Rutherford's VASCULAR SURGERY AND ENDOVASCULAR THERAPY

9TH EDITION

Anton N. Sidawy **Bruce A. Perler**

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VOLUME 1

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RUTHERFORD'S VASCULAR SURGERY AND ENDOVASCULAR THERAPY, NINTH EDITION

ISBN: 978-0-323-42791-3
Volume 1 Part Number: 999611774X
Volume 2 Part Number: 9996117804

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Library of Congress Cataloging-in-Publication Data
Names: Sidawy, Anton N., editor. | Perler, Bruce A., editor.
Title: Rutherford's vascular surgery and endovascular therapy / [edited by] Anton N. Sidawy, Bruce A. Perler.
Other titles: Rutherford's vascular surgery.
Description: Ninth edition. | Philadelphia, PA : Elsevier, [2019] | Preceded by Rutherford's vascular surgery / [edited by] Jack L. Cronenwett, K. Wayne Johnston. Eighth edition. 2014. | Includes bibliographical references and index.
Identifiers: LCCN 2018004364 | ISBN 9780323427913 (hardcover : alk. paper) | ISBN 9789996117749 (volume 1) | ISBN 9789996117800 (volume 2)
Subjects: | MESH: Vascular Surgical Procedures | Vascular Diseases—surgery | Endovascular Procedures
Classification: LCC RD598.5 | NLM WG 170 | DDC 617.4/13—dc23 LC record available at https://lccn.loc.gov/2018004364

Publisher: Russell Gabbedy
Senior Content Development Specialist: Joanie Milnes
Publishing Services Manager: Patricia Tannian
Senior Project Manager: Cindy Thoms
Book Designer: Ryan Cook

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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I dedicate this contribution to the memory of my parents, *Nicholas* and *Yvonne Sidawy*, who endeavored to instill in me at a very young age the values of hard work and persistence, along with the importance of pursuing a professional education. Their sacrifices enabled me to pursue my goal of becoming a surgeon and their selfless love, guidance, and unwavering support have always been my inspiration.

I dedicate my contribution to this book to the memory of my father and mother, *J. Leonard* and *Marcia Perler*. Although they never saw the inside of a college classroom, I learned more important life's lessons from them than from any school I ever attended; most important, the values of hard work, honesty, respect for others, and loyalty, which have always been the principles that have guided me in my career and in my life. Without their love, support, and lessons I would never have been this book's Editor.

We both dedicate this book to the patients with vascular disease, for the confidence they have expressed in all of us, allowing us the absolute privilege of caring for their vascular surgical needs. And to the trainees and to all those who care for the vascular patient by all means available—prevention, medical therapy, and surgical and endovascular techniques—and for whom the lessons of this book are intended.

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PREFACE

It is with a sense of deep professional pride and responsibility that we accepted our appointment as editors of *Rutherford's Vascular Surgery and Endovascular Therapy,* and by which we dedicated the past three years to build upon the unparalleled excellence of this textbook. This is *the definitive* reference text that has carried the name of one of the giants of our specialty, the late Dr. Robert Rutherford, who was a dear friend whose impact on the education of students, trainees, and practicing clinicians has been immeasurable. We are indebted to Dr. Rutherford, and to our colleagues, Drs. Jack Cronenwett and Wayne Johnston, who edited the seventh and eighth editions, for handing over to us a superb text to build on; a book that is without question the *bible* of vascular surgery.

Technology is advancing at a faster rate than at any time in our history, in terms of both the diagnosis and treatment of vascular disease, especially with respect to the endovascular treatment of aneurysmal and occlusive disease. Therefore, we decided to revise the title of this ninth edition to more accurately reflect the evolution of our specialty from purely open surgery to incorporating endovascular therapy in our armamentarium. Indeed, the content of these two volumes reflects the totality of care delivered by vascular surgeons in contemporary practice; namely, open surgery, endovascular therapy, and medical management of patients with the entire spectrum of circulatory disease, as well as presenting the most valuable diagnostic modalities.

This ninth edition contains 200 chapters organized in 31 sections. A concerted effort has been made to create shorter and more focused chapters to allow easier access to the desired information; having that in mind, we also included at the beginning of every chapter a listing of the topics discussed in that chapter. The roster of authors in this text includes the innovative leaders from all over the world who have been engaged in the advancement of the scientific basis and management of vascular disease to provide an unparalleled insight into the most appropriate contemporary and future treatment of these conditions. No other text can match the level of expertise assembled in this one book. Optimal patient outcomes increasingly are achieved through multidisciplinary care; therefore, we have recruited a unique roster of the most respected experts from the entire spectrum of medical specialties as well as vascular surgery and basic science, to provide the most comprehensive presentation of up-to-date knowledge and future directions in the care of circulatory disease. Likewise, in an increasingly global health care system, the authorship is decidedly international in scope to an unprecedented degree.

In many countries reimbursement for clinical services is being linked to quality outcomes rather than volume. The editors have tailored the presentation of information in each chapter so that the reader can practically apply the information provided to achieve the optimal outcomes at the least risk for the patient. This includes basing the content of each chapter on an evidence-based approach to the presentation of information.

Overall, we increased the number of the chapters in the book while we worked with our associate editors and contributors to make the chapters shorter and more focused so the overall number of pages did not significantly increase. We felt that the expansion in the number of chapters was necessary to incorporate new topics, reflect the rapid generation of new information, reorganize information on topics that gained more relevance over the years, or add topics that have not been included in past editions. For example, since many of today's vascular surgeons and interventionalists are being called upon to consult on vascular issues of the pediatric population, we added a section dedicated exclusively to pediatric vascular disease and its management. Recognizing the increasing regulatory and financial pressures faced by contemporary clinicians, this text includes an entire section on the business of vascular practice with a focus on the development and successful operation of outpatient vascular centers, multidisciplinary cardiovascular centers, importance of maintaining a vascular registry for the practice, and effective marketing strategies. Also, some sections have been strengthened by adding chapters that cover conditions being encountered more frequently in the daily practice of our practitioners, such as medial arcuate ligament syndrome and its contemporary management, vascular reconstructions in oncologic surgery, management of complex regional pain syndrome, and management of chronic compartment syndrome, among others. With the increasing performance of endovascular interventions, exposure to open surgery is decreasing while the contemporary vascular surgeon must continue to possess open vascular surgical skills. This text directly addresses that need by adding new chapters devoted to open surgical exposure and operative techniques with extensive illustrations and videos. In total, the ninth edition includes over 35 new chapters.

We are indebted to our twelve excellent associate editors who were each responsible for editing specific sections of the book; these are Drs. AbuRahma, Blankensteijn, Eidt, Forbes, Henke, Hoballah, Killewich, LaMuraglia, Mills, Rockman, Upchurch, and Weaver. Their diligence in working with the contributors to control the size and direct the focus of each chapter was instrumental in allowing us to execute our vision of increasing the number of chapters in the book while meeting our page allotment. We would like to thank our contributors who managed to produce the most up-to-date information available; they are the ones who did the majority of the work while following our, sometimes, burdensome instructions to make the book look and feel as one entity despite the participation of over 350 authors. We also greatly appreciate the hard work and attention to details by the production team at Elsevier, in particular, Joanie Milnes, Senior Content Development

Specialist; Cindy Thoms, Senior Project Manager, Books; and Russell Gabbedy, Publisher.

Finally, we would like to thank the Society for Vascular Surgery and its Publications Committee for putting their trust in us; we hope we were able to deliver what the readership will find educationally valuable, but most important, beneficial in improving the care of the vascular patient.

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COMMON ABBREVIATIONS

2,3-DPG, 2,3-diphosphoglycerate
2D, two-dimensional
3D, three-dimensional
5-HT, serotonin
AAA, abdominal aortic aneurysm
ABFB, aortobifemoral bypass
ABI, ankle-brachial index
ACA, anterior cerebral artery
ACE, angiotensin-converting enzyme
ACT, activated clotting time
ADA, American Diabetes Association
ADP, adenosine diphosphate
AEF, aortoenteric fistula
AF, atrial fibrillation
AFB, aortofemoral bypass
AGE, advanced glycosylation end product
AHA, American Heart Association
AHRQ, Agency for Healthcare Research and Quality
AI, aortoiliac
AIDS, acquired immunodeficiency syndrome
AKA, above-knee amputation
AMP, adenosine monophosphate
APC, activated protein C
APG, air plethysmography/ic
aPTT, activated partial thromboplastin time
ARB, angiotensin receptor blocker
ARDS, acute respiratory distress syndrome
ARF, acute renal failure
ASA, acetylsalicylic acid
ATN, acute tubular necrosis
ATP, adenosine triphosphate
AV, arteriovenous
AVF, arteriovenous fistula
AVG, arteriovenous graft
AVM, arteriovenous malformation
AVP, ambulatory venous pressure
bFGF, basic fibroblast growth factor
BKA, below-knee amputation
BSA, body surface area
BUN, blood urea nitrogen
CABG, coronary artery bypass grafting
CAD, coronary artery disease
cAMP, cyclic adenosine monophosphate
CAS, carotid artery stenting
CAVH, continuous arteriovenous hemofiltration
CAVHDF, continuous arteriovenous hemodiafiltration
CCA, common carotid artery
CCB, calcium channel blocker
CDC, Centers for Disease Control and Prevention
CEA, carotid endarterectomy
CEAP, clinical, etiologic, anatomic, pathologic [staging system]
CFA, common femoral artery
CFV, common femoral vein
cGMP, cyclic guanosine monophosphate
CI, confidence interval
CIA, common iliac artery
CK-MB, MB isozyme of creatine kinase
CKD, chronic kidney disease
CLI, critical limb ischemia
CMS, Centers for Medicare and Medicaid Services
CNS, central nervous system
CO, carbon monoxide
CO_2, carbon dioxide
COPD, chronic obstructive pulmonary disease
COX, cyclooxygenase
CRI, chronic renal insufficiency
CRP, C-reactive protein
CRPS, complex regional pain syndrome
CSF, cerebrospinal fluid
CT, computed tomography
CTA, computed tomographic angiography/ic
CTD, connective tissue disease
CTO, chronic total occlusion
CTV, computed tomographic venography/ic
CVD, cerebrovascular disease
CVI, chronic venous insufficiency
CVP, central venous pressure
CVVH, continuous venovenous hemofiltration
CVVHDF, continuous venovenous hemodiafiltration
DBI, digital-brachial index
DBP, diastolic blood pressure
DDAVP, desmopressin
DES, drug-eluting stent
DFU, diabetic foot ulcer
DIC, disseminated intravascular coagulation
DM, diabetes mellitus
DNA, deoxyribonucleic acid
DRIL, distal revascularization–interval ligation
DSA, digital subtraction angiography/ic
DSE, dobutamine stress echocardiography/ic
DTAA, descending thoracic aortic aneurysm
DUS, duplex ultrasound
DVT, deep venous thrombosis
EC, endothelial cell
ECA, external carotid artery
ECG, electrocardiogram
EC-IC, extracranial-intracranial [bypass]
ECM, extracellular matrix
ED, erectile dysfunction
EDS, Ehlers-Danlos syndrome
EDV, end-diastolic velocity
EEG, electroencephalography/ic
EF, ejection fraction
EIA, external iliac artery
ELAM-1, endothelial leukocyte adhesion molecule-1
ELISA, enzyme-linked immunosorbent assay
ELT, euglobulin lysis time
EMG, electromyography/ic
eNOS, endothelial nitric oxide synthase
ePTFE, expanded polytetrafluoroethylene
ESR, erythrocyte sedimentation rate
ESRD, end-stage renal disease
EVAR, endovascular aneurysm repair
FDA, U.S. Food and Drug Administration
FDP, fibrin/fibrinogen degradation product
FEV_1, forced expiratory volume in 1 second
FFP, fresh frozen plasma
FGF, fibroblast growth factor
FMD, fibromuscular dysplasia
FRC, functional residual capacity
FVC, forced vital capacity
G6PD, glucose-6-phosphate dehydrogenase
GA, general anesthesia
GFR, glomerular filtration rate
GI, gastrointestinal
GMP, guanosine monophosphate
GP-IIb/IIIa, glycoprotein IIb/IIIa
GSM, gray-scale median
GSV, great saphenous vein
GSW, gunshot wound
GTP, guanosine triphosphate
GUI, graphic-user interface

GW, guide wire
HD, hemodialysis
HDL, high-density lipoprotein
HIPAA, Health Insurance Portability and Accountability Act
HIT, heparin-induced thrombocytopenia
HIV, human immunodeficiency virus
HLA, human leukocyte antigen
HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A
HR, hazard ratio
HRQoL, health-related quality of life
hsCRP, high-sensitivity C-reactive protein
HTN, hypertension
I/R, ischemia-reperfusion
ICA, internal carotid artery
ICAM-1, intercellular adhesion molecule-1
ICAVL, Intersocietal Commission for the Accreditation of Vascular Laboratories
ICD, implantable cardioverter-defibrillator
ICH, intracerebral hemorrhage
ICU, intensive care unit
IDL, intermediate-density lipoprotein
IEL, internal elastic lamina
IFN, interferon
IFU, instructions for use
IGF, insulin-like growth factor
IH, intimal hyperplasia
IL, interleukin
IL-6, interleukin-6
IMA, inferior mesenteric artery
iNOS, inducible nitric oxide synthase
IOM, Institute of Medicine
IPC, intermittent pneumatic compression
IPG, impedance plethysmography
IPPB, intermittent positive pressure breathing
ISI, international sensitivity index
IVC, inferior vena cava
IVUS, intravascular ultrasound
JAK-2, Janus kinase-2
JNK, jun *N*-terminal kinase
KDOQI, Kidney Disease Outcomes Quality Initiative
KM, Kaplan-Meier
LAO, left anterior oblique
LDL, low-density lipoprotein
LMWH, low-molecular-weight heparin
LOS, length of stay
Lp(a), lipoprotein (a)
LS, lumbosacral
LV, left ventricular
LVEDP, left ventricular end diastolic pressure
LVEDV, left ventricular end diastolic volume
LVH, left ventricular hypertrophy
MAP, mean arterial pressure
MCA, middle cerebral artery
MI, myocardial infarction
MIP, maximum intensity projection
MMP, matrix metalloproteinase
MOF, multiple organ failure
MR, magnetic resonance
MRA, magnetic resonance angiography
MRI, magnetic resonance imaging
MRSA, methicillin-resistant *Staphylococcus aureus*
MRV, magnetic resonance venography
MTHFR, 5,10-methylenetetrahydrofolate reductase
NAC, *N*-acetylcysteine
NAD^+, oxidized nicotinamide dinucleotide
NADH, reduced nicotinamide adenine dinucleotide
NADPH, reduced nicotinamide adenine dinucleotide phosphate
NAIS, neo-aortoiliac system
Nd:YAG, neodymium:yttrium-aluminum-garnet
NF-κB, nuclear factor κB
NIH, National Institutes of Health
NIS, National Inpatient Sample
NOS, nitric oxide synthase
NPV, negative predictive value
NSAID, nonsteroidal anti-inflammatory drug
NSQIP, National Surgical Quality Improvement Program
OR, odds ratio
OTW, over-the-wire
PA, pulmonary artery
PAD, peripheral arterial disease
PAI, proximalization of arterial inflow
PAI-1, plasminogen activator inhibitor-1
PAOD, peripheral arterial occlusive disease
PAU, penetrating aortic ulcer
PBI, penile-brachial index
PBRCs, packed red blood cells
PCA, posterior cerebral artery
PCI, percutaneous coronary intervention
PCNA, proliferating cell nuclear antigen
PCWP, pulmonary artery wedge pressure
PD, peritoneal dialysis
PDE, phosphodiesterase
PDGF, platelet-derived growth factor
PE, pulmonary embolism
PECAM-1, platelet–endothelial cell adhesion molecule-1
PEEP, positive end-expiratory pressure
PEG, polyethylene glycol
PET, positron emission tomography/ic
PF4, platelet factor 4
PFA, profunda femoris artery
PFT, pulmonary function test/testing
PGE_2, prostaglandin E_2
PGI_2, prostaglandin I_2
PICCs, percutaneously inserted central catheters
PKC, protein kinase C
PMN, polymorphonuclear neutrophil
PPG, photoplethysmography
PPV, positive predictive value
PRBCs, packed red blood cells
PSA, pseudoaneurysm psi, pounds per square inch
PSV, peak systolic velocity
PT, prothrombin time
PTA, percutaneous transluminal angioplasty
PTFE, polytetrafluoroethylene
PTT, partial thromboplastin time
PVI, peripheral vascular intervention
PVR, pulse volume recording
QALY, quality-adjusted life year
QoL, quality of life
RAAA, ruptured abdominal aortic aneurysm
RAGE, receptor for advanced glycosylation end products
RAO, right anterior oblique
RAS, renal artery stenosis
RBC, red blood cell
RCT, randomized controlled trial
Re, Reynolds number
RFA, radiofrequency ablation
RGD, Arg-Gly-Asp
RI, resistive index
RIND, reversible ischemic neurologic deficit
RP, retroperitoneal
RR, relative risk
RS, Raynaud syndrome
rt-PA, recombinant tissue plasminogen activator
RUDI, revision using distal inflow
SBP, systolic blood pressure
SD, standard deviation
SE, standard error
SEPS, subfascial endoscopic perforator surgery
SF-36, Short Form (36) Health Survey
SFA, superficial femoral artery
SFJ, saphenofemoral junction
SK, streptokinase
SLE, systemic lupus erythematosus
SMA, superior mesenteric artery

SMC, smooth muscle cell
SOD, superoxide dismutase
SPECT, single-proton emission computed tomography
SPJ, saphenopopliteal junction
SSV, small saphenous vein
STEMI, ST-segment elevation myocardial infarction
SVC, superior vena cava
SVS, Society for Vascular Surgery
TAA, thoracic aortic aneurysm
TAAA, thoracoabdominal aortic aneurysm
TAAD, thoracic aortic aneurysm and dissection
TAO, thromboangiitis obliterans
TASC, Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease
TCD, transcranial Doppler
TEE, transesophageal echocardiography/ic
TEVAR, thoracic endovascular aortic repair
TF, tissue factor
TGF-β, transforming growth factor-β
TIMP-1, tissue inhibitor of matrix metalloproteinase-1
TIPS, transjugular intrahepatic portosystemic shunting
TLR, target lesion revascularization
TLR, Toll-like receptor
TMA, transmetatarsal amputation
TNF-α, tumor necrosis factor-α
TOS, thoracic outlet syndrome
t-PA, tissue plasminogen activator
TT, thrombin time
TTE, transthoracic echocardiography
TXA_2, thromboxane A_2
UFH, unfractionated heparin
UK, urokinase
u-PA, urinary (urokinase) plasminogen activator
USPSTF, U.S. Preventive Services Task Force
VATS, video-assisted thoracoscopic surgery
VCAM-1, vascular cell adhesion molecule-1
VEGF, vascular endothelial growth factor
VFI, venous filling index
VLDL, very-low-density lipoprotein
VSMC, vascular smooth muscle cell
VSS, Venous Severity Score
VTE, venous thromboembolism
vWF, von Willebrand factor
WBC, white blood cell
WIQ, Walking Impairment Questionnaire

1 CHAPTER

Epidemiology and Research Methodology

LOUIS L. NGUYEN and REBECCA E. SCULLY

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The goal of this chapter is to introduce the vascular surgeon to the principles that underlie the design, conduct, and interpretation of epidemiology and clinical research. Disease-specific outcomes otherwise detailed in subsequent chapters are not covered here. Rather, this chapter discusses the historical context, current methodology, and future developments in epidemiology, clinical research, and outcomes analysis. This chapter serves as a foundation for clinicians to better interpret clinical results and as a guide for researchers to further expand clinical analysis.

EPIDEMIOLOGY

The word *epidemiology* is derived from Greek terms meaning "upon" *(epi)*, "the people" *(demos)*, and "study" *(logos)* or "the study of what is upon the people." It exists to answer the four major questions of medicine: diagnosis, etiology, treatment, and prognosis.

Brief History

Hippocrates and his disciples not only marked the beginning of western medicine but were also among the first to begin to contemplate the role of external factors in disease. Sparking the beginnings of epidemiology, a great deal of time was spent investigating the progression of illness in their patients and their prognoses.[1] John Snow is often cited as the first modern epidemiologist. In the middle of a cholera epidemic in the summer of 1854, Snow, a physician, by mapping the geographic distribution of incident cases, successfully identified the source of the outbreak as contaminated water from the Broad Street pump.

Abstract

Evidence-based medicine seeks to guide the practice of medicine by using evidence from research studies. Basic understanding of epidemiology and clinical research methodology, therefore, is critical in interpreting research results and identifying its limitations. The application of research findings to practice and policy also is a key step in translating science into the care of patients.

Keywords

Epidemiology
Clinical Research
Statistics
Methodology

He then convinced local officials to remove the pump handle, thus shutting down the pump and stopping the outbreak.[2]

Modern Developments

The study of epidemiology continues the work of Hippocrates and Snow, working to investigate the cause and impact of disease. To achieve this goal and to be able to speak to causality, the ideal experiment often involves introducing an at-risk population to an exposure of interest and observing the results. In order to determine causality, one must then compare these results to what would have happened had that population not received the exposure. The first, or the observed outcome, is often referred to as the *factual outcome* and the alternative is the *counterfactual outcome.* Ideally one would be able to observe the outcome of the same individual in both the presence and absence of the exposure. However, lacking the ability to create multiple parallel universes, it must fall to clinical research and statistical methods to approximate this ideal.

CLINICAL RESEARCH METHODS

The choice of study design and statistical analysis technique depends on the available data, the hypothesis being tested, and patient safety and/or ethical concerns. Multiple options exist, each with their strengths and weaknesses.

Study Design

Clinical research can be broadly divided into observational studies and experimental studies. Observational studies are characterized by the absence of a study-directed intervention. Experimental studies involve testing a treatment, be it a drug, device, or clinical pathway. Observational studies can follow ongoing treatments but cannot influence choices made in the treatment of a patient. Observational studies can be executed in a prospective or retrospective fashion, whereas experimental studies can be performed only prospectively.

Deciding between these approaches is influenced by a number of factors. A key first step is to determine how common the disease or exposure of interest is. The *prevalence* of disease is the ratio of persons affected for the population at risk and reflects the frequency of the disease at a single time point, regardless of the time of disease development. In contrast, the *incidence* is the ratio of persons in whom the disease develops within a specified period for the population at risk. For diseases with short duration or high mortality, prevalence may not accurately reflect the impact of disease because the single time point of measurement does not capture resolved disease or patients who died of the disease. Prevalence is a more useful parameter in discussing diseases of longer duration, whereas incidence is more useful for diseases of shorter duration.

Observational Studies

There are two main types of observational studies: cohort and case-control. A cohort is a group that has something in common; in epidemiology this is frequently risk of a developing a disease of interest. Cohort studies enroll a population at risk and follow them for a period of time. Individuals who develop the disease in that time are then compared with individuals who remain disease-free. Many prominent studies of the modern epidemiology era have been cohort studies, including the Framingham Heart Study (FHS), which enrolled 5209 residents of Framingham, Massachusetts, in 1948 and has been monitoring that group and their descendants prospectively since that time; this endeavor has contributed greatly to our understanding of heart disease.[3] Since cohort studies tell us about the risk of a disease in two populations, exposed and nonexposed, one can determine a *relative risk* of a disease from a cohort study. If one were interested in evaluating the impact of smoking on developing peripheral artery disease (PAD), one could not simply look at the rate of PAD in smokers, since a baseline rate of PAD exists in the population that is not related to smoking. Instead, one could look at the rate of PAD in smokers and the rate of PAD in nonsmokers and compare the two to determine a relative risk.

For rare diseases with low frequency, it is not cost-effective to use a cohort study design. Instead, a *case series* seeks to prospectively follow or to retrospectively report findings of patients known to have a disease. When linked to a group free of the disease in question, a case series becomes a *case-control study.* Case-control studies are often less costly and are an important tool in studying a rare disease or a disease with a long latency time, since the disease is present at the time of enrollment.

Risk factors correlated with disease can be deduced by comparisons between the case and control groups. In this retrospective design, an *odds ratio* (OR) is calculated from the ratio of patients exposed to patients not exposed to the risk factor. This differs from relative risk (RR), in that the starting cohort is estimated only in case-control studies. The use of ORs reflects *Bayesian inference*, in which observations are used to infer the likelihood of a hypothesis. Bayesians describe probabilities conditional on observations and with degrees of uncertainty. In contrast, the alternative *probability theory* of Frequentists relies only on actual observations gained from experimentation.

The main challenge in case-control studies is to identify an appropriate control group with characteristics similar to those of the general population at risk for the disease. Inappropriate selection of the control group may lead to the introduction of additional confounding and bias. For example, matched case-control studies aim to identify a control group "matched" for factors found in the exposure group. Unfortunately, by matching even basic demographic factors, such as gender and the prevalence of comorbid conditions, unknown coassociated factors can also be included in the control group and may affect the relationship of the primary factor to the outcome. Appropriate selection of the control group can be achieved by using broad criteria, such as time, treatment at the same institution, age boundaries, and gender when the exposure group consists of only one gender.

Experimental Studies

The other large class among study designs is the *experimental study*. Unlike observational studies, experimental trials involve

introducing participants to an exposure of interest. One benefit of experimental studies is the ability to randomize participants, commonly via the *randomized controlled trial* (RCT). Although randomization ensures that known factors are evenly distributed between the exposure and control groups, the importance of RCTs lies in the even distribution of *unknown* factors. Thus, in a well-designed RCT, complex statistical models are not necessary to control for confounding factors.

There are several ways of structuring a randomization to address potential issues including complete randomization of the entire study population, block randomization, and adaptive randomization. For *complete randomization*, each new patient is randomized without prior influence on previously enrolled patients. The expected outcome at the completion of the trial is an equal distribution of patients within each treatment group, although unequal distribution may occur by chance, especially in small trials. *Block randomization* creates repeated blocks of patients in which equal distribution between treatment groups is enforced within each block. Block randomization ensures better end randomization and periodic randomization during the trial. End randomization is important in studies with long enrollment times or in multi-institutional studies that may have different local populations. Because the assignment of early patients within each block influences the assignment of later patients, block randomization should occur in a blinded fashion to avoid bias. Intrablock correlation must also be tested in the final analysis of the data. *Adaptive randomization* seeks to achieve balance of assignment of randomization for a prespecified factor (e.g., gender or previous treatment) suspected of affecting the treatment outcome. In theory, randomization controls for these factors, but unique situations may require stricter balance.

Experimental studies face stricter ethical and patient safety requirements than their observational counterparts. One basic assumption of experimental trials is *clinical equipoise*, or the existence of more than one generally accepted treatment.[4] This must exist both to create the situation where the research that is being undertaken will lead to clinical relevant information and that the treatment options to which a participant is randomized will not be assuming risk of care that is known to be inferior. Whereas you could not randomize people to observation only for a ruptured aortic aneurysm, for certain populations you could make an argument for endovascular versus open repair. This type of situation often arises when clinical experts professionally disagree on the preferred treatment method.[4] It is worth noting that although the field may have equipoise, individual healthcare providers or patients may have bias for one treatment. In such a case, enrollment in an RCT may be difficult because the patients or their providers are not willing to be subject to randomization.

Although RCTs represent the pinnacle in clinical design, there are many situations in which RCTs are impractical or impossible. Clinical equipoise may not exist, or common sense could prevent randomization of well-established practices, such as the use of parachutes during free fall.[5] RCTs can also be costly to conduct and must generate a new control group with each trial. For this reason, some studies are single-arm trials that use historical controls similar to the case-control design. In addition, patient enrollment may also be difficult, particularly if patients or clinicians are uneasy with the randomization of treatment. RCTs can also have methodologic and interpretative limitations. For example, if study patients are analyzed by their assigned randomization grouping (*intent to treat*) studies with asymmetric or high overall dropout and/or crossover rates may not reflect actual treatment effects. Given the cost and time required, RCTs are often conducted in high-volume specialty centers; as a result, enrollment and treatment of study patients may not reflect the general population with the disease or providers in the community. Finally, as with any analysis, inaccurate assumptions made in the initial power calculations may lead to failure to capture a true effect.

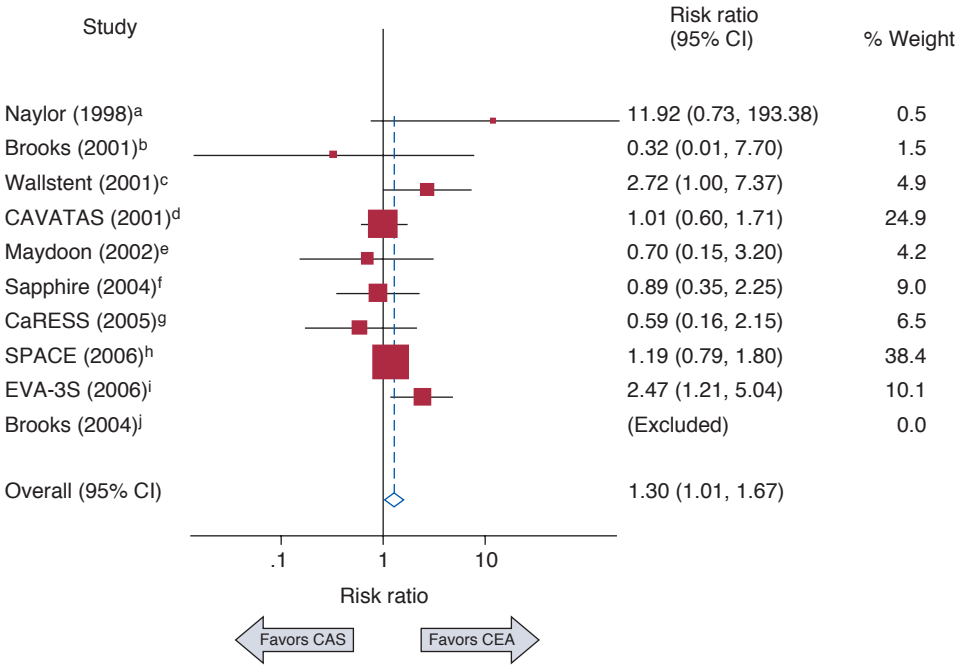
Special Techniques: Meta-Analysis

Meta-analysis is a statistical technique that combines the results of several related studies to address a common hypothesis. The first use of meta-analysis in medicine is attributed to Smith and Glass in their review of the efficacy of psychotherapy in 1977.[6] By combining results from several smaller studies, researchers may decrease sampling error and increase statistical power, thus helping to clarify disparate results among different studies.

The related studies must share a common dependent variable. *Effect size* specific to each study is then weighted to account for the variance in each study. Because studies may differ in patient selection and their associated independent variables, a test for heterogeneity should also be performed. Where no heterogeneity exists ($P > .5$), a fixed-effects meta-analysis model is used to incorporate the within-study variance for the studies included. A random-effects model is used when concern for between-study variance exists ($.5 > P > .05$). When heterogeneity among studies is found, the OR should not be pooled and further investigation for the source of heterogeneity may then exclude outlying studies.

The weighted composite dependent variable is visually displayed in a forest plot along with the results from each study included. Each result is displayed as a point estimate, with a horizontal bar representing the 95% confidence interval for the effect. The symbol used to mark the point estimate is usually sized proportional to other studies to reflect the relative weight of the estimate as it contributes to the composite result (Fig. 1.1). Classically, meta-analyses have included only RCTs, but observational studies can also be used.[7,8] Inclusion of observational studies can result in greater heterogeneity through uncontrolled studies or controlled studies with selection bias.

The strength of a meta-analysis comes from the strength of the studies that make up the composite variable. Furthermore, if available, the results of unpublished studies can also potentially influence the composite variable, because presumably many studies with nonsignificant results are not published. Therefore an assessment of *publication bias* should be included with every meta-analysis. Publication bias can be assessed graphically by creating a *funnel plot* in which the effect size is compared with the sample size or another measure of variance. If no bias is present, the effect sizes should be balanced around the population



[a] Naylor AR, et al: Randomized study of carotid angioplasty and stenting versus carotid endarterectomy: a stopped trial. *J Vasc Surg* 28:326-334, 1998.

[b] Brooks WH, et al: Carotid angioplasty and stenting versus carotid endarterectomy: randomized trial in a community hospital. *J Am Coll Cardiol* 38:1589-1595, 2001.

[c] Alberts MJ: Results of a multicenter prospective randomized trial of carotid artery stenting vs carotid endarterectomy. *Stroke* 32:325, 2001.

[d] Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 357:1729-1737, 2001.

[e] Madyoon H, et al: Unprotected carotid artery stenting compared to carotid endarterectomy in a community setting. *J Endovasc Ther* 9:803-809, 2002.

[f] Yadav JS, et al: Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 351:1493-1501, 2004.

[g] Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. *J Vasc Surg* 42:213-219, 2005.

[h] SPACE Collaborative Group, et al: 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 368:1239-1247, 2006.

[i] Mas JL, et al: Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 355:1660-1671, 2006.

[j] Brooks WH, et al: Carotid angioplasty and stenting versus carotid endarterectomy for treatment of asymptomatic carotid stenosis a randomized trial in a community hospital. *Neurosurgery* 54:318-324, discussion 324-325, 2004.

Figure 1.1 Example of a forest plot from a meta-analysis of carotid artery stenting *(CAS)* versus carotid endarterectomy *(CEA)* to determine 30-day risk for stroke and death. *CI*, confidence interval. (Redrawn from Brahmanandam S, Ding EL, Conte MS, et al. Clinical results of carotid artery stenting compared with endarterectomy. *J Vasc Surg.* 2008;47:343–349.)

mean effect size and decrease in variance with increasing sample size. If publication bias exists, part of the funnel plot will be sparse or empty of studies. *Begg's test* for publication bias is a statistical test that represents the funnel plot's graphic test.[9] The variance of the effect estimate is divided by its standard error to give adjusted effect estimates with similar variance. Correlation is then tested between the adjusted effect size and the meta-analysis weight. An alternative method is *Egger's test*, in which the study's effect size divided by its standard error is regressed on 1/standard error.[10] The intercept of this regression should equal zero, and testing for the statistical significance of nonzero intercepts should indicate publication bias.

OUTCOMES ANALYSIS

As physicians, we can usually see the natural progression of disease or the clinical outcome of treatment. Although these observations can be made for individual patients, general inferences about causation and broad application to all patients cannot be made without further analysis. Clinical analysis attempts to answer these questions by either observing or testing patients and their treatments. Because clinical analysis can be performed only on a subset or sample of the relevant entire population, a level of uncertainty will always exist in clinical analysis. Statistical methods are an integral aspect of clinical analysis because they

help the researcher understand and accommodate the inherent uncertainty in a sample in comparison to the ideal population. In the following sections, common clinical analytic methods are reviewed so that the reader can better interpret clinical analysis and also have foundations to initiate an analysis. Reference to biostatistical and econometric texts is recommended for detailed derivation of the methods discussed.

Bias in Study Design

In discussing statistical methods, it is important to remember that clinical analysis can estimate only the "true" effects of a disease or its potential treatments. Because the true effects cannot be known with certainty, analytic results carry potential for error. All studies can be affected by two broadly defined types of error: random error and systematic error. *Random error* in clinical analysis comes from natural variation and can be handled with the statistical techniques covered later in this chapter. *Systematic error*, also known as *bias*, affects the results in one unintended direction and can threaten the validity of the study. Bias can be further categorized into three main groupings: selection bias, information bias, and confounding.

Selection bias occurs when the effect being tested differs among patients who participate in the study as opposed to those who do not. Because actual study participation involves a researcher's determination of which patients are eligible for a study and then the patient's agreement to participate in the study, the decision points can be affected by bias. One common form of selection bias is self-selection, in which patients who are healthier or sicker are more likely to participate in the study because of perceived self-benefit. Selection bias can also occur at the level of the researchers when they perceive potential study patients as being too sick and preferentially recruit healthy patients.

Information bias exists when the information collected in the study is erroneous. One example is the categorization of variables into discrete bins, as in the case of cigarette smoking. If smoking is categorized as only a yes or no variable, former smokers and current smokers with varying amounts of consumption will not be accurately categorized. *Recall bias* is another form of information bias that can occur, particularly in case-control studies. For example, patients with abdominal aortic aneurysms may seemingly recall possible environmental factors that put them at risk for the disease. However, patients without aneurysms may not have a comparable imperative to stimulate memory of the same exposure.

Confounding is a significant factor in epidemiology and clinical analysis. Confounding exists when a second spurious variable (e.g., race/ethnicity) correlates with a primary independent variable (e.g., type 2 diabetes) and its associated dependent variable (e.g., critical limb ischemia). Researchers can conclude that patients in certain race/ethnicity groups are at greater risk for critical limb ischemia when diabetes is the stronger predictor. *Confounding by indication* is especially relevant in observational studies. This can occur when, without randomization, patients being treated with a drug can show worse clinical results than untreated counterparts because treated patients were presumably sicker at baseline and required the drug a priori. Confounding can be addressed by several methods: assigning confounders equally to the treatment and control groups (for case-control studies), matching confounders equally (for cohort studies), stratifying the results according to confounding groups, and multivariate analysis.

Statistical Methods

At the beginning of most clinical analyses, *descriptive statistics* are used to quantify the study sample and its relevant clinical variables. *Continuous variables,* or variables that can take on any value in a range between a minimum and a maximum, such as weight or age, are expressed as means or medians; *categorical variables*, or variables that have only a discrete value, such as institution of treatment or TASC Classification, are expressed as numbers or percentages of the total. A subset of categorical variables are *ordinal variables,* in which categories have some structure or relative value, such as good, better, best. Study sample characteristics and their relative distribution of comorbid conditions help determine whether the sample is consistent with known population characteristics and hence addresses the issue of generalizability of the clinical results to the overall population.

The next step in clinical analysis is *hypothesis testing*, in which the factor or treatment of interest is tested against a control group. The statistical methods used in hypothesis testing depend on the research question and characteristics of the data under comparison (Box 1.1). At its core, hypothesis testing asks whether the observable differences between groups represent true differences or if they just appear different because of random change. A wide variety of tests exist and each attempts to answer this question in a way that is appropriate to the data in question.

One major distinguishing characteristic of data is whether they fit a *normal*, or *Gaussian*, *distribution*, where the distribution of continuous values is symmetric and has a mean of 0 and a variance of 1. Gaussian distributions are one example of *parametric data* in which the form of the distribution is known. In contrast, *nonparametric data* are not symmetric around a mean, and the distribution of the data is more random. Nonparametric statistical methods make fewer assumptions about the shape of the distribution and trade power for accuracy. In general, nonparametric methods can be used for parametric data to increase robustness, but at the cost of statistical power. However, the use of parametric methods for nonparametric data or data containing small samples can lead to misleading results.

Regression Analysis

Among the statistical tests available, a few deserve special mention because of their common application to the clinical analysis of studies of vascular patients. *Regression analysis* is a mathematical technique in which the relationship between a dependent (or response) variable is modeled as a function of one or more independent variables, an intercept, and an error term. Models often describe a linear relationship between dependent and independent variables; however, they can also take on polynomial relationships, including quadratic and cubic functions. Regression analysis produces regression coefficients for each variable of

BOX 1.1 Choosing Statistical Tests Based on Research Question and Data Characteristics

Is There a Difference Between Means, Medians, and Proportions?

One Group

- Parametric data: one sample *t*-test
- Nonparametric data: sign test, Wilcoxon signed rank test, transform data for *t*-test
- Proportions: exact binomial test, z approximation to exact test

Two Independent Groups

- Parametric data: *t*-test
- Nonparametric data: Wilcoxon rank-sum test
- Proportions: chi-squared or Fisher's exact test

Two Related Groups

- Parametric data: paired *t*-test
- Nonparametric data: sign test, Wilcoxon signed-rank test
- Proportions: McNemar's test or kappa statistic

Three or More Independent Groups

- Parametric data: ANOVA
- Nonparametric data: Kruskal–Wallis test
- Proportions: chi-squared or Fisher's exact test

Three or More Related Groups

- Parametric data: repeated-measures ANOVA
- Nonparametric: ANOVA by ranks

Is There an Association?

Two Comparable Variables

- Nominal data: relative risk
- Ordinal data: Spearman's rank correlation test
- Continuous data: linear regression

One Dependent Variable and Two or More Independent Variables

- Binary dependent variable: logistic regression
- Categorical dependent variable: ANCOVA
- Continuous dependent variable: multiple linear regression
- Censored observations: CPH model
- Clustered or hierarchic parametric data: linear mixed models
- Clustered or hierarchic semiparametric data: GEE

ANCOVA, analysis of covariance; *ANOVA*, analysis of variance; *CPH*, Cox proportional hazards; *GEE*, generalized estimating equations.

interest. Regression coefficients, or *betas* (β), describe the magnitude of the effect that each independent variable *(x)* has on the dependent variable *(y)*. For binary dependent variables, a *logistic* (logit) *regression* is used, whereas for continuous dependent variables, a *linear regression* is used (see Box 1.1). The *goodness of fit* for the model is tested by using the R^2 value (R squared) and the analysis of residuals. R^2 is the proportion of variability that is accounted for by the model and has a range of 0 to 1. Although larger R^2 values imply better fit, there is no defined threshold for goodness of fit and R^2 can be artificially inflated by adding more variables to the model. Thus an adjusted R^2, which also accounts for the number of variables in the model, should be used.

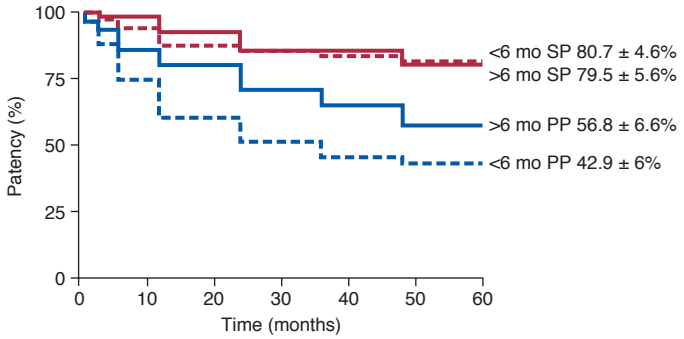


Figure 1.2 Example of life-table analysis of primary patency *(PP)* and secondary patency *(SP)* of bypass grafts after being revised before or after 6 months from the index operation. (Redrawn from Nguyen LL, Conte MS, Menard MT, et al. Infrainguinal vein bypass graft revision: factors affecting long-term outcome. *J Vasc Surg*. 2004;40:916–923.)

Survival Analysis

Survival analysis was developed to assess patient survival, and while death is often the primary event of interest, survival analysis can also be used to assess treatment failure, such as time to loss of graft patency or amputation. Rather than simply addressing frequency, survival analysis also captures an element of time to an event. It also incorporates *censorship*, in which data about the event of interest are unknown because of withdrawal of the patient from the study. Traditionally in clinical analysis, *death* is the event variable, and *loss to follow-up* is the censorship variable. In vascular surgery, where graft patency is more often the endpoint of interest, *graft patency* is treated as the event variable and *death* and/or *study withdrawal* is treated as the combined censoring variable. This assumes that censorship (death) is not due to the event (loss of graft patency); however, this assumption cannot be held true in other fields, such as oncology (death attributable to failure of cancer treatment) or cardiac surgery (death caused by loss of coronary artery bypass graft patency).

In essence, survival analysis accounts for event status between fixed periods of measurement. For example, in traditional methods, if graft patency is measured only after 1 year, a graft that fails at 30 days is statistically treated the same as a graft that fails on day 364. Similarly, a graft that was patent at 360 days but was lost to follow-up is treated the same as a graft that was patent but lost to follow-up at 60 days. In contrast, *life-tables* measure events at fixed intervals (e.g., every 30 days), so occurrences before 365 days are accounted for (Fig. 1.2).[11] Such analysis allows greater precision of events, but resolution is still limited to fixed time points. These limitations are addressed by using the *Kaplan–Meier* (KM) *method*. KM captures each event at the time of occurrence without the need for fixed time frames (Fig. 1.3).[12] Although the KM method allows more precise analysis of events and censorship, life tables are still appropriate when only predetermined periodic measurement of events is available or when arbitrary important milestones are of interest, such as 1-year graft patency or patient survival.

The strength of survival analysis lies in the ability to statistically account for censored data. The *KM estimator* (also known as the *product-limit estimator*) is the nonparametric maximum

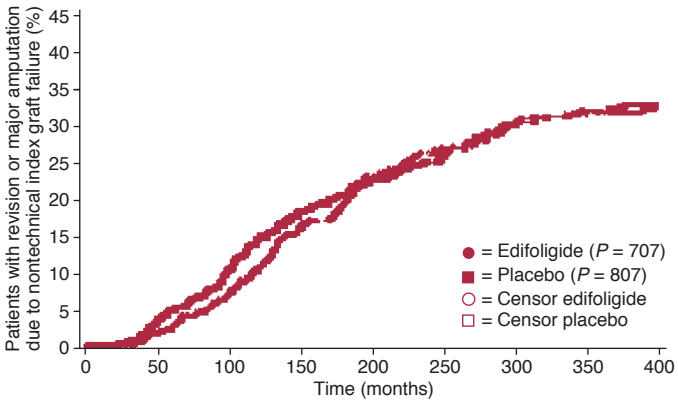


Figure 1.3 Example of Kaplan-Meier analysis of the effect of edifoligide on nontechnical graft failure. Each mark represents an event (graft failure) or censor (death or dropout). (Redrawn from Conte MS, Bandyk DF, Clowes AW, et al. Results of PREVENT III: A multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. *J Vasc Surg*. 2006; 43:742–751, discussion 751.)

likelihood estimator of the survival function, which is based on the probability of an event conditional on reaching the time point of the previous event. The *life-table method* (or *actuarial method*) treats censored events as though they had occurred at the midpoint of the time period. Most commonly, the Greenwood formula is used to calculate the standard error of the KM and life-table estimator for independent events.

Several tests are commonly used to test for differences between survival functions. The *log-rank test* adds observed and expected events within each group and sums them across all time points containing events. The log-rank statistic serves as the basis for the proportional hazards model (further on). In contrast, the *Wilcoxon test* is the log-rank test weighted by the number of patients at risk for each time point. Mathematically, the Wilcoxon test gives more weight to early time points and is thus less sensitive than the log-rank test to differences between groups that occur at later time points. Unlike the parametric log-rank and Wilcoxon tests, *Cox proportional hazards models* assume that the underlying hazard (risk) function is proportional over time, so that parameters can be estimated without complete knowledge of the hazard function. Other hazard models—such as the exponential, Weibull, or Gompertz distributions—instead assume knowledge of the hazards function. The Cox proportional hazards assumption allows the application of survival analysis techniques to multivariable models because individual hazards do not have to be specified for each independent variable in the model.

Longitudinal Analysis

Longitudinal data, or repeated measures from the same patient or patients over time, can be of interest in many situations, such as improvements in walking scores over time following exercise interventions for PAD. There are two aspects of longitudinal data that complicate statistical analysis. One is that repeated measures in the same patient are often positively correlated. For example, a patient who is obese at baseline is more likely to be overweight at the next measure no matter the intervention. The other issue is that that the degree of variability in repeated measures tends to vary over time. For example, the variability in individuals' response to a medication or treatment will become more apparent over time. This violates the assumption of homoscadicity, that variance around a regression line is the same for all values of a predictor. Several models exist to address these issues and to capture the covariance of repeated measures. *Mixed effects models* capture a more typical regression but also include terms for variability for individuals. Covariance structures, or assuming patterns to covariance rather than allowing them to be completely random, can capture covariance but preserve power.

Propensity Scoring

In comparing two groups that were not randomized, *propensity scoring* is a technique that can be employed to control for confounding and is often used when treatment groups are related to indication; for example, in comparing endarterectomy with stenting for carotid artery stenosis, as patients who underwent stenting may have more comorbidities or a different disease pattern than patients selected for carotid endarterectomy. Each individual included in the trial is assigned a propensity score that reflects the conditional probability of being in a treatment group based on selected variables. This balances the treatment groups for the variables on which the score is based.

There are two common methods of propensity scoring: trimming and reweighting. In trimming, patients at the extremes of the propensity score are eliminated from the analysis so that the remaining cohorts are more comparable matches. In reweighting, all patients are kept in the analysis, but their characteristics are reweighed to provide equivalency between groups.

As with other methods, propensity scoring can control only for known confounders, again falling short of the randomized controlled trial in its ability to balance unknown factors. Further, to appropriately balance but not confound the outcome, the variables used to create the propensity score should be related to treatment assignment but not to the outcome of interest.

Despite these drawbacks, when an RCT is not possible or practical, propensity scoring methods are useful for providing some insight in comparing treatment groups. Propensity score methods have also been used for other purposes, including nesting covariates for multivariable regression models and generating reweighted estimating equations to rebalance weights from missing data. RCTs further have the advantage of limiting the number of variables in a model and thus preserving power.

Errors in Hypothesis Testing

Important to an understanding of statistical methods is an appreciation of the potential pitfalls and shortcomings of the tools presented in the following paragraphs.

The default understanding of hypothesis testing, or the null hypothesis, is that there is no difference between the groups of patients in question. The alternative to this, called *the alternative hypothesis*, is that a difference does exist. Because you can only ever estimate the effect of various factors, you can never prove the alternative hypothesis. Instead, if the data suggest that a

difference does exist, you can reject the null hypothesis and conclude that there may be an effect. If the data suggest that there is no difference between groups, then you fail to reject the null hypothesis and conclude that there is likely no difference between them.

Two types of errors can be made in hypothesis testing. A *type I error* is rejection of the null hypothesis when the null hypothesis is in fact true. Alpha (α) is the probability of making a type I error. The *P* value is calculated from statistical testing and represents the probability of obtaining a result as extreme or more extreme than the results observed. Commonly, α is set at .05, and a *P* value less than α would reject the null hypothesis. Because 0.05 is a somewhat arbitrary setting, many will report actual *P* values to more precisely communicate statistical significance. Stricter α can be used when concern for a type I error is heightened, as in the testing of a large number of independent variables. For example, if 20 variables are tested, 1 variable (on average) is expected to be falsely positive with an α of .05. Accordingly, a stricter α of .01 or less may be required to reduce type I error. Conversely, a more relaxed α (typically .20) can be used in building stepwise regression models to be more inclusive of borderline variables.

A *type II error* is failure to reject the null hypothesis when the null hypothesis is false. Beta (β) is the probability of making a type II error. *Power* is defined as the probability of rejecting the null hypothesis when it is false (or concluding that the alternative hypothesis is true when it is true). In other words, power is the ability of a study to detect a true difference. Power is calculated as $1 - \beta$ and is closely related to sample size. Power analysis can be performed before or after data collection. *A priori power analysis* is used to determine the sample size needed to achieve adequate power for a study. *Post hoc power analysis* is used to determine the actual power of the study. Power analysis requires specification of several parameters, including α (usually 0.05), the level of power desired (usually 80%), expected effect size, and variance. Variance is simply estimated from previous measurements of related outcomes. However, the expected effect size is a parameter most susceptible to unintended influence. Setting the expected effect size too small decreases type I error but also decreases power and results in the necessity of enrolling larger numbers of patients. Setting the expected effect size too large allows lower enrollment numbers, but at the cost of type I error. The actual calculation for necessary sample size depends on the expected statistical test for the data and can be performed by using "power calculators" available at statistics websites or with statistical software packages.

Statistical and Database Software

Before the widespread use of computers, statistics were calculated by hand. Statistical software and computing power have greatly improved the ability and efficiency of statisticians and clinical researchers. Even rapid advancements in desktop computing allow for increasingly complex modeling. At its core, statistical software requires user coding of specific commands to perform data analysis and database manipulation. *SAS* (originally meaning Statistical Analysis System) was created by Anthony Barr from his work as a graduate student at North Carolina State University in the early 1960s. He and other collaborators later created the SAS Institute in 1976 to commercialize the statistical package. SAS statistical software is widely used in clinical analysis of large trials, epidemiology, the insurance industry, and other business applications of data mining. Frequently the development of new statistical techniques is included as new SAS commands or macros. *Stata* was created by Statacorp and is the other widely used statistical program, especially in the social sciences and economics.

Both SAS and Stata, in addition to their native coding interface, also have graphics user interfaces (GUIs) that automate or facilitate statistical analysis. Most other statistical packages, such as *SPSS* (originally Statistical Package for the Social Sciences), *JMP*, and *Minitab*, are promoted with GUIs and pulldown menus as the primary interface for performing statistical tests. Another statistical package that is rapidly gaining in popularity is *R*, particularly because it is both free and highly functional.

Economic Analysis

The concept of providing value in healthcare continues to gain traction in the current political and economic environment. Success following bypass graft or stent placement is not measured only in patency but also in improvements in a patient's ambulatory status and overall quality of life (QoL). This has driven an increasing interest in economic and cost-benefit analysis both in procedural fields and across medicine as a whole.

Utility Measures

In economic analysis and decision analysis, patients are considered to be in distinct "states" governed by specific diagnoses or symptoms; for example, asymptomatic versus symptomatic carotid artery stenosis or claudication versus critical limb ischemia. *Utility measures* capture the value a person places on a state of health. Such measures then can be used in decision trees and cost-effectiveness analysis. The Health Utilities Index and the EQ-5D are two widely used utility measures. The simplest method of determining utility is to ask patients to value their own health or a hypothetical state of health by using a rating scale. This information is then transformed into a utility measure by using data from a reference population. Transformations of health states from descriptive instruments (e.g., SF-36) have also been created, although low correlations between descriptive and preference measures have been demonstrated. For transformations to be meaningful, the reference population itself has to be subject to utility assessment.

Direct assessment of utility can be performed by using the *standard gamble*, in which, for a given health state, patients are asked whether they would choose to remain in that state or take a gamble between death and perfect health. The question is then repeated with varying gamble probabilities. The utility of the health state is then derived from the probability of achieving perfect health when the patient is at equilibrium (or indifferent between the choices) between taking the gamble or remaining in the known state of intermediate health. Another common

direct utility assessment method is the *time tradeoff*, in which the patient is asked to choose between a length of life in a given compromised state and a shorter length of life in a perfect state. The utility of the health state is then derived from the ratio of the shorter to the longer life expectancy at the point of equilibrium.

Because these utility assessment methods are artificial and do not actually expose subjects to decisions with true implications, variations in utility values exist between the methods. Generally, standard gamble methods generate the highest utility values because most patients are unwilling to accept a significant risk of sudden death, even if the alternative health state is poor. Utility values from time tradeoff methods are lower, which is consistent with the theory that decreased life expectancy is an easier price to pay for a chance to improve health. Rating scales usually generate the lowest utility values because there is no perceived penalty for underrating, as there is with the other methods.

Decision Analysis

Decision analysis is the formal methodology of addressing decisions by defining a problem, considering alternative choices, and then modeling the consequences of these alternatives based on an estimated risk of each alternative. This process has the potential to capture varying outcomes for individual types of patients and can also demonstrate critical factors that may alter their decisions.

One of the primary tools used in decision analysis is the decision tree, where the relevant factors are represented in chronologic relationship flowing left to right. The alternative choices (diagnostic tests, natural history states, treatments, etc.) are visually represented as branches of the tree, and each branch point is a decision node (usually represented as a square) in which a choice is possible, or a chance node (usually represented as a circle) in which the probability of a consequence is conditional on the events that preceded it. The end of each branch has an outcome that is based on the one that preceded it and their probabilities. Each outcome (life expectancy, quality-adjusted life years [QALYs], etc.) is given a value and the expected value for each alternative is then calculated on the basis of cumulative probabilities and outcome values. Decisions can then be made to optimize an outcome value, such as the lowest cost or highest QALYs.

The results from decision analysis are strongly influenced by the event probabilities and outcome values used. Ideally, these figures are derived from strong clinical studies in the field, although a consensus on precise figures and values can be difficult. *Sensitivity and threshold analysis* can then be performed to test the results of decision analysis under different probability and outcome assumptions. Sensitivity analysis is performed mathematically by setting the key probability as an unknown variable to be solved algebraically. This results in a probability value threshold around which the analysis can change to favor different decisions. If the threshold value (or probability) is within accepted estimated clinical probabilities for that event, researchers can have greater confidence in the applicability of the decision analysis results.

Markov Models and Monte Carlo Simulation

The decision trees discussed in the previous section work well for clinical situations in which one or a small number of decisions are made over a defined time frame. In reality, decision points may occur repeatedly, and the relevant factors influencing the outcome may also change over time. *Markov models* (named after the Russian mathematician Andrey Markov) assume that patients begin in one of a discrete number of possible mutually exclusive "states." For every cycle, each patient has a probability of remaining in the state or transitioning between one state and the next. Markov models also assume the Markov property, whereby future states are independent of past states. The model can then be analyzed by using matrixes, cohort simulation, or Monte Carlo simulation. *Matrix solutions* require matrix algebra techniques and can be used only when transition probabilities do not vary over time and costs are not discounted. *Cohort simulation* begins with a hypothetical large cohort of patients and subjects them to the Markov transition probabilities. A table is then generated with the new cohort distribution among the states. The process is repeated for the next and subsequent cycles until there is equilibrium or all patients are in a state without an exit, called *the absorbing state*. *Monte Carlo simulation* is similar to cohort simulation except that one patient at a time is simulated rather than the entire cohort. The simulation continues until the patient arrives at the absorbing state or the predetermined cycle is reached in models without absorbing states. Simulation of individual patients allows researchers to measure the variance of outcomes in addition to the mean.

Cost-Benefit and Cost-Effectiveness Analysis

At the heart of cost analysis is the assumption that resources are constrained. If unlimited resources are available, all testing and treatment would be offered as long as they were not harmful. However, in an environment of limited resources, cost analysis helps policymakers and clinicians decide on the greatest utility of the resources available. Cost analysis is certainly not the only or necessarily the best criterion for making health policy decisions. It is, however, an objective, quantitative tool that yields important information about the efficacy of clinical practice and does help to better clarify healthcare decisions.

From an economic standpoint, tests or treatments can be measured on two parameters: health improvement and cost savings. Treatments that both improve health and save costs are the goal and should be readily adopted. At the opposite end of the spectrum, treatments that worsen health and increase costs should be abandoned. Less clear cut are those interventions that fall within the spectrum—treatments that improve outcomes but also increase costs or those that save costs but fail to show improved outcomes. *Cost-effectiveness analysis* compares treatments based on a common measure of costs and effectiveness. The measure of effectiveness can be represented by the number of lives saved, cases cured, cases prevented, and preference-based utility measures such as QALYs. *Cost-benefit analysis* seeks to quantify costs and effectiveness in monetary

terms. Cost-benefit analysis is useful for comparing very different choices of treatments or interventions. Because many involved in healthcare are uncomfortable with the monetary valuation of life and life-years, cost-effectiveness is more commonly used in health-related analysis, whereas cost-benefit is more prevalent in economically oriented healthcare analysis.

The cost-effectiveness measure is the ratio of cost to effectiveness, typically dollars per QALY gained. Comparative choices (treatments, programs, tests) are subsequently ranked in order of lowest cost-effectiveness ratio to highest. These ratios can then be used to drive funding decisions. If funding is distributed to programs starting with the lowest cost per unit of efficacy, the cost-effectiveness ratio of the last funded program in this algorithm is defined as the *permissible cost-effectiveness threshold* for other programs to meet. In the United Kingdom, the National Institute for Health and Clinical Excellence has adopted a cost-effectiveness threshold range of £20,000 to £30,000 ($28,400-42,600 in US dollars) per QALY gained. In the United States, no official threshold has been adopted, although many in practice have used the threshold of $60,000 per QALY. This figure is based on the calculated average cost of hemodialysis per person per year and Medicare's special coverage of renal failure patients regardless of age.

The term *cost* is often misunderstood and misused. In economic analysis, cost is not limited to currency but can be applied to the use of other resources including time, personnel, and space. *Opportunity cost* is the loss or sacrifice incurred when one mutually exclusive option is chosen over another. Thus, if a plot of land is chosen to be developed into a hospital, the cost of that project includes the building cost as well as the lost opportunity to build a different facility at that site.

Specific to healthcare is the fact that cost must also be distinguished from "charges" by healthcare researchers because administrative accounting data often contain billing charges, which are based on the cost of materials and services but may also include indirect costs and a margin for profit. For most healthcare cost analyses, cost is stated from the perspective of the society. This utilitarian perspective differs from the perspective of the patient, provider, and institution. Although these other perspectives have validity, the societal perspective is more comprehensive and eliminates distortions, such as moral hazard and cost shifting.

Evidence in Practice

Evidence-based medicine is a relatively modern approach to the practice of medicine that aims to qualify and encourage the use of currently available clinical evidence to support a particular treatment paradigm. This practice encourages the integration of an individual practitioner's clinical expertise with the best currently available recommendations from clinical research studies.[2] Reliance on personal experience alone can lead to biased decisions, whereas reliance solely on results from clinical research studies can lead to inflexible policies. Evidence-based medicine stratifies the strength of the evidence from clinical research studies based on study design and statistical findings (Table 1.1). The criteria differ when the evidence is sufficient to support a specific therapeutic approach, prognosis, diagnosis, or other health services research. Criteria also differ among research institutions, including the US Preventive Services Task Force and the UK National Health Service. However, common themes can be seen among the different fields. Systematic reviews with homogeneity are preferred over single reports, whereas RCTs are preferred over cohort and case-control studies. Even within similar study design groupings, the statistical strength of each study is evaluated, with preference for studies with large numbers, complete and thorough follow-up, and results with small confidence intervals. Clinical recommendations are then based on the available evidence and are further graded according to their strengths (Table 1.2).

TABLE 1.1 Levels of Evidence for Therapeutics

Level	Evidence
1a	Systematic reviews of RCT studies with homogeneity
1b	Individual RCT with narrow confidence intervals
1c	"All or none" trials[a]
2a	Systematic reviews of cohort studies with homogeneity
2b	Individual cohort studies
2c	Clinical outcomes studies
3a	Systematic reviews of case-control studies with homogeneity
3b	Individual case-control studies
4	Case-series studies
5	Expert opinion without critical appraisal or based on bench research

[a]In which *all* patients died before the therapeutic became available, but some now survive with it, or in which some patients survived before the therapeutic became available, but now *none* die with it.
RCT, randomized controlled trial.
Modified from Oxford Centre for Evidence-Based Medicine (2001).

TABLE 1.2 Grades of Recommendation

Grade	Recommendation	Basis
A	Strong evidence to support practice	Consistent level 1 studies
B	Fair evidence to support practice	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Evidence too close to make a general recommendation	Level 4 studies or extrapolation from level 2 or 3 studies
D	Evidence insufficient or conflicting to make a general recommendation	Level 5 evidence or inconsistent studies of any level

Modified from U.S. Preventive Services Task Force Ratings (2003) and Oxford Centre for Evidence-based Medicine (2001).

OUTCOMES TRANSLATIONAL RESEARCH

The practice of surgery has changed greatly since its early beginnings. Issues of anatomy, physiology, and anesthesia gave way to improving technology and the refinement of surgical technique. As surgeons gained technical skill and collective expertise, clinical outcomes and evidence-based medicine began to take on increasing importance. The proliferation of surgical care (and medicine as a whole) does come with a cost, however. In the United States, healthcare expenditures for the year 2014 reached $3 trillion, or approximately $9523 per person or 17.5% of the gross national product. Other developed countries spend less, but their expenditures are increasing.

Although the actual care of patients will continue to challenge us, the way we conduct and finance healthcare will also have a profound impact. Healthcare is a continuum from advancements in basic sciences, patient applications, clinical outcomes, efficacy analysis, and policy. The ultimate goal of the many tools described here is to improve patient care. Where *translational research* captures the connection between the basic sciences and patient care, *outcomes translational research* can be thought of as the connection between clinical outcomes and healthcare policy. Policy decisions based on expenditure caps can control healthcare costs. However, if these decisions are made arbitrarily, the resulting distribution of resources may be inefficient. Ideally, healthcare policy should be based on clinical evidence and efficacy should maximize limited resources.

Outcomes translational research begins with a careful analysis of clinical results. Such an analysis should ideally incorporate carefully designed studies to elucidate the natural history of a disease and compare treatment options. Even the outcome measure itself needs thoughtful selection. For example, in the surgical treatment of claudication, the classic measure of outcome was bypass graft patency. With the greater adoption of percutaneous treatment methods, vessel patency has been adopted. However, vessel patency does not accurately reflect all outcomes. From the patient's perspective, symptom relief and improvement in QoL is the benchmark. Although vessel patency clearly influences walking function, a patent vessel does not confer improved walking if other comorbid conditions, such as severe arthritis or neuropathy, are limiting. Conversely, assessment of functional and QoL endpoints alone does not allow analysis of the components leading to patient-perceived improvements. Greater understanding of technical success, vessel patency, and treatment durability will allow further improvements in the treatments themselves. Therefore measurement of clinical outcomes is a multimodal technique involving the use of integrated components that measure several aspects of success and failure.

Although there is no doubt that the results of clinical trials have had an impact on the care of surgical patients, these trials are costly and may not have comprehensive generalizability. The majority of vascular surgery occurs outside of clinical trials, in institutions of varying size, and by practitioners of varying expertise. The outcomes of these "real world" efforts are not well studied and may not mirror the experience of large academic institutions. To begin to address healthcare at a population level, many have used large national or statewide administrative databases in an attempt to analyze care broadly. Although such efforts can be informative when they are used appropriately, it is often difficult to draw clinical recommendations from these databases, which are primarily based on billing rather than clinical information. Often limiting in vascular surgery, most administrative databases do not distinguish the left from the right extremity. Thus, two vascular procedures performed on an extremity within 1 year can represent a revision of the first procedure, or they can signify sequential bilateral procedures. Comprehensive registries that allow broader inclusion of patients who receive care within specific diagnostic groups have begun to address these issues. Although countries with single-payer healthcare are more easily able to establish national registries, databases comprising regional vascular surgery patients exist and have helped to inform vascular care. The cost of such endeavors is certainly a factor in achieving a nationwide database, although arguably the cost of not knowing the outcomes and efficacy of healthcare may be greater.

The use of economic analysis is an important component of outcomes translational research because healthcare, like all human effort, requires resources. Economics has often been maligned as being "cold"; however, this quality is its strength, not its weakness. Few of us can hope to be without bias in making healthcare decisions for ourselves, our patients, or our relatives, and each specialty group strives to increase resources that can be applied to their disease or cause. The economic analysis of healthcare allows assessment of outcomes as measured by a common comparable unit (cost). However, economics as a whole can shed light only on the tradeoffs between different alternatives and their impact. It is up to policymakers to assign value to these tradeoffs and, in the end, make decisions about the allocation of healthcare resources. In some ethical and societal frameworks, additional value may be assigned to the treatment of specific disease groups (e.g., dialysis care) not captured by traditional analytic methods. Nevertheless, without clinical and economic analytic tools, such decisions are made without reference to their impact on alternative decisions. Clinician researchers in outcomes translational research are well suited to contribute to the policies that affect healthcare because they can generate data to help formulate policy and they also see the effect of policy on the individual patients they are treating.

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2 CHAPTER

Embryology and Developmental Anatomy

ERIC D. ENDEAN

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The fundamental purposes of the vascular system are to supply the organism with oxygen and nutrients and to remove metabolic waste products. During the first 3 weeks of gestation, simple diffusion is sufficient to support the embryo; however, by the fourth week, a functional cardiovascular system must be in place to maintain the rapidly developing embryo. The cardiovascular system in the embryo is one of the first and earliest systems to appear and begin to function. Isolated blood vessels and blood components form in the yolk sac by day 17, while just a day later, isolated blood vessels begin to appear in the embryo proper. The heart begins to beat by day 22 and pumps blood by day 24. Failure of the vascular system to properly develop can result in the appearance of variations or abnormalities that can have clinical ramifications. By understanding the embryology of the vascular system, the vascular surgeon will be better able to recognize vascular anomalies and understand how they may have developed.

FORMATION OF EMBRYONIC BLOOD VESSELS

Molecular Signaling of Vasculogenesis and Angiogenesis

Historically the development of the vascular system has been thought to be no more than the growth of arteries, veins, and lymphatic vessels from a basic set of tubes. In reality, the development of the vascular system is a complex orchestration of signaling molecules, receptor molecules, and transcription factors. The initial step is the modification of splanchnic mesodermal cells into angioblasts that form vesicular aggregates in the splanchnic mesoderm of the embryo and extraembryonic regions, including the yolk sac, the connecting stalk, and the chorion.[1] Under the control of signaling molecules, these angioblasts develop into flattened endothelial cells that form

Abstract

The development of the vascular system is a complex but orderly process orchestrated by signaling and receptor molecules, transcription factors, and environmental factors. When normal development fails to occur, anatomic variations or anomalies ensue which in turn can have clinical implications. Normal development of the arterial, venous and lymphatic systems is outlined in the chapter. Common vascular anomalies that occur with failure of proper development of the vascular system are also highlighted.

Keywords

Aortic arch
Aortic arch, development of
Aortic arch, anomalies
Aorta, coarctation
Aorta, double aortic arch
Aorta, right aortic arch
Angiogenesis
Embryology
Limbs, development
Sciatic artery
Popliteal entrapment
Venous system, development
Superior vena cava, anomalies
Inferior vena cava duplication
Lymphatic system, development

small vessel cords, which will, in turn, coalesce with one another to form vessels. This process, termed *vasculogenesis*, begins first in the yolk sac at day 17. Hemangioblastic aggregates composed of an inner core of hematopoietic stem cells and an outer rim of endothelial cells form in the yolk sac.[2,3] The hematopoietic stem cells serve as the source of blood cells to the embryo until day 60, when the liver, spleen, thymus, and ultimately the bone marrow become the source of blood cells. Hemangioblastic aggregates also form in the connecting stalk and chorion at day 17, and coalesce to form the extraembryonic umbilical vessels that will act as the circulatory connection between the embryo and the maternal tissue.

Once endothelial cells are established as vascular elements, they begin to sprout and bud, forming simple capillary networks. These capillary networks remodel into arterial, capillary, and venous systems, as determined by the surrounding environment. In addition, some presumptive vessels will undergo vascular intussusception to remodel and generate additional vessels. Much of this growth is under the influence of vascular endothelial growth factor (VEGF), which activates a series of molecular and cellular events that ultimately lead to a stable vascular network.[4] Local hypoxia upregulates a number of genes and facilitates angiogenic sprouting from existing vessels. Signaling molecules also lead to endothelial specificity, such as vessels with a fenestrated endothelial layer found within the capillaries, as seen in endocrine glands and the kidneys, or tight junctions as seen in the capillaries of the brain (i.e., the blood-brain barrier).[4,5]

Veins and arteries have been used to describe vessels whose direction of blood flow is either toward (veins) or away from (arteries) the heart. Although there are morphologic differences in the walls of veins and arteries, it was not until recently that it has been demonstrated that arteries and veins are also different with regard to specific cell surface markers that trace back to the receptors found on angioblasts. The development of lymphatics is also under the control of specific genes that are expressed in a specific subpopulation of endothelial cells associated with the anterior cardinal veins. Cells from the cardinal veins bud, divide, and migrate to form lymph sacs and ultimately lymphatic vessels.[6,7]

Early Angiogenesis

As the major vascular structures including the heart, dorsal aortas, umbilical vessels, vitelline vessels, and cardinal veins are being formed by vasculogenesis, the embryo is already beginning to remodel this vascular system by the processes of angiogenesis and vascular intussusception. Other factors, especially related to the heart and dorsal aortas, have a profound effect on the definitive vascular system's configuration. By day 20, the growth of the neural tube forces the cardiogenic area ventrally and caudally to its final position in the thoracic region, whereas lateral folding of the embryo causes the two endocardial tubes to fuse along the midline, resulting in a single endocardial tube with a more cranially placed outflow and a more caudally located inflow region. As the developing heart lengthens, a series of swellings become visible. Beginning at the inflow end, these include the sinus venosus with its right and left horns, primitive atrium, primitive left ventricle, bulbus cordis (future right ventricle), and truncus arteriosus. The aortic sac, the rostral dilation of the truncus arteriosus, connects the developing heart to the dorsal aortas. Between days 22 and 24, the developing heart moves into its ventral position, and the attached dorsal aortas are forced into a dorsoventral bend that forms the first aortic arch. The first aortic arch is contained in the thickened mesoderm of the developing first pharyngeal arch surrounding the pharynx. Aortic arches 2 through 6 form from mesenchyme within their own pharyngeal arches in a rostral to caudal sequence between days 26 and 30. Lateral folding of the embryo also forces the paired dorsal aortas, beginning at the fourth thoracic somite, to fuse with one another as a common aorta; however, rostral to this level, the dorsal aortas remain as separate vessels. By the beginning of the fourth week, intersegmental vessels between each somite arise from the dorsal aortas. Each intersegmental vessel has a dorsal branch, a lateral branch, and a ventral branch that supply the individual somite regions.

Aortic Arch

Normal Arch Development

The vascular system in humans is symmetric, with the exception of the adult aortic arch. The right common carotid and right subclavian arteries arise from the brachiocephalic (innominate) artery, whereas the left common carotid and left subclavian arteries originate as separate vessels from the aortic arch. These differences are a consequence of the changes in the connections of the aortic arches, the dorsal aortas, and the aortic sac. Diagrammatic representation of these changes would suggest that the aortic arches are all present at the same time, but in reality, the first arches are already regressing while others are still developing.

The first two aortic arches appear and regress quickly and contribute very little to adult structures, whereas the fifth aortic arch never develops in humans (Fig. 2.1A). The third aortic arches become the common carotid arteries and proximal segments of the internal carotid arteries. The distal segments of the internal carotid arteries are derived from the dorsal aorta between the first and third arches. The external carotid arteries sprout from the common carotid arteries. The dorsal aorta on each side of the embryo between the third and fourth arches disappears, thus directing blood through the third aortic arch system to the head and neck regions (see Fig. 2.1B). The fourth aortic arches are asymmetrical with regard to their fate. The left aortic arch forms that part of the adult aortic arch between the left common carotid and left subclavian arteries, whereas the right aortic arch becomes the proximal segment of the right subclavian artery. The remainder of the right subclavian artery is derived from the right dorsal aorta and its right seventh intersegmental artery. The right dorsal aorta distal to the seventh intersegmental artery, but proximal to the fused common aorta, involutes (see Fig. 2.1C). The right horn of the aortic sac, connected to the right third and fourth aortic arches, elongates to become the brachiocephalic (innominate) artery, and the left horn becomes the initial portion of the aortic arch. The proximal portions of

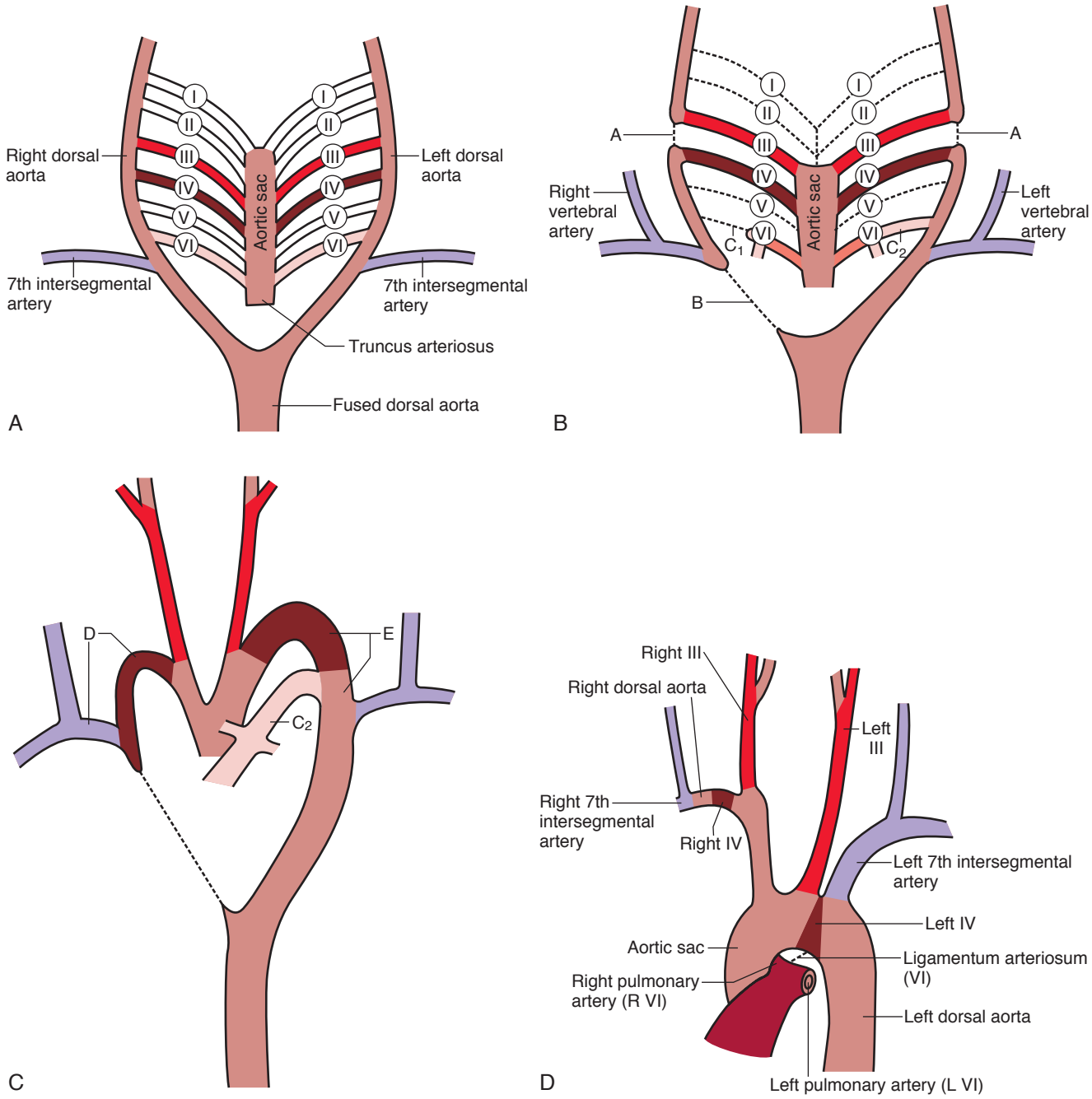


Figure 2.1 **(A)** The six primitive aortic arches. The first, second, and fifth arches disappear. The paired dorsal aortas fuse at the level of the seventh cervical vertebra to become the thoracic and abdominal aorta. **(B)** Differentiation of the aortic arches. The dorsal aorta between the third and fourth arches *(A)* involutes so that blood entering the third arch perfuses the head only. The third arch and its branches become the carotid system. The right dorsal aorta distal to the right seventh intersegmental artery *(B)* involutes so that blood entering the right fourth arch perfuses the right upper limb. This system becomes the right subclavian artery. The distal part of the right sixth arch *(C_1)* involutes, but the distal part of the left sixth arch *(C_2)* persists and becomes the ductus arteriosus. **(C)** Development of the aortic arches. The right fourth arch, the dorsal aorta distal to the right fourth arch, and the right seventh intersegmental artery become the right subclavian artery *(D)*. The left fourth arch and the left dorsal aorta distal to it become part of the aortic arch *(E)*. The left seventh intersegmental artery becomes the left subclavian artery. Pulmonary arteries form from the sixth arch with the ductus arteriosus *(C_2)* present. **(D)** Segments of the aortic arches that produce the adult aortic arch. The patent ductus arteriosus becomes the ligamentum arteriosum.

both sixth arches become the right and left pulmonary arteries. The distal segment of the right sixth arch disappears, but the distal segment of the left sixth arch becomes the ductus arteriosus during fetal life and atrophies after birth to become the ligamentum arteriosum (see Fig. 2.1D).

Aortic Arch Anomalies

In light of the complexity of events that must occur for normal development of the aortic arch and its branches, anomalies do occur.[8-14] Anomalies result when segments of the primitive aortic arch that should disappear persist or vice versa, when other parts that should persist disappear. Variations in the development of vessels as they arise from the aortic arch are relatively common. The most common developmental pattern considered to be "normal," as described in the preceding sections and illustrated in Fig. 2.1D, occurs in 65% of the population. In 22% of the population, the left common carotid artery originates from the brachiocephalic trunk rather than from the aortic arch, in what is termed a "bovine arch." In this case, the brachiocephalic trunk gives rise to the right subclavian, right common carotid, and left common carotid arteries, whereas the left subclavian artery originates from the aortic arch as normally expected. This variant accounts for 73% of all arch anomalies. Many other variations, each occurring in less than 3% of the population, have been described. Some of these anomalies include a very shortened brachiocephalic trunk that bifurcates immediately into the right subclavian and right common carotid arteries, with the left common carotid arising from the aortic arch at the base of the brachiocephalic trunk and a normal origin for the left subclavian artery from the aortic arch. The left vertebral artery can originate directly from the aortic arch between the left common carotid and left subclavian arteries. A left brachiocephalic trunk may be present, which bifurcates into left subclavian and left common carotid arteries.[8]

Patent Ductus Arteriosus

The ductus arteriosus develops from the distal portion of the left sixth aortic arch and is responsible for shunting blood from the immature, developing fetal lungs to the systemic circulation. A patent ductus arteriosus is the most common vascular anomaly. At birth, the ductus normally constricts in response to exposure of the now high oxygen content in the blood by oxygen-sensitive smooth muscle cells in its wall. By the age of 1 month, the ductus normally obliterates to become the ligamentum arteriosum. If the ductus arteriosus does not constrict and remains patent, blood is shunted from the high-pressure thoracic aorta to the low-pressure pulmonary system, eventually resulting in significant pulmonary hypertension (Fig. 2.2).

Coarctation of the Aorta

Aortic coarctation can be seen at any level of the aorta, but the most common location is postductal, just distal to the ligamentum arteriosum; the preductal type occurs immediately proximal to the ligamentum. The etiologic mechanism of coarctation remains unclear, but it is hypothesized that its development is similar to the process that results in normal, physiologic obliteration of the ductus arteriosus. It is thought that oxygen-sensitive

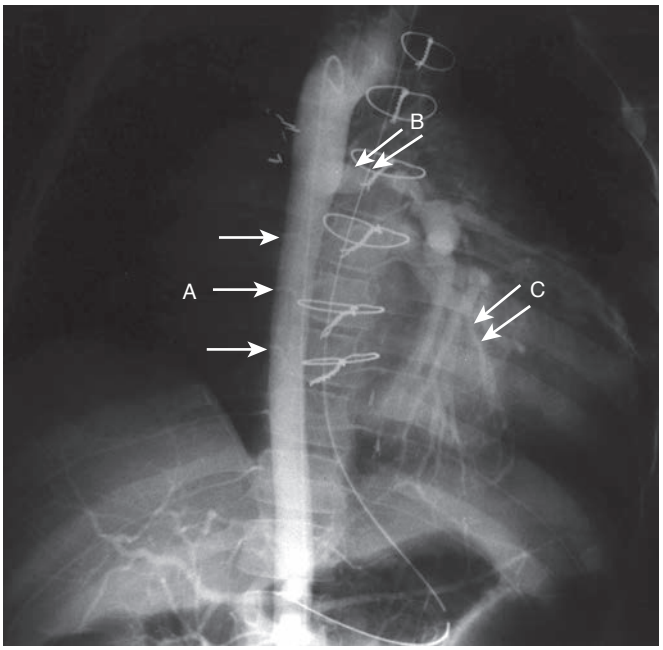


Figure 2.2 Right-sided aorta with a patent ductus arteriosus. *Arrows* point to the right-sided aorta *(A)*. A patent ductus arteriosus *(B)* is filling the pulmonary arteries *(C)*.

muscle tissue from the ductus arteriosus is incorporated into the wall of the aorta. This smooth muscle, which constricts when exposed to high oxygen tension, results in narrowing of the aorta at this level. Eventually chronic changes develop, and the constriction becomes permanent. Relative ischemia of the body below the constriction stimulates the development of collateral vessels. Radiographically, notching on the inferior aspect of the third to eighth ribs may be seen as a consequence of the increased collateral blood flow in the intercostal arteries (Figs. 2.3 and 2.4).[6,14,15]

Double Aortic Arch

The right dorsal aorta distal to the right seventh intersegmental artery may fail to involute, with the result being a double aortic arch. This segment passes posterior to the esophagus and joins the left aortic arch, which passes anterior to the trachea. As a result, a vascular ring forms around the esophagus and trachea. Symptoms may develop from compression of the esophagus and/or trachea (Fig. 2.5).

Right Aortic Arch

Involution of the left dorsal aorta distal to the left seventh segmental artery with persistence of the right dorsal aorta (opposite the normal sequence) creates a right aortic arch (Fig. 2.6). The ligamentum arteriosum arises from the distal right sixth arch instead of the distal left sixth arch, but still connects to the aorta. If the arch passes to the left side and posterior to the esophagus, a vascular ring is formed with the ligamentum arteriosum and is known as a right aortic arch, with an aberrant left subclavian artery or a retroesophageal component. If the right aortic arch passes anterior to the esophagus and trachea, a vascular ring is not formed, and it is considered to be a right

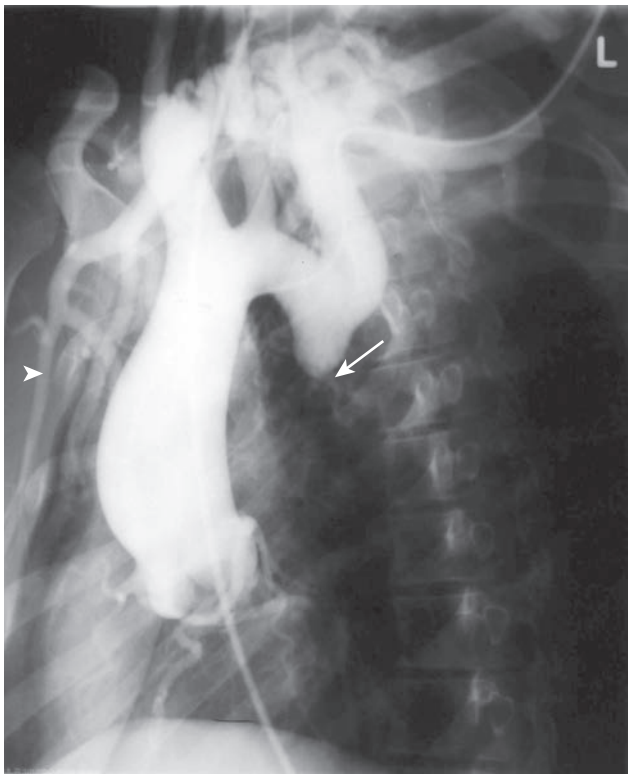


Figure 2.3 Coarctation of the aorta is identified by the *arrow*. Note the enlarged great vessels. The right internal mammary *(arrowhead)*, a major collateral vessel to the lower portion of the body, is very visible and enlarged.

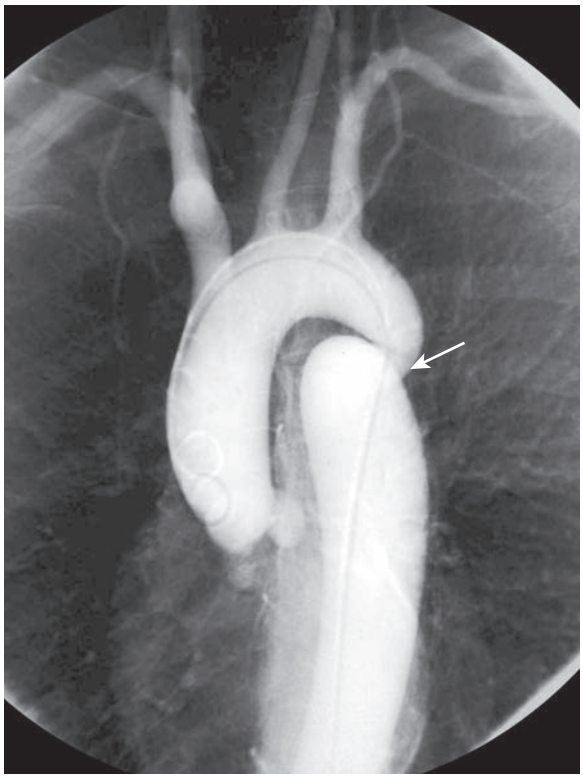
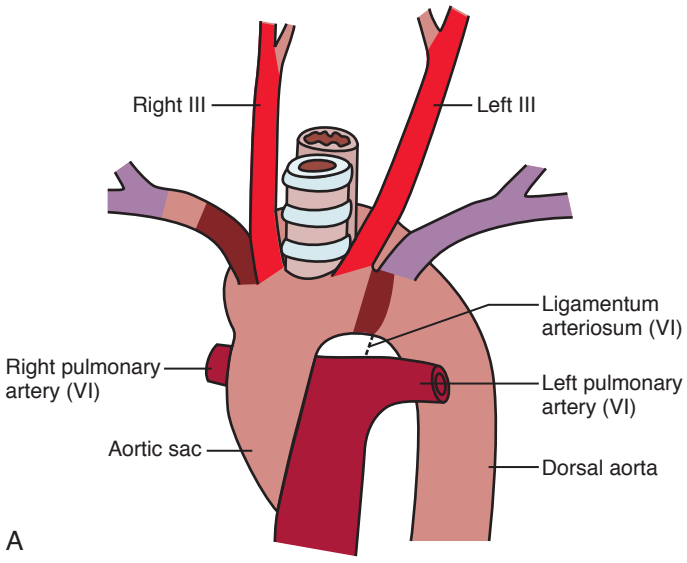


Figure 2.4 Coarctation of the aorta *(arrow)*, with poststenotic dilation of the aorta.



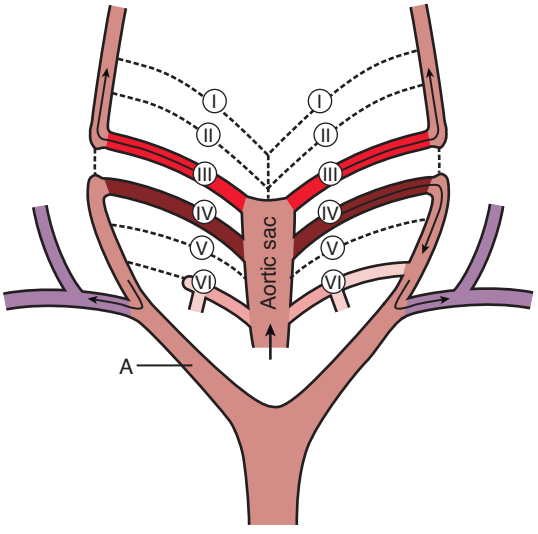


Figure 2.5 Double aortic arch. **(A)** The aortic arch passes anterior and posterior to the trachea and esophagus to form a vascular ring. **(B)** The right dorsal aorta distal to the right seventh intersegmental artery *(A)*, which normally involutes, persists to become part of the double aortic arch.

aortic arch with mirror image branching. The former anomaly may initially be a double aortic arch, in which the left dorsal aorta later regresses (see Fig. 2.2). The latter is a mirror image of normal anatomy and is associated with a higher incidence of heart malformations in which almost all infants are cyanotic. An example of a heart malformation associated with mirror image branching of the aortic arch is tetralogy of Fallot.[14]

Retroesophageal Right Subclavian Artery

The right subclavian artery normally forms from the right fourth aortic arch and the seventh intersegmental artery, connected by the intervening segment of the right dorsal aorta. A retroesophageal right subclavian artery forms as a result of abnormal involution of the right fourth aortic arch and the connected right dorsal aorta (Fig. 2.7). The right dorsal aorta distal to the

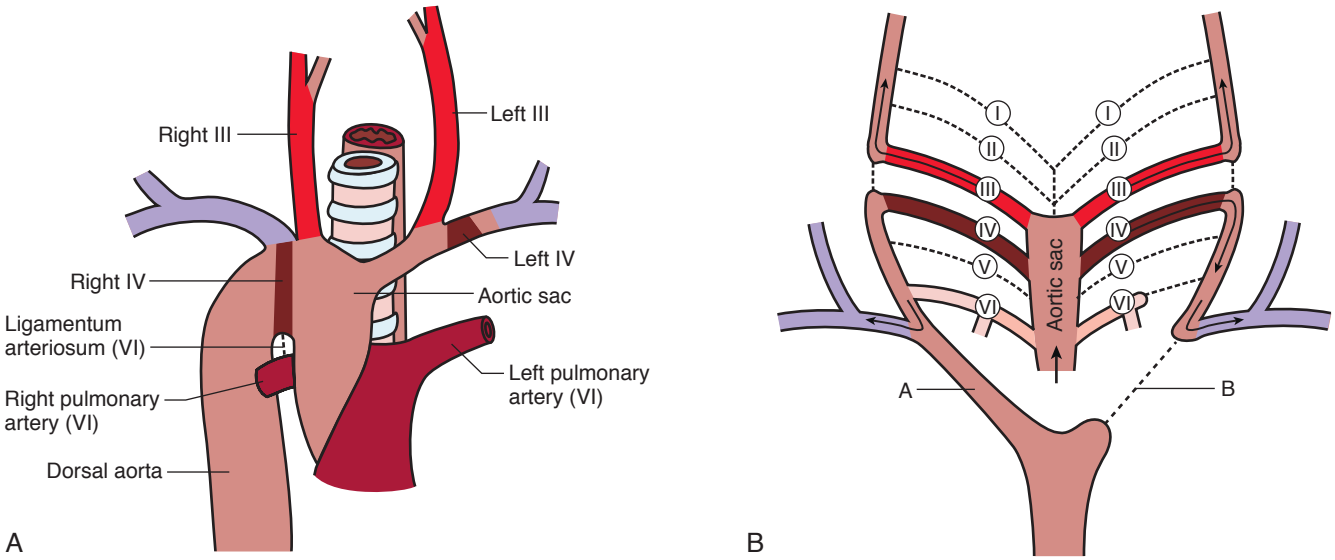


Figure 2.6 Right aortic arch. **(A)** One of two types in which the right arch passes anterior to the trachea and esophagus so that no vascular ring is formed. If the right arch passes posterior to the trachea and esophagus, the ligamentum arteriosum and the right arch form a vascular ring. **(B)** The right dorsal aorta distal to the right seventh intersegmental artery persists *(A)*, but the left dorsal aorta distal to the left seventh intersegmental artery involutes *(B)*, the opposite of the normal occurrence.

right intersegmental artery persists instead of involuting and joins the right seventh intersegmental artery to form the right subclavian artery. As the proximal portion of the aortic arch develops from the aortic sac, the right subclavian artery is forced to the left side and has an origin distal to the left subclavian artery. The right subclavian artery travels from the left side of the aorta behind the esophagus to supply the right upper limb. Most patients with this entity are asymptomatic, but about 5% have compression of the esophagus, resulting in difficulty with swallowing, a condition known as *dysphagia lusoria*.[10] In addition, this anomaly is prone to developing an aneurysm, a condition termed *Kommerell diverticulum*. These aneurysms can lead to compressive symptoms (dysphagia, cough, dyspnea), thromboembolism, or rupture (Fig. 2.8).

DEVELOPMENT OF THE DESCENDING (THORACIC AND ABDOMINAL) AORTA

During the fourth week, the paired dorsal aortas caudal to the level of the seventh cervical somite fuse to become the descending (thoracic and abdominal) aorta. At about the same time, the first of 36 to 38 segments or somites begin to form throughout the length of the embryo. At each somite level, segmental arteries continue to form dorsal, ventral, and lateral branches. The dorsal branches supply the developing neural tube and epimere (which becomes the epaxial muscle of the back), whereas the ventral branches supply the hypomere that become the intercostal muscles, external, and internal obliques, and transversus abdominus and overlying skin. In cervical regions, the dorsal intersegmental branches anastomose with one another to form the vertebral arteries, as well as the deep cervical and ascending cervical arteries. In thoracic regions, the dorsal branches form the intercostal arteries. Ventral branches anastomose with one another and contribute to the formation of the superior thoracic artery, internal thoracic artery, and the superior epigastric arteries. At the lumbar level, the dorsal intersegmental branches become lumbar arteries, with the fifth lumbar pair remaining as the common iliac arteries. The lumbar ventral branches form allantoic and vitelline vessels. The segmental arteries forming the allantoic vessels become the umbilical arteries, whereas the other paired ventral segmental vessels connect to the yolk sac and develop into the vitelline arteries. As the gastrointestinal tract develops, the vitelline arteries become its blood supply and fuse to become the three unpaired gut vessels: the celiac artery supplying the foregut, the superior mesenteric artery supplying the midgut, and the inferior mesenteric artery supplying the hindgut. The embryonic-derived components of the umbilical arteries are originally the ventral branches of the dorsal aorta. The bases of these segmental vessels later connect with the fifth intersegmental branches. The proximal portions involute, ultimately leading to the formation of the internal iliac arteries in the adult.

The lateral segmental arteries supply the primitive urogenital ridge, which is the source of the gonads and kidney. The most rostral part of the urogenital ridge develops two sets of primitive kidneys, the pronephros and mesonephros, which over time disappear. The most caudal part of the urogenital ridge becomes the metanephros, which develops into the adult kidney. At the seventh week of gestation, the "rostrally migrating" metanephros establishes and loses connection with a series of arteries, each of which will eventually regress. The metanephric kidneys establish connections with several rostral lateral segmental arteries that persist and fuse with one another to form definitive renal arteries. Not surprisingly, considerable variations exist in the

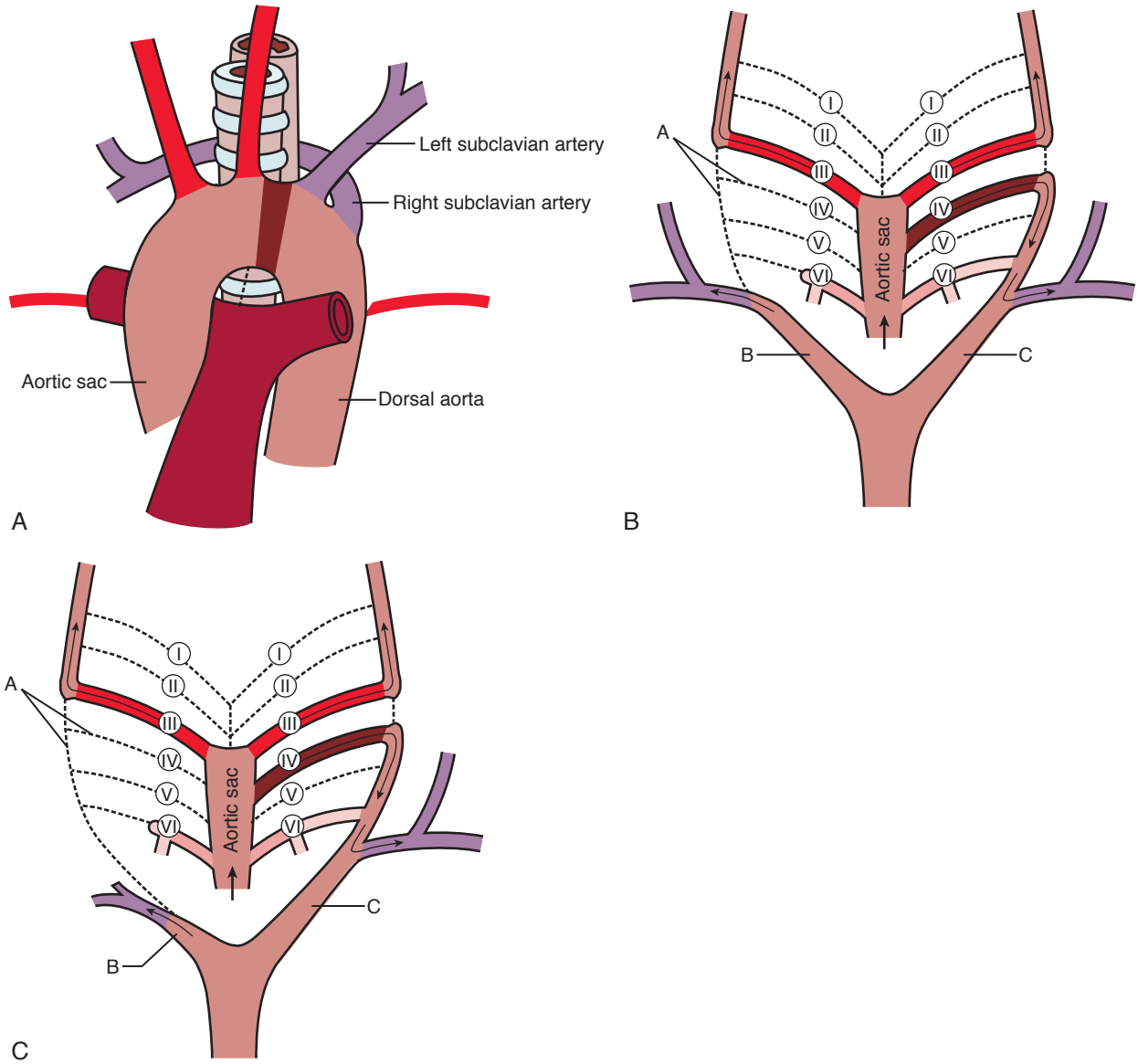


Figure 2.7 Retroesophageal right subclavian artery. **(A)** The right subclavian artery originates distal to the left subclavian artery and reaches the right upper limb by passing posterior to the trachea and esophagus. **(B)** The right fourth arch and the dorsal aorta distal to the right fourth arch *(A)* abnormally involute, and therefore cannot contribute to formation of the right subclavian artery. The right subclavian artery is then formed by the right dorsal aorta distal to the right seventh intersegmental artery *(B)*, which normally involutes *(C)*. This becomes part of the thoracic aorta. **(C)** The left dorsal aorta *(C)* elongates, enlarges, and moves craniad to become the thoracic aorta. The right dorsal aorta *(B)* shortens considerably to become a branch of the thoracic aorta leading to the subclavian artery *(A)*. This section abnormally involutes (see **B**).

arterial supply to the kidney.[16,17] Most individuals (71%) have a single artery to each kidney, whereas remaining individuals have a variety of combinations of hilar and accessory branches to the poles of the kidneys. Horseshoe kidneys develop with fusion of the caudal kidney poles. Such fusion arrests rostral migration of the kidney, and multiple segmental arteries persist to provide blood supply to the fused kidney. Similarly, ectopic kidneys frequently have several segmental arteries instead of a single renal artery. Therefore, when a patient is found to have either a horseshoe or an ectopic kidney, the clinician should suspect that the patient is likely to have an anomalous arterial blood supply.[18] Other lateral segmental branches become the adrenal and gonadal arteries.

DEVELOPMENT OF THE LIMBS

The limbs begin as an outgrowth of tissue originating from the embryonic trunk, called a *limb bud*. Within each limb bud, an apical ectodermal ridge is formed along the anteroposterior plane that differentiates ventral structures (e.g., palm of the hand) from dorsal structures (e.g., back of the hand). The first structure to differentiate in the limb bud is the skeletal tissue

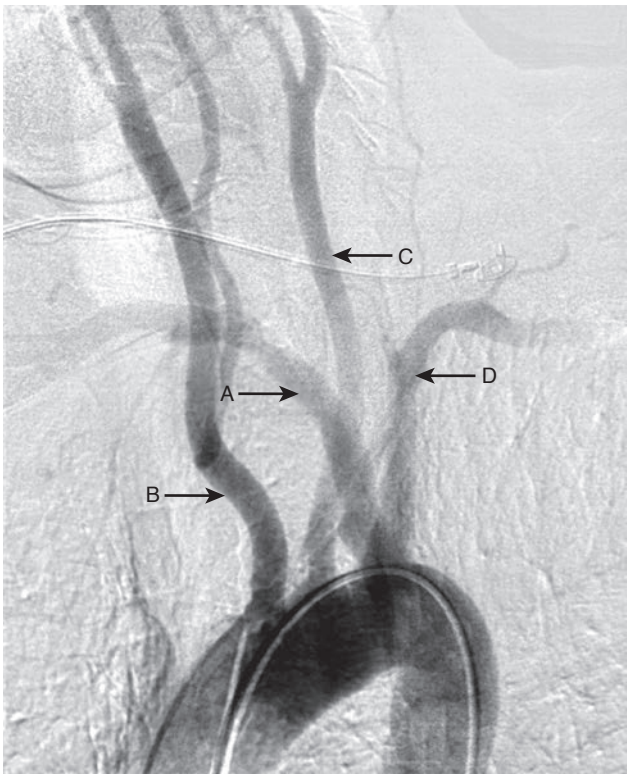


Figure 2.8 Aberrant origin of the right subclavian artery. The right common carotid artery *(B)* is the first branch of the arch, followed by the left common carotid *(C)*, left subclavian *(D)*, and then the right subclavian artery *(A)*.

from a cluster of mesenchymal cells. Shortly thereafter, muscle tissue develops from myogenic cells located in the ventral portion of the dermomyotome of the somite. Motor neurons appear in the limb muscles around the fifth week, followed by sensory neurons. The blood vessels that arise from endothelial cells in the segmental branches of the aorta, cardinal veins, and angioblasts within the limb bud mesoderm are the last tissue to be differentiated within the limb bud. Initially, a fine capillary network provides blood supply to the limb, but preferential enlargement of vessels gives rise to a single large central artery. Blood from this central artery feeds into a peripheral capillary bed and then collects in a marginal sinus located beneath the apical ectodermal ridge.[19]

Upper Limb

Normal Development

Development of the arterial supply to the upper limb is relatively simple (Fig. 2.9). The arterial supply to the upper limb is derived from the seventh cervical intersegmental artery, which supplies the upper limb by joining with the axial artery that develops within the limb bud. The developing axial artery becomes the brachial artery, whereas the portion of the axial artery in the forearm becomes the anterior interosseus artery. In the hand, a portion of the axial artery persists as the deep palmar arch. The ulnar, radial, and median arteries sprout from the axial artery to take over the supply of the forearm as the interosseous artery begins to regress. By the eighth week, the definitive vascular morphology of the arm is in place and consists of the subclavian artery, arising directly (left subclavian) or indirectly (right subclavian as a branch of the brachiocephalic) from the aortic arch. The subclavian artery continues into the arm as the axillary artery and next as the brachial artery. The deep brachial artery forms as a bud from the brachial artery and supplies blood to the posterior aspect of the arm. The brachial artery gives rise to the radial and ulnar arteries, a common interosseous artery that further bifurcates into anterior and posterior interosseous arteries, and a median artery.[19,20] Over time, the radial and ulnar arteries replace the anterior interosseous artery as the dominant arteries in the hand, whereas the median artery regresses.

Upper Limb Vascular Anomalies

There are some variations in vascular anatomy but very few anomalies of the arm vasculature. The main variations are a high origin of the radial artery proximal to the level of the elbow at the cubital fossa, which occurs in 14.2% of the population, and persistence of the median artery into the palm, which is present in up to 12% of the population.[20]

Lower Limb

Normal Development

Development of the arterial supply to the lower limbs is more complex than that in the upper limb (Fig. 2.10).[21] The axial artery of the lower limb initially is a distal continuation of the internal iliac artery, a ventral branch of the fifth lumbar intersegmental artery. During the fourth week, the right and left umbilical arteries connect with the paired dorsal aortas in the sacral region. The umbilical arteries join with the proximal portion of the fifth lumbar dorsal intersegmental arteries, giving rise to the common iliac arteries. The external iliac artery forms as a second branch of the fifth lumbar intersegmental artery, developing into the iliofemoral artery. The axial (sciatic) artery arising from the internal iliac artery regresses by the beginning of the eighth week, although parts of it persist as the sciatic (ischiadic) artery, part of the popliteal artery, and a portion of the peroneal artery. The remainder of the lower limb arteries develops as sprouts of the external iliac artery.

In the lower part of the thigh, the sciatic artery joins the iliofemoral system at the level of the popliteal fossa. The popliteal artery develops from the union of two arteries: (1) the deep popliteal artery, which is part of the sciatic system and lies anterior to the popliteus muscle, and (2) the later-developing superficial popliteal artery from the iliofemoral system (Fig. 2.11). The distal section of the deep popliteal artery regresses, whereas the superficial popliteal artery unites with the proximal portion of the deep popliteal artery to form the definitive popliteal artery and lies posterior to the popliteus muscle.

Lower Limb Vascular Anomalies

Persistent Sciatic Artery

If the iliofemoral artery fails to develop, the sciatic artery may persist as the dominant vessel supplying blood to the thigh.

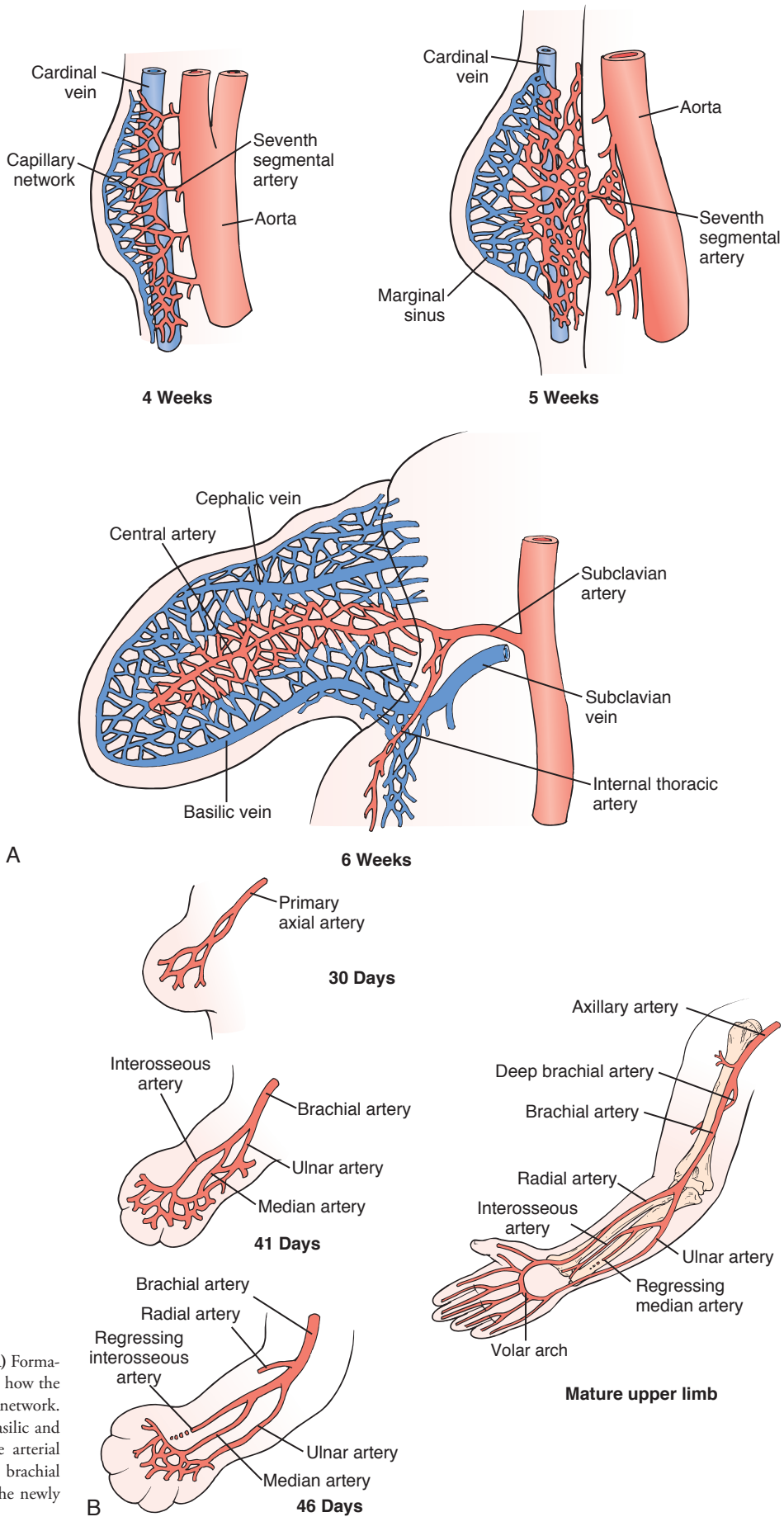


Figure 2.9 Arterial supply to the right upper limb. **(A)** Formation of the vascular system within the limb bud. Note how the capillary bed separates into an arterial and a venous network. At about 6 weeks, the marginal sinus becomes the basilic and cephalic veins, and a central artery forms from the arterial network. **(B)** The primary axial artery becomes the brachial artery, which gives rise to a number of branches in the newly developing forearm.

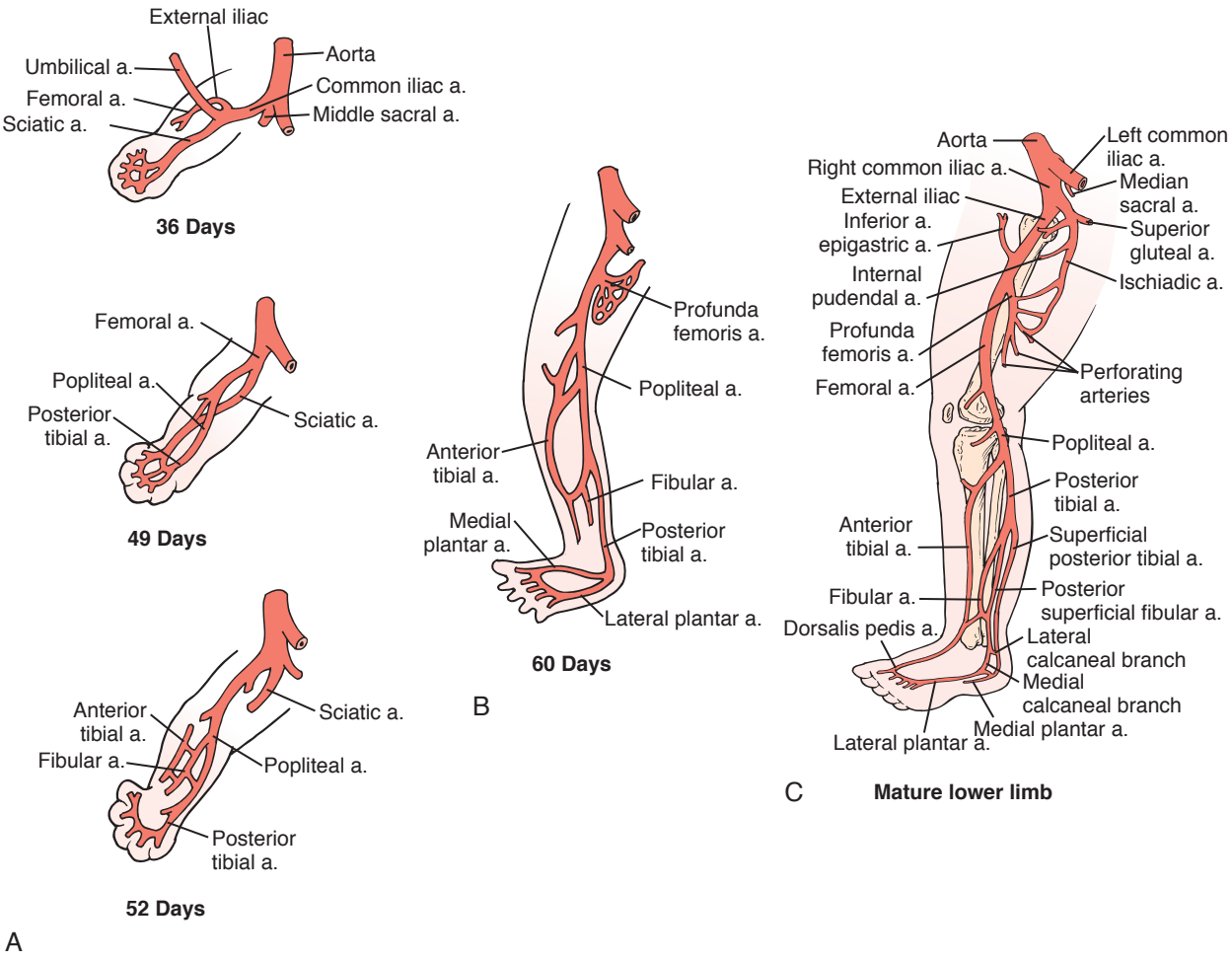


Figure 2.10 Arterial supply to the left lower limb. **(A)** The sciatic artery forms as a branch of the umbilical artery and initially supplies the entire leg. **(B)** The sciatic artery regresses, and the external iliac artery develops into the common femoral artery to supply the thigh. Note that the sciatic artery communicates with the popliteal artery just above the knee. **(C)** The sciatic artery disappears, although small portions remain to form the popliteal and peroneal arteries.

This is a rare anomaly, with an incidence of 0.05%[22] with variable morphologically, ranging from a persistent sciatic artery that is complete from its origin at the internal iliac artery to its union with the popliteal artery, to an incomplete sciatic artery that connects with the internal iliac or popliteal artery through small collaterals. A persistent sciatic artery is anatomically located next to the sciatic nerve and thus passes into the thigh through the sciatic notch and remains posterior to the adductor magnus until the insertion of that muscle, where it enters the popliteal fossa to join the popliteal artery. On physical examination, patients with a complete persistent sciatic artery may have an absent femoral pulse but a normal popliteal pulse. A persistent sciatic artery is superficial in the buttocks and can be traumatized by normal activity such as sitting. This causes early atherosclerotic changes and, possibly, aneurysm formation of the artery in the buttocks.[23-25] An aneurysm in a sciatic artery can compress the sciatic nerve and result in neurologic symptoms (Fig. 2.12).

Popliteal Entrapment Syndrome

Popliteal entrapment syndrome is caused by displacement of the popliteal artery medial to the medial head of the gastrocnemius. It results from migration of the medial head of the gastrocnemius that forces the vessels across the popliteal fossa and entraps them against the medial condyle of the femur.[21,26] Normally, at the time of attachment of the medial head of the gastrocnemius, the deep popliteal artery has involuted, and the mature popliteal artery has already formed in its normal location. No case of compression of the popliteal artery on the lateral epicondyle has been observed, most likely because the lateral head attaches well before the popliteal artery forms. Clinically, compression of the artery against the femur by the medial head of the gastrocnemius can cause claudication and formation of a popliteal artery aneurysm. Popliteal entrapment syndrome tends to be diagnosed in patients at an early age.

DEVELOPMENT OF THE VENOUS SYSTEM

Within 4 weeks of gestation, a cluster of capillary networks begins to enlarge and develop into the definitive veins of the embryo.[1] Greater anatomic variation is possible within the venous system because there are many multichanneled beginnings and a myriad of options for the venous channels to develop and

flow. At 4 weeks, three paired venous systems form. The vitelline veins drain the yolk sac, the umbilical veins return oxygenated blood from the placenta, and the cardinal veins return blood to the embryonic heart (Fig. 2.13).

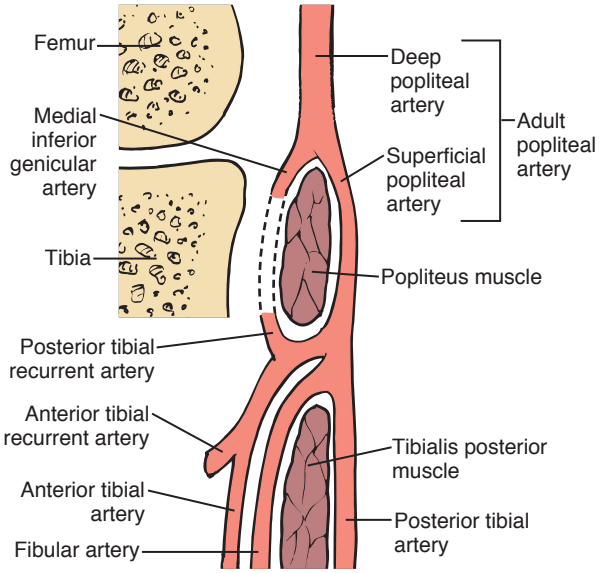


Figure 2.11 Embryologic development of the popliteal artery. The deep popliteal artery anterior to the popliteus muscle regresses, and the superficial popliteal artery posterior to the popliteus muscle becomes the mature popliteal artery. (From Gibson MHL, Mills JG, Johnson GE, et al. Popliteal entrapment syndrome. *Ann Surg*. 1977;185:341; modified from Senior HD. The development of the arteries of the human lower extremity. *Am J Anat*. 1919;25:55.)

The right and left vitelline veins drain blood from the yolk sac and the developing gastrointestinal tract. Before the vitelline vein enters the sinus venosus (the venous end of the heart), it forms a venous plexus in the developing liver, resulting in the formation of the liver's hepatic sinusoids (Fig. 2.14).[1] The left vitelline vein regresses, resulting in blood being shunted to the enlarged right vitelline vein as it passes through the developing liver. The enlarged right vitelline vein in the liver becomes the

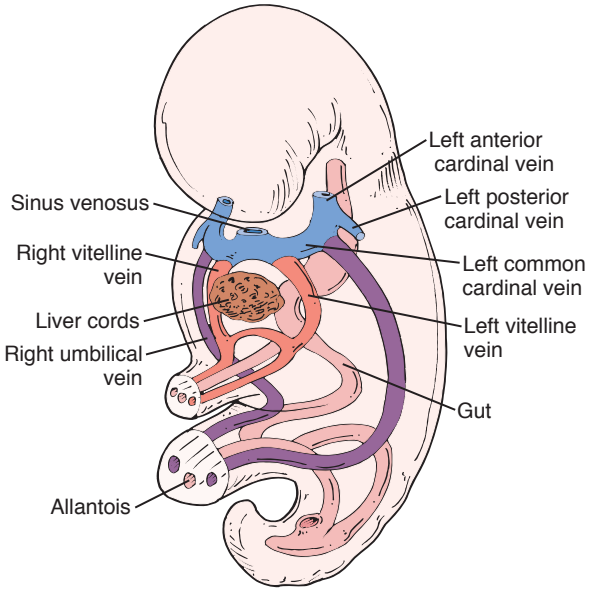


Figure 2.13 Venous system of a 4-week-old embryo.

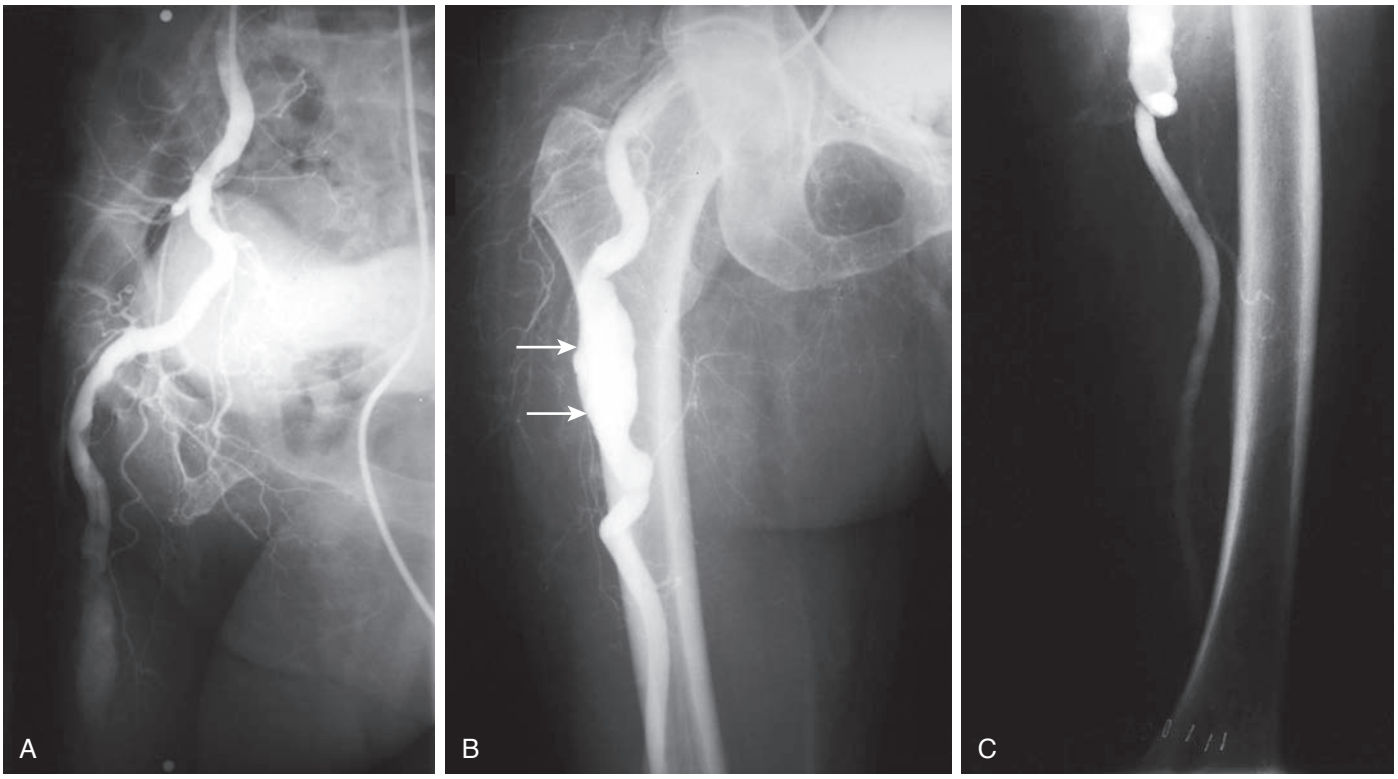


Figure 2.12 Persistent sciatic artery. **(A)** The sciatic artery in the pelvis is coursing posteriorly. **(B)** In the thigh, the sciatic artery has developed aneurysmal changes *(arrows)* and courses lateral to the normal location of the femoral artery. **(C)** More distally in the thigh, the sciatic artery is located laterally and ultimately joins the popliteal artery in the popliteal fossa (not seen on the radiograph).

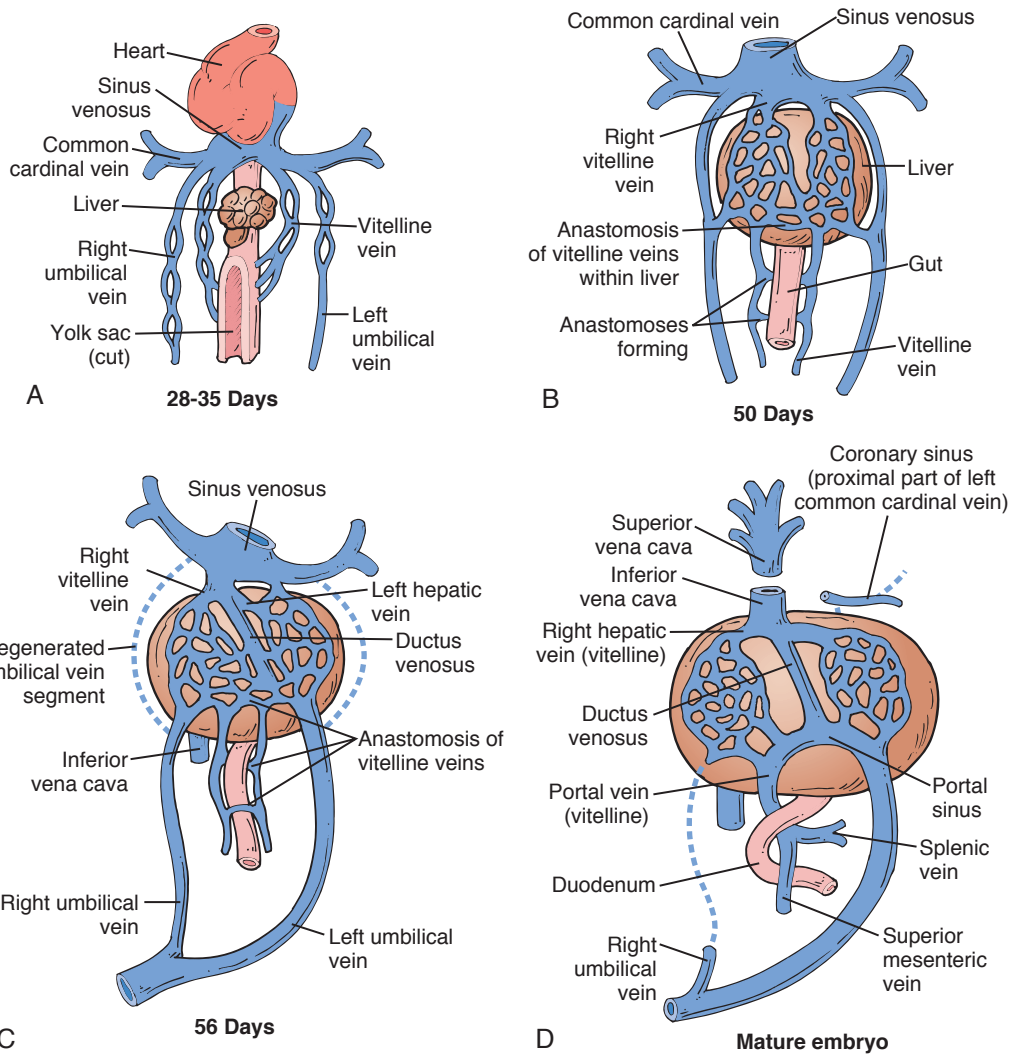


Figure 2.14 **(A-D)** Development of the umbilical and hepatic portal veins and the intrahepatic circulation.

ductus venosus, and the cranial portion develops into the inferior vena cava between the liver and heart. The portion of the right vitelline vein caudad to the liver becomes the portal vein and superior mesenteric vein. Left-to-right vitelline anastomoses remodel to form the splenic and inferior mesenteric veins, bringing blood from the foregut and hindgut, respectively, to the distal end of the portal vein.

The umbilical veins bring oxygenated blood from the placenta to the heart. Initially the umbilical veins are paired, but as the fetus develops, the right umbilical vein regresses, while the left persists. The left umbilical vein forms a direct anastomosis with the ductus venosus, which bypasses oxygenated blood from the placenta around the liver's sinusoids to directly enter the inferior vena cava. After birth, the ductus venosus atrophies and becomes the ligamentum venosum, whereas the left umbilical vein also atrophies to become the ligamentum teres (hepatis) contained within the falciform ligament.

The paired cardinal veins provide the blueprint for development of the intraembryonic venous system. The anterior cardinal veins, located cranial to the heart, join the posterior cardinal veins, located caudal to the heart, to form the paired short common cardinal veins, which drain blood into the right and left horns of the heart's sinus venosus. The paired anterior cardinal veins will eventually become the superior vena cava and its major tributaries; the posterior cardinal veins, subcardinal veins, and supracardinal veins contribute to formation of the inferior vena cava, its tributaries, and the azygos system.[1]

Superior Vena Cava

The cranial portions of the paired anterior cardinal veins become the internal jugular veins and connect with the external jugular veins, which develop from venous plexuses of the face.[1] The subclavian veins are formed from venous plexuses of the upper limb bud and empty into the proximal anterior cardinal veins. At the seventh week of gestation, an anastomosis develops obliquely between the left and right anterior cardinal veins. This anastomosis becomes the left brachiocephalic vein in the adult. The portion of the left anterior cardinal vein caudal to the developing left brachiocephalic vein and the left posterior

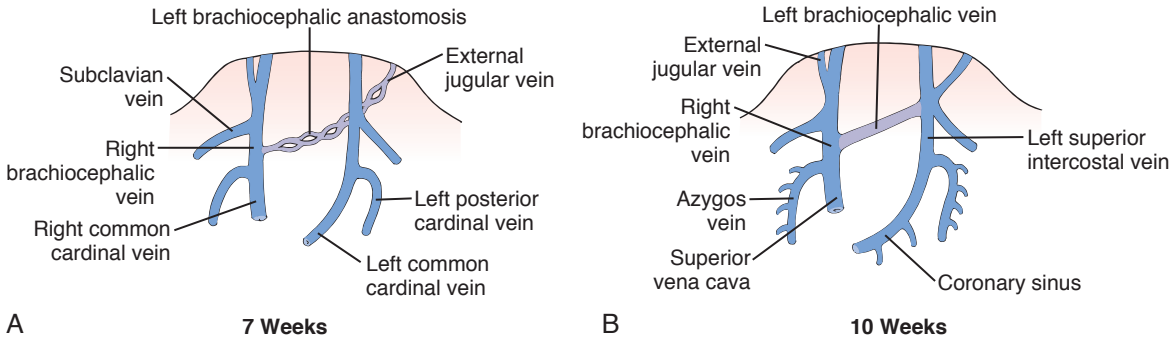


Figure 2.15 **(A)** Development of the superior vena cava and its major branches. **(B)** Completed development of the superior vena cava and its major branches.

cardinal vein regresses, directing blood from the left side of the head and neck to enter the heart through the left brachiocephalic vein to the superior vena cava. The superior vena cava, which develops from the junction of the left and right brachiocephalic veins and then enters the right atrium, is an enlargement of the right anterior cardinal and right common cardinal veins. The left common cardinal vein becomes the coronary sinus (Fig. 2.15).

Inferior Vena Cava and Associated Vessels

The inferior vena cava, common iliac veins, renal veins, and gonadal veins develop from a series of veins that have multiple anastomoses with one another and eventually coalesce to shunt the blood from the left to the right side of the embryo.[1] The inferior vena cava develops from four different embryonic vessels. The most rostral part (first part) of the inferior vena cava is formed from the enlargement of the right vitelline vein in the liver. The remainder of the inferior vena cava arises from parts of three parallel, but different, sets of veins that appear sequentially between the sixth and tenth weeks of gestation (Fig. 2.16A and B). The veins go through various changes, but eventually parts of each set coalesce to form the inferior vena cava and other veins of this region. The paired posterior cardinal veins appear first and are located on the posterior aspect of the fetus but eventually regress, with the exception of (1) the most distal portion of each, which fuse with one another to become the future most caudal portion (fourth part) of the inferior vena cava and the common iliac veins; and (2) the most proximal part that connects directly to the two horns of the sinus venosus and persists as the root of the azygos vein. The next pair of veins, the subcardinal veins, arise from the posterior cardinal veins before the latter regresses. They are located anterior and medial to the posterior cardinal veins and drain the mesonephric kidneys. The subcardinal veins anastomose with one another at the level of the metanephric kidneys. The right subcardinal vein enlarges and becomes the renal portion of the inferior vena cava (second part), whereas the left subcardinal vein forms an anastomosis with the right subcardinal vein at the level of the kidneys to form the left renal vein. This anastomosis has both anterior and posterior components that surround the aorta. The posterior vein regresses, whereas the anterior vein persists to become the left renal vein (see Fig. 2.16C and D). The left subcardinal vein rostral to the subcardinal anastomosis regresses, whereas the caudal portion remains as the left gonadal vein. The right renal vein and right gonadal vein sprout from the renal segment of the right subcardinal vein. The last pair of veins to appear, the supracardinal veins, also sprout from the posterior cardinal veins. They become the primary veins that drain the body wall. The thoracic and abdominal portions of the supracardinal veins have different fates. In the abdomen, the right supracardinal vein anastomoses with the right subcardinal portion of the inferior vena cava, thus becoming the infrarenal portion of the inferior vena cava (third part). At its caudal end, it will anastomose with the fused left and right posterior cardinal veins (fourth part of the inferior vena cava). The left abdominal supracardinal vein regresses. The thoracic portion of the supracardinal veins drains the posterior wall by a series of intercostal veins. They drain into the left and right horns of the sinus venosus by way of the rostral remnants of the posterior cardinal veins. Eventually the left supracardinal vein loses its communication with the left horn of the sinus venosus and instead anastomoses with the right supracardinal vein before its entrance into the right horn of the sinus venosus. The right supracardinal vein becomes the azygos vein, whereas the left supracardinal vein becomes the hemiazygos vein.

Anomalies

Superior Vena Cava

Two anomalies that can occur from development of the superior vena cava are described: double superior vena cava and left-sided superior vena cava. Neither anomaly is clinically important, except that they produce unusual shadows on chest radiographs. A double superior vena cava develops when the caudal section of the left anterior cardinal vein fails to regress.[27] This anomaly may occur with or without development of the brachiocephalic vein. A left-sided superior vena cava occurs if the caudal section of the right anterior cardinal vein regresses, but the caudal section of the left anterior cardinal vein remains open—the opposite of normal development.[28] A brachiocephalic vein forms, but in this anomaly, it connects the right anterior cardinal vein to the left anterior cardinal vein, becoming a left-sided superior vena cava (Fig. 2.17).

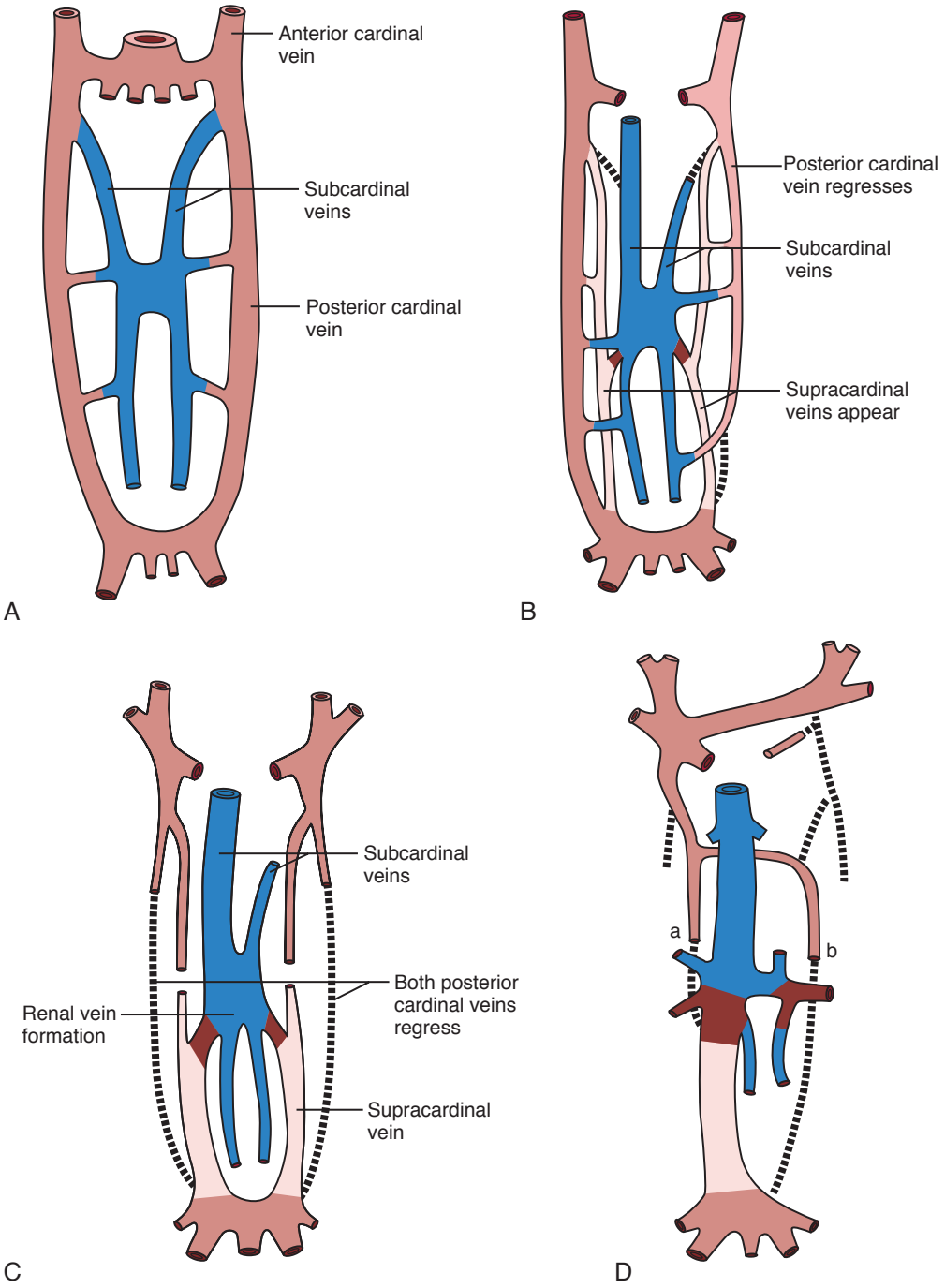


Figure 2.16 Development of the inferior vena cava. **(A)** At 6 weeks of gestation, the posterior cardinal veins are dominant and the subcardinal system is beginning to appear. **(B)** At 7 weeks of gestation, the subcardinal veins are dominant and the supracardinal system begins to appear. The posterior cardinal veins are beginning to regress. **(C)** At 8 weeks of gestation, the subcardinal veins form the suprarenal inferior vena cava. The supracardinal veins form the infrarenal inferior vena cava. The posterior cardinal veins regress. **(D)** The adult inferior vena cava. Portions of the posterior cardinal veins persist to form the azygos system *(a)* and the hemiazygos system *(b)*. (From Giordano JM, Trout HH, III. Anomalies of the inferior vena cava. *J Vasc Surg*. 1986;3:924–928.)

Inferior Vena Cava Duplication/Left-Sided Inferior Vena Cava

Duplication occurs if the left supracardinal vein fails to regress. If both supracardinal veins persist and join at the level of the renal arteries, a double inferior vena cava is observed. If the left supracardinal vein persists and the right supracardinal vein regresses (the opposite of normal), a left-sided inferior vena cava is seen. In this anomaly, the vein crosses to the right side at the level of the renal arteries and is a mirror image of normal anatomy. In the case of a left-sided inferior vena cava, the right adrenal and gonadal veins, instead of emptying into the inferior

Figure 2.17 Duplicated superior vena cava. Note the right-sided central venous catheter *(arrow)* entering the right atrium, indicative of the presence of a right-sided vena cava in addition to a left-sided vena cava.

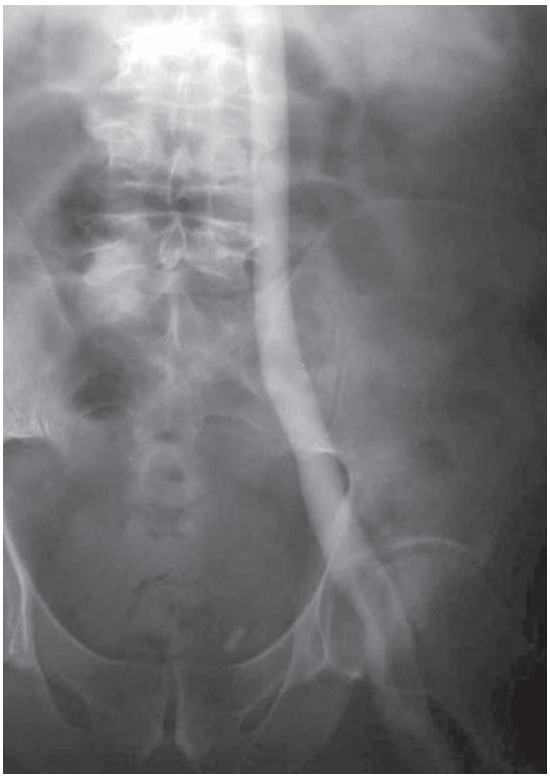


Figure 2.18 Left-sided inferior vena cava. The left-sided vena cava crosses over the midline at the level of the renal vein.

vena cava as normal, empty into the right renal vein; likewise, the left adrenal and gonadal veins empty into the inferior vena cava instead of the left renal vein. Recognition of a duplicated inferior vena cava or a left-sided vena cava is important when placing an inferior vena caval filter (Fig. 2.18).[29-35]

Renal Vein Anomalies

The most common venous anomaly is persistence of the posterior component of the left renal vein. This results in either a retro-aortic left renal vein if the anterior component regresses (the opposite of normal) or a left circum-aortic renal vein if both anterior and posterior renal veins persist. In cases of circum-aortic renal veins, both veins join before entering the inferior vena cava, resulting in a venous collar around the aorta. Awareness of a retro-aortic renal vein is important during dissection of the aorta at the level of the renal arteries to avoid injuring the vein (Fig. 2.19).[29-35]

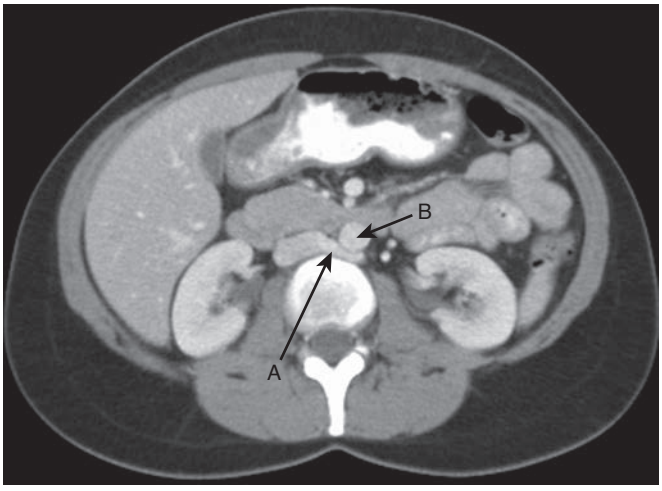


Figure 2.19 Retroaortic left renal vein. The left renal vein *(A)* can clearly be seen coursing posterior to the aorta *(B)*.

Development of the Lymphatic System

The Italian anatomist, Gasparo Asellius, first described the lymphatic system as a network of milky veins surrounding the intestines of a recently fed dog. The lymphatic system is important not only for the absorption of lipids from the intestines but also for the removal of interstitial fluids, and serves as a pathway for lymphatic cells involved in the immune response. Until recently, the mechanism responsible for the development of the lymphatic system was unclear. During the early twentieth century two hypotheses were proposed for its development: first, the "centrifugal theory," which proposed that in very specific regions, the lymphatic system budded from the developing venous system to form discrete lymph sacs; and second, the "local origin theory," which proposed that the lymphatic system developed de novo from embryonic mesoderm adjacent to the developing venous system.[35,36] Recent evidence supports the hypothesis that the lymphatic system buds from the developing venous system, as opposed to the concept that it develops from a mesodermal origin.

Development of the lymphatic system (Fig. 2.20) begins as six lymph sacs, two paired and two unpaired, that begin

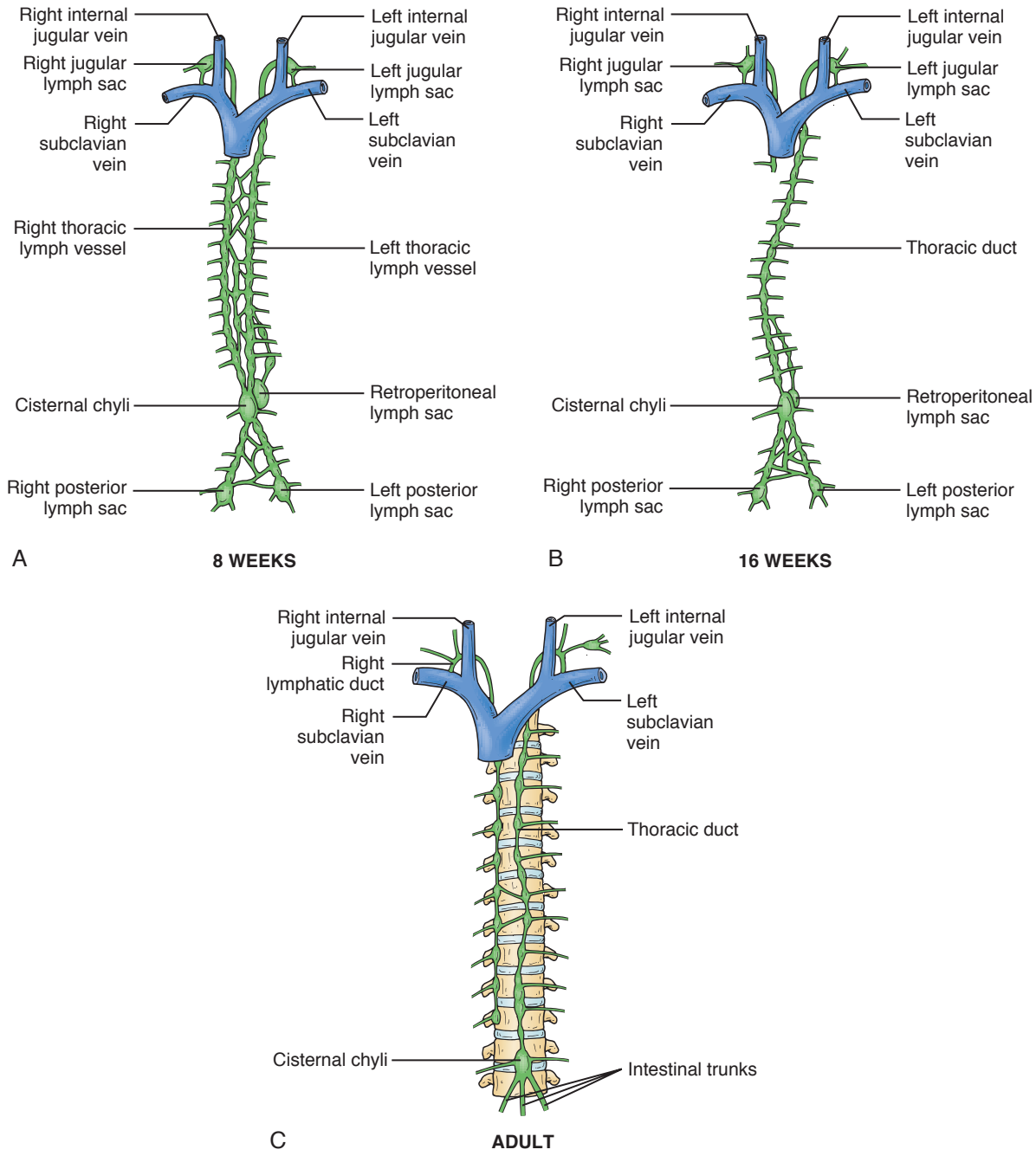


Figure 2.20 Development of the lymphatic system. **(A)** By 8 weeks, lymphatic vessels are established as outgrowths of the six lymph sacs that budded off of the vascular system. At this point in time the embryo has a pair of thoracic lymph vessels that connect the cisterna chyli to the venous system superiorly. **(B)** By 16 weeks, portions of the right and left thoracic lymph vessels have been remodeled to form a single thoracic duct. **(C)** By the adult stage, all the embryonic lymphatic sacs have regressed with the exception of the cisterna chyli. The definitive thoracic duct and right lymphatic duct are present.

to develop in a cranial to caudal sequence. These lymph sacs begin to appear in the fifth week and are complete by the end of the sixth week in the human embryo.[37] First to appear are a pair of jugular lymph sacs that bud off from the anterior cardinal veins (at the junction of the presumptive subclavian veins and internal jugular veins), whereas a second pair, the posterior lymph sacs, bud from the caudal segment of the posterior cardinal veins (at the junction of the internal and external iliac veins). The posterior lymph sacs appear late in the sixth week of development. The remaining lymph sacs, the retroperitoneal lymph sac and cisterna chyli, are unpaired and appear between the end of the fifth week and beginning of the sixth week. The retroperitoneal lymph sac develops from the part of the mesonephric venous system near the developing suprarenal gland, whereas the cisterna chyli buds from veins at lumbar levels 3 to 4.

Additional lymphatic vessels sprout from these six initial lymph sacs and follow the course of the developing veins.

Extensions of the two jugular sacs extend caudally to meet with rostral extensions of the cisterna chyli, forming a pair of thoracic lymph vessels that empty into the venous system at the internal jugular and subclavian junction on both the left and right sides. Later in development, these two thoracic vessels fuse at midthoracic levels, whereas the caudal portion of the left thoracic vessel and thoracic portion of the right are lost, leaving a right to left directed definitive thoracic duct, formed from the caudal part of the right thoracic duct and rostral part of the left thoracic duct. The right jugular sac remains connected to the venous system and will eventually form the right lymphatic duct. Additional lymphatic vessels bud from existing lymphatic vessels to form deep lymphatic vessels. Superficial lymphatic vessels develop as sprouts from these deep lymph vessels. Lymphatic vessels and nodes do not invade the central nervous system, meninges, eye, internal ear, cartilage, epidermis, or spleen. All the lymph sacs except the rostral part of the cisterna chyli develop connective tissue bridges and are seeded with lymphatic cells, which, in turn, form lymph nodes. The lymphatic connections to the venous system are lost, with the exceptions of the final connections of the right lymphatic duct and thoracic duct.

The previous sections have addressed the development of the arterial, venous, and lymphatic systems in isolation. However, it should be apparent that these systems develop simultaneously and likely interact with each other. As the initial fine capillary network forms (the retiform plexus stage), errors in morphogenesis can result in various vascular malformations. For example, persistence of capillary networks could explain the development of port-wine stains. Alternatively, failure of regression of arteriovenous communications could result in the development of arteriovenous malformations. Such malformations would have a greater venous component with persistence of the venous morphology, whereas the opposite would be true with persistence of the arterial morphology. Failure of the main vascular trunks to develop in the later phases of development can give rise to conditions in which there may be hypoplasia or aplasia of these vessels, as can be seen in Klippel-Trenaunay syndrome. Likewise, abnormal lymphatic system development can be manifested concurrently or separately as the venous and arterial systems develop. Failure of normal lymphatic development can lead to aplasia and hypoplasia that appears clinically as lymphedema.

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CHAPTER 3

Vessel Wall Biology

BAUER SUMPIO and JASON CHIN

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Complex organisms rely on the fluid, nutrient, and waste transport capabilities of the cardiovascular system whose subdivisions each have unique structure and biology to perform crucial metabolic and mechanical functions. The arterial network reacts to hemodynamic forces through constriction or dilation and also via activation of signaling pathways. Its venous counterpart is an adaptable system with unique mechanisms for accommodating the hemodynamic stresses of the body. The lymphatic system is a distinct but closely related network that augments fluid transport and immunologic functions (Table 3.1).

ARTERIAL WALL ANATOMY

The arterial wall exhibits a common organizational structure throughout the body, although proportions of components fluctuate through different regions. It consists of cells and matrix fibers arranged in three tunicae: intima, media, and adventitia (Fig. 3.1).

Intima

The intima, the innermost luminal layer, extends from the lumen to the internal elastic lamina (IEL). The intimal luminal surface is lined by the endothelium. The actual intimal layer is very narrow, consisting primarily of a few scattered leukocytes, smooth muscle cells (SMCs), and connective tissue fibers. The matrix fibers consist mainly of elastic and collagen fibers and proteoglycans.

Endothelium

The vascular endothelium is a continuous layer of flat polygonal endothelial cells (ECs) in direct contact with blood flow. The

Abstract

The circulatory system of the human body is composed of three main subdivisions: arterial, venous, and lymphatic. The vessel wall in and throughout each of these subdivisions has varying compositions directly related to and responding to their hemodynamic environment. This chapter describes the biologic structure of the vessel wall in these subdivisions and how this biology relates to each subdivision's function.

Keywords

Fenestrated continuous endothelium
discontinuous endothelium
shear stress
mechanotransduction
COUP TFII
endothelial microvalve

TABLE 3.1 Vessel Wall Characteristics of Circulatory Systems

	Arterial Wall	Venous Wall	Lymphatic Wall
Collagen content	Moderate	High	Mixed
Elastic fiber content	High	Moderate	Mixed
Central pressure	High	Very low	Low
Shear stress	High	Low	Low
Stretch force	High	Low	Low
Pulsatility	High	Low	Low
Compliance	Moderate	High	High
Oxygen tension	High	Low	Low
Intrinsic propulsion	None	None	Predominant
Valves	None	Some	Many

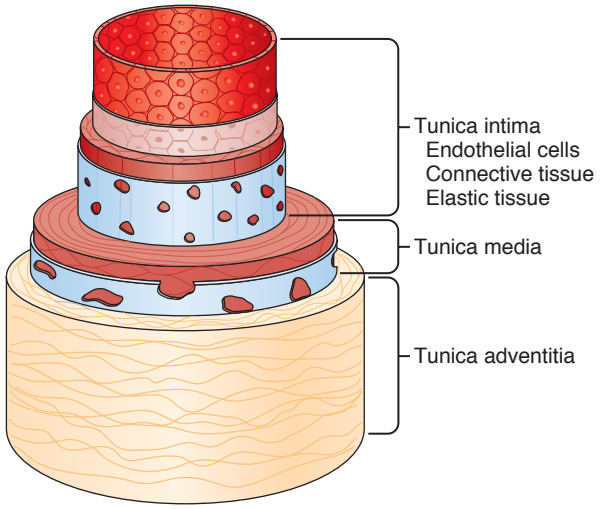

Figure 3.1 Anatomy of the Vessel Wall. Arteries and veins maintain the same basic structure, which consists of the tunica adventitia, tunica media, and tunica intima, although capillaries consist of no more than endothelium, connective tissue, and support cells called pericytes. (Redrawn from Hast J. *Self-mixing interferometry and its applications in noninvasive pulse detection* [dissertation]. Finland, University of Oulu; 2003.)

endothelium participates in both physiologic and pathologic processes and reacts to physical forces, chemical signaling, and immunologic mediators.[1] The endothelium interacts with its cellular and acellular environments and is an important regulator of vasomotor tone, hemostatic balance, permeability, cell proliferation, survival, and immunity.[2]

The endothelium provides a continuous lining throughout the arteries, capillaries, veins, heart valves, and endocardial surfaces. Cell thickness varies from less than 0.1 µm in the capillaries and veins to 1 µm in the aorta.[2] The luminal surface of ECs is smooth and regular.[3] The cells are covered by a glycocalix responsible for the antithrombogenic properties of the endothelial surface.[4] The glycocalix reduces friction from blood flow and serves as a barrier for fluid loss through the vessel wall. Its thickness varies across the vascular tree.[5] During inflammation, the glycocalix is sheared off, permitting the attachment of leukocytes and the transport of water from microvessels, and possibly initiating the development of atherosclerotic lesions.[6]

ECs, which are typically aligned in the direction of blood flow, tend to overlap immediately adjacent cells. The nature of the cell bonding is relevant to both the mechanical strength and the permeability of the endothelial layer. Membranes of adjacent cells are mainly parallel and separated by an intercellular space of 15 to 20 nm in size.[4] Sites of firmer attachment include tight junctions (zona occludens) and adherens junctions (zona adherens). Tight junctions form a barrier to transport between ECs and help maintain polarity between the luminal and abluminal sides of the cells. At these sites, opposing cell membranes form a continuous band around the side of the cells, forming a zona occludens. This tight seal prevents the passage of molecules between the lumen and cell base. Large artery ECs have a well-developed system of tight junctions due to high rates of pulsatile blood flow, whereas junctions become progressively looser as the system transitions to arterioles, capillaries, and venules. Postcapillary venules possess a less dense system of tight junctions to mediate the inflammation-induced extravasation of leukocytes and plasma constituents. In contrast, the blood-brain barrier, protecting neural tissue from fluctuations in blood composition, has rigid tight junctions.[2] Adherens junctions are less common and exist primarily in large arteries. Their primary role is to permit inter–EC communication via movement of ions, metabolites, and regulatory factors.[4]

The ECs contain pinocytic vesicles, which regulate the permeability of the endothelial layer. The pinocytic vesicles are responsible for the movement of material from the lumen of the vessel into its wall. The vesicles exist primarily in muscular small blood vessels and are found in large numbers in the heart and lung and to a lesser extent in the retina and the brain.[7]

The endothelium may be nonfenestrated continuous, fenestrated continuous, or discontinuous (Fig. 3.2).

Nonfenestrated Continuous

Nonfenestrated continuous endothelium functions as a selective filter, and exists in the arteries, veins, and capillaries of the brain, skin, heart, and lung. Highly selective microcirculations, such as the brain, with its tight blood-brain barrier, and luminal and abluminal plasma membranes fused only at the tight junctions, dictate the vascular permeability.[8]

Fenestrated Continuous

Fenestrated endothelium occurs in locations of increased filtration or transendothelial transport, including the capillaries of exocrine and endocrine glands, gastric and intestinal mucosa, choroid plexus, glomeruli, and renal tubules. Fenestrae are transcellular pores approximately 50 to 70 nm in diameter that extend through the entire endothelial layer.[2] The majority of fenestrae have a 5- to 6-nm nonmembranous diaphragm across their openings, although fenestral density varies in differing vascular beds and increases with greater need to absorb or secrete.[9-11] Cultivation of ECs on an extracellular matrix (ECM) derived

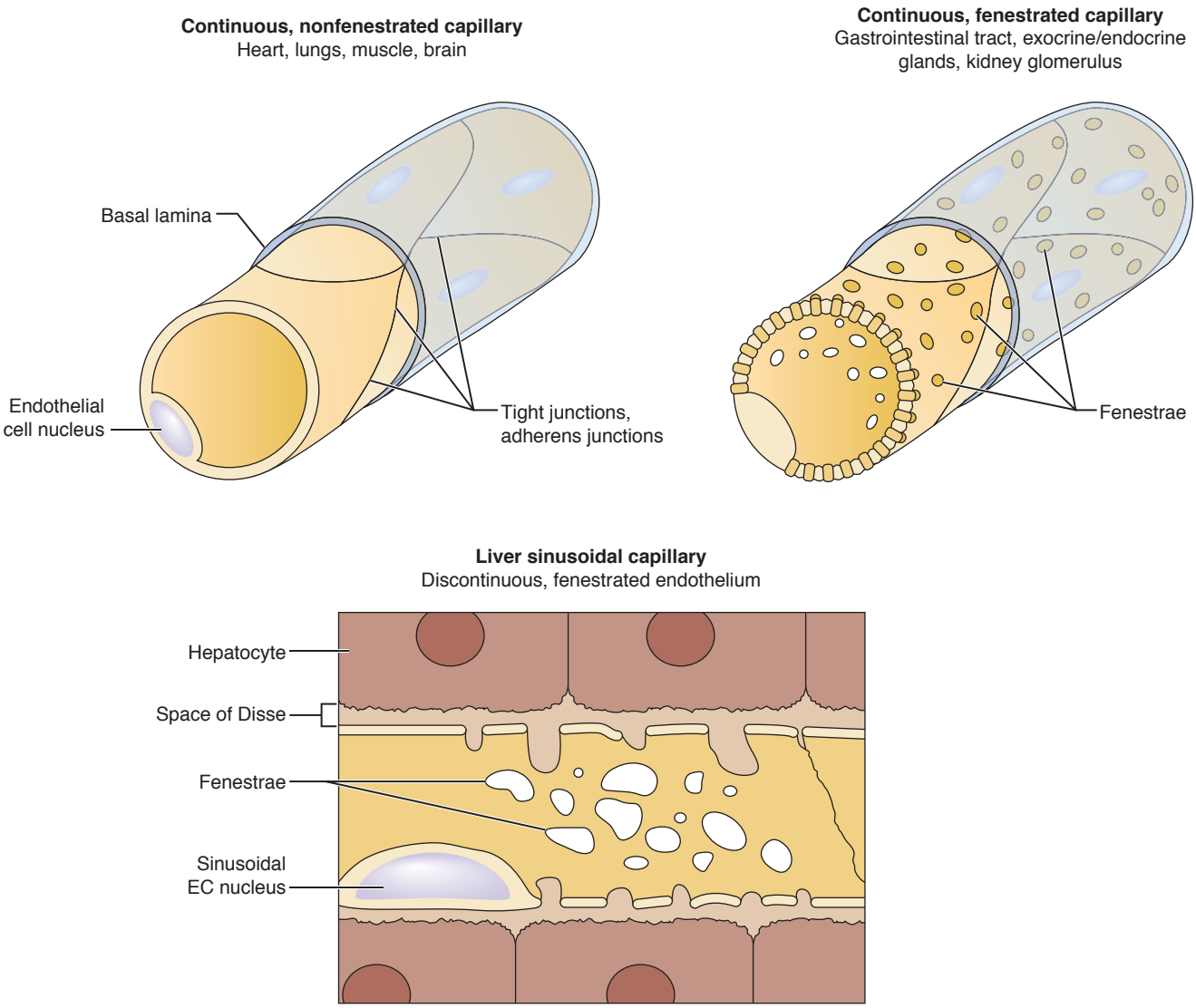

Figure 3.2 Nonfenestrated continuous, fenestrated continuous, and discontinuous capillary endothelium. These configurations affect the vascular permeability of the capillary bed with highly selective circulations such as the blood-brain barrier having continuous nonfenestrated capillary endothelium, and high fluid and macromolecule exchange circulations such as the liver having discontinuous capillary endothelium. (Redrawn from Kanasty RL, Whitehead KA, Vegas AJ, Anderson DG. Action and reaction: the biological response to siRNA and its delivery vehicles. *Mol Ther.* 2012;20(3):513-524.)

from renal epithelium results in diaphragmed fenestrations,[12] which allow the filtered reabsorption of ultrafiltrate from the tubular system.

Discontinuous

Discontinuous endothelium possesses larger fenestrations, ranging from 100 to 200 nm in diameter. These fenestrations lack a diaphragm and contain gaps or pores within individual cells.[13] Large intercellular and intracellular gaps with an incomplete basal lamina may be up to 0.1 to 1 μm in diameter and may also undergo dynamic changes.[8] Such capillaries form large irregularly shaped vessels, such as the sinusoids of sinusoid capillaries. In hepatic sinusoids, endothelial gaps are clustered in sieve plates to control the exchange of fluids, solutes, and macromolecules between the sinusoid and space of Disse.

Basal Lamina

The basal lamina, which borders the ECs on their abluminal surfaces, forms a generally continuous boundary between the endothelium and the immediately underlying intimal structure. It is involved in the regeneration and attachment of the endothelial layer, blood vessel permeability, initiation of blood clotting, and provides a barrier to cellular migration.[14] It connects the EC compartment to subjacent cell layers and SMCs.[15]

The basal lamina consists of two zones: a clear inner zone (lamina rara) and a dense fibrillar zone (lamina densa) adjacent to the interstitial connective tissue.[1] The clearer inner layer contains the glycoprotein laminin, whereas the dense layer is composed of type IV collagen. The basal lamina provides a pliable extensive bond, which permits ECs to comply with

changes in configuration related to cardiac pulsation and to vessel torsion and flexion.[4,16] Furthermore, discrete adhesion points of increased electron density have been observed between basal peripheral cytoplasmic dense bodies of ECs and the IEL, which prevent slippage of the lining cells when shear stress increases.[16]

The basal lamina is formed by glycoproteins; adhesion molecules, such as laminin, fibronectins, entactin, and thrombospondin; various proteoglycans, such as heparan sulfate, that can influence viscoelasticity, permeability, hemostasis, and thrombosis; and microfibrils of collagen types IV and V secreted by the endothelium.[14,17]

Mechanically, the basal lamina strengthens the vascular wall. Collagen type IV chains form a covalently stabilized framework and provide mechanical resistance. Laminin forms a second polymer network and connects ECs as well as heparan sulfate to the collagen.[15,18] Entactin binds laminin and collagen. Fibronectin transmits mechanical forces between integrin receptors on SMCs and the ECM to redistribute the mechanical load within the arterial wall.[19]

The monolayer of endothelium is normally quiescent with cell-cell contact inhibiting proliferation, resulting in a low mitotic index contributing to the stability and integrity of the vessel wall.[1] In this state, the ECs form cell-to-cell junctions, synthesize, and secrete ECM and basement membrane components, including fibronectins, laminin, proteoglycans, and collagen.

The underlying reticular layer of the endothelium is composed of collagen types I and III, which are produced by both ECs and SMCs and are the most abundant of all interstitial collagen. Evidence suggests that the ECM components influence cell phenotype in ECs and SMCs. In culture, EC phenotype is influenced by growth media, surface, and the age of the cultures. Further, cultures of these cells on various surfaces, including collagens, fibronectins, and reconstructed basement membranes, demonstrate different rates of production of gap junctions, actin, messenger RNA (mRNA), protein, cell proliferation, and membrane specialization.[20-22]

Internal Elastic Lamina

The IEL is a layer of elastic fibers 70 to 100 nm in thickness. Experimental evidence suggests that both abluminal SMCs and luminal ECs are collaboratively responsible for elastin formation and IEL synthesis.[23,24] The IEL separates the subendothelial intimal layer from the medial layer. Collagen- and proteoglycan-based fenestrations permit flow, driven by a pressure gradient, across the arterial wall tissues into the intimal layer.[4,25,26]

Elastin is organized into fenestrated cylindrical lamellae that are separated from neighboring lamellae by single layers of SMCs.[27] Lamellar units are determined prenatally, and postnatal changes in thickness or circumference of the media accompany parallel changes of the thickness and circumference of the elastic lamellae.[28,29]

The IEL and elastic lamellae in large arteries may function as barriers to macromolecular accumulation in the vascular wall. Structural defects within the IEL are directly implicated in the onset of intimal thickening in human arteries.[25] Fragmentation of the IEL and disruption of medial layers is common in advanced plaques in apolipoprotein E knockout mice.[30] Defective IEL may result in abnormal attachment with ECs, causing gaps in the endothelial surface facilitating the entry of macromolecules, lipids, and leukocytes into the intima.[25,31,32]

Although macromolecules are believed to cross the normal arterial EC layer through vesicular transport, macromolecules are believed to cross the IEL via diffusion through the fenestrations. The diffusion rate is inversely dependent on its size. Therefore, as the size of the macromolecule increases, the resistance of the endothelium does not change, but IEL resistance strengthens.[33] Owing to this difference in transfer rate, the IEL most likely plays a significant role in regulating macromolecular accumulation in the intima, restricting plasma-borne macromolecules from entering the media, and regulating discrete microenvironments between the intima and the media.[33]

Media

The tunica media extends from the IEL to the adventitia. The medial layer is a porous heterogeneous medium consisting of an ECM phase with embedded SMCs. Under normal conditions, SMCs in the tissue matrix beneath the IEL are shielded from the direct shear forces of flowing blood. At low and physiologic pressures, the media is the chief determinant of arterial wall properties. Its composition and microarchitecture ensure arterial stability. Arterial media elasticity dictates arterial distensibility and the capacitive effects of larger arteries.[34] Its elasticity also affects the mechanical load-bearing of the arterial wall. The metabolic state of the media also plays an important role in the pathogenesis of atherosclerotic lesions.

The media consists of vascular SMCs, elastin, and collagen fibers arranged in a highly organized fashion.[35] Closely packed layers of SMCs associated with elastin and collagen fibers distinguish the outer layer of the media in all intact arteries. The SMCs are surrounded by a basement membrane composed mainly of laminin, collagen IV, heparan sulfate proteoglycan, entactin/nidogen, and fibronectins, which prevent the proliferation and migration of the SMCs. This arrangement maintains the SMCs in a contractile state as opposed to the synthetic state.[36] In the contractile state in normal arterial vessels, SMCs are differentiated and contain abundant contractile and intermediate filament proteins. In certain physiologic and pathologic conditions, the SMCs abandon the contractile phenotype for an immature synthetic phenotype. This change permits migration into the intima, proliferation, and secretion of ECM components.[37]

The SMC layers consist of groups of similarly oriented cells, each surrounded by a common basal lamina in a closely associated interlacing basketwork of type III collagen fibrils. The fibrils are arranged to tighten around the cell groups as the media is brought under tension. This configuration holds the groups of cells together and prevents excessive stretching or slippage. At low and physiologic pressures, collagen fibers are slack and not substantially load-bearing.[35] The thickness and abundance of collagen bundles depends largely on vessel diameter with the

average tangential tension per medial layer approximately 2000 dynes/cm, regardless of species.[38]

Arteries are classified as either elastic or muscular according to the proportion of cellular and fibrous components.[39] In elastic arteries, well-defined elastic lamellae and collagen bundles are prominent in the media, whereas connective tissue fibers are less frequent. The prominent elastic arteries are those with large diameters and in close proximity to the heart—the aorta, the brachiocephalic trunk, and the iliac arteries. Elastic arteries consist of lamellar units, which are close associations of elastin, collagen, and SMCs. Between the lamellae, SMCs, collagen fibers, elastin microfibrils, and glycosaminoglycans are organized into functional units. Although the number of lamellar units depends on the arterial diameter, humans have from 40 to 60 units in the aorta, which are located approximately 12 to 17 μm in distance from the lumen of the artery. The number of lamellar units decreases from the heart to the peripheral arteries.[4]

Muscular arteries predominate in the second- or third-order branch arteries. The media consists primarily of SMCs with fewer connective tissue fibers. Nonparallel branching elastin strands increase the capacity to change diameter under neurohumoral stimulation.

Electron microscopy has illuminated a further structural breakdown of arterial microarchitecture in elastic and muscular arteries. The media is composed of groups of fascicles, which are jointly oriented, elongated SMCs within an encompassing network of branching elastic fibers.[35] Bundles of slack collagen fibers are interposed between the adjacent elastic fibers. Each fascicle is invested by a sheath of basal lamina and collagen fibrils oriented in the same direction as the fascicle cells.[4] Each fascicle is oriented in the direction of imposed tensile stress.[34] In straight segments of aortas and arteries, fascicles are uniform in size and oriented primarily circumferentially. At bends and branching points, fascicles are smaller and less uniform in size and orientation.[38]

Adventitia

The adventitia extends from the external elastic lamina to an ill-defined boundary usually contiguous with the perivascular connective tissue. The adventitia varies in thickness and organization. Whereas the aorta has minimal adventitial fibrous connective tissue, large muscular arteries contain prominent adventitial elastic and collagen fibers. Here, adventitia may be more prominent than media. Generally, adventitial cells are sparse and consist mainly of fibroblasts.

The adventitia contains vasa vasorum and nerves, which provide nutrition to the adventitia and media and contribute to the regulation of the medial smooth muscle function. The vasomotor nerve fibers induce vasoconstriction or vasodilation via adrenergic receptors. Nervous stimuli are transmitted to the outer SMCs through neuromuscular junctions. The signal is transmitted to the inner cells by electrical coupling between adjacent SMCs.

Vasa vasorum are present in arteries with diameters larger than 200 μm. Also, when the medial layer has more than 29 lamellar units, the outer part of the media is irrigated by the vasa vasorum. Nutrients may also be provided from the luminal blood flow for the inner part of the media. The vasa vasorum are composed of small arteries, arterioles, capillaries, and venous channels, as well as nerves that mediate smooth muscle tone. Vasa vasorum arise from the parent artery at branch junctions and arborize in the adventitia. In thick-walled arteries, mural stresses and deformations may affect the vasa vasorum. Hypertension may impair vasa flow. A lymphatic network in the adventitia collects the proteins, ions, and water from the blood and transports these substances through the vessel wall.

ARTERIAL WALL SYSTEM

Large Arteries

The arterial system commences with the aorta and its branches whose primary function is to provide a conduit for blood flow to the peripheral tissues and to smooth out the pulsations of intermittent ventricular ejection. The large arteries cushion the pulsations during ventricular ejection. This cushioning function is characterized by the relationships between oscillatory pressure, flow, and frequency, which in turn depend on arterial diameter and elasticity.[4]

The aorta is the main trunk of the vascular system, originating at the upper section of the left ventricle. It arches backward over the root of the left lung and descends within the thorax on the left side of the spine. It then flows into the abdominal cavity through the aortic hiatus in the diaphragm and ends opposite the lower border of the fourth lumbar vertebra. At this point, it is decreased to 1.75-cm in size and divides into the right and left common iliac arteries.

Medial cells in the aorta are organized into groups of overlapping elongated cells, bracketed by elastic fibers. Successive layers of cells and surrounding elastic fibers are separated from one another by a narrower, intervening acellular zone containing thick, crimped bundles of collagen.

Because of their significant size, the aorta and the large arteries offer little resistance to blood flow. Large arteries store a large portion of the blood volume during systole and drain it during diastole. They are able to accommodate the stroke volume ejected with each contraction of the heart. This ability allows for propagation of the pulse and also offers dynamic resistance to the oscillatory components of pulsatile flow.

Blood pressure is the highest at the origin of systemic circulation, although decreases in blood pressure are not linear with vessel diameter or distance down the vascular tree.[4] Blood pressure decreases to 30% to 40% of aortic pressure in vessels 250 to 50 μm in diameter. Significant pressure drop occurs in the terminal arterioles, which branch into small capillaries with diameters less than 100 μm (Fig. 3.3). In vessels smaller than 60 μm, no correlation has been found between central arterial pressure and microvascular pressure, suggesting that perfusion pressure is controlled directly in these blood vessels and those with smaller diameters.[40]

The larger arteries are predominantly under control of downstream resistance vessels, and there is little evidence that vasomotor changes in large arteries occur independently of

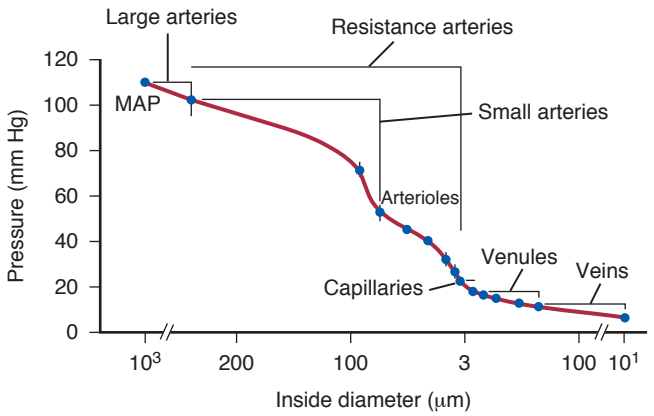

Figure 3.3 Pressure Drop Through Hamster Cheek Pouch Circulation. *MAP*, Mean arterial pressure, measured in the femoral artery. Bars indicate standard error. (Redrawn from Mulvany M, et al. Structure and function of small arteries. *Physiol Rev.* 1990;70:922-949.)

those in small resistive arteries.[41] Changes in caliber of large arteries occur passively through changes in transmural pressure and actively through changes in vascular SMC contraction. Arteriolar vasomotion may induce systemic or local blood pressure changes that alter the diameter of the artery and its viscoelastic properties. Arteriolar constriction or dilation may also modify arterial SMC tone through the endothelium-dependent mechanism of high-flow dilation.

Chemical stimulation may exert significant influence on arterial tone. Studies in isolated vessels, animals, and humans suggest that large arteries respond directly to both autonomic reflex and neurohumoral stimulation.[42] There are significant differences in the response to adrenoreceptor stimulation between large and small arteries. The aorta is poorly innervated in comparison with peripheral arteries. However, in conjunction with highly sensitive vascular SMCs and an excess of α_1-adrenoreceptors, larger arteries are sensitive to adrenergic stimulation.[43] Sympathetic control of vascular tone in large arteries is more sensitive to α-adrenergic blockade than that of smaller vessels.[44]

Small Arteries

Small arteries are the principal regulators of peripheral resistance with the ability to change diameter markedly in response to stimuli. The diameter of individual arteries in peripheral regions decreases, while the percentage of total blood volume increases, leading to a fall in blood pressure. The amount of elastic fibers in the tunica media decreases owing to these physiologic changes, in addition to having the lowest proportion of medial fibrous connective tissue. Initially, it was believed that resistance arteries consisted solely of arterioles with only one layer of SMCs and diameters of less than 30 to 50 μm. However, it has been shown that approximately 50% of precapillary resistance lies proximal to the arterioles and to vessels with diameters of 100 μm.[45]

Small arteries are considered muscular arteries. The tunica intima is thinner than in elastic arteries. ECs form a normal continuous layer; however, the subendothelial connective tissue, aside from a fenestrated IEL, is difficult to discern. The ECs of small arteries often project through fenestrations in the IEL and may come into contact with vascular SMCs in the tunica media.[46] The tunica media demonstrates numerous concentric layers of SMCs and few elastic fibers and collagen fibers. The external elastic lamina is clearly marked, though incomplete in various areas. The thickness of the adventitia in the arterial wall is variable, being small in cerebral small arteries and taking up approximately half of the wall in other regions. Nerves remain within the adventitia and do not penetrate the media.[47] The nerves, which are primarily adrenergic, consist of unmyelinated axons along which are interspersed varicosities. Axons remote from the adventitia-media border exist in bundles of up to 50. Closer to SMCs, axon bundles contain 1 to 11 axons. Although there are multiple junctions between axons and SMCs, the neuromuscular junctions in small arteries are less developed than in skeletal muscle.[45]

The number of SMC layers within the media of small arteries decreases relative to vessel diameter from approximately six layers in 300-μm vessels to a monolayer in 30- to 50-μm arterioles. The volume fraction of SMCs in the media of small arteries as seen by electron micrographs is from 70% to 85%, a fraction that is greater than in larger vessels.[45]

The resistance provided by a small artery is a function of the diameter-pressure relation. This compliance depends on the amount, arrangement, and characteristics of the connective tissues and SMCs and on the activation level of SMCs.[45]

Coronary Arteries

A special mention should be made of the coronary artery wall, given the prevalence and importance of coronary artery disease with regard to diagnosis and treatment in patients undergoing vascular surgery. The adventitia is thicker in proportion to other muscular arteries and includes a mix of collagen and elastic fibers, as well as adipose tissue. Collagen predominates in the adventitia compared with elastic fibers, in order to provide greater tensile strength and low stretch. Richly innervated SMCs in the media and adventitia are bundled longitudinally and circumferentially to respond to the repeated deforming forces caused by the contraction of the heart. Branching sites in the arteries also show normal, periodic thickenings of intima, termed musculoelastic cushions, that may contribute to atherosclerosis in these areas.[48]

Arterioles

Arterioles are the chief source of vascular resistance and control the distribution of flow. Abnormal constriction and dilation cause systemic hypertension and hypotension, respectively. The smooth muscle of arterioles, and small arteries to lesser extent, regulate tissue blood flow.

Small arteries and arterioles are controlled by both sympathetic and parasympathetic innervation. The response of small arteries and arterioles to neurohumoral activation under normal conditions largely depends on the type of stimulus and the arterial bed. Vasomotor responses depend on arteriolar territory, as in the case of emotional stress. Emotional stress dilates arterioles of skeletal muscles through activation of cholinergic vasodilator

fibers and release of epinephrine, while it constricts the splanchnic and renal arterioles.[4] In large arteries, emotional stress increases pressure and flow velocity, but does not change arterial diameter.[4,49]

Capillaries

Capillaries are responsible for the transfer of nutrient materials and waste products between blood and tissues. The low rate of blood flow and large surface area facilitate the provision of nutrients and oxygen to surrounding tissue; the absorption of nutrients, waste products, and carbon dioxide; and the excretion of waste products from the body.

The blood volume of all capillaries is significantly larger than that of the aorta, causing a decrease in blood pressure and flow rate. The capillaries have a very large surface-area-to-volume ratio, allowing for nutrients to cross the capillary wall. Diameter ranges from 4 to 15 μm. Only the tunica intima is present in capillaries and typically only consists of endothelium, its basal lamina, and an incomplete layer of cells surrounding the capillary called pericytes. Pericytes have contractile properties and are able to regulate blood flow in the capillaries. During vascular remodeling and repair, pericytes differentiate into ECs and SMCs.

Capillaries have a wide variety of configurations dependent on the structure of the endothelium, which is in turn related to the function of their specific vascular bed. They may be nonfenestrated continuous, fenestrated continuous, or discontinuous, as previously mentioned.

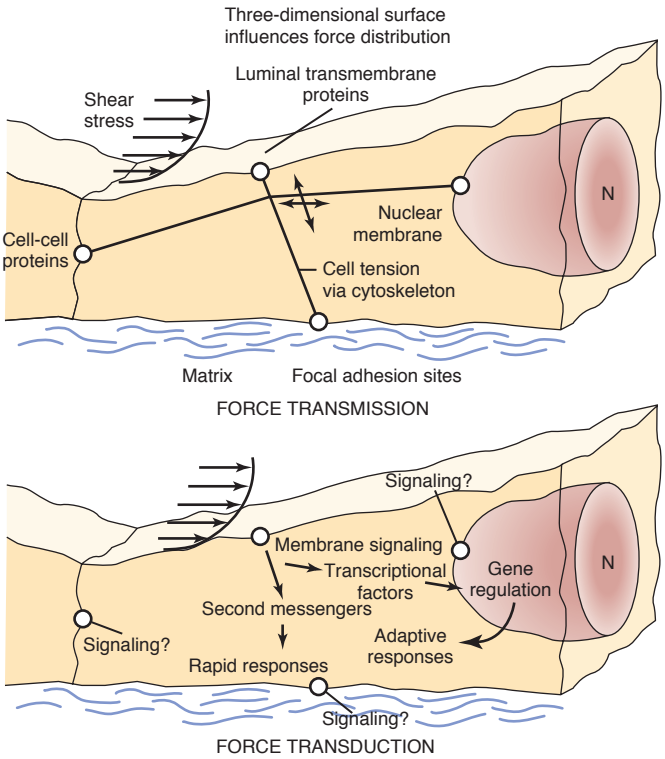

Figure 3.4 Transmission of Mechanical Force to Arterial Wall Surfaces. Extracellular fluid mechanical forces acting on the luminal surface are transmitted by the cytoskeleton to remote intracellular locations, such as cell-cell junctions, focal adhesion sites, and the nucleus *(N)*. (Redrawn from Helmke B, Davie P. Cytoskeleton under external fluid mechanical forces: hemodynamic forces acting on the endothelium. *Ann Biomed Eng.* 2002;30:284-296.)

HEMODYNAMICS AND VASCULAR WALL BIOLOGY

Blood vessels constantly experience the mechanical forces of cyclic strain and shear stress. Blood pressure is the primary determinant of cyclic strain as radial and tangential forces in the vessel wall work to counteract the intraluminal pressure. Hemodynamic forces have long been viewed as important modulators of protein synthesis, cell morphology, migration, differentiation, and proliferation. The tension per unit of thickness of the wall, which represents the stress exerted on the wall in the circumferential direction, is given as $\sigma = Pr/h$, where P is blood pressure, r is vessel radius, and h is wall thickness. Shear stress results from the flow of blood against the vessel wall and the stress acts parallel to the vessel surface. Shear stress is expressed as $\tau = 4\mu Q/\pi r^3$, where μ is viscosity, Q is flow rate, and *r* is the vessel radius. Cyclic strain affects all cell types in the vessel wall, whereas shear stress principally exerts its frictional forces on ECs at the interface of the blood and vessel wall (Fig. 3.4).

Shear Stress

Normal stress involves pulsatile pressure and flow, which includes changes in pressure and blood velocity throughout the duration of the cardiac cycle. Pulsatile flow induces both long- and short-term reactions, which vary among different regions of the vasculature. During changes in stress, the vessel wall compensates to restore the vessel to basal levels of tensile and shear stress. Acute changes in stretch and shear stress induce transient changes, including the release of vasoactive agents and alterations in vessel diameter. Chronic changes in mechanical forces demand vascular remodeling—and significant adaptive alterations in vessel wall shape and composition.

Shear stress is a determinant in the release of relaxing factors. Long-term increases in shear stress enhance the L-arginine/nitric oxide (NO) pathway in ECs. Marked increases in NO synthase mRNA and cyclic guanosine monophosphate occur with chronic increases in shear stress and, joined with matrix metalloproteinases (MMPs), can lead to apoptosis, enlargement, and vascular remodeling. An increase in flow rate through an isolated artery induces the release of endothelium-derived hyperpolarizing factor, prostaglandin I_2 (PGI_2), and NO. This finding suggests that flow-induced dilation depends on the release of endothelium-derived factors.[4,50-52] Further, long-term exposure to increased shear stress upregulates the expression of type III NO synthase in cultured ECs. NO and superoxide anions help activate MMPs. It is believed that MMPs are induced in the vessel wall in response to increased blood flow and are involved significantly in arterial wall remodeling. Increased shear stress stimulates the production of MMP-2 and MMP-9 in the arterial wall, inducing matrix degradation, tears in the IEL, and increases in arterial

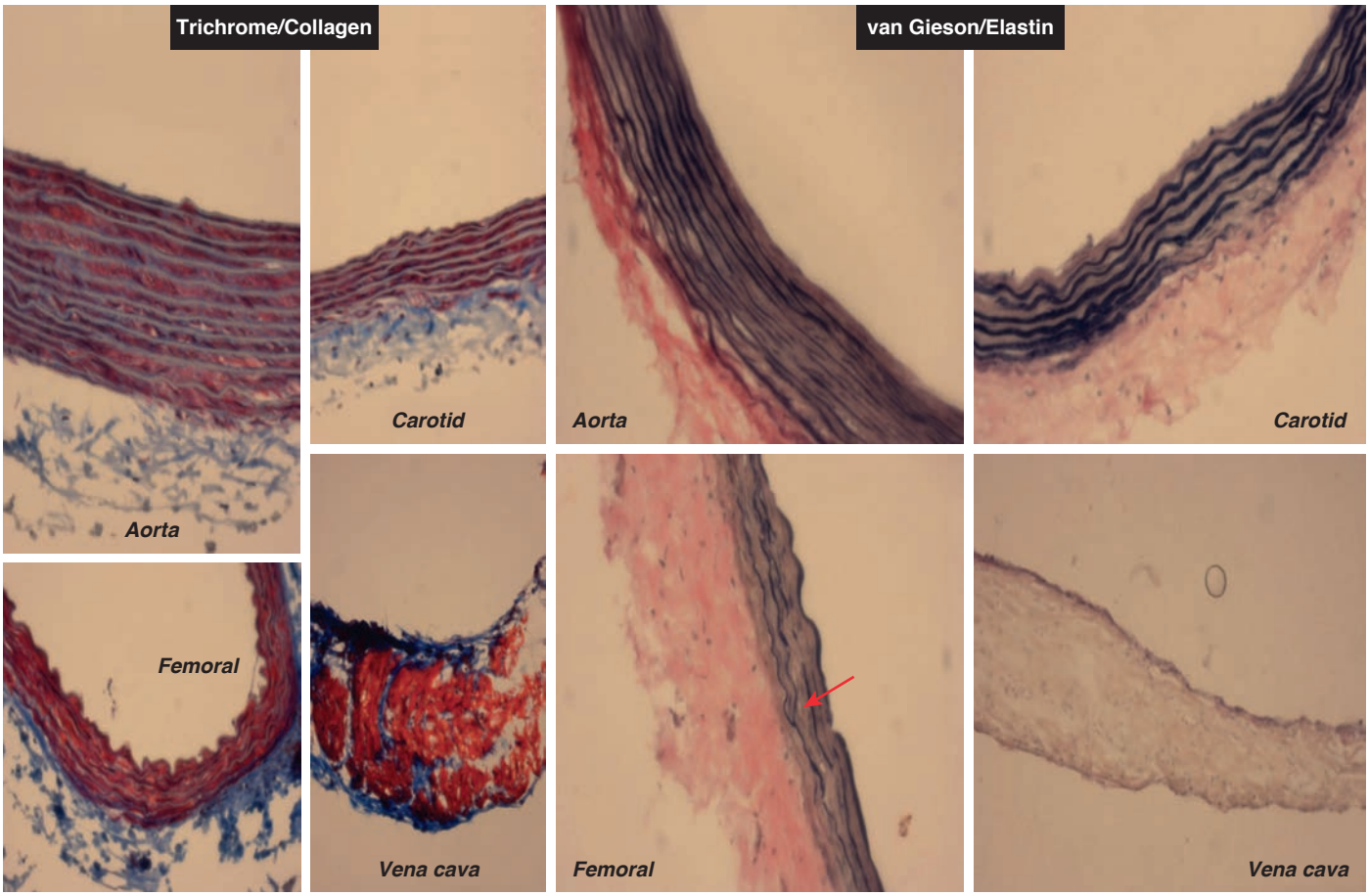

Figure 3.5 Masson trichrome blue staining of collagen, and van Gieson staining of elastin in different vessels. Blue represents collagen on the trichrome staining. There is a relative abundance of collagen in large veins such as the vena cava, as well as certain arteries such as the femoral artery, while there is minimal collagen expression in the aorta and carotid. Blackish-brown represents elastin on the van Gieson staining. The aorta and carotid have higher levels of elastin compared to the femoral artery and vena cava. The *red arrow* also indicates the broken structure of the elastin in the femoral artery specimen, which in this case could be associated with the higher level of expression of MMP-9 in the femoral artery compared to other vessels. (Redrawn from Basu P, Sen U, Tyagi N, Tyagi SC. Blood flow interplays with elastin: collagen and MMP: TIMP ratios to maintain healthy vascular structure and function. *Vasc Health Risk Manag*. 2010;6:215-228.)

diameter and distensibility (Fig. 3.5). MMP-induced remodeling will continue until arterial caliber has increased to such a point that wall shear stress is normalized. In contrast, restriction of blood flow, and thus a decrease in shear stress, causes a significant delay in the growth of the carotid artery, a 25% reduction in diameter in the carotid artery, and a decrease in elastin content in young rats.[53] Mean physiologic shear stress on the vascular endoluminal surface ranges from 10 to 15 dynes/cm^2 throughout the arterial, venous, and capillary networks.

Studies have shown that arterial circumference increases with age, but under normal physiologic conditions maintains consistent tensile stress. Medial thickness remains unchanged and intimal thickness demonstrates a pronounced increase. A study found that although wall thickness increases with age, lumen diameter also increases, thus maintaining stress levels. In a study comparing rats aged 6 to 30 months, there were significant increases in aortic wall elastin and collagen concomitant with aortic enlargement. There were also ruptures and lack of continuity in the elastic lamellae, resulting in significant decreases in wall distensibility. Thus, the walls of large arteries are stiffer in older animals. This decrease in distensibility is counterbalanced by a subsequent increase in lumen and overall vascular volume.

When there is limited vascular stretch, arteries experience an increase in intraluminal pressure, resulting in pressure-induced arterial wall crush. For instance, in percutaneous balloon angioplasty, the arterial wall is subjected to high intraluminal pressure, leading to pressure-induced crush. Sustained pressure leads to increased DNA synthesis and cell proliferation via autocrine or paracrine fibroblast growth factor-2 (FGF-2) in human vascular smooth muscle.[50] It has also been associated with an increase in *c-fos* expression in the rat model, which is associated with a proportional increase in SMC proliferation. Thus, pressure-induced crush may be involved significantly in vascular remodeling regarding the proliferation of smooth muscle.

Endothelium

Shear stress primarily affects ECs, although long-term changes in shear stress encourage vascular remodeling throughout the

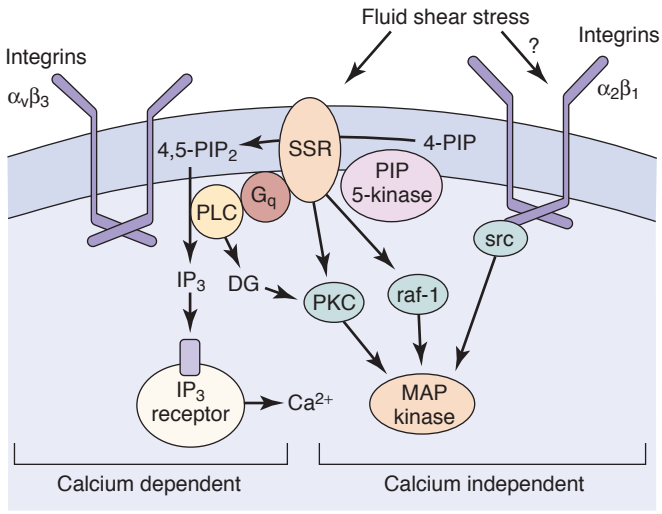

Figure 3.6 Signal Transduction Activated by Fluid Shear Stress in Endothelial Cells. Calcium-dependent and calcium-independent pathways are shown. *DG*, Diacylglycerol; G_q, G-protein; *IP$_3$*, inositol 1,4,5-triphosphate; *MAP*, mitogen-activated protein; *PIP*, phosphatidylinositol 4-phosphate; *PKC*, protein kinase C; *PLC*, phospholipase C; *SSR*, shear stress receptor.

arterial wall. ECs align in the direction of stress, and the greater the shear stress, the more elongated the cells.[54,55] Such changes are correlated with a redistribution of intracellular stress fibers and fiber quantity. In areas of high shear stress, ECs express higher amounts of stress fibers, including actin, myosin, and other contractile proteins. Although arterial levels of shear stress induce significant changes in stress fiber expression, venous levels of shear stress induce no change. Further, bovine aortic ECs retain their polygonal shape and do not develop actin stress fibers, either under oscillatory shear stress or in static culture (Fig. 3.6).

It is believed that transient changes in laminar shear stress do not permanently alter protein levels, although they may lead to the reorganization of cytoskeletal proteins and changes in cell shape. Shear stress dictates genes encoding for many growth factors, vasodilators, vasoconstrictors, and adhesion molecules. Cyclic strain interacts with shear stress, in that the strain reduces EC sensitivity to shear stress. In vivo, however, it is difficult to distinguish between shear stress and cyclic strain–induced changes in endothelium function.

Mechanotransduction begins on the luminal side of the ECs, causing deformation at the level of individual cells. This deformation is transduced through the cytoskeleton to other points on the cell, including basal adhesion points where the cells are attached to the ECM, cell junctions, and the nuclear membrane. The redistribution of forces stimulates immediate and delayed processes. The cell membrane responds by activation of stretch-induced ion channels, phospholipids, and integrins.[56,57] The nuclei upregulate the production of platelet-derived growth factors α and β, tissue plasminogen activator (tPA), transforming growth factor-β, endothelin-1, nitric oxide synthase III, and intercellular adhesion molecule-1 (ICAM-1).[58,59] Increased shear stress upregulates ICAM-1, steady shear stress upregulates vascular cellular adhesion molecule-1 (VCAM-1), and oscillatory stress decreases levels of both molecules.

It has been suggested that potassium channels, as opposed to calcium channels, are the mechanoreceptors by which ECs respond to shear stress and pressure.[60] A decrease in fluorescent dye used to measure potassium ion concentrations in bovine ECs was observed after exposure of the ECs to increases in shear stress. This decrease was due to an influx of potassium ions from the cells. An increase in inositol 1,4,5-triphosphate (IP_3) was also observed in conjunction with the onset of shear stress. This finding implies that phospholipase C (PLC) is activated by flow and that protein kinase C (PKC) activation occurs in flow-stimulated ECs.

Shear stress functions as an important modulator of arterial diameter through the release of vasoactive substances by the endothelium. Though ECs do not synthesize arachidonic acid, it is a crucial precursor to PGI_2, a vasodilator and platelet inhibitor released by ECs. It has been found that the percentage of arachidonic acid incorporated into diacylglycerol and phosphatidylinositol is significantly increased in ECs exposed to arterial levels of shear stress. Further, studies have shown that shear stress–induced PGI_2 release is significantly dependent on the PLC/diacylglycerol lipase pathway for arachidonic acid supply.[61-63]

Media

In the arterial media, vascular SMCs remain in a contractile phenotype, underscored by its spindle-shaped morphology, helical organization, contractile protein expression, low rate of proliferation, and ability to contract.[64]

Medial thickening occurs in response to hypertension and general increases in pressure and wall tensile stress. In resistance arteries, pressure increases induce medial thickening due primarily to SMC hyperplasia and changes in the proportion of contractile and matrix proteins. Such hypertrophy causes a decrease in lumen diameter and results in increased hemodynamic resistance. The increase in media-to-lumen ratio ensures that the media stress, or force exerted by the vascular smooth muscle per unit area, does not increase.

Circumferential Stretch

Cyclic or circumferential stress represents the constant, rhythmic deformation of the vascular wall caused by pulsatile, hydrostatic pressures linked to the oscillations of systole and diastole. Both ECs and underlying vascular SMCs are subjected to such forces and are susceptible to altered phenotype and changes in morphology.

In ECs, cyclic stretch has been shown to induce cell proliferation, with maximum proliferation occurring during day 1 of exposure. ECs also demonstrated an increase in total protein content. Endothelin release and gene expression in vascular ECs are stimulated by both shear stress and cyclic strain. Prostacyclin production in stretched cells has been shown to be double that in unstretched cells after incubation with arachidonic acid, although this difference also depends on the tissue source of ECs. Chronic cyclic strain for 3 to 5 days causes doubling in tPA secretion.[65]

SMCs, like ECs, when subjected to cyclic strain, change their orientation. They uniformly align perpendicular to the

direction of the strain vector—in an annular fashion. When exposed to cyclic strain, SMCs increase in proliferation rate but also fail to align. SMC hypertrophy in major arterial trunks tends to develop only when the distending pressure reaches a threshold level.[4] Cyclic stretch at low intraluminal pressure demonstrated decreased levels of smooth muscle marker proteins h-caldesmon and filamin. Physiologic intraluminal pressure, 80 mm Hg, maintained these levels. Further cyclic stretching of cultured SMCs increased expression of smooth muscle myosin heavy chains and myosin light chain kinase,[66] augmented smooth muscle myosin heavy chain SM-1 and SM-2 protein content, and decreased nonmuscle myosin NM-A. It is believed that certain levels of stretch are needed to maintain SMCs in a quiescent state and that excessive stretching triggers an increase in protein synthesis and hypertrophy.

In regard to ECM production, cyclic stretch induces an increase in collagen production in the cells and media of porcine aortic SMCs. Cyclic strain will also increase smooth muscle production of types I and III collagen, while in fibroblasts, it will increase the ratio of type II to type I collagen production. Elastin levels are markedly elevated in stretched SMCs. ECs subjected to the identical regimen demonstrated inhibition of collagen production.

In summary, increases in circumferential stress induce increases in SMC hypertrophy and in collagen and elastin production. Inversely, a decrease causes the wall to atrophy.[67] As the diameter of a blood vessel increases, the number of lamellar units and the overall wall thickness increase in order to maintain circumferential stress. In elastic large arteries, the adaptive response works to normalize tensile stress. Sustained hypertension is associated with an ongoing response in large arteries and arterioles, including increased medial wall thickness, changes in wall composition, altered arterial function, and increased SMC size and number.[68]

VEIN WALL ANATOMY

The venous system is an adaptable and variable system from person to person. In spite of the common basic function of arteries and veins in transporting blood, significant distinctions continue to be found in the organic backgrounds of the two types of vessels.

The basic cellular structure of the venous system in general conforms to the same three-layer (tunica) morphology present throughout the arterial system.[69] The IEL further separates the intima and media, and the external elastic layer separates the media and adventitia.

Intima

The intima consists of one layer of ECs sitting on an incomplete elastic basement membrane.[48] Under normal healthy conditions, the ECs have essential roles in venous wall integrity and function. These cells produce vasorelaxants and platelet inhibitors, such as PGI_2 and NO. NO also negatively affects the expression of chemical mediator secretion and inflammatory cell adhesion molecules including ICAM-1 and VCAM-1.[70-72] These functions of the venous intima and ECs in their normal state play important roles in pathologic processes such as neointimal hyperplasia when under arterial pressure.

Media

The media is composed of circularly arranged SMCs, and varies greatly according to location; however, in general it is less developed than that of the arterial system. This may contribute to the development of varicosities in lower extremity veins. The SMCs of this layer are held in a quiescent state in the normal venous environment by various factors.[73] Transforming growth factor-β downregulates their mitogenesis and stabilizes the ECM against SMC migration. In addition, heparin and heparin-like molecules neutralize FGF to downregulate cell proliferation. This process is important because these factors keep the normal vessel wall in a state of low cell turnover with low rates of proliferation and apoptosis. Injury or changes to the environment, as when veins are exposed to arterial flow, can increase rates of proliferation or apoptosis.[73]

Adventitia

The adventitia is generally the thickest layer in large veins, sometimes blending with the media. Bundles of longitudinally oriented SMCs are interspersed with collagen and elastic fibers. Collagen fibers may be particularly abundant in large veins as well and can have either a longitudinal or helical orientation. Compared with the vasa vasorum of arteries, vasa vasorum are much more extensive in venous adventitia and penetrate into deeper regions as well.[48] Lower oxygen tension in venous blood is a possible explanation for this phenomenon.

Developmental Concepts in Distinct Vein Wall Anatomy

Until 2005, vein was thought to be the default vascular state for undifferentiated vascular tissue development. The discovery of COUP transcription factor-2 (COUP-TFII) provided a direct molecular pathway to illustrate that the morphology of the vein wall is not due solely to environmental factors.[74] In the specification stage of embryonic vascular development, it was already known that the Sonic Hedgehog/vascular endothelial growth factor (VEGF) cascade in ECs activated the Delta-Notch signaling cascade, ultimately inducing expression of ephrin-B2, an arterial marker, and limiting expression of EphB4, a venous marker. COUP-TFII actively inhibits the VEGF receptor in venous development, thus suppressing Notch signaling and ephrin-B2 expression while increasing expression of EphB4.[74,75]

The decreased ephrin-B2 and increased EphB4 both contribute to the thinner, less cellular wall of veins in comparison with arteries. Ephrin-B2, a cell surface–anchored ligand for Eph receptor tyrosine kinases, regulates mural-cell migration, spreading, and adhesion during wall assembly; therefore, its deficiency in the venous development cascade may limit mural cell recruitment.[76] EphB4 expression is associated with decreased

intimal and medial thickening, largely composed of mature SMCs that otherwise localize to areas of decreased EphB4.[77] EphB4 also limits cell proliferation by extracellular-signal-regulated kinase (ERK) dephosphorylation.[73]

Physiologic Implications of Vein Wall Composition

In general, veins have thinner walls than arteries because their cellular and fibrous components are more limited in quantity. The composition of vein walls is also different, with a relative abundance of collagen fibers, particularly in large veins, and a relative paucity of elastic fibers—as might be assumed from the diminished elastic laminae (see Fig. 3.5).

This wall composition leads to the properties of veins as "capacitance vessels" and arteries as "resistance vessels." Compliance is extremely high for veins in comparison with arteries. A relaxed vein can increase in volume by up to 200% for a small increase in transmural pressure from 0 to 10 mm Hg. This increase reflects a change in geometry, with a low-pressure vein having an ellipsoidal cross-section that becomes circular with a small pressure increase—greatly enlarging the cross-sectional area.[78] The abundance of adventitial collagen and lack of medial elastin allow the vein wall to accommodate 60% to 80% of the body's blood volume.

VEIN WALL SYSTEM

The venous system begins from the capillary beds and drains blood from the extremities and body to transport it back to the heart. The vein wall changes in structure throughout its course.

Venules

Postcapillary venules are the smallest of venous vessels and form from the confluence of several capillaries. Their dimensions have ranges of 50 to 650 µm in length and 10 to 50 µm in diameter. Similar in structure to large capillaries, they have an endothelium and pericytes but no SMC layer. The attenuated endothelium is 0.2 to 0.4 µm wide. The endothelium is loosely organized and leaky with only a few intercellular junctions linking cells. A thin basal lamina is present. Given these characteristics and their slow flow, they are the main sites for white blood cell diapedesis and tissue exudate from circulation to interstitial tissue during inflammation.[48,69]

Postcapillary venules drain into collecting venules, which are larger but structurally similar with more pericytes. These continue to drain into muscular venules, which have a clearly defined intimal layer with no elastic fibers and a tunica media with one or two layers of SMCs.[69]

Veins

Veins form from the confluence of multiple venules. Typical small and medium-sized veins are 1 to 9 mm in diameter. Although these veins have three tunicae, the boundaries are less distinct than those in arteries. They may have a poorly developed IEL enclosed by a thicker media made of up to three layers of circumferentially oriented SMCs. This thicker media is still thinner than that of arteries. The adventitia, usually the thickest layer, consists primarily of longitudinally oriented collagen fibers. It may be continuous with the surrounding collagen of the supporting tissue. Large muscular veins, such as the femoral veins, exhibit a narrow intima but a substantial media with several layers of SMCs separated by collagenous tissue and scant elastic fibers.

Venae Cavae

The superior and inferior venae cavae are the largest veins and deliver deoxygenated blood into the right atrium of the heart. Other large systemic veins, such as the portal, pulmonary, azygos, splenic, and mesenteric veins, have similar features. A distinct intima of fibroelastic tissue is present. The media is narrow and composed of predominantly circumferentially oriented SMCs. A thick adventitia is most notable for the numerous bundles of longitudinally oriented collagen and smooth muscle fibers. Elastic fibers may be scattered throughout all the layers.

At the entrance to the heart, venae cavae and pulmonary veins can have a small amount of cardiac tissue in the adventitia. An extensive vasa vasorum is also present in the adventitia.[48]

Venous Valves

An important structural distinction found in veins and not present in arteries is valves. They are characteristic of small and medium-sized veins more than 2 mm in diameter.[69] Composed of local semilunar infoldings of wall intima, the valves project into the lumen in the direction of blood flow and prevent backflow as the blood returns to the heart against gravity. A reverse velocity of 30 cm/s appears required for valve closure.[79] Structurally, valves are composed of a mixed collagen-elastic fiber core of connective tissue covered by thin endothelium, making them stronger and more elastic than the vein wall.[48] They are typically found distal to the confluence of venous branches forming larger veins. The valve sinus is wider than the lumen above and below the cusps. Generally, valves assist in the caudal-to-cephalad flow of blood, but also ensure the flow from the superficial veins to the deep system. A notable exception to this is in the feet, where flow is from the deep muscles in the sole to the superficial veins in the dorsum of the foot.[80] Valves disappear more proximally in the venous system and are absent in the common iliac veins and inferior vena cava, as well as the veins of the head and neck.

It is the normal physiology of valves to disrupt the laminar flow of blood through the vein. This is important considering that this disruption occurs to a greater extent in high-flow states, such as when healthy vein is used in an arterial bypass. Turbulence caused by valves is known to induce endothelial injury in this setting and may contribute to intimal hyperplasia.[73]

The exact starting point for the development of venous diseases such as chronic venous insufficiency and varicose veins is not completely clear; however, there is little doubt that venous

valve incompetence plays a role. A reduction in the number of valves per unit length has been seen in chronic venous insufficiency.[81] The normal architecture of valve leaflets is also changed in chronic venous insufficiency, with significant infiltration by monocytes and macrophages.[82] Also, valves exposed to abnormally high pressures experience increased MMP-2 and MMP-9 levels, favoring the accumulation of ECM. Remodeling with reductions in leaflet height, width, and total disappearance also occurs.[81]

LYMPHATIC WALL ANATOMY

Although lymphatic vessels have been long known, the absence of large, consistent vessels has delayed more active research into the realm of lymphatics. However, advances in imaging and tissue engineering have revealed distinct structural and functional differences of lymphatics.

The lymphatic wall morphology has distinct anatomy at different levels. These differences play important roles in the drainage and propulsion of lymph through vessels. Briefly, at the level of the capillaries and initial lymphatics, a single layer of ECs is present, with large gaps between cells and an incomplete basal lamina.[48] These smaller lymph vessels coalesce into large vessels with thin walls that resemble veins. Like veins and arteries, large lymph vessels have three concentric tunicae. These layers, however, are not as readily delineated as they are in the cardiovascular system.[48] As in veins, valves are present within the lymph vessel lumen but are also much greater in number.

LYMPHATIC WALL SYSTEM

The lymphatic system is a unidirectional flow network originating in the interstitial space throughout the body, draining fluid from the ECM into initial lymphatics, which in turn contribute to gradually larger precollecting lymphatics, collecting lymphatics, trunks, and ducts (Fig. 3.7).[83] Lymph is pumped by the contraction of larger vessel walls containing smooth muscle.

Initial Lymphatics

The lymphatic system starts in connective tissue spaces at blind-ended vessels called initial lymphatics. These are most abundant in the connective tissue of the skin; beneath the mucous membranes of the respiratory, gastrointestinal, and genitourinary tracts; and in the connective tissue of the liver.[48] Skin on the lower extremities has a denser network of lymphatics than other areas. The capacity for transport is also higher in the lower extremities to compensate for increased interstitial fluid filtration due to gravity.[84]

Initial lymphatics are 10 to 60 μm in diameter with a wall thickness of 50 to 100 nm. The wall is composed of a monolayer of nonfenestrated ECs.[85] On electron microscopy, these blind-ended vessels are usually collapsed and have a discontinuous or completely absent basal lamina.[83] The ECs of the initial lymphatics are rich in actin filaments, which are contractile. These filaments may contribute to forward propulsion, although there is no proof yet of this ability.

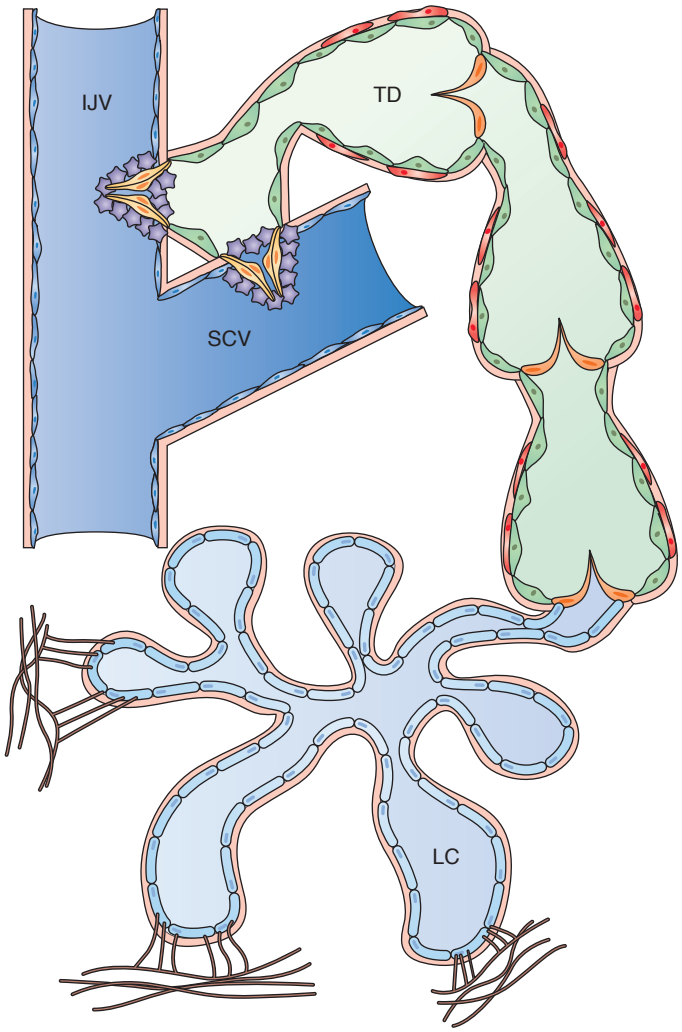

Figure 3.7 Schematic Diagram of the Lymphatic System. Lymphatic capillaries *(LC)*, also known as initial lymphatics, have endothelial cells with anchoring filaments connected to the surrounding connective tissue to form endothelial microvalves. These LCs drain into precollecting lymphatics and collecting lymphatic vessels, which have perivascular cell coverage to propel lymph and valves to prevent regurgitation. The thoracic duct *(TD)* is the longest collecting lymphatic vessel and returns lymph to the blood circulation by draining into the junction of the left subclavian *(SCV)* and left internal jugular veins *(IJV)*. (Redrawn from Chen H, Griffin C, Xia L, Srinivasan RS. Molecular and cellular mechanisms of lymphatic vascular maturation. *Microvasc Res*. 2014;96:16-22.)

Endothelial Microvalves

Because initial lymphatics have no complete basal lamina, gaps between ECs up to 10 μm wide provide an entry for lymph. When the vessels are collapsed, the ECs have overlapping extensions of cell membrane interconnected by discontinuous buttonlike junctions containing few intercellular tight junctions or adherens junctions.[86] Gaps are made possible by anchoring filaments, 6 to 10 nm in diameter, that anchor the ECs externally to the surrounding connective tissue.[87,88] When the interstitial fluid pressure increases and the surrounding matrix expands, the ECs anchored to this matrix are prevented from collapsing and allow fluid to flow through the resultant gaps between them.[83] As the interstitial fluid decreases and internal pressure

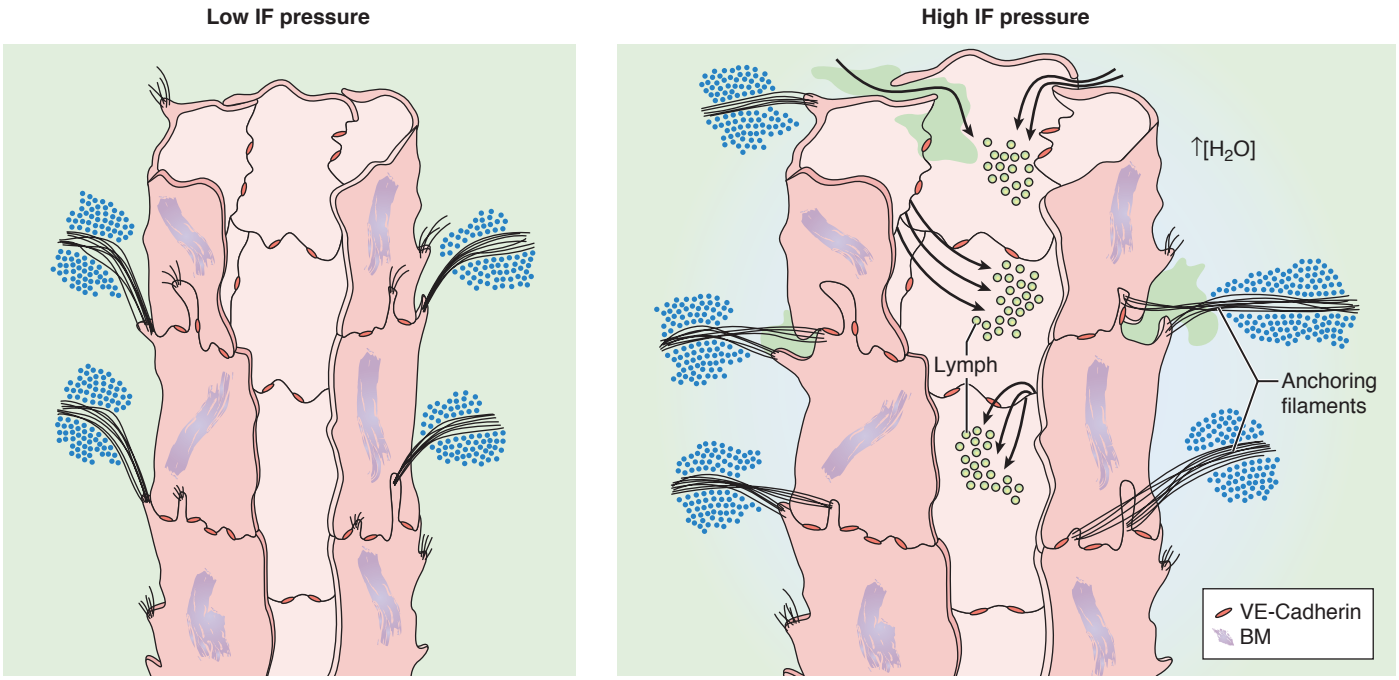

Figure 3.8 Endothelial Microvalve Drainage Response to Fluid Pressure Changes. When interstitial fluid *(IF)* pressure is low, junctions between endothelial cells are closed, not allowing flow into the lumen. When IF pressure is high, anchoring filaments pull the overlapping junctions apart and allow fluid entry into the lumen. (Redrawn from Bazigou E, Wilson JT, Moore JE Jr. Primary and secondary lymphatic valve development: molecular, functional and mechanical insights. *Microvasc Res*. 2014;96:38-45.)

rises, the ECs come together, overlap, and the gaps close (Fig. 3.8). In this way, the unidirectional flow of lymph into the lymphatics is ensured.[89] This complex is an endothelial microvalve or primary valve.

Secondary Valves

As in venous system, secondary valves are a prominent feature of the lymphatic system. They are generally bicuspid and present at regular intervals along the collecting lymphatics.[83] At the valve location, the vessel wall bulges to accommodate the opening and closing of the lymphatic valves, allowing them to form a tight seal. When viewed in vivo, lymphatic vessels often resemble a string of pearls because of these abrupt diameter changes.[90] Structurally, they are composed of a monolayer of ECs on a collagen matrix.[91] A buttress structure formed by the fusion of opposing leaflets has been observed in rat spinotrapezius lymph vessels, which has been theorized to allow the valve to close without inversion. Additional studies in other species have not demonstrated a buttress structure, and for now the valves appear to be passive structures closing in response to pressure gradients alone.[83]

Precollecting Lymphatics

Precollecting lymphatics are segments of vessels connecting the initial lymphatics to collecting vessels. Like vein walls, lymphatic walls project bicuspid, one-way valves (termed secondary valves) into the vessel lumen. Unlike in larger collecting lymphatics, these valves are irregularly spaced and sometimes constitute only a single leaflet. At this level, SMCs also start to appear around the vessels in one or more layers. These smooth muscle layers may contract and begin the forward propulsion of lymph through the system. However, many areas still are without any muscular layer or basal lamina and can act as a primary valve. Therefore, precollecting lymphatics fulfill a dual function in absorbing more lymph and also propelling it forward.[83,92]

Collecting Lymphatics

At the level of the collecting lymphatics, the basal lamina surrounding the endothelium of the lymph vessel becomes complete. Here the three typical layers of vessel wall also become more evident. The luminal side is bordered by an intimal monolayer of ECs. The media contains one to three layers of SMCs intermixed with collagen and elastic fibers. The muscle bundles are arranged in a helicoidal manner. This is all surrounded by an adventitia composed of fibroblasts, connective tissue, and nerve terminals.[93] Secondary valves also become more regularly spaced.

Lymphangions each represent the vessel space between two of these secondary valves. In humans, lymphangions of collecting lymphatics in the head and neck average 0.2 mm in diameter with a length of 2 mm. Those of the lower extremities may have a diameter of 1 to 2 mm with a similar 2-mm length. Lymphangions are innervated by sympathetic and parasympathetic nerves and rhythmically contract to propel lymph forward.[83]

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CHAPTER 4

Atherosclerosis

CHRISTOPHER D. OWENS and KAREN J. HO

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Vascular surgeons care for a diverse set of clinical manifestations related to atherosclerosis—from symptomatic transient cerebral ischemic attacks to aortoiliac occlusions to aortic aneurysms repairs to mesenteric ischemia and to lower extremity arterial occlusive disease. However, despite the wide range of manifestations, culprit lesions are more alike than different. Accumulation of large amounts of cholesterol ester in the arterial wall and formation of complex advanced plaque are common to all these lesions. Although the formation of atherosclerotic lesions is insidious and spans decades, the lesions can reach a clinical dénouement within minutes and manifest as catastrophic myocardial infarction (MI), stroke, or limb ischemia. Atherosclerotic-related cardiovascular disease (CVD) is the leading cause of death in every region of the world except sub-Saharan Africa.[1] However, during the last two decades, CVD age-specific death rates fell by more than 40% in high-income countries.[2] The improved survival has translated into growing disease prevalence and a staggering financial burden. It is estimated that 81,000,000 Americans have CVD with an estimated annual cost of treatment of $449 billion.[3] Globally, 202 million people have peripheral arterial disease (PAD), which disproportionately affects blacks and individuals living in low- to middle-income countries.[1,3] Particularly troubling is the high prevalence of CVD risk factors in children and young adults.[4,5] A sedentary lifestyle, abdominal obesity, and poor diets contribute to dyslipidemia and high blood pressure. Autopsy studies in children and young adults demonstrate a link between these risk factors and early lesions.[4]

This chapter outlines the existing theories of the pathophysiology of atherosclerosis and the relationship to traditional and emerging risk factors. It also describes our current conceptual understanding of the fundamental biology of atherosclerotic plaque.

ATHEROSCLEROTIC LESIONS

Lesions of the arterial wall have been divided into six types based on their histopathologic features.[6,7] However, although the classification system is useful for comparing pathologic specimens, it has limited clinical practicality.

Autopsy studies from the Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth study demonstrate that atherosclerotic lesions form in early childhood and increase with age.[4,8-10] In an intravascular ultrasound (IVUS) study of heart donors, 17% of individuals younger than 20 years had evidence of atherosclerosis.[11] Notably, both the Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth study emphasize that the number and severity of early lesions are directly related to known cardiovascular risk factors, thus suggesting that a paradigm shift is needed to address

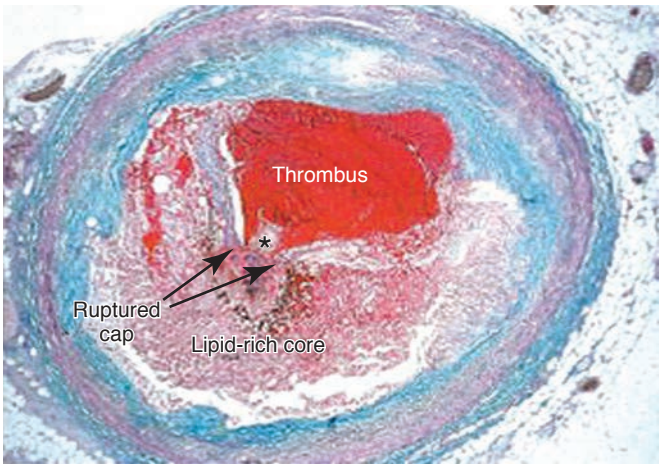

Figure 4.1 Thrombotic complication of a fibroatheroma seen on a trichrome-stained (thrombus and intraplaque hemorrhage stain *red*; collagen stains *blue*) cross-section of a human coronary artery. The fibrous cap has ruptured (area between the *arrows*), and the highly thrombotic lipid core is exposed to circulating blood with the subsequent production of acute occlusive thrombosis.

risk factors in childhood rather than pharmacologic therapy later in the disease process.

Diffuse intimal thickening has been identified in the atherosclerotic-prone areas of coronary arteries as early as 36 weeks of gestation.[12] Although the fatty streak—dominated by lipid-filled macrophages—is itself benign, it is the precursor of the more clinically relevant late lesion. The fatty streak is the first lesion visible to the naked eye. Its yellow color is attributed to lipid in the form of cholesterol and cholesterol esters within macrophages and smooth muscle cells (SMCs).

Advanced lesions, or fibrous plaque, are characterized histologically by the amount of extracellular lipid and fibrous connective tissue. They are whitish in gross appearance and are elevated so that they protrude into the lumen. These fibroatheromas are prone to provoking clinical sequelae by erosion of the surface endothelial cells, rupture of the fibrous cap, erosion of a calcium nodule, or intraplaque hemorrhage (Fig. 4.1).[6,13] Plaques differ in consistency and may be relatively soft and friable or densely sclerotic and calcific. Likewise, some have well-formed fibrous caps, whereas others are covered by a narrow zone of loose connective tissue or by endothelium alone.

The necrotic core usually occupies the deeper central regions of the plaque and contains amorphous lipid and cholesterol crystals. The term *atheroma* is derived from the Greek word *athere*, meaning "porridge-like gruel." SMCs and inflammatory cells are located adjacent to the necrotic core and at the shoulders of the plaque, where it is most susceptible to rupture.

The fibrous caps contain varied levels of SMCs adjacent to the collagen and basement membrane. These cells have reduced proliferative ability and may be regarded as senescent. However, the fibrous cap of ruptured plaque is often infiltrated with foam cells, which are largely of macrophage origin[14] and thus indicative of active inflammation and vulnerability to rupture. A priori identification of these so-called thin-cap fibroatheromas is an active area of cardiovascular imaging research.[15]

THEORIES OF PATHOGENESIS

Each of the well-regarded theories of atherosclerosis discussed in this section attempts to explain the underlying pathogenesis of atherosclerotic plaque. Each theory has undergone a steady evolution since the time that it was initially proposed, a consequence of advancements in our scientific inquiry from histologic descriptions to discernment of powerful molecular mechanisms. Each theory, held accountable over time, must incorporate new scientific data within a clinical context of risk factors and biomarkers to result in a model of atherosclerotic lesion formation.

Lipid Hypothesis

Cholesterol has been one of the most studied molecules in biomedical research. The modern era of cholesterol research began in St. Petersburg, Russia, at the turn of the 20th century, when Nikolai Anitschkow produced vascular lesions in rabbits by feeding them purified cholesterol dissolved in sunflower oil.[16,17] These lesions closely resembled those seen in human atherosclerosis. He hypothesized that they were caused by elevated serum cholesterol and also noted a distinctive pattern consisting of the location of the lesions near arterial branch points and concluded that this was probably determined by hemodynamic factors. Nevertheless, this work was criticized because the levels of cholesterol produced were too high and could not be experimentally reproduced in more conventional animal models such as rats and dogs.[16,17]

Cholesterol is insoluble in water, and the early work done in Russia provided no clues as to how it was transported to the arterial wall and formed plaques. The discovery that cholesterol was associated with proteins that allowed it to be transported in the aqueous environment led to investigations into lipoproteins. The first investigation in which the lipoprotein content in whole serum was accurately quantified involved analytic ultracentrifugation and was led by John Gofman of the Donner Laboratory at University of California at Berkeley.[18] Lipoprotein fractions were isolated and characterized by their densities and floatation characteristics.[18] Of note, this group noted that it was not simply the total cholesterol that was important but the species of lipoprotein contained within the cholesterol.[19]

Cholesterol is transported in the aqueous environment by esterification of the sterol of long-chain fatty acids and packaging of these esters with the hydrophobic cores of plasma lipoproteins. With its polar hydroxyl group esterified, cholesterol remains sequestered within this core, which is essentially an oil droplet composed of cholesteryl esters and triglycerides, solubilized by a surface monolayer of phospholipid and unesterified cholesterol and stabilized by protein. In persons who are fasting, lipids circulate in plasma as lipoprotein particles that are defined on the basis of their density as very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, and high-density lipoprotein (HDL). The protein of the VLDL, IDL, and LDL molecule is apoB-100, which has β-electrophoretic mobility.

The major milestone in the lipoprotein field was the discovery of the defective gene associated with familial hypercholesterolemia

by Goldstein and Brown. In fibroblasts cultured from normal human subjects, the activity of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-controlling enzyme in cholesterol biosynthesis, is regulated by the content of LDL (but not HDL) in the culture medium. Goldstein and Brown found that HMG-CoA was not sensitive to normal feedback regulation by LDL in cultured skin fibroblasts from homozygous familial hypercholesterolemia patients.[20,21] They then determined that the defect was related to deficient binding of LDL to the cells of patients with familial hypercholesterolemia and that suppression of HMG-CoA activity was related to the amount of bound LDL.[22] Therefore, these patients had overproduction of cholesterol because they lacked the appropriate receptor. They demonstrated that cellular uptake of LDL absolutely requires the LDL receptor, without which the LDL cholesterol concentration builds up to 800 to 1000 mg/dL (20.7-25.9 mmol/L). This important work culminated in a Nobel Prize in Physiology and Medicine for Goldstein and Brown in 1985.

Epidemiologic evidence from numerous studies, including the Japanese migration studies[23,24] and the Framingham Heart Study,[25] demonstrated the association between cholesterol and incident CVD. Other studies showed that diets rich in unsaturated fats resulted in lowered cholesterol and reduced cardiovascular events.[26]

Widespread acceptance of the causative role of cholesterol began with publication of the Coronary Primary Prevention Trial, sponsored by the National Institutes of Health.[27,28] This trial demonstrated that lowering cholesterol with the bile acid punding resin cholestyramine reduced cardiovascular events. A decade later, this trial was reinforced with powerful data that emerged from the statin era.[29] Although the primacy of the "cholesterol hypothesis" has been called into question, there is no doubt that lipids play a critical role in the pathogenesis of atherosclerosis.

Response-to-Injury Hypothesis

The basis of this hypothesis lies in the similarities between atherosclerosis and the response of arteries to experimental injury. Although the origins of the hypothesis date back to Virchow, the modern version of the hypothesis builds on earlier work by Duguid,[30] Poole and Florey,[31] and French[32] and was formally advanced in 1973 by Ross and Glomset,[33] who emphasized the importance of injury to the endothelium as a seminal event in the development of atherosclerosis lesions. Even though the definition of the term *injury* has been modified over the last three decades,[34] all response-to-injury hypotheses have emphasized the primacy of the endothelium in stimulating the cascade of events leading to lesion formation.[33-38]

Endothelial injury may result from mechanical disruption, exposure to toxic or infectious agents, or endogenous inflammatory signals. Injury to the endothelium allows adhesion of platelets and an influx of LDL and other serum factors into the subendothelial space. Platelets release their alpha granules and stimulate migration of SMCs into the intima, where they proliferate and form a thickened neointima responsible for narrowing of the arterial lumen. Restoration of a healthy endothelial cell layer abates the process. During work on this hypothesis, Ross et al. performed experiments leading to the discovery of platelet-derived growth factor (PDGF).[39,40]

Other investigators have countered that it is not injury to the endothelium that is the initiating event but rather retention of inflammatory lipids in the subendothelial space that renders a particular area susceptible to atherosclerosis. The observation that LDL accumulates in the intima within two hours after a bolus infusion[41] and that the accumulation occurs before the formation of fatty streaks[42,43] led to the conclusion that retention of LDL is the initiating event of atherosclerosis. The so-called "response-to-retention" theory purports that retained apoB–containing lipoproteins stimulate a macrophage- and T cell–dominated inflammatory response in the arterial wall.[44,45]

Monoclonal Hypothesis

This hypothesis suggests that each lesion of atherosclerosis is derived from a single SMC that serves as a precursor for the clonal expansion of proliferating SMCs.[46] The hypothesis put forth by Benditt and Benditt used the concept that in every female cell there is only one active X chromosome and the progeny of that cell will express the same X chromosome as the parent cell. Glucose-6-phosphate dehydrogenase (G6PD) has two isoforms that can be separated by electrophoresis. Its gene is located on the X chromosome and can therefore be used to identify the progeny of a parent cell. This approach was used to determine that uterine leiomyomas are composed of cells with the same active X chromosome, whereas adjacent normal myometrium is composed of a mixture of cells containing both G6PD isoforms, implying that both X chromosomes are active.[47]

The Benditts examined a series of atherosclerotic plaques from four black females and compared them with adjacent normal areas of arterial wall. They determined that SMCs from the plaque contained only one G6PD isoform, whereas adjacent control areas contained a mixture of isoforms. This allowed them to conclude that each lesion is a clonal outgrowth derived from a single precursor SMC located in the intima. It is noteworthy that SMCs within individual neonatal intimal thickenings are monoclonal in origin, whereas cells from the subjacent media are polyclonal.

Others challenged the hypothesis by noting that identification of a single enzyme phenotype does not necessarily imply clonal origin.[48,49] Regardless, the work was importantly heuristic, and hinted toward the role that modern molecular biology would play in unraveling the genetic basis of atherosclerosis.

ATHEROSCLEROSIS AS A CHRONIC INFLAMMATORY DISEASE

The original version of the response-to-injury hypothesis of atherosclerosis proposed that endothelial denudation was the first step in atherosclerosis.[33] Subsequent versions of the hypothesis proposed that an endothelium chronically bathed in serum with high concentrations of LDL or exposed to other

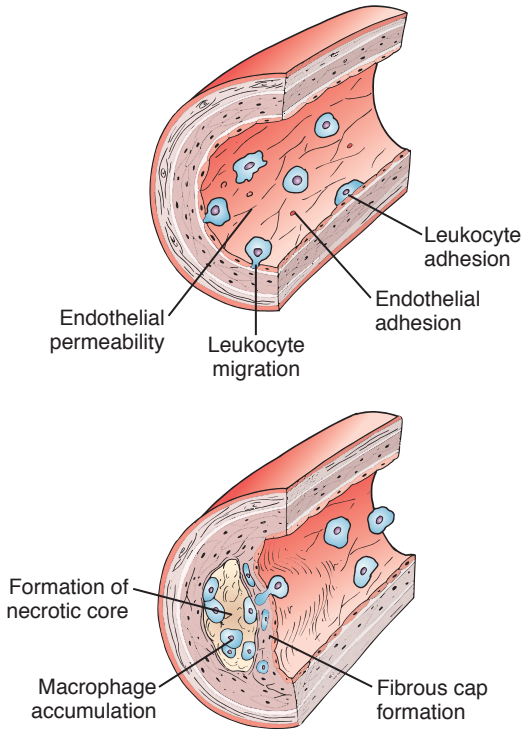

Figure 4.2 Initiation and progression of atherosclerotic plaque. Cardiovascular risk factors, hemodynamic forces, toxins, and infectious agents interact with the vessel at the level of the endothelium to produce injury, resulting in decreased nitric oxide production and increased permeability. Once injured, the endothelium increases the expression of leukocyte adhesion molecules such as vascular cell adhesion molecule-1, intracellular adhesion molecule-1, and P- and E-selectin, which increases the adherence of macrophages and other leukocytes. Permeability of the endothelium also increases and permits entry of leukocytes and lipoproteins into the subendothelial space. Chemokines and cytokines such as monocyte chemotactic protein-1 and interleukin-8 further enhance the recruitment of leukocytes and smooth muscle cells (SMCs) into the subendothelial space. Lipoproteins retained in the subendothelial space are biochemically modified such that they can be taken up by macrophages and SMCs to form foam cells. Foam cells at the central-most position of the developing atheroma become necrotic and form the central lipid core, whereas the shoulder regions contain SMCs, macrophages, and other leukocytes. Platelet-derived growth factor and transforming growth factor-β stimulate SMC migration and collagen formation in the subendothelial space, as well as formation of the fibrous cap.

cardiovascular risk factors would render susceptible areas of the endothelium dysfunctional or activated.[37] Indeed, an intact endothelium may be a necessary factor for lesion progression, and it is now clear that developing atheromas are covered by an intact endothelium throughout most stages of lesion progression.[7,34,50-52] In humans, only the most advanced ulcerated lesions are focally devoid of endothelium. The injury results in increased adhesiveness and an increase in permeability of the endothelium to inflammatory cells (Fig. 4.2).

Atherosclerosis is now recognized as an inflammatory disease, and components of the innate and adaptive immune system are involved in every step of the atherosclerotic process. Much of our modern understanding comes from examination of human pathology specimens and transgenic animals. Genetic deletion of apolipoprotein E *(ApoE$^{-/-}$)* or the LDL receptor *(Ldlr$^{-/-}$)*, which produce mice with severe hypercholesterolemia and atherosclerotic lesions with features of mature human atheroma, have become cornerstones in atherosclerosis research laboratories.[53-55] The importance of the LDL receptor in cholesterol regulation was noted by Goldstein and Brown when studying patients with familial hypercholesterolemia. Apolipoprotein E suppresses atherosclerosis, and *ApoE$^{-/-}$* mice have very low levels of pre-β HDL and their plasma is poor at promoting the efflux of cholesterol from lipid-laden macrophages.[56] Crossbreeding these mice with other strains carrying null mutations in immunologically relevant genes produces a robust research tool to dissect out the contribution of individual components of immune pathways in atherosclerosis. For example, some of the earliest approaches using compound mutant mice involved the global loss of the entire adaptive immune system. *Rag1$^{-/-}$* and *Rag2$^{-/-}$* mice lack the V(D)J recombinase required to form lymphocyte antigen receptor genes and hence have a complete loss of B and T cells. *ApoE$^{-/-}$* mice fed a regular chow diet developed plasma cholesterol levels between 390 and 470 mg/dL. Double knockout *ApoE$^{-/-}$/Rag1$^{-/-}$* mice had a 40% reduction in aortic atherosclerotic lesion reduction compared with immunocompetent animals, thus demonstrating the role cellular immunity plays in the pathogenesis of atherosclerosis.[57]

Low-Density Lipoprotein Retention

Trafficking of circulating LDL into and out of the subendothelial space is probably a function of concentration gradients and endothelial permeability.[58,59] Normal intima does not retain LDL particles, thus suggesting that most particles return to plasma or are degraded in situ. However, subendothelial retention of apoB-100–containing lipoproteins is an early event in atherosclerosis.[59] Factors favoring net retention include a balance of uptake and degradation of LDL by macrophages, egress of LDL-containing macrophages into the circulation, and complex interaction with proteoglycans such that the LDL particles are sufficiently modified to maintain the gradient. Once bound to the matrix, the lipoprotein is modified so that it becomes oxidized.[58,60] Oxidized LDL, unlike native LDL, is chemotactic to monocytes and rapidly taken up by macrophages to form foam cells by scavenger receptors.

Monocytes

As early as 1958, Poole and Florey noted that macrophages adhere to the surface of endothelial cells overlying atheroma.[31] In studies of hypercholesterolemic monkeys, monocytes are seen attached to the endothelium within 12 days of initiation of an atherogenic diet.[61] It is now apparent that monocytes play a very early role in atheroma formation.[62,63] Endothelium, which is rendered activated, expresses adhesion molecules that interact with circulating leukocytes, principally monocytes and lymphocytes. E- and P-selectins slow monocytes, mediate rolling, and loosely tether them to the endothelium.[64] More permanent fixation is due to members of the immunoglobulin superfamily—vascular cell adhesion molecule-1 (VCAM-1)[65] and intercellular adhesion molecule-1 (ICAM-1)—which are soon upregulated and firmly fix the leukocytes to the wall. The importance of the selectins, VCAM-1, and ICAM-1, in the pathogenesis of

atherosclerosis is evident in either ICAM-1 or VCAM-1 mutant mice exhibiting, which exhibit far less atherosclerosis than wild type control mice.[66-68] The adherent leukocytes are stimulated to migrate into the subendothelial space by a number of chemokines, including monocyte chemoattractant protein-1 and oxidized LDL.[69-71]

Macrophages

Once within the subendothelial space, monocytes undergo a series of phenotypic modulations and become resident tissue macrophages that take up oxidized LDL via the scavenger receptor A (SR-A), as well as CD36.[72] One of the key signals for macrophage activation, macrophage colony-stimulating factor, can enhance scavenger receptor expression and promote replication of macrophages and their production of proinflammatory cytokines. Experiments in mutant mice deficient in macrophage colony-stimulating factor have shown the importance of this factor in atheroma formation.[73,74] Although most foam cells are macrophage in origin, SMCs also take up lipids via scavenger receptors and CD36.

In mice, proinflammatory subsets of macrophages called M1-macrophages, induced by hyperlipidemia, produce the inflammatory cytokines IL-1β and TNF-α. The IL-1 gene family encodes three major proteins. The first two, IL-1α and IL-1β, exert proinflammatory effects by binding to the IL-1 receptor type 1. The third is IL-1 receptor antagonist (IL-1Ra), an endogenous inhibitor that competitively blocks the binding of IL-1α and IL-1β to the IL-1 receptor. Direct evidence for the proatherogenic role of IL-1 was obtained in experiments in which *ApoE*$^{-/-}$ mice received subcutaneous injection of recombinant IL-1 receptor antagonist. Mice injected with IL-1 receptor antagonist displayed a marked reduction in atherosclerotic lesion size. Similarly IL-18, previously called interferon-γ (IFN-γ)–inducing factor, is a Th1-promoting cytokine and therefore has the capacity to promote inflammation through the innate and the adaptive immune pathways.[75,76] Knockout of IL-18 in atherosclerosis-prone animals reduces aortic atherosclerotic lesion size.

Macrophages also contribute to thrombosis in several pivotal ways. As discussed later, atherosclerotic lesions that have ruptured characteristically contain abundant macrophages underlying a thin and collagen-poor fibrous cap. Specific collagenases matrix metalloproteinase (MMP)-1, MMP-8, and MMP-13, co-localize with macrophages in human atheroma. Rupture of the fibrous cap may be a balance between collagen synthesis by SMCs and collagen breakdown by interstitial (matrix metalloproteinases) collagenases generated by activated macrophages. Studies in collagenase-resistant mutant "knock-in" mice crossbred with *ApoE*$^{-/-}$ mice demonstrated increased intimal collagen and SMC content.[77] Similarly, compound mutant *ApoE*$^{-/-}$ mice crossed with MMP-13/collagenase-3$^{-/-}$ mice have increased fibrillar collagen that is thicker and more aligned in aortic atherosclerosis.[78] Hence, interstitial collagenases produced by activated macrophages greatly influence the structure and integrity of the fibrous cap overlying atherosclerotic plaques. Macrophages and SMCs within atherosclerotic plaques also overexpress the potent procoagulant tissue factor in response to C-reactive protein or CD40 ligand. Hence, inflammation links atherosclerosis and thrombosis, leading some to refer to it as "atherothrombosis."

Lymphocytes and Adaptive Immunity

The finding in the early 1980s that macrophages expressed the major histocompatibility class II antigens needed for antigen presentation to CD4$^+$ T cells suggested that adaptive immunity was involved in the atherosclerotic process.[79] T lymphocytes, which account for as much as 10% to 20% of the leukocyte population, are found most abundantly in the shoulder and fibrous cap region of the atheroma. In advanced lesions, these T cells display markers of chronic activation and produce the prototypical Th1 cytokine, (IFN-γ), which further stimulates expression of class II major histocompatibility antigens in SMCs and macrophages. The crossbreeding of severe combined immunodeficiency (SCID) mice that lack T and B cells with *ApoE*$^{-/-}$ mice produces offspring that are both hypercholesterolemic and immunodeficient. When lesions in these mice were compared with those in the immunocompetent *ApoE*$^{-/-}$ animals, a dramatic 70% reduction of lesion size was observed. However, transfer of oxidized LDL-reactive T cells to *ApoE*$^{-/-}$/SCID mice is more efficient at lesion acceleration than the transfer of T cells with no specificity to a plaque-derived antigen, demonstrating the importance of antigen presentation in the pathogenesis of atherosclerosis.[80]

Because of the participation of all components of the innate and adaptive immune system, atherosclerosis resembles other inflammatory and autoimmune diseases such as rheumatoid arthritis and type 1 diabetes mellitus. Potential endogenous autoantigens that activate T cells include LDL or heat shock protein 60.[80,81] Cellular and humeral immune responses are mounted toward these antigens in humans and mice, and protective immunization strategies in mice have provided encouraging results.

In mice, functionally distinct T cell subsets appear to exist in atheroma. Natural killer T cells appear to accelerate atherosclerosis when recognizing lipid antigens presented through CD1 molecules.[82] Conversely, regulatory T cells may suppress Th1 effector cells through production of antiinflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β).[83] T cells, although far fewer in number than macrophages, likely serve as key regulators of the concerted immune response.

Mast cells are located at the shoulder and more central area of the cap, where they may participate in rupture or erosion of the cap.[84] Once recruited to the subendothelial space in the intima, they can perpetuate and amplify the ongoing inflammatory response that led to their recruitment.[85] The CD40 receptor and CD40 ligand are expressed by several inflammatory cells, including macrophages and B and T lymphocytes.[86] It is thought that this system contributes to leukocyte adhesion, matrix degradation, and cytokine-induced inflammation. Interruption of the CD40 signaling pathway reduces progression of atherosclerosis in experimental models.

Smooth Muscle Cells

Proinflammatory mediators can stimulate the migration of SMCs from the tunica media into the intima. Growth factors produced locally provide a paracrine stimulus for SMC proliferation and activation. Activated SMCs appear capable of producing growth factors (e.g., PDGF, fibroblast growth factors) that can stimulate their own proliferation and that of their neighbors in an autocrine and paracrine fashion.[87] TGF-β stimulates the production of matrix and collagen in the subendothelial space. As the plaque matures, necrotic foam cells contribute to the central lipid core, whereas collagen contributes to the overlying fibrous cap of a mature fibroatheroma.

Calcification

Bone morphogenetic protein-2 (BMP-2), a member of the TGF-β family, and inorganic phosphate induce the osteochondrogenic phenotype in SMCs.[88] BMP-2, in turn, is produced by endothelial cells exposed to hypoxia, reactive oxygen species, turbulent flow, high pressure, or inflammation.[88] Atherosclerotic calcification proceeds through a process similar to chondrogenesis, whereby cartilaginous metaplasia precedes osteoblast induction. This is distinct from medial artery calcification, which proceeds through a process similar to intramembranous bone formation. The latter is common in patients with diabetes or chronic kidney disease. The reason that some plaques undergo calcific changes whereas others do not is not clear.

Thus, the inflammatory reaction stimulated by modified LDL and white blood cells in the subendothelial space provides a nidus for the subsequent events leading to the formation of mature fibrocalcific atherosclerotic plaque. Notably, this process, which probably begins in childhood, is silent until sufficient arterial stenosis exists or until a catastrophic plaque-destabilizing event occurs and produces a clinical symptom.

Putting It All Together: The Inflammasome

Clinically, cholesterol is an established causative risk factor for atherosclerosis. Recent evidence has shown that crystalline cholesterol is present early in the formation of atherosclerotic lesions and coincides with the presence of immune cells.[89,90] Cells of innate immunity are equipped with receptors that detect pathogen-associated molecular patterns and endogenous danger signals. Once these receptors are activated, monocytes and macrophages secrete inflammatory cytokines such as IL-1β into the arterial wall. In the last 10 years, considerable efforts in several laboratories have established a role for the interleukin 1 family in complex diseases, including atherosclerosis, diabetes mellitus, rheumatoid arthritis, and gout. As discussed earlier, IL-1β has several layers of regulation and is synthesized as pro-IL-1β and requires activated caspase-1 to cleave pro-IL-1β and IL-18 into their active and secreted form. Caspase-1 activation requires a second signal mediated through a complex of intracellular proteins known as inflammasomes. The nucleotide-binding domain leucine-rich (NLR) family pyrin domain–containing 3 (NLRP3) inflammasome has been most extensively studied. When NLRP3 receptors are activated, they oligomerize and recruit caspase-1 through the adapter protein ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) and autocatalytically activate caspase-1, which cleaves pro-IL-1β into its mature forms.[91] NLRP3 inflammasome activation historically included pore-forming toxins, extracellular adenosine triphosphate, viral DNA, and gout-associated uric acid crystals. However, recent evidence demonstrates that cholesterol crystals can also activate the inflammasome and therefore increase secretion of the potent proinflammatory cytokines IL-1β and IL-18. These data argue that cholesterol crystals are not solely an inert byproduct within the wall of the artery but an active contributor to atherosclerosis.[89,90]

Moreover, hypercholesterolemic *Ldlr*$^{-/-}$ mice reconstituted with bone marrow from mice deficient in NLRP3, ASC, or IL-1β have significantly reduced aortic lesion sizes compared with those reconstituted with wild-type bone marrow.[89] These mice showed significantly lowered levels of IL-1β and IL-18. The implication of caspase-1 was evaluated recently in atherosclerosis as a pathogenic enzyme because this deficiency decreases atherosclerosis in apoE-deficient mice.[92] Hence, within the vascular wall, lipids and inflammation appear to be inextricably linked.

C-Reactive Protein

The clinical detection of inflammation within the vascular wall is limited to the measurement of spillover circulating biomarkers of the inflammatory process. Many prospective studies have established an association between biomarkers of inflammation and first and recurrent cardiovascular events. For example, studies have noted that the circulating soluble ICAM-1 and VCAM-1 are elevated in the plasma of patients before the development of peripheral arterial disease.[93] Similarly, the inflammatory cytokines IL-6 and IL-1β, as well as acute-phase reactants C-reactive protein, fibrinogen, and serum amyloid A, have all been associated with peripheral arterial disease and its progression.[94,95] Among the many inflammatory biomarkers evaluated, high-sensitivity C-reactive protein (hsCRP) has emerged as the leading biomarker for clinical application. This is because CRP is a very stable analyte over time, has a relatively long half-life, has no diurnal variation, and requires no special processing for sampling.[96] In addition, very low (<0.5 mg/L) and very high (>10 mg/L) values of hsCRP both provide important prognostic information on cardiovascular risk.[97,98]

Currently, more than 20 large prospective studies across North America and Europe demonstrate the relationship between the baseline inflammatory state, as measured by hsCRP, and the risk for future cardiovascular events. Furthermore, in 28,000 apparently healthy women, hsCRP was a stronger predictor of cardiovascular events (including coronary events, stroke events, and cardiovascular death) than LDL cholesterol, total cholesterol, or other markers of inflammation and thrombosis.[99,100] Prediction models for future cardiovascular risk demonstrate that hsCRP enters the model just behind high blood pressure but ahead of smoking and total and LDL cholesterol.[101] The predictive value of hsCRP for cardiovascular

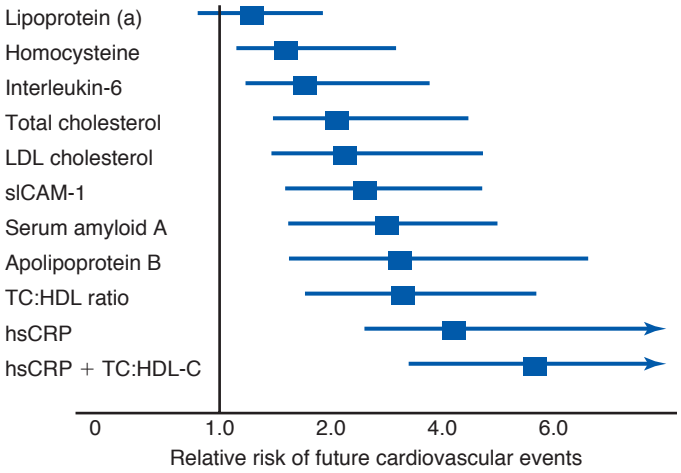

Figure 4.3 Comparison of lipid and nonlipid risk factors for cardiovascular disease (CVD) in 28,000 women enrolled in a nested case-control study from the Women's Health Study cohort of postmenopausal, apparently healthy women. hsCRP adds to the total predictive value of cholesterol. Note that lipoprotein (a) and homocysteine are relatively weak predictors of CVD. *HDL,* High-density lipoprotein; *hsCRP,* high-sensitivity C-reactive protein; *LDL,* low-density lipoprotein; *sICAM-1,* soluble intercellular adhesion molecule-1; *TC,* total cholesterol.

risk is similar in the United States and Europe, thus demonstrating consistency in different populations.[102] hsCRP is predictive in both primary and secondary prevention. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study, patients with acute coronary syndromes and the fewest subsequent events were those who reached LDL cholesterol levels of less than 70 mg/dL (1.81 mmol/L) and those who reduced their CRP levels to less than 2 mg/L (19.1 mmol/L).[103,104] Accordingly, hsCRP is at least as robust a biomarker for predicting future cardiovascular events as are traditional cholesterol-based biomarkers (Fig. 4.3).

The recently completed Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) adds further circumstantial evidence of the role inflammation plays in atherosclerosis. The primary objective of JUPITER was to determine whether treatment with rosuvastatin would reduce the rate of first major cardiovascular event in patients with normal cholesterol levels but high levels of inflammation.[105] The inclusion criteria of the trial stipulated that patients have a median hsCRP greater than 2.0 mg/L (median 4.2 mg/L) and LDL levels less than 130 mg/dL (median, 108 mg/L). The trial was terminated early because rosuvastatin resulted in a 44% reduction in the composite primary endpoint of MI, stroke, hospitalization for unstable angina, arterial revascularization, and cardiovascular death. Of particular interest to the surgical community was the 46% reduction in arterial revascularization and 48% reduction in stroke in patients allocated to rosuvastatin. The latter is particularly intriguing given the favorable data for statins in patients with carotid stenosis.[106-108] Thus, the JUPITER trial determined that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable. Further, individuals at increased risk due to inflammation benefit from therapy they otherwise would not have received.[109] Whether or not reducing inflammation with a drug that does not also modify lipids is an intriguing hypothesis that is currently being tested.[110]

LOCALIZATION OF ATHEROSCLEROSIS

The propensity of atherosclerosis to occur at specific sites in the arterial tree has been observed since the time of Anitschkow's cholesterol-fed rabbits.[108] Other investigators noted increased incorporation of 3H-thymidine into endothelial cells at branch sites in animals not exposed to injury; this was thought to be due to hemodynamic consequences.[111-113] Insull and colleagues found that atherosclerosis was predominantly located at intercostal branch points of the human thoracic aorta.[114]

Only recently have the molecular mechanisms underlying this phenomenon become elucidated. Areas of well-developed laminar shear stress are relatively resistant to atheroma formation, whereas areas of turbulent or low shear stress (such as the carotid bifurcation) are more susceptible to atherosclerosis. Shear stress response elements occur in the promoter regions of a number of atheroprotective genes. Endothelial nitric oxide synthase (eNOS) is the product of one such gene. Laminar shear increases eNOS activity and thus nitric oxide (NO) production, which renders endothelial cells more thromboresistant and results in less adhesion molecule expression and decreased SMC migration. NO reduces VCAM-1 gene expression through a novel pathway involving the inhibition of nuclear factor κB (NF-κB). Superoxide dismutase is expressed at higher shear stress and may reduce oxidative stress by catabolizing the highly reactive superoxide anion O_2^-. Thus, areas of high laminar shear stress have antiinflammatory and antioxidant properties and exhibit less adhesion to circulating leukocytes.

Branch points, bifurcations, and major curvatures disrupt laminar flow and cause boundary layer separation, flow reversal, and shifting stagnation points. Such areas are characterized by increased particle contact time with the luminal surface, which may favor lipid deposition. Hemodynamic forces may predispose specific areas of the arterial tree to atherosclerosis when the appropriate risk factors are present. Areas of arterial branch points demonstrate elevated NF-κB activity.[115] CAM-1, an NF-κB–dependent protein, is expressed on the endothelium at arterial branch points even in normocholesterolemic animals. Disrupted laminar flow may promote a phenotypic transition in arterial cells that favors a proliferative state. NF-κB binds to several areas in the cyclin D1 promoter and stimulates the G1-to-S transition in the cell cycle.[116] Alternatively, laminar shear stress induces the cyclin-dependent kinase inhibitor p21 and suppresses the G0/G1-to-S phase transition.[117]

Hence, fluid mechanical forces influence endothelial gene expression through certain response elements sensitive to shear stress. Endothelial dysfunction, characterized by decreased NO production, promotes vessel wall entry and modification of circulating LDL. Therefore, it is possible that the differential regulation of endothelial genes by distinct flow profiles allows

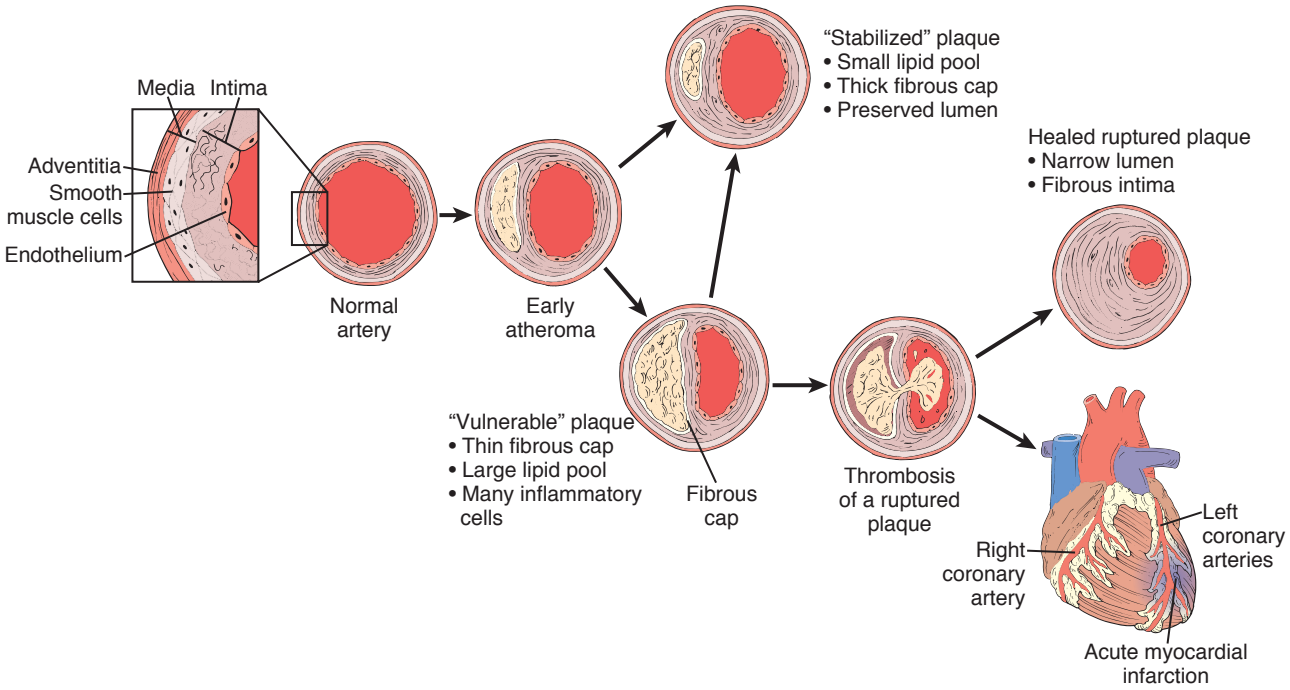

Figure 4.4 Life cycle of human atherosclerotic plaque. Rather than relentless progressive enlargement, human atherosclerotic plaque may undergo periods of progression, regression, and growth spurts. As the plaque extrudes into the lumen, the vessel undergoes compensatory enlargement, which preserves the lumen. The so-called vulnerable plaque consists of a relatively large lipid core and a thin (<100 mm) fibrous cap. Thrombotic complications can occur as a result of cap rupture, superficial endothelial erosion, intraplaque hemorrhage, or erosion of a calcified nodule in which circulating blood elements come in contact with the thrombogenic lipid core. The fate of such an event may be manifested as a myocardial infarction, transient ischemic attack, or in situ thrombosis of a lower extremity artery. Far more commonly, however, they result in a nonocclusive thrombus inciting a healing response. These healed ruptures result in a fibrous plaque with a narrowed lumen. (From Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340.)

certain areas of the vasculature to more effectively resist the influence of risk factors such as hyperlipidemia and diabetes.

PROGRESSION/REGRESSION OF PLAQUES

DePalma and others, in an important series of experiments, noted progression and regression of atherosclerosis in canines and subhuman primates by serial laparotomy and autopsy examinations.[118-121] The observation that plaque reduction correlated with a reduction in serum cholesterol paved the way for cholesterol-lowering trials in laboratory animals with bile acid sequestrants to test the hypothesis that reduced serum cholesterol would reduce plaque burden.[120,121] The success of these early animal trials engendered considerable optimism that atherosclerosis was not universally progressive and eventually leads to lumen occlusion. Hence our current understanding of atherosclerotic plaque emphasizes a dynamic evolution.

Serial angiographic studies of human coronary arteries demonstrate periods of intermittent growth spurts followed by relative quiescence.[122,123] What may account for the nonuniform progression of these atherosclerotic lesions? One prevailing theory suggests that most plaque disruptions with in situ thrombus formation do not always proceed to total occlusion and clinical sequelae, but instead are clinically silent (Fig. 4.4). Though unnoticed by the patient or clinician, they are far from benign. The local nonocclusive platelet thrombus induces a healing response with local inflammatory cytokine and growth factor production. TGF-β and PDGF stimulate SMC collagen production and migration. Thrombin production accelerates SMC migration and proliferation, and fibrin stimulates wound contraction and progressive luminal narrowing.[124,125] Healed fibrous cap ruptures can be detected microscopically by the identification of breaks in the fibrous cap with a surrounding repair reaction consisting of a proteoglycan-rich mass or collagen-rich scar.[126] Thus, in contrast to slow steady plaque growth in which compensatory enlargement of the vessel may protect from luminal encroachment, acute plaque rupture with nonocclusive thrombosis may signal a cascade of events leading to a fibrous atheroma and constrictive remodeling. Whether this mechanism is operative in peripheral vessels (e.g., femoropopliteal arteries) remains to be determined.

The use of cross-sectional images by IVUS reveals that segments of arteries that appear normal by angiography may nonetheless harbor substantial atherosclerotic disease.[127] Through morphometric studies of nonhuman primates and detailed autopsy studies of human coronary arteries, we understand that

vessels undergo compensatory enlargement (remodeling) and recognize that lumen encroachment is a relatively late occurrence in the evolution of atherosclerotic plaque.[128,129]

More recently, IVUS has been used to document plaque progression/regression in human coronary arteries with intensive statin treatment.[130,131] The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial measured the rate of disease progression in patients treated with either 40 mg of pravastatin or 80 mg of atorvastatin. LDL was reduced to 79 mg/dL (2.05 mmol/L) in the atorvastatin arm versus 110 mg/dL (2.85 mmol/L) in the pravastatin arm, and CRP was reduced 36.4% versus 5.2%. This resulted in a significant change in the primary endpoint of total atheroma progression of −0.4% in the atorvastatin arm versus 2.7% in the pravastatin arm.[131] In an open-label trial known as A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasoundr Ultrasound to EvAtheroma Burden (ASTEROID), 80 mg of rosuvastatin resulted in a change in atheroma volume of −0.98% over a 24-month treatment period. Collectively, these trials suggest that atherosclerotic plaque, far from being fixed, is a dynamic and mutable lesion that may regress in response to intensive hypolipidemic therapy. These trials also reflect the clinical benefit seen in the intensive treatment arms in trials such as PROVE IT-TIMI 22 and provide further rationale for recommendations of reducing LDL cholesterol below 100 mg/dL (2.59 mmol/L).[132] Further effort is needed to determine whether intensive statin therapy can reduce the progression of atherosclerotic disease in other vascular territories, such as the femoral arteries.

THROMBOTIC COMPLICATIONS OF ATHEROSCLEROSIS

A significant amount of resources in vascular surgery are expended in caring for the acute thrombotic events complicating atherosclerosis and in situ thrombosis of the peripheral circulation. These catastrophic clinical syndromes often occur suddenly and without warning.

In the coronary circulation, various lines of evidence reveal that generally the culprit lesions are not necessarily those associated with the tightest stenosis.[133-135] This is not to say that high-grade stenosis does not undergo thrombotic complications; on a per-lesion basis, the individual probability of a complication from a high-grade lesion is higher than the probability from a less severe lesion.[136] However, because noncritical stenoses outnumber lesions producing critical stenosis, the total probability of a thrombotic complication attributable to the noncritical stenosis is higher. It must also be remembered that these assessments are based on standard planar angiography and do not take into account compensatory enlargement. Thus, low-grade stenosis does not necessarily equate with smaller lesions. Other variables such as inflammation also contribute to plaque rupture.

Physical disruption of the atherosclerotic plaque rather than critical stenosis can commonly precipitate arterial thrombosis. Four mechanisms of plaque disruption may cause thrombosis or rapid plaque expansion.[13] Each may be operative in different vascular territories or with a different constellation of risk factors. For example, complete fracture of the plaque's fibrous cap causes most cases of fatal coronary thrombosis.[137] Plaque rupture is probably caused by both mechanical and biologic factors.[138,14] Physical forces acting on the shoulder region of the plaque, where circumferential wall stress and cap fatigue are the greatest, render this area particularly vulnerable, especially when the central lipid core accounts for greater than 40% of the total lesion area and the cap is relatively thin, (less than 100 μm).[139] Inflammation within the plaque may destabilize the cap and potentiate injury by hemodynamic factors. Macrophages and mast cells degrade the extracellular matrix by phagocytosis and secretion of proteolytic enzymes.[140] SMCs and macrophages, when stimulated by inflammatory cytokines, produce MMPs including collagenases, elastases, gelatinases, and stromelysins, which degrade the matrix of the fibrous cap and result in thinning and weakening.[141-146] It is now apparent that endothelial cells, SMCs, and macrophages all increase the expression of the CD40 ligand and its receptor under the direction of the inflammatory cytokines. Ligation of CD40 in turn upregulates the production of MMPs, inflammatory cytokines, and tissue factor, thus emphasizing the autocrine and paracrine nature of the local inflammatory response of the fibrous cap.[143-146]

Once the plaque is fractured, blood is exposed to the underlying thrombogenic substrate and thrombosis ensues. Tissue factor initiates the extrinsic clotting cascade and is a major regulator of coagulation and thrombosis. Thrombus formation and platelet adhesion create further stenosis and thrombotic occlusion. As previously mentioned, most thrombotic complications of plaque lead to progression of stenosis rather than occlusion of the artery. Cigarette smoking, hyperglycemia, and elevated LDL cholesterol all increase blood thrombogenicity.[147] These same risk factors are characterized by endothelial abnormalities such as increased generation of superoxide anion and decreased endothelium-derived NO.[148,149-151] Thus risk factors are linked to progression of atherosclerosis and to its thrombotic complications at susceptible areas in the vascular tree through abnormalities in blood coagulation, as well as endothelial function.

Although complete fracture of the fibrous cap may be the most common cause underlying coronary thrombosis, other mechanisms may be more important in the periphery. Intraplaque hemorrhage can transform an asymptomatic carotid plaque into a symptomatic lesion and produce transient ischemic attacks or stroke. Neovascularization and proliferation of the vasa vasorum, as in diabetic retinopathy, may produce a local microvascular network that is fragile and friable. Intraplaque hemorrhage can cause rapid plaque expansion and thinning or disruption of the cap. Superficial plaque erosion producing in situ thrombus without plaque rupture is prevalent in patients with diabetes and in women.[13,152] Apoptosis of endothelial cells may promote superficial erosion, and various inflammatory stimuli may promote apoptosis.[153] In particular, macrophage-derived myeloperoxidase may be operative in that it promotes both tissue factor generation and endothelial cell apoptosis, thus linking superficial erosion and in situ thrombosis.[154] Finally, erosion through the intima of a calcified nodule represents another

less common form of atherosclerotic thrombosis that may be relevant in both the coronary and peripheral circulations.

Distinct artery-dependent patterns of atherosclerosis probably account for differences in the pathogenesis of thrombotic-related complications.[155] Both coronary and carotid atherosclerotic plaques appear to be laden with foam cells and to have large lipid cores; plaque rupture or intraplaque hemorrhage is common. In the femoral artery, plaque is more commonly fibrous without extensive foam cells. Here, it is likely that superficial plaque erosion and erosion of a calcific nodule more commonly lead to thrombosis.

IDENTIFICATION OF VULNERABLE LESIONS

How does one predict a priori which patients may be more likely to progress from an asymptomatic carotid lesion to one with symptoms? Who will develop an MI following noncardiac vascular surgery or the progression of a stenosis in the superficial femoral artery at Hunter's canal? After all, many patients do perfectly fine with stable 60% carotid bifurcation disease or stable claudication. Understanding of the in vivo structural, functional, and biologic aspects of an atherosclerotic lesion may identify plaques that are "vulnerable" to either progression or symptomatic transformation.

Identification of such vulnerable lesions has been an area of intense recent work. As discussed previously, IVUS evaluation determines the true extent of the size of the atherosclerotic plaque as opposed to what is visible on angiography, the latter of which dramatically underestimates the true dimensions of the lesion. IVUS can detect the degree to which an artery has remodeled in response to a plaque. For instance, it has been determined that excessive expansive remodeling may result in a thin vulnerable plaque.[156]

Impaired endothelial vasodilator function is seen in patients with cardiovascular risk factors, and cardiovascular risk factors predict coronary events and stroke. Brachial artery flow-mediated vasodilation has been used as a surrogate for the more relevant coronary circulation.[157,158] Impaired flow-mediated vasodilation is seen in patients with inflammation and in those with classic risk factors,[159,160] and it is often present before symptoms of peripheral or coronary arterial disease are evident.[161] Impaired flow-mediated vasodilation has also been demonstrated to predict adverse events in patients undergoing vascular surgery.[162-164] Hence, the classic Framingham risk factors, as well as inflammation, appear to impair endothelial function and promote atherosclerosis.

Finally, molecular imaging is on the immediate horizon to help identify vulnerable plaque. For example, plaque with active inflammation may be identified by extensive accumulation of macrophages. Successful detection of plaque inflammation with magnetic resonance imaging was possible with gadolinium-loaded micelles coupled with antibodies to the scavenger receptor.[165] Alternatively, computed tomography may be used with a novel iodinated nanoparticulate contrast agent to detect inflammation in atherosclerotic plaque.[166] Contrast-enhanced ultrasound may also be used by attaching VCAM-1 to microbubbles and identifying areas of active adhesion molecule expression.[167]

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CHAPTER 5

Intimal Hyperplasia

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Intimal hyperplasia is the universal response of vessels and grafts to injury and describes a chronic structural change occurring in denuded arteries and arterialized vein and prosthetic bypass grafts. Intimal hyperplasia has been more narrowly defined as the abnormal migration and proliferation of vascular smooth muscle cells with the associated deposition of extracellular connective tissue matrix that is then followed by remodeling of this new tissue (Table 5.1). Its development can be chronologically subdivided into hyperacute, acute, and chronic stages reflecting the timelines of classical wound healing. Macroscopically the chronic lesion appears firm, pale, and homogeneous. The involved area in the vessel is smooth and uniformly located between the endothelium and the internal elastic lamina of an artery or between the endothelium and the medial smooth muscle cell layer of a vein graft. The distribution pattern of intimal hyperplastic lesions may be diffuse throughout a vessel, focal at an anastomosis, or focal within the body of the vessel. The biology of a vessel's response to injury is complex and has many biologic targets that testify to the therapeutic dilemma it poses to control. Arterial injury, venous injury, and prosthetic graft incorporation share many common mechanisms (coagulation, inflammation, cell proliferation, cell migration, proteases and extracellular matrix [ECM], and remodeling) but should be considered distinct biologies.

RESPONSE OF THE ARTERY TO INJURY

Angioplasty may be considered a controlled injury to the vessel wall (Figs. 5.1 and 5.2). The immediate response of the vessel to injury is the hemostatic response. Endothelial denudation exposes the subendothelial matrix and leads to platelet adherence and aggregation. Platelet accumulation occurs in a rapid but time-dependent manner which appears to last approximately 8 to 10 hours after injury.[1] The rationale for the use of aspirin across the cardiovascular specialties and the short-term use of dextran infusions after carotid endarterectomy stem from this important observation. Platelet levels on the surface have been noted to decrease from days 3 to 7. Platelet adhesion requires the interaction of subendothelial collagen with three platelet membrane glycoprotein receptors (GPIb, GPIc/GPIIa, and GPIa/GPIIa), plasma von Willebrand factor, and fibronectin. These observations have been used as the biologic rationale for the use of glycoprotein IIb/IIIa inhibitor class of drugs after percutaneous coronary interventions.[2,3] Elements of the coagulation cascade (tissue factor, factor V, factor VIIa, factor Xa, or α-thrombin) will modulate intimal hyperplasia development following angioplasty. Controlling the coagulation cascade early is the key to preventing the phenomenon of early stent thrombosis within 30 days. Coupled to the hemostatic response on the surface, apoptosis (programmed cell death) can be identified at 1 to 2 hours within the wall and appears to abate by 4 hours.[4] No apoptosis can be identified in the wall after injury at 3 days, but by day 7, 50% of the cells again show signs of apoptosis and by day 14, the number of apoptotic cells is again markedly decreased. Enhancing immediate apoptosis is one of the biologic benefits attributed to cryoangioplasty.[5]

Following vessel wall injury, there is a robust inflammatory response with polymorphonucleocytes (PMNs) and monocytes adhering to the subendothelial surface. There is a predictable

sequential expression of inducible cell surface molecules in both endothelial cells and smooth muscle cells after experimental angioplasty.[6,7] Compared with the uninjured endothelium, regenerating endothelial cells show high levels of VCAM and ICAM expression; this pattern of expression appears to follow the leading edge of the regenerating endothelium. Within 10 days, smooth muscle cells show expression for both ICAM and class II MHC antigens. However, by 30 days the expression of adhesion cell molecules in endothelial cells and smooth muscle cells returns to the pattern observed in uninjured vessels. Chemokines and their family of receptors have been shown to participate at every step of the remodeling process.[8] The monocyte chemotactic protein (MCP)-1/CC motif receptor 2 (CCR2) axis induces monocyte infiltration of the injured vessel wall and can stimulate smooth muscle cell proliferation. The RANTES (Regulated upon activation, normally T-cell expressed, and presumably secreted) receptors CC motif receptor 1 (CCR1) and CC motif receptor 5 (CCR5) help to regulate this monocyte infiltration into the injured vessel and expansion of the intimal hyperplasia. Reconstitution of the endothelium over the injured area appears to depend on CXC motif ligand 1 (CXCL1), which is augmented by stromal cell–derived factor (SDF)-1 alpha and its receptor CXC motif receptor 4 (CXCR4) recruiting VSMC progenitor cells to the injured vessel wall during the early phases of the injury response.

Cytokines including tumor necrosis factors, interleukins, lymphokines, monokines, interferons, colony-stimulating factors, and transforming growth factors (TGFs) are produced by both the inflammatory infiltrate and the cells of the vessel wall after injury.[9] The various cytokines interact with specific receptors on various cell types and activate JAK-STAT, NF-κB, and Smad signaling pathways leading to an inflammatory response, cell adhesion, proliferation migration, and apoptosis. Cytokines are also linked to increase production of mitochondrial reactive oxygen species, activation of Ca^{2+}, and multiple intracellular protein kinase pathways. Cytokines also interact with integrins and matrix metalloproteinases (MMPs) and modify ECM composition, a key component of the developing neointima.[10] In humans, targeted therapy against interleukin-1α has shown a trend toward lower incidence of restenosis following SFA interventions in humans.[11] Exogenous G-CSF will increase the

TABLE 5.1 Stages of Intimal Hyperplasia Development

	Vessel Lumen	Vessel Wall
Stage 1		
Hyperacute (minutes–hours)	Endothelial cell denudation	SMC injury
	Platelet aggregation	Activation of SMC
	Release of growth promoters	Proto-oncogene expression
		Release of growth promoters
Stage 2		
Acute (hours–weeks)	Organization of thrombosis	Medial SMC replication
	Endothelial cell ingrowth	Medial SMC migration
	Release of growth inhibitors	Infiltration of leukocytes
	Progenitor cell deposition	Infiltration of adventitial cells
		Infiltration of progenitor cells
		Synthesis of growth promoters
		Synthesis of growth inhibitors
Stage 3		
Chronic (weeks–months)	Re-endothelialization change of luminal dimensions	Intimal SMC replication
		Intimal SMC synthesis of ECM
		Remodeling of ECM
		Synthesis of growth inhibitors
		Vessel remodeling

ECM, Extracellular matrix; *SMC*, smooth muscle cell.

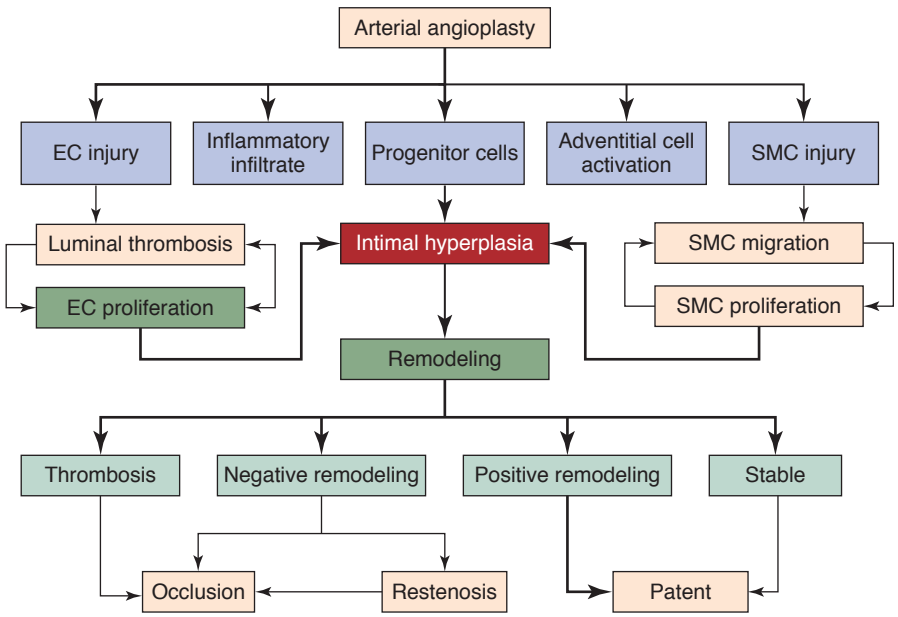

Figure 5.1 Pathobiology of the Injury Response After Angioplasty. Flow diagram demonstrating the key elements in the vessel's response to arterial injury. Endothelial cell (EC) injury leads to luminal thrombosis, inflammatory cell infiltration, cellular proliferation, and clearance of the thrombotic material on the surface with development of a neoendothelium. Injury to smooth muscle cells (SMCs) and adventitial cells leads to cell proliferation and migration. Progenitor cells are recruited to the vessel wall. With the migration of proliferation of SMC and adventitial cells, the appearance of progenitor cells and the deposition of extracellular matrix, intimal hyperplasia develops. Over time this lesion remodels and may either remain stable or demonstrate positive remodeling with an in luminal diameter or negative remodeling with a decrease in luminal diameter. These chronic changes in the intimal lesion can lead to continued patency, restenosis, or occlusion.

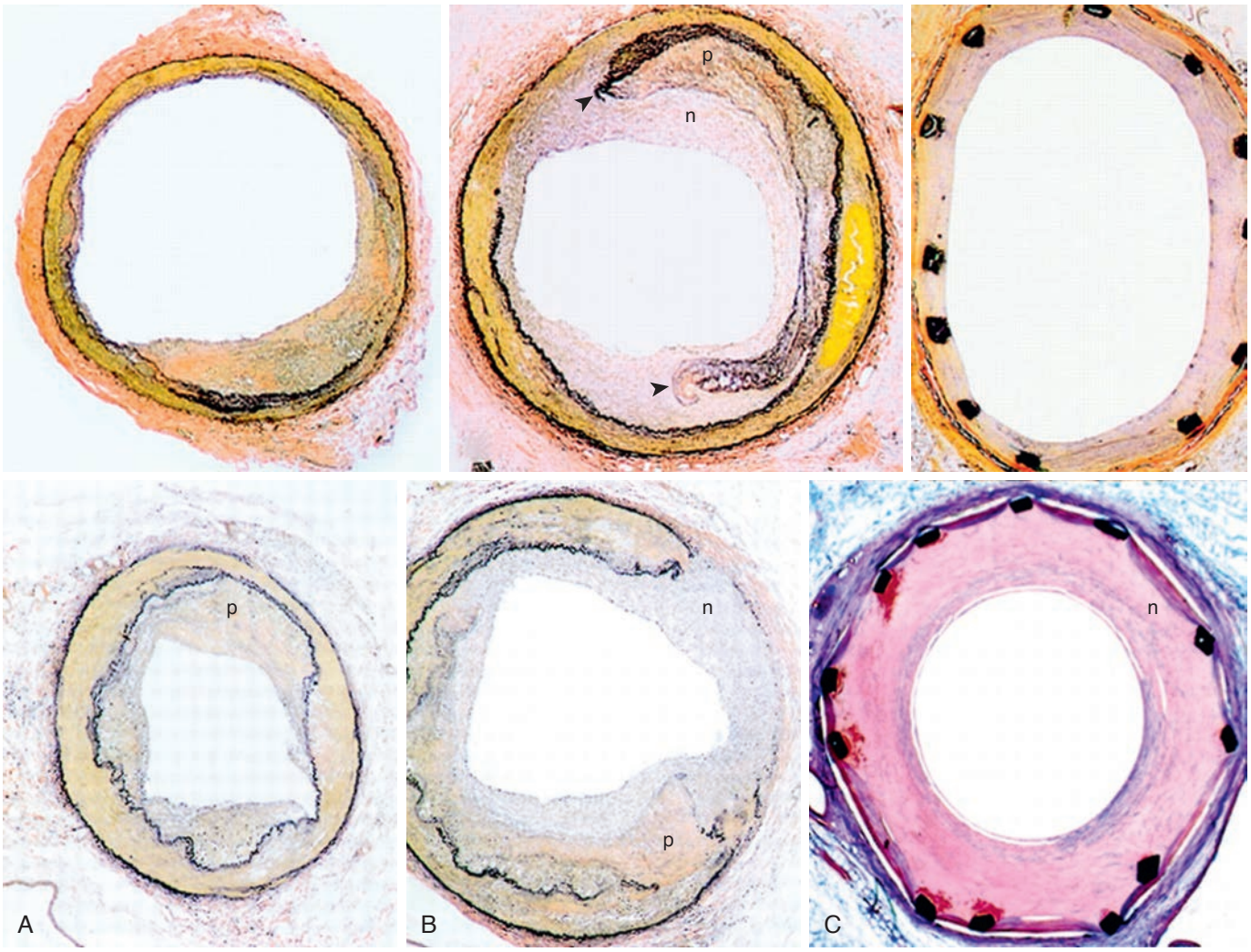

Figure 5.2 **Photomicrographs of Stented Vessel. Upper Panel:** Atherogenic diet induced complex intimal lesions shown in uninjured iliac artery **(A)**. Contralateral iliac artery was removed 35 days after experimental angioplasty **(B)**. Angioplasty has fractured the preexisting plaque (p; *arrowheads*) and injured the overlying media, with neointimal ingrowth (n). Palmaz stents were deployed in the proximal left subclavian artery, and after 35 days, neointimal ingrowth has covered the underlying plaque and stent struts **(C)**. Original magnification: **A** and **B,** ×40; **C,** ×100. All panels, Verhoeff-van Gieson stain. **Lower Panel:** Composite photomicrograph demonstrates a typical response 4 weeks after angioplasty and stenting. **A** and **B** show the uninjured and injured common iliac arteries, respectively, and panel **C** shows the stented external iliac artery. Animals consumed an atherogenic diet for 2.5 years, thus creating complicated plaques (p). **B** shows fractured plaque (p) and overlying media that have healed with neointimal ingrowth (n). **C** shows a stented external iliac artery with a typical neointimal lesion (n). Vessels were from a single treated animal. **A** and **B,** Verhoeff-van Gieson stain; **C,** trichrome stain; original magnification all panels, ×40. (**Upper Panel:** Reproduced with permission from: Deitch JS, Williams JK, Adams MR, et al. Effects of beta3-integrin blockade (c7E3) on the response to angioplasty and intra-arterial stenting in atherosclerotic nonhuman primates. *Arterioscler Thromb Vasc Biol*. 18(11);1998:1730–1737. **Lower Panel:** Reproduced with permission from: Cherr GS, Motew SJ, Travis JA, et al. Metalloproteinase inhibition and the response to angioplasty and stenting in atherosclerotic primates. *Arterioscler Thromb Vasc Biol*. 2002;22(1):161–166.)

number of circulating EPCs and result in rapid and nearly complete (>90%) reendothelialization of the angioplastied artery. This is paralleled by a decrease in inflammation in the vessel wall and a reduction in neointimal thickness.[12]

Smooth muscle cell proliferation within the media, which is normally less than 1%, increases to more than 20% within 48 hours after angioplasty.[13-17] The exact mechanisms, whereby smooth muscle cell proliferation is initiated, controlled, reduced, and eventually suppressed, are still not fully understood. Growth factors can regulate the proliferation of endothelial cells, the proliferation and migration of smooth muscle cells and adventitial cells, and the secretion of ECM throughout the vasculature. The first phase of smooth muscle cell proliferation appears to be driven by bFGF released from dead and damaged cells in the vessel wall following injury. The plasminogen activator, urokinase, also plays a role in bFGF activation and release.

Four weeks after injury the medial proliferative response returns to baseline levels. Intracoronary radiation after angioplasty inhibits this first wave of cell proliferation and prevents adventitial proliferation but also prevents reendothelization.[18]

By day 8 after the injury, smooth muscle cells are observed on the luminal side of the internal elastic lamina and appear to have migrated to the luminal surface through fenestrations in the internal elastic lamina. The mass of cells in the wall is augmented by circulating mesenchymal cells *(vide infra)* that subsequently differentiate into smooth muscle cells. The number of smooth muscle cells in the intima increases to a maximum at 2 weeks after injury, and approximately 30% of medial smooth muscle cells may migrate from the media to the intima. This migration of cells requires the degradation of the cage of matrix surrounding each cell by proteases and the synthesis of new matrix molecules. Migration of the smooth muscle cells from the media to the intima across the internal elastic lamina is mediated in part by both the receptor tyrosine kinase–linked agonists (PDGF, basic fibroblast growth factor, and hepatocyte growth factor) and the G-protein coupled receptor agonists (vascular endothelial cell growth factor, chemokines, LPA, thrombin, and uPA). Inhibition of the PDGR receptor PDGFR-β/β with parenteral chimeric antibodies that have been shown to be effective in animal models has failed to limit restenosis in human trials.[19-21] Smooth muscle cell migration is unaffected by irradiation and antimitotic drugs.

Once within the intima, approximately 50% of the smooth muscle cells proliferate, and this second phase of smooth muscle cell proliferation is first noted at day 7 and reaches a maximum at 14 days before returning to baseline by 28 days.[17] However, it may continue for up to 12 weeks in those areas where reendothelialization takes longer to complete. Thus a potential weakness of drug-elution techniques is inhibition of reendothelialization and a reinforcement of the proliferative responses. The second phase of smooth muscle cell replication in the intima appears to be mediated by autocrine and paracrine factors and remains poorly understood. It also appears that the thickness of the intimal hyperplasia peaks within 1 month, and its rapid development is due to both cellular elements and the production of the ECM (i.e., proteoglycans). Although the total number and volume of smooth muscle cells in the intima remains unchanged after 12 weeks, there is a decrease in the cellular fraction of the intima composed of smooth muscle cells as the ECM volume rises. This continued slow increase in intimal hyperplasia is the result of the synthesis and the accumulation of connective tissue components such as collagen and proteoglycans. In human restenotic lesions, staining for hyaluron was inversely related to collagen I and III staining. Little proteoglycan accumulation occurs over the first 1 to 2 months but dramatically increases from 3 to 6 months after balloon injury and then decreases gradually thereafter in restenotic human coronary atherosclerotic plaques.[22] In atherectomy specimens, zones of collagen and proteoglycan can be identified. The collagen-rich zone contains elongated smooth muscle cells closely packed together, and in these zones, collagen I, elastin, and biglycan predominate. In contrast, proteoglycan-rich zones contain both elongated and stellate smooth muscle cells, which are widely spaced. Versican and biglycan predominate in these areas, whereas elastin is sparsely identified.[23]

Changes in the ECM do not occur independent of changes in the smooth muscle cells. The cells sense these changes through integrins. Integrins are essential cell surface proteins that allow cells to interact with their environment and more particularly with the individual components of the ECM. There is an inverse correlation between the expression of the higher affinity form of β1 integrin and the migration and proliferation of smooth muscle cells and endothelial cells after arterial injury.[24] One of the principal cytokines involved in controlling ECM responses is TGF-β.[25] As collagen products increase in the ECM, "contractile" intimal smooth muscle supported by increased fibroblasts in the adventitia can lead to contraction and "negative" remodeling. This final event in the development of intimal hyperplasia has been used as a rationale for stent placement because it can prevent the luminal loss due to contraction of the vessel.

Bone marrow cells do contribute to the pathogenesis of lesion formation after mechanical vascular injury.[26-28] Associated with the changes in the intima and media, there are substantial changes in the adventitia, as evidenced by an increased cell proliferation and growth factor synthesis after angioplasty. Within the adventitia a marked infiltrate of cells termed "myofibroblasts" is observed by day 2, which by day 14 can represent up to 50% of cells within the intima.[29,30] The presence of myofibroblasts is common in wound healing and leads to contraction of the wound. A similar phenomenon may occur in the healing vessel. Injured vessels may undergo chronic elastic recoil or negative remodeling, which results in loss of luminal dimensions without a further increase in neointimal area. Retrieved atherectomy material from primary and restenotic lesions has shown that the proportion of cells that can be demonstrated to be proliferating in the restenotic lesion is low[31] but that the migratory activity and collagen synthesis of the human smooth muscle cells from the restenotic lesions are greatly elevated, strongly supporting that remodeling is important in the final determination of luminal diameter.[32,33]

The degree of intimal hyperplasia that develops in a vessel is dependent on the length and depth of the injury.[34] Minimal intimal proliferation occurs when the media is uninjured, but intimal hyperplasia increases in proportion to the depth of the medial injury, indicating that the proliferative response reflects the direct injury to the smooth muscle cells.[35,36] In addition, distension of smooth muscle cells without significant endothelial cell injury has been shown to result in smooth muscle cell proliferation. The length of the injury influences the duration of the reendothelialization process. Reendothelialization occurs from the margins of the denuded area and possibly from the endothelial cells of the vasa vasorum. The longer there is an incomplete endothelial cell covering, the greater time the smooth muscle cells are without the modulating influence of the endothelial cells and the longer the replication phases of the smooth muscle cells will be.[37,38] After deep vessel wall injury, luminal narrowing may be less dependent on intimal hyperplasia formation and more dependent on vessel wall remodeling.[39] Medial damage is accompanied by a massive adventitial cell

proliferation,[40] which in time provides cells capable of contraction and negative remodeling.

Hemodynamics

Acute distension of a vessel without substantial endothelial cell damage results in a low level of smooth muscle cell proliferation.[41] Deformation of smooth muscle cells leads to activation of protein tyrosine kinases, which may be an additional mechanism, whereby smooth muscle cell proliferation occurs.[42] Furthermore, limited vessel wall injury without associated subintimal dissection or direct media exposure increases transmural fluid flux, thus allowing soluble proliferogenic mediators to gain access to the media of a vessel.[43] Changes in hemodynamic parameters have been shown to affect the arterial structure of both normal and diseased vessels.[44] Clinical studies have suggested that after femoral angioplasty in patients with extensive distal disease, the rate of restenosis is increased. In an experimental study, Hehrlein confirmed that reduced vascular runoff after angioplasty results in the increased development of intimal hyperplasia.[45] Blood flow (closely associated with shear stress) is best associated with the formation of intimal hyperplasia, whereas deformation of the vessel wall in a circumferential direction is best associated with medial thickening.[46] Kohler[47,48] has shown a correlation between a reduction of intimal thickness, which forms early after angioplasty and an increase in flow, and between an increase in intimal hyperplasia and a decrease in flow, suggesting a direct effect of flow on smooth muscle cell function. However, they did not observe a similar change in mature intimal hyperplastic lesions, which had developed under conditions of normal flow, and were then subjected to either increased or decreased blood flow conditions.

Systemic Vascular Diseases

The development of intimal hyperplasia in a vessel with an already established atheromatous or hyperplastic lesion has considerable implications on the use of angioplasty as a primary endovascular procedure due to the fact that it mirrors the clinical situation. There is a limited understanding on the effects of preexisting vascular diseases on the subsequent development of intimal hyperplasia in the postoperative period. Clinically, hyperlipidemia and diabetes are associated with higher rates of post PTCA restenosis.[49-52] Exposure to cigarette smoke increases the development of experimental intimal hyperplasia by two fold.[53] Cholesterol reduction therapies with statins have been shown in some studies to reduce the development of restenosis,[54,55] whereas others have suggested that such therapy carries no long-term effect on restenosis because of the complex biology leading to a more acute restenotic response.[56]

Diabetes is a predictor for restenosis. Tissue from restenotic plaques in diabetic patients is composed primarily of atherosclerotic plaque rather than hypercellular tissue. This might suggest that recoil/remodeling may be predominant.[57] The medial response is more pronounced in the diabetic balloon-injured rat carotid.[58] Advanced glycosylation end products (AGEs) accumulate in vascular tissues with aging and at an accelerated rate in diabetes. AGEs are particularly abundant at sites of atherosclerotic lesions.[59] AGEs interact with specific receptors (RAGEs) present on all cells relevant to the restenosis process, including inflammatory cells and smooth muscle cells. AGE-RAGE interaction in the vessel wall may lead to inflammation, smooth muscle cell proliferation, and ECM production, culminating in exaggerated intimal hyperplasia and restenosis. Following arterial injury, the interaction of AGEs with monocytes expressing RAGEs can promote migration of inflammatory cells into the lesion and subsequent release of growth factors and cytokines. Binding of AGEs-RAGEs on smooth muscle cells increases chemotactic migration and cellular proliferation and can augment ECM production by upregulating TGF-β. Thus accumulation of AGEs in the vessel wall provides a common mechanism for the high restenosis rates of patients with diabetes.

Intravascular Bare Metal Stents

The biology of in-stent restenosis is different from that seen after balloon angioplasty.[60] A stent is generally used if the result of balloon angioplasty is technically unsatisfactory or if there is arterial occlusion, immediate elastic recoil, dissection, or restenosis (Fig. 5.3; see also Fig. 5.2). The response of a vessel to a stent is dependent on the stent design, length, composition, delivery system, and deployment technique.[61] In-stent restenosis is classified on the basis of length of restenosis in relation to stented length. Four categories of in-stent restenosis have been defined: (1) focal (≤10-mm length), (2) diffuse (>10-mm length), (3) proliferative (>10-mm length and extending outside the stent), and (4) occlusion.[62] After balloon angioplasty, there is thrombus formation, intimal hyperplasia development, elastic recoil, and negative remodeling. In contrast, after stent placement, elastic recoil and negative remodeling are eliminated[63] and thrombus formation followed by intimal hyperplasia development are the main contributors to in-stent restenosis.[64,65] Patients with diabetes and prior restenosis have a higher rate of in-stent restenosis,[66] and there is a correlation with in-stent thrombus and prolonged hyperglycemia.[67] Stent placement in a vessel results in both a generalized injury to the length of the vessel exposed and more focal injures at the areas of strut apposition to the wall.

Intravascular ultrasound has demonstrated that stents do not always completely appose the vessel wall along their entire length, thus resulting in uneven injury along the length of the stent.[63] After stent placement, the surface of the metal implanted into the vessel is covered by a strongly adherent monolayer of protein within 5 seconds. After 1 minute the surface is covered by fine layers of proteins, predominantly fibrinogen.[68] The holes between the stent struts are filled with thrombus, and the adherence of platelets and leukocytes is enhanced by disturbance of electrostatic equilibrium.[69,70] The basic mechanisms of smooth muscle cell proliferation and migration after stent placement are the same as those after balloon injury.[71] The intimal hyperplastic process in a stent is more prolonged and robust than in a balloon-injured artery and is proportional to the depth of injury the recipient vessel sustains[72] and the inflammatory response induced[73]; it can often be much more significant at the ends than in the body of the stent (see Fig. 5.2). In addition, the adventitial

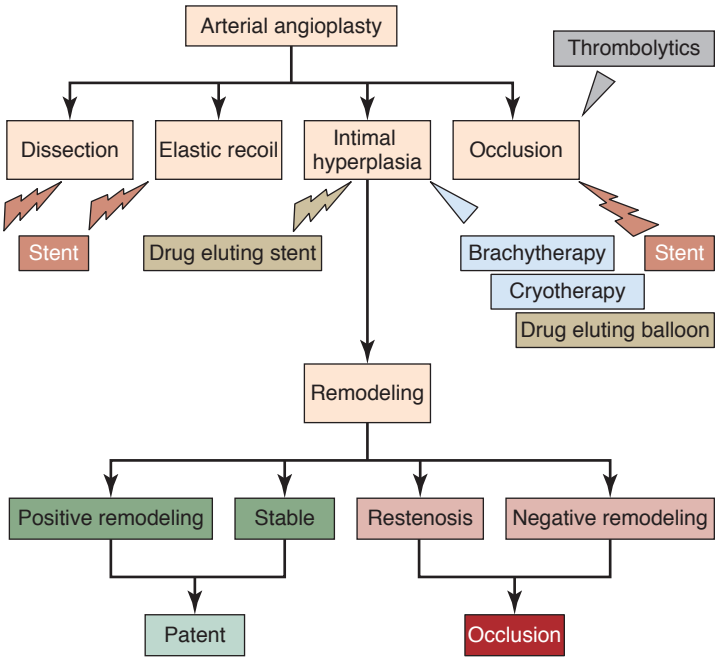

Figure 5.3 Consequences and Cures of Angioplasty. Flow diagram demonstrating the outcomes of a vessel's response to balloon angioplasty and the therapeutic maneuvers to correct the adverse outcomes. If a technical failure occurs after angioplasty due to elastic recoil or dissection, a stent is placed. If there is concern for the development of intimal hyperplasia, brachytherapy or cryotherapy may be applied. Sudden occlusion is corrected with thrombolysis or primary stenting. Remodeling will be influenced by placement of stents, drug-eluting stents, brachytherapy, or cryotherapy.

response is prolonged, with adventitial giant cell body formation being noted. Stents prevent chronic elastic recoil and cause progressive atrophy of the media.[74] Risk factors for late stent thrombosis include penetration of necrotic core, malapposition, overlapping stent placement, excessive stent length, and bifurcation lesions. Early after stenting in humans (≤11 days), fibrin, platelets, and acute inflammatory cells are always present in association with stent struts.[75] The degree of stent–arterial wall interface influences the severity of associated inflammation; increased numbers of inflammatory cells were seen when the stent strut is adjacent to injured media or lipid core rather than fibrous plaque. Chronic inflammation occurs adjacent to stent struts at all time points, especially greater than 12 days after stenting. Plaque compressed by stent struts is seen in 91% of vessel sections with penetration of the stent struts into the lipid core a common event.[75] A neointima containing smooth muscle cells develops within 2 weeks, and histologic success or failure of the stent is determined by neointimal growth within the stent and not influenced by artery or stent size. Neointimal thickness is increased when medial damage is present compared with struts in contact with atherosclerotic plaque or an intact media. Furthermore, increased intrastent neointimal growth is found in histologic failures, and increased neointimal area correlates with increased stent size relative to the proximal reference artery lumen. Therefore stent oversizing relative to the reference lumen appears to be an undesirable goal in deployment. Despite these histologic changes, neointimal cell density and the composition of the proteoglycan deposition in coronary stents were similar to those in matched PTCA coronary vessels.[75,76]

Intravascular Drug-Eluting Stents

Current successful drug-eluting stents (DESs) require a polymer coating for drug delivery.[77] Sirolimus-, paclitaxel-, and more recently, ABT-578–eluting stents are commercially available; each has demonstrated marked reduction in restenosis through decreases in smooth muscle cell proliferation. However, endothelial cell migration and proliferation are also decreased, and induction of tissue factor expression through specific interaction with signal transduction mediators occurs. These effects lead to an increased thrombogenic potential of DES.[78] The presence of a DES also decreases proliferation, differentiation, and homing of endothelial progenitor cells, which are believed to contribute to reendothelialization after stent implantation.[79] Furthermore, both rapamycin and paclitaxel have been demonstrated to induce endothelial dysfunction in the coronary vasculature distal to the stent.[80] Finally, the polymer used for DES can be associated with hypersensitivity reactions, which may, at least in some cases, favor stent thrombosis.[81]

Intravascular Drug-Eluting Balloons

The use of drug-eluting balloons (DEBs) is driven by the findings that short exposure of an artery to a drug (e.g., paclitaxel) delivered by a coated angioplasty balloon is sufficient for the attainment of an adequate tissue concentration of paclitaxel.[82] The chief benefit cited for DEBs is the avoidance of additional metal and polymer barriers, the presence of which may disrupt or hinder vascular healing, as discussed. However, DEB-treated vessels show delayed vascular healing characterized by dose-dependent increases in fibrin deposition, delayed re-endothelialization, lower number of neointimal cells, and increased medial VSMC loss.[83-85] The differences in reendothelialization may explain the observations that DEB-treated arteries behave generally similarly to plain balloon–treated vessels, regarding the endothelium-dependent vasodilation, but similarly to DES-treated arteries, and lead to proneness to vasoconstriction at 7 days and slow normalization of endothelium-independent vasodilation.[84]

RESPONSE OF VEIN TO INJURY

Saphenous veins demonstrate a spectrum of preexisting pathologic conditions ranging from significantly thickened walls to postphlebitic changes and varicosities at the time of harvest. Histologically, 91% of saphenous veins have moderate to severe fibrosis in the vein wall. In one study, 2% to 5% of veins were unusable and up to 12% can be considered "diseased."[86] These "diseased" veins have a patency rate one-half that of "nondiseased" controls. The etiology of the venous diseases observed are multifactorial in origin, and without gross morphologic evidence of disease there is currently no clear prognostic indicator to discriminate those veins that should be rejected as grafts.[86,87]

Intimal hyperplasia is the universal response of a vein graft to insertion into the arterial circulation and results from both the migration of smooth muscle cells out of the media into the intima and proliferation of these smooth muscle cells (Fig. 5.4). Whether the same series of events occurs in a vein graft as an injured artery remains to be determined. Progenitor cells may play a larger role in the vein graft than in the artery. It appears that in experimental models, many endothelial cells of vein grafts are derived from circulating progenitor cells and up to one-third appear to be derived from bone marrow progenitor cells.[88] In general, intimal hyperplasia is a self-limiting process that does not produce luminal compromise and usually becomes quiescent within 2 years of graft insertion. However, in focal areas the intimal hyperplastic process can proceed to significant stenosis.[89-92] Studies of peripheral vein grafts have documented that the majority of stenotic lesions that develop in a graft are composed of intimal hyperplastic tissue.[91,92] Graft stenoses develop at sites of unrepaired defects or early appearing conduit abnormalities[93] but not at the sites of valves or tributary ligation.[94]

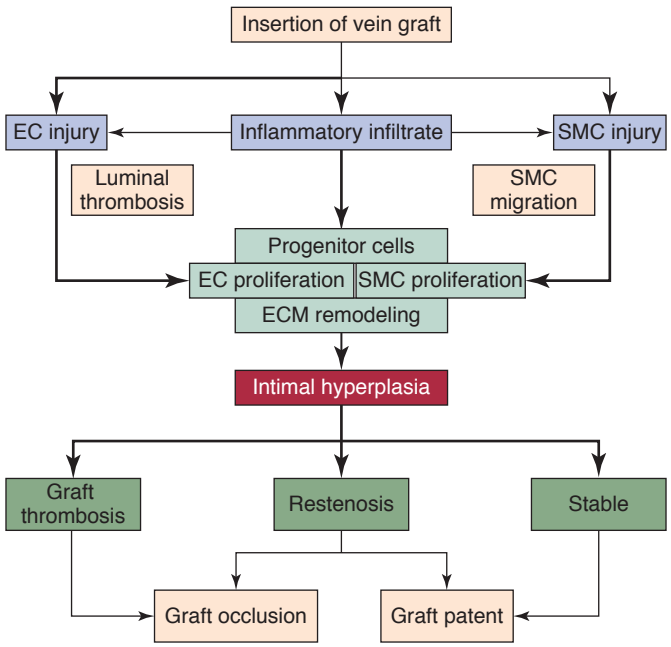

Figure 5.4 Pathobiology of the Vein Graft Response to Implantation. Flow diagram demonstrating the key elements in the vein's response to insertion into the arterial circulation. Denudation of the endothelium is dependent on the degree of implantation injury. Endothelial cell (EC) injury leads to luminal thrombosis, inflammatory cell infiltration, cellular proliferation, and clearance of the thrombotic material on the surface with restoration of the endothelium. If this fails to progress adequately, graft thrombosis may occur. Injury to smooth muscle cells (SMCs) leads to cell proliferation and migration. Progenitor cells are recruited to the vessel wall. With the migration of proliferation of SMC, the appearance of progenitor cells and the deposition of extracellular matrix (ECM), intimal hyperplasia develops to reestablish the tangential stress across the wall. Over time this lesion remodels and may produce a stenotic lesion due to the bulk of neointima or due to negative remodeling restenosis. This may result in graft occlusion.

Perioperative manipulations of veins prior to their insertion have been shown to produce significant tissue damage. Such implantation injury leads to endothelial dysfunction, endothelial cell injury, endothelial denudation, and smooth muscle cell injury, all of which are important factors in the initiation of intimal hyperplasia. It is now recognized that every effort should be made to reduce the degree of implantation injury that a vein graft suffers.[95-98] There appears to be a direct relationship between the morphologic integrity of the vein graft prior to grafting and its later histopathologic appearance and function.[96,98] Poorly prepared vein grafts develop significantly greater intimal hyperplasia and increased smooth muscle cell contractility compared with carefully prepared vein grafts.[96,98] Evidence suggests that deformation of smooth muscle cells by arterial hemodynamics can lead to activation of protein tyrosine kinases and thereby initiate smooth muscle cell proliferation.[42] Vein grafts with lower flows are associated with greater intimal thickening.[99] For example, a 50% reduction in arterial blood flow increased intimal hyperplasia by 60% and medial hypertrophy by 17% in arterial vein grafts after 4 weeks.[100] Other studies have suggested a role for increased wall tension in the development of intimal hyperplasia.[101,102]

With few exceptions, patients who undergo vein bypass grafting have a significant degree of arteriopathy and concomitantly have one or more atherogenic risk factors present. Hypertension in both human and experimental models does not affect the development of intimal hyperplasia in the short or long term.[103-106] Furthermore, it appears that hypertension is not associated with the later development of vein graft atherosclerosis.[103] In contrast, both experimental and clinical studies have shown an association of hyperlipidemia with the development of intimal hyperplasia/atherosclerosis and with higher vein graft failure rates.[103,107,108] Clinically, diabetes does not appear to impact significantly on vein graft patency, but experimentally it does increase short-term intimal hyperplasia development.[103,109] In cases of combined hypertension and hyperlipidemia, there appears to be no additive effect on intimal hyperplasia development in vein grafts compared with hyperlipidemia alone. However, in contrast, the combined presence of diabetes and hyperlipidemia has a significant additive effect on the formation of intimal hyperplasia in experimental vein grafts. The intimal hyperplastic lesions of vein grafts retrieved 1 month after aortocoronary bypass in humans have been shown to consist of proliferating smooth muscle cells with only scattered macrophages in the subendothelium.[110] With particular regard to peripheral vein graft stenoses, no association has been found with patient age, sex, presenting symptoms, hypertension, diabetes, or the condition of the outflow vessel. The incidence of stenosis appears higher the more distal the anastomosis is placed.[111]

Several peripheral factors may also play a role. Increased plasma fibrinogen concentrations have been identified as a potent risk factor for vein graft stenosis.[112] Increased homocysteine concentrations are also associated with increased incidence of vein graft stenosis.[113] Antibodies to cardiolipin are associated with infrainguinal vein bypasses failure.[114] Other studies have suggested that platelet dysfunction and lipoprotein (a) may be associated with an increased risk of stenosis development.[115,116] Smoking and plasma fibrinogen, lipoprotein (a), and serotonin concentrations are associated with the development of postoperative infrainguinal graft stenosis.[111,116,117] Others have suggested that there is no association between preoperative serum lipoprotein (a) and homocysteine levels and the frequency of 1-year graft occlusions.[118]

Lower serum cholesterol levels are associated with lower rates of vein graft occlusive disease for up to 7 years,[119] and high patency rates can be achieved in familial hypercholesterolemia in association with aggressive lipid-lowering therapy.[120] The Post CABG NHLBI study has shown that although saphenous vein graft atherosclerosis worsens with increasing age, lipid-lowering therapy can significantly reduce the probability of saphenous vein graft disease, regardless of the time of initiation of lipid-lowering therapy.[121] Glemfibozil retarded the progression of coronary atherosclerosis and the formation of bypass graft lesions after CABG in men with a low level of HDL cholesterol.[122]

Vein grafts retrieved from patients with angiographic evidence of occlusive disease demonstrate histologic features of atherosclerosis.[104,105,123-126] The earliest these lesions have been seen is 6 months after implantation. Thus, it appears that these late occlusions of vein bypass grafts are due to the development of a rapidly progressive and structurally distinct form of atherosclerosis which has been termed "accelerated atherosclerosis" to distinguish it from "spontaneous atherosclerosis."[90] Accelerated atherosclerosis is morphologically different from spontaneous atherosclerosis in that its lesions appear to be diffuse and more concentric and have a greater cellularity with varying degrees of lipid accumulation and mononuclear cell infiltration. The syndrome of accelerated atherosclerosis shares many of the pathophysiologic features of intimal hyperplasia; however, the prime mediators of this type of atherosclerosis are likely to be the macrophage. In addition, the endothelium overlying accelerated atherosclerotic lesions expresses the class II antigens, which are not observed in spontaneous atherosclerosis.

HEALING RESPONSE OF THE PROSTHETIC GRAFT

Studies of retrieved human polytetrafluorethylene (PTFE) grafts have shown that between 5 and 24 days after implantation, red blood cells and fibrin cover the anastomotic lines and some of the luminal surface. Macrophages can be found scattered throughout these thrombi. Between 11 and 48 months, one finds either a single layer of endothelial cells or a thin layer of fibrin covering the anastomotic segments of the graft. At this time, smooth muscle cells and collagen can be identified as a developing anastomotic intimal hyperplasia. From 94 to 149 months after implantation, this anastomotic intimal hyperplasia is relatively unchanged, with the same thickness and length as that seen in grafts retrieved between 11 and 36 months. Chronic inflammatory cells (macrophages, lymphocytes monocytes, and giant cells) can be identified in incorporated ePTFE grafts.[127] Perigraft tissue infiltration and tissue encapsulation occurs mainly in the external region of the prosthetic graft and increases with duration of implantation. Fibrous tissue penetrates the wall and partitions off the outer layer. The presence of external reinforcement does not effect this tissue infiltration.[128] Luminal surfaces of graft explanted between 94 and 149 months are covered by a connective tissue matrix with superposed scattered thrombi.[129] No current evidence exists that prosthetic grafts inserted into the human circulation are able to fully develop an endothelialized intima along the entire flow surface, which is in contrast to the majority of experimental models studied.[128] Rather, endothelial cells manage to populate the luminal surface in just the few centimeters near the anastomoses. The remainder of the graft is usually covered with a thin irregular layer of organized fibrin, containing platelets and leukocytes, interspersed with areas of exposed PTFE.[128,130] The incidence of lipid and cholesterol deposits is high,[131] and atheromatous changes have also been detected in retrieved PTFE grafts.[132] Staining for collagen type III is predominant, although collagen subtypes I, IV, and V can also be identified. No type II collagen is detectable. Elastin fibrils are seen within the anastomotic neointimal hyperplasia.[133]

Formation of the neo-endothelium in a PTFE graft can occur through two processes, transmural endothelialization by capillary ingrowth and endothelialization by migration from the anastomoses. Capillary ingrowth through the graft wall depends upon the porous characteristics of the graft. The porosity of the PTFE has a significant effect on these phenomena. In low-porosity grafts (10- and 30-μm internodal distance) placed in the aortoiliac position in the baboon, luminal endothelial coverage is limited to small areas near the anastomoses.[134] In higher-porosity grafts (60 and 90 μm), luminal endothelial coverage is complete.[135,136] A second process whereby endothelialization of PTFE grafts occurs is ingrowth from the anastomoses. Transmural fibrocapillary incorporation of PTFE vascular grafts provides a key supporting structure essential to the progression and attachment of endothelial cell ingrowth from the anastomoses. Porosity of the graft is important because nonporous grafts have a ragged and friable endothelial advancement zone.[137] New evidence in a canine model supports fallout endothelialization from the blood stream as a third possible mode of graft healing.[138] The process of neoendothelial healing can be divided into six stages: platelet aggregation phase (stage I), fibrin network phase (stage II), bridging phase (stage III), progression phase (stage IV-A), transmural migration phase (stage IV-B in thin wall long fibril length), intimal closure phase (stage V), and endothelial thromboresistance phase (stage VI).[139] In the ovine model, mural thrombosis is a prominent feature extending several centimeters from the venous anastomosis for up to 3 months after PTFE fistula placement. Over this 3-month period the thrombus is actively organized by invasion of macrophages and capillaries from adjacent areas of neointima and in places becomes covered by endothelial cells.[140] The process of healing

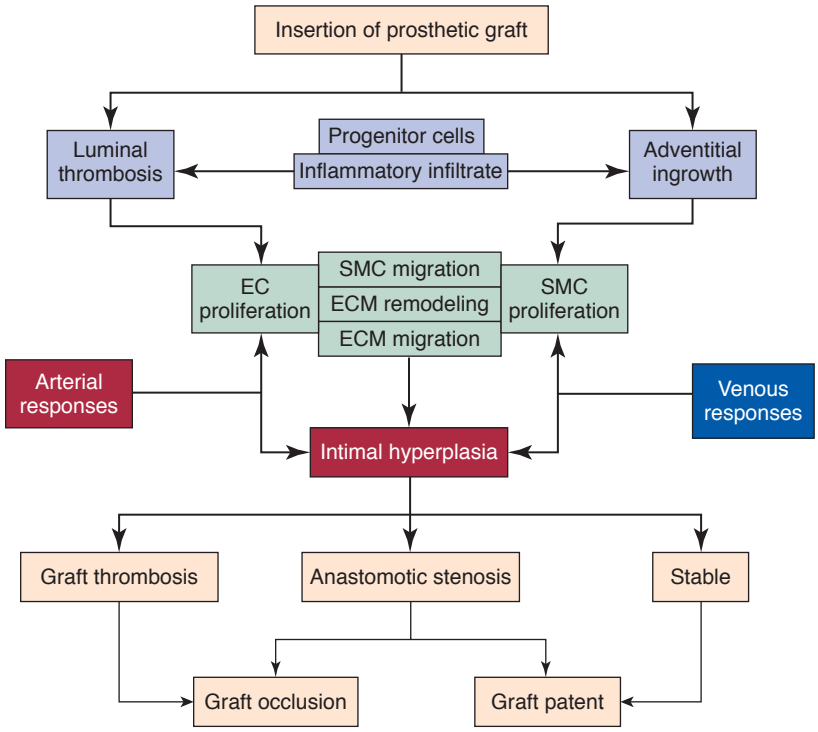

Figure 5.5 Pathobiology of the Prosthetic Graft Response After Implantation. Flow diagram demonstrating the key elements of the body's response to implantation of a prosthetic graft into the arterial or venous circulation. Luminal thrombosis and adventitial infiltration are associated with an inflammatory response and recruitment of progenitor cells. Injury to the endothelial cells (ECs) and smooth muscle cells (SMCs) at either the venous or arterial anastomosis leads to the development of intimal hyperplasia within the native vessel and ingrowth into the prosthetic conduit as a result of EC and SMC migration and proliferation occurs with the laying down of an extracellular matrix (ECM). Over time these lesions remodel and may produce a multifocal stenotic lesion at the anastomoses and in the floor of the recipient vessel.

in a prosthetic graft is shown in Fig. 5.5. Chronic administration of acetylsalicylic acid can prevent graft thrombosis between 2 and 4 weeks post implantation but does not appear to decrease distal anastomotic intimal hyperplasia development.[141]

INTIMAL HYPERPLASIA AND DIALYSIS ACCESS

Dialysis access grafts reflect an amalgamation of arterial, prosthetic, and venous intimal hyperplasia. Needle puncture sites are healed as a result of being filled in by surrounding connective tissue, and thus pseudoaneurysm formation is common at the puncture sites in the first 2 years.[142] Within the fistula, circumferential and valvular stenoses, and mural thrombi at needle sites can be identified angioscopically.[143] The anastomoses appear to be the areas of maximal intimal hyperplasia as a result of surgical trauma and the presence of flow disturbance. Two distinct regions of intimal thickening have been noted: one at the anastomotic site, which is greater in PTFE grafts than native vein, and the second in the floor of the artery, which is the same for both PTFE and native vessels.[144] The high failure rate of PTFE dialysis grafts is ascribed to problems in the venous distal outflow tract. The majority of stenoses occur at the venous anastomoses and within 1 cm of the anastomosis.[145] A greater initial mismatch in elastic properties between the vein and the graft and elevated local peak systolic velocity at the venous PTFE anastomoses correlates with the occurrence of anastomotic stenosis within the first 2 years.[146,147] Graft geometry can have a significant impact on internal hemodynamics and the development of venous intimal hyperplasia. The volume of the vibration signal set up by blood flowing through the relatively rigid PTFE graft has a better correlation with venous anastomotic intimal-medial thickness than either pressure or flow velocity.[148]

An end-to-end or end-to-side anastomosis has no impact on the intimal hyperplastic response in the recipient vein because flow stability, turbulence, and kinetic energy transfer are equivalent.[148] Venous anastomotic intimal hyperplasia develops in unbanded grafts, where flow is 100% greater than a banded equivalent and there is a direct correlation between the Reynold number and subsequent intimal hyperplasia development in the outflow vein.[149] Five anatomic stenotic lesions in arteriovenous fistula grafts have been categorized: stenosis in the draining vein proximal to the venous anastomosis (36%), stenosis in the central vein (24%), stenosis at the venous anastomosis (25%), stenosis at the arterial anastomosis (11%), and intragraft hyperplasia (4%).[150] The stenoses in these veins are intimal hyperplastic consisting of smooth muscle cells with extensive ECM. Proteoglycan was identifiable in the ECM close to the lumen, whereas collagen and elastin predominate deeper in the wall of the vein.[129] These venous intimal hyperplasia segments have significant neovascularization, and perivascular macrophages can be readily identified. There is intense staining for proliferating cell nuclear antigen (PCNA) in association with neovascularization. These PCNA-positive cells are both microvascular endothelial and smooth muscle cells and intimal hyperplasia smooth muscle cells.[151] In areas with a higher staining for PCNA within the intimal hyperplasia, there is intense perivascular staining for tenascin, prompting suggestions that there is an association of neovascularization with intimal hyperplasia formation.[152]

CONCLUSION

In summary, intimal hyperplasia remains a significant complication of vascular procedures, whether performed open or percutaneously. Substantial advances in our understanding of vessel wall physiology, biology, pharmacology, and pathology as it relates to the development of intimal hyperplasia have been made in the past two decades. However, we have not, as yet, managed to translate this knowledge into effective therapeutic regimens to allow us to control the progression of this disease. Therefore intimal hyperplasia remains the major short-term obstacle to patent angioplastied vessels and bypass grafts.

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CHAPTER 6

Ischemia-Reperfusion

ROBERT J. BEAULIEU, JOSHUA C. GRIMM, and HEITHAM T. HASSOUN

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Recognition of ongoing lower extremity necrosis following successful revascularization in patients presenting with acute ischemia prompted the first reports of ischemia-reperfusion (I/R) injury in the 1950s.[1] Following these initial reports, canine models of cardiac I/R were used to correlate the ischemic time with subsequent risk of hemorrhagic necrosis.[2] These findings were further correlated with human adults undergoing aortic valve surgery, implicating I/R injury after cardiopulmonary bypass as a cause of death in these patients. Since these initial reports, I/R injury has been observed in multiple types of operations, including cardiac, vascular, transplant, and reconstructive, as well as following traumatic injury and heart failure. The clinical manifestations of I/R injury are a direct result of the biochemical aberrations that develop as a consequence of the two components of I/R injury—ischemic injury and reperfusion injury.

PATHOPHYSIOLOGY OF ISCHEMIA-REPERFUSION INJURY

The two phases of I/R injury—ischemic injury and reperfusion injury—are marked by unique cellular and systemic consequences. Understanding the complex interaction between the biologic responses during two phases informs the clinician to the expected clinical manifestations, as well as potential mechanisms to treat, and even prevent, these injuries.

Injury During Ischemia

The ischemic phase of I/R injury is marked by tissue hypoxia or anoxia and stasis of the microcirculation (Fig. 6.1). The temporal pattern of injury after ischemic injury depends largely on the baseline metabolic demands of the affected tissue. For instance, ischemic injury in the jejunum results after only 30 minutes, whereas human skeletal muscle can tolerate ischemic times beyond 2 hours.

Tissue ischemia results in shift from aerobic mechanisms of cellular respiration toward anaerobic because the mitochondria no longer have adequate O_2 levels to effectively produce adenosine triphosphate (ATP). ATP production no longer meets the metabolic needs of the cell, and, as a result, intracellular pH increases as lactic acid levels rise. The resultant change in intracellular pH inhibits further glycolysis and activates Na^+/H^+ antiporter in an attempt to return the intracellular pH to normal values. Due to ongoing ATP deficits, the Na^+,K^+-ATPase cannot adequately pump Na^+ out of the cell to deal with the influx. High intracellular Na^+ inhibits the Na^+/Ca^+ antiporter, resulting in high intracellular Ca^{2+} levels, activating degradative enzymes, such as phospholipase A2, and proteases, such as calpains. Prolonged ischemia results in cell membrane damage and necrotic cell death.

Mitochondrial injury during the ischemia phase not only results in decreased ATP production, but also contributes to the production and accumulation of reactive oxygen species

Abstract

Ischemia-reperfusion injury (I/R injury) represents a complex mechanism by which changes in both the intracellular composition and local tissue environment during periods of ischemia lead to ongoing cellular injury in the setting of reperfusion. Creation of reactive oxygen species and priming of the mitochondrial membrane permeability transition pore during ischemia are primary factors in determining cellular damage when perfusion is restored. These mechanisms, as well as the role of pro-inflammatory molecules, hypothermia and anticoagulants, are outlined here. Additionally, the clinical manifestations of I/R injury, especially within the lower extremity and renal vasculature, are discussed. Understanding of the factors contributing to I/R injury at the cellular level and familiarity with methods of treatment and prevention of I/R injury are essential to reduce the devastating impact on postoperative morbidity and mortality. Finally, the areas of ongoing research are explored, including the use of mesenchymal stem cells and storage advances within the transplant community.

Keywords

Ischemia-reperfusion injury
reactive oxygen species
compartment syndrome

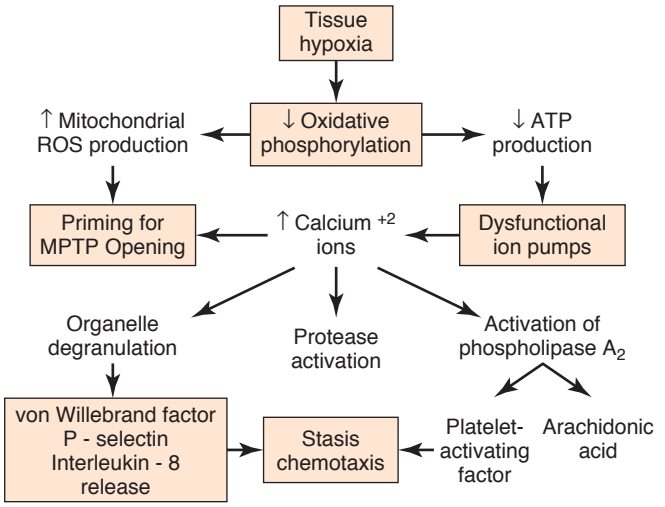

Figure 6.1 Injury During Ischemia. Decreased oxygen supply activates a complex cascade of metabolic, inflammatory, and prothrombotic pathways and sets the conditions for MPTP opening during reperfusion. *ATP*, Adenosine triphosphate; *MPTP*, mitochondrial membrane permeability transition pore; *ROS*, reactive oxygen species.

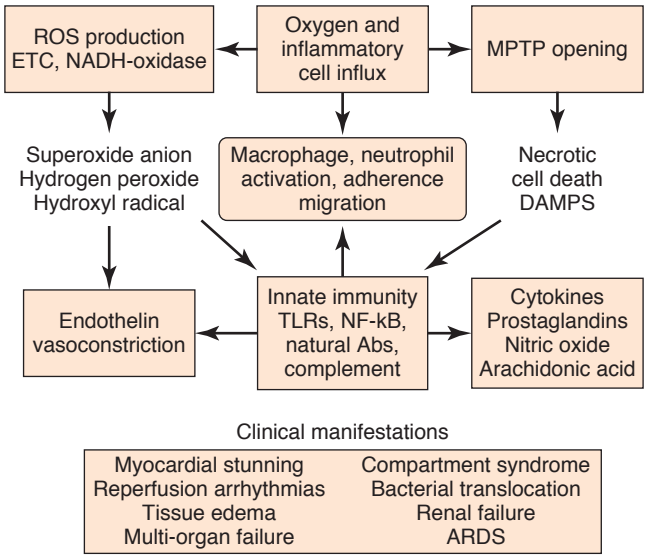

Figure 6.2 Injury During Reperfusion. The return of oxygen, influx of inflammatory cells, and washout of metabolites contribute to cell death and an inflammatory, prothrombotic milieu that exacerbates tissue injury. *Abs*, Antibodies; *ARDS*, acute respiratory distress syndrome; *DAMPS*, danger-associated molecular patterns; *METC*, mitochondrial electron transport chain; *MPTP*, mitochondrial membrane permeability transition pore; *NADH*, reduced nicotinamide adenine dinucleotide; *NF-κB*, nuclear factor kappa B; *ROS*, reactive oxygen species, *TLRs*, toll-like receptors.

(ROS).[3,4] Increases in the mitochondrial ROS concentration, in the setting of increased intracellular Ca^{2+} and elevation Pi levels, contribute to the priming of the mitochondrial membrane permeability transition pore (MPTP), an important component leading to necrotic cell death.[5,6] Indeed, data from Halestrap et al. indicate that the degree of ROS accumulation during ischemia is a key factor to determine the opening of the MPTP during reperfusion and the subsequent degree of tissue injury.[6a] During the ischemic phase, the low intracellular pH inhibits the MPTP opening. Pore opening upon return to normal intracellular pH during the reperfusion phase is a significant driver of necrotic cell death.

Tissue hypoxia results in movement of neutrophils and macrophages into the interstitium through the action of hypoxia-adaptive pathways.[7-9] Activated neutrophils subsequently release molecular mediators, including glutamate and adenine nucleotides, which contribute to the production of adenosine on the vascular endothelial surface, a protective factor that restores endothelial integrity.[10-12] Activated leukocytes also have significant proinflammatory consequences. Neutrophils release soluble factors that increase endothelial permeability and cytoskeletal rearrangement.[13] Data are emerging regarding the important role tumor necrosis factor-α (TNF-α), released from activated macrophages. TNF-α serves as an important proapoptotic agent through the induction of multiple cellular pathways, including NF-κB.[14] In addition, mechanisms that block TNF-α production have demonstrated protective effects against renal I/R injury in rat models.[15]

Injury During Reperfusion

Restoration of blood flow to an ischemic tissue bed results in a complex cellular and systemic response (Fig. 6.2). Paradoxically, this response often leads to further tissue injury than is seen during the ischemic phase alone. Insight into the mechanisms of reperfusion injury has led to the targeted studies for the prevention and mitigation of the deleterious effects of restoring blood flow to ischemic tissues.

Intracellular changes associated with reperfusion following ischemia include increased ROS production, increased sequestration of intracellular Ca^{2+} into mitochondria via the Na^{+}/Ca^{2+} antiporter and return toward normal intracellular pH.[5] As discussed with ischemic injury, mitochondrial damage is the primary determinant of tissue loss due to reperfusion.[16] Mitochondria are mediators of the multiple apoptotic and necrotic cell death pathways that result from ROS. ROS directly activate a family of proapoptotic proteins known as BH3-only proteins or trigger MPTP pore opening, resulting in increased permeability of the outer mitochondrial membrane and the release of proapoptotic proteins, such as cytochrome c.[17] Despite the MPTP typically being closed at normal pH, the combination of factors associated with the I/R injury, including ROS concentration, induces its opening and contribution to cellular injury.[18] Cytochrome c release may further be potentiated through the peroxidation of the mitochondrial protein cardiolipin, located on the inner mitochondrial membrane.[19] Loss of cytochrome c in the mitochondrial membrane results in decreased aerobic cellular respiration and increased ROS and ultimately stimulates increased apoptosis.[13,20-22]

Programmed cell death is further mediated by signaling from the TNF death receptor pathway.[23-25] Binding of circulating TNF to the TNF receptor 1 results in a conformational change in the receptor that promotes binding of cytosolic TNF receptor–associated death domain (TRADD) to the cytosolic domain of the receptor. The conformational change leads to the internalization of the receptor and production of secondary

cytosolic complexes, such as the necrosome. Two components of the necrosome, receptor-interacting protein 1 (RIP1) and receptor-interacting protein 3 (RIP3) undergo ROS-dependent phosphorylation and are thought to play a role in MPTP opening and subsequent cell death.[23,24] Evidence from cardiac models of I/R injury has outlined RIP3 activation of Ca^{2+}-calmodulin-dependent protein kinase II (CaMKII) as a trigger for MPTP opening and regulated cell death.[26] In these models, deficiencies in RIP3 and inhibition of CaMKII reduce myocardial necrosis resulting from I/R injury. In addition, TNF binding to the TNFR1 receptor may initiate the nuclear factor kappa B (NF-κB) proinflammatory pathway, described later.[24]

Activation of cell death pathways leads to the release of proteins and protein fragments that are typically sequestered within the cell, as well as cell surface accumulation of oxidatively modified proteins and lipids on the cell surface, triggering an immune response. Recognition of these surface moieties by the innate immune system as "danger-associated molecular patterns" (DAMPS) through activation of the toll-like receptors (TLRs) results in subsequent proinflammatory pathways.[27,28] Multiple reperfusion-associated DAMPS and their associated TLR targets have been identified, including heat shock protein 60 (HSP60), a ligand for TLR4; high-mobility group protein B1 (HMGB1), a ligand for TLR2, 4, and 9; low-molecular weight hyaluronic acid, a ligand for TLR2 and 4; and cardiac myosin, a ligand for TLR2 and 8.[29] Ligand binding to TLRs initiates TLR signaling pathways that result in cell necrosis through apoptosis or potentiation of the inflammatory response through signaling mediated by NF-κB.[29] NF-κB is a transcription factor in the cytosol in an inactive complex with inhibitor of NF-κB (I-κB). TLR signaling cleaves the I-κB component of the complex, allowing NF-κB to translocate to the nucleus and initiate the transcription of genes encoding multiple proinflammatory proteins, including TNF-α, interleukin-1β (IL-1β), IL-6, and intercellular adhesion molecule-1 (ICAM-1).[28,30,31] The presence of upregulated TLR-mediated apoptosis and cellular necrosis has been demonstrated in I/R injury in nearly all tissue types, including intestinal, cerebral, cardiac, hepatic, and renal.[32-36]

Activation of the complement cascade is also a significant mediator of tissue injury during ischemia and reperfusion. DAMPS also play an important role in antibody-mediated pathways of complement activation in I/R injury.[31] The dominant antibody class is immunoglobulin M (IgM).[27] The antibodies recognize epitopes formed by the oxidative modification of lipids and proteins that were translocated to the cell surface during reperfusion. In addition, cell damage sustained during I/R injury results in presentation of self-antigen that would have normally been sequestered from the immune system, such as myosin heavy chain II.[37] IgM binding to extracellular or cell surface epitopes induces the complement cascade, resulting in cell targeting via C3b binding and neutrophil chemotaxis via C5a binding.[31] Antibody-independent complement activation occurs with the binding of mannose-binding lectin (MBL) to cell surface carbohydrates.[38] MBL and C3 colocalization at the cell surface is significantly increased in the setting of ischemia and reperfusion and serves to further induce cell damage and necrosis.[39,40]

Reactive Oxygen Species Generation and Mitochondrial Injury

Mitochondrial injury due to derangements of the aerobic cellular respiration via the mitochondrial electron transport chain plays an important determinant role in tissue damage with I/R injury. During cellular respiration, ROS superoxide anions ($O^{\bullet -}$) are generated as a small percentage (2%-5%) of the O_2 consumed in the electron transport chain and may leak from the complex along the mitochondrial inner membrane.[40] The excess accumulation of ROS is mitigated by mitochondrial superoxide dismutase, which catalyzes the conversion to H_2O_2, which is subsequently converted to H_2O and O_2 by catalase.[40] In the setting of decreased O_2 tension, such as the ischemic phase of I/R injury, ROS generation paradoxically increases and overwhelms the compensatory mechanisms of the mitochondria. In addition, complexes along the electron transport chain, flavin mononucleotide (FMN) of complex I in particular, become saturated with electrons, due to the loss of O_2 as a final electron acceptor. With restoration of blood flow, the cell is saturated with O_2, which becomes a sink for electrons from FMN, leading to a burst of $O^{\bullet -}$. The increased concentration of mitochondrial ROS induces further damage of the mitochondrial cardiolipin and inner membrane complexes, driving further ROS formation.[41] High levels of ROS can lead to mitochondrial injury, protein misfolding, and cellular demise through the induction of apoptotic pathways, including triggered opening of the MPTP and release of cytochrome c.[42] Evidence suggests a beneficial role for intermediate levels of ROS to build tolerance to metabolic and oxidative stressors, although rampant dysregulation and accumulation in I/R injury can have devastating consequences.[40]

Nitric Oxide

Nitric oxide (NO) has contrasting impacts in I/R injury due to its potent antiinflammatory and antithrombotic properties, as well as potentially toxic, concentration-dependent effects.[15,43] NO results in stimulation of guanylate cyclase, causing increased intracellular concentrations of guanosine monophosphate and resultant smooth muscle relaxation, decreased cardiac contractility, and reduced platelet and inflammatory cell activation, due to increased intracellular calcium concentrations in these tissues. Increased NO levels may mitigate tissue damage in I/R injury through multiple mechanisms. NO activation, and more specifically the peroxynitrite ($ONOO^-$) molecule created by the interaction of NO and ROS, leads to increased membrane permeability through lipid peroxidation.[41] $ONOO^-$ contributes to activation of mitochondrial-dependent apoptosis and may increase NF-κB levels, discussed earlier as an inducer of apoptosis through the TNF pathway.[18,41] However, in vitro evidence suggests that $ONOO^-$ may inhibit NF-κB production, so the role of this pathway in the deleterious effects of NO remains unclear.[44,45] There are also beneficial properties of NO.

In vivo and ex vivo models of intestinal, neuronal, and hepatic injury when provided with NO donors show reduced injury.[46-48] NO induction of autophagy in ischemic-preconditioning additionally provides protection from tissue injury in hepatic

I/R.[49] Endogenous NO also inhibits vascular permeability and neutrophil adhesion to endothelium.[14,50] The complex interplay between the protective and deleterious effects of NO during I/R injury is likely impacted by duration of ischemia, magnitude of the injury, and the specific organ bed in which the I/R occurs.

Hypothermia

Hypothermia results in decreased rates of cellular metabolism and, specifically, reduces the rate of ATP breakdown more than the reduction in synthesis imposed by ischemia.[30] Accordingly, hypothermia is posited to have a protective effect against tissue damage in I/R injury. In animal models of skeletal muscle injury (canine) and spinal cord ischemia secondary to thoracoabdominal aortic occlusion (murine), hypothermia has been found to reduce damage secondary to I/R injury. The beneficial effect of hypothermia in spinal cord ischemia has also been demonstrated in humans in multiple studies. Animal models of renal I/R injury have shown beneficial effects of hypothermia, with temporary reduction in renal perfusion that does not result in permanent damage, as well as reduction of ROS production.[51,52] Lampe et al. have suggested two windows for the use of hypothermia in I/R injuries: at the time of ischemia to reduce mitochondria-free ROS production and upon reperfusion, when mitochondrial complexes formed during ischemia result in irreversible pathways toward apoptosis and necrosis.[53] The effect of cooling for reduction of infarct size in myocardial infarction was an area of recent interest, prompting the performance of multiple randomized clinical and feasibility trials, including the COOL MI, NICAMI, and LOWTEMP trials.[24,54,55] Although these trials have found only nonsignificant reductions in infarct size, they do support the safety and feasibility of both endovascular[24,37] and noninvasive[55] cooling strategies to lower core temperature to less than 35°C, which may have roles in mitigating I/R injuries in other tissue beds. The extent of benefits from hypothermia must be weighed with its contribution to potentially profound coagulopathy when deciding the utility of this strategy.

Anticoagulants

Anticoagulants are the mainstay of treatment during both phases of I/R injury, typically initiated on the suspicion of arterial occlusion and continued through restitution of flow. Unfractionated heparin and low-molecular-weight heparin are most commonly used. Unfractionated heparin has been shown to modulate endothelial cell permeability and pH. Despite reduced markers of local thrombosis, administration of enoxaparin does not appear to increase the rates of skeletal muscle salvage in a hind limb ischemia model. These results are in contrast to those seen in traumatic brain injury, in which administration of enoxaparin 30 hours after the onset of injury can reduce edema and infarct size in a rat model. A newer antithromboic agent, activated protein C (APC), has demonstrated a lower rate of inflammatory changes during I/R injury in models of renal I/R, through thrombomodulin activation resulting in a subsequent decrease in thrombin activity. Thrombin may represent a potential target to affect tissue damage in I/R injury. In a rodent model, pretreatment with antithrombin nanoparticles reduced creatinine increase, infarct size, and histologic evidence of microvascular thrombosis following 45 minutes of warm ischemia.[11] Evidence with neuronal damage in cerebral ischemia demonstrates increased thrombin expression in the affected neuronal bed and a decrease in neuronal loss after the administration of nafamostat mesilate, a serine protease inhibitor thought to act on the thrombin pathway.[56] Antithrombin, a serpin inhibitor that regulates proteolytic activity in the clotting cascade, has been shown to reduce infarct size following myocardial infarction in a murine model, although its effects appear independent of its anticoagulation properties and are due to an inhibition of the NF-κB pathway.[50]

CLINICAL MANIFESTATIONS OF ISCHEMIA-REPERFUSION INJURY

The clinical manifestations of I/R injury depend on the tissue bed affected, the duration of ischemia, and the ability to reperfuse. The time each tissue type can remain ischemic and maintain viability, known as the critical ischemia time, varies. The following discussion provides an overview to these clinical manifestations, highlighting the diagnosis and treatment by tissue type.

Lower Extremity Compartment Syndrome

Acute compartment syndrome of the lower limb can develop in multiple patient populations in which the arterial inflow or venous outflow are disrupted. In recent retrospective reviews, acute limb ischemia results most commonly from arterial embolism (39.5%) or thrombosis (50.23%), placing these patients at particular risk following reperfusion.[57] In patients who undergo arterial bypass, thrombosis of the graft is the most common cause of a repeated episode of acute limb ischemia.[57] Patients who undergo reperfusion following acute arterial injury or blunt/crush injury are at particular risk. Isolated injuries to either the artery or the vein can result in limb compartment syndrome. Aortic dissection, especially with extension into the iliac vessels, can result in limb compartment syndrome, as well as visceral compartment syndrome presentations.[58] Within the limb, muscle tissue is at the highest risk for I/R injury because it has the lowest critical ischemia time, at 4 hours, compared with ischemic time for bone (4 days).[31]

Compartment syndrome results from a reduction in the arteriovenous pressure gradient, a theory first posited in the 1970s.[59] Edema and increased intracompartmental pressure result in increased venous pressure, which results in a decrease in the flow gradient from lower extremity arteries to lower extremity veins. The increased interstitial pressure drives further increases in venous pressures and decreases venous drainage, contributing to worsening edema and thereby exacerbating the problem. Arteriolar compression may develop as interstitial pressure rises, resulting in nerve compression and the sensation of paresthesias and/or eventual numbness. These symptoms

may develop within 30 minutes of onset of ischemia. Irreversible damage results within 12 to 24 hours.[60]

In the conscious patient able to communicate, physical exam findings alone, including a swollen, tight limb with paresthesias, numbness, pain on passive flexion, and absent pulses, are enough to diagnose compartment syndrome. However, sedated patients, especially following large surgical procedures or trauma, may have equivocal findings that make it difficult to diagnosis compartment syndrome. In these patients the use of direct transduction of intracompartmental pressures can provide the diagnosis. Early research in the field defined 30 mm Hg as a critical compartmental pressure, above which treatment is necessary.[43] Despite nearly 40 years since these initial investigations, the 30-mm Hg threshold has persisted as a cutoff for surgical intervention in acute compartment syndrome.[61] Investigation into biomarkers for compartment syndrome has revealed elevated levels of inflammatory biomarkers, in particular matrix metalloproteinases (MMPs)-1, -2, -3 and -9, as well as neutrophil gelatinase-associated lipocalin (NGAL), in patients requiring fasciotomy for limb compartment syndrome.[19] The role of these biomarkers in directing therapy remains to be evaluated.

Left untreated, compartment syndrome of the lower extremity can result in multisystem organ failure through the action of inflammatory cytokines, myoglobinuria, and electrolyte abnormalities, especially following reperfusion and return of these molecules to systemic circulation. Accordingly, treatment is focused on decompressing the affected compartments to return blood flow and halt the ischemic insult. Initial nonsurgical management involving removal of any restrictive dressings (i.e., cast) may help; however, definitive management of compartment syndrome of the limb involves decompression with four-compartment fasciotomy.[61] Decompressive fasciotomy is performed through either one- or two-incision techniques. The single-incision technique involves a long incision along the anterolateral calf, terminating within 5 cm of the end of the fibula at either end, and can successfully decompress all four compartments while maintaining increased soft tissue stability for any underlying fracture.[16,29] The more traditional two-incision procedure decompresses through both a lateral and medial incision, with care taken to divide the intramuscular septum on the lateral incision to prevent incomplete decompression.[62] The use of vacuum-assisted closure (VAC) devices following either method may improve wound edema and facilitate easier closure.[63]

Beyond decompression for the treatment of I/R injury in the lower extremity, the initial ischemic insult may be addressed through catheter-based thrombolytic techniques or open revascularization. However, previous large, randomized trials have not focused on rates of I/R injury following reperfusion as a primary end point. However, the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial did enroll patients with 14 days or less of ischemic symptoms from either thrombosis or embolic occlusion of the lower extremity and found that distal embolization of thrombotic material occurred frequently during catheter-based thrombolysis techniques, although it could commonly be addressed through continued thrombolysis in most cases. This finding was further demonstrated in a recent Cochrane meta-analysis in which patients with lower extremity ischemia treated by thrombolytic techniques were more likely to have distal embolization within 30 days compared with patients who underwent open bypass.[65] However, DNA-based assays have demonstrated damage to DNA on the molecular level without phenotypic manifestations when using a tourniquet during surgical bypass.[64] Thus, regardless of reperfusion technique, a high degree of suspicious for I/R injury following treatment of lower extremity ischemia should be maintained.

Gastrointestinal Ischemia-Reperfusion Injury

Due to the high metabolic rate of the liver and small and large intestines, the gastrointestinal system is particularly susceptible to I/R injury. Ischemia to the mesenteric distribution may result from multiple sources, including low flow through decreased cardiac output or the administration of alpha-adrenergic agents, as well as embolic and thrombotic events.[47] In addition, mesenteric venous occlusion may result in ischemic insults similar to that seen in arterial etiologies. In the intestines the injury associated with reperfusion may be even greater than that of ischemia alone. In particular, in feline models a reduction in mucosal thickness and reduction of villi height has been observed following 3 hours of ischemia and 1 hour of reperfusion compared with 4 hours of ischemia alone.[65] The combination of ischemia and reperfusion in the intestinal tissue results in NO-induced damage to the mucosa and submucosa, contributing to loss of integrity of the intestinal wall, allowing for bacterial translocation.[17] Bacterial translocation into the portal and systemic circulation demonstrates a time-dependent increase even following reperfusion, highlighting the ongoing effects of I/R injury even after flow has been restored. Release of bacteria into the systemic circulation, as well as the accumulation and release of toxic metabolites, may have drastic systemic implications.

The liver has important roles in metabolism, detoxification, and the immune response, and, as such, there can be devastating consequences with hepatic I/R injury.[10] The bacterial burden and concentration of inflammatory molecules within the portal circulation is significantly increased after intestinal I/R. Within 2 hours of liver reperfusion, there is a significant increase in TNF-α and IL-1β concentrations within the liver, and neutrophils into the liver with resultant liver injury. Similarly, due to increased expression of ICAM-1 and the leukocyte adhesion protein CD11/CD18, there is a leukocyte-dependent increase in oxidative stress in the liver following intestinal ischemia.[66,67] Therefore the liver may demonstrate tissue damage following either as a result of ischemia to the liver itself or as collateral damage following intestinal ischemia and reperfusion.

The relatively high incidence of intestinal and hepatic I/R injury, as well as the detrimental systemic effects, have prompted investigation into factors that may mitigate the tissue damage of I/R injury in these tissue beds. Regional hypothermia may have benefits on limiting intestinal tissue damage, as well as systemic effects of intestinal ischemia. Within the gut, regional hypothermia has been shown to reduce the concentrations of NF-κB and rates of PMN priming within intestinal mucosa following I/R injury.[39] Systemically, therapeutic hypothermia has been shown to reduce distant organ damage following intestinal I/R injury in a rat model.[45]

Although PMN priming via ischemia preconditioning has been shown to increase superoxide production, it has also demonstrated augmented PMN bacterial killing and phagocytosis during intestinal I/R.[32] Decreases in the inflammatory response through modulation of the heme-oxygenase 1 (HO-1) pathway via ischemic preconditioning or regional hypothermia has improved outcomes in animal models, suggesting the possible future role for pharmaceuticals targeting the HO-1 pathway.[2,48] Administration of low-dose ethanol has been shown to decrease the liver damage associated with intestinal I/R injury via NO-dependent reduction in hepatic apoptosis.[68] Another alcohol analogue (dexpanthenol) has demonstrated protective effects against I/R injury in rat models and has shown preserved peristalsis in small intestines following I/R injury.[9] These experimental studies highlight the importance of novel mechanisms, in combination with surgical reperfusion, to mitigate the damage caused to the gastrointestinal system in I/R injury.

Renal Ischemia-Reperfusion Injury

Renal I/R injury significantly contributes to the morbidity and mortality of a large number of diseases.[69] The mechanism behind renal injury following renal I/R appears similar to other tissue beds discussed previously, namely, the activation of proinflammatory pathways, induction of ROS generation, mitochondria-mediated apoptosis signaling, and neutrophil accumulation in injured tissue beds.[25,46,69,70] The structure of the kidney leads to differential effects in the kidney. The outer medulla experiences a disproportionate reduction in blood flow during I/R, contributing to epithelial injury in the proximal tubule.[6] Renal I/R also induces damage and impaired healing in renal vasculature and microcirculation, through downregulation of vascular endothelial growth factor (VEGF) and upregulation of angiogenesis inhibitors, resulting in increased tubular fibrosis and higher risk of chronic kidney impairment after an episode of renal I/R.[3,71] Renal I/R injury also appears to alter the renin-angiotensin-aldosterone system (RAAS), toward an increased level of angiotensin II and aldosterone, promoting systemic hypertension, even following resolution of the acute renal I/R injury.[72]

Renal I/R can result in profound local and systemic disturbances (Fig. 6.3). In the kidney, medullary hypoxia due to ischemia results in salt wasting and vasoconstriction.[8] Reperfusion is marked by endothelial swelling, resulting in an initial "no reflow" phenomenon, followed by loss of endothelial integrity and resulting neutrophil invasion and tissue damage.[46] The distant organ effects may be the primary mediators of morbidity and mortality following renal ischemia and reperfusion. Renal ischemia induces apoptosis in the lung in murine models.[73] Systemic release of TNF-α, IL-1, and ICAM-1 are thought to play a role in cardiac injury due to neutrophil infiltration during renal I/R and increased rates of cardiac myocyte apoptosis have been observed in animal models of renal I/R.[74] In the central nervous system, increased concentrations of glial fibrillary acidic protein (GFAP) in the cerebral cortex may recruit neutrophils and result in neuronal damage, which may potentiate the effect of uremia to result in mental status changes in renal I/R.[75] Increased oxidative stress, apoptosis, and tissue damage have been experimentally demonstrated in hepatocytes following renal I/R injury, likely in part due to increased presence of systemic proinflammatory cytokines.[76] These manifestations help to explain the profound detrimental effect that even brief periods of renal I/R may have on patient morbidity and mortality in a wide variety of diseases.

Strategies to reduce the clinical manifestations of renal I/R injury have been studied in many populations, including the transplant population and patients undergoing juxtarenal aortic aneurysm repairs. In allografted organs, cold ischemic times are an important factor in determining the viability of a transplanted organ, with increased rates of delayed graft function associated with prolonged cold ischemic times.[77] Methods of machine preservation with pulsatile perfusion result in improved outcomes compared with static cold preservation, highlighting the importance of flow-responsive endothelial characteristics, including preservation of the endothelial barrier, for reducing the effect of renal I/R injury.[78] In vascular surgery, renal ischemia is of particular concern, especially with the high burden of preexisting renal disease among vascular patients. Renal dysfunction occurs in approximately 12% of patients undergoing thoracoabdominal aortic repair, although this represents a significant improvement from historical reports, likely due to the increased use of renal protective bypass methods (maintaining a perfusion pressure of at least 60 mm Hg) and cold perfusion strategies.[1] In addition, ischemic preconditioning has been shown to reduce tissue damage in a rat model of renal I/R, through a decreased inflammatory response following ischemic insult.[27,79]

Myocardial Ischemia-Reperfusion Injury

Following acute myocardial infarction, cardiac myocytes are susceptible to at least two different types of I/R injury. The first is known as myocardial "stunning" and refers to a reversible, transient dysfunction that persists following reperfusion despite the absence of irreversible damage. Myocardial stunning likely results from a complex interplay of multiple factors, including decreased ATP synthesis following reperfusion, microvascular spasm and plugging, and cytotoxic injury due to ROS and altered calcium metabolism. Stunning may result in malignant cardiac arrhythmias that result in sudden death following cardiac revascularization due to sudden changes in the intracellular ionic composition resulting in altered electrical coupling. In addition, following reperfusion of culprit lesions, a component of the cardiac microvasculature may remain nonperfused in up to 50% of patients, via a "no reflow" mechanism.[80] Ischemic time alone accounts for only a small component of morphologic changes following I/R injury, and tissue damage following cardiac ischemia depends on reperfusion time as well. In a rat model, ventricular wall thickness was significantly reduced in the group who experienced 30 minutes of ischemia followed by 60 minutes of reperfusion, compared with the groups experiencing either 30 minutes of ischemia or 90 minutes of ischemia without subsequent reperfusion.[80] Ventricular wall loss and altered electrical conduction have obvious implications on the clinical manifestations of myocardial I/R injury.

Multiple mechanisms have been explored to reduce the detrimental effect of I/R injury in cardiac myocytes. Rivaroxaban, the factor Xa inhibitor, delivered in high doses for 14 days

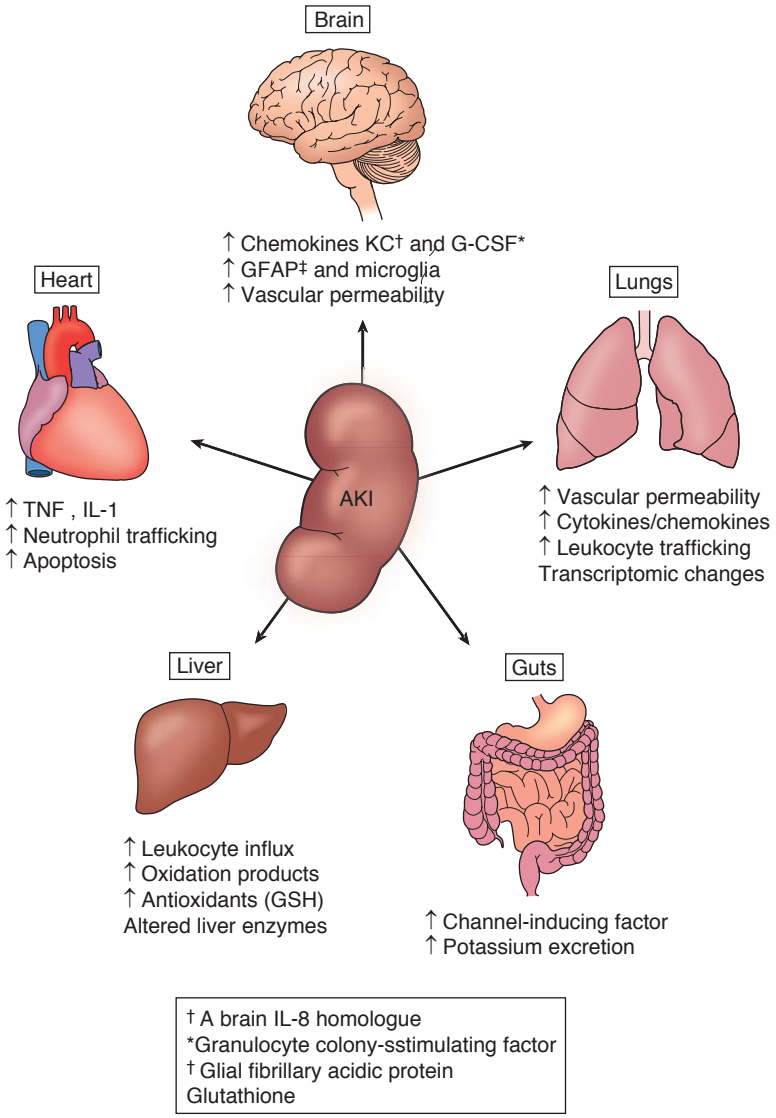

Figure 6.3 Systemic Effects of Acute Kidney Injury (AKI) Associated With Ischemia-Reperfusion (I/R) Injury. Systemic effects are responsible for the majority of morbidity and mortality associated with renal I/R injury. Universally, proinflammatory biomarkers are increased in distant organs, resulting in heart, brain, pulmonary, hepatic, and intestinal manifestations of renal I/R. Interesting, gut excretion of potassium may be responsible for the variable presence of hyperkalemia in AKI. *CSF*, Cerebrospinal fluid; *GFAP*, glial fibrillary acidic protein; *GSH*, growth stimulating hormone; *IL-1*, Interleukin-1; *KC*, CXCL1 chemokine; *TNF-α*, tumor necrosis factor alpha. (From White, LE, Hassoun, HT. Inflammatory mechanisms of organ crosstalk during ischemic acute kidney injury. *Int J Nephrol.* 2012;1–8.)

following myocardial I/R injury has been shown to increase survival compared with both no therapy and low-dose rivaroxaban therapy in a murine model.[38] These effects may be due in part to the pleomorphic effects of rivaroxaban, including antiinflammatory and antifibrotic effects. The incidence of malignant arrhythmias may be reduced through staged gradual reflow or transient acid reperfusion. New insights into the molecular pathway of myocardial I/R injury, including the role of the signal transducer and activator of transcription (STAT) pathway, may reveal individual molecular targets toward which pharmaceuticals may be directed, although such research is in preliminary stages only.[81]

Results from a multicenter randomized, prospective trial examining ischemic preconditioning for heart surgery have become available in the *New England Journal of Medicine*. In this trial, remote ischemic preconditioning was induced through four cycles of upper limb ischemia, each lasting 5 minutes. The concept is based on earlier reports in which infarct size within the heart is reduced through attenuation of endothelial dysfunction through exposure to previous ischemic periods.[82] However, Meybohm et al. report no significant difference in the rates of primary end points (death from any cause, nonfatal myocardial infarction, new stroke, or acute renal failure) in the groups with or without ischemic preconditioning prior to elective cardiac surgery.[83] These results echo the findings of myocardial protection for patients undergoing elective vascular surgery.[84] Thus it appears that despite the benefits seen in animal models, human use of ischemic preconditioning for the protection of myocardium during elective operations remains unproven.

FUTURE DIRECTIONS IN ISCHEMIA-REPERFUSION INJURY

Given the extensive clinical impact of I/R injury, reducing its effects remains an area of intense basic science and clinical research. Among patients with myocardial infarction, the use of mesenchymal stem cells has garnered increased attention. In murine models, delivery of adipose-derived stem cells following myocardial infarction results in decreased fibrosis and

improvements in left ventricular function.[85] In rat models, repeated transplantation of allogenic stem cells not only consistently reduces infarct size with each administration, but also does so without generating a rejection-like picture.[44] Mechanisms for transmyocardial delivery of stem cells with or without associated CABG in humans have been elucidated.[86] However, the ability to replicate beneficial findings from animal models in humans, and the role of stem cell delivery in other vascular beds, including the lower extremity, gastrointestinal system, and kidneys, remains to be seen.

Techniques for preservation of organs in transplantation may serve to improve outcomes in I/R injury. Cold storage solutions that incorporate the p38 MAPK inhibitor FR 167653 (with antiinflammatory) properties have been shown to reduce ATP depletion and intracellular calcium accumulation during I/R injury after transplantation. Furthermore, methods of organ procurement that involve pretreatment with low-dose dopamine have demonstrated reduced rates of dialysis in renal transplants, possibly due to membrane stabilization of the endothelial cell. Further investigation into this pathway may reveal potential pharmaceutical targets for reduction of tissue damage following I/R injury in other tissues, especially because alterations in endothelial barrier function are a hallmark to nearly all types of I/R injury. Finally, hypothermic machine perfusion with pulsatile flow in deceased donors may reduce the rates of delayed graft function following renal transplantation, highlighting the potential role for mechanical mechanisms to reduce tissue damage in I/R injury.[87,88]

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CHAPTER 7

Arteriogenesis and Angiogenesis

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Peripheral arterial disease (PAD) of the limbs can progress to critical limb ischemia (CLI), characterized by rest pain and tissue loss, including nonhealing ulceration and gangrene.[1,2] The body compensates via neovascularization, forming collateral circulation to bypass the obstructed vessel (arteriogenesis) or increasing capillary density (angiogenesis) to deliver oxygen and nutrients to ischemic tissue. Despite these responses, disease progression can lead to amputation, decreased quality of life, comorbidity, and death and is an economic burden to the healthcare system.

Traditional treatment of PAD includes risk factor modification (tobacco abuse, diabetes, hypertension, hyperlipidemia), exercise programs, and medical therapy (antiplatelet agents, phosphodiesterase inhibitors).[1-3] As atherosclerosis progresses, more invasive intervention may be necessary, including endovascular therapies and surgical bypass. Patients with CLI may not be candidates for surgical intervention because of severe medical comorbidity or nonreconstructable disease. This patient population may be candidates for biologic treatments, including gene-based, molecular, and cell-based therapies designed to promote healing and prevent amputation.

Advances in basic science research have developed these biologic therapies over the past two decades. Early clinical trials focusing on gene and molecular therapies, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), have demonstrated limited benefit. More promising results have been observed using cell-based therapies, including endothelial progenitor cells (EPCs) and bone marrow–derived mononuclear cells (BM-MNCs).

Herein, the basic science and processes involved in neovascularization (specifically arteriogenesis and angiogenesis), as well as recent human clinical trials designed to promote neovascularization for CLI, are discussed.

NEOVASCULARIZATION

Neovascularization refers to the formation of new blood vessels and includes vasculogenesis, arteriogenesis, and angiogenesis.[4]

Vasculogenesis is the de novo formation of embryonic blood vessels from vascular progenitor cells or hemangioblasts, which develop into hematopoietic precursors and endothelial cells.[5] These cells induce differentiation of discrete vascular layers as cells transform into endothelial cells, smooth muscle cells (SMCs), and adventitial pericytes. Although vasculogenesis primarily occurs during the embryonic stages of development, postembryonic adaptive vasculogenesis results from either arteriogenesis or angiogenesis.[6,7]

Arteriogenesis involves growth of collateral vessels and remodeling from preexisting arterial-arteriolar connections.[6,8] Arteriogenesis is induced by a change in hemodynamic forces (fluid shear stress [FSS]) resulting from pressure differences within an artery narrowed by atherosclerosis. FSS activates the endothelium, leading to increased transcription of the promoter regions of a variety of proteins contributing to vessel growth (Table 7.1).[4] With progressive arterial stenosis, blood follows the path of least resistance and is shunted into collateral vessels.[4] Collateral vessel formation maintains a degree of flow beyond the obstruction.

Angiogenesis, which refers to the sprouting of new capillaries from preexisting ones, is stimulated by decreases in oxygen tension secondary to reduced tissue perfusion. Local ischemia stimulates an increase in hypoxia-inducible factor-1 (HIF-1), which results in increased production of VEGF, a potent angiogenic factor. VEGF induces endothelial cell proliferation and increases endothelial permeability.[8] Matrix metalloproteinases (MMPs) locally degrade basement membrane and extracellular matrix (ECM), allowing vessel growth and increased tissue perfusion.[9-11] Although this increased flow provides greater delivery of oxygen and nutrients to ischemic tissues, it is often not sufficient to overcome major arterial obstruction.[8,11,12]

Postembryonic arteriogenesis and angiogenesis occur over a continuum of vascular adaptations (Fig. 7.1).[7]

ARTERIOGENESIS

Chronic, progressive arterial stenosis leads to generation of a collateral network by remodeling preexisting arterial-arteriolar connections (Fig. 7.2). Arteriogenesis is the formation of this collateral circulation, primarily in response to an increase in FSS with a contribution from increased circumferential wall stress. For example, femoral artery occlusion results in up to a 200-fold increase in shear stress in the arteriolar network.[5]

FSS is proportional to flow velocity and inversely proportional to the radius cubed, whereby small changes in radius can normalize shear stress.[11] Increased FSS activates the endothelium.[5,8,13] Nitric oxide (NO) is liberated by endothelial cells (via endothelial NO synthase [eNOS]) in addition to macrophages and SMCs in the adventitia (via inducible NOS). NO induces SMC relaxation and vasodilatation beyond the arterial occlusion, thereby improving blood flow.[12,14,15] NO also stimulates endothelial VEGF secretion, leading to the release of endothelial cell adhesion molecules (CAMs) and monocyte chemotactic protein-1 (MCP-1) by endothelial and SMCs.[5,6,15] Both molecules mobilize to the cell surface, generating a "sticky" endothelium that enhances leukocyte attraction, adhesion, and invasion of arteriolar collaterals and periadventitia.[6,8]

Monocytes either attach to CAMs to be incorporated into the lumen of the developing vessel, or accumulate in the adventitia.[15] Activated monocytes release tumor necrosis factor-α (TNF-α), further enhancing monocyte attraction. Platelet adherence and activation stimulates growth factor and interleukin-4 production, enhancing monocyte adhesion. Monocytes stimulate production of growth factors, chemokines, and cytokines, in addition to immune cells, leading to the proliferation of collateral arterioles (Fig. 7.3).[5] Macrophages contribute to remodeling of the collateral vessel by liberating proteases.[6,8,9] Endothelial cell proliferation and endothelial permeability increase, while

TABLE 7.1 Transcription and Growth Factors Influencing Arteriogenesis and Angiogenesis

Factor	Characteristics	Role in Arteriogenesis and Angiogenesis	Induced by
Transcription Factors			
HIF-1[118-126]	Helix:loop:helix structure Mainly involved in angiogenesis but possible role in VEGF stimulation in arteriogenesis	Induces gene transcription to promote angiogenesis in ischemic environment Is involved in hypoxic vasodilation, cell growth, proliferation, migration, sprouting, recruitment of pericytes/SMCs, vascular remodeling, mobilization of angiogenic cells and EPCs Also induces MMPs for ECM digestion	Hypoxia
EGR-1[142-147]	Increased expression in endothelial cells, SMC, fibroblasts, leukocytes	Required for expression of cyclin D1, a regulator of the cell cycle in vascular cells	Shear stress, mechanical injury, hypoxia, PDGF, FGF-1, FGF-2
Post-Transcriptional Regulators			
MicroRNAs[71,77,79,83,148,149,150,151]	~22 nucleotides in length, binds to 3′ UTR of target mRNA, single stranded RNA Post-transcriptional gene regulation	Promote and/or inhibit angiogenesis and arteriogenesis through interactions with various transcription factors, cytokines, and cell adhesion molecules	Varies with each miRNA

Continued

TABLE 7.1 Transcription and Growth Factors Influencing Arteriogenesis and Angiogenesis—cont'd

Factor	Characteristics	Role in Arteriogenesis and Angiogenesis	Induced by
Growth Factors/Cytokines			
VEGF[85-94]	Survival factor for endothelial cells Involved in angiogenesis and arteriogenesis	Promotes proliferation, migration, lumen formation Induces monocyte chemotaxis via binding to VEGFR1 on monocytes	Hypoxia and shear stress
FGF[85,87-92,100-102]	Perivascular macrophages are source of FGF-2 during collateral growth[7] Role in arteriogenesis and angiogenesis	Induces endothelial/SMC proliferation Stimulates endothelial cell migration/differentiation, and increases EGR-1 expression Potentiates VEGF and may be synergistic with VEGF-B	Shear stress, endothelial activation
TGF-β[11,16,123,152-154]	Expressed in areas of collateral formation	Expressed in developing collateral arteries Stimulates arteriogenesis by effects on endothelial cells, vascular SMCs, monocytes, macrophages	Shear stress, endothelial activation
TNFα[155-158]	Proximal mediator of inflammation	Angiogenic effects from TNFR2R Enhances activation and adhesion of monocytes by upregulating cell adhesion molecules Upregulates GM-CSF Necessary for migration/adhesion of BM-hematopoietic cells to endothelium via NO synthase-dependent mechanisms	Stimulated by endothelial activation by shear stress and LPS Lipopolysaccharide Ischemia stimulated TNFR2 expression
GM-CSF[6,11,159,160]	Enhances arteriogenesis through effects on circulating cells	Enhances release, proliferation, and differentiation of hematopoietic stem cells, mobilization of endothelial progenitor cells Amplifies effects of MCP-1,[11] promotes survival of monocytes and macrophages	Stimulated by endothelial activation by shear stress
HGF[106-109]	Augments arteriogenesis by enhancing endothelial cell function Role in angiogenesis and arteriogenesis	Activates Dll4-Notch-Hey2 pathway for inducing proliferation and migration of endothelial cells	Hypoxia, shear stress
ECM Proteins			
Del-1[109,115-117]	Involved with angiogenesis		Ischemia
Chemokines and Chemokine Receptors			
MCP-1 (or CCR2)[6,161-164]	CCR2 axis: MCP-1 binds CCR2 receptor on monocytes Potent stimulator of arteriogenesis and angiogenesis	Increases attraction/adherence of monocytes and tube formation. May attract endothelial progenitor cells to sites of vascular injury	Hypoxia and shear stress
ELR-containing CXC[161-163,165]	Binds receptors on CXCR1/2/3 Potent stimulator of angiogenesis, some forms inhibit angiogenesis via inhibition of VEGF/FGF	Binds chemokines MIG, IP-10, I-TAC, and PF-4 Decreases formation of collaterals and restoration of perfusion in knockout mice Perfusion improved with infusion of bone marrow mononuclear cells	Hypoxia
Cell Adhesion Molecules			
ICAM, VCAM-1, PECAM-[113,166-171]	Enhance attraction and adhesion of monocytes	Support diapedesis of monocytes, while enhancing cell signaling and activation of mechanosensory complexes that activate intracellular changes in response to shear stress	Shear stress

TABLE 7.1 Transcription and Growth Factors Influencing Arteriogenesis and Angiogenesis—cont'd

Factor	Characteristics	Role in Arteriogenesis and Angiogenesis	Induced by
Proteases			
MMPs[9,10,167,172-180]	Macrophages and monocytes are source of MMPs in ischemic/nonischemic tissue Involved in angiogenesis and arteriogenesis	Allow for ECM remodeling via proteolytic degradation of ECM/BM, enabling collateral vessel/capillary growth and endothelial cell migration Liberate growth factors and stimulate endothelial proliferation ECM/BM breakdown by MMPs promotes SMC proliferation and migration	Shear stress and hypoxia; MCP-1 activates macrophages to secrete MMPs MMPs activate release of more MMPs from macrophages
Immune Cells			
Monocytes/ Macrophages[6,9,48,155,167,168,177,178,181-188]	Induce vascular cell proliferation and wall remodeling via paracrine effects	Promote vascular growth and secrete growth factors (MMP, NO, VEGF, FGF-2, GM-CSF, TGF-β, TNFα) that stimulate arteriogenesis Monocytes accumulate in wall of growing collateral and differentiate into macrophages, liberating MMPs to digest ECM; encourages migration and proliferation of endothelial cells and SMCs	Shear stress-activated endothelium expresses MCP-1, leading to adhesion of monocytes
T cells/NK cells[4,170-200]	Immune Cells	CD4 and CD8 mononuclear cells migrate to collateral vessel, initiating arteriogenesis/ angiogenesis by cytokine activation Athymic mice have higher rates of autoamputation than heterozygotes NK cell deficient mice are unable to form collaterals	Shear stress
Mast Cells[10,11,200-202]	Present in adventitia of collateral arteries	Release TGF-β, VEGF, FGF-2, MMPs, histamine, serotonin	
Other Cells			
BM-EPCs[160,195-197,203-211]	BM-derived cells	Attracted to sites of neovascularization, differentiate into endothelial cells	Shear stress, ischemia Release stimulated by VEGF, SDF-1
Pericytes[211-213]	BM-derived cells	Release VEGF, FGF-2, MCP-1 and MMPs, promoting endothelial cell migration, proliferation, and survival	Shear stress
Vascular SMCs[11,213-216]	Derived from endothelial cells, mesenchymal cells, and BM-derived cells	Collateral vessel stabilization via ECM production	SMCs attracted by PDGF/VEGF Proliferation stimulated by ECM breakdown

BM, Bone marrow; *BM-EPCs,* bone marrow–derived endothelial progenitor cell; *CCR2,* CC chemokine receptor 2; *CXCR,* CXC chemokine receptor; *Del-1,* Developmental endothelial locus-1; *ECM,* extracellular matrix; *EGR-1,* early growth response protein-1; *eNOS,* endothelial nitric oxide synthase; *EPC,* endothelial progenitor cell; *FGF,* fibroblast growth factor; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *HGF,* hepatocyte growth factor; *HIF-1,* hypoxia-inducible factor-1; *ICAM,* intracellular adhesion molecule; *IL,* interleukin; *IP-10,* interferon gamma–induced protein 10; *I-TAC,* interferon-inducible T-cell alpha chemoattractant; *LPS,* Lipopolysaccharide; *MCP-1,* monocyte chemotactic protein-1; *MIG,* monokine inducible gamma-interferon; *MMP,* matrix metalloproteinase; *NK,* natural killer; *NO,* nitric oxide; *PDGF,* platelet-derived growth factor; *PECAM,* platelet endothelial cell adhesion molecule; *PF-4,* platelet factor 4; *SDF-1,* stromal cell-derived factor-1; *SMC,* smooth muscle cell; *TGF-β1,* transforming growth factor-β1; *TNF-α,* tumor necrosis factor-α; *TNFR2R,* tumor necrosis factor receptor 2R; *UTR,* untranslated region; *VCAM,* vascular cell adhesion molecule; *VEGF,* vascular endothelial growth factor; *VEGFR,* VEGF receptor.

Adapted from Huang P, Li S, Han M, et al. Autologous transplantation of granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cells improves critical limb ischemia in diabetes. *Diabetes Care.* 2005;28:2155–2160.

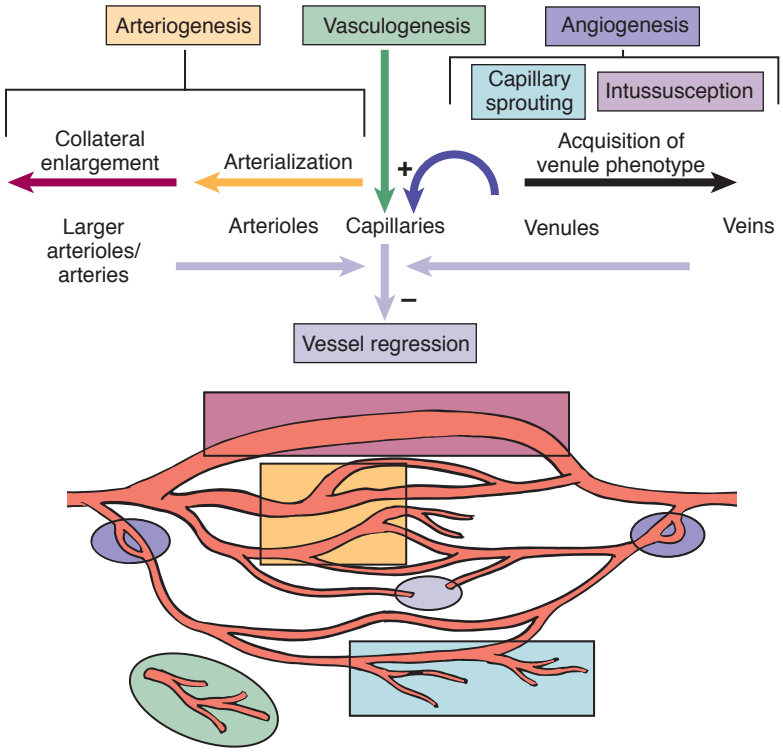

Figure 7.1 Vascular Development. Postembryonic vascular remodeling occurs in response to hypoxia and fluid shear stress and involves a complex continuum of vascular adaptations. (Redrawn from Peirce SM, Skalak TC. Microvascular remodeling: A complex continuum spanning angiogenesis to arteriogenesis. *Microcirculation.* 2003;10:99–111, with permission from Taylor & Francis Ltd. Available at http://www.tandf.co.uk/journals.)

vascular SMCs proliferate and change from a contractile to a proliferative phenotype.

Circumferential wall stress also plays a role in inducing arteriogenesis. As part of a second phase of arteriogenesis, vascular SMC growth is induced by circumferential wall stress. Increased intravascular pressure leads to SMC proliferation and increased vessel thickness. Increased vessel thickness enables normalization of circumferential wall stress at low blood pressure, which can lead to cessation of collateral vessel growth prior to the complete resolution of ischemia.[11]

The final phase of arteriogenesis involves "pruning" or regression of vessels. Poiseuille's law states that flow is proportional to radius and predicts that greater flow is observed within fewer larger arterioles rather than many smaller ones. As such, the process of "pruning" leads to regression of smaller collaterals, with persistence of a few larger collateral vessels. Vessel regression is the result of proliferation of the intima that leads to occlusion of the collateral.[11]

Cardiovascular Risk Factors Associated With Impaired Arteriogenesis

A variety of disease states perturb arteriogenesis, leading to impairment of endothelial or macrophage function. The recruitment of EPCs or growth factor production may also be impaired (Fig. 7.4). Aging itself affects arteriogenesis secondary to an overall decrease in endothelial production of NO[16] and by a higher rate of HIF degradation, along with decreased levels of VEGF, platelet-derived growth factor (PDGF), FGF-2, and chemokine signaling. Growth factor release is also impaired with aging.[16,17]

Diabetes mellitus retards vessel formation in relation to an attenuated response to the mobilization of mononuclear cells induced by granulocyte-macrophage colony-stimulating factor (GM-CSF)[18] and to impaired monocyte chemotaxis in response to VEGF.[16,17,19,20] This overall decrease in circulating EPCs leads to endothelial dysfunction and poor collateral artery formation.[16,20] In addition, eNOS is inhibited by an increase in free radicals related to diabetes.[17]

Hypertension can have a variety of effects on arteriogenesis. Elevated blood pressure can cause an increase in FSS, which stimulates arteriogenesis. Hypertension is also associated with activation of the renin-angiotensin system and subsequent activation of arteriogenesis. Angiotensin's role in regulating the inflammatory response can lead to initiation of arteriogenesis induced by inflammation. Angiotensin also stimulates increases in circulating VEGF, PDGF, and FGF, all of which stimulate arteriogenesis. Conversely, activation of angiotensin by hypertension is associated with endothelial cell dysfunction as a result of increased oxidative stress due to activation of NADPH (reduced nicotinamide adenine dinucleotide phosphate) oxidase activity. The increase in oxidative stress increases reactive oxygen and superoxide levels. These oxygen radicals uncouple eNOS, thereby reducing the availability of NO.[16,21,22]

Hyperlipidemia affects various steps in arteriogenesis and has direct toxic effect on both endothelial cells and vascular SMCs.[17] Oxidized low-density lipoprotein (LDL) cholesterol interferes with VEGF function, leading to disordered endothelial cell migration via eNOS inhibition.[17,22] In addition, endothelial cell FGF and T-lymphocyte migration are reduced, as is

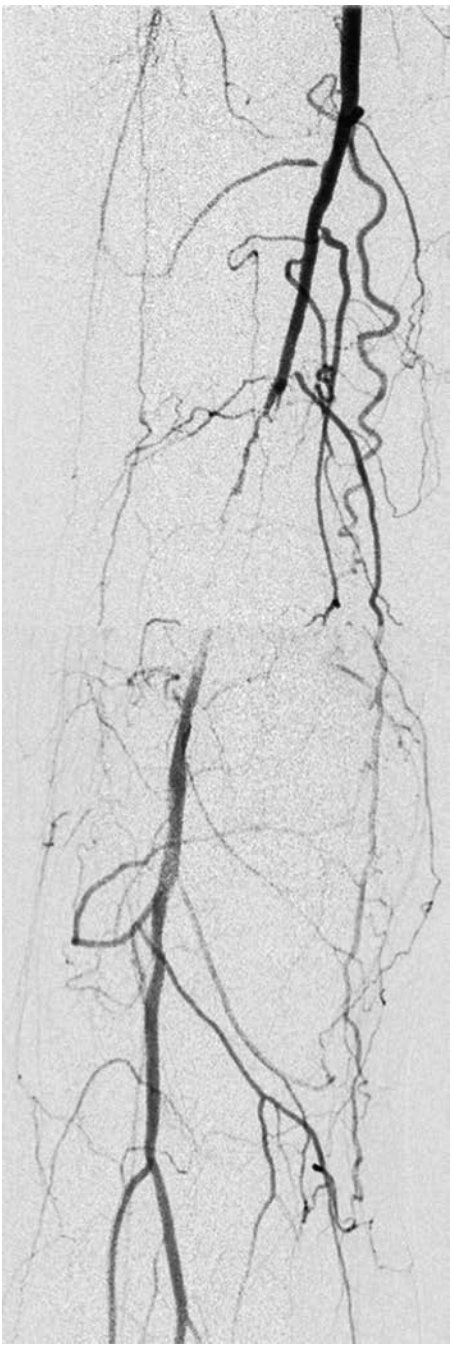

Figure 7.2 Clinical Example of Arteriogenesis. Digital subtraction arteriography of the right lower extremity in a patient with claudication. A distal superficial femoral artery (SFA) occlusion with reconstitution via collateral circulation is demonstrated. These collaterals formed via arteriogenesis in response to progressive SFA stenosis, allowing blood flow beyond the occlusion. The patient underwent successful angioplasty with stent placement, as these collaterals were insufficient to prevent symptomatic claudication (not shown). (Courtesy Paul DiMuzio, MD, Division of Vascular and Endovascular Surgery, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania.)

endothelial cell replication. Expression of FGF receptors, HIF-1, and VCAM-1 is impaired, leading to impairment of monocyte chemotaxis.[23]

Lastly, tobacco abuse impairs EPC number, function, migration, and adherence. Monocyte migration in response to VEGF is disordered with smoking. Decreased levels of VEFG and HIF-1 further impair EPC function.[16,17,22]

ANGIOGENESIS

Arteriogenesis involves the formation of collateral arteries stimulated by FSS related to upstream arterial stenosis or occlusion; in distinction, angiogenesis involves new capillary formation induced by distal tissue ischemia. Angiogenesis occurs via sprouting and nonsprouting (intussusceptive microvascular growth [IMG]) mechanisms.[24-26]

Sprouting Angiogenesis

Sprouting angiogenesis involves endothelial cell projections into surrounding connective tissue. Breakdown of the basement membrane occurs along with interendothelial junction formation, enabling endothelial cell projection.[26-28] Endothelial cells migrate along the projection's front with further sprouting, ultimately developing a complex capillary meshwork.

Sprouting angiogenesis requires specialization of cells along the migrating projection into "tip," "stalk," and "phalanx" cell phenotypes on the basis of the interaction of factors promoting or inhibiting angiogenesis.[29-34] Tip cells are polarized migratory cells that are at the forefront of the endothelial sprout. These cells branch at the tip of the stalk as they extend filopodia toward the stimulus; this is accomplished with minimal proliferation. Stalk cells conversely exhibit a proliferative phenotype responsible for the lengthening of the endothelial sprout. These cells are also responsible for secretion of basement membrane along the stalk and formation of vascular lumina from the initial luminal slit.[32,34,35] Additional stability to the proliferating stalk is provided by pericytes, which surround the basement membrane and provide further vessel coverage and decrease leakage from the vessel.[35-37] Initially, the process of sprouting requires minimal endothelial cell proliferation, although this demand increases with continued sprouting.[29,30,35]

Phalanx cells are endothelial cells that become quiescent after completion of the vascular branch. These cells deposit basement membrane and form tight cellular junctions via increased expression of vascular endothelial cadherin (VE-cadherin). These cells are ultimately responsible for delivery of oxygen and nutrients to surrounding tissues.[35,38]

Regulation of Angiogenesis

Angiogenesis is initiated by ischemia, leading to increased VEGF expression. VEGF is a potent angiogenic factor, serving to encourage endothelial cell binding to VEGF receptor 2 (VEGFR-2), which promotes endothelial chemotaxis. VEGF expression induces extension of tip cells and proliferation of stalk cells with concomitant synthesis of basement membrane components.[39-41] In addition, pericytes are attracted and contribute to capillary network formation. Whereas VEGF induces sprouting, Notch signaling pathways function to limit tip migration. Notch signaling occurs by increasing expression of VEGFR-1, competitively binding VEGF and thereby limiting

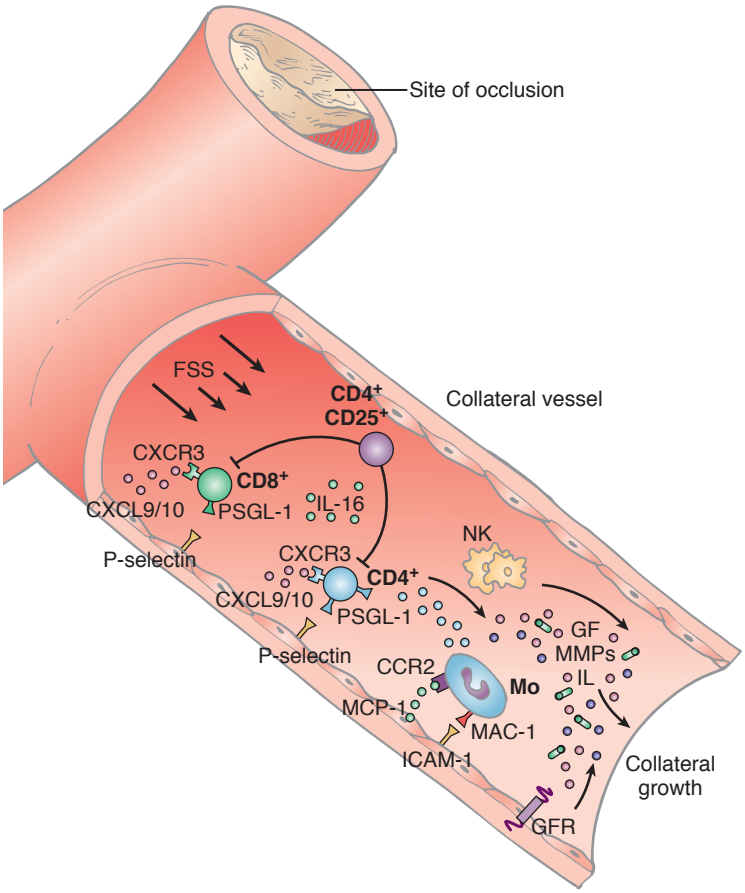

Figure 7.3 Role of Immune Cells in Arteriogenesis. With ischemia, CD8+ T cells are attracted to the growing collateral vessel and recruit CD4+ cells, which subsequently augment arteriogenesis in association with natural killer (NK) cells. Monocytes are recruited, initiating vessel growth by synthesis of angiogenic/arteriogenic cytokines. *CCR2*, CC chemokine receptor 2; *CXCL 9/10*, CXC chemokine ligand 9/10; *CXCR3*, CXC chemokine receptor 3; *FSS*, fluid shear stress; *GF*, growth factor; *GFR*, growth factor receptor; *ICAM-1*, intercellular adhesion molecule-1; *IL*, interleukin; *MAC-1*, membrane attack complex-1; *MCP-1*, monocyte chemotactic factor-1; *MMPs*, matrix metalloproteinases; *Mo*, monocytes; *PSGL-1*, P-selectin glycoprotein ligand 1. (Redrawn from Silvestre JS, Mallat Z, Tedgui A, Lévy BI. Post-ischaemic neovascularization and inflammation. *Cardiovasc Res.* 2008;78:242–249, with permission from Oxford University Press.)

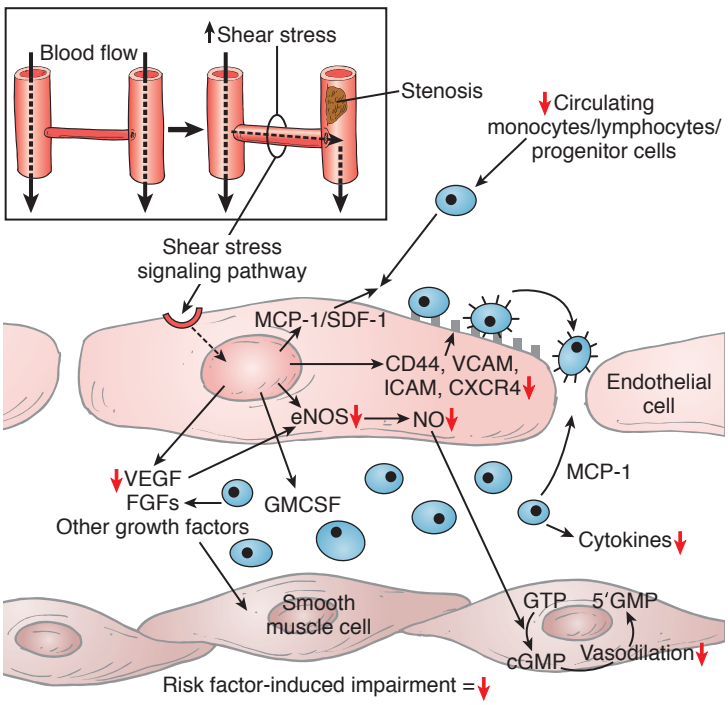

Figure 7.4 Impact of Cardiovascular Risk Factors on Arteriogenesis. With arterial stenosis or occlusion *(inset)*, there is a drop in pressure and subsequent increase in fluid shear stress (FSS). FSS initiates activation of the intracellular signaling cascade, thereby stimulating arteriogenesis. *Red arrows* indicated steps that may be negatively influenced by cardiovascular risk factors. *cGMP*, Cyclic guanosine monophosphate; *CXCR4*, CXC chemokine receptor 4; *eNOS*, endothelial nitric oxide synthase; *FGFs*, fibroblastic growth factors; *GMCSF*, granulocyte-macrophage colony-stimulating factor; *GMP*, guanosine monophosphate; *GTP*, guanosine triphosphate; *ICAM*, intercellular adhesion molecule; *MCP-1*, monocyte chemotactic factor-1; *NO*, nitric oxide; *SDF*, stromal cell-derived factor-1; *VCAM*, vascular cell adhesion molecule; *VEGF*, vascular endothelial growth factor. (Redrawn from Kinnaird T, Stabile E, Zbinden S, et al. Cardiovascular risk factors impair native collateral development and may impair efficacy of therapeutic interventions. *Cardiovasc Res.* 2008;78:257–264, with permission from Oxford University Press.)

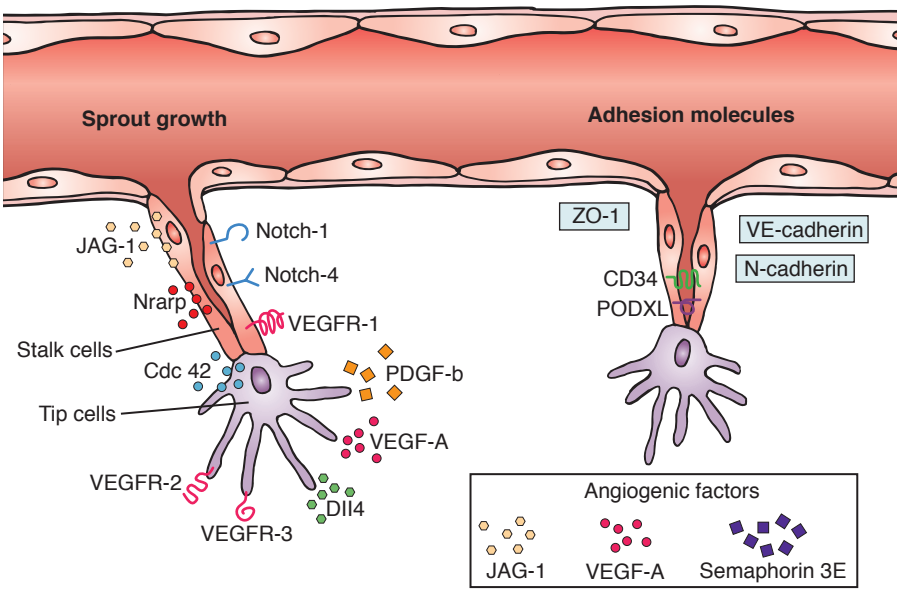

Figure 7.5 Specialization of Cell Phenotypes During Sprouting Angiogenesis. Proangiogenic and antiangiogenic factors regulate phenotypic specialization of cells into "tip," "stalk," and "phalanx" cells. Tip cells are responsible for migration of the developing vessel and formation of filopodia. Stalk cells are responsible for proliferation, lumen formation, and providing length to the developing vessel. Phalanx cells are quiescent. *Cdc 42*, Cell division control protein 42 homolog; *JAG-1*, jagged 1 gene; *Nrarp*, notch regulated ankyrin-repeat protein; *PDGF-b*, platelet-derived growth factor; *PODXL*, podocalyxin; *VEGF*, vascular endothelial growth factor; *VEGFR*, VEGF receptor; *ZO-1*, zonula occludens protein-1. (From Ribatti D, Crivellato E. "Sprouting angiogenesis," a reappraisal. *Dev Biol.* 2012;372:157–165.)

its availability.[25,31-33,42] The balance of VEGF and Notch signaling therefore regulates sprouting-related vessel development.

Transformation to a tip cell phenotype is induced by exposure of endothelial cells to VEGF. Delta-like ligand 4 (Dll4), a Notch binding ligand, is highly expressed by tip cells, increasing sensitivity to VEGF and binding to VEGFR-2.[31,32,39,43-46] Increased VEGF-VEGFR-2 binding upregulates Dll4, leading to downregulation of VEGFR-2 on adjacent endothelial cells. This process allows the tip cell to competitively maintain its position.[29,33,41,47] These adjacent cells transform into a stalk cell phenotype and express Notch, which is induced by Dll4.[31,46,48] Whereas tip cells have low Notch signaling, stalk cells express higher Notch signaling and higher expression of the jagged protein-1 (JAG-1), counteracting Notch-Dll4 activity and limiting tip cell migration (Fig. 7.5).[31,39,47-50]

Lumen Formation

Tubulogenesis, or lumen formation, is responsible for transforming endothelial stalks into vessels capable of carrying blood and nutrients to surrounding tissue. This process initially involves establishing endothelial cell apical-basal polarity, mediated by VE-cadherin. Apical borders face apposing cells, whereas the basal border faces the periphery. Beyond this first step, three proposed mechanisms may explain lumen development. The first process involves development of intracellular pinocytotic vesicles and vacuoles, which progressively fuse within the endothelial cell and then with adjacent cells, leading to lumen formation along the length of the stalk. The second mechanism is similar but involves exocytosis of these vacuoles between endothelial cells along the length of the growing stalk. These vacuoles then coalesce and form a lumen.

The third mechanism for lumen formation is by reorganization of intracellular junctions, mediated by VE-cadherin. Endothelial cells adhere to each other and become polar cells as VE-cadherin localizes CD34-sialomucins to the apical cell surface.[32,51-55] The negative charges of sialomucins lead to repulsion of adjacent surfaces of the endothelial cells, inducing lumen slit formation (Fig. 7.6).[32,51] As the lumen develops, the CD34-sialomucins are rearranged to the lateral surfaces of the cells and F-actin is attracted to the exposed lumen. VEGF attracts nonmuscle myosin II to the cell surface, with formation of an actinomyosin complex along the apical endothelial cell surface. This cytoskeletal interaction encourages cellular morphologic shape changes and further luminal expansion.[32,51-53] Beyond tubulogenesis, further increases in lumen diameter are primarily related to FSS.[29,51]

Intussusceptive Angiogenesis

Intussusceptive angiogenesis involves the formation of transcapillary tissue pillars that fuse to form new vessels. This leads to a rapid increase in the complexity of the capillary plexus and increased surface area for gas and nutrient exchange.[56-59] Initially cell contact is created between opposing capillary cells, followed by formation of a bilayer with reorganization of endothelial cell junctions. A pillar core then develops as the result of this activity. Pericytes, myofibrils, and interstitial cells are responsible for perforating the endothelial bilayer to define discrete vessels,[24,59,60] while collagen fibrils are deposited as a foundation for the developing meshwork.[60] After initial capillary formation by either vasculogenesis or sprouting angiogenesis, intussusception is initiated to allow for rapid capillary expansion and remodeling by three basic mechanisms: IMG, arborization, and intussusceptive branching remodeling (IBR).[24,59-61]

IMG initially involves formation of tissue pillars, which provides an increase in the surface area available for exchange of oxygen, carbon dioxide, and nutrients.[24,58-60]

The next phase, intussusceptive arborization, involves the development of "vertical pillars," which transform well-perfused capillary segments into arterioles and venules. This process

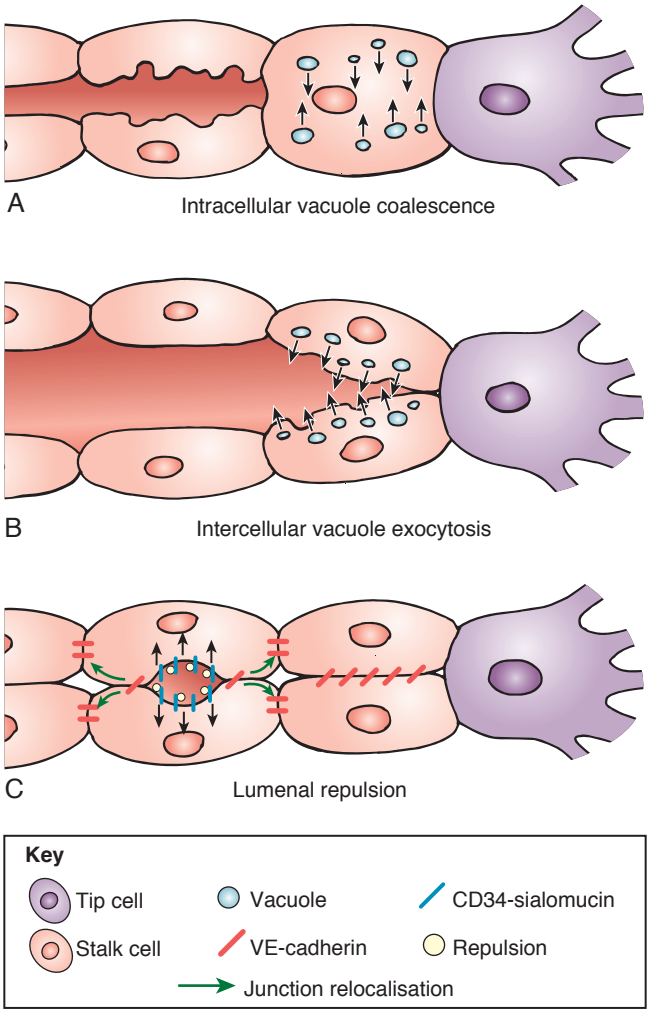

Figure 7.6 Paradigms of Lumen Formation in Angiogenesis. (A) Endothelial cells (ECs) form intracellular pinocytotic vesicles and vacuoles, which fuse within ECs and between adjacent cells, forming a lumen. (B) ECs exocytose vacuoles between cells along the growing stalk. (C) Polarization of ECs by vascular endothelial (VE)-cadherin–mediated localization of CD34-sialomucins to the EC apical surface, leading to apical-basal polarity and subsequent repulsion and lumen formation. (From Geudens I, Gerhardt H. Coordinating cell behavior during blood vessel formation. *Development.* 2011;138:4569–4583.)

decreases the distance between arteries and veins as the capillary plexus expands. Pillars form from endothelial cell reorganization and merging of developing tissue septa (Fig. 7.7). Horizontal folds develop and lead to pillar detachment from any remaining connections, ultimately separating the feeding vessel from the capillary plexus. Hemodynamic forces therefore have a role in further development of the arterial tree.[59,60,62]

IBR is the final process by which intussusception alters the vascular network. It involves adaptation of the angulation at branch points to optimize fluid hemodynamics in response to shear stress. Although this process has a role in branch remodeling, it is not involved in the formation of new capillary branches.[63] Vascular pruning also occurs with IBR because luminal obstruction leads to regression of the vessel in response to oxygen tension and growth factors, including VEGF, PDGF, and angiopoietin-1 (Ang-1).[30,59,64,65] Pruning encourages the predominance of more perfused capillaries with regression of less perfused ones (Fig. 7.8).[24,59,66]

There are multiple benefits of intussusceptive growth. One is that minimal endothelial proliferation is required given capillary expansion occurs primarily by rearrangement or remodeling of existing endothelial cells. Other advantages include low vascular permeability and minimal tissue disruption leading to less porous capillaries.[29,59,60]

Remodeling and Pruning

Remodeling of the capillary network occurs in response to the nutritional needs of local tissue. It involves growth of those vessels preferentially receiving flow, with regression of others. Vessels undergo alterations to increase in luminal diameter and mature their walls. Pruning is a dynamic process and involves vessel regression in response to luminal blood flow and possibly a reduction in VEGF. Areas with low wall shear stress undergo pruning to allow blood flow into larger bore vessels.[29,64,67]

After proliferation and remodeling are complete, blood vessels mature and stabilize largely on the basis of signaling from endothelial cells, pericytes, SMCs, and the ECM.[29,41] Pericytes invade and surround capillaries; subsequently, and likely in relation to interaction with the pericytes, the endothelial cells wrap around pericytes to stabilize the vessel.[68-70]

Postnatal angiogenesis is a dynamic process involving capillary growth related to sprouting and remodeling as directed by blood flow and the action of intussusceptive angiogenesis. Functional specialization of the endothelial cells during sprouting, regulation by VEGF and Notch signaling, and functional remodeling related to tissue metabolic needs are all hallmarks of angiogenesis.

ROLE OF MICRORNAS IN NEOVASCULARIZATION

MicroRNAs (miRNAs) are a class of short endogenous noncoding RNA molecules that regulate gene expression through inhibition of target gene translation.[71] These molecules are approximately 22 nucleotides in length and bind to the 3′-untranslated region (UTR) of target messenger RNA (mRNA).[72,73] The 3′-UTR is a specific section of mRNA following the stop codon of the coding region that contains regulatory regions which can influence post-transcriptional gene expression. The first miRNA identified was *lin-4* in 1993; they were subsequently recognized as a distinct class of regulatory RNAs in 2001.[72-74] A single miRNA can downregulate the expression of multiple target genes and thereby influence multifactorial physiologic processes.[75] In recent years, much has been discerned about miRNA and the important role it plays in post-transcriptional gene expression.

miRNAs influence both arteriogenesis and angiogenesis through interactions with various transcription factors, cytokines, and CAMs. The same miRNAs that are involved in adaptive vascular remodeling are also key regulators in maladaptive processes, such as atherosclerosis and aneurysm formation.[76] A few of the miRNAs involved include miR-126, miR-155, and

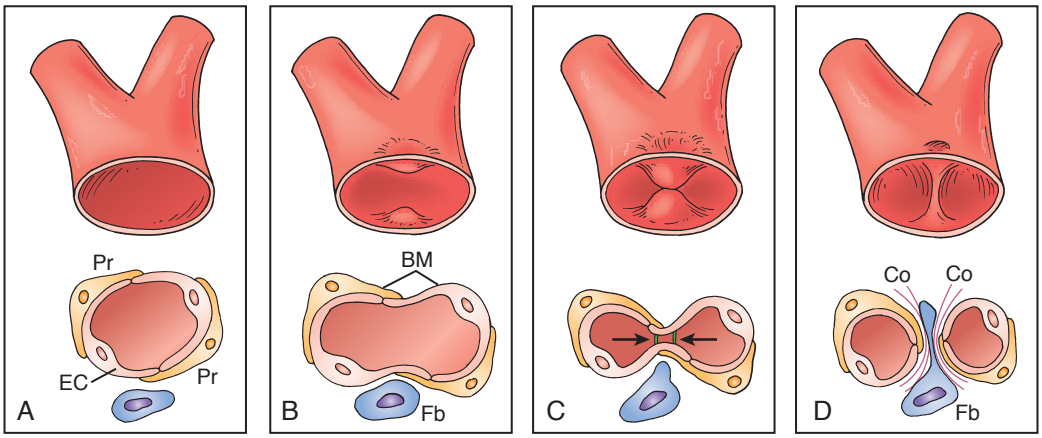

Figure 7.7 Intussusceptive Growth. (A and B) Impingement of endothelial cell wall into lumen, leading to creation of bilayer. This bilayer then develops perforations (C) leading to pillar formation (D). *BM*, Basement membrane; *Co*, collagen fibrils; *EC*, endothelial cell; *Fb*, fibroblasts; *Pr*, pericytes. (A through D from Kurz H, Burri PH, Djonov VG: Angiogenesis and vascular remodeling by intussusception: from form to function. *News Physiol Sci* 18:65-70, 2003; published by Int Union Physiol Sci/Am Physiol Soc. Entire figure is reproduced from Djonov V, Baum O, Burri PH. Vascular remodeling by intussusceptive angiogenesis. *Cell Tissue Res.* 2003;314:107–117. Published by Springer-Verlag.)

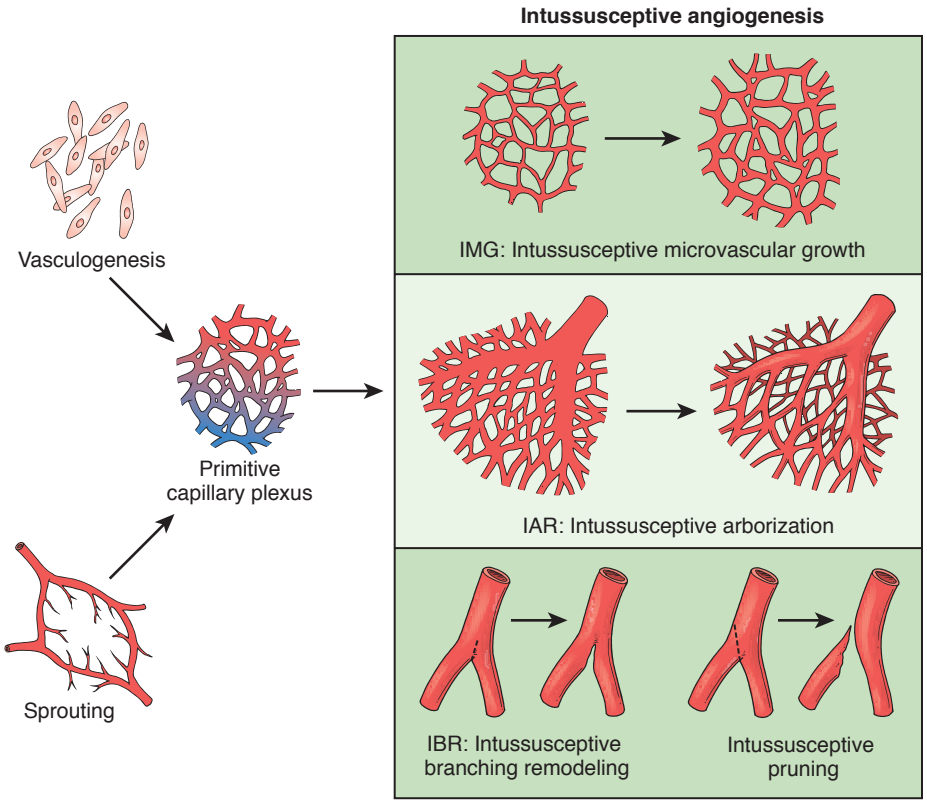

Figure 7.8 Intussusceptive Angiogenesis. The primitive capillary plexus undergoes organization and development into mature vessels via intussusceptive angiogenesis. Pillars develop by apposition of opposing capillary walls. "Vertical" pillars form and fuse, later definitively separating from the capillary plexus and forming new vessels. Local tissue demand promotes further modifications. Small diameter vessel pruning occurs due to low shear stress and possibly a decrease in vascular endothelial growth factor. (From Djonov V, Baum O, Burri PH. Vascular remodeling by intussusceptive angiogenesis. *Cell Tissue Res.* 2003;314:107–117, Springer-Verlag.)

the miRNA families miR-17/92 and miR-23/24/27.[77] The miR-126 gene is located on chromosome 9 and is one of the most abundantly expressed miRNAs in endothelial cells.[78] VCAM-1 expression has been shown to be inhibited by miR-126, which decreases leukocyte adherence to ECs and inhibits angiogenesis.[79] MiR-126 also promotes angiogenesis through inhibition of SPRED1 and PIK3R2, which are inhibitors of the VEGF signaling pathway.[80] The miR-155 gene is located on chromosome 21 and is highly expressed by activated B and T cells, as well as monocytes and macrophages.[81,82] MiR-155 has antiangiogenic as well as proarteriogenic functions through its interactions with AT1R and SOCS1, respectively.[83] It is coexpressed on SMCs with AT1R, where it inhibits the expression of AT1R and limits cell responsiveness to angiotensin II.[84] The

proarteriogenic effect of miR-155 is thought be mediated through SOCS1, which is upregulated in miR-155–deficient mice. These mice show significantly reduced levels of proarteriogenic cytokines.[83] These are only a few examples of the influence miRNAs have on neovascularization. As further progress is made in this area of study, the multifactorial role of miRNAs is certain to be expounded upon.

CLINICAL TRIALS

For a variety of reasons, patients with vascular disease may not be safe candidates for surgical intervention owing to comorbidities or extent of arterial disease. In this challenging patient population, stimulation of neovascularization via gene, protein or cell-based therapies has been proposed. Initial results of gene and protein therapies have been disappointing (Table 7.2); however, more encouraging results have been observed with cell-based therapies (Table 7.3).

Gene and Protein-Based Therapies

Vascular Endothelial Growth Factor

One of the first growth factors to be investigated was VEGF. This growth factor is responsible for promoting endothelial cell proliferation, migration, and lumen formation while inducing monocyte chemotaxis. It has been demonstrated to play an integral part in both arteriogenesis and angiogenesis.[85-94] VEGF was initially investigated in phase I clinical trials by Isner et al.[95] and Baumgarten et al.[96] With intraarterial administration of VEGF, these groups were able to demonstrate an increase in collateral vessels on arteriography, a significant improvement in ankle-brachial index (ABI), improvement in ischemic wounds, and limb salvage in three patients,[96] with the side effect of peripheral edema of the affected limb.[95] Since then several phase II clinical studies have further investigated the use of both intraarterial and intramuscular administration of VEGF.[97-99] Mäkinen et al.[97] in the VEGF peripheral vascular disease (VEGF-PVD) trial, found an increase in collateralization and an improvement in the ABI. Rajagopalan et al.[98] in the RAVE (Regional Angiogenesis with Vascular Endothelial Growth Factor) trial were unable to demonstrate any significant improvement in exercise tolerance or other quality of life indicators and found peripheral edema as a side effect. Kusumanto et al.[99] confirmed an improvement in both ABI and wound healing in a diabetic population, although no significant reduction in amputation rate was identified.

Fibroblast Growth Factor

FGF is a potent stimulator of angiogenesis and arteriogenesis. It induces proliferation, migration, and differentiation of endothelial cells and potentiates VEGF.[85,87-92,100-102] Several phase II and phase III clinical trials have studied the safety and efficacy of intraarterial and intramuscular injections of FGF. The Therapeutic Angiogenesis with Recombinant Fibroblast Growth Factor-2 for Intermittent Claudication (TRAFFIC) trial noted an improvement in exercise tolerance at 90 days, with more improvement observed in smokers, although this improvement did not persist to 180 days.[103] ABI improvements were also noted and did persist to 180 days.[103] The Therapeutic Angiogenesis Leg Ischemia Study for the Management of Arteriopathy and Non-Healing Ulcer(TALSIMAN) trial demonstrated a twofold risk reduction for all amputations and major amputations with FGF therapy, although the therapy achieved no improvement in ulcer healing when compared with placebo.[104] However, a nonsignificant trend toward a reduced mortality with intramuscular FGF was noted in the treatment population.[104] TAMARIS, the phase III trial to follow TALISMAN, was unable to replicate the reduction in amputations or mortality shown in TALISMAN.[105]

Hepatocyte Growth Factor

Hepatocyte growth factor is influential in angiogenesis because it enhances endothelial cell function by activation of the Dll4-Notch signaling pathway, inducing proliferation and migration of endothelial cells.[106-109] Investigation of intramuscular HGF injection in the HGF-STAT trial demonstrated increased transcutaneous oxygen tension ($tcPO_2$) when administered in high/moderate doses,[110] although there was no improvement in ABI, wound healing, or amputation rates. In a phase III trial by Shigematsu et al.,[111] there was 100% improvement in ulcer healing at 12 weeks and a significant improvement in quality of life, although no improvement in rest pain. Henry et al.[112] and Gu et al.[113] were both able to show an increase in median ABI and decrease in pain among patients with significant PAD using a novel form of intramuscular HGF. VM202 is a nonviral DNA plasmid that expresses two isoforms of HGF.[112,113] A more recent phase II trial involving VM202 showed significant reduction in ulcer size and an increase in $tcPO_2$ but failed to demonstrate an improvement in ABI.[114]

Developmentally Regulated Endothelial Locus-1

Developmentally regulated endothelial locus-1 (Del-1) is an angiomatrix protein capable of producing a highly angiogenic response by initiating $\alpha_v\beta_3$-dependent endothelial cell attachment and migration, upregulating an angiogenic phenotype.[108,115-117] In the DELTA (Del-1 for Therapeutic Angiogenesis) trial, intramuscular injection of Del-1 led to improvement in exercise tolerance, delayed the onset of claudication, and improved both quality of life and ABI, as demonstrated by Grossman et al.[117]

Hypoxia-Inducible Factor

HIF-1 is a transcriptional factor that regulates neovascularization in response to hypoxia. It induces gene transcription of VEGF and eNOS, promoting angiogenesis in ischemic environments. It induces vasodilatation, as well as cell proliferation and migration for sprouting angiogenesis. VEGF also recruits pericytes and SMCs and initiates ECM digestion via activation of MMP.[118-126] Creager et al.[127] have investigated HIF in the WALK (effect of HIF-1 gene therapy on walking performance in patients with intermittent claudication) trial to evaluate the effects in patients with claudication. These investigators were unable to demonstrate an improvement in exercise tolerance, claudication, quality of life, or ABI.

TABLE 7.2 Phase II/III Clinical Trials of Gene/Protein-Based Therapy

Trial (Phase)	Therapeutic Intervention	Study Group	Results
VEGF			
Mäkinen (2002)[97] VEGF in chronic limb ischemia (II)	IA VEGF-165 adenovirus/plasmid, after percutaneous transluminal angioplasty Control: LR	54 patients (18 VEGF-Ad, 17 VEGF-p, 19 LR)	Improved vascularity and ABI Rutherford class increased in both treatment and placebo groups
Rajagopalan (2003)[98] RAVE (Regional Angiogenesis with Vascular Endothelial growth factor trial) (II)	IM VEGF-121 adenovirus Control: placebo	105 patients (40 high dose, 32 low dose, 33 placebo)	No improvement in PWT Increased peripheral edema in treatment group
Kusumanto (2006)[99] VEGF in diabetes and chronic limb ischemia (II)	IM VEGF-165 adenovirus Control: NSS	54 patients with diabetes mellitus (27 VEGF-Ad, 27 NSS)	Significant improvements in ABI and ulcer healing, no reduction in amputation rates
FGF			
Lederman (2002)[103] TRAFFIC (Therapeutic Angiogenesis with Recombinant Fibroblast Growth Factor-2 for Intermittent Claudication) (II)	IA FGF-2 Control: placebo	174 patients (63 single dose, 54 double dose, days 1 and 30; 59 placebo)	Improvement in ABI at 90 and 180 days Improvement in PWT at 90 days (more improvement in smokers), not persisting to 180 days
Nikol (2008)[104] TALISMAN (Therapeutic Angiogenesis Leg Ischemia Study for the Management of Arteriography and Non-Healing Ulcer) (II)[a]	IM NV1FGF (FGF-1) Control: placebo	107 patients (51 NV1FGF, 56 placebo)	Reduction in risk of amputations, no significant improvement in ulcer healing Trend toward decrease mortality (NS)
Belch (2011)[105] TAMARIS (III)[a]	IM NV1FGF (FGF-1) Control: placebo	525 patients (259 NV1FGF, 266 placebo)	No improvement in death or major amputation
HGF			
Powell (2008)[110] HGF-STAT	IM plasmid HGF Control: placebo	106 patients (27 low dose, 26 middle dose, 27 high dose, 26 placebo)	$tcPO_2$ increased at 6 months in high/mid-dose group No improvement in ABI, TBI, pain relief, wound healing, major amputation
Shigematsu (2010)[111]	IM naked plasmid HGF Control: placebo	44 patients (30 HGFp, 14 placebo)	Improvements in ulcer healing and QOL Unable to demonstrate improvement in either ABI or rest pain
Henry (2011)[112] (I)	IM VM202(non-viral DNA plasmid) Control: none	12 patients (Dose escalation from 2-16 mg)	Improved ABI/TBI, wound healing and decreased pain
DEL-1			
Grossman (2007)[117] DELTA (Del-1 for Therapeutic Angiogenesis) (IIa)	IM VLTS-589/poloxamer 188 plasmid encoding Del-1 Control: poloxamer plasmid	105 patients (52 Del-1, 53 poloxamer 188 only)	Improvements in PWT, onset of claudication, ABI, QOL
HIF			
Creager (2011)[127] WALK (Effect of HIF-1 gene therapy on walking performance in patients with intermittent claudication) (II)	Induces gene transcription, vasodilation, and endothelial/SMC migration and proliferation to promote angiogenesis	289 patients (3 graded dosing or placebo)	No improvement in PWT, claudication, QOL, ABI

[a]TAMARIS is the phase III trial of the same group who performed TALISMAN, a phase II trial; although results in two studies were different.

ABI, Ankle-brachial index; *Ad,* adenovirus; *Del-1,* developmentally regulated endothelial locus-1; *eNOS,* endothelial nitric oxide synthase; *FGF,* fibroblast growth factor; *HGF,* hepatocyte growth factor; *HGFp,* plasmid HGF; *IA,* intraarterial; *IM,* intramuscular; *LR,* lactated Ringer solution; *NS,* nonsignificant; *NSS,* normal saline solution (0.9%); *NV1FGF,* nonviral 1 FGF; *p,* plasmid; *PVD,* peripheral vascular disease; *PWT,* peak walking time; *QOL,* quality of life; *TBI,* toe-brachial index; *$tcPO_2$,* transcutaneous oxygen tension; *VEGF,* vascular endothelial growth factor.

From Idei N, Soga J, Hata T, et al. Autologous bone-marrow mononuclear cell implantation reduces long-term major amputation risk in patients with critical limb ischemia: a comparison of atherosclerotic peripheral arterial disease and Buerger disease. *Circ Cardiovasc Interv.* 2011;4:15–25.

TABLE 7.3 Cell-Based Therapy, Human Trials[220]

Trial (Phase)	Therapeutic Intervention	Study Group	Results
EPCS			
van Royen (2005)[128] START (STimulation of ARTeriogenesis) trial (II)	SC rhGM-CSF Control: placebo	40 patients (20 rhGM-CSF, 20 Placebo)	Increased microcirculatory flow in treatment group No improvement in ABI or exercise tolerance
Kawamoto (2009)[129] EPOCH-CLI (I/IIa)	IM EPCs ($CD34^+$) Control: none	17 patients (6 low dose, 8 middle dose, 3 high dose)	Improvements in pain, TBI, pain-free walking distance, ulcer healing
Burt (2010)[130](I)	IM EPCs ($CD133^+$) Control: none	9 patients	Improvements in amputation rate, QOL
Zhang (2016) [131](II)	IV EPCs ($CD133^+$) Control: placebo	53 patients (27 treatment, 26 placebo)	Improvements in Rutherford Class, $tcPO_2$, ABI, ulcer healing, and amputation rate
BM-MNC/MSC			
Huang (2005)[217](I)	PB-MNCs Control: IV PGE_1	28 patients (14 PB-MNCs, 14 PGE_1)	Improvements in limb pain, ulcer healing, ABI, TBI, laser Doppler blood perfusion Angiogenic evidence of new vessel development
Powell (2011)[135] RESTORE-CLI (II)	IM BM-MNCs Control: placebo	46 patients (32 BM-MNCs, 14 Placebo)	Improvements in time to treatment failure, amputation free survival
Walter (2011)[134] PROVASA (II)	IA BM-MNCs Control: placebo	40 patients (19 BM-MNCs, 21 placebo), both groups received BM-MNCs at 3 months	Improvements in ulcer healing and rest pain, associated with repeat administration and BM-MNC number/function
Idei (2011)[218](I)	IM BM-MNCs Control: placebo	97 patients (25 w/atherosclerotic PAD, BM-MNCs; 26 w/ Buerger disease, BM-MNCs; 30 w/ atherosclerotic PAD, placebo; 16 w/ Buerger disease, placebo)	Buerger disease: improvements in ABI and $tcPO_2$ at 1 month and 3 years PAD: improvement in ABI at 1 month, gradual return to baseline
Iafrati (2011)[139,140] BMAC (Bone Marrow Aspirate Concentrate)(III)	IM BM-MNCs Control: placebo	48 patients (34 BM-MNCs, 14 placebo)	Improvement in amputation, pain, QOL, Rutherford classification, ABI
Lasala (2012)[136](II)	IM BM-MNCs/MSCs Control: placebo	26 patients (BM-MNCs/MSCs in more ischemic leg, placebo in contralateral)	Improvements in exercise tolerance, ABI; improved perfusion with Tc 99m tetrofosmin scintigraphy
Losordo (2012)[219](I)	IM $CD34^+$ cells—high/low dose, placebo	28 patients	Increased amputation free survival, further increase in high dose group
Fully Differentiated Cells			
Grossman (2016)[141](I) MultiGeneAngio(MGA)	IA MGA(fully differentiated venous ECs expressing Ang-1[angiopoetin-1] and SMCs expressing VEGF-165) Control: none	12 patients (Dose increases across 3 cohorts)	Improvement in mean PWT, COT ABI did not decrease over study period
Ongoing or Recruiting Phase III Clinical Trials (clinicaltrials.gov)[a]			
Maggi SCELTA (III) NCT02454231 Recruiting	Randomized, single center study evaluating IM BM-MNCs vs PB-MCs	(BM-MNCs vs. PB-MCs)	Primary outcome: Improvement in perfusion, evaluated by ultrasound Secondary outcomes: ABI, $tcPO_2$, QOL, rest pain, amputation
Dong (III) NCT02089828 Recruiting	Randomized, single blinded study evaluating purified $CD34^+$ cells vs. PB-MNCs	($CD34^+$ EPCs vs PB-MNCs)	Primary outcome: major amputation free survival Second outcomes: $tcPO_2$, peak pain-free walking time

[a]First researcher's name, trial acronym, and study number given. Information available online from clinicaltrials.gov.

ABI, Ankle-brachial index; *BM,* bone marrow; *BM-MNC,* bone marrow–derived mononuclear cell; *BM-MNCs/MSCs,* bone marrow–derived mononuclear and mesenchymal stem cells; *CLI,* critical limb ischemia; *COT,* claudication onset time; *EC,* endothelial cell; *EPCs,* endothelial progenitor cells; *IA,* intraarterial; *IM,* intramuscular; *MGA,* MultiGeneAngio; *NS,* nonsignificant; *PAD,* peripheral arterial disease; *PGE_1,* prostaglandin E_1; *PWT,* peak walking time; *QOL,* quality of life; *rhGM-CSF,* recombinant human granulocyte-macrophage colony-stimulating factor; *SC,* subcutaneous; *TBI,* toe-brachial index; *$tcPO_2$,* transcutaneous oxygen tension.

From Cooke JP, Losordo DW. Modulating the vascular response to limb ischemia: angiogenic and cell therapies. *Circ Res.* 2015;116(9):1561–1578.

Cell-Based Therapies

Endothelial Progenitor Cells

EPCs are derived from bone marrow or peripheral blood and are responsible for initiating postnatal vasculogenesis, given their ability to proliferate and provide both cytokines and growth factors necessary for vessel development.[108,128] Investigation has focused on using recombinant human GM-CSF (rhGM-CSF) to stimulate release of these cells from bone marrow into the peripheral blood for use in initiating angiogenesis in the patients with PAD.

The START (STimulation of ARTeriogenesis using subcutaneous application of GM-CSF as a new treatment for peripheral vascular disease) trial, a phase II clinical trial conducted by van Royen et al.[128] described efficacy of the use of rhGM-CSF in 40 patients with moderate to severe claudication. There was a tendency toward higher peak flow and peak-minus rest flow in the group treated with rhGM-CSF, thought to be related to enhanced endothelial function at the level of the microcirculation. These researchers were able to demonstrate only a temporary increase in monocyte and CD34 stem cell counts over the study period. In addition, a large placebo effect was experienced because both the treatment and placebo groups experienced an increase in walking distance over a 2-week period.[128]

Another phase I/IIa clinical trial, conducted by Kawamoto et al.,[129] concentrated on the use of GM-CSF–mobilized CD34 EPCs in patients with CLI and no options for vascularization or with Buerger disease and CLI. GM-CSF apheresis was used to mobilize the EPCs for use as intramuscular injections in a population of 17 patients. The findings indicated that use of CD34 EPCs was safe and effective because patients experienced improvements in pain, in pain-free walking distance, and wound healing. In addition, toe-brachial index and $tcPO_2$ were improved.[129]

EPCs were also studied by Burt et al.[130] in a phase I trial using GM-CSF–mobilized CD133+ cells from patients with CLI and no other options for revascularization. Intramuscular injection of CD133+ EPCs was found to be safe and was able to prevent amputation in seven of nine patients. In addition, quality of life improved at 3 and 6 months, but effects did not persist at 1 year. A trend toward improvement in symptom-free ambulation and increased exercise capacity was noted at 1 year, although there was no improvement in ABI.[130] Zhang et al.[131] used intraarterial CD133+ cells to improve microvascular circulation and promote angiogenesis in patients with CLI. They first improved flow on a macroscopic level by performing angioplasty on infraaortic and infrapopliteal lesions. In patients with restored flow through either the anterior/posterior tibial or peroneal arteries, significant improvements in ABI, $tcPO_2$, and Rutherford classification were seen at 18 months.[131] Overall, the therapeutic use of EPCs has been shown to achieve modest enhancement of angiogenesis and microcirculatory flow.

Bone Marrow–Derived Cells

BMCs include endothelial stem and progenitor cells, hemangioblasts, angioblasts, and mesenchymal and hematopoietic stem cells. Some of these cell lines are able to differentiate into endothelial cells for angiogenesis,[108,132,133] whereas others, including mesenchymal and hematopoietic stem cells, are not. Most BMCs, regardless of ability to transform into endothelial cells, are proangiogenic and participate in angiogenesis via paracrine signaling and/or the ability to take on endothelial cell–like characteristics.[132]

Phase II clinical trials have been conducted focusing on the safety and efficacy of intraarterial or intramuscular injection of BM-MNCs with or without bone marrow–derived mesenchymal stem cells (BM-MSCs). Initial results have been promising in the treatment of patients with CLI. In the PROVASA trial, a multicenter, double-blinded, randomized phase II trial, Walter et al.[134] examined 40 patients with severe CLI who received intraarterial BM-MNCs or placebo. At 3 months, all patients (treatment and placebo groups) received intraarterial BM-MNCs. In the treatment group a significant improvement was seen in ulcer healing and rest pain within 3 months. Both increased number and functionality of the BM-MNCs and repeated administration were associated with greater improvements in wound healing, which then correlated with limb salvage. There was no difference in amputation-free survival or improvement in ABI between the groups.[134]

Two trials have been conducted using a combination product of BMCs. In the RESTORE-CLI trial (a randomized, double-blind multicenter phase II trial comparing expanded autologous bone marrow-derived tissue repair cells[TRCs] and placebo), Powell et al.[135] evaluated patients with CLI and no options for revascularization. Bone marrow aspiration was performed in 46 patients, and the aspirate was processed to obtain a population of TRCs. This cell population represents a collection of nucleated cells, including endothelial, mesenchymal, and hematopoietic stem and progenitor cells.[133,135] With intramuscular injection of TRCs, improvement was seen in time to treatment failure and in amputation-free survival. There was also a nonsignificant trend toward wound healing in the treatment group.

Lasala et al.[136] also conducted a single-center, prospective, nonrandomized, placebo-controlled phase II clinical trial of the intramuscular injection of a similar combination bone marrow product. Their findings demonstrated improvement in walking time and ABI as well as increased perfusion when evaluated with technetium (Tc 99m) tetrofosmin scintigraphy. The purpose of using a BMC combination product, as in these two trials, is to provide growth factors, ECM molecules, and pericytes that are provided by MSC to interplay with EPCs for enhanced vascular growth and repair.[135-137]

A meta-analysis was conducted of 37 trials (controlled/noncontrolled and randomized/nonrandomized) using G-CSF–mobilized peripheral blood cells (PBCs) or autologous BMCs in patients with PAD.[138] Intramuscular administration, rather than intraarterial, and the use of BMCs, rather than PBCs, were found to be more effective and safe. BMCs were found to improve subjective symptoms, including pain and pain-free walking distance. There was also a significant improvement in ulcer healing. $tcPO_2$ was greater in the treatment group, as was ABI. Comparatively, only a slight and nonsignificant improvement in pain scale was seen with PBCs mobilized by G-CSF.[138]

Although early clinical trials using PBCs mobilized by G-CSF did not yield promising results, clinical trials using BMCs are continuing to demonstrate exciting and promising results in the treatment of CLI. Iafrati et al.[139,140] conducted a randomized, placebo-controlled, phase III trial using BM-MNCs in a group of 48 patients with Rutherford classification 4 and 5. Follow-up at 3 months showed an improvement in pain, quality of life, ABI, and Rutherford classification, as well as decreased rates of amputation in the study group. Further follow-up at 6 months demonstrated a decrease in amputation rates among study patients.[140]

Fully Differentiated Cells

There have been few studies evaluating the role of fully differentiated cells and their use in PAD. Grossman et al.[141] used a combination of fully differentiated autologous venous SMCs expressing VEGF-165 and endothelial cells expressing Ang-1 in a phase I trial. These cells were isolated from a short superficial vein segment, either basilic or cephalic, from the individual's arm. The endothelial and SMCs were transduced ex vivo using pseudo-typed retroviral vectors encoding Ang-1 and VEGF-165, respectively. Following cell processing, the therapeutic combination was administered intraarterially in the subject's most symptomatic leg, and they were monitored for 1 year. This trial demonstrated an increase in mean peak walking time and claudication onset time, as well as no decrease in ABI over the study period. Phase II trials using this unique combination, termed MultiGeneAngio (MGA), are currently ongoing.

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8 CHAPTER

Arterial Hemodynamics

R. EUGENE ZIERLER

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Based on contributions from previous editions by R. Eugene Zierler and David S. Sumner.

Obstruction of the vessel lumen is the primary physiologic abnormality in arterial disease—whether it be the result of atherosclerosis, fibromuscular dysplasia, thrombi, emboli, dissection, trauma, or external compression. The consequences of arterial obstruction are related to the degree of narrowing and can be analyzed in terms of hemodynamic principles. Effects on the distal vascular bed depend not only on the severity of the local obstructive lesion but also on the ability of the body to compensate by increasing cardiac work, dilating peripheral arterioles, and recruiting collateral pathways. Except for thrombus formation and occasional dissection, aneurysms seldom produce symptoms of obstruction. The tendency for aneurysms to rupture is determined by both intraluminal pressure and arterial diameter.

BASIC CONCEPTS

Fluid Energy

Although the motion of the blood is generally attributed to pressure gradients, blood flows through the arterial system in response to differences in total fluid energy. The pressure in a fluid system is defined as force per unit area, with units such as dynes per square centimeter (dyn/cm^2) or millimeters of mercury (mm Hg). Intravascular arterial pressure (P) has three components: (1) dynamic pressure produced by cardiac contraction, (2) hydrostatic pressure, and (3) static filling pressure.[1] Hydrostatic pressure depends on the specific gravity of blood and the height of the point of measurement above or below a specific reference level, which is usually considered to be the right atrium. The hydrostatic pressure is given by

$$P(\text{hydrostatic}) = -\rho g h, \qquad \textbf{(8.1)}$$

where ρ is the specific gravity of blood (~1.056 g/cm^3), g is the acceleration due to gravity (980 cm/sec^2), and h is the distance in centimeters above or below the right atrium. The magnitude of hydrostatic pressure may be relatively large. For example, in a man 5 feet 8 inches tall, the hydrostatic pressure at ankle level is approximately 90 mm Hg. In contrast, static filling pressure is low, usually about 7 mm Hg, and is determined by the volume of blood and the elastic properties of the vessel wall.[2]

Total fluid energy (E) consists of potential energy (E_p) and kinetic energy (E_k). The components of E_p are intravascular pressure (P) and gravitational E_p. Gravitational E_p represents the ability of blood to do work because of its height above a

specific reference level. The formula for gravitational E_p is the same as that for hydrostatic pressure but with an opposite sign: $+\rho gh$. Because the static filling pressure is relatively low, and the gravitational E_p and hydrostatic pressure usually cancel each other out, the predominant component of E_p is the dynamic pressure of cardiac contraction. Potential energy can be expressed as

$$E_p = P + (\rho gh). \quad \textbf{(8.2)}$$

E_k represents the ability of blood to do work because of its motion and is proportional to the specific gravity of blood and the square of blood velocity (v):

$$E_k = \tfrac{1}{2}\rho v^2. \quad \textbf{(8.3)}$$

When fluid flows from one point to another, the total fluid energy (E) remains constant, provided that flow is steady and there are no frictional energy losses. This is in accordance with the law of conservation of energy and constitutes Bernoulli's principle. This explains some apparent paradoxes of fluid flow. For example, in Fig. 8.1A, fluid with the density of blood enters the top of an inclined tube at a pressure of 100 mm Hg and flows out at a pressure of 178 mm Hg. Thus fluid moves against a pressure gradient; however, the total fluid energy remains constant because the gravitational E_p decreases by an amount exactly equal to the increase in pressure. In the horizontal diverging tube shown in Fig. 8.1B, steady flow between the entrance and exit is accompanied by an increase in cross-sectional area and a decrease in flow velocity. The widening of the tube results in conversion of E_k to E_p in the form of pressure. Although the fluid moves against a pressure gradient of 2.5 mm Hg and therefore gains E_p, the total fluid energy remains constant because of the decrease in velocity and a proportional loss of E_k. This phenomenon is seldom observed in the human circulation, because associated energy losses effectively mask the rise in pressure. The fluid energy lost in moving blood through the arterial circulation is dissipated mainly in the form of heat.

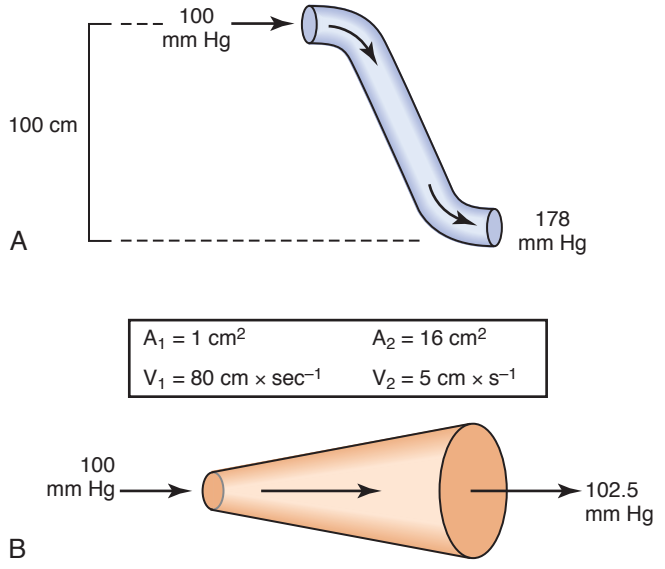

Figure 8.1 (A) Effect of vertical height on pressure in a frictionless fluid flowing downhill. (B) Effect of increasing cross-sectional area on pressure in a frictionless fluid system. A_1 and A_2, areas at the entrance and exit of the system, respectively; V_1 and V_2, velocities at the entrance and exit of the system, respectively.

Poiseuille's Law and Vascular Resistance

Energy losses in flowing blood occur either as viscous losses resulting from friction or as inertial losses related to changes in the velocity or direction of flow. The term *viscosity* describes the resistance to flow that arises because of the intermolecular attractions between fluid layers. Fluids with particularly strong intermolecular attractions offer a high resistance to flow and have high coefficients of viscosity. Because blood viscosity increases exponentially with increases in hematocrit, the concentration of red blood cells is the most important factor affecting the viscosity of whole blood. The viscosity of plasma is determined largely by the concentration of plasma proteins. Poiseuille's law describes the viscous energy losses that occur in an idealized flow model. This law states that the pressure gradient between two points along a tube (P_1–P_2) is directly proportional to the mean flow velocity ($\bar{V}$) or volume flow (Q), the tube length (L), and the fluid viscosity (η), and is inversely proportional to either the second or the fourth power of the radius (r):

$$P_1 - P_2 = \bar{V}\frac{8L\eta}{r^2} = Q\frac{8L\eta}{\pi r^4}. \quad \textbf{(8.4)}$$

This equation is often simplified to (pressure = flow × resistance), where the resistance term (R) is

$$R = \frac{8L\eta}{\pi r^4}. \quad \textbf{(8.5)}$$

The hemodynamic resistance of an arterial segment increases as the flow velocity increases, provided the lumen size remains constant, and these additional energy losses are related to inertial effects or changes in kinetic energy and are proportional to the square of blood velocity (Eq. 8.3).

The strict application of Poiseuille's law requires steady (nonpulsatile) laminar flow in a straight, rigid, cylindrical tube. Because these conditions do not exist in the arterial circulation, Poiseuille's law can only estimate the minimum pressure gradient or viscous energy losses that could be expected in arterial flow. Energy losses due to inertial effects typically exceed viscous energy losses, particularly in the presence of arterial stenoses. In the human circulation, approximately 90% of the total vascular resistance results from flow through the arteries and capillaries, whereas the remaining 10% results from venous flow. The arterioles and capillaries are responsible for over 60% of the total resistance, whereas the large and medium-sized arteries account for only about 15%.[3] Therefore the arteries that are most commonly affected by atherosclerotic occlusive disease are normally very low resistance vessels.

Normal Pressure and Flow

As the arterial pressure pulse moves distally, the systolic pressure rises, the diastolic pressure falls, and the pulse pressure becomes wider. The decrease in mean arterial pressure between the heart and the ankle is normally less than 10 mm Hg. In normal

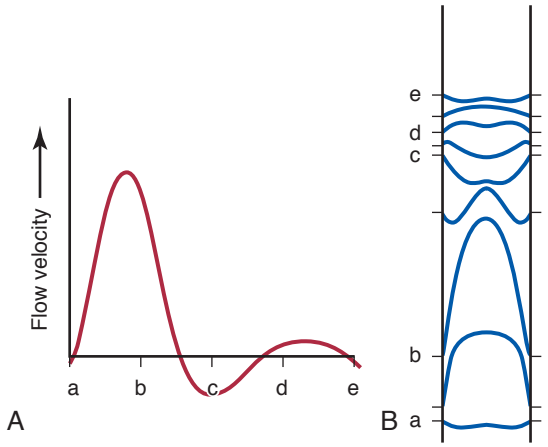

Figure 8.2 Phases of a normal femoral arterial flow pulse (A) and the corresponding velocity profiles (B). *Lowercase letters* indicate corresponding points in the cardiac cycle. For all profiles, the velocity at the wall is zero. At point *b,* forward flow is nearly maximal and the profile is almost parabolic. At the next point, flow near the wall is reversed but that in the center continues forward. Several profiles, both forward and reverse, are blunt in shape. (Adapted from McDonald DA. *Blood Flow in Arteries.* 2nd ed. Baltimore: Williams & Wilkins; 1974.)

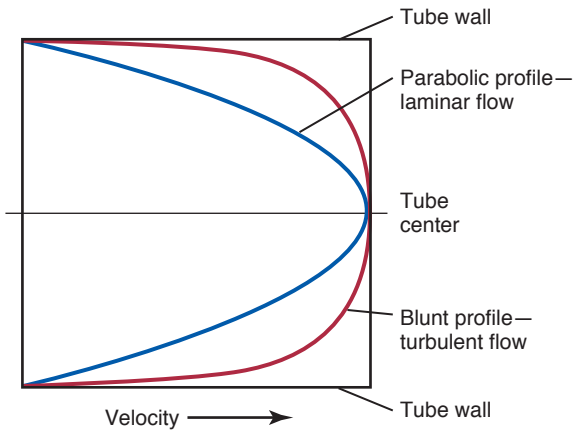

Figure 8.3 Velocity profiles of steady laminar and turbulent flow. Velocity is lowest adjacent to the tube wall and maximal in the center of the lumen. (From Sumner DS: The hemodynamics and pathophysiology of arterial disease. In Rutherford RB, ed. *Vascular Surgery.* Philadelphia: WB Saunders; 1977.)

individuals, the ratio of ankle systolic pressure to brachial systolic pressure (ankle-brachial index) has a mean value of 1.11 ± 0.10 in the resting state.[4] Moderate exercise in normal extremities produces little or no drop in ankle systolic pressure. Very strenuous effort may be associated with a relatively mild decrease in ankle systolic pressure; however, pressures return rapidly to resting levels after cessation of exercise.[5]

The velocity or flow pulse in the major arteries of the leg is normally described as *triphasic*, as shown in Fig. 8.2A. An initial large forward flow phase resulting from cardiac systole is followed by a brief second phase of reversed flow in early diastole and a third smaller phase of forward flow in late diastole. The phase of reversed flow is caused by reflected waves produced when the initial surge of forward flowing blood encounters the high resistance imposed by the arterioles, and these reflected waves subtract from the forward flow. As will be discussed, this triphasic flow pattern is modified by a variety of factors, including proximal arterial disease and changes in peripheral resistance. For example, body warming, which causes vasodilatation and decreased resistance, tends to eliminate the second phase of flow reversal; on exposure to cold, resistance increases and the reversed flow phase becomes more prominent.

The average blood flow in the normal human leg is in the range of 300 to 500 mL/minute under resting conditions.[6] Blood flow to the muscles of the lower leg is approximately 2.0 mL/100 g/minute. With moderate exercise, total leg blood flow increases by a factor of 5 to 10, and muscle blood flow rises to around 30 mL/100 g/minute. During strenuous exercise, muscle blood flow may reach 70 mL/100 g/minute.

Blood Flow Patterns

Laminar and Turbulent Flow

In the idealized flow conditions specified by Poiseuille's law, the flow pattern is *laminar*, with all flow streamlines moving parallel to the tube walls and the fluid arranged in a series of concentric layers or laminae. The velocity within each lamina remains constant, with the lowest velocity adjacent to the tube wall and increasing velocity toward the center of the tube. This results in a velocity profile that is parabolic in shape (see Figs. 8.2B and 8.3).

In contrast to the uniform, linear streamlines of laminar flow, *turbulence* is an irregular flow state in which velocity varies randomly with respect to location and time. These irregular velocity changes result in the dissipation of fluid energy as heat. When turbulence is the result of a stenotic arterial lesion, it generally occurs immediately downstream from the stenosis and may be present only during the systolic portion of the cardiac cycle when velocities are highest. Under conditions of turbulent flow, the velocity profile changes from the parabolic shape of laminar flow to a rectangular or blunt shape (see Fig. 8.3). Because of the random velocity changes, energy losses are much greater for a turbulent flow state than for a laminar flow state.

Boundary Layer Separation

When fluid flows through a tube, the portion of fluid adjacent to the tube wall is referred to as the *boundary layer*. This layer is subject to both frictional interactions with the tube wall and viscous forces generated by the more rapidly moving fluid toward the center of the tube. When the tube geometry changes, such as at points of curvature, branching, or alteration in lumen diameter, small pressure gradients are created that cause the boundary layer to stop or reverse direction. This results in a complex, localized flow pattern known as an *area of flow separation* or *separation zone*.[7,8] Boundary layer separation has been observed in models of arterial anastomoses and bifurcations (Fig. 8.4).[8-10] In the diagram of a carotid bifurcation shown in Fig. 8.5, the central rapid flow stream of the common carotid artery is compressed along the inner wall of the bulb, producing a region of high shear stress, with an area of flow separation along the outer wall of the carotid bulb that includes helical flow patterns and flow reversal. The region of the carotid bulb adjacent to the separation zone is subject to relatively low shear

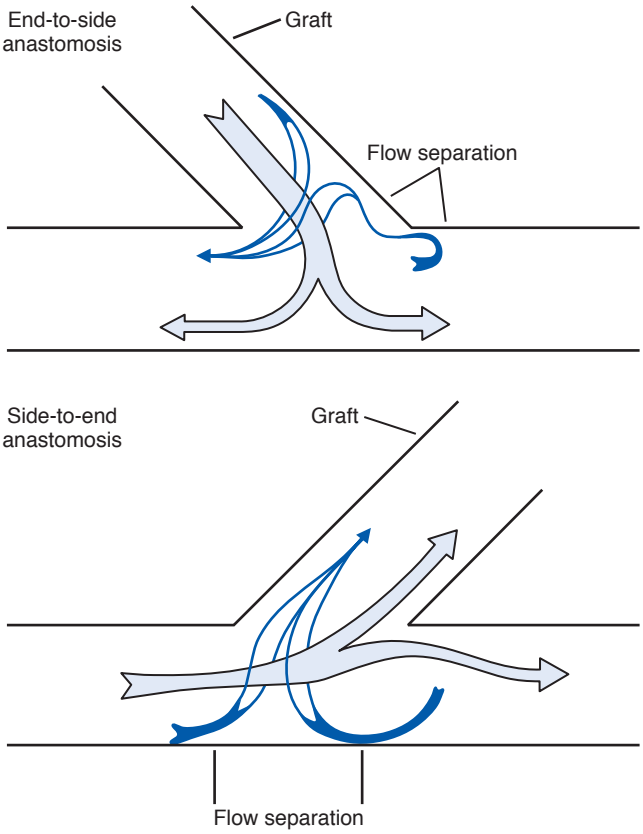

Figure 8.4 Flow patterns at end-to-side and side-to-end anastomoses. Near the wall, blood flow may reverse and travel circumferentially to reach the recipient conduit. Areas of flow separation are prone to the development of neointimal hyperplasia. (Redrawn from Sumner DS: Hemodynamics of abnormal blood flow. In: Veith FJ, et al., eds. *Vascular Surgery: Principles and Practice.* 2nd ed. New York: McGraw-Hill; 1994.)

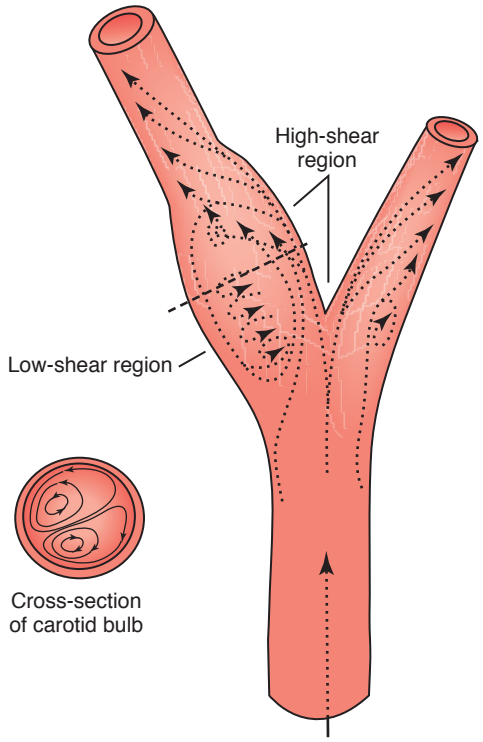

Figure 8.5 Carotid artery bifurcation showing an area of flow separation (low shear region) adjacent to the outer wall of the bulb. Rapid flow along the inner wall of the bulb is associated with high shear stress. *Arrows* indicate direction of flow. (Redrawn from Zarins CK, et al: Atherosclerotic plaque distribution and flow velocity profiles in the carotid bifurcation. In: Bergan JJ, Yao JST, eds. *Cerebrovascular Insufficiency.* New York: Grune & Stratton; 1983.)

stresses. Within the internal carotid artery distal to the bulb, flow reattachment occurs and a more laminar flow pattern is present.

The complex flow patterns described in models of the carotid bifurcation have also been documented in human subjects by pulsed Doppler studies.[9,10] As shown in Fig. 8.6A, the Doppler spectral waveform obtained near the inner wall of a normal carotid bulb is typical of the forward flow pattern found in the internal carotid artery. However, sampling of flow along the outer wall of the bulb demonstrates lower velocities with periods of both forward and reverse flow that are consistent with flow separation. Flow separation in the carotid bulb can also be seen with color-flow imaging, as shown in Fig. 8.6B. This is considered to be a normal finding and is particularly common in young individuals.[5] Wall-thickening in the carotid bulb and alterations in arterial distensibility with increasing age make flow separation less prominent in older individuals.[11]

The clinical importance of boundary layer separation is that these localized flow disturbances may contribute to the formation of atherosclerotic plaques.[12] Examination of human carotid bifurcations, both at autopsy and during surgery, indicates that intimal thickening and atherosclerosis tend to occur along the outer wall of the carotid bulb, whereas the inner wall is relatively spared. These findings suggest that atherosclerotic lesions form near areas of flow separation and low shear stress.

Pulsatile Flow

In a pulsatile system, pressure and flow vary with time, and the velocity profile changes throughout the cardiac cycle. The hemodynamic principles that have been discussed are based on steady flow, and they cannot be applied to pulsatile flow in the arterial circulation; however, they can be used to determine the minimum energy losses that would be expected in a specific flow system. The resistance term of Poiseuille's law (Eqs. 8.4 and 8.5) estimates viscous energy losses in steady flow, but it does not account for the inertial effects, arterial wall elasticity, and wave reflections that influence pulsatile flow. The term *vascular impedance* is used to describe the resistance or opposition offered by a peripheral vascular bed to pulsatile blood flow.[6]

Bifurcations and Branches

Although the branches of the arterial system produce sudden changes in the flow pattern that are potential sources of energy loss, the effect of branching on the total pressure drop in normal arterial flow is relatively small. Arterial branches commonly take the form of bifurcations. Flow patterns in a bifurcation are determined mainly by the area ratio and the branch angle. The area ratio is defined as the combined area of the secondary

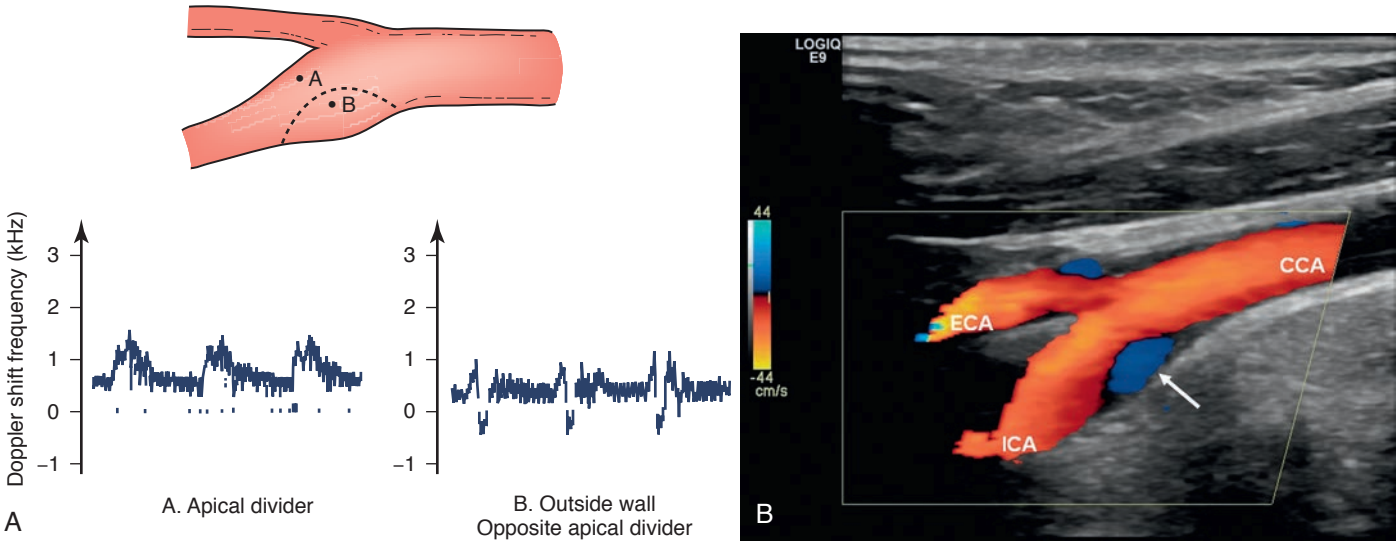

Figure 8.6 (A) Flow separation in a normal carotid bulb shown by pulsed Doppler spectral analysis. The flow pattern near the apical divider *(point A)* is forward throughout the cardiac cycle, but near the opposite wall *(point B)*, the spectral waveform contains both forward (positive) and reverse (negative) components. The latter pattern indicates an area of flow separation. (B) Color-flow image of a normal carotid bifurcation showing an area of flow separation *(white arrow)* adjacent to the outer wall of the proximal internal carotid artery *(ICA)*. The area of flow separation appears blue owing to the presence of reverse flow. *CCA,* Common carotid artery; *ECA,* external carotid artery.

branches divided by the area of the primary artery. Bifurcation flow can be analyzed in terms of pressure gradient, velocity, and transmission of pulsatile energy. According to Poiseuille's law, an area ratio of 1.41 would allow the pressure gradient to remain constant along a bifurcation. If the combined area of the branches equals the area of the primary artery, then the area ratio is 1.0 and there is no change in the velocity of flow. For efficient transmission of pulsatile energy across a bifurcation, the vascular impedance of the primary artery should equal that of the branches, a situation that occurs with an area ratio of 1.15 for larger arteries and 1.35 for smaller arteries.[13] Human infants have a favorable area ratio of 1.11 at the aortic bifurcation, but the ratio gradually decreases with age. This decline in the area ratio of the aortic bifurcation leads to an increase in both the velocity of flow in the secondary branches and the amount of reflected pulsatile energy. For example, with an area ratio of 0.8, approximately 22% of the incident pulsatile energy is reflected back to the infrarenal aorta. This mechanism may play a role in the localization of atherosclerosis and aneurysms in this arterial segment.[14]

The curvature and angulation of an arterial bifurcation can also contribute to the development of flow disturbances and energy loss. As blood flows around a curve, the rapidly moving fluid in the center of the vessel tends to flow outward and be replaced by the slower fluid originally located near the arterial wall. This can result in complex helical flow patterns, such as those observed in the carotid bifurcation.[9] As the angle between the secondary branches of a bifurcation widens, the tendency to develop turbulent or disturbed flow increases. The average angle between the human iliac arteries is 54 degrees; however, with diseased or tortuous iliac arteries, this angle can approach 180 degrees, and flow disturbances are particularly likely to develop.

ARTERIAL STENOSIS

Energy Losses

According to Poiseuille's law (Eq. 8.4), the radius of a stenosis has a much greater effect on viscous energy losses than its length. Inertial energy losses, which occur at the entrance (contraction effects) and exit (expansion effects) of a stenotic segment, are proportional to the square of blood velocity (Eq. 8.3). Energy losses are also influenced by the geometry of a stenosis. A gradual vessel tapering results in less energy loss than an irregular or abrupt change in lumen size. The energy lost at the exit of a stenosis may be quite significant because of the sudden expansion of the flow stream and dissipation of kinetic energy in a zone of turbulence. Fig. 8.7 illustrates the energy losses related to a 1-cm-long stenosis. The viscous energy losses are relatively small and occur within the stenotic segment. Inertial losses due to entrance and exit effects are much greater. Because most of the energy loss in this example results from inertial effects, the length of the stenosis is relatively unimportant.

Critical Stenosis

The extent of arterial narrowing required to produce a significant reduction in blood pressure or flow is called a *critical stenosis*. Because the energy losses associated with a stenosis are inversely proportional to the fourth power of the radius (Eq. 8.4), there is an exponential relationship between pressure drop and reduction in lumen size. When this relationship is illustrated graphically (Fig. 8.8), the pressure curves have a single sharp bend, and further narrowing results in a rapid increase in the magnitude of the pressure drop.[15,16] In peripheral arteries with physiologic flow rates, the critical stenosis value is reached at approximately

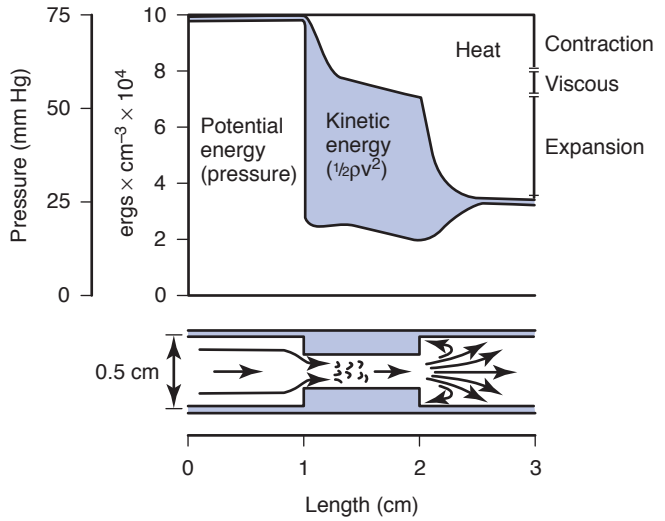

Figure 8.7 Diagram illustrating the energy losses that occur when blood passes through a stenosis 1 cm long. Flow is assumed to be unidirectional and steady. Very little of the total energy loss is attributable to viscous effects, so application of Poiseuille's law will greatly underestimate the drop in pressure across an arterial stenosis. Inertial energy losses due to entrance and exit effects are much greater.

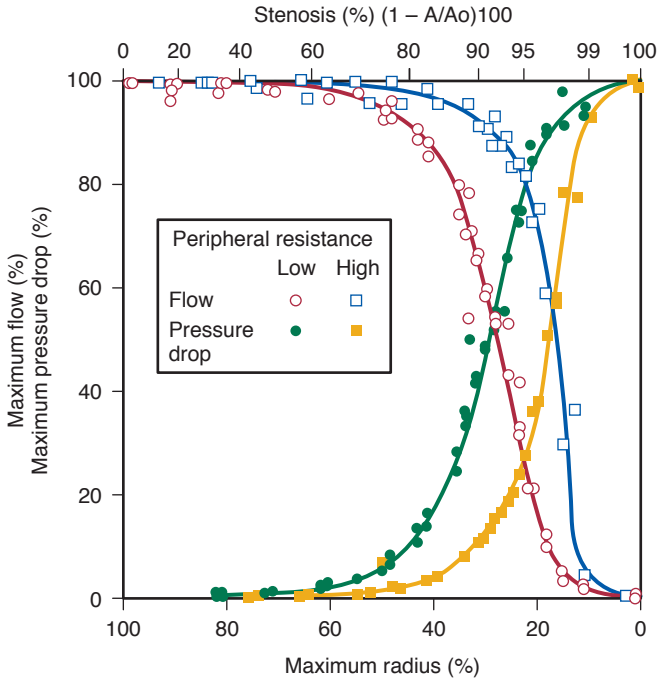

Figure 8.8 Relationship of pressure and flow to the degree of stenosis in a canine femoral artery. When peripheral resistance is high, the curves are shifted to the right. The percentage change in flow through the stenosis is essentially a mirror image of the percentage maximal drop in pressure across the stenosis.

a 50% reduction in lumen diameter or a 75% reduction in cross-sectional lumen area.

Whereas lumen size is the most prominent feature of an arterial stenosis, blood flow velocity is also a major determinant of fluid energy losses, and the pressure drop across a stenosis varies with the flow rate (Eq. 8.4). Consequently, a stenosis that is not significant at low or resting flow rates may become critical when flow rates are increased by reactive hyperemia or exercise. Because flow velocity depends on the distal vascular resistance, the critical stenosis value varies with the resistance of the runoff bed. In Fig. 8.8, a system with a high flow velocity (low resistance) shows a reduction in pressure with less narrowing than a system with low flow velocity (high resistance). The higher flow velocities produce curves that are less sharply bent, making the point of critical stenosis less distinct.

The decrease in flow with progressive arterial narrowing is linearly related to the increase in pressure gradient, as long as the peripheral resistance remains constant.[16] In this situation, the curves for pressure drop and flow reduction are mirror images of each other, and the critical stenosis value is the same for both (see Fig. 8.8). Many vascular beds are able to maintain a constant level of blood flow over a wide range of perfusion pressures by the mechanism of autoregulation. This is achieved by constriction of resistance vessels in response to an increase in blood pressure and dilatation of resistance vessels when blood pressure decreases (Fig. 8.9). For example, autoregulation permits the brain to maintain normal flow rates down to perfusion pressures in the range of 50 to 60 mm Hg.[17]

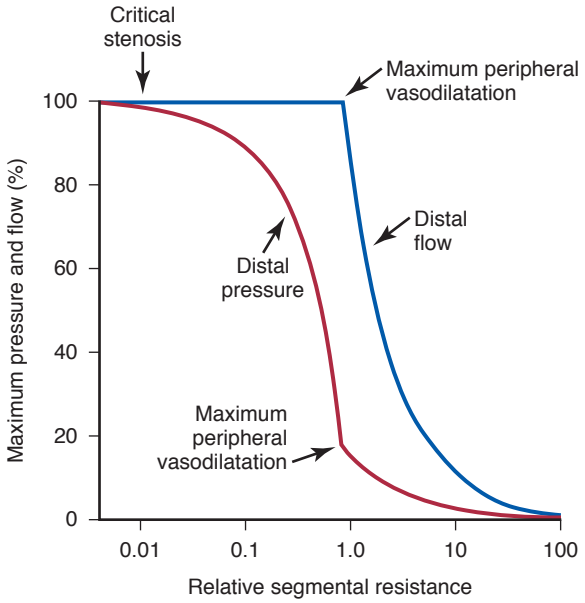

Figure 8.9 Although blood pressure distal to a critical stenosis falls progressively with increasing stenosis severity, autoregulation maintains normal blood flow until maximum peripheral vasodilatation is reached. Beyond this point, pressure and flow are linearly related; increasing stenosis results in marked decreases in both pressure and flow (compare with Fig. 8.8). (Redrawn from Sumner DS: Correlation of lesion configuration with functional significance. In: Bond MG, Insull WJ, Glagov S, et al., eds. *Clinical Diagnosis of Atherosclerosis: Quantitative Methods of Evaluation.* New York: Springer-Verlag; 1983.)

Stenosis Length and Multiple Stenoses

Poiseuille's law predicts that the radius of a stenosis has a much greater effect on viscous energy losses than its length (Eq. 8.4). Doubling the length of a stenosis results in a doubling of the

associated viscous energy losses; however, reducing the radius by half increases energy losses by a factor of 16. Because inertial energy losses are primarily due to entrance and exit effects, they are independent of stenosis length (see Fig. 8.7). Thus separate short stenoses tend to be more significant than a single longer stenosis. It has been shown experimentally that when stenoses that are not significant individually are arranged in series, large reductions in pressure and flow can occur.[18] In other words, multiple subcritical stenoses may have the same effect as a single critical stenosis.

Effect of Stenosis on Waveforms

As shown in Fig. 8.10, the compliant arterial wall and a stenosis create a situation analogous to a "low-pass filter." Passage of a pressure or flow pulse through this circuit attenuates the high-frequency or rapidly changing components of the pulse and results in a damped waveform. The arterial pulse pressure distal to a stenosis is reduced to a greater extent than the mean pressure.[19] In addition to the reduction in pulse pressure, the contour of the pressure pulse is changed radically: the upslope is delayed, the peak becomes more rounded, the "notch" on the downslope disappears, and the downslope becomes bowed away from the baseline. These changes are reflected in the plethysmographic (volume pulse) waveform and thus provide a sensitive indicator of the presence of arterial disease.[20] Similar changes are observed in the flow pulse waveform distal to a stenosis. In contrast to the normal flow pattern, the upslope rises more slowly in systole, the peak is rounded, and the downslope declines more gradually toward the baseline during diastole. The normal reverse flow component of the triphasic waveform also tends to disappear, and the waveform becomes monophasic.[21]

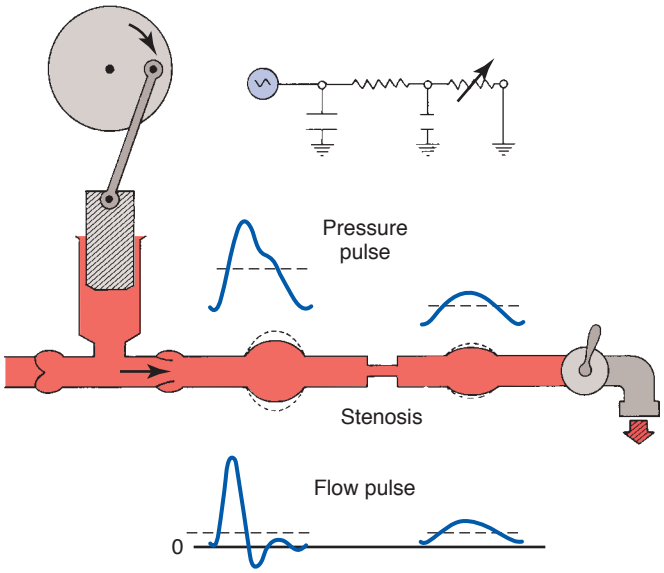

Figure 8.10 Effect of a stenosis and compliant vessels on the contour of arterial pressure and flow pulses. Mean pressure (*dashed lines* on the pressure pulses) is reduced, but mean flow (*dashed lines* on the flow pulses) is unchanged. The faucet represents the variable peripheral resistance. (Redrawn from Sumner DS: Correlation of lesion configuration with functional significance. In: Bond MG, Insull W Jr, Glagov S, et al., eds. *Clinical Diagnosis of Atherosclerosis: Quantitative Methods of Evaluation.* New York: Springer-Verlag; 1983.)

Abnormal Pressure and Flow

If an arterial lesion is hemodynamically significant at resting flow rates, there will be a measurable reduction in distal blood pressure. In general, limbs with a lesion at one anatomic level (e.g., aortoiliac, femoropopliteal, or tibioperoneal) have ankle-brachial indices between 0.90 and 0.50, whereas limbs with lesions at multiple levels have ankle-brachial indices less than 0.50. The ankle-brachial index also correlates to some extent with the clinical severity of disease; in limbs with intermittent claudication, the index has a mean value of 0.59 ± 0.15; in limbs with ischemic rest pain, 0.26 ± 0.13; and in limbs with impending gangrene, 0.05 ± 0.08.[4] Because of the increased vascular resistance produced by an arterial lesion and any associated collateral vessels, the ankle systolic pressure falls dramatically during leg exercise. The extent and duration of this pressure drop are proportional to the severity of the arterial lesions (Figs. 8.11 and 8.12).[22]

As mentioned previously, when blood flows through an arterial stenosis or a high-resistance collateral bed, the distal pulse pressure is reduced to a greater extent than the mean pressure.[19] This suggests that the systolic pressure distal to a lesion is a more sensitive indicator of hemodynamic significance than the mean pressure. It is well known that patients with superficial femoral artery stenosis can have palpable pedal pulses at rest that disappear after leg exercise; this occurs when increased flow through abnormal high resistance vessels causes a reduction in systolic pressure.

Resting leg or calf blood flow in most patients with intermittent claudication is not significantly different from values obtained in normal individuals. However, the capacity of these patients to increase limb blood flow during exercise is quite

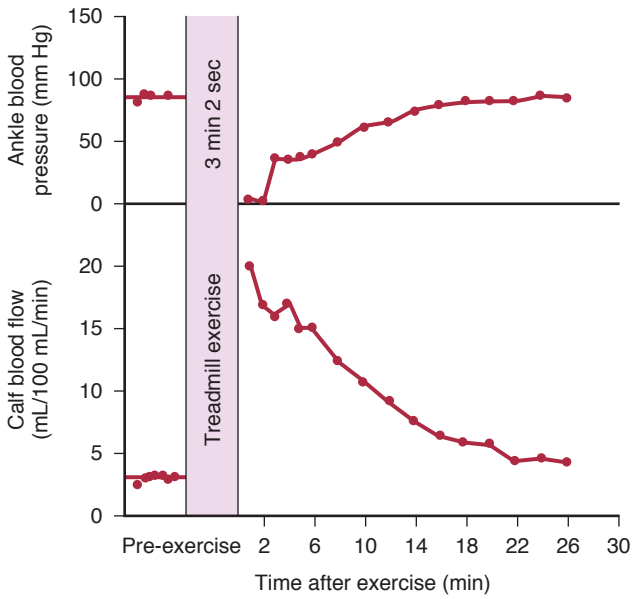

Figure 8.11 Ankle blood pressure and calf blood flow before and after exercise in a patient with stenosis of the superficial femoral artery. (Redrawn from Sumner DS, Strandness DE Jr. The relationship between calf blood flow and ankle blood pressure in patients with intermittent claudication. *Surgery.* 1969;65:763.)

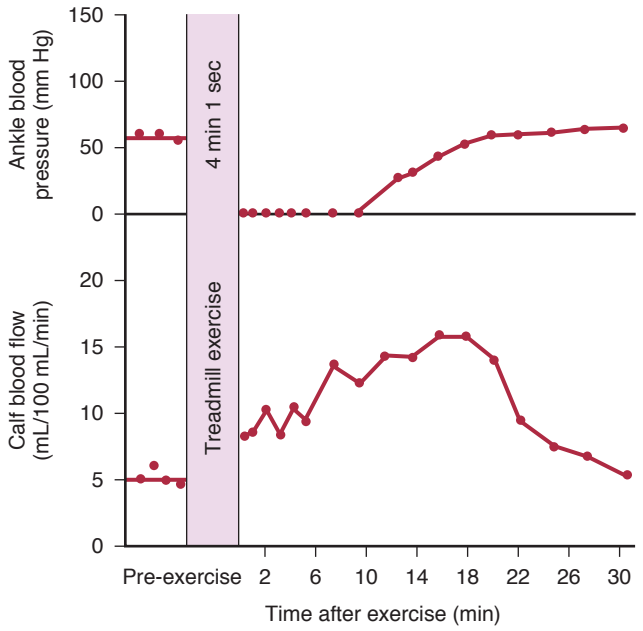

Figure 8.12 Ankle blood pressure and calf blood flow before and after exercise in a patient with stenosis of the iliac artery and occlusion of the superficial femoral artery. Note the more prolonged decrease in ankle pressure and slow return to resting baseline pressure compared to Fig. 8.11. (Redrawn from Sumner DS, Strandness DE Jr. The relationship between calf blood flow and ankle blood pressure in patients with intermittent claudication. *Surgery.* 1969;65:763.)

limited, and pain occurs in the muscles that have been rendered ischemic. As the occlusive process becomes more severe, a decrease in peripheral vascular resistance can no longer compensate, and resting flow drops below normal levels. When this occurs, signs and symptoms of ischemia at rest appear. With increasing degrees of disease, the hyperemia that follows exercise becomes more prolonged, and the peak calf blood flow is both decreased and delayed.[22]

Collateral Circulation

The development of collateral circulation is one of the major mechanisms that compensates for the hemodynamic effects of an obstructed artery. Collateral vessels are preexisting pathways that enlarge when flow through the parallel major artery is reduced. The functional capacity of a collateral system depends on the level and extent of the occlusive lesions. For example, the profunda-geniculate network can compensate to a large degree for an isolated superficial femoral artery occlusion; however, the addition of an iliac artery lesion severely limits collateral flow.

A collateral system consists of three components: (1) stem arteries, which are large distributing branches, (2) a midzone of smaller intramuscular channels, and (3) reentry vessels that join the major artery distal to the point of obstruction.[6] The main stimuli for collateral development are an abnormal pressure gradient across the collateral system and increased velocity of flow through the midzone vessels. Collateral vessels are smaller, longer, and more numerous than the major arteries that they replace. Although considerable enlargement may occur in the midzone vessels, collateral resistance is always greater than that of the original unobstructed major artery. In addition, the acute changes in collateral resistance during exercise are minimal.[23] Therefore the resistance of a collateral system can be considered as fixed. Unlike collateral resistance, the resistance of the peripheral runoff bed is quite variable.

Building on these concepts, vascular resistance in the lower limb can be divided into *segmental* and *peripheral* components. Segmental resistance consists of the relatively fixed parallel resistances of the major artery and any bypassing collateral vessels. Peripheral resistance includes the highly variable resistances of the distal arterioles and cutaneous circulation. The total vascular resistance of the limb can be estimated by adding the segmental and the peripheral resistances. Normally, the resting segmental resistance is very low and the peripheral resistance is relatively high.

Using the superficial femoral artery and profunda-geniculate collateral system as an example, the pressure drop across a normal femoropopliteal arterial segment is minimal. With exercise, the peripheral resistance falls, and flow through the segmental arteries increases by a factor of up to 10, with little or no pressure drop. With moderate arterial disease, such as an isolated superficial femoral artery occlusion, the segmental resistance is increased as a result of collateral flow, and an abnormal pressure drop is present across the thigh. Because of a compensatory decrease in peripheral resistance, the total resistance of the limb and the resting blood flow often remain in the normal range.[24] During exercise, the segmental resistance remains high and fixed, whereas the peripheral resistance decreases further. However, the capacity of the peripheral circulation to compensate for a high segmental resistance is limited, and exercise flow is less than normal. In this situation, exercise is associated with a still larger pressure drop across the diseased arterial segment, and the clinical consequence is calf muscle ischemia and claudication.

Vascular Steal

A vascular "steal" may arise when two runoff beds with different resistances must be supplied by a limited source of arterial inflow. One example of the steal phenomenon involves a limb with lesions in both the iliac and superficial femoral arteries. Between the fixed resistances of these two arterial lesions is the orifice of the profunda femoris artery, which supplies the variable resistance of the thigh. The resistance of the distal calf runoff bed is also variable. Under resting conditions, normal leg blood flow can be maintained by a nearly maximal decrease in calf resistance and a moderate decrease in thigh resistance. This is apparent clinically as abnormally low ankle systolic pressure. With the greater metabolic demands of exercise, thigh resistance can decrease further, but calf resistance has already reached its lower limit. The result is a further drop in pressure across the proximal iliac lesion, which reduces the pressure perfusing the calf. Blood flow to the calf is decreased until thigh resistance rises and thigh blood flow begins to fall. In this situation, the effect of exercise is to increase thigh blood flow, decrease calf blood flow, and decrease distal blood pressure. The thigh steals

blood from the calf because the proximal iliac lesion restricts inflow to both runoff beds.

When an extraanatomic bypass graft is performed, a single donor artery must supply several vascular beds. In the case of a femoral-femoral crossover graft, one iliac artery is the donor artery, the leg ipsilateral to the donor artery is the donor limb, and the contralateral leg is the recipient limb. Studies of crossover grafts in animal models have shown that the immediate effect of the graft is to double flow in the donor artery.[25] These experimental observations are consistent with hemodynamic data from patients with femoral-femoral grafts.[26] Improvement in the ankle-brachial index on the recipient side can be achieved, even when there is significant occlusive disease in both the donor and recipient limbs. Although the ankle-brachial index may decrease slightly on the donor side, a symptomatic steal is uncommon. The most important factor contributing to vascular steal with a femoral-femoral graft is stenosis of the donor iliac artery. With iliac artery stenosis, steal is most likely to occur during exercise, when flow rates are increased. A mildly stenotic iliac can be used as a donor artery when high flow rates are not needed, such as in the treatment of ischemic rest pain. However, when increased flow rates are required to improve the walking distance of a patient with claudication, stenosis of the donor iliac artery may result in steal from the donor limb. Occlusive disease in the arteries of the donor limb distal to the origin of the graft does not result in steal, provided that the donor iliac artery is normal.

Therapeutic Considerations

Arterial Occlusive Disease

Based on the preceding discussion, it is apparent that the high fixed segmental resistance of the diseased major arteries and collaterals is responsible for decreased peripheral blood flow. Therefore, to be most effective in improving peripheral blood flow and relieving ischemic symptoms, therapy must be directed toward lowering this abnormally high segmental resistance. Because the peripheral resistance has already been lowered to compensate for the increased segmental resistance, attempts to further reduce the peripheral resistance will not result in a significant increase in flow.[27]

Walking exercise therapy can lead to an increase in the speed, distance, and duration of walking, with decreased claudication symptoms.[28] Although walking exercise programs can improve walking ability, there is usually little change in the ankle pressure.[29] This finding suggests that the benefits of exercise are due in large part to metabolic changes and alterations in gait, rather than the development of new collateral vessels. In general, exercise therapy is best suited for patients with mild, stable claudication who are not considered as candidates for direct intervention.

A historical method for improving peripheral blood flow in limbs with arterial disease is medically induced hypertension.[27] The administration of mineralocorticoid and sodium chloride raises systemic blood pressure and increases the head of pressure perfusing the diseased arterial segment. Due to the obvious adverse effects of hypertension, this technique has not been widely applied; however, it has been used successfully in patients with severe distal ischemia and ulceration.

Arterial Grafts and Anastomoses

The most effective approach to reducing the abnormally high fixed segmental resistance is direct intervention on the obstructed arterial segments by open surgical or catheter-based techniques. In patients with occlusive disease involving a single anatomic level, a successful procedure should return all hemodynamic parameters to normal or near normal. This should be evident as an increase in the ankle-brachial index and an improvement in the ankle pressure response to leg exercise.[30] When occlusions involve multiple levels, the treatment of one level should result in significant improvement, and the persisting hemodynamic abnormality should then reflect the remaining untreated disease. In such cases, the improvement is usually sufficient to increase claudication distance or relieve ischemic rest pain.

When an arterial graft is required, decisions must be made regarding the choice of graft material, graft diameter, and anastomotic configuration (end-to-end or end-to-side). The factors required for optimal function of arterial grafts can be analyzed in terms of hemodynamic principles. As previously noted, vessel diameter is the main determinant of hemodynamic resistance, so the diameter of a graft is considerably more important than its length. Therefore the graft selected should be large enough to carry all the flow required at rest without causing a drop in pressure, and it should also be large enough to accommodate any increased flow likely to be required during exercise. Another factor to consider is that prosthetic grafts typically develop a thin layer (0.5 to 1.0 mm) of pseudointima on the luminal surface, so after implantation, a 6-mm prosthetic graft might have an internal diameter of only 4 to 5 mm.

Graft diameter is often limited by the size of the native arteries. To minimize energy losses associated with entrance and exit effects, the diameter of a graft should approximate that of the adjacent artery. When arteries of unequal size must be joined, a gradual transition is preferable. Thus the graft should be slightly smaller than the proximal artery and slightly larger than the distal artery. Theoretically, end-to-end anastomoses are preferable to those done end-to-side, because the end-to-end configuration eliminates energy losses due to curvature and angulation. However, these losses appear to be relatively small under physiologic conditions, and in most clinical situations the anastomotic angle is determined by local technical factors. For example, reversed angulation has been used successfully in the construction of aortorenal and femorofemoral bypass grafts. Nevertheless, as a general rule, the smallest anastomotic angle that is technically feasible should be used. The width of an end-to-side anastomosis should be approximately equal to the diameter of the graft; the length of an anastomosis is less important but does serve as the main determinant of anastomotic angle.

Bifurcation grafts, such as those used for aortobifemoral bypass, are subject to the same general hemodynamic considerations as arterial bifurcations and branches. Most commercially available bifurcation grafts have limbs with diameters that are

one-half that of the main body, resulting in an area ratio of 0.5. In this configuration, each of the limbs has 16 times the resistance of the main body of the graft, and in parallel they offer 8 times the main body resistance. The flow velocity in the limbs is doubled, and almost 50% of the incident pulsatile energy is reflected at the graft bifurcation.[6] As previously discussed, the area ratio determines the hemodynamic characteristics of a bifurcation with respect to pressure gradient, flow velocity, and transmission of pulsatile energy. However, the optimal area ratio for bifurcation grafts has not been established, and the geometry of bifurcation grafts has received relatively little attention. Despite their theoretical disadvantages, commercially available bifurcation grafts have functioned extremely well in a variety of clinical applications.

Aneurysms and Arterial Wall Stress

When the structural components of the arterial wall are weakened, aneurysms may form. Rupture occurs when the tangential stress within the arterial wall becomes greater than the tensile strength. The tangential stress (τ) within the wall of a fluid-filled cylindrical tube can be expressed as:

$$\tau = P\frac{r}{\delta}, \qquad \textbf{(8.6)}$$

where P is the pressure exerted by the fluid, r is the internal radius, and δ is the thickness of the tube wall. Thus tangential stress is directly proportional to pressure and radius but inversely proportional to wall thickness. Stress (τ) has the dimensions of force per unit area of tube wall (dynes per square centimeter). Eq. 8.6 is similar to Laplace's law, which defines tangential tension (T) as the product of pressure and radius:

$$T = Pr. \qquad \textbf{(8.7)}$$

Tension is given in units of force per tube length (dynes per centimeter). The terms *stress* and *tension* have different dimensions and describe the forces acting on the tube wall in different ways. Laplace's law can be used to characterize thin-walled structures such as soap bubbles; however, it is not suitable for describing the stresses in arterial walls.

Fig. 8.13 shows a tube with an outside radius of 1.0 cm and a wall thickness of 0.2 cm, dimensions similar to those of atherosclerotic aortas. If the internal pressure is 150 mm Hg, the tangential wall stress is 8.0×10^5 dynes/cm^2. Expansion of the tube to form an aneurysm with an outside radius of 3.0 cm results in a decrease in wall thickness to 0.06 cm. The increased radius and decreased wall thickness increase the wall stress to 98.0×10^5 dynes/cm^2, assuming that the pressure remains constant. In this example, the diameter has been enlarged by a factor of 3, and the wall stress has increased by a factor of 12.

Although the tensile strength of collagen is very high, it constitutes only about 15% of the aneurysm wall.[31] Furthermore, the collagen fibers in an aneurysm are sparsely distributed and subject to fragmentation. The tendency of larger aneurysms to rupture is readily explained by the effect of increased radius on tangential stress (Eq. 8.6) and degenerative changes in the arterial wall. The relationship between tangential stress and blood pressure accounts for the contribution of hypertension to the risk of rupture. Another factor is that in about 55% of ruptured abdominal aortic aneurysms, the site of rupture is in the posterolateral aspect of the aneurysm wall.[32] The posterior wall of the aorta is relatively fixed against the spine, and repeated flexion in that area could result in structural fatigue and a localized area of weakness that might predispose to rupture.

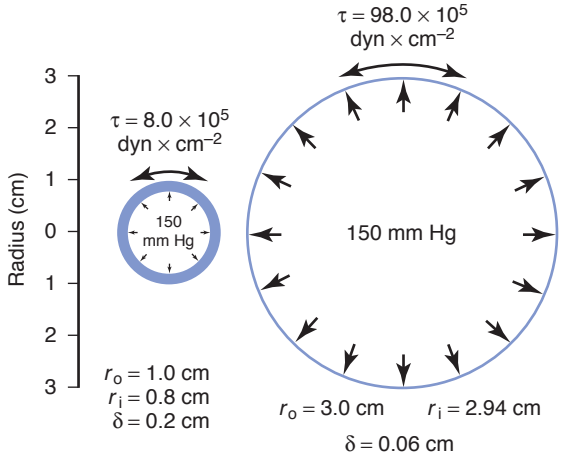

Figure 8.13 End-on view of a cylinder 2 cm in diameter before *(left)* and after *(right)* expansion to a diameter of 6 cm. Wall area remains the same in the two cases, but wall stress (τ) is greatly increased because of both the decrease in wall thickness (δ) and the increase in inside radius (r).

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9 CHAPTER

Venous Pathophysiology

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INTRODUCTION

The veins are complex "organs" and much like arteries are well suited to their physiologic purpose. Venous diseases represent a major concern in the general population and are influenced by genetics, environment, and acquired conditions. Understanding the basic physiologic and molecular responses to venous injury is essential for designing effective and safe therapies. Deep vein thrombosis (DVT) refers to the formation of one or more thrombi within the deep veins, most commonly in the lower limbs. The thrombus may cause partial or complete blockage of the circulation, which may lead to characteristic symptoms such as pain, swelling, tenderness, discoloration, or redness of the affected area, and skin ulcers. In 2008 The Surgeon General's Call to Action to Prevent DVT and pulmonary embolism (PE), states *"**the disease disproportionately affects older Americans, and we can expect more suffering and more deaths in the future as the population ages, unless we do something about it,**"* inviting multiple stakeholders, to come together in a coordinated effort to reverse this dramatic projected trend.[1]

BASIC CONSIDERATIONS

Endothelium and Hemostasis

The endothelium forms the inner cell lining of all blood vessels in the body and is a spatially distributed tissue. In an average individual the endothelium weighs approximately 1 kg and covers a total surface area of 4000 to 7000 square meters.[2] The endothelium has been described as a primary determinant of pathophysiology or as a target for collateral damage in most, if not all, disease processes.[2,3] Endothelial cells play a critical role in the balance between procoagulant and anticoagulant mechanisms in healthy individuals. The endothelium is integrally involved in mediating hemostasis.[4]

Most of the thrombosis-thrombolysis processes occur in juxtaposition to the endothelium, and hence the endothelium is one of the pivotal regulators of homeostasis. Under normal conditions, endothelial cells maintain a vasodilatory and local fibrinolytic state in which coagulation, platelet adhesion, and activation are suppressed. A nonthrombogenic endothelial surface is maintained by a number of mechanisms, including

(1) endothelial production of thrombomodulin and subsequent activation of protein C; (2) endothelial expression of heparan sulfate and dermatin sulfate, which accelerate antithrombin (AT) and heparin cofactor II activity; (3) constitutive expression of tissue factor pathway inhibitor (TFPI); and (4) local production of tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). In addition, the production of nitric oxide (NO) and prostacyclin by the endothelium inhibits the adhesion and activation of leukocytes and produces vasodilation.[5] Tissue factor (TF) production is also inhibited by NO.[6]

In addition, von Willebrand factor (vWF) is expressed to a greater extent on the endothelium of veins compared with arterial endothelium, and tPA is less commonly expressed in venous endothelium.[7] Systemic inflammatory insults, such as conferred by tumor necrosis factor-α (TNF-α), may cause endothelial activation and result in increased surface expression of cell adhesion molecules (CAMs) such as P-selectin, E-selectin, and intracellular CAM (ICAM), thereby promoting the adhesion and activation of leukocytes as well as platelets.[8]

Venous Biomechanics

Veins allow a very large volume capacitance and tonal regulation to rapidly redistribute overall blood volume. Approximately 60% to 80% of circulating blood is stored in the venules and systemic veins at any given time. The function of the blood capacitance system via vasoregulation is to maintain the filling of the heart, as well as to compensate for orthostatic changes. The physiology of venous blood flow in the limb related to the calf muscle pump and other actions is detailed in Chapter 22.

Everyday activities and changes in body position cause large changes in venous pressure. The average venous pressure at the foot is approximately 100 mm Hg in a person 5 feet 10 inches tall weighing 75 kg. This pressure drops significantly with ambulation and during recumbence. The venous valves are endothelium-lined folds of tunica intima that allow unidirectional flow, contribute to this pressure reduction, and maintain blood flow. To accommodate pressure and volume changes, veins undergo complex alterations in shape, depending on the blood volume, resistance, and the amount of blood flow within the system. Less vascular resistance occurs with a circular shape than an elliptical shape, and thus as venous volume increases, resistance to flow lessens.

Unlike arteries, large veins lack an extensive elastic lamella (composed of elastin) but exhibit marked distensible properties. Veins have a much smaller ratio of wall thickness to radius and higher incremental distensibility in the low-pressure range than arteries, thus indicating that the elastic modulus of veins can greatly exceed the stress modulus of arteries. As a result, veins have a high breaking pressure, nearly four atmospheres.[9] Much of the stress-bearing function of the vein wall may depend on its smooth muscle cell and elastin content, in contrast to the abundance of collagen in the arterial wall. Indeed, vein wall compliance is decreased after experimental venous thrombosis (VT) injury, which correlates with its increased collagen content,[10] and disrupted elastin, as measured histologically.[11]

Deep Venous Thrombosis

Venous thromboembolism (VTE) is a significant healthcare problem in the United States, with an estimated 900,000 cases of VT and PE, causing approximately 300,000 deaths yearly.[12] For the past 150 years, understanding the pathogenesis of VTE has centered on Virchow triad of stasis, changes in the vessel wall (now recognized as injury), and thrombogenic changes in the blood. Stasis is probably permissive, and not a direct cause, whereas systemic infection and systemic inflammation may be more causal than previously thought.[13,14]

Venous Thrombosis Pathways

Coagulation Cascade

Hemostasis is typically initiated by damage to the vessel wall and disruption of the endothelium, although it may be initiated in the absence of vessel wall damage, particularly in VT (Fig. 9.1).[15] Vessel wall damage simultaneously results in release of TF, a cell membrane protein, from injured cells and circulating blood, with subsequent activation of the extrinsic pathway of the coagulation cascade. These two events are critical to the activation and acceleration of thrombosis. Differences in local organ mechanisms may cause region-specific susceptibility to thrombosis. For example, hemostasis in cardiac muscle may be more dependent on the extrinsic pathway for thrombosis, whereas skeletal muscle may be more dependent on the intrinsic pathway for thrombosis (see Fig. 9.1).[16]

Coagulation can be activated through the intrinsic pathway with activation of factor XI to XIa, which subsequently converts factor IX to IXa and promotes formation of the Xase complex and ultimately thrombin. Another mechanism by which this occurs in vitro is through the contact activation system, whereby factor XII (Hageman factor) is activated to XIIa when complexed to prekallikrein and high-molecular-weight kininogen (HMWK) on a negatively charged surface; factor XIIa then activates factor XI to XIa. Both thrombin and factor XIa are also capable of activating factor XI.[17]

Thrombin (factor II) is central to coagulation through its action of cleavage and release of fibrinopeptide A (FPA) from the α chain of fibrinogen and fibrinopeptide B (FPB) from the β chain of fibrinogen. This causes fibrin monomer polymerization and cross-linking, which stabilizes the thrombus and the initial platelet plug (see Fig. 9.1). Thrombin also activates factor XIII to XIIIa, which catalyzes the cross-linking of fibrin, as well as that of other plasma proteins, such as fibronectin and α_2-antitrypsin, resulting in their incorporation into the thrombus and increasing resistance to thrombolysis.[18] In addition, factor XIIIa activates platelets, as well as factors V and VIII, further amplifying thrombin production (see Fig. 9.1).

Platelets

Platelet activation and the formation of an effective hemostatic "platelet plug" is a primary thrombotic event, extensively studied in both arterial thrombosis but VT. Two platelet activation routes are thought to exist physiologically.[19] Without direct vessel damage, platelet activation may occur via TF de-encryption

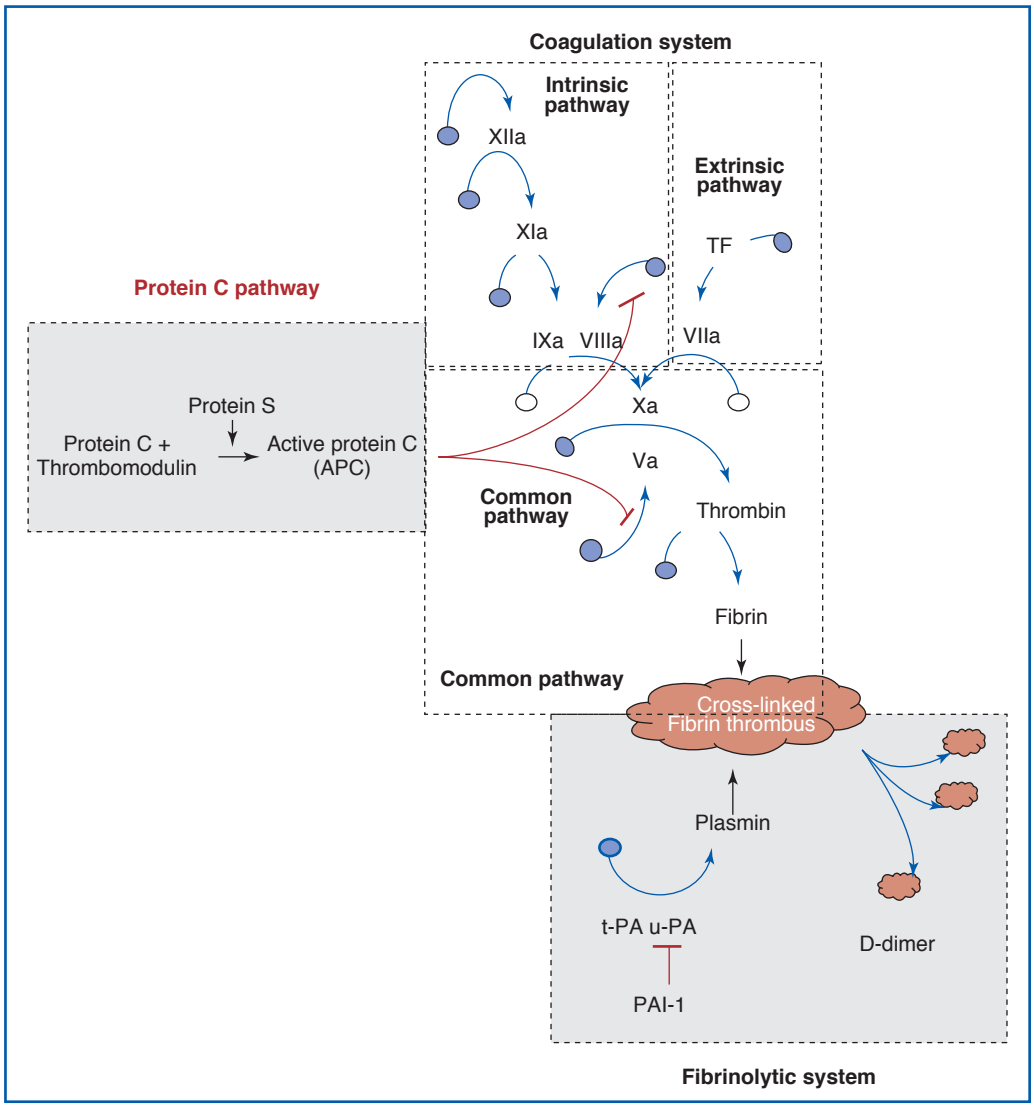

Figure 9.1 Fig. 9.1 shows an integrated representation of the coagulation cascade and the main players for the intrinsic, extrinsic, and common pathways, the natural anticoagulant protein C pathway, and the fibrinolytic system with the degradation product D-dimer. *PAI-1*, Plasminogen activator inhibitor-1; *TF*, tissue factor; *tPA*, tissue plasminogen activator; *uPA*, urokinase-type plasminogen activator.

and activation by protein disulfide isomerase, with factor VIIa generation and activation of platelets. Alternatively, subendothelial collagen may directly bind to glycoprotein (GP) VI and vWF, leading to platelet capture and activation.

Platelet interactions and activation are mediated by vWF, whose receptor is GPIb, via GPIIb/IIIa to fibrin.[20] Activation of platelets leads to the release of the prothrombotic contents of platelet granules, which contain receptors for coagulation factors Va and VIIIa. In addition, platelet activation also leads to the elaboration of arachidonic acid metabolites, such as thromboxane A_2, further promoting platelet aggregation (as well as vasoconstriction). Changes in platelet shape result in exposure of negatively charged procoagulant phospholipids normally located within the inner leaflet of the platelet membrane.[21] Platelets also release microparticles (MPs), rich in TF and other procoagulants, which accelerate and concentrate the thrombus generation. Interestingly, circulating TF may be more important in VT than in arterial thrombosis.[15,22]

Natural Anticoagulants

Several interrelated processes localize thrombotic activity to sites of vascular injury. First, AT is a central anticoagulant protein that binds to thrombin and interferes with coagulation by three major mechanisms: (1) inhibition of thrombin prevents removal of FPA and FPB from fibrinogen, limiting fibrin formation; (2) thrombin becomes unavailable for activation of factors V and VIII, thus slowing the coagulation cascade; and (3) thrombin-mediated platelet activation and aggregation are inhibited. In the presence of heparin the accelerated inhibition of thrombin by AT results in systemic anticoagulation. AT has been shown to directly inhibit factors VIIa, IXa, Xa, XIa, and XIIa. Thus patients with a genetic deficiency of AT are at much higher risk for development of VTE than the normal population.

A second natural anticoagulant is activated protein C (APC), which is produced on the surface of intact endothelium when thrombin binds to its receptor, thrombomodulin, and endothelial

protein C receptor (EPCR; see Fig. 9.1). The thrombin-thrombomodulin complex inhibits the actions of thrombin and also activates protein C to APC. APC, in the presence of its cofactor protein S, inactivates factors Va and VIIIa, therefore reducing Xase and prothrombinase activity (see Fig. 9.1).[23]

The third innate anticoagulant is TFPI. This protein binds the TF-VIIa complex, thus inhibiting the activation of factor X to Xa and formation of the prothrombinase complex. Interestingly, factor IX activation is not inhibited. Finally, heparin cofactor II is another inhibitor of thrombin whose action is in the extravascular compartment. The activity of heparin cofactor II is augmented by glycosaminoglycans, including both heparin and dermatan sulfate, but its deficiency is not associated with increased VTE risk.[24]

Thrombolysis

Physiologic thrombus formation is balanced by controlled thrombolysis to prevent pathologic intravascular thrombosis. Plasmin, the central fibrinolytic enzyme, is a serine protease generated by the proteolytic cleavage of the proenzyme plasminogen. Its main substrates include fibrin, fibrinogen, and other coagulation factors. Plasmin also interferes with vWF-mediated platelet adhesion by proteolysis of GPIb.[25]

Activation of plasminogen occurs through several mechanisms. In the presence of thrombin, vascular endothelial cells produce and release tPA as well as α_2-antiplasmin, a natural inhibitor of excess fibrin-bound plasmin (see Fig. 9.1). As a thrombus is formed, plasminogen, tPA, and α_2-antiplasmin become incorporated into it. In contrast to free circulating tPA, fibrin-bound tPA is an efficient activator of plasminogen. A second endogenous activator of plasminogen is through the uPA, also produced by endothelial cells but with less affinity for fibrin. Activation of uPA in vivo is not completely understood. However, it is hypothesized that plasmin in small amounts (produced through tPA) activates uPA, leading to further plasminogen activation and amplification of fibrinolysis.[26]

The third mechanism of plasminogen activation involves factors of the contact activation system; activated forms of factor XII, kallikrein, and factor XI can each independently convert plasminogen to plasmin. These activated factors may also catalyze the release of bradykinin from HMWK, which further augments tPA secretion. Finally, APC has been found to proteolytically inactivate plasminogen activator inhibitor type 1 (PAI-1), an inhibitor of plasmin activators that is released by endothelial cells in the presence of thrombin.[27]

The degradation of fibrin polymers by plasmin ultimately results in the creation of fragment E and two molecules of fragment D, which are released as a covalently linked dimer (D-dimer).[28] Detection of D-dimer in the circulation is a marker for ongoing thrombus metabolism and has been shown to accurately predict ongoing risk of recurrent VTE.[29] Interestingly, the resting state of the fibrinolytic system within the vein wall is lower in the area of the valvular cusps.[30] In comparison with other anatomic locations, the deep veins of the lower limb have the lowest fibrinolytic activity in soleal sinuses, as well as in the popliteal and femoral vein regions. This observation underlies a popular hypothesis as to why DVT most commonly originates in the lower limb.

Plasminogen Inhibitors and Thrombosis

Activation of plasminogen provides localized proteolytic activity,[31–33] and in plasma, PAI-1 is the primary inhibitor of plasminogen activators. It is secreted in an active form from liver and endothelial cells and is stabilized by binding to vitronectin (and inhibits thrombin in this form). PAI-1 is stored in the alpha granules of quiescent platelets.[34] PAI-1 levels are elevated by hyperlipidemia, and PAI-1 elevation appears to synergize with factor V Leiden genetic abnormalities.

Studies on the role of elevated PAI-1 in VT have been contradictory,[35,36] although it is plausible that elevated PAI-1 could suppress fibrinolysis and increase thrombosis potential. In humans, genetic polymorphisms correlate with increased risk of VTE. The highest levels of PAI-1 have been noted in those individuals carrying the 4G/4G polymorphism. Studies have found an eightfold higher risk for VTE in patients with the 4G allele in combination with other thrombophilic markers,[37] and a 4.5-fold higher risk for PE in patients with 4G/4G polymorphism and protein S deficiency.[38]

Inflammation and Thrombosis

The relationship between thrombosis and inflammation was first suggested in the early 1970s.[39] Inflammation increases TF, membrane phospholipids, fibrinogen, and the reactivity of platelets while decreasing thrombomodulin and inhibiting fibrinolysis (Fig. 9.2).[40]

Several circulating markers of inflammation once thought to be soluble are actually carried by small (<1 μm) phospholipid vesicles called MPs.[41] MPs, which are shed from platelets, leukocytes, and endothelial cells in a calcium-dependent fashion, are involved in the initiation and amplification of thrombosis (see Fig. 9.2).[42] MPs lack DNA and RNA, but subpopulations of MPs rich in TF and phosphatidylserine have been identified.[43] Fusion of MPs with activated platelets results in decryption of TF and the initiation of thrombosis.[44] These vesicles have direct exogenous procoagulant activity, as shown by normalization of tail bleeding times in hemophilic mice.[45] Moreover, MPs shed from platelets express PAI-1, and these MPs add to the growing thrombus via interactions between P-selectin and its receptor, P-selectin glycoprotein ligand-1 (PSGL-1; see Fig. 9.2). In this manner, platelet MPs not only are prothrombotic but also inhibit fibrinolysis, facilitating thrombus growth.[46] The results of these studies provide evidence that MPs are associated with VT; however, their role in thrombogenesis and also their potential role as biomarkers for VT was recently studied.[47]

Galectin 3 (gal3) and galectin 3 binding protein (gal3bp) play important roles in a number of pathologies, such as cancer, infections, diabetes, atherosclerosis, and wound healing, and in inflammatory disorders, such as asthma and rheumatoid arthritis, but their role in VT has not been defined.[48–56] Gal3bp was found to be upregulated in MPs collected from human patients diagnosed with DVT (see Fig. 9.2).[57] Gal3bp is a

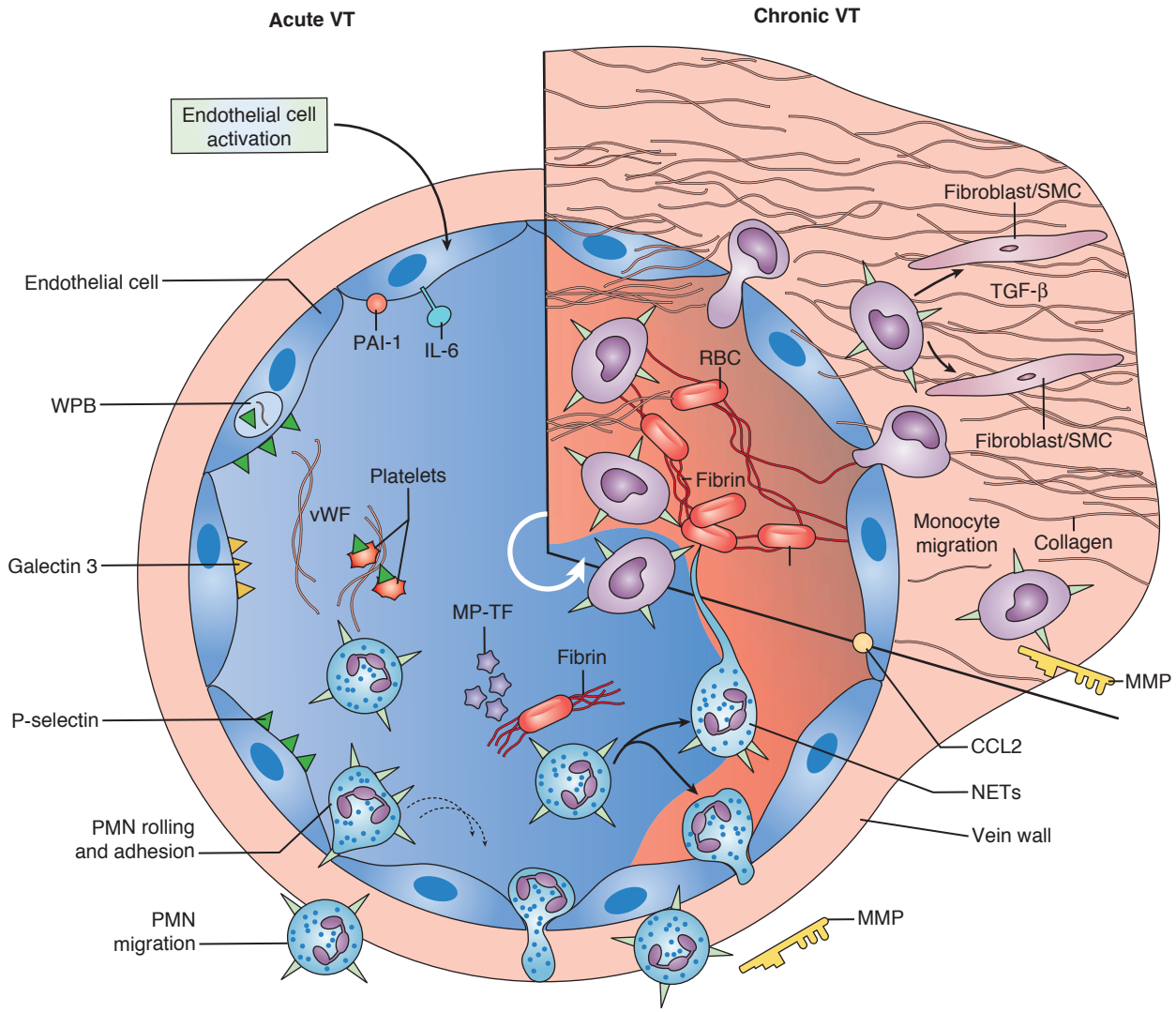

Figure 9.2 Fig. 9.2 shows a schematic representation of the inflammatory events during acute and chronic venous thrombosis in an anticlockwise fashion. The initial inflammatory events involve endothelial activation with secretion of cytokines and plasminogen activator inhibitor-1 (PAI-1) and release of von Willebrand factor (vWF) and P-selectin. This platform favors polymorphonuclear (PMN) recruitment. Platelet activation also contributes to the initial steps, and the fibrin red blood cell (RBC)-rich thrombus *(in light red)* forms. Vein wall, in *gray*, increases thickness over time. *CCL2*, CC motif ligand 2; *IL-6*, interleukin-6; *MMP*, matrix metalloproteinase; *MP-TF*, microparticle-tissue factor; *NETs*, neutrophil extracellular traps; *SMC*, smooth muscle cell; *TGF-β*, transforming growth factor-β; *VT*, venous thrombosis; *WPB*, Weibel-Palade body.

member of the lectin family, associated with integrin-mediated cell adhesion.[58] Gal3 and gal3bp were discovered to be associated with murine thrombogenesis. In addition, gal3 could be a potential biomarker in patients with acute DVT.[47] Gal3bp and gal3 were found in all tissue and blood elements pertinent to the thrombi that were examined (MPs, red blood cells, platelets, vein wall, thrombus), with the exception of leukocytes. In addition, increased circulating gal3bp and gal3 were observed during VT conditions in both mice and humans, showing parallelism between these two species and their potential to be biomarkers.[47] A detailed review of galectins and their potential role in venous thrombogenesis, inflammation, and fibrosis was published.[59]

Thrombus Resolution and Vein Wall Remodeling

Regardless of the location and extent of acute DVT, the resolution process is complex.[60] In humans the natural fibrinolytic mechanisms break down the thrombus over time at variable rates.[61] Resolution of experimental VT resembles wound healing, involving profibrotic growth factors, collagen deposition, and activation of matrix metalloproteinase (MMP; see Fig. 9.2). The fact that leukocytes invade the thrombus in a specific sequence suggests their importance in normal thrombus resolution.[62] Real-time in vivo imaging has also shown that leukocyte concentration and MMP activity colocalize to areas of recanalization.[63,64]

The first leukocyte subtype arriving to the thrombus is the polymorphonuclear neutrophil (PMN; see Fig. 9.2). Although PMNs may cause vein wall injury, they contribute to both early thrombus amplification and early thrombus resolution. The role of PMNs in promoting early DVT by release of neutrophil extracellular traps (NETs) has been shown in primate and murine models of thrombosis.[65] Inflammatory activation of PMNs causes degranulation of nucleic DNA, which is complexed with antimicrobial peptides and allows platelets and coagulation factors to assemble in juxtaposition to the vein wall. Consistently, DNAse treatment can directly accelerate VT resolution.

The monocyte is likely the most important cell for later DVT resolution (see Fig. 9.2).[62] In mice, monocyte influx into the thrombus correlates with elevations of monocyte chemotactic protein-1 (MCP-1), one of the primary CC chemokines that direct monocyte chemotaxis and activation[66,67]; MCP-1 has also been associated with DVT resolution.[68] Targeted deletion of CC receptor 2 (CCR2 KO) in the mouse model of stasis thrombosis is associated with late impairment of thrombus resolution, probably via impaired interferon-γ–inducible proteinase activity, which may be independent of monocytes.[69]

The local venous environment is by definition hypoxic. A major angiogenic growth factor is hypoxia-inducible factor-1α (HIF-Iα). Murine stasis models of VT have shown that thrombosis stimulates HIF-Iα, which thus accelerates thrombus resolution.[70] VEGF has also been associated with increased thrombus recanalization in smaller venous thrombi from rat models of DVT. VEGF was also correlated with higher numbers of thrombus monocytes.[71] Thus thrombus resolution is in part dependent on neovascularization. The effect of mechanical stretch, such as by a venous thrombus, may also stimulate HIF-Iα as well as MMP-2 and MMP-9, all of which lead to reduced vein contractility.[72]

As the thrombus resolves, a number of proinflammatory factors are released into the local environment, including interleukin-1β (IL-1β) and TNF-α.[73] The cellular sources of these different mediators have not been specifically defined but probably include leukocytes and smooth muscle–like cells within the resolving thrombus and adjacent vein wall. Leukocyte kinetics in the vein wall during DVT are similar to what is observed in the thrombus, with an early influx of PMNs followed by monocytes (see Fig. 9.2). On the basis of experimental studies, elastinolysis and collagenolysis seem to occur early, as measured by an increase in vein wall stiffness persisting through 14 days, and are accompanied by elevated MMP-2 and MMP-9 activities.[10,11] In addition, the protective effect of P-selectin inhibition is not yet know but probably does not involve leukocyte migration blockage, because no differences in influx of monocytes into the vein wall were observed.[74]

Loss of venous endothelium likely also contributes to vein wall fibrosis, as well as the predisposition to recurrent thrombosis. An experimental model of DVT showed lower expression of homeostatic endothelial gene products such as NO and thrombomodulin compared with controls, which correlated with loss of vWF-positive cell luminal staining.[75] Other investigators have found that prolonged venous stasis is associated with decreased plasminogen activators, probably related to the loss of endothelium.[76]

The profibrotic growth factor TGF-β is present in the thrombus and is activated with normal thrombolysis (see Fig. 9.2).[76] TGF-β may be a key mechanism promoting vein wall fibrosis. Late fibrosis has been observed in a mouse model of DVT, which demonstrated a significant increase in vein wall collagen.[59] Correlating with this increase in fibrosis is an increase in collagen I and III gene expression, as well as increases in MMP-2 and MMP-9 gene expression and activity. Genetic deletion of MMP-2 or MMP-2/9 is associated with decreased vein wall fibrosis, possibly by modulating vein wall elastin/collagen metabolism as well as monocyte influx.[77] Thus early vein wall injury is associated with active matrix remodeling that seems to promote late fibrosis, not unlike many organ responses to inflammation burnout.[78]

Chronic Venous Insufficiency

The common mechanism of chronic venous insufficiency (CVI) is venous reflux between the superficial and deep systems, either at the site of perforators or through other deep and superficial system connections, which accounts for the increased venous hydrostatic pressure transmitted to the superficial veins and tissues. An obstructed vein segment worsens this process. Experimentally, venous hypertension activates leukocytes,[79] although the activation is probably a local phenomenon.[80] The process of vein wall fibrosis plays a contributing role in valvular damage, which then worsens the hydrostatic pressure regulation and consequently promotes greater venous hypertension while in the upright position. Molecular and cellular events seem to point to adaptive responses to injury, as well as abnormal healing.

Historical Perspective and General Background

Several important theories have been postulated regarding the etiology and pathophysiology of CVI. In 1917 John Homans[81] produced a clinical treatise on the diagnosis and the management of patients with CVI and coined the term "post thrombotic syndrome." Alfred Blalock[82] put forth the hypothesis that local hypoxia precipitated CVI. Local tissue hypoxia and alterations in nutrient blood flow were proposed as an underlying etiology by Browse and Burnand.[83] Their important study directly demonstrated the effect of venous hypertension on the venous microcirculation, and they observed histologically the occurrence of pericapillary fibrin deposition in large capillaries, which they called the "fibrin cuff." Coleridge proposed that leukocyte trapping in slow-flow and distended venous segments may underlie much of CVI development.[84] Burnand et al.[85] also showed a positive correlation between the number of capillaries in the skin and the inability of the calf pump to reduce foot vein pressure during exercise.

Varicose Veins

Varicose veins (VVs) have been described since before the Common Era and are obvious on the lower limbs of many

people. The fact that VVs primarily affect the lower limb directly implicates the upright nature of humans—specifically, the effect of hydrostatic pressure on the pathophysiology of such veins. The relationship between body weight and the extent/symptoms of VVs is variable. Limb symptoms are generally local and consist of pruritus and swelling. Occasionally, VVs can erode and bleed. Conversely, most such veins do not thrombose, despite relatively slow blood flow through these torturous structures, pointing to the natural anticoagulant nature of venous endothelium even in structurally abnormal vessels.

Initially, VVs are typically located in the great and small saphenous distributions and their tributaries in the superficial system.[86] Related risk factors are multiple, including primary etiologies associated with pregnancy, prolonged standing, female gender, and, rarely, congenital absence of valves.[87] In addition, varicosities may develop as a result of prior DVT or trauma. Studies support a genetic predisposition to VVs.[88] In a prospective study of 402 subjects the risk of development of VVs was 90% if both parents were affected, 25% for males and 62% for females if one parent was affected, and 20% if neither parent was affected.[89] These data suggest an autosomal dominant with a variable penetrance mode of genetic transmission.

VVs lead to matrix dysregulation with altered expressions of collagen types I and III, with varying dysregulation patterns. The observed pathology suggests a net effect of matrix deposition. One mechanism for these changes may be local upregulation of MMPs and fibrinolytic activity within the microenvironment.[90] Overall differences in MMP-9 protein have also been identified, and it is likely, with the inflammatory influx, that MMP-9 is released primarily from PMNs and may be less important than MMP-2.[91]

This disordered vein structure also correlates with altered vasoreactivity. The contractual response of varicose and normal great saphenous rings to various alpha-adrenergic and non–alpha-adrenergic receptors has shown decreased contractility as compared with controls.[92] This lower contractility may be due to repeated overdistention or impaired contractility related to persistent vein wall tension. However, the response is segmental and likely adaptive.[93] Defining whether VVs involve an initial wall defect and a secondary hemodynamic factor or vice versa is still under debate.

Pathophysiology of Stasis Dermatitis and Dermal Fibrosis

Stasis venous dermatitis is a disease of chronic dermal inflammation due to persistent and sustained cutaneous and dermal injury secondary to venous hypertension. The primary injury may be extravasation of macromolecules and red blood cell products into the dermal interstitium, which creates a secondary inflammatory response, and multiple pathophysiologic hypotheses have been proposed.[94] The clinical appearance is that of brawny induration, skin thickening, swelling, and tissue breakdown with ulceration in the gaiter regions. Alteration in the extracellular matrix is clear on histologic assessment, with extracellular disorganized collagen deposition in the dermal space and perivascular tissue cuffs.

Skin hypoxia occurs on the gaiter areas of limbs with severe venous disease and is significantly different from controls, oxygen tension ($tcPo_2$) differing by more than 20 mm.[95] Although leukocyte trapping within the capillaries is probably not the sole cause, it is likely that leukocytes become activated, transmigrate into the vein walls, and mediate some of the observed tissue damage. Consistently, findings in punch biopsy specimens of ulcers suggest that leukocytes play a role in the dermal manifestations of CVI.[96] Leukocytes, macrophages, and mast cells have all been observed in immunohistochemical and electron microscopic examinations of affected dermal tissue.[97]

The dermal fibroblast may also be dysfunctional and allow perpetuation of the ulcer. Decreased motility, in part mediated by the microenvironment, plays a role in the impaired healing process of ulcer tissue.[98] Comparison of venous ulcer fibroblasts with control fibroblasts with stimulation with TGF-β suggested that there are differences in collagen production.[99]

An interesting but unanswered question is "why are patients with similar degrees of reflux and hydrostatic pressures from CVI more predisposed to venous ulcers?" Data now suggest that iron metabolism and ulcer development are interrelated. Although commonly thought of as a consequence of all the other mechanisms of CVI, the iron deposition itself may cause tissue damage.[100] More convincingly, the risk of ulcer development among patients with class 4 to 6 CVI was sevenfold higher in those with the C282Y genotype, a mutation related to iron processing.[101] This is an interesting area where the efforts between basic scientists and clinicians are devoted to providing new information to better understand the disease and improve patient treatment.

THROMBOPHLEBITIS

Thrombophlebitis, or venous wall inflammation associated with thrombosis, may be sterile or associated with a bacterial infection.[102] Most often it involves the superficial venous system, such as the great saphenous or cephalic vein, and occurs after placement of an intravenous catheter or other superficial trauma. Symptoms include pain, redness, swelling, and tenderness to palpation (often like a cord) present in the affected limb. A systemic febrile response is usually absent in noninfected cases, whereas bacterial thrombophlebitis may be a source of postoperative fever.

It is unclear whether there is a specific genetic predisposition to thrombophlebitis, but clinical factors and environment likely play the biggest roles. Migratory thrombophlebitis is a special case, which was described by Trousseau in the 1800s, and is specifically linked to patients with pancreatic cancer. Thrombophlebitis can also manifest superficially through Mondor disease, in which the veins of the breast tissue particularly in the upper outer quadrant are affected.

Sterile phlebitis may occur in varicosities, as well as after venous stripping or endovenous ablation. An experimental study of sterile thrombophlebitis showed a typical sequence of early PMN attachment followed by transmigration and inflammatory changes. Approximately 25% of the time, thrombosis occurs before symptoms. The histologic pathology is an acute vasculitis

with marked thickening, inflammatory cells, and fibrin deposition.[103] Later resolution involves fibrotic changes and recanalization of the venous segment at variable rates over weeks to months. One study has shown that anticoagulation for 45 days significantly decreased proximal venous thrombus propagation by approximately 85%.[104]

The role of bacterial infection in directly promoting thrombosis has been described in various clinical settings.[105] The pathophysiology of infectious thrombophlebitis is similar to that of any closed-space infection, and bacterial antigens and proteins may directly stimulate VT and the extrinsic pathway. Organisms can be diagnosed by cultured from infectious thrombophlebitis, including both gram-positive and gram-negative species.

CONCLUSION

It is an exciting time to study venous thrombogenesis and the pathophysiology of the resulting vein wall damage, in part because it has been relatively neglected compared with arterial disease. Fortunately, the National Institutes of Health has put forth two requests for funding applications in the past several years to better study the clinical and basic pathobiology of venous disease and the surgeon general has approved a call to action against VTE. Adjuncts to or replacement therapies for anticoagulants hold tremendous promise and will hopefully decrease the early risk of PE and the late complications of PTS for the benefit of the patient.

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10 CHAPTER

Lymphatic Pathophysiology

MARLYS H. WITTE and MICHAEL J. BERNAS

Dedicated to the memory of Charles L. Witte, MD (1935-2003), beloved husband and father, and great teacher, researcher, and clinician. He was the primary author of the previous version of this chapter and an internationally recognized authority in the field of lymphology.

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In a narrow sense, the lymph circulation is a unidirectional vascular system that merely transports surplus tissue fluid back to the bloodstream. In a broader sense, however, this network stabilizes the mobile intercellular liquid and extracellular matrix microenvironment to ensure parenchymal cellular integrity and function.

In its entirety, the lymphatic system is composed of vascular conduits: lymphoid organs, including the lymph nodes, spleen, Peyer patches, thymus, and nasopharyngeal tonsils; and cellular elements that circulate in the liquid lymph, such as lymphocytes and macrophages. These migrating cells cross the blood-capillary barrier along with a multitude of immunoglobulins, polypeptides, plasma protein complexes, and cytokines and enter the lymphatics to return to the bloodstream. Although body water circulates very rapidly as a plasma suspension of red blood cells within the blood vascular compartment, it percolates slowly outside the bloodstream as a tissue fluid-lymph suspension of lymphocytes through lymph vessels and lymph nodes. As a specialized subcompartment of the extracellular space, therefore, the lymphatic system completes a closed loop for the circulation by returning liquid, macromolecules, and other blood elements that "escape" or "leak" from blood capillaries (Fig. 10.1).

ANATOMY

Although, historically, identification of lymphatic vessels has long been hampered by lack of readily identifiable structures, early physicians from Hippocrates (460–377 BC) to Aristotle (384–322 BC) and Erasistratus (310–250 BC) did describe vessels and nodes and on occasion visible intestinal lymphatic vessels in recently fed animals (see Kanter[1] for details). After a period of little scientific advancement, discovery of chylous mesenteric lacteals in a well-fed dog by Gasparo Asellius early in the 17th century set off a flurry of anatomic dissections in England and continental Europe that established the nearly ubiquitous presence of lymphatics throughout the body and their

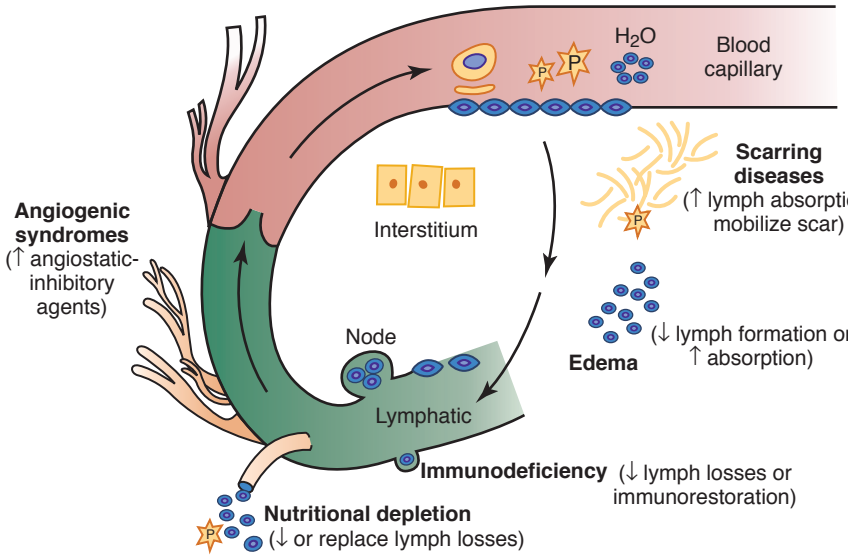

Figure 10.1 Blood-Lymph Circulatory Loop. Within the bloodstream, liquid flows rapidly as a plasma suspension of erythrocytes; outside the bloodstream, it flows slowly as a tissue fluid–lymph suspension of immunocytes through the lymphatics and lymph nodes. Small and large molecules, including plasma protein, trafficking cells, particulates, and respiratory gases, cross the blood–capillary endothelial barrier, percolate through the tissues, enter the lymph stream, and return to the central venous system to complete the loop. Clinical disorders of the blood-lymph circulatory loop are manifested as swelling, scarring, immunodeficiency, nutritional depletion, and uncontrolled lymphangiogenesis and angiotumorigenesis. Current and potential future therapeutic approaches are in parentheses.

BOX 10.1 Landmarks in Lymphology

1. Discovery of chyliferous vessels and "imaging" of the lymphatic system—Gaspar Asellius, 1627
2. Lymph as the milieu intérieur (internal environment)—Claude Bernard, 1878
3. Transcapillary exchange of liquid, lymph formation, and edema—Ernest Starling, 1895
4. Embryology and phylogeny of lymphatic system—F. Sabin, O. Kampmeier, 1903
5. Transcapillary protein movement and lymph absorption—A. Krogh, C. Drinker, H. Mayerson, F. C. Courtice, 1925
6. Lymphangiogenesis in vivo, 1932, and in vitro, 1984
7. Lymphocyte migrant streams—J. Yoffey, B. Morris, J. Gowans, 1939
8. Lymphatic imaging/classification—J. Kinmonth, M. Servelle, F. Kaindl, 1950
9. Intrinsic contractility and distinctive ultrastructure of lymphatics—J. Hall, I. Roddie, J. Casley-Smith, L. Leak, 1962
10. Lymphostatic disorders and/or edematous states—I. Rusznyak, G. Szabo, M. E. Foldi, W. Olszewski, A. Dumont, M. C. Witte, 1960
11. Lymphoscintigraphy, including sentinel node mapping, 1970
12. Highly specific molecular and/or histochemical markers—LYVE-1, Prox-1, podoplanin, 5′-nucleotidase, VEGFR-3, 1990
13. Lymphatic growth factors and/or genetics—K. Alitalo, 1996; teams from the University of Pittsburgh and University of Connecticut/St George; University of Arizona and University of Michigan, 1998, 2000

VEGFR, Vascular endothelial growth factor receptor.

important role in absorption of nutrients (Box 10.1).[2] These lymphatic "absorbents" accompany venous trunks everywhere, except in the central nervous system and cortical bony skeleton.

Macroscopic Anatomy

In general, lymph from the lower part of the torso and viscera enters the bloodstream via the thoracic duct at the left subclavian-jugular venous junction (see Figs. 10.1 and 10.2). Lymphatics from the head and neck and from the upper extremities enter the central veins either independently or by a common supraclavicular cistern. Numerous interconnections exist within this rich vascular network, and subvariant anatomic pathways are plentiful. For example, the bulk of cardiac and pulmonary lymph empties into the great veins in the right side of the neck. In contrast, intestinal lymph, which transports cholesterol, fat-soluble vitamins, and long-chain triglycerides as chylomicra, courses retroperitoneally to the aortic hiatus and with other visceral and retroperitoneal lymphatics forms the multichannel cisterna chyli and thoracic duct. The bulk of lymph formed in the liver flows retrograde or countercurrent to portal blood and joins intestinal lymph collectors just before the origin of the thoracic duct. Although these topographic variants influence development and progression of peripheral (lymph) edema only indirectly, they are nonetheless essential for a broad understanding of edema syndromes, including those accompanied by abnormal visceral lymphatics, celomic effusions, and chylous reflux.

Although the retina and brain do not technically have lymphatic apparatuses, they possess analogous circulations, such as the aqueous humor canal of Schlemm (the anterior chamber of the eye) or the cerebrospinal fluid/subarachnoid villus (pacchionian bodies) connections (the brain). Glial elements and non–endothelial-lined intracerebral perivascular (Virchow-Robin) spaces probably also serve to transport interstitial fluid to nearby intracranial venous sinuses. Extensive interruption of the cervical lymphatic trunks (e.g., after bilateral radical neck dissection) therefore causes prominent facial suffusion and a transient neurologic syndrome resembling pseudotumor cerebri,[3] whereas an infusion of crystalloid solution directly into the canine cisterna magna causes an elevation in intracranial pressure and increases lymph flow from draining neck lymphatics.[4,5] Although abundant lymphatic pathways thus exist for surplus tissue fluid to return to the bloodstream, homeostasis still depends on an unimpeded, intact, interstitial-lymph fluid circulatory system (see Figs. 10.1 and 10.2).

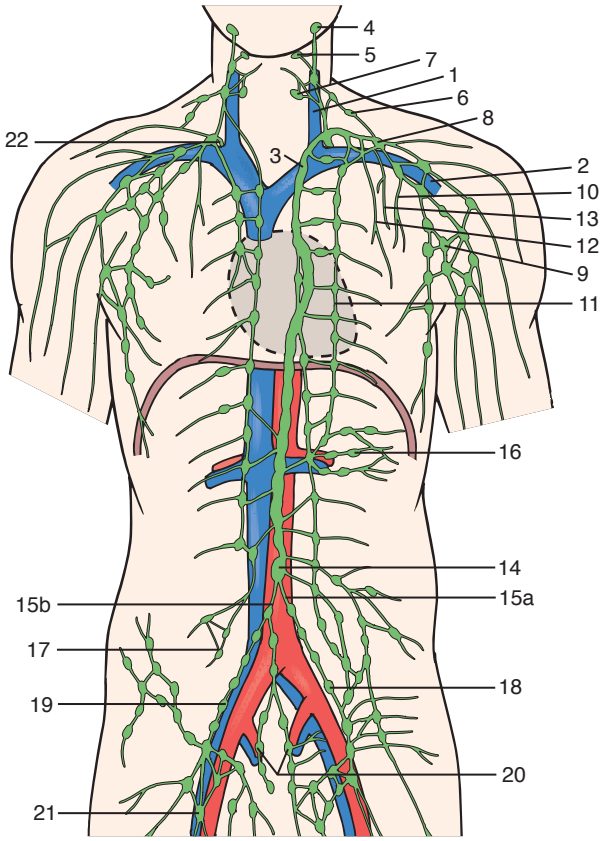

Figure 10.2 **Macroscopic Anatomy of the Lymphatic System Including Major Vessels, Structures, and Nodes in Relation to Major Arteries and Veins.** *1*, Left internal jugular vein; *2*, left subclavian vein; *3*, thoracic duct; *4*, parotid lymph nodes; *5*, submandibular lymph nodes; *6*, accessory and comitant lymph nodes of the accessory nerve; *7*, internal jugular lymph nodes with left jugular trunk; *8*, supraclavicular lymph nodes with left supraclavicular trunk; *9*, axillary lymph nodes with left subclavian trunk; *10*, intercostal lymph nodes with left intercostals trunk; *11*, parasternal lymph nodes with parasternal trunk; *12*, anterior mediastinal lymph nodes with left anterior mediastinal trunk; *13*, tracheobronchial lymph nodes with left tracheobronchial trunk; *14*, cisterna chyli; *15a*, left lumbar trunk; *15b*, right lumbar trunk; *16*, mesenteric lymph nodes; *17*, lumbar lymph nodes; *18*, left common iliac lymph nodes; *19*, right external iliac lymph nodes; *20*, internal iliac; *21*, inguinal lymph nodes; *22*, right lymphatic duct. (Modified from Kubik S. In: Földi M, Földi E, eds. *Foldi's Textbook of Lymphology.* 3rd ed. Munich: Urban & Fischer; 2012.)

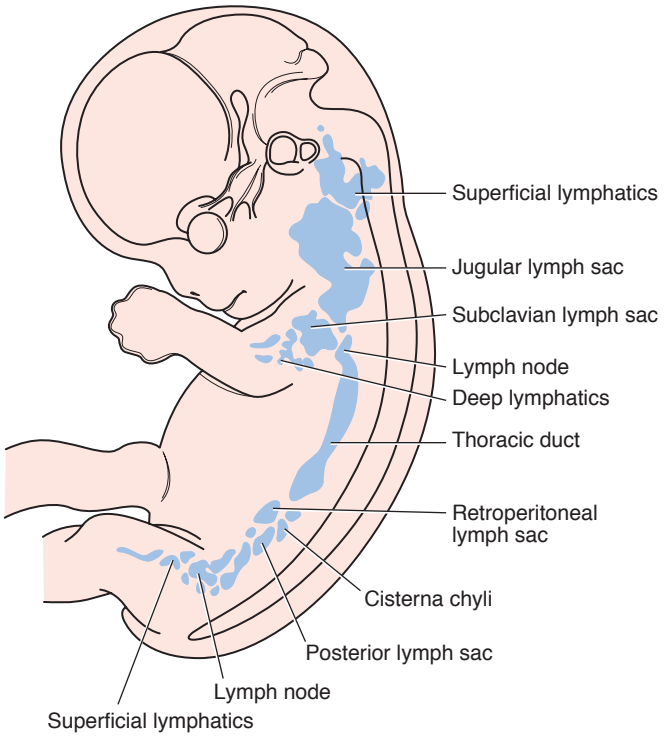

Figure 10.3 The developing lymphatic system showing the primary lymph sacs and the thoracic duct primordium, as well as several lymph nodes of a 2-month-old human embryo. (Modified from Sabin FR. On the origin and development of the lymphatic system from the veins and the development of the lymph hearts and the thoracic duct in the pig. *Am J Anat.* 1902;1:367, and Yoffey JM, Courtice FC. *Lymphatics, Lymph and the Lymphomyeloid Complex.* New York: Academic Press; 1970.)

Embryonic Development

Controversy has persisted since the early 1900s about the embryologic origin of lymphatics, that is, lymphovasculogenesis (endothelial precursors or stem cells, such as lymphangioblasts, differentiate and proliferate into a primitive tubular network) and subsequent lymphangiogenesis (sprouting from existing vessels; see Box 10.1).[6] According to Sabin, the primary lymphatic plexuses derive from central veins and their growth progresses centrifugally by sprouting toward the periphery and ultimately forming the superficial lymphatic system (Fig. 10.3).[7] In contrast, Kampmeier,[8] after a review of serial tissue sections, including Sabin's original human embryo preparations, and phylogenetic considerations, proposed the centripetal theory that the lymphatic system arises independently from tissue mesenchyme in peripheral tissues and the surrounding primary lymph sacs and only later joins the central venous system.

Although recent studies of the growth regulatory gene *PROX1*[9] and the receptor for lymphatic vascular endothelial growth factor (VEGFR-3)[10] have tended to support the centrifugal theory (origin from venous spouting), other elegant work has demonstrated a substantial centripetal contribution from mesenchymal lymphangioblasts in the engrafted wing lymphatic system of chimeric quail chick embryos[11] and early avian embryos through *PROX1* staining.[12] Both processes may contribute in various degrees to the ultimate link between the lymph and blood vasculature (e.g., the cervical thoracic duct/venous junction in humans).

Light Microscopic Anatomy

As an afferent vascular system, the lymphatics originate within the interstitium as specialized capillaries, although in certain organs, such as the liver, they seem to emanate from nonendothelialized precapillary channels (e.g., the spaces of Disse).[13] Lymphatic capillaries are remarkably porous and readily permit the entry of even large macromolecules (molecular weight >1000 kD). In this respect, they resemble the uniquely "leaky" fenestrated sinusoidal blood capillaries of the liver but are in distinct contrast to most other blood capillaries, which are relatively impervious to macromolecules even the size of albumin (molecular weight, 69 kD).[14]

Under light microscopy without treatment, it is difficult to distinguish between blood and lymph vessels, although the latter are usually thin walled and tortuous, have a wider, more

irregular lumen, and are largely devoid of red blood cells. Many staining features have been advocated to differentiate between blood and lymph microvasculature, such as the endothelial marker factor VIII–related antigen: von Willebrand factor (vWF). Although staining characteristics vary in both normal and pathologic states and at different sites (perhaps related to endothelial cell de-differentiation), in general, lymphatic staining resembles but is less intense than its blood vessel counterpart. In other words, the staining differences have been more quantitative than qualitative.[15-17] Most recently, several new markers have been proposed that appear to be more lymphatic specific, particularly antibodies to lymphatic endothelial hyaluronan receptor-1 (LYVE-1; a homologue of CD44 glycoprotein),[18] podoplanin,[19] PROX1,[9] and to less degree, VEGFR-3 (the endothelial receptor for VEGF-C, the so-called lymphatic growth factor),[20,21] as well as 5′-nucleotidase.[22]

Lymphatic-Specific Markers

Lymphatic vessels can increasingly be distinguished from blood vessels in tissue sections by whole-mount staining with specific markers. Only 15 years ago, little histochemical specificity existed to distinguish lymphatic vessels from blood capillaries and veins, and identification was based primarily on morphology, distinctive ultrastructure, or both. One of the most commonly used and most specific markers in use today is LYVE-1.[19,23] It has been applied to tissues ranging from early mouse embryo to adult human and highlights collecting vessels and lymphatic capillaries (but not larger-caliber vessels). Another strong marker localizing to the nucleus of lymphatic endothelial cells and adaptable to multiple tissues is the transcription factor PROX1.[23] Podoplanin recognizes a transmembrane glycoprotein[24] in lymphatics but not blood vessel endothelial cells in the mouse, whereas its human analogue, D2-40,[25] also sharply distinguishes lymphatic from blood vessel endothelium but stains other distinguishable cells. This feature has been useful in identifying preexisting and new lymphatics in tumor specimens and in generating quantitative differentials from blood vessels and indices of lymphatic invasiveness and tumor dissemination.[26] 5′-Nucleotidase staining is used by research laboratories for its lymphatic specificity[22,27] and other common markers showing some cross reactivity to veins include VEGFR-3[10] and neuropilin-2[28] (reviewed elsewhere).[29,30] Thus an array of lymphatic markers are now available to distinguish lymphatic from blood vessels, although there is overlap of cell types in normal conditions and even more so in pathologic states.

Ultrastructure

Ultrastructurally, lymph capillaries display both "open" and "closed (tight)" endothelial junctions, often with prominent convolutions[31] and these capillaries can dramatically adjust their shape and lumen size. Unlike blood capillaries, a basal lamina (basement membrane) is tenuous or lacking altogether in lymph capillaries.[31,32] Moreover, complex elastic fibrils, termed *anchoring filaments,* tether the outer portions of the endothelium to a fibrous gel matrix in the interstitium.[33-35] These filaments allow the lymph microvessels to open wide, which causes a sudden increase in tissue fluid load and pressure, in contrast to the simultaneous collapse of adjacent blood capillaries (Fig. 10.4). Just beyond the lymph capillaries are the terminal lymphatics. In contrast to more proximal and larger lymph collectors and trunks, the terminal lymphatics are devoid of smooth muscle, although the endothelial lining is rich in the contractile protein actin.[15] Intraluminal bicuspid valves are also prominent features and serve to partition the lymphatic vessels into discrete contractile segments termed *lymphangions*.[36] These specialized microscopic features support the delicate lymphatic apparatus's functions of absorbing and transporting elements and the large protein moieties, cells, and foreign agents of the bloodstream (e.g., viruses, bacteria) that gain access to the interstitial space (Figs. 10.5 and 10.6).

Structural-Functional Imaging

Early physicians were able to visualize the lymphatic system only by observing chyle-filled mesenteric lymphatics. Asellius's initial publication[37] included what has been reported as the first color anatomic plate in history.[1] This was followed by intralymphatic injection of mercury into cadavers by Nuck in 1692, which depicted fine channels,[38] then the detailed and elegant work of Mascagni in 1787,[39] and subsequently, the classic images of both subcutaneous and deep vessels by Sappey in 1874.[40] von Recklinghausen used silver nitrate, which allowed imaging to take place without removal of surrounding tissue and facilitated visualization of lymphatic vessels as distinct from blood capillaries.[41] Gerota developed a technique in 1896 of injecting a mixture of Prussian blue and turpentine to highlight the vessels,[42] and this was followed in 1933 by the intracutaneous injection of vital dyes that bind to tissue proteins by Hudack and McMaster,[43] which is a technique still used today for investigation and in the clinic (Fig. 10.7).

Modern imaging techniques also include direct (intralymphatic) injection of oily contrast agents, termed lymphangiography, first described by Kinmonth in 1954,[44] and whole-body lymphangioscintigraphy after subcutaneous or intradermal injection of protein-bound radiotracers (see Witte et al.[45] for an overview; see Fig. 10.7). Other agents used for indirect lymphography include various fluorescent or magnetic particles,[46,47] infrared particles and dyes,[48-50] immunoglobulin conjugates,[51] and microbubbles[52] for detection with fluorescent microscopes, optical imaging systems, computed tomography (CT), magnetic resonance imaging (MRI; with and without contrast),[53] and ultrasound,[54,55] with an expanding potential for highly specific molecular imaging. New contrast agents and techniques continue to be developed.[56-58]

PHYSIOLOGY

Any protein which leaves these vessels…is lost for the time to the vascular system…it must be collected by lymphatics and restored to the vascular system by way of the thoracic or right lymphatic duct.

–PHYSIOLOGIST ERNEST STARLING, 1897

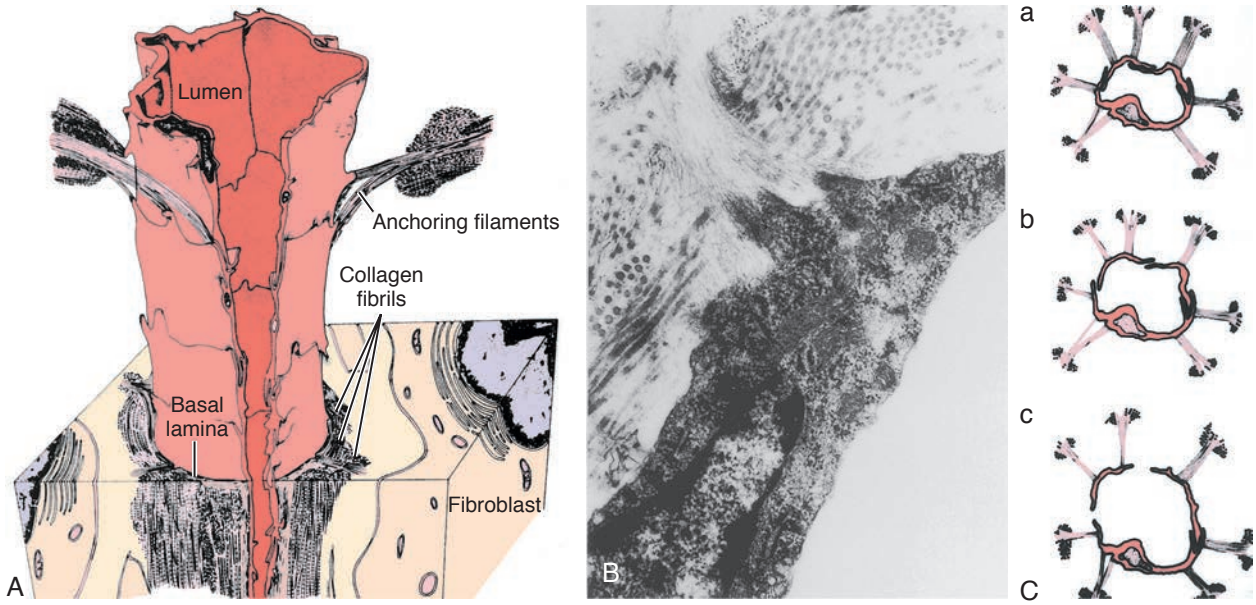

Figure 10.4 (A) Lymphatic capillary reconstructed from collated electron micrographs. The lymphatic anchoring filaments originate from the albumin surface of the endothelial cells and extend into adjacent collagen bundles, thereby forming a firm connection between the lymphatic capillary wall and the surrounding interstitium. (B) Transmission electron micrograph demonstrating anchoring filaments (AF) that derive from the lymphatic endothelium and join nearby collagen bundles. (C) Response of lymphatic capillaries to an increase in interstitial fluid volume. As the tissue matrix expands, tension on the AF rises, and the lymph capillaries open widely to allow more rapid entry of liquid and solute (*a* to *c*). In contrast to stretching of the lymph capillaries, a rise in matrix pressure collapses the blood capillaries, thereby restricting further plasma filtration. (From Leak LV, Burke JF. Ultrastructural studies on the lymphatic anchoring filaments. *J Cell Biol.* 1968;30:129–149; and Leak LV. Electron microscopic observation on lymphatic capillaries and the structural components of the connective tissue–lymph interface. *Microvasc Res.* 1970;2:361–391.)

General Principles

As a fine adjuster of the tissue microenvironment, the lymphatic system is often neglected in most treatises on vascular diseases. Yet this delicate system, so inconspicuous during life and collapsed after death, helps to maintain the liquid, protein, and osmotic equilibrium around cells and aids in absorption and distribution of nutrients, disposal of wastes, and exchange of oxygen and carbon dioxide in the local milieu intérieur.

Interstitial (Lymph) Fluid

Two-thirds of the body is composed of water, and most of this liquid volume is contained within cells. However, the remainder that exists outside cells continuously circulates. In a series of epochal experiments conducted more than a century ago, the English physiologist Ernest Starling outlined the pivotal factors that regulate partitioning of the extracellular fluid.[59,60] In brief, the distribution of fluid between the blood vascular compartment and tissues and the net flux of plasma escaping from the bloodstream depends primarily on the transcapillary balance of hydrostatic and protein osmotic pressure gradients as modified by the character (i.e., hydraulic conductance) of the filtering microvascular surface (Fig. 10.8; also see Box 10.1). Normally, a small excess of tissue fluid forms continuously (net capillary filtration), and this surplus enters the lymphatic system and returns to the venous system. In contrast to blood, which flows in a circular pattern at several liters per minute, lymph flows entirely in one direction and at rest at a rate of only 1.5 to 2.5 L/24 hour. This limited volume derives from a slight hydrodynamic imbalance that favors movement of fluid, salt, and macromolecules from plasma into tissue spaces. Although blood capillary beds vary in hydraulic conductance, in general, disturbances in the transcapillary hydrostatic and protein osmotic pressure gradients (Starling forces) tend to promote edema that is low in protein content (<1.0 g/dL [10 g/L]), whereas impedance to lymph flow (lymph stasis) promotes (lymph) edema that is high in protein content (>1.5 g/dL [15 g/L]).

Unlike blood flow, which is propelled by a powerful and highly specialized muscular pump (the heart), propulsion of lymph originates predominantly from spontaneous intrinsic segmental contractions of larger and probably also small lymph trunks,[61-63] and to less extent, from extrinsic "haphazard forces" such as breathing, sighing, yawning, muscular squeezing (e.g., alimentary peristalsis), and transmitted arterial pulsations (Table 10.1).[63,64] As noted, the contractions of lymphatic segments between intraluminal valves (i.e., the lymphangions) are highly responsive to lymph volume. Thus an increase in lymph formation is accompanied by more frequent and more powerful lymphangion contractions, a lymphodynamic response that resembles Starling's other major physiologic principle, the law of the heart.[36,65]

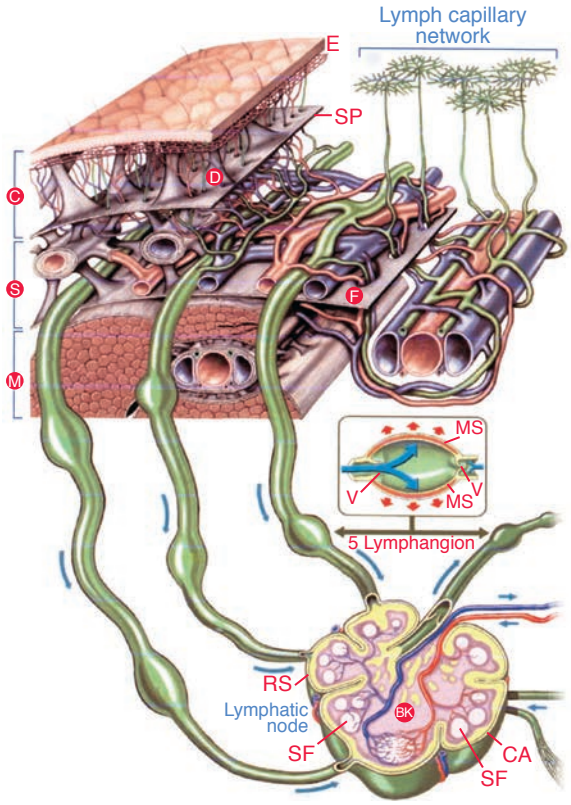

Figure 10.5 The lymphatic system consists of an initial superficial valveless network of endothelium-lined vessels connected to a deep valved collector system (lymphangion pumping segments defined by the valves). The deeper vessels run alongside major blood vessels and drain through lymph nodes to the main collectors; they ultimately empty into the thoracic duct or the right lymphatic duct. *BK*, Blood capillary network; *C*, cutis; *CA*, capsule; *D*, dermis; *E*, epidermis; *F*, fascia; *M*, musculature; *MS*, muscle layer; *RS*, marginal sinus; *S*, subcutis; *SF*, second follicle; *SP*, subcutaneous pseudofascia; *V*, lymphatic valves. (Modified with permission from BSN-Jobst Emmerich Conception, 2002.)

Lymphatic truncal contraction, like venous and arterial vasomotion, is mediated by sympathomimetic agents (both α- and β-adrenergic agonists),[66,67] byproducts of arachidonic acid metabolism (thromboxanes and prostaglandins),[68-71] and neurogenic, even pacemaker stimuli.[72,73] Oddly, in different regions of the body, lymphatic trunks exhibit varying sensitivity to different vasoactive and neurogenic stimulants.[67,74,75] Although the importance of truncal vasomotion as mediated by tunica smooth muscle is well established, it remains unclear whether terminal lymphatics or capillaries are also capable of vasomotion or are simply passive channels.

Lymph Nodes

In addition to their central immunologic role, lymph nodes are a potential site of impediment to the free flow of lymph. Unlike frogs, which lack lymph nodes but possess four or more strategically placed lymph hearts that propel large quantities of peripheral lymph back to the bloodstream,[76,77] mammals possess immunoreactive lymph nodes, which, when swollen, fibrotic, or atrophic, may act to initiate or perpetuate lymph stasis.[78,79]

Flow-Pressure Dynamics

Although lymphatic vessels, like veins, are thin-walled flexible conduits that return liquid to the heart, the flow-pressure relationships in the venous system and the lymphatic system are different. The energy to drive blood in the venous system derives primarily from the thrust of the heart. The cardiac propulsive boost maintains a pressure head through the arteries and blood capillaries into the veins. In contrast, lymph vessels in tissues are not directly contiguous with the blood vasculature, and the chief source of energy for propulsion of lymph emanates from the intrinsic lymphatic truncal wall

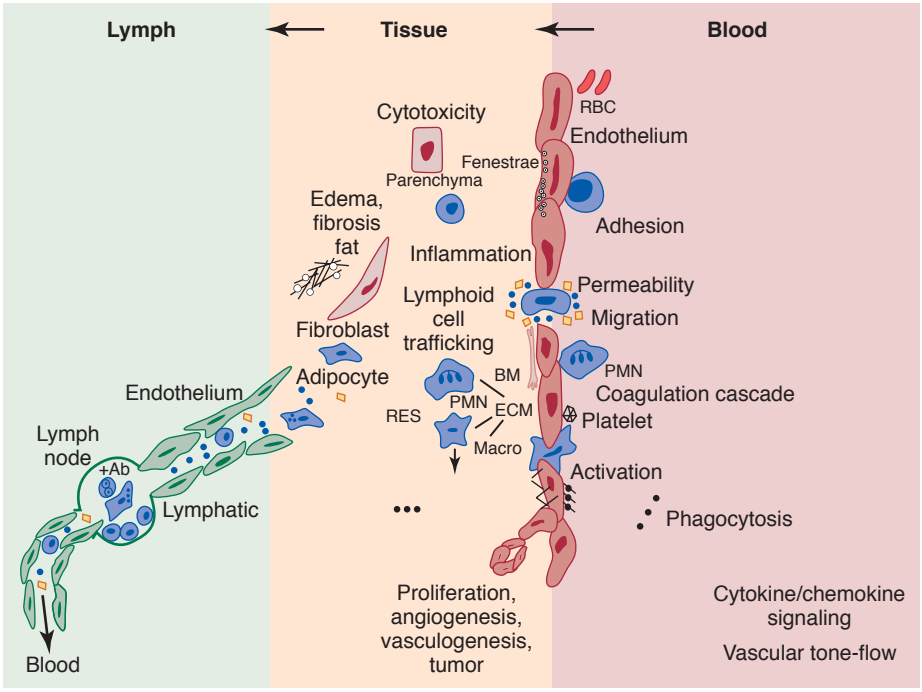

Figure 10.6 The postulated role of endothelial processes in microcirculatory events that have a bearing on angiogenesis in the blood-lymph loop. Such processes include macromolecular and liquid permeability, vasoresponsiveness, leukocyte adhesion and transmigration, coagulation cascading, particulate phagocytosis, antigen presentation and cytokine activation, lymphoid cell trafficking, and proliferative events leading to new vessel or tumor growth. Many mediators of these events have been identified by studying processes implicated at the blood vascular endothelial surface, which are likely to also occur at the lymphatic endothelial interface. The relative anatomic and dynamic relationships between blood and lymph vascular endothelium, parenchymal and extravascular connective tissue, and transmigrating leukocytes are shown. *Black circle*, exogenous particulates; *black square*, macromolecules; *open circles*, fluid (plasma, interstitial, or lymph). *Ab*, Antibody; *BM*, basement membrane; *ECM*, extracellular matrix; *macro*, macrophage; *PMN*, polymorphonuclear neutrophil; *RBC*, red blood cell; *RES*, reticuloendothelial system. (Modified from Witte MH, Dellinger MT, Papendieck CM, Boccardo F. Overlapping biomarkers, pathways, processes and syndromes in lymphatic development, growth, and neoplasia. *Clin Exp Metastasis.* 2012;29:707–727.)

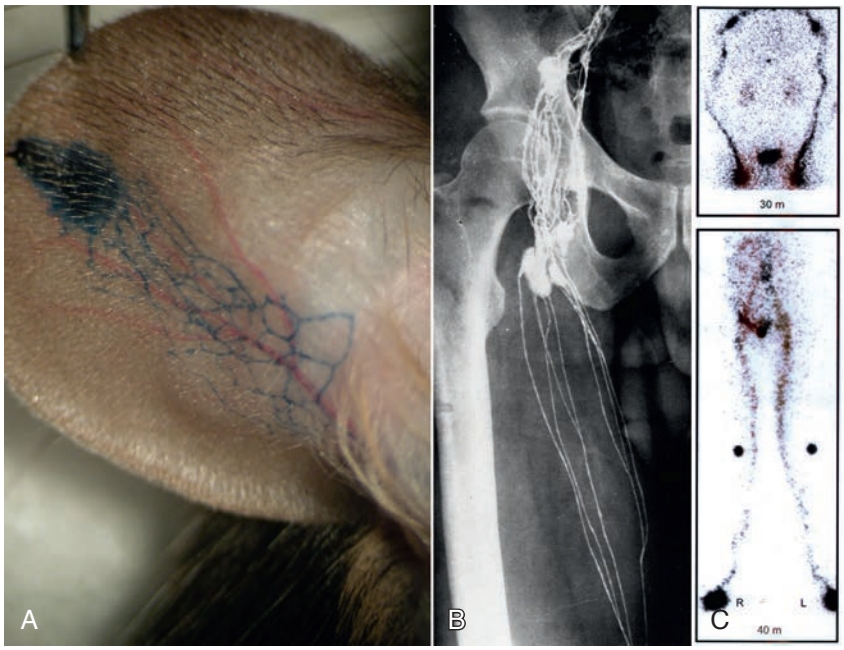

Figure 10.7 Imaging Techniques to Delineate the Structure and Function of the Lymphatic System. (A) Evans blue dye injected intradermally in the tip of a mouse ear rapidly displays the draining lymphatic channels. A similar vital dye (lymphazurin blue or isosulfan blue) is used in the clinic. (B) Classic lymphography image from Kinmonth clearly depicting the fine lymphatic vessels of the upper part of the thigh in an adult human.[44] (C) Radioisotope lymphangioscintigraphy displaying normal lymphatic tracer transport in the arms *(upper panel)* and the legs *(lower panel)*. A single injection into each hand or foot is seen at the bottom of each image, with markers at the knees in the lower panel. (Modified from Witte CL, Witte MH, Unger EC. Advances in imaging of lymph flow disorders. *Radiographics.* 2000;20: 1697–1719.)

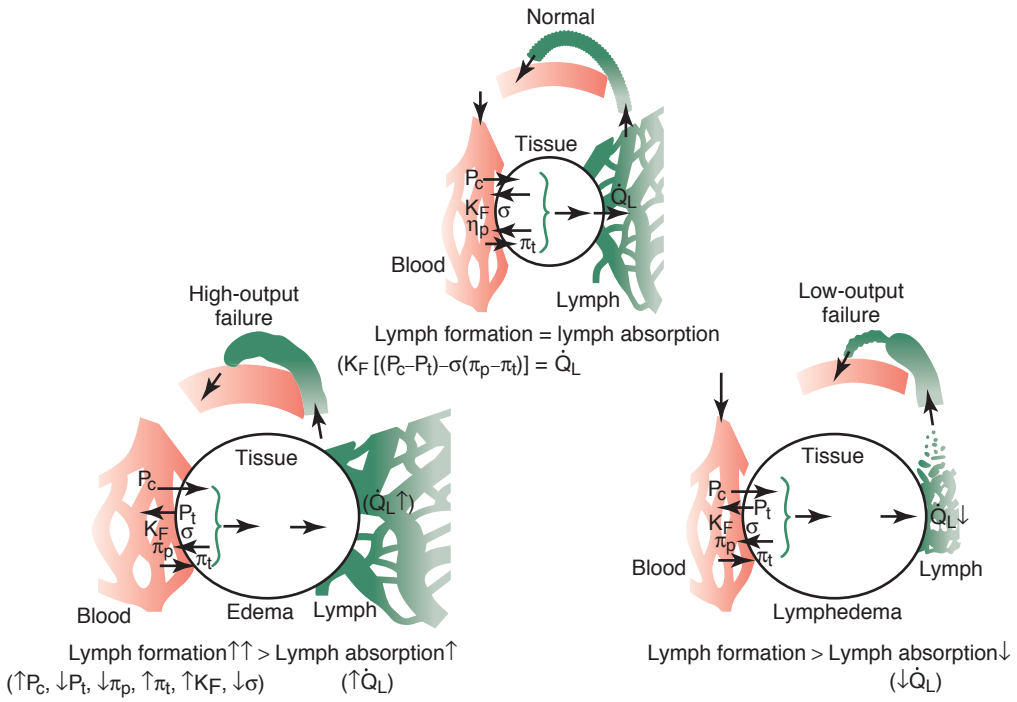

Figure 10.8 Primary forces regulating fluid flux into the interstitium and the importance of lymph flow in maintaining steady-state interstitial fluid volume, and hence, stable partitioning of extracellular fluid between the bloodstream and the interstitium (Starling's equilibrium). Edema may occur as a result of high-output failure of lymph circulation (lymph overload with increased lymph flow) *(lower left)* or, less commonly, low-output failure (lymphedema) caused by interruption in lymph transport capacity *(lower right)*.

contractions (propulsor lymphaticum).[61-77,80] Like amphibian lymph hearts (cor lymphaticum), mammalian lymphatic smooth muscle beats rhythmically, and in the presence of a well-developed intraluminal valve system, facilitates transport of lymph.[81] In a sense, the lymphatic structures function as micropumps that respond to fluid challenges with increases in both rate and stroke volume.[36,68] Ordinarily, resistance to flow in the lymphatic vessels is relatively high in comparison to the low resistance in the venous system,[82] but the pumping capacity of the lymphatics is able to overcome this impedance by generating intraluminal pressures of 30 to 50 mm Hg and sometimes even equaling or exceeding arterial pressure.[61,82,83] This formidable lymphatic ejection force is modulated not only by filling pressure but also by temperature, sympathomimetics, neurogenic stimuli, circulating hormones, and locally released paracrine and autocrine cytokine secretions.[84]

It is often mistakenly thought that lymph return, like venous return, is directly enhanced by truncal compression from skeletal muscle and other adjacent structures. Although muscular contraction and external massage clearly accelerate lymph return in the presence of edema,[83] under normal conditions, peripheral lymph flow is regulated primarily by spontaneous contraction

TABLE 10.1 Circulatory Dynamics of Vascular Conduits

	Lymphatic	Vein	Artery
Primary propulsive unit	Lymphangion	Heart	Heart
Secondary propulsive force	Haphazard[a]	Skeletal muscle	Vasomotion
Distal (upright) pressure (mm Hg)	2-3	90-100	20
Central pressure (mm Hg)	6-10	0-2	100
Flow rate	Very low	High	High
Vascular resistance	Relatively high	Very low	High
Intraluminal valves	Innumerable	Several	None
Impediment to flow	Lymph nodes	None	None
Conduit fluid column	Incomplete	Complete	Complete
Conduit failure	Edema (>1.5 g/dL) with brawny induration and acanthosis	Edema (<1.0 g/dL) with skin pigmentation and "stasis" ulceration	Claudication, rest pain, tissue necrosis

[a]Breathing, sighing, yawning, peristalsis, and transmitted arterial pulsation; skeletal muscle contraction also increases the amplitude and frequency of lymphatic contractions and squeezes interstitial fluid into the initial lymphatics (i.e., lymph capillaries).

of the lymphatics themselves.[83,84] In peripheral lymphatics, unlike peripheral veins, the column of liquid is incomplete. Accordingly, with normal intralymphatic pressure, external compression is ineffective in propelling lymph onward, although it may increase the frequency and amplitude of lymphatic contractions. In other words, lymphatics, in contrast to veins, are not sufficiently "primed."[85] During lymphatic obstruction and persistent lymph stasis, the fluid column in the lymphatics becomes continuous, and skeletal muscle or forceful external compression then becomes an effective pumping mechanism that aids lymph transport.[83,85]

Studies of the effect of gravity on peripheral lymphatic and venous pressure confirm these findings. Although assuming an erect position sharply raises distal venous pressure, peripheral intralymphatic pressure is unaffected, although lymphatic truncal pulsation increases in both frequency and amplitude.[85] This arrangement favors removal of tissue fluid by the lymphatics during dependency because, unlike veins, the lymphatics operate at much lower hydrostatic pressure. After the lymphatics become obstructed, truncal contractions quicken at first, but then the intraluminal valves gradually give way, and as the lymph fluid column becomes continuous, this mechanical advantage is lost, and chronic lymphedema supervenes.

Lymphatic Transport Route

The lymphatic route of transport of liquid, protein, and macromolecules, particularly chylomicra originating in the small intestine, is well recognized, albeit underappreciated, and the lymphogenous route of cancer spread forms the conceptual basis for most current treatment approaches to solid organ cancers. The role of lymphatic uptake and clearance of microorganisms in the clinical manifestations (e.g., lymphangitic streaking), pathogenesis, inflammatory and other tissue responses, and immune defense has been underemphasized, particularly in recent years. From the 1930s to the 1960s (see Box 10.1), a number of carefully performed studies examined the critical lymphatic route in the initial and later phases of viral and bacterial infection and the dynamic physiology of the afferent and efferent arms of the immune response.[86] The lymphologist Joseph Yoffey laid the groundwork for recognition of the importance of the "inert" lymphocyte and the discovery of lymphoid cell trafficking, which are fundamental to the principles of modern immunology.[87,88] Recasting these older investigations with more modern physiologic techniques and molecular tools may yield new translational insight into disorders ranging from AIDS and tuberculosis to parasitic disorders while also elucidating the lymphatic spread of cancer (Fig. 10.9).[81,89-92]

MOLECULAR LYMPHOLOGY

With improvement in methods of studying chromosomes, unexpected light may be shed on Milroy's disease and other hereditary lymphedemas.

–Lymphatic/Vascular Surgeon John Kinmonth, 1972

Advances in molecular biology and the development of new techniques from the Human Genome Project have ushered in the era of molecular lymphology.

Lymphangiogenesis

In contrast to uncontrolled new growth (lymphangiosarcoma), programmed proliferation of lymphatic endothelium with tube formation (lymphangiogenesis) is critical to a host of physiologic and pathologic processes. During the past several decades, since the phenomenon of angiogenesis was first reproduced in endothelial cell and mixed vascular tissue cultures,[93,94] considerable attention has been directed toward furthering understanding of this process, but largely in the context of blood vessel growth (hemangiogenesis).[95,96] The lymphatic counterpart (i.e., lymphangiogenesis) has received scant attention until recently,

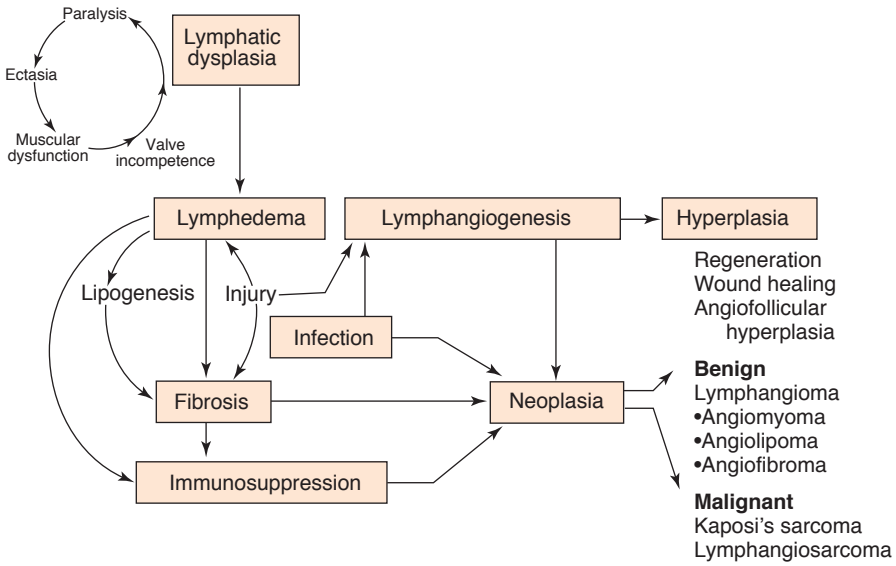

Figure 10.9 The Pathogenesis of Peripheral Lymphedema and Some of Its Sequelae. According to this scheme, congenitally deficient or obstructed lymphatics promote lymph stasis, which is accompanied by deranged truncal contractility, progressive valve incompetence, destruction of contractile elements (lymphangioparalysis), and gradual ectasia of lymphatic collectors. After a variable period (occult lymphedema), sometimes aggravated by environmental trauma, a series of events is set into motion that culminates in chronic lymphedema. This clinical state is characterized not only by progressive swelling but also by fat and scar deposition, immunodysregulation, a propensity for cellulitis, and microvascular proliferation; these processes are essential for repair and regeneration but may result in bizarre and poorly understood new vascular growths.

although lymphatic (re)generation is essential to health, and disorders of lymph flow and lymphatic growth are common, often disfiguring, and sometimes life- and limb-threatening.[95]

In now classic studies, Clark and Clark documented the extension of lymphatic capillaries by outgrowth from preexisting lymph vessels in rabbit ear transparent chambers (Fig. 10.10A).[97] Later, Pullinger and Florey emphasized that despite the similar appearance of each vascular endothelium, lymphatics are consistently connected to lymphatics, veins to veins, and arteries to arteries without intermingling (see Fig. 10.10B).[98]

After experimental hind limb circumferential skin incision, new lymphatics traverse the integumentary gap by postoperative day 4. By the eighth day, lymphatic continuity is restored anatomically (delineated by distribution of intradermal India ink particles) and physiologically (remission of transient peripheral edema).[99,100] Bellman and Odén meticulously documented, by Thorotrast microlymphangiography, the time course and extent of newly formed lymphatics in circumferential wounds in the rabbit ear, including lymphatic bridging through newly formed scar (see Fig. 10.10C).[101,102] As lymphatics increased in caliber, intraluminal valves and sinuous dilatations appeared. Subsequent studies documented restoration of distinctive ultrastructural features in newly regenerated lymphatic vessels, including characteristic overlapping junctions and Weibel-Palade bodies (storage depots for vWf [factor VIII–related antigen]).[103-105]

Like the more than 1 trillion blood vascular endothelial cells that are normally dormant,[106,107] lymphatic endothelial cell turnover is also miniscule.[108] However, with injury, incorporation of tritiated thymidine into proliferating lymphatic endothelium sharply increases.[108] Moreover, fetal lymphatics show greater labeling than do neonatal and adult lymphatics, whereas visceral lymphatic endothelium proliferates more rapidly than does peripheral lymphatic endothelium.[109]

Lymphatic endothelium was first isolated in vitro from bovine mesenteric lymphatics[17] and in the same year, from a patient with a large cervicomediastinal hygroma,[110] and subsequently, from another patient with a retroperitoneal lymphangioma,[15] as well as from canine and human thoracic ducts.[16] Lymphatic endothelial cells from sheep, dog, mouse, rat, and ferret lymphatic collectors have now been isolated, passed in culture, and studied by techniques similar to those used for blood large-vessel and microvessel isolation. Putative lymphatic endothelium has also been isolated from mixed microvascular cultures of human foreskin and skin by separation with magnetic beads and labeling with lymphatic markers such as LYVE-1.[111] Lymphangiogenesis in vitro was first demonstrated more than 2 decades ago with the formation of tubes and cystlike structures spontaneously[110] or after the addition of collagen matrix to tissue culture.[112]

Lymphovascular Genomics

Growing evidence has confirmed that lymphangiogenesis is under genetic control (Fig. 10.11 and Table 10.2; also see recent reviews).[6,29,30] For example, a gene or genes expressed from nonactivated portions of the inactivated X chromosome or from the Y chromosome are probably involved in lymphatic development, and a deficiency in this gene or its product(s) is responsible for Turner syndrome (XO ovarian dysgenesis), which exhibits a variety of lymphatic and other cardiovascular anomalies. Other chromosomal aneuploidies, such as trisomy 21 (Down syndrome), and rearrangements (additions, deletions, translocations) also occasionally manifest as strangulating fetal cystic hygroma, lymphedema, and intestinal lymphangiectasia and are commonly associated with early fetal demise (see Fig. 10.11).[113]

Both forward and reverse genetic techniques have provided clues to sites of "lymphangiogenesis genes," and a spectrum of developmental and other hereditary lymphedema-angiodysplasia syndromes (often with autosomal dominant inheritance) have been catalogued (see Fig. 10.11).[6,12,114-117] They include mutations in a subpopulation of patients with Milroy syndrome *(VEGFR-3)*,[118] mutations in the transcription factor *SOX18*[119] in two families with autosomal recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia syndrome, and mutations in the transcription factor *FOXC2*[120] uniformly

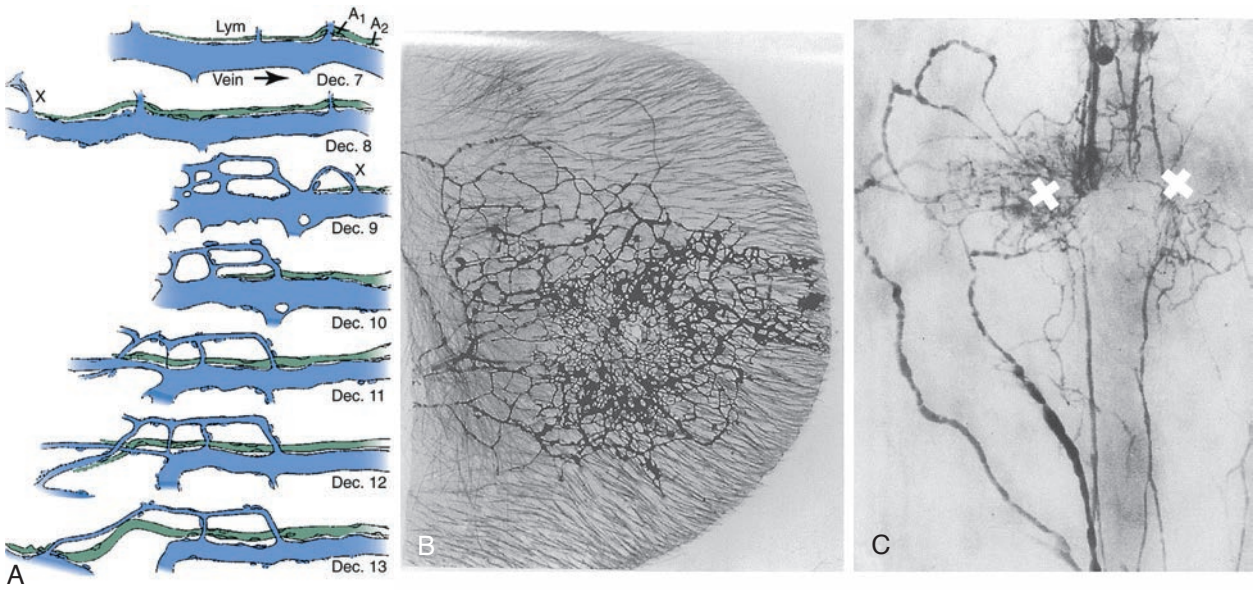

Figure 10.10 Classic Observations on Lymphangiogenesis in vivo. (A) Series of camera lucida, oil immersion records showing growth of an individual lymphatic capillary in the rabbit ear (LYM). Corresponding parts of a lymphatic and vein have been placed below one another in drawings of December (Dec) 7, 8, and 9 to 13. The drawings of Dec 9 to 13 have been moved to the right so that X represents the same spot on Dec 8 and 9. During growth of the lymphatic, there has been conspicuous retraction and disappearance of branches and loops of the blood vessel. Retraction of a short lymphatic tip is seen between Dec 11 and 13. Lymphatic endothelial nuclei are stippled. A1 and A2 are two daughter nuclei after a mitotic division (×177; magnification of original drawing, ×700). (B) Twenty-one days after making a turpentine abscess that perforated a mouse's ear, a dense new network of lymphatic capillaries surrounds the hole (×8). (C) In vivo microlymphangiogram 24 days after a short transverse incision in the skin of a rabbit ear. The extent of the incision is depicted by the *crosses*. The distal part of the ear is uppermost. Several arcading vessels around the incision and numerous fine connections through the scar are seen. ([A] From Clark ER, Clark EL. Observations on the new growth of lymphatic vessels as seen in transparent chambers introduced into the rabbit's ear. *Am J Anat.* 1932;51:49–87. [B] From Pullinger DB, Florey WH. Proliferation of lymphatics in inflammation. *J Pathol Bacteriol.* 1937;45:157–170. [C] From Bellman S, Oden B. Regeneration of surgically divided lymph vessels: an experimental study on the rabbit's ear. *Acta Chir Scand.* 1959;116:99–117.)

in hundreds of patients with lymphedema-distichiasis (LD) syndrome. Interestingly, the genetically engineered haploinsufficient (±) Foxc2 mouse[121] exhibits a double row of eyelashes and a hyperplastic lymphatic phenotype like human LD. More recently, additional mutations have been identified, including inherited generalized lymphatic dysplasia (Hennekam syndrome; *CCBE1*),[122] lymphedema type 1C *(GJC2),*[123] lymphedema-choanal atresia *(PTPN14),*[124] Emberger syndrome *(GATA2),*[125] microcephaly-lymphedema-chorioretinopathy *(KIF11),* Milroy-like lymphedema *(VEGF-C),* and oculodentaldigital lymphedema *(GJA1)* (see review)[117] Other genes (*HGF* and *MET*) have been associated with inherited lymphedema; however, no syndrome has been linked with these genes.[126] These known mutations pinpoint just a small portion of the more than 45 distinct Online Mendelian Inheritance in Man (OMIM) and non-OMIM familial disorders affecting the lymphatic segment of the "vasculature,"[112,127] suggesting that genes involved in normal and pathologic lymphatic growth and development span the entire genome (see Fig. 10.11).

Growth/Inhibitory Factors

Although the underlying mechanisms governing lymphangiogenesis are only beginning to be understood, a variety of stimulatory (e.g., VEGF-C and VEGF-D) and inhibitory factors, including the angiopoietin-1–angiopoietin-2 yin-yang interaction, modulate growth, development, and remodeling of the lymphatic vasculature (see Table 10.2),[29,30,128,129] and others modulate vascular development, with dysfunction/function of the lymphatic vasculature in common with or distinct from the blood vasculature.[6,12] Insights have been gained from the invaluable transgenic, spontaneous, and chemical- and/or radiation-induced mutant mouse models (see Table 10.2). These angiomodulatory factors should be crucial to understanding clinical conditions as diverse as cystic hygroma, Klippel-Trénaunay syndrome, (lymph)angiosarcoma, elephantiasis, and a constellation of peripheral and visceral disorders characterized by swelling, scarring, immunodysregulation, and malnutrition (Fig. 10.12; also see Figs. 10.1 and 10.9).

PATHOPHYSIOLOGY

Overview

Because both congenital absence and radical excision of regional lymph nodes (and hence, lymphatics) are associated with edema, it seems straightforward that lymphedema is simply the end result of insufficient lymphatic drainage (low-output failure of the lymphatic circulation). This scenario contrasts with the

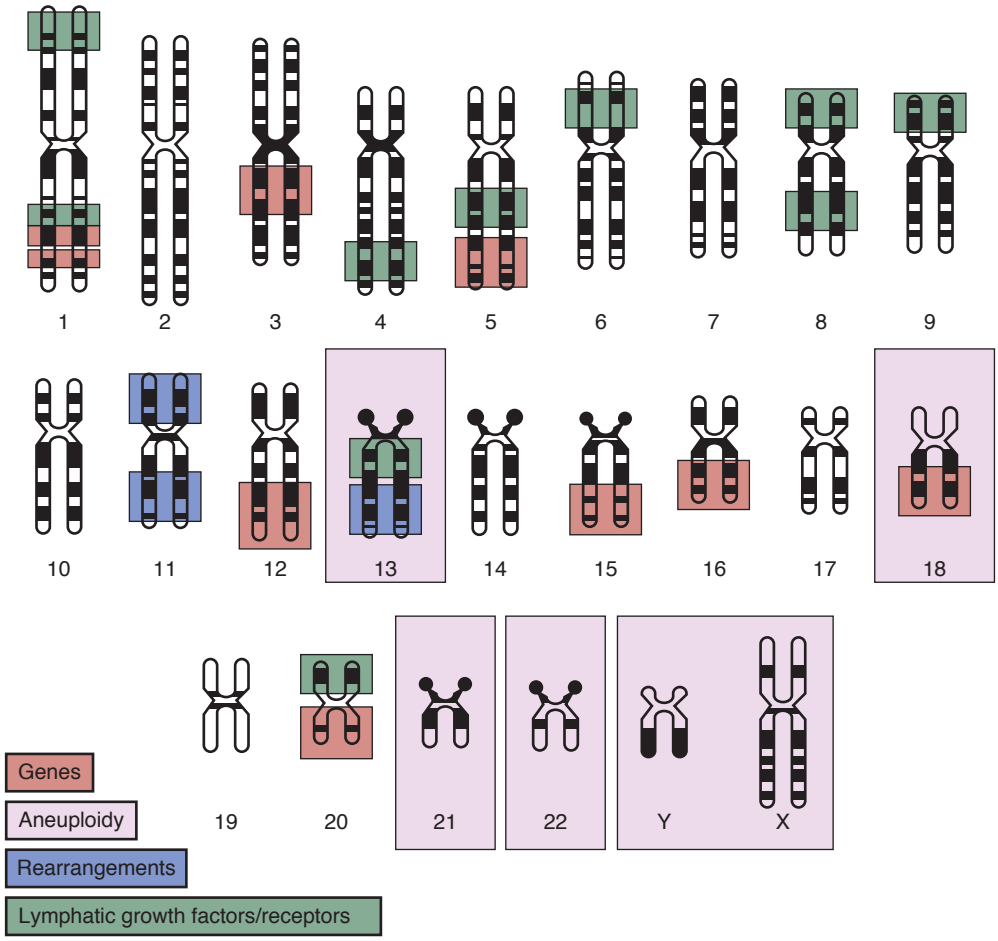

Figure 10.11 Genomics-proteomics of lymphedema-angiodysplasia syndromes displaying mutations of known genes *(pink boxes)* for a familial Milroy lymphedema subpopulation (VEGFR3 at chromosome 5q34-35), lymphedema-distichiasis (FOXC2 at chromosome 16q24), hypotrichosis, lymphedema, and telangiectasia (SOX18 at chromosome 20q13), generalized lymphatic dysplasia (Hennekam syndrome) (CCBE1 at 18q21), inherited lymphedema type 1C (GJC2 at 1q41), lymphedema-choanal atresia (PTPN14 at 1q32), and Emberger syndrome (GATA2 at 3q21) as well as linkage locations for Aagenaes syndrome (chromosome 15) and Noonan syndrome (chromosome 12). In addition, aneuploidies *(purple boxes)* and rearrangements *(blue boxes)* involving other chromosomes are associated with additional lymphedema-angiodysplasia syndromes. Examples include trisomy 13, 18, 21, and 22; Klinefelter XXY; Turner XO; and chromosomal abnormalities of addition 11p and deletions 11q and 13q, all associated with lymphedema-angiodysplasia syndromes. Locations of lymphatic-specific growth and/or modification proteins and receptors *(green boxes)* involved in development of the lymphatic system are also displayed. (Modified from Northup KA, Witte MH, Witte CL. Syndromic classification of hereditary lymphedema. *Lymphology.* 2003;36:162–189.)

TABLE 10.2 Mouse Lymphedema-Angiodysplasia Syndromes From Abnormalities and/or Altered Levels of Specific Proteins and/or Chromosomes

Molecular Description		Lymphatic Phenotype
Extracellular Proteins		
Angiopoietin-2	Ligand for the receptor tyrosine kinase Tie-2	*Ang2*$^{-/-}$ mice exhibit chylous ascites, lymphedema, and lymphatic hypoplasia. The mesenteric collecting lymphatic vessels of *Ang2*$^{-/-}$ mice lack complete coverage with smooth muscle cells, and the lymphatic capillaries in the digestive organs are associated with pericytes (Gale et al., 2002; Shimoda et al., 2007). Ang-1 can correct these mutant phenotypes (Gale et al., 2002; Shimoda et al., 2007)
Fasting-induced adipose factor	Glycosylated secreted protein	*Fiaf*$^{-/-}$ mice have dilated, blood-filled lymphatics in the small intestine. This phenotype begins postnatally and is not observed in *fiaf*$^{-/-}$ embryos (Bäckhed et al., 2007)
VEGF-C	Ligand for VEGFR-2 and VEGFR-3	*Vegfc*$^{-/-}$ mice lack jugular lymph sacs. *Vegfc*$^{+/-}$ mice have chylous ascites, lymphedema, and lymphatic hypoplasia (Karkkainen et al., 2004)

Continued

TABLE 10.2 Mouse Lymphedema-Angiodysplasia Syndromes From Abnormalities and/or Altered Levels of Specific Proteins and/or Chromosomes—cont'd

	Molecular Description	Lymphatic Phenotype
VEGF-D	Ligand for VEGFR-3	*Vegfd*$^{-/-}$ mice do not exhibit a striking lymphatic phenotype (Baldwin et al., 2005)
TgVEGF-C156S	Overexpression of the VEGFR-3–specific form of VEGF-C in the skin of mice using the keratin-14 promoter	Transgene-induced hyperplasia of lymphatic vessels (Veikkola et al., 2001)
TgVEGF-D	Overexpression of VEGF-D in the skin of mice using the keratin-14 promoter	Transgene-induced hyperplasia of lymphatic vessels (Veikkola et al., 2001)
Membrane and Intracellular Proteins		
Ephrin B2	Transmembrane ligand for the Eph receptor	*EphrinB2*$^{\Delta V/\Delta V}$ mice develop chylothorax and fail to undergo proper postnatal lymphatic remodeling (Mäkinen et al., 2005)
$\alpha_9\beta_1$ Integrin	Receptor for extracellular matrix	$\int 9^{-/-}$ mice develop chylothorax (Huang et al., 2000)
LYVE-1	Lymphatic hyaluronan receptor	The lymphatic system develops normally in *Lyve1*$^{-/-}$ mice (Gale et al., 2007)
Neuropilin-2	Receptor for semaphorins and VEGF family members	*Nrp2*$^{-/-}$ mice have a reduction in lymphatic capillaries during development (Yuan et al., 2002)
Podoplanin	Membrane glycoprotein	*Podoplanin*$^{-/-}$ mice have lymphedema, defects in lymphatic patterning, and dilated lymphatic vessels (Schacht et al., 2003)
SLP-76 and Syk	Adaptor protein and tyrosine kinase, respectively	Proposed that lymphatic and blood vessels in SLP-76 and Syk mutant mice fail to separate (Abtahian et al., 2003; Sebzda et al., 2006)
Spred1/2	Signaling proteins that negatively regulate ERK activation	*Spred1/2* double-knockout embryos die because of severe hemorrhage and edema. The lymphatic vessels of *Spred1/2* double-knockout mice appear dilated and contain blood (Taniguchi et al., 2007)
VEGFR-3	Receptor tyrosine kinase for VEGF-C and VEGF-D	*Chy* mice have chylous ascites, lymphedema, and hypoplasia of cutaneous lymphatic vessels (Karkkainen et al., 2001)
Connexin 37 and Connexin 43	Gap junction proteins	Connexin 37 and 43 deficiencies in mice disrupt lymphatic valve development and result in lymphedema and chylothorax (Kanady et al., 2011)
PI3K	Regulatory subunit of PI3-kinases	Organ-specific (gut) lymphangiectasia, arrested lymphatic sprouting, and maturation defects (Mouta-Bellum et al., 2009)
Tie1 receptor	Receptor for Tie1	Loss of Tie1 receptor impairs lymphatic vessel development, resulting in developmental edema (D'Amico et al., 2010)
Nuclear Proteins		
Foxc2	Transcription factor	*Foxc2*$^{+/-}$ mice exhibit lymphatic reflux, extralymphatic vessels and lymph nodes, and distichiasis (Kriederman et al., 2003). *Foxc2*$^{-/-}$ mice show defective lymphatic valves and abnormal mural cell coverage of lymphatic vessels (Petrova et al., 2004)
Net	Transcription factor. Net$^{\delta/\delta}$ mice lack a specific DNA-binding domain	*Net*$^{\delta/\delta}$ mice develop chylothorax and have dilated lymphatic vessels (Ayadi et al., 2001)
Prox1	Transcription factor	*Prox1*$^{-/-}$ mice fail to develop lymphatic vessels (Wigle and Oliver, 1999). *Prox1*$^{+/-}$ mice exhibit lymphedema, chylous ascites, mispatterned lymphatic vessels, and generalized obesity (Harvey et al., 2005)
Sox18	Transcription factor	*Sox18*$^{-/-}$ mice manifest chylous ascites, depending on the genetic background (Pennisi et al., 2000)
Vezf1	Zinc finger transcription factor	Lymphatic hyperplasia is observed in the jugular region of E13.5 *Vezf1*$^{+/-}$ embryos. Lymphatic abnormalities were not observed at later time points (Kuhnert et al., 2005)
Tbx1	Transcription factor	Lymphatic hyperplasia and chylous ascities. Regulates Vegfr3 (Chen et al., 2010)
Chromosomal Abnormalities		
Chy3	Large deletion of chromosome 8. The gene for VEGF-C is located within this deleted region	*Chy3* mice show chylous ascites, lymphedema, and lymphatic hypoplasia (Cattanach et al., 1993; Dellinger et al., 2007)
Ts16	Trisomy 16	Nuchal edema and distended jugular lymph sacs (Gittenberger-De Groot et al., 2004)

ERK, Extracellular signal–related kinase; *VEGF*, vascular endothelial growth factor; *VEGFR*, vascular endothelial growth factor receptor.

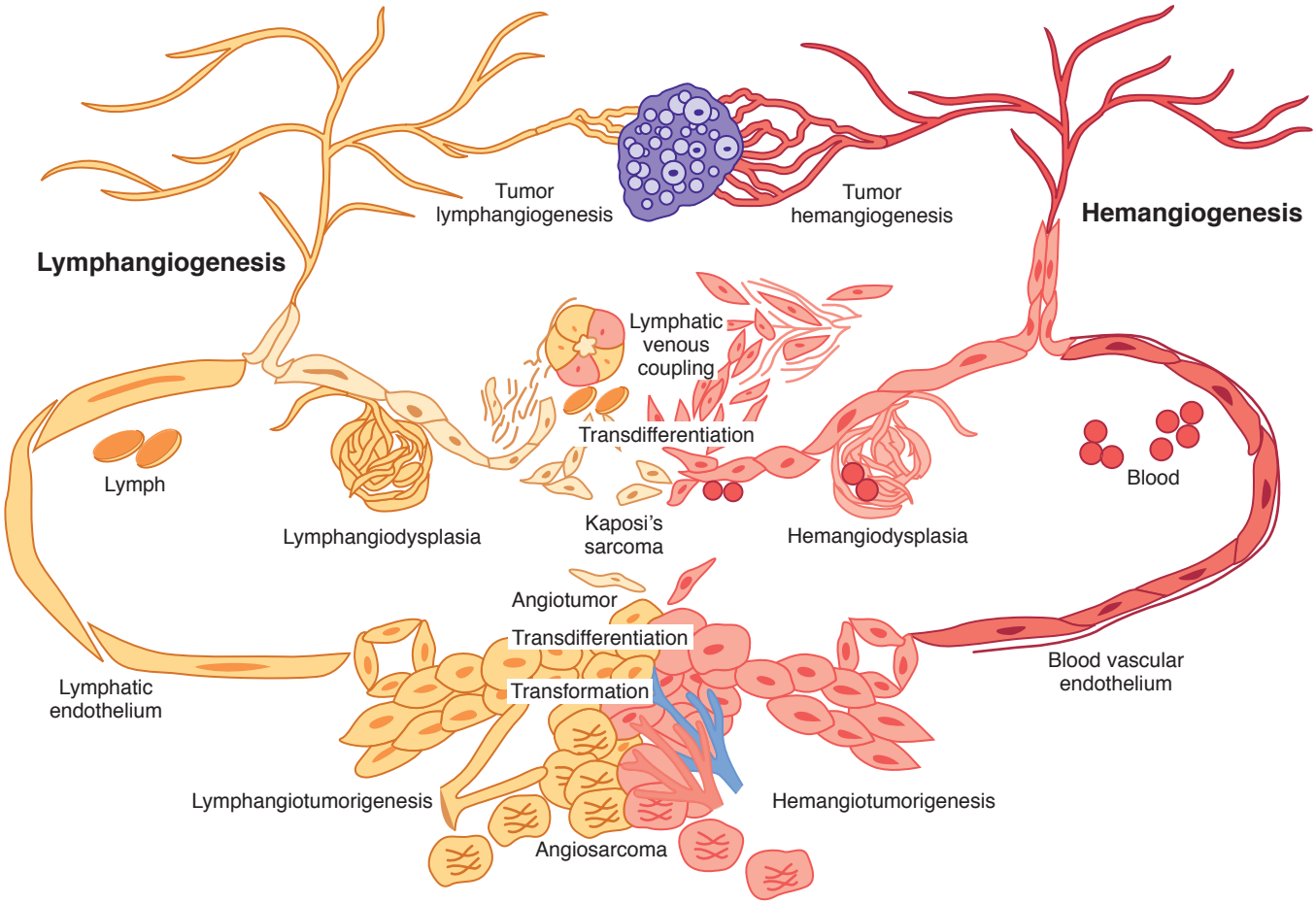

Figure 10.12 Physiologic and pathologic processes common to and linking the lymphatics with blood vessels and involving the growth of lymphatic vessels (lymphangiogenesis) analogous to and often accompanied by the growth of blood vessels (hemangiogenesis). Normally, these two vasculatures remain separate and connect directly only at a few strategic sites. In a variety of disorders, including tumor-associated angiogenesis, angiodysplasias, Kaposi sarcoma, and angiotumorigenesis, the two vasculatures come to resemble one another, interdigitate, and even merge indistinguishably. (Modified from Witte MH, Dellinger M, Bernas M, et al. Molecular lymphology and genetics of lymphedema-angiodysplasia syndromes. In: Földi M, Földi E, eds. *Textbook of Lymphology.* 6th ed. Munich, Germany: Urban & Fischer; 2006:497–523.)

more common local or generalized edemas (high-output; see Fig. 10.7) from venous occlusion, heart failure, and hepatic cirrhosis. Despite this reasonable conclusion and its pathophysiology, peripheral lymphedema has proved both hard to reproduce experimentally and difficult to treat. Initial experimental attempts to simulate the clinical condition by lymphatic sclerosis and radical excision were notoriously unsuccessful and revealed a remarkable capacity of obstructed lymphatics to regenerate and "bridge the gap" or bypass the induced blockage with spontaneous opening of auxiliary lymphatic-venous shunts.[98,130] Although transient swelling was common, these compensatory mechanisms precluded the development of chronic lymphedema solely based on obstruction of lymphatic drainage.

The general failure of early lymph stasis experiments to reproduce unremitting peripheral edema reinforced a long-held theory that overt or subclinical bacterial infection (lymphangitis) was indispensable for evolution of chronic lymphedema.[131] By disrupting microvascular integrity and promoting lymphatic obliteration, recurring infection was thought to exaggerate tissue scarring and cause unremitting lymphedema. This widely held belief was consistent with the commonly observed delayed onset and unpredictability of arm and leg edema after radical mastectomy and groin dissection, respectively, and the grotesque deformities of tropical lymphedema (so-called elephantiasis) from filariasis (Wuchereria bancrofti and Brugia malayi).

Lymphedema and Lymphangiodysplasia

Although understanding is still incomplete, it is now nonetheless clear that nonpitting, brawny extremity edema can arise from lymph stasis alone and by the unremitting accumulation of protein-rich fluid in the extracellular matrix. By using repeated intralymphatic injection of silica particles, Drinker et al.[132] first succeeded in simulating chronic lymphedema in dogs through extensive lymphatic sclerosis. Subsequently, Danese

et al.,[133] Olszewski,[79] and Clodius and Altorfer[134] established that refractory lymphedema could result solely from mechanical interruption of peripheral lymphatics. In an experimental model of circumferential lymphatic transection, tissue swelling was found to be prompt at first (acute lymphedema), disappeared by 4 to 6 weeks, and remained absent for months to years (latent lymphedema), but thereafter reappeared and persisted (chronic lymphedema). If radiation is combined with circumferential excision, the lymphedema is more severe and persists, as shown in rodent models of secondary lymphedema.[135-137] A similar sequence of events occurs in experimental filariasis (caused by Brugia malayi).[138] During the latent phase, when edema is not visible, conventional oil lymphography corroborates ongoing lymphatic destruction.[79] Progressive truncal tortuosity and dilatation give way to massive lymphangiectasis, valvular incompetence, and retrograde flow (dermal backflow). Serial microscopy discloses mononuclear cell infiltration, intramural destruction of lymphatic collectors, and collagen deposition throughout the soft tissues. Eventually, the lymph trunks lose their distinctive smooth muscle and endothelial lining, and the boundary lines between lymph collectors and the surrounding matrix progressively blur.[79,134]

These studies definitively demonstrate that extensive impairment of lymph drainage is sufficient by itself to cause chronic lymphedema (see Fig. 10.9). The key observation is the long interval between disruption of the lymph trunks and the development of refractory edema, which helps to explain the inconstancy and unpredictability of limb swelling after radical operations for treatment of cancer and other disorders of defective lymphatic drainage. As with deep venous occlusive disease, which is associated with valve destruction, venous stasis, and eventually overt edema (post-thrombotic syndrome) with characteristic trophic skin changes (hyperpigmentation and ulceration), absence or obliteration of the lymphatic vessels is associated with lymphatic valve incompetence, lymph stasis, and eventually, intractable edema (postlymphangitic syndrome) with its characteristic trophic skin changes (thickened toe skin folds or Stemmer sign, warty overgrowth, and brawny induration).[139]

Other lymphangiodysplasias were described long ago but remain poorly understood and treated. They often involve both the lymphatic and blood vascular systems and range from simple birthmarks to syndromes consisting of mixed lymphatic and venous components with benign tissue overgrowth to malignant lymphangiosarcoma (Box 10.2; also see Fig. 10.12).

These pathologic conditions and the biochemical and/or tissue composition changes (see Fig. 10.9 and Box 10.2) can be evaluated and imaged for diagnosis, prognosis, and intervention by a variety of modalities (e.g., circumferential measurements for limb volume, bioimpedance spectroscopy for fluid measurement, tonometry for tissue hardness, CT, MRI, dual energy x-ray absorptiometry [DEXA], and ultrasound for deep and superficial tissue analysis), depending on the clinical findings (Fig. 10.13). The current "gold standard" for lymphatic system imaging is whole-body lymphangioscintigraphy (Fig. 10.14), which provides both anatomic and functional imaging and is useful for most clinical manifestations.[45]

BOX 10.2 Clinical Examples of Hemangiodysplasia/Lymphangiodysplasia

A bewildering, poorly classified constellation of angiogenic, angioproliferative, and angiotumorigenic (benign/malignant) manifestations consisting of the following:

- Vascular "birthmarks"
- Capillary, cavernous, etc., hemangiomas, lymphangiomas, and mixed angiomas
- Angiomatosis, including "benign metastasizing" lymphangioma
- Histiocytoid hemangioma
- Malignant endovascular papillary angioendothelioma
- Epithelioid hemangioendothelioma(tosis)
- Kaposi sarcoma, kaposiform eruptions
- (Lymph)angiosarcoma

Chylous and Nonchylous Reflux

Abnormal retrograde transport of lymph is termed reflux. When the lymph fluid derives from outside the intestine (e.g., from the limbs, where it is generally straw-colored to clear), it is termed nonchylous reflux, whereas lymph arising from the intestines (generally milky in color) and flowing retrograde is termed chylous reflux. The phenomena of lymph reflux was observed and recorded as far back as Cruikshank,[140] but he was not sure of its significance and speculated that it was a post-mortem event in cadavers. In 1878 Busey described patients with both chylous and nonchylous reflux syndromes with accompanying lymphedema.[141] His failure to cure or even substantially benefit these patients persists even nowadays for many of these complicated conditions. Because cholesterol and long-chain triglycerides in the form of chylomicra are absorbed exclusively by the lymphatic system, dysfunction (in the form of disruption, compression, obstruction, or fistulization) of mesenteric lacteals, the cisterna chyli, and the thoracic duct is directly linked to chylothorax, chylous ascites, chyluria, chylometrorrhagia, and protein-losing enteropathy. In some patients with high-grade blockage of intestinal lymph flow, the peripheral lymphatics gradually dilate, and with progressive valvular incompetence, lactescent lymph refluxes into the soft tissues of the pelvis, scrotum, and lower extremities (chylous vesicles and chyledema) or even into the bronchial tree, manifesting as chyloptysis (see Fig. 10.14). Transgenic (particularly the angiopoietin-2 knockout mouse),[142] radiation-induced,[128] and spontaneously arising mouse models with chylous effusions are available to further study these chylous reflux syndromes (see Table 10.2). Dynamic imaging of both chylous and nonchylous lymph reflux can usually be accomplished by adjusting the whole-body protocol for lower, and rarely, upper limb lymphangioscintigraphy and can be applied in newborn infants to adults to identify the source, timing, and locations of the lymph reflux (see Fig. 10.14).[45]

Infection

Recurrent cellulitis is a devastating sequela of peripheral lymphedema. Erysipelas resulting from β-hemolytic streptococcal

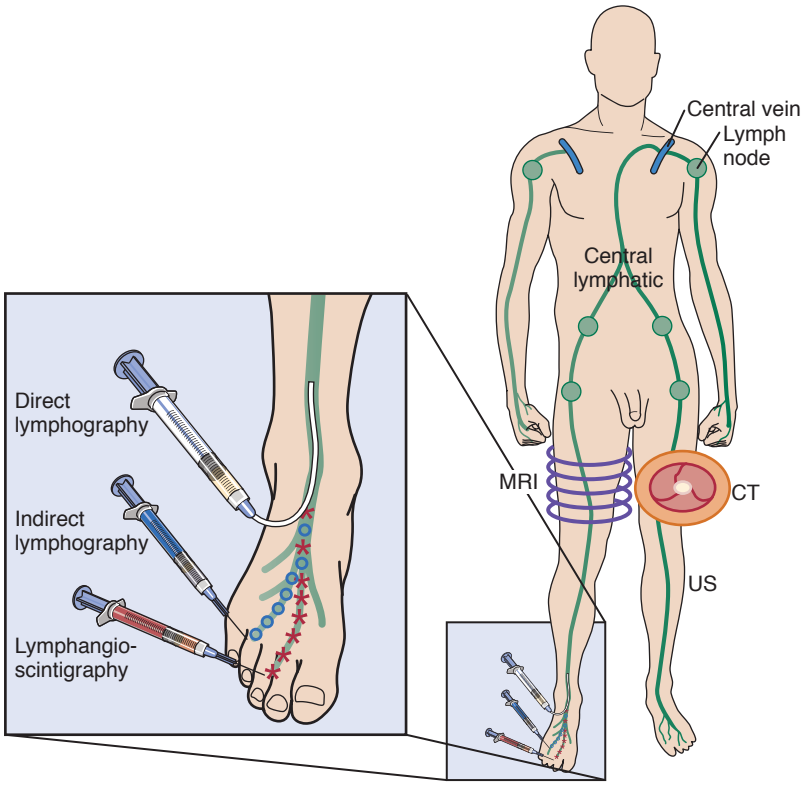

Figure 10.13 Techniques used for structural and functional imaging of the lymphatic system include direct lymphography with an oily contrast agent directly instilled into a lymphatic vessel and indirect lymphography with color vital dyes, fluorescent particles, or radioactive isotope (lymphangioscintigraphy) injected intradermally. Other useful techniques include magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound (US), including photoacoustic refinements.

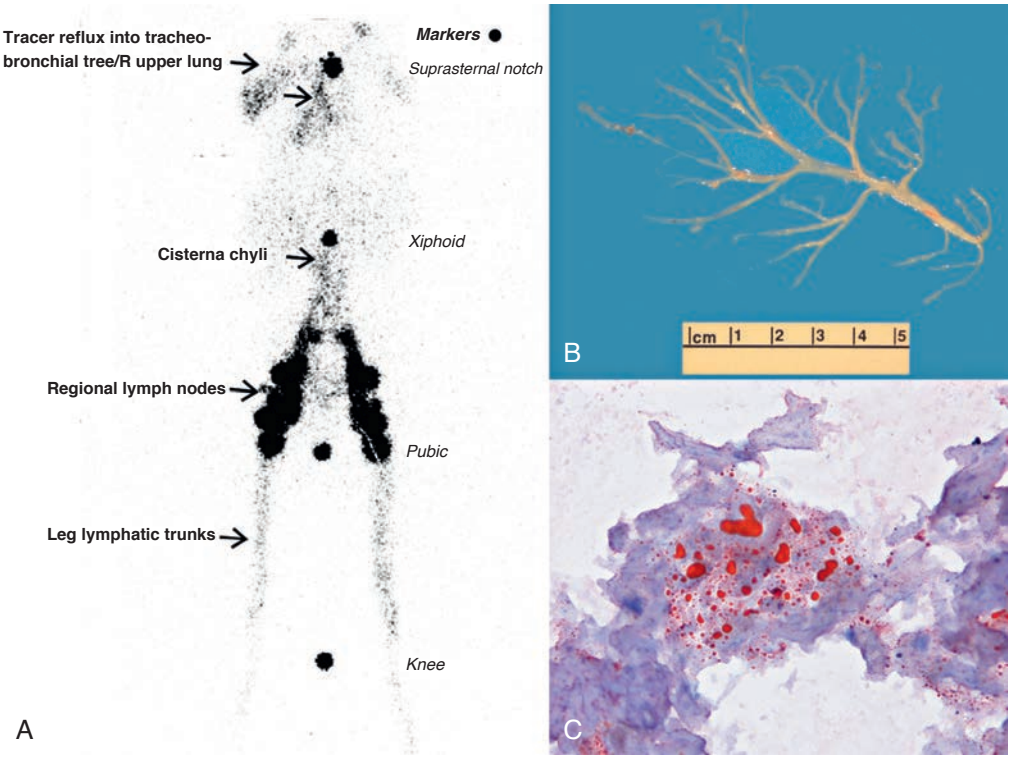

Figure 10.14 Chylous Reflux Syndrome Manifesting as Chyloptysis in an 11-Year-Old Boy With Congenital Heart Disease Following Fontan Repair. (A) Bilateral lower extremity technetium 99m sulfacolloid lymphangioscintigram. Note prompt cephalad tracer transport from foot injection sites into peripheral and central lymphatic trunks and regional inguinal and retroperitoneal lymph nodes up to the level of the cisterna chyli with demonstrable retrograde reflux of tracer *(arrow)* into the tracheobronchial tree and right upper lung field. Radioactive markers placed at key anatomic landmarks: knee, pubic, xiphoid, and suprasternal notch. (B) Large arboreal bronchial cast preserved following expectoration. (C) Acellular cast with oil red O positive lipid droplets, original magnification ×200. (Modified from Parikh K, Witte MH, Samson R, et al. Successful treatment of plastic bronchitis with low fat diet and subsequent thoracic duct ligation in child with Fontan physiology. *Lymphology.* 2012;45(2):47–52.)

infection is most common, but fulminant infection occurs with a variety of microorganisms.[143] To a certain extent, vulnerability to superimposed infection exists whenever tissue fluid stagnates. Patients with lymphedema (in contrast to edematous states arising from imbalances in transcapillary hydrodynamic forces) are so prone to recurring dermatolymphangitis that at one time it was mistaken as the sine qua non of lymphedema.

The reasons for extraordinary susceptibility of a lymphedematous extremity to bacterial infection remain perplexing. Studies

of canine-induced and human filarial lymphedema implicate defective complement activation and immunodysregulation.[79] In addition, dampened monocyte function has been reported in microfilaremic patients.[144] Alternative hypotheses include depopulation of regional lymph nodes with replacement by fat and scar[47] and deficient protease activity of extravascular macrophages.[145] Notwithstanding, the onset of overt lymphedema is often precipitated by sudden infection or injury in an extremity already exhibiting defective lymphatic function. In other words, in an extremity with marginal lymphatic drainage (and therefore dysregulated lymphocyte, monocyte, and dendritic cell trafficking and/or recirculation), even minor trauma and infection may initiate a protracted pernicious cycle that in the extreme culminates in a pachyderm-like deformity, and on rare occasion, leads to a highly aggressive vascular malignancy (see Fig. 10.9). Some strategies for bacterial and/or fungal prophylaxis, particularly in endemic filarial regions, have been undertaken. However, the value of long-term prophylaxis in Western and/or nontropical countries (demonstrating lower rates of infections) has not been well studied, nor has prophylaxis been widely practiced.

Fibrosis

Like the sequelae of superimposed infection, the complications of progressive interstitial fibrosis also set lymphedema apart from other edematous states. Although the pathogenetic sequence is still unclear, it has long been recognized that conditions associated with edema high in protein content (e.g., lymphedema) are characterized by fibrous proliferation and propagation of other cell types, including adipocytes. Altered cytokine production, perturbed immunoreactivity, accumulation of abnormal complexed plasma protein moieties, including growth factors in the extracellular matrix, proliferation of mast cells with release of vasomediators such as histamine,[146,147] alteration in the matrix sol-gel state, and activation of a complement cascade with "fixation" to immunocomplexes may exert, singly or with both microvascular and chemotactic effects that facilitate cell mobility and tissue infiltration of chronic inflammatory cells (e.g., lymphocytes and macrophages).[148] As fibrin- and cell-binding circulating fibronectins accumulate in the stagnant edema fluid, they act as the scaffolding and support glue for the migration of fibroblasts and deposition of collagen.[149] In addition, lymph stasis and the buildup of plasma proteins trapped in the interstitium overwhelm intrinsic neutrophil and macrophage proteases and provoke diffuse scarring.[150] Ironically, these same processes are also critical for the repair of wounds, for which scar formation is also the final common pathway.

Adipogenesis

Although the connection between the lymphatic system and fat absorption and/or deposition has been recognized by clinicians for well over a hundred years, the subject received relatively little interest until publications suggested mechanisms. It has long been recognized that a lymphedematous limb accumulates fat at an increased rate in comparison with the rest of the body and that, conversely, when weight loss is undertaken, the lymphedematous limb loses fat at a slower rate than the body does. The reasons for these observations are not understood. A report and accompanying comment studying Prox1 haploinsufficient mice proposed that lymph itself is stimulatory to fat cells.[151,152] More recent studies using the mouse tail have reported that lymph stasis stimulates adipogenesis and upregulation of fat differentiation genes.[153,154] Questions that still need to be answered include why other transgenic mouse models (e.g., angiopoietin-2 knockout) with more severe and sustained lymph accumulation do not exhibit the obesity phenotype and why severely obese (leptin knockout) mice have normal lymphatics.

In humans, it is known that adipogenesis occurs both prenatally and postnatally (particularly in relation to the modern lifestyle of excessive caloric consumption and epidemic obesity).[155] Obesity also can lead to significant changes in the skin, microcirculation, collagen structure and function, and lymphatics.[156] In humans, there is evidence that the presence of static lymph itself can also influence localized adipocyte hypertrophy.[157]

Adipocytes vary in function and growth potential. The fat pads on the soles of the feet rarely enlarge, whereas those in the midsection can enlarge greatly in number and size. These distinct regions also are likely to have different profiles of cytokine production and growth factors in response to the local environment and in turn to influence it. A factor from human preadipocytes has been shown to preferentially stimulate lymphatic endothelial cell growth in vitro,[158] and other work in rabbits has demonstrated that preadipocytes differentiate more completely when lymph is added to the culture medium.[159] In addition, multipotent mesenchymal stem cells give rise to adipocytes (as well as bone, muscle, and cartilage).[160]

The permanent accumulation of large amounts of fat in limb lymphedema is a poor prognostic factor for physical treatment methods and has given rise to therapeutic approaches such as liposuction to directly and effectively remove the fat.[161]

Lymphatic Tumors and Tumor Lymphatics

A rare but revealing sequela of long-standing peripheral lymphedema is the occurrence of lymphangiosarcoma and/or angiosarcoma and perhaps also other opportunistic neoplasms. This aggressive vascular malignancy was once thought to arise exclusively after radical mastectomy and irradiation for local control of breast cancer (Stewart-Treves syndrome).[162,163] However, lymphangiosarcoma has now been documented in other secondary lymphedemas and even in congenital or primary lymphedema.[164] Because preexisting swelling has usually persisted for many years and may occur in either primary or secondary lymphedema or in the presence or absence of previous radiotherapy, the lymphedema process itself has been thought to be the prime cause. More recently, Kaposi sarcoma, a vascular tumor akin to Stewart-Treves syndrome and allied closely with AIDS, has been linked to an origin from virally transformed lymphatic endothelium.[165-168] Perhaps immunodysregulation underlies a wide range of common and bizarre vasoproliferative and lymphologic syndromes, including hemolymphangioma (representing "angiotumorigenesis"), Klippel-Trénaunay syndrome, Gorham-Stout

syndrome (bony lymphangiomatosis or "disappearing bone disease"), angiofollicular hyperplasia (epithelioid hemangioma), lymphangioleiomyomatosis, and tumor lymphangiogenesis and lymphangitic metastatic carcinomatosis (see Fig. 10.12).[169,170]

Tumor angiogenesis, which generally refers to hemangiogenesis, has been extensively studied since Folkman's original observations[171] and has also become a major therapeutic target, including a target of blockbuster drugs such as Genentech's bevacizumab (Avastin).[172,173] Tumor lymphangiogenesis,[174] a phenomenon whose very existence until recently was questioned, has now become a hot topic. Yet cells giving rise to the two vasculatures overlap and may interchange in specific pathologic settings and resemble each other more in regional settings. Now, various biotechnology companies, stimulated by thought leaders in the angiogenesis field, are vigorously pursuing pharmaceuticals with antilymphangiogenic properties and testing them in preclinical models for application to patients with cancer.[169,170,172,175]

Other Lymphangiogenic Disorders

Although the specific disturbances in lymphangiogenic processes have not been pinpointed for a variety of syndromes and disorders, likely lymphatic growth and remodeling initiating or secondary events are affected in inflammation, infection, and immunodysregulation. In primary disorders such as lymphangioleiomyomatosis, lymphangiectasia, and lymphangiomas, the lymphatic disturbances are clear, but their lymphatic structural and functional details, range of clinical phenotypes, and molecular bases have not been well delineated.

CLINICAL OVERVIEW

Disturbances in microcirculatory perfusion and exchange of liquid, macromolecules, and cells across intact and abnormal microvessels and deranged lymphatic growth patterns and lymph kinetics are, individually and together, associated with disorders of tissue swelling. Low-output failure of the lymph circulation manifested as peripheral lymphedema is characteristically indolent for many years before lymphatic insufficiency and tissue swelling accelerate and become persistent. Nonetheless, impedance of lymph flow by itself is sufficient to explain at least mild to moderate forms of lymphedema. Chronic lymphedema is characterized by trapping of fluid and extravasation of plasma proteins and other macromolecules in the skin and subcutaneous tissues. It is typical to find impaired immune cell trafficking (lymphocytes, Langerhans cells, monocytes), abnormal transport of autologous and foreign antigens, probably intact hydrodynamic (Starling) transcapillary forces,[176] and an increased propensity for superimposed infection. Additional characteristics include progressive obliteration of lymphatics (lymphangiopathy "dieback" or lymphangitis), defective lymphangion contractility, mononuclear cell infiltrates (chronic interstitial inflammation), epidermal cell-fibroblast proliferation, collagen deposition, altered immunoreactivity, and vasoactive mediator imbalance with increased production of local cytokines and growth factors, including autocrine and paracrine hormones.

Transdifferentiation and transformation of endothelium and other vascular accessory cells associated with lymph stasis may also be pivotal factors in a wide range of dysplastic and neoplastic vascular disorders, including Stewart-Treves syndrome, AIDS-associated Kaposi sarcoma, recurrent lymphangiomatosis, and lymphangitic metastatic carcinomatosis. These phenomena have their origin in controlled and uncontrolled lymphangiogenesis and apparently are regulated at specific sites across the genome. Their manipulation may offer new avenues of therapy for both primary and secondary lymphedema and related angiodysplasia syndromes, as well as a variety of neoplasms. These new approaches include gene therapy to supply the normal gene and angiomodulatory therapy to promote lymphangiogenesis when inadequate (as in lymphedema) or inhibit lymphatic growth when excessive (as in lymphangioma). Stem cell therapy to grow new vessels from undifferentiated embryonic or adult stem cells (e.g., lymphangioblasts) and new biomaterials for artificial lymphatics and scaffolding to drain the tissues also hold promise for the future (Fig. 10.15).

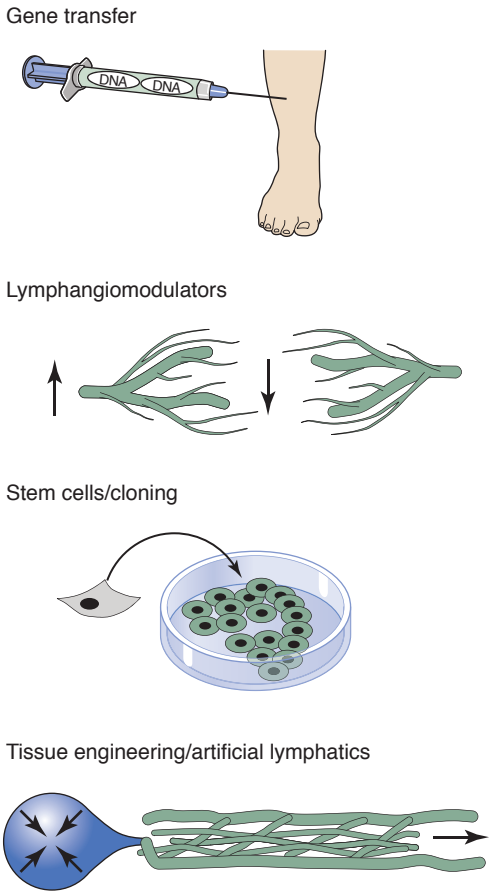

Figure 10.15 Future approaches to the treatment of patients with lymphedema-angiodysplasia disorders may include gene and/or protein transfer, modulation of growth and/or inhibitory factors, "reprogramming" with stem cells, or artificially engineered vessels/systems. (Modified from Witte MH, et al. Molecular lymphology and genetics of lymphedema-angiodysplasia syndromes. In: Földi M, Földi E, eds. *Foldi's Textbook of Lymphology.* 3rd ed. Munich, Germany: Urban & Fischer; 2012:444–466.)

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11 CHAPTER

Atherosclerotic Risk Factors: Smoking

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Called "one of the greatest public health catastrophes" of the 20th century in the Surgeon General's semicentennial report, smoking has had profound health consequences that continue to be felt even as its North American prevalence decreases.[1] For vascular surgeons in particular the association with aneurysm formation and arterial occlusive disease means that smoking remains one of the most critical modifiable risk factors.

EPIDEMIOLOGY

Smoking is the foremost cause of preventable morbidity and mortality in the United States. Annually, more than 480,000 premature deaths and more than $300 billion dollars in lost productivity and direct costs are attributed to smoking.[2]

Although the prevalence of smoking in the United States has decreased by more than half since the Surgeon General's seminal report on smoking in 1964, it remains significant.[1] Based on the National Health Interview Survey of almost 37,000 Americans at least 18 years of age, 16.8% smoked regularly in 2014. The prevalence was higher in males than females (18.8% vs. 14.8%). Adults aged 25 to 44 years had the highest rate of 20.0% compared with the lowest rate of 8.5% in those who were 65 years or older. There were also differences based on racial groups, education, and economic status. Namely, cigarette use was highest among American Indian/Alaska natives (29.2%) and lowest among Asians (9.5%). Caucasians had an intermediate rate of 18.2%. Americans with graduate degrees had a mere 5.4% use compared with 43% in those with a general equivalency diploma. Finally, people living below the poverty line had a use rate of 26.3% versus 15.2% in those living above the poverty line.[2]

It is important to recognize that patients may use tobacco products besides cigarettes. The 2012–2013 National Adult Tobacco Survey demonstrated that the following products were used daily or some days: snuff, dip, and other smokeless tobacco (2.6%); cigars and cigarillos (2.0%); water pipes and hookahs (0.5%); and pipes (0.3%).[3]

A recent increasingly popular cigarette alternative is the electronic cigarette or e-cigarette, used by 3.7% of adults daily or on some days.[4] E-cigarettes, while tobacco-free, are battery-operated devices that deliver aerosolized nicotine. They are marketed both as cigarette alternatives and as smoking cessation tools. Although more than half of smokers who attempted to quit had used e-cigarettes in 2014,[4] no such device has been FDA approved for smoking cessation, and the United States Preventative Services Task Force has found inadequate evidence to support e-cigarettes as cessation tools.[5] As a corollary, data regarding potential long-term harms from inhaling nicotine vapors are also absent. Finally, there is concern that e-cigarette use in minors may translate into long-term nicotine addiction for future generations.

Abstract

Despite the declining prevalence in American tobacco use, it remains a significant and relevant risk factor for the development of aneurysms and arterial occlusive disease. The epidemiology, molecular mechanisms, and clinical effects on arterial vasculature are reviewed. In addition, we consider approaches to smoking cessation.

Keywords

Tobacco
smoking
smoking cessation
nicotine

BIOLOGIC EFFECTS OF SMOKING ON THE VASCULATURE

Cigarette smoke has adverse effects on vascular biology through a variety of mechanisms. First, it creates endothelial dysfunction, including reduction of the availability of nitric oxide, and activation of enzymes leading to the increased production of reactive-oxygen species. Flow-mediated dilation, a common measure of endothelial function, is diminished in active smokers and even nonsmokers exposed to secondhand smoke for less than 1 hour.[1]

Second, smoking creates a prothrombotic environment. Smoking leads to the increased production of thromboxane A2 and decreased levels of prostacyclin, thus overall promoting platelet aggregation. Smoking is also associated with elevated levels of prothrombotic substances such as von Willebrand factor, thrombin, and fibrin, while simultaneously reducing antithrombotic and fibrinolytic substances such as tissue plasminogen activator and plasminogen activator inhibitor-1. Smokers also have higher markers of platelet activation, which decline after smoking cessation.[1]

Last, smoking promotes an inflammatory state, which has been associated with vascular disease. Compared with nonsmokers, smokers have higher levels of leukocytes, C-reactive protein, interleukin-6, tissue necrosis factor-α, interleukin-1-β, and other inflammatory markers.[1]

It should also be noted that nicotine itself plays an important role in known drivers of vascular disease. Not only does it act as a sympathomimetic substance that raises blood pressure, but it is also associated with insulin resistance, altered lipid metabolism, and endothelial dysfunction.[1] Finally, vascular surgeons have for generations passed on the observation of differential disease distributions patterns between patients who smoke versus those with diabetes. Smokers tend to have aorto-iliac and superficial femoral disease, while occlusive atherosclerosis generally strikes the profunda and tibials in diabetic patients.[6] However, rigorous documentation of these broad and frequently variable differential disease patterns is sparse.

NONVASCULAR CLINICAL EFFECTS

Smoking has causal links with numerous diseases across several organ systems. Most prominently, smoking is associated with cancers of the lungs, oropharynx and larynx, esophagus, stomach, pancreas, kidney, bladder, and cervix. More recently, it has been implicated in liver and colorectal cancers as well.[1]

Cigarette smoking also has been linked to diabetes, cataracts, macular degeneration, chronic obstructive pulmonary disease, asthma, and rheumatoid arthritis, among others.

VASCULAR CLINICAL EFFECTS

Development of Peripheral Arterial Disease

Cigarette smoking has an unequivocal positive association with the development of peripheral vascular disease in multiple large epidemiologic studies. For example, the original Framingham Study, which followed 5209 subjects, showed that smoking was more allied with the development of intermittent claudication than even coronary artery disease and stroke.[7] Similarly, the Speedwell study followed 2348 men starting in 1979 and found that smoking was the strongest risk factor for the development of claudication, more so than diabetes and hypertension.[8]

The Women's Health Study provided additional insights into the development of PAD. This study prospectively followed nearly 40,000 healthy women health professionals at least 45 years of age beginning in 1993.[9] During a median follow-up of 12.7 years, 178 subjects developed symptomatic peripheral arterial disease. Multivariate analysis showed that the risk of this developed in stepwise fashion with smoking. Compared with never smokers, the hazard ratio for symptomatic PAD development was 3.16 for former smokers, 11.94 for current smokers using fewer than 15 cigarettes, and 21.08 for those using 15 or more cigarettes daily.

Interestingly, the Women's Health Study also showed that smoking cessation was beneficial with respect to PAD development, and that these benefits were proportional to the duration of cessation. Using current smokers as the reference group, the hazard ratios for PAD development in those who had fewer than 10 years of cessation, 10 to 19 years of cessation, 20 or more years, and never smokers were 0.39, 0.28, 0.16, and 0.08, respectively.[9] Not all studies, however, have found that cessation reduces atherosclerotic disease burden risk. The Atherosclerosis Risk in Communities study showed that after controlling for pack-years of smoking, there was no difference in atherosclerotic disease between past and current smokers as measured by carotid artery intimal-medial thickness.[10]

Graft Failure and Amputation

Willigendael et al. conducted a meta-analysis to determine the effects of smoking on the patency of lower extremity arterial grafts.[11] On basis of a total of 20 prospective and retrospective studies, the hazard ratio for graft failure was 2.35 in smokers compared with nonsmokers. Studies that used biochemical tests to determine smoking status found an even higher hazard ratio of 3.8, implying that studies based on self-reported smoking status may underestimate effects. Interestingly, three component studies that looked at the effect of patient age all found that smoking in patients less than 65 years old had a higher risk of graft failure than older patients. Smoking had similarly negative effects on autogenous grafts and polyesters grafts.

Willigendael's meta-analysis also found that there was a graft patency benefit to smoking cessation. Former smokers had patencies superior to those of current smokers and comparable to never smokers.[11]

In a corollary study, Lassila et al. prospectively examined the impact of heavy smoking, defined as 15 or more cigarettes daily on amputation risk and survival in 190 patients undergoing lower extremity arterial reconstruction for PAD. At 3 years, heavy smokers had diminished survival and increased major amputation rates (21% vs. 2% in non–heavy smokers, $P < .001$).[12]

Smoking and Other Vascular Disease

Although this chapter focuses on atherosclerotic occlusive peripheral vascular disease, it should be noted that smoking is also intimately associated with two other diseases of concern to the vascular surgeon: thromboangiitis obliterans (Buerger disease) and aortic aneurysms. Both of these are common and important pathologies worldwide and are described in more detail in separate chapters.

SMOKING CESSATION

Smoking cessation can have positive health effects, including an improvement in all-cause mortality.[13] Although duration of cessation counseling from a healthcare provider correlates with likelihood of abstinence, providers would be mistaken to believe that extensive time investments are necessary to have an impact: even individualized interventions as short as 1 minute have been shown to increase quitting success.

Although a full treatment of cessation interventions is beyond the scope of this work, some essential guidelines follow. The Agency for Healthcare Research and Quality recommends that smoking interventions should consists of five key elements, the five As: ask, advise, assess, assist, and arrange.[13] Physicians should ask about and document tobacco use at every patient visit. They should directly advise every tobacco user to quit. Each tobacco user should be assessed for his or her willingness to quit. Patients willing to quit should receive assistance, detailed below, and finally healthcare providers should arrange for follow-up.

For patients who are unwilling to quit, physicians should be sure to use motivational interview strategies along with the five R's.[13] Physicians should point out the **r**elevance of quitting to the patient with regard to his or her social situation, health concerns, and so forth. They should delineate the **r**isks of ongoing tobacco use and point out the manifold **r**ewards of quitting. Finally, the physician should ask the patient to identify **r**oadblocks to success and attendant solutions, and **r**epeat this intervention at each visit.

For patients interested in quitting, physicians should provide contemporary practical advice (Table 11.1), and select medication adjuncts. There are currently seven FDA-approved first-line therapies consisting of five nicotine-replacement medications—gum, inhaler, lozenge, nasal spray, and lozenge—and two nonnicotine pharmaceuticals, bupropion SR, and varenicline (Table 11.2).[13] Bupropion SR blocks neuronal reuptake of dopamine and norepinephrine while also serving as a nicotinic acetylcholinergic

TABLE 11.1 Practical Advice in Smoking Cessation

- Aim for total abstinence after the chosen quit date.
- Alcohol decreases success rates; consider reducing alcohol intake.
- Others in the patient's household should consider attempting to quit or not smoking in the presence of the patient to maximize success.
- Identify triggers for smoking and avoid them.
- Anticipate withdrawal symptoms—problems with mood and concentration, nausea, headache—which will peak at 1-2 weeks but may persist for longer periods.

TABLE 11.2 Nicotine and Non-Nicotine Therapy for Smoking Cessation[15-19]

Medication	Directions	Dosing	Major Side Effects
Nicotine Replacement Therapy for Smoking Cessation			
Gum Nicorette (available over the counter in generic form)	Chew gum until it tingles, then park between cheek and gums until tingle disappears, then chew again until tingle returns. Repeat until most of tingle is gone (~30 min).	Use 2-mg pieces for <25 cigarettes daily or 4-mg pieces for >25 cigarettes daily. Smokers should use at least one piece every 1-2 h for the first 6 weeks; the gum should be used for up to 12 weeks with no more than 24 pieces to be used per day.	Throat and mouth irritation, increased salivation, hiccupping, jaw muscle ache Use with caution in patients with oral or pharyngeal inflammation and in patients with a history of esophagitis or peptic ulcer.
Lozenge Commit (available over the counter in generic form)	Use 2-mg lozenges for first cigarette use >30 min after waking or 4-mg pieces for <30 min after waking. Allow lozenge to dissolve (~20-30 min) in mouth. Do not chew or swallow lozenge. Occasionally move lozenge from one side of mouth to the other.	Use at least 9 lozenges per day in the first 6 weeks; the lozenge should be used for up to 12 weeks, with no more than 20 lozenges per day.	Throat and mouth irritation, increased salivation, hiccupping, indigestion Use with caution in patients with oral or pharyngeal inflammation and in patients with a history of esophagitis or peptic ulcer.

Continued

TABLE 11.2 Nicotine and Non-Nicotine Therapy for Smoking Cessation—cont'd

Medication	Directions	Dosing	Major Side Effects
Inhalation Nicotrol	10-mg cartridges (4 mg is delivered) to be used for inhalation	Initial 12 weeks, 6-16 cartridges per day, then gradual reduction during 6-12 weeks	Throat and mouth irritation, coughing, rhinitis, sinusitis, pain in jaw and neck
	Inhale deeply into back of throat or puff in short breaths. Nicotine in cartridge is used up after 20 min of active puffing.		
			Use with caution in patients with bronchospastic disease.
Nasal spray Nicotrol NS	50-μL spray containing 0.5 mg of nicotine per actuation. One dose is 1 mg of nicotine (2 sprays, one in each nostril).	Initially 1-2 doses per hour up to 5 doses per hour (40 doses per day) for 8 weeks, with tapering during next 4-6 weeks.	Use with caution in patients with bronchospastic disease, known chronic nasal disorders (allergy, rhinitis, nasal polyps, sinusitis).
	Spray once in each nostril, do not sniff or inhale while spraying.		
Transdermal patch Habitrol Nicoderm CQ (available over the counter in generic form)	Wear patch 16 or 24 hours, 24 h if cravings on awakening, otherwise remove at bedtime and apply fresh patch on a clean, nonhairy area of skin between neck and waist in the morning. Do not reapply patch to a previously used skin site for at least 1 week. Do not cut patch into smaller pieces.	10-week therapy for >10 cigarettes a day, 8-week therapy for <10 cigarettes a day	Skin irritation
		10-week therapy: 21 mg for 6 weeks, 14 mg for 2 weeks, 7 mg for 2 weeks	
		8-week therapy: 14 mg for 6 weeks, 7 mg for 2 weeks	

Medication	Mechanism of Action	Dosing	Major Side Effects
Nicotine- and Nonnicotine Therapy for Smoking Cessation[12,14]			
Bupropion (Zyban)	Atypical antidepressant with dopaminergic and adrenergic actions	Start with 150 mg daily for first 3 days and increase to 150 mg twice daily. The maximum dose of bupropion is 300 mg per day.	Seizures, worsening depression, anxiety, agitation, irritability, insomnia, unusual changes in behavior, development of suicidal ideation/behavior, hypertension, dry mouth
		Treatment should be started while the patient is still smoking; the patient should set a target quit date, usually for the second week of treatment.	Contraindicated in patients with seizure disorder already taking bupropion for another reason as risk of seizures are dose dependent with bulimia or anorexia undergoing abrupt discontinuation of alcohol or sedatives taking monoamine oxidase inhibitors allergic to bupropion.
		Continue treatment for 7-12 weeks. Patients abstinent within 7-12 weeks may continue with 300 mg daily maintenance therapy.	
			Use with extreme caution in patients with hepatic dysfunction.
		May be used in combination with nicotine replacement therapy.	
			Boxed warning: Patients should be closely monitored for signs of serious neuropsychiatric side effects.

TABLE 11.2 Nicotine and Non-Nicotine Therapy for Smoking Cessation—cont'd

Medication	Mechanism of Action	Dosing	Major Side Effects
Varenicline (Chantix)	$\alpha_{4\beta2}$ Nicotinic acetylcholine receptor partial agonist	Treatment should be started while the patient is still smoking; the patient should set a target quit date, usually for the second week of treatment. Days 1-3: 0.5 mg once daily 4-7: 0.5 mg twice daily 8-end: 1 mg twice daily Adjust dosage for severe renal impairment or side effects to maximum dose of 0.5 mg twice daily. Initial therapy for 12 weeks with an optional additional 12 weeks for maintenance therapy	Nausea, insomnia, unusual or vivid dreams, constipation, headaches, weight gain, gas, changes in behavior, agitation, depressed mood, suicidal ideation. Boxed warning: Patients should be closely monitored for signs of serious neuropsychiatric side effects.

TABLE 11.3 Outcomes of Selected Smoking Cessation Interventions[13]

Medication	Estimated Odd Ratio of Abstinence Success (95% CI)	Estimated abstinence rate (95% CI)
Placebo	1.0	13.8
Varenicline (2 mg/day)	3.1 (2.5-3.8)	33.2 (28.9-37.8)
Bupropion SR	2.0 (1.8-2.2)	24.2 (22.2-26.4)
Nicotine Patch (6-14 weeks)	1.9 (1.7-2.2)	23.4 (21.3-25.8)
Long-Term Nicotine Patch (>14 weeks)	1.9 (1.7-2.3)	23.7 (21.0-26.6)
Nicotine Nasal Spray	2.3 (1.7-3.0)	26.7 (21.5-32.7)
Nicotine Inhaler	2.1 (1.5-2.9)	24.8 (19.1-31.6)
Nicotine Gum	1.5 (1.2-1.7)	19.0 (16.5-21.9)
Nicotine Patch (>14 weeks) + Nicotine Gum or Spray	3.6 (2.5-5.2)	36.5 (28.6-45.3)
Nicotine Patch + Bupropion SR	2.5 (1.9-3.4)	28.9 (23.5-35.1)
Nicotine Patch + Nicotine Inhaler	2.2 (1.3-3.6)	25.8 (17.4-36.5)

receptor antagonist. Varenicline functions as a partial mixed nicotine receptor agonist and antagonist. Unfortunately, there is no consensus on how to choose among first-line therapies, and the final decision may ultimately reflect personal preference and practical matters such as insurance coverage.

It should be noted that evidence does not support the use of any of these therapies in smokers who use fewer than 10 cigarettes daily. Also, several combinations of first-line therapies have been demonstrated to be effective: nicotine patch for more than 14-weeks and nicotine gum or spray, nicotine patch and nasal inhaler, and nicotine patch and bupropion SR.[13] Effectiveness of individual therapies and combinations are listed in Table 11.3.

Since the first evidence linking smoking and lung cancer more than 60 years ago, there have been extraordinary efforts to elucidate the clinical effects, mechanisms of disease, and public health impact of smoking. Concerted efforts to curb smoking rates based on broad scientific consensus on the adverse effects of smoking have produced steady declines in smoking rates. Nevertheless, there remains much to be done. As surgeons, we are uniquely positioned and obligated to counsel patients not only during "teachable moments" in their lives, as before surgery, but also longitudinally.[14] Indeed, smoking cessation must be seen by surgeons to be as crucial to improving patients' health as any surgical intervention.

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12 CHAPTER

Atherosclerotic Risk Factors: Diabetes

LIDIE LAJOIE and SUBODH ARORA

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Diabetes is characterized by chronic hyperglycemia resulting either from a lack of insulin production (type 1) or from insulin resistance (type 2). In the past several decades an alarming rise in the global prevalence of diabetes has been seen. The cost to the health care system is enormous because the medical expenditures of people with diabetes are 2 to 3 times higher than those of the rest of the population. In 2012 the total cost of diabetes in the United States alone was estimated at $245 billion, including $176 billion in direct medical costs and $69 billion in indirect costs due to disability, work loss, and premature death.[1]

The health consequences of diabetes are primarily vascular and are routinely divided into microvascular and macrovascular categories. The most important microvascular complications are retinopathy and nephropathy; people with diabetes have a 20-fold increased relative risk of blindness and a 25-fold higher relative risk of end-stage renal disease compared with people without diabetes. Macrovascular disease is characterized by atherosclerosis.[2] Diabetes is an important risk factor for the development and severity of all forms of atherosclerosis, including peripheral artery disease (PAD), coronary artery disease (CAD), and cerebrovascular disease (CVD). Most of the 230,000 diabetes-related deaths in the United States every year are due to CAD.[1] Diabetes also increases the risk of ischemic stroke twofold to threefold and accounts for 60% of nontraumatic lower-limb amputations.[3-7] These financial and physical costs are expected to increase in the next few decades as the prevalence of diabetes continues to rise worldwide.

EPIDEMIOLOGY

Over the past several decades, the global prevalence of diabetes has nearly quadrupled, with an estimated 422 million people worldwide currently diagnosed with the condition.[8] This number is predicted to exceed 500 million by 2030, which equates to an annual increase in diabetes prevalence that is 1.7 times faster

than the annual growth of the world's population. In the United States 9.3% of the population, or 29.1 million people, have diabetes and 86 million people have prediabetes (characterized by insulin resistance).[1] Although the prevalence of diabetes is shifting to a younger demographic as the overall population becomes more obese, the risk of diabetes continues to increase with age, and as many as 25.9% of all Americans over the age of 65 have diabetes.[1] The prevalence rate is highest for American Indians/Alaska Natives (15.9%), followed by non-Hispanic blacks (13.2%) and Hispanics (12.8%), and lowest for Asian Americans (9%) and non-Hispanic whites (7.6%).[1]

Global demographic changes and lifestyle factors that directly affect the incidence of diabetes are the major contributors to the increasing prevalence of diabetes worldwide. More than one-third of the increase in number of persons with diabetes worldwide over the past 30 years can be attributed to increases in population size and aging of populations, particularly in India and China. Lifestyle changes related to increasing industrialization and economic development, and the interaction between demographic changes and lifestyle factors explain the remainder of this trend.[8] Industrialization has led to both the abundance of cheap high-calorie food and adoption of a sedentary lifestyle in the same countries with the greatest population growth, leading to an epidemic of obesity worldwide. The prevalence of obesity in the United States is increasing at an alarming rate and directly corresponds to the number of new diagnoses of diabetes. In fact, from 2000 to 2005 the rate of obesity increased by 24%. During that same time period, the prevalence of diabetes in the United States increased from 12% to 16.3%.[1] However, recent data point to the specific role and direct relationship of sugar consumption and other types of food intake, independent of obesity and the risk of development of diabetes.[9]

CLASSIFICATION OF DIABETES

Type 1

Type 1 diabetes is characterized by an absolute deficiency in insulin secretion and accounts for 5% to 10% of diabetes diagnoses.[10] It results from cellular-mediated autoimmune destruction of the pancreatic beta cells and requires both genetic and environmental factors to cause the disease state. Markers of immune destruction of the beta cell are present in 70% to 90% of patients and can aid in the diagnosis. These include islet cell autoantibodies, autoantibodies to insulin, antiglutamic acid decarboxylase antibodies, and autoantibodies to tyrosine phosphatase IA-2 and IA-2β.[11]

Typically, type 1 diabetes presents with acute hyperglycemia or ketoacidosis as the first disease manifestation. Type 1 diabetes (previously known as "juvenile-onset" diabetes) often presents in children and adolescents but can present at any age. It also frequently develops in patients who have other autoimmune diseases such as lupus, rheumatoid arthritis, and Hashimoto thyroiditis.[10] Because patients with type 1 diabetes have an absolute deficiency in insulin secretion, their treatment is reliant on insulin replacement therapy.

Type 2

Type 2 diabetes results from a combination of insulin resistance and inadequate compensatory insulin secretion, accounting for 90% to 95% of patients with diabetes.[10] Although type 2 was previously referred to as either "adult-onset" or "noninsulin-dependent" diabetes, these terms are less accurate because many patients may require insulin treatment and because it can develop at practically any age. In the United States more than 20% of new diagnoses of diabetes in people under the age of 20 are due to type 2.[1]

The pathogenesis of type 2 diabetes is heterogeneous, with both environmental and genetic causes. Obesity is strongly related to insulin resistance and is the most important environmental factor. The heritability of insulin sensitivity is approximately 40% to 50%. Although insulin resistance is clearly necessary for the development of type 2 diabetes, incomplete compensatory rise in insulin secretion (relative deficiency) must also be present for hyperglycemia to result. This concept was illustrated by DeFronzo et al., who demonstrated that plasma insulin response to ingested glucose increases progressively in individuals who have fasting glucose concentration less than 120 mg/dL. Having a fasting glucose greater than 120 mg/dL is progressively associated with a corresponding decline in insulin secretion.[12] Genomic studies have identified more than 88 gene loci associated with the risk of developing type 2 diabetes. Most of these loci are primarily associated with insulin secretion and beta cell function, with few genes (e.g., *NAT2*) linked to insulin resistance that is independent of obesity.[13] In type 2 diabetes the hyperglycemia tends to develop slowly, and therefore the symptoms are more subtle. These include polyuria, polydipsia, weight loss, and polyphagia. Because people with type 2 diabetes have varying levels of insulin resistance and deficiencies in insulin secretion, they require the titration of different medications to achieve appropriate glycemic control.

DIABETES AND VASCULAR DISEASE

Vascular disease is the most significant cause of morbidity and mortality in people with diabetes.[3] There is a direct relationship between level of hyperglycemia and disease severity in microvascular diseases such as retinopathy, nephropathy, and neuropathy; thus these diseases are more prominent in type 1 diabetes, with its long duration of hyperglycemia exposure.[3] On the other hand, macrovascular complications such as CAD, PAD, and CVD, although responsible for the majority of deaths in patients with diabetes, have a modest relationship to glycemia.[14]

Coronary Artery Disease

Diabetes is associated with a significantly increased risk of developing CAD, and patients with diabetes and CAD have been shown to have worse outcomes. People with diabetes tend to present with CAD at a younger age than patients without diabetes. It is estimated that diabetes leads to clinically evident CAD as much as 15 years earlier than otherwise expected.[15]

Once diagnosed with CAD, persons with diabetes have a higher risk of cardiovascular death, recurrent myocardial infarction (MI), stroke, and coronary stent thrombosis.[16] Furthermore, people with diabetes account for a disproportionate number of those presenting with acute coronary syndromes.[17] Following MI, people with diabetes have higher rates of morbidity and mortality, with a 58% higher mortality than in nondiabetics at 30-days[18] and nearly 50% higher mortality at 1 year.[19]

Cerebrovascular Disease

There are more than 2 million people with diabetes in the United States who have survived a stroke.[1] Diabetes is associated with at least twice the risk for stroke, a 2-year earlier age of onset of CVD symptoms, and worse functional outcomes compared with nondiabetics.[17] The duration of diabetes, but not the quality of glycemic control, is an independent predictor for risk of ischemic stroke. For patients treated with thrombolytic therapy for acute stroke, hyperglycemia is associated with a higher failure of recanalization and increased risk for hemorrhagic conversion.[20] After a completed stroke, diabetes doubles the risk for a recurrent event.[21] Although stroke is responsible for 20% of mortalities among people with diabetes, no significant difference has been demonstrated in the mortality rate after stroke among diabetics compared with nondiabetics. Among diabetic survivors of ischemic stroke, half will have long-term disability and are less likely than nondiabetics to be discharged home and are more likely to suffer loss of independence in the short and long term (3, 6, and 18 months).[21]

Peripheral Artery Disease

An estimated 10 million Americans are affected by PAD, and more than 80,000 are hospitalized each year for the condition.[1,22] The prevalence of PAD varies significantly based on the age of the population studied, from 0.9% in patients between 40 and 49 years old to 14.5% in patients older than 69 years in the National Health and Nutrition Examination Survey (NHANES)[23] Targeted screening can more clearly identify a population at risk. In the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) trial, nearly 7000 subjects were screened in primary care practices, provided they met one of the following criteria: age 70 years or older or ages 50 to 69 years with a history of diabetes and/or smoking.[24] Using these criteria, 29% of subjects were found to have PAD. In patients with diabetes, risk of PAD is increased by older age, smoking, duration of diabetes, and presence of peripheral neuropathy. In patients with diabetes the prevalence of PAD may be as high as 40%.[25] The risk of PAD is also known to be higher in African Americans and Hispanic Americans with diabetes.[5]

Diabetes significantly increases both the incidence and severity of limb ischemia because of several associated factors.[26] Insulin resistance is independently associated with PAD, after adjustment for demographic factors and medical comorbidities.[27] The distribution of PAD is different in patients with diabetes compared with those without it. Patients with diabetes and PAD tend to have involvement of the more distal arteries, particularly the popliteal and tibial arteries, making limb-salvage revascularization more challenging.[5,6] The neuropathy that often develops in people with diabetes presents several additional challenges. First, sensory neuropathy reduces the ability to avoid injury by decreasing normal sensation and withdrawal to pain. In addition, symptoms common to advanced ischemic disease may be less appreciated and may lead to delay in diagnosis.[6] Diabetic peripheral neuropathy also leads to limited joint mobility (due to motor neuropathy), decreased proprioception and pain sensation (due to sensory neuropathy), and decreased sweating (due to autonomic neuropathy). The motor neuropathy fosters the formation of a swan neck foot deformity, resulting in disproportionate increases in pressure points to the metatarsal heads and other parts of the foot, making ulceration more likely.[28,29]

As a result, diabetes is the most common cause of nontraumatic lower extremity amputation in the United States, accounting for 55% of amputation-related hospitalizations.[30] For people 65 to 74 years old, the risk of amputation is increased more than 20-fold compared with those without PAD and diabetes.[31] The combination of PAD and diabetes is of additional clinical importance given its association with cardiovascular events. Patients with both diabetes and PAD are at extremely high risk of adverse cardiovascular events. In the Linz Peripheral Arterial Disease (LIPAD) study, the mortality rate from cardiovascular disease over a 10-year period was 5% for people with diabetes, 14% for those with PAD, and 31% for patients with both.[32] The mortality for patients with diabetes and PAD who require a lower extremity amputation is 50% at 2 years.[25]

PATHOPHYSIOLOGY OF VASCULAR DISEASE IN DIABETES

Diabetes leads to increased atherosclerotic vascular disease by a number of mechanisms, including metabolic derangements, hypercoagulability, inflammation, vascular dysfunction, and neuropathy. These alterations result in a phenotypic change in the blood vessel from one of homeostasis to an atherogenic phenotype characterized by endothelial cell dysfunction, oxidative stress mediated by increased production of free radicals, and vascular smooth muscle dysfunction.[33]

Dysmetabolism and Vascular Dysfunction

The cardinal metabolic derangements in diabetes are each associated with a wide variety of insults that attenuate the vasculature's ability to maintain equilibrium and foster an environment permissive for the development of atherosclerosis. The two fundamental derangements include hyperglycemia and insulin resistance, which are both associated with the development of atherosclerosis. Increases in the rate of atherosclerotic events begin with modest increases in fasting glucose levels in the normal range. Insulin resistance, independent of hyperglycemia, is associated with atherosclerosis and predicts cardiovascular events.[33]

The impact of diabetes on the vascular endothelium represents an important link between the dysmetabolism of diabetes and

the atherosclerosis that causes the majority of morbidity and mortality. The vascular endothelium plays a fundamental role in vascular homeostasis, regulating vascular tone, platelet activity, leukocyte adhesion and diapedesis, and vascular smooth muscle cell migration and proliferation.[34] The endothelium regulates vascular homeostasis through the elaboration of autocrines and paracrines that modulate the structure and function of vascular cells. An endothelium-derived vasodilator, nitric oxide (NO), is constitutively produced in healthy endothelial cells by endothelial NO synthase (eNOS). The production of NO is closely adjusted by a wide variety of chemical and biomechanical stimuli. In addition to its potent vasodilatory properties, NO reduces production of proinflammatory chemokines and cytokines through inhibition of inflammatory transcription factors, which subsequently limits platelet activation. In contrast, decreased bioavailability of NO enhances an environment of vascular injury and atherogenesis.[35] NO bioavailability is reduced in basic investigations, animal models, and humans with insulin resistance and frank diabetes mellitus.[36-39] Endothelial dysfunction, found in both hyperglycemia and impaired endothelial insulin signaling, may link insulin resistance to its heightened risk of atherosclerosis, MI, and death. Thus endothelial dysfunction participates in the development and progression of atherosclerosis and may facilitate its adverse sequelae.

Hyperglycemia impairs vascular function through an increase in the production of reactive oxygen species (ROS), oxidative stress, and consequent impairment in endothelial function.[40] Hyperglycemia-induced ROS inactivates endothelium-derived NO.[40] Reduced NO bioavailability fosters atherogenesis and predicts a heightened risk of cardiovascular outcomes.[41,42] Through a variety of mechanisms, hyperglycemia increases ROS production and impairs endothelial function. Hyperglycemia increases mitochondrial generation of the superoxide anion, leading to cellular mitogenic pathway activation including polyol and hexosamine flux, advanced glycation end products (AGEs), protein kinase C (PKC) activation, and nuclear factor kappa B (NF-κB)-mediated vascular inflammation.[43,44] Indeed, ROS lead to upregulation and nuclear translocation of NF-κB subunit p65 and transcription of proinflammatory genes encoding for monocyte chemoattractant protein-1 (MCP-1), selectins, vascular cell adhesion molecule-1 (VCAM-1), and intracellular adhesion molecule-1 (ICAM-1). These events facilitate adhesion of monocytes to the vascular wall and their translocation into the subendothelium with subsequent formation of foam cells (Fig. 12.1).

The second cardinal marker of dysmetabolism in diabetes is insulin resistance. Insulin resistance likely precedes the onset of hyperglycemia by many years. In diabetes, insulin resistance affects many tissues, including skeletal muscle, liver, adipose, and blood vessels. One possible mechanism by which insulin resistance can impair vascular function is the byproduct of the resistance on adipose tissue. Adipose tissue is an important source of inflammatory mediators and free fatty acids (FFAs),[45] which are elevated in the plasma of obese patients with type 2 diabetes.[46] Impaired endothelial cell insulin signaling may also be salient in insulin resistance. In mice a loss of insulin signaling in the vascular endothelium leads to diminished endothelial

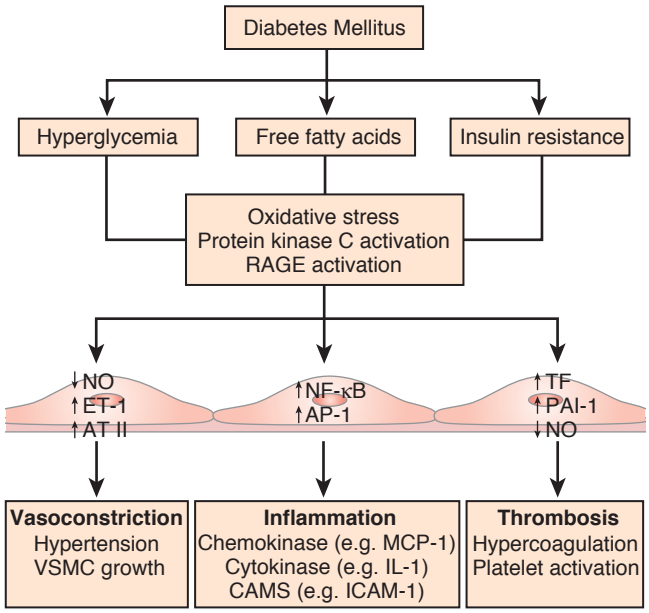

Figure 12.1 The metabolic abnormalities that characterize diabetes—particularly hyperglycemia, free fatty acids, and insulin resistance—provoke molecular mechanisms that alter the function and structure of blood vessels.

NO synthase levels, endothelial dysfunction, expression of adhesion molecules, and atherosclerotic lesions.[47] Another study confirmed the importance of endothelial insulin signaling by showing that genetic disruption of endothelial insulin receptor substrate 2 (IRS-2) reduces glucose uptake by skeletal muscle, whereas restoration of insulin-induced eNOS phosphorylation restored capillary recruitment as well as insulin delivery.[48] These novel findings strengthen the central role of endothelium in obesity-induced insulin resistance, suggesting that blockade of vascular inflammation and oxidative stress may be a promising approach to prevent metabolic disorders. Notably, pharmacologic improvement of insulin sensitivity in patients with type 2 diabetes and metabolic syndrome is associated with restoration of flow-mediated vasodilation.[49-51]

The atherogenic effects of insulin resistance are also due to changes in lipid profile such as high triglycerides, low HDL cholesterol, increased remnant lipoproteins, elevated apolipoprotein B (ApoB), and small and dense LDL.[52] Once circulating FFAs reach the liver, VLDL are assembled and made soluble by increased synthesis of ApoB. VLDL are processed by cholesteryl ester transfer protein (CETP), allowing transfer of triglycerides to LDL, which become small and dense and hence more atherogenic. Atherogenic dyslipidemia is a reliable predictor of cardiovascular risk, and its pharmacologic modulation may reduce vascular events in subjects with type 2 diabetes and metabolic syndrome.[53-55]

Platelet Dysfunction and Coagulation Cascade

Platelet dysfunction has also been shown to play a role in thrombosis, complicating atherosclerotic plaque rupture in diabetes. Glycoprotein Ib and IIb/IIIa expression is upregulated in diabetes, which leads to increased amounts of von Willebrand

factor and platelet-fibrin interaction.[56] Hyperglycemia also impairs calcium homeostasis, which alters calcium-dependent platelet aggregation and activation.[57] Procoagulant factors (factor VIII, thrombin, and tissue factor) are increased and endogenous anticoagulants and fibrin inhibitors (thrombomodulin, protein C, plasminogen activator inhibitor 1) are decreased in a chronic hyperglycemic state.[58-61] Diabetes therefore leads to increased platelet aggregation and a shift in favor of the procoagulant portion of the thrombotic cascade. These alterations contribute to the propensity not only for atherosclerosis, but also for thrombosis in pathologic plaque rupture resulting in acute coronary syndrome, ischemic stroke, and acute limb ischemia, which are known to be more common in people with diabetes.

VASCULAR EVALUATION OF PATIENTS WITH DIABETES

The vascular evaluation of patients with diabetes is a challenge for providers and requires additional evaluation for a comprehensive assessment, particularly regarding the evaluation of neuropathy, thorough foot examination, and noninvasive physiologic testing. The examination should focus on inspection of the extremities and feet for signs of skin change, hair loss, ulceration, or increased dryness. Full sensory and motor exam should then be performed with the addition of monofilament testing plus vibration sensation (using 128-Hz tuning fork), pinprick sensation, or ankle reflexes.[62]

The presence of neuropathy is an important risk multiplier not seen with other risk factors. Diabetic peripheral neuropathy is characterized by a symmetric sensorimotor polyneuropathy.[63] It starts distally, moves proximally, and results in a typical "glove and stocking" distribution.[64] Motor deficits are rare in the early stages of diabetic peripheral neuropathy. Burning, tingling, and shooting pains are frequently described and are typically worse at night.[64] Of note, the degree of pain and subjective symptoms are not reliable indicators of sensory nerve damage. Careful peripheral neurologic examination is recommended annually in patients with diabetes.[62]

The American Podiatric Medical Association and the Society for Vascular Surgery recommend that patients with diabetes have ankle-brachial index (ABI) measurements performed when they reach 50 years of age. Furthermore, patients with a prior history of diabetic foot ulcer, known atherosclerotic cardiovascular disease, prior abnormal vascular examination, or prior intervention for PAD should have a clinical examination of the lower extremities and noninvasive physiologic testing (ABI and/or toe pressures) annually.[25] However, one important diagnostic consideration is the increased likelihood of noncompressible pedal vessels and subsequent falsely elevated ABI results in patients with diabetes.

The Wound, Ischemia, and foot Infection (WIfI) classification system is a framework for stratifying amputation risk and revascularization benefit in patients with PAD that is useful in the evaluation of diabetic foot ulcers which is reviewed in Chapter 116.[65]

TREATMENT OF PATIENTS WITH DIABETES AND PERIPHERAL ARTERY DISEASE

The two most important goals in the treatment of patients with PAD and diabetes are improving limb outcomes (i.e., improving claudication symptoms and preventing progression to critical limb ischemia) and decreasing morbidity and mortality from cardiovascular disease and stroke. An aggressive approach to risk factor modification and medical treatment is the cornerstone to achieve both goals. Target-driven medical intervention can reduce the risk of cardiovascular events by as much as 50% in patients with type 2 diabetes.[66] A sample treatment algorithm for patients with PAD and diabetes is available in Box 12.1.

Preventive Foot Care

Peripheral neuropathy, ischemia, and infection form the etiologic triad of diabetic foot complications.[67] Proper foot care and hygiene are the hallmarks of preventive therapy. Commonly, diabetic foot ulcers and infections begin as small wounds that are not recognized and treated in the early stages because symptoms may be masked by sensory neuropathy. Therefore careful screening and early intervention are important in preventing diabetic foot complications. The American Diabetes Association (ADA) recommends annual foot examination to identify high-risk conditions before complications develop.[68] The SVS and APMA provide more specific recommendations for prevention of diabetic foot ulceration including: (1) annual foot

BOX 12.1 Treatment Algorithm for Peripheral Artery Disease in Patients With Diabetes

1. Refer to smoking cessation program
2. Treatment of hypertension with blood pressure reduced to <140/90 mm Hg
3. Control diabetes mellitus with hemoglobin A1c level reduced to <7.0%
4. Treat dyslipidemia and reduce serum LDL level to <70 mg/dL
5. Antiplatelet drug therapy with aspirin or clopidogrel
6. Treatment with angiotensin-converting enzyme inhibitor
7. Treatment with beta blockers in patients with coronary artery disease in the absence of contraindications
8. Use of statins
9. Treatment with cilostazol in patients with intermittent claudication
10. Exercise rehabilitation program
11. Foot care
12. Consider percutaneous angioplasty or bypass surgery for
    - Incapacitating claudication interfering with work or lifestyle
    - Limb salvage in persons with limb-threatening ischemia
    - Vasculogenic impotence
13. Amputation of lower extremities should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations diminish the benefit of limb salvage

Adapted from Aronow WS. Peripheral arterial disease of the lower extremities. *Arch Med Sci*. 2012;8:375-388.

examination by a provider with training in foot care, (2) inclusion of the Semmes-Weinstein test for peripheral neuropathy as a component of the foot exam, (3) patient and family education about preventative foot care, (4) custom therapeutic footwear in high-risk patients, including those with significant neuropathy, foot deformities, or previous amputation, and (5) glycemic control (hemoglobin A1c <7%).[25]

Glycemic Control

The study of glycemic control and the impact on macrovascular events has been investigated in three large trials performed to determine whether tight glucose control (hemoglobin A1c <6.5%) was better than standard control (hemoglobin A1c of 7%). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a strategy of targeting a hemoglobin A1c of 6% versus 7% to 7.9% to reduce adverse cardiovascular events was evaluated in 10,251 patients.[69] The study was stopped early because the intensive glucose-lowering strategy was found to increase cardiovascular mortality without reducing other major cardiovascular events. The Action in Diabetes and Vascular Disease (ADVANCE) study and the Veterans Affairs Diabetes Trial (VADT) both also failed to demonstrate a reduction in cardiovascular outcomes in patients with improved glycemic control.[70,71] Based on the lack of success in these large trials, the ADA recommended targeting a hemoglobin A1c of 7.0%.[72]

In addition to lowering glucose, insulin-sensitizing agents have been studied in relation to cardiovascular events. Metformin, a biguanide, has demonstrated improvements in cardiovascular outcomes. In United Kingdom Prospective Diabetes Study (UKPDS), among obese subjects, metformin reduced diabetes-related death and all-cause mortality by 42% and 36%, respectively.[3] In the 10-year follow-up of UKPDS, metformin reduced MI by 33% and mortality by 27% compared with subjects treated with sulfonylureas, despite a lack of difference in glycemic control.[73] In a Danish study, patients treated with insulin secretagogues had an approximate 20% increase in all-cause mortality compared with patients treated with metformin.[74] Thus metformin is the recommended first line hypoglycemic agent to be used in patients with type 2 diabetes. The thiazolidinediones have a mixed cardiovascular outcomes record. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), pioglitazone did not demonstrate macrovascular benefits in terms of reduction of cardiovascular events at 10-year follow-up.[75] Rosiglitazone, on the other hand, was shown to be associated with a reduction in overall cardiovascular events and cardiovascular death in the VADT.[76] Table 12.1 briefly reviews the different classes of medications available to treat hyperglycemia.

Although it has not been proven to improve PAD symptoms or amputation rates, the ACC/AHA consensus guidelines on PAD treatment also support a hemoglobin A1c goal of 7.0%.[77] When insulin-providing therapy was compared with insulin sensitization therapy for glycemic control in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, the insulin sensitization strategy was shown to be superior in the reduction of PAD, need for lower extremity revascularization, and lower extremity amputation.[78] The PROactive trial, despite failing to demonstrate an effect of pioglitazone on cardiovascular outcomes, did show a significant decrease in leg amputations at 10-year follow up (4.1% for pioglitazone compared with 5.6% for placebo).[75]

With so many medication classes, the choice of agent for each patient may seem daunting. The ADA published *A Consensus Algorithm for the Initiation and Adjustment of Therapy* in 2009 to aid in these decisions. According to this algorithm, lifestyle interventions are the first step of treatment, followed by metformin, if still necessary. If lifestyle interventions and maximal tolerated dose of metformin do not achieve a hemoglobin A1c less than 7%, another medication should be added. Either sulfonylurea or insulin is the suggested second medication for this step. If glycemic control is still not achieved, insulin therapy should be started or intensified until goal hemoglobin A1c is achieved. The ADA therefore relegates the other oral and subcutaneous medications to a "second-tier" algorithm, which it states is appropriate in certain individualized circumstances.[72]

Risk Factor Control

Aggressive risk factor modification is the cornerstone for reductions in atherosclerosis-related events. Much of this therapy is discussed in other chapters in the text; here we provide diabetes-specific data for risk factor reduction.

Dyslipidemia

The American College of Cardiology and American Heart Association guidelines on the treatment of blood cholesterol strongly recommend the use of moderate-intensity statin therapy for primary prevention of atherosclerotic cardiovascular disease in diabetics 40 to 75 years of age with LDL greater than 70 mg/dL.[79] This recommendation is based on numerous large-scale clinical trials which have shown a significant benefit of statin therapy in patients with diabetes and elevated LDL or even average LDL.[80,81] In the Heart Protection Study (HPS), 3000 subjects with diabetes and without evidence of atherosclerotic disease at entry but with total cholesterol greater than135 mg/dL were randomized to simvastatin or placebo. A 34% risk reduction was observed in the combined endpoint of coronary heart disease, stroke, and revascularization in simvastatin-treated group.[82] The Collaborative Atorvastatin Diabetes Study (CARDS) enrolled participants with diabetes without evidence of vascular disease but with one other cardiovascular risk factor (hypertension, retinopathy, smoking, or microalbuminuria or macroalbuminuria) and randomized these subjects to 10 mg/day of atorvastatin versus placebo.[83] The mean LDL level in this trial was 117 mg/dL. The results showed a 30% reduction in the composite primary endpoint of major cardiovascular events in the atorvastatin-treated group. The most significant finding of this trial is that the benefit occurred irrespective of baseline LDL levels in both treated and placebo patients. Despite numerous trials and recent efforts at targeted drug development, to date, no lipid-lowering medications other than statins have been shown to reduce the incidence of stroke, MI, or cardiovascular mortality. Indeed, niacin, fenofibrate, and novel agents

TABLE 12.1 Summary of the Most Common Oral Hypoglycemic Agents

Agent	Mechanism of Action	Expected A1C Reduction	Adverse Effects	Outcome Data/CV Safety Concerns
Biguanides Metformin	Decrease hepatic glucose production	≈1%-2%	Diarrhea, nausea, lactic acidosis, decreased B12 levels	May improve CVD outcomes; contraindicated in decompensated or unstable HF due to risk of lactic acidosis
Sulfonylureas Glyburide Glipizide Glimepiride	Bind to sulfonylurea receptors on pancreatic islet cells, cardiac K_{ATP}, stimulating insulin release	≈1%-2%	Hypoglycemia, weight gain	Hypoglycemia may precipitate ischemia or arrhythmia; cardiac K_{ATP} channel closure may impair ischemic preconditioning
Glinides Nateglinide	Bind to sulfonylurea receptors on pancreatic islet cells	≈1%-2%	Hypoglycemia, weight gain	Hypoglycemia may precipitate ischemia or arrhythmia; cardiac K_{ATP} channel closure may impair ischemic preconditioning
α-Glucosidase inhibitors Acarbose Miglitol	Slow gut carbohydrate absorption	≈0.5%-1%	Gas, bloating	Improves postprandial glucose excursions, which are more tightly associated with CVD than fasting glucose
Thiazolidinediones Rosiglitazone Pioglitazone	Activates the nuclear receptor PPAR-γ, increasing peripheral insulin sensitivity and reduces hepatic glucose production	≈1%-1.5%	Weight gain, edema, possible bone loss in women	May precipitate clinical HF in predisposed individual;
Incretin modulators GLP-1 mimetics Exenatide	Increase glucose-dependent insulin secretion, decrease glucagon, and delay gastric emptying	≈1%	Nausea, vomiting	
DPP-4 inhibitors Sitagliptin Saxagliptin	Inhibit degradation of endogenous GLP-1, thereby enhancing the effects of incretins	≈0.6%-0.8%		
Amylin analogues Pramlintide	Decrease glucagon secretion and delay gastric emptying	≈0.4%-0.6%	Nausea, vomiting	
Insulins	Increased insulin supply	No limit (theoretically)	Hypoglycemia, weight gain, edema (at high doses)	

CVD, Cardiovascular disease; *GIP-1*, glucose-dependent insulinotropic peptide; *GLP-1*, glucagon-like peptide 1; *HF*, heart failure; *MI*, myocardial infarction.
Adapted from Inzucchi SE, et al. New drugs for the treatment of diabetes: part II: incretin-based therapy and beyond. *Circulation*. 2008;117:574.

that raise HDL (CETP inhibitors) have all been shown in large-scale clinical trials to provide no benefit beyond statins in cardiovascular risk reduction.[84-86]

Hypertension

Control of hypertension has been shown in multiple studies to decrease the risk of macrovascular disease and death in patients with diabetes. Indeed, blood pressure control was the first treatment to show reductions in mortality. In UKPDS, "tight blood pressure control" (a mean blood pressure of 144/82 mm Hg in the treatment arm compared with 154/87 mm Hg in the control arm) was associated with a 32% risk reduction in death related to diabetes and 44% risk reduction in strokes.[87] In the Appropriate Blood-Pressure Control in Diabetes (ABCD) trial, normotensive patients with diabetes were randomized to intensive diastolic blood pressure control (with a goal of decreasing the diastolic blood pressure by 10 mm Hg from the baseline value) or moderate blood pressure control.[88] The intensive blood pressure control group was treated with either nisoldipine (a calcium-channel blocker) or enalapril (an angiotensin-converting enzyme [ACE] inhibitor). Intensive diastolic blood pressure control resulted in improved cardiovascular outcomes in the ACE inhibitor group and had a beneficial effect on albuminuria, retinopathy, and strokes in patients treated with either medication.[89] When patients with PAD were specifically analyzed, a significant and dramatic reduction (38.7% compared with 13.6%) was seen in MI, stroke, and cardiovascular death in the patients in the intensive blood pressure control groups.[90] In response to these and other studies showing similar outcomes, the current Joint National Committee (JNC) guidelines for the management of hypertension involves pharmacologic therapy with a goal blood pressure lower than 140/90 mm Hg for all adult patients with diabetes.[91]

Further studies have shed light on the importance of the renin-angiotensin axis in patients with diabetes. More than 20 high-quality studies have investigated the effect of ACE inhibitors on cardiovascular events in patients with diabetes, and meta-analysis of these data demonstrates that ACE inhibitor therapy significantly reduces the risk of all-cause mortality by 13%, cardiovascular deaths by 17%, and major cardiovascular events by 14%, including MI (reduced by 21%) in patients with diabetes.[92] The effect of ACE inhibitors and angiotensin II

receptor blockers on diabetic foot ulcers and lower extremity amputations in patients with diabetes and PAD was studied by Margolis et al.[93] They found significant reduction in diabetic foot ulcers and lower extremity amputations in patients treated with angiotensin II receptor blockers for 1 year compared with those who received ACE inhibitors. However, this finding requires further validation.

Antiplatelet Therapy

Antiplatelet therapy is a key component of secondary prevention measures in patients with diabetes and known atherosclerotic vascular disease. However, the role of aspirin therapy for primary prevention of cardiovascular disease is less clear. Three trials have been conducted specifically in patients with diabetes (Early Treatment Diabetic Retinopathy Trial, Prevention of Progression of Arterial Disease and Diabetes [POPADAD], and Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes [JPAD]), and six trials included large proportions of patients with diabetes with a wide range of study duration and aspirin dosage.[94] Meta-analysis of these data suggests a modest (9%) relative risk reduction in risk for cardiovascular events and more than twofold increased risk of bleeding. Based on this evidence, in 2015 the ADA and the AHA jointly recommended low-dose aspirin therapy (75 to 162 mg/day) for primary prevention in patients with diabetes when the 10-year risk of cardiovascular events is greater than 10% and the baseline risk of gastrointestinal bleeding is not increased.[95] This includes men older than 50 years and women older than 60 years with one or more of the following risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, or albuminuria.

Numerous studies have demonstrated the benefit of antiplatelet therapy in patients with known PAD for reducing cardiovascular events. A subgroup of the Antithrombotic Trialists' Collaboration meta-analysis included 9214 patients with PAD and found a significant reduction in serious vascular events with aspirin therapy.[96] In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, patients with non–ST-elevation MI, ischemic stroke, or PAD were randomized to treatment with aspirin versus clopidogrel. A subset analysis demonstrated that the 3866 patients with diabetes had a 12.5% reduction in major cardiovascular events with clopidogrel versus aspirin.[97] The SVS guidelines recommend antiplatelet therapy with either aspirin 75 to 325 mg or clopidogrel 75 mg in individuals with PAD with a grade 1 level of evidence.[22] However, more recent data question the benefits of this therapy specifically in patients with diabetes. In the JPAD trial, patients with diabetes were randomized to low-dose aspirin (81-100 mg) versus placebo, with no reduction found in the risk of major cardiovascular events.[98] The POPADAD trial evaluated aspirin efficacy in patients with both diabetes and PAD. The 1276 patients with diabetes and PAD (based on ABI <0.99) were randomized to low-dose aspirin plus antioxidant treatment, low-dose aspirin plus placebo, antioxidant plus placebo, or double placebo. No significant difference was seen among the four groups in death from coronary heart disease, nonfatal MI, stroke, above-the-ankle amputation, or critical limb ischemia.[99] The clinical standard will likely be to continue aspirin or other antiplatelet therapy in these patients pending further studies in a larger number of patients.

Medical Treatment for Symptomatic Improvement of Peripheral Artery Disease

After a diagnosis of PAD has been made, therapies to preserve exercise tolerance and improve symptoms should be initiated. Exercise therapy is the most beneficial intervention for these goals, and cilostazol may also improve exertional capacity and symptoms.

Exercise Therapy

Exercise therapy is effective in improving the symptoms of intermittent claudication. Randomized controlled trials of supervised exercise training programs have repeatedly supported this benefit, including increasing the distance to onset of claudication and increasing the distance to maximum claudication pain.[100,101] The optimal exercise program, based on a meta-analysis by Gardner et al., includes walking for at least 30 minutes, more than 3 times per week for 6 months.[102] In another meta-analysis of supervised exercise for PAD, Bendermacher et al. found an average improvement in maximum walking time of 6.5 minutes with supervised exercise, which is superior to any medication studied to date.[103] Although patients with diabetes typically have more impairment at baseline, exercise therapy increases walking distance in patients with diabetes as well as in claudicants without diabetes.[104] The Claudication: Exercise versus Endoluminal Revascularization (CLEVER) study randomized patients (approximately 25% of whom had diabetes) with aortoiliac PAD to optimal medical care, optimal medical care plus supervised exercise, or optimal medical care plus stent revascularization.[105] The primary endpoint was a graded treadmill test at 6 months compared with baseline. The supervised exercise group had the greatest improvement in walking time, but quality of life assessment by questionnaire was most improved in the stenting group. This finding will be further evaluated in the larger SUPERvised Exercise Therapy or Immediate PTA for Intermittent Claudication In Patients with an Iliac Artery Obstruction (SUPER) trial, which is ongoing.[106] Consistent with these data, the SVS recommends a supervised exercise program as the initial treatment modality for patients with intermittent claudication consisting of walking a minimum of 3 times per week (30 to 60 min/session) for at least 12 weeks or a home-based exercise program of similar intensity when a supervised exercise program is unavailable or has been completed.[22]

Cilostazol

Cilostazol is a phosphodiesterase-3 inhibitor that has vasodilator, antiproliferative, and antiplatelet effects.[107] Although it has not been shown to have any effect on mortality, it improves symptoms of claudication in approximately 50% of patients with and without diabetes.[108] A Cochrane Review of seven randomized double-blind trials evaluating the use of cilostazol found significantly increased walking times in patients with stable intermittent claudication.[109] The SVS guidelines for treatment

of PAD state that a 3-month trial of cilostazol at a dose of 100 mg twice daily is recommended to alleviate symptoms and improve walking distance in patients with lifestyle-limiting symptoms who do not have congestive heart failure.[22] In one study that compared the effects in subjects with and without diabetes, cilostazol increased walking distance similarly in both groups.[110] Cilostazol is generally well tolerated, with adverse effects of headaches, nausea, diarrhea, pain, infection, upper respiratory symptoms, palpitations, arrhythmias, and peripheral edema occurring in approximately 5% of people based on a meta-analysis.[109] Cilostazol is contraindicated in patients with congestive heart failure or moderate to severe renal or hepatic impairment.

Pentoxifylline

Pentoxifylline is a methylxanthine derivative that acts by inhibiting phosphodiesterase and by potentiating the effects of endogenous prostacyclin.[111] Numerous studies have been performed comparing pentoxifylline treatment with both placebo and other therapies. A Cochrane Review of these studies concluded that the data were poor, the results varied widely, and definitive evidence of efficacy was lacking.[111] When evaluated head to head, cilostazol significantly improved walking distances compared with placebo, whereas pentoxifylline was no different from placebo.[112] The SVS guidelines state that a trial of pentoxifylline may be considered for patients who cannot tolerate or have a contraindication to cilostazol to improve pain-free walking in patients with intermittent claudication.[22]

Statins

Beyond their reduction of cardiovascular events, statins have also been shown to improve walking distance and reduce the progression of symptomatic claudication. In one prospective trial of patients with PAD randomized to atorvastatin 10 mg/day, atorvastatin 80 mg/day or placebo, the patients in the high-dose atorvastatin group experienced improvement in pain-free walking distance and subjective physical activity questionnaire scores.[113] A retrospective analysis of the Scandinavian Simvastatin Survival Study (4S) found that patients with dyslipidemia and CAD had a 38% risk reduction in developing new or worsening claudication symptoms when treated with simvastatin.[114] A randomized trial of simvastatin versus placebo for intermittent claudication found that at 6 months the pain-free walking distance had increased 90 m more in the stimvastatin group.[115] With these data in mind, the SVS recommends the inclusion of statin pharmacotherapy for patients with symptomatic PAD.[22]

Angiotensin-Converting Enzyme Inhibitors

Six small randomized controlled trials have evaluated the role of ACE inhibitors in pharmacologic therapy to improve symptoms of PAD. Meta-analysis of these studies demonstrates that treatment with ACE inhibitors improves maximum walking distance by 121 m and pain-free walking distance by 75 m compared with placebo.[116] The greatest benefits were seen in the three trials that used ramipril. The most common side effect of treatment with ACE inhibitors is persistent cough.

Referral for Revascularization

When medical therapy fails, revascularization (either surgical or percutaneous) may be necessary. Indications for peripheral revascularization procedures for PAD are the same in patients with and without diabetes. In PAD, these include disabling claudication, critical limb ischemia (rest pain or tissue loss), or nonhealing or infected foot ulcers that are expected to benefit from revascularization, which is reviewed in Chapter 105.

SUMMARY AND FUTURE DIRECTIONS

Diabetes increases the risk of vascular disease, including cardiovascular, cerebrovascular, peripheral vascular, and microvascular diseases. CAD is responsible for the majority of the deaths in patients with diabetes, but stroke, claudication, critical limb ischemia, diabetic foot ulcers, retinopathy, and nephropathy all contribute to the overall health care expenditures and morbidity in patients with diabetes. Numerous metabolic, thrombotic, and vascular derangements occur in diabetes and explain the accelerated atherosclerosis and increased rate of thrombosis characteristic of diabetic vascular disease. Treatment of PAD in patients with diabetes involves therapies to improve claudication symptoms and aggressive risk factor modification aimed at improving cardiovascular outcomes and overall mortality. As the worldwide incidence of diabetes grows, these complications will become more and more important to global health care delivery.

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CHAPTER 13

Atherosclerotic Risk Factors: Hyperlipidemia

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Cardiovascular disease is the leading cause of death in industrialized countries and accounts for over 31% of deaths globally.[1] Over the last century, a multitude of discoveries and intense research have elucidated the mechanisms of atherosclerosis, a word derived from the Greek *atheros*, meaning gruel and *sclerosis*, meaning hard. It has been well established, for over six decades now, that the major atherosclerotic risk factors include hyperlipidemia, hypertension, cigarette smoking, and a positive family history of the disease.[2-4] Diabetes mellitus, obesity, lack of exercise, and poor dietary habits can also be added to the previous list (Box 13.1). At the molecular level, hypercholesterolemia and inflammatory cells play a key role in the development of atherosclerotic plaque.[5,6] Numerous large-scale studies have confirmed that lowering low-density lipoproteins (LDL) levels by 30% to 50% will significantly reduce cardiovascular mortality. Between 1980 and 2000, therapeutic cholesterol reduction has decreased mortality from atherosclerotic cardiovascular disease (ASCVD) by one third. The focus of this chapter is on the

Abstract

Hyperlipidemia is a recognized risk factor for the development of atherosclerosis. Over the last century, lipid metabolism and the pathophysiology of plaque formation have been elucidated. Low-density lipoprotein (LDL) level in the blood is the most important determinant for the development and progression of atherosclerosis. Therapeutic interventions have been devised to lower LDL serum levels in patients at risk. Several pharmaceuticals agents have been developed to treat hyperlipidemia but statins play a dominant role in this therapeutic goal. Lowering LDL serum levels <70 mg/dl in high-risk patients is associated with a decreased risk of stroke and coronary events, as well as improved survival. In addition to lipid-lowering agents, diet and exercise have been shown to be effective in managing hyperlipidemia. Recently, PCSK9 inhibitors were approved to treat patients who are refractory to the other lipid lowering therapies.

pathophysiologic role of hyperlipidemia in causing atherosclerosis, the physiology and metabolism of lipids, and the diagnosis and management of hyperlipidemia.

HISTORICAL PERSPECTIVE

The notion that dietary fat had something to do with atherosclerosis has existed for some time. In 1910, a German scientist found that human aortic plaque had 25 times more cholesterol than a "normal" aorta. Three years later, a Russian pathologist induced atherosclerosis in rabbits fed a high cholesterol diet. In 1919, an American clinician correlated electrocardiographic changes in patients suffering from angina caused by ASCVD.[2] Subsequently, familial hypercholesterolemia was diagnosed and the cholesterol synthesis pathway described. Over the last 50 years, the LDL receptor was discovered and pharmaceutical agents, the statins which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, were approved and prescribed to treat patients with hyperlipidemia (Table 13.1). More recently, the transcription factor sterol regulatory element-binding protein-1 (SREBP-1) was identified as well as its complex interaction with intracellular and nuclear elements to regulate LDL.

BOX 13.1 A Century of Cholesterol and Coronaries

First Half—The Era of Cholesterol

1910 Human and atherosclerotic plaques contain cholesterol
1913 High cholesterol diet causes atherosclerosis in rabbits
1919 Heart attacks recognized in humans
1933 Feedback inhibition of cholesterol synthesis demonstrated
1938 Familial hypercholesterolemia described
1950 Cholesterol biosynthetic pathway elucidated
1951 High-fat diets raise plasma cholesterol in humans
1953 Risk factor concept advanced

Second Half—The Era of LDL

1955 LDL identified as risk factor for CHD
1973 LDL receptor discovered
1976 HMG CoA reductase inhibitors (statins) discovered
1981 Statins increase LDL receptors in vivo
1987 First statin (Mevacor) approved for human use
1994 Statins decrease heart attacks and prolong life
1997 SREBP pathway elucidated
2006 PCSK9: Destroyer of LDL receptors

CHD, Coronary heart disease; *HMG CoA,* 3-hydroxy-3-methylglutaryl coenzyme A; *LDL,* low-density lipoproteins; *PCSK9,* proprotein convertase subtilisin/kexin type-9; *SREBP,* sterol regulatory element-binding protein.

PHYSIOLOGY AND METABOLISM OF LIPIDS

Lipids are hydrophobic and are chemically insoluble in blood. They are transported as lipoproteins in which the hydrophobic lipid components are surrounded by an envelope of hydrophilic phospholipids and proteins known as apolipoproteins (apo). This creates a water-soluble spherical particle that can be carried in the blood (Fig. 13.1). The principal function of lipoprotein particles is transporting lipids from the intestine and liver through the bloodstream to the cells of the body, where they can be stored, used for synthetic processes, and metabolized to yield energy. The various apolipoproteins, such as apo B, apo A, apo E, and apo C, serve as cofactors in metabolism of the contained lipid and as ligands to facilitate binding of lipoproteins to receptors on the surface of cells throughout the body. Five major lipoproteins are recognized.

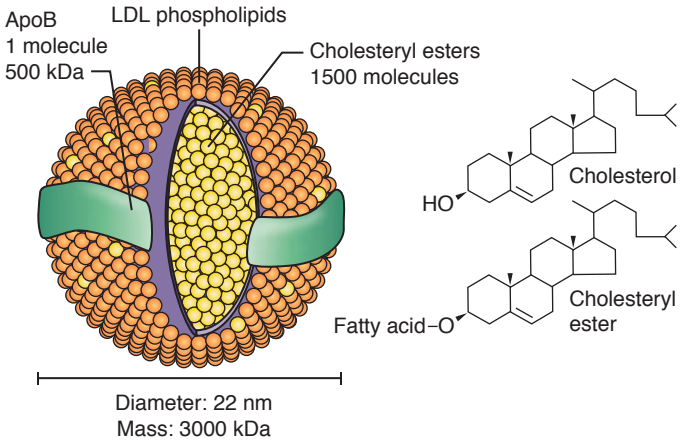

Figure 13.1 The low-density lipoprotein *(LDL)* molecule. *ApoB,* Apolipoprotein B. (From Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell.* 2015;161(1):161-172.)

TABLE 13.1 Critical Historical Events That Led to the Discovery and Development of the Statins

Year	Scientist(s)	Discovery
1913	Nikolai Anitschkow	Fed pure cholesterol to rabbits and demonstrated development of hypercholesterolemia and extensive aortic atherosclerosis
1950	John Gofman	Described the major classes of plasma lipoproteins using ultracentrifugation. Demonstrated direct and inverse association of LDL-C and HDL-C levels respectively, with incidence of myocardial infarction
1964	Konrad Bloch and Feodor Lynen	Received Nobel Prize for unraveling the metabolic pathway of cholesterol synthesis
1972	Akira Endo	Discovered compactin, the forebearer to the first statin, from a blue-green mold
1973	Michael Brown and Joseph Goldstein	Received the Nobel Prize for the discovery of the LDL receptor and its feedback regulation

HDL-C, High-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol.

Chylomicrons

Lipoprotein metabolism can be divided into exogenous and endogenous phases. During the exogenous phase, both dietary lipids and recirculated lipids within bile are absorbed into enterocytes and packaged as very large lipoproteins called chylomicrons. Although dietary cholesterol and triglycerides are absorbed by different mechanisms within the gastrointestinal (GI) tract, they are combined in this single chylomicron particle for transport from the GI tract through the thoracic duct and into the circulation to the rest of the body. Triglycerides constitute approximately 90% of the chylomicron's lipid content. When present in significant concentration, chylomicrons account for the turbidity or "milkiness" of plasma, known as postprandial lipemia, which is seen in some individuals with metabolic and inherited disorders of lipid metabolism. Chylomicrons are distinguished by the presence of one apo B-48 molecule in each particle. In the bloodstream, the enzyme lipoprotein lipase (LPL) hydrolyzes the triglyceride contained within the chylomicron into free-fatty acids (FFAs). FFAs are taken up by peripheral tissues and used for energy. In adipose and muscle cells, FFAs can also be re-esterified into triglycerides and stored for future energy production. The remaining triglyceride-poor chylomicron remnant contains only the absorbed dietary cholesterol, which is then transported to the liver for storage. Although chylomicrons are typically considered a transport lipoprotein, evidence suggests atherosclerotic lesions contain apo B-48 within plaque, thus implicating these chylomicron remnants as atherogenic particles.[7,8]

Very-Low-Density Lipoproteins

The endogenous phase of lipoprotein metabolism involves the hepatic formation of very-low-density lipoproteins (VLDLs) containing cholesterol and triglycerides derived from stores within the liver and adipocytes (Table 13.2). Each VLDL particle contains apos C and E as well as one molecule of apo B-100 per particle. Similar to chylomicrons, the predominant lipid component of VLDL is triglyceride, which accounts for approximately 70% of its lipid content. Although not as large as chylomicrons, VLDL is large enough to cause lipemia when present in very high concentrations. VLDL is released from the liver into the bloodstream, where LPL again facilitates removal of the triglyceride component of VLDL and presents it to the muscle cell as fuel for energy production. Through this endogenous mechanism, triglycerides stored in adipocytes, hepatocytes, and muscle cells can be used for energy during fasting or starvation as a more energy-rich alternative to glucose. As the triglyceride is removed, two additional atherogenic lipoprotein particles are formed: VLDL remnants and intermediate-density lipoproteins (IDLs).

Intermediate Density Lipoprotein (Remnant Lipoprotein)

IDLs carry cholesterol esters and triglycerides. IDLs, similar to LDL, have been shown to increase the risk of cardiovascular disease. These triglyceride-rich lipoprotein particles are present in patients with metabolic syndrome and type 2 diabetes mellitus. The MARS study showed that IDL is associated with increased carotid artery intima-media thickness (CIMT).[9]

TABLE 13.2 Adult Treatment Panel III Guidelines for the Evaluation of Fasting Lipid Profile

	Conventional Units (mg/dL)	SI Units (mmol/L)
Low-Density Lipoprotein Cholesterol		
Optimal	<100	<2.59
Near optimal	100-129	2.59-3.34
Borderline high	130-159	3.37-4.12
High	160-189	4.14-4.90
Very high	>190	>4.92
High-Density Lipoprotein Cholesterol		
Low	<40	<1.04
High	>60	>1.55
Triglycerides		
Normal	<150	<1.70
Borderline	150-199	1.70-2.25
High	200-499	2.26-5.64
Very high	>500	>5.65

SI, Standard international.

Low-Density Lipoprotein

In addition to LPL, hepatic lipase participates in the conversion of IDL to LDL, the most atherogenic of all lipoprotein particles. Although a number of other apolipoproteins are attached to the original VLDL particle, only one, apo B-100, is present in each LDL particle (see Fig. 13.1). LDL binds to specific LDL receptors on the surface of each cell, facilitating transfer of the remaining cholesterol to these cells, where it can be stored and used as cell membranes, steroid hormones, and bile acids. The number of exposed LDL receptors is regulated by the intracellular concentration of cholesterol within each cell. When excess plasma LDL is present, atherosclerosis can possibly increase in proportion to the concentration of circulating LDL.

Nabel and Braunwald received the Nobel Prize in 1985 for discovering the LDL receptor.[10,11] They were able to demonstrate that the circulating LDL concentration in plasma is determined by the number of LDL receptors on the various cells of the body, with the liver accounting for more than 70% of this total receptor number.[12] When the intracellular cholesterol content of the cells is low, LDL receptor synthesis is upregulated, receptor numbers increase, and the LDL plasma concentration decreases. In contrast, when intracellular cholesterol is increased, LDL receptor synthesis is downregulated, receptor numbers diminish, and circulating LDL rises. Humans are born with a maximum number of LDL receptors and a very low circulating LDL level

of 25 to 30 mg/dL (0.65 to 0.78 mmol/L).[13] Over a lifetime, the Western lifestyle of excessive calories, cholesterol, and saturated fat intake, along with inactivity, results in increasing intracellular cholesterol levels, causing secondary downregulation of LDL receptors. Therefore observed increases in excess plasma LDL-C levels coincide with the epidemic of atherosclerosis seen worldwide.

High-Density Lipoproteins

High-density lipoprotein (HDL) is synthesized by the liver and intestine as apo A-I, which is released into the bloodstream as a lipid-poor discoid particle. Stored cholesterol released from peripheral cells through the action of a specific transporter known as adenosine triphosphate–binding cassette (ABC) transporter A1 is absorbed by the discoid apo A-I and converted to cholesterol ester under the influence of lecithin-cholesterol acyltransferase (LCAT).[14] During this process, HDL becomes a spherical particle. Additional cellular cholesterol is then added by another cassette transporter, ABCG1, and through the action of the scavenger receptor B1 (SR-B1). The HDL particle can then return to the liver, where it binds to hepatic SR-B1 and releases its cholesterol, or it can exchange a portion of its cholesterol content for triglyceride from VLDL through the chemical action of the cholesterol ester transfer protein (CETP). This removes triglyceride from VLDL, converting it into LDL, which is then removed from circulation through the hepatic LDL receptor. This process is known as "reverse cholesterol transport" and plays an important role in the antiatherogenic properties of the HDL particle.[15,16]

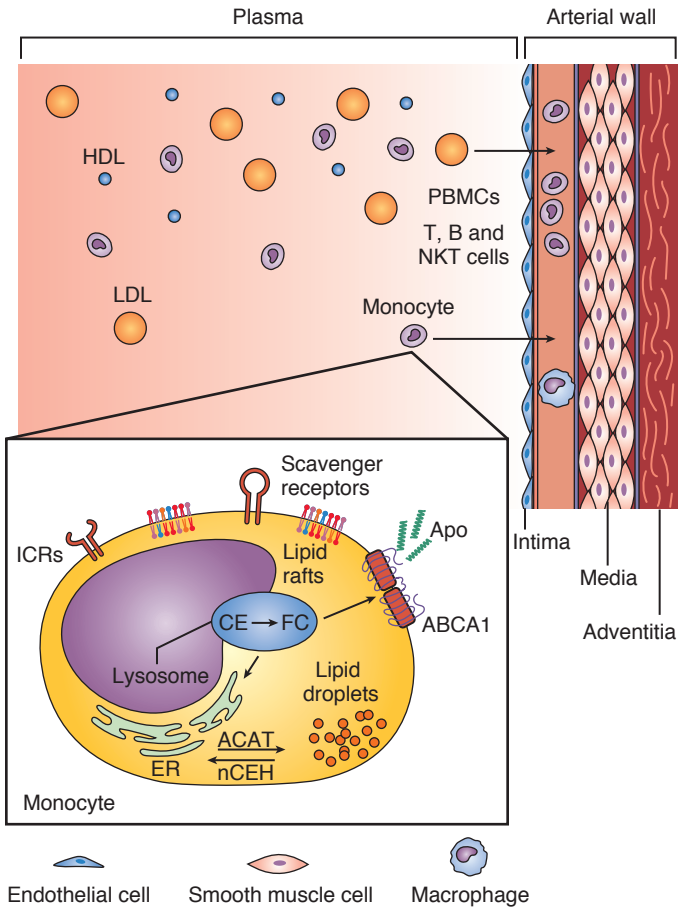

Figure 13.2 Low-density lipoprotein and monocytes invade the endothelial layer. *Apo,* Apolipoproteins; *ER,* extended-release; *HDL,* high-density lipoprotein; *LDL,* low-density lipoproteins. (Sorci-Thomas MG, Thomas MJ. Microdomains, inflammation, and atherosclerosis. *Circ Res.* 2016;118(4):679-691.)

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Atherosclerosis is a pathologic process that begins in the arterial endothelial layer. Normal endothelium is smooth and repels circulating blood elements. On the other hand, damaged endothelium attracts various cellular elements. After the initiation of an atherogenic diet, patches of endothelial cells express selective adhesion molecules that bind to various classes of leucocytes.[5] Vascular cell adhesion molecule-1 (VCAM-1) binds to monocytes and T-lymphocytes detected in human atheromas.[3] In the setting of elevated LDL and low HDL, peripheral blood mononuclear cells become cholesterol enriched (Fig. 13.2). Intracellular droplets of cholesterol ester accumulate in these engorged cells, and give them a characteristic appearance, "foam cells."[17] Foam cells are more apt to adhere to damaged endothelium and then migrate into the intima layer and become macrophages. In response to this, VSMC proliferate and cause thickening of the intima.[6] As the process is repeated, plaque thickness increases and a fibrous cap is formed (Fig. 13.3).[18] This pathologic process is the same in the peripheral and cerebrovascular circulation as it is in the coronary arteries. To varying degrees, the traditional risk factors are also similar, regardless of the location of atherosclerotic disease, including hyperlipidemia.[19]

Damaged endothelium also becomes permeable to LDL and other circulating atherogenic lipoproteins (VLDL remnants, IDL, and chylomicron remnants). Once inside the vessel wall, LDL is oxidized by free radicals, furthering the inflammatory immune response and initiating the pathologic process of atherosclerosis. Oxidized LDL is subsequently absorbed through specific scavenger receptors into fixed tissue macrophages, thereby transforming them into lipid-filled foam cells (Fig. 13.4). Groups of foam cells accumulate underneath the endothelium and become the initial lesion of atherosclerosis (the fatty streak).[4] As this process continues, the foam cells undergo apoptosis (programmed cell death) allowing the lipid contained in them to spill out to form the lipid core of an atherosclerotic plaque. The initial response of the arterial wall is to expand, a process known as positive remodeling. As the plaque increases in thickness, it begins to encroach on the arterial lumen, thereby reducing the blood flow to points distal.[20] The concept of stable and unstable plaque has been developed, with stable plaques possessing a thick fibrous cap and solid lipid core. Plaques accumulating a large lipid core trigger an intense local inflammatory reaction as this lipid is oxidized resulting in the infiltration of additional macrophages and inflammatory cells. The vulnerable or unstable plaque usually remains small and does not critically

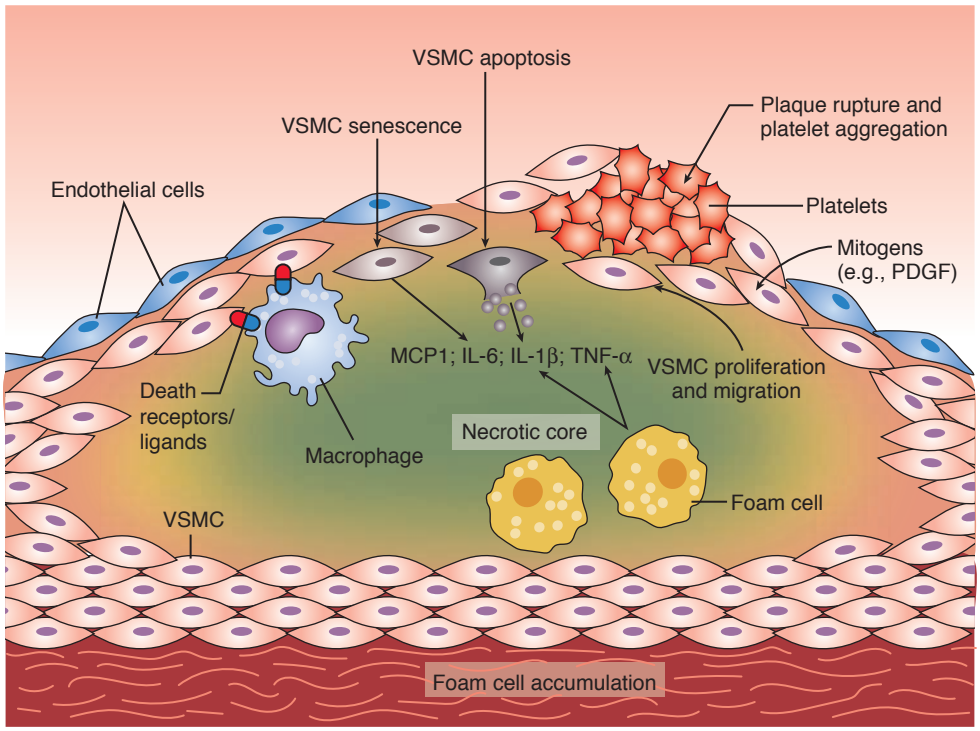

Figure 13.3 Interaction of cellular elements to form the lipid core and fibrous cap. (Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. *Circ Res.* 2016;118(4):692-702.)

compromise the luminal diameter (Fig. 13.5). However, the thin fibrous cap is prone to ulceration or rupture. When this occurs, a platelet-rich clot rapidly forms on top of the plaque and produces complete obstruction of the involved artery and subsequent acute clinical infarction or ischemia.

DIAGNOSIS OF ATHEROGENIC LIPID DISORDERS

The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) recommended that all adults older than 20 years be screened for hyperlipidemia every 5 years with a fasting lipoprotein profile.[21,22] Blood levels should include total cholesterol (TC), triglycerides, HDL cholesterol (HDL-C), and LDL-C. It is recommended that patients be in their usual state of health and fast for 12 hours before testing. Blood should be drawn after sitting comfortably for 5 minutes and with less than 1 minute of tourniquet time. If TC is greater than 200 mg/dL (5.18 mmol/L) or HDL is less than 40 mg/dL (1.04 mmol/L), a fasting lipoprotein profile should be obtained to better quantify the patient's atherosclerotic risk.

Fasting Lipid Profile

ATP III recommended new guidelines for the evaluation of a fasting lipid profile (see Table 13.2). TC is not a good risk predictor because it can be increased by elevated HDL, which is usually a lower risk lipid profile, or decreased by low HDL, which is a higher risk lipid profile. The presence of very high triglyceride levels can also elevate TC and suggest a higher risk lipid profile than actually may be present.

LDL-C has been shown to be the most predictive lipoprotein fraction for determining atherosclerosis risk in both epidemiologic and interventional studies, and the associated risk is directly proportional to the LDL-C concentration over a wide range of values.[23,24] HDL-C is equally predictive in epidemiologic studies, with an inverse relationship between the HDL-C concentration and risk for atherosclerosis. The risk associated with each of these lipoprotein fractions is additive in individuals with increased LDL-C and decreased HDL-C.[25] The role of elevated triglycerides in risk assessment is tougher to discern. When very sophisticated analyses of triglyceride-rich lipoproteins are performed, it is evident that large chylomicrons and VLDLs are not atherogenic, but the smaller remnant forms of both these lipoproteins and the presence of IDL definitely confer increased atherogenicity.[26]

Clinically, elevated triglycerides in the presence of type 2 diabetes, metabolic syndrome, or familial combined dyslipidemia should indicate an increase in the risk for ASCVD. Very high levels of triglycerides (>1000 mg/dL [11.3 mmol/L]) are also associated with an increased risk for pancreatitis. Atherogenic dyslipidemia is a characteristic lipoprotein pattern frequently observed in patients with type 2 diabetes mellitus and the metabolic syndrome. In this condition, the LDL-C is often unimpressive or frankly low, but it is associated with elevated triglycerides with a decreased HDL-C concentration. More important, however, is the change in the number and composition of LDL particles associated with the metabolic syndrome

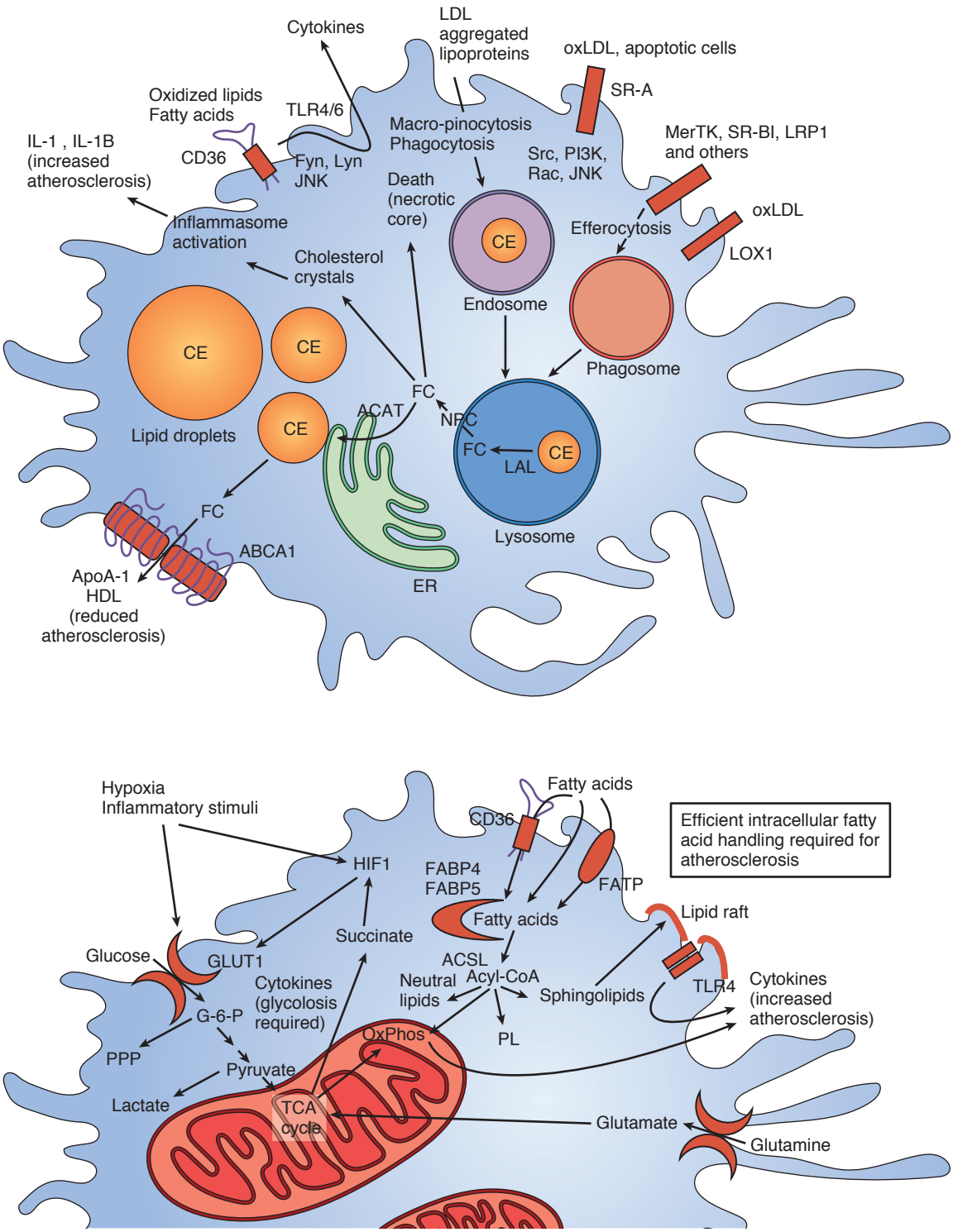

Figure 13.4 Complex interaction of lipids and macrophages in atherosclerosis. *ApoA-1,* Apolipoproteins A-1; *ER,* extended-release; *HDL,* high-density lipoprotein; *LDL,* low-density lipoproteins. (Tabas I, Bornfeldt KE. Macrophage phenotype and function in different stages of atherosclerosis. *Circ Res.* 2016;118(4):653-667.)

and type 2 diabetes, rendering them more atherogenic. This LDL is described as "small, dense LDL," which is an increased number of particles that contain less cholesterol per particle. Studies have shown that it is the number of LDL particles (LDL-P) that truly reflects the risk related to this profile.[27] LDL-P can be determined by lipid analysis using nuclear magnetic resonance (NMR) studies. Because each LDL-P contains one apo B-100 molecule, another method of more accurately assessing the risk conferred by an individual's LDL profile is to measure the apo B-100 level. Complete analysis

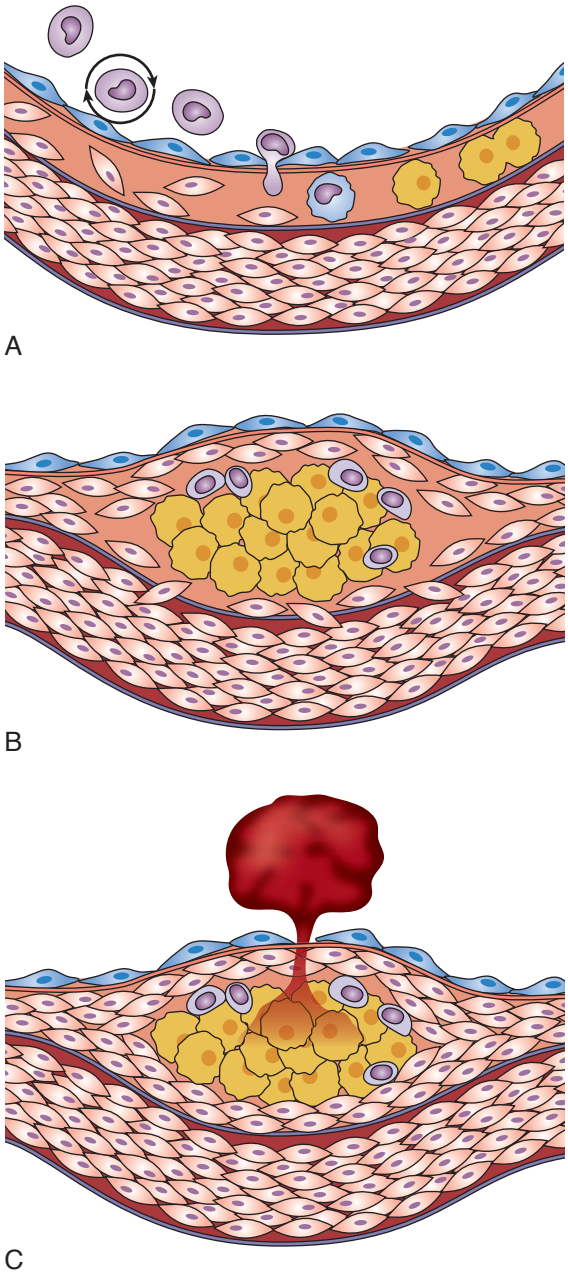

Figure 13.5 Initiation of plaque: the stable versus vulnerable plaque. A, Recruitment of leucocytes in a developing plaque; B, t-lymphocytes and macrophages in the intima and plaque formation; C, plaque rupture and thrombus formation, may lead to vessel occlusion. (Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105(9):1135-1143.)

may provide a better risk assessment because the individual risks associated with each lipoprotein abnormality in type 2 diabetes mellitus and metabolic syndrome are additive.

Non–High-Density Lipoprotein Cholesterol in Risk Assessment

Non-HDL-C has been recognized in epidemiologic studies as one of the better predictors of atherosclerotic risk.[28] Non-HDL-C is easily calculated by subtracting HDL-C from TC. ATP III recommended the use of non-HDL-C (Box 13.2) as a way to more accurately assess risk in patients with increased triglycerides and made this a secondary target of therapy after the primary therapeutic goal for LDL-C is attained (vide infra). Non-HDL-C essentially represents the cholesterol content in all of the apo B–containing atherogenic lipoproteins: non-HDL-C = LDL-C + IDL cholesterol + VLDL-C + lipoprotein (a) (Lp[a]). However, these more specialized studies of cholesterol fractions are significantly more expensive than a routine lipid profile. Therefore it is recommended that the initial risk evaluation and lipid management be performed with the standard LDL-C, HDL-C, and non-HDL-C measurements and that specialized testing be reserved for unusual situations or for fine tuning of therapy.

BOX 13.2 Importance of Non–High-Density Lipoprotein Cholesterol

- Known predictor of CHD in epidemiology
- Equivalent to total apo B-100 and TC/HDL
- Represents the sum of LDL, Lp(a), IDL, and VLDL: all atherogenic apo B–containing lipoproteins
- Lipid equivalent of hemoglobin A_{1c}

Non-HDL cholesterol = TC – HDL cholesterol.
CHD, Coronary heart disease; *HDL,* high-density lipoprotein; *IDL,* intermediate-density lipoprotein; *Lp(a),* lipoprotein (a); *TC,* total cholesterol; *VLDL,* very low-density lipoprotein.

Lipoprotein (a)

Epidemiologic studies have established that Lp(a) is associated with increased atherosclerotic risk and risk of cardiovascular events, particularly ischemic stroke.[29,30] However, little is known about the metabolism of this hybrid lipoprotein particle. There is a lack of interventional data to establish Lp(a) as a legitimate modifiable atherosclerotic risk factor, and there are few effective therapies for lowering levels of this lipoprotein. The European Atherosclerosis Society recommends checking Lp(a) levels in patients at moderate or high risk of cardiovascular disease, including patients with a personal or family history of premature atherosclerosis, familial hypercholesterolemia, family history of elevated Lp(a), recurrent atherosclerotic events despite statin therapy and meeting accepted goals for therapy, and patients with increased 10-year risk for major cardiovascular events according to European or U.S. guidelines.[30]

EVOLUTION OF THE GUIDELINES FOR MANAGEMENT AND THERAPEUTIC GOALS FOR LIPOPROTEIN DISORDERS

Adult Treatment Panel I

The NCEP was launched in 1988. It has served as the driving force for lipid management guidelines since the publication of the ATP I report and recommendations for standardization of clinical measurement of lipids.[31] ATP I sought to educate the

BOX 13.3 Risk Factors for Coronary Heart Disease in Addition to Low-Density Lipoprotein Cholesterol

- Cigarette smoking
- Hypertension (>140/90 mm Hg)
- Low HDL cholesterol (<40 mg/dL) (1.04 mmol/L)
- Family history:
  - CHD in male first-degree relative younger than 55 years
  - CHD in female first-degree relative younger than 65 years
- Age (men older than 45 years, women older than 55 years)

CHD, Coronary heart disease; *HDL*, high-density lipoprotein.

U.S. population regarding coronary heart disease (CHD) risk and to encourage cholesterol reduction. The focus of ATP I was education and lifestyle intervention. Interventional therapy was reserved for individuals at increased risk, including those with an LDL greater than 190 mg/dL (4.92 mmol/L) or those with an LDL-C greater than 160 mg/dL (4.14 mmol/L) and two or more additional CHD risk factors (Box 13.3).

Adult Treatment Panel II

The NCEP published the ATP II report in 1993 after the introduction of HMG-CoA reductase inhibitors (statins).[22] The NCEP guidelines adopted the ATP I recommendations and added secondary prevention of CHD in patients with known CAD. Several small trials verified the benefit of modifying diet and using statins. Lowering LDL-C was the main goal; however, significant increases in HDL-C were observed, and this lipid change was thought to contribute to the positive outcomes of these surrogate endpoint trials. On the basis of these secondary prevention studies, ATP II recommended that patients with known CHD have the more aggressive therapeutic goal for LDL-C of 100 mg/dL or less.[32]

Another observation made in these trials was that coronary events were frequent in patients with coronary stenosis less than 70%. This introduced the concept of a "vulnerable plaque."[33] This is a small plaque with a large lipid core and a thin fibrous cap, with less than critical stenosis but a potential for inducing intraluminal thrombosis. It was suggested that statin therapy "stabilized" this plaque by helping prevent rupture or ulceration of the fibrous cap.

On the basis of these secondary prevention studies, ATP II recommended that patients with known CHD have the more aggressive therapeutic goal for LDL-C of 100 mg/dL or less.

Adult Treatment Panel III

Initially published as an executive summary and later as a full report in 2002, ATP III was the first evidence-based report from the NCEP that focused on large clinical trial data.[21] Four large trials examined primary and secondary prevention strategies.[34-37] As a result, ATP III recommended a more aggressive approach to risk assessment and management of lipid levels. Table 13.2 shows the new classification recommended by ATP III for LDL-C, HDL-C, and triglyceride levels in the initial risk assessment of individuals based on lipid levels. ATP III also recommended more aggressive goals of therapy for lipid management in patients with both established CHD and CHD risk equivalents. In addition to continuing the evaluation of additional risk factors (see Box 13.3) recommended by ATP I and II, ATP III added an emphasis on 10-year risk assessment for CHD by using the Framingham risk assessment algorithm.[38]

BOX 13.4 Coronary Heart Disease Risk Equivalents

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease)
- Diabetes
- Multiple risk factors that confer a 10-year risk for coronary heart disease greater than 20%

Coronary Heart Disease Risk Equivalents

Another feature of ATP III was the designation of three conditions as "CHD risk equivalents," in that each carried a 10-year risk for a major coronary event that was equal to that of patients with established CHD (>20% per 10 years). Diabetes mellitus, other atherosclerotic diseases including PAD, carotid artery disease, and abdominal aortic aneurysm, and the presence of multiple cardiovascular risk factors that conferred a 10-year risk of greater than 20%, as judged by the Framingham risk assessment tool, received the designation of "CHD risk equivalent" (Box 13.4). Although discussed in the ATP II report, ATP III was the first formal recognition of the importance of PAD as a significant indicator of CHD.

Risk Stratification

ATP III suggested patients be categorized into one of three risk strata and that aggressiveness matched therapeutics to the assessed risk level. These three categories are as follows: (1) high risk—established CHD and CHD risk equivalents; (2) intermediate risk—multiple (2+) risk factors; and (3) low risk—0 to 1 risk factor. In addition to the goals recommended for LDL-C, in individuals with triglyceride levels greater than 200 mg/dL, a secondary goal was recommended for management of non-HDL-C (discussed previously). Table 13.3 shows the LDL and non-HDL-C goals for the treatment of individuals in each of these three risk categories. Although ATP III introduced the issue of basing lipid management on an individual's 10-year risk assessment, management of individuals with very high LDL levels or severe individual risk factors that conferred a high lifetime risk was continued as recommended by ATP I and II.

The 2013 ACC/AHA Guidelines

After ATP III was published, trials of very aggressive lipid lowering in very high-risk individuals were conducted, and the LDL-C levels reached were considerably lower than those recommended by ATP III.[39,40] The positive clinical outcomes of these aggressive lipid-lowering trials resulted in an addendum to

TABLE 13.3 Comparison of Low-Density Lipoproteins Cholesterol and Non–High-Density Lipoprotein Cholesterol Therapeutic Goals by Categories of Risk

	LDL CHOLESTEROL GOAL		NON-HDL CHOLESTEROL GOAL	
Risk Category	(mg/dL)	(mmol/L)	(mg/dL)	(mmol/L)
CHD and CHD risk equivalent (10-year risk for CHD >20%)	<100	<2.59	<130	<3.37
Multiple (2+) risk factors and 10-year risk <20%	<130	<3.37	<160	<4.14
0-1 Risk factor	<160	<4.14	<190	<4.92

CHD, Coronary heart disease; *LDL,* low-density lipoprotein; *non-HDL,* non–high-density lipoprotein.

TABLE 13.4 Adult Treatment Panel III Low-Density Lipoproteins Cholesterol and Non–High-Density Lipoprotein Cholesterol Therapeutic Goals by Risk Category

	LDL CHOLESTEROL		NON-HDL CHOLESTEROL	
Risk Category	(mg/dL)	(mmol/L)	(mg/dL)	(mmol/L)
CHD or equivalent (10-year risk >20%)	<100	<2.59	<130	<3.37
≥2 Risk factors (10-year risk ≤20%)	<130	<3.37	<160	<4.14
Very high risk (optional)	<70	<1.81	<100	<2.59

CHD, Coronary heart disease; *LDL,* low-density lipoprotein; *non-HDL,* non–high-density lipoprotein.
Modified from National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106:3143-3421.

the ATP III report published in 2004 that recommended lower therapeutic goals for LDL-C and non-HDL-C in patients with very high-risk CHD (Table 13.4).[41] In 2005, the ACC/AHA published guidelines specifically directed to the management of patients with PAD. Patients with established PAD should be treated with statins to achieve a target LDL of less than 100 mg/dL (class I recommendation). Treatment goals of less than 70 mg/dL are reasonable in patients with lower extremity PAD who are at high risk for events (class IIa recommendation).[19]

The most recent guidelines and recommendations from the ACC/AHA were published in 2013.[42] These guidelines reaffirmed the more aggressive therapeutic goals for LDL-C and non-HDL-C and recommended targeting 4 statin benefit groups: individuals with clinical ASCVD, those with LDL >190 mg/dL, diabetics and non-diabetics between 40 and 75 years, and LDL in the 70 to 189 mg/dL and ASCVD risk >7.5%.

CLINICAL TRIALS OF THE MANAGEMENT OF DYSLIPIDEMIA IN PERIPHERAL ARTERIAL DISEASE

Most clinical trials were designed to test the efficacy of statins and the benefit of driving down LDL levels in reducing cardiovascular mortality. The secondary benefit of improving PAD was realized post hoc. Patients with PAD generally receive less intensive risk factor modification than do patients with coronary disease, although they share similar vascular risk profiles.[43] As few as a third of patients with PAD receive statin therapy. The Heart Protection Study (HPS) data are provocative (see the next section); they indicate that aggressive lipid management produces a definite reduction of approximately one sixth in the risk for peripheral vascular events not only in patients with preexisting PAD but also in high-risk individuals without previously diagnosed PAD. This finding highlights the need for further clinical trials that have prevention of peripheral vascular disease as their primary endpoint. These additional trials should also include patients with early forms of PAD.

Early Trials Linking Lipid Therapy to Atherosclerosis

The Program on the Surgical Control of the Hyperlipidemias (POSCH) and the Cholesterol Lowering Atherosclerosis Study (CLAS) established the basis for future studies examining dyslipidemia.[44,45] Both studies used angiographic evidence to support the conclusion that lipid therapy is effective in controlling the progression of atherosclerosis.

POSCH used ileal bypass surgery to lower lipid levels and demonstrated a reduction in the progression of atherosclerosis. At the formal closure of the POSCH trial, no significant difference was noted between the control and active therapy groups in the progression of PAD. However, all participants were observed for an additional 5 years after the trial ended. At the 5-year follow-up evaluation, an ankle-brachial index (ABI) of less than 0.95 was present in 41 of 120 control patients and in 24 of 126 ileal bypass patients, thus conferring a 44% risk reduction for development of an abnormal ABI. Furthermore, the risk of development of clinical manifestations of PAD was reduced by 30%.[46]

TABLE 13.5 ATP III Low-Density Lipoproteins Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Change and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

Risk Category	LDL Cholesterol Goal	Initiate TLC	Consider Drug Therapy[a]
High risk: CHD[b] or CHD risk equivalents[c] (10-year risk >20%)	<100 mg/dL (2.59 mmol/L) (optional goal: <70 mg/dL [1.81 mmol/L])[d]	≥100 mg/dL (2.59 mmol/L)[e]	≥100 mg/dL (2.59 mmol/L)[f] (if <100 mg/dL, consider drug options)[a]
Moderately high risk: 2+ risk factors[g] (10-year risk of 10%-20%)[h]	<130 mg/dL (3.37 mmol/L)[i]	≥130 mg/dL (3.37 mmol/L)[j]	≥130 mg/dL (3.37 mmol/L) (if 100-129 mg/dL [2.59-3.34 mmol/L], consider drug options)[j]
Moderate risk: 2+ risk factors[g] (10-year risk <10%)[h]	<130 mg/dL (3.37 mmol/L)	≥130 mg/dL (3.37 mmol/L)	≥160 mg/dL (4.14 mmol/L)
Lower risk: 0-1 risk factor[k]	<160 mg/dL (4.14 mmol/L)	≥160 mg/dL (4.14 mmol/L)	≥190 mg/dL (4.92 mmol/L) (if 160-190 mg/dL [4.14-4.92 mmol/L], LDL-lowering drug optional)

[a]When LDL-lowering drug therapy is used, it is advised that the intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL cholesterol levels.
[b]CHD included a history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.
[c]CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks, stroke of carotid origin, or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with a 10-year risk for hard CHD >20%.
[d]Very high risk favors the optional LD cholesterol goal of <70 mg/dL (1.81 mmol/L) and, in patients with high triglyceride levels, non-HDL cholesterol <100 mg/dL (2.59 mmol/L).
[e]Any person at high risk or moderately high risk who has lifestyle-related risk factors (e.g., obesity, physical inactivity, elevated triglycerides, low HDL cholesterol, or metabolic syndrome) is a candidate for TLCs to modify these risk factors regardless of LDL cholesterol level.
[f]If baseline LDL cholesterol is <100 mg/dL (2.59 mmol/L), institution of an LDL-lowering drug is a therapeutic option on the basis of available clinical trial results. If a high-risk person has high triglyceride levels or low HDL cholesterol, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.
[g]Risk factors include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or taking antihypertensive medication), low HDL cholesterol (<40 mg/dL [1.04 mmol/L]), family history of premature CHD (CHD in male first-degree relative <55 years of age, CHD in female first-degree relative <65 years of age), and age (men ≥45 years; women ≥65 years).
[h]Electronic 10-year risk calculators are available at www.nhlbi.nih.gov/guidelines/cholesterol.
[i]Optional LDL cholesterol goal, <100 mg/dL (2.59 mmol/L).
[j]For moderately high-risk persons, when the LDL cholesterol level is 100-129 mg/dL (2.59-3.34 mmol/L) at baseline with lifestyle therapy, initiation of an LDL-lowering drug to achieve an LDL cholesterol level of <100 mg/dL (2.59 mmol/L) is a therapeutic option on the basis of available clinical trial results.
[k]Almost all people with zero or one risk factor have a 10-year risk of <10%, and 10-year risk assessment in people with zero or one risk factor is thus not necessary.
ATP III, Adult treatment panel III; *CHD,* coronary heart disease; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *TLC,* therapeutic lifestyle change.
From Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation.* 2004;110:227-239.

Anatomic assessment of the effect of lipid-lowering therapy was also evaluated in the CLAS trial.[47] One hundred sixty-two nonsmoking men between the ages of 40 and 59 years who had previously undergone coronary artery bypass graft surgery were randomized to a combination of colestipol, niacin, and diet, or to placebo and diet. Coronary angiography after 2 years demonstrated a significant reduction in the progression of atherosclerosis in the group that received therapy with colestipol plus niacin.

NONPHARMACOLOGIC THERAPY FOR DYSLIPIDEMIA

ATP III issued evidence-based guidelines on cholesterol management.[41] Therapeutic lifestyle change (TLC) was recommended as an essential modality in the clinical management of hypercholesterolemia. The ATP III report recommends initiation of TLC based on the LDL goal stratified by risk category (Table 13.5). Any person at high risk or moderately high risk who has lifestyle-related risk factors is a candidate for TLC to modify these risk factors, regardless of LDL-C level.

Dietary Changes

Individuals at low risk should initiate TLC at an LDL-C level of greater than 160 mg/dL (4.14 mmol/L); those with two or more risk factors and a Framingham 10-year CHD risk assessment of less than 10% should initiate TLC at an LDL-C level of greater than 130 mg/dL (3.37 mmol/L); and individuals with two or more risk factors and a 10-year CHD risk assessment of 10% to 20% should initiate TLC at an LDL-C level of 130 mg/dL (3.37 mmol/L). Finally, any high-risk patient with CHD or a CHD risk equivalent and a 10-year CHD risk assessment of greater than 20% should initiate TLC at an LDL-C level of greater than 100 mg/dL (2.59 mmol/L).

TABLE 13.6 Essential Components of Therapeutic Lifestyle Changes

Component	Recommendation
LDL-Raising Nutrients	
Saturated fats[a]	<7% of total calories
Dietary cholesterol	<200 mg/day
Therapeutic Options for LDL Lowering	
Plant stanols/sterols	2 g/day
Increased viscous (soluble) fiber	10-25 g/day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal/day

[a]*Trans* fatty acids are another LDL-raising fat that should be kept at low intake.

LDL, Low-density lipoprotein.

From National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106:3143-3421.

Dietary modifications include high amounts of fruits and vegetables, legumes, and whole grains as part of a low-fat diet. These modifications have been shown to reduce LDL and TC.[48] ATP III recommends a reduction in saturated fats to less than 7% of total calories and cholesterol to less than 200 mg/day. The addition of other dietary products containing plant sterols or stanols, which are available on the shelves of most grocery stores, has been shown to reduce TC and LDL-C by 10% to 15%.[49] Soluble fiber supplements are also suggested as adjuncts to dietary therapy. ATP III outlines maximal dietary therapy, including balancing energy intake and expenditure to maintain desirable body weight and prevent weight gain, which together can reduce LDL-C by 25% to 30% (Table 13.6). The PREDIMED study in Spain enrolled 7447 with increased CVD risk and demonstrated that a Mediterranean diet supplemented with olive oil or nuts decreased the incidence of major cardiovascular events.[50] A meta-analysis of gastric bypass studies showed an improved lipid profile in a majority of patients.[51]

Exercise

At least moderate daily physical activity, to expend approximately 200 kcal/day is recommended. Physical activity has been reported to lower LDL and triglyceride levels, raise HDL-C, and improve insulin sensitivity. Inactivity impairs cardiovascular fitness and coronary blood flow. These effects can be readily reversed by regular activity. Physical activity in accord with a patient's overall health status should be encouraged. Additional benefits may be realized in the management of metabolic syndrome. Exercise specialists in addition to nutrition and diet professionals may be able to assist patients in achieving TLC (see Table 28.5). The ACC/AHA goals for exercise include 30 to 60 minutes of moderate physical activity 5 to 7 days a week in addition to increased activity in daily lifestyle activities.[52,53]

PHARMACOLOGIC THERAPY FOR DYSLIPIDEMIA

There are many classes of drugs available for treating dyslipidemia. Newer drugs and classes of drugs are under development and briefly mentioned.

Statins

The HMG-CoA reductase inhibitors (statins) are the most effective class of drugs for treating elevated LDL-C levels. This class of drugs has been shown to reduce LDL-C by 18% to 60%, raise HDL-C by 5% to 20%, and decrease triglycerides by 7% to 30%. Statins have been proven to reduce the risk of CHD, stroke, and PAD, as well as improve mortality. They have also proved to be safe, with very low occurrences of major adverse events. The reduction in LDL-C is dose-dependent and log-linear. The starting dose of each statin produces 75% to 80% of the maximal reduction in LDL-C, and with each subsequent doubling of the dose, an additional 6% reduction is LDL-C is typically achieved.

Statin therapy has been demonstrated to be safe and effective in lipid management. Transient elevation of transaminase level occurs infrequently and is usually self-limiting. Minor musculoskeletal side effects (myalgia without CPK elevation) have been reported in clinical practice but not detected in randomized trials. Rhabdomyolysis is rare (4 in 10,000) and if strongly suspected, warrants measurement of total creatine phosphokinase, and if significantly elevated (>10× the upper limit of normal), discontinuation of the medication (Table 13.7). Excess risk of myopathy with the 80-mg dose of simvastatin was identified in the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, especially in the first 12 months of use.[54] This led the Food and Drug Administration (FDA) to recommend safety label changes, with recommendations regarding the prescription of the 80-mg dose of simvastatin, as well as adjusting the list of drugs to which the use of simvastatin is contraindicated.

Statin therapy is associated with an increased risk of new onset diabetes, and appears to be dose-dependent, with higher incidence in patients receiving high doses. In randomized trials, there was no evidence of a causal relationship between statins and malignancy or cognitive dysfunction.[1,55]

Statin therapy has also proved to be effective in improving pain-free walking time in patients with intermittent claudication.[56,57] In a multicenter randomized controlled trial of 354 people with claudication attributable to PAD, patients were randomized to placebo or to 10- or 80-mg doses of atorvastatin. There was an improvement in pain-free walking in 63% of patients but significant change in ABI.[58]

TABLE 13.7 Summary of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors

Available Drugs	Lovastatin, Pravastatin, Simvastatin, Fluvastin, Atorvastatin, Rosuvastatin
Lipid/lipoprotein	LDL cholesterol: decrease of 18%-60%
Effects	HDL cholesterol: increase of 5%-25%
	Triglycerides: decrease of 7%-30%
Major use	To lower LDL cholesterol
Contraindications	
Absolute	Active or chronic liver disease
Relative	Concomitant use of cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P-450 inhibitors (fibrates and nicotinic acid) should be undertaken with appropriate caution
Efficacy	Reduce risk for CHD and stroke
Safety	Side effects minimal in clinical trials
Major side/adverse effects	Myopathy, increased liver transaminases
Usual Starting Dose	**Maximum FDA-Approved Dose**
Lovastatin: 20 mg	Lovastatin: 80 mg
Pravastatin: 20 mg	Pravastatin: 80 mg
Simvastatin: 20 mg	Simvastatin: 40 mg[a]
Fluvastatin: 20 mg	Fluvastatin: 80 mg
Atorvastatin: 10 mg	Atorvastatin: 80 mg
Rosuvastatin: 5 mg	Rosuvastatin: 40 mg
Pitavastatin: 2 mg	Pitavastatin: 4 mg
Available dosing	Lovastatin: 10-, 20-, 40-mg tablets Pravastatin: 10-, 20-, 40-mg tablets Simvastatin: 5-, 10-, 20-, 40-, 80-mg tablets Fluvastatin: 20-, 40-mg capsules; 80-mg XL tablets Atorvastatin: 10-, 20-, 40-, 80-mg tablets Rosavustatin: 5-, 10-, 20-, 40-mg tablets Pitavastatin: 1-, 2-, 4-mg tablets

[a]Patients already on the 80-mg dose for more than 12 months may continue at this dose. New patients started on simvastatin should not exceed 40 mg daily.

CHD, Coronary heart disease; *FDA,* Food and Drug Administration; *HDL,* high-density lipoprotein; *HMG-CoA,* 3-hydroxy-3-methylglutaryl coenzyme A; *LDL,* low-density lipoprotein.

The Scandinavian Simvastatin Survival Study (4S) was the first trial of lipid-lowering therapy in patients with established CHD to show a decrease in all-cause mortality and a reduction in CHD mortality and morbidity with statins compared with placebo. Patients exhibited a 30% reduction in CHD mortality and a 42% reduction in the incidence of nonfatal coronary events, with both outcomes being directly proportional to the reduction in LDL-C and TC levels. In addition, new or worsening intermittent claudication symptoms were reduced by 38% in patients who received statin therapy versus those given placebo in 4S.[59]

The HPS, a trial of simvastatin, 40 mg/day, versus antioxidant vitamins or placebo in 20,536 participants at high risk for a CHD event, demonstrated an overall 19.8% risk for a first major vascular event on statin treatment compared with a 25.2% risk in the placebo group (a 24% relative risk reduction).[39] The average LDL-C difference between the two groups was 39 mg/dL (1.01 mmol/L) during a mean follow-up of 5 years. The event reduction was due mainly to a 20% reduction in noncoronary revascularization, including a decrease in the number of carotid endarterectomies. The HPS was also the most comprehensive evaluation of the effects of cholesterol-lowering therapy on major vascular events in patients with PAD. More than 6000 patients with PAD were included in this study. Risk reduction benefits were similar between PAD patients and CHD patients, and were reported in a separate subset analysis.[60] The HPS included more than 5900 diabetics who experienced similar benefits in clinical outcomes as nondiabetics. HPS was a landmark trial in the treatment of patients with PAD, given the large number of participants with preexisting disease. The results of HPS support the treatment of all patients with PAD with a statin agent for lipid-lowering therapy.

The high-risk elderly population was examined in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study.[61] A total of 5800 patients, ages 70 to 82 years, with a history of preexisting vascular disease (coronary, cerebral, or peripheral), or at increased risk for such disease because of smoking, hypertension, or diabetes, were randomized to 40 mg/day of pravastatin or placebo. Treated patients had a 34% reduction in their LDL-C level and a reduction in the rate of major coronary events by 19% and CHD mortality by 24%. The authors concluded that the study results allowed statin therapy to be safely extended to older persons.

The Treating to New Targets (TNT) study examined the safety and efficacy of aggressive LDL lowering. More than 10,000 patients with established CHD and LDL less than 130 mg/dL were randomized to atorvastatin either 10 or 80 mg daily. After nearly 5 years of follow-up, LDL levels were substantially lower in the patients treated with 80 mg daily (77 mg/dL) compared with patients taking atorvastatin 10 mg daily (101 mg/dL; $P < .001$). In addition, major cardiovascular events were 22% lower in the patients taking atorvastatin 80 mg (8.7%) versus 10 mg (10.9%) ($P < .001$).[62]

The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial enrolled 17,802 apparently healthy people with LDL levels less than 130 mg/dL and hs-CRP levels equal to or more than 2.0 mg/L to rosuvastatin or placebo. The trial was terminated early after a median 1.9 years of follow-up. Rosuvastatin reduced LDL-C by 50%; hs-CRP was decreased by 37%. The primary endpoint of major cardiovascular events or cardiovascular death decreased from 1.36 per 100 person-years with placebo to 0.77 per 100 person-years with rosuvastatin ($P < .00001$).[63]

Niacin

Niacin (nicotinic acid) was the first pharmacologic agent demonstrated to reduce cholesterol in clinical trials. It favorably affects all lipids and lipoproteins, with 15% to 35% increases in HDL-C and 5% to 25% decreases in LDL-C. Niacin inhibits lipoprotein synthesis, improves the clearance of triglyceride-rich lipoproteins from the circulation, and is also the most effective agent for raising HDL-C levels.

Adverse events are more common with niacin than with other lipid-lowering agents, and regular evaluation of liver function, glucose, and uric acid is indicated. Aspirin 30 minutes before niacin administration helps prevent flushing.[64] In addition, extended-release (ER) and enteric-coated ER niacin in which the frequency and intensity of flushing is reduced are available. Niacin is available over the counter, although over-the-counter forms of delayed-release or long-acting niacin should not be used because of a significant increase in hepatotoxicity.

Niacin is typically poorly tolerated at higher doses and is often used in combination with statins or other pharmacologic agents. The initial dosage should be 500 mg ER niacin by mouth nightly for 4 weeks and then increased by 500 mg/day every 4 weeks based on effect and tolerance. The maximum dose is 2 g/day ER niacin. Data from the Comparative Effects on Lipid Levels of Niaspan and Statins versus Other Lipid Therapies (COMPELL) study of 292 patients at high risk of MI and with mixed dyslipidemia (mean baseline LDL-C, 197 mg/dL [5.10 mmol/L]; HDL-C, 49 mg/dL [1.27 mmol/L]; and triglycerides, 168 mg/dL [4.35 mmol/L]) support this combination.[65] In this study, patients were randomized to treatment with either ER niacin (1 to 2 g daily) plus moderate doses of a statin (rosuvastatin, 10 to 20 mg daily, or atorvastatin, 20 to 40 mg daily), high-dose statin therapy (rosuvastatin, 20 to 40 mg daily), or combination therapy with simvastatin and ezetimibe (20/10 mg increasing to 40/10 mg daily). Although all treatments lowered LDL-C and non-HDL-C levels by about 50% or more, the combination of niacin plus statins resulted in substantially greater decreases in triglyceride levels and up to 3.5-fold greater increases in HDL-C levels than with the other regimens. Despite demonstrable improvements in the lipid profile, the role of niacin in lipid management has been questioned. Several large trials failed to show significant improvement.[66]

Fibrate

The fibrates, gemfibrozil and fenofibrate, are peroxisome proliferator receptor-α agonists used for treating hypertriglyceridemia and to increase HDL-C.[67] The therapeutic effect of these drugs is a 25% to 50% decrease in triglyceride levels and a 5% to 15% increase in HDL-C. In addition, fenofibrate may also decrease LDL-C by 10% to 20%, whereas an increase in LDL-C is often seen when gemfibrozil is used to treat very high levels of triglycerides. Gemfibrozil is taken 30 minutes before morning and evening meals as a 600-mg tablet. Fenofibrate is started at 54 mg by mouth with food once daily, and the dosage can be increased to 160 mg daily. Several trials demonstrated reduction in the progression of atherosclerosis but had no impact on decreasing mortality.[68,69]

Bile Acid Sequestrants

Bile acid sequestrants include colestipol, cholestyramine, and a more recently developed form, colesevelam. Historically, cholestyramine and colestipol were among the first drugs available to treat high TC and LDL-C. These drugs may be used as monotherapy in concert with dietary modification to achieve enhanced LDL-C lowering, but are more often used in combination with statin therapy. As noted earlier, doubling the dose of a statin may achieve only a 6% further reduction in LDL-C, but adding a sequestrant to a statin can further lower LDL-C by 12% to 16%.[70] Sequestrants have extremely low rates of systemic toxicity. Dyspepsia and constipation are known side effects. Colesevelam (WelChol, Daiichi-Sankyo, Inc., Basking Ridge, New Jersey) has significantly reduced these side effects and increased the compliance in the use of these drugs. It also has the advantage of being formulated as a tablet. Colesevelam comes in 625-mg tablets and should be started at three tablets twice daily with meals followed by liquid. In addition to the previously listed GI side effects, bile acid sequestrants may significantly increase triglycerides and are known to bind certain other drugs in the GI tract.

Ezetimibe

Ezetimibe is the first in a new class of pharmacologic agents for reducing TC and LDL-C. It specifically interferes with the absorption of cholesterol from the GI tract and results in a 15% to 20% reduction in LDL-C as monotherapy.[71] Ezetimibe is often used with a statin to achieve a further reduction in LDL-C of 20% to 25%, with added beneficial effects on triglycerides and HDL-C. The efficacy of ezetimibe in reducing atherosclerosis has been questioned, but the National Lipid Association endorsed its use because of its proven efficacy.[72]

Omega-3 Fatty Acids

Polyunsaturated fatty acids of the omega-3 type are found in fish and other marine animals, as well as in soybeans and other vegetables. Varying strength of evidence exists to support consumption of omega-3 fatty acid. ATP III supports the AHA's recommendation that fish, particularly fish high in omega-3 fatty acids, be included as part of a CHD risk reduction diet.[73] Fish is also low in saturated fat and may be cardioprotective. A number of observational studies have suggested that regular consumption of fish reduces the risk for CHD.[74,75] An Italian trial showed that the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) at a dose of 1 g daily reduced the risk of sudden death.[76] Other trials showed mixed results.[77-79] It is important to note that higher doses of EPA and DHA, 3 g or more daily, have a significant hypotriglyceridemic effect without significant adverse events. However, more definitive trials are necessary before strongly recommending high doses of omega-3 fatty acids.

Cholesterol Ester Transfer Protein Inhibitors

In addition to lowering LDL-C, the ability to raise HDL-C is a tangible therapeutic target. Endogenously, the transfer of cholesterol ester from HDL-C to apo B–containing lipoproteins, VLDL, and LDL, in exchange for triglycerides is mediated by CETP. This is deemed a heterotypic transfer. Homotypic transfer or the transfer of cholesteryl ester between HDL subtypes is also mediated by CETP. Of the developed CETP inhibitors, torcetrapib and anacetrapib inhibit both homotypic and heterotypic transfer, whereas dalcetrapib inhibits only heterotypic transfer.[80]

Novel Therapeutic Agents

Proprotein convertase subtilisin/kexin type-9 (PCSK9) increases LDL by interfering with hepatic LDL receptor recycling (Fig. 13.6). Monoclonal antibodies directed against PCSK-9 have been developed and tested in trials. Alirocumab, evolocumab, and bococizumab, PCSK9 inhibitors, have been effective in lowering LDL in patients.[81] The FDA has recently approved alirocumab and evolocumab in patients with clinical ASCVD or heterozygous familial hypercholesterolemia.

Combination Drug Therapy

Combination therapy has been shown to be effective in obtaining LDL, HDL, and triglyceride targets in patients with dyslipidemia. A combination of a statin plus an agent that blocks the intestinal absorption of cholesterol is particularly effective in decreasing LDL-C levels. Both ezetimibe and the bile acid sequestrants can be safely added to the maximal dose of a statin or can be used with lower doses to reach LDL-C therapeutic goals. Some patients will not tolerate the maximal dose of any statin, and one or both of these intestinally acting agents will allow the attainment of LDL-C goals when added to a submaximal dose of a statin. In addition, ER niacin can be combined with a statin or one of the intestinally acting drugs, or can be used in combination with both classes of drugs to reach LDL-C targets in patients with very high LDL-C levels, such as those with heterozygous familial hypercholesterolemia. Statin therapy may also be combined with fenofibrate, niacin, or omega-3 fatty acids to achieve control in patients with combined hyperlipidemia; the combination yields superior results over monotherapy. In general, gemfibrozil should not be used with a statin because of its inhibition of statin metabolism, which increases the potential toxicity of all statins.[82] Fenofibrate is a better choice when statin and/or fibrate combination therapy is required.[83] The SANDS (Stop Atherosclerosis in Native Diabetics) trial used the endpoint of change in CIMT as a surrogate for the control of atherosclerosis. In the most aggressive group with lipid goals of less than 70 mg/dL (1.81 mmol/L) for LDL-C and less than 100 mg/dL (2.59 mmol/L) for non-HDL-C, CIMT regression was achieved. However, larger prospective studies with clinical endpoints that include cardiovascular morbidity and mortality and PAD-related outcomes are still needed to evaluate the outcome benefits of combination therapy.

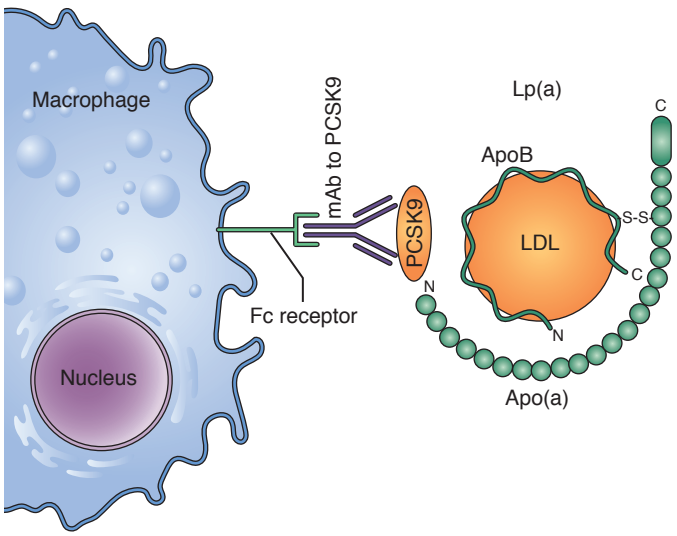

Figure 13.6 Mechanism of action of proprotein convertase subtilisin/kexin type-9 (PCSK9) to decrease low-density lipoprotein (LDL). *Apo(a),* Apolipoproteins (a); *Lp(a),* lipoprotein (a). (Shapiro MD, Fazio S. From lipids to inflammation: new approaches to reducing atherosclerotic risk. *Circ Res.* 2016;118(4):732-749.)

Homozygous Familial Hypercholesterolemia

In 1972, Goldstein and Brown treated two young siblings, aged 6 and 8, who were hospitalized at the NIH for acute coronary syndromes due to LDL levels eightfold above normal. They were diagnosed with homozygous familial hypercholesterolemia (HFH) and became the impetus for scientists to elucidate the LDL receptor mechanism.[2] Even with combination therapy, patients with HFH have a difficult time reducing LDL. LDL apheresis is available in some clinical centers and may be used when high-risk patients fail to meet target goals, despite dietary management and maximum tolerated lipid-lowering regimens. In addition, lomitapide, a microsomal triglyceride transfer protein inhibitor, and mipomersin, an antisense oligonucleotide inhibitor of apo B-100 synthesis, have been approved, but are presently available only through Risk Evaluation and Mitigation Strategy (REMS). Now PCSK9 inhibitors have been shown to effectively reduce LDL levels in HFH patients.[81]

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Additional lipid reduction trials involving more than 50,000 patients resulted in new optional therapeutic targets that defined optional lower target cholesterol levels for very high-risk coronary heart disease patients, especially those with acute coronary syndromes, and expanded indications for drug treatment.

Heart Protection Study Collaborative Group. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular disease and other major vascular outcomes in 20,536 people

with peripheral arterial disease and other high-risk conditions. *J Vasc Surg*. 2007;45:645–654.

The HPS is a landmark trial in the treatment of patients with PAD, given the large number of participants with preexisting disease. The results of the HPS support the use of lipid-lowering therapy in all patients with PAD.

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A complete reference list can be found online at www.expertconsult.com.

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14 CHAPTER

Atherosclerotic Risk Factors: Hypertension

PAUL N. FIORILLI and EMILE R. MOHLER III

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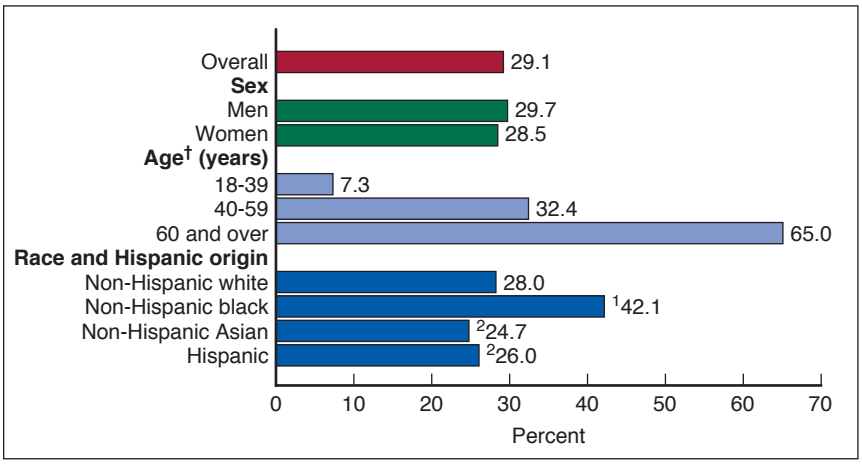
Hypertension is a key risk factor in the pathophysiology of atherosclerosis and the development of peripheral artery disease (PAD). Available evidence related to PAD and hypertension is largely extrapolated from subgroup analyses of larger trials of patients with atherosclerotic vascular disease and cardiovascular risk factors. Consequently, there are no current concrete within-class comparison studies of the effects of the treatment of hypertension on PAD-related disease outcomes. Patients with PAD have a high mortality from cardiovascular disease (CVD) and cerebrovascular disease, and thus treatment of hypertension is recommended in this population despite the lack of prospective, randomized clinical trial data showing that antihypertensive therapy alters the course of PAD.

EPIDEMIOLOGY

Scope of the Problem

The prevalence of hypertension is high in the United States, with nearly one-third of the US adult population affected.[1] The



† Significant linear trend. [1]Significantly different from non-Hispanic white.
[2]Significantly different from non-Hispanic black.

NOTE: Estimates were age-adjusted by the direct method to the Census 2000 population, using the age groups 18-39, 40-59, and 60 and over.

SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey, 2011–2012.

Figure 14.1 Age-specific and age-adjusted prevalence of hypertension among adults aged 18 and over: United States, 2011–2012. (From Center for Disease Control and Prevention [CDC], http://www.cdc.gov/nchs/data/databriefs/db133.pdf; National Health and Nutrition Examination Survey [NHANES].)

National Health and Nutrition Examination Survey (NHANES, 2011–2012) estimates that the age-adjusted prevalence of hypertension among US adults aged 18 and over was 29.1% (Fig. 14.1).[2] In this study, hypertension was defined as either a systolic blood pressure (SBP) of 140 mm Hg or higher, a diastolic blood pressure (DBP) of 90 mm Hg or higher, or the current need for antihypertensive medications. The prevalence of hypertension is similar to recent NHANES data from 2009 to 2010, but overall, has increased compared to the previous data from 1988 to 1994.[3,4] Despite a higher awareness of the problem over the past decade, the prevalence of hypertension in the adult U.S. population has remained unchanged.

The prevalence of hypertension increases with increasing age, with approximately 7.3% of adults between the ages of 18 and 39 affected, as compared with 32.4% of adults between the ages of 40 to 59 affected, and 65.0% of adults aged 60 and older affected.[2] Similarly, PAD increases in prevalence with increasing age.[5] Hypertension is similarly prevalent between men and women (29.7% vs. 28.5%), and the prevalence is highest among non-Hispanic black adults (42.1%).[2] PAD also has a higher prevalence among non-Hispanic male and female black adults as compared with non-Hispanic white adults (men 33% vs. 11%, women 34% vs. 22%) based on data from the genetic epidemiology network of arteriopathy (GENOA) study.[6] A similar trend in ethnic differences in epidemiology of PAD was observed in data from the NHANES survey.[5]

Elevation of SBP, DBP, and pulse pressure (PP) are associated with increased cardiovascular risk.[7] The relative importance of each of these factors as a predictor of cardiovascular risk varies with age. Based on data from the Framingham Heart Study, in adults younger than 50 years of age, DBP is the strongest predictor of cardiovascular risk.[7] In adults between the ages of 50 and 59, all three factors (SBP, DBP, PP) are comparable predictors of risk, and SBP is the strongest predictor in adults 60 years of age and older.[7] Isolated systolic hypertension is more prevalent in an older population,[8] and this may be responsible for predictive value of SBP of cardiovascular risk in older adults. SBP rises more than DBP with aging, which results in a widened PP.[9]

Hypertension, along with smoking, diabetes, and dyslipidemia, is strongly associated with PAD.[10] The high prevalence of hypertension in the US adult population, particularly among older adults, makes hypertension a significant contributor to the overall burden of PAD in the US adult population. Quantifying the risk of PAD among patients with hypertension depends, in part, upon the manner in which PAD is defined. For example, data from the Framingham Heart Study, which defined PAD by intermittent claudication (IC), showed that the risk for PAD increases with increasing systolic and DBP in both men and women.[11] Long-term 38-year follow-up of data from the original Framingham Heart Study cohort demonstrated that hypertension was a risk factor for both symptomatic and noninvasively determined PAD in both men and women, and was associated with a greater than twofold increase in the risk of PAD.[12] Data from the NHANES study, which also used IC to define PAD, found that hypertension that was untreated, or hypertension that was treated but still uncontrolled were both associated with PAD.[5] Although these studies demonstrated the risk of both SBP and DBP on PAD, other studies that used ankle-brachial index (ABI) to define PAD have shown slightly different results and have implicated SBP more than DBP in hypertensive risk of PAD. This may be attributable to the fact that not all patients with PAD (as defined by an ABI of <0.9) exhibit classic symptoms of IC.[13]

Traditionally, an ABI of less than 0.9 has been considered diagnostic for PAD; however, several studies have used more conservative criteria using an ABI of less than 0.80 or less than 0.75. In addition, patients with an ABI of 0.91 to 0.99 are considered borderline. NHANES data has shown that hypertension was strongly associated with PAD (when defined as an ABI of <0.90) in patients 40 years of age and older.[14] In the Cardiovascular Heart Study, an inverse relationship was

demonstrated between hypertension and ABI (the higher the blood pressure, the lower the ABI, consistent with more significant PAD).[15] However, after the study investigators controlled for confounders, the inverse relationship persisted for SBP but not for DBP. In the Rotterdam Study of PAD (which defined PAD by ABI of <0.9), SBP, and not DBP, was strongly associated with PAD.[16] Overall, there appears to be a stronger association between PAD and SBP than PAD and DBP.

Unfortunately, hypertension tends to be undertreated in the general population. According to the NHANES 2011–2012 data, 82.7% of patients with hypertension were aware of their diagnosis and 75.6% were currently taking prescribed antihypertensives, but only 51.8% of patients had their blood pressure controlled.[2] In addition, there is some data to suggest that blood pressure control is worse in patients with PAD than in the general coronary heart disease population.[17] In the PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) study, hypertension was treated less frequently in PAD patients with both newly diagnosed hypertension as well as known PAD and hypertension, as compared with patients with hypertension and no PAD.[18]

A secondary cause of hypertension, renal artery stenosis (RAS), is prevalent in patients with PAD. In a prospective cohort of 629 consecutive patients with PAD undergoing digital subtraction angiography (DSA), renal artery disease was found in 33%, and 9.6% of patients had a significant RAS (> or = 60%).[19] In patients with PAD and hypertension, RAS is an important consideration in the diagnostic evaluation, as it has implications for subsequent blood pressure management.

In summary, hypertension is prevalent in the adult U.S. population, and is a major risk factor for atherosclerotic diseases—specifically PAD. The high prevalence of hypertension in the PAD population, the association of hypertension with risk of cardiovascular events, as well as the undertreatment of hypertension in this population, all make the identification and treatment of hypertension an important target for the management of patients with PAD.

DIAGNOSIS

Definition

Previous epidemiologic studies and therapeutic trials have used different criteria to define hypertension in populations. In December of 2013, the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure released the eighth report and guidelines for the management of hypertension (JNC 8).[20] The JNC 8 guidelines did not address the definition of hypertension, but rather addressed the threshold for initiating pharmacologic treatment. In the previous guidelines (JNC 7), stage 1 hypertension was defined as a SBP of 140 to 159 mm Hg or a DBP of 90 to 99 mm Hg, and stage 2 hypertension was defined as a SBP of greater than or equal to 160 mm Hg or a DBP of greater than or equal to 100 mm Hg (Table 14.1).[21] JNC 8 guidelines recommend a blood pressure of less than 150/90 mm Hg in patients aged 60 years or older, and less than 140/90 mm Hg in patients aged 30 to 59 years of age.[20] The blood pressure should be based on the average of two or more properly measured, seated readings on each of two or more office visits.

TABLE 14.1 JNC 7: Definition of Hypertension

Stage	Systolic (mm Hg)	Diastolic (mm Hg)
Normal blood pressure	<120	<80
Prehypertension	120-139	>80-89
Stage 1 hypertension	140-159	>90-99
Stage 2 hypertension	>160	>100

Adapted from the National Heart Lung and Blood Institute: The Seventh Report of the Joint National Committee on Prevention, detection, Evaluation, and Treatment of High Blood Pressure (JNC-7). http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf.

Blood Pressure Measurement Technique

Routine blood pressure measurements should be made with an appropriate-sized cuff (cuff bladder encircling at least 80% of the arm) to ensure accuracy. At least two measurements should be made. The patient should be seated comfortably, with feet on the floor and back supported, for at least 5 minutes in a quiet room prior to taking measurements. The arm should be supported at the level of the heart. Ideally, patients should be free of caffeine and smoking for 30 minutes before measurements are taken.

Ambulatory blood pressure monitoring (ABPM) is another technique that can be used to verify the diagnosis of hypertension in certain situations. ABPM can be used to identify hypertension, masked hypertension, normotension, or white coat hypertension (WCH). In addition to suspected cases of WCH, the previous JNC 7 guidelines recommended ABPM for resistant hypertension (uncontrolled blood pressure despite adequate doses of three drugs including a diuretic), episodic hypertension, autonomic dysfunction, and those with symptoms of orthostasis on therapy.[21]

According to ABPM measurements, hypertension is defined as a 24-hour average of greater than 130/80 mm Hg or a daytime average of greater than 140/85 mm Hg.[22] WCH is defined as an elevated blood pressure in the physician's office of greater than or equal to 140/90 mm Hg and a 24-hour blood pressure of less than 130/80 mm Hg.[23] Although WCH has been traditionally thought to be a benign condition, there are now data indicating an increased, albeit small, risk of CVD.[23] No randomized trial data or guidelines exist addressing this group, so practitioners should use judgment in evaluating these patients from evidence of end-organ damage and counsel them regarding lifestyle modifications. Lastly, patients with masked hypertension have normal blood pressure in the office, but are hypertensive at home. This group of patients is more difficult to identify, and may be discovered by participation in research studies or through home blood pressure monitoring. These patients may also have an increased risk of CVD.[24]

Secondary Causes

Patients who have uncontrolled blood pressure despite adequate doses of three antihypertensive medications (including a diuretic) meet criteria for resistant hypertension. These patients should be evaluated for secondary causes of hypertension. First, patients with resistant hypertension should have a careful and detailed history taken, with specific attention paid to the use of exogenous substances that may lead to elevations in blood pressure (e.g., corticosteroids, weight loss supplements, herbal medication, NSAIDs). Next, the patient's current medication list should be reviewed to ensure that all antihypertensives are adequately dosed and include the use of a diuretic. The patient should also be assessed for adherence to the current medication regimen. If all of the above are unrevealing, then the patient should be evaluated for secondary causes of hypertension.[25]

The causes of secondary hypertension and association signs and symptoms are reviewed in Table 14.2. The physical examination of patients with suspected secondary hypertension should include auscultation for abdominal bruits, palpation of the thyroid gland, and assessment of pulses in the upper and lower extremities. The laboratory evaluation should include a complete blood count, serum blood urea nitrogen, glucose, calcium, creatinine, electrolytes, and a urinalysis.[26] A uric acid level may also be checked in patients that may undergo diuretic therapy, as this class of medications may cause hyperuricemia. Plasma renin activity may be checked in patients with hypokalemia with suspected primary hyperaldosteronism.

Renovascular hypertension is a cause of secondary hypertension and should be included in the evaluation of patients with difficult to control hypertension. It is most commonly due to the development of renal artery atherosclerosis and ultimately RAS. RAS leads to decreased blood flow to the kidney, and the renin-angiotensin-aldosterone system is thus activated. A proposed hypothesis of the model of renovascular hypertension is that humoral factors activated by the renin-angiotensin-aldosterone system in patients with RAS may accelerate and promote the atherosclerotic process in these patients, thus creating a vicious cycle.[27] In addition, studies of pigs with secondary hypertension due to RAS showed that increased oxidative stress resulted from this condition and was a stimulus for atherosclerosis independent of cholesterol levels.[28] Overall, clinical evidence is also supportive of this hypothesis, and this may explain the relatively high prevalence of RAS in patients with CVD and atherosclerosis in other arteries.

TABLE 14.2 Secondary Causes of Hypertension

Cause	Signs and Symptoms
Primary aldosteronism	Hypokalemia
Cushing syndrome	Striae, abdominal obesity
Pheochromocytoma	Labile blood pressure, tachycardia, sweats, headaches
Renal artery stenosis (atherosclerotic or due to fibromuscular dysplasia)	Smoking history, flash pulmonary edema, abdominal bruits
Thyroid disease	Goiter
Oral contraceptive pills	Women of child-bearing age
Obstructive sleep apnea	Snoring
Coarctation of the aorta	Children, disparate blood pressures in upper and lower extremities
Kidney disease	Elevated serum creatinine, proteinuria

PATHOLOGIC MECHANISMS OF HYPERTENSION AND ATHEROSCLEROSIS

The association of hypertension with the development of atherosclerosis has long been known, but the molecular mechanisms involved are not completely understood. This is likely due to the complex nature of the development of atherosclerosis. Many factors contribute to the development of atherosclerosis, including genetics, behavioral tendencies (e.g., smoking), and environmental factors.

Animal Models of Hypertension

Much insight into the interaction of hypertension and atherosclerosis has been gained from genetically engineered mouse models. Previous research has demonstrated that most mouse models of hypertension shown an increase in atherosclerotic lesion size.[29] It has also been demonstrated in mice that reducing blood pressure reduces atherosclerotic lesion size. Other studies have shown decreases in atherosclerosis without decreases in blood pressure.[29] These findings point to the complex interplay between blood pressure and development of atherosclerosis.

Renin-Angiotensin System and Atherosclerosis

A theme that has consistently been observed in the literature is that blood pressure alterations from the manipulation of the renin-angiotensin system has a direct impact on the size of atherosclerotic lesions.[29] The renin-angiotensin system is responsible for homeostatic control of arterial pressure, tissue perfusion, and extracellular volume. Renin is produced from the juxtaglomerular cells in the nephron. Angiotensinogen, which is primarily produced in the liver, is converted to angiotensin I by renin. Angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor, specifically on the efferent arteriole, and mediator of aldosterone secretion.

Previous mouse models have shown that angiotensin II, via chronic infusion, promotes atherosclerosis independent of changes in arterial pressure.[30] In addition, other studies have shown that pharmacologic inhibition of the renin-angiotensin system decreases the development of atherosclerosis independent of blood pressure lowering.[29] Consequently, this axis is a

prime target for pharmacotherapy for both hypertension and atherosclerosis.

A correlation between hypercholesterolemia and hypertension has been observed in humans. Vascular angiotensin II receptor type 1 (AT1) expression is upregulated in patients with hypercholesterolemia, and this is associated with a more prominent blood pressure response to angiotensin II in these patients. In one study, angiotensin II was administered to patients with hypercholesterolemia and to patients with normocholesterolemia, and the blood pressure response was exaggerated in the hypercholesterolemia group.[31] Administration of statins mitigated this response.[31] Animal studies have shown that renin-angiotensin inhibition, along with statin therapy, reduces atherosclerosis as compared with renin-angiotensin inhibition alone.[32] In addition to improved reduction in atherosclerosis with both renin-angiotensin inhibition and statins, the combination may also result in better blood pressure control as compared with renin-angiotensin inhibition alone.[33] In addition, statins have a role in improving endothelial function and in vascular elasticity.[32]

Endothelial Dysfunction and Hypertension

Hypertension is associated with endothelial dysfunction in the coronary, renal, and peripheral circulation. Endothelial dysfunction occurs early in the atherosclerotic process. Maintenance of normal endothelial function and appropriate vasodilation is important to both blood pressure control as well as the development of atherosclerosis. Previous studies have shown that the presence of hypertension blunts the effects of an agonist-induced vasodilatory response.[34] Nitric oxide (NO) is important in maintaining normal endothelial function and is critical to the vasodilator response. Reductions in endothelial-derived NO result in a reduced vasodilatory response, and may also result in a proinflammatory, prothrombotic, and procoagulant phenotype (Fig. 14.2).

The enzyme responsible for generating NO is endothelial NO synthase. In a mouse knockout model, the deletion of this enzyme resulted in significantly increased SBP (128 ± 3 vs. 108 ± 5 mm Hg; $P < .001$), and decreased heart rate (531 ± 22 vs. 629 ± 18 bpm; $P < .001$), as compared with wild-type controls.[35]

Although endothelial dysfunction is related to hypertension and appears to be a consequence of it, the data regarding endothelial dysfunction as a precursor to hypertension is mixed. In one study, investigators evaluated forearm blood flow modifications by administering intrabrachial acetycholine (an endothelium-dependent vasodilator), and sodium nitroprusside (an endothelium-independent vasodilator) to offspring of patients with essential hypertension.[36] A blunted vasodilatory response was found in those who were offspring of hypertensive patients, suggesting that impairment in NO may precede the onset of essential hypertension.[36] However, another study of black young adults with and without a family history of hypertension did not show a significant difference in brachial artery reactivity, and there was no evidence of early endothelial dysfunction in the offspring of those with essential hypertension.[37] In this study, women did show more brachial artery vasodilation compared with men and irrespective of family history of hypertension. Overall, more research is needed to help identify subject who are predisposed to developing hypertension.

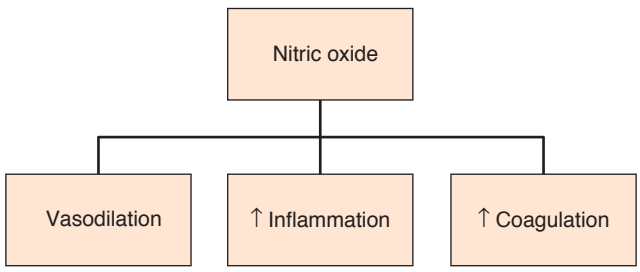


Figure 14.2 Pathologic mechanism of action associated with endothelial dysfunction. A reduction on nitric oxide may lead to reduced vasodilation, increased inflammation, and increased coagulation.

MANAGEMENT

General Principles

The goals of treating hypertension are to lower blood pressure and reduce CVD risk as well as to reduce progression of atherosclerosis. Effective treatment of hypertension includes lifestyle modifications as well as pharmacotherapy.

Lifestyle Modifications

Lifestyle modifications have been demonstrated to decrease blood pressure and to reduce CVD risk.[38] The relationship between weight loss and blood pressure reduction appears to be linear, and a reduction in every 1 kg of body weight is associated with an approximate reduction in blood pressure by 2/1 mm Hg.[39] Lifestyle modifications, including diet and exercise, can lead to improved overall health in addition to the benefits of blood pressure reduction. Most major medical societies recommend lifestyle modifications of weight loss, limiting sodium intake, engaging in aerobic physical activity for at least 30 minutes daily, and limiting alcohol intake to one to two servings daily. A diet that is commonly recommended and has been demonstrated to effectively lower blood pressure is the Dietary Approaches to Stop Hypertension (DASH) diet, which is low in fat and sodium and high in fruits and vegetables.[40]

Antihypertensive Therapy

CVD risk increases progressively with increasing blood pressure, beginning at 110/75 mm Hg.[41] Previous clinical trials have demonstrated that lowering blood pressure reduces the risk of CVD.[42,43] The benefits of treating hypertension with regards to lowering cardiovascular risk have also been demonstrated in patients with PAD. In the Heart Outcomes Prevention Evaluation (HOPE) study, the subset of patients with PAD (as defined by an ABI < 0.9), and treatment with an ACE inhibitor (specifically, ramipril), showed an overall reduction in cardiovascular events in patients with hypertension and PAD.[44] The Appropriate Blood Pressure Control in Diabetes study evaluated blood pressure control in patients with both diabetes and PAD. The

results demonstrated that a reduction in blood pressure to a mean of 128/75 mm Hg in this population was associated with a significant reduction in cardiovascular events.[45]

Although it is known that treatment of blood pressure reduces the risk of cardiovascular events in patients with hypertension and PAD, there is no clear data that antihypertensive treatment significantly modifies the disease process of PAD. The United Kingdom Prospective Diabetes Study Group (UKPDS) trial evaluated tight blood pressure control in patients with diabetes and hypertension, and there was an association in this study with reductions in cardiovascular endpoints, but not in the risk of incident PAD.[46] There is some evidence that treatment with ACE inhibitors may improve symptoms of PAD, including improved walking times.[47]

The 2005 American College of Cardiology and American Heart Association guidelines on the management of patients with PAD recommend treating blood pressure with antihypertensive therapy to a goal of less than 140/90 mm Hg.[48] The 2011 focused update to these guidelines did not address blood pressure control.[49] The Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC-II) also recommends treating to a goal blood pressure of less than 140/90 mm Hg.[50] As previously described, the JNC 8 guidelines for the management of hypertension recommend treating a blood pressure to less than 150/90 mm Hg in patients aged 60 years or older, and to less than 140/90 mm Hg in patients aged 30 to 59 years of age.[20] More recently, the results of a large, randomized trial, the SPRINT study, were published, which call into question the appropriate treatment goals for blood pressure in adults.[51] In this study, 9361 patients with hypertension and an increased cardiovascular risk (but without diabetes), were assigned to a blood pressure target of less than 120 mm Hg versus a target of less than 140 mm Hg. The primary outcome was myocardial infarction, acute coronary syndrome, heart failure, or death from cardiovascular causes. The trial, notably and surprisingly, was stopped early due to a significantly lower rate of fatal and nonfatal major cardiovascular events, as well as death from any cause in the group of patients treated to a SBP of less than 120 mm Hg.[51] The results of this trial argue for more aggressive blood pressure control than what is in the current guidelines. Importantly, this trial excluded patients younger than 50 years of age, those with previous strokes, and those with diabetes which is important to note, as only approximately 20% of the adult hypertensive population would have been eligible for this trial.[52] If this more aggressive approach to management of hypertension based on the SPRINT study is pursued, then it is important to discuss the possible side effects with patients such as presyncope or even syncope that may occur with lower blood pressure targets.

Pharmacotherapy

General Considerations

Patients with prehypertension (blood pressure >120-139/80-89) should be counseled regarding lifestyle modifications, as this group has a high risk for progression to hypertension. Currently, guidelines do not recommend treating pre-hypertensive patients with pharmacotherapy. However, a seminal study in 2006 demonstrated that treatment of prehypertensive patients with an angiotensin receptor blocker (ARB) reduced the incidence of hypertension.[53]

The first step in treatment of hypertension is lifestyle modifications. For patients who are unable to reach blood pressure goals with lifestyle modifications alone, or if there is evidence of end-organ injury, then antihypertensive medications should be initiated. The first-line therapy for most patients with uncomplicated, essential hypertension is a thiazide diuretic (typically chlorthalidone). If blood pressure is greater than 160/90 mm Hg on presentation, then combination therapy should be initiated with at least two antihypertensive agents. With the goal of patient adherence in mind, consideration should be given by the clinician to fixed-dose combination pill therapy. The second agent, after a thiazide diuretic, depends on the patient's other co-morbid conditions. In patients with uncomplicated, essential hypertension, the second-line agent may be an ACE inhibitor, an ARB, a beta blocker, or a calcium channel blocker.

For patients with other co-morbid conditions, the second medication chosen should be picked for specific benefits related to the co-morbid conditions. For example, in patients who have diabetes mellitus or chronic renal disease in addition to hypertension, ACE inhibitors and ARBs have superior benefit to the other medication classes. In addition, patients with coronary artery disease or heart failure derive greater benefits from beta blockers.

No specific antihypertensive medication class has shown superior benefit in patients with PAD.[54] Therefore medications should be chosen based on the patient's other comorbidities. The available agents for antihypertensive therapy, organized by medication class, are listed in Table 14.3.

Thiazide Diuretics

Thiazide diuretics act in the distal convoluted tubule by blocking sodium and chloride transport. Thiazides tend to be more effective in patients with lower renin levels, and this situation tends to be more common in African American patients and older hypertensive patients.[55] The landmark trial that demonstrated the beneficial effects of thiazides was the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and this largely led thiazides to be considered as first-line treatment for hypertension in most patients.[56,57] The ALLHAT study was a large, randomized, double-blind controlled trial of more than 33,000 participants with hypertension. Patients were assigned to receive either chlorthalidone (a thiazide diuretic), amlodipine (a calcium channel blocker), or lisinopril (an ACE inhibitor). In this study, patients treated with chlorthalidone had a lower average blood pressure, and was shown to be equivalent to both lisinopril and amlodipine. Given the low cost of thiazide diuretics, coupled with their sustained clinical benefits, the authors of the ALLHAT study concluded that thiazide diuretics should be considered as first-line therapy.[57]

In addition, thiazide diuretics lead to decreased calcium excretion, and therefore can be of benefit in preventing calcium-containing kidney stones. The positive calcium balance associated with thiazides may also be beneficial in patients with osteoporosis.

TABLE 14.3 List of Available Antihypertensive Agents by Class

Class	Drugs	Indications	Side Effects
Thiazide diuretics	Chlorthalidone Hydrochlorothiazide Indapamide Metolazone	First-line therapy Low renin Blacks Elderly	Hyperuricemia, hypokalemia, insulin resistance, erectile dysfunction
Loop diuretics	Bumetanide Ethacrynic acid Furosemide Torsemide	CHF Impaired kidney function	Hypokalemia, volume depletion
Potassium-sparing diuretics and aldosterone antagonists	Amiloride Eplerenone Spironolactone Triamterene	Hypokalemia from thiazide diuretics Primary aldosteronism CHF Proteinuria	Hyperkalemia, GI side effects, gynecomastia
Beta blockers	Acebutolol Atenolol Betaxolol Bisoprolol Carvedilol Labetalol Metoprolol Nadolol Nebivolol Pindolol Propranolol Sotalol	CAD Atrial fibrillation CHF	Hyperlipidemia, bradycardia, insulin resistance, depression?
ACE inhibitors	Benazepril Captopril Enalapril Fosinopril Lisinopril Moexipril Perindopril Quinapril Ramipril Trandolapril	CAD CHF LVH Proteinuria Younger patients	Angioedema, cough, hyperkalemia, acute kidney injury
ARBs	Candesartan Eprosartan Irbesartan Olmesartan Losartan Telmisartan Valsartan	CAD CHF LVH Proteinuria	Angioedema, hyperkalemia, acute kidney injury
Renin inhibitor	Aliskiren	Hypertension with elevated renin, (see ACE, ARB)	Angioedema, hyperkalemia, GI side effects
CCB	Dihydropyridine: Amlodipine, felodipine, isradipine, nicardipine, nimodipine, nifedipine Nondihydropyridine: Diltiazem, Verapamil	Blacks Elderly	Lower extremity edema, constipation, bradycardia
Alpha blockers	Doxazosin Terazosin	Hypertension with benign prostatic hypertrophy	Dizziness, fatigue
Central alpha agonists	Clonidine Methyldopa	Resistant hypertension Pregnancy	Rebound hypertension, fatigue, dry mouth, erectile dysfunction
Vasodilators	Hydralazine Minoxidil	Resistant hypertension with CHF or impaired kidney function	Fluid retention, tachycardia

ACE, Angiotensin converting enzyme; *ARB*, angiotensin receptor blockers; *CCB*, calcium channel blockers.

In patients with impaired renal function, thiazide diuretics are generally not effective (serum creatinine >1.5 mg/dL). In patients with decreased renal function, loop diuretics are preferred. Lastly, the efficacy of thiazide diuretics is reduced in the presence of excessive dietary sodium intake, as well as nonsteroidal anti-inflammatory drug use.

Complications/Side Effects

Thiazide diuretics must be used with caution, as they can lead to hypokalemia. Hypokalemia associated with thiazide diuretics is dose-dependent. This class is also associated with an increased risk of hypercalcemia, hyperuricemia, hyperlipidemia, and hyperglycemia. In addition, caution must be taken with the use of thiazide diuretics in elderly patients as they may cause volume depletion, and in patients with RAS. Lastly, there is an association of thiazide diuretics with erectile dysfunction.

Overall, thiazide diuretics are efficacious in the lowering of blood pressure and are considered to be first-line therapy. The use of this class must be balanced with the risks associated with their many metabolic side effects. Many of the side effects listed above are dose-dependent, and may be reduced and/or avoided by using low to moderate doses of these medications.

Angiotensin Converting Enzyme Inhibitors

ACE inhibitors block the enzyme that is responsible for converting angiotensin I to angiotensin II (Fig. 14.3). As previously discussed, angiotensin II is a potent vasoconstrictor. ACE inhibitors lack many of the metabolic side effects that are more commonly present with thiazide diuretics as well as beta blockers. This class is considered first-line therapy for patients with certain comorbid conditions, including congestive heart failure, anterior wall myocardial infarction, left ventricular hypertrophy, diabetes mellitus, and proteinuric renal disease.

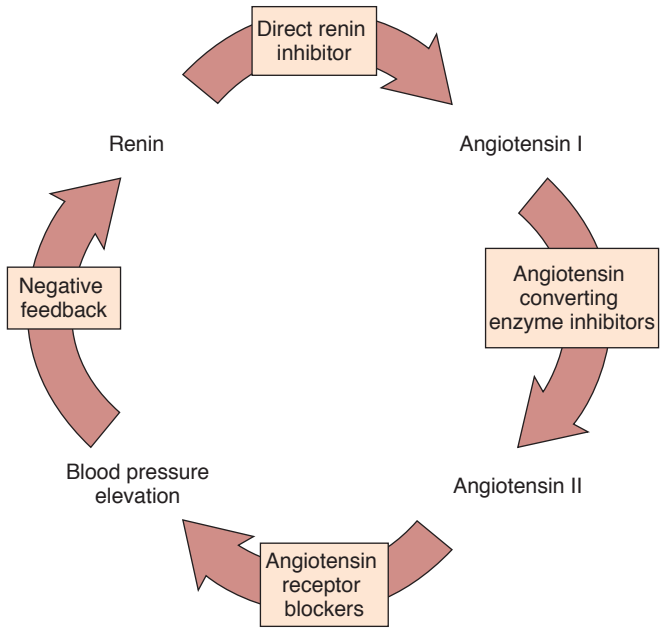


Figure 14.3 Site of action of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors within the renin-angiotensin system.

ACE inhibitors work synergistically with thiazide diuretics. In addition to the blood pressure lowering effects of ACE inhibitors, this class may be of particular benefit in patients with PAD, as they have been shown to improve endothelial dysfunction and vascular remodeling.[58] ACE inhibitors reduce cardiovascular morbidity and mortality, as has been observed in several randomized clinical trials.[42] In the HOPE study, patients with atherosclerotic vascular disease or diabetes had a reduction in the endpoints of acute myocardial infarction, stroke, and all-cause mortality when treated with an ACE inhibitor (ramipril), as compared with placebo.[59] This class of antihypertensives is of particular benefit for patients with hypertension and diabetes mellitus. In the UKPDS trial, which examined tight blood pressure control in patients with hypertension and diabetes, there was a reduction in the risk of death related to diabetes, as well as complications related to diabetes including progression of diabetic retinopathy and deterioration in visual acuity.[46] In addition, ACE inhibitors are beneficial to patients with diabetes, as they increase insulin sensitivity and may delay the onset of overt diabetes in patients with impaired fasting glucose.

Complications/Side Effects

A common side effect of ACE inhibitors is a dry cough, which is thought to be bradykinin mediated. ACE inhibitors are also associated with the rare, but potentially life-threatening, side effect of angioedema. Due to the common co-existence of renovascular disease in patients with PAD, caution must be used with the initiation of ACE inhibitors in this population to avoid the complication of acute kidney injury.[60] Hyperkalemia may also result from ACE inhibitor therapy, and this is of specific concern in patients with impaired renal function. Lastly, ACE inhibitors are contraindicated in pregnancy due to the known increased risk of cardiovascular and central nervous system congenital malformations.[61]

Angiotensin Receptor Blockers

Angiotensin II binds to the angiotensin (AT1) receptor, which triggers its downstream vasoconstrictive effects. ARBs work by inhibiting AT1 receptor. ARBs have similar indications to ACE inhibitors in regard to patient co-morbidities. Like ACE inhibitors, ARBs have significant benefits in regard to reduction in cardiovascular endpoints. The ARB, losartan, was studied in the Losartan Intervention for Endpoint reduction in hypertension (LIFE) trial, and in this large, randomized trial, patients with hypertension and left ventricular hypertrophy treated with losartan had a lower incidence of cardiovascular morbidity and mortality as compared with those treated with the beta blocker atenolol.[62] The ONgoing Telmisartan and in combination with Ramipril Global Endpoint Trial (ONTARGET) evaluated the ARB telmisartan in comparison to ramipril, and patients treated with telmisartan had equivalent outcomes with regard to cardiovascular events, and had a lower risk of angioedema.[63] The combination use of ACE inhibitors and ARBs was also evaluated in the ONTARGET study, and the combination was associated with an increased risk of adverse events without an improvement in clinical benefit.[63] In general, ARBs are better tolerated than

ACE inhibitors due to lower incidence of cough, and they carry a lower overall risk of hyperkalemia and angioedema.

Complications/Side Effects

Similarly to ACE inhibitors, ARBs have a risk of congenital malformations, and are therefore contraindicated during pregnancy.[64]

Calcium Channel Blockers

Calcium channel blockers (CCBs), work by interacting with the L-type voltage gated plasma membrane calcium channels to disrupt calcium transport. CCBs are subdivided into two groups: the dihydropyridines and the non-dihydropyridines. The dihydropyridines (e.g., amlodipine, nifedipine) are potent vasodilators. The non-dihydropyridines (e.g., diltiazem, verapamil) are negative chronotropic and inotropic agents. The dihydropyridines increase salt excretion and thus may be effective in patients who are unable to adhere to salt-restricted diets or those taking nonsteroidals (for which thiazide diuretics would be less effective). In addition, there is some evidence that CCBs may be of benefit to patients with claudication.[65] However, clinical guidelines do not support the use of CCBs as treatment for claudication. Patients with Raynaud's phenomenon also benefit from CCB treatment.

Complications/Side Effects

CCBs, specifically the non-dihydropyridines, must be used with caution in patients with underlying cardiac conduction abnormalities, as they will lower the heart rate. In addition, the dihydropyridines may cause lower extremity edema. The side effect of lower extremity edema can be reduced when CCBs are used in combination with a diuretic. Clinicians should be cautious when using these agents in combination with beta blockers due to the risk of bradyarrhythmia. Other common side effects include constipation and flushing.

Beta Blockers

The mechanism of action of beta blockers is to inhibit the beta adrenergic receptors. There are different categories of beta blockers, including nonselective beta blockers (e.g., propranolol), cardioselective beta blockers (e.g., atenolol, metoprolol), and beta blockers with alpha blocking properties (e.g., carvedilol). Beta blockers were previously considered first-line therapy for essential hypertension. However, several meta-analyses have been conducted that have called into question the role of beta blockers in the treatment of hypertension, and consequently, they are no longer recommended as first-line therapy.[66-70] Although no longer considered first line for treatment of hypertension, beta blockers are indicated for patients with the coexisting co-morbidities of coronary artery disease, congestive heart failure, angina, and atrial fibrillation. In addition, beta blockers may be useful in patients with hyperthyroidism as well as migraine headaches.

Complications/Side Effects

Beta blockers may cause reduced exercise tolerance and fatigue, which may be treatment limiting. Beta blockers also antagonize the bronchial beta receptors that mediate bronchodilation, and consequently, they may not be tolerated in patients with co-existing asthma or severe chronic obstructive pulmonary disease. Beta blockers also may cause metabolic derangements, including dyslipidemia and worsening insulin resistance. Caution must be used with regard to heart rate, especially in patients with underlying cardiac conduction abnormalities. This class of medications can mask hypoglycemic symptoms in diabetic patients, and may also predispose patients to depression. Previously, beta blockers were thought to be contraindicated in PAD due to the risk of exacerbating peripheral vasoconstriction; however, there is now evidence that beta blockers are safe in PAD.[71]

Loop Diuretics

Loop diuretics work in the thick ascending limb of the loop of Henle by blocking the reabsorption of sodium, chloride, and potassium. Because of their effectiveness at blocking sodium, and therefore water, reabsorption, and loop diuretics (e.g., furosemide, torsemide, bumetanide, ethacrynic acid), are particularly useful in patients in states of salt and volume excess (e.g., heart failure, renal failure). Generally, loop diuretics are thought to be less potent from an antihypertensive standpoint than thiazide diuretics, but they cause fewer metabolic derangements.

Complications/Side Effects

Volume depletion, as well as electrolyte abnormalities (specifically, hypokalemia), may occur with the use of loop diuretics. In addition, this class is associated with allergic reactions, especially in patients who are allergic to sulfa.

Potassium-Sparing Diuretics

The potassium-sparing diuretics, amiloride and triamterene, work in the distal convoluted tubule or collecting tubule, where they block the reabsorption of sodium without blocking potassium reabsorption. This class of medications is often used in combination therapy with diuretics to prevent the side effect of hypokalemia that is seen with diuretic therapy. These agents are frequently used in patients with hypertensive disorders associated with low potassium (e.g., primary aldosteronism).

Complications/Side Effects

Gastrointestinal side effects are associated with amiloride. Triamterene acts as a folate antagonist and is therefore contraindicated in pregnancy. Patients treated with this class of medications should be monitored for evidence of hyperkalemia.

Aldosterone Receptor Antagonists

Spironolactone and eplerenone, the aldosterone receptor antagonists, are effective at treating hypertension in patients particularly when it is associated with aldosterone excess. This class of medications is well studied in patients with heart failure with reduced ejection fraction, and has a mortality benefit in those patients.[72,73] Eplerenone is more selective than spironolactone, and has less of an impact on androgen and progesterone.

Complications/Side Effects

Spironolactone is associated with painful gynecomastia, erectile dysfunction, and irregular menses. These side effects may be treatment limiting. Eplerenone has an improved side effect

profile. Both medications are associated with hyperkalemia, and patients should be carefully monitored for this effect.

Alpha Blockers

Alpha blockers work by blocking the alpha adrenergic receptors. The use of this class of medications has decreased over time, particularly after the ALLHAT study showed an increased risk of heart failure in patients treated with the alpha blocker doxazosin.[56] The alpha blockers (e.g., terazosin, doxazosin) are of particular use in men who also have benign prostatic hypertrophy, as they have smooth-muscle relaxation properties and can relieve lower urinary tract obstructive symptoms. These medications may cause sodium retention, and concomitant use of a diuretic is often necessary. Nonselective alpha antagonists (e.g., phenoxybenzamine and phentolamine) are used primarily for the management of patients with pheochromocytoma.

Complications/Side Effects

The alpha blockers are associated with dizziness, orthostatic hypotension, fatigue, nasal congestion, and headache.

Centrally Acting Alpha Antagonists

The centrally acting alpha antagonists, clonidine and methyldopa, work to lower blood pressure by inhibiting sympathetic activity. Clonidine can be administered transdermally, which has the benefits of continuous drug delivery and improved adherence. Methyldopa is safe to use in pregnancy, and is most commonly used to manage hypertension in that setting.

Complications/Side Effects

Clonidine can cause fatigue and dry mouth, as well as impotence. The side effects of dry mouth and fatigue are attenuated with the transdermal preparation. An important consideration when using clonidine is the risk of rebound hypertension if the medication is abruptly stopped. Methyldopa also may cause fatigue, orthostatic hypotension, fluid retention, hepatotoxicity, and hemolytic anemia.

Direct Vasodilators

The role of direct vasodilators in the treatment of patients with hypertension is most commonly as a fourth-line agent in patients with refractory hypertension. These include direct arterial vasodilators like hydralazine. Hydralazine is commonly used in conjunction with nitrates for afterload reduction in patients with heart failure with reduced ejection fraction. It is approved as a fixed-dose combination drug with isosorbide dinitrate as BiDil, which is indicated in African American patients with systolic heart failure.[74] Another direct vasodilator, minoxidil, is generally used only in resistant hypertension and particularly in patients with impaired renal function. To prevent edema and tachycardia associated with minoxidil use, administration of alpha and beta blockers is frequently necessary.

Complications/Side Effects

Hydralazine is associated with sodium retention, reflexive tachycardia, and may also cause drug-induced lupus. Minoxidil is associated with fluid retention, tachycardia, and hirsutism.

Renin Inhibitors

Aliskiren, a direct renin inhibitor, was approved for use in the treatment of hypertension by the Food and Drug Administration in 2007. Aliskiren blocks the first step in the renin-angiotensin-aldosterone system. It has been shown to have equal efficacy in reducing blood pressure as compared to ACE inhibitors, ARBs, and diuretics.[75] When aliskiren is used in combination with ACE inhibitors or ARBs, the blood pressure reduction is greater than with monotherapy.[76,77] However, the use of combination therapy has been called into question, and as a result, the U.S. Food and Drug Administration (FDA) has cautioned against the use of aliskiren in combination therapy with ACE inhibitors or ARBs. This is largely based on the results of the Aliskiren trial in type 2 diabetes using cardiorenal endpoints (ALTITUDE) trial that showed that patients treated with combination therapy had a higher rate of adverse events (cardiovascular and renal events), and had higher rates of hyperkalemia.[78,79] Given the side effect profile of this medication, it is not commonly used.

Complications/Side Effects

Aliskiren is associated with angioedema, hyperkalemia, and diarrhea. This medication is also contraindicated in pregnancy.

Emerging Therapies

Experimental Invasive Therapies

In addition to lifestyle modifications and antihypertensive pharmacotherapy for hypertension, new technologies are currently being evaluated.

The carotid sinus baroreceptors play an important role in blood pressure regulation. Stimulation of the carotid sinus, via an implanted device, has been under investigation as an option for treatment of patients with resistant hypertension. The first generation of carotid sinus simulators, the Rheos device, is a surgically implanted pulse generator, bilateral carotid leads, and a programmer system.[80,81] The Rheos system was evaluated in the Phase III Rheos Pivotal Trial which was a double-blind, randomized, placebo-controlled trial.[82] This trial showed a significant benefit for patients who had the Rheos device implanted with regards to efficacy and device safety, but the trial did not meet the endpoints for acute responders or procedural safety.[82] As a result, the usage of this technology has been limited. Currently, a second-generation carotid sinus baroreceptor activation system is under evaluation, the Neos system. Further trials are necessary to evaluate the safety and role of carotid baroreceptor therapy for the treatment of patients with resistant hypertension.

In patients with resistant hypertension, increased sympathetic nervous system activity is present and can be difficult to treat pharmacologically.[83] A concept which grew out of this idea was that the sympathetic renal innervation could be interrupted, and thus blood pressure would be reduced due to the decrease in sympathetic activity. Renal denervation is a minimally invasive, catheter-based procedure that uses radiofrequency pulses in the adventitial layers of the renal arteries to ablate the nerves in the vascular wall and reduce sympathetic tone (Fig. 14.4). Renal

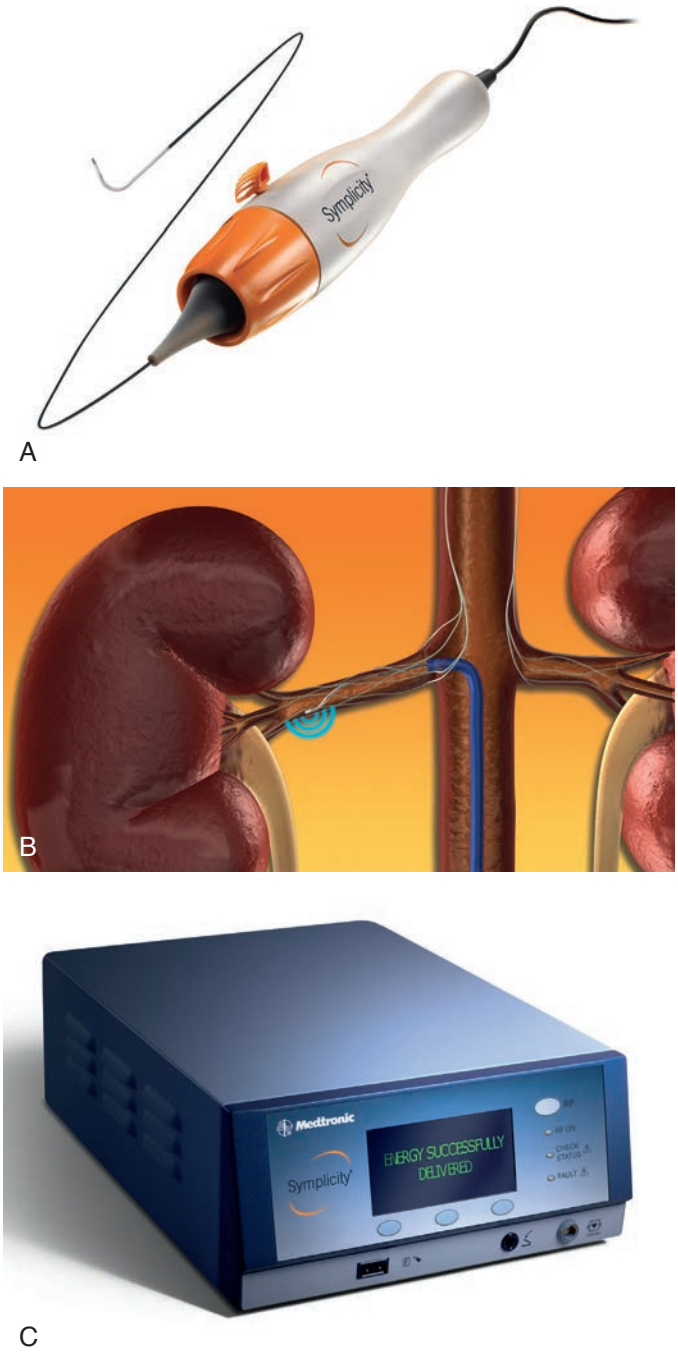


Figure 14.4 Ardian Symplicity Catheter System (A-C) which delivers radiofrequency energy from within the renal artery (B) to block conduction in the surrounding renal nerves, thereby counteracting chronic activation of the sympathetic nervous system. (Courtesy of Medtronic Simplicity Catheter System, www.whichmedicaldevice.com.)

denervation results in a decrease in renal sympathetic afferent and efferent activity, which indirectly results in a reduction in blood pressure.[84] The initial clinical trials involving catheter-based renal denervation, SYMPLICITY HTN-1 and -2, showed significant and sustained reductions in blood pressure.[84,85] These trials were open label, uncontrolled trials, which showed reductions in SBP by as much as 33 mm Hg for up to 3 years post-denervation. These initial results were very promising. To further evaluate the role of this technology, the SYMPLICITY HTN-3 was conducted, which was designed as a prospective, single-blinded randomized controlled trial with a sham procedure arm.[86] The results of SYMPLICITY HTN-3 stand in contrast to the previous two studies. In this trial, patients who received renal denervation had a reduction in SBP of only 2 mm Hg more than sham-operated patients at 6 months.[86] The explanation for the significant discrepancy between the first two SYMPLICITY trials and the third trial is not clear, but some have surmised that the extent of renal denervation may have not been adequate and there may have been significant variation in the extent of denervation within the trial.[87] Consequently, new technologies are currently being developed to improve the denervation procedure. Overall, catheter-based renal denervation is a novel, minimally invasive technique that may have a role in the future in the treatment of resistant hypertension.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 15

Atherosclerosis Risk Factors: Familial Arteriosclerosis

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Atherosclerosis is a disease in which plaque builds up inside of artery wall, causing the thickening and narrowing of arteries, thereby reducing blood supply to the end organs. Plaque is made up of fatty substances, cholesterol, cellular waste products and debris, calcium, fibrin, inflammatory cells, and platelets.[1,2] It can affect any artery in the body, including arteries in the heart, brain, kidneys, and legs.

Atherosclerosis is the result of nonresolving interactions of inflammation, oxidative stress, lipid deposition, and genetic predisposition.[3] In addition, a novel concept for atherosclerosis risk implicates a lack of endothelial progenitor cell (EPC)–dependent arterial repair in the development of the disease, secondary to the exhaustion of repair-competent EPCs. Molecular evidence derived from genetic techniques indicates that atherosclerotic lesions may begin to form as arterial repair fails, rather than merely following arterial injury. Thus chronic arterial injury may overwhelm the ability of EPCs to maintain arterial homeostasis, particularly when EPCs capable of arterial repair become exhausted. Imbalance between arterial damage and repair leads to atherosclerosis (Fig. 15.1).[4,5]

Atherosclerosis is probably one of the most complex of all disorders, with multiple genetic and environmental contributions. Of the major genetic risk factors, family history is the most significant independent one.[6-8] Familial hypercholesterolemia (FH), familial hypertension, familial diabetes, and familial obesity are at the top of the list of heritable and genetic risk factors. Moreover, these multiple heritable and genetic risk factors can cluster, in many cases, in families. Although FH is the best-characterized heritable risk factor in familial arteriosclerosis, it explains only a small percentage of disease susceptibility. Most of the clinical atherosclerotic diseases result from the interactions of multiple genetic and environmental factors, none of which usually can cause disease by itself.

FAMILIAL HYPERCHOLESTEROLEMIA

FH is an inherited metabolic disorder characterized by severe hypercholesterolemia due to the accumulation of low-density lipoprotein (LDL) in the plasma with cholesterol deposition in tendons and occasionally in skin and an increased risk of premature atherosclerosis manifesting almost exclusively as precocious CAD.

FH is an autosomal dominant disease caused by mutations in the genes encoding the LDL receptor (LDLR), which normally removes LDL from the circulation; apolipoprotein B (ApoB), which is the part of LDL that binds with the receptor; or proprotein convertase subtilisin/kexin type 9 (PCSK9), which induces degradation of LDLR; and the adaptor protein, or autosomal recessive hypercholesterolemia (ARH) protein (LDLRAP), which facilitates the clearance of circulating LDL

Abstract

Atherosclerosis is the principal cause of coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral artery disease (PAD) and represents a leading global cause of death and disability. Atherosclerosis is one of the most complex disorders with multiple genetic and environmental contributions. This chapter reviews numerous genetic and environmental risk factors for cardiovascular diseases associated with atherosclerosis. Of the major genetic risk factors, family history is the most significant independent one. Familial hypercholesterolemia, familial hypertension, familial diabetes and familial obesity are at the top of the list of heritable and genetic risk factors. Moreover, these multiple heritable and genetic risk factors also cluster, in many cases, in families. Although familial hypercholesterolemia is the best-characterized heritable risk factor in familiar arteriosclerosis, it explains only a small percentage of disease susceptibility. On the other hand, the major environmental risk factors are cigarette smoking, unhealthy diet, physical inactivity and infection. Most cases of myocardial infarction and stroke result from the interactions of multiple genetic and environmental factors, none of which can cause disease by itself.

Keywords

Atherosclerosis
Arteriosclerosis
Familial Arteriosclerosis
Genetics of Cardiovascular Disease
Familial Hypercholesterolemia

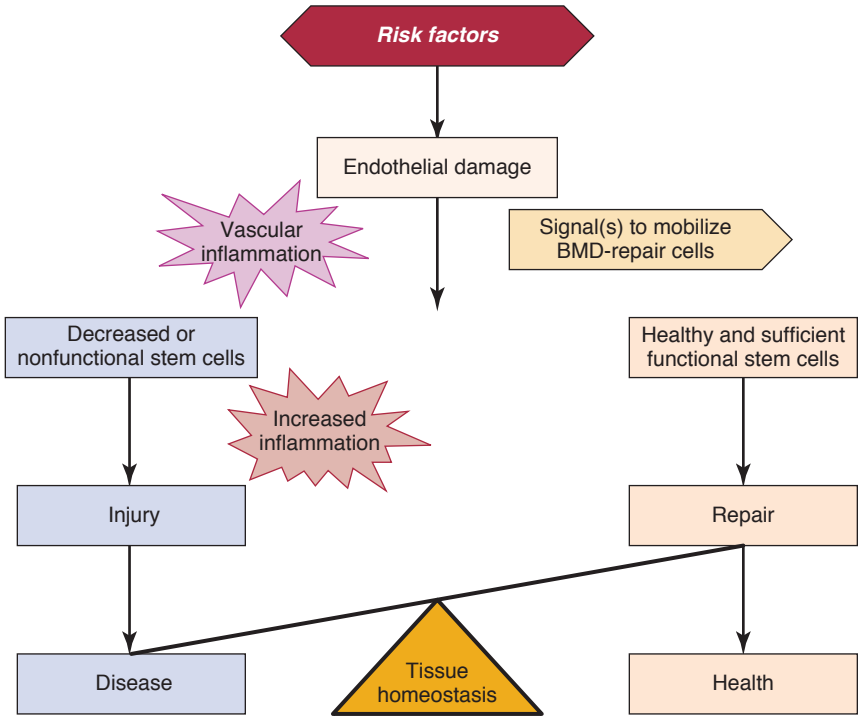

Figure 15.1 Imbalance between arterial damage and repair leads to atherosclerosis. Dysfunction of bone marrow–derived (BMD) stem cells or EPC-dependent arterial repair likely tips the balance toward the development of atherosclerosis.

(Fig. 15.2).[9] Mutations in these genes result in loss of function of these molecules and contribute to elevated plasma levels of LDL. Defects on the first three genes cause both homozygous and heterozygous phenotypes, whereas defects on the latter cause only the homozygous phenotype. People who have one abnormal copy (are *heterozygous*) in one of three genes *(LDLR, ApoB, PCSK9)* may have premature CAD at the age of 30 to 40. Having two abnormal copies (being *homozygous*), either biallelic pathogenic variants in one of these known genes or one pathogenic variant in each of two different genes, may result in severe CAD in childhood.

Heterozygous FH (HeFH) is more common and accounts for 60% to 80% of FH, with a prevalence estimated at 1 per 200 to 500 of persons with FH. Persons with untreated FH are at an approximately 20-fold increased risk for CAD. Untreated men are at a 50% risk for a fatal or nonfatal coronary event by age 50 years; untreated women are at a 30% risk by age 60 years. In contrast, homozygous FH (HoFH) is much rarer with a prevalence of about 1 per 160,000 to 1 million. Most individuals with HoFH experience severe CAD by their mid-20s. The rate of death or coronary bypass surgery by the teenage years is high. Severe aortic stenosis is also common.[10,11]

Cholesterol is a fatlike substance used by cells to synthesize hormones, vitamin D, and substances that help with food digestion. However, if too much cholesterol is present in the bloodstream, it builds up in artery walls and increases the risk of atherosclerosis. All nucleated cells can synthesize the enzymes to produce cholesterol. This synthetic pathway produces cholesterol as well as other isoprene products involved in the prenylation of proteins and the synthesis of ubiquinone. The rate-limiting enzyme in this pathway is 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The product of HMG-CoA reductase, mevalonic acid, appears in plasma and urine and may be used as a guide to cholesterol synthetic activity.

Cholesterol is carried in the bloodstream in small packages called lipoproteins, which are made up of lipid on the inside and proteins on the outside. There are two main kinds of lipoproteins: LDL and high-density lipoprotein (HDL). People who have FH have high levels of LDL because they cannot properly remove the LDL from the bloodstream. HDL carries cholesterol from other parts of the body to the liver, where it is removed from the body. Higher levels of HDL lower a person's chances for getting CAD.

LDL binds to LDLR, a well-characterized transmembrane protein that resides on the cell's surface.[12] Upon LDL binding with LDLR, the bound complex of LDL/LDLR is internalized. Once in the endosome, the LDLR dissociates from the lipoprotein during acidification. Thereafter, the lipoprotein proceeds to the lysosome for enzymic degradation into its constituent cholesterol, fatty acids, and amino acids. The dissociated LDLR can be retransported back to the cell surface and recycles approximately 150 times before degradation.[13]

The defect of LDLR results in accumulation of LDL in the bloodstream, leading to FH. Numerous defects in the LDLR have been divided into six classes, depending on the impact of the mutation on the presence of mRNA, receptor maturation in cells, disparity between LDL and immunoglobulin binding on the cell surface, and LDLR degradation and trafficking.[14] Class 1 defects, mainly due to promoter mutations, leave no detectable miRNA and no detectable LDLR. Class 2 defects are due to mutations that retard the maturation of the LDLR by glycosylation, either in a limited fashion (class 2B) or completely (class 2A). Mutations such as D206E have persistent folding defects, demonstrable on nuclear magnetic resonance

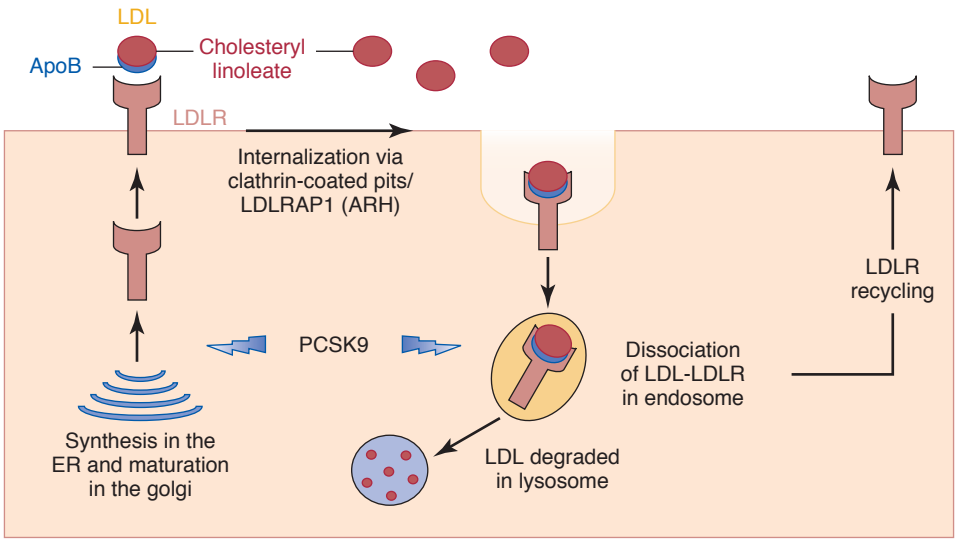

Figure 15.2 The LDL-receptor pathway for uptake and degradation of LDL. The LDL receptor is a cell-surface glycoprotein that is synthesized as an immature protein and processed in the Golgi apparatus, producing the mature form that is transported to the cell surface. There, the receptor specifically binds apoB in LDL particles present in the extracellular fluid. The receptor–ligand complex is then internalized by endocytosis via clathrin-coated pits through interactions involving LDLRAP1 (ARH). The complex is transported via early endosomes to the late endosomal compartment, where the acidic environment causes dissociation of the receptor–ligand complex. The receptor is recycled to the cell surface while the LDL particle is degraded in the lysosomal compartment. Accumulation of free cholesterol released by hydrolysis of cholesteryl esters in the core of LDL inactivates sterol regulatory element binding protein (SREBP), a transcription factor that drives expression of genes for enzymes involved in cholesterol synthesis and the LDL receptor. Thus the LDL-receptor pathway maintains intracellular cholesterol homeostasis. The PCSK9 normally reduces the LDL–protein content of cells by a post-translational mechanism that is not yet fully understood. Mutations in *LDLR, ApoB, LDLRAP1,* or *PCSK9* are known to result in FH. *ApoB,* Apolipoprotein B; *ARH,* autosomal recessive hypercholesterolemia; *FH,* familial hypercholesterolemia; *LDL,* low-density lipoprotein; *LDLRAP1,* low-density lipoprotein receptor 1; *PCSK9,* proprotein convertase subtilisin/kexin type 9.

spectroscopy, which will influence maturation.[15] In class 3, the defective LDLR mature normally but have defects in binding the ligand. In class 4, mutated LDLR mature normally to occupy the cell membrane but are not internalized, typically due to mutations in the cytoplasmic tail. Class 5 mutations relate to LDLR degradation that prevents receptors from reaching the cell surface and from recycling to the cell surface. Class 6 mutations are due to a failure of directing LDLR to the basolateral surface of polarized cells.[16] Although defective hepatic LDL uptake is the main and most direct consequence, other metabolic perturbations may contribute to the metabolic characteristics and accelerated atherosclerotic disease associated with FH.

The defective apoB100 is another common reason for FH. Compared with the numerous mutations found in the LDLR and its pathway, very few mutations have been reported in apoB100 that will disrupt the binding of LDL to the LDLR. Individuals with heterozygous familial binding defective apoB100 (FDB) exhibit cholesterol levels of about 300 mg/dL due to defective LDL clearance.[3] In homozygous FDB, there appears to be no significant gene dose effect.[17] Two homozygotes for FDB were reported to have cholesterol concentrations in the range of heterozygotes for LDLR mutations.[18] The binding affinity for LDLR of very low density lipoprotein (VLDL) was normal in these subjects, whereas LDL affinity was 10% of normal.

An alternative mechanism for FH is mutations in the *PCSK9* gene. PCSK9 protein binds to LDLR and induces LDLR degradation.[19] PCSK9 degrades LDLR by preventing the hairpin conformational change of LDLR.[20] Reduced LDLR levels result in decreased clearance of LDL, which can lead to hypercholesterolemia. Mutations in *PCSK9* have been known to cause autosomal dominant hypercholesterolemia.[21]

Mutations in ARH, the adaptor protein, can impair the internalization of LDLR.[22,23] Disruption of LDLR endocytosis in some FH patients affects the clearance of LDL by the liver and is therefore responsible for the HoFH phenotype.

FAMILIAL HYPERTENSION

Hypertension is a well-known risk factor for atherosclerosis.[24] Over time, this extra pressure can damage the arteries, making them more vulnerable to the plaque buildup associated with atherosclerosis. Hypertension tends to be familial and is likely to be the consequence of an interaction between genetic and environmental factors. About 30% to 50% of the variance in blood pressure readings is attributable to genetic heritability and about 50% to environmental factors.[25] The heritability of blood pressure frequently ranges about 50% to 70% in twins, with considerably lower estimates (around 20% to 25%) in family studies.[26-28] In spite of substantial efforts and progress

in elucidating the genetic basis for heritable hypertension, the genetic factors contributing to common forms of hypertension remain largely unknown. The genetics of hypertension is complex, with no known single gene playing a major role but rather many genes, each with mild effects, reacting to different environmental stimuli and thus contributing to elevated blood pressure. Early studies in hypertension identified specific enzymes, channels, and receptors implicating sodium handling in the regulation of blood pressure, including genes involved in the renin-angiotensin-aldosterone system (RAAS), controlling blood pressure and saltwater homeostasis, proteins in hormonal regulation of blood pressure (enzymes and receptors of the mineralo- and glucocorticoid pathways), and proteins coded by genes involved in the structure and/or regulation of vascular tone (endothelins and their receptors).[29] RAAS plays an important role in regulating blood pressure and during hypertensive crises (Fig. 15.3).[30] The enzyme renin acts on angiotensinogen (AGT) to generate angiotensin I (Ang I). Ang I is further converted to angiotensin II (Ang II) by angiotensin converting enzyme (ACE). Ang II exerts its effects by binding to two major types of receptors—AT1R and AT2R.[31] Functions like vasoconstriction, cellular proliferation, cellular hypertrophy, fibrosis, atherosclerosis, antinatriuresis, and the release of aldosterone, endothelin, norepinephrine, and vasopressin are initiated by the binding of Ang II to AT1R. In addition, Ang II directly stimulates vascular smooth muscle cell (SMC) growth and extracellular matrix production. Studies with spontaneously hypertensive rats indicate that raised blood pressure stimulates the expression of platelet-derived growth factor (PDGF), a potent mitogen for SMC.[32] Furthermore, both renin receptors (recently identified) and functionally active Ang II-derived peptides like Ang 1 to Ang 7 have been shown to play pathologic roles in the development of hypertension.[33] Both linkage and association studies have provided strong evidence for the role of the AGT gene in hypertension in Caucasian and African/Caribbean populations as well as in pregnancy-induced hypertension.[34]

The kidney is known to be the dominant, long-term regulator of blood pressure,[35-37] highlighting the need for an appreciation of its pathophysiology in considering genetic factors potentially contributing to hypertension. Moreover, pheochromocytoma is a rare cause of hypertension that may be familial.

FAMILIAL DIABETES

Cardiovascular disease (CVD) is more prevalent in type 1 and type 2 diabetes (T1D and T2D) and continues to be the leading cause of death among adults with diabetes. T2D, commonly referred to as insulin resistance, is partly inherited.[38]

Insulin resistance is also associated with the enhanced generation of reactive oxygen species (ROS). In addition, insulin resistance decreases NO production,[39-41] and increases the release of free fatty acids from adipose tissue. Increased circulating

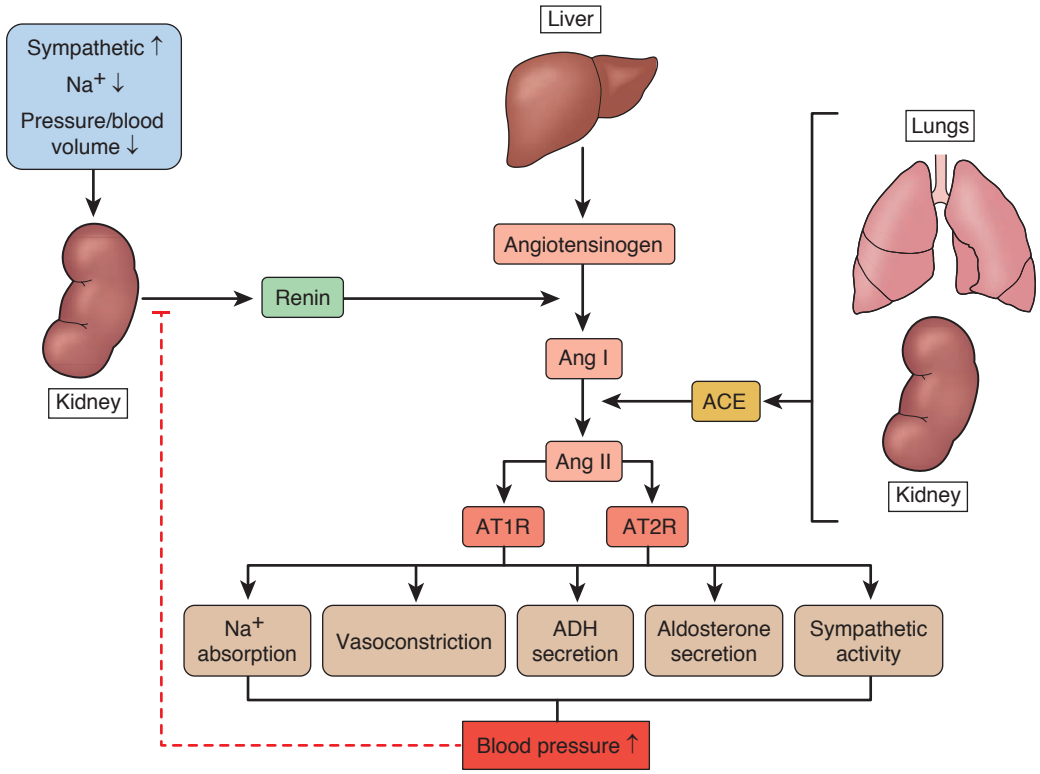

Figure 15.3 Renin-angiotensin-aldosterone system (RAAS). When renin is released into the blood, it acts upon angiotensinogen, which undergoes proteolytic cleavage to form Ang I. Vascular endothelium, particularly in the lung and kidney, produces ACE, which cleaves off two amino acids to form Ang II. Ang II binds with AT1R and AT2R to exert its effect on increasing blood pressure. High blood pressure inhibits renin production by kidney. *ACE,* Angiotensin converting enzyme; *Ang I,* angiotensin I.

levels of free fatty acids may impair endothelial function[40-42] and induce low-grade inflammation.[41,42] Hyperinsulinemia augments VLDL synthesis in liver; increases cholesterol transport/synthesis in cultured arterial SMCs; stimulates the proliferation of arterial SMCs; augments collagen synthesis and turns on multiple genes involved in inflammation.[43,44] Although insulin receptors are expressed on endothelial cells, vascular SMCs, and macrophages, it remains unclear whether the vascular insulin receptors contribute directly to the vascular pathology of metabolic insulin resistance.[45]

A subset of insulin-resistant individuals develop non–insulin-dependent diabetes mellitus (NIDDM), characterized by an insufficient insulin secretory capacity to maintain normal glucose levels. A genome scan identifies a major NIDDM susceptibility locus, designated NIDDM1, on chromosome 2q. Using linkage disequilibrium mapping, scientists have shown that an intronic polymorphism in the calpain-10 gene is strongly associated with the disease.[46] A second locus for diabetes has been identified on chromosome 1q.[47-50] It is interesting to note that the chromosome 1 locus was initially linked with familial combined hyperlipidemia (FCH) in a set of Finnish families, and that FCH overlaps with diabetes.[51]

Advances in genotyping technology have facilitated rapid progress in large-scale genetic studies. Genome-wide associated studies (GWAS) and linkage analyses have identified greater than 120 genetic variants associated with T2D and diabetes-related traits.[52-55] Most of these variants are noncoding variants; therefore, their functional consequences are challenging to investigate. However, many of the variants identified to date regulate insulin secretion and not insulin action in insulin-sensitive tissues.

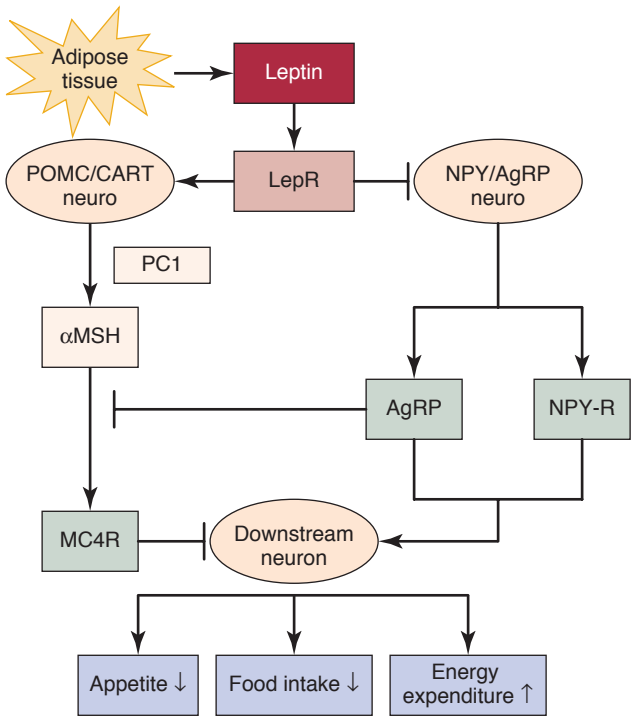

Figure 15.4 Influence of the leptin-melanocortin pathway on food intake and energy expenditure. Leptin secreted from adipose tissue binds to the leptin receptor (LepR) in the hypothalamus. Leptin binding inhibits the neuropeptide Y/agouti-related protein (NPY/AgRP) production and stimulates pro-opiomelanocortin (POMC) production, which undergoes posttranslational modifications to produce peptides such alpha-melanocyte-stimulating hormone (αMSH) via the processing of prohormone convertase 1 (PC1). αMSH binds to melanocortin 4 receptors (MC4R) and induce downstream events of food intake and energy consumption.

FAMILIAL OBESITY

Although some studies have suggested that obesity is not an important contributing cause of atherosclerosis and CAD,[56,57] recent evidence indicates that obesity is a major contributor to CVD risk and mortality.[58-60] Obesity exhibits considerable metabolic overlap with the abnormalities present in individuals with T2D and is associated with other cardiovascular factors such as hypertension, hyperlipidemia, and insulin resistance.[61,62]

Obesity is a complex disease resulting from the interaction of a wide variety of hereditary and environmental factors. Clustering of cases within a family, the congruence of body weight in monozygotic twins, and the discovery of genes associated with obesity all suggest genetic involvement in obesity. Obesity risk is 2-8 times higher for a person with a family history as opposed to a person with no family history of obesity, and an even higher risk is observed in cases of severe obesity. Occurrences of monogenic types of obesity are evidence that obesity may be caused by genetic mutations (http://obesity.ulaval.ca/obesity/generalities/genetic.php). Eight monogenic genes and four polygenic genes have been associated with obesity.[63] The cloning of the mouse ob gene and its human homologue, leptin,[64] has proved to be a paradigm for the field, resulting in the identification of many genes involved in the regulation of appetite, food intake, and energy expenditure via the leptin–melanocortin pathway (Fig. 15.4). These variants account for some 5% of morbid human obesity and include leptin[65] and its receptor,[66] the α-melanocortin–stimulating hormone receptor (MC4R),[67,68] pro-opiomelanocortin (POMC),[69] and prohormone convertase-1.[70] Moreover, the association of additional genes with obesity has recently been identified by GWAS (*SH2B1, KCTD15, MTCH2, NEGR1,* and *BDNF*) with dietary intake and nutrient-specific food preferences.[71] This is in line with the fact that food intake–related parameters are heritable[72] and are strongly correlated with body mass index (BMI).[73]

Other genes such as *fat mass and obesity-associated (FTO); PCSK1;* and *catenin, beta-like 1 (CTNNBL1)* are also associated with obesity. In addition, more than 150 loss-of-function coding mutations have been associated with monogenic obesity,[74] and two infrequent gain-of-function coding polymorphisms (V103I and I251L) have been associated with protection from obesity.[75,76]

GENETICS OF PERIPHERAL ARTERY DISEASE

PAD is a disease characterized by reduced blood flow to the lower extremities, most often because of atherosclerosis and

can be considered a marker of widespread atherosclerosis. However, PAD is a distinct subtype of atherosclerotic vascular disease that differs from CAD and CVD in its clinical manifestations. Thrombus formation resulting from acute rupture or erosion of a vulnerable plaque in the coronary or cerebral arterial beds leads to acute events such as myocardial infarction (MI) or stroke. Such acute events are relatively uncommon in PAD, and symptoms most often result from progressive arterial narrowing because of ongoing atherogenesis. The underlying reasons for the differences remain unknown. It is therefore likely that risk factors, both genetic and environmental, and the intermediate biochemical pathways through which they act contribute differently to PAD than to CAD or CVD. Although traditional cardiovascular risk factors have been associated with the development of PAD, relatively few genetic variants that influence susceptibility to PAD have been discovered. This may be partly because of the greater clinical and genetic heterogeneity in PAD.[77] Phenotypic heterogeneity seems to be a major challenge in investigating the genetic basis of PAD.

PAD is complex and heterogeneous; it is not a uniform entity. Two broad subtypes of PAD, proximal and distal, are associated with distinct risk factor and comorbidity profiles.[78] Female sex, smoking, hypertension, and dyslipidemia are more significantly associated with proximal disease, whereas older age, male sex, and diabetes are more significantly associated with distal, small vessel disease. The candidate genes include β-fibrinogen,[79] apoB,[80] endothelial nitric oxide synthase (eNOS), methylene tetrahydrofolate reductase,[81] G protein β3, α-adducin,[82] IL-6,[83] and glutathione S-transferase.[84] However, any reported associations between variants in these genes and PAD have not been confirmed in independent cohorts or in GWAS. Moreover, genetic analyses do not appear to be as useful as in CAD in determining progression of the disease or its tendency to remain stable.[85]

A linkage analysis using a 10-cM genome-wide scan in 272 PAD patients from 116 extended families has identified a region on chromosome 1 between 100 and 110 cM (logarithm of the odds score, 3.93; $P = 1.04 \times 10^{-5}$) associated with PAD. Several candidate genes (in pathways of inflammation, coagulation, lipid metabolism, blood pressure regulation, and vascular matrix regulation) for atherosclerosis are present under the linkage signals, but the causal variants cannot be identified.[86] Association studies using the GWAS approach identified only a few loci having weaker associations with PAD.[87]

Similar to CAD, several Mendelian disorders are associated with PAD. These include familial lipoprotein disorders, such as chylomicronemia resulting from mutations in the lipoprotein lipase gene and FH,[88,89] hyperhomocysteinemia,[90] and pseudoxanthoma elasticum.[91] In a family history study including 2296 PAD cases and 4390 controls, the prevalence of a family history of PAD was significantly higher among patients with PAD than in controls, resulting in a doubling of the odds of the presence of PAD in those with family history of PAD.[92] The association is stronger in individuals less than 68 years of age and in those with a greater number of affected relatives. In another study conducted in a twin population, the odds ratio of having PAD among individuals whose twins had PAD compared with individuals whose twins did not have PAD was 17.7 for monozygotic twins and 5.7 for dizygotic twins.[93]

INFLUENCE OF NONGENETIC FACTORS

Although the critical roles of genetic factors in atherosclerotic vascular disease have increasingly being recognized, the specific etiology in many cases remains unknown, with nongenetic risk factors believed to be important contributors. It is now generally considered that atherosclerosis results from a variety of genetic causes, with added epigenetic modulation and the interaction of genetic and environmental factors. None of these triggers is sufficient to cause atherosclerosis on its own.

Environmental Factors

Accumulating evidence strongly supports the existence of gene-environment interactions in atherosclerosis.[94-99] The genetics of atherosclerosis-induced CVDs involves a large number of genes having weak effects on disease risk, but possibly interacting with each other and with environmental factors could act synergistically in the pathogenesis of atherosclerosis and its complications. Gene-environment interactions can be either complementary or antagonistic.[100] Complementary gene-environment interactions may play a substantial role in CAD risk only when an individual with a high-risk genetic profile enters a high-risk environment; that is, the effect on risk will then be so great that premature CAD develops. Indeed, a large number of studies have shown significant gene-environment interactions in the etiology of obesity as well as in the pathogenesis of T2D and CAD.[101-103]

Epigenetic Factors

Epigenetics plays important roles in the modulation of gene expression and activity. Epigenetics represents a critical link between genomic coding and phenotype expression that is influenced by both underlying genetic and environmental factors. Epigenetic modifications may contribute to subclinical and clinical CAD, CVD, and PAD.[104] *Epigenetics* refers to changes in gene expression resulting from factors other than a direct change in the DNA sequence of the genome. Epigenetic mechanisms for the regulation of gene expression include DNA methylation, posttranslational histone modifications, and post-transcriptional modifications such as small noncoding miRNA (Fig. 15.5).[105] Alteration of gene expression regulated by epigenetics is heritable. Epigenetic inheritance is an essential mechanism that allows the stable propagation of gene activity states from one generation of cells to the next.[106]

RISK ASSESSMENT AND DIAGNOSIS

The Framingham Risk Score (www.bestsciencemedicine.com/chd/calc2.html) is a popular tool for risk assessment in patients without inherited CAD-associated diseases. For patients with

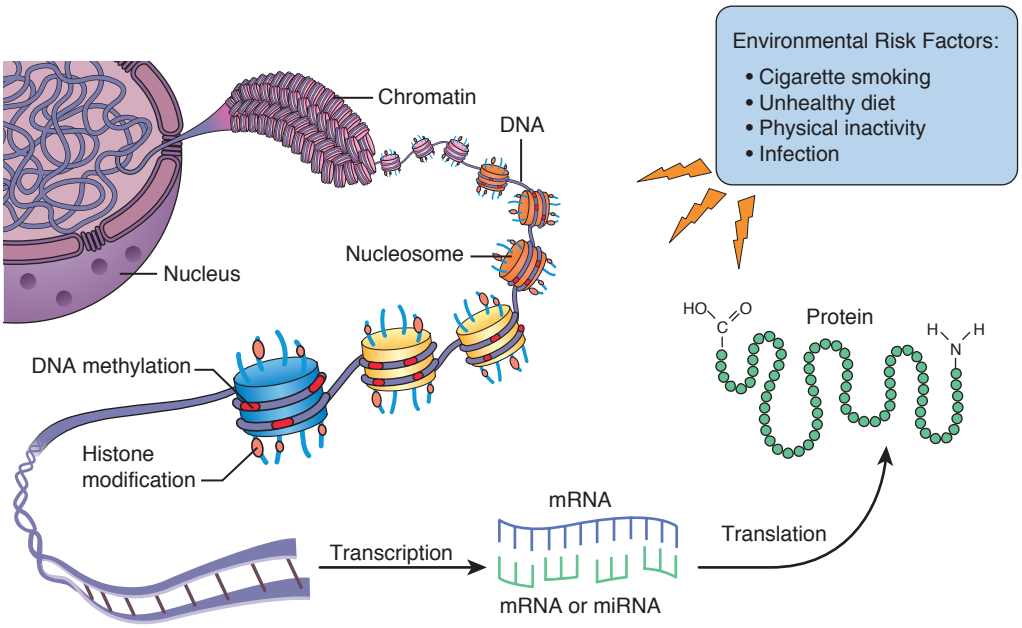

Figure 15.5 Overview of gene expression regulated by epigenetic mechanisms. Histone modifications, DNA methylation, and noncoding (micro)RNAs mediate influence from environment on gene transcription and translation. (Modified from Dr. Clarissa Gerhäuser. Cancer Prevention and Nutrition. *Lab&More int* 4, 2014.)

genetic susceptibility to CAD, family history plays a critical role in assessing the risk. Pedigree is a commonly used family history assessment tool. Family history along with emerging new genetic markers and traditional biomarkers—including lipid profile, glucose, and hormone level and established physiologic biomarkers such as serum ferritin, triglyceride-HDL ratio, lipophorin-cholesterol ratio, lipid-lipophorin ratio, lipophorins-LTPs ratio, LDL, HDL and apolipoprotein levels, sphingolipids, omega-3 index, and ST2 level—are employed in the prediction and diagnosis of a variety of familial inherited diseases.

Familial Hypercholesterolemia: The diagnosis of both HoFH and HeFH is based primarily on the finding of severe LDL elevations in the absence of secondary causes of hypercholesterolemia (Table 15.1). Findings on lipid analysis in patients with FH include the following:

Homozygous Familial Hypercholesterolemia: Severely elevated cholesterol levels (total cholesterol and LDL levels >600 mg/dL). Triglyceride levels remain within the reference range. A substantial increase in serum triglyceride levels should raise the possibility of another lipid disorder. Patients with a HoFH phenotype should be referred to specialized centers for diagnostic workup and management.

Heterozygous Familial Hypercholesterolemia: If the LDL level is commonly greater than 250 mg/dL, HeFH is suggested; in patients less than 20 years old, an LDL level greater than 200 mg/dL is highly suggestive of HeFH or, possibly, a familial ligand defective apoB-100; in adults, LDL levels greater than 300 mg/dL suggest HeFH. If tendon xanthomas are present in a patient with an LDL level above the 95th percentile, a probable diagnosis of HeFH can be made.

A careful family history is essential for the comprehensive assessment of possible FH in general and HoFH in particular. In the case of autosomal dominant mutations (in *LDLR*, *PCSK9*, and *APOB* genes), both parents are obligate heterozygotes and therefore display elevated LDL levels (frequently >95th percentile) and a strong positive family history of premature CVD (<55 years in men and <60 years in women among first-degree relatives). In the case of *LDLRAP1* mutation–induced ARH, parents may exhibit normal LDL levels, and determination of an extended family pedigree may reveal an autosomal recessive pattern of inheritance. Systematic cascade or opportunistic screening offers prospective parents with HeFH the possibility of making informed decisions prenatally and

TABLE 15.1 Diagnostic Criteria for Familial Hypercholesterolemia

Fm Family history	Premature CAD (>55 years in men and <60 years in women among first-degree relatives) >95 percentile for age and gender in first- or second-degree relatives)
Cli Clinical history	Pat Patient with premature CAD and/or CVD
La Laboratory examination	Ge High LDL levels (>250 mg/L in adult; >200 mg/L in patients <20 years old)
P Physical examination	Tendonxanthomas: arcus cornealis
Ge Genetic test	Ge Gene mutation in LDLR, ApoB, or PCSK9.
No No secondary causes of hyperlipidemia	Ge Normal liver enzymes, renal function, thyroid hormones No hyperglycemia or albuminuria

ApoB, Apolipoprotein B; *LDL,* low-density lipoprotein; *LDLR,* low-density lipoprotein receptor; *PCSK9,* proprotein convertase subtilisin/kexin type 9.

identifying HoFH patients at birth, thereby allowing for the early initiation of treatment. Identification of HoFH can also guide reverse cascade screening for parents and relatives to identify patients with FH.

Definitive diagnosis can be made only with gene or receptor analysis. The genetic diagnosis is popularly made by polymerase chain reaction (PCR) for LDLR and ApoB defects. Only a few mutations are known in ApoB, but there are more than 750 mutations in LDLR. New technology, such as next-generation sequencing and RNA-seq, may provide in-depth evaluation for many mutations. These new technologies are currently available in some medical centers for genetic diagnosis. In populations with founder effects, genetic diagnosis is easier. In other populations, where hospitals can sequence the genes in affected families, genetic diagnosis can be made in family members. Moreover, cell culture is more reliable in identifying LDLR defects. In fibroblast cultures, LDLR mutations will result in low binding, whereas adaptor protein mutations will not. It is worth considering measurement of plasma phytosterols for phytosterolemia and cholestanol for cerebrotendinous xanthomatosis and investigating the genes influencing the concentration of these products.

Familial Hypertension

A family history of hypertension is twice as common in the hypertensive population than in those who are normotensive. As described earlier, a polygenic model of inheritance has been found. Genetic factors include an inherited defect in cellular sodium transport as well as abnormal response to psychogenic stress. Therefore family history and genetic markers are included in the family hypertension workup. Other factors to be investigated include T2D, dyslipidemia, BMI, sex, age, smoking, and psychological factors (e.g., stress levels), as multiple factors are more often involved in high-risk CAD associated with family hypertension. Laboratory genetic test may consider *AGT*, which is the first gene to show linkage with human essential or primary hypertension,[107] ACE,[108] and α-adducin (ADD1).[109] More information about genetics and hypertension is available at the website of the Centers for Disease Control Office of Public Health Genomics.

Familial Diabetes

Family history is increasingly recognized as a powerful, cost-effective, and readily available tool for detecting diabetes. Such information can be used to classify individuals or groups of people according to different levels of familial risk, such as average, moderate, and high.

In most cases of T1D, people must inherit risk factors from both parents. In many people the development of T1D seems to take many years. Early onset suggests a major role for genetic factors, with a strong inverse association between age at diagnosis and prevalence of HLA alleles conferring susceptibility.[110,111] High genetic susceptibility in the proband implies increased genetic susceptibility and disease risk in his or her parents and siblings. This has been confirmed by many family studies.[112] Because genetic risk is inversely correlated with age at onset, it might be anticipated that this would also apply to familial risk. Most whites with T1D have genes called HLA-DR3 or HLA-DR4. If you and your child are white and share these genes, your child's risk is higher. (Suspect genes in other ethnic groups are less well studied. The HLA-DR7 gene may put African Americans at risk, and the HLA-DR9 gene may put Japanese at risk.) Individuals at high risk can be identified using immunologic, genetic, and metabolic parameters. In addition, circulating antibodies to pancreatic β-cell antigens are markers of islet autoimmunity. In first-degree relatives of persons with T1D, the levels and range of antigen specificities of these islet antibodies reflect the risk for clinical diabetes.[113] Besides, severe metabolic decompensation, rapid failure of C-peptide secretion, and high levels of glutamic acid decarboxylase are useful parameters.[110]

T2D accounts for some 90% of all cases of diabetes.[114] It has a stronger link to family history and lineage than T1D, although it also depends on multiple environmental.[115-118] T2D tends to run in families, based on sociologic and genetic factors. In general, the lifetime risk of developing the disease is about 40% in the offspring of one parent with T2D, greater if the mother is affected,[119] and approaching 70% if both parents have diabetes. It also shows that first-degree family history is associated with a twofold increased risk of future T2D.[120,121] People with certain rare types of T2D have different risks. If patients have the rare form called maturity-onset diabetes of the young (MODY), their child has a 50% chance of getting it too. The concordance of T2D in monozygotic twins is about 70%, compared with 20% to 30% in dizygotic twins.[122,123]

It should be noted that various single genetic variants have been found to be associated with increased risk for T2D, as mentioned earlier; however, the magnitude of increased risk conferred by each variant is relatively small. Thus genetic testing for the prediction of T2D in high-risk individuals is currently of little value in clinical practice.

Familial Obesity

Obesity also tends to run in families; hence family history is a basic tool in assessment.

BMI is the most common way to estimate body fat based on comparing a person's weight to height. Body fat can be measured in other ways in addition to BMI, including waist circumference, calculation of waist-to-hip circumference ratios, measuring the thickness of a skinfold (a pinch of skin and fat), and techniques such as ultrasound, which are more precise than BMI. Obesity is defined differently for children and teens than for adults. Children are still growing, and boys and girls mature at different rates. BMI for children and teens compares their heights and weights against growth charts that take age and sex into account. This is called a BMI-for-age percentile. A child's or teen's BMI-for-age percentile shows how his or her BMI compares with that of other boys and girls of the same age. For more details, see http://www.nhlbi.nih.gov/health/health-topics/topics/obe/diagnosis. Heritability estimates for obesity are high (typically >0.70). In addition, the use of

quantitative obesity subphenotypes that can be accurately measured has resulted in significant measures of heritability for skinfold thickness,[124-126] waist circumference,[127] and total and regional fat distribution.[128]

The location of fat deposition, variation in the secretion of adipokines, and other factors govern whether a particular obese person is more predisposed to obesity-associated diseases and thus is "at risk." Physiologically, metabolically deleterious and life-threatening forms of obesity are associated with a preferential accumulation of fat in the visceral adipose tissue and with ectopic fat deposition in insulin-sensitive tissues such as muscle, liver, and pancreas. This aberrant fat content strongly correlates with severe generalized insulin resistance and the development of a chronic inflammatory state, partly due to the infiltration of the adipose tissue by macrophages.[129] An anti-inflammatory adiponectin is known to strongly modulate the risk of the metabolic syndrome and T2D associated with obesity (diabesity).[130] Variation within the adiponectin gene is reported to modulate plasma adiponectin levels and also to predict risk for diabesity and associated CAD.[131] Paradoxically, the adiponectin variant alleles that protect against the development of diabesity by maintaining high adiponectin concentrations are also associated with obesity risk in both adults and children.[132] Individuals with high adiponectin levels can be severely obese but seem to enjoy metabolic protection.[133] The same alleles—together with the T2D protective PPARγ-12Ala allele—associate with a CAD-protective risk factor pattern, elevated adiponectin and insulin sensitivity, but also with a dramatic increase of 3 units of BMI.[134]

Several biomarkers have been used for assessing the development of obesity and its sequelae. These markers include ACE, AGEs, aldo-keto reductase family 1, member B10 (AKR1B10), alpha-methylacyl-CoA racemase (AMACR), cocaine- and amphetamine-regulated transcript (CART), collagen type I alpha 1, cannabinoid receptor 1 (CR1), ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), MC4R, MTHFR (5,10-methylenetetrahydrofolate reductase [NADPH]), NRs (nuclear receptors), POMC, PPARγ (peroxisome proliferative activated receptor γ), TCF7L2 (transcription factor 7-like 2 [T-cell specific]), TGFβ1 (transforming growth factor β1), VDR (vitamin D3 receptor).[135] However, the value of these biomarkers in risk assessment remains limited.

RISK MANAGEMENT

Familial Hypercholesterolemia: If they are diagnosed and treated early in childhood, individuals with FH can have a normal life expectancy. Early treatment of FH can reduce LDL burden, improve endothelial function, substantially attenuate the progression of atherosclerosis, and offer health and socioeconomic benefits.[136-141] Furthermore, long-term follow-up from statin trials, albeit not specifically in FH patients, suggests a legacy effect—that is, better CAD outcomes in those initially randomized to statin treatment.[142,143]

Children with HeFH should be treated with a fat-modified, heart-healthy diet at diagnosis and begin statins at age 8 to 10 years. For children aged 8–10 years, it is recommended to reduce LDL by 50% from pretreatment levels. For children above age 10, especially if there are additional cardiovascular risk factors including elevated lipoprotein(a), the target LDL should be less than 3.5 mmol/L (130 mg/dL). In HoFH, pharmacologic treatment should start at diagnosis. Children with HoFH should be referred to and cared for at a specialized center.

Diet and lifestyle underpin the management of FH in children. In considering dietary fat content, the major dietary drivers of serum cholesterol levels are saturated fats and trans fats with a small contribution from dietary cholesterol.[144,145] Limitation of foods high in saturated fat will secondarily limit dietary cholesterol intake; cholesterol-containing foods without saturated or trans fats may be allowed (http://www.health.gov/dietaryguidelines/2015-scientific-report/). There should be annual or biannual monitoring of weight, growth, and developmental milestones. Physical activity should be promoted and smoking strongly discouraged. Identifying children with FH early ensures that adherence with lifestyle interventions is established before puberty. Other cardiovascular risk factors should be monitored and treated if indicated.

The most powerful cholesterol-lowering agents for FH are the statins. By inhibiting de novo cholesterol synthesis at HMG-CoA reductase, compensatory upregulation of LDLR lowers plasma LDL concentration. Statins are the cornerstone of FH management. Simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, and rosuvastatin are approved in the United States and Europe for use in children with FH. Treatment should be initiated at the lowest recommended dose and titrated upward according to the LDL-lowering response and tolerability. Ezetimibe, a recently developed drug that limits cholesterol absorption, lowers LDL by about 15%. In addition, bile acid sequestrants that waste more bile acids for the patient result in a reduction of the cholesterol pool in cells. Thus the addition of ezetimibe or a bile-acid sequestrant may be required to attain the LDL goal in some patients.[146-148]

Modern pharmacotherapy can achieve desirable concentrations of LDL in HeFH, but treatment for HoFH remains problematic. Patients with HeFH respond as do normal subjects to lipid-modifying treatment as there is a functional LDLR that will clear LDL from plasma. In 2013, both mipomersen, an ApoB antisense oligonucleotide, and lomitapide, a microsomal triglyceride protein inhibitor, were approved for the treatment of HoFH in the United States.[149] Lomitapide was also approved in Europe. Also, PCSK9 inhibitors, including evolocumab and alirocumab, were approved in Europe and United States in 2015. Besides, liver transplantation (alone or in combination with a heart transplant) may be considered for young HoFH patients, although the disadvantages of this approach include the high risk of posttransplantation complications and mortality as well as the limited availability of donors. Other options, such as partial ileal bypass and portocaval shunting, are not recommended for this population but may be considered for patients with very severe disease in whom other conventional options are not effective.[150,151] In addition, several other novel options for the treatment of HoFH, such as gene therapy, are being investigated. Gene therapy is a strategy used to correct

defective genes responsible for the development of disease. For example, replacement of the *LDLR* gene has the potential to decrease LDL levels while also making patients with HoFH more responsive to conventional therapies.[152] Preclinical studies using mouse models of HoFH and HeFH have yielded promising results.[153] Additional studies and clinical trials of these gene replacement strategies are warranted before they can be considered for general use.

Familial Hypertension

Treatment of familial hypertension should comprise both lifestyle modification and pharmacologic therapy.

Pharmacologic therapy follows the guidelines for the treatment of essential hypertension. The best strategy is to formulate a combination therapy that targets different physiologic mechanisms and accounts for patient comorbidities. Based on either the approved responses of the family members to a given drug or genetic testing in the patient's family, the medication targets the factor related to the primary genetic alteration should be tested first rather than following the general guideline for hypertension treatment, in which the preferred initial drug choices are ACE inhibitor in patients less than 55 years old, or a dihydropyridine calcium channel blocker (CCB) in patients greater than 55 or black patients of any age. These options can then be trialed in combination and titrated as necessary before adding a thiazide, including a recently approved thiazide-like diuretic such as chlorthalidone and indapamide as the third medication. Spironolactone is recommended as the fourth antihypertensive drug.[154,155] Vasodilating β-blockers—that is, carvedilol and labetalol—are the fifth-line drug therapy.[156] Other options include α-blockers, clonidine, methyldopa, and direct vasodilators such as hydralazine or minoxidil. These seldom form part of the routine management and should be prescribed only with expert advice. Adequate monotherapy controls hypertension in 30% of cases.[156] If monotherapy is insufficient, the regimen could be modified by altering dose or adding an additional class of drug. Triple therapy must be optimized before selecting further add-on therapy because optimal dosing and drug selection can see blood pressure normalize in many patients. Patients must be approached in a stepwise manner, beginning with traditional antihypertensive therapy followed gradually by additional agents to reach a quadruple or five-drug compound regimen if necessary. In those who remain hypertensive despite thorough medical management, there are interventional options currently under development, such as renal denervation and carotid sinus stimulation, which are promising but require further research. The primary aim of antihypertensive treatment is to reduce the blood pressure to less than the 95th percentile and to less than the 90th percentile in the presence of comorbid conditions like diabetes, heart disease, or kidney disease.

Familial Diabetes

Risk management of familial diabetes requires continuous medical care with multifactorial risk reduction strategies beyond glycemic control. The management plan should be formulated as a collaborative therapeutic alliance among the patient and family, the physician, and other members of the healthcare team. The management plan should recognize the role of education in diabetes self-management and ongoing diabetes support as integral components of care.

Familial Obesity

The treatment of familial obesity should also focus on changing health behaviors to achieve effective weight management. Studies demonstrate modest weight loss of 5% to 10% with improvement in cardiometabolic parameters. Lifestyle interventions incorporating dietary change, increased physical activity, and decreased sedentary behaviors, with the involvement of family and adoption of a developmentally appropriate approach, should be used as the first line of treatment.

Drug treatment for obesity is an evolving branch of pharmacology. Several antiobesity drugs are under testing. Sibutramine (a centrally acting serotonin/noradrenaline reuptake inhibitor that mainly increases satiety), orlistat (a pancreatic lipase inhibitor that reduces fat absorption by partially blocking the hydrolysis of dietary triglycerides), and rimonabant (a selective antagonist of cannabinoid type 1 receptor) are three examples. When properly used, these medicines contribute to the reduction of body weight and undoubtedly improve cardiometabolic risk factors. Patients who might benefit from antiobesity treatment are those with a BMI ≥30 or 27 to 29.9 kg/m^2.[157] It should be pointed out that the pharmacologic approach is a complement to the behavioral strategy aimed at changing a person's lifestyle. But to treat extreme obesity—that is, in persons with an overweight of more than 100 lb (BMI > 40)—only bariatric surgery can be effective.

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CHAPTER 16

Less Commonly Considered Causes of Atherosclerosis

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Atherosclerotic disease is the leading cause of mortality in developed countries. Better understanding of the pathophysiology of atherosclerosis has led to successful therapies and preventative strategies; however, treatment of conventional risk factors for atherosclerotic disease may only prevent 50% of cardiovascular events.[1] A more complete understanding of atherosclerotic risk factors and the atherosclerotic process has the potential to yield improved therapies and preventative strategies. Several less commonly considered areas of investigation have added insights into the development and progression of atherosclerosis.

First, the atherosclerotic lesion itself appears to be more complex than previously described, and the roles of macrophages, vascular smooth muscle cells (VSMCs), and endothelial cells are not as distinct and static as once thought. Second, the effect of hyperlipidemia on atherosclerosis formation appears to involve more than just low- and high-density lipoprotein (HDL) levels. Finally, many less commonly considered environmental exposures seem to be associated with atherosclerosis and conventional atherosclerotic risk factors such as diabetes mellitus (DM; Table 16.1).

THE ATHEROSCLEROTIC LESION

The prevailing model for the progression of the atherosclerotic lesion from fatty streak to mature plaque has been well described.[2,3] In short, injury to the vascular endothelium allows for adherence and transmigration of bone marrow–derived monocytes into the arterial wall. Monocytes within the arterial wall differentiate into macrophages that phagocytose oxidized LDL (ox-LDL), and become lipid-rich foam cells. VSMCs within the arterial media migrate toward the luminal surface of the plaque to form a fibrous cap. The degree of inflammation, lipid content, and fibrous cap thickness within the lesion affect the stability of the plaque.

Recent evidence suggests that the roles of endothelial cells, VSMCs, and macrophages may not be as static as suggested by this model. Under atherogenic conditions, endothelial cells can transition into fibroblast-like cells, while VSMCs can transition to an inflammatory phenotype resembling macrophages.[4] The transition of endothelial cells into a fibroblast-like cell was first shown in cardiac fibrosis.[5] The role of endothelial

Abstract

Conventional atherosclerotic risk factors do not fully account for the development of atherosclerosis and atherosclerosis-related morbidity. Many less commonly considered environmental exposures seem to be associated with atherosclerosis and conventional atherosclerotic risk factors such as diabetes mellitus. The atherosclerotic lesion also appears to be more complex than previously described, and the roles of lipids, macrophages, vascular smooth muscle cells, and endothelial cells are not as distinct and static as once thought. Better understanding of the atherosclerotic lesion and interactions between conventional and less commonly considered risk factors for atherosclerotic development may lead to improved therapies and preventative strategies.

Keywords

apolipoprotein a
atherosclerosis
diabetes
foam cell
persistent organic pollutant
Toll-like receptor
trimethylamine-N-oxide

TABLE 16.1 Less Commonly Considered Causes of Atherosclerosis

Residual Hyperlipidemia
Lipoprotein a
Infection
Bacteria
Chlamydia pneumoniae, Helicobacter pylori
Periodontitis-causing bacteria
Viruses
HSV, CMV, EBV, HCV, enteroviruses
Diet
Trimethylamine oxide (TMAO)
Environmental
Persistent organic pollutants
Dioxins
Polychlorinated biphenyls (PCBs)
Air pollution
Heavy metals
Arsenic, cadmium, mercury

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HSV,* herpes simplex virus; *HCV,* hepatitis C virus.

cell transformation in atherosclerosis formation is not clear, but it does highlights the phenotypic flexibility of cells within the arterial wall. On the other hand, the transition of VSMCs into a macrophage-like phenotype seems to be an important component of atherosclerotic plaque formation. Recent evidence suggests that VSMCs do more than proliferate to wall off the atherosclerotic lesion. VSMCs may also differentiate into an inflammatory phenotype that can phagocytose ox-LDL to become lipid-rich foam cells.[6,7] It is difficult to determine the degree to which foam cells are derived from macrophages versus VSMCs in vivo, as the two cells are difficult to distinguish based on traditional cell surface markers. VSMC-derived foam cells express cell surface markers typically seen on macrophages, such as CD68 and Mac-2 antigen, while downregulating typical VSMC markers, such as alpha-smooth muscle cell actin.[8-11] VSMC-derived macrophages may accelerate the pathogenesis of atherosclerosis due to the decreased uptake of ox-LDL, increased cellular apoptosis, and dysfunctional reverse cholesterol transport.[7,12] However, it also appears that premature senescence of VSMCs leads to decreasing thickness of the fibrous cap, increasing lesion size, and a larger necrotic core area.[13] Therefore it seems that VSMCs can undergo both compensatory and pathologic changes during the atherosclerotic process, and it is not clear whether the overall effect of changes in the VSMC phenotype are beneficial or detrimental in atherosclerotic disease. The varying effects of VSMCs in atherosclerotic lesions may be partially explained by the fact that VSMCs are not a homogenous population derived only from the arterial media. Rather, VSMCs can be derived from precursor cells in the bone marrow, adventitia, or arterial media, with VSMC of different origins producing different effects within the atherosclerotic lesion.[14-16] A better understanding of the role of various VSMC populations in the formation of atherosclerosis may potentially lead to new therapies that can enhance the protective effects of VSMCs while decreasing the harmful effects.

HYPERLIPIDEMIA

Hyperlipidemia is one of the most well-known risk factors for atherosclerotic disease and a primary target of pharmacologic intervention for preventing or slowing the atherosclerotic process. High LDL cholesterol and low HDL cholesterol have been the most-studied lipid components related to atherosclerotic disease. Total cholesterol and LDL reduction has been the cornerstone for medical treatment and prevention of ischemic heart disease with an abundance of randomized control trials that attest to efficacy of cholesterol lowering therapy in preventing ischemic heart disease.[17-20] However, additional lipid variables have emerged as risk factors for atherosclerotic heart disease and potential routes of residual risk reduction.

Lipoprotein a

Lipoprotein a, or Lp(a), is an LDL molecule linked to apolipoprotein (a), or Apo(a). There are several different isoforms of Apo(a) and therefore of Lp(a) as well. Lp(a) levels correlate with both primary and secondary cardiovascular events independent of LDL and HDL levels.[21-24] Statin medications and niacin can reduce Lp(a) levels modestly.[25-28] Further reductions in Lp(a) can be achieved through apheresis, which can be used to remove both LDL and Lp(a) particles or Lp(a) particles alone.[29] Apheresis can be considered for persistently high levels of LDL cholesterol despite maximal medical therapy or isolated Lp(a) elevation in the setting of progressive atherosclerotic disease. Given the powerful LDL-lowering effect of statins and newer proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, apheresis is rarely needed for residual LDL reduction. However, Lp(a)-specific apheresis may be able to prevent progression of angiographically measured coronary atherosclerosis compared with medical therapy alone.[30] Major adverse cardiovascular events (MACEs) are also lower when apheresis is added to maximal medical therapy in patients with progressive cardiovascular disease.[31,32] Given that conventional therapy with statins may reduce only half of cardiac adverse events,[1] there seems to be a potential role for the consideration of lipid parameters beyond HDL and LDL and additional lipid-based interventions.

DIET

A diet low in meats and animal products is a component of a low-fat, low-cholesterol diet. However, there may be a link between diet and atherosclerosis beyond dietary cholesterol intake. Trimethylamine-N-oxide (TMAO) is a proatherogenic molecule that is derived from carnitine, which is predominantly found in red meats, and phosphaditylcholine (PC), which is found in most animal products including dairy and eggs. Intestinal bacteria synthesize trimethylamine (TMA) from

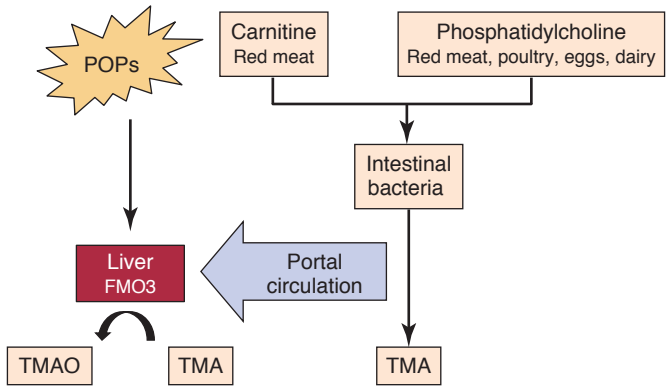

Figure 16.1 Interaction between diet and environment. Carnitine and phosphatidylcholine are converted into trimethylamine (TMA) by intestinal bacteria. TMA is oxidized by the flavin mono-oxygenase 3 (FMAO3) in the liver into trimenthylamine-N-oxide (TMAO). FMO3 is also upregulated by persistent organic pollutants (POPs).

carnitine and PCA. TMA is transported to the liver via the portal circulation, where it is converted to the proatherogenic molecule TMAO by a family of enzymes known as the flavin mono-oxygenases (FMO), particularly FMO3. The FMOs also oxidize a wide range of drugs and environmental toxins, such as persistent organic pollutants (POPs) in pesticides, and there may be a synergistic effect of diet and environmental toxins on atherosclerosis formation (Fig. 16.1).

The production of TMAO from dietary precursors is dependent on intestinal bacterial metabolism and can be suppressed by antibiotic administration.[33] The amount of animal products in the diet affects the intestinal microbiome and the amount of TMAO produced. Vegetarians and vegans produce significantly less TMAO than omnivores, and even short-term changes in diet can alter intestinal microbial populations.[34,35]

Blood TMAO levels are associated with increased rates of PAD, MI, and CAD.[33] Dietary TMA and choline supplementation also induce atherosclerosis in animal models.[36] TMAO levels are also associated with increased mortality or major adverse cardiac events (MACEs) in patients with heart failure, CAD, and renal failure.[37-39] Increased PC consumption has been associated with increased cardiovascular-specific mortality in the Nurses Health Study and the Health Professionals Study (encompassing over 110,000 participants).[40] Finally, carnitine and its immediate breakdown products, which are the TMAO precursors found in red meat, have also been shown to associate with atherosclerotic disease and cardiovascular mortality in both human and animal studies.[41,42]

On the whole, the observational and animal data are highly suggestive of a role for PC, carnitine, and TMAO in atherosclerosis formation. Some studies of meat consumption have suggested that an increased risk of cardiovascular disease and diabetes is not associated with fresh or frozen meat consumption, but is limited to consumption of processed meats.[43-45] However, determining the effect of TMAO production on cardiovascular risk may require assessment of all animal products that lead to TMAO production, not just meat consumption. Finally, there is some seemingly contradictory evidence that L-carnitine supplementation may prevent atherosclerosis in animal models,[46] and L-carnitine supplementation in patients with acute MIs decreases all-cause mortality.[47] Further studies and perhaps randomized interventional trials that assess TMAO as a risk factor for MACEs are needed to further clarify the link between diet, TMAO levels, and atherosclerotic disease.

INFECTION

Efforts to link atherosclerosis with infectious etiologies have spanned decades. Although enthusiasm for an infectious etiology of atherosclerotic disease may have waned after several negative trials of antibiotics, the association and potential causal link between infectious pathogens and atherosclerosis remains an active area of investigation. Numerous viral and bacterial pathogens have been examined as potential causes of atherosclerosis. The most commonly studied viral pathogens potentially linked to atherosclerosis are herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis C virus (HCV), and enteroviruses. The most commonly studied bacterial pathogens are *Chlamydia pneumoniae, Helicobacter pylori,* and the oral pathogens.

Potential mechanisms by which bacteria and viruses may cause atherosclerosis development include upregulation of adhesion molecules in vascular endothelium and foam cell formation.[48,49] The effect of many pathogens on foam cell formation seems partially dependent on Toll-like receptors (TLRs), which are present on inflammatory cells and bind to bacterial and viral pathogen–associated molecular patterns (PAMPs) as part of the innate immune system. However, they also bind endogenous compounds, such as ox-LDL, and cause macrophages to transform into foam cells (Fig. 16.2).[48-51]

Although the association between atherosclerosis and any single pathogen has been inconsistent, the concept of an increased pathogen burden may better explain the potential link between infection and atherosclerosis. The pathogen burden hypothesis postulates that exposure to an increased number of pathogens creates an increased systemic inflammatory response, which promotes the development of atherosclerosis. This hypothesis is supported by studies demonstrating a higher risk of CAD in patients with antibodies to a larger number of pathogens.[52-55]

Viruses

Herpes Simplex Viruses 1 and 2

Data linking HSV infection to atherosclerosis are mixed. A meta-analysis of 17 studies investigating the association of HSV-1 and 7 studies investigating HSV-2 seropositivity showed a significant association between both HSV-1 and HSV-2 with atherosclerotic disease. However, there was significant heterogeneity among studies with regard to the populations studied, the definition of exposure and disease outcomes, and the results.[56]

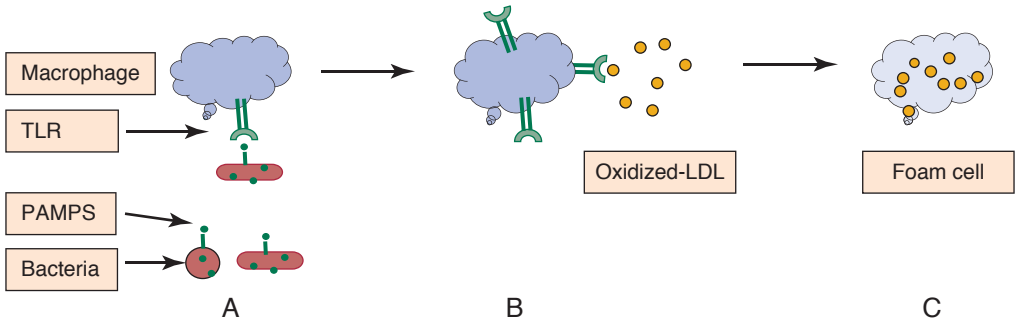

Figure 16.2 Potential mechanism of atherosclerosis formation by infectious pathogens. (A) Pathogens associated molecular patterns (PAMPs) are recognized by Toll-like receptors (TLRs) on macrophages. (B) Macrophages upregulate TLRs, which can also bind oxidized low-density lipoprotein (LDL). (C) Uptake of oxidized LDL by macrophages causes foam cell formation.

Enteroviruses, Hepatitis C, Cytomegalovirus

The association of cardiovascular events and antibodies to enteroviruses is also inconclusive, with some prospective studies showing a correlation between antibody levels and cardiovascular events[57] and others studies demonstrating no association.[58,59] Similarly, HCV infection has been shown to be associated with CAD in one study[60] and to have no association with MI in another.[61] The data regarding CMV infection are mainly composed of small case studies, with a meta-analysis of these studies suggesting a modest association between CMV exposure and CAD.[62]

Bacteria

Helicobacter pylori

H. pylori is best known as a cause of peptic ulcer disease, but it has also been associated with atherosclerotic disease. *H. pylori* DNA can be detected in up to 30% of coronary artery atherosclerotic plaques.[63] Its detection in coronary artery plaques by PCR techniques has been criticized for potential false-positive rates, but use of the internal mammary arteries as a control has lessened this concern.[63] *H. pylori* has been associated with increased risk of CAD, MI, and stroke, with the more virulent CAG A strains possibly conferring the highest risk.[64-68] However, the data are inconsistent, with several large studies not demonstrating a positive association between seropositivity to CAG A–positive *H. pylori* and cardiovascular mortality.[52,69] Inconsistent results may stem from variability in classifying exposure, disease endpoints, and confounding factors such as past and present socioeconomic status.[70]

Chlamydia pneumoniae

Many case-control[71-74] and a few prospective[75,76] studies have suggested an association between seropositivity or high serum titers to *C. pneumoniae* and atherosclerotic heart disease and ischemic stroke. However, other large prospective cohort trials have failed to show an association between seropositivity to *C. pneumoniae* in healthy individuals and the subsequent development of cardiovascular events.[77,78] Differences in the definition of exposure, definition of outcomes, and duration of follow-up in prospective trials may explain some of the differences between these trials.

Despite the possible association between *C. pneumoniae* infection and subsequent atherosclerosis, causation has been difficult to prove. The use of antibiotics effective against *C. pneumonia*, such as azithromycin[76,79-82] or gatifloxacin,[83] has not shown any benefit in the secondary prevention of cardiovascular events. The largest of these trials, totaling almost 16,000 patients,[81-83] had mean follow-up times of 2.0 to 3.8 years and included a fairly lengthy antibiotic regimen that continued for 1 to 2 years.[81,83] However, there may be a benefit in decreasing secondary cardiovascular event rates using broader antibiotic regimens of either azithromycin and metronidazole or amoxicillin and metronidazole[84] and in preventing the progression of carotid plaque using roxithromycin.[85] Interestingly, the benefit of using antibiotics to lower cardiovascular event rates appears to be independent of seropositivity to *C. pneumoniae*, suggesting that additional pathogens or mechanisms may be involved.[84]

Oral Pathogens

Oral pathogens have received substantial interest as a potential cause of atherosclerosis development and progression. Oral bacteria are detected in the blood after normal daily activities such as tooth brushing and therefore have access to the systemic circulation. There is a strong association between periodontitis, defined as chronic inflammation leading to bone loss, and clinical atherosclerosis. Periodontitis is associated with an increased risk of MI[86-91] and ischemic stroke.[91] Patient-specific oral bacteria have also been detected in and cultured from coronary atherosclerotic plaques.[92]

The relationship between oral pathogens and atherosclerosis appears to depend more on the entire oral microbiome rather than any specific pathogens, with an increasing number of oral pathogens exerting a synergistic effect on atherosclerosis development.[55] However, although the association between periodontitis and atherosclerosis is well established, causality is not clear.

The benefit of treating periodontitis with regard to cardiovascular events has been inferred through changes in cardiovascular disease biomarkers, such as C-reactive protein (CRP) levels but not demonstrated through decreases in clinical

endpoints, such as MI or stroke. Results of individual trials are mixed, with some showing no benefit in CRP and interleukin-6 (IL-6) reduction[93,94] whereas others demonstrate CRP and IL-6 reductions with periodontal therapy regimens.[95,96] Reductions in CRP levels occur regardless of whether antibiotics are added to the mechanical treatment of periodontitis, but the two modalities may exert synergistic effects.[95,97,98] Finally, the PAVE study[99,100] evaluated the effect of periodontal treatment on secondary prevention of cardiovascular events. This study did not show any benefit in CRP levels or cardiovascular event rates from treatment of periodontitis. However, a large portion (48%) of the "control group" also received treatment for periodontitis, and the treatment arm sustained only a short-term, modest improvement in the participants' periodontal disease status. Therefore despite the association between periodontitis and atherosclerosis, it is not known whether periodontitis causes atherosclerosis or if treatment of periodontitis will decrease major adverse cardiac events.

ENVIRONMENTAL TOXINS

Persistent Organic Pollutants

Emerging evidence suggests that some long-lasting environmental toxins, collectively known as POPs, are associated with both atherosclerosis and type II DM. POPs include many industrially produced compounds such as herbicides and dioxins. The toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the dioxin contaminant in the Agent Orange herbicide used during the Vietnam War, are well characterized, and the toxic effects of all other dioxins are expressed in relation to that of TCDD. TCDD is found as a by-product of industrial waste incineration, a contaminant in herbicides, and a by-product of pulp and paper mills and metal production.[101] Dioxins are highly lipophilic substances that accumulate in the fat stores of animals and humans due to their long biological half-lives of 7 to 11 years.[102,103] Polychlorinated biphenyls (PCBs) are another well studied class of POPs with similar mechanism of action and disease associations as dioxins.

The National Academy of Science, Engineering and Medicine routinely examines evidence linking POPs to diseases, including ischemic heart disease, stroke, and type II DM. In 2000 this institution's report on veterans and Agent Orange exposure stated that there is "limited or suggestive" evidence of an association between these chemicals and type II DM, ischemic heart disease, hypertension, and stroke.[104] Subsequent updates of this report at 2-year intervals have upheld this conclusion, although not all individual studies confirmed the association between these chemicals, atherosclerotic disease, and DM.[98,105,106]

More recent studies have also supported the association between POP exposure, atherosclerotic disease, DM II, and metabolic syndrome. They have demonstrated that both estimated exposure and blood level concentrations of POPs are associated with type II DM and serum glucose abnormalities in military veterans.[107-110] Many studies also show an association between occupational and environmental exposure to POPs and DM,[111-117] although others show mixed results or no such association.[105,106,118,119] In addition, exposure to POPs appears also to be associated with metabolic syndrome and stroke.[110,118,120]

The aryl hydrocarbon receptor (AhR) is the most studied mediator of the proposed mechanism by which POPs exposure exerts toxic effects, including the development of type II DM. POPs can bind the AhR and cause downstream effects affecting the regulation of the cell cycle and promoting inflammation. There is also an AhR-independent pathway that affects results in the upregulation of inflammatory mediators by altering intracellular concentrations of calcium ions.[121,122] Another mechanism by which some POPs can contribute to atherosclerosis is via the upregulation of flavin monoxygenase-3 (FMO3), the hepatic enzyme responsible for producing the proatherogenic compound TMAO from dietary precursors (see the earlier section titled "Diet"). Exposure to some POPs has recently been shown to cause upregulation of FMO3 as well as increased TMAO production in response to PC supplementation,[123] indicating that diet and environmental contaminants may synergistically lead to atherosclerotic disease (see Fig. 16.1).

Heavy Metals

Heavy metals are another source of environmental contaminants that may negatively affect cardiovascular health and promote atherosclerosis. Activities such as the burning of coal, municipal waste incineration, smelting, and the production of paper have led to the accumulation of arsenic, cadmium, and mercury in the environment.

Arsenic

The contamination of drinking water with arsenic is a major problem in the developing world. Blood arsenic levels are associated with multiple atherosclerotic risk factors, such as DM II and hypertension. Initially, only high levels of exposure and prolonged exposure times were associated with DM II[124]; however, arsenic seems to be associated with DM II even at "low" levels of 50 to 100 μg/L in drinking water.[125,126] There is also an association between levels of arsenic in blood and urine and hypertension (HTN).[118,127,128] Exposure to arsenic is also linked with coronary artery disease, stroke, and PAD.[129]

Cadmium

Cadmium exposure can occur through the ingestion of contaminated vegetables or smoke inhalation. The association of between cadmium exposure and tobacco smoke had previously made it difficult to determine whether cadmium exposure is linked with atherosclerosis independent of exposure to tobacco.[130] However, subsequent studies have demonstrated that cadmium exposure is associated with an increased incidence of MI, stroke, CAD, and PAD independent of smoking status.[131-133]

Cadmium levels may also affect the progression of atherosclerotic plaques, with higher cadmium levels being associated with the progression of carotid atherosclerois.[134] High levels of cadmium in symptomatic carotid plaques and the association between cadmium levels and the increased density of macrophages in carotid plaques has led some investigators to suggest that cadmium exposure can affect plaque behavior and stability

as well.[135,136] The association between cadmium exposure and atherosclerotic disease may be more pronounced in women than in men.[131,133] Potential mechanisms by which cadmium exposure can lead to atherosclerosis may include disruption of vascular endothelial integrity and endothelial cell junctions[137,138] as well as free-radical production and the depletion of endogenous free-radical scavengers.[139,140]

Mercury

Mercury vapor from the burning of fossil fuels, waste incineration and other industrial causes is eventually deposited in lakes, rivers, and oceans, where it can be converted to organic methyl mercury. Methyl mercury bioaccumulates in aquatic life, especially large predatory fish, such as shark, swordfish, and tuna.[141] The protective effect of fish consumption on cardiovascular health due to omega-3 polyunsaturated fatty acids, has the potential to obscure some of the detrimental effects of exposure to organic mercury. However, a large, prospective study of a Finnish population has demonstrated a strong association between levels of mercury in hair and MI and death from CAD at 6-, 10-, and 14-year follow-up intervals.[142-144] In addition, mercury appears to attenuate the protective effect of omega-3 fatty acids on the incidence of MI.[143,144] However, not all studies have corroborated the association between mercury levels and CAD.[119,145-147]

Air Pollution

Air pollution from automobiles and industrial production consists of free radicals, reactive aldehydes, and particulate matter. The association between air pollution, atherosclerosis, and atherosclerotic risk factors is controversial. There are methodologic challenges, such as quantifying the length and intensity of pollution exposure, accounting for confounders, and determining the true rates of outcomes. However, overall, multiple studies suggest an association between air pollution and the development of DM II.[148-154] In addition, the association between air pollution exposure and DM may be exaggerated in women and nonsmokers.[148,150,154] Increased exposure to air pollution is associated with increased levels of high-sensitivity CRP (hsCRP) and other inflammatory markers[155-157] as well as an increased prevalence of coronary artery disease, stroke, ischemic heart disease, and congestive heart failure.[149,158]

Multiple theories exist regarding potential mechanisms by which air pollution can cause atherosclerosis. Animal and human studies demonstrate increased markers of systemic inflammation, insulin resistance, and activation of the innate immune system through the activation of TLRs.[159–162] Additionally, free-radical stress from air pollution has also been linked to signs of mitochondrial dysfunction, which may be associated with atherosclerosis through increased intracellular oxidative stress, mutations in mitochondrial DNA, and decreasing metabolic rates due to reduced mitochondrial numbers.[160]

SUMMARY

There continues to be progress in understanding atherosclerosis and its risk factors. The behavior of the atherosclerotic lesion, the role of various cells within the atherosclerotic lesion, and the effect of hyperlipidemia are more complex than previously demonstrated. Many less commonly considered factors such as infection and environmental exposures may also contribute to atherosclerotic disease. As our understanding of the links between diet, infection, environmental exposures, and traditional atherosclerotic risk factors expands, there will be opportunities to develop new therapies and preventive strategies through improved pharmacotherapy and public health measures.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 17

International and Ethnic Trends in Vascular Disease

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The 21st century has ushered in a number of changes in the distribution of vascular disease worldwide, primarily due to demographic changes and trends in atherosclerotic risk factors. These global trends require concerted efforts at the patient, provider, and public health level to adequately care for the increasing burden of vascular disease worldwide. Similarly, significant advancements in the understanding of ethnic differences in the epidemiology of vascular disease, delivery of care, and outcomes of treatment modalities have also been made in the past decade. The disparities identified have prompted the development of a number of strategies to improve the care of the diverse population of patients with vascular disease.

INTERNATIONAL TRENDS

Globally, atherosclerosis is a leading cause of vascular disease, including ischemic heart disease (IHD), ischemic stroke, and peripheral arterial disease (PAD). Based on large-scale population-based studies, there is an increased burden of disease resulting primarily from the increasing trends of risk factors of atherosclerosis, primarily smoking and diabetes. A multifaceted approach including environmental and legislative interventions for health promotion, primary intervention, and access to affordable evidence-based evaluation and treatment of major risk factors are required to combat the growing burden of vascular disease worldwide.

Risk Factors

Smoking

There are currently more than 1 billion smokers worldwide.[1] Fortunately, the global prevalence of daily tobacco smoking has declined over the past 30 years but varies by gender and region (Fig. 17.1).[2] Men smoke more than women in all regions, with the largest disparity between the genders in the Western Pacific region and lowest in the Americas. Regionally, the highest smoking prevalence is in the European region, with nearly 30% daily tobacco use, followed by the Western Pacific (including China), Southeast Asia, Americas, then Eastern Mediterranean regions. The only region with smoking prevalence less than 10% is Africa.[1] The last quarter of the 20th century saw an increase in smoking in a number of developing regions, including parts of Latin America, the Eastern Mediterranean, and Southeast Asia.[3]

More than 6 million people die from tobacco use and exposure each year, which is projected to increase to 8 million by 2030. Smoking is estimated to cause nearly 10% of cardiovascular deaths worldwide. The highest proportion of cardiovascular deaths attributed to smoking is observed in North America (22%), Eastern Europe (17%), Western Europe (13%), and Southeast Asia (10%). Based on gender, the effects on men have demonstrated a relative risk of 1.6 for IHD mortality and 1.6 for stroke morality among current smokers compared with

Abstract

The 21st century has ushered in a number of changes in the distribution of vascular disease worldwide, primarily due to demographic changes and trends in atherosclerotic risk factors. These global trends require concerted efforts at the patient, provider, and public health level to adequately care for the increasing burden of vascular disease worldwide. Similarly, significant advancements in the understanding of ethnic differences in the epidemiology of vascular disease, delivery of care, and outcomes of treatment modalities have also been made in the past decade. The disparities identified have prompted the development of a number of strategies to improve the care of the diverse population of patients with vascular disease.

Keywords

international
global
ethnic
trends
epidemiology
disparities
public health

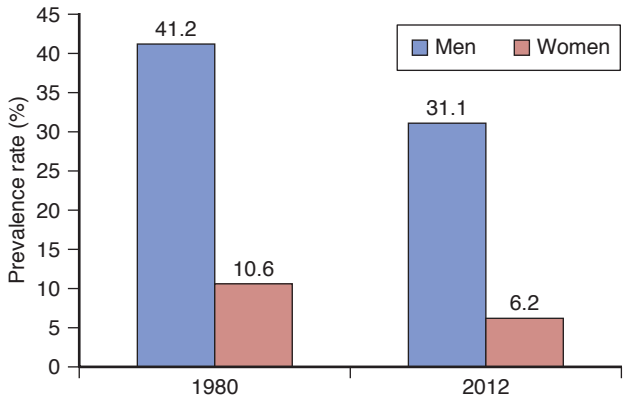

Figure 17.1 Trends in global prevalence of current tobacco use by gender, 1980 and 2012.

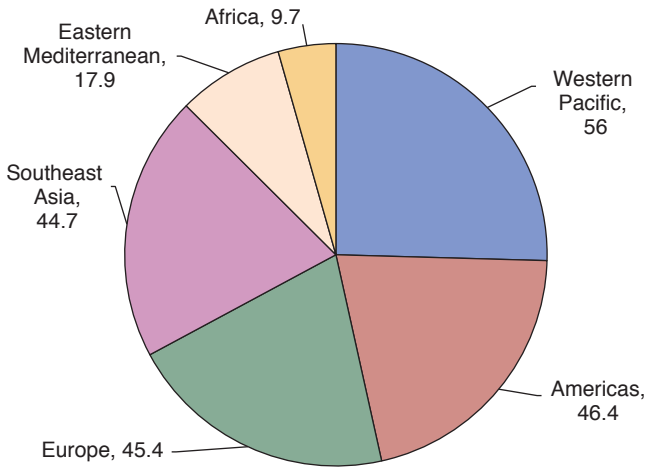

Figure 17.2 Prevalence (millions) of diabetes mellitus by World Health Organization Regions, 2004.

never-smokers.[4] Among women, current smokers were found to have 3 times the risk of mortality from IHD, 3 times increased risk of stroke mortality, and 6 times increased risk of death from aortic aneurysm compared with never-smokers.[5] Looking forward, it is expected that the countries with both the highest smoking prevalence rates and high consumption rates (>20 cigarettes per day) will likely face the greatest health consequences among current smokers: China, Greece, Ireland, Italy, Japan, Kuwait, Korea, Philippines, Uruguay, Switzerland, and Russia.[2]

Diabetes

The global epidemic of diabetes is expanding as rapidly growing populations, particularly in India and China, adopted Western lifestyles. These studies projected that the number of adults worldwide with diabetes will more than double from 2000 to 2030 due to the combined forces of improved survival from communicable diseases, abundance of food, and less physically demanding lifestyles.[6] As of 2004 the WHO estimated the prevalence of diabetes mellitus at 220.5 million, with the highest prevalence in the Western Pacific region and lowest in Africa (Fig. 17.2). By 2008 an estimated 10% of adults older than 25 years were living with diabetes worldwide.[1] Population growth and aging alone accounted for 70% of the 198 million new cases of diabetes between 1980 and 2008.[2] The prevalence of diabetes is relatively consistent among income groupings of countries, ranging from 8% in low-income countries to 10% in upper-middle-income countries.[1] The highest prevalence rates (>20%) were found in a mix of low- and high-income countries (HICs): Marshall Islands, Kiribati, Saudi Arabia, Cook Islands, and Samoa.[2] Large-scale meta-analysis of prospective observational studies quantified that diabetes mellitus increases vascular mortality rates by a factor of 2.[7] Therefore these regions with the greatest increase in diabetes prevalence can also anticipate an associated increase in vascular morbidity with its associated costs as the population ages.

Ischemic Heart Disease

IHD is the leading cause of death from noncommunicable diseases worldwide. In 2010 the highest mortality rates from IHD were reported for Eastern Europe (including Russia) and Central Asia, with these regions demonstrating nearly 10 times the mortality rate observed in the regions with the lowest rates: the high-income Asia Pacific region and Eastern Sub-Saharan Africa.[7]

Globally, the age-standardized incidence of acute myocardial infarction (AMI) and prevalence of angina and ischemic heart failure decreased from 1990 to 2010. Regionally, the greatest decline in age-standardized incidence of AMI during this period was observed in Australasia, Western and Central Europe, and North America high-income regions. However, Eastern Europe was noted to go against the trend of worldwide decline in age-standardized incidence of AMI, demonstrating an increased incidence of 62 per 100,000 in males and 17 per 100,000 in females during this time period.[8]

Cerebrovascular Disease

In 2004 the World Health Organization estimated a worldwide incidence of 9 million strokes per year, with the greatest incidence in populations of the Western Pacific (3.3 million), Europe (2 million), and Southeast Asia (1.8 million). Stroke incidence was lowest in the Eastern Mediterranean (0.4 million), followed by Africa (0.7 million) and the Americas (0.9 million).[9] The global trend in age-standardized incidence of stroke indicated a decrease from 1990 to 2010 by 12% in HICs but suggested an increase of the same degree in low- and middle-income countries (LMICs) (Fig. 17.3).[10]

Stroke is the second leading cause of death worldwide. Stroke-related mortality and disability-adjusted life-years (DALYs) lost also increased over the past 2 decades, with most of the burden in LMIC. These trends are represented in Fig. 17.3. Age-adjusted mortality rates for stroke decreased significantly globally and in both HIC and LMIC regions. This discrepancy between rising absolute numbers of stroke mortality and decreasing age-adjusted mortality rates for stroke globally can be explained by a 36% decrease in stroke-related mortality among persons older than 75 years.[10] Measures to improve stroke prevention and care (i.e., smoking cessation programs, blood pressure control, acute stroke units) that have been adopted in

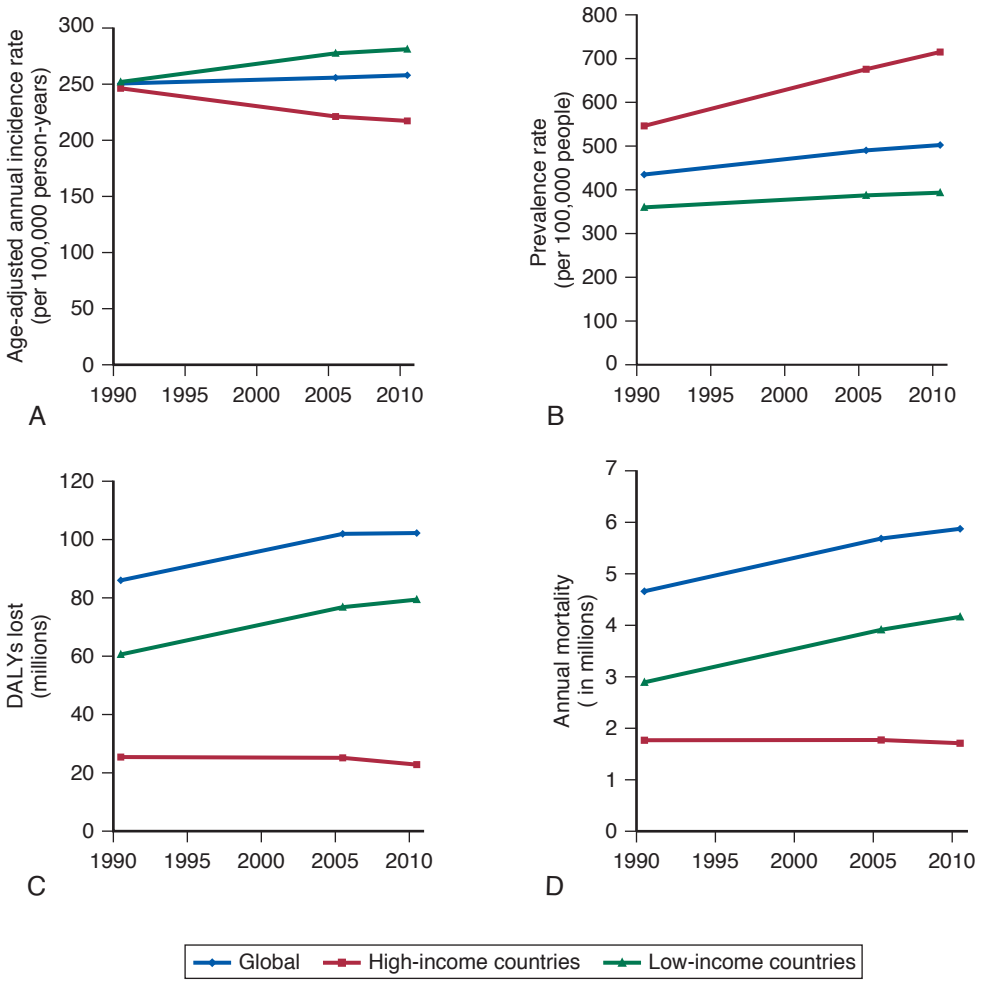

Figure 17.3 **Trends in Global Burden of Cerebrovascular Disease, 1990 to 2010.** (A) Age-adjusted annual incidence rate (per 100,000 person-years). (B) Prevalence rate (per 100,000 people). (C) Disability-adjusted life-years *(DALYs)* lost. (D) Annual mortality.

HIC are the most likely explanation for the decreasing incidence and mortality rates observed in the past 20 years. In countries like China, Russia, and India with very high stroke-related mortality attributable to tobacco use, even a modest reduction in the number of current smokers could prevent millions of deaths.[11]

Peripheral Arterial Disease

Lower extremity PAD, including intermittent claudication and critical limb ischemia, is the third leading cause of atherosclerotic vascular morbidity after IHD and stroke. Globally, more than 200 million people are living with PAD, with more than two-thirds of these persons residing in LMICs. In the past decade the number of people with PAD has increased both in HICs by 13%, and LMICs by 29%.[12] The regions with the highest incidence of PAD as of 2010 were Southeast Asia, LMIC Western Pacific, and Europe, whereas the lowest numbers of people living with PAD were in the Eastern Mediterranean, Sub-Saharan Africa, and HIC Western Pacific regions (Fig. 17.4). The increase in PAD prevalence over the past decade was highest in the elderly, thereby expecting the global prevalence of PAD to grow rapidly, because of an aging world population and increased prevalence of atherosclerotic risk factors, particularly smoking and diabetes.

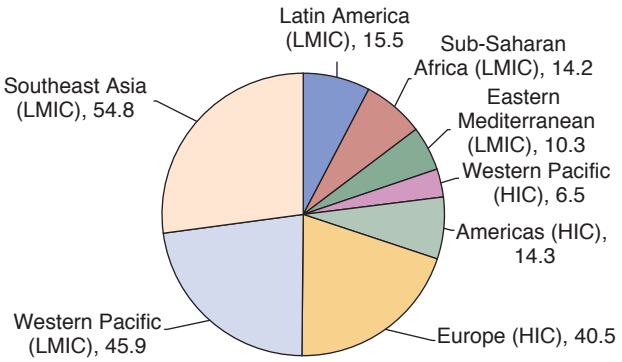

Figure 17.4 Prevalence (millions) of peripheral arterial disease by geographic regions, 2010. *HICs*, High-income countries; *LMICs*, low- and middle-income countries.

In addition, PAD, as opposed to IHD and stroke, has a lower associated mortality, accounting for only 1% to 2% of cardiovascular deaths globally each year.[7] The high-income

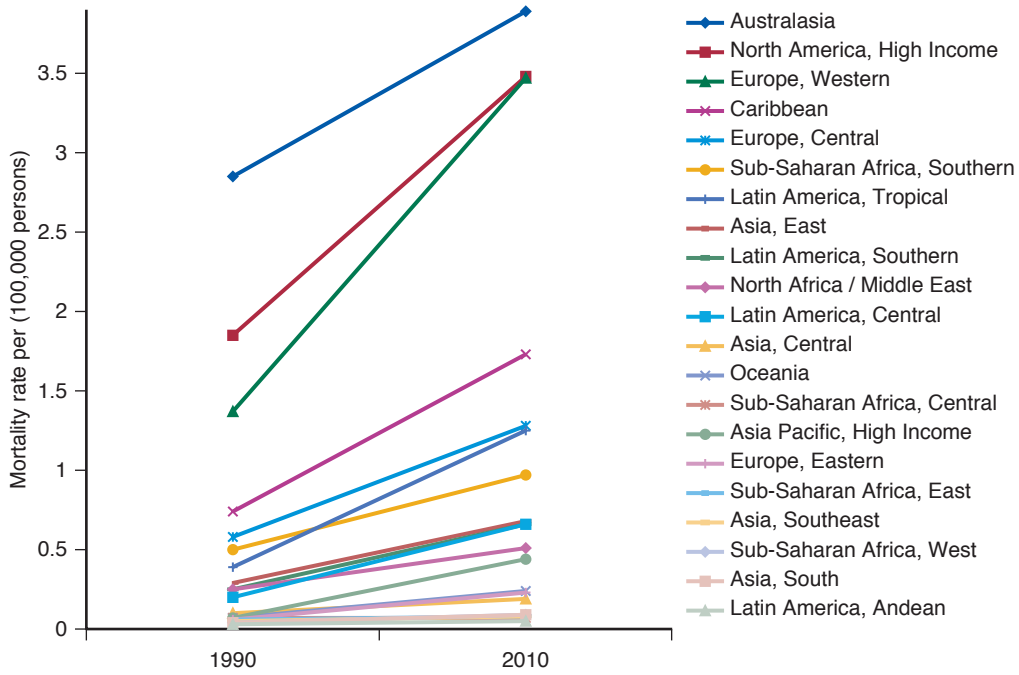

Figure 17.5 Trends in mortality rates attributed to peripheral arterial disease by geographic regions, 1990 to 2010.

regions of Australasia, North America, and Western Europe have consistently demonstrated the highest regional mortality rates from PAD but have also been noted in LMIC regions of the Caribbean, Central Europe, Southern Sub-Saharan Africa, tropical Latin America, and East Asia (Fig. 17.5).[13]

These trends pose a significant public health challenge in LMIC due to both the rapid rise in prevalence of PAD on healthcare resources and the dependence of the population on walking substantial distances for activities of daily living.[12] The limited availability of healthcare services in these regions is predicted to lead to significant number of limb amputations with their associated social needs in the coming decades.

Aortic Aneurysm

A consistent increase in the incidence and mortality from both thoracic and abdominal aortic aneurysm (AAA) were noted in many HICs during the second half of the 20th century, with a prevalence estimated at 5% by the turn of the century.[14] In 1990 to 2010 the highest global prevalence was in Australasia and North America HIC regions despite a decrease of prevalence over the past 20 years, whereas Oceania, tropical Latin America, Asia Pacific HIC, Central Asia, South Asia, and the Sub-Saharan African regions all demonstrated an increase in aortic aneurysm prevalence.[14]

Despite a net decline in the global prevalence of aortic aneurysm, mortality rates have increased worldwide over the same time period: from 2.49 per 100,000 in 1990 to 2.78 per 100,000 in 2010.[15] The highest mortality rates from aortic aneurysms have been consistently observed in the Australasia and Western Europe regions over the past few decades[15]; however, other studies have documented a decline in mortality rates in many HICs, likely due to a combination of comprehensive tobacco use reduction efforts and implementation of targeted screening programs.[14,16]

Global Strategies

A number of strategies have proven effective in decreasing the global burden of vascular disease. Public health measures to treat hypertension, high cholesterol, and diabetes and reduce smoking can further reduce the burden of IHD, cerebrovascular disease, PAD, and aortic aneurysm disease.

Interventions that are highly cost effective, feasible, and culturally acceptable to reduce tobacco use include increases in prices of tobacco products, policies designating smoke-free work and public spaces, mass media campaigns providing education about tobacco dependence and health effects, and bans on tobacco advertising, promotion, and sponsorship. The cost of implementation of these interventions is estimated at less than $0.50 per capita and has been effective when implemented; however, only 180 countries have ratified the WHO Framework Convention on Tobacco Control (Table 17.1). As of 2008, less than 10% of the world population was fully covered by any of these tobacco control reduction measures.[1]

Several evidence-based interventions for the management of diabetes have proven cost effective while improving health[1] and are reviewed in Chapter 12.

Approaches to improve cardiovascular health globally can be categorized as policy strategies, provider-level interventions, or patient-level interventions (Table 17.2). Primary prevention of atherosclerotic disease with a regimen of aspirin, statin, and blood pressure–lowering agents may significantly reduce the risk of mortality in people at high cardiovascular risk for a modest cost. In high-risk patients between 40 and 70 years of

TABLE 17.1 WHO Framework Convention on Tobacco Control

Price and Tax Measures to Reduce the Demand for Tobacco

- Tax increases that result in an increase of the sales price of tobacco products
- Prohibition or restriction of sales of tax- and duty-free tobacco products

Nonprice Measures to Reduce the Demand for Tobacco

- Comprehensive smoke-free policies to provide protection from exposure to tobacco smoke in indoor workplaces, public transport, and indoor and other public spaces
- Regulation of the contents and emissions of tobacco products and the methods by which they are tested and measured
- Disclosure of the constituents and emissions of tobacco products by manufacturers and importers
- Requirement that tobacco product packaging carry large health warnings and messages describing the harmful effects of tobacco (constituting more than 50% of the principal display areas)
- Education, communication, training, and public awareness campaigns
- Comprehensive ban on all tobacco advertising, promotion, and sponsorship
- Provision of support for reducing tobacco dependence and cessation, including counseling, psychological support, nicotine replacement, and education programs

Measures to Reduce the Supply of Tobacco

- Elimination of illicit trade in tobacco products by marking of tobacco packaging to enable tracking and tracing, monitoring of cross-border trade, and confiscation of proceeds derived from illicit trade in tobacco products
- Prohibition of sales of tobacco products to children and limitation of access of underage persons to tobacco products through elimination of distribution of free tobacco products, tobacco vending machines accessible to minors, and the sales of tobacco products individually or in small packets

TABLE 17.2 Comprehensive Strategy to Address Cardiovascular Disease[a]

Policy Approaches (Global, National, Local)

- Comprehensive tobacco control policies
- Food, agricultural, and trade policies that promote consumption of fruits and vegetables
- Environmental policies to limit meat, dairy, and palm oil production
- Urban planning policies to promote active transport to work and leisure-time activity

Healthcare Delivery—Provider-Level Approaches

- Creation of systemic infrastructure by establishment of disease management programs
- Adherence to clinical practice guidelines, with audit and feedback mechanisms to improve quality of care

Healthcare Delivery—Patient-Level Approaches

- Registration, recall, reminding, reinforcing, and review of patients with linked, simplified, stepped-care algorithms
- Fixed-dose combination or polypill therapy to increase adherence to multidrug regimen

[a]Modified from Huffman MD. Cardiovascular health in low- and middle-income countries. *Curr Probl Cardiol*. 2014;39:399–419.

age, providing this regimen has been estimated to avert approximately 20% of cardiovascular deaths over 10 years at a cost of less than $1 per person in low-income countries and less than $3 per person in middle-income countries.[1]

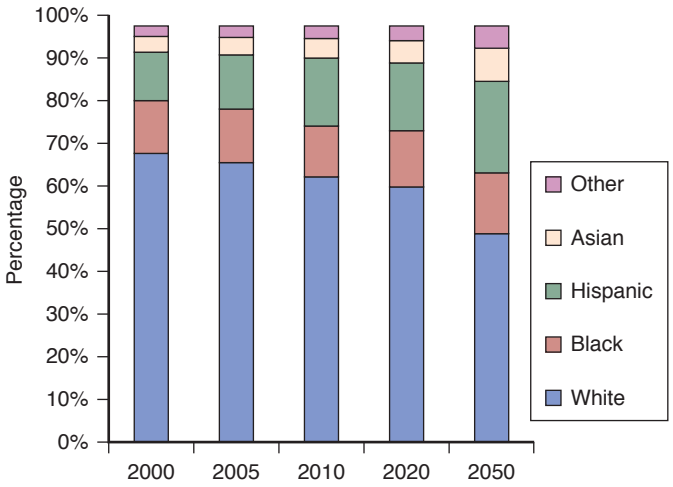

Figure 17.6 Percentages of projected US population by race/ethnicity.

ETHNIC TRENDS

Current demographic trends in the United States indicate that significant changes are occurring in the proportion of racial/ethnic groups represented in the overall population. Compared with estimates in 2000, the proportion of whites is expected to decrease, while proportions of Hispanics and Asians will nearly double by 2050 (Fig. 17.6).[17]

Trends in the Risks for Cardiovascular Disease

Racial and ethnic trends in the risk factors for and occurrence of cardiovascular and related diseases in the United States have been documented in the past few decades, and provide insights in the morbidity and mortality that can be expected in the years to come. It is important to note that the major broad racial/ethnic categories used to describe populations (white, black, Hispanic, Asian) represent genetically heterogeneous groups of diverse origins in these broad categories, resulting from migration and genetic intermixing. Rather than genetic factors, it is the psychosocial factors, particularly nutritional behaviors and disparities in access and delivery of healthcare, that have the most powerful effect on trends of vascular disease within these racial/ethnic constructs. Notable differences in cardiovascular risk factors—obesity, diabetes, hypertension, hypercholesterolemia, and smoking—have all been described.

The epidemic of obesity in the United States is not distributed equally among racial/ethnic groups. The highest obesity rates

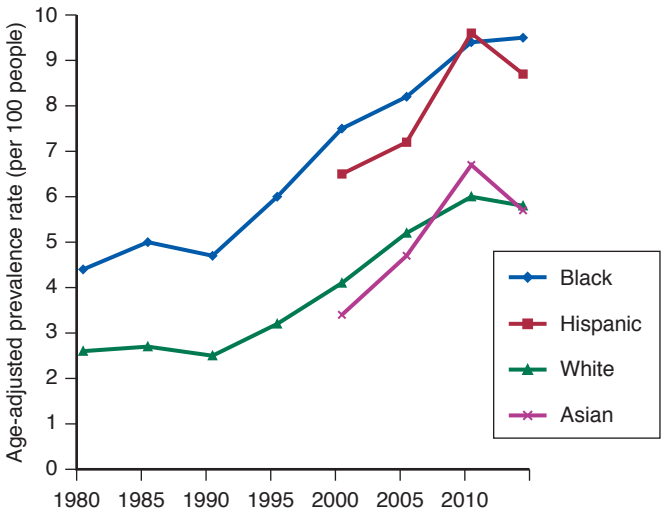

Figure 17.7 Racial/ethnic trends in age-adjusted rates of diagnosed diabetes per 100 persons in the United States, 1980 to 2014.

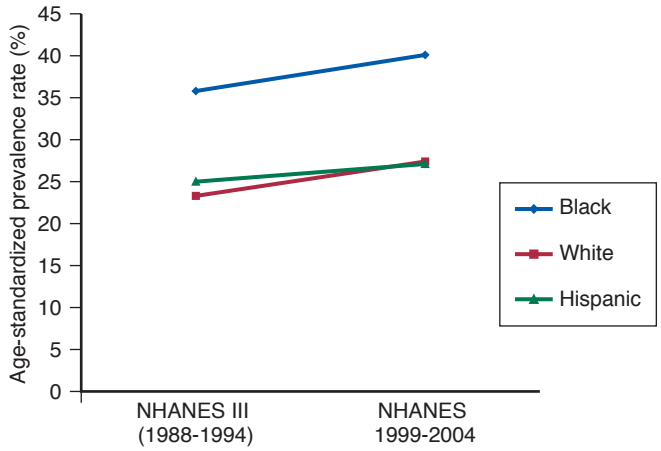

Figure 17.8 Racial/ethnic trends in age-standardized prevalence rates of hypertension in the United States, The National Health and Nutrition Examination Survey *(NHANES)*.

(BMI ≥ 30 kg/m^2) are seen among blacks (47.8%) and Hispanics (42%), followed by non-Hispanic whites (33.4%), whereas Asians have been much less affected (10.9%).[18] A parallel trend is seen in the age-adjusted prevalence of diabetes, which have risen at a similar rate in all racial/ethnic group categories (Fig. 17.7).[19,20] Trends for Asians may not accurately predict diabetes because the cutoff points of BMI indicating high risk for hypertension, dyslipidemia, and cardiovascular morbidity are lower than for other groups (obesity defined as BMI = 27.5 kg/m^2 for Asians).[21] However, after adjusting for age, gender, and BMI, Asians are 60% more likely to have diabetes than whites.[22]

The National Health and Nutrition Examination Survey (NHANES) noted an 18% relative increase in age-standardized prevalence rate of hypertension between the 1988–1994 survey and the 1999–2004 survey, with highest rates among blacks and lowest rates among Hispanics at both time points (Fig. 17.8).[23] Increases in BMI accounted for nearly all of the increase in hypertension in men, and much (but not all) of the increased prevalence in women. Greatest relative increases in prevalence rates were observed among white and black women. Among whites, awareness, treatment, and control of hypertension have improved significantly among men but not women between the survey periods. Blacks had the highest awareness and treatment rates in both surveys, and significant improvements were noted in both measures between the two time periods. However, rates of hypertension control among blacks have consistently lagged behind those of whites. Hypertension awareness, treatment, and control have been consistently lowest among Hispanics (60%, 39%, and 16%, respectively), and no demonstrable improvements have been made from 1988 to 2004.

NHANES has also tracked the prevalence of hypercholesterolemia among whites, blacks, and Hispanics and found that within these groups there has been no significant increase from 1999 to 2006. The prevalence of hypercholesterolemia in NHANES was highest for whites, at 57%, and similar for Hispanics (47%) and blacks (49%).[24] However, significant disparities existed in that blacks and Hispanics were less likely than whites to have had their cholesterol checked by their doctor, and if laboratory values demonstrated hypercholesterolemia, these groups were less likely to report having been told by a healthcare provider that they had high cholesterol, leading to substantially lower rates of treatment and control. Once told about their hypercholesterolemia, blacks, whites, and Hispanics were equally likely to report use of cholesterol-lowering medication.

Cigarette smoking has declined among US adults overall but still remains quite prevalent among American Indian/Alaska Natives (29.2%) (Fig. 17.9). Blacks and whites demonstrate similar rates of tobacco use and decline in prevalence. Despite studies suggesting that Hispanic smokers are half as likely as whites to be advised on or offered assistance with smoking cessation,[25] the largest reduction in smoking prevalence by racial/ethnic group has been seen among Hispanics.[26]

Cerebrovascular Disease

Stroke is a leading cause of death and disability in the United States,[27] with the highest age-adjusted prevalence in blacks (3.9%) compared with Hispanics (2.5%) and whites (2.5%).[25] A number of studies have suggested that there is a decreased utilization of surgical and nonsurgical interventions, as well as worse outcomes following these interventions, among racial/ethnic minority groups. The disparity in treatment of high-grade extracranial carotid artery stenosis with carotid endarterectomy is greatest for Asians compared with whites, where the ratio of intervention in Asians/whites is 0.08, whereas the Hispanic/white disparity ranges from 0.06 to 0.28, and the black/white ranges from 0.36 to 0.39.[27] These differences may result from unmeasured differences in patient preferences or disparities in access to care, the latter of which is substantiated by two large prospective cohort studies of racial/ethnic differences in carotid endarterectomy rates within the VA healthcare system (an equal access system). These studies did not find evidence of racial disparities in CEA use rates.[28,29] Negative outcomes after carotid endarterectomy have also disproportionately affected blacks and Hispanics, because studies have reported a higher rate of postoperative stroke and death in blacks and Hispanics

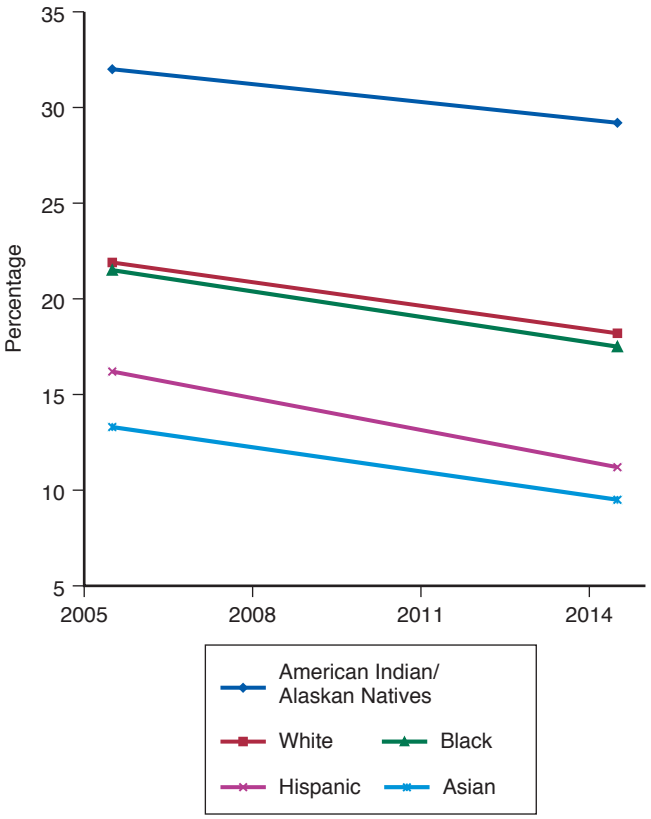

Figure 17.9 Racial/ethnic trends in prevalence of adult cigarette smokers in the United States, 2005 to 2014.

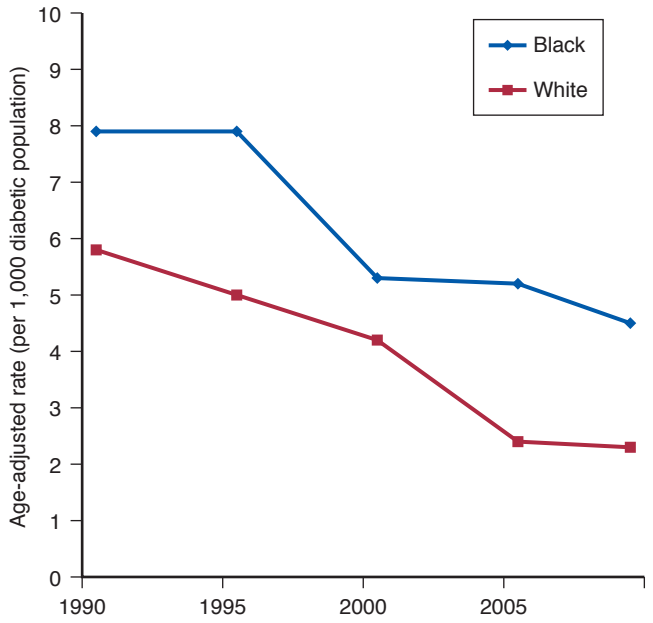

Figure 17.10 Racial trends in age-adjusted hospital discharge rates for nontraumatic lower extremity amputation per 1000 diabetic population in the United States, 1990 to 2009.

compared with whites.[30-32] Limited access to optimal surgical care may play a role in these racial/ethnic differences in outcomes after carotid endarterectomy, because these studies failed to adjust for hospital or surgeon volume.[27]

Peripheral Arterial Disease

The prevalence of PAD in the United States (defined by ankle-brachial index <0.9) is highest among blacks (7.2%), followed by whites (3.6%), Hispanics (2.4%), and Asians (2%).[25] There are more than 3.5 million people living in the United States with diagnoses of diabetes and PAD, and the diagnosis of PAD among diabetics has grown at a more rapid rate for blacks than for whites.[33] Approximately 2.5% of these patients undergo a vascular procedure each year. More white patients with claudication are treated with endovascular intervention compared with blacks and Hispanics.[34] Studies have demonstrated that, although 30-day mortality and complication rates are similar among blacks, whites, and Hispanics, a higher rate of early graft failure has been demonstrated among blacks and Hispanics.[34-36] Primary assisted patency and secondary patency are markedly inferior in black patients, suggesting a more aggressive process of neointimal hyperplasia leading to elevated rates of graft occlusion in the first postoperative year.[35] Biology has been postulated as a contributor to these poor outcomes, but no reliable histologic or genetic data exist to support this hypothesis.

Blacks and Hispanic Americans with PAD have a disproportionately high rate of 2 to 4 times higher nontraumatic lower extremity amputations, compared with whites (Fig. 17.10).[25,37] The incidence of lower extremity amputations is consistently reported as being higher in racial/ethnic minority populations even when controlled for atherosclerotic risk factors, severity of PAD, rate of infection, and income.[38-40] Because the decision to amputate is based in large part on the stage of disease at presentation, disparities in disease awareness, medical management, and access to tertiary care and vascular specialists may be key factors affecting these outcomes. Regarding optimal medical management, black patients with PAD are significantly less likely to have been treated with statins compared with whites.[35] A smaller proportion of black patients with diabetes report receiving recommendations on aspirin use from their physicians compared with whites (61% vs. 76%, respectively).[41] There is also evidence that blacks are less aggressively treated with lower extremity bypass and endovascular interventions for PAD.[37,38,42] Data from the Nationwide Inpatient Sample of patients admitted for PAD confirm that blacks and Hispanics are significantly less likely to undergo open vascular bypass or endovascular revascularization than whites when age, gender, comorbidities, and insurance status are controlled for.[40] Even among patients in the Medicare database, when patient characteristics are controlled for, black amputees were significantly less likely than whites to have undergone at least one lower extremity revascularization in the 2 years prior to major amputation.[37] There is no empiric evidence to suggest that black patients are less inclined to attempt limb salvage prior to proceeding with amputation; rather, differences in presentation or physician decision-making may explain these findings.[37]

Census data have consistently demonstrated higher levels of poverty and lower rates of insurance in black and Hispanic communities. Patients with less coverage face higher out-of-pocket costs for surgery and therefore may be less likely to opt

for intervention. Minorities are often treated in safety net hospitals, where providers may be overworked and less able to provide adequate treatment for patients with severe disease.[42] The role of hospital and physician volume has not been well explored, but data from the National Surgical Quality Improvement Program demonstrate that relatively more procedures performed in black patients involved resident trainees compared with procedures performed among white and Hispanic patients. This factor has previously been identified as a contributor to complication rates due to prolonged operative times.[36] Underinsurance may also lead to disparities in access to follow-up care after vascular intervention, including use of antiplatelet and lipid-lowering therapy postoperatively and surveillance duplex imaging.

Aortic Aneurysm

Population studies have shown that the disease burden of aortic aneurysm is greater among whites than Hispanics and blacks. However, even when the disease prevalence is controlled for, black and Hispanic patients are less likely to undergo elective repair of AAA and more likely to present emergently compared with whites.[43] This disparity may be secondary to lower rates of access to primary care and decreased rates of screening in minority communities. Blacks, Asians, and Hispanics are also more likely to receive treatment of AAA at low-volume facilities compared with whites. Numerous studies have demonstrated a higher morbidity and mortality from elective and ruptured endovascular aneurysm repair among blacks and Hispanics compared with whites, even when patient and facility factors are controlled for.[43-45]

When examining open repair of thoracic aortic aneurysms, blacks have a higher perioperative mortality compared with whites, even when adjusting for hospital volume.[46] Black, Hispanic, and Native American populations are more likely to undergo thoracic endovascular aortic repair compared with whites, with no racial/ethnic differences in complications or mortality rates.[47,48]

Hemodialysis Access

Blacks have more than 3 times the incidence of end-stage renal disease (ESRD) compared with whites.[48] A genetic basis for this difference has been identified. An increased risk for progression of chronic kidney disease (CKD) is seen among patients with high-risk variants of the gene encoding apolipoprotein L1 *(APOL1),* which appear at a high allele frequency in populations of West African ancestry.[49] Response to hypertension treatment does not differ by *APOL1* variant group. The risk of CKD progression among blacks even in the low-risk APOL1 variant group is higher than in whites, suggesting that genetic factors alone do not explain these racial disparities.[50] Limited access to specialist care and lack of medical insurance may explain why black and Hispanic patients with CKD are less likely to receive nephrology care prior to progression to ESRD compared with whites. As a result, white patients have a 22% greater chance than black patients and 32% greater chance than Hispanic patients of initiating hemodialysis with an arteriovenous fistula.[51]

Addressing Disparities

Addressing racial and ethnic disparities in the prevalence, delivery, and outcomes of care of vascular patients in the United States requires a multilevel approach. At the systems level, the Institute of Medicine has identified the operation of healthcare systems and the legal and regulatory climate in which they operate as a primary source of disparities in care. Federal, state, and institutional policies should be directed at changing the culture within healthcare facilities.[52] Addressing these disparities in access to healthcare at the policy level has been shown to reduce racial and ethnic disparities in outcome. In 2006 Massachusetts expanded healthcare coverage to include 98% of residents and noted significant reductions in racial disparities in vascular disease. Prior to healthcare expansion in that state, nonwhite patients were 12% more likely to present with severe PAD, 7% less likely to receive revascularization, and 9% more likely to receive an amputation compared with whites. After the insurance expansion to all Massachusetts residents, these measured disparities by patient race were no longer statistically significant.[53]

At the provider level, bias and uncertainty in clinical communication and decision-making have been identified by the Institute of Medicine as major sources of disparities. Healthcare providers must continue to develop cultural competency to improve clinical communication and therefore the provision of healthcare in cross-cultural situations. Cognitive shortcuts subconsciously introduce bias into medical decision-making. These rapid assessments of patients allow our minds to process complex environmental information in a short period of time by relying on preconceived notions of how a patient is expected to behave. However, they may be detrimental to the choice of the paradigm of care and ultimately affect the medical outcome of the patient.[52] The adherence to evidence-based guidelines allows physicians to rely on logical cognitive processes rapidly, thus reducing reliance on cognitive shortcuts to manage time pressures in the delivery of care. This may be particularly helpful for primary care providers to improve the use of antiplatelet and statin medications for risk reduction in patients with vascular disease. Much like how electronic clinical reminders have been shown to increase detection of AAA,[54] there is excellent evidence to support the use of tracking/reminder systems aimed at providers of racial/ethnic minority patients.[55] Protocols to alert providers to consider referral to a vascular specialist for specific diagnoses can help to address disparities in referral for timely vascular care among racial/ethnic groups.

Patient-level interventions include educational programs to improve patient awareness of interacting with and engaging the healthcare system.[52] Studies suggest that minority patients may be less communicative when the encounter is race discordant and more likely to report medical complaints with race-concordant providers.[56] This may contribute to decreased rates of intervention for claudication and rest pain if these symptoms are underreported by patients. Efforts have recently been made

to increase the presence of minorities in the health profession to facilitate members of minority communities to take advantage of treatment options.[42] Improving patients' knowledge of specialty services offered at high-volume centers particularly for aggressive limb salvage may be helpful to reduce outcome disparities if combined with efforts to improve the ability of patients to take advantage of these opportunities.

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18 CHAPTER

Clinical Evaluation of the Arterial System

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This chapter will focus on the role of patient history and physical examination in evaluating the various disease states associated with arterial, venous, and lymphatic pathology. In general, the lower extremities provide a model for the clinical evaluation of patients with peripheral vascular disease and can be used to demonstrate the value of an organized approach to the history and physical examination of the patient.

OVERVIEW OF THE CLINICAL EVALUATION

The patient's chief complaint should be determined; the physical examination should be correlated with the history and should provide a bridge to the pathophysiology of the disease process.[1-3] As an example, aortoiliac obstructive disease will often be associated with more proximal symptoms of claudication involving the buttock, hip, or thigh. If the clinical history is accurate, the examiner should expect that the femoral pulse will be absent or decreased. If it is not, the history and assumptions regarding pathophysiology should be questioned.

When the history and physical examination are completed, diagnostic studies can be ordered, if necessary, to further localize the disease or quantify the extent of the process. Therapy is ultimately driven by the natural history of the disease process and its impact on quality of life, as well as by the patient's risk factors and functional status. A relatively benign natural history or significant and unmodified patient risk factors may indicate an initial course of medical management, risk factor modification, and observation, whereas a threat of tissue loss may indicate the need for a more aggressive intervention.

Abstract

This chapter will focus on the role of patient history and physical examination in evaluating the various disease states associated with arterial, venous, and lymphatic pathology. This work will demonstrate the value of an organized approach to the history and physical examination of the patient.

Clinical History

Typically, the symptoms of arterial and venous disease can be broadly classified into the following categories: pain; weakness; neurosensory complaints, including warmth, coolness, numbness, and hypersensitivity; discoloration; swelling; tissue loss and ulceration; and varicosities. Critical elements include the initial onset of symptoms (acute or chronic); progression or changes since the initial onset; location (unilateral, bilateral, proximal, distal); character or quality of the symptom or complaint; some measure of the extent of disability or limitation; the context or factors precipitating or aggravating the symptoms (activity, position, temperature, menses, vibration, pressure); factors mitigating or relieving symptoms; and associated signs, symptoms, or risk factors. In the assessment of vascular disease, the history is important. As will be seen, variations from the expected history or pattern of findings may suggest additional disease processes that might be included in the differential diagnosis.

Physical Examination

The physical examination links the clinical history and the pathophysiology of the arterial, venous, or lymphatic disease process. The pathology associated with arterial disease can be broadly classified into inflammation-mediated arterial wall changes, arterial wall irregularity or ulceration, stenosis/occlusion, and dilation and aneurysmal degeneration. Veins are normally patent and competent, with functioning valves. Pathologically, intraluminal thrombus can partially or completely obstruct veins. With recanalization of thrombus, veins can become incompetent and lose their valvular function. Valvular incompetence can also develop primarily, independent of previous thrombosis. Finally, if flow through the lymphatic system is disturbed by obstruction, compression, or absence of the lymphatic channels, lymphedema may result.

The physical examination should progress from inspection, to palpation, to auscultation. On inspection, the extremity should be assessed for evidence of skin changes, including atrophy, cyanosis or mottling, pallor, and rubor; hair distribution; and abnormalities in nail growth. The presence and location of edema should be identified and quantified. Tissue loss and ulceration should be noted and fully described, including the location, size, and depth, and the presence of associated cellulitis and inflammation should be documented. Motor function should be documented. On initial palpation, changes in temperature and sensation should be noted and compared with the contralateral extremity. All accessible pulses should be evaluated. At a minimum, pulses should be classified as absent, decreased, or normal. A prominent or widened pulse may suggest aneurysmal degeneration.

Synthesis of the History and Physical Examination

Assessment of a patient with vascular disease is unique in that it is frequently possible to make a diagnosis and predict the underlying anatomic pathology on the basis of history and physical examination alone. This is important because the anatomy of the disease process can often correlate with the location of symptoms. The history and physical examination should be thought of as a system of checks and balances. Symptoms should correlate with the physical examination and suspected pathology.

The Evolving Role of Telemedicine in History and Physical Exam for Vascular Disease

As with many aspects of healthcare, technology has changed the landscape in which we practice. Many fields rely heavily on remote interaction between treating physicians and their patients. While many believe that telemedicine in vascular surgery is a new and evolving concept, it has been studied for more than 20 years. For example, Endean and colleagues described vascular evaluation by teleconference, remote Doppler assessment, and the use of physician extenders in a manuscript published in 2001.[4,5] The barriers they described at the time sound strikingly familiar to the challenges we all face, and electronic health records today comfort with technology and successful execution of technology-based assessment strategies. While this is an evolving strategy, future advances will undoubtedly change the way we perform physical examination in the future.

HISTORY IN PATIENTS WITH ARTERIAL DISEASE

Patients with peripheral arterial disease (PAD) may initially be seen after acute arterial occlusion or with symptoms of chronic arterial insufficiency. Regardless of whether the onset of symptoms is acute or chronic, the chief complaint is generally pain or discomfort. As part of the initial history, it is important to determine the acuteness of onset, the character and intensity of the pain or discomfort, changes in the character and intensity since onset, and its location.

Acute Arterial Occlusion

Acute arterial occlusion may be either embolic or thrombotic in etiology (see Chapter 100 and Chapter 101). Classically, acute arterial occlusion is associated with the six P's: pain, pallor, pulselessness, paresthesias, paralysis, and poikilothermy (meaning changing to room temperature; i.e., a cold extremity). Symptoms can occur within minutes to hours after acute arterial occlusion and are associated with a sudden, dramatic decrease in perfusion. Classically, a patient will complain of generalized pain, severe, and not well localized. The patient will notice a change in the color of the extremity, a decrease in sensation, and coolness to touch. Absent motor function is consistent with severe limb-threatening ischemia.

Acute Arterial Occlusion of the Lower Extremity

As a rule, patients with acute arterial occlusion secondary to an embolic etiology will not have a history of claudication or symptoms suggestive of chronic occlusive arterial disease. Embolic

occlusion of the iliac, femoral, or popliteal arteries is frequently associated with a history of atrial fibrillation, and the patient may have had a previous embolic event. Patients with thrombotic occlusion of the iliac, femoral, or popliteal arteries will frequently have a history of claudication and may have previously undergone arterial bypass or intervention.

Atheroembolism: "Blue Toes Syndrome"

Atheroembolic debris arising from atherosclerotic plaque or ulcerations in the aorta, as well as the iliac, femoral, and popliteal arteries, can result in distal small-arterial occlusion (see Chapter 103). Progressive renal insufficiency can be associated with atheroemboli originating in the thoracic or suprarenal aorta. Patients may have undergone some form of catheter-based procedure involving manipulation of a catheter in the aortic arch or the thoracic and abdominal aorta, or the embolism may be spontaneous.

Acute Arterial Occlusion of the Upper Extremity

While less common, acute arterial occlusion may also occur in the upper extremities. The onset and symptoms are similar to those seen in the lower extremities. Emboli associated with atrial fibrillation or recent myocardial infarction are more common, but may also originate from aneurysmal disease of the arch or upper extremity arteries. Atheroemboli involving the hand or digits may arise from atherosclerotic irregularity and plaque in the aortic arch, or from thrombus associated with a subclavian artery aneurysm.

Chronic Obstructive Arterial Disease

Patients with PAD most commonly have long-standing symptoms. Chronic PAD can be categorized according to the Rutherford classification system of occlusive arterial disease, which encompasses a spectrum of symptoms, beginning with effort discomfort (claudication) and progressing to pain at rest and tissue loss.[6] Claudication is derived from the Latin word *claudicare*, which means to limp or be lame. Thus, claudication involves the lower extremities and is associated with walking. Effort-induced discomfort with activity involving the upper extremity can be associated with stenosis or occlusion of the subclavian and axillary arteries.[7] The Rutherford classification system—a clinical staging system—ranges from asymptomatic (Stage 0), to mild or moderate claudication (Stage 3), to severe (Stage 6).

Lower Extremity Claudication

Claudication symptoms are associated with walking, and relief occurs promptly after the cessation of activity. Complete relief of symptoms should occur within 5 to 10 minutes, and it should not be necessary for the patient to sit to obtain relief. Symptoms may be described as cramping, aching, fatigue, or numbness, and the common denominator is an association with exercise or activity.

Symptoms may have been present for months or years. Anatomically, lower extremity PAD is broadly classified as aortoiliac, femoropopliteal, or tibial. Depending on the location of the arterial obstruction, the patient may have pain in any of the three major muscle groups of the lower extremity: the buttock, thigh, or calf. Symptoms may involve one or more of these muscle groups and may progress from the proximal to the distal part of the extremity or from the calf to the thigh with continued activity. Symptoms will often occur in the muscle group immediately distal to the obstruction. Whereas obstruction of the superficial femoral artery will cause calf discomfort, aortoiliac disease will result in symptoms involving the buttock or thigh. However, patients with aortoiliac disease can also have associated or isolated discomfort of the calf because the calf is the most distal large muscle group and is used extensively in walking. The triad of intermittent claudication, impotence, and absent femoral pulses is associated with aortoiliac occlusion and is often referred to as Leriche's syndrome. In his initial descriptions of the disease process, Leriche also identified widespread atrophy of the lower extremities and a pale appearance of the extremities and foot.[8]

Some patients with PAD confirmed by noninvasive vascular testing may not complain of claudication because comorbid conditions may limit their exercise tolerance. Conversely, other patients may have classic symptoms of claudication but a normal pulse examination. Because initial assessment generally occurs while the patient is at rest on the examining table, it is important to remember that the claudication occurs with walking. In cases when there is a mismatch between the history and physical examination, the physical examination may need to be repeated after exercise.

Conditions Mimicking Arterial Claudication

Classically, claudication is associated with arterial stenosis or occlusion; it is induced by exercise and relieved by rest, and has an onset that is consistently reproducible. Inconsistencies in the history should suggest the possibility of other causes of the patient's symptoms. Included in the differential diagnosis of claudication are musculoskeletal, neurologic, and venous pathologies—the most common of which are osteoarthritis, spinal stenosis, and venous outflow obstruction. Symptoms that occur at rest, occur with standing, or are associated with positional changes may suggest osteoarthritis, spinal stenosis, radiculopathy, or venous claudication (Table 18.1).

Patients with atypical claudication of nonarterial etiology will often note pain with exertion, yet the pain does not stop the individual from walking, may not involve the calves or other major muscle groups in the leg, or does not resolve within 10 minutes of rest.[9-11] Patients may report the same type of pain in both legs regardless of the associated presence of occlusive disease. Frequently, patients with atypical symptoms often report walking impairment because of joint pain or shortness of breath.[9,10]

Ultimately, in the evaluation of an individual with leg pain, the examiner has to be cognizant of the patient's comorbid conditions in an effort to offer the most complete treatment. Newman and colleagues compared answers to the Rose Questionnaire in patients with and without arthritis, all of whom had a decreased ankle-brachial index and exertional leg pain.[11] Both groups had pain in the calf or calves on walking at a normal

TABLE 18.1 Differential Diagnosis of Claudication

Condition	Location of Pain or Discomfort	Characteristic Discomfort	Onset Relative to Exercise	Effect of Rest	Effect of Body Position	Other Characteristics
Arterial Conditions						
Intermittent claudication of the calf	Calf muscles	Cramping pain	After same degree of exercise	Quickly relieved	None	Reproducible
Intermittent claudication of the hip, thigh, buttock	Hip, thigh, buttocks	Aching discomfort, weakness	After same degree of exercise	Quickly relieved	None	Reproducible
Popliteal artery entrapment	Calf muscles	Cramping pain	After exercise	Quickly relieved	Aggravated by extension of the foot	Typically seen in younger patients
Venous Conditions						
Venous claudication	Entire leg, but usually worse in the thigh and groin	Tight, bursting pain	After walking	Subsides slowly	Relief speeded by elevation	History of iliofemoral deep venous thrombosis, signs of venous congestion, edema
Venous compartment syndrome	Calf muscles	Tight, bursting pain	After much exercise (e.g., jogging)	Subsides very slowly	Relief speeded by elevation	Typically, heavily muscled athletes
Neurologic Conditions						
Nerve root compression (e.g., herniated disk)	Radiates down leg, usually posteriorly	Sharp lancinating pain	Soon, if not immediately after onset	Not quickly relieved (also often present at rest)	Relief may be aided by adjustment of back position	History of back problems
Neurospinal root compression	Hip, thigh, buttocks (follows dermatome)	Weakness more than pain	After walking or standing for same time	Relieved by stopping only if position changed	Relieved by lumbar spine flexion (sitting or stooping forward)	Common history of back problems; provoked by increased intra-abdominal pressure
Orthopedic Conditions						
Hip arthritis	Hip, thigh, buttocks	Aching discomfort	After variable degree of exercise	Not quickly relieved (and may be present at rest)	Patient is more comfortable sitting with weight taken off legs	Variable; may relate to activity level, weather changes

pace, while in a hurry, or when walking uphill. However, the patients with arthritis had a higher incidence of pain when standing still or sitting, were less likely to continue walking after the onset of pain, and required more than 10 minutes to obtain relief after they had stopped walking (Table 18.2).

Several prior reports have examined the sensitivity and specificity of the Rose Questionnaire for patients with intermittent claudication. Geoffrey Rose at the London School of Hygiene designed the original questionnaire, which was used to identify patients with intermittent claudication.[12] While the original questionnaire was highly specific (>90%), it was not very sensitive (<70%). Several investigators, including those described above, have worked to refine the sensitivity of this instrument and others like it. These tools are critical in the attempt to discern patients with and without significant claudication from those with other conditions that cause leg pain.

Neurogenic Claudication

Neurogenic claudication due to spinal stenosis can result from a wide range of conditions causing compression of the spinal cord or its nerve roots in the region of the lumbar spine. It may be associated with aging, arthritis, or inherited deformities of the spine. The symptoms of spinal stenosis are frequently inconsistent in their relationship to exercise or activity.

Venous Insufficiency/Venous Claudication

In an individual with venous claudication, the symptoms are associated with a proximal venous obstruction resulting in impaired venous outflow. When an individual begins to exercise or engage in some activity, venous outflow cannot accommodate the increase in arterial flow to the extremity, and high venous pressure develops. The veins become engorged and tense, which

TABLE 18.2 Answers to the Rose Questionnaire by Patients With or Without Arthritis, With a Low Ankle-Brachial Index and Exertional Leg Pain, but Without Positive Rose Questionnaire Findings for Intermittent Claudication (N 234)

	THOSE WITHOUT ARTHRITIS (N 73)		THOSE WITH ARTHRITIS (N 156)		
Question	Number	Percentage	Number	Percentage	*P* Value
Do you have pain in either leg on walking?	73	100	156	100	—
Does the pain begin when standing still or sitting? Answer = No	57	78.1	60	38.5	.001
Do you get this pain in your calf/calves? Answer = Yes	55	75.3	118	76.1	.897
Do you get it if you walk uphill or hurry? Answer = Yes	55	82.1	86	72.3	.133
Do you get it when you walk at an ordinary pace on the level? Answer = Yes	46	62.2	97	65.5	.620
Does it ever disappear while walking? Answer = No	22	29.7	76	50.7	.003
What do you do if you get it while walking? Answer = Stop or slow down	54	72.0	123	83.7	.041
What happens to the pain if you stand still? Answer = Relieved in 10 minutes or less	59	95.2	82	72.6	.001

From Newman AB, Naydeck BL, Sutton-Tyrrell K, et al. For the Cardiovascular Study Research Group. The role of comorbidity in the assessment of intermittent claudication in older adults. *J Clin Epidemiol*. 2001;54:294–300.

causes a bursting sensation or pain that is slowly relieved by rest. The same symptoms can be seen in individuals with chronic venous insufficiency, where persistent venous thrombosis or valvular insufficiency can cause an increase in ambulatory venous pressure that results in chronic lower extremity edema, as well as evidence of postphlebitic skin changes. In these patients, swelling is frequently minimal in the morning but progresses throughout the day with increased activity and dependency of the extremity.

Other Considerations in Young Patients

Claudication of a vascular etiology most commonly occurs in patients 50 years or older. In younger patients, symptoms of effort discomfort can be associated with popliteal artery obstruction from muscular or tendinous entrapment or mucinous degeneration of the artery. Popliteal artery entrapment[13] is a condition commonly seen in patients younger than 50 years (see Chapter 143). Another condition that can be seen in younger patients is chronic compartment syndrome, an overuse syndrome that is often symmetric and bilateral (see Chapter 197).[14,15] The most common complaints are muscle cramping and swelling, with focal paresthesias on the plantar or dorsal aspect of the foot. The pain or discomfort is associated with tightness in the calf and is precipitated by exercise. The patient is often an athlete or a runner with large calf muscles. Muscle swelling, increased compartment pressure, and impaired venous outflow constitute a vicious circle. The pain usually starts after considerable exercise and does not quickly subside with rest.

Rest Pain

Progressive, frequently multilevel atherosclerotic obstructive disease results in ischemic rest pain. In the absence of acute embolic or thrombotic arterial occlusion, the onset of symptoms is gradual. In most cases, the patient will have a history of claudication. With injury or minor trauma, the patient may have associated nonhealing ulcers. Pain at rest represents a significant decrease in circulation and involves the most distal aspect of the lower extremity, which is farthest from the central source of circulation and blood flow. The forefoot and digits are most commonly involved. In the absence of acute arterial occlusion, patients do not have pain in the thigh or calf at rest. The symptoms are classically relieved with dependency because gravity tends to facilitate circulation. The symptoms are aggravated if the patient lies down and elevates the extremity, which further increases the work of pushing blood against gravity to the foot. Patients will complain that the pain awakens them at night or develops soon after lying down. It is not uncommon for patients to be unable to describe the character of the pain. It is easiest to quantify the severity of rest pain relative to the sleep that patients are able to obtain. Early in the course, patients may awaken only occasionally and are able to get back to sleep after sitting up or walking about the room. With time, patients must sleep with their foot constantly hanging over the edge of the bed.

The clinical distinction between rest pain and tissue loss—which represent the two clinical conditions described as critical limb ischemia—is a matter of constant debate.[16] While both

syndromes require urgent attention, the clinical risk for amputation implied by the latter is presumed to be much higher. However, the magnitude of this difference remains a topic of discussion.[17]

Conditions Mimicking Rest Pain

Clinicians should note, and investigate, other etiologies of leg pain, especially when noninvasive tests fail to reveal evidence of PAD. As shown in several examples below, inconsistencies in the history can suggest an alternative diagnosis.

Diabetic Neuropathy

Diabetic patients are prone to a distal arterial occlusive process that frequently involves the tibial and digital arteries and can result in severe ischemia and pain at rest. Diabetic patients can also have associated peripheral neuropathy (see Chapter 12). Diabetic neuropathy can involve the forefoot and digits, and is often described as a burning pain, hyperesthesia, or a "pins and needles" sensation. A careful history should permit differentiation between ischemic rest pain and neuropathy because neuropathic pain is constant and unrelieved by dependency.

Complex Regional Pain Syndrome

Complex regional pain syndrome (or reflex sympathetic dystrophy or causalgia) is described in detail in Chapter 193. Often the pain originates after soft issue or nerve injury. Pain is the most common and prominent feature. The pain is frequently burning and can be worse in the distal aspects of the extremity.

Upper Extremity Effort Discomfort

Effort discomfort involving the upper extremity can be associated with stenosis or occlusion of the subclavian or axillary arteries. Like claudication, symptoms are induced by exercise and relieved by rest. A careful history should allow the examiner to make a distinction between symptoms related to arterial disease and those associated with thoracic outlet syndrome (see Chapter 120). In neurogenic thoracic outlet syndrome, the nerve roots that form the brachial plexus and its trunks are compressed within the scalene triangle (see Chapter 121). While the diagnosis of these patients can be especially difficult, careful attention to physical exam and a reliable history will add to the ability to decide whether or not surgical treatment is the best course.

PHYSICAL EXAMINATION IN PATIENTS WITH ARTERIAL DISEASE

Regardless of the suspected vascular pathology, physical examination of an individual with suspected arterial disease should be complete because of the systemic nature of the atherosclerotic process underlying the arterial disease.

Inspection

The examination begins with the observation or inspection of the extremities. Significant PAD can be associated with atrophy of the calf muscles; loss of hair growth over the lower part of the leg and foot is also a common sign of arterial insufficiency, as is thickening of the nails. With more advanced changes, atrophy of the skin is seen; there is a decrease in subcutaneous tissue, and the skin assumes a fragile, shiny appearance. With severe ischemia, dependent rubor is observed, and the distal part of the leg, the foot, and the digits may appear reddish. On elevating the lower extremity, the rubrous appearance is replaced with pallor.

Ischemic Ulcers

With increasing ischemia, the formation of ischemic ulcers can be observed. These ulcers are small and circinate, with pale, grayish granulation tissue in the base. They are noted specifically on the toes, heels, or fingertips, and if found more proximally, they are usually secondary to trauma. When examining the foot and digits for ischemic ulcers, care should be taken to examine between the toes because skin breakdown and small fissures can frequently begin in these intertriginous areas. Ischemic ulcers are usually painful and can progress to tissue necrosis and frank gangrene. Gangrene can consist of dry eschar, or be "wet" due to purulent or serous drainage at the margins of the eshar. Table 18.3 provides a model that can be used to describe and document ischemic ulcers and wounds in a uniform fashion.

Livedo Reticularis

Close examination of the skin may reveal abnormalities, such as livedo reticularis, which is a discoloration of the skin consisting of macular, violaceous, connecting rings that form a netlike or lacelike pattern. Decreased flow leading to hypoxia and collateral formation are thought to cause the cutaneous findings. Livedo reticularis can be due to PAD and be found in areas of ischemia. More often it is secondary to vasculitis, calciphylaxis, atheroemboli, hyperviscosity syndromes, endocrine abnormalities, infection, or any combination of these causes. In these latter forms, the lesions are usually more diffuse. In situations in which the microcirculation is affected, splinter hemorrhages, focal areas of cyanosis, or punctate violaceous lesions can be indicative of microemboli. These lesions can often be multiple, but they can also occur in single form. The lesions are generally

TABLE 18.3 Documentation of Wound Characteristics

Characteristic	Observations to Be Documented
Wound size	Length, width, depth, area, volume
Undermining	Presence, location, measurement
Appearance	Granulation tissue, sloughing, necrotic eschar, friability
Exudate	Amount, color, type (serous, serosanguineous, sanguineous, purulent), odor
Wound edge	Presence of maceration, advancing epithelium, erythema, even, rolled, ragged

From Lawrence PF, Caswell DR. The wound care center and limb salvage. In: Moore WS, ed. *Vascular and Endovascular Surgery. A Comprehensive Review*. 7th ed. Philadelphia: Saunders Elsevier; 2006:876–889.

small in overall diameter and are frequently found to be painful.[18,19]

Acrocyanosis

While a precise definition of acrocyanosis remains elusive, it is a generalized term used to describe painless, symmetric, cyanotic discoloration of the hands, feet, and occasionally face and central portions of the body, such as the tips of the ears or nose.[20] Episodes of acrocyanosis are often triggered by cold exposure.[21,22] Distinction from Raynaud's-like phenomena is difficult to discern.

Pulse Examination

Palpation of pulses should be performed in a relatively consistent manner and should be complete. Comparing a pulse with that in the contralateral extremity can demonstrate important relative differences. In addition to pulses in the neck and the upper and lower extremities, the abdominal aortic pulse also should be assessed. The carotid pulse can best be palpated in the midneck region, anterior to the sternocleidomastoid muscle. Superficial temporal artery pulses should also be documented, particularly when evaluating temporal arteritis. The subclavian pulse is usually found in the supraclavicular fossa, and the axillary pulse is found lateral to the clavicle along the course of the deltopectoral groove or in the axilla. Upper extremity pulses are examined in the antecubital fossa and at the wrist. Both the brachial and radial pulses can generally be felt with superficial palpation. The ulnar pulse, in contrast, does require firmer palpation because this artery follows a deeper course than the radial or brachial arteries. In the lower extremity, the common femoral, popliteal, dorsal pedal, and posterior tibial artery pulses are examined. The common femoral artery pulse can usually be found in the medial aspect of the groin, just below the inguinal ligament, and can be felt with light palpation in a thin person; but deeper palpation is necessary in an obese individual. Popliteal artery pulses are more difficult to palpate because they are generally located lateral to the popliteal fossa. The patient's knee should be partially flexed and relaxed to allow the examiner to palpate the pulse; firm pressure is required. The posterior tibial artery pulse is typically found in the hollow posterior to the medial malleolus, and usually, gentle pressure allows adequate palpation. Increased pressure, particularly in patients with poor arterial perfusion, can obscure the pulse. The dorsal pedal pulse is generally found on the dorsum of the foot between the first and second metatarsal bones. In 10% of patients, the dorsal pedal pulse is absent congenitally. In patients with suspected popliteal artery entrapment, tibial pulses should also be evaluated during active plantar flexion of the foot or during passive dorsiflexion.

Arterial Aneurysms

During the course of the pulse examination, the size of the artery should be assessed. Typically, an aneurysm is first suspected by a prominence of the palpated pulse. If a prominent pulse is appreciated, the artery should be further evaluated to determine whether aneurysmal dilation is present, and if it is, the size of the aneurysm should be estimated and noted. Peripheral aneurysms are most commonly found in the popliteal, common femoral, and subclavian arteries. The abdominal aorta can be palpated in thin individuals by having them relax their abdominal musculature and then palpating deeply.

Auscultation

After palpation, the arteries should be auscultated. Although, typically, nothing is heard on auscultation, the presence of a bruit, which is indicative of turbulent blood flow, is a marker of underlying pathology. Generally speaking, the pitch and duration of a systolic bruit are correlated with increasing severity of arterial narrowing, but it is difficult to quantify the degree of stenosis. Bruits extending into diastole may suggest the presence of an arteriovenous fistula. Although uncommon in the past, arteriovenous fistulae are being seen with increasing frequency because of the rising number of arterial catheterizations.

Palmar Circulation

In patients with upper extremity arterial disease, it may be of value to assess the patency of the palmar arch. Typically, circulation to the hand is supplied by both the radial and ulnar arteries. These two arteries merge to form the palmar arch. In approximately 10% of the population, the arch is congenitally incomplete. The Allen test can demonstrate the presence of an incomplete arch or occlusion of the arch. In this test, pressure is applied at the wrist to occlude the radial and ulnar arteries. The patient is asked to open and close the hand, making a fist. After several repetitions, the palmar aspect of the hand blanches and becomes pale. With release of pressure over the radial or ulnar artery, normal skin color should return within seconds.

THE ULCERATED LEG

Chronic ulcers can be associated with arterial ischemia, venous stasis, and neuropathy (Table 18.4). The history and physical examination are critical because the causes are not mutually exclusive. A history of arterial insufficiency, including claudication and rest pain, should be sought. Ischemic ulcers and tissue loss represent the far end of the spectrum of arterial disease. Diabetics can have arterial disease and peripheral neuropathy. Neuropathy can predispose diabetic patients to neurotrophic ulcers over the weight-bearing prominences of the plantar surface of the foot. Venous stasis disease can result in characteristic ulcerations, but associated arterial disease can affect healing and influence treatment. All areas of ulceration and tissue loss should be fully characterized with respect to location and size (Table 18.5).

Ischemic Ulcers

Ischemic ulcers are usually painful, and there is likely to be typical ischemic rest pain in the distal part of the forefoot that occurs nocturnally and is relieved by dependency. At first, these ulcers may have irregular edges, but when chronic, they are more likely to be "punched out." They are commonly located distally over the dorsum of the foot or toes but may occasionally

TABLE 18.4 Differential Diagnosis of Common Leg Ulcers

Type	CHARACTERISTIC					
	Usual Location	Pain	Bleeding With Manipulation	Lesion Characteristics	Surrounding Inflammation	Associated Findings
Ischemic ulcer	Distal, on the dorsum of the foot or toes	Severe, particularly at night; relieved by dependency	Little or none	Irregular edge; poor granulation tissue	Absent	Trophic changes of chronic ischemia; absence of pulses
Neurotrophic ulcer	Under calluses or pressure points (e.g., plantar aspect of the first or fifth metatarsophalangeal joint)	None	May be brisk	Punched out, with a deep sinus	Present	Demonstrable neuropathy
Venous stasis ulcer	Lower third of the leg (gaiter area)	Mild; relieved by elevation	Venous ooze	Shallow, irregular shape; granulating base; rounded edges	Present	Lipodermatofibrosis, pigmentation

TABLE 18.5 Characterization of Areas of Ulceration and Tissue Loss

Ulcer Location	Ulcer Etiology	Clinical Appearance	Treatment
Toes, distal forefoot	Arterial Insufficiency	Dry/Wet Gangrene	Revascularization
Weight bearing surface	Diabetic Neuropathy	Callus, "heaped up"	Offloading
Medial malleolus	Venous insufficiency	Beefy red, brown staining of skin	Compression, venous intervention

be pretibial. The ulcer base usually consists of poorly developed, grayish granulation tissue. The surrounding skin may be pale or mottled, and the previously described signs of chronic ischemia are invariably present. Notably, the usual signs of inflammation that one would expect surrounding such a skin lesion are absent, because it is the lack of adequate circulation to provide the necessary inflammatory response for healing that underlies ischemic ulcers. For the same reason, probing or debriding the ulcer causes little bleeding.

Neurotrophic Ulcers

Neurotrophic ulcers are completely painless but bleed with manipulation. They are deep and indolent and are often surrounded not only by acute but also by chronic inflammatory reaction and callus. Their location is typically over pressure points or calluses (e.g., the plantar surface of the first or fifth metatarsophalangeal joint, the base of the distal phalanx of the great toe, the dorsum of the interphalangeal joints of toes with flexion contractures, or the callused posterior rim of the heel pad). The patient generally has long-standing diabetes with a neuropathy characterized by patchy hypoesthesia and diminution of positional sense, two-point discrimination, and vibratory perception.

Stasis Ulceration

The so-called venous stasis ulcer, actually secondary to ambulatory venous hypertension, is located within the gaiter area, most commonly near the medial malleolus. It is usually larger than the other types of ulcers and irregular in outline, but it is also shallower and has a moist granulating base. The ulcer is almost invariably surrounded by a zone containing some of the hallmarks of chronic venous insufficiency—pigmentation and inflammation ("stasis dermatitis"), lipodermatofibrosis, and cutaneous atrophy.

Other Types of Ulcers

More than 95% of all chronic leg or foot ulcers fit into one of the previously described recognizable types. However, leg ulcers may also be produced by vasculitis and hypertension. Vasculitis frequently produces multiple punched-out ulcers and an inflamed indurated base, which, on biopsy, suggests fat necrosis or chronic panniculitis. Hypertensive ulcers represent focal infarcts and are very painful. They may be located around the malleoli, particularly laterally. Long-standing ulcers that are refractory to treatment may represent underlying osteomyelitis or a secondary malignant lesion. Finally, most patients with ulcers identify trauma as an initiating cause. In diabetics, ulcers may also be related to poorly fitting shoes that result in persistent irritation or trauma, or uneven weight distribution on the plantar surface of the foot.

Ulcer Assessment: What's Next

The presence of an ulcer can be a risk factor for amputation. However, as outlined above, there is significant heterogeneity in ulcer types, and with it, heterogeneity in amputation

risk. Categorizing and assessing ulcers has proven challenging, and several wound assessment mechanisms beyond physical examination have evolved. The testing and validation of these assessment systems, which usually involve digital photography, electronic health records, and a rating system, is an active area of investigation.[23]

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A complete reference list can be found online at www.expertconsult.com

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CHAPTER 19

Clinical Evaluation of the Venous and Lymphatic Systems

JASON JOHANNING and THOMAS G. LYNCH

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INTRODUCTION

Clinical evaluation of the patient with suspected venous or lymphatic disease can be challenging due to common presenting symptoms, varied pathophysiology, and the potential for associated comorbidity. Symptoms can range from mild to severe, impairing quality of life and threatening limb viability.

The vascular surgeon is typically consulted in order to establish a diagnosis in addition to developing and initiating a therapeutic plan. The evaluation begins with a history of the present illness. From the history, it should be possible to determine whether the problem is acute or chronic and whether the patient requires immediate intervention or there is time to complete a more extensive evaluation (Fig. 19.1). After obtaining the history, the next step is a complete physical examination, which should allow the practitioner to identify well over 90% of venous and lymphatic syndromes prior to any confirmatory studies. The emphasis of this chapter is on the use of the history and physical examination to identify the various disease states associated with venous and lymphatic pathology and the varying classification systems commonly used in clinical practice. In general, the lower extremities provide a model for the clinical evaluation and can be used to demonstrate the value of an organized approach to the history and physical examination. When appropriate, correlations with related pathology and presenting symptoms in the upper extremities are discussed. There are few areas in

Keywords

clinical presentation
swelling
anatomy
DVT
lymphedema
CEAP
scoring systems

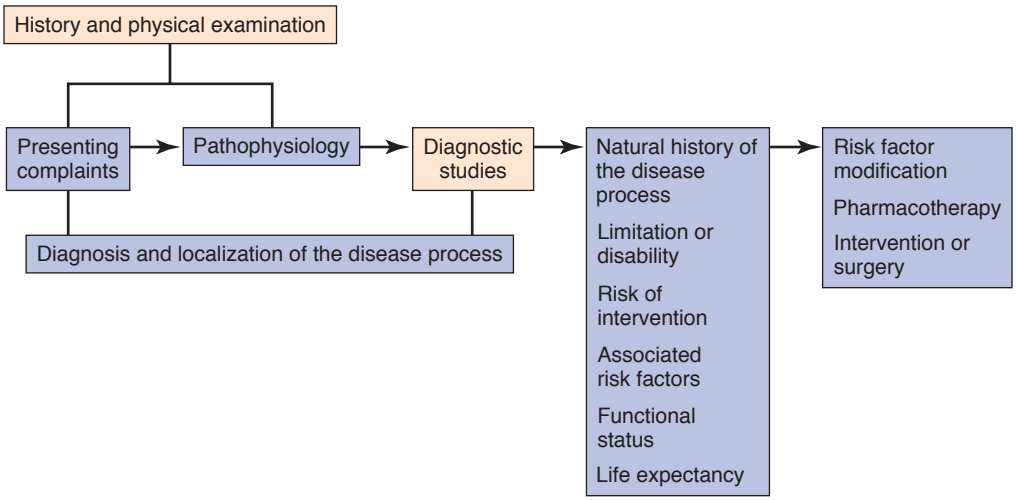

Figure 19.1 This algorithm illustrates the stepwise evaluation and management of patients presenting with arterial, venous, or lymphatic disease. The diagnosis and localization of the disease process involves the history and physical examination and any indicated diagnostic studies. The history and physical examination identify the presenting findings and provide a bridge to potential pathology and pathophysiology. Therapy is dependent upon the natural history of the disease process and its impact on the patient's quality of life as well as the patient's associated risk factors and functional status. (From Rutherford, 7th edition, Fig. 13.1, p. 204.)

medicine where conditions lend themselves so readily to diagnosis solely on the basis of a thoughtful, organized history and a careful physical examination.

Therefore the goal of this chapter is to present in a systematic fashion the classic presentation of the most common venous and lymphatic diseases. By correlating the clinical presentation with an understanding of the anatomy and pathophysiologic alterations, the clinician should be able to make a presumptive diagnosis that can be confirmed with common noninvasive tests and, if necessary, the sparring use of invasive procedures.

ANATOMIC CONSIDERATIONS

The anatomy of the veins and lymphatics provides the basis for understanding the pathophysiology of common disease states. With the primary purpose of the veins to return blood to the heart in a unidirectional fashion and for the lymphatics to carry excess interstitial fluid and particulate matter back to the central circulatory system, any interruption in normal flow patterns forms the basis for venous and lymphatic pathology.

Deep Veins of the Lower Extremity

The deep veins of the leg are bounded within their muscular compartments and enveloping fascia; they run together with the corresponding arterial and lymphatic structures.[1,2] The anterior tibial, posterior tibial, and peroneal veins are paired and coalesce to form the popliteal vein or veins, which may also be paired. The popliteal vein passes superiorly through the adductor canal, becoming the femoral vein (previously referred to as the superficial femoral vein), which then merges with the deep femoral vein to form the common femoral vein. Superior to the inguinal ligament, the common femoral vein becomes the external iliac vein. The external and internal iliac veins merge to form the common iliac vein. The left common iliac vein passes beneath the right common iliac artery and joins the right common iliac vein to become the inferior vena cava.

Superficial Veins of the Lower Extremity

The superficial veins, lying above the muscular fascia, are bounded superficially by the saphenous fascia. The great saphenous vein originates at the level of the ankle and continues medially to the level of the saphenofemoral junction to empty into the common femoral vein. Accessory saphenous tributaries arise from the saphenofemoral junction in variable anteromedial and anterolateral distributions (Fig. 19.2). The small saphenous vein originates over the ankle, lying above the muscular compartment, and is bounded by saphenous fascia superficially. It empties into the popliteal vein at the saphenopopliteal junction (Fig. 19.3). Two anatomically important veins are the intersaphenous vein, connecting the great and the small saphenous veins, and the posterior accessory great saphenous vein, draining the subcutaneous tissue and skin overlying the medial calf.[2,3]

Perforating veins can be found along the length of the lower extremity, with the majority located below the knee.[4,5] These veins traverse the muscular fascia and connect the deep and superficial veins, with flow normally occurring from the superficial veins into the deep venous system. These perforators (Fig. 19.4) are located from the level of the heel to the upper thigh along the medial leg in a narrow band and are often described based on named anatomic location or distance from the proximal medial malleolus.

The remaining veins lying above the muscular fascia and underneath the dermis are best described as communicating veins, which form a variable network that interconnects the named superficial veins.

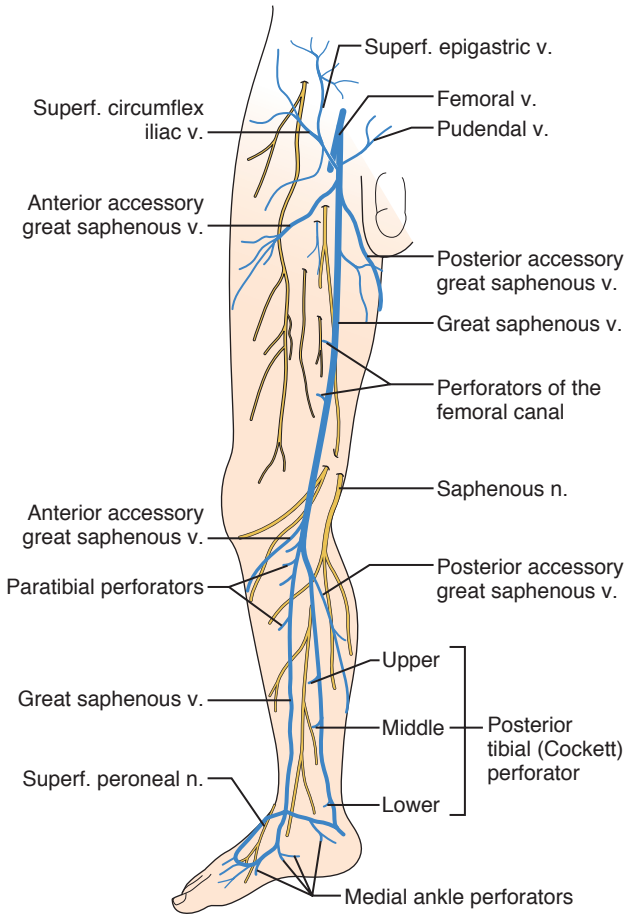

Figure 19.2 Anatomy of medial superficial and perforating veins of the leg. (From Rutherford, 6th edition, Fig. 158–151, p. 2269.)

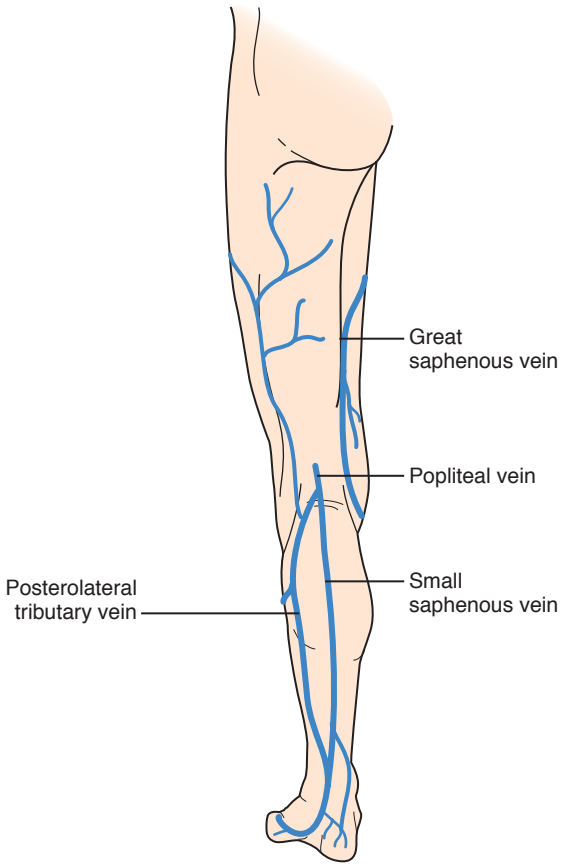

Figure 19.3 The small saphenous vein dominates the posterolateral superficial venous drainage and originates in the dorsal venous arch. At the posterolateral ankle, it is intimately associated with the sural nerve. Note the important posterolateral tributary vein and the posterior thigh vein, which ascend and connect the small saphenous venous system with the great saphenous venous system. (From Mozes G, Carmichael SW, Gloviczki P. Development and anatomy of the venous system. In: Gloviczki P, Yao JST, eds. *Handbook of Venous Disorders*. 2nd ed. London: Arnold; 2001:11–24. (From Rutherford, 6th edition, Fig. 158–152, p. 2269.)

Deep Veins of the Upper Extremity

Similar to those in the lower extremity, the deep veins of the upper extremity run in a paired fashion along with the radial and ulnar arteries, coalescing to form the brachial veins at the level of the antecubital fossa and bounded by the bicipital aponeurosis. Traversing the upper arm, the brachial vein or veins become the axillary vein or veins at the lower margin of the teres major muscle and subsequently the subclavian vein at the lateral edge of the first rib.[6]

Superficial Veins of the Upper Extremity

Superficial veins arising at the wrist include the cephalic and basilic veins, which lie above the muscular fascia underneath the skin and invariably become invested in superficial fascia at the level of the middle forearm. The cephalic vein continues along the lateral aspect of the arm, coursing to the level of the deltopectoral groove and finally emptying into the subclavian vein. Similarly, the basilic vein lies medially at the level of the wrist underneath the skin and courses to the level of the upper arm, where it subsequently pierces the muscular fascia to join the brachial or axillary vein.

Lymphatics of the Lower Extremity

In the lower extremity the lymphatics can be divided into vessels and nodes. There are two sets of lymphatic vessels, which correspond to the deep and superficial veins. The vessels follow the courses of the corresponding veins. There are a significantly increased number of superficial lymphatic vessels as compared with the deep lymphatic vessels. The vessels drain into lymphatic glands or lymph nodes. These are primarily found in the popliteal region, where it is common to see five to seven of them embedded within the popliteal fossa. In the inguinal region 10 to 20 nodes are present and are primarily found in the femoral triangle (Fig. 19.5).[7]

Lymphatics of the Upper Extremity

The lymphatic vessels of the upper extremity also follow the superficial and deep vascular structures. As in the lower extremity, the lymph node numbers increase as one moves proximally, with a significant number at the level of the axillary and supraclavicular region (Fig. 19.6).

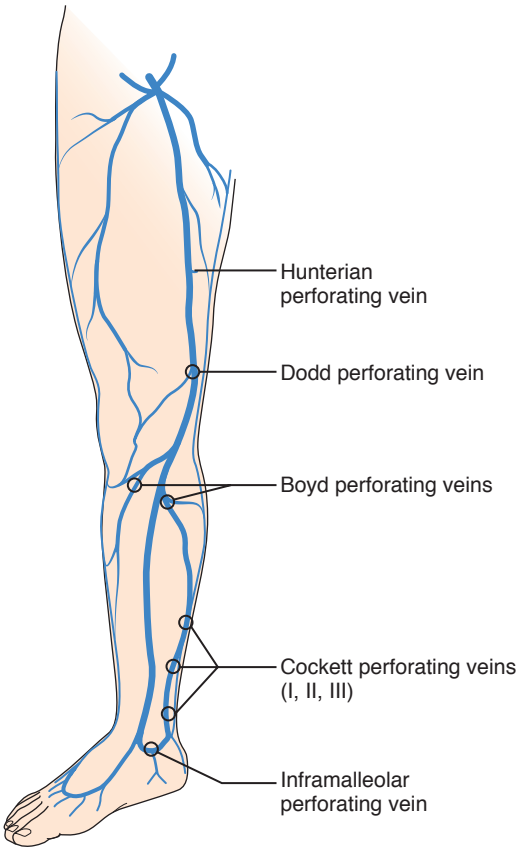

Figure 19.4 The location of the most important perforating veins associated with the great saphenous vein is shown. The Cockett and inframalleolar perforating veins are actually separate from the great saphenous system. The Boyd perforating vein is constantly present, but it may drain the saphenous vein or its tributaries. Perforating veins in the distal third of the thigh are referred to as "Dodd perforators," whereas those in the middle third of the thigh are referred to "Hunterian perforators." (From Rutherford, 6th edition, Fig. 157–152, p. 2252.)

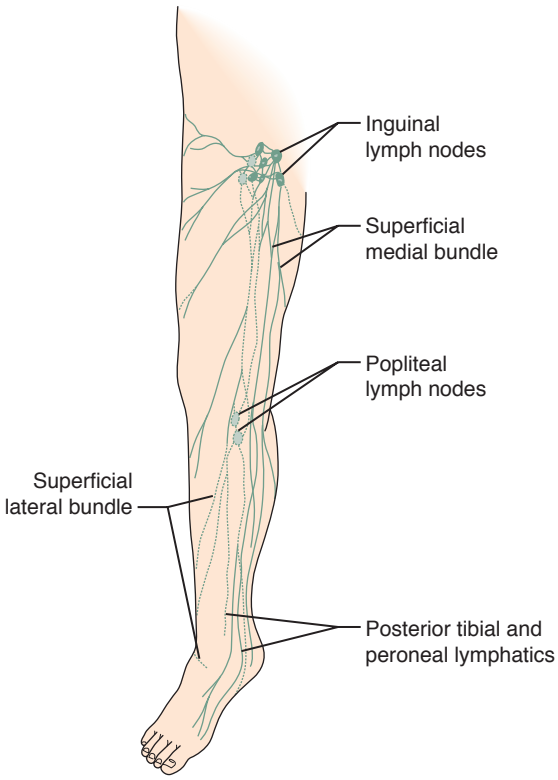

Figure 19.5 The lymphatic system of the lower extremity. (From Rutherford, 6th edition, Fig. 169.4, p. 2434.)

THE CLINICAL EVALUATION

Whether the examiner is familiar with vascular disease or not, most venous and lymphatic problems can be approached in an organized and sequential fashion. First, the presenting complaint should be determined; physical examination should correlate with the presenting history and should also provide a bridge to the pathophysiology of the disease process. When the history and physical examination have been completed, diagnostic studies can be ordered, if necessary, to further localize the disease or quantify the extent of the process. Therapy is ultimately driven by the natural history of the disease process and its impact on the patient's quality of life as well as the patient's risk factors and functional status. A relatively benign natural history, or significant and unmodified patient risk factors, may indicate an initial course of medical management, risk-factor modification, and observation; threat of significant hemodynamic consequences or tissue loss may indicate the need for a more aggressive intervention.

Typically, the presenting symptoms can be broadly classified into the following categories: pain; weakness; neurosensory

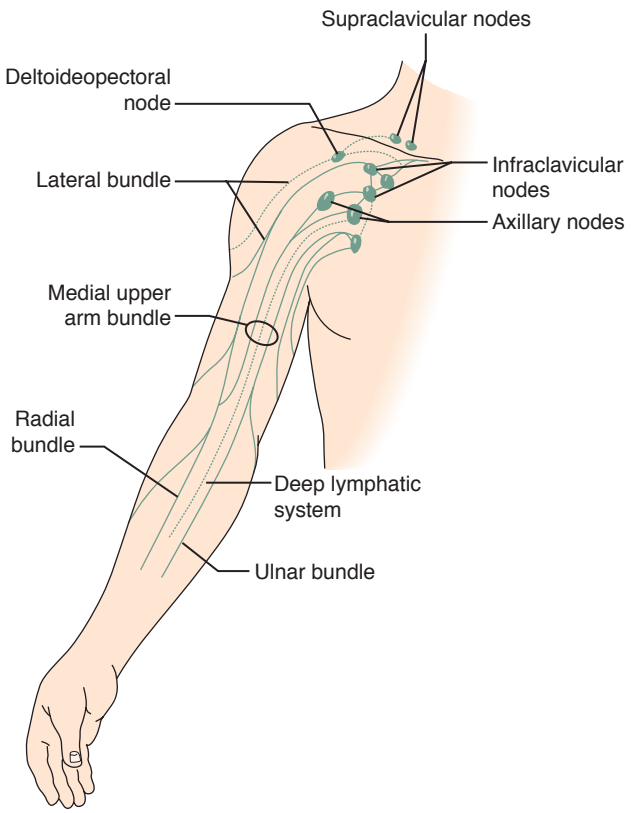

Figure 19.6 The lymphatic system of the upper extremity. (From Rutherford, 6th edition, Fig. 169.6, p. 2434.)

complaints including warmth, coolness, numbness, and hypersensitivity; discoloration; swelling; tissue loss and ulceration; and varicosities. The history should attempt to identify and characterize the location of the symptoms (unilateral, bilateral, proximal, distal); acuity of onset (sudden/gradual); duration; character, including frequency of symptoms and temporal patterns (continuous, intermittent); course or progression (better, worse, unchanged); and factors that aggravate and ameliorate the symptoms, including position, activity, temperature, menses, vibration, and pressure.

The physical examination should progress from observation and inspection to palpation. On observation, the extremity should be assessed for evidence of skin changes, including atrophy, cyanosis or mottling, pallor, and rubor. The presence and location of edema should be identified and quantified by measurement of circumference. Tissue loss and ulceration should be noted and fully described, including the location, size and depth, and presence of associated cellulitis and inflammation. On initial palpation, changes in temperature and sensation should be noted and compared with the contralateral extremity. All accessible pulses should be evaluated. At a minimum, pulses should be classified as absent, decreased, or normal, with use of the Doppler when pulses are nonpalpable, especially in patients with marked edema, to confirm adequate arterial inflow.

The severity of venous diseases can be classified using multiple models that have been shown to be of value for clinical and research purposes. These include anatomic location (Table 19.1; the Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) classification system (Table 19.2), the Venous Clinical Severity Score (VCSS) (Table 19.3), the Venous Segmental Disease Score (VSDS) (Table 19.4), and the Venous Disability Score (VDS) (Table 19.5).[8-10] Table 19.6 outlines available chronic venous disease–specific and health-related quality-of-life measures.

TABLE 19.1 Segmental Localization of Chronic Venous Disease of the Lower Extremity

Number	Segment		
	Superficial veins (AS1-5)		
1		Great saphenous vein	
2			Above knee
3			Below knee
4		Small saphenous vein	
5	Deep veins (AD6-16)	Nonsaphenous	
6		Inferior vena cava Iliac	
7			Common
8			Internal
9			External
10		Femoral	Pelvic: gonadal, broad ligament
11			Common
12			Deep
13		Superficial	
14			Popliteal
15		Tibial (anterior, posterior, or peroneal)	
16	Perforating veins (AP17-18)	Muscular (gastrocnemius, soleal, other)	
17		Thigh	
18		Calf	

From Rutherford, 6th edition, Table 155.2, p. 2234.
From Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. *J Vasc Surg.* 1995;21:635–645; with permission from Society for Vascular Surgery.

Venous Obstruction

Veins are normally patent and competent, with functioning valves. Pathologically, intraluminal thrombus can partially or completely obstruct a vein. Venous obstruction can remain asymptomatic, often associated with isolated tibial vein thrombosis, or can present with a symptomatic painful, swollen extremity. The latter is frequently associated with progression of the obstructing thrombus proximally. Untreated thrombosis, initially with minimal symptoms, can potentially lead to phlegmasia cerulea dolens and limb loss.

Isolated venous obstruction secondary to anatomic compression, such as that associated with May–Thurner syndrome, can result in mild to incapacitating swelling. Symptoms can be associated with compression, acute or chronic venous thrombosis, or postobstructive valvular incompetence and venous reflux.[11]

Deep Venous Thrombosis

Patients with deep venous thrombosis (DVT) can present with varying symptoms and signs, depending on the extent of obstruction, the degree of inflammatory reaction, the location and anatomic extent of the obstruction, and associated comorbidities. DVT most commonly presents with unilateral swelling, discomfort, and a sense of fullness or pressure in the affected extremity. The symptoms are acute in onset and the pain is often characterized as an aching discomfort. There may be a sensation of tightness or heaviness. Patients will note that the symptoms are exacerbated with ambulation or when the legs are kept in a dependent position. Leg elevation, however, will often relieve the discomfort. Hospitalized patients with DVT can be asymptomatic, and approximately half of nonhospitalized

TABLE 19.2 Overall Classification System for Chronic Venous Insufficiency: Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP)

Category	Finding	Classification
Clinical	Asymptomatic	C0
	Telangiectasias, reticular veins, malleolar flare	C1
	Varicose veins	C2
	Edema, no skin changes	C3
	Skin changes (pigmentation, venous eczema, lipodermatosclerosis)	C4
	Skin changes as above with healed ulcer	C5
	Skin changes as above with active ulcer	C6
Etiologic	Congenital: present since birth	EC
	Primary: undetermined cause	EP
	Secondary: known cause (postthrombotic, etc.)	ES
Anatomic	Superficial veins (AS)	
	Telangiectasias/reticular veins	AS1
	Greater saphenous vein	
	Above the knee	AS2
	Below the knee	AS3
	Lesser saphenous vein	AS4
	Nonsaphenous vein	AS5
	Deep veins (AD)	
	Inferior vena cava	AD6
	Iliac veins	
	Common	AD7
	Internal	AD8
	External	AD9
	Pelvic; gonadal, broad ligament	AD10
	Femoral veins	
	Common	AD11
	Deep	AD12
	Superficial	AD13
	Popliteal	AD14
	Tibial; anterior, posterior, or peroneal	AD15
	Muscular; gastrointestinal, soleal	AD16
	Perforating veins (AP)	
	Thigh	AP17
	Calf	AP18
Pathophysiologic	Reflux	PR
	Obstruction	PO
	Reflux and obstruction	PR,O

From Rutherford, 6th edition, Table 6.6, p. 47.

patients presenting with symptoms of DVT will not have venous pathology.[12]

In assessing the patient with suspected DVT, it is most important to determine any predisposing risk factors that may be present. Multiple risk factors can be associated with an increased threat of DVT, including advanced age; prolonged immobility, including hospitalization or recent travel; recent surgery, pregnancy, significant trauma, cancer, a previous history of DVT, or a family history of venous thrombosis and hypercoagulability (see Chapter 38). The presence or absence of risk factors can markedly influence the duration of treatment and the potential need for lifelong anticoagulation.[13,14]

The differential diagnosis can include systemic causes of lower extremity swelling, which generally result in bilateral lower extremity edema. Congestive heart failure and cirrhosis (liver failure) are common systemic etiologies and may also be seen in patients with chronic renal insufficiency. The common denominator among systemic causes of lower extremity swelling is fluid overload or retention. The first manifestation of heart failure is progressive swelling of the legs, but it may also be associated with dyspnea and orthopnea.

Localized trauma or injury is most often associated with unilateral swelling. The differential diagnosis also includes cellulitis, muscle strain or tear, a Baker cyst, hematoma, or dermatitis. Although the diagnosis of DVT can be suspected on the basis of pain, swelling, and associated risk factors, noninvasive imaging remains a necessary adjunct in order to confirm a suspected diagnosis.

In attempts to improve diagnostic accuracy in the case of a patient with suspected DVT, various models for risk stratification have been developed, since the signs and symptoms of DVT are often nonspecific. The most commonly used probability model is that of Wells (Table 19.7) (See Chapter 147). The Wells criteria include both subjective and objective elements, resulting in a score that indicates a low, moderate, or high risk of DVT.[15] The Wells criteria have been prospectively validated and are in use clinically, especially in emergency departments, where routine use of vascular ultrasound is not practical and a low pretest probability is associated with only a 2% to 3% incidence of DVT. Unfortunately the Wells scoring model still incorporates a subjective determination of alternative diagnoses, which, if present, significantly lower the clinical probability of DVT. Similarly, the Caprini Risk Assessment model is specific to surgical patients, factoring in clinical variables based on a point system. This assessment has been validated to be accurate in appropriate populations (Table 19.8).[16,17]

Regardless of the presentation or physical findings, one of the most important factors in the initial assessment of the patient presenting with DVT is the necessity to determine whether there is a proximate cause of the thrombotic event. This allows the provider to classify the event as either a provoked or unprovoked DVT. The duration of anticoagulation is markedly altered in those patients who present with an unprovoked DVT. They are by default considered potentially hypercoagulable, even in the presence of a negative laboratory workup, and consideration for lifelong anticoagulation should be entertained. The American College of Chest Physicians has provided ongoing evidence-based guidelines for the treatment of DVT.[18,19]

DVT may also involve the subclavian and axillary veins in the upper extremity. Onset is typically acute and associated with swelling of the entire arm. There has always been a strong relationship between venous thrombosis and compression of the subclavian vein at the thoracic outlet, and patients will frequently note an association with upper-body exercise and activity (see Chapter 123). More recently, subclavian and axillary

TABLE 19.3 Venous Severity Scoring: The Venous Clinical Severity Score

Attribute	Absent: 0	Mild: 1	Moderate: 2	Severe: 3
Pain	None	Occasional; not restricting activity or requiring analgesics	Daily; moderate activity limitation; occasional analgesics	Daily; severely limiting activities or requiring regular use of analgesics
Varicose veins[a]	None	Few, scattered: branch varicose veins	Multiple: GS varicose veins confined to calf or thigh	Extensive: Thigh and calf or GS and LS distribution
Venous edema[b]	None	Evening ankle edema only	Afternoon edema above ankle	Morning edema above ankle and requiring activity change, elevation
Skin pigmentation[c]	None or focal, low-intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower 1/3 of leg) or recent pigmentation (purple)	Wider distribution (above lower 1/3 of leg) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involving most of gaiter area (lower 1/3 of leg)	Severe cellulitis (lower 1/3 of leg and above) or significant venous eczema
Induration	None	Focal, circummalleolar (<5 cm)	Medial or lateral, less than lower	Entire lower 1/3 of leg or more
No. of acute ulcers	0	1	2	>2
Active ulceration;	No	Yes; <3 months	Yes; >3 months, <1 year	Yes; not healed > 1 year duration
Active ulcer, size	No	Yes; <2 cm	Yes; 2-6 cm	Yes; >6 cm (diameter)
Compressive therapy	Not used or not compliant	Intermittent use of stockings	Patient wears elastic stockings most days	Full compliance: stockings and compliant elevation

[a]"Varicose" veins must be >4 mm in diameter to qualify so that differentiation is ensured between C1 and C2 venous disease.
[b]Presumes venous origin from characteristics (e.g., brawny [not pitting or spongy] edema), with significant effect of standing/limb elevation and/or other clinical evidence of venous etiology (i.e., varicose veins, history of deep venous thrombosis). Edema must be regular finding (e.g., daily occurrence). Occasional or mild edema does not qualify.
[c]Focal pigmentation over varicose veins does not qualify.
GS, Greater saphenous; *LS*, lesser saphenous.
From Rutherford, 6th edition, Table 155.3, p. 2235.
Modified from Rutherford RB, Padberg FT, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg.* 2000;31:1307–1312; with permission from Society for Vascular Surgery.

vein thrombosis has been increasingly associated with subclavian vein catheters placed for central access.

Physical Examination

The presence of any swelling or edema should be noted and described. Unilateral or bilateral involvement should be noted, as well as the extent of involvement (i.e., is the entire extremity swollen, or just the calf and foot?). Swelling associated with acute DVT is frequently unilateral. The entire extremity may be swollen in patients with iliofemoral venous thrombosis, while femoropopliteal venous obstruction frequently results in swelling of the distal extremity or calf. The left leg is more commonly affected, as noted in multiple studies of patients presenting with DVT.[20] If there is unilateral swelling, it should also be determined if this results in a measureable discrepancy in the size of the leg relative to the other extremity. In patients with unilateral swelling resulting in a difference in leg circumference of more than 2 cm at the level of the thigh or 3 cm in the calf, the potential for a deep venous thrombotic process is high.[21] In contrast, absence of a significant change in limb circumference is associated with a very low likelihood of a deep venous thrombotic process. Physical examination should also include the joints as well as other skin changes, as joint pain and localized cellulitis are rarely associated with DVT.

The Homans sign describes the association between calf vein thrombus and calf pain with passive dorsiflexion of the foot. Other clinical findings that have been associated with acute DVT include the Bancroft sign, or tenderness on anteroposterior but not lateral compression of the calf, and the Lowenberg sign, which is calf pain associated with inflation of a blood pressure cuff about the calf. Unfortunately these "signs" persist in the literature and within medical documentation despite the fact that none of them are diagnostic of DVT.[12]

Phlegmasia

In the patient with DVT, the extremity may appear cyanotic secondary to venous congestion. Phlegmasia alba dolens, or "milk leg of pregnancy," describes a pale, white extremity, which was frequently seen in the postpartum period. Homans[22,23] attributed the finding to an underlying iliofemoral venous thrombosis. Collateral veins were noted over the upper thigh and abdomen. The swelling was frequently associated with fever as well as pain in the calf, popliteal fossa, or groin. The absence

TABLE 19.4 Venous Severity Scoring: The Venous Segmental Disease Score (Based on Venous Segmental Involvement With Reflux or Obstruction[a])

Reflux[b] Score	Vein(s)	Obstruction[bc] Score	Vein(s)
1/2	Small saphenous	0[d]	
1	Great saphenous	1	Greater saphenous (only if thrombosed from groin to below knee)
1/2	Perforators, thigh	0[d]	
1	Perforator, calf	0[d]	
2	Calf veins, multiple (posterior tibial alone = 1)	1	Calf veins, multiple
2	Popliteal vein	2	Popliteal vein
1	Femoral vein	1	Femoral vein
1	Profunda femoris vein	1	Profunda femoris vein
1	Common femoral vein and above[d] 1 1	2 Iliac vein Inferior vena cava	Common femoral
10	Maximum reflux score	10	Maximum obstruction score[e]

[a]As determined by appropriate venous imaging (phlebography or duplex ultrasonography scan). Although some segments may not be routinely studied in some laboratories (e.g., profunda femoris and tibial veins), points cannot be awarded on the basis of presumption without scanning of the segments for obstruction or reflux.

[b]*Reflux* means that all the valves in that segment are incompetent. *Obstruction* means there is total occlusion at some point in the segment or >50% narrowing of at least half of the segment. Most segments are assigned 1 point, but some segments have been weighted more or less to fit with their perceived significance (e.g., increasing points for common femoral or popliteal obstruction and for popliteal and multiple calf vein reflux and decreasing points for lesser saphenous or thigh perforator reflux). Points can be assigned for both obstruction and reflux in the same segment; this is uncommon but can occur in some postthrombotic states, potentially giving secondary venous insufficiency higher severity scores than primary disease.

[c]The excision, ligation, or traumatic obstruction of deep venous segments counts toward obstruction points just as much as their thrombosis.

[d]Normally there are no valves above the common femoral vein, so no reflux points are assigned to them. In addition, perforator interruption and saphenous ligation/excision do not count in the obstruction score, but as a reduction of the reflux score.

[e]Not all of the 11 segments can be involved in reflux or obstruction; 10 is the maximum score that can be assigned, and the maximum might be achieved by complete reflux at all segmental levels.

From Rutherford, 6th edition, Table 155.4, p. 2236.

Adapted from Rutherford RB, Padberg FT, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg.* 2000;31:1307–1312; with permission from Society for Vascular Surgery.

TABLE 19.5 Venous Severity Scoring: The Venous Disability Score

0	Asymptomatic
1	Symptomatic but patient is able to carry out usual activities[a] without compressive therapy
2	Patient can carry out usual activities[a] only with compression and/or limb elevation
3	Patient is unable to carry out usual activities[a] even with compression and/or limb elevation

[a]Usual activities = patient's activities before onset of disability from venous disease.

From Rutherford, 6th edition, Table 155.5, p. 2236.

Adapted from Rutherford RB, Padberg FT, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg.* 2000;31:1307–1312; with permission from Society for Vascular Surgery.

of bluish discoloration was attributed to the rapid development of collateral venous flow. Phlegmasia cerulea dolens is associated with extensive proximal venous obstruction and minimal collateralization. The leg is massively swollen and cyanotic in appearance. The affected extremity begins to sequester fluid in the interstitium, and massive swelling ensues. The examiner should perform a bedside Doppler examination to confirm the presence of multiphasic flow in the tibial arteries; the swelling and edema are often so significant that palpation of pulses is rendered useless. As interstitial fluid accumulates within the muscular compartments, findings consistent with compartment syndrome may be present.

A prompt diagnosis of phlegmasia cerulea dolens is critical, as the limb is salvageable with appropriate and aggressive therapy; however, progression to venous gangrene and limb loss in this setting can occur despite maximal medical and surgical therapy.

Superficial Thrombophlebitis

Thrombosis of the superficial veins results in localized inflammation surrounding the affected vein or veins. As opposed to deep venous obstruction, venous hemodynamics in the deep veins of the lower extremity are not usually affected by a superficial thrombophlebitis. Patients who present with superficial thrombophlebitis of the great saphenous vein, however, do have an approximate 10% risk of progression to DVT primarily involving the common femoral vein of the affected extremity.[24]

TABLE 19.6 Quality-of-Life Assessments

Outcome Assessment	Focus on CVD	QoL Score[a]	Construct
SF-36	Generic, applicable to a spectrum of nonvenous and venous diseases	Ascending	36 items Physical and mental health 8 domains
AVVQ—Aberdeen Varicose Vein Questionnaire	Varicose veins, CVD	Descending	13 items Weighted scoring Patient draws varices onto template
CIVIQ—Chronic Venous Insufficiency Questionnaire	General venous	Ascending	20 items Diagnosis based on clinical and subjective symptoms; no objective confirmation of venous etiology
VEINES—Venous Insufficiency Epidemiologic and Economic Study	General venous	Ascending	35 items, 2 categories VEINES-QoL measures the effect on QoL VEINES-Sym measures symptoms
CCVUQ—Charing Cross Venous Ulcer Questionnaire	Venous ulcer	Descending	20 items Venous etiology confirmed with clinical examination and Duplex ultrasonography

[a]Ascending scores indicate that a higher score means a better QoL, whereas a descending score indicates that a lower score has a better QoL.
CVD, chronic venous disease; *QoL*, quality of life; *SF-36*, short form health survey (36 items).
From Rutherford, 7th edition, Table 53.3, p. 837.

TABLE 19.7 Stratification of Pretest Probability: The Wells Criteria

Clinical Feature	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within 4 weeks	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely as or more likely than that of deep venous thrombosis	−2

Low probability, ≤0 points; moderate probability, 1–2 points; high probability, 3 points.
From Rutherford, 6th edition, Table 148.3, p. 2151.
Modified from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997;350:1795–1798. Reprinted with permission.

Similar to any thrombotic process, risk factors for superficial thrombophlebitis include advancing age, obesity, history of DVT, previous history of superficial thrombophlebitis, and recent cannulation of the affected vein. The latter is most common in the upper extremity, where it can be associated with a fever of unknown origin.

Physical Examination

Patients presenting with superficial thrombophlebitis will generally complain of pain, tenderness, and warmth over the involved vein with a cord palpable subjacent to the area of the pain. Additionally, erythema with proximal streaking is not uncommon. The presence of erythema is often misconstrued as a cellulitis, and it is not uncommon for patients to be placed on antibiotics because of a presumptive diagnosis of skin infection. If conservative therapy does not produce expected resolution of the thrombotic process in patients with extensive involvement of the extremity along the length of a named superficial vein, consideration should be given to a limited trial of full-dose anticoagulation.

For a discussion of postthrombotic (postphlebitic) syndrome, see Chapter 156.

Pathophysiology and Clinical History

Chronic venous insufficiency (CVI) is generally thought to be secondary to venous valvular dysfunction following an episode of DVT, resulting in apposition of the vein valve to the wall of the vein with subsequent incompetence after recanalization. Unfortunately, although the majority of patients have recanalization of their previously occluded veins, almost half of such patients have residual partial thrombosis, which also contributes.[25] The combination of venous obstruction and valvular incompetence can be associated with worsening symptoms with physical activity to the point of effort discomfort, often referred to "venous claudication." Thrombotic obstruction of the venous outflow and venous insufficiency can also result in ambulatory venous hypertension and edema. Long-standing symptoms of venous hypertension and swelling can ultimately result in the development of venous stasis ulceration (Fig. 19.7).

Initial presenting symptoms include mild swelling and discomfort at the end of the day relieved by rest and limb

TABLE 19.8 Venous Thromboembolism Risk-Factor Assessment

Patient's Name: _____ Age: _____ Sex: _____ Wt, lb:_____ Ht, in: _____

Choose All That Apply

Each Risk Factor Represents 1 Point

- ☐ Age 41-59 years
- ☐ Minor surgery planned
- ☐ History of prior major surgery
- ☐ Varicose veins
- ☐ History of inflammatory bowel disease
- ☐ Swollen legs (current)
- ☐ Obesity (BMI >30)
- ☐ Acute myocardial infarction (<1 month)
- ☐ Congestive heart failure (<1 month)
- ☐ Sepsis (< 1 month)
- ☐ Serious lung disease incl. pneumonia (< 1 month)
- ☐ Abnormal pulmonary function (COPD)
- ☐ Medical patient currently at bed rest
- ☐ Leg plaster cast or brace
- ☐ Central venous access other risk factor_____

For Women Only (Each Represents 1 Point)

- ☐ Oral contraceptives or hormone replacement therapy
- ☐ Pregnancy or postpartum (<1 month)
- ☐ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score ☐

Please see following page for prophylaxis suggestions and safety considerations

Each Risk Factor Represents 2 Points

- ☐ Age 60-74 years
- ☐ Major surgery (> 60 min)[a]
- ☐ Arthroscopic surgery (>60 min)[a]
- ☐ Laparoscopic surgery (>60 min)[a]
- ☐ Previous malignancy
- ☐ Morbid obesity (BMI >40)

Each Risk Factor Represents 3 Points

- ☐ Age 75 years or more
- ☐ Major surgery lasting 2-3 h[a]
- ☐ BMI > 50 (venous stasis syndrome)
- ☐ History of SVT, DVT/PE
- ☐ **Family history of DVT/PE**
- ☐ Present cancer or chemotherapy
- ☐ Positive factor V Leiden
- ☐ Positive prothrombin 20210A
- ☐ Elevated serum homocysteine
- ☐ Positive lupus anticoagulant
- ☐ Elevated anticardiolipin antibodies
- ☐ Heparin-induced thrombocytopenia (HIT)
- ☐ Other thrombophilia type _____

Each Risk Factor Represents 5 Points

- ☐ Elective major lower extremity arthroplasty
- ☐ Hip, pelvis or leg fracture (< 1 month)
- ☐ Stroke (< 1 month)
- ☐ Multiple trauma (< 1 month)
- ☐ Acute spinal cord injury (paralysis)(< 1 month)
- ☐ Major surgery lasting over 3 hours[a]

[a]Select only one from the surgery category.

In: A validation study of a retrospective venous thromboembolism risk scoring method. Bahl V, Hu HM, Henke PK, et al. *Ann Surg*. 2010;251(2):344–350.

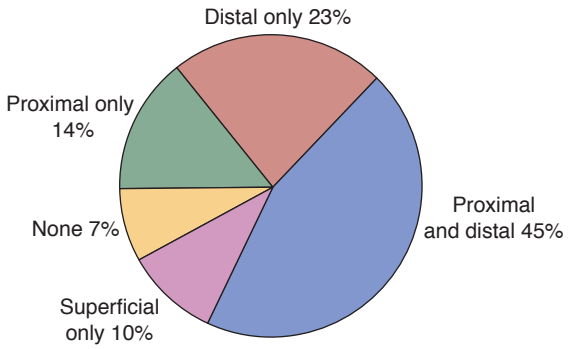

Figure 19.7 Distribution of venous valvular incompetence in limbs with stasis ulcers and pigmentation. (From Rutherford, 6th edition, Fig. 9.51, p. 113.)

elevation. The wearing of compression stockings, in general, will significantly improve the patient's symptoms at this stage. As the duration and severity of deep venous insufficiency increases, mild symptomatology is replaced by late findings, which include brawny edema, venous eczema, lipodermatosclerosis (hemosiderin deposition typically in the gaiter distribution), and eventual progression to venous stasis ulceration, commonly occurring at the level of the medial malleolus.

Physical Examination

Patients presenting with deep venous insufficiency exhibit mild to significant swelling depending on the stage of presentation. Unilateral swelling is more likely to be venous in nature, whereas bilateral swelling may more likely be associated with a central cardiac and hepatic dysfunction. In the late stages edema should be pitting and is often 3 to 4+ in nature, although the presence of brawny edema and chronic fibrosis may impede pitting at the level of the ankle or in the gaiter distribution (Fig. 19.8). The latter term is derived from the gaiter, or spat, which were garments worn over the shoe and the lower leg below the knee. The patient may have associated varicosities, although these are not a requirement and would be secondary to coexistent superficial venous insufficiency. The presence of active or healed ulcerations should be documented with regard to size, depth, and location. Classically ulcers associated with deep venous insufficiency are located primarily over the medial malleolar region, although in long-standing and severe cases these can be multiple and located throughout the gaiter distribution. Determination of ulcer etiology can be complex and should be made in conjunction with pulse assessment and neurologic examination for sensory deficits.

Chronic ulcers can be associated with arterial ischemia, venous stasis, and neuropathy (Table 19.9). A history of arterial insufficiency, including claudication and rest pain, should be sought. Ischemic ulcers and tissue loss represent the far end of the spectrum of arterial disease. Diabetic patients can present with arterial disease and peripheral neuropathy. Neuropathy can predispose such patients to neurotrophic ulcers over the weight-bearing prominences of the plantar foot. Venous stasis disease can result in characteristic ulcerations, but associated arterial disease can affect healing and influence treatment. The history should be accompanied by a complete physical examination, beginning with observation and inspection of the extremity. All areas of ulceration and tissue loss should be fully characterized with respect to location and size, and the status of all pulses should be documented.

Ischemic ulcers are usually quite painful, and there is likely to be typical ischemic rest pain in the distal forefoot that occurs nocturnally and is relieved by dependency. At first, these ulcers may have irregular edges, but when chronic, they are more likely to be "punched out." They are commonly located distally over the dorsum of the foot or toes but may occasionally be pretibial. The ulcer base usually consists of poorly developed grayish granulation tissue. The surrounding skin may be pale or mottled, and the previously described signs of chronic ischemia are invariably present. Notably, the usual signs of inflammation one would expect surrounding such a skin lesion are absent, for it is the lack of adequate circulation to provide the necessary inflammatory response for healing that underlies ischemic ulcers. For the same reason, probing or debriding the ulcer causes little bleeding.

Figure 19.8 The "gaiter" distribution of stasis dermatitis and leg ulcers. (From Rutherford, 6th edition, Fig. 1.3, p. 1.)

Neurotrophic ulcers, however, are completely painless but bleed with manipulation. They are deep and indolent and are often surrounded by both acute and chronic inflammatory reactions and callus. Their location is typically over pressure points or calluses (e.g., the plantar surface of the first or fifth metatarsophalangeal joint, the base of the distal phalanx of the great toe, the dorsum of the interphalangeal joints of toes with flexion contractures, or the callused posterior rim of the heel pad). The patient usually has long-standing diabetes with a neuropathy characterized by patchy hypoesthesia and diminution of positional sense, two-point discrimination, and vibratory perception.

The so-called venous stasis ulcer, actually secondary to ambulatory venous hypertension, is located within the gaiter area, most commonly near the medial malleolus. It is usually larger than the other types of ulcers and irregular in outline but also shallower and with a moist granulating base. The ulcer is almost invariably surrounded by a zone containing some of the hallmarks of chronic venous insufficiency—pigmentation and inflammation ("stasis dermatitis"), lipodermatofibrosis, and cutaneous atrophy, as already described. Ulcerations of long duration should undergo biopsy to rule out malignancy.

May-Thurner Syndrome

May-Thurner syndrome is a specific anatomic diagnosis arising from stenosis or obstruction of the left common iliac vein as it crosses under the right common iliac artery with a concomitant band or web found at the site of obstruction. It is commonly seen in young female patients although also not infrequently

TABLE 19.9 Differential Diagnosis of Common Ulcers

Type	Usual Location	Pain	Bleeding with Manipulation	Lesion Characteristics	Surrounding Inflammation	Associated Findings
Ischemic ulcer	Distal, on the dorsum of the foot or toes	Severe, particularly at night; relieved by dependency	Little or none	Irregular edge; poor granulation tissue	Absent	Trophic changes of chronic ischemia; absence of pulses
Neurotrophic ulcer	Under calluses or pressure points (e.g., plantar aspect of the first or fifth metatarsophalangeal joint)	None	May be brisk	Punched out, with a deep sinus	Present	Demonstrable neuropathy
Venous stasis ulcer	Lower third of the leg (gaiter area)	Mild; relieved by elevation	Venous ooze	Shallow, irregular shape; granulating base; rounded edges	Present	Lipodermatofibrosis, pigmentation

From Rutherford 7th edition, Table 13.5, p. 214.

found in asymptomatic patients.[26] The presentation is usually a unilateral swelling of the left lower extremity that is aggravated by exercise and activity. "Venous claudication" described as an intense pain, or a bursting sensation, is induced by exercise and relieved by rest and elevation of the limb. This is in contrast to arterial claudication, where the cessation of activity and standing rest result in relief.

Physical Examination

The classic presentation is a young female, past puberty, who presents with either provoked or unprovoked DVT of the left leg. Without treatment, limb swelling and venous claudication may develop. Alternatively and less commonly, unilateral swelling of the left leg, varicose veins, and venous ulcers may occur. However, many patients with May-Thurner anatomy remain entirely asymptomatic throughout their adult lives.[26,27]

Superficial Venous Insufficiency

Pathophysiology and Clinical History

Superficial venous insufficiency is classically thought to be caused by incompetent valves at the saphenofemoral and saphenopopliteal junctions, with subsequent loss of valvular function along the length of the great and small saphenous veins, respectively. Findings of superficial venous insufficiency include telangiectasias, reticular varicosities, and large ropey varicose veins. The large varicose veins can generally be traced back to the great or small saphenous veins. The majority of patients with varicose veins are women with a significant hereditary component as well as specific risk factors including multiple pregnancies, with general worsening of the varicosities with each successive pregnancy. Patients with varicose veins usually do not complain of severe pain; typically, the discomfort is described as burning or throbbing in character and is localized to the varicosities. Swelling of the calf, and rarely the proximal foot, can often be associated with varicosities. The symptoms associated with varicose veins are relieved with elevation of the extremity, and patients frequently note an absence of symptoms in the morning.[28] They also observe that symptoms increase during the course of the day, particularly if the patients are ambulatory and active with episodes of standing and sitting for long periods of time. Compression stockings are usually effective and significantly improve the symptoms in patients with superficial venous insufficiency.

Physical Examination

The patient with varicose veins should be examined in the standing position. The location of all varicosities should be noted. The presence of ankle flare or corona phlebectatica should be noted. Additional venous abnormalities may include telangiectasias, which are dilated intradermal venules about 1 mm in size. Reticular veins are nonpalpable subdermal veins measuring 1 to 3 mm in size.

Varicosities along the medial leg are generally related to the great saphenous vein or its perforating branches; varicosities over the posterior calf are in the distribution of the small saphenous vein, which begins on the lateral aspect of the foot and ascends along the posterior midline of the calf. Venous reflux in the great saphenous vein may be associated with incompetence at the saphenofemoral junction or related to incompetent deep and perforating veins. The great saphenous vein can communicate with the Dodd, Boyd, Cockett, Sherman, and Hunterian perforating veins (see Fig. 19.4). Hunterian perforator incompetence can be associated with varicosities in the middle third of the thigh. The Dodd perforator is located in the medial and distal third of the thigh; the Boyd perforators are along the medial aspect of the knee; the Cockett and Sherman perforators are located at the ankle.

In moderate to morbidly obese patients varicosities may not be visible but may be palpable. Physical examination should include an assessment of varicosities throughout the upper and lower extremities. Prominent veins, especially in the upper extremity, can signal the presence of normal but prominent veins in the lower extremities.

The Trendelenburg and Perthes tests are described here for completeness, however, they are used infrequently in clinical practice, given the ubiquitous use of duplex Doppler examination for patients with superficial venous insufficiency; this renders the test useful in only very selected circumstances. During the Trendelenburg test, the patient is initially supine, with the extremity elevated. Manual compression or a tourniquet is used to occlude the proximal great saphenous vein. The patient then stands upright. In the absence of significant deep venous insufficiency and perforator incompetence, the superficial varicosities will fill slowly over approximately 20 seconds. On repeating the maneuver when the patient first stands, release of compression will result in rapid filling of varicosities in the presence of significant proximal incompetence. With the Perthes test, a tourniquet is used to occlude the proximal superficial veins. As the patient ambulates, the varicosities enlarge if there are incompetent perforating veins. Use of a handheld Doppler in conjunction with these tests markedly improves the diagnostic accuracy.[29]

Klippel-Trenaunay Syndrome

Pathophysiology and Clinical History

Klippel-Trenaunay syndrome comprises a constellation of findings including varicose veins, port wine stain, and associated hypertrophy of the bone and soft tissue, resulting in limb-length discrepancy. With associated arteriovenous malformations, the condition is more correctly termed Parkes Weber syndrome or Klippel-Trenaunay-Weber syndrome.

The majority of patients present with unilateral limb involvement, with the lower extremity being the most frequent site. A port wine stain is the most common finding, followed by the presence of varicosities and then by limb hypertrophy. The varicose veins and port wine stain are invariably congenital and present at birth. Venous involvement can be associated with pain or venous ulcerations.[30]

Physical Examination

The patient's extremity should be examined for the presence or absence of other defining arteriovenous malformations or limb abnormalities. In isolated Klippel-Trenaunay syndrome, the port wine stain is most frequently located on the affected limb. The varicosities associated with the condition are classically described

as arising from the foot or the lower leg, extending proximally into the thigh or gluteal area. The varicose veins can be prominent or may only present with ambulation. In some cases varicosities may not be present until the onset of puberty. The veins often spare the saphenous distribution. Prior to treating the varicosities, it is essential to ensure the presence of a patent deep venous system, as often these patients can have atretic deep veins.

Lymphedema (See Chapter 168)

Overview/Pathophysiology

Lymphedema results from obstruction of the lymphatics, with resultant accumulation of protein and fluid in the interstitial tissues of the extremity. Lymphedema may be classified based on underlying etiology, genetic predisposition, morphology, and age of onset. Clinically, lymphedema is grossly classified as primary/intrinsic or secondary to other contributing factors (Table 19.10).[31-33] Primary etiologies are characterized by the age of onset; lymphedema may present as a congenital condition at birth, at puberty through adolescence, or later in life. Genetically, lymphedema may be familial or sporadic. Morphologically, lymphedema is the result of lymphatic aplasia, hypoplasia, hyperplasia, or less commonly the incompetence of the lymphatic system. Genetic predisposition and lymphatic morphology are most useful in predicting clinical severity and guiding potential therapies.

Primary Lymphedema

Primary lymphedema can present at birth as a congenital condition and is more common in males, with the vast majority of patients presenting with involvement of the lower extremity (>80%). Milroy disease is a familial variant.[34] It is more common in women and is associated with a mutation of the *VEGFR-3* or *FLT4* gene. It is frequently bilateral. Males can have an associated hydrocele, and males and females can have papillomas. Primary lymphedema can be associated with other syndromes including Turner syndrome, Noonan syndrome, Klinefelter syndrome, hemangiomas, trisomy 13, trisomy 18, neurofibromatosis type 1, yellow nail syndrome, congenital nail absence, distichiasis, lymphedema syndrome, and xanthomatosis.

Lymphedema praecox (or its familial variant, Meige disease) is the most common form of lymphedema, primarily affecting females between the ages of 10 and 35. It is commonly associated with puberty. It accounts for over 80% of all patients with lymphedema. Lymphedema tarda generally presents in patients over 35 years of age and also occurs more commonly in women.[35]

TABLE 19.10 Etiologic Classification of Lymphedema

I. Primary Lymphedema
A. Congenital (onset before 1 year of age)
1. Nonfamilial
2. Familial (Milroy disease)
B. Praecox (onset at 1-35 years of age)
1. Nonfamilial
2. Familial (Meige disease)
C. Tarda (onset after 35 years of age)
II. Secondary Lymphedema
A. Filariasis
B. Lymph node excision ± radiation
C. Tumor invasion
D. Infection
E. Trauma
F. Other

From Rutherford, 6th edition, Table 167.1, p. 2397.

Secondary Lymphedema

Secondary lymphedema is more common than primary lymphedema and results from any process leading to lymphatic injury, such as infection and filariasis. Patients who present with a sudden onset lymphedema later in life should be questioned about international travel.[36] In developed countries the most common cause of secondary lymphedema is direct injury or surgical dissection of regional lymph nodes and also trauma, cancer (tumor, surgery, or radiation), and infection.[37]

Physical Examination

Lymphedema most commonly involves the lower extremities. In the upper extremity, it can be associated with prior mastectomy and axillary lymph node dissection. It is unilateral, and elevation of the extremity generally does not result in resolution of the edema.[38] In the lower extremity, swelling generally begins distally, involving the area about the ankle; it rarely spares the toes and foot, which differentiates lymphedema from other conditions. At onset, the swelling begins as mild pitting edema, slowly increasing in extent, that is relatively painless in character. The edema may progress to involve the proximal extremity, including the genitalia and trunk. Stemmer sign describes the inability to pinch and lift the dorsal skin of the foot between the first and second toes; if the skin fold cannot be lifted, the test is indicative of lymphedema. Additionally, with lymphedema, the toes can become squared, suggesting the appearance of "boxcars."[39] With progression of the lymphedema, fibrosis develops in the subcutaneous tissues, with subsequent ulcerations, fissures, and lymphorrhea. Not infrequently, patients may present with inflammation secondary to lymphangitis and red streaks in the distribution of the lymphatic channels (Table 19.11).

TABLE 19.11 Clinical Staging of Chronic Lymphedema

Grade I	Early pitting prevalent that reduces with elevation No fibrotic skin thickening
Grade II	Skin thickened and fibrotic pitting only to deep prolonged pressure Often no pitting No reduction with elevation overnight
Grade III	Skin fibrotic and sclerotic in subcutaneous tissues Often secondary hyperkeratosis Verrucal development These changes are permanent

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The Wells criteria remains to this day a classically tested and clinically useful tool to risk assess patients in clinical settings.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 20

Vascular Laboratory: Arterial Physiologic Assessment

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Peripheral arterial occlusive disease (PAD) can usually be diagnosed by a careful history and physical examination. Arterial physiologic testing adds a degree of objectivity to the subjective clinical evaluation. With the advances in direct physiologic testing of specific arterial sites by duplex scanning and noninvasive imaging evaluation (see Chapters 27 and 28), the approximate localization of extent of disease provided by indirect physiologic testing is now less critical.

Nevertheless, physiologic testing is helpful when the diagnosis is uncertain, such as in patients with possible pseudoclaudication. These tests are also useful in determining the extent to which arterial disease limits walking in patients who have concomitant orthopedic or neurologic problems contributing to their disability. Noninvasive testing can be used to detect PAD in otherwise asymptomatic patients, which is significant because PAD is an independent risk factor for cardiac events.[1-3] These tests are uniquely able to identify intermittent arterial obstructions, such as those arising from entrapment syndromes, and to distinguish between fixed arterial obstructions and obstructions caused by vasospasm. In patients with advanced disease, physiologic testing helps to determine the ability of ischemic ulcers to heal or provides guidance for the optimal level of amputation. This chapter reviews the theory, methods, interpretation, and applications of the various indirect physiologic arterial tests available in the vascular laboratory.

DOPPLER ULTRASONOGRAPHY

The development of Doppler ultrasound to detect blood flow and analyze velocity waveforms revolutionized the ability to detect and quantitate peripheral vascular disease noninvasively.[4] This chapter discusses the use of basic continuous wave Doppler and waveform analysis. Pulsed Doppler combined with B-mode imaging in duplex ultrasound machines that allows analysis of velocity waveforms from specific sites along visualized vessels is described in Chapter 21.

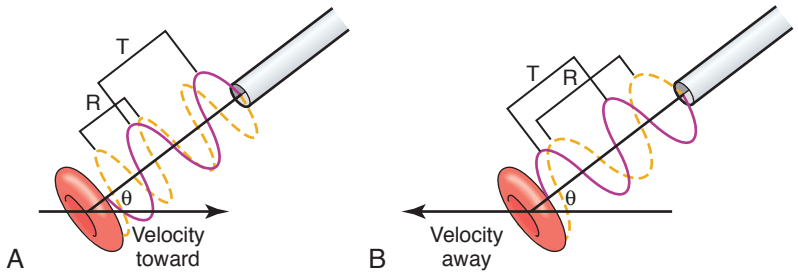


Figure 20.1 The Doppler device compares the frequency of backscattered sound from moving red blood cells with the transmitting frequency to determine the frequency shift, which is proportional to the speed of the flowing blood, the transmitting frequency, and the cosine of the Doppler angle, θ. The drawing shows a Doppler probe transmitting ultrasound at a wavelength *T* to a red blood cell moving in a direction indicated by an *arrow*. The red cell is moving toward the probe in (A) and away from the probe in (B). The angle between the ultrasound beam and the direction of red cell velocity is given by θ. The frequency of the ultrasound that is transmitted is the same in both cases *(red line)*. The ultrasound signal that is received *(yellow line)* has a shorter wavelength *(R)* and thus a higher frequency in (A) and a longer wavelength and lower frequency in (B).

Principles of Doppler Ultrasound

The hand-held continuous wave "pocket Doppler" devices typically have a transmitting frequency between 5 and 10 MHz, suitable for more superficial arteries due to the limited penetration depth of ultrasound waves at this frequency. The tip of the probe has a transmitting piezoelectric crystal that converts electrical energy into ultrasound waves, as well as a receiving piezoelectric crystal that detects reflected ultrasound waves. The probe converts detected frequency shift and sends it to the speakers for an audible signal. A fluid interface, generally an aqueous gel, is required between the probe and the skin to allow penetration of ultrasound waves into the tissue without significant loss of energy from impedance mismatch (difference in density causing significant reflection of ultrasound waves, thus preventing further tissue penetration).

Moving red blood cells act as reflectors that backscatter ultrasound waves. The frequency of the reflected ultrasound wave is shifted from the transmitted frequency in direct proportion to the velocity of the blood flow due to the Doppler effect (Fig. 20.1). The magnitude of the frequency shift (Δf) is given by the following Doppler equation:

$$\Delta f = \frac{2V f_0 \operatorname{Cos}\theta}{C}$$

where V is blood velocity in centimeters per second, f_0 is the transmitted frequency, θ is the angle between the velocity vector and the path of the ultrasound beam (known as the Doppler angle), and C is the velocity of sound through blood (1.54×10^5 cm/s). This equation can be rearranged to solve for V when the Doppler angle is known, or it can be estimated, as it is in duplex scanning.

Aural Interpretation of the Doppler Waveform

The velocity of blood flow is proportional to the frequency shift, which is heard as a change in pitch of the audio signal. Loudness (amplitude) is proportional to the volume of red blood cells moving through the Doppler signal path. Turbulence causes nonuniform velocities and imparts a harsh quality to the audible Doppler signal. An experienced listener can identify increased pitch, which corresponds to luminal narrowing causing increased velocity of flow. The listener can also perform elementary waveform analysis by taking note of the contour of the velocity waveform. Normal peripheral arteries at rest have a triphasic or biphasic quality with a brisk upstroke of forward flow in systole, a brief reverse flow component in diastole caused by the reflection of the flow wave from the high resistance periphery, and finally, in most, but not all peripheral arteries, a small forward component in late diastole (Fig. 20.2A and B). When the peripheral vascular resistance is low, either due to the arterial bed downstream such as the kidneys, brain, or liver, or after exercise, hyperemia, or intraarterial administration of vasodilating drugs, the velocity waveform loses the reverse flow component and becomes monophasic with forward flow throughout the entire cardiac cycle.

Arterial obstruction causes dampening of the waveform, which becomes monophasic (see Fig. 20.2C). The low-amplitude, monophasic Doppler signals that result from extensive occlusive disease may be difficult to distinguish from venous signals. Gentle compression of the foot causes a rush of venous blood from emptying the veins that is easy to appreciate in the Doppler signal. Directional Doppler can also be useful to distinguish arterial from venous signals because it will indicate whether blood is flowing toward or away from the ultrasound probe.

Qualitative and Quantitative Waveform Analysis

The earliest change at the site of stenosis is widening of the waveform (spectral broadening) in early diastole, when flow is decelerating and least stable. More severe stenosis produces a marked increase in systolic velocity in addition to spectral broadening. Critical stenosis limits flow and pressure and generally occurs when the lumen is narrowed by 50% or more. Waveforms at the site of stenosis are associated with a doubling of peak systolic velocity when compared with the adjacent segments (Fig. 20.3). Downstream from significant stenoses, waveforms become blunted and monophasic with widening as a result of turbulence.

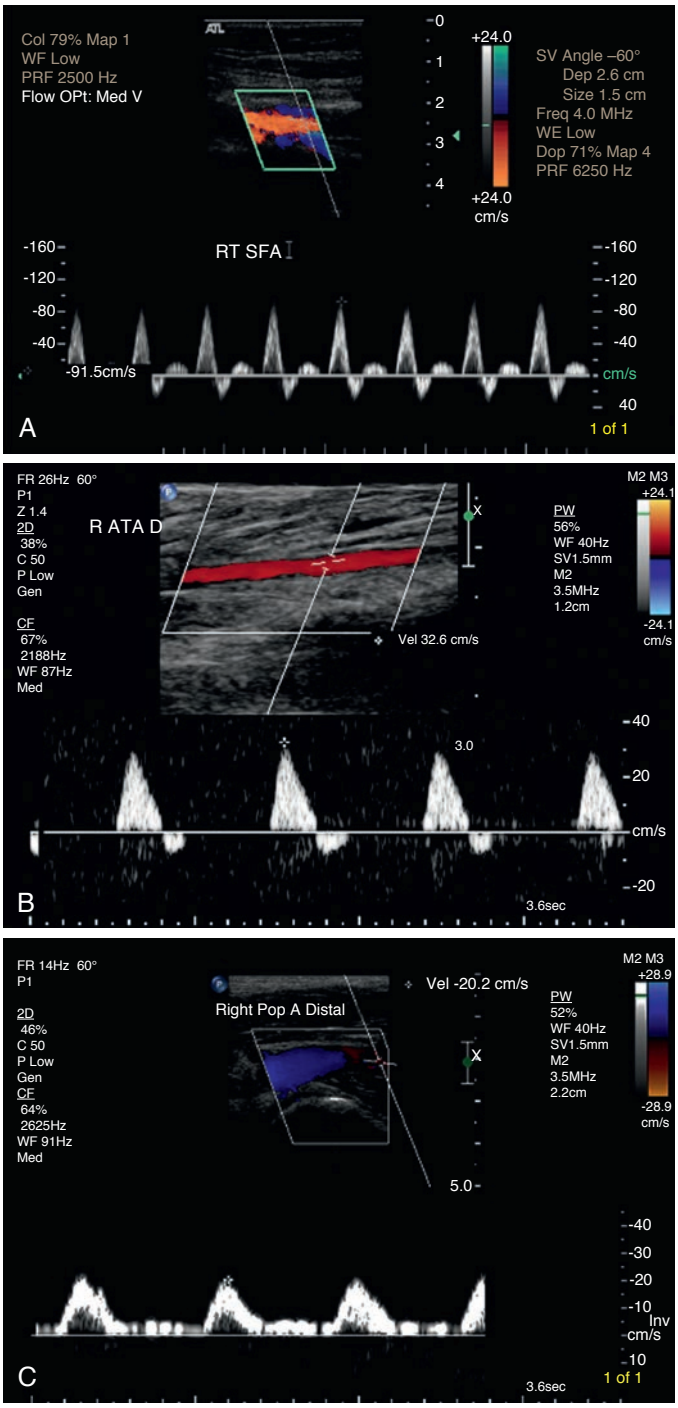


Figure 20.2 Normal and Dampened Velocity Waveforms Obtained With a Duplex Scanner. (A) Normal triphasic velocity waveform. (B) Biphasic velocity waveform. (C) Monophasic velocity waveform.

The result is a noisy, high-pitched Doppler signal at the site of stenosis. This signal can be heard for several vessel diameters downstream from the site of stenosis because of transmission of the high-velocity jet over this distance. A few centimeters upstream from the stenosis, the waveform is affected by the high resistance of the stenosis. This results in less forward flow and a large, reflected wave following the lower frequency systolic peak. It is heard as a "to-and-fro" signal pattern. Extremely low flow may not be detectable by hand-held Doppler instruments because of inadequate signal generation or cutoff of very low frequencies by the filter that is used to eliminate wall motion artifacts.

To overcome the subjective, operator-dependent nature of qualitative waveform analysis, spectrum analyzers can be used. These instruments have a frequency analyzer that uses fast Fourier analysis or similar methods to give a full picture of the entire spectrum of frequencies present in each sampling interval. Frequency shifts are displayed on the vertical axis and time on the horizontal axis. The amplitude of the reflected signal at each frequency is represented by a gray scale (see Fig. 20.2). The intensity of the gray scale is proportional to the number of red blood cells traveling at a particular velocity at each point in time. These devices, which are used in all duplex scanners, permit identification of features, such as uniformity of flow (narrow band of velocities) or nonuniformity (widening of the velocity waveform, known as spectral broadening). When the angle of insonation is known, the output can be displayed as velocity over time and various parameters can be measured, such as peak and end-diastolic velocity and ratios of various velocity components. Duplex scanners also use pulsed Doppler with time-gated reception of the reflected ultrasound to allow the operator to select the depth at which velocity information is obtained. This permits interrogation of Doppler information within a visualized vessel and thereby more precise categorization of the degree and location of stenosis (see Chapter 21). In the absence of Duplex scanning, indirect analysis of waveforms obtained at the common femoral artery level such as peak-to-peak pulsatility index (calculated as $(V_{max} - V_{min})/V_{mean}$ where V stands for velocity, max for maximum, and min for minimum), Laplace transform, power frequency spectral analysis, pulse wave velocity, and pulse transit time have been used to determine whether significant aortoiliac occlusive disease is present. However, these indirect methods are prone to false-negative interpretations because waveforms can return to a normal contour within only a few vessel diameters downstream from a significant stenosis.[5,6]

PRESSURE MEASUREMENTS

Strandness and coworkers developed noninvasive pressure measurement in the 1960s when continuous wave Doppler instruments became available to detect blood flow.[4] Since pressure differentials drive flow, decreased pressure results in decreased flow. In most instances, therefore, pressure is an acceptable surrogate measure for flow and is easier to measure.

The higher-frequency components of the pressure waveform are more sensitive to the dampening effect of stenoses, and therefore decreases in systolic pressure are more sensitive than changes in mean or diastolic pressure for detecting stenosis. The reduction in pressure is caused by viscous losses from flow through narrow channels and by kinetic energy losses secondary to turbulence (which is the dominant source of loss in all but the smallest arteries). Turbulence occurs when kinetic forces are much greater than the viscous forces that produce ordered, laminar flow. The relationship between these forces is estimated by the Reynold number (Re):

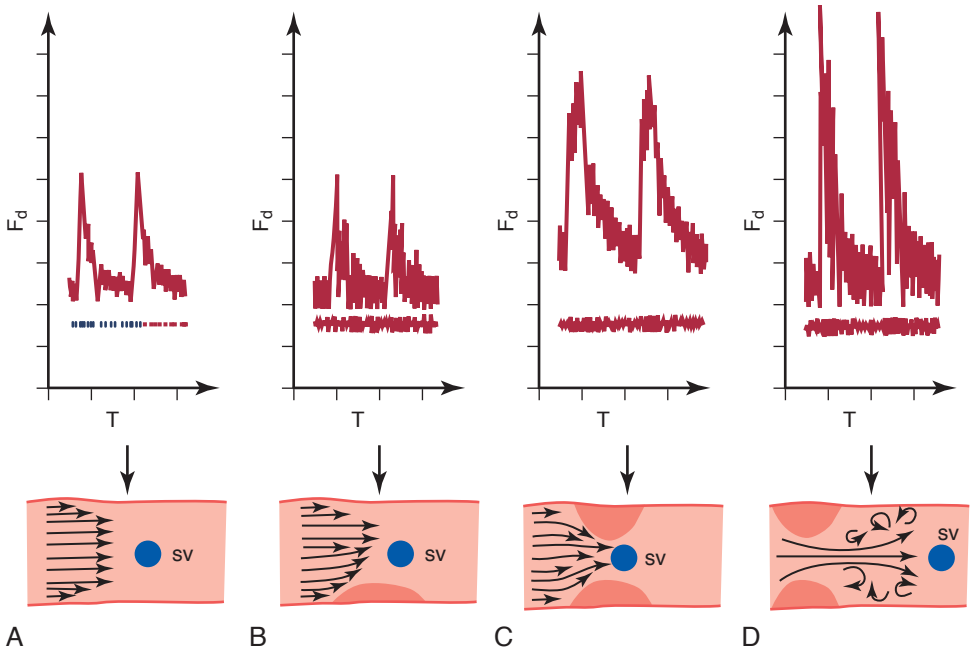


Figure 20.3 Changes in the Velocity Waveform Caused by Arterial Stenosis. (A) Normal waveform with relatively low and uniform velocity (frequency shift). (B) Mild stenosis causes disturbed flow in diastole (broadened waveform) and little increase in velocity. (C) Significant narrowing (>50%) causes at least a doubling of the peak systolic velocity. (D) Beyond a significant narrowing, post-stenotic turbulence causes marked widening of the waveform. F_d, Frequency shift; *SV*, sample volume; *T*, time. (Compliments of Jean Primozich.)

$$Re = Vd/\nu$$

where V is velocity in centimeters per second, d is diameter of the vessel, and ν is viscosity (which varies with velocity; in other words, blood is a non-Newtonian fluid). As flow increases, velocity increases, and flow becomes less stable as both viscous and kinetic losses increase. Greater than Reynold numbers of approximately 2500, turbulence develops (at least in straight tubes with nonpulsatile flow, conditions that are not met in the normal human vasculature) and energy is lost (as imperceptible heat generation). Thus resting flow and velocity may not be associated with a reduction in pressure. However, a pressure gradient may develop when flow increases, resulting in increased turbulence.

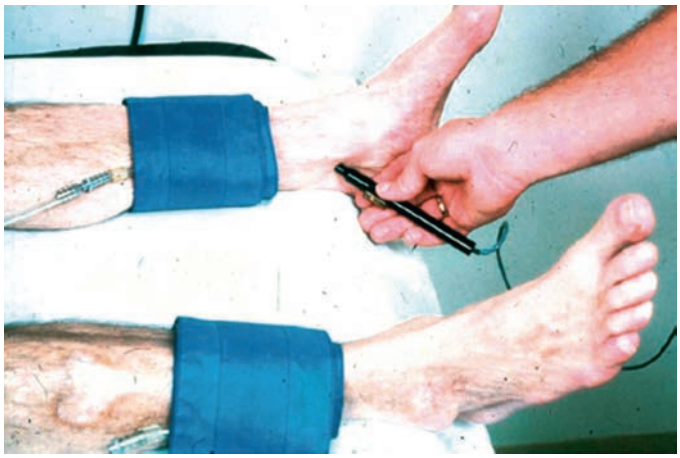
Mild stenoses that do not cause a drop in pressure at rest may become evident when flow is increased. A peak systolic pressure drop across an arterial segment of 10 mm Hg at rest or 15 mm Hg after hyperemia induced by exercise, ischemia, or the administration of vasodilators indicates increased resistance in this segment sufficient to reduce flow by a clinically meaningful amount. Conversely, significant proximal lesions (e.g., in the iliac system) may not be evident even after vasodilation if the outflow vessels (superficial and profunda femoral arteries) are so diseased that outflow is severely restricted. Without flow, there is no pressure drop across a vessel no matter how stenotic.

Ankle-Brachial Index Measurement

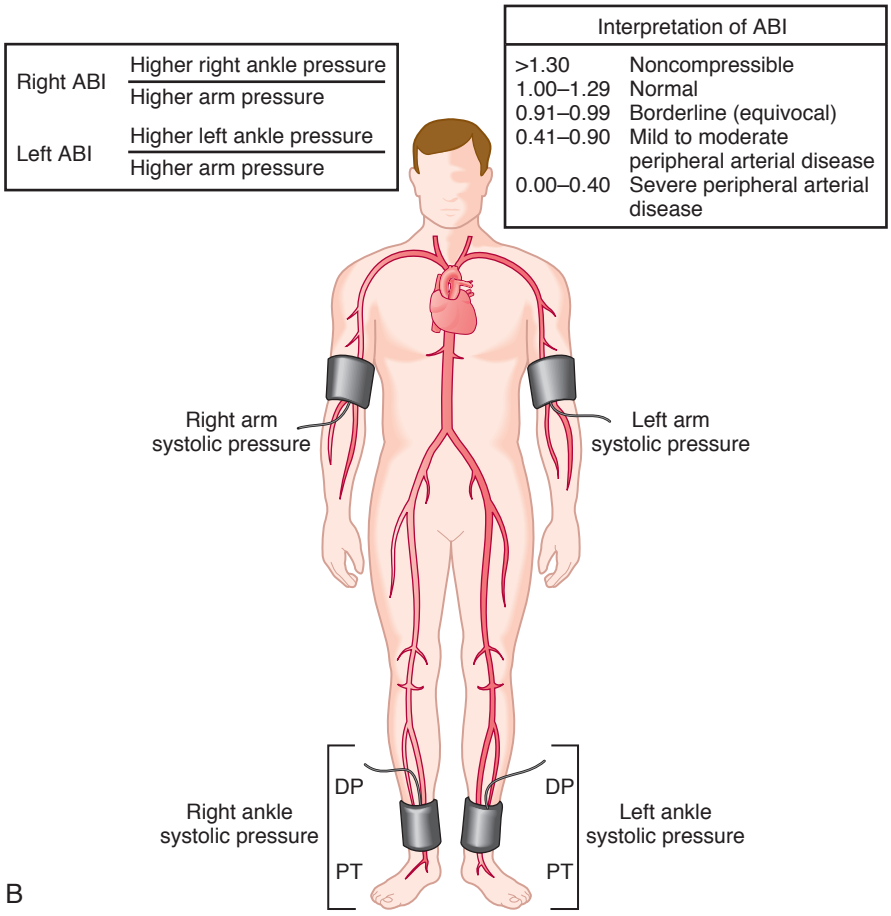
Basic Technique

Significant arterial occlusive disease anywhere between the heart and a blood pressure cuff will cause a decrease in systolic pressure at the cuff level. The simplest noninvasive method for documenting the presence of lower extremity arterial occlusive disease is the ankle-brachial index (ABI).[7] The cuff is placed as low as possible on the leg above the ankle, inflated above systolic pressure, and then slowly deflated while the Doppler probe is held over the posterior tibial artery, just behind the medial malleolus (Fig. 20.4A), or the dorsalis pedis artery, slightly lateral to the extensor hallucis longus tendon approximately a centimeter distal to the ankle joint. The ankle pressure is recorded as the highest pressure at which the Doppler signal returns. If no signal can be obtained over these arteries, the examiner should check for the terminal branch of the peroneal artery (the lateral tarsal artery), which is just anterior and medial to the lateral malleolus. However, pressure in this artery may not be as good a measure of pedal flow as in the other two tibial arteries because it does not connect directly to the pedal arch.

The brachial pressure, measured with a manual blood pressure cuff and continuous wave Doppler at the distal brachial or radial artery, is used as the denominator for the ABI and serves as a surrogate for central aortic pressure, which cannot be measured noninvasively. As upper extremity occlusive disease may lower brachial pressure, the higher of the two arm measurements should be used. Bilateral upper extremity occlusive disease renders the ABI nondiagnostic. The ABI for each lower extremity is the highest of the detectable ankle pressures divided by the higher of the two brachial pressures (see Fig. 20.4B). The ABI is less variable than ankle pressure, with a standard deviation of approximately 0.07, so a measurement greater than two standard deviations is considered significant. Normalizing to the brachial pressure accounts for the normal variation in central pressure and allows a better appreciation of the extent of arterial



A



B

Figure 20.4 (A) Method for measurement of ankle pressure. The cuff is placed just above the ankle, and pressure is measured over the dorsalis pedis and posterior tibial arteries. The higher of the two is used to estimate perfusion pressure at the ankle. (B) Method for measurement of the ankle-brachial index (ABI). The higher of the two brachial pressures and the higher of the two ankle pressures are used for calculation of the index. The patient should be supine and resting for at least 5 minutes before the measurements are made. *DP*, Dorsalis pedis; *PT*, posterior tibial. (From Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med.* 2001;344:1608–1621.)

occlusive disease in the presence of systemic hypotension or hypertension.

The pressure waveform changes as it moves through the vasculature (Fig. 20.5). Peak systolic pressure is accentuated by the additive effect of reflected pressure waves from the periphery. In addition, the lower extremity vasculature remodels in reaction to increased intraluminal pressure from gravity and upright posture to have increased wall thickening and unchanged inner radius, leading to increased arterial stiffness.[8] Thus, although mean pressure decreases as the pressure wave travels distally, peak systolic pressure increases. As a result, ankle systolic pressure is normally approximately 10% higher than brachial pressure

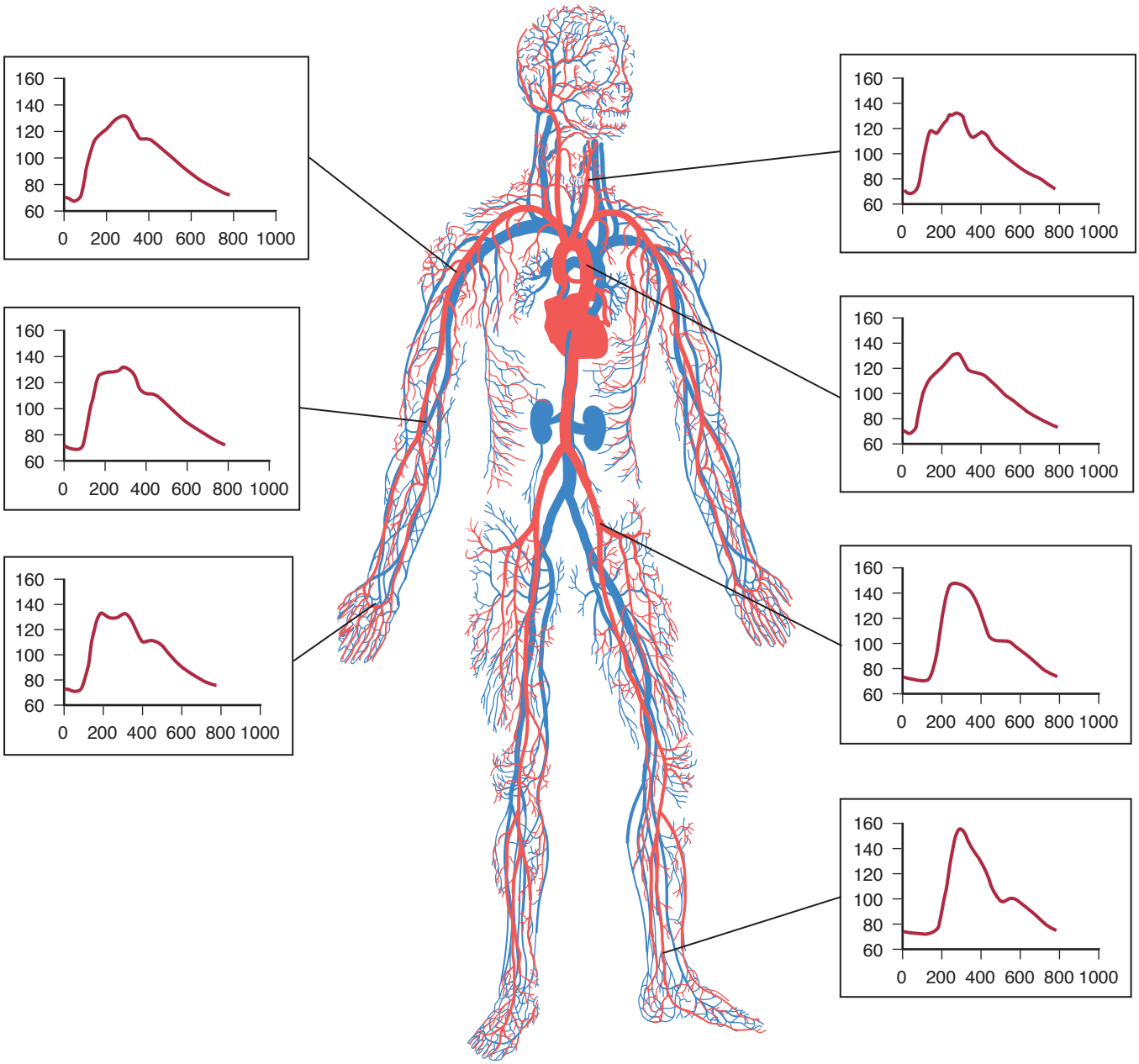


Figure 20.5 The pressure wave changes as it moves distally through the vasculature. Peak systolic pressure is accentuated, and mean arterial pressure decreases.

(ABI of 1.1). Significant PAD decreases this ratio. Because of the known variance of this test, ABIs in the range of 0.9 to 1.29 are considered normal. However, a value of 0.9 to 1 should be considered borderline because these patients have been demonstrated to have increased lower extremity and cardiovascular risk.[9] As the extent and severity of PAD increases, ABI decreases (Fig. 20.6A).

ABI has been well validated against contrast-enhanced angiography for its ability to detect stenosis of greater than 50%.[8,10,11] The sensitivity of this test depends on the lower limit of normal that is chosen, with higher limits detecting more disease, as well as the population being tested, with lower sensitivity in more elderly populations or with a higher percentage of diabetic or chronic kidney disease patients. Using an average of the two measurements has been found to correlate better with walking distance than using either the lower or higher ankle pressure.[12] In general, the sensitivity of ABI in detecting PAD ranges from 80% to 95% and the specificity from 95% to 100%, with positive and negative predictive values in excess of 90%.[10,13]

The automated blood pressure instruments commonly used in hospitals and clinics to determine arm blood pressures may also be used at the ankle level. The machine detects oscillations of pressure, caused by changes in volume in the extremity as a result of influx of blood with each systolic pulse, in the cuff as it deflates. Oscillation begins while the cuff is well above systolic pressure and continues until it is well below diastolic pressure. Maximum oscillation occurs at mean arterial pressure. Each

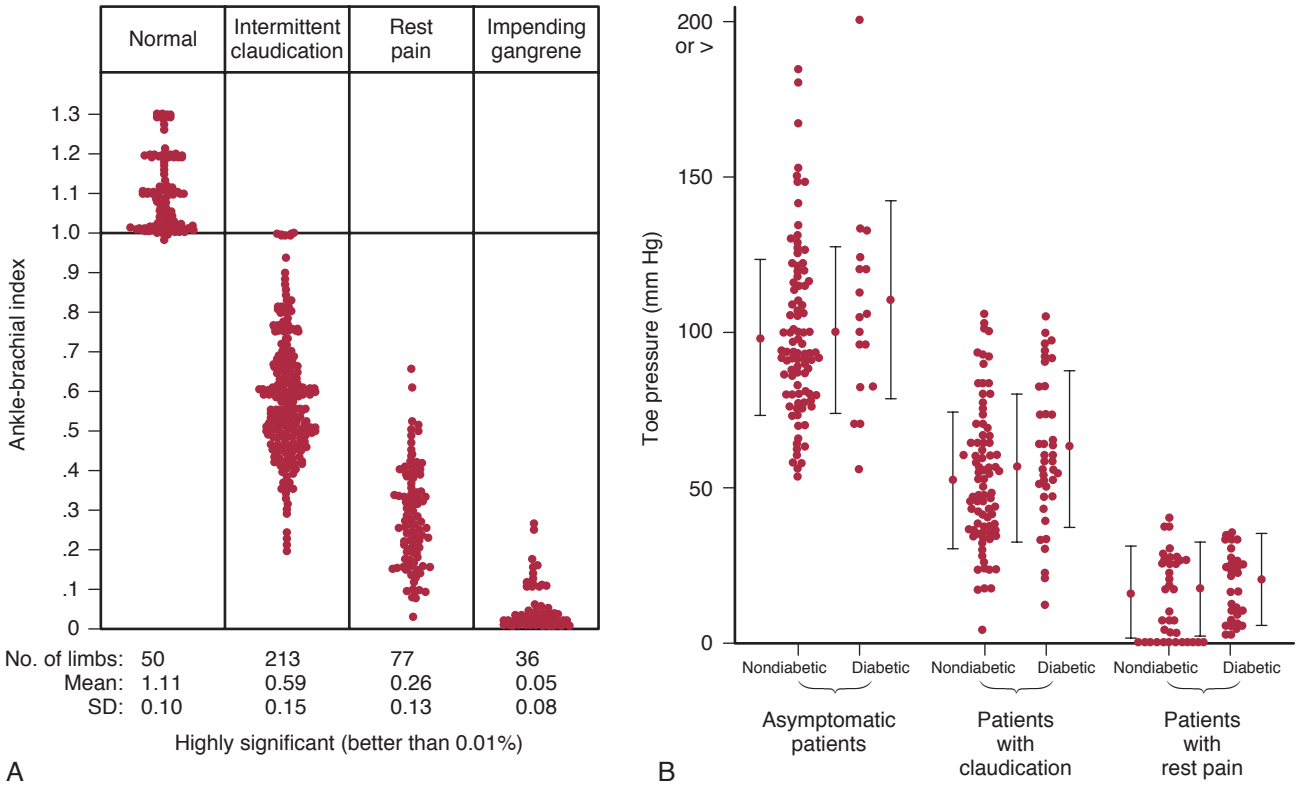


Figure 20.6 (A) Relationship of the ankle-brachial index to functional impairment produced by the occlusive process. *SD*, Standard deviation. (B) Toe blood pressure grouped according to symptoms and the presence of diabetes in patients with arterial disease. Mean and SDs for the nondiabetic and diabetic subgroups and for the two groups combined are indicated by *vertical bars*. ([A] Modified from Yao JST: Hemodynamic studies in peripheral arterial disease. *Br J Surg* 57:761, 1970; [B] Modified from Ramsey DE, Manke DA, Sumner DS. Toe blood pressure: a valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease. *J Cardiovasc Surg.* 1983;24:43–48.)

manufacturer has its own proprietary algorithm, empirically derived, to determine systolic and diastolic pressure from oscillometry. These algorithms were developed for measurement of arm pressure but can also be used for ankle pressure. Like standard Doppler methods, oscillometry has good concordance for normal ankle pressure, but it overestimates pressure when there is moderate disease and is unable to determine pressure in severe disease due to the significantly diminished pulse pressure. Nevertheless, this method may be useful to screen for PAD in primary care clinics because it is rapid and requires no specialized training or equipment.[8,14]

Noninvasive tests can help to make the diagnosis of entrapment syndrome. A change in ankle plethysmography and ABI with stress maneuvers suggests entrapment. The limb is examined with the knee extended and the foot in the neutral, forced plantar-flexed, and forced dorsiflexed positions. The test is considered positive if the ABI drops more than 0.5 or there is flattening of the plethysmographic tracing with forced dorsiflexion or plantar flexion.[15,16]

Prognostic Value of Ankle-Brachial Index

ABI has some predictive value; measurements greater than 0.5 are infrequently associated with progression to critical limb ischemia over the next 6 years.[17] Decreased ABI and the presence of diabetes mellitus were the two factors associated with the development of chronic limb ischemia in a 15-year study of 1244 patients with claudication.[18] Abnormal ABI (either <0.60 or >1.30) has been associated with increased overall mortality, as has decline in ABI over time.[19-22] ABI is useful as an office screening tool for PAD in asymptomatic patients older than 65 years of age, for whom an ABI < 0.90 is associated with a high mortality and vascular event risk.[23] The American Diabetes Association has recommended similar screening with ABI for diabetic patients older than 50 years of age.[24] Although detection of PAD can identify patients at risk for cardiac events, there are no data demonstrating that screening leads to prevention of such events. Nor is there evidence that ABI adds significantly to Framingham Risk Score or other assessments of cardiovascular risk.[25-27] Routine surveillance of ABI is not indicated in untreated patients with PAD unless they develop new or worsening symptoms.[28]

Technical Errors

Although measurement of ABI is straightforward, errors are often made, particularly by those unfamiliar with vascular pathophysiology. A common mistake made by the uninitiated is to use the left brachial pressure for calculation of the left ABI and the right brachial pressure for the right ABI. Once it is understood that brachial pressure is a surrogate for systemic

pressure and that atherosclerosis may lower pressure to an upper extremity, the correct practice of using the higher of the two brachial pressures becomes obvious.

Failure to have the patient supine for long enough to allow stabilization of blood pressure, preferably for ≥5 minutes, is the next most common error, particularly when it is difficult to assist nonambulatory patients from a wheelchair onto an examination table. Because hydrostatic pressure is equal to "ρgh" (where ρ is the density of blood, g is acceleration as a result of gravity, and h the height in centimeters of the blood column measured from the right atrium, also known as the phlebostatic level), ankle pressure will be increased by 0.74 times the height in centimeters from the right atrium to the cuff. If the patient is sitting or standing, this distance is on the order of 100 cm; ankle pressure would be elevated by 74 mm Hg above the supine value—a significant difference.

Accurate measurement requires that the cuff pressure reflect the actual pressure in the tissue underneath it. Use of a cuff that is too small will result in poor conduction of pressure to the extremity and falsely elevated readings. Conversely, a cuff that is too wide may cause an underestimation of pressure. The American Heart Association recommends that the bladder length of the cuff be 80% and the width be 40% of the circumference of the extremity (for a length-to-width ratio of 2:1).[29] It may not be possible to measure upper arm pressure accurately in obese patients because the width of a properly sized cuff exceeds the length of the upper part of the arm. In such cases, forearm pressure may be more accurate.

If the artery wall is stiffened by medial calcinosis, as often occurs in diabetics and patients with chronic kidney disease, increased pressure may be required to collapse the wall and stop the flow of blood. An ABI greater than 1.3 should raise suspicion that the wall is stiffened. In the extreme, blood flow is never occluded even at the highest cuff pressure. Stiff arteries may also reopen when cuff pressures are still well above intraluminal pressure, resulting in falsely elevated ankle pressure. There are several ways to suspect that such is the case. First, the quality of the Doppler waveform, which would be brisk and triphasic in a normal vessel, may be blunted and monophasic as a result of the occlusive disease (see later). Second, the pulse may not be palpable even though the measured pressure is well above the palpable level. Third, the remainder of the clinical picture, such as ischemic ulceration or a clear history of claudication or pain at rest in a patient with known atherosclerosis, may be strongly suggestive of significant PAD. Fourth, the Doppler signal may diminish if the ankle is elevated while the patient is supine. (Using the aforementioned equation, the ankle pressure in millimeter of mercury [mm Hg] may be estimated as 0.74 times the height of the ankle above the bed in centimeters when flow is no longer detectable by Doppler.) Because digital arteries are less commonly involved with calcification, toe pressure measurements can be useful when ankle pressure is falsely elevated.

Segmental Pressures

An estimate of the level of disease in the lower extremity can be made by measuring blood pressure with cuffs placed at the arm, upper thigh, above-knee, below-knee, and ankle levels (Fig. 20.7). A Doppler device is used to detect blood flow at the ankle as each individual cuff is inflated and then slowly deflated. Typical segmental pressures from normal subjects and patients with various levels of occlusive disease are shown in Table 20.1. Upper thigh pressure is normally higher than brachial pressure, particularly when the relatively narrow, 10-cm standard thigh cuff is used. In this case, upper thigh pressure may be as high as or somewhat higher than brachial pressure, even in the presence of significant iliac disease. False negatives may also result from restriction of outflow into the thigh because of occlusion of vessels by the cuff. The resulting limitation of flow across a stenotic iliac segment can prevent a pressure drop across it. A decrease in pressure of 20 mm Hg or more at any one level in comparison to the level above indicates significant disease. Because the most distal cuff is at the ankle, disease below this level is not detected.

Segmental pressure measurements do not detect disease in nonaxial vessels, such as the profunda femoris. Because of the difficulty in detecting stenoses when flow is restricted, multilevel disease can be difficult to identify when a proximal stenosis is causing a significant decrease in distal pressure and flow. Side-to-side comparisons should be made and are meaningful when there is a difference, but they may be misleading in patients with symmetric disease in the two extremities.

Figure 20.7 Segmental pressure is measured with the same technique as ankle pressure, but with cuffs placed at the upper part of the thigh, at the lower part of the thigh, below the knee, and at the ankle.

TABLE 20.1 Typical Segmental Systolic Arterial Pressures (mm Hg)

	ARTERIAL DISEASE				
	Normal	Iliac	Superficial Femoral	Iliac and Superficial Femoral	Below-Knee
Arm	120	120	120	120	120
Upper thigh	160	110	160	110	160
Above knee	150	100	100	70	150
Below knee	140	90	90	60	140
Ankle	130	80	80	50	90

An estimate of the extent of collateralization around the knee in patients with superficial femoral artery occlusion can be made using the profundapopliteal collateral index (PPCI).[30] PPCI is calculated as the difference between the above-knee and below-knee blood pressure divided by the above-knee pressure. A low index indicates good collateral development (little pressure drop across the knee). In general, a PPCI of less than 0.25 predicts a good result from profundaplasty without infrainguinal bypass, whereas a PPCI of greater than 0.50 predicts no improvement with profundaplasty alone.[31]

Use of segmental pressure does not add to simple ABI in improving the accuracy of Doppler waveform analysis in the diagnosis of PAD.[32] Segmental pressure measurement is frequently combined with pulse volume recording (see later) to provide a more accurate method for diagnosing PAD. Disadvantages include lack of exact anatomic detail, patient discomfort, and the potential to damage balloon-expandable peripheral arterial stents.

Digital Pressure Measurement

Pressure in a digit can be measured in much the same way as arm and ankle measurements. An appropriately sized minicuff is placed around the base of the digit and attached to a standard manometer. Any type of flow detector can be used to determine when flow returns as the inflated cuff is slowly deflated. Most commonly used are photoplethysmography (PPG) probes and continuous wave Doppler flow detectors placed on the distal phalanx, but laser Doppler probes have also been used and may be more sensitive to extremely low flow.[33] As digital arteries are less commonly calcified than tibial arteries, toe pressures are most useful in patients prone to arterial calcification, such as diabetics and patients with chronic kidney disease. Toe pressure is also sensitive to disease at the level of the pedal arch and digital vessels, which is not detectable by ankle pressure measurements.[34] However, even digital arteries can be calcified and noncompressible, at which point waveform analysis or transcutaneous oxygen tension ($tcPO_2$) measurements may be helpful.

Normal toe pressure is 20 to 40 mm Hg less than ankle pressure, possibly because of the measurement technique. A toe-brachial index less than 0.7 is considered abnormal.[11] Pressures of 30 mm Hg or lower are associated with ischemic symptoms (see Fig. 20.6B). Foot lesions usually heal when the toe pressure is greater than 50 mm Hg (or slightly higher in diabetics). The correlation between foot wound healing and toe pressure is shown in Fig. 20.8. Unfortunately, toe pressures often cannot be obtained in patients with forefoot and digital gangrene for whom transmetatarsal amputation is contemplated. For more detail on methods to predict amputation healing at various levels, see Chapter 111, Lower Extremity Amputations: Epidemiology, Procedure Selection, and Rehabilitation Outcomes.

Stress Testing

As noted earlier, the pressure reduction across a stenosis depends on the rate of flow through it. This is the basis of exercise testing to detect stenoses that may not cause abnormalities at rest. It is a useful, practical method for quantitating the functional effect of arterial insufficiency.

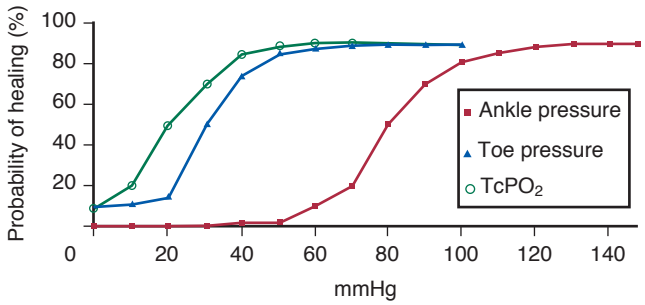


Figure 20.8 A schematic estimate of the probability of healing of foot ulcers and minor amputations in relation to ankle blood pressure, toe blood pressure, and transcutaneous oxygen pressure (tcPO2) based on selected reports. (From Bakker K, Apelqvist J, Schaper NC; International Working Group on the Diabetic Foot Editorial Board. Practical guidelines on the management and prevention of the diabetic foot 2011. *Diabetes Metab Res Rev.* 2012;28:225–231.)

Exercise Testing

Because most patients with claudication and those with ischemic symptoms have decreased ABI at rest, exercise testing is only rarely required to diagnose PAD. This test is most useful when it is difficult to distinguish between true arterial claudication and pseudoclaudication or when patients have both. It also helps to determine the extent to which cardiopulmonary, orthopedic, and vascular disease contributes to the patient's difficulty walking.

For standard exercise testing the patient rests supine for 20 minutes, after which resting ABI is measured. Blood pressure cuffs are left in position at both ankles and the upper extremities, and the patient is asked to walk at 2 miles/h on a treadmill at a 12-degree inclination for 5 minutes or until forced to stop because of symptoms (Fig. 20.9A). Note is taken of the time to initial symptom onset, the nature of the symptoms, and the time until stopping, which may be influenced by many factors, such as shortness of breath, patient motivation, and muscular pain. The patient is then asked to lie down, and ankle and arm pressures are measured immediately and then every 2 minutes for 10 minutes or until the pressure returns to resting levels.

Clinically significant lower extremity PAD can be reliably ruled out in patients who can walk the entire time without symptoms or a decrease in the ABI. The severity of PAD is reflected by the extent of the post-exercise drop and the length of time required to return to baseline levels (see Fig. 20.9B). Patients with mild disease may have normal resting pressure but a mild drop in pressure after exercise that returns within minutes to baseline levels. Those with moderate to severe disease have abnormal resting ABIs with further decreases after exercise that persists throughout the post-exercise observation period of 10 to 15 minutes. Patients who have less than a 20-mm Hg pressure drop at the ankle in comparison with the upper extremity rarely benefit from vascular reconstruction. The exception to this is a patient with a mild or no arterial stenosis at rest and vasoconstriction induced by intense exercise as seen in iliac endofibrosis. A standard walking test does not result in a drop

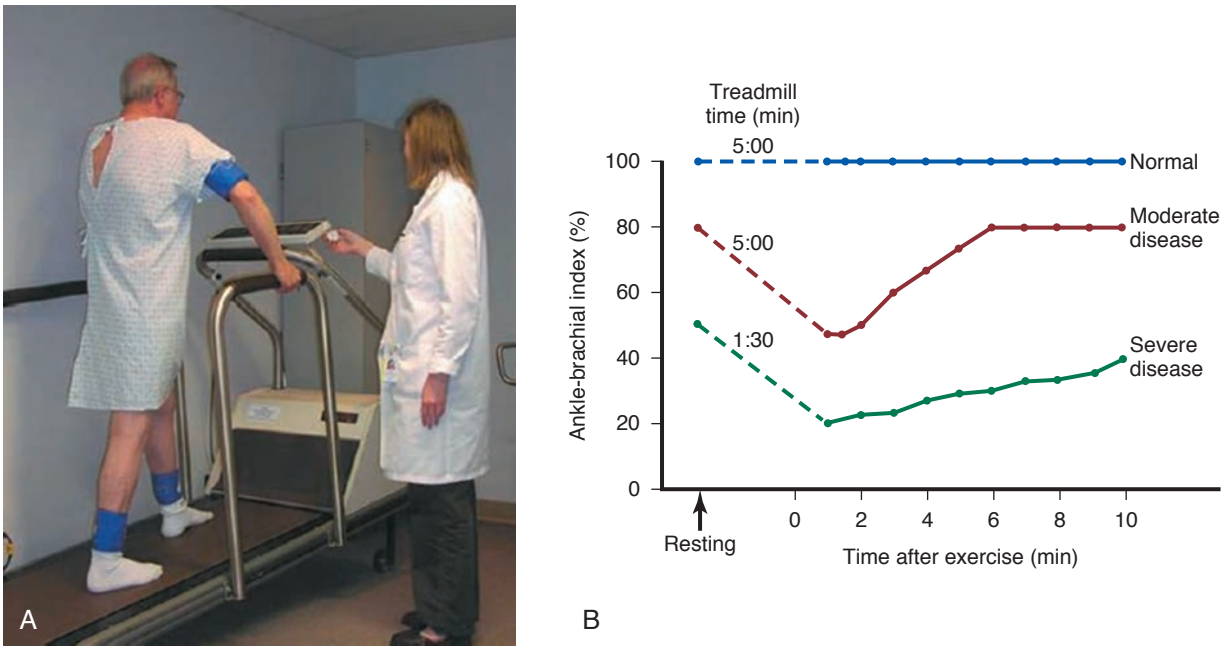


Figure 20.9 (A) Patient undergoing a standard treadmill test. Pressure cuffs are left in position at the arms and ankles to allow immediate measurement on stopping. (B) Examples of exercise test results in patients with various degrees of peripheral arterial occlusive disease. The resting ankle-brachial indices are noted, followed by similar measurements immediately after exercise and for several minutes thereafter.

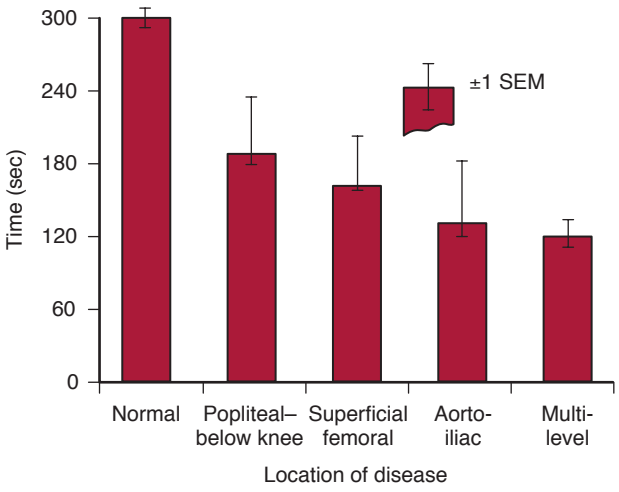


Figure 20.10 Treadmill walking times in patients with occlusive arterial disease. Normal individuals can almost always exceed 5 minutes (300 seconds). (Modified from Strandness DE Jr, Sumner DS. *Hemodynamics for Surgeons.* New York: Grune & Stratton; 1975.)

in ankle pressure in these young athletes; and a more intense exercise protocol may be required to elicit symptoms and a pressure drop.[35]

The treadmill test tends to be more positive with proximal disease than with distal disease (Fig. 20.10). The aortoiliac vessels supply all the musculature of the lower extremity, including the large muscular groups of the buttock and thighs, so the effect of lesions in these vessels is greater than the effect of isolated occlusion of an infrainguinal vessel. Exercise testing is not effective for detection of disease below the level of the popliteal artery because the sural branches to the gastrocnemius muscle come off at or proximal to this level. This is the same reason that revascularization of tibial arteries is not generally indicated for patients whose only complaint is claudication.

Reactive Hyperemia

There are times when exercise testing is not possible because of comorbid conditions or during situations when walking is not possible. In these situations, flow may be increased by reactive hyperemia or vasodilators. Reactive hyperemia is induced by occlusion of blood flow to the extremity by the tourniquet effect of a proximal blood pressure cuff inflated above the systolic pressure level for 3 to 5 minutes. When the cuff is released, peripheral vascular resistance is reduced, and flow is increased. This test is used infrequently because it is uncomfortable and does not produce sustained increases in flow. Reactive hyperemia can also be used to assess endothelial function in the brachial artery reactivity test.[36]

For the standard lower extremity reactive hyperemia test, a cuff placed around the thigh is inflated above systolic pressure for 3 to 7 minutes. After cuff deflation, ankle pressure is monitored two or three times a minute for up to 6 minutes or until measurements return to resting levels. In normal individuals, ankle pressure drops immediately to approximately 80% of resting levels but recovers within minutes to nearly normal levels. In patients with PAD the drop in pressure is approximately the same as that occurring after exercise, but recovery is more rapid, presumably because there is less oxygen debt. The magnitude of the drop in pressure correlates with the severity of disease, as does the length of recovery time, although less closely. This test has advantages over treadmill testing, such as being faster and less cumbersome, not needing a treadmill, not depending on patient motivation, being more easily standardized,

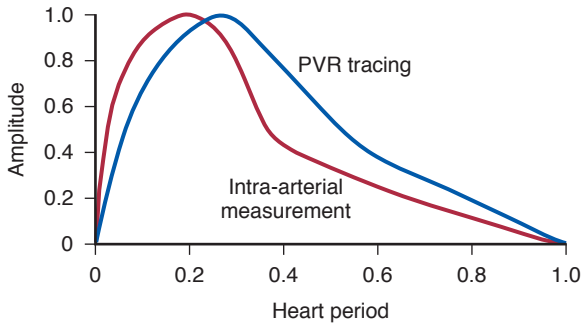


Figure 20.11 Comparison of pressure contours obtained with the pulse volume recorder (PVR) and direct cannulation of the common femoral artery. Axes normalized: y = fraction of maximal amplitude; x = fraction of one cardiac cycle. (Redrawn from Darling RC, Raines JK, Brener BJ, Austen WG. Quantitative segmental pulse volume recorder: a clinical tool. *Surgery.* 1972;72:873–877.)

and not being affected by cardiovascular or orthopedic conditions. Disadvantages include less specificity and sensitivity than exercise testing, patient discomfort, and more operator dependence because of the need for rapid pressure measurements, and it does not directly test the patient's ability to walk. These factors tend to outweigh the advantages of this technique, particularly because duplex scanning provides greater anatomic detail without patient discomfort.

Direct Pressure Measurement

In some cases it is difficult to determine either by imaging or indirect testing whether a segment of artery has clinically significant narrowing. In such cases the most definitive test is direct pressure measurement, which can be done intraoperatively or at the time of percutaneous angiography. Vasodilators can be used when results are equivocal. Measurement of pressure along the course of a bypass can be a useful, rapid means of locating technical problems. The technique is simple. The artery at the level of interest (generally the common femoral artery when the aortoiliac segment is being assessed) is punctured with a 19-gauge needle and connected to a standard strain gauge with stiff tubing. When comparing with a reference pressure, such as the radial artery, the same pressure transducer is used to make it easy to switch between the two pressure lines and to eliminate errors that may be caused by having the two transducers at different heights. Direct pressure measurement is the gold standard to which indirect methods are compared (Fig. 20.11).

Penile Pressure

Of the three paired penile arteries, which all arise from the internal pudendal artery (Fig. 20.12), the cavernosal artery is the most important for erectile function. Proximal occlusive disease can be responsible for vasculogenic impotence. Measurement of penile blood pressure is performed by applying a pneumatic cuff 2.5 cm in width to the base of the penis. Return of blood flow when the cuff is deflated can be detected by a mercury strain-gauge plethysmograph, a PPG probe applied to the anterolateral aspect of the shaft, or a Doppler flow probe.

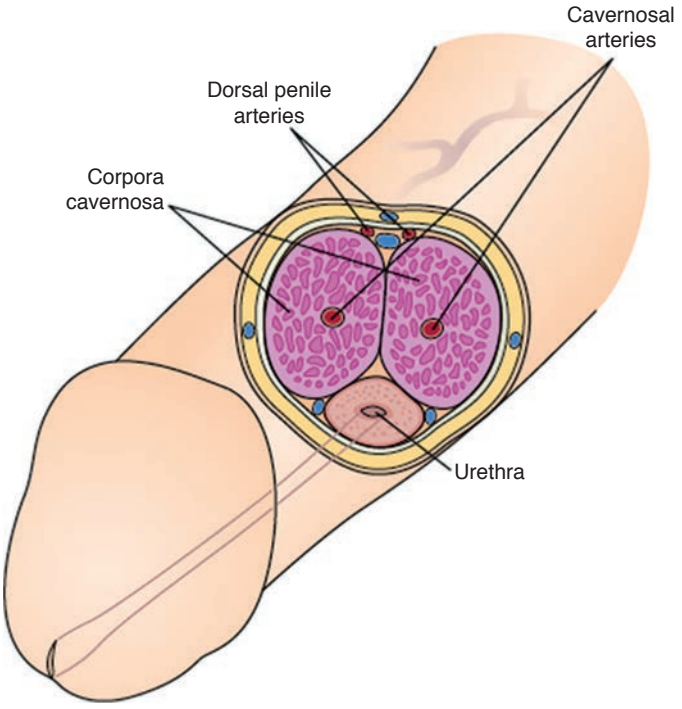


Figure 20.12 The paired penile arteries *(urethral arteries not shown).*

Although some investigators have positioned the probe over the dorsal penile arteries, others have emphasized the importance of detecting flow in the cavernosal artery.[37]

Penile pressure and brachial pressure are normally equivalent, but penile-brachial index declines with age. Penile-brachial indices greater than 0.75 to 0.80 are considered compatible with normal erectile function; an index of less than 0.60 is diagnostic of vasculogenic impotence, especially in patients with peripheral vascular disease. A brachial-penile pressure gradient of less than 20 to 40 mm Hg suggests adequate penile blood flow. Gradients in excess of 60 mm Hg suggest arterial insufficiency. For a more detailed discussion of the assessment of erectile dysfunction, including other diagnostic modalities, see Chapter 192.

PLETHYSMOGRAPHY

Plethysmography is based on measurement of change in volume of the extremity caused by the cyclic nature of arterial inflow. The technique was developed using a mercury strain gauge placed around the extremity. Change in volume causes a change in circumference and therefore in the length and electrical resistance of the strain gauge. The resistance is easily measured and plotted on a strip chart, which results in a waveform that has the same basic contour as the pressure wave (see Fig. 20.11).[38] Impedance plethysmography works on similar principles; it monitors electrical impedance, which is inversely proportional to volume. These devices have largely been replaced by air plethysmography, which monitors pressure in a cuff placed around the extremity and inflated to 65 mm Hg, because the cuffs are more rugged and easier to use. Raines and colleagues, who developed these instruments, called them pulse volume recorders (PVRs).[39,40]

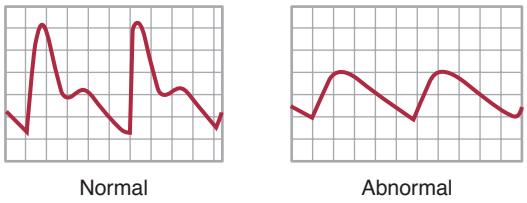


Figure 20.13 Normal and abnormal pulse volume contours recorded at the ankle level. The normal form shows a prominent dicrotic wave on the downslope. Cuff pressure, 65 mm Hg; cuff volume, 75 mL.

TABLE 20.2 Definition of Pulse Volume Recorder Categories

CHART DEFLECTION (mm)			DV (mm^3)		
Category	Thigh and Ankle	Calf	Ankle	Calf	Thigh
1	>15[a]	>200[a]	>160	>213	>715
2	>15[b]	>20[b]	>160	>213	>715
3	5-15	5-20	54-160	54-213	240-715
4	<5	<5	<54	<54	<240
5	Flat	Flat	0	0	0

[a]With reflected wave.
[b]No reflected wave.
DV, Maximal segmental volume change per heartbeat.

Pulse Volume Recording

Like segmental pressure measurements, PVR waveforms obtained at various levels of the lower extremity can be used to infer the presence and location of arterial occlusive disease. The normal pulse contour has a rapid upslope, a sharp systolic peak, a dicrotic notch, and a downslope that bows toward the baseline (Fig. 20.13). Downstream from stenotic segments, the waveform becomes dampened—the upstroke becomes less steep, the dicrotic notch is lost, and the overall amplitude is decreased. Thus a decrease in pulsatility (either the amplitude or upstroke) from one segment to the next indicates the presence of stenosis upstream. The extent of the changes in the waveform is related to the severity and extent of the proximal disease. Similar waveform changes may be also caused by downstream disease, confounding results.

Although the amplitude of the plethysmographic pulse is reduced by arterial occlusive disease, it alone is not a useful parameter for determining the extent of disease. Amplitude is fairly constant within an individual; however, intersubject variability is large because of differences in body and limb size, blood pressure, peripheral resistance, and cardiac output. A classification scheme has been devised to rate arterial disease from normal (1) to mild (2, 3) to severe (5), based on amplitude and changes in the waveform (Table 20.2). Pulse amplitude increases in normal limbs after exercise. As with pressure measurements, waveform contours that are normal at rest may become abnormal with increased flow. Flow-limiting stenosis causes deterioration of the waveform and reduction of the PVR amplitude at the ankle. PVR tracings from limbs with various combinations of disease are shown in Fig. 20.14.

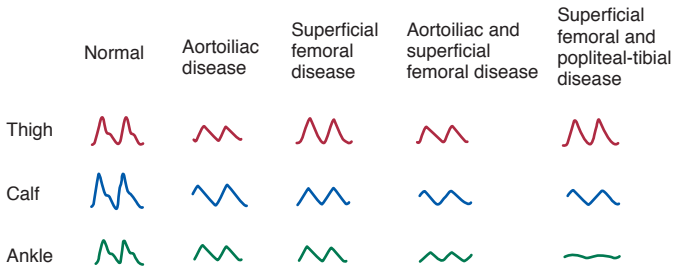


Figure 20.14 Pulse volume recorder tracings from a normal limb and from limbs with various combinations of peripheral vascular disease. (Modified from Rutherford RB, Lowenstein DH, Klein MF. Combining segmental systolic pressures and plethysmography to diagnose arterial occlusive disease of the legs. *Am J Surg.* 1979;138:216.)

PVR is less affected than pressure measurements by arterial calcification. The combination of segmental pressure measurements and PVR is more accurate than either method alone for detecting PAD.[41] There is current debate regarding whether these indirect physiologic tests should be completely replaced with arterial duplex scanning; however, they require less technologist expertise, allow assessment of the adequacy of the collateral circulation, and may be more appropriate for screening purposes.

Digital Plethysmography

As mentioned earlier, digital pressure measurements are useful when calcification of tibial vessels causes false elevations in ankle pressure or when patients have occlusive disease distal to the ankle level. The PPG probe commonly used for this application sends an infrared light into the tissue and has a detector for backscattered light that corresponds to the variation of blood volume over time.[42] The pulse oximeter is a form of PPG probe.

Pulse Contour

Changes in the plethysmographic waveform in the digit reflect any proximal disease. Significant disease documented by digital pressure and abnormal plethysmographic waveforms may be present despite adequate ankle pressure. Digital PVR is also useful for determining the extent of sympathetic activity in patients with cold sensitivity or the presence of significant steal syndrome caused by dialysis access grafts. Comparison of waveforms and digital pressures with and without access flow occlusion demonstrates the hemodynamic effects of the access.

The pulse contour in the digits is similar to that described previously for the lower extremity with the normal waveform having a rapid upslope, a sharp systolic peak, a dicrotic notch, and a downslope that bows toward the baseline. Occlusive disease causes dampening of the waveform with flattening and loss of the dicrotic notch. In extreme cases there may be no detectable waveform. Conversely, the presence of a normal digital waveform indicates that there is no clinically significant arterial disease in the arteries supplying the digit.

Reactive Hyperemia

Because resistance vessels in extremities with significant flow-limiting PAD are already maximally dilated to compensate for reduced flow, there is little additional response to reactive

hyperemia. A cuff is placed at the ankle or above, inflated above systolic pressure for 3 to 5 minute then, and rapidly deflated while the digital PVR is monitored. In normal limbs the pulse returns rapidly, attains half its baseline amplitude within a few seconds, and then rises quickly to twice baseline (Fig. 20.15A). With PAD, reappearance of the waveform and return to half the resting value are markedly delayed in proportion to the severity and extent of the disease (see Fig. 20.15B–D, Table 20.3).

The response to reactive hyperemia requires resting sympathetic tone. Therefore this test is useful for predicting the response to sympathectomy, which increases blood flow by decreasing peripheral resistance. If the increase in PVR amplitude is less than twice the resting level, sympathectomy likely will not improve skin blood flow. However, the response to reactive hyperemia is not dependent on intact sympathetic innervation, so this test cannot be used to determine if the sympathetic nerves are intact. Instead the deep breath test can be used for this purpose. Sympathetic innervation is intact if there is a decrease in pulse volume in response to a deep breath.

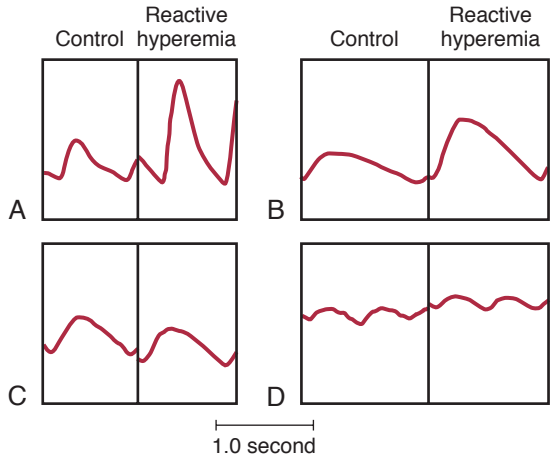


Figure 20.15 Reactive Hyperemia Test; Digit Pulse, Second Toe. Digit pulse volume more than doubles with a normal response *(upper panels)*. Little hyperemic response in pulse volume is evident with an abnormal response *(lower panels)*. (A) Normal circulation. (B) Superficial femoral occlusion. (C) Diabetic for 20 years. (D) Iliac and superficial femoral arterial disease.

TABLE 20.3 Pulse Reappearance Time After Release of Arterial Occlusion

Location of Occlusive Disease	Pulse Reappearance Time (s)	Time Required to Reach Half Control Volume (s)
No occlusion	0.2 ± 0.1	3.4 ± 0.8
Aortoiliac	7.2 ± 4.0	23.9 ± 6.7
Femoropopliteal	3.7 ± 3.7	26.5 ± 12.7
Popliteal trifurcation	15.2 ± 9.3	23.9 ± 9.4
Multilevel	45.3 ± 5.5	71.2 ± 5.5

Modified from Fronek A, Coel M, Bernstein EF. The pulse-reappearance time: an index of over-all blood flow impairment in the ischemic extremity. *Surgery*. 1977;81:376.

OTHER METHODS

Several methods can be used to evaluate the effects of PAD on the microcirculation, including $tcPO_2$, laser Doppler, hyperspectral imaging, cold testing, vasoreactivity, and capillaroscopy. The first two are briefly discussed in this chapter. The others are less commonly performed, and the reader is referred to the literature to learn more about their role in the diagnosis of PAD.[43,44]

Transcutaneous Oxygen Tension

$TcPO_2$ measurements reflect the metabolic state of the target tissues. Electrodes containing a circular silver–silver chloride anode surrounding a central platinum cathode are placed on the skin at the dorsum of the foot, the anteromedial aspect of the calf 10 cm below the patella, and the thigh 10 cm above the patella. The subclavicular region of the chest has been used as a reference site to calculate a regional perfusion index in an effort to control for variation caused by age, cardiac output, and arterial partial pressure of oxygen (PO_2). This index is not widely used. Oxygen diffusing to the surface of the skin is reduced at the cathode to produce a current proportional to the PO_2 within the sensor. The electrode has a heating element that raises the skin temperature to 45° C for optimal blood flow and diffusion of oxygen, from vasodilatation, rise in capillary PO_2, liquefaction of lipids in the stratum corneum, and a right shift in the oxyhemoglobin dissociation curve.[45]

Transcutaneous oxygen measurement is relatively insensitive to mild or moderate degrees of PAD because the oxygen supplied to the skin is far greater than the demand. Furthermore, because the oxyhemoglobin dissociation curve does not change rapidly until oxygen saturation drops to less than 80%, capillary oxygen tension does not decrease until inflow is severely restricted and oxygen demand equals or exceeds supply. When values are low, $tcPO_2$ is not linearly related to flow. A value of zero means all the available oxygen has been consumed rather than the absence of flow. Measurement of $tcPO_2$ must be interpreted cautiously as it is affected by many factors that are difficult to measure or to control and therefore is unreliable (Box 20.1). For this reason and because the method is time consuming, it has not gained wide popularity.

BOX 20.1 Factors Affecting Transcutaneous Oxygen Tension

Skin temperature
Sympathetic tone
Body temperature
Cellulitis
Hyperkeratosis
Obesity
Edema
Metabolic activity
Oxygen diffusion through tissue
Oxyhemoglobin curve
Increased venous pressure
Vertical position of the site of measurement relative to the heart
Age

Measurement of $tcPO_2$ is most helpful for evaluating cases of severe ischemia, particularly when determining the optimal level for amputation. It is especially useful in diabetic patients because it is not affected by arterial calcification. Normal $tcPO_2$ values depend on age (higher for younger patients) and position (higher for more proximal locations). In general, values greater than 55 mm Hg are considered normal. Proximal locations are less sensitive than more distal locations to PAD, with the foot being the most sensitive. Wound healing is not reliable when the local $tcPO_2$ is between 20 and 40 mm Hg (see Fig. 20.8).[46]

Various enhancement procedures have been proposed to improve the discriminative value of $tcPO_2$. Among these are observing the change in $tcPO_2$ with dependency.[47] Advanced disease is associated with a larger increase when the patient moves from the supine position to sitting or standing. This increase in $tcPO_2$ may be related to the increased hydrostatic pressure that dilates capillaries and resistance vessels, thereby increasing flow. This phenomenon may explain why dependency relieves rest pain.[48] Exercise is followed by a decrease in skin $tcPO_2$ because of shunting of blood away from the foot by dilatation of intramuscular vessels. The $tcPO_2$ response to hyperemia is similar to that of ankle pressure; it decreases after inflow obstruction and is much slower to recover in patients with severe PAD. Finally, oxygen inhalation has been used in attempts to improve the accuracy of $tcPO_2$ for determining the amputation level and predicting the effectiveness of hyperbaric oxygen therapy. A greater than 10 mm Hg increase after the inhalation of 100% oxygen is considered normal.[49] Patients with severe PAD have a much smaller increase in $tcPO_2$ than do normal individuals upon oxygen inhalation. None of these enhancement techniques have improved the reliability of the test enough to make transcutaneous oxygen measurement a routine part of most vascular laboratory practices.

Laser Doppler and Skin Perfusion Pressure

The laser Doppler uses monochromatic light to detect motion of red blood cells to a depth of approximately 1.5 mm in the skin.[50] The actual depth depends on the power of the laser beam, the thickness of the epidermis, and skin pigmentation. Cutaneous blood flow includes vessels in a complex, interlacing network. Light is backscattered by the tissues after transmission and again after it is reflected back to the receiving system. As a result the frequency shifts are a composite of multiple vessels with multiple velocities and multiple angles. The output, measured in millivolts, is approximately proportional to the average blood flow in a 1.5-mm^3 volume of skin lying 0.8 to 1.5 mm below the skin surface. The signal tracing has pulse waves that coincide with the cardiac cycle and vasomotor waves at a frequency of four to six times per minute. The instrument cannot be calibrated to give an exact estimate of blood flow because of the multiple factors that affect the signal. It is useful when only qualitative information is needed.

Resting values in the lower extremity vary anatomically and are highest in the great toe and lowest in the proximal part of the leg. PAD causes attenuation of the waveform, a reduction in velocity, and loss of vasomotor waves. Like $tcPO_2$ and ankle pressure, the response to hyperemia is diminished, and the time to recovery is increased. The ability of this test to predict amputation healing is not as good as that of transcutaneous oxygen measurements. Laser Doppler can be used with blood pressure cuffs to measure skin perfusion pressure.[33] The probe can be placed distally as a flow detector for similar results in obtaining segmental pressures, or beneath the cuff, which is then inflated. The pressure at which skin blood flow returns is noted as the cuff is slowly deflated. Normal pressures of 50 to 70 mm Hg are decreased to 10 to 20 mm Hg with significant PAD. Pressures less than 30 mm Hg are predictive of critical limb ischemia.[51] A combination of skin perfusion pressure greater than 40 mm Hg and toe blood pressure greater than 30 mm Hg has been associated with successful lower extremity wound healing.[52]

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Comprehensively reviews the literature regarding ABI measurement as well as provides guidance on standardized methods of measurement and interpretation of results.

Abularrage CJ, Sidawy AN, Aidinian G, Singh N, Weiswasser JM, Arora S. Evaluation of the microcirculation in vascular disease. *J Vasc Surg*. 2005;42:574–581.

Outline of the various methods used to assess the effect of PAD on the microcirculation.

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21 CHAPTER

Vascular Laboratory: Arterial Duplex Scanning

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Duplex ultrasound (DUS) is an integral component of diagnostic testing for the evaluation and management of arterial disease. This technology, which combines the acquisition of blood flow (pulsed Doppler spectral analysis) and anatomic (B-mode and color Doppler imaging) information, was developed under the guidance of D. Eugene Strandness, Jr., at the University of Washington in the 1970s.[1] The initial clinical application of arterial duplex scanning assessed the extracranial carotid artery bifurcation for the presence and extent of atherosclerotic plaque and developed velocity criteria to estimate internal carotid artery (ICA) stenosis on the basis of correlations with angiographic measurements.[2] Commercial duplex scanners became available by the 1980s, and the clinical use of DUS rapidly expanded into peripheral arterial, visceral arterial, and peripheral venous applications. The development of real-time, color-encoded Doppler imaging was an important technologic advance that simplified patient testing, enhanced diagnostic accuracy, and led to additional clinical applications in the areas of screening for arterial disease, intraoperative assessment, and surveillance after arterial intervention.

Modern DUS systems provide high-resolution B-mode ultrasound imaging of tissue and vessel anatomy, including three-dimensional vessel reconstruction and evaluation of atherosclerotic plaque morphology. Detailed assessment of blood flow characteristics can be made in real time by one of several techniques, color Doppler imaging, power Doppler imaging, B-flow imaging, or pulsed Doppler spectral analysis.

Test interpretation is based on both imaging and Doppler findings with classification ranging from normal to clinically relevant disease categories. Duplex testing is noninvasive and cost-effective and thus suitable for serial examination; because it not only permits the identification of disease, but also reveals its natural history, including progression, regression, and response to intervention. In many patients, duplex testing can establish a definitive diagnosis and can allow interventions, such as carotid endarterectomy or peripheral artery angioplasty, to be based solely on the B-mode imaging and velocity spectral changes recorded from diseased arterial segments. In the upper and lower limbs, duplex testing should be performed in conjunction with indirect physiologic testing (measurement of systolic blood

pressure, pulse volume plethysmography) to assess arterial hemodynamics (see Chapter 20). When peripheral arterial disease is identified, DUS can be used to map the site or sites of occlusive or aneurysmal lesions, analogous to contrast-enhanced arteriography. Arterial duplex test interpretation combined with the patient's clinical history and physical examination is often sufficient to counsel the patient on the advisability of intervention and whether it can be performed by an endovascular or conventional open surgical procedure.

The reliability of arterial duplex testing depends on several factors, including the expertise of the examiner (vascular technologist, physician) and the knowledge and experience of the interpreting physician. Testing performed and interpreted in an accredited vascular laboratory has sufficient diagnostic accuracy for clinicians to rely on the final interpretation provided and often avoid performing more invasive, expensive diagnostic testing, such as computed tomography, magnetic resonance imaging, or catheter-based contrast-enhanced angiography, to confirm disease severity.

INSTRUMENTATION AND BASIC CONCEPTS

DUS systems use transducers fabricated from piezoelectric crystals to convert electrical activity to mechanical energy (ultrasound) and vice versa, thereby allowing the same device to transmit and receive ultrasound signals to and from the patient to produce images of tissue anatomy as well as to characterize blood flow. Transducers consist of multiple elements that enable focusing of the ultrasound beam, steering of the beam, and resolution sufficient for detailed tissue imaging at depths of less than 1 cm to more than 20 cm. To perform detailed arterial mapping, DUS instrumentation for carotid and peripheral testing should be equipped with linear array transducers with frequencies ranging from 5 to 12 MHz. For visceral artery or abdominal imaging and transcranial Doppler (TCD) examination, lower frequency transducers are needed because of the higher tissue attenuation; typically, 2.5- or 3.5-MHz curved linear or phased array transducers are appropriate. Newer generation transducers have an ultrawide bandwidth that enables harmonic imaging, with its increased resolution and freedom from artifacts, and dynamic frequency tuning for improving image quality at greater tissue depths. Moreover, the development of two-dimensional transducer arrays enables the beam to be focused at a specific depth and steered, which facilitates the use of three-dimensional imaging.

A duplex B-mode, or brightness mode, ultrasound image is displayed as gray-scale pixels reflecting the amplitude and position of returning ultrasound echoes. By processing up to 200 or more separate ultrasound beam signals retrieved from the transducer array, a scan converter organizes both horizontal and vertical pixels to yield a two-dimensional view of the tissue being scanned. Optimal arterial anatomic imaging is achieved when the transducer scan lines (beam) are directed perpendicular to the vessel wall. A 90-degree imaging angle is best used for measuring vessel diameter, identifying intima-media thickening, and assessing atherosclerotic plaque composition. Transmit power and receiver gain should be adjusted to produce a gray-scale image with the best tissue signal-to-noise ratio so that subtle differences can be perceived by the human eye. The examiner can modify image appearance by adjustment of the instrument's time gain compensation, which is designed to correct for the effects of increasing attenuation with depth. When duplex arterial imaging is performed, the left side of the image should be oriented toward the patient's head.

There are two types of Doppler ultrasound displays. In one form, a color-flow Doppler image shows the flow velocity distribution over a wide area displayed as a color-encoded map superimposed on the gray-scale B-mode tissue image. The second type, often referred to as spectral Doppler, shows the time-varying flow velocity distribution at a selected sample volume. Spectral Doppler provides quantitative information on the peak velocity within the sample volume, whereas color-flow Doppler provides semiquantitative information on the distribution of velocities over an entire region.

To obtain reliable information from spectral Doppler, it is best to use scan line angles (i.e., Doppler angles) of 60 degrees or less relative to the transducer insonation beam and arterial wall (Fig. 21.1). Assignment of the Doppler angle is controlled by the examiner. Because calculation of blood flow velocity is determined by the Doppler equation, which is proportional to the cosine of the Doppler angle, recording velocity spectra at large Doppler angles results in reduced Doppler frequency shift and thereby increases flow velocity error as a result of uncertainty in knowing the true Doppler angle. For example, an error in Doppler angle assignment such as 5 degrees higher than the recommended 60 degrees (i.e., at 65 degrees) will result in a 15% measurement error in flow velocity, whereas if a 55-degree angle was assigned, an 8% error results. The velocity measurement error caused by incorrect or imprecise assignment of the Doppler angle by the examiner is a common duplex testing inaccuracy that can result in overestimation or underestimation of the severity of the stenosis when disease classification is based on

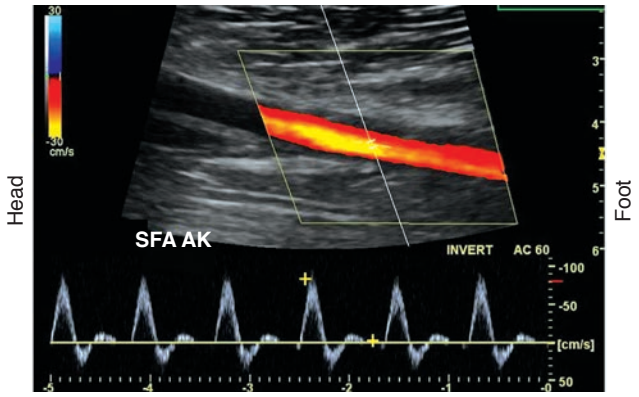

Figure 21.1 Color duplex image with velocity spectra of normal superficial femoral artery (SFA) flow recorded from the above-knee segment (AK) with a 60-degree Doppler beam angle. Note that the pulsed Doppler sample volume is positioned in the center stream of flow, where color-flow pixels indicate the highest flow velocity.

peak systolic velocity (PSV) or end-diastolic velocity (EDV) criteria. When pulsed Doppler flow signals are recorded, the instrument sample volume should be sized to encompass less than a third of the flow lumen and should be positioned in the center stream of flow.

Blood Flow Imaging Techniques

Blood flow detection can be performed with one of three imaging techniques: color Doppler, power Doppler, and B-flow.

Color Doppler Imaging

Color Doppler imaging refers to pixel encoding of blood flow based on a color bar that depicts both flow direction (toward and away from the transducer) and mean velocity (MV). The examiner adjusts the velocity scale, color priority, and saturation of the color bar as well as instrument color gain to show the appearance of normal, laminar arterial flow as homogeneous regions varying in color-coded pixels during the pulse cycle. To set the color gain correctly, the examiner should increase the gain until a noise speckle appears within the flow region and then reduce it slightly. This technique will optimize the display of weak or lower velocity blood flow signals, such as those adjacent to the artery wall. Excessive color gain causes color-coded flow pixels to bleed into or beyond the artery wall, thus making the flow lumen appear larger than reality. Interpretation of real-time color Doppler flow is based on the color bar settings (peak MV, baseline, wall filter, and color assignment of flow toward or away from the transducer). In tortuous vessels, blood flow is color-coded according to its direction relative to the transducer scan lines. When blood flow velocity exceeds the mean peak velocity threshold of the color bar, color aliasing occurs, because the sampling rate as defined by the pulse repetition frequency is no longer sufficient (the Nyquist limit). With aliasing, blood flow is erroneously encoded as the "wrap-around" color shown in the color bar, and the color image display will show flow in the opposite direction. Increasing the pulse repetition frequency and increasing the Doppler angle are two techniques that can be used to reduce the color-flow "aliasing" artifact.

Arterial stenosis is recognized by color Doppler imaging as a reduction in the color-encoded flow lumen, imaging of a high-velocity flow region with color bar aliasing, and development of a mosaic flow pattern in the lumen signifying turbulent flow. At the site of a high-grade (>75% diameter reduction) stenosis, real-time color Doppler flow will appear as a whitened, color-desaturated "flow jet" with mosaic color flow extending for several vessel diameters downstream corresponding to post-stenotic turbulence (Fig. 21.2). A tissue bruit may appear as low-velocity flow signals outside the artery lumen and is caused by vibration of the arterial wall. The presence of persistence of color, color bar aliasing, and changes in flow lumen diameter on color Doppler imaging is indicative of abnormal flow patterns produced by stenosis. The examiner should then carefully interrogate this diseased arterial segment with pulsed Doppler spectral analysis to measure changes in flow velocity, which are then used to estimate the severity of the stenosis.

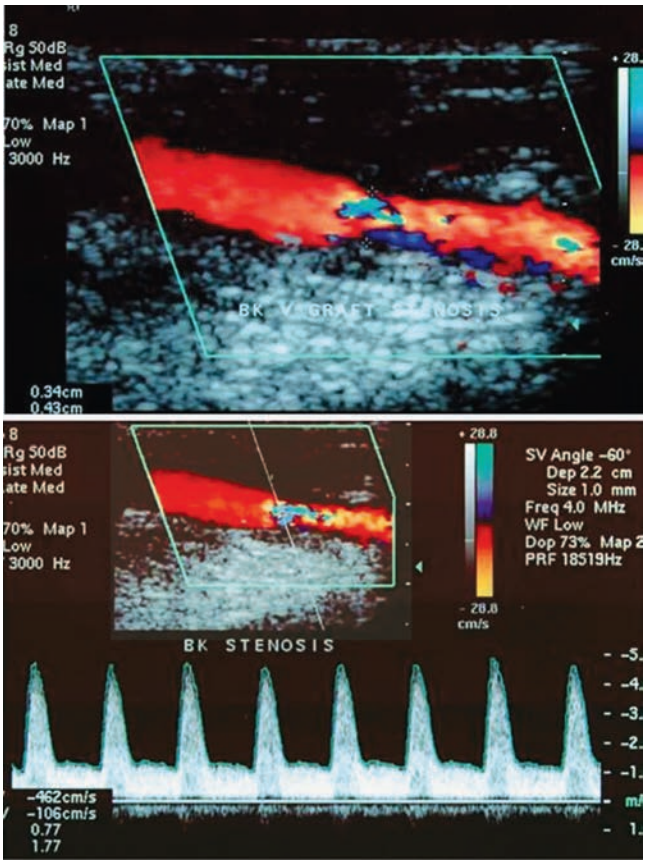

Figure 21.2 Color duplex image and velocity spectra of an arterial vein bypass graft stenosis. *Top image,* Color aliasing occurs at the stenosis when mean velocity is greater than 28 cm/s and extends for several vessel diameters downstream. *Bottom image,* Velocity spectra recording at the stenosis "flow jet" indicates a peak velocity of 426 cm/s and spectral broadening of highly disturbed, turbulent flow.

Power Doppler Imaging

Power Doppler imaging is a technique in which the display of blood flow is based on the amplitude of the backscattered Doppler signal; it increases the sensitivity of flow detection three to five times with respect to color Doppler imaging. This imaging mode is termed "color angio" and is used by the technologist for imaging of small-diameter vessels, detection of slow flow, assessment of residual lumen diameter at a stenosis, and detection of "trickle" flow associated with high-grade stenosis. Flow direction is not evident with the power Doppler imaging option, and the flow signal is less dependent on the Doppler angle.

B-Flow Imaging

B-flow imaging shows blood flow in gray scale; that is, flowing blood and the surrounding structures are depicted in shades of gray. The imaging technique is a visual depiction of flow hemodynamics and should not be confused with color Doppler imaging, because no velocity information is provided. B-flow imaging relies on the amplification of weak echoes from moving red blood cells and is most useful during arterial imaging to show boundary layer flow adjacent to the vessel wall and traversing atherosclerotic plaque. B-flow imaging can demonstrate the

complex flow patterns seen at bypass graft anastomoses and arteriovenous fistulae and within dialysis access conduits where color Doppler artifacts can obscure flow patterns.

Pulsed Doppler Spectral Analysis

Pulsed Doppler velocity spectra recorded from a normal artery have a narrow range of velocities throughout the pulse cycle, which indicates that red blood cells are moving at a similar speed and direction in a nondisturbed, or laminar, flow pattern. If the "sample volume" of the pulsed Doppler is too large relative to the diameter of the artery or positioned adjacent to the arterial wall, low-velocity flow signals will be displayed as "broadening" or increased width of the velocity spectra.

Spectral broadening in the pulsed Doppler signal can also indicate "disturbed" flow or flow turbulence when it is recorded center-stream at bifurcations, regions of abrupt diameter change, and sites of stenosis. The "normal" appearance of arterial duplex flow varies with the artery being studied (peripheral, carotid, renal, or mesenteric) but should demonstrate rapid flow acceleration in systole, narrow spectral width, and varied diastolic flow corresponding to the vascular resistance of the arterial bed.

The velocity spectrum of a normal peripheral (aorta, iliac, extremity, external carotid) artery is triphasic or multiphasic (see Fig. 21.1) and consists of high outflow resistance with a systolic flow component, early diastolic flow reversal, and late diastolic forward flow. Low-resistance arterial flow, such as in the internal carotid, vertebral, renal, celiac, splenic, and hepatic arteries, is characterized by continuous flow throughout the pulse cycle with only a single (systolic) phasic flow component producing a monophasic pulsed Doppler spectral waveform. Changes in flow resistance of the microcirculation are primarily reflected as an increase or decrease in diastolic flow velocity.

Measurements

The pulsed Doppler spectral parameters of acceleration time, pulsatility index (PI), resistive index (RI), and maximum spectral velocity measured at peak systole (PSV) and end-diastole (EDV) constitute the primary criteria used for test interpretation. The PSV measurement is reproducible and thus the most common velocity spectral parameter used for the interpretation of normal arterial flow and critical limb ischemia and for the grading of arterial stenosis. The EDV measurement is used in conjunction with PSV for evaluating high-grade stenosis (>70% diameter reduction; see Table 21.1).

RI is calculated by subtracting EDV from PSV and then dividing by PSV. It is used clinically to assess the renal and cerebral circulations for abnormal peripheral resistance. Normal values are less than 0.7, and levels higher than 0.85 are associated with increased vascular bed resistance and decreased end-organ perfusion.

PI is calculated by dividing the peak-to-peak velocity spectral shift by the average (mean) velocity. The PI of normal peripheral arteries is greater than 4.0 (femoral artery, >6; popliteal artery, >8). PI values lower than 4 may reflect proximal inflow or occlusive disease, and change in PI or spectral waveform damping is diagnostic of multilevel occlusive disease. Division of distal artery PI by proximal artery PI calculates the "damping factor;" a normal value is 0.9 or higher, and a value of less than 0.9 is diagnostic of occlusive disease.

TABLE 21.1 Velocity Spectra Waveform Parameters Used for Interpretation of Duplex Tests

Testing Area	PSV	EDV	RI	AT	PI	Mean Flow Velocity
Carotid duplex	X	X	X	X		
Transcranial Doppler	X		X		X	X
Peripheral duplex	X	X		X	X	
Duplex draft surveillance	X	X	X	X	X	
Renal duplex	X		X		X	
Mesenteric duplex	X	X	X	X	X	

AT, Systolic acceleration time; *EDV*, end-diastolic velocity; *PI*, pulsatility index; *PSV*, peak systolic velocity; *RI*, resistive index.

The systolic acceleration time during systole can also be used to diagnose occlusive disease proximal to the pulsed Doppler recording site. A normal value is less than 133 ms. As systolic acceleration time increases to longer than 200 ms, the spectral waveform develops a rounded upslope configuration, termed tardus-parvus, because of the prolonged time to PSV. Diagnostic accuracy of the systolic acceleration time is influenced by cardiac conditions (cardiomyopathy, aortic valve disease), but downstream occlusive disease has minimal influence on diagnostic sensitivity.

Artifacts and Errors

Artifacts and errors in ultrasound measurement can limit the effectiveness of the evaluation and create inaccurate results. Various artifacts include mirror image artifacts, shadowing from overlying vessel calcification, inaccuracy due to refraction, and aliasing. Most errors can be attributed to the technologist, because studies using flow models have found that adjustment of Doppler angle, sample volume placement, and Doppler gain were the most significant sources of error in PSV measurement.

Spectral Doppler aliasing is the most common artifact and, similar to color Doppler aliasing, is recognized by a "characteristic" signal wraparound in the spectral display. Adjustment of the velocity scale (i.e., pulse repetition frequency) to above the Nyquist limit or a reduction in the baseline level can shift the spectrum downward and eliminate the artifact. Shadowing from overlying calcification impedes adequate visualization of underlying vessel anatomy with B-mode imaging and interferes with accurate velocity measurement. Mirror image artifacts, created when a tissue structure is reproduced at an incorrect location, occur when a strongly reflecting surface is further reflected by other strongly reflecting surfaces.[3] Refraction can cause misregistration of the image and the Doppler sample volume and occurs when an ultrasound beam passes through mediums with different propagation speeds. Crosstalk, found only in Doppler evaluation, creates a mirror image where identical spectra appear above and below the baseline. It is

usually caused by an excessive receiver gain setting or an incident angle near 90 degrees. Ghosting occurs when low-velocity motion from pulsating vessel walls produces small Doppler shifts that can cause color flashing into the surrounding anatomy; it can be fixed with wall filters.

Variability of diagnostic criteria between laboratories stems from methods for defining the percentage of stenosis, different machines, and differences in technique.[3] Factors such as gender and physiologic condition of the patient can also affect the outcomes of DUS evaluations. Studies have found that carotid PSV measurements in women average 10% higher than in men.[4] Congestive heart failure, dysrhythmias, and artificial support measures (ventilators, intraaortic balloon pumps, or pacemakers) can alter cardiac output, which in turn can affect PSV measurements. Regarding technologist error, the largest source is error in accurately aligning the cursor of the sample volume. Even small errors in angle measurement can result in significant errors in velocity measurement and severity of the stenosis.[3] Sample volume assumes that flow is parallel to the walls; however, flow is not usually parallel in tortuous vessels or beyond an asymmetrical stenosis, and these situations can make correct sample volume positioning and true velocity readings difficult. Finally, the most accurate measurement of PSV at a stenosis is within the narrowest portion of the stenosis, and reproducible measurements can be best obtained only if the sample volume is placed at or very near this area.

Duplex Velocity Spectral Classification of Arterial Stenosis

A significant or "critical" arterial stenosis is a lesion that is associated with a resting systolic pressure gradient of more than 15 mm Hg and reduces volume flow. In the peripheral arterial circulation, this correlates with a 50% or larger diameter reduction stenosis or greater than 75% reduction in cross-sectional area. Stenosis produces losses in blood energy primarily as a result of losses in inertial energy caused by the development of turbulent flow; such losses are much greater than the friction energy losses predicted by Poiseuille law.

By measuring changes in velocity proximal to and across an arterial stenosis, duplex testing can noninvasively estimate its hemodynamic significance and predict reductions in diameter within specified ranges (e.g., 0%-49% diameter reduction, ≥50%, 50%-79%, ≥80%). The relationship between the increase in flow velocity and the reduction in diameter by stenosis is nonlinear, especially with stenoses greater than 50% diameter reduction (Fig. 21.3). The DUS characteristics of greater than 50% diameter reduction arterial stenosis include elevated PSV in comparison to adjacent normal segment, a color Doppler mosaic flow pattern, and pulsed Doppler spectral broadening of highly disturbed flow (i.e., post-stenotic turbulence with simultaneous forward and retrograde velocity spectra during systole).

The ratio of PSV (Vr) across a stenosis is a useful parameter for grading the severity of a stenosis; a Vr value higher than 2 indicates a greater than 50% diameter reduction, and a value higher than 4 correlates with greater than 70% diameter reduction. Typically, a pressure-reducing (peak systolic pressure >20 to 30 mm Hg) and flow-reducing arterial stenosis is associated with a Vr above 3.5, a PSV higher than 250 to 300 cm/s, and an elevation in EDV of 40 cm/s or more. Downstream of a "significant" pressure-reducing arterial stenosis, the spectral waveform should appear damped and monophasic with prolongation of the acceleration time and a decrease in PSV to below normal levels.

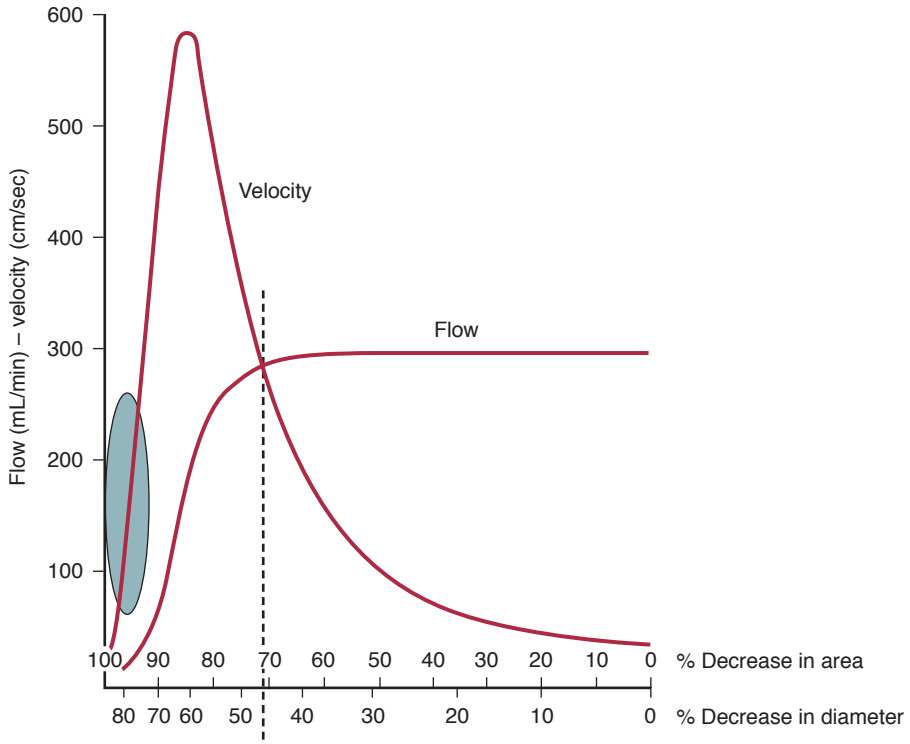

Figure 21.3 Correlation of percent diameter reduction with increases in blood flow velocity (cm/s) and reduction in volume flow (mL/min) in arteries. Note that a high-grade (>95%) diameter-reducing stenosis causes volume flow to decrease toward zero, whereas the velocity within the stenosis may be minimally elevated.

As stenosis severity increases beyond greater than 90% diameter reduction, volume flow through the stenosis tends toward zero, which can produce PSV at the stenosis in a minimally elevated range (100-200 cm/s) and low-velocity (<10 cm/s) trickle flow downstream. The atherosclerotic plaque associated with greater than 50% stenosis is typically irregular and may be calcified, which produces an acoustic shadow on the image and makes measurements of residual artery diameter or reduction in cross-sectional area too inaccurate on transverse imaging to classify the severity of an arterial stenosis. Correlation studies between duplex testing and angiographic measurements have found that PSV and Vr are the best predictors of the severity of stenosis when it is expressed as percentage diameter reduction.

Validation studies comparing duplex interpretation of stenosis severity with angiographic measurements have reported different threshold PSVs for lesions with greater than 50% diameter reduction.[5-19] PSV measurement variation is in the ±15% range, similar to other biologic measurements. This variation is related to the type of ultrasound system used and differences in Doppler angle assessment and sample volume positioning by the examiner. This limitation of duplex scanning can be minimized by reporting stenosis (i.e., diameter reduction) within a specified range (e.g., 0%-49%, 50%-75%, and 76%-99%). In each clinical application, it is recommended that the vascular laboratory conduct ongoing quality assurance studies to confirm that the diagnostic accuracy of stenosis interpretation in their laboratory in comparison to angiographic reports.

Patient Testing

Arterial duplex scanning can be performed as a portable bedside or vascular laboratory examination. Scanning should be conducted on a height-adjustable table or stretcher with the patient in a supine position. The bed and room environment should provide a comfortable, quiet atmosphere for patient examination, a warm room temperature (75-77°F) to avoid vasoconstriction of the extremities, and sufficient space to permit bilateral body access for ultrasound scanning. The typical examination time ranges from 30 to 60 minutes. Patients should refrain from tobacco use for at least 1 hour before the examination, and if abdominal scanning or visceral artery testing is planned, the patient should have fasted for 4 hours, and the examination should be performed in the morning to minimize accumulation of intestinal gas. Assessment of visceral artery flow before and after a test meal may be required for the evaluation of patients with symptoms of mesenteric ischemia.

Peripheral Arteries

Vascular specialists should be familiar with the spectrum of testing available as well as the information provided in conjunction with other hemodynamic tests. The duplex testing performed in the vascular laboratory is an extension of clinical assessment and is used to verify the presence and extent of disease. Numerous studies have analyzed the role of DUS, computed tomography, or MRA for preoperative assessment in efforts to limit the need for digital subtraction arteriography. In contemporary vascular practices, imaging with contrast-based modalities is generally limited to interventional procedures. This is because less invasive alternative imaging techniques can usually determine whether interventional treatment is possible without the performance of diagnostic arteriography. In patients with peripheral arterial disease, duplex imaging can determine disease location and length of lesions and help guide interventions.

Indications

DUS evaluation is beneficial for the following: patients with suspected symptomatic, chronic peripheral arterial disease[5-10]; patients with suspected acute limb ischemia; patients with pedal infection without a palpable pulse; patients with atheroembolic or thromboembolic disease states; and patients who require surveillance after revascularization procedures.

Technique

The extent of duplex arterial mapping should be individualized to the indication for peripheral arterial testing. Screening for aneurysm and imaging to identify tibial artery calcification are appropriate indications for testing in selected patients. Evaluation of patients with symptoms of claudication or other signs of peripheral arterial disease can localize sites of occlusive disease. Arterial scanning proceeds from proximal to distal, with notation of artery diameter, wall morphology, plaque or thrombus accumulation, and velocity spectral waveform; it can include both upper and lower extremities.

Abdominal imaging is optimally performed after fasting to minimize intestinal gas artifact. Lower limb testing should include imaging (3- to 5-MHz phased, curvilinear, or linear array transducer) of the abdominal aorta and iliac arteries for aneurysm and occlusive disease and the common femoral arteries for the presence of normal (i.e., triphasic) velocity spectra. Multiple scan windows are used to image the aorta at the level of the renal arteries, proceeding to the tibial arteries at the ankle. From the inguinal ligament distally, a 5- to 7-MHz linear array transducer is used to map the arterial tree. PSV and EDV should be reported in the arteries evaluated, with ratios of PSV compared with a more proximal segment of designated healthy vessel.

The findings on duplex mapping should be recorded in a schematic of the extremity arterial tree, analogous to an arteriogram, with notation of the site or sites of aneurysm or occlusive disease and measurements of velocity spectra at nondiseased arterial segments (common femoral, superficial femoral, popliteal, and tibial arteries) and at sites of stenosis (Fig. 21.4). Standardized values for arterial diameter and PSV in the lower limb arteries have been reported for healthy subjects under resting conditions (Table 21.2).[5-9] Duplex mapping allows classification of atherosclerotic occlusive disease in the aortoiliac, femoral-popliteal, and popliteal-tibial arterial segments based on Trans-Atlantic Inter-Society Consensus (TASC) guidelines for grading of lesions from A through D according to lesion length and morphology.[10]

Interpretation

Duplex-derived data to estimate severity of stenosis of the lower extremity have not undergone a consensus recommendation

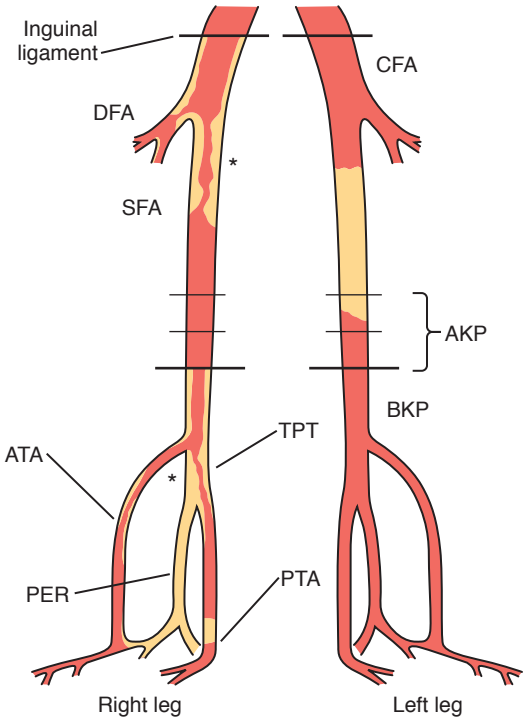

Figure 21.4 Schematic of the lower limb arteries for recording of arterial duplex map findings. Occlusion is denoted by a filled-in lumen and stenosis by an asterisk at the lesion. *AKP*, Above-knee popliteal; *ATA*, anterior tibial artery; *BKP*, below-knee popliteal; *CFA*, common femoral artery; *DFA*, deep femoral artery; *PER*, peroneal artery; *PTA*, posterior tibial artery; *SFA*, superficial femoral artery; *TPT*, tibioperoneal trunk.

TABLE 21.2 Artery Diameters and Peak Systolic Velocities in Healthy Subjects

Artery	Diameter (cm)*	Velocity (cm/s)*
Infrarenal aorta	2 ± 0.2	55 ± 12
Common iliac	1.5 ± 0.18	70 ± 18
External iliac	0.8 ± 0.13	115 ± 21
Common femoral	0.8 ± 0.14	114 ± 24
Superior femoral	0.6 ± 11	90 ± 14
Popliteal	0.5 ± 0.1	68 ± 14
Tibial arteries	0.3 ± 0.4	55 ± 10

*Values are means ± standard deviation.

process. Velocity-based criteria have been recommended by Cossman et al.[17] since 1989 (Table 21.3).

The PSV/EDV ratio should be calculated from an adjacent segment of a nonstenotic artery. Although the PI can aid in grading severity of stenosis, this number is not routinely independently used.

Fig. 21.5 depicts the classic progression of deterioration of ankle-brachial index (ABI), decreasing PSV, and decreasing PI.

Classification of peripheral arterial stenosis is based on duplex-derived criteria, similar to carotid duplex testing (e.g., PSV, EDV, and PSV ratio across a stenosis identified by color Doppler imaging) (Fig. 21.6; see Table 21.3). A doubling or

TABLE 21.3 Duplex Classification of Peripheral Artery Occlusive Disease

Stenosis Category	Peak Systolic Velocity (cm/s)	Velocity Ratio (Vr)	Distal Artery Spectral Waveform
Normal	<150	<1.5	Triphasic, normal PSV
30%-49%	150-200	1.5-2	Triphasic, normal PSV
50%-75%	200-400	2-4	Monophasic, reduced PSV
>75%	>400	>4	Damped, monophasic, reduced PSV
Occlusion	No flow; length of occlusion estimated by distance from exit and reentry collaterals		Damped, monophasic, reduced PSV

PSV, Peak systolic velocity.

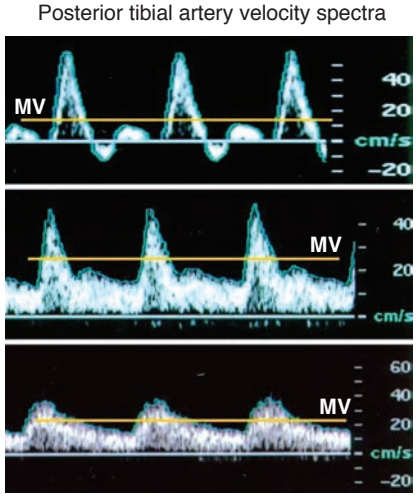

Figure 21.5 Velocity spectra, ankle-brachial index (ABI), and pulsatility index (PI) recorded from the posterior tibial artery of limbs with normal (ABI > 0.9, PI > 4), moderate (ABI = 0.5-0.8), and severe (ABI < 0.5, PI < 1.5) limb ischemia. *MV*, Mean velocity; *PSV*, peak systolic velocity.

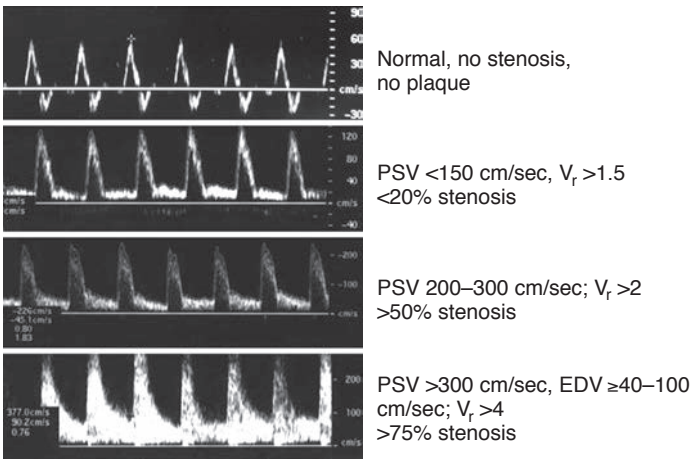

Figure 21.6 Duplex categories of peripheral artery stenosis based on velocity spectral waveform interpretation. *EDV*, End-diastolic velocity; *PSV*, peak systolic velocity.

step-up in PSV to more than 150 cm/s (Vr > 2) indicates 50% or greater diameter reduction stenosis. Duplex criteria for a critical flow-limiting stenosis include loss of the triphasic waveform, spectral broadening with an increase in velocity (PSV > 200 cm/s, EDV > 0 cm/s), and Vr greater than 3 across the stenosis. Higher degrees of stenosis (>75%) are associated with an EDV higher than 100 cm/s and a Vr above 4.[12]

Accuracy

A prospective comparison of DUS to contrast-enhanced MRA was performed with 152 patients, with conventional digital subtraction angiography as the "gold standard." A PSV ratio of more than 2.5 was used to define a significant stenosis. Duplex had sensitivity, specificity, and overall accuracy of 76%, 93%, and 89%, respectively, whereas MRA had a sensitivity of 84%, a specificity of 97%, and an overall accuracy of 94%, with statistically significant improvements in MRA sensitivity ($P = .002$) and specificity ($P = .03$).[13] Collins et al.[14] performed a systematic review of the literature comparing the three different imaging modalities. In detecting a greater than 50% stenosis, contrast-enhanced MRA demonstrated a median sensitivity and specificity of 95% and 97%, respectively; CTA showed a sensitivity and specificity of 91% and 91%, respectively; and DUS showed a sensitivity and specificity of 88% and 96%, respectively. For detection of occlusions, contrast-enhanced MRA was more sensitive and specific than CTA or DUS.

Iliac Arteries

The iliac arteries can be evaluated either by direct assessment via interrogation of the iliac artery or by indirect measures of common femoral artery waveform and velocity assessment. Direct assessment requires lower frequency abdominal probes and is limited by body habitus as well as by other factors (e.g., tortuosity, deep vessels) compared with indirect assessment of the femoral arteries.

Interpretation

Direct Imaging Criteria

Direct imaging criteria for iliac artery stenosis include the following: for greater than 50% stenosis: PSV higher than 200 cm/s or PSV ratio of 2.5 or more; for greater than 75% stenosis: PSV ratio above 5.0 and EDV higher than 40 cm/s. PSV of 400 cm/s or more is suggestive of greater than 75% stenosis.[15]

Indirect Imaging Criteria

Reduced velocities in the common femoral artery (<45 cm/s) with an associated monophasic waveform pattern are nearly 90% accurate in identifying a proximal iliac artery lesion without direct iliac artery evaluation. In addition, Shaalan et al.[16] did not find any statistical difference in velocities of the common femoral artery by gender or in the presence of significant ipsilateral superficial femoral artery or contralateral iliac artery disease.

Accuracy

The accuracy of DUS for detection of iliac artery disease is as follows.

Direct Imaging

For greater than 50% stenosis (PSV > 200 cm/s): 95% sensitivity, 55% specificity, 68% PPV, 91% NPV, and 75% accuracy; for greater than 75% stenosis (EDV > 40 cm/s): 70% sensitivity, 90% specificity, 64% PPV, 92% NPV, and 86% accuracy; for greater than 75% (with Vr > 5.0): 65% sensitivity, 91% specificity, 65% PPV, 91% NPV, and 86% accuracy.[15]

Indirect Imaging

An abnormal common femoral artery waveform contour (monophasic or biphasic) differentiated ipsilateral iliac artery stenosis of less than 50% from stenosis of greater than 50%, with 95% sensitivity, 89% specificity, 89% PPV, 95% NPV, and 92% accuracy. In differentiating between groups with greater than 50% stenosis and occlusion of the ipsilateral iliac artery, the specificity, PPV, and accuracy for PSV lower than 45 cm/s combined with a common femoral artery monophasic waveform are 97%, 92%, and 88%, respectively (Fig. 21.7).[16]

Femoral-Popliteal and Tibial Arteries

Studies, including a prospective blinded comparative study, have shown good agreement in the femoral-popliteal segment between DUS and digital subtraction angiography with use of a Vr of more than 2 for defining a greater than 50% stenosis by DUS. Agreement was better in the supragenicular than in the infragenicular segments.[17] In a comparison of the agreement with digital subtraction angiography, specific areas had poor correlation: profunda femoral artery, tibioperoneal trunk, peroneal artery, and crural arteries. In addition, a report has recommended the combined use of a PSV higher than 200 cm/s and a Vr above 2 to predict a greater than 70% femoropopliteal stenosis.[18]

The sensitivity and specificity of DUS in the femoral-popliteal arteries depend on criteria used to determine the degree of stenosis. With use of a Vr above 2.4 in detecting a greater than 50% stenosis in the femoral artery, the sensitivity, specificity, PPV, and NPV were 81%, 93%, 84%, and 91%.[16] A combined Vr above 2.0 and a PSV higher than 200 cm/s was associated with a sensitivity, specificity, PPV, and NPV of 79%, 99%, 99%, and 85% in detecting a greater than 70% stenosis.[18]

In the tibial arteries, the largest series reporting the accuracy of DUS in detecting 50% stenosis found a sensitivity of 88%, specificity of 75%, PPV of 83%, and NPV of 81% in 1690 infrageniculate segments correlated with conventional angiography (see Table 21.3).[19]

Limitations

For the aortoiliac disease segment, body habitus is the main limitation. For infrainguinal stenosis, the major limitation of

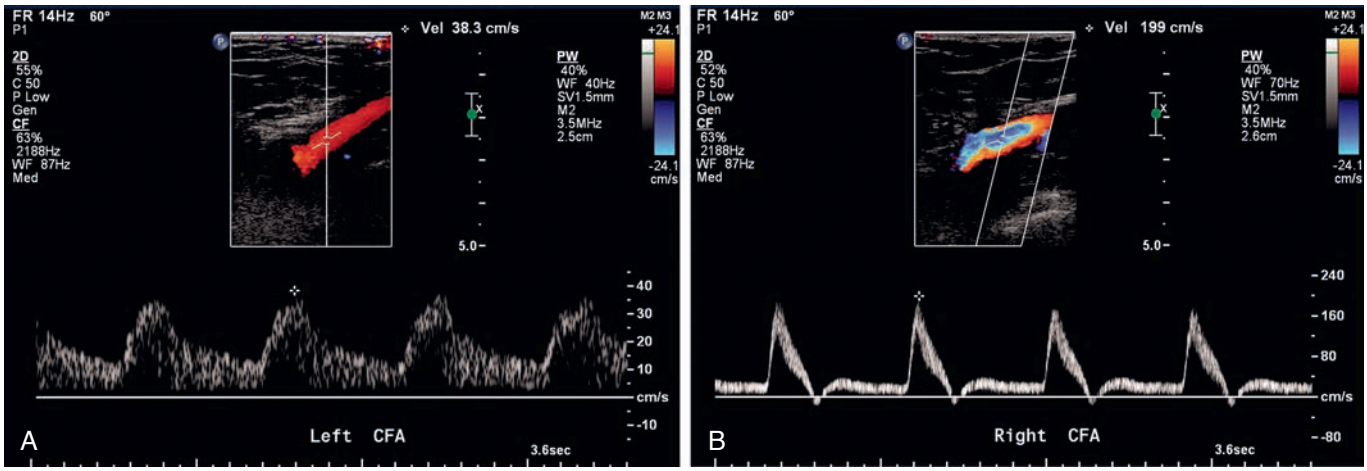

Figure 21.7 Indirect imaging of iliac arteries. **A,** Common femoral artery (CFA) with damped low-velocity waveform. **B,** Common femoral artery triphasic waveform for comparison.

accuracy is the presence of a proximal stenosis, which can falsely decrease distal velocities. Consequently, the velocity ratio may more accurately identify focal areas of stenosis. DUS may signify a high-grade stenosis instead of occlusion if a collateral vessel is visualized therefore falsely demonstrating flow adjacent to an occluded vessel. Incomplete vessel imaging may occur as a result of poor patient cooperation or acoustic shadowing caused by plaque calcification. Arterial segments difficult to image include the proximal external iliac artery, internal iliac origin, and tibioperoneal trunk. Calcific changes in the tibial arteries can decrease the accuracy of velocities.

DUPLEX SURVEILLANCE

Bypass Graft and Intervention Surveillance

Vein Grafts

A surveillance program after lower limb vein bypass grafting is recommended, but the extent of testing, including routine duplex testing, remains controversial.[20] Current recommendations include a baseline examination within 30 days of surgery, if it is not performed intraoperatively, subsequent examinations at 6-month intervals, and then annually after the first year for vein grafts.[21] However, an opposing view by TASC II recommended surveillance with physical examination and ABI only.[10] Duplex surveillance has been strongly advocated by the University of South Florida group. The latest recommendations for duplex surveillance of infrainguinal vein grafting reported improved efficacy of duplex surveillance with rigorous imaging for high-risk bypasses.[20] When it is conducted appropriately, a graft surveillance program should result in a graft failure rate of less than 3%/y. It can be anticipated with DUS surveillance that approximately 20% of infrainguinal vein bypasses will have either a residual operative stenosis or developing graft stenosis within 1 year of reconstruction.

Technique

Similar to native infrainguinal arterial examination, B-mode, color-flow, and pulsed Doppler imaging should be performed of the inflow, conduit, and outflow vessels. B-mode imaging can often identify early technical issues (i.e., retained valves or sclerotic vein segments). Pulsed Doppler with waveform analysis should be mapped of the lower limb with PSV, EDV, and Vr recorded. Specifics of the stenosis should also be recorded: diameter of the vein in transverse imaging above and below the stenosis, including length of stenosis in centimeters and anatomic location.

Interpretation

A combination of ABI, PSV, and Vr has been used to stratify patients into risk of subsequent vein graft failure. A PSV higher than 180 cm/s with associated Vr of 2.0 and no change in ABI correlates well with a 50% stenosis. A critical vein graft stenosis with impending failure has a PSV higher than 300 cm/s, a Vr of more than 3.5, and a decrease in ABI by 0.15 or more. Refer to Table 21.4 for risk stratification of failure.

Vein graft lesions with the duplex-derived velocity spectra of a high-grade stenosis (PSV > 300 cm/s, EDV > 20 cm/s, Vr across the stenosis > 3.5) correlate with a greater than 70% diameter reduction stenosis and should be repaired (see Fig. 21.2). In a prospective study, application of these threshold criteria identified all grafts at risk for thrombosis, and only one lesion with high-velocity criteria regressed. Multiple investigators have observed an approximately 25% incidence of graft thrombosis in stenotic bypasses when a policy of no intervention was followed.[20]

The risk for graft thrombosis is predicted by using the combination of high- and low-velocity duplex criteria and decreases in ABI (see Table 21.4). In the highest risk group (category I), the development of a pressure-reducing stenosis produces low flow in the graft, which will result in thrombosis if it is decreased below the "thrombotic threshold velocity." Prompt repair of category I lesions is recommended, whereas category II lesions can be scheduled for elective repair within 1 to 2 weeks. A category III stenosis (PSV of 180-300 cm/s, Vr < 3.5) does not reduce pressure or flow in the resting limb. Serial scans at 4- to 6-week intervals are recommended to determine hemodynamic progression of these lesions. An

TABLE 21.4 Risk Stratification for Vein Graft Occlusion by Duplex Criteria

Category	High-Velocity Criteria, Peak Systolic Velocity	Velocity Ratio (Vr)	Low-Velocity Criteria, Graft Flow Velocity	Change in ABI
I: Highest risk* (>70% stenosis with low graft flow)	>300 cm/s	>3.5	<45 cm/s or staccato graft flow	>0.15
II: High risk* (>70% stenosis without change or normal graft flow)	>300 cm/s	>3.5	>45 cm/s	<0.15
III: Moderate risk† (50%-70% stenosis with normal graft flow)	180-300 cm/s	>2.0	>45 cm/s	<0.15
IV: Low risk (normal bypass or <50% stenosis with normal graft fl ow)	<180 cm/s	<2.0	>45 cm/s	<0.15

ABI, Ankle-brachial index.
*Likelihood of progression of stenosis or graft thrombosis within 3 to 6 months is 40% to 50%.
†Of early (<3 months) lesions, 20% to 30% regress, 10% to 20% remain stable, and 40% to 50% progress to greater than 70% stenosis.

important feature of a "graft-threatening" stenosis is its propensity to progress in severity, to reduce graft flow, and to form surface thrombus, which are events that can precipitate thrombosis. By use of serial duplex scans, a category III stenosis that does not progress can be distinguished from a progressive lesion that needs to be repaired. The majority (approximately 80%) of bypass grafts will have no stenosis identified (i.e., category I scan). For these patients, surveillance at 6-month intervals is recommended. In patients with category I scans, a graft flow velocity lower than 40 cm/s indicates a "low-flow" bypass that is at increased risk for thrombosis by the concept of the thrombotic threshold velocity, which is lower in autologous vein than in prosthetic bypasses. Prescribing an anticoagulation regimen of warfarin to maintain the prothrombin time at an international normalized ratio of 1.6 to 2 and antiplatelet therapy (aspirin, 81 mg/day, or clopidogrel bisulfate, 75 mg/day) may reduce the incidence of low-flow vein bypasses.[20] Patients who are at high risk for development of vein graft stenosis[20] include those with abnormal results on baseline testing (PSV, 180-300 cm/s; Vr, 2-3.5), multisegment venous conduit, repeated bypass grafting, and need for warfarin therapy (Fig. 21.8).

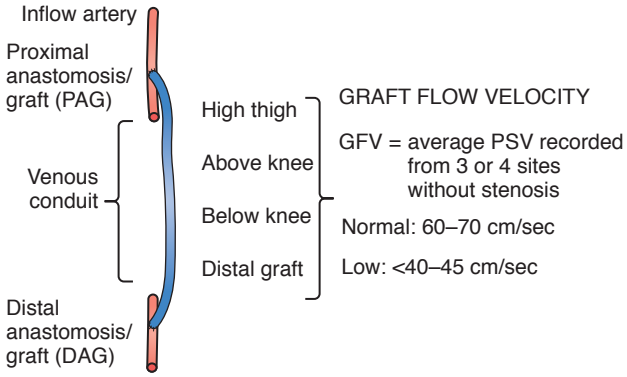

Figure 21.8 Schematic of a lower limb bypass graft indicating the duplex recording site and calculation of mean graft velocity (MGV). *PSV,* Peak systolic velocity.

Prosthetic Grafts

Although it is not supported by the TASC II recommendations, Mohler et al.,[21] in a consensus document, support the surveillance of prosthetic reconstructions at baseline and at 6-month intervals, similar to vein reconstructions. Duplex criteria were recommended by Stone et al.[22] for patients after femoral-femoral bypass grafting, with a PSV higher than 300 cm/s in the inflow iliac artery and midgraft velocity lower than 60 cm/s predictive of graft failure. When duplex-directed intervention was performed, patency at 5 years (assisted patency) was 88%. Patency appeared to be improved in comparison to most reports in the literature of patency without surveillance.

Duplex surveillance of prosthetic grafts does not appear to detect correctable lesions as in vein bypass grafts. Surveillance appears to serve more as a predictor of graft thrombosis by the detection of midgraft velocities below 45 cm/s. It has been shown that prosthetic grafts with low velocity benefit from warfarin to improve patency, which may justify surveillance. Brumberg et al.[23] recommended the use of warfarin if the mean graft velocity was below 60 cm/s to reduce the incidence of polytetrafluoroethylene bypass graft thrombosis.

Peripheral Interventions

Current guidelines recommend routine surveillance of peripheral arteries after percutaneous interventions.[21] However, the role of duplex examination after percutaneous peripheral interventions has been reported sparsely in the literature. Threshold criteria for repeated angiography included a PSV above 300 cm/s and a Vr of 2, which is commonly predicated on a clinical deterioration, an ABI decrease by 0.15, or an abnormal common femoral artery waveform analysis suggesting inflow disease. DUS after iliac artery interventions may serve a limited role. Back et al.[24] evaluated 67 patients with a mean follow-up of 1 year, finding a 4% stent thrombosis and only 20% of patients with potentially failing stents.

Similar to iliac artery percutaneous interventions, data are limited to support the routine use of duplex surveillance of

femoral-popliteal endovascular interventions. Several studies have evaluated DUS in determining recurrent stenosis of the femoral-popliteal segment after catheter-based procedures, with conflicting results.[25]

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CHAPTER 22

Vascular Laboratory: Venous Physiologic Assessment

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Chronic venous insufficiency (CVI) of the lower extremity is most often characterized by venous hypertension caused by valvular reflux, obstruction, or a combination of both.[1] Just as in the treatment of arterial disease, appropriate management of venous disease is predicated on accurate assessment of the anatomic abnormality, as well as the physiologic impact of the disease. The development of therapies for patients with CVI was historically hampered by inadequate tools for objective clinical and noninvasive anatomic and hemodynamic evaluation of the venous system.

Currently available clinical and laboratory evaluations address the physical findings, underlying etiology, anatomic distribution, and mechanism of disease. The results of these evaluations provide the essential elements of the clinical, etiologic, anatomic, pathophysiologic (CEAP) classification, detailed in Chapter 156.[2] Introduction of this system has advanced the evaluation of CVI from a subjective clinical impression based on physical examination alone to a more objective process similar to that followed for arterial disease.

As B-mode imaging technology has improved, it has assumed an important role in the anatomic diagnosis of CVI. By using the techniques outlined in Chapter 23, physicians can gain extensive knowledge of the anatomic sites and extent of disease noninvasively with B-mode imaging. Furthermore, the increasing sophistication of Doppler waveform analysis enables assessment of certain local physiologic measurements, such as the extent of segmental reflux. Many physicians base their clinical decisions on this combination of B-mode and Doppler waveform information (duplex ultrasonography) alone. However, duplex ultrasonography cannot define the importance of anatomic abnormalities in the context of global venous function of the limb.[3] Clearly, one patient with gross reflux in the greater saphenous vein may have no resultant symptoms, whereas another may have an active ulcer. An objective measurement of the hemodynamic performance of the lower extremity's venous system would greatly improve our ability to evaluate patients and recommend treatment.

Several noninvasive techniques are available to evaluate the global hemodynamic function of the venous system. However, they have not gained widespread use. The same considerations that exist in arterial disease are important in the diagnosis of CVI and assessment of treatment efficacy.[4,5] Furthermore, for clinical research on the treatment of venous disease, hemodynamic evaluation should and will progressively become an important expectation in reporting standards.

This chapter focuses on methods of evaluating the hemodynamic significance of CVI. It details the instrumentation, techniques, interpretation, accuracy, and limitations of these

tests. It also offers a perspective on appropriate clinical situations in which each test may provide clinically relevant information.

AMBULATORY VENOUS PRESSURE

Venous insufficiency most often results in elevated venous pressure and may be due to the net result of outflow obstruction, valvular incompetence, arteriovenous malformations, or any combination of these conditions. Pollack and Wood first described venous pressure changes in 1949, when they noted that muscle contraction increased the outflow of blood from the lower extremities during exercise, thereby lowering venous pressure.[6] They also documented the gradual return to resting venous pressure when the activity ceased. When Arnoldi and associates demonstrated that variations in venous pressure in the superficial venous system reflected those in the deep venous pathways,[7] it validated the use of a dorsal foot vein for the evaluation of venous hemodynamics.

The sum of the hemodynamic factors involved in venous insufficiency can be quantified by the measurement of ambulatory venous pressure (AVP). AVP is defined as the venous pressure in a dorsal foot vein after the execution of 10 tiptoe maneuvers in a standing position. A direct measurement of AVP is considered the "gold standard" measure of venous hemodynamics.[8,9]

Technique

To measure AVP, a catheter or butterfly needle is placed in a dorsal pedal vein and connected to a pressure transducer, and baseline standing pedal venous pressure is recorded. The patient then performs 10 tiptoe maneuvers at a rate of 1 per second to empty the calf veins and returns to the standing position. The pressure recorded at the end of the tiptoe maneuvers is defined as AVP. Refill time is measured as the time required to return to 90% of baseline venous pressure after cessation of calf muscle contraction.

Interpretation

In normal subjects, standing venous pressure is around 90 mm Hg (depending on the individual's height). During exercise it should fall to around 30 mm Hg, and after exercise it should rise slowly back to standing pressure. Usually 90% of baseline pressure is achieved in about half a minute (Fig. 22.1A). There are a number of possible abnormal results. The pressure may not fall normally during exercise, which indicates that the calf pump is not working effectively (see Fig. 22.1B). AVP may return to the standing pressure too quickly, which would indicate reflux in the deep or superficial veins (see Fig. 22.1B). Pressure may also rise rather than fall during exercise, which indicates that the deep veins are occluded.

A higher AVP is generally indicative of more severe CVI. Nicolaides and associates correlated AVP values to the incidence of limb ulceration and severity of CVI and showed a progressive increase in the incidence of skin ulceration as the mean values of AVP increased.[8] They also reported differences in the AVP based on the anatomic pattern of venous reflux. Patients with deep venous insufficiency had higher AVPs than did those with superficial insufficiency. Perforator incompetence and outflow obstruction also increased AVP, with the highest AVP reported in patients with deep valvular incompetence and proximal obstruction.

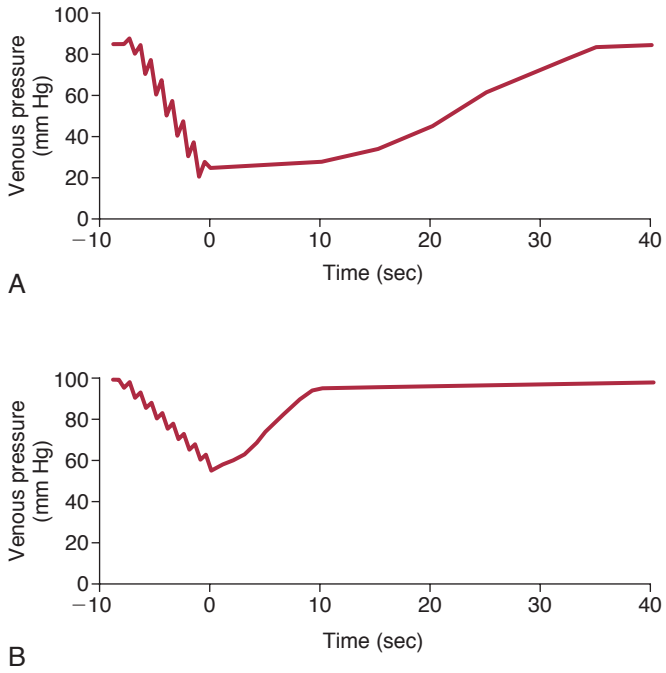

Figure 22.1 (A) Tracing of ambulatory venous pressure (AVP) in a normal subject. Note the rapid fall in pressure during 10 calf contractions, indicative of good venous outflow and calf muscle pump function. Also note the slow rise to baseline pressure on completion of the calf contractions, indicative of absence of venous reflux. (B) Tracing of AVP in a patient with chronic venous insufficiency. Note the higher baseline pressure, slow fall in pressure with tiptoe maneuvers, and high pressure on completion of the contractions, indicative of venous outflow obstruction and poor calf muscle pump function. Also note the rapid rise to baseline on completion of the calf contractions, indicative of severe venous reflux.

Accuracy

Overlap can exist between the AVP values of normal limbs and those with varying clinical categories of CVI. Up to 25% of patients with ulceration can have AVP values within normal limits.[8,10] The use of tourniquets to occlude the superficial venous system during the study may help define the contribution of the superficial and perforator veins to refill time. In theory, a thigh tourniquet should occlude reflux occurring in the superficial system. If AVP and refill time correct after tourniquet application, the superficial system is probably the primary source of abnormal function. A lack of correction implicates the deep venous system. However, this aspect of the test has not proved to be reliable,[11] and AVP should not be routinely used to identify the differential contribution of the deep and superficial systems to global venous hemodynamic dysfunction.

Limitations

Although AVP is generally perceived to be the gold standard measure of venous function, there is concern that pressure at the pedal vein may not accurately reflect changes in venous pressure within the leg, particularly in the deep venous system.[12] Furthermore, it is an invasive and time-consuming procedure that may be difficult to perform in many patients, particularly

those with active ulcers. Severe edema or dermal thickening and inflammation often accompany advanced CVI and may obscure the pedal veins, thus making access difficult. Therefore it has been largely supplanted by techniques that measure venous hemodynamics noninvasively. These techniques also depend on a protocol of calf contraction and rest, much like the one used for measurement of AVP.

PLETHYSMOGRAPHY

Plethysmography is a noninvasive method of estimating changes in volume in an extremity.[13] Because all other tissues maintain constant volume during the short period of testing, any recorded volumetric differences reflect changes in blood volume. Several plethysmographic techniques with different sensors have been used to measure changes in blood volume in a limb, including strain-gauge plethysmography (SGP), impedance plethysmography (IPG), photoplethysmography (PPG), and air plethysmography (APG).

These tests rely on the fact that the lower extremity veins are not filled to maximum capacity when the patient is in the supine position. With positional changes or when outflow is occluded by a pressure cuff, the venous system can accommodate increased volume before reaching maximal venous capacitance. With subsequent rapid positional changes or release of an externally inflated pressure cuff, patients with normal outflow exhibit rapid emptying of their lower extremity veins. These tests now routinely use an occlusion cuff, which has increased standardization by avoiding active patient movement and positional changes.

Positioning of the patient is critical in these tests. The patient is placed supine with the leg elevated 20 to 30 degrees on a soft heel support to enable venous drainage. The knee is flexed 10 to 20 degrees to prevent obstruction of popliteal vein outflow. The plethysmographic sensor is applied and a thigh occlusion cuff is inflated to above venous pressure (50 to 60 mm Hg) and maintained until limb volume increases to a stable level. The cuff is then released rapidly to allow the tracing to return to baseline readings (Fig. 22.2A). The rise in the recording to the plateau during cuff inflation measures calf venous volume (VV), whereas the fall in the recording after rapid deflation measures venous outflow (VO). The rate at which this outflow occurs is inversely proportional to the resistance to VO. In the presence of VO obstruction or venous insufficiency, VV and VO are reduced (see Fig. 22.2B).

Strain-Gauge Plethysmography

SGP is designed to detect changes in calf volume after inflation and then rapid deflation of a thigh occlusion cuff. A change in calf volume stretches a mercury-filled Silastic conductor tube with a proportional change in its resistance, which results in a corresponding change in voltage output signal. SGP provides an estimate of VO obstruction and has primarily been used in the past for the diagnosis of deep venous thrombosis (DVT). Although estimates of VV have not proved to be reliable diagnostic indicators of DVT, an estimate of VO in the form of MVO provides improved sensitivity.[14] Barnes and coauthors reported that MVO had a sensitivity of 90% for above-knee DVT but only 66% for below-knee DVT, whereas its overall specificity was 81%.[15] Successful recordings from SGP require full cooperation from the patient. It cannot be performed on patients who are unable to lie flat. Prolonged recumbency, muscle wasting, and cardiac failure may result in measurement errors. Patients with limb injuries, bandages, casts, or severe edema are unsuitable candidates for SPG. Today its use has been largely supplanted by duplex sonography.

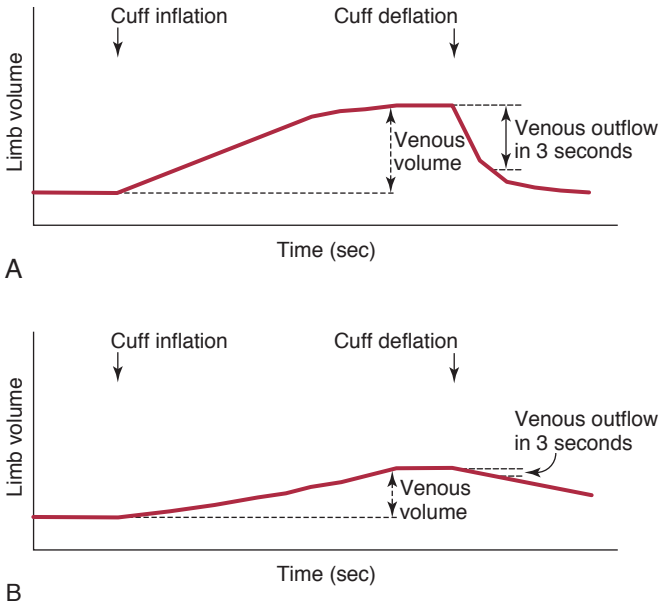

Figure 22.2 (A) Representative plethysmographic tracing in a normal subject during inflation and deflation of proximal thigh occlusive cuff. (B) Representative plethysmographic tracing in a patient with chronic venous insufficiency. Note the significantly reduced venous outflow recorded during the 3 seconds after cuff deflation (3-second venous outflow), indicative of severe venous outflow obstruction. The slope of the outflow curve (maximum venous outflow) is also reduced in comparison with the normal tracing in A.

Impedance Plethysmography

IPG is a technique that measures changes in electrical resistance in tissues of the extremity in response to changes in volume. Two electrodes are placed on the calf and the voltage output is used to derive the resistance. A thigh occlusion cuff is inflated and then rapidly deflated to provide an estimate of VO. IPG has primarily been used for the diagnosis of acute DVT. The sensitivity of IPG in diagnosing DVT ranges from 33% to 96%, with accuracy reduced in asymptomatic patients or those with DVT below the knee.[16] For these reasons, given the reliability of duplex ultrasound techniques, IPG is now rarely used to diagnose DVT. Neither SPG nor IPG has been well characterized as a diagnostic technique in the hemodynamic evaluation of CVI.

Photoplethysmography

PPG uses light absorbance by hemoglobin as a reflection of blood volume in the venous and capillary networks of the skin to estimate the degree of venous stasis.

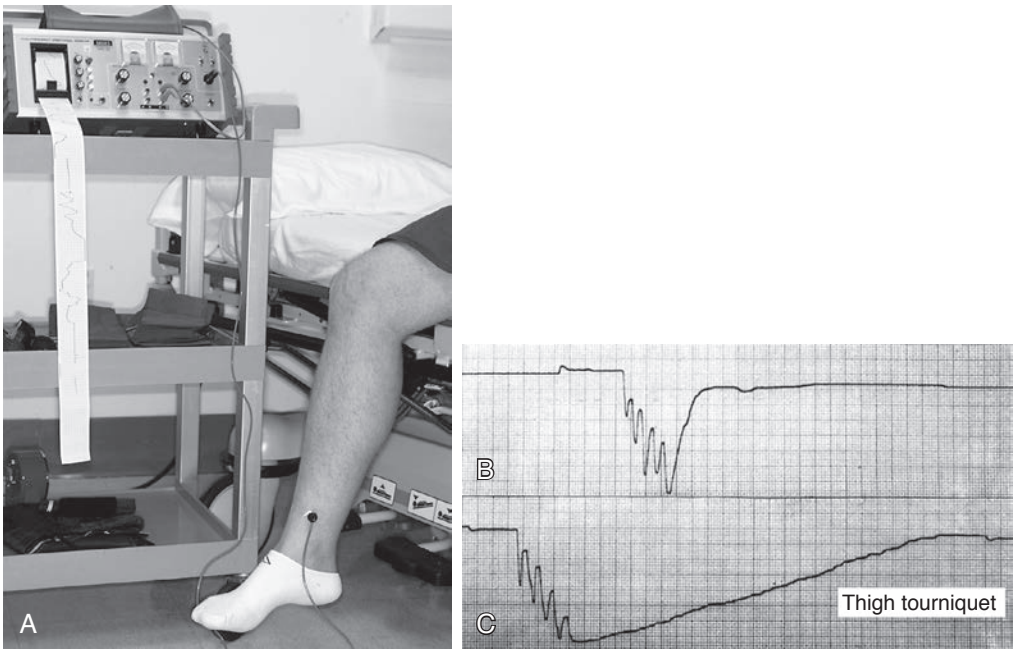

Figure 22.3 (A) Standard position for photoplethysmography (PPG), with the phototransducer located above the medial malleolus. (B) Tracing of PPG refill time in a patient with chronic venous insufficiency. Note the rapid refill time, indicating severe venous reflux. (C) Repeat test with a thigh tourniquet in place indicating correction of refill time to normal. This suggests that venous reflux is limited to the superficial system.

Technique

PPG uses a transducer that emits infrared light from a light-emitting diode into the dermis. Hemoglobin absorbs light and is the most abundant chromophore in the skin. The amount of light absorbed from the transducer is therefore a good estimation of blood volume in the venous and capillary networks of the skin.[17] The backscattered light is measured by an adjacent photodetector, and net absorption is displayed as a line tracing. Absorption of light is high when skin venous and capillary blood is increased during sitting or standing; conversely, it is decreased during exertion when venous blood is expelled from the limb by the action of the calf muscles.

The patient is asked to sit comfortably with the legs hanging freely. The transducer is applied to the leg (Fig. 22.3A) and a baseline recording is obtained. The patient is then asked to perform five consecutive ankle flexion/extension maneuvers. The tracing drops as the calf muscles empty the veins. The time taken to recover to 90% of the original baseline tracing after the exertion is completed is recorded as the venous refill time (VRT) (see Fig. 22.3B).

Interpretation

In normal individuals, VRT tends be longer than 20 seconds and can extend to as long as 60 seconds. Significant venous reflux results in a VRT of less than 20 seconds,[18] and reducing times generally reflect increasing severity of reflux (see Fig. 22.3C).[19] In the presence of abnormal findings, the test can be repeated with a tourniquet inflated (50 mm Hg) alternately above and below the knee to identify the source of reflux.

Accuracy

Although PPG can provide an assessment of the overall physiologic function of the venous system, it is most useful as a relatively simple measure to detect the presence of venous reflux. Duplex ultrasonography provides detailed information on segmental reflux, and PPG provides an estimate of the global effect of reflux on the limb. Quantitative measurements are not obtained, so each laboratory should define its own standard for a normal refill time based on the equipment used. PPG measurements have not been proved to be a strong discriminator of the severity of CVI. Nicolaides' group has reported that abnormal limbs demonstrated refill times of less than 18 seconds with their protocol.[20] However, within this group, VRT could not differentiate between degrees of CVI, with similar times obtained in patients with AVP measurements ranging from 45 to 100 mm Hg.

Limitations

In addition to being inversely proportional to the degree of reflux, refill time is also affected by arterial inflow. In the presence of occlusive arterial disease, VRT may be reduced despite an absence of venous reflux. This test also requires full patient cooperation, and inability to perform the contraction maneuvers or inability to access the calf for proper placement of the transducer will preclude accurate results. VRT can vary depending on the site of photosensor placement, the size of the sample area obtained, and the type and amount of exercise performed during the recording.[21] Placement near the site of a varicose or perforating vein may also affect the results. The test has limited reliability in

differentiating deep from superficial reflux despite the addition of tourniquet testing. Because of its inability to reliably grade the severity of CVI, PPG has limited utility for assessing the results of corrective venous surgical procedures. Therefore PPG is a reasonable measure of the presence or absence of CVI that is best used when no further information concerning the venous hemodynamic situation is desired. If information on the severity of CVI or evaluation of improvement after venous surgery is required, a quantitative test will be more useful.

Air Plethysmography

APG is a technique that measures changes in size in a large sample area of the lower part of the leg by using an air-filled cuff snugly applied to the extremity.

Technique

APG can potentially measure each individual component of clinical venous hemodynamics—namely reflux, calf muscle pump function, and outflow obstruction.[22-24] It uses a technique to improve on the shortcomings of PPG and other types of plethysmography that have limited sampling areas. A low-pressure air-filled cuff measuring 30 to 40 cm in length is applied to the lower part of the leg from the knee to the ankle. It is connected to a plethysmograph and serves as the sensor for changes in volume. This approach enables precise quantitation of the changes in volume of the entire lower leg region from the knee to the ankle. The test is performed with the patient resting supine with the leg elevated and supported in the same fashion as for SGP or IPG (Fig. 22.4A). The cuff is inflated to a pressure of 6 mm Hg to provide snug apposition to the limb without compressing the superficial veins. A baseline volume is obtained with the patient resting. A proximal occluding thigh cuff is inflated to 80 mm Hg to assess outflow obstruction.[19] Subsequent testing focuses on detection of reflux and calf muscle pump function. The patient moves to a standing position supported by a walker to remove weight from the tested limb (see Fig. 22.4B). The volume tracing gradually increases until a plateau is reached, which is recorded as VV. The time required to achieve 90% VV is described as the 90% venous filling time. The patient then performs one calf contraction with a tiptoe maneuver, followed by rest. The extent to which the volume reduces is defined as the ejected volume. The volume is then allowed to return to baseline, at which time a subsequent series of 10 tiptoe maneuvers completes the test procedure. The volume drops as venous blood is expelled from the leg. The amount of volume remaining in the limb after the tiptoe maneuvers is defined as the residual volume. Fig. 22.5A describes the measurements obtained during cuff inflation/deflation; Fig. 22.5B describes the recordings and indices obtained from the standing/tiptoe testing.

Three important indices can be derived from these APG measurements. The venous filling index (VFI) defines the rate of increase in volume on standing. Expressed in milliliters per second, VFI measures the mean filling rate of the dependent leg and is slow in normal limbs. The ejection fraction (EF) is the percentage of volume removed from the leg with one calf contraction. Finally, the residual volume fraction (RVF) is the residual volume expressed as a percentage of the baseline volume of the leg. The test protocol may be repeated with the use of a thigh tourniquet to isolate the deep venous system from the superficial system.

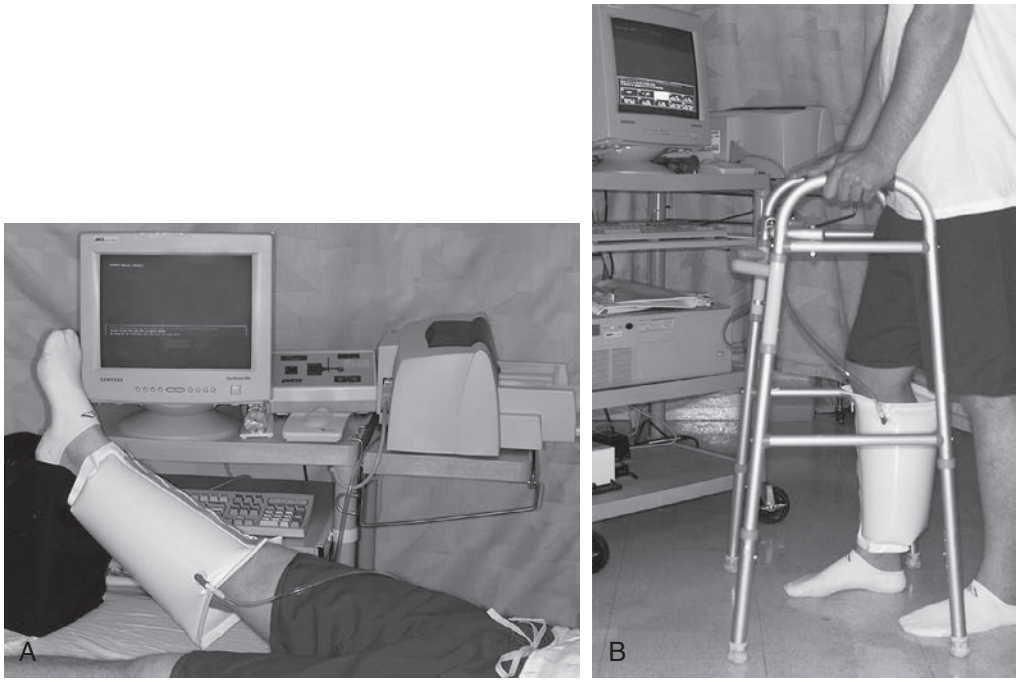

Figure 22.4 (A) Recording of baseline leg volume at the onset of air plethysmography (APG) testing with the patient supine and the leg elevated to minimize venous volume. Note the APG cuff over the leg. (B) Patient demonstrating a tiptoe maneuver during APG and the use of a walker to allow the limb under examination to remain relaxed.

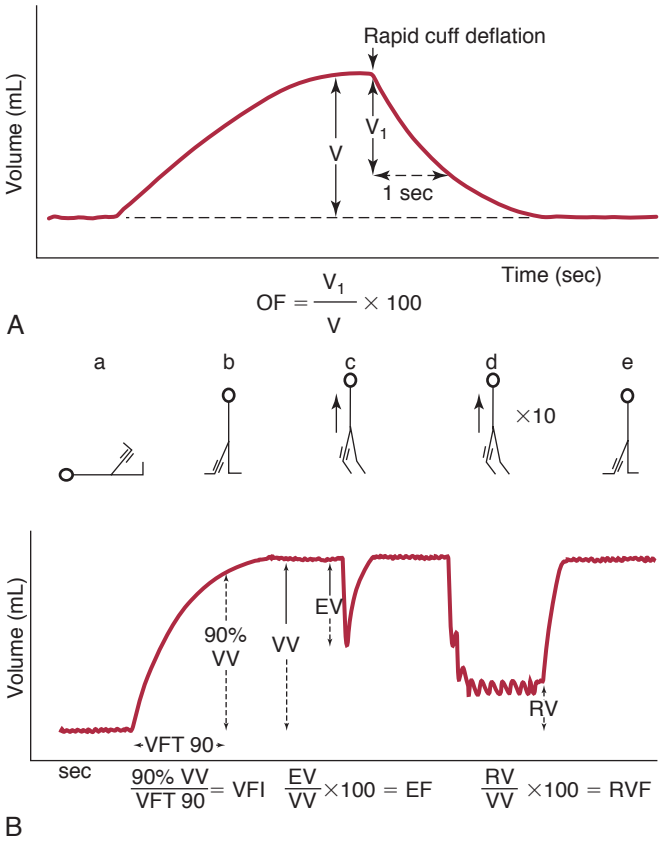

Figure 22.5 (A) Typical outflow fraction tracing obtained with air plethysmography (APG). After venous congestion is created with a thigh occlusion cuff, rapid deflation allows venous emptying. The outflow fraction (OF) is obtained by dividing the amount of venous volume emptied in 1 second (V_1) by the venous volume (V) and multiplying by 100. (B) APG data obtained from tracings. The figures along the top indicate the patient's position and maneuvers performed during the recording. *EF*, Ejection fraction; *EV*, ejected volume; *RV*, residual volume; *RVF*, residual volume fraction; *VFI*, venous filling index; *VFT*, venous filling time; *VV*, venous volume. (Redrawn from Christopoulos DG, Nicolaides AN, Szendro G, Irvine AT, Bull ML, Eastcott HH. Air plethysmography and the effect of elastic compression on venous hemodynamics of the leg. *J Vasc Surg.* 1987;5:148–159.)

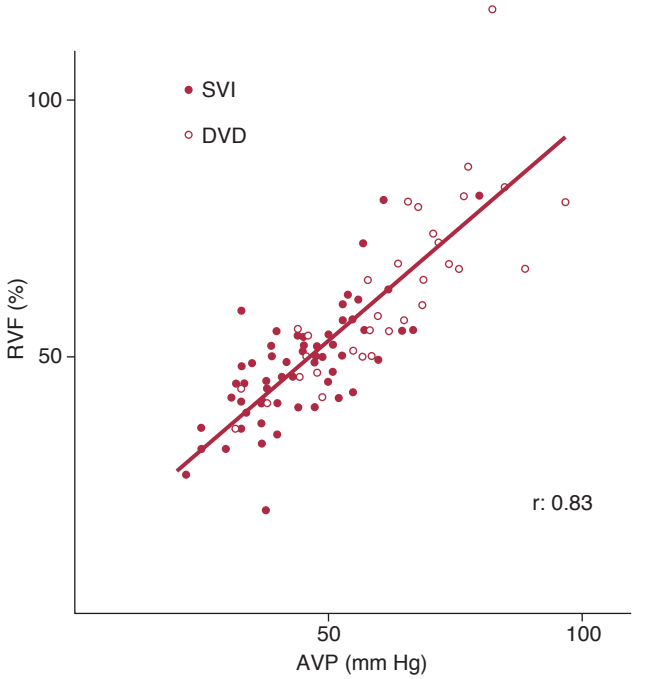

Figure 22.6 Correlation of residual volume fraction (RVF) obtained by air plethysmography to ambulatory venous pressure (AVP). *DVD*, Deep venous disease; *SVI*, superficial venous incompetence. (Redrawn from Nicolaides AN, Sumner DS, eds. *Investigation of Patients with Deep Vein Thrombosis and Chronic Venous Insufficiency*. London: Med Orion; 1991:39–43.)

TABLE 22.1 Prevalence of the Sequelae of Venous Disease in Relation to Venous Filling Index in 134 Limbs With Venous Disease Studied With Air Plethysmography

	SEQUELAE OF VENOUS DISEASE		
VFI (mL/s)	Swelling (%)	Skin Changes (%)	Ulceration (%)
<3	0	0	0
3-5	12	19	0
5-10	46	61	46
>10	76	76	58

VFI, Venous filling index.

Interpretation

The VFI provides a reasonable estimate of the global function of the lower extremity venous system and venous reflux. A VFI of less than 2 mL/s is associated with clinically normal limbs. The VFI may be increased to 30 mL/s in severe reflux, and increasing VFI values indicate more severe reflux, more symptoms, and higher grades of CVI (Table 22.1).[23]

EF and RVF provide measures of the efficacy of the calf muscle to pump blood out of the leg. RVF correlates closely with AVP throughout the range of AVP measurements (Fig. 22.6), with lower RVF values representing better calf pump function (normal RVF is defined as <35%).[25]

Like other plethysmographic measurements, APG can also provide estimates of VO obstruction. A cuff is placed around the proximal part of the thigh and inflated to 80 mm Hg. VV in the limb is measured until a plateau is reached. The cuff is rapidly deflated, and an outflow curve is recorded as limb volume decreases (see Fig. 22.5A). The recordings are similar to those obtained with SGP or IPG. The increase in volume recording above baseline is the VV, whereas the volume expelled after cuff deflation in 1 second is the 1-second VO. Using these measurements, Nicolaides and Sumner have calculated the outflow fraction by dividing the 1-second VO by VV.[26] Nicolaides has reported that the outflow fraction is higher than 38% in limbs with normal VO, 30% to 38% in patients with partial VO obstruction, and less than 30% in limbs with severe obstruction.[27]

Accuracy

Indices derived from APG measurements are useful in predicting the clinical severity of CVI. The VFI provides a particularly

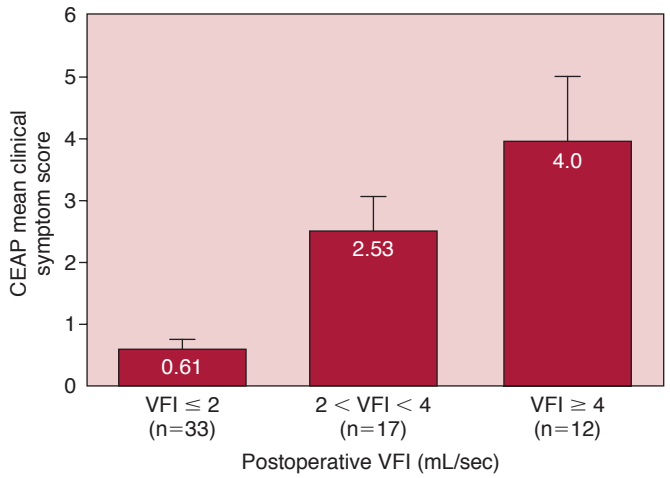

Figure 22.7 Correlation of the venous filling index (VFI) obtained by air plethysmography at early postoperative follow-up to symptom score at late follow-up. Mean values and numbers in each group are shown. *CEAP*, Clinical, etiologic, anatomic, pathophysiologic. (Redrawn from Owens LV, Farber MA, Young ML. The value of air plethysmography in predicting clinical outcome after surgical treatment of chronic venous insufficiency. *J Vasc Surg.* 2000;32:961–968.)

good estimate of disease severity and can assist in the selection of patients for venous surgery. Criado and colleagues showed that 93% of limbs with a VFI of less than 2 mL/s were CEAP class 0, and only 9% of patients with a VFI higher than 5 mL/s were CEAP class 0.[23] VFI was found to have 80% sensitivity and a 99% positive predictive value for detecting abnormal reflux.

The VFI also predicts recurrence of venous ulcers. In patients with healed leg ulcers, a VFI higher than 4 mL/s was associated with an increased risk of recurrence as compared with those with a VFI lower than 4 mL/s. For each 1 mL/s greater than 4 mL/s, the risk of ulcer recurrence increased 17%.[5] Based on this information, APG parameters can be used to assist in the selection of patients at higher risk for recurrent ulceration who may wish to consider corrective venous surgery.

The VFI is also useful for monitoring improvement in venous function and in predicting long-term outcome after venous surgical procedures.[28] In a review of 71 patients undergoing venous surgery, Owens and associates reported that 94% of patients in whom the VFI corrected to less than 2 mL/s after venous surgery were asymptomatic after a mean follow-up of 44 months (Fig. 22.7).[29]

APG, by sampling a large portion of the calf area, provides a better measure of the global venous function of the limb than PPG does.[27] Bays and coworkers reported that APG accurately separated normal limbs from those with CVI, and the parameters that significantly differentiated the two groups were VFI, VV, EF, and RVF.[4] PPG refill times had a sensitivity of 100% in identifying reflux; however, the specificity was only 60%. Furthermore, the κ coefficient between duplex and APG was 0.83, whereas it was 0.47 between duplex and PPG.

Limitations

The accuracy of APG depends on the ability of patients to stand unassisted and perform vigorous tiptoe maneuvers. Furthermore, in patients with advanced CVI, particularly CEAP classes 5 and 6, ankle range of motion is frequently limited. It is possible that some of the changes in EF and RVF seen in these groups are related to intrinsic dysfunction of the calf muscle pump or the patient's inability to activate the pump because of reduced ankle range of motion. APG is also limited in obese patients as a result of cuff size limitations; PPG may be the only option in such patients. Despite the use of a thigh tourniquet, APG is less reliable in differentiating superficial from deep reflux.

SELECTIVE USE OF VENOUS PHYSIOLOGIC TESTING

Several factors must be considered in determining the use of physiologic testing in the vascular laboratory.[30] The clinical manifestations (acute versus chronic) of the patient, the questions being asked of each individual patient, the ability of the patient to comply with the requested study, the use of vascular laboratory resources, and the examiner's facility with the testing procedures are all important considerations.

If the only question asked is whether venous disease is present and no details concerning anatomy or the severity of CVI are necessary, PPG is relatively rapid to perform and a reasonable choice. If the primary question concerns the anatomic site of reflux to plan intervention, duplex ultrasound evaluation should be performed. If the primary question concerns the severity of CVI or whether improvement has occurred after intervention, APG measurements should be performed.

Physiologic assessment with PPG or APG can provide evidence of global venous dysfunction, thereby separating CEAP class 2 patients with a primarily cosmetic problem from class 3 and 4 patients with more significant venous dysfunction. Once that determination has been made, duplex examination will be required to identify the sites of reflux, evaluate the deep and perforator systems, and guide intervention. In these patients, APG can also serve to document improvement and predict long-term outcome after intervention. CEAP class 5 and 6 patients should also undergo duplex evaluation to determine their candidacy for surgical or endovascular intervention. APG measurements are helpful in identifying patients at high risk for recurrent ulceration after intervention.

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CHAPTER 23

Vascular Laboratory: Venous Duplex Scanning

DAVID L. DAWSON and EDWARD RONNINGEN

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The use of Doppler ultrasound for the evaluation of lower extremity veins was pioneered in 1960s.[1,2] In 1968, David Sumner, Dennis Baker, and D. Eugene Strandness described use of an ultrasonic flow detect to assess venous flow patterns.[3] In 1972, Strandness and Sumner published their observations on the use of Doppler ultrasound for the diagnosis of venous thrombosis.[4] Steven Talbot, a vascular technologist, published his description of the use of B-mode (2-D gray-scale) imaging for the diagnosis of deep vein thrombosis (DVT) in 1982.[5,6]

Early validation studies that compared venous ultrasonography with venography identified limitations of B-mode imaging when it was used as a sole modality. Imaging of deeper structures was limited. Moderate probe compression did not collapse some normal vein segments (e.g., femoral vein at the level of the adductor hiatus) and vein compressibility could also be limited by obesity, edema, or tenderness. It was soon recognized that the accuracy of the examination was improved by combining imaging *and* Doppler-derived information about the presence and nature of venous flow in the interrogated segments.[7,8] Within a few years, venous duplex scanning had been accepted as a primary diagnostic modality, not just a screening method.

Duplex scanning is now readily available, noninvasive, and relatively inexpensive. It is the primary means for diagnosis of DVT and venous insufficiency.[8a,8b,9-12] There are limitations, however. The accuracy and reliability of venous duplex scanning still depend on the thoroughness of the examination, the skill of the vascular technologist performing the study, and the competence of the interpreting physician.

Variation is reduced by exam standardization and by the use of appropriate study procedures and interpretation criteria.[12a] Accreditation recognizes facilities that provide quality vascular testing services by compliance with relevant standards. It also serves as an educational tool to improve overall quality. The Intersocietal Accreditation Commission (IAC) accredits imaging facilities specific to vascular testing. The IAC publishes accreditation standards that are regularly updated, and they represent a consensus on what constitutes an appropriate vascular laboratory examination.[13] These standards include appropriate training and credentials of technologists and interpreting physicians, and the use of established, consistent examination protocols (Tables 23.1 and 23.2).

Abstract

Venous duplex scanning is readily available, inexpensive, safe, and reliable for most clinical situations. Duplex ultrasound is the primary diagnostic method for evaluation of suspected deep vein thrombosis, chronic venous insufficiency, and other disorders of the venous system.

Keywords

Ultrasonography, Doppler, color
Ultrasonography, Doppler, duplex
Veins/diagnostic imaging
Venous insufficiency/diagnosis
Venous thrombosis/diagnostic imaging

TABLE 23.1 Vascular Laboratory Standards for Peripheral Venous Testing

INDICATIONS: Peripheral venous testing must be performed for appropriate clinical indications
- Testing indication must be documented

Equipment: Equipment must provide accurate data.
- Imaging equipment: duplex ultrasound with color flow Doppler, with
  - imaging frequencies appropriate for the structures evaluated
  - Doppler frequencies appropriate for the vessels evaluated
  - range-gated spectral Doppler with ability to adjust the depth and position of the range gate in the area of interest
  - Doppler angle which is measurable and adjustable
  - visual display and permanent recording of images
  - visual display, audible output, and permanent recording of Doppler waveforms and corresponding images
- Equipment quality control: equipment used for diagnostic testing must be maintained in good operating condition

PROTOCOLS: There must be a written protocol for each examination, including:
- Equipment to be used
- Proper technique
- Anatomic extent of a complete examination, generally includes entire course of the accessible portion of each vessel
- Variations in technique following vascular interventions, including dialysis access
- Variations in technique and documentation for limited exams
- Routine documentation and additional documentation that must be acquired to describe abnormalities
- Description of how color Doppler or other flow imaging modes (e.g., power Doppler) are used to supplement grayscale imaging and spectral Doppler measurements

TECHNIQUES: Appropriate techniques to document their severity, location, extent and (whenever possible) etiology. Elements of proper technique include:
- Performance of an examination according to a specific written protocol
- Proper patient positioning
  - limb must be in dependent position when examined for valvular function
  - standing preferred, if not constrained by the patient's physical condition
  - sitting or reverse Trendelenburg may be used if the patient cannot stand
  - patient position should be noted in the final report
- Patient preparation
  - appropriate equipment and transducer selection
  - appropriate transducer positioning and orientation
  - proper Doppler sample volume size and positioning
  - optimization of equipment gain and display settings
- Proper vein diameter measurements:
  - acquired with the limb in a dependent position
  - measured anterior wall to posterior wall
  - no external pressure is applied to the vein during measurement
  - identification of vessels by imaging and Doppler, using appropriate terminology for vessel nomenclature and anatomic level
  - transverse grayscale imaging without and with transducer compressions

DOCUMENTATION
- Grayscale images
- Color Doppler images
- Doppler spectral waveforms
- Velocity measurements
- Valve closure time, reflux duration
- Abnormalities will require additional images and waveforms that demonstrate the severity, location, extent, and etiology
  - trace superficial reflux to source
  - areas of suspected obstruction must include representative Doppler waveforms recorded at and distal to the obstruction

Vascular laboratory standards for peripheral venous testing (modified from: Intersocietal Accreditation Commission—Vascular Testing. IAC Standards and Guidelines for Vascular Testing Accreditation. *Section 4B: Peripheral Venous Testing*, revised January 15, 2018. (https://www.intersocietal.org/vascular/standards/IACVascularTestingStandards2018.pdf)

NORMAL B-MODE IMAGING FINDINGS

Venous duplex scanning may be performed with most ultrasound systems. Transducer selection depends on the depth of the veins to be scanned. A 5 to 10 MHz linear array transducer is sufficient for most extremity venous examinations, but a 3 to 5 MHz curved linear transducer may be needed to evaluate deeply located vessels, such as the inferior vena cava (IVC) and iliac veins, or to evaluate obese or edematous extremities. High-frequency transducers may be used for mapping or guiding access to superficial veins.

Blood is not an effective reflector of ultrasound. Thus with conventional B-mode imaging the lumen of normal vein is typically anechoic (black). The interface between blood and

TABLE 23.2 Components of Venous Duplex Scans: Peripheral Venous Documentation

LOWER EXTREMITY VENOUS DUPLEX FOR THROMBOSIS AND PATENCY

- Transverse grayscale images without and with transducer compression, including:
  - common femoral vein
  - saphenofemoral junction
  - proximal femoral vein
  - mid femoral vein
  - distal femoral vein
  - popliteal vein
  - posterior tibial veins
  - peroneal veins
  - additional images to document areas of suspected thrombus (including superficial veins and muscular calf veins)
- Spectral Doppler waveforms demonstrating spontaneous venous flow, phasicity and/or flow augmentation, including:
  - right and left common femoral veins
  - popliteal vein
  - additional waveforms, as appropriate
  - abnormalities require additional images, waveforms and velocity measurements

LOWER EXTREMITY VENOUS DUPLEX FOR REFLUX

- Transverse grayscale images of diameter measurement, including:
  - common femoral vein
  - saphenofemoral junction
  - mid femoral vein
  - great saphenous vein
  - popliteal vein
  - small saphenous vein
- Spectral Doppler waveforms with the leg in a dependent position, demonstrating baseline flow and response to distal augmentation; if reflux is present, duration of retrograde flow is measured with calipers:
  - common femoral vein
  - saphenofemoral junction
  - great saphenous vein
  - femoral vein, mid thigh
  - popliteal vein
  - saphenopopliteal junction
  - small saphenous vein
- Transverse grayscale images without and with transducer compression, including:
  - saphenofemoral junction
  - great saphenous vein at proximal thigh
  - great saphenous vein at knee
  - small saphenous vein (at saphenopopliteal junction)

UPPER EXTREMITY VENOUS DUPLEX FOR THROMBOSIS AND PATENCY

- Transverse grayscale images without and with transducer compression, including:
  - internal jugular vein
  - subclavian vein
  - axillary vein
  - brachial vein(s)
  - basilic vein
  - cephalic vein
  - additional images to document areas of suspected thrombus
  - brachiocephalic vein should be imaged, if possible, but compression maneuvers are not used for intrathoracic veins
- Spectral Doppler waveforms demonstrating spontaneous venous flow, phasicity and/or flow augmentation, including:
  - internal jugular vein
  - right and left subclavian veins
  - axillary vein
  - additional waveforms (e.g. brachiocephalic veins), as appropriate

VEIN MAPPING

- Assessment of the veins (distended with use of superficial tourniquet)
- Vein patency and diameter

VENOUS STENTS

- Spectral Doppler waveforms with color Doppler images, including:
  - proximal stent
  - mid stent
  - distal stent
  - native vessel adjacent to the proximal end of the stent
  - native vessel adjacent to distal end of the stent

Components of venous duplex scans: Peripheral venous documentation (modified from: Intersocietal Accreditation Commission—Vascular Testing. IAC Standards and Guidelines for Vascular Testing Accreditation. *Section 4B: Peripheral Venous Testing*, revised January 15, 2018. (https://www.intersocietal.org/vascular/standards/IACVascularTestingStandards2018.pdf)

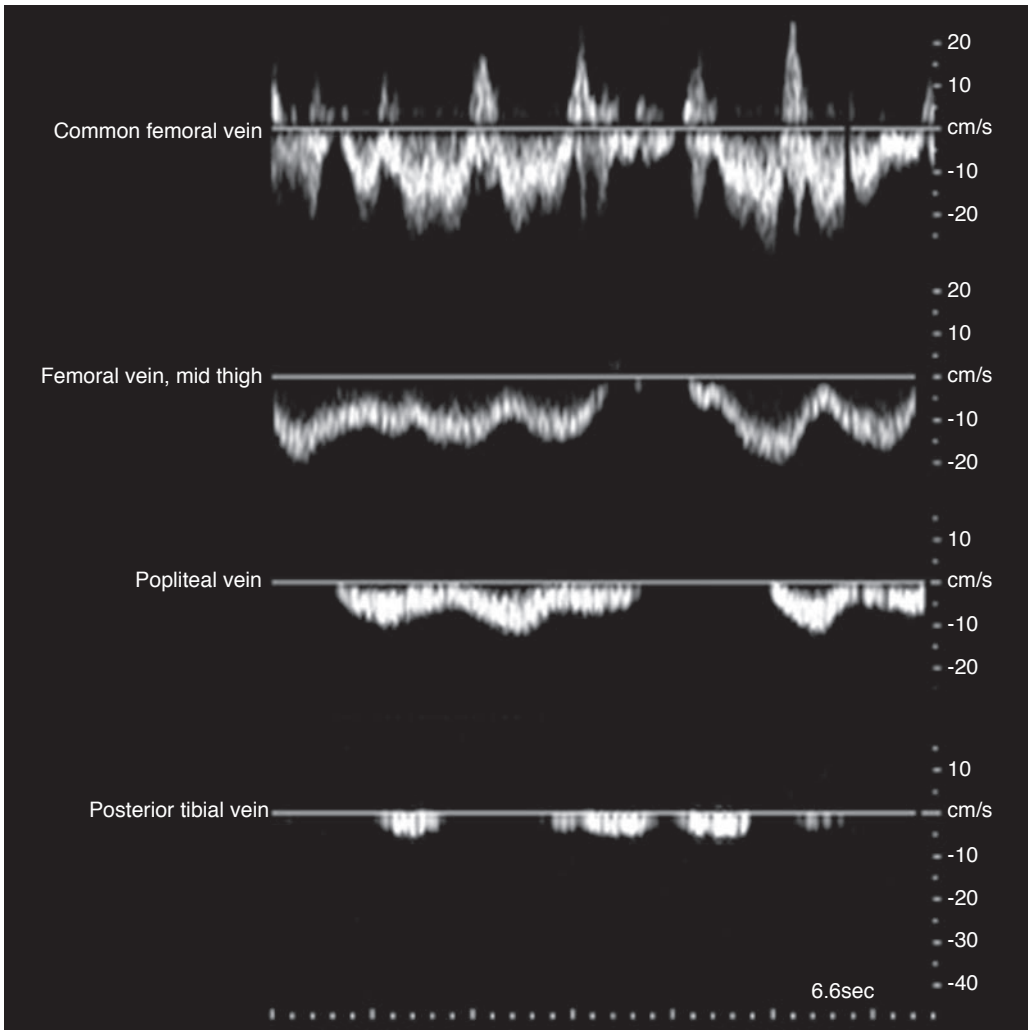

Figure 23.1 Normal flow in the lower extremity veins is spontaneous (occurring without calf pump function or other augmentation maneuvers) and phasic with respiration. Flow patterns differ at proximal and distal locations, with less spontaneous flow observed in the smaller veins in the distal limb. The presence or absence of thrombus within an imaged vein can be confirmed with probe compression. (Image from Dawson DL, Gray HM. Acute lower extremity deep vein thrombosis. In: Zierler RE and Dawson DL, editors: *Strandness's Duplex Scanning in Vascular Disorders*. 5th ed. Philadelphia: Wolters Kluwer; 2016: 235 [Chapter 19, Fig. 19.8].)

the vein wall is echogenic (bright), especially when specular reflections are created when the ultrasound angle of incidence is close to 90 degrees. The wall of a vein appears thinner than the wall of the adjacent artery. Flowing blood may sometimes be seen within veins, especially when a high-frequency transducer is used to examine a vein that is close to the skin surface. This may be most apparent when slow flow conditions result in red blood cell aggregation with rouleaux formation, creating greater echogenicity.[14]

Extremity veins may vary in size and profile. With hypovolemia, veins may appear ovoid or collapsed. Because of the normally low pressure in veins, they are easily collapsed with extrinsic compression. (Of note, normal arteries may also be compressible if sufficient probe pressure is applied.) When venous pressure is high (heart failure, more central obstruction, etc.), veins may be distended. Extremity veins may appear collapsed when the limb is elevated above the phlebostatic axis (level of the right atrium), and they will be full and dilated when the limb is dependent. Lower extremity examinations are typically done with some reverse-Trendelenburg (foot down) positioning to make the veins easier to identify.

NORMAL FLOW PATTERNS IN VEINS

Color flow Doppler and pulsed Doppler spectral waveform analysis are used to evaluate venous flow characteristics (Fig. 23.1).

In the arterial system, the pumping action of the heart is the primary driving force for blood flow, but in the low-pressure venous system, the antegrade movement of venous blood flow is substantially affected by other factors. Normal venous flow is **phasic** with respiratory movements. During inspiration, the diaphragm moves downward and intraabdominal pressure is increased. This decreases venous return from the lower extremities. Flow increases during expiration. In the upper extremity veins, respiratory phasicity has a different pattern. Intrathoracic pressure is decreased during inspiration; antegrade flow in upper extremity veins is increased. The cardiac cycle has greater effects on venous flow patterns in more central veins.

Spontaneous antegrade venous flow is seen under resting conditions, but flow velocity is dramatically augmented with voluntary muscle contraction or by manual compression by the examiner. Muscle contraction transiently increases compartment

pressures, compresses deep veins and venous sinuses within the muscles, and thereby functions as a peripheral pumping mechanism in the circulation. Venous obstruction interferes with the flow **augmentation** produced by compression or other provocative maneuvers.

DIAGNOSIS OF DEEP VEIN THROMBOSIS

Direct ultrasound visualization of thrombus within a vein is the most obvious finding associated with DVT (see Chapter 147). Deep veins that are acutely occluded by thrombosis are often distended, appearing round and larger than the adjacent artery. Thrombus echogenicity increases as the clot organizes, making it easier to detect with B-mode imaging over time. Acute thrombus may be adherent to the vein wall, or it may be loosely attached and mobile, a "free floating thrombus" or "thrombus tail."

B-mode imaging alone has limited sensitivity. Fresh thrombus may be hypoechoic. It can also be difficult to recognize intraluminal thrombus if the imaging quality is suboptimal, as can be the case with an uncooperative patient, greater imaging depth (obesity), failure to optimize imaging settings, or other technical factors.

For better detection of thrombus in the lumen, venous scanning is done with compression maneuvers (Fig. 23.2). Pressure is manually applied with the imaging probe. Normal vein walls are coapted with modest compression. Vein walls will not collapse when there is thrombus in the lumen, though soft thrombus may deform with firm pressure. Partial compressibility may be seen with non-obstructive acute thrombosis or as recanalization of an occluded segment occurs over time.

B-mode imaging is not a stand-alone modality for DVT diagnosis. Imaging of deeper structures can be limited, and some normal venous segments may not collapse with probe pressure (e.g., femoral vein at the level of the adductor hiatus). Venous compressibility can also be limited by obesity, edema, or tenderness. Calf veins may be difficult to visualize.

Duplex scanning, the combination of imaging *and* Doppler-derived information about the presence and nature of venous flow, improves the accuracy of the examination (Fig. 23.3).[7] The addition of flow information makes it possible to identify veins that are not well demonstrated with B-mode alone and to determine patency. Color flow Doppler helps confirm the patency of venous segments that were incompletely evaluated with B-mode imaging. It can help to distinguish between occluding and non-occluding thrombus and identify anechoic thrombus by visualization of the flow around it. The color velocity scale (pulse repetition frequency or PRF) should be at a low setting to detect low velocity venous flow.

The diagnostic accuracy of duplex ultrasound scanning is good enough that it has replaced contrast venography as the definitive diagnostic test for DVT, except in limited situations. A systematic review found 100 publications from 1966 to 2004 that compared ultrasound with venography in patients with suspected DVT. Meta-analyses of data from these studies confirmed that the best results were obtained with examinations that combined B-mode, pulsed Doppler, and color Doppler imaging.[15] The pooled sensitivity was 96% for proximal limb DVT, 75% for distal DVT, and a pooled specificity of 94%. Sensitivity was found to be higher in the more recently published studies, in cohorts with higher pretest probability of DVT and more proximal DVT, and was lower in cohorts that reported interpretation by a radiologist. Specificity was higher in cohorts that excluded patients with known prior DVT.

Imaging techniques and provocative maneuvers need to be used in combination to correctly distinguish normal flow variations from DVT (Fig. 23.4). The presence of intraluminal echoes from rouleaux formation can be distinguished from thrombus by the disruption of the echogenic erythrocyte aggregates by flow augmentation and by vein wall collapse with compression. The absence of spontaneous flow (pulsed Doppler or color Doppler) may be normal in the distal limb, or it may be the result of more central obstruction. Augmentation maneuvers (calf pump, manual distal compression) will demonstrate flow.

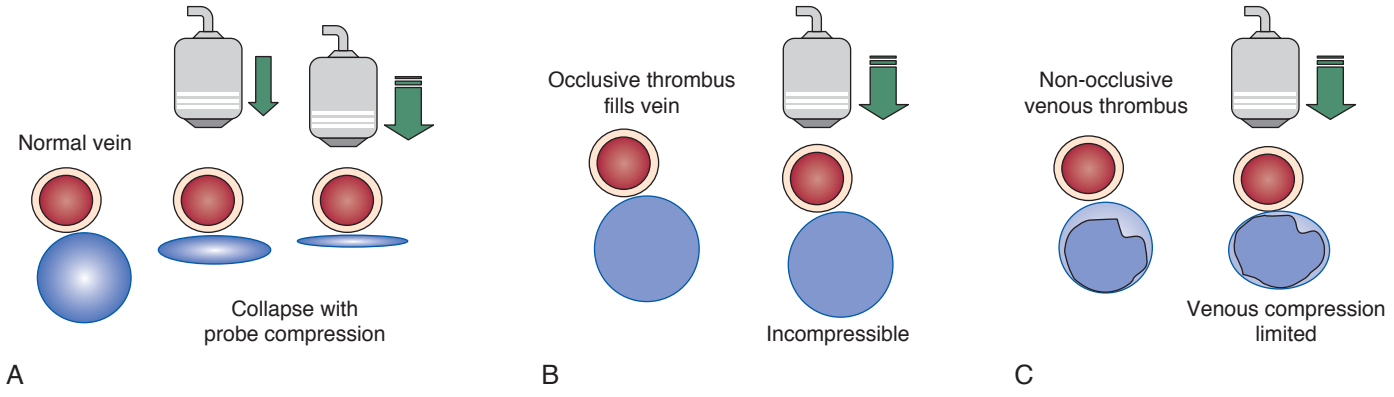

Figure 23.2 The presence or absence of thrombus within an imaged vein can be confirmed with probe compression. (A) Normal vein collapses with probe pressure. (B) Thrombosed vein does not compress. (C) Partial vein compressibility with non-occlusive venous thrombosis. (Modified from Dawson DL, Gray HM. Acute lower extremity deep vein thrombosis. In: Zierler RE and Dawson DL, eds. *Strandness's Duplex Scanning in Vascular Disorders*. 5th ed. Philadelphia: Wolters Kluwer; 2016:233 [Chapter 19, Fig. 19.2].)

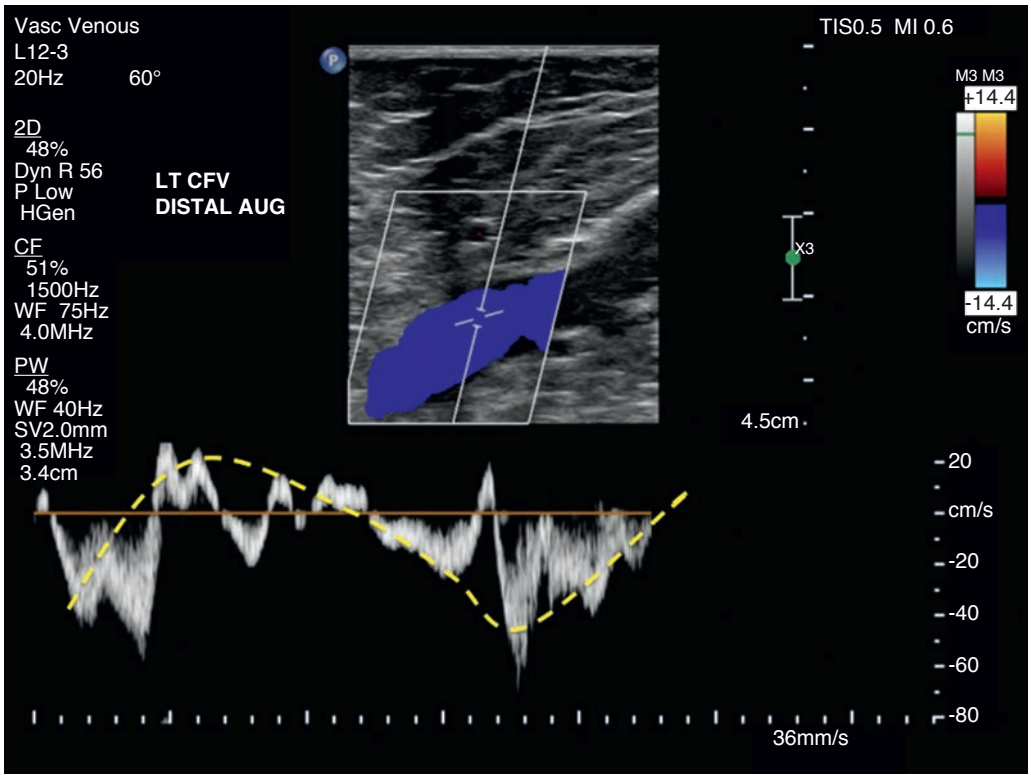

Figure 23.3 Color Doppler Image of a Normal Common Femoral Vein. There is complete color filling of the vein lumen. The flow velocity waveform demonstrates spontaneous flow that is phasic with respiration (highlighted by *dashed yellow line*). Cardiac effects are also seen in the waveform.

CALF VEIN THROMBOSIS

All lower extremity deep veins should be examined as part of a complete DVT examination, including infrapopliteal veins: peroneal, posterior tibial, soleal, and gastrocnemius veins. Calf vein thrombosis is common in patients with acute DVT and often occurs as an isolated finding.[16] The peroneal and posterior tibial veins are involved in the majority of cases. Anterior tibial vein thrombi are less common.

Duplex scanning can reliably evaluate for calf vein DVT, but there are some differences in examination technique and interpretation. Spontaneous flow is not always detected, but there will be Doppler-detectable flow with augmentation by distal manual compression. Calf veins may be difficult to visualize with B-mode imaging, especially in the obese or those with significant edema. Detection of venous flow with color Doppler, with or without augmentation maneuvers, can confirm calf vein patency (Fig. 23.5).

Isolated calf vein thrombi rarely cause clinically relevant pulmonary emboli (PE), but patients with calf vein DVT are at risk for progression to involve the femoropopliteal veins (see Chapter 147). Symptomatic calf-vein DVT is associated with progression or recurrent thrombosis in 15% to 20% of patients within 3 months.[17,18] Calf vein DVT is a marker for increased thromboembolic risk, for which anticoagulation may be indicated.[19] Few patients with calf vein DVT are at high risk for progression or PE.[20] Risk is higher when thrombus is isolated to calf veins,[21-23] if the DVT was a second or subsequent venous thromboembolism (VTE) episode, in patients with recent orthopedic procedures, in patients with malignancy, and in those who are immobile.[24-26]

When anticoagulation is not used to treat acute, isolated calf vein thrombi, follow-up duplex scanning over at least 2 weeks is recommended to evaluate for progression.[27]

Thrombosis of intramuscular veins, those within the gastrocnemius or soleus muscles, can be associated with localized calf tenderness. In rare cases, there can be propagation and subsequent pulmonary embolism, but isolated muscular calf vein thrombosis has a low risk of extension. If extension is not observed within 2 weeks, it is very unlikely.[27-30] Patients with muscular calf vein thrombosis, with only transient risk factors, do not require anticoagulation, but they should be re-evaluated with duplex scanning 1 week after diagnosis to confirm thrombus resolution or the absence of progression.[31]

ILIAC VEIN AND INFERIOR VENA CAVA

The IVC and iliac veins, like other intraabdominal and retroperitoneal vessels, can be difficult to evaluate due to overlying abdominal bowel gas and the decreased resolution of ultrasound when evaluating deeper structures. When possible, patients should fast for 6 hours prior to the examination to help reduce bowel gas. B-mode imaging and transverse probe compression maneuvers are seldom effective when evaluating abdominal or

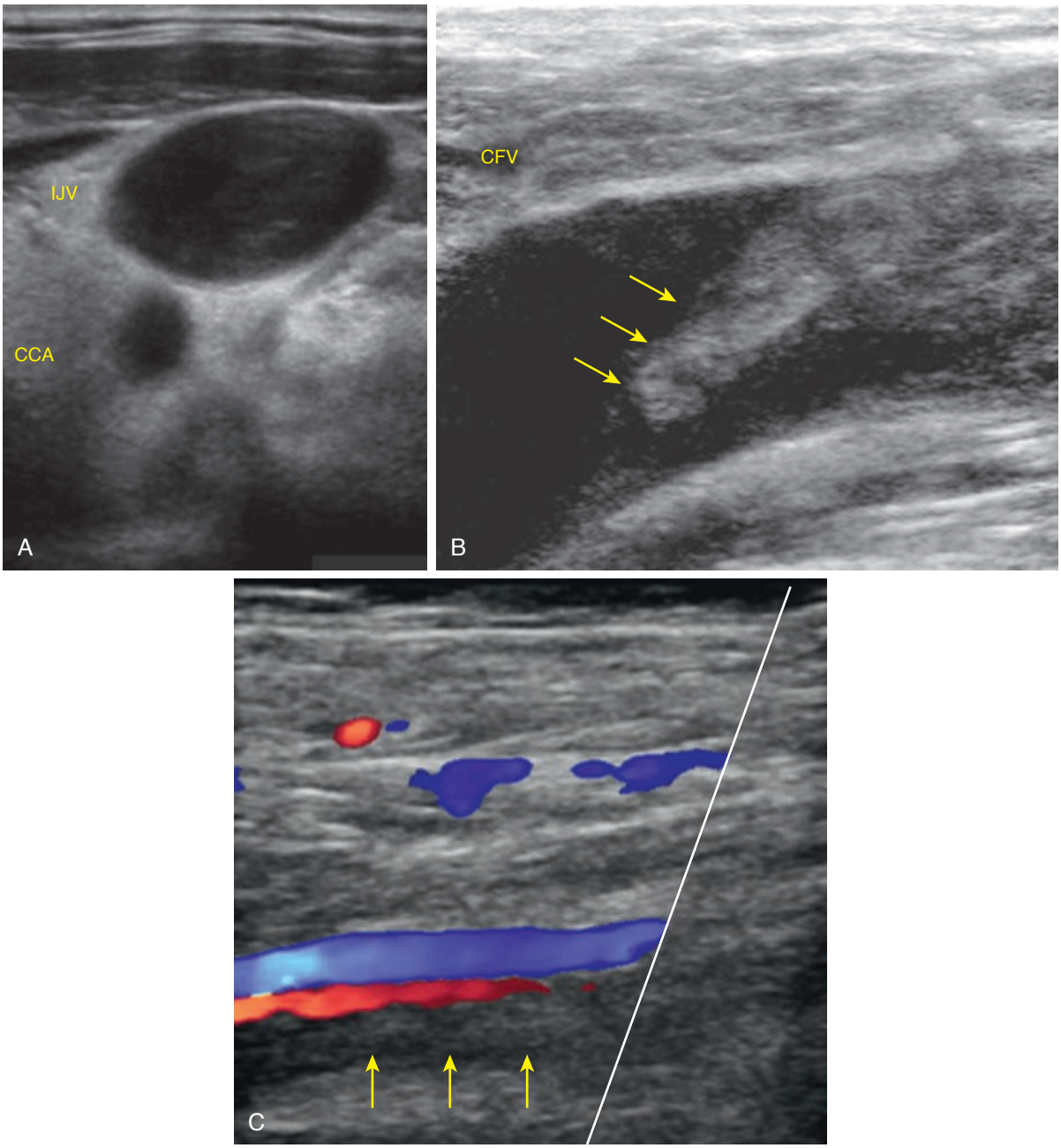

Figure 23.4 Examples of Acute Deep Vein Thrombosis. (A) Dilated internal jugular vein with hypoechoic lumen. (B) Intraluminal thrombus in the common femoral vein with a "free floating tail" *(yellow arrows)* extending cephalad. (C) Absence of color filling in one of two peroneal veins, with the presence of intraluminal echogenic thrombus *(yellow arrows)*.

pelvic veins. Therefore color flow and Doppler spectral waveforms are the primary modalities for evaluation of the IVC and iliac veins. Color scale and gain settings are adjusted for depth.

IVC flow should be spontaneous and phasic throughout. Greater pulsatility is seen in the IVC due to its proximity to the heart. Absence of detectable flow by pulsed Doppler and color Doppler imaging suggests IVC occlusion or thrombosis.

External iliac and common iliac veins can be evaluated from the inguinal ligament to the level of the IVC. Augmentation of flow is produced with thigh compressions. Internal iliac veins are identified at their confluence with the external iliac veins. Complete or partial absence of color flow within the iliac veins may indicate intraluminal thrombus. Absence of spontaneous flow or lack of respiratory phasicity (continuous flow) may indicate a more central venous obstruction. Comparison of venous flow characteristics to the contralateral side may show indirect findings that indicate common iliac vein obstruction or compression (Fig. 23.6). Continuous venous waveforms with elevated flow velocities may be seen with venous stenosis.

Abnormal flow patterns in lower extremity veins may reflect abnormal (central) cardiovascular abnormalities. Heart failure

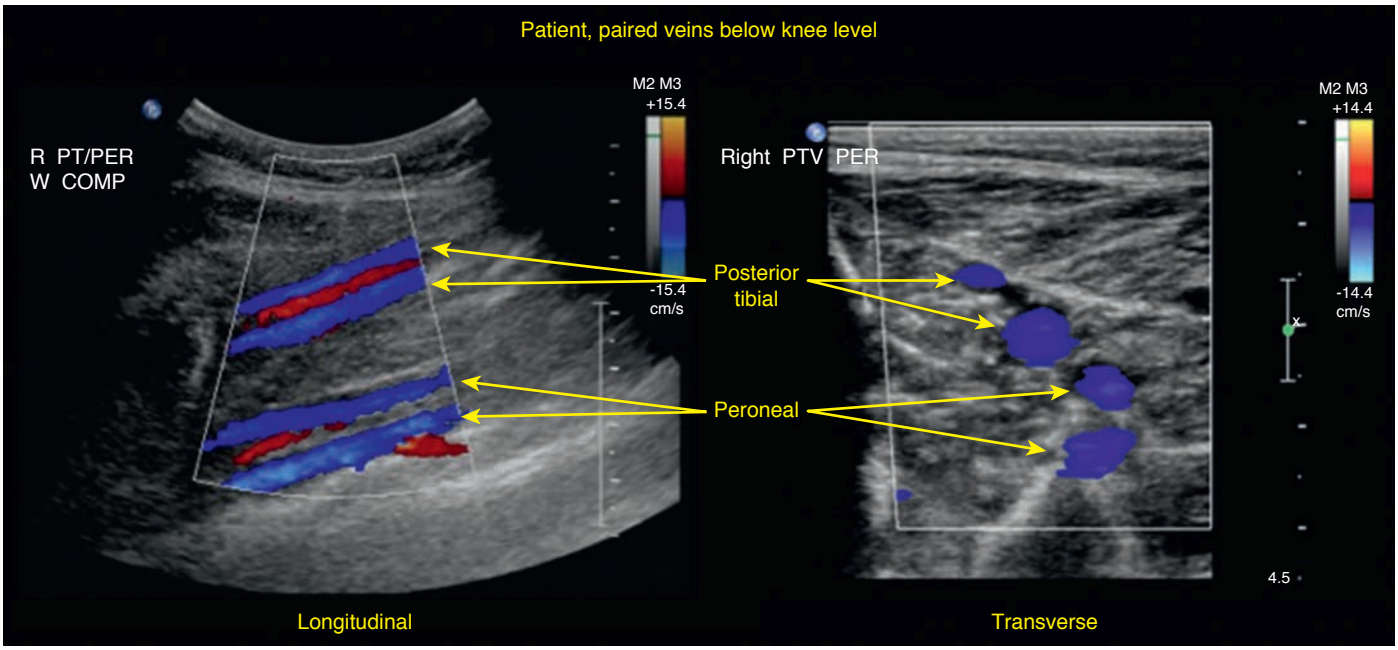

Figure 23.5 **Imaging of the Posterior Tibial and Peroneal Veins.** *Left,* longitudinal view; *right,* transverse view. Color flow imaging can confirm patency of the posterior tibial and peroneal veins. This can help to rule out calf deep vein thrombosis when vein wall coaptation with compression maneuvers is difficult to demonstrate. (Image from Dawson DL, Gray HM. Acute lower extremity deep vein thrombosis. In: Zierler RE and Dawson DL, eds. *Strandness's Duplex Scanning in Vascular Disorders.* 5th ed. Philadelphia: Wolters Kluwer; 2016:240 [Chapter 19, Fig. 19.17].)

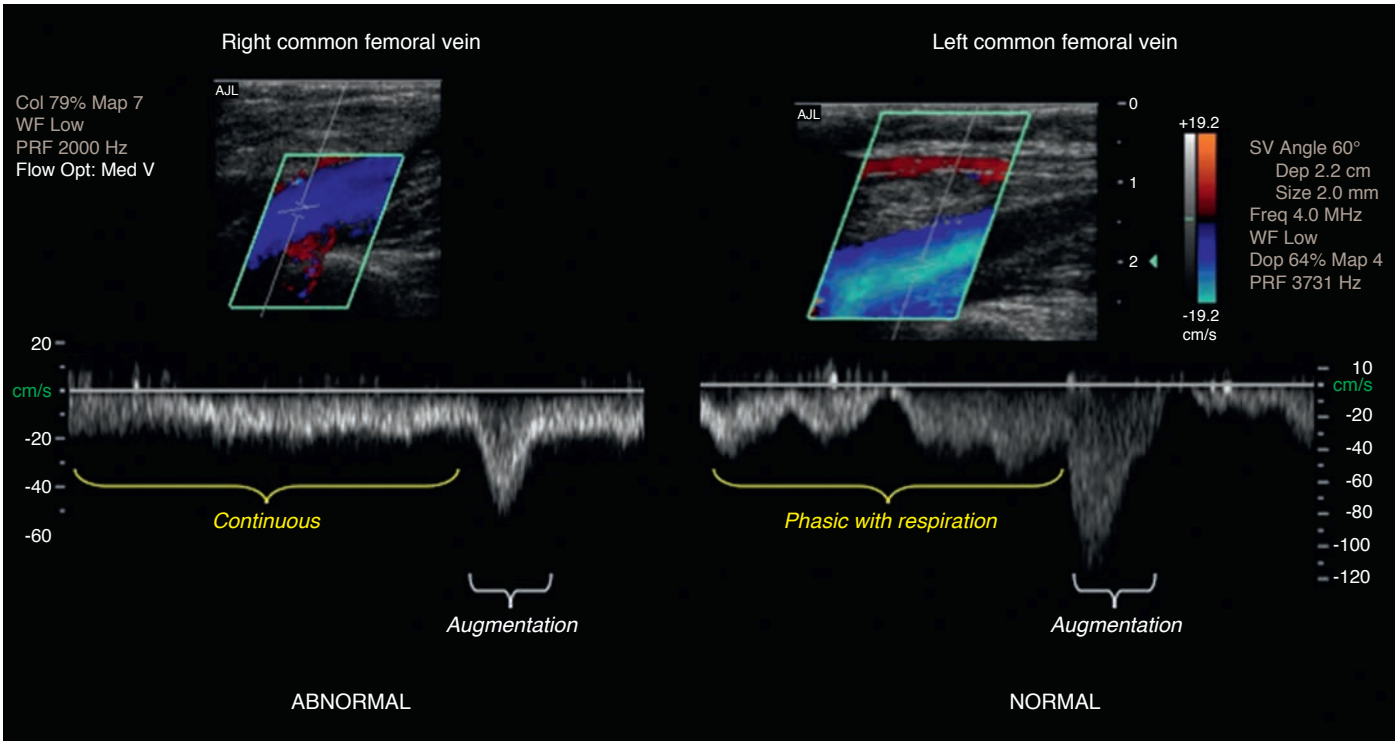

Figure 23.6 Continuous venous flow (loss of normal respiratory phasic variation) indicates venous outflow obstruction. This indirect finding does not distinguish occlusion, non-occlusive thrombosis, chronic narrowing, or extrinsic compression. When seen in one common femoral vein, as shown, it indicates iliac vein obstruction. (Image from Dawson DL, Gray HM. Acute lower extremity deep vein thrombosis. In: Zierler RE and Dawson DL, eds. *Strandness's Duplex Scanning in Vascular Disorders.* 5th ed. Philadelphia: Wolters Kluwer; 2016:233 [Chapter 19, Fig. 19.2].)

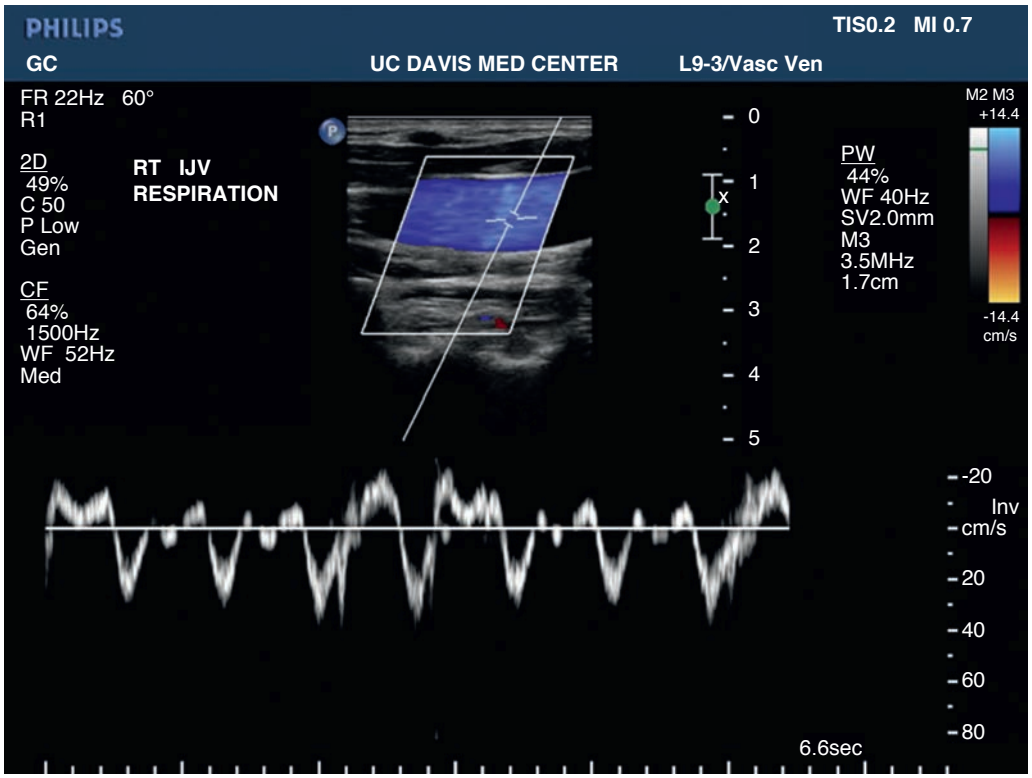

Figure 23.7 The normal flow pattern in the internal jugular vein (IJV), like other veins close to the heart, is more affected by the cardiac cycle than phasic respiratory variation.

or tricuspid valve regurgitation can increase venous flow variations with each cardiac cycle.

DIAGNOSIS OF UPPER EXTREMITY DEEP VEIN THROMBOSIS

Compared with the lower extremities, the upper extremities are less frequently affected by deep venous thrombosis.[32-34] Upper extremity DVT usually develops secondary to an identified inciting factor, such as the presence of central venous catheters (Fig. 23.7), pacemaker wires, or malignancy (see Chapter 149).[34,35] Primary upper extremity venous thrombosis, when it does occur, is most commonly due to extrinsic compression at the level of the thoracic outlet (Paget-von Schrötter syndrome; see Chapter 123).[34-40]

Catheter venography may be performed for diagnosis or as part of an intervention to treat upper extremity or central venous thrombosis or stenosis, but duplex scanning is the primary diagnostic modality in clinical practice.

Upper extremity venous duplex scanning, compared with lower extremity studies, has both similarities and differences. Venous incompressibility is similarly used in upper extremity examinations as a sign of vein thrombosis, but compression techniques are not practical for evaluation of veins under the clavicle or more centrally. The presence or absence of Doppler detectable flow can be used to assess for patency, but anatomic features

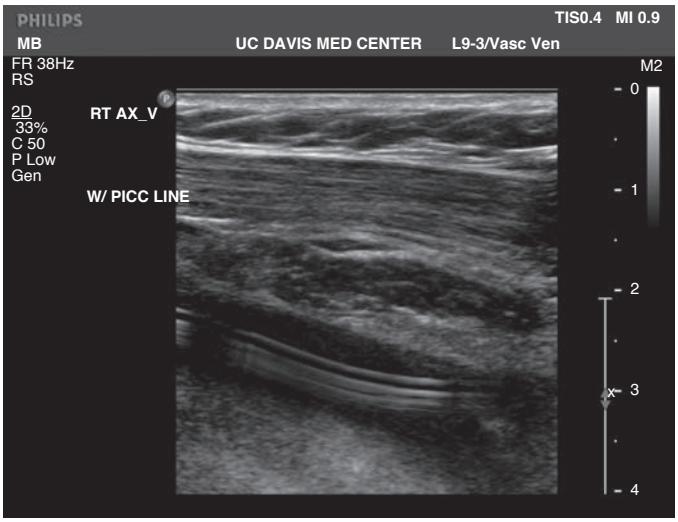

Figure 23.8 Intraluminal foreign bodies can be visualized with B-mode gray-scale ultrasound imaging. In this example, the echogenic walls of a catheter are seen within the anechoic lumen of the axillary vein. The echogenicity of the catheter produces the reverberation artifact, seen here. Upper extremity venous thrombosis is often associated with the presence of an indwelling catheter.

limit direct B-mode imaging of the central venous outflow from the upper extremities (brachiocephalic veins and superior vena cava). Greater pulsatility is a normal finding in central veins or proximal upper extremity veins (Fig. 23.8). Indirect findings, such as asymmetry of venous flow velocity waveforms,

may suggest the presence of central venous obstruction, but robust collateral formation may develop around chronically occluded segments, limiting the reliability of indirect findings. In some cases, occluded axillo-subclavian venous segments may be incorrectly identified as patent due to the prominence of adjacent collateral veins.

A systematic review of diagnostic tests for clinically suspected upper extremity DVT found 84% to 97% sensitivity and 93% to 96% specificity for venous ultrasound techniques, including compression ultrasonography, Doppler ultrasonography, or combinations of techniques.[41] Methodologic limitations, differences between studies, and small sample sizes limited the strength of the evidence.

LIMITED OR POINT-OF-CARE ULTRASOUND EXAMINATIONS

Point-of-care ultrasound (POCUS) examinations have become more common as ultrasound imaging systems become smaller, less expensive, and more user-friendly. POCUS examinations can be used to evaluate for DVT in outpatient clinics or offices, emergency rooms, or inpatient settings.[42] It is anticipated that venous POCUS applications will have increasing importance in clinical practice.

With appropriate training and testing procedures, it appears that the diagnosis of femoropopliteal DVT by providers at the point of care may approach the accuracy of vascular laboratory professionals.[43] While some have suggested the use of an abbreviated "two-point" compression ultrasound examination that only evaluates the common femoral and popliteal veins, this approach does not identify thrombus limited to the femoral vein in the thigh or thrombosis of calf veins, reducing exam sensitivity.[44] While this shortcoming may not be a major problem in ambulatory patients with low suspicion for DVT who have appropriate follow-up,[45] it is clinically relevant in high-risk patients (e.g., severely ill hospitalized patients).[44,46]

A systematic review that included meta-analysis of 16 studies with 2379 patients compared emergency department POCUS examinations with a reference examination (a color flow duplex scan performed by a radiology department or vascular laboratory, or angiography) for the diagnosis of DVT. The prevalence of DVT was high in these studies: 23% (498 in 2379 patients). The weighted mean sensitivity of emergency department POCUS, compared with the reference imaging test, was 96% with a weighted mean specificity of 97%, suggesting that with appropriate patient selection and testing procedures, POCUS can be a useful tool for DVT diagnosis.[47] The differences in the clinical characteristics of patients in various settings will substantially affect the pretest probability of DVT; and the training and experience of the clinicians performing the examinations will affect the accuracy of the results.

In vascular laboratories, routine bilateral evaluation is not standard in the absence of bilateral symptoms or other indications.[48,49] Unilateral studies are a common and accepted practice, except when a prothrombotic state is suspected, there are systemic symptoms, or there is a suspicion of pulmonary embolism.[50,51] The incidence of unilateral thrombus in an asymptomatic extremity in an otherwise healthy individual approximates 1%.[52]

DETERMINATION OF THROMBUS AGE

The manifestations and clinical significance of venous thrombus change over time. Acute thrombus in the deep veins is associated with the highest risk of thromboembolism. As the thrombus ages, it becomes less friable, increasingly fibrotic, and more firmly attached to the vein wall. Embolic risk declines over time. The age and characteristics of venous thrombus also affect the potential for success with thrombolysis or thrombus extraction procedures. Thrombus age may also affect the clinical manifestations of DVT. Thus diagnostic assessments need to consider whether identified abnormalities reflect acute or chronic disease. The vascular laboratory needs to have diagnostic criteria for the interpretation and evaluation of thrombus and its age.

Typical features of acute DVT and its late sequelae are summarized in Table 23.3. The sonographic appearance of fresh thrombus is relatively hypoechoic. Acute thrombus may have some deformability that can be demonstrated with probe compression. The vein may be occluded or there may be some residual flow around the thrombus, which may not be firmly attached to the vessel wall. In some cases, there may be a cephalad tail of free-floating thrombus that may be visualized moving in the lumen. As time passes, soft acute thrombus becomes firmer and more echogenic. Fibrin cross-links are formed, and thrombus becomes more organized and adherent to the vessel wall. Subsequently, there may be thrombolysis and vein recanalization, or inflammatory changes in the thrombus and vessel wall may lead to fibrosis (Figs. 23.9 and 23.10).[53,54]

TABLE 23.3 Ultrasound Features That May Determine Venous Thrombus Age

Feature	Early (Acute Deep Vein Thrombosis)	Late
Thrombus appearance	Hypoechoic, may be mobile or loosely attached to vein wall	Echogenic
Vein lumen size	Larger, distended	Smaller than adjacent artery, irregular
Vein wall	Thin, smooth luminal surface	Thickened, hyperechoic
Compressibility	Slightly deformable, "spongy" (may or may not occlude lumen)	Rigid, incompressible (may be partially recanalized)
Flow	Absent, or abnormal on color Doppler, with filling defects	Varying degree of recanalization
Collateral veins	Absent	Present
Valvular function	Competent (usually)	Incompetent (reflux)

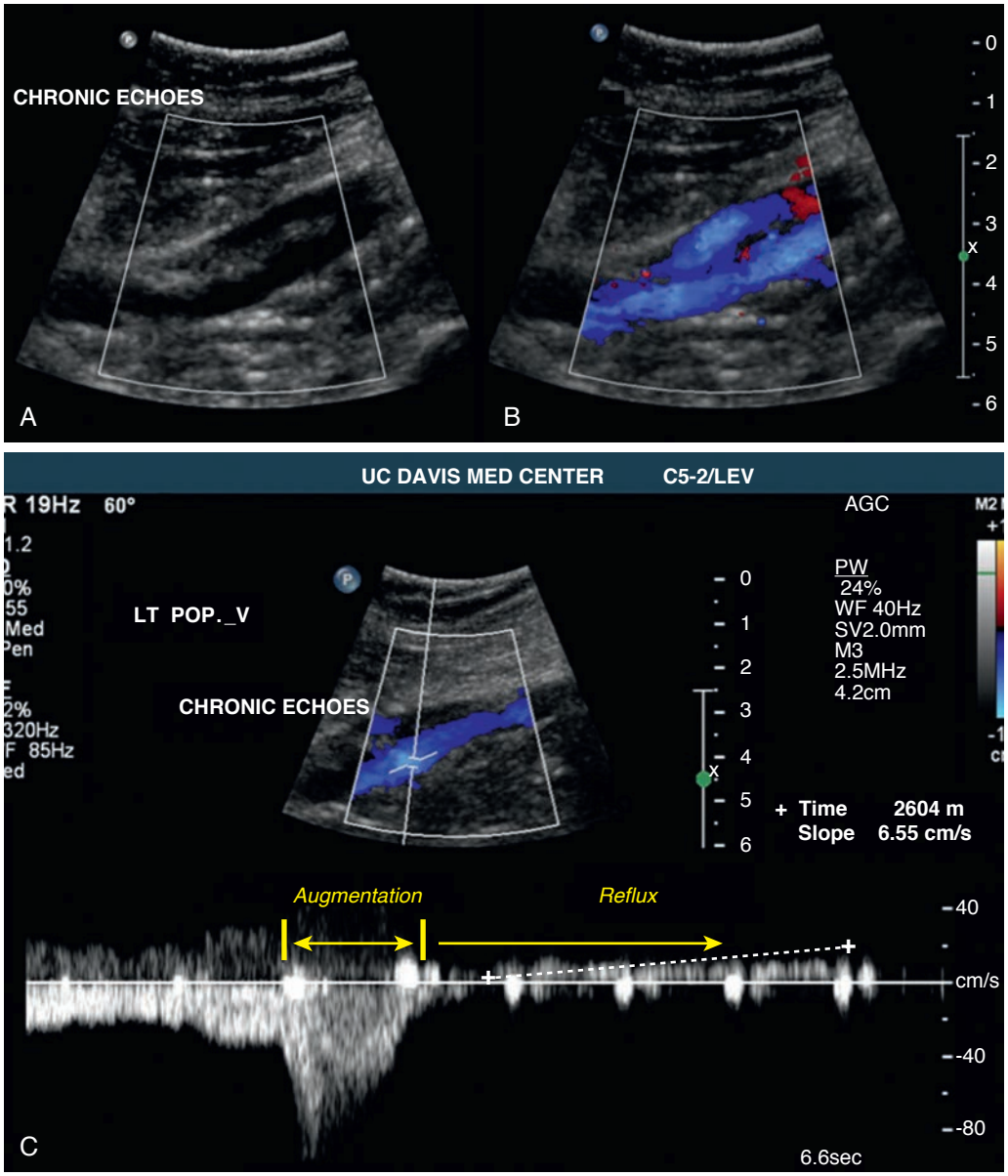

Figure 23.9 Chronic Postthrombotic Changes in the Popliteal Vein. (A) Echogenic material is seen in the lumen. (B) Color flow Doppler shows partial recanalization. (C) Venous reflux indicates valvular incompetence (though retrograde flow is slow in this example from a supine patient).

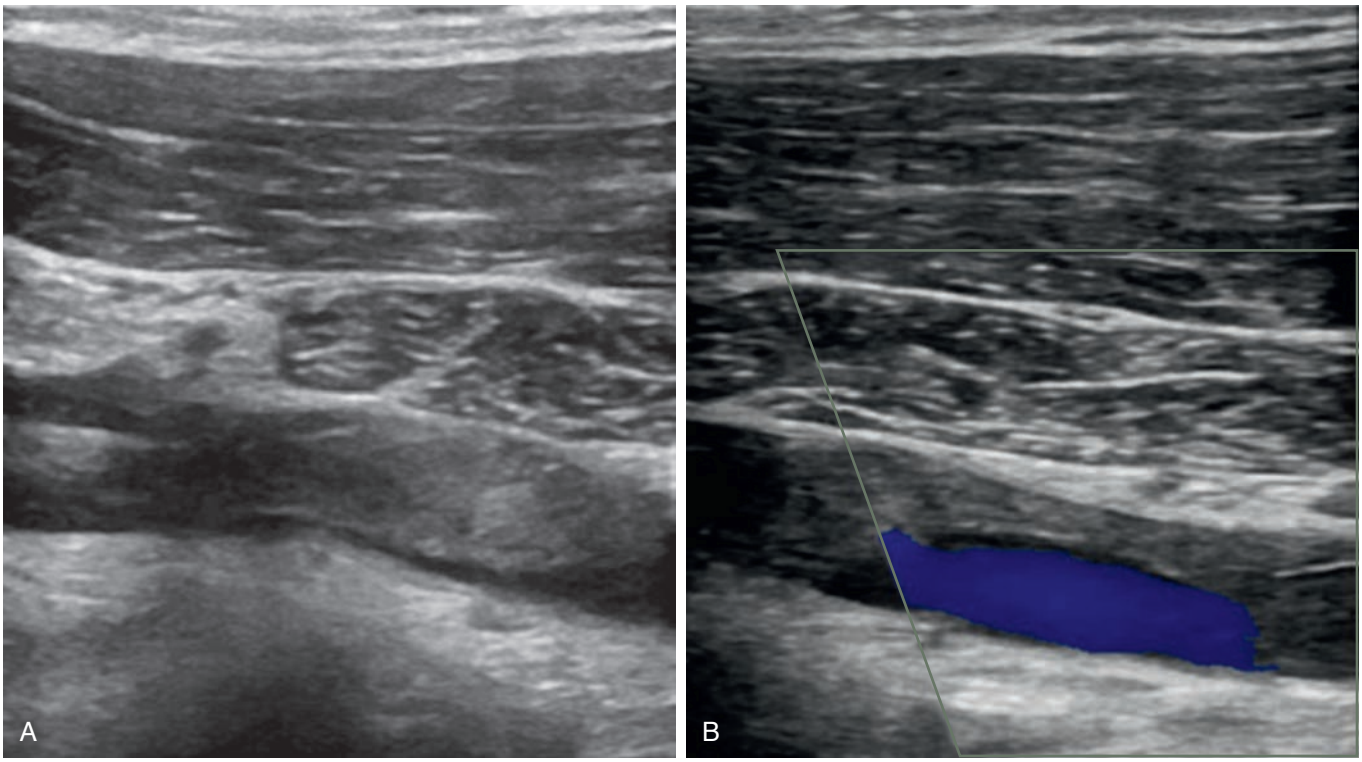

Figure 23.10 Chronic Postthrombotic Changes in the Right Axillary Vein. (A) Echogenic material is seen in the lumen. (B) Color flow Doppler shows partial recanalization.

Thrombus extent in deep veins generally regresses over time after acute DVT, but the rate and extent of thrombus resolution is variable.[55]

Venous thrombosis is appropriately described as "acute" when it first occurs. Chronic venous thrombosis has been used to describe the appearance of late intraluminal obstruction after acute DVT, but the term may be inaccurate and confusing. Fibrotic tissue, not thrombus, may be the principal content of residual intraluminal material. Abnormal findings may be seen with ultrasound months or years after DVT.[56] Some providers mistakenly assume that anticoagulation needs to be prescribed when these findings are reported as "chronic DVT." In the absence of recurrent thrombosis, there is generally no need for anticoagulation. Therefore **chronic postthrombotic change** has become the preferred term to describe what is seen months after an acute DVT. This nomenclature emphasizes the pathophysiology and may reduce misunderstandings about the implications of the diagnosis. Postthrombotic changes may be associated with a variety of manifestations of chronic venous disease, including swelling, pain, skin change, and secondary varicosities.

The term "subacute venous thrombosis" is nonspecific, and its use is no longer recommended. There is no standard definition for the duration of the acute period. There are no verified ultrasound criteria that can be used to determine the age of thrombus in the weeks or months after acute venous thrombosis. Further, the term does not have clinical significance. For the purposes of ultrasound diagnosis, when the findings are not clearly acute or chronic, the preferred terminology for reporting is **venous thrombosis, indeterminate age**. Therapeutic decisions consider individual circumstances and risk factors. If DVT is found in an asymptomatic patient in the absence of clinical history to help establish when the thrombosis occurred, it may be reasonable to consider anticoagulation, though no randomized trials have evaluated the value of anticoagulation for incidentally found VTE. The benefit of anticoagulation may be less than for patients with symptomatic DVT, as the extent of the thrombosis may be less. Clinical assessment of DVT risk is especially important in this setting.

NOVEL ULTRASOUND TECHNIQUES: ELASTOGRAPHY

Ultrasonic elastography uses ultrasound imaging to measure soft tissue strain to objectively assess the mechanical properties of tissues, such as hardness or stiffness.[57,58] This may be considered a correlate to the palpation of tissue to determine its characteristics. Several ultrasonic elastography methods have been used to characterize tissues in research and clinical applications (liver, breast masses, etc.), and elastography has been studied as an additional diagnostic modality for the characterization of venous thrombus.[57-63]

Elasticity is the tendency of a material to resume its original size and shape after deformation by a force. Fluids possess only volume elasticity, resisting changes in volume, but not shape. Solids resist changes in shape and volume, as they have both shear elasticity (rigidity) and volume elasticity. **Strain** is term

that describes changes in size or shape. Deformational forces produce strain. It is the ratio of the change in length per unit length. Force acting on an area is **stress**. When a material is stressed, thickness may decrease as length extends.

For a homogeneous isotropic (uniform) solid, the ratio of stress/strain is a constant, the modulus of elasticity. There are three moduli that describe elasticity: the Young modulus (longitudinal elasticity), the ratio of stress to strain; shear or torsion modulus (rigidity); and bulk or volume modulus (volume elasticity).

Compression elastography (quasistatic elastography or strain imaging) uses ultrasound imaging with and without external probe compression. Ultrasound images are recorded with and without compression. Areas of interest are compared—evaluated to determine relative deformation. Less deformation is seen in tissues or thrombi that are more rigid.[57,64,65] Tissue strain is determined by relative distortion.

Acoustic Radiation Force Impulse (ARFI) imaging uses energy of the insonated ultrasound to move tissues at the microscopic level. A focused ultrasound beam passing though soft tissues is primarily attenuated through absorption, but some of the acoustic pressure of the beam creates tissue movements that cause deformational stress, with greater effects on softer tissues. This is the basis of ARFI mapping of tissue stiffness. AFRI provides a qualitative stiffness value along the axis of the beam. The magnitude, location, spatial extent, and duration of acoustic radiation force can be manipulated for the evaluation of different tissues. This technique is most widely used for the evaluation of hepatic fibrosis, but studies of venous thrombus have used variations of this modality.[63]

In addition to the compression waves that propagate acoustic energy through tissue, there are also shear waves (transverse waves) created by oscillations at right angles to the direction of the ultrasound beam. The compressional wave speed through tissue is related to the bulk modulus, while the shear wave speed is related to the shear modulus. Because variations in tissue characteristics have a greater effect on the shear modulus than the bulk modulus, changes in the shear wave speed indicate structural differences in tissues. Because of this, several advanced imaging modalities use shear waves for tissue characterization. Feasibility studies with shear wave elasticity imaging (SWEI), or shear wave induced resonance elastography (SWIRE), have shown that thrombus elasticity can be quantitatively assessed.[63,66,67]

To date, however, elastography for thrombus characterization has not been standardized or sufficiently validated for their practical use in the vascular laboratory.

DETERMINING THE DURATION OF THERAPY FOR ACUTE DEEP VEIN THROMBOSIS

Benefits and risks of anticoagulant therapy should be considered when choosing the duration of anticoagulation for a first episode of unprovoked VTE.[27] Isolated calf vein DVT has half the risk of recurrence compared with proximal DVT and PE. One the other hand, a second or subsequent episode of VTE is estimated to have a 50% higher of recurrence risk compared with a first-time VTE.[27]

Venous ultrasound findings may have some value in predicting recurrence risk. Residual vein thrombosis (RVT) may indicate a continuing prothrombotic state.[68] The Duration of Anticoagulation based on Compression UltraSonography (DACUS) study found residual thrombus in the proximal veins was associated with an increased risk of recurrent thrombosis after a first episode of DVT. Conversely, the absence of RVT identified patients at very low risk for recurrence. A subsequent study similarly found that in the absence of RVT, a short period of DVT treatment may be sufficient. For those with persistent RVT, treatment extended to 2 years substantially reduced, but did not eliminate, the risk of recurrent thrombosis.[69] Among 409 patients with unprovoked DVT, 33% did not have RVT, and anticoagulation was stopped after 3 months, with a recurrent DVT rate of only 1.4%. Patients found to have residual thrombus (n = 273) received anticoagulants for an additional 21 months. Anticoagulation was stopped after a total of 24 months, and the subjects were again evaluated for residual thrombus. The rate of recurrent thrombotic events in the following year was 1.4% in those with no RVT after extended therapy, but 10.4% in those with persistent RVT.

The Cancer-DACUS study evaluated the association of RVT with recurrent VTE in patients with lower extremity DVT and cancer.[70] In cancer patients with a first DVT, treated for 6 months, the overall risk of thrombosis after cessation of anticoagulation was 15% at 1 year. The absence of RVT identified a subgroup at low risk for recurrent thrombosis, but this study's findings were not considered compelling enough to warrant a change in the guideline for long-term anticoagulation treatment for VTE in patients with cancer.[27]

The D-dimer level is another predictor of recurrent thrombosis in patients after an unprovoked first episode of VTE. Recurrence rates were found to be higher for patients with positive D-dimer results compared with those with a normal D-dimer level (3.5% vs. 8.9%).[71] The PROLONG study looked at residual venous obstruction, alone and in combination with D-dimer, to predict risk for recurrence after anticoagulation withdrawal following a first episode of DVT. An elevated D-dimer at 1 month after anticoagulation withdrawal appeared to be a risk factor for recurrence, while residual venous obstruction at the time of anticoagulation withdrawal was not.[72,73]

DIAGNOSIS OF RECURRENT THROMBOSIS

The diagnosis of recurrent venous thrombosis can be challenging.[74,75] Previous DVT is a known predictor of risk for venous thrombosis, particularly when the predisposing factor was a nonsurgical condition or if no clinical risk factor was identified.[76] Previous DVT is also a cause for symptoms occurring months or years after the acute event.

Patients with prior DVT may undergo venous duplex ultrasound to evaluate newly recognized (or chronic) leg pain

or swelling; however, abnormal findings may not be indicative of acute thrombosis. Visualized abnormalities may be residua of prior DVT (chronic postthrombotic changes). Residual vein incompressibility or other postthrombotic abnormalities can be found in approximately 80% of DVT patients at 3 months[77,78] and up to 50% at 1 year.[77,79,80]

Distinguishing acute from chronic findings is important, as postthrombotic syndrome is not treated with anticoagulation (in the absence of recurrent thrombosis or another indication). If venous reflux is demonstrated, postthrombotic syndrome may fully explain chronic or persistent symptoms.

There can be recurrent acute thrombosis in an abnormal segment ("acute on chronic" DVT), or there may be new acute DVT in a previously normal venous segment. Imaging findings typical of acute thrombosis, in combination with other chronic postthrombotic changes, suggest the recurrent, acute DVT.

Findings from a single ultrasound imaging study may be insufficient to make the diagnosis of recurrent DVT. Comparison with a prior venous duplex scan is the most reliable means to distinguish new from chronic abnormalities.[81] A study performed after completion of a course of anticoagulation establishes a new baseline for future comparison.[82] This examination can determine the posttreatment status of venous segments previously shown to have acute thrombus, including whether there is persistent occlusive thrombus, partial recanalization or postthrombotic change, or if there has been complete recanalization of the segment. If a subsequent examination is abnormal, comparison with the posttreatment baseline study allows the interpreting physician to distinguish persistent abnormalities from new ones. Late recanalization (9-12 months) after DVT may occur, so imaging findings after DVT should not be assumed to be static over time.[83,84]

When a posttreatment study is unavailable for comparison, the clinical, laboratory, and imaging findings should be considered together.[85] Recurrent DVT is more likely when there are new or persistent risk factors (including malignancy, acute illness, injury, recent surgery, etc.). A normal D-dimer level is a strong indicator that abnormal venous imaging findings are due to chronic postthrombotic changes. An elevated D-dimer level is not diagnostically useful, though.[73] D-dimer testing frequently yields false positive results associated with other conditions (cancer, chronic diseases, advanced age, inflammatory status, infections, etc.).

SUPERFICIAL VEINS

Patients may be referred to the vascular laboratory when symptoms prompt concern for DVT, but other venous problems, including superficial vein disorders, may also need to be considered.[86,87] Examination of the great saphenous vein at the level of the saphenofemoral junction is a routine part of a lower extremity veins evaluation for DVT, but a more thorough evaluation of the superficial veins is needed when patients report symptoms of localized pain, swelling, erythema, palpable venous cord, or painful varicosities. Imaging of superficial veins is also used to determine the suitability of venous segments as conduits for vascular reconstruction.

"Superficial venous thrombosis" (SVT) is the most broadly applicable term to describe thrombotic occlusion of a superficial vein. The term "superficial thrombophlebitis" may be used clinical findings of inflammation are present (pain, tender venous cord, erythema; see Chapter 150).

Inflammation is more common with superficial vein thrombosis than with DVT. The term "suppurative thrombophlebitis" is used when there is bacterial infection of a thrombosed vein.

Thrombosis of lower extremity superficial veins is commonly associated with varicose veins, but 5% to 10% of patients with SVT may have nonvaricose veins. In this setting, phlebitis may be a marker for hypercoagulable conditions, malignancy, vasculitis, or other systemic disease.[73] The Trousseau sign of malignancy, characterized by recurrent, migratory thrombosis in superficial veins, including uncommon sites, such as the torso and upper extremities, is associated with adenocarcinoma, especially of pancreas or lung origin.[88] Inherited (Factor V Leiden, prothrombin G20210A mutation, and MTHFR C677T mutation) and acquired thrombophilias are associated with an increased risk of superficial vein phlebitis and thrombosis, as well as an increased risk of thrombus progression to involve the deep veins.[89] Thrombophlebitis of upper extremity superficial veins most commonly occurs as a complication of venipuncture and intravenous catheter use.[90]

The ultrasound findings used to diagnose SVT are similar to those for DVT: venous distension, incompressibility, intraluminal echogenic material, and the absence of Doppler flow. With inflammation, there can also be vein wall thickening, perivascular edema, and tenderness with examination.

It is important to determine the extent of superficial vein thrombus, as progression of thrombosis on serial examinations, or the proximity of the thrombus to the confluence with the deep system (i.e., saphenofemoral junction), may help guide therapy. Anticoagulation for SVT reduces the incidence of thrombus extension or recurrence in high-risk cases.[89,91] In a single center series of patients with SVT who were not anticoagulated, progression to involve the deep veins was seen in 11%, most commonly though the saphenofemoral junction.[92] Based on observations like these, it has been recommended that great saphenous vein thrombosis in the proximal thigh should be treated with anticoagulation or at least followed by serial duplex ultrasound evaluation.

In a cross-sectional, prospective epidemiologic cohort study of consecutive patients with symptomatic lower extremity SVT, 10% developed thromboembolic complications at 3 months (pulmonary embolism, 0.5%; DVT, 2.8%; extension of SVT, 3.3%; and recurrent SVT, 1.9%), despite therapeutic anticoagulation of more than 60%.[93] Risk factors for complications at 3 months were male sex, history of DVT or pulmonary embolism, previous cancer, and absence of varicose veins.

Evaluation of lower extremity superficial veins is an integral component of examinations of patient with chronic venous insufficiency (CVI). Varicose axial veins (great saphenous and short saphenous veins) and varicose tributaries are assessed for patency, diameter, and their course. As superficial vein anatomy and patterns of varicose vein development are variable, a worksheet with a diagram to illustrate the sonographer's findings

TABLE 23.4 Characteristic of Superficial Vein Segments to Consider Prior Use as Bypass Conduit (Great Saphenous, Short Saphenous, Cephalic, and Basilic Veins)

	Compressibility	Diameter	Other Factors to Be Considered
Findings considered **suitable** for use as bypass conduit	• Fully compressible at all levels • No intraluminal echoes	≥0.25 cm	Vein should be of uniform caliber, without tortuosity
Findings considered **unsuitable** for use as bypass conduit	• Intraluminal echoes • Incompressible • Thickened walls	<0.20 cm	Tortuosity; varicose segments, multiple branches, location superficial to fascia

is particularly useful. Prior to procedures to treat varicose veins, duplex scanning to define the venous segments with reflux and to demonstrate the relationships of varicosities or symptomatic sites to the sources of reflux is needed.

Preoperative imaging helps determine suitability of superficial veins that might be used for creation of an arteriovenous fistula (AVF). Routine preoperative vascular ultrasound improves AVF outcomes in terms of patency and use for dialysis.[94] It can guide the selection of which vein segment to use and which type of procedure to perform. In a randomized, prospective study, the addition of ultrasound imaging to the preoperative assessment was found better than physical examination alone, with a significantly lower rate of immediate technical failure and better rates of fistula maturation to usability. Assisted primary patency at 1 year was significantly better for the ultrasound group (80% vs. 65%, $P = .012$).[95] Upper extremities veins 2.5 mm or greater in diameter are sought for AVF creation,[96,97] although there is no consensus about an absolute threshold. A 2 mm vein may be usable. A larger vein is better.

Ultrasound vein mapping prior to revascularization procedures can assess superficial veins for potential suitability as bypass conduits (Table 23.4).[98] Preoperative vein mapping reduces costs and improves outcomes for patients undergoing infrainguinal bypass surgery.[99,100] Vein mapping in the vascular laboratory or a POCUS examination prior to arteriography provides practical information that can help select between an endovascular intervention or an open surgical approach.

Guidelines for lower extremity vein mapping recommend examinations be performed with the patient in reverse Trendelenburg position using a high frequency transducer.[101] For standard vein mapping, the entire length of the great saphenous and small saphenous vein (if indicated) are evaluated with diameter measurements in transverse views. The vein is evaluated for anomalies or anatomic variants, and large branches are noted. In addition to measuring diameter, the vein is assessed for evidence of prior thrombosis or phlebitis, checking for compressibility, wall thickening, intraluminal echoes, and sclerotic valve leaflets (Fig. 23.11). It may be helpful to mark the course of the superficial veins facilitate positioning of skin incisions.

A venous tourniquet is used to dilate the veins for upper extremity vein mapping.[102] An elastic tourniquet is placed at the axilla for upper arm vein mapping and at the antecubital fossa for the forearm. The diameters of the brachial, cephalic, and basilic veins are measured in transverse view, throughout their course.

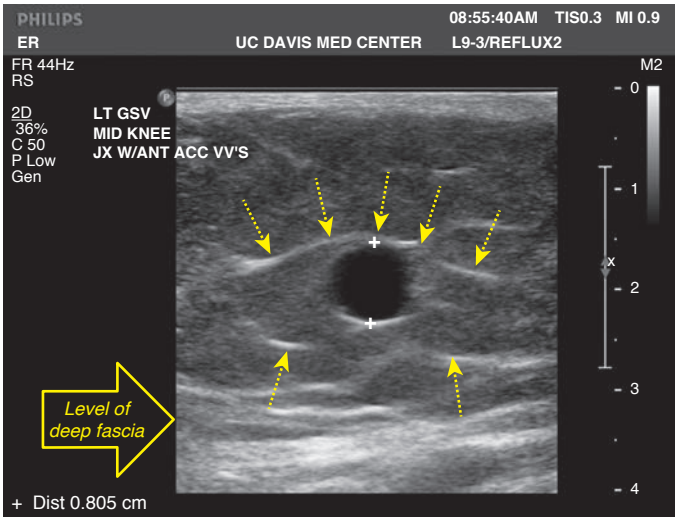

Figure 23.11 Lower extremity superficial veins are measured with electronic calipers. Measurements are performed with the leg in a dependent position. Superficial veins are distinguished from deep veins by their location between the skin and muscular fascia. A layer of subcutaneous fascia envelops the great saphenous vein *(dashed arrows)*.

EVALUATION FOR CHRONIC VENOUS DISEASE: VENOUS INSUFFICIENCY

The vascular laboratory has an integral role in the evaluation of patients with CVI (see Chapter 156).[102a,102b,103-107]

The CEAP system (Clinical-Etiology-Anatomy-Pathophysiology) is a descriptive classification that standardizes reporting and clinical documentation of chronic venous disease.[108] The diagnostic assessments for chronic venous disorders are organized into levels of testing, which may be included in the reporting of CEAP classification:

Level I: office visit, with history and clinical examination, which may include use of a handheld Doppler

Level II: noninvasive vascular laboratory testing, including duplex color scanning and plethysmographic methods

Level III: invasive investigations or more complex imaging studies, including ascending and descending venography, venous pressure measurements, computed tomography venous scanning (CTV), or magnetic resonance imaging (MRV).

The Level II assessment with duplex ultrasound scanning allows for objective evaluation of the affected anatomic levels and locations (A), as well as the pathophysiology (P) involved.

The scanning techniques for venous insufficiency testing evolved from the techniques developed for DVT diagnosis, with increased emphasis on the Doppler evaluation of flow patterns.[50,104,109] The limb swelling and pain associated with acute DVT are due to venous obstruction. CVI is the result of abnormally elevated venous pressure due to outflow obstruction (similar to acute DVT), pathologic reflux, or a combination of the two. Chronic venous stenosis or occlusion can be the cause of continued symptoms. Venous hypertension due to outflow obstruction worsens when limb blood flow is increased. This is the pathophysiologic mechanism of venous claudication.[110,111]

Incompetence of venous valves is the most common etiology of CVI.[112] Valvular incompetence can be primary (without an underlying or antecedent disorder) or secondary, where valvular dysfunction is the result prior venous thrombosis or injury.[113] Competent venous valves and muscular pumping of venous blood are needed to move blood from the lower extremities to the central circulation when upright.[114] When valves are incompetent, the musculovenous pump becomes ineffective. Distal limb pressure is not decreased with walking as it should, and ambulatory venous hypertension results.

A duplex scan for CVI directly evaluates for obstruction by examining the appearance and compressibility of the vein, as well as flow patterns, including assessment with provocative maneuvers to augment antegrade flow or to cause retrograde flow. Indirect findings that may indicate more central venous obstruction include asymmetry in flow velocity, lack of respiratory flow variation, or lack of spontaneous flow.

A 4- to 7-MHz linear array transducer is commonly used, though a lower frequency curved array probe may be useful for large or obese patients. A higher-frequency probe is best for scanning superficial veins. Testing for deep and superficial vein reflux is properly performed with the patient upright, with the lower extremity externally rotated (Fig. 23.12). The heel may be on the ground, with weight bearing on the opposite limb, or a step may be used to offload examined side.[105]

Though some venous valves may be visualized with high-resolution B-mode imaging, the functioning of the bicuspid venous valves is determined observing the direction of blood flow. Normally, in the supine position, venous flow is phasic with respiration. Retrograde flow may be physiologic, as valve closure may not occur if the velocity of the retrograde flow is less than 30 cm/s, too slow to close the valve leaflets. In the upright position, vein valves open to allow antegrade flow, and then snap shut as forward flow ceases and flow reversal commences.

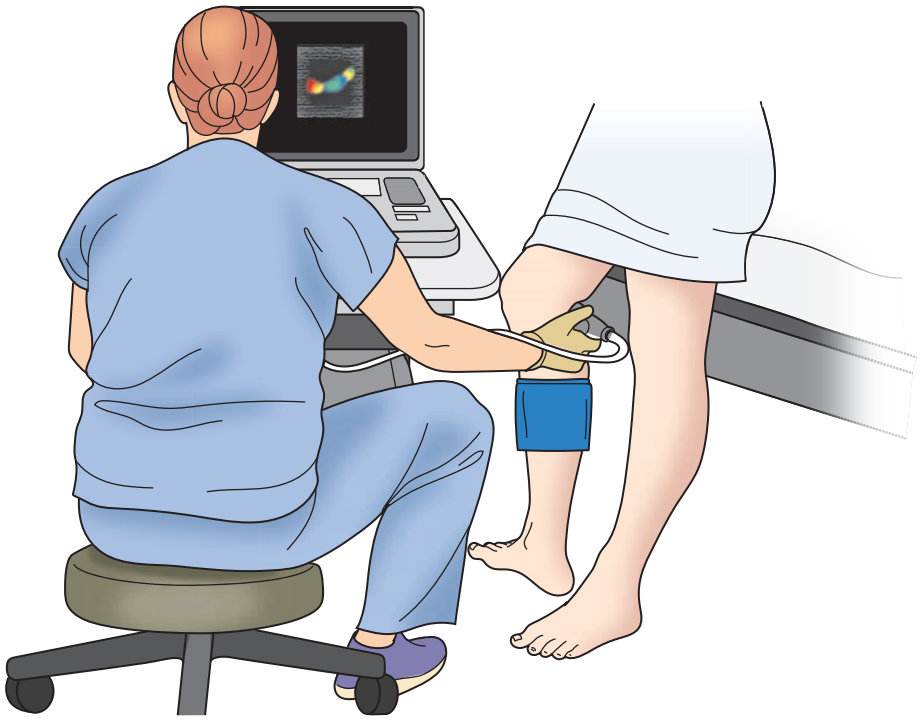

Figure 23.12 Examinations to evaluate for reflux (valvular incompetence) in lower extremity veins should be performed with the patient standing. Reflux is elicited with release of a pneumatic cuff, while imaging the vein approximately 5 cm above the cuff.

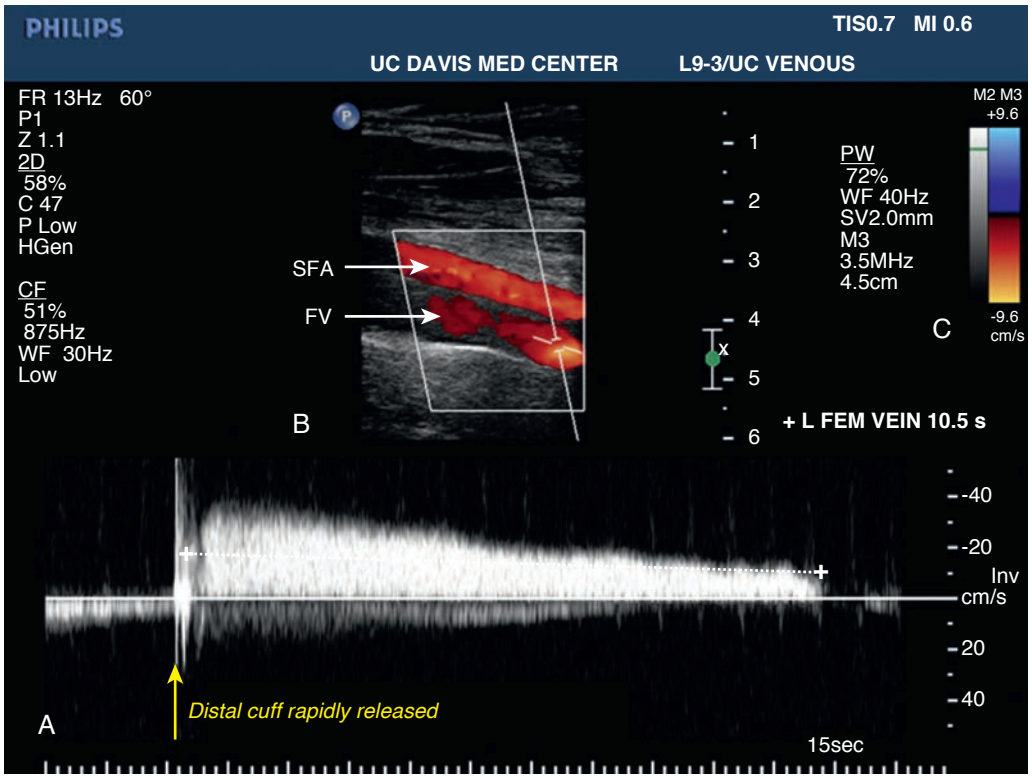

Figure 23.13 Deep Vein Reflux With Standing Examination. (A) Slow antegrade flow is demonstrated with pulsed Doppler waveform. Rapid reversal of flow (negative values shown above baseline) immediately after release of pneumatic cuff on distal thigh. (B) Color flow image shows the same direction of flow in the superficial femoral artery *(SFA)* and the adjacent femoral vein *(FV)*. (C) The color map with red colors below the baseline indicates red color Doppler display indicates flow vector away from the transducer (cephalad to caudal direction in this example).

Venous reflux is defined as retrograde flow of abnormal duration (Fig. 23.13). Venous reflux can be characterized as axial if there is uninterrupted retrograde flow from the groin to the calf. Segmental reflux involves only some segments of the venous system, while other segments retain competent functioning valves.[115]

Techniques to elicit reflux include increasing intraabdominal pressure using a Valsalva maneuver (for the common femoral vein or the saphenofemoral junctions) or by manual compression and release of the limb distal to the point of examination. The preferred method, however, is to use a standardized technique with calibrated inflation and rapid (less than 0.3 seconds) deflation of a pneumatic cuff applied distally on the limb.[116] The advantage of the distal cuff deflation technique was emphasized by van Bemmelen et al.[117] This technique, when performed in the standing position, ensures sufficient retrograde flow to achieve the closure of normal valves. The supine position should not be used for reflux testing, as both false-positives and false-negatives result.[116,118]

A prospective study to establish the upper limits of normal for the duration of retrograde flow in lower extremity veins suggested that the cutoff value should be 1.0 seconds for identifying deep vein reflux in the femoral and popliteal veins; the cutoff value to define reflux should be greater than 0.5 seconds in the superficial veins and the deep veins of the calf; and outward flow in perforating veins should be considered abnormal if greater than 350 ms.[119] A different multicenter study suggested a 0.5 second threshold for defining reversed venous flow as abnormal could be used for all veins.[120] Use of this standard value may provide diagnostic sensitivity. Diagnostic reports should include the measured reflux time in each examined vein, the patient's position (if not standing, the reason), and the provoking maneuver used.

PERFORATING VEINS

Perforating veins in the lower extremities connect the superficial veins to the deep veins.[120a] They pass through the fascia that separates the muscular compartments from the subcutaneous tissue. Normal venous flow is from superficial to deep, but valves are only present in larger perforators. Perforating veins less than 1 mm in size do not have valves.

Scanning of perforators is best done with imaging in the transverse plane, focusing on boundary between the deep and superficial compartments, looking for the interruptions in the fascia through which the perforating veins pass. Flow in perforating veins may be bidirectional, but reflux is diagnosed when there is net outward (deep to superficial) flow (Fig. 23.14).

Perforating veins may be evaluated selectively, for example, for patients with advanced disease or when evaluating recurrent varicose veins.[109] The finding of a perforating vein greater than 3.5 mm is associated with demonstrable perforator reflux in 90% of patients.[121]

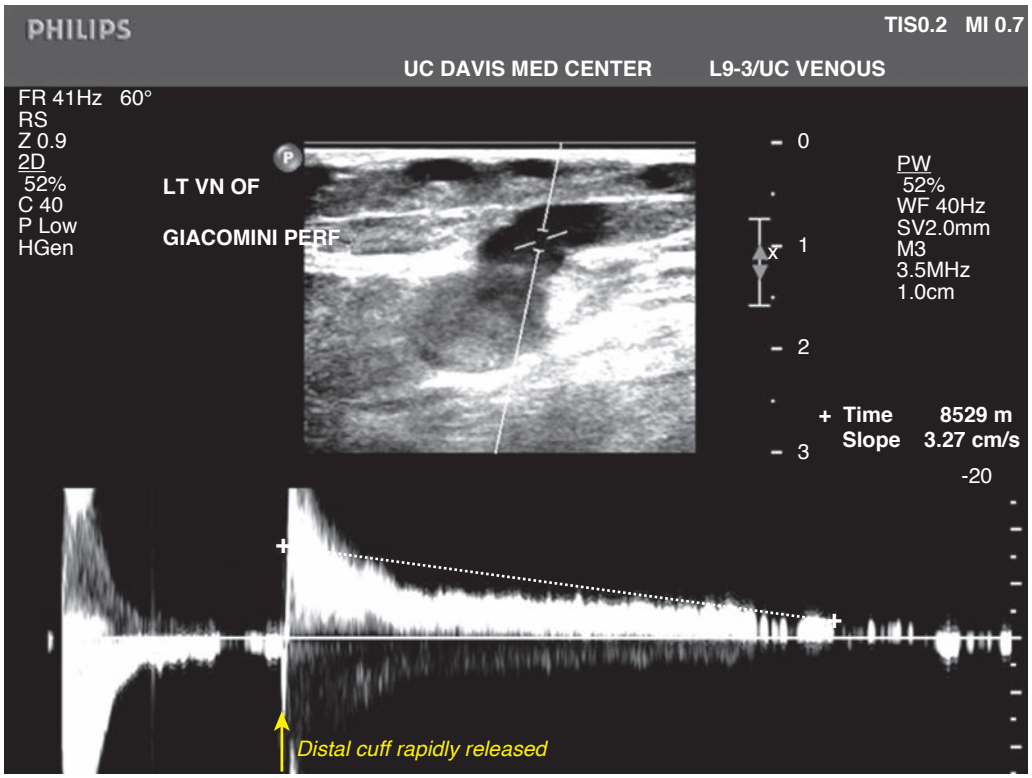

Figure 23.14 Reflux in an Incompetent Perforating Vein. Rapid reversal of flow (negative values shown above baseline) immediately after release of pneumatic cuff on proximal calf. Though the lumen of the vein deep to the fascia appears echogenic, this is an artifact from high gray-scale gain setting. The fascial gap measured 0.52 cm. Large perforators often have incompetent valves.

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Liem TK. Duplex ultrasound for acute venous disease. In: Gloviczki P, ed. *Handbook of Venous and Lymphatic Disorders: Guidelines of the American Venous Forum*. 4th ed. Boca Raton, FL: CRC Press, Taylor & Francis Group; 2017:141–150, [chapter 12].

The American Venous Forum (AVF) is a multidisciplinary, international medical society that promotes research, education, and clinical care for all aspects of venous disease, including diagnosis, pathophysiology, and treatment. The fourth edition of the AVF Handbook of Venous and Lymphatic Disorders *serves as an up-to-date reference for vascular surgeons and specialists in vascular medicine. Chapter 12 addresses the diagnosis of deep vein thrombosis.*

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Chapter 13 of the AVF Handbook of Venous and Lymphatic Disorders *addresses duplex scanning for venous insufficiency.*

Section V. Peripheral Venous. In: Zierler RE, Dawson DL, eds. *Strandness's Duplex Scanning in Vascular Disorders*. 5th ed. Philadelphia: Wolters Kluwer; 2016:223–283.

Dr. D. Eugene Strandness, Jr., first published his textbook on duplex scanning and its applications in 1990. Dr. Strandness died in 2002, just as the third edition was published. Subsequent editions by his former trainees and colleagues expanded and updated the content. The Strandness textbook now includes clinical perspectives, techniques of scanning, and discussions of applications and pitfalls of vascular laboratory tests. The book is intended as a comprehensive text for residents, fellows, and vascular laboratory professionals. Section V includes chapters on acute lower extremity DVT, upper extremity venous thrombosis, and chronic venous disorders.

Clinical Practice Guidelines

American Institute of Ultrasound in Medicine; American College of Radiology; Society of Radiologists in Ultrasound: Practice guideline for the performance of peripheral venous ultrasound examinations. *J Ultrasound Med*. 2011;30(1):143-150.

Guidelines for venous duplex scanning developed by ultrasonographers and radiologists, with representation from several organizations, including the American Institute of Ultrasound in Medicine (AIUM). The AIUM was established in 1952 as a multidisciplinary organization when uses of ultrasound for medical diagnosis were first being explored.

Barleben A, Bandyk DF. Interpretation of peripheral venous duplex testing. *Semin Vasc Surg*. 2013;26(2–3):111–119. doi:10.1053/j.semvascsurg.2014.01.001.

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Coleridge-Smith P, Labropoulos N, Partsch H, et al. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs—UIP consensus document. Part I. Basic principles. *Eur J Vasc Endovasc Surg*. 2006;31(1):83–92.

This paper reports on an initiative of the Union Internationale de Phlébologie (UIP) to establish a consensus on the methods to be used for duplex

ultrasound examination, the interpretation and reporting of images and measurements obtained, and recommendations on training vascular laboratory personnel.

Cavezzi A, Labropoulos N, Partsch H, et al. Duplex ultrasound investigation of the veins in chronic venous disease of the lower limbs—UIP consensus document. Part II. Anatomy. *Eur J Vasc Endovasc Surg*. 2006;31(3):288–299.

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Intersocietal Accreditation Commission—Vascular Testing. IAC Standards and Guidelines for Vascular Testing Accreditation. *Section 4B: Peripheral Venous Testing* 2018; http://intersocietal.org/vascular/standards/IACVascularTestingStandards2018.pdf.

The Intersocietal Accreditation Commission—Vascular Testing (previously the Intersocietal Commission for the Accreditation of Vascular Laboratories) has been the primary organization for vascular laboratory accreditation since 1991. IAC standards, developed by subject matter experts in vascular surgery and other specialties, represent standards of practice in noninvasive vascular testing, including venous duplex scanning.

Lee BB, Nicolaides AN, Myers K, et al. Venous hemodynamic changes in lower limb venous disease: the UIP consensus according to scientific evidence. *Int Angiol*. 2016;35(3):236–352.

The Union Internationale de Phlébologie (UIP) commissioned a large group from member societies, including the European Venous Forum (EVF), American Venous Forum (AVF), American College of Phlebology (ACP), and Cardiovascular Disease Educational and Research Trust (CDERT), to provide a comprehensive review of venous hemodynamic concepts underlying the pathophysiology of lower limb venous disorders. Chapters include basic hemodynamic concepts and normal venous physiology; the mechanism and magnitude of hemodynamic changes in acute deep vein thrombosis; hemodynamic changes that occur with chronic venous disease; and hemodynamic changes resulting from treatment by compression, drugs, and surgical or endovenous ablation, as well as other topics.

A complete reference list can be found online at www.expertconsult.com.

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24 CHAPTER

Radiation Safety

AMY B. REED

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Advances in radiation have led to a significant increase in its use for diagnostic, interventional, and therapeutic purposes. With the ever-increasing utilization of endovascular techniques, concern has grown regarding the potential harmful effects of radiation delivered to both the patient and the operator. Although radiation exposure from diagnostic procedures is generally low and comparable to natural background doses, therapeutic use of radiation involves a higher level of exposure, which can be harmful if not controlled.[1] Surgeon education on appropriate use of fluoroscopic equipment has been shown to be beneficial in decreasing radiation exposure.[2]

Radiation poses risk to workers and patients alike. Many medical specialists operate medical x-ray equipment frequently. Operating room assistants are often not properly educated regarding the potential damaging effects of radiation and are not trained to minimize exposure to themselves or to the patient. Patients may undergo procedures without being properly informed of the risks. These deficiencies may result in unnecessary exposure to both patients and staff.

The concern about radiation exposure is particularly pressing in the field of vascular surgery, where endovascular procedures have evolved to be the mainstays of clinical practice. Percutaneous angioplasty and stenting of peripheral and carotid arteries, as well as endovascular stent-grafts for treating abdominal and thoracic aortic diseases are now first-line treatment options. Advanced techniques such as fenestrated and branched endografts for complex thoracoabdominal aneurysms may carry significant radiation exposure to surgeons and the patient. Computed tomography angiography (CTA) as a primary modality of investigation and follow-up has become widely accepted in vascular surgery and is emerging in cardiology with the advent of coronary CT scanning. Given the incidence of coronary disease in a vascular surgery patient population, the potential exists for significant radiation exposure over the patient's lifetime.

Abstract

Vascular surgeons are performing an increasing number of endovascular treatments for their patients. These procedures vary from straightforward peripheral interventions to complex branched aortic endovascular aneurysm repair. As the complexity increases, concern grows with regard to radiation exposure for both patient and physician. Surgeon education is paramount in reducing radiation exposure and decreasing possible radiation-induced injuries.

Keywords

minimizing dose
stochastic effects
deterministic injury
skin injury

The principles of radiation safety have been well addressed by a number of national bodies—for instance, the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP). These organizations provide valuable resources and publications that disseminate information and recommendations about radiation exposure and protection. This chapter serves to familiarize vascular surgeons with terminology, metrics regarding dose, radiation-induced injury, and techniques to lower radiation dose.

TYPES OF RADIATION

Radiation is a form of energy emitted as electromagnetic waves or particles. It can be classified as nonionizing (ultrasound, magnetic resonance, laser, microwaves) or ionizing (x-rays, gamma rays). Nonionizing radiation does not possess the energy to ionize atoms of the absorbing matter. Ionizing radiation consists of alpha and beta particles, neutrons, and energetic photons (ultraviolet and above), which contain sufficiently high energy to interact with atoms and produce biologic injury. The most common forms of ionizing radiation used in medicine are x-rays, gamma rays, beta rays, and electrons.

MEASUREMENT

The amount of ionization that radiation produces in air, measured in roentgens (R), does not accurately reflect its potential to cause biologic injury. More important, the actual damage or biologic effect of radiation depends on the total energy of radiation absorbed per unit mass, the sensitivity of the organ, and the actual strength of the radiation. To quantify radiation for the purposes of risk assessment and setting standards and limits, the terms *absorbed dose*, *equivalent dose*, and *effective dose* are commonly used (Table 24.1).

Absorbed Dose

The absorbed dose is a measure of the amount of energy deposited in a medium by ionizing radiation per unit mass of matter and is equal to the amount of heat generated by the radiation per tissue weight in a specified material. The International System (SI) unit for absorbed dose is the gray (Gy), named after Louis Harold Gray, a British physicist. One gray equals 1 joule (J) of energy absorbed per kilogram (J/kg). Previously, the unit most commonly used was the "radiation absorbed dose (rad)" (1 Gy = 100 rad). The absorbed dose is not a good indicator of biologic effect because different ionizing radiation produces different degrees of damage.

TABLE 24.1 Units of Radiation

Measurement	Unit	Measures	
Radioactivity	Curie	Number of particles/sec from 1 g of radium	
Ionizing radiation	Roentgen (R)	Charge/unit mass	1 R = 2.58 × 10^{-4} C/kg
Absorbed dose	Rad	1 rad = 0.01 J/kg	1 rad = 0.01 Gy
	Gray (Gy)	1 Gy = 1 J/kg	1 Gy = 100 rad
Equivalent dose/ effective dose	Rem	Rem = rad × W	1 rem = 0.01 Sv
	Sievert (Sv)	Sv = Gy × W	1 Sv = 100 rem

W, Weighting factor.

Equivalent Dose

The equivalent dose is a measure of the radiation dose to tissue and takes into account the different degrees of damage by different types of radiation by introducing a radiation weighting factor (W_R). The SI unit of equivalent dose is the sievert (Sv), named after Rolf Sievert, a Swedish physicist. Thus equivalent dose = absorbed dose × W_R. (Another unit, the roentgen equivalent man, or rem, is still sometimes used; 1 Sv = 100 rem.)

W_R is calculated by the type of radiation (1 for x-rays and gamma rays and 3-10 for protons and neutrons). The sievert better describes the biologic effect of radiation and is commonly used when risk from ionizing radiation is assessed. It also allows quantification of risk and comparison to other commonly encountered modes of exposure. For fluoroscopic interventions in vascular surgery, the sievert and gray are roughly equal (absorbed dose = equivalent dose).

Effective Dose

Because different tissues and organs have different sensitivity to radiation, the concept of effective dose is introduced to take into account the part of the body irradiated and the volume and time over which the dose is applied. The effective dose is formed by weighting the equivalent dose by another tissue weighting factor (W_T), according to the distribution of radiation and the radiosensitivity of various organs. To avoid confusion, W_R and W_T are sometimes grouped together into one single weighting factor (W). The effective dose is also measured in sieverts.

Effective dose in radiation protection can be used prospectively for planning and optimization of radiation protection, as well as retrospectively for assessment of risk. It is mainly used as a protective and regulatory quantity and not for epidemiologic study of populations. It does not give a precise indicator of an individual patient's risk; there is no consideration of patient age, gender, or other confounding factors.

Because grays and sieverts quantify relatively large amounts of radiation, in medical use radiation is typically described in milligrays (mGy) or millisieverts (mSv).

BIOLOGIC EFFECTS OF RADIATION

Ionizing radiation damages living cells, which can repair themselves, die, or undergo a mutation. The effects of radiation on biologic tissue are generally classified as two types: deterministic effects and stochastic effects.

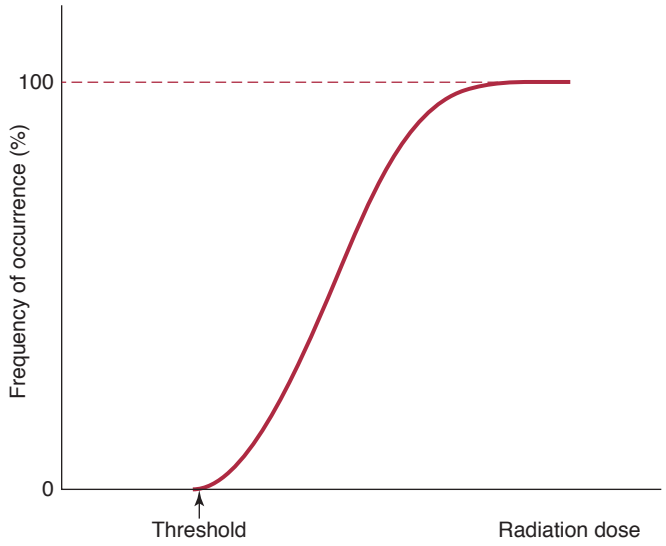

Figure 24.1 General dose-response curve for the deterministic effects of radiation.

TABLE 24.2 Deterministic Effects and Threshold Doses of Radiation

Organ	Effects	THRESHOLD EFFECTIVE DOSE (Sv)	
		Single Dose	Multiple Yearly Doses
Gonads	Temporary sterility	0.1	0.4
	Permanent sterility	3-6	2
Eye	Cataracts	0.5	0.2
Bone marrow	Marrow depression	0.5	0.5
Skin	Transient erythema	2	—
	Desquamation	2-10	—
	Temporary hair loss	4	—
	Dermal necrosis	25	—
	Skin atrophy	10	1
Whole body	Acute radiation sickness	1	—

Modified from the International Commission on Radiological Protection guidelines.

Deterministic Effects

Deterministic effects are dose dependent and result in cell death, impacting hair follicles, skin, subcutaneous tissues, and the lens of the eye. These are acute events when a threshold level of radiation has been exceeded, and the higher the dose, the greater the injury (Fig. 24.1). The threshold is not absolute and can vary among individuals. Table 24.2 shows some threshold levels of human organs with corresponding deterministic effects. Doses required to produce deterministic effects are often large and exceed 1 to 2 Sv. Symptoms arise when a significant proportion of cells are killed by radiation, and subsequent inflammation or fibrosis may produce additional damage to the organ. Examples of deterministic effects include radiation dermatitis, cataracts, infertility, and organ atrophy or fibrosis (Figs. 24.2 and 24.3). Recently, concerns have increased about the late manifestation of cataracts from low doses of ionizing radiation, and the recommended threshold of the lens has been lowered to 0.5 Sv.

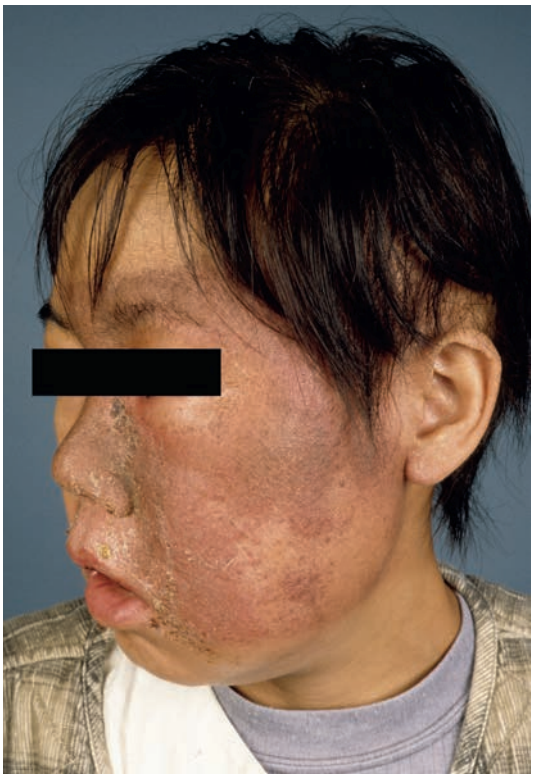

Figure 24.2 Radiation dermatitis of the face.

Whole-body exposure to 10- to 20-Gy high-energy radiation, delivered at one time, can be fatal to humans. For acute whole-body equivalent doses, 0.5 to 1 Sv may produce light radiation sickness; 1 Sv causes slight blood changes; and 2 to 3 Sv causes nausea, hair loss, and hemorrhage. An acute dose of 3 Sv causes death in 50% of individuals within 30 days, and with doses higher than 6 Sv, survival is unlikely.

Stochastic Effects

Stochastic (or probabilistic) effects cause DNA damage to single cells, which results in mutation. This is an all-or-none phenomenon, with the probability of occurrence increasing as the cumulative radiation exposure increases without an established threshold level (Fig. 24.4). The severity of the effect of mutation is unrelated to the dose. Mutations lead to cancer and heritable genetic defects. Theoretically, stochastic effects can occur even at low doses, but it is assumed that with radiation doses of less than 100 mSv/yr, the probability of stochastic effects is very low. At such low doses, it is assumed that the probability of incurring cancer or heritable effects will be directly proportional to the equivalent dose. This is known as the linear-nonthreshold model of incremental risk.

Leukemia and other cancers have been shown to be associated with radiation exposure. It is estimated that the probability of

Figure 24.3 Radiation-induced skin necrosis.

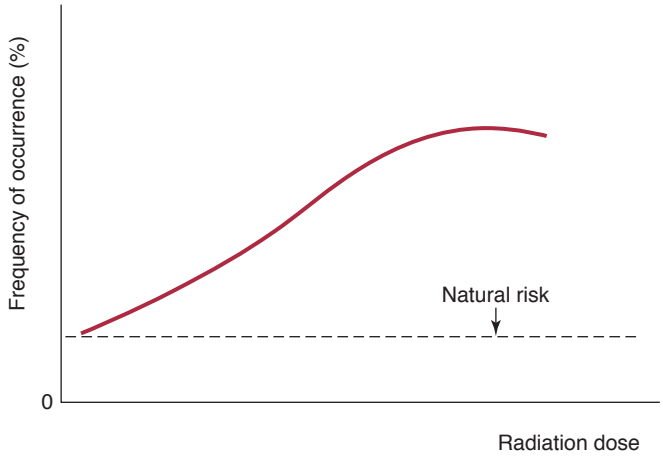

Figure 24.4 General dose-response curve for the stochastic effects of radiation.

fatal cancer developing as a result of radiation exposure is 4% per 1 Sv of lifetime dose equivalent (or 0.004% per mSv). The background risk of spontaneous fatal cancer is around 20%. The nominal nonfatal cancer risk has been estimated at 0.8% per sievert. Radiation-induced cancer risks from relatively low-dose exposure are difficult to interpret. A statistically significant increase in cancer risk has not been demonstrated in populations exposed to doses of less than 100 mSv. Studies of atomic bomb survivors showed an increased incidence of leukemia and other tumors of the lungs, thyroid, breast, skin, and gastrointestinal tract. There is usually a latent period of 2 to 5 years for leukemia, about 5 years for thyroid cancer, and 10 or more years for other cancers to become manifested. The risk with antenatal exposure and for children and adolescents is slightly higher by a factor of 2 to 3, whereas for older adult patients, the relative risk of malignancy is lower. Fetal effects are discussed in the "Radiation and Pregnancy" section later in this chapter.

Hereditary effects from radiation exposure have not been observed in humans from studies of the offspring of atomic bomb survivors. Based on extrapolation from animal studies, the ICRP proposed a nominal risk of heritable effects of 0.1% per sievert.

TABLE 24.3 Background and Occupational Exposure

Occupation	Effective Dose (mSv/Yr)
Natural background radiation	3
Aircrew (1000 h)	5
Frequent flyer (75,000 miles/200 h)	1
Catheterization laboratory physician	2-60
Catheterization laboratory nurse	8-16

EXPOSURE AND RECOMMENDED LIMITS

Background Radiation

We are constantly exposed to radiation through naturally occurring radioactive materials, as well as by cosmic radiation and human activities. The average annual natural background radiation, which varies depending on the geographic location, is around 3 mSv/yr in the continental United States. Living at higher altitude is associated with a higher dose. The greatest source of domestic radiation is radon gas (about 2 mSv/yr). Radon arises from the decay of radium; it seeps out of the soil and may concentrate in poorly ventilated concrete homes because of its high density. Radon is the second most frequent cause of lung cancer after cigarette smoking. Other manmade radiation sources include building materials, fuel, televisions, smoke detectors, and various fluorescent devices.

Occupational and Medical Exposure

For the general public, about 80% of lifetime exposure to radiation comes from natural sources and the rest from manmade sources such as medical radiographs and CT scans. The total average exposure for Americans is about 3.6 mSv/yr. In the United Kingdom, the average yearly dose is about 2.2 mSv. Some of the common occupation-related radiation dosages are addressed in Table 24.3. Pilots, who are exposed to solar radiation, are at a higher risk. On average, the amount of cosmic radiation doubles with every 2000-mile increase in altitude; cosmic radiation is strongest at the poles. Taking a long-haul commercial flight results in about 0.1 mSv of radiation.

The typical doses of common diagnostic radiology examinations are given in Table 24.4. These values vary, depending on the machine and manufacturer, the study technique, and patient's build.

TABLE 24.4 Typical Effective Dose in Common Diagnostic Procedures

Examination	Effective Dose (mSv)
Chest radiograph (PA)	0.02
Chest radiograph (lateral)	0.04
Skull radiograph	0.03
Pelvic radiograph	0.7
Abdominal radiograph	1.0
Thoracic spine (AP)	0.4
Lumbar spine (AP)	0.7
Mammogram	0.1
Barium swallow	1.5
Barium enema	7.0
CT of the head	2
CT of the thorax	8
CT of the abdomen	10
CT of the pelvis	10
Cardiac CT (calcium score)	2
Coronary angiogram	5-15

AP, Anteroposterior; *CT*, computed tomography; *PA*, posteroanterior.

TABLE 24.5 International Commission on Radiological Protection Safety Dose Limits

	Occupational	Public (mSv/yr)
Whole-body effective dose	20 mSv/yr averaged over 5 years	1
Ocular lens	20 mSv/yr	15
Skin	500 mSv/yr	50
Extremities	500 mSv/yr	—
Pregnant women	1 mSv to the fetus	—

Recommended Dose Limits

The ICRP recommends a dose limit of 1 mSv/yr to the general public. For radiation workers, an effective dose limit is 20 mSv/yr, averaged over 5 years and not exceeding 50 mSv in any single year. Additional exposure limits for the ocular lens and extremities of workers are defined separately (Table 24.5). It is generally believed that for occupational exposure, the risk of health effects is too small to be observed at doses below 50 to 100 mSv/yr.

PRINCIPLES OF RADIATION PROTECTION

The ICRP system of protection in medical practice stresses the fundamental principles of justification, optimization of protection, and dose and risk limits. The use of radiation in medicine must be justified—that is, the diagnostic information or therapeutic use should produce more benefit than harm. It is the responsibility of the hospital and medical personnel to ensure that the radiation equipment is properly maintained to deliver the lowest possible dose of radiation and to ensure that safety instructions and protective measures are available and adopted. All procedures involving ionizing radiation should be monitored and the risk limits determined for patients and staff beforehand. A system of reporting and remedial measures should be in place whenever the recommended limit is exceeded. In addition, special operating procedures should be available for high-risk individuals, such as pediatric patients and pregnant workers.

RADIATION SAFETY: DIAGNOSTIC PROCEDURES

For diagnostic procedures, an alternative imaging modality that does not involve radiation, such as magnetic resonance imaging or ultrasound scans, should be considered whenever possible. Certain routine radiographs and screening tests, such as chest radiographs on hospital admission and skull radiographs for minor head injuries, are shown to be nonbeneficial and should be avoided.

CT has become one of the most commonly used diagnostic tools, largely because of the availability of faster, more powerful machines with multislice capabilities, thus reducing examination time and increasing accuracy. Contrary to common belief, the effective dose of spiral CT and multislice detector CT can be 10% to 30% higher than that for older CT scanners, depending on the protocol and machine. In less essential situations, the physician should request lower-dose examinations, wider pitch, and partial rotation instead of large numbers of overlapping scans of extensive body regions. A number of techniques such as automated tube current modulation or attenuation-based kilovoltage selection algorithm can be used to reduce radiation exposure for CT angiograms after endovascular aneurysm repair (EVAR).

Many patients receive CT angiography and also serial CT scans for follow-up of endovascular aortic procedures. The effective dose of a CT scan of the chest is about 8 mSv, and for the abdomen and pelvis it is about 10 to 20 mSv (see Table 24.4). Repeated examinations of large areas may deliver an effective dose that can approach harmful levels. The excess relative risk of a patient acquiring solid organ malignancy from postoperative CT scans in EVAR surveillance is higher in young patients, women, and multiple examinations. A policy of switching to standard or contrast-enhanced ultrasound scans for postoperative EVAR surveillance has been shown to be equally effective even for fenestrated grafts; this will further reduce exposure to radiation.[3]

Three-dimensional rotational angiography (DynaCT) has recently found a role in preoperative planning, especially under emergency situations, and also in postoperative identification of endoleaks. The mean dose area product for a DynaCT is in the region of 3500 to 4000 μGy m^2, which is seven to eight times less than the radiation from a standard multidetector CT.[4]

Consideration should be given to the patient as a whole during imaging. Sometimes higher-risk organs may be exposed to unnecessarily high doses even if they are not the targets of the examination. For example, the lens, thyroid, and breast in CT examinations of the head and thorax often receive doses as high as 30 to 40 mSv. The gonads are also at risk during CT scans of the pelvis. This is particularly important for younger patients and females of childbearing age. Every effort should be made to shield radiosensitive organs whenever possible—in particular when they are adjacent to but not part of the actual radiographic examination.

RADIATION SAFETY: ENDOVASCULAR PROCEDURES

Modern coronary interventional procedures incur an average dose of 0.05 mSv per procedure. Radiation exposure for an operator in modern catheterization laboratories can amount to 5 to 60 mSv/yr. The hands are at particular risk. One minute of unprotected screening time leads to 20 mSv of skin dose, and transient skin erythema can result from doses of 2 Sv. Higher doses of radiation can lead to eye damage characterized by cataract formation in the posterior pole of the lens. Chronic exposure will increase the risk of cancer, in particular in the thyroid, brain, and skin.

Although most endovascular procedures are usually performed on older patients, in whom the perceived stochastic risks are relatively small, one must always be conscious of the radiation dosage to reduce the probability of deterministic effects to skin, soft tissue, and the eyes. The typical exposure of a patient in a catheterization laboratory with 10 minutes of fluoroscopic time is estimated to be equivalent to 200 to 400 chest radiographs.

The operator in an interventional suite is responsible for the amount of radiation exposure to the patient and coworkers. Fluoroscopy should be intermittent and never used unless the operator is looking at the monitor. Only essential personnel should be in the room, and ample warning signs should be displayed at all entrances. All staff not essential to the procedure should leave the room during serial exposure sequences or stand behind a barrier shield. Good practice in minimizing patient exposure will also cut down exposure to the operator and assistant staff.

Radiation equipment should be regularly serviced and inspected by a medical physicist and calibrated at proper intervals. Standard radiation checklists should be used regularly for self-inspection. The radiation dose varies among different machines and room setups. In general, newer machines and fixed systems generate lower energy because of a better image intensifier. They also incorporate more dose-reducing features such as pulse fluoroscopy and provide better-quality images, thus further reducing imaging time. Operators should try to familiarize themselves with these safety features to maximize radiation protection.

High dosages during interventional procedures are often due to inappropriate use of equipment or poor technique. The following are essential practice guidelines to reduce radiation exposure.

Emission Control

The voltage of the fluoroscopic tube controls the penetration of the beam and contrast, whereas the current determines the number of photons produced by the tube. Most machines have an automatic exposure control based on the feedback from the image receptor. Using higher tube voltage (kVp) and less current (mA) will reduce radiation and will not usually affect image quality. Lower frame rates should be adopted, and pulsed fluoroscopy instead of continuous fluoroscopy should be used for less critical maneuvers. In pulsed fluoro the x-ray generator emits short bursts of energy, which decreases the exposure time compared with continuous fluoroscopy. Higher dose fluoroscopy modes often increase the pulse rate, thereby further increasing dose. A large image intensifier requires less radiation than does a small one. The use of magnification should be limited because magnified views incur two to three times the radiation of a normal view. The use of high-level fluoroscopy should be kept to a bare minimum. X-ray field collimation and filters should be used whenever possible. This helps in focusing the beam of radiation by decreasing the field of view, thereby allowing for a clearer image. A large patient will expose the operator to more radiation because of an automatic increase in voltage and current from the machine to obtain a satisfactory image.

Time

Every effort should be made to minimize fluoroscopy and screening time. A conscientious operator will refrain from continuous activation of the beam-on switch and instead perform intermittent short exposures only when necessary. When the table position must be changed, it should be done before confirming with fluoroscopy. Liberal use of fluoroscopy often accounts for the largest radiation exposure during a procedure. Safety features are built into modern equipment to alert the operator to excessive use. A timer usually produces an audible warning at the end of a 5-minute interval. Making a habit of noting the total fluoroscopy time and patient absorbed dose at the end of the procedure may increase awareness and motivate improvement in practice.

Digital subtraction angiography is used to acquire images and generate a permanent record, and it requires high-dose rapid-sequence screening. This procedure can result in 10 times more radiation than fluoroscopy and accounts for 60% of total personnel doses. The use of cinefluoroscopic acquisition should be limited and an attempt made by operators to maintain a distance (or leave the room) when activating this function.

Distance

Personnel should always maintain a distance from the x-ray tube and keep the image intensifier as close to the patient (and the tube as far away) as possible to reduce patient skin dosage.

The amount of scatter radiation decreases with the square of the distance from the tube (exposure = $1/d^2$); thus the radiation dose will diminish fourfold if the distance from the operator doubles. Transfemoral procedures will therefore incur less exposure than transbrachial procedures will.

Radiation exposure varies according to the angulation of the tube. The left anterior oblique view exposes the operator (on the right of the patient) and the anesthetist to the greatest amount of radiation because the tube is closest to the operator. This view can account for three to five times more radiation than a right anterior oblique view. Steep gantry angulations also increase exposure by increasing the length of the radiation path and the thickness of tissue penetration. Changing the beam angulation during prolonged procedures can help spread out the radiation and reduce the skin dose to a particular area.

Maximizing the source (radiation) to the patient distance decreases as a function of the inverse square law. Raising the fluoroscopic table as high as possible from the source decreases the radiation. Once the table is raised to a comfortable height as high as possible away from the source, the image intensifier should be lowered as close as possible to the patient. A recent study on scatter radiation levels using cadavers showed that operator radiation exposure is lowest with a detector-to-patient distance of <5 cm, a source-to-image distance of <15 cm, and a 10-cm vertical collimation. The assistant's exposure is 23% to 46% of the operator's.[5]

Barriers

Radiation scatter is not uniform but propagates in isodose curves and decreases exponentially with the distance from the table. The highest scatter exposure is at the table level. A modern interventional suite should be equipped with tableside lead shields and additional mobile shields to reduce scatter. Ceiling-mounted mobile acrylic shields are very effective and will reduce doses to the brain and eye by a factor of 20. The first operator should always try to stand behind a barrier for the entire procedure.

Properly worn personal protective equipment is essential. Staff members should wear protective aprons with at least a 0.25-mm lead equivalent; many modern lightweight models provide wraparound designs to maximize frontal protection. A 0.25-mm lead apron will attenuate approximately 96% of the dose, and a 0.5-mm apron, 99%. The front of the apron should be kept toward the x-ray tube at all times. Lead glasses and thyroid shields should always be worn. Protective gloves should be at least a 0.35-mm lead equivalent but are less widely used because of reduced tactile sensitivity. All protective gear should be inspected at least yearly and replaced if defective.

Technique

The primary operator should possess the necessary endovascular skills to perform the procedure. Even a straightforward procedure can result in significant radiation exposure if the operator's technique and protection practice are poor.

Monitoring Exposure

In a work environment, radiation dosage should be monitored by dosimeters—one worn at waist level under the apron and, ideally, a second one worn on the thyroid shield. These are usually film-badge–based, thermoluminescent dosimeters that measure an absolute dose received over a specific period of time. An investigation is necessary when the cumulative total dose during a year reaches recommended ICRP limits, and temporary withdrawal from radiation work should be enforced.

Informed consent and proper recording of patient exposure should be ensured if the anticipated dose of a complicated procedure is high. Discussion should be undertaken with the patient and family immediately after a complicated procedure to inform them of the high use of radiation and possible development of skin reactions or changes on the back or side. If a patient is exposed to a higher dose (>3 to 5 Gy), follow-up should be arranged within 1 to 2 weeks to determine whether any harmful effects have developed.

RADIATION AND THE ENDOVASCULAR SURGEON

Endovascular therapy has become more complex, and many hospitals have modern hybrid suites installed to replace mobile C-arms. Although these fixed units provide much better image quality and have no overheating issues, operators may become oblivious to fluoroscopy time and the use of image acquisition and magnification during a more complex case.

Few studies have been completed on the radiation exposure of vascular surgeons undertaking endovascular procedures. Ho and colleagues conducted a prospective study on an active endovascular practice in an academic unit over a 12-month period.[6] All endovascular procedures were performed with mobile fluoroscopic units in an operating room setting, using tableside barriers, standard 0.5-mm lead aprons, thyroid shields, and protective eyewear. The workload consisted of an average of 150 endovascular procedures, including 30 endovascular aneurysm repairs, 60 diagnostic angiograms, and 60 peripheral angioplasty and stenting procedures. With an average of 500 to 700 minutes of annual fluoroscopy time, the median yearly effective doses that the surgeons received were 0.2, 0.2, and 1 mSv for the body, eye, and hand, respectively—these amounts are significantly below ICRP recommended dose limits. It was extrapolated that a vascular surgeon has to perform 2600 endovascular aneurysm repairs or 6500 peripheral procedures annually to reach the dose limit.

Provided that a stringent protection policy is used, the amount of radiation absorbed by vascular surgeons appears to be lower than that absorbed by cardiologists and interventional radiologists, who reportedly receive up to 60 and 10 mSv annually. However, the study also revealed significant individual variations in dosage, probably related to technique and habit. This difference was most marked for doses to the hand, in which case less experienced surgeons accumulated up to 3.3 times the dosage per minute for the same procedure used by more experienced

surgeons. Regular use of eye protection also reduced eye doses by a factor of 3.

Recently, a number of studies focused on the radiation exposure of patients during EVAR, using indirect dose area product (DAP) measurement.[7-11] An estimated average effective dose of 12.4 mSv was reported based on DAP estimation in 111 EVAR cases, and average peak skin dose was 0.69 Gy, with 99% of patients having a peak skin dose of <2 Gy.[7] Significantly higher exposure was reported in patients with a high body mass index (>30),[8] those with complex anatomy,[8] and for those undergoing fenestrated and branched procedures.[10] For a standard EVAR, the average fluoroscopy time is about 20 minutes, with approximately 50% in a magnified view. The incurred entrance skin dose is 0.85 Gy, with a DAP of 60 to 150 Gy cm^2 and a patient effective dose of 8 to 27 mSv. Skin injury is still possible, but it is unlikely at these levels. These dosages can be further decreased by the usage of low-dose and pulse mode, especially for fenestrated and branched grafts, procedures in which mean DAP values of 860 and 1890 Gy cm^2 are to be expected.[8]

Modern imaging systems, which provide multiple high-resolution video screens and give the operator full motorized control of the C-arm, patient position, and imaging mode, have been shown to reduce radiation exposure, operation and screening time, and contrast volume.[12] State-of-the-art equipment now allows for off-table planning, precision of cannulation, and remote control. The use of three-dimensional (3D) navigation software by fusion of preoperative CT with DynaCT images obtained on table will allow a 3D real-time visualization of catheter position with respect to the target vessels. In complex endograft procedures this would reduce radiation exposure and the use of contrast media by facilitating branch cannulation. Also in development is a robotic system for peripheral vascular interventions, allowing distal 3D catheter tip control by a surgeon from a remote workstation, thus protecting him or her from radiation exposure.

RADIATION AND PREGNANCY

With the increasing use of medical radiation, many women who are pregnant or potentially pregnant will be exposed to ionizing radiation. In most instances, the radiation risk to the fetus is small in comparison to the risk of spontaneous abortion (15%), genetic abnormalities (4%-10%), and malformations (2%-4%) in the general population. However, undue anxiety and termination of pregnancy may result if the patient and staff are not properly educated.

Declaration of Pregnancy

Under federal law a pregnant woman can choose to continue to incur occupational radiation exposure at the level allowed for adult workers. However, it is recommended that an occupationally exposed pregnant woman declare pregnancy for the purpose of reducing the risk to the unborn child. Once pregnancy is declared, additional precautions should be adopted to protect the fetus and limit the radiation exposure to recommended levels.

Fetal Risk From Radiation

Risks to the fetus from radiation depend on the dosage and the stage of pregnancy, the risk being highest during organogenesis in the first trimester and least in the third trimester. Whenever possible, diagnostic tests or procedures that involve radiation should be deferred or replaced with safer options. In all cases, the patient should be adequately informed of any chances of radiation exposure. Estimated fetal radiation doses for diagnostic tests vary based on the type of procedure and the stages of the pregnancy; doses are generally highest in the later trimesters. A plain anteroposterior radiograph of the pelvis carries a dose of about 1.5 mSv. A lumbar spine anteroposterior radiograph at 3 months of gestation results in about 2 mSv of exposure; this increases to 9 mSv when performed near term. A CT scan of the head of the mother delivers less than 0.005 mSv, but an abdominal CT scan can lead to 8 mSv of fetal exposure.

The major adverse effects on the fetus include abortion, teratogenicity, mental retardation, intrauterine growth retardation, and the induction of cancer. Normal diagnostic procedures would seldom involve sufficient dosage to induce malformations, fetal death, or central nervous system defects, but the threshold may be exceeded with complicated interventional procedures.

Malformations and Mental Retardation

Based on animal studies, malformations after in utero exposure to doses below 100 mSv are not expected. Central nervous system malformations may appear if a dose threshold of 100 mSv has been exceeded (Table 24.6). Fetal doses of 100 mSv or higher, especially if incurred between 8 and 16 weeks of pregnancy, can be associated with reduction of intelligence and microcephaly. As an example, in victims exposed to in utero radiation during the 1945 atomic bombing of Hiroshima, the risk of mental retardation has been estimated to be about 0.04% per mSv of exposure, with an estimated loss of 2 to 3 IQ points/mSv.

Cancer Risk

The main issue with prenatal exposure at lower levels is cancer. Radiation has been shown to increase the risk of leukemia and cancer in children and the fetus. The threshold of childhood

TABLE 24.6 Probability of Fetal Risk as a Function of Radiation Dose

Fetal Dose (mSv)	Probability of Malformation (%)	Probability of Development of Cancer (%)
1	3	0.3
5	3	0.3
10	3	0.4
50	3	0.6
100	3	0.9

Modified from the International Commission on Radiological Protection guidelines.

cancer induction is not clear. For in utero exposure of 10 mSv, a 1.4-fold increase in leukemia and cancer and 1 excess cancer death per 1700 have been reported.

From studies of atomic bomb survivors and patients receiving radiotherapy, preconception exposure of the gonads to radiation has not been shown to result in a significant increase in the risk of cancer or malformations in children. The risk of serious birth defects was estimated at 2^{-6} per 1-mSv gonadal dose.

Recommendations for Pregnant Workers

Pregnant healthcare workers may work in a radiation environment as long as it is determined that the fetal dose can be kept below 1 mSv during the course of pregnancy. With such doses, radiation should have negligible effects on the fetus. Properly sized protection should be worn at all times, although lead aprons may present other health hazards, such as back strain, in pregnant women. Fetal doses approaching 100 mSv pose a small risk of radiation-induced cancer or leukemia, but the risk is minimal in the third trimester. The National Nuclear Commission guideline calls for no more than 5 mSv of equivalent dose exposure during the entire pregnancy, or less than 0.5 mSv/mo. If a worker has declared pregnancy while having been exposed to radiation, it should be ensured that any additional dose to the fetus would not exceed 1 mSv during the remainder of the pregnancy.

A unique concern to female vascular surgeons and trainees is radiation exposure during pregnancy. The author was involved in a multiinstitutional study in 2013 aimed to evaluate the dosages recorded on fetal dosimeter badges and compare them to the external badges worn by the same cohort of 81 women.[13] The average fetal dosimeter recording during the pregnancy rounded to zero. Only two women had positive fetal dosimeter recordings; one had a single reading of 3 mrem and the other had a single recording of 7 mrem. No significant difference between maternal exposure prior to, during, and postpregnancy was noted. This documentation of negligible radiation exposure on fetal monitoring suggests that with appropriate safety precautions, heightened concerns during pregnancy may be unfounded.

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CHAPTER 25

Arteriography

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Despite many advances in the quality and availability of less invasive arterial imaging modalities, arteriography remains the "gold standard." Alternative modalities, such as duplex arterial mapping, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA), are being used with increasing frequency because of improved image quality and minimal risk.[1-6] For some clinical scenarios, such as duplex surveillance of lower extremity vein bypass grafts, these imaging techniques have supplanted arteriography as the preferred test.[7-9] However, arteriography remains an indispensable tool for the vascular surgeon. A comprehensive understanding of basic to advanced techniques permits a wide array of arteriographic imaging studies to be performed optimally. In addition, a wide breadth of knowledge about arterial anatomy, equipment and materials, potential complications, and sources of interpretation error are required for becoming an expert in performing arteriography.

The goal of this chapter is to impart a broad overview of modern arteriography. Clinical acumen about vascular disease and operative experience also play important roles in determining how to optimize arteriographic imaging. This chapter provides evidence-based guidance, as well as practical experience, for safe performance of high-quality arteriography.

EQUIPMENT

The task to determine what equipment is needed to perform high-quality arteriography can seem overwhelming. The necessary components can be divided into venue, imaging hardware, catheters, contrast agents, devices for delivery of contrast agents, and digital software used to assist in the processing of arteriographic images. Image processing closely relates to techniques of arteriography and is discussed later in the chapter.

Abstract

Arteriography is an indispensable tool of the vascular surgeon. Despite the proliferation and advancement of enodovascular procedures, exposure to basic principles and techniques of arteriography is somewhat variable during vascular surgical training. This chapter describes the various options available to the vascular surgeon with regards to equipment, venue and acquisition techniques. Recent advances in equipment are highlighted as are potential pitfalls and complications associated with various arteriography agents and techniques.

Keywords

Arteriography
Image processing
three-dimensional fusion computed tomography
carbon dioxide angiography
contrast-induced nephropathy

Operating Room Versus Imaging Suite

Depending on facility-specific logistics, angiography can be performed with a portable fluoroscopy unit or in a designated interventional radiology suite with a fixed imaging unit. In addition, many centers now contain "hybrid operating rooms," featuring a fixed-mount imaging unit combined with all the features of an operating room, a fully equipped endovascular stock (catheters, guide wires, and devices), and a trained staff that is comfortable with endovascular and open vascular surgery.

The advantages of an operative-endovascular or hybrid suite are clear. Combined endovascular and open procedures are commonplace. Aortic endograft procedures, common femoral endarterectomy with concomitant retrograde or antegrade stenting and hybrid approaches to acute limb ischemia are evolving into the "standard of care." Lastly, complications that arise during any endovascular procedure, albeit rarely, can be managed by immediate and seamless conversion to open surgery, as opposed to the need for emergency transport from an angiography suite to the operating room.

Fixed-Mount Versus Portable Equipment

The two principal types of radiographic imaging units that can provide state-of-the-art arteriography are the fixed-mount unit physically attached to one suite (Fig. 25.1) and the portable fluoroscopy unit equipped with wheels so that it can be moved from room to room (Fig. 25.2). Each type has the basic components, including a power generator for fluoroscopy, a C-arm with image intensifier, screens for viewing real-time and reference images, and digital image processing software. In experienced hands, both types of imaging units have their advantages and disadvantages.

In general, fixed-mount units have more powerful generators that allow more detailed imaging. More power allows greater depth of fluoroscopic penetration and thus the ability to discern finer detail. Depending on the types of imaging units compared, fixed-mount units can provide upward of 10 times the resolution of portable units. Although this greater resolution may not be needed in persons of ideal body weight, increased power for improved penetration is important when arteriography is performed on obese patients. Another distinct advantage of a fixed-mount unit is a larger field of view. Modern fixed-mount units now have flat detector image intensifiers as large as 22 inches (57-cm image projection). This increased size translates into the ability to cover more imaging area during arteriography with less radiation exposure and less total volume of contrast material. In addition, fixed-mount units have tableside controls that allow precise and easily directed movement of the C-arm and table. This feature is useful during visceral and cerebrovascular arteriography inasmuch as subtle manipulations in C-arm angulation can result in significantly improved arterial visualization.

A portable fluoroscopy unit designed for high-quality arteriography is advantageous by the mere ability to move the equipment from room to room. This may be important in trying to fulfill the needs of different types of vascular surgical practices, operating rooms, specialty procedure rooms, and intensive care units. Typically, portable fluoroscopy units require only one technician in addition to the vascular surgeon for arteriography to be adequately performed. Fixed-mount units require, in addition to the angiographer, three or four specially trained staff, including a technician who is gowned and gloved with the vascular surgeon, a circulator attending to material needs, a technician coordinating image acquisition and processing, and a certified nurse who is responsible for monitoring the patient and administering medications. Finally, portable

Figure 25.1 Dedicated fixed-mount imaging suite. (Courtesy Siemens Medical Solutions USA, Inc.)

Figure 25.2 Mobile C-arm portable unit. (Courtesy Philips Healthcare.)

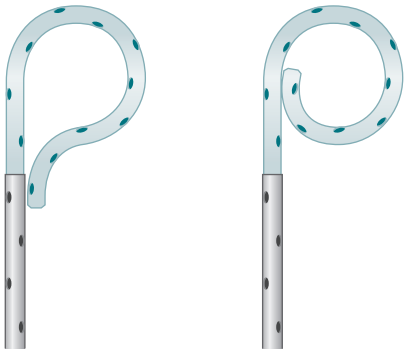

Figure 25.3 Flush catheters in various shapes with multiple side holes, as opposed to end-hole catheters (not pictured), are ideal for power injections.

units are much less costly than fixed-mount units. Not only are fixed-mount units expensive (ranging from $1.5 to $5 million), but construction of such a suite may require major structural modifications to an existing room, which can be a significant additional cost.

Catheters

The type of catheter used also plays an important role in optimizing the arteriographic image and avoiding injury to the vessel. Intraarterial catheters come in virtually all shapes, sizes, and lengths. Given this variety, attention should be paid to whether the catheter has just an end hole or multiple side holes in addition to the end hole (Fig. 25.3). The latter, known as a flush catheter, is designed for safe, quick, and even dispersion of contrast material at high injection pressures to image large arteries with high flow. End-hole catheters, with their greater variety of shapes, are often all that can be used after remote arterial access is achieved. Care should be taken whenever a power injection is performed with an end-hole catheter in a medium-sized muscular artery. Problems may include loss of a tenuous catheter crossing because of pressure forcing the catheter out of the arterial lumen, creation of intimal flaps, and arterial rupture. Direct power injection into very small arteries, such as the vertebral or tibial arteries, should be avoided with any type of catheter. Hand injection with a manifold should also be performed gently to avoid injury to these vessels.

Contrast Agents

The concept of angiographic imaging relies on the presence of an intravascular contrast agent. To maximize vascular anatomic detail, this agent needs to have a radiodensity that is distinct from that of the tissue being imaged. Typical contrast agents have greater radiodensity than surrounding tissue and therefore appear markedly darker on imaging. However, an agent significantly less radiodense than surrounding tissue, such as carbon dioxide (CO_2) gas, can also provide adequate contrast to image intravascular anatomic detail,[10,11] albeit with less quality in some cases. The underlying concept is to provide adequate visual contrast between the intravascular space and the extravascular space. Selecting the appropriate contrast agent and adjusting the imaging equipment and technique accordingly are essential for patient safety and imaging quality.

Iodinated Contrast Agents

Conventional contrast agents are composed of molecular compounds containing iodine. These iodinated agents can be categorized as ionic or nonionic.

Ionic contrast agents dissociate into anions and cations when they are placed in solution, which includes flowing blood. The anion is a benzene ring fully substituted with three iodine atoms. Iodine atoms absorb the x-ray photons and are responsible for contrast visualization, or radiopacity, of the artery visualized. The cation can be sodium, methylglucamine, or a combination thereof. When iodinated contrast agents dissolve, their osmolality doubles because of the presence of two ions. The osmolality of these agents ranges from 1500 to 1700 mOsm, thus making them significantly more hyperosmolar than plasma (285 mOsm).

Nonionic contrast agents have considerably less osmolality. Because dissolution of the benzene compound into two ions is prevented, the osmolality remains half that of ionic contrast agents. However, because the number of iodine atoms remains the same, radiopacity remains comparable to that of conventional ionic agents but with much less ionic charge. Osmolality can be further reduced by a compounding method that creates a *dimeric* ionic contrast agent, whereby two benzene rings are attached to each cation. With this formulation, twice the number of iodine atoms are present with the same level of osmolality (ranging from 320 to 880 mOsm). Doubling of the iodine atoms leads to a greater amount of x-ray photon absorption, and thus comparable arteriographic images are achieved with less volume of contrast material (Table 25.1).

Carbon Dioxide Arteriography

Another contrast agent with novel properties and applications is CO_2.[10,11] Injection of this gas with its decreased radiodensity creates radiographic contrast by transiently displacing blood from the artery being imaged. Improvements in equipment, technology, and image-processing software, coupled with the significant number of vascular patients who have compromised renal function, have led to increased use of CO_2 arteriography.[11-13] Digital subtraction technology has greatly enhanced anatomic definition and visualization with this contrast agent. However, despite improved techniques, image quality still remains inferior to that of conventional contrast agents.

Many techniques can enhance the quality of CO_2 arteriography. Because of the image settings developed to enhance visualization of intravascular CO_2, the presence of bowel gas can especially degrade image quality in this acquisition mode. Because CO_2 rapidly displaces blood and then dissolves quickly, frame rates are increased during image acquisition (four to eight frames per second). Modern arteriographic imaging systems now feature prescribed settings that depend on the type of contrast agent and area of the body to be imaged. Further image enhancement can be achieved by selective catheterization and magnified views of smaller-caliber vessels (Fig. 25.4). Contrast injections may be performed rapidly by hand or with an automatic pump system. They should be spaced 3 to 5

TABLE 25.1 Characteristics of Commonly Used Contrast Agents

Contrast Agent	Manufacturer	Structure	Iodine Content (mg/mL)	Osmolality (mOsm/kg)	Average Wholesale Cost (50 mL)
Hexabrix	Mallinckrodt Medical	Ionic dimer	320	600	$53.50
Isovue-200	Bracco Diagnostics	Nonionic	200	413	$53.75
Isovue-300	Bracco Diagnostics	Nonionic	300	524	$57.49
Isovue-370	Bracco Diagnostics	Nonionic	370	796	$62.50
Optiray 160	Mallinckrodt Medical	Nonionic	160	355	$39.60
Optiray 320	Mallinckrodt Medical	Nonionic	320	702	$57.60
Omnipaque 140	GE Healthcare	Nonionic	140	322	$38.94
Omnipaque 300	GE Healthcare	Nonionic	300	672	$54.00
Omnipaque 350	GE Healthcare	Nonionic	350	844	$58.81
Oxilan 300	Cook Corporation	Nonionic	300	585	$45.00
Oxilan 350	Cook Corporation	Nonionic	350	695	$50.00
RenoCal-76	Bracco Diagnostics	Ionic	370	2188	$24.25
Renografin-60	Bracco Diagnostics	Ionic	292	1549	$44.13
Ultravist 150	Bayer	Nonionic	150	328	$19.80
Ultravist 240	Bayer	Nonionic	240	483	$22.80
Ultravist 300	Bayer	Nonionic	300	607	$25.20
Ultravist 370	Bayer	Nonionic	370	774	$28.80
Visipaque 270	GE Healthcare	Nonionic	270	290	$63.80
Visipaque 320	GE Healthcare	Nonionic	320	290	$69.48

Modified from *Drug Topics Red Book 2008,* Montvale, NJ, 2008, Thompson Healthcare.

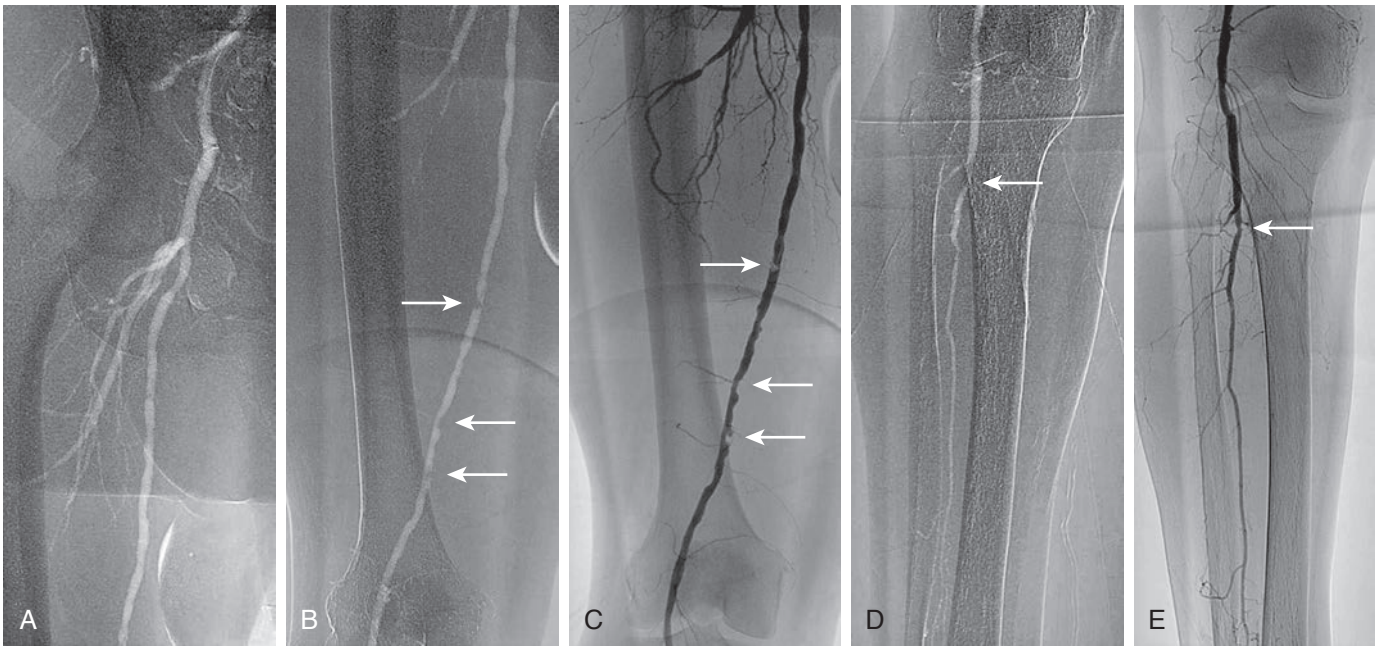

Figure 25.4 (A) Angiogram of the femoral bifurcation visualized with CO_2 contrast and selective placement of the catheter in the common femoral artery. (B) Opacification of the superficial femoral artery reveals multiple stenoses *(arrows)*. (C) Comparison of the same vessel opacified with iodinated contrast material shows much better characterization of each stenosis *(arrows)*. (D) Distal views show relatively well-visualized popliteal and single-vessel peroneal runoff with CO_2; significant disease is evident at the proximal peroneal artery *(arrow)*. (E) Again, better characterization with iodinated contrast material reveals only a mild stenosis at the proximal peroneal artery *(arrow)*.

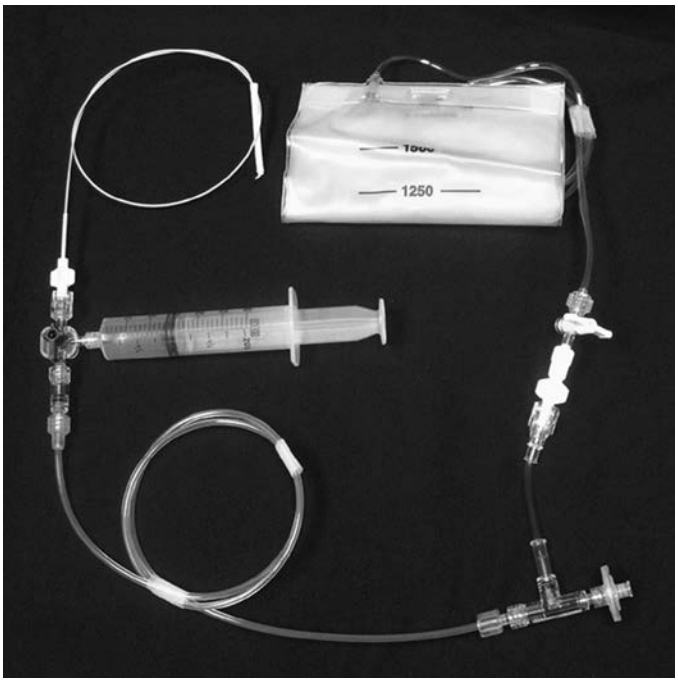

Figure 25.5 CO_2 System Connected to a Diagnostic Catheter. The delivery system uses a three-way stopcock, check valve, and filter port connected to the gas tank (not shown). A 1500-mL bag is attached to the delivery system with low-pressure tubing and a two-way stopcock. A large Luer-Lok syringe is required for hand injection.

minutes apart to allow complete dissolution before the next injection. Overestimation of the degree of stenosis can occur when one is unable to completely fill the diameter of the artery with CO_2.[14] For lower extremity arteriography, Trendelenburg positioning or elevation of the extremity to approximately 20 to 30 degrees will slow distal blood flow and promote concentration of the CO_2, thus slowing the dispersion rate as CO_2 exits the catheter and travels distally.

The CO_2 delivery system includes a 30- to 60-mL Luer-Lok syringe, tubing with a two-way distal stopcock and two one-way check valves, a 1500-mL fixed-volume gas bag, and the CO_2 tank (Fig. 25.5). After assembly of the system, purging of the tubing with three syringe volumes (90 to 180 mL) of gas prevents the possibility of accidental injection of air. Nitrogen gas in ambient air is not soluble and can lead to gas embolization. Once the gas bag is filled with CO_2 directly from the gas tank, the syringe is pulled back to be filled with gas from the gas bag. Because of a one-way valve distal to the syringe, only gas from the bag can be withdrawn. Another reversed one-way valve proximal to the syringe forces gas to travel only to the patient on injection.

Devices for Injection of Contrast Agents

Injection of liquid contrast material can be performed with a power injector or manually. For optimal arteriography, the ability to perform both methods is preferable because both have distinct advantages, depending on which arteries are being imaged.

Power Injection

Power injectors allow rapid high-pressure injection of contrast material into the catheter. Precise control exists with regard to the pressure setting (psi), amount of contrast material used during a set period, timing of injection in relation to fluoroscopic imaging and catheter position, and rate of rise of the injection. Typically, use of a power injector allows rapid filling of large arteries at high flow rates. This produces equal distribution of contrast material and hence a higher-quality image. Power injectors can also be used for prolonged injections, generally ranging from 3 to 6 seconds, when the catheter can be placed only in a very proximal position and the target artery is remote. Imaging of the dorsal pedal artery with the catheter placed in the ipsilateral common femoral artery is one such example. When a power injector is used, settings must be adjusted to manipulate pressure and the rate of rise of the injection, depending on the vessels being imaged. Large high-flow arteries require high pressure (800 psi) and rapid rise of the injectate to quickly disperse the contrast agent for a proper image. Smaller arteries, such as the superficial femoral artery, can be traumatized by such settings and require a lower pressure setting (300 to 600 psi) and reduced rate of rise of the injectate. For every power injection, the vascular surgeon will determine what volume of contrast material is to be given during what time. For example, typical aortic arch arteriography may require 20 mL of contrast material per second for a total of 2 seconds. Common jargon in the endovascular suite before such an injection would be "20 for 40," or 20 mL of contrast material injected per second for a total volume of 40 mL.

Manual Injection

Manual injection of contrast material can be performed by use of a simple syringe with full-strength contrast agent or a manifold device that allows more precise and rapid loading of contrast material (Fig. 25.6). Manifolds are also equipped with the ability to dilute contrast material with saline, to evacuate air and liquid waste, and to perform real-time intraarterial pressure measurements. The ability to perform high-quality arteriography with the use of dilute contrast material should not be underestimated. Contrast agents, many of which are nephrotoxic, should always be used conservatively regardless of renal function. Establishing this habit helps to prevent injury to patients with mild renal disease not yet manifested by abnormal laboratory values. In smaller arteries (e.g., the common carotid artery or tibial arteries), 3 to 4 mL of diluted contrast material (1 : 1 mixture of contrast material and saline) should be sufficient to give a high-quality arteriographic image. The learning curve for maximizing proper use of a manifold is not very steep, and after it is mastered, optimal arteriographic images can be obtained rapidly with minimal volume of contrast material. Typical injection methods, rates, and volumes of contrast agent are detailed in Table 25.2.

TECHNIQUES

Arteriographic imaging in the modern era is synonymous with digital subtraction angiography (DSA). The basic concept behind

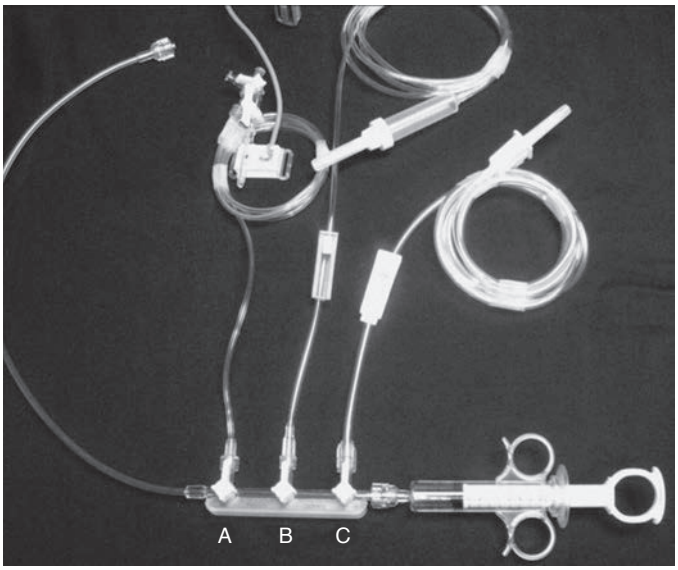

Figure 25.6 Rapid, Convenient Device for Mixing and Delivery of Contrast Material. The control syringe and manifold allow quick reloading after each injection of contrast agent, with one hand operating the syringe and the other regulating the proportions of contrast material *(C)* and saline *(B)* being drawn up via the stopcocks on the manifold. Between injections, the saline line can be left on flush to keep the catheter irrigated. The third stopcock *(A)* allows continuous monitoring of pressure when it is connected to a transducer.

TABLE 25.2 Typical Injection Method, Rate, and Volume of Contrast Agent for Various Vascular Regions

Location	Suggested Method	Injection Rate (mL/s)	Total Volume (mL)
Aortic arch	Power injection	20	40
Selective carotid	Hand or power injection	3-5	5-10
Selective vertebral	Hand injection	2-4	2-4
Selective subclavian or brachial	Hand or power injection	5-10	10
Abdominal aorta	Power injection	20	40
Renal or mesenteric	Hand injection	3-5	5-10
Iliac artery	Hand or power injection	10	10
Infrainguinal segments	Hand or power injection	5-10	10
Aorta to pedals, stepped run	Power injection	20	90[a]

[a]Full-strength contrast agent; all others typically performed with a half-strength contrast agent when digital subtraction angiography is used.

DSA involves a recording technique by which the captured fluoroscopic image is amplified and digitized. With advanced computer data processing capability, multiple manipulations of the stored data can be performed to optimize image quality.

Image Processing

Some of the commonly used postprocessing capabilities are subtraction, masking, pixel shifting, and view tracing. Other tools, such as roadmapping and unsubtracted image referencing, can assist in guiding wires and catheters during the actual procedure.

Subtraction Tool and Masking

The subtraction tool is the single most effective characteristic of this technology that enhances and improves image quality. This technique subtracts all visible radiodensities on the current image to create a mask image, represented as a blank screen. Once the mask has been established, any motion in the field during the fluoroscopic run will be highlighted as a dynamic image on this blank background. All radiodense tissues subtracted on the mask image will remain subtracted as long as they remain in the same position and alignment as in the mask image. After subtraction is achieved and the mask image is created, the contrast agent is injected and visualized because it is radiodense and moves with blood flow through the vessels of concern. By subtraction of the surrounding tissue and vessel wall from the contrast images, the quality of visualization of intraluminal contrast is greatly enhanced. In an ideal image capture, there is no movement between creation of the mask and injection of contrast material. This would produce the purest image derived solely from flow of the contrast agent. However, such is often not the case, and unintended motion can greatly compromise imaging. If the mask has been created and the patient then changes position, breathes, or even has bowel peristalsis, this skeletal or visceral motion will be seen on the contrast images because it was not part of the original mask image. Therefore it is essential for the patient to remain very still during image capture.

Masking can be used beyond the original subtraction maneuver to improve image quality. If a patient moves during an injection, any image prior to contrast appearance or after contrast washout can be used as the mask image to improve image quality and minimize motion artifact. A trial of different mask images is often an effective way of finding the best possible result.

Pixel Shifting

Pixel shifting provides a valuable tool when movement occurs after contrast material has already entered the field of view. Instead of creating a new mask, one can take the existing mask and slide it in a bidirectional plane (vertical, horizontal, or both) to realign the surrounding tissue (Fig. 25.7). This realignment of the existing mask to the patient's current position on the contrast image erases the discrepancy and minimizes the motion artifact. Software programs allow automatic or manual pixel shifting. In the automatic mode the computer will try to

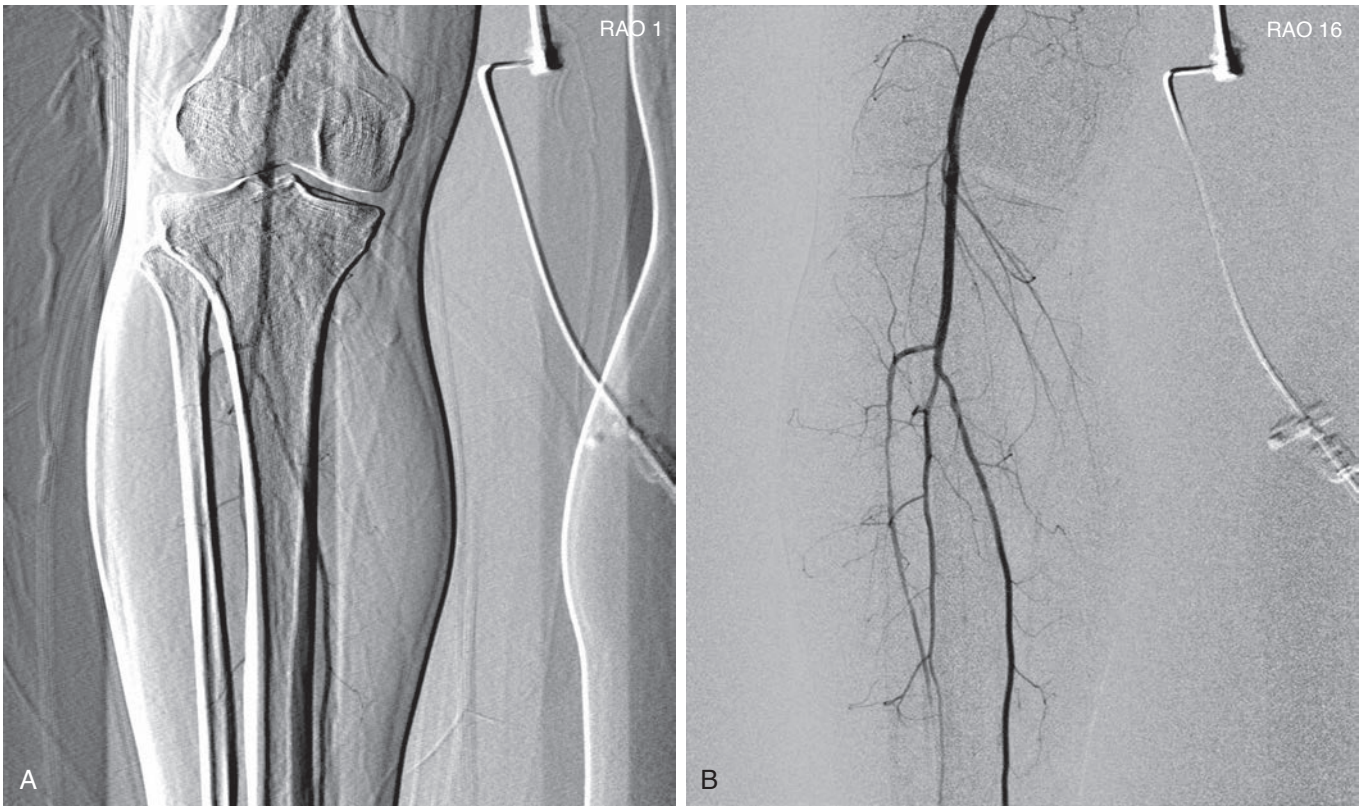

Figure 25.7 (A) Patient motion during contrast opacification significantly degrading image quality. (B) Pixel shifting during postprocessing realigns the mask image with the contrast image and thereby results in optimal visualization of the artery. If the motion occurs before contrast injection as opposed to during it, reassigning the mask image can accomplish a similar result. *RAO,* Right anterior oblique.

realign the mask image to create the best subtracted result for that particular region of the field. In manual mode, the pixel shifting can be done freehand in real time by sliding the cursor vertically, horizontally, or both until the optimal image is achieved.

View Tracing

Because arteriography is a dynamic imaging modality, obtaining one static image from a series during injection of contrast material will often fail to provide complete visualization of the target vessel. As the contrast agent opacifies one segment of the blood vessel, a previous segment may already have washed out and a distal segment may not yet have filled with the contrast agent. This property can be ameliorated using view tracing.

View tracing, sometimes referred to as opacification, allows consolidation or "stacking" of different time points by overlaying consecutive static images in a series to provide one cumulative arteriographic image. The first image in which contrast appears may be designated the first image in a view-traced series. Each subsequent image that is stacked over the previous one will show further progression of contrast and further visualization of the vessel distally (Fig. 25.8). However, with each additional view-traced image, any motion artifact will also be superimposed, thereby degrading the image more and more with sequential stacking. To circumvent this problem, each individual static image can first be optimized by pixel shifting to minimize artifact in the final cumulative image.

After broad manipulations with the techniques just discussed, images can be further enhanced by finer adjustments. Image contrast, brightness, edge enhancement, sharpness, and even color of the contrast agent (image invert) can be modified to create a final optimized image. These finalized images can then be stored in the patient database along with the dynamic DSA runs.

Roadmapping and Measuring

Other useful techniques involving DSA can help with guidance during the actual procedure. Roadmapping allows a previously constructed image of a contrast-filled vessel to be displayed on the working monitor. Real-time fluoroscopic imaging can then be superimposed on the monitor so that the contrast image can be used as a "roadmap" to direct guide wires and catheters. This technique is effective as long as table and patient positions do not change. The roadmap mask is extremely sensitive to motion, and image quality will degrade during use. Another valuable guiding tool during arteriography is the simple use of unsubtracted image referencing. Disabling subtraction from a contrast image allows identification of native tissue reference points, most often bone landmarks, near vessel bifurcations (Fig. 25.9). This image can then be displayed on a reference

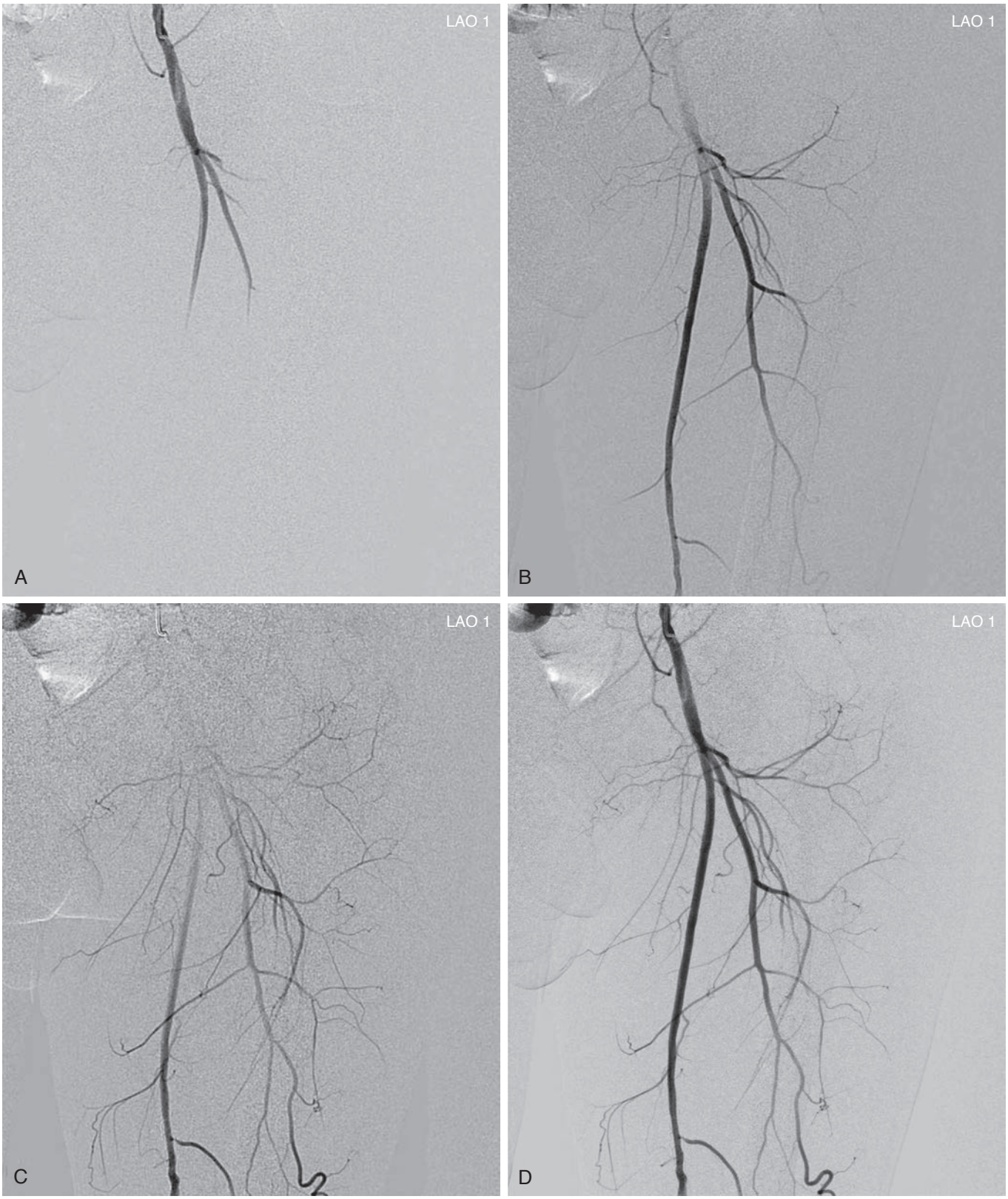

Figure 25.8 (A) Femoral arteriogram early after injection of contrast material illustrating only proximal opacification of the vessels. (B and C) Progress of contrast opacification through the femoral vessels with improved distal but poor proximal visualization. (D) View tracing allows stacking of sequential images to give a comprehensive view of the vessels with all areas opacified during the different time points of the contrast run. *LAO,* Left anterior oblique.

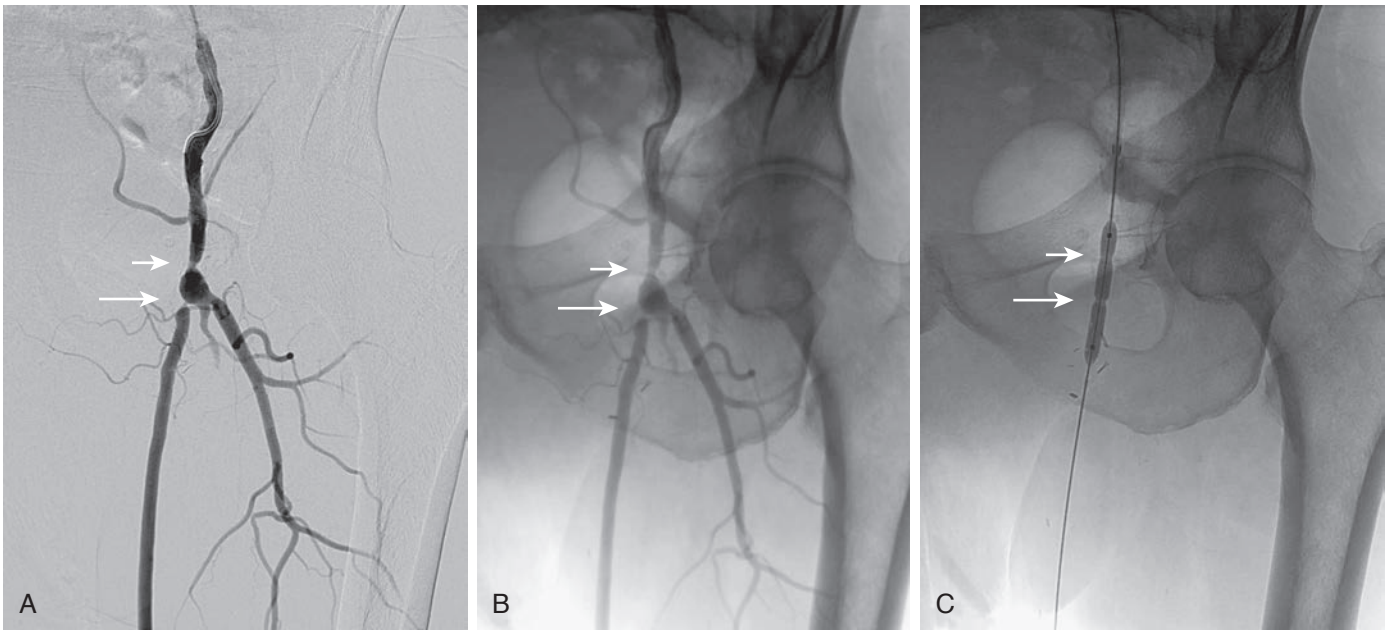

Figure 25.9 (A) A femoral arteriogram to evaluate a lower extremity bypass graft shows a stenosis at the proximal anastomosis *(short arrow)* and a second stenosis in the proximal graft *(long arrow)*. (B) Viewing of the same image in an unsubtracted mode allows the use of bone structures, such as the pubic rami and obturator foramen, to serve as reference landmarks. (C) On the unsubtracted reference image, localization and treatment of the target lesions can be performed accurately with guidance from these bone landmarks.

monitor alongside the working monitor so that the angiographer can manipulate catheters or wires on the basis of these reference points.

Finally, imaging units' software includes measurement tools. These tools can be autocalibrated on the basis of estimated distances from the image intensifier to the center of the patient's body, or they can be manually calibrated by measuring an object with known dimensions, such a known distance between radiopaque markers on catheters. This allows more accurate interpretation of stenoses and vessel dimensions than is possible with mere visual estimation or "eyeballing."[15]

Single-Injection Multiple–Linear Field Arteriography

The technique, which allows imaging of both lower extremities with a single injection of contrast agent, is referred to as single-injection multiple–linear field or bolus chase arteriography. With this method, contrast material is injected into the abdominal aorta and imaging proceeds sequentially down the entire length of both lower extremities. Image intensifiers larger than 15 inches are required to view both extremities in one field with this technique. After a single bolus injection of contrast agent, imaging must follow the progression of contrast in a dynamic manner.

Stage Technique

In the stage technique the operator sets the image intensifier at a certain number of sequential positions, or stages, from the lower part of the abdomen to the feet. Four or five stages with some overlap between stages is usually required, depending on the size of the image intensifier. When the imaging process is initiated, the image intensifier starts at the feet and travels proximally from stage to stage to acquire a mask image for each particular position. Once the final mask is obtained in the lower part of the abdomen, a bolus of contrast material is injected and continuous imaging proceeds in a staged manner from the abdominal aorta back down to the feet. In essence, the image intensifier "chases" the bolus of contrast material as it travels distally. On completion, the images can then be viewed at each stage individually and processed in the standard manner (Fig. 25.10). Because the mask images are obtained before the run, the contrast imaging is viewed in subtracted mode, which enhances visualization during the actual run.

Stepping Technique

In the second technique, referred to as stepping, the image intensifier remains stationary while the fluoroscopic table moves for proper imaging. This method uses a large number of small incremental advancements in position, or steps, as opposed to the smaller number of large position changes in the stage method. The process begins with injection of contrast material into the abdominal aorta as the table is stepped sequentially from the abdomen to the feet. Because the incremental changes in position are smaller than with staging, fluoroscopic imaging can more precisely follow the progression of contrast material down the extremities. Stepping can be slowed or even stopped by the operator, depending on the rate of travel of the contrast agent. Once the contrast run is completed, the table returns to the

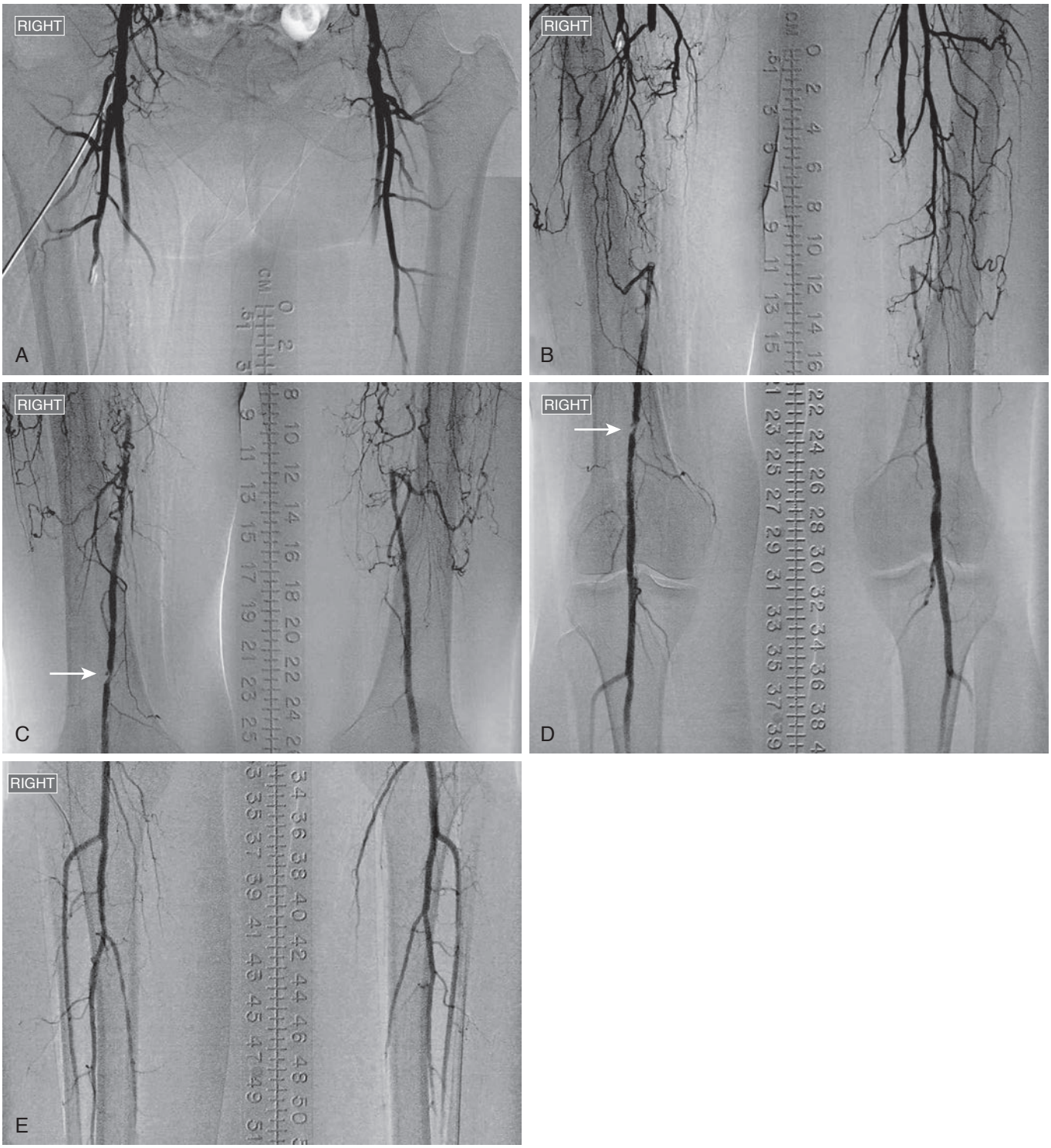

Figure 25.10 Single-injection multiple–linear field (bolus chase) arteriogram of both lower extremities showing bilateral mid-superficial femoral artery segmental occlusion (A and B), right popliteal artery stenosis *(arrow)* (C and D), and bilateral patent tibioperoneal trunks and three-vessel runoff with posterior tibial artery disease on the right (E). Because disease severity appears similar in both lower extremities, there is no discrepancy in contrast transit time between the two; hence imaging appears to have adequate and equal bilateral vessel opacification at each level.

original position and automatically proceeds through the same step sequence used to acquire the mask images.

Limitations of Single-Injection Multiple-Field Arteriography

There are two significant limitations of single-injection multiple-field arteriography. First, as with any DSA imaging, patient movement can significantly compromise image quality. Because the time required to complete this type of study is considerably longer (often lasting 2 minutes) than a standard single-field run, the possibility of motion artifact is significantly increased. A second limitation occurs in patients with a discrepancy in the severity of arterial occlusive disease between the two extremities. More severe occlusive disease on one side will cause delayed contrast transit time and decreased visualization on that side because the image follows the progression of contrast in the more rapidly filling extremity. In this case, it will be necessary to obtain unilateral images separately. Although this technique of arteriography can be performed for each leg individually, the amount of contrast agent needed to do so must be considered. Typical bolus chase arteriography requires 80 to 100 mL of full-strength contrast material, whereas selective single-field imaging of each extremity can be performed in sequential fashion with a manifold and a diluted contrast agent to provide quality images with significantly less volume of contrast material. In the presence of severe unilateral disease, this is the preferred injection technique.

Rotational Arteriography

Rotational arteriography involves rotational image capture and incorporates specific computer software to record the fluoroscopic image series in multiple planes. Preset algorithms are then used to convert the data acquisition into a comprehensive three-dimensional (3D) image. The final reconstructed image can be rotated and manipulated to fully visualize the vessel from any angle, thereby addressing the limitations of single-plane arteriography. Figs. 25.11 and 25.12 illustrate examples of single-plane and rotational arteriography.

Rotational arteriography is similar to the bolus chase technique in that a single injection of contrast material is administered as images are captured from a series of varying positions. The target vessel is first centered on the fluoroscopic image. As contrast material is injected, the image intensifier rotates between two predetermined points (usually 90 to 213 degrees, depending on the system) and captures a broad spectrum of imaging angles with each frame of acquisition during the rotation. The final reconstructed image can be viewed with or without subtraction, and further "cutting" of surrounding tissue artifact can be performed with postprocessing tools (see Fig. 25.12). More recent software even allows roadmapping with 3D imaging for catheter guidance, which may prove especially useful in the cerebral vasculature.

Three-Dimensional Fusion Computed Tomography

With the advent of complex aortic endograft procedures, the need to minimize contrast loads and radiation exposure is more critical than ever. Three-dimensional fusion computed tomography (CT) imaging allows for the patient's preoperative CTA to be used as an overlay roadmap image during the procedure. Briefly, the areas of interest, such as the visceral artery origins, are manually marked on the preoperative CTA. Next an intraoperative "CT scan" is obtained by performing a rotational imaging spin of the patient. Available commercial software packages align the bony landmarks and aortic calcifications of the preoperative CTA and the intraoperative rotational image, allowing the preoperative image to overlay the intraoperative image as a roadmap to guide endograft orientation and target vessel cannulation (Fig. 25.13A and B). Use of this imaging technique does require additional training of the surgeon and hybrid room staff but has been shown to reduce procedure times, radiation exposure, and contrast use in fenestrated aortic endograft procedures and coronary angiography.[16,17]

Maximizing Image Quality During Arteriography

Limiting patient movement is essential to maximize the quality of an arteriographic image. To effectively do so, the angiographer must pay special attention to the patient's comfort and anxiety. Pain and anxiety can cause a patient to make even subtle position changes that can translate to deleterious artifact on imaging. Explaining each step of the procedure ahead of time can help to alleviate anxiety during imaging. Administration of anxiolytic and narcotic medications before and during the procedure is the most effective tool to minimize patient motion. Midazolam (Versed), 1 to 2 mg, and fentanyl, 25 to 50 μg, intravenously can be used before the start of most arteriography procedures. Depending on the patient's condition and tolerance and the length of the procedure, additional small doses can be given as needed. Use of conscious sedation usually requires certification in advanced cardiac life support and also necessitates adequate patient monitoring and the presence of nursing staff during the procedure.

Breathing maneuvers are also important to ensure quality imaging because motion of surrounding tissue secondary to breathing can result in significant image degradation, especially on imaging of the chest, abdomen, or pelvis. Patients should be asked to hold the breath as imaging is initiated, because vessel position can be significantly altered with deep inspiration or expiration. Alternatively, patients can be asked to hold the breath at the midbreath cycle to minimize significant vessel displacement, compared with a deep inspiration, which can cause downward displacement of visceral vessels. When the neck is being imaged, such as the extracranial carotid and vertebral vessels, asking patients to avoid swallowing will likewise prevent significant motion artifact in this area.

Proper positioning of the patient and the imaging equipment is also necessary to maximize information during a study. For example, the legs can be placed closer together during bolus chase angiography to include both of them in the field of view (see Fig. 25.10). Some tables may offer tilt features to increase the capability of patient positioning. However, the majority of positioning relies on adjustment of the image intensifier,

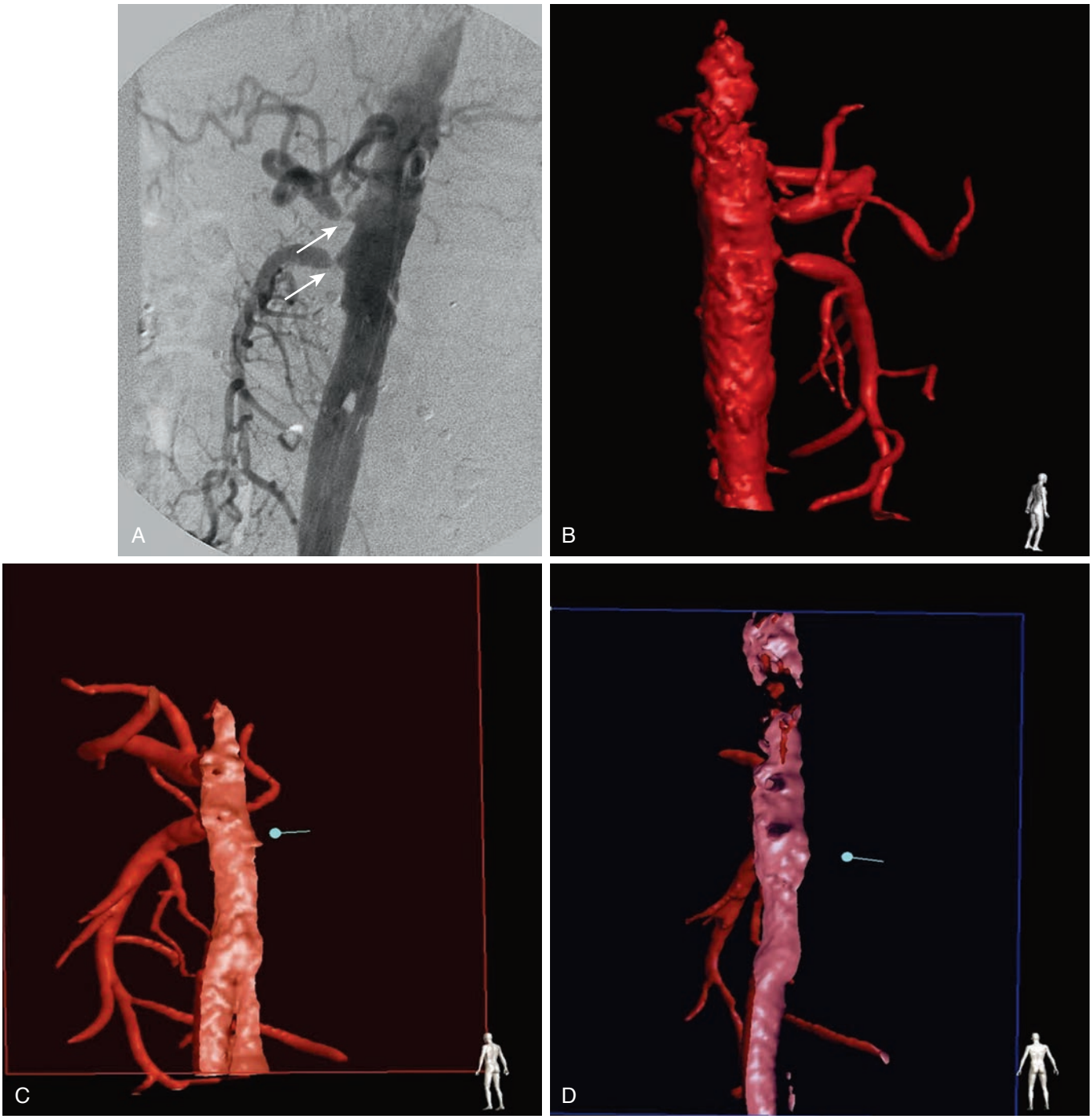

Figure 25.11 (A) Lateral view arteriogram of the aorta showing proximal celiac and superior mesenteric artery stenoses *(arrows)*. (B) Rotational arteriography with three-dimensional reconstruction allows improved characterization of the lesions and rotating views of the image. The images can also be manipulated to view an intraluminal perspective of the aorta, which reveals significant orificial narrowing of both mesenteric vessels before stenting (C) and improved orificial diameter after stenting (D).

including both lateral angular rotation (anteroposterior versus oblique versus lateral views) and craniocaudal angulation. General recommended filming projections for viewing of some commonly imaged arteries are listed in Table 25.3. Depending on the particular vessels being imaged and the patient's individual anatomy, varying degrees of rotation are preferred for optimal visualization (Figs. 25.14 and 25.15).

The maximum size of available image intensifiers has increased significantly in recent years, and current equipment may allow a broad field of view on imaging at maximum projection. This feature is especially useful in performing abdominal and lower extremity angiography because it allows complete evaluation with less contrast agent and shorter radiation exposure times. However, smaller vessels and subtle lesions may be difficult to

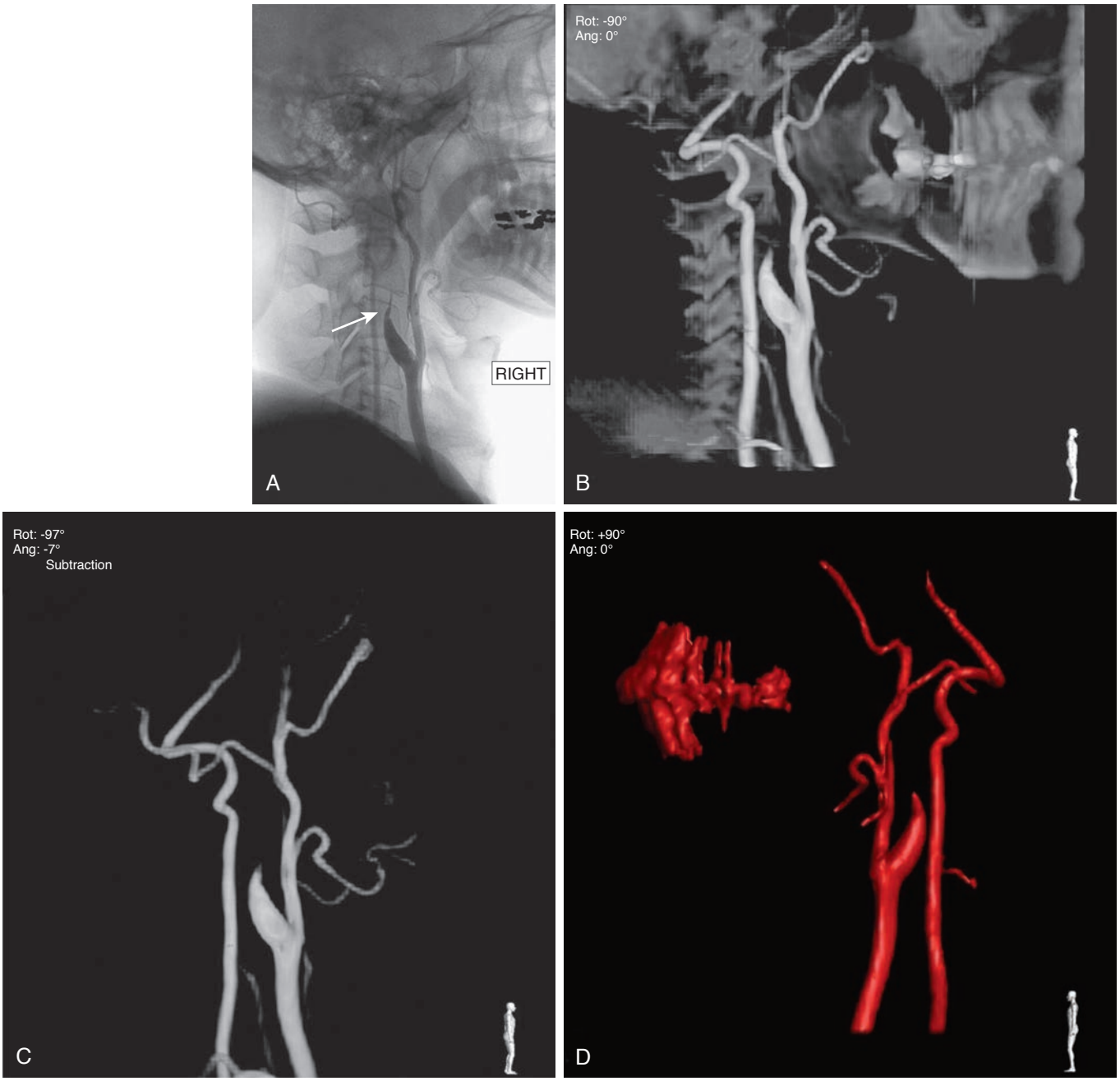

Figure 25.12 (A) Selective carotid arteriogram showing the typical "tapering" appearance of an internal carotid artery dissection *(arrow)*. (B) Preliminary three-dimensional (3D) reconstructed image from a rotational arteriogram showing the same lesion. (C and D) After color manipulation and "cutting" of surrounding bony tissue, the final 3D image can be rotated for different viewing angles.

characterize at such a wide view. By reduction of the projected image dimension, a magnified view focused on the vessel of interest can be obtained (Fig. 25.16).

CLINICAL APPLICATIONS

The quality of MRA and CTA has improved immensely during the past 10 years, and in many clinical scenarios, MRA or CTA can become the preferred choice for planning of either endovascular or operative procedures. Nevertheless, arteriography still has a major role as the primary modality to provide a first diagnostic vascular image. Although arteriography remains the criterion standard, variability exists among all three modalities with respect to quality of imaging and useful information that is gained. CTA and MRA continue to improve in ease of use, accuracy, and speed, but they are still dependent on the physicians and technicians who oversee the production of those images. Therefore variability exists from center to center, which can influence the path that a vascular surgeon will take in obtaining the best vascular images for treatment decisions. Possible

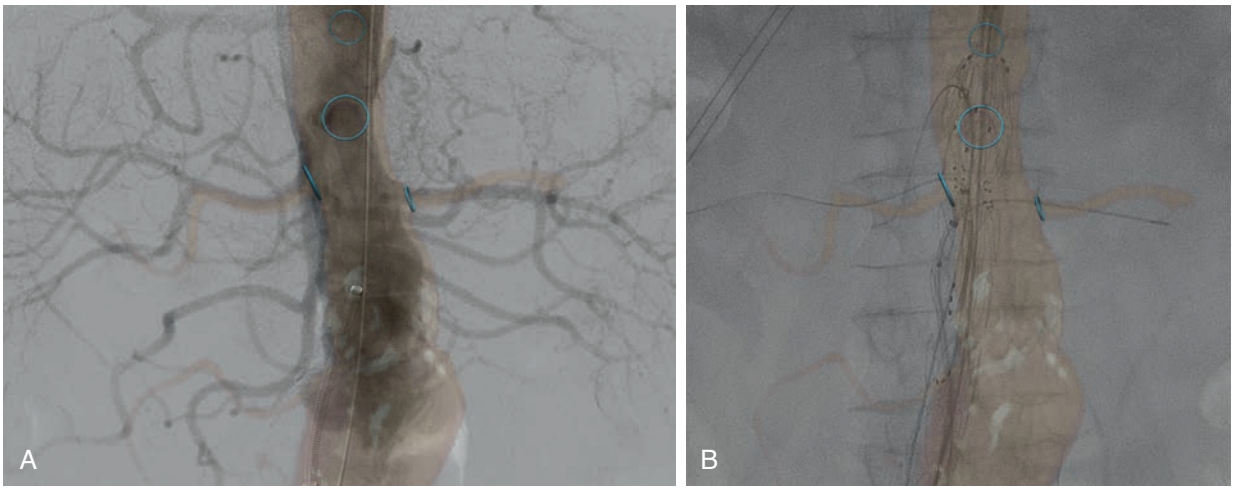

Figure 25.13 (A) Intraoperative aortogram with overlay of preoperative computed tomography (CT) scan showing good alignment of visceral vessels. (B) Three-dimensional CT scan overlay is used to orient fenestrated aortic endograft and cannulate visceral vessels.

TABLE 25.3 Recommended Radiographic Filming Projections for Optimal Branch Separation

Location	Recommended Filming Projection
Aortic arch	30-degree left anterior oblique
Cervical carotids	AP, lateral, and 45-degree ipsilateral anterior oblique
Intracranial carotids	AP and lateral
Vertebrobasilar system	AP and lateral
Right subclavian	Right anterior oblique
Renal artery origins	AP ± 10 degrees
Celiac artery and SMA origins	Lateral
Iliac bifurcation	20- to 30-degree contralateral anterior oblique
Femoral bifurcation	20- to 30-degree ipsilateral anterior oblique
Trifurcation and tibial arteries	Anatomic AP (or 20-degree ipsilateral anterior oblique with feet in the neutral supine position)

AP, Anteroposterior; *SMA*, superior mesenteric artery.

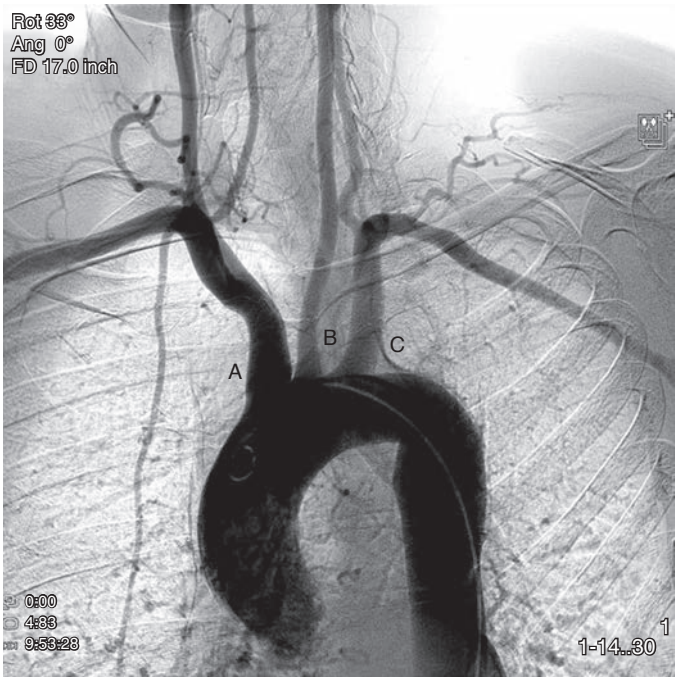

Figure 25.14 Viewing the aortic arch from an approximately 30-degree left anterior oblique angle splays out the arch anatomy with good visualization of the origins of the innominate *(A)*, left common carotid *(B)*, and left subclavian *(C)* arteries.

variability of MRA and CTA make it all the more important that vascular surgeons be highly adept at performing high-quality arteriography to include such small vascular beds as the foot, hand, viscera, pelvis, and brain.

A thorough history and physical examination have become even more important in an era surrounded by cost consciousness and minimization of risks to the patient from unnecessary radiologic evaluation. From a vascular examination perspective, the history and the physical examination in association with routine noninvasive vascular laboratory testing may guide the vascular surgeon directly to primary diagnostic arteriography, particularly if endovascular treatment is anticipated at the time of the diagnostic. There are several clinical scenarios in which CTA or MRA is necessary before arteriography: when diagnosis of a vascular problem is in question and CTA or MRA can provide a diagnosis that will avoid arteriography; in the diagnosis and treatment of aneurysmal disease; when the route of optimal percutaneous access is uncertain; and when other juxtaposition body imaging information is necessary in addition to vascular imaging. Other advantages of arteriography that may affect clinical decision-making include the ability to obtain physiologic testing of differing blood pressures proximal

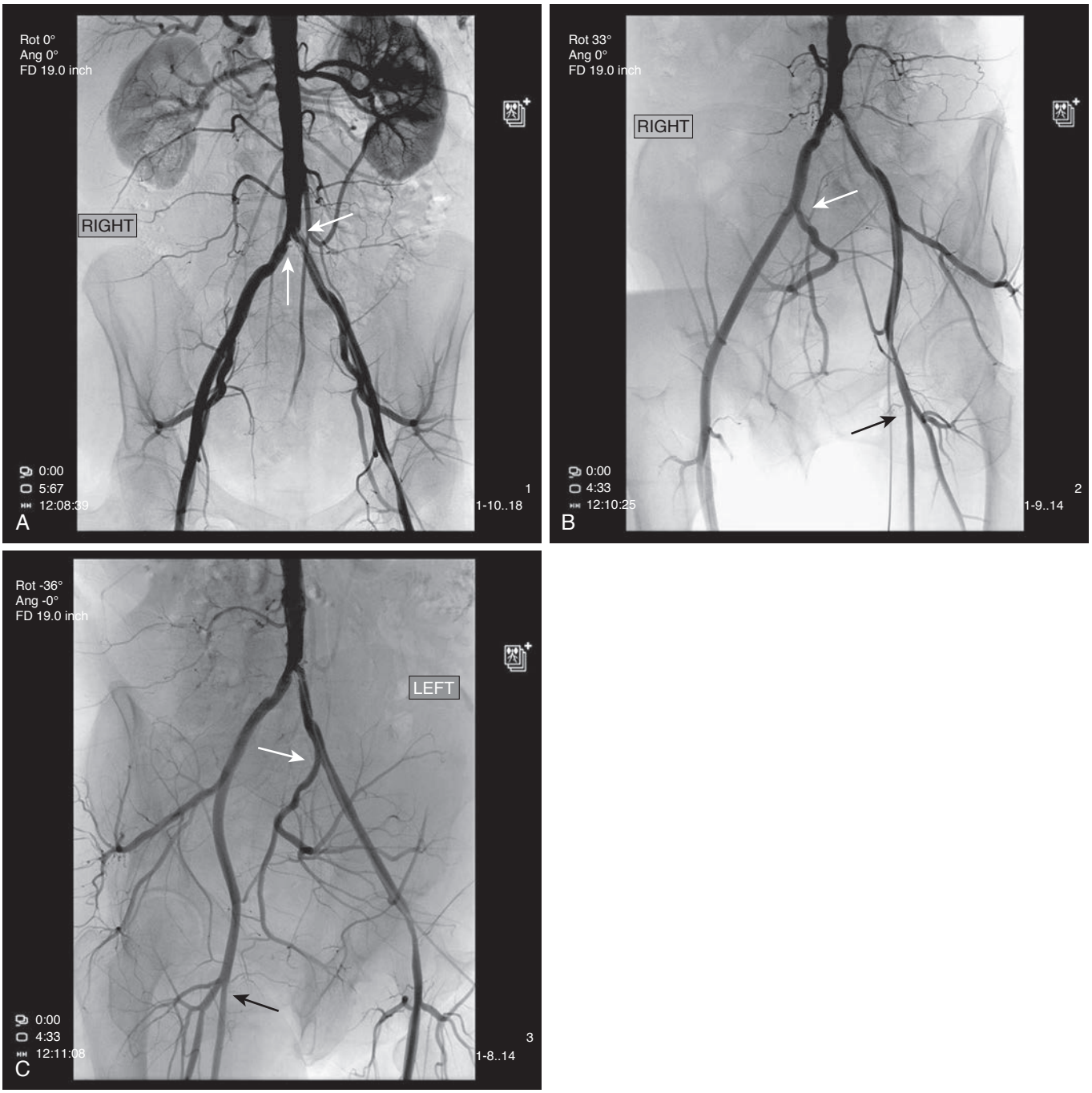

Figure 25.15 (A) An anteroposterior view of an aorta-iliac-femoral arteriogram is the ideal orientation to visualize the aortic bifurcation and bilateral common iliac arteries. Mild stenosis is present in the proximal right common iliac artery, and moderate in-stent restenosis is present in the proximal left common iliac artery *(arrows)*. (B) A 30-degree left anterior oblique view splays out both the right iliac bifurcation *(white arrow)* and the left femoral bifurcation *(black arrow)*. (C) Alternatively, a right anterior oblique view is ideal for visualizing the left iliac bifurcation *(white arrow)* and the right femoral bifurcation *(black arrow)*.

and distal to stenoses, the ability to directly affect a specific vascular bed with a vasodilator drug, and the ability to take blood samples from certain vascular beds for a certain diagnosis to be made.

Studies comparing arteriography with CTA and MRA conflict as to whether the two are equivalent to the criterion standard.[18-27] More important, in making clinical decisions, some studies have shown benefit of CTA or MRA, whereas others have not. Hingorani et al.[19,21] compared CTA and MRA with contrast arteriography in patients with chronic lower extremity ischemia requiring revascularization. Accuracy of CTA and MRA were poor in femoropopliteal and tibial segments compared with contrast arteriography. In these studies, CTA and MRA could not provide equivalent imaging to ensure the optimal clinical

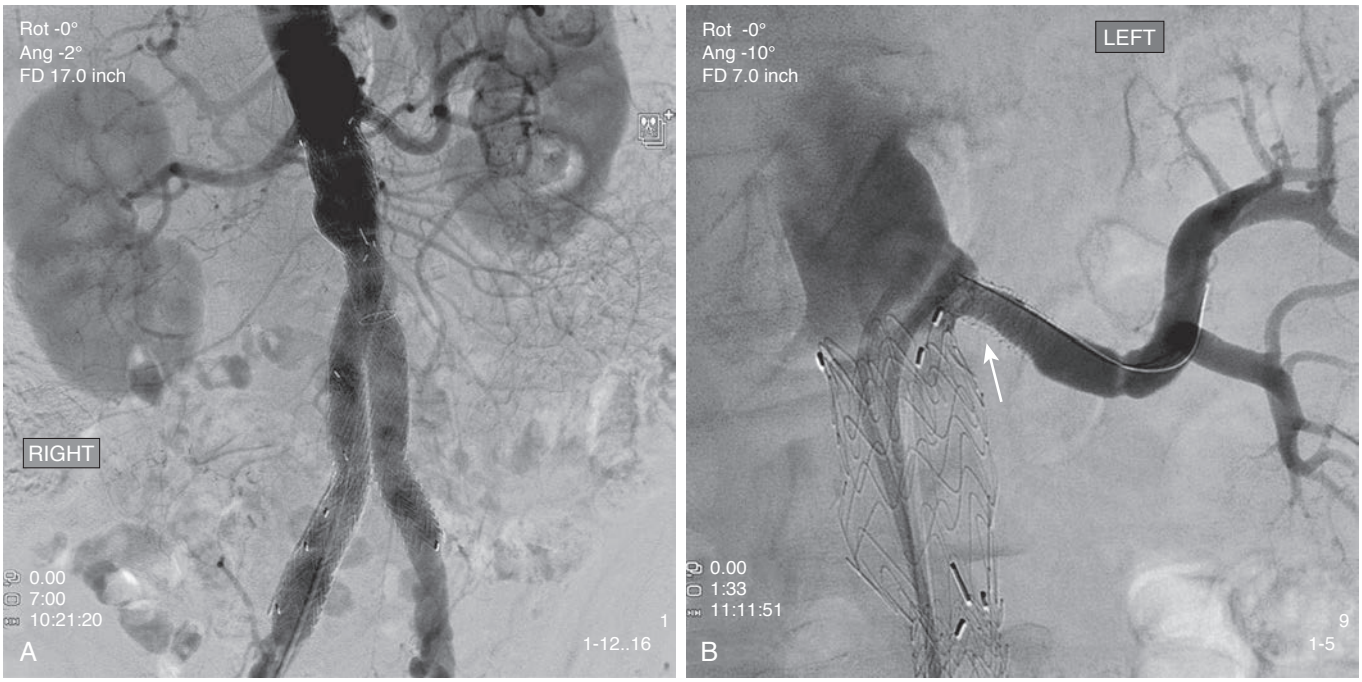

Figure 25.16 (A) Flush aortic arteriogram showing an adequately sealed aortic endograft and patent left renal artery stent. (B) Adjustment of the image intensifier, or flat detector, from a 17-inch to a 7-inch projection gives a much clearer magnified view of the left renal artery and reveals mild in-stent restenosis *(arrow)*.

decision for lower extremity revascularization. In contrast, MRA may have a role in identifying patent tibial target vessels for lower extremity bypass that are not seen on DSA due to very low flows (Owen et al., 1993).[24,25] All studies comparing CTA and MRA with DSA for lower extremity arterial occlusive disease are fraught with small numbers of patients and differing methodologies of stenosis criteria and techniques, and the selection of optimal imaging remains somewhat case-, center-, and surgeon-specific.

LIMITATIONS AND RISKS

Sources of Error With Arteriography

Motion artifact is the most common source of degradation of image quality and can be devastating to accurate visual interpretation. However, other potential sources of image compromise involve the patient's anatomy. Bone, bowel gas, surgical clips, implanted devices, shrapnel or other foreign bodies, and any other surrounding tissue densities can obscure true anatomic detail of a vessel. This problem is addressed by obtaining images from multiple angles and thereby separating the target vessel from the interfering tissue density. Vital interpretations and interventions are almost never based on a single-plane image. Superimposed contrast columns in overlying arteries can also obscure anatomic detail. This often occurs at vessel bifurcations and in vessels that are angulated in a plane parallel to the angle of view. Because significant occlusive lesions commonly occur at vessel bifurcations, this scenario can seriously adversely affect accurate disease diagnosis and proper management decisions. Recognizing subtle differences in the density of contrast in areas of artery overlap will help to prevent misinterpretation. Again, emphasis should be on changing the angle of view to splay out such a bifurcation and better visualize each individual vessel (Fig. 25.17).

An extremely important concept in angiography is the limitation of expecting a two-dimensional image to accurately represent a 3D structure. Relying solely on single-plane imaging, in an anteroposterior-only view, for example, may lead to underestimation of significant arterial disease in some instances. This is highlighted by some of the aforementioned scenarios. Posterior plaques are another notorious example of this potential source of error (Fig. 25.18). In one view, a vessel may appear to have uniform diameter and no evidence of stenosis; but in an oblique or lateral view, hidden ulceration or a profound stenosis may be evident, a so-called pancake lesion as opposed to a circumferential lesion. This underscores the importance of multiplanar arteriography to truly highlight its accuracy over other imaging modalities.

Risks From Contrast Agents

Systemic Toxicity

The toxic side effects of iodinated contrast agents are primarily thought to be due to hyperosmolality. The most common adverse symptoms are nausea, vomiting, and pain in the distribution of the specific arterial bed that is injected. The discomfort seems to become more significant as the osmolality increases,[28] especially when it is greater than 400 to 500 mOsm. Furthermore, nonionic agents tend to cause fewer adverse symptoms than ionic agents

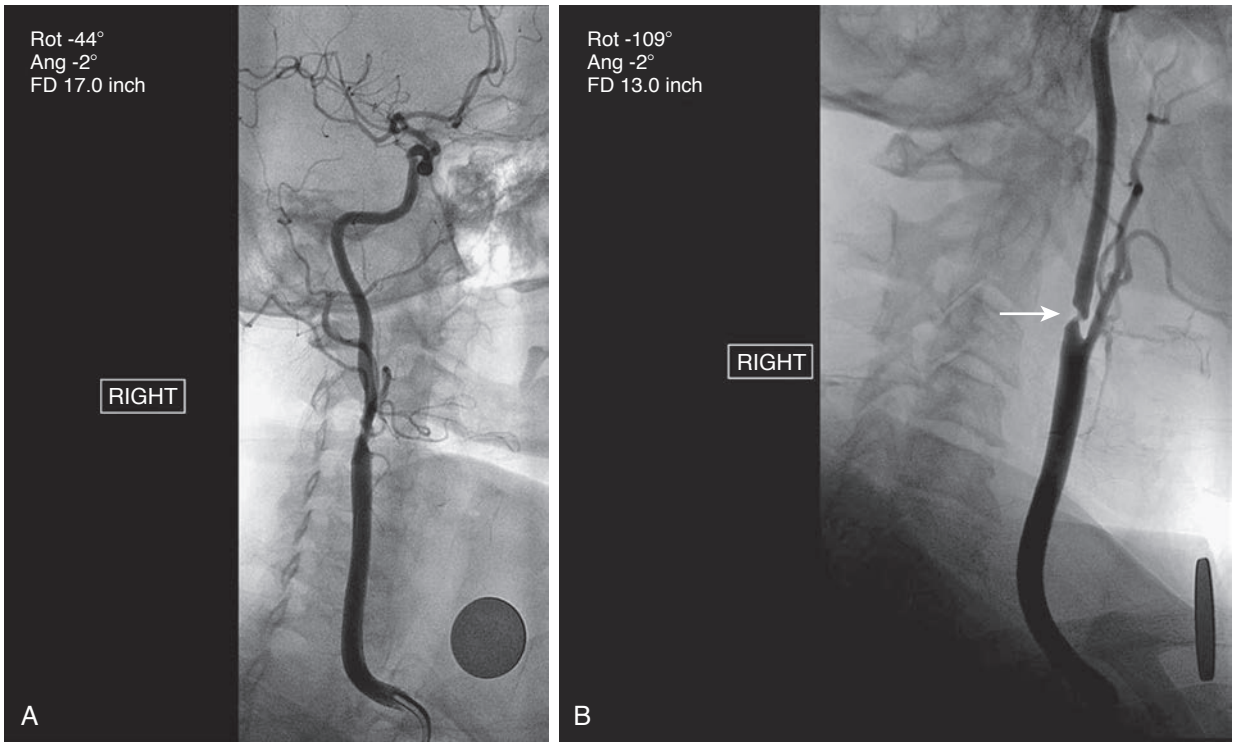

Figure 25.17 (A) Selective carotid arteriogram showing poor characterization of the carotid bifurcation on an oblique view because of superimposed vessels. (B) Adjustment of the angle of projection opens the bifurcation to clearly visualize the internal and external carotid arteries, revealing a significant proximal internal carotid stenosis *(arrow)* that previously was not apparent.

Figure 25.18 Selective Carotid Arteriogram Highlighting the Importance of Multiplane Imaging to Unmask Suspicious Posterior Vessel Lesions. (A) An oblique view seems to demonstrate good visualization of the carotid bifurcation with some mild irregularity of the internal carotid artery *(arrow)*. (B) Repeated imaging with a lateral projection, however, unveils a high-grade stenosis of the internal carotid artery with an ulcerated posterior plaque *(arrow)*.

do, which is why there has been a significant trend toward formulating lower osmolality, nonionic agents.

Other adverse systemic effects of contrast administration are related to nonspecific reactions involving histamine release. Such reactions are usually treated with antihistamines alone in minor cases, such as urticaria. For more severe reactions, such as laryngeal edema or bronchospasm, treatment starts with inhaled adrenergic medications such as albuterol and, if that is ineffective, intravenous administration of epinephrine. Finally, cardiopulmonary arrest may require full hemodynamic support with vasopressors in addition to mechanical ventilation for respiratory support. It is important to distinguish hemodynamic instability caused by cardiopulmonary collapse from the more common vagally mediated hypotension, which may be due to such causes as anxiety or catheter manipulation and is best treated with intravenous fluid and close observation. In cases of severe bradycardia and hemodynamic instability, atropine (0.5 to 1.0 mg intravenously) should also be administered. Patients with a history of asthma, other allergies, reactions to contrast media in the past, or anxiety are predisposed to the aforementioned side effects.[29,30]

After a patient has suffered an adverse reaction from exposure to an iodinated contrast agent, it is imperative to minimize this risk in the event of subsequent exposure. Multiple studies have shown corticosteroids to be effective for prophylaxis in these patients.[31-37] Lasser and colleagues demonstrated a significant reduction in reactions related to hyperosmolar agents with the administration of 32 mg of methylprednisolone 12 and 2 hours before injection of the contrast agent. In a similar regimen, these investigators also found that use of a nonionic contrast agent with lower osmolality reduced adverse events from 4.9% in the untreated group to 1.7% in the pretreated group.[32,33] Other studies have shown that premedication with 50 mg of prednisone given at 13, 7, and 1 hour prior to contrast administration, often in conjunction with diphenhydramine, is an effective method of preventing contrast-induced allergic reactions, with breakthrough reactions occurring only 2.1% of the time.[38,39] Katayama and associates found a reduction in adverse reactions from 12.6% to 3.1% with use of ionic, high-osmolality contrast agents, as opposed to nonionic, low-osmolality agents.[40] Steroid premedication should be administered to all patients who have a history of reaction to contrast media or who are otherwise at high risk for such. Some authors assert that despite prophylaxis, albeit at lower doses than described previously, and the use of low-osmolality contrast agents, as many as 10% of patients may still suffer a breakthrough reaction.[41]

Cardiac Toxicity

Contrast agents can adversely affect cardiac function, particularly during coronary angiography and ventriculography. These physiologic disturbances are spurred by electrolyte imbalances of sodium and calcium in the coronary system caused by passive washout after the injection of contrast material. Even in noncoronary arteriography, some older contrast agents were able to bind calcium and induce arrhythmias by reducing levels of free ionized calcium.[42] The most common hemodynamic effect is a decrease in heart rate and blood pressure, usually temporary and self-limited. However, this can be much more pronounced in patients with severe underlying cardiac dysfunction, aortic stenosis, or direct exposure of the heart to the contrast agent. Use of low-osmolality agents has been shown to reduce the incidence of such adverse hemodynamic effects.[43]

Hematologic Toxicity

Conventional iodinated contrast agents have been shown to inhibit multiple coagulation factors and antithrombin activity, as well as to exhibit antifibrinolytic properties.[44] The clinical significance of these findings is unclear within circulating blood. However, red blood cells do aggregate when in contact with contrast media.[45] This can present a compromising situation with stasis of blood and contrast material within the catheters and sheaths used for injection. To prevent the possible introduction of fresh thrombus into the circulation, it is strongly advised that one remain vigilant about frequent flushing of catheters and sheaths with saline. Anticoagulation (heparin, 2500 to 5000 units) during endovascular procedures should be considered on a case-by-case basis. In cases in which heparin is used, measuring activating clotting times and possibly reversing heparin effects with protamine administration may be necessary before sheath removal. There is some evidence that use of nonionic contrast agents may reduce these adverse hematologic effects.[46]

Nephrotoxicity

Contrast-induced nephropathy is perhaps the most commonly cited and studied adverse reaction to iodinated contrast agents and carries with it significant morbidity and mortality. It continues to be the third leading cause of acute renal failure in hospitalized patients.[47,48] The severity of clinical manifestations in these patients ranges from a mild reversible rise in serum creatinine concentration to end-stage renal failure and death. Multiple clinical trials have shown the deleterious effect of iodinated contrast agents on renal function.[49-51] Many risk factors for the development of contrast-induced nephropathy have been identified, of which preexisting renal dysfunction remains the most important.[52] Other risk factors include advanced age,[53] congestive heart failure, dehydration, hyperosmolar states (e.g., multiple myeloma), and severe proteinuria. In such patients the volume of contrast material should be minimized and adequate hydration should be administered. Interestingly, neither the type of contrast agent used nor the total volume infused seems to play a significant role in the development of this complication in patients with normal renal function.[52,54-56] Although administration of contrast agents to patients already suffering from complete renal failure may be done without fear of inducing further nephropathy, these patients are at risk for hyperosmolar volume overload and should be scheduled for dialysis after the angiography procedure.

All iodinated contrast agents are primarily excreted by the kidneys. It was originally thought that the high osmolality and ionization of conventional contrast agents were responsible for contrast-induced nephropathy. However, there is no difference in such occurrence with ionic and nonionic contrast agents.[57] However, there does appear to be reduced risk with the use of low-osmolality contrast agents as opposed to those with high

osmolality.[57-59] After infusion, contrast material is filtered by the glomerulus with little or no evidence of tubular reabsorption. The principal site of contrast-induced nephropathy is the renal tubule secondary to transient local ischemia.[60] Because contrast material is filtered without reabsorption, an osmotic gradient is created that results in increased intratubular pressure, afferent arteriolar vasoconstriction, and decreased glomerular filtration rate. This decrease in glomerular filtration rate results in regional tubular ischemia.

The incidence of contrast-induced nephropathy in patients with normal renal function is only 1% to 2%.[52] This risk increases to 10% in patients with creatinine levels of 1.3 to 1.9 mg/dL (115 µmol/L to 168 µmol/L) and to as much as 62% in patients with levels higher than 2 mg/dL (177 µmol/L). The incidence of contrast-induced nephropathy is high in the diabetic population, although diabetes is not considered an independent risk factor. It is probably an unmasking effect of subclinical renal insufficiency, which is common in these patients. Patients with type 1 diabetes are more prone to the development of contrast-induced nephropathy than are patients with type 2 diabetes.[61,62] Moreover, diabetics with renal insufficiency in whom acute contrast-induced renal failure develops are less likely to recover than are nondiabetics with baseline renal insufficiency, and they are at greater risk of permanently requiring dialysis.[61-63]

Metformin

Diabetic patients taking metformin (dimethylbiguanide), an oral hypoglycemic agent, require special consideration when receiving iodinated contrast material. Metformin is excreted by the kidneys, and continuing to take this drug in the setting of renal dysfunction can result in lactic acidosis. This is a rare complication resulting from impaired drug clearance in patients in whom nephropathy develops as a result of iodinated contrast material. There have been published guidelines pertaining to the use of contrast material in these patients.[64] Only low-osmolality contrast agents should be used, and creatinine levels should be checked before and after the procedure. Patients with normal preprocedure and postprocedure renal function should refrain from taking metformin for a period of 48 hours after the procedure. Patients with baseline renal insufficiency that remains stable should refrain from taking the drug for 48 hours before and 48 hours after the procedure. In an emergency setting, patients with renal insufficiency should be well hydrated for 24 hours after the procedure while being monitored for the development of lactic acidosis. Findings can include nausea, vomiting, somnolence, epigastric pain, anorexia, lethargy, diarrhea, thirst, pH less than 7.25, lactic acid level greater than 45 mg/dL (5 mmol/L), anion gap greater than 15 mEq/L (15 mmol/L), and increase in the lactate-to-pyruvate ratio.

Prevention of Contrast-Induced Nephropathy

Prevention of contrast-induced nephropathy has been the subject of many research trials and studies. Intravenous hydration appears to be the most effective tool,[65,66] with 0.9% normal saline offering better protection than 0.45% normal saline.[67] Intravenous sodium bicarbonate administered before exposure to contrast material may also significantly reduce renal dysfunction.[68] Another agent that may offer protection against contrast-induced nephropathy in patients with renal dysfunction is the antioxidant *N*-acetylcysteine[69-73] given at a dose of 600 mg for 2 days before and after the procedure. Tepel and colleagues found that the incidence of contrast-induced nephropathy was reduced from 22% to 2% in patients receiving *N*-acetylcysteine with hydration versus those receiving hydration alone.[70] Other trials have failed to show a clear benefit, and therefore the recommendation for routine use remains controversial.[74-77] Many other agents have been studied for possible protective effects against contrast-induced nephropathy through the actions of increasing vasodilation, renal perfusion, or diuresis (or any combination of these mechanisms). Such agents include fenoldopam, theophylline, prostaglandin E_1, endothelin antagonists, calcium channel blockers, dopamine, and diuretics. However, none of these agents can be recommended for the prevention of contrast-induced nephropathy on the basis of current scientific evidence.[50,51,65,78-96] The development of strict protocols with adherence to low dosing of contrast agents has also been shown to further improve results in the prevention of contrast-induced nephropathy. Although many of these protocols have been developed for CT, they are equally applicable to arteriography.[97-99]

Limitations and Risks of CO_2 Contrast

Because CO_2 gas tends to rise, visualization of vessels with posterior origins may sometimes be difficult in the supine position. A typical example is the left renal artery, which often has a posterolateral takeoff from the aorta. To address this issue, patients can be positioned with the left flank slightly elevated, either by placing a roll under the left side or by tilting the table in that direction if such a feature is available. This will raise the left renal artery above the plane of the catheter and allow better filling with CO_2.

Complications from CO_2 injection for angiography are extremely uncommon, with only a handful of serious adverse events reported in the literature.[100-104] Most of them were related to mesenteric ischemia secondary to gas trapping. CO_2 dissipates rapidly in the bloodstream, but gas trapping can occur in any vessel and lead to ischemia. The most important consideration when CO_2 is used for intraarterial injection is the potential risk of neurotoxicity. An animal study involving direct injection of CO_2 into the carotid vessels resulted in multiple ischemic infarcts and subsequent neurologic deficits.[105] However, other animal studies found no adverse reactions when CO_2 was injected into the thoracic aorta or carotid vessels.[106,107] Although there is no strong evidence in humans, this potential risk demonstrated in animals has led to the general recommendation to avoid use of CO_2 as a contrast agent when injection is above the diaphragm.

FUTURE ADVANCES

Arteriography is an essential tool in the practice of vascular surgery, and the outlook of future advances is promising. Arteriography will be integrated with other modalities to create improved images, provide physiologic information, and deliver novel therapies in a targeted manner. The possibilities will

continue to grow as scientists and vascular surgeons alike move to treat standard problems in ways previously thought not possible. A sound education and training in arteriography, with the commitment to modernize as standards of care change, is necessary as vascular surgery continues to evolve.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 26

Venography

RICHARD H. PIN, MICHEAL T. AYAD, and DAVID GILLESPIE

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Since the early 1970s contrast-enhanced venography has been the "gold standard" for the diagnosis of deep venous thrombosis (DVT). Early leg venography required venous cut-down for access to the deep venous system, but this technique has evolved such that contrast material is injected percutaneously into a superficial vein in the foot, with a tourniquet applied above the ankle to prevent filling of the superficial veins that often obscure the deep system. As equipment and contrast agents have improved, so has the safety and efficacy of venography in evaluating DVT. However, in recent decades, duplex ultrasonography has emerged and become readily available as a noninvasive means of accurately diagnosing DVT. This modality has largely supplanted venography for the diagnosis of extremity venous disease; however, venography remains important in evaluating the proximal iliofemoral or axillosubclavian veins and integral in the endovascular treatment of DVT. It also remains an effective imaging tool for evaluating venous structures within the thoracic and abdominal cavities.

Keywords

venous
venography
reflux
obstruction
thrombosis

BASIC PRINCIPLES

The two primary techniques of venography that we currently use are ascending and descending venography. Ascending venography is more common and is used to elucidate the presence of DVT in the lower extremity. Descending venography predominantly evaluates incompetent valves in patients with chronic venous insufficiency. This requires direct access to the deep venous system. The techniques of ascending and descending venography are described in the next section on clinical applications.

CLINICAL APPLICATIONS

The current indications for venography are detailed in Box 26.1. Despite the availability of less invasive techniques, venography is still considered the gold standard against which all examination modalities are compared to determine the presence of DVT. This is particularly true in instances in which duplex ultrasound is inconclusive or unavailable. Venography also continues to have a higher sensitivity and specificity in detection of infrapopliteal thrombotic disease. Venography is indicated in evaluation of valvular insufficiency and venous malformations, and it has been shown to be helpful in planning adjunctive techniques in the operating room. Relative contraindications to venography are also listed in Box 20.1. Other common modalities used in detection of thrombosis and reflux are compared in Table 26.1.

BOX 26.1 Current Indications for and Relative Contraindications to Venography

Current Indications for Venography

1. Diagnosis of DVT in a patient
   a. With a nondiagnostic duplex ultrasound examination or for whom a duplex examination is not technically feasible
   b. With a high clinical suspicion for DVT but with a negative duplex examination
   c. When duplex ultrasound is not available
2. As an adjunct during venous intervention (thrombolysis, thrombectomy, angioplasty, and stenting)
3. Evaluation of valvular insufficiency prior to stripping or ligation of superficial varicose veins
4. Venous mapping prior to or following a surgical interventional procedure
5. Evaluation for venous stenosis or venous hypertension
6. Evaluation for venous malformations
7. Preoperative evaluation for tumor involvement or encasement

Relative Contraindications (Included But Not Limited to)

1. Evidence of active cellulitis of the extremity to be imaged
2. Iodinated contrast allergy
3. Renal insufficiency in patients who are not on dialysis, particularly those with diabetes or congestive heart failure

DVT, Deep venous thrombosis.
Reproduced from ACR-SIR practice guideline for the performance of diagnostic infusion venography, revised 2008.

Ascending Venography

Ascending venography has been used for many indications, including DVT, incompetent perforating veins, and venous aneurysms and malformations.

Deep Venous Thrombosis

DVT cannot be reliably diagnosed by clinical examination. Indications for ascending leg venography include a nondiagnostic ultrasound study and a need for better imaging of calf veins in the setting of high clinical suspicion of DVT.[1] Because of its high diagnostic accuracy, a leg venogram is immediately useful for evaluation of the presence of deep venous disease in these circumstances. Another indication is delineation of DVT during endovascular intervention, such as thrombolysis, thrombectomy, or angioplasty.

Technique

Diagnostic ascending venography requires a 22-gauge catheter, three 25-mL syringes, two tourniquets, a tilting fluoroscopic table with footrest, C-arm fluoroscopy, contrast agent, and normal saline. In addition, a 4F micropuncture sheath should be available for direct access to the venous system through the popliteal vein if needed. It begins with placement of a catheter in a peripheral vein. The access device is usually a 22-gauge intravenous catheter inserted into a superficial vein on the dorsum of the foot. When the affected extremity has significant edema, percutaneous catheterization of peripheral veins becomes difficult. In such cases, we use ultrasound to guide vascular access. It is important that access for ascending venography not be through the saphenous vein adjacent to the medial malleolus at the ankle because contrast material may preferentially fill the superficial system without demonstrating the deep venous systems adequately. The likelihood of this problem can be decreased by placing a tourniquet at the ankle and one at the knee, which will drive the contrast material into the deep venous system. However, these tourniquets should be released just before image acquisition to relieve extrinsic compression and to avoid occlusion of the deep veins.

The patient is placed on a tilting fluoroscopic table and a footrest to enable near-upright positioning. With the patient initially in a reverse Trendelenburg position, the table is tilted to recumbency as the bolus is tracked. This approach enhances visualization of the large-capacity lower extremity venous anatomy as gravity delays the outflow of contrast material. The contralateral leg is supported with a small platform so that no weight is borne on the leg to be examined. Side grip handles can be placed on the table as needed, depending on the patient's comfort and security in the semiupright position.

The examination is begun with the patient in a 40- to 60-degree semiupright position. The bolus is followed by radiographic imaging as the material flows to the central veins. As the contrast agent ascends, additional filming of the deep and superficial femoral veins is performed. At least two projections are needed in the tibial and popliteal locations. Approximately 50 to 100 mL of contrast material is needed to fill the deep venous system adequately from ankle to groin.

TABLE 26.1 Comparison of Various Modalities for the Detection of Venous Disease

Technique	Pros	Cons
Venography	Good confirmatory test with diagnostic uncertainty and in detection of asymptomatic DVT Good diagnostic ability below the knee Descending venography demonstrates the location of the valve as well as valvular competence or incompetence	Invasive Not as readily available Expensive Potential for patient discomfort Risk of phlebitis Intravenous administration of contrast material Risk of nephrotoxicity Allergic reactions Increased cost Need for adequate intravenous access
Duplex ultrasound	Noninvasive Portable Readily available Absence of ionizing radiation High sensitivity and specificity above the elbow and above the knee	Operator dependent Detection of calf DVT is variable Greater accuracy in detecting DVT in symptomatic versus asymptomatic patients Does not permit accurate localization of the levels of valve stations and specific identification of incompetent segments Difficult to ascertain in those with massive edema, wounds, or obesity
Computed tomography venography	Noninvasive Technically simple Time requirement to ascertain the examination is low High sensitivity and specificity	Contrast agent required Risk of nephrotoxicity Radiation exposure Requires patient participation with breathing techniques Flow artifacts may complicate results
Magnetic resonance venography	Noninvasive Improved image quality	Expensive Long examination requirements Radiation exposure Caution in renal disease Inability to be used in patients with metal-based implanted devices

DVT, Deep venous thrombosis.

Additional contrast material can be injected, as needed, to visualize problem areas.

Even with appropriate venous access and the use of tourniquets, adequate opacification of the deep veins of the lower extremities may be difficult because of dilution of the contrast agent and preferential flow from deep to superficial regions, which allows contrast material to escape to the superficial system. In such cases, we place the patient in the prone position, access the popliteal vein under ultrasound guidance, insert a 4F micropuncture sheath, and inject contrast material into the deep venous system. At completion of the examination, the veins are flushed with 50 mL of normal saline to minimize contact of the contrast agent with the venous endothelium and the chance for development of thrombophlebitis.

Interpretation

The classic venographic sign of venous thrombosis is a luminal filling defect with a surrounding rim of contrast (Figs. 26.1-26.6). This appearance of parallel lines of contrast material around the thrombus is referred to as the "tram-track" sign. Other indicators of thromboembolism are an abrupt termination of intravascular contrast or the formation of a meniscus. However, correct and consistent interpretation of lower extremity venography to rule out DVT may be difficult. Intraobserver disagreement about the probable presence or absence of thrombus has been shown to occur in up to 10% of venographic cases.[2] The invasive nature of the technique, the exposure to radiation, and the upsurge of ultrasound technology have made venography a secondary technique for the detection of acute and chronic venous thrombosis. However, venography does play a primary role in the treatment of DVT, allowing for localization and use of mechanical thrombectomy devices for acute venous clot and placement of stents in the setting of chronic venous scarring.

Incompetent Perforating Veins

The normal outflow from veins of the lower extremity includes pathways from the superficial system to the deep system through perforating veins. Perforating veins possess unidirectional valves, which, when competent, prevent reflux of blood from the deep into the superficial veins of the leg. Perforating veins with incompetent valves contribute to the development of venous hypertension in the superficial system, which results in the formation of varicose veins and venous ulceration.

Normal perforating veins are small, thin, and smooth. However, incompetent veins are dilated, irregular, and valveless. Historically, ascending venography has been a reliable technique for identifying incompetent perforating veins. This invasive technique, although useful, has largely been replaced by color-flow duplex examination of the lower extremity.

Figure 26.1 Normal right leg venogram. (A) Lateral calf projection. (B) Anteroposterior projection of the knee. The anterior tibial veins *(small arrow),* peroneal veins *(short arrow),* posterior tibial veins *(arrowhead),* gastrocnemius veins *(open arrow),* great saphenous vein *(curved arrow),* and popliteal vein *(long arrow)* are indicated.

Technique

Ascending venography for incompetent perforating veins involves the injection of contrast material into a foot vein with a tight tourniquet around the ankle to occlude the superficial veins such that reverse flow from the deep veins into the superficial veins through the incompetent perforating veins can be seen. A translucent ruler is then used to measure the location of the incompetent perforating vein from the tip of the medial or lateral malleolus. The table is next moved through the horizontal position and then into Trendelenburg position, and flow of contrast material is followed under fluoroscopy. Lateral views are especially important in the thigh for accurate localization of a midthigh perforating vein. After a perforating vein is identified, a tourniquet can be used above that level to direct the contrast agent into any incompetent perforating vein.

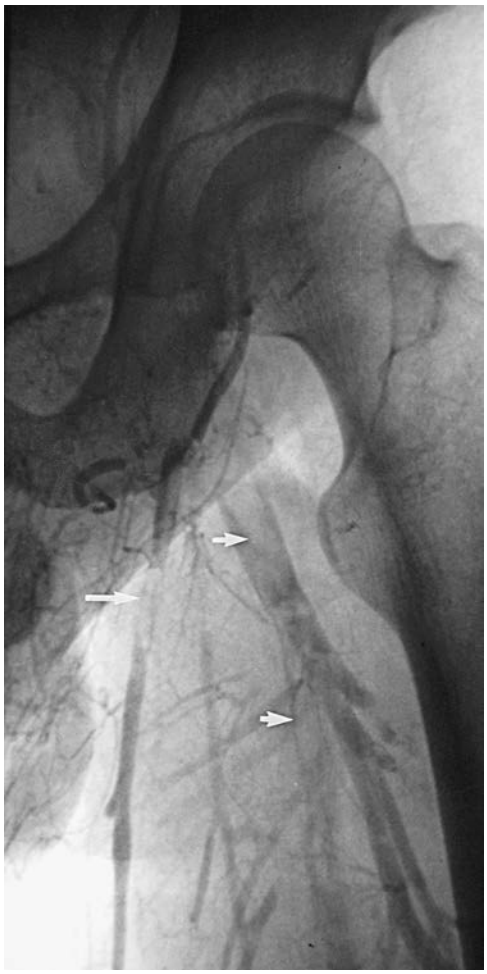

Figure 26.2 Acute thrombus in the deep femoral and great saphenous veins. The deep femoral vein *(short arrows)* and the great saphenous vein *(long arrow)* are shown. The femoral vein is occluded.

Interpretation

Thomas and Bowles compared ascending venography with varicography for identification of incompetent perforating veins.[3] Sixty-one legs of 50 patients were examined with both methods. Incompetent perforating veins of the gastrocnemius muscle and midthigh were more accurately shown with varicography than with ascending venography (Fig. 26.7).

Venous Aneurysms and Malformations

The most serious complication associated with lower extremity venous aneurysms is the development of thrombus within the aneurysm and subsequent embolization. Pulmonary embolization has been reported to occur frequently in extremity venous aneurysms, most notably in those involving the popliteal vein (Fig. 26.8). Aldridge and coauthors in 1993 reported 24 cases of popliteal venous aneurysm in which all patients had experienced thromboembolic events.[4] Aggressive treatment with immediate anticoagulation and preoperative planning has become the standard of care for this reason. Venography is a useful method for preoperative planning before resection and interposition grafting or lateral suture repair of these aneurysms.

Figure 26.3 Acute thrombosis of the soleal veins. *Arrows* indicate fresh thrombus filling the soleal veins.

Figure 26.4 Subacute thrombus in the popliteal vein. *Arrows* denote retracted thrombus, indicative of subacute thrombosis.

Venous malformations may take the form of isolated venous lakes or diffuse venous aneurysm formation, such as Klippel-Trénaunay syndrome (Fig. 26.9). Patients often become symptomatic from mass effect, reflux, or venous thromboembolism. Operative or interventional management may be indicated in symptomatic patients. Most patients do well without treatment or with elastic compression only. Surgical treatment of the vascular malformation in Klippel-Trénaunay syndrome is rarely needed and continues to be controversial.[5] Preoperative venous imaging with ascending venography or direct stick varicography is useful for planning treatment.

Technique

The technique used is the same as when ascending venography is performed. Direct stick varicography is most useful for the evaluation of venous malformations (see Figs. 26.8 and 26.9). Ultrasound-guided access provides the ability to perform direct stick venography. In patients being treated for venous malformations, access can be difficult and painful. In such cases, either general or regional anesthesia may be useful.

Interpretation

Focal dilation of the deep or superficial venous system is diagnostic of venous aneurysms and malformations (see Figs. 26.8 and 26.9). Because of the small number of venous aneurysms included in most individual series, no single diagnostic method has been reported to be superior to another. However, most series do report color-flow duplex examination to be extremely valuable in the diagnosis of popliteal venous aneurysms and to provide information on the presence of mural thrombus.[6] Gillespie and associates found in their series that venous aneurysms were correctly diagnosed in 85% of patients with imaging techniques: phlebography (60%), color-flow duplex scanning (27%), and magnetic resonance imaging (10%).[7]

Passive filling of the vascular tree after compressive exsanguination of an extremity, extrinsic occlusion of its arterial supply, and venous drainage has been shown to be a useful technique for evaluation of venous malformations.[8] Closed-system venography was performed in 17 patients, and it correctly identified 11 of 12 surgically confirmed vascular abnormalities. There were no false-positive findings.

Descending Venography

As with ascending venography, lower extremity descending venography is no longer used as a screening study. It has largely been replaced by color-flow duplex study, which has shown good agreement with descending venography in the grading of deep and superficial vein reflux.[9] However, duplex examination is limited in that it does not permit accurate localization of the levels of valve stations and specific identification of incompetent segments. For this reason, descending venography remains the definitive test for identifying incompetent valves in patients

Figure 26.5 Chronic popliteal venous thrombosis. Note the extensive recanalization of the popliteal vein *(open arrows)* and relatively large caliber of the great saphenous vein *(solid arrow)*.

Figure 26.6 Chronic deep venous thrombosis. Note the extensive collateral channels and no visualization of normal deep venous structures.

with chronic venous insufficiency who are candidates for venous valve repair or valve transplantation.

Descending venography is used for evaluation of the anatomy and function of the venous valves in the lower extremities. It shows the location of the valves in the veins and also demonstrates the competence or incompetence of these valves. Kistner[10] and Herman[11] and colleagues developed a classification system used commonly to categorize the severity of deep venous reflux and the functional integrity of the venous valves (Table 26.2).

Technique

Descending venography requires a tilt radiographic table, C-arm fluoroscopy, a short 4F or 5F straight catheter with distal side holes, syringes, and contrast agent. It is performed on a tilt radiographic table to allow examination in the 40- to 60-degree upright position. Descending venography always requires direct catheter access into the deep veins. In most cases the venous access site is the common femoral vein contralateral to the side of interest. The catheter is advanced to the inferior vena cava (IVC) and then to the iliac vein and common femoral vein of

Figure 26.7 Incompetent medial calf perforating veins. A single-frame image of a videotape shows free flow of contrast material from the posterior tibial vein through the incompetent perforating veins *(arrows)* into the superficial varicose veins.

Figure 26.8 Popliteal venous aneurysm. (Courtesy Mitch Cox, MD.)

Figure 26.9 Tibial venous malformation in a patient with Klippel-Trénaunay syndrome. (From Gillespie DL, Villavicencio JL, Gallagher C, et al. Presentation and management of venous aneurysms. *J Vasc Surg*. 1997;26:845–852.)

TABLE 26.2 Grades of Venous Reflux

Grade	Description
0	Normal valvular function with no reflux
1	Minimal reflux confined to the upper part of the thigh
2	More extensive reflux, which may reach the lower part of the thigh; a competent valve is present in the popliteal vein, and there is no reflux to the calf level
3	Reflux as above but associated with popliteal valvular incompetence and leakage of contrast material into the calf veins
4	Virtually no valvular competence with immediate and dramatic reflux distally into the calf; this type of reflux often opacifies incompetent calf perforating veins

From Kistner RL, Ferris EB, Randhawa G, Kamida C. A method of performing descending venography. *J Vasc Surg*. 1986;4:464–468; and Herman RJ, Neiman HL, Yao JS, et al. Descending venography: a method of evaluating lower extremity venous valvular function. *Radiology*. 1980;137:63–69.

the symptomatic lower extremity. A short 4F or 5F straight catheter with distal side holes is positioned at the junction of the external iliac vein and common femoral vein (Fig. 26.10). For unilateral examination the catheter is placed from the ipsilateral femoral vein, and for bilateral examination a single femoral vein puncture is used. A transjugular approach may be used to direct the retrograde catheter into both lower extremities from a single access site. The contralateral leg is supported with a small platform, as with ascending venography, so that the leg being examined will be relaxed and bear no weight.

With the catheter tip in the common femoral vein, the table tilted to a 60-degree semiupright position, and the patient bearing weight on a block placed under the nonexamined leg, contrast material is injected and tracked by fluoroscopy as it flows caudad through the incompetent venous valves. A total of 10 mL of contrast material is slowly injected by hand at a rate of 5 mL/s. As the contrast material is injected, the patient breathes normally, after which the patient is instructed to bear down and perform a Valsalva maneuver to enhance evidence of valvular incompetence. Specific areas of interest can be further studied by sequential injections of contrast material to optimize image capture of valve location and function and the extent of reflux.

Interpretation

Although superficial varicosities are frequently present, they are rarely a prominent feature of symptomatic advanced chronic venous disease.[12] Most patients with symptoms of chronic venous insufficiency who undergo venography have reflux into the deep venous system. The two main abnormalities that cause venous valve reflux are postphlebitic valvular incompetence and primary valvular incompetence, with primary valvular incompetence being responsible more frequently.[13] Although venous duplex evaluation is a widely used screening modality for venous reflux, the use of descending venography provides the degree of detail and specificity that allows selection of candidates for deep venous valve repair or transplantation. These procedures are offered to patients with grade 3 or grade 4 reflux who have

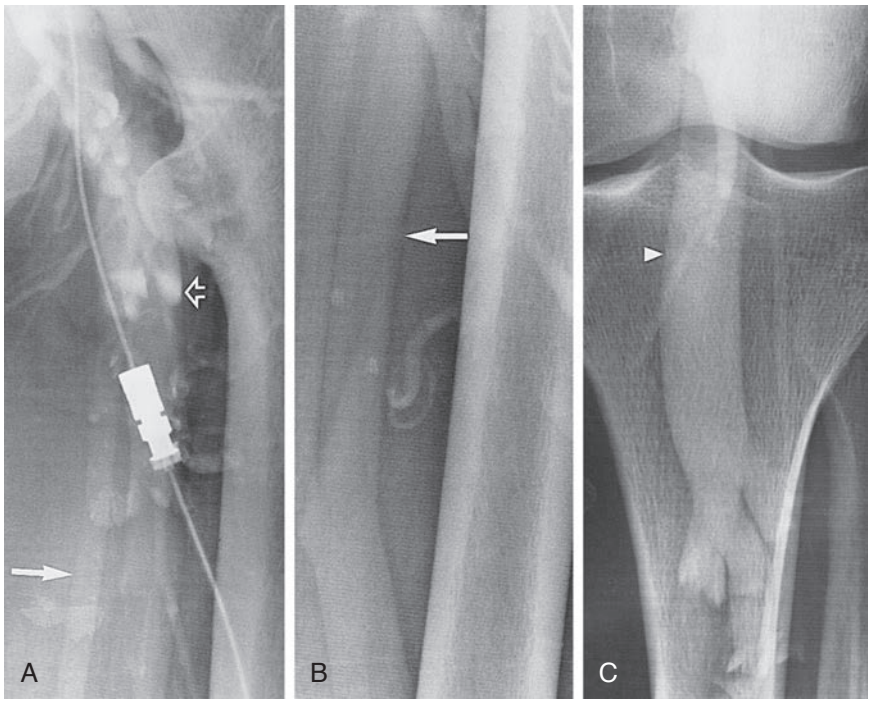

Figure 26.10 (A-C) Descending left leg venogram showing grade 4 reflux. Note the lack of valves in the femoral vein *(solid arrow)* and the large caliber of the popliteal vein *(arrowhead)*. The deep femoral vein *(open arrow)* is shown.

recurrent symptoms of venous insufficiency after treatment of superficial varicosities and perforating vein incompetence (see Fig. 26.10 and Table 26.2).

ILIAC VEIN ASSESSMENT AND INFERIOR VENACAVOGRAPHY

IVC anatomy and patency are routinely assessed as part of IVC filter placement. Phlebography allows assessment of caval anatomy and evaluation for the presence of caval thrombus. In addition, there are several anomalies of the IVC, as outlined in previous chapters. Duplicated cavae, megacavae, and left-sided venae cavae are but a few of these anomalies. Although these anomalies are uncommon, it is important to routinely assess the vena cava with venography before placement of IVC filters to avoid complications caused by either filter misplacement or leaving the patient vulnerable to pulmonary embolism through alternative pathways.

Technique

Access to the venous system is achieved through the internal jugular or common femoral vein. Puncture of just a single wall is facilitated by ultrasound guidance, and a micropuncture kit is used to minimize access size. After access is achieved, a 4 or 5F sheath is placed and proper placement confirmed by free flow of venous blood from the sheath and during femoral access, confirmation that there is no iliac vein thrombus prior to inserting a larger sheath in the vena cava.

From the groin, a 0.035-inch J wire is passed into the common iliac vein. A 5F pigtail catheter is advanced over this wire into the common iliac vein, and cavography is performed.

An alternative method of cavography is to proceed with placement of the IVC filter kit, which consists of a sheath, usually 6.5F to 8F. The insertion track is serially dilated to the appropriate French size. The IVC filter sheath is advanced over the wire to the level of the common iliac vein, and a cavogram is performed.

From the neck a 0.035-inch J wire is passed through the right atrium to the common iliac vein. Passing the J wire through the right atrium into the IVC can sometimes be a challenge. If simple manipulation fails, an angled glidewire and angled glide catheter can be useful. After the J wire is in position, an iliocavogram is performed using a protocol of 10 mL/s for a total of 20 mL of nonionic contrast agent.

Interpretation

The iliocavogram is reviewed for the diameter of the vena cava, the anatomic level of the bifurcation, the level of the renal veins, and any other anomalies (Figs. 26.11 and 26.12). Typically, the renal veins will not fill with contrast material and instead will be identified by a characteristic flow pattern of the mixing of blood filled with contrast material and unopacified blood. The confluence of the common iliac veins is usually identified by the spilling over of contrast material into the contralateral side. The IVC filter can then be placed at a level between the lowest renal vein and the common iliac vein junction.

Some centers advocate first-order selective venography instead of or as a supplement to nonselective venography. Danetz and coworkers found that when selective venography was used in conjunction with nonselective venography, 23% of patients had either an abnormal finding or aberrant anatomy, and most of these patients required a major change in vena cava filter position.[14]

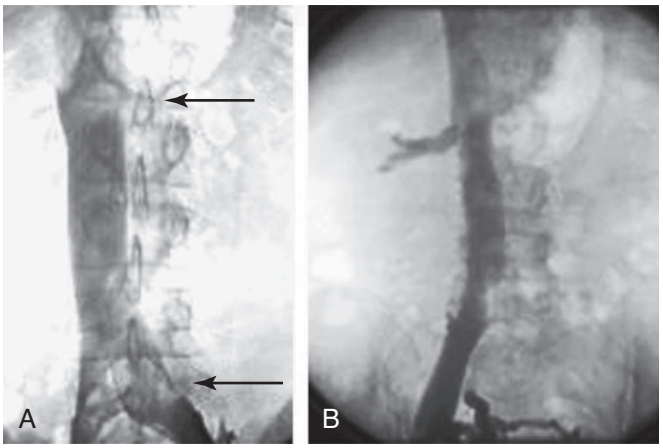

Figure 26.11 (A) Inferior venacavogram demonstrating confluence of the common iliac veins and a normal flow pattern formed by mixing of unopacified renal vein blood with contrast material in the inferior vena cava *(arrows)*. (B) Inferior venacavogram demonstrating filling of the renal veins.

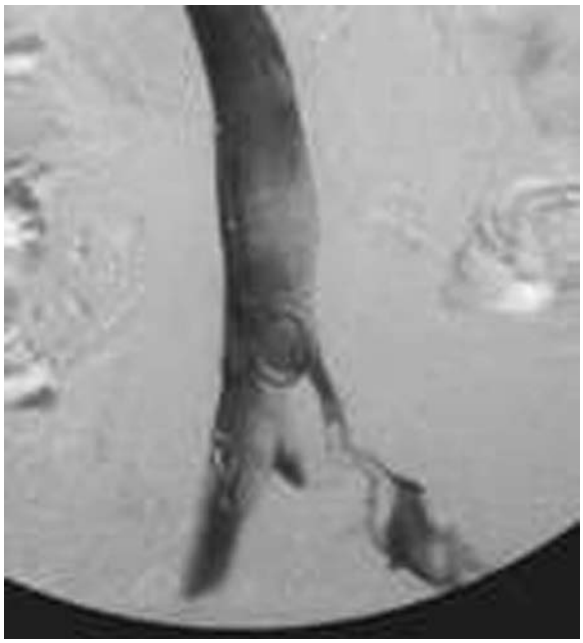

Figure 26.12 Inferior venacavogram demonstrating left common iliac vein deep venous thrombosis (unknown source).

In terms of IVC filter retrieval the surgeon should examine whether the filter has retained thrombus, penetrated the IVC, migrated, or angulated (Fig. 26.13). Severely angulated temporary filters with more than 20 degrees of tilt are more likely to make removal unsuccessful, and filters with retained thrombus should not be percutaneously retrieved unless the operator can lyse the thrombus prior to retrieval.[15]

VENOGRAPHY DURING TREATMENT OF ILIOCAVAL STENOSIS

Advances in angioplasty and stent technology have led to percutaneous treatment of acute and chronic iliocaval occlusion due to thrombosis or external compression (May-Thurner

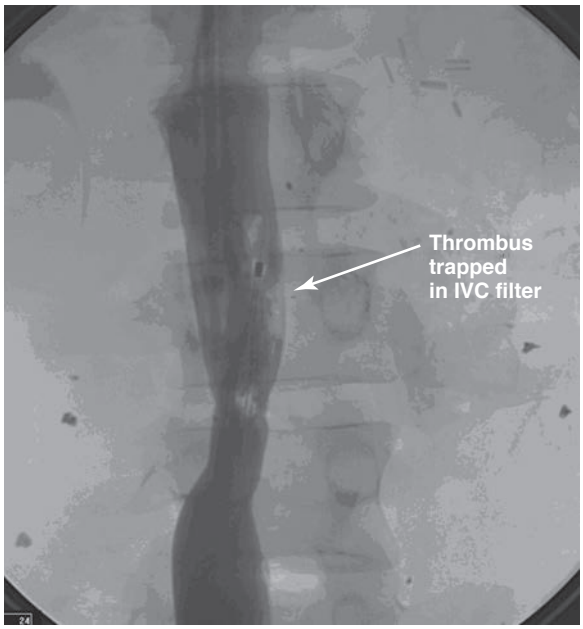

Figure 26.13 Venogram of the inferior vena cava *(IVC)* before attempted retrieval of a prophylactic IVC filter with trapped thrombus *(arrow)*. (Courtesy Eric Adams, MD.)

syndrome). Many authors have written on the efficacy of this method of treating lower extremity venous outflow obstruction.[16-39] Investigation of the safety and efficacy of this treatment has led to refinements of the technique. Neglen and Raju have shown that ensuring adequate inflow into the common femoral vein segment is critical to long-term patency.[27-30,40-44]

Technique

To facilitate visualization of the confluence of the profunda femoral vein and the superficial femoral vein, it is recommended that access be obtained at the midthigh or popliteal level.[45] Ultrasound guidance facilitates placement of a 5F sheath into either of these deep veins. Access to the superficial femoral vein is best achieved in the supine position. However, to obtain popliteal venous access, the patient is placed in the prone position. Once venous access has been achieved, a J wire is advanced to the level of the common femoral vein. A catheter is then advanced over this wire, and iliocavography is performed in the usual fashion. The surgeon can use either a hand injection technique or power injection.

Interpretation

Accurate hemodynamic tests for detecting and grading venous outflow stenosis are currently unavailable. Diagnosis and treatment must be based on morphologic findings. Single-plane transfemoral venography is often used as a standard investigation (Fig. 26.14). These studies may show definite obstruction and the development of collaterals. However, findings are often subtle and only suggestive of an underlying obstruction. Subtle findings of significant venous stenosis include widening of the iliac vein, pancaking, "thinning" of the contrast dye, partial

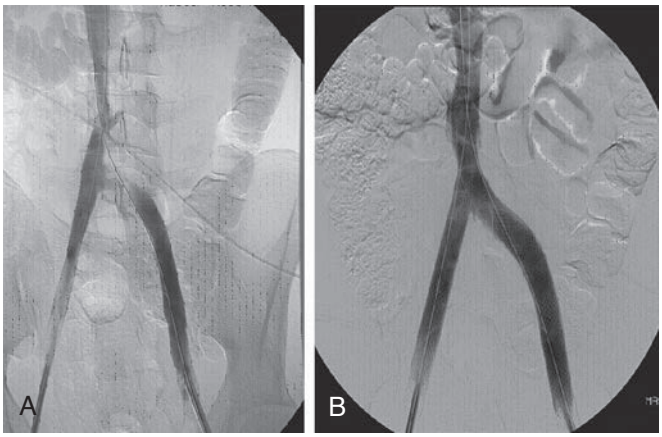

Figure 26.14 Venacavogram revealing left common iliac vein stenosis before (A) and after (B) stenting.

intraluminal defects, septa, and transpelvic collateral formation.[28] To increase the overall accuracy of detecting iliac vein stenosis, the use of intravascular ultrasound can complement venography in these circumstances by providing a cross-sectional view of the area of interest.

DIAGNOSTIC VENOGRAPHY OF PELVIC CONGESTION SYNDROME

Pelvic venous congestion syndrome is characterized by symptoms of pelvic pain, dysmenorrhea, dysuria, dyspareunia, vulvar and pelvic varices in women, and varicoceles in men.[46] Sources of pelvic venous plexus congestion include ovarian vein reflux, pelvic varices, and hypogastric venous insufficiency.

The ovarian veins provide drainage of the parametrium, cervix, mesosalpinx, and pampiniform plexus. Two or three trunks form a single vein at L4, with the right ovarian vein draining directly into the IVC and the left into the left renal vein. These veins have an average diameter of 3.1 mm and possess two or three valves.

In addition to primary valvular incompetence of the ovarian vein valves, pelvic congestion syndrome may also result from obstruction of ovarian vein outflow. This obstruction is most often caused by compression of the left renal vein between the superior mesenteric artery (SMA) and the aorta, also known as the nutcracker syndrome, and it can also occur with a renal vein that travels posterior to the aorta with compression of the vein between the aorta and spine. Distal obstruction leads to increased venous pressure and subsequent venodilation, valvular incompetence, and tortuosity of the ovarian vein. The development of numerous pelvic collateral pathways concurrently allows venous drainage around the point of obstruction. Distal obstruction of ovarian vein outflow leads to the development of an elevated gradient between the left renal vein and the vena cava. Normally, there is minimal or no gradient between the left renal vein and the vena cava, so the presence of an elevated gradient is diagnostic of nutcracker syndrome.[47]

Vulvar varices may arise from the lower extremity veins, the pelvic veins, or both. Varicose veins of the lower extremities are a frequent source of venous hypertension resulting in pelvic congestion. Almost half of vulvar varices arise from an incompetent great saphenous vein through the superficial external pudendal or posteromedial tributaries. Less often, they arise from a tributary communicating directly with the common or deep femoral vein. The remaining varices arise from the pelvic veins through branches of the internal iliac, including the internal pudendal vein, the obturator vein, and the inferior gluteal vein. The internal pudendal tributaries communicate with the ovarian vein. Rarely, the veins arise from the round ligament.[48]

Technique

Diagnostic venography of the ovarian vein is achieved with standard catheter-based techniques. After access to the venous system has been achieved, a 4F angled glide catheter is advanced into the vena cava. The right ovarian vein drains into the IVC just inferior to the renal veins. The left ovarian vein drains into the left renal vein. Selective catheterization of each ovarian vein is then achieved with an angled glide wire and catheter system. After the catheter is placed in the ovarian vein, the angiographic table is tilted into reverse Trendelenburg. Then, after hand injection, the patient is asked to perform a Valsalva maneuver as images are obtained. Venography can be performed through either the jugular or femoral approach.

The diagnosis of nutcracker syndrome is made by determining the retrograde renocaval gradient. To do so, a glide catheter is placed in the distal left renal vein and the pressure transduced. This pressure is compared with the pressure in the vena cava. An elevated renocaval gradient is one clue in making the diagnosis. In addition, contrast-enhanced visualization of the gonadal system and its pelvic and extrapelvic connections should be performed to look for ovarian vein reflux. Intravascular ultrasound can be a useful adjunct in providing a cross-sectional view of the area of extrinsic compression. Patients with the clinical and radiologic diagnosis of nutcracker syndrome can be studied in both the supine and prone positions. Placing the patient in the prone position theoretically decreases the renocaval gradient and displaces the SMA forward with the intestinal mass.

Interpretation

The venographic criteria for pelvic congestion syndrome were established by Beard and colleagues in 1984.[49] The criteria for pelvic congestion syndrome include (1) an ovarian vein diameter of 6 mm or greater, (2) retention of contrast material for longer than 20 seconds, (3) congestion of the pelvic venous plexus or opacification of the ipsilateral or contralateral internal iliac vein (or both veins), and (4) filling of vulvovaginal and thigh varicosities (Fig. 26.15). Each variable is assigned a value of 1 to 3, depending on the degree of abnormality, and scores higher than 5 indicate pelvic congestion syndrome.[49]

Diagnostic criteria for ovarian vein reflux include a left ovarian vein diameter of 6 mm or greater and retrograde left ovarian vein flow (Fig. 26.16). Valvular incompetence exists in up to 47% of all women. In a study of preoperative aortography in

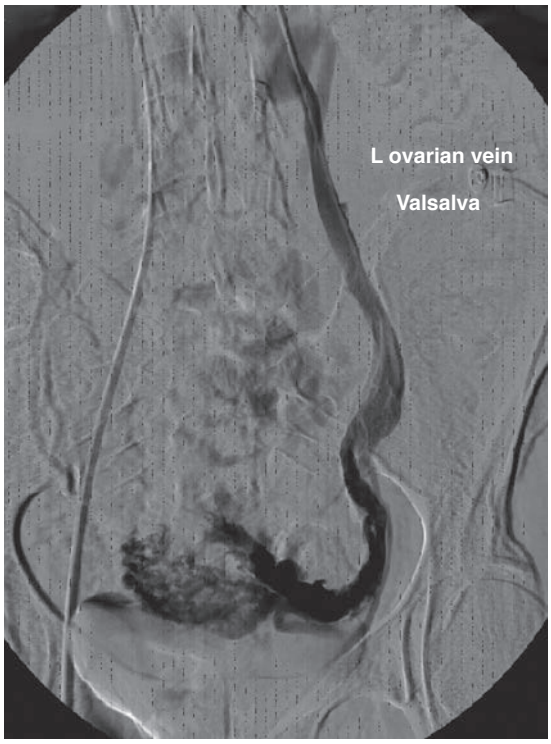

Figure 26.15 Pelvic congestion syndrome resulting from common iliac vein reflux. (Courtesy Mark Meissner, MD.)

Figure 26.16 Pelvic congestion syndrome resulting from ovarian vein reflux *(arrows)*. (Courtesy Charles Fox, MD.)

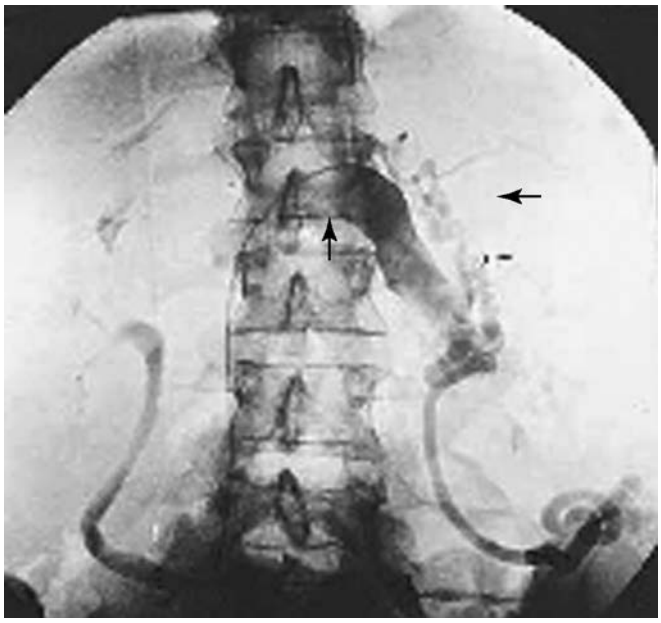

Figure 26.17 Nutcracker syndrome. Retrograde catheterization of the left renal vein shows mesoaortic compression *(vertical arrow)* of the left renal vein and perirenal varicosities *(horizontal arrow)*. Obstruction of gonadal outflow is evident. Kinking and curls of the gonadal vein are the radiographic manifestations of obstruction. This patient had left flank pain and hematuria. (From Scultetus AH, Villavicencio JL, Gillespie DL. The nutcracker syndrome: its role in the pelvic venous disorders. *J Vasc Surg*. 2001;34:812–819.)

273 female kidney donors, Belenky and coworkers found incompetent left ovarian veins in 27 (9.9%).[50] Fifty-nine percent of these patients had pelvic symptoms. A secondary cause arising from iliac artery or left renal vein compression of the left ovarian vein was noted in 20% of these patients.

Venographic evidence of SMA compression of the renal vein may be seen on an anteroposterior view of midstream venacavography (Fig. 26.17). Further delineation is aided by selective catheterization of the left renal vein and looking for proximal compression or pancaking. However, definitive documentation requires measurement of the retrograde renocaval gradient and contrast visualization of the gonadal system, as well as of its pelvic and extrapelvic connections. A renocaval gradient greater than 1 mm Hg is consistent with the presence of nutcracker syndrome.[51]

VENOGRAPHY FOR VARICOCELES

Abnormal distention of the pampiniform venous plexus, the venous drainage from the testicle, results in varicocele formation. Varicocele can be due to absence of testicular vein valves; however, it is generally due to retrograde flow in or impaired drainage of the testicular vein. Veins of the testes, along with tributaries from the epididymis, converge to form the pampiniform plexus. This plexus begins in the scrotum and extends into the spermatic cord and ascends along the cord in front of the ductus deferens. Below the inguinal ring, the pampiniform plexus unites to form three or four veins that enter the abdomen through the inguinal ring and further coalesces to form two gonadal veins. Intraabdominally, on the right side, the gonadal vein drains

directly into the infrarenal IVC; on the left side, the gonadal vein drains into the left renal vein. The left renal vein then drains into the IVC. Collateral pathways for venous drainage of the testis include perirenal, retroperitoneal, and lumbar veins.

Varicocele predominantly occurs on the left side. It is suspected that this is related to the indirect drainage of the testicular vein to the IVC through the left renal vein. Bilateral and right-sided varicoceles account for approximately 10% to 15% of varicoceles.[52] An isolated right-sided varicocele is less frequent, and its presence should prompt an evaluation for obstructive disease like renal tumors or adenopathy.

Patients presenting with varicocele will often report pain and reduced sperm count. Varicoceles have been associated with a time-dependent decrease in size and function of the testes, and this is assumed to contribute to male infertility. The physical examination is the cornerstone in diagnosis of this entity. The patient should be examined in the standing position after he has been upright for at least 5 minutes. Visual inspection of the scrotum should occur first, and obvious distention of the spermatic cord is noted. Next, the patient is palpated before and after a Valsalva maneuver. Previous descriptions of varicocele have described a "bag of worms" or a thickened cord on palpation. Although the physical examination is key in diagnosis, it is subjective. Therefore imaging should be obtained to assist in diagnosis. A duplex ultrasound study can be performed to confirm the physical examination findings. On ultrasound, the presence of two prominent tortuous veins in the pampiniform plexus that measure at least 2 mm in diameter and that increase with the Valsalva maneuver is diagnostic. Other potential imaging modalities include computed tomography and magnetic resonance imaging. However, venography remains the gold standard in diagnosis of varicocele, and reflux of more than 2 seconds is determined to diagnose it.[52]

Indications for treatment include an infertile man with a palpable varicocele and an abnormal sperm count, prophylactic repair in adolescent men with a reduction in testicular size, bilateral varicoceles, and impaired spermatogenesis in patients older than 18 years.[52]

Technique

Access may occur through the femoral or jugular approach. Access through the femoral vein generally requires a sheath or guiding catheter to stabilize the renal vein access and to allow passage of a catheter into the testicular vein. We obtain a venogram from the midpoint of the renal vein to determine renal vein patency and testicular vein incompetence. Venography with a Valsalva maneuver or preferably a tilt table with the patient placed in the reverse Trendelenburg position is performed of the testicular vein, and retrograde flow and collaterals can be visualized. Visualizing the entire anatomy of the testicular vein and pampiniform plexus is necessary to evaluate retrograde and collateral flow, as well as aberrant blood supply to the varicocele. At times during instrumentation, the gonadal vein may spasm, and nitroglycerin is used. If reflux is not demonstrated with this technique, renal venography with a Valsalva maneuver may be used, or an internal iliac study with an occlusion balloon may be warranted. This technique, described before, is used to determine a right- or left-sided varicocele.

Treatment

The goal of treatment is to stop the retrograde flow from the gonadal vein or collateral veins to the pampiniform plexus. Occlusion of the testicular vein should extend from just above the inguinal ligament to 5 cm below the convergence of the testicular vein with the left renal vein on the left side. This technique eliminates all collateral and aberrant vessels. Several techniques for occlusion are available: coil embolization, sclerosing agents, and open surgical repair. Coil embolization is commonly used, owing to its painless ease of use. Coils must be sized correctly to at least 10% larger than the diameter of the spermatic vein at the level of deployment. If the coils are undersized, there is a risk of embolization to the pulmonary artery. Other groups, particularly those in Europe, use sclerosants exclusively. In general, if the right side does not evidence reflux, it is not routinely treated. Open surgical options for repair involve retroperitoneal or inguinal access to the testicular vein for ligation. The traditional open approach usually requires general anesthesia and a 2- to 3-day hospitalization.

Complications associated with treatment of varicocele include spasm, dissection, and perforation. Venous puncture–associated complications such as false aneurysms or hematomas are generally rare. Phlebothrombosis and phlebitis are the most common complications of embolization specific to embolization of the spermatic vein. Patients may present with fever, pain, and scrotal swelling within 24 to 48 hours of intervention. Patients with this complication should undergo an immediate duplex ultrasound examination followed by a repeated study 6 weeks later for evaluation of signs of testicular necrosis, which rarely occurs. Patients may also be treated with a short course of steroids and nonsteroidal antiinflammatory drugs. Antibiotics may also be prescribed if there is difficulty in differentiating phlebitis from infection.

RENAL VENOGRAPHY

The renal veins may be evaluated for anatomic verification or assessment of congenital anomalies or tumor invasion before resection. Renal venography is also useful for the evaluation of suspected renal vein thrombosis in both native and transplanted kidneys. Patients typically have generalized malaise, flank pain, hematuria, and hypertension. Renal vein thrombosis affects men more than women and most often involves the left renal vein.[53] Renal vein thrombosis may arise from four separate causes: (1) thrombus propagating from below to obstruct the IVC and renal veins; (2) caval obstruction or invasion from malignant neoplasms with compromise of the renal veins; (3) primary renal vein thrombosis, which usually occurs in infants; and (4) renal vein thrombosis secondary to nephritis.[54] Catheter venography may be especially useful in patients with acute renal vein thrombosis because it may be followed by therapeutic intervention consisting of catheter-directed thrombolysis.

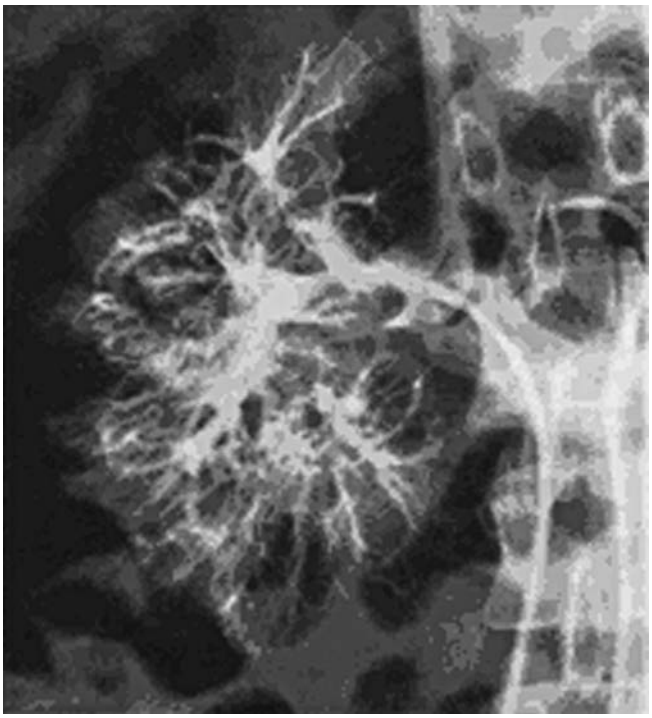

Figure 26.18 Epinephrine renal venogram. The thrombus in the intrarenal veins and the main renal vein is well seen. (From Martin EC, Gordon DH. Selective renal venography in patients with primary renal disease and the nephrotic syndrome. *Cardiovasc Intervent Radiol.* 1980;3:175–179.)

Technique

Midstream venacavography results in characteristic flow voids seen at the L2-3 level as a result of mixing of unopacified renal vein blood with contrast material in the vena cava. However, detailed evaluation of the renal veins is best achieved by selective catheterization. Renal vein selection is easily achieved with standard glide wires and angled catheters. After access to the renal veins has been attained, venography is usually accomplished by hand injections of 5 to 10 mL of dilute contrast material. Improved visualization of the renal veins has been reported with the injection of 10 μg of epinephrine into the renal artery or balloon occlusion of the renal artery (Fig. 26.18).[54]

Interpretation

Although renal venography is a useful technique for demonstrating renal vein anomalies such as a retroaortic left renal vein or circumaortic venous collar, computed tomography and magnetic resonance imaging are currently more commonly used. Venographic diagnosis of renal vein thrombosis depends on the demonstration of a persistent filling defect within the renal vein. Acute renal vein thrombosis may be partial or complete. Detection of intraluminal defects showing partial occlusion and no collateral formation is consistent with acute thrombosis. Chronic renal vein thrombosis would appear as main renal vein obstruction with numerous collaterals around the obstruction. The risk for pulmonary embolism during renal venography and treatment has been reported to be low.[53,55]

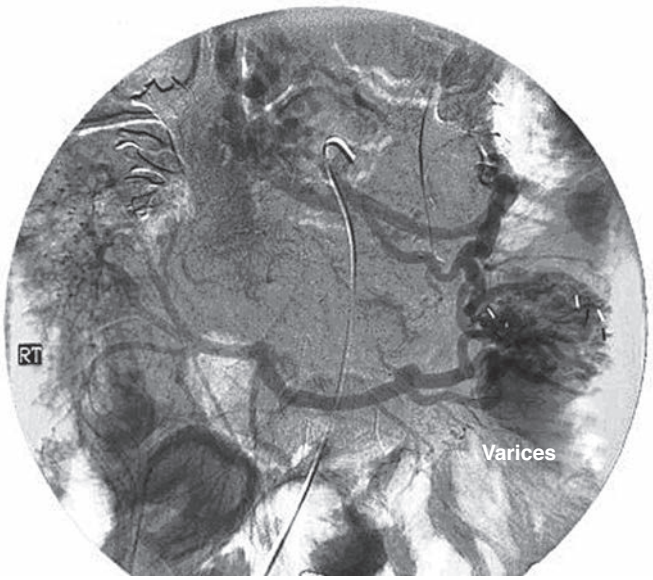

Figure 26.19 Venous phase of a superior mesenteric arteriogram showing occlusion of the superior mesenteric vein. *RT*, Right. (From Ozkan U, Tang SJ, Jutabha R, Jensen DM. Push enteroscopy for recurrent gastrointestinal hemorrhage due to jejunal anastomotic varices: a case report and review of the literature. *Endoscopy*. 2002;34:735.)

Definitive exclusion of renal vein thrombosis requires selective catheterization of the renal veins if an initial midstream venacavogram is normal. Martin and Gordon found that only 6 of 15 (40%) patients with documented renal vein thrombosis had caval thrombus, whereas the cava was completely normal in 46%. The authors suggest that inferior venacavography lacks specificity in the diagnosis of renal vein thrombosis when it is associated with primary renal disease and nephrotic syndrome.[54]

DIAGNOSTIC ANGIOGRAPHY OF MESENTERIC OR PORTAL VENOUS THROMBOSIS

The signs and symptoms of acute mesenteric or portal venous thrombosis are varied and include vague abdominal pain, nausea, vomiting, melena, bloody diarrhea, and ultimately circulatory collapse.[56] The diagnosis is usually accomplished with computed tomography or magnetic resonance imaging but can be made with angiography. High clinical suspicion plus early diagnosis may be lifesaving because it allows systemic anticoagulation or thrombolysis (or both) to be performed.[57]

Technique

Visualization of the superior mesenteric veins may be accomplished either indirectly by review of the venous phase of a superior mesenteric arteriogram (Fig. 26.19) or by direct access (Figs. 26.20 and 26.21). Direct access to the superior mesenteric veins can be accomplished through a transjugular-intrahepatic or transhepatic approach and allows percutaneous intervention.

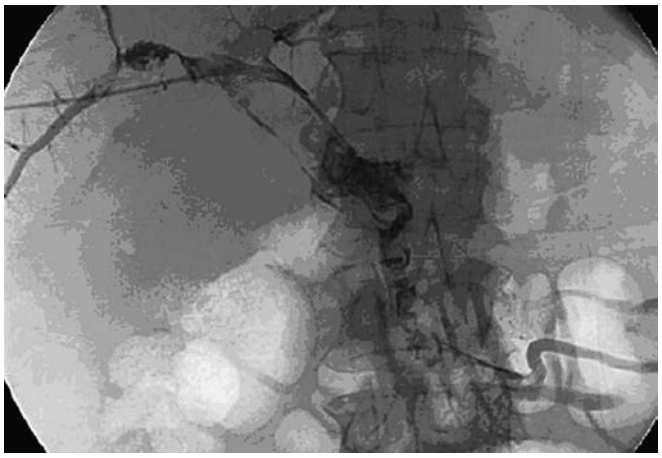

Figure 26.20 Transhepatic venogram showing filling defects attributable to thrombus in the small mesenteric vein, main pulmonary vein, right pulmonary vein, and left pulmonary vein. (From Ozkan U, Oguzkurt L, Tercan F, Tokmak N: Percutaneous transhepatic thrombolysis in the treatment of acute portal venous thrombosis. *Diagn Interv Radiol.* 2006;12:105–107.)

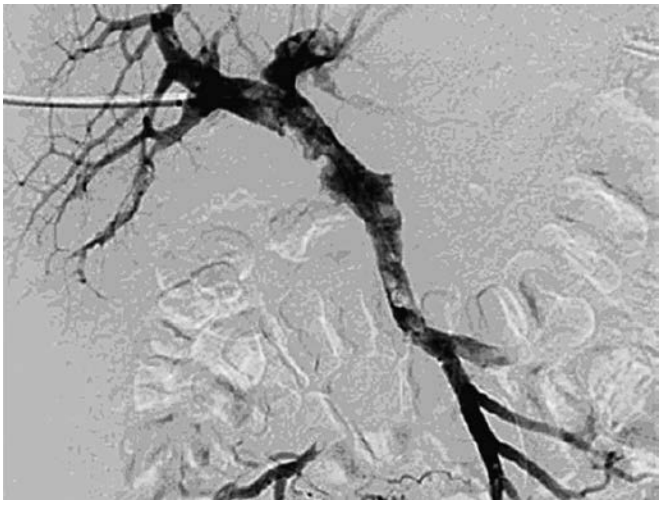

Figure 26.21 Control venography after balloon angioplasty and infusion of recombinant tissue plasminogen activator shows 90% reduction of the thrombus in the superior mesenteric vein and main portal vein, although prominent thrombus is still present in the left pulmonary vein branch. (From Ozkan U, Oguzkurt L, Tercan F, Tokmak N. Percutaneous transhepatic thrombolysis in the treatment of acute portal venous thrombosis. *Diagn Interv Radiol.* 2006;12:105–107.)

The venous phase of an SMA injection provides visualization of superior mesenteric drainage into the portal venous system. After arterial access is achieved, a 5F Simmons 1 catheter is advanced into the aorta. Once the tip is shaped so that it is aimed caudad, the catheter is manipulated into the orifice of the SMA. Hand-injected half-strength contrast dye is helpful in confirming placement of the catheter. Injection of contrast material with a power injector is useful for improving imaging. An injection protocol of 5 mL/s for a total of 10 mL is appropriate. Imaging of the venous phase is accomplished either by delaying acquisition until after injection or by continuing to image after the arterial phase has been completed.

The transcutaneous transhepatic approach is a useful direct technique for access to the portal venous system. Under sonographic guidance, the skin is marked at the point where the right portal vein and the right hepatic vein are aligned in one plane with the portal vein closer to the sonography probe. By use of aseptic technique, the right portal vein is punctured with an 18-gauge needle. After imaging, the superior mesenteric vein has been shown to allow thrombolysis, angioplasty, and stenting in a highly select group of patients.[58]

The transjugular intrahepatic approach to portal venography was popularized in the 1960s by Rösch, who modified the technique of liver biopsy and developed the technique of transjugular intrahepatic portosystemic shunting.[59-62] Transjugular intrahepatic portosystemic shunting is best performed under general anesthesia or heavy intravenous sedation. A 10F introducer sheath is placed through the right internal jugular vein into the IVC. A curved angiographic catheter is used to select a hepatic vein, and the tip of the sheath is then introduced into the hepatic vein. A 16-gauge, 55-cm Colapinto transjugular needle is passed from the hepatic vein through the liver parenchyma into a portal vein branch. A 0.035-inch Amplatz extrastiff guide wire is placed into the superior mesenteric vein and the needle exchanged for a 5F angiography catheter. Portal venography is then performed through a multihole diagnostic catheter placed in the portal vein.[63] Postdiagnostic angiographic embolization of the track formed has routinely been performed, although this is changing.

Interpretation

The superior mesenteric vein joins with the splenic vein to form the portal vein. In general, noninvasive methods of imaging are used as the initial diagnostic modality in the case of portal or mesenteric vein disease. Indirect visualization of the portomesenteric system can be achieved during mesenteric arteriography by prolonged imaging of the venous phase. However, this method does not provide great detail or access for treatment. Advances in percutaneous technology have led to increased use of the transjugular and transhepatic approaches.[57,58,64] These methods carry increased risk for subcapsular or intraabdominal bleeding complications, especially if they are combined with thrombolytic therapy.

DIAGNOSTIC VENOGRAPHY OF BUDD-CHIARI SYNDROME

Normal hepatic venous outflow occurs from the right and left hepatic veins into the retrohepatic vena cava and then into the right atrium (Fig. 26.22). Budd-Chiari syndrome results from thrombosis of hepatic venous outflow, which gives rise to portal hypertension and its sequelae. The liver becomes congested and enlarged, and as the hepatic congestion progresses, hepatic function deteriorates and failure results. For unclear reasons, some patients have mild initial symptoms, whereas others exhibit fulminant hepatic failure and massive hepatic necrosis.[65] Budd-Chiari syndrome can result from various causes, including membranous obstruction of the IVC, pregnancy, oral contraceptive use, tumors, infections, and blood dyscrasias, or it can be

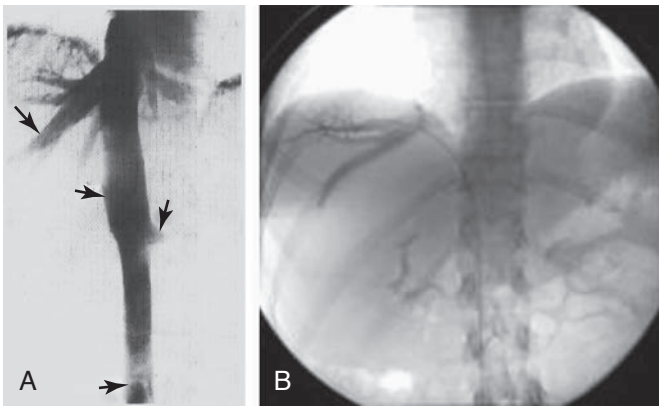

Figure 26.22 (A and B) Normal hepatic venous outflow *(arrows)* demonstrated by cavography and selective catheterization of the hepatic veins. (B courtesy Charles Fox, MD.)

idiopathic. The most useful initial test is a color-flow duplex scan of the portal vein, which will establish the diagnosis. This scan should then be followed by venacavography and portal vein venography with portal venous and vena cava pressure measurements, as well as liver biopsy, to help determine further management.[66]

Technique

The diagnosis of Budd-Chiari syndrome may be confirmed by demonstrating obstruction of hepatic venous outflow, most often by selective catheterization of the right or left hepatic vein. This can easily be accomplished through a transfemoral or transjugular approach. From the groin, a curved catheter, such as a Simmons 1, is manipulated into the suprahepatic cava and then used to select the hepatic vein. From the jugular vein, a straight or angled catheter is easily manipulated into the hepatic outflow tract. Hand injection of 5 to 10 mL of contrast material should reveal a characteristic spiderlike appearance of the occluded hepatic venous system.

In some cases, such as membranous obstruction of the vena cava, imaging is best accomplished with venacavography. A pigtail catheter is placed at the level of the distal IVC. Power injection at 15 mL/s for a total volume of 30 mL would be used. The surgeon should look for filling defects in the distal IVC.

Interpretation

Thrombosis of the hepatic venous outflow tract may be detected by direct catheterization of the hepatic veins. A characteristic spiderlike appearance of the occluded or recanalized hepatic veins is seen (see Fig. 26.22). Distal obstruction of the IVC may take the appearance of a weblike band or stenosis (Figs. 26.23 and 26.24).

UPPER EXTREMITY VENOGRAPHY

Upper extremity venography is the procedure of choice for most clinicians in the evaluation of central thoracic veins and

Figure 26.23 Wedged hepatic venogram showing a fine-meshed spiderweb pattern resulting from an intrahepatic network. (Available at www.emedicine.com.)

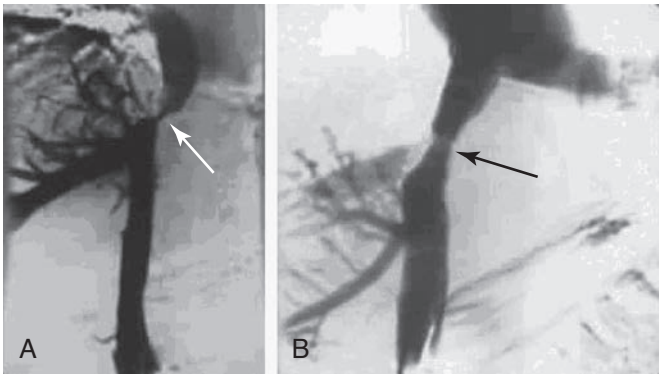

Figure 26.24 (A and B) Inferior venacavogram showing upper inferior vena cava stenosis with reflux of contrast material *(arrow)* into the vena cava. (Available at www.emedicine.com.)

for investigation of upper extremity edema. Upper extremity edema can be caused by acute or chronic venous thrombosis, external venous compression by a tumor of the lymph nodes, venous obstruction secondary to fibrosis after radiation therapy or surgery, superior vena cava (SVC) obstruction, and lymphatic obstruction. Although primary axillary-subclavian vein thrombosis is relatively uncommon (<2% of all cases of DVT), the incidence of central venous occlusion is still rising because of the increasing long-term use of central venous catheters and transvenous cardiac pacers (Fig. 26.25).[67,68]

Upper extremity venography is most commonly used in the investigation of arm edema in patients with primary axillary-subclavian venous thrombosis who are candidates for thrombolytic therapy. The examination is performed to show the extent of thrombosis and to guide placement of infusion catheters for the administration of lytic agents. Other common indications are to evaluate patients with suspected central venous occlusion who are not candidates for magnetic resonance angiography (e.g., because of a cardiac pacemaker or claustrophobia) and to rule out venous injuries from trauma.

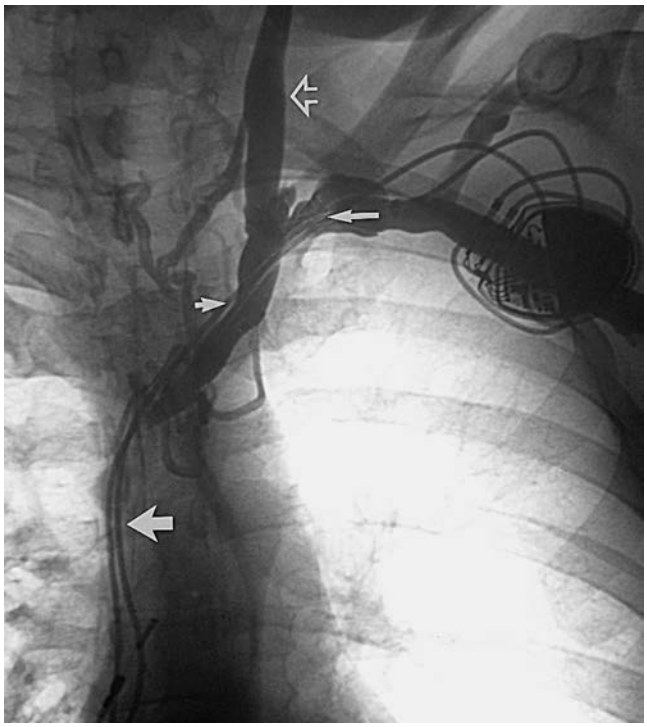

Figure 26.25 Chronic thrombosis of the superior vena cava, the innominate veins, and the subclavian veins caused by cardiac pacer wires. Chronic subclavian venous thrombosis *(long arrow),* the innominate vein *(short arrow),* and the expected location of the superior vena cava *(wide arrow)* are shown. Note the reflux of contrast material up the left internal jugular vein *(open arrow)*.

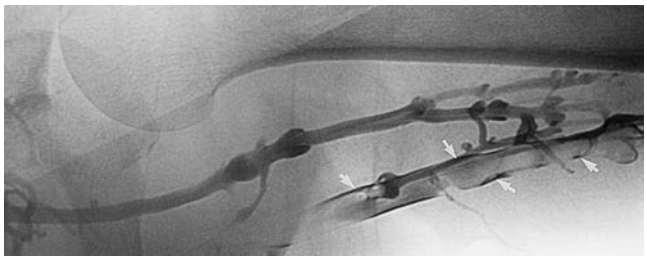

Figure 26.26 Acute thrombosis of the left brachial vein. *Arrows* denote fresh thrombus in the brachial vein.

Technique

Arm venography techniques were initially described in 1971 by Thomas and Andress.[69] The most common method involved accessing the median antecubital vein or a peripheral hand vein and positioning the upper extremity by the side of the patient in 5 to 10 degrees of abduction without the use of tourniquets (Fig. 26.26). Natu and associates modified this technique by abducting the arm 90 degrees, introducing the catheter into a hand vein or forearm vein, and injecting 50 mL of contrast material (Renografin-60) in 5 seconds.[70] If a simultaneous intervention, such as thrombolysis or percutaneous mechanical thrombectomy is contemplated, ultrasound-guided access of the basilic vein in the upper arm is preferred. This site allows for larger sheath placement, as well as a short distance between sheath access site and area of stenosis for improved catheter pushability and control. The arm may be imaged in an adducted position or with less than 90-degree abduction. This can be done with either a hand injection or small volume power injection. The venous system is then reimaged with the arm fully abducted and extended. That position should narrow the thoracic outlet to help diagnose venous thoracic outlet syndrome in patients without axillosubclavian thrombosis.

Interpretation

Significant findings in subclavian venous thrombosis include nonopacification of the vein with filling of collaterals and visualization of the thrombus within the vein. Stenosis or occlusion of the subclavian vein associated with thoracic outlet syndrome typically occurs as the vein enters the chest at the sternoclavicular junction. This point of impingement is often due to hypertrophy of the subclavius muscle. The stenosis is usually more pronounced with the arm in a provocative maneuver (arm abduction and extension). Large collateral vein formation is seen and allows venous outflow from the arm around the point of obstruction. In patients with pacemaker wires, subclavian vein stenosis will typically occur more distally. Patients with central venous catheters will have stenosis or occlusion from the midclavicle, centrally.

CENTRAL THORACIC VENOGRAPHY

Contrast-enhanced venography is considered the diagnostic method of choice for evaluation of SVC obstruction.[71] SVC evaluation is necessary in patients with clinical suspicion of SVC or innominate vein obstruction (or both), many times associated with malignancy.[72,73]

Technique

Sharma and colleagues described their technique for evaluation of the SVC, which involves access in a peripheral vein of each upper extremity and injection of 20 mL of contrast material at a rate of 5 mL/s and a pressure of 150 psi.[74] We perform central thoracic venography similarly by injecting through an intravenous site in the antecubital fossa or forearm with the arm in a neutral position at the patient's side. For each projection needed, 20 to 30 mL of contrast material is injected by hand. Digital images of the mediastinum are obtained at one frame per second until contrast material is seen within the veins, and the frame rate is then increased to three per second. The imaged field should include the upper mediastinum and shoulders for careful evaluation of the site of venous obstruction, collateral channels, and reconstitution of the SVC distal to the obstruction. If central veins are not well opacified with a peripheral IV, then similar to peripheral venography sheath placement can be accomplished percutaneously into the basilic vein with ultrasound guidance. A catheter can then be introduced into the proximal axillary vein, and venography can be performed through a catheter hand injection in closer proximity to the central vein of interest.

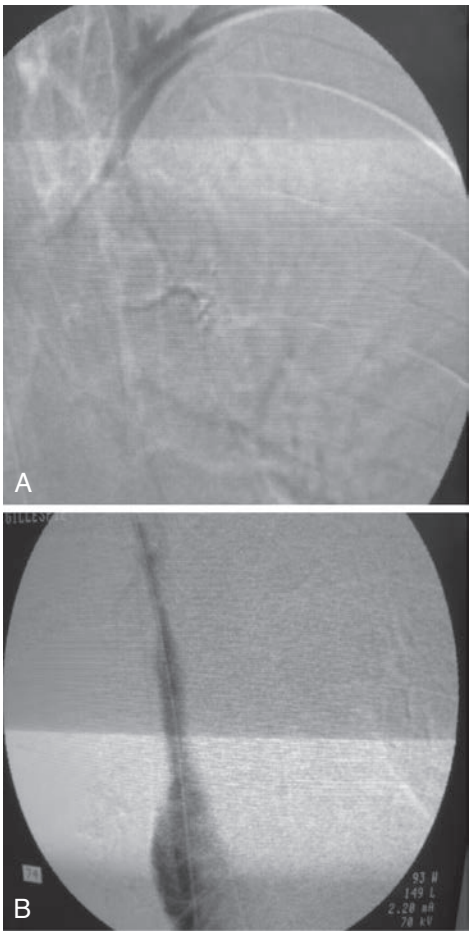

Figure 26.27 High-grade superior vena cava stenosis diagnosed by left (A) and right (B) internal jugular vein catheterization.

In general, contrast material is injected unilaterally for suspected subclavian vein obstruction and bilaterally for suspected SVC obstruction (Fig. 26.27). This helps to compensate for washout of contrast material in the SVC by unopacified blood from the opposite innominate vein. Images are acquired at one frame per second, and the duration of injection and acquisition is determined by opacification of the SVC, brachiocephalic veins, and medial third of the subclavian veins. These structures are commonly obscured within the mediastinal shadows on conventional venography.

Interpretation

Obstruction of the central veins may be associated with either benign or malignant processes. Benign processes are most often related to indwelling catheters for hemodialysis or other infusions. Malignant tumors of the chest may also cause SVC syndrome through external compression or tumor invasion. The existence of large collateral veins arising from the innominate veins and reconstituting in the SVC is indicative of significant obstruction. One may also see less degree of obstruction from extraluminal compression or intraluminal thrombus. Options for treatment of central venous obstruction include operative reconstruction with spiral vein grafts, angioplasty and stenting in select patients, or both (Fig. 26.28).

Figure 26.28 Widely patent superior vena cava after percutaneous transluminal angioplasty and stenting of both the innominate veins and superior vena cava.

PULMONARY ARTERIOGRAPHY

In situations in which there is a strong clinical suspicion of pulmonary embolus and computed tomographic angiography or magnetic resonance angiography is nondiagnostic or the patient has a contraindication to these imaging modalities, pulmonary arteriography should be performed. Pulmonary arteriography is superior to computed tomographic angiography or magnetic resonance angiography for identification of small or subtle peripheral or chronic emboli and has the advantage of being able to measure pulmonary arterial pressure.[75] Another indication for pulmonary arteriography is imaging with intent to treat patient with massive pulmonary embolism through thrombus fragmentation and thrombolysis.

Technique

Selective catheter pulmonary arteriography is performed by advancing a pigtail catheter through the right atrium and ventricle. Angulated pigtail catheters such as the Grollman catheter are preshaped to facilitate advancement from the right ventricle into the pulmonary outflow tract with the guidance of an angled glidewire. Caution should be exercised when the catheter is advanced through the right ventricle because this maneuver can produce transient right bundle branch block. In patients with left bundle branch block, it may cause complete heart block. One should consider the use of a temporary pacemaker in this subset of patients when pulmonary angiography is performed. After the target artery has been selectively catheterized, baseline pulmonary arterial pressure measurements are obtained. The right and left pulmonary artery trunks are

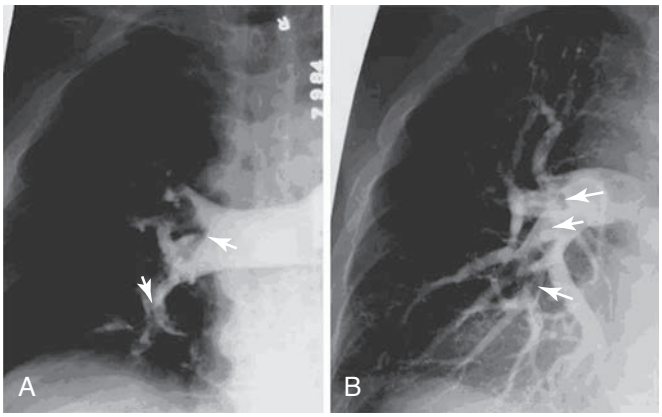

Figure 26.29 (A and B) Pulmonary artery arteriograms showing multiple pulmonary emboli *(arrows)*. (From Santilli JG. Venous thromboembolism in trauma. *Semin Intervent Radiol.* 2003;20:111–124.)

normally evaluated separately. Contrast material is injected at 15 to 25 mL/s for a volume of 30 to 50 mL per injection. Fluoroscopy should be set at high frame rates (4-15 frames per second), and patients should be holding their breath during image acquisition. For complete evaluation, frontal and oblique views of each pulmonary artery should be obtained.

In patients with pulmonary hypertension, injection of large volumes of contrast material into the pulmonary artery is contraindicated. However, patients with chronic compensated pulmonary hypertension can tolerate pulmonary arteriography without difficulty. A right ventricular end-diastolic pressure of greater than 20 mm Hg is considered a relative contraindication to high-volume injection of contrast material, and only small amounts should be injected by hand in such cases.

Interpretation

The classic angiographic sign of acute pulmonary embolism is an intraluminal defect with diminished distal contrast enhancement (Fig. 26.29). Main and segmental pulmonary artery emboli should be easily detectable. Smaller subsegmental pulmonary emboli may be missed with this technique unless digital spot films are obtained. This is often time consuming and less successful. As treatment for massive and submassive pulmonary embolus shifts to percutaneous catheter–directed thrombolysis and mechanical thrombectomy, the use of simultaneous pulmonary angiography will rise despite the widespread use of CT angiogram for its initial diagnosis. Chronic pulmonary emboli are more difficult to detect than acute occlusion and are typically identified as stenosis, webs, or mural thickening consistent with organized thrombus.

GENERAL LIMITATIONS AND RISKS OF VENOGRAPHY

Although venography is still considered the gold standard in diagnosis of DVT and reflux disease, several limitations and risk accompany its use.

Limitations include the invasive nature of the technique, radiation exposure, differences in intraobserver interpretation of the presence or absence of thrombus, and inability to cannulate the appropriate vein in the setting of extremity edema. Several technical issues, such as incomplete filling of the vein, may lead to a 5% to 15% inadequacy of this study. In instances in which the external or common iliac veins are not well visualized, access through the common femoral or iliac vein for venography may need to be accomplished.

Risks of venography can range from minor to major and include pain at the site of injection, local infection at the injection site, extravasation of contrast material, contrast-induced allergic reaction, thrombophlebitis, intraabdominal bleeding complications with the transhepatic approach to evaluate mesenteric or portal vein thrombosis, DVT, and pulmonary embolism. Risks specifically associated with pulmonary angiography include transient right bundle branch block. In those with an already present left bundle branch block, complete heart block may ensue.

FUTURE ADVANCES

It is difficult to ascertain what future role venography will play in the diagnosis of thrombosis or reflux disease. Vascular surgery is a rapidly evolving field, and improvements in less invasive methodologies for diagnosis of disease are evolving. Currently, venography is still the reference by which diagnostic imaging modalities are compared, and its use is preferred in particular instances described earlier in the chapter. As the demand for less invasive diagnostic technology continues, the use of more invasive diagnostic techniques like venography may become more limited. However, the treatment of venous disease is likewise becoming less invasive, shifting from open venous procedures to endovascular techniques. The introduction of intravascular ultrasonography and its utility in venous management had increased the sensitivity and specificity of venography in imaging the venous system, offsetting some of its limitations and yielding more accurate diagnosis and intervention. Venography plays a paramount role in these minimally invasive treatment options, and therefore the knowledge and skill in venography becomes an even greater asset in the vascular surgeons' armamentarium.

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27 CHAPTER

Computed Tomography

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Conventional contrast-enhanced arteriography is no longer considered the standard imaging modality for vascular disease.[1-6] As with many technologic advances, however, the process of image creation continues to become more difficult for the average end user to understand. Although the typical vascular surgeon can perform clinical evaluation and can make decisions without an understanding of the basic principles behind computed tomography (CT), these concepts remain important. A better understanding of the imaging process and terminology also aids collaboration between radiologists, radiographers, and the surgeons who use the images to plan interventions. Finally, an understanding of the basic concepts enhances the ability of the surgeon to understand technologic advances as they become the new standard of care.

BASIC PRINCIPLES

In the early 1930s, the Dutch radiologist Ziedses des Plantes first devised a technique that reduced the problem of superimposition of structures in basic radiography (x-ray tube and plain film). Physically connecting the x-ray tube and film opposite each other and rotating the combination around a body segment sharpens the image created by the points on the focal plane, whereas the images of points outside the focal plane are blurred, thereby creating less superimposition artifact. This technique was called "planigraphy" or "tomography," derived from the Greek words *tomos*, which means "a section" or "a cutting," and *graphein,* meaning "to write." Tomography played an important role in diagnostic radiology until the 1970s, when invention of the transverse axial scanning method together with the availability of minicomputers, which allowed computational reconstruction of images, led to the development of so-called computed axial tomography (CAT scan, or later, CT scan).

Two similar methods for transverse axial scanning and image reconstruction were independently invented by Sir Godfrey Newbold Hounsfield in Hayes, United Kingdom, at Elector-Musical Instruments (EMI) Limited Central Research Laboratories, and Allan McLeod Cormack of Tufts University in Massachusetts. A combination of hardware, mathematical algorithms, and computer software resulted in the cross-sectional images. The first so-called EMI scanner was installed in Atkinson Morley's Hospital, Wimbledon, England, in 1971.[7] In the United States, the first installation was at the Mayo Clinic in Rochester, Minnesota. These machines would acquire two adjacent brain tomographic sections in about 4 minutes and needed about 7 minutes of computation time per picture. This was such a leap forward in imaging technology that Hounsfield and Cormack shared the Nobel Prize in 1980.

Many of the principles used in this first-generation CT scanner are still in use today and provide a framework for understanding the technology. The fundamental unit for this scanning method consists of an emitter and a detector. The emitter produces a thin x-ray beam. The beam is transmitted through the tissue and detected on the other side. The attenuation (the rate of reduction of x-ray energy recorded at the detector) of multiple x-ray beams traversing the same point in the matrix from different angles is collected and an ingenious method applied to calculate backward to the density or CT number that must be present at each location in the matrix.

The resulting CT number is expressed in Hounsfield units (HU). CT numbers range from the extremes of air (−1000 HU) to dense bone (>1000 HU), but fat (−20 to −100 HU), water (0 HU), and muscle and blood (40 to 60 HU) tend to lie in a much narrower range. Differences in factors such as the energy level of the beam and tissue thickness prevent the density in HU from being absolutely uniform from one CT scan to another, but the ranges are similar. When the range of CT numbers for a scan is determined, it can be broken up into smaller ranges for graphic display by a set of gray-scale values. Each gray-scale data point in the matrix is known as a pixel because it represents a "picture element." When displayed as a whole, this matrix of gray squares becomes an interpretable image.

Types of Scanners

Single-Slice Sequential Computed Tomography

A first-generation CT scanner is capable of producing a cross-sectional image with a 160 × 160 matrix. These CT scans were applicable only to parts of the body with limited motion (e.g., the head). To obtain useful scans in areas such as the chest and abdomen, subsequent generations of CT scanners were designed to decrease the time required to obtain a complete cross-sectional image.

Spiral (Helical) Computed Tomography

With development of a so-called slip-ring gantry, the emitter and detector array can rotate continuously in the same direction, and at the same time, the computer can acquire data continuously. If the table moves in a continuous linear motion through the gantry while the x-ray emitter and detector rotate continuously over 360 degrees, data can be acquired in a single sweep over the entire volume of interest. In this technique the emitter traces out a spiral relative to the patient, which is referred to as a spiral CT or helical CT scan.

Spiral or helical CT technology has several important ramifications beyond a simple decrease in scan time. A spiral CT scan collects data over a continuous volume rather than discontinuous slices (Fig. 27.1). The most obvious advantage of acquiring data

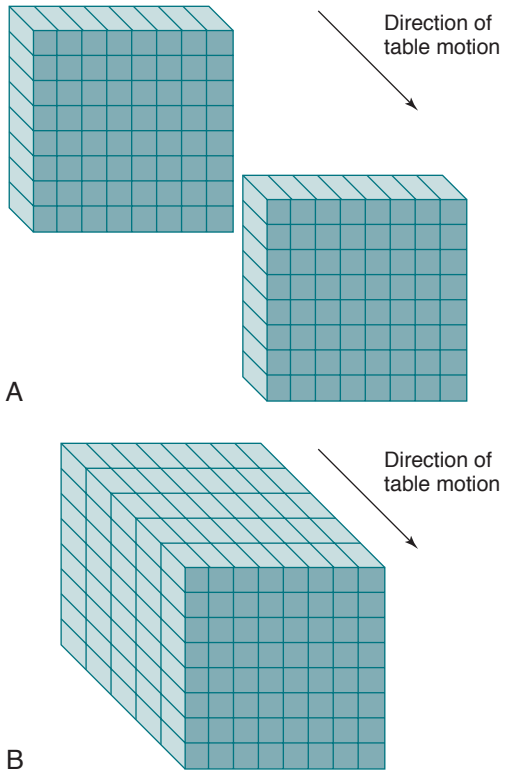

Figure 27.1 Discontinuous data collection (A) versus continuous data collection (B) for conventional and spiral computed tomography.

over a continuous volume is that thin axial slices can be reconstructed from the digital data set at arbitrarily small intervals without additional radiation exposure. Single-slice sequential CT can produce similar overlapping or adjacent axial slices, but the tradeoff is increased scan time and additional radiation exposure. The advantage of sequential scanning, however, is a lower level of reconstruction artifacts because table movement along the z-axis during scanning does not need to be corrected in the acquired data sets. This is the main reason why sequential scanning is often used for brain imaging.

Multislice (Multidetector) Computed Tomography

Multidetector scanners have multiple rows of detectors in craniocaudal direction (z-direction), so that the volume to be scanned can be covered more quickly. Whereas a single-slice detector acquires one slice per rotation, multidetector CT scanners are capable of acquiring multiple separate slices or 1 big volume per rotation. Each slice can be acquired at 1-mm or even smaller with rotation times in the range of 0.2 to 0.3 seconds. Complete imaging of the abdominal vasculature can be accomplished in a fraction of the time required with previous-generation scanners. This diminishes or eliminates many artifacts or compromises that must be dealt with in single-row detector scanners, as discussed subsequently. For this reason, multidetector or multirow scanners have almost completely replaced the earlier-generation single-row scanners.

Advances in hardware and computer software technology have also greatly improved the graphic image display despite the reduction in scan times. A first-generation CT scanner produced a cross-sectional image with a 160 × 160 matrix, but current scanners typically generate a 512 × 512 matrix. Each data point in the matrix is mapped to a gray scale for display, so the size of the matrix and the field of view (FOV) have a direct impact on spatial resolution of the display (the smallest distinguishable element). Data points are displayed as a two-dimensional (2D) picture, and each point in the display matrix is a pixel (picture element). Data points are acquired in three dimensions, however, and each data point in the matrix actually represents a voxel (volume element). The size of the voxel is determined by multiple factors, including FOV (x, y direction) and detector design (x, y, z direction).

Computed Tomography Angiography

Visualization of vessels on CT is limited by the similar densities of blood and soft tissue. Administration of iodine intravenous contrast material highly overcomes this problem, However, optimal visualization of the vessels (computed tomographic angiography [CTA]) was not possible until the availability of fast spiral CT: faster scan times and increased numbers of detectors will allow a larger part of the body to be imaged as the contrast bolus passes.

Timing of the initiation of image acquisition relative to injection of the contrast agent is crucial for maximizing opacification of vessels in the scanned volume. Various dedicated bolus tracking algorithms have been developed by the CT scanner manufacturers to detect contrast arrival in the vessel of interest in order to start the scan on an appropriate time. These algorithms are all based on a stationary, continuous scan of a single slice in which contrast density is measured in an area of interest (usually a large vessel) marked by the operator. Only after a sufficient increase in density is measured is the spiral CT run initiated.

The iodine concentration, injection rate, and the length of the contrast bolus are important parameters. Bolus length should be balanced against the length of the volume to be imaged. Because large distances must often be covered, CTA generally previously required a significant infusion of contrast material. In the past, a typical CTA study from the celiac axis down to the external iliac arteries would require 120 to 180 mL of 300 mg/mL nonionic contrast.[8,9] For optimal arterial enhancement, fast injection rates are important.

Optimization of scanning and power injector protocols, faster scanning times, and the use of saline push bolus techniques reduced this volume significantly, and often volumes do not exceed 100 mL and can only be several milliliters.

Split-bolus techniques are alternative ways of administering intravenous contrast. These techniques employ multiple phases—for instance, enhancement of venous and arterial structures—in one single scan. This is achieved by splitting the contrast bolus volume into one early bolus of contrast and one late bolus of contrast administration before obtaining the CT scan. This technique decreases ionizing radiation dose since fewer scanning phases are needed per patient.

Another factor that increases contrast enhancement is lowering of beam energy (kvpeak) which increases iodine density on scans.[10]

Acquisition Parameters

A scan protocol consists of a series of settings of acquisition and contrast parameters, reconstruction parameters, technician and patient instructions, and maneuvers to generate a set of images that is optimal for the specific anatomy and indication for the CT scan. The protocol includes the setting of x-ray emitter parameters (i.e., beam energy expressed in kilovolts peak [kVp] and tube current expressed in milliampere-second [mAs]), rotation time, length of helical exposure, pitch, collimation, patient instructions (i.e., breath-hold), dosage of contrast material, delay, volume and infusion rates, reconstruction interval and reconstruction algorithm, parameters of radiation dose optimization tools, and FOV.

Prescan and postscan parameter settings should be distinguished from each other. Various postscan settings, such as the reconstruction algorithm or interval, can be applied to the raw image data. This is not true for the prescan settings. Obviously, an improper prescan setting cannot be corrected after the images have been acquired. Particularly in multislice scanners, proper prescan settings are important and have a direct impact on the diagnostic value of the scan.

Scan parameter settings are also important for optimization of the scan protocol in relation to the clinical question because this may be the only way to limit the radiation dose delivered by the scan.

Prescan Parameters

kVp and mAs

Tube voltage, measured in kVp, is the value that determines the energy level of the x-ray tube. Higher tube voltage renders better tissue penetration but leads to decreasing relative contrast differences between the various tissues. High kVp settings (120 kV) are recommended to allow sufficient photons to reach the detector elements in obese patients. In children or slim patients, low kVp settings (80 kV, or even lower) should suffice and also produce increased contrast differences.

mAs values describe the tube current time product. The mAs value is linearly related to the duration and amount of radiation. Higher mAs represents more radiation delivered by the x-ray tube and leads to a decrease in image noise because more photons will reach the detector. However, this decreased noise is achieved at the expense of an increased radiation dose to the patient. kVp and mAs settings are closely linked, and a change in one may dictate a change in the other.

Collimation

Collimation is a method of reducing the thickness of the x-ray beam. Collimation has a direct impact on spatial resolution in the z-axis and determines the smallest possible slice thickness.

Table Feed and Pitch

Pitch (P) is defined as the ratio of table feed (the speed at which the table moves during tube rotation) and collimation. Values above 2 will result in undersampling of the region of interest and might result in artifacts. Values below 1 will result in overlapping scans, which might be beneficial for three-dimensional (3D) reconstructions but will also increase the dose significantly if other scanning parameters are kept constant. For multislice CT scanners, pitch calculations are different, depending on whether single collimation of one detector ring or total collimation of the whole detector array is chosen. An asterisk indicates that total collimation of the detector array is being described; for a four-slice scanner, a pitch of 2 corresponds to a P* of 8.

$$P = TF/SC$$

$$P^* = TF/(N \times SC)$$

where P = pitch, TF = table feed, N = number of detectors, and SC = single-section collimation.

To give an example for a 64-slice scanner, if pitch is set at 2 and collimation is set at 1 mm, the resulting TF—according to the formula P* = TF/(N × SC)—will be 64 mm/s.

Scanning time is the maximum duration of a scan that a certain tube allows while not exceeding the maximum permissible heat capacity. Older scanners are limited to approximately 20 seconds, whereas newer scanners allow scan times of up to 100 seconds.

Patient Positioning

Proper, central positioning of the patient in the gantry can significantly improve image quality and decrease radiation dose.

Figure 27.2 Beam-hardening artifacts caused by the humerus as a consequence of scanning with the patient's arms alongside the upper part of the chest.

A clear example is raising the arms of the patient when scanning the upper part of the chest (Fig. 27.2).

Contrast Protocols

With the newer scanner types, good timing of the administration of contrast material has become an essential part of the examination. Depending on the indication and parameter settings (pitch), optimization of total volume of contrast, contrast iodine density, volume, and speed of injection is required.

Dual Energy/Source Computed Tomography

Dual energy/source CT was introduced as a novel new technique in 2006. Instead of one x-ray tube, the system was equipped with two x-ray tubes each working at a different kVp. The application of dual-energy computed tomography offers two advantages. The simultaneous availability of high and low peak kilo voltage gives improved visualization of the aorta due to an improved conspicuity of contrast media at lower kVp CT imaging. This, in turn, permits an improved aortic visualization or allows for a reduction in volume or rate of the contrast administration. The inherent increased image noise at low kVp is compensated by the simultaneously acquired high kVp images. The second advantage is the potential to calculate material-specific densities from the simultaneous availability of attenuation measurements at 2 distinct energies. Improved visualization of bone, contrast, or even soft tissue might improve visualization and might decrease the need for multiphasic imaging and allows for the application of bone subtraction resulting in subtracted angiographic like images.[11]

It is still uncertain whether dual energy/source CT will become the gold standard. The use of two different x-ray tubes does have inherent hardware design issues. Also, the inherent advantages of dual energy might also be acquired by smart software algorithms with a single source CT.

Postscan Parameters

Increment

The increment or reconstruction index defines the spacing of the reconstructed images from the raw data set. One could, for instance, decide to reconstruct only a 1-mm slice every 3 mm. The main advantage would be the fewer number of reconstructed slices than if a 1-mm slice had been reconstructed for every position. If the raw data are saved, it is possible to obtain reconstructed images at different positions retrospectively.

Slice Width

Slice width or section collimation defines the thickness of the slice. Slices of various thickness ranging from 0.5 to 10 mm can be calculated from the raw data. The minimum slice thickness, however, is defined by the prescan collimation setting. The main advantage of a thicker slice is a lower noise level and a significant reduction in the data load.

Field of View

As mentioned previously, the size of the display matrix and FOV have a direct impact on axial resolution of the display. By keeping FOV to the minimum necessary, pixel size is decreased. If FOV is 30 cm and the matrix size is 512 × 512, each pixel in the display of axial slices is 0.6 mm. If FOV is reduced to 20 cm, pixel size is improved to 0.4 mm, but the tradeoff is that a higher radiation dose is required because of an increase in detector noise.

In general, a small FOV is important only when detailed measurements are necessary (e.g., in endovascular surgery, calculation of carotid artery stenosis or intracerebral aneurysms). In addition, factors such as contrast density, timing of administration of contrast material, window level (WL), and window width (WW) more strongly affect the ability to distinguish different structures and the edges of these structures.

Windowing

WW sets the number of gray scales displayed, and WL defines the middle gray-scale value of the width. Windowing sets the contrast and the brightness of the image.

Reconstruction Algorithms: Filtered Back Projection and Iterative Reconstruction

Reconstruction algorithms are used to reconstruct the raw data. Basically during a rotation of the tube, obtained one-dimensional (1D) data sets (raw data) are reconstructed in a 2D data set (back projection). Obtained images in this way are very fuzzy and additional filters need to be applied in order to improve image quality (filtered back projection). Initially, filtered back projection was the algorithm of choice. The algorithm determines the relation between spatial resolution and noise and thus contrast resolution. Changing of parameter settings allows optimization of the images. For instance, if a high spatial resolution (bone or lung pathology) is needed, high-resolution convolution kernels (HR kernels) are applied. This will result in a significant increase in spatial resolution and improved imaging for bone or lung, but at the expense of a significant increase in image noise.

With the increasing computational power of current systems, iterative reconstruction has became the major reconstruction algorithm for clinical practice.

With iterative reconstructions mathematical calculations of the cone shape of the x-ray beam, the shape of the voxels, focal spot, nature of the x-ray beam, and detectors are all taken into account. By doing this, image noise can be reduced significantly compared to the filter back projection algorithm (70% to 90%).

The initial iterative reconstruction algorithms were in part based on filtered back projection, but the most recently introduced iterative reconstruction algorithms are fully model based, which means that no filtered back projection is necessary. The major advantage of these algorithms is a substantial decrease in noise and therefore lower radiation doses with an inherent higher noise level can be used, and this will be compensated by the algorithm. The major disadvantage, however, is the high demand on computational power, which, with the ever increasing improvements in computational power, is becoming less of a problem.

Dynamic Computed Tomography Scanning

With the increased number of detector rings in the new multislice scanners, dynamic CT scanning has become an option.[12] The basic concept is that of obtaining CT images at a fixed location (in other words, without moving the table) during the injection of contrast material. After injection of a contrast agent, imaging at a fixed position with continuous rotation of the CT gantry will provide insight into passage of contrast material through the arterial, capillary, and venous phases, representing tissue perfusion. The maximum anatomic area covered by this type of imaging is determined by the z length of the detector area. The 256 and 320 scanners are better suited for this technique and are currently used predominantly for brain and cardiac perfusion studies.

Electrocardiogram Triggered and Gated Scanning

Techniques that couple the electrocardiogram (ECG) signal to scan acquisition can be used to obtain images without cardiac pulsation artifacts at the level of the heart, coronaries, and the ascending aorta. Retrospective ECG-gated CT acquisition is a scanning technique in which the ECG is registered during the scan and coupled to the raw data obtained.[13] By partial reconstruction of the images, it is possible to obtain an image at, for instance, 10 different phases of the ECG. The technique is now available on almost all 64-slice scanners and is most often used for coronary imaging.[14] Because partial reconstructions are used, a major drawback of this technique is that the resulting images are substantially noisier than the full reconstructions. In prospective ECG-gated CT acquisition, the x-ray beams are turned on during preselected phases of the cardiac cycle. The main benefit of this way of sampling is the far lower radiation dose, which, in comparison with retrospective gating, proved to be reduced by 52% to 85%. The main disadvantage is that only preselected phases can be reconstructed.

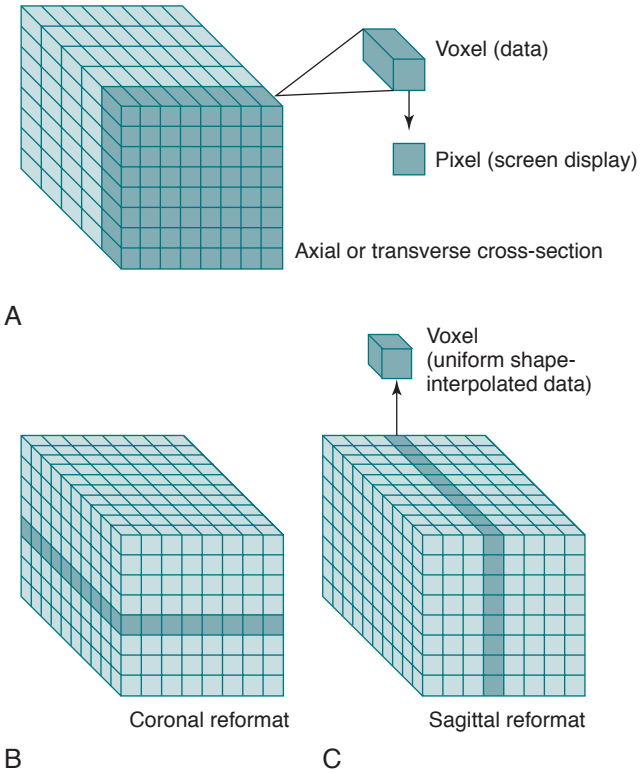

Figure 27.3 (A to C) Because spiral computed tomography (CT) data are acquired and stored over a continuous volume, they can be used to create axial (A), coronal (B), and sagittal (C) sections. For display purposes, the nonuniform voxel can be interpolated into a cube, but the quality of the data still depends on the length of the original voxel (which is determined by the collimation). Reformatting CT data into coronal, sagittal, or other nonaxial planes is often referred to as multiplanar reformatting.

Postprocessing

Multiplanar Reformatting

Reformatting CT data into coronal, sagittal, or other nonaxial planes is often referred to as multiplanar reformatting or multiplanar reconstruction (MPR). A schematic representation of this process is shown in Fig. 27.3. The ability of spiral CT to view the data in coronal, sagittal, or arbitrarily defined planes often gives more insight into vascular anatomy than possible with axial views alone.[15]

Measurements

Simple axial CT slices often do not cut through planes perpendicular to the vessel, which results in elliptical cross-sections that can make measurements of diameter difficult (Fig. 27.4). Generally, the narrowest diameter of the elliptical cross-section is the "true" arterial diameter, but this is not always the case because the aorta does not always have a simple cylindrical or conical shape.[16] Conventional CT may lead to a slight overestimation of diameter on axial slices, whereas spiral CT slices reconstructed perpendicular to the vessel tend to be more accurate.[3,20] Simply using sagittal or coronal reconstruction is not always adequate because these sections may not be perpendicular to the vessel or may not cut through the center of the vessel over an adequate length. Curvilinear reformats continue to improve, but they make measurements of length difficult and straighten out angles, which may affect an endovascular repair. Spiral CT with 3D reconstruction and CT reformats perpendicular to the vessel lumen eliminate the diameter measurement problems associated with the other techniques (see Fig. 20.4).[3,17-20] CTA with 3D reconstruction offers several other important benefits that are key for imaging before endovascular surgery. In conjunction with spiral CTA and MPR, 3D reconstruction speeds assimilation of the CT data and makes the extent of an aneurysm rapidly apparent.[3,18,19] More important, specialized measurement software and unique aspects of the 3D reconstruction can eliminate most of the measurement problems associated with conventional techniques.[3,17-20] Software algorithms can be used to display the centerline of the blood flow channel in the infrarenal aorta and iliac arteries and allow measurements of length along the vessel centerline in tortuous aortic or iliac segments.[17] In some systems, graft paths along a line other than the centerline can also be defined by the user, which is necessary because an endovascular graft may not follow the centerline of the blood flow channel throughout its entire course.

3D reconstructions can be used to calculate the volume of any structure in the 3D model, and data on imaging of tumors and other 3D structures indicate that volume measurements are much more sensitive to changes in size than measurements of maximal diameter.[21-23] Multiple institutions have confirmed that volume measurements are much more sensitive than maximum diameter measurements for the detection of changes in size of abdominal aortic aneurysms (AAAs) after endovascular AAA repair, and it seems that volume is the "gold standard" for early detection and accuracy regarding aneurysm growth or shrinkage.[24-29] Early detection of aneurysm enlargement can be crucial in follow-up of endovascular repair because it indicates that the aneurysm is still at risk for rupture and usually precedes evidence of endoleak or overt rupture.[26,30-32] CT volume measurements may become a standard postoperative test for aneurysm exclusion or risk of rupture either routinely or if the aneurysm is not clearly shrinking.[24-29] These same studies indicate that there may also be a role for early volume measurements within the first 6 months to more clearly identify decreasing aneurysms that may need less frequent imaging or may be able to avoid secondary interventions.

Several systems providing all of the aforementioned display and measurement tools (and more) are commercially available or in development.

Three-Dimensional Reconstruction

The combination of rapid scanning over the volume of interest, new software algorithms, and advances in computer technology has made it possible to create 3D-like reconstructions from spiral CT data. The reconstruction can be limited to individual structures that meet certain parameters, such as density or location within the scan volume. If bony structures are of primary interest, the computer algorithm can select only the elements of the CT (voxels) that are of bone density (i.e., CT numbers representing bone). For vascular structures, CTA produces

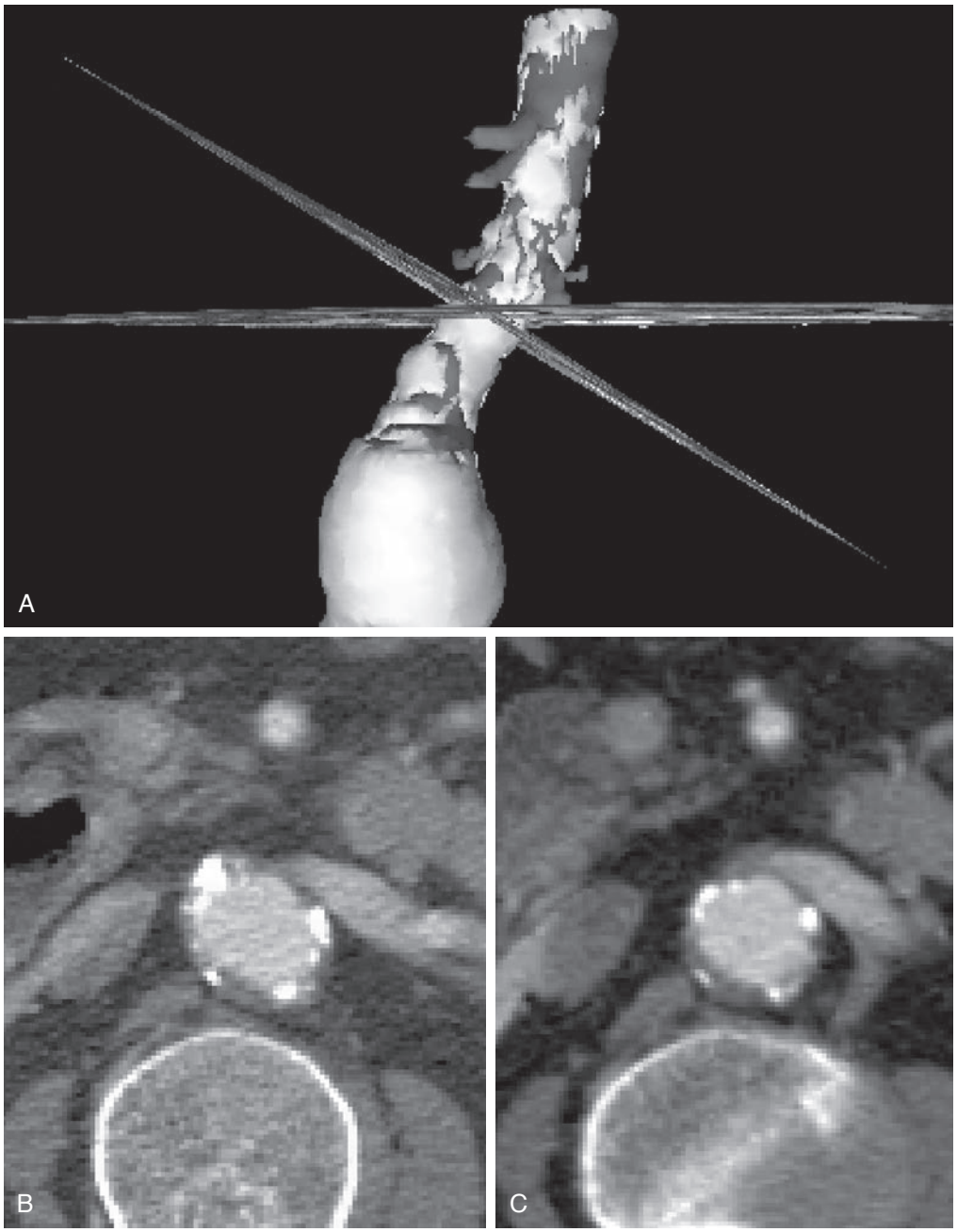

Figure 27.4 Diameter measurement issues and solutions using computed tomography (CT). (A) Three-dimensional (3D) reconstruction with simultaneous display of CT slices in 3D space. The CT slices shown here are a standard axial reformat and a reformat perpendicular to the aorta. The 3D model was rotated to show the intersection of the two CT slices at the same location on the aorta. (B) The same axial CT slice as shown in (A). The axial slice does not intersect the aortic neck perpendicular to its axis, thereby creating an elliptical cross-section. Although the smaller diameter (minor axis of the ellipse) is usually similar to the true diameter, elliptical cross-sections also occur in noncylindrical vessels and at the margins of aneurysms. Viewing multiple cross-sections in sequence can help with this problem, but evaluation is still difficult. (C) The CT slice reformatted perpendicular to the aorta (shown in A) accurately depicts the essentially circular lumen and provides a diameter measurement without ambiguity. This cross-section of the aorta also provides a more correct impression of thrombus thickness, which is artifactually enhanced on an elliptical cross-section. The renal vein and vertebrae help verify the magnification, location, and orientation of the slices.

contrast density within the vessel lumen so that 3D reconstruction of the vessel lumen can be performed. When this type of 3D reconstruction (or 3D model) is created, the density (CT numbers) of vascular contrast and bone may overlap. Bone structures are either included in the model or "cut away" manually. Calcium within the vessel wall cannot be cut away easily, however, and is usually included in a reconstruction of the contrast-enhanced vessel lumen. This produces the typical computer-generated 3D reconstruction, which most often is displayed as a shaded surface display (SSD). In an SSD, the

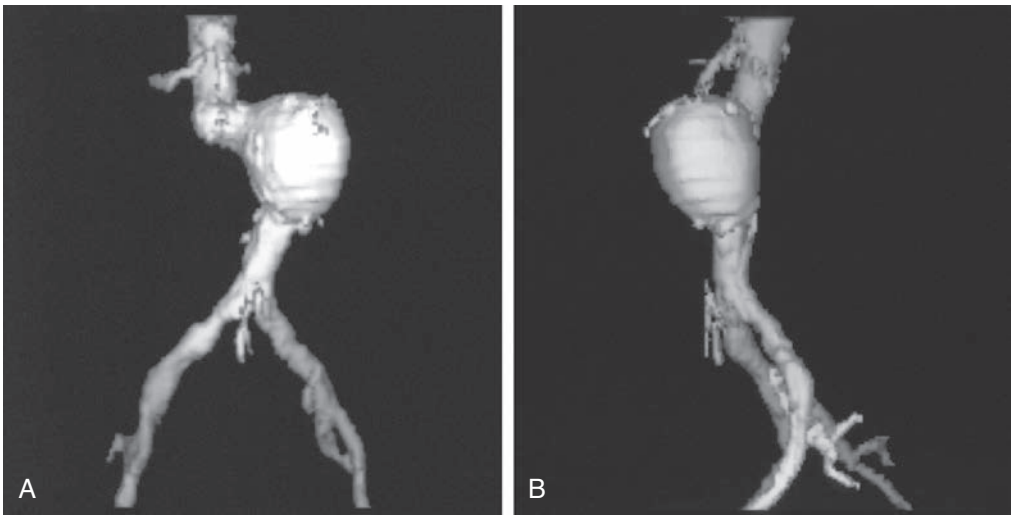

Figure 27.5 Computer-generated shaded surface display (SSD) of computed tomography data. The three-dimensional (3D) relationships of the aneurysm and surrounding structures are immediately apparent in these anteroposterior (A) and left lateral (B) views. In this typical single-object 3D SSD, the threshold for reconstruction is the density of contrast-enhanced blood. Because calcified plaque is denser than contrast-enhanced blood, it is included in the reconstruction. The spine was removed electronically before making the 3D reconstruction. An infinite number of views are possible on the workstation used to create the views, but a limited number of views are printed as hard copy to show the anatomy.

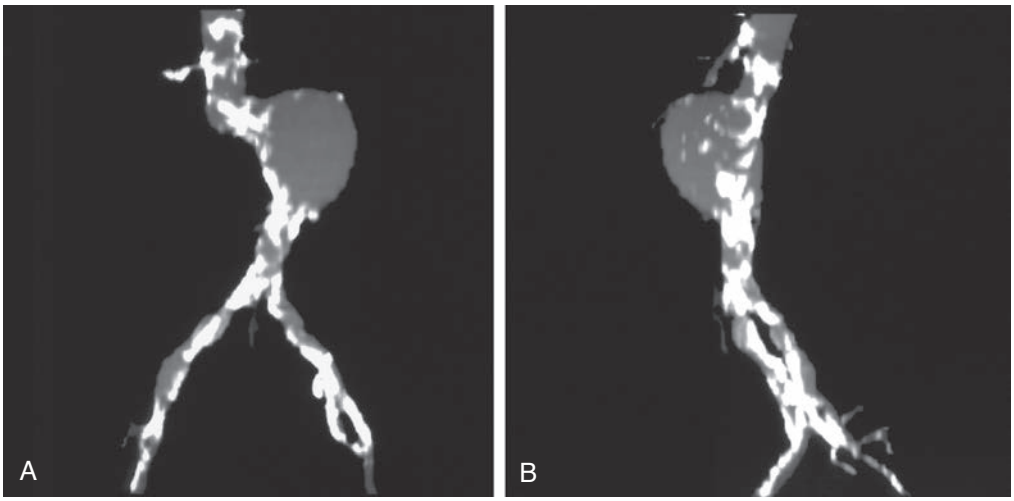

Figure 27.6 Maximum intensity projection (MIP) images of the same abdominal aortic aneurysm shown in Fig. 27.5, anteroposterior (A) and left lateral (B) views. Because this reconstruction represents a two-dimensional projection of the structure along a line defined in three-dimensional space, the MIP appears to be similar to an arteriogram. Only the structure with maximum intensity is projected, so calcified plaque is displayed prominently. MIP images display calcified plaque well, but this same feature can obscure the residual lumen in locations where the vessel is heavily calcified (note the iliac arteries in particular).

exterior of the structure is opaque and shaded to provide an appreciation of depth (Fig. 27.5). The 3D reconstruction can greatly aid in the interpretation of difficult anatomy. Although it lacks the detail of CT scans, morphology within the 3D image is easily recognizable in far less time than it takes to review the CT data. This depiction of 3D relationships is probably most helpful in surgical planning for complicated open procedures or endovascular procedures.[18,19,33,34]

One problem with the SSD of 3D models is that the bulk of structures, such as calcified plaque, cannot be fully appreciated because all CT numbers (physical densities) included in the model are given the same opaque color in the display. One method that better displays different physical densities is called the maximum intensity projection (MIP). MIP images display the 2D projection that would result if one could see only the densest structures (structures that project the maximum intensity). Although an MIP image is created from 3D volume data, it is a projection—similar to an angiogram—and must be defined from a particular point of view (Fig. 27.6). MIP images are relatively familiar to surgeons and interventional radiologists,

and they display calcified plaque well. Adequate evaluation of the structure requires many views, however, and even then a heavily calcified vessel may obscure important details regarding the vessel lumen and degree of stenosis.

Another method developed to improve the display of structures with different physical densities involves the SSD of multiple objects simultaneously. In vascular surgery, the most clinically relevant structures are the contrast-enhanced vessel lumen, calcified plaque, noncalcified plaque, and thrombus. Noncalcified atherosclerotic plaque and thrombus have essentially identical CT numbers and cannot be distinguished as separate objects. The latter two structures are distinct from contrast-enhanced blood flow, however, and blood flow can be distinguished from calcified plaque to a reasonable degree. With proper CT protocols and software algorithms, these structures can be displayed separately on the basis of density. The resulting 3D reconstructions display information that is not available in any other imaging modality (Fig. 27.7). Because the separate elements can be viewed in combination or separately, this type of reconstruction has the advantages of single-object SSD and MIP without most of their disadvantages. This 3D method can display best the extent of an aneurysm (because thrombus is visible), degree of calcification, and lumen narrowing secondary to plaque (especially if structures of differing density can be made invisible or transparent) (Fig. 27.8).

It is important to realize that a 3D SSD is a representation of a real 3D data set, unlike the "fake" 3D created in pictures (or movies) whereby a pair of 2D photographs, each taken from the same point but at a slightly different angle, emulate

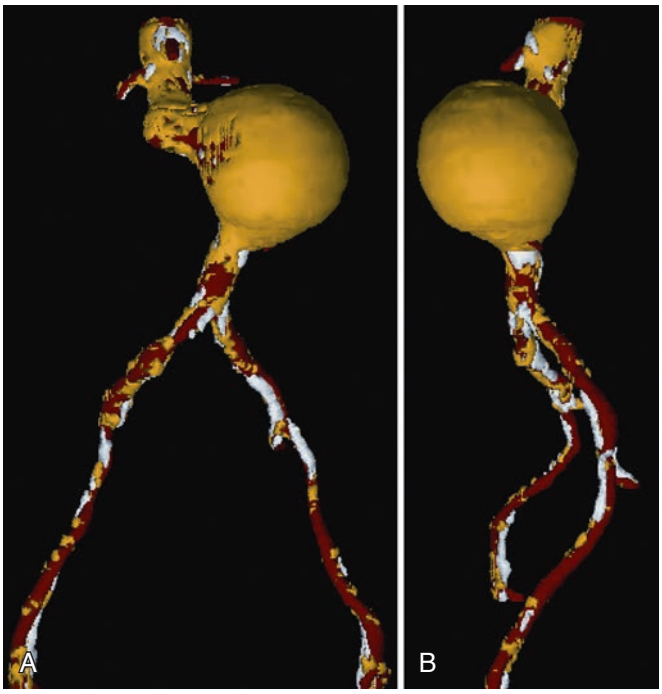

Figure 27.7 Multiple-object shaded surface display, anteroposterior (A) and left lateral (B) views of the same abdominal aortic aneurysm seen in Figs. 27.5 and 27.6. Contrast-enhanced blood flow is displayed in *red*, thrombus and noncalcified plaque in *yellow*, and calcified plaque in *white*. In this type of three-dimensional reconstruction, all the components of the aneurysm are seen. Multiple views are helpful, and it is preferable if the display can be rotated and viewed at will on a computer screen. This type of display is most helpful in determining the true extent of an aneurysm because thrombus is clearly visible.

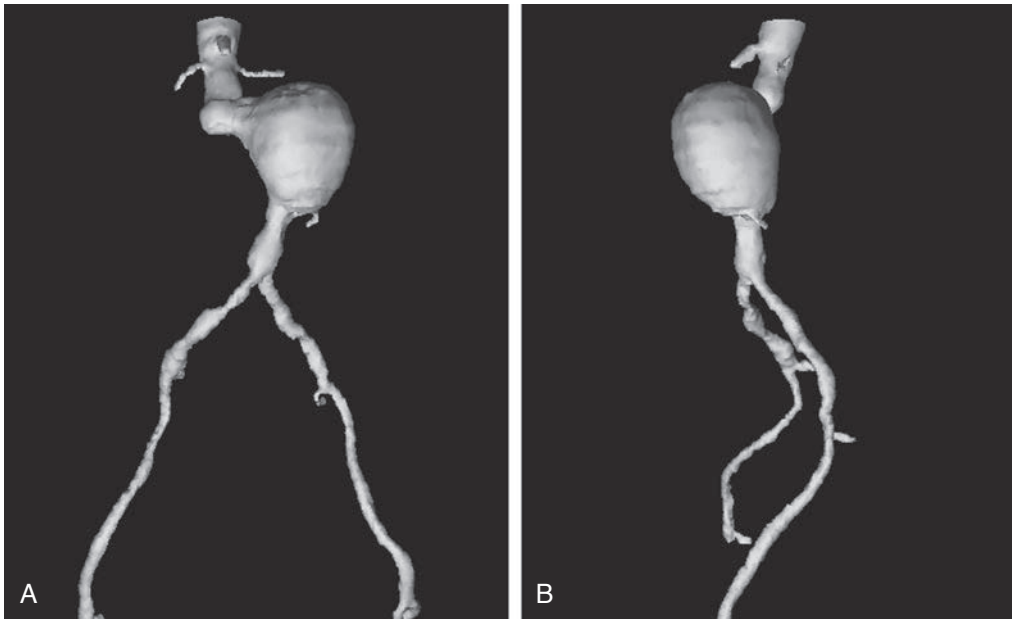

Figure 27.8 Multiple-object shaded surface display (SSD) from Fig. 27.7 with the same anteroposterior (A) and left lateral (B) views and all structures made invisible except blood flow. With calcified plaque made invisible, the degree of occlusive disease becomes apparent in the iliac arteries. A key point is that calcified plaque was modeled separately and has been made invisible so that this three-dimensional reconstruction does not have the same appearance as the typical single-object SSD shown in Fig. 27.5. For surgical planning, it is preferable if the objects can be made visible or invisible at will on a computer screen. An alternative is to print hard-copy images in multiple views with the various components sequentially highlighted, transparent, or invisible.

the physiologic parallax of binocular real 3D vision. Still, this 3D SSD model is displayed in 2D, and real visual depth information is therefore missing. To add the value of depth, several solutions have been proposed. One is the use of sophisticated software programs that add perspective to the 3D CT data (Dextroscope, Bracco AMT, Princeton, California). The main limitation of this technology is that the observer is required to wear dedicated polarizing glasses to see this effect. With the development of 3D monitors, however, this problem seems to be solved. The end result will be real 3D data sets that can be manipulated, viewed, and analyzed with perspective and that will give the observer an optimal feel for the depth information in the 3D model.

CLINICAL APPLICATION

The most common noncardiac, nonbrain vascular imaging indications for CTA are aortic disease (aneurysm, dissection, trauma), peripheral arterial occlusive disease, renovascular disease, venous disease, and, rarely, vascular malformations.

Aortic Disease

In general, CTA has become the primary imaging modality for aortic disease. The excellent spatial resolution and the potential of 3D image reconstruction allow for highly accurate measurements of aortic aneurysms in the preoperative planning of endovascular repair, as well as postoperative follow-up. CTA also allows for imaging of small branches such as the intercostal arteries (important for prevention of spinal cord infarction during thoracic aortic repair) and for tiny contrast enhancements in thrombus (important for identification of endoleak). The CTA acquisition speed of the entire aorta (currently, within 1 minute; in newer scanners, within a few seconds) allows accurate imaging of the aorta in acute cases such as ruptured aneurysm, aortic dissection, and trauma. Endovascular repair of these acute diseases currently relies on acute CTA (Fig. 27.9A and B). ECG gated or triggered CTA aids in detecting and exclusion of pathology of the ascending aorta.

Apart from the acquisition speed, an important advantage of CTA over MRA in both the acute and elective setting is the ability of CTA to image calcium, for instance, in aortic landing zones of endovascular devices that depend on penetrating hooks and barbs or access arteries that may render endovascular repair difficult or impossible (Fig. 27.10). CTA is preferred over MRA when endovascular devices are in place because metal artifacts are rarely a problem.

Figure 27.10 Example of heavily calcified iliac access arteries, coronal reconstruction.

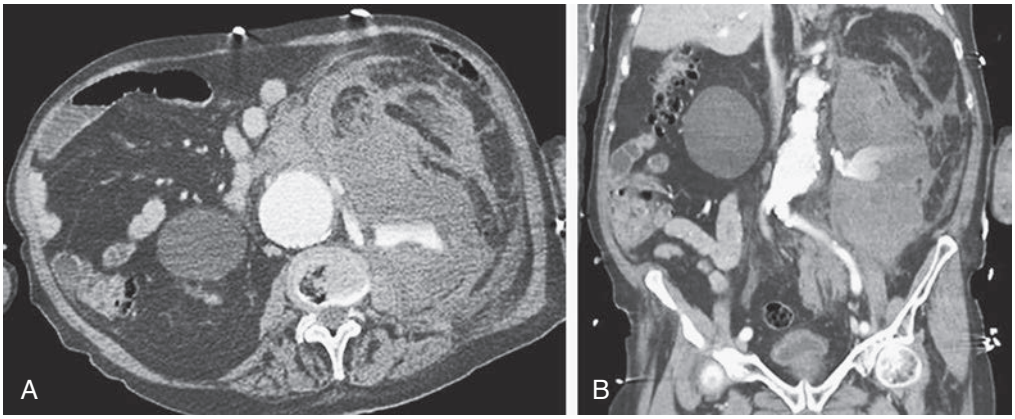

Figure 27.9 Computed tomographic angiography of ruptured abdominal aortic aneurysm. (A) Axial view. (B) Coronal reconstruction.

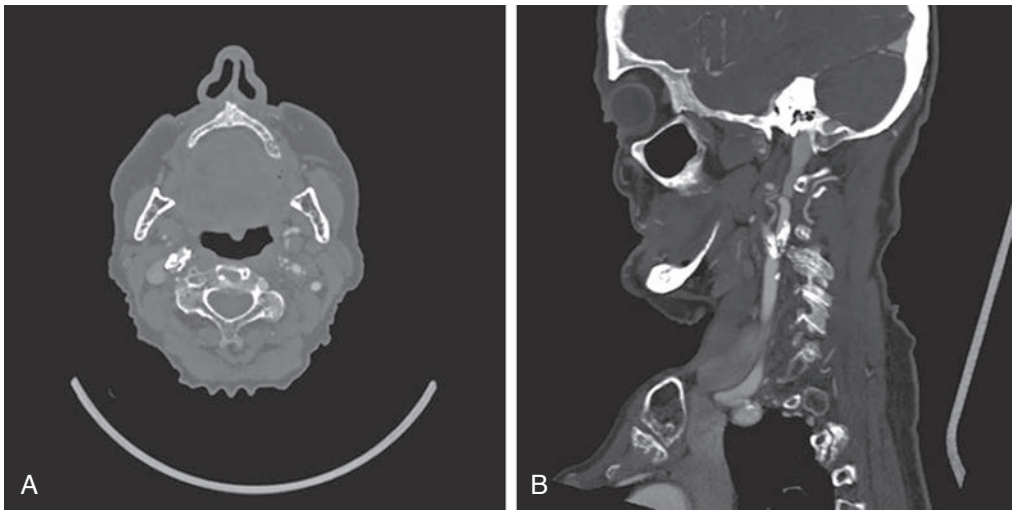

Figure 27.11 Example of carotid artery computed tomographic angiography imaging. (A) Axial view. (B) Sagittal reconstruction.

Peripheral Arterial Occlusive Disease

CTA can be used to image the arterial tree from the aorta through the pedal vessels in a single contrast-enhanced acquisition run. However, accurate timing of contrast injections is essential. The high resolution of CTA allows for accurate delineation of stenotic segments and planning for open and endovascular intervention. It has been shown to be highly accurate in imaging tibial artery runoff.[35] On the downside, interpretation of CTA images and reconstructions of small arteries (tibial vessels) can be very tedious, particularly the distinction between calcium and contrast. Overestimation of the severity of a calcified stenosis is common.[35] Carotid artery stenosis can be accurately defined by CTA. Although duplex-ultrasound imaging can be impeded by calcified plaques, the accuracy of CTA imaging of the carotid artery is hardly affected by calcium (Fig. 27.11A and B). In addition, it can help differentiate occlusion from high-grade stenosis, and it provides better anatomic reference than duplex. CTA also provides the option of adjacent imaging of the aortic arch and intracranial arteries, which may be of help in the diagnosis and treatment of neurovascular disease.[36] CTA can also often be used for diagnosis of mesenteric artery stenosis and aneurysms and for preinterventional planning.

Renovascular Disease

CTA and MRA are comparable in sensitivity for the detection of proximal renal artery stenosis. However, if evaluation of more peripheral abnormalities is needed, MRA suffers significantly from respiratory movement of the kidney.

The main benefit of MR for renal artery imaging is the fact that contrast-induced renal nephropathy is avoided, although a limiting factor is the rare occurrence of interstitial fibrosis due to gadolinium in patients with renal failure. Valid alternatives include time of flight or comparable MR techniques that allow for flow imaging without the use of gadolinium; however, these techniques provide less optimal imaging quality.

Venous Disease

Provided that a proper injection protocol with sufficient delay and contrast volume is chosen, CT is able to evaluate a variety of venous pathologies, including mesenteric venous thrombosis. For the evaluation and detection of pulmonary emboli, CT has replaced lung perfusion and ventilation studies. However, for peripheral evaluation of venous disease (in legs, iliac veins, subclavian veins), the optimal imaging modality is still duplex ultrasound because this also provides essential flow information. If cross-sectional imaging is required MRV is an excellent alternative to CT.

Vascular Malformations

The role of CTA in the evaluation of vascular malformations is limited. Only in cases of high-flow malformations (AVM, AVF) can CTA support a proper diagnosis; the extent and composition of the nidus cannot be adequately evaluated without the use of four-dimensional (4D) imaging. For low-flow malformations there is virtually no role for CT imaging. The limited soft tissue contrast and the extremely low-flow situation make a venous malformation very difficult to characterize with CT. Instead, ultrasound and MRI are the modalities of choice.

LIMITATIONS AND RISKS

Radiation Dose

The radiation dose of CT has attracted attention in the recent decade because of the increased frequency of use and recognition of cancer risks.[37] With the development of the new CT technology (spiral and multidetector), the initial hope was that the radiation dose to the patient could be decreased relative to the old single-slice sequential technique. It soon became apparent, however, that this would be true only if the less optimal image quality of the older technique (often 10-mm slices) were still

acceptable. However, the advent of CTA, 3D reconstructions, and MPR has led to optimal use of the new technology, often with imaging at the smallest collimation possible to allow use of the advanced postprocessing techniques. Furthermore, as image quality improved and the diagnostic value of CT became more apparent, an exponential growth in the *number* of CT examinations occurred. As CT rapidly became a major diagnostic instrument, not all physicians ordering CT scans were aware of the long-term carcinogenic potential, particularly in the pediatric group. Additionally, large-scale screening programs for asymptomatic patients based on CT have emerged. The most well known are CT colonography, coronary calcification screening, CT lung screening, and whole-body screening.[37]

Although it is difficult to validate the calculated radiation risk data because they rely heavily on assumptions based on follow-up data from atomic bomb survivors, it is estimated that between 1991 and 1996, 0.4% of all cancers in the United States were attributable to CT studies. As a result of the increased use of CT in the last decade, this figure has increased to 1.5% to 2%.[37] Awareness of the potentially harmful side effects of radiation is important and should play an important role in the clinical decision of whether to order a CT scan, particularly in children. In addition, radiation risk should influence the choice of parameter settings and scan protocol.

Contrast-Induced Nephropathy

Contrast nephropathy has long been considered as an important cause of iatrogenic acute renal failure.[38] This has led to large-scale programs to prevent this entity. During the last years, the debate on less strict criteria for CIN prevention has emerged.[39] However, final conclusions have not yet been drawn. Nephrotoxicity of contrast agents, contrast-induced nephropathy, associated risk factors, prevention, and alternative imaging options are described in detail in Chapter 25.

COMMON ARTIFACTS

Partial-Volume Effects

Partial volume refers to a situation in which objects are only partly included within the scan plane. The resulting image simulates a lesion where none exists. A good example of this effect is, for instance, the appearance of a "nonexistent" lung nodule adjacent to the anterior attachment of the first rib (Fig. 27.12).

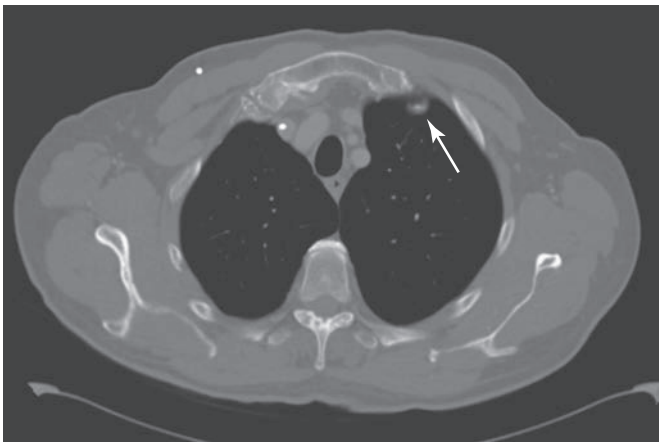

Figure 27.12 Example of a partial-volume effect, here responsible for the appearance of a nonexistent "lung nodule" adjacent to the anterior attachment of the first rib *(arrow)*.

Beam-Hardening Artifacts

Streak artifact or scatter artifact arises from interfaces between materials with large differences in density from the surrounding structures. This artifact is commonly seen with dense materials such as prosthetic hips or metallic stents in endografts. Different materials cause varying levels of artifact. Tantalum and gold stents cause significant beamlike artifacts, whereas platinum has almost no influence on the image. Steel lies in the middle of the spectrum. These artifacts can result in the erroneous interpretation of vessel lumen narrowing—sometimes by 25% to 50%. Tantalum and gold cause few effects on MRI images. Knowledge of the type of stent helps determine the preferable imaging modality.[40,41] Scatter also can occur as a result of dense intravenous contrast material in the subclavian or brachiocephalic veins because dense contrast is often infused rapidly into these veins during the scan. If the aortic arch vessels are the focus of the CT scan, the contrast agent should be infused into the arm opposite the vessel of interest or into the inferior vena cava.

Beam-hardening artifacts can also be seen if both arms are left alongside the body while scanning the chest. To avoid these artifacts, the patient should be positioned with at least one arm, preferably both arms, above the head (see Fig. 27.2), or iterative reconstruction should be used. Another way to reduce this type of artifact is by using metal reducing reconstruction algorithms.

Motion Artifacts

Different types of motion artifact exist, but the most pronounced is due to movement of the patient during the scan. Other well-known motion artifacts are respiratory and pulsation artifacts. The degree of degradation of the resulting image depends on the degree of movement and ranges from a double contour to double visibility of the body. To avoid respiratory artifacts in dyspneic patients, the general recommendation is to ask these patients to *not* hold their breath during scanning, because this will often result in a sudden deep inhalation during the scan and subsequent severe motion artifacts and less contrast enhancement. Instead, the patient should be requested to maintain shallow respiration.

Other Common Artifacts

Averaging artifact has already been mentioned with regard to "missing" a small vessel because of surrounding soft tissue, but it can also work in the opposite fashion. In this type of artifact, comparable to partial volume artifacts, the large attenuation from a small piece of calcified plaque within a CT slice "averages" with thrombus-density material to produce a display with an

intermediate density—similar to intraluminal contrast. This artifact often occurs within aortic aneurysms and should be suspected when contrast-density material appears with no apparent inflow or outflow vessel and when a piece of calcium or metal is nearby. This type of artifact is reduced by using a small reconstruction interval.

Stair-step artifact occurs when the reconstruction interval on a spiral CT scan is too large and a stepped appearance in the vessels is created. This artifact is most likely to occur in vessels oriented away from the z-direction of the scan (e.g., renal or iliac arteries). If such an appearance is noted in a multiplanar reformat, it is difficult to evaluate potential occlusive disease. Some of these artifacts are shown in Fig. 27.13.

A number of scanner-related artifacts are also possible. Most are related to scanner malfunction, improper calibration (ring artifacts), tube malfunction, or detector malfunction.

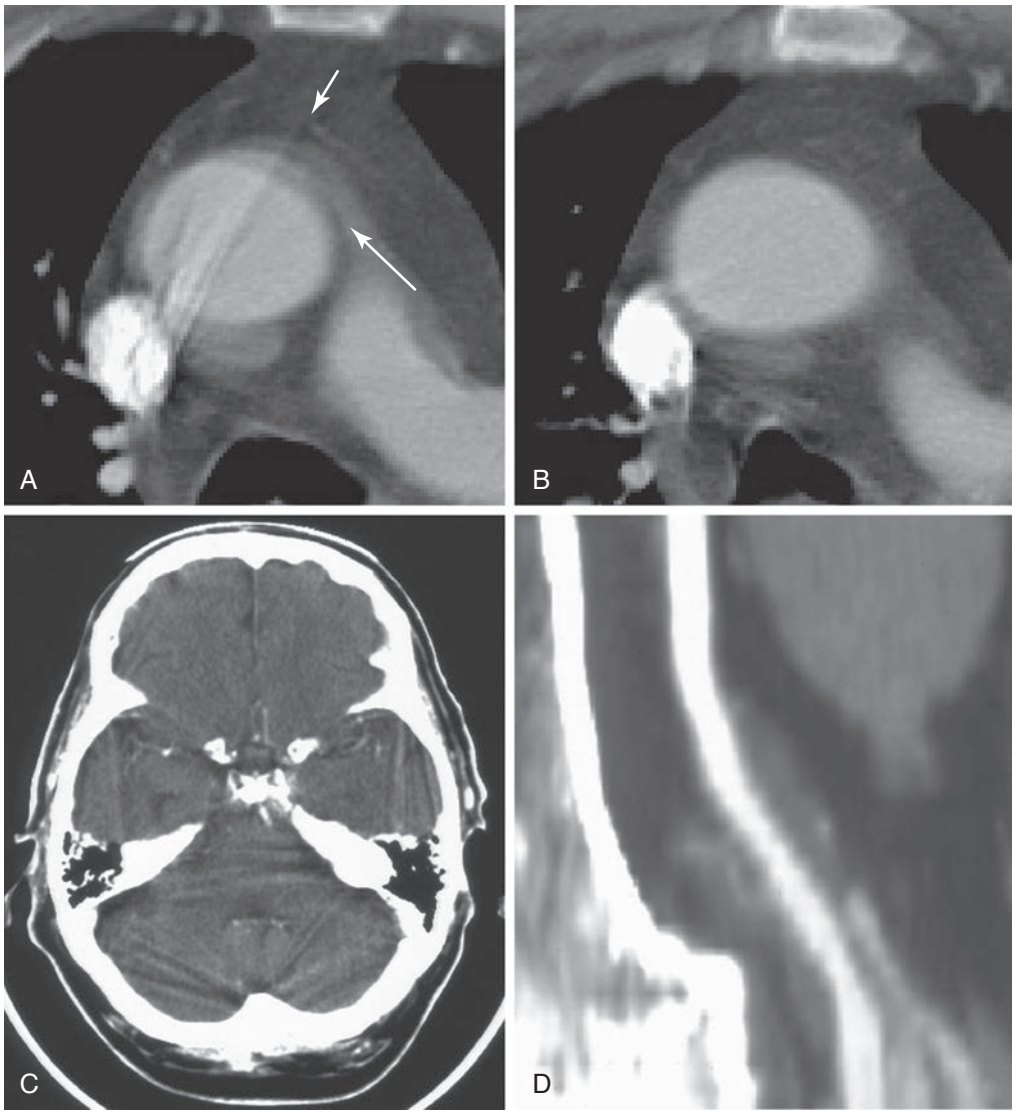

Figure 27.13 Computed tomography (CT) artifacts. (A) Motion artifact in the thoracic aorta creating the impression of an intimal flap or dissection *(long arrow)*. The position of these artifacts is usually due to aortic motion from the left anterior to the right posterior position. Streak artifact is also seen arising from dense contrast within the superior vena cava. The longer streak is clearly artifact because it extends beyond the vessel wall *(short arrow)*, but the shorter streak could be misinterpreted as an intimal flap. One clue is the appearance of an obvious streak artifact in the same vessel. Another clue is the interface between structures with large differences in density. Other clues to the true nature of the aorta come from the benign patient history and the immediately adjacent CT slice. (B) The apparent pathology (artifacts) shown in A is not present in this immediately adjacent CT slice. (C) An intracranial streak artifact can make it difficult to detect infarcts in locations surrounded by dense bone. Beam-hardening artifact is also common on head CT and occurs when low-energy portions of the x-ray beam are absorbed by thick, dense structures, such as the skull. The residual beam that proceeds through the dense bone has higher energy and may cause a small area of adjacent tissue to appear less dense (darker) than it should be. This can create an artifact resembling an ischemic infarct immediately adjacent to the skull. (D) A stair-step artifact creates a stepped appearance in the vessel (see text). This artifact is unique to spiral or helical CT.

Finally, window and level setting errors affect the ability to visualize contrasting objects. A window setting too narrow will result in a significant increase in visible noise that will degrade the visualization of fine structural details, whereas a window too wide will abolish small differences in contrast.

SPECIAL PEDIATRIC CONSIDERATIONS

CT scanning should be avoided in the pediatric age group, if at all possible, to avoid the radiation exposure. Alternative imaging techniques, such as ultrasound and MR, can often replace CT. If CT is necessary, strict adherence to the As Low As Reasonable Achievable (ALARA) principle must guide selection of the scan parameters that determine the radiation dose relative to the image quality. A lower image quality can and should be accepted if this is sufficient for a proper diagnosis.

FUTURE ADVANCES

4D imaging will be incorporated further into clinical practice, and diffusion and perfusion imaging could become an integral part in the evaluation of many organs (e.g., renal transplants). Improved detector designs (with higher-detection quantum efficiency and lower noise levels) combined with noise-reduction iterative algorithms will lower the radiation dose significantly.

Computer-aided diagnostic programs will further expand and be used to assist the clinician in evaluating the huge data sets currently being produced by the 256 and 320 scanners.

Computed Tomography Versus Duplex Ultrasound and Magnetic Resonance

Duplex ultrasound is a noninvasive technique and an excellent screening modality in patients with PAOD. However, duplex ultrasound is hampered by the fact that it is operator-dependent and of limited value in patients with heavily calcified arteries or extensive, multilevel disease. Also, evaluation of the abdominal and pelvic vessels can be quite challenging in the obese patient. In the era of progressive application of endovascular techniques, detailed pretreatment information is essential, and duplex ultrasound alone frequently fails in that respect because of the previously described limitations. CTA and MRA each have their own pros and cons. CTA is an excellent modality for the evaluation of the aorta in case of endovascular treatment and provides detailed and often essential information on calcification in the access arteries and in the wall at the level of landing zones for endografts. MRA is, in this respect, less useful because of its limited ability to visualize calcium. On the other hand, if information about tibial arteries is required, MRA is preferable over CTA because the presence of heavy calcifications in small vessel walls hampers the evaluation of the CTA.

Although the quality of periprocedural imaging in the operating theater is rapidly improving, detailed preprocedural imaging is essential and cannot be replaced by periprocedural imaging without lengthy procedures and high radiation doses.

Positron Emission Tomography With Computed Tomography

Use of positron emission tomography (PET) in concert with CT combines valuable physiologic information from the PET scanner with anatomic information from CT. In oncology imaging, PET/CT is one of the major evaluation tools for detection of malignancy and inflammation. PET/CT might play a role in vascular imaging for the detection of infected grafts. Furthermore, growing evidence indicates that PET/CT may have additional value in identifying inflammatory responses in atherosclerotic plaque, which may allow noninvasive assessment of disease activity.[42,43] In Chapter 29, vascular nuclear imaging is described in detail.

Mobile Computed Tomography and C-Arm Computed Tomography

The new angiographic C-arms, equipped with flat-panel detectors, also offer the possibility of C-arm CT. At present, the quality of acquired CT images is comparable to that of the first- and second-generation CT scanners. Further improvements are to be expected because the technique offers interesting options for incorporating interactive CT models into fluoroscopic images in real time.[44,45] This form of image fusion may be used to improve endovascular therapy and other invasive procedures.

ACKNOWLEDGMENT

Monique Brink, Gijs Bloemsma, and Maarten Truijers are greatly acknowledged for their help in preparing this chapter.

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28 CHAPTER

Magnetic Resonance Imaging and Arteriography

JEFFREY P. CARPENTER, HAROLD LITT, and MAMATHA GOWDA

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Abstract

Magnetic resonance angiography (MRA) allows evaluation of the vascular system without ionizing radiation and if needed without contrast in patients with contraindications. Recent advances in MRA are discussed in this chapter for evaluation of vascular diseases, including technical developments, applications, artifacts, and novel contrast and noncontrast methods.

Keywords

Magnetic Resonance Angiography
Magnetic Resonance Venography
Aortic Vascular Disease
MRI artifacts
MR contrast agents

BASIC PRINCIPLES

Magnetic resonance imaging (MRI) is performed by using a large external magnetic field, magnetic field gradients, and an applied oscillating magnetic field known as the radiofrequency field (RF). The combination of these three types of applied magnetic fields allows the user to produce signals from inside patients, which in turn can be used to create MR images.

The details of the external magnetic field, magnetic field gradients, and RF determine many of the characteristics of MR images. The goal of the external magnetic field is to magnetize the subject by making the protons within the subject align parallel with the external field. The physical characteristics of the protons and the size of the external magnetic field define the resonance frequency of the proton. If the external magnetic field is uniform, all the protons will resonate at the same frequency. Most MRI machines operate at an external field strength of 1.5 or 3 tesla (T); the potential advantages of 3-T magnetic resonance angiography (MRA) are discussed later in the chapter. Lower field systems, those less than 1.0 T, tend to produce images at a slower rate or at a lower resolution than is typically desirable for MRA examinations.

Magnetic field gradients are used to alter the otherwise uniform external magnetic field in a linear fashion in any of three directions. The gradients ramping on and off produce the noise heard when an MR image is being made. When the gradient fields are applied, the protons resonate at a frequency that is a function of the magnetic field gradient's position. This is analogous to a radio station's frequency corresponding to a specific position on the dial. The speed and strength of the gradients determine the size of the images and may be a rate-limiting step in imaging speed.

Resonant coils placed adjacent to the region of interest produce the RF. These fields are tuned to match the resonant frequency of the protons inside the patient. The applied RF in combination with the gradients is used to manipulate the protons inside the patient to produce a signal. This signal is detected with a receiver RF coil, also tuned to the resonant frequency of the protons. Once detected, the signal is sent to an amplifier and receiver, where it is digitized and processed with a mathematical algorithm known as a Fourier transform to produce the MR image.

Characteristics of Magnetic Resonance Images

The contrast in MR images depends on the characteristics of the object being imaged and on the specifics of the sequence itself. Images are typically referred to as either T1 weighted or T2 weighted. T2-weighted images display simple fluids such as urine, bile, or cerebrospinal fluid as bright and other tissues as lower signal. T2-weighted imaging is one of the basic sequences for imaging of tumors but is not used for angiographic imaging. MRA and magnetic resonance venography (MRV) are performed with T1-weighted image sequences. Objects that are bright on T1-weighted images, including fat, methemoglobin, flow effects, and MRI contrast, will often also be seen on MRA.

Magnetic Resonance Pulse Sequences

The MR pulse sequence is a label that refers to the particular combination of RF and gradients that are used to create the image. There is a large variety of MR pulse sequences, but almost all are variations of spin-echo or gradient-echo sequences. Spin-echo pulse sequence methods use RF alone to produce the MR signal, whereas gradient-echo pulse sequences use RF and applied gradients to produce the signal. As a rough generalization, spin-echo pulse sequences are used to produce T2-weighted images and gradient-echo sequences are used to create T1-weighted images.

Pulse Sequence Parameters

The characteristics of a tissue that determine its appearance on MR images are the T1 and T2 parameters of the tissue. Some tissues are bright on T1-weighted images and others bright on T2-weighted images. How then do we create a T1- or T2-weighted image? All pulse sequences have fundamental parameters known as echo time (TE) and repetition time (TR) that determine image contrast. T2-weighted images have a longer TE, in the range of 80 ms or greater, and a longer TR, in the range of several seconds. Because of the long TE and TR, these sequences are slower and not appropriate for contrast-enhanced MRA. However, T1-weighted images have a very short TR and TE, with a TE of 1 ms or less and a TR ranging from hundreds of milliseconds to less than 10 ms for MRA sequences. These fast T1-weighted gradient-echo sequences are used for most angiographic examinations.

Other parameters used in all MR image sequences include the field of view (FOV) and image matrix. FOV is the size of the imaged region. In a two-dimensional (2D) image, FOV may be 40 × 30 cm with a slice thickness of 5 mm. The resolution of the image in that 5-mm slice will depend on the number of pixels within the 30 × 40-cm region. However, most MRA is performed with a three-dimensional (3D) image sequence. In this case, FOV is specified with three dimensions, such as 40 × 30 × 30 cm. If we have an image matrix of 256 × 192 × 64, we have a voxel (or 3D pixel) size of 1.56 × 3.26 × 4.7 mm. Image postprocessing is usually performed on 3D data to make the last dimension twice as small as specified by the pulse sequence. In this case, such processing would yield a voxel size of 1.56 × 3.26 × 2.35 mm.

Magnetic Resonance Angiography and Venography

Non–Contrast-Enhanced Magnetic Resonance Angiography

Non–contrast-enhanced MRA methods, most notably time-of-flight (TOF) imaging, have largely been supplanted by superior contrast-enhanced methods.[1-5] However, the description of nephrogenic systemic fibrosis (NSF) in patients with poor renal function who have received gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)[6,7] (see section "Contrast-Enhanced

Magnetic Resonance Angiography" for further details) has led to renewed interest in non–contrast-enhanced techniques.

TOF angiography uses a rapid T1-weighted pulse sequence in either sequentially acquired 2D slices or a 3D imaging slab. In a single-slice image when data are gathered rapidly, the protons within the slice lose much of their magnetization. Thus there is much less signal from these protons, and the corresponding tissues are not well seen. However, the rapid imaging does not degrade any protons outside the slice. When fully magnetized protons in a vessel flow into the slice of interest, they produce much greater signal than the surrounding tissue. This results in an image in which the blood flowing into the slice is much brighter than surrounding tissue.

For example, if the image were obtained in an axial slice through the mid abdomen, the aorta and inferior vena cava (IVC), as well as some of the mesenteric arteries and veins, would be bright. To remove either the arteries or veins, a special RF pulse is applied to the tissue either above or below the slice to eliminate magnetization from that tissue. If an inferior saturation pulse were used in our example, only the protons flowing into the slab from above (the aorta and mesenteric arteries) would be bright. A series of such images obtained sequentially would produce a 2D TOF abdominal angiogram.

Additional noncontrast MRA techniques such as ECG-gated steady-state free precession (SSFP),[8] ECG-gated arterial spin labeling (ASL),[9] Navigator-gated SSFP, and half-Fourier fast spin-echo imaging (HASTE) with flow-spoiled gradients[10] are used. These techniques use combinations of several different methods that accentuate the signal of flowing blood and attenuate the signal from nonmoving structures and tissue with signal characteristics different from blood. For example, the SSFP technique provides rapid imaging of both large and small vessels, such as the aorta,[11] carotids,[12] and renal arteries,[13] without the need for administration of a contrast agent. Examples of thoracic aorta, noncontrast SSFP MRA and renal arteries, noncontrast MRA using newer methods are shown on Figs. 28.1 and 28.2A and B. In SSFP imaging the signal of a particular tissue is related to the T2/T1 ratio for that tissue, and flowing blood appears bright.

Figure 28.1 Oblique sagittal non–contrast-enhanced steady-state free precession magnetic resonance angiogram of the thoracic aorta. The signal from flowing blood appears bright.

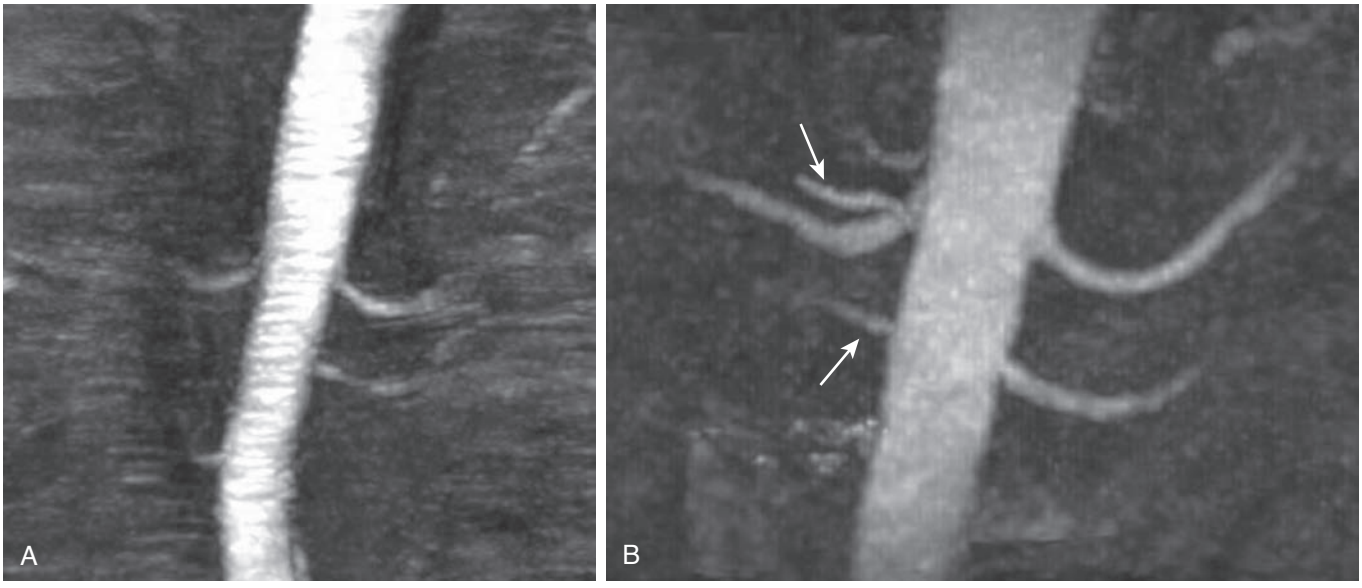

Figure 28.2 (A) Coronal maximum intensity projection (MIP) of time-of-flight (TOF) magnetic resonance angiography (MRA) of the renal arteries. (B) Coronal MIP of noncontrast MRA acquired with a newer method that uses ECG gating to subtract diastolic from systolic images, leaving only arterial systolic flow. Note markedly improved visualization of accessory right renal arteries compared to TOF technique *(arrows)*.

Newer techniques for non–contrast-enhanced MRA include fresh blood imaging (FBI): ECG -gated 3D half Fourier FSE, which relies on the signal difference between systolic and diastolic triggered acquisitions. The arterial signal in systole is dark due to spin-dephasing effects of fast arterial flow. In contrast, venous blood is bright throughout the cardiac cycle because of constant slow flow. By applying flow-spoiling pulses to this technique, arteries can be separated from veins in the peripheral runoff region.[13] Two alternative approaches using the SSFP approach include Flow-sensitive dephasing (FSD) and Quiescent-interval single-shot (QISS). QISS MRA is performed using 2D ECG-gated single-shot SSFP acquisition. Initial saturation pulses suppress in-plane background tissues and venous inflow from below the imaged segment of the body. Advantages of QISS are short acquisition times and ease of use, allowing imaging of fast flowing vessels such as the aorta, and renal arteries; however, this technique requires good magnetic field homogeneity.[13]

Fig. 28.1 shows a non–contrast-enhanced SSFP MR angiogram of the thoracic aorta.

Fig. 28.2A and B shows a noncontrast MRA study of the renal arteries, comparing TOF MRA with images obtained with a technique that uses ECG gating and subtracts diastolic from systolic images, leaving signal only in arteries. Evaluation of these techniques is ongoing[14]; however, they have the potential to replace contrast-enhanced MRA in many circumstances.

Contrast-Enhanced Magnetic Resonance Angiography

Currently, MR contrast agents approved by the US Food and Drug Administration (FDA) include several in which the rare earth element gadolinium is chelated with another substance to avoid release of toxic free gadolinium into the body. These agents are designed to shorten the T1 of the protons in the vicinity, thereby making them more conspicuous on T1-weighted imaging sequences.

There are several important differences between MR contrast and the iodinated contrast used for computed tomographic angiography (CTA) or catheter angiography. First, as suggested, MRI is designed not to image the agent itself but to image its effect on protons in the surrounding water. This has a subtle implication that is important in certain circumstances. That is, a very small amount of MR contrast material may be detected by its effect on multiple water molecules, whereas an equivalently small amount of iodinated contrast is simply not detectable directly by CTA or catheter angiography. This is one reason that the volume of MR contrast can be much less than the volume of iodinated contrast used for CTA or diagnostic angiography. Other advantages of gadolinium-based contrast include decreased nephrotoxicity and a lower incidence of contrast reactions.[15-19]

Step-Table Magnetic Resonance Angiography

For applications involving imaging of a large volume, such as the entire aorta or a peripheral runoff study, acquisition of data from the entire volume of interest is impractical and may lead to decreased image quality. The spatial resolution of the acquired images is inversely proportional to the image matrix size, and the image matrix size has a direct impact on the duration of the acquisition, so a higher resolution image requires longer to acquire. If the FOV is very large, a long acquisition time may be required to achieve the necessary spatial resolution for visualization of the vessels of interest, which may be beyond breath-holding capacity of the patient and lead to respiratory motion artifact. In addition, intravenously administered contrast will flow from the aortic root to distal vessels in a time dependent on the rate and volume of injection, the patient's cardiac output, and the presence of any proximal occlusive disease; thus not all portions of the arterial system will be enhancing optimally at the same time. For these reasons, it is desirable to use a step-table acquisition in which portions of the anatomy of interest are imaged sequentially, with the scanner table moving between stations to place the specific anatomy of interest near the isocenter of the magnet.

A peripheral runoff study may include four step-table stations—abdomen/pelvis, thighs, calves, and feet—each imaged with a coil, FOV, spatial resolution, and orientation optimized to the particular vascular anatomy in that station. For example, whereas the abdominal and pelvic vessels may best be imaged in the coronal plane with a larger FOV and a large array coil, the smaller pedal vessels would optimally be acquired in an oblique plane oriented along the foot, with a small FOV, high spatial resolution, and smaller coils for an improved signal-to-noise ratio (SNR). Although step-table examinations are generally performed in a proximal-to-distal direction, there may be circumstances in which a "reverse step-table" protocol is preferable (e.g., when imaging a patient with known abdominal aortic pathology in whom there is less suspicion of thoracic aortic disease). In this case the abdominal aorta could be imaged first, in the coronal plane, followed by the thoracic aorta, imaged in a more advantageous oblique sagittal plane. This would provide higher resolution imaging of both regions of the aorta, in two shorter breath-holds, than possible with a single large FOV acquisition with imaging of the area of greatest interest in a pure arterial phase and perhaps some venous filling for the less critical thoracic portion.

Step-table MRA requires additional hardware, including a set of MRI coils for optimal imaging of each anatomic segment and (usually) optional software to control the automated table motion. As mentioned before, a disadvantage of the step-table technique may be a longer total acquisition time, which can lead to venous contamination in the later stations. Techniques for minimizing venous contamination are discussed later under section "Continuous Moving Table and Time-Resolved Magnetic Resonance Angiography."

Three-Dimensional Image Processing

Contrast-enhanced MRA is performed as a 3D imaging sequence. Three-dimensional imaging sequences are typically faster and of higher resolution than non–contrast-enhanced angiograms and provide the same coverage. A 3D image can be viewed as a stack of 2D images, but the higher resolution of 3D methods allows the use of multiplanar reformatting (MPR). MPR involves manipulation of the data to create images from multiple views

that optimize visualization of the anatomy or pathology. Images can be processed with many types of algorithms to display the 3D data to best advantage. Because contrast within is designed to have the highest intensity, an algorithm that displays the maximum intensity of the voxels, known as maximum intensity projection[20] (MIP), is the most commonly used for reformatting 3D MR angiograms. Volume rendering (VR) has become a popular evaluation and display method and has been demonstrated to be equivalent or superior to MIP for both MRA and CTA of several vascular territories.[21,22]

Hardware and Software for Magnetic Resonance Angiography

MRA is performed optimally on a 1.5- or 3-T MR system with the fastest and strongest gradients available. This will result in shorter acquisition times with higher spatial resolution and improved SNR. Dedicated coils for specific vascular beds are also useful and include at least a neurovascular coil for head and neck MRA and a peripheral angiography coil covering the pelvis to the ankles or toes for runoff studies. MRA of the thoracic, abdominal, and pelvic vessels is performed with multiple flexible phased-array coils that can be placed over the anatomy of interest; multichannel coils and RF receivers allow parallel imaging (described later under section "Parallel Imaging") for faster acquisitions. Digital and pedal vessels can be imaged either with small local extremity coils or by placing both extremities in a dedicated head coil that is designed for high-resolution and SNR imaging.

An MR-compatible dual-chamber power injector is needed for rapid administration of contrast, followed by a saline chaser (which can decrease the amount of contrast used). MR-compatible patient monitoring equipment is also useful, especially when imaging hospitalized patients or when sedation is needed. Additional software may be needed for step-table and parallel imaging, as well as newer non–contrast-enhanced and contrast-enhanced MRA techniques, so it is important when purchasing MR systems to investigate which sequences are included in the base MR system package and which are optional. MR-compatible blood pressure cuffs can be useful for reducing venous contamination in extremity MRA. For example, placing cuffs around both thighs while inflating to half to two-thirds systemic arterial pressure effectively delays venous return and allows improved visualization of calf arteries.[23]

A postprocessing workstation with MPR, MIP, and VR capability is the minimum necessary for visualization and interpretation of MRA studies. Additional software, such as automated vessel analysis with curved planar reformatting, vessel centerline extraction, automated segmentation, and bone removal, may also be useful for specific applications but is more relevant for CTA than for MRA.

CLINICAL APPLICATIONS OF MAGNETIC RESONANCE ANGIOGRAPHY

Aortic Vascular Disease

Contrast-enhanced 3D MRA has been used to assess the aorta[24-27] in patients with many different types of disease. Assessment of the aortic arch by contrast-enhanced MRA may be superior to any other technique.[28] Several examples are shown in Fig. 28.3. Other diseases that are routinely evaluated by MRA at some centers include aortic dissection,[24,29-31] as shown in Fig. 28.4, and aneurysms.[24,32] MRA is also used to evaluate patients with other vascular diseases, as shown in Figs. 28.5 and 28.6, such as connective tissue disorder—Ehlers Danlos syndrome,[33] and for vascular stent-graft placement,[34,35] as well as for endoleak in those with a nitinol-based stent-graft.[36,37]

Carotid Vascular Disease

MRA is becoming an increasingly used method for evaluating carotid artery atherosclerosis. It has proven to be a very sensitive

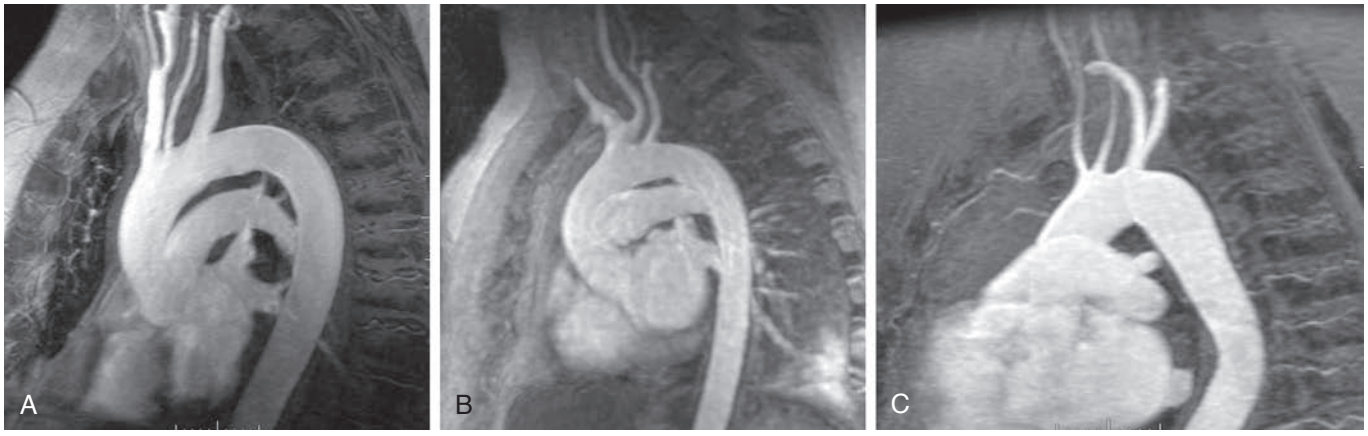

Figure 28.3 (A) Sagittal oblique reformatted magnetic resonance (MR) angiogram of a normal aortic arch. (B) Sagittal oblique reformatted MR angiogram of a bovine arch. (C) Sagittal oblique reformatted image of a rare arch anomaly, bicarotid truncus. All four vessels arise separately from the arch. The carotids arise anteriorly and the subclavians posteriorly.

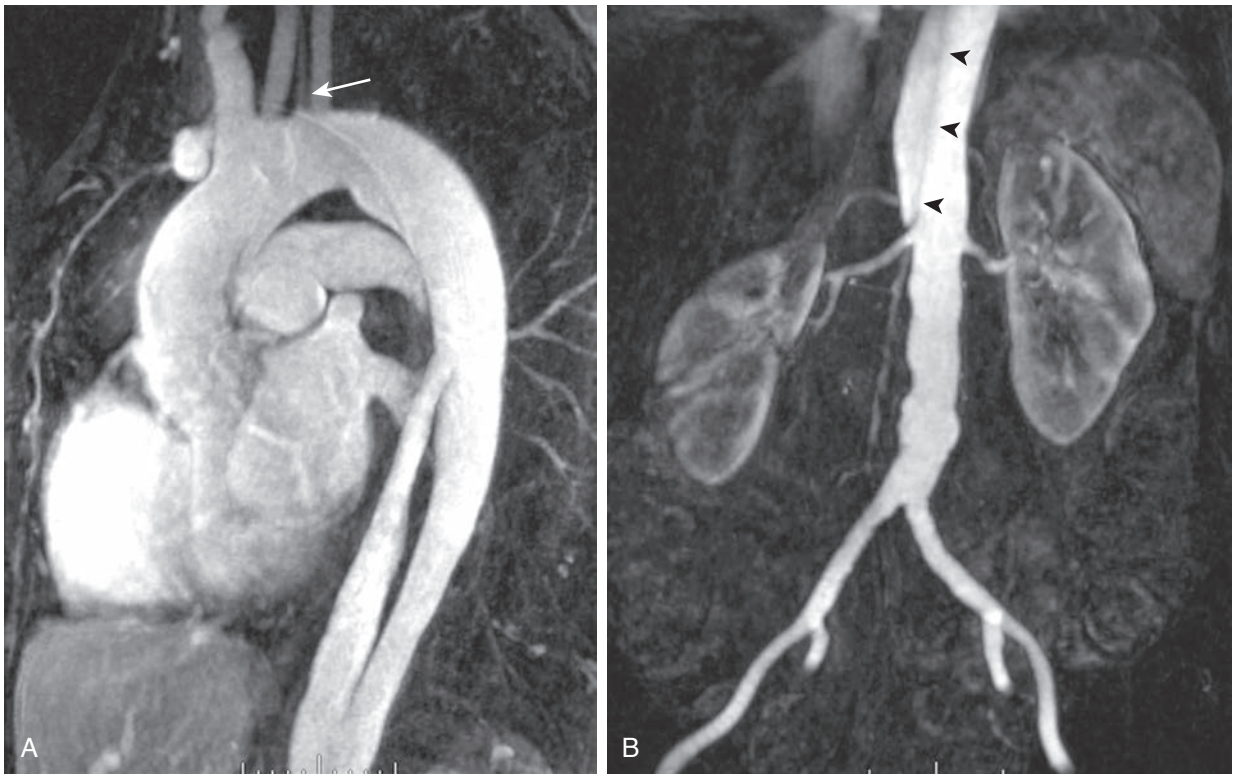

Figure 28.4 (A) Sagittal oblique reformatted magnetic resonance (MR) angiogram showing a type B dissection. The origin of the flap and filling of the proximal false lumen are seen. A separate origin of the left vertebral artery is seen from the aortic arch *(arrow)*. (B) Coronal three-dimensional MR angiogram obtained during the same examination as the chest-station image by using the step-table technique. The dissection flap *(arrowheads)* terminates just above the origin of the right renal artery.

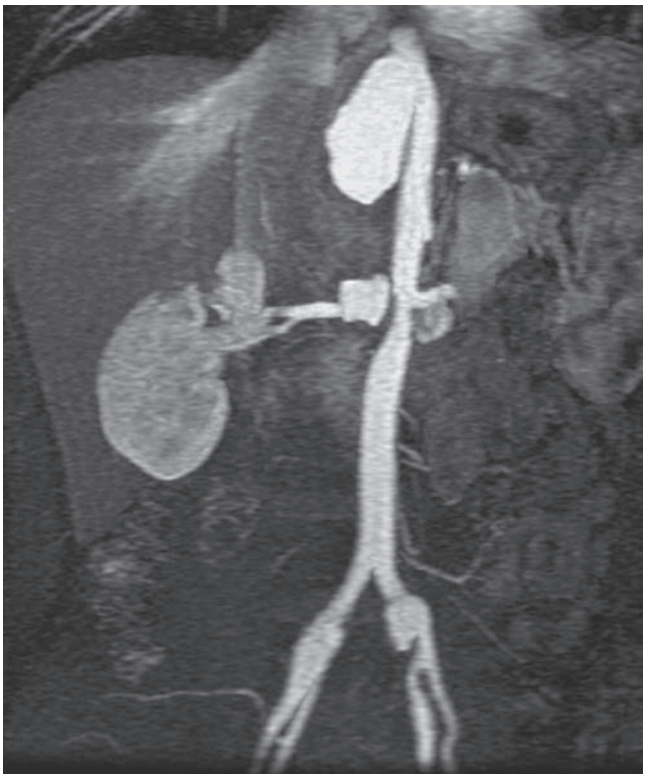

Figure 28.5 Coronal three-dimensional magnetic resonance angiogram in a patient with suspected Ehlers-Danlos syndrome. Saccular aneurysms are seen from the upper abdominal aorta and both renal arteries. An irregular fusiform aneurysm of the left common iliac is also present.

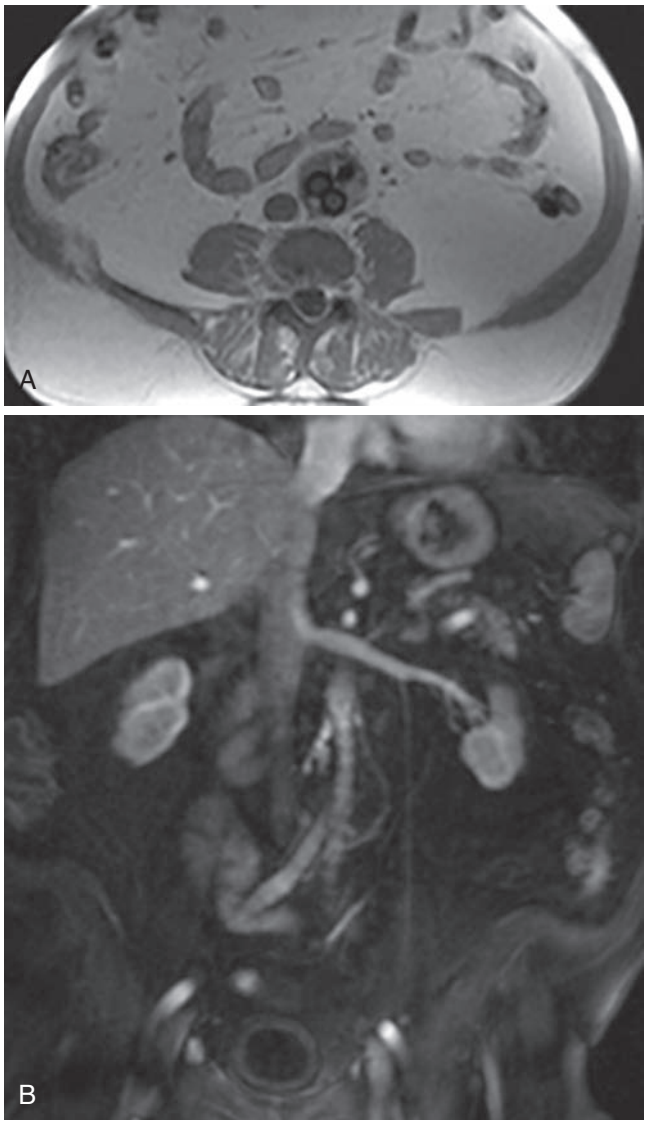

Figure 28.6 Axial (A) and coronal magnetic resonance angiogram (B) images show stented infrarenal abdominal aortic aneurysm with type 1a endoleak.

method of detecting significant stenoses. For stenosis of between 70% and 99% narrowing, MRA has a reported sensitivity of 95% and a specificity of 90%.[38] For all stenoses, MRA has a reported sensitivity of 98% and a specificity of 86%.[39] Several authors conclude that the performance of MRA warrants its use as a tool to plan operative or interventional revascularization.[40,41] A 3D MR angiogram of the carotid and vertebral arteries is shown in Fig. 28.7.

Peripheral Vascular Disease

MRA has become a standard method for evaluation of peripheral vascular disease.[42] Peripheral vascular disease is extremely common in the middle-aged and elderly population. Its prevalence is approximately 3% in those older than 55 years but increases to 11% in those older than 65 and is as high as 20% in individuals older than 70 years.[42] MRA has been demonstrated to be effective in the preoperative assessment of patients[43-45] with peripheral vascular disease, including imaging of inflow vessels[46] and evaluation of stenoses,[46] as shown in Fig. 28.8. Its sensitivity for detecting hemodynamically significant stenoses is 99.5% with a specificity of 98.8% compared with digital subtraction angiography (DSA).[46] In addition, MRA is effective in imaging suitable target vessels, including vessels not seen by catheter angiography.[45,46] MRA is also a cost-effective method for evaluation of patients with peripheral vascular disease.[43]

With the continued advancement in MR technology, MRA evaluation of peripheral vascular disease continues to improve.[3,4,47-49] Improvements in step-table examination have increased the speed and resolution of the examination. This has allowed improved visualization of smaller distal vessels and permitted arterial-phase dedicated imaging of the feet, as shown in Fig. 28.9. As mentioned previously, MRA has been shown to be superior to DSA for the evaluation of distal vessels in some cases.[40] In a study of 37 patients, MRA depicted significantly more vascular segments in the foot than DSA did ($P \approx .0001$).[49]

In addition to the value of MRA for diagnosis and pretreatment planning, it may be used for the evaluation of patients after therapy.[50-52] MRA can be used to assess graft patency and stenosis. Fig. 28.10 demonstrates narrowing at the distal end of a femoral-to-popliteal bypass graft. MRA is also a useful technique for demonstrating complications of graft placement such as pseudoaneurysm formation, as shown in Fig. 28.11.

Renovascular Disease

For the evaluation of renovascular disease, 3D gadolinium-enhanced MRA has become a clinical standard.[53] The most common such disease is atherosclerotic renal artery stenosis. However, MRA has also demonstrated that it is a powerful technique for evaluating more subtle renal vascular conditions such as fibromuscular dysplasia, renal artery aneurysms, and accessory renal arteries.[1] Detection of accessory arteries is particularly important for assessment of potential living renal donors.[54-55]

Approximately 25% of the middle-aged white and African-American population in the United States has high blood pressure.[55] Renal artery stenosis is the most common cause of secondary hypertension, and approximately 1% of people with hypertension will have renal artery stenosis.[56] Because renal artery stenosis is so common and potentially curable,[57-59] it is critical that appropriate screening tests exist for those at risk. 3D contrast-enhanced MRA has a sensitivity of 94% and a specificity of 93%.[1] In addition, it has been shown that when MRA is used to plan a renal artery intervention, both the number of pretreatment angiograms and the total amount of contrast are reduced.[58]

As shown in Fig. 28.12, the majority of renal artery stenoses are located in the ostial or proximal[60,61] segments. As methods for 3D contrast-enhanced MRA have improved, diseases that are not typically near the renal artery origin have more commonly been diagnosed by MRA. Such diseases include another curable

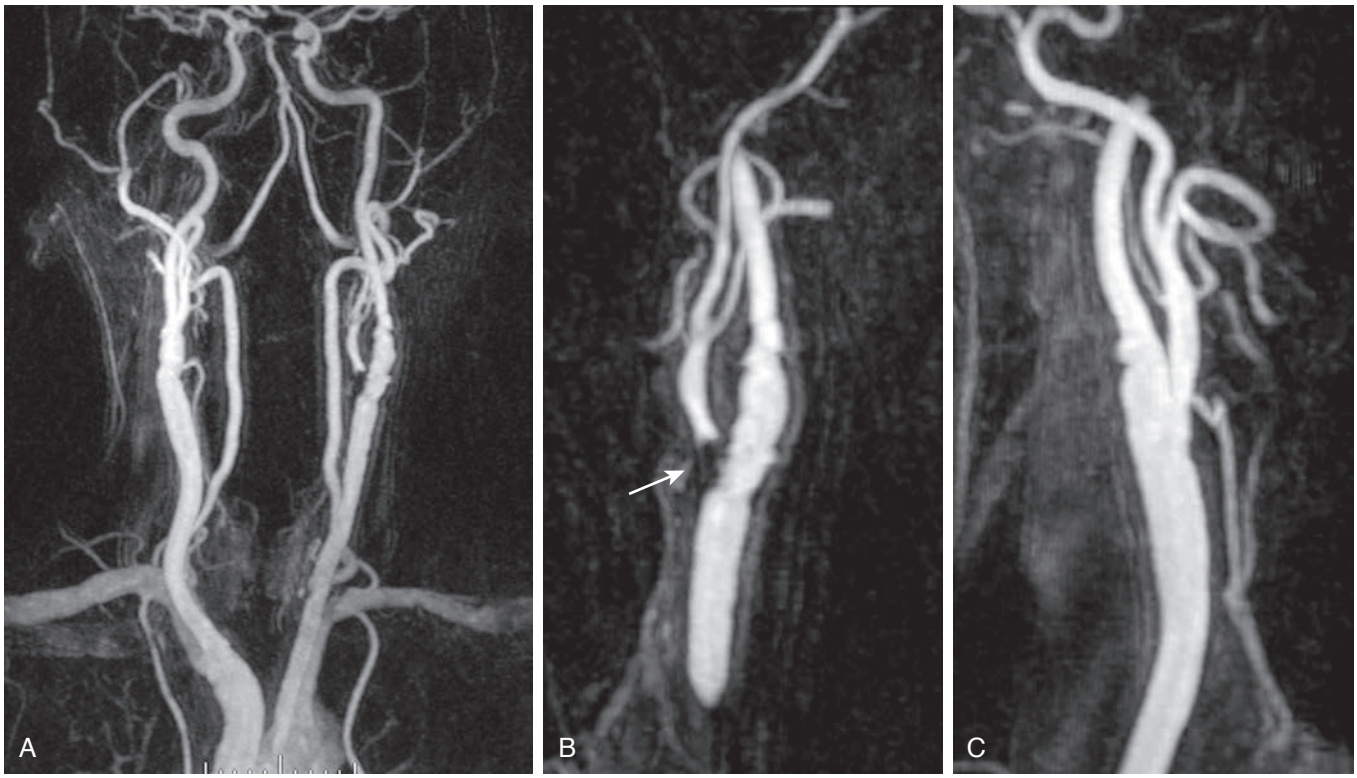

Figure 28.7 (A) Coronal three-dimensional magnetic resonance (MR) angiogram of the carotid and vertebral arteries. (B) Oblique sagittal reformatted MR angiogram showing high-grade narrowing at the origin of the left external carotid artery *(arrow)* and mild disease of the left internal carotid artery. (C) Oblique sagittal reformatted MR angiogram showing the right carotid bifurcation with only mild disease in the proximal right internal carotid.

cause of hypertension, fibromuscular dysplasia,[62] shown in Fig. 28.13.

Accessory renal arteries occur in nearly 45% of patients,[63] and their diagnosis can be important in screening candidates for renal donation.[54,55] MRI and MRA have been shown to be cost-effective methods for evaluating potential renal donors.[62] Fig. 28.14 demonstrates an individual with six total renal arteries.

Mesenteric Vascular Disease

The most common use of MRA in patients with mesenteric vascular disease is to evaluate those with suspected intestinal angina or chronic mesenteric ischemia.[64,65] MRA is between 95% and 97% accurate for characterizing proximal disease of the superior mesenteric artery[66] in cases of chronic mesenteric ischemia.

MRA is also useful to evaluate more complex diseases of the mesenteric vasculature. The median arcuate ligament passes anterior to the descending aorta near the T12 level. During end-expiration the ligament can compress the proximal portion of the celiac axis, which can lead to a false impression of proximal celiac stenosis. MRA can be helpful in demonstrating the effect of the arcuate ligament during a single examination,[67] as shown in Fig. 28.15.

In cases of suspected mesenteric venous thrombosis, MRV can be an extremely useful tool and has been suggested to be superior to mesenteric catheter angiography.[68] MRV is particularly successful because of the ease of detecting small amounts of MR contrast. Central injection of MR contrast will be easily visualized in the veins, even after several cycles of circulation. An example of postcontrast 2D MRI is shown in Fig. 28.16; the portal vein, splenic vein, superior mesenteric vein, and even inferior mesenteric venous branches occluded with thrombus are clearly depicted.

Venous Vascular Disease

MRV is a useful technique for evaluating both central[69,70] and deep[71-73] venous structures. Central venous structures, in particular the superior vena cava, can be evaluated with 3D methods, with 100% sensitivity for the detection of thrombus when compared with DSA.[70] For pelvic and deep venous structures, it is more common to use 2D TOF angiography.[71,72] In cases of suspected deep venous thrombosis (DVT), this method showed that 20% of patients had pelvic DVT that could not be diagnosed by ultrasound.[73] This same study also demonstrated that in cases of known pulmonary embolism and negative lower

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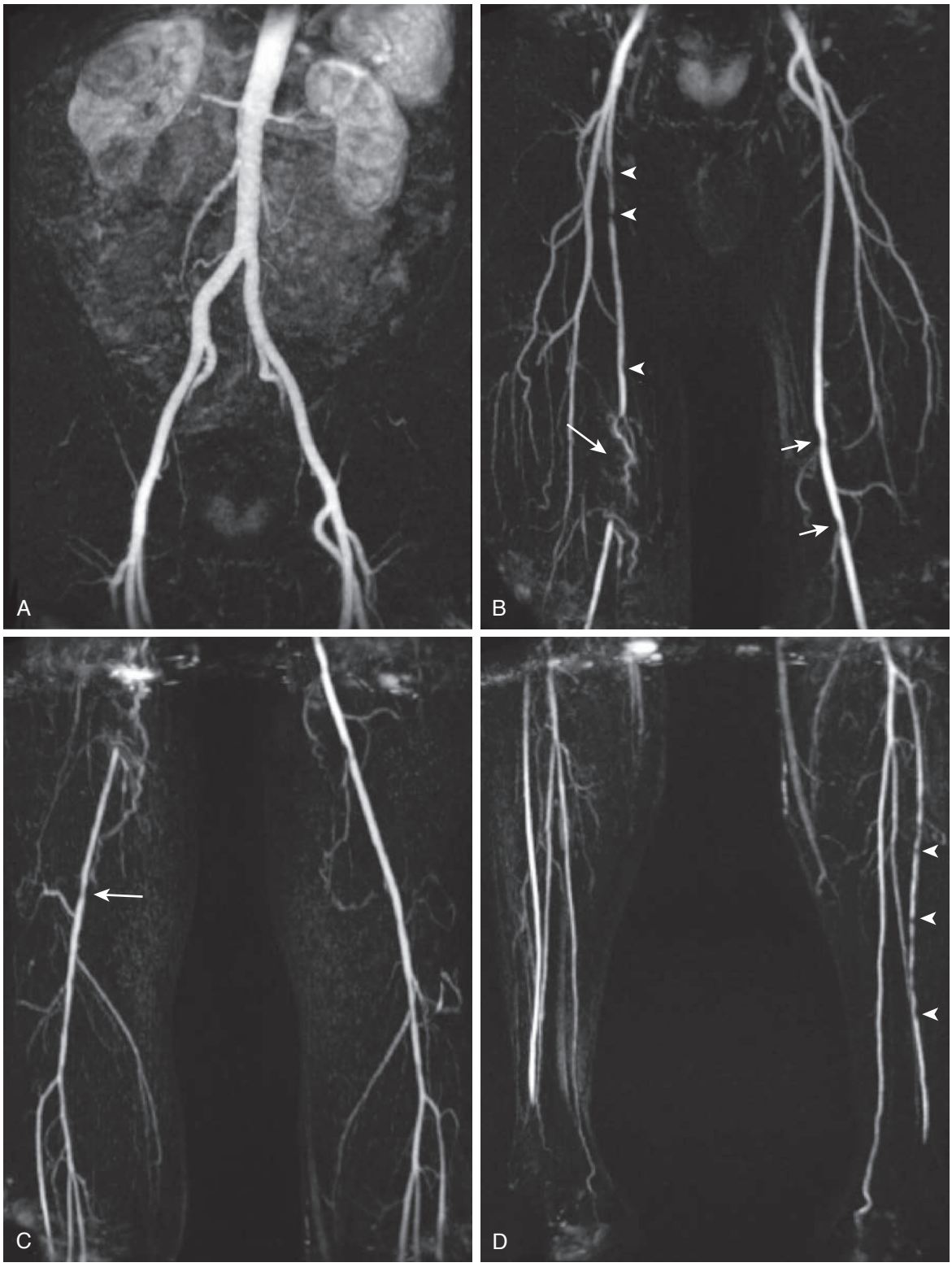

Figure 28.8 Coronal three-dimensional magnetic resonance angiography step-table examination showing (A) normal inflow vessels, (B) right proximal superficial femoral artery (SFA) stenoses *(arrowheads)*, segmental occlusion of the right distal SFA/popliteal *(long arrow)*, and mild left popliteal stenoses *(short arrows)*, with (C) mild right popliteal artery stenosis *(arrow)* and (D) multiple stenoses of the left anterior tibial artery *(arrowheads)*.

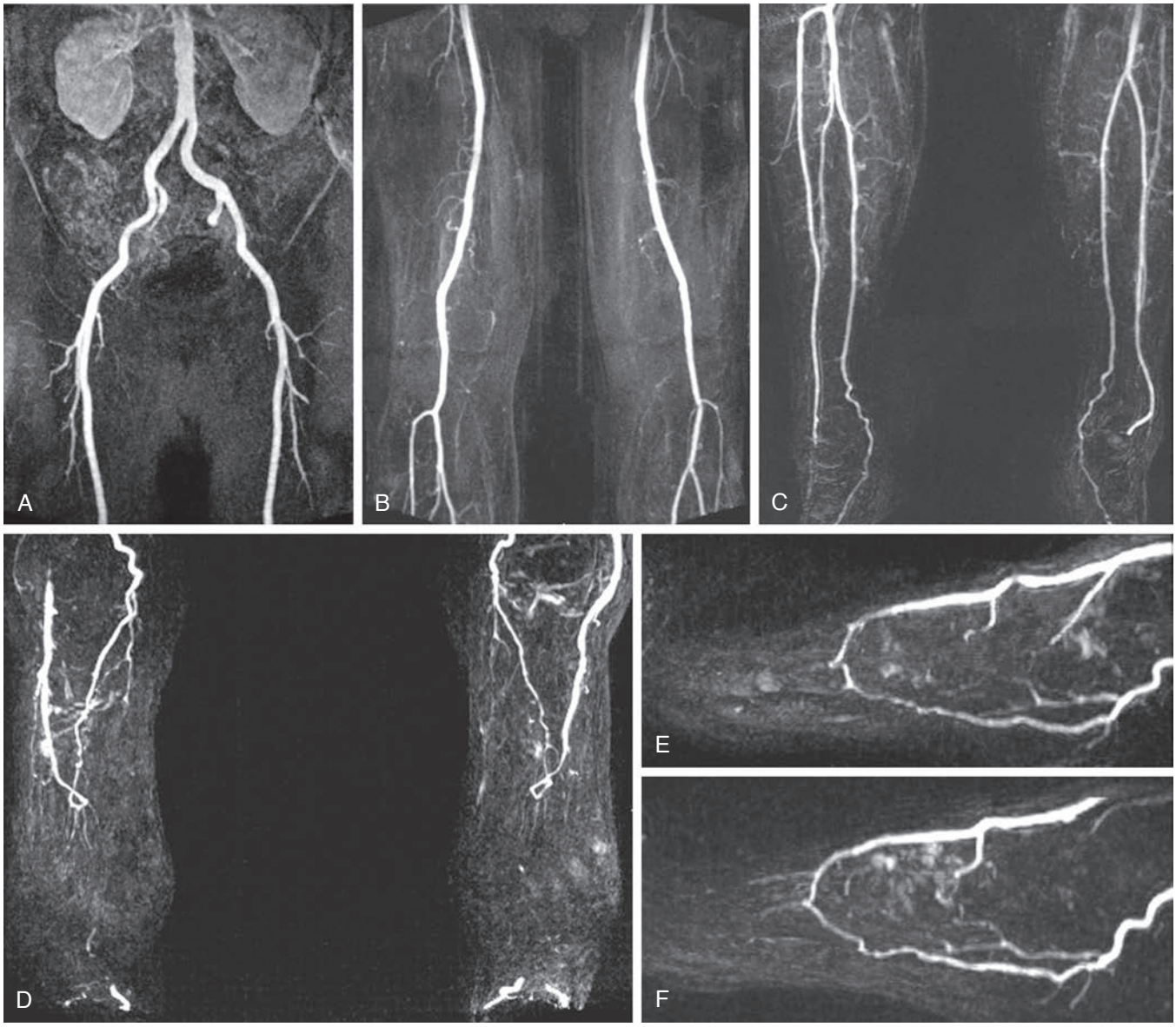

Figure 28.9 Five-station step-table examination showing normal inflow vessels to the lower extremities (A), normal thigh vessels (B), normal calf vessels (C), and normal vessels in both feet (D). The high-resolution three-dimensional data allow reconstruction of each foot in the sagittal plane (E and F), which shows a patent plantar arch in each.

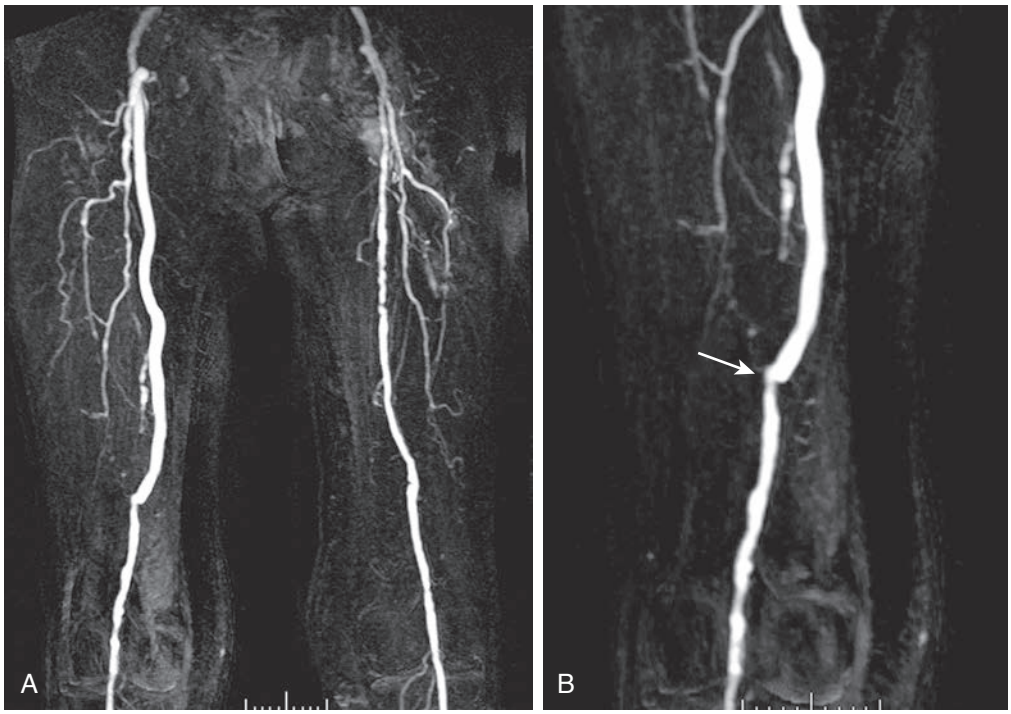

Figure 28.10 (A) Coronal three-dimensional thigh-station magnetic resonance angiogram of a femoral-to-popliteal bypass graft. Note the contralateral disease in the superficial femoral artery. (B) An oblique reformatted image shows narrowing at the touchdown of the graft *(arrow)*.

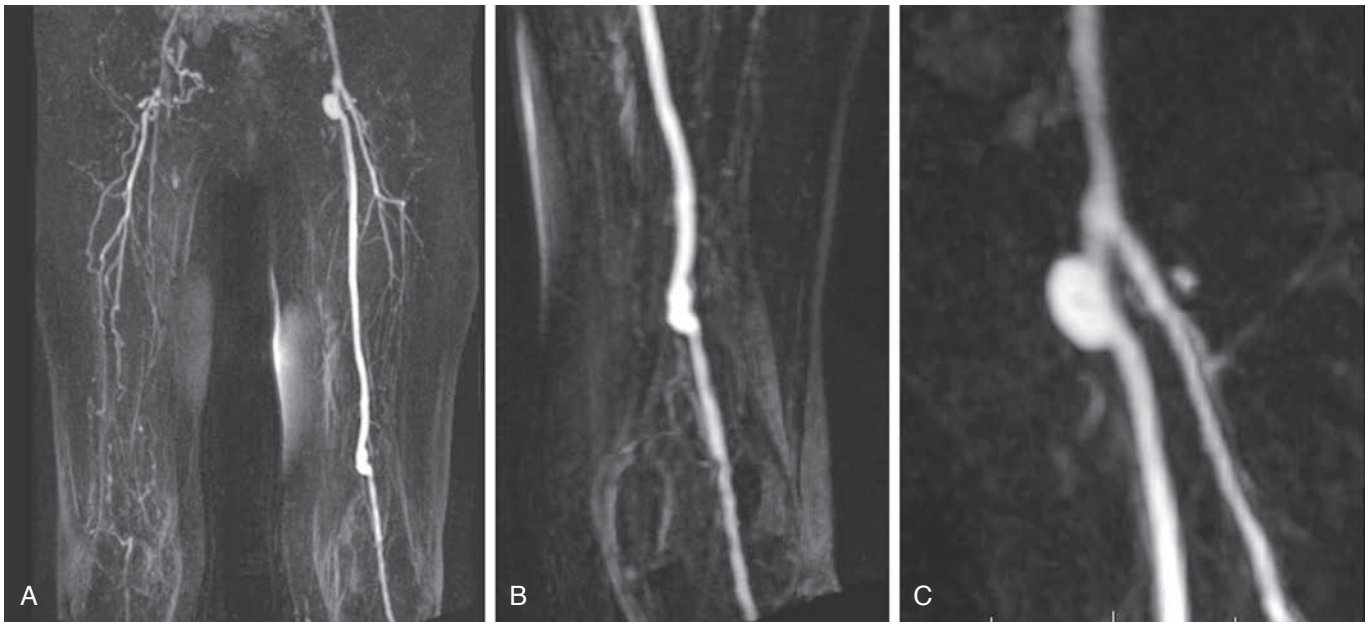

Figure 28.11 (A) Coronal three-dimensional thigh-station magnetic resonance angiogram of a left femoral-to-popliteal bypass graft. Note the contralateral disease in the superficial femoral artery and visualization of multiple collaterals above the right knee. (B) An oblique reformatted image shows the distal end of the graft. (C) Another oblique reformatted image shows a probable pseudoaneurysm at the origin of the graft.

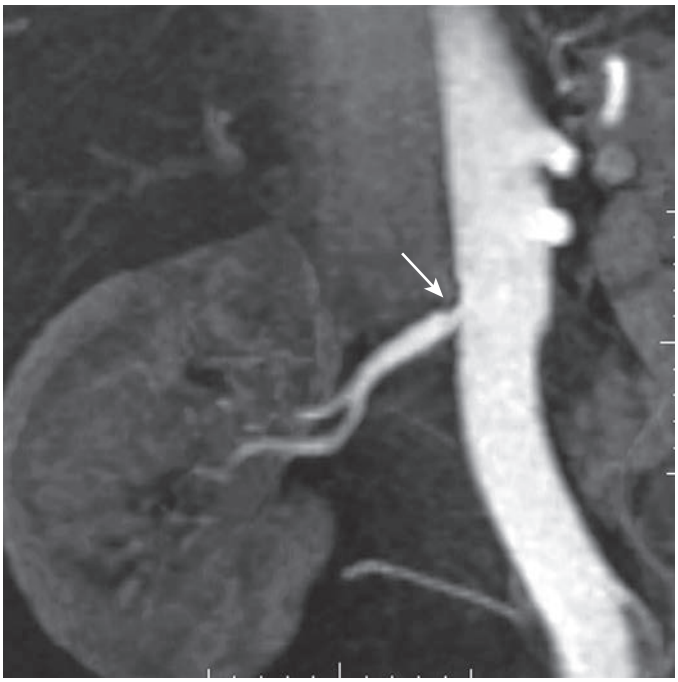

Figure 28.12 Coronal three-dimensional magnetic resonance angiogram showing an ostial renal artery plaque *(arrow)*.

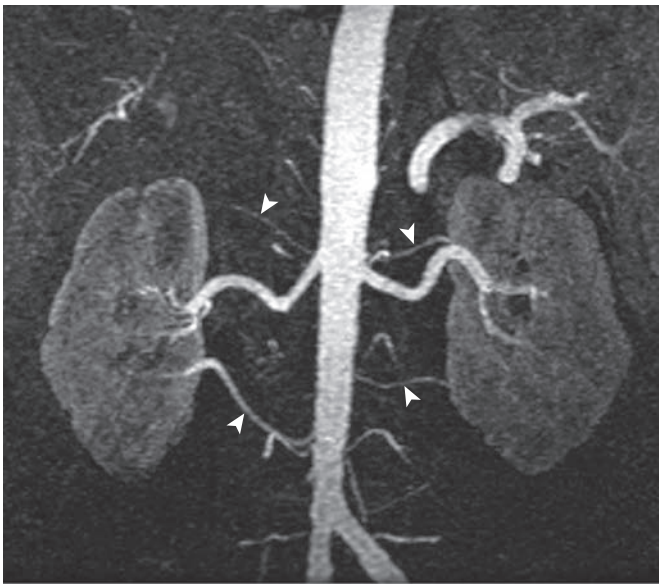

Figure 28.14 Coronal three-dimensional magnetic resonance angiogram showing two main renal arteries and four accessory arteries *(arrowheads)*. Note that the accessory arteries may enter the renal hilum or perforate the cortex.

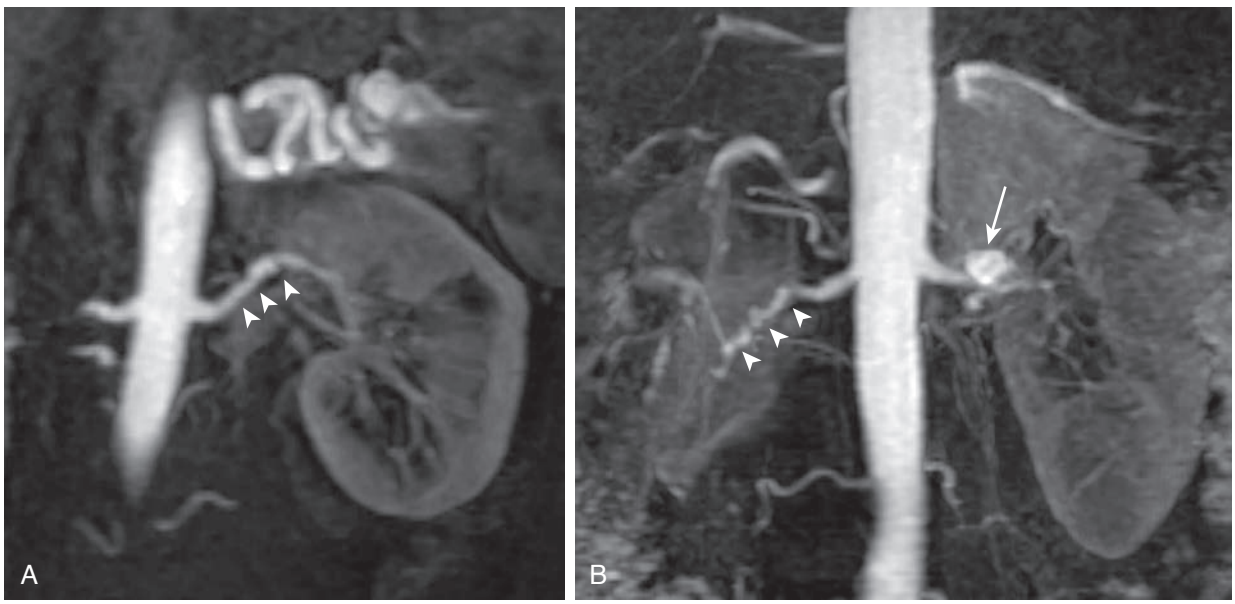

Figure 28.13 (A) Coronal three-dimensional (3D) magnetic resonance (MR) angiogram showing subtle fibromuscular dysplasia *(arrowheads)*. Note that the disease is isolated to the distal portion of the main renal artery. (B) Coronal 3D MR angiogram showing right-sided fibromuscular dysplasia *(arrowheads)* and a left-sided renal artery aneurysm *(arrow)*. Renal artery aneurysms may occur in patients with fibromuscular dysplasia.

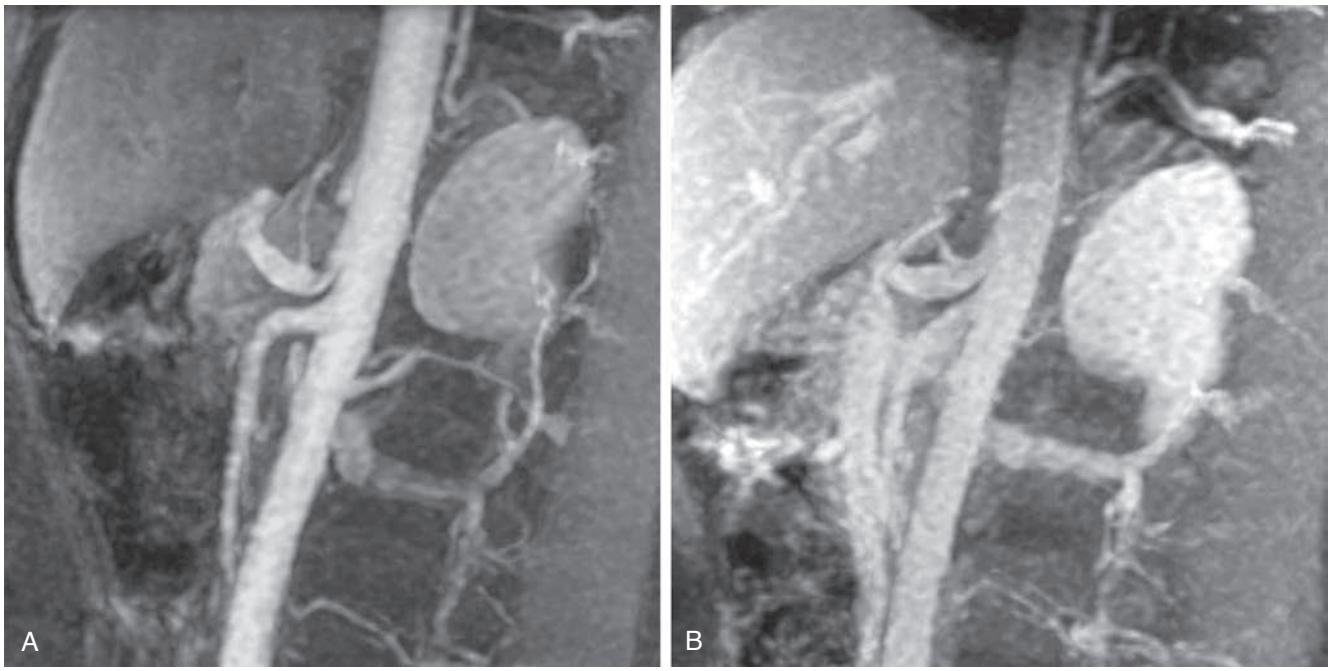

Figure 28.15 (A) Arterial-phase sagittal three-dimensional (3D) magnetic resonance (MR) angiogram at end-expiration showing the impression of the arcuate ligament just proximal to the origin of the left gastric artery. Notice the quality of the evaluation of the proximal superior mesenteric artery as well. (B) Venous-phase sagittal 3D MR angiogram at end-inspiration showing no narrowing of the proximal celiac axis. During the delayed phase, there is still sufficient contrast within the aorta and branch vessels for adequate visualization.

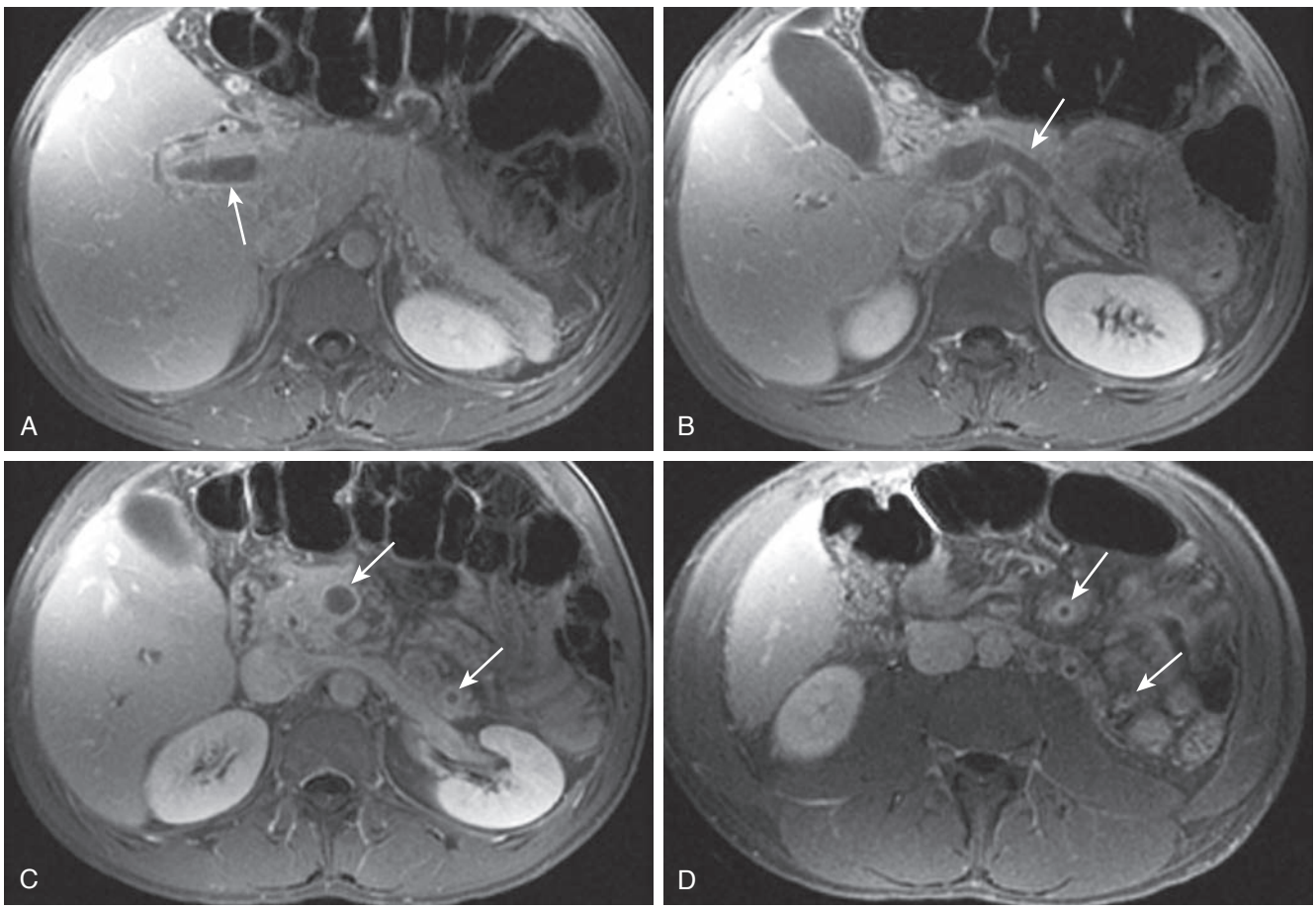

Figure 28.16 (A) Two-dimensional (2D) T1-weighted postcontrast magnetic resonance (MR) image showing a portal vein thrombus *(arrow)*. (B) 2D T1-weighted postcontrast MR image showing a splenic vein thrombosis *(arrow)*. (C) 2D T1-weighted postcontrast MR image showing superior mesenteric vein (SMV) and inferior mesenteric vein (IMV) thrombi *(arrows)*. (D) 2D T1-weighted postcontrast MR image showing small distal branches of the SMV and IMV filled with thrombi *(arrows)*.

extremity Doppler ultrasound, 29% of patients had residual pelvic DVT.

An example of 2D TOF imaging of an IVC thrombus is shown in Fig. 28.17 with corresponding 2D postcontrast MR images. Both types of imaging are useful for detecting DVT in the abdomen, pelvis, and lower extremities.

Other Applications

A large variety of vascular conditions may be evaluated by MRA. The capability of performing the evaluation may depend on the experience of the physicians and technologists performing the study. For example, MRA may be performed to assess patients with suspected thoracic outlet syndrome if the appropriate image sequences can be combined with maneuvers to elicit the symptoms.[74] A case of thoracic outlet syndrome is shown in Fig. 28.18, where compression of the subclavian vein is clearly seen when the ipsilateral upper extremity is raised above the head.

In centers in where transplants are performed, MRA is useful for assessment of potential renal donors,[54,55,62] as mentioned earlier. In addition, MRA can be useful in the assessment of suspected failure of the arterial or venous anastomoses of the transplant graft.[5,75] Fig. 28.19 demonstrates evaluation of a pancreas transplant graft in the postoperative phase and in a later phase in which graft rejection was occurring.

MRA is also useful to assess less common diseases (e.g., to diagnose and assess the response to therapy in cases of large-vessel and medium-vessel vasculitis).[76,77] An example of Takayasu arteritis is shown in Fig. 28.20. Example of Takayasu arteritis involving subclavian artery is shown in Fig. 28.21. Another example of more esoteric disease that has easily been assessed by MRA is pulmonary arteriovenous malformations,[78,79] as shown in Fig. 28.22. In such cases, MRA has 100% sensitivity for imaging pulmonary arteriovenous malformations greater than 5 mm in size, and all feeding arteries and draining veins are also characterized.[79]

LIMITATIONS AND RISKS

Scan Artifacts

Several common artifacts and pitfalls are associated with MRA. Knowledge of these limitations will allow the user to approach diagnostic MRA with increased confidence that any abnormal findings do represent actual pathology.

Fat Saturation in Chest Magnetic Resonance Angiography

Suppressing the signal from fat may be advantageous in that fat will have high signal on the T1-weighted images used for MRA. The so-called fat sat method is an RF suppression pulse that takes advantage of the small difference in resonance frequency between water protons and the protons that are part of long-chain hydrocarbon fat groups. Within the chest there are intravascular water protons in blood vessels directly adjacent to the lungs. When such geometry exists, the resonance frequency of the water protons may be shifted to the precise range at which the fat protons normally resonate. In this case the selective method of fat suppression will result in suppression of the water signal instead.[80] Thus a vessel that is entirely patent may appear entirely occluded, or a vessel that is occluded may not be accurately assessed, as shown in Fig. 28.23.

Susceptibility Artifact From Concentrated Gadolinium

MRA contrast contains a chelated form of the rare earth element gadolinium. The chelate serves several different purposes in the contrast agent. First, it isolates the gadolinium, which is necessary because in its unbound form gadolinium is toxic. Second, the chelate provides multiple binding sites at which surrounding water molecules may remagnetize. Hence the chelate potentiates the T1 relaxation effects of the gadolinium. However, unbound gadolinium would not only shorten the T1 of water but would also shorten the T2 of the surrounding water. The chelate prevents close contact between water and gadolinium, thus minimizing the T2-shortening effects of the gadolinium. However, when the contrast is at high enough concentrations, there is still a T2-shortening effect that reduces the MR signal. In effect, at high concentrations, MR contrast behaves like a small piece of metal and produces a susceptibility artifact on the surrounding tissues. These concentrations occur only during the injection of pure contrast and are typically seen in the area of the origin of the great vessels[81] or in the subclavian artery during initial passage of injected contrast through the adjacent vein,[82] as shown in Fig. 28.24. If this artifact is suspected to be the cause of an apparent stenosis, repeating the sequence immediately should demonstrate resolution because contrast in the adjacent vein becomes more dilute.

Susceptibility Metal Artifacts

Metal produces large signal void and extensive distortion around the implant in MR imaging. Presence of metal also degrades CT studies by metal streaky artifact. Metal artifact reduction sequence (MARS) optimizes in reduction of metal artifact by using selection-selection gradient and increased radiofrequency bandwidth, by increasing read gradient and by applying view angle tilt. These parameter changes can be used in any spin-echo sequence without any increase in imaging time.[83]

Multiacquistion with variable resonance image combination (MAVRIC) and slice-encoding metal artifact correction (SEMAC) are two recently developed metal artifact reduction techniques that significantly reduce susceptibility artifacts near metallic hardware.[84] In CT imaging modality, dual energy CT removes metal artifacts along with use of iterative reconstruction algorithm.[85]

High Intravascular Signal From Thrombus Containing Methemoglobin

Clotted blood has a widely varying appearance on MR images, depending on both the redox state of the hemoglobin molecule and the integrity of the red blood cell wall. At a certain state

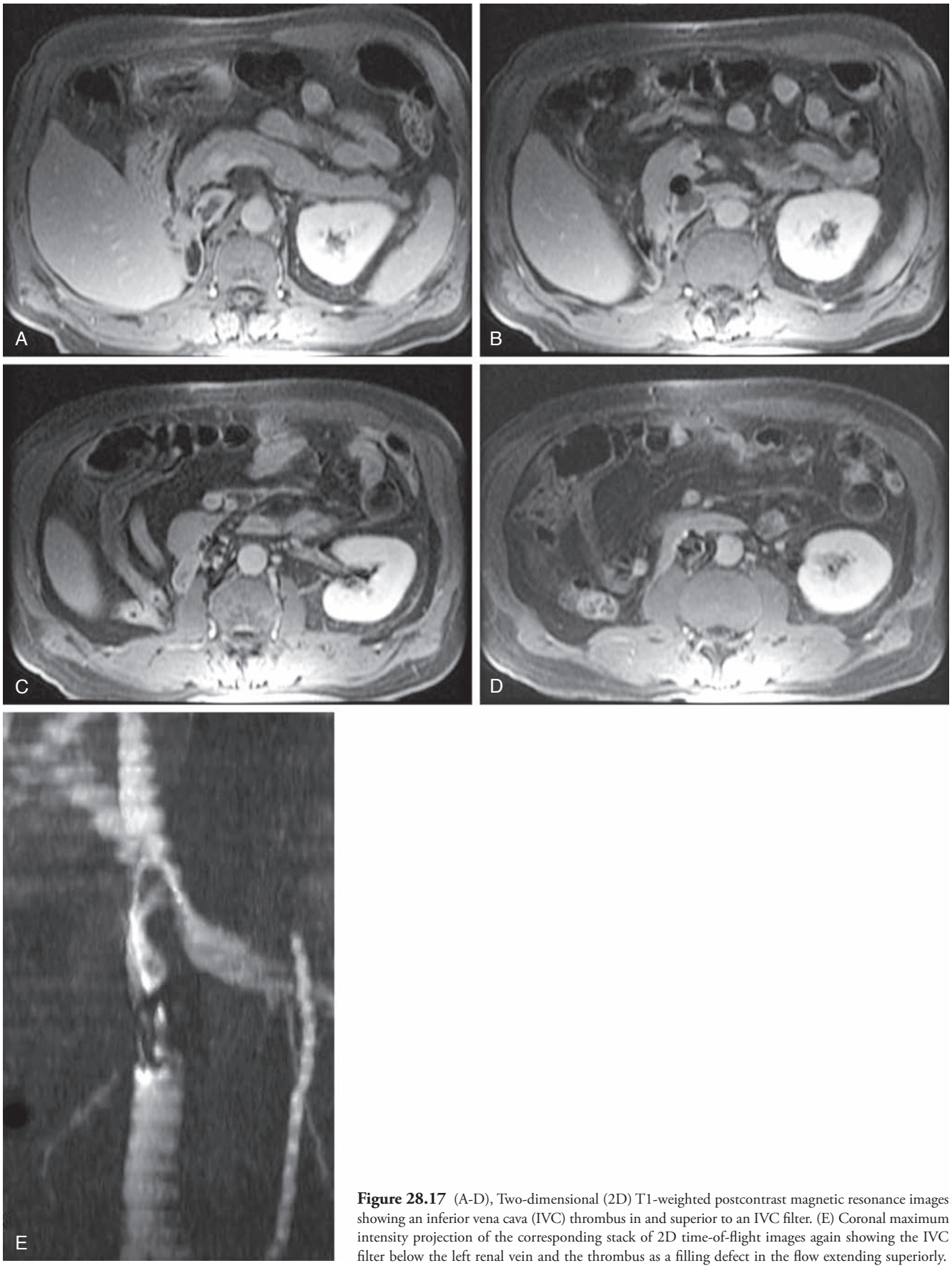

Figure 28.17 (A-D), Two-dimensional (2D) T1-weighted postcontrast magnetic resonance images showing an inferior vena cava (IVC) thrombus in and superior to an IVC filter. (E) Coronal maximum intensity projection of the corresponding stack of 2D time-of-flight images again showing the IVC filter below the left renal vein and the thrombus as a filling defect in the flow extending superiorly.

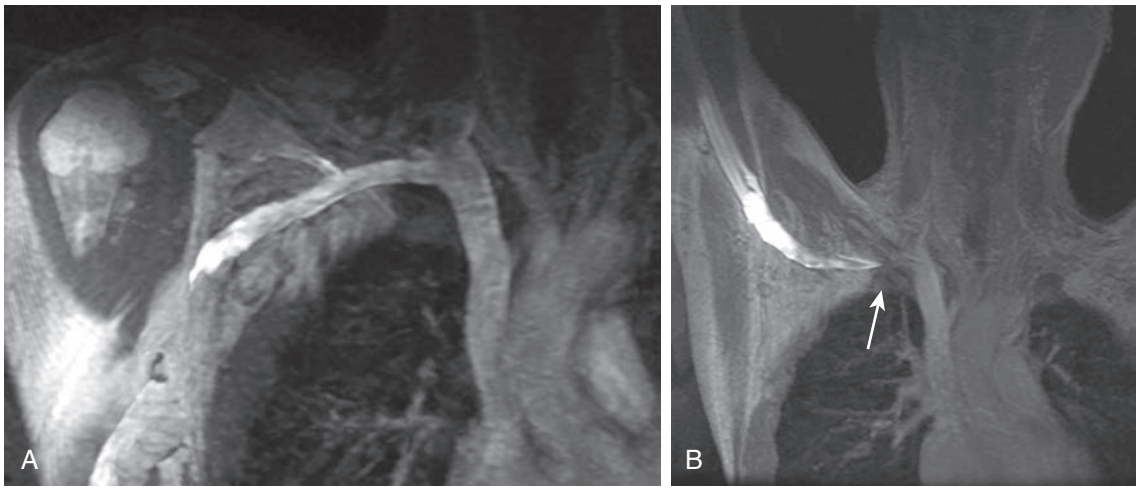

Figure 28.18 (A), Coronal three-dimensional (3D) magnetic resonance angiogram showing a normal right subclavian vein with the patient's arm lowered. (B) Coronal 3D MR angiogram showing occlusion of the subclavian vein near the junction with the axillary vein *(arrow)*. Note the pooling of very concentrated contrast material in the arm.

Figure 28.19 (A) Coronal three-dimensional (3D) magnetic resonance (MR) angiogram showing the anastomosis between the donor external iliac limb of the y-graft and the donor splenic artery feeding the pancreatic body *(arrow)*. (B) Coronal 3D MR angiogram performed later during transplant rejection showing narrowing of the donor splenic artery *(arrow)*. There is also a renal transplant partially seen in the left hemipelvis.

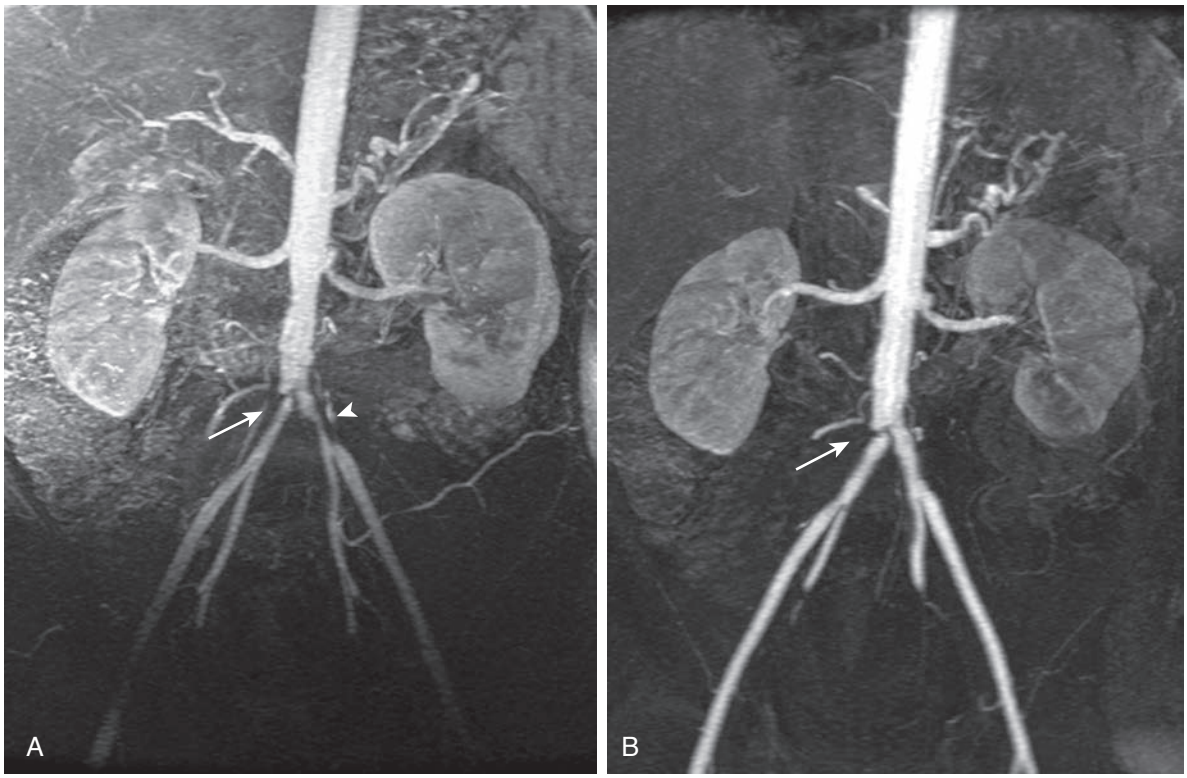

Figure 28.20 (A) Coronal three-dimensional (3D) magnetic resonance (MR) angiogram showing narrowing of the proximal common iliac arteries bilaterally (*arrow* and *arrowhead*) in a patient with Takayasu arteritis. (B) Coronal 3D MR angiogram showing complete resolution of the left common iliac narrowing and residual disease *(arrow)* in the right common iliac after treatment.

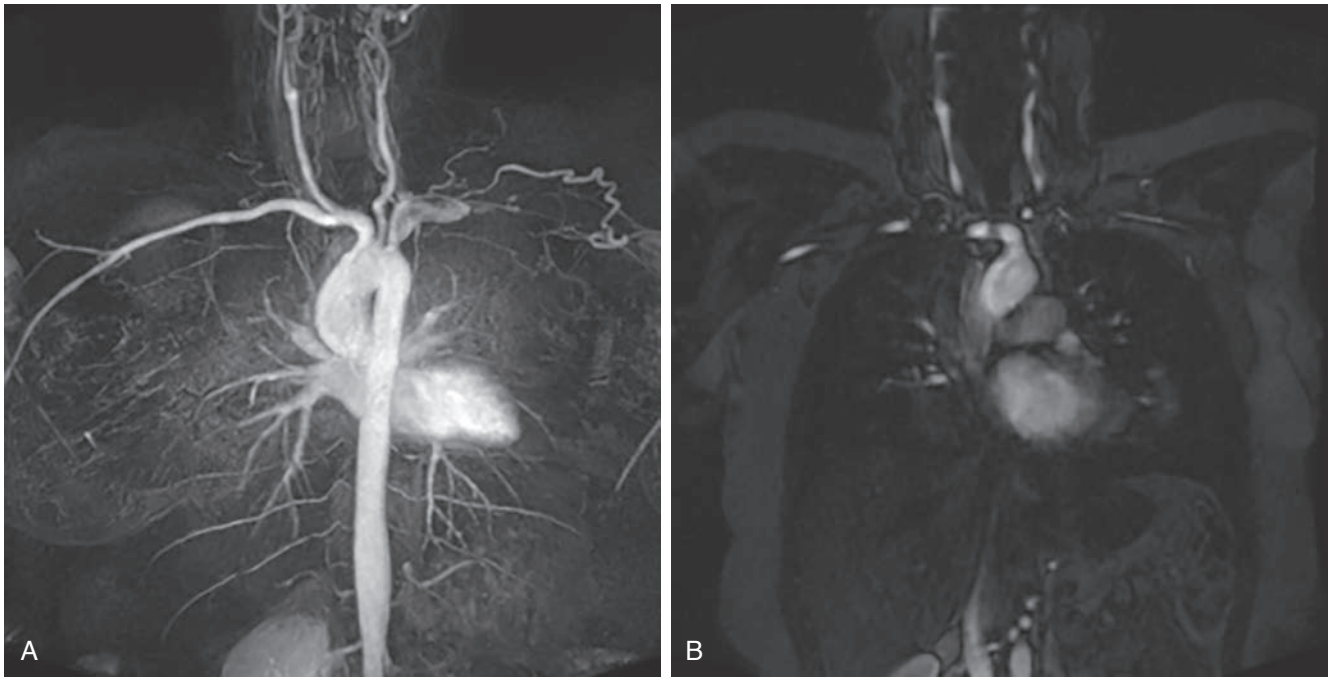

Figure 28.21 (A) Three-dimensional magnetic resonance maximum intensity projection coronal image shows collaterals from chronic severe narrowing and occlusion of left subclavian artery in a patient with Takayasu arteritis. (B) MR angiogram shows severe narrowing of left subclavian artery in a patient with Takayasu arteritis.

in its evolution, clotted blood will pass through a state of either intracellular or extracellular methemoglobin. This state typically occurs in the subacute phase (1-14 days) of a blood clot.[86] When the clot contains large amounts of methemoglobin, particularly extracellular methemoglobin, the signal may be high on the T1-weighted images used in MRA. This signal can be high enough to mimic intravascular contrast, as shown in Fig. 28.25. The use of precontrast T1-weighted imaging can identify the thrombus, as shown.

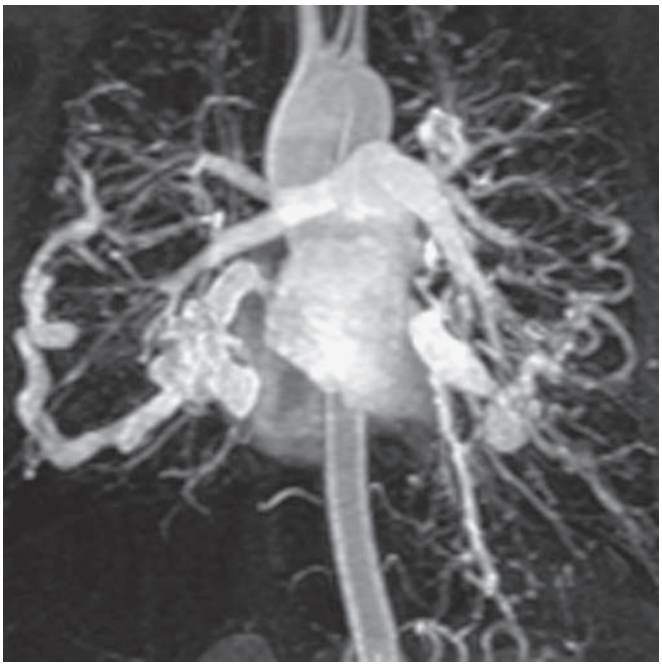

Figure 28.22 Coronal three-dimensional magnetic resonance angiogram showing a large right-sided pulmonary arteriovenous malformation and several smaller left-sided malformations.

Contraindications to Magnetic Resonance Imaging

Impaired Renal Function and Nephrogenic Systemic Fibrosis

As noted earlier, gadolinium-containing contrast agent had long been thought to be safer for patients with impaired renal function because they are associated with a much lower incidence of contrast-induced nephropathy than iodinated contrast material is at the dose used for clinical imaging.[16,18] Because the radiodensity of Gd-DTPA is one-half to one-third that of the same dose of iodinated contrast material at the energies used for fluoroscopy, a large dose of contrast material may be necessary to obtain diagnostic images, which may engender higher risk for contrast-induced nephropathy than a dose of iodinated contrast material of equivalent radiodensity.[87]

NSF, previously known as nephrogenic fibrosing dermopathy, is a disease with primarily dermatologic manifestations, although findings in other organs have now been elucidated.[6] NSF is characterized by skin thickening and hyperpigmentation of the extremities and trunk; patients with more severe involvement may have contractures and organ fibrosis, in some cases leading to death. All reported cases to this point have occurred in patients with renal insufficiency, primarily in those with very poor kidney function in the setting of chronic renal failure, although cases have been described with milder renal dysfunction in acute renal failure. Whereas concomitant liver failure was previously thought to be an additional risk factor, longer-term studies have not supported this finding. There is no specific treatment of NSF other than improving renal function, such as through kidney transplantation; steroids and other antiinflammatory treatments have been used, along with hemodialysis and photopheresis.[88]

Although the first cases of NSF were described in 2000,[6] a possible association between NSF and exposure of patients with

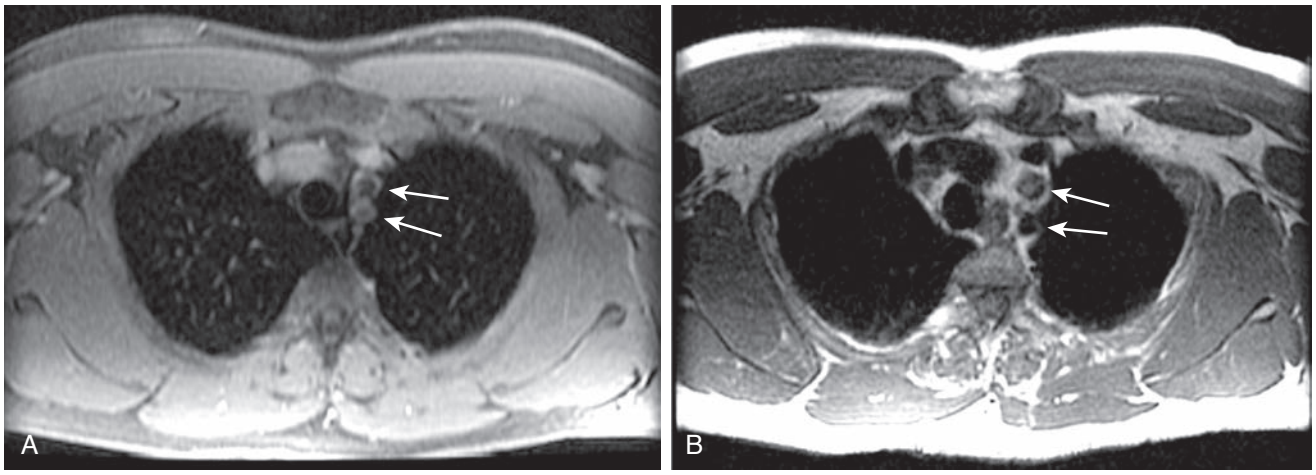

Figure 28.23 (A), Axial two-dimensional postcontrast fat-saturated T1-weighted image showing no contrast within the left subclavian and left common carotid arteries *(arrows)* in a patient with a type A dissection. (B) Axial T2-weighted dark blood imaging showing flow void within the left subclavian but signal within the left common carotid arteries *(arrows)*, findings indicative of thrombosis.

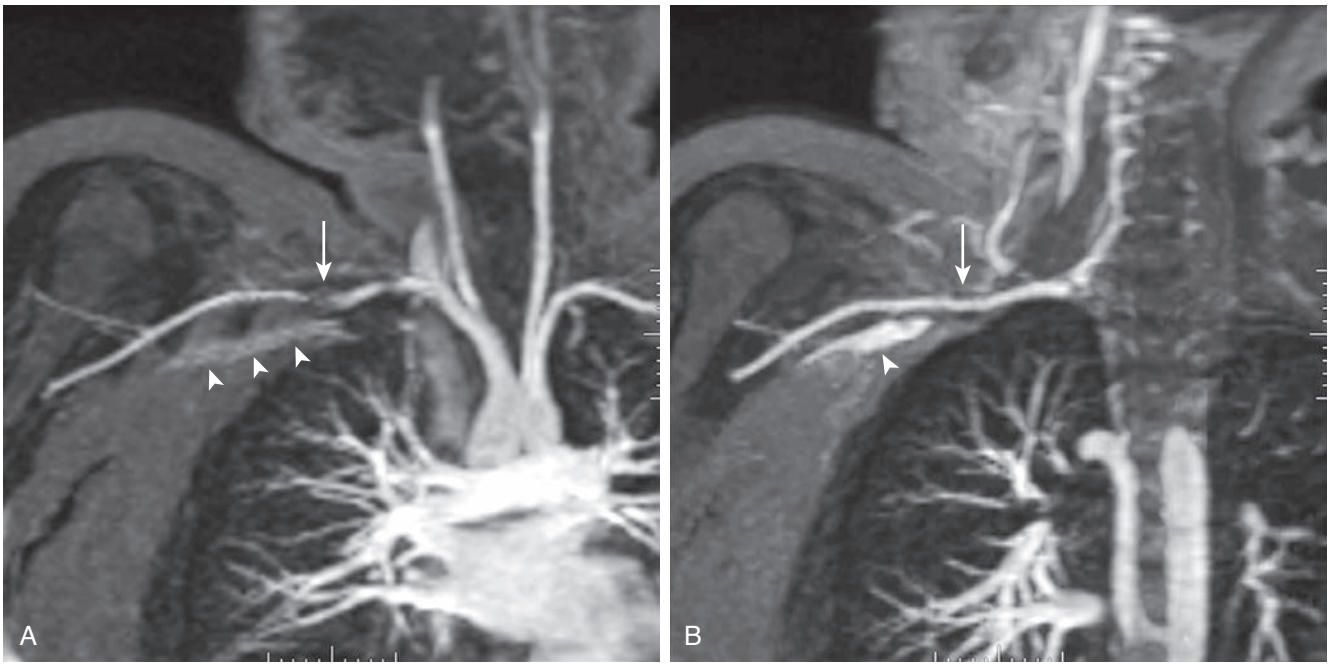

Figure 28.24 (A) Arterial-phase coronal three-dimensional (3D) magnetic resonance (MR) angiogram showing apparent stenosis *(arrow)* in the right subclavian artery. Note that the signal from the pure contrast in the left subclavian vein *(arrowheads)* is not as high as the signal from the dilute contrast in the adjacent artery. (B) Delayed-phase 3D MR angiogram showing no stenosis in the subclavian artery *(arrow)*. Note that the signal from the dilute venous contrast is now much higher than that from pure contrast *(arrowhead)*.

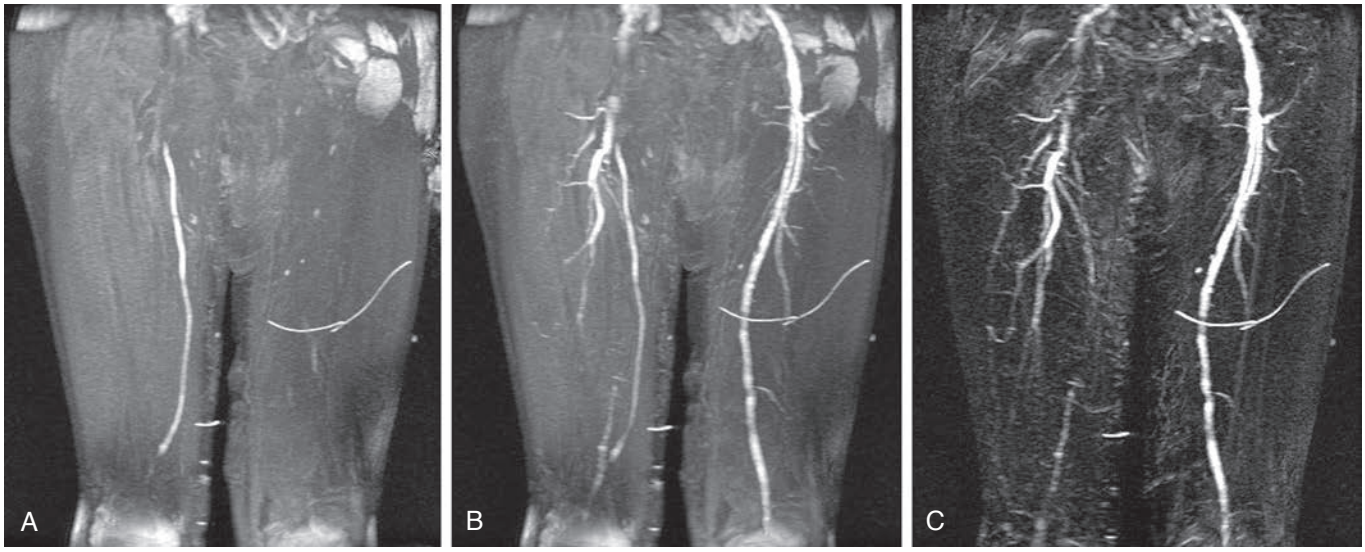

Figure 28.25 (A) Precontrast coronal T1-weighted image showing high intravascular signal from a thrombosed femoral bypass graft. The high signal is from methemoglobin in the thrombus. (B) Coronal three-dimensional magnetic resonance angiogram showing that the signal from the thrombus is as high as the signal in the contralateral superficial femoral artery. There are signal voids at the origin and touchdown of the graft, suggesting stenosis, when in fact the entire graft is occluded. (C) Subtraction image of the arterial-phase image minus the precontrast image showing only the contrast-enhancing arteries.

renal insufficiency to gadolinium-containing contrast agents was not proposed until 2006, when five cases were reported in a cohort of dialysis patients who had undergone MRA.[7] Since that time, approximately 1600 cases have been reported in dialysis and nondialysis patients,[89] and several predisposing factors have come to light, including metabolic acidosis, administration of a larger dose of gadolinium contrast agent, repeated contrast-enhanced studies (i.e., the effect may be cumulative), proinflammatory conditions, and recent vascular procedures, including surgery. All but five documented cases of NSF have occurred in patients exposed to gadolinium contrast agents, and thus far, there have been no documented cases of NSF in patients with normal renal function.[88] Although gadolinium agents are cleared rapidly by the kidneys in those with normal renal function, residence time may be increased 100-fold in those with markedly impaired renal function. It is currently unknown whether repeated exposure to gadolinium agents could induce NSF even in those with normal renal function.

Several new gadolinium-containing contrast agents have become available, and both the FDA and European Society of Uroradiology (ESUR) changed their policies and guidelines with respect to administration in patients with renal failure.[89,90] The FDA requires a boxed warning on all gadolinium-containing contrast agents, stating that the use of these agents should be avoided in patients with impaired elimination of drugs, that patients should be screened for acute kidney injury and other conditions that may reduce renal function (age > 60 years, hypertension, or diabetes), and to estimate glomerular filtration rate (GFR) with laboratory testing. The vast majority of NSF cases have been reported in association with gadodiamide, with small numbers associated with gadopentetate dimeglumine and gadoversetamide, and the use of these agents in patients with severe chronic kidney disease or acute kidney injury is contraindicated by the FDA. There was a single case after exposure to gadobenate dimeglumine, although this patient had also previously received gadodiamide[89]; this and other agents are not contraindicated, although caution is advised as described previously. Of all of these compounds, gadodiamide has the weakest binding of gadolinium ions to the chelating agent, which is consistent with a current theory for the pathogenesis of NSF, that it is caused by a reaction to free gadolinium ions. The histologic finding of gadolinium in affected tissues supports this mechanism, as does the association with proinflammatory states.

For permanently dialysis-dependent patients, CTA should almost always be the examination of choice for vascular imaging. If contrast-enhanced MRI is a clinical necessity, such as for postoperative imaging of brain tumors, repeated hemodialysis within 24 hours of the study has been proposed. In patients with poor renal function who are not dialysis dependent, a temporary dialysis catheter can be placed to allow immediate hemodialysis.[87]

Pacemakers and Other Implanted Devices

Although MRI is extremely safe, the degree of safety is ensured only by maintaining the appropriate environment around the magnet and by careful screening of patients.[91,92] There are a number of implanted metallic devices that are not safe in or near an MRI magnet. The more common include implanted pumps or neurostimulators, some cochlear implants, and some intracranial aneurysm clips. Because of the large variety of implanted devices, sources of information regarding which are safe have been developed. Such sources include books,[93] published articles,[94] and websites,[95] and consultation of these resources is highly suggested before considering MRI in a patient with an implanted device.

Implanted pacemakers and defibrillators had long been considered absolute contraindications to MRI; however, several studies have demonstrated that some patients with pacemakers and defibrillators can be imaged safely under carefully controlled conditions.[96-100] The risks in imaging patients with pacemakers or defibrillators include patient- and device-related complications, although the factor of greatest concern is whether the patient's underlying cardiac rhythm would be able to tolerate the pacemaker's ceasing to function while in the magnet, where immediate treatment may be more difficult. In general, factors that entail greater risk include a pacemaker-dependent patient, pacemaker generator implanted before 2000 (some older models appear to be more susceptible to an electrical reset to default parameters while in the magnet),[98] presence of an implantable cardioverter-defibrillator (ICD), and inclusion of the pacemaker/ICD generator or leads in the RF field. At our institution, we follow a protocol in which the device is interrogated before MRI and pacing parameters altered so that they are less susceptible to interference from the RF and gradient,[98] and an electrophysiologist physician is present throughout the MRI examination. The ICD's antitachycardia therapy capabilities are turned off during the examination, and thus the device would be unable to respond to episodes of tachycardia that would benefit from shocks.[100] We will perform MRI on patients with pacemakers or defibrillators that are not FDA approved as MRI conditional under the following circumstances:

1. There is a compelling clinical need for the scan, and the information to be gained from the examination has a high likelihood of altering patient management or prognosis.
2. There is no other acceptable imaging alternative.
3. An electrophysiologist concurs that the patient will not be harmed by the temporary modifications to pacemaker/ICD programming just noted.

Given the availability and utility of high-quality CTA, there are very few situations in which these conditions would be met in vascular imaging, and the majority of cases reported in the literature involve neurologic, musculoskeletal, and abdominopelvic imaging. However, the recent availability of devices that are approved by the FDA as MRI conditional may mean that MRA of the patients with implanted pacemakers and ICDs will become more routine.

Vascular Stents, Filters, and Coils

The majority of implantable vascular stents, filters, and coils have been shown to be "MRI safe" or, using newer terminology developed by the American Society for Testing and Materials

International, "MRI conditional"[101,102]; that is, they are not subject to significant force when placed inside the magnet and have been demonstrated to pose no known hazards. One exception was the Zenith AAA stent graft system (Cook Inc, Bloomington, Indiana), which is made of stainless steel and was shown to be subject to significant forces in in vitro testing, and was therefore previously characterized as MR unsafe.[103] This stent has not been systematically studied in vivo; however, retrospective results have been reported for a small cohort of 11 patients with Zenith stent grafts who underwent a total of 20 MR exams (including 10 of the abdomen, pelvis, or spine) and suffered no ill effects,[104] and nonclinical testing at field strengths of up to 3 T demonstrated no significant heating or torqueing. Therefore it is now classified as MR conditional at up to 3 T, beginning immediately after placement.[103]

IVC filters and vascular embolization coils are composed of either nonferromagnetic alloys such as nitinol or weakly ferromagnetic stainless steel. Neither of these materials is subject to significant force when exposed to MRI, and all IVC filters tested are classified as MRI safe or conditional. As with stents, many manufacturers recommend waiting up to 8 weeks after placement of the device before performing MRI because this period is thought to be the amount of time needed for stable incorporation into the vessel wall; however, there are no specific data to justify this policy. Stents, filters, and coils composed of nonferromagnetic material may be safely imaged immediately after placement. For weakly ferromagnetic devices, the decision to perform MRI within 6 to 8 weeks after placement should be accompanied by consideration of the potential risks versus the benefits of the information that the studies will provide.[102]

Although it may be safe to perform MRI on patients with stents, IVC filters, or coils, the presence of such devices may cause severe image artifacts related to distortion of the magnetic field by the metal, thus rendering portions or the entire MR study uninterpretable. Stainless steel devices in particular, as well as platinum and some other materials, will cause large areas of signal void on gradient-echo imaging sequences, the primary type of imaging used for MRA. These artifacts extend beyond the region of the device, and thus, for example, MRI of the right kidney may not be the appropriate examination for someone with a stainless steel IVC filter. Nitinol and other alloys will produce less degrees of artifact, and the vessel lumen may be evaluable even inside a stent[35] or adjacent to an IVC filter. Although vessel patency can usually be evaluated, some artifact will still be present, and therefore these images may not reliably demonstrate vessel diameter or the degree of stenosis.

RECENT ADVANCES

3-Tesla Magnetic Resonance Angiography

As noted earlier, MR systems with magnets up to 3 T have now been approved by the FDA. Because the degree of magnetization produced is linearly related to the magnetic field strength, use of a 3-T magnet can result in an improvement of up to a factor of 2 in image signal greater than 1.5 T. This increased signal can then be traded for decreased imaging time or increased spatial resolution. Although the first applications demonstrated to benefit from 3-T imaging were imaging of the brain and spine and musculoskeletal imaging, the entire range of MRI is now being performed at 3 T, including breast, body, and cardiac MRI, as well as MRA.[105-108]

MRA at 3 T has several other advantages over 1.5 T. T1 relaxation times are longer at 3 T than at 1.5 T, which results in an increased degree of enhancement from the same amount of gadolinium contrast or the ability to use less contrast to obtain the same degree of enhancement, which may be relevant for those with impaired renal function. Preliminary studies have shown improved image quality and accuracy of 3-T MRA over 1.5-T MRA for imaging of the renal, carotid, and infrapopliteal arteries.[109-111]

The principal disadvantage of 3-T imaging is a fourfold increase in deposition of RF energy into the patient, known as the specific absorption rate (SAR). There are FDA-mandated limits on SAR, which are encountered more commonly at 3 T than at 1.5 T. Although this is not an important problem for contrast-enhanced MRA because of the types of pulse sequences used, it can be an issue when using non–contrast-enhanced SSFP techniques and in applications such as cardiac MRI. Additional concerns include higher cost for 3-T MR systems than for 1.5-T systems and an increase in certain types of image artifacts related to inhomogeneity of the magnetic field, which requires careful shimming (adjustment) of the gradient magnetic fields to maintain even signal across the image.[112] Despite these difficulties, more MRA studies will be performed at 3 T as radiology practices switch to this new technology because of its advantages for general MRI.[113]

Parallel Imaging

Parallel imaging refers to a collection of MR acquisition and processing techniques that use multiple coils and RF receiver channels to accelerate the acquisition of image data.[114,115] In parallel imaging, multiple receiver coils are placed around the object, and RF signals may be read independently from each coil. Because the different coils are at different positions relative to the object being imaged, analysis of the subtle differences in signal acquired by each coil can provide spatial information about the object. This type of spatial information can be used to reduce the number of different gradient settings (called phase-encoding steps) at which RF signal must be acquired to obtain an image, thus reducing acquisition time. The amount by which the acquisition time is reduced is referred to as the "acceleration factor" and is theoretically proportional to the number of independent coil signals that are acquired. However, in practice, acceleration factors are currently limited to 2 or 3 because the SNR of the resultant images is decreased by the square root of the acceleration factor. As such, the use of parallel imaging is usually confined to high-SNR applications, including MRA, and most contrast-enhanced MRA examinations done on newer scanners are now performed with parallel imaging.[116]

Advantages of parallel imaging include

1. Faster imaging—which may lead to fewer motion artifacts and shorter breath-holding time.
2. Higher resolution imaging in the same acquisition time.
3. Lower SAR—especially important for 3-T imaging.
4. Improved image homogeneity and slightly better SNR because multiple smaller coils are more evenly distributed around the body part being imaged than a larger single coil would be.

Disadvantages of parallel imaging include

1. Need for more expensive multielement coils and multiple–receiver channel MR systems. Newer MR systems may have to 32 receiver channels, which allow the acquisition of 32 simultaneous signals from up to 76 separate coil elements. Although all MR systems are capable of performing parallel imaging, some are limited in the number of coils that may be connected simultaneously, which can have implications when performing step-table examinations.
2. Increase in image noise as a result of acquisition of less information.
3. Image artifacts related to parallel data processing may occur.

Compressed sensing[117-119] is a mathematical framework that provides reconstruction of data from highly undersampled measurements to gain acceleration of acquisition time. The k-space is undersampled to allow reconstruction of an image from less data. This method is useful in pediatric imaging and where shorter breath-hold sequences are required. Compressed sensing approaches are now available from several manufactures and will be incorporated into routine MRA protocols in the coming years.

Continuous Moving Table and Time-Resolved Magnetic Resonance Angiography

One limitation of 3D contrast-enhanced MRA is that signal from the entire volume of data is acquired simultaneously, so respiratory or other motion at any point during the acquisition may result in artifacts throughout the imaged volume. A solution to this difficulty is continuous moving table MRA, in which, as occurs in helical computed tomography (CT), the table moves throughout the acquisition in a proximal-to-distal direction. As in helical CT, data from only a small volume of tissue are being acquired at any moment, and motion artifacts will affect only the region being acquired at the time of the motion. In addition, continuous moving table techniques may truly permit "bolus chasing" because the speed of table motion can be adjusted to match the transit time of contrast in the arteries.[120] This technique has shown promising results for peripheral vascular imaging, particularly when combined with parallel imaging techniques to allow decreased scan time and increased resolution, without venous contamination.[121] Fig. 28.26 demonstrates a continuous table motion MRA runoff obtained at 3 T with parallel imaging.

Another limitation of typical contrast-enhanced MRA methods is that they average the appearance of a vessel over a long acquisition time, typically 20 seconds to 2 minutes, thus providing a static view without insight into the dynamic physiology of blood flow. For example, one may not be able to tell whether an artery distal to a high-grade stenosis is filling in an antegrade fashion or retrogradely through collaterals. Long acquisition times may also result in venous contamination if there is rapid transit of contrast through an organ with early venous filling, such as in the kidney. In addition, if two extremities are imaged simultaneously, the optimal imaging time may be different for each if one extremity has early arteriovenous shunting related to cellulitis, varicose veins, or arteriovenous malformations. Time-resolved MRA methods obtain multiple, more rapid acquisitions throughout passage of the contrast from arteries to veins.[122] Typically, time-resolved methods

Figure 28.26 Coronal maximum intensity projection of a continuous table motion magnetic resonance angiography runoff examination acquired at 3 T with parallel imaging from the abdomen to the toes in a patient with bilateral iliac stenoses and segmental left superficial femoral artery occlusions. The acquisition time was approximately 90 seconds. Note the lack of venous contamination in the calves and feet.

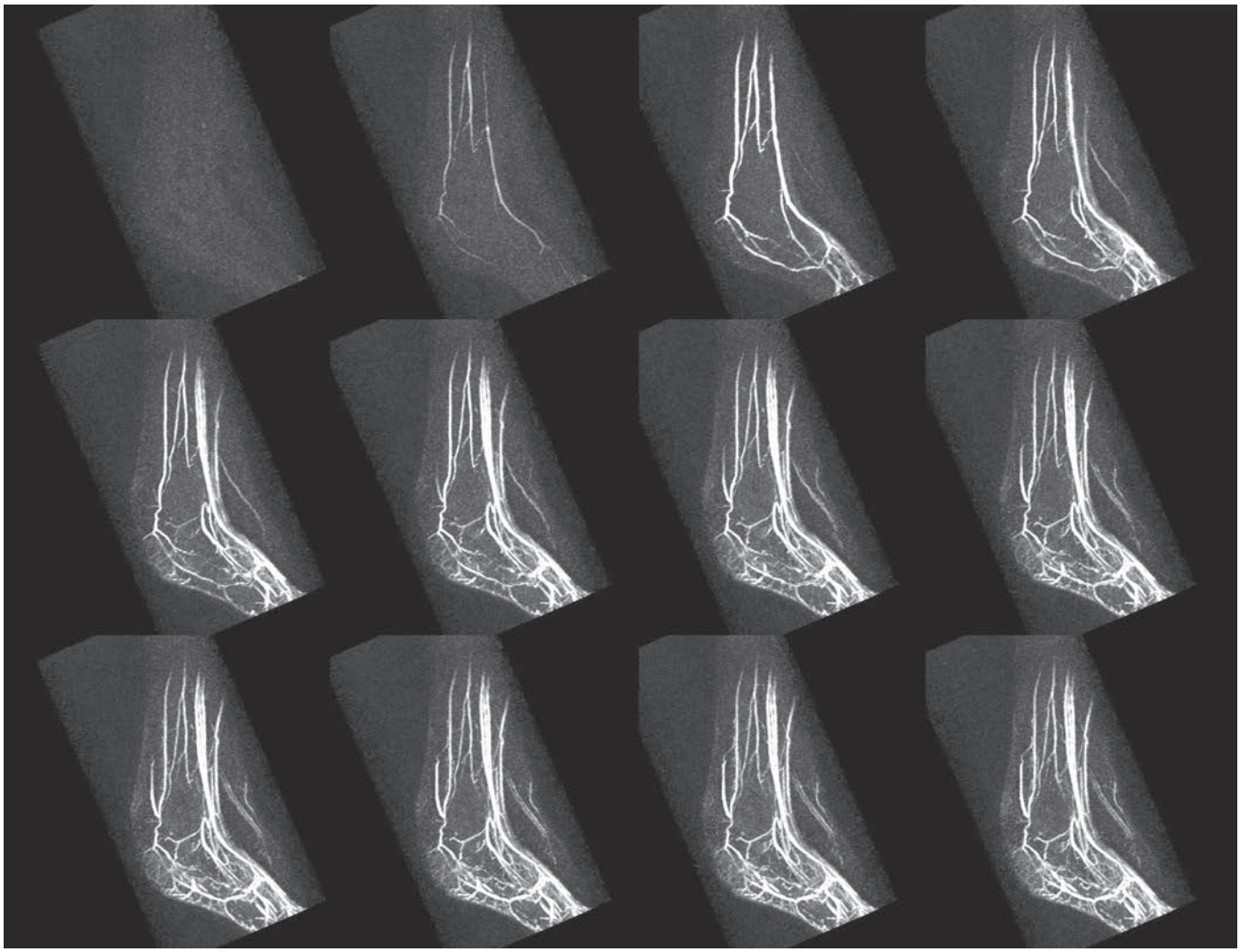

Figure 28.27 Coronal maximum intensity projection images of successive frames from a time-resolved magnetic resonance (MR) angiography examination of the feet. Each frame requires approximately 6 to 8 seconds to acquire, and thicker slices are obtained than with a static MRA.

acquire thicker slices than static high-resolution MRA does; some spatial information is sacrificed for improved temporal resolution, but complete 3D data sets are acquired in 2 to 10 seconds instead of 20 to 120 seconds. In this way, images can demonstrate the dynamic flow of contrast into an artery, followed by venous filling. The multiple frames of the resulting time-lapse movie can be viewed to choose the time with optimal arterial filling and minimal venous contamination (Fig. 28.27).

Blood Pool Contrast Agents

Gd-DTPA– and Gd-BOPTA–based contrast agents are extracellular or interstitial contrast agents (i.e., they do not enter cells with intact membranes); however, they rapidly equilibrate in the extracellular space after intravascular injection, with predominantly renal clearance, although some hepatic clearance also occurs. This property results in a narrow time window for MRA before the decreased concentration of contrast in the vessels and the increased background tissue signal make further imaging of little value, thus limiting the spatial resolution that can be obtained.

Blood pool contrast agents (BPCAs) remain intravascular for extended periods, which allows longer high-resolution imaging, albeit at a static steady state in which both arteries and veins are filled with contrast. Two principal types of BPCA have been developed—compounds of gadolinium bound to macromolecules and ultrasmall superparamagnetic iron oxide (USPIO) particles[123,124]—both of which may allow up to 1 hour of imaging time. Gadofosveset (Ablavar in the United States, Vasovist outside the United States), previously known as MS-325, is the only BPCA currently approved for clinical use. Gadofosveset binds noncovalently to albumin in plasma and results in an increased degree of enhancement for the same concentration when compared with Gd-DTPA compounds, so a lower dose may be used in imaging (0.03 mmol/kg gadofosveset

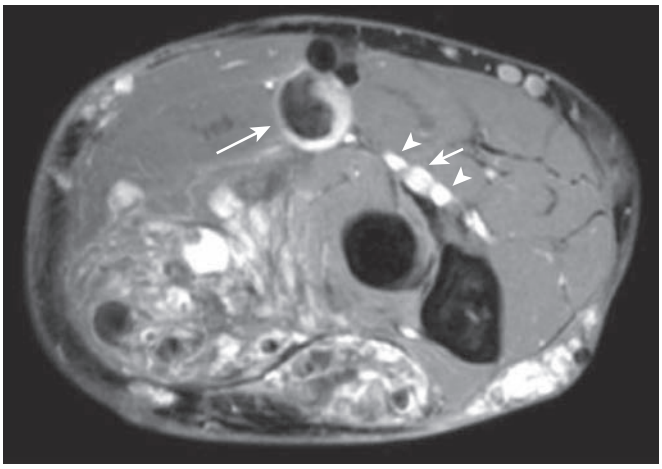

Figure 28.28 High-resolution axial T1-weighted image obtained more than 5 minutes after the administration of a blood pool contrast agent demonstrates contrast filling both arteries and veins, and outlining thrombus in an enlarged draining vein *(arrow)* in a patient with a large forearm vascular malformation.

vs. 0.1 mmol/kg Gd-DTPA).[124] One advantage of gadofosveset over some other BPCAs is the ability to obtain a dynamic arterial-phase acquisition in addition to steady-state imaging.

BPCAs have been evaluated for imaging of many vascular territories.[125,126] In most applications, steady-state imaging is performed at isotropic high spatial resolution, from 1 mm to 0.5 mm or less—such high resolution is necessary to be able to distinguish adjacent arteries and veins, both of which are filled with contrast. Imaging of abdominal and thoracic vessels (e.g., the renal arteries) is currently limited by breath-hold length and may not benefit as much from a BPCA, although the non–breath-hold respiratory or navigator-gated techniques currently used for non–contrast-enhanced MRA could be applied in these situations.[127] Fig. 28.28 shows a high resolution axial image T1-weighted image obtained through the forearm in a patient with a large vascular malformation more than 5 minutes after administration of a BPCA; contrast remains in both arterial and venous structures. Unfortunately, it was announced in early 2016 that Ablavar would no longer be available for purchase in the United Staes because of manufacturing difficulties.

Iron-based superparamagnetic nanoparticle MR contrast agents, SPIONS are used in scanning patients who have infection or inflammation. These agents are safe to be used in patients who have chronic renal failure where gadolinium-based contrast are contraindicated. SPIONS when injected are phagocytosed by macrophages and show prolonged T2 and T2* effects on contrast-enhanced MR images in macrophage-infiltrated tissues.[123] These agents are beginning to be studied for use in MRA, showing promising initial results.

Imaging of Blood Flow

All of the above discussion has concentrated on anatomic imaging of blood vessels, using native or exogenous contrast to allow visualization of the vessel lumen. In these techniques, signal within a vessel is relatively independent of flow, although vessels with poor flow may not fill with exogenous contrast or provide enough signal for noncontrast methods. However, MRI can also be used to visualize and measure flow velocities in a vessel using phase-contrast techniques, in which signal intensity is actually proportional to flow velocity. In cardiac MRI, 2D methods have long been used to measure valvular flow and regurgitation and to calculate shunt fraction, using ECG gating to acquire velocity maps through the cross-section of a vessel such as the aortic root. The instantaneous flow at each phase of the cardiac cycle is determined by multiplying the average velocity by the area of the cross-section, which is then integrated over the cardiac cycle to provide total flow.[128] The same 2D methods were used in the precontrast enhanced MRA era as an alternative to TOF imaging, allowing both anatomic and physiologic characterization of the significance of a stenosis.[129] Generalizing these methods to 3D velocity measurement over time has become possible, with acquisition times dramatically decreased by application of acceleration methods such as parallel imaging and compressed sensing.

After the complete 4D dataset has been acquired, it can be visualized in a variety of different ways. One popular method creates time-resolved 3D particle traces or pathlines, following the fate of a massless particle released from a specific point over the cardiac cycle (Fig. 28.29). This method has been applied to many different vessels; however, the ascending aorta has received the most study, allowing visualization and characterization of altered flow dynamics in patients with aneurysms, bicuspid valve, coarctation, and disorders such as Marfan syndrome.[130] Although 4D flow has proven useful for generation of hypotheses concerning a variety of pathophysiologies, whether it will demonstrate value in clinical routine remains to be seen.[131]

Plaque Imaging

A primary aim of MRA throughout the body is to image arterial stenosis caused by atherosclerotic disease; for this application, the principal advantages of MRI over catheter angiography are its noninvasive character and lack of ionizing radiation. However, stenosis imaging by itself fails to use one of the most powerful capabilities of MRI, soft tissue contrast imaging, which potentially allows visualization of the cause of the arterial stenosis (i.e., atherosclerotic plaque).[132] Several methods are available for imaging plaque, including non–contrast-enhanced techniques, the use of Gd-DTPA and other typical contrast agents, and imaging with contrast agents that concentrate specifically in atherosclerotic plaque.

The carotid bifurcation has been the subject of many investigations of plaque imaging techniques given its superficial location, lack of pulsatile motion, high prevalence of atherosclerotic disease, and clinical importance. So-called multispectral imaging, which combines information from sequences with T1, T2, and proton density weighting, has been shown to allow reliable discrimination of the various components of carotid atherosclerotic plaque, including the lipid core and fibrous cap, and distinction between necrotic, calcified, and hemorrhagic plaque.[133,134] Similar techniques have begun to be applied to

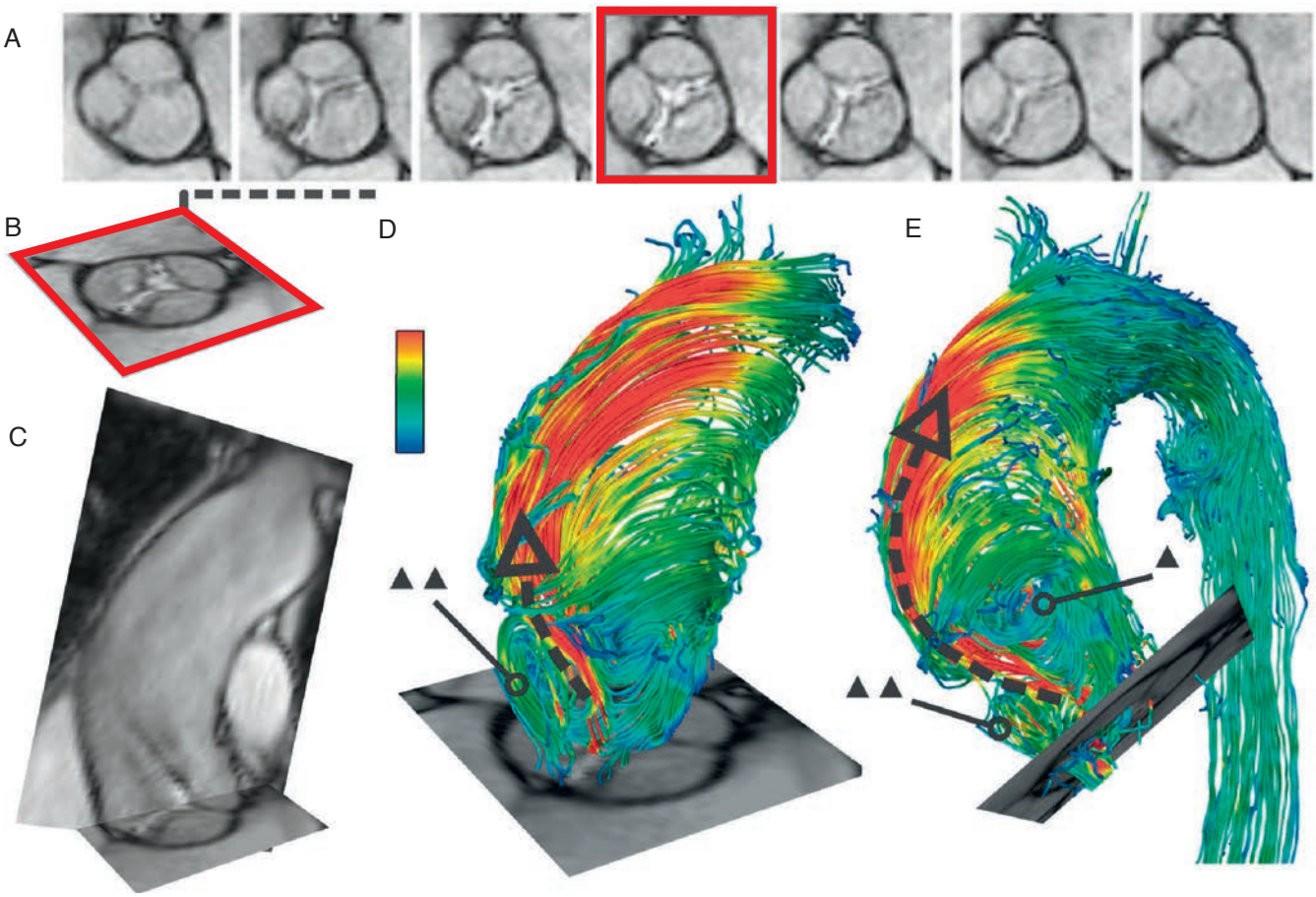

Figure 28.29 Several representations of data obtained during a single four-dimensional phase-contrast flow acquisition in a patient with a bicuspid aortic valve and dilated ascending aorta. (A and B) Two-dimensional cine images through the aortic valve demonstrate fusion of the left and right cusps and small opening area during systole. (C) Hybrid short-axis and oblique multiplanar reformatting long-axis anatomic view of dilated ascending aorta with high velocity flow jet visible. (D and E) Pathline reconstructions demonstrate high-velocity flow along the anterior border of the ascending aorta *(large arrow)* and abnormal flow vortices at the aortic root *(arrowheads)*. (Courtesy Alex J. Barker, PhD, Northwestern University.)

other vessels, including the aorta[135] and coronary arteries,[136] but imaging of atherosclerotic plaque in these vessels is limited by small diameter or pulsatile motion, or both.

Contrast-enhanced imaging has been used to quantify the degree of neovascularity of atherosclerotic plaque, which may be related to vulnerability to or likelihood of rupture.[137,138] In addition to their properties as BPCAs, injected USPIO particles are eventually taken up by macrophages and thus allow visualization of macrophage-laden plaque, which may be more vulnerable to rupture.[139] One preliminary study has demonstrated increased uptake of gadofosveset, the BPCA described earlier, in inflamed arterial walls adjacent to atherosclerotic plaque.[140] Currently under development are MR molecular imaging agents that specifically bind to components of atherosclerotic plaque or vessel walls, such as integrins.[141]

Recent studies have also shown that noninvasive MR angiography allows assessment of presence or absence of greater than 50% coronary artery stenosis with diagnostic accuracy comparable to that of multidetector computer tomography.[142]

Computed Tomographic Angiography Versus Magnetic Resonance Angiography

The development of multidetector CT technology over the past several years has led to a dramatic improvement in the quality and reproducibility of CTA examinations. The latest generation of 64-, 128-, 256-, and 320-slice scanners permit the rapid acquisition of high-resolution data over a large volume, which allows arterial-phase acquisitions at isotropic submillimeter resolution. Although the utility of CTA versus MRA for specific vascular applications will be discussed in later chapters, general advantages and disadvantages of each technique are mentioned here.

Acquisition Speed

Despite advances in MRI such as 3-T systems and parallel imaging technology (see earlier), a major advantage of CTA is speed of acquisition. Newer machines allow scanning of the entire aorta in under 2 seconds, scanning of the chest for

evaluation of pulmonary embolism in 1 second, imaging of peripheral runoff from the diaphragm to the toes in less than 10 seconds, and imaging of the coronary arteries in 150 ms. More important than the specific speed of acquisition is the fact that spatial resolution is independent of acquisition time and limited only by detector thickness, focal spot size, and the transit time of contrast down a vessel. Outrunning the contrast bolus is a potential complication in CTA,[143] especially in patients with poor cardiac output, large aneurysms with stagnant flow, or proximal occlusive disease. Unlike MRA, there is a cost associated with a repeat scan to allow filling of unopacified vessels, namely, increased radiation dose, although a second scan through the calves will not add much to the overall examination dose given their comparative insensitivity to radiation.[144]

Dynamic Imaging

Lack of dependence of spatial resolution on acquisition speed in CT can also be a disadvantage in that it is not possible to trade off these parameters for applications such as time-resolved imaging. As noted earlier, MRA can be performed in a dynamic fashion to provide physiologic information about direction and speed of blood flow, albeit at lower resolution, whereas CTA generally allows only static full-resolution snapshots at one or two time points during the contrast bolus. New wide detector CT systems can image up to 16 cm at each gantry rotation (< 0.3 seconds), thereby potentially allowing full-resolution dynamic imaging as well. Although this technique has shown some initial promise in neurovascular imaging, where it can also capture brain perfusion, it is not yet clear that the information gained will be worth the substantial penalty in radiation dose engendered by repeated scans.

Calcification and Other Imaging Artifacts

MR is limited in its ability to image vascular calcification because it tends to have very low signal on all pulse sequences used for MRA. Although this disadvantage limits the utility of MRI for detection of vascular calcification, it also means that MRA is in general not subject to the artifacts from vascular calcification seen with CTA. Therefore MRA may be more appropriate for patients with known or a high likelihood of heavily calcified vessels,[145] particularly for distal runoff imaging in diabetics. However, because these patients are also more likely to have renal disease, all options should be carefully considered, including non–contrast-enhanced MRA. Dual energy CT, also known as spectral CT, is a novel technique in which CT data are acquired at two different x-ray energies, exploiting the fact that the difference in x-ray attenuation at the two different energies is characteristic of an element, with chemical binding exerting only a small effect. By examining the difference in attenuation for each pixel at the two different energies, one can determine the material in that pixel. Using this method, pixels containing calcium can be separated from those containing iodine, even if their attenuation (in Hounsfield units) is very similar, allowing more accurate subtraction of calcium in bones and vessels from CT angiographic studies.[146] However, although these methods may allow improved removal of vascular calcification, they do not decrease the artifacts associated with the calcification, and therefore the degree of stenosis may still be overestimated in a vessel adjacent to a large calcified lesion.

As discussed earlier, MRA may be suboptimal in the presence of vascular stents, filters, or coils, depending on their composition. CTA also is subject to artifacts in these circumstances, although to a lesser degree.[147-150] Fig. 28.30 demonstrates the ability of CT to visualize the stent lumen, as well as the presence of stent artifact on MRA. Specific exceptions include coils containing platinum and stents or other metallic implants made of titanium or gold, all of which can cause severe streak artifacts on CTA.[151,152] Orthopedic hardware can cause artifacts in both modalities, but MRA may provide a better option, depending on the specific device and anatomy being imaged. As noted,

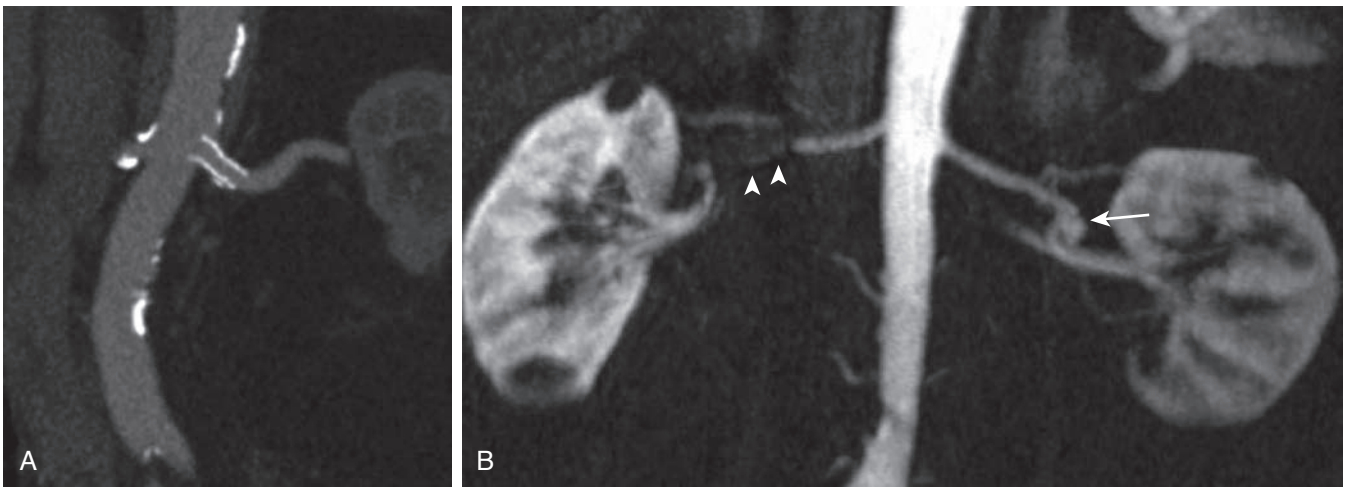

Figure 28.30 (A) Coronal multiplanar reconstruction (MPR) from a computed tomographic angiography examination demonstrating a patent stent in the left renal artery. (B) Coronal maximum intensity projection from three-dimensional magnetic resonance angiography in a patient with history of previous stent placement for right renal artery aneurysm. Note artifact from the stent obscuring the midportion of the renal artery *(arrowheads)*; we can infer stent patency from enhancement of right kidney. A left renal artery aneurysm is also present *(arrow)*.

CTA is almost always preferred in patients with implanted pacemakers or defibrillators.

Radiation Dose and Contrast Concerns

With increasing use of CT, and of CTA in particular, has come increased concern for the effects of exposure to ionizing radiation. Several high-profile journals and the mainstream media have published reports evaluating the cancer risk engendered by exposure to radiation from CT.[153,154] Although one can disagree with the assumptions behind many of the calculations of cancer risk in these reports, it is clear that repeated CT studies do come with some risk. Therefore consideration should be given to the use of MRA in radiation-sensitive populations (children, young women, etc.) and in those who will undergo repeated surveillance studies over many years.

As discussed previously, gadolinium contrast agents are not without risk, particularly in patients with renal dysfunction. However, the incidence of contrast-induced nephropathy (CIN) is still greater with iodinated contrast (at the doses of each used for clinical imaging), and there is a higher rate of reactions and complications after iodinated contrast agents.[16,18,19] As stated earlier, contrast-enhanced MRA should not generally be performed in dialysis-dependent patients without a compelling clinical need.

Dual energy CT may provide an opportunity for both radiation and contrast dose reduction in CT angiography. As mentioned previously, this technique can be used to determine the material content of an object (e.g., the amount of iodine in a specific pixel). The amount of iodine can then be subtracted, leaving what is called a "virtual noncontrast" or water image. This has two potential benefits: (1) obviating the need for an actual precontrast acquisition (e.g., saving radiation dose in stent-graft follow-up exams)[155] and (2) improving the contrast-to-noise ratio (CNR) of contrast enhanced exams, allowing the reductions in iodinated contrast dosage.[156]

Ease of Use and Convenience

CTA examinations are generally performed much more quickly than MRA, in less than 5 minutes of table time versus 30 minutes or more. This is a result of increased positioning and setup time before data acquisition, increased duration of each acquisition performed during the study, and the increased number of acquisitions per study for MRA versus CTA. The increased number of acquisitions is related both to the ability to acquire multiple phases during the contrast bolus without a radiation penalty and to the multiple pulse sequences acquired to obtain the different soft tissue contrast (T1 versus T2) that are available with MRI. Our typical CTA protocol requires four breath-holds (topogram, precontrast, arterial phase, and delayed phase), whereas a typical MRA protocol would entail approximately 10 (localizers [2], axial T1 in- and out-of-phase imaging [2], axial T2 in- and out-of-phase imaging [2], precontrast imaging [1], arterial- and delayed-phase MRA [2], and postcontrast T1-weighted imaging [1]), which can be completed in less than 15 minutes in most patients. However, CT would still be the recommended initial study for acutely symptomatic vascular disease, such as acute aortic syndromes.

Until recently, CTA gantries were larger and more "open" than MR systems; however, the availability of short-bore MRI machines and 64-slice and greater CT has virtually erased that gap, with 70-cm openings and 450-lb or higher table capacity being standard on most CT and MR systems. The presence of the magnetic field does continue to limit the types of monitoring equipment and patient attachments that can be brought into the scan room, as well as ease of access for staff to respond to medical emergencies in the magnet room. Although MR systems tend to be more expensive and less available than CT systems, these differences have also narrowed recently.

MR angiograms tend to be easier to interpret and postprocess than CT angiograms because of the background suppression techniques used in MRA pulse sequences. This allows rapid 3D visualization without the need for the bone removal techniques used in CTA. In addition, there are usually many fewer images in 3D Gd-MRA than in corresponding CTA of the same volume because the MR angiogram can be acquired in the plane that is most advantageous for the specific anatomy, such as oblique sagittal for the aorta, whereas all CT images are acquired axially and then reformatted to the desired orientation.

Both CTA and MRA can provide excellent-quality imaging in almost all clinical circumstances. In the end, the decision concerning whether to perform CTA or MRA may often be most influenced by the local availability of the technology and expertise in performing and interpreting these studies, as well as the experience and comfort of the referring vascular surgeon with the two modalities and the interpreting radiologists.

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A complete reference list can be found online at ExpertConsult.com

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29 CHAPTER

Vascular PET/CT and SPECT/CT

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Traditional imaging modalities for the assessment of blood vessels have focused on size, irregularity of the vascular lumen, and anatomic changes in adjacent structures. The ability of these morphologic imaging techniques to identify physiologic changes such as active inflammatory processes and plaques at risk for rupture is, however, limited. Molecular imaging has the advantage of enabling noninvasive physiologic assessment of these processes with radionuclides, very often early in the course of disease. Such early assessment can lead to subsequent changes in clinical management, potentially affecting patients' outcomes. The limitations of traditional nuclear medicine techniques, mainly low spatial resolution and lack of anatomic details, have been overcome in the last decade with the introduction of the hybrid single-photon emission computed tomography/computed tomography (SPECT/CT) and positron emission tomography (PET)/CT imaging devices. A large body of evidence has accumulated on the use of molecular probes for the assessment of vascular inflammation and infection (especially in vascular graft infections and vasculitis), early diagnosis, precise determination of the extent of disease, and assessment of response to therapy.

BASIC PRINCIPLES

Single-Photon Emission Computed Tomography, Positron Emission Tomography, and Hybrid Imaging

In nuclear medicine imaging, radiopharmaceuticals are administered to the patient intravenously. Images are obtained from radiation, which is emitted at the location of disease processes in the patient's body. Two main camera systems, the gamma camera and the PET camera, convert this radiation into images.

The gamma camera forms the basis of conventional nuclear medicine and provides two-dimensional imaging of the body.

Abstract

This chapter provides an overview of the basic principles of nuclear medicine, the most commonly used tracers, and the clinical applications of these tracers in atherosclerosis, aortic pathology, vasculitis and vascular graft infections.

Keywords

Nuclear Medicine
PET/CT
SPECT/CT
atherosclerosis
vasculitis
vascular graft infection

Image contrast of this planar imaging is rather low due to the presence of overlying structures that interfere with the region of interest. This limitation can be overcome by collecting images from different angles around the patient, the so-called SPECT, which leads to better spatial resolution, higher contrast, and improved sensitivity.

PET is an imaging tool based on radionuclides that emit positrons to become stable. For example, decay of the radioisotope fluorine-18 (18F) leads to emission of a positron that collides with an electron after traveling a short distance in tissue, thereby generating a pair of 511-keV annihilating photons (in opposite directions) that can be detected by the PET imaging device. The major advantage of PET over SPECT is that the PET camera system is more effective in detecting photons and provides better spatial resolution (around 3-4 mm). Furthermore, quantification is easier with PET. Uptake of PET radiopharmaceuticals can be quantified by standardized uptake values (SUVs), which measure the tracer uptake within a region of interest in relation to the injected dose and patient's body weight.[1]

However, both modalities provide only very limited morphologic information. Therefore PET as well as SPECT are now combined with CT in a single imaging modality. Hybrid SPECT/CT, PET/CT, and now also emerging PET/magnetic resonance imaging (MRI) improve the sensitivity by anatomic detection of small structures, such as plaques, and may also improve the specificity, confirming active disease in these small lesions.[2] Other advantages of combining radiologic and nuclear medicine techniques in one imaging modality are reduced costs, perfect correlation of pathophysiologic with anatomic information, and the one-stop-shop principle, which is convenient for the patient and reduces waiting time.

Most Commonly Used Tracers for Vascular Diseases

^{18}F-Fluorodeoxyglucose

Fluorodeoxyglucose (FDG) is an analogue of glucose, taken up by and accumulating in cells in proportion to their metabolic activity. The transfer of glucose into cells is facilitated by glucose transporters (GLUTs) and sodium glucose cotransporters (SGLTs). After entering the cell, glucose undergoes phosphorylation by hexokinase, forming glucose-6-phosphate. After its glycolysis by hexose-6-phosphate isomerase, fructose-6 phosphate is formed. In contrast, the analogue 2-deoxy-D-glucose cannot undergo conversion by hexose-6-phosphate isomerase; therefore, FDG becomes trapped in the cytosol. Glucose and FDG have otherwise similar properties, and the rates of phosphorylation in vivo are proportional to each other, reflecting the general rates of glucose metabolism.[3]

FDG imaging is today the "gold standard" in the assessment of patients with cancer, for staging tumors, monitoring response to treatment, and diagnosing recurrence. FDG can also be used in infectious and inflammation diseases, since many cells involved in infection and inflammation (activated leukocytes, monocytes, lymphocytes, macrophages, and giant cells) use glucose for their metabolism. This tracer is extensively used in vascular imaging.

^{18}F-Sodium Fluoride

Sodium fluoride (NaF) is mainly used for skeletal imaging, since it has the desirable characteristics of high and rapid bone uptake accompanied by a very rapid blood clearance, which results in a high bone-to-background ratio.[4] Its use in vascular imaging is, however, at this time limited to plaque imaging. Since NaF is not physiologically taken up in the myocardium and blood vessels, it could also potentially be a better agent than FDG in assessing the coronary vessels.

Labeled White Blood Cells

Scintigraphy using autologous white blood cells—also called leukocyte scintigraphy—is still considered the gold standard nuclear imaging modality for infections. In using the correct acquisition protocols and interpretation criteria, this technique is highly accurate. Limitations, however, are the needs for a laborious labeling procedure and for imaging at several time points. White blood cell scintigraphy is primarily used in musculoskeletal infections but has also been extensively evaluated in vascular diseases, such as vascular graft infections.

Other Available Tracers

Besides the already mentioned commonly used tracers, various other radiopharmaceuticals have been developed and tested, most of them in atherosclerosis. SPECT and PET imaging of atherosclerosis takes advantage of the wide array of biologic mechanisms involved in the different stages of atherosclerosis and plaque formation. Tracers have been developed for targeting the atherosclerotic lesion components, such as technetium-99m (^{99m}Tc)–labeled low-density lipoprotein (LDL), ^{99m}Tc-labeled oxidized LDL, and labeled antibodies against plaques and degradation products. Since an unstable plaque with rupture or erosion of the fibrous cap demonstrates activation of platelets and of the clotting cascade, other studies have focused on labeled platelets and fibrins. Apoptosis has also been demonstrated in macrophages as well as in smooth muscle cells of atherosclerotic plaques and is often observed in the fibrous cap of a ruptured plaque. Therefore ^{99m}Tc-labeled annexin V has also been used for specifically targeting the atherosclerotic plaque. Also matrix metalloproteinases (MMPs), excreted by macrophages and activated by plasmin as part of the inflammatory process in active atherosclerotic lesions, were labeled and tested. Many of the molecular probes developed for plaque imaging are linked with inflammation, a major component of vulnerable plaques. Labeled macrophages, monocytes, and lymphocytes were all used for imaging the inflammatory process. An overview of all the possible radiopharmaceuticals for imaging atherosclerosis can be found in a recent review.[5]

Challenges

There are a number of challenges in the molecular imaging of vascular plaques. Their small size (most are less than 5 mm in diameter) is close to the resolution limit of SPECT and

PET. Also, some arteries are located deep within the body, and in some regions, such as the coronary arteries, imaging is of lower quality because of artifacts related to cardiac and respiratory motion.[6] Most of the radiopharmaceuticals labeled with single-photon emitters have unfavorable imaging properties, including slow blood clearance and a low ratio of target (atherosclerotic plaque) to background (blood pool); they may also demonstrate affinity with nonspecific binding sites. Despite the large variety of probes labeled with single-photon emitters, none is being widely used in the clinical setting to identify vulnerable plaques. More research is needed to identify a suitable probe that will also yield a robust clinical imaging tool.

CLINICAL APPLICATIONS

Molecular Imaging of Atherosclerosis

Fluorodeoxyglucose Uptake in Carotid Plaque

In patients undergoing FDG PET/CT scans for cancer imaging, increased FDG uptake was reported in the vascular walls of 31% to 59% of patients older than 50 years,[7-9] the uptake being more evident with advancing age, male sex, and the presence of cardiovascular risk factors such as hypertension and hypercholesterolemia.[7,8,10,11] Rudd et al.[12] were the first to show, in a prospective study in eight patients imaged shortly after a transient ischemic attack (TIA), that FDG uptake was 27% higher in the symptomatic carotid artery than in the asymptomatic contralateral artery. Autoradiography confirmed the location of uptake in macrophages.[12] Coregistration of FDG PET and MRI indicated the presence of increased tracer uptake in arterial plaques in 10 of 12 patients with an embolic event, consistent with clinical symptoms. In addition, 25% of lesions determined to be nonstenotic by magnetic resonance angiography (MRA) in symptomatic patients had increased FDG activity in significantly inflamed plaques.[13] Plaques with unstable features, such as a large lipid core and intraplaque hemorrhage on MRI or echolucency on ultrasound, show higher FDG uptake than more stable lesions.[14-17] Lipid-rich necrotic plaques show higher FDG uptake than collagenous or calcified plaques.[14] In patients with severe carotid stenosis imaged prior to endarterectomy, an excellent correlation of FDG activity was reported with macrophage staining but not with plaque thickness, plaque area, or smooth muscle staining. This confirms that FDG can be used to assess the severity of inflammation in patients with carotid plaques.[18,19] Significantly increased carotid FDG activity had been demonstrated in patients with stroke.[20,21] FDG uptake in carotid vessels correlates with serum levels of C-reactive protein, a marker of systemic inflammation.[22,23] This observation is consistent with the definition of the "vulnerable patient" rather than "vulnerable plaque": the finding of one vulnerable lesion may increase the likelihood of other vulnerable lesions.[24] FDG activity in vessels was greater in patients with more than one cardiovascular risk factor and known coronary artery disease.[23] In addition, patients with type 2 diabetes mellitus and/or metabolic syndrome also demonstrated increased carotid FDG uptake.[25,26]

Monitoring Treatment With Fluorodeoxyglucose Uptake

Sequential PET/CT studies can be used to monitor the effect of lipid-lowering treatment on FDG uptake in atherosclerotic plaques. Reduced plaque inflammation after treatment with probucol, a lipid-lowering antioxidant, has been shown in an experimental rabbit model.[27] In human studies, high-resolution MRI has demonstrated that more than 12 months of simvastatin treatment were required to show regression of atherosclerotic plaques.[28-30] In a group of 43 patients with cancer who had increased FDG activity in the thoracic aorta or carotid arteries, half of the subjects who were subsequently randomly assigned to treatment with simvastatin showed reduced FDG uptake in the arterial wall as well as a decrease in LDL cholesterol by 30% and an increase in high-density lipoprotein (HDL) cholesterol by 15%. The second half of the study group received dietary management and did not show any change in FDG uptake.[30] On the other hand, dietary and lifestyle modifications in asymptomatic subjects caused a 65% reduction in the number of FDG-positive vascular regions.[31]

Fluorodeoxyglucose-Avid Arterial Wall Calcifications

Colocalization of FDG on PET and arterial calcifications on CT has been previously studied using PET/CT, with FDG-avid arterial wall calcifications observed in 2% to 14% of lesions.[7-9] Findings in the vascular wall of patients more than 50 years of age showed three different patterns: PET-negative and CT-positive, PET- and CT-positive, and PET-positive and CT-negative. Although there were many CT-positive atherosclerotic lesions (in 82%-92% of patients), FDG uptake indicating active inflammation was variable (15%-74%). Lesions with evidence of both past (CT-positive) and current (PET-positive) inflammation were seen in 10% of patients.[8,32] Other researchers have described none or a negative correlation between areas of calcification and FDG uptake.[33] The incongruence between FDG PET and CT findings may represent variations in the stage of the atherosclerotic process. The presence and extent of calcifications on CT define morphologic changes likely consistent with advanced disease, whereas FDG avidity demonstrates transient plaque inflammation, possibly indicating future complications.

Change in Plaque Fluorodeoxyglucose Uptake Over Time

Changes in vascular wall uptake over time in 50 patients with cancer and a mean age of 68 years who had repeat PET/CT scans 8 to 26 months apart were also reported. Changes in the pattern of vascular findings were observed in 48% of FDG-positive sites, compared with 4% of PET-negative foci and 7% of CT-positive lesions (Fig. 29.1).[32] Transient FDG uptake in the arterial wall was found in a group of 205 studies from 50 patients with a mean age of 49 years who underwent at least four PET/CT scans for a mean follow-up of 27 months.[33] The variable FDG uptake in the vascular wall suggests that inflammation may be a transient feature of a dynamic process, whereas calcifications may represent a chronic process or stable atherosclerosis.[32] This

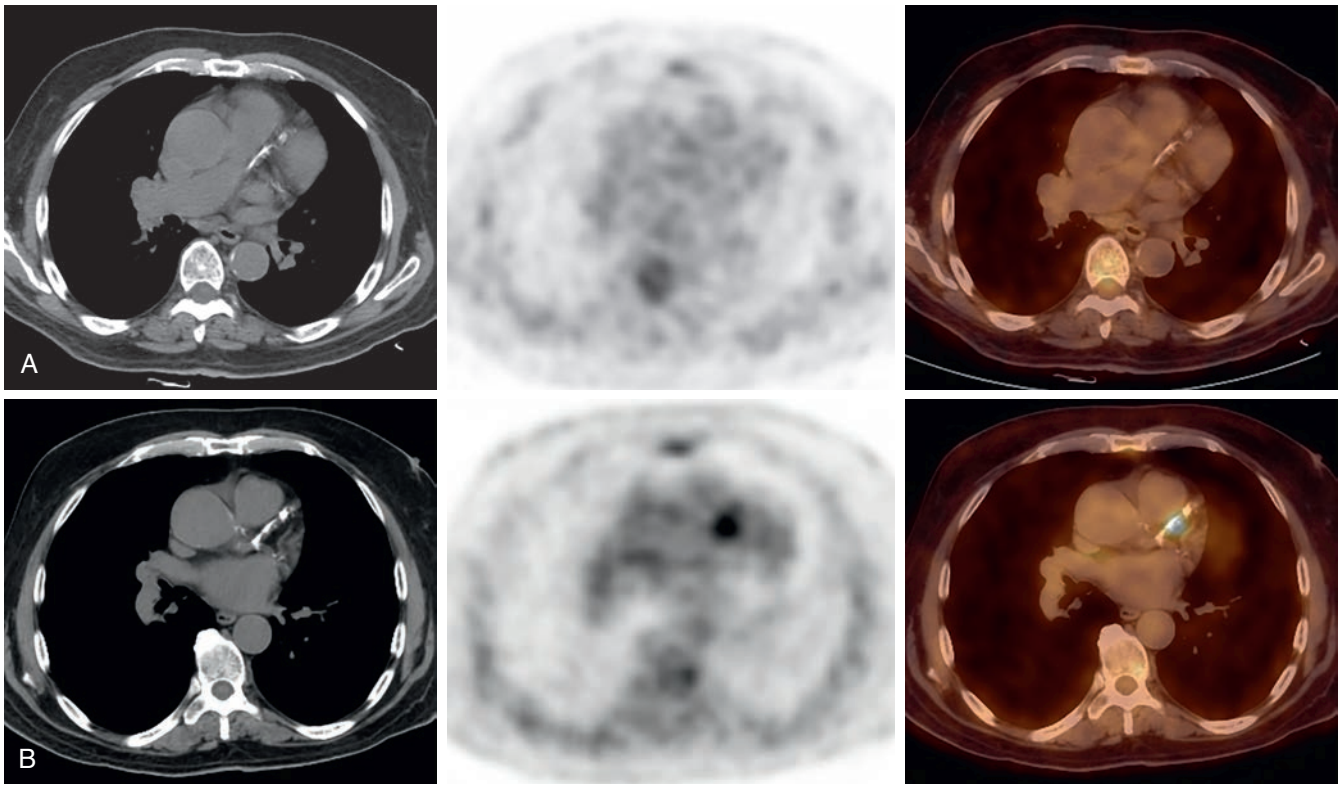

Figure 29.1 Changing pattern of vascular wall fluorodeoxyglucose (FDG) uptake in 70-year-old patient referred for routine follow-up after completion of chemotherapy for diffuse large B-cell lymphoma. Whole-body FDG positron emission tomography/computed tomography (PET/CT) images showed no evidence of FDG-avid disease. (A) Selected axial slice shows left anterior descending (LAD) coronary artery calcifications on CT *(left)* with no focal increased FDG activity on PET *(center)* or on the fused PET/CT image *(right)*. (B) On follow-up scanning 8 months after the previous study, CT shows that LAD calcifications have progressed *(left),* and there is also focal FDG activity in the LAD calcifications on the PET *(center)* scan and localized activity on the fused PET/CT scan *(right)*.

observation may have potential future implications for the design of trials for monitoring the response of vascular inflammation to therapeutic interventions.

Other Tracers for Plaque Imaging

The majority of data related to metabolic imaging of atherosclerosis refer to the use of FDG, mainly because of its wide availability and the vast clinical experience with its use accumulated over the last few decades. Because of the limitations of FDG, including the nonspecific nature of its uptake in various types of cells that metabolize glucose as well as the technically challenging imaging of the coronary vessels, other tracers are being sought and evaluated.

Active plaque calcification can contribute to plaque instability[34] and can be assessed with NaF, which can potentially better assess the coronary vessels than FDG owing to the lack of significant physiologic myocardial uptake and its high target-to-background ratio. It has been shown that NaF adsorbs to calcified deposits within plaque with high affinity and is selective and specific.[35] NaF PET/CT imaging can distinguish between areas of macro- and microcalcification. A group of 45 patients with cancer were assessed with FDG, NaF, and CT for the presence of inflammation, active calcium deposition, and calcifications, respectively. Of 105 lesions with NaF uptake, 77% showed calcification on CT and 14% showed increased FDG activity.[36] It has been hypothesized that in early atherosclerosis, only inflammatory changes and therefore only FDG uptake can be seen, whereas later during the course of this process, there is also active calcification, reflected by uptake of both FDG and NaF. At a late stage, when the density of calcium deposits exceeds a certain threshold, calcifications would also become visible on CT. When calcification and mineralization exceed the inflammatory process, uptake of NaF but not of FDG would be found in calcified lesions seen on CT. At the final stage of dense calcification with no significant calcium turnover, lesions would be seen only on CT.[24]

^{99m}Tc-labeled LDL has been shown to accumulate in experimental atherosclerotic plaques in rabbits.[37] In clinical studies, a fourfold greater uptake was found in carotid endarterectomy macrophage-rich specimens than in fibrotic specimens.[38] Owing to slow blood clearance, however, this tracer was not suitable for in vivo imaging. ^{99m}Tc-labeled oxidized LDL is taken up by macrophages and has a more rapid blood clearance. It was detected at 150% higher levels in 10 of 11 plaques than in normal arterial segments and therefore provides better image quality.[39] Indium-111 (^{111}In)- or ^{99m}Tc -labeled antibodies against plaque and its degradation products, fibrin and platelets, have also been used for the imaging of atherosclerosis in an experimental setting.[40] ^{111}In–labeled polyclonal human immunoglobulin (Ig) G contains an Fc unit that binds to macrophage receptors.

It showed a poor target-to-background ratio in rabbits, whereas in humans uptake was found in carotid atheromas in 86% of patients, with no correlation with ultrasound findings.[41]

In patients with known cardiovascular events, imaging with ^{111}In-labeled platelets correlated with plaque burden and ulcerations seen on ultrasound.[42,43] However, blood clearance of labeled platelets is slow, so imaging cannot be performed until 48 hours after the injection. In addition, discontinuation of antiplatelet medication is needed, which cannot be considered in patients with suspected vascular events. Fibrin fragment E1 labeled with ^{123}iodine and ^{99m}Tc can detect thrombi in animals with deep venous thrombosis.[44] This agent clears rapidly from the circulation and has good imaging qualities. At present there are no reports on the use of this tracer in the evaluation of atherosclerosis.

^{99m}Tc–labeled annexin V has been used for specific targeting of active atherosclerotic lesions. Uptake of ^{99m}Tc–annexin V has been reported in experimental models of aortic lesions[45] as well as in patients with carotid artery disease.[46] The role of this substance to assess apoptosis is limited by the lack of specificity. ^{99m}Tc–annexin V binds to phosphatidylserine on platelets within the thrombus, but because thrombosis occurs in vulnerable plaques, this feature represents only a relative limitation for imaging with ^{99m}Tc–annexin V.[47]

Lymphocytes constitute at least 20% of infiltrating cells in vulnerable plaques. Therefore the interleukin-2 (IL-2) receptor, being overexpressed on activated T lymphocytes, may represent an attractive biomarker for plaque vulnerability. Radiolabeled IL-2 was therefore tested for imaging the lymphocytic infiltration in carotid plaques. ^{99m}Tc-IL-2 was found specific for imaging activated T lymphocytes in the carotid plaque. A significant correlation was found between the number of CD25+ lymphocytes and the total number of CD25+ cells in the plaque and the tracer uptake in the plaque.[48]

Preliminary work using ^{11}C-PK11195, a selective ligand of a translocator protein with 20 times greater density expression on macrophages than on vascular smooth muscle cells, has been reported. This tracer binds to macrophage-rich regions in human carotid plaques,[49] and promising results have been reported in patients with vasculitis.[50]

Other potentially useful tracers include ^{68}Ga-DOTATATE, which binds to somatostatin receptors subtype 2 expressed by macrophages,[51] and ^{11}C– or ^{18}F–labeled choline, which is taken up by macrophages, undergoes phosphorylation and metabolism to phosphatidyl choline, and is incorporated into the cellular membrane.[52,53] In an experimental model, ^{18}F–labeled choline uptake correlated better than FDG uptake with fat staining and macrophage-positive areas.[53] In patients with cancer, ^{11}C–labeled choline was not taken up by the normal vascular wall or by calcified vascular wall lesions.[52]

Molecular Imaging of Aortic Pathology

Abdominal Aortic Aneurysm

Increased FDG activity has been reported in patients with asymptomatic abdominal aortic aneurysms (AAAs), probably owing to the presence of transmural inflammation and the accumulation of FDG in macrophage aggregates.[54,55] A possible association between increased FDG uptake and AAA expansion and rupture has been suggested.[56] Higher FDG uptake in AAA has been associated with higher wall stress[57] and correlated with instability and macrophage infiltration.[58] Aneurysmal dilatation develops after an inflammatory phase with increased FDG activity.[59] An inverse relationship between FDG uptake and future expansion of the aneurysm, as measured by Doppler ultrasound, was found in 25 patients with AAAs who underwent routine surveillance over a period of 12 months.[60] In patients with asymptomatic AAAs, no increase in FDG uptake was observed in large lesions referred to surgery.[61] A marked reduction in cell density in AAAs correlated with low FDG activity.[61] Increased FDG activity is more frequent in small aneurysms and in lesions with inflammatory changes, which are more often symptomatic and require direct surgical intervention (Fig. 29.2).[58]

Aortic Dissection

Thoracic aortic dissections are uncommon but are associated with high mortality rates, 10% to 30% within 30 days of diagnosis.[62,63] The disease is mediated by inflammatory changes.[64] In one study, FDG PET/CT was performed in 33 patients with acute aortic syndrome. Increased FDG activity (positive result) was seen in one-third of the patients, 82% of whom showed progression of disease; 55% of patients with negative PET results showed stable disease on follow-up.[65] In another study, FDG uptake in 28 patients with acute or chronic dissection was compared with that in a group of 14 age-matched controls for prediction of adverse outcomes. Patients were followed for up to 6 months after PET/CT. Within a subgroup of eight patients with unfavorable outcomes (death from cardiovascular causes, rupture or progression of aortic dissection, requirement for surgical repair, or cardiovascular events during or after initial hospitalization), FDG uptake was significantly higher in those with acute dissecting aneurysms than in controls. It was also higher at the site of maximum dissection in patients with unfavorable outcomes than in those with favorable outcomes. Multivariate analysis showed that the mean SUV of FDG uptake at the site of maximum dissection independently predicted an unfavorable outcome. The investigators concluded that FDG PET/CT may play a role in predicting the prognosis of patients with type B aortic dissection and may also be useful in selecting patients at high risk for near-term complications requiring early surgery.[66]

More clinical data from larger and longitudinal patient cohorts will establish the role of FDG PET/CT in guiding patient selection for surgery and for follow-up of patients with aortic pathology.

Molecular Imaging of Vasculitis

In vasculitis, molecular imaging techniques can assist in the early diagnosis of inflammatory changes in the vascular walls, which are potentially reversible. This inflammatory process precedes anatomic changes; therefore, at the early stage, anatomic imaging modalities are unreliable. MRI is probably the best method to

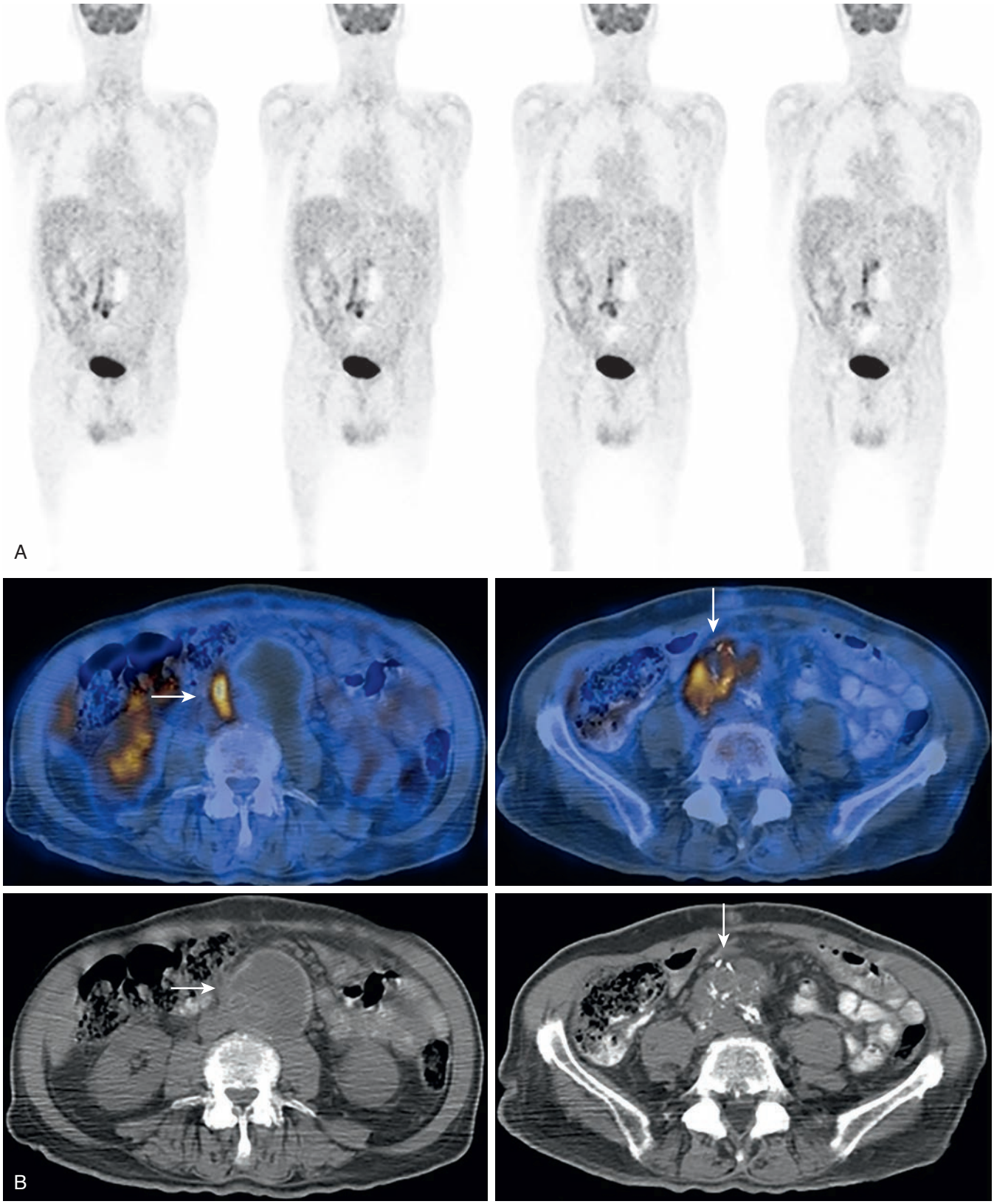

Figure 29.2 Fluorodeoxyglucose (FDG) uptake in an infected graft inserted in an abdominal aortic aneurysm (AAA). The patient, a 79-year-old diabetic man, had undergone surgical repair of a dissecting AAA and implantation of a bi-iliac vascular graft 10 years prior to the current examination. He presented with severe abdominal pain. Computed tomography (CT) angiography demonstrated a thickened posterior wall of the aneurysm. (A) Selected coronal positron emission tomography (PET) slices demonstrate a linear area of intense abnormal FDG uptake in the lower abdomen and upper pelvis. (B) The uptake is localized by PET/CT at its upper level to a thickened AAA wall (left column, *arrows*), consistent with active inflammation, and at the pelvic level to a soft tissue mass surrounding the right component of the graft and surgical clips (right column, *arrows*), consistent with an infected right vascular graft.

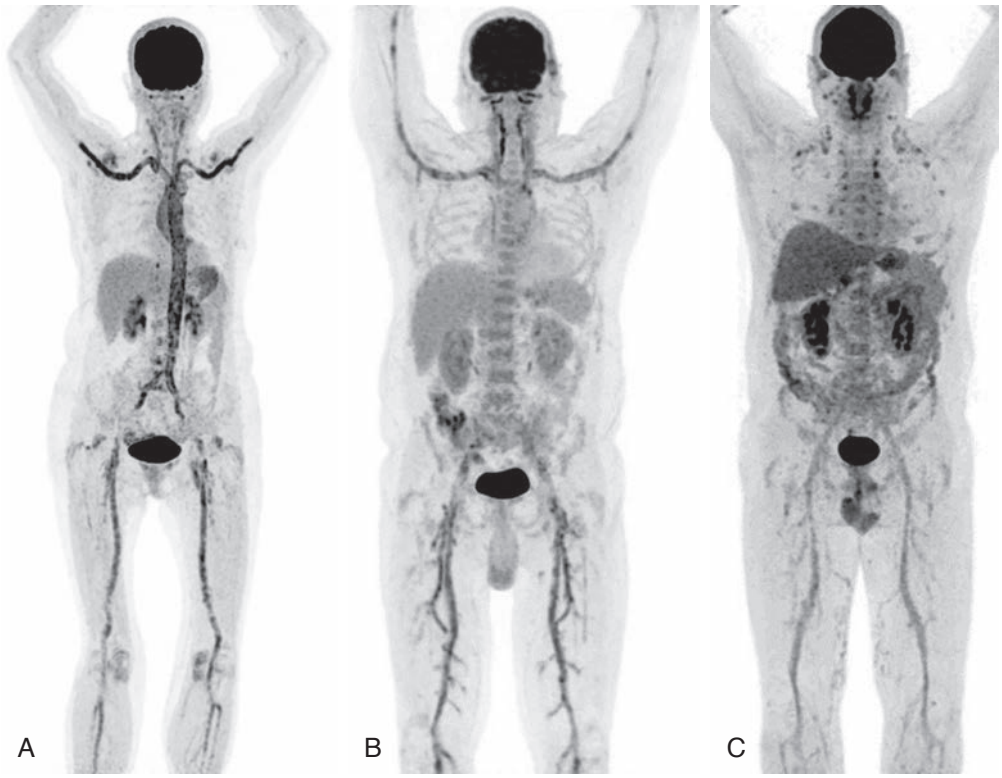

Figure 29.3 Fluorodeoxyglucose uptake patterns in different vasculitis types and associated diseases. (A) Giant cell arteritis with intense uptake in the aorta and all the large vessels. This scans also shows increased uptake in the shoulders, hips, and knees, pointing to polymyalgia rheumatica. (B) Uptake in both large (subclavian and femoral arteries) and medium-sized arteries in the legs, pointing to polyarteritis nodosa. (C) Another example of polyarteritis nodosa, but also notice the uptake in the costochondral and costovertebral joints and the ears, indicating polychondritis.

evaluate and reveal structural vascular abnormalities. However, in the early setting without anatomic changes, MRI cannot detect inflammation. FDG PET is able to identify vasculitis at an early stage, but because of the limited spatial resolution of the imaging device (4-5 mm), it is able to visualize only inflammation of the aorta and the large and medium-sized arteries. Based on which vessels are involved, FDG PET is able to diagnose giant cell arteritis (GCA) (involvement of the aorta and all large vessels), Takayasu arteritis (mainly involvement of the vessels in the thoracic region), and polyarteritis nodosa (involvement of the medium-sized arteries, which can be visible in the upper legs and arm (Fig. 29.3).[67] Moreover, FDG PET is able to diagnose associated diseases, such as polymyalgia rheumatica (PMRI) or polychondritis (see Fig. 29.3). For these reasons, FDG PET is accepted as a major imaging technique for the early detection of vasculitis.[68] In addition, FDG PET has been shown to be superior to anatomic imaging modalities and is being increasingly used to assess response to therapy in documented cases of vasculitis.[68,69]

FDG PET has become increasingly important for the diagnosis of large vessel vasculitis, particularly in cases with nonspecific presentation, such as fever of unknown origin, malaise, and weight loss. Vasculitis can be diagnosed early with FDG PET because the inflammatory process precedes morphologic changes.[68] Also, FDG PET detects more involved regions than MRI.[68,70] The overall reported sensitivity and specificity of FDG imaging in untreated patients with large vessel vasculitis and increased inflammatory markers are in the range of 77% to 92% and 89% to 100%, respectively.[69,71-74] In the largest prospective study involving 35 patients with biopsy-proven GCA, the sensitivity of FDG imaging was 83%.[75] Increased FDG activity at the level of the aortic arch and subclavian arteries has been reported in 56% and in the lower limbs in 64% of cases.[76-79] In TA, increased FDG activity was noted in the aorta and brachiocephalic, carotid, and subclavian arteries and less frequently in the pulmonary arteries.[80] False-negative results have been reported in patients with temporal arteritis, caused either by high physiologic FDG uptake in the brain or the adjacent skin or by the small diameter of the involved vessel.[73] One study compared FDG PET, contrast-enhanced CT, MRI, and angiography in 18 patients with biopsy-proven TA. FDG PET had a sensitivity of 92%, a positive predictive value of 85%, and specificity and negative predictive value of 100% and was superior to morphologic imaging both in early diagnosis of inflammatory changes and for monitoring treatment effectiveness.[73] In another study, the role of FDG PET/CT was assessed in 39 patients with TA and 40 controls; it correlated with disease activity as defined by clinical and biochemical markers. Maximum SUV (SUV_{max}) was significantly higher in patients with active disease than in those with inactive disease and controls. For an SUV_{max} cutoff of 2.1, active TA was detected with a sensitivity of 92.6%, specificity 91.7%, a

positive predictive value of 96.2%, and a negative predictive value of 84.6%. SUV_{max} was also significantly higher in patients in whom relapse occurred during treatment than in patients with stable disease during treatment.[80]

A correlation between the intensity of vascular FDG activity and inflammatory markers has been found in GCA.[81] In TA, SUV measurements were found to be useful only for serial follow-up studies, showing a decrease in patients whose disease responded to therapy.[82] FDG PET/CT was superior to MRI in monitoring GCA disease activity during immunosuppressive therapy. FDG imaging reliably detected the earliest improvement after treatment, in good correlation with inflammatory markers and clinical symptoms, whereas morphologic changes seen on MRI, such as wall thickening, resolved only later.[66] In a small number of patients with fever of unknown origin and negative workup results, FDG PET correctly diagnosed GCA, demonstrating findings that disappeared on follow-up studies after the administration of steroids (Fig. 29.4).[83] In patients who have previously received immunosuppressive therapy, FDG imaging is unreliable for assessment of inflammation.[74,81]

FDG PET/CT is a sensitive and specific imaging modality in the diagnosis of large vessel vasculitis. It can assist in visualizing early inflammatory changes in patients with active disease, earlier than morphologic imaging techniques, thus enabling prompt treatment and possibly preventing occlusive complications. It can also be used as an index of disease activity and response to immunosuppressive therapy, but it appears to be unreliable in diagnosing vasculitis in patients receiving steroids.

Molecular Imaging of Vascular Graft Infection

Molecular imaging modalities have a major role in the assessment of vascular graft infection; the basic principles already described for other vascular diseases apply also here.

Both labeled white blood cells (WBCs) and FDG PET have been used for the detection of infected vascular grafts, with FDG PET having several advantages over labeled WBC scintigraphy (higher target-to-background ratios, shorter study duration, no need for handling of the blood of potentially infected patients, and quantification possibilities).

Because of the relatively high incidence of nonspecific morphologic abnormalities in patients with infected vascular grafts, molecular imaging modalities have been used to assess the clinical and functional significance of anatomic findings with significant clinical consequences on optimized early diagnosis, defining the best therapeutic strategy. The major advantages of molecular imaging are related to its ability to define functional or metabolic alterations. However, it provides only scarce morphologic data. Therefore hybrid SPECT/CT and PET/CT are of particular value in patients with suspected infections of vascular prostheses.[84,85] Accurate spatial localization of abnormal radiotracer foci to a graft or only to the adjacent soft tissues may be impossible unless these highly specific functional or metabolic images with low background activity and therefore limited structural information are combined with an anatomic road map. Precise alignment of metabolic and anatomic images is crucial, particularly in the extremities and in regions prone to even involuntary patient motion between imaging sequences, which may harbor an infectious process in a structure located very close to several others (as is the case with vascular grafts).

Radiolabeled White Blood Cell Imaging

Scintigraphy with radiolabeled WBCs has been used for assessment of suspected prosthetic graft infection. The overall sensitivity of WBCs for diagnosis of infected grafts ranges between 53% and 100%.[86,87] Although the circumstances have not been described in detail, false-negative results may be related to previous or concomitant antibiotic treatment or to the duration of symptoms.[86] The specificity of WBC scintigraphy ranges between 50% and 100% as well.[86,87] False-positive results have been reported in the presence of uptake in lymphocele, hematoma, thrombosis, bleeding, and pseudoaneurysms. Physiologic tracer uptake can be found in recently placed noninfected grafts within 1 month after surgery.[88] Many of the false-positive or false-negative studies can be overcome by using the correct acquisition criteria (at least dual time-point imaging) and the correct interpretation criteria (only uptake increasing over time is consistent with infection).

A study of 40 patients with suspected infection of abdominal aortic grafts compared the performance indices of ^{111}In–labeled WBCs and MRI. The positive predictive value of MRI was higher than that of WBC scintigraphy, although the negative predictive values were similar, around 80%.[89] SPECT studies performed with ^{99m}Tc–labeled WBCs are of better quality and therefore easier to interpret than studies using ^{111}In-labeled WBCs. ^{99m}Tc WBC imaging has reported sensitivity and specificity in the range of 82% to 100% and 75% to 100%, respectively.[86,87] The modality is of significant clinical value in cases where findings of other imaging modalities are inconclusive. False-positive results can be due to cross-labeling of red blood cells and platelets and by nonspecific perivascular accumulation of granulocytes early after surgery in healing wounds or graft anastomoses.[86,87]

In a study involving 82 patients with suspected infection, the use of labeled WBC SPECT/CT contributed significantly to the precise anatomic localization of suspicious foci of increased tracer uptake, thus confirming the diagnosis of infection and subsequently the precise localization and delineation of its extent in up to half of the patients.[84] This study included 24 patients with suspected vascular graft infection who were scanned with ^{111}In WBCs, with confirmed infected vascular implants in 10 patients. Overall, SPECT/CT provided more accurate data than planar imaging and contributory information in 67% of patients with suspected vascular graft infection. In one patient, SPECT/CT was falsely positive, showing focal vascular graft uptake that was unconfirmed by further follow-up and clinical outcome.[84] The role of ^{99m}Tc WBC SPECT/CT was also assessed retrospectively in 11 patients with suspected arterial graft infection. On the basis of clinical outcome, ^{99m}Tc WBC SPECT/CT identified 6 patients as having infection (true-positive results) and 4 as not having infection (true-negative results). One false-positive result was seen in a patient imaged 2 years after insertion of a thoracoabdominal aortic endograft.[90]

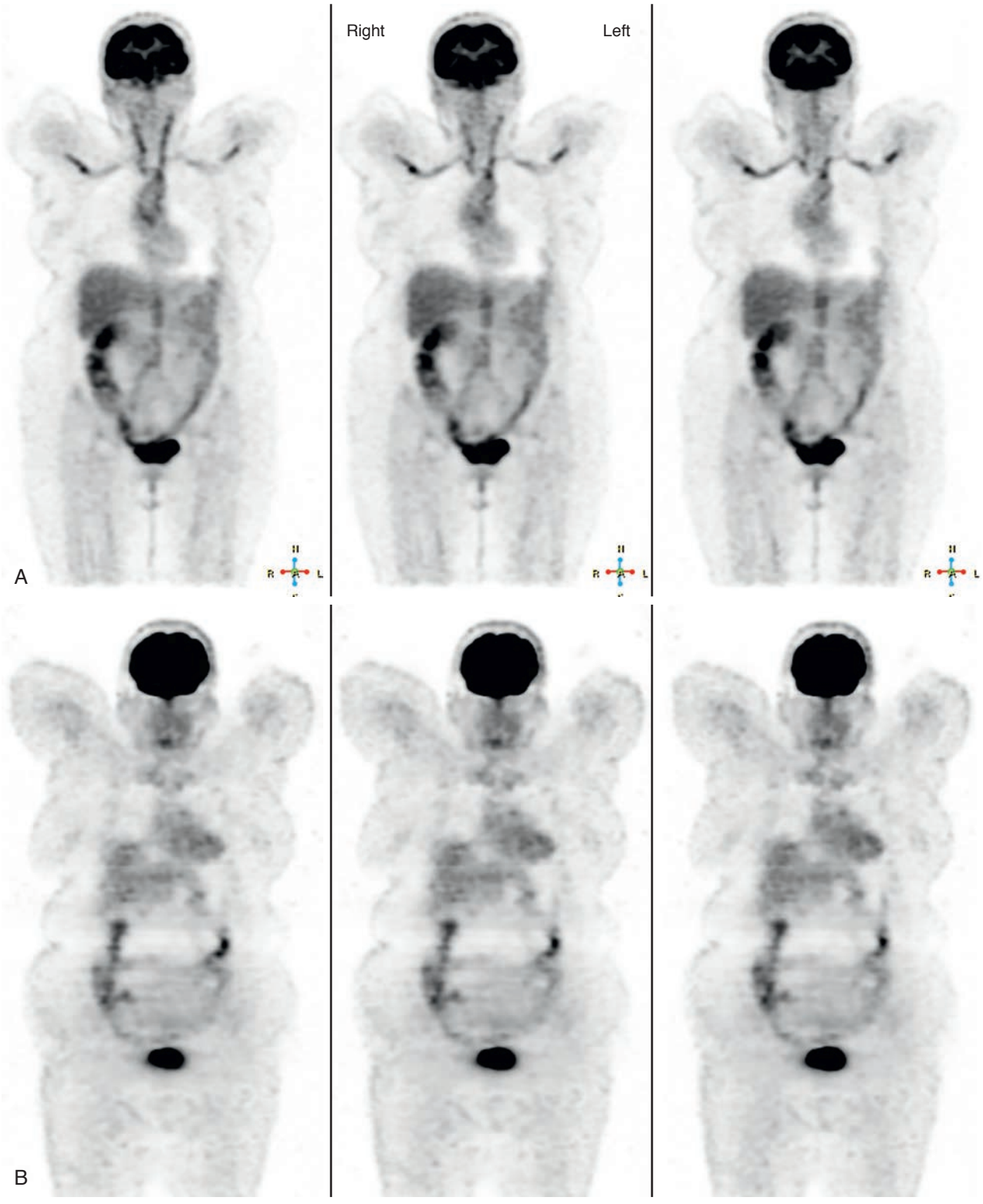

Figure 29.4 Fluorodeoxyglucose (FDG) uptake in the diagnosis and follow-up of vasculitis. A 65-year-old woman was referred for the assessment of fever of unknown origin. Results of computed tomography (not shown) were negative. (A) Selected coronal positron emission tomography slices demonstrate intense abnormal FDG uptake along the large vessels, including the ascending thoracic aorta, aortic arch, and subclavian and carotid vessels bilaterally. Less intense uptake can be seen along the abdominal aorta and iliac vessels, consistent with large vessel vasculitis. Biopsy confirmed Takayasu arteritis. (B) Follow-up imaging a year after treatment shows significant improvement.

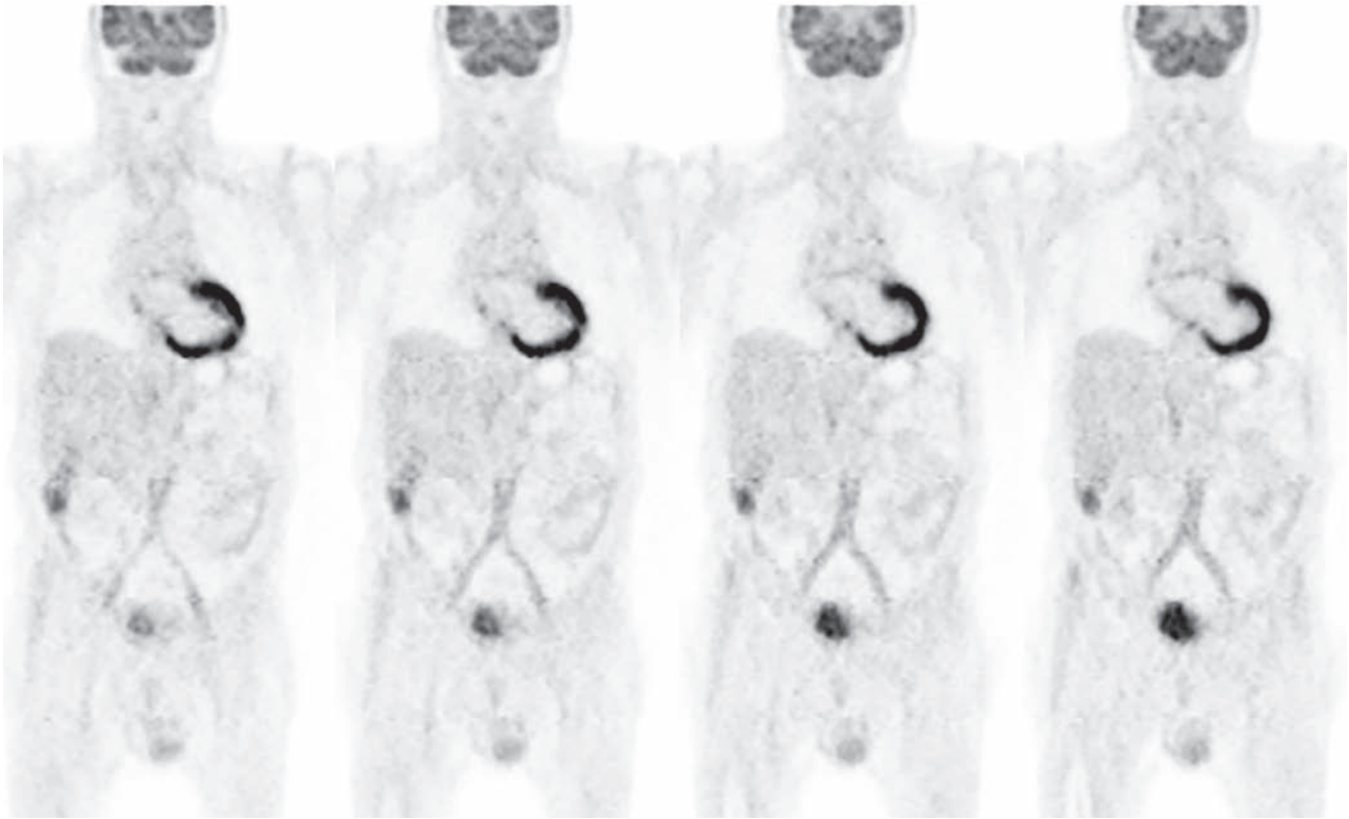

Figure 29.5 Diffuse linear fluorodeoxyglucose (FDG) uptake along a noninfected aortobifemoral graft. This 82-year-old man was diagnosed with cancer of the larynx 2 years prior to the current examination. He was referred for reevaluation at completion of radiochemotherapy. FDG positron emission tomography/computed tomography (selected serial coronal slices) does not demonstrate pathologic uptake consistent with residual viable tumor. There is increased linear FDG uptake in the abdominopelvic region along an aortobifemoral Dacron graft implanted 16 years earlier, representing an inflammatory "foreign-body reaction." The patient had no evidence of infection of the vascular prosthesis during a follow-up of 48 months. (Note also the physiologic FDG activity in the ascending colon.)

Fluorodeoxyglucose Positron Emission Tomography

Stand-alone FDG PET has a high sensitivity for vascular graft infection, but specificity is low in comparison with CT.[91] Increased FDG uptake may also occur in native vessels. False-positive results can be due to increased radiotracer activity along implants, grafts, and stents or in healing postoperative scars as well as to the presence of known or unknown malignant disease.[92] A pattern of linear FDG uptake of mild to moderate intensity found along a vascular graft with no evidence or suspicion of infection can be attributed to a chronic aseptic inflammatory reaction to a synthetic graft that is mediated by macrophages, fibroblasts, and foreign-body giant cells (Fig. 29.5). This pattern is observed more frequently in recently implanted grafts but can persist for years after surgery.[93] Keidar et al. studied FDG uptake in 107 noninfected vascular graft prostheses in patients scanned for other, mainly oncologic reasons. Diffuse, homogeneous uptake was found in more than half of the grafts, more prevalent in Gore-Tex than in Dacron grafts. The FDG uptake in these synthetic grafts showed no change in intensity for a follow-up of up to 16 years.[94] Although a focal pattern of intense abnormal FDG uptake is indicative of infection, the use of PET alone is limited for diagnosis of an infected vascular graft mainly by its inability to precisely define the anatomic location of the increased radiotracer focus. Correlation of functional information provided by FDG PET with the anatomic data of CT or MRI in separately performed imaging procedures of the lower limbs is not accurate enough for localizing a focus of increased FDG uptake to the vascular prosthesis itself or to the surrounding soft tissues.

Hybrid PET/CT has improved the specificity of FDG imaging. The presence, intensity, and pattern (focal or diffuse) of increased radiotracer activity is defined on the PET component, and the precise localization of abnormal FDG foci to the graft or to adjacent soft tissues is determined by the CT component (Figs. 29.6 and 29.7). In patients with complicated regional anatomy after multiple surgical procedures, PET/CT can pinpoint to the infected implant and differentiate between various suspicious findings on CT. In patients with multiple grafts, PET/CT can diagnose or exclude infection involving one or more specific prostheses.

Keidar et al. studied 39 patients with suspected graft infections. FDG-avid foci were noted in 30 of 39 patients on PET/CT, allowing for the accurate localization of 16 foci to the grafts with a sensitivity of 93%, specificity of 91%, positive predictive value of 88%, and negative predictive value of 96% for the diagnosis of prosthetic involvement. This enabled accurate

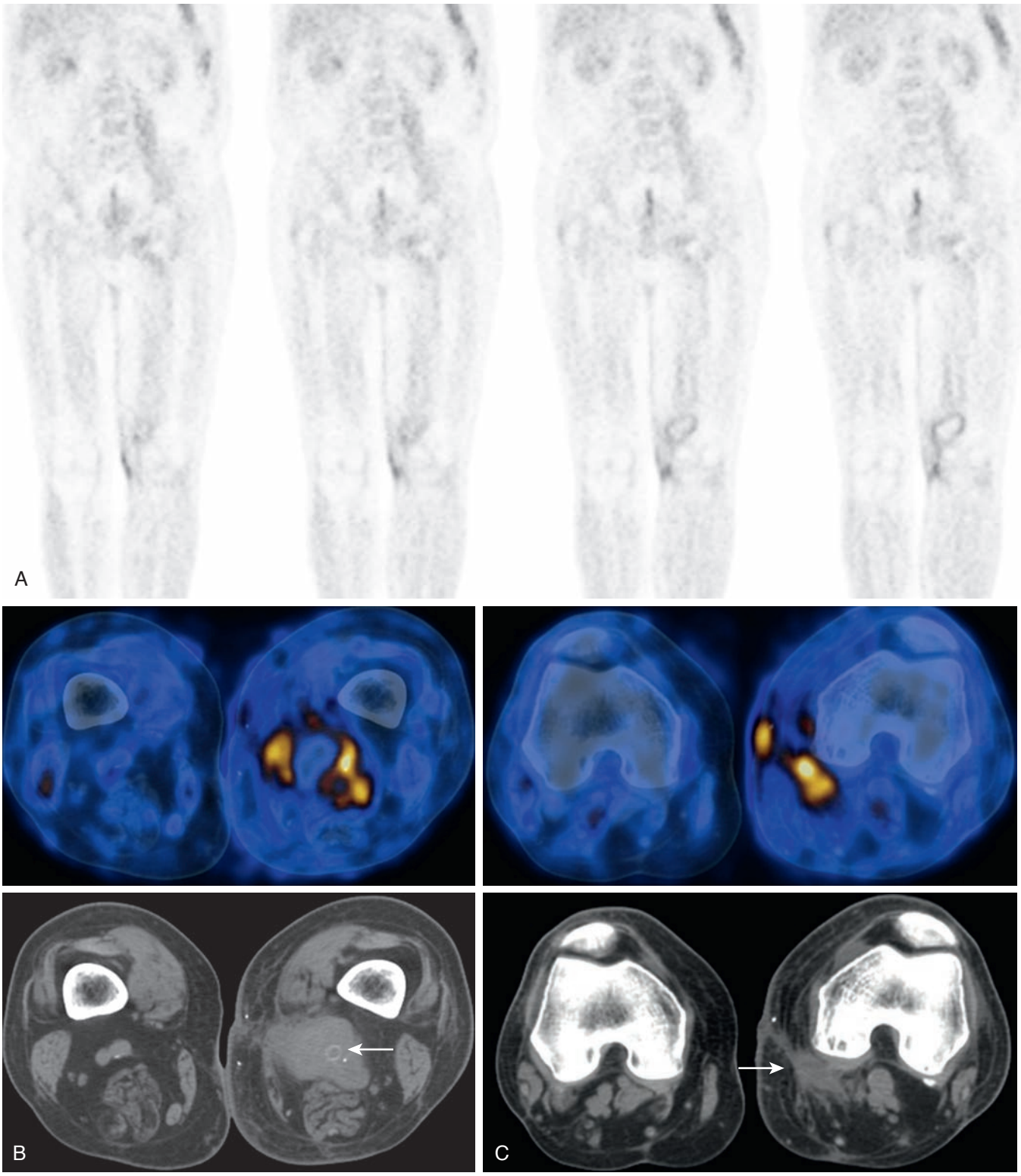

Figure 29.6 Abnormal focal fluorodeoxyglucose (FDG) uptake in an infected graft and soft tissue. The patient, a 65-year-old diabetic man with severe peripheral vascular disease, underwent implantation of a left femoropopliteal synthetic vascular graft 2 months prior to the current examination. The patient presented with pain and swelling and a pus-secreting surgical wound at the lower anastomosis of the graft at the level of the proximal left calf. (A) Coronal positron emission tomography (PET) slices demonstrate the presence of focal intense FDG uptake at the medial aspect of the proximal left calf. (B) and (C) The uptake is localized by PET/computed tomography to a soft tissue edematous mass surrounding and involving the lower end of the prosthesis (B, *arrow*) as well as in postsurgical soft tissue changes at the level of the infected surgical wound (C, *arrow*).

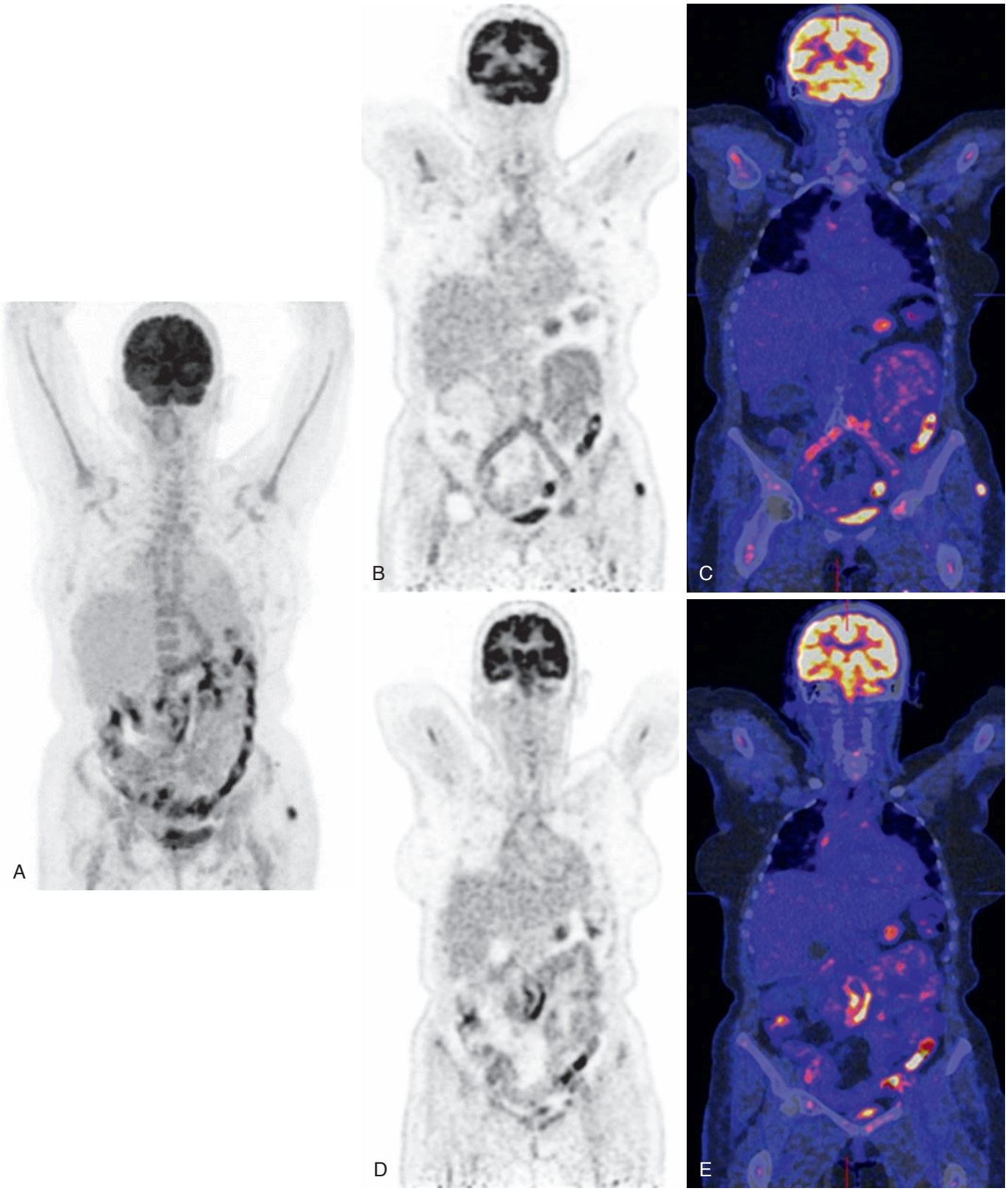

Figure 29.7 Normal and abnormal fluorodeoxyglucose (FDG) uptake in an aortobifemoral vascular graft. (A) Coronal maximum intensity projection showing heterogeneous uptake at the graft and diffuse physiologic uptake in the colon. (B and C) Selected coronal FDG positron emission tomography (PET) and fused PET-computed tomography (CT) images of the iliac part of the prosthesis showing homogeneous uptake because of reactive inflammation. (D and E) Selected coronal FDG PET and fused PET-CT images of the aortic part of the prosthesis showing heterogeneous focal and intense uptake. This part of the prosthesis is infected.

differentiation between graft and surrounding soft tissue infection.[95] In a prospective study of 96 suspected infected grafts in 76 patients, focal FDG uptake had a positive predictive value of 93% for the diagnosis of graft infection and a negative predictive value of 97%, compared with 89% and 67%, respectively, for a pattern of inhomogeneous tracer activity. Only focal FDG uptake and irregular graft boundaries on CT were significant predictors of vascular graft infection, whereas smooth lesion boundaries with no focal FDG uptake had a positive predictive value of less than 5%. The overall diagnostic accuracy of FDG PET/CT was more than 95% in 75% of vascular grafts.[96] The incremental value of fused images of FDG PET and CT was assessed in 25 patients with suspected vascular graft infections. In 15 patients, infection was proven by culture. FDG PET had a sensitivity of 93%, a specificity of 70%, a positive predictive value of 82%, and a negative predictive value of 88%; for CT, these values were significantly lower: 56%, 57%, 60%, and 58%, respectively. The results were improved when FDG and CT data were fused.[97]

LIMITATIONS AND RISKS

The limited resolution of the current technology of molecular imaging procedures, around 4 to 5 mm, is overcome by the unique information this technique offers on both function and structure, which is often unattainable with morphologic imaging.

Another important limitation is the development of new molecular probes for imaging. There is significant difficulty in the radiolabeling of new substrates and in the development of new radiopharmaceuticals for clinical indications. Novel molecular probes for SPECT and PET are currently in the pipeline of basic and clinical research.

The combined modalities, SPECT/CT and PET/CT, offer greater detail and a higher level of accuracy. These studies, however, are associated with higher radiation exposure for the patient. For instance, most molecular imaging procedures result in radiation doses between 1 and 10 mSv and the effective dose for FDG PET/CT is around 4 mSv. With the use of hybrid devices, the burden of radiation derives from both the radiopharmaceuticals and the CT component. Advances in PET/CT scanner technology allow reduced injected activity of FDG and hence lead to a decrease in the effective dose. In addition, advances in CT technology, as well as careful planning of CT for either attenuation correction or diagnostic purposes can further lower the overall radiation dose.

FUTURE ADVANCES

Vascular imaging is challenging to manage. It is therefore important to gather a wide expertise in a multidisciplinary vascular team approach involving vascular internal medicine and surgery and experienced nuclear (hybrid) imagers to perform the optimal diagnostics resulting in dedicated treatment and follow-up for each individual patient. It is also important to standardize the acquisition protocols and interpretation criteria throughout the world, not only to provide the nuclear medicine physicians with criteria indicating when to declare a scan positive but also to be able to better compare research results. Some efforts to provide this standardization have recently been taken.[98] Hybrid PET/MR technology has been developed and is now available for clinical use. The total radiation exposure in a combined PET/MR study is limited to that resulting from the administration of the PET tracer only. The combination of PET, with its sensitivity in the picomolar range, with the high soft tissue contrast offered by MRI may play an important role in future imaging algorithms.[99] Bini et al. have recently compared PET/MR with PET/CT for carotid artery imaging and have also assessed various technical variables associated with the new technology (i.e., MR-based attenuation correction, carotid coil for PET/MR). Excellent correlations were reported, supporting the use of PET/MR for quantitative assessment of the inflammatory burden of the carotid arteries.[100]

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30 CHAPTER

Intravascular Ultrasound

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INTRODUCTION

Catheter-based endovascular techniques are increasingly being used in vascular surgery, with demand for detailed intraoperative imaging increasing accordingly. Intravascular ultrasound (IVUS) is a catheter-based endoluminal guidance system that was initially utilized in interventional cardiology in the 1980s.[1-5] Various trials and analyses of IVUS-guided versus angiographic-guided percutaneous coronary intervention (PCI) have concluded that IVUS-guided PCI results in similar or improved outcomes overall.[6-15] In fact, IVUS has been shown to be effective in improving procedural results and reducing restenosis and the need for reintervention in PCI. Since its initial clinical use in coronary artery interventions, IVUS has been shown to have a variety of applications in vascular intervention because of its ability to provide detailed pretreatment diagnostic information on the extent and severity of disease, to guide treatment intraoperatively, and to immediately assess the treatment's success.[16]

Abstract

The use of intravascular ultrasound (IVUS) has broadened from its initial use in percutaneous coronary interventions to become applicable and beneficial in the treatment of aortic, arterial, and venous pathologies as well. The benefits of IVUS include its ability to be used intraoperatively to provide superior visualization of arterial wall and plaque morphology, to aid in choosing appropriately sized balloons and stent-grafts by providing accurate luminal measurements, and its capacity to evaluate the effectiveness of treatment postoperatively.

Key Words

intravascular ultrasound
IVUS
imaging
imaging modalities
endovascular imaging
arterial imaging
venous imaging
vascular diagnostics
vascular imaging

BASIC PRINCIPLES

Creating the Image

Technology

IVUS creates axial images perpendicular to the long axis of the catheter by transmitting sound waves covering 360 degrees around the tip of the catheter, which is delivered into the lumen of the vessel over a guidewire. This is achieved either mechanically or electronically. The mechanical system, produced by Boston Scientific Corporation, utilizes a flexible high-torque catheter with a quickly rotating ultrasound transducer located at the tip. Electronic systems, produced by Volcano Corporation, utilize 64 miniaturized transducer elements located circumferentially around the tip of the catheter that are activated in sequence to produce an array of images. Information collected by IVUS transducers is reconstructed, displayed, and recorded visually on a separate console. This workstation facilitates the collection of measurements such as the diameter, circumference, and area of a vessel and allows for the capture of still images and video loops (Fig. 30.1).

In working with IVUS, it is important to choose the appropriate catheters and ultrasound frequencies to obtain

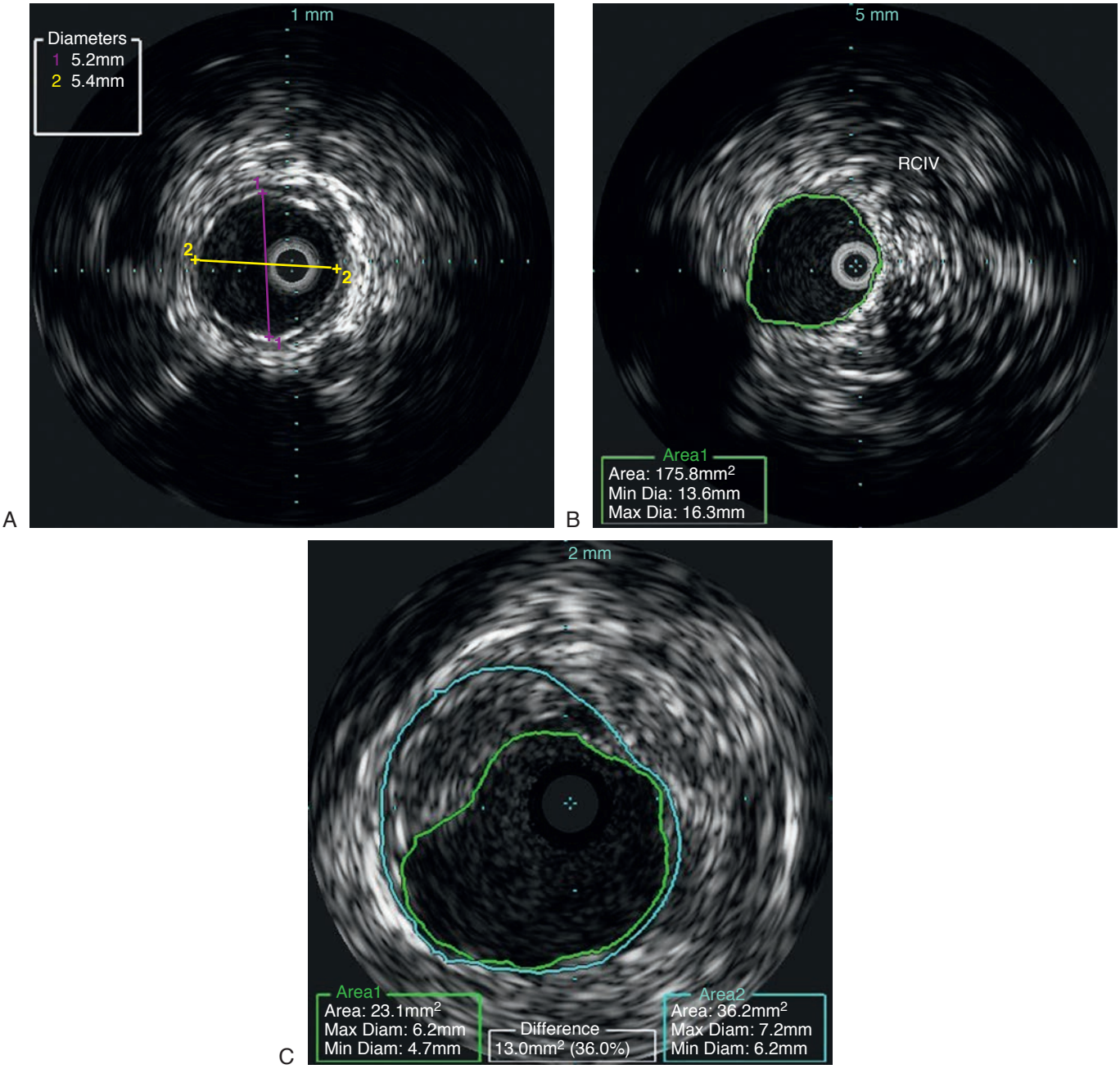

Figure 30.1 It is possible to take a variety of measurements on the intravascular ultrasound console, including diameters (A) and area (B). It is also possible to find the amount of thrombus present in a vessel by measuring the area of the lumen and the area of the vessel (C). *RCIV*, Right common iliac vein.

TABLE 30.1 Table of Catheters for Noncoronary Vascular Imaging[a]

Catheter	Guidewire (in)	Frequency (MHz)	Sheath (F)	Working Length (cm)	Imaging Diameter (mm)	Manufacturer
Opticross	0.018	30	6	135	12	Boston Scientific
Eagle Eye Platinum	0.014	20	5	150	20	Volcano
Visions PV 014	0.014	20	5	150	20	Volcano
Visions PV 018	0.018	20	6	135	24	Volcano
Visions PV 035	0.035	10	8.5	90	60	Volcano

[a]In the United States, Boston Scientific Corporation and Volcano Corporation are the major manufacturers of FDA-cleared intravascular ultrasound (IVUS) systems.

the best possible imaging.[17] Higher frequencies improve image resolution but decrease the depth of penetration. This makes them ideal for smaller vessels, as they provide more detail, with probes delivering 45 MHz being well suited to coronary vessels. Probes with frequencies around 20 MHz are ideal for larger peripheral vessels or occlusive branched vessels, whereas probes with lower frequencies around 10 MHz are well suited for imaging vessels such the aorta, inferior vena cava, and iliacs (Table 30.1). These catheters must be delivered with larger sheaths and provide less detail, but they can scan the entire circumference of a vessel.

Interpreting the Image

Gray Scale

As with other forms of ultrasound, IVUS displays two-dimensional images in gray scale. Ultrasound's ability to penetrate the material and the resultant amplitude of the returning signal determine the relative brightness or darkness of the vessel wall, reflecting its echogenicity or echolucency, respectively (Fig. 30.2).[18,19] It is also possible to visualize different types of plaques using IVUS. Heavily calcified plaques are highly echogenic and characterized by brightness and posterior shadowing. Fibrotic plaques are slightly less bright and lack the posterior shadowing of calcified plaques. Soft, lipid-filled plaques are echolucent and appear darker. Software allowing further characterization and analysis of vessels is also available with IVUS.

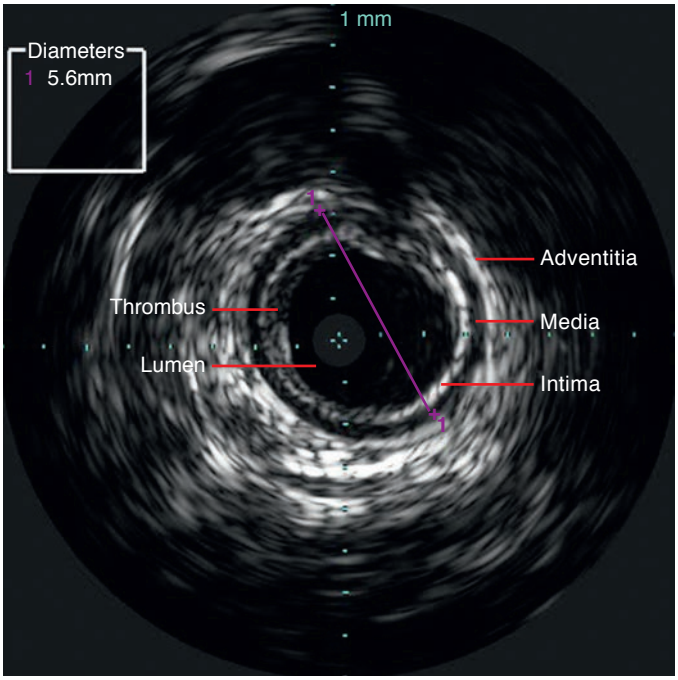

Figure 30.2 In gray scale, the layers of the arterial wall are visualized clearly, with the intima and adventitia appearing bright and echogenic, while the media is darker and echolucent. The blood-filled lumen appears very dark, with the clear demarcation between the arterial wall and the lumen allowing measurements to be obtained.

Volumetric Three-Dimensional Intravascular Ultrasound

In order to overcome the limitations of two-dimensional visualization, three-dimensional IVUS has been developed to more accurately describe arterial morphology and atheroma distribution. Conventional methods have relied on a longitudinal reconstruction similar to an angiogram, created through an automated "pullback" of the IVUS probe and compiling a pixel-based two-dimensional longitudinal reconstruction. Because the catheter tip is not reliably in the center of the lumen, it is difficult to obtain accurate diameter and length measurements in longitudinal reconstructions.[20] However, in recent years more sophisticated three-dimensional reconstruction algorithms have been developed, such as a novel method allowing for simultaneous registration of two IVUS pullbacks of the same vessel.[21] This type of technology is likely to continue to improve, offering fewer errors in location and orientation registration.

Color-Flow Intravascular Ultrasound

It is also possible to characterize blood flow with IVUS using color-flow software. This software, such as Volcano's ChromaFlo, compares adjacent frames at 30 frames per second and identifies the movement of blood cells, coloring any normal blood flow red and faster blood flow yellow. Unlike Doppler, color-flow IVUS cannot measure flow velocities. However, it does provide more information about the interface between the vessel wall and the bloodstream, allowing for more accurate volumetric measurements and the ability to assess completeness of treatment (Fig. 30.3 and Video 30.1).[22,23]

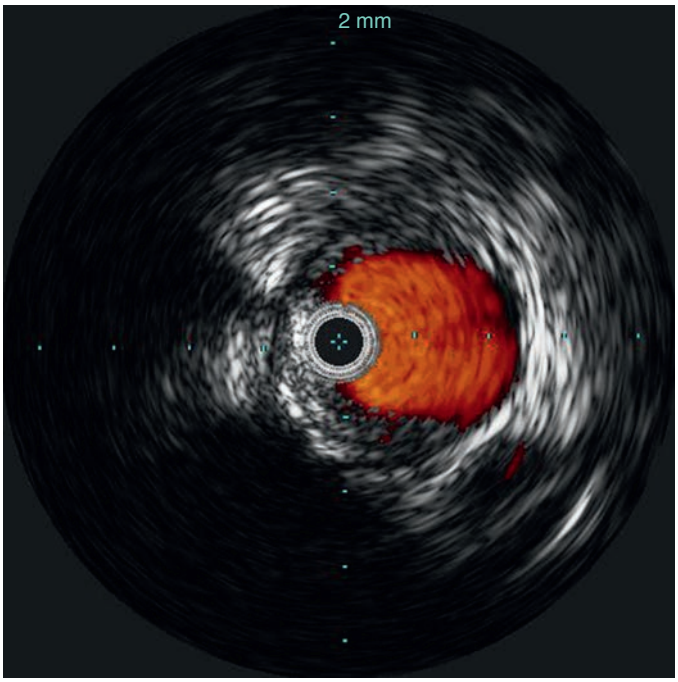

Figure 30.3 Color-flow intravascular ultrasound.

Virtual Histology Intravascular Ultrasound

Virtual histology (VH) IVUS utilizes the frequency of the returned signal as well as its amplitude to produce a color-coded map of a lesion based on the different frequencies at which various tissues reflect ultrasound. This allows histopathologic analysis of plaques based on their composition (Fig. 30.4). The Carotid Artery Plaque Virtual Histology Evaluation (CAPITAL) study, which compared 153 VH IVUS images with true histopathology sections from endarterectomies, found that VH IVUS was able to accurately diagnose 99.4% of thin-cap fibroatheromas, 96.1% of calcified thin-cap fibroatheromas, 85.9% of fibroatheromas, 85.5% of fibrocalcific plaques, 83.4% of pathologic intimal thickening, and 72.4% of calcified fibroatheromas.[24] A 2013 study analyzing 276 atherosclerotic plaques also found that VH IVUS had high sensitivities for various types of plaques (87% for noncalcified thin-cap fibroatheromas, 92% for calcified thin-cap fibroatheromas, 85% for noncalcified fibroatheromas, 89% for calcified fibroatheromas, and 79% for pathologic intimal thickening).[25] Although the accuracy of VH IVUS varies in identifying different types of plaque, it is overall able to provide insight into the morphology of

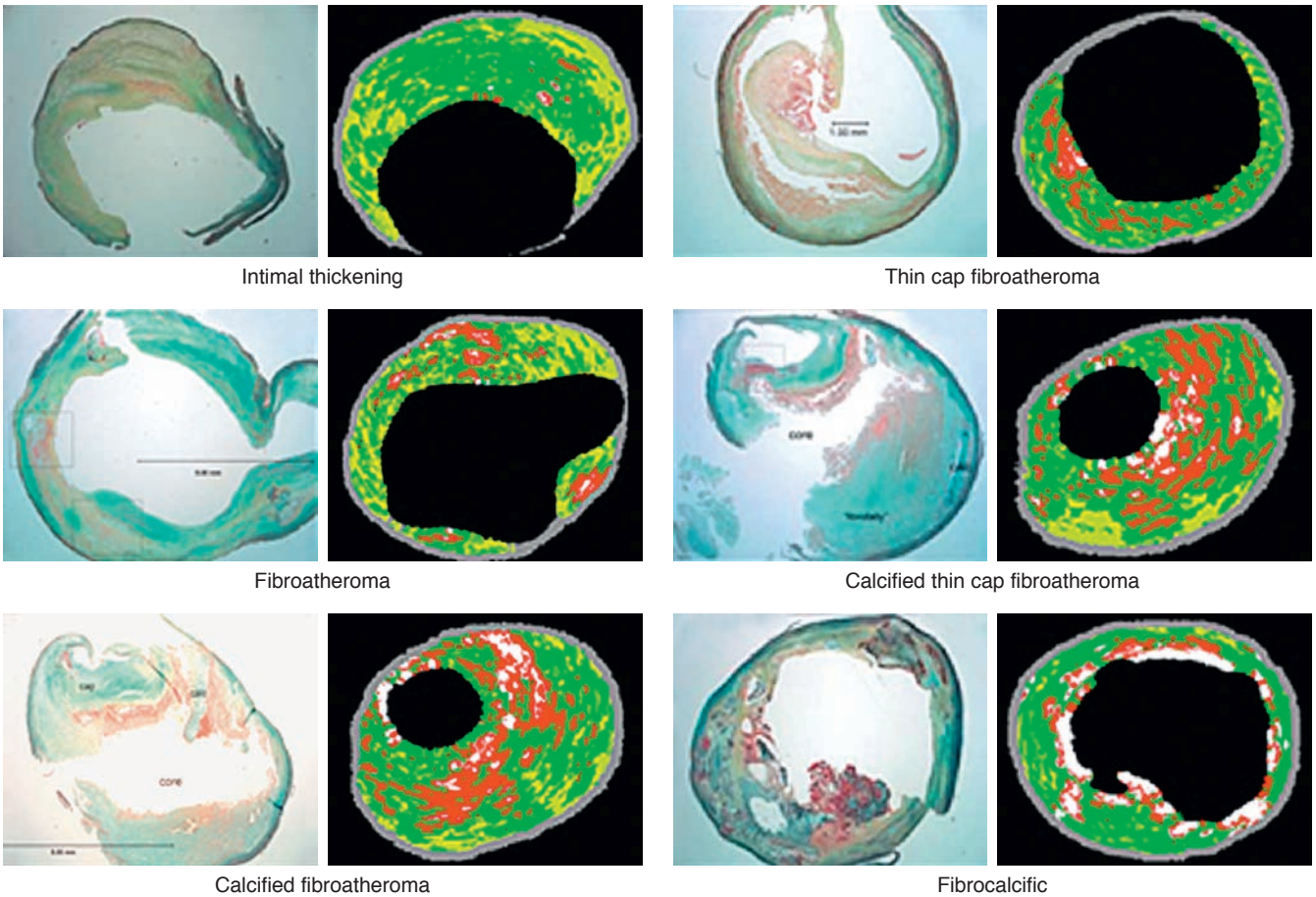

Figure 30.4 Virtual histology intravascular ultrasound software color codes images of atherosclerotic plaques based on their histologic components: dark green = fibrous, yellow/green = fibrofatty, white = calcified, red = necrotic lipid core.

lesions. The information about plaque composition offered by VH IVUS may improve outcomes by allowing physicians to predict plaque behavior in response to treatment, determining whether plaques may resist treatment or embolize when grafts or balloons are expanded.[26-31] Histopathologic analysis using IVUS is currently available only for smaller vessels, since the maximum fields of display are less than 20 mm, but future advances in VH IVUS technology may improve plaque characterization in larger vessels.

CLINICAL APPLICATIONS

Effectiveness of Intravascular Ultrasound

Cost Versus Benefits

As of 2009, IVUS systems were listed at between $100,000 and $200,000, while the disposable IVUS catheters cost between $600 and $1000 each.[32] These can represent significant added costs to procedures. However, the benefits of using IVUS suggest that it is cost-effective, because increased effectiveness of treatment can prevent reintervention and improve morbidity/mortality rates, especially in complex cases.[33] In a study examining the cost-effectiveness of IVUS in PCI, results demonstrated that use of IVUS was cost-effective, especially in patients at greater risk of restenosis, who benefit from more accurate stent implantation.[34] Improved long-term clinical outcomes can certainly decrease costs, and IVUS has been shown to improve clinical outcomes in many studies. Studies of aortoiliac artery stenting found that clinical outcomes were improved with IVUS guidance.[35,36] Studies investigating peripheral and branch vessel stenting found that IVUS was able to detect unsatisfactory deployment of stents, allowing further measures to be taken immediately and preventing later reintervention.[37] Similarly, IVUS-guided treatment of lower limb endovascular interventions was found to be predictive of lower postprocedural complications and significantly improved limb salvage rates.[38] Overall, the benefits of IVUS use tend to outweigh additional procedural costs.

General Benefits of Intravascular Ultrasound

IVUS is most often used because of its ability to provide additional diagnostic information to accurately assess vascular pathology, a benefit that has been well documented.[39] Intraoperatively, the dynamic imaging provided by IVUS allows for accurate deployment of grafts and assessment of successful therapy. The improved measurement ability of IVUS helps to determine proper stent graft sizing as well as in making last-minute adjustments based on intraoperative measurements.[40] Although measurements taken with IVUS have been found to be accurate overall, it is important to remember that because the catheter may not always be in the center of the lumen, it may provide a distorted oblique slice that does not reflect the true center-line diameter, especially in tortuous sections of the aorta.[41]

A significant benefit of IVUS is that it does not require the use of contrast. Because of this, patients with contrast allergies or renal impairment may benefit from preoperative imaging with IVUS instead of computed tomography angiography (CTA).[42,43] Intraoperatively, the use of IVUS is especially recommended as an alternative or adjunct to angiography because of its ability to decrease the volume of contrast injected as well as the radiation exposure.[44] It was shown in one comparison study that use of IVUS decreased fluoroscopy time from 39 to 19 minutes in comparable procedures.[45] In 2002, a study evaluating outcomes of endovascular aneurysm repair (EVAR) with IVUS as compared with angiography concluded that IVUS was accurate and reliable enough to be used for EVAR without additional angiographic assessment.[46] This ability to perform a procedure while eliminating or reducing contrast load and radiation exposure recommends the use of IVUS in patients with life-threatening contrast allergies or renal complications.[47] Because of its many benefits, IVUS has proven useful in a variety of vascular applications, including in the treatment of peripheral arterial disease, abdominal aortic aneurysm, thoracic aortic disease, dissection, and venous disease.

Arterial Applications: Carotid and Peripheral Arterial

Peripheral Arterial Disease

It has been shown that residual stenosis of greater than 60% after peripheral balloon angioplasty is associated with decreased patency rates.[48] Studies have also shown that more accurate sizing, especially with balloon-expandable stents, leads to better patency rates.[49] IVUS assessment of lumen diameter and degree of stenosis allows for accurate sizing of the vessel to be treated, thereby informing decisions regarding balloon and stent sizing.[50] One Japanese study found that 5-year overall patency rates were improved at 65% versus 35% when IVUS was used in the treatment of femoropopliteal lesions.[51] IVUS is also able to assess the initial results of balloon angioplasty and determine the need for further intervention, ensuring proper dilation of stents to improve apposition to vessel walls. In one study, 40% of patients had underexpanded stents after initial deployment and balloon expansion, but these were able to be further expanded with larger balloons because the lack of apposition was identified with IVUS.[52] Arteriography or angiography alone does not always visualize this type of problem, whereas IVUS is able to identify stent struts because of their echogenicity and assess the extent of stent expansion and apposition, allowing physicians to act to improve patency rates and overall success of treatment (Fig. 30.5).

In a study of popliteal aneurysms, researchers found that use of IVUS allowed accurate characterization of vessel morphology, including location and extent of thrombus burden. This improved outcomes in endovascular procedures because measurement of the diameter and location of desired landing zones allowed for appropriate sealing of the aneurysm proximally and distally.[53] In patients with drug-eluting stent placement for treatment of femoropopliteal lesions, IVUS guidance and postprocedural IVUS assessment was able to offer predictors of restenosis at 1 year.[54] In another study, IVUS use was associated with higher primary patency rates following nitinol stenting of TASC II

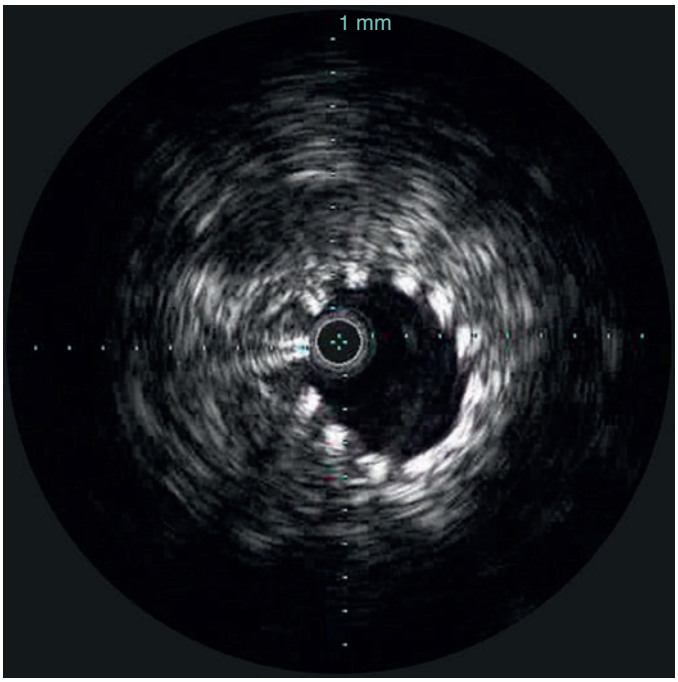

Figure 30.5 The echolucency of stent grafts allows for evaluation of graft apposition.

A-C lesions.[55] As these studies demonstrate, the information provided by IVUS has shown clear benefits in treatment of the peripheral vasculature.

Intravascular Ultrasound-Guided True Lumen Reentry

Endovascular revascularization to recanalize peripheral arteries is often unsuccessful because of a failure to reenter the true lumen after crossing an occlusion subintimally. Use of a device such as the Pioneer Plus,[56,57] which combines IVUS with reentry technology, can ensure true lumen reentry and improve outcomes, as shown in several studies. In one study of patients with chronic total occlusion of the iliac arteries, the use of the Pioneer device (a precursor to the Pioneer Plus) was able to decrease procedure time and improve precision of reentry, resulting in improved technical success of the recanalization procedure.[58] Another study found similarly positive outcomes in longitudinal follow-up of use of IVUS reentry devices for iliac and infrainguinal CTO.[59] Use of IVUS in conjunction with reentry devices ensures accurate needle placement and reentry.

Carotid Applications

IVUS can also be useful in the treatment of carotid arteries. A study of endarterectomy patients found that use of IVUS allowed correct identification of the distal ends of stenotic lesions, increasing the amount of information available to physicians that may not have been initially available with preoperative angiograms.[60] Similarly, a study of patients undergoing carotid angioplasty and stenting found that IVUS provided complementary information to allow more detailed characterization of lesions and thus to inform choice of type and size of stent.[61]

Endovascular Repair: Abdominal Aortic Aneurysms

Preoperative Intravascular Ultrasound

Abdominal aortic aneurysms (AAA) are increasingly being treated endovascularly.[62,63] Preoperative planning for such procedures requires high-quality imaging to characterize arterial morphology, particularly for accurate assessment of landing zones proximally and distally. Most of this planning is done using CTA. However, the use of IVUS preoperatively may be beneficial in several instances. It has been shown that IVUS provides accurate measurements of the length and diameter in landing zones, aiding in the proper selection and sizing of endografts.[64,65] In the case of patients with tortuous vessels, the combination of information from IVUS and CTA preoperatively can improve the ability to accurately assess and plan for cases that may be technically challenging.

Intraoperative Intravascular Ultrasound

For patients with abdominal aortic aneurysm, IVUS is most effectively used intraoperatively. Prior to stent graft deployment, IVUS can help to assess access anatomy in patients with questionable suitability for percutaneous endografting as seen on CTA. Prior to endograft delivery in patients with difficult access, IVUS can guide rotational atherectomy or balloon angioplasty or determine whether a conduit may be necessary. This assessment of access vessels can limit complications such as iliac dissection or rupture. During deployment, IVUS can visualize side branches for accurate placement of the graft. In the event that a bifurcated graft is being deployed, IVUS can also be used to ensure that the contralateral gate has been properly cannulated.

After Repair

After deployment of the stent-graft, IVUS can determine the completeness of treatment by assessing apposition to the vessel walls proximally and distally as well as apposition between overlapping stent-grafts. Potential endoleaks can thus be visualized and characterized. The use of IVUS for immediate intraoperative assessment of treatment can facilitate decision making about the necessity of further interventions such as ballooning, placement of proximal cuffs, or additional stent grafts, thus preventing the need for later reinterventions.

Endovascular Repair: Thoracic Aortic Disease

Endovascular thoracic aortic stent grafts are being used to treat a variety of thoracic aortic pathologies, including aneurysm, dissection, penetrating aortic ulcer (PAU), intramural hematoma (IMH), coarctation, and thoracic aortic injury secondary to trauma.[66-69] IVUS can clearly identify and characterize all those pathologies along with providing additional information that may not have been provided in CTA imaging. Unlike imaging for abdominal aortic pathologies, CTA imaging for thoracic disease often does not include abdominal and pelvic visualization. IVUS can therefore be used to provide information about access sites. Thoracic grafts often require larger sheath diameters,

thus increasing the risk for access-related complications and the need for accurate assessment to evaluate need for a conduit or additional treatment prior to delivering the main graft. IVUS can also provide information about arch vessel involvement that may not have been available on CTA, informing decisions about landing zones and any additional stenting that may be necessary.

Thoracic Aneurysms

The benefits of IVUS use in the treatment of thoracic aortic aneurysm are similar to the benefits provided in the treatment of abdominal aortic aneurysm, with the addition of the aforementioned benefits that are general to IVUS use in thoracic aortic disease. Before intervention, it can assess the access vessels, determine the amount of graph coverage necessary, guide graft sizing, and identify branch vessels and landing zones (Fig. 30.6 and Video 30.2). Of note, IVUS is especially beneficial in detecting any sources of potentially embolic material, such as calcific plaques or mobile atheroma in the aortic arch. This can allow physicians to limit ballooning in the arch so as to prevent embolic stroke.[70]

Blunt Traumatic Aortic Injury

Although CTA remains essential as a diagnostic tool for blunt traumatic aortic injuries (BTAIs), such as rupture, intimal tears, or transection, additional imaging is sometimes required. A study of BTAI patients with equivocal CTAs found that IVUS was more sensitive than angiography in these cases, with 3 out of 25 patients having had a negative angiogram, being diagnosed

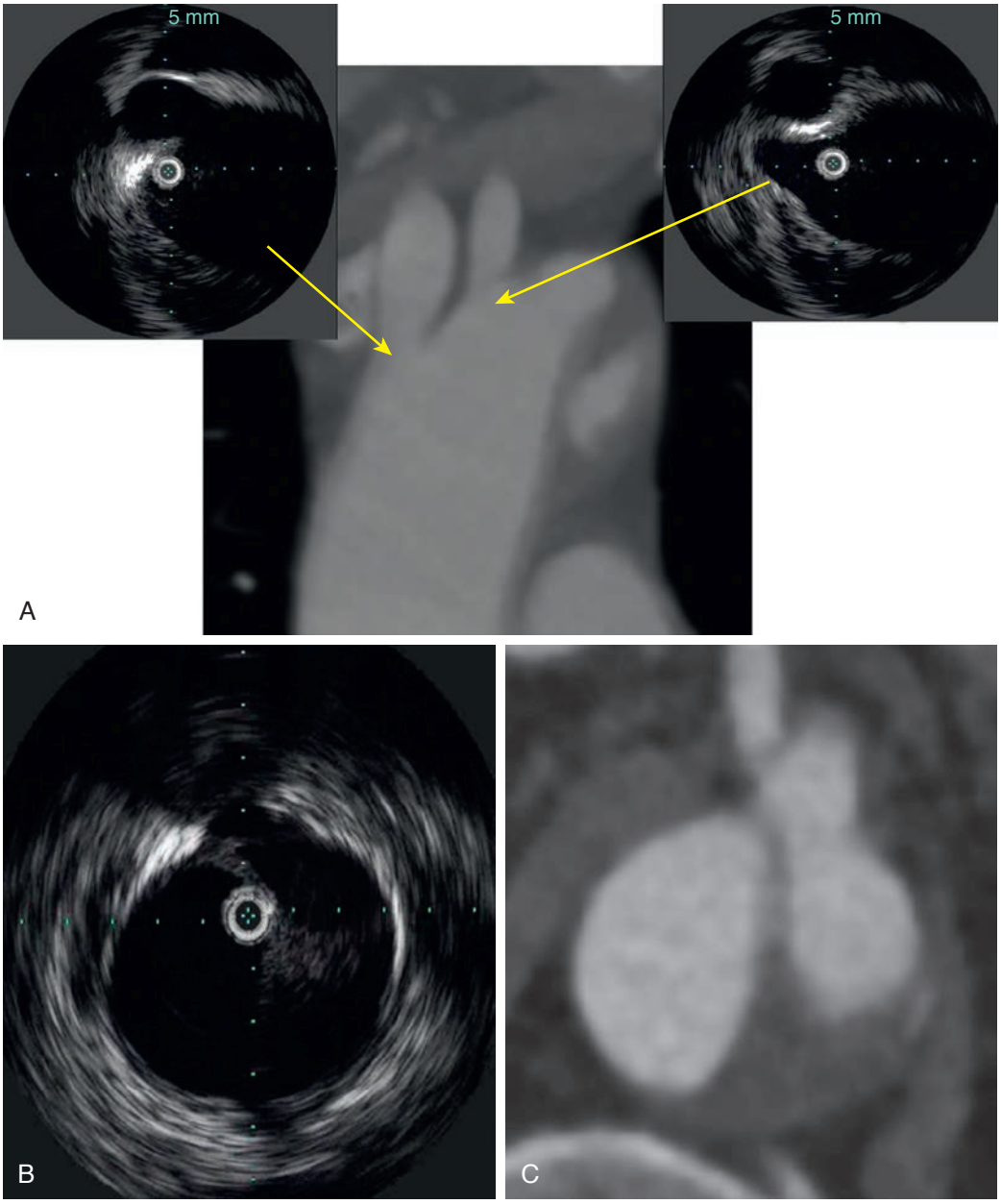

Figure 30.6 Branched vessels. On IVUS, it is possible to see the take-off of the great vessels (A, arrows indicate location of IVUS images captured at innominate and carotid arteries). IVUS image (B) and correlating CTA (C) show the celiac artery perfused by a partially thrombosed false lumen.

only by IVUS.[71] Additionally, the aortic diameter in patients with traumatic aortic injury often increases from the time of initial CTA to the time of repair due to hypovolemic shock and subsequent resuscitation, thus highlighting the need for intraoperative reassessment and real-time measurement to guide device sizing.[72] This accurate sizing of the true aortic luminal diameter can prevent graft infolding or bird-beak configuration and ensure proper apposition.[73] This is especially critical for BTAI patients, who are often younger, necessitating the anticipation of changes that come with aging and appropriate planning to promote longer-term durability of treatment.[74]

Coarctation

IVUS has emerged as an important imaging technique in endovascular repair of coarctation of the aorta. In a study examining balloon dilation for native and recurrent coarctation of the aorta, it was found that IVUS was more sensitive than angiography in providing detail regarding vascular wall changes, remodeling, and intimal tears.[75] Not only intraoperatively useful, it may also be beneficial in the diagnosis of arch anomalies or coarctation. In 2000, a total of 20 infants and children with arch anomalies were examined, and it was determined that it is possible to diagnose arch anomalies accurately using IVUS catheters from a transesophageal approach with three-dimensional image reconstruction.[76]

Dissection

Pre- and Intraoperative Intravascular Ultrasound

The benefit of IVUS in endovascular treatment of thoracic aortic dissections is most clearly seen in its ability to identify the true and false lumens (Fig. 30.7). Characterization of the dissection is

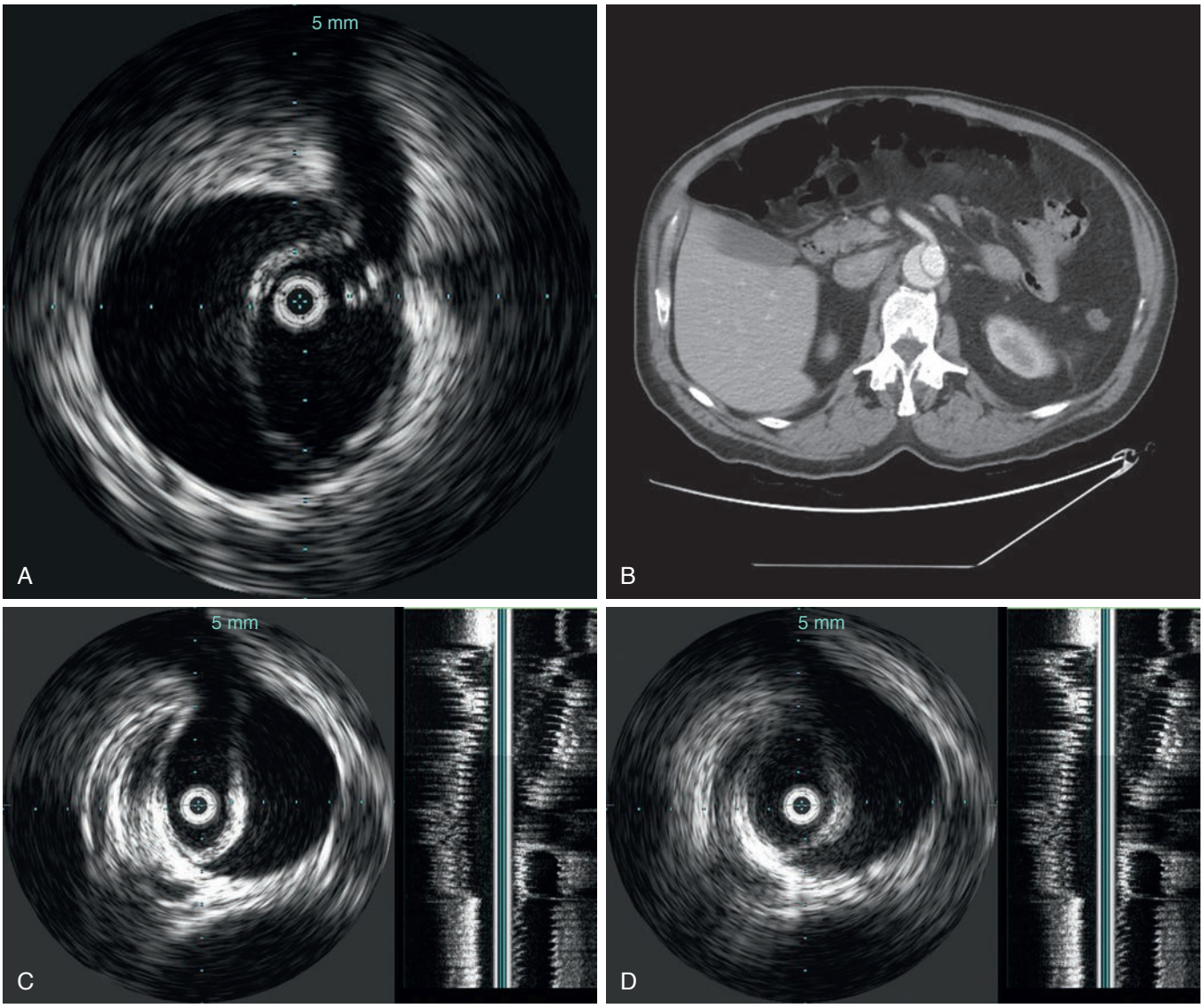

Figure 30.7 (A) It is possible to see the intima separating the true and false lumens and the superior mesenteric artery (SMA) coming off the true lumen. (B) Computed tomography angiography of dissection and SMA coming off true lumen. (C and D) Dynamic obstruction as seen on intravascular ultrasound with longitudinal reconstruction.

also possible, with the ability to identify the entry tear and other fenestrations between the true and false lumen. Movement and thickness of the dissection flap can be visualized, facilitating the diagnosis of dynamic obstruction due to flap motion (Videos 30.3 and 30.4). The benefit of IVUS in treating Stanford type B dissections, especially "complicated" type B dissections, is clear in its ability to identify visceral vessels.[77] Not only can dynamic obstruction be clearly seen, but it is also possible to assess through which lumen each artery is perfused, guiding further therapies if visceral stents are required (Fig. 30.8). Identification of the celiac artery with IVUS can also assist in placement of the graft, as the origin of this artery is sometimes difficult to identify solely with aortography.[78] Because it provides accurate measurements of vessel diameter and exact locations of branched vessels and fenestrations, the use of IVUS in treating dissections can facilitate the identification and characterization of proximal and distal landing zones, determining the amount of coverage required, and guiding selection of the appropriate size and length of the device to be used. As in other aortic pathologies, IVUS can also guide wires. This is especially important in the case of

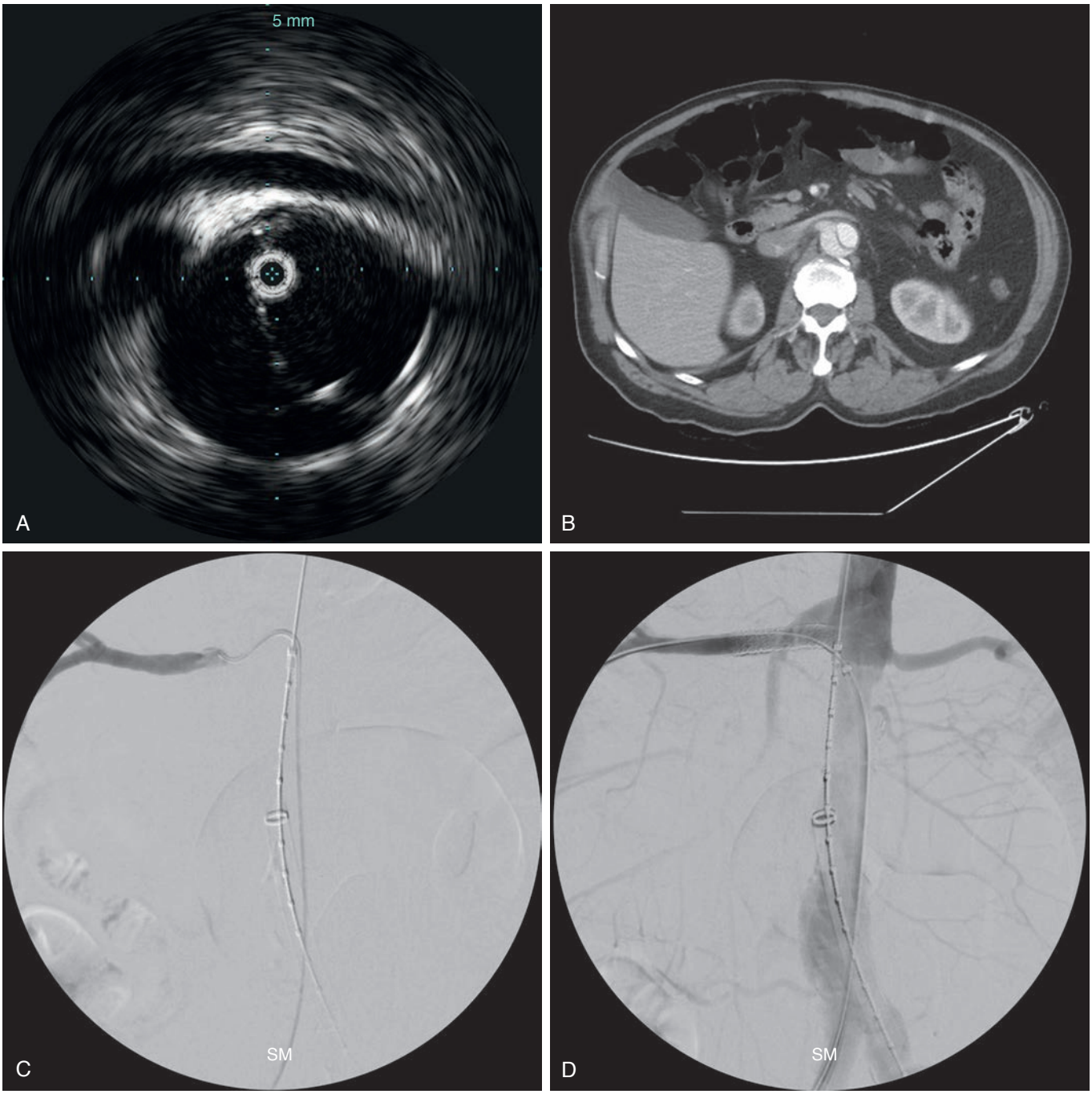

Figure 30.8 (A) The right renal artery coming off the false lumen. (B) Computed tomography angiography of dissection with the right renal artery coming off the false lumen. (C) Selective cannulation of the right renal artery. (D) Final placement of graft across the septum of the false lumen into the true lumen.

dissection, as it is difficult to determine by angiography alone whether a wire is in the true or false lumen. IVUS thus becomes especially useful in appropriately guiding wires into the arch, because it can confirm true lumen access. Where percutaneous fenestration of the intimal flap becomes necessary, IVUS may also guide this therapy.[79]

After Deployment

After deployment, IVUS can assess the completion and success of treatment. In Stanford type B dissections, IVUS can be used to examine the proximal deployment zone of the stent-graft and ensure that arch vessels are patent. It can also assess the ascending aorta for the presence of a retrograde dissection. IVUS can also be beneficial in the further evaluation of visceral vessels after the main stent-graft has been deployed, as it can identify continued malperfusion and guide further treatment. Postoperatively, expansion of the true lumen can be determined and the false lumen assessed for extent of thrombosis. In the case of type A dissections, IVUS has also been shown to be valuable in follow-up for patients with ascending arch replacement.[80]

Penetrating Aortic Ulcers and Intramural Hematoma

As with dissection, IVUS can be beneficial in the treatment of PAU and IMH.[81,82] The exact location and size of the ulcer can be visualized with IVUS, allowing appropriate proximal and distal landing zones to be determined. As in the treatment of other aortic pathologies, this information guides the choice of appropriate graft size and length. In the case of IMH, IVUS is especially useful in visualizing the arterial wall and distinguishing the intima and adventitia, allowing appropriate sizing to be obtained. After intervention, stent apposition can be clearly seen, ensuring that the ulcer is completely covered.

Venous Imaging and Applications

The ability of IVUS to characterize the extent and composition of lesions and provide information about vessel morphology is well documented in arterial and aortic pathology. However, IVUS is also well suited to the particular needs of venous imaging and has advantages over both single and multiplanar venography.[83,84] Although venography can characterize hemodynamics and visualize secondary veins, it does not allow for dynamic imaging, cannot accurately evaluate intraluminal pathologies, and does not provide accurate sizing information. IVUS can identify plaque morphology, trabeculae and intraluminal webs, neointimal hyperplasia, degree of thrombosis, immobile or inverted valves, and other deformities and abnormalities.[85] It can also provide measurements that may be difficult to obtain with venography. This is especially important in treatment of veins, since veins often have irregular circumferences and unusual contours, making the analysis of stenoses and vessel diameters difficult. By measuring cross-sectional areas and diameters of veins and evaluating the degree of disease or compression, IVUS can guide treatment and assist in the sizing of balloons or stents.

Venous Thromboembolism

In the case of deep venous thrombosis, IVUS can be useful in providing additional diagnostic imaging to identify lesions that may not be visualized by venography.[86,87] It has also been shown to be more sensitive than venography in detecting residual thrombus, thus recommending its routine use in thrombolytic regimens.[88] However, IVUS is more frequently utilized to treat venous thromboembolism in the inferior vena cava than in the peripheral vessels. Because IVUS can obtain accurate sizing measurements and identify branch vessels, it can guide the placement of filters.[89] Recent studies examining the use of IVUS instead of contrast venography for the placement of inferior vena caval (IVC) filters have found it to be a safe and effective technique.[90] Additionally, IVUS guidance in placing IVC filters can also eliminate the need to transport patients to an endovascular suite.[91] These benefits can be significant, especially for critically ill patients, as bedside IVC filter placement reduces the amount of contrast or fluoroscopy required while also eliminating the need for patient transfer.

Chronic Cerebrospinal Venous Insufficiency

As in other venous applications, IVUS aids in the diagnosis and treatment of chronic cerebrospinal venous insufficiency (CCSVI) because of its ability to assess and characterize vessel size and intraluminal abnormalities. The ability to evaluate valve abnormalities and endoluminal structures and constrictions is especially important in visualizing the jugular and azygos veins, as the nature of stenoses detected in major cerebrospinal veins is not always clearly seen in venography.[92] On IVUS, abnormal valves are easily seen because of the high echogenicity of thickened areas. One study assessing the accuracy of catheter venography as compared with IVUS and color Doppler (CD) sonography found that catheter venography was inferior to both IVUS and CD sonography in detecting jugular endoluminal malformations and that CD sonography underestimated the cross-sectional areas of internal jugular veins (IJV) as compared with IVUS.[93] Especially for the treatment of stenosis in an IJV, accurate sizing is difficult to obtain owing to the vessel's lack of a uniform circular shape. IVUS can therefore aid in proper balloon sizing, traditionally a challenge in treating IJV stenoses, and prevent complications secondary to improper sizing.

Venous Compression Syndromes

The use of IVUS in venous compression syndromes can allow for improved diagnosis and more effective treatment (Fig. 30.9). In studies of patients with May-Thurner syndrome, it was found that IVUS had a higher success rate than venography in identifying obstructions and in many cases was able to confirm diagnosis and influence endovascular management.[94,95] Similarly, a study evaluating IVUS and venography for patients with lower extremity venous stasis disease and for iliofemoral vein stenosis/obstruction found that IVUS was more sensitive and accurate than venography.[96] In the case of nutcracker syndrome, IVUS has been recommended to provide precise vessel sizing intraoperatively.[97] In 1994, a study examining the use of IVUS in

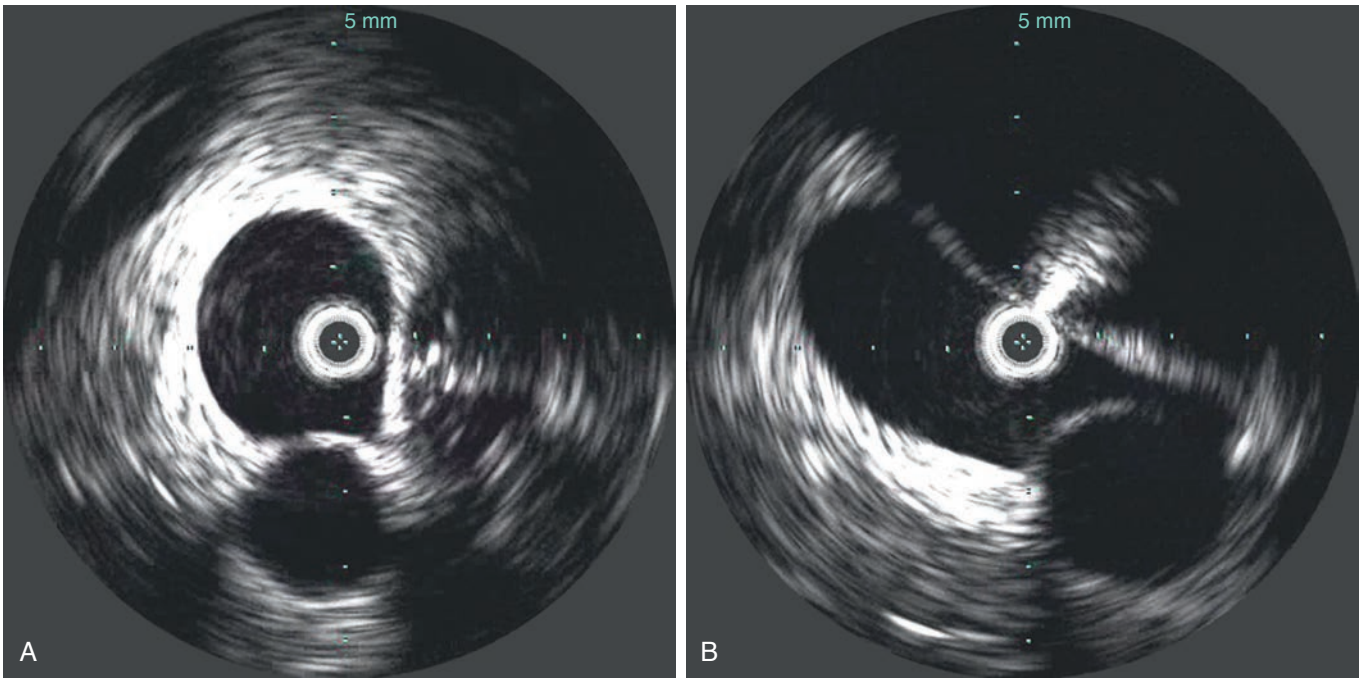

Figure 30.9 Intravascular ultrasound demonstrates an uncompressed vein (A) and a vein compressed by an artery (B) in venous compression syndrome.

the treatment of thoracic outlet syndrome found that IVUS was able to limit the extent of dissection necessary by providing real-time imaging of the release of extrinsic compression.[98] Several more recent studies of patients with thoracic outlet syndrome found that IVUS was able to provide a more detailed evaluation of the subclavian vein than venography, allowing for better identification of high-grade stenosis.[99,100] Overall, the precise imaging provided by IVUS recommends its use in venous compression syndromes.

LIMITATIONS AND RISKS

Comparison of Intravascular Ultrasound With Other Imaging Modalities

Intraoperative imaging options are limited. Although CTA and MRI provide high-quality imaging, they are not usable during a procedure. Imaging modalities besides IVUS that may be used intraoperatively include intravenous magnetic resonance imaging (IV MRI), optical coherence tomography (OCT), transesophageal echocardiography (TEE), near infrared spectroscopy (NIRS), angiography, and fractional flow reserve (FFR). Compared with other intraoperative imaging modalities, IVUS has clear benefits in some cases, while other modalities may be more suited for providing other types of information.[101]

Although angiography and venography are useful in that they provide details of blood flow and vessel contour, allowing visualization of collateral circulation and quality of flow, they are limited in that they do not allow characterization of wall disease and cannot accurately describe size or composition of lesions.[102] Similarly, FFR provides meaningful information about hemodynamic measures of lesion severity but cannot provide information about plaque composition.[103] It was found that in comparing IVUS with angiography for the evaluation and treatment of peripheral arterial disease, IVUS was superior in measuring diameter, areas of stenosis, plaque concentricity, plaque morphology, and calcification.[104] In terms of identifying plaque morphology, intravenous (IV) MRI is also able to characterize the composition of lesions and has been shown to be accurate in measuring vessel wall area.[105] However, although there have been significant improvements to decrease scan time and improve resolution, the associated cost, scan time, and presence of significant movement artifacts has thus far limited the effectiveness of IV MRI.[106,107] Many studies evaluating the efficacy of OCT have found that it is accurate and beneficial in characterizing plaque components in small arteries, such as coronary and infrapopliteal arteries, since it has significantly better spatial resolution than other intraoperative imaging modalities.[108] However, OCT's lack of penetrative depth, small field of view, use of contrast, and the fact that it requires blood removal from the vessel at the time of imaging diminish its usefulness with increased vessel size.[109-111] Overall, its ease of use and increased depth of penetration recommend IVUS for measurements and lesion identification in aortic and peripheral treatments.

Limitations and Risks of Intravascular Ultrasound

Although the risks associated with the use of IVUS are minimal, IVUS does require an invasive procedure and thus carries the risk of bleeding or clotting in the area of catheter insertion and possible damage to blood vessels. However, since IVUS is often performed in conjunction with other invasive procedures, its use adds little additional risk. Major complications are reported to occur in less than 0.5% of procedures and usually occur

during surgical intervention rather than diagnostic imaging.[112] Similarly, the use of IVUS does add additional cost to a procedure, with basic system implementation costing $70,000 to $120,000 and an additional cost per patient of around $600 for a disposable catheter tip.[113] However, studies of the long-term clinical outcomes of IVUS use suggest that the decreased number of postoperative complications and reduced need for reintervention may offset these costs.[114-116]

Another limitation of IVUS is the quality of imaging. A 2014 study of IVUS, OCT, and IV MRI compared the three imaging modalities and found a comparatively lower quality of imaging with IVUS, with low signal-to-noise ratios and significant artifacts and interference.[117] Normal ultrasound systems have frame rates between 50 and 750 frames per second, whereas current IVUS systems run at about 30 frames per second, accounting for the difference in image quality, a common complaint of vascular physicians using IVUS. The quality and utility of IVUS images is also user-dependent. Appropriate catheter and frequency selection is key, but other system settings such as gain, compression and rejection (specific to certain mechanical scanners), time-averaging and persistence, and gamma curves must also be adjusted properly to reduce image artifacts and decrease noise while ensuring that targets are not blurred or obscured and that inaccurate measurements are not introduced.[118] Physicians utilizing IVUS must recognize potential pitfalls in interpreting images, being aware of near-field and motion artifacts as well as artifacts created by transducer position, taking into account catheter obliquity and vessel curvature as well as angle-dependent artifacts that may be created by catheter eccentricity.[119,120] Technician support should be available and standards, protocols, and education should be established to ensure that IVUS use is as effective and efficient as possible.

FUTURE ADVANCES

In the future, technological advances may overcome some of the limitations of IVUS, allowing for improved imaging and ease of use. Currently, IVUS creates images with axial slices at 90 degrees to the probe, which limits its usefulness in guiding wires through chronic total occlusions. Recent advances in technology to overcome this limitation include the development of a single-chip forward-looking imaging system created by integrating capacitive micromachined ultrasonic transducer (CMUT) arrays with front-end electronics.[121-123] This type of array may also allow for IVUS use on guidewires, thus simplifying procedures by eliminating the need for separate catheters.[124,125]

Identification and characterization of plaques with IVUS may also be improving. The PROSPECT II trial is currently under way to evaluate the efficacy of a cardiac catheter combining IVUS with NIRS to help identify and characterize vulnerable lipid-rich coronary plaques.[126] NIRS has been shown to be more accurate than IVUS in characterizing soft plaques, so its combination with IVUS contributes to the accurate characterization of vulnerable plaques by providing precise information about lesion morphology.[127-129] Combination technologies, such as systems that integrate FFR or NIRS with IVUS, along with other types of technology that integrate IVUS with treatments such as angioplasty or ablation, may be the most promising developments for IVUS in the years ahead.[130]

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31 CHAPTER

The Future of Imaging for Endovascular and Open Surgery

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BACKGROUND

Vascular surgery has pioneered the development of various novel, minimally invasive catheter-based endovascular procedures within the confines of the open surgical operating room (OR). Portable image-intensifier–based C-arm imaging systems were the original imaging platforms on which catheter-based therapies have evolved in the hands of vascular surgeons. Thus far, the portable C-arm imaging system has been the signature imaging tool in the OR that heralded the entry of open vascular surgeons into the endovascular interventional space. With the advent and rapid evolution of imaging technologies in the OR, vascular surgeons are now required to have an increased understanding of both basic and advanced imaging techniques.

As the complexity of endovascular interventions has evolved—with advancements in endovascular devices such as catheters, stents, and stent grafts—so imaging technologies have evolved in parallel. Image intensifiers in the portable C-arm imaging systems have been replaced with flat-panel–based digital image detector systems and provide better image quality, signal-to-noise ratio, and dynamic range with little to no geometric distortions.[1] However, the portable nature of these C-arm systems is still a limitation for having a more powerful x-ray tube with better cooling capabilities. Because of the advanced imaging demands for longer and more complex vascular procedures, fixed angiography imaging suites, traditionally the province of cardiologists and interventional radiologists, have become commonplace within the operating environment. Often referred to as *hybrid rooms*, they allow for both "open" surgical procedures and catheter-based endovascular interventions to be satisfactorily performed in the same operating suite. Although expensive, hybrid ORs, for the very first time, have paved way for intraoperative 3D imaging in the hybrid OR.[2-4] This has been followed by technologies like flexible endovascular robotics and integration of multimodal imaging modalities such as transesophageal echocardiographic imaging (TEE), intravascular ultrasound (IVUS), preoperative computed tomography (CT), and magnetic resonance imaging (MRI) within the hybrid OR. Indeed, the rapid evolution of imaging and endovascular devices is symbiotic and synergistic. Along with this evolution of

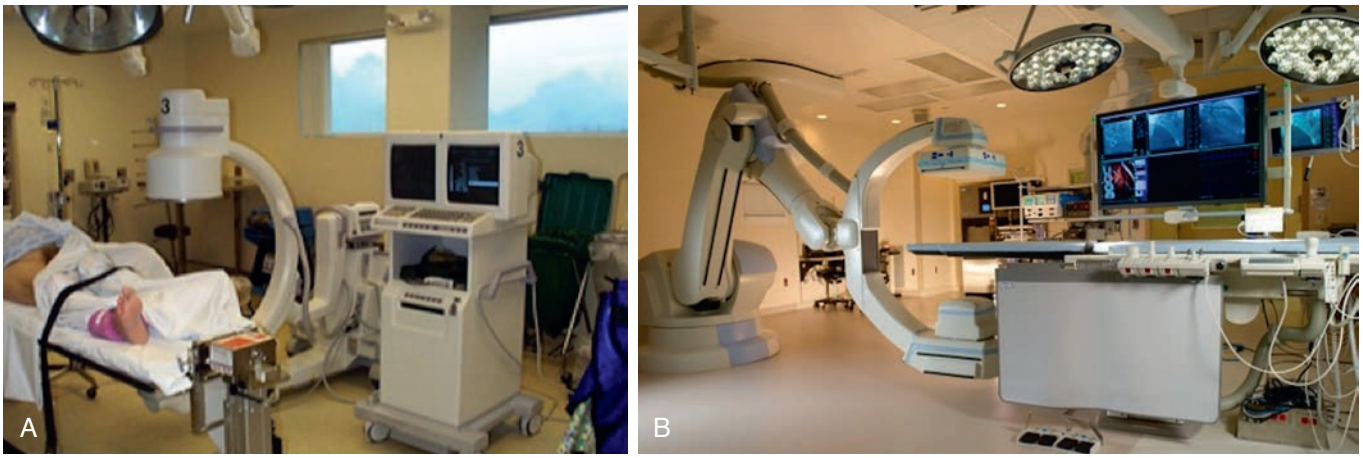

Figure 31.1 Figure illustrating the imaging (r)evolution in a vascular operating room from a portable C-arm with radiolucent patient table (A) to a robotic angiographic imaging suite with advanced intraoperative 3D imaging and image fusion capabilities (B).

intraoperative imaging, however, there is an increasing concern about the amount of radiation to which surgeons and interventionalists are being exposed. Consequently, new methods have been developed for monitoring radiation exposure and minimizing the amount of radiation employed during these procedures.

The goal of this chapter is to impart a broad overview of the recent evolution of advanced x-ray and multimodality imaging techniques for vascular surgery and to provide a glimpse into potential future imaging and catheter navigation technologies that could improve the safety and efficacy of minimally invasive endovascular procedures while minimizing the amount of radiation used in hybrid ORs.

X-RAY IMAGING AND HYBRID OPERATING ROOMS

Although alternate imaging modalities such as ultrasound and MRI are available and less invasive, diagnostic imaging for endovascular interventional and surgical procedures has primarily been superseded by multislice CT imaging and invasive 2D x-ray fluoroscopy and angiography. Despite lacking depth, the primary advantage of invasive x-ray angiography is better spatial resolution of around 0.2 mm in imaging smaller vessels with temporal resolution of ~20 ms after injecting iodinated contrast agent as a bolus into the vessel of interest.[5]

Portable C-Arm Imaging Systems

Although the portable image-intensifier–based C-arm imaging system has been the staple imaging modality for vascular surgery for many years, it has continued to evolve with technological advancements. For example, the image-intensifier–based x-ray detector system has been replaced by the flat-panel–based digital detectors; these have better sensitivity and lower noise levels, potentially offering better distortion-free image quality at a lower radiation dose.[1] In addition, newer x-ray tubes in mobile C-arms with higher power generators—in the order of 25 kW—and better cooling capabilities enable higher penetration power even in obese patients. Moreover, these allow uninterrupted imaging for longer endovascular procedures than was possible with fixed C-arm angiographic imaging systems.[6,7] Radiation exposure to both patients and the surgery team needs to be carefully considered during the usage of mobile C-arm imaging systems in the OR.[7,8] Perhaps the most revolutionary development is 3D imaging in upcoming mobile-C-arm imaging systems. Although there has been some preliminary work using this 3D imaging technique during spine and orthopedic procedures,[4,9,10] routine clinical use of this technology for vascular imaging is still in our future.

Recent advancements in mobile C-arm imaging systems, including image fusion and overlay capabilities, are very relevant. In most vascular surgery practices, the portable low-end mobile C-arm imaging system continues to be the primary imaging modality or a backup imaging option to the fixed hybrid OR. Moreover, portable-C-arm-imaging–based interventional suites have been increasingly used to set up office-based vascular practices (Fig. 31.1). With the technological gap between portable and fixed C-arm imaging systems narrowing, portable C-arms could represent a very practical and economical option for an outpatient interventional or endovascular suite, permitting both the technical and professional revenues to be captured in an office-based vascular surgery practice.

Fixed C-Arm Angiographic Imaging Systems

Typically the concept of a hybrid OR is one where high-resolution angiography can be performed in the same room—even concomitantly—as complex open surgical procedures. Over time, the concept of hybrid OR has been generalized, and not all hybrid ORs are equal. In this context, a modern, high-end hybrid OR often references one that is equipped with a fixed C-arm imaging system that can enable open, endovascular, or hybrid minimally invasive surgical procedures. A typical fixed C-arm angiographic imaging system can be floor- or ceiling-mounted

and is integrated to the OR table, with the option of surgical tables to improve the utilization of the hybrid suite across various surgical specialties.[11] In addition, fixed C-arm angiographic imaging systems mounted on a robotic arm offer versatility and the option of bringing the imaging system to the patient whenever needed during the surgical procedure (see Fig. 31.1).[12]

Concept of As Low As Reasonably Achievable and "Low"-Dose Radiation to the Patient

Monitoring radiation dose delivered to the patient and training and awareness of radiation safety for the entire OR team is critical but often overlooked. Adherence to ALARA (As Low As Reasonably Achievable) strategies should be a key part of training and must not be seen as a matter of convenience. However, in a recent anonymous survey of vascular surgery trainees, 45% had no formal training in radiation safety and 43% were unaware of annual maximum acceptable levels of radiation exposure.[13] In the same study, the vascular trainees also perceived themselves as practicing ALARA strategies, when they perceive that their attending physicians as regularly practicing ALARA strategies.[13,14] This further highlights the value and immediate need for improvement in radiation safety measures to optimize the radiation dose delivered to both patient and the operating team.[15-20]

Protection From Radiation Scatter

One of the challenges associated with radiation safety education is that the training is based on non-intuitive understanding of radiation scatter patterns in the OR. However, in certain scenarios, stepping away from the patient to respect inverse square law is not always feasible. The scenarios related to radiation safety must be redefined from an OR perspective. Recent studies have attempted to map radiation scatter patterns in the OR using personal wireless dosimeters,[21-23] which would pave a great step into the future of radiation safety training measures.

Designing a Hybrid Operating Suite

When designing a high-end hybrid OR, it is very important to consider the following factors: (1) type of procedures that will be performed in the room; (2) adequate area and ceiling height of the room; (3) location and proximity to other ORs or preexisting interventional suites and intensive care units; (4) recruiting experienced specialist architects, local hospital planning, and construction team; (5) involvement of all primary users and surgical and anesthesia departments throughout planning and execution process; (6) including strategic vendors; (7) determining appropriate staffing with dedicated OR managers, nurses, x-ray technologists, and a backup team; and more importantly, (8) adequate communication, education, and training of the entire OR team. Building a hybrid OR service typically take a few months to years from design to construction and being fully operational. It involves cohesive interaction between various clinical disciplines working together with specialist architects, imaging equipment vendors, OR equipment vendors, and hospital biomedical engineers. Therefore detailed planning that accounts for ergonomics, clinical workflow considerations, integration of imaging and informatics, and adequate risk management strategies is paramount. After all, these are some of the most expensive ORs built in the hospital and require careful planning and execution.[11,24,25]

Although installation of the imaging system may often seem like the most important decision, it is not the main challenge. Configuring and installing all the other OR accessories including overhead lights and booms, anesthesia equipment, imaging equipment, and cardiopulmonary bypass pumps all require careful planning and workflow considerations. Adequate staffing and training is another major often overlooked factor in the final functioning of a hybrid OR. Dedicated, highly trained interventional technologists and OR nurses familiar with both x-ray and multimodality 3D imaging are essential. It is also important to train some of the technologists to act as "special procedure" technologists and nurses to ensure adequate exposure and to maintain experience and skills training. In summary, tight integration of patient scheduling, audio, video, imaging, patient monitoring, and hospital informatics systems in a hybrid OR should enable seamless display and access to all the preoperative, intraoperative, and postoperative information during the surgical interventions.

Advanced 3D Imaging and Image Guidance Techniques

Preoperative Imaging and Why This Impacts Procedural Performance

Until recently, preoperative CT or MRI scans were used as tools for diagnosis and decision-making. However, for presurgical planning, a surgeon needs to review the images in multiplanar (Fig. 31.2), volume-rendered reconstructions (Fig. 31.3) and plan the endovascular or open surgical intervention. The evolution of endovascular stent grafting spurred parallel development of third-party, postprocessing software packages that facilitate advanced image visualization techniques, including multiplanar reconstructions, and now even provide advanced virtual stent graft planning software.

The latest generation of hybrid ORs has evolved with advanced imaging techniques such as acquiring three-dimensional cone-beam CT imaging, and advanced image fusion techniques such as 3D-3D image fusion and 2D-3D image fusion to incorporate preoperative imaging data. Consequently, the technique and quality of preoperative imaging is increasingly important not just for diagnosis but also for intraoperative use. This should be kept in mind during acquisition of preoperative images using CT and MRI protocols that generate high-resolution, thin-slice acquisitions that facilitate accurate 3D rendering and image fusion techniques. For example, during imaging for type-II endoleak evaluation, acquiring high-resolution 3D datasets encompassing both arterial and delayed phase enables the surgeon to understand and target the inflow and outflow patterns within the endoleak-feeding vessels. Once endovascular targets are defined on the preoperative CT images, these same targets can be overlaid onto the fluoroscopic image to guide interventions such as selective embolization.[26-28] In the long run, this will

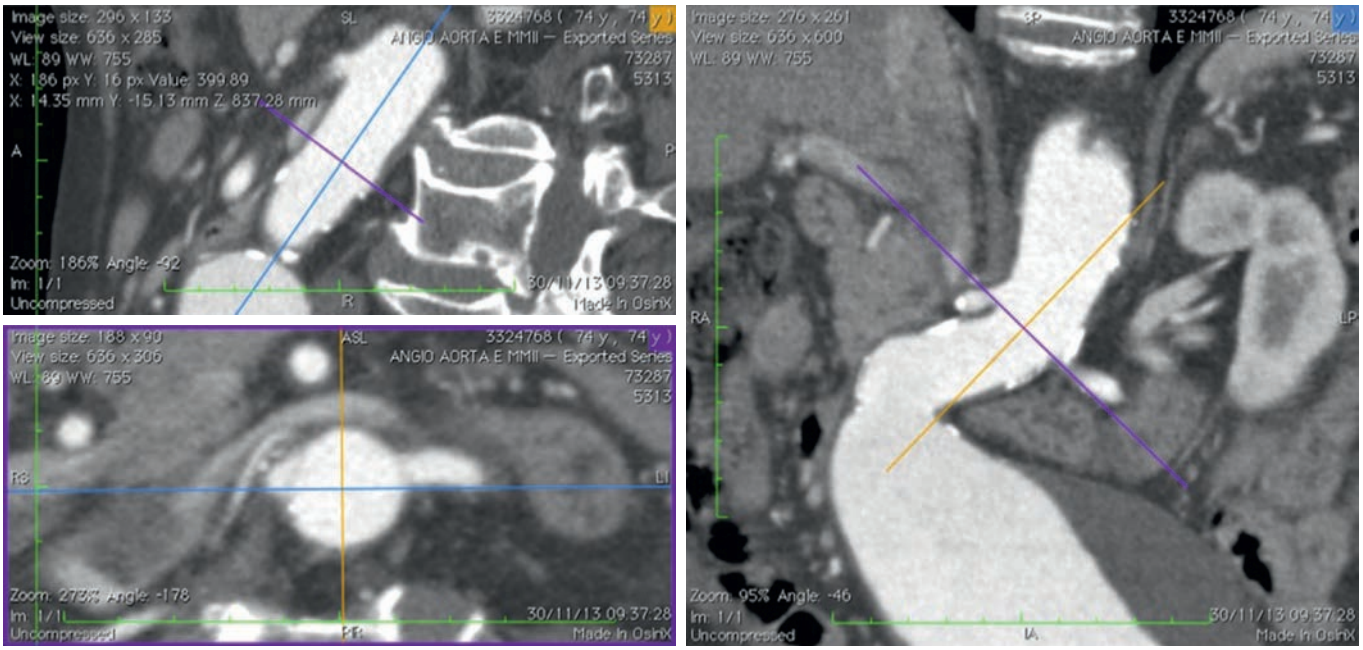

Figure 31.2 Standard multiplanar reconstruction (MPR) of three-dimensional CT dataset using commercially available software (OsirixMD). Angulation of aorta and other branches can be inferred accurately from such MPR rendering techniques and can be used to optimize the C-arm angulations during imaging and stent deployment.

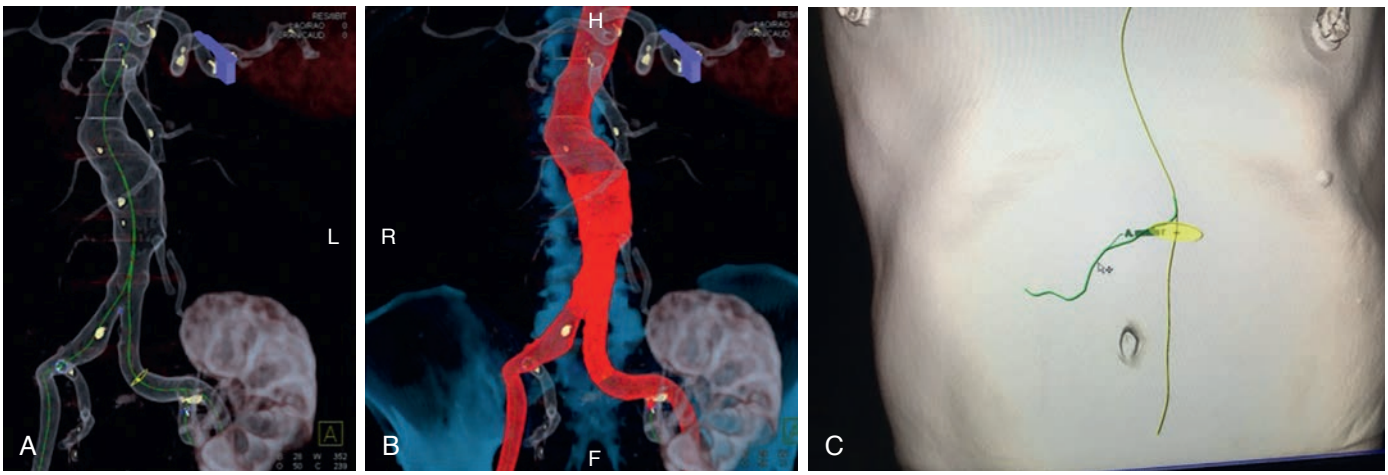

Figure 31.3 (A and B) Volume rendered reconstructions of CT datasets using a transparent visualization preset after segmentation of aortic centerlines using a prototype software (Siemens Healthcare GmbH). Transplanted kidney in the left iliac fossa can be seen, and the angulation for left internal iliac artery was defined using the CT datasets during the endovascular repair. (C) Surface rendering reconstruction of patient from the CT datasets overlaid with centerlines of aorta and right renal artery after image segmentation.

optimize judicious usage of radiation and contrast agents in patients during diagnosis and interventions.

Even when an open surgical procedure is planned, surface rendering of a CT scan will show the surface features of the patient such as prior surgical scars, nipples, and umbilicus (see Fig. 31.3C). This can be directly used for surgical incision planning after a surface-to-surface image co-registration process.[29] Understanding how to interact with the 3D imaging datasets can transform endovascular procedural planning and optimize incision planning and targeted approaches for minimally invasive open surgical procedures.

In summary, preoperative imaging and planning helps with achieving appropriate device sizing, avoiding parallax by selecting optimal C-arm angulation and providing a 3D roadmap during interventions after image fusion. Finally, the cardiovascular system is highly dynamic: the aorta varies in diameter and position with cardiac and respiratory cycle, the inferior vena cava (IVC) varies in diameter with respiration, and the aortic dissection septum moves extensively during systole and diastole. The emerging role of dynamic multimodality imaging such as CT and MRI in understanding the cardiovascular system is undisputable.[30,31] Increasingly, these dynamic images are being

incorporated into both diagnosis and interventional procedure guidance, such as endovascular stent grafting for complex aneurysms and dissections of aortic arch and ascending aorta.

C-Arm Cone-Beam Computed Tomography Imaging

In addition to 2D x-ray fluoroscopy and angiography, recent fixed C-arm angiographic imaging systems provide the additional capability of intraoperative 3D imaging by acquiring a series of 2D projections while the C-arm rotates around the patient for 200 degrees and reconstructing them as 3D cone-beam CT images. The development of high-contrast 3D angiographic imaging within the interventional neuro-radiology suites, and more recently, 3D cone-beam CT imaging capabilities, have revolutionized minimally invasive catheter-based interventions.[28,32-34] This cone-beam CT imaging technology and associated clinical applications have historically been well adopted and integrated in neuro-interventional and interventional radiology suites. To ensure consistency, the term CBCT will been used from here on to refer to intraoperative cone-beam CT imaging technique. Of course, different imaging vendors tend to use their own trademark terms—such as *syngo* DynaCT (Siemens Healthcare GmbH, Germany) or XperCT (Philips Medical Systems) or InnovaCT (General Electric Medical Systems)—adding to confusion surrounding individual room capabilities and adequate training. However, the penetration of these intraoperative 3D imaging and image fusion techniques into the ORs is rather recent and comes with its own challenges and opportunities. Evolution of such 3D imaging modalities in the OR could impact both the conduct of open surgical and endovascular procedures and could support the surgical community's further development of incremental technologies such as flexible-catheter robotics. Consequently, CBCT is a very versatile intraoperative imaging tool that can be considered the gateway for application of very sophisticated CT imaging applications in the future.[2,11,28,35,36] Along with this heavy dependence on x-ray imaging, however, there is an increasing concern about the amount of radiation exposure for surgeons and OR personnel.[19,37] Consequently, newer methods have been developed for monitoring radiation exposure and minimizing the amount of radiation delivered to the patient and surgical team during these procedures.[38,39] Nevertheless, the potential complementary role of other radiation-free tracking or imaging techniques, such as optical or electromagnetic device tracking and ultrasound and MRI, needs to be explored, especially for complex open and endovascular surgical procedures.

Image Fusion and Guidance Techniques

While having access to a fixed hybrid OR with its multiple advanced imaging capabilities is necessary for the conduct of complex endovascular procedures, the ability to perform a CT in the OR represents the next huge technological leap for vascular surgeons. It allows them to understand the intraoperative status of vasculature and stent grafts immediately after deployment to rule out potential endoleaks, kinking, and beaking of stents, thus potentially avoiding a future reintervention.

However, the core functionality of such an intraoperative imaging system is the ability to create a 3D DICOM dataset in the hybrid room. Until the real CT imaging capability in the OR is adopted into routine, image fusion of preoperative datasets can be performed using 2D3D and 3D3D image fusion techniques.[20,40,41] This minimizes additional radiation, avoids giving additional iodinated contrast usage, and allows the operator to use the entire prior computed tomographic angiography (CTA) dataset, which is often much more extensive than that which can be obtained using CBCT.

3D3D image fusion technique involves co-registration of a noncontrast CBCT dataset with a preoperative CT or MR dataset. After image fusion, the structures of interest electronically annotated in the preoperative dataset can be overlaid on the fluoroscopic image during intervention.[36,42,43] The significant advantage of this 3D3D image fusion is that relevant structures can be matched between two 3D datasets and no additional angiographic contrast is necessary during intervention. Additional nonradiation imaging such as IVUS or low-dose carbon-dioxide (CO_2) angiography can be used to verify and complement 3D3D fusion imaging. Furthermore, automated image segmentation algorithms can extract relevant vascular landmarks such as aortic centerlines, renal artery, and internal iliac artery ostia and overlay them onto fluoroscopy (see Fig. 31.3A and B). To demonstrate this image fusion process, we describe our workflow for endovascular abdominal aortic aneurysm repair (EVAR) using endografts. First, the patient is typically evaluated using outpatient thin-cut multislice CTA (MSCT). Next, after the patient arrives in the hybrid OR and is prepped and draped, a low-dose noncontrast CBCT is typically performed. A 3D postprocessing workstation was used to fuse noncontrast CBCT with the preoperative MSCT. An automated image segmentation algorithm then segments the vascular structures and relevant landmarks consisting of the aorta and its major branches. Then, after image fusion, all the relevant vascular structures segmented were immediately overlaid on the live fluoroscopy, even before the first injection of contrast agent during the procedure. Image fusion is typically achieved by aligning and fusing bony structures between CBCT and MSCT datasets. In theory, if the ribs, vertebrae, and pelvis are aligned, then the vascular structures should also be aligned. Bony structures are used to perform fusion because they are easily visible on noncontrast CBCT. However, there are a few limitations: if the patient is positioned differently during preoperative imaging and during the intervention, aligning bony landmarks may not achieve accurate alignment of vascular structures. Typically patients' arms are positioned abducted above their heads during preoperative CT imaging and are positioned adducted by their sides in the OR. Therefore dedicated context-specific image fusion techniques based upon vascular wall calcifications have been developed.[41,44,45] The vascular wall calcifications can be thought of as the bones of the blood vessels. This technique is possible and reliable because most of our elderly EVAR patients have extensive calcification easily visible on MSCT and CBCT. Based on our preliminary experience, we have found this to be a highly accurate method for fusing vascular structures.[44]

Another recently available image fusion technique can co-register preoperative images to fluoroscopy without the need for acquiring noncontrast CBCT imaging. This 2D3D image fusion technique works by acquiring two fluoroscopic images acquired at least 30 degrees apart and fusing them with digitally reconstructed radiographs derived from preoperative 3D images.[40,46] Although this 2D3D image fusion simplifies the image fusion workflow, the accuracy of this technique needs to be further validated.[47] In the future, it is likely that the image fusion technique will be chosen based upon the clinical context and accuracy necessary for conducting the procedure safely. For the time being, until robust automated workflow specific algorithms are routinely available, injection of dilute contrast agent or CO_2 angiography is typically performed to confirm image fusion accuracy before device deployment.

Needle Guidance

Not all procedures performed by vascular surgeons are endoluminal and permit target access via the peripheral vasculature. A typical example of a needle-based procedure is translumbar embolization of aneurysmal sac for treatment of type 2 endoleaks.[27,48,49] Conventionally this has been performed using bony landmarks, as seen on fluoroscopy, and carefully avoiding the puncture of the stent-graft.

Here the workflow for 3D needle guidance has been illustrated using CBCT imaging and dedicated needle guidance software (*syngo* needle guidance, Siemens Healthcare GmbH). The ability to perform intraoperative CBCT and fuse with a previously acquired MSCT or MRI in which the endoleak and feeding vessels are delineated is beneficial. Even with the patient placed prone on the hybrid OR table, the stent grafts from two datasets can be aligned to achieve accurate image fusion. The target endoleak site is typically electronically marked in the preoperative CT dataset (arterial or delayed phase). This virtual needle path electronically marked on the CT dataset is overlaid on 2D fluoroscopy during needle progression. In addition, the integrated laser crosshairs built in the detector helps with guidance of needle entry point in the skin to achieve ideal bull's-eye trajectory to reach the target endoleak site. Availability of virtual needle path overlay in all C-arm angulations helps with accurate 3D guidance and needle progression to the endoleak site (Fig. 31.4). Once the target is accessed by the needle, confirmation can be achieved by retrograde blood aspiration from endoleak site or by a repeat CBCT imaging. Then, a guidewire was placed and a sheath can be positioned to continue with the embolization procedure in standard fashion using embolization coils or liquid embolic agent.

Challenges and Next Steps

One of the current challenges associated with image fusion is that most solutions do not typically consider the vascular deformation caused by stiff wires, devices placed inside the lumen of the blood vessels. There are two approaches currently being evaluated to limit this problem: (1) acquiring an intraoperative 3D dataset (CBCT) after the device induced vessel deformation has occurred, and (2) deriving deformable registration of the preoperative dataset by acquiring biplane fluoroscopic images of device and reconstructing the 3D device followed by development of algorithms that automatically compensate for iliac straightening and can predict the final position of the internal iliac artery origin. In addition, patient-related movements need to be handled appropriately during image fusion.

A few more important practical challenges include optimization of appropriate preoperative imaging protocols, adequate training of the OR technologists and personnel in using these advanced imaging, and image fusion capabilities.

Optical and Electromagnetic Tracking for Image Fusion and Guidance

Although image fusion is currently performed by fusing two DICOM datasets using 3D3D fusion or using two fluoroscopic images using 2D3D fusion, there are other methodologies for fusing preoperative datasets in the OR. For example, non-radiation-based methods may be used: (1) electromagnetic tracking of sensors placed in the instruments and electromagnetic field generator placed in the surgical suite or (2) optical scanning of the patient's surface contours and fusing the surface to the surface-rendered from the CT datasets. Such non-radiation-based fusion techniques could be much more cost-effective than using a conventional hybrid room and could potentially be used in every OR for surgical procedure guidance. For example, the incisions for minimally invasive cardiac surgical procedures could be optimized, such as localizing the left internal mammary artery to left anterior descending coronary artery bypass graft prior to surgical incision for a minimally invasive MICS-CABG procedure.

ENDOVASCULAR NAVIGATION AND CATHETER ROBOTICS

The use of endovascular catheter robots represents yet another technological leap and could potentially transform endovascular navigation, providing a level of accuracy, maneuverability, and stability that cannot be achieved using manually controlled catheters. This endovascular robotic technology leverages a combination of minimally invasive remote catheter interventions with the ability to operate catheters from a distance (removing the need for the interventionist to be tableside) and to provide precise endovascular robotic control and navigation.[50-52]

Currently there are two endovascular catheter-based robotic systems (Fig. 31.5):

a. *CorPath precision vascular robotics system* (Corindus, Waltham, Massachusetts) is currently approved only for coronary interventions: Any off-the-shelf catheter mounted onto the robotic console is steered manually to the coronary arteries, and the robotic system enables the delivery of balloons and stents to the target vessel to facilitate therapeutic interventions.
b. *Magellan endovascular robotic system* (Hansen Medical Inc., Mountain View, California): Dedicated telescopic robotic catheter with four pull wires built into the catheter and sheath lumen enables precise robotic control and stability

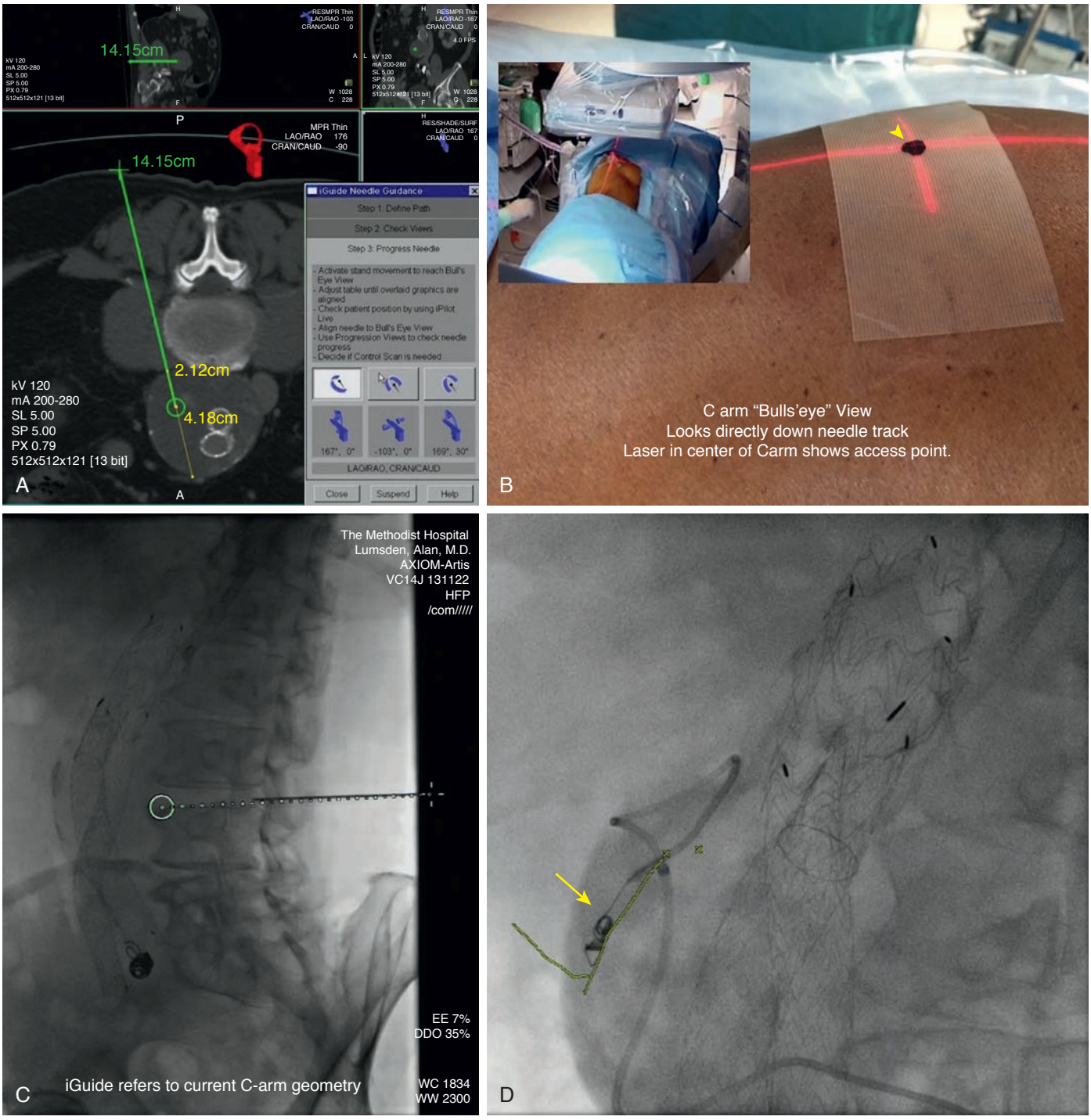

Figure 31.4 Workflow for 3D Needle Guidance for Type-2 Endoleak Embolization. (A) 3D planning of virtual needle trajectory *(green line)* in the 3D postprocessing workstation, and computation of bull's-eye and needle progression views. (B) Integrated laser cross-hairs in the x-ray detector projected onto patient's skin defining the ideal skin entry site *(yellow arrow head)* and trajectory for obtaining bull's-eye needle trajectory. (C) Real-time overlay of virtual needle trajectory on real-time live fluoroscopy across various angulations. (D) Fluoroscopic overlay of endoleak target vessel (e.g., inferior mesenteric artery) annotated from CT datasets, providing guidance for deploying embolization coils *(yellow arrow)*.

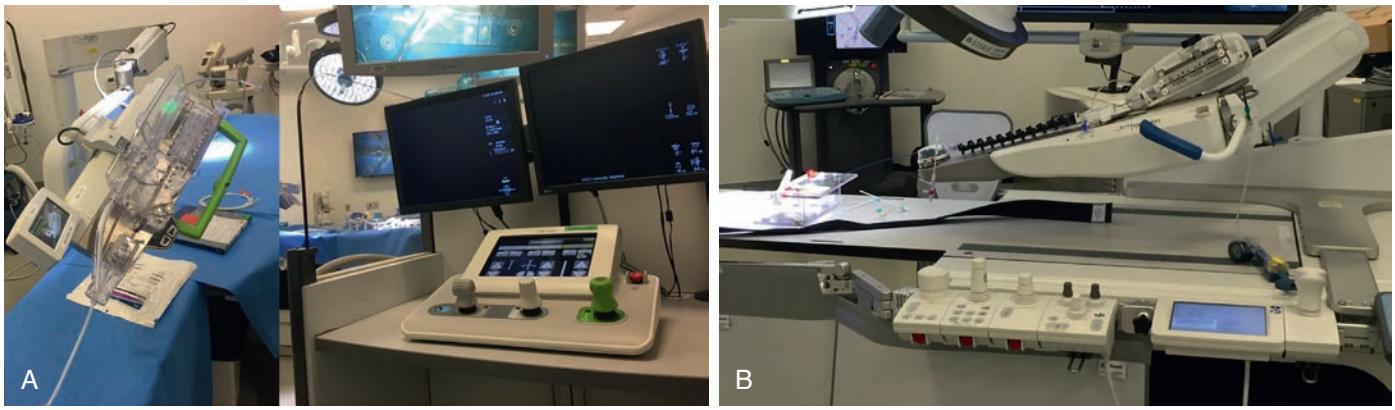

Figure 31.5 Endovascular Robotic Systems Commercially Available. (A) CorPath precision robotic system (Corindus, Massachusetts) and (B) Magellan Robotic System (Hansen Medical Inc., California).

of catheter, sheath, and guidewire steering, enabling target vessel cannulation.

Until recently, robotic catheters have not been integrated into the imaging system upon which all endovascular interventions are dependent. We are, however, beginning to see developments that allow path planning from 3D reconstruction models, followed by semiautonomous movement of the catheter to a target, termed as "assisted navigation." This, in our opinion, is the ultimate opportunity to integrate precise 3D navigation with high-resolution 3D imaging.[53] This novel "assisted" robotic navigation capability has recently been demonstrated by Schwein et al. in an ex-vivo aortic aneurysm model. Continuous electromagnetic tracking provides feedback on catheter localization, shape, and motion using EM sensors embedded within the robotic catheter. Such electromagnetic triangulation of an EM enhanced robotic system permits feedback on catheter motion, correction of catheter movement, and autonomous movement along a predetermined trajectory. Future endovascular navigation will be enhanced by non-radiation-based endovascular device localization, possibly facilitated by optical fiber based or electromagnetic-sensor–based tracking or other upcoming tracking technologies.

THE FUTURE HYBRID OPERATING SUITES

While the development of CBCT imaging capability fundamentally enhanced the functionality of the hybrid OR, performing the CBCT can be challenging at times and requires increased technical support. To bolster the intraoperative imaging capabilities, some future hybrid ORs are now increasingly being installed with integrated fully functional conventional multislice CT imaging systems. These CT imaging systems reside in the OR, mounted on the rails and slide over the patient whenever cross-sectional imaging is required. This could be a transformational technological development for minimally invasive image guided surgery that can impact patient care directly. For example, unstable patients with suspected pulmonary embolism may go straight to such a hybrid OR, where intensive care can be continued, a diagnosis can be confirmed or refuted, and therapy from lysis to open pulmonary thrombectomy can be immediately instituted. Such a room can transform trauma management, allowing immediate angiography, CT imaging, and appropriate therapy—either interventional or open surgical procedures instituted. However, these rooms also present some operational challenges in that cross-trained radiology technicians, knowledgeable in both angiography and CT scanning, and careful consideration of surgical workflows are necessary.

An additional imaging combination being explored is combined angiography suite and MRI imaging systems. An MRI must be kept in a magnetically isolated environment, separate from the main angiography suite or OR. Patients must be transported into the adjacent MRI imaging system using a dockable table transfer system whenever imaging is needed. Although having a dynamic imaging modality such as MRI is attractive, currently there are few uses for such a combination system in cardiovascular interventions; however, they are now being actively used in neurosurgery.

While the possibilities are endless, and "chance favors only the prepared mind," it may be prudent to say that the future of minimally invasive endovascular and open surgery is bright at the very cusp of upcoming "novel imaging and navigation" technologies on the horizon.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 32

Preoperative Evaluation and Management

G. MATTHEW LONGO and THOMAS G. LYNCH

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Preoperative assessment and management of vascular patients are of utmost importance because patients with vascular disease have multisystem involvement, including cardiac, cerebrovascular, renal, and peripheral arterial disease, as well as multiple other comorbid conditions. Consequently, they are at high risk for complications after surgery. A focused preoperative evaluation should identify potential treatable risk factors so that complications can be minimized and optimal choices can be made for the timing of elective surgery.

GENERAL PREOPERATIVE RISK ASSESSMENT

Every patient undergoing elective vascular surgery should have a preoperative assessment that includes a thorough history and physical examination, blood analysis, and electrocardiogram (ECG). In addition, if there are patient-specific areas of concern, these should receive a more detailed, directed evaluation. A complete blood count should be obtained to screen for the presence of infection, to ensure an adequate red blood cell volume, and to rule out a serious hematologic abnormality. Serum electrolyte concentrations should be evaluated and corrected when abnormalities exist. Of special importance are serum potassium, calcium, and magnesium levels because if they are abnormal and not corrected, they can lead to deleterious cardiac effects. Furthermore, because renal disease is so prevalent in vascular patients and some vascular interventions may compromise renal function, a baseline creatinine level should be obtained. All patients should also have serum glucose concentration measured, and in diabetic patients, glucose levels should be controlled before, during, and after intervention. Measures of coagulation, such as the partial thromboplastin time and the prothrombin time (PT) and international normalized ratio (INR), should be determined to identify coagulation abnormalities, and in patients taking warfarin or other anticoagulants, an appropriate anticoagulation scheme should be decided on before surgery (Box 32.1). Chest radiography may be helpful in some patients if undiagnosed underlying disease is suspected based on the history and physical examination. Finally, overall assessment of health can be quantified by the American Society of Anesthesiologists (ASA) classification (Table 32.1).

Cardiac Evaluation

In addition to a thorough cardiac history, physical examination, and baseline ECG, advanced cardiac testing may be appropriate for selected patients undergoing elective vascular procedures. The American College of Cardiology (ACC) Foundation and the American Heart Association (AHA) have provided recommendations with regard to preoperative cardiac workup (Fig. 32.1).[1] Most major vascular procedures are classified as "high

Abstract

Preoperative assessment and management of vascular patients are of utmost importance because patients with vascular disease have multisystem involvement, including cardiac, cerebrovascular, renal, and peripheral arterial disease, as well as multiple other comorbid conditions. Consequently, these patients are at high risk for complications after surgery. A focused preoperative evaluation should identify potential treatable risk factors so that complications can be minimized and optimal choices can be made for the timing of elective surgery. Furthermore, a discussion regarding both the potential benefits and risks of any intervention viewed through the patient's current functional state allows both the surgeon and the patient to choose the optimal treatment strategy.

Keywords/phrases

cardiac evaluation
diabetes
chronic renal failure
frailty
pulmonary function

BOX 32.1 Preoperative Checklist for Elective Vascular Surgery

For All Patients

History
Physical examination
Ankle-brachial index
Complete blood count
Serum electrolyte values
Blood urea nitrogen/creatinine
Glucose concentration
Prothrombin time and international normalized ratio
Electrocardiogram
Chest radiograph
Informed consent

TABLE 32.1 American Society Anesthesiologists Classification

ASA I	Normal, healthy patient with good exercise tolerance
ASA II	Controlled medical conditions without significant systemic effects
ASA III	Medical conditions with systemic effects; functional compromise
ASA IV	Medical condition with significant dysfunction; potential threat to life
ASA V	Critical medical condition; little chance of survival with or without surgery
ASA VI	Brain death, anesthesia performed for organ donation

ASA, American Society Anesthesiology.

risk" except for carotid endarterectomy and endovascular aneurysm repair, which are classified as "intermediate risk." In patients with adequate functional capacity (>4 METs), further cardiac testing is not generally recommended. Furthermore, those who have undergone coronary revascularization within 5 years or have normal findings on coronary angiography or cardiac stress testing within 2 years may also undergo surgery without further cardiac evaluation provided there have been no significant functional changes since that time. Dipyridamole-thallium imaging or dipyridamole stress echocardiography may be indicated for patients at intermediate or high cardiac risk with poor or unknown functional capacity (<4 METs).

In patients with cardiac implantable electronic devices (CIEDs), pacemaker, or an implantable cardioverter-defibrillator (ICD), it should be determined if monopolar electrocautery is going to be used. If so, the device may require reprogramming or application of a magnet over the CIED to prevent the transient inhibition of pacing or the inappropriate triggering of shocks. Furthermore, the surgical team should be familiar with the type of CIED, its manufacturer, response of device following reprogramming or magnet application, and the patient's underlying rhythm. External defibrillation equipment with transcutaneous pacing ability should be readily available in the operating room for these patients.

PREOPERATIVE MEDICAL VERSUS INTERVENTIONAL THERAPY FOR CARDIAC DISEASE

An extended discussion on cardiac complications and the preventions of these is in Chapter 42. Perioperative use of beta blockers has long been the standard of care for most patients with cardiac disease undergoing vascular surgery. However, their use has engendered significant controversy during the past several years. The POISE (PeriOperative Ischemic Evaluation) trial confirmed a reduction in primary cardiac events with perioperative beta-blockade therapy.[2] Nearly 8000 patients undergoing noncardiac surgery were randomized to fixed higher-dose, extended-release metoprolol started the day of surgery or no treatment. Whereas patients receiving beta blockers experienced a reduction in cardiovascular death, MI, and cardiac arrest, this benefit was offset by an increased risk of stroke and total mortality. The results suggested that the administration of high-dose beta blockers in the absence of dose titration may be harmful in beta-blocker naive patients. In the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography trial (DECREASE-IV), patients were randomized to receive beta blockade only, statin only, beta blockade and statin, or neither medication before elective noncardiac surgery.[3] Beta-blocker use, initiated well before surgery and titrated for heart rate (50-70 beats/min), proved to be cardioprotective in intermediate-risk patients, without an increase in perioperative stroke or death. However, the results of both trials have been called into question.[4] In a separate systematic review, it was noted that the preoperative use of beta blockers was associated with a reduction of cardiac events, but support was lacking regarding the effectiveness of preoperative administration of beta blockers to reduce the risk of surgical death.[5] Furthermore, there is a clear association between beta-blocker administration and adverse outcomes, such as bradycardia and stroke. Thus the best recommendations for beta-blocker use are that they should be continued in patients who have been on them chronically. In patients with intermediate- or high-risk myocardial ischemia on preoperative risk stratification tests or having three or more Revised Cardiac Risk Index (RCRI) risk factors (e.g., diabetes mellitus, heart failure, coronary artery disease, renal insufficiency, cerebrovascular accident), it is reasonable to begin perioperative beta blockers. In these patients, beta blockers should be started long enough in advance to assess safety and tolerability. Beta-blocker therapy should generally not be started on the day of surgery.

Most other "home" medicines, including aspirin, statins, and antihypertensives, should be continued throughout the perioperative period.[1] There is evidence that statins reduce the risk of adverse cardiovascular events among high-risk patients through effects on endothelial function, reduction in vascular inflammation, and stabilization of atherosclerotic plaque.[6] In the absence of a specific contraindication, statins should be initiated prior to surgery and be continued throughout the perioperative period.

Although many surgeons prefer to discontinue clopidogrel or other $P2Y_{12}$ inhibitors due to a perceived risk of increased bleeding at the time of surgery, there are scant objective data

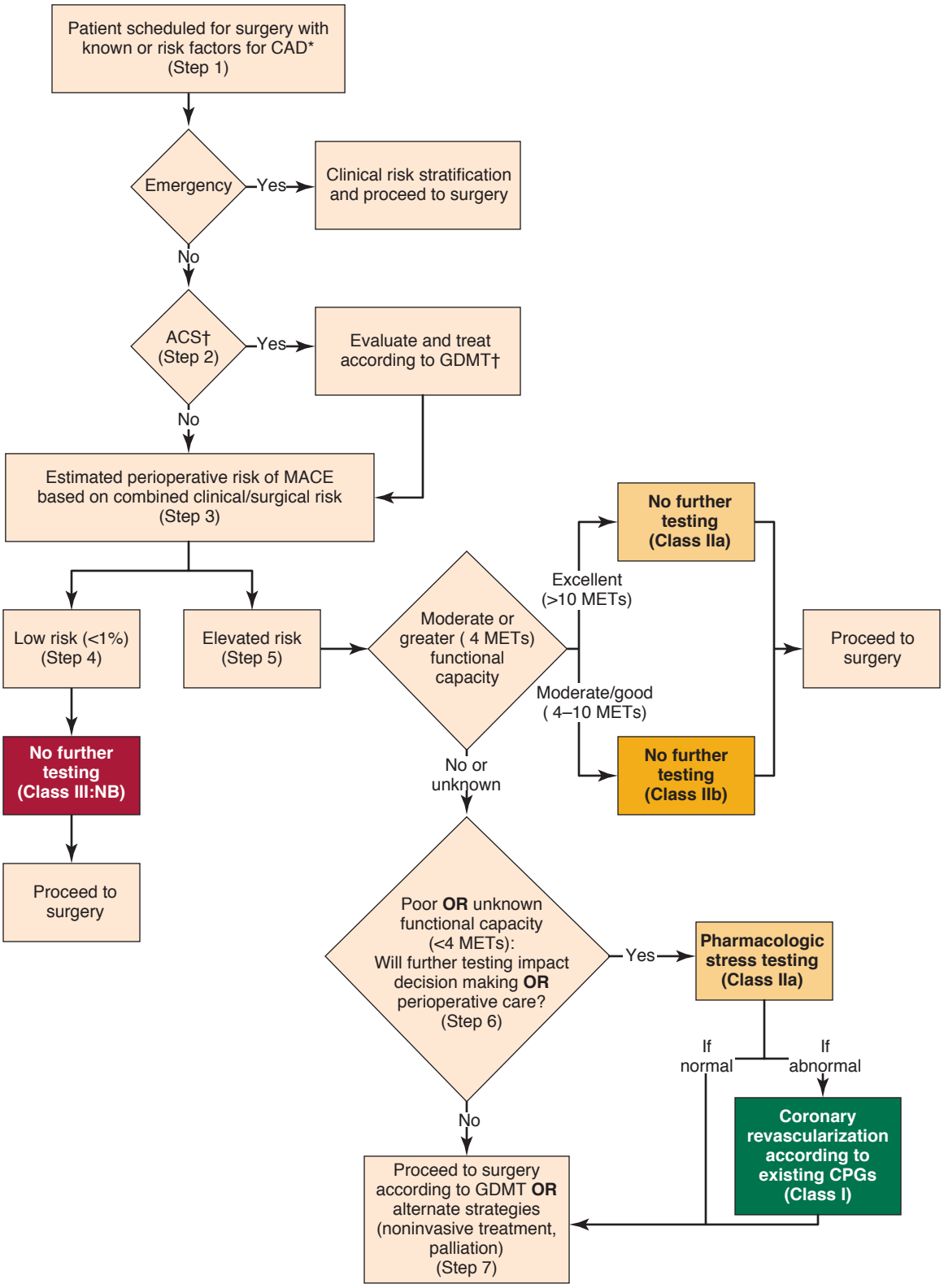
Patient scheduled for surgery with known or risk factors for CAD* (Step 1)
Emergency
Yes
Clinical risk stratification and proceed to surgery
No
ACS† (Step 2)
Yes
Evaluate and treat according to GDMT†
No
Estimated perioperative risk of MACE based on combined clinical/surgical risk (Step 3)
Low risk (<1%) (Step 4)
Elevated risk (Step 5)
Moderate or greater (4 METs) functional capacity
Excellent (>10 METs)
No further testing (Class IIa)
Moderate/good (4–10 METs)
No further testing (Class IIb)
Proceed to surgery
No further testing (Class III:NB)
Proceed to surgery
No or unknown
Poor OR unknown functional capacity (<4 METs): Will further testing impact decision making OR perioperative care? (Step 6)
Yes
Pharmacologic stress testing (Class IIa)
If normal
If abnormal
Coronary revascularization according to existing CPGs (Class I)
No
Proceed to surgery according to GDMT OR alternate strategies (noninvasive treatment, palliation) (Step 7)

Figure 32.1 Stepwise Approach to Perioperative Cardiac Assessment for CAD. Colors correspond to the Classes of Recommendations in Table 32.1. **Step 1:** In patients scheduled for surgery with risk factors for or known CAD, determine the urgency of surgery. If an emergency, then determine the clinical risk factors that may influence perioperative management and proceed to surgery with appropriate monitoring and management strategies based on the clinical assessment. **Step 2:** If the surgery is urgent or elective, determine if the patient has an ACS. If yes, then refer patient for cardiology evaluation and management according to GDMT according to the UA/NSTEMI and STEMI CPGs (18,20). **Step 3:** If the patient has risk factors for stable CAD, then estimate the perioperative risk of MACE on the basis of the combined clinical/surgical risk. This estimate can use the American College of Surgeons NSQIP risk calculator (http://www.surgicalriskcalculator.com) or incorporate the RCRI with an estimation of surgical risk. For example, a patient undergoing very low-risk surgery (e.g., ophthalmologic surgery), even with multiple risk factors, would have a low risk of MACE, whereas a patient undergoing major vascular surgery with few risk factors would have an elevated risk of MACE. **Step 4:** If the patient has a low risk of MACE (<1%), then no further testing is needed, and the patient may proceed to surgery. **Step 5:** If the patient is at elevated risk of MACE, then determine functional capacity with an objective measure or scale such as the DASI (133). If the patient has moderate, good, or excellent functional capacity (≥4 METs), then proceed to surgery without further evaluation. **Step 6:** If the patient has poor (<4 METs) or unknown functional capacity, then the clinician should consult with the patient and perioperative team to determine whether further testing will impact patient decision-making (e.g., decision to perform original surgery or willingness to undergo CABG or PCI, depending on the results of the test) or perioperative care. If yes, then pharmacologic stress testing is appropriate. In those patients with unknown functional capacity, exercise stress testing may be reasonable to perform. If the stress test is abnormal, consider coronary angiography and revascularization depending on the extent of the abnormal test. The patient can then proceed to surgery with GDMT or consider alternative strategies, such as noninvasive treatment of the indication for surgery (e.g., radiation therapy for cancer) or palliation. If the test is normal, proceed to surgery according to GDMT. **Step 7:** If testing will not impact decision making or care, then proceed to surgery according to GDMT or consider alternative strategies, such as noninvasive treatment of the indication for surgery (e.g., radiation therapy for cancer) or palliation. *ACS,* Acute coronary syndrome; *CABG*, coronary artery bypass graft; *CAD*, coronary artery disease; *CPG*, clinical practice guideline; *DASI*, Duke Activity Status Index; *GDMT*, guideline-directed medical therapy; *HF*, heart failure; *MACE*, major adverse cardiac event; *MET*, metabolic equivalent; *NB*, No Benefit; *NSQIP*, National Surgical Quality Improvement Program; *PGI*, percutaneous coronary intervention; *RCRI*, Revised Cardiac Risk Index; *STEMI*, ST-elevation myocardial infarction; *UA/NSTEMI*, unstable angina/non-ST-elevation myocardial infarction; *VHD*, valvular heart disease. (Reprinted with permission from Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64:e77–e137.)

to support this practice. Furthermore, the role of dual antiplatelet therapy (DAPT) in the management of coronary artery disease continues to evolve. Current ACC/AHA guidelines[7] support the use of DAPT following percutaneous coronary intervention (PCI) with both bare metal stents (BMSs) and drug-eluting stents (DESs). The duration of DAPT is dependent on the indication (acute coronary syndrome vs. stable angina) and PCI technique (BMS vs. DES), balanced against the estimated risk of bleeding. If the risk of surgical bleeding is believed to be high, elective vascular procedures should generally be postponed until DAPT can be safely withheld.

For urgent vascular procedures, DAPT should be continued unless the risk of bleeding outweighs the risk of stent thrombosis, particularly during the first 4 to 6 weeks following BMS or DES implantation. Consultation with cardiology is appropriate prior to discontinuing DAPT. If the procedure is time sensitive or urgent, and coronary revascularization is absolutely necessary, coronary artery bypass grafting (CABG) combined with the surgery or preceding the surgery may be considered.

The role of coronary revascularization prior to vascular surgery is uncertain. The Coronary Artery Revascularization Prophylaxis (CARP) trial demonstrated that in patients with stable coronary artery disease, coronary artery revascularization (with either CABG or PCI) before elective major vascular surgery does not improve long-term cardiac outcomes or reduce short-term postoperative outcomes such as death, MI, or length of hospital stay.[8] In addition, preoperative coronary artery revascularization in vascular patients is associated with increased risk for procedure-related complications and may lead to delay in the intended vascular procedure. Furthermore, patients who have recently (<5 years) undergone CABG or PCI before vascular surgery do not have an obvious survival advantage over patients at high cardiac risk without previous coronary interventions. Only the subset of patients with unprotected left main disease (the left main trunk is defined as unprotected when there is a >50% stenosis and the absence of at least one patent bypass graft to the left circumflex [LCX] or left anterior descending [LAD] artery) showed a benefit from preoperative coronary artery revascularization. CABG showed improved outcomes versus PCI.[9]

Preoperative Management of Hypertension

Elective surgery should generally be delayed if systolic blood pressure is greater than 200 mm Hg or if diastolic blood pressure is greater than 120 mm Hg, and acute control within hours of surgery is inadvisable. Pain can elevate blood pressure; therefore, appropriate analgesia with nonsteroidal antiinflammatory drugs or opioids should be administered to alleviate pain. Agents with minimal hemodynamic effects should be considered, such as fentanyl rather than morphine. Before induction of anesthesia, patients should also be well hydrated because volume loading can minimize the drastic swings in blood pressure that are characteristic of hypertensive patients.

There is general consensus that "home" antihypertensive medications should be continued during the perioperative period, with the possible exception of angiotensin-converting enzyme inhibiters (ACEIs) and angiotensin receptor blockers (ARBs). The incidence of intraoperative hypotension appears to be increased in patients receiving ACEIs or ARBs on the day of surgery, and this has been reflected in an increased risk of all-cause death, stroke, and MI.[10]

Pulmonary Evaluation

Pulmonary complications are reported in 1% to 2% of minor surgeries and up to 20% in upper abdominal or thoracic operations (see Chapter 43).[11] As such, preoperative pulmonary

evaluation should be completed in all patients and should begin with a history and physical examination, which is the most sensitive evaluation to identify "at-risk" patients. Patient-related risk factors for postoperative pulmonary complications include chronic obstructive pulmonary disease, age older than 60 years, ASA class II or higher, functionally dependent, smoking, forced expiratory volume in 1 second (FEV1) <1 L, congestive heart failure, and obesity. Patients with a BMI ≥ 40 kgm^2 have a 30% chance of developing atelectasis and/or pneumonia. The surgeon should pay particular attention to any history of smoking, exercise intolerance, unexplained dyspnea, or coughing. On physical examination, decreased breath sounds, wheezes, crackles, or a prolonged expiratory phase should be noted. Procedure-related risks should likewise be assessed. The duration of surgery (surgical time greater than 3 hours), the need for emergent surgery, and the surgical site all influence the risk of perioperative pulmonary complications. Aortic aneurysm repair, thoracic surgery, abdominal surgery, upper abdominal surgery, and emergency surgery all increase the risk of pulmonary complications. Obstructive sleep apnea is present in up to 22% of the adult population undergoing surgical procedures, and a large number of patients are undiagnosed prior to the preoperative assessment.[12] The presence of obstructive sleep apnea increases the chances of postoperative hypoxemia and reintubation in the postoperative period.

In some situations the at-risk patient will require further pulmonary evaluation and risk stratification. Although clinicians frequently obtain chest radiographs as part of a routine preoperative evaluation, few show unexpected abnormalities or influence the management of the patient. Despite this, there is some evidence that chest radiographs may be helpful for patients with known cardiopulmonary disease and those older than 50 years who are undergoing upper abdominal, thoracic, and open abdominal aortic aneurysm surgery.[13]

The value of pulmonary function testing before lung resection surgery and in determining candidacy for coronary artery bypass is well documented. However, its value outside of these cases remains controversial. Currently the American College of Physicians recommends preoperative pulmonary function testing only in patients who are thought to have undiagnosed chronic obstructive pulmonary disease.[9] Low serum albumin (<35 g/L) is a powerful, independent marker of increased risk for postoperative pulmonary complications. Several indices incorporating multiple factors can be used to stratify pulmonary risk. These typically incorporate the type of surgery, age, functional status, weight loss/nutritional status, COPD, smoking, and whether the surgery is emergent. After a patient is identified as at risk for pulmonary complications, risk reduction strategies should be used. These include smoking cessation, respiratory physiotherapy, respiratory muscle training, optimization of nutritional status, intraoperative strategies, and postoperative lung expansion techniques when appropriate.

Patients who currently smoke have a twofold increased risk for postoperative complications, with the highest risk in patients who have smoked within the past 2 months. Smoking abstinence can reduce the rate of such complications. Patients who have quit smoking for more than 6 months have a risk similar to those who do not smoke, and the beneficial effects of smoking cessation, including improvement in ciliary function and a decrease in sputum production, occur gradually over a period of several weeks. Strategies to improve the quit rate for smoking include counseling, nicotine replacement therapy, bupropion, hypnosis therapy, and varenicline. Nicotine replacement therapy is available in several formulations, including transdermal patch, gum, nasal spray, inhaler, and lozenge. Bupropion is an atypical antidepressant, and varenicline is a partial agonist of the α4β2 nicotinic acetylcholine receptor. Second line agents are nortriptyline, a tricyclic antidepressant, and clonidine, an antihypertensive drug. All of the available treatments appear to be similarly effective, with the exception of varenicline, which has been shown to offer significant improvement in abstinence rates over antidepressants.

Patients with a history of bronchospasm and chronic obstructive pulmonary disease should also be optimized before surgery. International guidelines suggest the use of inhaled bronchodilators, β2 agonists, and anticholinergics as the mainstay of symptomatic therapy for patients with bronchial hyperreactivity. These interventions should begin at least 5 days before surgery. Systemic corticosteroids are recommended when the FEV1 is less than 80% of predicted. In addition, it has been demonstrated that the instances of bronchospasm during intubation in patients with bronchial hyperreactivity who were not previously receiving bronchodilators is reduced with the use of albuterol and steroids. The safety of perioperative corticosteroid use has been established, and it is not associated with death or serious infections. Lung expansion techniques, such as incentive spirometry, chest physical therapy, cough, postural drainage, ambulation, and continuous positive airway pressure, have been used to limit postoperative pulmonary complications. Available data suggest that for patients undergoing abdominal surgery, any type of lung expansion intervention is better than no prophylaxis at all, although no one modality is clearly superior and there is little benefit to combining modalities.[13] Despite the association of hypoalbuminemia with the development of postoperative pulmonary complications, the use of preoperative nutritional supplementation (either parenteral or enteral) has not been demonstrated to reduce postoperative pulmonary complications and should not be instituted solely for this purpose.

Renal Evaluation

Vascular patients are frequently found to have kidney dysfunction at initial evaluation because of the shared risk factors of diabetes, hypertension, atherosclerosis, obesity, alcohol, nicotine abuse, and hypercholesterolemia. One-third of all vascular surgery patients suffer from stage III or higher chronic kidney disease (CKD).[14,15] Therefore kidney function must be carefully evaluated preoperatively. The preoperative evaluation should include an assessment for the presence of renal failure symptoms such as fatigue, dry skin, muscle cramps, decreased urine output, recurrent urinary tract infections, edema, history of renal disease, and history of dialysis or transplantation. The examination should focus on signs of hyperkalemia, volume status, anemia, and bleeding.

In all patients a baseline creatinine level and glomerular filtration rate (GFR) should be obtained to identify problems with renal clearance preoperatively and to establish baseline renal function should renal compromise occur. Serum cystatin C level should be measured in patients with an estimated GFR of 45 to 59 mL/min for confirmation of CKD. In addition, as noted previously, laboratory tests should assess electrolyte status, the presence of anemia, and coagulation status; the chest radiograph should be examined carefully for signs of fluid overload. If the patient is being maintained with dialysis, careful examination of the vascular access site should be performed. If a dialysis catheter is present, it should be inspected for signs of infection, and functionality of the catheter should be verified. If an arteriovenous fistula or graft is present, the fistula or graft should be assessed for thrill and bruit, infection should be excluded, and the examiner should verify that there is adequate blood flow to the hand. The fistula or graft should also be protected before and during surgery, commonly by wrapping the site in loose gauze. The nursing and technical staff should also be advised to avoid drawing blood from the arm used for access.

Hyperkalemia is common in patients with chronic renal insufficiency or end-stage renal disease (ESRD). It is important to correct potassium levels before surgical intervention because hyperkalemia may cause cardiac instability. Treatment options include polystyrene binding resins, insulin in combination with intravenous dextrose, calcium carbonate for cardiac stabilization, intravenous bicarbonate, and dialysis. Polystyrene binding resins can be given orally or as retention enemas and, like dialysis, remove excess stores of potassium; although retention enemas should be used with care to prevent colonic necrosis. Patients maintained with dialysis should undergo dialysis the day before surgery. In addition to correction of electrolytes, acid-base balance should be achieved before surgery because acidosis can decrease the effectiveness of some local anesthetics.

A clinical history of prolonged bleeding and frequent bruising can suggest a potential coagulation abnormality. In the patient with renal dysfunction, uremia can be associated with platelet dysfunction, which may result in an increased incidence of perioperative bleeding. If confirmed, options to improve platelet function include dialysis, desmopressin, cryoprecipitate, conjugated estrogens, and transfusion of red blood cells or platelets (or both). Antiplatelet agents, including aspirin, clopidogrel, and dipyridamole, should be accounted for and recommendations made before surgery in patients with ESRD. In addition, drug-induced minor platelet effects may be exaggerated in ESRD patients, and drugs associated with such problems include diphenhydramine, nonsteroidal antiinflammatory drugs, chlordiazepoxide, and cimetidine.

Anemia is of particular concern in patients with ESRD because of decreased production of erythropoietin. If necessary, red blood cells can be transfused to correct the hematocrit before surgery. However, unnecessary transfusion should be avoided because antibody formation may result in higher rejection rates if the patient is a candidate for future renal transplantation. In addition, transfusion may result in red blood cell lysis and contribute to hyperkalemia. If surgery is elective, it should be delayed until erythropoietin can be administered and the hematocrit allowed to increase in response to the patient's own production of red blood cells.[16] Erythropoietin is also an important option for patients who refuse transfusion for religious reasons.

Contrast-induced nephropathy (CIN) is the third most common cause of hospital-acquired acute renal injury and the leading cause of iatrogenic renal failure. It is a significant problem as more patients are receiving iodinated contrast media for computed tomography, angiography, and endovascular therapies.[17] Strategies to reduce the risk of CIN include (1) avoidance of iodinated contrast completely by using alternative imaging techniques (e.g., MRA, ultrasound, or CO_2), (2) limit the volume of iodinated contrast agents and use only nonionic, low osmolar agents (e.g., iodixanol [Visipaque]), and (3) judicious periprocedural hydration with isotonic saline. Some authors recommend the use of oral N-acetylcysteine (Mucomyst) on the day before and the day of the procedure, although the evidence supporting this practice is conflicting. Recent evidence suggests that the use of sodium bicarbonate and N-acetylcysteine is of no addition value. There are insufficient data to recommend the use of ascorbic acid, statins, low-dose dopamine, or fenoldopam. The use of a gadolinium-based agent, such as those used in magnetic resonance imaging, should be avoided in the setting of compromised renal function. It has been associated with the development of nephrogenic systemic sclerosis, a rare but serious syndrome that involves fibrosis of the skin, joints, eyes, and internal organs. A detailed review of renal complications is presented in Chapter 44.

Diabetes

Surprisingly, the prevalence of undiagnosed diabetes in surgical patients is high despite the association of diabetes with multiple perioperative complications.

Preoperatively, the surgeon should elicit a complete diabetic history, including a history of metabolic control and diabetic complications such as heart disease, nephropathy, neuropathy, retinopathy, and previous episodes of diabetic ketoacidosis or hyperosmolar hyperglycemic nonketotic coma. In addition, evidence of diabetic autonomic neuropathy should be sought because this predisposes patients to perioperative hypotension, and gastroparesis increases a patient's risk for aspiration.

High glucose levels are associated with increased morbidity and mortality after surgery and in the intensive care unit. Independent of previous cardiac disease, diabetes, or other comorbid conditions, hyperglycemia at the time of carotid endarterectomy has been associated with an increased risk for perioperative stroke, MI, and death. In addition, poor perioperative glycemic control is associated with an unfavorable outcome after peripheral bypass surgery. Therefore it is imperative that blood glucose be controlled during and after vascular surgery. If necessary, every effort should also be made to ensure that glucose levels are controlled preoperatively. When possible, glucose control should be attained weeks before surgery; hemoglobin A1c (HbA1c) is a useful diagnostic test for assessing long-term glucose control. However, some patients will require

preoperative hospitalization and endocrine consultation to ensure diabetic control before surgery. When necessary, an insulin drip with hourly glucose monitoring can be used to stabilize blood glucose levels.

Several studies add additional perspective to perioperative diabetic management. Dronge et al. conducted a retrospective observational study of 490 diabetic patients using the Veterans Affairs National Surgical Quality Improvement Program (now VASQIP).[18] With primary outcomes of infectious complications, including pneumonia, wound infection, urinary tract infection, or sepsis, they observed that a preoperative HbA1c (within 180 days of surgery) of less than 7% was significantly associated with a decrease in infectious complications with an adjusted odds ratio of 2.13. Although this association was not observed in a subsequent larger study of more than 55,000 diabetic patients undergoing a variety of noncardiac operations, King et al. did report that higher rates of postoperative infection were associated with mean 24 hour postoperative serum glucose concentrations of 150 to 250 mg/dL (incidence rate ratio of 1.22) and greater than 250 mg/dL (incident rate ratio of 1.43).[19]

Glucose control should also be considered even in the nondiabetic patient. In a 2010 study, Frisch et al. studied morbidity and mortality in 3184 noncardiac surgery patients.[20] Using multivariate analysis, the risk of death increased in proportion to perioperative glucose levels; however, the relationship was only significant for patients without a history of diabetes. O'Sullivan and associates also found a link between poor preoperative glucose control in nondiabetics and perioperative mortality.[21] They studied preoperative HbA1c in 165 patients undergoing vascular surgery procedures; 43 had diabetes, and 122 did not. In diabetics, a HbA1c of greater than 7 was associated with a significantly higher incidence of 30-day mortality. In nondiabetics a suboptimal HbA1c (>6 to ≤7) was an independent predictor of 30-day morbidity.

Although there has been substantial observational evidence linking hyperglycemia in hospitalized patients with or without diabetes to worsening health outcomes, the optimal blood glucose range remains ill defined. Until recently, achievement of nearly normal glycemia was considered beneficial in the intensive care unit setting and during the postoperative period, predominantly on the basis of studies evaluating outcomes after cardiac surgery. Subsequent trials have not replicated the initial findings with tight glycemic control using intensive insulin therapy. The use of intensive insulin therapy has been demonstrated to have no effect on mortality, sepsis, or wound infection.[22] Similarly, the need for strict intraoperative glycemic control has not been demonstrated. There is insufficient evidence to provide definitive recommendations for glycemic targets for hospitalized patients. The American Diabetes Association,[23] the Canadian Diabetes Association,[24] and others have recommendations on inpatient glycemic control.[25] In the intensive care unit, the glucose goal should be maintained between 140 and 180 mg/dL. For general medical and surgical patients, a premeal glucose target less than 140 mg/dL and a random blood glucose concentration less than 180 mg/dL should be obtained.

Different regimens have been recommended for routine preoperative treatment of diabetic patients undergoing surgical procedures. Patients with type 2 diabetes who are being treated by diet alone are to abstain from oral intake overnight, and hydration may be maintained with intravenous solutions. Hyperglycemia is treated with supplemental short-acting insulin. In patients treated with oral agents, these medications are generally withheld the day of surgery, and hyperglycemia can be corrected with insulin. Metformin should be stopped 24 hours before surgery to prevent the possibility of lactic acidosis if the patient's renal function becomes compromised. For patients receiving insulin therapy and for the postoperative patient, recommendations are listed in Box 32.2. Specific sliding scale insulin regimens are typically standardized on the basis of hospital practices.

Adrenal Evaluation

Patients who have been chronically treated with steroids may not be able to mount a stress response and will thus be at risk for perioperative adrenal crisis. Therefore a careful history should be performed to screen for steroid use. Hypothalamic or pituitary dysfunction should be considered in patients with tumor, previous brain irradiation, or sarcoidosis. Furthermore, primary adrenal insufficiency may be present in patients with tuberculosis, acquired immunodeficiency syndrome, and autoimmune endocrine syndromes.

Following reports of adrenal suppression associated with chronic glucocorticoid pharmacotherapy in the 1950s, protocols for stress steroid coverage to prevent surgically induced adrenal insufficiency were initiated. However, studies through the late

BOX 32.2 Recommendations for Perioperative Glycemic Management With Insulin Therapy

Determine level of glycemic control.

Avoid alterations of long-acting basal insulin the day before surgery (unless hypoglycemia or on diet restrictions).

Reduce evening dose of intermediate-acting (NPH) insulin the day before surgery to 75%. The day of surgery, use 50%-75% of the morning dose.

Do not administer prandial insulin while the patient is fasting.

Maintain intraoperative glucose ranges between 100 and 180 mg/dL.

In nonintensive care unit settings

Preferable method for control is the use of subcutaneous basal-bolus-correctional insulin.

For noneating patients: use of basal insulin in combination with correctional insulin.

The use of sliding scale as monotherapy is inadequate and should be avoided.

Use standardized subcutaneous insulin protocols as clinically applicable.

Patients receiving intravenous insulin who are not insulin naïve, safely transition to subcutaneous insulin when appropriate. Use 60%-80% of total daily calculated insulin requirement based on the final 6 h of the infusion rate.

In patients receiving intravenous insulin who are previously insulin naive, the conversion can be more complex but is frequently based on 50% of the total daily need when instituted at glucose levels ≥140 mg/dL.

1990s began to suggest that stress steroid protocols might not be routinely necessary. In 2008 Marik and Varon published a review of the literature with the purpose of determining the requirement for perioperative supplemental stress doses of corticosteroids in patients receiving long-term corticosteroid therapy.[26] They identified nine studies, two randomized controlled trials (RCTs), and seven cohort studies. In the two RCTs, there was no advantage for those patients receiving stress doses of corticosteroids, and in five of the cohort studies there were no hemodynamic consequences in patients continuing to receive their daily dose of steroids without additional stress supplementation. In the remaining two studies, one patient in each (1% and 5% of the respective cohorts) had unexplained hypotension when steroids were discontinued before surgery. In each case the patients responded to steroid administration. The authors concluded that patients receiving therapeutic doses of corticosteroids do not require supplemental coverage if daily doses are continued. Patients receiving physiologic replacement doses because of hypothalamic-pituitary-adrenal axis dysfunction should receive supplemental steroids perioperatively. In these patients the authors recommend 50 mg of hydrocortisone intraoperatively, continued every 8 hours for 48 to 72 hours postoperatively.

There is significant individual variation in the dose and duration of steroid therapy that leads to suppression of the hypothalamic-pituitary axis. In evaluating the need for perioperative steroid coverage, the patient's steroid history and the complexity of surgery should both be considered. If patients are taking less than 5 mg of prednisone (4 mg of methylprednisolone, 0.5 mg of dexamethasone, 20 mg of hydrocortisone) in the morning, have been treated for less than 3 weeks, or are taking less than 10 mg of prednisone (or its equivalent) every other day, they should not require intraoperative steroid coverage. However, they should continue to receive their regular daily dose of steroids.[26a] Patients taking greater than 20 mg per day of prednisone (or equivalent) should receive supplemental perioperative steroid coverage. Recommendations for perioperative coverage vary. Marik and Voran[24] recommended 50 mg of hydrocortisone intraoperatively, continued every 8 hours for 48 to 72 hours for patients receiving physiologic replacement doses because of hypothalamic-pituitary-adrenal axis dysfunction. Other authors[27-29,29a] have based coverage on surgical complexity. Excessive steroid use may be associated with impaired wound healing, increased blood glucose concentration, or increased susceptibility to infection, and therefore steroids should be given based on the minimum requirement. Some have recommended that patients undergoing minor surgery (inguinal hernia equivalent) should receive 25 mg of hydrocortisone (or its equivalent) at the start of the procedure and then their usual replacement dose after the procedure. Others advocate no preoperative steroids for minor procedures. Patients undergoing moderately complex surgery (lower limb revascularization) should receive 50 to 75 mg of hydrocortisone on the day of surgery, tapered to the patient's usual replacement dose over 1 to 2 days. For major surgery (cardiothoracic surgery of its equivalent) patients should receive 100 to 150 mg of hydrocortisone on the day of surgery, which is tapered to the patient's usual dose over 2 to 3 days. As recommendations vary, it is best to coordinate planned steroid coverage with anesthesiology prior to any surgical procedure.

Patients taking 5 mg of prednisone a day or greater (or equivalent), less than 5 mg of prednisone (or equivalent), but in the evening, or patients who have discontinued glucocorticoids in the year prior to surgery should be evaluated for adrenal insufficiency by measuring a morning cortisol level or assessing the results of a corticotropin stimulation test. Corticotropin stimulation testing uses 250 μg of cosyntropin administered intravenously or intramuscularly and measures cortisol at baseline and then at 60 minutes. A plasma cortisol level greater than 20 μg/dL (552 nmol/L) at either time is diagnostic of adequate function. As an alternative, the low-dose stimulation test uses 1 μg cosyntropin intravenously and measures cortisol at baseline and 30 minutes. A plasma cortisol level greater than 18 μg/dL (497 nmol/L) is diagnostic of adequate function in the low-dose stimulation test.

Deep Venous Thrombosis Prophylaxis, Thrombotic Risk Factors, and Antithrombotic Therapy

The potential for deep venous thrombosis (DVT) in surgical patients can be stratified by risk factors and the type of operation. Prior to surgery, the surgeon should obtain a history of the patient's coagulation status and previous history of thrombotic events. A family history or a previous episode of DVT may indicate a genetic predisposition to abnormal clotting, such as factor V Leiden or prothrombin gene mutations. A pharmacologic history, including current and previous exposure to drugs that modify coagulation, such as aspirin, antiplatelet therapy, warfarin, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and direct thrombin and factor Xa inhibitors, should also be obtained. Particular attention should be paid to adverse reactions, such as aspirin allergy or previous development of heparin-induced thrombocytopenia (HIT). In addition, physicians should be aware of the possibility of other procoagulant states, such as antithrombin III deficiency, protein C and S deficiency, antiphospholipid syndrome, disseminated intravascular coagulation, and abnormal platelet function, all of which may confound the underlying disease process responsible for the vascular insult (see Chapter 38).

Pharmacologic prophylaxis for venous thromboembolism includes UFH, LMWH, fondaparinux, warfarin, antiplatelet therapy, and direct thrombin or factor Xa inhibitors. Mechanical devices, such as graduated compression stockings, intermittent pneumatic compression, and venous foot pumps, are also effective modalities for prophylaxis of venous thromboembolism (see Chapter 146). Updated guidelines for DVT prophylaxis have been reported.[30] Recommendations specific to vascular surgery are limited because of the lack of large randomized trials evaluating outcomes in patients undergoing specific vascular procedures. Given this, recommendations for vascular surgery are pooled with recommendations for patients undergoing general, urologic, gynecologic, bariatric, and plastic or reconstructive surgeries (Table 32.2).

TABLE 32.2 Recommendations for Thromboprophylaxis in Various Risk Groups

Risk and Consequences of Major Bleeding Complications		
Risk of Symptomatic VTE	Average Risk (–1%)	High Risk (–2%) or Severe Consequences
Very low (<0.596)	No specific prophylaxis	
Low (~1.596)	Mechanical prophylaxis with IPC	
Moderate (~3.096)	LDUH, LMWH, or mechanical prophylaxis, preferably with IPC	Mechanical prophylaxis, preferably with IPC
High (~6.096)	LDUH or LWMH plus mechanical prophylaxis with ES or IPC	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added
High-risk cancer surgery	LDUH or LMWH plus mechanical prophylaxis with ES or IPC and extended-duration prophylaxis with LMWH postdischarge	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added
High risk, LDUH and LMWH contraindicated or not available	Fondaparinux or low-dose aspirin; mechanical prophylaxis, preferably with IPC; or both	Mechanical prophylaxis, preferably with IPC. until risk of bleeding diminishes and pharmacologic prophylaxis can be added

ES, Elastic stockings; *IPC*, intermittent pneumatic compression; *LDUH*, low-dose unfractionated heparin; *LMWH*, low-molecular-weight heparin; *VTE*, venous thromboembolism.

Reproduced with permission from Gouid MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(suppl):e2275–e2775.

With the increasing use of heparin and heparin-containing solutions in hospitalized patients, a history of HIT has become more common in the preoperative evaluation of patients. The reported incidence is variable, although HIT can occur in up to 5% of patients exposed to heparin.[31] Greinacher suggests an incidence of 1 in 5000 hospitalized patients. The risk is greatest after the use of UFH and can be seen in 1% to 3% of patients after coronary bypass. Thrombocytopenia is the result of autoantibodies to the heparin–platelet factor 4 complex (see Chapter 38).

The literature predominately addresses the significance of HIT relative to planned cardiac surgery and PCI. However, Warkentin et al. reviewed records over a 30-year period, identifying patients with a diagnosis of HIT who underwent vascular surgery while positive for heparin-dependent platelet activating antibodies using a serotonin release assay.[32] Most of the surgeries were necessitated by acute arterial thrombosis, and patients were divided into two groups, those receiving intraoperative anticoagulation with either UFH or an alternative non–heparin-based strategy. Limb amputation was the primary outcome. Fourteen patients were identified; 10 received intraoperative UFH, and four were managed with alternative strategies, including saline flushes, danaparoid, lepirudin, or argatroban. Two of the 10 receiving UFH underwent subsequent amputation, and three of four receiving alternative therapies had amputation. The review extended from 1981 to 2010, was observational, and included only a small number of patients. Patients were not randomized or matched. Nonetheless, the authors concluded that UFH administration to patients with SRA-positive HIT did not necessarily lead to adverse outcomes. Welsby et al. reported on the use of intraoperative plasmapheresis and heparin anticoagulation in cardiac surgical patients.[33] Three of 11 patients died of causes unrelated to HIT 3 months to 1 year after surgery. Only one patient developed foot ischemia, associated with cardiogenic shock and not thought to be HIT related. Current recommendations from the American College of Chest Physicians[34] are to use nonheparin anticoagulants, such as bivalirudin, lepirudin, or argatroban over heparin or LMWH in patients with a history of HIT who continue to have heparin antibodies present and who require cardiac surgery. In patients with a history of HIT but without heparin antibodies, heparin anticoagulants may be used.

Direct thrombin inhibitors, including argatroban, lepirudin, and bivalirudin, have been used during PCIs in patients with HIT.[35] The agents are valued because of their small molecular size, their ability to inhibit bound and unbound thrombin, and their lack of cross reactivity with HIT antibodies. Current recommendations from the American College of Chest Physicians suggest the use of bivalirudin (a grade 2B recommendation) or argatroban (a grade 2C recommendation) for percutaneous interventions.[34]

Previously perioperative management of anticoagulation has focused on the need to discontinue warfarin and the necessity to initiate bridge anticoagulation prior to and after surgery. Current consensus recommendations advocate the discontinuation of warfarin 5 days prior to surgery.[30] Patients should be assessed at least 7 days prior to surgery, should be provided with a calendar outlining the perioperative timing of warfarin discontinuation, and should undergo INR testing on the day before surgery. Warfarin can be resumed 12 to 24 hours after surgery.

Consensus recommendations support the use of bridging anticoagulation with therapeutic doses of LMWH in high-risk patients.[30] High-risk patients include those with any mitral valve prosthesis, any caged or tilting disc aortic prosthesis, or

recent (within 6 months) stroke or TIA. Patients with atrial fibrillation are at high risk if they have a $CHADS_2$ score of 5 or 6, have had a recent (within 3 months) stroke or TIA, or have a history of rheumatic valvular heart disease. Patients with a recent (within 3 months) history of venous thromboembolic disease or thrombophilia are also at high risk. The use of therapeutic dose, subcutaneous LMWH appears to have a lower incidence of arterial thromboembolic events. Protocols suggest that LMWH should be started 3 days prior to surgery and stopped the day of surgery. Bridging is resumed 12 to 24 hours after surgery depending on the risk of bleeding.[36]

When managing bridging anticoagulation, prior to the use of spinal or epidural anesthesia, prophylactic LMWH should be discontinued 10 to 12 hours prior to placement of the catheter and should be resumed 6 to 8 hours after catheter removal. When using therapeutic doses of LMWH, treatment should be discontinued 24 hours prior to catheter placement and restarted 24 hours after catheter removal.

The use of bridging anticoagulation in patients not at high risk is unclear, and individual risk factors for thromboembolic complications and perioperative bleeding need to be considered. Two recent studies have examined the value of periprocedural heparin bridging. Siegal et al. reported on a systematic review and meta-analysis, concluding that vitamin K antagonist (VKA)-treated patients receiving periprocedural heparin bridging appeared to be at increased risk of overall and major bleeding and at a similar risk of thromboembolic events.[37] The study did not define the risk of the patients reported. Furthermore, an accompanying commentary did caution that the study reflected a heterogeneous database because of a high variation in clinical practice and that uniform bridging protocols were not used.[38] A more recent randomized, double-blind placebo-controlled trial, in which patients with atrial fibrillation were assigned to receive LMWH bridging (100 IU of dalteparin per kilogram subcutaneously twice a day) or placebo after interruption of warfarin therapy, was reported by Douketis et al.[39] Bridging extended from 3 days before the procedure until 24 hours before the procedure. Patients with atrial fibrillation associated with valvular heart disease were excluded. The study showed that forgoing bridging anticoagulation was noninferior to perioperative bridging with LMWH with respect to the prevention of arterial thromboembolism and a decreased risk of bleeding.

With the advent of novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban, there are additional considerations. The newer agents are frequently not monitored; have dependable therapeutic profiles; and have more rapid onset and shorter half-lives, altering the time needed to clear the anticoagulant effect and the time needed to achieve clinical anticoagulation. Of the newer anticoagulants, dabigatran has been studied most extensively. Healey and others showed dabigatran facilitated shorter interruption of oral anticoagulants prior to surgery.[40] Depending on the renal function and risk of perioperative bleeding, dabigatran could be stopped 24 to 96 hours prior to surgery. Schulman et al. reported resuming dabigatran therapy on the day of the procedure in 40% of 541 cases studied.[41] Bridging was not used preoperatively but was used in nine patients (1.7%) postoperatively. Postoperative bridging was associated with bowel surgery and vascular surgery. For patients receiving neuraxial anesthesia, the American Society of Regional Anesthesia recommends stopping dabigatran 5 days prior to surgery.[42]

Management of the other non-VKA anticoagulants generally reflects the management protocols used for dabigatran. Discontinuation is dependent upon the risk of bleeding and renal function but generally can occur 2 to 4 days prior to surgery. Bridging anticoagulation has not been used preoperatively. Postoperatively, anticoagulants can be resumed, at preoperative dosages, once hemostasis has been ensured. Postoperative bridging may be necessary if the slow return of bowel function prevents oral intake in high-risk patients for arterial thromboembolism, stroke, or venous thromboembolic disease.

Infection

Patients with infection in the preoperative period should be identified because of their increased risk for surgical site infection. Common sources of infection, both preoperatively and postoperatively, include the urinary tract, the pulmonary system, and an ischemic extremity. If any prosthetic material has been implanted, it can also be a nidus for infection. A careful history should be performed to elicit signs of infection, such as recent fever, cough, sputum production, urinary symptoms, tenderness or erythema over a graft site, or purulence from an open wound or ischemic extremity. The physical examination should assess abnormal breath sounds, and careful inspection of the extremities and feet should identify any ulceration, tenderness, or erythema. Urinalysis, a chest radiograph, and a white blood cell count should be obtained to evaluate for specific sites of infection if indicated. If infection is identified, elective surgery should be delayed until the patient's health has been optimized. Choice of antibiotics should be tailored to the specific microbe and sensitivities identified from microbiology laboratory cultures. In the absence of an acute infection, perioperative prophylactic antibiotic administration is recommended in patients undergoing vascular surgery. Antibiotics should be administered within 1 hour before incision and should be discontinued within 24 hours postoperatively unless an underlying infection is being treated. Acceptable prophylactic antibiotics include cefazolin and cefuroxime. Vancomycin is an acceptable alternative in the setting of β-lactam allergy, methicillin-resistant *Staphylococcus aureus* (MRSA) colonization or infection, chronic wound care or dialysis, acute inpatient hospital extended care or nursing home care in the previous 12 months, or preoperative length of stay of 24 hours or longer.

Antibiotic resistance is a growing problem, in particular with MRSA, which has become a predominant cause of *S. aureus* infections in both healthcare and community settings, with up to 65% of healthcare–associated *S. aureus* infections due to MRSA. Unlike for traditional *S. aureus* infection, treatment options for MRSA infection are limited and less effective. MRSA is typically transmitted person to person, and colonization generally precedes infection. Colonization is frequently long lasting (months to years). Successful prevention of MRSA transmission is possible

through Centers for Disease Control and Prevention–recommended core and supplemental strategies. Core strategies target preventing transmission from colonized to uncolonized persons and preventing infection in colonized patients. Core preventive strategies include assessing hand hygiene practices, implementing contact precautions of MRSA-colonized/infected patients, recognizing previously colonized patients who have not met criteria allowing discontinuation of isolation, rapid laboratory reporting of MRSA identification, and providing MRSA education to healthcare providers. Supplemental strategies including active surveillance testing and decolonization have been recommended by many but met with controversy. Although several successful MRSA preventive collaboratives have used active surveillance testing, studies evaluating its utility have demonstrated mixed results. Active surveillance testing involves culture or polymerase chain reaction testing (frequently from the nares) done at the time of patient admission, typically focusing on high-risk patients such as those admitted to the intensive care unit. However, after it is identified, no data to date exist to support programs of pharmacologic decolonization.

Preoperative Anemia and Coagulation Assessment

Preoperative anemia increases the postoperative morbidity and mortality for patients undergoing noncardiac surgery. A history of chronic renal disease or anemia, such as sickle cell disease or thalassemia, should alert the physician to the potential for anemia, and a preoperative hematocrit level should always be obtained to provide information on the red blood cell status of the patient. Ideally, preoperative anemia should be identified and treated if possible. Bleeding from the upper and lower gastrointestinal tract or the genital-urinary tract should be considered and investigated. There are three types of iron-restricted erythropoiesis that should be considered: absolute iron deficiency, iron sequestration secondary to inflammation, and iron deficiency due to insufficient erythropoiesis stimulating agents.[43] Nutritional deficiencies also need consideration. These forms of anemia can be treated with pharmacologic interventions, including iron, vitamin and folate supplementation, or erythropoiesis-stimulating agents. Transfusion of blood preoperatively should be limited to patients who are symptomatic, bleeding with severe anemia, or poor physiologic reserve with insufficient time to correct the physiologic abnormality. However, because transfusion is not without side effects and blood is costly with limited availability, anemic patients should be carefully evaluated to determine whether transfusion is likely to be of benefit. In addition, the patient's cardiac status may influence the decision to transfuse inasmuch as anemia worsens outcomes in patients with coronary artery disease who undergo cardiac or noncardiac surgery. Although recommendations for transfusion have been debated, most current guidelines recommend adhering to a restrictive transfusion strategy when possible.[44] In adult and pediatric intensive care unit patients, transfusion should be considered at hemoglobin concentrations of 7 g/dL or less. In postoperative surgical patients, transfusion should be considered at a hemoglobin concentration of 8 g/dL or less or for symptoms including chest pain, orthostatic hypotension, and tachycardia unresponsive to fluid resuscitation.[45] For elective surgery, autologous transfusion or administration of erythropoietin should be considered to boost the patient's red blood cell volume from endogenous sources.

Due to the nature of most vascular surgical interventions and the fact that the majority of vascular patients are on antiplatelet agents or anticoagulants, coagulation studies are routinely checked. However, the medical history remains the most important tool for detecting inherited and acquired bleeding disorders that would increase the risk of perioperative bleeding. This includes a medication history, questions regarding a known coagulopathy, unexplained epistaxis, hematomas, prolonged bleeding following cuts or abrasions, or abnormal requirements for blood products after previous surgeries. Routine tests include an activated partial thromboplastin time (aPTT), a PT, which allows the generation of the standard INR, and a platelet concentration. Unfortunately, these values are poor predictors of perioperative bleeding and mortality, although an INR greater than 1.8 and a platelet count less than 50×10^3 have been associated with adverse outcomes and may delay surgery or prompt an intervention to correct the abnormality.[45]

Nutrition

Up to half of surgical patients have preoperative malnutrition that contributes to an increased risk for postoperative complications, such as impaired wound healing and infection, pulmonary complications, longer hospital stay, higher health cost, and overall increased morbidity and mortality. Vascular surgical patients are an elderly population with poor mobility and diet and multiple comorbidities that contribute to a higher prevalence of malnutrition, which may be exacerbated by specific vascular disease processes such as diabetes, chronic mesenteric ischemia, and renal failure. Lower preoperative nutritional indices are associated with more severe systemic inflammatory responses after major vascular surgery. Serum albumin is the standard laboratory assessment of nutritional status, and hypoalbuminemia (<3.5 g/dL) from malnutrition is an independent predictor of major adverse events and death after major open vascular surgery.[46] However, a similar relationship was not observed for endovascular procedures, suggesting that other preoperative factors (congestive heart failure, preoperative hematocrit level, and creatinine concentration) were more predictive of postoperative complications.

A nutritional assessment should be performed for all vascular surgical patients, including a history evaluating changes in weight and appetite as well as the patient's functional status (which may impair the ability to obtain or prepare food). Symptoms of nausea, vomiting, dysphagia, constipation, diarrhea, and related gastrointestinal complaints should be assessed, particularly in patients with suspected mesenteric ischemia. In general, weight loss of more than 5% in 1 month or 10% in 6 months can signify an increased risk for postoperative complications.[47] The physical examination should focus on body habitus and findings of general weakness, edema, pallor, decubitus ulcers, petechiae, ecchymoses, poor skin turgor, fissured tongue,

inflamed gums, ulceration of the oral mucosa, brittle hair, and nail abnormalities.

A number of laboratory values can be used to assess nutritional status, but serum albumin is the most appropriate. Albumin is the most abundant plasma protein and has a long half-life (18-21 days); it is a marker of chronic protein status and a better evaluation of nutritional status than anthropometric measurements. Serum prealbumin and transferrin levels have a shorter half-life and are more sensitive to the short-term response to nutritional support than are assessment tools for chronic malnutrition. The prognostic nutritional index, which relates operative risk to nutritional status, is determined on the basis of nutritional parameters including serum albumin, serum transferrin, triceps skinfold measurement, and skin test of delayed hypersensitivity.[48] It is seldom used in clinical practice.

Despite the nutritional assessment's ability to predict poor outcomes, there are no clear guidelines as to who would benefit from preoperative nutritional support, especially in patients undergoing vascular surgery. There is evidence that preoperative nutritional support can lower postoperative complication rates in patients undergoing intraabdominal surgery, particularly in those with severe malnutrition (albumin <2.1 g/dL). Up to 25 to 35 kcal/kg per day, based on adjusted body weight in obese patients, should be provided, incorporating 1.5 to 2 g/kg per day of protein. A Cochrane evaluation of preoperative nutritional support in patients undergoing gastrointestinal surgery demonstrated that the use of parenteral nutrition significantly reduced postoperative complications.[47] Similar results with oral supplementation or enteral nutrition were not observed, although most experts agree that enteral nutrition is preferred to parenteral because it is safer and more cost-effective. It is recommended that nutritional support be provided for 10 to 14 days before major surgery.[48] Interestingly, immune-enhancing nutritional supplementation can significantly reduce postoperative complications. Immune-enhancing formulas intend to bolster function of the immune system by providing immunonutrients, including arginine, glutamine, and ω-3 polyunsaturated long-chain fatty acids. However, the generalizability of these modalities to vascular surgical patients is unknown.

ETHICAL AND LEGAL CONCERNS/ FRAILTY ASSESSMENT

As part of the decision to proceed with surgery, both the physician and patient must consider ethical and legal matters. In the preoperative evaluation, situations pertaining to patient confidentiality, reporting of abuse, and informed consent may arise. Furthermore, should issues arise in the perioperative or postoperative period that ultimately result in legal action, a medical damages claim must establish three things to prove successful: it must be shown that (1) the provider had a duty to care for the patient, (2) the duty of care was breached in a deviation from the standard of care, and (3) this breach caused loss or damage to the patient. Therefore the preoperative setting is ideal for both the patient and the physician to come to a mutual understanding about the expectations of the physician-patient relationship and the treatment decided on to minimize the chance that legal action will be initiated.[49]

Patient confidentiality is an important topic since the passage of the Health Insurance Portability and Accountability Act (HIPAA) in the United States to address the privacy and release of health information. Physicians have a duty to maintain confidentiality with their patients, which means that they may not disclose any medical information discovered in connection with the treatment of a patient, thereby protecting the physician-patient relationship. Information contained in a patient's medical record may be released to third parties only if the patient provides consent. Breaches in confidentiality can lead to mistrust, lawsuits, or disciplinary action. Exceptions can be made if patients threaten bodily harm to themselves or to others. Federal and state laws vary on the reporting of suspected child, elder, or spousal abuse. It is the responsibility of the physician to be aware of these laws.

Informed consent must be obtained from all patients before surgical intervention and is a process of communication that results in the patient's agreement to undergo a medical intervention. To provide consent, the patient must have an understanding of the diagnosis, the purpose of a proposed procedure, the risks and benefits associated with the procedure, the alternative treatments, and the risks and benefits of not undergoing a procedure. This may seem straightforward, but it has been shown that surgeon characteristics influence how risks are presented to vascular patients.[50] Care must be taken while discussing the risks and benefits of the surgery so that patients do not think that they are being coerced into a specific decision. The informed consent, although not designed as such, is an instrument through which trust between physician and patient can be further enhanced.[48] Although informed consent is a process, for the purpose of protection from litigation it is important that this communication be documented. If the patient does not have decision-making capacity, a family member or someone with power of attorney will need to be designated to make decisions on behalf of the patient. A patient need not have the same level of awareness at all times to provide legally adequate informed consent. In these situations, consultation with the psychiatry and ethics teams can be helpful. Regardless, physicians should make themselves familiar with federal and state laws regarding confidentiality, reporting of abuse, and informed consent (Box 32.3).

The final step in risk assessment is brought about by the changing demographics of an aging population. Many of the classic risk stratification tools have failed to take into account

BOX 32.3 Key Components of Informed Consent

Date and time
Diagnosis explained
Risks and benefits of the proposed procedure explained
Alternative treatment options explained
Consent form must be read by the patient
Patient must be given the opportunity to ask questions
Patient must express understanding and wish to proceed

the physiologic reserve of elderly patients. This decreasing physiologic reserve, frailty, which is manifested in functional impairment and multiple comorbidities has been shown to indicate an inability to recover from major stresses and predict poor outcomes in several studies. The concept of frailty represents the increased vulnerability of a patient due to the loss of physical and mental function and the decline of several organ systems. The application of a frailty assessment preoperatively has the ability to engage the patient into a discussion on the risk of a procedure, and the potential outcomes from an intervention. Currently, research is attempting to identify what factors can guide decision-making in the frail and elderly patient. These considerations are necessary to take into consideration when evaluating and providing informed consent for patients.[51]

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A complete reference list can be found online at www.expertconsult.com.

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33 CHAPTER

Intraoperative Management

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Vascular patients are some of the most challenging to manage intraoperatively. These patients, even if known to the medical system, present with multiple comorbidities necessitating extensive preoperative evaluation and preparation. If new to the medical system, their surgical procedures can unmask unknown, often life-threatening medical conditions making their intraoperative management complex. Rarely do these patients present with an isolated vascular issue. Not infrequently, their procedures are complicated requiring long operative times, large incisions, and greater volume and blood loss compared to equally complex general surgery interventions. Frequently, these patients are elderly and lack the physiologic capability to rebound from homeostatic variations. Often only the slightest of insults can lead to their demise. The aim of this chapter is to review some of these intraoperative considerations the surgical team will face during vascular surgery.

ANESTHESIA

General Principles of Anesthesia

The term *anesthesia* refers to the practice of medicine that utilizes the three constituents of analgesia, amnesia, and relaxation. *Analgesia* refers to the absence of pain in the conscious or

TABLE 33.1 Continuum of Depth of Sedation: Levels of Sedation/Analgesia

	Minimal Sedation (Anxiolysis)	Moderate Sedation/Analgesia (Conscious Sedation)	Deep Sedation/Analgesia	General Anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful response to verbal or tactile stimulation	Purposeful response after repeated or painful stimulation	Unarousable, even with painful stimulation
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

From American Society of Anesthesiologists Task Force on Sedation/Analgesia. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology*. 2002;96:1004. Developed by the American Society of Anesthesiologists; approved by the ASA House of Delegates October 13, 1999.

unconscious state. The goal of *amnesia* is to block consciousness and memory formation. With *relaxation*, the aim is to block voluntary motor activity and suppress autonomic reflexes. Each of these components is addressed separately, often by specific agents or techniques in a balanced manner to achieve the level of anesthesia necessary for the planned procedure.

Proper anesthesia is tailored appropriately for the procedure and allows safe, comfortable, and humane conduct of interventions that the patient would otherwise not tolerate. Surgeons are well aware that the physiologic impact of our invasive therapies extends beyond the intraprocedural period into the following days and weeks. As such, the supportive treatments through the perioperative period form a continuum, and many therapeutic interventions initiated in the operating room may have ongoing or even greater importance in the postoperative period. Selection of an anesthetic approach for a particular patient must therefore integrate the preexisting status of the patient, the expected impact of the planned intervention, and the predicted needs of the patient during convalescence. A breakdown of the levels of anesthesia as described by the American Society of Anesthesiologists (ASA) is presented in Table 33.1.[1] Practitioners intending to produce a given level of sedation should be able to rescue patients whose level of sedation becomes deeper than initially intended.

A balanced approach is required as there is no single ideal anesthetic agent that can achieve each of the specific goals with complete safety in all patients. The spectrum of activity of every anesthetic agent can extend beyond the specific effect desired. Many agents induce disturbances in homeostasis that can impair autonomic responses and augment the detrimental impact of surgical trauma. The concept of balanced anesthesia is to administer a sequence of drugs with specific actions at safe dosing ranges without undesirable side effects of any particular agent (see Table 33.1).

Anesthesia Levels

Local/Regional Anesthesia

Local anesthetics produce their effects by interfering with nerve conduction through blockade of neuronal sodium channels.[2,3] The inward sodium current is an essential component for propagation of the action potential along nerve fibers. Most local anesthetics contain an aromatic ring, and are basic and lipid soluble. They are made soluble in an acid aqueous vehicle for administration. In tissue, neutral pH is required to promote neuronal interaction. This is the theoretical explanation for the diminished effect of local infiltration agents in the relatively acidic environment in regions of inflammation or infection.

A variety of agents are available for local anesthesia. These agents have structural homology but different functional properties (potency, onset, duration of action) that influence their selection for clinical applications (Table 33.2).[4] In clinical practice, most vascular surgeons use lidocaine or bupivacaine. Though less potent than lidocaine, bupivacaine has a longer duration of action that extends well into the postprocedural period and thus may enhance recovery comfort.

Systemic local anesthetic toxicity is the result of rapid drug absorption and uptake into the circulation. Beyond the occasional inadvertent intravenous administration, systemic toxicity may occur as a result of absorption from mucosal surfaces, peritoneal or pleural spaces, and muscle. Co-administration of a vasoconstrictor (epinephrine) will reduce these effects somewhat. A Bier block, in which a relatively high dose of local anesthetic is administered intravenously into an isolated limb, can deliver a dangerous systemic dose if the tourniquet is prematurely removed. Ester-containing local anesthetics are cleared by plasma cholinesterase rapidly, but amide-based local agents, including lidocaine and bupivacaine, require liver metabolism. Toxic central nervous system effects follow a dose-related progression from vertigo and tinnitus, to anxiety and fear, and subsequently to tremors, seizures, and coma.[5] Benzodiazepines may mask the early neurologic signs of local anesthetic toxicity, so particular care is needed in the setting of concomitant sedation. Direct cardiovascular toxicity is seen at levels exceeding the threshold for seizure and is manifested as arrhythmia and myocardial depression.

Moderate Sedation

The term *moderate sedation* (formerly referred to as "conscious sedation") describes a drug-induced depression of consciousness that facilitates intervention but does not depress the ability of patients to protect their airway. Moderate sedation does not impair independent respiration and normal cardiovascular function and may be administered by specifically trained individuals with appropriate credentialing. The Joint Commission has developed standards for healthcare facilities that conduct

TABLE 33.2 Clinical Features of Individual Local Anesthetic Drugs

	Drug	Main Use	Potency[a]	Onset	Duration[a]	Toxicity	Maximal Single Dose	Comments
Esters	Cocaine[a]	Topical	1	slow	30-60 min	Very high	150 mg	Addictive, vasoconstriction, "fight or flight response"
	Benzocaine	Topical	NA	slow	30-60 min	Low	200 mg	Topical only
	Procaine	Infiltration, nerve block	2	fast	30-60 min	Low	1000 mg	Allergic potential
	Chloroprocaine	Infiltration, nerve block	1	fast	30-60 min	Low	1000 mg	No longer available
	Tetracaine	Topical	4	slow	30-60 min	High	20 mg	No longer available
Amides	Lidocaine	Topical, infiltration, nerve block, epidural	1	fast	1-2 h	Medium	300-500 mg	Versatile agent
	Mepivacaine[a]	Infiltration, nerve block, epidural	1	fast	1-3 h	Medium	400-500 mg	No longer available
	Prilocaine	Infiltration, nerve block, epidural, intravenous regional	1	fast	1-3 h	Low	600 mg	Methemoglobinemia at >600 mg
	Ropivacaine	Infiltration, nerve block, epidural	4	slow	2-12 h	Medium	20 mg	Enantiomer of Bupivacaine
	Bupivacaine	Infiltration, nerve block, epidural	4	fast	2-12 h	Medium	225 mg	Ventricular arrhythmias, cardiovascular collapse at high doses
	Etidocaine	Infiltration, nerve block, epidural	2	fast	2-12 h	Medium	300-400 mg	No longer available

[a]Relative to lidocaine.

moderate sedation and the ASA has published detailed guidelines for the administration of moderate sedation.[1,5,6] The principal hazard of moderate sedation is induction of excessive sedation with a deeper than desired level of anesthesia and the potential for hypoventilation and hypoxia.

In preparation for moderate sedation, patients should be fasting. A careful history of allergies, adverse reactions, current medications, and conditions recognized to compromise cardiopulmonary function under sedation (e.g., sleep apnea) should be elicited. The facility should have devices and medications for rescue in the event of oversedation. Intraprocedural and postprocedural monitoring is critical to safety. The ASA strongly recommends monitoring the following: level of consciousness; oxygenation with pulse oximetry; arterial pressure with automated oscillometry every 5 minutes; respiration with an apnea monitor; and electrocardiogram in patients with cardiac disease or undergoing deep sedation. Table 33.3 lists basic information on several agents used in modern practice.[7,8] Reversal agents, naloxone for opiates and flumazenil for benzodiazepines, must be immediately available. These receptor antagonists may have durations of action shorter than the agents that they are used to block, and therefore continued careful observation of patients after any use of rescue agents is mandated as repeat dosing maybe required.

Dexmedetomidine is also being used with increasing frequency for procedural sedation. Dexmedetomidine is a centrally acting, alpha-2 adrenergic agonist that decreases anxiety while simultaneously providing pain relief and sedation. This agent induces sedation with limited respiratory depression and has a half-life of 2 to 3 hours. Dexmedetomidine has potential sympatholytic effects including hypotension, bradycardia, and decreased circulating norepinephrine. Patients receiving maintenance anesthetics (sevoflurane, isoflurane, propofol, and fentanyl) with dexmedetomidine, as opposed to those without, were found to have significantly lower heart rates, mean arterial blood pressures, less nausea and emesis, and decreased restlessness.[9] Patients given dexmedetomidine require close hemodynamic monitoring. Patients with hypovolemia and heart block should not receive dexmedetomidine. Atropine should be available to treat unwanted associated bradycardia. The sympatholytic effects have been shown to attenuate the stress response during emergence from general anesthesia specifically for vascular procedures.[10]

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist and dissociative anesthetic, may also be used for procedural sedation and to decrease the postoperative need for opioid analgesics. This agent increases cerebral blood flow and metabolism and has actions on both monoamine and opioid receptors. Ketamine can also increase systemic and pulmonary arterial pressure, heart rate, cardiac output, and myocardial oxygen requirements via stimulation of the central nervous system. Because of these actions, this agent should be avoided in patients with ischemic heart disease, congestive heart failure, cerebrovascular disease, increased intracranial or intraocular pressure, epilepsy, and psychotic illness. Therapeutic dosing is often reached after one dose. The initial dose is 0.5 mg/kg which can be repeated if the effect is inadequate after five minutes. Critically ill patients may experience negative cardiac inotropic effects with an unexpected drop in arterial pressure and heart rate if their sympathetic responses and endogenous catecholamines are exhausted.[11-13]

Regional Anesthesia

Regional anesthetic techniques include peripheral nerve blocks, cervical and brachial plexus blocks, spinal anesthesia, and epidural

TABLE 33.3 Properties of Drugs Commonly Used for Moderate Sedation

Drug	Pharmacologic Class	Pharmacologic Effects	Onset of Action	Duration of Action	Adverse Effects
Midazolam	Benzodiazepine	Sedation Amnesia Anxiolysis	1-5 min, peak in 3-5 min	1-3 h	Hypotension, hypoventilation, decreased tidal volume, increased respiratory rate, apnea, increased upper airway resistance
Diazepam	Benzodiazepine	Sedation Amnesia Anxiolysis	1-5 min	20-60 min	Hypotension, hypoventilation, respiratory depression
Meperidine	Opioid	Sedation Analgesia	5 min, peak in 10 min	2-4 h	Hypoventilation, hypotension, lower seizure threshold, respiratory depression, decreased tidal volume, nausea, vomiting
Propofol	Ultrashort-acting sedative, hypnotic	Sedation Hypnotic	30-60 s	3-10 min	Dose-dependent hypotension, hypoventilation, respiratory depression, pain at injection site
Droperidol	Neuroleptic	Neuroleptic Anxiolytic	30 min	1-4 h	Hypotension, tachycardia, hypoventilation, prolonged QT interval
Fentanyl	Opioid	Sedation Analgesia	<1 min, peak in 5-8 min	30-60 min	Hypoventilation, respiratory depression, decrease in tidal volume

Modified from Lubarsky DA, Candiotti K, Harris E. Understanding modes of moderate sedation during gastrointestinal procedures: a current review of the literature. *J Clin Anesth.* 2007;19:397.

anesthesia. Peripheral nerve blocks are frequently utilized for extremity and digital procedures with effects lasting well after the surgery is complete.

Spinal and Epidural Anesthesia

Spinal anesthesia refers to the injection of medications through the dura directly into the cerebrospinal fluid from lumbar levels. The specific agents chosen are based on time of onset, potency, and duration of action. Lidocaine and bupivacaine are often used for spinal anesthesia and have durations of action of 60 and 100 minutes, respectively. Patient positioning and solution density are also important factors that should be considered for successful spinal anesthesia. Spinal anesthesia is contraindicated when hemodynamic instability is expected since this technique often produces a variable degree of sympathetic blockade with some loss of arterial and venous tone and fluid sequestration. A decrease in systemic vascular resistance of >30% has been reported in older patients with known cardiac disease.[14] Hypotension associated with spinal anesthesia is treated with fluid resuscitation, Trendelenburg positioning, or inotropic or pressor agents if the patient has underlying heart failure. Severe coagulopathy, increased intracranial pressure, and infection at the injection site are other contraindications to spinal anesthesia.

Complications of spinal anesthesia include postdural puncture headache, nausea and emesis resulting from unopposed parasympathetic efferents, and respiratory depression particularly in patients with high punctures and chronic obstructive pulmonary disease. These patients rely on accessory muscles for respiration which can be compromised by a high spinal block. Other complications include direct neurologic injury, cauda equine syndrome, arachnoiditis, spinal hematoma, meningitis, and idiopathic cardiovascular collapse. Complications are rare with the exception of postdural puncture headache which may occur in 25% of patients undergoing spinal anesthesia. The headache may be associated with cranial nerve symptoms such as diplopia, tinnitus, and nausea and is classically relieved by the supine posture. Patients are treated with bed rest, caffeine, hydration, and analgesics.[15] This complication may be treated by the administration of an epidural blood patch which is thought to work by sealing the meningeal puncture site.[16,17]

Epidural anesthesia refers to the placement of a catheter into the epidural space around the distal thoracic or lumbar spine, frequently with the delivery of larger quantities of anesthetic required for absorption between the spinal ligament and dura (epidural space). Vascular specialists must be familiar with the advantages and limitations of these approaches, particularly as they affect postoperative management and analgesia. A major advantage of epidural anesthesia is the ability to continually deliver postprocedural analgesia via an indwelling catheter. Effective epidural postoperative analgesia obviates the need for systemically administered opioids and the accompanying risk for respiratory depression, excessive sedation, and gastrointestinal side effects. Epidural anesthetic infusions can be maintained in most patients safely for 3 to 4 days.

The technique of catheter placement is critical to properly enter the epidural space at the appropriate level without injury to the veins of Batson's plexus. Local anesthetic infused into the epidural space acts on the spinal nerve roots which are mixed nerves with somatosensory, somatomotor, and autonomic fibers. These component nerve fibers usually have different sensitivity to the blocking effect of anesthetic agents with the greatest effect on sympathetic autonomic fibers and the least effect on somatic motor nerves. Thus, the extent of autonomic, sensory, and motor blockade with a given epidural infusion may differ by several vertebral levels.

Contraindications to epidural catheter placement are similar to those for spinal block with the exception that recent anticoagulation is not an absolute contraindication. The American

TABLE 33.4 Recommended Time Interval Before and After Neuraxial Block or Catheter Removal

Drug	Time Before Neuraxial Manipulation	Time After Neuraxial Manipulation
Unfractionated heparin, subcutaneous prophylaxis	4 h	>60 min
Intraoperative therapeutic heparinization	2-4 h after the last heparin dose, check partial thromboplastin time	>60 min (Note intravenous anticoagulation should not be continued with neuraxial catheter in place)
Low molecular weight heparin	12 h for prophylactic doses 24 h for therapeutic doses	Prophylaxis should be delayed 24 h after neuraxial manipulation and should be limited to once a day dosing Delay prophylaxis until adequate hemostasis is achieved if blood is present during neuraxial manipulation Prophylaxis can be started 2 h after neuraxial catheter removal
Warfarin	When INR < 1.4	When INR < 1.4
Dabigatran	5 days	6 h
Apixaban	3 days	6 h
Rivaroxaban	3 days	6 h
Prasugrel	7-10 days	6 h
Ticagrelor	5-7 days	6 h
Aspirin, NSAIDs COX-2 inhibitors	Can be continued	Can be continued
Clopidogrel	7 days (if needed before, can perform P2Y12 assay to assess residual antiplatelet activity)	Should be held until after removal

Modified from Horlocker TT, Wedel DJ, Rowlingson JC, et al: Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (3rd edition) *Reg Anesth Pain Med.* 2010;35:64-101.

Society of Regional Anesthesia and Pain Medicine recently released a consensus statement suggesting that epidural blocks may be performed four hours after the last subcutaneous dose of unfractionated heparin and 12 hours after the last subcutaneous dose of low-molecular-weight heparin (LMWH).[18] Treatment with nonsteroidal antiinflammatory drugs or aspirin is not considered a contraindication if placement is atraumatic. Clopidogrel should be discontinued 7 days before puncture. Systemic heparinization can be started one hour after catheter insertion. If a traumatic puncture occurs, elective vascular surgery should be delayed for 12 to 24 hours (Table 33.4).

Complications of epidural anesthesia are similar to those of spinal anesthesia. Accidental dural puncture can lead to postdural puncture headache, but this generally occurs less frequently with epidural anesthesia than with spinal techniques which naturally always involve dural puncture. With misplacement of epidural access, it is possible to inject agents into the subdural or the subarachnoid space, potentially resulting in total spinal anesthesia and even blockade of the brainstem, which can induce cardio-pulmonary reflexes, coma, and shock. This complication is extremely rare but special care must be exercised with high epidurals.

General Anesthesia

The term *general anesthesia* refers to a loss of consciousness with patients unarousable to painful stimuli. Patients under general anesthesia cannot protect their airway and in most cases require assisted ventilation. Patients receiving general anesthesia often have depressed cardiovascular function and require support by specially trained anesthetists. A complete discussion of the agents and techniques of general anesthesia are beyond the scope of this text; however, a few of the more commonly used agents are discussed below. A comprehensive review can be found in specialized work listed.[19] This text focuses on the aspects of general anesthesia of special interest to vascular surgeons and highlights the optimal anesthetic techniques to manage common vascular procedures.

Agents used in general anesthesia can induce peripheral vasodilation and inhibit sympathetic autonomic regulation, leaving the patient with the reduced ability to autoregulate circulation and tissue perfusion. Resulting hypotension is frequently noted between anesthesia induction and skin incision. The loss of vasoconstriction in the periphery leads to redistribution of blood flow to the skin, loss of thermoregulation, a decrease in core temperature. The patient can become dependent on therapeutic interventions with fluid and inotropes.

Succinylcholine is a depolarizing muscle relaxant with rapid onset and short action. Adverse effects of succinylcholine include malignant hyperthermia, sepsis, arrhythmias, elevated intracranial pressure, elevated intraocular pressure, elevated intragastric pressure, and transient increases in serum potassium. It should be avoided in patients with large-surface area burns, spinal cord injury, neuromuscular disease, cerebrovascular accident, and severe chronic debility, as the associated hyperkalemia can lead to cardiac arrest.

If malignant hyperthermia is suspected, the surgical procedure should be stopped as soon as possible. Intravenous dantrolene at 2.5 mg/kg can be given through a large bore IV. Doses can

be repeated until decreases in end-tidal CO_2, heart rate, and muscle rigidity are noted. Dantrolene dosing may need to be increased to 10 mg/kg if muscular contractions persist. The patient should be hyperventilated on 100% oxygen at greater than 10 L/min to lower end-tidal CO_2 and flush volatile anesthetics. Activated charcoal filters can be placed in the ventilator circuit and replaced frequently to remove inhaled anesthetic. The patient should be cooled if temperature is greater than 38°C. Metabolic acidosis should be corrected with bicarbonate. Calcium chloride 10 mg/kg or calcium gluconate 30 mg/kg, sodium bicarbonate 1 to 2 mEq/kg IV, 50% glucose 50 mL, and regular insulin 10 units IV can be used to treat hyperkalemia. Refractory hyperkalemia should be treated with albuterol, kayexalate, or dialysis. Avoid calcium channel blockers for treatment of arrhythmias.

Commonly used inhaled agents for general anesthesia in vascular surgery include nitrous oxide, desflurane, halothane, sevoflurane, and isoflurane. Nitrous oxide use has decreased with the availability of safe, more potent and short-acting agents. Significant cardiovascular depression with decreased myocardial contractility can occur when nitrous oxide is given with opioids. These actions can be exacerbated in patients with congestive heart failure. However, nitrous oxide as a component of balanced general anesthesia has no greater risk of death and cardiovascular complications in patients with known or suspected increased cardiac risk undergoing major noncardiac surgery. Absolute contraindications include respiratory compromise and patients with air-filled cavities including pneumothorax, pulmonary blebs, and bowel obstruction.

All halogenated inhalants can decrease mean arterial pressure. Halothane decreases myocardial contractility while desflurane, isoflurane, and sevoflurane decrease systemic vascular resistance. Small increases in desflurane dosing, however, can dramatically affect sympathetic nervous system activity and indirectly affect the cardiovascular responses. Therefore desflurane should not be used in patients in whom increased heart rate and blood pressure could be detrimental. Isoflurane does not have the same effect on the sympathetic nervous system at usual general anesthetic doses. Halothane and sevoflurane depress the sympathetic response. Halothane increases myocardium sensitivity to catecholamines and therefore should not be used in patients with prior history of arrhythmias. All halogenated inhalant agents cause respiratory depression, airway vasodilation, and irritation. These agents have different solubilities, metabolisms, and decrement times that allow for selection of the most appropriate agent for procedures of different lengths. All should be avoided in patients with a history of malignant hyperthermia.

Propofol is a rapidly acting intravenous sedative-hypnotic agent that decreases cerebral blood flow and metabolic oxygen requirements. It rapidly reaches an equilibrium between the plasma and brain but is not absorbed and metabolized in other tissues, explaining its rapid onset and sometimes prolonged effects. Propofol-associated hypotension occurs because of three separate mechanisms: inhibition of the sympathetic nervous system, impairment on the baroreflex regulatory mechanisms, and a dose-dependent decrease in potassium-induced tone in the veins and arteries.[20,21] Propofol is also frequently used for procedures requiring only moderate sedation; however, the ASA and the American Association of Nurse Anesthetists believe that only persons trained in the administration of general anesthesia, not concurrently involved with the procedure, should administer propofol to nonventilated patients.

Etomidate, another hypnotic agent frequently used upon induction, preserves hemodynamic stability and might be a better choice for some patients because it does not affect the sympathetic and autonomic reflexes as much as propofol. Etomidate can inhibit cortisol production by the adrenal glands in critically ill patients and therefore should be limited to induction of general anesthesia and not be used as a maintenance anesthetic in such patients.[22]

Vascular Anesthesia Technique and Outcomes

There is a great deal of interest in determining anesthetic approaches that minimize the physiologic impact of surgery, enhance vascular reconstruction durability, and improve patient survival. Some of the research efforts related to the anesthetic management for specific frequently performed vascular operations are considered here.

Elective Aortic Surgery

The use of epidural analgesia arose in the 1970s and 1980s as an attractive alternative to standard therapy with balanced general anesthesia and postoperative systemic opioid analgesia. Epidural techniques, generally supplemented with light general anesthesia during the procedure, were applied to high-risk vascular patients with apparent success. A fair number of trials were conducted in this period to compare the relative outcomes of these techniques in high-risk patients.[23-26] Unfortunately, these studies produced conflicting results. Three major randomized clinical trials have been published that directly address this question.

The first study is the Veterans Affairs (VA) Cooperative Study #345, reported by Park and associates in 2001.[27] This prospective randomized trial was conducted at 15 VA Medical Centers to compare outcomes in high-risk patients (ASA class III or IV) undergoing elective major abdominal surgery (gastric, biliary, colonic, and aortic). Patients were randomized to one of two anesthetic schemes: (1) balanced general anesthesia and postoperative pain management or (2) epidural combined with light general anesthesia and postoperative pain management with epidural supplemented with intravenous morphine as needed. The study was powered to detect a 50% reduction in relative risk of a projected 15% major complication rate. No differences were noted in the occurrence of any of the complications between the two anesthetic groups. Although epidural catheters were in use for only a mean of 55 hours, pains scores were significantly less in the epidural group. Of the 984 patients who entered the study, approximately 38% underwent major aortic surgery. A post hoc subgroup analysis of the aortic patients ($n = 374$) showed that occurrence of any complication was reduced significantly in patients managed with the epidural technique (22% vs. 37%, $P < .01$), mostly as a result of a reduction in the rate of new myocardial infarction, respiratory

failure, and stroke. The data suggest that the two anesthetic approaches are equivalent across the range of major abdominal surgery, but there could be advantages of epidural approaches in aortic surgery. The study suffers from the lack of blinding of the treating physicians, lack of proscribed guidelines for postoperative hemodynamic management, and less than optimal analgesic administration in the standard-therapy group.

A single-institution, prospective randomized double-blinded study performed at Johns Hopkins Hospital was reported in 2001.[28] The study was designed to evaluate intraoperative anesthesia technique and postoperative analgesic management in high-risk patients undergoing abdominal vascular surgery. Patients were randomly assigned to one of four groups: (1) general anesthesia with postoperative intravenous patient-controlled analgesia (PCA), (2) general anesthesia with postoperative epidural PCA, (3) epidural anesthesia and supplemental general anesthesia with postoperative intravenous PCA, and (4) epidural anesthesia and supplemental general anesthesia with postoperative epidural PCA. All randomized patients had an epidural catheter placed before surgery and the epidural was kept in place for at least 72 hours postoperatively. The primary endpoint was length of hospital stay, and the study was powered to detect a 20% reduction in an expected 12.7-day stay. There were detailed protocols for hemodynamic management, fluid administration, transfusion, and extubation. The study was closed prematurely when a preliminary conditional power analysis showed minimal likelihood of detecting a significant difference among the treatment groups. The data collected showed no differences in death, myocardial infarction, myocardial ischemia, reoperation, pneumonia, and renal failure between the treatments. Similarly, ICU length of stay, time to initiation of diet, time to independent ambulation, and pain scores were not different in the four groups. Epidural PCA was associated with a significantly shorter time to extubation. These data demonstrate that in a controlled setting with well-designed and managed treatment protocols there are no measurable differences in outcomes among these techniques.

The third study is the Multicentre Australian Study of Epidural Anesthesia (MASTER Anesthesia Trial), reported by Rigg and coauthors in 2002.[29] This multicenter, randomized controlled trial recruited 920 patients and was intended to confirm the benefit of epidural anesthesia noted in an earlier Australian trial while using more consistent anesthetic technique.[30] High-risk patients who were to undergo elective major abdominal surgery or esophagectomy were eligible for recruitment. Patients were randomized to either control, consisting of balanced general anesthesia with postoperative intravenous opioid analgesia, or epidural procedural anesthesia with postoperative epidural analgesia. Detailed protocols were included for the management of each aspect of care throughout the study period. There was no masking of treatment in this study. Primary outcomes were combined 30-day mortality and morbidity. Three quarters of patients were recruited in Australian centers and 18% of patients underwent major aortic surgery. The data showed no difference between the two treatments with regard to overall 30-day outcome. However, there were significant differences in pain score and respiratory failure that favored the epidural group. The MASTER Anesthesia Trial was limited by poor protocol compliance, specifically in the epidural group with only 225/447 patients fully completing the protocol. Further subgroup analysis of aortic surgery patients (n = 164) revealed no significant differences in cardiovascular complications between the two anesthetic techniques (4.5% vs. 4.7%, P = NS).

Since then, multiple reviews have attempted to compile the data from these trials and others to draw working conclusions. In 2012, a Cochrane Library meta-analysis was performed comparing the use of postoperative epidural or systemic analgesia in patients undergoing elective abdominal aortic surgery. The study included 15 randomized trials including 1297 patients receiving either postoperative epidural analgesia or postoperative systemic analgesia with opioids. Most patients receiving postoperative epidural analgesia also had the epidural in place during their surgical procedure. The epidural group had significantly lower postoperative pain scores, and the duration of postoperative intubation and mechanical ventilation was shortened by 48%. Rates of myocardial infarction, gastrointestinal complications, and renal complications were also significantly lower in the group treated with postoperative epidural.[31]

The benefits of epidural anesthesia in aortic surgery are observed with thoracic as opposed to lumbar epidurals. In the meta-analysis performed by Beattie in 2001, the superiority of thoracic epidural anesthesia was highlighted.[32] Thoracic regional anesthesia specifically reduces sympathetic activation and increases myocardial oxygen supply via coronary dilation.[33-35] The same effects are not seen with lumbar regional anesthesia which may actually result in a compensatory increase in sympathetic activity.[36] Thoracic epidural anesthesia also protects against splanchnic hypoperfusion during periods of ischemia and reperfusion resulting in decreased duration of postoperative ileus. Intestinal perfusion and bowel motility is not protected by lumbar epidural anesthesia.[37,38] Better pulmonary and diaphragmatic function with epidurals might also be explained by epidural anesthesia's ability to block inhibitory effects of abdominal surgery and general anesthesia on the phrenic nerve and diaphragm.[38,39]

Generally, the supplementation of general anesthesia with the epidural technique has advantages for the patient, especially in the postoperative phase with improved patient comfort and a reduction in cardiovascular, pulmonary, and other systemic complications.[31,40] The intraoperative use of epidural anesthesia in comparison with general anesthesia has not been proven to reduce mortality associated with aortic surgery and has not been shown to improve revascularization durability.

Ruptured Abdominal Aortic Aneurysms

The primary goal for anesthetists treating a patient with a ruptured abdominal aortic aneurysm is to maintain sufficient arterial pressure for vital organ perfusion. Careful resuscitation with intravenous fluids is paramount, because aggressive volume resuscitation to pressures higher than 100 mm Hg has been found to be associated with increased perioperative mortality.[41] As long as the patient is awake and exhibits mentation, permissive hypotension with systolic arterial pressure between 70 and 80 mm Hg should be tolerated. Transfusion of blood products

is also discouraged unless the patient is suffering from a concurrent myocardial infarction.[41] Pain control should be managed with small intravenous doses of narcotics until surgical arrangements are made.

Because the induction of anesthesia is associated with a reduction in sympathetic tone and myocardial depression, the anesthetist should be prepared for large volume resuscitation and transfusion. Furthermore, the relaxation of abdominal muscles may result in loss of the tamponade of the rupture and positive pressure ventilation will decrease venous return, either of which can further exacerbate hypotension. Systemic arterial pressure lability can be reduced with the use of a large volume endovascular balloon positioned proximal to the site of rupture prior to induction (Resuscitative Endovascular Balloon Occlusion of the Aorta, REBOA).[42] Such balloons can be inserted under local anesthesia from groin access. The patient should undergo sterile prep and draping prior to induction so that immediate incision is feasible once anesthetic is given. Once cross clamp control of the aorta is obtained, the anesthetic team should be allowed to catch up with blood losses.

No particular anesthetic technique has been shown to be superior for ruptured abdominal aortic aneurysms. Hemodynamically stable patients with contained ruptures should be evaluated for epidural placement as there are potential postsurgical advantages. Endovascular repair of ruptured abdominal aortic aneurysms can be initiated, if not always completed with local anesthetic and intravenous sedation.[43] Reasons cited for converting to general anesthesia included patient discomfort, loss of consciousness, and movement during the procedure. The technique of utilizing local anesthetic for ruptured abdominal aortic aneurysm repair might be a crucial factor for preventing large hemodynamic disturbances and improved patient survival.[44]

Infrainguinal Reconstructions

Anesthetic technique has also been studied in patients having infrainguinal vascular surgery, but the data are less extensive and few firm conclusions can be drawn.[45-49] Some evidence suggests that epidural anesthesia could impact early infrainguinal bypass graft patency. Christopherson and colleagues reported a prospective randomized study comparing general and epidural anesthesia in 100 patients undergoing elective lower extremity bypasses.[49] Although the data showed no evidence of an effect of anesthetic method on mortality or major morbidity, these authors found an unexpected dramatic reduction in postoperative graft thrombosis from a high rate of 43% with general anesthesia to 8% with the epidural technique over six-month follow-up. Additional investigators suggested that this may be due to an effect of epidural anesthesia on coagulation and fibrinolysis.[50,51] Epidural anesthesia does not affect fibrinogen or plasminogen activator inhibitor (PAI) levels, however PAI levels were significantly increased in the first 24 hours postoperatively in patients receiving general anesthesia for lower extremity bypass. These findings suggest an early prothrombotic effect of general anesthesia and that epidural anesthesia possibly promotes fibrinolysis.[52] This fibrinolytic effect was not found to be significant beyond 30 days after surgery.[53]

A large retrospective review of the National Surgical Quality Improvement Program database was recently performed comparing outcomes by the anesthetic technique used in patients who had infrainguinal arterial bypass. Not surprisingly, general anesthesia was the most common type of anesthesia, outnumbering both regional techniques, spinal and epidural, by more than three to one. When spinal anesthesia was compared to general anesthesia, early graft failure, early return to the operating room, cardiac morbidity, and pneumonia were significantly lower in the spinal anesthesia group. When spinal anesthesia was compared to epidural anesthesia, no statistically significant differences were noted in early graft failure or 30-day morbidity. No significant difference was noted in 30-day mortality among the three groups.[49]

Carotid Surgery

The optimal mode of anesthesia for carotid surgery has been a topic of interest for decades and numerous attempts have been made to determine whether general or local/regional anesthesia techniques are superior. A major benefit of performing carotid surgery under regional anesthesia is the ability to continuously monitor cerebral function in the conscious patient during carotid clamping. A Cochrane meta-analysis comparing patients undergoing carotid endarterectomies randomized to regional or general anesthesia demonstrated no significant differences in death, stroke, and other serious cardiopulmonary complications. However, nonrandomized patients undergoing the procedure with regional anesthesia did have a significant reduction in these serious complications.[54] The GALA (General Anesthesia versus Local Anesthesia) trial was designed to determine if this benefit persisted with a larger cohort of randomized patients. Over 3500 patients undergoing carotid endarterectomies were randomized to general versus local anesthesia over 8 years, but no difference in mortality and major morbidity was detected between the two groups at 30 days.[54] Critics of the study and proponents of regional anesthesia argue that successful regional anesthesia requires a dedicated team of surgeons, anesthesiologists, nurses, and support staff and the variability associated with randomizing does not allow for optimal patient care (see Chapter 91).[55,56]

INTRAOPERATIVE MONITORING

Continuous monitoring of the patient response to the surgical intervention is critical. This allows both the surgeon and the anesthesiologist to recognize deviations from the expected course and adapt to the changing condition of the patient.

Electrocardiography

Monitoring of the electrical activity of the heart should be applied throughout the perioperative period in almost all types of interventions. The rationale for electrocardiographic (ECG) monitoring is detection of arrhythmias and myocardial ischemia. Arrhythmias, common during vascular interventions, are related primarily to the choice of anesthetic agents, intraoperative variations in blood gases and serum electrolytes, direct autonomic

stimulation, activation of cardiovascular reflexes (endotracheal intubation, vagal stimulation, peritoneal traction, sinus nerve), or direct stimulation of the myocardium (central venous cannulation, cardiac retraction). Myocardial ischemia is usually the result of underlying coronary heart disease combined with increased myocardial work secondary to the neuroendocrine responses to surgical trauma and hemodynamic conditions that may reduce global myocardial perfusion (hypovolemia).

A five-electrode system with four limb leads and a single unipolar precordial lead (generally V_5) is standard for most vascular procedures. This configuration allows monitoring of any of the standard six bipolar limb leads, as well as the anterolateral chest wall lead in the distribution of the left anterior descending coronary artery. Leads II and V_5 are monitored continuously in most vascular cases. Some evidence suggests that V_3 or V_4 may have greater sensitivity for detection of myocardial ischemia in this setting.[57] Invasive leads (esophageal, endotracheal, or central venous) may have higher sensitivity for detection of arrhythmia and ischemia but are not used in routine clinical practice.[58,59]

Pulse Oximetry

Pulse oximetry is a noninvasive technique of monitoring oxygen saturation with probes placed peripherally, often on fingers, earlobes, and/or toes. It measures the absorption of different wavelengths of light that undergo preferential absorption by either oxyhemoglobin or deoxyhemoglobin. Monitoring with pulse oximetry is continuously performed throughout the perioperative period, but evidence to support its efficacy or impact on outcomes in patients undergoing general anesthesia is scant.[60,61] The potential benefit of intraoperative pulse oximetry is a continuous index of tissue perfusion. Pulse oximetry is prone to a number of artifacts and may be particularly misleading in patients with vascular disease.[62] Risk factors for discordant pulse oximetry include ASA physical status III, IV, or V; orthopedic, vascular, or cardiac surgery; and intraoperative hypothermia, hypotension, or hypertension. Furthermore, pulse oximetry cannot detect changes in PaO_2 above 100 mm Hg and thus is insensitive to potentially clinically relevant changes in gas exchange in the lungs.

When vascular surgery patients have compromised extremities that are not easily monitored with standard pulse oximetry, reflectance cerebral oximetry can be used. The reflectance monitor uses an emitter and light detector that measures the backscatter of light. Such probes can be placed on the forehead, which receives blood flow from the internal carotid and ophthalmic artery rather than peripheral arteries. Standard pulse oximetry probes and reflectance probes readings were compared and found to be comparable in patients undergoing vascular surgery.[63]

Capnography

Continuous monitoring of the end-tidal CO_2 using infrared absorption spectroscopy is the standard of care for the assessment of ventilation during general anesthesia. This information is displayed most commonly as a continuous plot of the partial pressure of CO_2 versus time (time capnogram). Exhaled gases can be sampled either by a sensor placed directly within the respiratory circuit or by a sensor placed remotely with gases aspirated. It is important to bear in mind that the gradient between end-tidal CO_2 and $PaCO_2$ (normally about 5 mm Hg) may be affected by disease states and that the measurement of end-tidal CO_2 using capnography is subject to artifacts. The clinical applications of capnography have been reviewed recently.[64,65] In 2011, the ASA updated its statement on Standards for Basic Anesthetic Monitoring to recommend the addition of continuous monitoring of end-tidal CO_2 during both moderate and deep sedation.[66,67]

Arterial Pressure

Noninvasive Methods

The high incidence of cardiac disease in vascular patients and the dramatic effects of vascular procedures on afterload and blood volume make monitoring arterial pressure especially important in vascular interventions. All patients should have periodic measurement of arterial pressure with noninvasive techniques throughout the perioperative period. This is accomplished with automated oscillometric devices with a single cuff that measure the amplitude of oscillations as the cuff is slowly deflated. The pressure at which oscillations are maximal is the mean arterial pressure, and systolic and diastolic pressures are calculated by various proprietary algorithms.[68] Such devices correlate well with invasive arterial pressure measurements, although the decreased arterial compliance in the elderly and in diabetics may lead to overestimation of systolic pressure and underestimation of diastolic pressure.[69] Automated oscillometry may be less useful in the setting of atrial fibrillation, bradycardia, and in patients with severe vasoconstriction.

Invasive Methods

Real-time measurement of arterial pressure is extremely useful, particularly in the case of vascular surgery procedures with aortic clamping and release resulting in sudden changes of afterload, intentional pharmacologic manipulation of arterial pressure (hypotension during the thoracic endograft procedure, hypertension in occasional carotid cases), and manipulation of critical cardiovascular reflex arcs (with carotid angioplasty, endarterectomy, or both). In clinical practice today, intraarterial pressure is usually measured with a fluid-filled catheter, tubing, and an electromechanical pressure transducer system. The accuracy of these systems is limited by the length and compliance of the tubing and the presence of small air bubbles in the tubing. The fluid-filled systems have the added benefit of being able to repeatedly sample arterial blood.

The arterial cannula is commonly inserted into the radial artery. Stenosis, thrombosis, and occlusion of the radial artery are possible complications of cannulation and ischemia of the hand can result.[70] The ulnar artery is the dominant supply of arterial perfusion to the hand in approximately 90% of people.[71] Assessment of the adequacy of collateralization through the ulnar artery by way of the Allen test is a critical step before safe use of the radial artery for monitoring pressure. Alternatively,

monitoring catheters can be placed in the brachial, axillary, and femoral arteries. Femoral lines can be placed at the time of arterial exposure or cannulation for diagnostic or adjunctive arteriography and can be discontinued at the end of the procedure. Brachial catheters should be avoided because of the poor collateralization around the elbow in the event of thrombosis, and axillary lines may be complicated by axillary sheath hematoma which can produce devastating neurologic consequences if not promptly identified and treated.

Insertion should be assisted with either a separate or integral guidewire using Seldinger technique.[72] Ultrasound imaging provides the proceduralist with the advantage of real-time assessment showing needle location in relationship to the vessel. Ultrasound imaging can also show vessel patency and atherosclerotic disease helping to determine if the vessel is appropriate for catheter placement. The use of ultrasound for the placement of arterial catheters has been shown to improve the likelihood of successful cannulation.[73,68]

Advanced Hemodynamic Monitoring

Systemic arterial pressure is a derived variable and is a physiologic result of the interaction of cardiac output and peripheral arterial resistance. Cardiac output is the product of heart rate and stroke volume and is determined by myocardial contractility and left ventricular end-diastolic volume (LVEDV). Central venous and pulmonary artery (PA) catheterization have been performed historically to measure pressures that may have a useful relationship to left ventricular filling and thus to cardiac output. It is important to understand the function of these devices. However, the development of less invasive monitoring technology has reduced the role of real-time monitoring of hemodynamic parameters by these methods.

Central Venous Catheterization

Central venous catheterization can be used to measure central venous pressure (CVP) and to theoretically provide a real-time estimate of intravascular volume and venous return. Unfortunately, CVP is affected by a large number of confounding variables which limits its value. CVP correlates well with left ventricular filling pressure only in patients with normal cardiac and pulmonary function. The correlations are further weakened with the use of positive pressure ventilation during surgery and by patient positioning. Absolute values of CVP have little meaning but changes in the parameter with intervention are valuable. The ASA has recently published comprehensive practice guidelines to enhance the safety of central venous catheterization.[69] The use of central venous catheterization to regularly measure CVP intraoperatively and estimate intravascular volume for moderate to high-risk surgery has largely been replaced by other techniques including transesophageal echocardiography and minimally invasive hemodynamic monitoring.

Pulmonary Artery Catheterization

Some of the shortcomings of CVP monitoring were overcome by the development of PA catheters. Basic flow-directed balloon-tipped PA catheters can be used to measure both pulmonary artery diastolic pressure (PADP) and pulmonary capillary wedge pressure (PCWP). PA catheters also allow estimation of cardiac output by several different methods and permit sampling of mixed venous blood, which enables calculation of total body oxygen delivery (Do_2) and total body oxygen consumption (Vo_2).

The PA catheter was developed to optimize cardiac function in critically ill patients and was used extensively in the ICU during the perioperative period in high-risk patients. This practice was the result of an observation by Shoemaker and others that the metrics of systemic perfusion and oxygen delivery (cardiac output and Do_2) were closer correlates of survival than were more traditional cardiovascular parameters, such as heart rate, arterial pressure, and CVP.[74-77] The PA catheter was an essential tool for implementing the strategy of hemodynamic optimization before elective major vascular surgery.[77]

However, several large prospective studies have suggested that the use of PA catheters in critically ill patients may offer little objective benefit and this conclusion has been further supported by meta-analysis.[78-89] In brief, the evidence is insufficient to recommend preoperative hemodynamic optimization for high-risk surgical patients and there is no evidence of benefit for the routine use of PA catheters during high-risk general or vascular surgery. Guidelines from both the American College of Cardiology/American Heart Association (ACC/AHA) and the ASA reflect these data and advise against the routine use of PA catheters in vascular surgery but suggest that these devices may be of some benefit in high-risk subsets.[90,91]

Minimally Invasive Hemodynamic Monitoring

Minimally invasive hemodynamic monitoring refers to a number of devices that can provide real-time assessment of cardiac output without the need of inserting a PA catheter. Some of the more commonly used devices evaluate the arterial pressure tracing and percent changes in pulse pressure to calculate stroke volume and systemic vascular resistance. The underlying principle of these devices is that stroke volume is proportional to arterial pressure. When an algorithm was developed to determine aortic compliance, the ability to calculate stroke volume based on the area under the systolic phase of the arterial curve became possible.[92]

There are a variety of devices that use the pulse pressure analysis method to extrapolate cardiac output, some of which are "autocalibrated" and some of which are externally calibrated. Autocalibrated minimally invasive devices use an indwelling arterial monitor and include the FloTrac sensor (Edwards Lifesciences, Irvine, California), ProAQT sensor with Pulsioflex monitor (Pulsion Medical Systems, Munich, Germany), and LidCO rapid system (LidCO Ltd., Cambridge, UK).[93]

Calibrated minimally invasive devices include those using thermodilution similar to PA catheters and lithium dilution. Transpulmonary thermodilution utilizes an injection of cold fluid into the superior vena cava via a central venous catheter. A thermistor in a main (femoral, axillary, or brachial) arterial branch subsequently measures temperature change over time and CO is extrapolated.[94] The two commercially available devices using this technique are the PiCCO plus monitor (Pulsion Medical Systems, Munich, Germany) and

EV1000/VolumeView monitor (Edwards Lifesciences, Irvine, California). Lithium dilution is performed with small volume lithium chloride injections via a peripheral or central venous catheter. Lithium concentration is measured by aspirating arterial blood. A lithium-sensitive electrode at the tip of the catheter generates a voltage corresponding with a change in lithium concentration.[95] Lithium dilution hemodynamic monitoring is not accurate in patients treated with lithium or muscle relaxants. Muscle relaxants can incorporate a positively charged quaternary ammonia ion that can trigger the lithium electrode and cause an overestimation of CO. Commercially available lithium dilution hemodynamic monitors include the LidCOplus (LidCO Ltd., Cambridge, UK).

Minimally invasive hemodynamic monitoring to calculate CO correlates well with the gold standard of PA catheters in patients with a regular cardiac rhythm, stable respiratory patterns, and without abrupt hemodynamic changes. The minimally invasive monitors are not as accurate calculating continuous CO in patients with abrupt hemodynamic changes, specifically including those treated with norepinephrine or those having off-pump coronary artery bypass surgery or open abdominal aortic aneurysm repair. However, newer generation software with upgraded algorithms is improving the correlation between the two techniques and research is on-going.[96-98]

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) has become a mainstay of the intraoperative management for patients undergoing surgery on the heart and thoracic aorta.[99,100] In this application, TEE allows not only monitoring of cardiac function in real time but also can provide information that may modify the conduct or extent of surgery. TEE provides two-dimensional gray-scale images of the cardiac chambers in a wide spectrum of projections. In addition, pulsed, continuous wave, and color-flow Doppler capabilities allow physiologic measurement of flow and global cardiac dynamics. In particular, TEE can provide direct information on ventricular systolic function. The contribution of asymptomatic LV dysfunction to mortality in vascular surgery highlights the value of direct observation with TEE.[101] Some data indicate that TEE-derived LVEDP correlates better with cardiac output than do PA catheter-derived data (PCWP).[102] Myocardial contractility is best assessed with the ejection fraction calculated from two-dimensional data by standard formulas. Diastolic function (left ventricular relaxation) is assessed by pulsed Doppler examination of flow through the mitral value. Intraoperative TEE allows appropriate diagnosis of hemodynamic changes (e.g., hypovolemia vs. reduced ejection fraction in hypotension) and provides prompt feedback on therapeutic interventions. Myocardial ischemia may be detected by early diastolic dysfunction and regional wall motion abnormalities.

No published reports to date demonstrate an outcome-based improvement with TEE.[103-108] This may be related to the generally poor correlation between TEE findings of myocardial ischemia, ECG data, and eventual cardiac outcome. The ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery suggest that intraoperative or perioperative TEE is reasonable for investigating acute, life-threatening hemodynamic disturbances.

NEUROLOGIC MONITORING

Central Nervous System

Monitoring of central nervous system function is critical to optimize neurologic outcome with carotid interventions. Regardless of the anesthetic technique or the use of an intracarotid shunt during clamping, these procedures can be completed safely only with a clear understanding of cerebral perfusion. Placement of an intracarotid shunt does not guarantee that the shunt is functioning or that perfusion of the brain is satisfactory. The adequacy of cerebral perfusion has been assessed by a wide range of approaches including conscious monitoring of the neurologic responses of the patient, continuous electroencephalography, and transcranial Doppler measurements of flow in the middle cerebral artery (see Chapter 91).

Spinal Nervous System

Monitoring of spinal nerve function is useful in procedures that involve possible disruption of perfusion to the spinal cord, most commonly through temporary clamping of thoracic aortic segments or ligation or exclusion of intercostal arteries giving rise to the great radicular artery. Such monitoring is generally accomplished with sensory- and/or motor-evoked potentials to test the integrity of the spinal segments (see Chapter 77).

INFECTION CONTROL AND MAINTENANCE OF HOMEOSTASIS

Perioperative Antibiotics

Surgical Site Infection (SSI) has been estimated to account for at least 25% of all nosocomial infections in hospitals and has been associated with increase mortality, length of hospital stay, and cost.[109-111] Kirkland et al. found that patients with SSI experienced twice the mortality (7.8% vs. 3.5%), a greater likelihood of requiring ICU care (29% vs. 18%), and a higher incidence of readmission (41% vs. 7%) than matched controls.[112-116]

The tenets of SSI prophylaxis were established in the 1960s and have been noted in numerous reviews.[117-121] The fundamental requirement for effective SSI prophylaxis is maintenance of an effective concentration of an antibiotic suitable for the probable organisms in tissue at the site and time of inoculation (wounding). The critical role of timing of antibiotic administration is illustrated in the report by Classen.[121] When compared with the group who received antibiotics within 2 hours of incision (0.6% incidence of SSI), those who were treated early (>2 hours before incision), perioperatively (within 3 hours after incision), and late (3 to 24 hours after incision) had relative risks for SSI of 6.7, 2.4, and 5.8, respectively.

The Centers for Disease Control and Prevention (CDC) published formal guidelines in 1999, and in 2002, the Centers

for Medicare and Medicaid Services (CMS) and the CDC implemented the national Surgical Infection Project (SIP).[114,122,123] The strategy was to reduce the incidence of SSI by monitoring three specific performance measures: (1) the number of patients receiving parenteral SSI prophylaxis within 1 hour of incision, (2) the proportion of patients receiving SSI prophylaxis with an agent consistent with published guidelines, and (3) the proportion of patients whose prophylactic antimicrobial therapy is discontinued within 24 hours of completion of surgery.[124] In 2004, the SIP was incorporated into a more comprehensive surgical quality initiative, the Surgical Care Improvement Project (SCIP). According to the SCIP guidelines, the approved antibiotic agent for SSI prophylaxis during vascular procedures was cefazolin. Vancomycin and clindamycin were appropriate substitutes in the event of β-lactam allergy. Additional recommendations included preoperative dosing 60 minutes before surgical incision, dosing adjustments for body weight, intraoperative redosing to ensure adequate serum and tissue concentrations, shortened postoperative course of antimicrobials to a single dose or for continuation less than 24 hours.[123,124] Despite the retirement of the SCIP in December 2015, these recommendations continue.

Risk factors for postoperative surgical site infections in patients undergoing vascular procedures include lower extremity surgical sites, delayed procedures after hospitalization, diabetes mellitus, and history of prior coronary or vascular bypass.[125,126] Richet et al. prospectively evaluated 561 vascular surgery patients undergoing a revascularization procedure with prosthetic and found a surgical site infection rate of 4.1% and Ross et al. found a similar rate of surgical site infections (3.85%) in over 200 patients undergoing peripheral arterial revascularization.[126,127]

The appropriateness of prophylactic antibiotics in endovascular interventions has not been determined by prospective randomized controlled trials. The Society of Interventional Radiology (SIR) Standards of Practice Committee has developed recommendations for the use of antibiotic prophylaxis during percutaneous vascular interventions.[128] Prophylactic antibiotics for the placement of stent grafts is recommended not because of high stent graft infection rate but rather the mortality associated if an infection occurs. Recommendations are extended for thoracic, abdominal, and extremity stent grafts.[127,129-131] Prophylactic antibiotics are not recommended for angiograms, angioplasty, placement of bare metal stents, venous procedures, thrombolysis, and closure devices.[127,129,132-136] In cases of endovascular re-intervention defined as within 7 days, interventions in the presence of hematoma, procedures lasting more than two hours, immunosuppressed patients, and interventions in the presence of another intravascular implant, prophylactic antibiotics should be considered.[137-141]

Adrenergic Agents

A great deal of research has been performed on the potential role of cardiotonic drugs in reducing the cardiac risk associated with major general and vascular surgery.[142] Administration of beta-blockers through the perioperative period has the theoretical benefit of reducing myocardial work through control of heart rate and anti-inotropic actions. The 2014 ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery recommended beta-blocker therapy be continued throughout the perioperative period if patients have been taking it longitudinally and it is well tolerated (see Chapters 32 and 42).[143-150]

Recommendations for patients undergoing vascular surgery with intermediate or high risk for myocardial ischemia as determined preoperatively can be started on beta blockade therapy, especially if at risk for stroke.[151-154] Such intermediate and high-risk patients with uncompensated heart failure should not be started on beta blockade therapy without heart failure optimization. Therapy should be started at least 2 to 7 days prior to surgery to titrate dosing and should not be started on the day of surgery.[155-158] There is no proven benefit to starting beta blockade therapy greater than 30 days prior to surgery. For patients with three or more revised cardiac risk index risk factors (diabetes mellitus, heart failure, coronary artery disease, renal insufficiency, and prior cerebrovascular accident), the safety and efficacy of starting beta blockade in the preoperative setting is less clear.[144,150,159]

Beta-blockers are contraindicated in patients with asthma, sick sinus syndrome, and second- and third-degree heart block. Potential adverse intraoperative effects include augmented intraoperative hypotension and bradycardia, which may be significant in vascular patients with impaired cardiac reserve. In such cases, there is evidence that a similar reduction in periprocedural cardiac morbidity may be obtained with α_2-adrenergic agonists.[160]

Maintenance of Normothermia

The combination of anesthesia and surgery leads to major increases in convective heat loss in patients. The loss of peripheral vasoconstriction resulting from anesthesia diverts perfusion from the visceral organs to the extremities and the skin where heat is lost to the environment through thermal radiation. Similar heat loss occurs in large open surgical wounds, especially those of the chest or abdominal cavity where heat loss is augmented by evaporative cooling. For clinical purposes, normothermia is a core temperature higher than 36°C and lower than 38°C. Mild hypothermia refers to core temperatures between 34°C and 36°C. The physiologic responses of awake humans to mild hypothermia include peripheral sympathetic activation with increased circulating norepinephrine, shivering with increased metabolic rate, oxygen consumption, and mean arterial pressure.[161] In patients undergoing anesthesia with sympathetic blockade, these normal responses to hypothermia are blunted.

Hypothermia is associated with a number of potentially serious complications in surgical patients including wound infection, immune dysfunction, coagulopathy, increased blood loss, increased transfusion requirements, major adverse cardiac events, and death.[162-170] The most significant concern in patients with coronary heart disease is an increased risk for perioperative myocardial ischemia.[171] Frank and associates assessed myocardial ischemia in the first postoperative day in 100 patients undergoing lower extremity bypass surgery and divided the population into

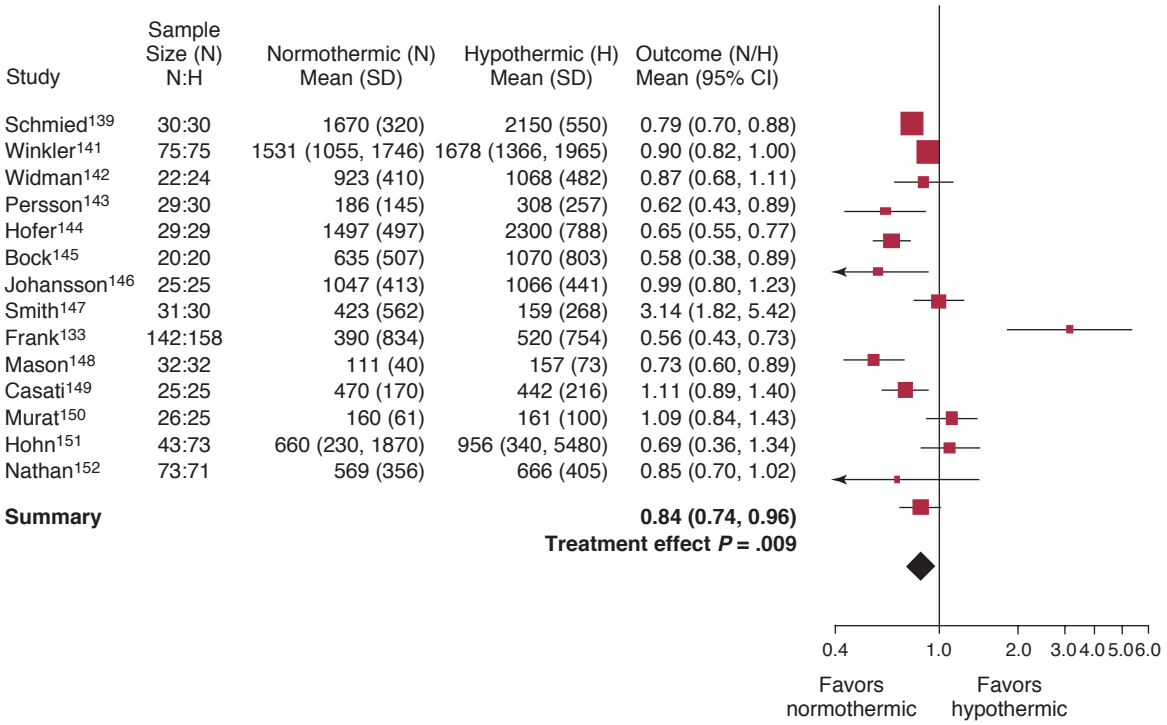

Figure 33.1 Total Blood Loss: Meta-Analysis and Forest Plot. Treatment effect is expressed as the ratio of geometric means of blood loss for normothermic *(N)* versus hypothermic *(H)* patients. Results indicate an estimated 16% (95% confidence interval *[CI]*, 4% to 26%) lower average blood loss in normothermic than in hypothermic patients, P = .009. *SD*, Standard deviation.

hypothermic (<35°C) and normothermic (≥35°C) groups on the basis of immediate postoperative body temperature.[171] ECG changes indicative of myocardial ischemia were three times more likely to occur in the hypothermic group (36% vs. 13%), and multivariate analysis showed that temperature was an independent risk factor for myocardial ischemia. A subsequent prospective RCT of supplemental warming of at-risk cardiac patients undergoing vascular, abdominal, and thoracic surgery by these investigators confirmed that hypothermia is an independent predictor of morbid cardiac events with a relative risk of 2.2.[162] This and other studies have shown a clear relationship between postoperative hypothermia and ventricular tachycardia and atrial fibrillation.[172]

Hypothermia also has a significant effect on coagulation. Many coagulation factors are temperature-sensitive proteases whose activity is reduced by hypothermia. Measurement of this effect in vivo is complicated by the fact that the common clinical assays of coagulation (prothrombin time and partial thromboplastin time) are performed at 37°C and thus results do not reflect the impact of actual body temperature at the site of bleeding.[173] Generally, in the absence of major hemorrhage or consumptive coagulopathy, the functional impact of mild hypothermia on coagulation is relatively mild.[174] There is also clear evidence of platelet dysfunction with hypothermia.[175] Platelet margination occurs with dropping temperature because hypothermia concentrates blood cell volume, induces a change in platelet shape, decreases rate of blood flow, and increases expression of adhesion molecules such as thromboxane A2. The drop in platelet count can be reversed with restoration of normal body temperature.[176-178]

The clinical impact of mild hypothermia on perioperative bleeding was determined in the report of Schmied estimating that mild hypothermia (1°C) may increase blood loss by 16% and the increase relative risk for transfusion by 22% (Fig. 33.1).[162,168,179-190]

Hypothermia is also a major risk factor for SSI. This effect is mediated by a combination of vasoconstriction at the site of wounding (inoculation) and a generalized effect on immune function. Local vasoconstriction affects the delivery of antibiotics to the wound and may produce relative hypoxia.[165] The impact on immune function involves mitogen-induced responses of lymphocytes, and alterations of cytokine production, neutrophil phagocytosis and oxidative killing.[191-193] Kurz and colleagues studied the clinical effect of core temperature on SSI in a prospective randomized trial of 200 patients undergoing colorectal surgery.[194] SSI occurred in 6% of normothermic patients (36.6°C ± 0.5°C) and 19% of hypothermic patients (34.7°C ± 0.6°C). Furthermore, sutures were removed 1 day earlier in normothermic patients and normothermic patients had a shorter hospital stay (2.6 days, about 20% less).

Other undesirable effects of hypothermia include variable and drug-specific effects on the distribution and metabolism of both muscle relaxants and anesthetic agents, enhanced cardiotoxicity of bupivacaine, mild hypokalemia, and thermal discomfort. Despite these data, there may be a protective role for mild hypothermia in certain specific clinical situations that

involve tissue ischemia.[195] Skepticism may, however, be warranted based on the inability of recently released systematic reviews to show any clear benefit of hypothermia as a preventive strategy for brain injury associated with head trauma, stroke, cerebral aneurysm surgery, and cardiac surgery.[196-199] Passive hypothermia is often used as an empirical component of visceral and spinal cord protection during repair of thoracoabdominal aneurysms. This topic is covered in Chapter 77.

Intraoperative normothermia is maintained thorough a comprehensive strategy to reduce radiant heat loss and provide active warming. Components of this approach include prewarming to reduce the core-to-periphery thermal gradient, passive insulation, active heating (circulating water, forced air, radiant heat), fluid warmers, and airway heating and humidification. The ambient temperature in the operating room is an important factor in reducing radiant heat loss. The recommended temperature range for the operating room is between 68°F and 75°F.[200,201] Maintenance of normothermia has been recognized as a quality metric.

Glycemic Control

Although the potential benefit of close glycemic control on the incidence of long-term complications of diabetes has been known for some time, it has become increasingly clear that acute hyperglycemia can have short-term detrimental effects on surgical and critically ill patients. Krinsley et al. performed a retrospective review of the impact of glycemia on outcomes in a mixed medical/surgical ICU at a university-affiliated community hospital between 1999 and 2002.[197] Among 1826 consecutive patients studied, hospital mortality was directly related to the mean glucose value and nearly doubled between those with a mean glucose level of 80 to 99 and 140 to 159 mg/dL (9.6% vs. 18.8%).[202]

Hyperglycemia can be a problem in nondiabetic surgical patients because the normal hormonal response to even uncomplicated surgery involves glycogenolysis, gluconeogenesis, and relative insulin resistance. Furthermore, as many as 6% of cardiothoracic surgical patients with no history of diabetes are found to have diabetes, and an additional significant proportion of such patients will have abnormally elevated hemoglobin A_{1c} values.[203,204] There is a clear relationship between hyperglycemia and SSI. Latham and associates showed a history of diabetes and postoperative hyperglycemia (defined as glucose >200 mg/dL) were independent risk factors for SSI (OR = 2.76 and 2.02, respectively). In theory, this association is related to the impact of hyperglycemia on immune function. Specific effects of hyperglycemia may include impaired vasodilatory responses in the wound; changes in expression of adhesion molecules, cytokines, and chemokines; enhanced responses of complement; and depressed neutrophil chemotaxis, phagocytosis, and release of reactive oxygen species. The basic and clinical data supporting these effects have been reviewed recently.[205,206] In a study of 995 general and vascular surgery patients, Ramos et al. discovered postoperative hyperglycemia increased the risk of postoperative infections by 30% with every 40-point increase from normoglycemia (<110 mg/dL).[207]

There is substantial evidence that aggressive therapy to maintain normoglycemia can have a beneficial effect on mortality in surgical patients. Van der Berghe and colleagues compared either routine glycemic management or intensive glycemic control.[208] The intensive-treatment group was managed with insulin infusion to maintain blood glucose between 80 and 110 mg/dL. Overall ICU mortality was 8% with conventional care and 4.6% with intensive management ($P < .04$). The greatest difference in mortality was seen in patients who required more than 5 days of ICU care (10.6 vs. 20.2%, $P < .005$). Similar substantial differences were noted in the rates of in-hospital mortality, bloodstream infection, and acute renal failure. Others have reported similar findings.[209,210]

Recent studies have shown that there is an increased incidence of hypoglycemia among intensive care patients undergoing strict glycemic control with an increased mortality rate. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial randomized 6104 patients within 24 hours of admission to ICU to see if strict glucose control defined as blood glucose of 81 to 108 mg/dL and 3050 patients assigned to undergo conventional glucose control defined as 180 mg/dL or less. There was a significantly higher mortality rate in the strict glucose control group (27.5%, 829 patients) versus the conventional group (24.9%, 751 patients).

No specific performance measures have been issued regarding postoperative glycemic control for general or vascular surgical patients to date and there are to date no randomized controlled trials specifically addressing the monitoring and treatment of hyperglycemia during major vascular surgery. Recommendations are based on studies evaluating comparable groups. The current guidelines for the perioperative care of patients with peripheral arterial disease is to maintain a blood glucose level of <200 mg/dL.[211]

ANTICOAGULATION/ANTIPLATELET THERAPY

All vascular interventions involve interruption of blood flow and some disruption of the vascular wall, risking local and distant arterial thrombosis. Although the use of systemic anticoagulation and antiplatelet therapy during and after vascular interventions seems logical, the efficacy of this strategy has not been tested rigorously. There is evidence that systemic anticoagulation is not necessary to prevent local thrombotic complications with aortic aneurysm surgery, although most vascular surgeons treat such patients with anticoagulants. The need for anticoagulation probably varies inversely with the diameter of the arteries and the rate of blood flow.[212] Newer anticoagulants with more favorable therapeutic ratios and enhanced safety profiles are now available (see Chapter 39).[213,214]

Anticoagulation

Anticoagulation is generally initiated at the time of arterial clamping by bolus administration of unfractionated heparin

via either an empirical, fixed-dose regimen (3000 to 5000 units is the common fixed-dose range seen in practice) or a weight-based dosing scheme (100 to 150 units/kg). The half-life of unfractionated heparin is dose-dependent since clearance has both a rapid saturable phase due to binding to endothelial cells and blood elements and a slower first-order elimination phase. The effective half-life in most individuals is 30 to 90 minutes so repeat dosing (500 to 1000 units, or 50 units/kg) every 45 to 60 minutes is required to maintain effect.[215,216] There is considerable variability in the anticoagulation responses to unfractionated heparin, and several studies support monitoring the level of anticoagulation during certain procedures, which is typically accomplished with the activated clotting time (ACT) at the point of care.[217,218]

Although the degree of anticoagulation seen with fixed-dose regimens will vary among patients, the clinical impact of such variation is small. Poisik and colleagues measured ACT values during 140 carotid endarterectomies receiving a fixed-dose regimen (5000 units).[219] This regimen in effect delivered weight-based heparin doses of 44 to 116 units/kg and produced ACTs of 175 to 425 seconds with no measurable differences in neurologic outcome or wound hematoma. An ACT longer than 350 seconds appears to be associated with the least risk for ischemic events during percutaneous coronary intervention, and similar values may be appropriate for small-artery interventions in the legs or carotid angioplasty.[220] Intraprocedural anticoagulation may also have benefits beyond avoidance of thrombosis in the treated arteries. Some data show a reduction in both fatal and nonfatal periprocedural myocardial infarction after abdominal aneurysm repair when unfractionated heparin was administered systemically at the time of aortic clamping.[212]

There is controversy regarding the benefit of anticoagulation reversal in vascular procedures. Reversal is generally used in shorter duration procedures to speed closure or after intra-cavitary operations, where the risk of unrecognized hemorrhage can be substantial. Administration of protamine has some risk with anaphylaxis reported in up to 3% of patients. The risks associated with protamine administration have been reviewed recently.[221] Protamine does not counteract the anticoagulant effect of LMWH. Guidelines from the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy support the use of unfractionated heparin during vascular interventions but state that the benefit of reversal has not yet been demonstrated.[222] The 9th edition of the American College of Chest Physicians (ACCP) does not address this question.[223] Some suggest that a single measurement of ACT with reversal for high values (>400 seconds) may be a reasonable approach.[219]

For patients with anti-heparin antibodies or heparin-induced thrombocytopenia, several direct thrombin inhibitors are marketed, including hirudin derivatives and argatroban. These agents may not be immediately available in all hospitals. As recommended in the literature describing its use with percutaneous coronary interventions, anticoagulation with argatroban can start with a bolus of 350 μg/kg administered over 3 to 5 minutes followed by an infusion of 25 μg/kg per minute. For a subtherapeutic ACT, an additional 150 μg/kg/bolus can be given and the infusion rate can be increased to 30 μg/kg per minute. An ACT should be rechecked in 5 to 10 minutes. For supratherapeutic ACT (>450 seconds), the infusion rate should be decreased to 15 μg/kg per minute. Initial doses in the patient with hepatic impairment should be 0.5 μg/kg per minute.[224] Effective means of argatroban reversal have not been established. Bivalirudin initial bolus dosing is 0.75 mg/kg followed by and immediate infusion of 1.75 mg/kg/hour. ACT should be checked in 3 to 5 minutes and if subtherapeutic, an additional bolus of 0.3 mg/kg should be given if required.[225] Bivalirudin reversal can be accomplished with recombinant factor VIIa and can be eliminated with hemodialysis.

Table 33.5 reviews some of the target-specific anticoagulants and their nonspecific and specific reversal options. Prothrombin complex concentrate (PCC) is a nonspecific reversal agent derived from plasma composed of vitamin K-dependent coagulation factors II, VII, IX, and X with variable amounts of protein C and S. PCC is approved by the FDA to be used for the reversal of vitamin K antagonists (warfarin) associated bleeding. Activated prothrombin complex concentrate (aPCC) was developed to treat hemophilia patients and contains activated forms of the coagulation factors II, VII, IX, and X. It is important to note that none of the nonspecific reversal agents are Food and Drug Administration (FDA) approved to reverse target specific anticoagulants with the exception of Praxbind. Activated charcoal can be used if ingestion of an oral agent occurred within two hours. Hemodialysis is generally only effective for clearance of dabigatran.[226-228]

Antiplatelet Therapy

The overwhelming majority of arterial interventions are performed to treat advanced atherosclerosis. Accordingly, virtually every patient undergoing a vascular procedure should be treated with an effective antiplatelet agent to reduce the greater incidence of myocardial infarction and ischemic stroke.[229] The general recommendation in at-risk patients is low-dose aspirin (81 mg) daily. Although clopidogrel is often added empirically as a second antiplatelet agent in many patients, there is little evidence to support the benefit of this agent in low-risk patients who can tolerate aspirin.[230] On the other hand, clopidogrel has an important role together with aspirin in enhancing the patency of percutaneous coronary interventions. In general, dual platelet therapy is recommended for a minimum of 1 month after coronary angioplasty with a bare-metal stent and for a minimum of 12 months after the use of a drug-eluting stent.[92] These recommendations are based on the theoretical time required for endothelialization of the stent. The significant risk for stent thrombosis and fatal myocardial infarction with premature discontinuance of dual platelet therapy has prompted the publication of the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery and the Joint Advisory on Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients with Coronary Artery Stents.[231-233] These guidelines suggest (1) delay of elective surgical procedures associated with significant risk for periprocedural bleeding until the appropriate course of dual platelet

TABLE 33.5 Target-Specific Anticoagulants

Agent	Mechanism	Half Life	Metabolism	Coagulation Assay	Nonspecific Reversal	Specific Reversal Agents
Dabigatran **Pradaxa**	Direct thrombin inhibitor Blocks fibrinogen →fibrin	12-17 h	85% renal excretion	• Prolonged thrombin time (TT) • Prolonged ecarin clotting time (ECT) • Range of effect on activated partial thromboplastin time (aPTT)	• Hemodialysis is effective • Activated charcoal • Prothrombin complex concentrates (PCC, KCentra) not effective—Erenberg ES, et al. 2011 • Recombinant factor VIIa (rFVIIa, Novoseven) effective—Marlu R, et al. 2012 • Activated prothrombin complex contrite (aPCC, FEIBA) effective—Khoo TL, et al. 2013	• **Anti-Dabi-Fab** (Idarucizumab/ Praxbind)—Humanized monoclonal antibody fragment • 5 g IV • **FDA approved** • **PER977** (Aripazine/ Ciraparantag)—binds Xa and IIa • Phase 2 clinical trials
Rivaroxaban **Xarelto**	Factor Xa inhibitor Blocks prothrombin → thrombin	5-9 h	66% renal excretion 33% hepatic excretion	• Anti-factor Xa activity assay • May elevate prothrombin time (PT) • Prolonged aPTT	• Hemodialysis is not effective • Activated charcoal • 4 factor PCC (KCentra) is effective, 50 units/kg (max 5000 units)—Erenberg ES, et al. 2011, Marlu R, et al. 2012, Dinkelaar J, et al. 2013 • aPCC (FEIBA) effective, 8-25 units/kg	• **PRT064445** (Andexanet Alfa/ AndexXa)—binds to Xa inhibitor site • Phase 3 clinical trials • **PER977** (Aripazine/ Ciraparantag)—binds Xa and IIa • Phase 2 clinical trials
Apixaban **Eliquis**	Factor Xa inhibitor Blocks prothrombin → thrombin	7-14 h	66% hepatic excretion 33% renal excretion	• Anti-factor Xa activity assay • Prolonged aPTT	• Hemodialysis is not effective • Activated charcoal • 4 factor PCC (KCentra) is effective, 50 units/kg (max 5000 units) • aPCC (FEIBA) effective, 8-25 units/kg	• **PRT064445** (Andexanet Alfa/ AndexXa)—binds to Xa inhibitor site • Phase 3 clinical trials • **PER977** (Aripazine/ Ciraparantag)—binds Xa and IIa • Phase 2 clinical trials
Fondaparinux **Arixtra**	Binds to antithrombin III and causes neutralization of Factor Xa	17-21 h	renal	• Anti-factor Xa activity assay	• Hemodialysis is not effective • rFVIIa, Novoseven, 90 µg/kg • aPCC (FEIBA) effective, 8-25 units/kg	• None

Modified from Hu TY, Vaidya VR, Asirvatham SJ. Reversing anticoagulant effects of novel oral anticoagulants: role of ciraparantag, andexanet alfa and idarucizumab. *Vasc Health Risk Manag*. 2016;12:35-44.

therapy has been completed and (2) continuation of aspirin throughout the perioperative period in any cases requiring major intervention for which clopidogrel must be discontinued. Naturally, these considerations play a large part in decision making regarding the role of coronary intervention as a risk reduction strategy for high-risk cardiac patients needing urgent vascular interventions.

The risk of bleeding complications with vascular procedures performed on patients treated with aspirin is measurable but small.[234] Neilipovitz and associates estimated that continuation of aspirin through the perioperative period would reduce periprocedural mortality from 2.78% to 2.05% with an associated 2.46% increase in bleeding complications.[235,236] The 2012 ACCP guidelines on Perioperative Management of Antithrombotic Therapy recommend continuing aspirin in the perioperative period for patients at high cardiovascular risk.[223] Bleeding during surgery in patients treated with both aspirin and clopidogrel can be a significant problem.

Periprocedural clopidogrel has been reported to increase the risk of intraoperative bleeding, as well as the risk of reoperation (OR = 5.1 and 6.9, respectively).[237-239] Like aspirin, clopidogrel must be discontinued for 5 to 7 days for complete resolution of its effect.[240] Most vascular surgeons discontinue clopidogrel in preparation for major open operations. If significant diffuse, punctate platelet-type bleeding occurs intraoperatively, platelet transfusion is often administered. However, there are no real clinical data to support the efficacy of platelet transfusion in this setting.[239,241]

Desmopressin (DDAVP) is a V2 receptor agonist analogue of arginine vasopressin that may enhance platelet function through the stimulated release of von Willebrand factor from endothelial cells, although the precise mechanism of its action

is not known.[242] This agent has been used for many years to control platelet-related bleeding in patients with end-stage renal disease and after cardiac surgery.[243] The true impact of this agent on surgical bleeding is not known because of conflicting reports and an inconclusive meta-analysis by the Cochrane group.[244] DDAVP has been associated with a 2.4-fold increase in postprocedural myocardial infarction in cardiac surgical patients.[245] Similarly, recombinant factor VIIa is an approved drug to treat bleeding in patients with hemophilia and acquired hemophilia. This agent also enhances thrombin generation by platelets and may control bleeding in the setting of thrombocytopenia or platelet dysfunction. Anecdotal reports of the administration of recombinant factor VIIa in cases of refractory surgical bleeding or trauma suggest that it could also have a role in these difficult situations. However, reports indicate that this agent carries an increased risk for thromboembolic complications, and its availability is restricted in many centers.[246,247]

Intraoperative Fibrinolysis

Although intraoperative fibrinolysis as an adjunct to mechanical thrombectomy in patients with acute limb ischemia was originally reported in the 1980s and has been widely adopted, there are no systematic data to support the optimal dose ranges for specific agents in this application.[248-253] Consensus recommendations for intraoperative dosing from the Working Party on Thrombolysis in the Management of Limb Ischemia are available.[254,248,255-263] Although surgical bleeding may not be an issue, the risk for potentially fatal intracranial hemorrhage is real, and rates ranged from 1.2% to 2.1% in the STILE and TOPAS trials.[264,265] Intracranial hemorrhage may be difficult to detect intraoperatively and special caution is thus warranted. Recombinant tissue plasminogen activator (rt-PA) is the most commonly used agent and is typically administered as a catheter-directed bolus into the thrombus often followed by a continuous transcatheter infusion at rates of 0.05 to 0.1 mg/kg per hour until lysis of the thrombus is confirmed. Generally, rt-PA infusions are only continued 12 to 48 hours until the presence of the thrombus can be re-evaluated angiographically (see Chapter 41).

CONTROL OF BLOOD LOSS/TRANSFUSION

Compensatory Responses to Anemia and Blood Loss

Allogenic transfusion of blood components is performed to restore specific functions that are lost by either failure of synthesis of blood components or increased losses. These functions fall into two broad categories: oxygen transport and coagulation. The initial physiologic responses to anemia are an increased stroke volume as a result of decreased impedance to ventricular ejection secondary to reduced blood viscosity and increased venous return because of reduced peripheral vascular resistance. Activation of aortic and carotid chemoreceptors will initiate reflex autonomic hemodynamic compensatory mechanisms to maintain oxygen delivery in the presence of decreased oxygen content of the blood. These autonomic reflexes further increase cardiac output through increases in myocardial contractility and heart rate. The capacity for compensation is substantial in normal healthy subjects with normal blood volume. Data from humans undergoing clinical hemodilution for surgery and from studies of anemic patients who were not transfused for religious reasons suggest that healthy individuals can survive blood loss that reduces the hemoglobin concentration to 5 to 6 g/dL (50 to 60 g/L).[265-270] However, these mechanisms depend on maintenance of adequate resuscitation in the setting of active bleeding and result in increases in myocardial work and oxygen demand that may be poorly tolerated by vascular patients with significant coronary heart disease.

Risks Associated With Allogeneic Transfusion

Allogeneic transfusion exposes the recipient to a myriad of cellular, lipid, and protein antigens that can evoke a wide range of immune-mediated adverse events, including anaphylaxis, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and both acute and delayed hemolytic reactions. The leading causes of transfusion-related mortality are TRALI, fatal hemolytic transfusion reactions, and transfusion associated sepsis (TAS).[271]

TRALI is an acute respiratory distress syndrome characterized by noncardiogenic pulmonary edema and hypoxia occurring within six hours of transfusion.[271-273] It is defined as acute hypoxemia with a ratio of partial pressure of arterial oxygen to fractional inspired oxygen concentration (PaO_2/FiO_2) of <40 kPa (300 mm Hg) with bilateral infiltrates on chest radiograph without pulmonary vascular overload. The risk of TRALI is highest after the infusion of plasma and platelets, but due to the shear number of units transfused, the majority of TRALI cases occur after the transfusion of red cells. The estimated incidence is 1.12% per unit transfused and in at-risk populations, the incidence may be as high as 8%. The mortality rate ranges from 5% to 45%.[274] The etiology of TRALI has not been defined, but there are two main theories.[273] The first postulates that donor antibodies to recipient leukocyte antigens result in leukocyte activation and lung injury. The other involves a two-hit concept consisting of sensitization of the recipient's pulmonary endothelium by stimuli such as sepsis, trauma, cardiopulmonary bypass, and ischemia-reperfusion with resultant pulmonary sequestration of neutrophils, followed by exposure to donor antibodies or inflammatory lipid mediators, or both. Treatment is supportive with cessation of transfusion and respiratory support with lung protective mechanical ventilation if indicated (see Chapter 43).

TACO is a common transfusion reaction in patients typically receiving a large volume of blood products. However, patients receiving less than a unit of blood have been reported to have developed TACO suggesting its etiology is more complex than simple volume overload.[275] TACO complicates 1% to 8% of transfusions. Cardiopulmonary dysfunction with TACO is characterized by hydrostatic pulmonary edema in the presence

of increased pulmonary artery and left atrial pressures and it often occurs in patients with a history of left ventricular failure. This syndrome is also diagnosed within six hours of transfusion. Clinical symptoms include acute respiratory distress, tachycardia, increased blood pressure, acute or worsening pulmonary edema, jugular venous distention, or any other signs of positive fluid balance. The chest radiograph will also reveal bilateral infiltrates. Elevated brain natriuretic peptide has a positive predictive value of up to 78%.[276] Treatment includes providing telemetry monitoring, supplemental oxygen, elevating the head of the bed, noninvasive positive pressure ventilation, diuresis, vasodilation with nitrates to reduce preload especially if hypertensive, and renal replacement therapy if indicated.

The greatest risk for transfusion-associated transmission of disease arises from bacterial contamination of platelets.[277] Platelet packs are an ideal culture medium for small inocula of bacteria because the protein-rich plasma may be stored for up to 5 days at 20°C to 24°C. The frequency of bacterial contamination of platelets may be as high as 1 in 1000 or 2000. Bacterial contamination of RBC units is much lower with an estimated rate of less than 1 in 1,000,000. The most common organism in RBC bacterial contamination is *Yersinia enterocolitica*, which carries a mortality rate of 60% and is often fatal in less than 24 hours.[278] The combination of donor screening programs and nucleic acid testing has progressively lowered the rate of transmission of lipid-encapsulated viruses such as human immunodeficiency virus and hepatitis C to less than 1 in 1,000,000, rates similar to those of major acute hemolytic transfusion reactions.[279] Transmission rates of hepatitis B virus are somewhat higher at about 1 in 50,000 to 150,000.[277] Other infectious agents can also be transmitted through blood products, but rates of transmission in the United States are extremely low. Included in this category are hepatitis D, hepatitis A, hepatitis E, syphilis, leishmaniasis, Lyme disease, brucellosis, parvovirus B19, tick-borne encephalitis virus, Colorado tick fever virus, West Nile virus, and human herpesviruses, as well as parasitic diseases (e.g., malaria, babesiosis, toxoplasmosis, and Chagas disease). Certain diseases are transmitted by transfused leukocytes, including Epstein-Barr virus, human T-lymphotropic virus type I, and cytomegalovirus.

Fatal hemolytic transfusion reactions caused by the infusion of ABO-incompatible blood occur at an estimated incidence of 1 in 1,000,000 and are most commonly due to preventable human error.[280] Acute hemolytic transfusion reactions may be difficult to identify intraoperatively and should be suspected in the event of circulatory decompensation or acute coagulopathy. Management of anaphylaxis intraoperatively involves maintenance of the airway and oxygenation, aggressive fluid resuscitation, and administration of pressors (epinephrine and vasopressin).[281]

Infusion of allogeneic leukocytes may cause a number of immunologic effects, including alloimmunization-related febrile nonhemolytic transfusion reaction (FNHTR), graft-versus-host disease, and immunomodulation. FNHTR frequency is unknown with a great deal of variability in the rates reported; however, the risk associated is increased with platelet transfusion (with some groups reporting over 20%) as compared to RBC transfusion. The median rates for FNHTR are 4.6% for platelets and 0.33% for RBCs.[282] These immunologic reactions have been attributed to leukocytes either directly via infusion of intact immunologically competent allogeneic leukocytes or indirectly as a result of infusion of biologically active substances released from leukocytes during storage. These latter substances include histamine, eosinophil cationic protein, myeloperoxidase, plasminogen activator inhibitor-1, and a host of proinflammatory cytokines and chemokines, including interleukin-1, tumor necrosis factor, and interleukin-6. The downregulation of immune system responses after transfusion has been referred to as transfusion-related immunomodulation (TRIM). Immunotolerance has long been recognized in the setting of renal transplantation with increased transplant survival in recipients who had received multiple previous allogeneic transfusions.[283,284] TRIM has been invoked as the cause of several other deleterious conditions associated with allogeneic transfusion, including an increased rate of recurrence of solid tumors, increased nosocomial infections, and increased mortality.[285-287] These and other possible detrimental effects of TRIM have been the subject of an extensive body of basic and clinical research.[285,286]

Leukocyte reduction has been shown to decrease the incidence of these immunologic complications of allogenic blood transfusion, as well as reduce transmission of cytomegalovirus in populations at high risk.[288,289] Based on the data available, several countries have adopted universal leukocyte reduction programs for all blood transfusions, and data suggest that such an approach can decrease fever, mortality, and antibiotic use in at-risk patients.[290] There is evidence that the use of leukocyte-depleted blood transfusion may have particular benefit in surgical patients, such as a decrease in the risk for multiple organ system failure and shorter length of stay.[277,290-292] The impact of leukocyte depletion on the incidence of postoperative infection is less clear and remains controversial.[293,294] Leukocyte reduction may also have a beneficial impact on a number of changes that affect RBCs during storage, collectively referred to as the "RBC storage lesion."[295-297] Such changes include a decrease in RBC survival, morphologic alterations, increased osmotic fragility, loss of deformability, conversion of hemoglobin to methemoglobin, and depletion of 2,3-diphosphoglycerate with a resultant decrease in oxygen-carrying capacity and an increase in oxygen affinity.[298,299] There has been a great deal of controversy regarding the potential detrimental effect of RBC storage lesions on the value of RBC transfusion and on the outcomes of patients receiving transfusion. Several small observational studies in patients after trauma or with sepsis have suggested that transfusion of "old blood" (stored between 17 and 25 days) is associated with a greater risk for complications than is transfusion of "fresh blood."[300-303] Koch and coauthors reported a retrospective series of patients who underwent cardiac surgery receiving "newer blood" (stored 14 days or less) and "older blood" (stored longer than 14 days).[304] Patients receiving older blood had higher in-hospital mortality (2.8% vs. 1.7%) and higher rates of prolonged intubation, renal failure, and sepsis. Large prospective studies will be required to determine the accuracy of these retrospective observations, which if true, clearly have profound implications for the current

practice of blood banking and maintenance of the blood supply.

Transfusion Triggers

Although the benefit of replenishment of RBC volume through transfusion in ill anemic patients seems intuitive, the data regarding the impact of RBC transfusion on morbidity and mortality in surgical patients are mixed. There is a lack of clarified threshold for transfusion of RBCs in either critically ill or postsurgical patients.[305-308] The data from patients who refused transfusion would indicate that most patients can tolerate a postoperative hemoglobin concentration of 7.1 to 8.0 g/dL without mortality.[265-270] In contrast, Carson and coworkers demonstrated a clear relationship between mortality and the degree of anemia in the postoperative period, with a 2.5-fold increase in the odds of death for each gram decrease in hemoglobin below 8.0 g/dL.[309] Separate investigators found no evident increase in perioperative mortality in elderly patients undergoing surgical repair of hip fracture who received RBC transfusion based on a trigger of 8.0 to 10 g/dL versus those transfused at a trigger value of 10 g/dL or greater.[310]

Reports of the Transfusion Requirements in Critical Care (TRICC) investigators support the safety of lower transfusion triggers. This multicenter study compared the effects of a "liberal" transfusion strategy (transfusion trigger of 10 g/dL) and a "restrictive" transfusion strategy (transfusion trigger of 7 g/dL) on outcomes of critically ill, euvolemic patients.[311] The in-hospital mortality rate was somewhat lower in the restrictive-strategy group (22.2% vs. 28.1% for liberal), but 30-day mortality in the two groups was not different (18.7% for restrictive vs. 23.3% for liberal). Analysis of participants with cardiovascular disease was published separately, and similar results were reported with no differences in 30-day, 60-day, or in-hospital mortality between the two transfusion strategies.[312] There was a suggestion (not statistically significant) that the liberal transfusion strategy led to slightly better survival in the subgroup with severe ischemic heart disease (257 patients). A comprehensive meta-analysis of data available in 1999 and a recent practice guideline from the American Association of Blood Banks generally support restrictive transfusion triggers in patients without cardiac disease but highlighted the need for additional data in higher risk groups.[310]

On the other hand, there is clear evidence of silent and evident perioperative myocardial ischemia in patients with anemia, particularly those with coronary heart disease and intraoperative or postoperative tachycardia.[313,314] A retrospective report of observational data from the VA National Surgical Quality Improvement Program (NSQIP) indicated a 1.6% increase in 30-day postoperative mortality with each percent decrease in hematocrit below 39%, although any conclusions from this data set must be tempered by the nature of the data.[315] The best evidence and analysis suggest that the hemoglobin concentration must be assessed in light of the overall condition of the patient and, in particular, the adequacy of circulating blood volume and perioperative resuscitation.[316] The recommendations of a number of authoritative bodies indicate consensus that transfusion is required frequently in patients with a low hemoglobin concentration (<6 to 8 g/dL) and rarely in those with a hemoglobin concentration greater than 10 g/dL and point to the important role of physiologic assessment of the patient as a major determinant for transfusion in the intermediate range (7.0 to 10 g/dL).[280,285,291,296,317-320] Hebert and colleagues have suggested a reasonable set of transfusion triggers based on current evidence (Table 33.6).[308]

TABLE 33.6 Transfusion Recommendations

Variables	TRANSFUSION TRIGGERS[a]		GOAL	
	g/L	g/dL	g/L	g/dL
General critically ill (no acute bleeding)	70	7	70-90	7-9
Critically ill with septic shock (>6 hr)	70	7	70-90	7-9
Critically ill with septic shock (<6 h)	80-100	8-10	100	10
Critically ill with chronic cardiac disease	70	7	70-90	7-9
Critically ill with acute cardiac disease	80-100	8-10	100	10

[a]Administer 1 unit of red blood cells at a time and re-measure hemoglobin concentrations.

From Hebert PC, Tinmouth A, Corwin HL. Controversies in RBC transfusion in the critically ill. *Chest*. 2007;131:1583.

Bursi et al. performed a retrospective review of 359 consecutive patients undergoing major elective vascular surgery (carotid endarterectomy, aortic surgery, and infra-inguinal surgery) to assess for an association between postoperative transfusion and early mortality and myocardial infarction, and demonstrated an increased hazard ratio for early death and myocardial infarction in patients receiving transfusion that were not anemic even after adjustment for surgical risk and postoperative bleeding. The study also did not show that anemic patients receiving postoperative transfusions experienced less myocardial infarctions or early deaths as compared to those anemic patients not receiving a transfusion.[321] Currently, there is a Danish prospective clinical trial appropriately named *The Transfusion Triggers in Vascular Surgery Trial* to determine the appropriate transfusion triggers for vascular surgery patients.[321a,b]

TRANSFUSION STRATEGIES

Given the considerable risks associated with allogenic blood transfusion (ABT), a number of proactive strategies have been developed to reduce or replace the need for transfusion. Key components common to all approaches focus on limiting blood loss and include selection of the proper procedure, meticulous surgical hemostasis, limited phlebotomy, maintenance of normothermia, aggressive management of coagulopathy, and careful resuscitation.[322,323]

The first option is to accept a lower transfusion trigger, carefully resuscitate, monitor cardiac status, and accelerate innate

RBC synthesis and replenishment. Wallis and coworkers studied 30 patients after hip arthroplasty and demonstrated evidence of increased erythropoiesis (increased reticulocytes and erythropoietin) 7 days postoperatively and recovery of about two thirds of the drop in hemoglobin concentration by 28 days postoperatively.[324] Appropriate attention to replenishment of iron stores is important.[325] Preoperative treatment with erythropoietin may be helpful in anemic patients, as has been demonstrated in elective orthopedic surgery.[326-329] These approaches can reduce but not absolutely eliminate the need for ABT.

The other strategies involve autogenous transfusion via a number of different techniques. Interest in these approaches arose in the 1980s, primarily because of heightened concern regarding viral transmission by transfusion. There are three main methods: preoperative autologous blood donation (PAD), acute normovolemic hemodilution (ANH), and intraoperative autologous blood recovery and transfusion (IAT). The basic concept of PAD is that the patient can donate sufficient RBC units to meet the expected perioperative need preoperatively and reconstitute the lost RBC mass before the planned surgery. In practice, the time interval between collection and surgery has rarely been sufficient, and the effect is chronic hemodilution with the potential for an increased incidence of transfusion (both autogeneic and allogeneic).[330] The use of PAD increased rapidly in the late 1980s and early 1990s but has subsequently declined.[331-335] PAD has limited utility in vascular surgery because of the relatively high incidence of anemia and the urgent nature of many interventions.

ANH involves removal of whole blood from the patient immediately before surgery with maintenance of normovolemia by infusion of crystalloid or colloid solutions. This technique has several clear benefits. Any intraoperative blood loss entails a lesser loss of RBC mass because of the lower hematocrit. The blood thus collected requires no testing, has a low risk for bacterial contamination, requires no storage cost, contains clotting factors and platelets, and has virtually eliminated the chance of misadministration. Studies in urologic and orthopedic patients suggested similar reductions in the need for periprocedural ABT with PAD and ANH, but a more recent meta-analysis of available data questions the overall benefit of this approach.[336-339] ANH increases the demands on the anesthesia team intra-operatively and is not well suited to many vascular patients with baseline anemia and significant fixed coronary heart disease. However, there is evidence of clear benefit of ANH combined with IAT in several reports of patients treated for AAA.[340,341]

IAT uses one of several commercially available devices to collect, wash, and concentrate RBCs shed during surgery. The in vivo survival of recovered RBCs is similar to that of allogeneic RBCs.[342] The washing process does not completely remove malignant cells, bacteria, or potentially toxic substances such as antibiotics, cytokines, or vasoactive substances, so malignancy, gross infection, and ascites may limit use of this technique. There are reports indicating that IAT can reduce the need for ABT in cardiac, orthopedic, and vascular surgery and recent meta-analyses of available data support this conclusion, at least with regard to orthopedic and possibly cardiac surgery.[343,344] Several studies have evaluated the role of IAT in aortic surgery. RCTs have shown variable benefits with four studies demonstrating a reduction in the frequency and amount of ABT with the use of IAT in patients undergoing aortic surgery. Two recent meta-analyses support the conclusion that IAT reduces ABT in the periprocedural period in patients undergoing AAA repair, although a previous meta-analysis suggested no clear benefit.[345-348] A number of cost analyses have been reported with varying methodology and rigor.[349-355] Huber and coauthors reported a decision tree assessment of the cost versus benefit (quality-adjusted life years) of IAT and concluded that routine use of IAT was not justified in surgery for AAA unless the expected blood loss was 5 or more units.[355,356] More recent studies have suggested a decrease in perioperative morbidity and reduced length of stay with IAT for AAA surgery, and the impact of these considerations will need to be incorporated into any future economic analysis.[357,356] Nevertheless, use of IAT is common practice for infrarenal AAA repair and routine for thoracoabdominal aortic surgery in most centers today.

VENOUS THROMBOEMBOLIC PROPHYLAXIS

Surgery is a major risk factor for venous thromboembolism (VTE). Moreover, vascular surgery patients often have other well-recognized VTE risk factors including advanced age, decreased mobility, cardiac disease, obesity, and smoking. Vascular surgery in many ways reduces the risk for VTE. Most vascular patients are treated with antiplatelet agents and virtually all receive full therapeutic anticoagulation during intervention. Postoperatively, some are treated with systemic anticoagulation. VTE prophylaxis has been the subject of call to action by the Surgeon General and was a major component of the Surgical Care Improvement Project (SCIP) and is included in several schemes of value-based reimbursement.[358]

INTRAOPERATIVE SAFETY

The operating room is a hazardous environment in which anesthetized patients are subjected to potentially lethal medications and treatments with well-recognized safety concerns. As physicians, protecting our patients from harm is our responsibility. The magnitude of the challenge became evident in the well-publicized report of the Institute of Medicine (IOM): To Err Is Human.[359] This report estimated that at least 44,000 people die in US hospitals each year as a result of preventable medical errors and injuries. The report emphasized that most errors are not intentional or malicious, but rather are the result of "faulty systems, processes and conditions" that either lead to mistakes or fail to safeguard against them.

The idea that safety is primarily a "systems" or "process" problem has led to research designed to modernize healthcare using models taken from other fields. Viewing a medical procedure as a "process" rather than an assemblage of interacting independent practitioners has profound implications on the

mode of practice in the operating room. Attention has been focused on two main ideas: (1) team development and shared management of patient care and (2) policies/procedures/protocols to reduce error.

Our current concept of the surgical team is based on management concepts developed in the military.[360,361] Crew Resource Management (CRM) describes a model of high-performance team interaction that has evolved out of the findings of a joint National Aeronautics and Space Administration (NASA)/industry conference to address human issues associated with airline disasters.[362] The basic concept is that "error is an inevitable result of the natural limitations of human performance and the function of complex systems."[363] Essential components of CRM implementation include a nonpunitive approach to error, team education on sources of error, and accurate error reporting. CRM team training focuses on empowerment of all team members. It also focuses clear protocols, flattening of hierarchical structures, education on effective communication techniques, and mandatory status reporting. The essential components of this approach are standard operating polices and guidelines, briefings, and checklists.[322] CRM concepts have been applied as well to the care of the surgical patient. This approach expands the duties, responsibilities, and competencies required of the team leader (i.e., the surgeon), and also has important implications for surgical education, credentialing, and maintenance of competency.[363-370]

In the decade leading up to the IOM report and since, a large number of healthcare organizations have issued suggested guidelines to improve the surgical patient safety. In the United States, the National Patient Safety Goals and the Core Measures of the Joint Commission are standards that must be met for accreditation of healthcare facilities. The partnership between the Center for Disease Control (CDC) and Centers for Medicare and Medicaid Services (CMS) led to the comprehensive quality initiative, the Surgical Care Improvement Project (SCIP).[371] Many of these measures are followed currently as best practices and included as standards for hospital accreditation today. More information and tools provided by the Joint Commission to avoid wrong site surgery and surgical infections can be obtained at: http://www.ihi.org/resources/Pages/Tools/WHOSurgicalSafetyChecklistGettingStartedKit.aspx.

The World Health Organization (WHO) and the Harvard School of Public Health in collaboration with more than 200 national and international societies implemented the "The Safe Surgery Saves Lives Initiative" proving checklists utilized in the surgical setting can dramatically reduce complication and mortality associated with surgical procedures.[372] The checklist focuses on three phases of the surgical setting: preanesthesia, preincision, and postprocedural. The developed checklist reinforces safety practices and fosters better communication and leads to teamwork between clinicians caring for surgical patients. The World Health Organization (WHO) Surgical Safety Checklist and additional information can be found at http://www.ihi.org/resources/Pages/Tools/WHOSurgicalSafetyChecklistGettingStartedKit.aspx.

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CHAPTER 34

Postoperative Management

GIUSEPPE PAPIA

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Keywords

postoperative care
ICU
monitoring
complications

Vascular surgery patients remain at high risk for the development of complications in the postoperative period because of the complexity of their surgical procedures and their preoperative comorbidities. This chapter addresses management issues in the postoperative period with an emphasis on issues in the intensive care unit (ICU) and specially monitored high-dependency step-down units.

POSTOPERATIVE TRIAGE

An important aspect of postoperative medical care involves identifying patients at highest risk for postoperative complications and triaging them to the appropriate care environment. The safest postoperative environment for patients undergoing vascular surgical procedures is determined by their preoperative medical comorbid conditions (see Chapters 9, 33, 37, 47, 43, and 44), the inherent risks of the type of operation performed, and the ability to maintain the patient's intraoperative and postoperative homeostasis. Emergency operations, such as those for a ruptured abdominal aortic aneurysm (AAA), have an increased risk for mortality.[1]

Admission to the Intensive Care Unit and High-Dependency Step-Down Unit

The need for invasive hemodynamic monitoring and observation remains the most common criterion for the admission of selected patients to an ICU or step-down unit. The main distinction between these two environments in most institutions is the severity of critical illness and need for invasive positive-pressure ventilation. These environments can provide patients with the following: decreased myocardial oxygen demand through expeditious rewarming, effective fluid resuscitation, effective analgesia, meticulous control of hemodynamics, and careful monitoring and appropriate nursing care to aid in the early diagnosis and treatment of complications. In a cohort study of patients after elective aortic surgery, Lawlor et al.[2] demonstrated that care in an ICU decreased mortality in patients with preoperative severe coronary artery disease, defined as an ejection fraction of less than 40%, congestive heart failure, or New York Heart Association class III or IV angina. Consideration of direct admission to the ICU should also be given to patients with significant chronic obstructive pulmonary disease (COPD, defined as forced expiratory volume in 1 second of less than 1 L) and those who are dialysis-dependent or have a need for continuous renal replacement therapy. Hemodynamically unstable patients (systolic blood pressure <90 mm Hg or inotropic support at the end of the operation), intubated patients with an ongoing need for ventilatory support, those with clinically significant perioperative cardiac ischemia, patients with pulmonary artery catheters, patients with spinal drains, patients with hypothermia (temperature <35°C), and those who required massive transfusion of blood products (>3 L) during the procedure should be admitted to the ICU.

Selective use of high-dependency step-down units and rationing of ICU resources can be safe and cost-effective with appropriate patient risk stratification.[3,4] Each patient must be individualized according to preoperative comorbid diseases, perioperative hemodynamic stability, and the surgical procedure performed. Patients undergoing less invasive vascular procedures associated with fewer fluid shifts and lower surgical morbidity can safely be managed in a step-down unit. This is the case with patients undergoing peripheral arterial bypass, elective repair of infrarenal AAAs, and carotid endarterectomy. Several scoring models predicting risk in vascular patients have been studied and validated as predictors of high-risk patients undergoing vascular surgery.[5]

Organizational Structure of the Intensive Care Unit

The organizational structure of the ICU, independent of a patient's medical factors, has a direct impact on outcomes.[6-11] In looking at outcomes after abdominal aortic surgery, Pronovost et al.[7,12] showed a relationship between increased in-hospital mortality and the absence of a full-time ICU director, less than 50% of ICU attending physicians certified in critical care, no daily rounds by an ICU physician, and decreased ICU nurse-patient ratio in the evening (<1:2). In patients undergoing abdominal aortic surgery, intensivists not making routine ICU rounds is associated with an increase in hospital mortality (odds ratio [OR], 3.0; 95% confidence interval [CI], 1.9-4.9), cardiac arrest (OR, 2.9; 95% CI, 1.2-7.0), acute renal failure (OR, 2.2; 95% CI, 1.3-3.9), septicemia (OR, 1.8; 95% CI, 1.2-2.6), platelet transfusion (OR, 6.4; 95% CI, 3.2-12.4), and reintubation (OR, 2.0; 95% CI, 1.0-4.1). Dang et al.[6] also demonstrated that ICUs with decreased nurse staffing had increased rates of cardiac and respiratory complications after abdominal aortic surgery.

HEMODYNAMICS AND PRESSURE MONITORING

Monitoring is required to intervene in abnormal physiology with the goal of improving outcomes. However, even patients with normal hemodynamic parameters may have inadequate organ perfusion.[13] Distributive hypoxia is a state that results from inadequate oxygen delivery to tissues; it is exacerbated by increased metabolic demands, with resultant multiorgan dysfunction.[14] Indicators of organ perfusion to guide resuscitation[15] include blood pressure, heart rate, central venous pressure (CVP), pulmonary capillary wedge pressure, cardiac output,[16] urine output, blood lactate concentration, tissue carbon dioxide levels, base deficit, mixed venous oxygen levels, and mixed venous carbon dioxide levels.[15,17] The key to interpreting and managing these indicators appropriately is to follow trends over time rather than individual measurements.

Central Venous Catheters and Central Venous Pressure

Central venous catheters are used primarily to infuse fluids, administer vasoactive drugs, and assess intravascular volume.

The most common sites for the placement of central venous catheters are the internal jugular veins, subclavian veins, and femoral veins. To measure CVP, internal jugular or subclavian central venous catheters must be positioned with the catheter tip in the distal segment of the superior vena cava. More distal placement in the right atrium is associated with a potential risk for erosion, perforation, and cardiac tamponade. CVP measures right atrial pressure, providing an estimation of preload. This measurement, however, is inaccurate in patients with COPD or in those with valvular heart disease. Femoral lines are good for resuscitation but not for CVP measurements because of the effect of intra-abdominal pressure (IAP) on measurements.

The transducer must be zeroed at the level of the midaxillary line, and normal values of CVP are between 6 and 12 mm Hg. In patients being managed with positive pressure ventilation, CVP should be measured at end-expiration, when pleural pressure in the chest is approximately zero.[18] The addition of positive end-expiratory pressure (PEEP) in a ventilated patient is another important consideration in measuring pressure in the chest. In normal lungs and with low levels of PEEP (between 5 and 8 cm H_2O), intrapleural pressure, which affects CVP, is only slightly affected.[18] The effect on CVP of high levels of PEEP (>12 to 15 cm H_2O) when the lungs are probably not compliant is unclear.[19] High levels of PEEP prevent the backflow of fluid outside the chest to the heart, thus decreasing venous return. If sudden changes in CVP occur, a cardiorespiratory cause such as pneumothorax or cardiac tamponade should be considered. Further discussion of CVP monitoring can be found in Chapter 33

Peripheral Arterial Lines

Peripheral arterial catheters are the "gold standard" for direct assessment of blood pressure and allow direct vascular access for blood sampling. Complications include bleeding, hematoma, line-related infection, thrombosis, and, rarely, limb ischemia.[20] These complications occur to varying degrees, depending on the cannulation site. The most common site for cannulation is the radial artery, followed by the femoral artery, axillary artery, brachial artery, and, less commonly, dorsalis pedis and ulnar arteries. The radial and the femoral arteries have similar cannulation complication rates[22]; some prefer the femoral artery as the primary cannulation site because of ease of insertion. The most common complication of radial artery cannulation is temporary arterial occlusion, which occurs approximately 20% (1.5%-35%) of the time; however, the occlusion is temporary in most cases and rarely causes acute ischemia.[20] In contrast to the radial artery, cannulation of the femoral artery is associated with a higher risk of bleeding (1.58% vs. 0.53%) and pseudoaneurysm (0.3% vs. 0.09%) but a lower risk of thromboembolism.[20] Cannulation of the axillary artery has a complication rate similar to that at other sites, and it may be the only site available for arterial access in some patients. In the ICU, however, it is not commonly used because of lack of familiarity with the approach and the potential, albeit unproven, risk for carotid embolization.[20] In the hands of experienced operators, the brachial artery also has a low reported complication rate. Yet because it requires meticulous attention to technique and anatomy, it is not commonly used.[21] The level of the transducer relative to the pressure being measured will determine the measured value of the arterial pressure, thus making its position critical for obtaining an accurate measurement. The standard level is the midpoint of the right atrium, approximately 5 cm below the sternal angle in the midaxillary line. This is the area where the preload pressure of the heart is determined.[23]

The distance of the measuring catheter from the heart, the length and compliance of the tubing, and the presence of air bubbles affect systolic and diastolic measurements in the system. These variables affect systolic and diastolic pressure proportionately in opposite directions and have no net effect on the measurement of mean arterial pressure (MAP). For this reason, measurement of MAP is a more accurate reflection of mean aortic pressure. MAP is manually calculated with the formula MAP = 1/3 ([2 × diastolic blood pressure] + systolic blood pressure). Electronic monitoring systems, however, measure MAP as the area under the pulse wave, often averaged over three or more cycles.

Pulmonary Artery Catheters

Pulmonary artery catheters provide central hemodynamic measurements, waveform tracings, and specific blood gas calculations such as mixed venous oxygen and carbon dioxide saturation (also see discussion of pulmonary artery catheter use in Chapter 33). Pulmonary artery catheters were initially used to assess and treat patients with acute myocardial infarction (MI); however, their use has declined significantly because several randomized trials have failed to demonstrate a reduction in mortality.[24-26] Pulmonary artery catheters are typically inserted in the ICU in situations where the clinician believes that measuring cardiac output, cardiac pressure, and mixed venous oxygen saturation will aid in guiding therapy and for direct assessment of the effect of and response to various treatments, such as the administration of fluids and vasopressors.[27] Included in this category are patients in cardiogenic or refractory shock and those in whom right ventricular dysfunction, such as infarction, is suspected.[18,28] Pulmonary artery catheters may induce arrhythmias, which are usually transient and not life-threatening.[29] Left bundle branch block is a relative contraindication to the use of pulmonary artery catheterization because it can induce a temporary right bundle branch block and the potential for subsequent complete heart block.[29] Other catheter-related complications include catheter knotting, pulmonary artery rupture, catheter fragmentation, and cardiac rupture secondary to forceful insertion. Long-term placement, more than 72 to 96 hours, can also lead to thrombosis and infection.

Echocardiography

Echocardiography is used to assess cardiac function by measuring ventricular contractility, chamber size, valve function, and flow.[30,31] Global assessment of ventricular function with transthoracic echocardiography can be helpful in guiding hemodynamic management because one can easily differentiate between

left and right ventricular dysfunction and adjust treatment appropriately.[32] For instance, a patient with a poorly functioning left ventricle may benefit from an inotropic agent, whereas the presence of a hyperdynamic left ventricle and evidence of tissue hypoxia may indicate the need for fluid challenge and vasopressors.[30] Echocardiography is helpful in the case of normotensive shock in a patient who has been adequately fluid resuscitated and who may require afterload-reducing agents such as nitroglycerin.[33] Calculation of ejection fraction, pulmonary artery pressure, and cardiac output is also possible, but specific expertise is required and such measurements may not be reliable in ICU settings.[32]

Transesophageal Doppler ultrasound is a noninvasive modality for measuring cardiac output.[34] Cardiac output is calculated by using the diameter of the descending aorta, the distribution of flow to the descending aorta, and the measured flow velocity of blood.[15] The accuracy of the calculated cardiac output may be affected by the position of the ultrasound probe, which is inserted blindly in the esophagus. Poor positioning of the probe most commonly results in underestimation of the cardiac output.[15]

Intra-Abdominal Pressure

Abdominal compartment syndrome is defined as clinically relevant organ dysfunction caused by intra-abdominal hypertension. IAP is the steady-state pressure concealed within the abdominal cavity. For most critically ill patients, an IAP of 5 to 7 mm Hg is considered normal.[35] Morbidly obese and pregnant individuals may have chronically elevated IAP without adverse consequences. Intra-abdominal hypertension is defined as IAP in excess of 12 to 20 mm Hg.[36,37] Abdominal perfusion pressure is calculated as MAP minus IAP. Elevated IAP may reduce blood flow to the abdominal viscera. Abdominal compartment syndrome is diagnosed by the combination of intra-abdominal hypertension and evidence of organ malperfusion. Specifically, it is a constellation of symptoms consisting of new attributable organ dysfunction, such as cardiovascular (decreased cardiac output), respiratory (high peak airway pressure), and renal (oliguria) malperfusion in the context of a sustained IAP of 20 mm Hg or higher.[36] Patients at increased risk for abdominal compartment syndrome are those who received large volumes of fluid for resuscitation (>10 L of crystalloid, >5 L of colloid) or transfusion of more than 10 units of packed red blood cells (PRBCs) during a 24-hour period.[37]

IAP is most commonly measured by the intravesicular technique.[38] An indwelling bladder catheter is connected to a pressure transducer. A defined volume of fluid (25-50 mL of normal saline) is instilled into the catheter and used to distend the bladder and eliminate bladder wall coaptation.[37] Volumes greater than 50 mL falsely elevate IAP values. IAP is then measured at end-expiration with the patient in the supine position and the manometer or other pressure measuring system at the level of the symphysis pubis. Another technique of IAP measurement uses a nasogastric or orogastric tube.[39] This technique involves a lower risk for sepsis secondary to iatrogenic urinary tract infection as a result of catheter manipulation, but it is a more cumbersome method and rarely used. The timing and frequency of IAP monitoring are not standardized, but the highest risk for the development of abdominal compartment syndrome is during and shortly after resuscitation. The main reason for monitoring IAP is that the early recognition and treatment of abdominal compartment syndrome appears to improve survival.[37]

CARDIOVASCULAR COMPLICATIONS

Hypertension

Hypertension is common after surgery and may be caused by hypoxia, hypercapnia, hypervolemia, hypothermia, gastric or bladder distention, agitation, and pain. Furthermore, a common cause of postoperative hypertension is simply neglecting to restart preoperative antihypertensive medications. Sedation, analgesia, and rewarming often resolve most cases of mildly elevated blood pressure. However, hypertension increases myocardial oxygen consumption and can potentially cause myocardial ischemia. In addition, in the immediate postoperative period, it may contribute to increased bleeding from raw surfaces or through vascular anastomoses. After all possible causes have been evaluated and addressed, drug treatment may be considered. In general, blood pressure treatment targets should center on systolic blood pressure values 20 mm Hg above or below preoperative pressure.[40] Deviations in MAP greater than 20% from preoperative values should also be treated.[41,42] Several agents may be used; the surgeon should become familiar with a few for an effective and safe approach to hypertensive patients in the postoperative period. Nitrates, beta blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and vasodilators are the most common classes of drugs used (see Chapter 14).[43]

Hypertensive crisis causes acute damage to end organs (heart, brain, retina, and kidney); it is associated with a systolic blood pressure higher than 179 mm Hg or diastolic blood pressure higher than 109 mm Hg. In the absence of evidence of end-organ damage, these elevations in blood pressure constitute hypertensive emergencies.[44] When such an emergency is diagnosed, short-acting intravenous antihypertensive agents should be used; the reduction in blood pressure should occur within 1 hour in hypertensive crisis and within 24 hours in a hypertensive emergency.[9] The goal is to reduce the patient's diastolic blood pressure to less than 110 mm Hg within 30 to 60 minutes.[45] Hypertensive patients in these circumstances will manifest natriuresis, which causes intravascular fluid depletion requiring the administration of fluid along with antihypertensive medications. Several agents can be used in hypertensive emergencies; one of the most common and effective is labetalol because it is a combined α_1-adrenergic and nonselective β-adrenergic receptor blocker.[46]

Hypotension

Hypotension is dangerous and is associated with an increased risk for end-organ dysfunction (MI, cerebrovascular events, and

renal failure) and possibly bypass graft thrombosis. Common causes of hypotension after surgery are hypovolemia, cardiac dysfunction, and a diffuse vasodilatory state with or without sepsis. The management strategy for the correction of hypotension involves the administration of fluids and vasoactive agents. A fluid challenge should be the first line of treatment of postoperative hypotension. Surgical bleeding should be excluded as a cause to prevent delays in returning the patient to the operating room.[47]

In administering fluids for resuscitation, one must first determine whether the patient is on the ascending portion of the Frank-Starling curve and will benefit from a fluid challenge. If the patient is on the flat portion of the curve, fluid loading will only increase tissue edema and worsen tissue dysoxia, with little effect on cardiac output.[15] A large pulse pressure–stroke volume ratio (>10%:15%) is indicative of hypovolemia and predictive of volume responsiveness.[15] A fluid challenge in these circumstances will increase preload and subsequently increase stroke volume.[48] Similarly, in patients with a pulse pressure variation greater than 12%, a fluid challenge is likely to have a positive effect on cardiac output.[49] If the hypotension does not respond to fluid resuscitation, cardiac output must be optimized by pharmacologic means. Short-acting peripheral vasoconstrictors, such as phenylephrine and dopamine, are readily available on crash carts and can be given peripherally and titrated to effect. Once adequate central intravenous access has been established, the patient should be switched from dopamine to more definably titratable vasopressors.

In cardiogenic shock, peripheral vasoconstrictors may increase myocardial workload and dysfunction. In this setting, inotropic agents may be necessary to increase cardiac output. Patients in cardiogenic shock secondary to acute MI have mortality rates higher than 50%.[50] In these situations, volume must be optimized, rhythm must be controlled, and beta agonists should be administered to enhance contractility.[51] Finally, intra-aortic balloon pump counterpulsation may be necessary to aid the heart in generating cardiac output when pharmacologic agents fail. Beta blockers and calcium channel blockers have a negative inotropic effect and are relatively contraindicated in this setting.

Arrhythmias

Patients with preexisting structural heart disease are at highest risk for postoperative arrhythmias.[52] Common triggers for postoperative arrhythmias are hypoxia, hypercapnia, acid-base imbalances, electrolyte abnormalities, and myocardial ischemia. Treatment must focus on predisposing factors, and the goal should be hemodynamic stabilization, control of the ventricular response, and restoration of rhythm.[52]

Tachyarrhythmias

The most common tachyarrhythmias are sinus tachycardia, atrial fibrillation (AF), ectopic atrial tachycardia, junctional tachycardia, multifocal atrial tachycardia, atrioventricular (AV) nodal reentry tachycardia, ventricular tachycardia (VT), and ventricular fibrillation. Tachyarrhythmias that traverse the AV node can often be controlled pharmacologically by altering conduction through the AV node.[52] Tachyarrhythmias that are conducted by accessory pathways and ventricular tachyarrhythmias are more difficult to control pharmacologically than those that transverse the AV node. Supraventricular tachyarrhythmias are common after surgery, with an incidence of approximately 4% to 13%,[52] and after AAA repair, with an incidence of 3.2%.[53] Short bursts of atrial tachycardia do not require treatment. It is important, however, to correct any underlying causes, such as electrolyte imbalances. For sustained atrial tachyarrhythmia in a hemodynamically stable patient, the rate may be slowed with beta blockers or calcium channel blockers. Caution should be exercised with these agents, however, when they are used in patients with poor left ventricular function or congestive heart failure. Alternatively, in monitored settings, treatment can be switched to intravenous amiodarone. In stable patients with nodal reentrant rhythms, adenosine (6-12 mg intravenously) can also be used instead of beta blockers or calcium channel blockers. If patients are hemodynamically unstable, they should be electrically cardioverted regardless of the type of atrial tachyarrhythmia.

Ventricular tachyarrhythmias are also managed according to their duration and hemodynamic consequences. In the presence of coronary artery disease, these rhythms are ominous. Furthermore, the presence or absence of structural heart disease has prognostic significance[52]; it is important when the treatment of runs of premature ventricular contractions and nonsustained VT is being considered. Prompt evaluation and treatment of predisposing factors—such as hypokalemia, hypomagnesemia, hypoxia, and myocardial ischemia—are important to prevent sudden death. In addition, unstable VT is an indication for immediate electrical defibrillation. In contrast, hemodynamically stable monomorphic VT should be treated with antiarrhythmics such as intravenous amiodarone, followed by prompt cardiac evaluation.

Polymorphic VT and ventricular fibrillation occur most commonly in the setting of acute MI and can rapidly lead to hemodynamic instability. These arrhythmias are also treated with urgent defibrillation and intravenous antiarrhythmics. Polymorphic VT with prolonged QT intervals is called torsades de pointes. The most common cause of this rhythm is drug-related or QT prolongation secondary to electrolyte abnormalities. Intravenous magnesium should be given empirically for suspected torsades de pointes. Positive chronotropic agents such as isoproterenol or temporary overdrive pacing to shorten the QT interval can also be used.

Atrial Fibrillation

AF is the most common arrhythmia encountered in the postoperative period; it affects 10% of patients undergoing major noncardiothoracic operations.[54,55] Onset is often within the first few days after the operation, and AF is associated with increased 30-day postoperative mortality, increased ICU stay, and increased overall hospital length of stay. Common risk factors for the development of AF include advanced age, male gender, valvular heart disease, and previous history of AF.[54] AF can be precipitated by hypokalemia, hypomagnesemia, volume overload, withdrawal of beta blockers or angiotensin-converting enzyme inhibitors,

COPD, obesity and obstructive sleep apnea, and infections, especially pulmonary infections.[54,56,57] A rapid heart rate limits ventricular filling, and loss of the atrial component of the cardiac cycle—the so-called atrial kick—decreases left ventricular stroke volume by 20% to 35%.[58] This is especially important in patients with diastolic dysfunction and dilated left ventricles, whose cardiac output is volume-dependent.[59]

Treatment focuses on controlling the heart rate, restoring normal sinus rhythm, and preventing thromboembolic complications.[59] Patients who are hemodynamically unstable, have pulmonary edema, or have ongoing chest pain should undergo urgent electrical cardioversion. Hemodynamically stable patients should have their heart rates pharmacologically controlled with beta blockers, amiodarone, digitalis, or calcium channel blockers. Chemical cardioversion can also be used in hemodynamically stable patients, and one-third of patients will convert to normal sinus rhythm with amiodarone loading alone.[60]

Before electrical cardioversion, one must consider the patient's risk for thromboembolic complications. If the patient has been in AF for longer than 48 hours or for an unknown period, intracardiac thrombus must be excluded.[61] This is obviously not feasible in the event of acute hemodynamic instability, in which case one should proceed with electrical cardioversion to stabilize the patient and subsequently monitor for thromboembolic complications. If an intracardiac thrombus cannot be excluded and the patient is hemodynamically stable, the safest course is anticoagulation with unfractionated heparin before cardioversion.[54]

Bradyarrhythmias

Bradyarrhythmias are not generally a diagnostic challenge and treatment options are straightforward. Those associated with sinus node dysfunction are sinus bradycardia, sinus pause, sinoatrial block, and sinus arrest.[62] Postoperatively, these rhythms are most often due to increased vagal tone and myocardial ischemia. If the bradyarrhythmia is transient and not associated with hemodynamic instability, it does not require treatment. Treatment of sustained bradyarrhythmias and hemodynamic compromise is with antimuscarinic agents such as atropine. If there is no response with continued bolus doses of atropine, the patient must be paced either externally or with a temporary transvenous pacer.

Postoperative Myocardial Infarction

Diagnosis

MI is the most common cause of cardiac complications and mortality in patients with peripheral vascular disease.[47,63-66] The three modes of detecting clinically meaningful postoperative cardiac ischemia are symptoms, the electrocardiogram (ECG), and evaluation of myocardial enzymes. Symptoms elicited from the patient, often in the form of anginal chest pain, are not a frequent manifestation of postoperative myocardial ischemia but are more commonly found in those with acute coronary syndrome.[67] In the postoperative period, these symptoms are also difficult to distinguish from distracting postoperative pain and are influenced by the concomitant use of analgesia and anesthetics. The presence of ST-segment changes on the ECG may indicate an MI. However, after major vascular surgery, approximately one-third of patients will have ST changes on the ECG in the absence of clinically significant myocardial ischemia.[68] Regardless, the presence of such changes correlates with an approximately 9- to 16-fold increased risk for MI and death.[68] The third method of diagnosing postoperative MI is through the detection of myocardial proteins released into the circulation as a result of myocardial cellular injury. The most common enzymes evaluated are the MB isoenzyme of creatine kinase (CK-MB) and the myocardial-specific cardiac protein troponin I.[69] In vascular surgery patients, increased cardiac troponin I levels in the absence of clinical symptoms have also been demonstrated to be useful in the risk stratification of postoperative patients for cardiac morbidity.[69] Elevated levels after major vascular surgery are associated with an increased risk for perioperative MI and increased risk for mortality at 6 months.

ST-Segment Elevation Myocardial Infarction

ST-segment elevation MI (STEMI) is most commonly caused by acute rupture of atherosclerotic plaque and thrombosis of the involved coronary arteries. For this diagnosis to be made, the ECG must show ST-segment elevation of at least 0.1 mV (1 mm) in two consecutive leads.[70] In patients with preexisting left bundle branch block, diagnosis of STEMI is difficult. Biochemically, CK-MB levels are elevated 3 to 12 hours after infarction, peak at 24 hours, and can be elevated for 3 days. Cardiac troponin levels can be detected 4 to 12 hours after infarction, peak at 12 to 48 hours, and can remain elevated for 1 week.

Treatment involves rapid resuscitation with administration of supplemental oxygen, afterload-reducing agents, antiplatelet therapy, anticoagulation with unfractionated heparin (if at low risk for bleeding), and urgent reperfusion therapy with either fibrinolysis or primary percutaneous coronary intervention (PCI). Postoperatively, fibrinolysis may be relatively contraindicated, but this decision must be individualized to the patient according to the extent of surgery and time after the operation. For clinically significant ischemia and patients in cardiogenic shock in the postoperative period, urgent PCI and revascularization are indicated. Primary PCI is associated with primary patency rates of greater than 90%. Emergency coronary artery bypass surgery is reserved for patients who have failed to respond to PCI or fibrinolysis or who have a complication that requires surgery, such as ventricular septal rupture, cardiac rupture, or severe mitral valve insufficiency.[71] Beta blockers should also be started unless patients are hypotensive or bradycardic, are in congestive heart failure, have advanced AV block, or have reactive airway disease. In addition, an angiotensin-converting enzyme inhibitor should be started in the first 24 hours after infarction. In the long term, patients also benefit from treatment with statins.

Non–ST-Segment Elevation Myocardial Infarction

Non–ST-segment elevation MI (non-STEMI) is characterized by the presence of biomarkers indicative of myocardial injury in the absence of ST elevation on the ECG. The key difference

from STEMI is myocardial ischemia in the absence of significant coronary obstruction, such as occurs with acute plaque rupture. The myocardial ischemia in this setting is due to a transient reduction in coronary blood flow that causes an imbalance in myocardial oxygen supply and demand, often with shortness of breath and decompensated heart failure. The ECG can demonstrate nonspecific T-wave inversion or ST depression, and the key to diagnosis is the presence of circulating biomarkers (CK-MB, troponin I, troponin T) indicative of myocardial cellular necrosis.[72] Mortality risk is directly proportional to troponin levels.[73]

Treatment is medical and centered on optimizing myocardial oxygen delivery and demand and preventing reinfarction and death.[72] Supplemental oxygen should be administered, and pharmacologic agents to decrease preload and cardiac afterload should be given. Treatment can be thought of as the ABCs (acetylsalicylic acid, angiotensin-converting enzyme inhibitor, beta blockers, and cholesterol lowering). Administration of unfractionated heparin is also associated with a mortality benefit,[72] but its use must be balanced with the risk of bleeding. Statin therapy should also be instituted and treatment continued in the long term. In the setting of ongoing chest pain, the most recent American College of Cardiology/American Heart Association guidelines recommend the use of sublingual nitroglycerin if the systolic blood pressure is higher than 90 mm Hg and the heart rate is not less than 50 beats per minute or more than 100 beats per minute. If further analgesia is needed after nitroglycerin is given, morphine sulfate or meperidine can be used.[74]

PULMONARY MANAGEMENT

Respiratory insufficiency can be divided into either oxygenation failure or ventilation failure. Oxygenation failure is typically associated with hypoxia and ventilation failure with hypercapnia. Management of patients with acute respiratory failure and acute respiratory distress syndrome is discussed extensively in Chapter 40. The following comments focus on pulmonary support provided for the mechanically ventilated patient.

Ventilatory Support

Mechanical Ventilation

Mechanical ventilators affect oxygenation by controlling airway pressure and fraction of inspired oxygen and affect ventilation by controlling tidal volume and respiratory rate. Patients are ventilated primarily in two modes: controlled and supported. In controlled ventilation, the ventilator initiates and delivers a set amount of tidal volume; in supported mode, the breath is initiated by the patient and supported by the ventilator. Ventilators may deliver either a fixed tidal volume with variable pressure (volume control) or a variable tidal volume at a fixed pressure (pressure control). The combination of these two general modes of ventilation (controlled versus spontaneous) with either of these two settings (volume control versus pressure control) accounts for the majority of modes with which patients are ventilated. Patients with hemodynamic instability or in severe respiratory distress should be placed on a controlled mode of ventilation to limit the work of breathing. Either volume control or pressure control ventilation will be adequate, and practitioners should select the mode with which they are most familiar. Pressure support mode is generally used in patients who are more stable. It is also used as a weaning mode (discussed in the next section).

It is important to ventilate patients with use of a lung protective strategy to reduce ventilator-induced lung injury, which can occur through two main mechanisms. The first is referred to as volutrauma, which causes overdistention of alveoli due to high tidal volume and high alveolar pressure and can lead to barotrauma (pneumothorax, pneumomediastinum). The second main mechanism is caused by shear forces on alveolar endothelium.[75] These shear stresses are created in alveoli by cyclic opening and closing, and the resultant injury is called atelectatic trauma.[76] PEEP applied throughout the ventilatory cycle serves to stent alveoli open, which prevents atelectatic trauma and facilitates gas exchange. The ideal level of PEEP is unknown, but an accepted range, depending on the clinical situation, is 5 to 15 cm H_2O.

In ventilating patients at increased risk for volutrauma, such as those with acute respiratory distress syndrome, a lung protective strategy using pressure control ventilation to reduce peak airway pressure is most appropriate (Fig. 34.1). In this mode, inspiratory time can also be lengthened to allow increased alveolar recruitment, and alveolar distending plateau pressure and transpulmonary pressure are to be kept below 30 cm H_2O by use of tidal volumes that should not exceed 6 to 8 mL/kg ideal body weight.[77] However, low tidal volume ventilation causes decreased clearance of carbon dioxide, with associated respiratory acidosis. However, this "permissive hypercapnia" and acidosis are well tolerated if the patient's pH is above 7.2.[78] One caveat is that permissive hypercapnia is contraindicated in patients with cerebral edema.

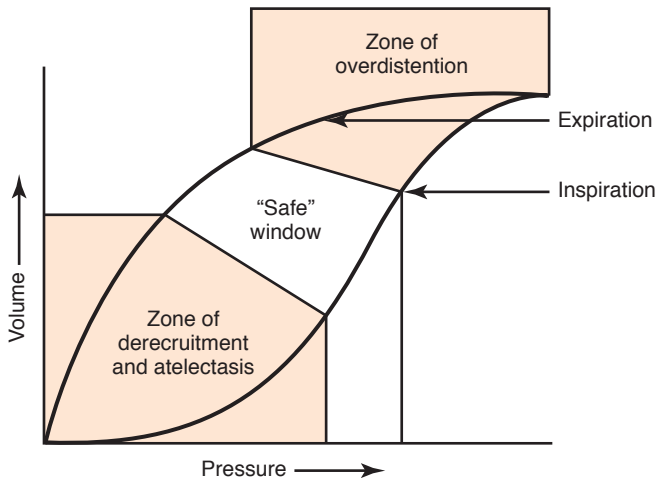

Figure 34.1 Protective Ventilation. Ventilation of a patient with parameters on the left side of the pressure-volume curve places the patient at risk for atelectatic trauma, and ventilation of a patient with parameters on the right side of the curve places the patient at risk for barotrauma. (Redrawn from Froese AB. High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time. *Crit Care Med.* 1997;25:906–908.)

Weaning

There are two main considerations in the weaning process. The first is weaning the support provided by the ventilator, and the second is removing the endotracheal tube (liberation from the ventilator). Patients should be assessed daily for readiness to be weaned, which can be done only after interruption of sedation.[79] This method has been called "wake up and breathe." Several randomized trials have revealed that weaning method influences the duration of ventilation.[80,81] The traditional approach to weaning has been a progressive reduction in ventilatory support over time according to a protocol.[82] A second technique is the use of spontaneous breathing trials without progressive withdrawal of ventilatory support, which may be associated with earlier extubation.[83] With the traditional approach to weaning, patients are switched from a controlled to a spontaneous mode of ventilation, such as pressure support ventilation. The amount of ventilatory support and PEEP is then decreased according to oxygen saturation, respiratory rate, and tidal volume. If the patient is not ready for weaning, a decrease in tidal volume and an increase in respiratory rate will be noted.[84] When a spontaneous breathing trial is used, patients are allowed to breathe spontaneously with little or no assistance. Most often, patients will be placed on minimal support (pressure support at 5-8 cm H_2O, PEEP at 5 cm H_2O) for 30 minutes to 2 hours. In a successful trial, the patient does not demonstrate respiratory distress (respiratory rate >35 for >5 minutes), desaturation (SaO_2 <90% for >30 seconds), increase or decrease in heart rate (±20% for >5 minutes), systolic blood pressure higher than 180 mm Hg or lower than 90 mm Hg, or other signs of agitation and distress (paradoxical breathing, use of accessory muscles, diaphoresis).[85]

Indications for Extubation

Once patients are weaned from the ventilator and have successfully spent a prolonged time with minimal PEEP and on minimal pressure support, they can be assessed for the potential for extubation. If any indication for intubation exists, it is a contraindication to extubation. Contraindications to extubation are sedation, inability to protect the airway, presence of copious secretions, and lack of a cough reflex. Consideration must also be given to how difficult it would be to reestablish the airway if needed. Failure of extubation is associated with increased mortality and a need for long-term ventilation.[86] The harm of reintubation must be balanced by the harm created by prolonged mechanical ventilation. Reintubation rates of 10% to 15% are within the normal range in most ICUs.[87]

Tracheostomy

Tracheostomy relieves the patient of the portion of the work of breathing required to overcome the resistance of the endotracheal tube and the upper airway. It also allows better oral hygiene and secretion management and improves patient comfort. The major disadvantages of a tracheostomy are procedure-related complications, stomal complications, formation of a tracheoinnominate fistula, and formation of a tracheoesophageal fistula. Early tracheostomy within the first week in patients who are thought to require ventilation for more than 10 days facilitates weaning and is associated with a shorter length of stay in the hospital.[87] Jubran et al.[80] found that in patients who required prolonged mechanical ventilation, unassisted breathing through a tracheostomy resulted in shorter median weaning time compared with pressure support. However, in a retrospective observational study after abdominal and thoracoabdominal repair, Diedrich et al.[88] found that, overall, tracheostomy correlated with worse outcomes but that patients with preexisting COPD who received a tracheostomy had improved survival.

Tracheostomy can be done either by an open surgical procedure or percutaneously. Percutaneous tracheostomy is as safe as open surgical tracheostomy, with the advantage that the patient does not require transport to the operating room; operating room resources are thus conserved.[89] Furthermore, no difference in long-term outcomes between percutaneous and open surgical tracheostomy has been shown.[89] However, percutaneous tracheostomy is relatively contraindicated in patients who are hypoxic and have high PEEP requirements, those who are obese with short necks, those who are coagulopathic, and those with recent (<10 days) anterior cervical spine fixation.[90]

BLEEDING

Evaluation of Bleeding Patients

Patients with greater than expected fluid requirements postoperatively must be urgently evaluated for bleeding.[47] The physiologic response to hypovolemia includes tachycardia, hypotension, low CVP, decreased urine output, and signs of peripheral vasoconstriction.[91]

Surgical Bleeding

Surgical bleeding can worsen coagulopathy and render it resistant to medical correction. A thorough patient examination is necessary to evaluate for possible sources of bleeding. Coagulopathy is generally assessed with a hemoglobin level, platelet count, prothrombin time (usually expressed as the international normalized ratio [INR]), activated partial thromboplastin time (aPTT), and fibrinogen assay. A blood sample for typing and screening should also be drawn to ensure that blood is available for transfusion if needed. Hemoglobin level may not show an initial drop when the patient is bleeding acutely. The role of imaging is dependent on the stability of an acutely bleeding postoperative patient. If the patient is stable and the bleeding source is not clear, computed tomography, ultrasonography, and angiography may be helpful.

Coagulopathy

For a summary of coagulopathy, see Table 34.1. Early in the postoperative period, coagulopathy is often dilutional or caused by incomplete reversal of the heparin administered during surgery (or both). Assessment of the coagulation system by measurement of the aPTT, prothrombin time (expressed as the INR), platelet count, and fibrinogen should be done immediately to guide

TABLE 34.1 Postoperative Coagulopathy

	Possible Problems	Treatment
Prolonged aPTT and normal INR	Heparin Hemophilia A Hemophilia B Hemophilia C	Protamine Factor VIII Factor IX Factor XI
Normal aPTT and increased INR	Warfarin Vitamin K deficiency Drugs	FFP or vitamin K or prothrombin complex concentrates Vitamin K
Normal aPTT and normal INR	Platelet dysfunction Thrombocytopenia	Platelet transfusion Platelet transfusion
	Hypothermia	Warm patient
Prolonged aPTT and increased INR	Primary fibrinolysis Disseminated intravascular coagulation	Treat underlying cause Cryoprecipitate if fibrinogen <100 mg/dL (<150 to 200 mg/dL in severe bleeding) Tranexamic acid FFP if factors <25% of normal Keep platelets >50 × 10^9

aPTT, Activated partial thromboplastin time; *FFP,* fresh frozen plasma; *INR,* international normalized ratio.

therapy. The etiology, diagnosis, and management of specific coagulopathies are discussed in Chapter 37. Included here is a practical approach to the management of coagulopathic patients in the postoperative period.

Prolonged Activated Partial Thromboplastin Time and Normal International Normalized Ratio

If the patient has a prolonged aPTT and a normal INR, potential residual heparin effect may be reversed with protamine sulfate, which should be administered slowly to avoid inducing hypotension.[92] However, the heparin effect may not be reduced by the administration of fresh frozen plasma (FFP) because it may increase the level of antithrombin III, and most of the effect of heparin is mediated through activation of this factor. A normal INR and a prolonged aPTT may also be found in factor VIII deficiency (hemophilia A) or von Willebrand disease. This may be treated with administration of the specific factor and, in mild cases, desmopressin (DDAVP). An increased aPTT with an often normal INR may also be found in patients with hemophilia. Diagnosis of the three types of hemophilia is made through specific factor analysis. Type A involves a deficiency of factor VIII, type B involves a deficiency of factor IX, and type C involves a deficiency of factor XI.[91] In these patients, transfusion of the missing factors may be necessary. For further discussion of hemophilia, see Chapter 37.

Increased International Normalized Ratio and Normal Activated Partial Thromboplastin Time

An increased INR with a normal aPTT may be caused by warfarin administration or by vitamin K deficiency secondary to chronic illness or malnutrition or as a side effect from treatment with broad-spectrum antibiotics. The coagulopathy in this setting is due to a reduction in vitamin K–dependent coagulation factors (factors II, VII, IX, and X), and FFP; vitamin K may be necessary to reverse this coagulopathy. In situations where rapid reversal is required within 6 hours, FFP or prothrombin complex concentrates may be required.

Normal International Normalized Ratio and Activated Partial Thromboplastin Time

In patients with a normal INR and aPTT, the bleeding diathesis may be caused by platelet dysfunction. This, in turn, may be due to lack of a sufficient number of platelets or, in the presence of a normal number, to a defect in their function. Other less common causes of coagulopathy associated with a normal INR and aPTT are factor XIII deficiency and hyperfibrinolysis. Causes of thrombocytopenia include bacterial infection, drugs (other than heparin), and bone marrow disease. Platelet dysfunction can also result from hypothermia. The level at which platelets should be transfused is controversial in an actively bleeding patient, but general guidelines for platelet transfusion are discussed later (and also in Chapter 37). Platelet dysfunction may be caused by platelet inhibitors or uremia. Platelet transfusion and DDAVP may be helpful in these settings. In the immediate postoperative period, patients need to be rewarmed expeditiously because platelet function is enhanced at normothermic body temperatures.[47]

Increased International Normalized Ratio and Increased Activated Partial Thromboplastin Time

Primary fibrinolysis and disseminated intravascular coagulation (DIC) rarely occur in the postoperative period. DIC is usually associated with an increased INR and aPTT as well as thrombocytopenia. The hallmark of this condition is excessive stimulation of the coagulation system with an imbalance between thrombosis and fibrinolysis. The severity of the coagulopathy is dependent on the level of fibrinogen. Microthrombi are formed and induce the body's natural mechanism of fibrinolysis. This, in turn, causes bleeding, and bleeding results in the release of tissue factors, including activation of factor VII, which increases coagulation. This scenario creates a vicious circle leading to depletion of stores of coagulation factors and subsequent consumptive coagulopathy. DIC can result from shock liver secondary to massive hypotensive episodes in the postoperative period, especially in the setting of chronic liver failure. Other common causes in postoperative patients are massive occult hemorrhage and sepsis. DIC has also been rarely associated with the administration of different blood products, including factor VII, in a dose-dependent manner.[93]

DIC is a clinical diagnosis, and laboratory tests are confirmatory.[94] They show low fibrinogen levels, increased fibrin degradation products, and thrombocytopenia. The principles of management include treating the underlying cause, such as debridement of devitalized tissue and source control for sepsis or disseminated bacterial infection. Replacement of blood products is reserved for patients actively bleeding or at high risk for bleeding, not in response to laboratory abnormalities.

It may be appropriate to administer cryoprecipitate when fibrinogen levels are less than 100 mg/dL (<150 to 200 mg/dL in severe bleeding), to transfuse FFP when other factor levels are below 25% of normal or the INR is abnormal, to transfuse platelets to increase counts to greater than 50,000/mm^3, and to replace blood volume as needed.[91,94]

FLUIDS

Infusion of Fluids

Fluid administration in the postoperative period must be tailored to the individual patient. A balance must be reached between adequate tissue perfusion by replacing fluid loss at surgery and avoidance of fluid overloading. Hypervolemia is as detrimental to the patient as hypovolemia because it causes unwanted tissue edema and impedes tissue oxygenation. If large volumes of crystalloid solution are administered for resuscitation, it is recommended that a balanced salt solution such as lactated Ringer's solution be given instead of normal saline to reduce the development of iatrogenic hyperchloremic metabolic acidosis. Restricted fluid regimens based on physiologic response versus standard fluid administration based on fluid algorithms and fixed rates have been associated with improved outcomes and decreased lengths of hospital stay after major gastrointestinal surgery and decreased pulmonary morbidity after thoracic surgery.[95,96] We favor the administration of intravenous fluids in the postoperative period at low maintenance rates of 75 to 100 mL/h and small boluses of crystalloid (500-1000 mL) as needed, with titration to low blood pressure, increased heart rate, or low urine output (Fig. 34.2). Colloids are commonly used for fluid resuscitation because they have the theoretical benefit of expanding intravascular volume and their osmotic activity reduces third spacing. However, there appears to be no survival benefit when albumin is used in severely ill patients and no difference among the different types of colloid used.[97]

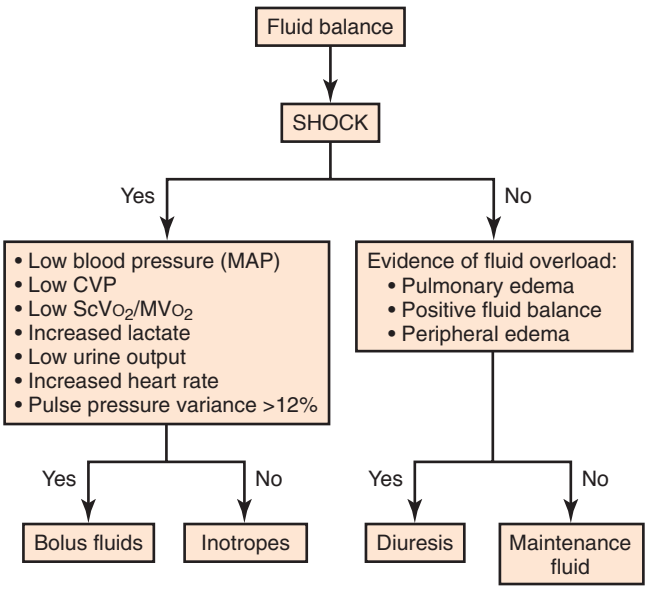

Figure 34.2 Fluid balance. *CVP,* Central venous pressure; *MAP,* mean arterial pressure; *MVO_2,* mixed venous oxygen saturation; *$ScVO_2$,* central venous oxygen saturation.

Electrolyte Management

In the immediate postoperative period, it may be dangerous to add routine electrolytes, such as potassium, to maintenance fluids because of perioperative fluid shifts. Routine testing of sodium, potassium, magnesium, calcium, and phosphate should be performed. Electrolytes should then be replaced individually as needed, and this can safely be done by protocol. Magnesium and potassium levels must be maintained in the normal range to avoid cardiac arrhythmias. Maintenance of calcium and phosphate levels is also important for cardiac function as well as for several cellular functions. The serum sodium level is a reflection of total body water. Both hyponatremia and hypernatremia require assessment of the patient's volume status and careful treatment to avoid adverse neurologic complications.

Transfusion of Blood Products

For a summary of blood product transfusion, see Table 34.2. The evidence for guiding transfusion practices is sparse with respect to the timing and volume of product administration and the ideal ratio of red blood cells (RBCs), platelets, and FFP. It is accepted that giving a disproportionate amount of one product over another can exacerbate dilutional coagulopathy. In addition, relying on laboratory tests to guide transfusion may be misleading because of the delay in obtaining results and the fact that normal levels do not equate to normal function. Additional discussion of the following topics can be found in Chapter 33.

TABLE 34.2 Transfusion of Blood Products

	Clinical Scenario	Transfusion Threshold
Red blood cells	Stable patient, absence of CAD	Hb <7.0 g/dL (<70 g/L)
	Stable patient with CAD	Hb 8.0-9.0 g/dL (80-90 g/L)
Platelets	Major cardiac surgery and unexplained bleeding	$<100 \times 10^9$
	Coagulopathy and active bleeding	$<50 \times 10^9$
	No active bleeding, febrile, with coagulopathy	$<20 \times 10^9$
	No active bleeding, low risk for hemorrhage, no fever	$>10 \times 10^9$
Fresh frozen plasma	Active bleeding and INR >1.5	INR >1.5
Cryoprecipitate (factor VIII, factor XIII, vWF)	Active bleeding and fibrinogen <100 mg/dL (<2.9 µmol/L)	<100 mg/dL

CAD, Coronary artery disease; *Hb,* hemoglobin; *INR,* international normalized ratio; *vWF,* von Willebrand factor.

Red Blood Cells

The transfusion threshold for RBCs has decreased for all patients on the basis of a randomized nonblinded study in critically ill euvolemic patients in the intensive care setting by Hébert et al.[64] They compared 418 patients treated with a restricted transfusion strategy to maintain the hemoglobin concentration between 7.0 and 9.0 g/dL (70 and 90 g/L), in whom PRBCs were transfused when the hemoglobin level was lower than 7.0 g/dL (70 g/L), with 420 patients in whom the hemoglobin target was 10.0 to 12.0 g/dL (100-120 g/L), who were administered PRBCs when the hemoglobin level fell below 10.0 g/dL (100 g/L). The restrictive strategy resulted in a 54% reduction in the number of units of PRBCs transfused. Overall, 30-day mortality and organ dysfunction were similar in the two groups. Mortality at 60 days was significantly less in the restrictive group ($P = .05$). Furthermore, subgroup analysis suggested improved 30-day mortality in patients with an Acute Physiology and Chronic Health Evaluation (APACHE) score of less than 20 and age younger than 55 years for the restricted group ($P = .02$). No difference was found in patients with a primary or secondary diagnosis of cardiac disease. Thus, for clinically stable patients not at risk for coronary artery disease, transfusion of RBCs is likely to be beneficial when the hemoglobin level is less than 6.0 g/dL (60 g/L) but not when it is greater than 7.0 g/dL (70 g/L) as long as normal blood volume is maintained and the patient is carefully monitored.

In contrast to critically ill patients, guidelines state that for those at risk for coronary artery disease, transfusion may be indicated when hemoglobin is less than 8.0 to 9.0 g/dL (80-90 g/L). In acute blood loss, the lower limit of tolerance has not been established, but oxygen delivery will probably be adequate with a hemoglobin level of 6.0 to 8.0 g/dL (60-80 g/L). With ongoing blood loss, however, the measured hemoglobin concentration may be misleading, because by the time that the hemoglobin value is reported, the actual oxygen-carrying capacity may have changed. In these circumstances, the decision to administer RBC transfusions should be determined by evaluating the rate of ongoing blood loss, evidence of end-organ dysfunction, and risk for or presence of coronary artery disease.[91]

Platelets

The definition of a threshold for platelet transfusion would be relatively easy if there were consistent, well-defined relationships between platelet count, platelet function, and bleeding manifestations. However, 10 review articles and 12 guidelines for platelet transfusion therapy were published between 1966 and 1999, thus suggesting that such a relationship is less than clear. One unit of platelets from whole blood contains 5.5 to 10×10^{10} platelets, whereas 1 unit from platelet pheresis contains 40×10^{10} platelets and is equivalent to 6 units from whole blood.

In nonsurgical patients, spontaneous bleeding is uncommon with platelet counts greater than 20×10^9/L. In contrast, the platelet count at which surgical patients are likely to experience increased bleeding is unknown. Regardless, in 1994, the College of American Pathologists recommended platelet transfusion for patients with platelet counts less than 50×10^9/L.[98] For major surgery with life-threatening bleeding, this guideline also concluded that transfusions might be indicated at higher platelet counts to maintain a concentration greater than 50×10^9/L. In addition, it indicated that some experts recommend platelet transfusion after cardiopulmonary bypass in patients with normal coagulation values and platelet counts below 100×10^9/L when major unexplained bleeding occurs because platelets are dysfunctional. Similarly, the American Society of Anesthesiologists Task Force concluded that bleeding risk in surgical patients is defined by the type and extent of surgery, ability to control the bleeding, consequences of uncontrolled bleeding, actual and anticipated rate of bleeding, and presence of factors that adversely affect platelet function (e.g., extracorporeal circulation, renal failure, medications). Moreover, in the absence of contradictory evidence, the opinion of the task force is that platelet transfusion is justified at higher platelet counts in bleeding patients than in nonbleeding patients because of the increased risk for complications from bleeding in surgical patients. Similarly, massively transfused patients with microvascular bleeding that is suspected to be secondary to platelet deficiency may benefit from empiric platelet therapy. However, the task force indicates that surgical patients with microvascular bleeding will usually require platelet transfusion if the platelet count is less than 50×10^9/L but rarely require therapy if the count is greater than 100×10^9/L. With intermediate platelet counts (50-100 $\times 10^9$/L), the decision to transfuse platelets should be based on the patient's risk for more significant bleeding.

In summary, for patients who are actively bleeding after major surgery, platelet counts should be maintained at a level greater than 50,000/mm^3. In nonbleeding patients and those in whom the risk for hemorrhage is low, platelet counts can be maintained above 10,000/mm^3. However, if patients have a fever or are coagulopathic, the target should be a level greater than 20,000/mm^3.

Fresh Frozen Plasma

According to the American Society of Anesthesiologists, after major transfusion, defined as transfusion of more than 10 units of RBCs, or after major surgery with active bleeding, FFP should be given to reduce the INR to a level below 1.5, because pathologic microvascular bleeding does not tend to occur until coagulation test results are greater than 1.5 times normal. In massive resuscitation, as for trauma, it has also been suggested that FFP be given in a 1 : 1 ratio with RBCs to reduce the risk of dilutional coagulopathy, although definitive evidence supporting this practice is lacking. FFP is also indicated for warfarin overdose, but it will not correct the anticoagulant effect of heparins because it contains antithrombin, which is augmented by both unfractionated heparin and low-molecular-weight heparin.

Cryoprecipitate

Cryoprecipitate consists of fibrinogen, factor VIII, factor XIII, and von Willebrand factor. The majority of acquired hypofibrinogenemias are due to consumptive coagulopathy and fibrinolysis. With postoperative bleeding, administration of cryoprecipitate should be reserved for patients with fibrinogen

levels less than 100 mg/dL (2.9 μmol/L). Each unit of cryoprecipitate contains approximately 150 mg of fibrinogen and is compatible only with normal saline. The volume needed to raise fibrinogen concentration 0.5 to 1.0 g/L can be estimated as 1 unit of cryoprecipitate per 5 to 10 kg of body weight.[99]

Summary of the Transfusion of Blood Products

For clinically stable patients not at risk for complications of coronary artery disease, transfusion of PRBCs is likely to be beneficial when the hemoglobin level is less than 7.0 g/dL (70 g/L) as long as normal blood volume is maintained and the patient is carefully monitored. Critically ill patients and those at risk for coronary artery disease will probably benefit from maintenance of hemoglobin in the range of 8 to 9 g/dL (80-90 g/L). In acute blood loss, the lower limit of tolerance has not been established, but oxygen delivery will probably be adequate with a hemoglobin level between 6 and 8 g/dL (60 and 80 g/L). With ongoing blood loss, however, the measured hemoglobin concentration may be misleading; by the time the hemoglobin value is reported, the actual oxygen-carrying capacity may have changed. In this circumstance, the decision to administer RBC transfusions should be determined by evaluating the rate of ongoing blood loss, evidence of end-organ dysfunction, and risk for or presence of coronary artery disease. FFP should be administered in the context of massive transfusions if there is microvascular bleeding associated with a significant (>1.5 times the normal value) increase in INR or aPTT. If these tests are not readily available, however, plasma may be transfused in an attempt to stop diffuse nonsurgical bleeding. Cryoprecipitate should be given when the fibrinogen level is less than 100 mg/dL (2.9 μmol/L) or possibly when time or the intravascular volume does not allow transfusion of FFP. Platelets should be transfused to patients who are bleeding from nonsurgical causes and have a platelet count of 50×10^9/L or less. Clinical circumstances may also require transfusion of platelets at a higher threshold.

Adjuncts in Hemostasis

Several adjuncts may be used with the aim of improving hemostasis. Recombinant activated factor VII (VIIa) has been used to control bleeding in patients with hemophilia types A and B. Recombinant factor VIIa also generates thrombin at the site of vessel injury and induces coagulation.[100] It has been used in the treatment of patients with hemorrhage from blunt trauma, thrombocytopenia, warfarin overdose, obstetric bleeding, and intracranial bleeding.[100,101] It is no longer recommended for off-label use in patients without hemophilia because of increased thromboembolic arterial events and lack of mortality benefit.[102]

Antifibrinolytic agents such as tranexamic acid and aminocaproic acid have been successfully used to treat postoperative hemorrhage.[103] These synthetic lysine analogues inhibit plasminogen and plasmin-mediated fibrinolysis.[92] Similarly, serine proteases such as aprotinin—which neutralize trypsin, plasmin, and kallikrein—have been used when fibrinolysis contributes to bleeding.[104] These agents have been shown to decrease transfusion of blood products in cardiac, hepatic, and orthopedic surgery.[104] Aprotinin has also been used prophylactically in coronary artery bypass surgery, but there has been concern because of an increased incidence of renal failure and increased risk for MI in these patients; this led to its temporary removal from the market.[100] Finally, DDAVP, a synthetic vasopressin analogue that stimulates endothelial release of factor VIII and von Willebrand factor, has been used to enhance platelet aggregation.[105] It is used mainly in patients with hemophilia and those with both congenital and acquired platelet disorders, but its value in surgical hemostasis is unproven. Thus its use in postoperative patients who do not have bleeding disorders is not recommended.[100]

Complications of Massive Transfusion

The definition of massive transfusion is replacement of 50% of a patient's blood volume in 3 hours or one blood volume in 24 hours.[106] The major complication of massive transfusion is the development of coagulopathy from multiple causes, including hemodilution, hypothermia, acidosis secondary to tissue hypoxia, and DIC.[106] Hemodynamically unstable patients are initially resuscitated with crystalloids, which are acellular and dilute the blood components, thereby aggravating the coagulopathy. Hypothermia associated with the infusion of large volumes of cold solution also inhibits the enzymatic coagulation cascade, synthesis of coagulation factors, and platelet function.[107] Administration of large volumes of fractionated blood products also causes coagulopathy by complex mechanisms, some known and some unknown: dilution of coagulation factors (particularly factors V and VIII:C, which have a limited shelf life), hypocalcemia because of the citrate used as an anticoagulant, and platelet dysfunction as a result of aging and metabolic alterations caused by storage.[91] Furthermore, when RBCs are stored, their extracellular potassium levels increase over time, so patients receiving large volumes of RBCs are at risk for hyperkalemia.

One of the most common sequelae of massive transfusion is acute lung injury secondary to congestion caused by overload, alveolar inflammation, and increased permeability.[108] Passive transfer of leukocyte antibodies in donated blood resulting in immune-mediated transfusion-associated lung injury can also occur.[109] Finally, massive transfusion has been described as an immunosuppressant leading to sepsis and sepsis-induced lung injury.[108] (See Chapter 33 for further discussion of transfusion-associated lung injury.)

RENAL FAILURE

A detailed discussion of renal failure can be found in Chapter 44. Therefore this discussion focuses on issues related primarily to the care of patients with postoperative renal failure. Briefly, patients with preoperative renal insufficiency are at the highest risk for postoperative renal failure. After vascular surgery, the major cause of postoperative renal failure is perioperative hypotension and ischemic injury leading to acute tubular necrosis.[47] Unfortunately postoperative renal failure is a marker for increased mortality, with rates of 60% to 80% after major

vascular surgery.[47] Physiologically patients are found to have oliguria or anuria and rising creatinine concentration despite volume resuscitation.

Few strategies have proven effective in reducing the incidence of this complication in the postoperative period. Diuretics may improve diuresis but they have no demonstrated effect on the prevention of renal failure. Low-dose dopamine has also been used, but without a reduction in morbidity or mortality.[110] In small studies, the use of fenoldopam (a renal vasodilator with natriuretic effect) given intraoperatively and postoperatively has been associated with some beneficial effect in patients with preexisting renal insufficiency.[111,112]

Early management of postoperative renal dysfunction should focus on reperfusion of the kidneys, which is most often achieved by fluid resuscitation. Forced diuresis has also been used in addition to fluid loading, but diuresis can be detrimental because it increases oxygen demand in the kidney and exacerbates ischemic injury.[113] Loop diuretics are the drugs of choice when forced diuresis is used because they offer the theoretical benefit of decreased oxygen consumption by the kidney by inhibiting adenosine triphosphatase in the medullary thick ascending limb.[114] In patients with renal dysfunction, doses of many drugs used in intensive care (particularly antibiotics excreted through the kidneys) should be adjusted according to creatinine clearance.

GENERAL ISSUES

Gastrointestinal Ischemia

Postoperative gastrointestinal ischemia is a rare but potentially lethal postoperative complication. Colonic ischemia occurs in 2% of patients after elective AAA repair and carries an overall mortality of 40% to 60% if it is transmural.[115] The incidence of ischemic colitis in patients undergoing repair of a ruptured AAA is reported to be 15% to 65%.[116] A high index of suspicion for colonic ischemia is necessary after aortic repair in patients with persistent acidosis and shock with no other obvious cause, greater than expected fluid requirements, new onset of gastrointestinal bleeding, or simply bloody bowel movements. Laboratory investigations often demonstrate anion gap acidosis and leukocytosis. In advanced cases, a plain abdominal radiograph may demonstrate free air in the peritoneal cavity or in the portal venous system. Abdominal computed tomography may demonstrate evidence of pneumatosis intestinalis. Bedside flexible sigmoidoscopy or colonoscopy can be diagnostic of colon ischemia. Stable patients with colonoscopic results suggesting ischemia limited to the mucosa may be treated conservatively with hydration and broad-spectrum intravenous antibiotics. However, immediate exploration is warranted in such patients if the condition worsens or hemodynamic instability ensues. Unstable patients with evidence of bowel ischemia should undergo urgent surgical exploration to reduce mortality. In selected cases of colon ischemia that has not progressed to gangrene, reimplantation of the inferior mesenteric artery can be considered. In the setting of frank gangrene, the colon should be resected and a colostomy created.

Nutrition

The nutritional state of critically ill patients has a direct effect on outcome. This is due to the catabolic stress that critical illness creates. Malnutrition in this patient population is associated with increased morbidity and mortality as well as increased length of stay in the hospital. In the general medical and surgical ICU population, it has been shown that commencing enteral nutrition within 24 to 48 hours of ICU admission is associated with improved outcomes.[117] It has been associated with reduced infections, increased protection against stress ulceration as well as intestinal ischemia, maintenance of gut flora, decreased catabolism, and decreased mortality.[118] Nutritional support in the ICU has had the goals of maintaining lean body mass to preserve immune function and avert metabolic complications.[119] This includes delivery of both micronutrients and macronutrients and meticulous glycemic control.[119] Early enteral nutrition has been shown to be safe in patients admitted to the ICU after major abdominal surgery.[120]

Several studies have also shown that patients undergoing major vascular surgery have a significant incidence of preoperative and postoperative malnutrition.[121] Patients undergoing surgery for AAAs have higher nutritional depletion and increased rates of postoperative infection compared with those having carotid or peripheral vascular surgery.[122] Interestingly, after AAA surgery, it has also been demonstrated that small bowel function returns to normal by 18 hours and starting enteral nutrition within 3 hours of surgery can promote activity in the small intestine, that fasting would not. This suggests that enteral nutrition may in fact aid the return of normal bowel function.[123] As suggested by others, it is our practice to initiate oral or enteral feeding within the first 48 hours after AAA surgery even in the absence of traditional clinical markers for readiness to feed (presence of bowel sounds, flatus, bowel movement, or volume of gastric aspirate).[124] Most ICUs use enteral nutrition protocols and guidelines for critically ill patients for this reason.[118] Although there are few studies of the applicability of these protocols specifically to vascular patients, both our vascular surgeons and intensivists think that these guidelines are safe and beneficial in this patient population.[125]

There are several newly updated North American and European guidelines available to help guide the assessment of nutrition and support therapy in critically ill adult patients.[118,119] These patients represent a heterogeneous population, and their nutritional needs should be individualized. These guidelines are intended for patients who are expected to require more than 2 or 3 days of ICU care and who have had significant metabolic or surgical stress. They are not intended for those patients who require only temporary monitoring or who have had minimal surgical stress. Some of the general highlights of the guidelines are reviewed here.

Nutrition in the ICU can be subdivided between dosing and route of administration. Several predictive equations exist that are used to estimate calorie requirements for patients in the ICU. However, these predictive equations are often less accurate than indirect calorimetry. These predictive equations are also more problematic in making accurate assessments of

nutritional goals for obese patients. Once goal calories are determined, patients should be given 50% to 65% of goal calories in their first week of ICU admission, thereafter increasing to goal rate. In obese patients (body mass index >30) with critical illness, permissive underfeeding or hypocaloric feeding with enteral nutrition is recommended. The target in obese patients should remain at 60% to 70% of ideal weight.

The two main routes of administering nutrition in critically ill patients are the enteral route and the parenteral route. As a general rule, the enteral route has the most benefit for the patient. In patients who are unable to eat, enteral nutrition is preferred to parenteral. As mentioned before, feeding should be started within the first 24 to 48 hours of admission to the ICU and advanced toward goal during the next 48 to 72 hours. Enteral feeding can be started through either a gastric tube or small bowel tube in the absence of traditional markers of bowel function (bowel sounds, flatus, or passage of stool). Patients are often challenged with trickle feeding at 10 mL/h to ensure tolerance before increasing rapidly toward goal.

It is recommended that either parenteral or enteral nutrition be provided to critically ill patients who are unable to voluntarily maintain their nutritional needs. In general, enteral feeding is preferred to parenteral feeding because of its superior nutritional efficacy and better safety profile. Enteral feeding through a nasogastric tube or small bowel feeding tube should be started within the first 24 to 48 hours after admission to the ICU and continued until adequate oral intake is firmly established. Placement of a feeding tube in the proximal small bowel should be considered in patients with inadequate gastric emptying as evidenced by residual gastric volumes in excess of 500 mL. If early enteral feeding is not feasible, parenteral nutrition should be considered if the anticipated duration of nutritional support will exceed 7 days. Shorter periods of parenteral nutrition (e.g., <5 to 7 days) expose the patient to a variety of vascular access, metabolic, and infectious risks without proven benefit. Even in patients stabilized on parenteral nutrition, periodic efforts should be made to start enteral feeding. Parenteral nutrition should not be stopped until enteral nutrition is providing at least 60% of target requirements. Recommended nutrition doses based on guidelines are up to 20 to 25 kcal/kg actual body weight per day in the acute phase of critical illness (72-96 hours) and 25 to 30 kcal/kg body weight per day in the recovery phase.[118]

Pain Management

Effective postoperative analgesia is important and may be associated with a reduction in the incidence of myocardial ischemia after surgery.[63] This reduction in incidence of MI does not appear to be related to changes in heart rate, blood pressure, or requirement for postoperative vasoactive agents compared with patients with inadequate pain control.[63] In nonintubated patients who are able, patient-controlled analgesia is preferred to intermittent on-demand narcotic dosing because patients can be in a significant amount of pain while waiting for the next narcotic dose. Epidural analgesia can also be effective in the postoperative period, and it offers the potential benefit of reducing the dose of opiates, which improves gastric emptying and ileus and increases patient mobility.[126] Patients who are mobilized earlier can benefit from reduced thrombotic events and pulmonary complications. However, care must be taken to prevent significant hypotension, which can be caused by the administration of epidural anesthesia. The balance between analgesia and sedation is discussed in the earlier section on sedation and delirium in the ICU.

Deep Venous Thrombosis Prophylaxis

The etiology, treatment, and prophylaxis of deep venous thrombosis (DVT) are reviewed in depth in Chapter 147. Thus only issues relevant to the prophylaxis and treatment of DVT after vascular surgical procedures are discussed here. Because most vascular surgery involves the intraoperative administration of heparin, it has been suggested that these patients do not carry the same postoperative risk for DVT as other surgical patients do. However, the incidence of DVT after aortic surgery has been reported to be between 2% and 18%[127]; therefore, all patients undergoing vascular surgical procedures should receive postoperative DVT prophylaxis.

General measures in postoperative care—such as elevation of the lower extremities, early ambulation, and leg exercises—may reduce the incidence of DVT.[128] Graduated compression stockings, intermittent pneumatic compression, and venous foot pumps have also been shown to decrease the incidence of DVT, but they have not been proved to prevent fatal pulmonary embolism when used as monotherapy.[128] It is also generally accepted that aspirin is not effective in the prevention of DVT.[129] In contrast, treatment with either low doses of subcutaneous unfractionated heparin (5000 units subcutaneously two or three times per day) or subcutaneous low-molecular-weight heparin at prophylactic doses is effective and safe in the prevention of postoperative DVT.[128] The potential benefit of prophylaxis with low-molecular-weight heparin is a reduced rate of heparin-induced thrombocytopenia. Prophylaxis is generally given until patients become ambulatory and mobile. This topic is extensively reviewed in Chapter 147.

Bridging Postoperative Oral Anticoagulation

Patients taking oral anticoagulants in the preoperative period require specific considerations. The most common strategy is to interrupt the oral anticoagulation and use either subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin.[130]

The American College of Chest Physicians has published guidelines with regard to patient risk for thromboembolic events.[131] Patients are categorized as being at low, moderate, or high risk. Bridging with full-dose anticoagulation is recommended only for patients at high risk. Such patients include those with mechanical mitral valves or old-model mechanical aortic valves. However, in patients at low risk for stroke and thromboembolism, such as those with atrial fibrillation (AF) and no other risk factors for stroke such as rheumatic valve disease, bridging may be unnecessary and potentially harmful.[132]

In these patients, oral anticoagulation can be stopped several days before the procedure and restarted several days after it. Although limited data regarding benefit are available, a prophylactic dose heparin may be used for such patients.

In patients taking oral anticoagulants who are at high risk for perioperative stroke, such as those with mechanical mitral valves or old-model mechanical aortic valves, oral anticoagulants should be stopped 4 days before and heparin started 2 days before surgery, when the oral agent is assumed to become subtherapeutic.[130] In the absence of postoperative bleeding, bridging doses of heparin can be restarted 12 to 24 hours after the surgical procedure. If unfractionated heparin is used, it should be restarted without a bolus dose. However, the risk of bleeding caused by restarting anticoagulation after major vascular surgery must be carefully considered. If anticoagulation is delayed because the risk of bleeding is deemed too high, prophylactic doses of heparin may be given.[130] After minor surgical procedures, oral anticoagulation can be restarted on the evening after surgery. In any case, clinicians must decide on a strategy that balances stroke risk with bleeding risk in each individual.

Alcohol Withdrawal Syndrome

Alcohol is the most abused drug worldwide.[133] Autonomic hyperactivity—including tremulousness, sweating, nausea, vomiting, anxiety, and agitation—appears within the first 24 to 48 hours after withdrawal in patients who abuse alcohol.[133] Symptoms can peak between the third and fifth postoperative days. Serious complications that may develop are delirium tremens and grand mal epileptiform seizures. Delirium tremens, which occurs in less than 5% of patients abusing alcohol, is associated with an increase in postoperative mortality[134] and characterized by fever, tachycardia, hypertension, tremors, diaphoresis, hallucinations, disorientation, agitation, and urinary incontinence. Physicians must exclude other life-threatening causes of confusion, such as myocardial ischemia, congestive heart failure, hypotension, pulmonary embolism, bleeding, stroke, metabolic and electrolyte disorders, and sepsis. Before sedation is initiated for presumed alcohol withdrawal, hypoxia must be ruled out, because hypoxia is the most common cause of confusion and agitation in the postoperative period.

Patients can be identified preoperatively to be at risk by the quantity and frequency of their alcohol consumption. Preoperative detoxification or abstinence before elective surgery may prevent adverse postoperative complications, but data in this regard are lacking. Patients known to be at risk should be administered prophylactic doses of benzodiazepines throughout the entire perioperative period to prevent the development of alcohol withdrawal syndrome.[134] Patients who regularly consume alcohol at dependency levels (determined by how alcohol consumption affects relationships, jobs, educational goals, and family life and not by the specific quantity consumed) have been shown to have increased postoperative morbidity and mortality.[135]

The first-line treatment for patients with alcohol withdrawal syndrome is benzodiazepines.[136] They mimic the central nervous system effects of alcohol on γ-aminobutyric acid receptors and suppress the withdrawal response.[137] Alcohol replacement therapy with oral or intravenous alcohol is still used but is controversial and has not been shown to be superior to benzodiazepine treatment.[138] Treatment of severe acute alcohol withdrawal may require intubation and admission to the ICU. Beta blockers may also be used to reduce sympathetic overactivity and cardiac complications. Seizures should be treated with intravenous benzodiazepines. All patients should also be given daily thiamine and multivitamins to prevent Wernicke-Korsakoff syndrome.

Sedation and Delirium in the Intensive Care Unit

Emphasis on sedation and analgesia in critically ill patients has recently come to the forefront of patient care in the ICU. The primary goal is to achieve adequate pain control and anxiolysis with appropriate sedation and analgesia. Unfortunately, in critically ill patients on mechanical ventilation, this is very challenging and can lead to oversedation, delirium, and harm to the patient.[139] It is very important to titrate the medications used for analgesia and sedation in a goal-directed manner so as to safely provide comfort without impeding recovery, affecting weaning from the ventilator, and prolonging length of stay. Several sedation monitoring systems have been developed in the ICU, such as the Sedation Agitation Scale, the Motor Activity Assessment Scale, and the Richmond Agitation-Sedation Scale (RASS).[139] A multidisciplinary team at Virginia Commonwealth University in Richmond has developed the RASS; it is a validated method used to avoid oversedation in the ICU. It is unique in that it separates verbal from physical stimulation in generating the score, thereby assessing the patient's arousal with varying potency of stimulus.[140] The RASS assesses consciousness by the use of a 10-point scale from −5 to +4 (−5, unarousable, to 0, alert and calm, to +4, combative), with three defined steps that incorporate the duration of eye contact to determine arousal and content of thought.[141] The entire assessment takes approximately 20 seconds.[139] The first step is simply to observe the patient; if he or she is alert, restless, or agitated, a score of 0 to +4 is given accordingly. If such a patient is not spontaneously alert, he or she is asked to look at the rater, with duration of eye contact rated (more or less than 10 seconds) and scored from −1 to −3 accordingly. If the patient does not respond to verbal stimulation, a physical stimulus is given and a score of −4 or −5 assigned accordingly.[141] However, if the patient is calm but not alert before verbal and physical stimulation, a score from −1 to −5 is given even if he or she becomes agitated on stimulation.

Ely et al.[139] compared the RASS with the Glasgow Coma Scale, which is a trauma-specific consciousness assessment tool; they demonstrated excellent correlation and discrimination between the scores in assessing levels of consciousness. They also compared RASS with cumulative lorazepam, propofol, fentanyl, and morphine doses of the prior 8-hour and 24-hour periods before RASS assessment. Interestingly, they found significantly different correlations with RASS between opiates (analgesics) and benzodiazepines (sedatives), with a higher likelihood of reintubation with deeper sedation measured by RASS. There

was further agreement in this study that RASS provided a consensus target for goal-directed sedation and improved team communication regarding sedation management.

Consciousness is considered a combination of level of arousal plus the content of that consciousness, such as delirium.[142] Unaddressed pain and anxiety in critically ill patients has been shown to lead to increased morbidity and mortality as well as posttraumatic stress disorder over the long term.[143] RASS is used to assess the level of arousal, but another key to patient outcome is delirium, a key feature of which is the presence or absence of inattention. Because the RASS incorporates eye contact as part of its assessment, it also correlates with the onset of inattention and delirium. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is a delirium-monitoring tool that complements the RASS and is used to assess acute brain dysfunction.[144] Whereas RASS measures the level of consciousness, CAM-ICU determines the content of that consciousness and the presence or absence of delirium. Delirium is a common but underdiagnosed form of organ dysfunction in the ICU. It was once thought to be a normal part of the process as patients arose from coma to consciousness, but it also occurs in the absence of this process or preexisting coma. Critically ill patients at risk for the development of delirium are those with preexisting cognitive impairment, advanced age, use of psychoactive drugs, mechanical ventilation, untreated pain, and sleep deprivation.[144]

Three subtypes of delirium are described: hyperactive, hypoactive, and mixed. Hyperactive delirium is represented by the patient who is agitated and attempting to pull out lines and tubes; patients with hypoactive delirium typically are characterized by a flat or withdrawn affect; and those who fluctuate between the two have mixed delirium. ICU physicians have concentrated on treating multiorgan dysfunction, often dismissing delirium as an unavoidable, often iatrogenic consequence of critical illness with little long-standing ill effect. However, the development of delirium has been shown to be an independent predictor of higher 6-month mortality and longer hospital stay in mechanically ventilated patients.[145] In this study, the investigators demonstrated that the development of delirium and the number of days spent in a delirious state were associated with a threefold increase in mortality in mechanically ventilated patients compared with those who did not develop delirium. Current guidelines suggest, in fact, that critically ill patients should be monitored daily for delirium.[146]

The assessment for delirium combines the RASS score with inattention and either disorganized thinking or an altered level of consciousness.[144] If patients respond to verbal stimulation (RASS score of −3 to +4) and have a positive CAM-ICU assessment, they are found to be delirious. Monitoring delirium with the CAM-ICU daily takes approximately 1 to 2 minutes, and nurses can easily be trained to perform it along with their routine assessments.[145] One important aspect in daily assessment for delirium is identifying patients with the hypoactive delirium subtype. As mentioned before, this subtype is characterized by a flat affect present in a calm, seemingly alert patient.[147] These patients have normal or nearly normal arousal compared with the agitated patients with delirium, which is likely why they are underdiagnosed and may have a worse outcome. Outcomes can be improved by reducing the unnecessary use of sedatives and analgesics.

Treatment of delirium can be divided between the use of nonpharmacologic and pharmacologic agents. Nonpharmacologic methods concentrate on minimizing risk factors with repeated reorientation of patients, early mobilization and activity, nonpharmacologic sleep protocol, and timely removal of catheters and lines; unnecessary noise and stimuli are minimized, and patients are given their normal aids, such as glasses and hearing aids. Pharmacologic strategies first involve the reduction or removal of unnecessary sedatives and analgesics. Many drugs, such as benzodiazepines, used to treat confusion often exacerbate it; lorazepam is a well-recognized offender. Pharmacologic agents with a procognitive advantage, such as haloperidol, have also been recommended for the treatment of delirium, although this is based on sparse data in the ICU population.[146] Other antipsychotic and neuroleptic agents—such as risperidone, quetiapine, and olanzapine—are often used in both hyperactive and hypoactive delirium, but patients receiving these agents must be closely monitored for adverse cardiac and extrapyramidal events. An important resource for physicians is available at www.icudelirium.org. Fig. 34.3 gives an overall approach to balancing both pharmacologic and nonpharmacologic approaches in critically ill patients. It attempts to improve patient outcomes

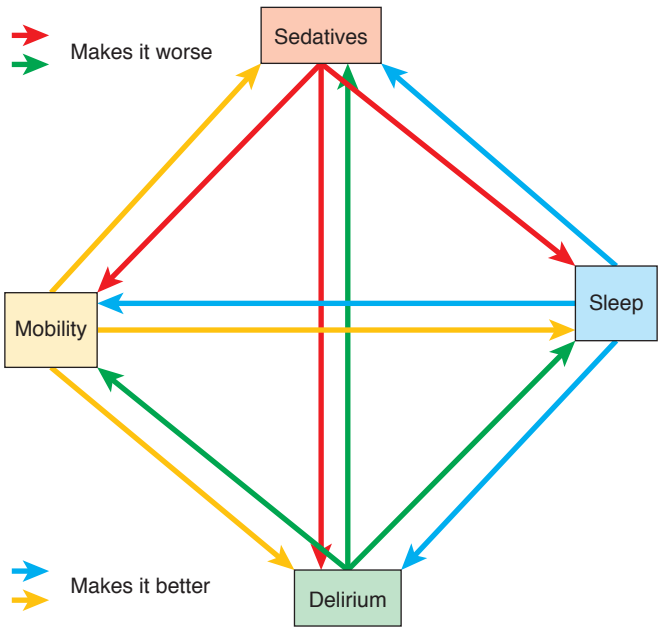

Figure 34.3 Sedation, Mobility, Sleep, Delirium Harm-Reduction Model. This diagram demonstrates the interrelationship between unrecognized delirium, oversedation, immobility, and lack of sleep. The red and green denote pathways that make this problem worse, whereas the blue and yellow pathways make this problem better. For example, the overuse of sedation decreases the likelihood of mobility, increases delirium risk, and decreases restorative sleep. Alternatively, mobilizing patients can make apparent a decreased need for sedation, improve sleep, and help to clear delirium. (From Clemmer T. *Rethinking critical care: reducing patient harm from sedation, immobility, and delirium*. 2001; Institute for Healthcare Improvement.)

by addressing oversedation, immobilization, and delirium simultaneously in high-risk critically ill patients.

Outside the ICU, postoperative delirium requires a hypoxic, metabolic, and septic workup. Medications and medication interactions must be ruled out. Older patients, such as vascular patients, suffer from multisensory deprivation, which makes them particularly vulnerable to extreme confusion at night.

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A complete reference list can be found online at www.expertconsult.com.

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35 CHAPTER

Hospital Readmissions in Vascular Surgery

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INTRODUCTION

The United States spends over $3 trillion annually on healthcare, or over 17% of the nation's Gross Domestic Product (GDP) (Fig. 35.1).[1] This is projected to reach nearly 20% of GDP by 2024.[2] This unsustainable spending has driven a keen interest in cost containment and the concept of increasing value in healthcare.[3] An area that has come under increasing focus in recent years is the issue of unplanned readmission. Readmission is a common occurrence that results in increased costs both to the patients and to the healthcare system as a whole. It has been estimated that potentially preventable readmissions cost Medicare approximately $12 billion annually.[4] Under the assumption that at least a fraction of these readmissions are related to breakdown in care and poor transition from the inpatient to the outpatient setting, readmissions have become a marker of quality of care, and reducing readmissions has become a focus of healthcare reform and the Affordable Care Act (ACA).[5] This focus on readmissions, specifically 30-day readmissions, as well as the financial penalties that are now tagged to this metric, have driven physicians, hospitals, and healthcare organizations to devote substantial time and effort to minimizing readmission. While on its face avoiding expensive hospitalizations is a good thing, emphasizing 30-day readmission as a primary quality metric—and tagging to it what can be steep financial penalties for hospitals—obscures what could be a holistic view to patient care and moves focus from clinical outcomes to what many have deemed a somewhat arbitrary measure.

Particularly for surgeons, how to best quantify and report quality has been a challenge. As stated by Lord Kelvin, the 19th century mathematical physicist who calculated the point of absolute zero on the thermodynamic temperature scale, "when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind."[6]

HISTORY

The Centers for Medicare and Medicaid Services (CMS) uses a diagnosis-related group (DRG) payment scheme for hospital reimbursement. DRGs were introduced by CMS in 1983 as an alternative to the initial payment model for CMS, which had no incentive to control cost.[7] The DRG system has been revised multiple times and, in its current incarnation, attempts to capture patient illness severity, comorbidities, risk of mortality, interventions, and likely resource use.[8] Payments are calculated by multiplying the fees by the DRG code plus modifiers for hospital factors, including teaching institutions, low-volume

Abstract

Thirty-day readmissions after vascular surgery is a blunt metric for capturing quality in patients with complex medical comorbidities. Avoiding this penalty may lead to unintended practices. Better quality metrics may lead to more meaningful incentives and outcomes.

Keywords

Re-admission
quality
metrics
complications
discharge

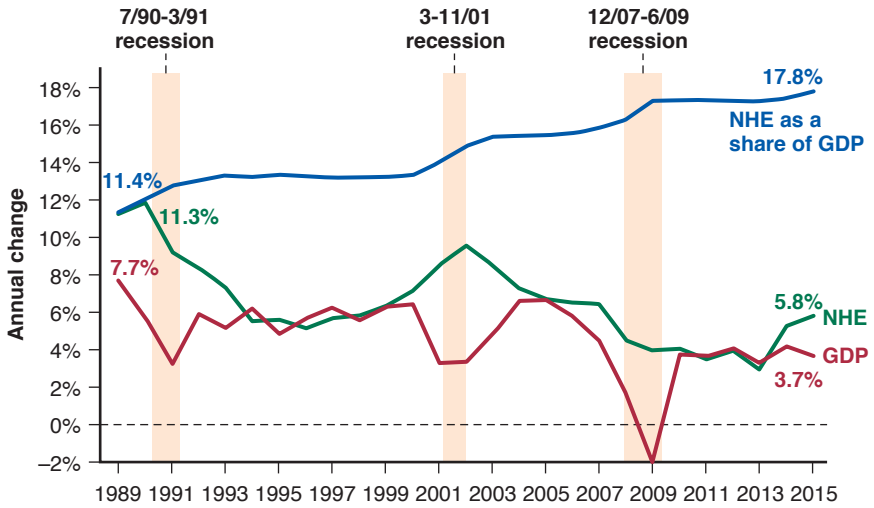

Figure 35.1 Growth in national health expenditures *(NHE)* and gross domestic product *(GDP)*, and NHE as a share of GDP, 1989 to 2015. (From Martin AB, Hartman M, Washington B, Catlin A. National Health Expenditure Accounts Team: National health spending: faster growth in 2015 as coverage expands and utilization increases. *Health Aff (Millwood)*. 2017;36(1):166-176. Data sources Centers for Medicare and Medicaid Services, Office of the Actuary, National Health Statistics Group; US Department of Commerce, Bureau of Economic Analysis; and National Bureau of Economic Research Inc.)

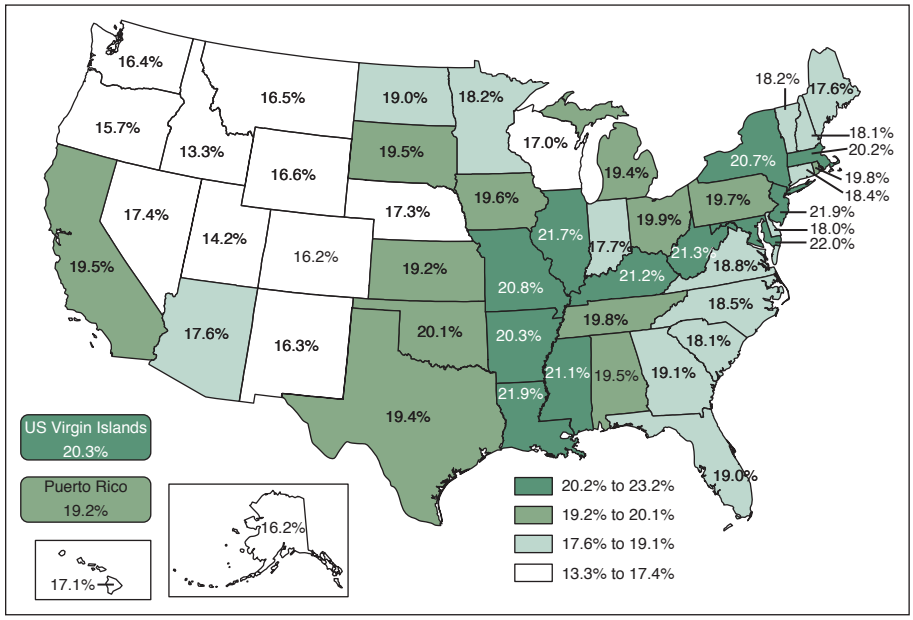

Figure 35.2 Rates of re-hospitalization within 30 days after hospital discharge. The rates include all patients in fee-for-service Medicare programs who were discharged between October 1, 2003, and September 30, 2004. The rate for Washington, DC, which does not appear on the map, was 23.2%. (From Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med*. 2009; 360(14):1418-1428.)

hospitals, transfers, and outliers. While unlike direct billing, DRGs attempt to control costs by limiting payments to adjusted but set amounts, and they continue to incentivize hospitals to operate at or near capacity in order to bill for patients treated. In addition to the many changes that came with the ACA, a focus of cost control was also implemented, and one aspect of that was a focus on 30-day readmissions under the Hospital Readmissions Reduction Program (HRRP).[9] To capture this, CMS calculated anticipated readmission rates based on performance over the prior 3 years and then instituted penalties for institutions that were above that calculated benchmark. The readmission period is defined as 30 days from discharge rather than from procedure date, an important nuance particularly in surgical specialties, and captures readmission to any part of the hospital, to either surgical or nonsurgical specialties. In 2012, readmission measures began with acute myocardial infarction (AMI), heart failure (HF), and pneumonia. Also pertinent to surgeons, in 2014 CMS began to adjust for planned readmissions. Beginning in 2015, chronic obstructive pulmonary disease (COPD) became a tracked condition, as well as elective total hip arthroplasty (THA) and total knee arthroplasty (TKA). Coronary artery bypass graft (CABG) was added in 2017. Once expected risk-adjusted readmissions are calculated, the excess readmission ratio is calculated, and reimbursement for each targeted DRG is then discounted by that ratio to a maximum penalty of now 3% of the hospital's annual DRG payments.[9]

READMISSION IN VASCULAR PATIENTS

Work by Jencks et al.[4] provides much of the basis of our current understanding of the issue of 30-day readmissions (Fig. 35.2). While the average estimated readmission rate for Medicare patients for all-comers is as high as 18% of patients, readmission rates vary by geographic area and by specialty, with an average 11.1% of surgical patients readmitted within

30 days of discharge.[4] Within surgical specialties, readmission rates also vary. In a recent study within the VA population, 16% of vascular patients were readmitted within 30 days of discharge compared to only 9.6% of orthopedic patients.[10] Indeed, unplanned readmission rates for vascular surgery patients are high, and range from 9.3%[11] to 24%[4] (Table 35.1). Surgery for peripheral vascular disease had the third highest rate of 30-day readmission behind only congestive HF and psychosis.[4] Ninety-day readmission rates climb significantly higher, to an average 17.9% for vascular patients tracked in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP).[12] This can be as high as 48% following outpatient upper extremity hemodialysis access creation.[13] Readmissions were often associated with surgical site infections, treated deep vein thrombosis (DVT), cerebrovascular or cardiovascular events, and increased direct hospital costs 61% over the index hospitalization.[12]

TABLE 35.1 Readmission Rates for Vascular Procedures by Procedure Type

Procedure	30-Day Unplanned Readmission Rates	References
Carotid endarterectomy	6.5%-9.6%	48,49
Endovascular aortic repair	7.6%-13.3%	26,48
Open AAA repair	8%-12.8%	26,48
Open aortoiliac bypass	12.3%	50
Endovascular infrainguinal procedures	13.1%	50
Infrainguinal bypass graft	15.7%-30%	48,51-53
AV fistula	26%	13

AAA, Abdominal aortic aneurysm; *AV*, arteriovenous.

A number of factors have been identified that increase 30-day unplanned readmissions in the vascular population. Estimates of 30-day unplanned readmission following carotid endarterectomy were approximately 6.5%, with cardiac issues being the most frequent reason for readmission (followed by headache, bleeding complications, and stroke). Medical complications other than cardiac, both possibly related to the surgery or unrelated, were also among the most frequent reasons for unplanned readmission following carotid endarterectomy (CEA) (Fig. 35.3).[14]

Capturing this information is further complicated by the fact that patients are often readmitted to hospitals that did not perform their index procedure. Using a statewide database, following complex thoracic and thoracoabdominal aortic aneurysm repair, 79% of readmitted patients were readmitted to a hospital different from that at which their index procedure occurred.[15] Readmissions at the index hospital were more likely to be related to their aneurysm repair, as opposed to readmission to other hospitals, which were more likely to be related to medical morbidities.[15] Costs associated with readmissions were lower at nonindex hospitals, although this was possibly related to the increased likelihood of these readmissions being for medical complications. Indeed, in a single institution study, Orr et al.[16] found that readmissions potentially requiring repeat intervention, including endoleaks and graft occlusion, were associated with significantly higher median costs than complications that could potentially be managed nonoperatively including surgical site infections, which, while more common, had a median cost of only $4500 rather than $23,000 for endoleaks and $17,700 for graft occlusion. Interestingly, no difference has been seen between readmissions for open compared to endovascular procedures on average. In a single institution trial, among 605 open procedures and 421 endovascular procedures there was no significant difference between the two groups in terms of index hospitalization institutional cost ($27,653 vs. $23,999),

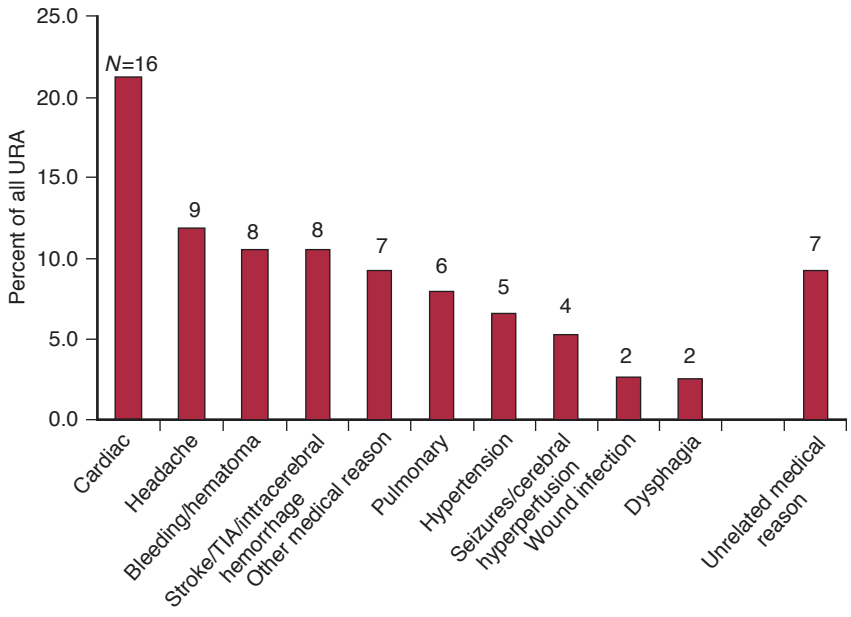

Figure 35.3 Reason for 30-day readmission following carotid endarterectomy (CEA). Frequency of reasons for unplanned readmission (URA) after CEA. *TIA*, Transient ischemic attack. (From Ho KJ, Madenci AL, Semel ME, et al. Predictors and consequences of unplanned hospital readmission within 30 days of carotid endarterectomy. *J Vasc Surg*. 2014;60(1):77-84.)

unplanned readmission rates (16.9% vs. 17.8%), or cost of readmission ($19,117 vs. $17,887).[17]

Risk Factors for Readmission

Primary preoperative predictors of readmission include American Society of Anesthesiologists (ASA) operative class, preoperative open wound, inpatient operation, dialysis dependence, and a history of diabetes mellitus. However, as with many surgical patients, the strongest predictors of readmission remain postoperative factors, meaning that they cannot be used to improve patient selection prior to the operating room.[11,18,19] Among vascular patients, postoperative complications are the most significant predictor of readmission and the complications with this best predictive ability were postdischarge deep space infection, superficial surgical site infections, pneumonia, myocardial infarction (MI), and sepsis.[18] Given that these complications often require hospitalization for management, it is not surprising that they predicted readmission.

INTERVENTIONS TO DECREASE READMISSIONS IN VASCULAR SURGERY

Brooke et al.[20] reported a framework to address the issue of readmissions in vascular surgery across various phases of care from patient selection to postprocedure follow-up, and point out the various opportunities for complications in patient care as well as research at each phase (Fig. 35.4).

Within patient selection, multiple patient level factors exist that have been associated with increased risk of readmission, including diabetes and advanced age. Preoperative health optimization programs are becoming increasingly popular and focus on increased activity, smoking cessation, weight loss, and sleep training among other factors.[21]

At the provider level, while the decreased rates of death and stroke following carotid endarterectomy is a classic example of the impact of surgeon volume on patient outcomes, the link between surgeon volume and readmission remains tenuous.[22] Among pancreatic surgeons, there does appear to be a link between the increasing volume of procedures performed and the decreased rates of readmission, ranging from 23% for low volume surgeons to 12% for those with higher operative volumes.[23] However, the vast majority of variation in readmission appears to be due to patient-related factors, with surgeon-level factors explaining only approximately 3% of variability.[24] At the hospital level, following surgical procedures, higher volume institutions do appear to have lower rates of readmissions: 16.8% for lower volume hospitals compared to 12.7% for higher volume hospitals.[5]

Patient discharge is also a transition point that influences the rates of readmission. Within the state of Maryland, in a study of hospital discharges across multiple services including surgical subspecialties, discharge summaries that were greater than 3 days delayed in completion were associated with an increased risk of readmission and each additional 3-day delay in discharge summary completion was associated with an increase in the adjusted odds of readmission of 1%.[25]

Postoperative care also has a predictably significant impact on readmission rates. Among individuals undergoing open and endovascular abdominal aortic aneurysm (AAA) repairs, the odds of readmission more than doubled for those individuals with a postoperative wound infection and were significantly higher if patients required discharge to a skilled nursing facility rather than their own home.[26] What is perhaps most disconcerting was that readmission was also associated with a significant increase in 1 year mortality rates, going from 4.5% to 23.4%.[26]

There has been concern that a move toward enhanced recovery pathways and earlier discharge may drive increases in readmission rates. However, in both cases, this has not been seen.[27,28] In fact, it appears that standardizing care likely leads to better coordination and fewer deviations from care pathways and that stronger adherence to pathways are associated with better outcomes and decreased readmissions.[29]

LIMITATIONS OF 30-DAY READMISSIONS

Focusing on 30-day readmissions appears to have at least, in part, had a positive impact on readmission rates. While readmission rates decreased across the board between 2012 and 2015, the rates for targeted conditions appeared to decline more than nontargeted conditions.[30] Furthermore, this occurred without a corresponding increase in observation admissions, which is a potential loop-hole to readmission penalties.[30]

Despite this improvement, 30-day readmission remains a proxy measure for larger issues and the impact of readmission reduction programs on quality of care is less clear. Looking at six major procedures, including CABG, pulmonary lobectomy, colectomy, hip replacement, endovascular aneurysm repair (EVAR), and open AAA repair, an association was seen between 30-day readmission rates and other commonly accepted measures that are felt to correlate with a higher quality of surgical care, including higher surgical volume and lower operative mortality.[5] However, adherence to surgical process measures as measured by Hospital Quality Alliance (HQA) score was not significantly associated with better outcomes.[5]

Specific to vascular surgery, an additional weakness of readmission as a quality indicator for hospitals is the fact that there is little year-to-year reliability in the readmission rank for hospitals. Looking at readmissions following open and endovascular AAA repair and lower extremity bypass within Medicare for 63% of hospitals, the change in their year-to-year rank moved across quintiles, with the previous 2 years' readmission rank explaining only 32% of the variation.[31] The magnitude of this variation is much larger than one would expect, based on the quality of the hospital alone and suggests that a substantial degree of year-to-year variability may be random.[31]

Measuring readmissions also has the potential to penalize hospitals when, in reality, it is often community-level factors that influence readmission.[32] Among safety-net hospitals, 30-day

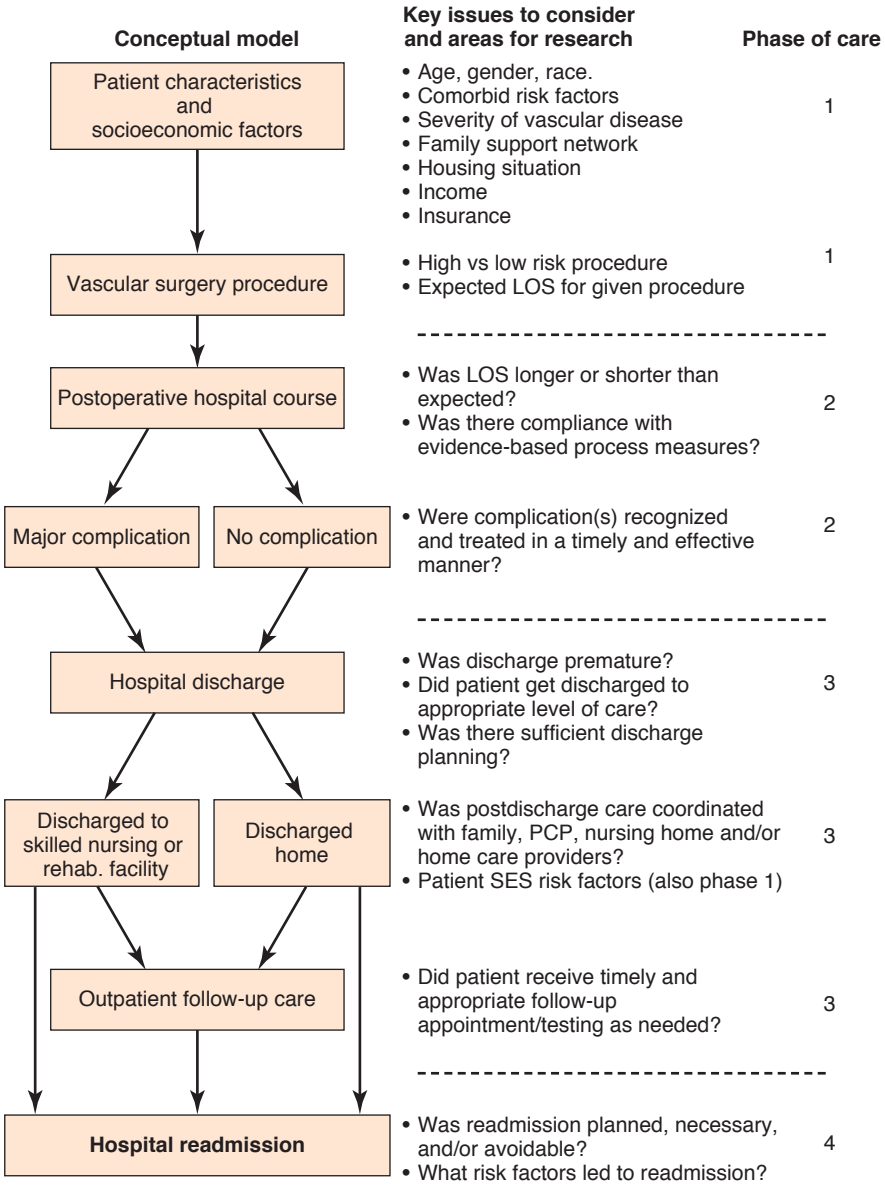

Figure 35.4 Conceptual model of readmission in vascular surgery. Conceptual model of prevental readmission in vascular surgery. There are multiple risk factors and key issues to consider at four separate phases of care for a patient readmitted following a vascular surgery procedure. These represent points where variability in clinical pathways and decision making may be associated with increased risk for readmission, and where future research may be targeted. *LOS*, Length of stay; *PCP*, primary care provider; *SES*, socioeconomic status. (From Brooke BS, De Martino RR, Girotti M, Dimick JB, Goodney PP. Developing strategies for predicting and preventing readmissions in vascular surgery. *J Vasc Surg*. 2012;56(2):556-562.)

readmission following discharge from a general surgical service only appeared to be linked to the index hospitalization in a minority of cases, with the vast majority of the readmissions being related to patient and disposition issues, and only 9.2% of all readmissions being related to the initial injury or condition.[32] In one study, the most frequent reasons for readmission included new soft tissue infections, either related to intravenous drug use (16.8%) or de novo (13.3%), or to disposition support issues (14.5%).[32] Furthermore, the degree to which readmissions are preventable—even those that are related to the index hospitalization or hospital-level factors—has also been raised as a concern. Some estimates report that less than one-third of all readmissions are actually preventable.[33,34]

Safety-net hospitals are also disproportionally burdened by the 30-day readmission penalty given the severity of the disease faced by many of the patients for which they care. While safety-net hospitals have been able to respond to readmission penalties by reducing readmission rates,[35] the CMS has acknowledged this issue with proposed adjustment to penalties based on the socioeconomic demographics of a hospital's patient mix.[35]

An additional concern regarding readmission as a measure of quality is that often factors leading to patient readmission are tied to perioperative complications. If wound complications are captured during the index hospitalization, leading to quality penalties, and then lead to a later readmission, clinicians are potentially being doubly penalized.

This is further complicated by the fact that readmission data vary widely by their source. In analyzing the extent to which readmissions are preventable, the data varied from 59% for reports based on administrative data to only 12% for those studies that relied on clinical data.[33,34] In another study, when based on administrative claims, readmission diagnosis varied from clinical diagnosis 30% of the time and miscategorized a

significant proportion of planned readmissions as unplanned.[36] This raises significant concerns regarding the achievability and appropriateness of lowering 30-day readmissions as a quality metric. Furthermore, where Medicare defines readmission as 30 days from discharge, the ACS-NSQIP starts the 30-day clock on the day of surgery. This creates what has been described as an immortal time bias, in that individuals with prolonged postoperative admissions are not at risk for readmission.[37] This leads to a systematic underreporting of 30-day readmissions when compared to Medicare data, and this is exacerbated by longer hospitalizations.[37]

Both longer and shorter timeframes for readmission penalties have been suggested, with those arguing for a longer duration of surveillance pointing out that 30 days likely fails to capture the entirety of postdischarge complications. Shorter timeframes, often 3 to 7 days, have also been suggested as being more directly linked to factors that hospitals have the potential to control.[34] In hierarchical modeling, the impact of hospital-level quality factors on readmission rate nadirs at 7 days postdischarge.[38] It has also been suggested that clinicians feel more personal responsibility for early readmissions and, therefore, are committed to improving care transitions.[34,39]

Existing Interventions to Reduce 30-Day Postprocedure Readmissions and Alternative Metrics

While the body of literature surrounding the issue of hospital readmissions has grown exponentially, interventions designed to reduce 30-day readmission, particularly following surgical procedures, are lacking, and those that are reported are often quite limited in their generalizability.[40] The vast majority focus on improving transitional care.

Rather than focus on readmissions as a quality metric, some groups have begun to propose alternative means of measuring quality and value in healthcare.[41] Financial incentives, bundled payments, risk sharing, accountable care organizations, and a focus on the concept of value in care have all come to the forefront. Particularly pertinent to procedural care, bundled, or episode-based payments create a single payment for the complete episode of care.[42] Rather than penalizing hospitals for unplanned readmissions, it is thought that bundles create a financial incentive to minimize low value care or expensive complications. Bundles are mandatory for joint replacement within Medicare and Medicaid, and capture the index hospitalization, procedure, plus 90 days following discharge. Voluntary oncology care bundles, as well as four variations of bundled payment models that address 48 different conditions and procedures and attempt to capture both in-hospital and postacute care costs, are also being piloted.[42] In addition to their impact on costs, in early data these bundles appear to be associated with a decreased length of stay and 30-day readmissions.[42]

It is important to note that—as with readmission penalties and other novel reimbursement strategies—safety-net hospitals, which carry a larger burden of patients with more advanced disease, face disproportionate financial losses in the bundling environment. Patients managed at safety-net hospitals for diabetic foot wounds are more likely to require an amputation and more complex disease, meaning that safety-net hospitals would face significantly higher penalties for their care compared to other institutions.[43]

Patient-centered outcomes have also become increasingly prevalent, particularly as patient satisfaction begins to play a greater role in the perception of quality care.[44] Within vascular surgery, while graft patency and amputation-free survival are widely accepted outcomes, patient quality of life, independence, and ambulatory status capture a more nuanced picture of the patient experience, and help to allow patients and providers to speak a similar language around expected outcomes and benefits for procedures.[45]

Multidisciplinary care centered around conditions rather than the current specialty-centric silos that exist within clinical medicine has been proposed as a means of decreasing costs and increasing value to patients and the healthcare system.[3] It has been proposed that this would decrease the duplication of effort that plagues the current system.[3] Many areas of vascular surgery lend themselves well to this approach. Within orthopedic surgery, setting a common goal and mobilizing a multidisciplinary team was associated with increased early mobilization, discharge home, and decreasing costs.[46] A multidisciplinary approach to care for patients with critical limb ischemia was associated with a twofold increase in amputation-free survival.[47]

CONCLUSIONS

The issue of cost containment in healthcare has led to a focus on the issue of unexpected readmissions as a potential area of intervention. While a great deal of work has been done in this area, 30-day readmissions remain an imprecise metric in measuring quality. It is undeniable that unplanned readmissions are costly and can be the result of complications during the index hospitalization, but the degree to which they are a stable measure of quality, or are within the ability of physicians or institutions to improve, seems less clear. A number of alternatives to readmission penalties have been proposed that each attempt to incentivize improved value in care. As the healthcare system continues to evolve, it is likely that readmissions will remain a factor in assessing quality of care. However, as our understanding of this process further develops, the interventions to improve transitions of care will become more prevalent and the quality metrics more refined.

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The key references represent a subset which we feel are the best foundation references or are a more contemporary discussion of the topic.

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CHAPTER 36

Normal Coagulation

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INTRODUCTION

Vascular endothelial cells, blood, and extravascular tissue maintain blood flow fluidity or produce an integrated response to attenuate blood leakage by localized clotting at the site of vascular injury. The processes of blood coagulation and fibrinolysis are the primary defense systems of the vasculature. The opposing forces of fibrin clot formation and dissolution maintain hemostasis and preserve vascular function and integrity. Procoagulant events that culminate in the generation of thrombin and the formation of a fibrin clot protect the vasculature from perforating injury and excessive blood loss. Fibrinolysis removes the clot and initiates mechanisms involved in tissue repair and regeneration. Therefore, hemostasis refers to multiple discrete processes that center on

Abstract

The blood coagulation process is essential to maintaining hemostasis and preventing hemorrhage. Excessive or aberrant activation of the coagulation process can lead to unwanted thrombosis. It is necessary to closely monitor patients to minimize the risks of hemorrhage and thrombosis in a surgical setting.

Keywords

Blood
Coagulation
Thrombosis
Hemostasis
Anticoagulants
Coagulation tests
Fibrinolysis

thrombin generation, fibrin clot formation, and fibrin clot dissolution.

Hemostasis is not a passive state, but instead it is actively maintained by the vascular system. Specific cellular and protein interactions are required to maintain a state of equilibrium. When the system is perturbed, an integrated series of processes are required to initiate procoagulant events and to promote fibrinolysis and tissue repair. Each individual process that contributes to hemostasis must operate properly or the entire system is compromised. A balance among procoagulant, anticoagulant, and fibrinolytic factors is required to prevent uncontrolled bleeding or, conversely, excessive clot formation.[1]

PROCOAGULANT, ANTICOAGULANT, AND FIBRINOLYTIC PROTEINS, INHIBITORS, AND RECEPTORS

History and Nomenclature

Current knowledge of the components involved in the complex process of blood coagulation (Fig. 36.1) is the result of observations that date back to the second century.[2] Many hypotheses were envisioned about the transformation of fluid blood to a gel-like mass as it escaped the body,[3] but the realization that clots stem blood loss did not occur until the beginning of the 18th century,[3,4] and it was not until the 19th century that the existence of thrombin, the key enzyme in blood coagulation, was recognized.[3,5] Four clotting factors were initially identified[6]: factor I, fibrinogen; factor II, prothrombin; factor III, thromboplastin; and factor IV, calcium ions (or Ca^{2+}). As more coagulation factors were identified, initially by bleeding pathology and subsequently by laboratory clotting tests,[7,8] they were assigned consecutive Roman numerals, with activated forms distinguished by an *a* after the Roman numeral designation.

To describe the multiple simultaneous processes involved in generation of a hemostatic response, we identify an inventory of the procoagulant, anticoagulant, and fibrinolytic participants in blood coagulation. Subsequently, we describe the connections between these components and the dynamics of this process.

Vitamin-K-Dependent Proteins (See Chapter 39: Anticoagulant Drugs)

The vitamin-K–dependent proteins, synthesized in the liver, play central roles in both the procoagulant or anticoagulant pathways. The family includes the procoagulant factors VII, IX, X, and prothrombin and the anticoagulants protein C, protein S, and protein Z (Fig. 36.2 and Tables 36.1 and 36.2). Except for proteins S and Z, these proteins in their active forms are serine proteases. The cleavage of specific peptide bonds converts the vitamin-K-dependent zymogens to their active serine protease forms. All share noncatalytic domains, each of which is characterized by highly conserved regions that provide

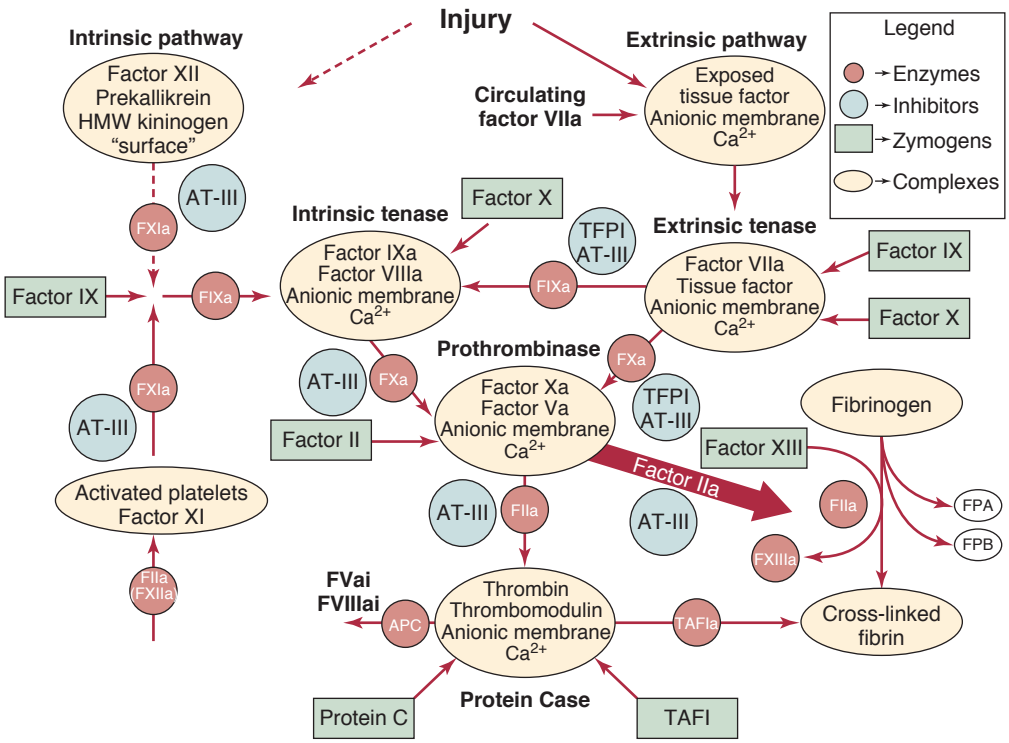

Figure 36.1 Overview of hemostasis. Two pathways can be used to initiate coagulation: the primary extrinsic pathway (shown on the right) and the intrinsic pathway (shown on the left). *AT,* Antithrombin; *HWM,* high-molecular-weight; *TAFI,* thrombin-activatable fibrinolysis inhibitor; *TFPI,* tissue factor pathway inhibitor. (Modified from Brummel-Ziedins K, et al. In: Lee GR, et al, eds. *Wintrobe's Clinical Hematology*. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2003: Chapter 21.)

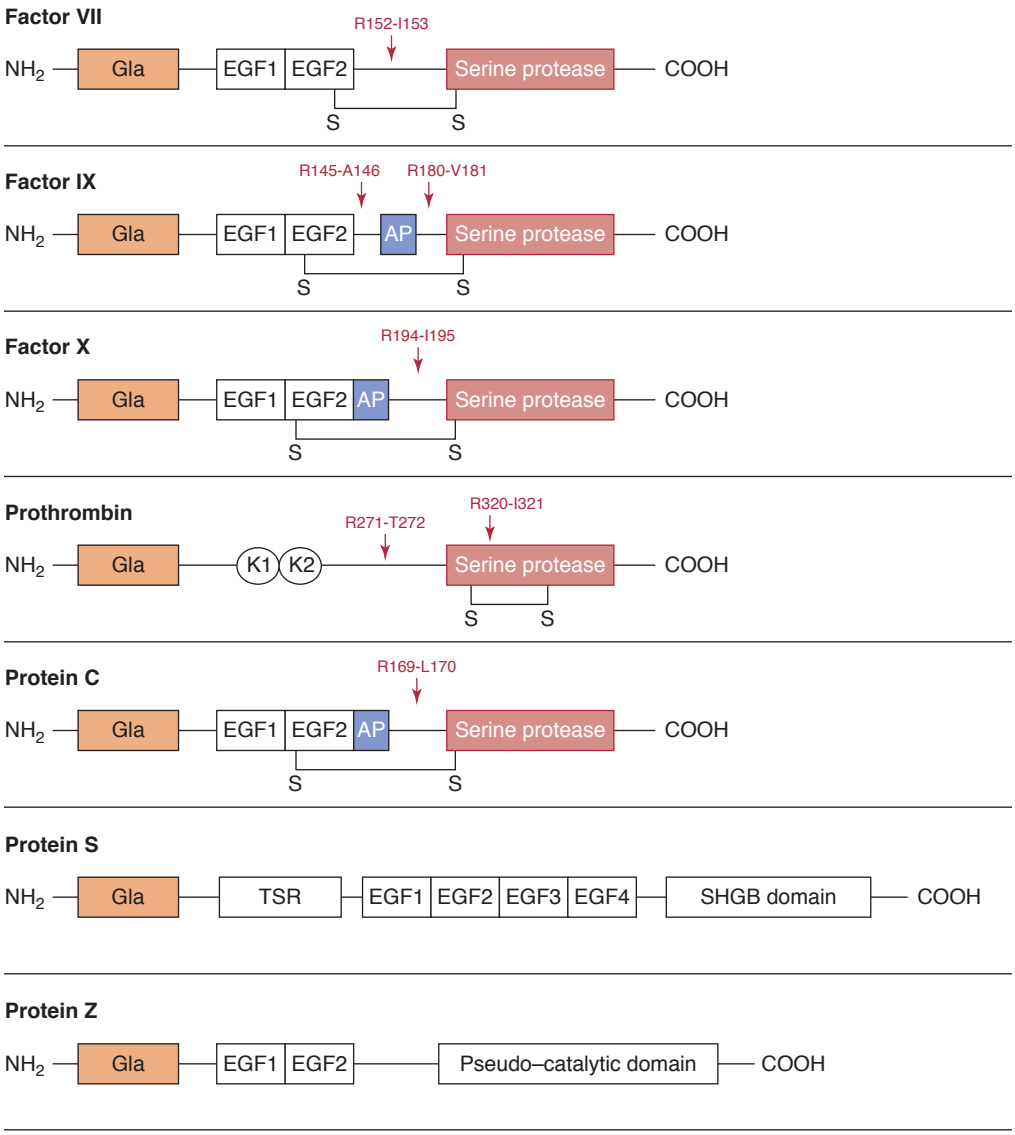

Figure 36.2 Schematic representation of the vitamin-K-dependent proteins. The building blocks for these proteins include an NH_2-terminal Gla domain with 9 to 13 γ-carboxyglutamate residues followed by either an epidermal growth factor *(EGF)*-like domain in factor VII, factor IX, factor X, protein C, protein S, and protein Z or kringle *(K)* domains in prothrombin. Activation cleavage sites, disulfide bonds (–S–S–), and activation peptides *(AP)* are illustrated. The sex hormone-binding globulin *(SHBG)* and thrombin-sensitive regions *(TSR)* are also represented in proteins.

specific binding characteristics essential for their function. The domain organizations of the vitamin-K-dependent proteins are illustrated in Fig. 36.2.[9-13]

Vitamin K is essential for the biosynthesis of these clotting factors by participating in a cyclic oxidation and reduction process that converts 9 to 13 amino-terminal glutamate residues into γ-carboxyglutamate (Gla) residues.[12,14,15] This posttranslational modification enables the vitamin-K-dependent proteins to interact with Ca^{2+} (or calcium ions) and appropriate membranes.[16-18] Inhibition of the Gla residue modification is the basis for "blood-thinning" anticoagulant therapy with coumarin derivatives (e.g., warfarin) that interfere with the redox cycle. The level of anticoagulation achieved with vitamin K antagonist therapy in individuals taking the same dose regimen is variable.[19,20] For instance, altered sensitivity to warfarin has been identified in patients when it is prescribed after surgery.[21] Factors affecting the efficacy of treatment include liver function in the synthesis of clotting factors, the influence of other medications, and the dietary intake/absorption of vitamin K[22]; therefore, monitoring of warfarin therapy is essential.[19,20]

NH_2-terminal Gla domains are followed by either a Kringle domain or an epidermal growth factor-like domain (see Fig. 36.2). Protein S is not a serine protease precursor but instead contains a thrombin-sensitive region before the epidermal growth factor domain and a sex hormone-binding globulin-like domain in the COOH terminus.[23] Protein Z contains a

TABLE 36.1 Procoagulant Proteins

Protein	Molecular Weight (kD)	Plasma Concentration (nmol/L)	Plasma Concentration (μg/mL)	Plasma $t_{1/2}$ (Days)	Clinical Phenotype Associated With Deficiency	Functional Classification
Factor XII	80	500	40	2-3	None	Protease zymogen
HMW kininogen	120	670	80		None	Cofactor
LMW kininogen	66	1300	90			Cofactor
Prekallikrein	85/88	486	42			Protease zymogen
Factor XI	160	30	4.8	2.5-3.3	Sometimes bleeding	Protease zymogen
Tissue factor	44			N/A		Cell-associated cofactor
Factor VII	50	10	0.5	0.25	Bleeding (occasionally thrombotic)	VKD protease zymogen
Factor X	59	170	10	1.5	Bleeding	VKD protease zymogen
Factor IX	55	90	5	1	Bleeding	VKD protease zymogen
Factor V	330	20	6.6	0.5	Bleeding[a]	Soluble procofactor
Factor VIII	285	1.1-1.5[d]	0.3-0.4	0.3-0.5	Bleeding	Soluble procofactor
vWF	255	Varies	10		Bleeding	Carrier for factor VIII
Factor II	72	1400	100	2.5	Bleeding[b]	VKD protease zymogen
Fibrinogen	340	7400	2500	3-5	Bleeding[c]	Structural clot protein
Factor XIII	320	94	30	9-10	Bleeding	Transglutaminase zymogen

[a]Factor V Leiden mutation associated with thrombosis.
[b]Prothrombin 20210A mutation associated with thrombosis.
[c]Some fibrinogen mutations associated with thrombosis.
[d]Butenas S, Parhami-Seren B, Mann KG. The influence of von Willebrand factor on factor VIII activity measurements. *J Thromb Haemost*. 2009;7:132–137; Butenas S, Parhami-Seren B, Undas A, Fass DN, Mann KG. The "normal" factor VIII concentration in plasma. *Thromb Res*. 2010;126:119–123.
HMW, High-molecular-weight; *LMW*, low-molecular-weight; *VKD*, vitamin-K-dependent; *vWF*, von Willebrand factor.

TABLE 36.2 Anticoagulant Proteins, Inhibitors, and Receptors

Protein	M_r (kD)	Plasma Concentration (nmol/L)	Plasma Concentration (μg/mL)	Plasma $t_{1/2}$ (Days)	Clinical Phenotype Associated With Deficiency	Functional Classification
Protein C	62	65	4	0.33	Thrombotic	Proteinase zymogen
Protein S	69	300	20	1.75	Thrombotic	Inhibitory cofactor
Protein Z	62	47	2.9	2.5	Sometimes thrombotic	Inhibitory cofactor
Thrombomodulin	100	N/A	N/A	N/A		Cofactor/modulator
Tissue factor pathway inhibitor	40	1-4	0.1	minutes		Proteinase inhibitor
Antithrombin	58	2400	140	2.5-3	Thrombotic	Proteinase inhibitor
Heparin cofactor II	66	500-1400	33-90	2.5	Often thrombotic	Proteinase inhibitor
α_2-Macroglobulin	735	2700-4000	2-3000	<1 h		Proteinase inhibitor
α_1-Proteinase inhibitor	53	28,000-65,000	1500-3500	6		Proteinase inhibitor
Endothelial protein C receptor						Receptor

"pseudo-catalytic domain" in the COOH terminus and is not a zymogen.[24]

Cofactor Proteins

Cofactor proteins (Fig. 36.3A, B) either circulate in plasma (factor V and factor VIII) or are the cell-bound tissue factor (TF) and thrombomodulin (TM).

Soluble Plasma Procofactors

Factor V

Factor V (see Fig. 36.3A and Table 36.1) is a large single-chain glycoprotein[25-28] found in plasma or platelet alpha granules (18%-25% of the total factor V pool)[29] and is secreted upon platelet activation. It is proteolytically activated by thrombin to form the cofactor factor Va (Fig. 36.3A).[30] Factor Va functions

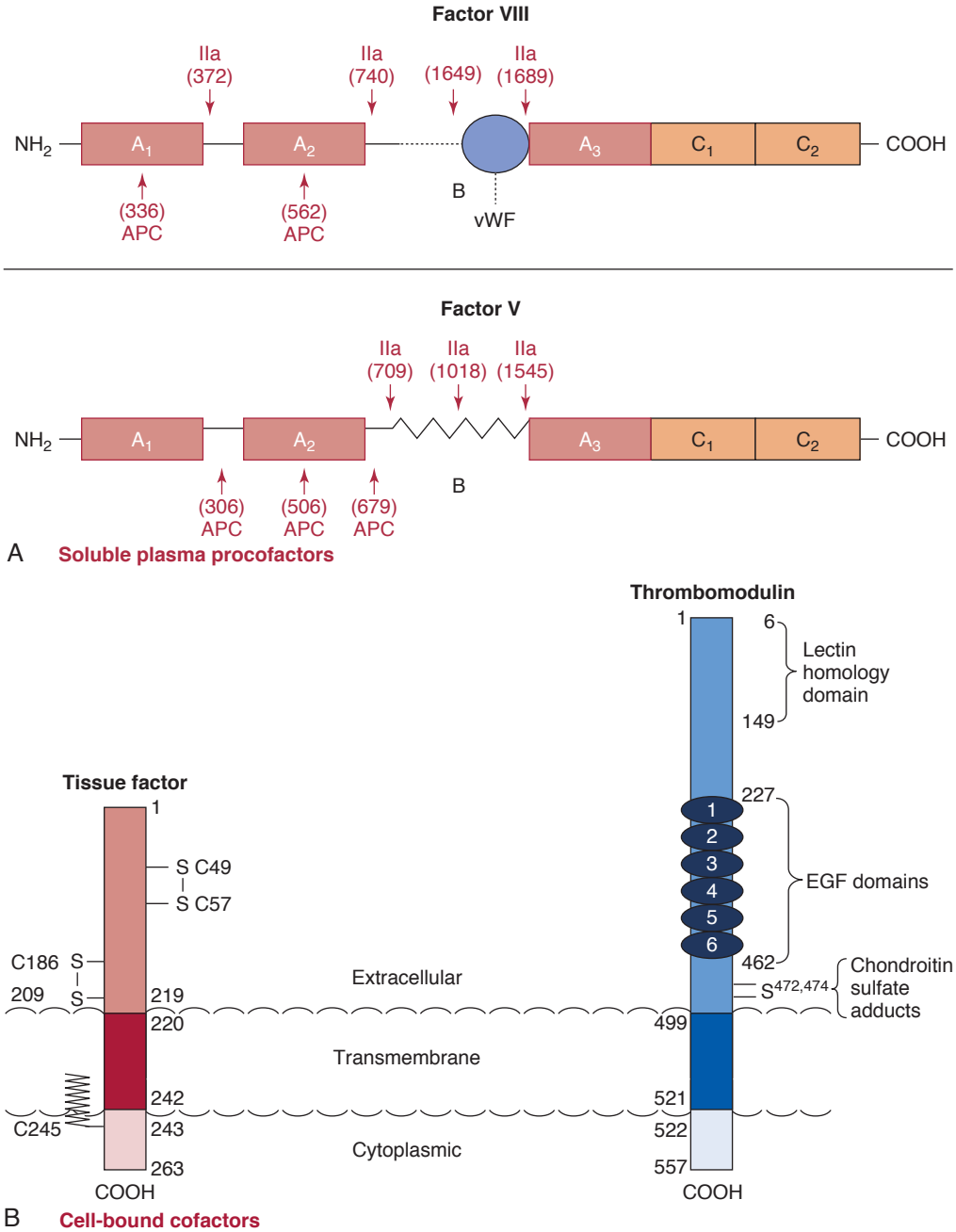

Figure 36.3 Cofactors. **(A)** Plasma procofactors factor VIII and factor V. The linear domain structures (A_1-A_2-A_3-C_1-C_2) are represented. *APC,* Activated protein C; *vWF,* von Willebrand factor. **(B)** Cell-bound cofactors tissue factor and thrombomodulin. Epidermal growth factor (EGF), transmembrane, and cytoplasmic domains are illustrated.

as positive modulator of factor Xa's catalytic potential in the prothrombinase complex in the presence of Ca^{2+} and an appropriate membrane surface.[31] It is proteolytically inactivated by activated protein C (APC) (see Fig. 36.3A).[32,33] Cleavage at Arg^{506} by APC reduces factor Va activity, while the slower cleavage at Arg^{306} eliminates activity. The importance of this regulatory mechanism is illustrated by the factor V Leiden, characterized by an $Arg^{506}Gln$ mutation.[34] Therefore, despite normal activity in the prothrombinase complex, factor Va Leiden is more slowly inactivated resulting in a prothrombotic phenotype.

Factor VIII

The procofactor factor VIII circulates in plasma in complex with the large multimeric protein von Willebrand factor (vWF; see Fig. 36.3A). It is homologous (40% identity) with factor V,[35,36] but circulates in plasma as a two-chain molecule.[37] Factor VIII is activated by thrombin cleavage at three sites to generate the heterotrimeric cofactor factor VIIIa that lacks a vWF binding site.[38] Factor VIIIa enhances the enzymatic activity of the factor IXa in the presence of Ca^{2+} and an appropriate membrane surface, forming intrinsic tenase complex. Its function is downregulated

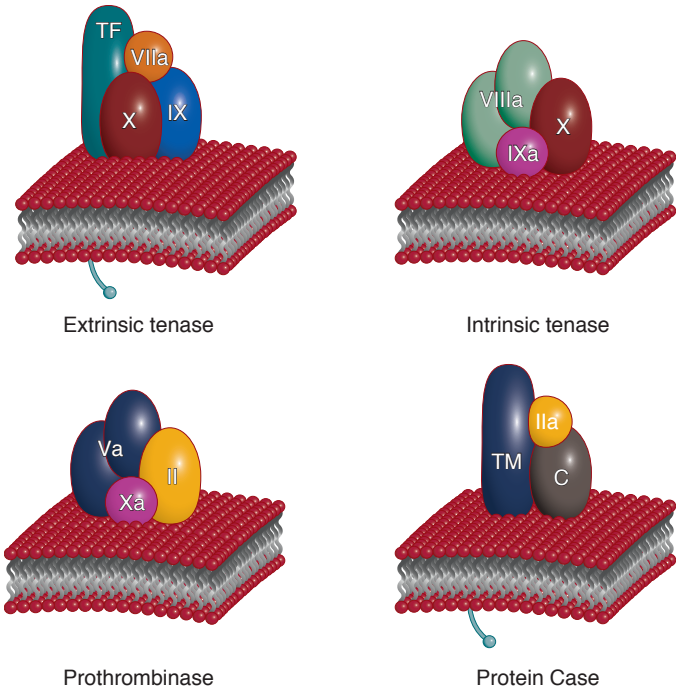

Figure 36.4 Vitamin-K-dependent complexes. Three procoagulant complexes (extrinsic tenase, intrinsic tenase, and prothrombinase) and one anticoagulant complex (protein Case) are illustrated. Each serine protease is shown in association with the appropriate cofactor protein and zymogen substrate or substrates on the membrane surface. Calcium ion is not shown. *TF,* Tissue factor; *TM,* thrombomodulin. (Redrawn from Mann KG. *Coagulation explosion,* Vermont Business Graphics; 1997.)

by the rapid and spontaneous dissociation of the noncovalently bound A_2 subunit or proteolysis of the factor VIIIa light chain by APC. Deficiency of factor VIII (hemophilia A) is a well-characterized bleeding disorder linked to the X chromosome.[39]

Cell-Bound Cofactors

Tissue Factor

TF is a transmembrane protein that functions as a nonenzymatic cofactor with factor VIIa in the extrinsic tenase complex that activates both factors IX and X (Fig. 36.4).[40] TF is not expressed in blood in the absence of injury or inflammatory stimulus, and its presentation triggers the extrinsic pathway for hemorrhage control (see Fig. 36.1).[41-43] Functional TF is presented following vascular damage that exposes the subendothelium or cytokine stimulation of monocytes.[44-46] There are no known deficiencies of human TF, and the absence of TF in mice is lethal during embryonic development.[47]

Thrombomodulin

TM is a high-affinity receptor for α-thrombin and acts as a cofactor for the activation of protein C (see Fig. 36.3B).[48] The endothelial cell protein C receptor provides cell-specific binding sites for both protein C and APC.[49,50] Once thrombin is bound to TM, its procoagulant activities are neutralized and the rate of inactivation of α-thrombin by antithrombin (AT) is increased.[51-53] Protein C activation by the thrombin-TM complex (protein Case) leads to inactivation of the cofactors factor Va and factor VIIIa, suppressing thrombin formation (see Fig. 36.2).[54] The protein Case complex also has an antifibrinolytic role through activation of thrombin-activatable fibrinolysis inhibitor (TAFI).[55-57] TM activity on the surface of endothelial cells is decreased by inflammatory cytokines[58]; this decrease may contribute to hypercoagulation in inflammatory states.

Complexes

Vitamin-K-dependent protein complexes are essential for establishing hemostatic balance (see Fig. 36.4). Each complex is composed of a serine protease (factor VIIa, factor IXa, factor Xa, or thrombin [factor IIa]), a cofactor that functions as a receptor/enhancer for the enzyme (factor VIIIa, factor Va, TF, TM), Ca^{2+}, and an appropriate anionic phospholipid membrane of cellular origin. There are four vitamin-K-dependent enzyme complexes (see Fig. 34.4): the extrinsic tenase complex (factor VIIa–TF), the intrinsic tenase complex (factor IXa–factor VIIIa), the prothrombinase complex (factor Xa–factor Va), and the anticoagulant protein Case complex (thrombin-TM). These membrane-bound complexes serve to localize enzymatic activity to the appropriate regional site for their required enzymatic functions and result in the only biologically relevant enzymatic activity for factor VIIa, factor IXa, and factor Xa—10^4-fold to 10^9-fold faster reaction rates than the enzyme in solution.[59]

Intrinsic (Accessory) Pathway Proteins

Deficiencies of proteins associated with the intrinsic pathway (factor XII, prekallikrein, and high-molecular-weight kininogen [HMWK]) are not associated with abnormal bleeding, even after surgical challenge.[60-62] In contrast, deficiencies of the protein components of the extrinsic or primary pathway (prothrombin and factors V, VII, VIII, IX, and X) can lead to severe bleeding diatheses.[63-67] The physiologic significance of the intrinsic pathway is still debated, but mounting evidence suggests that it serves as the link between inflammation and innate immunity.[68]

Factor XI represents an intersection point for the two pathways. Individuals with factor XI deficiency (hemophilia C) express variable bleeding with surgical challenge,[69,70] thus establishing a role for factor XI in hemostasis. During the hemostatic process, formation of factor XIa appears to be catalyzed by thrombin as part of a positive feedback loop.[71] Factor XIa then functions in the propagation phase of thrombin generation in association with the primary pathway by activation of factor IX.[72]

Three proteins, factor XII, prekallikrein, and HMWK, are required for activity of the intrinsic pathway. Factor XII and prekallikrein are zymogens that are activated to generate serine proteases, and HMWK is a nonenzymatic procofactor (Fig. 36.5). Activation of this pathway in vitro is accomplished when factor XII autoactivates to factor XIIa with exposure to a foreign surface (e.g., glass, kaolin, dextran sulfate, sulfatides).[73-75] The substrates for factor XIIa, prekallikrein and factor XI, exist in a noncovalent complex with HMWK and become activated to kallikrein and factor XIa, respectively.[76] This pathway is positively and negatively regulated via cleavage of HMWK by

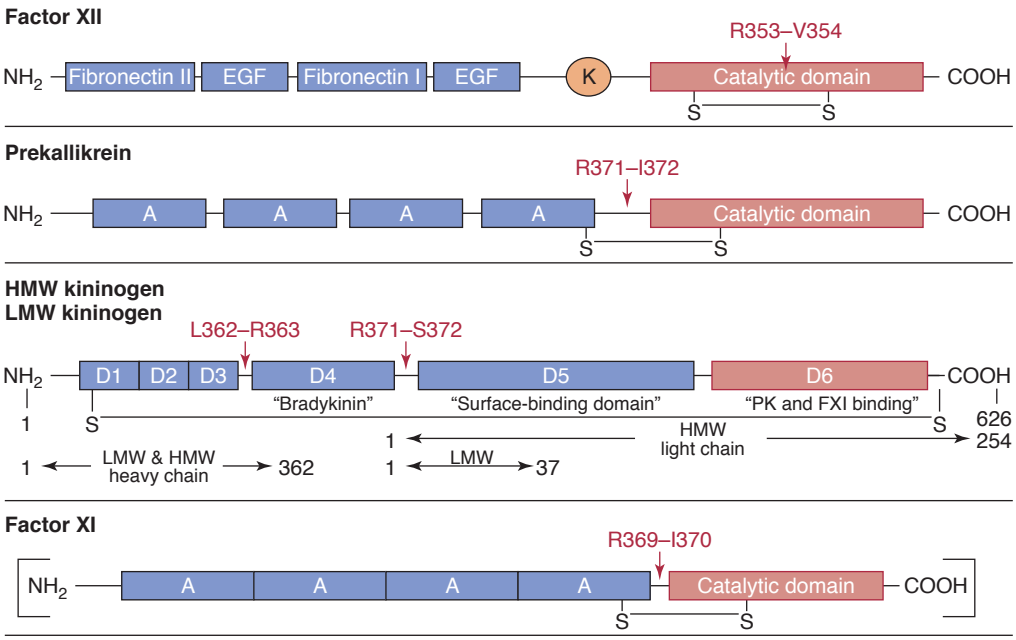

Figure 36.5 Schematic representation of the intrinsic pathway proteins. Factor XII, prekallikrein *(PK)*, high-molecular-weight kininogen *(HMWK)*, low-molecular-weight kininogen *(LMWK)*, and factor XI *(FXI)* are shown with their various domains depicted. *A,* Apple domain; *EGF,* epidermal growth factor domain; *K,* kringle domain. Cleavage sites and key interchain disulfide bonds (S–S) are shown. For the kininogens, *horizontal arrows* indicate the amino acid residues defining heavy- and light-chain regions of the activated forms of the cofactors. The factor XI molecule is a dimer of the illustrated monomer. Factor XI is a disulfide-linked homodimer with each subunit containing four apple domains, which provide binding sites for high-molecular-weight kininogen, thrombin, factor XIIa, platelets, and heparin. Activation of factor XI (by thrombin or factor XIIa) results in a conformational change that permits factor IX binding to the apple 3 domain.

kallikrein and FXIa, respectively.[77,78] It has also been reported that the intrinsic pathway is activated by inorganic polyphosphates[79,80] or the assembly of these proteins on endothelial cell membranes.[81,82] Activation of the intrinsic pathway is important in cardiopulmonary bypass because of contact between blood components and synthetic surfaces.[83]

Stoichiometric Inhibitors

An array of inhibitors is present in blood with both specific and broad-spectrum actions. Inhibitors of clot formation are AT, tissue factor pathway inhibitor (TFPI), heparin cofactor II, and protein C inhibitor (Fig. 36.6).

Antithrombin

AT is a member of the serpin proteinase family and circulates in blood as a single-chain glycoprotein (see Fig. 36.6).[84,85] Congenital AT deficiency exhibits an autosomal dominant pattern of inheritance, with an incidence of 1 in 2000 to 5000.[86] Individuals with this deficiency have partial expression of AT and are prone to thromboembolic disease.[87] The complete absence of AT is lethal. AT is a broad-spectrum anticoagulant, interacting with most proteases participating in the coagulation cascade (see Fig. 36.1), including thrombin, factor Xa, factor IXa, factor VIIa–TF, factor XIa, factor XIIa, plasma kallikrein, and HMWK.[88-90] Heparins and heparan sulfates potentiate these reactions and are used in the treatment of thrombosis. When AT is complexed with heparin, its rate of inhibition of several coagulation proteases is accelerated by up to 10,000-fold as heparin induces structural changes that expose its reactive center loop. Antithrombin also displays antiproliferative and anti-inflammatory properties that primarily derive from its ability to inhibit thrombin. In addition, latent or cleaved forms of AT have antiangiogenic activity.[91]

Tissue Factor Pathway Inhibitor

TFPI (also called extrinsic pathway inhibitor or lipoprotein-associated coagulation inhibitor) is a multivalent, Kunitz-type inhibitor that circulates in plasma as a heterogeneous collection of partially proteolyzed forms (see Fig. 36.6).[92-95] Ninety percent of circulating TFPI is found associated with lipoproteins.[94,96,97] Circulating TFPI is cleared principally by the liver and has an unusually short half-life compared with other proteinase inhibitors.[98]

Complete deficiency of TFPI is incompatible with birth and survival in transgenic mice;[18] however, this lethality can be rescued by heterozygous or homozygous factor VII deficiency.[99] Mice bred to have a combined heterozygous TFPI deficiency and homozygous apolipoprotein E deficiency exhibit an increased atherosclerotic burden, suggesting a role for TFPI in protection from atherosclerosis and as a regulator of thrombosis.[100]

TFPI is the principal stoichiometric inhibitor of the extrinsic tenase complex (factor VIIa–TF).[101] Effective TFPI inhibition

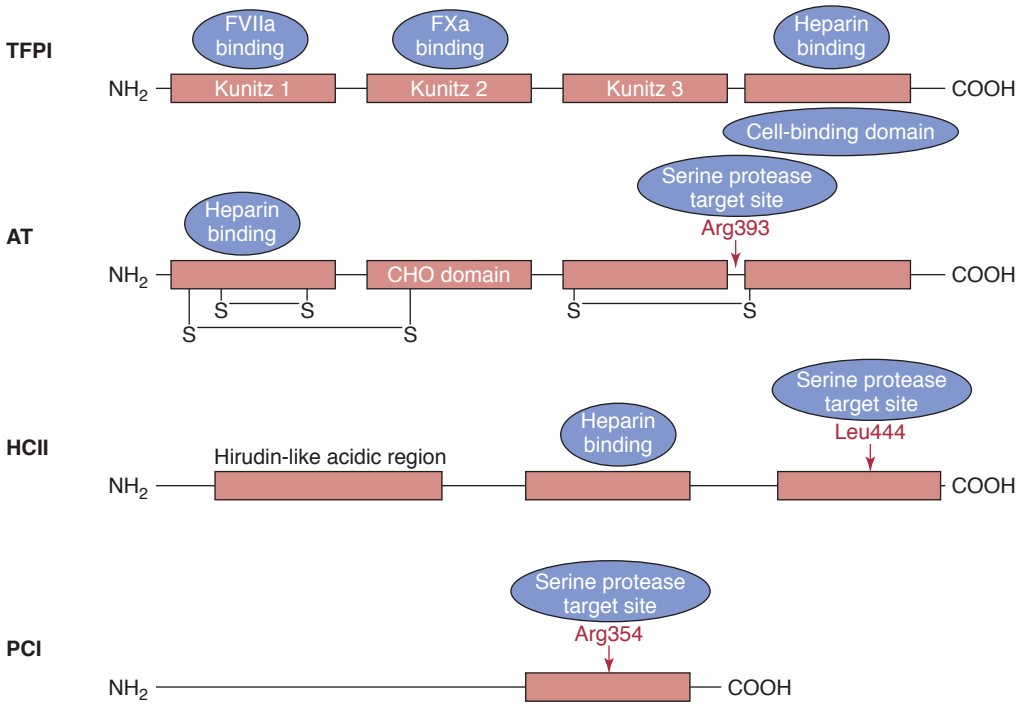

Figure 36.6 Stoichiometric inhibitors. Tissue factor pathway inhibitor *(TFPI)* has three Kunitz domains. The Kunitz 1 domain binds factor VIIa, the Kunitz 2 domain binds factor Xa, and the Kunitz 3 domain has been reported to bind protein S. The COOH terminus of TFPI contains a basic region, the cell-binding domain that also binds to heparin and some forms of factor Va. Antithrombin *(AT)* has two intrachain disulfide bonds (-S-S-) at its NH_2 terminus and one in its COOH terminus with a carbohydrate-rich domain (CHO) in between. The region of interaction between the active sites of target proteases and AT is called the reactive center loop, R393-S394. Heparin binding occurs in the NH_2 terminus. Heparin cofactor II *(HCII)* contains an NH_2-terminal hirudin-like region, a heparin- or dermatan sulfate-binding region, and a reactive center loop. The reactive site is Leu444.

of the factor VIIa–TF complex depends on the presence of factor Xa; thus, inhibition of the extrinsic factor tenase by TFPI occurs only after significant generation of factor Xa. The TFPIα splice variant can also bind to some forms of factor Va formed early in the coagulation process and inhibit the prothrombinase complex.[102] This interaction is the basis of the east Texas bleeding disorder, which is associated with life-threatening bleeding after trauma or surgery due to the production of a factor V splice variant that binds tightly to TFPIα.[103,104]

Heparin Cofactor II

Heparin cofactor II is a member of the serpin family (see Fig. 36.6). Like AT, heparin cofactor II inhibits thrombin in a reaction that is accelerated more than 1000-fold by heparin.[105] However, unlike AT, thrombin is the only coagulation enzyme inhibited by heparin cofactor II.[106] Heparin cofactor II and dermatan sulfate levels increase during pregnancy,[107-109] and decreased heparin cofactor II is associated with preeclampsia.[110,111]

Endothelium and Platelets (See Chapter 40: Antiplatelet Agents)

Blood cells and the vasculature are crucial to normal hemostasis, in part because they supply appropriate anionic surfaces to support the coagulation process. Additionally, interactions between the vessel wall, the circulating platelets, and the plasma protein moieties are essential for maintaining blood fluidity (Fig. 36.7AB). The biologic elements contributing to the phospholipid requirement of the coagulation process include damaged vascular tissue, activated platelets, and inflammatory cells.[101,112,113] Mechanically damaged cells can provide the anionic membrane required to support general procoagulant complex formation, but more subtle cellular activation events also generate selective complex-forming sites on intact cells, as is the case with platelets.[114,115] Therefore, pathologic hemorrhage is associated with thrombocytopenia, and is also seen in Scott's syndrome in which there is improper presentation of these platelet-binding sites.[116]

Endothelium

The endothelium plays key roles because of its strategic interface with organs, tissues, and circulating blood, and varies considerably in morphology and physiologic function in different parts of the vasculature. This complex cellular network not only provides a structural barrier to contain flowing blood, but also actively regulates blood pressure, vascular tone, permeability, and processes involving other cells. It also has roles in inflammation, immune responses, and angiogenesis.[117] Therefore, defects in vascular endothelial function have profound physiologic implications. Excessive bleeding can result from structural

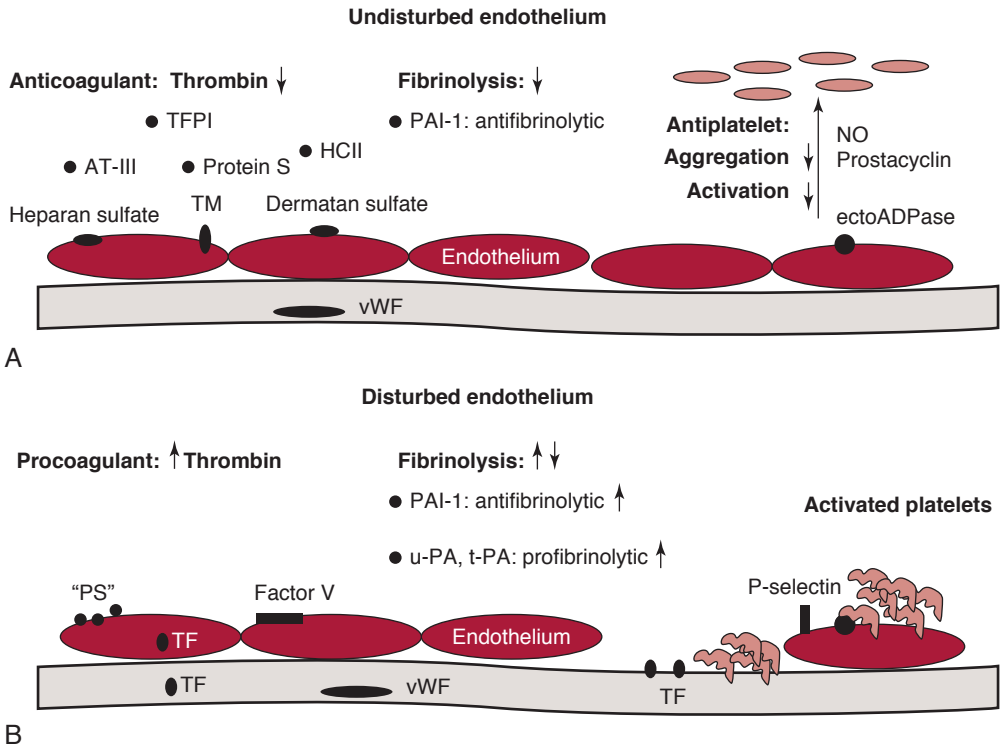

Figure 36.7 The endothelium in hemostasis. **(A)** Under normal conditions and in the absence of injury or chemical stimulus, the undisturbed endothelium actively downregulates thrombin generation through production of tissue factor pathway inhibitor *(TFPI)*, antithrombin *(AT)*, protein S, heparin cofactor II *(HCII)*, heparan sulfate, thrombomodulin *(TM)*, and dermatan sulfate. The undisturbed endothelium is also antifibrinolytic and secretes plasminogen activator inhibitor-1 *(PAI-1)*. In the absence of stimulus, the endothelium is likewise antiplatelet and prevents platelet adhesion activation, secretion, and aggregation through production of nitric oxide *(NO)*, prostacyclin, and the membrane-associated protein ectoADPase. **(B)** When the endothelium is disturbed, the endothelium becomes procoagulant and accelerates thrombin formation by exposing or expressing anionic phospholipid *("PS")*, limited tissue factor *(TF)*, and factor V. The fibrinolytic response is modulated by the release of both antifibrinolytic and profibrinolytic molecules. Urokinase (urinary plasminogen activator, *u-PA*) and tissue plasminogen activator *(t-PA)* are profibrinolytic and serve to activate plasminogen, whereas PAI-1 inhibits both enzymes and is antifibrinolytic. Platelet activation, secretion, and aggregation are also promoted under conditions in which the endothelium is disrupted. Exposure of von Willebrand factor *(vWF)* in the subendothelial matrix allows platelets to attach to the surface of the vessel. P-selectin likewise promotes platelet attachment.

abnormalities of the endothelial cell layer or supporting matrix. For example, impaired plasminogen activator inhibitor-1 (PAI-1) expression and/or secretion by the endothelium promotes bleeding through increased fibrinolytic activity.[118]

Platelets

Platelets are vital to procoagulant events and contribute to the fibrinolytic process as well. Like the endothelium, the undisturbed platelet presents a nonthrombogenic surface. Important components of platelet physiology are surface adhesion protein complexes and platelet secretory granules: alpha granules, lysosomes, and dense granules. The contents of alpha granules include procoagulant, adhesive, fibrinolytic, and antifbrinolytic proteins, among others.[29,119-127] In the unstimulated platelet, the granule contents remain internalized, and anionic phospholipids are sequestered in the inner leaflet of the plasma membrane.

When the vascular system is perturbed, platelet plug formation occurs in stages. Initially, platelets adhere and are activated by exposure to collagen, vWF, and other matrix components (Fig. 36.8). However, thrombin is the most potent activator of platelets; it is able to overcome most pharmacologic and cytokine inhibitors that depress platelet function.[128] During platelet activation, the cytoskeleton spreads, platelet-fibrinogen aggregates are formed, and the contents of the granules are secreted.[129-131] The activated platelets adhere to each other, and to endothelial cells, leukocytes, and components of the subendothelial matrix.[132] The phosphatidylserine-rich internal face of cell membranes is exposed and presents a highly procoagulant surface to the circulation. In addition, activated platelets express specific receptors and/or binding sites for assembly of both the prothrombinase and intrinsic tenase complexes.[114,133-137]

During the extension phase of platelet plug formation, activated platelets accumulate on top of the initial monolayer of platelets bound to collagen. The presence of receptors on the platelet surface allows agonists, such as thrombin, adenosine diphosphate, and thromboxane A_2 to further recruit circulating platelets into the growing hemostatic plug. During this phase

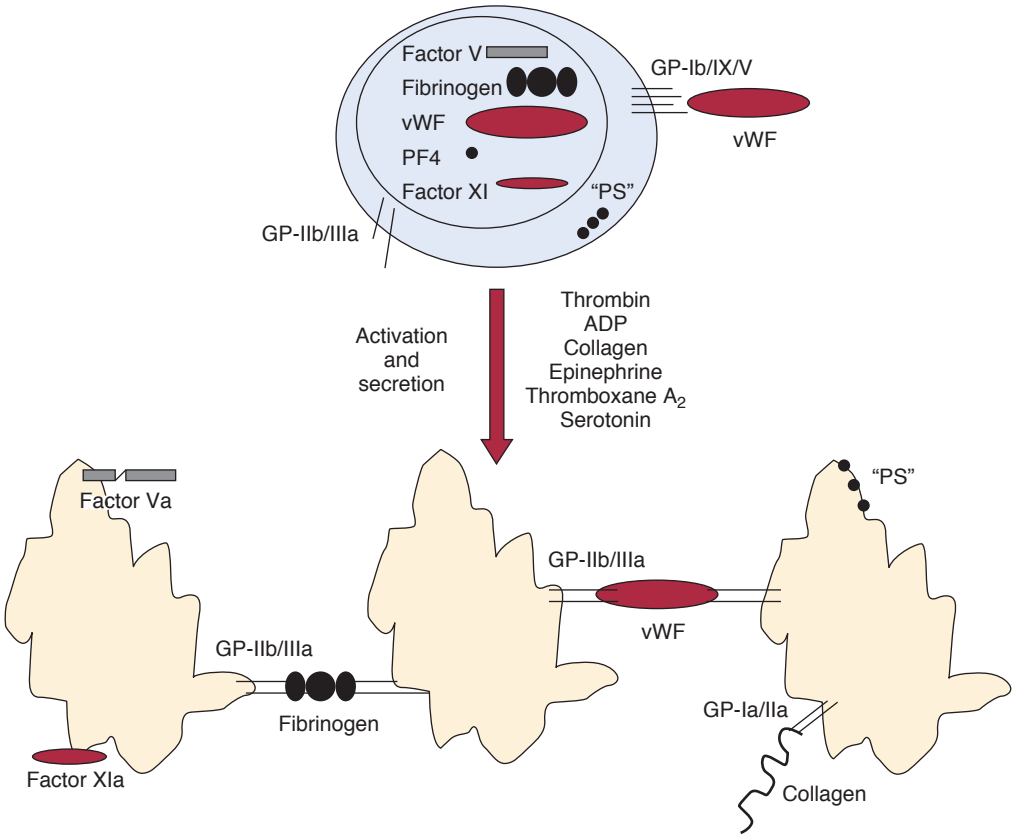

Figure 36.8 Activation, secretion, and aggregation of platelets. Platelets have multiple functions in hemostasis. They serve as reservoirs of factor V, fibrinogen, von Willebrand factor *(vWF)*, platelet factor 4 *(PF4)*, and factor XI. Platelets also contribute a significant portion of the anionic phospholipid *("PS")* necessary for membrane-dependent complex formation and function. In the unstimulated state, proteins and other molecules are sequestered in the platelet granules. Anionic phospholipid is found only in the inner leaflet of the platelet membrane and is not exposed to flowing blood. The glycoprotein Ib/IX/V *(GP-Ib/IX/V)* complex that recognizes vWF is an active receptor, whereas the GP-IIb/IIIa receptor that recognizes a variety of molecules, including fibrinogen and vWF, is not active. The GP-Ib/IX/V receptor probably allows unstimulated platelets to attach to exposed subendothelial vWF and promotes procoagulant events before platelet activation. On activation by a variety of agonists, platelets secrete granule contents, activate and bind factor V/Va and factor XI/XIa, and expose anionic phospholipid. The GP-IIb/IIIa receptor serves to link platelets to each other and the vessel wall. Collagen receptors, such as GP-Ia/IIa, promote both platelet activation and aggregation.

of clot growth, close contact between platelets that stimulates growth and stabilization of the hemostatic plug, in part through contact-dependent signaling mechanisms.[128,138]

Clot Proteins

The primary proteins of the clot are fibrin and the transglutaminase factor XIIIa. A central event in blood coagulation is the conversion of soluble fibrinogen to insoluble fibrin (see Fig. 36.1).[139,140] Fibrinogen serves as a molecular bridge to support interplatelet aggregation, and is the precursor of fibrin, the protein scaffolding component of the hemostatic plug (Fig. 36.9). Platelet aggregation critically depends on fibrinogen binding to activated the platelets, and depends on fibrin adhesion. Fibrinogen/fibrin also regulates thrombin activity by sequestering thrombin via an exosite mediated interactions.[141,142] Although it is primarily recognized for its role in hemostasis, fibrinogen is also associated with inflammation. Fibrinogen is an acute-phase reactant, with levels increasing during inflammation where it functions as a bridging molecule in cell-cell interactions.[143]

The fibrin clot is stabilized by the transglutaminase factor XIIIa,[144-146] whose function is to cross-link fibrin and other adhesive proteins, including integrin receptors, thereby providing a stable network (Fig. 36.10). The protransglutaminase factor XIII circulates in plasma as a tetramer and is also present as a dimer in platelets. Activation of the protein by thrombin cleavage and Ca^{2+} binding yields the transglutaminase factor XIIIa that cross-links fibrin by forming exopeptide bonds between the ε-amino group of lysine and the γ-carboxamide group of glutamine residues.[147,148] The resulting stable fibrin clot creates an insoluble network that, along with the primary platelet plug, seals the perforation in the blood vessel with a temporary scaffold, stopping further blood loss.

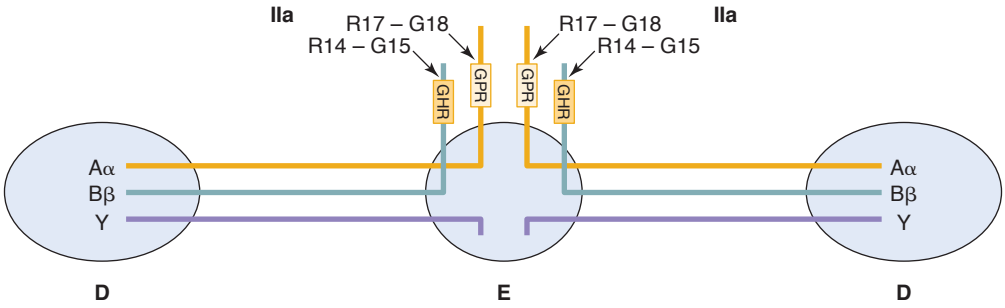

Figure 36.9 A schematic representation of human fibrinogen. Fibrinogen is composed of six polypeptide chains (two Aα, two Bβ, and two γ). These are organized into two identical half-molecules. All six NH_2 termini are linked by disulfide bonds in the central or E domain. The three chains extend out from this domain through coiled coils in either direction, terminating in the globular D domains. Thrombin *(IIa)* cleavage sites at the N termini of the Aα and Bβ *(arrows)* are indicated, with the new N termini *(box)* that associate with "holes" in the D domains to form fibrin.

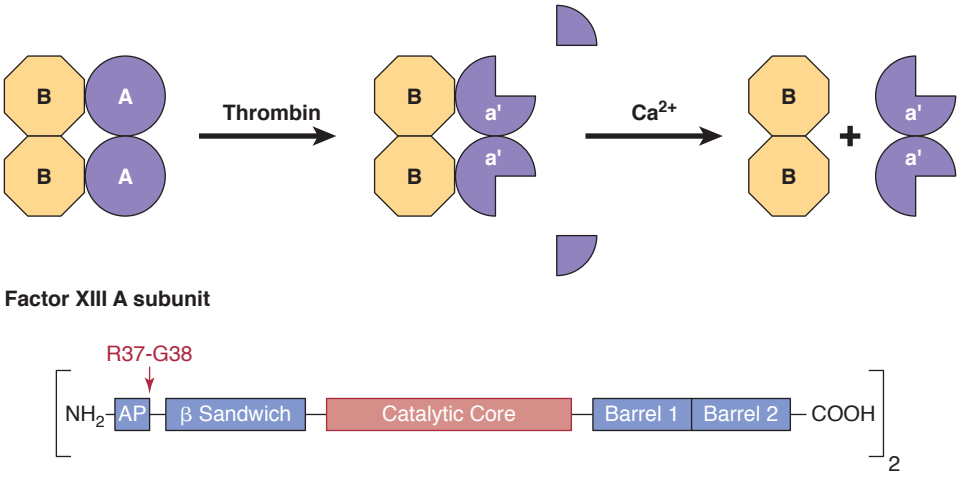

Figure 36.10 Plasma factor XIII. Thrombin-catalyzed activation of plasma factor XIII (A_2B_2; 320,000 Da) occurs in two steps. First, thrombin cleaves the R37-G38 bond. This releases the activation peptides (residues 1-37) from the A chains, producing the inactive intermediate a'_2B_2. In the second Ca^{2+}-dependent step, the B chains dissociate from the a'_2B_2 intermediate, exposing the active site cysteine, Cys314, of the a′ subunits. The enzyme a'_2 catalyzes the formation of isopeptide bonds between glutamine residues and lysine residues of adjoining polypeptide chains.

Fibrinolysis Proteins (See Chapter 41: Thrombolytic Agents)

Clot formation is integrated with clot dissolution. The mechanisms of clot dissolution center on fibrin-specific reactions. The key proteins involved are plasminogen; the plasminogen activators tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA); thrombin; and the inhibitors PAI-1, α_2-antiplasmin, and TAFIa (Fig. 36.11 and Table 36.3).

Fibrinolysis Activators

Plasminogen/Plasmin

Plasminogen is the inactive precursor of the enzyme plasmin, the primary catalyst of fibrin degradation.[149] Hereditary plasminogen deficiency is described either as a deficiency of plasminogen antigen and activity (type I) or as a normal antigen level but reduced activity (type II, dysplasminogenemia).[150] Plasminogen is also an acute phase reactant protein.[151,152] Homozygous plasminogen-deficient mice are viable, but exhibit severe thrombosis with systemic fibrin deposition and die prematurely.[153] The zymogen is converted to the serine protease plasmin following cleavage at Arg^{561}, primarily by t-PA and u-PA in vivo although pharmacologic agents can also exogenously activate plasminogen. Plasminogen activation is primarily inhibited by PAI-1, which targets u-PA and t-PA.[154] Congenital deficiency of PAI-1 is rare, with homozygous individuals displaying abnormal bleeding in response to trauma.[155] Once formed, plasmin cleaves after basic amino acid residues. The lysine analogues ε-aminocaproic acid and tranexamic acid can compete with lysyl residues in proteins for binding to plasminogen and hence are inhibitors of fibrinolysis.[156,157] Inhibition of plasmin by α_2-antiplasmin is the primary route for the regulation of plasmin's hemostatic function in vivo; suppression of plasmin activity beyond the locale of fibrin deposition is imperative if systemic fibrinogenolysis is to be prevented; therefore, plasmin bound through its lysine binding sites to fibrin reacts more slowly with α_2-antiplasmin than when it is free in solution.

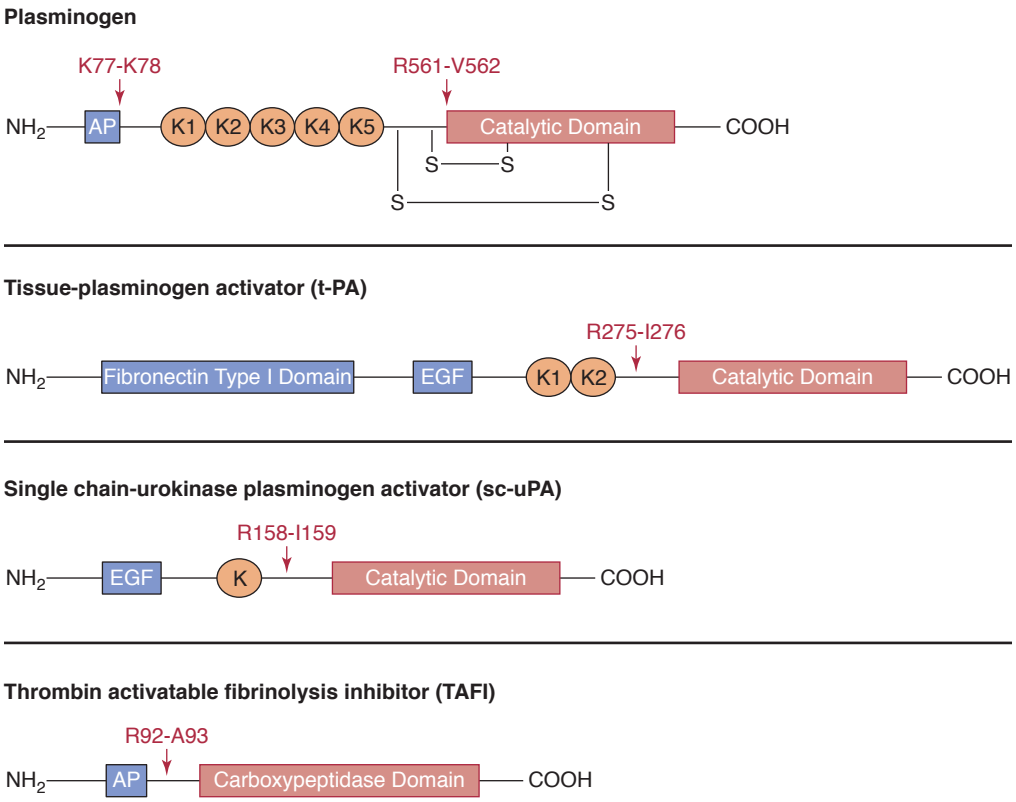

Figure 36.11 A schematic representation of proteins of the fibrinolytic system. Plasminogen, tissue-type plasminogen activator, urokinase plasminogen activator, and thrombin-activatable fibrinolysis inhibitor are shown with their various domains depicted. Cleavage sites with the specific amino acid residues are shown. *AP,* Activation peptide; *K,* kringle domain; *EGF,* epidermal growth factor.

TABLE 36.3 Fibrinolytic Proteins, Inhibitors, and Receptors

Protein	M_r (kD)	Plasma Concentration (nmol/L)	Plasma Concentration (μg/mL)	Plasma $t_{1/2}$ (Days)	Clinical Phenotype Associated With Deficiency	Functional Classification
Plasminogen	88	2300	210	2.2		Proteinase zymogen
t-PA	70	0.07	0.005	<5 min		Proteinase zymogen
u-PA	54	0.04	0.002	5 min		Proteinase zymogen
TAFI	58	75	4.5	10 min	Thrombotic	Carboxypeptidase
FSAP	64	190	12			Fibrinolytic zymogen
PAI-1	52	0.2	0.01	<10 min	Bleeding	Proteinase inhibitor
PAI-2	47/60	<0.070	<0.005	–		Proteinase inhibitor
α-Antiplasmin	70	500	70	2.6	Bleeding	Proteinase inhibitor
u-PAR	55					Cell membrane receptor

FSAP, Factor VII–activating protease; *PAI,* plasminogen activator inhibitor; *TAFI,* thrombin-activatable fibrinolysis inhibitor; *t-PA,* tissue plasminogen activator; *u-PA,* urinary plasminogen activator (urokinase); *u-PAR,* urokinase-type plasminogen activator receptor.

Tissue Plasminogen Activator

t-PA manifests its full fibrinolytic potential only when it is bound to fibrin.[158-160] This binding interaction aligns t-PA and plasminogen on the fibrin surface so that the catalytic efficiency of t-PA is enhanced several-hundred-fold. This is vital to the localization of plasmin generation at the site of fibrin deposition. Release of t-PA from the vessel wall is another important regulator of fibrinolysis.[161,162] The rate at which clots lyse depends on how rapidly t-PA is secreted by the relevant cells in the vicinity of an injury.[163,164] For example, activated platelets secrete serotonin, which can induce endothelial cells to release t-PA; they also release PAI-1 from their alpha granules. Although only a fraction of this PAI-1 is in the active form, it functions to downregulate plasminogen activation.[165,166] No cases of congenital deficiency of t-PA have been reported.

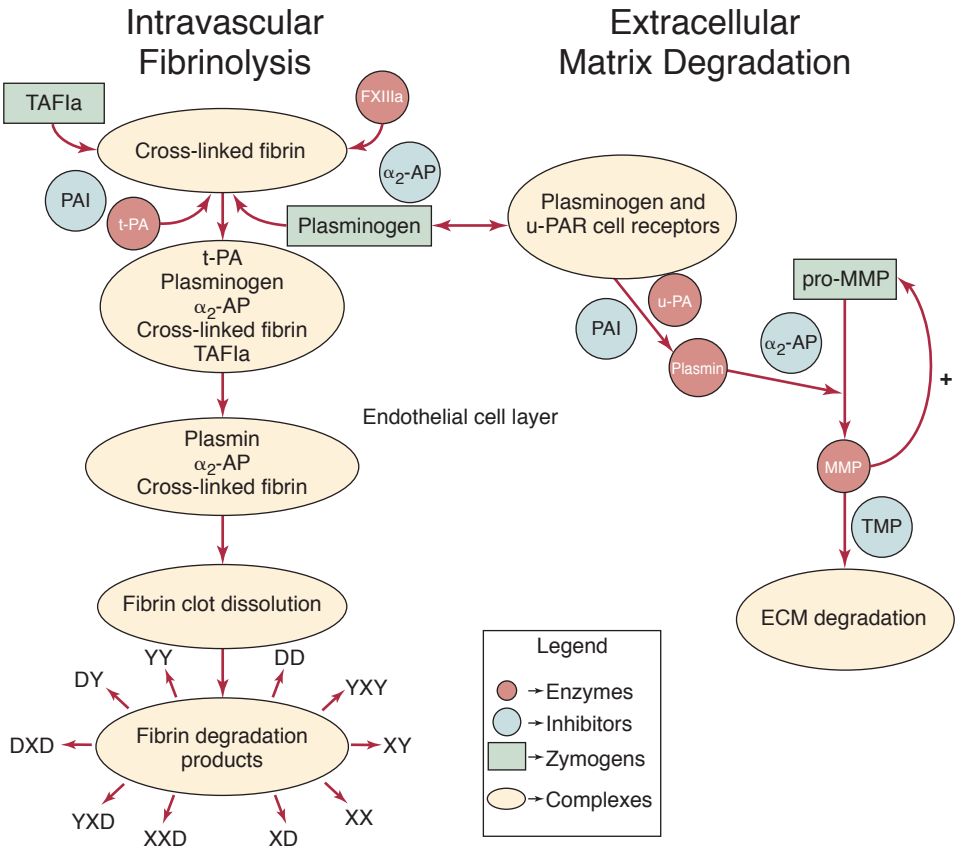

Figure 36.12 Schematic of the dynamic interaction between the proteins and inhibitors of intravascular fibrinolysis and extracellular matrix degradation. Cross-linked fibrin formation *(left)* is integrated with fibrin clot dissolution and degradation of its products. Two pathways are shown: intravascular fibrinolysis and extracellular matrix degradation, separated by an endothelial cell layer. The enzymes, inhibitors, zymogens, and complexes are illustrated in simplified form to show this multicomponent process. Degradation of fibrin occurs by cleavage of plasmin at the D-E-D domains of fibrin polymers to yield a variety of polymers, as illustrated. Plasminogen can cross the endothelial cell layer and become converted to plasmin by urokinase (urinary plasminogen activator; u-PA) *(right)*. Plasmin can convert latent matrix metalloproteinases (pro-MMP) to their active form (MMP). MMPs themselves can act in a positive feedback mechanism to convert pro-MMP to more MMP and ultimately degrade the extracellular matrix. Plasmin-mediated effects are inhibited by plasminogen activator inhibitor (PAI) and α_2-antiplasmin. MMP-mediated effects are inhibited by tissue inhibitors (TMP). *α_2-AP,* α_2-Antitrypsin; *ECM,* extracellular matrix; *t-PA,* tissue plasminogen activator; *TAFI,* thrombin-activatable fibrinolysis inhibitor; *u-PAR,* u-PA receptor.

Urokinase Plasminogen Activator

The main site of urokinase-driven plasminogen activation appears to be extravascular, where it has an important role in promoting degradation of the extracellular matrix by triggering the activation of plasminogen and, possibly, matrix metalloproteinases. The regulation of urokinase is important for normal and pathologic processes, including embryogenesis, wound healing, tumor cell invasion, and metastasis.[167-169] Inhibitors of urokinase have been shown to suppress the growth of primary tumors and to interfere with metastasis of tumor cells.[170-177] t-PA appears to be the primary plasminogen activator in the vasculature, with u-PA amplifying rather than initiating plasmin formation.[178,179] Transgenic mice lacking a functional t-PA gene develop normally and display a normal basal hemostatic phenotype.[180] Mice in which both the t-PA and u-PA genes are disabled have shortened life spans and experience severe spontaneous thrombotic episodes.[180,181]

Fibrinolysis Inhibitors

Plasminogen Activator Inhibitor-1

PAI-1, the primary physiologic inhibitor of plasminogen activation in blood, targets u-PA and t-PA (Fig. 36.12). Congenital deficiency of PAI-1 is rare, with homozygous individuals displaying abnormal bleeding in response to trauma.[182-186] In the normal population, plasma PAI-1 concentrations vary over a 15-fold range (6-80 ng/mL; mean, 10 ng/mL [0.2 nmol/L])[187,188] and exhibit circadian variations.[189] Some of this variability stems from polymorphisms in the PAI-1 gene; however, a larger fraction of the variability appears to derive from the responsiveness of PAI-1 gene expression to a wide variety of physiologic effectors and conditions as well as pharmacologic agents.[190] Higher levels of plasma PAI-1 delay fibrin removal by shortening the functional lifetime of plasminogen activators, delaying fibrinolysis.[191]

α_2-Antiplasmin

α_2-Antiplasmin (or α_2-plasmin inhibitor) is the primary plasmin inhibitor[192-195] and thus is an important regulator of fibrinolysis (see Fig. 36.12). Congenital deficiency of α_2-antiplasmin is rare, with homozygous individuals displaying a moderate to severe bleeding disorder.[196] The primary site of synthesis is the liver, although the kidney may be another contributing source;[197] its in vivo half-life is 2.6 days.[198,199]

Thrombin-Activatable Fibrinolysis Inhibitor

TAFI is a plasma procarboxypeptidase B synthesized in the liver and is thought to circulate in blood in complex with plasminogen.[200] Activation of TAFI yields an exopeptidase (TAFIa) that catalyzes the removal of basic amino acids (arginines, lysines) from the COOH termini of polypeptides. Its primary physiologic activator appears to be the thrombin-TM complex.[201] The COOH-terminal lysyl residues of peptides produced during fibrin degradation are the primary substrates for TAFIa. In the initial phase of plasmin proteolysis of fibrin, peptides are produced that amplify activation of plasminogen by t-PA. These fibrin degradation products contribute to a positive feedback process that accelerates clot lysis. Removal of these terminal lysine residues by TAFIa reduces the number of plasminogen binding sites, thus downregulating the rate of plasmin generation and, thereby, the rate of clot lysis.

CONNECTIVITY AND DYNAMICS OF BLOOD COAGULATION

In the healthy state, the three-compartment system consisting of vascular endothelium, blood, and extravascular tissue functions to maintain fluidity or to produce an integrated response to attenuate leakage of blood by localized activation at the site of vascular injury. When the endothelium is disrupted, the extravascular compartment and blood interact to rapidly produce a vigorous local coagulation response that attenuates blood loss and initiates the vascular repair process in four phases: initiation, propagation, termination, and elimination/fibrinolysis, which overlap.

Initiation

Exposure of subendothelial TF activates blood coagulation by binding to circulating plasma factor VIIa.[40,202] Before binding to TF, the plasma serine protease factor VIIa is essentially inert from the catalytic perspective and is, therefore, impervious to the abundant protease inhibitors in plasma.[203] Factor VII competes with factor VIIa for TF binding, thus serving as a negative regulator, buffering the overall reaction. The TF VIIa-factor Xa product complex is under tight supervision by TFPI.[204,205] If the initiating procoagulant stimulus is sufficient to overcome the level of this anticoagulation, a threshold is exceeded and the downstream complexes can form and lead to an explosive burst of thrombin generation. The small amounts of factor Xa produced that escape inhibition by TFPI and AT can activate small amounts of prothrombin to thrombin on an activated membrane surface.[206] Although this process is inefficient, this initial thrombin is essential to the acceleration of the process by serving as the activator for platelets, the procofactors factor V and factor VIII, and factor XI.[72] The initial thrombin also begins activating factor XIII to factor XIIIa[207] while converting some fibrinogen to fibrin,[142] and at this point clot formation is observed.

Propagation

Once the factor VIIIa is formed, it combines on activated platelets with IXa generated by the factor VIIa–TF complex to form the intrinsic tenase complex. This complex is the major activator of factor X; it is 50 times more efficient than factor VIIa–TF in catalyzing the activation of factor X[208,209] and is not under the control of TFPI.[210,211] In the absence of factor VIII or factor IX, the intrinsic tenase complex cannot be assembled; therefore, no amplification of factor Xa generation occurs. This is the principal defect observed in hemophilia A and hemophilia B.[212,213]

Factor Xa combines with factor Va on the activated platelet membrane and other surfaces at specific receptor sites[114,214,215] to form the prothrombinase complex, the principal generator of thrombin. This process serves as a major amplification loop of blood coagulation. Factors Xa and IXa, of the prothrombinase and intrinsic tenase complexes, respectively, are protected from inhibition by AT and other plasma inhibitors in their complexed form.[216] Furthermore, these membrane-bound enzyme complexes execute the propagation phase of the reaction, during which massive amounts of thrombin are produced efficiently and continuously, as long as more blood enters the wound site to resupply the procoagulant catalytic process.[217,218]

Termination

Once flow has ceased because of the formation of a fibrin-platelet "dam," the velocity of thrombin formation diminishes and the overwhelming concentration of inhibitors present in blood can "catch up" and inhibit the various proteases as they dissociate from their respective complexes. In the intact vasculature surrounding the growing thrombus, procoagulant enzymes and cofactors escaping the wound site are quenched rapidly under normal circumstances by the stoichiometric and dynamic inhibitory systems of blood in cooperation with elements of the vascular endothelium. Any thrombin escaping from the wound site may bind resident TM constitutively present on vascular endothelial cells. When it is TM bound, thrombin is converted from a procoagulant enzyme to an anticoagulant enzyme as part of the protein Case complex. Activation of protein C downregulates the intrinsic tenase and prothrombinase complexes by cleaving factors VIIIa and Va, whereas TAFI activations act to prolong clot lysis[53,219] When it is operating properly, this system of attenuation of blood leakage displays the appropriate level of procoagulant required to obstruct blood loss, but it is precluded from systemic activation of the coagulation system.

Elimination/Fibrinolysis

The thrombus restricting blood flow is structurally composed of aggregated platelets and cross-linked fibrin. Other plasma proteins and blood cells are also trapped within the clot. Clot formation is integrated with clot dissolution by plasmin to maintain hemostatic balance. The lytic system has two roles: t-PA generates plasmin at the fibrin surface and governs fibrin homeostasis, whereas u-PA binds to a cellular u-PA receptor and generates pericellular plasmin, which plays an important role in tissue remodeling and cellular migration. The latter function is, to a great extent, mediated by plasmin activation of matrix metalloproteinases, which degrade the extracellular matrix. t-PA and u-PA are secreted by vascular endothelial cells and regulated by cellular cytokines and components produced during the clotting cascade, including thrombin.

The elimination phase begins the process of tissue repair by dissolving the fibrin-platelet clot generated in the earlier phases of hemostasis. The damaged vascular tissue requires plasmin not only to clear the fibrin clot but also to initiate removal of damaged tissue so that cells can migrate into the injured area.[220,221] Plasmin activates a variety of matrix metalloproteinases that degrade subendothelial matrix components and extricate the damaged tissue.[222,223] These processes mark the beginning of the final stages of the hemostatic response: repair and regeneration.

The importance of tight regulation of these processes is perhaps best illustrated by malfunctions of the hemostatic response. An inappropriate response can lead to one of two opposing but equally undesirable outcomes. Failure to form a sufficient hemostatic plug to arrest blood flow subsequent to vascular injury can result in pathologic hemorrhage. Excessive clot formation or failure to efficiently lyse a clot may result in thrombosis with consequent vascular obstruction. Under normal circumstances, the vascular endothelium together with the aforementioned positive and negative feedback loops within the procoagulant pathways prevents these negative outcomes by actively controlling the coagulation process until a triggering stimulus of sufficient magnitude threatens vascular integrity. Initiation of the procoagulant response also initiates the fibrinolytic response simultaneously with the repair and regeneration processes.

BLOOD COAGULATION MONITORING

Most clinical assays use fibrin clot formation as a means to assess hemostasis (e.g., the prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT) assays). These clinical clot-based assays were designed to be rapid; where the formation of a visible clot occurs during the initiation phase of coagulation at only 3% to 5% of the total amount of thrombin produced.[217,224] These clot end point assays have advanced our detection of clinical risk by being able to quickly distinguish certain protein defects in either the intrinsic or extrinsic pathways (Fig. 36.13); however, the majority of thrombin (>95%) is generated after clot formation during the propagation phase,[217] during which most hemostatic and thrombotic physiology is occurring, and is not captured by the fibrin clotting endpoint assays. The development of assays that capture the propagation phase dynamics are

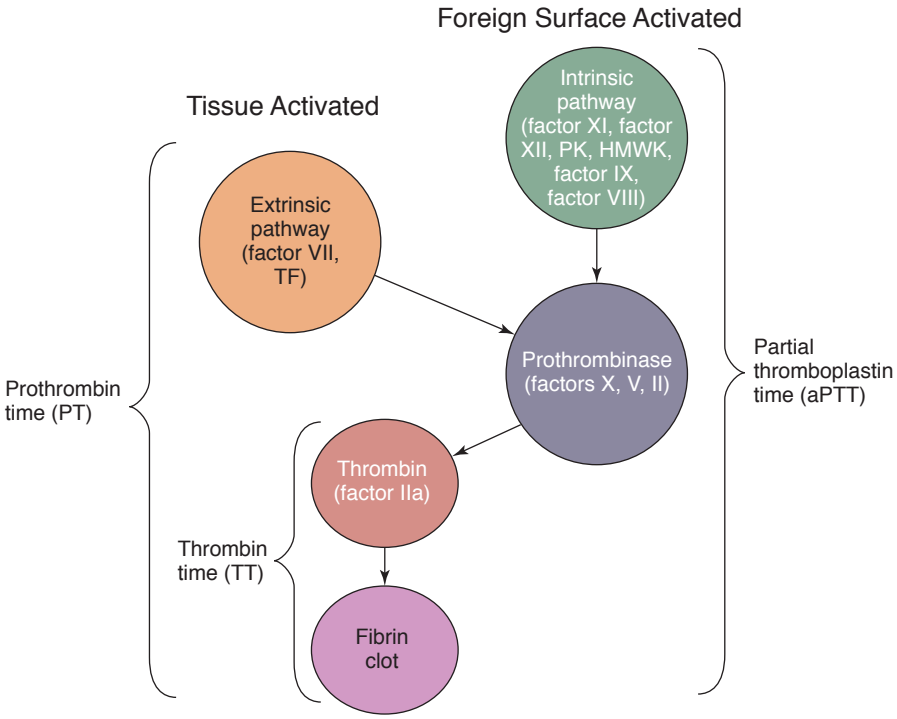

Figure 36.13 Schematic of plasma coagulation tests. The prothrombin time evaluates the tissue factor *(TF)* or extrinsic activated pathway of blood coagulation. This test uses thromboplastin as an initiator of blood coagulation. The plasma test for evaluation of the intrinsic (contact or accessory) pathway is referred to as the partial thromboplastin time. This test uses a foreign surface (e.g., kaolin or silica) as the activator of blood coagulation. The thrombin time, also known as the thrombin clotting time, specifically evaluates conversion of fibrinogen to fibrin through the action of thrombin. *HMWK,* High-molecular-weight kininogen; *PK,* prekallikrein.

leading to a more holistic view of each individual's clinical risk profile.

Plasma Clotting Tests

Fig. 36.13 represents a simplified continuity diagram for the coagulation system and interrogation of that system by common plasma assays, including the PT, aPTT, and TT. These tests are conducted with citrated plasma.

Prothrombin Time

The three main uses of the PT assay are the monitoring of warfarin therapy, the assessment of liver function in patients with severe liver disease, and the screening for deficiencies in the extrinsic and common pathways. This assay depends on the infusion of Ca^{2+} and exogenous TF-lipid preparation (thromboplastin, recombinant, or prepared from human placenta or rabbit brain) to citrated plasma. The intrinsic pathway contributions to coagulation in the PT assay are negligible because of the large amount of TF-lipid used. PT results are standardized by the international normalized ratio (INR).[225] This assay is most sensitive to factor II, factor V, factor VII, factor X, and fibrinogen; however, mild deficiencies in any of these factors can go undetected with the PT assay.

Activated Partial Thromboplastin Time

The continuity of the intrinsic pathway of coagulation is assessed by the aPTT, which involves adding phospholipid, Ca^{2+}, and a foreign "surface" (e.g., kaolin or silica) to citrated plasma in the absence of TF.[8] This test evaluates the ability of the intrinsic pathway catalysts (i.e., factor XII, prekallikrein, HMWK, factor XI, factor VIII, and factor IX) and components of the common pathway (i.e., fibrinogen, prothrombin, factor V, and factor X) to produce a clot. The primary utility of the aPTT is that it provides identification of the congenital hemostatic defects associated with hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency). The aPTT is also used to monitor therapy with unfractionated heparin and to detect the lupus anticoagulant.

Thrombin Time

The TT test detects direct inhibitors of thrombin or fibrin polymerization. It is particularly sensitive to heparin, fibrin degradation products, and hypofibrinogenemia or dysfibrinogenemia. Thus, this screening test is useful in evaluating a prolonged PT or aPTT by discriminating between a problem in thrombin generation and the inhibition of thrombin activity.

Thrombin Generation Assays

Aberrations in thrombin generation can affect the critical balance of many hemostatic processes that ultimately can result in bleeding and/or clotting. An integrated view of the ability of recalcified platelet-rich or platelet-poor plasma samples to generate thrombin on stimulation with either contact pathway activator or TF has more recently come into use. In the thrombin generation assay (TGA), thrombin, once produced, hydrolyzes a specific substrate to give a fluorescent signal that is continuously recorded and to provide an evaluation of the phases of thrombin generation.[226-228]

This assay has recently been adapted for use in whole blood,[228] and continued adaptations of TGA will ultimately lead to improved correlation between the diagnostic value of these tests and clinical outcome.[229,230]

Platelet Function Tests

Platelet function tests are used to aid diagnosis (e.g., impaired platelet function or thrombocytopenia), predict risk (e.g., hemorrhage or thrombosis), and monitor antiplatelet therapy. If platelets are not functioning normally or a thrombocytopenia is present, a patient is at an increased risk of excessive bleeding. A platelet count continues to be utilized as a first-line test, but the overall function of the platelet is more difficult to measure. Platelets are sensitive to manipulation and are prone to spontaneous activation in vitro. Assays to test platelet function include platelet aggregometry, platelet function analyzers, flow cytometry, and molecular biology techniques.[231-233]

Platelet Aggregometry

Platelet aggregometry allows the laboratory to test how particular stimulators (agonists) affect platelets in the milieu of plasma or whole blood. This test is used to diagnose inherited and acquired platelet function disorders. It is affected by aspirin and a variety of other drugs that alter platelet function. Platelet aggregometry does not mimic the physiologic processes of platelet adhesion, activation, and aggregation that occur during hemostasis in vivo. Other tests have been developed to simulate the in vivo processes that occur during vessel wall damage.

Instruments That Simulate Platelet Function in Vitro

The Plate Function Analyzer-100 (PFA-100) is the mainstay for platelet function screening in hospitals and screens platelet adhesion and aggregation under high shear conditions in response to defined agonists.[234,235] This test is sensitive to both platelet count as well as hematocrit. Although abnormal results are indicative of platelet dysfunction, they are not specific for any disorder. Furthermore, it has not been shown to be able to predict the likelihood that a patient will bleed excessively during surgery, and its full clinical utility is still being established.

Other platelet function tests have been developed to address existing gaps in our ability to analyze platelet function:[235] the Clot Signature Analyzer (CSA) can detect abnormalities in both global hemostasis and platelet function under high shear conditions,[236,237] while the Thrombotic Status Analyzer (TSA) measures both thrombotic and thrombolytic activities within nonanticoagulated blood[238] and is capable of detecting defective or excessive platelet function, and monitoring both antiplatelet and thrombolytic therapy. The VerifyNow system was developed to address the need for monitoring platelet receptor blockade in order to ensure optimal dosing of anti-GPIIb/IIIa therapy.[239] Finally, thromboelastography (described below) also tests platelet function in the context of the coagulation process.

Whole-Blood Assays

There is renewed interest in "global coagulation testing" with methods enabling on-site measurements of coagulation that provide rapid and continuous information on coagulation. The use of whole blood gives a better picture of the situation in vivo because all the blood components are allowed to interact during the test. The whole-blood, on-site assays in common use in surgery and cardiovascular percutaneous interventions are the activated clotting time (ACT) and thromboelastography.

Activated Clotting Time

The ACT, introduced by Hattersley in 1966,[240] is an adjusted aPTT test for samples of citrated whole blood. The ACT assay can evaluate the influence of coagulation inhibitors, such as heparin and the direct thrombin inhibitors.[241,242] It is one of the most frequently performed coagulation assays and has shown utility as a point-of-care evaluation of the hemostatic response in surgical and interventional suites to control treatment with intravenous unfractionated heparin during vascular procedures.[243]

Thromboelastography

Thromboelastography uses technology that has existed for more than 40 years.[244,245] The modern iterations of the thromboelastograph are computerized, user-friendly devices that provide on-site evaluations of clotting performance and the potency of in situ fibrinolysis. These devices are viscometers that measure the increasing viscosity of blood during the coagulation process, producing a time-based record. Viscoelastic measurements are currently being performed on one of two instruments using their proprietary reagents: rotational thromboelastography (ROTEM) and thromboelastometry (TEG). The thromboelastogram arises through movement of the cup (TEG) or the pin (ROTEM). As fibrin forms, this movement is impeded and transformed to a trace (Fig. 36.14) reflecting different phases of the clotting process from which different semiquantitative parameters that evaluate the quality and timing of clot formation and lysis are measured, including clot time (R), clot build-up and cross-linking (K and α), and overall strength of the fibrin clot (maximum amplitude, MA). Protracted evaluations yield parameters associated with clot lysis. To describe these viscoelastic changes, both systems have their own terminology. The viscoelastic measurement of a patient's blood sample is increasingly being used in clinical settings.[246] These settings include cardiac surgery,[247-250] liver transplantations,[251] sepsis trauma,[252-259] obstetrics,[260] anticoagulant activity,[261,262] and treatment with fibrinolytic agents.[263-267] Modifications of thromboelastography to measure platelet aggregation are also being utilized more in the clinical setting.[268,269]

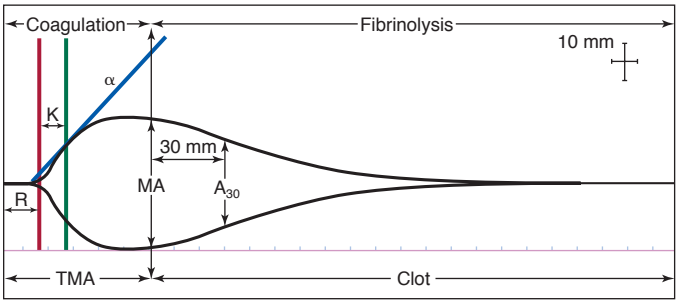

Figure 36.14 Representation of a thromboelastographic tracing. Evaluation of the quality and timing of clot formation and lysis is illustrated in terms of semiquantitative parameters: *R*, the reaction time, estimates the time to initial clot formation; *K* and α estimate the rate of fibrin formation and cross-linking; *MA* estimates the maximum amplitude of the fibrin clot and its strength; *TMA* calculates the time to MA. A_{30} is the amplitude at 30 minutes.

Future Coagulation Assays

Advancing technology will permit the translation of our ever-expanding understanding of blood coagulation physiology into even more refined and informative clinical assays. The advent of new, direct-acting procoagulants and anticoagulants is leading to the push for the development of new plasma-based and on-site whole-blood assays that will improve the reporting of the quality of an anticoagulant response, its monitoring, and its reversal.

ACKNOWLEDGMENT

The authors were supported in part by ARO-W911NF-10-1-0376, NHRC W911QY-15-C-0027 and 1-UM1-HL120877 and the University of Vermont Department of Biochemistry.

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37 CHAPTER

Coagulopathy and Hemorrhage

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Abstract

Coagulation is a physiologic defense mechanism aimed at maintaining the integrity of the circulatory system in the setting of vascular injury. There is a critical balance between coagulation and fibrinolysis aimed at preventing both pathologic hemorrhage and thrombosis. The surgeon is thus tasked with preventing adverse events by achieving adequate hemostasis without effecting extensive thrombosis. In this chapter, we review the pathophysiology of the coagulopathies that may lead to perioperative hemorrhage and highlight options for both diagnosis and treatment.

Keywords

Coagulation
Thrombosis
Bleeding
Hemostasis
Coagulopathy

Sealants 479
FloSeal, Tisseel, Evicel 479
Dry Fibrin Sealant Dressings 479
Tissue Glue 479
Newer Agents 479
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POSTOPERATIVE BLEEDING 479

Understanding the complex biology of coagulopathy and hemorrhage is imperative in the perioperative management of surgical patients. "Coagulopathy" is a term employed loosely in the literature and in the clinical setting. It is applied to patients without identifiable coagulation abnormality but with clinical bleeding or recurrent thrombosis as often as to patients with disseminated intravascular coagulopathy and significantly abnormal coagulation parameters, or those with specific inherited factor deficiencies. The *Gale Encyclopedia of Medicine* defines coagulopathy as a disorder in which blood is either too quick or too slow to coagulate (clot).[1] Coagulation is a physiologic defense mechanism aimed at maintaining the integrity of the circulatory system in the setting of vascular injury. There is a critical balance between coagulation and fibrinolysis aimed at preventing pathologic hemorrhage and thrombosis. The vascular surgeon is thus tasked with preventing adverse events by achieving adequate hemostasis without effecting extensive thrombosis, and an understanding of normal hemostasis is necessary to assimilate the pathophysiology of the coagulopathies and necessary treatments (see Chapter 36).

DIAGNOSIS AND PREOPERATIVE SCREENING FOR BLEEDING DISORDERS

Identifying patients preoperatively who are at risk for bleeding allows the surgeon to initiate corrective treatment before performing a surgical procedure and to plan for optimal perioperative management.

History and Examination

The key to minimizing perioperative hemorrhage is to identify patients at significant risk for hemorrhage or coagulopathy by means of a thorough history and physical examination. A detailed history should elicit any previous episodes of bleeding with prior surgery, dental extractions, or trauma as well as any easy bruising or epistaxis. A patient with a family history of significant hemorrhagic complications should be evaluated for increased bleeding risk. Complete drug and medication histories (including homeopathic or herbal remedies) are important to evaluate for agents that affect the clotting cascade. A history suggestive of hematuria or melena requires further investigation. Physical examination should identify any evidence of petechiae or excessive bruising.

Laboratory Testing

With the abundance of laboratory tests available for the evaluation of hemostasis, performing all of them is neither cost-effective nor necessary. One must adopt a systematic approach to selecting which, if any, laboratory studies a particular patient requires.

Risk Stratification

Rapaport devised the following four-level stratification scheme to determine the need for preoperative laboratory testing according to the patient's clinical status and bleeding history, and the planned operation[2]:

Level I

Patients who have no bleeding history and will undergo minor procedures, such as lipoma excision. No further hematologic evaluation is required because the cost of testing outweighs the probability of finding an abnormality and the risk of bleeding, even if one exists.

Level II

Patients who have no previous bleeding history but will undergo a major operation. Normal activated partial thromboplastin time (aPTT) and platelet count should effectively eliminate the risk of life-threatening bleeding.

Level III

Patients whose bleeding history raises concern for defective hemostasis and those whose procedure might impair hemostasis (e.g., cardiac or neurosurgical interventions). In these patients, preoperative evaluation of the following factors is appropriate:

1. Adequacy of hemostatic plug formation—bleeding time and platelet count
2. Adequacy of coagulation reactions—prothrombin time (PT) and aPTT
3. Size and stability of the fibrin clot—factor XIII deficiency and fibrinolysis screening

Level IV

A history or physical findings highly suggestive of abnormal hemostasis, and the surgical procedure is not a factor. In addition to performing the tests indicated for level III patients, the following should be considered (especially if the results of level III testing are normal):

1. Bleeding time after the administration of 600 mg of aspirin—to uncover von Willebrand disease (vWD) or a qualitative platelet disorder[3]
2. Factor VIII and factor IX levels
3. Thrombin time (TT)—to detect dysfibrinogenemia

Proper Blood Drawing

A properly drawn blood sample is paramount to interpreting the results of clotting tests; the specific methodology is beyond the scope of this chapter.[4] Whole blood is collected into an evacuated sample tube containing a fixed amount of citrate as an anticoagulant. The ratio of whole blood to citrate solution should be 9:1. An adult sample tube should be filled to at least 60% to 80% of its full collection volume to avoid excessive anticoagulation (a pediatric sample tube needs to be filled to 90% of its volume).[4] The anticoagulated blood should be mixed gently by being inverted three to four times. Testing should be done within 2 hours if the sample is kept at room temperature and within 4 hours if kept at 4°C. The screening tests used to determine the cause of coagulopathy are summarized on Table 37.1.

Specific Laboratory Tests (See Chapter 36)

Prothrombin Time

PT is used to assess the extrinsic pathway of clotting (factors II, V, VII, IX, and X and fibrinogen). The end point is the time required (in seconds) for a fibrin clot to form. Argatroban therapy and very high doses of heparin can also cause an elevated PT value secondary to thrombin (IIa) inhibition.[5]

Activated Partial Thromboplastin Time

The aPTT is used to assess the intrinsic pathway (factors VIII, IX, XI, and XII) and final common pathway (factors II, V, and X and fibrinogen) of clotting. Primary uses of aPTT include monitoring heparin therapy and detecting lupus anticoagulant, hemophilia A, and hemophilia B.

Thrombin Time

TT measures the conversion of fibrinogen to fibrin, which is the final step in the clotting pathway. Prolongation of TT is attributable to direct thrombin inhibitor (DTI) therapy, heparin, lytic administration, and dysfibrinogenemia.

Activated Blood Clotting Time

The activated clotting time (ACT) test is performed by addition of a coagulant-accelerating matrix (e.g., diatomaceous earth) to a sample of whole blood and measurement of the time required for clot formation. This method is generally used to monitor adequacy of heparinization in the operating room or interventional suite.

Bleeding Time

The bleeding time, or the time needed for a superficial wound to clot, is used to assess primary hemostasis. One measures bleeding time by making a controlled wound in the forearm or earlobe and subsequently measuring the time for clotting to occur.[6] Clotting that takes longer than 5 minutes is considered abnormal. Bleeding time is mainly affected by the number and function of platelets, although vasoconstriction or vasodilatation may affect the bleeding time as well. Other factors that prolong the bleeding time include heparin therapy (as a result of platelet inhibition), vWD, thrombocytopenia, aspirin or other antiplatelet therapy, and uremia.

Thromboelastography and Rotational Thromboelastometry

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are point of care tests which measure real-time clot

TABLE 37.1 Tests of Coagulation and Clinical Uses

Test	Measured Variable	Causes of Abnormalities	Clinical Use
Prothrombin time (PT)	Factors II, V, VII, IX, and X; proteins C and S; tissue factor; fibrinogen	Consumptive coagulopathy, warfarin therapy, vitamin K deficiency, liver disease	Identify coagulopathy, monitor warfarin therapy
Activated partial thromboplastin time (aPTT)	All coagulation factors except factor VII	Consumptive coagulopathy, heparin therapy, lupus anticoagulants	Identify coagulopathy, monitor heparin therapy
Thrombin time (TT)	Fibrinogen (functional)	Consumptive coagulopathy, fibrinolysis, dysfibrinogenemia	Monitor fibrinolysis
Activated clotting time (ACT)	Global clotting function	Heparin use	Monitor intraoperative heparin therapy
Bleeding time (BT)	Platelet number and function	Abnormal platelet function, antiplatelet therapy, thrombocytopenia, uremia, von Willebrand disease	Evaluate platelet function
Thromboelastography (TEG)	Clotting kinetics	Anticoagulants, platelet deficiency/dysfunction, fibrinolytics	Liver transplantation, monitoring during/after cardiopulmonary bypass
Fibrin degradation products (FDPs)	Fibrinolysis	Consumptive coagulopathy	Identify coagulopathy
Euglobulin lysis time (ELT)	Fibrinolysis	DIC, primary fibrinolysis	Monitor fibrinolysis, adjunct to diagnosing DIC or primary fibrinolysis

DIC, Disseminated intravascular coagulation.

characteristics, including formation and dissolution kinetics, as well as in situ fibrinolysis.[7] Due to rapid turnaround time for these tests, they are useful for intraoperative monitoring of anticoagulation (e.g., cardiac surgery) as well as in goal-directed hemostatic therapy in a bleeding patient after trauma, surgery, or post-partum hemorrhage.[7-8] There is emerging data to support the use of TEG/ROTEM to guide blood product administration in patients on extracorporeal membrane oxygenation (ECMO).[9] Future studies may establish the utility of TEG/ROTEM for guiding anticoagulation on ECMO, especially in the pediatric population.[10-11]

Fibrin Degradation Products

Fibrin degradation products (FDPs) occur as the result of primary or secondary fibrinolysis. Elevations of their levels are seen in disseminated intravascular coagulation (DIC), cirrhosis, eclampsia, and trauma, and following lytic therapy. The FDP assay has few specific clinical applications except in the attempt to identify primary fibrinolysis.

Euglobulin Lysis Time

The euglobulin lysis time (ELT) is an assay used to assess global function of the plasma fibrinolytic system. It measures the time required for a clot to lyse in a test tube (the normal value is 90-240 minutes). For this test to be useful, a patient must have adequate clot formation. This test is used as part of a panel to help differentiate a primary fibrinolytic state from DIC. A shortened ELT in patients without thrombocytopenia or schistocytosis is diagnostic of primary fibrinolysis, whereas a shortened ELT with thrombocytopenia or schistocytosis probably indicates DIC. Reports imply that ELT can also be used to determine the presence of excessive tissue plasminogen activator (t-PA) and deficiency of plasminogen activator inhibitor.[12] A drawback of this assay is its significant reported interlaboratory variability.[13]

INHERITED COAGULOPATHIES

Platelet Disorders

Inherited platelet disorders are rare conditions with varying degrees of phenotypic severity. These disorders affect multiple aspects of platelet function, namely aggregation, secretion, adhesion, and procoagulant activity. There are a large number of rare conditions, the most common of which are described in the following sections.

von Willebrand Disease

von Willebrand factor (vWF) plays an important role in primary hemostasis by binding to both platelets and endothelial components, effecting formation of an adhesive bridge between them. vWF also contributes to clot formation by acting as a carrier protein for factor VIII.[14]

von Willebrand disease (vWD) is the most common inherited bleeding disorder. Although it affects about 1% of the population, only 5% of affected patients are symptomatic.[15] Clinical manifestations range from nil to severe bleeding, depending on the level of functional, circulating vWF. Easily identifiable but nonspecific symptoms include easy bruising, mucous membrane bleeding, prolonged epistaxis, postoperative bleeding, gastrointestinal bleeding, and heavy menstrual bleeding.[16,17] Previously undiagnosed patients sometimes have the first manifestation of the disease after taking antiplatelet agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin.

vWD is classified into three major types on the basis of clinical laboratory test results and genetic mutations, as delineated in Table 37.2. Type 2 comprises at least four subtypes with variable inheritance patterns. Patients with type 2A vWD (≈15% of all with vWD) have decreased platelet-dependent functions owing to loss of high-molecular-weight multimers. Those with type 2B disease (≈5% of all with vWD) have vWF with increased affinity for platelet glycoprotein Ib (GP-Ib). Type 2M is less common and results in reduced binding of vWF to platelet GP-Ib despite the presence of large vWF multimers. Patients with type 2N disease have mutations that alter the vWF binding site for factor VIII. Impaired binding effects rapid clearance of factor VIII.[15]

If vWD is suspected, the initial screening tests are (1) bleeding time, (2) closure time (vWF-dependent platelet function), (3) platelet count, and (4) aPTT. If results of these studies are positive or suspicious, more specific testing is pursued (Table 37.3).[14,18-20]

Treatment decisions are based on severity of symptoms and type of vWD. Symptomatic patients should avoid NSAIDSs. Desmopressin (DDAVP) is effective in patients with type I vWD perioperatively and in those with mild to moderate bleeding episodes. Patients with type 3 and severe forms of type 2A, 2B, and 2M disease usually require replacement therapy with vWF, factor VIII–vWF concentrates, or cryoprecipitate. In general, the goal of treatment in these patients is to maintain

TABLE 37.2 Types of von Willebrand Disease

Type	Transmission	Percentage of Cases of vWD (%)	Defect	Phenotype
1	AD	75	Quantitative deficiency of vWF	Mild-moderate bleeding
2	Autosomal but varied	20%	Multiple qualitative defects (2A,2B, 2M, 2N)	Variable
3	AR	5	Absence/severe decrease in vWF	Severe bleeding

AD, Autosomal dominant; *AR,* autosomal recessive; *vWD,* von Willebrand disease; *vWF,* von Willebrand factor.

TABLE 37.3 Tests for von Willebrand Disease

Test	Evaluates	Type in Which Abnormality Seen
Plasma vWF antigen	Quantitative defects (presence)	1,3
Ristocetin cofactor activity	Agglutination requires largest vWF multimers	2A, 2M
Factor VIII coagulant activity	Factor VIII half-life and secretion depend on vWF	1,3
Ristocetin-induced platelet aggregation (RIPA)	vWF concentration and affinity for GP-Ib	2A, 2M, 3
vWF multimer distribution	Presence of high-molecular-weight multimers	2A, 2B
vWF: factor VIII binding assays	Affinity of factor VIII: vWF binding	2N (vs. hemophilia A)

the activity of factor VIII and vWF between 50% and 100% for 3 to 10 days to address episodes of serious bleeding or for major surgery.[16]

Giant Platelet Disorders

Giant platelet disorders are a group of rare disorders characterized by thrombocytopenia, large platelets, and variable bleeding symptoms. They are generally subcategorized into four groups: those with a structural defect (e.g., Bernard-Soulier syndrome with glycoprotein abnormalities), those with abnormal neutrophil inclusions (e.g., May-Hegglin anomaly), those with systemic manifestations (e.g., hereditary macrothrombocytopenia with hearing loss), and those with no specific abnormalities (e.g., Mediterranean macrothrombocytopenia).[21]

Bernard-Soulier syndrome, the most common of these platelet disorders, is characterized by thrombocytopenia, large platelets, and bleeding. It is attributed to dysfunction or absence of the GP-Ib/IX/V complex, which is a primary adhesion receptor of platelets.[21] The disorder manifests early in life as bleeding symptoms, most frequently epistaxis or gingival or cutaneous bleeding. Frequently, a severe hemorrhagic episode is noted after surgery (e.g., circumcision). Laboratory findings include thrombocytopenia ranging from less than 30 to $200 \times 10^3/\mu L$ (normal) and a prolonged bleeding time with normal clot retraction.[21,22] Management of patients with this syndrome usually entails education and avoidance of minor trauma. In the event of significant hemorrhage, platelet transfusion is generally indicated.[23]

Glanzmann's Thrombasthenia

Glanzmann's thrombasthenia is an autosomal recessive disease with a large number of reported mutations. A defect in GP-IIb/IIIa renders platelets unable to aggregate.[24,25] Normal GP-IIb/IIIa allows platelets to bind soluble proteins and vWF. In Glanzmann's thrombasthenia, platelets can attach to exposed endothelium but cannot form aggregates. A wide spectrum of phenotypic severity is reported, but mucocutaneous bleeding and the absence of platelet aggregation are classic findings.[26] Significant bleeding episodes typically require platelet transfusion.[21,24,27]

Storage Pool Disorders

Storage pool disorders result from platelet granule deficiencies. The granules are usually divided into two groups: alpha granules (which contain vWF, thrombospondin, fibrinogen, and platelet-derived growth factor) and dense granules (which release adenosine diphosphate [ADP] and serotonin). Gray platelet syndrome is an example of an alpha-granule storage disorder.[28] This autosomal recessive disorder results in granules deficient in secretory proteins. Manifestations are typically limited to mucosal bleeding, but trauma-associated hemorrhage can occur. Laboratory analysis reveals moderate thrombocytopenia and a prolonged bleeding time. Preprocedural DDAVP and platelet transfusions form the basis for treatment.

Dense-granule deficiencies include Chédiak-Higashi syndrome, Wiskott-Aldrich syndrome, and thrombocytopenia-absent radius syndrome.[29] Wiskott-Aldrich syndrome is an X chromosome-linked immunodeficiency manifested as thrombocytopenia with platelets of reduced size and function as well as eczema.[30] A defect in glycoprotein L115 (a leukocyte/platelet surface molecule) yields platelets that are unable to form aggregates.[30,31] Patients with the syndrome are typically diagnosed in early childhood with the constellation of thrombocytopenia, atopic dermatitis, and frequent infections. The only curative therapy is bone marrow transplantation. If platelet transfusion is required prior to transplantation, HLA-selected platelets should be used and all blood products should be irradiated.[31]

Hemophilia

The hemophilias are inherited bleeding disorders caused by low concentrations of specific coagulation factors.

Pathogenesis

The most common hemophilias are X-linked deficiencies of factor VIII (hemophilia A) and factor IX (hemophilia B).[32] Factor XI deficiency (hemophilia C) is a less common autosomally transmitted disorder. Factor VIII is a complex plasma glycoprotein produced by liver sinusoidal endothelial cells and by vascular endothelial cells.[33] It has a half-life of 12 hours in adults and is protected from premature degradation by vWF. Factor IX is a vitamin-K-dependent protein synthesized by the liver with a plasma concentration approximately 50 times that of factor VIII and a half-life of 24 hours.[34] Bleeding in hemophilia results from a failure of secondary hemostasis. Although a normal platelet plug forms, stabilization of the plug by fibrin is defective owing to inadequate amounts of thrombin.

Diagnosis

Hemophilias A and B are clinically indistinguishable. A diagnosis of hemophilia is confirmed by an assay for the specific factor. However, factor VIII deficiency secondary to hemophilia A

requires distinction from vWD by assays for vWF. Depending on the concentration of the factor, the bleeding tendency is classified as mild, moderate, or severe.[35] Mild disease has a factor VIIIc or IXc concentration between 0.05 and 0.40 IU/mL (5%-40% of normal) with bleeding manifestations after surgery, dental intervention, or trauma. Spontaneous bleeding is not seen. Moderate disease translates to a factor VIIIc or IXc concentration of 0.01 to 0.05 IU/mL (1%-5% of normal). This concentration can result in bleeding into muscles and joints following minor injury. Major surgical or dental intervention effects severe hemorrhage.[34] Severe disease is seen with a concentration of factor VIIIc or IXc of less than 0.01 IU/ml (<1% of normal).

Though most cases of hemophilia are identified via family history, some appear as de novo mutations. Whereas severe disease is typically diagnosed by 2 years of age, mild or moderate disease may not be recognized until adulthood. The hallmark of severe hemophilia is spontaneous bleeding into joints and muscles.

Management

The primary goal of treatment is to sufficiently increase the concentration of the missing factor to stop or prevent spontaneous, traumatic, or surgical hemorrhage. A critical aim is to aggressively treat and prevent joint bleeding, which otherwise can lead to crippling arthropathy and joint deformity.[36] Primary prophylaxis (prior to any episode of joint hemorrhage) to prevent this devastating complication is now recommended, with most centers recommending initiation prior to 3 years of age.

Although DDAVP can sufficiently raise factor VIII levels in patients with mild hemophilia A, factor concentrations are typically required for more significant disease. Multiple factor VIII and IX concentrations are available as either recombinant or plasma-derived products. For prophylaxis of a nonbleeding patient, a factor VIII concentration of 3% is considered adequate. A level of 30% is required for minor bleeding, and 50% for major bleeding. Prior to elective surgery, a factor VIII level greater than 80% is recommended, with a goal of 30% to 50% to be maintained in the first 2 postoperative weeks. The goals for hemophilia B include a factor IX level of 30% for minor bleeding and greater than 50% for major bleeding.[37]

In some patients who undergo long-term replacement therapy, antibodies against factors VIII and IX develop. For these patients, recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrates might be necessary to achieve hemostasis. These agents act by bypassing the need for factors VIII and IX to achieve coagulation. The long-term goal for patients with high antibody titers is immune tolerance induction therapy, which results in a gradual reduction of antibody titers and increased tolerance of factor replacement therapy.

ACQUIRED COAGULOPATHIES

Platelet Disorders

Acquired platelet dysfunction has myriad causes, including uremia, liver dysfunction, cardiopulmonary bypass, hypersplenism, hematologic malignancy, thrombotic thrombocytopenic purpura, and immune thrombocytopenic purpura. These processes can result in quantitative or qualitative platelet deficiencies and should be considered in any investigation of abnormal bleeding, especially that accompanied by thrombocytopenia.

Liver disease evokes thrombocytopenia via portal hypertension with splenic sequestration as well as by decreased thrombopoietin production. Cardiopulmonary bypass and mechanical assist devices place platelets in contact with nonphysiologic machine surfaces, which result in pathologic alterations in surface glycoprotein expression. Activation of these glycoproteins results in granule release as well as decreased endothelial adhesion and aggregate formation.

Uremia

Although bleeding diatheses secondary to uremia are not completely understood, it is clear that platelet dysfunction plays a critical role. Uremia results in both intrinsic platelet defects and alteration of platelet-endothelial interaction.[33] Changes have been described in GP-IIb/IIIa, in ADP release from alpha granules, and in the arachidonic acid pathway.[38]

Uremic patients can exhibit easy bruising and mucosal bleeding. Laboratory evaluations demonstrate a prolonged bleeding time in the setting of normal values for PT, aPTT, and platelet count. Directed treatment is typically reserved for major surgery or active bleeding, including correcting anemia to a hematocrit of 25% to 30% (to improve platelet aggregation and adhesion) and the administration of DDAVP (to enhance release of vWF) and/or conjugated estrogen (unknown mechanism).[39] Dialysis is the most effective treatment for uremic complications.

Vitamin-K-Related Disorders

Factors II, VII, IX, and X as well as proteins C and S require vitamin K for activation. Functional impairment of these factors is due to failure of vitamin-K-dependent carboxylation. The cause is typically lack of vitamin K (malnutrition or malabsorption due to biliary obstruction or gut bacterial overgrowth) or pharmacologic blockade of vitamin K (warfarin).

Treatment entails either functional factor replacement (FFP) or vitamin K (allowing carboxylation of patient's factors) to address active bleeding or in anticipation of surgical intervention. FFP acts quickly as a direct replacement without the need for enzymatic reactions; it has an immediate effect that lasts about 6 hours. Vitamin K takes at least 6 hours to take effect but exerts a more durable reversal.

Disseminated Intravascular Coagulation

DIC is systemic activation of the coagulation cascade that induces both thrombosis and hemorrhage.

Pathogenesis

DIC is primarily caused by uncontrolled production of thrombin, which leads to systemic intravascular deposition of fibrin. The inciting factor is generally vascular injury or intravascular exposure to a procoagulant, which results in initiation of normal

TABLE 37.4 Mechanisms for Common Causes of Disseminated Intravascular Coagulation

	Mechanism
Sepsis	Extrinsic pathway Thrombin generation Suppression of protein C/thrombomodulin system[36,37,126]
Major tissue injury	Direct endothelial injury Release of phospholipids and enzymes to circulation
Malignancy	Expression of tissue factor by circulating tumor cells Procoagulant: calcium-dependent cysteine protease[38] Directly activates factor X

hemostasis. Normally, thrombin generation is tightly regulated by a combination of intravascular and endothelial factors. In DIC, these inhibitory mechanisms become dysfunctional or overwhelmed, leading to the production of excess thrombin. The increased circulating levels of thrombin provoke greater fibrin production with microvascular deposition. Thrombosis of the microvasculature causes the end-organ damage seen in severe DIC. The systemic thrombosis activates t-PA, which causes thrombolysis, consumptive coagulopathy, and bleeding diathesis.

Etiology

The most common precipitants of DIC are sepsis, extensive traumatic tissue injury, cancer, amniotic fluid embolism, and placental abruption. The final common pathway for all of these entities is systemic activation of the coagulation cascade. Proposed specific mechanisms are delineated in Table 37.4.[40-43]

Clinical Phases

Even though DIC is a continuously progressing cascade of events, it can be described as three major clinical phases.[44] They are described here, and their typical laboratory findings are delineated in the Table 37.5.

Management

The overriding goal in the management of DIC is correction of the precipitating disease. Supportive therapy generally necessitates replacement of clotting factors and platelets while the inciting process is addressed. In patients with active bleeding, very aggressive replacement is pursued. Goals of resuscitation include a fibrinogen level over 100 mg/dL. Management also requires achieving and maintaining normothermia and adequate tissue perfusion. There is little evidence to support heparin therapy in acute DIC. During the supportive phase, emphasis should be put on correcting the underlying pathologic process, the achievement of which will, in turn, stop the activation of the cascade. For instance, in septic patients, broad-spectrum antibiotics, abscess drainage, and debridement of infected or necrotic tissues is critical.

TABLE 37.5 Coagulation Parameters in Disseminated Intravascular Coagulation

	Phases of DIC[a]		
	Phase I	Phase II	Phase III
Prothrombin time	Normal	↑	↑↑
Activated partial thromboplastin time	Normal	↑	↑↑
Platelet count	Normal	↓	↓↓
Thrombin time	Normal	Normal/↑	↑↑
Thombin-antithrombin complex (TAT)	↑	↑	↑
Prothrombin fragment F_{1+2}	↑	↑	↑
Fibrinogen	Normal	↓	↓↓
Fibrin degradation products	Normal	↑	↑↑

[a]Phases of DIC are defined as follows:
Phase I: Compensated activation of the hemostatic system. Patients are asymptomatic.
Phase II: Decompensated activation of the hemostatic system. Hemorrhage from injuries and venipuncture sites becomes evident. Renal, hepatic, and pulmonary function are impaired. Frequent laboratory analyses are indicated during this phase due to rapid ongoing changes.
Phase III: Complete DIC. Patients have numerous ecchymoses and multi-organ failure. Laboratory tests demonstrate consumption.

DIC, Disseminated intravascular coagulation; ↑, increased (no. of arrows indicates extent of increase); ↓, decreased (no. of arrows indicates extent of decrease).

Primary Fibrinolysis

Fibrinolytic system derangements can result in either excessive bleeding or thrombosis. It is essential to differentiate primary fibrinolysis from secondary fibrinolysis (DIC) because of their differing management strategies.

Fibrinolytic System (See Chapter 36)

Plasminogen circulates as an inactive zymogen. Activation of plasminogen by t-PA or urinary-type plasminogen activator (u-PA) results in its conversion to plasmin, a serine protease that degrades fibrin. Inhibitors of plasmin include plasminogen activator inhibitor (inhibits tissue and u-PA) and α2-antiplasmin (hepatic production). Thrombin-activatable fibrinolysis inhibitor (TAFI; a procarboxypeptidase activated by thrombin-antithrombin complex [TAT]) also constrains fibrinolysis by cleaving the C-terminal lysine residue of fibrin fragments. This disruption prevents recruitment of plasminogen to a partially digested clot, thereby inhibiting fibrinolysis.

Pathogenesis

In this complex plasmin-plasminogen activator system, excessive bleeding can result from hyperactivity of plasminogen activators

or deficient activity of fibrinolysis inhibitors. In primary fibrinolysis, there is pathologic direct activation of plasminogen. Excess circulating plasmin saturates plasminogen activator inhibitor-1 and α2-antiplasmin and cleaves fibrin and clotting factors, including factors V and VIII. Plasmin generated on the surfaces of platelets and endothelium inappropriately lyses hemostatic plugs. To counter the excess plasmin and fibrinolysis, excess thrombin is generated, resulting in microvascular thrombosis.

Etiology/Diagnosis

A primary hyperfibrinolytic state can develop in multiple clinical settings, including malignancy, liver failure, trauma, and congenital deficiency of fibrinolysis inhibitors.[45,46] Differentiating primary fibrinolysis from a secondary process, such as DIC, can be exceedingly difficult. The simplest laboratory findings to diagnose primary fibrinolysis are a short euglobulin lysis time in the absence of thrombocytopenia and the presence of schistocytes. Though challenging, the distinction between these two entities is critical as they require quite dissimilar treatments.

Management

The crux of treatment is the inhibition of fibrinolysis using lysine analogues. The lysine analogues, aminocaproic acid and tranexamic acid, act as competitive inhibitors of the conversion of plasminogen to plasmin.[42] Often, factor replacement is also required, typically factors V and VIII. Prior to its removal from the market, aprotinin was also used as a therapy for this disorder.[43]

DRUG-INDUCED COAGULOPATHIES

Heparins

Heparin is a naturally occurring, highly sulfated glycosaminoglycan. Heparin prevents clot formation and propagation by binding to and activating antithrombin. The resulting conformational change in antithrombin accelerates its ability to inactivate factors II (thrombin), Xa, and IXa.[47] Heparin can be monitored via ACT or aPTT, both of which demonstrate prolongation. Heparin is available for subcutaneous (half-life 8 hours) or intravenous (half-life 1.5 hours) administration. Intravenous heparin is frequently used for intraprocedural anticoagulation because of its short half-life, point-of-care monitoring, and ease of reversal (protamine at 1 mg per 100 U intravenous heparin).[48]

Enzymatic depolymerization of unfractionated heparin results in fragments that are approximately a third the size of heparin. These are marketed as low-molecular-weight heparins (LMWHs; such as enoxaparin and fondaparinux). Administered subcutaneously, these agents offer a longer half-life and greater bioavailability than heparin.[48] Benefits of LMWHs include ability to be given once or twice daily and decreased need for laboratory monitoring for therapeutic use. The risk of bleeding with LMWH prophylaxis is low and is comparable to that seen with prophylactic subcutaneous heparin. Withholding fully therapeutic LMWH for 24 hours prior to major surgical intervention is recommended. There is no described benefit in protamine for reversal of LMWHs.[49] The use of either type of heparin risks heparin-induced thrombocytopenia. Briefly, patients with this disorder form antibodies to the complex of heparin and platelet factor IV on platelet surfaces. The presence of the antibodies leads to uncontrolled platelet activation and pathologic thrombosis.

Thrombin Inhibitors

Intravenous DTIs include hirudin, lepirudin (recombinant hirudin), argatroban, and bivalirudin. The most common indication to use any of these agents is for the treatment of patients with heparin-induced thrombocytopenia. In contradistinction to heparins, these agents can bind to and inactivate clot-bound thrombin (a strong thrombogenic stimulus).[50] Furthermore, in comparison with heparins, DTIs have a more predictable response and are not impacted by acquired or inherent antithrombin deficiency. A brief review of these agents is shown in Table 37.6.

Oral Anticoagulants

Warfarin

Warfarin is an orally administered vitamin K antagonist (VKA). It acts by preventing vitamin-K-dependent carboxylation of factors II, VII, IX, and X and of proteins C and S. The liver synthesizes nonfunctional forms of these proteins, which require carboxylation to become active. Following initiation, warfarin typically requires 2 or 3 days to take effect. Owing to the relatively shorter half-lives of proteins C and S in comparison with the clotting factors, a heparin bridge is sometimes required at the initiation of warfarin therapy to prevent sequelae of a paradoxically hypercoagulable state. The earlier loss of the anticoagulant effect of protein C or S (more commonly problematic in patients with protein C or S deficiency) can result

TABLE 37.6 Intravenous Direct Thrombin Inhibitors

	Half-Life (min)	Monitoring Test	Disadvantages
Hirudin	40-50	aPTT	Expensive Narrow therapeutic window No antidote Problematic in renal dysfunction
Lepirudin	60-100	aPTT	Expensive Problematic in renal dysfunction Antigenic
Bivalirudin	25	aPTT Activated clotting time	Expensive
Argatroban	45	aPTT	Problematic in hepatic dysfunction Expensive

aPTT, Activated partial thromboplastin time.

in small vessel thrombosis, which manifests as warfarin-induced skin necrosis. This entity, if encountered, is treated with the cessation of warfarin and the initiation of therapeutic heparin.[51]

Direct Oral Anticoagulants

The impetus to find alternative agents included the need for frequent monitoring due to multiple food and drug interactions and a less predictable anticoagulant effect based on weight, requiring multiple adjustments. Two new classes of oral anticoagulants were developed with the goal of improving monitoring and safety: factor Xa inhibitors (rivaroxiban, apixaban, edoxaban) and DTIs (dabigatran and ximelagatran). The advantages of these agents, which have been termed direct oral anticoagulants (DOACs), include significant reductions in the need for laboratory monitoring, and shorter half-lives, which may aid in preoperative planning. The safety and efficacy of DOACs has been confirmed in randomized trials for multiple indications. These include perioperative prevention of venous thromboembolism (VTE), prevention of embolic events in atrial fibrillation, treatment of venous thromboembolism, thrombo-prophylaxis in major orthopedic surgery, and acute coronary syndrome.[50,52,53,54] However, further research is necessary to evaluate the efficacy of DOACs for the treatment of VTE associated with cancer or antiphospholipid syndrome, where the recurrence risk is high.[54] While the benefit of oral anticoagulation without frequent monitoring is obvious for the pediatric population, most trials to date have been in adults. No DOACs are currently approved for children, although several trials are currently ongoing.[55]

The disadvantages of DOACs compared with VKAs include the lack of a known effective reversal protocol with known antidotes and lack of a simple laboratory test to evaluate efficacy.[50] Since plasma and cryoprecipitate do not reverse the anticoagulation effect of DOACs, local management plans including mechanical compression, blood transfusion, and surgical and radiologic intervention must be developed. Life-threatening bleeding may require off-label use of hemostatic agents such as prothrombin concentration complex (PCC) and recombinant factor VIIa. Specific antidotes for DOACs are being developed, including the human monoclonal antibody idarucizumab specific for dabigatran, which has completed phase III clinical trials.[56] With increased attention to the need for reversal of the anticoagulant effects of DOACs, other promising antidotes are in clinical safety trials or drug development.[57]

Also, since many DOACs have yet to be compared in head-to-head trials, choosing a specific DOAC for an individual patient can be challenging.[58] Furthermore, dosing adjustments for renal impairment differ from agent to agent, requiring a high level of clinical knowledge and experience to prevent dosing errors. There has also been some controversy over the description of a possible increase in myocardial infarction rate in patients treated with dabigatran.[52]

Antiplatelet Agents (See Chapter 40)

Antiplatelet agents, such as aspirin, thienopyridines, clopidogrel, and ticlopidine, are most often used in patients who have had previous cerebrovascular events, recent acute coronary syndrome, or peripheral vascular disease, or who have undergone peripheral or coronary interventions. Aspirin irreversibly inactivates platelet cyclooxygenase with the resulting inhibition of platelet production of thromboxane A_2. Clopidogrel and ticlopidine block platelet ADP receptors, effecting decreased GPIIb/IIIa expression. The duration of effect of all of these agents is 5 to 7 days because reversal requires the synthesis of new platelets.

Decisions regarding perioperative cessation of antiplatelet agents are frequent areas of debate. Most later reports favor continuation of these agents when possible throughout the perioperative period. Ultimately, the determination depends on the indication for antiplatelet therapy as well as the extent of planned surgery and its attendant bleeding risk. Studies suggest that withdrawal of aspirin therapy in anticipation of coronary artery bypass grafting is associated with an elevated in-hospital mortality risk.[53,59] This finding was echoed in the analyses of the peripheral bypass population.[60]

Recommendations for patients with coronary stents who are taking clopidogrel are well-delineated. In this population, elective surgery should be postponed for at least 6 months for bare metal stents and 1 year for patients with drug-eluting stents in order to avoid interruption in therapy.[61] When therapy can safely be interrupted, cessation of clopidogrel or ticlopidine should occur 5 days prior to elective operation.

Abciximab and eptifibatide are antiplatelet agents that act via inhibition of GP-IIb/IIIa. Abciximab, frequently used during coronary procedures, is synthesized from Fab fragments of anti-GPIIb/IIIa immunoglobulins.[62] The result is inhibition of platelet aggregation. Platelet aggregation typically returns to normal 24 to 48 hours after cessation of therapy because of the agent's short half-life. Platelet transfusion can be used for emergency reversal because abciximab remains strongly bound to native platelets. Eptifibatide also decreases platelet aggregation and prolongs bleeding time.[63] It binds reversibly to GP-IIb/IIIa with a half-life of 2.5 hours. Platelet transfusion is not effective to reverse this agent.

A newer class of antiplatelet agents targets the platelet $P2Y_{12}$ receptor for ADP (collectively called $P2Y_{12}$ inhibitors). Agents are available for intravenous (elinogrel, cangrelor) or oral (ticagrelor, elinogrel) administration. These drugs are direct-acting inhibitors of the receptor. This alternative mechanism of action is important because about 30% of patients show inadequate platelet inhibition with clopidogrel therapy. The $P2Y_{12}$ inhibitors also have rapid onset and offset of platelet inhibitory action. This feature allows them to serve as a bridge therapy (when clopidogrel needs to be stopped in anticipation of an invasive intervention) as well as an alternative when clopidogrel fails. Although the efficacy of these agents is at least comparable to that of clopidogrel, there is some suggestion of higher bleeding complication rates with elinogrel.[64-66]

Therapeutic Thrombolysis

Thrombolytic agents are all plasminogen activators that directly or indirectly convert plasminogen to plasmin. Plasmin then

degrades fibrin and fibrinogen as well as additional factors, such as prothrombin and V and VII. The most commonly used agents are urokinase, tenecteplase, reteplase, and alteplase (t-PA). Thrombolytics are thoroughly discussed in Chapter 41. These agents can be used systemically or in a more directed fashion.

HYPOTHERMIA

Because coagulation factors are enzymes, their activity is substantially impaired by extremes of temperature or pH. Hypothermia in vascular surgery can result from insufficient ambient temperature, prolonged operative time, excessive blood loss, and the administration of cold fluid and blood products.[67] Results of laboratory studies can be falsely reassuring as the studies are routinely performed after sample warming to 37°C, which does not reflect the current patient condition.[68]

Maintenance of normothermia is critical during vascular procedures. Measures that should be undertaken to prevent heat loss include ambient temperature control, the use of warming blankets to cover the body except for the surgical field, and the use of warm, humidified air in the ventilator circuit. Intravenous fluids and blood products can also be warmed with countercurrent warming systems. Warming of inspired air can contribute significantly to maintenance of normothermia, increasing patient temperature as much as 3.5°C in 20 minutes.[69] Efforts to minimize the duration of the procedure and the extent of blood loss are also effective. Generally, active rewarming approaches, such as body cavity lavage, cardiopulmonary bypass, and continuous arteriovenous rewarming, are reserved for severe hypothermia related to trauma or submersion injuries.[70]

ACIDOSIS

It is well recognized that acidosis impairs normal coagulation. Later studies have suggested that its major inhibitory effect is on thrombin generation in the propagation phase of clotting, although the exact mechanism has yet to be fully elucidated. As in hypothermia, prolonged bleeding times in acidosis are believed to be related to the slowing of enzymatic reactions. For example, a pH decrease from 7.4 to 7.0 results in a reduction in factor VIIa activity by more than 90% and in factor VIIa–tissue factor complex by more than 60%.[70,71] Acidosis is often seen in surgical settings related to bacteremia, in septic or cardiogenic circulatory compromise, and in other hypoperfusing states. In vascular surgery, it is often seen following reperfusion of large ischemic areas.

The most effective treatment of coagulopathy related to acidosis is to identify and address the underlying cause of the acidotic state. In sepsis, this process generally involves broad-spectrum antibiotics and aggressive drainage and/or débridement of infected tissue. If hypoperfusion is the cause of acidosis, volume repletion and inotropic support may be required. If reperfusion injury is anticipated, preemptive induction of respiratory and metabolic alkalosis prior to arterial clamp removal can reduce resulting acidosis.

DILUTION

Coagulopathy secondary to dilution is common and is frequently overlooked. Large-volume resuscitation in the form of red blood cells (RBCs) or crystalloid or colloid fluids result in decreased plasma concentrations of coagulation factors and platelets. This relative depletion can lead to coagulopathy, especially in the setting of active bleeding. Some reports also suggest that hydroxyethyl starches, gelatins, and dextran solutions impair platelet function and interfere with fibrin polymerization. Hypertonic saline is also recognized to have anticoagulant and antiplatelet effects.[70] Literature from the military has emphasized dilutional coagulopathy in the setting of massive transfusion. Studies have also demonstrated the importance of high ratios of FFP to packed RBCs (PRBCs) and, to a lesser extent, of platelets to PRBCs to prevent this problem in trauma resuscitations.[72,73]

TREATMENT

Treatment of clinically significant bleeding prioritizes therapies tailored to the etiology of bleeding and the maintenance of adequate perfusion. The surgeon should emphasize the determination of the cause of bleeding to appropriately tailor therapy. The currently available resuscitation and product replacement factors are summarized in Table 37.7.

Packed Red Blood Cells

PRBCs are the most commonly transfused blood component. They are typically used to replace intraoperative or traumatic losses and to restore oxygen-carrying capacity. After blood donation, RBCs are separated out to create a concentrated product with 42.5 to 80 g of hemoglobin. The idea of a threshold hematocrit to trigger transfusion is debated. There is a move toward administering transfusion only in the presence of symptomatic anemia or ongoing or expected significant blood loss. The reasons for this paradigm shift are multifold. Studies have demonstrated that transfusing RBCs to a target hemoglobin of 7 g/dL rather than 10 g/dL did not adversely affect patient outcome.[74,75] In addition to concerns regarding infection transmission and transfusion reactions, data have been published describing problematic storage lesions in banked blood that may actually worsen patient oxygenation rather than improve it with transfusion.[76] There are also studies demonstrating significantly worse outcomes with a liberal compared to a conservative transfusion strategy. These outcomes include increases in postoperative infections, in-hospital mortality, lengths of stay in hospital and intensive care unit, and the duration of mechanical ventilation.[75,77-81] The American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies recommends that in otherwise healthy patients, hemoglobin levels be maintained at 6 g/dL (60 g/L) or above.[82] The adequacy of oxygen delivery must be assessed in individual patients, particularly those with limited cardiac reserve or significant atherosclerotic vascular disease. The initiation of transfusion should be based on developing signs of

TABLE 37.7 Blood/Coagulation Factor Replacements for Achieving Hemostasis

Resource	Dose and Effects	Product Content	Use
Packed red blood cells	1 unit (350 mL) increases hemoglobin level by 1 g/dL (10 g/L)	Red blood cells	Symptomatic anemia (guideline hemoglobin level <6 g/dL if healthy), massive hemorrhage, decreased oxygen-carrying capacity
Platelets	1 unit (250 mL) increases the platelet count by 30,000-60,000/μL	Platelets, clotting factors	Thrombocytopenia, massive hemorrhage, platelet function deficit
Fresh frozen plasma	1 unit (250 mL)	All coagulation factors, especially factors II, VII, IX, and X, proteins C and S, and antithrombin III	Bleeding from warfarin therapy, massive transfusion, thrombotic thrombocytopenic purpura, coagulation factor deficiencies, antithrombin III deficiency
Cryoprecipitate	20 mL contains 200 mg fibrinogen, 70-80 units of factor VIII	Fibrinogen, factors V, VIII, and XIII, and von Willebrand factor	Hypofibrinogenemia, massive hemorrhage
Desmopressin	0.3-0.4 μg/kg	Stimulates release of von Willebrand factor	Uremic platelet dysfunction, some von Willebrand disease cases with bleeding
Vitamin K	10 mg intramuscularly, intravenously, or subcutaneously	Restores the function of factors II, VII, IX, X, protein C, and protein S	Liver dysfunction, bleeding from warfarin therapy
Protamine sulfate	1 mg neutralizes 100 units of heparin	Heparin antagonist	Reversal of heparin therapy
Factor VII	50 μg/kg (20-90 μg/kg)	Recombinant factor VIIa	Hemophilia, massive hemorrhage
Aminocaproic acid	0.1 g/kg loading dose, 1 g/h	Plasminogen inhibitor	Primary fibrinolysis

organ ischemia, the magnitude and rate of bleeding, and the patient's intravascular volume status.

Platelets

Standard platelet transfusion doses are prepared by pooling concentrated platelets from whole blood donated by four to six patients. A unit of platelets approximately comprises 250 mL and 3.5 to 4×10^{11} platelets. Such a dose is expected to increase the platelet count by 30,000 to 60,000/μL^3.[83] Single-donor apheresis platelets are also available. Potential advantages of these products include decreased risk of infectious transmissions and reduced alloimmunization. With the improvements in infection screening and leukoreduction techniques, these are likely no longer actual benefits and the use of the products simply increases the cost of platelet transfusion.[84] Generally accepted indications for platelet transfusion include prophylactic use in a patient with a platelet count less than 10,000/mm^3, and planned surgery or active bleeding in a patient with a platelet count less than 50,000/mm^3.[85] Early administration of platelets in massive transfusion treatment of major hemorrhage is also now recommended. Although not always possible, platelet transfusions should be avoided in patients with thrombotic thrombocytopenic purpura or autoimmune thrombocytopenias.

Fresh Frozen Plasma

Plasma consists of the acellular portion of blood, which is separated and frozen after donation. FFP contains all coagulation factors. Accepted indications for its use are severe bleeding or a planned operation in a patient requiring replacement of multiple factors (as seen in liver disease or DIC); as part of a massive transfusion to treat or prevent dilutional coagulopathy; bleeding or the need for quick invasive intervention in a patient taking warfarin; and specific coagulation factor deficit for which no factor concentration or directed therapy is available. ABO compatibility is required.[86]

Cryoprecipitate

Cryoprecipitate contains concentrated levels of fibrinogen, factor VIII, vWF, factor XIII, and fibronectin as well as platelet microparticles.[87] In the current era of factor concentrates, the primary indication for cryoprecipitate treatment is for hypofibrinogenemia (often due to consumptive coagulopathy, primary fibrinolysis, or therapeutic thrombolysis).[86] A single unit of cryoprecipitate provides 150 to 250 mg of fibrinogen and 80 units of factor VIII.[86,87]

Desmopressin

DDAVP is an arginine vasopressin analogue that stimulates release of vWF from the vascular endothelium.[88] Its initial uses focused on decreasing bleeding in patients with mild hemophilia A and vWD who required invasive interventions. Although the finding that DDAVP administration raises plasma levels of vWF and factor VIII seems to support this practice, extension of the practice to general use has not resulted in improved hemostasis.[89] A 2008 *Database Systematic* update found no evidence that DDAVP decreased perioperative transfusion requirements or any other clinically relative outcomes in patients without congenital bleeding disorders. It is still possible that patients with specific

congenital or acquired platelet disorders may benefit from this agent.[89]

Vitamin K

Patients requiring operative intervention are not infrequently undergoing long-term oral VKA (warfarin) therapy (mechanism previously described). Whether vitamin K administration will offer adequate reversal of the effect depends on the urgency of the planned intervention. In a study of patients taking warfarin (international normalized ratio [INR] 1.4-1.9) administered 1 mg of oral vitamin K 1 day prior to surgery, 77% had INR values lower than 1.2 on the day of surgery.[90] However, vitamin K treatment by any route does not allow the immediate reversal required for more urgent or emergency interventions. These patients generally require FFP. The most rapid and effective reversal of VKAs may be provided by administration of either prothrombin complex concentrate, recombinant factor VIIa, or both.[91,92]

Protamine Sulfate

Protamine sulfate is a small arginine-rich protein derived from salmon sperm nuclei. In order to reverse heparin effects, one administers 1 mg of protamine per 100 units of heparin administered in the last 6 hours. The use of this agent is plagued by a multitude of adverse reactions ranging from mild rash to life-threatening cardiovascular collapse. Previous exposure to protamine in this form or as neutral protamine Hagedorn (NPH) insulin predisposes patients to adverse reactions.[93] Vasectomy may also raise the risk of protamine-related events owing to the formation of antisperm antibodies via the exposure of blood to sperm (normally immunologically isolated in the testes). In a study of 243 patients undergoing cardiac surgery who received protamine sulfate, 26 had immediate protamine reactions; of these, 21 had previous protamine exposure (cardiac catheterization or surgery).[94] The precise mechanism of adverse protamine reactions is not well elucidated, but is believed to involve mast cell activation, complement activation, and antiprotamine antibodies. The most severe reactions are attributed to immunoglobulin G or E antibodies to protamine.[93]

Factor VIIa

Recombinant factor VIIa (rFVIIa) (NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) was developed and is approved by the US Food and Drug Administration (FDA) for uses related to hemophiliac patients in whom antibody development limits the use of standard factor replacement therapies. Since its introduction, off-label uses of rFVIIa have steadily increased. Common off-label uses include cardiac surgery, trauma, and intracranial hemorrhage.[95] Although some reports suggest a decrease in transfusion requirement with its use, current evidence does not demonstrate reduction in mortality or other commonly measured outcomes in the off-label use of this agent. There also persists a concern regarding increased thromboembolic events associated with the administration of rFVIIa. Additionally, the cost associated with the use of this agent is not negligible; it is approximately $7000 (USD) for a single 90 μg/kg dose.[96] Combat situations in which blood product supplies are limited may offer a reasonable off-label indication for rFVIIa.

Antifibrinolytic Agents

Aminocaproic Acid and Tranexamic Acid

Lysine analogues such as aminocaproic acid (Amicar) and tranexamic acid prevent the conversion of plasminogen to active plasmin. A 2011 *Cochrane-Database review* confirmed the role of lysine analogues in reducing perioperative blood loss and the need for allogeneic transfusion. The evidence analyzed in the review suggested greater efficacy for tranexamic acid than for aminocaproic acid.[97] These agents are reported to have good safety profiles and cost-benefit analyses when used for surgical patients with a high bleeding risk.[98,99]

Aprotinin

Aprotinin is a serine protease inhibitor with antifibrinolytic effects. It was withdrawn from the U.S. market following the BART (Blood Conservation using Antifibrinolytics in a Randomized Trial), in which a significant increase in renal failure and mortality was associated with the use of this agent.[100]

INTRAOPERATIVE BLEEDING

Intraoperative and traumatic bleeding should be immediately managed with manual pressure. Mechanical pressure allows temporary control while the surgeon rationally evaluates the type and extent of vascular injury, gains adequate exposure, and assembles the equipment required for definitive control. In the case of arterial bleeding, achieving proximal and distal control is a critical initial step allowing fastidious vascular repair. If there is a discrete source of bleeding, the need for pronged clamping of an artery, and no coagulopathy, systemic heparin can be administered.

The approach to venous bleeding is quite different because of the fragile, thin wall of the vessel and the more frequent extensive tributaries and branches. The risk of tearing or otherwise injuring veins is higher than for arteries and results in significant bleeding that can be quite difficult to control. Most small venous injuries can be adequately controlled with pressure, packing, or topical hemostatics. Extensive collateralization of the venous system often allows more liberal ligation of these structures without significant clinical consequence in comparison with arteries. The following sections describe tools used for intraoperative hemostasis.

Mechanical Tools

Electrosurgery

William T. Bovie is the pioneer of electrosurgery (often inappropriately referred to as electrocautery, which would imply heating of a probe rather than heating of tissue).[100] He invented the prototype of the electrosurgical unit that was first used by

neurosurgeon Harvey Cushing in October of 1926. The basis of electrosurgery is the finding that high-frequency current passes through the body, producing heat rather than evoking neuromuscular stimulation. Ohm's law (Eq. 3.1) and Joule's law (Eq. 3.2) are essential to the understanding of electrosurgery. Recall that in a circuit, voltage is proportional to applied current and resistance. Furthermore, the heat generated is a function of the applied current density (squared), tissue resistance, and time (Eq. 3.2).[101]

$$\text{Voltage} = \text{Current} \times \text{Resistance} \quad \textbf{(Equation 3.1)}$$

$$\text{Energy} = (\text{Current/Cross} - \text{Sectional Area})^2 \times \text{Resistance} \times \text{Time} \quad \textbf{(Equation 3.2)}$$

$$\text{Power} = \text{Voltage} \times \text{Current} \quad \textbf{(Equation 3.3)}$$

Energy application in electrosurgery can be monopolar or bipolar. For monopolar electrosurgery, the current passes from the probe, through the tissue, to a grounding pad that returns it to the generator (completing the circuit). In bipolar electrosurgery, no return electrode is necessary because both electrodes are incorporated in the forceps between which the target tissue is held.

Electrosurgical unit settings include cutting and coagulation modes. The differences between these modes are in current continuity and voltage. The surgeon adjusts the mode (cut vs. coagulate) and power settings on the unit but cannot directly manipulate the current or voltage. For a given power setting, cutting mode minimizes the voltage but functions continuously, yielding a high current density that heats tissue very rapidly, resulting in vaporization. In contrast, the coagulate mode maximizes the voltage and applies the current in an interrupted fashion. This results in deeper tissue penetration with lower current density. The intermittent nature of the application generates less heat and produces a coagulum.

For monopolar electrosurgery, adequate sealing of the grounding pad is mandatory to prevent pad site burns resulting from increased current density over the reduced surface area caused by an insufficient seal. Alternatively, with very poor grounding pad application, the current can be directed to another site, such as electrocardiogram electrodes, resulting in burn injuries remote from the surgical field. A related caveat is that monopolar surgery should be avoided in locations with a limited cross-sectional area over which to spread the current (e.g., penis or finger). Monopolar electrodes are preferred, however, when deeper tissue heating is necessary.

When using bipolar devices, the surgeon grasps the target tissue between the tines of the forceps, allowing alternating current to flow from one tine to the other. This maneuver limits the production of heat to the small area of tissue grasped and effects the selective application of heat, avoiding injury to adjacent structures. Less power is required than for monopolar devices because the distance between the electrodes is significantly reduced. Bipolar devices are also effective in saline solution because of the smaller area of application. The LigaSure (Covidien AG, Boulder, Colorado) is a sealing device that combines bipolar electrocautery with pressure application designed to fuse collagen and elastin in vessel walls, producing a hemostatic seal.

Argon Beam Coagulator

Monopolar devices can be enhanced by the addition of a stream of argon gas.[101,102] The column of argon gas passes over the tip of the electrode in a line with it. This arrangement adds several functions. First, the fully ionized gas beam disperses pooled blood from the target area, allowing the electrical energy to have an effect where it otherwise would not. As a noble gas, argon also allows arcing of the current from the electrode along the gas beam to the target tissue, making possible diffuse coagulation of surfaces along the line of the argon column.[101] It is of particular use over raw bleeding surfaces, such as the liver or spleen.

Radiofrequency Devices

The TissueLink device (Salient Surgical Technologies, Inc., Boston, Massachusetts) combines radiofrequency with continuous saline irrigation. It is designed to hemostatically seal cut bone and soft tissue.[103] The continuous and simultaneous application of saline is intended to decrease the temperature of the treated tissue, favoring mechanical sealing of the vessels rather than the coagulation and associated burning and charring seen with conventional electrosurgery.[104] The saline keeps the tissue temperature below 100°C (compared with up to 300°C seen with conventional devices). Luminal narrowing of target vessels is ascribed to collagen shrinking caused by the device.

The device is available in monopolar or bipolar forms for either spot application or painting of large raw surface areas. A disadvantage is the potential for "steam popping," which can occur if the temperature of the subsurface tissue exceeds the desired 100°C despite a surface temperature of 100°C.[105] This complication may result in steam formation and tissue disruption. Constant moving of the probe over the target surface rather than continuous static application over a small area can prevent this complication.

Topical Hemostatic Agents

Pusateri et al.[106] described the ideal topical hemostatic as (1) able to stop large vessel arterial and venous bleeding within 2 minutes of application to a wound even in a pool of blood, (2) ready to use without the need for special preparation or mixing, (3) simple to apply with minimal training, (4) lightweight and durable, (5) stable and functional for 2 years at room temperature and for several weeks at extreme ambient temperatures, (6) safe to use without the risk of injury to tissue or the transmission of infection, and (7) inexpensive. Though we are yet to develop a single agent fulfilling all of these criteria, many advances have been made.[107,108]

Mechanical Agents

Gelatin

Gelatin foam provides a physical matrix for clotting initiation and is available as Gelfilm and Gelfoam (both produced by

Pfizer Inc., New York) in film, sponge, and powder forms. The powder is mixed with a sterile saline solution and applied as paste to sites of bleeding. Because Gelfoam paste is associated with less infection and inhibition of bone healing, it is a good alternative to bone wax for stopping bleeding from bony surfaces, such as a sternotomy incision.[109] It is important to note that Gelfoam swells more than collagen or cellulose products and can double its volume. Although this feature can enhance mechanical hemostatic action, swelling can also cause compressive complications, especially when the product is used near nerves or in confined spaces. Gelatin foam is absorbed within 4 to 6 weeks and is largely nonantigenic despite its origin from animal products. Unlike oxidized cellulose, the pH of gelatin foam is neutral; therefore, it can be used in conjunction with thrombin or other pH-neutral biologics to enhance hemostatic action.

Oxidized Cellulose

Oxidized regenerated cellulose is branded as Surgicel Fibrillar and Surgicel Nu-Knit (both produced by Ethicon, Inc., Somerville, New Jersey). The material offers handling characteristics superior to those of gelatin foam, and the knitted fabric can be trimmed to fit any size. It does not stick to instruments and can easily be held firmly against bleeding tissue until hemostasis is achieved. Surgicel Fibrillar resembles cotton in consistency and remains pliable when laid into a wound. These products should not be moistened before use because greater hemostatic effect is exerted when they are applied dry.

Oxidized cellulose products result in a decreased local pH. There are theoretical advantages to this effect, including antimicrobial effects and hemostatic effects. Disadvantages of acidity include inactivation of other topical agents, such as thrombin (which should not be used together with cellulose) and potential increases in inflammation resulting in delayed wound healing.[110]

The observed discoloration of cellulose products following blood contact are attributable to low pH resulting in RBC lysis and hematin generation. Only the minimal necessary amount of product should be applied, with any excess agent removed after hemostasis is achieved.

Collagen

Microfibrillar collagen (MFC) is derived from bovine corium and available in several forms:

- A powder form, which is a fluffy, white-appearing dry material that conforms well to irregular surfaces: Avitene Flour (C.R. Bard, Inc., Murray Hill, New Jersey), Helitene (Integra LifeSciences Corporation, Plainsboro, New Jersey), and Instat (Ethicon, Inc.)
- A nonwoven sheet: Avitene and EndoAvitene (both C.R. Bard, Inc.)
- A sponge: Avitene Ultrafoam and Avitene UltraWrap (both C.R. Bard) and Helistat (Integra LifeSciences Corporation)
- A pad: Instat (Ethicon, Inc.)

Platelets adhere to the fibrils on the collagen's surface, resulting in activation and granule release. This results in platelet aggregation and thrombus formation with expected hemostasis in 2 to 5 minutes. Because this mechanism depends on functional platelets, its utility is limited in severe thrombocytopenia but retained in the setting of heparinization.

MFC should be applied with dry instruments because it adheres to gloves. It does not swell significantly, though adherence to neural structures should be avoided. Excess material should be removed after adequate hemostasis is attained. Blood from areas where this product is used should not be returned to the patient because the material may pass through the filters of blood-scavenging systems.

Polysaccharide Spheres

The synthetic agents known as polysaccharide spheres—Arista (Medafor, Inc., Minneapolis, Minnesota) and Trauma Dex—are designed to absorb plasma or blood and to concentrate clotting factors and platelets on their surfaces, forming a matrix that promotes clot formation. They require no preparation or delay for use. Disadvantages of these agents include a tendency to swell as well as a high sugar content, which limit use in closed spaces and in diabetic patients, respectively.

Active Hemostatic Agents

Thrombin: Liquid/Gel Products

Thrombin promotes the conversion of fibrinogen to fibrin and forms the basis of a fibrin clot. The original thrombin products used medically were of bovine origin; however, despite their reported efficacy, they demonstrated a tendency to result in antibody formation, which negatively affected outcomes in cardiac surgery as well as hemodialysis access (mostly involving coagulopathy and bleeding issues).[111-114] Recombinant human (Recothrom, The Medicines Company, Parsippany, New Jersey) and human plasma-derived (Evithrom, Ethicon, Inc.) thrombins were developed in response to these issues. In a phase II, randomized, double-blinded, comparative trial of topical recombinant human thrombin with bovine thrombin in surgical hemostasis, recombinant human thrombin was found to have comparable efficacy, a similar safety profile, and significantly less immunologic response in comparison with bovine thrombin.[115]

Thrombin: Solid Products

TachoComb (NYCOMED Austria GmbH, Linz, Austria) is a collagen (equine) sheet coated on one side with human fibrinogen, bovine thrombin, and bovine aprotinin. The three components are distributed in layers that dissolve on contact with blood, allowing the formation of fibrin, which seals the wound by binding the collagen sheet to it.[116]

TachoSil (Takeda Pharmaceuticals International GmbH, Zurich) was developed in response to the realization that topical products containing aprotinin can have potential adverse effects, including anaphylaxis and renal injury. Therefore, TachoSil is made without aprotinin and with human rather than bovine-derived thrombin. This product is found to have equivalent hemostatic effects too, but has a lower risk of side effects than TachoComb.[117]

Sealants

FloSeal, Tisseel, Evicel

Fibrin sealants consist of two primary components that are mixed on application. Tisseel (Baxter International Inc., Deerfield, Illinois) combines human fibrinogen, human thrombin, and calcium chloride. Its mechanical strength is determined by the fibrin concentration. Thrombin concentration determines the speed of clot formation and tensile strength. This product does contain small amounts of aprotinin, which may carry the aforementioned risks of this agent. Evicel (Ethicon, Inc.) is a similar, later-developed product composed of fibrinogen and human-derived thrombin that lacks aprotinin.

FloSeal (Baxter International, Inc.) comprises a gelatin matrix of bovine collagen and microgranules cross-linked with glutaraldehyde and human thrombin.[118,119] The cross-linked gelatin granules swell on contact with blood, offering an additive tamponade effect. FloSeal was found to be superior to Gelfoam-thrombin in cardiac surgery and was shown to successfully reduce bleeding when used for open and laparoscopic nephrectomy.[118,120]

Dry Fibrin Sealant Dressings

A dry fibrin sealant dressing consists of gauze embedded with lyophilized fibrinogen and thrombin. It is a solid-phase delivery mode for the clotting factors to promote and support clot formation. Its advantages include a long shelf-life and a lack of requirement for pre-mixing. Its use is limited in some forums by the brittle nature of the material.

Tissue Glue

Several unique characteristics render tissue glues potential vehicles for drug delivery. They have a predictable pattern of biodegradability, can be applied in a site-specific manner, and are biocompatible.[58] BioGlue (CryoLife Inc., Kennesaw, Georgia) contains glutaraldehyde and bovine serum in addition to the tissue glue component. A scaffold is created by cross-linking of albumin to wound proteins.

Newer Agents

Chitins

The modified Rapid Deployment Hemostat (mRDH, Marine Polymer Technologies, Inc., Danvers, MA) bandage is a lyophilized matrix of acetylated, poly-N-acetyl glucosamine-containing nanofibers. The bandage rapidly binds and absorbs plasma proteins from blood. The nanofibers interact with receptors on platelets to stimulate activation and coagulation as well as agglutinating and activating RBCs. These interactions with platelets and RBCs result in the generation of thrombin and the deposition of a fibrin mesh. In addition to the formation of this hemostatic plug, thromboxane (from the activated platelets) and endothelin-1 (from endothelial contact with the bandage) effect vasoconstriction.[121] Case series from military use support the efficacy of this agent for at least temporary control of hemorrhage.[117,122]

Chitosans

Chitosans are a deacetylated form of chitin. The gauze base of agents such as HemCon (HemCon Medical Technologies, Inc., Portland, OR) and TraumaStat (Ore-Medix, Salem, OR) contains silica and polyethylene, which interact with wound blood and coagulation factors to promote rapid hemostatic plug formation in a manner similar to that displayed by chitins.[123]

Mineral Zeolite

Mineral zeolite agents such as QuikClot (Z-Medica, Wallingford, Connecticut) function by absorbing water, an action that concentrates platelets and clotting factors to accelerate hemostasis. They may also activate factor XII. Multiple studies have demonstrated this to be a very rapid and effective manner to achieve hemostasis.[124,125] However, this mechanism is realized via an exothermic reaction that has been demonstrated to cause nontrivial parenchymal thermal injuries in the region of application. A newer version, QuikClot Advanced Clotting Sponge, is intended to create a less exothermic reaction.[123]

Lysine Analogues

The topical application of lysine analogues has been best studied in cardiac and orthopedic procedures. These antifibrinolytic agents act by preventing the binding of plasminogen to fibrin (thus countering the action of t-PA released from endothelial cells in response to surgical trauma). Of the four randomized, controlled, blinded studies of tranexamic acid in cardiac surgery, all showed less postoperative bleeding than with placebo; only one demonstrated a reduction in the perioperative transfusion requirement. In orthopedic surgery, topical or intra-articular tranexamic acid similarly reduced blood loss. A sole study evaluated the use of aminocaproic acid in cardiac surgery. It demonstrated decreased blood loss in the first 24 postoperative hours (although accumulated loss prior to chest tube removal was not significantly different in the aminocaproic acid and the placebo arms) and a lower transfusion requirement in patients receiving aminocaproic acid. None of the studies evaluating topical lysine analogue use has been considered adequately tailored or powered to determine thrombotic or other potential risks (Table 37.8).[108]

POSTOPERATIVE BLEEDING

When patients demonstrate signs or symptoms of bleeding in the immediate postoperative period, a critical decision point is to determine whether it represents medical or surgical bleeding. Thus, while instituting aggressive, goal-directed resuscitation, the surgeon should be assessing the nature of the bleeding. Adjuncts in this process include coagulation parameters such as PT and aPTT, as well as the platelet count. If there is a suspicion or suggestion of consumptive coagulopathy, additional useful tests include fibrinogen, FDPs, and TT.

Management of postoperative bleeding hinges on its etiology. Surgical bleeding should be initially managed with manual pressure while the patient is transported back to the operating

TABLE 37.8 Intraoperative Hemostatic Tools: Advantages and Disadvantages

Hemostatic Agent	Products	Mechanism of Action	Specific Advantages	Specific Disadvantages
		Mechanical Agents		
Gelatin	Gelfoam Gelfilm Surgifoam (Ethicon, Inc.)	Matrix for clot formation Mechanical barrier to bleeding	Immediately available for use; stored at RT Can be used with thrombin/saline Conforms to wounds	Not for use in infected fields or near neural elements due to swelling risk Intravascular use should be avoided
Oxidized cellulose	Surgicel Surgicel NuKnit Surgicel Fibrillar BloodSTOP (LifeScience PLUS, Inc., Mountain View, CA)	Matrix for clot formation	Immediately available for use; stored at RT Small pieces easy to manipulate into small spaces	Not for use in closed spaces due to swelling risk Cannot be combined with thrombin
Microfibrillar collagen	Avitene Helitene Instat	Matrix for clot formation/strengthening Enhances platelet activity	Immediately available for use; stored at RT	Not for use in closed spaces Cannot be combined with saline/thrombin
Polysaccharide spheres	Arista	Hydrophilic effect dehydrates blood Concentrates solid components, resulting in barrier	Immediately available for use; flexible storage temperature	Not for use in closed spaces due to swelling risk Not for ophthalmologic, neurologic, or urologic procedures Limitations in diabetes due to sugar content of spheres
	TraumaDex (microporous polysaccharide hemospheres)	Absorbs plasma-concentrating coagulation factors and platelets, forming gel matrix for clot formation	No preparation	With sterilization, no risk of infection
		Active Hemostatic Agents		
Synthetic or plasma-derived	Recothrom (recombinant human)	Actively converts fibrinogen to fibrin	Stored at RT and reconstituted with saline	Cannot be used in patients hypersensitive to hamster/snake proteins
	Evithrom (plasma-derived)	Actively converts fibrinogen to fibrin		Frozen liquid form (takes at least 1 h to prepare) Contraindicated in patients with human blood product allergies
	TachoSil (equine collagen patch with human fibrinogen and thrombin)	Human thrombin converts fibrinogen to fibrin and polymerization yields coagulation effect; mechanical collagen effect	Stored at RT Patch placed directly on bleeding Modification of TachoComb (aprotinin should be avoided)	Human plasma-derived Infection risks Cannot be used in neurologic or urologic procedures
	TachoComb (sponge)	Collagen sheet, one side coated with human fibrinogen and bovine thrombin and aprotinin		Aprotinin content risks anaphylactic reactions and renal injury
		Sealants		
Polyethylene glycol	Coseal	Polyethylene glycol matrices cross-link in and with wound	Fast-acting Not exothermic	Not for use in closed spaces due to significant swelling

TABLE 37.8 Intraoperative Hemostatic Tools: Advantages and Disadvantages—cont'd

Hemostatic Agent	Products	Mechanism of Action	Specific Advantages	Specific Disadvantages
Fibrin sealants	Tisseel	Fibrinogen source	Does not need active bleeding to polymerize (prophylactic)	Frozen: 5-105 min to thaw
	Evicel	Fibrinogen source	No mixing required Does not need active bleeding to polymerize (prophylactic)	Frozen: at least 10 min to thaw Should be avoided in patients with known severe reactions to human blood products
Thrombin sealants	FloSeal (gelatin thrombin suspension)	Human and bovine thrombin formulation resulting in mechanical and active hemostasis contributions	3-min reconstitution Stored at RT	Should be avoided in ophthalmologic procedures
	Dry Fibrin Sealant Dressings (gauze embedded with lyophilized fibrinogen and thrombin)	Provides fibrinogen and thrombin	Has longer shelf-life than other sealants and does not require mixing	Brittle material causes handling and packaging issues
Bovine-derived factors	BioGlue (glutaraldehyde and bovine serum; glue)	Glutaraldehyde cross-links bovine albumin to wound proteins to make scaffold	Fast-acting Flexible use environment (temperature, moist)	Hypersensitivity reactions Theoretic mutagenic potential
		Newer Agents		
Chitin	mRDH (Modified Rapid Deployment Hemostat) (gauze)	Mobilizes clotting factors, platelets, RBCs Mechanical sealant Vasoconstrictive	Very portable	No known significant adverse effects Gauze backing and small size[101] Varied results with severe injuries
Chitosan (deacetylated form of chitin)	HemCon, TraumaStat (granules) Chitogauze (HemCon Technologies), Celox (MedTrade Products Ltd., Crewe, United Kingdom), Hemogrip (Remedium Technologies, Inc., College Park, MD)(gauze)	Hemostatic plug forms on thrombin and fibrin mesh formed on gauze by receptor-based contact with RBCs and platelets	Antimicrobial properties Immediately available for use, stored at RT	No known adverse effects Cannot be used in patients with shellfish allergy Very user dependent
Mineral zeolite	QuikClot (combat gauze, granules, mesh bags)	Absorbs water from blood, thus concentrating platelets and clotting factors and promoting rapid local hemostasis Activates factor XII	Stored at RT, immediately available for use	Exothermic (burn) Foreign body reaction
Lysine analogues[102]	Tranexamic acid Aminocaproic acid	Antifibrinolytics block the binding of plasminogen to fibrin		

RBCs, Red blood cells; *RT,* room temperature.

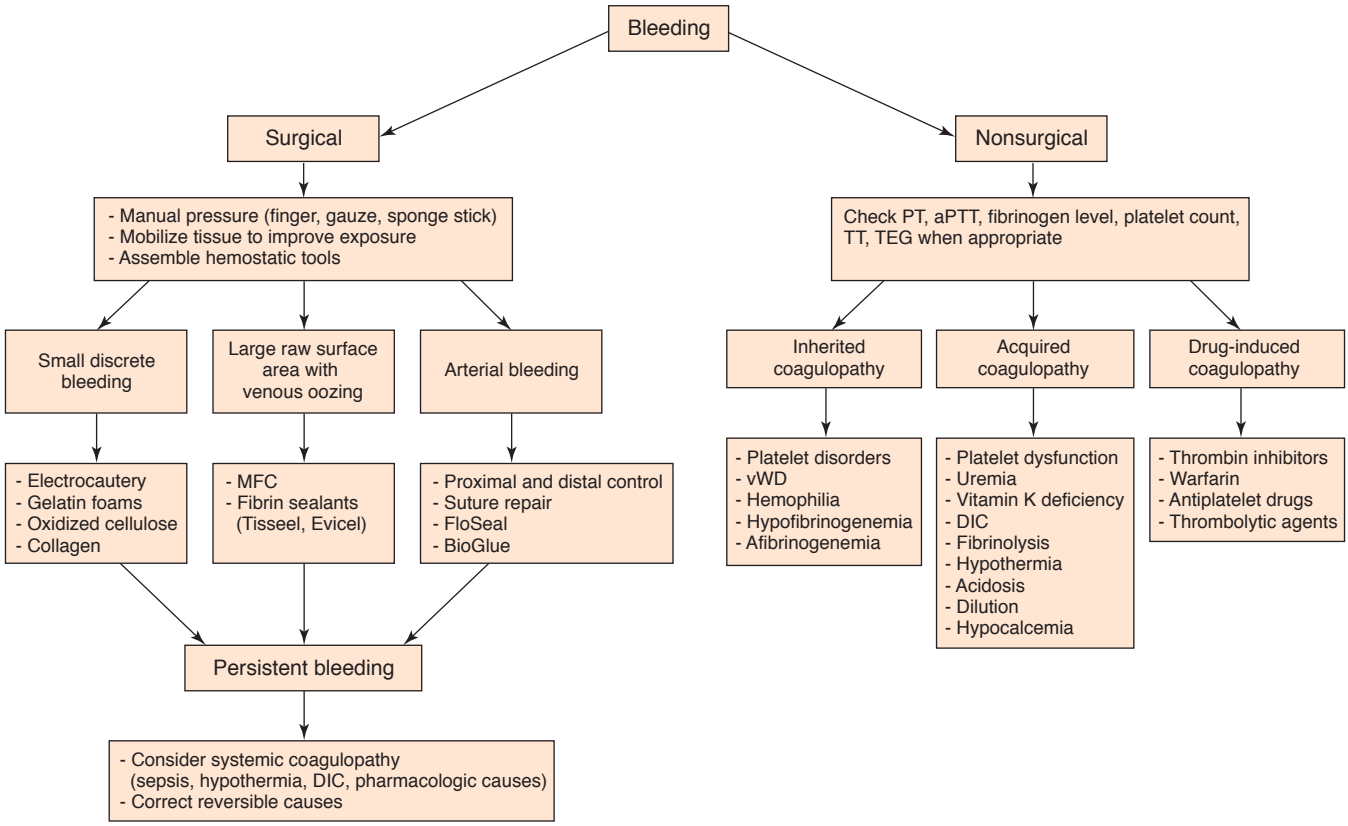

Figure 37.1 Causes and management of perioperative bleeding. *aPTT,* Activated partial thromboplastin time; *DIC,* disseminated intravascular coagulation; *MFC,* microfibrillar collagen; *PT,* prothrombin time; *TEG,* thromboelastography; *TT,* thrombin time, *vWD,* von Willebrand disease.

room. Here, small discrete bleeding may require a topical hemostatic, sutures, or a simple electrosurgery application. Large raw surfaces with venous oozing may be best managed with argon beam therapy or conventional electrosurgery application rather than a topical agent. Arterial bleeding is best addressed by rapid attainment of proximal and distal control followed by suture repair with or without the addition of topical agents.

Nonsurgical/medical bleeding is generally due to an isolated inherited or acquired coagulopathy or a diffuse coagulopathy related to surgery, sepsis, or massive resuscitation. Specific factor or blood element deficiencies can be treated with replacement. Drug-induced coagulopathies can sometimes be directly reversed. Homeostasis-related or diffuse coagulopathies require the correction of all involved factors, normothermia, and the correction of acidosis and dilution. Coagulopathy-related bleeding events are generally not best served by a return to the operating room. Fig. 37.1 summarizes the causes of and treatment strategies for perioperative bleeding.

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CHAPTER 38

Hypercoagulable States

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Thromboembolism is an enormous problem across the spectrum of medicine. Approximately 10 million individuals in the United States have symptomatic peripheral artery disease, and approximately 100,000 arterial reconstructive procedures are performed annually.[1] In the United States and Europe, more than 600,000 people will experience a venous thromboembolism (VTE), and nearly 20% will die as a result.[2] The incidence of arterial embolism and VTE is highly age dependent, contributing significant morbidity and mortality to an aging population.[3-5]

More than 150 years ago, the great German pathologist, Rudolf Virchow, proposed the concept known as *Virchow's triad.* He observed that thrombosis occurred when the following three situations were present; vascular wall (endothelial) injury, stasis of blood, and changes in the consistency of blood that enhances coagulation (hypercoagulability). An understanding of the latter, now termed the hypercoagulable state, was least apparent and could not be further characterized until there was a greater understanding of the normal mechanisms of hemostatic regulation (see Chapter 36). In the last 40 years, a number of inherited

and acquired hemostatic disorders have been characterized that are associated with an increased risk of venous and/or arterial thrombosis. In most circumstances, the relationship between specific hemostatic defect and the hypercoagulable state is readily apparent by the respective role in normal hemostasis. However, the mechanism(s) by which other well-documented hypercoagulable defects (e.g., the antiphospholipid syndrome or elevated homocysteine) contribute to an increased risk of venous and arterial thrombosis remain poorly understood. The interactions of these hypercoagulable defects, alone or in combination, or when combined with other transient factors, such as vascular injury from surgery or trauma, can result in a significant increased risk of thrombosis. The interaction between inherited hypercoagulable defects and acquired additional factors, such as age or acute illness, can result in what has been termed an increased "thrombosis potential," which, upon reaching a "thrombosis threshold," can result in symptomatic thromboembolism.[6]

PATHOPHYSIOLOGY

Hemostasis is a highly organized series of reactions involving platelet adhesion and activation to form the platelet plug, followed by activation of coagulation proteins in a series of controlled enzymatic reactions to generate thrombin. Thrombin potentiates platelet aggregation and activation, and acts on fibrinogen to generate the insoluble fibrin clot. Under normal conditions, these reactions occur on the endothelial surface only at sites of endothelial injury. This limits the size of the clot and allows blood to remain liquid and flowing. When this balance is altered, excess thrombin is generated, and abnormal thrombosis may occur. Therefore, thrombosis can result from defects in normal hemostasis that either increase the procoagulant activity or decrease the naturally occurring anticoagulants. These hypercoagulable defects have been termed thrombophilic syndromes and have been further classified as either congenital or acquired thrombophilias.[6,7]

In addition, there is a group of other disorders whose prothrombotic mechanisms are poorly understood. These include elevations of homocysteine (hyperhomocysteinemia) and lipoprotein(a) (Lp[a]). The management of patients with thrombosis with these disorders remains controversial.[8-13]

Arterial thrombosis, unlike VTE, is associated with conditions that primarily affect the vascular wall and endothelium. Endothelial disruption, which occurs with atherosclerosis, vasculitis (vascular inflammation), infection, trauma, or surgery, is most often associated with an arterial thrombotic event. In well-controlled population studies, the majority of congenital hypercoagulable defects associated with venous thrombosis are not associated with a statistical increased risk of arterial thromboembolism.[14-17] The few congenital hypercoagulable defects that may be associated with an increased risk of both venous and arterial thrombosis, such as hyperhomocysteinemia or increased Lp(a), are also associated with an increased risk of arterial atherosclerosis.[8,9,18-20] Other defects associated with an increased risk of arterial thromboembolism, such as those observed with increased levels of fibrinogen and von Willebrand factor, are known to enhance platelet function.[21,22]

CONGENITAL HYPERCOAGULABILITY

Although the thrombosis potential or risk of thrombosis for inherited prothrombotic defects have been well characterized in a number of prospective and retrospective population studies, it is important to understand that thrombosis is a multigenetic and multifactor disorder. The thrombosis potential for specific congenital thrombophilic abnormalities is classically defined as a relative risk of thrombosis compared with a patient population without these abnormalities.[6,7,14-16] In most circumstances, patients who inherit more than one abnormality have a significantly higher risk of thrombosis potential or a relative risk of thrombosis.[6,7,14-16,23] However, patients may have additional risk factors, such as aging, oral contraceptive (OC) use, hormone replacement therapy (HRT), pregnancy, cancer, infection, trauma, or surgery. In these circumstances, a patient's individual risk also can be increased by a factor that is more than the sum of each individual risk factor.[23]

Classification

Crowther and Kelton[7] proposed a simple classification system that divides the congenital hypercoagulable (thrombophilic) states associated with VTE into two broad groups (Table 38.1). The first group constitutes defects associated with the reduced levels of the natural anticoagulants, such as antithrombin, protein C, and protein S.[7] The defects in this "loss of inhibition" group are much less common, but are associated with a significantly higher risk of thrombosis.[7] The second group is associated with defects that result in a "gain in procoagulant function" due to increased levels or function of coagulation factors.[7] These include factor V Leiden (activated protein C resistance [APCR]) and prothrombin G20210 mutations, increases in coagulation factors VIII, IX, and XI, and the dysfibrinogenemias. Although these defects have a lower thrombosis potential, they are more frequently found in the general population, and therefore, are more commonly associated with clinical thrombosis. The understanding that certain defects alone or in combination can be associated with a significantly higher risk of thrombosis may be important in determining the physician's approach to antithrombotic prophylaxis, the duration of anticoagulation after venous thrombosis, and family screening for patients with these defects.

Group 1 Thrombophilia

Group 1 includes deficiencies of the naturally occurring anticoagulant factors antithrombin, protein C, and protein S. All are rare, representing less than 1% of the population.[7] However, they are highly prothrombotic, with 30% to 50% of carriers (heterozygote) having a symptomatic thrombotic event before they reach 60 years of age.[7] A significant number of carriers will have had a spontaneous thromboembolic event before the age of 40 years. Frequently, there is a strong family history of venous thrombosis. Although the risk of thrombosis is high, routine prophylactic anticoagulation in ambulatory healthy individuals has not been demonstrated to be of benefit and

TABLE 38.1 Venous Thromboembolism and Inherited Thrombophilias

Abnormality	Frequency in General Population (%)	Frequency in Patients With VTE (%)	Relative Risk	Reference
Antithrombin	0.02	4-7.5	8.1-21	14-16, 23, 26-29
Protein C	0.2	2.5-6	7.3-11	15, 16, 23, 28, 29, 44, 45
Protein S	Unknown	1.3-5	8.5-32	15, 16, 23, 45
Factor V Leiden (APCR) heterozygote	2-7	10-19	2.5-7	6, 16, 17, 23, 67-73
Factor V Leiden homozygote	0.015	1.5	80	16, 70, 75
PT G20210A heterozygote	1-4	5-10	1.7-3	6, 86-90, 94
PT G20210A homozygote	Unknown	Unknown	Unknown	
Factor VIII	11	25	4.8	6, 99
Homocysteine	5-10	10	2-4	6, 118-122

APCR, Activated protein C resistance; *PT*, prothrombin; *VTE*, venous thromboembolism.
The Factor V Leiden and Prothrombin G20210A mutations are predominantly in populations of European descent.

should be reserved for high-risk situations, such as surgery, sepsis, pregnancy, and immobilization.[7] Because of the high risk of recurrence, with group 1 deficiencies and patients homozygous for certain group 2 abnormalities, lifelong anticoagulation may be recommended after a spontaneous thrombotic event.[7,24]

Antithrombin Deficiency

Pathogenesis and Incidence

Physiologically, antithrombin is the most important inhibitor of thrombin and other activated clotting factors (e.g., factors Xa, IXa, and VIIa). Antithrombin physiologic activity is enhanced 1000-fold by the binding of naturally occurring or administered heparin or heparin sulfates.[25] Antithrombin deficiency is rare, reportedly occurring in an estimated 0.02% of the general population in a study that screened samples from healthy blood donors.[26,27] It has been reported in 4% to 7.5% of patients with VTE.[14-16,28,29] Antithrombin inheritance is autosomal dominant.[30] More than 250 mutations within the molecule have been described.[31] Homozygosity, particularly for antithrombin deficiency types I and II, is extremely rare and appears to be incompatible with life. Homozygosity for antithrombin deficiency results in a severe thrombophilic phenotype.[32]

Types

There are three general subtypes of antithrombin deficiency.[31] Type I is characterized by decreased antithrombin functional activity and antigen. Type II defects are antithrombin mutations that have reduced functional activity, but normal antigen levels resulting from a mutation in the active inhibitory site on the protein. Type III antithrombin mutations are characterized by moderate decreased activity due to impaired interaction with heparin. Screening for antithrombin deficiency should always be undertaken using a functional assay, because screening with an antigen assay may fail to diagnose type II and III defects. In the presence of low antithrombin activity, further characterization can be made with an antigen assay.

Patients with antithrombin deficiencies are at a significantly higher risk of thrombosis than patients with other congenital deficiencies. Approximately 60% of carriers of type I and II deficiencies will have a thrombotic event by the age of 60 years. The risk for type III deficiency may be lower.[33,34] A strong family history of thrombosis is usually present. A Spanish Multi-Center study reported the relative risk of thrombosis in these thrombophilic families as 21-fold.[29] A multicenter, multinational European Prospective Cohort on Thrombophilia (EPCOT) study reported an adjusted relative thrombotic risk of 17.5 (95% confidence interval [CI], 9.1 to 33.8).[23] After the diagnosis of antithrombin deficiency is made in an individual with thrombosis, screening of family members is recommended.

Clinical Presentation and Management

The clinical presentation of antithrombin deficiency is predominantly lower extremity thrombosis with or without pulmonary embolism.[30,33,35] Recurrent events are common, and atypical thrombotic events involving the portal, mesenteric, and hepatic venous system, or cerebral veins have been reported.[29,36,37] Arterial events are rare, and patients are not at increased risk more than the unaffected adult population.[14-16,23] Pregnancy is a particularly high-risk situation, and prophylaxis with heparin is indicated throughout pregnancy and in the immediate postpartum period.[35,38] Patients with breakthrough events can receive antithrombin concentrates.[39] An acquired form of antithrombin deficiency has been reported in pregnant women with the fatty liver syndrome with disseminated intravascular coagulation (DIC).[40] Treatment with plasma or antithrombin concentrates rapidly reverses the coagulopathy.[40]

Protein C Deficiency

Pathogenesis and Incidence

Protein C is a vitamin K-dependent anticoagulation protein that is activated by thrombin to activated protein C (APC).[41] When thrombin levels are high, thrombin binds to the endothelial protein receptor, thrombomodulin (TM), which changes

the specificity of thrombin from cleaving fibrinogen or activating platelets to activating protein C. Protein C binds to its specific endothelial receptor, termed the endothelial protein C receptor, which enhances its activation. APC is a potent serine protease anticoagulant that cleaves the coagulant cofactors VIIIa and Va, thus modulating thrombin generation and subsequent clot formation.[41,42] Deficiency of protein C is found in 0.2% of the general population, and in 2.5% to 6% of patients with VTE.[28,29,43,44]

Types

Similar to antithrombin deficiency, multiple mutations resulting in protein C deficiency have been reported. These mutations have been classified into two general subtypes: type I mutations have reduced functional and antigenic protein levels; and type II mutations have reduced functional levels but preserved antigen levels of the protein.[45] Adult heterozygous patients with protein C deficiency usually have activity levels of less than 60%.

Clinical Presentation and Management

Patients who have VTE usually present in the lower extremities. Unusual sites of thrombosis have been reported and are similar to those seen with antithrombin deficiency.[41,42,44,45] Although rare arterial events have been reported, large cohort studies do not support an increased risk of arterial events.[46] In protein C deficient patients from thrombophilic families who present with an unprovoked (idiopathic) thrombosis, recurrent thrombotic events are frequent. Life-long anticoagulation should be considered in these patients, particularly those who present before the age of 40 years.

Homozygosity for protein C deficiency, with absent protein C activity, may present at birth as a neonatal disorder termed purpura fulminans.[47] This disorder is characterized by diffuse microvascular thrombosis of the skin and systemic organs. Immediate treatment with heparin, plasma, or protein C concentrates can be lifesaving.[47] The majority of homozygous neonates with protein C deficiency will have functional levels less than 20% of normal.[47]

A similar severe disseminated thrombotic disorder, characterized by skin necrosis, can occur in heterozygous patients with protein C deficiency treated with higher doses of warfarin, usually without concomitant anticoagulation with heparin.[48,49] The syndrome, termed warfarin necrosis, results from the disproportional decrease in protein C in comparison to other procoagulant vitamin K-dependent coagulation factors. Patients presenting with this disorder should be treated with fresh frozen plasma, vitamin K, and heparin.[48,49] The syndrome can be prevented by initiating oral anticoagulation with lower doses of warfarin and concomitant use of heparin.

Protein S Deficiency

Pathogenesis and Incidence

Protein S is the vitamin K-dependent cofactor necessary for the inactivation of factors Va and VIIIa by APC. A deficiency in protein S is phenotypically similar to protein C deficiency. Protein S exists in two forms: the functionally active free form that usually constitutes 20% to 40% of the total protein, and the remaining 60% to 80% that is active and bound to complement binding protein C4b.[50,51] Most patients with protein S deficiency will have activity levels between 50% and 75% of normal.[50-52]

Types

Similar to the other natural anticoagulant proteins, protein S deficiency can be classified into 3 subtypes: type I is characterized by reduced functional and antigen protein levels; type II has reduced functional activity, but normal antigen levels; and type III has normal antigen levels, but reduced free active protein S due to enhanced C4b binding.[53] Type I and type III protein S deficiencies are the most common forms of the deficiency encountered, and do not appear to differ in their risk of venous thrombosis.[54]

The measurement of protein S activity and antigen can be confounded by a number of physiologic and clinical conditions. In pregnancy, protein S levels fall in the second and third trimesters.[55,56] Reduced protein S levels have also been reported in patients with active cancer, lupus erythematosus, antiphospholipid antibody syndrome (APLAS), sepsis, chronic inflammatory disorders (e.g., inflammatory bowel disease) and in advanced HIV disease.[57-69]

Clinical Presentation and Management

Protein S deficiency is clinically characterized by venous thrombosis and has been frequently reported in association with venous thrombosis in atypical sites.[50-52,60,61] These reports may be confounded by other comorbidities in these patients that can be associated with acquired protein S deficiency. In addition, several reports have suggested a relationship between low protein S levels and arterial thrombosis, including a reported association between low free protein S and cardiolipin antibodies in stroke patients.[62]

Like protein C deficiency, homozygous deficiency can be associated with neonatal purpura fulminans. Approach to management is similar to that of homozygous protein C deficiency.[63] Warfarin necrosis can also develop in heterozygote protein S patients.[63]

Group 2 Thrombophilia

Although associated with a lower thrombosis potential than Group 1 thrombophilia, Group 2 hypercoagulable disorders are more frequently found in the general population and are found in a greater proportion of patients with VTE. They represent gain of function mutations resulting in increased thrombin generation. They are typified by either increased synthesis of specific coagulation factors or as observed with factor V Leiden, resistance to the inactivation of this cofactor by APC.

Factor V Leiden (Activated Protein C Resistance)

Pathogenesis and Incidence

Factor V is a cofactor that accelerates the conversion of factor II (prothrombin) to thrombin by factor Xa. Under normal

circumstances, factor V is degraded by the serine protease, APC, which cleaves the protein at two sites. Factor V Leiden has a mutation in the 506 position that results in a substitution of glycine for arginine. This renders one of the factor V cleavage sites resistant to the action of APC, which, like all coagulation serine proteases, cleaves arginine bonds.[64-66] This results in a slowing of the inactivation of the cofactor, which leads to increased thrombin generation.

Factor V Leiden is a common mutation, occurring in approximately 2% to 7% of individuals of European ancestry.[66-68] It can be found in nearly 10% of people with VTE and in 30% to 50% of individuals being evaluated for thrombophilia.[66-69] The mutation is very rare in native Asians and Africans.[68,69] The mutation is also rare in African Americans (0.6%) and has not been reported in Native Americans.[68,69] Compared with patients with group 1 thrombophilia, patients with factor V Leiden have a lower relative risk of thrombosis, estimated between 2.5- and 7-fold.[16,17,23,70-73] A cross-sectional study from Italy found that only 6% of carriers of the mutation developed a thromboembolic event by the age of 65 years.[74] Homozygotes are at much higher risk than heterozygotes, with an estimated relative risk of 80-fold.[16,70,75] However, heterozygotes with combined defects have a significantly increased risk of VTE.[16,23,74] A second, very rare, mutation of the second factor Va cleavage site (Arg306Thr) has also been reported to be associated with increased risk of thrombosis, whereas other studies have failed to find a relationship of this mutation with the development of VTE.[76]

Clinical Presentation and Management

The clinical presentation of thrombosis with factor V Leiden is overwhelmingly venous. Rare, unusual thrombosis sites, such as the cerebral vein and the retinal vein, have been reported.[77,78] The onset of thrombosis is frequently at an older age than seen in patients with type 1 thrombophilia.[17] In the Physicians Health Study, the risk of VTE in men with the factor V Leiden mutation did not become statistically significant until after the age of 50 years.[17] The study also found no association with the factor V Leiden and an increased risk of stroke or myocardial infarction.[17] Thrombosis is frequently triggered by transient risk factors, such as a prolonged plane flight, OC use, or pregnancy.[79-82] In women carriers of the mutation, the reported thrombosis risk associated with the use of second-generation OCs varies widely, ranging from 6- to 50-fold.[79-82] The wide variation reported in the thrombotic risk of OCs may be explained, in part, by a higher risk of thrombosis in women more than 30 years old who are taking OCs and some variation in the specific OCs used in the European studies, some of which contain prothrombotic progesterone substitutes.[82]

There is no excess mortality in carriers of the factor V Leiden mutation. No prophylaxis is recommended for carriers except what is recommended by guidelines for surgical interventions. Antepartum prophylaxis is not recommended for women who have not had a previous thrombotic event or a history of recurrent fetal loss.[83] The risk of recurrent VTE after cessation of oral anticoagulation is not greater than that observed in other patients with unprovoked VTE.[84]

Prothrombin Gene Mutation G20210A

Pathogenesis and Incidence

The prothrombin G20210A mutation is an abnormality located at the untranslated 3′ end of the prothrombin gene that results in increased plasma levels of prothrombin. The mutation affects the 5′ end cleavage signal, leading to increased prothrombin mRNA stability.[85] The thrombotic risk is relatively low.[86-88] The gene frequency in the European population is about 1% to 4%, with the greatest frequency in southern Europe and Spain.[89,90] It is present in 5% to 10% of patients with VTE, and 15% of patients with thrombophilia.[86-90] Similar to factor V Leiden, the prothrombin G20210A mutation is very rare in Native Asians, Native Africans, African Americans, and Native Americans.[91] Many carriers with a history of VTE have coinheritance of the factor V Leiden mutation.[23,92] The relative risk of thrombosis is low in carriers of the prothrombin mutation, ranging from two- to threefold higher in carriers compared with noncarriers of the mutation.[93,94]

Clinical Presentation and Management

The clinical presentation is predominantly venous thrombosis of the lower extremities, and unusual sites are rare.[86-88,93,94] Some controversy exists as to whether the prothrombin mutation is associated with an increased risk of arterial thrombosis.[94-96] In carriers of the mutation who develop thrombosis, studies to date have shown either no increase in risk or only a slight increased risk of recurrent VTE after discontinuation of anticoagulation.[94,97]

The risk of VTE in women on OCs has been reported to be significantly increased, similar to that reported for factor V Leiden.[93] Women who are carriers of both the prothrombin G20210A mutation and the factor V Leiden mutation have a markedly high risk of VTE.[93] An association between the development of cerebral venous thrombosis in women carriers of the prothrombin mutation taking OCs has been reported, in which 20% of patients carried the mutation versus only 3% of controls.[98]

Elevated Factors VII, XI, and IX

Pathogenesis and Incidence

Koster et al.[99] first reported an increased risk of VTE in patients with an elevated factor VIII coagulant protein of more than the 90th percentile (>150%). Factor VIII activity levels more than 150% were associated with an adjusted relative risk of 4.8% compared with factor VIII levels 100% or less.[99] These elevations appear to be independent of ABO blood type and were measured in patients without evidence of inflammation confirmed by a normal erythrocyte sedimentation rate (ESR) and C-reactive protein.[100,101]

Subsequent studies have supported this observation and found both a family and racial clustering suggestive of an inherited propensity for increased factor VIII levels.[100,102] A study of African American women found a statistically higher level of factor VIII compared with the white and Asian population in the United States.[103] Unlike female carriers of the factor V Leiden

and prothrombin mutations, the use of OCs did not appear to significantly increase the risk of VTE.[104] Elevations of factor VIII activity have also been associated with an increased risk of recurrent VTE.[105]

The measurement of factor VIII activity is confounded by the fact that factor VIII, along with its carrier protein, von Willebrand factor, is an acute phase reactant and increases with bleeding and inflammation.[100,101] Therefore, measurement of factor VIII activity should be performed with a simultaneous acute phase marker, such as the ESR or C-reactive protein. The assay should also be repeated at least twice at distant time intervals.[99-101] Each laboratory must define the 90th percentile range for its own population to determine the patient population at risk.

Clinical Presentation and Management

The clinical presentation of patients with elevations in factor VIII activity is predominantly VTE of the lower extremities.[99] Because factor VIII levels increase with inflammation, the elevation of this coagulation protein is an important cofactor in the development of thrombosis associated with infection, inflammatory bowel disease, and cancer. There is controversy as to whether increased levels of factor VIII are associated with arterial thrombosis, because elevations in factor VIII activity are associated with increases in von Willebrand factor. Increased levels of von Willebrand factor have been shown in population-based studies to be associated with an increased risk of arterial thrombosis.[106]

Increased levels of factors IX and XI have been associated with a twofold increase in the risk of VTE.[107,108] These are relatively weak risk factors for thrombosis, but if combined with other defects, they may become significant. To date, no molecular markers have been reported to characterize these elevations in factors VIII, IX, and XI.[109]

Other

Hyperhomocysteinemia

An association was made between markedly elevated levels of homocysteine and arterial vascular disease in individuals with homocysteinuria.[110,111] Additional studies confirmed this association and found additional evidence that individuals with homocysteinuria also experience an increased incidence of VTE.[110] Subsequent studies found an association between elevations of plasma homocysteine and an increased risk of atherosclerosis and arterial thrombosis in apparently healthy individuals.[112-120] Additional studies that focused on risk factors for venous thrombosis reported a similar association.[120-123]

Homocysteine metabolism involves two enzymatic pathways that require essential vitamin cofactors: folate, vitamin B_{12}, and vitamin B_6 (pyridoxine).[124] The vitamine B_6-dependent pathway involves the enzymatic conversion of homocysteine to cystathionine by the enzyme cystathionine-β-synthase (CBS).[111,124] The second pathway involves remethylation of homocysteine back to methionine requiring folate, vitamin B_{12}, and the two enzymes 5,10-methylenetetrahydrofolatate reductase (MTHFR) and methionine synthetase.[124] The primary mutations responsible for homocysteinuria are in the CBS gene.[111] However, in the general population, independent of deficiencies in the vitamin cofactors, a common mutation in the MTHFR gene at position 677 is most frequently associated with elevations in homocysteine.[124] This C to T mutation results in a 50% reduction in the enzymatic activity of the gene.[124] However, even in MTFR C677T homozygotes, folate supplementation or a diet intrinsically rich in folate can reduce homocysteine levels into the normal range.[124,125]

The reported mechanisms by which homocysteine increases the risk of both arterial and venous thrombosis include (1) a direct toxic effect on endothelium; (2) enhanced platelet activation; (3) oxidation of low-density lipoprotein cholesterol; (4) an inflammatory decrease in endothelial TM; and (5) an increase in von Willebrand factor and factor VIII.[124] However, no single reported effect of homocysteine adequately explains its prothrombotic effect in both the arterial and venous vasculature.

A number of cohort studies and some prospective studies have found a statistically significant association between elevated homocysteine and an increased risk for myocardial infarction and stroke with estimated risks of 2- to 7.8-fold for individuals in the highest quartile.[112-114] However, several prospective studies have failed to confirm this association.[115-117] Data from the Physicians' Health Study,[117] the Atherosclerosis Risk in Communities Study,[118] and the Women's Health Study[115,116] suggest a gender-defined risk for elevated homocysteine in which the risk is most significant in women. Elevations of homocysteine have also been found in case-controlled studies to be a weak risk factor for VTE, with a relative risk of only 2 to 4.[117-123] Meta-analyses further confirmed an increased risk in patients with homocysteine levels more than the 95th percentile.[123]

Complicating the issue of elevated homocysteine as a risk factor for both arterial and VTE disease is the lack of response, in randomized controlled trials, to lowering homocysteine in reducing the risk of recurrent arterial[10-12] and VTE[13] disease in patients treated with vitamin therapy.

The measurement of homocysteine in patients can be complicated by comorbid conditions, such as vitamin deficiency, renal insufficiency, and improper plasma collection and handling. Measurements are best performed using freshly collected plasma, preferentially with patients in the fasting state. It is reasonable to repeat the assay on at least two separate occasions. Studies to date do not support an advantage for determination of the MTHFR genotype over direct measurement of homocysteine.[125]

Lipoprotein(a)

Lp(a) is a serum lipoprotein composed of a low-density lipid particle with a disulfide link to a long polypeptide chain, apolipoprotein(a).[20,126] The protein has "kringle-like" domains that compete with tissue plasminogen activator, plasminogen, and plasmin for binding to fibrin and endothelial annexin II, thereby inhibiting fibrinolysis.[126,127] The plasma levels of Lp(a) vary greatly within and between different racial populations, with African Americans having higher levels.[128] Also, Lp(a) may increase as an acute phase reactant[129,130] and has been reported to be elevated in certain inflammatory rheumatologic disorders.[131]

Early retrospective studies suggested a relationship between elevated levels of Lp(a) and the risk of premature atherosclerosis and arterial thrombosis.[132-134] However, prospective studies have been less supportive and at the most suggest only a small increase in risk for individuals with elevated plasma Lp(a).[135-141] Additional reports have suggested a role for elevated Lp(a) as an independent risk factor for VTE,[142,143] although a failure to find an association has been reported by other investigators.[144]

Sticky Platelet Syndrome

Sticky platelet syndrome (SPS) is an inherited, autosomal dominant disorder associated with early-onset myocardial infarction and peripheral vascular disease.[145-147] Although most often associated with arterial vasculopathy, VTE has been reported.[145-147] A causal relationship to early miscarriage has also been reported. Patients usually present with a history of myocardial infarction or thromboembolism as young adults. The events often are precipitated by stress.[145-147] The defect appears to be common in patients with unexplained thromboembolic events. In an analysis of 200 patients and family members identified with SPS, 21% had arterial thromboembolic events and 13.2% had VTE events.[146] SPS platelets demonstrate hyperreactivity to epinephrine and adenosine diphosphate (ADP) even with dilution, but have normal responses to thrombin, collagen, and arachadonic acid.[145-147] Three types of platelet responses have been noted: type I is hyperreactive to both ADP and epinephrine; type II is hyperreactive to epinephrine only; and type III is hyperreactive to ADP only. Increased arterial events may be mediated through polymorphisms of glycoprotein IIIa allele PLA-A2.[148] Although other investigators have reported similar hyperreactivity of platelets in patients with ischemic stroke,[149] there remains controversy as to whether SPS represents a true congenital prothrombotic syndrome. In patients with documented platelet reactivity and thrombosis, low-dose acetylsalicylic acid (81 mg) appears to be effective in inhibiting platelet hyperreactivity.[147]

Idiopathic (Unprovoked) Venous Thrombosis

Unprovoked or idiopathic venous thrombosis is defined as the development of deep vein thrombosis and/or pulmonary embolism in the absence of known genetic prothrombotic mutations, permanent factors, or acquired risk factors. Patients who develop VTE provoked by surgery, trauma, immobilization, pregnancy, or female hormone intake are at low risk of recurrent thrombosis.[150,151] Patients with unprovoked VTE have a recurrence risk of 5% to 10% per year, with nearly 50% developing a recurrent event by 10 years.[150,151] A recent prospective clinical trial evaluated whether D-dimer screening 4 weeks after completion of 6 months of warfarin for unprovoked VTE could predict risk of recurrence off anticoagulation.[152] The study found males, even with low D-dimer levels continue to have a greater than 7% annual risk of recurrent VTE.[152] Women with low D-dimer levels and women with estrogen associated VTE have a significantly lower risk of recurrent VTE. A prospective study that screened 66 patients with idiopathic venous thrombosis found abnormalities in 26 (39.3%) patients when they were screened for thrombophilia (antithrombin, protein C, protein S, factor V Leiden, prothrombin G20210A, antiphospholipid antibodies).[153] Therefore, 60% of patients with unprovoked VTE have no underlying known major inherited or acquired thrombophilia and still remain at high risk of recurrent VTE. It has been proposed that an underlying inflammatory state may be responsible for the increased risk of VTE in patients with unprovoked events.[154,155] Laboratory assessment of patients with idiopathic VTE have demonstrated higher levels of interleukin (IL)-6 and IL-8 with low levels of IL-10 compared with age- and sex-matched controls.[156] It is notable that the same inflammatory markers are linked to an increased risk of atherothrombotic disease.[154-157]

ACQUIRED HYPERCOAGULABILITY

An increased risk of thrombosis can be associated with a variety of acquired abnormalities. Disorders such as the APLAS and cancer are significant prothrombotic syndromes.[158,159] Common clinical situations such as cancer, pregnancy, infection, and estrogen use are transient causes of hypercoagulability.[160-162] Surgery is a well-documented transient cause of hypercoagulability in which the risk of thrombosis is related to a number of factors, such as the type of surgery, the duration of surgery, the age of the patient, and other patient comorbidities.[162] A significant iatrogenic thrombotic disorder is heparin-induced thrombocytopenia (HIT), in which early diagnosis and treatment may be lifesaving.[163] Chronic inflammatory and autoimmune disorders, such as inflammatory bowel disease, Behcet's syndrome, or lupus erythematosus, with and without antiphospholipid antibodies, are also associated with a significant risk of thrombosis.[164-167]

Acquired elevations in factor VIII levels or depressions in protein S may be important contributing factors to a number of prothrombotic disorders, including cancer, pregnancy, infection, and chronic inflammatory disorders. In patients with cancer, the expression of tissue factor by the malignant cell further increases the thrombotic risk.[168,169] Paroxysmal nocturnal hemoglobinuria, a rare hemolytic disorder in which nearly half of the patients develop symptomatic thrombosis, has been shown to be associated with both increased platelet activation and increased leukocyte tissue factor expression.[170,171] Thrombosis in patients with myeloproliferative syndromes frequently involves unusual sites, such as the portal and hepatic veins, and is more often associated with syndromes associated with the Janus kinase-2 (JAK-2) mutation.[172-175] The presence of JAK-2 mutation has also been shown to be associated with thrombosis in the splanchnic, portal, and hepatic veins, even in the presence of normal blood counts.[175]

Antiphospholipid Antibody Syndrome

The APLAS is one of the more common causes of acquired hypercoagulability.[158,159] The syndrome is associated with an increased risk of both arterial and venous thrombosis.[158,159] Although the APLAS can occur with systemic lupus erythematosus (SLE), 50% of the patients do not fulfill criteria for lupus

or other autoimmune disorders.[176] The syndrome is characterized by the presence of antibodies that inhibit in vitro coagulation reactions, the lupus anticoagulant (LA), and antibodies that bind to anticardiolipin and β_2-glycoprotein.[158,159] Clinical criteria include a history of either thrombosis and/or pregnancy complications with fetal loss.[177]

Pathogenesis and Incidence

There is strong epidemiologic evidence to support a relationship between the presence of these antiphospholipid antibodies and thrombosis.[158,148,178] There appears to be a differential risk with the highest risk of thrombosis associated with the presence of an LA and high titer immunoglobulin-G (IgG) anticardiolipin antibody.[158,178] The Leiden Thrombophilia Study, a large population-based, case-control study of unselected patients with a first episode of venous thrombosis, found a 3.6-fold increased risk for deep venous thrombosis for individuals positive for LA (odds ratio [OR], 3.6; 95% CI, 1.2 to 10.9).[178] However, patients who were positive for both the LA and either antiprothrombin or anti-β_2-glycoprotein-1 antibodies had an estimated 10-fold increased risk of VTE (OR, 10.1; 95% CI, 1.3 to 79.8).

The syndrome is something of a paradox in that this thrombotic disorder is characterized by antibodies that prolong in vitro coagulation tests, most commonly, the activated partial thromboplastin time (aPTT). The mechanism(s) by which these antibodies result in thrombosis remains unclear.[179] Activation of monocytes, platelets, and endothelial cells by antibody/β_2-glycoprotein-1 complexes has been implicated in the etiology of thrombotic events.[180-183] Antibodies to annexin II on endothelial cells, tissue plasminogen activator, and plasmin have been proposed as additional antigenic targets.[182] Complement (C5a)-mediated inflammation has been demonstrated to be associated with increased thrombogenicity and recurrent fetal loss.[179,183]

Diagnosis

Laboratory diagnosis of the APLAS should include screening for LA with two different assay systems.[177] Assessment of anticardiolipin antibodies should include screening for both IgG and IgM antibodies.[177] Anti-β_2-glycoprotein-1 screening can provide further confirmatory evidence for the diagnosis.[177] Positive tests should be confirmed 12 weeks after the initial screen, because transiently positive values may be seen during infections, during autoimmune hemolytic anemia, and with malignancy.[177]

Clinical Presentation and Management

APLAS has been associated with both arterial and VTE.[158,159,176] No laboratory test can distinguish patients at risk for either an arterial or venous event. However, recurrent events most often recur in the vascular sites of previous thrombosis.[184] Thrombosis at unusual sites is well described with the APLAS, including multiple arterial emboli due to nonbacterial thrombotic endocarditis.[184] Retrospective studies have reported a risk of recurrence as high as 50%.[185,186] However, recent prospective treatment trials have estimated the risk to be somewhat lower, but still significant, with a relative risk of recurrence after stopping oral anticoagulants of 4- to 7.7-fold.[187-189] This has led to consensus recommendations to consider extended or indefinite anticoagulation for patients with the APLAS and thromboembolism.[24]

Two prospective randomized trials in patients with APLAS associated thrombosis compared moderate- to high-intensity warfarin (prothrombin time [PT] international normalized ratio [INR] 2.0 to 3.0 vs. 3.0 to 4.0) for secondary antithrombotic prophylaxis. Both trials demonstrated that moderate-intensity warfarin was equivalent to high-intensity treatment with a lower risk of bleeding complications.[188,189] Assessing adequate anticoagulation with the PT INR may, at times, be difficult in the rare patient with an LA that affects the PT test.

A catastrophic form of APLAS designated as CAPS is a life-threatening variant of the disorder characterized by diffuse macro- and microvascular thrombosis with multiple organ involvement.[190] Prompt recognition and treatment with corticosteroids and heparin, and in refractory cases, plasmapheresis, can be lifesaving.[190]

Cancer

Pathogenesis and Incidence

The etiology of thrombosis in patients with cancer is complex, including expression of tissue factor by tumor cells and malignancy-induced inflammation resulting in prothrombotic hemostatic changes in blood, such as increases in fibrinogen, factor VIII, and platelet count.[160,191,192] Additional prothrombotic risk factors frequently encountered by the cancer patient include compression and invasion of vessels by tumors, surgical procedures, indwelling catheters, and systemic chemotherapy.[161,191-193]

The association of cancer with an increased propensity for thrombosis has been recognized since 1861, when Armand Trousseau made his seminal presentation.[194] According to various studies, the incidence of clinically significant VTE ranges from 1% to 43% among cancer patients, depending on the type and stage of the tumor, the modality of cancer treatment, contributing risk factors, and comorbidities.[160,195-198] Cancer patients receiving chemotherapy are at a significantly higher risk of VTE.[160,194,195] In comparison to patients without cancer, cancer patients have an approximately 7-fold increased risk of VTE, and with metastatic disease, the risk may be as high as 20-fold.[161] Furthermore, the identification of unsuspected pulmonary emboli among cancer patients at autopsy and by highly sensitive computed tomography scanning, which is now used for routine staging, suggests that VTE remains an underdiagnosed phenomenon.[198,199]

Clinical Presentation and Management

Venous

Cancer patients with VTE have a threefold higher incidence of recurrent thrombosis and a higher risk of treatment-related bleeding than patients without cancer.[200,201] In a prospective study comparing patients with and without cancer who were newly diagnosed with VTE and treated with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) followed by oral warfarin, the 12-month cumulative incidence

of recurrent VTE among the cancer patients was 20.7% versus 6.8% among patients without cancer, although the degree of anticoagulation achieved was superior among the cancer patients.[201] Recurrences were more likely in patients with more extensive disease. The 1-year cumulative incidence of major bleeding was 12.4% in cancer patients, as opposed to 4.9% in patients without cancer, with no difference in the number of patients who had levels of anticoagulation above the therapeutic range.[201] The results of these retrospective studies resulted in a reassessment in the use of warfarin for secondary antithrombotic prophylaxis in cancer patients with VTE. Subsequent clinical trials[202,203] and resulting guidelines[204,205] now recommend against the use of warfarin in favor of long-term LMWH for the management of cancer-associated VTE.

Arterial

Arterial thromboembolic events account for 10% to 30% of the thrombotic complications in cancer patients.[160] Cancer patients, who, in general, represent an older age population, have the same risk factors for arterial thrombotic events, such as stroke or myocardial infarction, as older patients without cancer. However, the impression emerges of a greater risk imposed by the presence of a malignancy. As with VTE, systemic therapy of cancer may increase the risk of arterial thrombosis. In a meta-analysis of five completed cancer trials using chemotherapy plus the antiangiogenic agent, bevacizumab, the incidence of arterial thromboembolic events was 3.8%, twice that seen in patients who received chemotherapy alone.[205] The mortality associated with these events was 0.8%, again twice that seen with chemotherapy alone.

Cerebral emboli resulting in infarction may result from underlying nonbacterial thrombotic endocarditis (NBTE). NBTE may be the most common cause of stroke in patients with solid tumors.[206,207] NBTE is the cardiac manifestation of systemic hemostatic activation in the cancer patient, resulting in the formation of platelet and fibrin vegetations on cardiac valves. In one study, atherosclerosis accounted for 14.5% of symptomatic cerebral infarcts compared with 18.5% of thrombotic events associated with NBTE.[208] Of patients with NBTE, 30% to 70% have laboratory evidence of overt DIC.[206,207,209] Although NBTE is more frequently diagnosed with advanced malignancy, patients with localized or occult malignancy have been reported.[206,207] In autopsy series, NBTE has been detected in 0.9% to 1.3% of patients dying of cancer.[208-210] Antemortem diagnosis of NBTE with transesophageal echocardiography (TEE) has the greatest diagnostic yield.[207] However, a negative TEE cannot completely exclude the diagnosis of NBTE in cancer patients with new-onset stroke or other arterial thrombotic event. Hemostatic studies to look for DIC should be performed before NBTE is ruled out.[207-209]

Pregnancy and Oral Contraceptives

Pregnancy

Pathogenesis and Incidence

Pregnancy induces an acquired prothrombic state due to hormone-related elevations of fibrinogen, factor VIII, reduced protein S, and depressed fibrinolysis.[55,56] Therefore, it is not surprising that the incidence of VTE significantly increases for patients who have underlying inherited thrombophilia.[211] Patients with congenital deficiencies of AT-III and proteins C or S are eight times more likely to have thromboembolic complications during pregnancy compared with controls, and are more likely to have antepartum thromboembolism.[35,80,83,211] Heligren et al.[80] reported, in a noncontrolled study of northern European pregnant patients with VTE, that 60% had the factor V Leiden mutation. In a case-controlled study of 119 women with a history of VTE during pregnancy and postpartum, the prevalence of factor V Leiden was 43.7% compared with 7.7% among normal women.[212] The prothrombin G20210A mutation was detected in 16.9% of women with VTE compared with only 1.3% in the nonpregnant controls.[212] In an Italian case-controlled study, 39% of women presenting with their first venous thrombotic event during a pregnancy had a thrombophilic defect.[213] Factor V Leiden was the most commonly associated thrombophilia.[214]

The risk of VTE associated with pregnancy is increased four- to sixfold compared with comparable age-matched nonpregnant patients.[211-213,215,216] The overall incidence of VTE, as estimated by the Rochester Epidemiology Project (Olmsted County, Minnesota) from 1966 to 1995, was 199.7 per 100,000 woman-years.[211] Greer[215] estimated the acute antepartum risk of deep venous thrombosis to be 0.6 per 1000 in women younger than 35 years and 1.2 per 1000 in women older than 35 years. VTE is a leading cause of maternal mortality in the United States, representing 11% of maternal deaths.[216] Thromboembolism can develop any time during pregnancy; the lowest risk occurs in the first trimester, but the risk does not increase during the last 20 weeks of gestation.[212] The postpartum period accounts for greater than 50% of pregnancy-related VTEs.[212,216-218] The incidence is higher after cesarean section than vaginal delivery.[217] The left leg is affected in 90% of cases, which is felt to be due to a compressive effect on the left iliac vein by the right iliac artery where the two blood vessels cross.[219-221,214]

Clinical Presentation and Management

Women with a history of pregnancy-associated thrombosis without documented thrombophilia can have antepartum prophylactic anticoagulation withheld, but should be followed closely and receive prophylaxis in the immediate postpartum period.[83] Patients with congenital deficiencies, such as antithrombin, protein C, protein S, and antiphospholipid syndrome, should be considered for both ante- and postpartum prophylaxis, even if they have not had a previous thromboembolic event. Patients with the factor V Leiden mutation should receive prophylaxis in the peri- and postpartum periods (6 weeks), unless they have had an antepartum thrombosis with a previous pregnancy. Pregnant patients with active thrombosis should receive a full dose of LMWH.

Oral Contraceptives

Pathogenesis and Incidence

Estrogen alone as HRT or when used in combination with progestin in OCs is a well-documented risk factor for venous

thrombosis.[222-225] A reduction in the estrogen content of OCs from 150 μg to the present preparations containing 15 to 20 μg resulted in a reduction of arterial thrombotic events in American studies, but not European studies.[226-229] The progestagen component of OCs was changed from the second-generation compounds (levonorgestrel, norgestrione, norgestrel) to the third-generation agents (desgestrel, gestodene) in the hope of lower androgenic effects and beneficial effects on high-density lipoprotein cholesterol levels. However, these third-generation progestagen compounds were associated with a doubling of the risk of VTE compared with second-generation agents.[230-232]

The first-generation OCs were associated with a 10-fold increased risk of VTE that decreased to a 4-fold risk with the second-generation OCs.[232-234] The third-generation OCs containing the newer progestagen compounds have a two- to threefold increased risk of VTE over second-generation OCs.[232-234] A meta-analysis including case-controlled studies and cohorts performed before October 1995 estimated the overall adjusted ORs for third- versus second-generation OCs to be 1.7 (95% CI, 1.4 to 2.0).[234] The role of OCs in the development of venous thrombosis in unusual sites remains controversial. A meta-analysis of studies on risk factors associated with cerebral venous thrombosis estimated a sixfold increased risk for users of OCs,[235] whereas a study of risk factors for the development of portal vein thrombosis failed to document an increased risk for users of OCs.[236] Retrospective studies have demonstrated that the combination of OC use and inherited thrombophilia has a multiplicative effect on the risk of VTE.[81,82,93,237-239]

Case-controlled studies[240,241] and randomized clinical trials[242-244] of HRT in postmenopausal women demonstrated a two- to threefold increased risk of VTE without demonstrable benefit in the reduction of cardiovascular disease. The risk appeared to be the highest in the first year and significantly higher in women with thrombophilia.[245,246] A recent case-controlled study suggested that transdermal estrogen replacement might be associated with a lower risk of VTE, even in women with inherited thrombophilia.[247,248]

Heparin-Induced Thrombocytopenia

Heparin use in cardiac and vascular surgery patients is ubiquitous. Therefore, the differential diagnosis of thrombocytopenia in these patients must include consideration of HIT. HIT is the most significant adverse event associated with heparin use. It is an immunopathologic disorder that places patients at a significant higher risk of developing venous and arterial thrombotic complications and is associated with a substantial mortality.[163,249-255] Although HIT is associated with thrombocytopenia, it is not a bleeding disorder.

Pathogenesis and Incidence

HIT is an immunologic disorder in which there is a polyclonal antibody response against neoantigens expressed on platelet factor 4 (PF4) upon binding to heparin.[256,257] Platelet activation is mediated solely by IgG antibodies directed against the heparin-PF4 complex.[258,257,259] The larger heparin molecules contained in UFH induce larger PF4 bundles, resulting in greater antibody binding. This may explain the greater incidence of HIT observed with UFH as opposed to LMWH or fondaparinux.

Upon binding to the heparin-PF4 complex, the Fc domain of the HIT IgG antibodies activate platelets through the platelet Fc receptors.[260,261] Upon activation, platelets release significant membrane microparticles,[262] which express P-selectin capable of activating monocytes and inducing tissue factor expression, the initiator of the coagulation cascade.[263] However, heparin-PF4/HIT IgG complexes have also been reported to independently induce tissue factor expression and cytokine release from monocytes and macrophages.[264] The resulting activation of coagulation leads to significant thrombin generation, which, in turn, results in further platelet activation and thrombocytopenia. In many ways, clinical HIT can be viewed as similar to DIC because both syndromes are mediated by excessive thrombin generation.[265] Although venous thrombosis predominates over arterial thrombotic events at a rate of 4:1, the targeting of specific thrombotic events in patients with HIT can be explained, in part, by the clinical circumstances associated with the development of HIT.[251] Patients who develop HIT during the treatment of venous thrombosis are most likely to develop new or progressive VTE. Antecedent arterial events may precipitate additional arterial thromboses. If HIT is not diagnosed promptly and appropriately treated, thrombotic events at multiple sites can occur, as seen in patients with DIC.[266] The incidence of HIT varies depending upon the patient population, the duration and type of heparin utilized, and the medical or surgical procedure.[249-253,267,268-272]

Diagnosis and Management

The diagnosis of HIT is based upon clinical findings, including the development of thrombocytopenia and/or thrombosis during or immediately following heparin use.[163,250,251,256,267] Rapid-onset HIT can occur as early as 24 hours of heparin treatment in patients who have been exposed to heparin within the previous 100 days and have developed HIT antibodies.[273] Although the development of thrombocytopenia or an unexplained decrease in the platelet count (>50% of pretreatment baseline) during heparin exposure is the clinical hallmark of this disorder, thrombotic sequelae can develop in 30% to 70% of HIT patients, and this accounts for much of the morbidity associated with this diagnosis.[252,253,256,267] The thrombotic death rates in these retrospective studies are between 4% and 5%.[252,253,256,267] Thrombotic complications may occur even when the platelet count nadir remains greater than 150×10^9/L.[256] Severe thrombocytopenia (platelet count <20 K) is rare with HIT. In large clinical studies of HIT, the median platelet count nadir has been in the range of 50 to 60×10^9/L.[252,253,267] The development of new thrombosis or progression of an existing venous or arterial thrombosis in a patient receiving heparin, particularly if accompanied by a drop in the platelet count, is highly suggestive of HIT.

Appropriate platelet monitoring is essential to the early diagnosis of HIT. In heparin-naive patients, the platelet count should be monitored every other day, beginning 5 days after starting heparin. In patients with previous heparin exposure, the platelets should be monitored with the start of heparin use.

A 50% or greater decrease in platelet count from the pretreatment platelet count should alert the clinician to the development of HIT.[163,250,274] The development of platelet activating, noncomplement fixing IgG antibodies directed against the complex of heparin and PF4 is the hallmark of this immunopathic disorder.[273,259,258,274] Therefore, confirmation of a clinical suspicion of HIT requires serologic screening for HIT-associated heparin/PF4 antibodies.[273,259,257] Prospective studies of heparin/PF4 antibody formation indicate that clinical HIT occurs in a minority of patients who form antibodies.[275] Antibody detection can be performed by either the use of functional assays that detect antibodies capable of inducing platelet activation (serotonin release assay), or by a PF4/heparin immunoassay (enzyme-linked immunosorbent assay [ELISA]). The more readily available heparin/PF4 ELISA has significant sensitivity (>90% to 95%) and specificity (80% to 90%).[274] Therefore, a negative ELISA has a strong negative predictive value of more than 95%, suggesting an alternate diagnosis for thrombocytopenia. A strongly positive ELISA is also more likely to be associated with a positive functional assay as determined by either a washed platelet C^{14}-serotonin-release assay (SRA) or heparin-induced washed platelet aggregation assay.[274] A positive platelet SRA or platelet aggregation assay has a reported sensitivity of greater than 90% and specificity for clinical HIT of greater than 95%.[274] The combined use of both the PF4/heparin ELISA and a functional assay provide a diagnostic sensitivity approaching 100% for clinical HIT.[274]

Prompt recognition of the disorder, immediate cessation of all forms of heparin and rapid initiation of a direct thrombin inhibitor, such as argatroban, lepirudin, or bivalrudin, is essential in preserving life and limb (see Chapter 39). Approximately 50% of patients with HIT characterized by thrombocytopenia alone will develop thrombosis if managed with only the discontinuation of heparin.[251] The use of warfarin alone in these patients is not protective, and warfarin loading after a diagnosis of HIT can result in severe thrombotic complications, such as ischemic limb gangrene.[251,276] Other thrombotic complications reported in patients with HIT include overt DIC with hypofibrinogenemia, adrenal necrosis, and cutaneous necrosis at the sites of heparin injections.[163,256] HIT appears to be a unique event in many patients, without recurrence. However, patients within 100 days of diagnosis should not receive any form of heparin therapy.[273,277] Patients beyond 100 days may receive heparin if indicated, but they should have daily platelet counts monitored. Antibody testing should be closely followed to make sure the patient does not have a recurrence.

Obesity

Obesity, as defined by a body mass index (BMI) greater than 25 kg/m^2, has been shown to be a comorbidity and an independent risk for VTE. In a prospective study of risk factors, the Copenhagen City Heart Study, a BMI of more than 35 kg/m^2 was found to be associated with a hazard ratio of 2.1 versus patients with a BMI less than 20 kg/m^2.[278] In the Tromsø study, the combination of tall stature and obesity (BMI >30 kg/m^2) was associated with an increased risk of VTE in both men and women.[279] Tall, obese men had a fivefold increase in VTE (hazard ratio 5.16) and tall, obese women had a threefold increase (hazard ratio 2.89). Moreover, in an analysis of patients with idiopathic VTE, the presence of the "metabolic syndrome," defined as abdominal obesity, impaired glucose metabolism, arterial hypertension, and dyslipidemia, was detected in 23.5% of patients with idiopathic VTE (P =< .001; OR, 2.99).[280]

In association with other risk factors, such as family history, OCs, and surgery, the risk for VTE in obese patients increases significantly independent of age and sex.[281] Data stratified by age, regardless of race and family history of VTE showed obesity to be a statistically significant risk factor for VTE (age 18 to 44 years: OR, 3.5; 95% CI, 1.6 to 7.6; age 45 to 54 years: OR, 2.6; 95% CI, 1.3 to 5.0; age ≥55 years: OR, 2.6; 95% CI, 1.3 to 5.2). Further, when the association between family history and VTE was examined, among men and women, regardless of race, a family history of VTE was a statistically significant risk factor for VTE among both men and women who were obese (OR, 3.5; 95% CI, 1.8 to 6.6 vs. OR, 2.2; 95% CI, 1.3 to 3.7, respectively).[281] However, among obese patients, a family history of VTE in a relative before age 50 years was a statistically significant risk factor for VTE only among men (OR, 6.9; 95% CI, 2.2 to 21.6), although the OR was elevated among women (OR, 1.8; 95% CI, 0.86 to 3.6), but the P-value for interaction was not significant.[281]

EVALUATION OF THE PATIENT WITH SUSPECTED THROMBOPHILIA

The purpose for testing for thrombophilia in patients with venous thrombosis is to determine the risk of recurrent thrombosis, and, therefore, the duration of anticoagulation. Figs. 38.1 and 38.2 provide a suggested outline for hypercoagulable testing. Patients with significant prothrombotic defects alone or in combination can be at a significantly higher risk of recurrent VTE; therefore, extended or lifelong anticoagulation may be recommended. In patients in whom significant prothrombotic defects are detected, further testing of family members, who have not had a VTE, should be performed. This will allow asymptomatic carriers to be counseled regarding high-risk situations of increased hemostatic stress, such as surgery, pregnancy, OC pills, HRT, or prolonged travel. Patients with VTE who should be tested include those younger than 50 years with unprovoked (idiopathic) VTE, patients with unprovoked recurrent VTE, and patients who develop thrombosis, including those associated with a transient risk factor, if there is a strong family history of VTE.

In the younger patient (<50 years of age) without a history of diabetes, who has experienced an unprovoked arterial thrombotic event, a screening evaluation can lead to the identification of prothrombotic risk factors. This allows for effective treatment strategies to reduce the risk of a recurrent arterial event. Table 38.2 lists the recommended studies for the evaluation of patients with VTE and patients with arterial thrombotic events.

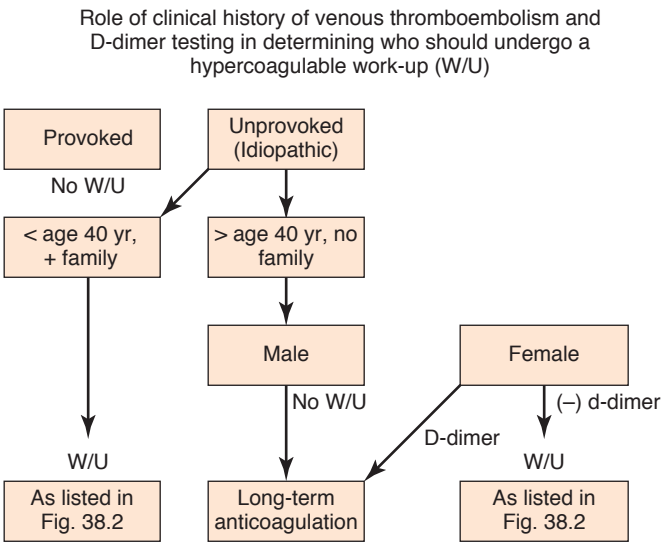
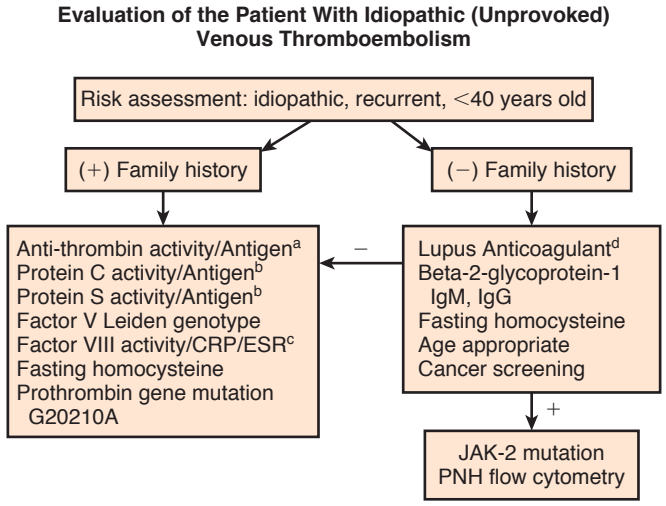


Figure 38.1 The role of clinical history and D-dimer screening before undertaking a hypercoagulable work-up. Based on the findings, a work-up as outlined in Fig. 38.2 may be indicated.



[a] Should not be tested in the setting of acute clot or heparin therapy
[b] Should not be tested in the setting of acute clot or warfarin therapy
[c] Should not be tested in the setting of acute clot
[d] Cannot be tested on unfractionated heparin therapy

Figure 38.2 Evaluation and laboratory testing for hypercoagulability in patients with venous thromboembolism. *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *Ig*, immunoglobulin; *JAK-2*, Janus kinase-2; *PNH*, paroxysmal nocturnal hemoglobinuria.

TABLE 38.2 Recommended Tests for Evaluation of Congenital and Acquired Prothrombotic Defects in Patients With Venous and Arterial Thrombosis

Thrombophilic Defect	Type of Test Available
Venous Thrombosis	
Factor V Leiden	Polymerase chain reaction
Prothrombin G20210A	Polymerase chain reaction
Antithrombin	Functional, then antigenic assay[a]
Protein C deficiency	Functional, then antigenic assay[a]
Protein S deficiency	Functional, then antigenic assay[a]
Elevated factor VIII, IX, and XI levels	Functional assay
Dysfibrinogenemia	Functional assay
Hyperhomocysteinemia	HPLC
Lupus anticoagulant	Coagulation-based assays[b]
Cardiolipin antibodies	Enzyme-linked immunoassay
β_2-Glycoprotein-1 antibodies	Enzyme-linked immunoassay
Arterial Thrombosis	
Lupus anticoagulant	Coagulation-based assays[b]
Cardiolipin antibodies	Enzyme-linked immunoassay
B2-glycoprotein 1 antibodies	Enzyme-linked immunoassay
Lipoprotein (a)	Enzyme-linked immunoassay[c]
Sticky platelet syndrome	Platelet aggregation studies

[a] Abnormal functional assays should be performed first, followed by antigen assays to subtype the defect.
[b] Two different coagulation-based assays should be performed in screening for a lupus anticoagulant.
[c] Screening for elevated lipoprotein (a) should be performed in conjunction with a full cholesterol and lipid panel.
HPLC, High-performance liquid chromatography.

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A complete reference list can be found online at www.expertconsult.com.

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39 CHAPTER

Anticoagulant Drugs

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INTRODUCTION

Arterial thrombi are rich in platelets because of the high shear in the injured arteries. In contrast, venous thrombi, which form under low shear conditions, contain relatively few platelets and are predominantly composed of fibrin and trapped red cells.[1] Because of the predominance of platelets, arterial thrombi appear white, whereas venous thrombi are red in color, reflecting the trapped red cells. Antithrombotic drugs are used for prevention and treatment of thrombosis. Targeting the components of thrombi, these agents include (1) antiplatelet drugs, which inhibit platelets; (2) anticoagulants, which attenuate coagulation; and (3) thrombolytic agents, which induce fibrin degradation. With the predominance of platelets in arterial thrombi, strategies to inhibit or treat arterial thrombosis focus mainly on antiplatelet agents (see Chapter 40), although, in the acute setting, they often include anticoagulants and thrombolytic agents. Anticoagulants are the mainstay of the prevention and treatment of venous thromboembolism (VTE) because fibrin is the predominant component of venous thrombi. Antiplatelet drugs are less effective than anticoagulants in this setting because of the limited platelet content of venous thrombi.

Anticoagulants are the focus of this chapter and are available in parenteral and oral forms. Parenteral anticoagulants include unfractionated heparin, low-molecular-weight heparin (LMWH), fondaparinux, a synthetic pentasaccharide, and parenteral direct thrombin inhibitors (bivalirudin, hirudin analogs, and argatroban). Oral anticoagulants include vitamin K antagonists (VKAs),

such as warfarin, and the direct oral anticoagulants (DOACs); dabigatran etexilate, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa.

Parenteral Anticoagulants: Indirect Inhibitors

Heparin

A sulfated polysaccharide, heparin is isolated from mammalian tissues rich in mast cells. Most commercial heparin is derived from porcine intestinal mucosa and is a polymer of alternating D-glucuronic acid and *N*-acetyl-D-glucosamine residues.[2]

Mechanism of Action

Heparin acts as an anticoagulant by activating antithrombin (previously known as antithrombin III) and accelerating the rate at which antithrombin inhibits clotting enzymes, particularly thrombin and factor Xa.[3] Antithrombin, the obligatory plasma cofactor for heparin,[3] is a member of the serine protease inhibitor superfamily. Synthesized in the liver and circulating in plasma at a concentration of 2.6 ± 0.4 μM, antithrombin acts as a suicide substrate for its target enzymes.

To activate antithrombin, heparin binds to the serine protease inhibitor via a unique pentasaccharide sequence that is found on one third of the chains of commercial heparin (Fig. 39.1). The remainder of the heparin chains that lack this pentasaccharide sequence have little or no anticoagulant activity.[4] Once bound to antithrombin, heparin induces a conformational change in the reactive center loop of antithrombin that renders it more readily accessible to its target proteases. This conformational change enhances the rate at which antithrombin inhibits factor Xa by at least two orders of magnitude but has little effect on the rate of thrombin inhibition by antithrombin.[5] To catalyze thrombin inhibition, heparin serves as a template that binds antithrombin and thrombin simultaneously.[6] Formation of this ternary complex brings the enzyme in close apposition to the inhibitor, thereby promoting the formation of a stable covalent thrombin-antithrombin complex.[6,7] Only pentasaccharide-containing heparin chains composed of at least 18 saccharide units (which corresponds to a molecular weight of 5400) are of sufficient length to bridge thrombin and antithrombin together.[8] With a mean molecular weight of 15,000 and a range of 5000 to 30,000, almost all of the chains of unfractionated heparin are long enough to effect this bridging function.[9] Consequently, by definition, heparin has equal capacity to promote the inhibition of thrombin and factor Xa by antithrombin and is assigned a 1:1 ratio of anti–factor Xa to anti–factor IIa (thrombin) activity.[3]

Heparin induces the release of tissue factor pathway inhibitor, a factor Xa–dependent inhibitor of tissue factor–bound factor VIIa, from the endothelium.[9-11] Tissue factor pathway inhibitor may contribute to the antithrombotic activity of heparin. Longer heparin chains induce the release of more tissue factor pathway inhibitor than shorter chains.[10,11]

Pharmacology

Heparin must be given parenterally. It is usually administered subcutaneously when given for prophylaxis and by continuous intravenous infusion when used for therapeutic purposes. If heparin is given subcutaneously for treatment of thrombosis, the dose of heparin must be high enough to overcome the limited bioavailability associated with this method of delivery.[3]

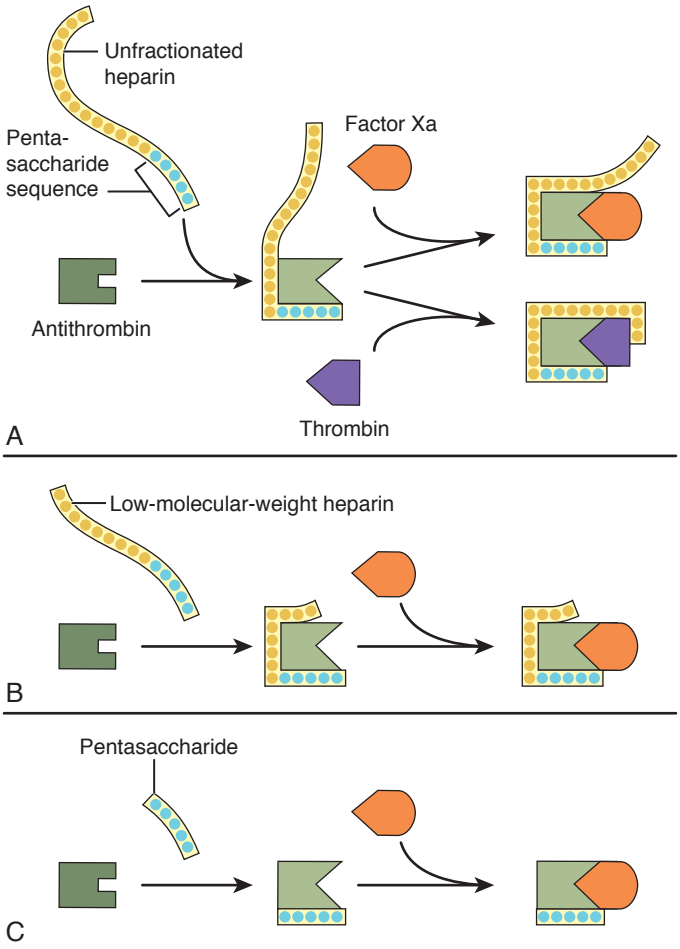

Figure 39.1 Mechanism of action of heparin, low-molecular-weight heparin (LMWH), and fondaparinux, a synthetic pentasaccharide. (A) Heparin binds to antithrombin via its pentasaccharide sequence and induces a conformational change in the reactive center loop of antithrombin that accelerates its interaction with factor Xa. To potentiate thrombin inhibition, heparin must simultaneously bind to antithrombin and thrombin. (B) LMWH has greater capacity to potentiate factor Xa inhibition by antithrombin than thrombin because at least half of the LMWH chains are too short to bridge antithrombin to thrombin. (C) Fondaparinux only accelerates factor Xa inhibition by antithrombin because it is too short to bridge antithrombin to thrombin.

In the circulation, heparin binds to the endothelium, and this explains its dose-dependent clearance. At low doses, the half-life of heparin is short because it rapidly binds to the endothelium.[3] With higher doses of heparin, the endothelium is saturated and the half-life is longer.[3] Because of this phenomenon, the plasma half-life of heparin ranges from 30 to 60 minutes with bolus intravenous doses of 25 and 100 U/kg, respectively.[3] Clearance of heparin is mainly extrarenal; heparin binds to macrophages, which internalize and depolymerize the long heparin chains and secrete shorter chains back into the circulation.

Once the endothelium is saturated, heparin enters the circulation, where it binds plasma proteins other than antithrombin,

a phenomenon that reduces the anticoagulant activity of heparin.[12] Some of the heparin-binding proteins in plasma are acute-phase reactants whose levels are elevated in ill patients.[12,13] Others, such as high-molecular-weight multimers of von Willebrand factor (vWF), are released from activated platelets or endothelial cells.[14,15] Activated platelets also release platelet factor 4 (PF4), a highly cationic protein that binds heparin with high affinity.[16] The large amounts of PF4 found in the vicinity of platelet-rich arterial thrombi can neutralize the anticoagulant activity of heparin.[17] This phenomenon may attenuate heparin's capacity to suppress thrombus growth.

Because the levels of heparin-binding proteins in plasma vary from person to person, the anticoagulant response to fixed or weight-adjusted doses of heparin is unpredictable. Consequently coagulation monitoring is essential to ensure that a therapeutic response is obtained. This is particularly important when heparin is administered for treatment of established thrombosis, because a subtherapeutic anticoagulant response renders patients at risk for recurrent thrombosis,[18,19] whereas excessive anticoagulation increases the risk of bleeding.[20,21]

The interaction of heparin with plasma proteins also contributes to the phenomenon of heparin rebound. Defined as the reappearance of anticoagulant activity after adequate neutralization of heparin with protamine, heparin rebound may contribute to excessive bleeding after cardiac surgery. This phenomenon likely reflects the slow release of protein-bound heparin after circulating heparin is neutralized by protamine. Heparin rebound can be managed by administration of additional protamine by intravenous bolus or as a low-dose continuous infusion.[22]

Monitoring

Heparin therapy can be monitored using the activated clotting time (ACT), activated partial thromboplastin time (aPTT), or anti–factor Xa level. The ACT, which is less sensitive than the aPTT and can be measured at the bedside, is used to monitor the high doses of heparin given during catheter-based or open cardiovascular surgical procedures. The aPTT is the test most often used to monitor therapeutic doses of heparin. aPTT reagents vary in their sensitivity to heparin, and the type of coagulometer used for testing can influence the results.[23] Consequently laboratories must establish a therapeutic aPTT range with each reagent-coagulometer combination by measuring the aPTT and anti–factor Xa level in plasma samples collected from heparin-treated patients. For most of the aPTT reagents and coagulometers in current use, therapeutic heparin levels are achieved with a two- to threefold prolongation of the aPTT.[24] Anti–factor Xa levels can also be used to monitor heparin therapy. With this test, therapeutic heparin levels range from 0.3 to 0.7 U/mL. Although this test is gaining in popularity, anti–factor Xa results can vary between laboratories.

Up to 25% of heparin-treated patients with VTE require more than 35,000 U/day to achieve a therapeutic aPTT. These patients are considered heparin resistant.[25] It is useful to measure anti–factor Xa levels in heparin-resistant patients because many will have a therapeutic anti–factor Xa level despite a subtherapeutic aPTT. This dissociation in test results occurs because elevated plasma levels of fibrinogen and factor VIII, both of which are acute-phase proteins, shorten the aPTT but have no effect on anti–factor Xa levels.[26] Heparin therapy in patients who exhibit this phenomenon is best monitored using anti–factor Xa levels instead of the aPTT.[25] Patients with congenital or acquired antithrombin deficiency and those with elevated levels of heparin-binding proteins may need higher doses of heparin to achieve a therapeutic aPTT or anti–factor Xa level. If there is good correlation between the aPTT and the anti–factor Xa levels, either test can be used to monitor heparin therapy.

Dosing

For prophylaxis, heparin is usually given in fixed doses of 5000 units subcutaneously two or three times daily. With these low doses, coagulation monitoring is unnecessary.[27] In contrast, monitoring is essential when the drug is given in therapeutic doses. Fixed-dose or weight-based heparin nomograms are used to standardize heparin dosing and to shorten the time required to achieve a therapeutic anticoagulant response. At least two heparin nomograms have been validated in patients with VTE; these reduce the time required to achieve a therapeutic aPTT.[28,29] Weight-adjusted heparin nomograms have also been evaluated in patients with acute coronary syndromes. After an intravenous heparin bolus of 5000 units or 70 U/kg, a heparin infusion rate of 12 to 15 U/kg per hour usually is administered.[29,30] In contrast, weight-adjusted heparin nomograms for patients with VTE use an initial bolus of 5000 units or 80 U/kg followed by an infusion of 18 U/kg per hour.[28] Thus patients with VTE appear to require higher doses of heparin to achieve a therapeutic aPTT than do patients with acute coronary syndromes. This may reflect differences in the thrombus burden. Heparin binds to fibrin, and the fibrin content of large deep venous thrombi is greater than that of small coronary thrombi. For interventions, heparin is usually given as a fixed intravenous bolus of 5000 to 10,000 units or as a weight-adjusted dose of 70 to 100 U/kg.[31,32]

Limitations

Heparin has pharmacokinetic and biophysical limitations (Table 39.1). The pharmacokinetic limitations reflect heparin's propensity to bind in a pentasaccharide-independent fashion to cells and plasma proteins. Heparin binding to endothelial cells explains its dose-dependent clearance, whereas binding to plasma proteins results in a variable anticoagulant response and can lead to heparin resistance.

The biophysical limitations of heparin reflect the inability of the heparin-antithrombin complex to (1) inhibit factor Xa when it is incorporated into the prothrombinase complex,[33,34] the complex that converts prothrombin to thrombin, and (2) to inhibit thrombin bound to fibrin.[35,36] Consequently factor Xa bound to activated platelets within platelet-rich thrombi has the potential to generate thrombin, even in the face of heparin.[37] Once this thrombin binds to fibrin, it too is protected from inhibition by the heparin-antithrombin complex.[38,39] Clot-associated thrombin can then trigger thrombus growth by locally activating platelets and amplifying its own generation through feedback activation of factors V, VIII, and XI.[38-40]

TABLE 39.1 Pharmacokinetic and Biophysical Limitations of Heparin

Limitations	Mechanism
Poor bioavailability at low doses	Limited absorption of long heparin chains
Dose-dependent clearance	Binds to endothelial cells
Variable anticoagulant response	Binds to plasma proteins whose levels vary from patient to patient
Reduced activity in the vicinity of platelet-rich thrombi	Neutralized by platelet factor 4 released from activated platelets
Limited activity against factor Xa incorporated in the prothrombinase complex and thrombin bound to fibrin	Reduced capacity of heparin-antithrombin complex to inhibit factor Xa bound to activated platelets and thrombin bound to fibrin

Further compounding the problem is the potential for heparin neutralization by the high concentrations of PF4 released from activated platelets within the platelet-rich thrombus.[18]

Side Effects

Bleeding. The most common side effect of heparin is bleeding. The risk of heparin-induced bleeding increases with higher heparin doses. Concomitant administration of drugs that affect hemostasis, such as antiplatelet or fibrinolytic agents, increases the risk of bleeding, as does recent surgery or trauma.[41] Heparin-treated patients with serious bleeding can be given protamine sulfate to neutralize the heparin. Protamine sulfate, a mixture of basic polypeptides isolated from salmon sperm, binds heparin with high affinity, and the resultant protamine-heparin complexes are then cleared. Typically, 1 mg of protamine sulfate neutralizes 100 units of heparin. Protamine sulfate is given intravenously. Anaphylactoid reactions to protamine sulfate[42] can occur, and drug administration by slow intravenous infusion is recommended to reduce the risk of these problems.[42,43]

Thrombocytopenia. Heparin-induced thrombocytopenia (HIT) is an antibody-mediated process triggered by antibodies directed against neoantigens on PF4 that are exposed when heparin binds to this protein.[44] These antibodies, which usually are of the IgG subtype, bind simultaneously to the heparin-PF4 complex and to platelet Fc receptors. Such binding activates the platelets and generates platelet microparticles. Circulating microparticles are prothrombotic because they express anionic phospholipids on their surface and can bind clotting factors, thereby promoting thrombin generation.[45]

The clinical features of HIT are illustrated in Table 39.2. Typically HIT occurs 5 to 14 days after initiation of heparin therapy, but it can manifest earlier if the patient has received heparin within the past 3 months.[46] Even a 50% decrease in the platelet count from the pretreatment value should raise the suspicion of HIT in those receiving heparin.[44] HIT is more common in surgical patients than in medical patients and, like many autoimmune disorders, it occurs more frequently in females than in males.

TABLE 39.2 Features of Heparin-Induced Thrombocytopenia

Features	Details
Thrombocytopenia	Platelet count of 100,000/μL or less or a decrease in platelet count of 50% or more
Timing	Platelet count falls 5-10 days after starting heparin
Type of heparin	More common with unfractionated heparin than low-molecular-weight heparin; almost never occurs with fondaparinux
Type of patient	More common in surgical patients than medical patients; more common in women than men
Thrombosis	Venous thrombosis more common than arterial thrombosis

TABLE 39.3 Management of Heparin-Induced Thrombocytopenia

Stop all heparin
Give an alternative anticoagulant, such as lepirudin, argatroban, bivalirudin, danaparoid, fondaparinux, or rivaroxaban
Do not give platelet transfusions
Do not give warfarin until the platelet count returns to its baseline level. If warfarin was administered, give vitamin K to restore the international normalized ratio to normal
Evaluate for thrombosis, particularly deep venous thrombosis

HIT can be associated with thrombosis, either arterial or venous. Venous thrombosis, which manifests as deep venous thrombosis and/or pulmonary embolism, is more common than arterial thrombosis. Arterial thrombosis can manifest as ischemic stroke or acute myocardial infarction (MI). Rarely, platelet-rich thrombi in the distal aorta or iliac arteries can cause critical limb ischemia.[44]

The diagnosis of HIT is established using enzyme-linked assays to detect antibodies against heparin-PF4 complexes or with platelet activation assays. Enzyme-linked assays are sensitive but can be positive in the absence of any clinical evidence of HIT.[44] The most specific diagnostic test is the serotonin release assay. This test is performed by quantifying serotonin release when washed platelets loaded with labeled serotonin are exposed to the patient's serum in the absence or presence of varying concentrations of heparin. If the patient's serum contains the HIT antibody, the addition of heparin induces platelet activation and subsequent serotonin release.[44]

Management of HIT is outlined in Table 39.3. Heparin should be stopped in patients with suspected or documented HIT, and an alternative anticoagulant should be administered to prevent or treat thrombosis.[47] The agents most often used for this indication are parenteral direct thrombin inhibitors (such as lepirudin, argatroban, or bivalirudin) or parenteral or oral factor Xa inhibitors (such as fondaparinux, danaparoid, or

rivaroxaban).[48] The alternative anticoagulant should be continued until the platelet count is normal or the diagnosis of HIT is excluded. Warfarin should be avoided in HIT patients because it can trigger skin necrosis and thrombosis. These complications occur because warfarin lowers the levels of protein C, and many HIT patients already have low levels of this anticoagulant protein as a consequence of increased thrombin generation.

Osteoporosis. Treatment with therapeutic doses of heparin for over a month can cause a reduction in bone density. This complication has been reported in up to 30% of patients given long-term heparin therapy,[48-51] and symptomatic vertebral fractures occur in 2% to 3% of these individuals.

Studies in vitro[52] and in laboratory animals[53-55] have provided insights into the pathogenesis of heparin-induced osteoporosis. These investigations suggest that heparin causes bone resorption both by decreasing bone formation and by enhancing bone resorption.[52-55] Thus heparin affects the activity of both osteoblasts and osteoclasts.

Elevated Transaminases. Therapeutic doses of heparin frequently cause modest elevation in the serum levels of hepatic transaminases, without a concomitant increase in the level of bilirubin.[56,57] The levels of transaminases rapidly return to normal when the drug is stopped. The mechanism responsible for this phenomenon is unknown.

Perioperative Management

When given subcutaneously for thromboprophylaxis, the last dose of heparin should be administered at least 2 hours before surgery. Full-dose intravenous heparin should be stopped 4 to 6 hours before surgery.[58] Low-dose heparin can be restarted 12 to 24 hours after surgery. Resumption of full-dose heparin should be delayed until hemostasis is secure. Often in this setting, heparin is started as an infusion without a loading dose.

Low-Molecular-Weight Heparin

Consisting of smaller fragments of heparin, LMWH is prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. The mean molecular weight of LMWH is 5000, one third the mean molecular weight of unfractionated heparin.[59] LMWH has advantages over heparin (Table 39.4) and has replaced heparin for most indications.

Mechanism of Action

Like heparin, LMWH exerts its anticoagulant activity by activating antithrombin. With a mean molecular weight of 5000, which corresponds to about 17 saccharide units, at least half of the pentasaccharide-containing chains of LMWH are too short to bridge thrombin to antithrombin (see Fig. 39.1). However, these chains retain the capacity to accelerate factor Xa inhibition by antithrombin because this activity is largely the result of the conformational changes in antithrombin evoked by pentasaccharide binding. Consequently LMWH catalyzes factor Xa inhibition more than thrombin inhibition.[59] Depending on their molecular weight distribution, the anti–factor Xa to anti–factor IIa ratios of the various LMWH preparations range from 2:1 to 4:1.

TABLE 39.4 Advantages of Low-Molecular-Weight Heparin Over Heparin

Advantage	Consequence
Better bioavailability and longer half-life after subcutaneous injection	Can be given subcutaneously once or twice daily for both prophylaxis and treatment
Dose-independent clearance	Simplified dosing
Predictable anticoagulant response	Coagulation monitoring is unnecessary in most patients
Lower risk of heparin-induced thrombocytopenia	Safer than heparin for short- or long-term administration
Lower risk of osteoporosis	Safer than heparin for extended administration

Pharmacology

Although usually given subcutaneously, LMWH can also be administered intravenously if a rapid anticoagulant response is needed. LMWH has pharmacokinetic advantages over heparin,[59,60] since shorter heparin chains bind less avidly to endothelial cells, macrophages, and heparin-binding plasma proteins.[61-63] Reduced binding to endothelial cells and macrophages eliminates the rapid, dose-dependent, and saturable mechanism of clearance characteristic of unfractionated heparin. Instead, the clearance of LMWH is dose independent and its plasma half-life is longer.[60] Based on measurement of anti–factor Xa levels, LMWH has a plasma half-life of about 4 to 6 hours. LMWH is cleared almost exclusively by the kidneys, and the drug can accumulate in patients with renal insufficiency.[59,60]

LMWH exhibits about 90% bioavailability after subcutaneous injection.[59,60] Because LMWH binds less avidly to heparin-binding proteins in plasma than heparin, LMWH produces a more predictable dose response, and resistance to LMWH is rare. With a longer half-life and more predictable anticoagulant response, LMWH can be given subcutaneously once or twice daily without coagulation monitoring.[59] These properties render LMWH more convenient to use than unfractionated heparin. Studies in patients with VTE have shown that home treatment with LMWH is as effective and safe as in-hospital treatment with continuous intravenous infusions of heparin.[64-66] Outpatient treatment with LMWH streamlines care, reduces healthcare costs, and increases patient satisfaction.

Monitoring

In the majority of patients, LMWH does not require coagulation monitoring. If monitoring is necessary, anti–factor Xa levels must be measured, because LMWH has little effect on the aPTT. Therapeutic anti–factor Xa levels with LMWH range from 0.5 to 1.2 U/mL when measured 3 to 4 hours after drug administration. When LMWH is given in prophylactic doses, peak anti–factor Xa levels of 0.2 to 0.5 U/mL are desirable.[67]

Potential indications for LMWH monitoring include renal insufficiency, obesity, and pregnancy. LMWH monitoring in patients with a creatinine clearance of 50 mL/min or less is prudent to ensure that there is no drug accumulation. Although

weight-adjusted LMWH dosing appears to produce therapeutic anti–factor Xa levels in patients who are overweight, this approach has not been extensively evaluated in those with morbid obesity. It may also be advisable to monitor the anticoagulant activity of LMWH during pregnancy because dose requirements can change, particularly in the third trimester.[67] Monitoring should also be considered in high-risk settings, such as in patients with mechanical heart valves who are given LMWH for the prevention of valve thrombosis.

Dosing

The doses of LMWH recommended for prophylaxis or treatment vary depending on the LMWH preparation. For prophylaxis, once-daily subcutaneous doses of 4000 to 5000 units are often used, whereas doses of 2500 to 3000 units are given when the drug is administered twice daily. For treatment of VTE, a dose of 150 to 200 U/kg is given if the drug is administered once daily. If a twice-daily regimen is employed, a dose of 100 U/kg is given. In patients with unstable angina, LMWH is given subcutaneously on a twice-daily basis at a dose of 100 to 120 U/kg.[59]

Side Effects

Bleeding. The major complication of LMWH administration is bleeding. Meta-analyses have suggested that the risk of major bleeding may be lower with LMWH than with unfractionated heparin.[68,69] HIT and osteoporosis are also less common with LMWH than with unfractionated heparin.[59] As with heparin, bleeding with LMWH is more common in patients receiving concomitant therapy with antiplatelet or fibrinolytic drugs. Recent surgery, trauma, or underlying hemostatic defects also increase the risk of bleeding with LMWH.[41]

Although protamine sulfate can be used as an antidote for LMWH, it incompletely neutralizes the anticoagulant activity of LMWH because protamine sulfate binds only the longer chains of LMWH.[70] Since longer chains are responsible for catalysis of thrombin inhibition by antithrombin, protamine sulfate completely reverses the anti–factor IIa activity of LMWH. In contrast, protamine sulfate only partially reverses the anti–factor Xa activity of LMWH because the shorter pentasaccharide-containing chains of LMWH do not bind to protamine sulfate.[71] Consequently patients at high risk for bleeding may be more safely treated with continuous intravenous unfractionated heparin than with subcutaneous LMWH.

Thrombocytopenia. The risk for HIT is about fivefold lower with LMWH than with heparin.[72,73] LMWH binds less avidly to platelets and causes less PF4 release. Furthermore, with lower affinity for PF4 than heparin, LMWH is less likely to induce the conformational changes in PF4 that trigger the formation of HIT antibodies.

LMWH should not be used to treat HIT patients[47] because most HIT antibodies exhibit cross-reactivity with LMWH.[74,75] This in vitro cross-reactivity is not simply a laboratory phenomenon; cases of worsening thrombocytopenia and thrombosis have been reported when HIT patients are treated with LMWH.

Osteoporosis. The risk for osteoporosis is lower with long-term LMWH than with heparin.[76] For extended treatment, therefore, LMWH is a better choice than heparin because of the lower risk for osteoporosis and HIT.

TABLE 39.5 Comparison of Features of Heparin, Low-Molecular-Weight Heparin, and Fondaparinux

Features	Heparin	LMWH	Fondaparinux
Source	Biologic	Biologic	Synthetic
Molecular weight	15,000	5000	1500
Target	Xa and IIa	Xa and IIa	Xa
Bioavailability (%)	30	90	100
Half-life (hr)	1	4	17
Renal excretion	No	Yes	Yes
Antidote	Complete	Partial	No
HIT	<5%	<1%	Never

Perioperative Management

When used in prophylactic doses, the last dose of LMWH should be given at least 12 hours before surgery. With treatment doses of LMWH, the drug should be held for 24 hours before surgery. Thromboprophylaxis with LMWH can be started 12 to 24 hours after surgery; if started 12 hours after major surgery, a half dose can be given provided that hemostasis has been secured. Resumption of full-dose LMWH should be delayed for 2 to 3 days.

Fondaparinux

A synthetic analog of the antithrombin-binding pentasaccharide sequence, fondaparinux differs from LMWH in several ways (Table 39.5). Fondaparinux is licensed for thromboprophylaxis in general surgical and high-risk orthopedic patients and as an alternative to heparin or LMWH for the initial treatment of patients with established VTE. Although approved as an alternative to heparin or LMWH in patients with acute coronary syndrome in Europe and Canada, fondaparinux is not licensed for this indication in the United States.

Mechanism of Action

As a synthetic analog of the antithrombin-binding pentasaccharide sequence found in heparin and LMWH, fondaparinux has a molecular weight of 1728. Fondaparinux binds only to antithrombin (see Fig. 39.1) and is too short to bridge thrombin to antithrombin. Consequently fondaparinux catalyzes factor Xa inhibition by antithrombin and does not enhance the rate of thrombin inhibition.[77]

Pharmacology

Fondaparinux exhibits complete bioavailability after subcutaneous injection. With no binding to endothelial cells or plasma proteins, the clearance of fondaparinux is dose independent and its plasma half-life is 17 hours.[78] The drug is given subcutaneously once

daily. Because fondaparinux is cleared unchanged via the kidneys, it is contraindicated in patients with a creatinine clearance less than 30 mL/min, and it should be used with caution in those with a creatinine clearance less than 50 mL/min.[77,78]

Fondaparinux produces a predictable anticoagulant response after administration in fixed doses because it does not bind to plasma proteins. The drug is given at a dose of 2.5 mg once daily for prevention of VTE. For initial treatment of established VTE, fondaparinux is given at a dose of 7.5 mg once daily. The dose can be reduced to 5 mg once daily for those weighing less than 50 kg and increased to 10 mg once daily for those over 100 kg. When given in these doses, fondaparinux is as effective as heparin or LMWH for the initial treatment of patients with deep venous thrombosis or pulmonary embolism and produces similar rates of bleeding.[79,80]

Fondaparinux is used at a dose of 2.5 mg once daily in patients with acute coronary syndrome. When this prophylactic dose of fondaparinux was compared with treatment doses of enoxaparin in patients with non–ST-segment elevation acute coronary syndromes, no difference was seen in the rate of cardiovascular death, MI, or stroke at 9 days.[81] However, the rate of major bleeding was 50% lower with fondaparinux than with enoxaparin, a difference that likely reflects the fact that the dose of fondaparinux was lower than that of enoxaparin. In patients with acute coronary syndrome who require percutaneous coronary intervention (PCI), there is a risk for catheter thrombosis with fondaparinux unless adjunctive heparin is given.[82]

Side Effects

Although fondaparinux can induce the formation of HIT antibodies, HIT is rare with fondaparinux. In contrast to LMWH, there is no cross-reactivity of fondaparinux with HIT antibodies. Consequently fondaparinux appears to be effective for the treatment of HIT patients,[83] although large clinical trials supporting its use are lacking.

The major side effect of fondaparinux is bleeding. There is no antidote for fondaparinux. Protamine sulfate has no effect on the anticoagulant activity of fondaparinux because it fails to bind to the drug. Recombinant activated factor VII reverses the anticoagulant effects of fondaparinux in volunteers,[84] but it is unknown whether this agent controls fondaparinux-induced bleeding.

Perioperative Management

When used in prophylactic or treatment doses, the last dose of fondaparinux should be given at least 36 hours before major surgery.

Parenteral Direct Thrombin Inhibitors

Heparin and LMWH are indirect inhibitors of thrombin because their activity is mediated by antithrombin. In contrast, direct thrombin inhibitors do not require a plasma cofactor; instead, these agents bind directly to thrombin and block its interaction with its substrates. Approved parenteral direct thrombin inhibitors include lepirudin and desirudin—recombinant forms of hirudin—as well as argatroban, and bivalirudin (Table 39.6). Lepirudin and argatroban are licensed for treatment of patients with HIT with or without associated thrombosis, desirudin is licensed for thrombophylaxis after elective hip arthroplasty, and bivalirudin is approved as an alternative to heparin in patients undergoing PCI, including those with HIT.[85]

TABLE 39.6 Comparison of the Properties of Hirudin, Bivalirudin, and Argatroban

	Hirudin	Bivalirudin	Argatroban
Molecular mass (Da)	7000	1980	527
Site(s) of interaction with thrombin	Active site and exosite 1	Active site and exosite 1	Active site
Renal clearance	Yes	No	No
Hepatic metabolism	No	No	Yes
Plasma half-life (min)	60	25	45

Lepirudin and Desirudin

Lepirudin and desirudin are bivalent direct thrombin inhibitors that interact with both the active site and exosite 1, the substrate binding site, on thrombin.[85] For rapid anticoagulation, lepirudin is given by continuous intravenous infusion, but the drug can be given subcutaneously for thromboprophylaxis. Lepirudin has a plasma half-life of 60 minutes after intravenous infusion and is cleared by the kidneys. Consequently lepirudin accumulates in patients with renal insufficiency.[86] A high proportion of lepirudin-treated patients develop antibodies against the drug.[87] Although these antibodies rarely cause problems, in a small subset of patients they can delay lepirudin clearance and enhance its anticoagulant activity. Serious bleeding has been reported in some of these patients.[87]

Desirudin is given subcutaneously at a dose of 15 mg twice daily. The dose is reduced in patients with a creatinine clearance less than 60 mL/min. In contrast to lepirudin, antibody formation is rare with desirudin, possibly because the drug is only administered subcutaneously.

Desirudin does not usually require anticoagulation monitoring. Lepirudin is monitored using the aPTT, and the dose is adjusted to maintain an aPTT that is 1.5 to 2.5 times the control. The aPTT is not an ideal test for monitoring lepirudin therapy because the aPTT plateaus with higher drug concentrations. Although the ecarin clotting time provides a better index of lepirudin dose than the aPTT does, the ecarin clotting time is not widely available.

Argatroban

A univalent inhibitor that targets the active site of thrombin, argatroban is metabolized in the liver.[85] Consequently, this drug must be used with caution in patients with hepatic insufficiency. Argatroban is not cleared via the kidneys, so this drug is safer than lepirudin for HIT patients with renal insufficiency.

Argatroban is administered by continuous intravenous infusion and has a plasma half-life of about 45 minutes. The aPTT is used to monitor its anticoagulant effect, and the dose is adjusted to achieve an aPTT 1.5 to 3 times the baseline value but not to exceed 100 seconds. Argatroban also prolongs the international normalized ratio (INR), a feature that can complicate the transitioning of patients to warfarin.[88] This issue can be circumvented by using the levels of factor X to monitor warfarin in place of the INR. Alternatively, argatroban can be stopped for 2 to 3 hours before INR determination.

Bivalirudin

A synthetic 20–amino acid analog of hirudin, bivalirudin is a divalent thrombin inhibitor.[89] Thus the NH2-terminal portion of bivalirudin interacts with the active site of thrombin, whereas its COOH-terminal tail binds to exosite 1, the substrate-binding domain on thrombin. Bivalirudin has a plasma half-life of 25 minutes, the shortest half-life of all the parenteral direct thrombin inhibitors.[85] Bivalirudin is degraded by peptidases and is partially excreted via the kidneys. When bivalirudin is given in high doses in the cardiac catheterization laboratory, its anticoagulant activity is monitored using the ACT. With lower doses, its activity can be assessed using the aPTT.

Studies comparing bivalirudin with heparin suggest that bivalirudin produces less bleeding.[90,91] This feature plus its short half-life make bivalirudin an attractive alternative to heparin in patients undergoing PCI.[92] Bivalirudin has also been used successfully in HIT patients who require PCI or cardiac surgery.[89]

Oral Anticoagulants

Current oral anticoagulant practice dates back almost 60 years to when the VKAs, such as warfarin, were discovered as a result of investigations into the cause of hemorrhagic disease in cattle. Over the past decade, however, a new class of oral anticoagulants has been licensed. Known as the non–vitamin K antagonist oral anticoagulants (NOACs) or DOACs, this class includes dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. The NOACs are now replacing warfarin for many indications.

Warfarin

A water-soluble VKA initially developed as a rodenticide, warfarin is the coumarin derivative most often prescribed in North America. Like other VKAs, warfarin interferes with the synthesis of the vitamin K–dependent clotting proteins, which include prothrombin (factor II) and factors VII, IX, and X. VKAs also reduce the synthesis of the vitamin K–dependent anticoagulant proteins, proteins C, S, and Z.

Mechanism of Action

All of the vitamin K–dependent clotting factors possess glutamic acid residues at their N-termini. A posttranslational modification adds a carboxyl group to the γ-carbon of these residues to generate γ-carboxyglutamic acid.[93] This modification is essential for expression of the activity of these clotting factors because it permits their calcium-dependent binding to negatively charged phospholipid surfaces.[94,95] The γ-carboxylation process is catalyzed by a vitamin K–dependent carboxylase. Thus vitamin K from the diet is reduced to vitamin K hydroquinone by vitamin K reductase (Fig. 39.2). Vitamin K hydroquinone serves as a cofactor for the carboxylase enzyme, which, in the presence of carbon dioxide, replaces the hydrogen on the γ-carbon of glutamic acid residues with a carboxyl group. During this process, vitamin K hydroquinone is oxidized to vitamin K epoxide, which is then reduced to vitamin K by vitamin K epoxide reductase (VKOR).[96]

Warfarin inhibits VKOR, thereby blocking the γ-carboxylation process.[96,97] This results in the synthesis of vitamin K–dependent clotting proteins that are only partially γ-carboxylated.[98] Warfarin acts as an anticoagulant because these partially γ-carboxylated proteins have reduced or absent biologic activity. The onset of action of warfarin is delayed until the newly synthesized clotting factors with reduced activity gradually replace their fully active counterparts.

The antithrombotic effect of warfarin depends on a reduction in the functional levels of factor X and prothrombin, clotting factors that have half-lives of 24 and 72 hours, respectively.[99] Because of the delay in achieving an antithrombotic effect, initial treatment with warfarin is supplemented by concomitant administration of a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux, in patients with established thrombosis or those who are at high risk for thrombosis.[99]

Pharmacology

Warfarin is a racemic mixture of *R*- and *S*-isomers. Warfarin is rapidly and almost completely absorbed from the gastrointestinal tract. Levels of warfarin in the blood peak about 90 minutes after drug administration.[99] Racemic warfarin has a plasma half-life of 36 to 42 hours, and more than 97% of circulating warfarin is bound to albumin. Only the small fraction of unbound warfarin is biologically active.[99]

Warfarin accumulates in the liver, where the two isomers are metabolized via distinct pathways. Oxidative metabolism of the more active *S*-isomer is mediated by CYP2C9 (see Fig. 39.2). Two relatively common variants, CYP2C9*2 and CYP2C9*3, have reduced activity. Patients with these variants require lower maintenance doses of warfarin. Polymorphisms in the C1 subunit of vitamin K reductase (VKORC1) can also influence the anticoagulant response to warfarin.[100,101] These findings have prompted the recommendation that patients starting on warfarin should be tested for these polymorphisms and that this information should be incorporated into their warfarin-dosing algorithms. However, whether warfarin-dosing algorithms that incorporate pharmacogenetics data improve clinical outcomes remains uncertain.

In addition to genetic factors, the anticoagulant effect of warfarin is influenced by diet, drugs, and various disease states. Fluctuations in dietary vitamin K intake affect the activity of warfarin. A wide variety of drugs can alter the absorption, clearance, or metabolism of warfarin.[99] Because of the variability in the anticoagulant response to warfarin, coagulation monitoring is essential to ensure that a therapeutic response is obtained.

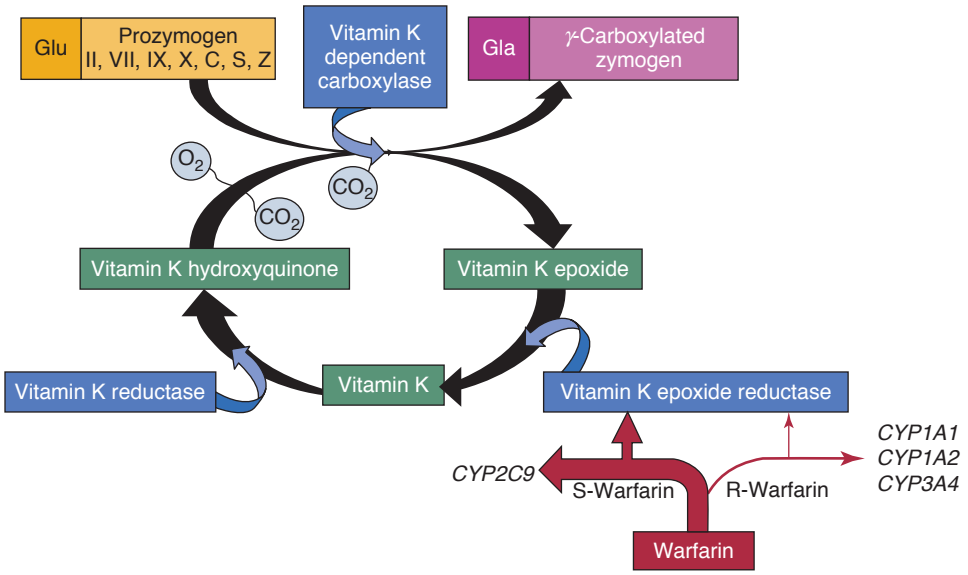

Figure 39.2 The vitamin K cycle and its inhibition by warfarin. Dietary vitamin K is reduced by vitamin K reductase to generate vitamin K hydroquinone. Vitamin K hydroquinone serves as a cofactor for the vitamin K–dependent carboxylase, which converts glutamic acid residues at the N-termini of the vitamin K–dependent precursors to γ-carboxyglutamic acid residues, thereby creating the so-called Gla-domain. By binding calcium, the Gla-domain is critical for the interaction of the vitamin K–dependent clotting factors with negatively charged phospholipid membranes. During vitamin K–dependent carboxylation, vitamin K is oxidized to vitamin K epoxide. Vitamin K epoxide is then converted to vitamin K by vitamin K epoxide reductase. Vitamin K antagonists, such as warfarin, interfere with this cycle by inhibiting vitamin K epoxide reductase. Supplemental vitamin K overcomes the inhibitory effects of vitamin K antagonists by providing more substrate for vitamin K reductase.

Monitoring

Warfarin therapy is most often monitored using the prothrombin time, a test that is sensitive to reductions in the levels of prothrombin, factor VII and factor X. The test is performed by adding thromboplastin—a reagent that contains tissue factor, phospholipid, and calcium—to citrated plasma and determining the time to clot formation. Thromboplastins vary in their sensitivity to reductions in the levels of the vitamin K–dependent clotting factors. Consequently less sensitive thromboplastins will trigger the administration of higher doses of warfarin to achieve a target prothrombin time. This is problematic because higher doses of warfarin increase the risk of bleeding.

The INR was developed to circumvent many of the problems associated with the prothrombin time. To calculate the INR, the patient's prothrombin time is divided by the mean normal prothrombin time, and this ratio is then multiplied by the international sensitivity index (ISI), an index of the sensitivity of the thromboplastin used for prothrombin time determination to reductions in the levels of the vitamin K–dependent clotting factors. Highly sensitive thromboplastins have an ISI of 1.0. Most current thromboplastins have ISI values that range from 0.9 to 1.4.

Although the INR has helped to standardize anticoagulant practice, problems persist. The precision of INR determination varies, depending on reagent-coagulometer combinations. This leads to variability in the INR results. Also complicating INR determination is unreliable reporting of the ISI by thromboplastin manufacturers.[99] Furthermore, every laboratory must establish the mean normal prothrombin time with each new batch of thromboplastin reagent. To accomplish this, the prothrombin time must be measured in fresh plasma samples from at least 20 healthy volunteers using the same coagulometer that is used for patient samples.[99]

For most indications, warfarin is administered in doses that produce a target INR of 2.0 to 3.0. An exception is patients with mechanical heart valves in the mitral position, in which case a target INR of 2.5 to 3.5 is recommended.[99] Studies in atrial fibrillation demonstrate an increased risk for cardioembolic stroke when the INR falls below 1.7 and an increase in intracranial bleeding with INR values over 4.5.[102] These findings highlight the fact that VKAs have a narrow therapeutic window. In support of this concept, a study in patients receiving long-term warfarin therapy for unprovoked VTE demonstrated a higher rate of recurrent VTE with a target INR of 1.5 to 1.9 compared with a target INR of 2.0 to 3.0.[103]

Dosing

Warfarin is usually started at a dose of 5 to 10 mg. The dose is then titrated to achieve the desired target INR. Because of its delayed onset of action, patients with established thrombosis or those at high risk for thrombosis are given concomitant treatment with a rapidly acting parenteral anticoagulant, such as heparin, LMWH, or fondaparinux. Initial prolongation of the INR reflects reduction in the functional levels of factor VII. Consequently concomitant treatment with the parenteral anticoagulant should be continued until the INR has been

therapeutic for at least 2 consecutive days. A minimum 5-day course of parenteral anticoagulation is recommended to ensure that the levels of prothrombin have been reduced into the therapeutic range with warfarin.[99]

Because warfarin has a narrow therapeutic window, frequent coagulation monitoring is essential to ensure that a therapeutic anticoagulant response is obtained. Even patients with stable warfarin dose requirements should have their INR determined every 2 to 4 weeks. More frequent monitoring is necessary when new medications are introduced because so many drugs enhance or reduce the anticoagulant effects of warfarin.

Side Effects

Bleeding. As with all anticoagulants, the major side effect of warfarin is bleeding. At least half of the bleeding complications with warfarin occur when the INR exceeds the therapeutic range. Bleeding complications may be mild, such as epistaxis or hematuria, or more severe, such as retroperitoneal or gastrointestinal bleeding. Life-threatening intracranial bleeding can also occur.[41]

To minimize the risk of bleeding, the INR should be maintained in the therapeutic range. In asymptomatic patients whose INR is between 4.5 and 9, warfarin should be withheld until the INR returns to the therapeutic range. If the INR is higher than 9, a therapeutic INR can be achieved more rapidly by administering low doses of sublingual vitamin K.[104,105] A vitamin K dose of 2 to 5 mg is usually adequate, but higher doses can be administered if more rapid reversal of the INR is required or if the INR is excessively high.

Patients with serious bleeding need more aggressive treatment. These patients should be given vitamin K to reverse the warfarin and prothrombin complex concentrate to replenish the missing clotting factors. Vitamin K should be administered by slow intravenous infusion at a dose of 10 mg; additional vitamin K should be given until the INR is in the normal range. Derived from pooled human plasma, three- and four-factor prothrombin complex concentrates are available. These differ in their content of factor VII; three-factor concentrate contains little or no factor VII, whereas four-factor prothrombin concentrate contains a full complement of factor VII as well as the other three vitamin K–dependent coagulation factors (factors II, IX, and X). Four-factor prothrombin complex concentrate is preferred over three-factor concentrate for warfarin reversal, but the three-factor form should be used if four-factor prothrombin concentrate is unavailable.[106] Prothrombin complex concentrate reverses the INR more rapidly than fresh frozen plasma and is associated with a lower risk of heart failure and transfusion-related lung injury because the required volume is much less. Recombinant factor VIIa should not be used for warfarin reversal because it supplements only one of the missing factors. In support of this concept, factor VIIa failed to attenuate warfarin-induced bleeding from punch biopsy sites in volunteers even though it normalized the INR.[107]

Warfarin-treated patients who experience bleeding when their INR is in the therapeutic range require investigation into the cause of the bleeding. Those with gastrointestinal bleeding often have underlying peptic ulcer disease or a tumor. Similarly, investigation of hematuria or uterine bleeding in patients with a therapeutic INR may unmask a tumor of the genitourinary system.

Skin Necrosis. A rare complication of warfarin, skin necrosis usually is seen 2 to 5 days after initiation of therapy. Well-demarcated erythematous lesions form on the thighs, buttocks, breasts, or toes. Typically, the center of the lesion becomes progressively necrotic. Examination of skin biopsies taken from the border of these lesions reveals thrombi in the microvasculature.

Warfarin-induced skin necrosis is seen in patients with congenital or acquired deficiencies of protein C or protein S.[108,109] Initiation of warfarin therapy in these patients produces a precipitous fall in plasma levels of proteins C or S, thereby eliminating this important anticoagulant pathway before warfarin exerts an antithrombotic effect by lowering of the functional levels of factor X and prothrombin. The resultant procoagulant state triggers thrombosis. Why the thrombosis is localized to the microvasculature of fatty tissues is unclear.

Treatment involves discontinuation of warfarin and, if needed, reversal with vitamin K. An alternative anticoagulant, such as heparin or LMWH, should be given to patients with thrombosis. Protein C concentrates can be given to protein C–deficient patients to accelerate healing of the skin lesions; fresh frozen plasma may be of value for those with protein S deficiency. Occasionally, when there is extensive skin loss, grafting is necessary.

Because of the potential for skin necrosis, patients with known protein C or protein S deficiency require overlapping treatment with a parenteral anticoagulant when warfarin therapy is being initiated. Warfarin should be started in low doses in these patients, and the parenteral anticoagulant should be continued until the INR is therapeutic for at least 2 to 3 consecutive days. Alternatively, a DOAC could be used in place of warfarin, but data with these agents in patients with protein C or protein S deficiency are lacking.

Pregnancy. Warfarin crosses the placenta and can cause fetal abnormalities or bleeding. The fetal abnormalities include a characteristic embryopathy, which consists of nasal hypoplasia and stippled epiphyses. The risk of embryopathy is highest if warfarin is given in the first trimester of pregnancy.[110] Central nervous system abnormalities can also occur with exposure to coumarin drugs at any time during pregnancy. Finally, maternal administration of warfarin produces an anticoagulant effect in the fetus, which can cause bleeding. This is of particular concern at delivery, when trauma to the head during passage through the birth canal can lead to intracranial bleeding. Because of these potential problems, warfarin is contraindicated in pregnancy, particularly in the first and third trimesters. Instead, heparin, LMWH, or fondaparinux can be given during pregnancy for the prevention or treatment of thrombosis. Warfarin does not pass into the breast milk. Consequently warfarin can safely be given to nursing mothers.

Special Problems

Patients being treated with a lupus anticoagulant or those who need urgent or elective surgery present special challenges.

Although observational studies have suggested that patients with thrombosis complicating antiphospholipid syndrome require higher-intensity warfarin regimens to prevent recurrent thromboembolic events, two randomized trials have demonstrated that the targeting of an INR of 2.0 to 3.0 is as effective as higher-intensity treatment and produces less bleeding.[111,112] Monitoring warfarin therapy can be problematic in patients with antiphospholipid syndrome if the lupus anticoagulant prolongs the baseline INR; factor X levels can be used in place of the INR to dose warfarin in such patients.

Periprocedural Management

Warfarin should be stopped 5 days before surgery or invasive procedures to allow the INR to return to normal levels. The INR should be determined before surgery to ensure that it is less than 1.5. Recent studies indicate that bridging with LMWH before and soon after surgery does not reduce the risk of thrombotic complications in patients with atrial fibrillation and increases the risk of bleeding after surgery.[113] However, few patients with atrial fibrillation and a prior history of stroke were included and patients with mechanical heart valves were excluded. Therefore bridging remains indicated in such patients. Bridging can be done with intravenous heparin or once- or twice-daily subcutaneous injections of LMWH when the INR falls below 2.0. Intravenous heparin should be stopped 4 to 6 hours before surgery, whereas the last dose of LMWH should be given 24 hours before surgery. Warfarin can be restarted 12 to 24 hours after surgery, and patients should receive prophylactic doses of heparin or LMWH after surgery until the INR is at least over 1.8.

In the case of urgent surgery, warfarin can be rapidly reversed with four-factor prothrombin complex concentrate and intravenous vitamin K. Prothrombin complex concentrate rapidly normalizes the INR; therefore patients can undergo surgery as soon as it is given.

Direct Oral Anticoagulants

The DOACs include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. All of these drugs have a rapid onset and offset of action and have half-lives that permit once- or twice-daily administration. Designed to produce a predictable level of anticoagulation, the DOACs are more convenient to administer than warfarin because they are given in fixed doses without routine coagulation monitoring.

Mechanism of Action

The DOACs are small molecules that bind reversibly to the active site of their target enzyme. Table 39.7 summarizes the pharmacologic properties of these agents.

Indications

The DOACs were compared with warfarin for stroke prevention in patients with nonvalvular atrial fibrillation in four randomized trials that enrolled 71,683 patients.[114-118] Compared with warfarin, the higher doses of the DOACs significantly reduced stroke or systemic embolism by 19% ($P = .001$), primarily driven by a 51% reduction in hemorrhagic stroke ($P < .0001$); they were associated with a 10% reduction in mortality ($P < .0001$).[119] The DOACs reduced intracranial hemorrhage by 52% compared with warfarin ($P < .0001$) but increased gastrointestinal bleeding by about 24% ($P = .04$).[119] Overall, therefore, the DOACs demonstrate a favorable benefit-to-risk profile compared with warfarin, and their relative efficacy and safety are maintained across a wide spectrum of patients with atrial fibrillation, including those over the age of 75 years and those with a prior history of stroke.[120] Based on these findings, DOACs are licensed as alternatives to warfarin for stroke prevention in nonvalvular atrial fibrillation, which is defined as atrial fibrillation that occurs in patients without mechanical heart valves or severe rheumatic valvular disease, particularly mitral stenosis and/or regurgitation.

The DOACs were compared with conventional anticoagulation therapy in 27,023 patients with acute VTE.[121-126] The primary efficacy endpoint in these trials was recurrent VTE, while the primary safety outcome was either major bleeding or the composite of major and clinically relevant nonmajor bleeding. In a pooled analysis of these trials, recurrent fatal and nonfatal VTE occurred in 2.0% of those given DOACs compared with 2.2% of those given VKAs (relative risk [RR]: 0.90, 95% confidence interval [CI]: 0.77–1.06).[127] Compared with VKAs, DOACs were associated with a 39% reduction in the risk of major bleeding (RR: 0.61, 95% CI: 0.45–0.83), a 63% reduction in intracranial bleeding (RR: 0.37, 95% CI: 0.21–0.68) and a 64% reduction in fatal bleeding (RR: 0.36; 95% CI: 0.15–0.84).[127] In addition, clinically relevant nonmajor bleeding was reduced by 27% with the DOACs compared with VKAs (RR: 0.73; 95% CI: 0.58–0.93).[127] Therefore the DOACs are noninferior to well-managed therapy with VKAs for the treatment of VTE but are associated with significantly less bleeding.

TABLE 39.7 Comparison of the Features of the Direct Oral Anticoagulants

Target	Dabigatran *Thrombin (IIa)*	Rivaroxaban *Factor Xa*	Apixaban *Factor Xa*	Edoxaban *Factor Xa*
Active drug	No	Yes	Yes	Yes
Onset time (h)	0.5-2	2-4	3-4	1-3
Half life (h)	12-17	5-13	~12	9-11
Renal excretion (%)	80	33	27	50

Whereas dabigatran and edoxaban were started after a minimum of a 5-day course of parenteral anticoagulant therapy, rivaroxaban and apixaban were administered in all-oral regimens starting with a higher dose for 21 days and 7 days, respectively. When used in this all-oral fashion, both agents were noninferior to conventional therapy and were associated with significantly less major bleeding. Therefore rivaroxaban and apixaban simplify treatment and facilitate out-of-hospital management of most patients with deep venous thrombosis and many with pulmonary embolism, thereby reducing healthcare costs. With these advantages, recent clinical guidelines now endorse the DOACs for first-line treatment of VTE in patients without active cancer. For those with active cancer, LMWH remains the preferred therapy.

Dabigatran, rivaroxaban, and apixaban have also been compared with enoxaparin for thromboprophylaxis after elective hip or knee arthroplasty, and although all three are licensed for this indication, dabigatran is rarely used.

Dosing

For stroke prevention in patients with nonvalvular atrial fibrillation, dabigatran is given at a dose of 150 mg twice daily with a dose reduction to 75 mg twice daily in those with a creatinine clearance of 15 to 30 mL/min; rivaroxaban is given at a dose of 20 mg once daily with a dose reduction to 15 mg once daily in patients with a creatinine clearance of 15 to 49 mL/min; apixaban is given at a dose of 5 mg twice daily with a dose reduction to 2.5 mg twice daily for patients with at least two of the following criteria; age of 80 years or more, body weight of 60 kg or less, and serum creatinine >1.5 g/dL; edoxaban is given at a dose of 60 mg once daily with a dose reduction to 30 mg once daily for patients with a creatinine clearance of 15 to 50 mL/min, body weight of 60 kg or less, or receiving potent P-glycoprotein inhibitors such as amiodarone or verapamil.

For the treatment of VTE, dabigatran is given at a dose of 150 mg twice daily after a minimum of a 5-day course of heparin or LMWH; rivaroxaban is started at a dose of 15 mg twice daily for 21 days and the dose is then reduced to 20 mg once daily thereafter; apixaban is started at a dose of 10 mg twice daily for 7 days and the dose is then reduced to 5 mg twice daily for the following 6 months, after which the dose can be further reduced to 2.5 mg twice daily; and edoxaban is given at a dose of 60 mg once daily after a minimum of a 5-day course of heparin or LMWH, with the dose reduced to 30 mg once daily for patients with a creatinine clearance of 15 to 50 mL/min, body weight of 60 kg or less, or receiving potent P-glycoprotein inhibitors.

For thromboprophylaxis after elective hip or knee replacement surgery, rivaroxaban is given at a dose of 10 mg once daily, whereas apixaban is given at a dose of 2.5 mg twice daily. These drugs are usually given for 14 days after knee arthroplasty and for 35 days after hip arthroplasty.

Monitoring

Although the DOACs are designed to be administered without routine monitoring, there are situations where determination of their anticoagulant activity can be helpful. These include assessment of adherence, detection of accumulation or overdose, identification of bleeding mechanisms, and determination of activity prior to surgery or intervention. For the qualitative assessment of anticoagulant activity, the prothrombin time can be used for factor Xa inhibitors and the aPTT for dabigatran.[128] Rivaroxaban and edoxaban prolong the prothrombin time more than apixaban. In fact, because apixaban has such a limited effect on the prothrombin time, anti–factor Xa assays are needed to assess its activity. The effect of the drugs on tests of coagulation varies depending on the time that the blood is drawn relative to the timing of the last dose of the drug and the reagents used to perform the tests. Chromogenic anti–factor Xa assays and a diluted thrombin clotting time with appropriate calibrators provide quantitative assays to measure the plasma levels of the factor Xa inhibitors and dabigatran, respectively.[129]

Side Effects

As with all anticoagulants, bleeding is the most common side effect of the DOACs. The DOACs are associated with less intracranial bleeding than warfarin. The increased risk of intracranial bleeding with warfarin likely reflects the reduction in functional levels of factor VII, which precludes efficient thrombin generation at sites of microvascular bleeding in the brain. Because the DOACs target downstream coagulation enzymes, they produce less impairment of hemostatic plug formation at sites of vascular injury.

A downside of the DOACs is the increased risk of gastrointestinal bleeding. This likely occurs because unabsorbed active drug in the gut exacerbates bleeding from lesions. Although dabigatran etexilate is a prodrug, only 7% is absorbed and the remainder passes through the gut, where at least two-thirds is metabolically activated to dabigatran by gut esterases.[130]

Dyspepsia occurs in up to 10% of patients treated with dabigatran; this problem improves with time and can be minimized by administering the drug with food. Dyspepsia is rare with rivaroxaban, apixaban, and edoxaban.

Periprocedural Management

Like warfarin, the DOACs must be stopped before procedures associated with a moderate or high risk of bleeding. The drugs should be held for 1 to 2 days or if renal function is impaired for longer. Assessment of residual anticoagulant activity before procedures associated with a high bleeding risk is prudent.

Management of Bleeding

The management of bleeding with DOACs is dependent upon the severity of bleeding and the drug that has been taken (Fig. 39.3). With minor bleeding, holding one or two doses of drug is usually sufficient. The approach to serious bleeding is similar to that with warfarin except that vitamin K administration is of no benefit. Thus, anticoagulant and antiplatelet drugs should be held, the patient should be resuscitated with fluids and blood products as necessary, and, if possible, the bleeding site should be identified and managed. Coagulation testing will determine the extent of anticoagulation, and renal

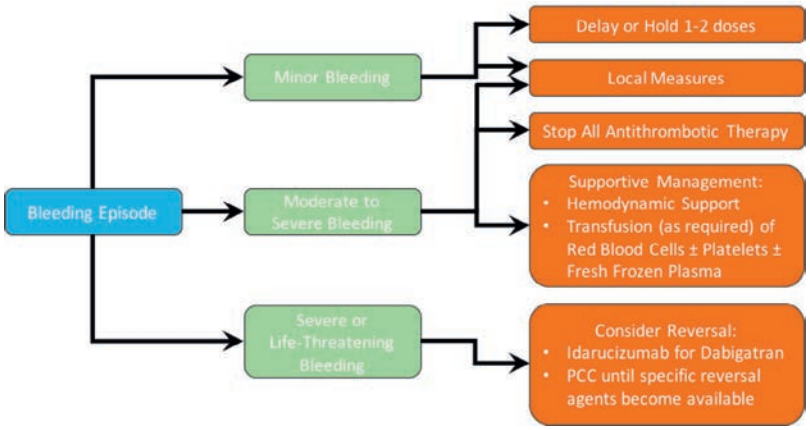

Figure 39.3 Flow diagram for the management of bleeding in patients taking DOACs.

function should be assessed so that the half-life of the drug can be calculated. Timing of the last dose of anticoagulant is important; administration of oral activated charcoal may help to prevent absorption of drug administered in the preceding 2 to 4 hours.

Anticoagulant reversal should be considered in patients with life-threatening bleeding, such as intracranial bleeding, bleeding that continues despite supportive measures, or if patients require urgent surgery. Idarucizumab is a specific reversal agent for dabigatran. A monoclonal antibody fragment, idarucizumab binds dabigatran with high affinity to form a 1 : 1 complex that is then cleared by the kidneys.[131] Idarucizumab is given as an intravenous bolus of 5 g.

Andexanet alfa and ciraparantag are under development for reversal of rivaroxaban, apixaban, and edoxaban, but neither is approved.[132] Until these reversal agents are available, intravenous prothrombin complex concentrate (25 to 50 U/kg) should be considered for reversal of the oral factor Xa inhibitors in patients with life-threatening or ongoing bleeding.

Special Considerations

In a phase II dose-finding study comparing dabigatran with warfarin in patients with mechanical heart valves, there was a trend for more ischemic strokes and more bleeding with dabigatran than with warfarin.[133] Consequently dabigatran and the other DOACs are contraindicated in patients with mechanical heart valves; such patients should receive warfarin. All DOACs pass through the placenta and should not be used in pregnancy. They should also be avoided in nursing mothers because it is uncertain whether they are excreted in breast milk. There is limited information about DOAC dosing in children.

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CHAPTER 40

Antiplatelet Agents

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INTRODUCTION

Platelets are the smallest blood cells in the human body, normally numbering 150–350 × 109/L, and play a central role in the normal homeostatic process of hemostasis and thrombosis. As first described in the 18th century,[1] platelets are involved in nearly all aspects of vascular occlusive disease. This includes the disruption of platelet- and fibrin-rich atherosclerotic plaques which lead to further platelet aggregation and deposition causing thrombus formation and, possibly, clinically relevant thrombotic events.[2] Antiplatelet agents modulate the role of platelets in these delicate processes. Thus a detailed understanding of platelet function and antiplatelet pharmacology is essential for the practicing vascular specialist.

NORMAL PLATELET FUNCTION AND PLATELET ACTIVATION

Normally platelets circulate without interacting with the blood vessel wall. This delicate balance is modulated by the interaction of platelets with the endothelium. The endothelium releases nitric oxide and prostacyclin to prevent platelet aggregation. In addition, endothelial cells express ADPase, which degrades adenosine diphosphate (ADP) released from activated platelets, further inhibiting platelet aggregation. A platelet life span ranges from 8 to 10 days.

Platelets are the essential components of primary hemostasis. Primary hemostasis is defined as the early stages of hemostasis to prevent blood loss. When vessel injury occurs, the subendothelium is exposed. Exposed tissue factor, subendothelial collagen, von Willebrand factor, and fibronectin interact with molecules expressed on the platelet surface *($\alpha_2\beta_1$, glycoprotein Ib/IX,* and *$\alpha_5\beta_1$)*. These interactions induce a conformational change in platelet morphology and stimulate platelet granule release of ADP and thromboxane A_2. Exposure of ADP receptors on activated platelets induces platelet aggregation by cross-linking ADP molecules. Thromboxane A2 induces vasoconstriction and further recruitment of platelets to the site of injury. Platelet activation also results in the expression of glycoprotein IIb/IIIa *(GP-IIB/IIIA)* on the platelet surface. *GP-IIB/IIIA* ligates divalent fibrinogen to bridge platelets, thus promoting aggregation. The platelet aggregates are woven into a fibrin mesh formed by the cleavage of fibrinogen by thrombin. This platelet plug forms the basis for the later stages of hemostasis. Antiplatelet agents modulate various steps in these intricate processes (Fig. 40.1).[3-5]

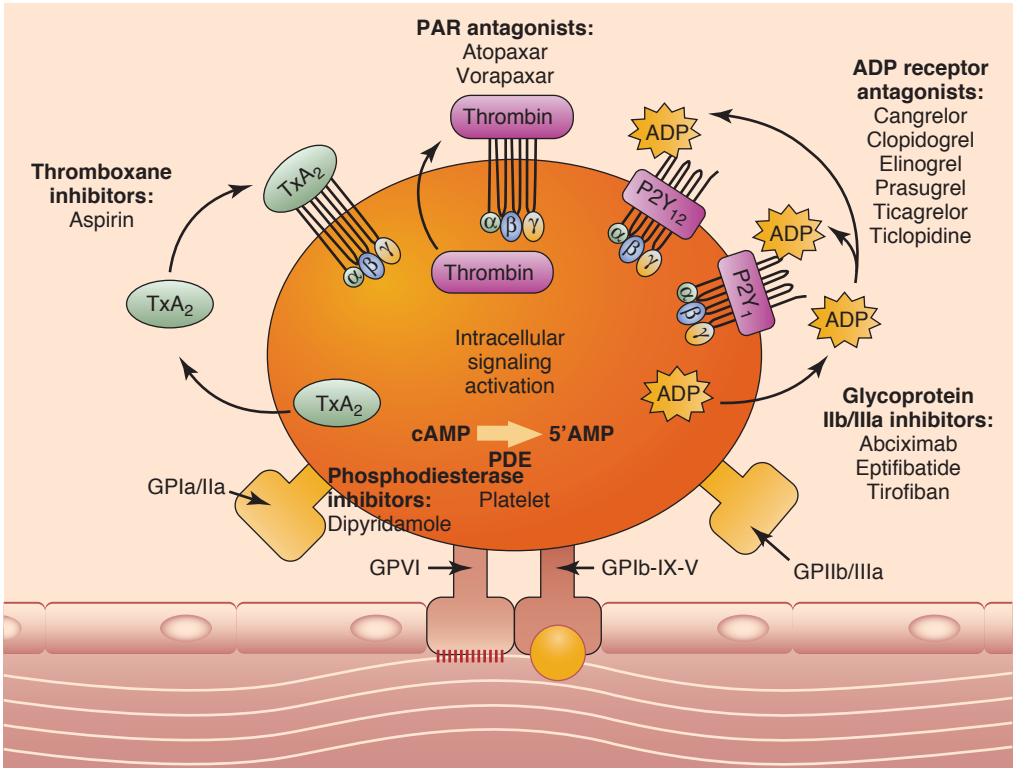

Figure 40.1 Platelet function and molecular targets of antiplatelet agents.[5] *ADP*, Adenosine diphosphate; *cAMP*, cyclic adenosine monophosphate; *TxA2*, thromboxane A2; *PAR*, protease-activated receptor.

Antiplatelet Agents

Thromboxane Inhibitors

Aspirin

Mechanism of Action. Aspirin is the most commonly used antiplatelet agent. It is a nonselective, irreversible cyclooxygenase enzyme *(COX)* inhibitor. It irreversibly acetylates *COX-1,* interrupting the production of prostaglandin H2 and the production of thromboxane A2 (TXA_2) to prevent platelet aggregation.[6,7] At higher doses, *COX-2* is also inhibited, promoting the antiinflammatory effect of aspirin.[8]

Indications and Dose. Aspirin is indicated for the prevention of cardiovascular events in patients with established coronary disease, peripheral arterial occlusive disease, or cerebrovascular occlusive disease.[9] More recently, the use of aspirin for primary prevention in patients without an established cardiovascular risk profile has been scrutinized.[10] Currently, there is no consensus recommendation regarding aspirin use for primary prevention of adverse cardiovascular events.[11,12]

Aspirin doses range from 75 to 325 mg/daily. Non–enteric-coated aspirin can achieve platelet inhibition approximately 1 hour after ingestion. Enteric-coated aspirin may achieve platelet inhibition at 3 to 4 hours after ingestion.[13] Chewing aspirin can result in inhibition as rapidly as 20 minutes after ingestion and is independent of the enteric coating of the pill.[14]

Side-Effect Profile. The most common side effects involve the gastrointestinal (GI) tract and range from dyspepsia to gastritis and ulcers, which may lead to bleeding and/or perforation. *Helicobacter pylori* infection may predispose to a higher risk of GI bleed. The risk of bleeding is estimated to be between 1% and 3% per year and increases with the addition of other antiplatelet agents (e.g., clopidogrel) or anticoagulants (e.g., warfarin).[13]

Allergy to aspirin is a rare phenomenon (~0.3% of patients). Bronchospasm can occur in patients allergic to aspirin, and this stands as a contraindication to aspirin administration. Allergy to aspirin may be more common in patients with asthma, urticaria, nasal polyps, or chronic rhinitis and thus administration should be undertaken with caution.[15]

Perioperative Management. Aspirin is generally discontinued 7 to 10 days before surgery in those at moderate to high risk for bleeding and a low estimated risk for cardiovascular events while off the medication. Otherwise, aspirin can be continued perioperatively in patients undergoing diagnostic or therapeutic interventions at low risk for bleeding. In patients undergoing vascular surgery, aspirin can be safely continued in the perioperative period.[16,17]

Thienopyridines (Adenosine Diphosphate Receptor Antagonists)

Clopidogrel

Mechanism of Action. Clopidogrel is a prodrug that is activated by the hepatic cytochrome-450 *(CYP450)* enzyme system (mainly *CYP2C19*). It irreversibly inhibits $P2Y_{12}$ (a key

ADP receptor) on the platelet surface.[18] Because it requires activation, the onset to therapeutic inhibition can be variable and can be influenced by genetic polymorphisms of the *CYP450* system.[19]

Indications and Dose. Clopidogrel is indicated for use in patients with unstable angina/non–ST-elevated myocardial infarction (UA/NSTEMI), ST-segment myocardial infarction (STEMI), recent myocardial infarction, recent cerebrovascular accident (CVA), or established peripheral arterial occlusive disease. Off-label use includes adjunctive therapy after percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, or peripheral artery percutaneous transluminal angioplasty. For patients with symptomatic carotid artery stenosis or with aspirin intolerance, clopidogrel is frequently used.

The usual daily dose of clopidogrel is 75 mg.[20] The time to platelet inhibition (the onset of action) is dose-dependent and may take to the second day of therapy to detect activity at the usual daily dose. During periods that require more rapid therapeutic levels (e.g., coronary stenting), a bolus dose between 300 and 600 mg of clopidogrel may be administered. This provides a more rapid onset of platelet inhibition (typically about 2 hours).[21,22]

Side-Effect Profile. The main side effect of clopidogrel is bleeding, and this can occur at any site. The incidence of severe GI hemorrhage is estimated to be 2%.[23] Other, less common side effects include pruritus and epistaxis.[23]

Perioperative Management. Clopidogrel should be discontinued 7 to 10 days prior to surgery (minimum of 5 days) before elective surgery, except in patients with coronary stents who have not completed a full course of dual antiplatelet therapy.

Drug-Drug Interactions. Clopidogrel's antiplatelet effect may be influenced by other drugs metabolized via the *CYP450* enzyme system.[24] Specifically, proton-pump inhibitors, which are inhibitors of *CYP2C19,* may lessen the ability of clopidogrel to inhibit platelet aggregation. This interaction may not be clinically relevant for most patients; however, current recommendations are to avoid the administration of *CYP2C19* inhibitors concomitantly with clopidogrel, whenever possible.[25]

Clopidogrel Resistance. The most important *CYP450* isoenzyme involved in clopidogrel metabolism (and thus activation) is *CYP2C19*. Patients with certain variant *CYP2C19* alleles *(CYP2C19*2 or CYP2C19*3)* may have reduced conversion of clopidogrel to the active metabolite compared with wild-type alleles *(CYP2C19*1),* which may result in reduced platelet inhibition,[26,27] This may result in a higher rate of adverse cardiovascular events.[28] Additional polymorphisms in *ABCB1* (a gene encoding the P-glycoprotein pump responsible for transporting molecules across intracellular and extracellular membranes) and *CYP3A4* can also reduce the effectiveness of clopidogrel and have been linked to adverse events.[29] However, there is insufficient evidence to recommend routine genetic testing. Tests are available to determine the *CYP2C19* genotype and may be used to determine therapeutic strategy (i.e., alternative treatment may be considered if the patient is identified as a poor metabolizer). Functional testing (e.g., the VerifyNow *P2Y12* assay) can be done after the initiation of treatment to determine a patient's clinical responsiveness to clopidogrel (i.e., assess for a nonresponder) and to further optimize antiplatelet strategy.[30,31] The GRAVITAS trial, however, did not show any benefit in individualizing the dose of clopidogrel in patients based on functional testing results.[32]

Ticlopidine

Ticlopidine is metabolized to an active metabolite that irreversibly blocks the *P2Y12* component of ADP receptors, reducing platelet aggregation. Like clopidogrel, it is metabolized via the *CYP450* system (mostly via *CYP3A4*).

Ticlopidine was previously approved for the prevention of ischemic stroke and for patients with recent coronary intervention. However, due to the incidence of severe neutropenia, aplastic anemia, and thrombotic thrombocytopenic purpura (TTP) associated with the drug, it is no longer available in the United States.

Ticagrelor

Mechanism of Action. Ticagrelor reversibly and noncompetitively binds the ADP *P2Y12* receptor reducing platelet aggregation. Due to the reversible nature of the receptor binding, the levels of platelet inhibition may fluctuate due to serum concentration of drug. It is metabolized via the cytochrome P450 enzyme system (the major isoenzyme is *CYP3A4*).[33]

Indications and Dose. Ticagrelor is indicated for acute coronary syndrome (ACS) to reduce the rate of cardiovascular death, myocardial infarction (MI), and stroke. Ticagrelor reduces the rate of in-stent thrombosis in patients stented during treatment of ACS. Off-label indications include use in patients with UA/NSTEMI and an allergy to or intolerance of aspirin.

Ticagrelor is initiated with a loading dose of 180 mg followed by a maintenance dose of 60–90 mg twice daily ($t_{1/2}$ = 7 to 9 hours).[34] Time to maximal inhibition of platelet aggregation is approximately 2 hours.

Side-Effect Profile. Side effects are similar to clopidogrel. Unique side effects specific to ticagrelor include elevated serum uric acid levels and transient dyspnea. Ticagrelor should, therefore, be used with caution in patients with a history of gouty arthritis or baseline hyperuricemia.[35,36] Dyspnea is typically self-limited and resolves within 1 week. It does not require any specific intervention nor does it warrant cessation of therapy unless the patient is intolerant to the medication-associated dyspnea.[37]

Perioperative Management. As with clopidogrel, ticagrelor should be discontinued 7 to 10 days prior to elective surgery (at least 5 days prior to procedure).

Drug-Drug Interactions. Strong inducers of the cytochrome P450 enzyme system (specifically inducers of *CYP3A4*) may decrease serum drug concentrations and reduce platelet inhibitory activity. Some examples of commonly used *CYP3A4* inducers include barbiturates, anticonvulsants (e.g., phenytoin), and glucocorticoids. Caution should be exercised when combining these classes of medications.

Prasugrel

Mechanism of Action. Prasugrel is a prodrug that is activated by the *CYP450* enzyme system. Its active metabolite irreversibly blocks the $P2Y_{12}$ component of ADP receptors on the platelet surface, reducing platelet activation and aggregation.[38]

Indications and Dose. Prasugrel is indicated for ACS managed with PCI or as an alternative for those patients intolerant to aspirin. It is contraindicated for use in patients with a history of transient ischemic attacks (TIAs) or stroke.[38]

Patients are usually started with a loading dose of 60 mg followed by a maintenance dose of 10 mg daily. For patients weighing less than 60 kg, the daily dose is typically 5 mg/day. Prasugrel administration is not recommended for patients above 75 years of age, though its use may be considered in high-risk situations.[38]

Side-Effect Profile. As with other thienopyridines, the major adverse side effect is bleeding. Other specific side effects include hypertension, hyperlipidemia, and thrombotic TTP.[39]

Perioperative Management. Similar to clopidogrel and ticagrelor, prasugrel should be discontinued 7 to 10 days prior to elective surgery (minimum 5 days prior).

Cangrelor

Mechanism of Action. Cangrelor reversibly binds to the *P2Y12* receptor to block ADP-induced platelet activation and aggregation.

Indications and Dose. It is used during coronary intervention to reduce the risk of periprocedural myocardial infarction, and stent thrombosis in patients who were not previously taking another *P2Y12* inhibitors.

The drug is administered with an intravenous 30 μg/kg bolus prior to PCI followed immediately by an infusion of 4 μg/kg per minute continued for at least 2 hours or for the duration of the procedure. The patient is then transitioned to an oral agent (clopidogrel, prasugrel, or ticagrelor) after the infusion is complete.

Side-Effect Profile. The major side effect of cangrelor is bleeding; however, in the Champion Phoenix study, the incidence of bleeding was no different from that seen in patients on clopidogrel. Dyspnea or breathlessness was the other adverse effect associated with cangrelor use and occurred in 1.2% of patients compared with 0.3% of patients on clopidogrel ($P < .001$).[40]

Perioperative Management. Cangrelor is approved for use in the periprocedural period only. After a bolus, platelet inhibition is almost immediate (<2 minutes). The half-life of cangrelor is 3 to 6 minutes, and platelet activity returns to normal within 60 minutes of cessation of the infusion.[41]

Glycoprotein IIB/IIIA (GPIIB/IIIA) Inhibitors

Mechanism of Action. Three intravenous *GPIIB/IIIAs* are available for clinical use: abciximab, eptifibatide, and tirofiban. Abciximab is a monoclonal antibody against the *GPIIB/IIIA* receptor, preventing activation and, thus platelet aggregation. Eptifibatide and tirofiban, on the other hand, are peptide antagonists of the *GPIIB/IIIA* receptor, which accomplish a similar effect in platelet inhibition.[42,43]

Indications and Dose. Abciximab is indicated for the prevention of ischemic complications in patients undergoing PCI and patients with UA or non–ST-elevation MI scheduled to undergo PCI. It is administered intravenously as a loading dose of 0.25 mg/kg given prior to starting PCI followed by an infusion of 0.125 μg/kg per minute.[43,44]

Eptifibatide is indicated for patients with ACS who are to be managed medically or those undergoing PCI. It is administered intravenously with a bolus of 180 μg/kg followed by a continuous infusion of 2 μg/kg per minute.[43,44]

Tirofiban is indicated for patients with UA/non–ST-elevation MI to decrease the rate of adverse cardiovascular events. It is administered intravenously as a loading dose of 25 μg/kg followed by a continuous infusion dose of 0.15 μg/kg per minute.[43,44]

Side-Effect Profile. The main adverse effect associated with all the *GPIIB/IIIA* modulators is bleeding, especially when these drugs are combined with other antiplatelet agents or anticoagulants. Other side effects associated with abciximab use include nausea, hypotension, and chest pain. Eptifibatide is associated with hypotension and tirofiban has been associated with coronary artery dissection. All the *GPIIB/IIIA* modulators are associated with thrombocytopenia. With abciximab, thrombocytopenia occurs in up to 5% of patients. Thrombocytopenia is less common with the two other agents (1% of patients).[45]

Perioperative Management. Abciximab provides inhibition of platelet aggregation greater than 80% at 10 minutes after administration. It has a plasma half-life ($t_{1/2}$) of 30 minutes; however, the dissociation half-life from the *GPIIB/IIIA* receptor can take up to 4 hours. Consequently, the infusion should be stopped at least 12 hours prior to surgery.[46,47]

Eptifibatide achieves more than 80% inhibition of platelet aggregation within 5 minutes after bolus dose and has a half-life of 2.5 hours. It should be stopped 2 to 4 hours prior to elective surgery.[47]

Tirofiban achieves inhibition of platelet aggregation greater than 90% within 10 minutes and has a half-life of 2 hours. It should also be stopped 2 to 4 hours prior to elective surgery.[47]

Phosphodiesterase Inhibitors

Dipyridamole

Mechanism of Action. Dipyridamole inhibits the activity of adenosine deaminase and phosphodiesterase to increase the concentration of adenosine and cyclic adenosine monophosphate *(cAMP),* which promotes vasodilation and inhibits platelet aggregation. At baseline, dipyridamole alone is a relatively weak antiplatelet agent. A combination medication of dipyridamole and aspirin (Aggrenox) has been used for prophylaxis against stroke.[48,49]

Indications and Dose. Dipyridamole is indicated as a pharmacologic agent for cardiac stress testing. The combination drug, Aggrenox, is indicated for stroke prevention.[50-52]

Dipyridamole alone can be administered orally or intravenously. Oral doses are typically between 50 and 100 mg three to four times daily. The intravenous dosing for cardiac stress testing is usually 0.14 mg/kg per minute for 4 minutes with a maximum dose of 60 mg. Aggrenox contains 200 mg of dipyridamole and 25 mg of aspirin, and is administered twice daily.[48]

Side-Effect Profile. Oral administration has been associated with headache most commonly, but also dizziness, skin rash, and GI upset. Intravenous administration is associated with worsening chest pain, dizziness, or headache.[48] The vasodilatory effect of dipyridamole may adversely affect cardiac perfusion; therefore caution should be exercised when using this medication

in patients with established coronary disease. Contraindications to dipyridamole for cardiac stress testing include bronchospastic lung disease with ongoing wheezing or significant reactive airway disease, hypotension (SBP < 90 mm Hg) or uncontrolled hypertension (SBP > 200 mm Hg), ingestion of caffeine within 12 hours of the procedure, or UA, ACS, or recent acute MI (PMID: 26914678).

Perioperative Management. The half-life of dipyridamole is 10 to 12 hours. Perioperative management of Aggrenox is dictated by the aspirin component, which produces irreversible *COX-1* inhibition to reduce platelet aggregation. This may be stopped 7 to 10 days in advance of surgery, if necessary.

Protease-Activated Receptor-1 Inhibitors

Vorapaxar

Mechanism of Action. Vorapaxar is a reversible antagonist of the protease-activated receptor-1 *(PAR-1)* to inhibit thrombin-induced and thrombin receptor agonist peptide *(TRAP)*–induced platelet aggregation.[53,54]

It achieves 80% or greater inhibition of TRAP-induced platelet aggregation within 1 week of starting therapy and has a half-life of 3 to 4 days.[54]

Indications and Dose. Vorapaxar is indicated to reduce adverse cardiovascular events in patients with a history of MI or with peripheral arterial disease (PAD).[55,56]

The approved dose of vorapaxar is 2.5 mg (vorapaxar sulfate) orally once daily in combination with aspirin and/or clopidogrel.[56]

Side-Effect Profile. Bleeding is the major adverse effect associated with vorapaxar use. In the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2P) study, any degree of bleeding was found in 25% of patients. Clinically significant bleeding (any bleeding requiring medical attention, including intracranial hemorrhage [ICH] or overt signs of bleeding with a drop in hemoglobin of ≥3 g/dL), occurred in 13.4% of patients.[56] Also, patients with a history of ischemic stroke had higher rates of ICH on vorapaxar compared with placebo. Consequently vorapaxar is contraindicated in patients with a history of stroke, TIA, or ICH.[56] Other, less common side effects include anemia, depression, and rash.[57]

Atopaxar

Similar to vorapaxar, atopaxar is a selective *PAR-1* antagonist that blocks thrombin-mediated platelet activation. It is currently in clinical trial and is not FDA approved.

CLINICAL USE OF ANTIPLATELET AGENTS IN VASCULAR DISEASE

Cardiovascular Death, Stroke, or Myocardial Infarction

The primary prevention of cardiovascular disease using antiplatelet agents is controversial. The most recent CHEST guidelines from 2012 recommend the use of low-dose aspirin (75 to 100 mg) over no aspirin in patients aged 50 years or older without symptomatic cardiovascular disease. This recommendation was based on the 2009 Antithrombotic Trialists collaboration study demonstrating a reduction in nonfatal MI (low-risk patients had 6 fewer MIs per 1000 patients treated, moderate-risk patients had 19 fewer nonfatal MIs per 1000 treated, and high-risk patients had 31 fewer nonfatal MIs per 1000 treated) and improved total mortality (six fewer deaths per 1000 treated in low-risk and moderate- to high-risk groups) in patients taking aspirin based on a 10-year risk estimate using the Framingham risk score. There was, however, an increase in major bleeding in all groups taking aspirin compared with those not taking aspirin.[12,58] In a more recent meta-analysis, aspirin reduced the incidence of cardiovascular events by 10%, driven mostly by a significant reduction in nonfatal MI. Cardiovascular death was not improved with intake of aspirin, and the incidence of bleeding was significantly higher in those patients. Consequently, the authors were not able to make a recommendation for aspirin use in the primary prevention of cardiovascular disease.[59]

Secondary prevention of adverse cardiovascular events in patients who have survived an occlusive episode is well validated.[9,60] Antiplatelet therapy reduced subsequent vascular events by 25% in patients with previous MI, by 30% in patients with an acute MI, by 22% in patients with previous CVA/TIA, and by 11% in patients with acute CVA (Fig. 40.2). The positive effects were independent of the aspirin dose used.[9,61]

The CAPRIE trial compared clopidogrel to aspirin in 19,185 patients with recent stroke, MI, or symptomatic PAD. The study found that patients treated with clopidogrel had an annual 5.32% risk of stroke, MI, or death compared with 5.83% in patients treated with aspirin (8.7% relative risk reduction favoring clopidogrel).[23]

It should be noted that there is some evidence that the sudden discontinuation of aspirin therapy may be associated with an increased risk of thrombotic events, especially within the first 5 to 7 days. These include ACSs, stent-associated thrombosis, acute MI, ischemic stroke, and limb ischemia. Although further study is needed, it appears that aspirin withdrawal may be associated with a prothrombotic state.[62]

Peripheral Artery Disease

Relative to the amount of evidence regarding cardiovascular death, stroke, and MI in patients taking antiplatelet agents, the literature on the impact of antiplatelet agents on the natural history of PAD is not as clear or robust.[63,64]

The recent TRA 2P trial assessing vorapaxar for the secondary prevention of ischemic events enrolled patients with stable atherosclerotic disease, including recent MI, CVA, and symptomatic PAD (claudication with an ABI ≤0.85 or previous revascularization for ischemia).[56] The patients with symptomatic PAD were studied separately regarding specific limb efficacy endpoints including acute limb ischemia (ALI), the need for peripheral revascularization (urgent and elective), or hospitalization for any vascular cause of an ischemic nature. Vorapaxar, in combination with other antiplatelet agents, reduced the risk

Category of Trial	No of Trials with Data	NO (%) OF VASCULAR EVENTS: Allocated Antiplatelet	Adjusted Control	Observed-Expected	Variance	% Odds Reduction (SE)
Previous myocardial infarction	12	1,345/9,984 (13.5)	1,708/10,022 (17.0)	−159.8	567.6	25 (4)
Acute myocardial infarction	15	1,007/9,658 (10.4)	1,370/9,644 (14.2)	−181.5	519.2	30 (4)
Previous stroke/transient ischaemic attack	21	2,045/11,493 (17.8)	2,464/11,527 (21.4)	−152.1	625.8	22 (4)
Acute stroke	7	1,670/20,418 (8.2)	1,858/20,403 (9.1)	−94.6	795.3	11 (3)
Other high risk	140	1,638/20,359 (8.0)	2,102/20,543 (10.2)	−222.3	737.0	26 (3)
Subtotal: all except acute stroke	188	6,035/51,494 (11.7)	7,644/51,736 (14.8)	−715.7	2,449.6	25 (2)
All trials	**195**	**7,705/71,912 (10.7)**	**9,502/72,139 (13.2)**	**−810.3**	**3,244.9**	**22 (2)**

Heterogeneity of odds reductions between:
Five categories of trial: $\chi^2 = 21.4$, $df = 4$; $P = 0.0003$
Acute stroke *v* other: $\chi^2 = 18.0$, $df = 1$; $P = 0.00002$

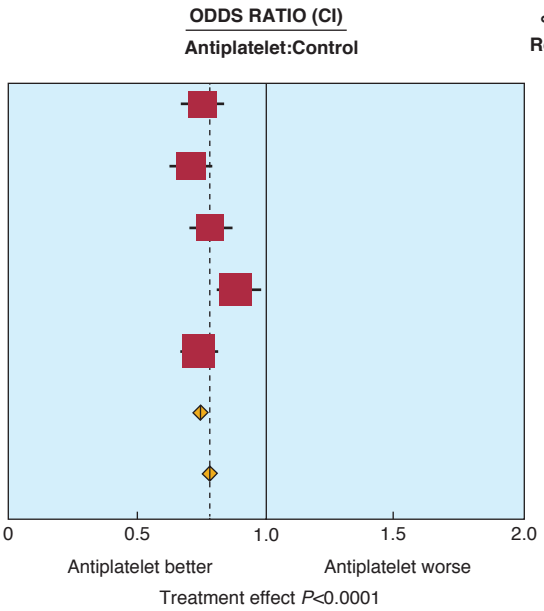

Figure 40.2 Proportional effects of antiplatelet therapy on vascular events.[9]

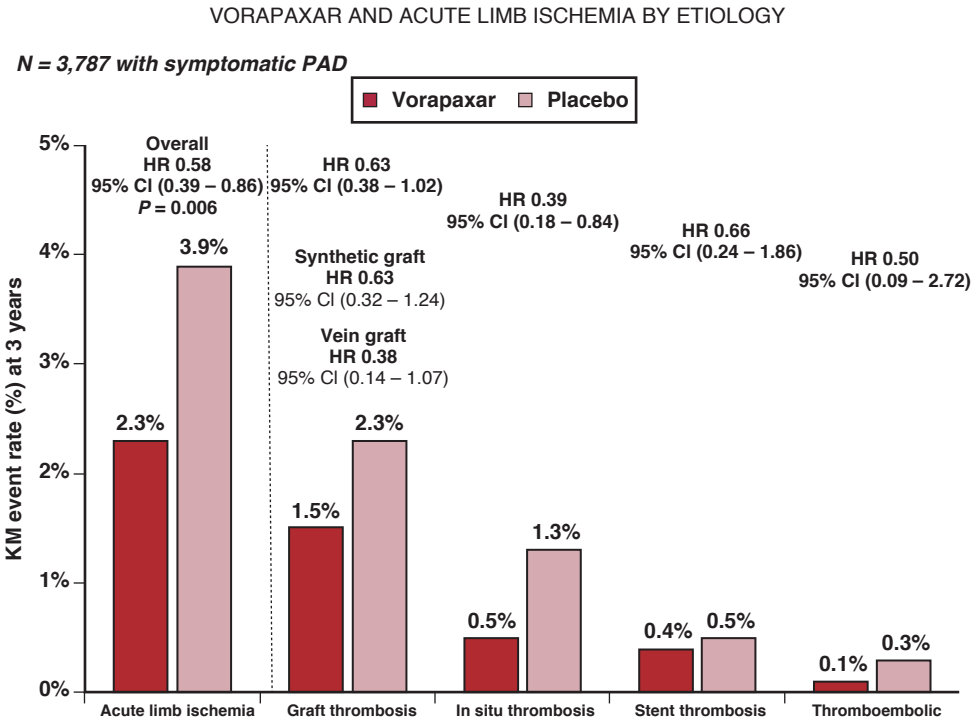

Figure 40.3 Vorapaxar and acute limb ischemia by etiology.[65] *PAD*, Peripheral arterial disease.

of hospitalization for ALI (2.3% vs. 3.9%) and the need for peripheral revascularization (18.4% vs. 22.2%) compared with placebo, respectively.[55] A follow-up study on ALI in this patient cohort showed that vorapaxar reduced the risk of a first ALI event by 42% and reduced total ALI events by 41% compared with the placebo arm. This reduction was evident for all etiologies of ALI (graft thrombosis, in situ thrombosis, stent thrombosis, or thromboembolism; Fig. 40.3).[65]

Given the paucity of data regarding antiplatelet agent use specifically for peripheral artery disease, the main indication for the use of antiplatelet agents in peripheral artery disease is to reduce the risk of cardiovascular death, stroke, and MI.

Perioperative Management of Dual Antiplatelet Therapy

Dual antiplatelet therapy (DAPT) generally refers to a combination of aspirin and a $P2Y_{12}$ inhibitor (a thienopyridine), such as clopidogrel. Patients with a coronary artery disease (CAD) and history of MI are at an increased risk of recurrent infarctions

as a result, in part, of enhanced platelet activation. Aspirin alone suppresses only one pathway of platelet activation. DAPT suppresses more than aspirin alone and has been shown to improve cardiovascular endpoints in patients with CAD. Coronary artery stenting is done with either bare-metal stents or drug-eluting stents (DESs). The 2014 American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommended DAPT in all patients with bare-metal coronary stents for at least 30 days after implantation. Discontinuing DAPT before 30 days is associated with an increased risk of stent thrombosis, adverse cardiovascular events, and mortality.[62] Thus the timing of procedures should take this risk into account. Elective procedures should be delayed until after the first 30 days after bare-metal stent implantation. For urgent, emergent, or nonelective operations, DAPT should generally be continued within the first 30 days after stent implantation unless the bleeding risk associated with the procedure is thought to be higher than the risk of stent thrombosis or adverse cardiovascular events. In these cases, aspirin alone should be continued.[66]

First-generation DESs were sirolimus- or paclitaxel-eluting stents. The newer DESs use everolimus or zotarolimus. The 2014 AHA/ACC guidelines for patients with DES recommended therapy for 12 months.[66] This recommendation was formed from the evidence of stent thrombosis within the first 3 to 6 months in the first-generation of DESs.[67-69] More recent studies on the newer generation of DESs have shown that they are associated with a lower risk of stent thrombosis.[70,71] A 2016 update to the AHA/ACC guidelines recommends that elective surgery be delayed for 3 months in patients treated with newer-generation DESs (Fig. 40.4).[71] For patients treated with greater than 3 months of therapy, DAPT may be discontinued for the procedure, if necessary, however with a slightly increased risk of thrombosis within the 3- to 6-month time frame. After 6 months, DAPT is safe to discontinue for procedures. In all cases, aspirin should be continued throughout the perioperative period, if possible. DAPT should be resumed as soon as the perioperative bleeding risk is considered low.[72]

For patients who require urgent or emergent surgery before the recommended minimum duration of DAPT, the risk of

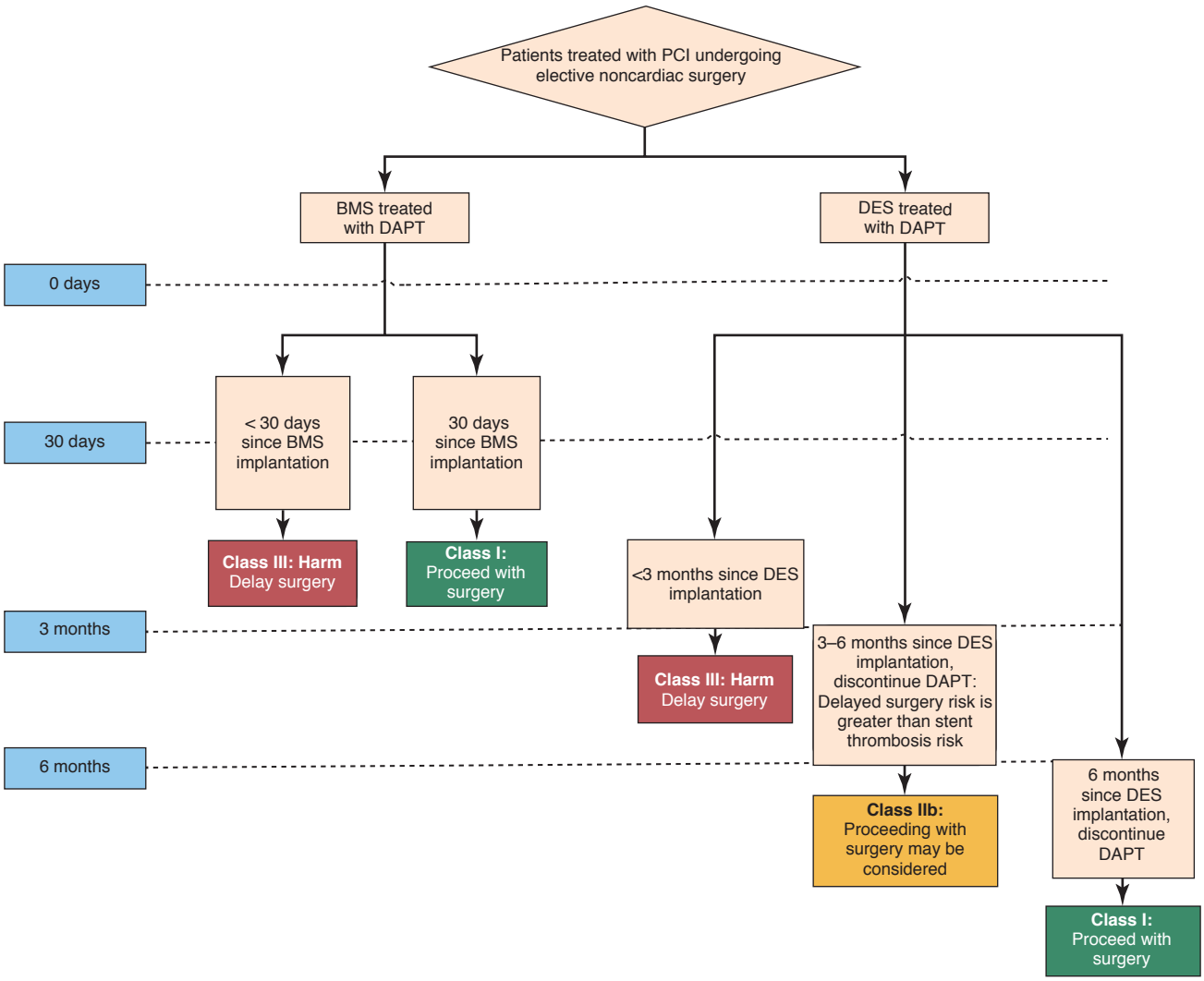

Figure 40.4 2016 ACC/AHA Guidelines for Perioperative Management of Dual Anti-Platelet Agents in patients undergoing noncardiac surgery. *DAPT*, Dual antiplatelet therapy; *DES*, drug-eluting stents; *PCI*, percutaneous coronary intervention.

discontinuing the DAPT should be weighed against the risk to the patient of not undergoing the procedure. Strategies to limit the risk of adverse cardiovascular events or perioperative bleeding include perioperative platelet transfusion and "bridging" with an intravenous platelet inhibitor. Platelet transfusion may be used to stem the risk of bleeding in patients with DAPT; however, no studies have been performed to develop an optimal management strategy. Perioperative intravenous antiplatelet bridging has been studied. It has not been proven to eliminate the risk of stent thrombosis and may, in fact, be associated with a higher incidence of bleeding complications.[73,74]

The long-term duration of DAPT has been a focus of more recent studies. The Dual Antiplatelet Study (DAPT study) assessed 12 months versus 30 months of DAPT after coronary stenting. It showed a significant reduction of late coronary stent thrombosis and less major adverse coronary or cerebrovascular events in patients treated with DAPT compared with aspirin alone. The Dual Anti-Platelet Score (http://www.daptstudy.org/for-clinicians/score_calculator.htm) was developed from this study and is a useful tool for assessing the benefit for continued DAPT in these patients.[71] In patients with bleeding complications, or with a relatively increased risk of bleeding (e.g., history of TIA or stroke, age ≥75 years, recent trauma or surgery, recent or recurrent GI bleeding, active peptic ulcer disease, severe hepatic impairment, body weight <60 kg, or use of oral anticoagulants), consideration can be given for treatment for less than 12 months with DAPT.[71,75]

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CHAPTER 41

Thrombolytic Agents

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Embolic and thrombotic events in the arterial and venous systems lead to end-organ malperfusion and dysfunction. In the past, open surgical procedures were used to restore vessel patency and organ function; however, with the advent of thrombolytic agents and endovascular techniques, intravenous thrombolysis (IVT) and catheter-directed thrombolysis (CDT) have become essential components in the contemporary management of acute arterial and venous thrombotic conditions.

Thrombolytic agents have evolved with time, and many of the original agents (streptokinase [SK] and urokinase [UK]) are no longer manufactured in the United States, although they still hold Food and Drug Administration (FDA) labels for use. In current practice, alteplase (recombinant tissue plasminogen activator [rt-PA]) is the agent most commonly used. Current FDA indications for thrombolysis include acute myocardial infarction (AMI),[1-4] pulmonary embolism (PE),[1,2,5] acute ischemic stroke (AIS),[2] arterial thrombosis and embolization,[1] deep venous thrombosis (DVT),[1] and central venous catheter occlusion (Table 41.1).[2]

HISTORY

Early theories on the process of clot lysis arose from observations that postmortem blood existed in both liquid and coagulated forms. In 1769, Morgagni noted this phenomenon occurred after traumatic death,[6] and in 1906, Morawitz found that postmortem liquid blood contained no fibrinogen and could liquefy coagulated blood.[7] It was postulated that an "inactive component" of blood, controlled by a "regulator," could be converted into a "fibrin-degrading agent."

The "inactive component" was first described by Milstone in 1941 as "lytic factor" and is now known as plasminogen.[8] Subsequently, Kaplan and Christensen separately identified the "fibrin-degrading agent" as plasmin.[9-11] The "regulator," or tissue plasminogen activator (t-PA), was the last to be isolated in 1957 by Albrechtsen.[12]

The discovery of the first thrombolytic agent, SK, came by chance at Johns Hopkins University in 1933 by Tillett. He observed that streptococcus in human plasma would

Abstract

Intravenous thrombolysis and catheter-directed thrombolysis (CDT) have become essential components in the contemporary management of acute arterial and venous thrombotic conditions. There has been significant growth in the area of CDT devices and thrombolytic agents, allowing for expansion in clinical applications and safety profile

Keywords

Thrombolysis
catheter-directed thrombolysis
embolic
deep venous thrombosis
acute myocardial infarction
limb ischemia
stroke
pulmonary embolism
urokinase
alteplase
reteplase
tenecteplase

TABLE 41.1 Thrombolytic Agents and Indications Approved by the US Food and Drug Administration as of 2012

Generic Name	Trade Name	Manufacturer	FDA Indication
Streptokinase[a]	Streptase Kabikinase	CSL Behring (King of Prussia, Pennsylvania) Pharmacia & Upjohn AB	AMI, PE, DVT, peripheral arterial thrombosis or embolism
Urokinase[a]	Kinlytic	Microbix Biosystems (Ontario, Canada)	PE
Alteplase	Activase CathFlo Activase	Genetech (South San Francisco, California) Genetech	AMI, PE, stroke Central venous catheter occlusion
Reteplase	Retavase	Cornerstone Therapeutics (Cary, North Carolina)	AMI
Tenecteplase	TNKase	Genetech	AMI

[a]Though still FDA approved, no longer available in the United States.
AMI, Acute myocardial infarction; *DVT*, deep venous thrombosis; *FDA*, US Food and Drug Administration; *PE*, pulmonary embolism.

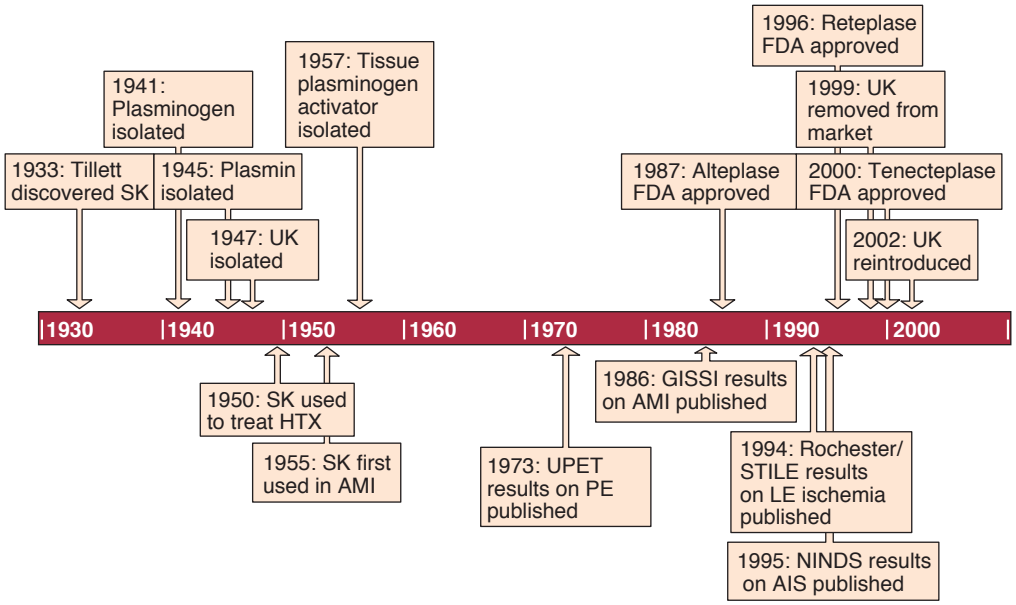

Figure 41.1 Timeline of key moments in thrombolytic history. *AMI*, Acute myocardial infarction; *AIS*, Acute ischemic stroke; *FDA*, US Food and Drug Administration; GISSI, Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; *HTX*, hemothorax; *LE*, lower extremity; *NINDS*, National Institute of Neurological Disorders and Stroke; *PE*, pulmonary embolism; *SK*, streptokinase; *STILE*, surgery or thrombolysis for the ischemic lower extremity; *UK*, urokinase; *UPET*, Urokinase Pulmonary Embolism Trial.

agglutinate, whereas streptococcus in human serum did not. He hypothesized that fibrinogen, present in plasma but not in serum, bound to the bacteria and caused agglutination. To test the hypothesis, he compared human plasma in test tubes as a control to human plasma in which streptococci were added. After addition of calcium, both tubes demonstrated clot formation. However, after the test tubes sat overnight, he noted the clot had liquefied in the streptococcal-containing tube. He attributed this finding to the production of "fibrinolysin" by streptococci.[13,14] A year later he isolated "fibrinolysin," which is now known as SK.[15]

In 1949, Tillett and Sherry reported the first clinical uses of SK in the thoracic cavity to treat empyema and retained hemothorax.[16,17] They reported the first human intravascular experience with SK in 1954.[18,19] Urokinase was the second thrombolytic agent discovered in 1946, and put into clinical use in 1961.[20] As experience with these two early agents grew and additional agents developed, large clinical trials encompassing many vascular applications soon followed, including two of the earliest, AMI and PE (Fig. 41.1).

THROMBOLYTIC DRUG ADMINISTRATION

Systemic/Intravenous Thrombolysis

When thrombolysis was first introduced, systemic delivery via a peripheral intravenous catheter was the only method of administration. Although this was effective in certain clinical scenarios, it required large doses of thrombolytic agent with an increased risk of hemorrhagic complications. The development of CDT has allowed a more targeted delivery of thrombolytic agents in smaller doses. However, IVT still remains a common

mode of delivery in applications in which preservation of end organ function requires rapid delivery (AMI, AIS).

Catheter-Directed Thrombolysis

CDT provides direct delivery of the thrombolytic agent into existing thrombus.[21,22] It is the preferred method of delivery for acute limb ischemia,[23,24] DVT,[25] and arteriovenous graft (AVG) occlusion.[26] The endovascular techniques used for CDT also permit concomitant percutaneous treatment of the underlying culprit lesions responsible for vessel or graft occlusion.[3]

CDT requires traversal of the occluded arterial or venous thrombosis with a guide wire, followed by placement of a multiple side-hole infusion catheter. An initial bolus is delivered via pulse spray technique. Depending on the particular vessel and end organ being treated, a continuous infusion for a specified period of time follows. To maximize the effectiveness and minimize systemic delivery of the thrombolytic, the infusion catheter side holes should be placed within the thrombus. Heparin is used as an ancillary drug during CDT and commonly infused through the indwelling arterial sheath. Administration of heparin is crucial to prevent propagation of thrombus around the indwelling catheter.[23,24,27] Full anticoagulation with heparin with an activated partial thromboplastin time (aPTT) of 60 to 80 seconds should be achieved before thrombolysis, but once CDT has begun, the heparin dose should be decreased to 500 to 1000 U/h. The heparin drip should be adjusted to maintain an aPTT no more than 1.5 times control. Full anticoagulation with larger doses of heparin during CDT has not improved outcomes, and evidence suggests that excessive anticoagulation can potentiate bleeding complications.[28]

Catheter-Directed Thrombolysis With Mechanical Thrombectomy

Percutaneous mechanical thrombectomy is a catheter-based therapy that disrupts the thrombus and allows better penetration of the clot by the thrombolytic agent. Its putative advantages include decreased thrombolytic dosing and shortened therapy time. Most mechanical devices were originally used for the treatment of AVG thrombosis,[29] but their use has been extended to the peripheral vasculature (discussed in greater detail in Chapters 101, 161, and 162).[30] A number of methodologies and devices exist for mechanical thrombectomy, each with advantages and disadvantages:

1. Hydrodynamic: Saline is infused and aspirated to create a local reduction in pressure (the Venturi effect).
2. Rotational recirculation: Rotating blades or propellers macerate the thrombus.
3. Mixing: Devices with a double-balloon catheter system confine the thrombolytic agent within a vessel, whereas a rotating, sinusoidal wire disrupts the clot.
4. Ultrasound: High-frequency, low-power ultrasound energy is delivered to loosen and separate fibrin strands to permit better penetration of the thrombolytic agent.
5. Aspiration: Aspiration of thrombus by a large suction catheter and syringe.

Monitoring

No existing laboratory test directly monitors the degree and effectiveness of thrombolysis. D-dimer and fibrin degradation products are elevated by thrombolysis, but levels do not correlate with the degree of thrombolysis. Thrombolytic therapy creates a dynamic fibrinolytic state consisting of both thrombus dissolution and thrombus formation. Formation occurs in an attempt to replace lysed clot, and coagulation factors and fibrinogen are consumed in the process. If fibrinogen drops below 100 mg/dL (2.9 mcmol/L) or the aPTT increases above 100 seconds, excessive consumption of coagulation factors is present and an increased risk of hemorrhagic complications exists. In these situations, it is prudent to reduce or temporarily stop the lytic infusion until fibrinogen increases or the aPTT decreases, or both.[31]

Other laboratory tests for indirect monitoring of the thrombolytic state include hemoglobin, platelet count, and creatinine. Patients treated by thrombolysis should be monitored in the intensive care unit or intermediate unit, where laboratory tests can be drawn at 4- to 6-hour intervals and patients assessed on an hourly basis.[1-5,31]

With CDT, serial angiography is performed through the indwelling catheter to assess the results of thrombolysis at 6- to 12-hour intervals over a 24- to 48-hour period. Restored pulse or Doppler signal or improved symptoms can be used as surrogates for successful treatment. CDT should be discontinued once organ perfusion has been adequately restored, and transition to full anticoagulation with heparin instituted.[23,24,27] Thrombolysis beyond the 48-hour window increases the risk of complications with little to no additional benefit.

Complications

Complications of thrombolytic therapy can be classified as hemorrhagic, antigenicity-related, catheter-related, or embolic.

Hemorrhagic

Bleeding is always a risk when thrombolysis is used. Major versus minor bleeding depends on the degree of bleeding and clinical consequence, but in general, major bleeding includes intracerebral, retroperitoneal, or gastrointestinal hemorrhage. Minor bleeding is usually at the puncture site for CDT and managed with local measures.[31,32] Puncture-site bleeding can become major if a large hematoma develops or if blood tracks into potential spaces such as the retroperitoneum. Ultrasound guidance can minimize multiple needle passes for vascular access and thus minimize this bleeding risk.

The risk of remote-site bleeding increases as more thrombolytic drug is administered and clotting factors and fibrinogen are depleted. In general, patients treated for pathologies that require longer infusions have a higher bleeding risk. Acute limb ischemia, PE, and DVT use more total thrombolytic when compared with AMI and AIS. AVG and catheter occlusion use the smallest doses.[33]

Intracerebral hemorrhage (ICH) is the most dreaded complication. AIS is associated with the greatest incidence of ICH (6.4%

to 8.8%). Thrombolysis provides reperfusion of a stunned penumbra, but it also lyses hemostatic plugs, leading to hemorrhagic reperfusion.[34] For other conditions, incidence of ICH varies depending on the thrombotic process: PE (0% to 4.5%), AMI (0.3% to 1.8%), and peripheral artery occlusion (1% to 2%).[32,33] The true incidence of other remote bleeding complications is difficult to determine, given inconsistent definitions and reporting. When major bleeding is defined as that causing permanent disability, increased hospital stay, or a requirement for blood transfusion, rates as high as 27% have been noted.[32,33] Major bleeding after thrombolysis is seen in 10% to 27% of patients with acute limb ischemia, 5% to 21% with PE, 0.3% to 5.9% with AMI, and 4% to 11% with DVT.

Antigenicity Related

This complication is mainly related to SK. Minor allergic reactions have been reported in 1% to 10% of cases, and life-threatening allergic reactions in less than 0.01%.[1] Pretreatment with 100 to 250 mg of methylprednisolone, antihistamines, or acetaminophen (or any combination of these drugs) can reduce the allergic response.[1] Other thrombolytics, such as UK and rt-PA, are naturally found in vivo, and allergic reactions are rare.[2,5]

Catheter Related

Catheter insertion for CDT poses the same risks associated with any endovascular procedure, including but not limited to dissection of the artery, pseudoaneurysm, dislodgment of thrombus during wire or catheter manipulation, and bleeding around the introducer sheath.[35]

Embolic

As a thrombus is lysed, fragments may embolize. Embolization is most often seen in patients with acute limb ischemia. Typically, after initial clinical improvement with restoration of a pedal pulse or Doppler signal, sudden clinical deterioration due to embolism occurs. In randomized clinical trials of patients with acute limb ischemia, embolic events occurred in 9% to 13% of patients. In most cases, advancing the catheter distally and continuing the thrombolytic infusion can effectively treat the embolic malperfusion.[35-37]

Embolic events occur less often in other applications. Clinically significant PE has been seen after thrombolytic treatment of DVT (0% to 10%), and though it is a hypothetical risk in catheter and AVG occlusion, PE has been rarely reported (<1%).[33]

Contraindications

Absolute contraindications to thrombolytic treatment include conditions that are likely to be associated with existing or very recent hemorrhage: (1) active internal bleeding; (2) recent (within 2 months) cerebrovascular accident, trauma, or intracranial or intraspinal surgery; (3) known intracranial neoplasm; (4) severe uncontrollable hypertension; (5) uncontrollable clotting disorders; (6) previous severe allergic reactions to the thrombolytic agent.

Relative contraindications include (1) recent (within 10 days) operative or obstetric procedures, biopsy, or procedure in a location that is not compressible, gastrointestinal bleeding, or trauma, including cardiopulmonary resuscitation; (2) left heart thrombus; (3) subacute bacterial endocarditis; (4) severe liver or kidney disease; (5) diabetic hemorrhagic retinopathy; (6) acute pancreatitis; (7) pregnancy; (8) any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its anatomic location.[1,2,5,27]

THROMBOLYTIC AGENTS

Currently, the most commonly used thrombolytic agents are the recombinant plasminogen activators and genetically modified variants (see Table 41.1). Characteristics of commercially available thrombolytic agents are listed in Table 41.2. A number of other investigational thrombolytic agents are being studied. Thrombolytic agents can be classified as follows:

TABLE 41.2 Pharmacology of US Food and Drug Administration—Approved Thrombolytic Agents

Name	Molecular Weight (kD)	Half-Life (Min)	Fibrin Specificity	Mechanism of Action	Cost ($US)[a]
Streptokinase	47	20	0	Plasminogen activator	NA
Urokinase	33	13	++	Plasminogen activator	NA
Alteplase	70	5	+++	Recombinant human tissue plasminogen activator	$40/mg
Reteplase	39	15	++	Same as alteplase but has extended half-life because of lack of carbohydrate side chains, finger domain, epidermal growth factor, and kringle 1 domain	$150/U
Tenecteplase	65	22	++++	Same as alteplase but has three single–amino acid and a tetra-alanine substitution, which extends its half-life	$70/mg

[a]Costs for thrombolytic agents vary depending on location and individual pricing agreements. These costs are from a tertiary hospital based in the Los Angeles, California, region.

NA, No longer manufactured in the United States.

1. Plasminogen activators: The mechanism of action for thrombolysis is indirect. These agents convert intrinsic plasminogen to active plasmin that cleaves linked fibrin. There are two types:
   a. Biologic, naturally occurring, such as SK and UK
   b. Recombinant and genetically modified variants
2. Direct-acting agents: The mechanism of action is direct cleavage of fibrin linked strands.

Biologic, Naturally Occurring Plasminogen Activators

Streptokinase

SK is FDA approved for use in most clinical applications: AMI, PE, DVT, peripheral arterial thrombosis, or embolism (see Table 41.1). It has been marketed under different names—Kabikinase (Pharmacia & Upjohn, Somerset County, New Jersey) and Streptase (CSL Behring, King of Prussia, Pennsylvania)—but in 2004, CSL Behring (the only manufacturer of SK in the United States) discontinued production. Despite its multiple FDA indications, it is rarely used in the United States because of its side effects. In developing countries, SK is still used because of its low cost. There are now recombinant technologies to produce SK via *Escherichia coli*, but these products can have variable lytic activity.[38-40]

SK is a 414–amino acid, single-chain protein with a molecular weight of 47 kD. Produced by β-hemolytic streptococci, it is present in the broth of cultured bacteria and can be purified and then isolated. After multiple strains of streptococci were tested, the Lancefield group C *Streptococcus equisimilis* was chosen for pharmaceutical production because it lacks production of the erythrogenic toxin and has fastidious growth requirements.[41]

SK has three main structural domains: α, β, and γ. The β domain is involved in forming the SK-plasminogen complex, and the γ domain assists in making the plasminogen within this complex active.[42] The SK-plasminogen complex has a half-life of 20 minutes and does not dissociate.[1,43] It can be inactivated by systemic plasmin inhibitors (α_2-antiplasmin and α_2-macroglobulin), but when administered as a therapeutic agent, concentrations are increased such that the SK-plasminogen complex overwhelms this inhibition.[44]

Because SK is derived from streptococci, previous bacterial infection or exposure to SK can cause antibody formation, which makes any SK administered in the future inactive. Neutralizing antibodies to SK last for a minimum of 4 days and can persist for up to 4 years in 50% of patients.[45,46] Minor hypersensitivity reactions to SK are uncommon, 4.4% in one study,[47] but cases of life-threatening anaphylaxis and serum sickness have been documented.[48,49] Readministration of SK can be attempted up to 4 days after the initial dose; however, repeat dosing after 5 days to a year is not recommended because of inactivation by an increased amount of antistreptococcal antibodies.[1]

Urokinase

Unlike SK, UK lacks antigenicity because it is normally present at low levels in human plasma (10 μg/L).[50] It is called urine plasminogen activator (u-PA) when found in vivo and is normally involved in intracellular signaling pathways and cell proliferation, adhesion, and migration.[51,52] Produced predominantly by kidney cells, commercially used UK was originally isolated from urine.

Native, or naturally occurring, UK exists in a number of forms in both plasma and urine. The precursor to all forms is prourokinase, a 55-kD, 411–amino acid single-chain protein also called single-chain urokinase plasminogen activator (scu-PA). It has little enzymatic activity, but in the presence of fibrin it is cleaved by plasmin into active forms.[53,54] The resultant high-molecular-weight urokinase is the predominant form of UK found in urine and is also called a two-chain urokinase plasminogen activator. It weighs 55 kD and is composed of a 22-kD light chain and a 33-kD heavy chain linked by a single disulfide bond.[55] The final form is the 33-kD, low-molecular-weight urokinase, which is an enzymatically degraded form of high-molecular-weight UK.[56]

Despite the poor fibrin/fibrinogen affinity of naturally occurring UK, it was once the only alternative to SK. UK was marketed as Abbokinase (Abbott, Abbott Park, Illinois). It is rapidly cleared by the liver, and its half-life is 6.4 to 18.8 minutes, with a volume of distribution of 11.5 L.[5] Current methods of production use donated human kidney cells from neonates who have died from noninfectious causes. The neonatal kidney cells can be cultured to secrete large quantities of UK.[5,57]

The trade name Abbokinase was stigmatized after the FDA halted its production in 1999 due to manufacturing issues and viral validation.[58] The FDA intervention created a relative shortage of UK and led to investigational development of other thrombolytic agents such as modified SK, rt-PA, and staphylokinase. In 2002, Abbokinase was reintroduced by Abbott Laboratories. In 2006, Abbokinase was sold to ImaRx, and a year later its trade name was changed to Kinlytic. Two years later, in September 2008, Microbix Biosystems (Ontario, Canada) acquired all the rights related to UK from ImaRx.[59] Of note, the only licensed indication for UK is PE (see Table 41.1), but before being taken off the market in 1999, UK was FDA approved for PE, AMI, and catheter occlusion.

Recombinant Plasminogen Activators

Recombinant Urokinase

To improve the yield of manufactured UK, investigators have produced recombinant UK from genetically engineered mouse hybridoma cells. Recombinant UK, or urokinase alfa, is a 48-kD, two-chain UK once marketed as Open-Cath-R (ImaRx). Despite successful clinical trials in treating catheter occlusion, it is not currently available in the United States.[60,61]

Alteplase

Currently alteplase, or rt-PA, is the most commonly used thrombolytic agent in clinical practice. It is identical to the naturally occurring t-PA, which is normally produced by endothelial cells. After sequencing of the native t-PA protein, recombinant technology now produces rt-PA from Chinese hamster ovary cells.[2]

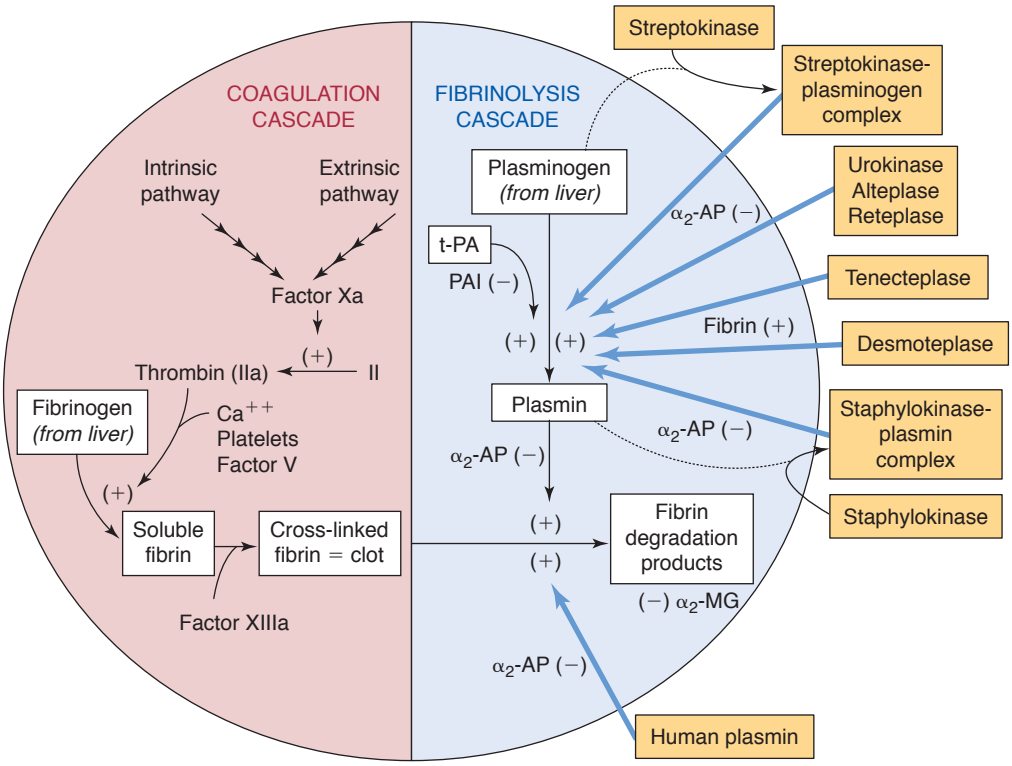

Figure 41.2 Coagulation and fibrinolytic pathway in relation to thrombolytic agents and the mechanism of action. α_2-*MG*, α_2-Macroglobulin; α_2-*AP*, α_2-antiplasmin; *PAI*, plasminogen activator inhibitor; *t-PA*, tissue plasminogen activator.

rt-PA and t-PA have the same molecular structure and characteristics (Fig. 41.2). Both are 70-kD molecules and contain five distinct functional domains. The carboxyl-terminal protease domain cleaves the plasminogen peptide bond, arginine 560–valine 561, which converts plasminogen to plasmin.[62] The fibronectin finger domain and the two kringle domains assist in binding to fibrin. Kringle domains are triple-looped, disulfide-bonded structures of about 80 amino acid residues that contain lysine-binding sites with different affinities for various molecules and receptors.[63] The epidermal growth factor (EGF) domain assists in liver binding and clearance and gives rt-PA a short half-life of 5 minutes and a terminal half-life of 72 minutes.[2] Because rt-PA is the same protein as native t-PA, it should lack antigenicity, but rare cases of hypersensitivity and allergic reactions have been reported.[64,65]

Alteplase was developed jointly by Genentech in the United States and Boehringer Ingelheim in Germany. Alteplase is marketed in the United States as Activase and Cathflo (Genentech, Inc., South San Francisco, California) and in Europe as Actilyse (Boehringer Ingelheim, Ingelheim, Germany). Activase has FDA approval for use in patients with AMI, PE, and AIS, whereas Cathflo (which is alteplase packaged into 2-mg vials) is approved for occluded central venous catheters (see Table 41.1).

Reteplase

Removal of the finger, EGF, and kringle K1 domains of rt-PA results in a protein called reteplase (see Figs. 41.2 and 41.3, and Table 41.2). This 355–amino acid protein also lacks carbohydrate side chains because it is produced from *E. coli* rather than from mammalian cells.[66] The changes remove the less desirable characteristics of native t-PA. Lack of the EGF and carbohydrate side chains decreases liver clearance and thus prolongs its half-life to 15 minutes and terminal half-life to 1.6 hours. This allows bolus dosing of reteplase, usually in two separate 10-unit intravenous doses 30 minutes apart.[67,68] Reteplase is cleared by both the renal and hepatic systems. Although reteplase lacks the EGF and K1 domains, retention of the K2 domain still gives it some fibrin/fibrinogen specificity.

Reteplase was originally developed by Boehringer Ingelheim, which merged with Roche. Abroad, reteplase was marketed as Rapilysin (Roche, Basel, Switzerland), but in the United States it was marketed as Retavase (EKR Therapeutics, Cedar Knolls, New Jersey). The rights to Retavase in the United States have gone from Roche to Centocor (Horsham, Pennsylvania), to PDL, Inc. (Redwood City, California), in 2006, to EKR Therapeutics in 2008, and since June 2012 to Cornerstone Therapeutics (Cary, North Carolina). It is FDA-approved for AMI (see Table 41.1).

Tenecteplase

Tenecteplase is another genetically modified rt-PA produced in Chinese hamster ovary cells. It differs from native t-PA in three ways. Threonine 103 is replaced by asparagine, asparagine 117 is replaced by glutamine (both within the K1 domain), and the amino acid sequence from positions 296 to 299 within the carboxyl-protease domain is replaced by four alanines.[4] The

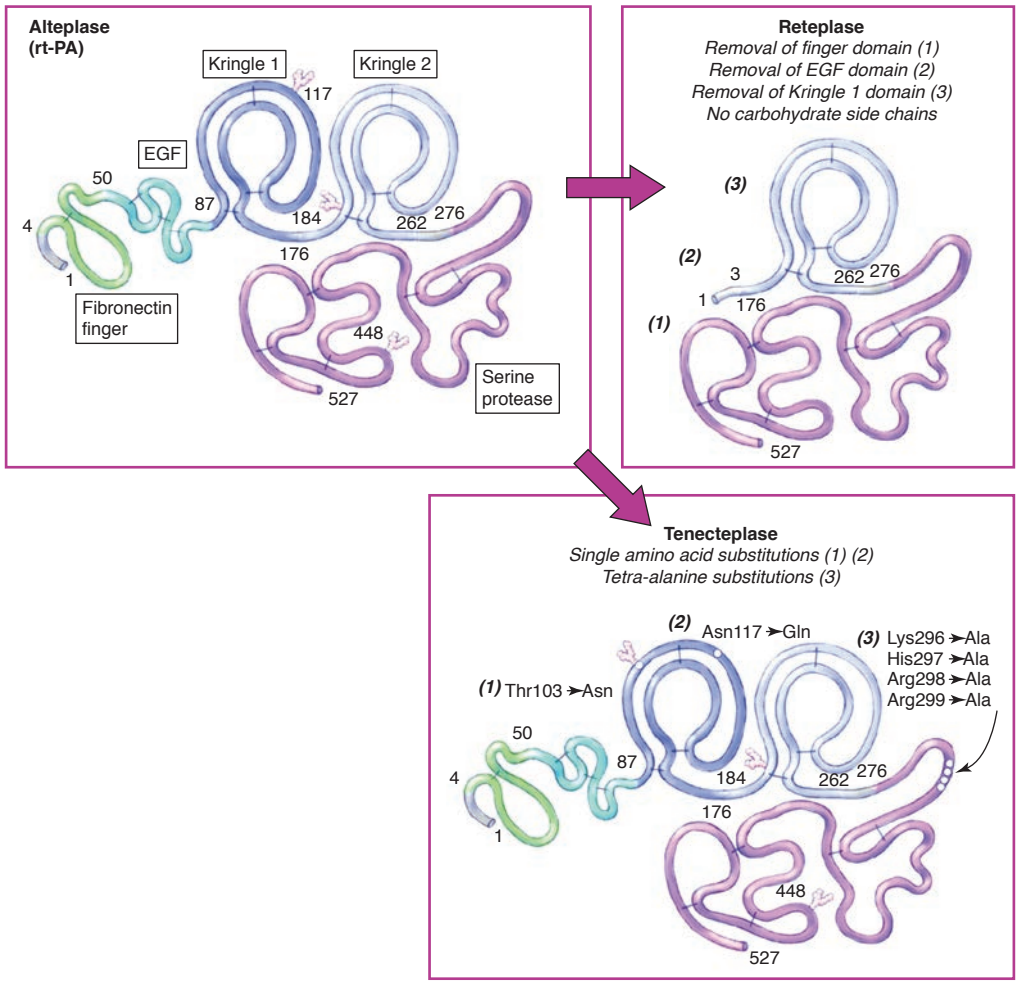

Figure 41.3 Molecular structure of the recombinant plasminogen activators. *EGF*, Epidermal growth factor. (Image modified with permission from Fig. 41.2 in Llevadot J, Giugliano RP, Antman E. Bolus fibrinolytic therapy in acute myocardial infarction. *JAMA*. 2001;286:442–449. Copyright © 2001, American Medical Association. All rights reserved.)

tetra-alanine substitution creates increased fibrin specificity. The substitution at position 103 allows decreased clearance, and the final position 117 exchange is needed to retain the thrombolytic effect of the entire protein (see Fig. 41.2 and Table 41.2).[68,69]

These modifications give tenecteplase a longer half-life than rt-PA, while retaining fibrin affinity. In vivo models demonstrate an 80-fold higher resistance to plasminogen activator inhibitor-1 (PAI-1) and 14-fold enhanced fibrin specificity when compared with rt-PA.[69] Tenecteplase half-life is 20 to 24 minutes, with a terminal-phase half-life of 90 to 130 minutes. Hepatic metabolism is the main method of clearance. Dose is based on weight and administered as a single bolus.[4] In 2000, tenecteplase was approved by the FDA for AMI and marketed as TNKase (Genentech). Abroad, tenecteplase is known as Metalyse (Boehringer Ingelheim; see Table 41.1).

Direct-Acting Agents

All the thrombolytic agents described to this point are plasminogen activators that convert intrinsic plasminogen to active plasmin, which cleaves linked fibrin. This "indirect" method of achieving thrombolysis results in a varied thrombolytic response. Direct-acting thrombolytic agents could theoretically eliminate this variability, since they act directly on the fibrin polymer. However, these "plasmin"-like compounds are inhibited by circulating inactivators and therefore cannot be delivered systemically. Thus catheter-directed administration of these agents to the offending thrombus is required for therapeutic effect.

Plasmin

The only direct-acting thrombolytic currently under investigation is plasmin. As early as 1960, research was conducted to investigate using human plasmin to treat thrombotic occlusion, but the initial clinical results were poor because of inactivation of systemically administered plasmin by α_2-antiplasmin.[70,71] Later animal studies demonstrated that plasmin directly delivered to the thrombus provides more rapid and effective thrombolysis than currently available plasminogen activators.[72]

Talecris (Barcelona, Spain), purchased by Grifols in 2011, is investigating two forms of plasmin: The first form is γ-Plasmin

(TAL-6003), a recombinant plasmin that is still in preclinical development. It is a simplified form of human plasmin, in which the K1 domain is directly attached to the serine protease domain. This modified plasmin can potentially be more active and fibrin specific.[73]

The other form is human plasmin. It is obtained from donors who are screened to rule out blood-borne pathogens. Phase I and II clinical trials in the Plasmin Revascularization by Intrathrombus Infusion for the Ischemic Lower Extremity (PRIORITY) study tested a total dose of plasmin from 25 to 175 mg, in 25-mg increments. Using CDT and pulse-spray delivery, 27% was given as a bolus; then 30 minutes later another 13% of the total dose was given as a second bolus, and the last 60% was infused over a period of 4.5 hours. Thrombus resolution (≥50%) occurred in 79% of subjects receiving 125 to 175 mg of plasmin, as compared with 50% who received 25 to 100 mg, with no trend toward more bleeding at higher dosages of plasmin. Major bleeding occurred in 4.8%, and minor bleeding in 15.7%.[74]

Phase II randomized trials comparing plasmin with placebo and rt-PA in peripheral artery obstruction are in different stages of development.[75] Phase I/II trials of CDT using plasmin (doses of 20, 40, 80 mg) in AIS within a 9-hour window are also being considered.[76]

CLINICAL APPLICATIONS

Each thrombolytic agent has been studied in a number of well-performed multicenter, randomized clinical trials, and although the FDA-licensed indications are limited for most agents, off-label use is common. The choice of agent is often based on the treating physician's experience and the availability in the hospital. In most facilities, rt-PA is the most readily available, followed by reteplase and tenecteplase.

Acute Myocardial Infarction

In most centers, emergency cardiac catheterization has replaced thrombolytic treatment of AMI, but in institutions without this capability, IVT still has a role. Furthermore, the development and dosing of almost every new thrombolytic agent has been tested in patients with AMI. The first trial to establish IVT as a useful treatment of AMI was reported in 1986 (see Fig. 41.1). The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) study randomized 11,806 patients seen within 12 hours of the onset of symptoms to receive intravenous SK or placebo. At 21 days, overall hospital mortality was 10.7% in SK recipients versus 13% in controls ($P = .0002$).[77] The International Study of Infarct Survival (ISIS) 2 not only confirmed the benefits of SK versus placebo in patients with AMI but also proved combination therapy with aspirin to be beneficial.[47]

Similarly, the use of rt-PA for AMI has been extensively studied. The results of the Anglo-Scandinavian Study of Early Thrombosis (ASSET) demonstrated the superiority of rt-PA over placebo in 5011 randomized patients with AMI.[78] In comparing rt-PA with SK, several trials have demonstrated superiority of rt-PA over SK in respect to coronary arterial flow[79] and relative risk of 30-day mortality.[79,80,81] Furthermore, reteplase and tenecteplase have been studied in a number of trials that ultimately established a licensed indication for AMI (Table 41.3).[82-88]

TABLE 41.3 Dosing of Currently Available Thrombolytic Agents for Acute Myocardial Infarction

Agent	Dose
Alteplase	100 mg in accelerated or 3-h infusion: Accelerated infusion: Give 15-mg bolus, then 50 mg over next 30-min period, then 35 mg over next 60-min period 3-h infusion: Give 60 mg during first hour (of which 6-10 mg is administered as a bolus), then 20 mg during second hour, then 20 mg during the third hour
Reteplase	10 U + 10 U double-bolus injection, each 10 U over 2-min period, 30 min apart
Tenecteplase	Weight-based dosing, single bolus (30-50 mg) over 5-s period, not to exceed 50 mg

Dosages are for adult use (≈70 kg) and intravenous injection.

Pulmonary Embolism

Multiple trials with different thrombolytic agents in various dosages have been undertaken for PE. Unlike AMI, IVT for the management of PE has not consistently demonstrated mortality benefits. Success thus far has been based on improved pulmonary angiography, lung scans, or pulmonary pressure (or any combination of these endpoints).[89-96]

In 2012, the Ninth American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy did not support the routine use of IVT for PE unless the patient was hemodynamically unstable or becoming unstable despite anticoagulation (grade 2C). IVT with the shortest infusion times are still recommended over CDT. However, whereas previously the ACCP recommended against CDT all together, they now weakly recommend CDT (in combination with mechanical thrombectomy) in patients with an acute PE, which is associated with hypotension and either contraindications to thrombolysis, failed thrombolysis, or shock that is likely to cause death before IVT can take effect.[25]

These ACCP recommendations are supported by evidence demonstrating that mechanical device assisted thrombolysis improves thrombus removal with a smaller dose of thrombolytic agent.[97,98] One such device, the Ekosonic Endovascular System (EKOS, Bothell, Washington), when used to assist thrombolysis has demonstrated the capacity to rapidly clear thrombus in patients with large pulmonary thrombi.[98,99] The ULTrasound Accelerated Thrombolysis of PulMonAry Embolism (ULTIMA) trial was one of the first randomized controlled trials comparing EKOS assisted CDT to anticoagulation alone. This trial included 59 patients with intermediate risk PEs and concluded that EKOS was superior to anticoagulation alone in reversing RV dilation at 24 hours.[100] Results from this trial led to the FDA

approval of EKOS for the treatment of PE in 2014. In 2015, the results of a single-arm multicenter prospective clinical trial (SEATLE II) concerning the safety and efficacy of EKOS assisted CDT in the treatment of acute massive and submassive PEs were published. The authors concluded that EKOS decreased RV dilation, reduced pulmonary hypertension, decreased thrombus burden, and minimized intracranial hemorrhage.[101] A systematic review and proportional meta-analysis done by Mostafa evaluated the use of EKOS in patients with acute PE. The main finding was that major bleeding rates were 2.3% with EKOS assisted CDT, in contrast to 10% seen in IVT. They also concluded that EKOS improved postprocedural RV/LV ratio, as compared with preprocedural values.[102] The PERFECT trial, published in 2015, also supported the above findings for CDT when used for treatment of massive and sub massive PE showing an improvement in mean pulmonary artery pressures from 51.17 ± 14 mm Hg to 37.23 ± 15.8 mmHg ($P < .0001$). There were no major bleeding or procedure-related complications, or hemorrhagic strokes.[103] Finally, EKOS Corporation, now owned by United Kingdom based company BTG, is currently sponsoring a clinical trial called OPTALYSE PE, which is recruiting participants to determine the optimum duration of EKOS CDT in acute sub massive PE.

Acute Ischemic Stroke

Well-controlled randomized clinical trials have established the benefits of IVT in patients with AIS.[109, 110, 112-114] The 2012 ACCP guidelines recommend administration in less than 3 hours (grade 1A), but have extended the window to 4.5 hours (grade 2C) based on new data.[25] Of note, the only FDA-approved agent is rt-PA, although a number of thrombolytic agents, either no longer commercially available or discontinued, have been used in case reports and even clinical trials.[104-107] Results of phase II clinical trials comparing alteplase to tenecteplase for the treatment of ischemic stroke suggest neurologic and radiologic outcomes do not differ.[108] A more recent randomized controlled trial compared low-dose (0.6 mg per kg of body weight) versus standard-dose (0.9 mg per kg of body weight) intravenous alteplase in AIS. The study showed low-dose alteplase to be noninferior to standard dose alteplase for the treatment of acute stroke. Low-dose alteplase had a lower incidence of symptomatic intracranial hemorrhage, and lower incidence of early fatal events.[109]

IVT with rt-PA administered within 3 hours of AIS in combination with CDT, or CDT plus EKOS for distal thrombus was studied in 81 patients in a phase II trial Interventional Management of Stroke (IMS)-II.[110] Compared with historic data from the National Institute of Neurological Disorders and Stroke, the 3-month mortality was lower (16%), but symptomatic ICH was higher (9.9%).[110] In the phase 3 trial (IMS-III), patients who received IVT with rt-PA within 3 hours after stroke symptom onset were randomly assigned to receive either additional IVT or CDT with rt-PA.[111] After randomizing 665 patients, the study was terminated, because no difference was demonstrated in stroke outcome between the two therapies. A concurrent study from the SYNTHESIS Expansion investigators also demonstrated no benefit to CDT with rt-PA when compared with IVT alone.[110,112] This is consistent with an earlier phase I study, the Emergency Management of Stroke (EMS) trial, which studied CDT alone against CDT plus IVT in 35 patients and found no difference in clinical outcomes or rates of symptomatic ICH.[113] However, a prospective observational study of 2650 patients with ischemic stroke showed that percutaneous mechanical thrombectomy plus CDT or IVT showed improved functional outcome (common odds ratio, 1.84; 95% confidence interval, 1.32 to 2.57) and decreased mortality (15% vs. 33%, $P < .0001$) when compared with IVT alone.[114]

The 2012 ACCP guidelines recommend intraarterial rt-PA in patients with AIS due to proximal cerebral artery occlusions who do not meet eligibility criteria for treatment with IV rt-PA (past the 3- to 4.5-hour window) but are still within 6 hours of symptom onset. They recommended against combined IVT and intraarterial rt-PA or mechanical thrombectomy, except in carefully selected patients willing to accept an increased risk with uncertain benefit. It should be noted that these recommendations were all grade 2C, weak with low quality of evidence (Table 41.4).[115]

TABLE 41.4 Dosing of Currently Available Thrombolytic Agents for Pulmonary Embolism

Agent	Dose
Alteplase	100 mg over 2-h period
Reteplase[a]	10 U + 10 U double-bolus injection, each 10 U over 2-min period, 30 min apart

[a]These dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses. Dosages are for adult use (≈70 kg) and intravenous injection.

Acute Limb Ischemia

Initial evidence that thrombolysis could effectively treat acute arterial occlusions of the extremity and delay or replace surgical interventions came from several nonrandomized case series.[116,117] Preliminary studies proved CDT to be safer and more efficacious than IVT for all the reasons discussed previously.[21,22] Three randomized, prospective clinical trials provided definitive evidence that in patients with acute limb ischemia of less than 14 days of duration, CDT was of clinical benefit.

The Rochester Trial randomized 114 patients with less than 7 days of limb-threatening ischemia to either open surgery or CDT with UK. The 12-month limb salvage rates (82%) were similar, but thrombolysis provided improved 12-month survival (84% with CDT vs. 58% with surgery, $P = .01$).[35]

The Surgery Versus Thrombolysis for the Ischemic Lower Extremity (STILE) trial included patients with up to 6 months of ischemic symptoms. It compared open surgical therapy with CDT using either rt-PA or UK. The study was stopped after 393 patients, due to adverse primary outcomes in the CDT group when compared with the surgical group. However, a subgroup analysis of patients with less than 14 days of ischemia

TABLE 41.5 Dosing of Currently Available Thrombolytic Agents for Acute Ischemic Stroke

Agent	Dose
Alteplase	Systemic: 0.9 mg/kg total dose (not to exceed 90 mg): Load 10% as a bolus over 1-min period and infuse remainder over 60-min period Catheter directed: 2 mg bolus (over 2 min) distal to thrombus, then 2 mg bolus (over 2 min) into the thrombus; then infusion 9 mg/h for up to 2 h—not to exceed 120 min (based on the IMS study[112])

Dosages are for adult use (≈70 kg).

showed a lower amputation rate at 6 months when treated with CDT than when treated surgically (CDT 11% vs. surgery 30%, $P = .02$).[36]

The Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial randomized 544 patients with acute (<14 days) arterial or bypass graft occlusion to open surgery versus CDT with UK. At 12 months, rates were similar for amputation-free survival (CDT 65% vs. surgery 75%) and mortality (CDT 20% vs. surgery 17%). However, CDT allowed 40% of patients to avoid a surgical intervention with the tradeoff being an increased rate of major bleeding (CDT 12.5% vs. surgery 5.5%, $P = .005$).[37]

Current recommendations support CDT in patients with Rutherford class I to class IIa limb ischemia of less than 14 days of duration.[23,24] In selected circumstances, treatment may also be of value in patients with Rutherford class IIb. The enthusiasm for this recommendation is tempered by the time required for successful CDT and the associated bleeding complications with currently available thrombolytic agents.[23,24] Contemporary dosing for CDT has evolved to a low-dose extended infusion (Table 41.5). A Cochrane review in 2009 found that although high-dose and forced-infusion techniques achieved vessel patency in less time than low-dose infusion; bleeding complications were more common, and at 30 days no improvement in patency rates or limb salvage was documented.[118]

CDT with EKOS may allow for even lower doses of thrombolytic agents to be used with equal efficacy and improved safety. A Dutch randomized trial (DUET) comparing CDT with EKOS assisted CDT for thromboembolic infrainguinal disease showed significantly reduced thrombolysis time for EKOS assisted CDT (17.7 ± 2.0 hours) compared with CDT alone (29.5 ± 3.2 hours, $P = .009$).[119]

A recent retrospective review analyzed 154 patients with acute limb ischemia who were treated with CDT or pharmacomechanical thrombolysis (PMT), with other adjunctive endovascular and surgical interventions. Technical success was achieved in 84% with a 30-day mortality rate of 5.2% and an overall rate of major amputation of 15%. CDT and PMT had equal benefit. Additional revascularization procedures, mostly endovascular (69%), were required in 89% of patients. End stage renal failure and poor pedal outflow were predictors of limb loss.[120] Early experimental studies looking at contrast-enhanced ultrasound to accelerate the thrombolytic effects of low-dose CDT in arterial occlusions have shown results in porcine models sufficient to warrant clinical studies.[121]

Deep Venous Thrombosis

Until recently, most data on thrombolysis in the management of DVT had been predicated on small randomized clinical trials or venous registries. In 1984, Goldhaber pooled data from six small, randomized studies (N = 185) of IVT with SK versus heparin for the management of DVT. Venous patency was achieved 3.7 times more often in patients treated with SK versus heparin, but bleeding was 2.9 times greater with SK.

A 2005 review by Janssen identified 18 randomized controlled trials of IVT for DVT. Twelve studies compared SK with heparin in 468 patients, two trials compared UK with heparin in 117 patients, and four trials compared rt-PA with heparin in 150 patients. Only one trial compared CDT with standard anticoagulation, and no trials compared PMT with conventional anticoagulation.[122] The conclusion, similar to that of Goldhaber, was that IVT can improve venous patency but with an increased risk of bleeding. A later Cochrane review of 17 randomized controlled trials involving 1103 patients demonstrated that when compared to anticoagulation alone, IVT was associated with lower risk of post thrombotic syndrome, and leg ulceration; but with a higher bleeding risk (RR: 2.23; 95% CI: 1.4 to 3.5, $P = .0006$).[123] To examine whether CDT could decrease the bleeding risk, Mewissen established a venous registry that included 63 institutions and 287 patients. A higher frequency of venous patency was reported for CDT than for anticoagulation, but major bleeding complications still occurred in 11% of the patients.[124]

Before 2012 only one randomized trial had compared CDT with anticoagulation. In 2002, Elsharawy randomized 35 patients with acute iliofemoral DVT and found that those treated with CDT as opposed to anticoagulation had an improved 6-month patency (72% vs. 12%, $P = .0001$) and less venous reflux (11% vs. 41%, $P = .04$).[125] In 2012, the Catheter-Directed Thrombolysis Versus Standard Treatment for Acute (<21 days) Iliofemoral Deep Vein Thrombosis (the CaVenT study) trial randomized 209 patients to CDT versus anticoagulation alone. After 6 months, iliofemoral vein patency was higher in the CDT group (66%) versus the anticoagulation group (47%, $P = .012$), and at 24 months, rates of postthrombotic syndrome were lower in the CDT group (41.1%) compared with the anticoagulation group (55.6%, $P = .047$). However, 20 bleeding complications related to CDT occurred, including three major bleeding complications.[126]

Engelberger performed a prospective single center study in 87 patients with iliofemoral DVT using EKOS assisted CDT. Primary and secondary patency rates at 1 year were 87% and 96%, respectively. PTS at 1 year was 6%, and the incidence of major bleeding was 1%.[127] They subsequently in a later open-label randomized controlled study of 48 patients compared EKOS assisted CDT with CDT alone and found that there was no difference in long-term outcomes.[128]

Debate continues on whether the DVT clearance and immediate patency achieved by thrombolysis translates into

TABLE 41.6 Dosing of Currently Available Thrombolytic Agents for Acute Limb Ischemia

Agent	Dose
Alteplase	Catheter directed: Low-dose (extended infusions >12 h): 0.5-2.5 mg/h High-dose: 0.05 mg/kg per hour up to 12 h (or until maximum of 100 mg administered)
Reteplase[a]	Catheter directed: 2-U bolus, then infuse 0.5-1 U/h (should not exceed a total administered dose of 20 U)
Tenecteplase[a]	Catheter directed: 0.25-0.5 mg/h; infusion stopped if no improvements on serial arteriograms

[a]These dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses. Dosages are for adult use (≈70 kg).

TABLE 41.7 Dosing of Currently Available Thrombolytic Agents for Venous Thrombosis

Agent	Dose
Alteplase[a]	Catheter directed: 0.25-2 mg/h
Reteplase[a,b]	Catheter directed: 0.75 U/h
Tenecteplase[a,b]	Catheter directed: 0.25-0.5 mg/h

[a]Infusions are stopped once no improvement is seen on serial venograms performed every 8 to 12 hours.
[b]These dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses. Dosages are for adult use (≈70 kg).

TABLE 41.8 Dosing of Currently Available Thrombolytic Agents for Arteriovenous Graft Occlusion

Agent	Dose
Alteplase[a,b]	Catheter directed: 2 mg
Reteplase[a,b]	Catheter directed: 1 U
Tenecteplase[a,b]	Catheter directed: 1 mg

[a]These dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses.
[b]The listed dosages are administered under fluoroscopic guidance. Dosing can be repeated if arteriovenous graft patency is not restored.
Dosages are for adult use (≈70 kg).

superior long-term outcomes. The current guidelines favor anticoagulation over CDT (grade 2C) for an acute proximal DVT. ACCP stipulates that CDT (with or without PMT) or IVT can be considered if patients attach a high value to the prevention of postthrombotic syndrome and a lower value to the initial complexity, cost, and risk of bleeding (Table 41.6).[25] DUTCH CAVA (NCT 00970619) and ATTRACT (NCT 0070035) trials are ongoing randomized controlled trials that will hopefully provide further clarification as to the use of CDT for DVT.

Arteriovenous Graft Occlusion

The use of thrombolysis in patients with AVG thrombosis was reported as early as 1983, when Rodkin used SK to successfully lyse eight of nine thrombosed AVGs.[129] Over the years, a number of techniques have been developed that have made thrombolysis quite efficient and clinically effective. The cross-catheter method uses two overlapping catheters placed at separate locations within the AVG, with their tips just past the arterial inlet and venous outlet.[26,130] The "lyse and wait" technique is a method in which the thrombolytic agent is infused into the graft while the arterial and venous ends are manually occluded. With the advent of PMT devices, thrombolytic agents are being used as more of an adjunct following thrombus extraction.[131,132] Although no FDA-approved thrombolytic agents are available for the treatment of AVG occlusion, case reports and series exist for almost every agent.[133-135] Thrombolytic doses of 2 mg of rt-PA, 1 mg of tenecteplase, and 1 unit of reteplase have all been used with success and minimal to no bleeding complications (Table 41.7).

Central Catheter Occlusion

The only FDA-approved thrombolytic for central catheter occlusion is rt-PA marketed in 2 mg vials as Cathflo. It was studied in 1064 patients in the Cardiovascular Thrombolytic to Open Occluded Lines (COOL) trial. Increased catheter patency was seen after 2 hours with one 2 mg dose of rt-PA (74%) versus placebo (17%, $P = .0001$).[136] Efficacy rates were similar among catheter types (single-, double-, and triple-lumen catheters and ports), and 30-day adverse events were rare: ICH (0.0%), embolic events (0.0%), gastrointestinal bleeding (0.3%), thrombosis (0.3%), and sepsis (0.4%).[137]

In children, rt-PA has also been found to be safe and effective through the Cathflo Activase Pediatric Study (CAPS). Patients weighing less than 30 kg received instillations of rt-PA (1 mg/1 mL) equal to 110% of the estimated internal lumen volume of the dysfunctional central venous catheter, not to exceed 2 mL.[26]

Hemodialysis catheters were excluded from all clinical trials on Cathflo; therefore hemodialysis catheters are not included in the FDA indication for catheter occlusion. However, the successful use of rt-PA (2 mg), reteplase (0.4 U) has been reported (Tables 41.8 and 41.9).[138-140]

Miscellaneous Uses

Intraoperative thrombolytic therapy used as an adjunct to open arterial thrombectomy or thromboembolectomy has been described and shown to be safe and effective in breaking down distal thrombus.[141] However, in patients with extensive distal clot burden, thrombolytic boluses given intraoperatively may not be enough. In these circumstances, isolated limb perfusion with high-dose thrombolysis has been described with or without a pump oxygenator. Another purported advantage of this

TABLE 41.9 Dosing of Currently Available Thrombolytic Agents for Catheter Occlusion

Agent	Dose
Alteplase[a]	≥30 kg: 2 mg in 2 mL; may repeat after 120 min if catheter still occluded <30 kg: 110% of the internal lumen volume (not to exceed 2 mg in 2 mL); may repeat above after 120 min if catheter still occluded
Reteplase[a,b]	0.4 U in 2 mL; may repeat after 30-60 min if catheter still occluded

[a]The volume instilled is not to exceed the internal lumen volume. Clamp the catheter and try to aspirate its contents in 30 minutes. If no result, a second dose can be attempted (see individual agents for timing).
[b]These dosing guidelines are based on case reports and series. Additional dosing schedules (not reported here) have been used. Given the lack of clinical trials, caution should be used if thrombolytic agents are administered at these doses. Dosages are for adult use (≈70 kg).

treatment is the mitigation of the systemic effects of reperfusion injury.[142] Although combining open surgical procedures with thrombolysis is infrequently employed, there may be selected patients in which knowledge of these techniques can be limb and/or life sparing.

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CHAPTER 42

Systemic Complications: Cardiac

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Abstract

Vascular surgery patients as a groups are the patients with the largest prevalence of cardiac disease among all non-cardiac surgery patients. As such, they are also at high risk of developing perioperative cardiac morbidity and mortality. This chapter will focus on understanding the pathophysiology of perioperative cardiac events in vascular surgery patients, on the methods to accurately define and diagnose preoperative cardiac pathologies and cardiac risks and on the possible measures that can be taken to improve perioperative cardiac risk.

Keywords

Myocardial infarction
Type-1
Type-2
Myocardial injury and troponin elevation
Cardiac risk indices

EPIDEMIOLOGY

Prevalence of Coronary Disease

Coronary artery disease (CAD) is highly prevalent in vascular surgical patients. Hertzer and colleagues drew attention to this by showing the small percentage of vascular surgery patients (8%) who were free of CAD.[1] In a study from the Cleveland Clinic from more than 30 years ago, 5% of patients had left main CAD and 11% had significant three-vessel disease. In fact, 15% of these patients had severe, yet unsuspected CAD. Since then, significant changes in both the primary and secondary prevention of coronary disease have occurred, including smoking cessation and the adoption of aggressive lipid lowering therapies. Subsequently, the incidence of myocardial infarction (MI) and cardiac death in nonsurgical populations decreased by 30%.[2] Conversely, patients presenting for vascular surgery in 2013 are on average a decade older, with more comorbidities, and the incidence of major coronary pathology in vascular patients may be even higher. Thus, despite clear advances in the treatment of CAD, it is conceivable that many patients presenting for vascular surgery have silent yet significant CAD. In the intervening years, our ability to identify patients with significant coronary disease has apparently been imperfect. This was demonstrated by Monaco and colleagues, where screening patients using the American Heart Association/American College of Cardiology (AHA/ACC) guidelines identified fewer patients with three-vessel or left main coronary disease than a randomized cohort having routine preoperative coronary angiograms.[3] In this chapter we will outline and define the pathology and document the incidence, the diagnostic criteria, risk stratification, and treatment options designed to limit the effect of postoperative cardiac adverse events.

Definition of Adverse Postoperative Cardiac Events

These can be classified using the following terms:

- Acute coronary syndromes (i.e., unstable angina pectoris [UAP], acute MI, or sudden cardiac death)
- Congestive heart failure (CHF)
- Myocardial injury
- Life-threatening arrhythmias

Myocardial Infarction

MI is one of the leading causes of death after surgical procedures. Since the introduction of cardiac troponin assays in the 1990s and the recognition of their high sensitivity, specificity, and prognostic value, the diagnosis of MI is based mainly on serum troponin elevations. The most recent universal definition of MI[4] endorsed by all major cardiology organizations defines MI as a rise and fall in cardiac troponin above the 99th percentile of the upper reference limit (for the specific troponin assay), in association with signs or symptoms of myocardial ischemia—that is, at least one of the following: (1) symptoms of myocardial ischemia (i.e., typical chest pain); (2) electrocardiographic evidence of acute ischemia, ST-T wave changes, or left bundle branch block; (3) development of new pathologic Q waves; (4) imaging showing loss of viable myocardium or a new abnormal left ventricular (LV) wall motion. The universal definition of MI identifies two main types of MI.[4]

Type-1 Myocardial Infarction

This is a sudden, spontaneous coronary event typically occurring in an unstable or "vulnerable" coronary plaque that has a large and highly inflammatory lipid core with a thin, weakened fibrous cap that suddenly undergoes acute disruption, leading to acute coronary thrombosis. Acute plaque rupture and coronary thrombosis that occur in a major coronary artery, supplying an area that was not significantly stenosed prior to the acute occlusion and lacks sufficient collaterals, typically results in ST-elevation-type MI (STEMI). STEMI, as a rule, is a medical emergency. It typically causes severe chest pain, dyspnea, and sweating, and requires an emergency intervention to reopen the occluded coronary artery, preferably by percutaneous coronary intervention (PCI). Even with the urgent coronary intervention, STEMI is associated with up to 10% early mortality. Other patients may have similar symptoms but no ST-segment elevations or, rather, ST-depression on electrocardiogram (ECG/EKG). These infarctions are defined as non-ST-elevation infarctions or NSTEMI. Pathologically, these are plaque ruptures and coronary thromboses in coronary arteries supplying smaller myocardial territories or territories supplied also by collaterals, or thromboses causing partial coronary occlusions. Patients with NSTEMI usually do not benefit from urgent coronary interventions, unless hemodynamic instability or progression of symptoms occurs. In the past, the proportions of STEMI and NSTEMI, in the general nonsurgical Western populations were approximately 50% each. Currently, with the older age of the population, with primary and secondary prevention strategies available, and with the better detection of MI by the high-sensitivity troponin assays, the absolute incidence of STEMI in the Western world is declining while the incidence of NSTEMI is increasing. Hence the current proportion of STEMIs of all infarctions is 30% or less.

Type-2 Myocardial Infarction

In contrast, type-2 MI often occurs in patients with severe yet stable CAD, usually due to extracardiac causes leading to a prolonged imbalance between myocardial oxygen supply and demand. The most common triggers for type-2 MI are prolonged tachycardia, hypotension or hypertension, anemia, and emotional or physical stress causing coronary vasospasm.[5] Type-2 MI is almost uniformly associated with ST-depression or non-ST-elevation type ischemia and is therefore indistinguishable from type-1 NSTEMI. The clinical circumstances (i.e., spontaneous, primary event in type-1 versus stress-induced, secondary event in type-2) can help distinguish between the two types of MI (Fig. 42.1).

Postoperative MI occurs in up to 24% of vascular surgery patients if MI is defined only based on troponin elevation and the low cutoff level of troponin elevations is used to define MI.[6] Postoperative ST elevation MI (STEMI) is usually less than 1% of all postoperative MIs.[7] Many more patients sustain

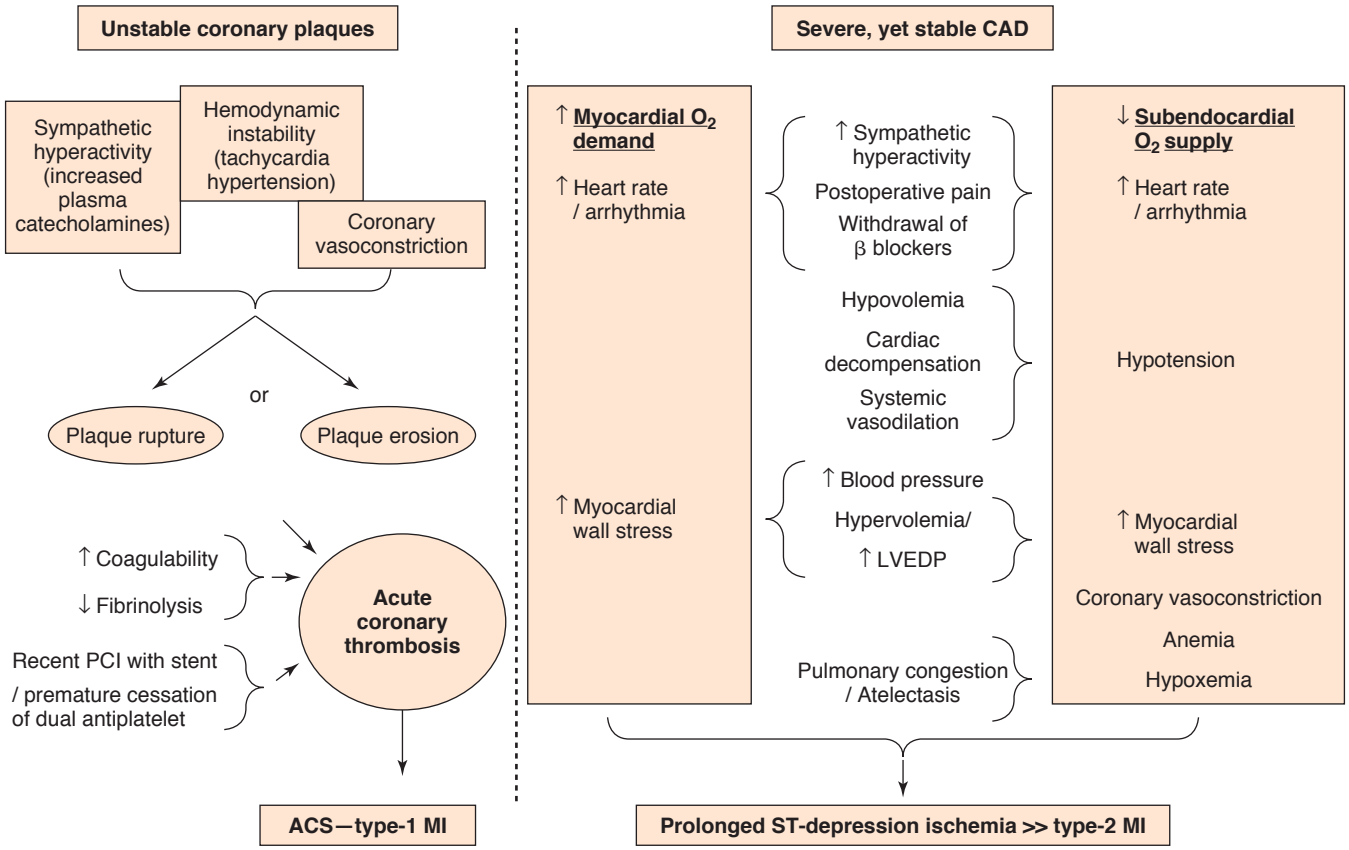

Figure 42.1 The two distinct mechanisms of PMI. *CAD*, Coronary artery disease; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention.

a biomarker rise with ST-segment depression or without any transient ST-T changes, which is analogous to a non-ST elevation myocardial infarction (NSTEMI) or myocardial injury.

Unstable Angina Pectoris

UAP occurs when a patient has recurrent or new onset typical chest pain, especially during rest, yet with no evidence of serum troponin elevations, since the presence of serum troponins elevation already makes the diagnosis of MI.

Congestive Heart Failure

Heart failure is the inability of the heart to provide adequate cardiac output to meet the normal metabolic requirements of all peripheral organs. Acute heart failure often leads to a drop in blood pressure and shock. Chronic, compensated heart failure is a situation in which the periphery adapts itself to the lower capacity of the heart to supply adequate cardiac output. Currently heart failure is divided into two main subtypes: (1) heart failure with reduced ejection fraction (HFrEF) or systolic heart failure (these are usually patients with dilated hearts due either to MIs or dilated cardiomyopathy and reduced systolic function), or (2) heart failure with normal or preserved ejection fraction (HFnEF) or diastolic heart failure (these are often patients with prolonged severe hypertension, left ventricular hypertrophy [LVH] and are more likely in female than males). Another type of heart failure is right ventricular failure, which is most commonly either secondary to LV failure, such as in the presence of severe mitral valve disease, or secondary to severe lung disease (i.e., cor pulmonale). In the perioperative setting, congestive failure is often ill defined and is frequently the result of fluid overload or transfusion-associated cardiac overload (TACO). The inability to handle excess fluids is a sign of a failing left ventricle. Postoperative CHF should be more thoroughly investigated with biomarkers (B-type naturetic peptide [BNP], N-terminal pro-B-type naturetic peptide [NT-proBNP]), chest x-ray, cardiac imaging, and particularly with echocardiography.

Life-Threatening Arrhythmia

Most life-threatening arrhythmias (ventricular tachycardia, ventricular fibrillation, high-degree A-V block) occur in the setting of acute myocardial ischemia and infarction, or in the presence of structural myocardial disease such as severely dilated cardiomyopathy. Fortunately, these LTAs are rare in the perioperative period, and if they do occur, it is mostly in patients with known predisposing factors such as severe CAD or cardiomyopathy. The more common arrhythmia in the perioperative setting is new onset or recurrent atrial fibrillation, and the most common causes of postoperative AF in patients with no known myocardial or valvular disease are severe diastolic dysfunction and chronic lung disease or pulmonary hypertension. Patients with new onset postoperative atrial fibrillation obviously have the worse prognosis.

Cardiac Death

Cardiac death has also been defined in the universal definition statement. Type-3 MI is death or cardiac arrest that is sudden and unexpected, with symptoms suggestive of myocardial ischemia, occurring before cardiac biomarkers could be obtained or before they appear in the blood.[4]

THE PATHOPHYSIOLOGY OF PERIOPERATIVE MYOCARDIAL INFARCTION

The high prevalence of CAD in vascular surgery patients and the strong perioperative physiologic and emotional stresses, including catecholamine surge, hemodynamic instability, vasospasm, reduced fibrinolytic activity, platelet activation, and hypercoagulability, predispose the vascular patients to a high incidence of postoperative cardiac complications. Interestingly, however, numerous studies showed that postoperative STEMI is disproportionately rare compared with the common occurrence of NSTEMI and that tachycardia is a frequent cause of postoperative myocardial ischemia.[6,8-10] Studies using continuous perioperative 12-lead ECG monitoring with online ST-segment analysis showed that prolonged, reversible episodes of ST-segment depression, indicative of subendocardial myocardial ischemia, occur in up to 41% of vascular surgery patients and precede the occurrence of troponin elevation.[11] These ST-depression-type ischemic events peak early after surgery and troponin elevations are maximal within the first 2 days.[12-14] In contrast, postoperative ST-elevation type ischemia is rare.[6-10] The data suggest, therefore, that perioperative MI is most commonly type-2 MI, caused by a prolonged ST-depression-type ischemia that is the result of an imbalance between myocardial oxygen supply and demand,[15] usually as a result of tachycardia and increase in myocardial load. Anemia, hypoxemia, increased myocardial oxygen demand, ventricular overload or underload, systolic or diastolic dysfunction, and neuroendocrine responses to the stresses of surgery all contribute to the decreased ischemic threshold early after surgery and with the increase in heart rate may lead to prolonged ischemia and infarction.[15] Although small pathologic studies showed that plaque disruption or hemorrhage can be found in postmortem analyses in up to half of patients who died after postoperative MI,[16,17] it is now well recognized that vulnerable plaques are ubiquitous in patients with CAD and most of them are not related to MIs.

Perioperative Myocardial Injury and Mortality

Studies that used routine postoperative troponin measurements showed that most patients with postoperative troponin elevations do not fulfill the additional diagnostic criteria necessary for the diagnosis of postoperative MI and that postoperative troponin elevation is predominately clinically silent. Landesberg and colleagues[8] first showed that almost 24% of all 447 patients who underwent major vascular surgery had at least minor postoperative troponin elevations (troponin-T > 0.03 ng/mL), yet only 30% of these patients with troponin elevations exhibited myocardial ischemia on continuous 12-lead EKG monitoring with ST-segment analysis and 82% of them had no symptoms related to MI (Tables 42.1 and 42.2). When a higher cutoff level of troponin elevation (troponin-T > 0.1 ng/mL) was selected, 8.7% of the patients had such troponin elevation yet 56% of these patients were still asymptomatic. Regardless if patients were symptomatic or not, even minor troponin elevation in the first 3 days after vascular surgery was associated with increased 5-year mortality, and higher postoperative troponin elevation was associated with worse long-term survival (Fig. 42.2). LeManach and colleagues studied more than 1100 patients undergoing open abdominal aortic aneurysmectomy.[14] Fourteen percent of these patients had troponin elevations, and in their study, too, minor troponin elevation was associated with greater 30-day postoperative mortality.[4] Van Waes and colleagues found similar results.[9,10] Similarly, the VISION prospective multicenter study that included more than 15,000 patients and the single center retrospective study that included more than 10,000 have confirmed that troponin elevations on the first 3 days after surgery predict early (30-day) mortality in a dose-dependent manner.[13,18,19]

The reasons for this lack of symptomatology in most patients with postoperative troponin elevations remain elusive. Elderly, diabetic, and vascular patients in particular are known to have a high incidence of silent ischemia. The concomitant use of narcotics and other competing somatic postoperative sensations may contribute to masking cardiac symptoms. The ECG, which is central for the diagnosis of MI, is less specific and sensitive in the presence of preexisting changes such as left or right bundle branch block, pacemaker rhythms, or baseline ST-T wave changes.[20,21] Moreover, the ischemic EKG changes may

TABLE 42.1 Universal Classification of Myocardial Infarction

Type 1: Spontaneous Myocardial Infarction

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, assuring, erosion, or dissection, with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but on occasion nonobstructive or no CAD.

Type 2: Myocardial Infarction Secondary to an Ischemic Imbalance

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-arrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH.

CAD, Coronary artery disease; *LVH*, left ventricular hypertrophy.

TABLE 42.2 Association of Longest Ischemia Duration With Biochemical Markers of Myocardial Infarction

Myocardial Infarction Defined As	Total n (%)[a]	Ischemia >15 min n (%)[b]	Ischemia >30 min n (%)[b]	Ischemia >60 min 11 (%)[b]	Symptoms Attributable to MI[c]
CK > 170 IU and MB >5%	34 (6.7)	17 (50.0)	14 (41.2)	12 (35.3)	7 (20.5)
CK > 170 IU and MB >10%	14 (2.9)	8 (57.1)	7 (50.0)	7 (50.0)	5 (35.7)
cTn-I >0.6 ng/mi and/or cTn-T >0.03 ng/mL	107 (23.9)	34 (31.8)	29 (27.1)	21 (19.6)	19 (17.7)
cTn-I >1.5 ng/mL and/or cTn-T >0.1 ng/mL	41 (8.7)	38 (87.8)	24 (58.3)	19 (46.3)	18 (43.9)
cTn-I >3.1 ng/mL and/or cTn-T >0.2 ng/mL	21 (4.2)	19 (90.5)	17 (81.0)	17 (81.0)	13 (61.9)

[a]Percent of all 501 vascular operations.
[b]All four biochemical criteria of infarction were significantly associated ($P < .001$) with both >30 min and >60 min ischemia duration using chi-square analysis.
[c]Prolonged chest pain, congestive heart failure, or new onset arrhythmia.
CK, Creatine kinase; *cTn-I*, cardiac troponin-I; *cTn-T*, cardiac troponin-T; *ID*, international units; *MB*, MB fraction; *MI*, myocardial infarction.
Adapted from Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol*. 2003;42:1547-1554.

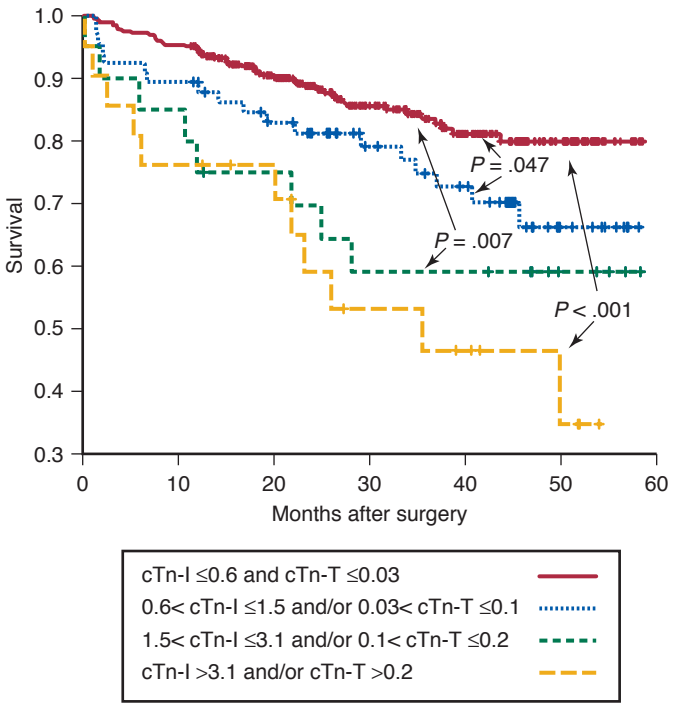

Figure 42.2 Long-term survival in 447 vascular surgery patients divided according to the highest troponin-T level in the first 3 postoperative days. (From Landesberg G, Luria MH, Cotev S, Eidelman LA, et al. Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. *Lancet*. 1993, JACC 2003;341:715-719.)

be of transient nature, and the lack of routine monitoring of postoperative 12-lead EKG with ST-segment analysis leads to underdetection of postoperative ischemia.[16]

Recently it has been shown that postoperative troponin elevations in patients undergoing major abdominal surgery predict not only cardiac but also noncardiac complications and mortality.[22] Noncardiac complications pose a higher demand on the patient's heart, and thus it is not surprising that mortality is increased in those with underlying heart disease. Conversely, primary cardiac injury may lead to cardiac failure and a deterioration in other important systems, such as the kidneys, leading to what may appear to be a noncardiac cause of death.[23]

Incidence of Cardiac Complications Following Major Vascular Surgery

Abdominal Aortic Surgery

The incidence of major cardiac complications is dependent on patient characteristics, risk factors, symptomatology, and type of surgery. The incidence of major cardiac complications is displayed in Table 42.3.

Aortic surgery has the highest incidence of cardiac morbidity, which ranges from 1% in endovascular repair to more than 14% in open abdominal aortic aneurysm repair.[31] Generally, the events rates in randomized trials are half of those in registries. In addition, the cardiac event rate is higher in patients with larger aneurysms, in open versus endovascular repairs, in patients with known preoperative cardiac comorbidity, and in operations requiring higher aortic cross clamps (e.g., suprarenal vs. infrarenal).[29] Recently a comprehensive systematic review of all studies reporting survival after abdominal aortic aneurysm repair in the last 25 years, including altogether 65,557 patients, was published.[32] It showed that chronic obstructive pulmonary disease (COPD) requiring supplementary oxygen and/or ESRD/dialysis was associated with the highest risk of long-term mortality. Increased age, female gender, cardiac failure, renal impairment, COPD, cerebrovascular disease, PVD, diabetes, and IHD also significantly increased mortality.

TABLE 42.3 Incidence of In-Hospital Cardiac Morbidity and Mortality by Surgery Type

	CARDIAC MORBIDITY		ALL CAUSE MORTALITY	
	Open (%)	Endovascular (%)	Open (%)	Endovascular (%)
Abdominal Aortic				
DREAM study[24]	2.9	2.9	4.5	1.2
OVER trial[25]	2.8	1.3	2.9	0.5
EVAR (1&2)[26,27]	2.7	1.4	6.2	2.1
VSG(NE)[28] AAA size <5.5 cm	9.5		2.5	
VSG(NE)[28] AAA size >5.5 cm	14.8			
Ferrante et al.[29]	12.8			
Low Extremity Bypass				
VGE(NE) claudication only[28]	3.4			
VGE(NE) critical limb ischemia	10.1			
Carotid				
CREST[30]	2.3	1.1	0.3	0.7
VGE(NE) asymptomatic	2.3			
VGE(NE) symptomatic	3.4			

OVER, Open versus endovascular repair; *VSG(NE)*, Vascular Study Group of New England.

Lower-Extremity Bypass

The cardiac event rate in lower extremity vascular surgery is dependent on symptoms, where patients with critical limb ischemia have more than 10% cardiac event rate that is three times that of patients with claudication only. One recent study reported that the presence of low-extremity arterial disease is associated with a twofold increase in the prevalence of CHF, and that CHF increases the complication rates for perioperative pneumonia, prolonged intubation, sepsis, return to the operating room, and mortality.[33]

Carotid Endarterectomy

Carotid surgery is associated with an approximately 2% to 3% rate of perioperative cardiac morbidity. The results from randomized trials are similar to those from registry data. The CREST trial[30] suggested a doubling in cardiac morbidity for surgery as opposed to a carotid stent procedure; however, this was offset by an increased stroke rate in patients having a stenting procedures.

PREOPERATIVE CARDIAC EVALUATION

Clinical Risk Assessment

Preoperative cardiac risk assessment is important, since it affects perioperative decision-making: (1) A high cardiac risk may influence both perioperative or long-term risk-benefit ratio of an elective vascular surgery and may therefore lead to its deferral. (2) Good cardiac risk assessment will enable preoperative optimization by using optimal medical therapy and in specific cases by preoperative coronary interventions to reduce perioperative and long-term cardiac risk. (3) Accurate preoperative knowledge of the patient's cardiac function and risk will allow better intraoperative and postoperative treatment and resource utilization, such as intraoperative monitoring and the need for postoperative intensive care unit (ICU) utilization. (4) Finally, understanding a patient's perioperative and long-term risks will allow the treating physician to provide the best possible consultation for optimal risk-benefit decision.

Cardiac Risk Indices

Numerous clinical risk indexes have been proposed. These include the seminal Goldman Cardiac Risk index,[34] the following Detsky's Risk index,[35] l'Italien,[36] and others. None of these has gained wide and lasting acceptance. In 1999, Lee and his colleagues constructed a simplified Revised Cardiac Risk Index (RCRI).[37] In a derivation cohort of 2893 consecutive patients, they identified six independent risk factors, including (1) a history of heart disease, (2) a history of CHF, (3) cerebral vascular disease, (4) insulin therapy, (5) chronic renal failure (defined as a preoperative creatinine of 177 mmol/L [2 g/L]), and (6) high-risk surgery (major vascular, thoracic, and upper abdominal). The validation cohort of 1422 patients showed that patients with none, one, two, and three of these factors had cardiac complications of 0.4%. 0.9%, 7%, and 11%, respectively. The overall accuracy ranged between 0.75 and 0.80, and was superior in their population to the other cardiac risk indices and the American Society of Anesthesiologists (ASA) classification. Since its publication, it has been widely used and adopted by the ACC/AHA guidelines committee for the preoperative stratification of patients perioperative cardiac risk.[38]

A recent meta-analysis of 24 studies including more than 750,000 patients showed that the RCRI discriminated moderately well in mixed surgical population with a sensitivity of 0.65 and

TABLE 42.4 Comparison of Two Cardiac Risk Indices

Revised Cardiac Risk Index[39]	Vascular Study Group of New England—CRI[28]
	Age 60-69 70-79 ≥80
	Smoking
Diabetes—insulin dependent	Diabetes—insulin dependent
CAD	CAD
CHF	CHF
Cerebrovascular disease	COPD
Creatinine ≥ 2 mg/mL	Creatinine ≥ 1.8 mg/mL
High-risk surgery	Abnormal cardiac stress test
	Chronic β-blockade

CAD, Coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *CRI*, cardiac risk index.

specificity of 0.76.[39] When this meta-analysis was limited strictly of studies of vascular surgical populations, the RCRI had an aggregate sensitivity and specificity of 0.70 and 0.55, respectively. Therefore the RCRI alone is inadequate to reliably screen vascular surgery patients, and further information gained through laboratory testing were proposed to increase the accuracy of the preoperative cardiac investigation.

In 2010, the Vascular Study Group of New England (VSGNE; Table 42.4) developed a vascular surgery-specific model for the prediction of cardiac events following vascular surgery.[28] The authors studied 10,081 total patients who underwent various major arterial vascular procedures. They found that the RCRI predicted risk after carotid endarterectomy (CEA) reasonably well, but substantially underestimated the other procedures for low- and higher-risk patients. In a multivariate analysis of the VSGNE cohort, the independent predictors of adverse cardiac events that were found included: increasing age, smoking, insulin-dependent diabetes, CAD, congestive heart failure, abnormal cardiac stress test, long-term beta-blocker therapy, COPD, and elevated creatinine. The rates of cardiac complications for patients with zero to three, four, five, and greater than or equal to six Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) risk factors were 3.1%, 5.0%, 6.8%, and 11.6% in the derivation cohort and 3.8%, 5.2%, 8.1%, and 10.1% in the validation cohort, respectively. The authors concluded that the VSG-CRI risk model more accurately predicted the actual risk of cardiac complications in vascular surgery patients than the RCRI.

Preoperative Laboratory Testing

Complete Blood Count

Preoperative anemia has been linked to increased cardiac morbidity.[40] Preoperative anemia is also linked to increased transfusion requirements that have been secondarily shown to increase cardiac morbidity. In particular, surgical patients chronically on beta-blockers do not tolerate acute anemia, which may lead to increased cardiac morbidity.[41]

Creatinine

The RCRI and the VSG-CRI show that chronic renal failure is independently associated with increased cardiac morbidity. However, creatinine is closely related to lean muscle mass. Thus many elderly patients with normal creatinine levels have chronic renal failure. The conversion of creatinine to glomerular filtration rate, through either the MDRD or Cockcroft-Gault equations that take account for patient age, may increase the sensitivity and specificity of the measurement.[42]

Blood Sugar

Diabetes is a common comorbidity in up to 50% of vascular surgical patients. Diabetes is strongly associated with most other risk factors, coronary disease, renal disease, and cerebral vascular disease. It is interesting to note that while insulin therapy was independently associated with cardiac morbidity in the derivation set of the RCRI, it was not in the validation set. Several observational trials have suggested that elevated levels of glycosylated hemoglobin (HbgA1c) are related to perioperative cardiovascular outcomes. Certainly HbA1c above 6.7% has been shown to be associated with increased morbidity after cardiac surgery[43] and PCIs. However, there is no good prospective data in vascular surgery to suggest that elevated HbA1c improves diagnostic accuracy over a history of diabetes alone. Tight glucose control in the perioperative period, the focus of several critical care randomized trials, failed to show any improvement in outcomes.[44]

Natriuretic Peptides

Increased preoperative levels of Plasma NT-proBNP and BNP have been associated with increased postoperative adverse outcomes. Rodseth and colleagues have completed a meta-analysis of six prospective observational trials of 850 vascular surgical patients.[45] Using a composite outcome of cardiovascular death and nonfatal MI, this meta-analysis showed that a BNP below 30 pg/mL has a low likelihood ratio of 0.11 for a postoperative cardiac event. For levels between 30 and 116 pg/mL, the positive likelihood ratio was 3.6. For levels above 116 pg/mL, the positive likelihood ratio was found to be 6.4.

Cardiac Troponin

The advent of high sensitivity troponin assays has led to the awareness that patients with cardiovascular anomalies have elevated troponin levels. Recently two studies have evaluated preoperative troponin levels as a prognostic indicator.[46,47] In a multicentered observational study, RCRI, BNP, and preoperative high sensitivity troponin elevation were associated with an increase in mortality. Preoperative troponin outperformed both RCRI and BNP as a prognostic indicator, suggesting that low-level troponin elevation existing before surgery represents preexisting cardiac abnormality or dysfunction.

C-Reactive Protein

Patients with systemic inflammation as evidenced by an elevated C-reactive protein (CRP; >5 mg/L) before surgery had higher major postoperative vascular event rates (60%) compared with a 32% rate in those with a baseline CRP of <5 mg/L (P = .004). Following multivariable analysis, elevated CRP correlated with adverse graft-related or cardiovascular events.[48] Vascular surgery patients with high preintervention values of both high sensitivity CRP and NT-BNP were 10.6 times more likely to experience major adverse cardiac events (MACE = stroke, MI, or death) than were patients with normal CRP and NT-BNP values.[49]

Rest Electrocardiogram

The resting EKG is mandatory tool for screening patients with suspected cardiac disease. ST-segment changes, either ST-elevation or depression, indicative of acute or recent ischemia, should be correlated with symptoms and compared with previous EKGs. Most other EKG changes represent chronic patterns of injury or conduction abnormalities. Pathologic Q-waves represent old MIs, and the more EKG leads with pathologic Q-waves, the wider the territory of infarcted myocardium. Tall R waves and wide QRS complexes with or without ST-T changes and inverted T-waves represent myocardial hypertrophy or dilation. EKG also detects and helps define abnormal rates and rhythms. These chronic pathologic ECG changes are associated with an increased risk for perioperative events.[37] In patients undergoing noncardiac surgery, Van Klei and colleagues found that while preoperative bundle branch blocks, Q waves, and ST-T changes were significant predictors of postoperative cardiac events, these EKG abnormalities did not remain predictive in a multivariable logistic regression that includes the six independent risk factors of the RCRI.[50] EKG changes are common in vascular surgery patients. A study in vascular surgery patients showed that 33% had pathologic Q-waves, 22% had baseline ST-segment changes, 38% had T-wave inversions, and 16% had voltage criteria for LVH. Patients with pathologic Q-waves or LVH are more likely to have perioperative ischemia or infarction[51]

Chest X-Ray

The chest x-ray is also an essential qualitative tool in screening cardiac patients, and its main value is to supplement the history and physical examination in identifying and assessing the severity of cardiac failure. Signs of cardiac failure on chest x-ray, recognizable by abnormal cardiac size and increased pulmonary vasculature, should trigger further examination to gain better understanding of the causes of cardiac dysfunction.

Echocardiography

Routine preoperative echocardiography is not recommended for routine screening in the absence of specific indications. Echocardiography is justified before major surgery to verify or evaluate significant valvular disease—in particular aortic stenosis. Severe aortic valvular stenosis is common in elderly patients and has been shown to correlate with perioperative complications and death. Severe aortic stenosis is also a relative contraindication for regional anesthesia. Significant mitral valvular disease predisposes the patient to congestive failure in the perioperative period, and its recognition before surgery may alter the approach to patients and their perioperative clinical management. Other important indications for preoperative echocardiography are to evaluate significantly reduced LV and/or right ventricular (RV) function, cardiomyopathies such as hypertrophic obstructive cardiomyopathy or dilated cardiomyopathy, and the presence and severity of pulmonary hypertension.[40] Resting echocardiography is not a good method to evaluate the severity of CAD and the risk of perioperative MI.

Ambulatory ST Segment Monitoring

Silent myocardial ischemia, defined as episodes of ST-segment depression on ambulatory EKG with ST-segment trend analysis that are not accompanied by chest pain, is a well-known phenomenon in elderly patients with CAD and has been shown to predict worse prognosis. Similarly, the detection of silent preoperative ischemia on preoperative Holter monitoring has been associated with increased postoperative morbidity. Raby and colleagues used Holter monitoring for 24 hours before vascular surgery and found that preoperative ischemia predicted postoperative cardiac complications with a sensitivity of 75% and specificity of 83%.[52] In contrast, however, meta-analysis of eight studies with more than 800 patients found a cumulative sensitivity of 52% and a specificity of 70%.[53] One major reason for this relative insensitivity is related to the fact that as many as 30% of vascular patients have preexisting ST-T changes, bundle branch block, or pacemakers, which make the interpretation of ST segments difficult. In addition, Holter monitoring uses only two, and rarely three modified EKG leads, and is susceptible to motion and other artifacts during normal daily activity.

Preoperative Investigation for Coronary Artery Disease

While coronary angiography is the gold standard for determining the existence and severity of CAD, its invasiveness and cost make it unsuitable for routine preoperative screening. Coronary angiography provides information on the major coronary anatomy but less so on the downstream minor vessels or on functional consequences of that anatomy. Nevertheless, Hertzer and colleagues performed routine coronary angiographies on all patients scheduled for major vascular surgery in the early 1980s, and patients with significant left main and triple vessel disease were treated with CABG.[51] In a retrospective analysis of 1522 of these patients, Ellis and Hertzer found that 81% of the patients with postoperative MI or cardiac death had at least one total coronary artery occlusion with collaterals compared with 29% in match-controlled patients without cardiac complications. In every other respect, patients with postoperative complications also had more severe CAD prior to surgery as compared with

the control group.[54] Based on this observation, it is possible to conclude that postoperative cardiac complications most likely occur in patients with preoperative long-standing severe CAD. This is also consistent with the previously described observations that postoperative MI and cardiac complications are the result of prolonged stress-induced ischemia in the presence of severe yet stable CAD. Therefore identifying patients with severe and often clinically silent coronary disease should be the focus of preoperative coronary investigations.

Noninvasive (Stress) Testing

The ACC/AHA guidelines suggest that patients who report limited functional capacity—that is, inability to climb at least two flights of stairs without chest pain or shortness of breath, the equivalent of four metabolic equivalents (METs)—are candidates for noninvasive cardiac stress testing before major noncardiac surgery.[40] Limited functional capacity is indeed a marker of higher perioperative risk. However, limited exercise tolerance may be due to numerous causes, including cardiac, pulmonary, orthopedic, neurologic, peripheral vascular, obesity, advanced age, or poor physical fitness. The noninvasive cardiac testing can help sort out the cardiac from other causes.

Exercise Stress Testing

The most common physiologic stress test for detecting myocardial ischemia uses a treadmill or cycle ergometer. Among its advantages, this test provides an estimate of functional capacity and hemodynamic response and detects myocardial ischemia through ST-segment changes. The accuracy of an exercise ECG varies widely among studies. A meta-analysis by Kertai and colleagues for the detection of myocardial ischemia with treadmill testing in vascular surgery patients showed a rather low sensitivity (74%) and specificity (69%).[54] The extremely low effort capacity in some vascular surgical patients limits the utility of this test and often leads to the use of pharmacologic stress testing. The most recent ACC/AHA guidelines (2014) designate only a Class IIb recommendation for preoperative cardiac exercise testing: (1) "In patients with elevated risk and unknown functional capacity, it may be reasonable to perform exercise testing to assess for functional capacity if it will change management (level of evidence: B)." (2) "In patients with elevated risk and poor (<4 METs) or unknown functional capacity, it may be reasonable to perform exercise testing with cardiac imaging to assess for myocardial (level of evidence: C)."[40]

Myocardial Perfusion Imaging

Single photon emission tomography (SPECT) with thallium-201 or technetium-based agents has been available since the 1970s and is still the most widely used noninvasive test. The test can be done with physiologic (treadmill/cycle ergometer) or pharmacologic (dipyridamole) stress. When the cardiac images acquired in a resting state are compared with the stressed state, the investigation is able to differentiate fixed from reversible filling defects in myocardial tracer uptake. These differences are suggestive of areas of infarct versus ischemia. A meta-analysis of 114 articles showed that the sensitivity and specificity of SPECT for detecting CAD with ≥50% stenosis are 88% and 61%, respectively[55] SPECT has a time-honored and important value in predicting long-term risk in patients with suspected CAD. A meta-analysis of 14 articles comprising more than 12,000 patients showed that negative and positive stress SPECT are associated with 0.6% and 7.4% annualized rate of hard events (nonfatal MI or death), respectively.[56] SPECT can also provide calculation of left ventricular ejection fraction during stress and rest. Transient left ventricular dilation and increased lung uptake during stress are additional parameters used to evaluate higher cardiac risk. A meta-analysis by Etchells and colleagues that investigated the prognostic value of semiquantitative dipyridamole myocardial perfusion imaging (MPI) for determining perioperative cardiac risk in patients undergoing vascular surgery found that reversible ischemia in less than 20% of the myocardial segments did not change the likelihood of perioperative complications, whereas greater extents of reversibility of myocardial perfusion defects were associated with increased risk of perioperative cardiac complications.[57] In contrast, however, a normal SPECT scan may occur in up to 15% of patients (false negative rate) with left main disease on account of balanced ischemia in multivessel disease. False positive tests are also common as a result of attenuation artifacts in obese patients, due to elevated diaphragm or breast artifacts.

Dobutamine Stress Echocardiography

This is a relatively low-cost, widely available test based on the assessment of increasing or new global or regional myocardial wall motion abnormalities during stress that are induced by increasing doses of dobutamine. Meta-analysis of 62 studies showed that the sensitivity of dobutamine stress echocardiography (DSE) is 83% in patients without prior MI but decreases to 74% when patients with prior MI were included. The specificity of DSE for detecting significant CAD is also approximately 80%. Long-term, a negative DSE test is associated with a 0.5% to 0.8% annualized risk of death or MI. A recent meta-analysis by Beattie and coworkers compared the value of DSE with MPI in predicting postoperative MI or in-hospital death.[58] This report included 25 studies (3373 patients) of mainly DSE, and 50 MPI studies with marked variability in results among the studies. The likelihood ratio for positive test was greater for DSE than for MPI, 4.1 versus 1.8, respectively, and the area under the ROC curve for the tests was 0.8 and 0.75, respectively. The recent ACC/AHA guidelines (2014) designate only a Class IIa recommendation for preoperative cardiac pharmacologic testing: "It is reasonable for patients who are at an elevated risk for noncardiac surgery and have poor functional capacity (<4 METs) to undergo noninvasive pharmacologic stress testing (either dobutamine stress echocardiogram [DSE] or pharmacologic stress MPI) if it will change management (level of evidence: B)."

Positron Emission Tomography

It is a newer, more expensive modality that is not widely available. Positron emission tomography (PET) includes both perfusion

(by Ru-82, N-13 ammonia or O-15 water) and functional metabolic (F-18 fluorodeoxyglucose [FDG]) imaging. Mismatch between perfusion and metabolism suggests viable ischemic area, while matched reduction in both blood flow and metabolism suggests an area of infarct. A meta-analysis of 19 studies showed that PET had a sensitivity of 92% and specificity of 85% for diagnosing significant CAD.[59]

Cardiac Magnetic Resonance Imaging

This is another new technology that may become the standard preoperative screening test in the future. Unlike SPECT and PET, cardiac MRI (CMR) has excellent spatial resolution and can provide accurate information on transient (ischemia) or fixed (infarction) hypoperfusion and scar tissue, even in small areas of the sub-endocardium. Myocardial perfusion is imaged during the first pass of a bolus of gadolinium during stress (achieved by adenosine or dipyridamole), rest and late gadolinium enhancement. In a meta-analysis, CMR was shown to have better sensitivity (89%) and specificity (76%) than SPECT for detecting significant CAD.[60] Contraindications to the CMR include patients with implanted metal, hypersensitivity to gadolinium, renal insufficiency, or sensitivity to the vasodilating agents, adenosine and dipyridamole, and patients with severe asthma or COPD.

Computed Tomography Coronary Angiography

This is an established noninvasive method for evaluating coronary anatomy as well as myocardial function. Studies showed that computed tomography coronary angiography (CTCA) has a high diagnostic accuracy for detecting the presence of coronary artery stenosis. A meta-analysis of 27 studies showed the sensitivity, specificity, PPV, and NPV were 97%, 91%, 93%, and 96% compared with conventional coronary angiography.[61] A more recent study showed that while the sensitivity of CTCA remains strong, the specificity declines to 66% in patients with coronary calcifications. One prospective study in 290 consecutive patients undergoing CTCA with a 64 row detector found that a higher RCRI, a high coronary artery calcium score (CACS >113), the presence of significant coronary artery stenosis, and multivessel CAD were significantly associated with postoperative cardiovascular events.[62] The promise of this technology will be realized with higher resolution scans.

Ahn and colleagues studied 239 patients who underwent CTCA before intermediate-risk noncardiac surgery, and noted that RCRI, CAC score, the presence of significant coronary artery stenosis (diameter stenosis ≥50%), and multivessel CAD were the strongest predictors of postoperative cardiac complications. Hwang and colleagues studied 844 patients who underwent coronary CTA for screening of CAD before noncardiac surgery.[63] The risk of perioperative major cardiac events was 14.0% in patients with significant CTA findings (>3 lesions), versus 2.2% in patients without significant CTA findings regardless of RCRI score. The sensitivity, specificity, positive, and negative predictive values were 76%, 73%, 8%, and 99%, respectively.

Preoperative Coronary Angiography and Revascularization

The detection of significant CAD by noninvasive testing is only the first step in investigating cardiac patients undergoing vascular surgery. The decision to proceed to coronary angiography based on the noninvasive testing depends on an assessment of whether the benefits of an intervention (prophylactic preoperative coronary revascularization) outweigh the risks associated with the intervention and delaying surgery.

Earlier retrospective studies suggested that preoperative coronary revascularization in vascular surgery patients was associated with better postoperative and long-term survival.[64,65] However, these studies suffered from the limitations of retrospective studies, among which was failure to include all patients who died or had serious complications from the preoperative revascularization and therefore could not undergo the expected vascular surgery. In 2004, McFalls and coworkers published the randomized Coronary Artery Prophylaxis (CARP)[3] trial that included 510 candidates for major vascular surgery.[66] After screening for cardiac risk, patients who had coronary angiography that showed one or more major coronary vessels with ≥70% stenosis were randomized to either coronary revascularization (by PCI or CABG) before vascular surgery or no coronary intervention prior to surgery. Patients were followed for a mean period of 2.5 years after surgery. The study showed no difference in survival between the two groups. However, this trial had two important limitations: (1) The screening process did not rigorously follow the ACC/AHA guidelines, so that only a minority of the patients had evidence of severe ischemia on noninvasive testing and the study was underpowered to assess this key aspect. (2) Patients with left main CAD and patients with severely reduced LVEF were excluded. Nevertheless, this trial had a strong impact worldwide on perioperative patient management by shifting the paradigm toward less coronary investigations and interventions before major noncardiac and vascular surgery. This trial coincided with the COURAGE trial,[67] which showed that PCI does not confer better survival than optimal medical treatment in patients with stable CAD, creating evidence that prophylactic re-vascularization by PCI was unwarranted in vascular surgery. Importantly however, subsequent publications from the CARP trial and registry reported that the following: (1) Patients who had CABG with more complete coronary revascularization had better survival than those revascularized by PCI.[68] (2) Patients with left main disease, excluded from the trial, had markedly better survival with coronary re-vascularization than without it.[69] (3) In a subset of 109 patients with ischemia on preoperative MPI, patients randomized to preoperative coronary revascularization had significantly better long-term survival free of MI than patients without revascularization, particularly if ischemia was in the anterior wall.[67]

Monaco and associates[3] randomized 208 consecutive patients with RCRI ≥ 2 scheduled for elective abdominal aortic surgery to either a "selective strategy" with coronary angiography only if their stress test was positive or a "systematic strategy" with routine

coronary angiography. The systematic strategy discovered 50% more patients with significant CAD than the selective strategy, had more subsequent coronary revascularizations (58% vs. 40%, respectively), and was associated with significantly better long-term survival and freedom from major adverse cardiac events. While this small study supports the concept of prophylactic preoperative coronary angiography and revascularization among patients at high clinical risk (RCRI ≥ 2), the routine use of coronary angiography without prior noninvasive screening is not established practice and merits further investigation. Another large sample (16,478 patients) representing real-world practice suggested that patients with a recent MI benefit from preoperative revascularization and that CABG improves outcomes more than coronary stenting, especially when surgery is deemed necessary within 1 month of the revascularization.[70] In contrast, another study that included 1104 vascular surgery patients confirmed the significance of ischemic heart disease (IHD) for postoperative survival of vascular surgery patients and that CR is associated with lower IHD-related death rates, yet CR in that study failed to provide an overall survival benefit because of increased rate of cardiovascular mortality unrelated to IHD.[71]

The latest ACC/AHA update "On Evaluation and Care for Non-Cardiac Surgery" (2014)[40] states the following:

CLASS I

Revascularization before noncardiac surgery is recommended in circumstances in which revascularization is indicated according to existing clinical practice guidelines (CPGs). (Level of Evidence: C)

CLASS III: NO BENEFIT

It is not recommended that routine coronary revascularization be performed before noncardiac surgery exclusively to reduce perioperative cardiac events. (Level of Evidence: B)

MEDICAL PROPHYLAXIS

Beta Blockade

Up to 25% of patients assessed for vascular surgery are taking beta-blockers. Beta blockade is indicated for the treatment of various comorbidities, including hypertension, CAD (both stable angina, and after acute MI), and congestive heart failure. Studies on stable angina pectoris show that beta-blockers provide excellent symptomatic improvement. Patients who are maintained on beta-blockers after MI show moderately improved long-term survival. In patients with congestive failure, beta-blockers also improve long-term survival. Nevertheless, there is a growing body of evidence showing that chronic beta blockade may also be harmful. A meta-analysis comparing beta blockade to other forms of antihypertensive therapies such as ASA and carotid endarterectomy (ACE) inhibitors and calcium channel blockers suggested that beta-blockers are associated with an increase in cerebral vascular accidents.[72] A recent large prospective observational trial showed that although chronic beta blockade in patients with prior MI is associated with improved long-term survival,[73] patients with CAD but without MI do not benefit after 4 years of follow-up, and patients with no CAD have an 18% increase in morbidity after 4 years compared with all other forms of therapy.

Postoperative MI is preceded by prolonged ST-depression type ischemia, and the ischemia itself is associated with a significant increase in heart rate. These findings gave impetus to the theory that perioperative beta blockade would reduce perioperative MI, leading to numerous clinical trials. In a high-quality meta-analysis of 33 trials involving more 12,000 patients, Bangalore and colleagues demonstrated that perioperative beta blockade was indeed associated with a 35% (95% CI 54% to 79%) reduction of nonfatal MI.[74] This was achieved, however, at the expense of a doubling in the stroke rate with no significant effect on all-cause mortality. The largest trial (POISE) in that meta-analysis showed that the beneficial effect on nonfatal MI was at the expense of both an increase in stroke and a 30% increase in all-cause mortality.[75] The POISE trial also showed that mortality was significantly higher in patients receiving beta-blockade if they developed serious infection or sepsis postoperatively. Lindenaurer, in an analysis of the Premier Prospective database, showed that postoperative mortality was reduced only in patients with RCRI of ≥2, but in patients with no risk factors mortality was increased by 30%.[74] A recent Cochrane meta-analysis also found no clear evidence that prophylactic perioperative beta-blockade reduces postoperative cardiac morbidity.[76]

On the basis of no improvement or even an increase in mortality and a doubling in postoperative strokes, the recommendation for prophylactic perioperative beta-blockade that was strongly advocated a decade ago (based on two relatively small, high-impact, yet questionable studies[77,78]) was stopped. Two independent investigations showed that major blood loss (or acute anemia) is associated with increased morbidity in beta-blocked patients.[43,79] Hence the increased mortality and stroke rate caused by prophylactic beta-blockade, despite the decrease in nonfatal MI, is most likely related to the potential detrimental effects of beta-blockade—that is, slowing heart rate and decreasing myocardial contractility in patients with postoperative anemia or infection who are at the greatest need for tachycardia and high cardiac output after surgery.

Statins

A recent meta-analysis in patients at risk of cardiovascular events, combining 27 prospective trials and over 174,000 patients, showed that for each 1 mmol decrease in LDL, statins reduced the long-term relative risk of a cardiovascular event by 24% (95% CI 21 to 27).[80] This reduction was seen across all risk populations, and reduced the need for revascularization, incidence of stroke, and other vascular events. Furthermore, these benefits far exceeded the risks of elevated liver enzymes, myopathy, or rhabdomyolysis. This study suggests that all vascular patients who have atherosclerosis should receive statins, if

tolerated, for management of their cardiovascular disease irrespective of the need for surgery. The Vascular Quality Initiative (VQI), including more than 14,000 patients who underwent major vascular surgery, found no association between the rate of in-hospital MI/death and the use of antiplatelet agents or statins.[81] Antiplatelet agents and statin medications appear to be more useful in reducing late mortality than early postoperative MI/death in VQI. However, they were not harmful, so their long-term benefit argues for continued use. Therefore regardless of the procedure or stress testing results, patients with symptomatic atherosclerosis (e.g., PAD, cerebrovascular disease) should be on antiplatelet and statin therapy according to the ACC/AHA guidelines.[81] Although no RCT showed improved in-hospital morbidity or mortality with statins, a recent meta-analysis of statin use in vascular surgery patients showed a significant risk reduction in postoperative cardiac morbidity as well as death.[82] In addition, a large institutional study including nearly 166 patients and a large registry study demonstrated a significant reduction in perioperative stroke and MI rates among patient undergoing CEA on statins compared to nonusers[83,84] Further, compliance with both antiplatelet therapy and statins in vascular surgical patients was associated with significantly improved long-term survival.[85] Currently, there is no clear prospective evidence to indicate how soon statins must be started preoperatively, if not administered chronically, to achieve a reduction in perioperative adverse events.

Aspirin

While the primary prevention of cardiovascular events by aspirin is still controversial,[86] the utility of aspirin as a secondary prevention of cardiovascular events is well established.[87] The benefits of aspirin in terms of reduction of re-infarction, stroke, and ischemia far outweigh the increased risks of bleeding in nonsurgical patients. The Anti-Thrombotic Trialist's Collaboration conducted a meta-analysis of 287 trials in more than 130,000 high-risk patients (with acute or previous vascular disease or some other predisposing condition) compared with a control group. MI was reduced by one-third, nonfatal stroke by one quarter, and vascular death by one-sixth. The absolute reduction in cardiovascular morbidity in high risk patients was 22 per 1000 patients after 2 years of therapy.[88] These results confirm that patients at risk of any recurrent vascular morbidity should be treated with ASA irrespective of their need of surgery.

In the perioperative setting, the large-scale POISE-2 RCT that included 10,010 noncardiac surgery patients (5% of them had vascular surgery) showed that aspirin given before surgery and throughout the early postsurgical period had no effect on composite death or nonfatal MI but increased the risk of major bleeding.[88] Among vascular surgery patients, the ACE (Aspirin in Carotid Endarterectomy) randomized trial compared four doses of aspirin in patients having elective CEA [89] and found that the risk of stroke, MI, and death within 30 days and 3 months of endarterectomy is lower for patients taking 81 mg or 325 mg acetylsalicylic acid daily than for those taking higher doses of aspirin. Unfortunately, the ACE trial did not have a placebo control. Another prospective two-arm comparative study in patients undergoing CEA showed that the overall cardiac and neurologic complication rate was lower in the aspirin group compared with the group not on aspirin (5.2% vs. 17.6%, respectively), with no significant increase of postoperative bleeding necessitating revision.[90]

Despite the clear advantages of secondary prevention, the effectiveness of low dose ASA, and grade 1A evidence of a low incidence of excess bleeding with a low dose ASA, this drug continues to be withdrawn prior to many nonvascular operations. Two meta-analyses of retrospective studies[91,92] demonstrated that aspirin withdrawal was associated with a threefold increased risk of a major adverse cardiovascular events on an average of 7 days after cessation. The major reason for withdrawal was an upcoming elective surgical procedure. The authors concluded that ASA should be maintained in all patients except for those who had the highest risk of bleeding. Unfortunately, there are no prospective studies assessing withdrawal of ASA in any surgical population.

Dual Antiplatelet Therapy After Coronary Stenting

More than 1 million PCI procedures are conducted annually in North America[93] alone, and more than 5% of these patients will undergo elective surgery within 1 year.[94] Patients who had recent revascularization using PCI and stents are treated initially with dual antiplatelet therapy for a variable period of time, aspirin, and a P2Y12 platelet receptor–inhibitor, usually clopidogrel, to prevent stent thrombosis. These patients require special consideration. Kaluza[95] drew attention to the increased mortality in patients having elective surgical procedures shortly after PCI. Mortality was related either to excessive bleeding due to continuation of the dual-antiplatelet therapy through surgery or to acute stent thrombosis and type-1 MI after the abrupt discontinuation of the antiplatelet medications. This case series was then quickly followed by a myriad of other case series showing increased morbidity when procedures were carried out within 90 days of PCI.[96,97] A retrospective analysis of 8116 stent patients from large a comprehensive stent registry linked to a Medicare administrative database confirmed that surgical procedures conducted within 45 days of a PCI are associated with high mortality.[98] However, after 45 days the risk was similar to patients with a RCRI of equal to or greater than 2% for both patients with bare metal or drug eluting stents. After 180 days, the risk of major cardiac morbidity is approximately 1%, which is similar to the morbidity of patients after PCI who do not undergo surgery. A recent retrospective study matched 20,590 surgical patients to 41,180 nonsurgical patients who underwent PCI in the Veterans Affairs (VA) hospital between the years 2000 and 2010.[99] During the 30-day interval following noncardiac surgery, the surgical cohort had higher rates of the composite cardiac endpoint (3.1% vs. 1.9%). The incremental risk of noncardiac surgery adjusted for surgical characteristics ranged from 3.5% immediately following stent implantation to 1% at 6 months, after which it remained

TABLE 42.5 Focused Update on Duration of Dual Antiplatelet Therapy

COR	LOE	Recommendations
I	B-NR	Elective noncardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation (101-103, 143-146).
I	C-EO	In patients treated with DAPT after coronary stent implantation who must undergo surgical procedures that mandate the discontinuation of $P2Y_{12}$ inhibitor therapy, it is recommended that aspirin be continued if possible and the $P2Y_{12}$ platelet receptor inhibitor be restarted as soon as possible after surgery.
IIa	C-EO	When noncardiac surgery is required in patients currently taking a $P2Y_{12}$ inhibitor, a consensus decision among treating clinicians as to the relative risks of surgery and discontinuation or continuation of antiplatelet therapy can be useful.
IIb	C-EO	Elective noncardiac surgery after DES implantation in patients for whom $P2Y_{12}$ inhibitor therapy will need to be discontinued may be considered after 3 months if the risk of further delay of surgery is greater than the expected risks of stent thrombosis.
III: Harm	B-NR	Elective noncardiac surgery should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively (101-103, 143-146).

stable out to 24 months. In addition, the authors observed that approximately 50% of the risk of adverse cardiac events was due to underlying cardiac risk factors and approximately 50% was due to surgical factors. After matching for cardiac risk factors, no significant difference was found in cumulative incidence of adverse cardiac event rates between the surgical population and the nonsurgical matches over the 24 months following stenting, although there was a higher mortality in the surgical population from noncardiac causes. There was also no significant difference in postoperative cardiac complications between patients with bare-metal stents and drug-eluting stents.

In patients undergoing CEA (the VQI)[100] patients on dual therapy were more likely to have multiple comorbidities, including CAD, congestive heart failure, and diabetes, and had increased rate of reoperation for bleeding but experienced a reduced rate of TIAs, stroke, and stroke/death.

See Table 42.5 for the most recent (2016) ACC/AHA guidelines for dual antiplatelet therapy in patients undergoing noncardiac surgery.[101]

TREATMENT

In treating patients at risk for postoperative cardiac complications, it is most important to recognize that the majority of postoperative cardiac complications are silent or begin as silent. High-risk vascular surgery patients have a high rate of silent ischemia, silent myocardial injury, and infarction, all of which are associated with higher in-hospital and long-term mortality.[102] Silent and overt cardiac complications are strongly linked to noncardiac complications, and both types precipitate each other.[103] For instance, perioperative hypotension,[104] systemic infection, serious bleeding, and anemia were all linked to postoperative cardiac morbidity and mortality. A high index of suspicion for silent cardiac complication is of greatest importance when dealing with cardiac patients undergoing major vascular surgery. If a patient is suspected of having postoperative ischemia or cardiac failure, the first diagnostic step would be to perform a 12-lead EKG. The presence of *ST-segment elevation ischemia or MI* is a medical emergency,[105] especially after surgery. A cardiologist must be consulted, and the possibility of immediate reperfusion with percutaneous transluminal coronary angioplasty with stenting should be considered. A special subset of patients who are prone to develop acute postoperative coronary thrombosis are those with fresh coronary stents in whom the antiplatelet therapy was stopped before surgery.

The more common situation is the occurrence of *ST-segment depression type ischemia or MI.* In these patients, diagnostic effort to find the potential causes for stress-induced, supply-demand imbalance type ischemia should be started and medical therapy should be implemented to relieve ischemia.[106] The importance of preventing even modest increases in heart rate cannot be overemphasized. The treatment of tachycardia and hypertension can be achieved with beta-blockers or calcium channel blockers or pain-killing medications. In contrast, treatment of tachycardia associated with hypotension is particularly challenging and requires an understanding of the patient's baseline and postoperative myocardial, valvular, and coronary physiology. These patients will require additional diagnostic tests, invasive monitoring, bedside echocardiography, and other imaging devices. Frequently, vasopressors to maintain blood pressure and beta-blockers to slow heart rate while fine tuning blood volume, postoperative pain, and respiratory function are necessary (Fig. 42.3). Management of patients with ischemia in the face of hypotension and hypoperfusion is often challenging, and the assistance of an intensive care unit and consultation with anesthesiologists, intensivists, and cardiologists is warranted.

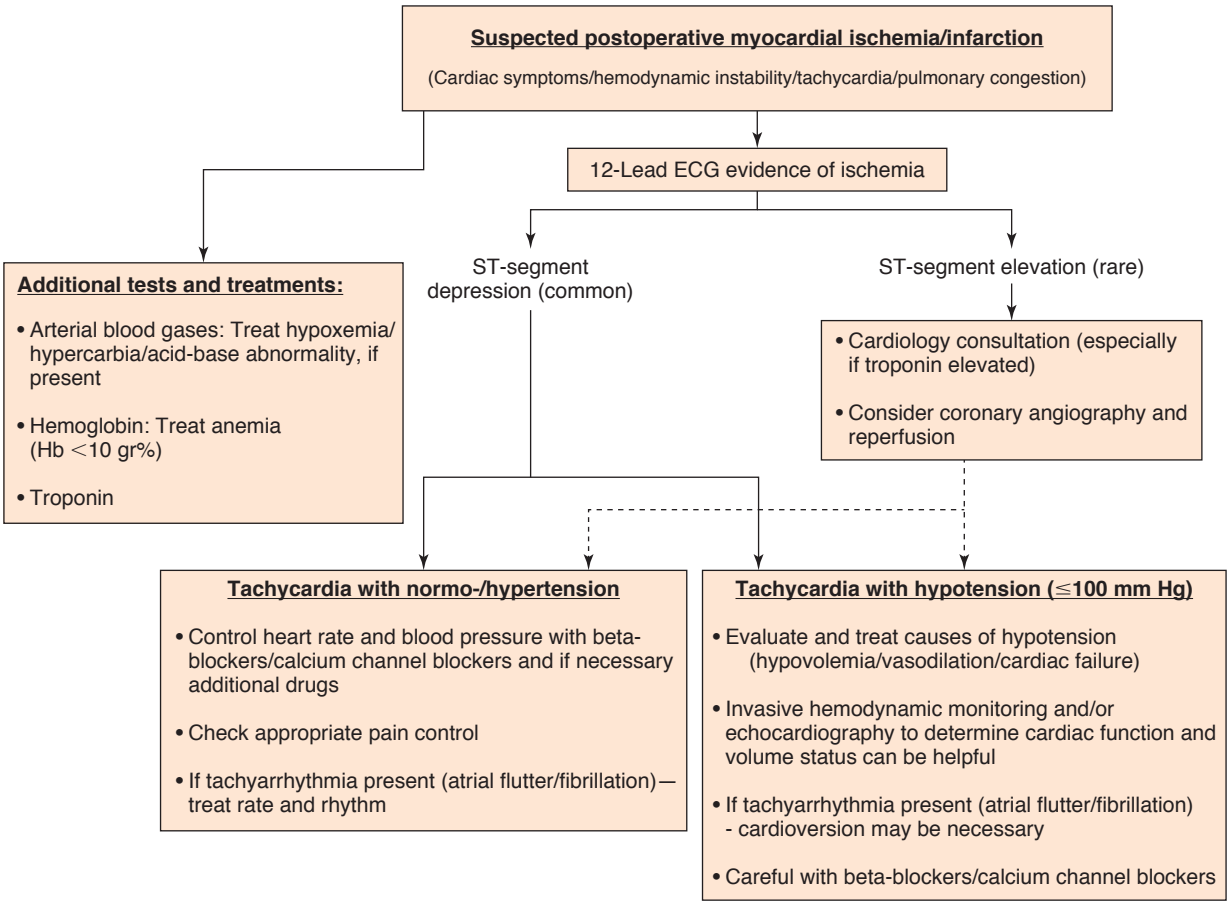

Figure 42.3 Suggested perioperative myocardial infarction treatment algorithm. *ECG*, Electrocardiogram.

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CHAPTER 43

Respiratory Complications

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Perioperative respiratory complications remain a major cause of morbidity and mortality in surgical patients.[1-10] Quality and safety of patient care relies on the anticipation and prevention of respiratory complications, as well as timely and effective management when complications do occur.[11-13] Broadly defined, perioperative respiratory complications include any conditions that affect the respiratory tract and adversely influence the course of a patient after surgery.[5] Common complications (Box 43.1) may include atelectasis, pneumonia, upper airway obstruction, acute respiratory distress syndrome (ARDS), and respiratory failure, which is often defined as mechanical ventilator dependence 48 hours after surgery.[5,10,14] This chapter will review approaches to preoperative risk stratification, perioperative risk reduction, and management of respiratory complications.

PREOPERATIVE RISK STRATIFICATION

Preoperative risk stratification for respiratory complications involves assessment of patient-related risk factors, procedure-related risk factors, and laboratory test risk factors (Table 43.1).[15-17] Pulmonary risk indices have been developed to assist with preoperative risk assessment and patient optimization prior to surgery.[7-10]

Patient-Related Risk Factors

A comprehensive systematic review conducted by Smetana et al. found good evidence to support advanced age, functional dependence, American Society of Anesthesiologists (ASA) Class II or greater, chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF) as risk factors for postoperative pulmonary complications in patients undergoing noncardiothoracic surgery.[8] Early studies identified advanced age as a potential risk factor for pulmonary complications after surgery, but they did not adjust for comorbid conditions and overall health of patients. The precise influence of age has not been clearly established, but the review by Smetana et al. adjusted for comorbidities and reported an independent incremental risk of postoperative pulmonary complications with increasing age.[8,18,19] Prospective studies have also identified advanced age as a risk factor, but age alone should not be considered a contraindication for a patient who is otherwise suitable for an operation.[7,9] Functional status and comorbidities, often assessed with the ASA classification system, are an important determinant of preoperative pulmonary risk. Several studies have shown that ASA class II or higher is associated with postoperative pulmonary complications.[2,8] Comorbidities of particular interest include COPD and CHF, as these may predict postoperative respiratory complications and associated mortality.[8,20-24] For patients undergoing endovascular aortic aneurysm repair (EVAR), preoperative COPD is a risk factor for mortality with hazard ratio 1.9 (95% CI 1.2-3.1).[25] Patients with COPD and CHF have a higher risk of mortality after below knee amputation (BKA) for critical limb ischemia when compared to patients without these comorbidities.[26] While comorbid disease should generally not preclude surgical intervention, patients should be carefully advised regarding risks.[27]

BOX 43.1 Common Postoperative Respiratory Complications

- Acute lung injury
- ARDS
- Aspiration/aspiration pneumonitis
- Atelectasis
- Bronchitis and tracheobronchitis
- Bronchospasm
- Exacerbation of chronic disease (e.g., chronic obstructive pulmonary disease)
- Healthcare-associated pneumonia (including hospital-acquired and ventilator-associated pneumonia)
- Hypoventilation (from analgesia or residual neuromuscular blockade)
- Pleural effusion
- Pneumothorax
- Pulmonary edema
- Pulmonary embolism
- Respiratory failure (ventilator dependence 48 hours after surgery)
- TRALI
- Upper airway obstruction

ARDS, Acute respiratory distress syndrome; *TRALI*, transfusion-related acute lung injury.

TABLE 43.1 Patient-Related, Procedure-Related, and Laboratory Test Risk Factors for Postoperative Pulmonary Complications

Patient-Related Risk Factors	Procedure-Related Risk Factors
• Advanced age • Functional dependence • ASA Class II or greater • COPD • CHF • Smoking/cigarette use • Poorly controlled asthma • Upper respiratory infection (during previous month) • OSA	• Surgery type (endovascular vs. open) • Surgical site • Duration of surgery 2 hours or longer • Upper abdominal or intrathoracic surgery • Type of anesthesia • Endotracheal intubation • Long-acting neuromuscular blockade • Perioperative blood transfusion • Emergency surgery

Laboratory Test Risk Factors

- Oxyhemoglobin saturation by pulse oximetry (SpO_2 < 90%)
- Albumin <35 g/L
- Blood urea nitrogen >21 mg/dL
- Anemia (preoperative hemoglobin ≤10 g/dL)

ASA, American Society of Anesthesiologists; *CHF*, Congestive Heart Failure; *COPD*, Chronic Obstructive Pulmonary Disease; *OSA*, Obstructive Sleep Apnea.

Current smoking increases the risk of postoperative pulmonary complications and a dose-dependent increase in pulmonary complications is based on pack-year exposure to cigarettes.[28,29] Some early studies suggested that recent smoking cessation (less than 4-8 weeks prior to surgery) actually *increased* the risk of postoperative pulmonary complications purportedly through increased sputum production.[29,30] However, a more recent meta-analysis determined that quitting smoking within 8 weeks of surgery was not associated with either an increase or decrease in overall postoperative complications or pulmonary complications.[31] Surgeons should encourage their patients to quit smoking as early as feasible and whenever possible in the preoperative setting.[32]

Well-controlled asthma is not considered a risk factor for postoperative pulmonary complications, although there is fair evidence that poorly controlled asthma is a risk factor.[8] While severe perioperative bronchospasm and other complications may occur in patients with asthma, the incidence is quite low.[33] The risk of these complications depends on the patient's airway hype-responsiveness, airflow obstruction, and history of prior surgeries which may predispose to latex and/or anesthetic agent sensitivity.[34] Patients with asthma should be maintained on their antiinflammatory and vasodilatory agents in the perioperative period and may benefit from a short course of oral corticosteroids to improve lung function preoperatively.

Obesity is associated with physiologic changes that affect pulmonary gas exchange including reduced lung volumes, ventilation-perfusion mismatch, and relative hypoxemia.[35-37] Upper airway obstruction and sleep-disordered breathing may also be common in this population.[37] However, whether obesity itself is a risk factor for postoperative pulmonary complications is debatable.[8,38-40] Thoughtful management is necessary to ensure the best outcomes for obese patients, which may include modified approaches to anesthesia and perioperative noninvasive ventilation or continuous positive airway pressure (CPAP).[37]

Obstructive sleep apnea (OSA) has been reported to be an independent risk factor for postoperative pulmonary complications.[41-43] A study using the National Inpatient Sample found significantly higher rates of postoperative pulmonary complications, including aspiration pneumonia and ARDS, among general surgery and orthopedic surgery patients with OSA compared to matched controls.[41] A recent meta-analysis concluded that patients with OSA have an increased risk of postoperative respiratory failure (OR 2.42 [95% CI 1.53-3.84]).[42]

Other patient-related risk factors may include recent acute upper respiratory infection (within 1 month), alcohol use, weight loss (>10% in previous 6 months), impaired sensorium, and abnormal findings on chest examination.[7,8,14,44] Careful assessment and optimization of modifiable risk factors in the preoperative setting is critical to ensure best outcomes.

Procedure-Related Risk Factors

Procedure-related risk factors include type of surgery, surgical site, duration of surgery, anesthesia considerations, perioperative blood transfusion, and emergency surgery.[7-9] Risk factors related to the procedure are perhaps more important than patient-related risk factors, but procedure risks are generally less modifiable.[1]

Good evidence suggests that vascular surgery, especially aortic surgery, confers a higher risk of postoperative respiratory complications than other types of surgery.[1,8] Open aortic surgeries were associated with the highest risk of pulmonary complications

in one review OR 6.90 (95% CI 2.74-17.36). A cohort study compared postoperative pulmonary complication rates for open versus endovascular repair of abdominal aortic aneurysms.[45] The multivariate odds ratio for pulmonary complications after endovascular repair was 0.14 (95% CI 0.04-0.47) compared with open surgery. More generally, surgical sites near the diaphragm such as upper abdominal and intrathoracic surgery have higher risk for postoperative pulmonary complications, likely through direct impairment of diaphragmatic and respiratory function.[7,46-48]

Operative duration 2 hours or longer is associated with higher risk of postoperative pulmonary complications.[7,8,49] The review by Smetana et al. identified five different studies evaluating extended duration of surgery, ranging from 2.5 to 4 hours, and determined the pooled odds ratio for respiratory complications was 2.26 (95% CI 1.47-3.47). This finding is in contrast with known risk factors for postoperative cardiac complications, where duration of surgery is not thought to increase the risk of cardiac complications.[50] When a less ambitious or briefer procedure is an option, it is prudent to avoid longer operative duration.

Select anesthesia considerations, including type of anesthesia and neuromuscular blockade, may confer increased risk of postoperative pulmonary complications.[51] Although these data are not definitive, neuraxial anesthesia, including spinal and epidural anesthesia, has been associated with fewer postoperative respiratory complications than general anesthesia alone.[52-57] Furthermore, postoperative pain relief may be superior with epidural analgesia compared to parenteral opioids.[57] A recent Cochrane review examined the use of neuraxial anesthesia for lower-limb revascularization procedures.[58] Postoperative pneumonia was lower with neuraxial anesthesia compared to general anesthesia, but no mortality benefit was identified. An older trial from our institution randomized patients undergoing abdominal aortic surgery to one of four treatment groups: thoracic epidural anesthesia combined with light general anesthesia or general anesthesia alone and either intravenous or epidural patient-controlled analgesia postoperatively.[59] Epidural patient-controlled analgesia correlated with a significantly shorter time to extubation, but otherwise, there were no significant differences in outcomes among the four groups, including postoperative pain scores. When possible, short or intermediate-acting neuromuscular blockade is preferred to limit residual neuromuscular blockade, which may perpetuate hypoxia through functional impairment of the diaphragm and muscles of the pharynx.[60]

Other procedure-related risk factors, including emergency surgery and perioperative blood transfusion, may also confer higher risk of pulmonary complications.[7-9] Emergency surgery appears to confer a modestly increased risk, OR 2.2 (95% CI 1.0-4.5).[7] Preoperative transfusion of 4 or more units of packed red blood cells, or intraoperative transfusion, appears to confer higher risk of postoperative pneumonia.[7,8] Although in many circumstances these factors may not be modifiable, it is important to recognize these risks and maintain a high index of suspicion to ensure timely diagnosis and management of postoperative complications.

Laboratory Test Risk Factors

Select laboratory tests or adjunct studies are not a substitute for appropriate clinical evaluation. However, some studies may be of use during the preoperative evaluation to assist with risk assessment for pulmonary complications. Preoperative oxyhemoglobin saturation by pulse oximetry (SpO_2) was found to be one of the strongest independent predictors of postoperative pulmonary complications in one large cohort of surgical patients.[7] Patients with a SpO_2 less than 90% (supine position on room air) had an odds ratio of 10.7 (95% CI 4.1-28.1) for pulmonary complications compared to patients with a preoperative SpO_2 greater than or equal to 96%. This study also identified preoperative anemia (hemoglobin ≤ 10 g/dL) as an independent predictor of pulmonary complications.[7] A systematic review found good evidence to support preoperative albumin level less than 35 g/L as a risk factor for pulmonary complications and at least fair evidence to support blood urea nitrogen (BUN) level greater than 21 mg per deciliter as a risk factor.[1,8]

Adjunct studies, including pulmonary function tests (PFTs), arterial blood gas measurements (ABG), and chest radiography, should not be considered routine preoperative studies. However, in specific circumstances, these studies may be helpful to assess risk in the preoperative setting. Among patients undergoing procedures other than pulmonary resection, there is considerable debate concerning the role of PFTs in preoperative risk stratification.[61-65] PFTs provide an estimate of forced expiratory volume (FEV_1) and forced vital capacity (FVC). Two scenarios may justify the use of preoperative PFTs in vascular surgery: (1) identification of patients for whom the risk of an open vascular surgical procedure may outweigh the benefit or for whom a percutaneous or endoluminal approach would be better tolerated, and (2) identification of patients at higher risk who would benefit from aggressive perioperative management. For example, PFTs may be useful in patients with COPD or asthma when clinical examination alone is unable to determine whether the patient is fully optimized for surgery. In some cases, these studies may change management by highlighting the need for perioperative corticosteroids or other treatments. However, most patients identified by PFTs as high risk are identified equally well by a careful history and physical examination.[22]

Similarly, ABG and chest radiography are not necessary for preoperative evaluation and should not be ordered routinely. No data suggest that hypercapnia identifies additional high-risk patients beyond those who would already be identified by clinical criteria. Chest radiographs are commonly ordered for preoperative evaluation, but these studies may add little to the clinical evaluation of healthy patients and very rarely influence preoperative management.[66] An older review included over 14,000 surgical patients and found abnormal chest radiographs in 10% of patients; however, only 1.3% of studies revealed an unexpected finding, and only 0.1% of studies influenced perioperative management.[67] Preoperative chest radiography should be considered in patients with known cardiopulmonary disease, especially among patients with a recent change in disease status. Patients older than 50 years who are current smokers should also be evaluated with preoperative chest radiography to evaluate for malignancy and pulmonary disease.[8]

Pulmonary Risk Indices

A thorough history and physical exam forms the basis of preoperative risk assessment. Pulmonary risk indices have been developed to assist in the evaluation and stratification of patient risk.[7-10] Canet et al. reported the development of a predictive index for postoperative pulmonary complications based on a prospective multicenter observational cohort study in a broad population of surgical patients.[7] This study identified independent risk factors for postoperative pulmonary complications including low preoperative SpO_2, acute respiratory infection during the previous month, age, preoperative anemia, upper abdominal or intrathoracic surgery, surgical duration of at least 2 hours, and emergency surgery. Using these seven predictors and assigning point values for each, the authors designed an index to predict postoperative pulmonary complications (Table 43.2). Arozullah et al. developed an index to predict the risk of postoperative pneumonia using the Veterans Administration database.[9] Risk factors were assigned points based on their strength in a multivariate analysis. Procedure-related risk factors dominate the index, but many modifiable risk factors are also identified including functional status, cigarette use, and alcohol use. A more recent risk calculator for postoperative respiratory failure was developed using the prospective National Surgical Quality Improvement Program (NSQIP) data set.[10] On multivariate analysis, five preoperative predictors were identified: type of surgery, emergency case, dependent functional status, preoperative sepsis, and higher ASA class. Many of the factors included in these indices are not modifiable or amenable to risk reduction strategies. However, these tools may best serve to predict risk and inform decisions about the magnitude of the planned procedure, timing of surgery, and candidacy for surgery.

TABLE 43.2 Prediction of Postoperative Pulmonary Complications

Preoperative Predictor	Odds Ratio (95% CI)	Point Value
Age (years)		
≤50	1	—
51-80	1.4 (0.6-3.3)	3
>80	5.1 (1.9-13.3)	16
Preoperative SpO_2 (%)		
≥96	1	—
91-95	2.2 (1.2-4.2)	8
≤90	10.7 (4.1-28.1)	24
Respiratory infection in last month	5.5 (2.6-11.5)	17
Preoperative anemia (≤10 g/dL)	3.0 (1.4-6.5)	11
Surgical Incision		
Peripheral	1	—
Upper abdominal	4.4 (2.3-8.5)	15
Intrathoracic	11.4 (4.9-26.0)	24
Duration of Surgery (hours)		
≤2	1	—
>2-3	4.9 (2.4-10.1)	16
>3	9.7 (4.7-19.9)	23
Emergency surgery	2.2 (1.0-4.5)	8

Class	*Point Total*	*Predicted Probability of Postoperative Pulmonary Complication (%)*
Low risk	<26	1.6 (0.6-2.6)
Intermediate risk	26-44	13.3 (7.6-19.0)
High risk	>45	42.1 (29.3-54.9)

CI, Confidence interval; *SpO_2*, oxyhemoglobin saturation by pulse oximetry breathing room air in supine position.
Modified from Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology*. 2010;113:1338–1350.

PERIOPERATIVE RISK REDUCTION

Some risk factors for perioperative pulmonary complications are modifiable and risk may be reduced with appropriate attention to detail in the preoperative setting, the operating room, and the postoperative setting.

Preoperative Risk Reduction

Patient optimization in the preoperative setting may help prevent respiratory complications associated with surgery. Surgeons should encourage their patients to quit smoking as early as feasible before surgery but whenever possible in the preoperative setting.[32] Patients with comorbid pulmonary conditions, including COPD and asthma, should generally be optimized for elective surgery in the same manner they would be optimized in nonoperative settings.[33,34,68-71] Clinicians should not employ treatments specifically for upcoming surgery unless these treatments are otherwise indicated. Systemic preoperative corticosteroids may be appropriate in patients for whom peak airflow is not at the optimal baseline despite appropriate treatment with other therapies.[33,72] Corticosteroids may be safely used preoperatively without undue risk of infection or wound complications.[73,74] There is no role for routine antibiotics patients for respiratory prophylaxis prior to surgery. However, when a recent change in the chest radiograph or the amount or character of sputum indicates a respiratory tract infection, the patient should be treated for infection, and surgery should be delayed when possible.

Multimodality approaches for patients with COPD, including chest physical therapy, bronchodilators, antibiotics, and corticosteroids, may reduce the risk of postoperative pulmonary complications.[1,22] Inhaled therapies (including anticholinergics, beta-agonists, and corticosteroids) are standard treatment for

COPD and often used in combination depending on patient symptoms.[75,76] Pulmonary rehabilitation may also be appropriate in the preoperative setting for patients with symptomatic disease and FEV_1 less than 50% of predicted value.[69]

There is some evidence that preoperative inspiratory muscle training may be of general benefit to patients undergoing elective cardiac or major abdominal procedures. A recent Cochrane review determined that preoperative inspiratory muscle training was associated with a reduction in postoperative atelectasis, pneumonia, and duration of hospital stay.[77] The preoperative setting may also be the appropriate place to begin patient education regarding the importance of postoperative lung expansion maneuvers.[6]

Patients with asthma should be evaluated preoperatively with a thorough clinical history including medication use, examination, and review of symptoms. Measurement of PFTs may be an appropriate consideration in the preoperative setting.[34] When possible, lung function should be optimized to either the patient's predicted values or personal best values using a short course of oral systemic corticosteroids. Consideration for stress doses of corticosteroids at the time of surgery and during the postoperative period are appropriate for patients treated with corticosteroids during the previous 6 months or for those patients previously treated with high doses of inhaled corticosteroids.[34]

Intraoperative Risk Reduction

Many intraoperative factors may increase the risk of pulmonary complications, including type of surgery, site of surgery, and operative duration, but many procedure-related risk factors are not easily modifiable. When feasible as an alternative to open procedures, the benefits and risks of endovascular procedures should be considered. There is at least fair evidence that endovascular procedures are preferred to open procedures for the prevention of pulmonary complications, but the balance between benefit and harm may be too close to justify a general recommendation.[1,78]

Avoidance of long-acting neuromuscular blockade is appropriate to reduce the risk of perioperative pulmonary complications. There is at least fair evidence that the benefits of using agents for short-acting neuromuscular blockade outweigh any associated harm.[1] Intraoperative neuraxial blockade may confer some benefit in terms of reduction of pulmonary complications, alone or in combination with general anesthesia, but the data are conflicting and no definitive recommendation can be made at this time.[78]

General anesthesia is known to cause atelectasis, which can lead to impairment in respiratory function and associated complications. This risk may be compounded by use of one-lung ventilation commonly used during open thoracoabdominal aortic surgery to achieve surgical exposure.[79] Severe hypoxemia may result from one-lung ventilation secondary to right-to-left transpulmonary shunt.[80] The use of positive end-expiratory pressure (PEEP) intraoperatively may increase functional residual capacity and prevent airway collapse and atelectasis. Data at this time are insufficient to make any conclusions about the association of intraoperative PEEP and postoperative respiratory complications.[80,81]

Postoperative Risk Reduction

Risk reduction in the postoperative setting should focus on a number of different strategies: limiting the duration of intubation, preventing aspiration, increasing lung volume, preventing poor inspiratory effort, and avoiding overfeeding. Every effort should be made to extubate patients expeditiously because intubation significantly increases the risk of nosocomial pneumonia.[82,83] Ventilator-associated pneumonia (VAP) is the most common nosocomial infection among patients receiving mechanical ventilation and may occur in as many as 9% to 27% of intubated patients.[83] Protocols for daily weaning of sedation and trials of spontaneous respiration should be used to assess readiness for extubation; many of these protocols have been incorporated into VAP prevention bundles.[84,85] VAP prevention bundles, often championed as an effective approach to improve the practice of evidence-based medicine, have been shown to reduce respiratory complications in intubated patients.[85]

Aspiration prevention also comprises a major focus of VAP prevention bundles.[85] Strategies include head of bed elevation and subglottic suctioning of endotracheal tubes. Several studies have demonstrated that patients in the supine position are predisposed to microaspiration of gastric contents and subsequent nosocomial pneumonia as compared to patients kept in a semirecumbent position.[86-88] Aspirated secretions may pool above the cuff of the endotracheal tube; subglottic suctioning of these secretions has been demonstrated to significantly reduce the risk of associated pneumonia.[89-92] Other factors associated with aspiration and pneumonia include overaggressive use of restraints, immobility, toxic or metabolic causes of altered level of consciousness, and presence of nasogastric or other tubes that stent open both the upper and lower esophageal sphincters.[93,94] It is important to identify a purpose for nasogastric tube use and consider removal as soon as possible to help prevent pneumonia. Aggressive chlorhexidine oral hygiene will reduce bacterial load and colonization in the oropharynx and this strategy has been shown to reduce the incidence of aspiration pneumonia.[95-98] Stress ulcer prophylaxis is recommended for critically ill patients at risk of upper gastrointestinal mucosal bleeding; typically this is someone who will remain on a ventilator for more than 48 hours. However, acid suppressive medications, such as proton pump inhibitors and H2 blockers, may predispose patients to VAP by raising gastric pH and allowing bacterial overgrowth. The risk of VAP associated with stress ulcer prophylaxis remains controversial.[99]

Two prospective randomized trials have confirmed early tracheostomy is not associated with improved mortality or decreased incidence of VAP, though length of stay in the intensive care unit (ICU) may be decreased with early tracheostomy.[1,100,101] The TracMan trial compared early (4 days) versus late (10 days) tracheostomy among 909 patients requiring prolonged mechanical ventilation and found no differences in outcomes.[101] Other considerations, such as inability to protect the airway or patient comfort, may serve as indication for earlier tracheostomy.

Lung expansion modalities in the postoperative period may serve as a strategy to reduce postoperative pulmonary complications. These modalities range from simple and effort-dependent,

such as deep breathing exercises and incentive spirometry, to complex, expensive, and effort-independent, such as CPAP. There is evidence from a randomized controlled trial among patients undergoing thoracoabdominal aneurysm repair to support use of nasal CPAP immediately after extubation to reduce pulmonary complications.[102-104] However, a recent Cochrane review did not find the current evidence to be sufficient to confirm the benefits or harms of CPAP during the postoperative period following major abdominal surgery.[105] The evidence currently does not support one type of modality over another, and any lung expansion intervention may be better than no intervention.[78] However, a recent Cochrane review even calls in to question the effectiveness of incentive spirometry.[106] Given the expense of CPAP, as well as a small risk of barotrauma, this should not be considered a routine intervention and is best employed in patients unable to cooperate with effort-dependent lung expansion strategies. Inspiratory effort can be augmented through adequate pain control and careful attention to incision location, patient position, immobility, and location of chest tubes or binders that impede full chest wall excursion.

Malnutrition is considered a risk factor for postoperative pulmonary complications including pneumonia, but the data generally do not support total parenteral nutrition (TPN) or total enteral hyperalimentation over no hyperalimentation.[78] Patients should resume oral intake after surgery as soon as feasible; intestinal villi atrophy quickly without enteral intake and this may increase risk for bacterial translocation and subsequent sepsis. Swallow function should be assessed after extubation by bedside assessment to limit risk of aspiration. In cases of prolonged intubation or history of swallowing difficulty, the expertise of speech-language pathologists should be sought. Conversely, overfeeding should be avoided as this produces excess carbon dioxide, which may exceed the patient's capacity for removal through exhalation. Electrolyte abnormalities should be aggressively sought and corrected as these may contribute to a patient's failure to wean from mechanical ventilation. In particular, hypophosphatemia may limit the patient's energy (adenosine triphosphate) available for muscle contractility and may directly impair diaphragmatic function.

CLINICAL MANIFESTATIONS

Atelectasis

Atelectasis refers to collapse or closure of alveoli and commonly affects dependent portions of the lung. General anesthesia causes loss of the normal coordinated activity of respiratory muscles. These changes cause alterations in the shape and motion of the chest wall, which result in reduced lung volumes, abnormalities in regional gas exchange, and atelectasis.[107] Atelectasis is present in up to 90% of anesthetized patients, independent of the type of anesthesia used or patient demographics.[108-112] A goal-directed approach to perioperative mechanical ventilation, utilizing low tidal volume, low plateau pressures, and PEEP, may help mitigate pulmonary complications associated with atelectasis.[107]

Bronchospasm

Bronchospasm is the result of increased tone in the bronchial smooth muscles; subsequent narrowing of the bronchi may cause severe and life-threatening hypoxemia. Although intraoperative acute bronchospasm is rare, this complication may occur in susceptible patients such as those with asthma.[33] Bronchospasm may be provoked by mechanical manipulation of the airway such as laryngoscopy, intubation, extubation, or airway suctioning. Perioperative medications may also cause bronchospasm through release of histamine, muscarinic activity, or allergic reactions. Acute management of bronchospasm may include administration of beta-2 selective agonist by nebulizer, intravenous steroids, and/or intravenous epinephrine.

Pneumonia

Pneumonia is an acute infection of pulmonary parenchyma. Among hospital-acquired infections, pneumonia is the leading cause of death.[84,85,113] Guidelines from the American Thoracic Society and Infectious Diseases Society of America categorize pneumonia as hospital-acquired pneumonia (HAP), VAP, and healthcare-associated pneumonia (HCAP).[114] Community-acquired pneumonia (CAP) should be distinguished from these other categories of pneumonia since the causative pathogens and empiric treatment will differ. HAP is defined as a pneumonia occurring greater than 48 hours after hospital admission. VAP is a specific type of HAP that develops after greater than 48 hours following endotracheal intubation. HCAP is defined as a pneumonia occurring in a patient who meets 1 or more of the following criteria: hospitalization for at least 2 days in an acute care facility within 90 days of the infection, resident of a nursing home or long-term care facility at time of infection, patient who has received hemodialysis within 30 days, patient who has received any intravenous treatment or wound care within 30 days of infection, and any patient who is a family member of a known patient with a multidrug-resistant pathogen.

The etiology of VAP is related to (1) bacterial colonization of the aerodigestive tract or (2) aspiration of contaminated secretions of the lower airway.[1] The leading pathogen identified in cases of VAP is *Staphylococcus aureus*.[115-117] Other common organisms include *Pseudomonas aeruginosa*, *Enterobacter* species, *Acinetobacter baumanii*, and *Klebsiella pneumoniae*. Of considerable concern, many multi-drug-resistant organisms have been isolated in cases of VAP.[118] Methicillin resistance has been identified in as many as 54% to 82% of *S. aureus* isolates in cases of VAP.[118,119] Causative pathogens may vary among different institutions, and clinicians should be aware of specific pathogens and sensitivities within their institution and especially their ICUs. The highest rates of VAP are found in surgical ICUs, especially in burn and trauma ICUs.[1,118]

Diagnostic strategies and associated controversies regarding HAP and VAP are beyond the intended scope of this chapter. However, it is important to recognize that these infections are difficult to diagnose because the clinical findings are nonspecific.[1,120] There is ongoing debate about whether an aggressive

TABLE 43.3 Clinical Pulmonary Infection Score for Ventilator-Associated Pneumonia

	0 Points	1 Point	2 Points
Temperature (°C)	36.5-38.4	38.5-38.9	≤36.0 or ≥39
Peripheral WBC	4000-11,000	<4000 or >11,000	<4000 or >11,000 and >50% bands
Tracheal secretions	None	Nonpurulent	Purulent
Pulmonary radiography	No infiltrate	Diffuse/patchy infiltrates	Localized infiltrate
Culture of ET suction	No growth	Heavy growth	Heavy growth and positive gram stain
Oxygenation (PaO_2/FiO_2)	>240 or ARDS		≤240 and no ARDS

CPIS Score >6 is consistent with ventilator-associated pneumonia.
ARDS, Acute respiratory distress syndrome; *°C*, degrees Celsius; *ET*, endotracheal tube; *FiO_2*, fraction of inspired oxygen; *PaO_2*, partial pressure of oxygen in arterial blood; *WBC*, white blood cell count in cells/cubic milliliter of blood.
Modified from Pugin J, Auckenthaler R, Mili N, Janssens J, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis*. 1991;143:1121–1129.

strategy employing bronchoalveolar lavage (BAL) should be utilized in addition to clinical criteria for diagnosis and treatment.[121-125] Although there does not appear to be a mortality benefit with use of BAL to diagnosis pneumonia, this technique may help with prescription and deescalation of antibiotic treatment. The Centers for Disease Control and Prevention (CDC) define VAP using a combination of radiologic, clinical, and laboratory criteria.[126] In common practice, the Clinical Pulmonary Infection Score (CPIS) has emerged as a useful diagnostic tool for VAP.[127,128] Points are assigned based on temperature, white blood cell count, tracheal secretion character, radiograph findings, culture data, and oxygenation (Table 43.3). Patients with a CPIS score greater than 6 are likely to have VAP.

Successful treatment of HAP and VAP requires initiation of early and appropriate empiric broad-spectrum antibiotics to cover all potential causative pathogens. The initial choice of empiric antibiotic therapy should be based on national guidelines while also considering institution and ICU-specific antibiograms. Guidelines recommend that patients with no risk factors for multi-drug resistant organisms may be treated empirically with second- or third-generation cephalosporins, extended-spectrum fluoroquinolones, aminopenicillins, or narrow-spectrum carbapenems.[114] Patients with risk factors for multi-drug-resistant organisms should be treated with initial combination therapy to cover both gram-negative infections and gram-positive infections. Coverage of *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA) is especially important. Linezolid or vancomycin should be added when MRSA is suspected. Antibiotic therapy should be tailored to specific pathogens and sensitivities when culture data become available. Duration of therapy should generally be 8 days.[129]

Acute Respiratory Failure

Acute respiratory failure may result from failure to protect the airway, failure to oxygenate, and/or failure to ventilate. In some cases, acute respiratory failure will result from a combination of these abnormalities. Loss of airway protection may result from a number of circumstances including traumatic brain injury, neurologic impairment, absent cough and/or gag reflex, laryngeal edema, or residual effects of anesthesia and/or neuromuscular blockade.

Hypoxemic respiratory failure may be identified by a low partial pressure of oxygen in arterial blood (i.e., PaO_2 of less than 60 mm Hg).[1] The etiology of hypoxemic respiratory failure is attributed to either diffusion defects or ventilation-perfusion mismatch at the interface between the pulmonary capillary and the alveolus. Fluid filling of alveoli, as in the case of pulmonary edema, impairs diffusion of oxygen. Causes of pulmonary edema may include increased hydrostatic pressure from left cardiac ventricular failure, decreased plasma oncotic pressure from liver failure, or increased capillary permeability commonly seen with burns or sepsis. Alveolar collapse affects gas exchange by decreasing the functional residual capacity of the lung and creating ventilation-perfusion mismatch. Lung volume loss decreases lung compliance and makes ventilation more difficult. In this setting, PEEP is commonly used to "recruit" alveoli, increase the size of the functional lung, and improve both compliance and oxygenation. Increasing the fraction of inspired oxygen (FIO_2) through administration of oxygen-enriched air (by high-flow nasal cannula, face mask, intubation and mechanical ventilation, etc.) is also an important strategy to improve oxygenation in the acute setting.

Hypercapnic respiratory failure may be identified by a high partial pressure of carbon dioxide in arterial blood (i.e., $PaCO_2$ greater than 50 mm Hg).[1] Hypercapnic respiratory failure results from central loss of ventilation (sedation, stroke, etc.), impairment of the diaphragm/respiratory muscles (trauma, neurologic changes, etc.), or changes in chest wall mechanics (pneumothorax, effusion, etc.). The approach to this type of respiratory failure involves improvement of minute ventilation through increased respiratory rate and/or tidal volume. Other strategies, such as chest tube placement or thoracentesis, may be directed at the underlying pathology.

A systematic approach should be utilized to recognize the etiology of acute respiratory failure. For most postoperative patients with acute respiratory failure, consideration should be made for intubation and mechanical ventilation. A trial of

noninvasive ventilation strategies may be appropriate for some patients with reversible causes of respiratory failure. All patients with acute respiratory failure should be treated in an ICU setting.

Acute Respiratory Distress Syndrome

ARDS was originally defined in 1994 as a diffuse inflammatory process involving both lungs and arising in the setting of illness with a severe systemic inflammatory response.[130] The original definition stated that the onset of ARDS must be acute, the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2:FIO_2 or P:F ratio) must be less than 200, chest radiograph must demonstrate new bilateral infiltrates (with no clinical suspicion of pneumonia), and left atrial pressure must be normal (with no clinical suspicion of cardiac failure). In cases of suspected left atrial pressure elevation, a pulmonary catheter wedge pressure less than 18 mm Hg was considered consistent with ARDS when the other criteria were also met. This definition was subsequently revised after a 2011 consensus conference reevaluated the reliability and validity of the definition of ARDS.[131] The revised definition, commonly known as the Berlin definition, introduced escalating stages of ARDS defined by mild, moderate, or severe oxygenation (Table 43.4). The escalating stages of ARDS, when empirically evaluated, were associated with incremental increases in mortality from 27% mortality for mild ARDS, 32% mortality for moderate ARDS, and 45% mortality for severe ARDS.[131]

TABLE 43.4 The Berlin Definition of Acute Respiratory Distress Syndrome

Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Pulmonary radiography	Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload
Oxygenation	Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Mild ARDS	200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O
Moderate ARDS	100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O
Severe ARDS	PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O
Mortality	
Mild ARDS	27% (CI 24%-30%)
Moderate ARDS	32% (CI 29%-34%)
Severe ARDS	45% (CI 42%-48%)

ARDS, Acute respiratory distress syndrome; *CI*, 95% confidence interval; *CPAP*, continuous positive airway pressure; *FiO_2*, fraction of inspired oxygen; *PaO_2*, partial pressure of oxygen in arterial blood; *PEEP*, positive end-expiratory pressure.
Modified from ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526–2533.

The global epidemiology of ARDS was recently reported in a large prospective cohort study of patients undergoing invasive or noninvasive ventilation in 459 ICUs from 50 countries across five continents.[132] This study, known as LUNG SAFE, enrolled over 29,000 patients in participating ICUs and determined that 10.4% of ICU admissions met criteria for ARDS and 23.4% of patients requiring mechanical ventilation met criteria for ARDS. Not only was ARDS very common, it was also underrecognized: clinicians only recognized 51.3% and 78.5% of mild and severe ARDS cases, respectively. Finally, this study reported high hospital mortality, ranging from 34.9% for mild, 40.3% for moderate, and 46.1% for severe cases of ARDS.

Conditions that may predispose to ARDS include sepsis, pneumonia, pulmonary contusion, cardiopulmonary bypass, pancreatitis, and other diseases associated with a systemic inflammatory response. The pathogenesis behind ARDS is marked by dysregulated inflammation, inappropriate accumulation and activity of leukocytes and platelets, uncontrolled activation of coagulation pathways, and altered permeability of the alveolar endothelial and epithelial barriers.[133] ARDS is typically progressive in distinct stages with different clinicopathologic and radiographic stigmata at each stage. The acute or exudative phase is manifested by the rapid onset of respiratory failure and arterial hypoxemia refractory to supplemental oxygen. Computed tomography shows alveolar filling, consolidation, and atelectasis predominantly in the dependent lung zones; other lung areas may be relatively spared. Although the disease may resolve in some patients after the acute phase, it progresses in other patients to fibrosing alveolitis with persistent hypoxemia, increased alveolar dead space, and further compromised pulmonary compliance.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is the onset of respiratory distress after transfusion of one or more units of blood.[134] TRALI is recognized as a leading cause of transfusion-related mortality.[135] TRALI should be suspected in patients with acute onset of respiratory failure within 6 hours of blood transfusion, bilateral infiltrates on chest radiography, PaO_2:FIO_2 less than 300, no evidence of pulmonary edema, and no other risk factors for lung injury.[136] TRALI is not easily distinguished from other causes of acute lung injury and ARDS, and clinical management does not differ. However, the time course of TRALI is usually shorter than ARDS, and resolution is frequently observed with appropriate supportive care. Mortality from TRALI is quite low (5%-10%) compared to ARDS, and long-term prognosis is excellent in those surviving the initial pulmonary insult.[135,137]

MANAGEMENT STRATEGIES

Perioperative pulmonary complications may be managed with a number of different noninvasive and invasive strategies. For those patients requiring intubation and mechanical ventilation,

a number of adjuncts are available to assist with recovery and optimization of respiratory function.

High-Flow Nasal Oxygen

High-flow nasal cannula oxygen therapy has emerged as an effective modality for management of respiratory insufficiency in the perioperative setting. The nasal prong device is capable of delivering up to 60 L/min of adequately heated and humidified oxygen with physiologic benefits including reduced anatomic dead space and PEEP.[138] A randomized trial recently reported statistically significant differences in post-extubation respiratory failure rates and reintubation rates among patients with low risk for reintubation who were randomized to either 24 hours of high-flow nasal oxygen or conventional oxygen therapy following extubation.[139] Only 4.9% of patients who received high-flow nasal oxygen required reintubation within 72 hours compared to 12.2% of patients who received conventional oxygen therapy ($P = .004$). Post-extubation respiratory failure occurred in 14.4% of patients managed with conventional oxygen therapy versus 8.3% of patients managed with high-flow nasal oxygen ($P = .03$). High-flow nasal therapy is generally well tolerated by patients, because it is considered more comfortable than standard high-flow oxygen masks or noninvasive ventilation.[140] Furthermore, since the patient can talk and eat with the nasal therapy in place, patients often utilize the therapy more consistently.

Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation (NPPV) refers to delivery of CPAP or bilevel positive airway pressure either by facemask or nasal cannula. These modalities utilize a combination of pressure support and PEEP and are used commonly in patients with reversible acute respiratory failure to avoid endotracheal intubation.[103,104,141,142] Through the application of extrinsic PEEP, NPPV counterbalances auto-PEEP in COPD and recruits flooded alveoli in pulmonary edema. Ultimately, this therapy serves to increase functional residual capacity, improve lung compliance, and optimize gas exchange.[143] NPPV is considered the best first approach for patients with COPD exacerbations and brings about rapid symptomatic and physiologic improvement as well as reduced rates of intubation and mortality.[144] For patients with asthma, data are inconclusive about the role of NPPV.[144] While a trial of NPPV may be warranted for asthmatic patients, close surveillance is critical, since these patients may deteriorate rapidly and require mechanical ventilation. NPPV may be of use in other patient populations including those with airway edema after extubation or in patients with OSA.[104,142] NPPV is associated with some complications including nasal bridge ulceration and gastric distention. Major complications, such as aspiration, are infrequent. A recent Cochrane review concluded that both CPAP and bilevel NPPV are effective and safe treatments for respiratory failure.[145] A randomized clinical trial has demonstrated that use of NPPV compared with standard oxygen therapy reduces the risk of reintubation among patients with hypoxemic respiratory failure after abdominal surgery.[146]

Mechanical Ventilation

Intubation and mechanical ventilation is generally required in most cases of ARDS and in cases of respiratory failure where noninvasive strategies have failed. Although mechanical ventilation is the cornerstone of respiratory failure management, this modality may also exacerbate lung injury through barotrauma such as pneumothorax or mediastinal emphysema. Ventilation strategies for ARDS protect the lungs by limiting barotrauma-associated injury.

Lung-protective mechanical ventilation utilizes low tidal volumes (6 mL/kg of predicted body weight), permissive hypercapnia, elevated PEEP, and use of pressure-limited ventilator modes.[147] This strategy recognizes that dependent, atelectatic portions of the lung do not open at normal physiologic tidal volumes. The remaining portion of the lung must accommodate the entire tidal volume, leading to elevated peak inspiratory and plateau pressures. Some alveoli may subsequently become overdistended, leading to increased vascular permeability, loss of surfactant, cytokine production, and further local and systemic injury. Through use of low tidal volumes and limited plateau pressures (less than 30 cm H_2O), further injury is limited or avoided. The seminal multicenter randomized trial by the ARDS Network compared traditional ventilation tidal volumes (12 mL/kg) with lower tidal volumes (6 mL/kg) and found that use of lower tidal volumes in ARDS resulted in fewer ventilator-dependent days and decreased mortality (39.8% with conventional versus 31.0% with protective lung ventilation, $P = .007$).[148] This strategy is used with the understanding that traditional goals of gas exchange must be modified with use of low tidal volumes, and permissive hypercapnia is often necessary.

Other advanced or nontraditional ventilatory modes have been proposed for management of ARDS, including high-frequency oscillatory ventilation (HFOV). However, the OSCAR trial found no mortality benefit for use of HFOV in patients with ARDS.[149] The OSCILLATE trial reported lack of efficacy of HFOV and possible harm to patients.[150] While there may be a role for HFOV in select rescue situations, this should not be considered a routine management strategy.

Adjuncts to Mechanical Ventilation

A number of adjunct strategies have been used in concert with lung-protective mechanical ventilation for the management of patients with acute respiratory failure and ARDS. Alveolar recruitment through use of higher PEEP has been suggested as a strategy to increase functional residual capacity, prevent alveolar collapse, and improve oxygenation. However, PEEP is also associated with circulatory compromise (from impaired venous return) and lung injury from overdistention. The ARDS Network group compared high versus low PEEP among patients with low tidal volumes and low plateau pressures and did not find a mortality benefit with use of high PEEP.[151]

Fluid management has also been an area of interest, since ARDS is marked by altered permeability at the level of the

alveolar endothelial and epithelial barriers with subsequent alveolar flooding. There has been some evidence that fluid restriction and use of furosemide may decrease duration of mechanical ventilation, but there is no mortality benefit.[152] High-volume hemofiltration may confer some benefits, but more data are needed.[153] Currently, the evidence does not support the use of any specific fluid strategy or invasive monitoring of fluid status in patients with ARDS.

Inhaled nitric oxide (iNO) has been used in some cases of severe, refractory hypoxemia, but this should not be considered a routine strategy and can only provide modest improvements in oxygenation over a short period. A meta-analysis has suggested that use of iNO confers no mortality benefit and may cause harm.[154]

Patients with ARDS and a PaO_2:FIO_2 less than 150 mm Hg may benefit from early treatment with a continuous infusion of cisatracurium for 48 hours. This treatment has been shown to reduce the rate of mortality at 90 days, increase the number of ventilator-free days, and decrease the number of ICU days.[155] The exact mechanism by which neuromuscular blockade improves outcomes in ARDS is unknown, but it is likely related to improvement in lung mechanics, uniform and synchronous lung recruitment, and improved lung compliance.

Prone positioning has been an area of considerable interest in the management of patients with ARDS. A number of randomized trials have evaluated the outcomes associated with this treatment strategy.[156-158] These studies have identified improvement in oxygenation with prone positioning, but the data are conflicting concerning any mortality benefit. Furthermore, there have been some safety concerns identified with use of prone positioning including endotracheal tube obstruction and pressure sores.[157] This strategy may best be employed when the critical care team is appropriately trained in this technique and has experience ensuring patient safety during prone positioning.

Veno-venous extracorporeal membrane oxygenation (ECMO) may be of benefit as salvage therapy in select patients with ARDS who continue to have profound gas-exchange abnormalities.[159-161] Generally, patients may be considered for this therapy when mechanical ventilation and the other available adjuncts are unable to maintain adequate oxygenation and removal of carbon dioxide to support life. The conventional ventilatory support versus ECMO for severe adult respiratory failure (CESAR) trial performed in the United Kingdom provided encouraging outcomes regarding the efficacy and economic assessment of this strategy.[162] However, this trial was criticized for methodological limitations: patients treated with ECMO were treated at a single center and those receiving conventional support were treated at a number of different centers where not all patients received best practice lung-protective ventilation strategies. The EOLIA trial is an ongoing effort comparing the efficacy of veno-venous ECMO in ARDS with tight parameters concerning the mechanical ventilation strategies employed in the control group.[163] ECMO remains an important rescue strategy in ARDS for select patients, but further evidence is needed to understand the benefits and risks of this therapy in larger populations.

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44 CHAPTER

Systemic Complications: Renal

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A basic comprehension of renal anatomy and physiology is necessary to understand the complex changes in renal function that can occur during treatment of vascular disorders. This chapter will provide a brief summary, and more detail can easily be obtained from several standard texts.[1]

RENAL ANATOMY

Specific kidney components include the nephrons, the collecting ducts, and the microvasculature. The human kidney contains approximately 1 million nephrons, which are established before birth. Injured or lost nephrons cannot be replaced, so nephron preservation is essential to maintain normal renal function. There are two basic types of nephrons: those with short loops of Henle and those with long loops. The long loops extend to the inner medulla, and the short loops to either the outer medulla or the cortex. The collecting ducts descend within the medullary rays of the cortex, entering the inner medulla to form papillary ducts (Fig. 44.1A).

The renal artery divides into the interlobar arteries, which enter the cortex. The interlobar arteries divide into the arcuate arteries at the junction of the cortex and the medulla. These vessels then divide into the cortical radial arteries, which ascend through the cortex. No arteries penetrate the medulla. The cortical radial arteries give rise to the afferent arterioles, which supply the glomeruli. The glomeruli are drained by efferent arterioles that can be cortical or juxtamedullary. The cortical efferent arterioles are derived from the superficial and midcortical glomeruli and supply the capillary plexus of the cortex. The juxtamedullary efferent arterioles supply the renal medulla. At the level of the outer stripe of the medulla, the juxtamedullary efferent arterioles divide into the descending vasa recta, and from these vessels, leave at different levels to supply the adjacent medullary plexus. Ascending vasa recta drain the renal medulla and ascend as unbranched vessels. They then ascend and traverse the outer medulla and form the capillary plexus of the outer stripe. The ascending vasa recta then empty into the arcuate veins.

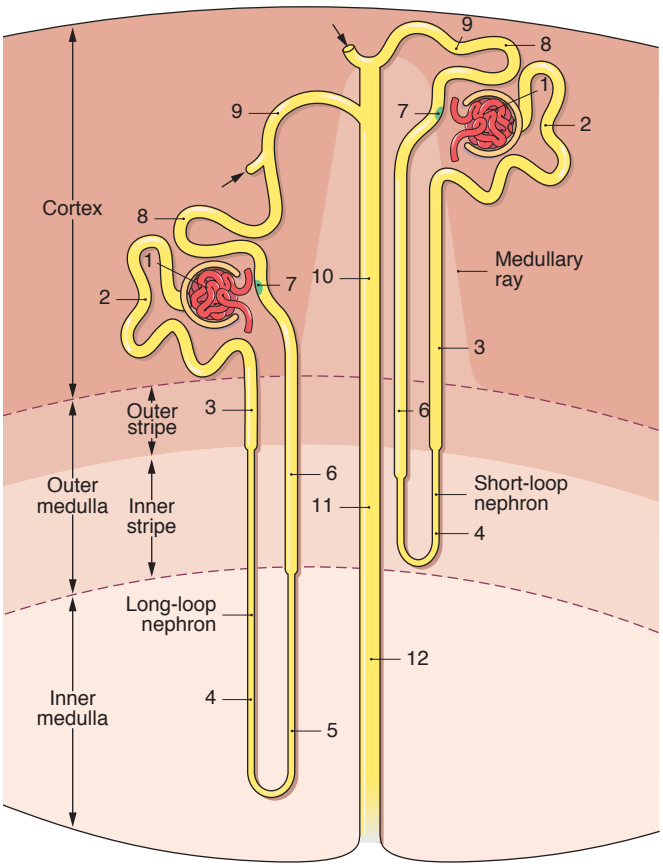
The microvasculature provides a unique countercurrent exchange between the blood entering and the blood leaving the medulla. The unique vascular anatomy also separates blood flow in the inner stripe from the inner medulla. The descending vasa recta supplying the inner medulla are not exposed to the tubules of the inner or outer stripe (outer medulla). Blood flow in the ascending vasa recta from the inner medulla and inner stripe perfuses the outer stripe. The physiologic significance has been postulated to be a mechanism to prevent loss of solute from the medulla. Venous drainage accompanies the arteries. Arcuate veins form anastomosing arches at the corticomedullary border and are fed by veins from the cortex and medulla. Arcuate

Abstract

A basic comprehension of renal anatomy and physiology to understand the complex changes in renal function that can occur during treatment of vascular disorders. Understanding the pathophysiology of renal injury can help the clinician identify those factors that predispose the patient to renal injury following open vascular surgery and endovascular procedures and thus help decrease rates of morbidity and mortality.

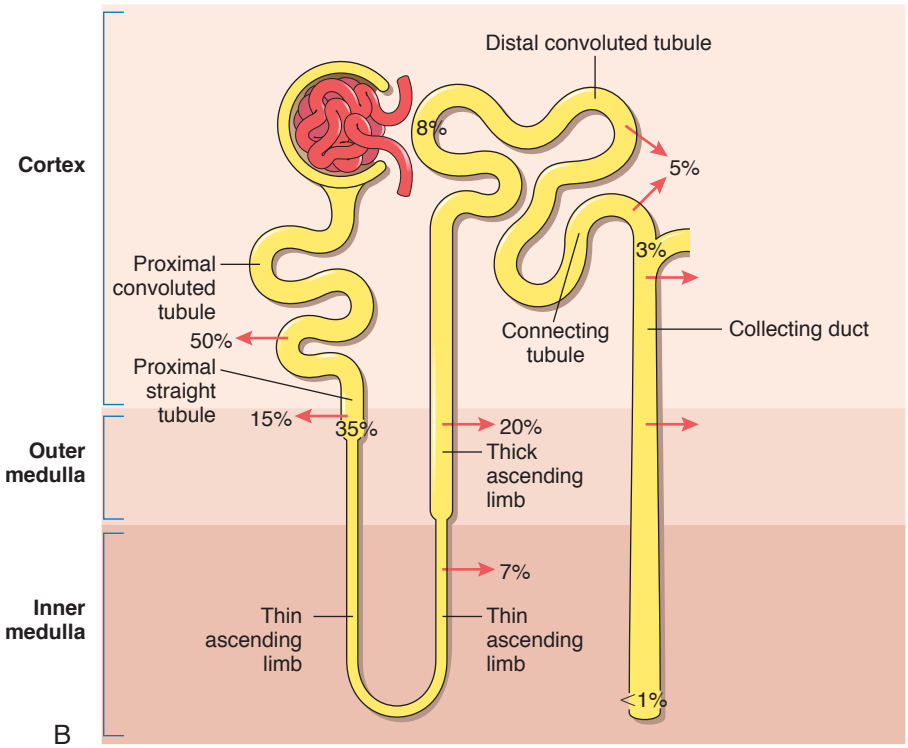
Keywords

Acute kidney injury
Postoperative renal complications
Contrast-induced nephropathy
Renal physiology
Endovascular associated renal injury



1. Renal corpuscle
2. Proximal convoluted tubule
3. Proximal straight tubule
4. Descending thin limb
5. Ascending thin limb
6. Distal straight tubule (thick ascending limb)
7. Macula densa
8. Distal convoluted tubule
9. Connecting tubule
10. Cortical collecting duct
11. Outer medullary collecting duct
12. Inner medullary collecting duct

A



B

Figure 44.1 (A) Nephrons and the collecting duct system. Short- and long-looped nephrons are shown together with a collecting duct (not drawn to scale). *Arrows* denote the confluence of further nephrons. (Adapted from Kriz W, et al. Renal anatomy. In: Floege J, Johnson R, Freehally J, eds. *Comprehensive Clinical Nephrology*. 4th ed. Philadelphia: Mosby Elsevier; 2010:4.) (B) Renal sodium handling by the nephron. Figures outside the nephron represent the approximate percentage of the filtered load reabsorbed in each region. Figures within the nephron represent the percentages remaining. (Adapted from Shirley DG, et al. Renal physiology. In: Floege J, Johnson R, Freehally J, eds. *Comprehensive Clinical Nephrology*. 4th ed. Philadelphia: Mosby Elsevier; 2010:21.)

veins join to form the interlobar veins, which are parallel to the interlobar arteries (see Fig. 44.1A).[2]

RENAL FUNCTION

The kidney is the major site responsible for maintenance of intravascular volume and composition under normal conditions. Toward this end, the kidney provides three basic physiologic processes: glomerular filtration, selective tubular secretion, and selective tubular reabsorption.[3,4] The kidney receives a fourth of the cardiac output, and based on a cardiac output of 5 L/min, the kidney receives approximately 900 L/day of plasma flow. The glomeruli filter 20% of renal plasma flow and must reabsorb 99% of the 180 L of plasma filtered per day to provide a urine output of 1.8 L/day (for a 70-kg man). This ultrafiltrate has the same electrolyte and solute concentration as plasma, and is almost totally reabsorbed.[5] The solute content and volume of urine that enters the renal pelvis are very different from the solute content and volume of the glomerular filtrate. The filtrate flows through the different portions of the tubule, where the solute content and volume are altered by tubular reabsorption and tubular secretion. When the direction of solute movement is from the tubular lumen to the peritubular capillary plasma, the process is termed *tubular reabsorption*. Movement in the opposite direction is termed *tubular secretion*. For any particular substance, there is a unique combination of filtration, reabsorption, and secretion. The combination of filtration, secretion, and reabsorption is under physiologic control, which can alter the relative rates of each process. For example, after drinking a large quantity of water, the excess will be excreted within 1 to 2 hours because of an increase in the glomerular filtration rate (GFR) and a decreased water tubular reabsorption.

The descending loop of Henle is permeable to water but only minimally permeable to sodium and chloride, whereas the ascending loop is not permeable to water but has active transport mechanisms that readily transport the chloride ion with concomitant passive transport of sodium. This is the underlying basis for the countercurrent mechanisms that produce the medullary osmotic gradient that is important in the regulation of urine osmolarity. Reabsorption of sodium from the distal tubule and from the proximal collecting ducts is controlled by aldosterone secretion. The mechanisms responsible for sodium reabsorption by the kidney are remarkable in that only 50 to 200 mEq of sodium is excreted per day of the 25,000 mEq of sodium filtered daily by the kidney (see Fig. 44.1B). Potassium is reabsorbed in the proximal convoluted tubule and the thick ascending limb of Henle. Ten percent of the filtered load reaches the early distal tubule. Potassium secretion by connecting cells in the late distal tubule and/or cortical collecting system is variable and represents the major determinant of potassium excretion.[3-6]

Neuroendocrine Modulators of Renal Function

Intravascular volume is regulated primarily by a series of baroreceptors located in the arterial tree and the atria. Because these receptors not only sense changes in pressure or volume (atrial receptors) but also monitor the rates of change during the cardiac cycle, they govern the effective circulating volume. Factors that decrease cardiac performance and intravascular volume are perceived by these receptors, which then alter renal function to retain salt and water and thereby increase the effective circulating volume. Similarly, when the concentration of circulating plasma proteins is reduced, there is a net diffusion of intravascular water into the extravascular space secondary to the decreased intravascular oncotic pressure. This net decrease in circulating volume is sensed by these same receptors, and neuroendocrine regulators of urinary output inhibit the excretion of water to correct the volume deficiency. When the baroreceptors perceive a reduction in circulating volume, their afferent signals are reduced, which decreases their tonic inhibition over the neuroendocrine system. This reduced inhibition leads to increased secretion of vasopressin, 13-endorphins, growth hormone, adrenocorticotropic hormone through the central nervous system, and an increased release of epinephrine from the adrenal medulla.

At the local renal level, a reduction in arterial pressure or central venous pressure (or both) results in an increase in renal sympathetic nerve stimulation that reduces urinary sodium excretion via three mechanisms: (1) constriction of afferent and efferent arterioles, which reduces renal blood flow and GFR; (2) reabsorption of sodium in the proximal tubule and the thick ascending loop of Henle; and (3) stimulation of renin secretion. At the level of the nephron, baroreceptors within the macula densa cells of the juxtaglomerular apparatus perceive a decrease in intravascular pressure or plasma ion concentration and stimulate juxtaglomerular cells to release renin. Renin is an enzyme that is stored in the specialized macula densa cells that constitute part of the juxtaglomerular apparatus. It is released in response to an increase in sympathetic nerve activity, reduced stretch of the afferent arteriole, and decreased transport of NaCl to the macula densa. Renin catalyzes the release of angiotensin I from angiotensinogen. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II has several important actions. First, it induces arteriolar constriction of the afferent and efferent arterioles and thereby causes an increase in blood pressure while decreasing renal blood flow; second, it stimulates renal sodium reabsorption in the proximal tubule; and third, it induces secretion of aldosterone from the zona glomerulosa of the adrenal cortex. Aldosterone secretion results in sodium reabsorption in the distal tubule and collecting duct.[1-6]

Paracrine and Endocrine Modulators of Renal Function

A number of endogenous and exogenous paracrine and endocrine substances influence renal function. An exhaustive list of these substances is beyond the scope of this chapter, but the major substances thought to be involved in normal and abnormal renal physiology are briefly presented. Eicosanoids are an important class of vasoactive metabolites of three different enzymes: cyclooxygenase (COX), lipoxygenase, and cytochrome P-450. COX is present as both constitutive (COX-1) and inducible forms (COX-2). Conversion of arachidonic acid to

prostaglandins and thromboxane occurs via both enzymes. The major renal eicosanoids are prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2). These potent vasodilators buffer renal vasoconstrictors such as thromboxane A2, angiotensin II, and norepinephrine. Decreased synthesis of the renal vasodilators PGE2 and PGI2 has been associated with renal vasoconstriction and has been demonstrated after a number of injuries, including renal ischemia, renal ischemia-reperfusion, and intestinal ischemia-reperfusion.[7-15] PGE2 has been shown to inhibit sodium reabsorption from the thick ascending limb of Henle and thus contributes to protecting the renal medulla during hypoxia. COX-2 expression has been found in the macula densa and is thought to contribute to the release of renin via PGE2. This could be one of the mechanisms responsible for the low renin levels found in patients taking nonsteroidal antiinflammatory drugs (NSAIDs). The loss of COX-2 expression can also reduce medullary blood flow and cause apoptosis of medullary interstitial cells.

Nitric oxide (NO) is another potent endogenous renal vasodilator that has been shown to contribute to the maintenance of normal renal blood flow and function under normal physiologic conditions.[12-23] Zou and Cowley24 demonstrated that NO was synthesized in both the medulla and the cortex.[23] They concluded that NO might play a role in the control of vascular tone and tubular function in the kidney.[23] Loss of endogenous NO synthesis has been suggested to contribute to renal vasoconstriction after renal ischemia-reperfusion injury from either local or systemic causes.[12,13,16-24] Similar to the vasodilator prostaglandins, NO is present in the macula densa as the neuronal synthase form (nNOS). Downregulation of nNOS may contribute to arteriolar vasoconstriction by downregulating COX-2 (and subsequent PGE2 synthesis) through an adenosine or adenosine triphosphate (ATP) pathway. NO has also been shown to help mediate the increased natriuresis following an increase in renal interstitial hydrostatic pressure (caused by acute increases in blood pressure) without incurring a transforming growth factor (TGF)–mediated decrease in GFR.[25] Atrial natriuretic peptide is released from atrial myocytes after atrial stretch, secondary to increased blood volume. Atrial natriuretic peptide increases sodium excretion directly and by downregulating renin and aldosterone secretion.

Endothelins are a potent family of vasoconstrictor peptides. The kidney is a rich source of endothelins, which function as autocrine and paracrine substances. Endothelin-1 (ET-1) is synthesized in the afferent and efferent arterioles, where it induces vasoconstriction, and in mesangial cells, where it induces contraction. Upregulation of ET-1 synthesis induces a marked reduction in renal blood flow and GFR. ET-1 can inhibit sodium reabsorption in the medullary thick ascending limb, and this may be mediated by NO. Renal ischemia/reperfusion injury in rats demonstrated a potential benefit of bosentan, an endothelin antagonist.[2]

Purines are another complex class of autocrine substances that may be involved in renal physiology. Purinoreceptors are divided into P1 and P2 receptors. Purinogenic signaling is believed to be concentration dependent, with basal levels acting as a mediator of normal physiology and growth, and elevated concentrations of purines signaling adaptive pathways in response to inflammation of the kidney. P1 receptors are activated by adenosine. Higher concentrations of adenosine, such as in pathologic states, activate low affinity A3 receptors that mediate cell signaling via the inhibition of adenylate cyclase. P2 receptors are stimulated by nucleotides such as ATP and adenosine diphosphate (ADP). P2 receptors are subdivided into P2X (ligand-gated ion channels) and P2Y (metabotropic) receptors. P1 and P2X receptors are located in the afferent arteriole and contribute to vasoconstriction. P1, P2X, and P2Y receptors are located along the nephron. Specifically, the P2X7 receptor has been linked to downstream coupling to proinflammatory cascades, and this is in response to much higher levels of ATP and ADP, thought of as a "danger signal" for excessive local cellular damage. Endogenous adenosine enhances proximal tubular reabsorption, whereas luminal ADP inhibits it. In the collecting duct, basolateral ATP inhibits vasopressin-sensitive water reabsorption, and basolateral and luminal ATP inhibits sodium reabsorption. Uric acid (the end product of purine metabolism) may cause renal vasoconstriction, possibly by inhibiting release of NO and stimulation of renin.[26] Further studies will provide insight into the role of purines in renal physiology.[2]

ACUTE KIDNEY INJURY AFTER VASCULAR AND ENDOVASCULAR PROCEDURES

Acute kidney injury (AKI) after vascular and endovascular procedures can vary from mild natriuresis to fulminant acute tubular necrosis (ATN) and acute renal failure (ARF), requiring dialysis. Postoperative AKI can be classified as prerenal, renal, or postrenal (Fig. 44.2). Although the incidence of AKI complicating vascular and endovascular procedures has decreased with the development of appropriate perioperative fluid resuscitation, better surgical and endovascular techniques, and fewer nephrotoxic radiocontrast agents, the mortality associated with ARF remains high, ranging from 10% to 80% depending on the associated presence of multiorgan system failure.[27,28]

General Approach to Patients With Renal Dysfunction

Postoperative AKI is usually identified by oliguria or increases in serum creatinine. The evaluation of patients should include a thorough physical examination. Prerenal causes of AKI are most frequently encountered in the early postoperative period. Assessment of the patient's intravascular volume status and cardiac performance is required. A patient with signs of volume depletion requires replenishment of intravascular volume with physiologic saline (without potassium supplement until renal failure is ruled out). If examination reveals that diminished cardiac performance is responsible for the oliguria, judicious inotropic support is provided while indices of cardiac performance are measured.[29,30]

If correction of filling pressures or myocardial performance fails to improve urinary output, samples of urine and blood

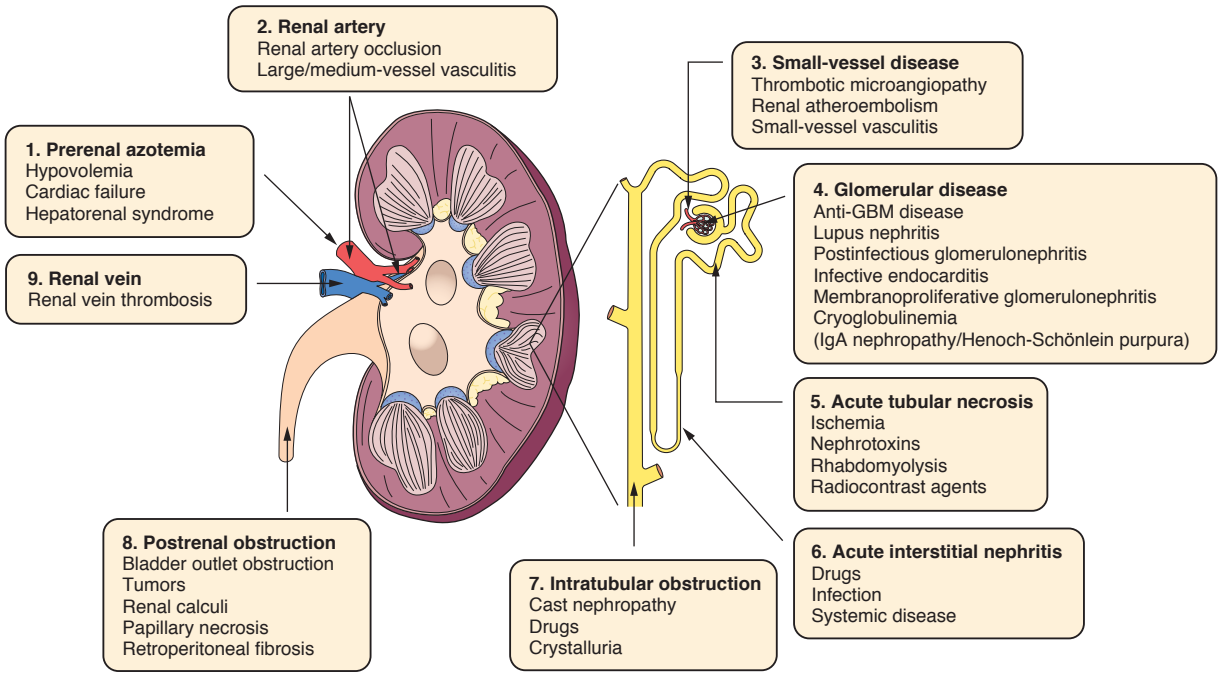


Figure 44.2 Causes of Acute Renal Failure. Acute renal failure is classified into prerenal, renal, and postrenal causes. *GBM*, Glomerular basement membrane; *IgA*, immunoglobulin A. (Adapted from Ashley J, et al. Pathophysiology and etiology of acute kidney injury. In: Floege J, Johnson R, Freehally J, eds. *Comprehensive Clinical Nephrology*. 4th ed. Philadelphia: Mosby Elsevier; 2010:798.)

are obtained, and diuretic therapy is considered. Serum electrolytes, blood counts, and urine studies (urinalysis, urine sodium, urea, creatinine, osmolality, estimation of the fractional excretion of sodium) allow evaluation of other possible sources of oliguria and renal failure, such as ATN or myoglobinuria.

Acute Kidney Injury: Causes—Prerenal

Prerenal causes are the most frequent source of AKI in the early postoperative period. Renal failure from a prerenal cause is usually the direct result of a contracted intravascular volume secondary to inadequate fluid replacement. Less commonly, it is secondary to a primary reduction in cardiac performance that triggers neurohormonal reflexes to enhance intravascular volume by increasing tubular reabsorption of sodium and water. In their pure forms, these two causes of reduced renal function are easily discernible. Hypovolemia is associated with flat neck veins, dry mucous membranes, and reduced pulmonary artery wedge pressure, whereas renal dysfunction secondary to poor cardiac performance is associated with distended neck veins, clinical fluid overload, and elevated pulmonary artery wedge pressure. Therapy for hypovolemic prerenal azotemia is to increase intravascular volume by administering balanced salt solution and red blood cells as needed. Therapy for renal dysfunction of cardiogenic origin is directed at improving myocardial performance by administering afterload-reducing and inotropic agents, and instituting diuretic therapy as needed to diminish the preload of the failing left ventricle.

Because an atherosclerotic patient who is undergoing major vascular and endovascular procedures frequently has associated coronary artery disease and impaired left ventricular function, distinction between these two causes of prerenal dysfunction (hypovolemic vs. cardiogenic) can be difficult. Preexisting heart disease may raise the baseline total body volume for an individual to higher central filling pressures, and apparently normal or low-normal cardiac filling pressures may reflect relative hypovolemia. In this clinical situation, one can maintain a constant infusion of afterload-reducing and inotropic agents (e.g., dobutamine) and cautiously administer small boluses of balanced salt solution while monitoring cardiac output and pulmonary artery wedge pressure. If no urinary response is noted when filling pressures begin to increase, diuretic therapy is added. Reliable estimates of cardiac function and filling pressures are needed before initiation of inotropic or diuretic therapy.[31,32]

Another important prerenal cause of acute and chronic renal insufficiency is renal artery stenosis. Also termed *ischemic nephropathy*, this diagnosis is made by exclusion of other causes. If other causes of prerenal dysfunction have been excluded, renal duplex sonography is used to determine whether renal artery occlusive disease is present. Hemodynamically significant renal artery stenosis or occlusion is characterized by a focal increase in peak systolic velocity (>1.8 m/sec), along with distal turbulent Doppler waveforms (i.e., stenosis) or absence of Doppler flow (i.e., occlusion; see Chapter 125). ATN is characterized by a marked decrease in diastolic velocity and an increased resistance index measured by spectral analysis of the renal artery. In the absence of acute or chronic renal parenchymal disease, diastolic velocity is increased as a result of a compensatory decrease in renovascular resistance. Correction of renal arterial stenosis or occlusion is contemplated, and the appropriate endovascular or operative intervention is instituted.[33]

Acute Kidney Injury Causes—Postrenal

Postrenal mechanisms represent the least frequent cause of postoperative oliguria leading to renal dysfunction. The pathophysiology involved in this process is obstructive, and it is usually at the level of the urethra or urinary catheter and less commonly at the level of the ureters. Hematuria or traumatic catheter insertion can predispose to clots and obstruction of indwelling urinary catheters. When rapid cessation of urine flow is detected, initial maneuvers should be directed toward catheter irrigation or replacement, which is usually successful in restoring urinary flow. Postrenal oliguria can also be caused by ureteral or renal pelvic obstruction, and these mechanisms should be investigated after exclusion of other causes of oliguria. Causes include iatrogenic injury or compression of the ureters associated with aortic surgery and stone disease. A preliminary diagnosis can be suggested on the basis of renal ultrasound or isotope renography, and can be confirmed with retrograde urography. Relief of obstruction may require the placement of ureteral stents or percutaneous nephrostomy.[29] Acute urinary retention from obstructive uropathy can rarely accompany removal of a urinary catheter. One important clinical situation occurs after urinary catheter removal in patients with epidural catheters placed for pain control and in patients with prostatic hypertrophy. Generally, one should allow 6 to 12 hours to elapse after epidural analgesia is discontinued before removal of urinary catheters. Prostatitis or traumatic urinary catheter insertion combined with general anesthesia can also precipitate acute urinary retention. If recognized early, both are easily treatable by catheter reinsertion.

Acute Kidney Injury Causes—Parenchymal

Parenchymal causes of AKI are diverse and pose the greatest risk for permanent renal failure. ATN describes all renal parenchymal causes of AKI. More specifically, the pathophysiologic mechanism of ATN involves a decrease in cellular ATP, which is associated with loss of the actin cytoskeleton; loss of the cytoskeleton causes a loss of renal tubular cell membrane polarity and subsequent loss of intercellular tight junctions. Shedding of the apical portion of tubular cells into the tubules can result in tubular obstruction and lead to a further reduction or cessation of glomerular filtration in the nephron. AKI is manifested clinically by an abrupt rise in serum creatinine, either with or without a change in urinary output (oliguria). Although ATN may be transient and self-limited, its causes related to vascular surgery include ischemic injury (shock, acute renal artery occlusion, multiorgan failure, and atheroembolic injury) and toxic injury (myoglobinuria, antibiotics, and contrast-related injury; Fig. 44.3).[29,30]

ISCHEMIC INJURY TO THE KIDNEY

Acute Ischemic Renal Injury

Postoperative acute ischemic renal injury is caused by either temporary periods of interruption of renal perfusion or periods of systemic hypoperfusion. The pathophysiology of acute ischemic injury is twofold. First, as a consequence of the magnitude and duration of ischemia, tubular cell swelling occurs after reperfusion. This swelling can cause tubular obstruction, leading to a further reduction or cessation of glomerular filtration in the nephron. Second, tubular cells either can lose their basement membrane attachment secondary to the interstitial edema that develops after reperfusion or can undergo cell death during ischemia and subsequently be sloughed into the tubule. The medullary thick ascending loop of Henle and the pars recta of the proximal tubule seem to be the tubular epithelium that are most sensitive to ischemia. After loss of the tubular cell, back leak of glomerular filtrate into the renal parenchyma occurs.[30-36] The risk for AKI after a vascular surgical intervention is greatest for aortic surgery.[37-47]

Acute renal artery occlusion (see Chapter 129) can be caused by emboli from a cardiac origin, by trauma, or by aortic or renal artery dissection. When related to a cardioembolic event, the diagnosis is often delayed, and ultimate recovery of renal function depends on the magnitude of the occlusion and the presence of preexisting collaterals to the kidneys. Back, flank, or abdominal pain; new onset of hypertension; hematuria; and elevated serum lactate dehydrogenase levels may provide a clue regarding the diagnosis and treatment.[48] Traumatic renal artery occlusion is suggested by the presence of hematuria and nonvisualization of the kidney on an intravenous pyelogram. Prompt angiography is necessary to confirm the process, although the success of revascularization largely depends on the duration of the ischemic period, which is frequently prolonged. Dissection of the renal artery can be due to catheter-related injury, or it can arise from preexisting disease (fibromuscular dysplasia). Treatment and the opportunity for functional recovery are based on the extent of the dissection, and in cases of complete occlusion of the renal artery, the time of ischemia.

Atheroembolism to the renal arteries has increasingly been recognized as a cause of AKI and can give rise to renal damage culminating in end-stage renal disease (ESRD). Catheter-based peripheral and coronary angiography and endoluminal interventions are well-recognized sources of renal atheroemboli. Up to 20% to 40% of patients with renal artery interventions have shown deterioration in GFR. It would seem logical to include the use of distal embolic protection during these procedures. This is supported by the study of Henry et al.,[49] which showed that 100% of the patients treated with renal artery angioplasty and stents with distal filter wire protection showed evidence of emboli on the filter. Cooper et al.[50] showed that, in addition to distal embolic protection, adjunct pharmacologic treatment (such as the platelet glycoprotein IIB/IIIa inhibitor, abciximab) may be required to minimize renal injury after endoluminal interventions. Atherosclerotic plaque from proximal diseased aortic segments can complicate suprarenal cross-clamping or manipulation of the aorta. Atheroembolism can also occur spontaneously from these proximal sources or from renal artery atherosclerotic plaque. The clinical diagnosis is suggested by deterioration of renal function in a patient who displays other extrarenal manifestations of atheroembolism (e.g., blue toe syndrome) and is highly suggested by the laboratory finding of eosinophilia (71%). The diagnosis is confirmed by renal biopsy, and treatment is supportive.[51-54]

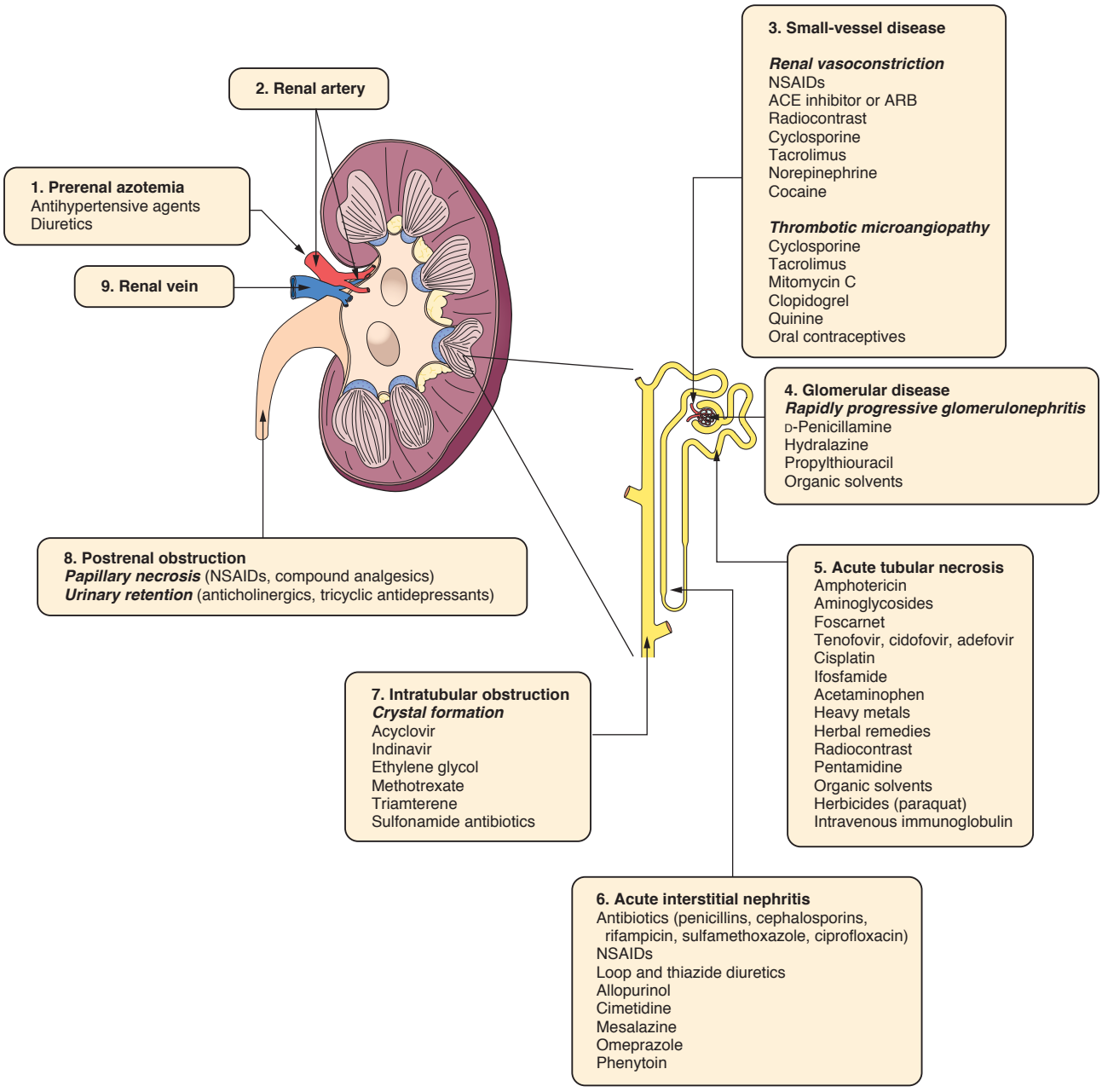


Figure 44.3 Nephrotoxic agents that lead to acute renal failure. *ACE*, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *NSAIDs*, nonsteroidal anti-inflammatory drugs. (Adapted from Ashley J, et al. Pathophysiology and etiology of acute kidney disease. In: Floege J, Johnson R, Freehally J, eds. *Comprehensive Clinical Nephrology*. 4th ed. Philadelphia: Mosby Elsevier; 2010:804.)

Vascular procedures complicated by sepsis, myocardial dysfunction, and reperfusion injury can result in transient or permanent renal dysfunction. In these instances, recovery of excretory renal function depends on the elimination of the septic focus and improvement in left ventricular performance to ensure adequate renal perfusion.

Chronic Ischemia and Ischemic Nephropathy

Chronic ischemic nephropathy describes reduced renal excretory function in conjunction with renovascular disease and is discussed in Chapter 125. Usually the renovascular disease is bilateral or involves a solitary kidney, and diminished renal artery perfusion has been implicated as the cause of elevated serum creatinine. This condition tends to be rapidly progressive and is thought to be responsible for up to 20% of these patients becoming dependent on dialysis, as well as a rapid rate of death during follow-up, with a median survival of only 27 months after the initiation of dialysis and a 5-year survival rate of just 12%.[55-59]

Toxic Injury and Angiography

Chemical injury to the kidney can result from many sources (see Fig. 44.3). Nephrotoxic agents should be identified and

used with caution, particularly in a vascular patient with compromised renal clearance. Aminoglycosides are some of the most common compounds responsible for such injury in the postoperative period; myoglobin and radiologic contrast media have also been implicated. Aminoglycosides appear to exert their renal toxicity at the tubular cell by causing mitochondrial damage, destruction of the cell membrane, activation of phospholipase, or alteration in lysosomes. Because of this relationship and the frequent history of reduced renal function in postoperative vascular surgery patients, it is important to identify risk factors that can contribute to nephrotoxicity before the administration of aminoglycosides. Such risk factors include preexisting renal insufficiency, advanced age, extracellular volume depletion, and concomitant use of other nephrotoxins. The routine use of aminoglycoside blood levels to predict or prevent nephrotoxicity is probably not warranted. Although alternative antibiotics with less nephrotoxicity have reduced the use of aminoglycosides, all pharmacologic agents should be administered with caution, and the dosage adjusted for renal clearance.[60-62]

Myoglobinuria is an important cause of renal failure in patients who undergo revascularization after prolonged periods of limb ischemia. Circulating as a breakdown product of muscle death, myoglobin is filtered freely by the glomerulus. Myoglobin exerts its toxicity through direct tubular cell injury and via precipitation and obstruction of the tubule. Hematuria after reperfusion of a profoundly ischemic extremity suggests pigment toxicity and should prompt urinalysis. Myoglobinuria is suggested when the urine is dipstick positive for blood but no red blood cells are present on urinalysis and can be confirmed by testing for urine myoglobin. When diagnosed, renal injury may be lessened by maximizing the urine flow rate through the infusion of intravenous crystalloid and diuretics (mannitol) and by alkalinizing the urine.[63]

Contrast-Induced Acute Kidney Injury Nephropathy

Administration of contrast media continues to be a frequent cause of hospital-acquired renal failure. Over the past few years, the increasing number of diagnostic and interventional procedures requiring contrast agents has paralleled the increasing incidence of CI-AKI. CI-AKI now accounts for more than 10% of cases of hospital-acquired renal failure and is the third leading cause of iatrogenic AKI in hospitalized patients. CI-AKI is associated with an increase in hospital mortality, length of stay, and cost.[64-73]

Conventional contrast agents have iodine incorporated into their structure to absorb x-ray photons, thereby achieving visualization of the vasculature. The nephrotoxicity of such iodinated contrast agents has been recognized for many years. The principal site of contrast-induced nephrotoxicity is the renal tubule from transient regional renal ischemia; the effects on glomerular function seem to be mild.[74] Nonionic contrast agents are now available and provide comparable absorption of x-ray photons, yet are significantly less charged than traditional agents. However, severe adverse renal events still continue to plague the use of nonionic contrast media.[71] Renal nephrotoxicity after exposure to ionic agents occurs most commonly in patients with preexisting renal insufficiency (relative risk of 3.3) alone or in combination with diabetes mellitus, especially diabetes type 1. Other risk factors, such as dehydration, volume of contrast agent used, and simultaneous exposure to other nephrotoxins, contribute to the likelihood of acute contrast-induced nephrotoxicity.[70] Additional risk factors include multiple myeloma and heavy proteinuria. Overall, the incidence of acute renal dysfunction after contrast-enhanced angiography varies from 0% to 10%, although these estimates are skewed by several studies that included only diabetes type 1 patients. In one study, hospital-acquired nephropathy occurred in 12% of patients. In patients with normal renal function, however, the incidence of CMIN is just 1% to 2%.[71] Although diabetic and nondiabetic patients with renal insufficiency are at increased risk for contrast-induced ARF, diabetics seem to recover less often and are at greater risk for permanent dependence on dialysis as a consequence of contrast-induced ARF.[74-79]

One of the difficulties in treating or preventing renal failure after the administration of contrast media is that the biochemical mechanisms of CI-AKI have not been identified. One group of studies has hypothesized that NO contributes to preservation of renal blood flow and function in normal and pathologic states. Several studies have shown that inhibition of NO, before the administration of radiocontrast material, results in abolition of the medullary vasodilatory response and contributes to regional hypoxic renal tubular injury.[80-83] Heyman et al.[81] also suggested that maintenance of local vasodilatory prostaglandins, in particular PGE2, is likewise important in maintaining regional blood flow to the medulla. Myers et al.[84-86] combined the use of in vivo microdialysis and laser Doppler blood flow analysis to identify the clinically relevant intrarenal vasodilators (cortical and medullary) that are required to maintain microvascular blood flow during exposure to contrast material. The ionic agent Conray decreased superior mesenteric artery (SMA) blood flow, whereas the nonionic agent Optiray (Mallinckrodt) did not. Neither Conray nor Optiray altered total renal or aortic blood flow. Conray caused a marked decrease in cortical and medullary blood flow and NO synthesis, but did not alter PGI2 or PGE2. Optiray decreased medullary and cortical blood flow and cortical NO synthesis. Unlike Conray, Optiray did not decrease medullary NO synthesis, but profoundly decreased medullary and cortical PGE2 and PGI2 synthesis. These findings suggest that both Conray (ionic contrast agent) and Optiray (nonionic contrast agent) decrease renal cortical and medullary blood flow and renal function, although the intrarenal mechanisms differ. The decrease in renal cortical and medullary blood flow occurred without a decrease in total renal blood flow, thus suggesting that the decrease in renal microvascular blood flow induced by ionic and nonionic contrast agents occurs as an early injury. The Conray-induced fall in SMA blood flow may contribute to intestinal ischemia-reperfusion and distant organ dysfunction, including the kidney. These findings suggest that contrast-induced renal injury is due to local and systemic mechanisms. Preservation of normal levels of renal cortical and medullary NO synthesis and SMA blood flow may be required to prevent or lessen contrast-induced renal injury.[86,87]

Specific measures to minimize the risk for CI-AKI are controversial, and the results from controlled studies are largely inconclusive. Nevertheless, the basic relationship between the

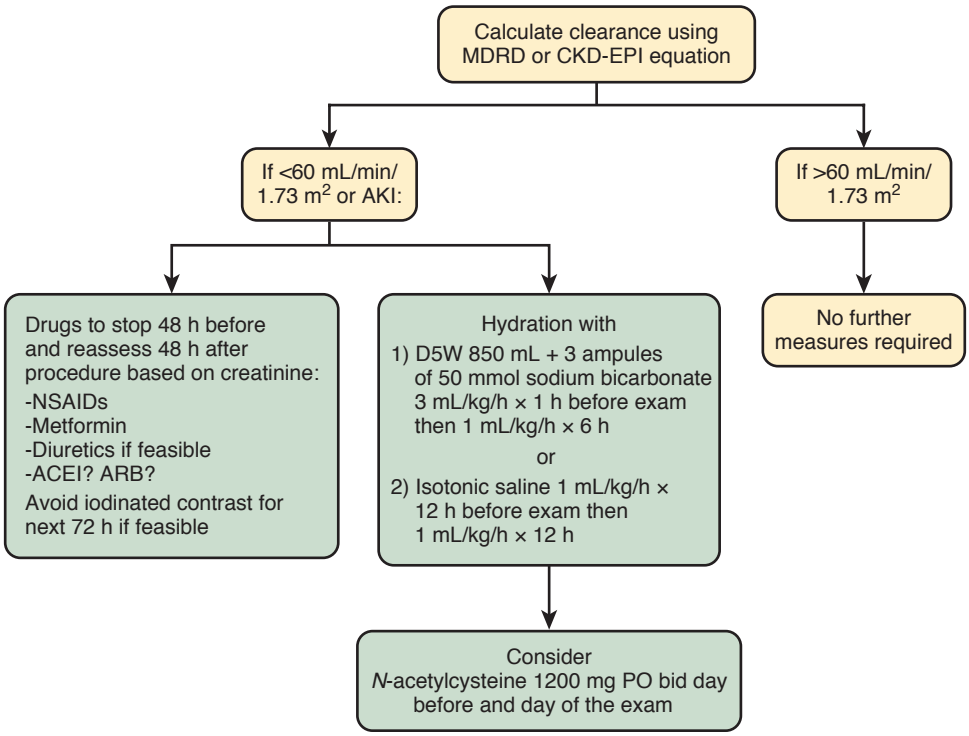


Figure 44.4 Management of patients receiving iodinated contrast media. *ACEI*, Angiotensin-converting enzyme inhibitor; *AKI*, acute kidney injury; *ARB*, angiotensin receptor blocker; *CKD-EPI*, Chronic Kidney Disease Epidemiology Collaboration; *D5W*, 5% dextrose in water; *MDRD*, modification of diet in renal disease; *NSAIDs*, nonsteroidal antiinflammatory drugs. (From Johnson RJ, Feehally J, Floege J. Prevention and nondialytic management of acute kidney injury. In: Macedo E, Bouchard J, Mehta R, eds. *Comprehensive Clinical Nephrology*. 5th ed. Philadelphia: 2015: 842–854.)

use of contrast material and the risk for contrast-induced nephropathy seems to be related to the amount of time that the kidney is exposed to the contrast material. The Prevention of C-I AKI Consensus working panel recommends that measures to reduce the AKI risk should be implemented in patients with a baseline estimated GFR (eGFR) below 60 mL/min per 1.73 m^2, and are presented in Fig. 44.4. Maximizing the urine flow rate during and immediately after angiography and limiting the quantity of contrast agent used are important considerations.[88] The rationale for the use of isotonic sodium bicarbonate is based on animal studies showing that bicarbonate is capable of scavenging reactive oxygen species and that the increased pH in the proximal tubule could reduce superoxide levels. Merten et al.[89] demonstrated the potential efficacy of sodium bicarbonate hydration before, during, and after the use of contrast agents. The current recommendation for sodium bicarbonate use is presented in Fig. 44.4. We have successfully used this protocol over a 10-year period.

Although attempts to calculate a safe upper limit of contrast material have met with some success, no definitive limit currently exists.[90] It seems prudent to limit the quantity of non-ionized contrast agent to less than 50 to 75 mL in patients with a significant reduction in GFR (<20-30 mL/min). In some instances, digital subtraction techniques have been useful in limiting the quantity of contrast material required. Other adjuncts or alternatives to conventional angiography include carbon dioxide gas,[91] and abdominal ultrasound with visceral and/or renal artery duplex sonography. MR angiography with gadolinium is no longer considered a viable option because of reports of nephrogenic fibrosis in patients with compromised renal function.[92]

By scavenging reactive oxygen species, N acetylcysteine (NAC) may protect against contrast-induced nephrotoxicity. Tepel et al.[93] studied patients with chronic renal dysfunction who required administration of nonionic contrast for computed tomography. They documented a significant reduction in serum creatinine with the use of oral acetylcysteine and hydration versus placebo and hydration.[93] However, there are as many studies showing either a benefit or no benefit from the use of acetylcysteine.[93-96] If NAC is to be used, the current recommendation is 1200 mg administered twice daily on the day before and the day of the procedure (see Fig. 44.4). ACE inhibitors and angiotensin II receptor antagonists are withheld for at least 72 hours before aortic reconstruction or exposure to arterial contrast agents. Selective beta-blockers and calcium channel blockers are substituted when necessary.

ALTERED RENAL FUNCTION DURING AORTIC SURGERY

Fluid Shifts Associated With Aortic Surgery

Reconstruction of the abdominal aorta is associated with volume shifts within fluid compartments. These shifts stem from the

local tissue trauma that occurs with operative dissection, from hemodynamic consequences that occur with aortic clamping and unclamping, and from operative blood loss. In large part, the changes are mediated through transcapillary and transcellular movement of fluid. The net movement of water and solutes from the intravascular, extracellular compartment (plasma) to the interstitium (extracellular or third space) normally takes place at the precapillary level secondary to increased hydrostatic pressure. Reentry of fluid back into the intravascular compartment in the distal capillaries is favored by intravascular protein albumin, which exerts an oncotic pressure gradient. Normally 7% of the intravascular albumin arriving at the capillary level crosses the capillary membrane into the interstitial space. This extravascular protein eventually enters the lymphatics and ultimately returns to the intravascular pool. The operative dissection results in the disruption of lymphatic channels and the release of inflammatory mediators that cause local and systemic alterations in tissue perfusion, contributing to increased capillary membrane permeability to albumin.[97] The exact mechanisms involved are not currently understood, but the resultant effects are a flux of albumin into the interstitium and subsequent decrease in water reabsorption into the intravascular space. The decrease in intravascular volume activates neuroendocrine mechanisms that decrease renal excretion of sodium and free water. In addition, there is net movement of sodium and water into the intracellular space from the extracellular compartment. This process is due to a relative decline in the normal cellular transmembrane potential after ischemia-reperfusion, shock, or both, secondary to blood loss.[98] The causes of the decline in transmembrane potential are unclear, but are due, in part, to impaired function of the Na^+, K^+-adenosine triphosphatase pump and loss of active ion transport. This cellular swelling is also governed by a change in intracellular calcium homeostasis and an increase in the intracellular level of calcium.[99] During resuscitation, the abnormalities in intracellular sodium concentration and water are reversed.

The normal response to decreased circulating intravascular volume is to mobilize extracellular (third-space) interstitial fluid. Temporary ischemia in tissue beds during aortic surgery, the shift in acid-base balance in the involved tissue beds, the adverse impact of unreplaced blood loss, the potential reductions in cardiac and renal performance during aortic cross-clamping, and stimulation of stress-induced neuroendocrine mechanisms contribute to the injury-induced shift of total body water from the functional circulating blood volume into the third space.[100,101]

Determination of intravascular volume and its associated solutes after major surgery has been of dramatic benefit to the intraoperative and early postoperative fluid management of patients undergoing major vascular surgery. The increased obligatory losses of intravascular volume associated with major surgery have led to the current use of balanced salt solutions (5% dextrose, lactated Ringer solution) for volume replenishment.[102] Hourly postoperative fluid requirements may be several-fold higher than requirements during the resting nonoperative state. The increased need for fluid replacement continues in the immediate postoperative period because of continued sequestration of fluid into areas of the operative site and the persistent effects of a complex array of inflammatory mediators.[103] Mobilization of the sequestered third-space fluid is delayed for 2 to 5 days, depending on the magnitude of operative and postoperative stress, cardiac performance, and intravascular oncotic pressure. Reabsorption of third-space fluid usually begins on postoperative day 2 or 3. If not managed with an appropriate reduction in maintenance parenteral fluid administration or the addition of diuretic therapy, reabsorption of third-space fluid can lead to intravascular volume overload and acute congestive heart failure.

Although renal insufficiency continues to be a complication after treatment of suprarenal aneurysms and renal artery occlusive disease, very few studies have assessed the effect on renal function of clamping the aorta above and below the renal arteries. A series of studies by Myers et al.[84,104-105] examined the simple question of whether suprarenal aortic clamping and reperfusion (renal-SRACR) preserves renal function as opposed to clamping the renal arteries above the superior mesenteric artery (SMA-SRACR). In an experimental model, both SMA-SRACR and renal-SRACR were shown to decrease medullary and cortical blood flow and NO synthesis. SMA-SRACR downregulated cortical iNOS, whereas renal-SRACR did not. The use of superoxide dismutase (inhibitor of oxygen-derived free radicals [ODFRs]) restored cortical and medullary NO synthesis after SMA-SRACR (but not renal-SRACR), suggesting that the ODFRs generated during mesenteric ischemia-reperfusion were one of the systemic mechanisms contributing to decreased renal NO synthesis. SMA-SRACR profoundly decreased creatinine clearance, far greater than the decrease in clearance that occurred after renal-SRACR. These data suggest that clinically relevant cortical and medullary vasodilators (NO and vasodilator prostanoids) are required to maintain microvascular renal cortical and medullary blood flow after both SMA-SRACR and renal-SRACR. The data also suggest that maintaining SMA blood flow and preventing ODFR production could help maintain renal microvascular blood flow.[84,85,104-105]

Renal Failure Associated With Aortic Surgery

Aortic repair requiring suprarenal cross-clamping poses a significant risk for an ischemic renal insult. Rates of AKI approaching 18% have routinely been quoted for elective repair of thoracoabdominal aneurysms in larger series. Contemporary series report the occurrence of AKI after repair of infrarenal aortic aneurysms range from 1% to 13%.[37-47] The evolution of AKI depends on the clinical circumstances of the operation, the age of the patient, blood loss, myocardial dysfunction, the presence of sepsis, the level of aortic repair, preoperative renal function, intraoperative and postoperative events, and overall previous health of the patient. Mortality in patients with postoperative renal failure as an isolated system failure ranges from 25% for nonoliguric renal failure to 70% for oliguric renal failure.[37-47,106-109] Determinants of outcome include the preexisting disease and precipitating events. When renal failure is only one of several system failures, mortality is extremely high, approaching 100% for three or more organs failing simultaneously.[110-113] Unfortunately, the pathophysiology and

thus the prevention of multiorgan system failure have not been elucidated.

A temporary isolated period of renal ischemia caused by suprarenal aortic cross-clamping, temporary renal artery occlusion, a single episode of hypovolemic shock, post-cross-clamp hypotension, or cardiogenic shock in the perioperative period is the most common cause of acute renal dysfunction and renal failure associated with aortic surgery.[114-120] Studies in patients with postischemic AKI have shown minimal, if any, disturbance in glomerular architecture, yet profound tubular disruption supports the notion that the injury is initiated through tubular luminal obstruction caused by sloughed tubular cells.

Clinically observed rates of renal failure after aortic surgery suggest that the incidence of AKI can be correlated with the level of aortic repair. Svensson et al.[107] Kashyap et al.[108] and Allen et al.[109] reported an 18% incidence of renal failure (serum creatinine >3 mg/dL [>265 μmol/L]) and a 9% rate of dialysis-dependent renal failure in patients who underwent thoracoabdominal aneurysm repair. Series using regional renal hypothermia for renal protection and a clamp-and-sew technique identified the occurrence of AKI in 11.5% of patients.[101] Factors that predicted renal dysfunction included a preoperative creatinine level greater than 1.5 mg/dL (133 μmol/L) and a total cross-clamp time of more than 100 minutes. These results do not seem to differ from series in which partial left heart bypass and distal aortic perfusion were used.[108] In cases of juxtarenal and suprarenal abdominal aortic aneurysm (AAA) repair, preservation of renal function may be enhanced by renal hypothermia.[109] For elective infrarenal aortic surgery, a preoperative creatinine clearance of less than 45 mL/min has been associated with a significant risk for subsequent AKI. In the same series, no patient with a preoperative serum creatinine concentration of less than 1.5 mg/dL (133 μmol/L) required postoperative dialysis, whereas 8% of patients with a preoperative serum creatinine level greater than 1.8 mg/dL did.[109]

Another important cause of AKI in aortic surgery is renal atheroembolism.[121,122] The quantity of microembolization produced during surgery depends on the emboligenic potential of the atheromatous debris and the operative techniques used to prevent such an event. The clinical impact of renal microembolization depends on the quantity of functioning renal units before the procedure and the presence of other causes of AKI. In the absence of other factors favoring AKI and a normal mass of functioning nephron units, relatively large amounts of atheromatous microemboli can accumulate without an immediate impact on renal function, whereas in patients with minimal renal reserve, even minor microembolization can lead to AKI.[122]

The use of endovascular aneurysm repair (EVAR) has also been associated with an increased risk of renal dysfunction. This can be secondary to direct trauma to the renal arteries with suprarenal fixation barbs or dissection of the renal artery during the repositioning of a mal-deployed aortic endograft with suprarenal barbs.[123-128] In one series describing open and endovascular repair of ruptured AAAs, the incidence of AKI was 36%, with a higher incidence of AKI and mortality seen in the group treated with open surgical repair.[129]

Recently, there has been increasing experience with the use of chimney snorkel/periscope techniques and the introduction of fenestrated grafts for treatment of thoracoabdominal aneurysms; juxtarenal aneurysms; aneurysms with a short, severe angled proximal neck; and asymptomatic, symptomatic, and ruptured aneurysms. These technologies have allowed repair of these complex aneurysms with far less morbidity and mortality than open repair. However, they have a significant impact on perioperative renal function with rates of AKI between 10% and 36%.[130-136] In one study, fenestrated EVAR had a higher incidence of perioperative AKI than open repair, yet by 1-year follow-up, renal function was the same in both groups.[130]

Protection of Renal Function During Aortic Surgery

Renal function protection strategies during aortic surgery include limiting the period of warm renal ischemia (<40 minutes), providing intravenous fluid hydration preoperatively, adequate blood volume replacement, avoiding repetitive or prolonged renal ischemia, and maintaining maximal parameters of cardiac performance. In addition, other protective measures (currently used and experimental) include the use of routine heparinization, mannitol, furosemide, dopamine, fenaldopanan, atrial natriuretic peptide other diuretics, renal hypothermia, and renal vasodilating drugs and during thoracoabdominal aortic surgery patient-specific surgical adjuncts, including renal endarterectomy and open stent placement.[137-163] Use of all these measures is directed toward minimizing renal tubular ischemia and metabolic needs during periods of ischemia, or prevention of tubular obstruction by sloughed tubular cells. No single modality or combination of modalities entirely prevents renal injury during aortic surgery.

Distal aortic perfusion may be used to maintain renal perfusion during repair of thoracoabdominal aneurysms. This technique is most attractive during the repair of an isolated thoracoabdominal aneurysm[160,161] or when complex disease precludes prompt completion of the proximal thoracic aortic anastomosis.[162] Distal aortic perfusion may be modified with "octopus" catheters to perfuse the renal arteries directly during distal reconstruction.[163] Because the routine use of distal aortic perfusion in these cases has been associated with an increased incidence of AKI, other strategies to provide renal protection may be considered.

Regional renal hypothermia has been used sporadically for many years to protect renal function during ischemia, based on the premise that decreases in core temperature significantly reduce metabolic needs. The technique usually involves the renal infusion of 500 mL to 1 L of cold (4°C-5°C) crystalloid solution, with or without other additives. Animal studies have shown that the first 10°C reduction in tissue temperature seems to provide the greatest protection. Postoperative serum creatinine levels and renal tubular morphology data revealed that a protective effect occurs with a minimal sustained decrease in core temperature to 35°C.[164]

Operative technique during aortic reconstruction should avoid repetitive aortic cross-clamping. Some authors use temporary renal artery occlusion immediately before application

of the aortic cross-clamp whenever the aortogram suggests the presence of complicated peri-renal atherosclerosis. These authors believe that this maneuver has been an important adjunct in minimizing the incidence of postoperative ARF in their patients.

It is not uncommon that infrarenal AAAs may extend superiorly to the level of the renal arteries. In these cases, the surgeon may facilitate the exposure of the suprarenal aorta and expedite repair by transecting the left renal vein divided (LRVD). Because of the collateral drainage of the left kidney, it is thought that permanent ligation of the LRV may be a safe procedure, without reconstruction.[165-167] Several series have shown increased renal and pulmonary complications following LRVD,[165-168] so this technique should only be used when necessary.

In performing ligation of the LRV, one must remember that the main tributaries are the left gonadal vein, the left ureteral vein, capsular veins, lumbar veins, and the ascending lumbar vein from above, and the left middle suprarenal vein and the inferior phrenic vein from below. LRVD toward the inferior vena cava will spare the tributaries and thus preserve renal function. If the case has gone well, I would recommend reconstruction of the LRV to prevent a reduction in renal function, although only seen in a small number of patients. For the medical treatment for chronic kidney disease, consult reference #1.

ACKNOWLEDGMENT

This text is supported by a Veterans Affairs Merit Grant.

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45 CHAPTER

Neurologic Complications

ADAM C. RING, JUDITH W. COOK, and FAISAL AZIZ

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In vascular surgery patients, nerve damage can result from acute or chronic ischemia, trauma, compression, and associated comorbid disease. This chapter describes the following:

1. Ischemic neuropathy—an under-recognized form of peripheral nerve damage that must be distinguished from ischemic pain
2. Nerve trauma—which can be prevented by knowledge of the relevant anatomy
3. Other neuropathies encountered in vascular patients consequent to systemic diseases

STRUCTURE OF A PERIPHERAL NERVE

The peripheral nerves are composed of nerve fibers, Schwann cells, collagen, small vessels, and endoneurial fluid. Large nerves derive their nutrient and oxygen supply from the vasa nervorum, whereas smaller nerves are able to rely on diffusion through the interstitial space to supply their metabolic demands. The oxygen requirement of a mammalian nerve is less than that of other tissues, even when the requirement is increased by activity.[1] Hence,

Keywords

Ischemic Neuropathy
Ischemic Monomelic Neuropathy
Iatrogenic Nerve Injuries

peripheral nerves have an inherent resistance to ischemia. The large nerves of the extremities contain multiple redundant collateral networks of vasa nervorum supplied by sequential branches of adjacent arteries, while the inner portions of the nerves contain an extensive pattern of epineural vessels.[2,3] Due to rich collateralization, interruption of the blood supply to a segmental portion of the nerve usually does not result in ischemic nerve injury.[4,5] One notable exception is ischemic monomelic neuropathy (IMN), an infrequent ischemic nerve injury following acute limb malperfusion, which is characterized by multiple distal axonal infarctions and resultant motor and sensory mononeuropathies.[6,7]

CAUSES OF NERVE DAMAGE

Ischemic Nerve Injury

The true incidence of ischemic neuropathy in patients with peripheral arterial disease (PAD) is difficult to determine; the symptoms of ischemic nerve injury may mimic either rest pain associated with arterial insufficiency or decreased sensation due to diabetic neuropathy. Historically, the incidence of clinically detectable ischemic neuropathy associated with PAD has been estimated to be as high as 88%.[8] This has been confirmed in contemporary studies reporting similar incidence of pain and sensory disturbances in this cohort,[9] with nearly universal presence of occult nerve dysfunction detectible by electrophysiologic nerve conduction studies.[10-12] Both acute and chronic ischemic conditions have the potential to cause nerve injury, although the mechanism of ischemic injury specific to PAD has not been fully elucidated.

Acute Ischemic Neuropathy

Animal models of acute limb ischemia have demonstrated the ability of injured mammalian nerve tissue to recover after short periods of ischemia subsequent to occlusion of large inflow arteries[13] and smaller vasa nervosum.[14] There is, however, a certain time threshold in animal models, between 6 and 10 hours, beyond which the neurologic damage is irreversible.[15,16] Peripheral nerve tissue initially recruits oxygen and nutrient supply from the surrounding interstitial fluid. The rich collateral circulation within the nerve bundle itself is also protective against ischemic nerve injury. Eventually persistent hypoxemia and hypercapnia lead to hyperkalemia and acidosis, which in the local milieu of the ischemic nerve may contribute to irreversible depolarization of the axon cell membrane.[17,18] Exactly how much ischemia the human peripheral nerve is able to tolerate without irreversible injury is still unknown.

IMN, a subcategory of acute neuropathy, is relatively uncommon and the mechanism of injury is not completely understood. The pathophysiology of IMN does not result in the characteristic Wallerian degeneration seen histologically with other severe nerve injuries, where fragmentation of both the axon and myelin are early responses. Consequently, nerve biopsies following IMN will not display axonal degeneration and demyelination.[19] It is believed that altered blood flow through the vasa nervorum causes acute but reversible conduction block. Persistent malperfusion leads to distal axonal infarction and manifests as multiple axonal-loss mononeuropathies in the extremity.[20] IMN has been proposed to result from acute ischemia superimposed on predisposing factors such as diabetic neuropathy and peripheral vascular disease.

Chronic Ischemic Neuropathy

Since reliable experimental models for chronic limb ischemia are nonexistent, researchers have focused on using histologic findings of peripheral nerve specimens obtained from patients with chronic PAD. These specimens show segmental demyelination and remyelination, as well as axonal degeneration and regeneration.[8] The mechanism by which chronic limb ischemia produces changes in the peripheral nerve is still not known; however, similar morphologic changes in peripheral nerves were observed following both acute and chronic ischemia, thus suggesting that the lack of blood flow and oxygen delivery have the same ultimate effect when present acutely or over time.[21] The severity of the chronic ischemia so far has not been shown to correlate with the degree of histologic damage found in peripheral nerves.[22] Furthermore, Lacroix et al.[23] suggest that the injury observed in chronically ischemic limbs may not be a result of slow progression of the ischemic process but rather the accumulation of multiple repeated episodes of acute ischemia in the setting of chronic PAD. This is supported by more recent evidence that ischemic preconditioning, which tends to be beneficial to skeletal muscle tissue, is harmful to peripheral nerve tissue.[24]

Traumatic Nerve Injury

Peripheral nerves with anatomic proximity to the major arteries and veins of the extremities are at risk for iatrogenic injury during vascular interventions. Without a commanding knowledge of the anatomic relationships of structures within the major neurovascular bundles, vascular surgeons may successfully restore flow to an extremity yet leave significant neurologic deficits because of surgical trauma. Fortunately, most peripheral nerve injuries that occur during operative exposure result in transient nerve dysfunction (neurapraxia) that recovers with time.

Traumatic injury can occur via several mechanisms, and direct division or ligation of a nerve renders the nerve immediately and permanently damaged. Although reconstruction of divided nerves is possible with acceptable rates of functional recovery, the outcome is variable.[25-29] Other mechanisms include stretch injury from improper retractor placement and thermal injury from electrocautery devices. Compressive injury can result from hematoma formation or from improper patient positioning on the operating table. Nerves can also be injured by clamps or entrapped by sutures. The ability to avoid nerve injury during operative procedures is based on a high level of technical precision with constant vigilance for anatomic relationships. Except where the nerve is completely severed, the peripheral nerves have remarkable capacity to regenerate and functional outcome in most instances is favorable.[29-31]

Other Causes of Nerve Injury

A proportion of patients evaluated by a vascular specialist will have peripheral neuropathy that is not due to ischemia or trauma

BOX 45.1 Examples of Common Types of Neuropathy: Causes

Commonly Unilateral

- Entrapment
- Trauma
- Ischemia
- Vasculitis

Commonly Bilateral

- Metabolic (diabetes, uremia)
- Toxic (alcohol, drugs, metal)
- Connective tissue disease, vasculitis
- Deficiency (Vitamin)
- Inflammatory
- Monoclonal gammopathies
- Human immunodeficiency virus infection

and it is important to include these other causes in the differential diagnosis (Box 45.1). Diabetic neuropathy is the most commonly encountered alternative cause of peripheral neuropathy seen by vascular specialists.[32] Risk factors include increasing age, increasing length of time being diabetic, poor overall glycemic control, poor lipid metabolism, inadequate blood pressure control, obesity, and metabolic syndrome.[32-34] The etiology of the nerve damage is multifactorial and not completely understood, but the metabolic derangements associated with chronically elevated blood glucose levels and abnormal insulin homeostasis are thought to be the major determinants.[35] Vascular disease in the microcirculation is also believed to play a role in nerve damage, thus making the difference between diabetic neuropathy and ischemic neuropathy less distinct.[36] Other causes of peripheral neuropathy include alcoholism, uremia, drug intoxication, medication side effects, vasculitis, autoimmune disorders, infectious causes, and inflammatory causes. Most often, these neuropathies are symmetric.

DIAGNOSTIC EVALUATION

History and Physical Examination

Ischemic pain at rest is most often unilateral, involves the foot, is usually worse at night, and is generally relieved by placing the extremity in a dependent position to allow gravity to assist in blood flow. Neuropathic pain is usually constant and typically has no identifiable aggravating or alleviating factors. It is often described as shooting or burning pain associated with the sensation of numbness and tingling, and it is most severe distally in the toes or foot. These symptoms are unilateral in ischemic neuropathy but are bilateral and symmetric in metabolic neuropathies. After revascularization of a severely ischemic limb, persistent pain due to neuropathy rather than ischemia often emerges. The neuropathic pain is burning and paresthetic, is frequently worse with rest and at night, and is either unaffected or relieved by walking. The patient may perceive the foot to be cold, although it is, in fact, warm. The patient may also remark on stiffness or loss of mobility of the toes. Physical examination should include a detailed vascular examination supplemented by noninvasive vascular testing to document the degree of arterial ischemia.

Vascular Testing

Ankle pressure greater than 50 to 60 mm Hg or toe pressure greater than 30 mm Hg suggests adequate peripheral circulation, and ischemic rest pain is unlikely. Flat or monophasic Doppler waveforms indicate severe arterial insufficiency. When perfusion is inadequate, the pain may be due to ischemia, neuropathy, or both, and treatment should be directed first toward improvement of limb blood flow. If no ischemia is present, a neurologic evaluation should be performed. If ischemia is present, efforts should be made to correct the ischemia in parallel with any indicated neurologic testing.

Neurologic Testing

Ischemic neuropathy in the lower extremity may be accompanied by slight ankle weakness and depressed ankle reflex. There is unilateral sensory loss in a "stocking" distribution, particularly vibration sense. The small muscles of the affected foot may become atrophied. Unlike the findings in neuropathies caused by diabetes, uremia, drug intoxication, or alcoholism, the findings in ischemic neuropathy are asymmetric; sensory and motor findings occur exclusively or prominently in the limb that is affected by severe ischemia.

The peripheral neuropathy associated with diabetes is characterized by bilateral sensory loss, numbness and tingling, and pain in the hands, feet, fingers, and toes. Distal muscle weakness and muscle wasting are common, and ankle reflexes are absent. The pattern of distribution is symmetric over the involved extremities, in contrast to the unilateral pattern of ischemic neuropathy. Evaluation of individual nerves is discussed later under "Specific Nerve Injuries."

Electromyography and Nerve Conduction Studies

Electrophysiologic testing including motor nerve conduction studies, sensory nerve conduction studies, and needle electrode examination can establish the diagnosis and severity of ischemic neuropathy. With ischemic neuropathy, patients typically have a unilateral axonal neuropathy involving the distal tibial and peroneal nerves. Motor nerve conduction studies show decreased or absent compound muscle action potential amplitude following nerve stimulation in the affected foot.[37] Distal latency and the velocity of conduction in the calf portion of these nerves are relatively well preserved. These findings are in sharp contrast to diabetic and uremic neuropathy, where distal latencies and conduction velocities tend to be reduced below normal velocities at an early stage and in a bilateral, symmetrical pattern.

Sensory nerve conduction studies in ischemic neuropathy show decreased or absent sensory potential amplitudes from the sural, superficial peroneal, and plantar nerves, whereas sensory conduction velocity, when recordable, is normal.[37,38] Needle

electrode examination reveals muscle denervation in the small muscles of the affected foot, particularly in the sole of the foot, with fibrillation potentials at rest and large motor units of long duration in much reduced numbers. If the ischemia has been severe, denervation changes of a lesser degree are also seen in the muscles of the calf.[39]

GENERAL PRINCIPLES OF TREATMENT

Acute Ischemic Neuropathy

If a patient has acute arterial ischemia, revascularization will often improve the motor and sensory symptoms of ischemic neuropathy either immediately or over the first few weeks. If symptoms persist and the revascularization is deemed adequate, a neurologic cause of the pain should be suspected. The pain should be treated, and a neurologic consultation should be obtained.

Pain Control

Ideally, a neurologist or other specialist familiar with treating this condition should manage the pain from ischemic neuropathy. Treating the pain of ischemic neuropathy is often difficult, because the typical narcotic regimens used for postsurgical pain may not be effective, and individual response to commonly used drugs is highly unpredictable. Anti-inflammatory drugs and opiate medications are generally ineffective, although opioids or tramadol may be used to augment initial treatment during titration of other medications. First line therapy may include tricyclic antidepressants (TCAs) or selective serotonin and norepinephrine reuptake inhibitors (SSNRIs). Secondary amine TCAs (nortriptyline and desipramine) are generally better tolerated in the elderly than tertiary amine TCAs (amitriptyline and imipramine); however, all TCAs have potential cardiac toxicity and should be avoided in patients with ischemic heart disease.[40] SSNRIs (duloxetine and venlafaxine) have a more favorable side effect profile and less risk of cardiac toxicity, but analgesic efficacy is inconsistent.[41] Calcium channel α2-δ ligands (gabapentin and pregabalin) are also used for first line therapy but do not provide reliable relief for all patients. The most common dose-limiting side effects include somnolence and dizziness, and renal insufficiency requires dose reduction. Although well tolerated if titrated properly, it may take weeks to establish effective dosage.[41]

TRAUMA

Partial loss of nerve function after surgery will generally recover since nerves have the ability to regenerate. The rate of axonal regeneration is estimated to be 1 mm per day; thus, the recovery period may be lengthy.[19] In a patient with severe loss of motor and sensory function, surgical re-exploration should be considered. If a major nerve or branch is found to be divided, repair is indicated. If a nerve is acutely compressed because of a hematoma, surgical decompression should be performed promptly and will often result in the recovery of function. In cases in which symptoms persist without signs of healing and nerve conduction studies indicate loss of nerve function, surgical exploration with neurolysis and nerve grafting offers some hope of recovery of function, with encouraging results being reported in contemporary series.[26-31]

SPECIFIC NERVE INJURIES

Brachial Plexus and Upper Extremity Nerve Injuries

Anatomy

The brachial plexus gives rise to the five main terminal nerves of the upper extremity: the axillary nerve (C5, C6), the musculocutaneous nerve (C5, C6), the median nerve (C5–T1), the radial nerve (C5–C8), and the ulnar nerve (C8, T1). The superior, middle, and inferior trunks of the brachial plexus are intimately associated with the axillary artery, as they make the turn along the shoulder joint and become the lateral, posterior, and medial cords. Great care must be taken during operative exposure of the axillary artery to not injure the cords of the brachial plexus, because they are located on three of the four sides of the artery (Fig. 45.1).

The musculocutaneous and axillary nerves terminate in the upper part of the arm and are not routinely encountered during vascular exposure there. Likewise, the radial nerve is rarely encountered in its deep location posterior to the humerus, as it courses toward the extensor compartment of the forearm. However, in the upper part of the arm, the median and ulnar nerves are intimately associated with the brachial artery and basilic vein (Fig. 45.2). Avoiding the median nerve as it wraps around the brachial artery in a lateral-to-medial direction and

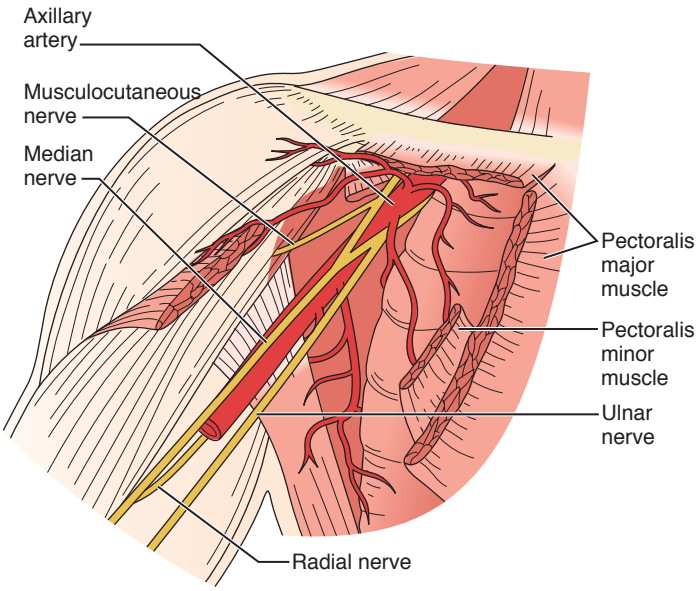

Figure 45.1 Relationship of the axillary artery to the brachial plexus nerves.

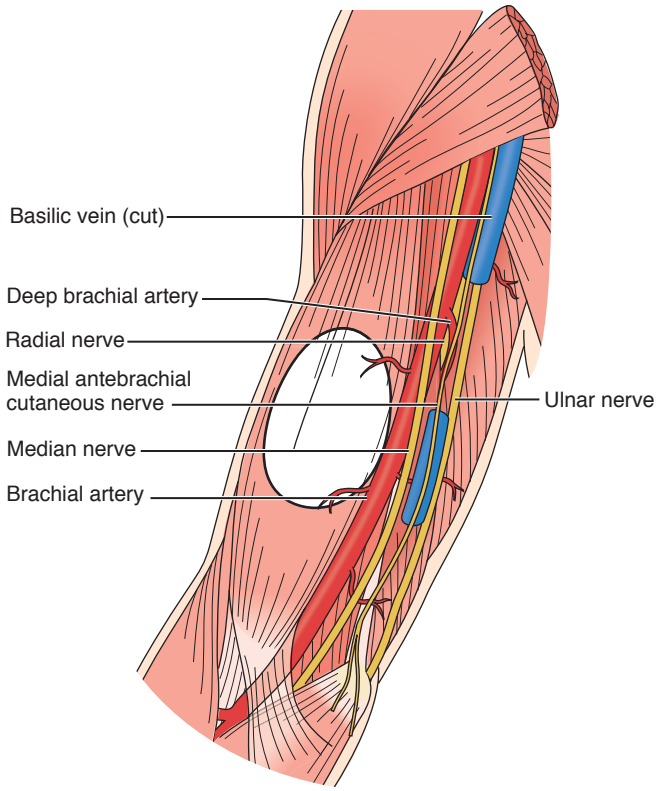

Figure 45.2 Relationship of the brachial artery and basilic vein to the median and ulnar nerves in the neurovascular bundle that runs deep to the medial brachial fascia.

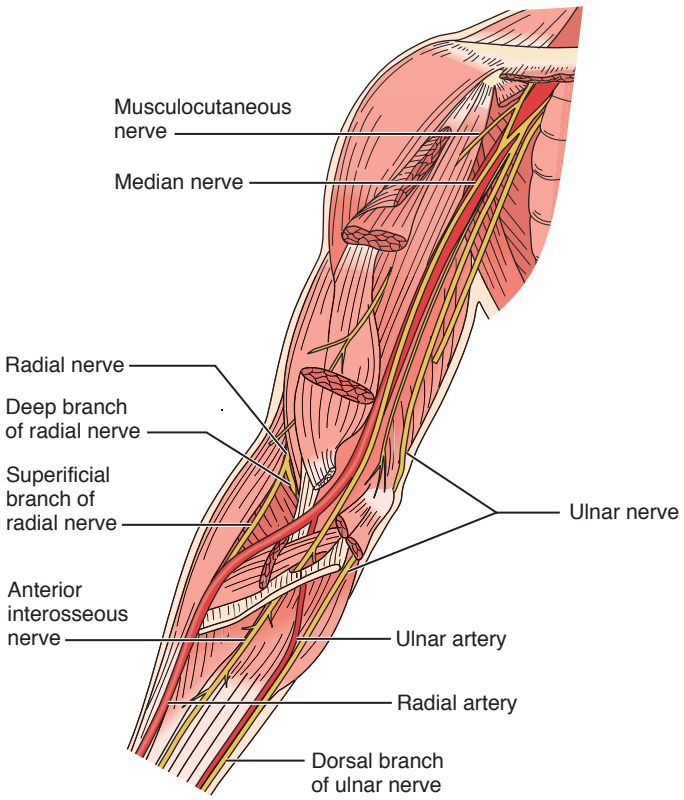

Figure 45.3 Relationship of named arteries and nerves of the upper extremity. Note that the ulnar nerve and ulnar artery are in close proximity at the wrist.

the ulnar nerve deep to the basilic vein is essential to prevent iatrogenic injury.

In the forearm, the median nerve is not routinely encountered, whereas the ulnar nerve, which runs adjacent to the ulnar artery into the hand, can be injured when the distal ulnar artery is exposed. The location of the ulnar nerve at the elbow also makes it vulnerable to compression injury from prolonged improper positioning (Fig. 45.3).

Etiology

The most common causes of injury to nerves in the upper extremities include direct surgical injury, compression, and traction. Procedures associated with injury include hemodialysis access, arterial puncture, radial artery harvesting, and venipuncture (Box 45.2).

Surgical Dissection

During thoracic outlet surgery, the brachial plexus can be injured by direct trauma or traction (see Chapter 124). Injury to the cords of the brachial plexus can also occur during exposure of the axillary artery, producing neurologic deficits in more than one peripheral nerve. In the upper part of the arm, the median nerve with its close proximity to the brachial artery and the ulnar nerve with its close proximity to the basilic vein can be injured by dissection of these vessels. The median and ulnar nerves in the upper part of the forearm can also be injured during surgical dissection of the major arteries.

BOX 45.2 Avoiding Upper Extremity Nerve Injuries

- Positioning patient: padding beneath elbow to avoid ulnar nerve injury
- Dissection: remember important anatomic relationships (median nerve/brachial artery, ulnar nerve/basilica vein)
- Careful hemostasis: avoid compression and nerve dysfunction secondary to hematoma
- Ultrasound guided percutaneous brachial access: avoid needle trauma to artery, leading to thrombosis/hematoma

Compression

The anatomic confines of the fascial compartments of the arm predispose the associated nerves to compression injury in the setting of compartmental swelling. Upper extremity nerves can be compressed by even a small hematoma, and peripheral neuropathy can occur secondary to hematoma formation in the neurovascular bundle following transaxial puncture.[39] Nerve injury during brachial artery catheterization has been reported at 0.2% to 1.4% resulting from direct needle trauma, compression from hematoma, and ischemia from brachial artery thrombosis.[42] Prompt surgical decompression of any postprocedure hematoma causing neurologic symptoms in the upper extremity may prevent permanent nerve damage.[43,44]

Hemodialysis Access

After hemodialysis access, patients may complain of pain and sensory loss in the hand and forearm from multiple causes. This may be the result of arterial steal syndrome or direct nerve compression by a hematoma or the arterialized vessel. Diagnosis, however, may be confounded in many patients because of coexistent diabetic or uremic neuropathy.[45-47] IMN is a distinct clinical entity characterized by severe neurologic impairment of multiple extremity nerves in the setting of normal or near normal blood flow. Although reported sporadically in the lower limb,[48] IMN is much more common after upper extremity procedures, particularly those involving the brachial artery.

Radial Artery Procedures

Studies evaluating the effects of radial artery harvest on the forearm have shown that neurovascular deficits in the immediate postoperative period usually resolve over time and suggest that ischemic injury is not very common.[49,50] The incidence of transient nerve dysfunction does not differ between harvest technique of sharp or electrocautery dissection.[51] Isolated nerve injury following transradial access for coronary artery catheterization is rare, but the use of larger sheath size may be associated with injury of the superficial radial nerve at the wrist.[52,53]

Clinical Findings

Upper extremity neuropathies are frequently misdiagnosed and mistaken for complications attributed to anesthesia or patient positioning. These types of nerve injury typically manifest in the immediate postprocedure period as motor and sensory deficits.

Axillary nerve injury results in weakness of shoulder abduction and sensory deficit over the deltoid muscle. Median nerve injury gives rise to sensory deficit in the first, second, third, and radial aspects of the fourth digits. There is concomitant weakness in the thenar muscles, which on occasion, extends to the flexors of the digits and wrist. Ulnar nerve injury results in numbness of the fifth digit and the ulnar aspect of the fourth digit, along with weakness of the hypothenar muscles. Abduction and adduction of all digits and flexion of the fourth and fifth fingers are also affected. Radial nerve injury results in weakness of wrist and finger extension.

IMN presents in the immediate postoperative period with intractable pain and variable, often severe, sensorimotor deficits which may involve any or all the upper extremity peripheral nerves. Arterial examination and noninvasive testing can be normal, but neurologic studies show decreased or absent amplitude with motor and sensory stimulation of the median, ulnar, and radial nerves in the presence of preserved conduction velocities.[54] Detailed evaluation with electrophysiologic studies helps determine the extent of involvement of the different peripheral nerves in these patients.

Treatment and Prognosis

Signs of nerve injury in the immediate postprocedure period warrant timely patient evaluation, assessment, and intervention. Any obvious sign of hematoma or bleeding complication in the presence of a neurologic deficit should prompt immediate wound exploration to relieve compression of the involved nerves. Occasionally, because small, clinically unapparent hematomas can cause compression and nerve dysfunction, exploration may be warranted even without external signs of hematoma. Imaging with ultrasound or computed tomography may aid in diagnosis. In patients with a delayed diagnosis or evaluation, the benefit of intervention decreases; however, operative reconstruction of traumatically injured nerves within 3 months of injury has shown acceptable rates of motor and sensory recovery.[55] Prompt recognition of IMN after arteriovenous fistula or graft with revision or ligation of the newly created access is essential; recovery of function and relief of pain is variable following access ligation, and in some individuals, sensory and motor deficits may be prolonged or permanent.[56]

SPINAL CORD AND LUMBOSACRAL PLEXUS INJURY

Anatomy

The spinal cord itself ends at L1–L2, but inferior to that level the thecal sac contains the branches of the cauda equina. The lumbosacral plexus provides the nerve fibers that supply innervation to the lower extremity. Fibers from the lumbar plexus form the lateral femoral cutaneous nerve (L2–L3), the femoral nerve (L2–L4), and the obturator nerve (L2–L4). Blood supply to the lumbosacral plexus is through five sets of paired lumbar arteries arising from the abdominal aorta, the deep circumflex iliac arteries (branches of the external iliac arteries), and the iliolumbar and gluteal branches of the internal iliac arteries. D fibers from the sacral plexus form the posterior femoral cutaneous nerve (S1–S3) and the sciatic nerve (L4–S3). The sciatic nerve divides in the posterior aspect of the mid-thigh into the common peroneal nerve (L4–S2) and the tibial nerve (L4–S3).

Etiology

Lower spinal cord injury and lumbosacral plexus injury can occur from dissection, traction, or compression after thoracic and aortoiliac interventions (Box 45.3). It is important to differentiate the two because the signs and symptoms are different, as are the outcomes.

Ischemia

Lumbosacral plexus neuropathy after aortobifemoral bypass grafting for aneurysm disease was described in 1970, evidenced by infarction of the plexus found on autopsy.[57] More recently, similar findings after open and endovascular aortoiliac procedures

BOX 45.3 Avoiding Lumbosacral Nerve Injury

- Dissection: iliac artery dissection—avoid nerves overlying psoas muscle
- Retraction: avoid self-retraining retractor compression of nerves
- Hemostasis: avoid hematoma compression of nerve structures

suggest that thrombosis of the internal iliac artery might play a causal role in the ischemic nerve injury.[58] The incidence of lumbosacral plexus injury after open aortoiliac operations may be as low as 0.3%, presumably secondary to pelvic ischemia, but the true incidence and risk factors remain ill-defined.[59-62] Case reports of lumbosacral nerve root injury and sciatic nerve injury have also been reported after endovascular stent-graft repair of the abdominal aorta,[63-65] with some authors reporting a lower incidence of nerve complications with endovascular repair compared to open repair.[66]

Trauma

The branches of the lumbosacral plexus are prone to direct injury during vascular surgical procedures. Exposure of the iliac arteries may require dissection and retraction of structures in the iliac fossa, with a corresponding risk of injury to the nerves coursing along the psoas major muscle. Improper or careless positioning of retractors (especially self-retaining devices) can lead to significant blunt injury to these nerve branches.

Compression

Another cause of lumbosacral plexus injury is acute compression from a retroperitoneal hematoma or chronic compression from iliac artery aneurysm or pseudoaneurysm.[67-69] Similarly, extraperitoneal hematomas from either surgical procedures or femoral catheterization may cause severe compression and injury to the femoral nerve in the iliac fossa.

Clinical Findings

Careful history and physical examination will reveal the level of injury when evaluating a patient with lower extremity sensory and motor dysfunction. Injury to the lumbosacral plexus most commonly produces unilateral motor and sensory loss and affects more than one peripheral nerve and dermatomal segment, unlike an injury in a peripheral nerve, which has a unique sensory and motor distribution. The weakness associated with a plexus injury may be in both the large proximal muscle groups and the smaller distal muscle groups, with flaccid paralysis, absence of reflexes, and a sensory deficit to pain, temperature, and vibration. Spinal cord injuries produce unilateral or bilateral dysfunction and spastic, hyperreflexic limbs with varying degrees of hip, knee, and ankle flexor weakness, along with an extensor plantar response. Typically, with an ischemic cord lesion, there is an identifiable sensory level deficit to pain and temperature, with preservation of position and vibration sense.

On electromyography, a lumbosacral plexus neuropathy will manifest as unilateral loss of sensory potentials, reduced motor conduction, absent paraspinal denervation, and the presence of denervation changes in muscles innervated by multiple nerves and roots. In spinal cord injuries, nerve conduction studies are normal, and there are no denervation changes.

Treatment and Prognosis

Overall, there is some evidence to suggest that lumbosacral plexus injury has a better prognosis than spinal cord injury, but definitive studies are lacking.[59] If the etiology can be determined, intervention may result in regaining nerve function. In the case of compression from hematoma or aneurysm, relief of the compression in the early stages of nerve dysfunction may improve the long-term outcome.[67-69] For nerves with ischemic injury, the likelihood of restoring nerve function with correction of the ischemia is less likely.

FEMORAL NERVE INJURY

Anatomy

The femoral nerve receives nerve fibers from L2 to L4, and it courses along the anterior surface or within the fibers of the psoas major muscle, passes deep to the inguinal ligament, and enters the femoral triangle immediately lateral to the common femoral artery. After exiting the femoral triangle, it forms multiple muscular branches to the muscles of the thigh and then continues to form its terminal branch, the saphenous nerve, which courses along the saphenous vein to the foot (Fig. 45.4). The main trunk of the femoral nerve receives its blood supply from the iliac branch of the iliolumbar artery, from the deep circumflex iliac artery, and from the lateral circumflex femoral artery in the femoral triangle.[4] This redundant blood supply provides protection against ischemic injury.

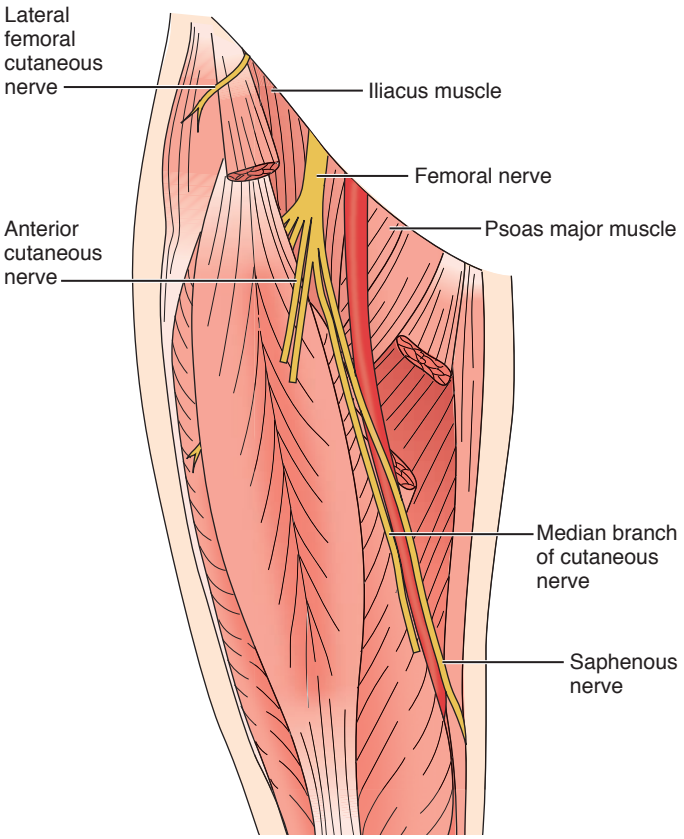

Figure 45.4 Anatomy of the femoral nerve.

BOX 45.4 Avoiding Femoral Nerve Injury

Traction: self-retaining retractors during pelvic surgery
Dissection: care in reoperative groin surgery
- Compression: postoperative and postcatheterization hematoma

Etiology

Femoral nerve injury is most commonly the result of traction injury, direct surgical trauma, electrocautery injury, compression injury, or ischemia (Box 45.4).

Traction

Most reported series suggest retraction injury to be the principal culprit, commonly from the use of self-retaining retractors placed to facilitate pelvic surgery. These injuries have been reported after urologic,[70] gynecologic,[71] colorectal,[72] laparoscopic,[73] orthopedic,[74] hernia,[75] spine,[76] and vascular[77] surgical procedures.

Surgical Trauma

The true incidence of iatrogenic femoral neuropathy remains unknown; most reports are retrospective and may not capture transient postoperative symptoms. Anecdotally, patients who undergo reoperative groin surgery may be at higher risk for postoperative femoral neuropathy, but conclusive evidence in the literature is lacking.[78] Electrocautery may be a factor in some cases; however, the impact of type of incision (vertical vs. oblique) on the development of a femoral neuropathy awaits further study.[79,80]

Compression

The presence of groin hematoma or retroperitoneal hematoma has been reported as a cause of femoral neuropathy.[40,81-83] Femoral neuropathy has been described following cardiac catheterization procedures using common femoral artery access in association with groin hematoma or false aneurysm at the access site.[84] Similarly, femoral neuropathy has also been associated with profunda femoris pseudoaneurysms compressing the adjacent femoral nerve following common femoral artery access.[85]

Ischemia

The true incidence of femoral neuropathy secondary to ischemia is unknown; it is presumably exceedingly low as the literature contains only case reports of femoral neuropathy caused by large-vessel occlusive disease.[86,87] Femoral neuropathy and lower extremity IMN have been reported with the use of intra-aortic balloon pump therapy.[48,88-90] It is unclear whether this is from prolonged presence of the large intra-arterial delivery system causing reduced flow, from thrombosis in the branch arteries that supply the femoral nerve, or from ischemic complications such as aortoiliac dissection and iliofemoral thrombosis.[89,91,92]

Clinical Findings

Femoral nerve injuries are manifested in the postoperative period as paresis or flaccid paralysis of the quadriceps muscle, diminished or absent extension of the knee, and reduced or absent patellar reflex. Loss of sensation is present along the course of the saphenous nerve, over the anteromedial aspect of the thigh and the inner aspect of the calf down to the medial malleolus. The discrete location of the signs and symptoms of femoral neuropathy are in contradistinction to a lumbosacral plexus lesion, which involves multiple peripheral nerves. The femoral nerve forms a medial cutaneous and an anterior cutaneous branch that produce isolated sensory symptoms when injury spares the motor branches.[93,94] The lateral cutaneous nerve of the thigh originates from the lumbosacral plexus directly and not from the femoral nerve and is more commonly injured during orthopedic pelvic surgery than vascular exposures.

Treatment and Prognosis

Additional testing consisting of motor and sensory nerve conduction studies and needle electrode examination is not usually necessary because the diagnosis can be made based on the history and physical examination. Fortunately, most femoral neuropathies from iatrogenic injury have an excellent prognosis. Treatment is conservative, and gradual return of nerve function is common.

SAPHENOUS NERVE AND SURAL NERVE INJURY

Anatomy

The terminal branch of the femoral nerve is the saphenous nerve. In the thigh, this nerve courses in the sub-fascial plane and accompanies the superficial femoral artery. In the proximal popliteal fossa, the saphenous nerve becomes more superficial as it penetrates the fascia and accompanies the great saphenous vein along the medial aspect of the extremity to the level of the ankle. The sural nerve arises from the tibial nerve in the popliteal fossa below the fascia, and descends laterally to the short saphenous vein in the groove between the medial and lateral heads of gastrocnemius muscle. A communicating branch from the peroneal nerve joins the sural nerve in the mid-calf, and there the nerve exits the fascia and courses down toward the lateral malleolus.

Etiology

The saphenous and sural nerves are closely associated with the great and short saphenous veins, respectively, in the lower leg and can be injured during vein harvest or venous extirpation with stripping and ablative procedures (Box 45.5).

Surgical Trauma

The saphenous nerve is prone to injury during harvesting and stripping of the great saphenous vein, especially below the knee. Over 60% of patients report some degree of sensory loss associated with great saphenous vein harvest incisions below the knee during lower extremity arterial reconstructions.[78] The rate of nerve injury was found to be 12.5% following endoscopic great

BOX 45.5 Avoiding Saphenous Nerve Injury

- Dissection: saphenous vein harvest, especially below the knee
- Thermal: endovenous ablation

saphenous vein harvest for coronary artery bypass grafting.[95] After great saphenous vein stripping, saphenous nerve injury was reported at rates from 27% to 40% based on subjective patient reports,[96-98] but with neurologic testing, the rate was found to be higher (58%).[97]

The sural nerve lies close and lateral to the short saphenous vein throughout its length and is at risk during harvest or stripping of the short saphenous vein, as well as dissection of the saphenopopliteal junction.[91,92] The occurrence of sural nerve injury with short saphenous vein surgery is thought to be lower than saphenous nerve injury following great saphenous vein harvest, although large series are lacking.[99]

Thermal Injury

The saphenous nerve is also prone to thermal injury during endovenous vein ablation, either with laser or with radiofrequency energy.[100] Some series have reported decreased incidence of saphenous nerve injury and duration of paresthesias with laser treatment compared to radiofrequency.[101,102] Ablation of the short saphenous vein may cause sural nerve injury in up to 4% of patients,[103] and nerve injury from ablation procedures can be mitigated with liberal use of circumferential tumescent anesthesia.[104]

Clinical Findings

Injuries to the saphenous nerve are uniformly manifested as sensory deficits (decreased sensation, paresthesias, and dysesthesias, in decreasing order of frequency)[105] in the anteromedial aspect of the calf to the level of the ankle.[78,95,97,98,105] Sural nerve injury presents with dysesthesias in the posterior calf or lateral ankle,[99] and there are no motor deficits associated with saphenous or sural nerve injury.

Treatment and Prognosis

Treatment of saphenous nerve injury is conservative, and the majority of patients report eventual resolution of symptoms[78,95,97,98,105] with infrequent reports (2.3%) of a negative impact on quality of life.[97] Rarely, patients with sural nerve injury may develop an unbearable chronic pain syndrome.[100]

TIBIAL AND PERONEAL NERVE INJURY

Anatomy

The sciatic nerve divides in the posterior portion of the midthigh into the common peroneal nerve and posterior tibial, or tibial nerve. The common peroneal nerve maintains a lateral course before dividing into superficial and deep branches. The tibial nerve accompanies the popliteal artery through the popliteal fossa and then continues distally within the posterior tibial neurovascular bundle (Fig. 45.5). The common peroneal nerve takes a lateral course from the posterior aspect of the midthigh, crosses the knee joint posterior to the fibular head, and wraps around the proximal fibula before dividing into the superficial and deep peroneal nerves. The superficial peroneal nerve runs deep to the fascia in the lateral compartment and extends to the foot unaccompanied by any major artery. In contrast, the deep peroneal nerve extends from its origin to enter the anterior compartment, where it descends along the intermuscular septum and accompanies the anterior tibial vessels to the foot. The tibial nerve continues its posterior course through the popliteal fossa adjacent to the popliteal artery before coursing through the deep posterior compartment and terminating in the medial and lateral plantar nerves that parallel the course of the posterior tibial artery and its branches.

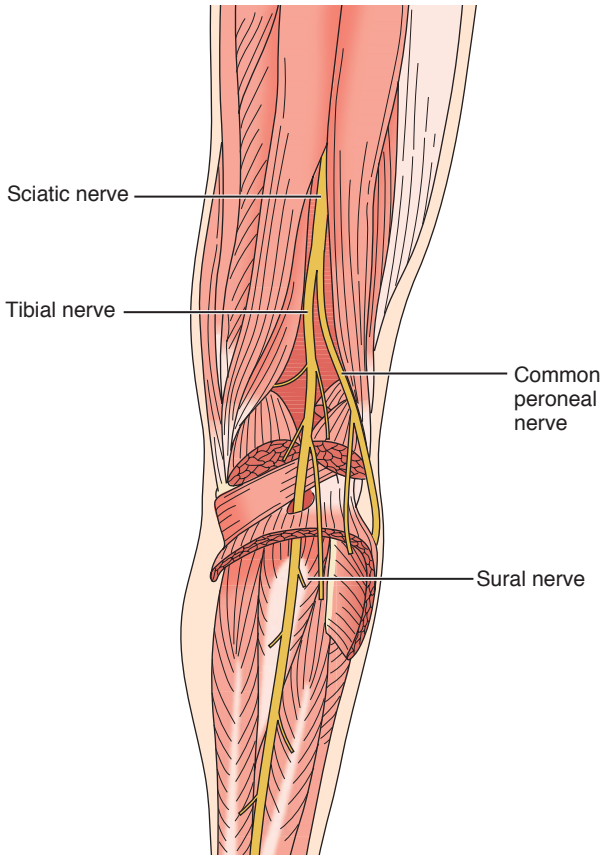

Figure 45.5 Anatomy of the sciatic, tibial, sural, and peroneal nerves.

Etiology

These nerves are vulnerable to iatrogenic injury due to proximity to the popliteal and tibial vessels and can be affected by episodic ischemia and high compartment pressure (Box 45.6).

Peroneal nerve injury is reported following surgical removal of the short saphenous vein (4.7%) and may be associated with

BOX 45.6 Avoiding Lower Leg Nerve Injury

- Dissection: popliteal/tibial exposure, lesser saphenous vein surgery
- Thermal: endovenous ablation lesser saphenous vein
- Compartment syndrome: prompt diagnosis and treatment

a saphenopopliteal junction located abnormally high above the popliteal skin crease.[106] Tibial and peroneal nerve injury complications have been reported in up to 20% of cases associated with short saphenous venous ablation techniques.[107] In a review by Drees et al.,[108] trauma and ischemia were the two most common causes of tibial neuropathy. Additionally, the deep peroneal nerve in the anterior compartment and the tibial nerve in the deep posterior compartment are at risk for injury from compartment syndrome in the leg, which is discussed in detail in Chapter 102.

Clinical Findings

Posterior tibial nerve injury causes weakness of plantar flexion of the ankle and toes with an absent ankle jerk and sensory loss on the sole and lateral aspect of the foot. Peroneal nerve injury is manifested as weakness of dorsiflexion, inversion, and eversion of the ankle, and weakness of dorsiflexion of the toes. These motor deficits are accompanied by loss of sensation in the dorsal aspect of the foot and toes with variable extension to the lateral aspect of the calf. Occasionally, these symptoms can be due to L5 or S1 nerve root compression; this can be differentiated by nerve condition studies and electromyography.

Treatment and Prognosis

The neurologic dysfunction associated with acute compartment syndrome can recover quickly with prompt decompression. Delayed decompression results in a greater degree of muscle damage and nerve injury and a poor prognosis for recovery. Ischemic peroneal and tibial neuropathies can only be managed expectantly, and accordingly, the prognosis for recovery is poor. Peroneal pressure palsies carry a good prognosis for recovery with conservative treatment. Traumatic injury to the peroneal and tibial nerves warrants surgical exploration if functional nerve loss is complete or if compression is suspected. Significant improvement in motor function and pain can be expected after operative repair of tibial and peroneal nerve injuries.

OTHER NERVES

Cranial nerve injury related to carotid artery surgery is described in detail in Chapter 91, and the autonomic nerves of the retroperitoneum and pelvis that are relevant to aortic surgery are discussed in Chapter 71 and Chapter 54.

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A complete reference list can be found online at www.expertconsult.com.

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46 CHAPTER

Graft Thrombosis

BJOERN D. SUCKOW and DAVID H. STONE

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Postoperative graft thrombosis remains a significant clinical challenge in contemporary vascular surgical practice. Whether early or delayed, graft thrombosis continues to account for significant morbidity, limb loss, and mortality in patients requiring vascular intervention. Specifically, at 1 year after infrageniculate bypass graft failure, more than 50% of patients will have undergone major amputations.[1,2] Among the remaining patients, ischemic pain at rest or ulceration will have developed in 25%, and more than 15% will have died. Accordingly, underlying risk factors associated with graft failure continue to be the focus of vascular surgical outcomes analyses and regional quality improvement groups alike.[3-5]

The causes of graft thrombosis are multifactorial and involve patient demographics, risk factors, natural history, and comorbid conditions, as well as technical issues associated with arterial reconstruction. Such risk factors and technical aspects of reconstruction have an impact on graft patency (Table 46.1) from the initial operation through the entire follow-up period. With this in mind, technical precision at initial reconstruction is imperative to achieve an optimal outcome because technical errors account for 4% to 25% of early failure after revascularization.[6-8] Furthermore, optimal long-term graft durability remains, in part, predicated on lifetime surveillance, timely re-interventions, and vigilant risk factor modification.[9-12] To facilitate intraoperative assessment of the technical adequacy of the reconstruction at the time of surgery, numerous diagnostic tools are available to the surgeon, which we review. Thereafter, the discussion focuses primarily on surgical revascularization, including autogenous and prosthetic conduits and factors associated with their failure. Understanding the etiology and clinical manifestations of graft thrombosis and current experience with available treatment options is crucial for achieving the best and most durable results after initial failure of revascularization.

PREVENTION: INTRAOPERATIVE GRAFT ASSESSMENT

To ensure optimal patency after revascularization, it is imperative that the surgeon determine the technical adequacy of the reconstruction before leaving the operating room.

Inspection, Palpation, and Measurement of Flow

The most convenient and readily available methods for graft assessment include inspection and palpation of pulses. These processes involve not only inspection of the graft itself for kinks, twists, and stenoses, but also examination of the distal target vessel and of the revascularized tissue, if possible. Is the foot

Abstract

Postoperative graft thrombosis remains a significant clinical challenge. Etiologies are often multifactorial and include patient demographics, natural history, comorbidity conditions, and technical issues associated with arterial reconstruction. We review intraoperative modalities that aid in the assessment of the technical adequacy of an arterial revascularization. Further, we discuss the assessment and therapeutic approaches of grafts that fail in the early (<30 days) and late (>30 days) period following bypass grafting.

Keywords

Graft thrombosis
graft failure
intraoperative graft assessment
graft imaging modalities
thrombolytic therapy

TABLE 46.1 Definitions of Graft Patency

Term	Definition
Primary patency	The bypass graft remains patent without any subsequent intervention.
Primary assisted patency	The bypass graft undergoes a pre-emptive intervention to maintain patency, such as endovascular balloon angioplasty or anastomotic revision; however, the graft has never thrombosed.
Secondary patency	The bypass graft has thrombosed and is patent again following lysis and/or thrombectomy. A concomitant endovascular intervention and/or open revision may also have been performed to aid with subsequent patency.

pink and perfused? Has capillary refill time been shortened? Is a pulse now palpable in the foot?

The process is facilitated by having the target organ, as much as possible, included in the sterile field and available to the surgeon for intraoperative examination. For example, for aortobifemoral or more distal bypasses, covering the sterilely prepared feet with clear plastic bags permits rapid examination after completion of the bypass. However, inspection and palpation are subjective and thus susceptible to observer bias. After a complex reconstruction, the surgeon's expectations may cloud the evaluation of capillary refill time in the feet. Calcified arteries, secondary to long-standing diabetes, may not adequately transmit an improved pulse. The effects of anesthesia combined with concomitant chronic occlusion of runoff arteries may delay the appearance of adequate lower extremity reperfusion. More importantly, false-negative results can occur when a graft has a strong pulse, often called a "Water Hammer Pulse," because of distal outflow obstruction.

Measurement of arterial flow may be significantly affected by anesthesia. Furthermore, small, seemingly hemodynamically insignificant defects in the graft may also result in failure. Low-flow measurements may accurately predict graft failure, but this finding alone does not localize the specific defect. Studies using an ultrasound flowmeter have confirmed the inability of graft flow as an isolated parameter to predict future graft function.[13] Measurement of flow by ultrasonically measured transit times has been reported to be sensitive and specific for graft defects.[14] Performance of these studies is cumbersome, however, and requires additional adjunctive measures to both localize and identify specific graft defects. In our practice, we prefer the use of duplex ultrasound, as explained here, because this modality can assess graft flow and at the same time help visualize areas of graft defect. Therefore ultrasound flowmeters are used less frequently and usually more as perfunctory diagnostic adjuncts.

Arteriography

Since its introduction, intraoperative completion arteriography has been the "gold standard" for anatomic evaluation of the technical adequacy of arterial reconstructions. One appealing feature of arteriography is its ability to assess anatomic arterial outflow—the "runoff." This is particularly important in the clinical context of preoperative studies that fail to reveal adequate target vessels in diffusely diseased vascular systems. Although completion arteriography is an invasive procedure associated with potential complications because of arterial puncture (intimal injury, dissection), injection (air embolism), use of radiographic contrast agents (renal failure, anaphylaxis), and radiation exposure, the actual observed complication rate has been negligible in large series.[15,16]

The technique varies according to individual application but generally involves insertion of an 18- to 20-gauge plastic angiocatheter or 4- to 5-Fr sheath into the arterial graft to allow subsequent injection of 10 to 30 mL of radiographic contrast agent. Temporary occlusion of arterial inflow maximizes the concentration of contrast agent without the need for excessively rapid injection. Digital subtraction angiography, rather than simple fluoroscopy with concomitant contrast injection, will then provide clearer images and allow for visualization of vessel patency and runoff (Fig. 46.1).

Several weaknesses are inherent in the technique of completion arteriography, however. In lower extremity bypass grafts, the proximal anastomosis is frequently not evaluated, which may obviate detection of a proximal technical defect. Air bubbles or overlying structures may lead to false-positive interpretations. A potential source of false-negative results is the use of a single plane of view to analyze a multidimensional target; this method can result in underestimation of the stenosis from a small defect, such as an intimal flap or platelet aggregate.[17]

Ultrasonography

The development of ultrasound technology has provided multiple noninvasive modalities for the intraoperative and subsequent longitudinal assessment of arterial reconstructions.

Continuous-Wave Doppler

The simple and inexpensive continuous-wave Doppler 8- to 10-MHz pencil probe is nowadays readily available for intraoperative use. Its small size allows insonation of arteries in areas less accessible to larger probes. It is frequently used to assess flow in the target or outflow vessel(s). Further, the probe can be passed along the graft and anastomoses, where localized increases in the audible sound frequency or audible turbulence could indicate a potential defect. Patent residual vein branches of in-situ saphenous vein bypasses can be readily identified by locally increased frequency, continuous flow, and flow outside the graft boundary. Successively compressing the graft from the proximal to the distal end while listening for residual proximal flow with a Doppler device can also localize these arteriovenous fistulae.

Use of the audible continuous-wave Doppler technique is subjective and operator dependent. Considerable experience is required for maximum accuracy. The presence of high-frequency sound waves within the graft or at the distal anastomosis is worrisome. However, some investigators have shown that the

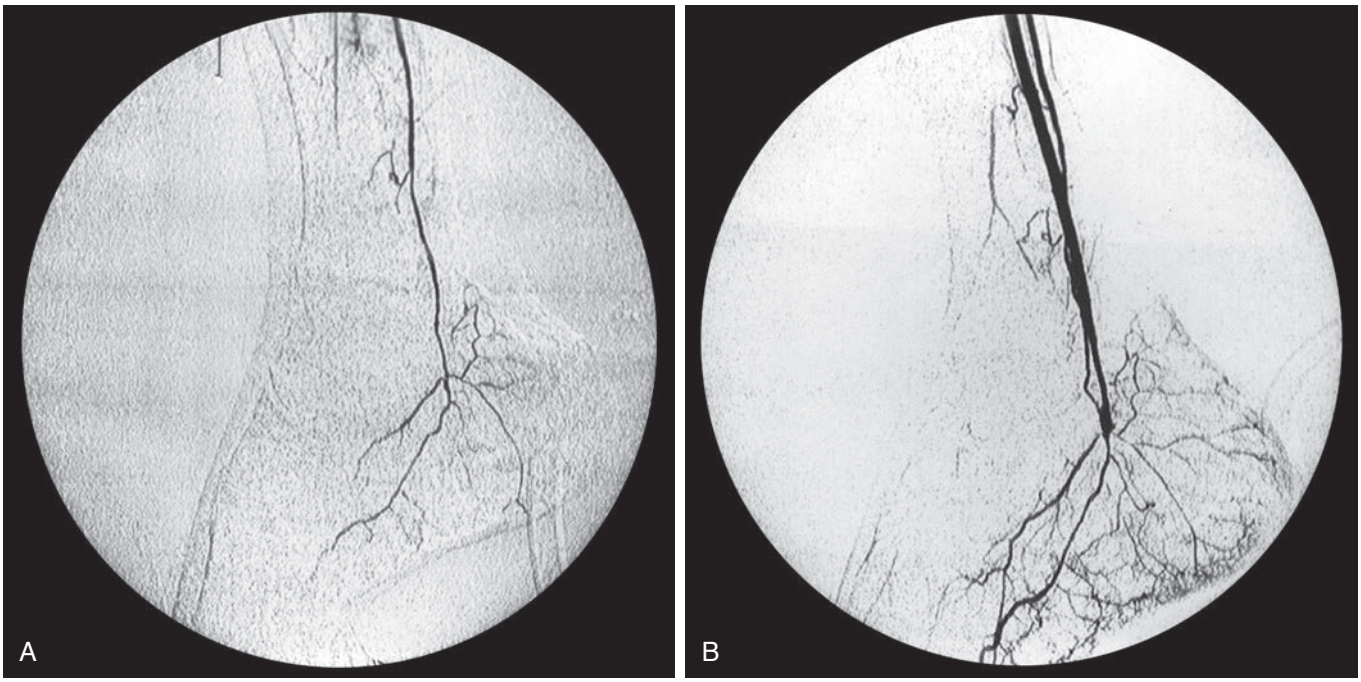

Figure 46.1 Intraoperative digital subtraction angiographic images of the plantar circulation performed (A) before and (B) after bypass.

continuous-wave Doppler device is not highly sensitive.[18] Most vascular surgeons use this modality as an easy, available, and inexpensive screening device to guide their use of a more precise evaluation technique.

B-Mode Ultrasonography

B-mode ultrasonography has been used intraoperatively to obtain anatomic images noninvasively, although it is more commonly used in conjunction with duplex ultrasonography. Initial experimental studies established that its ability to detect small defects in patients was comparable to that of arteriography.[19] In an evaluation of arterial defects created in dogs, both arteriography and B-mode ultrasonography were nearly 100% specific in excluding arterial defects. However, ultrasonography has significantly greater sensitivity in detecting defects, 92% overall, than serial biplanar arteriography at 70% and portable arteriography at 50%. These techniques have comparable accuracy in detecting stenoses.

B-mode ultrasonography has utility in assessing lower extremity arterial reconstructions. Kresowik et al.[20] reported that in 106 patients, intraoperative B-mode ultrasonography detected defects in 20% of patients, and that half of these defects were deemed important enough to warrant correction. In follow-up, there were no early graft occlusions in the B-mode group, and no residual defects were discovered with duplex scanning follow-up in the postoperative period.

Intraoperative use of B-mode ultrasonography, however, is not without its problems.[21] Because this modality does not evaluate blood flow, it cannot differentiate fresh thrombus from flowing blood, which has the same echogenicity. Compared with Doppler pencil probes, B-mode ultrasound probes are larger and cannot be sterilized, requiring a sterile covering containing a gel to maintain an appropriate acoustic interface. Significant operator experience is needed to obtain optimal images and make accurate interpretations.

Duplex Ultrasonography

With the addition of flow-measuring capability to B-mode ultrasonography, duplex scanning brings a more powerful tool to the operating room. Like B-mode ultrasound probes, duplex scanning probes are large, cannot be sterilized, and require considerable operator skill so that accurate velocity and imaging data can be obtained. Duplex color-flow technology provides continuous Doppler signals along the graft and artery at multiple points. Color imaging facilitates identification of areas of higher velocity, albeit at a significant increase in equipment cost.[22]

Duplex scanning provides an easier mechanism for identifying defects in proximal arterial anastomoses than arteriography does, because contrast-enhanced imaging of the proximal anastomosis from a more distally placed catheter is cumbersome and often difficult, and one would rather avoid an arterial puncture in the native inflow vessel due to potential later stenosis development or other complications at this site.[23] In addition, duplex scanning can identify low graft velocities that are undetectable by arteriography. Intraoperative experience with this imaging modality has shown greater sensitivity for detecting technical defects. Early results with intraoperative duplex scanning have demonstrated an association between these defects and suboptimal results in the postoperative period.[24,25] It is noteworthy that duplex scanning is unable to assess newly placed polytetrafluoroethylene (PTFE) and polyester (Dacron, Hemashield) grafts, because the graft walls contain air, which prevents penetration of the ultrasound waves.

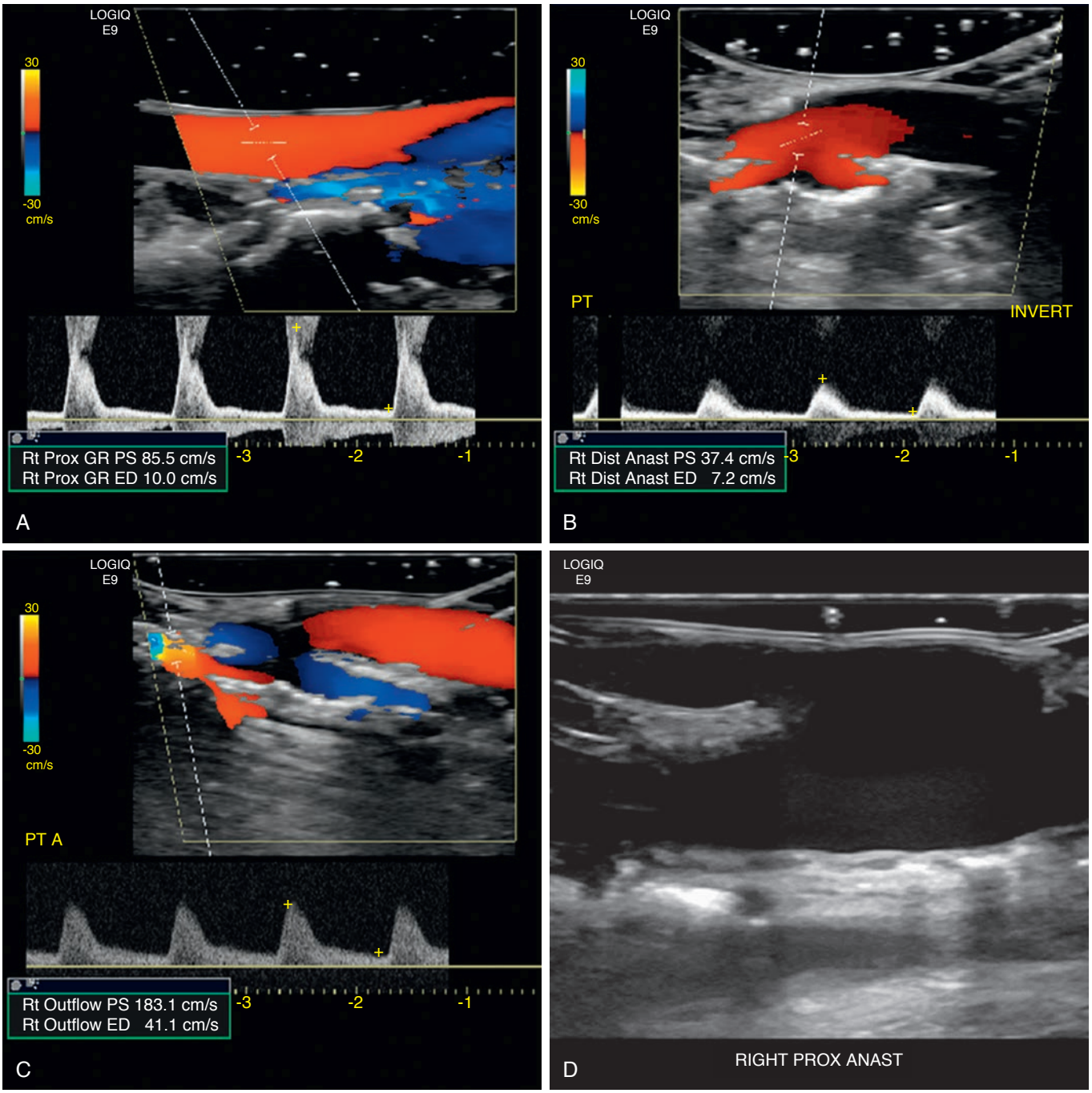

Figure 46.2 Intraoperative completion duplex ultrasound after a femoral to below-knee popliteal artery bypass graft with vein conduit. (A) The proximal part of the graft shows good diastolic flow as indicated by an end-diastolic (ED) velocity of 10 cm/s. (B) Patent distal anastomosis without stenosis as indicated by peak systolic (PS) velocity of 37.4 cm/s. (C) Antegrade blood flow in the native outflow artery with good diastolic flow as indicated by ED velocity of 41.4 cm/s. (D) No dissection flap, stenosis, or technical complication at the proximal anastomosis as seen on B-mode ultrasound.

A study by Rzucidlo et al.[26] reported intraoperative completion duplex scanning to be a useful tool after the completion of infrageniculate arterial reconstruction. Specifically, the authors documented that a 10-MHz, low-profile transducer could be used successfully to identify compromised grafts with a predilection for early failure. Moreover, it was determined that low end-diastolic velocity (EDV) was both associated with and predictive of early graft failure. Further, Scali et al.[27] validated the utility of intraoperative completion duplex scanning following distal bypass, documenting that EDV measurements less than 5 cm/s predicted early graft failure (Fig. 46.2).

Angioscopy

Intraoperative angioscopy has become an attractive technique for evaluation of arterial reconstructions and thorough interrogation

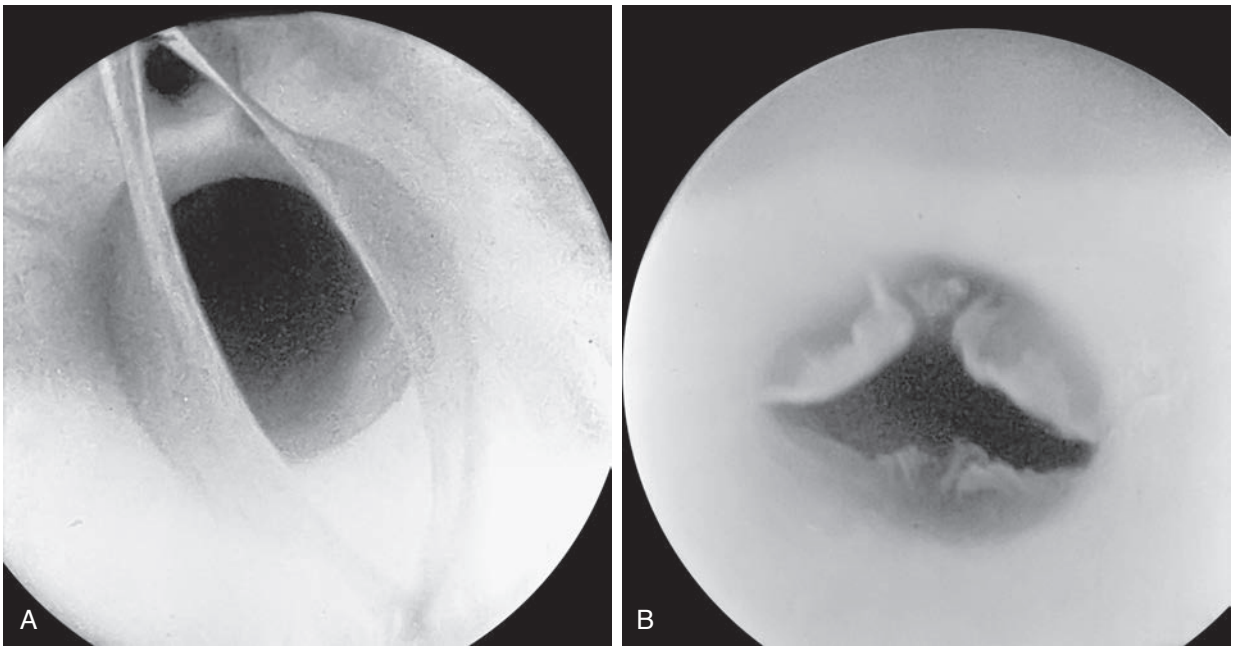

Figure 46.3 (A) Photograph of a valve via an angioscope before lysis. (B) Photograph of an angioscopic image of a valve after lysis. (B, From McCaughan JJ Jr, Walsh DB, Edgcomb LP, et al. In vitro observations of greater saphenous vein valves during pulsatile and nonpulsatile flow and following lysis. *J Vasc Surg*. 1984;1:356.)

of autogenous conduit. Angioscopy requires irrigation with saline accompanied by occlusion of inflow, and sometimes outflow, to provide a visually clear image. Many scopes have a separate lumen incorporated for irrigation or suctioning. The use of a specifically designed infusion pump with high- and low-flow rates has greatly facilitated angioscopy techniques.[28] As with duplex ultrasonography, experience is required to manipulate both the angioscope and the visual target to obtain adequate visualization.

Angioscopy has been most widely used for inspection of in-situ saphenous vein grafts to ensure complete valve lysis,[29] to exclude unligated venous branches, and to assess the quality of the venous conduit (Fig. 46.3). At our institution, vein graft valves are commonly lysed under direct visualization with the valvulotome and scope inserted at opposing ends of the conduit and following the valvulotome with the scope while the vein is irrigated and pressurized with heparinized saline. Angioscopy appears to be particularly important in detecting abnormalities within an arm vein conduit that may not be evident by external visual inspection, including important evaluations of venovenostomy anastomoses.[30-32]

It should be noted that experimental studies have documented that mild intimal injury may occur with angioscopy. However, such injury occurs only after multiple repeated passages of larger diameter scopes.[33] The long-term effects of this mild trauma have not been firmly established, but a few passes of a small-diameter (1.4 mm) angioscope in human vein grafts appear to have no significant late clinical consequences. Several studies have revealed that infusion of irrigation solution can be limited to 500 mL or less in most instances, an amount that has not been associated with complications, especially when planned as a part of the overall fluid administration during the procedure.[28,34] In a 2002 study from Lund, Sweden, the authors documented successful application of intraoperative angioscopy in a group of patients who underwent below-knee in-situ saphenous vein graft bypass; they demonstrated its utility in this setting and concluded that angioscopy has an impact on primary graft patency rates and therefore reduces the need for subsequent reintervention. Specifically, this adjunct was useful in identifying persistent saphenous vein branches, incomplete valve destruction, and partially occlusive intraluminal thrombus.[35]

Intravascular Ultrasonography

More frequently in contemporary practice, intravascular ultrasound (IVUS) has become a useful intraoperative imaging adjunct. This technology is based on a flexible catheter system and generates two-dimensional cross-sectional images through the circumferential rotation of a miniaturized (10 to 30 MHz) ultrasound crystal at the catheter tip. In experimental studies, IVUS has proved to be accurate in measuring luminal diameter and identifying stenoses caused by atherosclerosis or intimal hyperplasia.[36-38] This technology has significant appeal as an imaging modality in the setting of complex aortic procedures, in particular for acute aortic dissection.[39-41] Both IVUS and angioscopy were found to be 100% accurate in detecting 2-mm intimal flaps in canine femoral arteries, compared with only 60% accuracy for single-plane arteriography.[42]

Few clinical studies assessing the role of IVUS have established its efficacy and potential role in evaluating the technical adequacy of vascular surgical reconstructions. However, its utility appears

to be growing. Although IVUS appears to be useful in the evaluation of lesions appropriate for placement of devices such as bare-metal stents and stent-grafts,[43] it is unclear whether IVUS will provide information that is different and useful enough to justify its current cost in comparison to alternative intraoperative techniques. Nevertheless, this real-time, radiation-free, contrast-free dynamic imaging modality offers significant appeal.

Miscellaneous Modalities

Some indirect intraoperative methods can measure resistance within the graft or within the outflow bed, which may help evaluate the adequacy of revascularization. This is most easily accomplished with a continuous-wave Doppler probe placed over an outflow artery while the examiner listens for audible augmentation of the waveform after release of a temporary graft occlusion. This modality, however, provides little objective measure of the adequacy of reconstruction.

A more quantitative assessment can be obtained by measuring distal extremity pressure with a sterile blood pressure cuff during surgery. In patients with more proximal reconstructions and residual outflow abnormalities, ankle pressure may not be maximal immediately after revascularization, but rather may increase only gradually in the postoperative period. Thus this intraoperative pressure measurement does not provide absolute proof of the success of reconstruction, and therefore must be interpreted on the basis of the preoperative anatomy of each patient. Other similar modalities, including pulse volume recording (plethysmography), photoplethysmography, and even transcutaneous oxygen tension measurement, can be used intraoperatively as clinical adjuncts to evaluate the restoration of distal blood flow. In each, the surgeon should assess for a significant difference in magnitude with and without graft occlusion.

GRAFT THROMBOSIS: PATHOGENESIS

Despite meticulous attention to preoperative planning and to technical perfection in the operating room, revascularizations may be unsuccessful. Depending on the type of arterial reconstruction, between 0.3% and 10% fail in the early postoperative period, regardless of attempts by numerous groups to identify and abrogate factors associated with graft failure.[1,4,44] Early graft thrombosis has significant prognostic implications, in that a failed reconstruction is associated with poor clinical outcomes, particularly when performed for limb salvage indications.[45-47] Several studies have identified a variety of factors potentially contributing to graft failure, including patient demographics, risk factors, comorbid diseases, conduit characteristics, anesthesia type, adjuvant medical therapy, and technical precision.[4,48-52] A study from the Washington Hospital Center and Georgetown University Medical Center prospectively collected and analyzed the National Surgical Quality Improvement Program (NSQIP) database from 1995 to 2003 in an attempt to elucidate risk factors predictive of graft failure in patients who underwent infrainguinal arterial bypass. Multivariate logistic regression revealed that younger age (<60 years), African American race, and crural target vessel were associated with graft failure.[4] Furthermore, other modifiable factors predictive of graft failure have been identified and should be incorporated into treatment paradigms. Giswold et al.[1] documented that dialysis dependency, a known hypercoagulable state, ongoing smoking, and failure to undergo routine graft duplex surveillance were all independently associated with reversed vein graft occlusion. Further, Oresanya et al. added that a small vein graft diameter (<3 mm) and the nonadherence to ultrasound surveillance are independently associated with graft failure.[53] In addition, Nolan et al. indicate that bypass grafts performed in limbs where a previous endovascular intervention was performed have a significantly higher failure rate than grafts performed in limbs without a prior endovascular intervention (28% occlusion rate versus 18% occlusion rate).[54]

The role of hypercoagulability as a cause of graft failure has become increasingly recognized in contemporary practice. As the population ages, it has been hypothesized that the number of arterial reconstructions will increase.[1,45,55] This, coupled with the introduction and evolution of myriad percutaneous technologies, will lead to an increasing number of interventions that a typical patient will undergo, thereby compounding the impact of hypercoagulability in light of the inherent multiple previous exposures to heparin.[56-58]

Long-term follow-up has demonstrated that nearly 50% of vascular reconstructions are subject to some degree of restenosis or eventual occlusion,[44,59] and thus has confirmed the efficacy of aggressive graft surveillance and subsequent endovascular or conventional surgical revision in an attempt to identify and prospectively repair deteriorating grafts and prevent graft occlusion.[47,59-62]

When thrombosis does occur, therapeutic alternatives range from expectant supportive care to thrombectomy, thrombolysis, or placement of an entirely new arterial reconstruction. Optimal results in these most difficult circumstances require rapid decisions by the surgeon regarding the etiology of the graft failure and/or thrombosis, selection of either surgical or endovascular repair, timing of re-intervention, and assessment and modification of complex patient risk factors. This discussion summarizes therapeutic guidelines for the most frequently encountered scenarios after thrombosis of an arterial reconstruction.[63]

GRAFT THROMBOSIS: THERAPEUTIC APPROACH

Documentation of Graft Thrombosis

It is incumbent on the clinician to document graft thrombosis in a timely fashion. It may be as easy as noting the absence of a previously palpable pulse combined with dramatic progression or return of the patient's ischemic symptoms. In less obvious circumstances, noninvasive testing to measure the ankle-brachial index and the use of duplex ultrasonography to determine

patency and the location of the occlusion or restenosis may obviate the need for administration of contrast material. This is particularly germane in light of the fact that the patient will probably require further contrast as part of the definitive revision and/or reconstruction.

Assessment of Neurologic Status

A primary determinant of the necessity for and urgency of aggressive intervention is the patient's neurologic status at initial evaluation. As the level of neurologic dysfunction increases from dysesthesia to paralysis, the impetus for rapid resolution of the situation grows. Consequently, the time available for lengthy diagnostic or therapeutic measures outside the operating room decreases correspondingly. Considerable clinical judgment is required in these cases because delay in treatment may precipitate irreversible tissue injury and culminate in untoward outcomes, including limb loss or death. A standardized approach to and reporting of the acutely ischemic limb was published by Rutherford et al. in 1997.[64] We feel that the Rutherford criteria of acute limb ischemia based on sensory function, motor function, and presence or absence of ankle Doppler signals continue to provide a good measure of the degree of acute ischemia. This approach will aid the clinician in determining the rapidity with which revascularization is necessary or perhaps even contraindicated. A nonviable limb, Rutherford category III, would preclude an attempt at revascularization, while a Rutherford category IIb limb should prompt urgent revascularization.

If there is no neurologic compromise and the degree of tissue ischemia appears minimal, such as in Rutherford category IIa or category I, diagnostic or alternative therapeutic maneuvers, including thrombolysis, can be contemplated (see Chapter 41). This is predicated on recognition of the delayed therapeutic efficacy associated with thrombolytic therapy. Nevertheless, adequate clinical outcomes with thrombolytic therapy can be anticipated when applied in select clinical circumstances.[65-67] However, it should be emphasized that secondary patency after treatment of infrainguinal graft thrombosis is generally poor. If the initial reconstruction was performed for ongoing tissue loss, and the ulcer or amputation has subsequently healed, urgent revascularization may not be required. Likewise, graft failure in the setting of recurrent claudication may not warrant urgent reintervention, particularly if a patient has extensive medical comorbidities.

Anticoagulation

Once the diagnosis of graft thrombosis has been confirmed, immediate anticoagulation becomes imperative to minimize or halt thrombus propagation. A short interval to permit blood collection for determination of hypercoagulability is permissible. If regional anesthesia is preferred for a surgical attempt at graft salvage, systemic anticoagulation can be delayed until anesthesia is achieved. If immediate surgery is not required or regional anesthesia is contraindicated, either systemic heparinization or anticoagulation with an alternative agent, when appropriate, should be instituted to inhibit ongoing thrombosis.

Etiologic Assessment

Several factors that may contribute to any graft failure should be investigated. If not previously established, the patient's coagulation status should be determined. As noted earlier, graft thrombosis at any time after placement can be the consequence of a previously unrecognized hypercoagulable state (see Chapter 38).[57,68-70] A blood specimen should be collected and sent immediately (before anticoagulation) for measurement of standard coagulation parameters, including platelet count, functional activated protein C resistance, anticardiolipin antibodies, antithrombin III, and protein S. Previous exposure to heparin, with consequent heparin-associated antibodies causing platelet aggregation, should be investigated and routinely considered in current practice scenarios because previous exposure to heparin is becoming more common, perhaps secondary to the advent and application of less invasive percutaneous interventions.[57,71] Failure to recognize this insidious condition can lead to poor clinical outcomes and recurrent graft thrombosis.[68,72] As the incidence of heparin-induced thrombocytopenia becomes more prevalent, so too will the untoward effects of administration of unfractionated and low-molecular-weight heparin.[72] Alternatively, less likely causes of hypercoagulable complications leading to thrombosis include increased blood viscosity from dehydration, polycythemia, or sepsis, which can easily be diagnosed by physical examination and routine hematologic screening. Moreover, a multivariate analysis from NSQIP implicated thrombocytosis as being independently associated with early graft failure, although this has not been widely studied in other analyses.[3] Acute or chronic cardiac decompensation is an uncommon but real cause of failure of arterial revascularization; these conditions can be rapidly detected at initial patient evaluation with electrocardiography or echocardiography, as indicated. Rapid cardiac assessment is also critical in assessing the risk associated with various possible therapeutic options.

The first element fundamental to achieving successful treatment of a failed revascularization is accurate determination of the cause of the thrombosis. As noted previously, the incidence of technical errors as a cause of early graft failure has significantly decreased over the last 40 years. Technical errors now account for 20% or less of thromboses in arterial reconstructions in the early postoperative period, despite the historical supposition to the contrary. Other probable causes include inherent thrombogenicity of the graft conduit, underappreciated or unrecognized patient-related hypercoagulable states, and poor target artery selection with disadvantaged runoff.

One analysis of roughly 2500 patients from the regional Vascular Study Group of New England, a regional quality improvement initiative revealed several predictors of both early and late graft occlusion. Specifically, both a below-knee target and a tarsal distal target were predictive of diminished graft patency, as was a secondary reconstruction or "redo" revascularization in the early postoperative period. Analysis also determined that diabetes, preoperative tissue loss, greater body mass index (>35 kg/m^2), and reconstructions requiring early revision (primary-assisted patency) were predictive of diminished

long-term graft patency.[73] Similarly, a review of high-risk bypass grafts performed for critical limb ischemia by Rzucidlo et al.[26] found the rate of graft failure within 12 months to be 44%. Noted risk factors included compromised distal arteries that previously required thrombectomy, single-vessel outflow, inability to pass a 1 mm dilator into the outflow vessel, or disadvantaged vein conduits, such as venovenostomy, vein patch angioplasty, or prosthetic interposition.

An alternative approach to better determine the etiology of an unsuccessful arterial revascularization is to examine each of the elements required for effective durable graft patency. The five elements critical for sustained function of an arterial reconstruction are *inflow*, *outflow*, *conduit*, *operative technique*, and *coagulation profile*.

For any revascularization to function, blood pressure, and blood flow at the origin of the reconstruction must be the same as the systemic parameters. Compromised inflow noted by a gradient between the proximal reconstruction and central systemic arterial pressure demonstrates the existence of a significant proximal arterial stenosis. If uncorrected, suboptimal clinical outcomes and graft durability can be expected.

The quality of outflow for a revascularization can be extremely difficult to characterize. For example, in the setting of lower extremity revascularization, only a few small vessels may constitute the outflow runoff, which at arteriography appears too sparse to support durable graft function (Fig. 46.4). Despite attempts to correlate the radiographic features depicted on angiograms with impending graft thrombosis or failure, no consistent angiographic criteria have been determined to be reliable predictors of graft patency. In the limb shown in Fig. 46.4, the runoff bed is based on the lateral plantar artery. Despite conventional wisdom suggesting short-lived patency, this graft has remained patent for more than 5 years. However, this case proves the exception rather than the norm, as several large-cohort reviews have identified poor runoff as an independent risk factor for graft thrombosis.

When considering both the timing and the etiology of failed arterial reconstructions, two temporal categories should be taken into account as they dictate initial approach: early (within 30 days of placement) and late (after 30 days) (Table 46.2). This discussion focuses primarily on outcomes of infrainguinal revascularization, which forms the largest cohort of failed revascularizations.

Early Graft Failure (0 to 30 Days)

Despite improvement in infrainguinal vein graft revascularization techniques, 5% to 10% of grafts fail within 30 days of placement.[44] The time elapsed from initial revascularization is the single most important characteristic aiding in determination of the cause of the graft failure (Fig. 46.5). Early (<30 days) thrombosis of vascular reconstructions has historically been attributed to technical error.[6] In a review of the Dartmouth-Hitchcock experience, it was found that technical errors accounted for roughly 25% of early graft failures.[7] Since that time, the number of graft failures referable to technical error

TABLE 46.2 Classification of Graft Failure by Time Interval With Associated Causes and Treatments

Time	Etiology	Treatment
Early/mid-term failure	Technical Graft thrombogenicity Low flow Poor runoff	Thrombectomy Thrombolysis Patch angioplasty
Late failure	Graft abnormality Metachronous disease	Thrombolysis PTA Patch angioplasty Interposition graft

PTA, Percutaneous transluminal angioplasty.

Figure 46.4 Intraoperative completion arteriogram demonstrating sparse runoff from a lateral plantar artery.

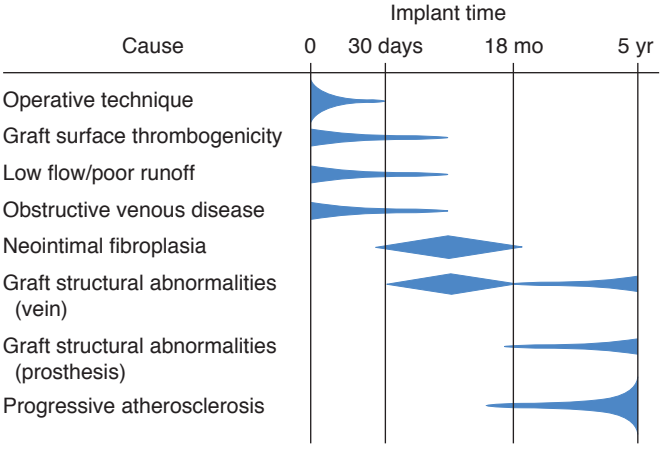

Figure 46.5 Factors Contributing to Graft Occlusion With Time. (Modified from Rutherford RB: The prevention and management of graft thrombosis. In Kempczinski RF, ed. *The Ischemic Leg*, Chicago, IL: Year Book Medical; 1985.)

has declined sharply (10%).[63] This improvement can be directly attributed to the routine use of angioscopy, duplex ultrasound scanning, and DSA to confirm the technical adequacy of the arterial reconstruction. Such confirmation also permits a prospective, qualitative determination of the likelihood that graft failure will occur, and a recognition that it is most likely related to the conduit or the quality of the runoff bed. In addition, thorough graft interrogation greatly simplifies further therapeutic clinical decision-making. For example, if a failed graft was constructed with the only available autogenous vein conduit to the only possible target runoff vessel, and it showed no evidence of an anastomotic or an intrinsic conduit problem at the time of placement, early amputation might represent the optimal strategy to achieve the best possible outcome. In other words, if such a patient undergoes further attempts at thrombectomy, revision of the anastomosis, replacement of the conduit, or substitution of the runoff, they are only likely to sustain increased morbidity, mortality, and expense, with little improvement in the chance for limb salvage.[45]

After diagnosis of a graft that failed early in the postoperative period, the surgeon must first determine whether to proceed with attempted salvage of the initial bypass graft. Commonly used options include either surgical thrombectomy or thrombolysis. The results of both techniques remain discouraging in the early postoperative time period, irrespective of the conduit used or the procedure performed. Furthermore, thrombolysis places the patient at significant bleeding risk, especially at recent surgical sites. A meta-analysis of three randomized studies and 14 review papers on thrombolysis for acute limb ischemia placed the risk of major hemorrhage associated with thrombolysis at nearly threefold higher than nonlytic therapy (OR 2.85).[74] A separate Cochrane review of thrombolysis for acute limb ischemia similarly identified a 200% increase in major bleeding risk.[75] The risk of major bleeding therefore could preclude a significant patient subset with graft thrombosis from undergoing thrombolysis.

After thrombolysis is attempted in the early postoperative period, the extended patency of thrombosed vein grafts ranges between 15% and 20% at 1 year.[67,76,77] In one series, 3% of patients died, 14% experienced bleeding complications requiring transfusion, and 13% developed thromboembolic complications. Despite these associated complications, 75% of the treated limbs had been salvaged at 1 year. Results with thrombolysis of prosthetic grafts are slightly better, although this difference is probably related to the better runoff than usually exists when prosthetic graft material is used as the conduit for the initial bypass procedure.[78] Vein graft longevity after thrombolytic intervention has been documented to correlate with the time interval since the vein graft was placed.[79] Specifically, a shorter interval to graft failure will have a diminished likelihood for success with thrombolytic therapy, particularly in patients with diabetes. Review of the Dartmouth experience found that no patient with diabetes and a recently placed graft achieved reasonable secondary graft patency with thrombolysis.[77] Of patients treated successfully with lytic therapy, 44% ultimately required early amputation, whereas in patients in whom thrombolysis failed, the amputation rate approached 69%.

Like lytic therapy, the results of surgical thrombectomy for early graft failure are also relatively disappointing, even with an adjunctive procedure such as patch angioplasty of the responsible lesion or lesions. Among 36 vein bypasses in which patency was reestablished within 1 month after surgery via mechanical thrombectomy, graft stenosis was noted in as many as 39% of arterial reconstructions. Such stenosis is possibly due to rapid degeneration of normal cellular function in the thrombosed vein wall.[80] Late bypass revisions, performed in 35% of grafts, did little to improve 1-year patency rates, which approached 38%.[81] Robinson et al.[45] reported a cumulative secondary patency rate of 47% at 1 year. In this series, 26% of the patients required amputation within 1 month of graft thrombectomy, and 41% required amputation by 1 year. The results of surgical thrombectomy were significantly improved if technical problems (e.g., a twist in the graft or a retained valve cusp in an in-situ saphenous vein bypass graft) were identified at exploration. Review of the Dartmouth experience was again similar, with long-term graft patency rates for grafts in which thrombosis occurred because of correctable, underlying technical problems approaching that for grafts without complications.

It should be reemphasized, however, that the incidence of graft failure referable to technical error has substantially decreased.[45] It is our practice to perform immediate reexploration in any patient with perioperative graft failure, irrespective of the conduit, when at initial surgery all components of the revascularization were judged technically optimal and in no way disadvantaged. In this setting, thrombolysis poses an additional risk of bleeding, delayed efficacy, and overall poor long-term results. Therefore, in such patients, thrombectomy, anticoagulation, and repair of any underlying potential technical problems yield superior results.[82-85]

In as many as 50% of patients who undergo reexploration for early graft failure, no underlying cause of thrombosis is found.[6] In such circumstances, when a correctable problem has not been detected, and poor conduit or disadvantaged runoff does not appear to be the cause of thrombosis, a 20-gauge polyethylene catheter can be placed in a proximal side branch of the vein graft after thrombectomy. Through this catheter, nitroglycerin (0.05 μg/min) and heparin (10 U/min) are infused while the patient is held in the postanesthesia recovery unit or the intensive care unit. This measure is an attempt to counteract potential underlying undocumented inherent thrombogenicity within the revascularization, whether related to runoff spasm or to graft harvest trauma. The catheter is removed at the bedside or in the operating room after 24 to 36 hours of infusion therapy. Although not routinely used, this adjunct has been documented to confer reasonable patency in 8 of 10 patients at a mean follow-up of 17 months.[7]

If attempts to salvage a thrombosed infrainguinal graft remain unsuccessful in the early postoperative period, two options remain. One management strategy includes expectant therapy and anticoagulation. Frequently, amputation will ensue, although limb loss is not inevitable.[85,86] An alternative strategy includes performing a second bypass procedure with the best available autogenous vein, assuming that there is adequate residual conduit length and an additional good quality target vessel. Although

seemingly difficult, this aggressive posture often leads to improved results.[87] In extenuating circumstances, alternative conduit options including cadaveric vein can be used though the results have not been particularly durable.[88] The advent and evolution of stem cell therapy for patients without additional reconstruction options may play a growing role in clinical practice in this circumstance; however, definitive results of clinical trials are still largely pending (see Chapter 7).[89-91]

Late Graft Failure (>30 Days)

Many of the aforementioned diagnostic and therapeutic decisions remain germane in the setting of delayed or late graft failure. There are, however, several distinctions. First, technical errors no longer constitute a significant cause of graft pathology. Second, thrombolytic therapy offers greater therapeutic utility in this time interval. Third, a greater magnitude of technical difficulty can be anticipated in the surgical dissection of previously operated vessels.

The time interval since arterial reconstruction can act as a positive predictor of the successful application of thrombolytic therapy. Specifically, the longer a graft has been in place, the greater the likelihood that thrombolytic therapy will confer graft patency. Two factors have been noted in the Dartmouth experience to be critical in predicting success after lytic therapy: graft age (since time of placement) of approximately 1 year or older, and the absence of diabetes. It was noted that although thrombolysis was successful in 15 failed grafts in patients with diabetes, only 1 graft was patent at 1 year. Conversely, in nondiabetic patients with at least 12 months of documented graft patency before thrombosis, 44% of patients achieved documented graft patency at 2 years.

After restoration of graft patency, it has been well-documented that further endovascular or surgical therapy may be required in up to 85% of cases to achieve sustained patency. Available therapeutic options in this setting include (1) balloon angioplasty of an intragraft or juxta-anastomotic stenoses, (2) open surgical vein patch angioplasty, and (3) interposition bypass reconstruction. Although the results of such techniques when applied to failed grafts successfully treated with lytic therapy (secondary patency) are not comparable to the documented outcomes observed when applied to maintain the patency of threatened grafts (assisted primary patency), the "threatened" group constitutes a larger cohort and provides a significant body of data from which the surgeon may guide clinical decision-making.

Several groups have reported patency rates from 40% to 86% following angioplasty or vein patch angioplasty for failing/threatened bypass grafts.[92,93] Our current policy reserves percutaneous transluminal angioplasty for maintenance of graft patency until operative repair can be undertaken, for the treatment of straightforward, short stenoses that are difficult to approach surgically, or for dilation of critical stenoses in patients with medical contraindications to anesthesia or surgery. Further, we have found cutting balloon angioplasty to be more effective than plain balloon angioplasty. In a patient with a failed prosthetic bypass graft secondary to progressive advanced atherosclerotic disease compromising outflow circulation, percutaneous treatment with angioplasty or other endovascular adjuncts is justified when no reasonable surgical alternatives are available.[94,95]

Selective application of patch angioplasty versus interposition grafting to address a vein graft lesion noted after successful thrombolysis should best be decided on the basis of lesion location and appearance, availability of adequate autogenous conduit, and surgeon preference. Review of both techniques demonstrates that similar results and outcomes can be expected.[38] Although some suggest superior outcomes with a vein interposition graft to treat an intimal hyperplastic lesion, the requisite additional anastomoses carry their own potential associated complications.

The optimal autogenous vein conduit for replacement of a short segment of vein graft is ideally derived from either the remaining ipsilateral saphenous vein or the lesser saphenous vein. Insertion of a segment of contralateral great saphenous or arm vein as a short interposition graft segment should be avoided to preserve these intact longer conduits for alternative or metachronous uses. In patients who have older grafts with acquired diffuse degeneration or in patients with diabetes whose grafts have failed in less than 1 year after implantation, thrombolysis is unlikely to confer any significant secondary graft patency. Rather, a repeat bypass is more likely to offer successful long-term patency. This supposition is predicated, however, on the availability of sufficient quality distal target vessels and adequate autogenous conduit. When these are available, there does appear to be an enhanced sustained benefit associated with repeat bypass when applicable.

The choice of conduit constitutes yet another example of the associated clinical decision-making complexity when confronted with a failed graft. Historically, the contralateral great saphenous vein has been thought to be the preferred source of conduit for bypass in the setting of an inadequate ipsilateral great saphenous vein because of either disease or previous use. Appropriate concern that the donor extremity will potentially require future bypass or that the saphenous vein might better be used for coronary artery bypass has traditionally been outweighed by the more immediate need and clinical gravity. However, there is reason to question this conduit selection algorithm. Review of the infrainguinal bypass experience at Dartmouth-Hitchcock Medical Center revealed that 20% of patients required contralateral lower extremity revascularization at a mean of 31 months after initial ipsilateral bypass.[96] The intervention rate in our patients, as calculated by life-table analysis, was nearly linear at 6% per year. Among these interventions, 83% were contralateral infrainguinal vein bypasses. Factors predictive of the need for future intervention at the time of initial ipsilateral revascularization included younger age, diabetes, coronary artery disease, and diminished contralateral ankle-brachial index.

By comparison, in patients with only unilateral lower extremity atherosclerosis warranting surgery, the likelihood of future contralateral intervention remained less than 10% during the following 5 years. Based on these findings, it could be argued that the contralateral saphenous vein should be utilized for revascularization of the index leg in elderly patients in whom atherosclerosis remains isolated to one limb. In these clinical

settings, the surgeon may proceed with confidence that the potential future requirement for use of this vein will be unlikely. Unfortunately, only 8% of patients who require infrainguinal revascularization have isolated unilateral lower extremity atherosclerosis.

In light of these findings, selection of the most appropriate bypass conduit, when the ipsilateral great saphenous vein is not available, remains a complex decision confronting the vascular surgeon. Arm veins, when deemed acceptable on preoperative duplex evaluation and intraoperative angioscopic examination, remain an appropriate alternative conduit for graft revision or secondary bypass. Although the need for graft revision remains greater in reconstructions in which an arm vein was used as the conduit, documented assisted primary patency rates approach 72% over 5 years.[97] Although alternative vein grafts spliced together from the lesser saphenous vein and the remaining ipsilateral saphenous vein have been documented to have equivalent patency to that of an arm vein, the associated added morbidity of distal incisions in an ischemic, previously operated limb should not be underestimated. Use of an arm vein conduit may also minimize the number of venovenostomies required in the scenario of small segments of a viable lower extremity conduit. Regular use of the profunda femoris artery and end-arterectomy of the superficial femoral artery to lessen the requisite conduit length for bypass are important surgical adjuncts that should be incorporated into treatment paradigms. Although some advocate repeat infragenicular bypass with either cadaveric vein or, more commonly, prosthetic conduit with or without a distal vein cuff or associated arteriovenous fistula, we seldom use these techniques unless confronted with dire limb salvage circumstances without other therapeutic alternatives.[98-101] In a comparative study of alternative graft conduits, Faries et al.[102,103] documented that autogenous arm vein grafts demonstrated better patency than prosthetic conduit when applied to below-knee popliteal and tibial configurations. Despite optimistic reports from other centers regarding the use of prosthetic conduit, results at Dartmouth-Hitchcock have not been comparable in similar cases to those of autogenous vein. In this setting, it is our continued preference to use autogenous vein when available and prosthetic grafts as a reasonable alternative to primary amputation, with cadaveric conduits reserved for extreme clinical circumstances in the setting of infection/tissue loss where less expensive prosthetic conduit might be at risk to become infected.

ACKNOWLEDGMENT

The authors would like to acknowledge Daniel J. Walsh, MD, Professor in Vascular Surgery at Dartmouth-Hitchcock Medical Center, for his mentorship and for his contribution to the evolution of this chapter.

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This study is a National Surgical Quality Improvement Program analysis of a large cohort of patients that identifies predictors associated with early graft failure.

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This study is a National Surgical Quality Improvement Program analysis of a large cohort of patients that identifies predictors associated with early graft failure.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 47

Graft Infection

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The incidence of infection involving vascular prostheses is relatively low because of routine antibiotic prophylaxis before surgical procedures, refinements in the sterilization and packaging of devices, and careful adherence to aseptic procedural and surgical technique.

When infection does occur, detection and definitive therapy of the vascular prosthesis are often delayed, with potentially catastrophic consequences. If it is not recognized or treated promptly, implant failure will occur as a result of sepsis, vessel disruption and hemorrhage, or thrombosis with end-organ ischemia.[1-6] The clinical manifestations of prosthetic vascular infection vary depending on the anatomic location and the virulence of the pathogen.[1,3,5,7-9] In general, surgical therapy is always required, often coupled with excision of the prosthesis, because antibiotics alone are insufficient to eradicate an established infectious process. An appropriate treatment plan is influenced by the clinical findings, anatomic location, time since initial implantation, type of graft/device material, extent of infection, virulence of infecting organism, and the patient's underlying comorbid conditions.

Keys to a successful outcome include use of accurate diagnostics to identify the infecting organism and the extent of the graft infection; administration of culture-specific antibiotic therapy; well-planned surgical intervention(s) to preserve, excise, or replace the infected graft; sterilization of the local perigraft tissues; and maintenance of adequate distal organ/tissue perfusion. Improved results have been reported in the past 30 years after both graft excision coupled with extra-anatomic bypass

Abstract

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Keywords

Vascular graft
Aortic graft infection
Biofilm infection
In-situ prosthetic replacement
cryopreserved allograft / homograft
neo-aorto-iliac system (NAIS)
femoral-popliteal vein graft
extra-cavitary graft infection
methicillin-resistant Staph aureus (MRSA)
aortic graft resection
extra-anatomic bypass

TABLE 47.1 Incidence of Prosthetic Graft and Endovascular Device Infection Relative to the Implant Site

Infection	Incidence (%)
Graft Implant Site	
Descending thoracic aorta/thoracoabdominal	0.5-1.9
Aortoiliac	0.2-1.3
Aortofemoral	0.5-3
Femorofemoral	1.3-3.6
Axillofemoral	5-8
Femoropopliteal	0.9-4.6
Femorotibial	2-3.4
Carotid patch	0.25-0.5
Carotid-subclavian	0.5-1.2
Axilloaxillary	1-4
Endovascular Device	
Aortic stent-graft	0.1-1.2
Peripheral stent	<0.1

BOX 47.1 Clinical Classifications of Prosthetic Graft Infections

Time of Appearance After Implantation

- Early: <4 months
- Late: >4 months

Relationship to Postoperative Wound Infection (Szilagyi's Classification)

- Grade I: cellulitis involving the wound
- Grade II: infection involving subcutaneous tissue
- Grade III: infection involving the vascular prosthesis

Extent of Graft Involvement (Bunt's Classification Modified)

- Peripheral graft infection:
  - P0 graft infection: Infection of a cavitary graft (e.g., aortic arch; abdominal and thoracic aortic interposition; aortoiliac, aortofemoral, iliofemoral graft infections)
  - P1 graft infection: Infection of a graft whose entire anatomic course is noncavitary (e.g., carotid-subclavian, axilloaxillary, axillofemoral, femorofemoral, femorodistal, dialysis access bridge graft infections)
  - P2 graft infection: Infection of the extracavitary portion of a graft whose origin is cavitary (e.g., infected groin segment of an aortofemoral or thoracofemoral graft, cervical infection of an aortocarotid graft)
  - P3 graft infection: Infection involving a prosthetic patch angioplasty (e.g., carotid and femoral endarterectomies with prosthetic patch closure)
  - Graft-enteric erosion (GEE)
  - Graft-enteric fistula (GEF)
  - Aortic stump sepsis after excision of an infected aortic graft

and in situ replacement procedures.[10-18] Because most patients with late manifestations have a low-virulence graft infection, in situ replacement therapy with autogenous venous conduits, cryopreserved allografts, or antibiotic-impregnated prostheses to replace the infected grafts has evolved to become a preferred treatment strategy.[10,12,13,18-26]

INCIDENCE

The reported incidence of infection involving a vascular prosthesis varies from 0.2% to 5% of open operations performed and is influenced by the implant site, indication for the intervention, underlying disease, and host defense mechanisms (Table 47.1).[1,4-6,8,25,27-34] Graft infection occurs much less frequently than wound infection, with the incidence of early (<30-day) graft infection being in the range of 1% to 2% of procedures. Infection is more likely to involve prosthetic grafts implanted during an emergency procedure, when the prosthesis is anastomosed to the femoral artery or placed in a subcutaneous tunnel. In a Canadian prospective multicenter trial of nonruptured AAA open repair, the incidence of graft infection was 0.2%,[23] similar to that reported after endovascular aneurysm repair (EVAR) employing a stent graft.[31,35-37] Infection can also develop after arterial deployment of a bare stent, but the incidence appears to be extremely low (<0.1%).

CLASSIFICATION

Prosthetic graft infections can be classified according to time of appearance after implantation, relationship to postoperative wound infection (Szilagyi's classification), and the extent of graft involvement (Bunt's classification) (Box 47.1).

Early (<4 months after graft implantation) infections correlate with Szilagyi grade III wound infections that involve vascular prostheses.[33] These infections are caused by virulent hospital-acquired bacteria and are associated with sepsis, manifested by fever, leukocytosis, bacteremia, and advanced wound infection. Early graft infections appear after patients have been discharged from the hospital and most involve extracavitary grafts. There is evidence that even Szilagyi grade I and II wound infections increase the likelihood of a late-appearing graft infection.

Late infections are the result of graft colonization by low-virulence organisms such as *Staphylococcus epidermidis* or, infrequently, *Candida* species.[1,10,17,19,28,38] The low titer of microorganisms on graft surfaces produces an indolent infection without signs of sepsis, and cultures of perigraft fluid or tissue may yield no growth. Most cavitary (i.e., aortic) graft infections occur as late (>4 months) infections with a mean time to appearance of more than 40 months.[6,10,39,40]

PATHOGENESIS

Etiology

The presence of a foreign body potentiates the infectivity of bacteria. In 1957, Elek and Conen[41] demonstrated that a single braided silk suture significantly reduces the inoculum of

staphylococci required to produce a local infection. The risk of foreign body infection is enhanced in the presence of a larger inoculum, more virulent bacterial strains, depressed host immune function, and invasion of sites more remote from host defenses.

Cellular and Biomolecular Events

The pathogenesis of biomaterial-associated infection involves the following fundamental steps: (1) adhesion of bacteria to graft or stent surfaces, (2) formation of microcolonies within a bacterial biofilm, (3) activation of host defenses (neutrophil chemotaxis, complement activation), and (4) an inflammatory response involving perigraft tissues and the graft-artery anastomoses.

After adherence of bacteria to the biomaterial surface, both graft and bacterial characteristics influence the likelihood of colonization. Bacterial adherence to polyester grafts is 10 to 100 times greater than adherence to polytetrafluoroethylene (PTFE) grafts. Gram-positive bacteria, such as staphylococci, produce an extracellular glycocalyx, or mucin, that promotes adherence to biomaterials in greater numbers than are seen with gram-negative bacteria. The increased adhesion of staphylococci to biomaterials is due to specific capsular adhesions that mediate the attachment and colonization of microorganisms.

The vascular prosthesis and adherent bacteria together stimulate the immune system through inflammatory cytokines. The local inflammatory response after implantation serves to establish connective tissue ingrowth ("incorporation") to the outer surface of the graft material. This healing process can be impaired by early perigraft seroma or hematoma formation, which increases the risk for bacterial adherence and colonization. The inflammatory response also creates an unfavorable healing environment characterized by local ischemia and an acidic pH that is potentially conducive to bacterial colonization. Local disruption of the fine balance between pro- and anti-inflammatory mediators may lead to excess production of matrix metalloproteinases (MMPs) by tumor necrosis factor–stimulated macrophages.[42] Excessive degradation of secreted extracellular matrix and angiogenic growth factors by MMPs may hinder optimal graft healing by restricting capillary ingrowth, tissue incorporation, and potential luminal endothelialization. Lack of perigraft ingrowth and vascularity also favors greater exposure of the implanted biomaterial to bacteria and sequestration within graft pores/interstices away from activated phagocytic cells. Neutrophil function can also be directly impaired in the presence of biomaterials. Decreased neutrophil opsonic, phagocytic, and bactericidal activity against *Staphylococcus aureus* has been observed in PTFE tissue cages implanted subcutaneously in guinea pigs.[43]

Clinical Sources of Infection

Exposure of a vascular prosthesis to microorganisms (bacteria or fungi) can result in clinical infection by any of four mechanisms: perioperative contamination via the surgical wound; bacteremic seeding; mechanical erosion into the bowel, genitourinary tract, or through the skin; and involvement in a contiguous infectious process. Underlying impairment of host defenses can further increase the risk for infection.

Perioperative Contamination

Skin and lymph nodes are major reservoirs of bacteria. Biomaterial surfaces can contact microorganisms (1) by a direct route during implantation, (2) through the surgical wound, or (3) by hematogenous or lymphatic sources arising from remote sites of infection. Potential sources of direct graft contamination include breaks in aseptic operative technique and contact with a patient's endogenous flora harbored within sweat glands, lymph nodes, diseased arterial walls (atherosclerotic plaque or aneurysm thrombus), disrupted lymphatics, and intestinal bag effluents as well as injury to the gastrointestinal or genitourinary tract. Reoperative and urgent/emergent vascular procedures and prolonged operative time also increase the risk of vascular surgical site infections (VSSIs).[44]

If the surgical wound does not develop a fibrin seal or heal promptly after surgery, the underlying vascular prosthesis is susceptible to colonization from any superficial wound complication (cellulitis, dermal necrosis, lymphocele). Wounds with persistent drainage indicate the presence of ischemia or tissue injury that can extend to deeper tissue and involve the prosthesis. Diseased arterial walls and reoperative wounds are an unappreciated source of bacteria, with microbiologic culture recovering pathogenic strains of staphylococci in 10% to 20% of cases.[1] Bacteria can be harbored in scar tissue or lymphoceles of healed wounds and can contact prosthetic grafts undergoing revision or arterial replacement. Culture of explanted graft material from such procedures has isolated microorganisms, typically *S. epidermidis*, from 50% to 70% of thrombosed grafts and from more than 80% of grafts associated with anastomotic aneurysms.[38]

Bacteremia

Bacterial seeding of the prosthesis via a hematogenous route is an uncommon but important mechanism of graft and stent infection. Experimentally, intravenous infusion of 10^7 colony-forming units of *S. aureus* administered within days of implantation produces a clinical graft infection in nearly 100% of animals.[45] Thus bacteremia arising from infected intravascular catheters, urinary tract infection, pneumonia, or infected foot wounds increases the risk of graft infection.

Parenteral antibiotic therapy has been shown experimentally to significantly decrease the risk of graft colonization from bacteremia; this is the rationale for both antibiotic prophylaxis and culture-specific antibiotic therapy in the patient with a known site of infection. As the prosthesis heals and becomes incorporated into surrounding tissue, susceptibility to bacteremic colonization decreases but vulnerability has been documented more than 1 year after implantation, with infection developing as a result of dental and gastrointestinal diagnostic procedures. Transient bacteremia, in conjunction with altered immune status, may account for some graft infections occurring years after the original operation.

Mechanical Erosion

Erosion of a prosthetic graft through the skin or into the gastrointestinal or genitourinary tract results in a perigraft infection that can spread along the length of the graft.

Graft-enteric erosion/graft-enteric fistula (GEE/GEF) can develop as a result of pulsatile movement of an aortic graft against adjacent bowel, most commonly without adequate intervening retroperitoneal soft tissue. Enteric erosion may involve the graft body or anastomotic sites with intact suture lines or pseudoaneurysm formation. A low-grade underlying graft infection has been found in a fraction of cases (confirmed by operative findings and recovery of staphylococcal species) and may provide an additional inflammatory stimulus for bowel adhesion.[46] The reported incidence of GEE/GEF after prosthetic aortic grafting is 0.4% to 2%.

Involvement by a Contiguous Infectious Process

Prosthetic grafts can become colonized as a result of an adjacent infection. The most common clinical scenarios are an aortofemoral graft limb infection associated with diverticulitis and a peripheral graft infection secondary to an infected lymphocele. Frequently the graft segment adjacent to the contiguous bowel or soft tissue infection may be involved.

Impaired Host Defenses

Impaired host defenses from underlying systemic conditions can also predispose patients to prosthetic graft infection.[47] The altered immune function associated with malnutrition, malignancy, lymphoproliferative disorders, autoimmune diseases, chronic renal insufficiency/uremia, advanced liver disease, drug administration (corticosteroids, antineoplastic and immune-modulating agents), and potentially diabetes mellitus may potentiate graft infection with lower numbers of contaminating bacteria.

Bacteriology

Although any microorganism can infect a vascular prosthesis, *S. aureus* is the most prevalent pathogen and accounts for 25% to 50% of infections, depending on the implant site (Table 47.2). Graft infections with *S. epidermidis* or gram-negative bacteria have increased in frequency. This change in the microbiology of graft infection is the result of reporting of both early- and late-appearing graft infections, including aortic graft infections associated with GEE/GEF. Coagulase-negative staphylococci are present in normal skin flora but have the ability to adhere to and colonize biomaterials, where growth occurs within a biofilm on the surface of prostheses. Surgeons have also become aware of microbiologic sampling errors in late infections because of low numbers of bacteria present within the graft surface biofilm and their slow growth.[48] Graft infections associated with negative culture results are caused by *S. epidermidis* or other coagulase-negative staphylococci and by *Candida* species. Infection with gram-negative bacteria such as *Escherichia coli* and *Pseudomonas*, *Klebsiella*, *Enterobacter*, *Serratia*, and *Proteus* species can be particularly virulent. The incidence of anastomotic dehiscence and arterial rupture is high because of the ability of the organisms to produce destructive endotoxins (elastase and alkaline protease) that compromise the structural integrity of the vessel wall. Fungal (*Candida* and *Aspergillus* species) and mycobacterial (tuberculous) infections of grafts are rare, and most patients with such infections are either severely immunosuppressed or have an established fungal or opportunistic infection elsewhere.

Plasmid-mediated genetic mutations have afforded *S. aureus* resistance against penicillin, β-lactams, and other antibiotics (aminoglycosides, erythromycin, tetracycline). Nosocomial and community-acquired infections caused by methicillin-resistant *S. aureus* (MRSA) have rapidly increased in prevalence over the past 15 years. Although estimates in the general population have shown MRSA skin colonization (nares and wounds) in less than 2% of individuals, a much higher prevalence is found in residents of long-term care facilities (23%-49%).[49-51] A study involving more than 13,000 surgical patients admitted to a tertiary hospital in Switzerland found that the overall incidence of MRSA carriers was 4%, but of those carriers, 64% were newly identified. Previous hospitalization, age greater than 75 years, and recent antibiotic treatment were each prognostic for unsuspected MRSA carriage.[52] The combination of increased prevalence, harboring in high-risk populations, multiple staphylococcal virulence factors, and rapidly evolving antibiotic resistance mechanisms makes emergence of MRSA a daunting

TABLE 47.2 Bacteriology of Prosthetic Vascular Graft Infections From Collected Series

	INCIDENCE (%)				
Microorganism	Thoracic Aorta	Graft-Enteric Erosion/ Graft-Enteric Fistula	Aortofemoral	Femoral/Popliteal/Tibial	Carotid
Staphylococcus aureus	32	4	27	28	50
Staphylococcus epidermidis	20	2	26	11	15
Streptococcus spp.	2	9	10	11	3
Pseudomonas spp.	10	3	6	16	6
Coliforms/gram-negative organisms[a]	14	49	28	29	9
Other species/*Candida*	10	15	1	3	5
No growth/no culture	12	18	2	2	12

[a]*Escherichia coli*; *Enterococcus*, *Bacteroides*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus* species.

medical challenge. British reports have documented MRSA as the most common pathogen involved in vascular wound and graft infections and concluded that it is associated with higher morbidity and mortality rates than infection with other microbes.[53,54] At the University of South Florida (USF), the prevalence of MRSA arterial graft infections increased fourfold over the past 25 years (from 11% before 2000 to 49% after 2000), with more than half of early extracavitary graft infections being the result of MRSA. Early mortality, limb loss, and infection recurrence rates have not been appreciably higher for MRSA in our experience. However, the future possibility of a higher overall incidence of graft or vascular device infections caused by more prevalent MRSA colonization in the vascular population is concerning.

Prevention Principles

Surgical site infection (SSI) guidelines have recently been updated and a comprehensive review has been generated by the American College of Surgeons and the Surgical Infection Society.[55]

VSSIs can be minimized if the following principles are applied:

1. Avoid a prolonged preoperative hospital stay to minimize the development of more resistant hospital-acquired bacterial strains.
2. Have patients shower, scrub, or wipe with an alcohol-based soap (e.g., chlorhexidine) for 1 to 3 days before the operation.
3. Control remote infections before an elective vascular operation.
4. Remove hair from the operative site immediately before the operation with care to avoid skin trauma.
5. Protect vascular grafts from contact with exposed skin in the operative field by using iodine-impregnated plastic drapes or antibiotic-soaked towels/sponges.
6. Avoid concomitant gastrointestinal procedures during cavitary grafting procedures.
7. Use prophylactic antibiotics (30-60 minutes before skin incision) prior to open surgical implantation of a prosthetic graft.
8. Longer (>24 hours) duration of periprocedural antibiotics may be considered when two or more patient-related high-risk factors for surgical wound infection are identified, including extremes of age, malnutrition, prolonged hospitalization, remote infections, immunosuppression, recent or "redo" operations, and previous irradiation of the surgical site.
9. Measures aimed at controlling MRSA include the use of disposable barriers (gowns, gloves, masks) by all individuals contacting MRSA carriers to reduce direct transmission within hospitals, routine MRSA screening (nares swab) of all admitted patients, and use of nasal mupirocin ointment and repeated chlorhexidine skin cleansing before operations.
10. Meticulous attention to sterile technique. Careful handling of tissues, prevention of hematoma formation, and closure of groin incisions in multiple layers to eliminate dead space with lymphatic resection/ligation are imperative to reduce wound complications. Skin reapproximation without tension minimizes the development of dermal ischemia and wound edge necrosis.

Topical Antibiotics

The addition of topical antibiotics (bacitracin or cefazolin) to irrigating solutions allows soaking of grafts before implantation and cleansing of wounds before closure and may contribute to decreased wound infection rates. Randomized clinical trials using rifampin-soaked (1 mg/mL) gelatin-impregnated polyester aortofemoral grafts have reported significantly reduced groin wound infection rates (4.4% without rifampin vs. 2.7% with rifampin), although the rates of subsequent graft infections were similar (0.6% vs. 0.3%).[56,57] All graft infections were caused by *S. aureus* in this study. On the basis of the absence of a longer-term benefit, routine rifampin treatment of polyester grafts for primary aortic reconstruction cannot currently be recommended.

Prophylactic Antibiotics

Prophylactic antibiotics should be infused before skin incision and at regular intervals during long procedures (>3 to 4 hours) to maintain tissue drug levels above the minimal bactericidal concentration for expected pathogens (Box 47.2). Prophylaxis should also be instituted before percutaneous puncture of existing prosthetic grafts (peripheral or coronary arteriography accessed through existing femoral grafts) or before selected endovascular interventions involving stent/stent-graft implantation. Culture-specific antibiotics should be prescribed for patients undergoing

BOX 47.2 Antibiotic Prophylaxis in Adults Undergoing "Clean" Prosthetic Graft or Patch Implantation and Selected Endovascular Procedures

- Precarotid endarterectomy, femoral patch, AAA open repair, or EVAR:
  Cefazolin 1-2 g IV 30 min before the procedure and repeated (1-2 g) q8h for 24 h or
  Cefuroxime 1.5 g IV and q12h for 24 h
- Single prophylactic dose before any endovascular procedure involving a prior access-site prosthesis, repuncture of a recent access site, prosthetic/device reintervention (secondary intervention), or an existing remote peripheral arterial device (e.g., prior stents, grafts):
  Cefazolin 1-2 g IV or cefuroxime, 1.5 g IV
- Before reoperation involving an existing prosthetic graft/patch:
  Vancomycin 1 g IV given 30-60 min before incision and continued q12h for 24-48 h
- Known patient MRSA colonization or prolonged or recurrent stay in hospital or chronic care facility (high MRSA risk):
  Vancomycin 1 g IV before the incision/procedure
- Alternatives for penicillin, cephalosporin, or vancomycin allergies:
  Daptomycin 4 mg/kg IV before procedure and daily for 24-48 h
  Levofloxacin 500 mg IV before the procedure and then daily for 24-48 h
  Clindamycin 900 mg IV before the procedure and then 450-900 mg q8h for 24-48 h

AAA, Abdominal aortic aneurysm; *EVAR*, endovascular stent-graft AAA repair; *IV*, intravenous; *MRSA*, methicillin-resistant *Staphylococcus aureus*.

vascular graft implantation who have coexisting infections of the leg or another remote site.

After implantation of a prosthetic graft, patients should be informed of the potential risk for graft colonization and infection from transient bacteremia, especially after dental work, colonoscopy, or cystoscopy. Antibiotic prophylaxis is recommended if these procedures are performed within 3 months of the vascular operation. Amoxicillin 2 g orally 1 hour before the procedure can be used. For patients with penicillin allergy, clindamycin 600 mg orally 1 hour before the procedure is an alternative.

DIAGNOSIS

The prompt diagnosis and treatment of prosthetic graft infections is essential to avoid major complications (advanced sepsis and hemorrhage) and death. Clinical manifestations are varied and may be subtle, particularly when associated with late-appearing cavitary graft infections. The urgency of diagnostic evaluation depends on the clinical findings and the status of the patient.

Clinical Manifestations

Vascular surgeons should maintain a low threshold for proceeding with additional diagnostic testing when any symptom or sign suggests graft infection. In aortic grafts confined to the abdomen, unexplained sepsis, ileus, or abdominal distention might be the only clinical sign. If infection involves an extracavitary graft, the initial sign of infection is usually overlying inflammation/cellulitis, a cutaneous draining sinus tract, or an anastomotic pseudoaneurysm. Any patient with gastrointestinal bleeding and an aortic graft should be presumed to have graft infection and GEE/GEF until either another source of bleeding is conclusively identified on endoscopy or no graft-bowel communication is verified at surgery.

In patients with vague suggestive symptoms and ultrasound or computed tomography (CT) evidence of perigraft fluid, a thorough clinical history may furnish clues that further support the diagnosis of graft infection and provide the rationale for invasive diagnostic testing. The patient should also be queried about recent medical illnesses that may have resulted in hematogenous or lymphatic seeding of the graft with bacteria. Early graft infections with *S. aureus* or other gram-negative bacteria typically manifest within weeks of the procedure as fever, leukocytosis, wound complications, and perigraft purulent drainage. Bacteremia is a sign of an advanced graft infection associated with arterial wall or mural thrombus infection or the secondary development of endocarditis. Patients with grafts infected by *S. epidermidis* are typically seen years after graft implantation with graft-healing complications (anastomotic aneurysm, perigraft fluid cavity, or graft-cutaneous sinus tract). Signs of systemic sepsis are frequently absent.

An elevated white blood cell (WBC) count with a left-shifted differential count and an increased erythrocyte sedimentation rate are common but nonspecific findings in patients with graft infection and fever. Routine laboratory testing should also include urinalysis, blood culture, and cultures of other clinical sites of infection such as foot ulcers and surgical wound drainage. Positive blood culture results are uncommon (<5%), but when present they indicate an advanced graft infection, virulent organisms, or both. All laboratory test results may be normal in patients with late-appearing perigraft infections with *S. epidermidis.*

Imaging Studies

Vascular imaging is essential for the diagnosis and treatment of graft infection and its sequelae. Anatomic signs of graft infection—such as perigraft abscess, anastomotic aneurysm, and GEE/GEF—can be accurately identified (with >90% sensitivity) through a combination of ultrasonography, CT, magnetic resonance imaging (MRI), and endoscopy. Vascular imaging studies permit localization of involved prosthetic infection, related operative sites/tissues for abnormal healing and facilitate planning of surgical treatment options.

Contrast-Enhanced Computed Tomography and Computed Tomographic Angiography

CT is the preferred initial imaging technique for suspected graft infections in aortofemoral and abdominal vessels as well as the thoracic aorta and major cavitary branch vessels (P0, P2). CT is also preferred for cavitary graft infections involving the neck, torso, and proximal parts of the limbs (P1, P3) (see Chapter 49). It should be performed with and without intravenous contrast and oral contrast agents (to detail the relationship of adjacent enteric structures) should be used only in patients in whom GEE/GEF is suspected. The exact location and extent of polyester and PTFE grafts can best be seen on initial non–contrast-enhanced imaging. Review of delayed arterial-phase images or the "bone" preset window for early arterial-phase imaging best separates the detail of prosthetic graft, arterial, and venous structures from perigraft tissues and aids in image interpretation.

Diagnostic criteria consistent with infection include the loss of normal tissue planes (fat density) of the retroperitoneal or subcutaneous perigraft structures (indicative of inflammation), collections of fluid or gas around the graft (Fig. 47.1), the formation of false aneurysms, hydronephrosis, and adjacent vertebral or bony osteomyelitis. Any gas in periprosthetic tissues beyond 2 or 3 months after implantation is an abnormal CT finding suggestive of graft infection. CT angiography provides an assessment of continuity of the arterial lumen, associated distribution of occlusive disease, and the presence of thrombus at planned clamp sites; it may also enable operative planning for arterial reconstruction without invasive arteriography.

Ultrasonography

Ultrasonography can be performed urgently as a portable bedside examination in severely ill patients. It should be the initial imaging study for extracavitary (P1, P2, P3) graft infections. Color duplex scanning can reliably differentiate a perigraft fluid collection from an anastomotic pseudoaneurysm, hematoma, and soft tissue masses (enlarged lymph nodes). Ultrasonography has the advantage of being the most accurate vascular imaging technique for verifying vessel or graft patency and assessing

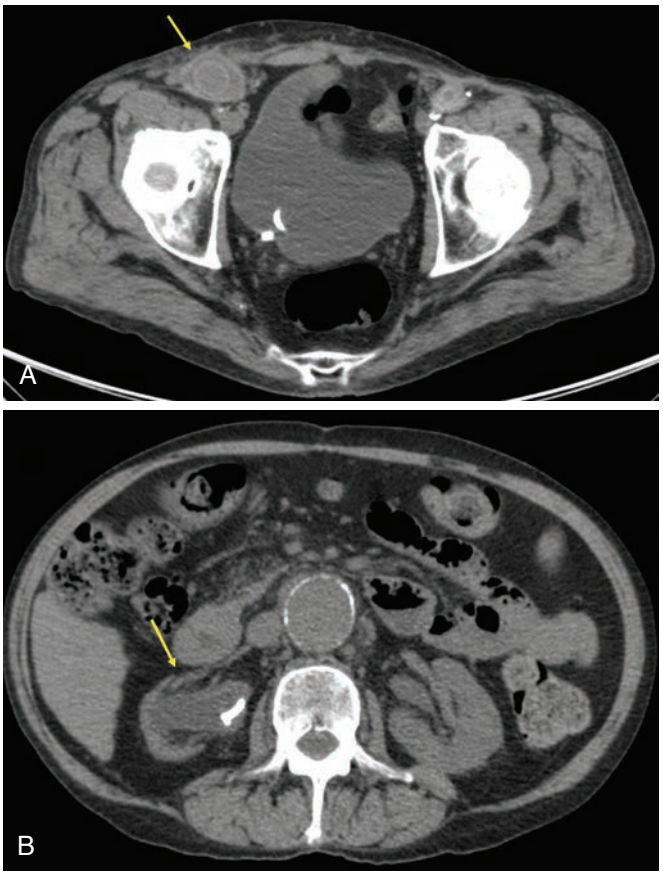

Figure 47.1 Non–contrast-enhanced CT scan showing an infected aortofemoral graft limb *(arrow)*. (A) Perigraft fluid and inflammation in the groin. (B) Infection-associated ipsilateral hydronephrosis, indwelling ureteral stent, and atrophic kidney.

pulsatile masses adjacent to grafts in the groin and limbs (see Chapter 48).

Magnetic Resonance Imaging

MRI provides anatomic imaging equivalent to that of CT but is better able to distinguish between perigraft fluid and fibrosis on the basis of differences in signal intensity between T1- and T2-weighted images. A gadolinium contrast agent enhances vascular luminal resolution (magnetic resonance angiography, or MRA) to allow planning of arterial reconstruction. Although less nephrotoxic than iodinated contrast agents, gadolinium has unfortunately been linked to a systemic fibrotic process in patients with renal insufficiency (see Chapter 28).

Functional White Blood Cell Scanning

All radionuclide imaging techniques aim to demonstrate abnormal accumulations of leukocytes in perigraft tissue for the diagnosis of graft infection, but they do not provide anatomic detail. However, they can be correlated with MRI and CT to delineate the anatomic extent of infection. The type of radionuclide used (gallium 67 citrate, indium 111–labeled leukocytes, technetium Tc 99m hexametazime–labeled leukocytes) can vary and will affect diagnostic accuracy. The accuracy (positive predictive value) of indium 111–labeled WBC scans approaches 80% to 90% in detecting graft infection.

Functional WBC scans are not useful, however, during the early postoperative course (3-6 months) because of nonspecific radionuclide uptake in the healing and inflamed perigraft tissue, resulting in a potential false-positive result. Normal scans (those showing no labeled WBC accumulation) have been reported in late-appearing aortic graft infection and documented cases of GEE/GEF (both false-negative results). Immunoglobulin G scans are sometimes preferred over WBC scans because of ease of preparation, lack of exposure to the patient's blood, absence of background red blood cell and platelet imaging, and the longer shelf life of IgG.

Endoscopy

With use of upper endoscopy, an important diagnostic modality for suspected GEE/GEF, the lumen of the esophagus, stomach, entire duodenum, and ideally the proximal jejunum can be inspected for sources of bleeding (a pediatric colonoscope should be used).

Computed Tomography—Guided Aspiration Versus Operative Findings

CT-guided aspiration of cavitary perigraft fluid collections is increasingly being used to differentiate uninfected seroma from abscess formation. Sampling error (limited sampling in septated perigraft fluid collections) is possible with percutaneous aspiration techniques, as is misinterpretation of negative culture results as indicating no graft infection in some cases of *S. epidermidis* biofilm infection. The definitive diagnostic test for suspected graft infection is operative exploration, especially with equivocal anatomic imaging results and suspected GEE/GEF. Direct exposure of the outer surface of the biomaterial through the typically thick fibrous capsule encompassing a polyester graft allows the detection of late indolent biofilm infections.

Culture Techniques

Standard swab cultures of material taken directly from the graft surfaces and perigraft fluid are usually sufficient in patients with obvious local or systemic sepsis caused by more virulent organisms, which are usually present in high numbers. However, surface swabs may not recover less virulent pathogens that do not invade perigraft tissues. An apparent negative result of Gram staining of tissue or fluid from around an unincorporated prosthetic graft showing no organisms (but typically the presence of WBCs) is not sufficient to exclude a low-grade graft infection because low numbers of slow-growing bacteria can reside within a surface biofilm.

For reliable recovery of microorganisms from within a biofilm infection, mechanical (tissue grinding) or ultrasound disruption of the biofilm of an explanted graft segment must be performed before incubation in a broth culture medium. Placement of a small graft segment in a trypticase soy broth medium is believed to maximize bacterial growth and recovery because the liquid medium allows submersion of the graft and optimal exposure of any adherent bacteria to the nutrient medium. The use of mechanical disruption and broth cultures is particularly helpful in confirming graft infection with *S. epidermidis.*

Culture tubes should be maintained for 5 to 7 days to exclude growth.

SURGICAL TREATMENT AND OUTCOMES

Treatment Considerations

The goals of managing vascular graft infections include initial and long-term eradication of the local and systemic septic process and maintenance of normal arterial perfusion to involved end-organ and limb tissues. Our USF group advocates a patient-specific treatment algorithm involving the use of conventional (total graft excision and extra-anatomic/remote bypass) or in situ replacement modalities and, occasionally, graft preservation techniques.[39]

Selection criteria for specific treatment modalities are based primarily on the clinical findings, extent of graft involvement, and microbiology (Table 47.3). Important adjuncts to attain wound sterilization for a VSSI, especially when in situ reconstruction or graft preservation is under consideration, include the use of multiple staged debridement and/or "washout" operative procedures (every 3-4 days) to minimize residual bacterial counts with more virulent infections; aggressive excision of involved arterial wall and perigraft tissues to healthy tissue planes; intraoperative mechanical and passive wound irrigation with cytotoxic agents (pulsed Clorpactin, passive dilute Betadine plus peroxide); temporary placement of antibiotic-loaded beads; soft tissue coverage of arterial repairs with uninfected, well-vascularized rotational muscle or fasciocutaneous flaps or omental pedicles; negative-pressure wound "sponge" therapy; closed suction drains and continuous dilute Betadine irrigation in grossly infected tissue beds; and culture-specific parenteral antibiotics.

Several general treatment tenets are imperative. Infection involving prosthetic biomaterials frequently requires partial or complete graft removal to eradicate the local septic process. Attempts to preserve prosthetic grafts are appropriate only in limited circumstances. Graft preservation is possible for most arterial infections involving autologous tissue reconstruction (vein bypass or patch). Like Calligaro and colleagues,[58] we at USF have seen more frequent successful graft preservation attempts with early-appearing extracavitary prosthetic infections and overall equivalent outcomes (operative mortality or limb loss) in early and late graft infections with use of a selected treatment regimen. The exception for preservation efforts is invasive infections (those producing local and systemic sepsis) caused by virulent *Pseudomonas*, *Klebsiella*, *Serratia*, *Proteus* spp., and *E. coli*. Autologous or prosthetic graft excision with ex situ revascularization is indicated in these scenarios.

Cavitary graft infections are less amenable than extracavitary infections to wound sterilization techniques involving multiple debridement procedures. Instead, a definitive procedure (simultaneous debridements) or two (staged) procedures that include total graft excision and in situ or ex situ reconstruction are required for cavitary infections. Because of the added invasiveness and physiologic stress of repeated cavitary exposure for the treatment of abdominal or thoracic graft infection, potential catastrophic cavitary graft disruption, and risk of development of enteric erosion or fistulization in the infected graft, preservation techniques should be attempted only rarely for cavitary graft infections.[59]

Graft Preservation

Attempts at graft preservation with just local measures are possible in limited circumstances. Patent grafts with infection involving a shorter length (segmental) and sparing anastomoses

TABLE 47.3 Selection Criteria for Appropriate Operative Management of Prosthetic Vascular Graft Infection

Treatment Option	Manifestations	Extent of Infection	Microbiology
Graft preservation/local therapy	Early infection, no sepsis	Not Dacron, graft body only, no anastomosis, segmental	Gram-positive organism, *Staphylococcus* spp.
Graft excision only	Graft thrombosis, viable limb, adequate collaterals	Any	Any organism
Excision and Ex Situ Bypass			
Simultaneous	Unstable patient, GEE/GEF, hemorrhage, severe sepsis	Invasive infection	Any organism
Staged	Stable patient, mild sepsis, GEE/GEF, no active bleeding	Invasive infection	Any organism
In Situ Replacement			
Prosthetic	No sepsis, no GEE/GEF	Biofilm infection, segmental	*Staphylococcus epidermidis*, gram-negative organism
Autologous vein	No sepsis, no GEE/GEF, severe occlusive disease	Invasive or biofilm, diffuse or segmental	Not *Pseudomonas*

GEE, Graft-enteric erosion; *GEF*, graft-enteric fistula.

(graft body only) can be considered for preservation. Results have been better with PTFE than with polyester conduits, with early (<4 months after implantation) rather than late (>4 months) infectious manifestations, with single gram-positive organisms than with polymicrobial or gram-negative infections, and with extracavitary rather than cavitary locations. Graft preservation should be attempted only for infections that are limited to the immediate perigraft region, caused by bacteria with low virulence and not associated with systemic sepsis.

Serial wound debridement in the operating room, use of cytotoxic irrigating solutions, and placement of antibiotic-loaded polymethyl methacrylate (PMMA) beads are necessary steps to minimize residual bacterial counts. Residual negative wound culture results are necessary for eventual rotational muscle flap coverage of the exposed graft segment, definitive skin closure, or both. More aggressive attempts at graft salvage by others, not necessarily adhering to the aforementioned criteria, have achieved complete graft preservation and wound healing in roughly 70% of patients with early aortofemoral graft limb[60] or infrainguinal prosthetic bypass infections.[21] However, initial treatment failures as a result of fatal graft disruption, persistent graft infection, and nonhealing wounds in 30% of cases limit broader application of this approach and emphasize the need to perform graft excision if local sepsis persists during serial treatments.[11] Mayer et al.,[61] advocating the use of debridement and negative-pressure wound therapy applied directly to exposed reconstructions for Szilagyi grade III (deep) infections, achieved 91% wound healing and 84% freedom from reinfection. However, in that cohort only 54% involved prosthetic graft infection. By comparison, with use of our stricter selection criteria, only 15% to 20% of our USF patients with early extracavitary prosthetic graft infections were deemed candidates, and they were successfully treated by preservation techniques.

Graft Excision and Extra-anatomic Bypass

Need for Revascularization

Graft excision without revascularization may be possible in some cases, including those in which claudication was the initial indication for intervention and when thrombosis of an infected graft does not result in critical limb ischemia. Arterial collaterals around a thrombosed or ligated bypass may take several weeks to develop, and inflow may be optimized by endovascular intervention if occlusive lesions are present in the native proximal vessels. Such an approach may be possible for a localized/segmental groin infection and aortofemoral graft via ligation of the affected limb through a clean retroperitoneal incision, segmental graft excision through the groin wound, endovascular recanalization of residual aortoiliac stenoses/occlusions, and femoral artery reconstruction (Fig. 47.2).

Intraoperative decisions regarding the need for immediate revascularization in patients with patent, infected grafts can be made with the use of temporary bypass occlusion, a sterile blood pressure cuff, and continuous-wave Doppler assessment of pedal outflow. Persistence of a pulsatile pedal arterial signal and ankle pressure greater than 40 mm Hg with bypass occlusion may allow initial graft excision and consideration of delayed revascularization after eradication of local infection. Absence of pulsatile pedal flow during temporary bypass occlusion would probably result in critical ischemic symptoms and risk of limb loss, thus mandating concomitant limb revascularization.

Graft Excision

Conventional management of an infected prosthetic arterial bypass involves total graft excision and revascularization via extra-anatomic/remote routes (ex situ) through uninfected tissue planes. This approach is generally required in patients with

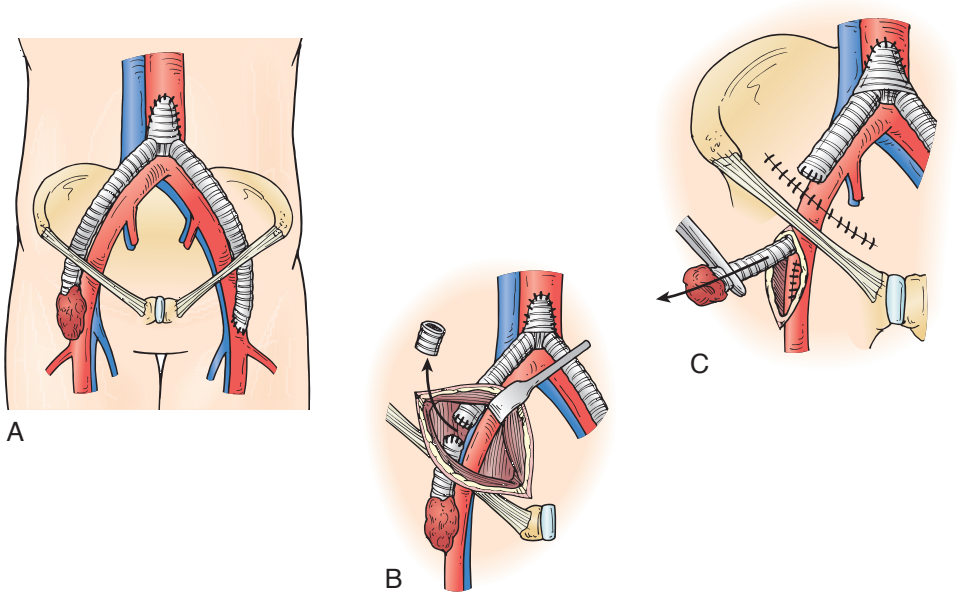

Figure 47.2 Excision of an infected distal aortofemoral graft segment. (A) Localized/segmental distal graft groin infection. (B) Retroperitoneal exposure of an uninfected graft limb through clean tissue planes. (C) Excision of an infected graft segment. In situ prosthetic or autologous vein replacement is performed if needed.

GEE/GEF and for more invasive infections associated with systemic sepsis or extensive perigraft infection (retroperitoneal/psoas abscess). Complete removal of diffusely infected aortoiliofemoral grafts (including anastomotic suture lines) is accomplished by repeat celiotomy or a left retroperitoneal exposure. The explanted graft material should always be cultured.

Proximal control/clamping of the supraceliac aorta may be necessary during exposure of an infrarenal anastomosis with significant retroperitoneal inflammation. Occluding Fogarty balloons may be used into patent iliac systems for hemostatic control. Ureters should be identified and protected during pelvic dissection, and preoperative placement of ureteral stents may be helpful to avoid injury when hydronephrosis and extensive retroperitoneal inflammation are present. The infrarenal aorta should be debrided back to normal-appearing wall. Pledgets of prosthetic material should be avoided, and a double layer of interrupted monofilament suture should be used for aortic ligation. A similar closure technique for the distal aortic or iliac arteries should be performed to maintain retrograde flow from extra-anatomic bypasses at the femoral level into at least one pelvic artery system (external iliac and hypogastric) to avoid pelvic ischemia.

Aggressive excisional debridement of infected perigraft tissue along with irrigation with cytotoxic agents and tunneling and placement of an omental pedicle to cover the aortic stump and retroperitoneal wound may reduce the risk of residual infection and later catastrophic "stump blowout." Temporary closed-suction drains and continuous dilute Betadine irrigation in the retroperitoneal wound bed can be considered in patients with abscess and extensive local infection. Repeat CT imaging within 7 to 10 days can confirm abscess cavity regression to allow removal of drains.

Timing of Limb Revascularization

In patients with aortic graft infection, the timing of limb revascularization depends on the clinical findings. Simultaneous ex situ bypass with graft excision is necessary in hemodynamically unstable patients with systemic sepsis, hemorrhage from dehiscence of the anastomosis, or GEE/GEF. However, staged management with initial axillofemoral PTFE bypass followed in 1 to 2 days by excision of the aortic graft has been associated with lower perioperative mortality than a simultaneous approach in stable patients.[15]

Several decades of experience with the conventional management of aortic graft infection has led to minimal changes in operative mortality but significant reductions in early limb loss, residual aortic stump infection and blowout, and recurrent infections involving ex situ prosthetic bypasses as well as improved midterm patient survival (Table 47.4).[62,63] The highest mortality rates continue to occur in patients with GEE/GEF or systemic sepsis; conventional management is preferred over in situ replacement techniques for such patients.

TABLE 47.4 Results of Treatment of Prosthetic Graft Infections Involving the Infrarenal Aorta or Aortoiliofemoral Bypass[a]

			GRAFT EXCISION AND EX SITU BYPASS				
Series	Year	Number of Patients	Operative Mortality (%)	Early Limb Loss (%)	Stump Blowout (%)	Survival >1 Year (%)	Extra-Anatomic Bypass[b] Infection (%)
O'Hara et al.[6]	1986	84	18	27	22	58	25
Reilly et al.[15]	1987	92	14	25	13	73	20
Yeager et al.[17]	1999	60	13	7	4	74	10
Seeger et al.[62]	2000	36	11	11	3	86	6
Bandyk et al.[39]	2001	31	22	10	0	81	3
			IN SITU REPLACEMENT				
			Operative Mortality (%)	Early Limb Loss (%)	1-Year Graft Patency (%)	Survival >1 Year (%)	Recurrent Infection (%)
Neo-aortoiliac System/Superficial Femoropopliteal Vein							
Nevelsteen et al.[25]	1995	29	9	6	90	83	1
Clagett et al.[12]	1997						
Ali et al.[69]	2009	187	10	7	92	77	5
Prosthetic:							
Bandyk et al.[39]	2001	25	0	0	100	100	12
Allograft							
Kieffer et al.[63]	2004	179	20	0.5	80	74	3

[a]Some series include cases involving graft-enteric erosion/graft–enteric fistula, which may influence the reported operative mortality.
[b]Cross-femoral, axillofemoral.

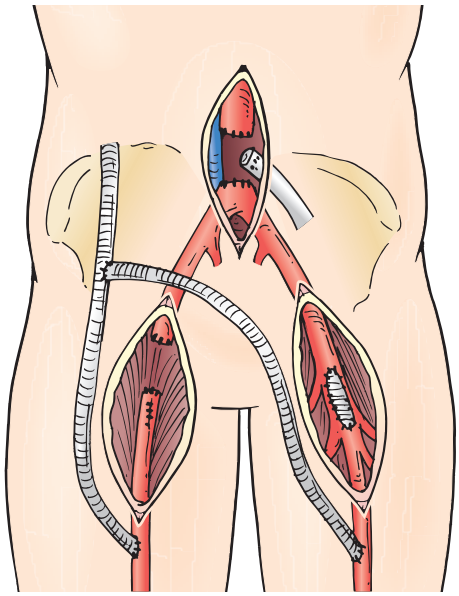

Figure 47.3 Excision of an infected aortobifemoral graft with extra-anatomic bypass.

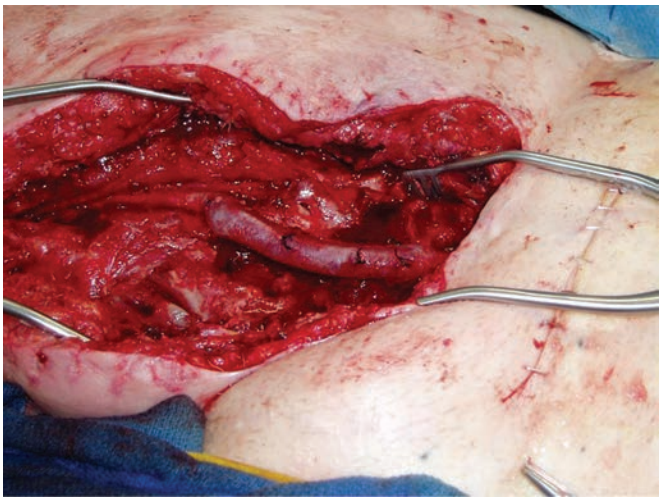

Figure 47.4 Interposition (in situ) replacement with a femoral vein segment after excision of an infected femoral prosthetic graft.

Diffuse aortobifemoral graft infections involving the groin region and with significant associated femoropopliteal occlusive disease can make ex situ approaches to revascularization challenging (Fig. 47.3). Limb loss is more frequent after aortofemoral graft infection than after aortoiliac reconstructions because of the higher risk for ex situ bypass thrombosis or recurrent infection. Unilateral axillofemoral bypasses to the profunda femoris or superficial femoral artery through an uninfected tissue plane have acceptable patency rates (94% at 6 months), but distal anastomoses to the popliteal artery are prone to early failure (42% at 6 months).[64] Preservation of retrograde flow into the common femoral artery by vein patching (and endarterectomy for occlusive disease) after excision of the infected aortofemoral graft is also important for maintaining pelvic flow. A further option for managing aortofemoral graft infection is a unilateral axillofemoral PTFE bypass through uninvolved/less involved tissue, autogenous deep vein cross-femoral bypass in infected fields, and total aortic graft excision.

In Situ Graft Replacement

Autologous Graft Replacement

The great saphenous vein (GSV) or a superficial upper extremity vein can be used for the reconstruction of infrainguinal, visceral, cervical, and upper extremity arteries after excision of an infected graft. However, use of GSV grafts for cross-femoral, iliofemoral, or common carotid/innominate replacement has resulted in limited patency because of size mismatch and occlusion from intimal proliferation.[65] Use of appropriate lengths of a femoropopliteal vein segment has allowed larger-diameter, autologous arterial reconstruction without causing significant morbidity in the donor limb (extensive deep venous thrombosis, limb edema, compartment syndrome) (Fig. 47.4). Preoperative ultrasonographic mapping of the GSV, arm vein, and the superficial femoropopliteal vein (SFPV) can be done in nonurgent scenarios to best match available autologous conduit and repair-site diameters. Adequacy of the femoral vein (absence of acute/chronic thrombus, diameter >5 to 6 mm) can be confirmed by ultrasound when a small-diameter GSV or arm vein (<4 mm) is seen.

Neo-Aortoiliac System Reconstruction

Construction of an in situ neo-aortoiliac system (NAIS) from SFPV after removal of an infected aortoiliofemoral graft was first described by Clagett et al.[66] and Nevelsteen et al.[25] Preoperative ultrasound mapping of the deep leg veins is recommended because long replacement lengths necessitate bilateral harvest. Longitudinal thigh incisions lateral to the sartorius muscle proximally and division of the adductor hiatus are needed, with double-ligation techniques to secure side branch origins. The vein is harvested distal to the profunda femoris origin of the common femoral vein, preserving collateral outflow. Prophylactic lower-dose anticoagulants (heparin, low-dose warfarin) are recommended, as are sequential compression devices applied to the calf regions to augment venous outflow and limit propagation of thrombus in the ligated segments. Patients with prior GSV harvest undergoing SFPV harvest are at higher risk for the development of calf compartment syndrome (up to 12% incidence), so a low threshold for calf fasciotomy should be maintained. Late venous insufficiency and chronic limb edema affects 15% of patients.

SFPV segments are used in a nonreversed configuration after vessel eversion and direct excision of valve cusps. In situ replacement after graft excision and perigraft debridement can be tailored depending on the length of reconstruction needed and available SFPV (Fig. 47.5). If a wide infrarenal aorta is present (18-26 mm), a "pantaloon" technique can be used, in which two SFPV segments are sutured together over half of their circumferences proximally to widen the conduit for end-to-end aortic anastomosis. Excessively large aortic necks (>28 mm) may require ligation and ex situ bypass. If bilateral aortofemoral

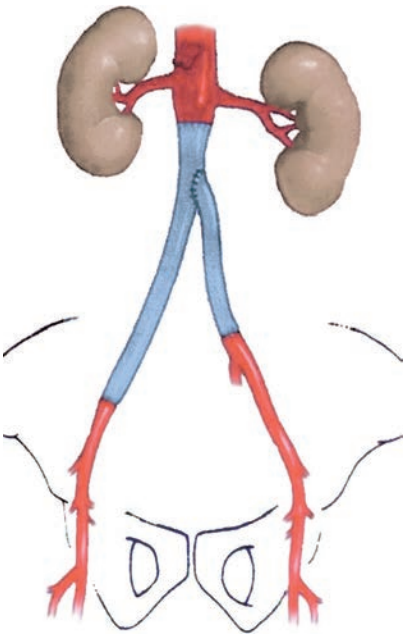

Figure 47.5 Schematic of deep venous replacement (neoaortoiliac system) after excision of an infected aortobi-iliac prosthetic graft. Shortening of the total bypass length (and necessary bilateral femoral vein harvest) is possible because the contralateral femoral vein segment (to the left leg) originates off the mid or distal region of the ipsilateral aortoiliofemoral graft (to the right leg). (From Jackson MR, et al. Excision and autogenous revascularization of an infected aortic stent graft resulting from a urinary tract infection. *J Vasc Surg.* 2002;36:622.)

reconstruction is needed in patients in whom limited lengths of SFPV are available, a unilateral aortofemoral SFPV segment can be used with a shorter cross-femoral SFPV segment between the longer limb and the contralateral groin.

When compared with excision/ex situ bypass, in situ SFPV replacement for diffuse aortoiliofemoral graft infection has been associated with lower mortality and amputation rates, improved graft patency rates, and a lower incidence of recurrent infection (see Table 47.4).[12] Longer-term audits of SFPV replacement by Clagett et al.[66-69] show a primary graft patency rate of 81%, a secondary/assisted patency rate of 91%, and a freedom from amputation rate of 89% at 6 years. This treatment approach has an operative mortality rate of 10% and a 5-year survival of 52%. Early deaths and/or recurrent/residual vein conduit infection and disruption occurred after treatment of GEE/GEF or identification of virulent gram-negative organisms. In situ SFPV replacement is contraindicated under these circumstances. Vein conduit restenosis has been more common with a smaller-diameter femoral vein (<7 mm) and in patients with coronary disease or a history of smoking.[67]

Antibiotic-Treated Prosthetic Grafts

Use of a prosthetic conduit for in situ replacement of infected grafts is a treatment option in selected circumstances. In situ prosthetic replacement with PTFE or polyester conduit has been associated with recurrent infection in 10% to 20% of cases, primarily with gram-negative bacteria and MRSA involvement. These results have increased interest in antibiotic-bonded prosthetic grafts to potentially improve results.[18,70,71]

BOX 47.3 Selection Criteria for and Treatment Components of In Situ Prosthetic Graft Replacement for Biofilm Graft Infection

Selection Criteria

- Clinical:
  - Evaluation months to years after graft implantation
  - No systemic signs of infection—afebrile, normal WBC count, sterile blood cultures
- Anatomic:
  - Limited local inflammation of tissue adjacent to the prosthetic graft
  - Perigraft cavity with absence of graft incorporation
  - Weakening of the graft-artery anastomosis (pseudoaneurysm)
- Microbiologic:
  - Perigraft fluid Gram stain with WBCs, no bacteria
  - Perigraft fluid culture with no growth
  - Graft biofilm culture—coagulase-negative staphylococci (*Staphylococcus epidermidis*)

Treatment Components

- Preoperative and perioperative administration of daptomycin or vancomycin beginning 3 days before replacement
- Wide debridement/excision of inflamed perigraft tissue and the sinus tract if present
- Excision of anastomotic sites
- Cleansing/debridement of tissues and the retained graft segment with cytotoxic wound irrigation
- Use of rifampin-soaked (60 mg/mL) polyester gelatin or collagen-impregnated polyester grafts
- Muscle flap coverage of the replaced graft segment in the groin, omental pedicle coverage of intra-abdominal aortoiliac graft
- Parenteral administration of culture-specific antibiotics for 6 weeks

WBC, White blood cell.

We have advocated graft excision and in situ prosthetic replacement for localized/segmental, low-grade biofilm infections caused primarily by coagulase-negative staphylococci *(S. epidermidis)* (see Table 47.3). More than 50% of late extracavitary graft infections met these criteria and were treated with in situ PTFE graft replacement, with a recurrent infection rate of less than 5%.

Limited morbidity has also been shown with in situ replacement using PTFE and rifampin-soaked (60 mg/mL) gelatin-sealed Dacron for low-grade aortoiliofemoral graft infections (see Table 47.4).[39] Recurrent infections were due to rifampin-resistant *S. epidermidis*, MRSA, or more extensive graft involvement (bilateral graft limbs or aortic graft body), thus emphasizing that optimal results appear to be confined to limited biofilm infections (distal aortofemoral graft). Despite the risk of recurrent/residual infection, in situ prosthetic replacement of a distal aortofemoral graft limb through a groin incision may be preferred over cavitary graft excision and aortic reconstruction in debilitated elderly patients presenting with low-grade biofilm infection and local groin sepsis. Our selection criteria and treatment specifics for in situ prosthetic graft replacement are detailed in Box 47.3. Alternatively, Oderich et al.[72] used in situ rifampin-soaked grafts with omental pedicle coverage to treat limited-involvement GEE/GEF (segmental enteric erosion onto aortic graft body or limb, no anastomosis/aneurysm, no

BOX 47.4 Operative Details of the Use of Cryopreserved Arterial Allografts for Aortic Infection

1. Excise the infected vascular segments and perform perivascular debridement.
2. Thaw and rinse allografts immediately before implantation.
3. Use an appropriate length of allograft to perform a tension-free anastomosis.
4. Perform through-and-through ligature of allograft side branches—avoid the use of metal clips.
5. Use end-to-end anastomosis to native arteries or the retained prosthetic graft—avoid allograft-to-allograft anastomoses and use a single aortoiliofemoral allograft segment to fit the needed anatomic replacement.
6. Provide anastomotic reinforcement with allograft strips.
7. Use gentamicin-impregnated fibrin glue at the suture lines.
8. Use aggressive wound irrigation; consider drainage catheters, muscle flap coverage of the groin allograft, omental pedicle coverage of aortic allograft.
9. Prescribe 6 weeks of parenteral culture-specific antibiotics.

retroperitoneal sepsis), reporting 9% early mortality and 4% reinfection rates. Partial excision of the existing aortic graft was possible in 43% of these selected cases.

Cryopreserved Arterial Allografts

A third option for in situ replacement is the use of aortic and iliofemoral arterial segments harvested from transplant donors and rendered nonantigenic by cryopreservation. Cryopreserved arterial allografts/homografts (CAHs) are now widely commercially available. Specific operative details for allograft implantation are provided in Box 47.4. Allograft replacement may have a primary role in mycotic or prosthetic graft infections of the thoracic or visceral aorta when in situ reconstruction is mandatory. Kieffer and colleagues reported an initial series in 1993 (36 patients)[24] and a more comprehensive experience in 2004 (179 patients)[63] with allograft replacement for infrarenal aortic graft infection. The higher operative mortality was influenced by adverse outcomes in the 30% of patients with GEE/GEF (see Table 47.4). The incidence of limb loss, recurrent infection, and midterm patient survival compares favorably with that for other methods of in situ replacement. However, allograft dilation/aneurysm formation (17%) or stenosis/occlusion (20%) occurred during late (>3 years) follow-up with earlier-generation CAH and fresh homografts. Three recent studies document in situ CAHs used in 151 total patients for arterial infectious pathologies (96 with infected prosthetic aortic grafts) with an overall operative mortality of 10% and a 5% conduit-related complication rate (graft occlusion/stenosis, reinfection, degeneration) during 1 to 3 years of follow-up.[73-75]

Treatment Adjuncts

Antimicrobial Agents

Parenteral antibiotics should be selected according to specific perigraft/graft culture results and adjustments should be made during serial/staged operations with repeated cultures obtained.

Upon presentation with suspected graft infection, empiric broad-spectrum parenteral therapy is indicated with vancomycin (dosing adjusted to renal function and serum levels) and piperacillin/tazobactam 3.375 g every 6 hours, cefepime 2 g every 8 to 12 hours, or levofloxacin 500 mg daily (for penicillin/cephalosporin allergy). On the basis of culture and Gram stain results, biofilm (*S. epidermidis* or *S. aureus*) infections are treated with parenteral vancomycin, and we have abandoned adjunctive oral or intravenous rifampicin (potential emergence of resistant *S. epidermidis* with continued use). Invasive and persistent MRSA soft tissue infection should be treated with higher-dose daptomycin, 6 mg/kg daily. Pseudomonal infections should be "double-covered" with combinations of third- or fourth-generation cephalosporins, piperacillin/tazobactam, aminoglycosides, fluoroquinolones, or carbapenem/monobactams. Parenteral antibiotics should be continued for a minimum of 2 weeks. More invasive infections require 4 to 6 weeks of parenteral antibiotics. Oral amoxicillin/clavulanate or a fluoroquinolone can be used for less invasive, non-MRSA infections after discharge. We use indefinite oral antibiotic therapy as prophylaxis against reinfection only in rare circumstances. Postoperative imaging (CT or ultrasound) should be performed out to 1 year to assure resolution of infection at the treated site.

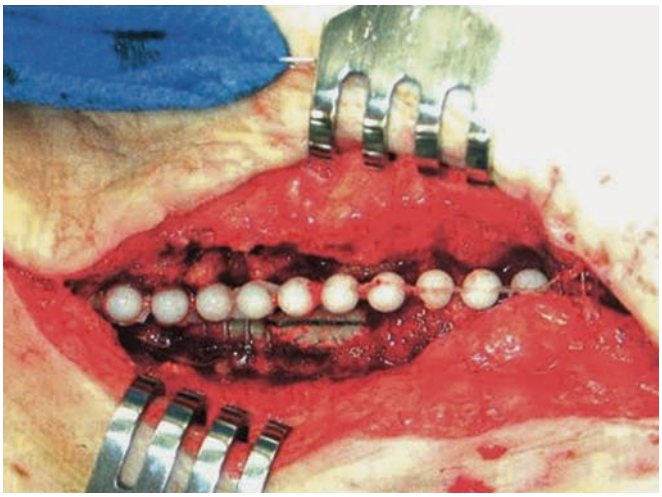

Figure 47.6 Antibiotic-loaded polymethyl methacrylate beads implanted adjacent to an infected polytetrafluoroethylene graft segment and polyester patch. Graft preservation will require further aggressive resection of the skin edges, subcutaneous abscess cavity, and perigraft tissue. (From Stone PA, et al. Use of antibiotic-loaded polymethylmethacrylate beads for the treatment of extra-cavitary prosthetic graft infection. *J Vasc Surg.* 2006;44:757.)

Antibiotic-Loaded Beads

We have used antibiotic-loaded PMMA beads in our wound sterilization algorithm to aid in the treatment of early and late extracavitary prosthetic graft infection.[76] Beads are made in the operating room with PMMA powder, liquid catalyst, and either vancomycin (1 g), daptomycin (1-1.5 g), tobramycin (1.2 g), or gentamicin (1 g) according to initial culture results. The hardening cement mix is molded into 5-mm beads on stainless steel wire mandrels and implanted in the depth of the wound with temporary skin closure and adjacent closed suction drainage (Fig. 47.6). MRSA was found in 44% of initial cultures in our series. After an average of 2.5 bead replacements (staged debridement/washout/beads every 3-4 days) per patient, culture-proven wound sterilization allowed graft preservation or

subsequent in situ reconstruction in all cases. Wound healing and avoidance of recurrent infection were achieved in 90% of cases during an average follow-up of 2 years.

Local Tissue Flap Coverage

Transfer or rotation of local soft tissue structures to provide coverage of preserved or new in situ grafts may be needed when surrounding tissues are inadequate or an excessive skin defect exists. Pedicles of omentum mobilized within the abdominal or lower thoracic cavity are useful for minimizing recurrence after the treatment of aortic graft infections. Use of sartorius muscle flaps has been the most commonly reported technique for groin wound involvement.[77] The muscle is typically exposed lateral to the femoral vessels, divided proximally from its iliac spine attachment, and mobilized medially without tension with preservation of as many segmental feeding vessels as possible (Fig. 47.7). Other muscle/fascial flaps can be used for groin wound VSSI adjuncts, including the rectus abdominis, rectus femoris, and gracilis.

We have used sartorius flaps in 21% (89/422) of groin-related, early and late VSSI cases, primarily as part of graft preservation or in situ replacement therapies.[78] Initial graft bed microbiology revealed 65% gram-positive, 20% gram-negative, and 15% mixed infections. An attempt was made to sterilize groin wounds with staged debridement and antibiotic-loaded beads to allow delayed application (after a mean 9 days) of sartorius flaps. However, immediate flap construction was required in 10% of patients because of extensive soft tissue loss with exposed graft/repair. Flap application was used in nearly half of the cases where the VSSI was improving clinically after staged debridement with no gross infection/exudate but with residual positive wound culture results. Six (7%) recurrent infections occurred over 4 to 5 years of follow-up. Sartorius flaps may not completely eliminate the risk of reinfection for incompletely sterilized graft beds, but muscle coverage can salvage complex groin wounds associated with VSSI.

Endograft Device Infection

The incidence of aortic endograft infection in large institutional experiences has been low (0.1%-1.2%),[79-81] but isolated case reports have evolved into multi-institutional modest-sized cohorts documented more recently (Fig. 47.8).[31,35-37,82,83] One-third of abdominal and thoracic aortic endograft infections manifest as

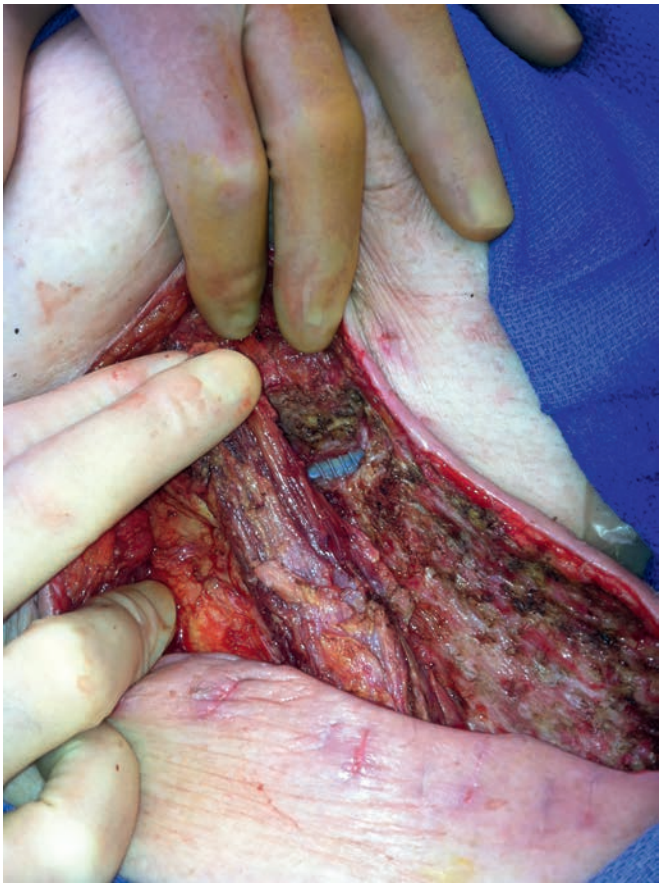

Figure 47.7 Sartorius muscle flap divided superiorly and mobilized toward the upper medial groin wound to cover exposed prosthetic cross-femoral graft after serial debridements of the abscess bed and adjunctive use of polymethyl methacrylate beads loaded with daptomycin plus tobramycin. Skin closure was possible over the sartorius flap, and a bulb-suction drain was placed in the lateral harvested sartorius bed. The patient's head is to the left of photo and the perineum is at the upper edge of the photo.

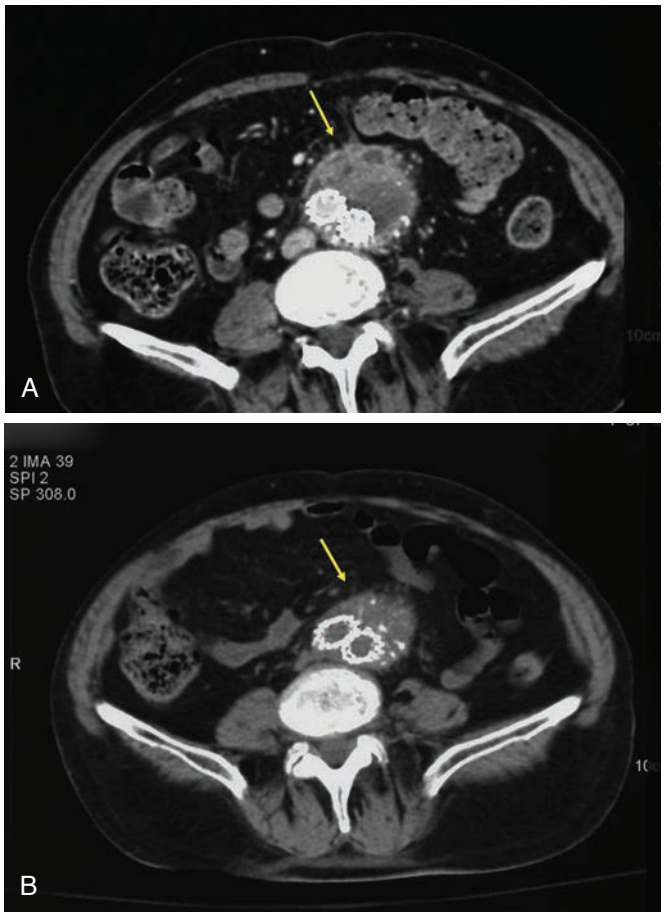

Figure 47.8 Infection associated with an abdominal aortic aneurysm endograft manifested as staphylococcal bacteremia and back pain. (A) Inflammation in the anterior region of the distal infrarenal sac with patent aortoiliac stent-graft limbs *(arrow)*. (B) Resolved inflammation/infection 16 months later, after a 3-month course of parenteral antibiotics *(arrow)*.

aortoenteric or bronchial fistulas, with speculation that residual inflammation results from large intact aneurysms with pulsatility, persistent endoleak, or sac pressurization. Bacteremic or direct seeding may be responsible for endograft infections associated with catheter-based endoleak embolizations.[84]

Definitive treatment of endoprosthesis infection after EVAR, similar to open aortic graft infections, has generally been managed by explantation of the device and ex situ bypass or in situ replacement with SFPV, cryopreserved allografts, or prosthetic graft. The operative mortality risk appears to be significant (10%-30%) for these definitive interventions, with reinfection occurring in 5% to 10% of patients. The potential use of endovascular techniques to treat endograft-related infected pseudoaneurysms or enteric erosions is extrapolated from limited experiences with endograft treatment of mycotic aneurysms or aortoenteric/bronchial fistulas.[85,86] Endovascular repair of primary and graft-related aortoenteric fistulas may be associated with lower morbidity but has shown limited durability and represents only a bridge to definitive open repair.[87]

Several reports have shown successful treatment of endograft infections without device explantation. This approach should be offered only to extremely high-risk patients without aortoenteric erosions who have a rapid, favorable clinical response to parenteral antibiotics (6 weeks' minimal duration). Recurrent or persistent sepsis mandates explantation.

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48 CHAPTER

Anastomotic Aneurysms

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In 1956, Birch et al. reported the first case of anastomotic aneurysm in a patient after prosthetic aortic graft placement.[1] Since then, anastomotic aneurysms have been recognized as an infrequent, although important, late complication of prosthetic arterial reconstruction. Although true native aneurysmal degeneration may occur at an anastomotic site, the majority of anastomotic aneurysms are false because they are composed of a fibrous pseudocapsule rather than the normal component layers of the arterial wall. Notably, anastomotic aneurysms have the potential for significant morbidity and mortality, and they present clinical challenges in their detection, evaluation, and management.

INCIDENCE AND ANATOMIC LOCATION

Overall, anastomotic aneurysms complicate 1% to 4% of arterial anastomoses.[2-5] The incidence of anastomotic aneurysms, however, is influenced substantially by anatomic location, surgical technique, time from anastomotic construction, integrity of the host artery at the original operation, and other local and systemic factors. When reporting incidence, anastomotic aneurysm formation may be described by the number of patients, or more accurately, by the number of anastomoses, as a patient with an aortobifemoral bypass, for instance, has one aortic anastomosis and two femoral anastomoses at risk.[6]

The interval to presentation of anastomotic aneurysm has increased.[7,8] Previously an early phenomenon, anastomotic aneurysms in most modern series present at a mean of 6 years following graft implantation,[8-13] although associated infection can shorten this interval dramatically.[14] Anastomotic aneurysms after reconstruction for aortoiliac occlusive disease are more likely to have late presentations (16 years vs. 9 years for aneurysmal aortic disease)[15] and are more likely to represent degeneration of the anastomosis rather than true aneurysmal change.[16]

The most common anatomic site of anastomotic aneurysm formation is the femoral artery, complicating from 0.5% to 24% of reconstructions. In a large retrospective analysis of

Keywords

anastomosis
pseudoaneurysm
complications
femoral artery
graft

anastomotic aneurysms after prosthetic reconstructions for aortoiliac occlusive disease, van den Akker et al.[17] reported an overall incidence per patient of 13% and an incidence per anastomotic site of 4.8%, 6.3%, and 14% for aortic, iliac, and femoral anastomoses, respectively. In addition, the cumulative freedom from anastomotic aneurysm formation at 15 years was 92%, 84%, and 76% for aortic, iliac, and femoral sites. This propensity of anastomotic aneurysms to form at the femoral location has been documented by others.[6,9]

Large retrospective studies of graft-related complications for abdominal aortic aneurysm repair report a cumulative incidence of anastomotic aneurysm of 1.3% to 3.0%.[18,19] The incidence of aortic and iliac anastomotic aneurysms, however, is probably underestimated because of inadequate surveillance, prolonged time to recognition, and their initially quiescent behavior.[20] Studies with routine radiologic surveillance estimate the incidence of anastomotic aneurysms of the aorta and iliac arteries to be approximately 10%, and may reach 36% by Kaplan-Meier analysis at 15 years.[17,21,22]

The documented incidence of anastomotic aneurysms following carotid endarterectomy (with or without patch angioplasty) is much less, at around 0.3%.[23] However, following repair of extracranial carotid aneurysms, anastomotic aneurysms can complicate 13% to 57% of cases.[24] The interval to presentation may occur as early as weeks following carotid intervention, although the majority of reported cases present from 5 to 12 years after reconstruction. With improved operative technique and the introduction of superior prosthetic materials, carotid anastomotic aneurysms are most commonly associated with surgical site infection and, more specifically, prosthetic infection (see Chapter 94).[25]

PATHOGENESIS

An anastomosis between two vascular structures is potentially subject to failure and hence aneurysm formation. Anastomotic aneurysms occur almost exclusively between prosthetic grafts and native arteries, with only rare occurrences in completely autogenous anastomoses.

When a suture line between two vascular structures is disrupted, an anastomotic aneurysm may form. The egress of blood from the defect forms a pulsatile hematoma that, while in continuity with the bloodstream, becomes lined peripherally with laminated thrombus that eventually becomes encapsulated by surrounding host tissue. A fibroblastic process that initiates the formation of a tissue capsule ensues. The capsule, essentially a false aneurysm cavity, is subjected to systemic arterial pressure and may gradually enlarge, occasionally resulting in local complications of expansion, distal embolization, or rupture.

Several etiologic factors have been implicated in the pathogenesis of anastomotic aneurysms, yet the relative importance ascribed to each factor varies substantially by author or institutional experience. Nonetheless, because anastomotic disruption is pivotal in anastomotic aneurysm formation, the pathogenesis may be conceptualized simplistically by considering local and systemic etiologic factors. Each factor may induce or contribute to anastomotic failure, and each has assumed prominence during various time periods. Because no robust data exist to corroborate the contribution of some of these factors to the development of anastomotic aneurysms, several factors are accepted on a theoretical basis alone (Box 48.1).

BOX 48.1 Factors Associated With the Development of Anastomotic Aneurysms

Local

- Arterial wall degeneration
- Suture line disruption
- Prosthetic graft failure
- Infection/inflammation
- Technical errors
- Mechanical stress

Systemic

- Smoking
- Hyperlipidemia
- Hypertension
- Anticoagulation
- Systemic vasculitides
- Generalized arterial weakness

Local Factors

Arterial Wall Degeneration

Degeneration of the host arterial wall is often associated with progression of atherosclerosis, which compromises vessel integrity and impairs a critical component of the vascular anastomosis.[18,25,26] A consistent operative finding at exploration for anastomotic aneurysm is an intact unit of suture and prosthesis that has nonetheless separated from an attenuated arterial wall. In a cohort of 45 patients with 49 anastomotic aneurysms, Skourtis et al.[12] demonstrated the contribution of host arterial degeneration. After operative treatment, 28 arterial specimens were examined microscopically and demonstrated a reduction or absence of elastic fibers in the media and replacement of smooth muscle cells by acellular fibrous connective tissue. Hyaline degeneration of the media and adventitia was also appreciated. In these instances, however, it can be difficult to differentiate anastomotic false aneurysm development from true aneurysmal degeneration of the native vessel.

Suture Line Disruption

Prosthetic graft anastomosis with a native artery depends indefinitely upon the integrity of the suture line, as no lasting union occurs as would between two native vessels. Suture material, particularly silk, was recognized as a central factor contributing to anastomotic aneurysm formation in early reports. Silk suture gradually dissolves and is eventually resorbed by phagocytosis and other processes. This discovery culminated in the abandonment of silk suture for vascular anastomosis. Unfortunately, several successors of silk, including polyethylene and nylon, were also implicated in anastomotic aneurysm development, in general because of loss of tensile strength and ultimate suture disruption.[26] Monofilament polypropylene (Prolene, Ethicon, Livingston, Scotland) suture was introduced

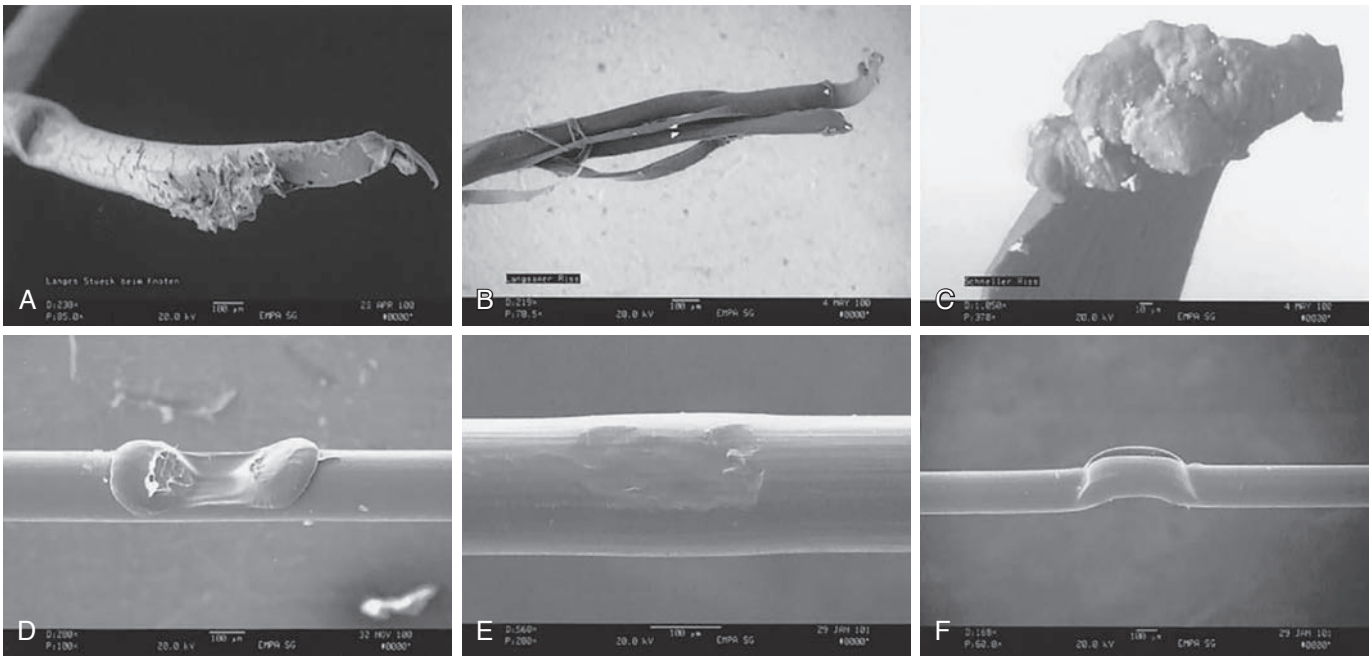

Figure 48.1 Electron Microscopy of Polypropylene Suture. (A) Unexplained suture rupture extracted from an anastomotic aneurysm. (B) Damage from manual slow pulling. (C) Damage from fast pulling. (D) Thermal damage from electrocoagulation with a very short contact time. (E) Damage after soft compression with surgical forceps. (F) Damage after arterial clamp placement. (Reprinted from Huber C, Eckstein FS, Halbeisen M, Carrel TP. Rupture of a polypropylene suture after aortic operation: a scanning electronic microscopical assessment of potential mechanisms. *Ann Thorac Surg*. 2003;75(4):1318–1321 with permission from Elsevier.)

commercially in 1969 and has enjoyed favor among vascular surgeons primarily because of its minimal tissue reactivity, low thrombogenicity, inherent resistance to infection, low coefficient of friction during suturing, and excellent maintenance of tensile strength without biodegradation.[27] Despite these advantages, polypropylene suture readily frays and fractures, particularly with instrumentation and indiscriminate handling (Fig. 48.1).[28] Polytetrafluoroethylene (PTFE) suture is preferred by some surgeons because of its favorable suturing characteristics and relatively inert behavior in tissues, although its breaking strength is half that of polypropylene.[29]

Nonsuture methods of vascular anastomosis that have recently been explored include rings, staples, clips, cuffs, stents, and adhesives.[30-34] Purported advantages of nonsuture methods include decreased tissue reactivity, diminished vessel trauma, and technical simplicity and efficiency. Only clips are associated with an acceptable complication profile.[35] However, these methods have been reported in only small case series, and before adoption can become widespread, long-term data are needed, especially regarding the incidence of anastomotic aneurysm formation.

Graft Failure

Both early and modern generations of prosthetic grafts have infrequently been incriminated as important factors in anastomotic aneurysm formation. Although knitted and, less commonly, woven polyester grafts dilate over time, they consistently maintain their structural integrity. Notwithstanding, several investigators have associated textile graft dilatation and compliance mismatch between the graft and host artery with development of anastomotic aneurysms. Thus prosthetic grafts may indirectly contribute to late anastomotic disruption.[13,36,37] A potential disadvantage of woven polyester grafts is their tendency to fray with handling. However, incorporation of a greater margin of graft into the anastomosis functionally eliminates this feature as a cause of late anastomotic failure (see Chapter 64).

Infection and/or Inflammation

Inflammatory states are recognized causes of anastomotic aneurysms, and are frequently the etiology of early postoperative anastomotic aneurysms. An inflammatory process may occur in response to implantation of prosthetic materials, postsurgical hematoma or lymphocele, or acquired vasculitides, such as Behçet's disease.[38] Inflammation caused by acute or indolent graft infection may also lead to anastomotic aneurysm formation (Fig. 48.2). Even in the absence of clinical signs of infection, bacterial isolates, especially coagulase-negative Staphylococci, have been isolated from as many as 60% to 80% of excised graft material.[39-41]

Technical Errors

Meticulous attention to suturing, including incorporation of generous portions of the arterial wall, especially in arteries subjected to concurrent endarterectomy, is paramount in preventing eventual anastomotic breakdown. Graft tension during construction of an anastomosis also contributes to late disruption and aneurysm formation. Incorrect suture handling, such as

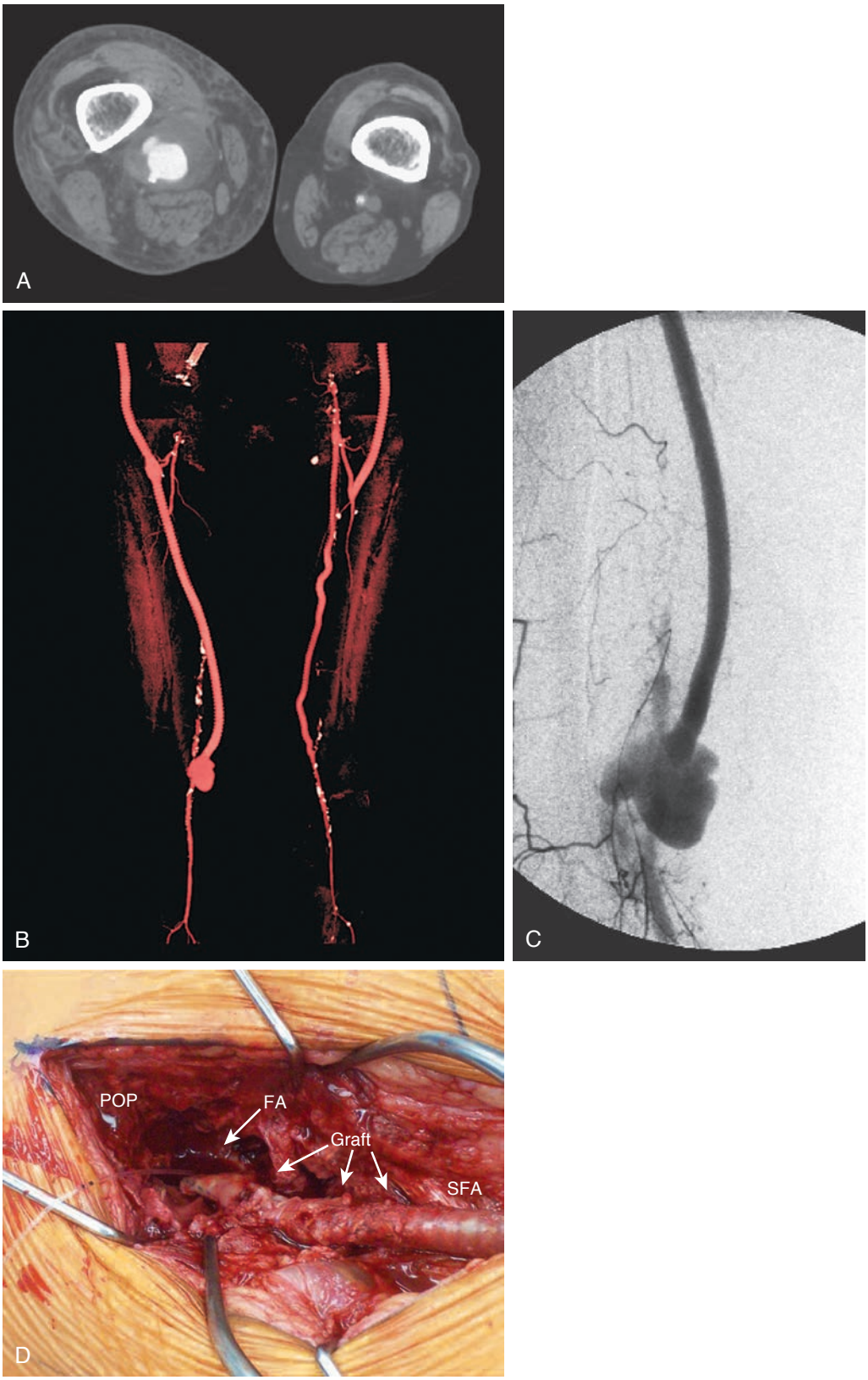

Figure 48.2 Infected Anastomotic Aneurysm Involving the Distal Femoropopliteal Bypass Graft. (A) Axial computed tomographic images from a preoperative angiogram. (B) Reconstructed images from a preoperative computed tomographic angiogram. (C) Intraoperative angiogram demonstrating a false aneurysm. (D) Degenerated polytetrafluoroethylene graft to the popliteal artery (POP) anastomosis. *FA*, False aneurysm; *SFA*, superior femoral artery.

grasping the suture with forceps or clamps, may fracture sutures and predispose an anastomosis to late failure. The use of sutures of adequate strength and size also assists in minimizing technical errors.

Mechanical Stress

Myriad mechanical forces operate at an anastomosis and may differentially contribute to anastomotic aneurysm development. Formation of an anastomosis between a prosthetic graft and an artery establishes compliance mismatch. The inherent properties of a prosthetic graft include nondistensibility and a tendency for latent dilatation, both of which impose mechanical, or shear, stresses on an anastomosis. Laplace's law states that wall tension increases proportionally with radius and pressure. By this, prosthetic dilatation may transmit tension to the suture line and adjacent host artery, resulting in anastomotic disruption. An additional application of this physical principle relates to the diameter of the anastomosis: the greater the diameter, particularly in end-to-side anastomoses, the greater the tension imposed on a suture line.[36,37] Extraneous tension on the anastomosis may result in elastic recoil of the graft, leading to separation from the vessel wall.

According to laws of fluid mechanics, the larger the incident angle between the graft and recipient artery, the lower the flow rate through the anastomosis and the greater the associated turbulence and shear stress on the suture line. Hence minimizing the angle between the host artery and the graft may impart a hemodynamic benefit and prevent late anastomotic complications. In particular, end-to-end, rather than end-to-side, anastomoses better establish optimal hemodynamic conditions and reduce anastomotic turbulence.[42]

Systemic Factors

Several systemic factors are thought to contribute to anastomotic aneurysm formation. Smoking, hypertension, and hyperlipidemia may facilitate anastomotic failure through local effects on arterial wall integrity. Perioperative systemic anticoagulation occasionally complicates the postoperative course through local wound hematoma, a recognized local etiologic factor in anastomotic aneurysm development. Acquired vasculitides are also associated with anastomotic aneurysm development. Behçet's disease, an autoimmune vasculitis, is a multisystem disorder characterized by severe arterial and venous manifestations (see Chapter 137). Operative intervention in patients with Behçet's disease is complicated by anastomotic aneurysm formation in 30% to 50% of these patients because of chronic vasculitis and arterial wall fragility.[38,43] Similar manifestations and complications are observed in Takayasu arteritis and in the connective tissue disorder Ehlers-Danlos syndrome type IV (see Chapter 139 and Chapter 140).[44]

Prevention

An understanding of the pathogenesis and risk factors associated with anastomotic aneurysms contributes to their prevention. Deliberate attention to surgical technique is paramount. Anastomoses must be constructed without excessive tension and by incorporating sufficient graft and arterial wall into the suture line, especially if concurrent endarterectomy is performed. Judicious use of adjunctive endarterectomy is advisable. When feasible, an end-to-end anastomosis should be selected unless preservation of critical vascular beds is required (e.g., retrograde iliac perfusion). If an end-to-side anastomosis is performed, a minimum incident angle should be achieved at the anastomotic site.[2] In the modern era, the choice of suture and graft material is probably irrelevant and subject to the surgeon's discretion. Nonetheless, it is recommended that the selected prosthesis have a diameter equal to that of the recipient artery. Strict attention to skin preparation and aseptic operative technique is critical, as is preoperative antibiotic administration. Additional prophylactic strategies include meticulously achieving hemostasis, minimizing lymphatic disruption, avoiding adventitial dissection (i.e., ex-arterectomy), and accurate wound closure.[9,11,42] Despite adherence to the aforementioned principles, anastomotic aneurysms may not be preventable, so periodic surveillance should be conducted to decrease related complications. All patients treated with graft material should undergo long-term evaluation, including clinical examination, color Doppler ultrasound, and if necessary, angiographic computed tomography (CT).

CLINICAL DIAGNOSIS

The diverse clinical manifestations of anastomotic aneurysms are determined largely by anatomic site. Because most anastomotic aneurysms are asymptomatic, they are generally discovered incidentally during routine surveillance or radiologic examinations for unrelated clinical problems.

HISTORY AND PHYSICAL EXAMINATION

A careful, systematic physical examination will detect most femoral and other superficially located anastomotic aneurysms. In clinical practice, an anastomotic aneurysm is detected by examination as a palpable, occasionally tender, pulsatile mass. Thus periodic clinical evaluation with directed physical examination is recommended indefinitely after construction of prosthetic femoral anastomoses. Over a 15-year period, Demarche et al.[9] retrospectively described their extensive experience with femoral anastomotic aneurysms. Of 142 anastomotic femoral aneurysms, 64% presented as an asymptomatic pulsatile mass, 19% presented with acute limb ischemia, 9% presented as a painful groin mass, and 7% presented with acute hemorrhage. Two patients (1%) presented with distal microemboli and limb edema, respectively. Overt infection complicated the presentation of 7% of anastomotic aneurysms. The majority of other series reported similar presentations.[11,13,45] Thrombosis, embolization, and venous or neurogenic compression are also well-documented complications of femoral anastomotic aneurysms.[14]

Intraabdominal anastomotic aneurysms may evade clinical detection until they cause symptoms or enlarge sufficiently that they become palpable. Most aortic and iliac anastomotic

aneurysms present as an asymptomatic pulsatile mass or with abdominal or back pain, but they can produce more threatening clinical manifestations such as rupture, infection, distal embolization, erosion with fistulization, or hemorrhage.[10,12] Occasionally, aortic and iliac anastomotic aneurysms are discovered incidentally during radiologic examinations for unrelated clinical problems. Many large intraabdominal anastomotic aneurysms are palpable on physical examination, particularly in nonobese patients. Small or intracavitary anastomotic aneurysms, however, are often not appreciated by physical examination and require focused radiologic studies for diagnosis. Despite the relatively high incidence of anastomotic aneurysms long-term from the operating room, there are no clear guidelines in place for routine imaging follow-up of patients with aortic and iliac artery anastomoses.

Many carotid anastomotic aneurysms display progressive asymptomatic enlargement, which is rarely appreciated on physical exam. However, local compression, distal embolization, neurologic symptoms, and even rupture are notable manifestations. Rupture is fortunately infrequent, but may occur in approximately 3% of cases.[24]

Imaging

During surveillance or when an anastomotic aneurysm is suspected but cannot be confirmed by examination, ultrasonography, computed tomographic arteriography (CTA), and magnetic resonance arteriography (MRA) are reliable diagnostic modalities. The quality and resolution of modern CTA and MRA often obviate the need for conventional catheter-based arteriography (Fig. 48.3). Moreover, conventional arteriography often cannot identify or provide size information for anastomotic aneurysms because the true diameter is obscured by thrombus.[46,47] To determine the validity of several current vascular imaging modalities in diagnosing aortic anastomotic aneurysms, Bastounis et al.[48] performed a cross-sectional study comparing B-mode ultrasonography, CT, magnetic resonance imaging (MRI), and digital subtraction angiography (DSA). Defining color-coded Doppler imaging as the "gold standard," they determined that all modalities had sensitivities of 100%, but only MRI, DSA, and enhanced CT possessed sufficient specificity, and only MRI possessed sufficient positive predictive value for diagnostic utility. Although interesting, this study's applicability is limited by the small number of anastomotic aneurysms encountered and by modern technologic improvements in CT and MRI scanners.

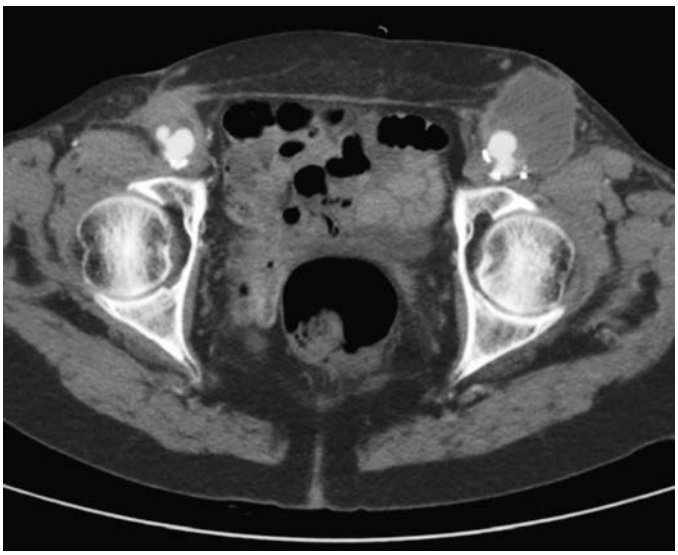

Figure 48.3 Axial computed tomographic image of bilateral femoral anastomotic aneurysm after aortobifemoral bypass.

The discovery of an anastomotic aneurysm at one site, particularly if femoral, necessitates definitive radiologic evaluation of the remaining anastomoses, because synchronous anastomotic aneurysms are often detected and may occur in up to 36% of patients.[17] Similarly, 13% of patients with abdominal anastomotic aneurysms concurrently harbor femoral anastomotic aneurysms.[49]

When an infected anastomotic aneurysm is suspected, nonspecific serum markers such as erythrocyte sedimentation rate and C-reactive protein levels may suggest a systemic inflammatory state. A technetium-labeled white blood cell scan may also assist in determining the probability of an infected anastomotic aneurysm.[50]

SURGICAL TREATMENT

Indications for Treatment

The indications for intervention when an anastomotic aneurysm is detected depend on several interrelated variables, including size, location, symptom status, and suspected etiology. Most concur that femoral anastomotic aneurysms may be safely observed until they achieve a diameter of 2 to 2.5 cm, or until they produce symptoms because of local expansion or distal embolization.[51] While data on rupture risk as a function of size are not available, it is generally accepted that this probability increases as they grow larger.[52] Early appearance of an anastomotic aneurysm often signals a more ominous etiology and frequently requires additional evaluation and earlier intervention. Urgent treatment is required for severe manifestations of anastomotic aneurysms, such as hemorrhage, graft thrombosis, and embolization.

Although less common, aortic and iliac anastomotic aneurysms should be considered for repair at discovery because of difficulties in surveillance and the seriousness of their potential complications.[3,21,22,53] However, some authors recommend selective intervention for aortic and iliac anastomotic aneurysms.[15,47] The decision for repair should be based on assessment of operative risk, and those who do not undergo immediate repair should undergo periodic clinical and radiologic surveillance. Saccular aortic and iliac anastomotic aneurysms represent a special population that historically behave more aggressively and thus may not be amenable to extended surveillance.[54]

Carotid anastomotic aneurysms are rarely encountered in clinical practice but deserve special attention. The morbidity and mortality attributable to these lesions obligate consideration for surgical intervention.[24,55] When infection is suspected or clinically apparent, expeditious intervention is warranted.

Principles of Treatment

Each anastomotic aneurysm should be approached after considering its etiology and how this factor influences its management. Infection should be presumed until definitively excluded by exploration and standard microbiologic techniques. The management of infected anastomotic aneurysms, suggested by perigraft fluid or poor tissue incorporation, often requires complex reconstruction and is associated with increased morbidity and mortality, especially under urgent circumstances.[14,53]

If using an open technique for repair, operative goals include safely obtaining proximal and distal vascular control, careful preservation of important arterial branches and collateral vessels, and replacement or exclusion of the aneurysm to prevent or limit complications. Tedious and hazardous dissection, often in a densely scarred, altered surgical field, is characteristic of such therapeutic endeavors. Care and judgment is required to prevent premature aneurysm disruption that may result in significant hemorrhage. Excessive mobilization should also be avoided to prevent dislodgement and distal embolization of mural thrombus. In particularly difficult dissections, intraluminal balloon occlusion may assist in controlling inflow or outflow arteries and circumvent an otherwise perilous situation.

Although open surgical techniques have predominated in the literature concerning management of anastomotic aneurysms, several authors have published reports of successful endovascular treatment. Endovascular techniques are particularly suitable for treatment of aortic and iliac anastomotic aneurysms, especially with the advent of fenestrated and branched endovascular devices, and in many circumstances they have supplanted conventional treatment strategies (Table 48.1; see Chapter 80).

Open Repair

When suture disruption is the apparent etiology, especially when anastomotic failure occurs early, simple repair of the anastomosis is an option. However, when arterial wall degeneration, or less commonly, graft deterioration is discovered, insertion of an interposition graft is preferred; this technique is associated with excellent patency and low risk of recurrence.

Femoral Anastomosis

Detailed preoperative arteriography assists in operative planning and provides critical information by documenting the patency and location of the involved arteries, the status of the pelvic circulation, and the likelihood of infection. The existing graft is identified through the previous incision and controlled for later occlusion (Fig. 48.4). Large femoral anastomotic aneurysms may necessitate proximal control through a suprainguinal incision. In this approach, an incision is made between the anterior superior iliac spine and a point halfway between the pubis and the umbilicus. The abdominal wall muscles are divided, and the preperitoneal plane is identified. Exposure is carried posteriorly using blunt dissection. The external iliac artery is identified in association with the vein. Circumferential dissection of the artery allows for loop control or clamping. Alternatively, it is often convenient to employ balloon occlusion of the external iliac artery after dissecting the false aneurysm in the groin. Distal control is next secured by careful dissection of the superficial and deep femoral arteries and other important collateral branches. Balloon occlusion may also be used for any branches that are obscured by dense scar tissue, including the profunda femoris artery.

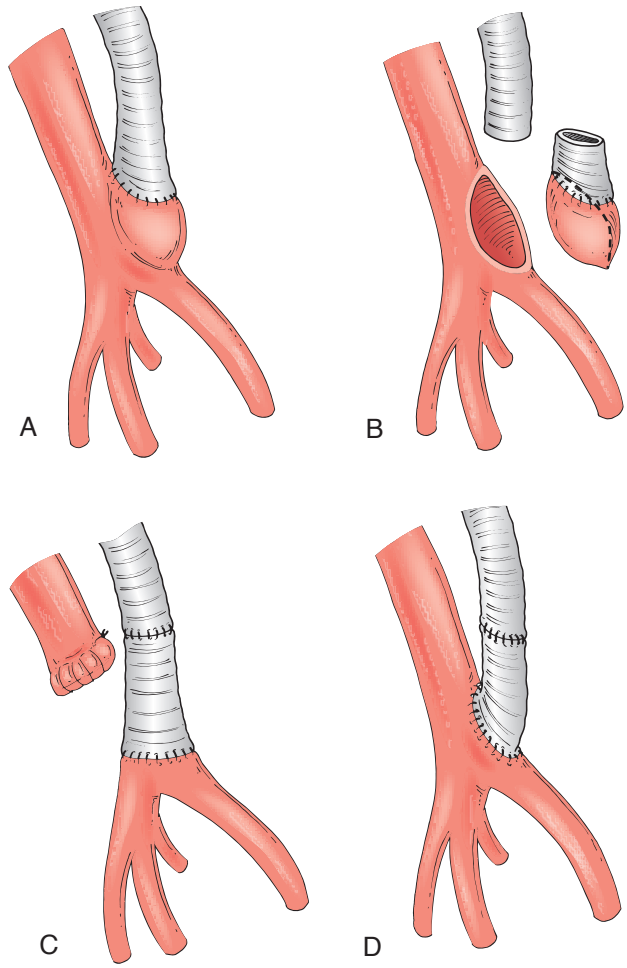

Figure 48.4 (A) Depiction of a femoral anastomotic aneurysm with arterial wall degeneration. (B) View of the femoral anastomotic aneurysm after excision of the false aneurysm. (C) Repair of the femoral anastomotic aneurysm with an interposition graft (end-to-end anastomosis). (D) Repair of the femoral anastomotic aneurysm with an interposition graft (end-to-side anastomosis).

Following systemic anticoagulation, inflow and outflow arteries are occluded atraumatically, and the anastomotic aneurysm is entered. Local signs of infection, such as purulence, perigraft fluid, and poor graft incorporation, are sought. In the absence of overt infection, a tissue or graft specimen is submitted for microbiologic analysis. If the etiology appears noninfectious, interposition graft replacement is performed. If overt infection is present, an extraanatomic reconstruction may be warranted.

The false aneurysm including the distal graft and degenerative native arterial wall is debrided, and an interposition graft of a diameter similar to that of the recipient artery is selected. Some authors prefer polytetrafluoroethylene in their choice of conduit

TABLE 48.1 Endovascular Management of Anastomotic Aneurysms

Series	Year	No. of Patients	Location	Technique	RESULTS (%)					Mean Follow-Up (Mo)
					Infected	Technical Success (%)	Major Complications (%)	30-Day Mortality (%)	Patency (%)	
Adam et al.[56]	2005	3	A	Fenestrated and branched	No	100	33	0	100	12
Beck et al.[57]	2009	18	A	Fenestrated and branched	No	94	11	0	95	23
Bosch et al.[58]	2011	58	A/I	Covered stent	No	95	13	2	74.1	41
Curti et al.[59]	2001	11	I	Covered stent	Yes	100	0	0	100	28
Derom and Nout[60]	2005	7	F	Covered stent	No	100	0	0	100	18.6
Di Tommaso et al.[61]	2007	6	A	Covered stent	No	100	0	0	100	26.1
Faries et al.[62]	2003	33	A/I	Covered stent	No	100	11	0	—	—
Gallitto et al.[63]	2016	20	A	Fenestrated and branched	No	95	25	0	98.7	15
Gawenda et al.[20]	2003	10	A/I	Covered stent	No	100	0	10	100	—
Lagana et al.[64]	2007	30	A/I	Covered stent	No	100	0	3	91	19.7
Magnan et al.[65]	2003	10	A	Covered stent	No	100	10	0	90	17.7
Mitchell et al.[66]	2007	10	A/I	Covered stent	No	100	10	0	—	—
Piffaretti et al.[67]	2007	22	A/I	Covered stent	No	100	5	0	96	16
Reyes et al.[68]	2016	34	A	Fenestrated, branched, and chimney	No	97	18	3	98	23.2
Sachdev et al.[15]	2007	65	A/I	Covered stent	Yes	98	9	3.80	94	18.1
Tsang et al.[69]	2009	11	A/I	Covered stent	No	100	4	0	—	—
van Herwaarden et al.[70]	2004	8	A/I	Covered stent	No	100	20	0	88	12
Wu et al.[71]	2016	24	A	Covered stent	No	100	21	0	0	43
Yuan et al.[72]	1997	12	A/I	Covered stent	No	100	17	0	100	16
Ziegler et al.[73]	2007	9	A	Fenestrated and branched	No	100	3	0	—	12

A, Aortic; *F*, femoral; *I*, iliac.

because of its reduced propensity for dilatation, potentially reducing the incidence of late anastomotic aneurysm recurrence. When permissible, an end-to-end anastomotic configuration is recommended. However, if an end-to-end anastomosis compromises flow to critical vascular beds, such as the pelvic circulation, an end-to-side anastomosis is constructed with care to maintain a minimal incident angle between the graft and host artery. When managing a large false aneurysm, vascularized soft tissue coverage can be achieved with rotational muscle flaps. Several authors strongly advocate similar management techniques.[14,74,75]

Aortic Anastomosis

Preoperative imaging with noninvasive radiologic studies provides vital information regarding signs of graft infection, selection of a proximal clamp location, aneurysm proximity to visceral branches (especially the renal arteries), and the location of retroperitoneal and intraperitoneal structures (Fig. 48.5). Operative approaches vary by surgeon experience and preference, but both retroperitoneal and transperitoneal approaches have distinct advantages and disadvantages. Frequently, a suprarenal clamp location may be necessary if the anastomotic aneurysm is juxtarenal, and proximal control may be more safely obtained, especially in the presence of scar tissue, via a retroperitoneal approach, especially if it helps avoid the previous operative field.

When open repair is contemplated, most frequently an aortoaortic bypass is performed with a tubular prosthesis that originates from the proximal normal, nonaneurysmal aorta to the existing graft distally. Occasionally, visceral branch bypass is required to ensure a secure proximal anastomosis. Less frequently, and if distal anastomotic revision is required concurrently, implantation of a bifurcated graft (aortobiiliac or aortobifemoral) is expeditious.[76] If an infectious etiology is discovered intraoperatively, graft excision with extraanatomic bypass or autogenous in situ reconstruction is performed. In cases of infected aortic grafts involving the visceral or renal branches, direct reconstruction with nonautologous conduit may be unavoidable.

Iliac Anastomosis

As with aortic anastomotic aneurysms, intervention for iliac anastomotic aneurysms relies on accurate, high-quality noninvasive imaging for operative planning. Often the aneurysm involves the distal anastomosis of a bifurcated prosthesis and is located at or close to the iliac bifurcation. A retroperitoneal (flank) approach provides adequate exposure. Operative principles parallel those employed at aortic locations. Preservation of the internal iliac artery often complicates reconstruction, but may be accomplished with a separate bypass. The ureter should be carefully identified and protected, especially when managing large or inflammatory anastomotic aneurysms. Methods of ureteral protection include identification of the ureter in proximal unaltered tissue planes and preoperative placement of a ureteral stent.

Carotid Anastomosis

Based on clinical experience with primary carotid artery aneurysms, anastomotic aneurysm management using nonoperative strategies is thought to yield excessive morbidity and mortality.[77] Traditional management of carotid anastomotic aneurysms depends largely on the clinical suspicion or subsequent intraoperative discovery of infection, especially when a prosthetic patch is present. The preferred method of reconstruction is resection of the aneurysm with interposition bypass grafting or repair with patch angioplasty. Resection with primary anastomosis, extracranial to intracranial carotid bypass, and carotid ligation have also been described.[23] When infection is the presumed etiology, reconstruction with the saphenous vein is indicated. Carotid ligation has generally been limited to use in failed reconstruction attempts, and has been associated with a mortality rate of 28% to 50%.[23,77,78]

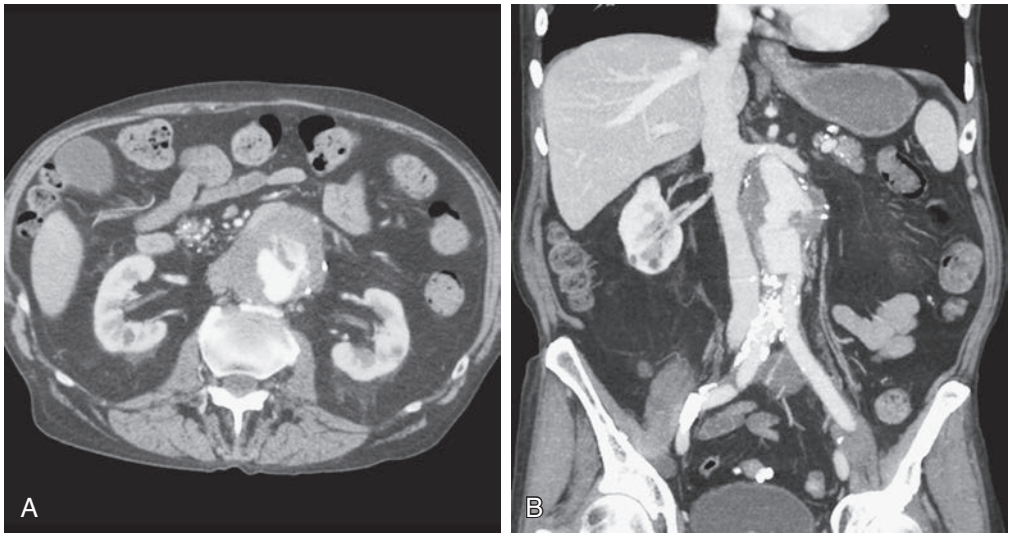

Figure 48.5 Proximal Aortic Anastomotic Aneurysm After Aortobifemoral Bypass. (A) Axial view. (B) Coronal view.

Endovascular Repair

Femoral Anastomosis

Open operation represents the traditional management strategy for femoral anastomotic aneurysms. Endovascular repair of anastomotic aneurysms at this location is problematic because of chronic hip motion that may cause deformation, fracture, or migration of implanted stents. Successful endovascular management of ruptured and nonruptured femoral anastomotic aneurysms, however, has been reported in cases of prohibitive operative risk.[78,79]

Aortic Anastomosis

Conventional open repair of aortic anastomotic aneurysms is formidable and is associated with mortality rates of 3% to 17%.[21,70] By avoiding the risks of re-operative aortic exposure and suprarenal aortic clamping, endovascular repair presents an attractive therapeutic alternative. Endovascular exclusion of aortic anastomotic aneurysms has been successfully described with both homemade and commercially manufactured stent-grafts, including tubular, bifurcated, and aortic uni-iliac stent-graft configurations.[15,64,70,80,81] Additionally, fenestrated, branched, and chimney devices are being increasingly used for proximal aortic anastomotic aneurysms involving the visceral vessels.[56-58,63,68,73,82-84] Stent-graft repair of ruptured anastomotic aneurysms is equally efficacious and advantageous.[73]

Important considerations include the ability to obtain detailed and high-definition CTA with multiplanar reconstructions for precise aortic measurement and graft selection. Particular attention is directed toward the proximal neck to ensure that adequate conditions exist for successful sealing. Neck diameter and length from the lowest renal artery to the flow divider of the existing graft are critical factors. A segment of nonaneurysmal aorta adjacent to the anastomotic aneurysm (the "neck") is vital to allow endograft fixation and aneurysm exclusion. The availability of a suitable neck is often the limiting factor in this form of therapy. Suprarenal fixation may provide additional proximal stability without an adverse effect on renal function.[73] Several investigators have noted late complications of endoleak and rupture when tubular endografts are employed because of insecure fixation to polyester graft and exclusive reliance on radial force.[19] However, sufficient graft oversizing (10%-20%) should permit secure sealing.[73]

When the distance from the lowest renal artery to the flow divider is insufficient to permit deployment of a modular bifurcated endograft, an aortic uni-iliac graft may be inserted with adjunctive femorofemoral bypass. As with endovascular repair of de novo aortoiliac aneurysms, internal iliac artery occlusion is occasionally necessary to achieve distal fixation without endoleak.[70,73] To avoid the risks of buttock claudication, pelvic ischemia, and rarely spinal cord ischemia, pelvic collateral circulation must be carefully investigated. Efforts to preserve at least one internal iliac artery are prudent.[57] When intentional internal iliac artery occlusion is planned, proximal embolization is recommended to prevent interruption of important collateral branches.

Increasing use of fenestrated and branched endovascular stent-grafts for the repair of proximal aortic anastomotic aneurysms has been reported, especially in cases where the length or quality of the proximal neck is insufficient.[56,84] Beck et al. described 18 patients with previous aortic reconstruction who developed juxtarenal aortic aneurysms from 2004 to 2008.[57] Technically successful treatment with fenestrated and branched endovascular stent-grafts occurred in all cases, and perioperative complications, including congestive heart failure and myocardial infarction, only occurred in two patients. Thirty-day and 1-year mortality were 0% and 11%, respectively. Mean follow-up was 23 months, with a cumulative primary patency at 95%. Zeigler et al. retrospectively reviewed their experience with the use of fenestrated and branched grafts for para-anastomotic aortic aneurysm repair in patients who were considered high risk for open surgical repair.[73] Of the nine patients who received fenestrated endoprostheses, technical success was achieved in all. Transient kidney injury was seen in three patients, and permanent renal impairment was seen in one. More recently, Reyes et al. reported on a series of 34 patients undergoing endovascular repair for pararenal aneurysms after prior open abdominal aortic repair.[68] While the majority of patients underwent fenestrated or branched graft repair, four patients underwent chimney-EVAR. The technical success rate was 97%, with a 3% 30-day mortality. During follow-up, six patients (18%) underwent reintervention, although primary patency of the target aortic branches was 98%. While short- and mid-term outcomes of fenestrated and branched EVAR are promising, long-term outcomes are still largely unknown. Furthermore, specific complications from using these complex techniques, such as target vessel occlusion and type III endoleaks at the side branch joints should be considered during the initial perioperative period and throughout follow-up.

In complicated cases in which the anastomotic aneurysm encroaches on the renal arteries, superior mesenteric artery or celiac trunk, an alternative to a completely endovascular fenestrated or branched repair is a hybrid repair.[83,85] In a review of their experience with complicated pararenal and thoracoabdominal aortic pathologies treated with hybrid approaches, Böckler et al. described two para-anastomotic aneurysms treated with commercially available endografts after open revascularization of visceral and renal arteries.[85]

Concurrent infection should generally be excluded before committing to an endovascular repair strategy, a decision that relies on clinical and radiologic data. When an aortoenteric fistula is present, stent-graft repair may function as a bridge until definitive therapy can be accomplished. If endovascular repair is performed as definitive therapy, it should be used in conjunction with extended antibiotic treatment with possible lifelong antibiotic prophylaxis.[16,57,86]

Isolated reports also chronicle the management of both aortic and iliac anastomotic aneurysms with percutaneous embolization using traditional coils, *n*-butyl cyanoacrylate, and Amplatzer (AGA Medical Corp., Plymouth, Minnesota) atrial septal defect occluder devices.[87-89] Badran et al. reported a case of embolization with transcatheter delivery of thrombin to a thoracic aortic pseudoaneurysm at the anastomosis between graft and native aorta patch.[90] It is important to note that the neck

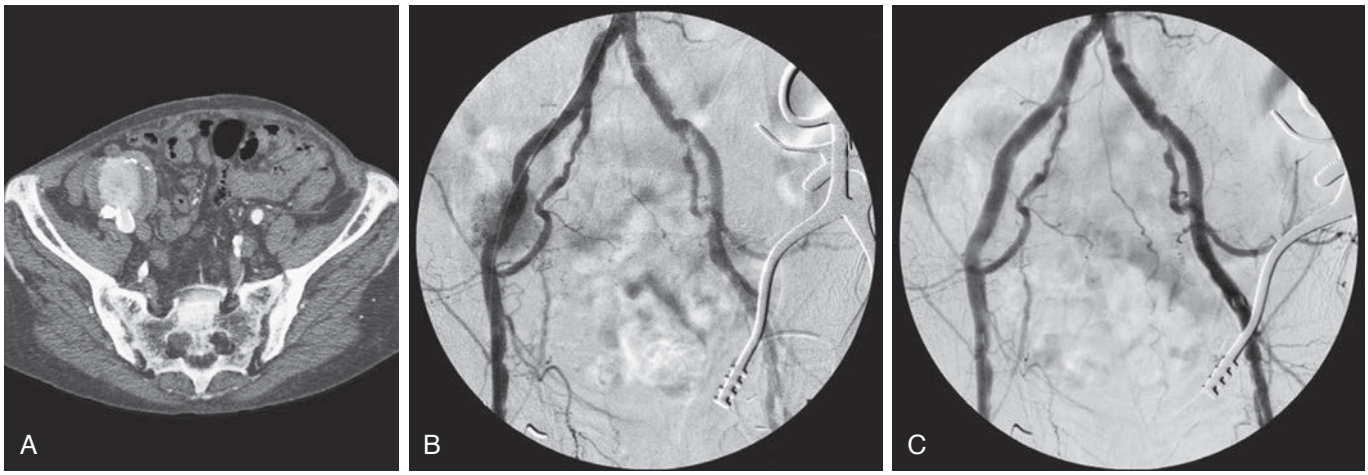

Figure 48.6 (A) Axial computed tomography of a right external iliac anastomotic aneurysm. (B) Diagnostic arteriogram demonstrating a right external iliac anastomotic aneurysm. (C) Successful exclusion of the external iliac anastomotic aneurysm with a covered stent.

of this pseudoaneurysm was narrow, and catheter placement actually occluded the neck, which allowed for successful intervention, emphasizing that practice must be tailored to well-suited cases.

Iliac Anastomosis

Open repair of iliac anastomotic aneurysms is also technically challenging and is associated with significantly higher morbidity and mortality than primary iliac aneurysm reconstruction.[91,92] Endovascular treatment principles are similar to those employed in the management of aortic anastomotic aneurysms, and successful intervention has been described (Fig. 48.6).[93] Management is frequently complicated by a patent internal iliac artery that requires embolization and coverage for successful aneurysm exclusion.[94] However, when preservation of the artery is necessary, separate revascularization with bypass is a durable solution. Hybrid techniques combining open and endovascular repairs have been successfully used in both symptomatic and ruptured iliac aneurysms.[95,96]

Carotid Anastomosis

Endovascular techniques recently have been adapted to the management of carotid anastomotic aneurysms. To avoid a difficult dissection and ameliorate the risk of cranial nerve injury, a few investigators have reported successful management of extracranial carotid aneurysms with stent-grafts, endovascular balloon occlusion, and bare-metal stents with adjunctive coil embolization. Zhou et al. reported their experience with the endovascular treatment of 14 carotid anastomotic aneurysms over a 10-year interval.[24] Length of hospital stay, cranial nerve injury, and 30-day mortality and stroke rates were significantly lower than those in patients managed with conventional open reconstruction during earlier and concurrent periods. Primary patency of endovascular intervention appears acceptable during early and intermediate follow-up,[97] and no progression of neurologic symptoms has been reported.[98] However, long-term results are currently unavailable.

OUTCOMES

Compared with treatment of de novo arterial aneurysms, therapy for anastomotic aneurysms is associated with greater morbidity and mortality primarily because of challenges associated with remedial intervention and advanced medical illness in elderly populations. Mulder et al., in a retrospective analysis of 220 noninfected anastomotic aortic aneurysms managed surgically, reported overall intraoperative mortality rates of 4.5% and 24% in elective and emergency circumstances, respectively.[53] Similarly, open repair involved an overall morbidity rate of 53% (50% in elective and 70% in emergency operations), with a 14% rate of re-intervention and a 2.6% amputation rate.

As with de novo aneurysms, the mortality rate associated with ruptured aortic anastomotic aneurysms is dismal, estimated at 67% to 100%.[47,53] The discrepancy in mortality and morbidity between elective and emergency repair of anastomotic aneurysms highlights the argument for early elective repair. For example, Bianchi et al. found 31 treated anastomotic aneurysms in their single institution review over a 25-year period.[99] The mortality rates among the elective and emergency cases were 5% and 66.6%, respectively, and the morbidity rates were 57.8% and 75%, respectively. In addition, the survival rate during follow-up was significantly higher for elective than emergency cases. While elective repair of anastomotic aneurysms carries a higher operative risk than the initial grafting procedure, it appears to be acceptable when compared with the risk of emergency repair following rupture.

Endovascular repair of aortic and iliac anastomotic aneurysms is associated with high technical success and reduced early- and intermediate-term morbidity and mortality compared with open repair. At intermediate follow-up, aneurysm exclusion is consistently observed without a significant incidence of endoleak or conversion to open repair.[73] Bosch et al. demonstrated the durability of endovascular repair of anastomotic aneurysms after previous open aortoiliac reconstruction.[58] The retrospective review of four centers' experience with anastomotic aneurysms

in 80 aortic and iliac anastomoses demonstrated high technical success rates and acceptable mortality and morbidity. Exclusion was successfully maintained in 86% of the anastomotic aneurysms over a mean follow-up of 41 months (range 0-106 months).

With modern techniques—namely, interposition grafting—recurrence rates after repair of femoral anastomotic aneurysms have improved.[11,83,100] Recurrences after initial operative repair occurred in 9.5% to 19% of patients.[53,101] The risk of recurrence increased with graft dilation and continued arterial wall degradation, as well as with local wound complications and female sex.[4,102] Compared with the primary operation, repair of femoral anastomotic aneurysms was associated with increased morbidity, including a significant incidence of perioperative hemorrhage and wound infection.[103] The effect of different repair techniques on postoperative complication rates has not been reported.

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49 CHAPTER

Local Complications: Aortoenteric Fistula

ROSS MILNER and SAMANTHA MINC

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Aortoenteric fistula (AEF) is defined as a communication between the aorta and gastrointestinal (GI) tract. AEF is classified as primary or secondary based on the underlying cause leading to the fistula development. Primary AEF is a communication between the native aorta and GI tract; secondary AEF is a communication between a reconstructed aorta (for either aneurysmal or occlusive disease) and the GI tract.

Sir Astley Cooper was the first to describe a primary AEF in a publication in 1829. He referred to it as a "sometimes but serious complication of an aneurysmal aorta."[1] Brock published the first report of a secondary AEF in 1953, wherein he described a fistula between the proximal anastomosis of an aortic homograft and the duodenum.[2] Zenker performed the first repair of a primary AEF in 1954 by primary closure,[3] and MacKenzie et al.[4] performed the first successful repair of a secondary AEF in 1958.

AEF presents a particularly complicated challenge for the vascular surgeon. When it is left untreated, the outcome is almost universally fatal. However, surgical repair is fraught with complications, and despite continued advances in medicine and critical care, morbidity and mortality rates remain high.

In addition to the difficulties encountered with surgical treatment, AEF is notoriously difficult to diagnose, and as such, a high index of suspicion is required in approaching any patient with GI hemorrhage and history of aortic disease. This chapter reviews the pathogenesis, etiology, diagnostic methods, and treatment options for AEF.

PRIMARY AORTOENTERIC FISTULA

Incidence, Etiology, and Pathogenesis

The incidence of primary AEF has been reported at 0.04% to 0.07% in large autopsy series.[5] The body of literature available on the subject of primary AEF is small, with approximately 251 cases available in the published literature.

Despite the rarity of primary AEF in the population overall, the incidence in patients with aneurysms of the abdominal aorta is 0.69% to 2.36%.[6] In the majority of cases (83%), an aneurysmal aorta is associated with primary AEF; foreign bodies, tumors, radiotherapy, infection (historically due to tuberculosis and syphilis but now most commonly caused by *Klebsiella* and

Salmonella), and GI tract disease (peptic ulcer disease and perforating biliary stones) account for the remainder of AEF. The mean diameter of the aorta with primary AEF is 6.2 cm; the mean age of patients is 64 years, with a male-to-female ratio of 3:1.[7]

The most commonly described GI tract location for primary AEF is the third and fourth portion of the duodenum (54%). It is presumed that this is due to the tethering effect of the ligament of Treitz, leaving this portion of the duodenum exposed to the direct pulsatile pressure of the aorta. Primary AEF has also been described in the following locations: esophagus (28%), small and large bowel (15%), and stomach (2%).[7]

Overall, the pathogenesis of primary AEF is uncertain. The proposed mechanisms are mechanical, infectious, and inflammatory (Fig. 49.1). In the majority of cases, the mechanical component is caused by the pulsatile pressure of an expanding aorta against the wall of the GI tract. This leads to local compression and ischemia, with weakening of the wall and eventual erosion with fistula formation.

SECONDARY AORTOENTERIC FISTULA

Incidence and Etiology

Secondary AEF is more common than primary AEF and is related to prior vascular surgery, with an incidence of 0.36%[8] to 1.6%[9] reported after open abdominal aortic graft reconstruction. The interval from aortic reconstruction to onset of symptoms is on average 2 to 6 years after graft placement. Secondary AEF involves fistulization between the GI tract and a prior vascular reconstruction for either aneurysmal or occlusive disease. Although it is typically described as occurring in the setting of a synthetic graft, secondary AEF has also been reported with aortic homograft reconstruction and allografts. Similar to primary AEF, the most common location described for secondary AEF is the distal duodenum and proximal jejunum. However, secondary AEF has been described at multiple GI sites depending on the location of the prosthetic graft.

Secondary AEF has been further classified based on the location of the fistula regarding the suture line of the graft (Fig. 49.2). A fistula that has a direct communication between the arterial circulation and the GI tract at the level of the suture line is classified as a graft enteric fistula. Communication between the GI tract and the graft interstices (but not at the suture line) is referred to as a graft enteric erosion. Both entities are highly morbid complications that require urgent management; however, the etiology and presentation may differ. The graft enteric fistula's

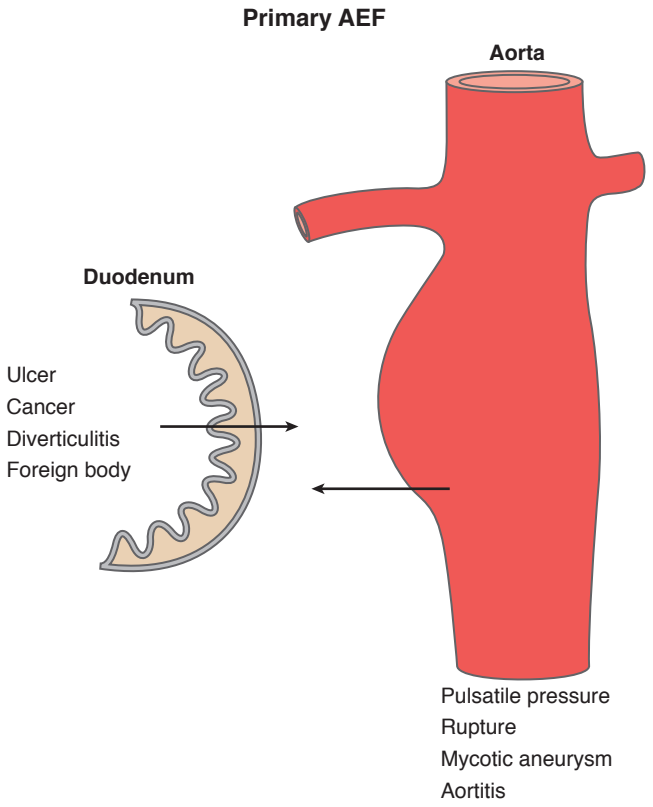

Figure 49.1 Etiologic factors for primary aortoenteric fistula (AEF). Pulsatile pressure from an expanding aneurysm is thought to be the predominant feature in the development of primary AEF. Other factors related to intrinsic bowel conditions may play a role in the development of primary AEF in a minority of cases.

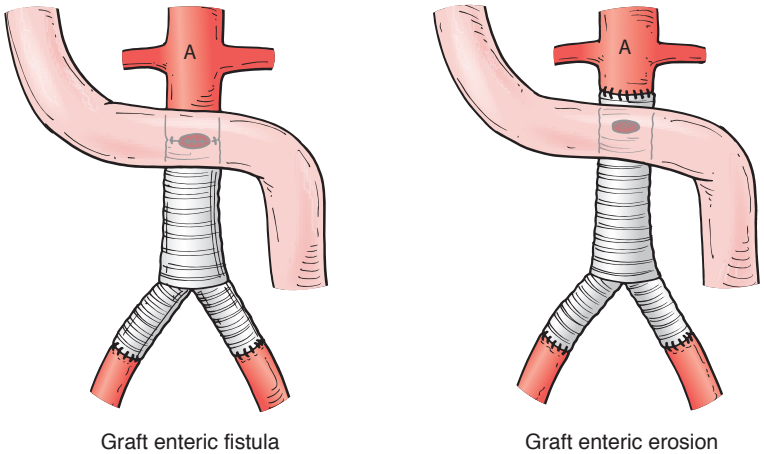

Figure 49.2 Graft enteric fistula versus graft enteric erosion. Graft enteric fistula has a communication between the bowel and the arterial circulation at the level of an arterial prosthetic suture line. Graft enteric erosion has a communication between the bowel and the interstices of an arterial prosthetic graft without involvement of the suture line.[10]

involvement of the suture line will disrupt the arterial anastomosis and causes dramatic hemorrhage, whereas graft enteric erosion may be manifested first with infectious symptoms as a result of direct contact of the graft material with the GI tract, allowing bacterial translocation to occur between the interstices of the graft from the GI tract.

The etiology of secondary AEF includes both patient and surgical factors that occur during the initial placement of the graft. A history of multiple vascular procedures, wound complications, infection, emergency operation, and technical error have been found to predispose to secondary AEF formation.[11]

Pathogenesis

The proposed mechanisms of secondary AEF pathogenesis are infection, pulsatile pressure, and technical error.

Infection

Infection, introduced either at the time of initial surgery or through bacteremia, is an important cause of secondary AEF formation. Graft infection leads to local inflammation and results in breakdown of the suture line, pseudoaneurysm (PSA) formation, and eventual rupture into surrounding structures. The majority of patients described in case reports with AEF have clinical and bacteriologic evidence of graft infection at the time of reoperation. A study by Busuttil et al.[12] demonstrated the role of infection in the pathogenesis of AEF with a canine model of 24 animals divided into four groups. In group 1, the duodenum was fixed to the proximal suture line of a Dacron aortic interposition graft. Group 2 underwent the same procedure but was subjected to an infusion of *Staphylococcus aureus*. In group 3, a false aneurysm was created with a patch of duodenum incorporated onto the anterior aspect of the proximal suture line. The same procedure was performed in group 4; however, this group was also subjected to *S. aureus* infusion. At the end of 6 weeks, no dogs in group 1 had an AEF, two of six dogs in group 2 had an AEF, three of six dogs in group 3 had an AEF, and five of six dogs in group 4 had an AEF. This study clearly demonstrated that infection is a key factor in the formation of AEF, independent of any mechanical or technical factors.

Pulsatile Pressure

Pulsatile pressure also remains a factor in the proposed mechanism of AEF formation. As described earlier, pressure from a noncompliant prosthesis against the bowel wall may lead to ischemia to the surrounding tissue and eventual erosion. Another mechanism described is suture line disruption, leading to the formation of an expanding PSA, compressing surrounding structures and eventually eroding into the bowel. Despite the intuitive nature of this mechanism, the majority of studies continue to point to the issue of infection as the root cause of AEF.

Technical Error

The final factor in the formation of AEF is technical error. This includes inoculation of the prosthesis at time of implantation as well as duodenal injury, serosal thinning, and ischemia during the operation. Changes in standards in patient preparation and appropriate antibiotic administration intraoperatively have decreased the overall rate of aortic graft infection. Operative trauma to the bowel, however, remains an issue. The bowel can be injured during the initial dissection and exposure either directly with sharp injury and heat transfer from cautery or indirectly by overretraction and tension. Retraction injury may occur from the retractor blades directly; however, it may also occur by overcompression of the bowel, causing ischemia, or by allowing the bowel to become dehydrated outside of the body. Methods to reduce bowel trauma include wrapping the bowel in warm moist laparotomy sponges during the procedure (being mindful to resoak the sponges intermittently), keeping the bowel intraperitoneal by packing it above the liver (which can be difficult in larger patients), and using an isolation bag to keep the bowel moist and protected (but still visible) while it is outside the abdomen. Another method to reduce bowel trauma is by using a retroperitoneal approach and interposing tissue between the aorta and the graft at the end. Proponents of the retroperitoneal approach believe that avoiding division of the parietal peritoneum to expose the aorta limits the devitalization of tissue and development of adhesions between the graft material and bowel. Regarding interposition of tissue between the aorta and graft, aortic sac closure followed by a second layer of retroperitoneal tissue and parietal peritoneum is the preferred approach. If that is unavailable, a flap of greater omentum or a layer of bovine pericardium patch material may be used. Omental coverage may be necessary more commonly in end-to-side graft anastomoses to the aorta, rather than in end-to-end anastomoses, and in thin patients.

Aortoenteric Fistula After Endovascular Repair

There is a growing body of literature documenting reports of AEF after endovascular aneurysm repair (EVAR) and thoracic endovascular aneurysm repair (TEVAR). There have been approximately 20 aortoenteric fistulae reported in the case of EVAR and 20 aortoesophageal and aortobronchial fistulae reported in the case of TEVAR. Proposed mechanisms in the case of endovascular repair include persistent endoleak with growth of the residual sac, multiple coiling efforts to repair an endoleak, erosion of the stent-graft through the aorta, endotension, and infection at the time of graft placement.[13,14] More recently, the Multicenter Study on Aortoenteric Fistulization After Stent Grafting of the Abdominal Aorta (MAEFISTO) study evaluated 3932 patients who underwent EVAR between 1997 and 2013 at eight Italian centers with EVAR programs. Of the patients who underwent EVAR at the participating centers, 22 presented with AEF on follow up, 15 of which underwent EVAR for atherosclerotic aneurysmal disease and 7 for postsurgical PSA. On subgroup analysis, they found that the incidence of AEF development of EVAR was 0.46% in patients undergoing EVAR for atherosclerotic aneurysmal disease and 3.9% when performed for PSA. Anastomotic PSA as indication for EVAR, and urgent/emergency EVAR were significantly associated with AEF development. There were no significant associations between choice of endograft and fistula

formation. The increased risk of AEF after EVAR for PSA does suggest that a preexisting infectious process or even subclinical AEF formation may have already been present at the time of EVAR placement in these cases. In urgent/emergency surgery, the presence of a hematoma compressing surrounding structures or the overall increase in local inflammation in emergency repair may contribute to the formation of AEF.[15]

CLINICAL PRESENTATION

The classic clinical triad for primary AEF as described by Sir Astley Cooper in 1829 consists of GI bleeding, abdominal pain, and a pulsatile mass. Recent reviews note the incidence to be 64% to 94% for GI bleeding, 32% to 48% for abdominal pain, and 17% to 25% for a pulsatile abdominal mass, with all three of these symptoms occurring concurrently in only 11% of cases.[16] Other symptoms reported include back pain, fever, and sepsis. Laboratory findings have been reported in only half of the studies, and only two thirds of patients demonstrated a hemoglobin level lower than normal (8 mmol/L). One-quarter of patients had leukocyte counts above the upper limit of normal (10×10^9).[12]

In the case of secondary AEF, hemorrhage remains an important feature of the presenting symptoms. In a recent retrospective review of 4137 patients who underwent aortic reconstruction between 2000 and 2008, 37 patients (0.08%) presented with secondary AEF. Of these patients, 73% presented with some form of hemorrhage, 41% with sepsis, 22% with abdominal or back pain, 14% with graft limb thrombosis, 11% with a groin fistula, 8% with a peripheral abscess, 5% with a femoral PSA, and 5% with peritonitis.[17]

In both primary and secondary AEF, a classic clinical feature is the "herald bleed." This is a minor bleed that is self-limited because of vasospasm and thrombus formation. Herald bleeds may lead to hospital admission immediately; however, some patients experience multiple episodes of recurrent bleeding. Regardless of the initial presentation, an untreated herald bleed is commonly followed by an exsanguinating bleed within hours to months.

DIAGNOSIS

The diagnostic approach to the evaluation of AEF is dependent on the patient's hemodynamic status on presentation. In general, a high level of suspicion should be maintained in approaching any patient with massive GI bleeding and a history of an aortic aneurysm or previous aortic revascularization. In such cases of massive bleeding, diagnosis will often be made during exploratory laparotomy. If the patient is stable, the three major diagnostic modalities are computed tomography (CT) with iodinated contrast enhancement, esophagogastroduodenoscopy (EGD), and angiography. There has been some controversy in the past about which study should be done first; some authors have recommended EGD, followed by CT scan, followed by visceral angiography if no source is found. However, with the improvements of radiologic imaging, CT scan has become a preferred initial diagnostic test; CT scans are less invasive than EGD or angiography, are easy to obtain, and do not risk thrombus dislodgment.[18]

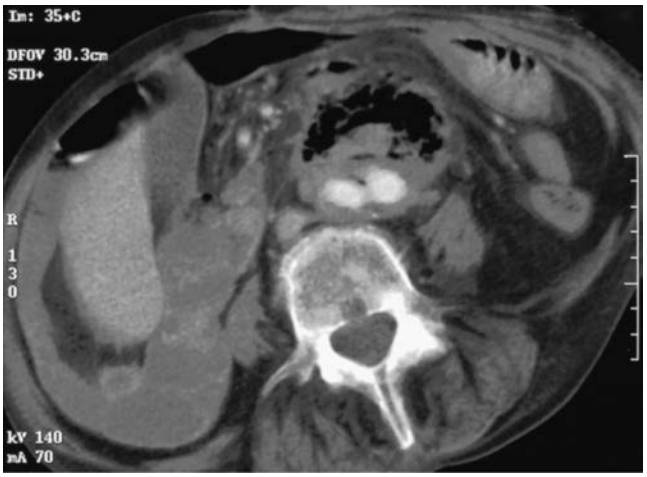

Figure 49.3 Contrast-enhanced computed tomography scan of a patient with a secondary aortoenteric fistula. Note the accumulation of gas and retroperitoneal inflammation surrounding a bifurcated aortic prosthesis.

Investigations

Computed Tomography

Common findings on CT scan include effacement of the fat planes around the aorta, perigraft fluid and soft tissue thickening, ectopic gas (Fig. 49.3), tethering of adjacent thickened bowel loops toward the aortic graft, and, in rare cases, extravasation of contrast material from the aorta into the involved segment of bowel.[19] The detection rate of CT for AEF is the highest of all modalities (61%),[13] and CT also can be used to assess the peripheral vasculature to assist with revascularization plans during repair.

Esophagogastroduodenoscopy

Endoscopy plays an essential role in the management of acute GI bleeding. Although it does not rule out AEF, it can exclude other sources of bleeding. The detection rate of AEF by EGD is 25%, and it is essential that the third and fourth portions of the duodenum be visualized for a complete study. Endoscopy may be facilitated by using a pediatric enteroscope or a side-viewing endoscope. A careful study by an experienced endoscopist with a high level of suspicion may reveal a graft (Fig. 49.4), ulcer, erosion with adherent clot, or extrinsic pulsatile mass. This is uncommon, however, and the primary purpose of EGD is to exclude other pathologic processes as the source of GI blood loss. Only hemodynamically stable patients should undergo EGD, and some surgeons recommend that EGD be performed in the operating room so that laparotomy can be done should a tamponading thrombus become dislodged during the study and lead to severe hemorrhage.

Angiography

The role of angiography as a diagnostic modality for AEF is limited. It may be useful to delineate arterial anatomy for

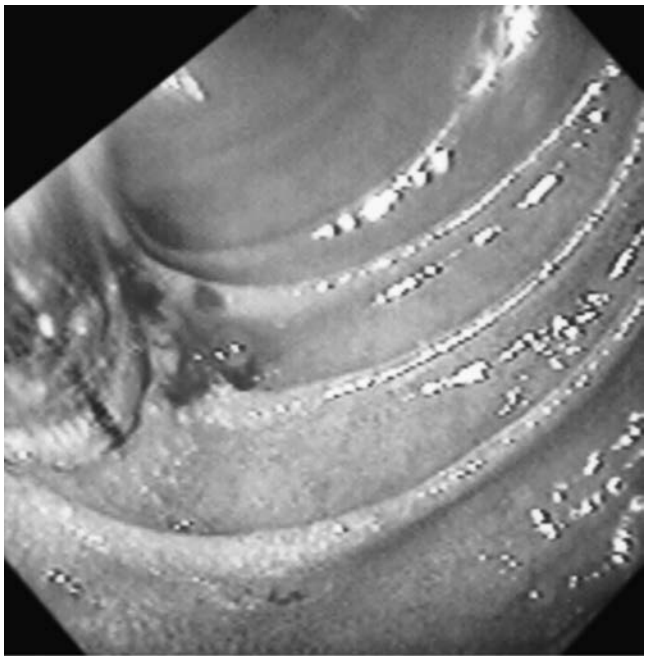

Figure 49.4 Esophagogastroduodenoscopy revealing an exposed Dacron graft that has eroded into the duodenum. Although this finding is unusual, esophagogastroduodenoscopy should be performed to visualize the fourth portion of the duodenum in most patients with gastrointestinal bleeding and previous aortic reconstruction.

Figure 49.5 Aortography revealing a secondary aortoenteric fistula arising from the proximal anastomosis of a bifurcated aortic prosthesis. Note the contrast material in the bowel lumen. Angiography is useful in planning reconstruction after graft excision but will only rarely document an aortoenteric fistula because most stable patients will have an occlusive thrombus sealing the fistula. (From O'Hara PJ. Surgical management of infected abdominal aortic grafts. In: Cowgill LD, ed. *Cardiac Surgery: State of the Art Reviews*. Philadelphia: Hanley & Belfus; 1987.)

potential reconstruction and to identify secondary AEF by finding PSA formation at the proximal anastomosis of grafts (Fig. 49.5), kinking of graft limbs, or bulges in deteriorating prosthetic material. However, because a stable patient is likely to have an occlusive thrombus sealing the fistula at the time of the examination, its use in diagnosis is limited, with an AEF detection rate of 26%. As part of a treatment modality, angiography can be useful to place a proximal occlusion balloon prior to laparotomy.

Other Tests

Other tests, including leukocyte- and erythrocyte-tagged nuclear scanning, magnetic resonance imaging, ultrasound, and contrast-enhanced GI studies, are potentially useful but usually less accurate and more time intensive. Both magnetic resonance imaging and magnetic resonance angiography may aid in the diagnosis of graft infection and AEF[20] but are more difficult to perform in critically ill patients. Nuclear imaging techniques using indium In 111–labeled leukocytes[21] or immunoglobulin G[22] and technetium Tc 99m hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO)–labeled leukocytes[23] have high sensitivity in detecting graft infection, but their role in detecting AEF is less clear. Contrast-enhanced GI studies should be avoided, because they rarely help make the diagnosis, are time intensive, and can obscure findings in subsequent angiographic or contrast-enhanced CT studies.

A rare type of AEF is an aortoappendiceal fistula, which, given the location of the fistula and the quick transit time of blood through the large bowel, can cause patients to have bright red blood per rectum. In this situation, colonoscopy and tagged red blood cell scans may be needed for the diagnosis to be made.[24] Rarely, plain skeletal radiography reveals changes consistent with systemic infection. Unilateral lower limb hypertrophic osteoarthropathy[25,26] and multifocal osteomyelitis[27] have also been associated with AEF.

TREATMENT

Conservative nonoperative therapy for AEF is uniformly fatal,[28] and surgery is the only treatment option with the potential for success. The important factors to be considered to coordinate effective surgical management are the presence of active hemorrhage, the classification of the AEF (primary or secondary), the presence of sepsis, and the anatomic distribution of the patient's aneurysmal or occlusive disease.

The first priority in treatment is to preserve the patient's life; the second is limb preservation. Whereas hemodynamically unstable patients with active GI hemorrhage or sepsis require urgent operative intervention, stable patients with a resolved herald bleed may be further evaluated and optimized. These patients must be monitored closely, however, and should proceed to surgery as soon as possible as the risk of fatal rebleeding is high; 30% of patients rebleed within 6 hours, and 50% of patients rebleed within 24 hours.[13]

Urgent Surgical Treatment of Hemorrhage

In instances of massive GI bleeding, central venous access, volume resuscitation, and broad-spectrum gram-negative and gram-positive

antibiotic therapy should be initiated. In both primary and secondary AEF, the operative approach should be a midline incision, followed by rapid proximal aortic control. Infrarenal aorta control is preferable; however, supraceliac clamping may be required initially. If fluoroscopy or a hybrid OR is available emergently, proximal control via balloon occlusion should be considered. Distal control may be obtained with iliac clamping or occlusion balloons. Once the aorta has been controlled, the bowel should be sharply dissected off of the aneurysm/prosthesis; noncrushing bowel clamps or sutures can be used to control enteric spillage. If the bowel defect is small, it may be closed primarily; otherwise, a bowel resection and anastomosis should be performed after the aorta has been managed.

It should be noted that a recent review of aortoduodenal AEF bowel repair found higher rates of recurrent fistula after simple closure compared to complex (resection or diversion) bowel repair (48.9% vs. 11.1% $P = .036$). This same study found that on multivariate analysis, omentum (or any other structure) interposition between the bowel repair and artery was associated with lower mortality regardless of the technique used to close the bowel wall (OR 0.385, 95% CI 0.221-0.669).[29] In cases in which there is no evidence of infection, in-situ repair may be performed with prosthetic graft, cadaveric artery, or femoral vein. Care should be taken to separate the graft from the GI tract with the posterior peritoneum or omentum. If there is evidence of local infection, the aortic stump should be oversewn and covered with omentum; this should be followed by retroperitoneal débridement, drain placement, and extraanatomic bypass.

Surgical Treatment in Stable Patients

In the case of a hemodynamically stable patient with no active bleeding, more time can be spent evaluating and planning the procedure. This allows the order of the operation to be reversed, with extraanatomic bypass performed first (although initially a concern, the issue of graft infection of the newly placed prosthesis in the presence of a known infected abdominal graft has not been realized).[14,30] This may be particularly useful in patients with known infection with a functional graft or in patients with anticipated prolonged clamp time, as it allows both limbs and the pelvic vasculature to remain perfused throughout the case, thereby reducing the risk of amputation and bowel ischemia. Cystoscopy with placement of ureteral stents can also be performed before laparotomy, which may assist in reducing ureteral injury during dissection in an inflamed retroperitoneum.

Primary Aortoenteric Fistula

Management of primary AEF depends on whether infection is present in the aortic bed at the time of surgical intervention. In the case of mild contamination, in-situ replacement of the aorta with local débridement and long-term antibiotic therapy is the favored approach. In the case of gross retroperitoneal contamination and sepsis, aneurysm resection, omentoplasty, retroperitoneal débridement, and extra-anatomic bypass should be performed. The latter approach is considered inferior because of higher reported rates of mortality and limb loss, and most authors agree that it should be reserved for cases of gross contamination (defined as widespread aortic or retroperitoneal gross purulence or inflammation[31]) if possible.[32]

The majority of primary AEFs are in the duodenum and proximal small bowel, which is associated with less bacterial contamination because of differing flora and bacterial loads compared with more distal locations such as the colon. Regardless, all primary AEFs should be treated with antibiotics in the postoperative period. Broad-spectrum antibiotics should be used until culture results are available, and then antibiotic therapy should be tailored appropriately. In the case of a negative culture, antibiotic therapy can be discontinued after 1 week; positive cultures necessitate a 4- to 6-week course.[33]

Secondary Aortoenteric Fistula

The available operative choices for secondary AEF are graft excision alone, in-situ replacement, graft excision and reconstruction with autogenous vein (i.e., the neo-aortoiliac system procedure), extraanatomic revascularization and graft excision, and endovascular repair with lifelong antibiotics.

It is generally agreed that all infected synthetic material must be resected if there is clear evidence of graft and retroperitoneal contamination, which is more likely with AEF involving the distal GI tract and fistulae that have been chronic. The infected arterial tissue should be debrided back to grossly healthy tissue and closed with monofilament permanent suture material, preferably in two layers. The defect in the GI tract should be repaired with conventional techniques appropriate for the location of the fistula and retroperitoneal drains placed to minimize the risk of persisting sepsis causing breakdown or PSA formation at the site of arterial closure. If it is feasible, a flap of omentum should be placed to separate the bowel from the aortic stump closure and to fill the dead space resulting from excision of the graft. Despite this additional procedure, there still remains concern for the integrity of the aortic closure when infection is present. The aortic closure is at risk of "blowout," which would lead to massive hemorrhage and a life-threatening emergency requiring emergent laparotomy.

Graft Excision Without Replacement

If the graft has been placed for occlusive disease or has been chronically occluded, it is possible to resect the graft without reconstruction. This will be possible only if the patient has sufficient collateralization, and CT or angiography may be helpful in assessing the patient preoperatively. If the original graft was placed in an end-to-side configuration, endarterectomy and patch angioplasty of the aorta and distal vessels may allow uninterrupted perfusion. Patch material such as vein or bovine pericardium should be considered. This approach should not be considered in patients with patent grafts, patients with grafts placed for aneurysmal disease, or patients with palpable distal pulses. The concern in these clinical scenarios is that removal of the graft will lead to profound ischemia and the risk of amputation. The patient needs to be critically assessed for a

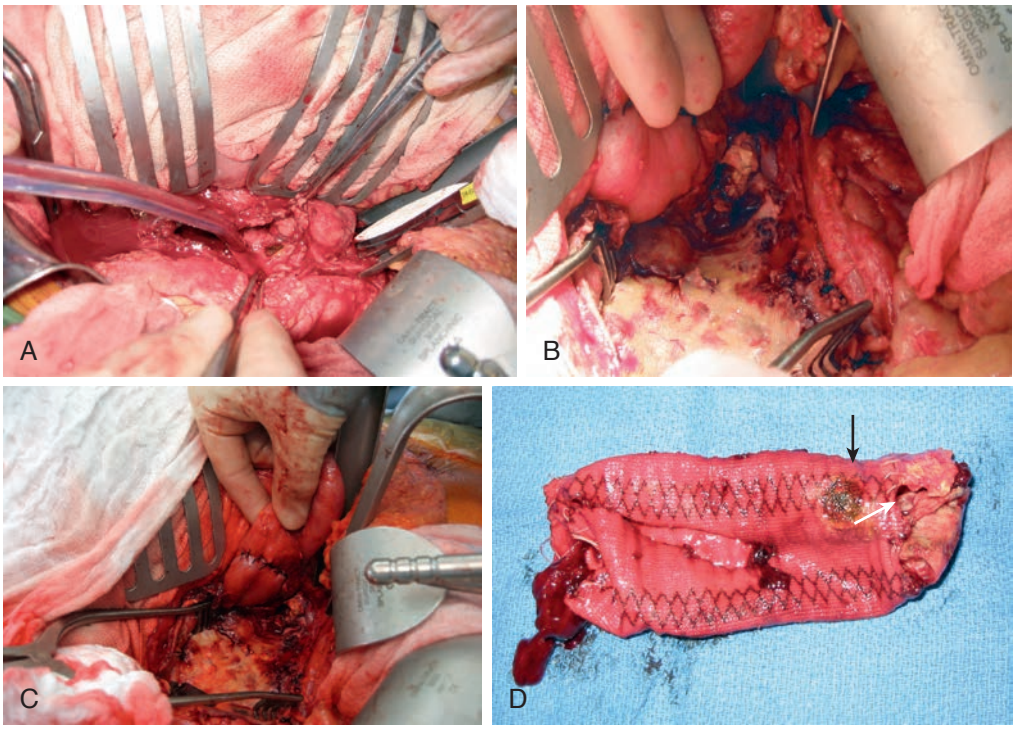

Figure 49.6 Intraoperative images of aortoenteric fistula repair with excision of aortic graft and extraanatomic revascularization: (A) aortoenteric fistula in situ, (B) remaining aortic stump, (C) duodenal closure, (D) remnant graft with fistula site *(arrow)* next to the former proximal anastomosis. (Courtesy Robert Steppacher, MD.)

means of arterial reconstruction that will allow adequate perfusion but not lead to a high risk of recurrent infection.

In-Situ Aortic Graft Replacement

In-situ reconstruction may be attempted with use of cryopreserved allografts (Fig. 49.6), antibiotic-soaked synthetic graft, or silver-coated Dacron. As previously discussed, this approach remains controversial; however, in recent years, it has become an increasingly accepted strategy. Advocates of in-situ reconstruction cite the following benefits: improved long-term patency, decreased risk of stump blowout, decreased risk of thrombosis ascending to the renal arteries after resection, and maintenance of blood supply to the colon and pelvis. Studies have also begun to demonstrate the potential benefit of in-situ reconstruction; a meta-analysis in 2006 demonstrated a lower operative mortality for in-situ reconstruction with rifampin-bonded prosthesis compared with extraanatomic reconstruction in patients with aortic graft infections,[34] and a retrospective study of in-situ reconstruction for secondary AEFs published in 2011 demonstrated no difference in operative mortality between in-situ reconstruction and extraanatomic reconstruction.[18] Another important factor crucial to the success of secondary AEF repair underlined by this study was the role of carefully performed, effective visceral repair, as bowel leakage was a significant predictor of fatal outcome.

Neo-Aortoiliac System Procedure

The neo-aortoiliac system procedure uses the femoropopliteal vein to reconstruct an autogenous neo-aortoiliac system. Chung et al.[35] have advocated this technique in the setting of graft infection, as it allows infection-resistant autologous tissue to be placed in the operative field and avoids the pitfalls of the aortic stump. Another benefit to this procedure is that use of autologous vein is relatively inexpensive compared with the use of cadaveric graft or other treated prosthetics, and it does not require lifelong anticoagulation as is the case with cadaveric allograft. The principal disadvantages of this procedure are the length of time required to harvest the deep vein and that it cannot be staged. Other drawbacks include the risk of venous insufficiency in the harvest limb leading to compartment syndrome and fasciotomy. These issues may be improved with multiple surgical teams and growing center experience. More data are required to determine if the benefits seen in patients with aortic graft infection with this approach can be extrapolated to patients with AEF.

Extraanatomic Revascularization

Extraanatomic revascularization is performed with externally supported (ringed) polytetrafluoroethylene and may be performed after abdominal closure with a fresh set of clean instruments to restore flow to the extremities. Alternatively, if the patient is stable and not actively bleeding, a preliminary extraanatomic revascularization may be performed before the aortic procedure. This allows uninterrupted flow to the extremities throughout the procedure and reduces the risk of limb ischemia and amputation. The interval between the procedures should not be too lengthy, however, as there is the potential for graft occlusion due to competitive flow as well as recurrent GI bleed.

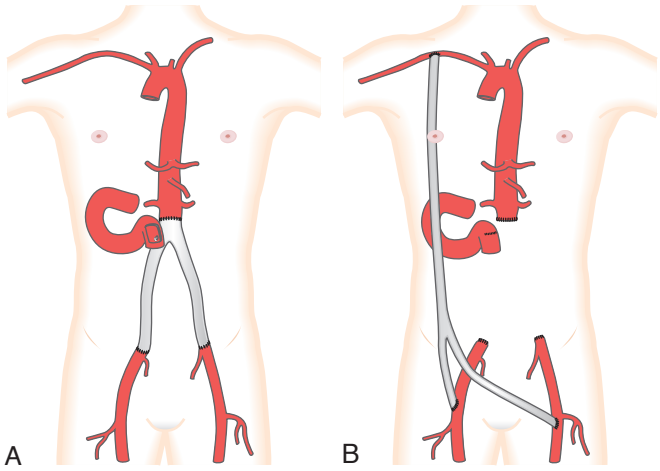

Figure 49.7 (A) Secondary development of aortoenteric fistula after synthetic aortobiiliac graft placement. (B) Surgical management includes extraanatomic bypass with an axillobifemoral graft, resection of all abdominal prosthetic material, retroperitoneal débridement, and closure of the bowel defect. (Modified from O'Hara PJ. Surgical management of infected abdominal aortic grafts. In: Cowgill LD, ed. *Cardiac Surgery: State of the Art Reviews*. Philadelphia: Hanley & Belfus; 1987.)

Regarding graft configuration, if the previous aortic synthetic graft reconstruction was intra-abdominal, axillobifemoral grafting is feasible (Fig. 49.7). However, if the graft infection has extended to the femoral arteries, as in the case of previous aortobifemoral graft placement, bilateral axillo-unifemoral grafts tunneled laterally to the available superficial femoral, profunda femoris, or popliteal arteries may be required. Tunneling of the left extraanatomic bypass may be a problem if a left retroperitoneal incision was used for the initial graft excision. A variation on this approach involves the use of a composite graft consisting of placement of a synthetic extraanatomic graft in a noncontaminated tissue plane with the autogenous graft component extending to the débrided, contaminated femoral vessels. Care must be taken to avoid contamination of the synthetic component, and the surgeon should be familiar with techniques such as sartorius muscle flap rotation to provide adequate soft tissue coverage of the femoral vessels. Appropriate antibiotic coverage is important to minimize the risk of seeding the extraanatomic bypass graft, which can occur in approximately 15% to 25% of patients.[14]

Endovascular Repair

With the technical difficulty and resulting morbidity and mortality of current open operative approaches, endovascular repair offers an appealing solution, as it allows rapid control of hemorrhage with minimal physiologic impact on the patient. In the last decade, a growing number of case reports have described endoluminal stent-grafting (EVAR) for AEF. The use of endografting is particularly interesting as it violates the basic principles of surgical treatment of AEF; the enteric fistula is not treated, the retroperitoneal tissue is not débrided, and the infected aorta/prosthetic graft is not removed. Despite this, a 2009 systematic review of the literature[36] identified 33 reports that included 41 patients with AEF who had EVAR as initial management. In this review, all patients underwent successful endograft implantation, and 20% had concurrent repair (open or endoscopic) of the contributing portion of the GI tract. Unfortunately, a significantly high complication rate was found after follow-up of 13 months, with 44% of patients developing persistent, recurrent, or new infection or hemorrhage and 29% of patients expiring, mainly as a result of septic complications. In the study, the major significant factors for poor outcomes were preoperative infection and complications that developed at any time after endovascular treatment. The overall conclusion of this study is that endovascular repair should be considered only a temporizing strategy until definitive repair can be performed. A similar conclusion was drawn from a multicenter retrospective study in 2011,[37] which reported the outcome of endovascular repair and open repair of AEF in 25 patients. The study found a statistically significant difference in overall morbidity in the short term (77% for open vs. 25% for endovascular); however, the early benefit of endovascular repair in the early operative period was lost by the second postprocedural year because of an increased recurrence of bleeding, sepsis, and AEF in the endovascular group. Despite these discouraging results, enthusiasm for endograft placement remains, and the practice of endograft placement with or without surgical management of the GI tract, long-term antibiotics, and "close surveillance" continues to be performed. This is particularly concerning, as recent reviews of the literature evaluating infectious complications after endograft placement have found that patients presenting with recurrent AEF or infection after endograft placement for the indication of AEF have uniformly fatal outcomes. In one study, which treated patients without explanation, but with antibiotics and surgical intervention for the bowel, 7/7 recurrent AEF patients died.[28] A second study, evaluating the outcomes of late open conversion for infected aortic endografts found that 6/6 recurrent AEF patients died.[38]

In the case of aortoesophageal fistula, there has been interest in TEVAR as a means to control bleeding and reduce the 55.5% mortality associated with open repair of this condition. A 2014 meta-analysis documented similar overall mortalities for TEVAR alone; however, there was a significant decrease in mortality (52.5% vs. 25% [$P = .029$]) on univariate analysis when the TEVAR was used as part of combined approach (e.g., with a staged graft excision and esophageal resection or staged esophageal resection and debridement). This paper also noted a decrease in mortality, bleeding, and AEF recurrence with the use of greater than 4 weeks of antibiotic on multivariate analysis (OR 0.03, 95% CI 0.001-0.21, $P = .0039$).[39]

In summary, endovascular repair should be reserved as a bridge to open repair once patients have stabilized and local infection control is established. It is also an acceptable treatment modality for patients with a limited life expectancy who would benefit from a short hospital stay and earlier discharge and will not be exposed to the long-term risks.[40]

RESULTS AND CONCLUSIONS

In primary AEF, standard aortic reconstruction with repair of the associated bowel defect has been successful. In a collective

review of 118 cases in the literature by Sweeney and Gadacz,[33] nonoperative management was uniformly fatal. Thirty-three patients were treated surgically, with an operative mortality of 36%. Standard aortic reconstruction with duodenal repair was performed in 19 of 22 survivors with minimal long-term sequelae. Similar results have been reported in an additional 35 cases in the Netherlands, thus indicating that placing a prosthesis in patients with primary AEF appears to be safe.[41]

The natural history of untreated secondary AEF is hemorrhage, continued sepsis, and eventually death. Operative mortality ranges from 13% to 86%, with an average mortality of 30% to 40%. Amputation rates hover at 10%, and long-term survival approximates 50% at 3 years. Taken together, these results attest to the tremendous physiologic stress from the AEF itself and the magnitude of operative repair of AEF. Of note, multiple authors have documented higher mortality rates in patients treated for AEF than in those treated for aortic graft infection alone. In a report of 61 patients, AEF operative treatment required longer hospitalization and more blood transfusion. Furthermore, operative mortality was higher (35% vs. 17%), and 12-month survival diminished (25% vs. 60%) for AEF versus aortic graft infection.[10]

Multiple strategies have been advocated for the operative management of AEF, and controversies continue to abound. In the appropriate patient with chronic graft occlusion or severe aortic occlusive disease, simple graft excision may be the only treatment required. In-situ repair with allograft, antibiotic-impregnated graft, or silver-coated graft has become an increasingly valid option in the appropriate patient population, as has the neo-aortoiliac system procedure. Extraanatomic reconstruction remains a safe alternative in the setting of gross contamination and can be particularly useful if it can be staged before the aortic graft resection. EVAR continues to make strides and has the greatest potential to minimize overall morbidity and mortality; however, it currently remains a temporary measure to bridge patients to definitive repair. In summary, the key features to successful treatment are timely intervention, appropriate patient selection, effective bowel repair, and long-term follow-up.

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CHAPTER 50

Local Endovascular Complications and Their Management

JEFFREY J. SIRACUSE and JAMES F. MCKINSEY

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INTRODUCTION

Endovascular procedures have become increasingly more common and in many cases are the first-line treatment for occlusive peripheral vascular disease.[1,2] Although less invasive, endovascular procedures can have unique complications differing from open repair that the surgeon should be prepared to treat.[3,4] These complications range from minor, which can be treated with minimally invasive intervention, to serious life- or limb-threatening conditions that require urgent operative or percutaneous interventions. Currently the majority of percutaneous peripheral interventions are performed with common femoral artery access.[5] Historical coronary data have shown an access site complication rate of up to 6.1%, with 2.3% requiring

Abstract:

Endovascular procedures have become increasingly more common. Although overall less invasive in nature, these procedures can have unique complications differing form open repair that the surgeon should be prepared to treat. These complications range from being to serious and life-threatening. Some of the most common complications are access site complications. These including a wide range of bleeding and occlusive complications. Complications during the procedure include vessel occlusion, dissection, rupture, and embolization. Device specific complications include device fracture and embolization. This chapter will outline complications unique to endovascular interventions and discuss treatment.

Keywords

Endovascular
complications
hematoma
dissection
embolism

TABLE 50.1 Risk Factors for Access Site Complications

Advanced age
Warfarin use
Congestive heart failure
Non–ultrasound-guided access
Large sheath size
Intervention performed
Emergent case
Chronic obstructive pulmonary disease
Antiplatelet use
Hypertension
Tibial interventions

See references 9, 10, 11.

surgical repair.[6] A higher complication rate has been reported when an intervention is performed, rather than it being just a diagnostic study.[7] Contemporary data from the Vascular Quality Initiative looking at patients with critical limb ischemia show the rate of access site hematoma was 3% overall and access site occlusion or stenosis was 0.2%.[8]

Predicting which patients are at greatest risk for access site injury is crucial for the interventionalist. Risk factors for access site complications are listed in Table 50.1.[9-11] By identifying higher-risk patient groups, risk reduction strategies can be implemented and complications can be decreased.

GROIN HEMATOMA

One of the most common complications of percutaneous access is the development of a groin hematoma. Contemporary rates for groin hematoma during peripheral interventions have been reported as 3%.[8] The clinical manifestation of a groin hematoma varies widely. In most circumstances, postprocedure groin swelling is the only clinical finding. Other common signs and symptoms include pain, skin ecchymosis, bleeding at the puncture site, neuropathy secondary to nerve compression, anemia, and in more advanced cases hypotension.

Etiology and Manifestations

Hematomas can develop from difficult access, multiple access attempts, or inadequate closure or compression at the completion of the procedure. For access, adequate compression should be used after an attempt to obtain hemostasis; this can be variable based on needle size. Further, back wall injury or leakage around the sheath can contribute to hematoma formation.

Routine ultrasound use has been shown to decrease the risk of postprocedure hematoma. Routine and selective ultrasound guidance was used by 27% and 73% of interventionalists in the Vascular Study Group of New England. The overall post-procedural groin hematoma rate after PVI was 4.5%. However, the rate of combined moderate and major hematoma was 0.8%. Routine ultrasound use was protective against hematoma overall and particularly in patients aged greater than 80 years, obese patients, and those with a sheath size greater than 6 F.[12]

Figure 50.1 Left groin hematoma *(arrow)* after percutaneous access.

Management

Treatment strategies for groin hematomas generally consist of observation as well as correction of any underlying coagulopathy. Transfusion may be required. Manual compression should be applied to hematomas that have been identified in the acute setting. Similarly, mechanical compression devices such as the FemoStop (Radi Medical Systems, Wilmington, Massachusetts) or C-clamp have demonstrated benefit in reducing bleeding complications.[13] Computed tomography (CT) is useful to gauge the extent of the hematoma and assess for active bleeding, as evidenced by a contrast-induced blush (Fig. 50.1). Moreover, imaging is prudent with large hematomas to rule out extension into the retroperitoneum, especially when associated with hemodynamic instability. Laboratory assessment of hematocrit levels should be performed every 4 to 6 hours until stabilization. Furthermore, interval duplex assessment should be performed to rule out the development of a pseudoaneurysm. Although most of these patients can avoid surgical exploration, the time to ambulation is delayed and length of stay increases.[14] The incidence of hematomas requiring transfusions in the coronary literature has been reported as 1.8%. This was associated with both in-hospital mortality and 1-year mortality.[15] Groin exploration with evacuation of the hematoma is warranted in the setting of hemodynamic instability, persistent anemia despite transfusions, skin necrosis, nerve compression, or severe pain.

RETROPERITONEAL HEMATOMA

High punctures at the groin, particularly above the most inferior border of the inferior epigastric artery, present increased risk for the development of access site complications, including retroperitoneal hematoma (RPH).[16] Though rare, RPH has the potential for severe morbidity and even death if not detected. Bleeding that extends into the retroperitoneum is less likely to be tamponaded by surrounding structures (Fig. 50.2). Independent predictors of RPH include male gender, low body surface area, less than 1.73 m^2, and higher femoral artery puncture.[14]

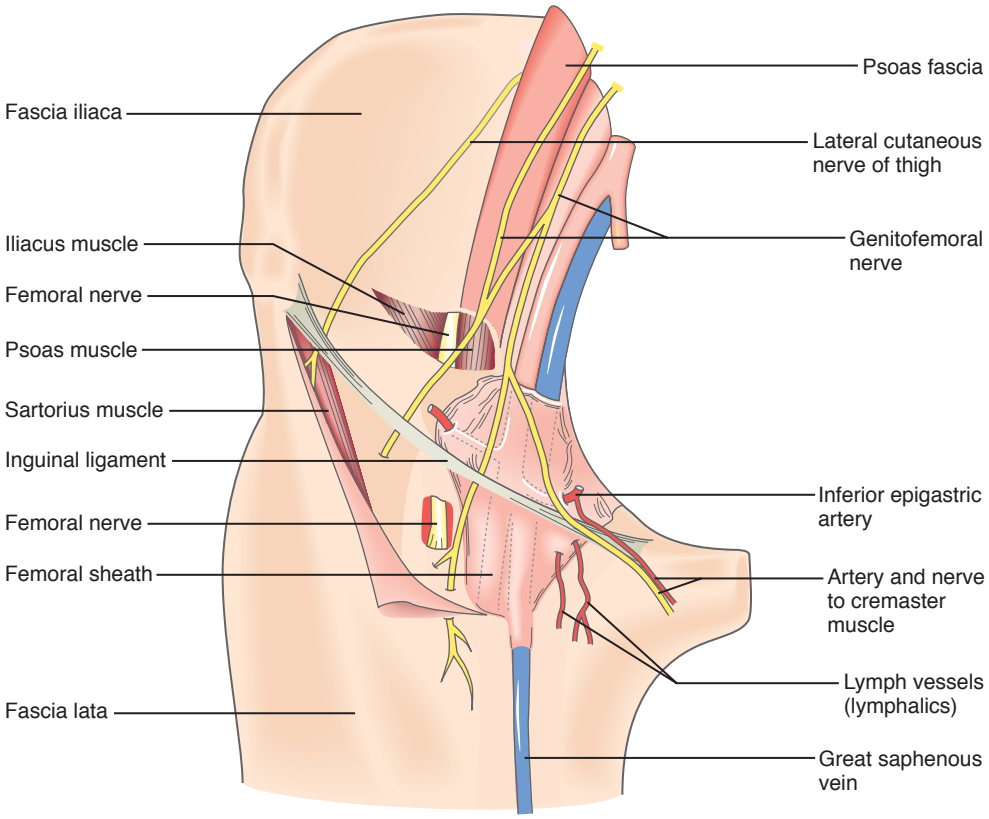

Figure 50.2 Relative anatomy of common few oral artery for access.

Manifestations and Diagnosis

Clinical findings of RPH are often subtle and less obvious than with groin hematomas. The most common symptoms are hypotension followed by diaphoresis, groin pain, abdominal pain bradycardia, and back pain.[14] The diagnostic test of choice for RPH is abdominopelvic CT (Fig. 50.3).

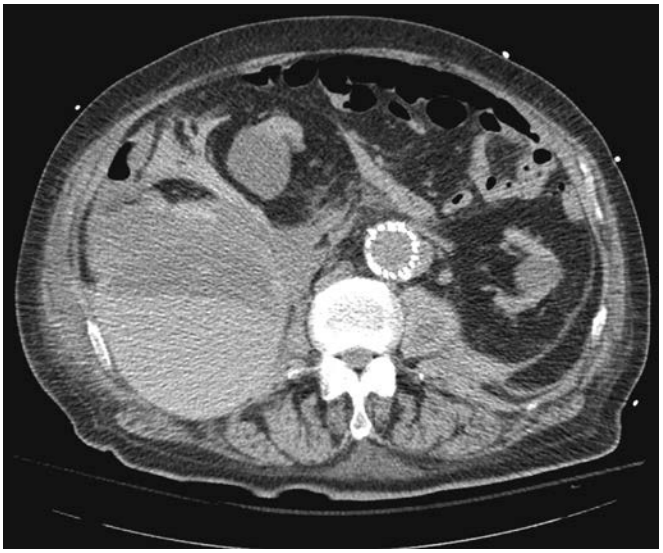

Figure 50.3 Computed tomography scan showing large retroperitoneal hematoma.

Management

Treatment for RPH is tailored to the clinical status of the patient. Indications for intervention include neurologic deficits in the affected extremity, hemodynamic instability, ongoing blood loss, and severe pain.[17] Decompression of an RPH can be performed either through a groin incision or through an incision above the inguinal ligament to gain direct access to the retroperitoneum and iliac vessels. Either way, the arteriotomy must be investigated and repaired for optimal therapy. A covered stent can also be used to obtain control of bleeding, especially if the arterial injury is above the inguinal ligament, avoiding a more morbid operation.[18]

ARTERIOVENOUS FISTULA

Etiology, Manifestations, and Incidence

An arteriovenous fistula (AVF) in the groin is a rare complication of percutaneous access and involves a communication between the femoral artery and vein. The incidence has been reported as 0.5% to 0.86%.[9,19,20] AVF after coronary interventions has been associated with high heparin dosage, warfarin use, left-sided access, hypertension, simultaneous femoral artery, and vein access and female gender. Within 12 months, 38% of all AVF closed spontaneously. None of the risk factors for AVF influenced the incidence or the rate of AVF closure.[19] AVF usually occurs

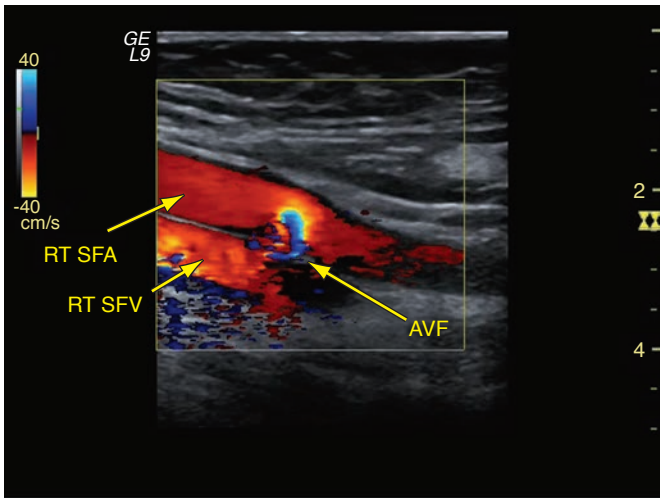

Figure 50.4 Duplex demonstrating the characteristic systolic-diastolic flow pattern seen with a femoral artery to vein arteriovenous fistula.

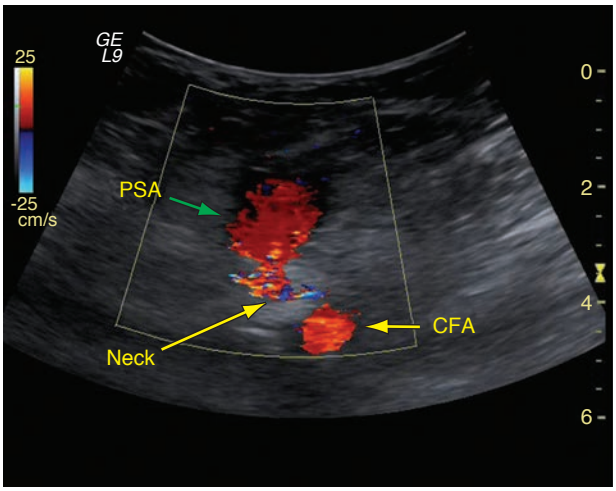

Figure 50.5 Duplex of a femoral artery pseudoaneurysm.

after inadvertent low puncture of the CFA bifurcation or the profunda femoris artery and vein, which run near the superficial femoral artery (SFA). However, AVF may also develop after through-and-through puncture of the CFA or SFA into the common femoral vein. Groin AVFs are generally asymptomatic and detected on physical examination by the presence of a palpable thrill in the groin or auscultation of a continuous bruit. Duplex ultrasound is the imaging study of choice and demonstrates the characteristic systolic-diastolic flow pattern with arterialization of the venous signal (Fig. 50.4).

Management

Treatment options include observation alone, surgical repair, and endovascular repair. While ultrasound-guided compression had historically been used to treat groin AVF, success rates are low.[21] If conservative management is implemented, patients should have follow-up duplex surveillance and physical examination. If symptoms do arise or the fistula increases in size, surgical treatment is indicated. Endovascular management of femoral AVFs has been reported with the advent of balloon-expandable stent-grafts.[22-24] Coverage of the fistula with a covered stent-graft results in immediate abolishment of the AVF without the need for surgery and therefore is optimal for high-risk candidates who may have failed conservative management. The decision whether to treat an AVF with open, endovascular, or conservative measures is still under debate and should be driven by surgeon experience and the patient's overall symptomatology and comorbid conditions.

PSEUDOANEURYSM

Etiology and Manifestations

PSAs develop postprocedure if the arteriotomy has not adequately sealed once the sheath is removed. There is communication with the arterial lumen, and blood spreads into the surrounding soft tissue. It is a "pseudo" aneurysm, in that no elements of the arterial wall are incorporated in the aneurysm sac; the wall of the PSA consists solely of compressed thrombus and surrounding soft tissue. PSAs can be differentiated from hematomas in that there is arterial flow into the PSA with a defined neck that tracks to the arteriotomy. The incidence of PSA formation after percutaneous procedures in contemporary series is less than 1%.[9,25]

The cause of a PSA is often related to an inability to adequately compress the vessel or closure device failure after removal of the sheath. This occurs most frequently with SFA or low CFA puncture because the femoral head sits more cephalic and compression is insufficient. On physical examination, a systolic bruit can be auscultated and is associated with the pulsatile groin mass. When there is clinical suspicion of a PSA, groin arterial duplex examination should be performed. The typical ultrasound appearance of a PSA is an echolucent sac that is pulsatile, and with the addition of color Doppler, a swirling flow pattern is noted within this sac (Fig. 50.5). On spectral waveform analysis, the characteristic "to-and-fro" flow pattern can be discerned and is pathognomonic for PSA.[26,27] If the PSA has significant extension into the retroperitoneum, abdominopelvic contrast-enhanced CT may be of benefit to evaluate its size, as well as to identify additional arterial injury sites.

Management

Before the 1990s, an operation was the primary recommended therapy for large or expanding PSAs, to decrease the complications of nerve compression, distal embolization, or skin necrosis. Subsequently, ultrasound-guided compression was performed. In the largest series published to date, success rates ranged from 74% to 93%.[28-30] The main factors impeding successful ultrasound-guided compression include anticoagulation at the time of compression, size of the PSA, and patient discomfort. Risks associated with ultrasound-guided compression include PSA rupture, distal embolization, and thrombosis of the femoral vein or artery.[28-30]

Ultrasound-Guided Thrombin Injection

The disadvantages of ultrasound-guided compression, including patient and ultrasound technician discomfort and only moderate success, prompted the development of the practice of injection of thrombin directly into the PSA under ultrasound guidance. The principle of this technique is based on the necessity of thrombin for conversion of fibrinogen to fibrin. When blood is exposed to high-dose thrombin within the aneurysm sac, fibrin clot forms and instantaneously results in thrombosis of the PSA. It should be noted, however, that this still remains an off-label use for thrombin, which was produced as a topical hemostatic agent.[31-34] Lonn et al. performed a randomized prospective study comparing thrombin injection to compression. Thrombosis within 24 hours was achieved in 15 (100%) patients given thrombin versus 2 (13%) in the compression group ($P < .001$). The most significant complications of this procedure include thrombosis of the native artery or vein if thrombin is inadvertently injected into these vessels. Anaphylaxis has also been reported anecdotally, especially with bovine preparations of thrombin, but this complication is very rare.[35] For PSAs that are small, observation alone is a reasonable treatment strategy.[36,37]

Surgical Management

Despite the excellent results with thrombin injection, there still remains a role for surgical repair of PSAs. These include larger pseudoaneurysms and those without a narrow neck, and those that have failed compression or thrombin injection. Techniques of PSA repair include direct surgical repair and endovascular options.[38,39] Endovascular options for postangiography PSA include using a covered stent, but they have not been adequately studied to date.[40,41]

Thrombosis

CFA thrombosis at the site of an endovascular procedure is a known complication of catheter-based interventions. Simple compression of the CFA after removal of the sheath can lead to thrombosis, especially in the presence of significant CFA atherosclerotic disease or previous groin reconstruction. CFA occlusion in a contemporary series in the treatment of critical limb ischemia in the Vascular Quality Initiative has been shown to be 0.2%.[8]

Thrombosis usually becomes apparent after the sheath has been removed and manual compression has been completed. Treatment consists of groin exploration with femoral endarterectomy, patch angioplasty, and thromboembolectomy. Alternatively, patients may benefit from endovascular interventions, including mechanical thrombectomy, thrombolysis, or atherectomy, to remove or dissolve the obstruction.

AXILLARY AND BRACHIAL ACCESS COMPLICATIONS

Although the vast majority of peripheral interventions are performed through the groin, severe atherosclerotic disease of the femoral or iliac vessels can often make this approach difficult. As an alternative, the brachial and axillary arteries have demonstrated adequacy as access vessels to perform lower extremity, visceral, or carotid interventions. These are becoming more frequent with complex aneurysm repair. In the Vascular Quality Initiative, brachial access was performed in 1.6% of vascular procedures. Brachial access was associated with an increased complication rate compared with femoral access (9.0% vs. 3.3%; $P < .001$), including more hematomas (7.2% vs. 3.0%; $P < .001$) and access site stenosis/occlusion (2.1% vs. 0.4%; $P < .001$). Neither the surgeons' overall peripheral vascular intervention experience nor prior experience with brachial access predicted likelihood of adverse events.[42] Larger sheath sizes (>5 F), percutaneous access, and female gender were risk factors for complications. In a cardiac catheterization study in which up to 7 Fr sheaths were used, the major complication rate was approximately 5%.[43] In evaluating the transaxillary approach, Chitwood and associates found a 2.3% incidence of complications, and the most common was nerve injury.[44] Risk factors identified for axillary artery injury included female gender, hypertension, periprocedural anticoagulation, thrombolysis, and prolonged (>90 minutes) procedures.

Nerve Injury

It is important to maintain high vigilance for nerve injury with transbrachial/transaxillary access because of the potential for permanent devastating disability of the upper extremity. When compared with the groin, where the incidence of nerve injury from percutaneous procedures is extremely low (0.2%), brachial access can be associated with clinically significant neuropathy of the various terminal nerves of the infraclavicular brachial plexus at an incidence ranging between 0.4% and 12.7%.[44-46] This neuropathy probably occurs because anatomically the median nerve and brachial artery are in close association and travel within the medial brachial fascial compartment (Fig. 50.6). Patients complain of pain radiating down the arm with associated muscle weakness and paresthesias. The most common and treatable

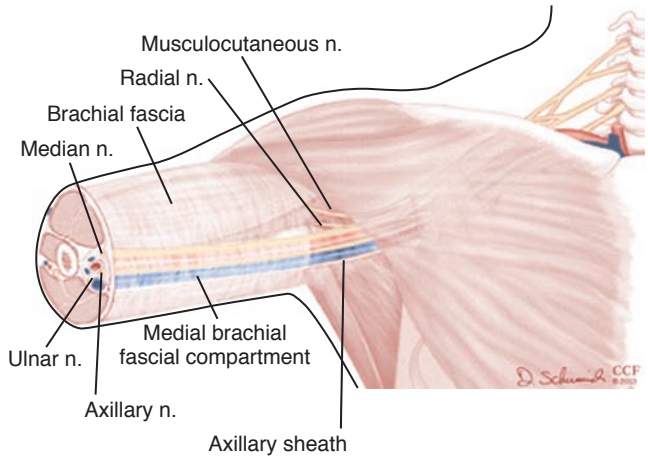

Figure 50.6 Relative anatomy of the brachial and axillary arteries.

cause of neurologic dysfunction is compression from an axillary sheath hematoma. Treatment involves decompression of the fascial compartment with exposure of the brachial artery and repair of the arteriotomy.

Thrombosis

The small diameter of the brachial artery makes it more prone to thrombosis. The diagnosis may become evident if the patient complains of hand symptoms, including pain, numbness, or tingling. This should prompt rapid removal of the sheath. For closure, manual compression should be applied with just enough pressure to prevent bleeding and hematoma while maintaining perfusion to the hand.

Radial artery access is becoming increasingly used for coronary interventions.[47] Radial artery occlusion has been seen postprocedure at a rate of 7.7% at 24 hours, which decreased to 5.5% at greater than 1 week follow-up. Higher doses of heparin, shorter compression time, advanced age, female gender, sheath size, and smaller diameter of radial artery have been shown to be associated with radial artery occlusion.[48] Radial artery occlusion is often without clinical sequelae due to collaterals in the hand.[49] Radial artery pseudoaneurysm has been shown to have an incidence of 0.08 %, with the majority of cases (80%) being treated with surgical repair.[50]

Pedal Access

Retrograde pedal access is more often used for tibial lesions that cannot be crossed antegrade or retrograde. Treatment could be accomplished either by snaring from above and treating antegrade or by placing a sheath in the pedal vessels. Although reports contain low numbers, pedal access appears safe with no local complications reported peri-procedurally, although the data is not clear about whether the target vessel for revascularization is altered.[51-53]

PERCUTANEOUS CLOSURE DEVICE COMPLICATIONS

Vascular closure devices (VCDs) allow for rapid arteriotomy closure after percutaneous interventions. They allow early ambulation and discharge after groin puncture and mitigate patient discomfort from extended manual compression. In addition, when compared with manual compression, which requires normalization of the activated clotting time (ACT) before pulling the sheath, VCDs are used immediately once the procedure has concluded. However, despite the obvious benefits of VCDs, they have not gained universal adoption among interventionalists. A Cochrane analysis of 52 studies showed that VCDs were associated with reduced time to hemostasis when compared with extrinsic compression. No deaths were reported secondary to VCDs. There were no differences in the incidence of infection between closure device type and extrinsic compression. Limited data were obtained when VCDs were compared with each other.[53]

TABLE 50.2 Risk Factors for "Preclose" Failure

Obesity
Thoracic aneurysm repair
Access calcification
Access depth >4 cm
Large sheath size (>20 Fr)

Hu G, Chen B, Fu W, et al. Predictors and treatments of Proglide-related complications in percutaneous endovascular aortic repair. *PLoS One*. 2015;10(4):e0123739.

Perclose

The primary suture-based closure device is the Perclose (Perclose, Abbott Vascular, Redwood City, California). It is a 6 Fr sheath mediated VCD that fires a single monofilament polypropylene suture. For sheath sizes greater than 8 Fr, more than one device is recommended. A prospective randomized study looking at the Perclose Proglide device compared with manual compression showed that there was shorter time to hemostasis, ambulation, and discharge with suture mediated closure. There was no difference in overall complication rate between the two treatment groups.[54]

Perclose is increasingly used to "preclose" the common femoral artery before endovascular aortic aneurysm repair (EVAR). Technical success rates of approximately 90% have been reported. Device failure can be treated with manual compression, additional Perclose use, or open repair. Predictors of failure include obesity, thoracic aneurysm repair, CFA calcification, CFA depth greater than 4 cm, and sheath size greater than 20 Fr, though the double closure technique has been effective for 24 F sheaths (Table 50.2).[55]

Starclose

The Starclose VCD delivers a nitinol clip to close the access site. A randomized prospective study comparing Starclose to manual compression showed no difference in complications. The results of the diagnostic Starclose cohort have been reported separately. Results for the interventional arm revealed major vascular complications occurring in 1.1% of Starclose subjects and 1.1% in manual compression subjects (P = 1.00). No infections were seen in either cohort. Minor complications in the Starclose interventional group occurred at a rate of 4.3% and with compression at 9.9% (P = .107). Procedural success ranges from 93.9% to 100%.[56-58]

Exoseal

Exoseal is a percutaneous vascular closure system based on an extravascular, bioabsorbable polyglycolic plug and comes in a 5 Fr device. A large retrospective review showed that immediate hemostasis was achieved in 93.9% of cases. Difficulty with deployment was attributable to malfunctioning of the device, massive vascular wall calcifications, postoperative scar tissue, or too steep a puncture angle. Minor complications were observed

in 7.4% of cases, with PSA (1%), inguinal hematomas (6.3%), and stenosis (0.1%).[59] Boschewitz et al. showed a 98% technical success rate with no major complications and a 0.7% minor complication rate.[60] A prospective analysis comparing Exoseal to manual compression showed no device failures and no major complications in the Exoseal group. Patient pain scores and satisfaction were higher with Exoseal than manual compression.[61]

Angio-Seal

Angio-Seal (St. Jude Medical, St. Paul, Minnesota) is a collagen plug closure device. Its use has been associated with less time to hemostasis and earlier ambulation compared to manual compression. The Angio-Seal device has been associated with ischemic complications when the device is deployed incorrectly.[62-65] However, the overall major complication rate is similar to other devices.[66,67]

Mynxgrip (Mynx)

The Mynxgrip (Mynx) closure device (Cordis, Milpitas, California) is a closure system that creates an immediate seal through the delivery of a polyethylene glycol plug external to the arteriotomy at the sheath access point. The sealant expands as red blood cells and platelets enter its porous membranes, further covering the access site, and within 30 days, the sealant is dissolved completely by hydrolysis, leaving no intravascular or foreign substances behind. In a registry report including 73,124 patients who had received Mynx devices after PCI procedures with femoral access from January 1, 2011, to September 30, 2013, the Mynx device was associated with a significantly greater risk of any vascular complication than alternative vascular-closure devices (absolute risk, 1.2% vs. 0.8%; relative risk, 1.59; 95% confidence interval [CI], 1.42 to 1.78; $P < .001$); there was also a significantly greater risk of access-site bleeding (absolute risk, 0.4% vs. 0.3%; relative risk, 1.34; 95% CI, 1.10 to 1.62; $P = .001$) and transfusion (absolute risk, 1.8% vs. 1.5%; relative risk, 1.23; 95% CI, 1.13 to 1.34; $P < .001$).[68]

BLEEDING COMPLICATIONS

The most common complication of VCD is device failure resulting in bleeding. For the Perclose Proglide, a wire can be replaced through the barrel of the device to permit replacement of a sheath or the use of another closure device. This allows time for normalization of the ACT, and removal with manual compression. However, if salvage of the sheath is not possible, adjunctive manual compression is required immediately. Protamine can also be given at this time to help facilitate hemostasis.

ISCHEMIC COMPLICATIONS

Less commonly, VCD malfunction can result in lower limb ischemia (Fig. 50.7). Either signs of ischemia develop immediately, or new-onset claudication or pain at rest may arise later.

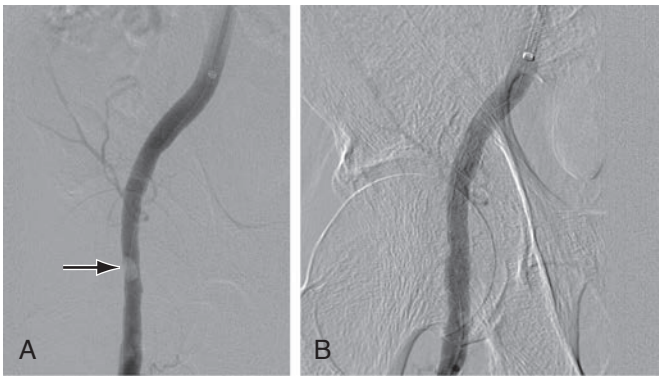

Figure 50.7 (A) Maldeployment of a vascular closure device causing arterial occlusion *(arrow)*. (B) Successful treatment of occlusion with atherectomy.

It is therefore prudent to obtain a baseline pulse and Doppler evaluation before an endovascular intervention and then recheck both lower extremities immediately after the procedure. The etiology of these adverse events is dependent on the device. On exploration, suture-mediated VCDs may have disrupted the back wall intima and caused an occlusive dissection flap that resulted in thrombosis. For the collagen or hydrogel matrix plug VCDs, ischemic complications occur when the prothrombotic material is inadvertently advanced through the arteriotomy, which can potentially embolize or cause local thrombosis. Treatment options for these complications include groin exploration with standard surgical thrombectomy, primary repair, or bypass.

PROCEDURE-SPECIFIC COMPLICATIONS

All endovascular procedures are dependent on the use of a combination of wires, catheters, sheaths, balloons, stents, and interventional devices. Complications caused by these devices can potentially be limb or life threatening, but in many cases they can be treated with adjunctive endovascular interventions. For a safe and successful intervention, it is critical that high-risk vessels be identified on either preoperative imaging or initial angiography. This may prompt earlier anticoagulation, use of protection devices, or use of smaller catheters and sheaths to prevent adverse outcomes.

Dissection

Balloon Angioplasty Dissection

One of the more commonly encountered problems during percutaneous procedures is intimal/medial dissection. This has been reported up to 7% of the time after balloon angioplasty.[69] Balloon angioplasty of atherosclerotic vessels almost always results in intimal dissection. Balloon inflation causes stretching and disruption of the plaque and overlying intima that result in a tear or dissection. Pulsatile arterial flow can then propagate the dissection distally and result in flow-limiting obstruction or arterial occlusion. Arteriography depicts the typical luminal

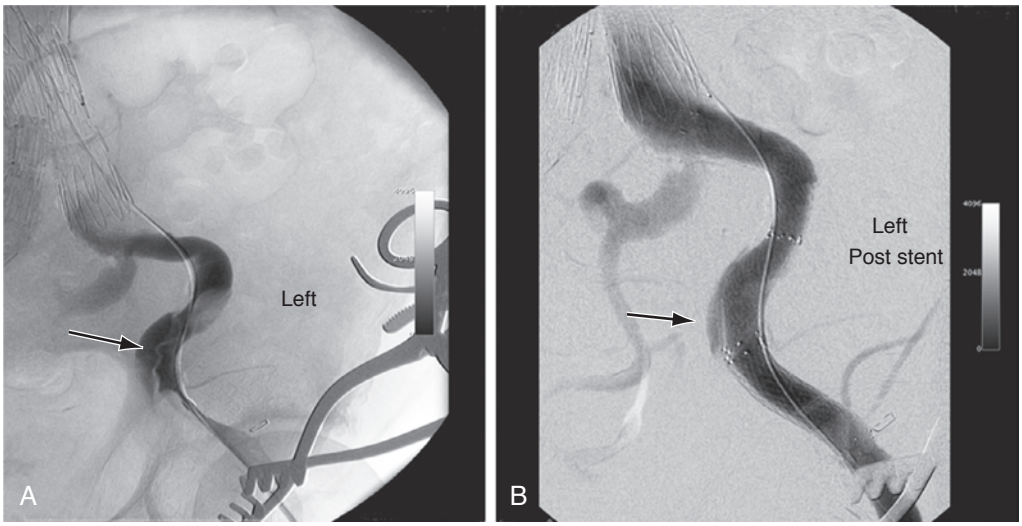

Figure 50.8 (A) Arterial dissection causing occlusion. (B) Successful treatment of occlusion with stent.

flap appearance with contrast media present on both sides of the dissection. Overdistention of a balloon in a normal vessel can also result in dissection. Postangioplasty dissections are initially treated by sustained inflation of a low-pressure angioplasty balloon in an attempt to "tack down" the dissection flap. If low-pressure angioplasty is unsuccessful and there is still a significant (>30% or flow-limiting) dissection, a self-expandable or balloon-expandable stent may be used to repair the dissection. Theoretically, the stent tacks the intima, increases the luminal diameter, and prevents further propagation of the dissection flap. Focal dissections in the infrainguinal vessels can also be treated by excision with a directional atherectomy device. If there is any question that a wire, catheter, or device is subintimal, the procedure should be halted and a low-profile catheter advanced to the point of resistance. If blood cannot be aspirated from the catheter, it is probably subintimal and should be withdrawn until blood can be aspirated. Low-pressure hand injection can then be performed. A subintimal position will be demonstrated by contrast material stagnating within the dissection plane without washout.

Small dissection planes that have been created in normal, nondiseased arterial segments, especially in large-caliber vessels such as the iliac arteries, can be tolerated if there has been no narrowing of the lumen and no evidence of thrombus development, particularly if the dissection is retrograde to the flow of blood. Alternatively, large iatrogenic dissections with a high probability of occluding the vessel or thrombosing require intervention (Fig. 50.8).

Subintimal Angioplasty

In certain circumstances, such as crossing chronic total occlusions, the creation of a dissection plane and subintimal advancement are done intentionally. It is critical that the point of reconstitution distal to the chronic total occlusion be exactly identified and the wire not be allowed to traverse more than 1 or 2 cm beyond the reconstitution point while in the subintimal plane. If accessing the native lumen is difficult, reentry devices such as the Outback catheter (Cordis, Johnson and Johnson, New Brunswick, New Jersey) can be used.[70,71] This has been associated with a low complication rate.

Figure 50.9 Distal embolization after proximal endovascular intervention.

Embolization

Embolization can be a devastating complication of endovascular procedures. It can transform a relatively straightforward procedure performed for claudication into a complex high-risk limb salvage endeavor (Fig. 50.9). In patients with large-volume atheromatous

disease, any wire, catheter, or sheath manipulation can result in distal embolization. Catheter movement across friable thrombus or atheromatous plaque, especially in aneurysmal vessels or a diseased aortic arch, can liberate embolic debris. Depending on location, this can result in "trashing" of runoff vessels, and if in the aortic arch, it can lead to stroke. The rates of lower extremity embolism have been reported from 1% to 3.8%, although not all are clinically significant if there is alternate distal flow. Atherectomy devices have been associated with higher distal embolization.[72] Also, the presence of thrombus in the lesion and TASC C and D lesions have also been shown to be associated with embolus.[72,73]

Management

Prevention of distal embolization is best achieved by recognition of high-risk vessels on preintervention imaging. It is then prudent to institute anticoagulation early and minimize manipulation across the lesion. Moreover, some groups have used embolic protection devices in lower extremity interventions by extrapolation from the carotid angioplasty and stenting experience, especially in the setting of large-volume plaque burden, significant thrombus burden, or single-vessel runoff.[74] If embolization does occur, endovascular rescue can be implemented for salvage of the vessel. First, the patient should be heparinized with confirmation of adequate anticoagulation by the ACT, and if needed, additional heparin should be administered. Aspiration catheters (Export catheter, Medtronic, Minneapolis, Minnesota; Pronto catheter, Vascular Solutions, Inc., Minneapolis, Minnesota) can then be used to remove obstructing thrombus or free-floating plaque.[75] Percutaneous embolectomy is another option that has demonstrated favorable results with acute embolic occlusions,[76] or AngioJet (Possis Medical, Minneapolis, Minnesota) can be used to diminish thrombus burden in the event of distal embolization. The Penumbra device is a newer thromboaspiration device that is being increasingly used in the periphery for embolectomy or thrombectomy.[77] Finally, thrombolytic agents can be administered as an adjunct to the aforementioned maneuvers to dissolve potential thrombotic emboli or if there is concern for possible in situ thrombosis after an embolus has occurred. If these techniques are unsuccessful and the patient has signs of acute ischemia, standard open surgical techniques are warranted, including open thromboembolectomy and, if necessary, surgical bypass.

Wire Perforation

Isolated wire perforations, especially in lower extremity vessels, usually seal with conservative management (Fig. 50.10). Stiffer wires have a higher propensity to perforate and should therefore be avoided as an initial navigation wire or in small, highly diseased vessels. Wires that have perforated a vessel can often be seen on fluoroscopy as traveling outside the normal course of the arterial anatomy, and the tip of the wire will curl abnormally as it enters the soft tissue planes. Once the wire is removed, angiography may reveal extravasation of contrast material. Recognition of this problem is essential before advancing catheters or devices, and the wire should be withdrawn and an attempt made to find a new subintimal plane to traverse the lesion.

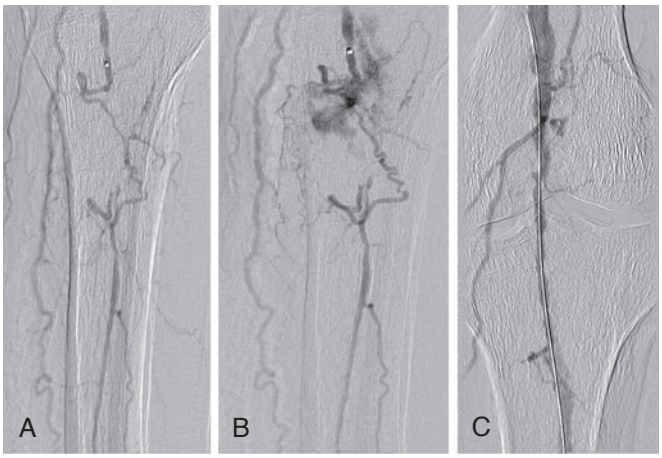

Figure 50.10 Wire perforation after attempted subintimal recanalization. A, Before attempting to cross occlusion; B, wire perforation of vessel; C, successful recanalization.

Figure 50.11 Right kidney iatrogenic perforation.

When performing interventions on the visceral arteries, wire advancement can lead to perforation of the end organ. For example, renal angioplasty requires positioning of a stiff wire in the distal renal artery to allow placement of a sheath and eventual angioplasty and stenting. In rare circumstances, the wire is advanced too far distally and can potentially perforate an intraparenchymal vessel or the kidney capsule itself. Such perforation inevitably results in trauma to the kidney with subsequent hemorrhage into the retroperitoneum (Fig. 50.11). Treatment of this complication depends on the patient's clinical status.

Angioplasty Perforation

Perforation secondary to angioplasty can result in life-threatening bleeding, especially in atherosclerotic vessels. Overdistention of a calcified vessel that has lost its elastic compliance can result

Figure 50.12 Retroperitoneal hemorrhage as seen by extravasation of contrast material.

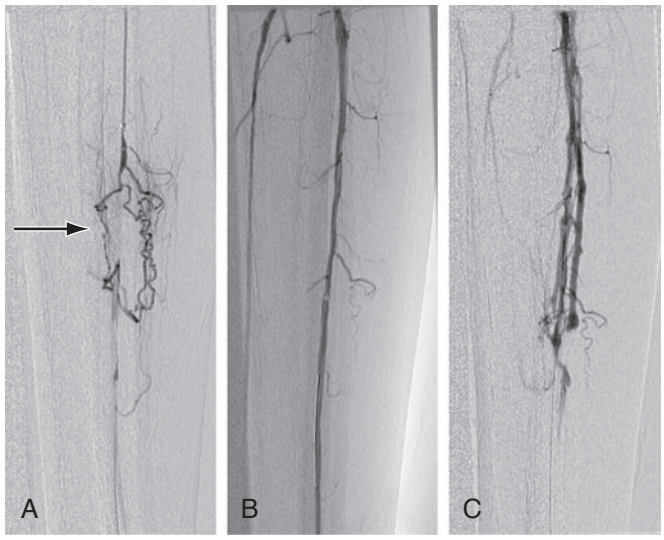

Figure 50.13 Atherectomy-induced arteriovenous fistula characterized on angiography by rapid venous filling. A, Before attempting to cross occlusion; B, successful recanalization; C, delayed filling showing arteriovenous fistula.

in disruption of all layers of the arterial wall and frank perforation. For iliac lesions, perforation can potentially cause massive hemorrhage into the retroperitoneum. Angiography will delineate the extent of rupture based on extravasation of contrast material (Fig. 50.12). Once the perforation is identified, a large compliant balloon should be placed across the injured segment and gently inflated until it tamponades the bleeding site. A covered stent can be used for repair, although sometimes open repair is required.[18,79] For aortic bifurcation lesions or proximal iliac perforation, aortic stent-grafting or aortouniiliac with femorofemoral bypass may be an option. If endovascular repair is not an alternative, the occluding balloon can be left in place while the patient is prepared for open surgical repair.

Angioplasty-induced rupture of the infrainguinal vessels is rarely a life-threatening condition, although it can result in PSA formation or arterial occlusion. In a study of 1409 patients undergoing peripheral angioplasty, 52 (3.7%) experienced arterial perforation.[80] Risk factors for perforation included advanced age, diabetes, and subintimal angioplasty. There were no deaths, and no patients required surgery at the site of perforation; of note, 27 of the 52 procedures were completed successfully, despite the complication.

Atherectomy Perforation

Atherectomy devices, when allowed to excise too deeply, can result in arterial perforation. Generally this is a rare phenomenon that occurs in less than 1% of cases.[5] Oversizing of the device and use near bifurcations can also result in perforation. Prevention of this injury rests on knowing the level of excision within the arterial wall. It is also useful to image the artery orthogonally; multiple views facilitate localization of the device relative to the arterial wall. Intravascular ultrasound can also be performed to determine the depth of plaque excision. Use in heavily diseased arteries with multiple passes along one plane causes an asymmetric excision that can thin the wall down to the subadventitial space. This places the vessel at high risk for the development of an acute or subacute AVF and, in rare cases, PSA formation.

Atherectomy-induced AVF is characterized on angiography by rapid venous filling and, with large AVFs, by diminished or abolished distal arterial outflow (Fig. 50.13). With involvement of the SFA, the majority of fistulae are of no clinical significance and will thrombose spontaneously. If the fistula causes compromised distal perfusion, treatment is warranted. Initial treatment is prolonged low-pressure balloon inflation. If this is unsuccessful, reversal of the anticoagulation is indicated, and if this fails, placement of a covered stent is an option. Under conditions of worsened ischemia that can be attributable to the fistula, surgery may be required if endovascular maneuvers fail. Surgical options include ligation of the vein above and below the site of the fistula or, if necessary, bypass.

Endovascular Aneurysm Repair Access Sites

Stent-graft implantation for the abdominal or thoracic aorta requires the use of large (18 to 24 Fr) sheaths for delivery of the device (see Chapter 73). Proper preoperative assessment of access site vessels, including the femoral and iliac arteries, is a requirement for safe deployment of these grafts. Despite appropriate planning, however, iliac tortuosity, vessel diameter, atherosclerotic disease, and calcification can be limiting factors. Contemporary incidence of iliac artery rupture reported in a single center review during EVAR was reported as 3%, with the common iliac artery being most affected. More than half of the patients became hypotensive after the rupture. The majority underwent endovascular repair, with 25% requiring open repair. There were no intraoperative deaths, but the postoperative mortality rate was 20%.[81] Fernandez et al. analyzed

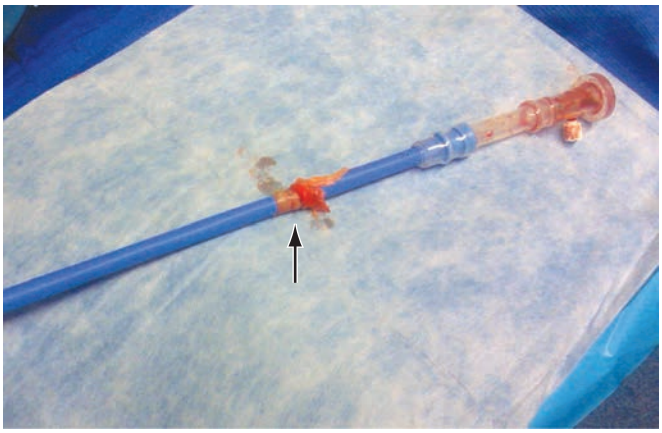

Figure 50.14 "Iliac artery on a stick"—an everted cast of the iliac artery is stuck to the sheath and avulsed on removal of the sheath.

rates with both EVAR and TEVAR. Iliac rupture was more likely to occur during TEVAR (8.9%) than EVAR (2.98%) and in women. Patients in the ruptured group had longer lengths of stay and a higher procedure-related mortality.[82]

Therefore with evolving experience with these devices, many investigators have instituted a lower threshold for using an iliofemoral or iliac artery conduit to gain larger, more proximal access, although this has been shown to increase perioperative morbidity and mortality.[83] Despite even the most diligent preparation, rupture of the access vessels can occur, and operators should be prepared to manage this devastating complication by having appropriately sized balloons and covered stents immediately available in the area where the aortic stent-graft surgery is being performed. Most ruptures are detected at the conclusion of the procedure when the sheaths are being removed from the iliac/femoral vessel. Before removal of the sheath, the sheath itself is occluding the ruptured iliac vessel. The patient will not begin to hemorrhage from the perforation until the sheath is removed. Ruptured iliac vessels will usually cause acute and profound hypotension. It is crucial that wire access be maintained to allow placement of an occlusion balloon in all cases until it is proved that the patient is hemodynamically stable after removal of the sheath. In extreme cases, operators may encounter the "iliac artery on a stick," in which an everted cast of the iliac artery is stuck to the sheath and avulsed on removal of the sheath (Fig. 50.14). Definitive treatment of this adverse event can be accomplished by placing multiple covered stents that span the area of rupture. At any time, however, surgical repair may be required to repair an injury that has not completely sealed or was not amenable to stent coverage.

OTHER COMPLICATIONS OF ENDOVASCULAR PROCEDURES

Thrombolysis

Catheter-directed thrombolysis has become the first line of treatment at many institutions for deep venous thrombosis, acute arterial ischemia, and pulmonary embolism.[84-86] Major complications have been associated with several thrombolytic agents (see Chapter 41). In two of the major trials comparing surgery and thrombolysis (TOPAS [Thrombolysis or Peripheral Arterial Surgery] and STILE [Surgery vs. Thrombolysis for Ischemia of the Lower Extremity]), the life-threatening hemorrhage rates were 13% and 5.6%, respectively.[87,88] The most common complication is a hematoma at the access site.[85] Intracranial hemorrhage has been reported 0.7% of the time and gastrointestinal hemorrhage in 1.6% of cases.[90] Treatment of minor bleeding is primarily application of continuous pressure locally. Patients receiving thrombolytic therapy should be monitored by serial hematocrit determination and coagulation studies. A profound decline in fibrinogen levels (<150 mg/dL) should at the minimum raise concern for increased bleeding risk. A drop in hematocrit, especially with hemodynamic instability, should prompt concern for retroperitoneal hemorrhage, and a CT scan should be obtained. If the bleeding is significant and requires transfusion, lytic treatment should be halted. Similarly, a change in mental status should prompt stoppage of thrombolytic therapy, given the risk for intracerebral bleeding, and imaging of the brain with either CT or magnetic resonance imaging should be performed.

Device Infection

Endovascular Stent-Grafts

Infections of EVAR and TEVAR grafts are rare but potentially devastating complications. The reported incidence ranges from 0.6% to 0.77% (see Chapter 72).[91,92]

Stents

Infection of bare-metal stents is also a rare complication of endovascular interventions. These have been reported more in noncoronary rather than coronary stents.[93] PET-CT has been helpful at identifying stent infections. Breaks in sterile technique, occult glove perforation, inadequate skin preparation, repeat puncture of the same arterial access site, prolonged use or reuse of an indwelling catheter, increased procedure time, puncture site hematoma, other sources of coincident bacteremia, and nonsterile angiography suites may contribute to this, although there are no clear data.[94] As noted, infections have also been reported in stent-grafts, with reports of stent-graft preservation with antibiotic therapy.[95,96]

Patients with stent infections often have clinical signs of bacteremia consisting of fever, chills, and rigors, and this should prompt a standard evaluation for other sources of infection. Once these are ruled out, stent infection should be considered, but the rarity of this complication makes it a diagnosis of exclusion. *Staphylococcus aureus* is the most common organism isolated in cases of stent infection.[94] Imaging modalities that are helpful in making the diagnosis include CT, angiography, duplex ultrasonography, and tagged white blood cell scans. Treatment should be aggressive and consist of removal of the stent and all surrounding infected tissue, which often includes a large portion of the artery. The principles of management of

prosthetic graft infection should be applied so that most patients will require bypass with autogenous conduit or extra-anatomic reconstruction with prosthetic material. Definitive preventive measures for stent infections are unknown at this time.

Device Fracture or Embolization

In view of the vast array of equipment used during complex percutaneous procedures, it is not uncommon to encounter device or instrument malfunction. For example, wires, catheters, or sheaths can break and leave residual, free-floating fragments within the arterial lumen. This necessitates prompt retrieval to avoid distal embolization or arterial thrombosis. The most common technique used to retrieve foreign bodies within the vasculature involves the use of endovascular snares or biopsy forceps. If a broken wire is positioned within a sheath, it is also possible to advance a balloon alongside the wire, inflate it, and drag the wire to the origin of the sheath. This technique can also be used to retrieve broken sheaths.[98]

Figure 50.15 Dislodged inferior vena cava filter.

Improper sizing of the vessel lumen can cause a mismatch between the stent diameter and the size of the vessel. If the stent is too small, it can migrate distally and essentially embolize and lodge at a branch point or a smaller portion of the vessel. Inadvertent displacement of a stent can occur during passage of the device. For example, in patients with iliac disease that has been stented in the past, passage of the device through these iliac vessels risks stent dislodgement and embolization. Balloon expandable stents should be advanced through the stenotic area in the sheath to avoid dislodging the stent from the balloon.

Venous

Angioplasty and Stenting

Venous angioplasty with stenting is a commonly performed procedure for patients with central venous stenosis (see Chapter 161). Vein rupture with aggressive angioplasty may occur in the setting of highly scarred or chronically occluded vessels. Generally, vein perforations can be managed conservatively because the low-pressure system allows the injury to seal spontaneously with manual compression therapy alone.

Venous stent migration has been reported to occur, and in the most severe cases these stents can embolize to the heart. This has been reported in the setting of iliac vein stenting, superior vena cava (SVC) syndrome, and stenting of the renal vein for Nutcracker syndrome.[99-101] Retrieval of migrated venous stents can usually be accomplished with snares; however, in some instances, open operation is required for stent removal.

Inferior Vena Cava Filter Complications

Inferior vena cava (IVC) filter placement is rarely associated with complications (see Chapter 152).[102] Procedure-related complications can occur either in the acute period or months to years later. Late filter complications carry the highest morbidity and mortality rates for filters and include embolization, vessel penetration, and thrombosis of the filter.[103-108] Embolization of the filter or filter struts can go into the heart or the pulmonary arteries and can potentially induce fatal arrhythmias.[103,104]

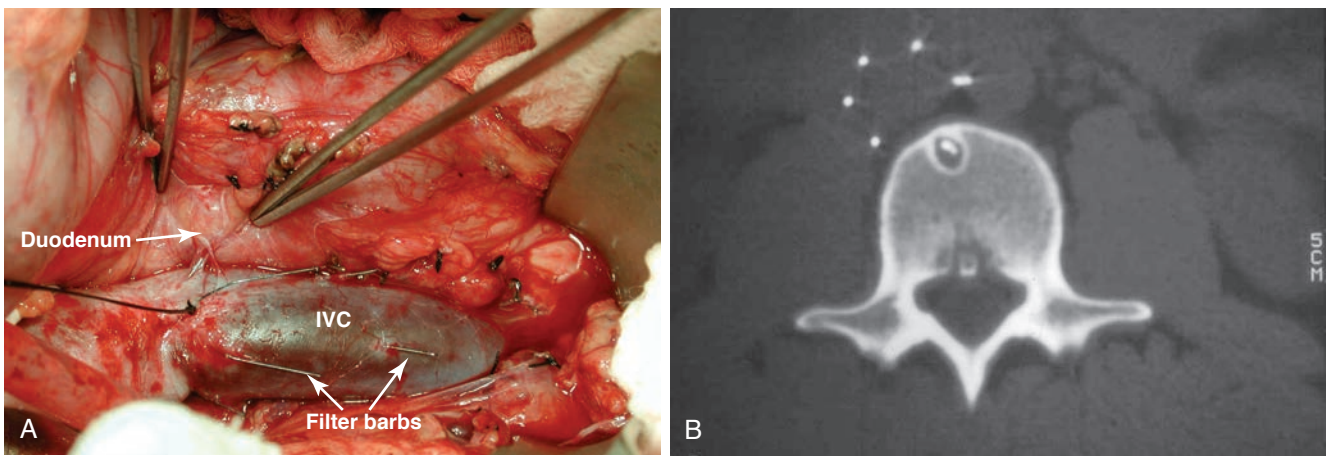

Figure 50.16 Protrusion of prongs of IVC filter into adjacent structures (A) bowel, (B) spine. IVC, Inferior vena cava.

Embolization or dislodgement can also occur during either internal jugular or lower extremity venous catheter exchange (Fig. 50.15).

Long term, the barbs on the filter erode through the IVC. Although most cases are asymptomatic, penetration into adjacent structures such as the duodenum, aorta, or vertebral bodies can occur (Fig. 50.16).[105] The duration of filter placement is associated with the risks of penetration. Treatment of bowel perforation involves open removal of the filter and repair of the intestinal injury and the caval wall.[106] The development of thrombus at the level of the filter is another complication that can cause complete occlusion of the IVC with resultant venous obstructive complications, including phlegmasia, recurrent deep venous thrombosis, and postphlebitic syndrome.[107] IVC filter occlusion has been associated with pulmonary embolism that has failed anticoagulation as an indication for placement.[108] This complication should be considered when planning filter placement in young individuals and provides justification for the placement of temporary filters.

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A complete reference list can be found online at www.expertconsult.com.

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51 CHAPTER

Venous Complications

ELLEN DILLAVOU and MISAKI KIGUCHI

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In vascular surgery, venous complications arise from different mechanisms, ranging from traumatic to iatrogenic injury, both directly and indirectly. Complications may present as bleeding and hematoma immediately after venous injury or as occult thrombosis or fistula detected only after many months following the incident. Presentations of venous complications are highly variable and can range from subtle to obvious. In general, the greater the severity of the clinical presentation of the venous complication, the greater the magnitude of the treatment required, and because of this, treatment options are often up for debate.

INCIDENCE OF VENOUS COMPLICATIONS

The most common venous complication after any type of surgery or illness is deep venous thrombosis (DVT) (see Chapters 147-149). Although not necessarily a direct venous injury, the incidence of DVT after vascular surgery has been reported as high as 20%.[1] The incidence of DVT after venous puncture is not widely reported but was found to be up to 60% without anticoagulation during cardiac procedures[2] and in 36% of patients with an existing clot who received an inferior vena cava (IVC) filter.[3]

Direct venous injury requiring dedicated repair is most commonly seen in trauma patients and as a procedural complication. These injuries can lead to bleeding, thrombosis or, more rarely, arteriovenous fistula (AVF). Venous injury in trauma has been reported as high as 28% of penetrating wounds and is usually associated with arterial injury.[4] Iatrogenic injuries during other surgeries are rarely reported, but the Mayo clinic reported on 44 injuries during major abdominal surgery over 17 years. Average blood loss from these injuries was nearly 4 L, and there was an 18% mortality rate.[5]

Direct Venous Injury

Direct venous injury involves trauma to a vein. The expanding field of endovascular therapy for the treatment of vascular disease has steadily increased the number of access site procedural complications. (See Chapter 50: Local Endovascular Complications and Their Management.) Since 1995, there has been approximately a 10-fold increase in the rate of peripheral vascular interventions.[6] Access site complications occur in 1.0% to 11% of these procedures.[7-10] Central line placement can also cause direct injury to the vessels. Injury is often obvious, but hypotension after a percutaneous intervention should always include the differential diagnosis of a remote hematoma. After femoral interventions, an acute drop in hemoglobin level and lower abdominal/flank pain should raise suspicion for a retroperitoneal hematoma.

Isolated venous injury during dissection of the adjacent arterial or nerve structures or other surgical exposures often goes unreported. Injuries are commonly repaired primarily, or the affected veins may be ligated, relying on collateral circulation. Direct venous injuries are often only diagnosed and reported when a life-threatening hemorrhage or hemodynamic instability occurs.

Abstract

Complications from venous injury can have varied clinical presentations, ranging from minor acute subtle hematomas occurring minutes after a procedure to large arteriovenous fistulas that progress to congestive heart failure months after an intervention. This chapter explores several specific types of venous complications, including direct and indirect venous injury from open and endovascular therapies, their diagnostic evaluations, and comprehensive management. A fuller understanding of the common pitfalls that cause venous injury often limits its occurrence, aids in immediate diagnosis, and improves clinical outcomes.

Keywords

Venous injury
Venous complications
Arteriovenous fistulas traumatic
Arteriovenous fistulas iatrogenic
Venous thrombosis
Venous stent complications
Retroperitoneal hematomas venous
Inferior vena cava filter complications

The risk of direct venous injury can be minimized by proper technique and recognition of high-risk patients. Predictors of groin complications from any vascular access have been well described. Obesity, large sheath size, previous catheterization, and anticoagulation are notable risk factors for all access site complications.[11] For percutaneous interventions, including central line placements, ultrasound guidance and the Seldinger technique are considered standard of care procedural steps.[12,13]

Diagnostic Evaluation of Direct Venous Injury

During percutaneous interventions, a hematoma is most telling of a complication from a venous injury. A hematoma may present as obvious swelling, but other more subtle signs and symptoms include access site pain, skin ecchymosis, continued bleeding through the puncture site, and hypotension. Duplex ultrasound of the localized hematoma is often necessary, especially if the hematoma is pulsatile, has a bruit over it, or is exquisitely tender, to rule out arterial pseudoaneurysm or AVF. Venous extravasation is generally not seen on ultrasound, but is instead seen as hematoma. Venous compression or thrombosis from the hematoma can also be seen.

Retroperitoneal hematomas are a clinical diagnosis. Retroperitoneal hematomas from femoral venous accesses are often subtle but can have severe morbidity and mortality if not identified. The retroperitoneal space accommodates a large amount of blood without tamponade from surrounding structures, and thus, complaints of back or lower abdominal pain, hypotension, tachycardia, and oliguria should raise suspicion to diagnose and manage urgently. Patients should promptly be considered for a CT scan. By using contrast, an abdominal and pelvic CT scan can readily identify arterial or venous injury and resulting hematoma, pseudoaneurysm, or extravasation (Fig. 51.1).

Venous injuries during open surgical approaches are often diagnosed by direct visualization. However, if clinically occult, computed tomography and magnetic resonance angiography in the delayed phase can provide a diagnosis.

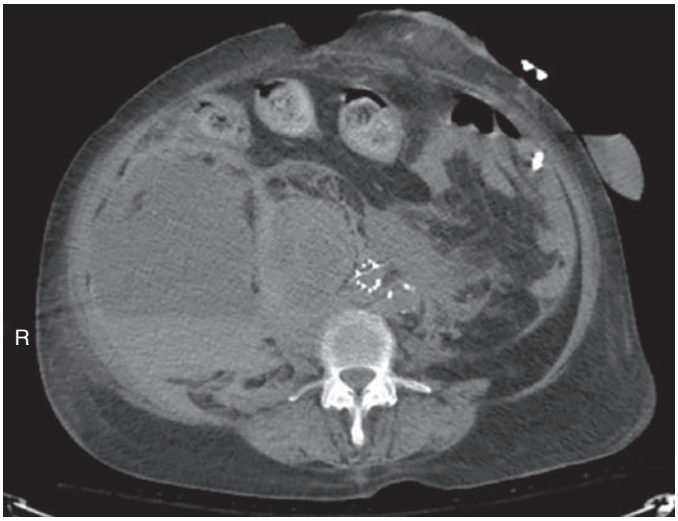

Figure 51.1 Large retroperitoneal hematoma. Note the indistinct border of the inferior vena cava (IVC). This patient had an IVC filter placed shortly before this scan.

Management of Direct Venous Injury

Venous access site injury during a percutaneous intervention often results in hematoma formation. Early recognition limits significant morbidity. Although often self-limiting, pressure over the puncture site is recommended. The area should be marked to evaluate for any expansion and be serially monitored. Monitoring serial hemoglobin levels and prolonging bedrest is recommended. Most hematomas resolve within a few weeks. Hematoma size varies, and if skin compromise is evident, evacuation and debridement of the affected area is necessary.

In coagulopathic patients, however, aggressive resuscitation with blood products may be required, especially if a retroperitoneal hematoma is suspected. Although most retroperitoneal hematomas can be managed with resuscitation, bedrest, and monitoring serial hematocrit levels, hemodynamic instability, ongoing blood loss, and neurologic deficits due to compression of adjacent nerves are indications for further imaging and possibly open surgical exploration. Complications from venous intervention remote from the access area are now recognized as increasingly common. Treatment of these complications is an evolving area of vascular surgery and is individually determined on a symptomatic basis.

Venous injury during open surgical procedure, such as an iliac vein injury during an aortobifemoral bypass, ranges from small adventitial hematomas to complete transections. Small injuries often are managed conservatively with direct pressure. However, tears and lacerations can be repaired with 5-0, 6-0, or 7-0 prolene sutures as appropriate for vein size. Proximal and distal control is often not necessary but can be done gently with sponge sticks if required. Encircling and clamping veins to assist in repairing injuries frequently causes additional trauma and bleeding as small branches may be sheared and large soft veins are susceptible to clamp trauma. In general, when severely injured and resulting in hemodynamic instability, the brachiocephalic, internal jugular, subclavian, and extremity veins can be ligated, especially if the contralateral side is patent. Open repair however, is preferred. Caval, femoral, brachiocephalic, or subclavian/axillary vein injuries can be closed with a transverse primary repair with 4-0 or 5-0 prolene suture if there is no loss of domain. With a loss of domain, it is necessary to replace this lost segment, usually with lateral venorrhaphy and a bovine pericardial patch in the IVC or vein patch in smaller vessels, to avoid tension or stricture. Large abdominal veins such as the renal or superior mesenteric veins should be repaired as needed. However, in the context of hemodynamic instability, vein ligation of even these vessels may be necessary.

For caval injuries, endovascular repair options include balloon occlusion or control, and even coverage with a covered stent or aortic cuff. These interventions are usually performed in a hybrid OR. Balloon occlusion with large, low-pressure balloons from above and below the injury, either inserted percutaneously from the jugular and femoral sites or inserted through the injury, can slow down blood loss and may allow enough

visualization for an open repair. If the injury is being managed percutaneously, there are reports of covered stent grafts in the IVC.[14-17] These are difficult to size, as the injured cava may have ill-defined walls and the size of the tear may be difficult to appreciate on CT or venogram. In addition, there may be spasm of the IVC or underfilling from blood loss that leads to placement of cuffs that could embolize once the cava is fully expanded.

In the event of a posterior vena caval injury, this difficult problem can possibly be managed by control of the cava and opening the cava on the anterior surface to visualize the posterior tear. This can then be repaired from inside the cava and the anterior exposure site can be primarily closed in a transverse manner. If there is a significant loss of domain in any of these large veins, and the patient is hemodynamically stable, the injured section of vein can be replaced with a Dacron prosthetic graft, usually 20–24 mm in diameter, or a spiral vein graft if time allows. If a prosthetic graft is used, consideration should be given to prolonged systemic anticoagulation, a distal arteriovenous fistula, or both to optimize patency. Severe venous injuries, especially in the infra or suprahepatic regions of the IVC, carry a very high morbidity and mortality.[18]

Arteriovenous Fistulas

An AVF is a direct communication between an artery and a vein. AVFs often can occur after penetrating trauma, where ongoing bleeding from an artery decompresses into an adjacent venous injury (Fig. 51.2). With increasing numbers of invasive percutaneous procedures, vascular cannulation accounts for most AVFs.[19] The incidence ranges from 0.0006% to 0.88%.[20-22] Total knee replacements, lumbar disc surgery,[23,24] and percutaneous biopsies, such as in transplant kidneys, may also result in AVFs.

Venous Thrombosis

The topic of DVT is extensively discussed in Section 22. DVTs can manifest with varied signs and symptoms but is particularly an important clinical diagnosis to keep in mind after any venous injury or intervention. After percutaneous interventions such as IVC filter placement, compression of the punctured vein after instrumentation predisposes to thrombus formation.[25] Furthermore, any instrumentation or catheter placement within the vein activates the clotting cascade by virtue of the venous trauma involved (Fig. 51.3).[26] Surgical repair after direct injury to a vein can also be a nidus for thrombus formation.

Diagnostic evaluation and management of venous thrombosis is discussed in detail in Chapter 146: Venous Thromboembolic Disease: Epidemiology, Pathophysiology, Natural History; Chapter 147: Acute Lower Extremity Venous Thrombosis: Presentation, Diagnosis, and Medical Management; Chapter 148: Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment; and Chapter 149: Acute Upper Extremity and Catheter-Related Venous Thrombosis.

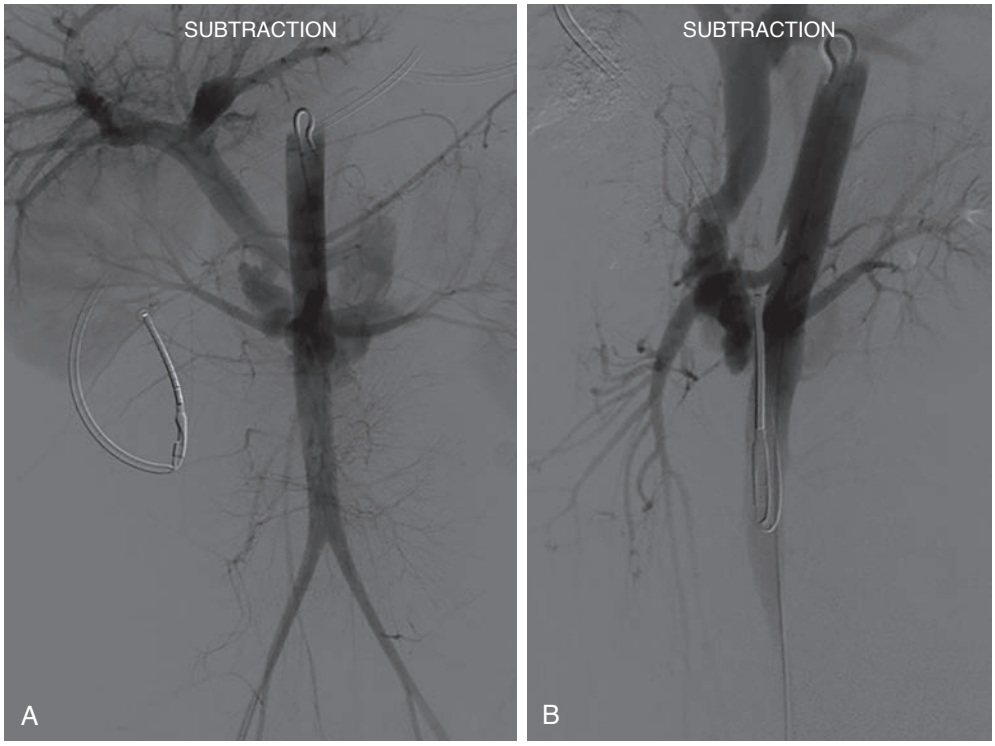

Figure 51.2 Aorto-superior mesenteric vein fistula draining into the portal vein in AP (A) and lateral (B) projections after a gunshot wound to the abdomen. Both vessels were repaired primarily. (Image courtesy of Mitchell W. Cox, MD.)

Endovascular Complications From Venous Interventions

Venous angioplasty and stenting are instrumental in salvaging hemodialysis access. Outflow and central venous stenosis are often treated with balloons and stents to improve secondary patency of hemodialysis fistulas and grafts. Left iliac vein angioplasty and stenting is common in relieving left leg swelling for patients with May-Thurner and postthrombotic syndromes. Caval recanalization and reconstruction with stents have been shown to improve venous ulcer healing.[27] Venous stenosis, especially within veins arterialized from hemodialysis access, may be difficult to dilate and require high-pressure balloons. However, not infrequently, high-pressure inflations cause venous rupture (see Chapter 161: Iliocaval Venous Obstruction: Endovascular Treatment).

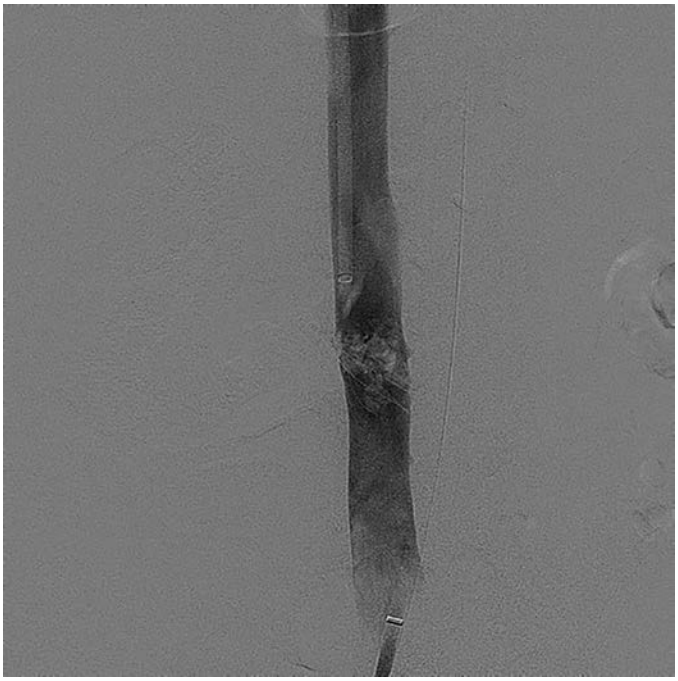

Figure 51.3 New thrombus after attempts to retrieve tilted inferior vena cava filter. Filling voids can be seen from the draining renal veins near the superior sheath tip, and new thrombus surrounds the tilted filter directly below. This thrombus occurred after prolonged attempt to remove the filter. (Image courtesy of Mitchell W. Cox, MD.)

Migration is another potential complication of endovascular intervention and is usually associated with central vein stent deployment.[28] Central veins are more compliant and thus, without adequate stent oversizing, venous stents are more prone to migration. Intravascular ultrasound aids in accurately measuring the diameters of these compliant lumens intraoperatively. In addition to adequate oversizing, accurate proximal and distal positioning of the stent with adequate anchors limits migration.[29]

Wire perforation from endovascular venous interventions is rare but can happen when recanalizing chronic occlusions, such as during iliocaval reconstructions. Stiffer wires have a higher propensity to injure the vessel and should be used cautiously. However, significant bleeding from wire perforation is uncommon, as the occluded veins have low flow.

Diagnostic Evaluation of Endovascular Complications From Venous Interventions

Most endovascular complications of venous interventions occur intraoperatively as, for example, when a venous stent "watermelon seeds" into the right side of the heart (Fig. 51.4). Therefore,

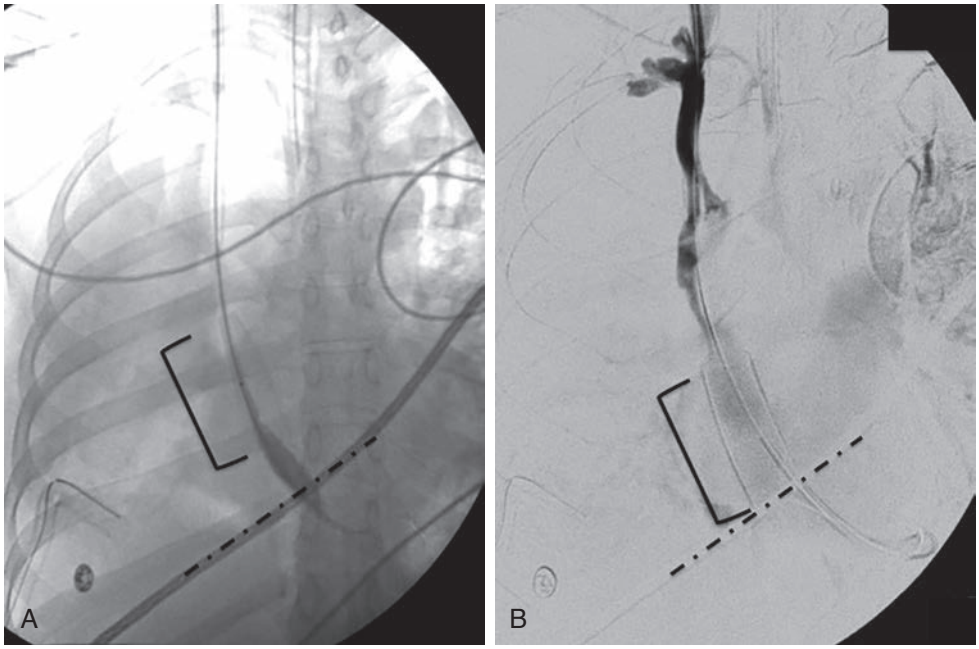

Figure 51.4 Embolization of a stent from the superior vena cava into the right atrium. Note the position of the stent *(brackets)* in relation to the fixed wire *(dashed line)* overlying the patient at deployment (A) and after ballooning (B).

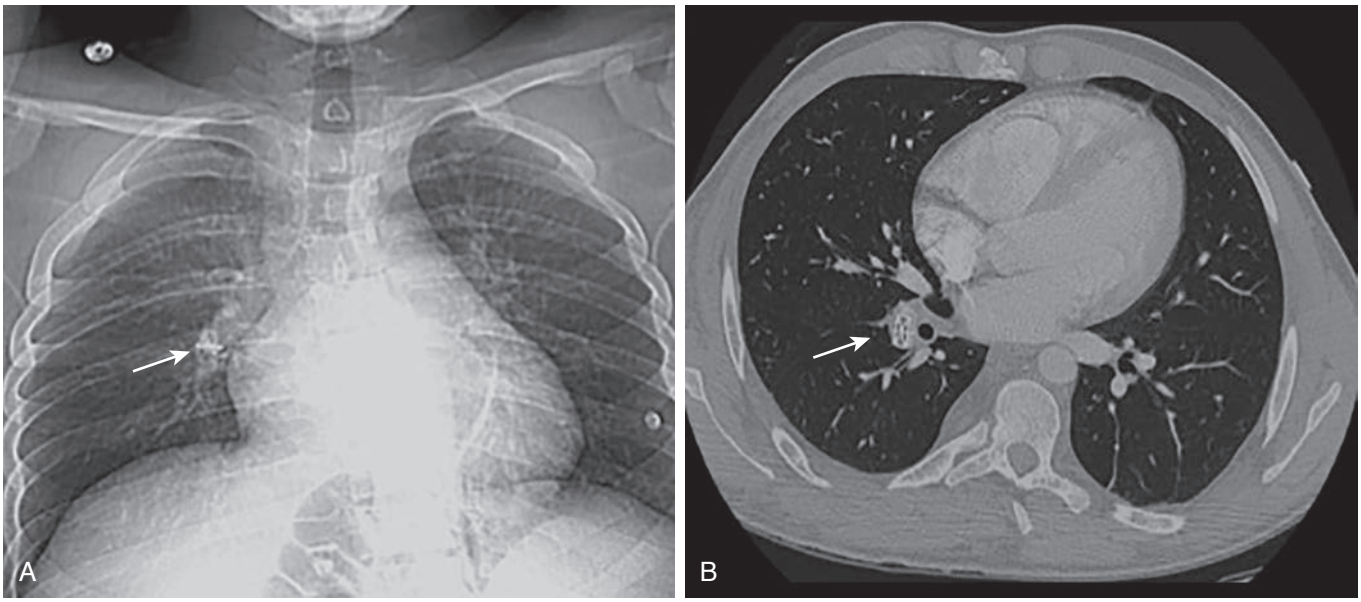

Figure 51.5 Embolization of an occlusion plug *(arrows)* from the right internal iliac vein into the pulmonary circulation, seen on chest x-ray (A) and CT scan (B).

diagnosis is immediate. Perforations after venous angioplasty are quite evident when a post-angioplasty image is taken and can be addressed immediately, and a hematoma may be present in the affected extremity.

Management of Endovascular Complications From Venous Interventions

Most venous ruptures are self-limiting due to the low pressure of the venous system and will seal after a brief period of balloon tamponade. A balloon slightly smaller than the surrounding venous diameter should be placed across the perforated venous segment and gently inflated to low pressure (<5 atm) for at least 5 minutes. If there is still extravasation after this maneuver is performed, a covered or even bare metal stent can be placed across the perforation to achieve hemostasis.

Migrated stents are often percutaneously retrieved with snares if they can be pulled into a large sheath. Migrated stents can also be removed through surgical cutdowns, and the venous system may need to be reconstructed.[30]

Venous embolization devices can also migrate. Coils and plugs have been found in the heart and lungs (Fig. 51.5), as the venous diameter has a large variation and may be in spasm at the time of instrumentation. Placing plugs or coils in the internal iliac veins should be done with great caution, as these can embolize.[31] If this vessel needs to be coiled, the ends of the coils should be anchored in branch vessels and extended into the larger veins (Fig. 51.6).

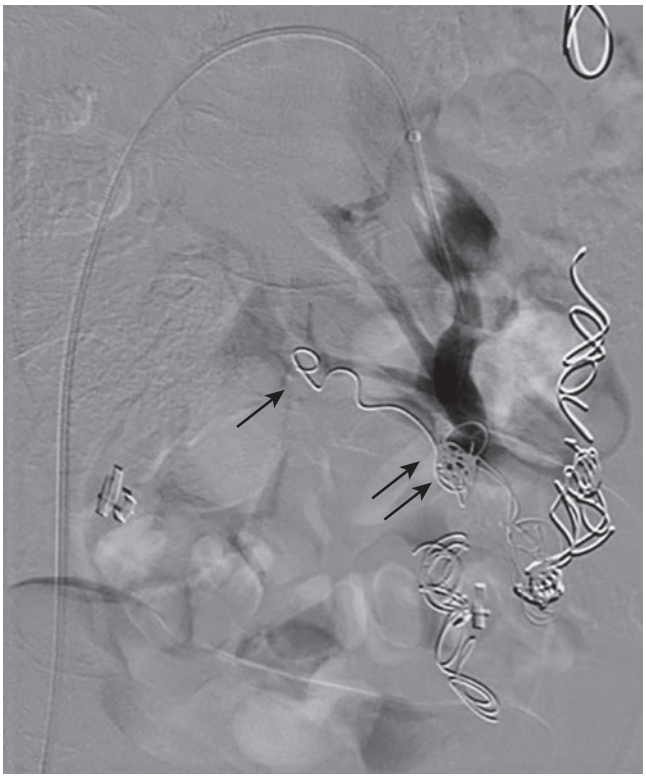

Figure 51.6 Internal iliac vein coiling in a patient with severe pelvic congestion. Sheath extends from the right iliac vein up and over to the left. Coils were anchored in the branches of the iliac vein *(single arrow)* and extended into the internal iliac *(double arrow)* for occlusion.

Inferior Vena Cava Filter Complications

Inferior vena cava filter (IVCF) placements are performed to prevent venous thromboembolism. These filters and procedure-related complications have been well studied (see Chapter 152: Vena Cava Interruption). Misplaced IVCFs, pneumothorax, hematoma, air embolism, AVF, insertion site thrombosis, and carotid puncture are a few of the well-described procedural complications.[32,33] Late complications include IVCF thrombosis, embolization from a thrombosed IVCF, and perforation into

adjacent structures.[34] Migration of IVCF into the right heart carries high morbidity and mortality,[35] and it often occurs when the cava is too large to anchor commercial IVCFs or wires manipulate the filter during venous catheter exchanges (Fig. 51.7).

Figure 51.7 Undersized inferior vena cava (IVC) filter placed near the hepatic veins in the IVC for caval thrombus extending above the renal veins.

Diagnostic Evaluation of Inferior Vena Cava Filter Complications

Migration of IVCFs often is diagnosed intraoperatively or when a diagnostic imaging scan is performed for subsequent symptoms resulting from the migration. Thrombosis of the IVCF can also be diagnosed with a CT scan in the venous phase or venography. Late complications such as perforation or migration are usually detected by a CT performed for symptoms or unrelated problems (Fig. 51.8).

Management of Inferior Vena Cava Filter Complications

IVCF migration can be largely prevented with appropriate sizing and preoperative planning. When wire exchanges are necessary for line exchanges in the context of a patient with an IVCF, direct fluoroscopic wire exchanges limit manipulation of the existing IVCF. Retrieval of a migrated IVCF usually involves percutaneous access of the internal jugular vein and femoral vein, while using large diameter sheaths to accommodate buddy wires, snares, and catheters. Filters may need to be crushed into large sheaths and extracted with a cutdown on the femoral or internal jugular vein. If percutaneous methods fail, surgical exploration and extraction may be required, especially if lodged in the pulmonary artery and causing cardiac complications.

Perforations of the IVCF legs are most often found incidentally on imaging studies. Most cases are asymptomatic, but symptoms from penetration into adjacent structures such as the duodenum can occur. Treatment may require removal of the offending IVCF and open repair of the organ injury.

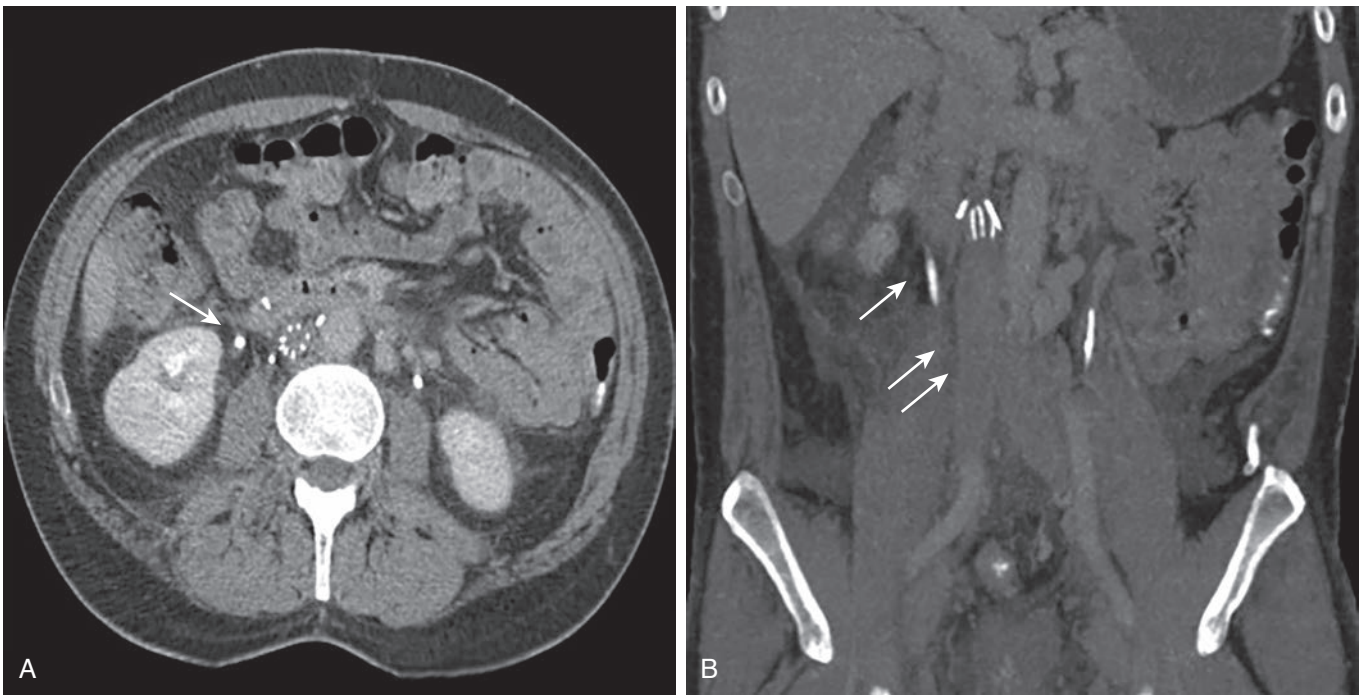

Figure 51.8 CT scan for abdomen and pelvis in sagittal (A) and reconstructed (B) views demonstrating strut fracture and migration *(single arrow)*, thrombosis of inferior vena cava inferior to the filter *(double arrows)* and perforation of filter struts in the bowel retroperitoneum and near the aorta.

Figure 51.9 Inferior vena cava thrombus at time of filter retrieval.

Thrombosed IVCF most often manifests with lower extremity swelling but can also be associated with chronic postphlebitic syndrome, phlegmasia, and renal failure. Patency rates of IVCFs decreases with time; thus, filters should be removed as soon as clinically possible.[36] Patients with IVCF thrombosis (Fig. 51.9) can be considered for thrombolysis and removal of the IVCF, assuming no contraindications. In addition, patients with chronic caval obstruction may be considered for iliocaval venous reconstruction, especially to address lower extremity symptoms.[37]

CONCLUSIONS

Venous complications typically arise because of trauma or iatrogenic injury. DVT is the most common venous complication and is treated with anticoagulation in most cases. Direct injury can be treated with repair or ligation, depending on the location. Late complications, such as AV fistula or migration of a venous device, are treated based on symptoms.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 52

Local Complications: Lymphatic

AUDRA A. DUNCAN

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Due to the close anatomic association between fine lymph vessels, lymph nodes, and corresponding arteries and veins, the possibility of lymphatic complications should always be considered when proceeding with vascular operations. Although the ability of transected or ligated lymphatics to regenerate and reestablish normal lymphatic transport is remarkable, extremity edema after vascular intervention is one of the most common complications. Injury to the lymphatics is a major contributor to the development of lower extremity edema after infrainguinal reconstruction.[1-11] Interruption of lymphatic vessels during surgical dissection may also cause a lymphatic fistula[12-17] or lymphocele.[17-27] Rarely, injury to the para-aortic or mesenteric lymphatics may result in chylous ascites.[22,28-46] Thoracic duct injury may occur during cervical, thoracic, or thoracoabdominal aortic reconstruction,[31,47-56] and chylothorax may occur after high translumbar aortography.[57]

This chapter reviews the pathophysiology, diagnosis, and management of the most frequent lymphatic complications after vascular reconstruction and suggests guidelines for prevention.

POST-BYPASS EDEMA

Lower extremity edema occurs in 50% to 100% of patients who undergo open infrainguinal arterial reconstruction for chronic ischemia.[2,7] Leg swelling after femoropopliteal or femorotibial bypass becomes evident with dependency, usually when the patient resumes ambulation. Pitting edema generally subsides within 2 to 3 months after reconstruction, although it may be persistent in some patients. Significant lymphedema can impair normal ambulation or delay wound healing despite successful arterial reconstruction.

Etiology and Pathogenesis

Lymphedema develops when the rate of production of protein-rich interstitial fluid exceeds the capacity of the lymphatic system to remove the increased lymph volume. When lymphatic transport fails, post-bypass edema occurs.[58] Lymphatic insufficiency has two main causes. First, increased production of interstitial fluid after successful revascularization results in a significant increase in the lymphatic load. Second, the transport capacity of the lymphatic system is reduced because of lymphatic injury and obstruction of deep and superficial lymph channels during dissection in the groin and popliteal space and along the great saphenous vein.

Increased capillary filtration results from elevated arterial pressure after revascularization, alterations in the regulation of microcirculatory flow, and probable endothelial and smooth

Abstract

Due to the close anatomic association between fine lymph vessels, lymph nodes, and corresponding arteries and veins, the possibility of lymphatic complications should always be considered when proceeding with vascular operations. This chapter reviews the pathophysiology, diagnosis, and management of the most frequent lymphatic complications after vascular reconstruction and suggests guidelines for prevention. Frequent complications such as extremity edema, as well as lymphatic fistula or lymphocele will be reviewed. In addition, central lymphatic injury resulting in chylous ascites or chylothorax will be discussed.

Keywords

Lymphatics
graft complications
thoracic duct
edema
chyle
lymphocele
chylothorax

muscle injury from chronic ischemia.[1,7] Eickhoff[8] demonstrated that abnormalities in local blood flow regulation normalize approximately within a week after reconstruction, whereas edema persists much longer in these patients. Although derangement of the microcirculation contributes to post-bypass edema to some degree, Eickhoff's experiments support the theory that lymphatic obstruction secondary to surgical injury is the most important cause of post-bypass edema.

If the number of functioning major lymph channels decreases to a critical level, lymphedema develops. In one study in which patients underwent lymphangiography after infrainguinal bypass, the average number of patent superficial lymph vessels visualized was reduced to 1.7 per patient compared with the normal average of 9.5.[1] In a similar series of 37 patients, edema was not significant when more than three intact superficial lymph vessels were visualized on the postoperative lymphangiogram.[4] AbuRahma et al.[9] examined the involvement of the lymphatic system in the pathophysiology of edema formation in patients who underwent femoropopliteal bypass grafting. Edema developed in 29 of the 72 patients (40%). Leg swelling occurred in 85% (17 of 20) of the patients treated by conventional dissection of the femoropopliteal arteries. When careful dissection preserving lymphatics was performed, edema developed in only 2 of 20 patients (10%). Postoperative lymphangiography showed normal anatomy in six of the eight patients without edema, but markedly abnormal anatomy was in all eight patients with edema.

Persson et al.[10] found less edema in patients who needed less dissection; that is, less edema in patients with prosthetic grafts compared to those with vein grafts. Patients with above-knee grafts also had less edema than those with below-knee bypasses.[10] Studies using albumin clearance in patients with edema after revascularization also supported the idea that edema is mainly lymphatic in origin. A reduction in the plasma albumin level with a concomitant increase in albumin content in the extremity was noted after femoropopliteal bypass.[59] The increase in albumin content was three times greater in limbs revascularized by femoropopliteal bypass than in those revascularized with aortoiliac grafts. These data correspond to the clinical observation that edema rarely develops after aortofemoral revascularization.

Lymphedema with lymphocele has also been reported following varicose vein surgery. There is an association of lymphatic dysfunction in patients with incompetent varicose veins, and therefore one must take the same care to protect lymphatics during open vein surgery.[60]

Although venous thrombosis has been proposed as a cause of postoperative leg edema,[61,62] studies have demonstrated a low incidence of deep venous thrombosis in patients with post-bypass edema.[63,64] In one series, normal venous hemodynamics and morphology were confirmed in 41 of 45 patients with leg edema after arterial bypass.[65] The incidence of deep venous thrombosis after femoropopliteal bypass was found to be similar in patients who had edema (7%) and in those who did not (10%).[9] Deep venous thrombosis therefore seems to play a minor role in post-bypass edema in most patients.[7,58,66]

Diagnosis

Mild, partially pitting ankle edema appears on the second or third postoperative day and resolves almost completely with leg elevation and bed rest. Lymphedema is frequently unilateral and involves the dorsum of the foot ("buffalo hump") and the toes ("squaring"). The differential diagnosis of postoperative limb swelling includes deep venous thrombosis, infection with cellulitis, and compartment syndrome. The history and physical examination can aid in identifying cellulitis or compartment syndrome, and duplex scanning of the deep veins is the test of choice for excluding deep venous thrombosis. If the cause of the edema is still in question, lymphoscintigraphy can confirm the presence of lymphedema (Fig. 52.1).

Management

Postoperatively, mild edema of the extremity should be treated by frequent elevation of the limb. Some surgeons advocate for strict bedrest. Cardiac failure should be treated promptly to help preserve the normal pressure gradient and allow venous return and lymph flow toward the heart. Moderate to severe post-bypass edema is treated with compression wrapping until the incisions have healed, followed by calf-length, 30- to 40-mm Hg compression stockings. For patients with a below-knee, in-situ bypass or any bypass to the distal tibial or pedal arteries, management is individualized to avoid direct compression of the subcutaneous vein graft. Attempts to prevent or limit post-bypass edema pharmacologically with steroids, mannitol, terbutaline, or furosemide have not proved effective[10] and are not recommended.

Prevention

Meticulous, lymph-preserving surgical dissection is needed to minimize post-bypass edema.[9,58] For infrainguinal bypass, a vertical groin incision slightly lateral to the femoral pulse should be made in an attempt to preserve the patency and integrity of the lymph nodes.[67] The inguinal lymphatics should be retracted medially, and a vertical incision should be made in the femoral sheath to dissect the femoral arteries. Loupe magnification facilitates identification of the lymph nodes and lymph vessels. The lymphatics should be carefully preserved; if they must be divided, they should be ligated to avoid leakage of lymph. Attempts should be made to preserve as much lymphatic tissue as possible between the saphenofemoral junction and the femoral artery.

Multiple short skin incisions to harvest the saphenous vein may disrupt fewer superficial lymphatics.[9] In theory, endoscopic video-assisted vein harvest may also cause less lymphatic injury and decrease wound-healing problems without compromising vein conduit quality. In a series of 68 lower extremity bypass procedures, only one bleeding complication was related to the video-assisted harvest, and two seromas developed at the arterial dissection sites.[68] The benefit of endoscopic versus open vein harvesting in terms of a reduced rate of lymphatic complications was confirmed in prospective randomized

Figure 52.1 (A) Edema of the left lower extremity in an 88-year-old man 4 weeks after left femoropopliteal saphenous vein bypass performed for severe chronic ischemia. (B) Lymphoscintigraphy confirmed severe lymphedema of the left leg with no visualization of the lymph vessels or inguinal lymph nodes. Lymphatic transport was normal on the right.

studies,[69,70] and such harvesting can result in a reduction in postoperative wound infections.[71,72] Dissection around the popliteal artery should be performed with the same care to avoid lymphatic disruption. The vascular sheath should be opened longitudinally without dissection of the popliteal vein or the posterior tibial nerve in the neurovascular bundle. Fibroadipose tissue, which contains the deep lymphatics in the popliteal fossa, should be left intact. Obara et al. reviewed 1580 open and endovascular surgery procedures and concluded that significant reductions in lymphatic complications occur with planned procedure, and endovascular procedures, as well as using minimal incision techniques for femoral artery exposures when possible.[73]

LYMPHATIC FISTULA

Because of the rich lymphatic network in the femoral triangle, lymphatic fistulae after vascular reconstruction most often occur at the groin. In 4000 vascular operations, Kalman et al.[16] observed lymphatic fistulae in 45 (0.1%) patients. The incidence of this complication was similar in other series and ranged from 0.8% to 6.4%.[13,74,75]

Etiology

Important factors that contribute to lymphatic leakage are failure to ligate or cauterize divided lymphatics and failure to approximate the tissue layers properly at closure. Lymphatic leakage occurs more frequently in older diabetic patients with poor wound healing. Excessive early limb motion, infection of the operated leg or foot, reoperation, and placement of a prosthetic graft to the groin are other possible causes.[16]

Diagnosis

Persistent leakage of clear or yellow fluid from a groin incision establishes the diagnosis. Lymphoscintigraphy to confirm that the fluid is of lymphatic origin is seldom necessary when the fistula develops within days or a few weeks after the operation. When lymphatic leakage occurs several months or years after vascular reconstruction, lymphoscintigraphy is helpful; in such cases, however, computed tomography (CT) white blood cell scanning, and sometimes fistulography, must be performed to exclude infection of an underlying vascular graft (see Chapter 47). CT is also valuable for the diagnosis of concomitant retroperitoneal lymphatic injury, because a retroperitoneal lymphocele or chylous ascites can manifest as a lymphatic fistula at the groin.[58]

Management

Early diagnosis and management of a lymphatic fistula are important to prevent prolonged hospitalization and delayed wound healing. Although infection of an underlying vascular graft may be rare, most studies have reported a small but definite risk of deep wound infection from persistent leakage of lymph.[13,16] Conservative management is indicated in the first few days and should include local wound care, administration of systemic antibiotics, and bed rest with leg elevation to reduce lymph flow. Ideally, all lymphatic leakage will cease 7 to 12 days after initial drainage with conservative measures.[73]

When the fistula continues to produce large volumes despite several days of conservative management, surgical closure in the operating room is the best therapeutic option.[13,16] Approximately 30 to 60 minutes preoperatively, 5 mL of isosulfan blue

(Lymphazurin; United States Surgical, Norwalk, Connecticut) dye is injected subcutaneously into the first and third interdigital spaces in the foot (Fig. 52.2).[15,58] A sequential compression pump is placed on the affected leg to increase lymphatic and venous drainage. The groin incision is then opened, and the site of the lymphatic injury is apparent by the leakage of blue fluid (Fig. 52.3). The area is oversewn, and the wound is closed in multiple layers. If isosulfan blue is not visualized, the incision is irrigated and closed in layers with interrupted suture. When it is impossible to oversew the damaged tissue, injection of fibrin glue may also be useful.

Recently, the widespread use of vacuum-assisted closure (VAC) therapy has been suggested in the use of lymphocutaneous fistulae.[76] By placing VAC devices on 10 patients with either lymphocutaneous fistulae (4 patients) or lymphoceles (6 patients), which converted to fistulae, the authors were able to treat all incisions without recurrence with a median outpatient VAC treatment duration of 16 days. Although this was an early study, it suggests that VAC therapy may be useful in recurrent lymphoceles or difficult-to-manage wounds.

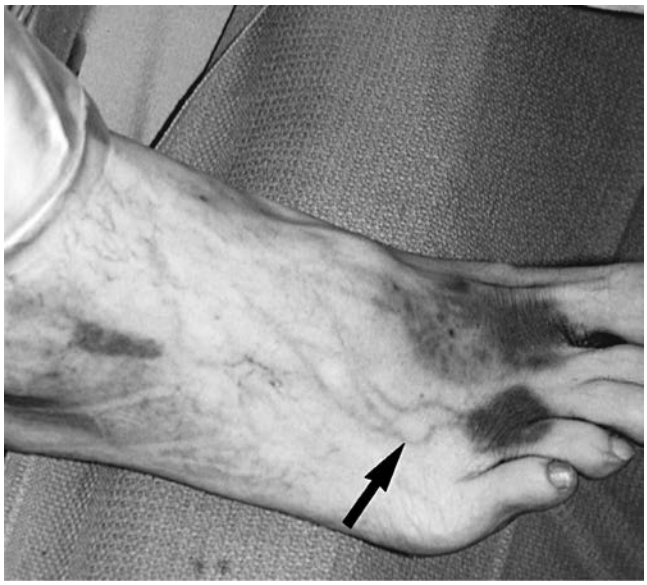

Figure 52.2 Injection of isosulfan blue (Lymphazurin) dye into the first and third interdigital spaces of the foot immediately visualizes the foot lymphatics *(arrow)* and during surgery helps identify the site of lymphatic injury at the groin.

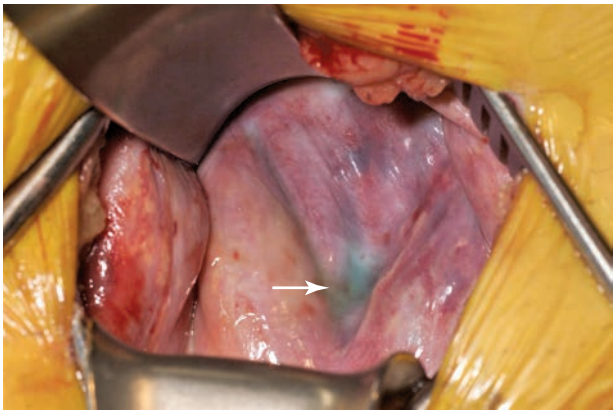

Figure 52.3 Intraoperative photograph of groin re-exploration demonstrating isosulfan blue (Lymphazurin) dye at the base of the incision *(arrow)*. The dye allows localization of the lymphatic injury to facilitate ligation and fistula control.

LYMPHOCELE

A lymphocele is a localized collection of lymph. Early after injury to the lymphatic pathways, the lymph collects between tissue planes. Unless the lymph is reabsorbed spontaneously or drains through a cutaneous fistula, a pseudocapsule develops. In contrast to a seroma, a lymphocele usually has a well-localized connection with one or more of the lymphatic channels. For this reason, lymphoscintigraphy can readily demonstrate a lymphocele (Fig. 52.4).

Groin Lymphocele

As with lymphatic fistulae, the most frequent site of lymphoceles after vascular reconstruction is the groin, often appearing within the first postoperative month. Large lymphoceles cause local discomfort, pain, and leg swelling. Hematoma, seroma, and wound infection should be considered in the differential diagnosis. The presence of a soft, fluid-filled cyst and intermittent drainage of clear lymph through a fistula confirm the diagnosis of lymphocele. Ultrasonography is helpful in distinguishing a solid, dense hematoma from a cystic lymphocele. CT is performed when a lymphocele develops several weeks to months after the operation by excluding graft infection or identifying a retroperitoneal lymphocele extending to the groin.

Small lymphoceles can be observed because they may reabsorb spontaneously. For enlarging or symptomatic lymphoceles or lymphoceles that lie close to a prosthetic graft, early surgery to reduce the chance of graft infection should be performed. Injection of isosulfan blue into the foot is helpful for identifying the lymphatic channels supplying the lymphocele. The lymphocele is excised, and the lymphatic pedicle is ligated or

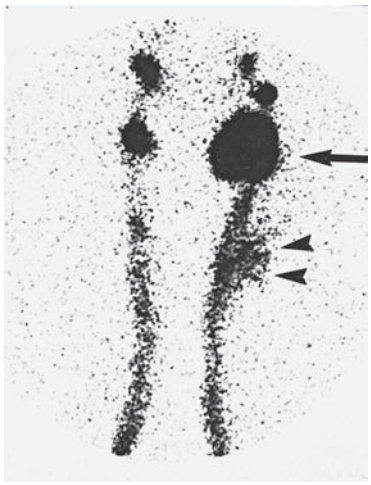

Figure 52.4 Bilateral lower extremity lymphoscintigraphy demonstrating a large left groin lymphocele *(arrow)* and extravasation of colloid in the left side of the thigh *(arrowheads)*.

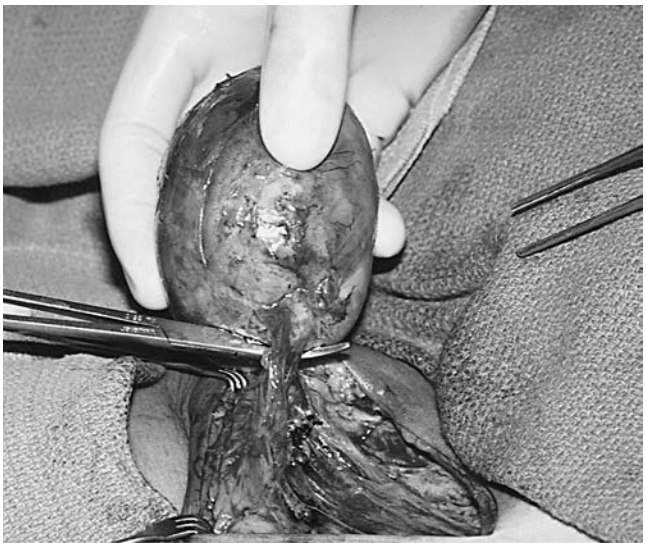

Figure 52.5 Intraoperative photograph of a dissected left groin lymphocele with an easily identifiable lymphatic pedicle. The pedicle was ligated, and the lymphocele was removed.

oversewn (Fig. 52.5). The wound is closed in multiple layers over a small subcutaneous drain. Sclerotherapy, performed more frequently for retroperitoneal lymphoceles, can also be used for groin lymphoceles.

Groin muscle flap coverage can be used to fill defects and provide a single-intervention management of lymphoceles. Shermak et al. reviewed the 22 muscle flaps (19 gracilis, 1 sartorius, 1 rectus abdominis, 1 rectus femoris) placed for lymphoceles. They found that biopsy specimens of the healed muscle at 1 year identified lymphatic channels, indicating that the muscle flap becomes a new path for lymphatic drainage.[77]

Retroperitoneal Lymphocele

Symptomatic retroperitoneal lymphoceles are rare. In a review of more than 4000 aortic reconstructions, an incidence of 0.1% was reported by Garrett et al.[25] In reviewing the literature,[18,19,21-23,25,58] 11 well-documented cases of this complication were found after aortic reconstruction. The number of unreported and asymptomatic cases is undoubtedly higher. Retroperitoneal lymphoceles have been reported more frequently after renal transplantation (incidence of 0.6%-18%).[26,78-80] In these patients, however, a lymphocele develops not only because of injury to the recipient pelvic lymphatics but also because of increased lymph production and leakage from the donor kidney.[26]

Diagnosis

The most common symptoms of retroperitoneal lymphocele are abdominal distention, nausea, and abdominal pain, and the most frequent finding is an abdominal or flank mass. Although signs or symptoms may develop early, in almost half of patients, the lymphocele is discovered a year or several years after the operation.[58] Patients with signs or symptoms of a retroperitoneal lymphocele should be examined with CT (Fig. 52.6). In 5 of 11 published cases of retroperitoneal lymphocele, a groin mass was also present.[58] Evaluation of these patients showed communication between the groin lymphocele and a retroperitoneal lymphocele. This observation illustrates the importance of CT when a groin mass develops after aortofemoral reconstruction. If infection is suspected, white blood cell scanning should also be performed, unless CT has already confirmed graft infection (see Chapter 47). Lymphoscintigraphy can be diagnostic of a retroperitoneal lymphocele and should distinguish it from perigraft seroma. Nevertheless, lymphoscintigraphic confirmation of a lymphocele does not rule out graft infection.

Figure 52.6 Computed tomography in a 70-year-old woman reveals a large left retroperitoneal lymphocele 9 months after repair of a thoracoabdominal aortic aneurysm.

Management

For patients with a small asymptomatic retroperitoneal lymphocele, observation with serial ultrasonography or CT is warranted. If the lymphocele enlarges or causes local compression of adjacent structures, needle aspiration under CT or ultrasound guidance is performed. This maneuver is both diagnostic and therapeutic. In 4 of 11 patients, aspiration alone was used with success.[58] Placement of an indwelling irrigation-drainage system is associated with a risk for infection. Garrett et al.[25] discussed two patients whose prosthetic grafts became infected after an irrigation-drainage system was placed for a retroperitoneal lymphocele. Therefore, when repeated aspiration is unsuccessful, sclerotherapy or operative repair should be considered. Abdominal exploration is performed after injection of 5 mL of isosulfan blue into the ipsilateral foot according to the technique detailed earlier. The lymphocele is unroofed, and the site of the lymphatic injury is oversewn, ligated, or both. If the prosthetic graft is exposed, it is covered by retroperitoneal tissue or omentum. When preoperative aspiration confirms the presence of chyle in the cyst, 24 oz of whipping cream is administered through a nasogastric tube 4 hours before exploration. Absorption of the cream helps identify the site of lymphatic leakage in the mesenteric lymphatics around the left renal vein or at the cisterna chyli (Fig. 52.7). Although the mesenteric lymphatic trunks

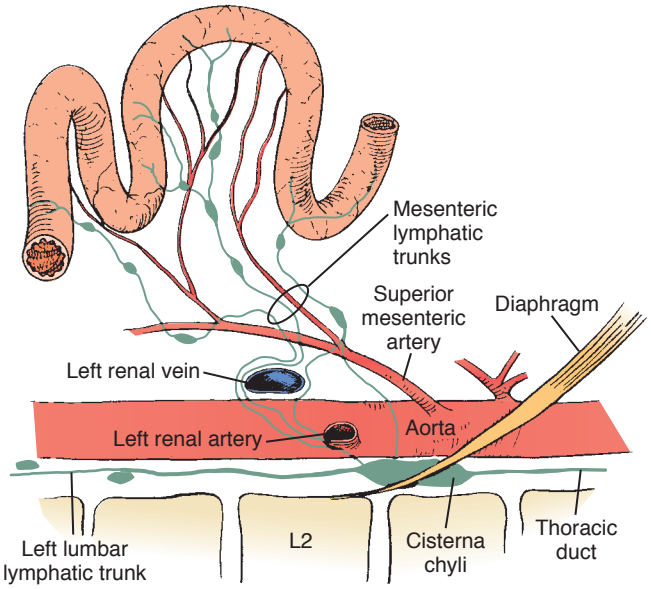

Figure 52.7 Anatomy of the mesenteric and ascending lumbar lymphatic trunks and the cisterna chyli. (Modified from Gloviczki P, Bergman RT. Lymphatic problems and revascularization edema. In: Bernhard VM, Towne JB, eds. *Complications in Vascular Surgery.* 2nd ed. St. Louis, MO: Quality Medical Publishing; 1991:366.)

should be ligated or oversewn, lateral closure of the cisterna may be attempted first with loupe magnification.

For post-transplant lymphocele, peritoneal fenestration has been recommended for treatment.[78-80] Since the advent of surgical laparoscopy, however, several reports have described aspiration and peritoneal fenestration under laparoscopic visualization.[79,80] A tongue of omentum is brought down and placed through the peritoneal window to prevent premature closure and recurrence of the cyst. One study analyzed the results of 12 laparoscopic and 23 open surgical internal marsupializations of pelvic lymphoceles. Laparoscopic lymphocelectomy required a longer operative time, but it resulted in a shorter hospital stay, faster convalescence, and fewer recurrences of the lymphocele.[78] Laparoscopic transperitoneal drainage may become a useful addition to the vascular surgeon's armamentarium for the occasional treatment of lymphoceles after vascular reconstruction.

Percutaneous sclerotherapy has been used with increasing success as the definitive treatment of lymphoceles. Injection of talcum, bleomycin, doxycycline, povidone-iodine, fibrin sealant, and absolute alcohol has been reported, with good results in most cases.[81-88] Treatment with repeated injections may be necessary.

CHYLOUS ASCITES

The development of chylous ascites after abdominal aortic reconstruction is rare, but the morbidity and mortality related to this complication can be significant. In a review of the literature, 23 patients were reported to have chylous ascites after aortic reconstruction.[22,28-46,80] Eighteen patients (78%) underwent repair of an abdominal aortic aneurysm, and five (22%) had surgery for occlusive disease. Ascites developed in the first 6 weeks after surgery in all but one patient.

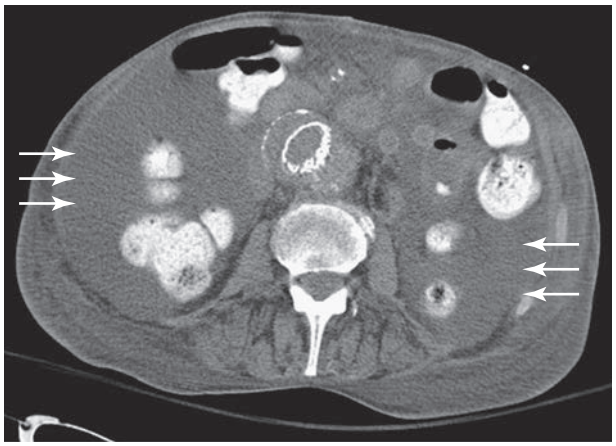

Figure 52.8 Computed tomography scan demonstrating diffuse ascites *(arrows)* in a patient 3 months after abdominal debranching and endovascular repair of a paravisceral aneurysm. Paracentesis confirmed the presence of chyle.

Diagnosis

Symptoms of chylous ascites include progressive abdominal pain, dyspnea, and nausea. Abdominal distention can be significant, and the loss of proteins and fat may result in malnourishment. Lymphopenia and anemia can also develop and frequently result in poor immune function. Ascites can usually be detected by physical examination and confirmed by ultrasonography or CT (Fig. 52.8). Paracentesis is necessary to verify the presence of chyle in the ascitic fluid. Chyle is an odorless, sterile, alkaline fluid that is milky in appearance. Its specific gravity is higher than 1.012. Its protein content is usually more than 3 g/dL, and its fat content ranges from 0.4 to 4 g/dL. The fat in the fluid stains with Sudan stain.

Management

Although chylous ascites in patients with abdominal malignancies carries an ominous prognosis, the outcome when chylous ascites develops after open aortic surgery is somewhat better. Nevertheless, in one series, 4 of 23 patients with this complication after open aortic surgery died (mortality rate, 17%).[22,31,47,89] The cause of death was sepsis in two patients, pulmonary embolism in one patient, and malnutrition in one patient.[22,31,42,89] Most patients with chylous ascites after aortic surgery can be treated successfully without an operation.[90] The mainstay of treatment in patients with mild to moderate ascites is a medium-chain triglyceride diet to decrease chyle formation.[90] For severe cases, however, complete bowel rest and total parenteral nutrition must be instituted. Repeated paracentesis results in resolution of the symptoms in most patients. Placement of a peritoneovenous shunt has been reported, but may cause sepsis, leading to death.[80,91] If repeated paracentesis is unsuccessful, exploration after ingestion of a fatty meal and closure of the site of the lymphatic injury should be performed (Fig. 52.9). Larger mesenteric or para-aortic lymphatic channels should be ligated or oversewn, but lateral closure of the injured cisterna chyli can be attempted with fine monofilament suture, as mentioned

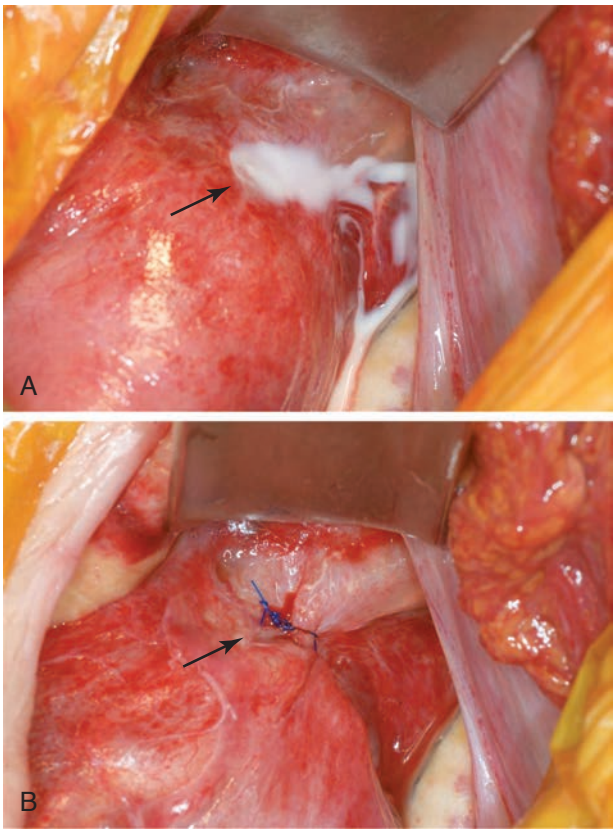

Figure 52.9 Intraoperative photographs of the patient described in Fig. 52.8. (A) After ingestion of a fatty meal, chyle is easily visualized at the base of the mesentery *(arrow)* during abdominal re-exploration. (B) Successful ligation of the chylous injury and control of leakage *(arrow)*.

earlier. Of six reported patients who underwent exploration and surgical closure of the fistula, all recovered without recurrence.[28,34,39,41,44,45]

Several case reports have described the use of laparoscopic techniques to control chylous ascites complicating nonvascular procedures.[92-95] It is possible that these techniques may be used in patients with chylous ascites who do not respond to bowel rest and total parenteral nutrition after vascular procedures. In these cases, the patient first ingests a fatty meal. Laparoscopic lymphostasis is performed with a combination of laparoscopic clipping, electrocautery, and fibrin glue. Somatostatin and a low-fat diet may be used adjunctively in the postoperative period.[92,95] Although these reports are preliminary, the concept of minimal-incision re-exploration is enticing, and early reports appear promising.

Prevention

Injury to the retroperitoneal and mesenteric lymphatics during aortic dissection should be carefully avoided. The cisterna chyli is formed by the right and left lumbar and the mesenteric lymphatic trunks; it is usually located at the level of the second lumbar vertebra, between the inferior vena cava and the abdominal aorta.[58] In half of patients, a well-developed cisterna chyli is absent. Several large mesenteric lymph vessels are located on the anteroinferior aspect of the left renal vein (see Fig. 52.7). Injury to these vessels results in leakage of chyle. Failure to close the divided lymphatics may lead to the development of chylous ascites or retroperitoneal lymphocele. All large lumbar, para-aortic, and mesenteric lymph vessels should be ligated or clipped when division is necessary during aortic dissection. Lateral closure of the injured cisterna chyli should be attempted with 7-0 monofilament suture.

THORACIC DUCT FISTULA

Injury to the thoracic duct may occur after dissection of the proximal left common carotid artery or after left subclavian or vertebral artery dissection.[22] Neglected cases of thoracic duct cutaneous fistula may lead to malnutrition, lymphocytopenia, anemia, or infection of an underlying prosthetic graft. Early surgery plus lateral closure with 7-0 or 8-0 nonabsorbable monofilament suture is the optimal treatment. If lateral closure is not possible, ligation of the thoracic duct at the neck is an accepted alternative because the collateral lymphatic circulation is usually adequate. The incision is closed over a subcutaneous drain, which is left in place for a short time postoperatively.

CHYLOTHORAX

Effusion of chyle into the pleural cavity after vascular procedures is uncommon; it occurs in just 0.2% to 1% of cases after cardiothoracic surgery.[55] It is more common in neonates and small children operated on for congenital vascular anomalies, most frequently for aortic coarctation.[51-56] Chylothorax after repair of a thoracic aortic aneurysm has been reported,[47-50] and in one patient it occurred after repair of an abdominal aortic aneurysm.[31] Chylothorax may develop as a complication of transthoracic dorsal sympathectomy[48] or after high translumbar aortography.[57]

Diagnosis

Pleural effusion is confirmed by chest x-ray studies or CT. Thoracentesis reveals milky fluid rich in albumin and lipids. Diagnostic criteria include a milky appearance, separation into a creamy layer on standing, absence of odor, specific gravity above 1.012, and triglyceride levels higher than 110 mg/dL (1.24 mmol/L).[96,97] Analysis of the fluid obtained by thoracentesis or through the thoracostomy tube confirms the diagnosis. Laboratory analysis of the milky or serous fluid is similar to that described for chylous ascites. CT is performed to confirm effusion and exclude malignancy, although dilated lymphatics may also be seen on magnetic resonance imaging. Lymphoscintigraphy or lymphangiography is rarely required to identify the source of the chyle leak.[98]

Management

Because respiratory embarrassment is frequent, drainage of the chylous fluid through a thoracostomy tube is usually necessary. The principles of treatment to decrease chyle formation are the

same as those for chylous ascites. Conservative management consisting of closed drainage through a thoracostomy tube and nutritional support has been effective in most cases. If a low-fat, high-protein diet with medium-chain triglyceride supplementation is not successful, intravenous hyperalimentation is started. Rarely, surgical closure of the site of leakage by oversewing or ligating the thoracic duct must be performed. Pleurodesis facilitates closure of the pleural space and decreases the potential for recurrence. Parietal pleurectomy is the most successful treatment when no distinct chylous leak can be identified.[96] Of six patients in whom chylothorax developed after aortic aneurysm repair, only one needed thoracotomy to treat a large chylous pseudocyst[47]; however, one patient who was treated conservatively died after a long postoperative course that was complicated by both chylous ascites and chylothorax.[31]

Cerfolio et al.[97] at the Mayo Clinic reported 47 patients in whom chylothorax developed after thoracic operations. Nonoperative therapy was successful in a third, but 32 patients required ligation of the thoracic duct, and 2 were treated with mechanical pleurodesis and fibrin glue. Reoperation was successful in 31 of the 34 patients (91.2%). These authors recommended early reoperation and ligation of the thoracic duct when drainage was more than 1000 mL/day.

Multiple case reports have been published illustrating the role of thoracoscopic thoracic duct ligation in the treatment of chylothorax.[99-107] With progress in thoracoscopic surgery, thoracoscopic clipping of the thoracic duct has replaced open thoracotomy in many patients.[98] An early report from Cope and Kaiser[100] described percutaneous cannulation of the cisterna chyli and embolization of the thoracic duct with microcoils, particles, and glue. They reported on 42 patients who underwent percutaneous transabdominal catheter embolization or needle disruption of the retroperitoneum.[100] Cure or improvement was documented in 74% of the patients. The authors recommend this procedure particularly for ill and high-risk patients. Although rare, chylous ascites occurring after lymphatic puncture for thorax duct embolization for chylothorax has been reported.[108] Recently, a technique of direct lymphangiography using hybrid CT and fluoroscopy imaging that allowed direct placement of a 21-gauge needle into the cisterna chyli was described in two patients.[109]

A summary paper from Kumar and Pawar in 2004 reported a total of 21 cases of video-assisted thoracoscopic surgery (VATS) for the treatment of chylothorax (16 patients), chylopericardium (4 patients), and cervical chylous leak (1 patient).[101] A trial of conservative therapy had failed in all patients, who then underwent clipping or ligation of the thoracic duct, except for one patient who had glue applied to the chylous leak site. All procedures were successful without complications. Ligation of the thoracic duct far above the diaphragm may be more successful than clipping of the cut near the diaphragm.[101] In addition, if extensive fibrosis is present, and the thoracic duct is not easily identified, VATS may be used to ligate the mass of tissue between the azygos vein and the aorta with good success.[101] One specific advantage of VATS for the treatment of chylothorax is that magnification of the thoracic structures can facilitate ligation. Because of the efficacy, low expense, and low morbidity of VATS for the management of chylothorax, early reoperation is recommended to avoid a lengthy conservative course with concomitant loss of chyle and a long hospital stay. Early intervention with VATS is recommended for patients with a high-output fistula (>1000 mL/24 hours), and a 1-week trial of conservative therapy is recommended in others.[101] However, if the chylous output remains greater than 200 mL/24 hours after 1 week, VATS intervention should be considered.[101]

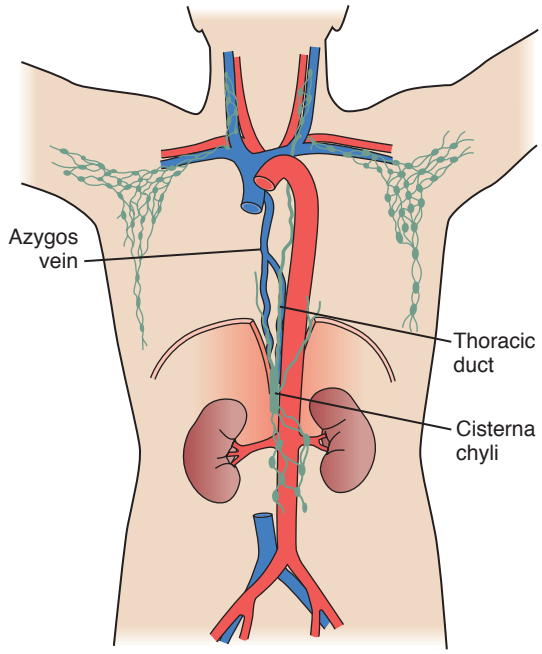

Figure 52.10 Anatomy of the thoracic duct. (By permission of the Mayo Foundation.)

Prevention

Injury to the thoracic duct during thoracic aortic dissection should be carefully avoided. The thoracic duct extends upward from the cisterna chyli and enters the posterior mediastinum through the aortic hiatus, slightly to the right of the aorta and to the left of the azygos vein (Fig. 52.10). In the posterior mediastinum, it is mostly a right-sided structure. The thoracic duct enters the superior mediastinum behind the aortic arch and subclavian artery, to the left of the esophagus. It is thus exposed to injury during dissection of the proximal thoracic aorta, the aortic arch, or the proximal subclavian artery. Once injury to the thoracic duct is recognized, an attempt at lateral closure with 7-0 monofilament suture should be made with loupe magnification. If it is not successful, ligation of the thoracic duct should be performed. Adequate collateral lymphatic circulation usually develops.

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A complete reference list can be found online at www.expertconsult.com.

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53 CHAPTER

Thoracic and Thoracoabdominal Vascular Exposure

ADAM Z. OSKOWITZ, MARK ARCHIE, and WILLIAM QUIÑONES-BALDRICH

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Surgical exposure of the aorta involves three main segments: the ascending aorta and aortic arch, the thoracic aorta, and the abdominal aorta. Depending on the pathology, either one or several of these segments will need exposure simultaneously. This chapter presents the various incisions, techniques, and key elements for exposure of each aortic segment or combinations of segments.

EXPOSURE OF THE ASCENDING AORTA AND AORTIC ARCH

Median Sternotomy

The median sternotomy exposure is an optimal method to access the chambers of the heart, the ascending aorta, and the aortic

Abstract

Aortic hybrid repair involves open surgical bypass and endovascular stent grafting to treat a number of aortic pathologies. Typical debranchings are done for the great vessels off the aortic arch, or the visceral vessels in the abdominal aorta

Keywords

hybrid
debranching
stent graft
thoracoabdominal aortic aneurysm
arch aneurysm

arch. As a result, it is the most common exposure technique for operations involving the ascending aorta and the great vessels.

Position

The patient is placed supine on the operating room table, with arms tucked along the patient's side to relax the musculature and allow opening of the mediastinum and chest space.

Incisions

An incision is made from just below the sternal notch to the tip of the xyphoid process. This incision can be extended for additional exposure of the aortic arch vessels, either along the anterior borders of the sternocleidomastoid muscle for exposure of the left or right common carotid arteries or superiorly along the midline for greater overall exposure. If additional exposure of the right subclavian artery is required, the incision can be carried along the superior border of the clavicle. Although an anterior 3rd or 4th intercostal space thoracotomy is the approach typically used for exposing the left subclavian artery, the very proximal part of the left subclavian artery can also be reached through a median sternotomy. Extension into a left supraclavicular incision may be needed for further distal control. An additional anterior 3rd or 4th intercostal space thoracotomy with creation of a trap door thoracotomy can be added to obtain exposure of the full continuum of the left subclavian artery in extremis patients with challenging traumatic injuries.

Dissection

Electrocautery is used to divide the subcutaneous tissue down to the pectoral fascia, which is also divided. The periosteum is then scored along the midline an equal distance from both sides of the intercostal space. The interclavicular ligament at the top of the sternal notch is divided. The tissues on one side of the xyphoid process are released, though some surgeons prefer to resect the entire process. Using a sternal saw, the sternum is divided along the midline. It is imperative to hold mechanical ventilation at this time to avoid inadvertent pleural tears. Electrocautery is then used to achieve hemostasis along the anterior and posterior edges of the sternum. Manual pressure and a small amount of bone wax can be used to achieve hemostasis of the bone marrow. Once the sternopericardial ligaments are divided and the pericardium is freed from the posterior sternum, the sternal retractor is placed and progressively opened to achieve homogeneous retraction. The vessels arising from the internal thoracic artery and draining into the brachiocephalic vein are identified and ligated. This allows full mobilization of the brachiocephalic vein. The superior portion of the pericardium is then opened vertically to access the ascending aorta and origin of the aortic arch vessels (Fig. 53.1). In certain circumstances, it may be necessary to ligate the left innominate vein, which is often well tolerated. Following these maneuvers, the ascending aorta, the aortic arch, and the innominate and left common carotid arteries can easily be identified and dissected free from surrounding tissues. The right vagus and right recurrent laryngeal nerves must be avoided during dissection of the distal portion of the innominate artery. It should be recognized that the vagus nerve courses anterior to the subclavian artery at its origin, with the recurrent laryngeal nerve originating from the vagus nerve and coursing posterior to the subclavian artery origin, creating a sling where the subclavian artery rests. Exposure of the innominate artery bifurcation can be obtained, often requiring caudal retraction of the left innominate vein. Small vessels draining into the innominate vein should be ligated prior to any manipulation of the innominate vein to avoid tearing of these vessels. Exposure beyond the proximal right common carotid artery and subclavian artery may require extending the incision.

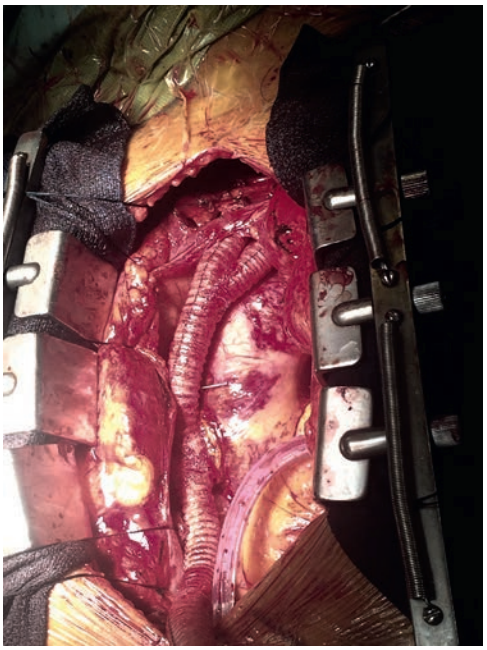

Figure 53.1 Exposure of the ascending aorta. The median sternotomy allows ample exposure of the ascending aorta and the proximal branches. This image shows an aorto-innominate graft with second limb traveling to the left carotid artery. A third limb traveling caudally will be used as a conduit to place an endograft. The two cranial limbs travel posterior to the brachiocephalic vein.

Mini-Sternotomy

The mini-sternotomy was first described in 1949 by Holman and Willett.[1] Today, it is commonly used for valve replacements, aortic root replacements, and ascending aortic aneurysm repairs. Its benefits include reduced trauma and a lower risk of sternal instability. It is also commonly used in re-operative cardiac surgery to reduce the risk of ventricular injury during sternal retraction. The advantages of this technique include decreased post-operative pain, decreased blood loss, and decreased adhesions around the right ventricle, as this region is not dissected during this exposure.[2] A number of studies have been conducted by Svensson and colleagues regarding minimally invasive sternotomy techniques. In one particular study, 54 patients underwent mini-sternotomy, 18 of which were redo sternotomies. Thirty-six patients underwent ascending aortic repair and 18 underwent ascending and aortic arch repair. Mortality and incidence of stroke were 4% and 3.7%, respectively, indicating that this method was safe for use in ascending and aortic arch repairs.[3]

Position

As with a full sternotomy, the patient is placed supine on the operating room table, with arms tucked along the patient's side.

Incision

There are various incisions for this approach, including the upper "T" and upper "J" incisions, which are the most commonly employed incisions to expose the superior mediastinum. Both incisions often provide adequate exposure to the aortic arch and the proximal portions of the innominate artery and vein. Moreover, conversion to a full median sternotomy is always an option when exposure is inadequate using this technique. An upper reversed "T" incision spans from the sternal notch caudally to the level of the 3rd or 4th intercostal space, while the "J" incision begins at the sternal notch and comes across the right 3rd or 4th intercostal space. Transesophageal echocardiography may be used to aid in determining the caudal extent of the incision.[2]

Dissection

The sternum is divided in the midline and then transected transversely taking care to avoid injuring the internal mammary arteries, which lie just lateral to the sternum. For additional exposure the internal mammary arteries can be ligated. A self-retaining retractor is then placed to separate the upper portion of the sternum and the dissection is continued in the same fashion as a full sternotomy.

EXPOSURE OF THE DISTAL AORTIC ARCH AND DESCENDING THORACIC AORTA

Trans-Sternal Bilateral Thoracotomy (Clamshell)

The trans-sternal bilateral thoracotomy incision is used in traumatic situations, lung transplantation, single-stage operations, as well as for repair of aortic arch and proximal descending aortic pathology. This technique is most useful for exposures that require not only arch access, but also access to the descending aorta. As with the mini-sternotomy, the clamshell incision may be used in redo operations. The major disadvantage of this exposure is the need for increased ventilatory support postoperatively as compared to a median sternotomy.

Position

The patient lies in the supine position with the right arm alongside the chest. The left shoulder and hip are slightly raised with bumps.

Incision

An incision is made from the medioclavicular line on the right to the anterior axillary line on the left at the level of the 4th intercostal space.[4]

Dissection

Dissection is carried down through the intercostal muscles in the fourth intercostal space, and both internal mammary arteries are ligated and then divided. The sternum is then divided transversely using a saw in the transverse plane. Using rib spreaders, the thoracic cavity is exposed. The pericardium and pleural reflections are dissected free from the posterior portion of the sternum. The left lung is mobilized and retracted away from the region of interest.

Left Posterolateral Thoracotomy

Exposure of both the distal aortic arch and proximal descending thoracic aorta may be accomplished using a left posterolateral thoracotomy. This incision requires tolerance for single lung ventilation.

Position

The patient is positioned in the right lateral decubitus position with the left arm placed above the head on a padded armrest. The right arm is extended at 90 degrees to the operating room table with the elbow partially flexed to avoid traction of the brachial plexus. Padding is placed between the legs with the right leg flexed at the knee and the left leg extended resting on top of the padding. An axillary roll is placed under the right shoulder to support the shoulder girdle.

Incision

A curvilinear incision is started at a point midway between the medial border of the scapula and the thoracic spine along the 4th intercostal space along the inframammary crease to the tip of the scapula. This can be extended medially for additional exposure of the aortic arch vessels. In cases involving the aortic root, the sternum can be transected but this requires sacrifice of the internal mammary artery.

Following skin incision, flaps are raised and the anterior edge of the latissimus dorsi is incised vertically. The plane between the latissimus and the serratus anterior is developed. Following this, the posterolateral edge of the serratus muscle is incised and the muscle is elevated. The latissimus dorsi is retracted posteriorly, and the serratus retracted anteriorly, thereby exposing the intercostal space.

The 4th intercostal space is identified and entered on the superior portion of the rib to avoid injury to the neurovascular bundle. The pleural sac is appreciated and opened with a fine-tipped scissors. A ratcheted, self-retaining chest wall retractor, such as a Finichetto retractor, is then carefully placed between the ribs at the incision site and slowly opened. If the distal portion of the descending aorta is involved in the operation, the fifth rib may be resected for adequate exposure. The left lung is deflated and retracted to expose the descending aorta. The vagus, recurrent laryngeal, and phrenic nerves are identified just proximal to the origin of the left subclavian artery. The aorta is then mobilized and intercostal arteries are ligated. In patients with thoracoabdominal aneurysms, the incision can be extended through the retroperitoneum, dividing the

costochondral margin that is described in detail later in this chapter.

EXPOSURE OF THE THORACOABDOMINAL AORTA

This approach will allow for exposure of the entire thoracic and abdominal aorta. The incision and dissection will vary depending on the level of exposure required. Due to the location of the aorta, this incision crosses both the thoracic and abdominal cavity, making it difficult to stay within anatomic boundaries. When possible more limited incisions should be utilized; it is important to note that the abdominal part of the aorta can be reached through an extraperitoneal (retroperitoneal) or transperitoneal approach. In the extraperitoneal approach, the aorta is exposed through the retroperitoneum without entering the peritoneal cavity, avoiding bowel manipulation and limiting fluid loss. In the transperitoneal approach, the abdominal cavity is entered and the aorta and its branches are exposed using a left medial visceral rotation. The latter is typically used when access to the distal visceral vessels, right renal artery, or right common iliac bifurcation is needed.

Position

The patient is placed in modified right lateral decubitus position with the shoulders at 60 degrees to the table (Fig. 53.2). The hips are rotated up to 45 degrees and partially flexed with the legs parallel to the bed. This allows access to both groins. The right arm is placed in a sling above the patient's head to enable proper rotation of the upper body, and a shoulder roll is placed under the chest to ensure the right shoulder is free from pressure. The operating table is hyperextended to open the space between iliac crest and costal margin. Once the patient is in the appropriate position, a moldable beanbag that was previously placed to sit between the patient and the operative table is secured by vacuum suction.

Figure 53.2 Positioning for exposure of the thoracoabdominal aorta. The body is placed in a lateral decubitus position with the operating table extended to provide maximum exposure.

Incision

Prepping and draping should allow for access to the left thorax, the abdomen caudal for exposure of the distal right common iliac artery. A gentle curve near the superior portion of the incision reduces the risk of tissue necrosis at the apex of the lower portion of the musculoskeletal tissue flap as the incision crosses the costal margin. The more superior the exposure of the aorta, the more medial and superior the incision travels, with the incision traversing the skin along the 5th, 6th, or 7th intercostal space according to the desired level of exposure (Figs. 53.3 and 53.4). To expose portions of the distal aortic arch, it may be necessary to enter the space between the 3rd and 4th rib through the same skin incision but as a separate thoracotomy incision (double thoracotomy).

Thoracic Dissection

To expose the thoracic aorta, the latissimus dorsi, anterior serratus, and rectus muscles are divided by electrocautery. The pleural space is entered after single right-lung ventilation is initiated. The subcostal margin is cut with either electrocautery or scissors at the lower intercostal space and the incision is linked downward with the abdominal portion of the incision. The entire rib or the posterior section of the rib of the particular interspace can be resected to aid in exposure. Once the pleural space is entered, the inferior pulmonary ligament is divided with cautery, ligating any vessels within it.

The lung can then be gently retracted superiorly and laterally to expose the distal portion of the thoracic aorta. Pulmonary

Figure 53.3 Incision used to repair a type 3 thoracoabdominal aortic aneurysm. Exposure of both the abdominal and thoracic aorta requires an incision that crosses anatomic boundaries.

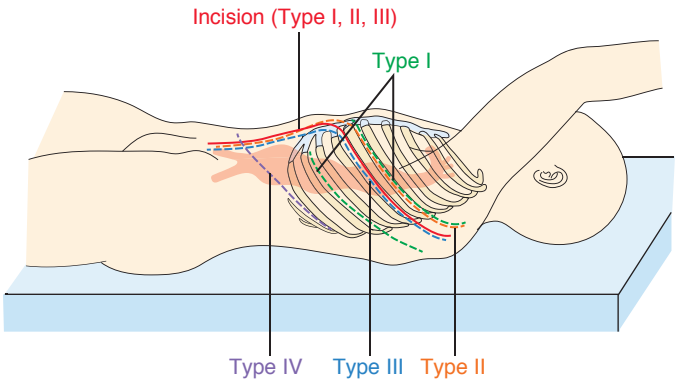

Figure 53.4 Skin incisions and superficial dissection for thoracoabdominal aortic (TAA) exposure. The red line indicates the skin incision for exposure of Type 1 to 3 TAA aneurysms. Manipulation of this skin incision allows for multiple entry points into the thoracic and abdominal cavities based on aneurysm location. The plane used for superficial dissection, including the appropriate rib space to enter the pleural cavity, is shown with the various green, gray, and orange dotted lines for TAA aneurysms 1 to 3. The blue dotted line indicates both the skin incision and the superficial dissection plane for type 4 TAA aneurysms.

manipulation should be kept to a minimum. The proximal descending aorta can be separated from the surrounding mediastinal tissue to expose the origin of the left subclavian artery. The vagus nerve and recurrent laryngeal never are in close proximity to the aorta just proximal to the subclavian artery, and care should be taken not to injure these structures during this portion of the dissection. The thoracic aorta is then circumferentially dissected from the esophagus, which lies just anterior and medial to the aorta. The diaphragm is radially divided to avoid injury to the phrenic nerve for several centimeters near its peripheral attachment to the anterior chest wall for maximal exposure. Some surgeons advocate partial division of the diaphragm in an attempt to decrease postoperative pulmonary complications. This decision is often dictated by the intraoperative anatomy and level of complexity of the exposure.

Abdominal Dissection

The abdominal aortic dissection is initiated by dissecting down to the abdominal wall musculature lateral to the rectus abdominus muscle and fascia.

Medially, the rectus muscle and associated fascia can be divided if additional exposure is required. It is often better to mobilize the rectus from medial to lateral after superior transection to avoid denervation. The anterior and posterior sheaths are divided longitudinally. This will allow two-layer closure of the anterior and posterior rectus sheath at the end of the procedure. Laterally, the dissection is continued by dividing the external oblique, internal oblique, and transversalis muscles to identify the peritoneum (Fig. 53.5). Great care must be taken not to disrupt the peritoneal lining, as it is thin and often difficult to distinguish from the transversalis fascia. Difficulty in separating the "peritoneum" from the abdominal wall is often due to incomplete division of the transversalis fascia. Once the peritoneum is identified, it is separated from the abdominal wall using a combination of manual dissection and gentle traction. The peritoneum and the abdominal visceral are retracted to the right to reveal the retroperitoneal fat. The plane between the retroperitoneal fat and the psoas muscle is then created and traced superiorly to the diaphragm. Gerotas fascia and the contained left kidney are included with the peritoneal contents and lifted anteromedially to expose the infrarenal and visceral segments of the aorta. The parietal peritoneum is dissected free from the periaortic fat and rolled medial to expose the anterior portion of the aorta and identify the proximal portions of the visceral vessels. The right renal artery will not be visible with this exposure unless the infrarenal aorta is either transected or fully mobilized. The left ureter will be on the back of the peritoneal sac and should be identified as it crosses the iliac artery (Fig. 53.6).

The left renal artery is identified to orient the visceral aortic dissection (Fig. 53.7). A relatively constant structure nearby the left renal artery origin is the reno-lumbar vein, which rises from the psoas groove to enter the renal vein, taking a course around the left side of the aorta. This vessel must be identified and ligated to allow the kidney to be retracted further medially. In rare circumstance, a retro-aortic left renal vein prevents this retraction. In that situation, the kidney can be left in its native position (see below) with the renal vein ligated distal to the adrenal and gonadal vein to allow collateral drainage. Ligation with planning of re-anastomosis is extremely difficult due to retraction, which creates tension during repair and should be avoided.

The peritoneal cavity is dissected free from the periaortic fat and rolled medial to expose the anterior portion of the aorta and identify the proximal portions of the visceral vessels.

The diaphragmatic crus is divided, freeing the visceral aorta and allowing greater mobility of the aorta during the operation (Fig. 53.8). Further mobilization is aided by dividing the median arcuate ligament. With these maneuvers, the origins of the left renal artery, the superior mesenteric artery, and the celiac artery can all be identified and circumferentially dissected (Figs. 53.9 and 53.10).

EXPOSURE OF THE DISTAL DESCENDING THORACIC AORTA AND VISCERAL AORTA

Transperitoneal Approach

A transperitoneal approach should be used to access the visceral and infrarenal aorta, both renal arteries, the hepatic artery, as well as the distal portion of the celiac and superior mesenteric artery. The origins of the superior mesenteric artery and celiac artery can also be exposed although extensive mobilization of the spleen and pancreas is needed. The approach requires significant manipulation of the abdominal viscera and thus should be used selectively.

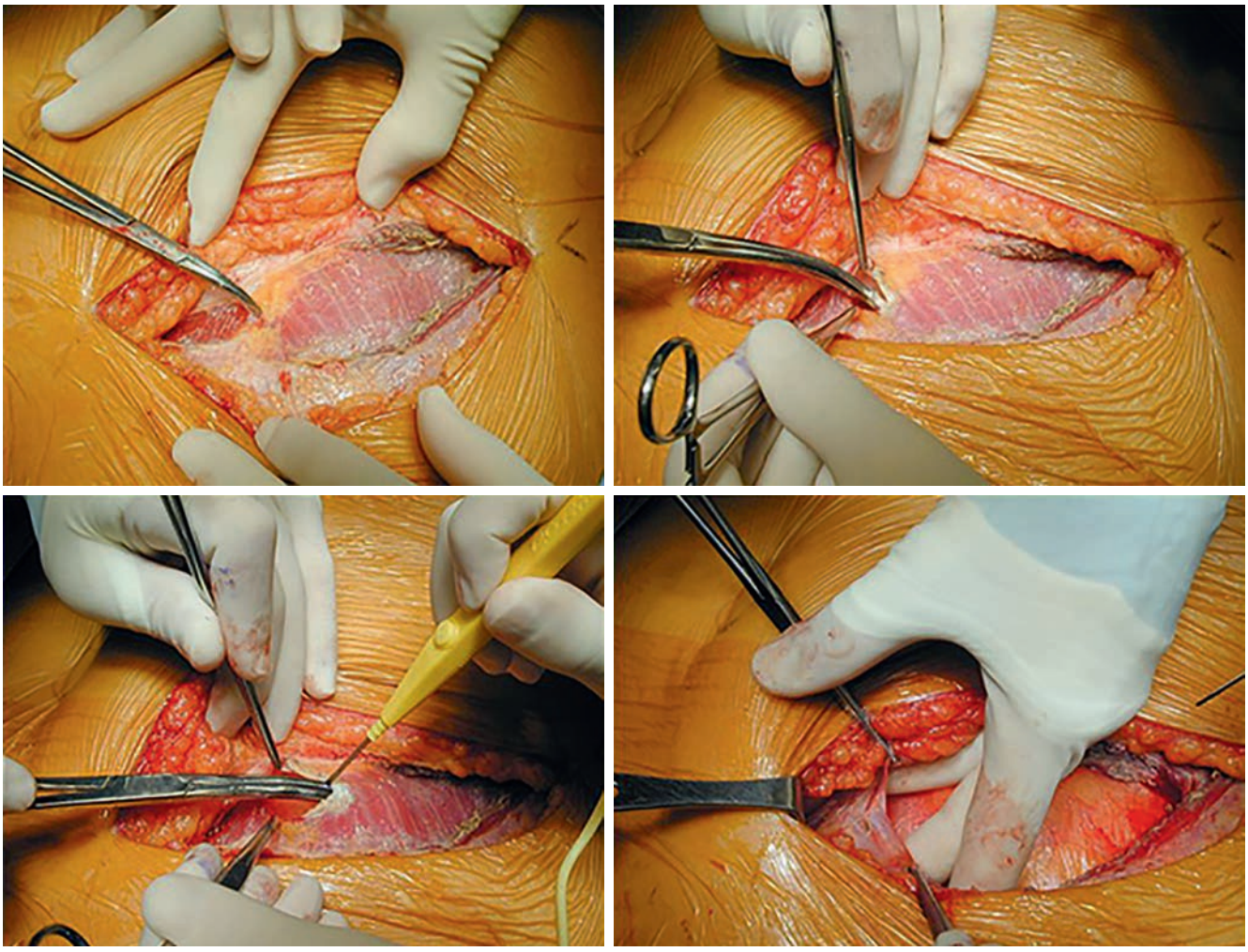

Figure 53.5 Layers of the abdominal wall. This panel shows the identification of the lateral border of the rectus muscle *(top left)*, followed by the dissection of the external oblique, internal oblique, and transversus abdominis musculature (*top right* and *bottom left*). Ultimately, the peritoneal lining is identified *(bottom right)*.

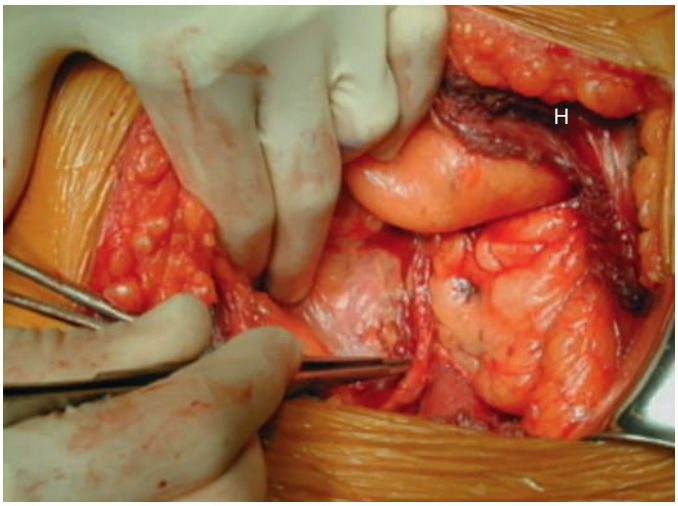

Figure 53.6 Ureter lying within the retroperitoneal fat. In this image, it is identified and reflected posteriorly to allow the left kidney to remain in its anatomic position.

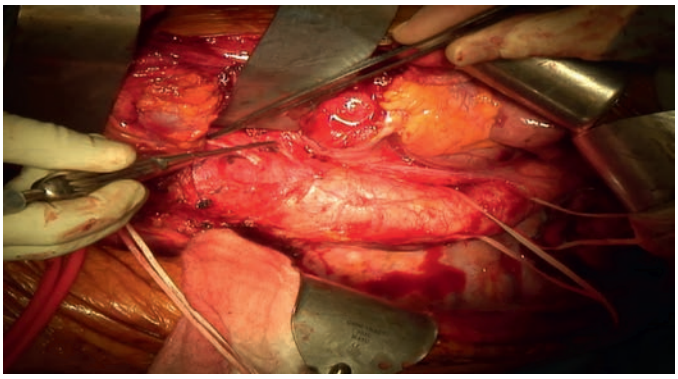

Figure 53.7 Exposure of the thoracoabdominal aorta. The left renal artery is identified at the tip of the surgeon's forceps as it courses posterior to a metal suction device. Identification of the left renal artery helps orient the surgeon to the remaining visceral vessels.

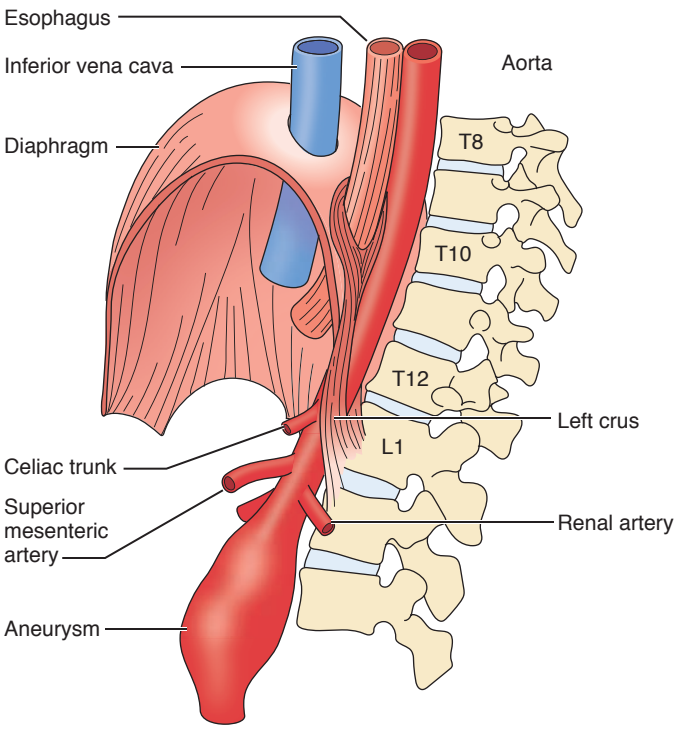

Figure 53.8 Sagittal view of the aorta and adjacent structures. The left crus of the diaphragm overlies the aorta proximal to the renal artery at the same level as the first lumbar vertebrae. Division of this structure allows access the paravisceral aorta and descending aorta from within the abdominal cavity.

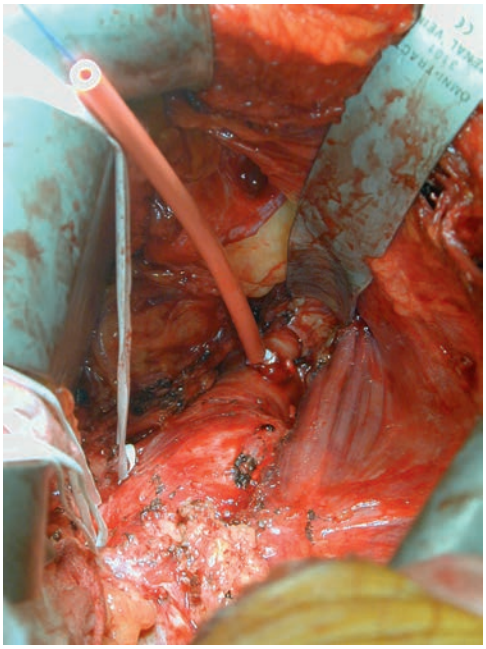

Figure 53.9 Exposure of the visceral aorta after dividing the diaphragmatic crus. A Rommel tourniquet is around the descending thoracic aorta.

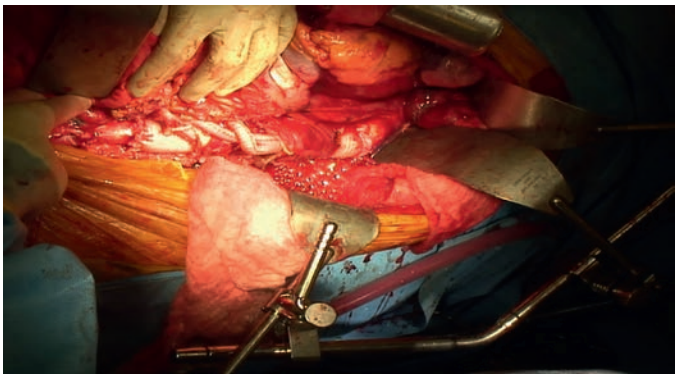

Figure 53.10 Complete replacement of the thoracoabdominal aorta. Note the three smaller caliber grafts anastomose with the left renal, superior mesenteric, and celiac arteries.

Position

The patient is placed supine with the arms extended laterally.

Incision

A midline laparotomy incision is made extending from the xiphoid process to the symphysis pubis. Alternatively, a transverse reversed "smile" incision can be used. The latter, however, divides the abdominal musculature and causes significant denervation of the abdominal wall muscles. Some surgeons, however, believe it is better tolerated by patients with pulmonary insufficiency.

Dissection

Once the midline fascia is incised the peritoneal cavity is entered and the abdominal contents can be inspected. The visceral aorta is exposed using a left medial visceral rotation. The splenic attachments to the abdominal wall are released and the spleen is mobilized superiorly and medially. This dissection is carried posteriorly along the space between the spleen and the left kidney by ligating the spleno-colic and spleno-renal ligaments. A plane is then developed following the lateral curvature of the spleen into the space posterior to the pancreas. The spleen and pancreas are then separated from the retroperitoneum and rotated medially until the suprarenal aorta is exposed. Dissection of the retroperitoneal and periaortic fat along with division of the left crus of the diaphragm provides additional proximal exposure of the suprarenal aorta. As with the retroperitoneal exposure, division of the medial arcuate ligament allows for identification of the celiac artery origin. The left kidney can be kept in the renal fossa or mobilized medially.

Retroperitoneal Approach

The retroperitoneal approach is used to expose the distal descending and abdominal portion of the aorta including the paravisceral segment. This allows for excellent exposure of the proximal abdominal aorta while not violating the peritoneal cavity, making it ideal for treating paravisceral aortic pathology and type 4 thoracoabdominal aneurysms.

Figure 53.11 Incision used for a retroperitoneal exposure of the aorta. Note the groin incisions used to expose the femoral arteries. When positioning a patient for a retroperitoneal exposure, both groins should be accessible.

Several studies have demonstrated reduced time in the intensive care unit and reduced time until return of bowel function using a retroperitoneal approach compared to a transperitoneal approach.[5,6]

Position

The patient is placed in modified right lateral decubitus position similar to the positioning for a thoracoabdominal exposure. However, in this case, the hips are rotated only 20 to 30 degrees and the right leg is partially flexed.

Incision

A curvilinear incision begins in the midline between the umbilicus and pubic symphysis and is carried laterally to the 10th or 11th intercostal space (Fig. 53.11). For exposure that focuses on the cranial portion of the abdominal aorta, the incision can be further extended along the intercostal space recognizing that the more cranial the incision, the more likely the pleural cavity will be entered. To avoid postoperative bulging, it is best to keep the incision within a single dermatome.

Dissection

The dissection is performed in a similar fashion to the abdominal portion of a thoracoabdominal exposure with the following exceptions. The anterior layer of the rectus sheath is divided

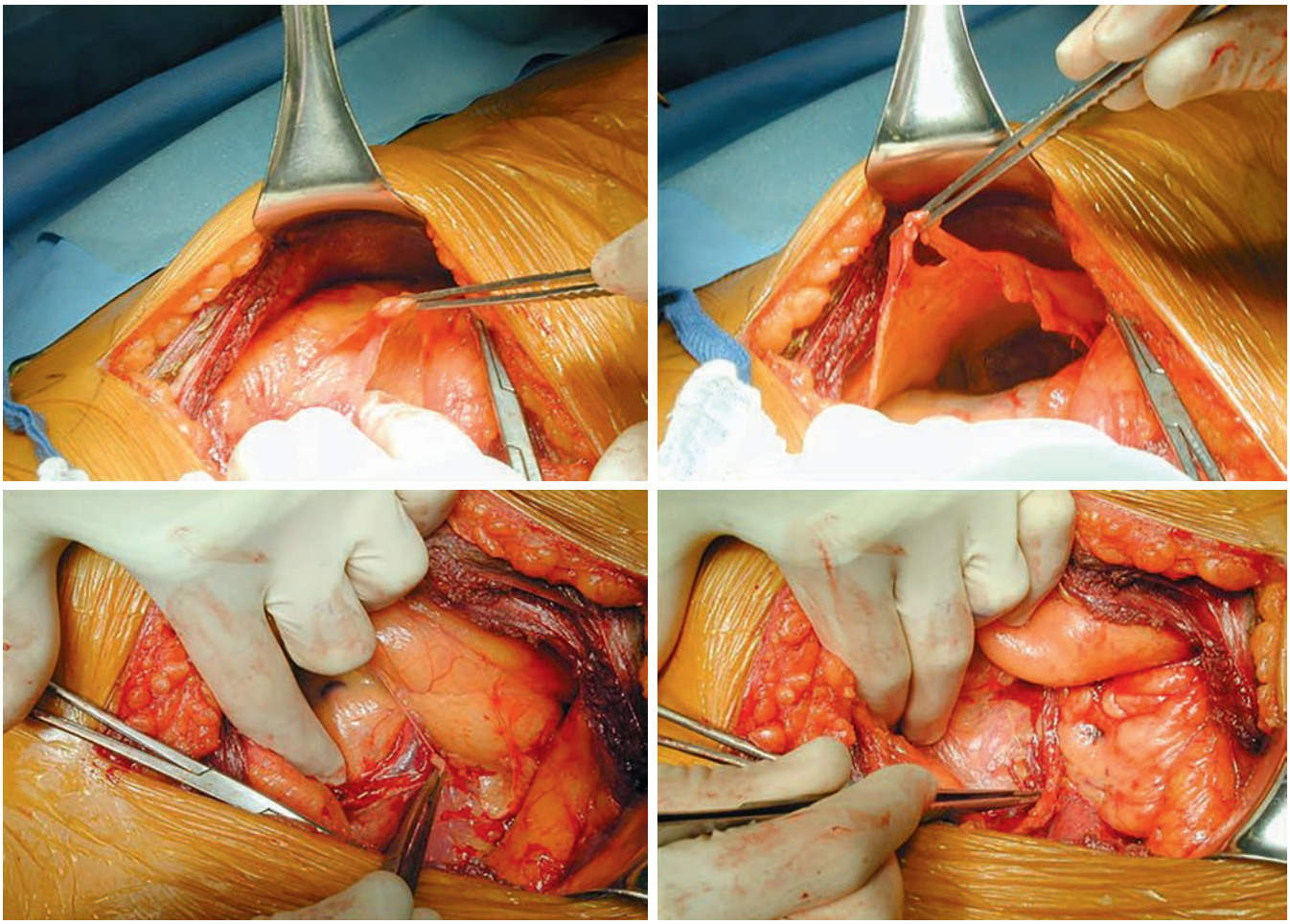

Figure 53.12 Dissection of the retroperitoneal space. The *top panels* demonstrate the plane between the pre-peritoneal fat and pro-peritoneal fat. Developing this plane will guide the surgeon down the aorta. The gonadal vessels and ureter can then be reflected posteriorly *(bottom panels)* while the peritoneal contents are retracted anteromedially. This allows the left kidney to remain in its anatomic position while still exposing the abdominal aorta.

after dissecting through the subcutaneous tissue; however, care should be taken not to divide the rectus muscle fiber, as this reduces hernia formation.[7] If exposure of the right common iliac artery is needed, division of the posterior rectus sheath can be performed, leaving the muscle fibers of the rectus intact. The lateral musculature is again divided down to the peritoneal cavity, keeping this division within a single dermatome.

Once the retroperitoneal space is created, the surgeon can continue the dissection in the pre-peritoneal space, the plane used in a thoracoabdominal incision, ultimately sweeping the contents off of the psoas muscle. Care should be taken to stay in the plane anterior to the psoas muscle. There is a tendency to go behind the psoas muscle, which leads to increased bleeding and injury to the ilioinguinal and genitofemoral nerves.

Alternatively, the plane between the pre-peritoneal fat and pro-peritoneal fat can be developed (Figs. 53.12 and 53.13). Developing this space allows the surgeon to sweep the pre-peritoneal fat and the peritoneal contents medially while leaving the pro-peritoneal contents in place, ultimately leaving Gerotas fascia and the left kidney undisturbed in its anatomic location. This approach reduces manipulation of the left kidney but limits the amount of cranial exposure that can be achieved. In both scenarios, the abdominal aorta is encountered, and the para-aortic fat is dissected free. When the pro-peritoneal fat is left in place, the gonadal vein and ureter should be identified to ensure it is not lifted medially with the peritoneal contents but rather left in their anatomic location. In cases where the kidney is left in its anatomic location, the gonadal vein can be ligated at its junction with the left renal vein to allow complete retraction

Once the aorta is encountered, the dissection of the infrarenal and paravisceral segments of the aorta can be completed as described in the thoracoabdominal section.

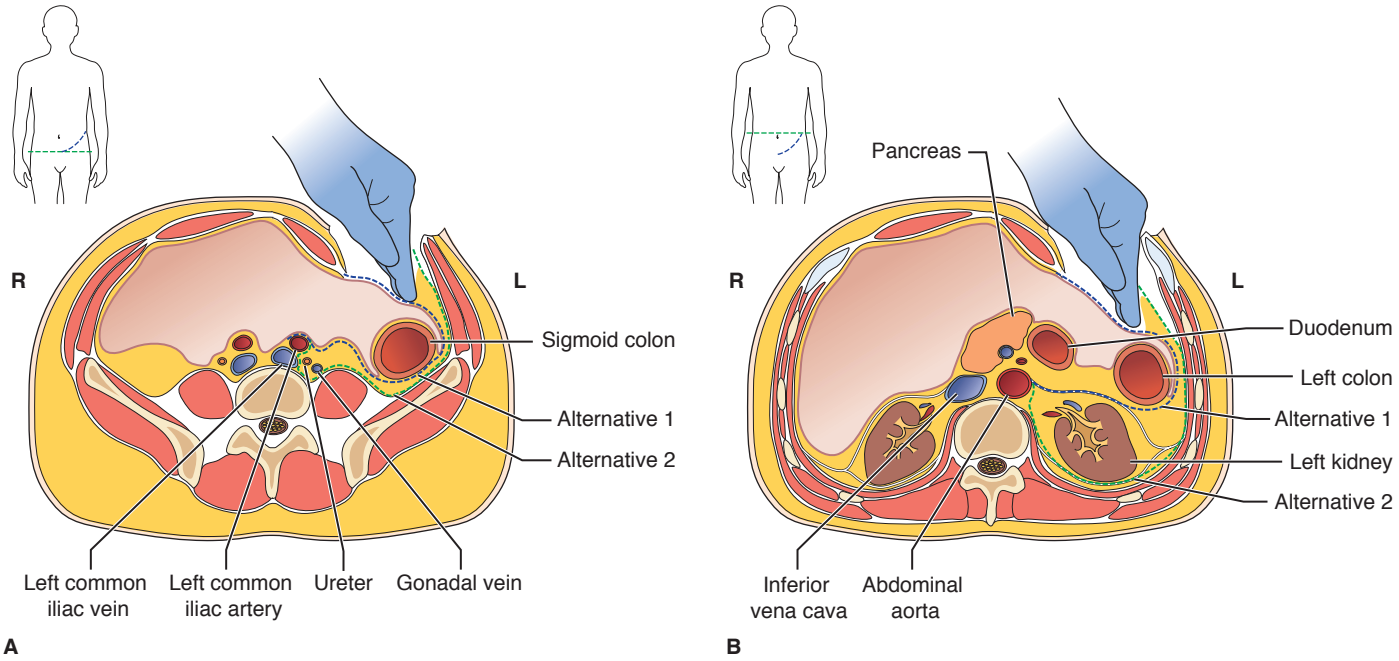

Figure 53.13 Cross sectional image of the abdominal cavity at the level of the abdominal aorta (A) and the iliac arteries (B). The schematic shows the surgeon's hand dissecting along the retroperitoneal plane. The dotted lines demonstrate alternate approaches to access the aorta within the retroperitoneal space.

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54 CHAPTER

Abdominal Vascular Exposures

LOAY S. KABBANI and ALEXANDER D. SHEPARD

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ANATOMIC CONSIDERATIONS

The aorta enters the abdomen through the aortic hiatus in the diaphragm at the level of T12 vertebra.[1] It is surrounded at this level by the right and left crura of the diaphragm and runs anterior to the spine. The first two branches off the aorta are the two phrenic arteries, which arise anterolaterally. The celiac axis refers to a short arterial trunk originating from the anterior surface of the proximal abdominal aorta as it passes between the diaphragmatic crura. The celiac trunk and its proximal branches are surrounded by tough, fibrous splanchnic ganglionic tissue, making dissection challenging. The celiac trunk splits 1 cm beyond its origin, most often (in 75% of patients) into three branches: the splenic, the common hepatic, and the left gastric artery.[2,3] The common hepatic arises from the celiac and runs on the posterior wall of the lesser sac, forming the lower boundary of the foramen of Winslow. It follows the upper border of the pancreas before it divides into the gastroduodenal and proper hepatic arteries. The proper hepatic lies anterior to the portal vein and gives rise to the right gastric before it divides into the left and right hepatics. In approximately 18% of cases the right hepatic artery is "replaced" and originates from the superior mesenteric artery (SMA). A "replaced" left hepatic artery originates from the left gastric artery in approximately 12% of cases. The SMA arises from the anterior aorta at the level of mid-L1, then courses inferiorly behind the pancreas and anterior to the third and fourth portions of the duodenum, to enter the root of the mesentery. Similar to the celiac trunk,

Abstract

This chapter explores the various approaches for exposure of the abdominal vasculature. It is an important reference for the vascular surgeon planning an open operation on vessels within the abdomen. It depicts the operative anatomy of the major abdominal arteries and veins and their relationship to surrounding structures and then walks the surgeon through the ideal exposure technique in an easy step-by-step fashion. The different approaches described along with advantages and pitfalls will help to guide surgical decision-making. The chapter starts with an anatomic overview, followed by a description of the variety of incisions available to expose the abdominal vasculature, and concludes by detailing the different approaches to each major vessel within the abdomen.

Keywords

Abdominal incision
transverse abdominal incision
subcostal incision
oblique flank incision
retroperitoneal approach
thoracoretroperitoneal approach
lower quadrant incision
abdominal aorta and iliac arteries
proximal abdominal aorta
visceral arteries
celiac artery
superior mesenteric artery
renal artery
hepatic artery
splenic artery
inferior vena cava
portal vein
superior mesenteric vein

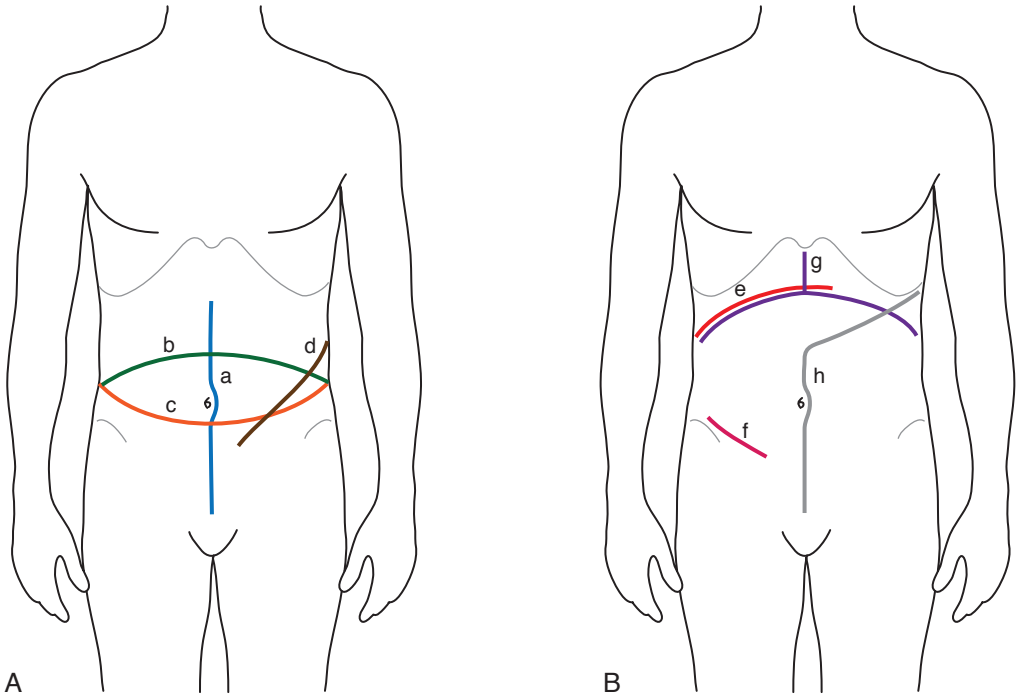

Figure 54.1 Abdominal Incisions on a Supine Patient. (A) *a*, Midline incision; *b*, Supraumbilical transverse ("frown") incision; *c*, Infraumbilical transverse ("smile") incision; *d*, Left flank retroperitoneal incision. **(B)** *e*, Right subcostal incision; *f*, Right lower quadrant "transplant" incision; *g*, Chevron incision; *h*, Thoracoabdominal incision.

its origin is usually associated with some ganglionic neural tissue and large lymphatics which can make exposure tedious. The main branches of the SMA are the inferior pancreaticoduodenal artery (which forms an arcade with the superior pancreaticoduodenal artery from the proper hepatic), the first jejunal branch (which is usually spared in embolic occlusions of the SMA[4]), the middle colic artery, and the ileocolic artery. There are extensive collateral networks between the celiac trunk, SMA, inferior mesenteric artery (IMA), and internal iliac arteries. The celiac axis and SMA collateralize through the superior and inferior pancreaticoduodenal arteries. The SMA and IMA collateralize through the meandering mesenteric artery and the marginal artery of Drummond.[1] The meandering mesenteric artery is a collateral vessel that develops in the presence of SMA stenosis. It lies at the base of the mesentery and is at risk of being ligated along with the inferior mesenteric vein during exposure of the infrarenal aorta.[1] The renal arteries usually arise at the level of first lumbar vertebra, but there is considerable variability.[5] For example, multiple renal arteries occur in up to 30% of patients.[6] The left renal artery runs posterior to the left renal vein (LRV), whereas the right renal artery courses posterior to the vena cava. The juxtarenal aorta is the segment of aorta between 1 cm above and 1 cm below the renal arteries and frequently overlaps the visceral segment. The aortic bifurcation is usually at the level of L4-L5, with the IMA arising 2 to 3 cm above this juncture. The IMA gives rise to the superior rectal artery, the sigmoid artery, and the left colic artery. The right common iliac artery runs anterior to the inferior vena cava (IVC) and the origin of the left common iliac vein. At the level of the iliac bifurcation each artery is crossed by the ureter. The cisterna chyli lies to the right of the aorta and passes beneath the right crus of the diaphragm.

Abdominal Incisions

Vascular surgeons need to be familiar with a variety of approaches for exposing the abdominal vasculature (Figs. 54.1 and 54.2). Transperitoneal exposure through a midline celiotomy incision is the most versatile and therefore remains the standard approach. Virtually every major artery and vein can be exposed through this incision. Disadvantages compared with transverse or oblique incisions are a greater degree of postoperative pain and a higher incidence of incisional hernia, which can reach as high as 20% to 35% when used for aortic aneurysm repair.[15a] Transverse and oblique incisions are less painful (helpful in patients with pulmonary compromise) and less prone to hernias but lack the versatility of a midline incision.[7-10] The following is a more detailed description of the various abdominal incisions used by vascular surgeons.

Midline Incision

As mentioned previously, this is considered the most versatile approach, allowing unrestricted exposure of the infrarenal aorta and its branches (see Fig. 54.1). It can also provide exposure to the suprarenal aorta when combined with medial visceral rotation. The patient is positioned supine, with one arm abducted to 90 degrees and accessible to the anesthesia team. Skin preparation should extend from the nipples to include both groins down to mid thighs for access to the femoral arteries, and saphenous veins if needed. The incision starts at the level

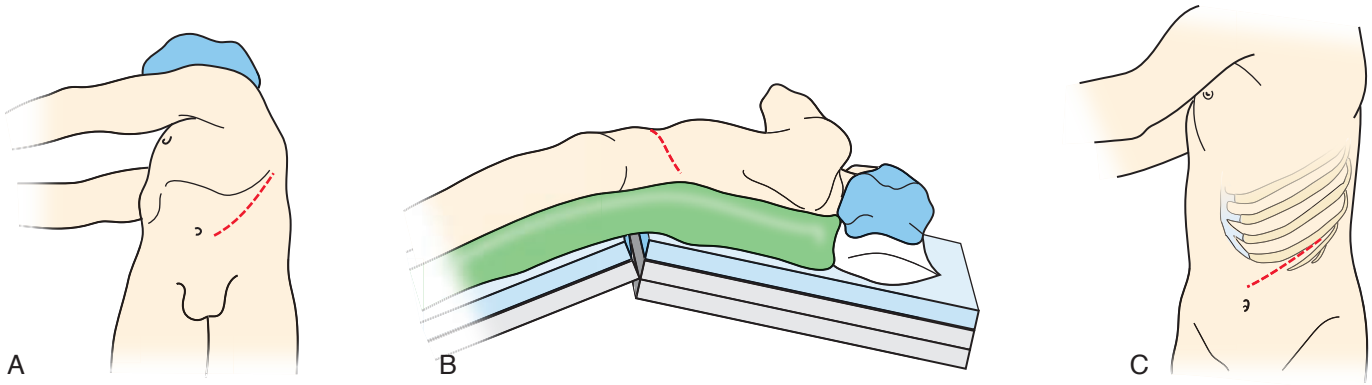

Figure 54.2 Patient Positioning for Left Flank Approach to Abdominal Aorta. (A) The shoulders are positioned at 50 to 70 degrees to the operating table and the pelvis rotated posteriorly as far as possible (corkscrew position). **(B)** The table can be jackknifed to widen the space between the left iliac crest and costal margin. **(C)** The incision can be carried into the 10th interspace for more proximal aortic exposure.

of the xiphoid in the upper abdomen and is carried down around the umbilicus. It can be extended to just above the pubic bone if the iliac vessels need to be exposed. The peritoneal cavity is entered through the linea alba, and the viscera are packed into the lower abdomen if one is working on the upper abdominal vessels, or in the right side of the abdomen if one is working on the infrarenal aorta. If the small bowel is eviscerated, it is placed in a bowel bag to keep the heat in and collect the transudate; a moist towel may also be used. A large mechanical retraction system (i.e., Omni Tract or Thompson) is useful to retract the bowel and help with exposure.

Transverse and Subcostal Incisions

The transverse and subcostal incisions are transperitoneal incisions (see Fig. 54.1). The transverse incision is carried across both rectus muscles from the contralateral anterior/mid-axillary line to the ipsilateral anterior/mid-axillary line (depending on the amount of exposure needed), midway between the costal margins and the iliac crests. When unilateral flank exposure is contemplated, the incision can be limited to one side and end at the contralateral midclavicular line. Transverse incisions can be supraumbilical ("frown") or infraumbilical ("smile"). The apex of the supraumbilical incision is centered halfway between the umbilicus and the xiphoid, and the center of the infraumbilical incision is 3 to 4 cm below the umbilicus. A supraumbilical transverse incision is good for infrarenal aortic exposure, particularly when concomitant distal renal artery exposure is necessary.[11] An infraumbilical incision provides excellent pelvic exposure (e.g., for large iliac/hypogastric aneurysms) but offers poor access to the pararenal aorta. When compared with a midline incision, some studies show a significant decrease in postoperative pain, pneumonia, and hernias,[12] whereas some show no difference in outcomes or complications.[10,13-15]

Subcostal incisions are transverse incisions infrequently used by vascular surgeons, which run parallel to the costal margins and two fingerbreadths below them. The most common variety is an extended right or left incision which begins at the lateral edge of the contralateral rectus sheath and is carried across the midline as far laterally on the ipsilateral side as necessary (usually the anterior axillary line). The subcostal incision is helpful in exposing the hepatic, splenic, and renal arteries, as well as upper abdominal venous structures.

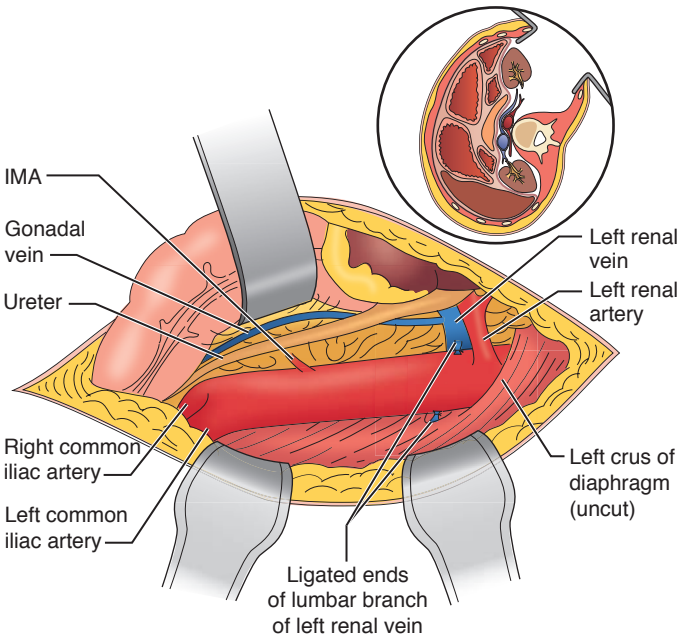

Figure 54.3 Left Flank Incision Retroperitoneal Dissection. The abdominal contents are retracted anteriorly and to the right. The left kidney is mobilized anteriorly, and the lumbar branch of the left renal vein is divided; inset is a cross sectional view demonstrating a retrorenal dissection plane. *IMA*, Inferior mesenteric artery.

Oblique Flank Incision

These incisions are retroperitoneal and helpful for exposing the aorta and its branches through the left flank, and the IVC through the right flank (see Figs. 54.1-54.3).

A left retroperitoneal flank incision (see Figs. 54.2-54.4) is excellent for patients with complex aortic anatomy.[15a] Different

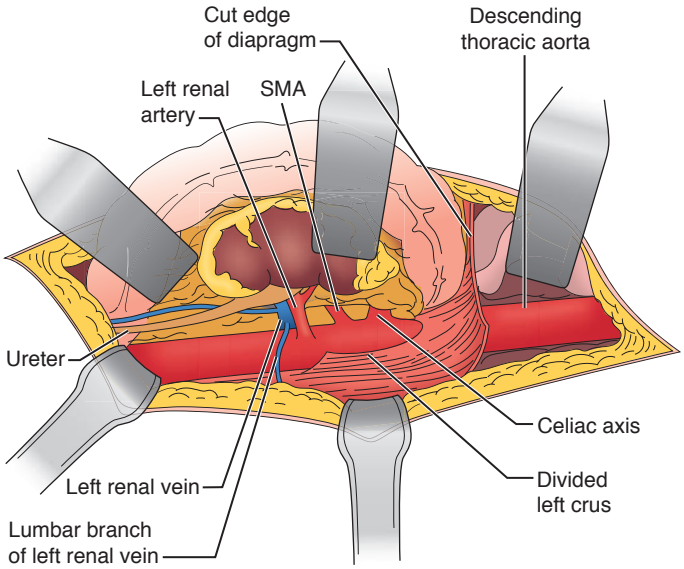

Figure 54.4 Left flank thoracoretroperitoneal approach with exposure of aorta from distal descending thoracic segment to aortic bifurcation. *SMA*, Superior mesenteric artery.

sections of the aorta from hiatus to bifurcation can be exposed based on which intercostal space is used. The restrictions of this incision are limited exposure of the right iliac system and poor visualization of nonostial right renal artery lesions. This approach is extremely helpful in redo-aortic operations, suprarenal aortic pathology, horseshoe kidney with multiple renal arteries, morbid obesity, inflammatory aneurysms, diastasis of the abdominal wall, and in patients with respiratory compromise (because the incision generates less pain). The patient is placed in a modified right lateral decubitus position, with the left shoulder at 30 to 70 degrees to the operating table, and the pelvis rotated posteriorly as far as possible (corkscrew position). A vacuum "bean bag" helps to maintain this position. The left arm is supported on an over-arm board. The table may be broken at the level of the umbilicus to open up the space between the left costal margin and iliac crest. An oblique incision is made from the lateral edge of the left rectus sheath, a centimeter or so above the midpoint between the umbilicus and pubis and extended a few centimeters into the 11th intercostal space. This incision is particularly good for infrarenal aortic exposure. Extension across the rectus to the midline aids in more distal right iliac exposure. For more proximal aortic exposure, the incision can be extended posteriorly or taken into a more proximal intercostal space (10th or 9th), which requires entry into the chest (a thoracoretroperitoneal approach; see Figs. 54.2 and 54.4). The external and internal oblique and transversus muscles are divided to the margin of the left rectus sheath medially, which is partially split. Posteriorly the intercostal muscles are divided on the superior aspect of the 12th (or 11th or 10th) rib, making no attempt to stay out of the chest. The retroperitoneal space is entered at the tip of the chosen rib, and the peritoneum stripped away from the musculature anteriorly (with or without the transversalis fascia). Dorsally, the peritoneum is stripped off the lumbodorsal fascia to the level of the psoas, and using blunt dissection, a retroperitoneal plane is developed by retracting the spleen, tail of pancreas, and left colon to the patient's right. This plane is developed either anterior or posterior to the left kidney depending on the nature of the procedure. A right flank incision can be performed in a similar fashion to expose the IVC. Shorter oblique incisions (extending from the lateral edge of the rectus just to the tip of the 12th rib) can also be used, but these provide very limited exposure.

Thoracoabdominal Incision (see Chapter 53)

This incision is used to expose the upper abdominal and lower thoracic aorta (see Figs. 54.2 and 54.4). It should be considered as an extended version of the retroperitoneal approach for exposure of the thoracic aorta. A double-lumen endobronchial tube is helpful when collapse of the left lung is needed during extensive work on the thoracic aorta; otherwise when only limited exposure is required the lung may be retracted out of the way. After intubation, the patient is rolled into a right lateral decubitus position and the scapula set between 60 and 90 degrees to the table, depending on the exposure needed. The hips are rotated as far posteriorly as 30 degrees to the table if access to the femoral arteries is necessary. A vacuum bean bag aids in maintaining the patient's torso in the ideal position. Other safety measures to minimize nerve injury include an axillary roll, and positioning of the lower extremities, with the bottom leg (the right) bent at the knee, the top leg (left) straight, and a pillow placed between the legs. The incision starts 2 cm below the tip of the scapula and extends to the midline. It is then deepened, preserving the latissimus dorsi if possible, and incising the serratus anterior muscle. Depending on the extent of the aneurysm, the thorax may be entered through any appropriate intercostal space (from the fifth interspace for an extent II thoracoabdominal aneurysm (TAAA), to the ninth interspace for an extent IV aneurysm). After entering the chest, the inferior pulmonary ligament is divided and the lung is mobilized and retracted. Distally, the incision may extend to the upper abdomen if the aneurysm involves only the upper visceral aorta (extent I and V TAAA), or it may extend down the midline to just above the pubis if it involves the iliac arteries. The abdomen can be entered through a retroperitoneal plane or transperitoneally, with left medial visceral rotation. The diaphragm is partially divided peripherally (50% of the circumference), 2 to 3 cm away from its attachments to the chest wall.[16,17] This avoids injury to the phrenic nerve. Leaving the diaphragm intact may result in earlier ventilator weaning.[17] A portion of the costochondral cartilage is excised to prevent postoperative costochondritis. Excising a 1.5 to 2 cm posterior segment of rib assists with the exposure and reduces pain postoperatively.

Lower Quadrant Incisions

Lower quadrant incisions are useful for exposure of the iliac arteries (see Fig. 54.1). The patient is placed supine, with a roll under his flank on the side of the incision. The classic transplant incision is a curvilinear ("hockey stick") incision, beginning one or two fingerbreadths above the symphysis pubis and lateral to the midline. This incision curves up laterally to the edge of

the rectus sheath and is then extended superiorly along the lateral edge of the rectus for a distance determined by how much of the iliac system needs to be exposed. The fascia at the edge of the rectus is divided along with the transversalis fascia to expose the peritoneum. The crossing inferior epigastric vessels caudally are ligated and divided. The spermatic cord should be preserved in male patients (freed up laterally and retracted medially), but the round ligament in females can be sacrificed if deemed necessary. A retroperitoneal plane is gently created laterally and the peritoneal sac and contents retracted medially to expose the iliac vessels from just below the aortic bifurcation to the inguinal ligament. Shorter suprainguinal incisions, running parallel to, and one or two fingerbreadths above, the inguinal ligament, provide excellent exposure for control of the distal external iliac artery, when femoral artery exposure is deemed hazardous (e.g., in the presence of a large femoral artery pseudoaneurysm).

Exposure of Infrarenal Abdominal Aorta and Iliac Arteries

Transperitoneal Approach

Inframesocolic exposure of the infrarenal aorta (Figs. 54.5-54.7) is the most common approach practiced by vascular surgeons.[5,14] It can be performed through a midline or transverse incision and is the preferred approach when access to the right renal artery, distal right iliac system, or intraabdominal organs is necessary. After entering the peritoneal cavity, the transverse colon is reflected superiorly out of the abdomen and the small bowel retracted to the right and protected with a moist towel, or placed in a plastic bag (see Fig. 54.5). Maintaining the small bowel within the abdominal cavity, as opposed to retracting it on to the abdominal wall, helps to reduce bowel wall edema. The peritoneal attachments of the third and fourth portions of the duodenum are divided and the mobilized duodenum reflected to the right. The retroperitoneum overlying the aorta, along with the paraaortic tissue, is incised. The inferior mesenteric

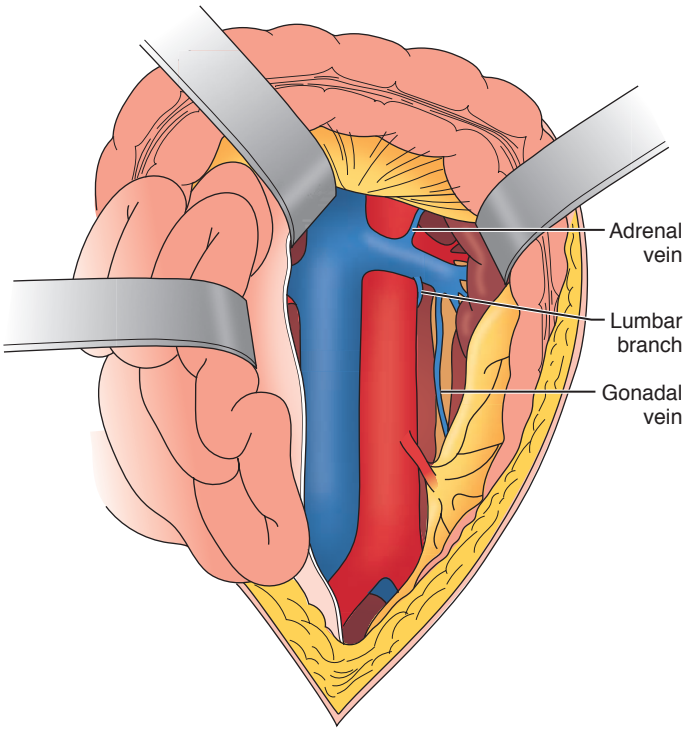

Figure 54.6 Inframesocolic approach to infrarenal aorta (II): Infrarenal aorta exposed from left renal vein to just below aortic bifurcation showing origin of the inferior mesenteric artery.

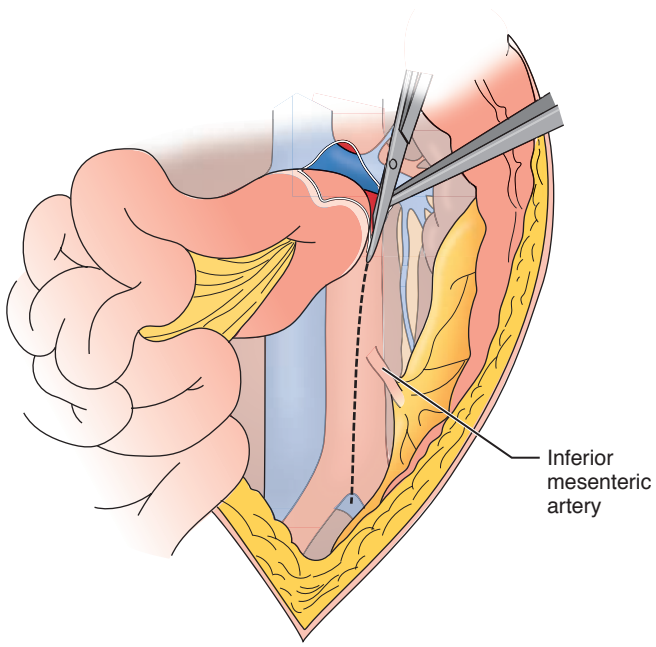

Figure 54.5 Inframesocolic approach to infrarenal aorta (I): Reflection of transverse colon superiorly, retraction of small bowel and duodenum to right after division of the ligament of Treitz.

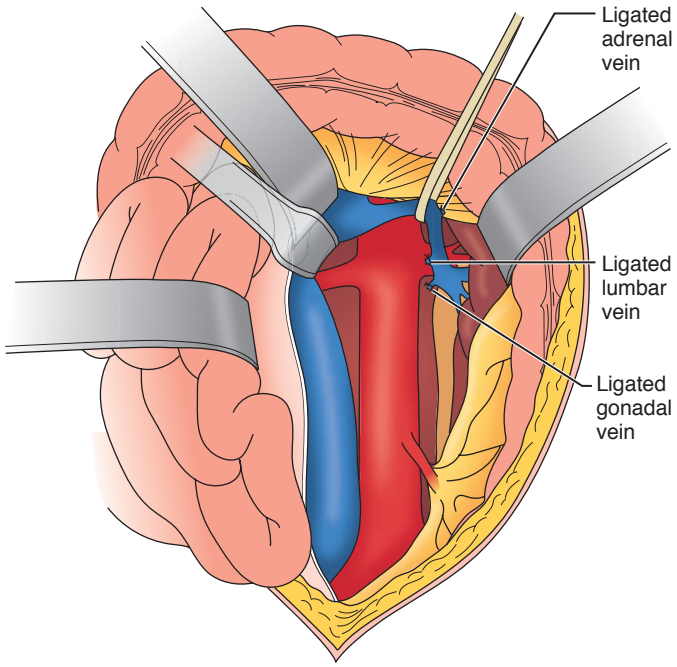

Figure 54.7 Inframesocolic exposure of the pararenal aorta with mobilization of left renal vein (following division of venous branches and retraction) to show renal artery origins.

vein is the most superficial venous structure encountered in the retroperitoneum superiorly and can be ligated and divided if necessary. The aorta is palpated and dissected out. The superior extent of the dissection is the LRV (see Figs. 54.6 and 54.7), where draining lymphatic channels are particularly abundant and should be ligated or divided with an ultrasonic scalpel, rather than cauterized, to avoid troublesome chyle leaks postoperatively. The anterior surface of the aorta can be cleared off distally to the level of the bifurcation, with the only structure at risk being the IMA. This vessel is surrounded by a plexus of nerves which should be avoided if possible. During mobilization of the duodenum and exposure of the retroperitoneal aorta, care must be taken to identify and protect any large visceral collaterals (e.g., the meandering mesenteric artery) that can sometimes course at this level.

Exposure of the pararenal aorta (see Fig. 54.7) more superiorly requires full mobilization of the LRV, again taking care to ligate adjacent lymphatics. The vein is freed up from its junction to the IVC to a point past its major branches, which include the left adrenal vein superiorly, the left gonadal vein inferiorly, and a lumbar branch posteroinferiorly. Ligating and dividing these branches allows the LRV to be retracted superiorly or inferiorly with an encircling Penrose drain, as needed. The LRV can be divided to improve exposure, but in this case, its branches (gonadal, adrenal, and lumbar branches) must be preserved to provide venous outflow for the left kidney. Division of the LRV should be performed close to the IVC to help preserve these collaterals. Whether LRV ligation is associated with an increased risk of renal dysfunction is controversial.[18,19] Exposure of the proximal left renal artery is accomplished by dissecting posterior to the mobilized LRV. The right renal artery courses posterior to the IVC, and its origin is visualized by freeing up the LRV-IVC junction. Crural fibers extending down from the diaphragm posterior to the renal arteries can be released to improve exposure. Aortic dissection can be carried superiorly to the origin of the SMA which is the cranial extent of this exposure. Again, large crossing lymphatics at this level should be ligated to avoid a chyle leak.

The origins of the iliac arteries (Figs. 54.8 and 54.9) can be exposed by slight distal extension of the retroperitoneal incision used for the infrarenal aorta. This extension can be continued over the course of the right iliac beyond the iliac bifurcation to expose the entire right iliac system. Exposure of the right bifurcation and hypogastric artery requires retraction of the cecum and small bowel laterally and superiorly. At the level of the iliac artery bifurcation, caution is taken to identify and protect the overlying ureter. Exposure of the external iliac artery is achieved by incising the peritoneum over it distal to the ureter.

Only a few centimeters of the left common iliac artery can be exposed as an extension of aortic exposure, because of the overlying sigmoid colon. The tissue crossing over the origin of the left common iliac artery contains parasympathetic nerve fibers (nervi erigentes), which should be carefully preserved and retracted rather than incised in sexually active male patients to avoid postoperative erectile dysfunction.[20] Circumferential dissection of the aortic bifurcation and most proximal common iliac arteries should be avoided unless absolutely necessary,

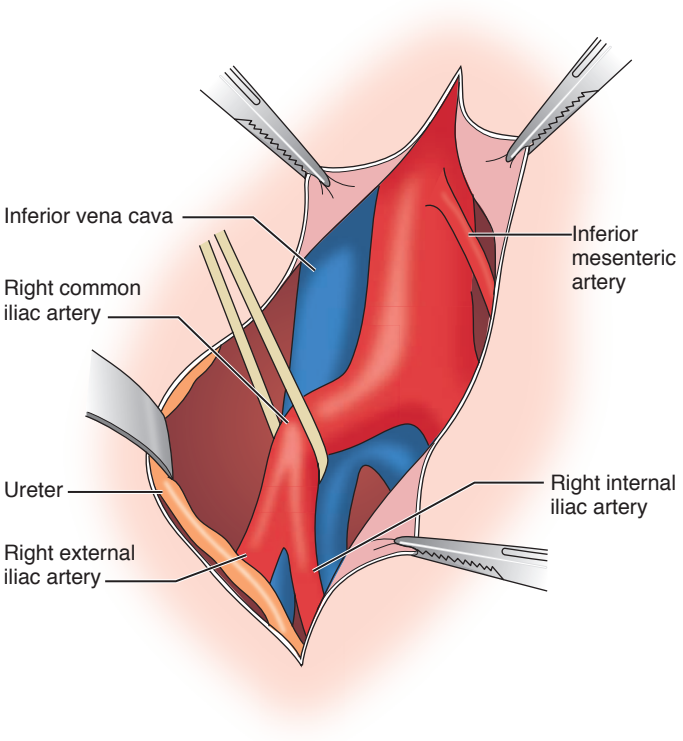

Figure 54.8 Exposure of right iliac artery bifurcation with ureter retracted distally.

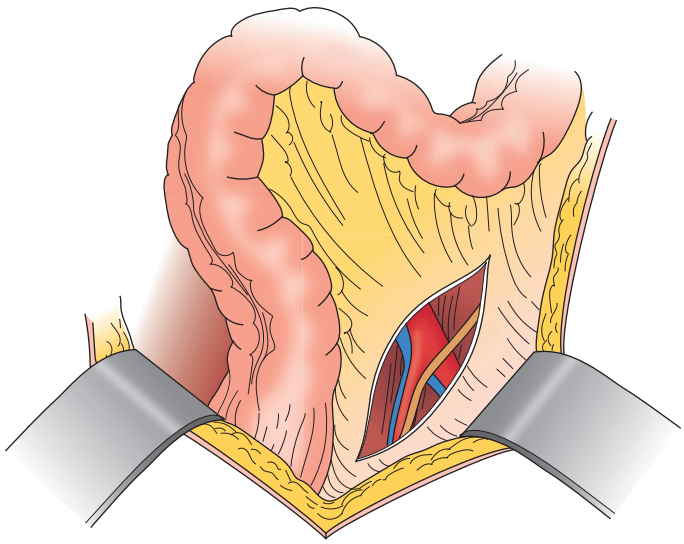

Figure 54.9 Exposure of left iliac artery bifurcation with crossing ureter after incising peritoneal reflection lateral to sigmoid colon.

because of the risk of injuring the underlying caval confluence, which can be quite adherent to diseased or aneurysmal arteries. Controlling the common iliac arteries just a few centimeters distally is usually safer. To access the left external and hypogastric arteries, the sigmoid colon is reflected medially after incising

its lateral peritoneal reflection. The external iliac artery is visually confirmed as traversing laterally and superiorly over the psoas muscles to form the common femoral artery beneath the inguinal ligament. The dissection is carried cephalad to identify the iliac bifurcation and crossing ureter. The hypogastric artery is confirmed as the branch coming off at right angles and coursing medially and inferiorly. Careful and meticulous dissection is performed to separate the internal iliac artery from the underlying vein.

Retroperitoneal Approach

As outlined previously, surgical exposure through a left flank retroperitoneal approach (see Figs. 54.2 and 54.3) offers a number of advantages.[7,8] Oftentimes the impediment to choose this approach is lack of surgeon's experience. An oblique left flank incision is made as described previously. After entering the retroperitoneal space, the surgeon must decide whether to expose the aorta anterior or posterior to the left kidney. A retrorenal plane is the one most commonly chosen, and the left kidney and ureter are reflected anteriorly along with the peritoneal sac and contents. When developing this plane, it is important to stay anterior to the lumbodorsal fascia covering the psoas and flank musculature, because of increased bleeding when this fascia is stripped off. As the viscera are retracted to the patient's right, the aorta should become palpable in the base of the wound. Initial efforts are focused on identification of the left renal artery because this is the only major structure that can be injured while clearing off the aorta from this approach. Identification does not necessarily require dissection of all the tissue around the pararenal aorta. A guide to this artery is provided by a large vein (the lumbar branch of the LRV) that crosses the left lateral wall of the aorta at this level; this vein usually requires division for exposure of the juxtarenal aorta. If this vein is quite large, the surgeon needs to be concerned that it may represent a retroaortic LRV, a possibility which can be confirmed by a review of preoperative imaging studies. In this instance the retrorenal approach should be abandoned in favor of an exposure plane anterior to the kidney, which will leave this vein undisturbed. Following division of the lumbar branch, dissection of the left lateral wall of the aorta is carried distally to the aortic bifurcation, watching for the origin of the IMA. During exposure of the aortic bifurcation, care should be taken to ensure that the left ureter has been mobilized and retracted out of harm's way. The entire left common iliac artery and its bifurcation are easily visualized through this approach, but only the proximal right common iliac artery is accessible. Division of the IMA can improve right iliac exposure, as can extension of the incision across the rectus to the midline, but exposure beyond the iliac bifurcation is rarely possible through this approach.

Exposing the aorta anterior to the left kidney is more tedious because a plane between the kidney and mesocolon must be developed with more sharp than blunt dissection. As the left colon and viscera are retracted anteriorly, the left kidney and ureter are left in their normal anatomic position posteriorly; the ureter must be carefully protected during subsequent left iliac dissection as it courses medially over the iliac bifurcation. Besides a retroaortic LRV, the only other indication for this approach is the need to expose a long segment of the SMA which is obscured by the crossing left renal artery when approached retrorenally.

As previously outlined, disadvantages of this approach include limited exposure of the distal right iliac system and right renal artery, as well as an inability to perform a complete abdominal exploration. However, a limited abdominal exploration is still possible by making a rent in the peritoneal sac.

Exposure of the Proximal Abdominal Aorta (Hiatus to Renals)

Transperitoneal Approach Through the Lesser Sac

Use of this approach is limited because the exposure provided is confined to 4 to 5 cm of supraceliac aorta, the celiac axis, and proximal SMA (Fig. 54.10). Indications include visceral bypasses and exposure for supraceliac aortic clamping. The segment of aorta proximal to the celiac artery is usually devoid of plaque and is used for aortic control when the lower aorta is not favorable for clamping (e.g., excessive thrombus, or plaque). Either a midline or supraumbilical transverse incision is used. The triangular ligament of the left lobe of the liver is divided, and the distal end of the left lobe retracted to the right. Care is taken not to injure the left hepatic vein while dividing the triangular ligament. The lesser sac is entered through a longitudinal incision in the gastrohepatic ligament. Identification of the esophagus is greatly aided by the presence of a nasogastric tube, particularly in hypotensive ruptured aneurysm patients, when the aorta is flaccid. During division of the gastrohepatic ligament, care is taken not to divide an aberrant (replaced) left hepatic artery, present in 10% to 15% of patients. When present, it usually runs in the cephalad portion of the ligament, coming off the left gastric artery. After retracting the esophagus and stomach to the left, the right crus of the diaphragm can be exposed, lifted off the aorta with a right-angle clamp and divided with electrocautery. The operator's index finger can then be inserted between the aorta and the median arcuate ligament, which is divided if necessary to expose the distal descending thoracic aorta. The pleural cavity is occasionally entered, which makes a chest radiograph in the immediate postoperative period necessary. Circumferential isolation of the aorta at this level is usually unnecessary and may injure posterior intercostal branches.

In an emergency requiring urgent proximal aortic control, a more rapid supraceliac aortic dissection is performed after entering the lesser sac (Fig. 54.11). The avascular portion of the gastrohepatic ligament is incised, and the esophagus is retracted to the left, guided by the nasogastric tube. The aorta is palpated and compressed against the spine. Blunt index finger dissection is used to separate the aorta from the crura of the diaphragm and from surrounding tissues. Once reasonable dissection is completed, the aorta is pinched between the index and middle fingers, while a long vascular clamp is applied.

The celiac axis is exposed by dissecting away the enveloping celiac plexus; this nerve tissue is thick and can be quite adherent

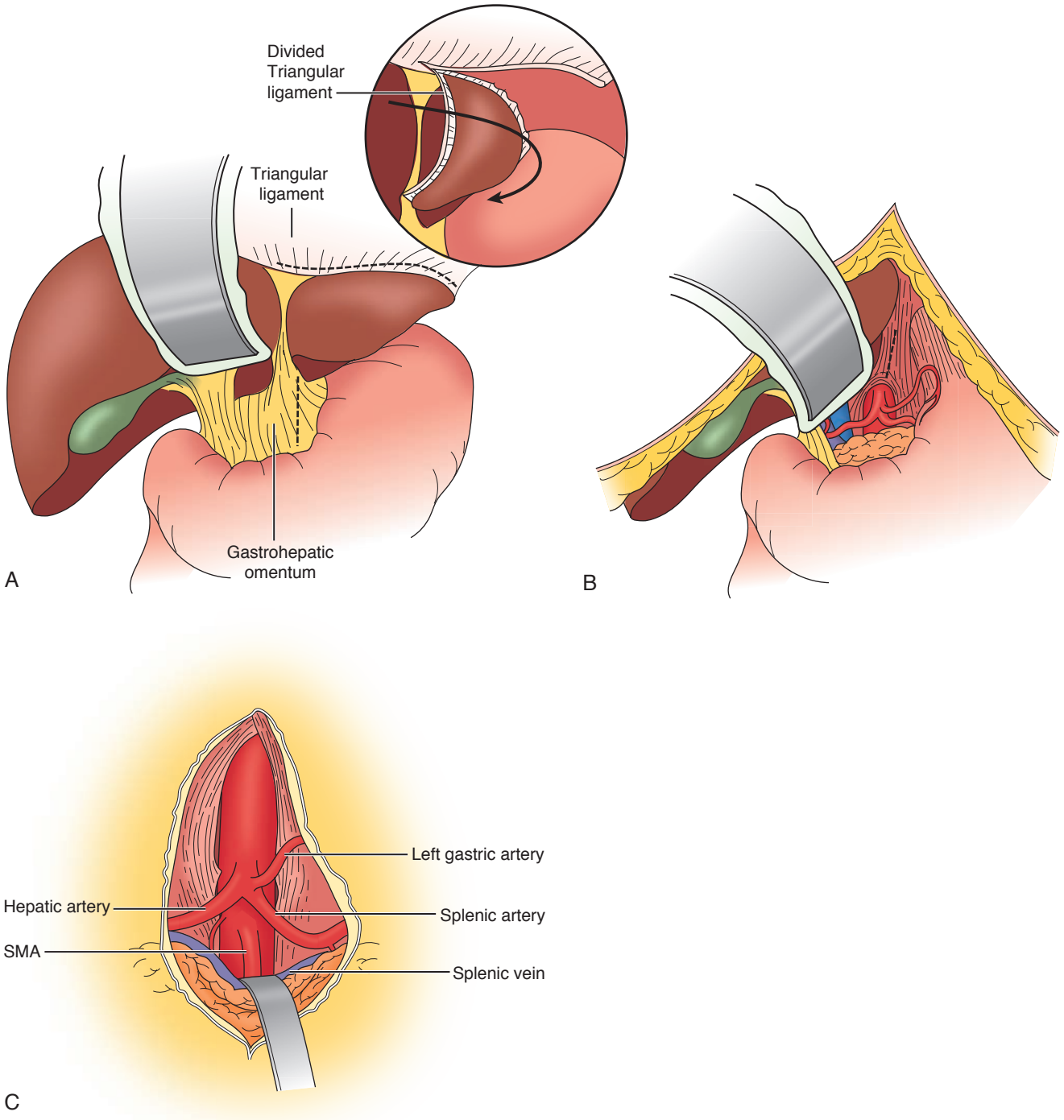

Figure 54.10 Exposure of the Celiac Trunk/Branches and the Superior Mesenteric Artery. (A) Division of gastrohepatic omentum and triangular ligament of left lobe of liver; inset shows lateral edge of left hepatic lobe folded back on itself to expose aortic hiatus. **(B)** Lateral segment of left hepatic lobe retracted to the right; dotted line shows division of median arcuate ligament and diaphragmatic crura over anterior surface of aorta; celiac artery and branches are typically covered by a thickened rind of neural/lymphatic tissue (not shown). **(C)** Exposure of celiac artery and proximal branches after division of crura, and resection of neural/lymphatic tissue; superior mesenteric artery is exposed by retracting the superior border of the pancreas distally. *SMA*, Superior mesenteric artery.

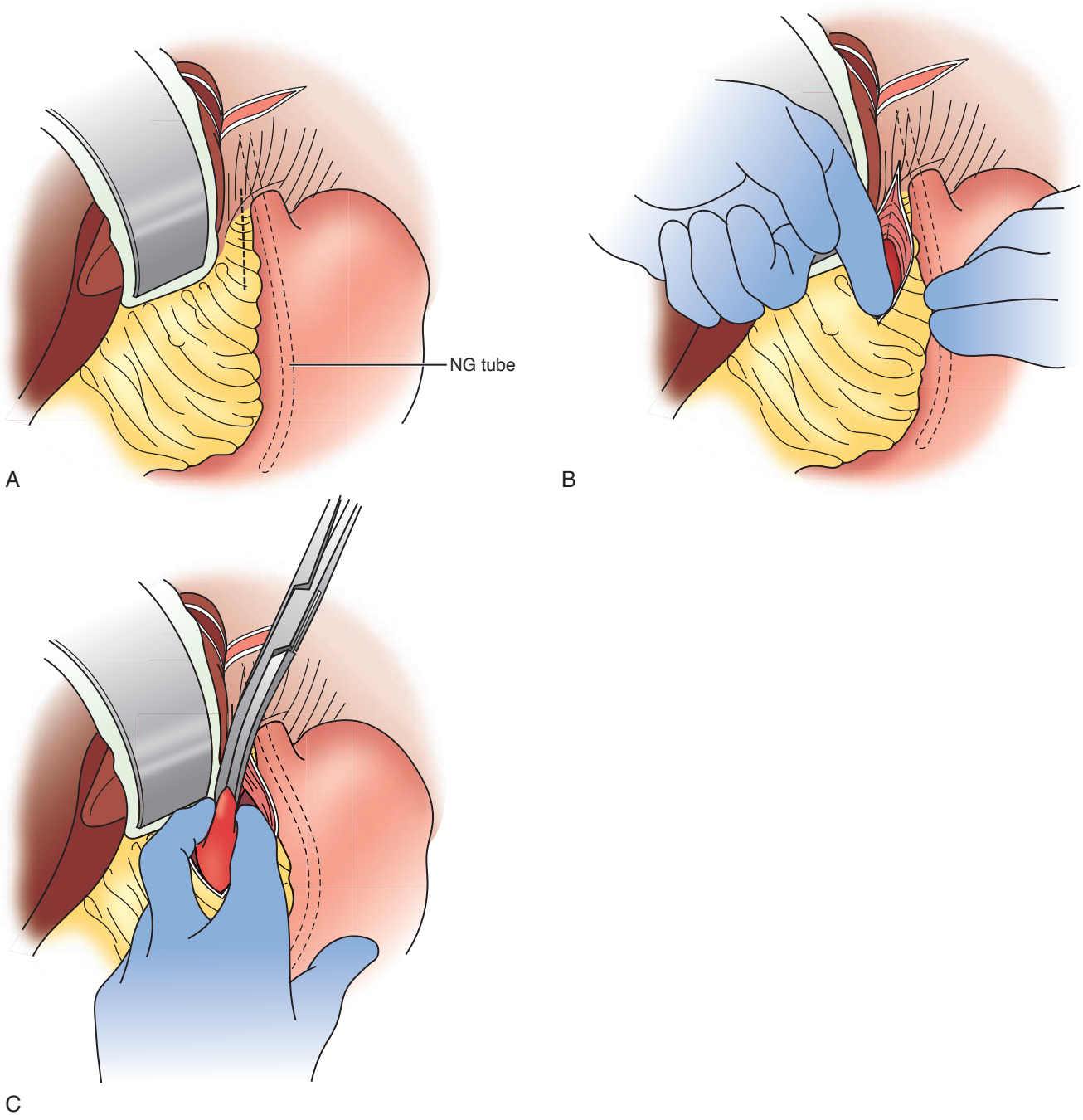

Figure 54.11 Rapid Control of Supraceliac Aorta. (A) Retraction of lateral segment of left hepatic lobe and division of gastrohepatic omentum (along *dotted line*). **(B)** Division of overlying diaphragmatic crural fibers and blunt index finger mobilization of supraceliac aorta; palpation of nasogastric tube and retraction of stomach to left reduces risk of inadvertent injury to stomach/esophagus during this maneuver. **(C)** Placement of large, vertically oriented clamp across supraceliac aorta.

to the aorta and celiac artery. As the dissection proceeds distally, the three branches of the celiac artery are encountered and should be treated with care because they are much thinner walled than the main trunk and can easily be damaged. The SMA can be identified just below the celiac; caudal retraction on the mid body of the pancreas provides exposure to up to 3 to 5 cm of this vessel. Surrounding lymphatics require careful attention to prevent postoperative chyle leaks.

Transperitoneal Approach With Medial Visceral Rotation

The entire proximal abdominal aorta can be exposed through a transabdominal approach by performing a medial visceral rotation (the so-called Mattox maneuver; Fig. 54.12).[21,22] This approach is challenging in obese patients and those with a narrow costal angle, but it does avoid a thoracic incision. The

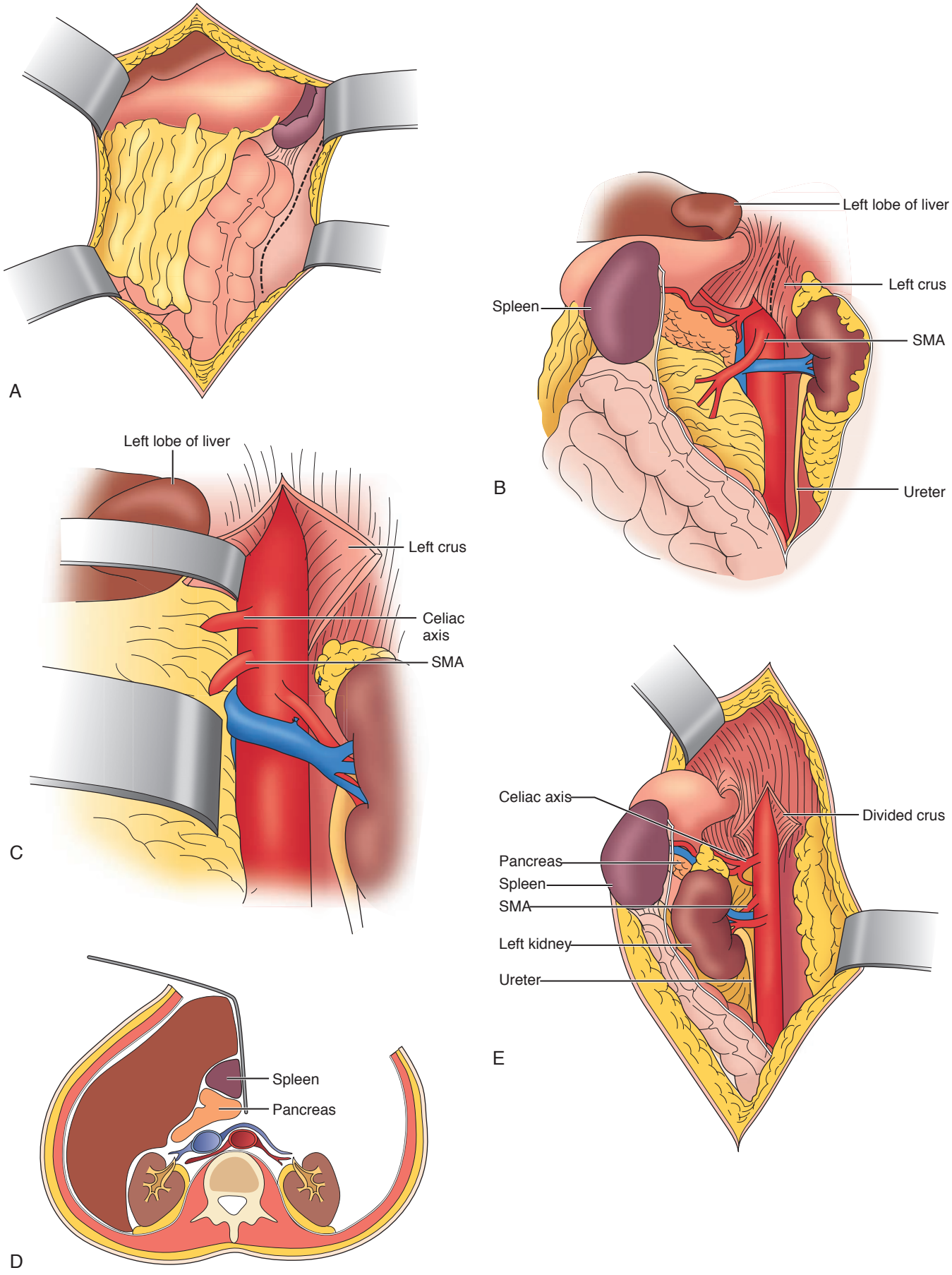

Figure 54.12 Left Medial Visceral Rotation. **(A)** Peritoneal incision lateral to descending colon and spleen. **(B)** Reflection/rotation of abdominal viscera from left to right (medially) in a plane anterior to left kidney leaving kidney in normal anatomic location with exposure of proximal abdominal aorta in base of wound. *Dotted line* is intended division line of left diaphragmatic crus. **(C)** Same exposure following division of left diaphragmatic crus and mobilization of left renal vein. **(D)** Cross-sectional view showing potential retraction injury of spleen and pancreas with this approach. **(E)** Same exposure but dissection plane is carried posterior to left kidney elevating it out of its bed and retracting it medially. *SMA*, Superior mesenteric artery.

lateral peritoneal reflection adjacent to the descending/sigmoid colon and spleen is incised cephalad, curving toward the aortic hiatus. Using largely blunt dissection, a retroperitoneal plane is developed, and the spleen, tail of pancreas, and left colon are retracted anteriorly and to the patient's right. The left kidney is usually elevated with these structures, and the avascular plane posterior to the left kidney is entered anterior to the psoas and flank musculature, taking care not to strip off the lumbodorsal fascia. When the left kidney is reflected upward, the origins of the celiac trunk, SMA, and the entire left renal artery can be visualized. However, exposure of the SMA beyond its first 2-3 cm is limited by the crossing left renal artery. In the case of a retroaortic LRV, or when exposure of a longer segment of proximal SMA is necessary, a plane anterior to the kidney may be developed. When the kidney is left down, a much longer segment of SMA (up to 10 cm) is accessible, but exposure of the left renal artery then requires wide mobilization of the LRV. Developing an anterior plane is more tedious than a posterior one, and care must be taken to avoid injury to the left adrenal gland.

Exposure of the supraceliac aorta is limited to just a few centimeters with this approach and requires division of the left diaphragmatic crus along the left lateral wall of the aorta. Besides the lack of access to the distal descending thoracic aorta, other disadvantages of this approach include a high incidence of splenic injury (up to 20%), and complications of excessive visceral retraction (e.g., bowel ischemia and pancreatitis; see Fig. 54.12D).[21] Nevertheless, when combined with standard transperitoneal exposure techniques, this approach provides the greatest versatility for exposing the entire abdominal aorta and all its branches.

Left Flank Retroperitoneal/Thoracoretroperitoneal Approach

The proximal abdominal aorta can also be exposed through a left flank incision in the 10th or 9th interspace, depending on how much proximal exposure is necessary (see Figs. 54.2-54.4). The 10th interspace is adequate for supraceliac clamping. However, pararenal exposure and paravisceral procedures are best accomplished through a ninth interspace incision. When going through a 10th or 9th interspace incision the left chest is entered, and it is necessary to divide the diaphragm to prevent tearing it when the ribs are retracted apart. A circumferential division 2 to 3 cm away from the chest wall avoids the risk of phrenic nerve injury, which may contribute to postoperative pulmonary dysfunction. The same remarks outlined earlier apply to exposure anterior or posterior to the left kidney, with a retrorenal plane preferred. Longitudinal division of the left diaphragmatic crus improves exposure of the left renal artery and is essential for revealing the celiac trunk and SMA origins. As previously mentioned, circumferential isolation of the aorta is not necessary.

Exposure of Visceral Arteries

Celiac Axis

Exposure of the proximal celiac through the lesser sac has been described previously (see Fig. 54.10).

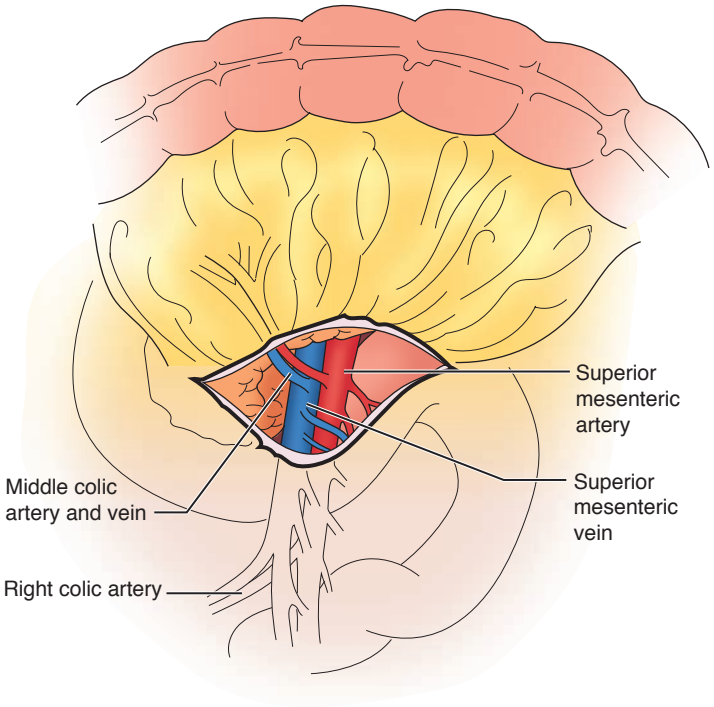

Figure 54.13 Superior mesenteric artery (and vein) exposure at base of mesentery.

Superior Mesenteric Artery

Exposure of the proximal SMA can be accomplished transperitoneally through the lesser sac (allowing for 3-5 cm of exposure; see Fig. 54.10), via medial visceral rotation, or through a left flank retroperitoneal approach (providing 8-10 cm of exposure; see Figs. 54.3, 54.4 and 54.12). Distal SMA exposure requires an inframesocolic approach (Fig. 54.13). Through a transperitoneal incision, the transverse colon is reflected superiorly and the small bowel retracted to the right and inferiorly. The SMA is dissected out to the right of the ligament of Treitz in the root of the mesentery, as it emerges from underneath the pancreas. In SMA embolism a proximal pulse is frequently present and serves as a guide to the artery; if not, an occluded SMA can usually be palpated as a firm tubular structure 5 to 6 mm in diameter. The superior mesenteric vein (SMV) lies immediately to the right of it. With this approach the surgeon can usually dissect out the SMA from just proximal to the middle colic artery to its distal ileocolic branches.

Hepatic Artery

A transperitoneal upper midline or an extended right subcostal incision is usually used (see Fig. 54.10). Elevation of the right flank on a rolled sheet may be helpful. The liver is retracted superiorly and the right transverse colon and small bowel inferiorly. The gastrohepatic ligament is incised transversely, and the lesser sac is entered. The common hepatic artery and proximal portion of the proper hepatic artery are easily palpated within the hepatoduodenal ligament. The common hepatic artery is dissected out as it passes over the pancreatic head and followed distally until the gastroduodenal artery is found. Gentle traction on the

common hepatic artery will facilitate exposure of its branches, the gastroduodenal and proper hepatic. The proper hepatic artery is located more distally within the porta hepatis, anterior to the portal vein and medial to the common bile duct.[2,3]

Splenic Artery

A transperitoneal upper midline or extended left subcostal incision is appropriate, with a rolled sheet placed under the left flank (see Figs. 54.10 and 54.12). The proximal third of the splenic artery is best approached through the lesser sac, which is entered either by dividing the gastrohepatic omentum above the lesser curvature of the stomach or dividing the gastrocolic ligament, after reflecting the greater omentum superiorly and the transverse colon inferiorly. The posterior gastric wall is then separated from the underlying pancreas, and the superior edge of the pancreas is exposed. The splenic artery is located along the superior surface of the body and tail of the pancreas. For distal splenic artery exposure, a partial medial visceral rotation is performed by incising the lateral peritoneal reflection of the descending colon and retracting the left colon medially. The pancreas and spleen are mobilized anteriorly and medially away from the left kidney, which is left in its normal anatomic location. The splenic artery is palpable and dissected out along the superior border of the pancreas.

Exposure of Renal Arteries

The origins (and first 2-3 cm) of the renal arteries can be exposed through an inframesocolic approach, as detailed in the section on infra/pararenal aortic exposure (see Fig. 54.7). The peritoneum over the aorta is incised, and the duodenum is reflected to the right. The avascular plane under the pancreas is entered. The LRV is mobilized, and the lumbar, gonadal, and adrenal branches are ligated and divided. This allows for cephalad or caudal retraction of the vein, depending on the exposure required. The left renal artery is typically posterior to the LRV. The left crus of the diaphragm may be divided to help with exposure. The proximal right renal artery is exposed by mobilizing the IVC-LRV junction. Usually a couple of lumbar veins need to be ligated to retract the vena cava to the right. The LRV is retracted superiorly, exposing the origin of the right renal artery. Overlying lymphatic vessels may need to be ligated and divided to enhance the exposure of the right renal artery origin. Again, dividing the right crus of the diaphragm helps with this exposure. More of the left renal artery (5-6 cm) than the right renal artery can be exposed from the inframesocolic approach with the IVC on the right.[14]

As previously described, the entire length of the left renal artery can be exposed with a full medial visceral rotation (see Fig. 54.12)[22] or through a left flank retroperitoneal approach (see Figs. 54.3 and 54.4). It should be noted that the left renal artery is put on considerable "stretch" when approached posteriorly; this should be kept in mind when retracting the left kidney anteromedially. Therefore bypasses to the left renal artery in this position should always be performed under some tension; otherwise, there is a risk of kinking when the kidney is returned to its normal anatomic position.

The right renal artery (in particular its mid to distal portion) requires a right medial visceral rotation (Cattell-Brasch maneuver), either through a midline or transverse transperitoneal incision (Fig. 54.14).[23,24] The lateral peritoneal reflection of the ascending colon from cecum to hepatic flexure is incised and the colon reflected medially and anteriorly. The underlying second portion of the duodenum and head of the pancreas are mobilized medially with a Kocher maneuver to expose the right kidney and the right renal vein is mobilized circumferentially from its caval junction as far distally as necessary, with the attendant ligation of the small proximal tributaries. This vein may then be easily retracted during dissection of the underlying renal artery. The right renal artery travels under the IVC to its origin off the aorta, and more proximal exposure requires mobilizing the IVC from the midline (see Fig. 54.7). Any lumbar veins encountered in this process should be divided with stitch ligatures on the caval side to avoid tie dislodgement during retraction.

EXPOSURE OF MAJOR ABDOMINAL VEINS

Inferior Vena Cava

Anatomic Considerations

The internal and external iliac veins converge at the sacroiliac joint to form the common iliac veins. The ureter, spermatic cord (male) and round ligament and ovarian vessels (female) cross the external iliac veins at this level. At the bifurcation of the aorta and vena cava, the iliac veins are closely related to the dorsal surface of the arteries. This makes them prone to injury during hasty exposure of these arteries, especially in trauma cases. The IVC starts at the level of L5 to the right of the midline, with the confluence of the common iliac veins. The aortic bifurcation is slightly more cephalad and anterior than the caval confluence, which results in the IVC bifurcation and left iliac vein being crossed anteriorly by the right common iliac artery. There can be significant "adhesions" between the back wall of the aortic bifurcation and the front wall of the caval bifurcation and proximal iliac veins in this overlap zone, which can make dissection in this area quite hazardous. The infrarenal IVC has several pairs of lumbar veins that arise, posteriorly tethering it to the psoas muscles. The renal veins enter the vena cava at the level of L1-L2 and are usually single. The retrohepatic IVC receives three large hepatic veins at the level of the dome of the liver and several small caudate lobe branches. The IVC then enters the chest at the level of T8 and drains into the right atrium.

Infrarenal/Suprarenal Inferior Vena Cava

A variety of incisions are available to expose the infrahepatic IVC, with the choice depending on the amount of exposure desired (Figs. 54.14 and 54.15). A midline, transperitoneal incision is standard in trauma cases and is the most frequent approach used. A right transverse transperitoneal or right flank retroperitoneal approach is also useful but is slightly more limited in visualizing branches beyond the caval bifurcation. A subcostal

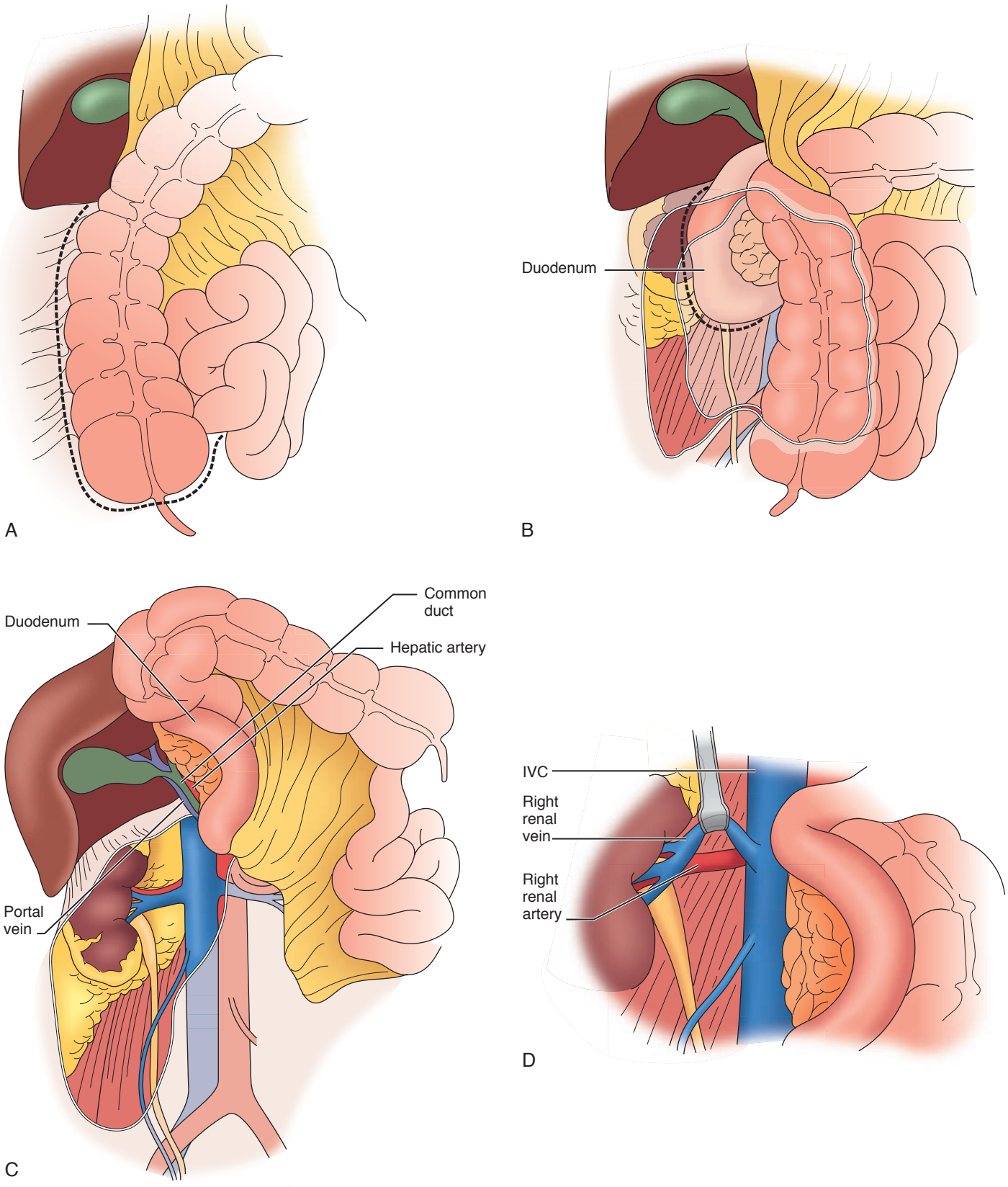

Figure 54.14 **Exposure of Subhepatic Inferior Vena Cava and Right Renal Artery Through Right Medial Visceral Rotation (Cattell-Brasch Maneuver).** **(A)** The lateral peritoneal reflection of the ascending colon is incised (from cecum to hepatic flexure). **(B)** The right colon is reflected medially and anteriorly. **(C)** The underlying second portion of the duodenum and the head of the pancreas are mobilized with a Kocher maneuver and reflected medially to expose the right kidney and inferior vena cava. The cecum can be reflected superiorly to expose the entire infrarenal vena cava to its bifurcation. **(D)** Mobilization of the right renal vein exposes the underlying right renal artery. *IVC*, Inferior vena cava.

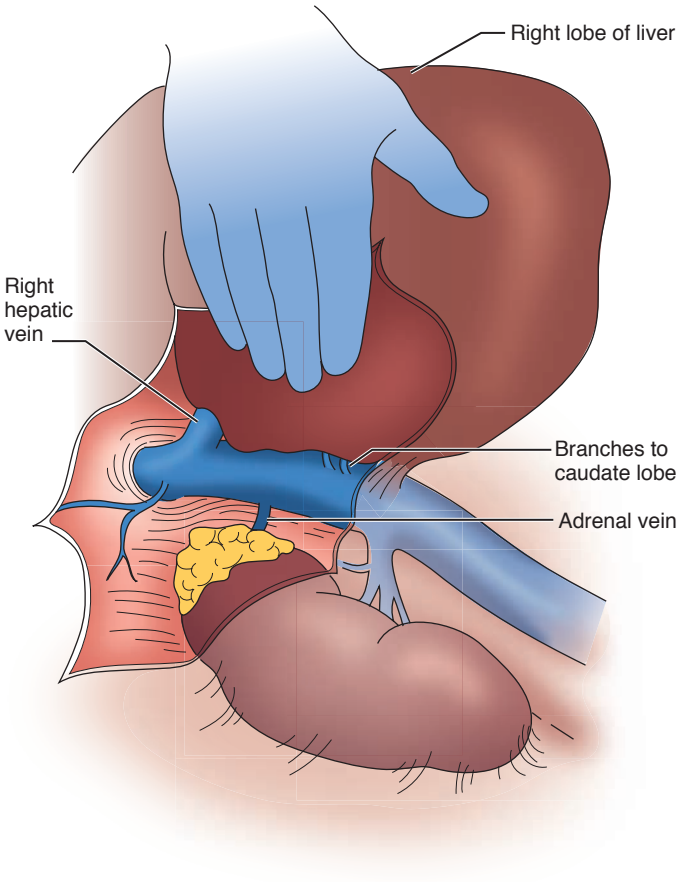

Figure 54.15 Exposure of retrohepatic inferior vena cava and right hepatic vein by mobilizing and retracting the right lobe of the liver to the left.

incision may also be used for limited exposure. With transperitoneal approaches, the small bowel is retracted to the left and a right medial visceral rotation is performed by incising the lateral peritoneal reflection of the ascending colon, as described previously. Following a Kocher maneuver, the pancreatic head and second and third portions of the duodenum are retracted to the left, exposing the IVC and renal veins. This also allows the porta hepatis and distal SMV to be dissected out behind the pancreas.[24] This dissection can be carried cephalad, exposing the retrohepatic vena cava. Some surgeons report that extending the incision into the ninth intercostal space of the right chest improves exposure of the retrohepatic IVC. Dividing the diaphragm can expose the juxtaatrial IVC, along with the major hepatic branches. For more distal exposure (caval confluence and both iliac veins), the peritoneal reflection of the cecum is incised to the level of the ileocecal junction, and the entire right colon is retracted leftward (Cattell-Brasch maneuver).[23,24] The IVC from the common iliac veins to the level of the caudate lobe can be visualized with this approach. Ligation/division of tethering lumbar veins permits mobilization of the IVC, but it is advisable to place suture ligatures on the caval side of these branches to prevent accidental dislodgement. One method to provide rapid exposure to the IVC bifurcation and proximal iliac veins in a trauma situation is to divide the overlying right iliac artery to expose the underlying injury. After venous repair, the artery is reanastomosed and distal blood flow reestablished (see Fig. 54.16)[25,26]

Retrohepatic and Suprahepatic Inferior Vena Cava

A midline approach with superior extension into a sternotomy is the most widely used incision to expose these IVC segments,

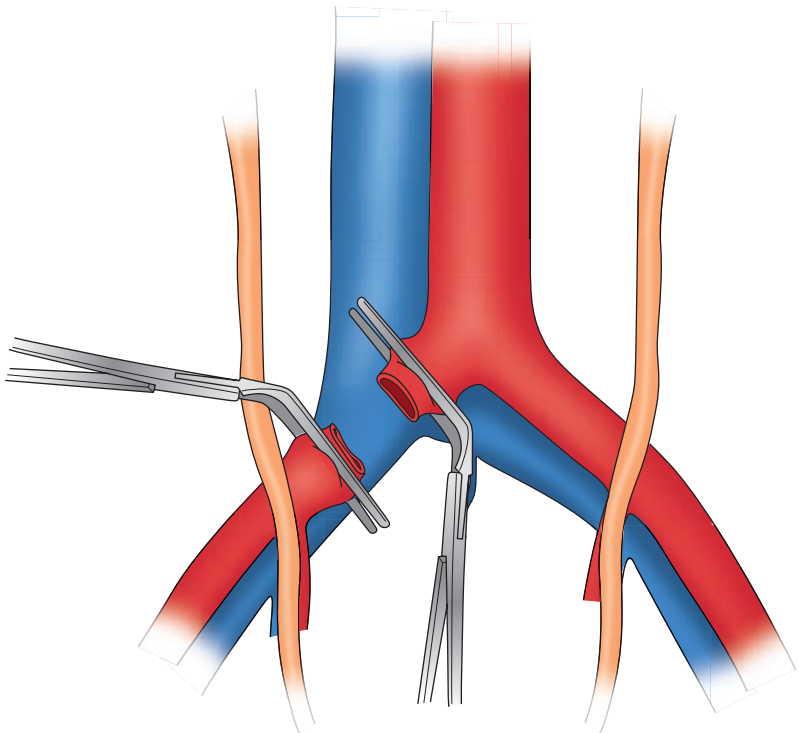

Figure 54.16 Exposure of the inferior vena cava–iliac vein confluence by dividing the right common iliac artery.

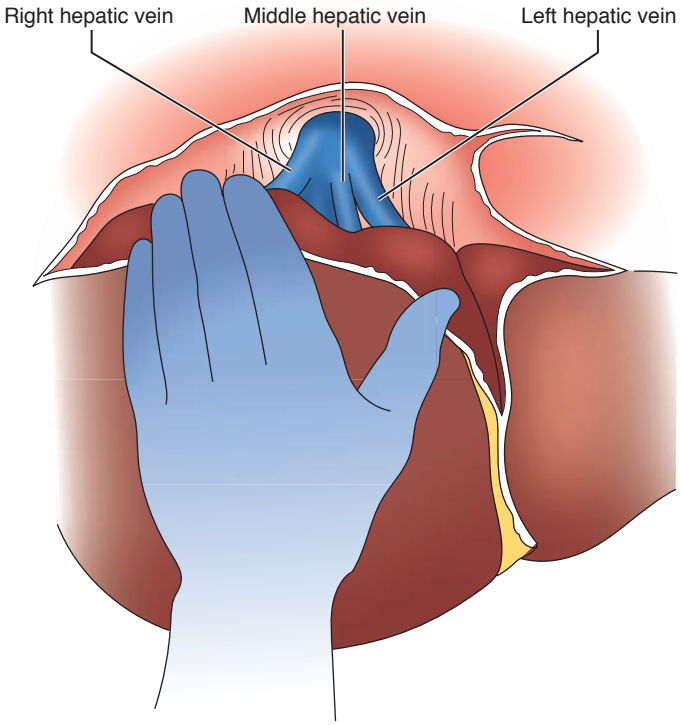

Figure 54.17 Exposure of suprahepatic inferior vena cava and hepatic veins after incising the coronary ligaments and retracting the liver caudally.

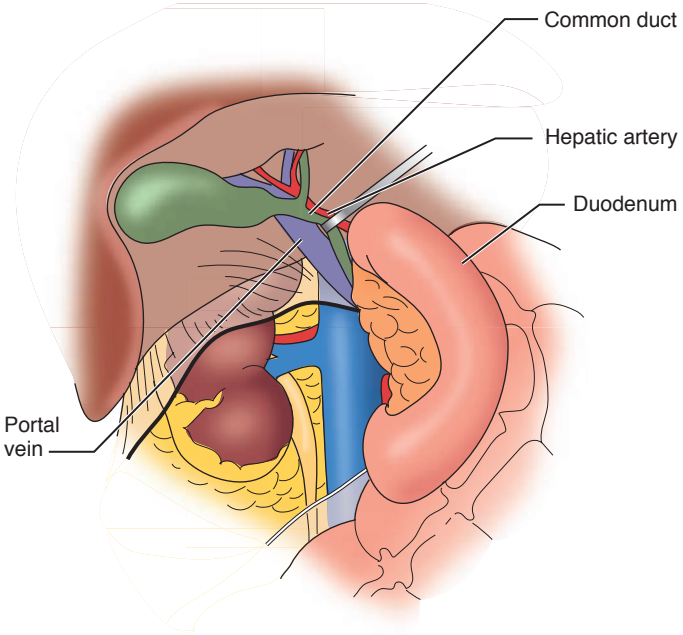

Figure 54.18 Portal vein exposure after mobilizing the hepatic flexure of the right colon and performing a Kocher maneuver on the duodenum. Small retractor is displacing common bile duct to patient's left.

particularly in trauma situations (see Figs. 54.15 and 54.17). A chevron incision ± sternotomy, or an eighth or ninth interspace right thoracoabdominal incision can provide excellent exposure in elective cases. A transperitoneal approach is greatly facilitated by upward and lateral retraction of the costal margins. After entering the peritoneum, the right triangular ligament is divided, along with the peritoneal attachments to the right lobe of the liver, and the right lobe is mobilized and retracted medially and anteriorly. This exposes the retrohepatic IVC. A number of small venous tributaries draining the caudate lobe and sometimes the posterior right lobe are encountered during this mobilization and should be carefully ligated and divided to prevent avulsion. Of the three hepatic veins, only the right can be reliably visualized from this approach. Exposure of the other hepatic veins and the suprahepatic IVC requires wider mobilization. The round and falciform ligaments have to be divided and all the superior peritoneal reflections of the liver (coronary ligaments) incised, to expose the "bare area" of the liver. The liver is then retracted caudally to visualize the suprahepatic IVC and hepatic veins. If control of the IVC between the hepatic veins and diaphragm proves difficult, intrapericardial control of the IVC can be accomplished after performing a sternotomy.

Portal Vein and Branches

Anatomic Considerations

The SMV lies to the right of the SMA in the root of the mesentery. It tracks over the third portion of the duodenum and uncinate process of the pancreas and dives under the neck of the pancreas to join the splenic vein, which runs in a groove along the back of the pancreas. The inferior mesenteric vein lies to the immediate left of the infrarenal aorta and crosses over it to drain into the splenic vein. The portal vein is formed by the confluence of the splenic and SMV at the level of L2 and courses toward the liver within the gastrohepatic ligament, posterior to the medially located hepatic artery and the laterally located common bile duct.

Portal Vein

A subcostal incision extending into the right flank or a midline incision is appropriate. After dividing the falciform ligament, the right lobe of the liver is retracted cephalad and the hepatic flexure of the colon caudally. After a partial Kocher maneuver, the first and second portions of duodenum are mobilized and retracted downward and slightly to the left, to expose the porta hepatis structures (Fig. 54.18). The portal vein is the most posterior structure of the hepatoduodenal ligament and is best isolated by longitudinally dividing the peritoneum along the right posterior aspect of the ligament to avoid injury to the common bile duct. After the lateral wall of the vein has been dissected free proximally and distally, the common bile duct can be gently retracted superiorly and to the left, enhancing exposure. A replaced right hepatic artery, if present, runs parallel and to the right of the vein and should be carefully preserved. Mobilization of the portal vein from the pancreas to its hepatic bifurcation can be accomplished by carefully isolating and dividing tributaries, which usually enter the vein medially and posteriorly. Mobilizing the right lobe of the liver by dividing the triangular ligament and pushing the liver down and forward with laparotomy pads packed behind it greatly improves exposure of the porta hepatis. Uncontrollable bleeding from the porta hepatis or liver

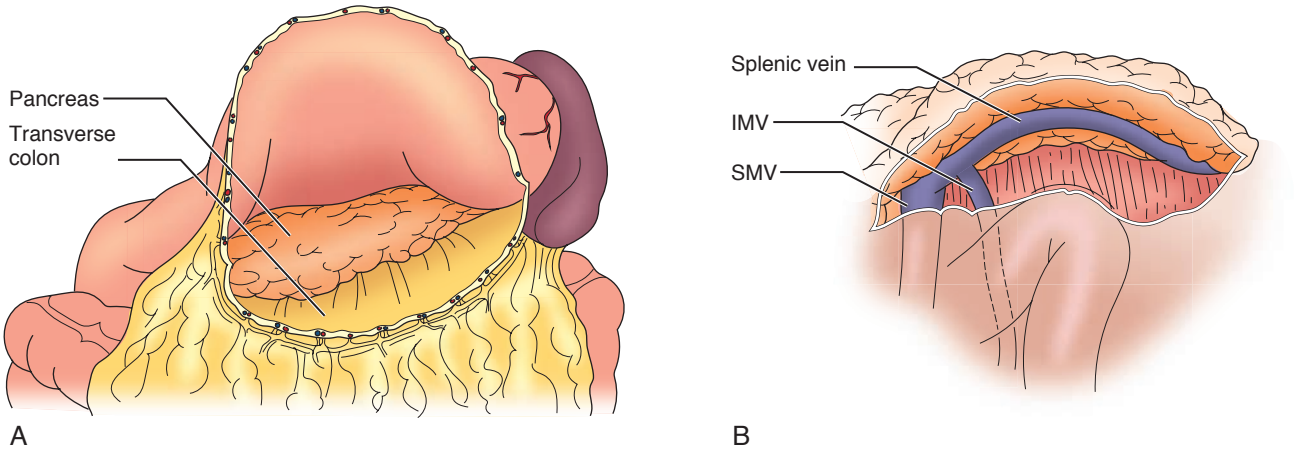

Figure 54.19 Exposure of Splenic Vein. **(A)** Lesser sac is entered by dividing the gastrocolic ligament. **(B)** Pancreas elevated superiorly with splenic vein under it; the splenic veins joins the superior mesenteric vein *(SMV)* to form the portal vein. The inferior mesenteric vein *(IMV)* drains into the splenic vein.

can be managed by inserting an index finger through the foramen of Winslow and pinching the entire porta hepatis between the thumb (on the anterior surface of the porta) and the index finger (Pringle maneuver[27]).

Superior Mesenteric Vein

Exposure of the SMV is similar to that of the SMA (see Fig. 54.13). After elevating the transverse mesocolon to expose the root of the mesocolon, the small bowel is retracted inferiorly, and the SMA is palpated. The SMV lies just to the right of the SMA.

Splenic Vein

The most direct approach to the splenic vein is through the lesser sac (Fig. 54.19). A subcostal incision extending to the left or a midline incision is used. After entering the peritoneum, the lesser sac is reached by dividing the gastrocolic ligament. The greater curvature of the stomach is elevated, and the inferior border of the pancreas is exposed. The splenic vein is dissected out under the inferior border of the pancreas. Multiple small branches drain into it, making the dissection tedious. This approach is useful for distal splenorenal shunts.

The splenic vein can also be approached below the transverse mesocolon. As discussed previously in exposure of the left renal artery through an inframesocolic approach, the transverse colon is elevated and the small bowel retracted to the patient's right. The ligament of Treitz is divided, mobilizing the third and fourth portions of the duodenum to the right. The LRV is identified as a landmark. The inferior border of the pancreas is identified and the inferior mesenteric vein running along the left side of the aorta traced cephalad to its junction with the splenic vein. The inferior border of the pancreas is rotated superiorly to expose the splenic vein running along its posterior surface.

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55 CHAPTER

Cerebrovascular Exposure

LINDA M. HARRIS and MACIEJ DRYJSKI

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GENERAL

Carotid interventions are among the most frequently performed vascular procedures (see Chapter 91). For revascularization involving cervical vessels, the patient should be positioned supine, with the head averted from the operative side and slightly extended. Extension is typically obtained by placing a small roll behind the shoulder blades transversely. Care should be taken not to hyperextend the neck or over rotate. The bed should also be placed slightly in a reverse Trendelenburg position to decompress the surrounding venous structures. Both arms can be tucked to allow for the surgeon and assistant to stand across from each other or with one at the head of the bed and one at the side of the involved vessel, depending on surgeon preference. The area to be prepped should include the jawline and the inferior aspect of the ear to below the clavicle, with more extensive prep if consideration is given to extending the incision for access to the origins of the great vessels. If regional anesthesia is being performed, this is done prior to prepping and draping. It is also advantageous to place a small squeeze toy in the contralateral hand to allow for neurologic assessment throughout the procedure. This allows the patient to demonstrate function of that limb when regional blocks are being utilized. If regional anesthesia is utilized, the skin should always be tested prior to making the incision to ensure adequate anesthesia. If high exposure is necessary, general anesthesia with nasotrachial intubation is performed to facilitate ear/nose/throat (ENT) assistance with subluxation of the mandible if needed.

EXPOSURE OF THE CAROTID ARTERY FOR ENDARTERECTOMY

Standard Approach

The standard skin incision for carotid exposure is approximately 12 to 15 cm long and is made parallel to the anterior edge of the sternocleidomastoid muscle (SCM) from the end of the

Abstract

This chapter provides descriptions of traditional and newer approaches to the cervical vessels, including the carotid artery, vertebral artery, and subclavian artery. Descriptions include high exposures of the carotid artery, access to various segments of the vertebral artery, and exposures for the resection of carotid body tumors. Mini-incisions as well as retrojugular and posterior approaches are some of the newer technical approaches described for carotid access.

Keywords

Carotid artery
subclavian artery
mini-incision
vertebral artery
carotid body tumor
exposures

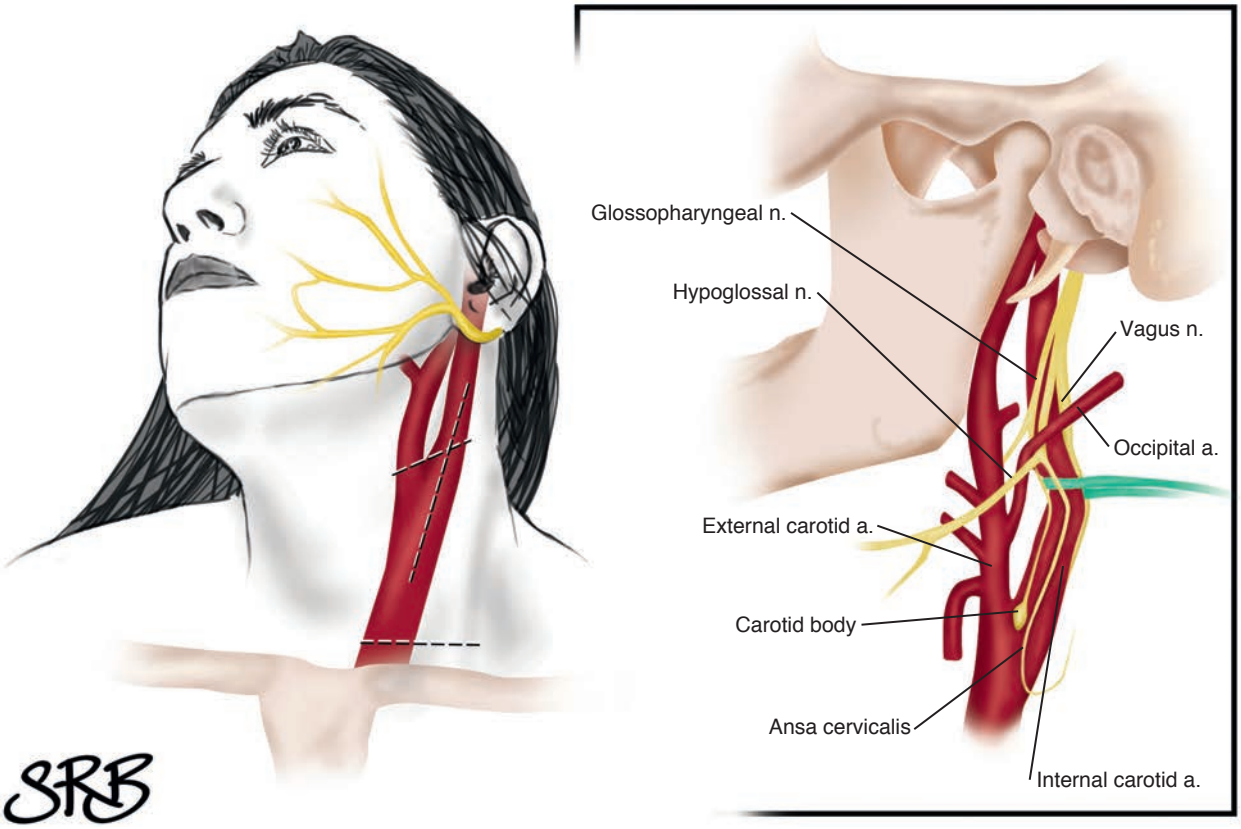

Figure 55.1 Incisions for standard carotid exposure, mini-incision carotid exposure, and subclavian artery exposure.

mastoid process to the medial end of the clavicle (Fig. 55.1). In recent years the much shorter incision over the carotid bifurcation as well as the transverse incision in the skin crease have become more popular, as both provide an adequate access to the bifurcation and to the internal and external carotid arteries.

1. Skin incision is made obliquely along the edge of the sternocleidomastoid, with both the standard and retrojugular approaches. At the level of the angle of the jaw, the incision is extended slightly more laterally to prevent injury to the parotid gland. Preoperative duplex can be utilized to identify the level of the carotid bulb and to decrease the length of incision needed.
2. Dissection is continued through platysma, typically with electrocautery. The external jugular frequently has to be divided. Several small nerves of the superficial cervical plexus may have to be divided, which may lead to areas of hypesthesia around the incision. The great auricular nerve may be visualized when the incision is high. The nerve should be protected if possible; if divided, it results in numbness to the ear lobe, which usually regresses within a few months. Care should be taken at the angle of the mandible to remain lateral to avoid dissection into the parotid gland. The dissection is continued through the tissues along the medial border of the sternocleidomastoid until the carotid sheath is encountered. During the dissection, a small sternomastoid branch of the superior thyroid artery usually has to be ligated; other small perforating vessels supplying the SCM can be divided with cautery. At this point one must avoid injury to the accessory nerve, which can be found at the superior aspect of the incision. Once the sternocleidomastoid has been retracted laterally, a Weitlaner or Henle retractor should be utilized to hold the tissues in place. If regional block is utilized, it is occasionally necessary to supplement with additional lidocaine at the carotid sheath.
3. The internal jugular vein is dissected along the medial border and retracted posteriorly. This maneuver requires division of the anterior facial vein (Fig. 55.2). Since the anatomy of the venous structures is quite variable, there may be a single vein or, alternately, two or three veins separately joining the internal jugular vein, in which case they must be separately ligated and divided. Usually the jugular vein is further dissected cephalad as far as the posterior belly of the digastric muscle. The connective tissue between the facial vein and the digastric muscle is rich in lymph nodes, which can be dissected from the vein and, if necessary, divided with cautery.
4. Next, after the vagus nerve in the space between the jugular vein and carotid artery is identified, dissection of the common carotid artery and its branches is performed. This often requires division of the ansa hypoglossi nerve. The common carotid is isolated first, using sharp dissection with attention given to protecting the vagus nerve as it encircles the vessel. Next, the internal carotid artery (ICA) is mobilized along the medial border of the internal jugular vein up to the

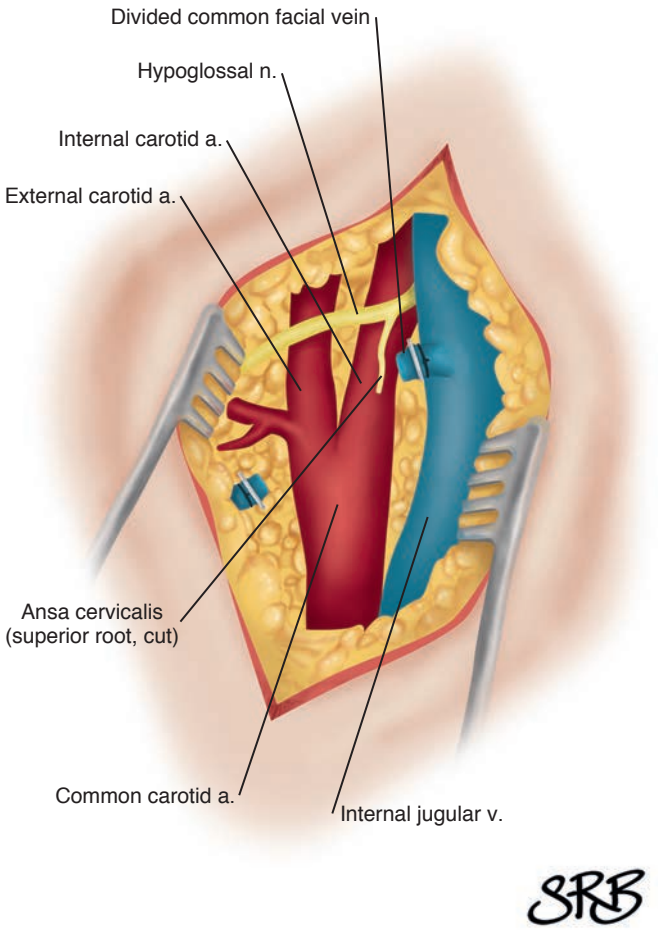

Figure 55.2 Traditional carotid exposure with division of facial vein and ansa cervicalis.

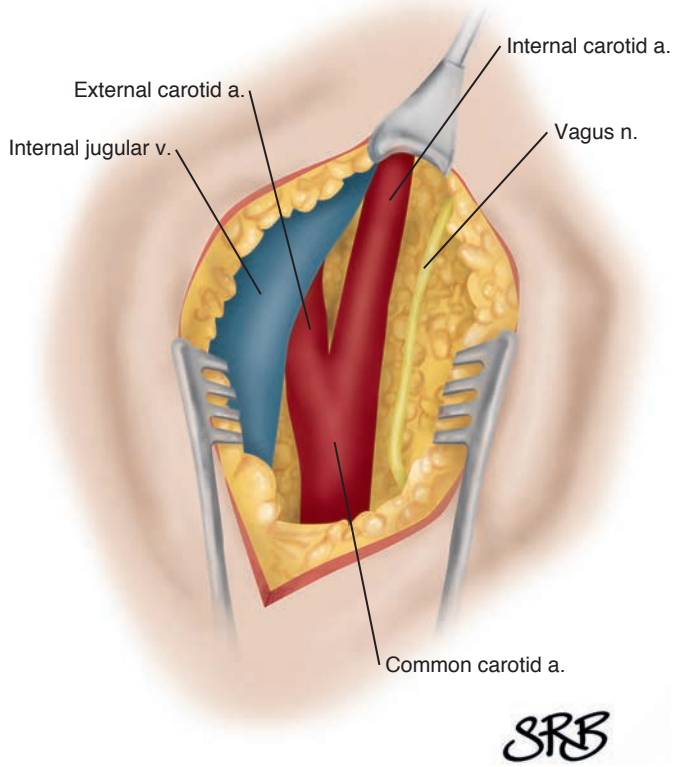

Figure 55.3 Retrojugular approach to carotid artery with medial rotation of internal jugular vein to expose internal carotid artery.

point where the vessel is completely normal. Usually small venous branches and the sternocleidomastoid branch of the occipital artery cross the ICA; once these vessels have been ligated and divided, the hypoglossal nerve can be mobilized cephalad. Finally, the external carotid artery is isolated at the bifurcation. It is important to encircle the artery close to the bifurcation to avoid injury to the superior laryngeal nerve, which runs behind the external carotid artery. The superior thyroid artery also requires dissection, particularly if it branches directly from the common carotid artery.

RETROJUGULAR APPROACH

With the standard approach, when bleeding occurs postoperatively, it is frequently venous, specifically related to the facial vein. The ICA is located more posteriorly with this approach, and it may be difficult to access more distal disease. The vagus nerve is also not well visualized during the standard approach, which can lead to clamp injuries. With the retrojugular approach, the ICA is anterior. Visualization of the external carotid artery (ECA) is slightly more limited, but the origin and superior thyroidal arteries are easily identified and controlled, with markedly better visualization of the ICA. There is no need for ligation or division of major venous structures, thus decreasing the potential for postoperative bleeding, and the ansa hypoglossi is also not divided.

1. Skin incision and initial approach are identical to the standard exposure. Once the sternocleidomastoid has been retracted and the carotid sheath exposed, the dissection diverges from the standard approach.
2. The sheath overlying the vessels is divided at the *lateral* border of the internal jugular vein. Once fully dissected, the vein is then retracted medially, using a blunt Weitlaner. Occasionally there may be small venous branches posteriorly that require ligation and division. The vagus nerve is visualized and left lateral to the carotid artery. This approach avoids division of the facial vein, ansa cervicalis, and the vascular bundle associated with the hypoglossal nerve, as all of these structures are retracted medially with the jugular vein. This approach allows greater visualization of the internal carotid artery (Fig. 55.3).
3. At this point, the dissection is the same as for the standard carotid approach, with mobilization of the ICA, ECA, and common carotid artery (CCA) for clamping as well as the superior thyroid artery. However, the vagus nerve has already been identified laterally and does not fall into the area of concern when encircling the CCA.
4. Carotid endarterectomy (CEA) is then performed in either standard fashion or with the eversion technique.
5. At completion of the procedure, after hemostasis has been verified, the jugular vein is allowed to return to its normal location, lateral to the artery, and the wound is closed in

the standard fashion with reapproximation of the platysma and subcuticular skin closure.

POSTERIOR APPROACH FOR CAROTID ENDARTERECTOMY

This technique has been described by Berguer. It allows exposure of the ICA, medial to the sternocleidomastoid, between the hypoglossal and vagus nerves.

1. The patient is placed prone/lateral with the contralateral arm placed under the head.
2. The incision is initially transverse, beginning at the occipital protuberance and extending to the mastoid process, where it is curved downward along the posterior border of the SCM for 2 to 3 cm.
3. The fibers of the trapezius, splenius capitis, semispinalis capitis, and longissimus capitis muscles are divided.
4. The greater occipital nerve, which is a dorsal ramus of C2 and courses over the semispinalis capitis muscle, may have to be divided.
5. At this point the internal jugular vein, carotid artery, and the accessory nerve are exposed.

PROXIMAL EXPOSURE FOR CAROTID ENDARTERECTOMY

More proximal control can be obtained of the CCA by division of the omohyoid muscle, and ligation of the associated vessels.

High Exposure

More distal exposure is also possible from the retrojugular or standard approach. This may be necessary for high lesions or reoperative surgery. The retrojugular approach will provide access to the artery to the level of the digastric belly without additional dissection of structures.

1. With the standard approach, more distal exposure may be obtained by mobilizing the hypoglossal nerve. This requires division of the sternomastoid artery and vein, which form a sling around the structure. This allows mobilization of the vessel up to the level where the vagus sheath joins the hypoglossal. Further dissection can also be performed above the level of the nerve, which can be gently retracted with a vein retractor or vessel loop.
2. For more distal exposure, the accessory spinal nerve should be identified as it enters the sternocleidomastoid; it can be followed proximally to the digastric, with care taken not to injure the nerve. To facilitate exposure, both the internal jugular (IJ) and the vagus nerve should be retracted medially, over the top of the carotid artery. The superior laryngeal nerve arises in this area and passes posterior to the ICA. Just above this level, the superior cervical sympathetic ganglion will be seen. Depending on the extent of exposure needed, the posterior belly of the digastric can be retracted or divided (Fig. 55.4). Such division should be done sharply to avoid thermal injury to the glossopharyngeal nerve, which would result in difficulty swallowing. Retraction can also result in nerve injury and should be performed cautiously. The nerve runs on top of the ICA and under the ECA and may present with either a single or double trunk. The muscle should be divided close to the attachment with the mastoid. If high access to the ICA is anticipated, this should prompt consideration for general anesthesia with nasotracheal intubation and preoperative consultation with ENT to allow for subluxation of the mandible if division of the digastric is insufficient (Fig. 55.5; see Chapter 91).

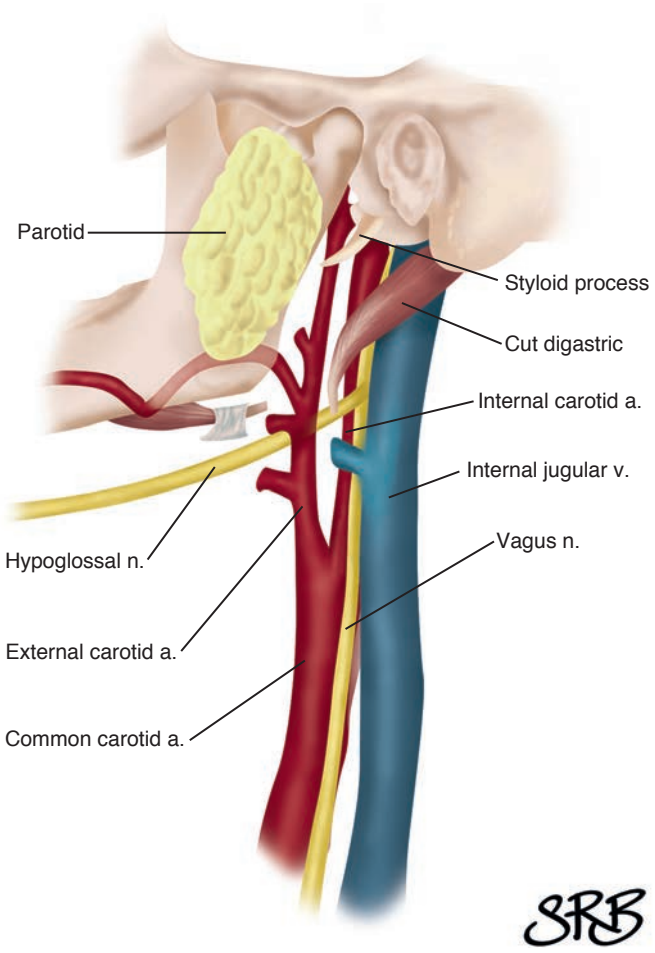

Figure 55.4 High exposure of internal carotid artery with division of digastric muscle.

Mini-Incisions for Carotid Endarterectomy

Short transverse and longitudinal incisions for eversion and standard patch endarterectomy have been popularized in the recent years. The outcome and operative time is generally the same as for standard, long incision.

Short Transverse Incision

Positioning is the same as for standard incision.

1. Duplex is recommended to identify and mark the skin at the carotid bifurcation before draping. If duplex is not used,

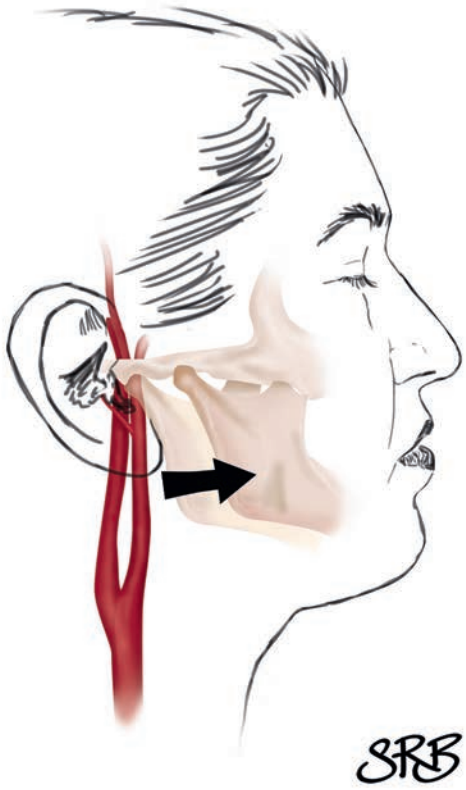

Figure 55.5 Subluxation of mandible for high carotid exposure.

the incision is made in the skin crease at the level of the upper margin of the cricoid medial to the sternomastoid muscle. The length of the incision is approximately 4 cm; it can be extended if exposure is inadequate.

2. After division of the platysma transversely, two self-retaining retractors are placed at 90-degree angles to each other and dissection is carried out in the same fashion as for the standard carotid exposure. Use of the self-retaining retractors allows exposure of up to 1.5 to 2 cm on each side of the carotid bifurcation.
3. Small bulldog clamps, which can be placed deep in the wound, allow the length of the exposed carotid arteries to be longer than the length of the skin incision both in the transverse and longitudinal mini-incision.

Longitudinal Mini-Incision of Skin

1. After appropriate positioning of the patient on the operating table and prior to prepping and draping, duplex is used to identify and mark on the skin the carotid bifurcation and the anticipated skin incision. Length of the incision depends on the depth and extent of the lesion and varies from 2.5 to 5 cm.
2. The dissection and approach to the carotid bifurcation is essentially the same as for the standard longitudinal incision. Use of two self-retaining retractors and skin laxity allow for traction and exposure of a longer segment of carotid arteries than the length of skin incision itself (see Fig. 55.1).

REOPERATIVE EXPOSURE FOR CAROTID STENOSIS

For intimal hyperplastic lesions occurring within the first 2 years of surgery, intervention is not indicated until the lesion is at least 80% or the patient is symptomatic. Lesions occurring late are treated in the same fashion as de novo atherosclerosis of the carotid artery. Morbidity of reoperative procedures is increased due to risk of cranial nerve (CN) injury from scarring, making the identification of critical structures more difficult. The surgeon must also be prepared to resect the involved segment and replace it with an interposition graft. Either autologous vein grafts, using the proximal great saphenous vein (GSV), or prosthetic grafts may be used.

The retrojugular approach may be preferred for reoperative procedures to decrease nerve mobilization and dissection and the ability to work in a field that has not previously been dissected. The surgeon should anticipate the need for more distal and more proximal exposures to an area of healthy artery.

EXPOSURE FOR SUBCLAVIAN CAROTID INTERVENTIONS

These interventions initially declined markedly in the era of endovascular intervention, with stenting of the subclavian or innominate arteries, but then there was a resurgence with the advent of TEVAR and the need for coverage of the left subclavian artery or additional great vessels with debranching procedures.

Transposition

1. The patient is placed supine, with a roll under the scapula transversely and the head averted toward the contralateral side, with care taken not to hyperextend the neck. A slight reverse Trendelenburg position is preferred. Both arms should be tucked.
2. A transverse incision is made one fingerbreadth above the clavicle, extending from medial to the lateral head of the SCM for about 6 cm (see Fig. 55.1). Superficial dissection includes division of the platysma and superficial cervical aponeurosis. The external jugular vein should be ligated and divided. The clavicular head of the SCM is usually divided but sometimes it can be retracted. The omohyoid is next divided. It is helpful to mobilize the internal jugular vein to facilitate both medial and lateral mobilization and exposure of various regions of the subclavian artery. The vein should be mobilized laterally to allow for visualization for transposition and access of the artery prior to the takeoff of the vertebral branch. On the left side, it is important to identify the thoracic duct, which can be ligated and divided if necessary. This structure passes over the subclavian artery and joins the internal jugular vein on the left. There may be one main duct or several smaller ducts. Right-sided thoracic ducts have been reported in patients with aberrant right subclavian arteries; care should be taken in patients with this anatomic

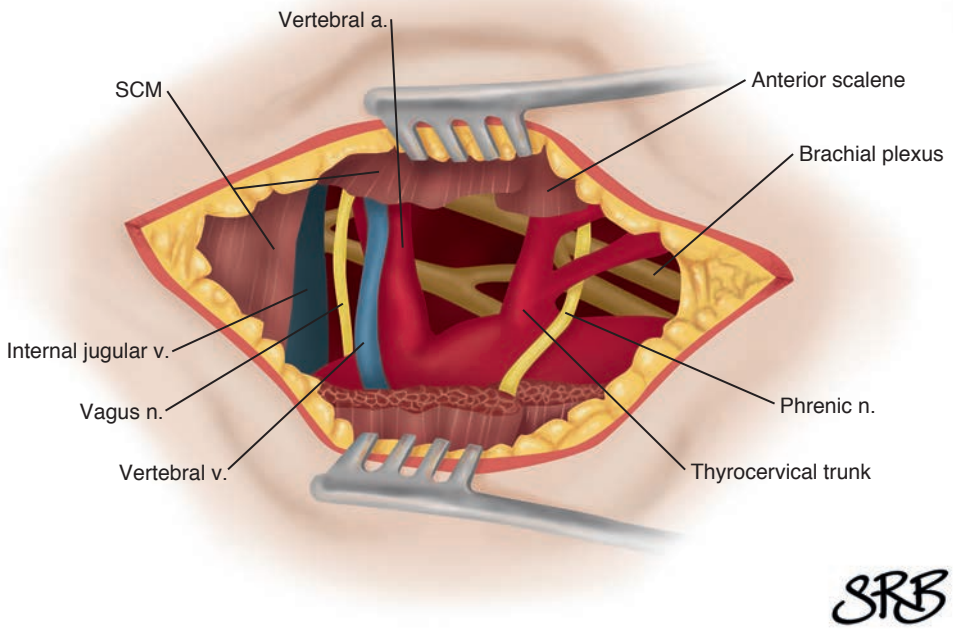

Figure 55.6 Traditional exposure of subclavian artery after division of anterior scalene muscle for carotid subclavian bypass. *SCM,* Sternocleidomastoid muscle.

variant to avoid injury. Inadvertent injury to the duct can lead to lymphatic leak, requiring reoperation. The sternal head of the SCM and subhyoid are retracted medially, as is the common carotid artery. The vertebral vein should be identified, ligated, and divided. The sympathetic ganglion or chain typically has fibers around the subclavian artery at this level just medial to the vertebral vein. Injury should be avoided if possible to prevent Horner syndrome. The vertebral artery superiorly and the internal mammary artery inferiorly should be controlled with vessel loops. At the more proximal aspect of the subclavian artery, the vagus, which crosses anteriorly, and the recurrent laryngeal nerve, which passes posteriorly to the subclavian, should be identified and preserved. The left subclavian artery is deeper than the right and can be slightly more difficult to access proximal to the vertebral artery. After adequate mobilization of the subclavian artery, the common carotid artery, which is in the medial portion of the field, is dissected to allow for a tension-free anastomosis and for adequate vascular control at the level of the subclavian artery. Care should be taken to avoid kinking the vertebral artery during transposition. It is also important to ensure complete hemostatic control of the subclavian stump prior to losing control of this segment as it retracts into the chest.

3. More proximal exposure of the subclavian artery can be gained by division and resection of the medial head of the clavicle. This facilitates exposure up to the junction with the carotid on the right. This is infrequently necessary today and is typically reserved for situations with hemorrhage, when endovascular maneuvers are insufficient or not available to control proximal bleeding. For right-sided proximal exposure of the subclavian artery, the incision can be extended to include a median sternotomy. This may require division of the innominate vein to facilitate full exposure of the more proximal subclavian and carotid arteries and the brachiocephalic trunk. On the left side, anterolateral thoracotomy can be performed to gain access to the origin of the left subclavian.

Subclavian Bypass

1. This dissection is similar to the supraclavicular approach for thoracic outlet syndrome (TOS). The incision is extended about 8 cm from the medial border of the clavicular head of the SCM one fingerbreadth above the clavicle. Superficial dissection is similar to transposition. The clavicular head of the SCM is divided. The scalene fat pad is mobilized inferiorly and medially and retracted superolaterally with a self-retaining retractor. The anterior scalene is next divided sharply after the phrenic nerve is first dissected; it is protected with a vessel loop. Electrocautery should be avoided to prevent thermal injury to the brachial plexus and surrounding nerves. The muscle should be divided as close to the insertion on the first rib as possible. The subclavian artery lies immediately beneath the anterior scalene. The thyrocervical trunk is typically visible and can be divided if necessary or controlled with vessel loops (Fig. 55.6). This exposure provides an adequate length of vessel for bypass with proximal control distal to the vertebral and mammary arteries.

VERTEBRAL ARTERY EXPOSURE

Traditionally, the vertebral artery has been exposed in four segments, a classification proposed by Berguer. The proximal

V1 segment involves vertebral artery from its origin at the subclavian artery to the point where it enters C6 transverse process. The V2 segment lies in the transverse process of C6 to C2 and is seldom exposed primarily for control of hemorrhage. V3 segment is between C2 and the base of the skull before the artery enters foramen magnum. The V4 segment is intracranial and begins at the atlanto-occipital membrane and terminates at the level where the vertebral arteries merge to form the basilar artery.

Exposure of the V1 Segment of the Vertebral Artery

Two approaches to exposure of V1 segment have been described. The more common supraclavicular approach is frequently used for transposition of the vertebral artery into the CCA. This approach allows the exposure of the origin of the vertebral artery but requires transection of the SCM and limits exposure of the distal V1 segment. In contrast, the anterior cervical approach does not require muscle transection and allows access to more distal V1 segment.

Supraclavicular Approach

1. The patient is placed supine, with the head turned away from the surgery site.
2. A transverse incision is made a fingerbreath above the clavicle, beginning at its head and extending laterally for 6 to 8 cm.
3. The platysma muscle, superficial fascia, and external jugular vein are divided.
4. Dissection is carried out between the two bellies of the SCM.
5. Alternatively, the clavicular head of the SCM may be divided, followed by division of the omohyoid muscle.
6. The internal jugular vein is then identified, dissected free on the medial aspect, and retracted laterally.
7. Subsequently the vagus nerve is identified and retracted either medially with the common carotid artery or laterally with the JV. The dissection is carried upward and downward between the JV, the subclavian vein, and the carotid artery.
8. On the left side, the thoracic duct is identified and divided between two ligatures. The dissection is medial to the prescalene fat pad that covers the phrenic nerve. On the right side large lymphatic channels may be identified; this is not uncommon. In such cases these channels should be ligated to avoid lymph leakage.
9. The inferior thyroid artery, which runs transversely, is ligated and divided. Subsequently the vertebral vein is identified. It often has some small branches that have to be controlled. The vertebral vein should be ligated and divided in its proximal aspect (Fig. 55.7).
10. At this point, the vertebral artery and sympathetic ganglion are easily identified in the center of the angle formed by the anterior scalene and longus colli muscles. The ganglion should be dealt with carefully to avoid a Horner syndrome. The vertebral artery should be dissected free from

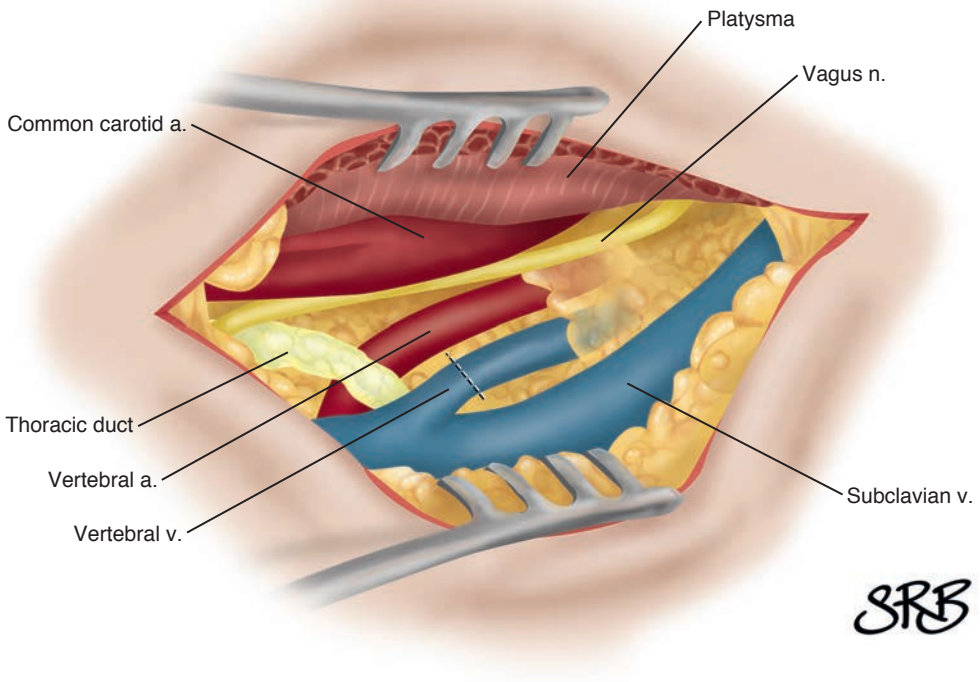

Figure 55.7 Supraclavicular approach to V1 segment of vertebral artery demonstrating overlying vertebral vein and thoracic duct.

sympathetic fibers and encircled with a vessel loop. This then allows for intervention on the V1 segment.

Anterior Cervical Approach

1. The positioning is the same as for the supraclavicular approach.
2. A vertical incision is made from the clavicular head up to the retromandibular area, on the anterior border of the SCM; the dissection is similar to that of standard carotid artery exposure.
3. The superior belly of the omohyoid muscle is often divided. The vagus nerve as well as sympathetic chain should be identified and protected.
4. In the lower aspect of the incision, the scalene fat pad is identified and retracted laterally, exposing the anterior scalene muscle and phrenic nerve.
5. The inferior thyroid artery should be ligated and divided, exposing the vertebral artery. The entire extraosseous vertebral artery (V1 segment) can be easily exposed to the level where it enters the transverse process of C6.

EXPOSURE OF THE V2 SEGMENT OF THE VERTEBRAL ARTERY

Exposure of the V2 segment is usually performed for bleeding control and has become less common in the endovascular area. Since the V2 segment runs through the forearm tranversaria, direct access is possible only by unroofing the transverse process. The exposed vertebral artery in the V2 segment is surrounded by a network of veins referred to as the vertebral transverse sinus. Injury to this vein system adherent to the adventitia and periosteum may lead to significant blood loss.

1. The incision is the same as that used for the anterior cervical approach to the V1 segment and extends from the clavicular head to the mastoid process.
2. The platysma muscle is divided and the SCM is retracted laterally to expose the carotid sheath.
3. Larynx, pharynx, and carotid sheath are dissected free from the prevertebral fascia and retracted medially, exposing the sympathetic ganglia and the anterior longitudinal ligament.
4. The ganglia are preserved and the ligament is incised vertically for the entire length of the incision.
5. The ligament is retracted laterally exposing the prevertebral fascia, longus colli, and longus capitis muscles, which are removed with a periosteal elevator from the transverse processes. In order to prevent cervical nerve injury, it is important to not extend the dissection beyond the lateral border of the transverse processes.
6. Access to the vertebral artery in the bony canal is obtained by carefully removing the anterior arch of the transverse process with a rongeur.

Exposure of the Atlantoaxial (V3) Segment of the Vertebral Artery

Access to V3 segment has been used for bleeding control resulting from traumatic injuries to the distal vertebral artery as well as to create the distal anastomosis in vertebral bypasses. Today exposure of V3 is rarely used since many of vertebral artery pathologies are treated with transcatheter techniques. At this level, the vertebral artery is fragile and susceptible to traumatic injury. In addition, the artery is encircled by the periarterial venous plexus. Thus it is recommended to dissect the artery at the subadventitial level.

1. The positioning of the patient is similar to that for carotid exposure, although some authors recommend a semiseated position to reduce venous pressure in the neck.
2. The vertical incision is carried on along the anterior aspect of the SCM from the level of the cricoid and curved posteriorly beneath the earlobe to cross over the mastoid. The platysma muscle is divided and the dissected carotid sheath is retracted medially and SCM laterally.
3. Partial or complete transection of the SCM at its origin significantly improves the exposure.
4. It is imperative to identify and preserve the spinal accessory nerve, which enters the sternocleidomastoid approximately 2 to 3 cm below the mastoid tip. The nerve should be retracted anteriorly and the transverse process of the first cervical vertebra identified by palpation. The C1 transverse process serves as the point of attachment for the levator scapulae, splenius cervicalis, and inferior oblique muscle, covering the interspace between C1 and C2, where an approximately 2-cm segment of the vertebral artery is readily accessible.
5. These three muscles are carefully divided, paying attention to avoid injury to the anterior ramus of the C2 nerve root, which lies on the anterior border of the levator scapulae muscle. In order to avoid nerve injury, the muscle division is performed over a right-angled clamp or small retractor, which is inserted between the C2 nerve and the muscles.
6. To increase exposure of the intertransverse space and vertebral artery, the cephalad muscle fibers are resected and the lower end of the divided muscle is either resected or retracted inferiorly.

POSTERIOR EXPOSURE OF THE SUBOCCIPITAL VERTEBRAL ARTERY (V4) SEGMENT

This technique, as described earlier for posterior carotid exposure, can also be used to treat dissections or aneurysms involving the most distal segment of the extracranial vertebral artery.

1. The patient is placed in the prone/lateral position with the contralateral arm placed under the head, with the incision as previously described for the posterior approach to the carotid.
2. Once the internal jugular vein and the accessory nerve are exposed, further dissection requires ligation and division of the condyloid emissary vein.
3. This is followed by partial division of the rectus capitis posterior muscle, allowing exposure of the vertebral artery, which is covered by a large venous plexus.

The overlying veins must be dissected away from the artery, which requires meticulous technique. Eventually the vertebral

artery can be dissected to the level of the atlanto-occipital membrane.

Exposure for Carotid Body Tumors

The major risk of intervention for carotid body tumors is injury to CNs (see Chapter 95).

Preoperatively, the diagnosis is made by duplex, CTA, or magnetic resonance angiography (MRA) assessment. Typical imaging demonstrates splaying of the carotid arteries with a highly vascularized tumor. The blood supply is primarily from the external carotid artery. For patients with very large tumors, preoperative embolization can be performed the day prior to decrease the size and potentially the bleeding from the tumor.

1. As with all cerebrovascular approaches, a roll is placed under the shoulders to allow for neck extension. The head is turned away from the operative side. The area is widely prepped, including the ear.
2. There are two possible incisions, depending on surgeon preference: The typical transverse incision or the C-shaped incision, which is more cosmetically appealing.
3. The platysma is raised as a flap.
4. After identifying the SCM and reflecting laterally, lymph nodes should be examined and sent for pathologic evaluation if any concern exists for metastatic disease.
5. The vagus nerve should be identified and protected.
6. Vascular control should be obtained of the common carotid, the external carotid above the tumor, and the internal carotid artery with vessel loops. Proximal ECA branches should be identified and controlled and may require ligation.

Size of the Tumor Determines Further Dissection

In the case of small tumors, such as Shamblin I, the ansa cervicalis is divided, as in a typical anterior approach to the carotid bulb. The tumor is dissected with bipolar electrocautery. The dissection is best started at the external carotid level. This allows one to devascularize the tumor from the external carotid artery branches supplying it. Any vessels identified as directly feeding the tumor are ligated and divided. Typically there is a major feeding vessel at the base of the bifurcation. Gentle tension on the tumor typically allows for better visualization of the plane between tumor and vessels. Care should be taken not to injure the hypoglossal nerve, which can be mobilized by division of the vascular bundle, and the superior laryngeal nerve, which is typically posterior to the tumor and close to the superior thyroid artery.

For Shamblin II tumors—which is defined as partially encompasing the vessels , and Shamblin III tumors—defined as encasement and vessel adherence, the approach is described below. Preoperative embolization can be helpful in decreasing bleeding for these patients. Patients should also be prepped with consideration of an interposition vein bypass. The great saphenous vein is typically utilized if of adequate size and should be mapped prior to surgery. Consideration should be given to ligation and even division of the ECA if needed to facilitate dissection. Only the periadventitial plane should be dissected if bypass is to be avoided. If the tumor invades the media, resection with bypass will be required. Cranial nerve transection may be necessary for larger tumors and should be discussed with the patient prior to surgery. The hypoglossal is typically tented over the tumor. The tumor can then be shaved off the bifurcation using bipolar electrocautery for the vast majority of lesions. With larger tumors, division of the digastric muscle is frequently necessary and should be approached as described previously.

Knowledge of the location and function of the CNs is critical to the exposure and surgery of a carotid body tumor (CBT) (see Chapter 91). The hypoglossal (CN XII) exits the skull from the hypoglossal canal, and runs between the internal jugular and the internal carotid arteries. It then runs medially over the ECA and ICA. Typically it is seen crossing about 2 cm above the carotid bifurcation.

The vagus nerve, CN (X) is posterolateral to the ICA, between the carotid and internal jugular vein. It joins the hypoglossal when followed cranially.

The superior laryngeal nerve lies posterior to the carotid arteries, frequently in direct communication with the tumor and adjacent to the superior thyroid artery.

The spinal accessory nerve (CN XI) and glossopharyngeal nerve (CN IX) run close to the base of the skull and are at risk for injury when division of the digastric is required. The spinal accessory runs over the distal ICA but behind the stylohyoid and then enters the SCM. The glossopharyngeal also crosses anterior to the ICA and to the jugular vein.

The marginal mandibular branch of the facial nerve (CN VII) runs along the masseter and can be injured with retraction.

TIPS

Awareness of CN location will decrease CN injury.

Bipolar electrocautery minimizes risk of thermal nerve injury and decreases blood loss.

Preoperative embolization should be considered for larger tumors but should be done in close proximity to the surgery, typically 1 day prior, to prevent development of new collateral vascularity to the tumor.

CHAPTER 56

Lower Extremity Arterial Exposure

FRANK B. POMPOSELLI Jr., SCOTT PRUSHIK, and KATE SHEAN

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INTRODUCTION

Operations involving the arteries and veins of the lower extremity are among the most frequently performed open vascular surgical procedures in clinical practice. Having good familiarity with both the usual and alternative surgical exposures used in the lower extremity should be part of every vascular surgeon's repertoire. Typically, exposure is made through linear, vertical incisions placed directly over the arterial or venous segments in question (Fig. 56.1). In bypass procedures done for treatment of intermittent claudication, femoral endarterectomy, profundaplasty, and when embolectomy or thrombectomy is done for acute limb ischemia, exposure is usually confined to the femoral artery in the groin and the medial approach to the popliteal artery above or below the knee. Not surprisingly, these are by far the most commonly employed exposures, familiar to all vascular surgeons. However, in procedures done for critical limb ischemia and in reoperative surgery, exposure of the more distal crural and pedal

Abstract

Operations involving the arteries and veins of the lower extremity are among the most frequently performed open vascular surgical procedures in clinical practice. Having good familiarity with both the usual and alternative surgical exposures used in the lower extremity should be part of every vascular surgeon's repertoire. This chapter describes the common and infrequently used exposures used in the lower extremity.

Keywords

Exposure
vascular surgical
lower extremity

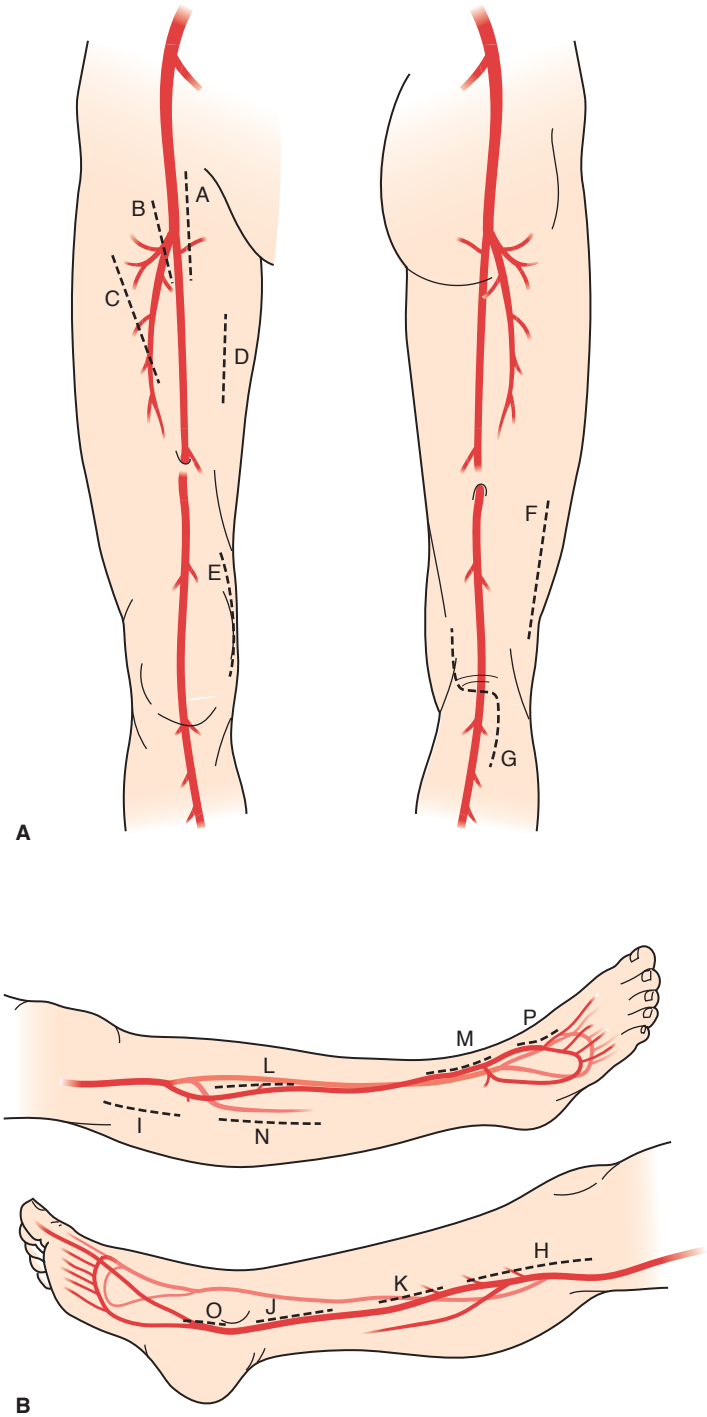


Figure 56.1 (A) Location of the vertical incisions to expose the arteries in the thigh: common femoral, deep femoral, superficial femoral, and popliteal arteries (B) and in the calf: popliteal, tibioperoneal trunk, anterior tibial, posterior tibial, and dorsalis pedis arteries. (Figures 67 and 68 from Rutherford RB. *Atlas of Vascular Surgery: Basic Techniques and Exposure*. Philadelphia: WB Saunders; 1993:114 and 115.)

vessels is frequently required. Moreover, in procedures done for or in the presence of infection, in obese patients, in many redo operations, and those performed for traumatic injury, it may be necessary to use incisions or exposure techniques not frequently employed in everyday practice.

Regardless of the exposure employed, we have found the following general principles to be critical:

Make an incision of adequate length—do not compromise exposure

Use self-retaining retractors whenever possible

Have a sterile continuous-wave Doppler probe available

Make liberal use of the cautery for dissection except in close proximity to adjacent nerves

Ligate all transected lymphatics

Ensure meticulous hemostasis

Adhere to the basic principles of traction/countertraction, bloodless field, meticulous blunt and sharp dissection as close to the artery as possible, obtain proximal and distal control with enough space to perform an anastomosis comfortably, avoid clamping or crushing of heavily calcified segments whenever possible.

Vein conduits should be handled gently and carefully; poorly prepared veins result in inferior outcomes.

Ensure good lighting and make use of magnification when anastomoses are being constructed.

FEMORAL ARTERY EXPOSURE

The common femoral artery (CFA) is located deep to the inguinal skin fold as a continuation of the external iliac artery as it passes beneath the inguinal ligament. It lies medial to the femoral nerve and lateral to the common femoral vein. The femoral neurovascular bundle is contained within the femoral sheath, which is formed by elements of the iliac, pectineus, and transversalis fascia in the femoral triangle.[1] The femoral triangle is covered by the tensor fascia lata and bound by the adductor longus muscle medially and the sartorius muscle laterally. The CFA bifurcates into the superficial femoral artery (SFA) and profunda femoris or deep femoral artery (DFA).

Common Femoral Artery—Longitudinal Approach

The CFA is usually exposed through a longitudinal incision over the femoral pulse just distal to the inguinal ligament. If no pulse is present, the artery is usually still palpable as a firm, cylindrical mass slightly medial to the midpoint of the inguinal ligament. The incision should be extended proximally to expose the inguinal ligament. The length of the incision varies based on the patient's body habitus and the extent of atherosclerotic disease, but typically about one-quarter to one-third of the incision should extend proximal to the ligament and the remainder distally. In very obese patients with a large overhanging pannus, it is important to identify the exact location of the inguinal ligament prior to making an incision. Often it is much more proximal than it may appear, making it possible to keep the distal end incision proximal to the fold in the pannus, which avoids the troublesome wound separation that invariably occurs when a vertical incision needlessly crosses this point. The subcutaneous tissue should be divided directly over the artery to avoid the creation of a medial or lateral flap, which can also lead to troublesome and occasionally

disastrous problems with wound healing. Any small venous or arterial branches of the superficial epigastric and superficial circumflex artery encountered should be ligated and divided. The authors also routinely ligate any divided lymphatics to minimize lymphatic leaks. The saphenous vein typically lies medial to the artery but is often encountered. Care should be taken to extend the dissection lateral to its course to prevent its injury.

The fascia lata lies deep to the subcutaneous tissue and is divided medial to the medial edge of the sartorius muscle over the artery to enter the femoral sheath. Most commonly, exposure will extend to the inguinal ligament. If more proximal exposure is needed, the inguinal ligament can be mobilized and retracted superiorly to increase visibility. Additional exposure can be obtained by dividing the ligament, which must always be repaired at the time of closure. If extended exposure of the proximal SFA is needed, the sartorius muscle can be mobilized and retracted laterally. The DFA typically arises somewhat lateral and posterior to the CFA (see further on). Care must be taken to avoid straying too far posterior and lateral to the CFA, which would risk injury to the femoral nerve. Medially, the common femoral vein is in very close proximity and not uncommonly adherent to the CFA. Careful sharp dissection is required to avoid its injury, especially in redo dissections.

Common Femoral Artery—Transverse Approach

The transverse approach is useful provided that only limited arterial exposure is needed, as for femoral embolectomy or a cutdown for endovascular aneurysm repair (EVAR). It begins with a horizontal skin incision 2 fingers' breadth above to the groin crease, parallel to the inguinal ligament. Once the incision has been made, it is deepened through subcutaneous tissue and Scarpa's fascia until the inguinal ligament is encountered. The ligament should be freed and mobilized to allow retraction superiorly. The dissection is deepened directly over the femoral pulsation until the femoral sheath is encountered, which is then incised longitudinally to expose the CFA. Self-retaining retractors are essential for adequate exposure. Although most of the CFA can usually be exposed through this approach, it provides only limited access to the superficial and deep femoral arteries.

Deep Femoral Artery—Conventional (Proximal) Approach

The DFA originates approximately 2 to 5 cm distal to the inguinal ligament and has a lateral course relative to the CFA in most patients. Exposure of the DFA begins with longitudinal exposure of the CFA, as previously described. As the CFA is exposed distal to the inguinal ligament, the origin of the DFA is usually encountered on the lateral or posterior lateral side of the CFA at the point where the CFA caliber becomes noticeably smaller as it bifurcates into the DFA and SFA. In most cases a few centimeters of the DFA can be exposed before the lateral femoral circumflex vein is encountered (Fig. 56.2); it crosses over its anterior surface and must be carefully divided and suture-ligated for additional exposure. Further dissection may require division of other crossing veins and lateral retraction of the sartorius muscle. Lymphatics are often encountered in extended exposure of the PFA and should be ligated. The femoral nerve is in close proximity and care should be taken to avoid its injury. The length of the proximal profunda varies in length from a few to as many as 8 cm. Branch points and bifurcations increase in frequency with more distal exposure. Both the medial and lateral circumflex arteries most commonly originate from the DFA, although either or both can originate from the CFA, usually near the DFA origin; they may be injured during careless posterior dissection of the CFA or DFA.

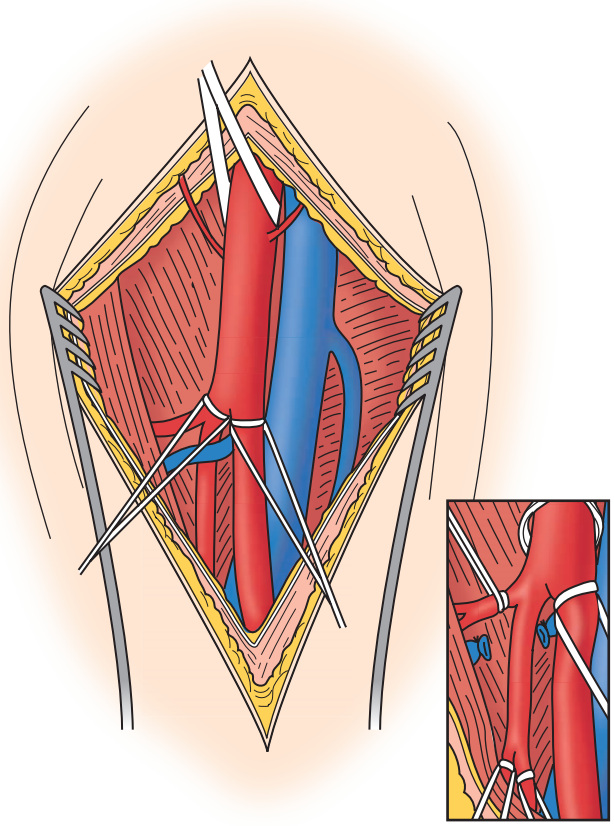


Figure 56.2 The proximal deep femoral artery origin is typically identified as a posterolateral branch of the common femoral bifurcation. Additional exposure is obtained by extending the vertical incision to expose the lateral femoral circumflex vein, which is divided where it crosses over the deep femoral artery. (Figure 71 from Rutherford RB. *Atlas of Vascular Surgery: Basic Techniques and Exposure*. Philadelphia: WB Saunders; 1993:123.)

Deep Femoral Artery—Lateral (Distal) Approach

The lateral approach to the DFA is useful in reoperative surgery as an alternative source of either inflow or outflow when the more proximal femoral vessels are encased in dense scar and/or infection or when a more distal inflow site is needed in the case of limited venous conduit.[2,3] The incision is made parallel to the course of the sartorius muscle usually 6 or 7 cm distal to the femoral pulsation or just distal to the end of a previous femoral

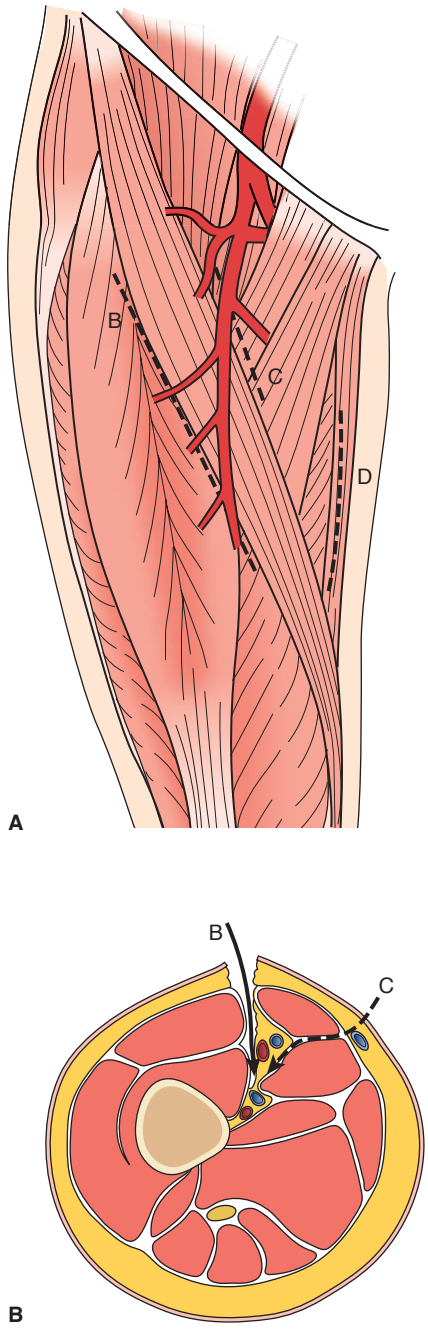


Figure 56.3 (A) The distal deep femoral artery can be approached from either medial or lateral to the sartorius muscle, depending on the course of the bypass. (B) In both cases, the dissection is performed lateral to the superficial femoral vessels. (Figure 73A and B from Rutherford RB. *Atlas of Vascular Surgery: Basic Techniques and Exposure*. Philadelphia: WB Saunders; 1993:128-129.)

incision. It can be placed on either the medial or lateral side of the sartorius depending on the situation and the likely course of the bypass graft; for example, lateral for a profunda-anterior tibial or axillary-profunda graft or medial for a femoral-profunda or profunda-popliteal graft (Fig. 56.3). Regardless of the chosen incision, approaching the distal PFA requires dissection lateral to the superficial femoral vessels and adjacent nerves, which can be easily injured with retraction, especially when Gelpi or sharp-toothed Weintlander retractors are being used. The dissection continues deep to the superficial femoral vessels in a plane between the vastus medialis and adductor longus muscles (Fig. 56.4). Usually a raphe created by the intersecting fibers of the fascia of these muscles is encountered, which, when opened, exposes the underlying deep femoral vein. The artery is usually found deep to the vein. In difficult cases, a handheld Doppler probe is useful for identifying the location of the artery.

Superficial Femoral Artery Exposure—Proximal Approach

The SFA is lies in a plane deep to the sartorius muscle, crossing over the adductor longus muscle. The proximal SFA is easily exposed by distal extension of the longitudinal incision made for exposure of the CFA. The SFA is located under the proximal sartorius muscle, which can be mobilized and retracted laterally. It can also be exposed in this fashion without exposing the CFA or DFA with a more distal incision placed along the anterior edge of the sartorius muscle (see later).

Superficial Femoral Artery Exposure—Mid-/Distal

The SFA follows a course between the anterior and medial compartments of the thigh in an aponeurotic tunnel, the adductor (Hunter) canal, created by components of the investing fascia of the vastus medialis, sartorius, and the adductor longus muscles.[1,4] In addition to the SFA, the Hunter canal contains the superficial femoral vein deep to the artery and two branches of the femoral nerve: the sensory saphenous nerve and the motor nerve to the vastus medialis muscle. To approach the SFA, the patient is placed with the leg externally rotated and the knee flexed to 30 degrees. A longitudinal incision is then made parallel to the anterior border of the sartorius to avoid disrupting the blood supply to the muscle, which enters on its inferomedial edge. The incision is carried down to the fascia lata, which is incised to expose the sartorius muscle. The muscle is then reflected in a posterior direction to reveal the roof of the Hunter canal. The fascia is opened to expose the SFA and vein. The vessels are often densely adhered to one another requiring careful dissection to separate them. Typically several large branches of the vein are encountered crossing over the artery, which should be divided. The SFA, even when widely patent on imaging, usually has some degree of atherosclerosis and is often calcified. In the authors' experience, the surgeon should be prepared to extend the initial exposure either proximally or distally to find the most suitable area for clamping and/or placing an anastomosis.

POPLITEAL ARTERY EXPOSURE

Anatomy

The popliteal artery is the extension of the SFA across the knee. It courses from the adductor hiatus at its superior border to

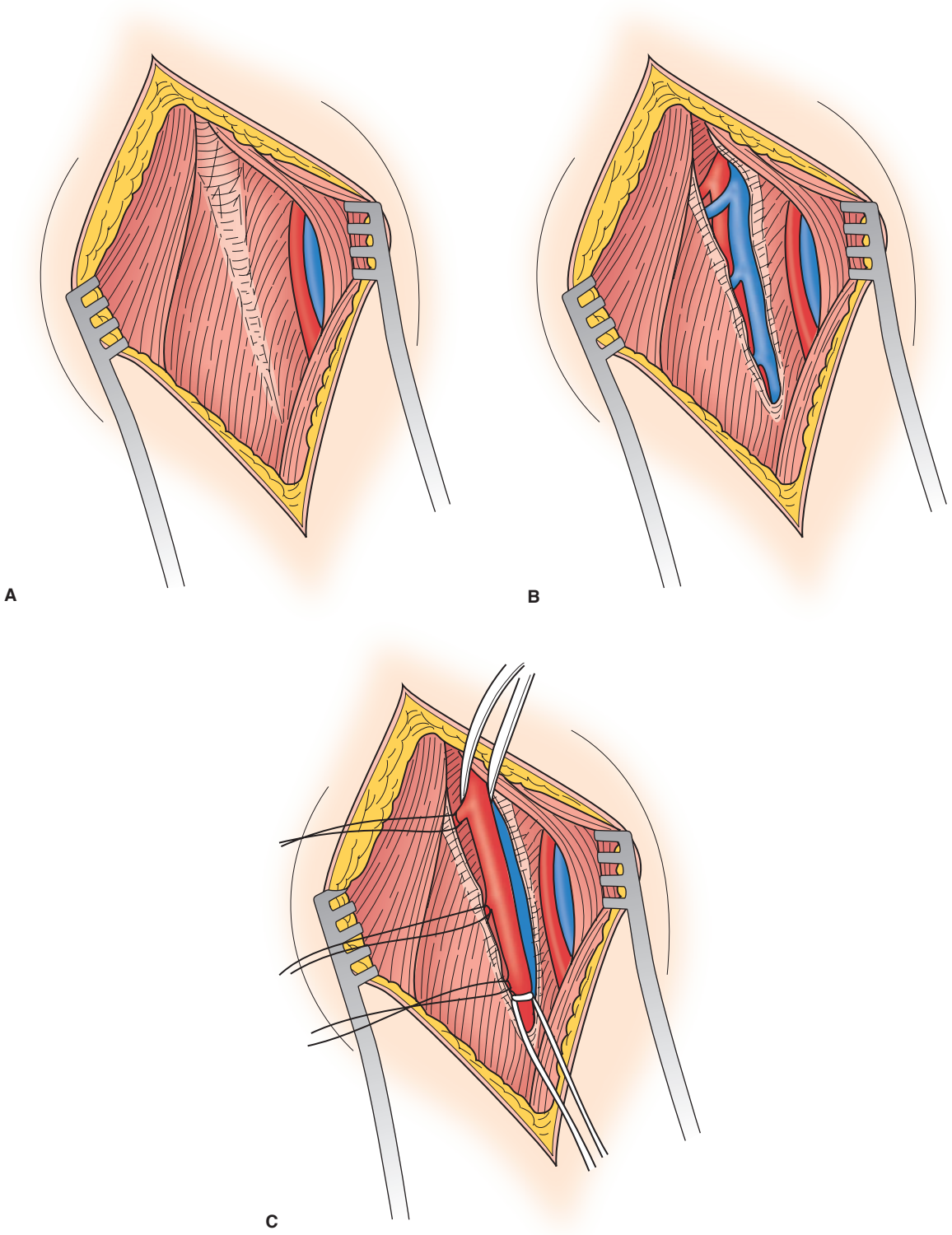


Figure 56.4 (A) There is a raphe formed by the intersecting fibers of the vastus medialis and the adductor longus muscles, which is divided to reveal the (B) deep femoral vessels with the vein lying superiorly. (C) The artery is dissected free from the vein with careful attention paid to the fibers of the femoral nerve. (Figure 73C to E from Rutherford RB. *Atlas of Vascular Surgery: Basic Techniques and exposure*. Philadelphia: WB Saunders; 1993:128-129.)

the popliteus muscle at its inferior border.[1,4] It is important to understand the relationships of the muscles, nerves, fascia, and arteries to perform adequate exposure for safe arterial reconstruction. The vessels are encased in a connective tissue sheath and are loosely adherent to the tibial nerve. The entire neurovascular bundle is enclosed within the fat pad of the popliteal space, which can be quite bulky and extensive, especially in obese individuals. The popliteal artery gives rise to several small arteries around the knee joint that form important collaterals with the DFA.

SUPRAGENICULATE POPLITEAL

Medial Exposure

The patient is placed supine with the leg externally rotated on a bump at the level of the knee. The incision is made in the distal third of the medial thigh along the anterior border of the sartorius muscle at the lower edge of the vastus medialis. Alternatively, the incision is made through the bed of the saphenous vein harvest incision, which results in a slightly more posterior approach. The fascia lata is incised and the sartorius muscle is retracted posteriorly. The deep fascia should be incised slightly inferior to the edge of the vastus medialis muscle. A small artery and vein is often encountered as well as a branch of the saphenous nerve. The artery and vein should be divided but the nerve can often be spared. Upon entering the popliteal space, the popliteal fat pad is encountered. The dissection commences in this envelope of fat in close proximity to the posterior aspect of the femur. The artery is usually firm or calcified and easily palpated even in the absence of a pulse. In obese patients the fat pad is thicker and more extensive and the artery can be difficult to find. In this case, palpation of the firm mass of the adductor magnus tendon is a good reference point, since the artery pierces the tendon to enter the popliteal space and is easily found at its edge. It should be encircled with a vessel loop or tape and placed on some traction by attaching the loop to a self-retaining retractor, which greatly facilitates its exposure, especially during the creation of an anastomosis. The popliteal artery is usually encountered anterior and medial to the vein, which is often paired, with multiple bridging veins across the popliteal artery that must be divided. Like the SFA, this artery is often heavily calcified and rarely free of some degree of atherosclerotic disease. Finding the best place for clamping may require exposure of the entire segment from the adductor hiatus to the point where it crosses under the medial head of the gastrocnemius muscle.

Lateral Exposure

The leg is internally rotated and the knee is flexed. The incision is made in the distal third of the lateral thigh between the iliotibial tract and the biceps femoris muscle. The fascia lata is incised posterior to where the iliotibial tract joins the lateral intramuscular septum. The popliteal space is entered between the short head of the biceps femoris muscle and the lateral femoral condyle. The neurovascular bundle can be palpated in the popliteal fat pad. The popliteal vein, which is located lateral to the artery, is usually encountered first (Fig. 56.5). When dissecting the popliteal artery free from the popliteal vein, careful attention must be paid so as not to injure the common peroneal nerve.[2]

MIDPOPLITEAL

Posterior Approach

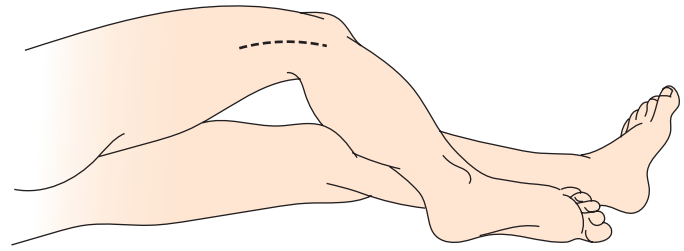
The posterior approach to the popliteal artery is especially useful in the repair of popliteal aneurysms[5-7] or for diseases confined to the midpopliteal artery, such as adventitial cystic disease.[8] The patient is placed prone on the operating table with the foot and ankle resting on a pad to slightly flex the knee. An S-shaped incision is chosen to avoid scar contracture across the posterior knee joint. The incision is made from the posterior medial aspect of the thigh across the skin crease and down the posterior lateral leg. The small saphenous vein is identified in the subcutaneous tissue; it can be ligated or dissected free and retracted to expose the deep fascia. The deep fascia is then incised vertically and the sural nerve retracted laterally. The tibial nerve is the most superficial of the neurovascular structures and should be retracted laterally along with the common peroneal nerve, which runs along the biceps femoris tendon. This will expose the popliteal vessels, which lie medial and deep to the nerves (Fig. 56.6). To facilitate distal exposure, the medial and lateral heads of the gastrocnemius muscle are retracted apart. The popliteal artery lies slightly deep and medial to the vein and can be readily dissected free.

The midpopliteal artery can also be exposed from the medial approach through an extended incision by dividing the tendinous attachments of the medial head of the gastrocnemius and sartorius muscles. These are best reattached with heavy-gauge sutures during closure.

INFRAGENICULATE POPLITEAL

Medial Exposure

The patient is placed in the supine position with the knee flexed, using a bump under the thigh. The incision starts at the knee joint, one finger breadth inferior to the medial border of the tibia, which is usually superior to the course of the great saphenous vein. The vein should be identified to avoid inadvertent injury. When the saphenous vein is planned for conduit, it should be mobilized first and the resulting incision used to expose the artery. The crural fascia is then incised to enter the popliteal space. At the proximal end of the incision the semimembranosus tendon is encountered; it can be divided to facilitate exposure. The medial head of the gastrocnemius is retracted posteriorly to reveal the neurovascular bundle, which lies under the medial edge of the tibia. The first structure encountered is the medial branch of the paired popliteal veins. The artery is then dissected circumferentially and encircled with vessel loops or tapes to elevate it into the incision.



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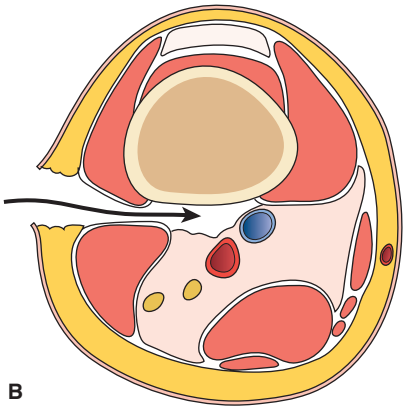

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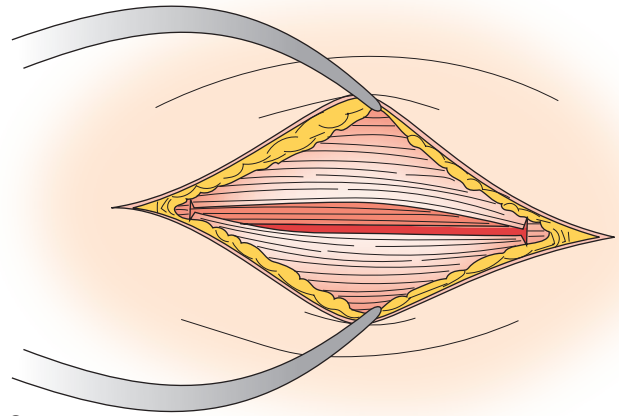

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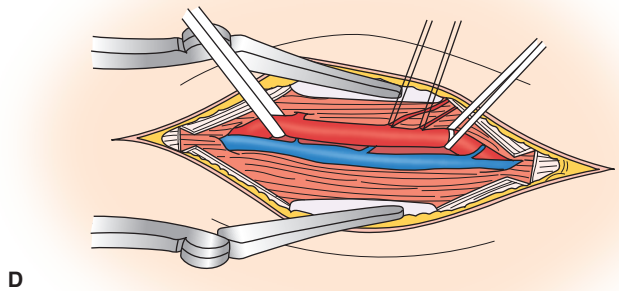


D

Figure 56.5 (A) With the leg internally rotated and the knee flexed, the incision is made in the distal third of the thigh between the iliotibial tract and the biceps femoris muscle. (B) The popliteal space is entered between the short head of the biceps femoris and the lateral condyle of the femur. (C) A cruciate incision is made through the tough fibers of the iliotibial tract to facilitate retraction. (D) The femoral vessels are identified in the popliteal fat pad and the artery is dissected free. ([A] Figure 17.7 (top picture) from Valentine JR, Wind GG. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:448. [B] Figure 76 (B to D) from Rutherford RB. *Atlas of Vascular Surgery: Basic Techniques and Exposure*. Philadelphia: WB Saunders; 1993:139.)

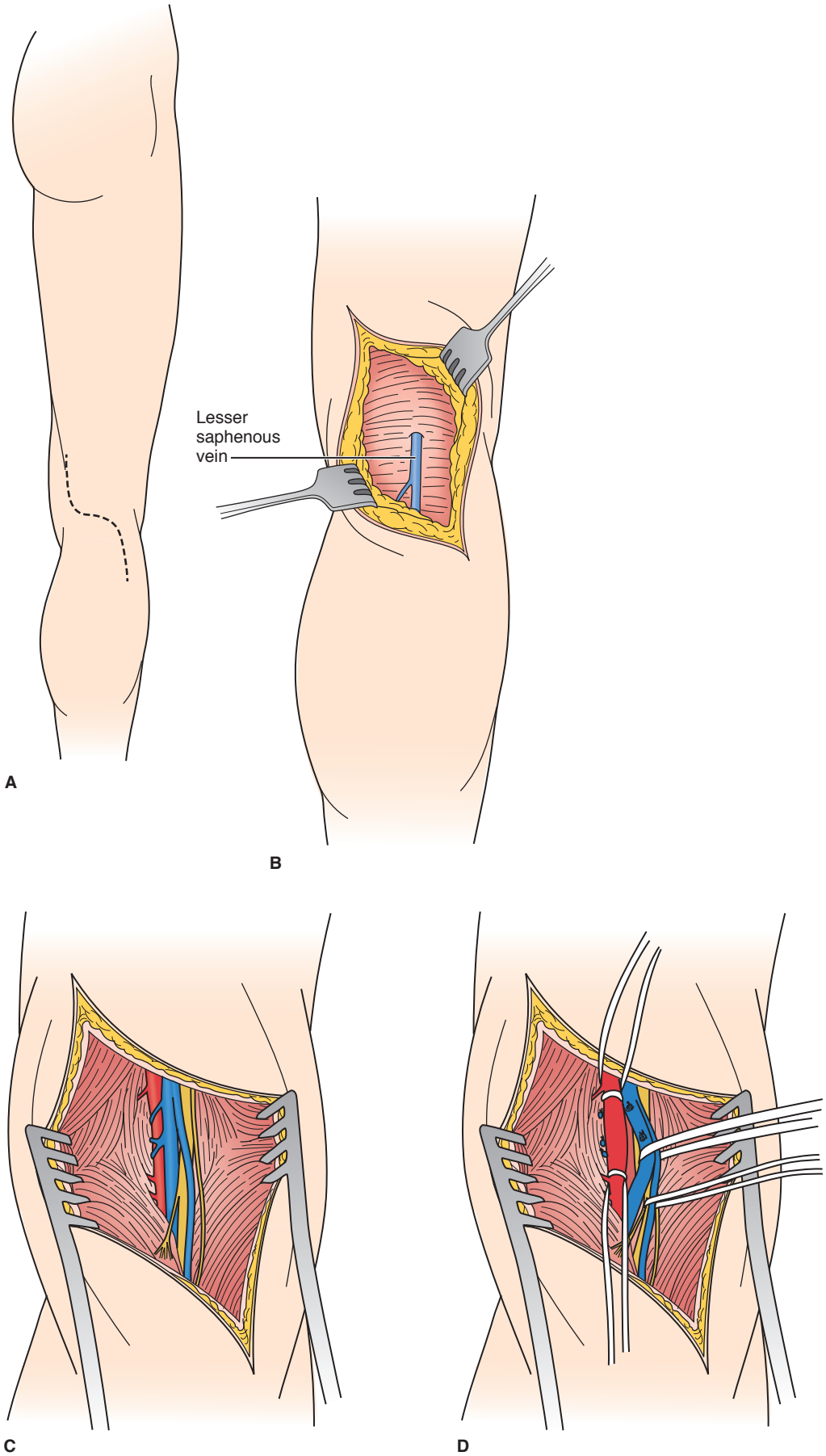


Figure 56.6 (A) The incision for the posterior exposure of the popliteal artery is made as a "lazy S" shape to avoid scar contracture across the knee. (B) The small (lesser) saphenous vein is identified in the subcutaneous tissue. (C) The deep fascia is incised and the sural nerve is gently retracted laterally to facilitate the dissection (D) of the popliteal artery from the popliteal vein and the tibial nerve, which lies most superiorly. ([A, B] Figures 17.35 and 17.36 from Valentine JR, Wind GG. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:462 and 463. [C, D] Figure 77C and D from Rutherford RB. *Atlas of Vascular Surgery: Basic Techniques and Exposure*. Philadelphia: WB Saunders; 1993: 142.)

The artery can then be separated from the veins with sharp dissection. Overlying crossing veins are uncommon but should be divided, while large collateral arterial branches should be preserved.

Lateral Exposure

The patient is placed in the supine position with the leg internally rotated and the knee flexed. A longitudinal incision is then made over the head of the fibula and extended distally. The common peroneal nerve is then identified posterior to the tendon of the biceps femoris muscle. The nerve should be gently dissected and retracted anteriorly as the tendon is divided to reach the fibula. The attachments to the fibula and fibular head are detached bluntly with a periosteal elevator. The proximal third of the fibula is then divided and removed. The popliteal artery is encountered deep to the fibula and can then be dissected free from the veins and encircled with vessel loops (Fig. 56.7).[2]

EXPOSURE OF THE TIBIAL AND PERONEAL ARTERIES

Anterior Tibial Artery Exposure

The anterior tibial artery is the most distal branch of the infrageniculate popliteal artery, arising from its lateral aspect and immediately passing through the interosseous membrane before entering the anterior compartment of the lower leg. Consequently the first 2 or 3 cm are most often not accessible for bypass and are frequently associated with significant atheromatous disease. Although a technique for medial exposure of the anterior tibial artery through the popliteal fossa has been described,[9,10] in the authors' experience it is rarely needed.

The proximal and middle third of the anterior tibial artery is exposed by a vertical incision on the anterolateral aspect of the calf and centered over the location of the planned anastomosis. The anterior tibial artery and vein lie on or in close

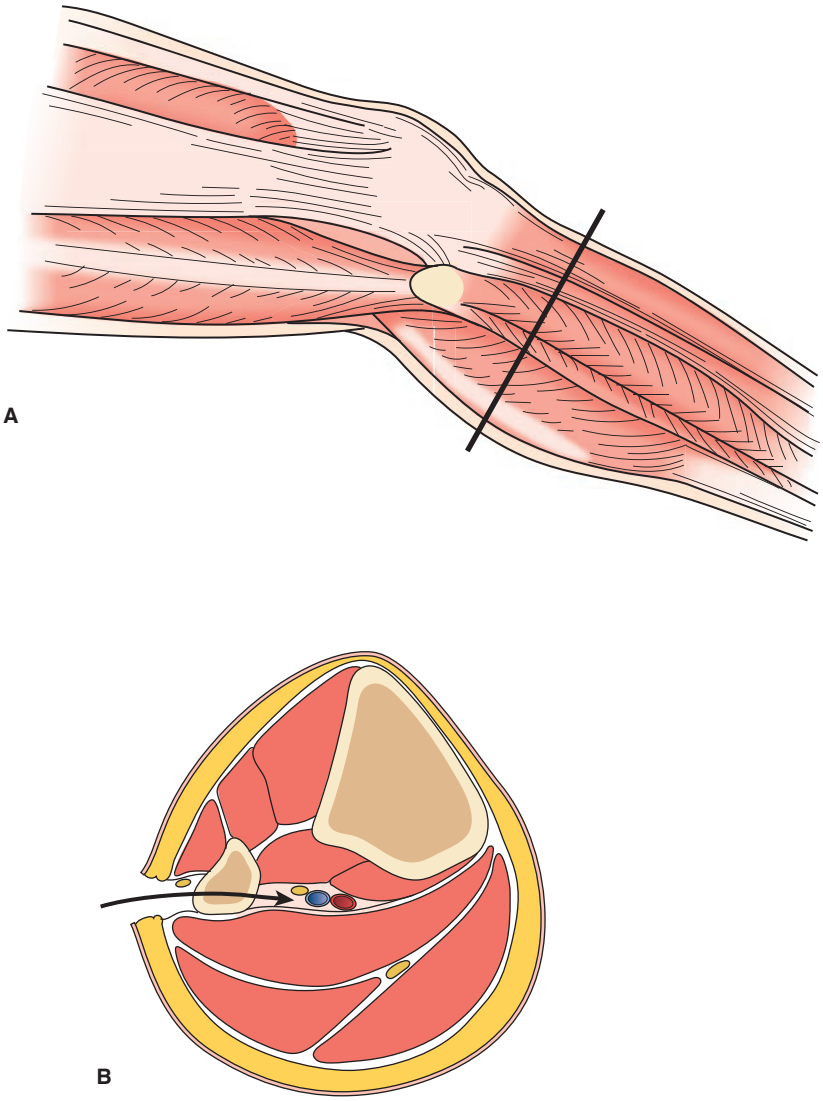


Figure 56.7 The lateral approach to the below-knee popliteal is performed by incising overlying the proximal third of the fibula. The common peroneal nerve is identified and gently retracted anteriorly. The attachments to the fibula are taken down bluntly with a periosteal elevator, and the fibula is then divided proximally and distally to reveal the neurovascular bundle. (Figure 79 from Rutherford RB. *Atlas of Vascular Surgery: Basic Techniques and Exposure*. Philadelphia: WB Saunders; 1993:149.)

proximity to the interosseous membrane. With the foot and ankle relaxed, it is often possible to palpate the cleft between the tibialis anterior and extensor digitorum longus muscles on the lateral calf approximately at the midpoint between the fibula and the tibia. The incision should be made directly over the cleft starting about 2 or 3 cm distal to the head of the fibula. The overlying fascia should be incised in line with the skin incision with the fascial incision extending for several centimeters distal and proximal to the skin incision to facilitate exposure, especially in heavily muscled individuals. Care must be taken to avoid injury to the peroneal nerve with this maneuver. Blunt finger dissection is used to separate the muscle bellies of the tibialis anterior and extensor digitorum longus muscles. Deep in the cleft at the level of the interosseous membrane, the anterior tibial artery and vein are usually easily identified (Fig. 56.8). Self-retaining retractors are crucial in this location. Small branches of the anterior tibial artery are often seen on the surface of the muscle bellies and are easily torn with overly aggressive blunt dissection or retraction. Quite often the vein is anterior to the artery and must be carefully dissected free from the underlying artery to facilitate exposure. A number of small crossing veins are often encountered on the anterior surface of the artery and should be ligated and divided to avoid troublesome bleeding. Similarly, great care should be taken in dissecting to free the artery, which has numerous small side branches; this can also lead to troublesome bleeding if they are torn during dissection. The authors prefer the use of a fine-tipped mosquito clamp to dissect along the surface of the artery and favor encircling the artery with small-caliber vessel loops for proximal and distal control. Heavily calcified anterior tibial arteries are better controlled with tourniquet occlusion after exsanguinating the lower leg with an Esmarch bandage.

The distal half of the anterior tibial artery can be exposed in similar fashion to the more proximal artery. However, if adequate conduit is available, the distal anterior tibial artery is best exposed at the ankle just proximal to the malleoli and flexor retinaculum. The tendons of the numerous extensor muscles of the ankle and foot come together in this location, and care must be taken in deciding the best way to expose the artery to avoid compressing or kinking the vein graft when the ankle is dorsiflexed. The best route is to separate the tendons of the extensor hallucis longus and extensor digitorum longus muscles. Once these tendons have been separated, the artery and vein are usually easily found and dissected free as previously described.

Because of its lateral location, vein grafts arising from the femoral triangle to the anterior tibial artery must be tunneled laterally, either subcutaneously or through the interosseous membrane. This anatomic reality can lead to graft thrombosis from kinking or twisting of the vein graft when done incorrectly.

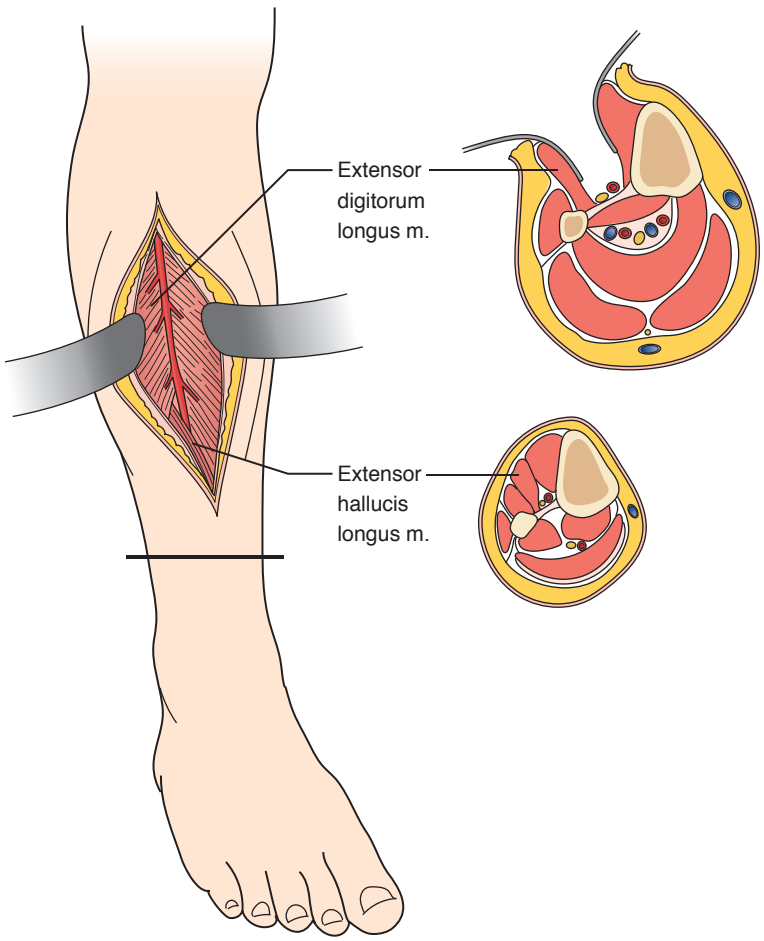


Figure 56.8 The proximal anterior tibial artery is exposed through an incision lateral to the tibia between the tibialis anterior and the extensor digitorum longus muscles. The anterior tibial artery is identified deep in the cleft between these two muscles along the interosseous membrane. (Figure 18.41 from Valentine JR, Wind GG. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:508.)

Subcutaneous vein grafts arising from the groin to the proximal anterior tibial artery can be easily tunneled across the anterior surface of the thigh (the authors' preferred approach), crossing the knee at the midpoint of the lateral femoral condyle and anterior to the head of the fibula, taking care to avoid injury to the peroneal nerve. The graft should not cross the knee joint in a more anterior location to avoid compressing the vein graft with flexion of the knee joint. When tunneling across the anterior thigh, it is important to place the tunnel in the subcutaneous tissue as close to the anterior fascia of the thigh muscles as possible to provide the maximal amount of soft tissue coverage and minimize kinking at the groin. Tunnels created too superficially, especially in obese patients, will result in a kink of the vein graft by the thick layer subcutaneous tissue of the femoral arterial exposure incision at the point where the graft exits the femoral triangle. Tunnels created too deeply may cross underneath the sartorius muscle, leading to graft compression. Often it is necessary and prudent to make a counterincision on the anterolateral thigh midway between the knee and groin dissection to facilitate the creation of the tunnel.

Tunneling an anterior tibial graft through the interosseous membrane has the advantage of needing a shorter length of vein conduit and also reduces the likelihood of graft exposure if there is wound breakdown, especially when the graft is also tunneled under the sartorius muscle and through the popliteal space. For in situ vein grafts and bypasses arising from the above- or below-knee popliteal artery, tunneling through the interosseous membrane is the only feasible pathway for bypasses terminating in the proximal or middle third of the anterior tibial artery. More distal bypasses to the supramalleolar anterior tibial artery can be tunneled across the anterior surface of the tibia. Although this approach is simpler, it may result in graft compression by the underlying tibia in patients where the skin and soft tissue in this location is thin and taut.

When creating the interosseous tunnel, the authors prefer to have the knee flexed at 90 degrees in the "sit up" position. The tunnel is created by simultaneous dissection medially from the below knee popliteal space and laterally from the anterior compartment with surgeon's finger and blunt tipped instrument (Fig. 56.9). The graft should be tunneled several centimeters proximal to the planned point of anastomosis to the anterior tibial artery. Many surgeons will expose the interosseous membrane from the lateral aspect of the leg and perform a cruciate incision to expand the space and prevent compression of the graft by the firm edge of the fascia. Once the membrane has been incised, the authors prefer to pass a gently curved clamp from the popliteal space in close proximity to the point where the anterior tibial artery crosses the membrane. The jaws of the clamp can be partially opened to widen the tunnel. Careless or overly forceful tunneling can lead to very troublesome venous bleeding from the anterior tibial vein.

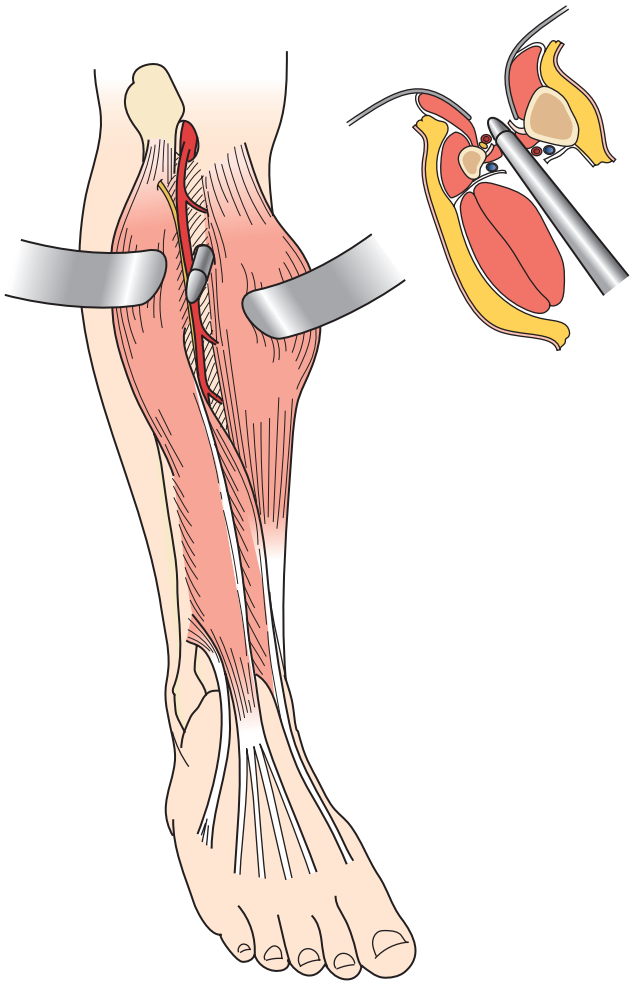


Figure 56.9 Bypass grafts originating from the medial leg can reach the lateral leg by traversing the interosseous membrane. The membrane is exposed with gentle blunt dissection from both the medial and lateral sides. The graft is then tunneled several centimeters proximal to the planned site of the distal anastomosis. (Figure 18.42 from Valentine JR, Wind GG. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:509.)

Tibioperoneal Trunk and Proximal Posterior Tibial and Peroneal Artery Exposure

The tibioperoneal (TP) trunk and proximal posterior tibial and peroneal arteries are found in the deep posterior compartment underneath the soleus muscle. The dissection commences with exposure of the below-knee popliteal artery from the medial aspect of the leg. Once the distal popliteal artery has been identified, the tip of a finger or the end of a right-angled clamp can be used to enter the potential space where the artery crosses beneath the soleus muscle, using cautery to divide the soleus about a finger breadth posterior to where it attaches to the tibia. Starting the dissection is the most difficult part, since large veins can be encountered; these must be carefully ligated or suture-ligated. Once the soleus has been divided, the arteries are usually easily identified. The TP trunk is often found posterior to its corresponding vein, which must be mobilized to facilitate its exposure. The distal TP trunk bifurcates into the posterior tibial and peroneal arteries. The posterior tibial artery is more superficial and easily dissected free from its adjacent vein in this location. Dissection of the peroneal artery can be more difficult, since it lies more deeply as it turns laterally to run in its typical course along the medial side of the fibula. Veins are

often encountered in this area, which must be carefully ligated to avoid troublesome bleeding.

Posterior Tibial Artery Exposure

Exposure begins with an incision on the medial aspect of the calf about one or two finger breadths posterior to the edge of the tibia. Alternatively the incision can be made through the base of the incision of the harvested great saphenous vein. Once the deep fascia has been incised, the soleus muscle will be encountered, which should be detached from the tibia using electrocautery to enter the deep posterior compartment. The posterior tibial vessels are then immediately encountered. The posterior tibial vein is usually slightly superior to the artery, whereas the posterior tibial nerve is usually posterior to both (Fig. 56.10). Crossing veins are often encountered and must be divided. The artery often has small side branches, which must be controlled. Soft arteries are easily controlled with vessel loops, while heavily calcified arteries are best controlled with a tourniquet after exsanguination of the lower leg.

Distal exposure of the posterior tibial artery beyond the lower edge of the soleus muscle is easily accomplished in most cases and is the preferred location for in situ femoral posterior tibial bypasses, since the vein harvest incision can be used to expose the artery as well. The artery is exposed through an incision made posterior to the tibia and anterior to the Achilles tendon (Fig. 56.11). Once the fascia has been incised, the artery and vein will be encountered in an investing layer of fatty tissue. A Doppler probe is useful for identifying the precise location of the artery in this location. Numerous crossing veins are almost always present; these should be divided to expose an adequate length of artery.

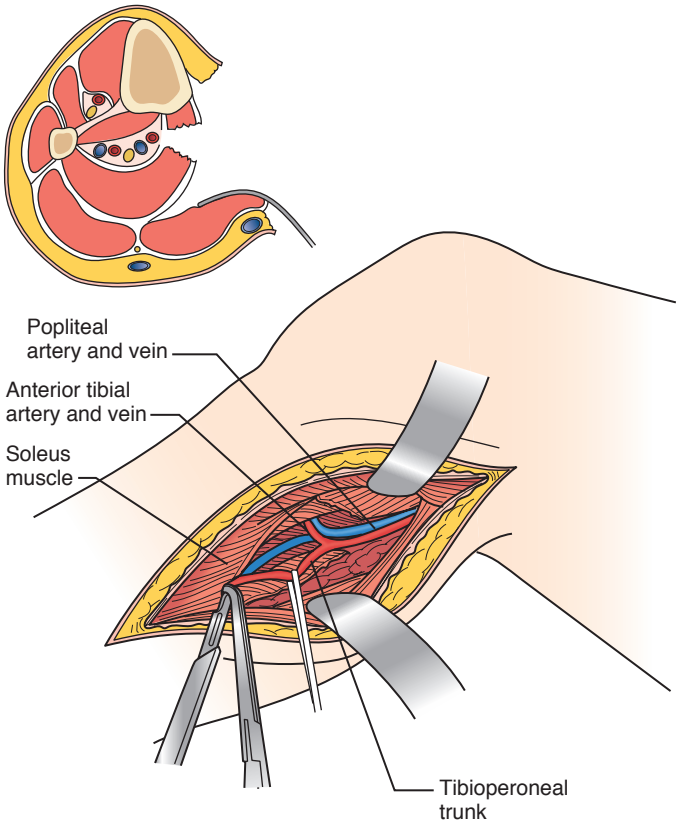


Figure 56.10 Exposure of the posterior tibial artery begins with an incision one to two finger breadths posterior to the edge of the tibia. The deep fascia is incised, and the soleus is detached from the tibia to enter the deep posterior compartment. The posterior tibial vessels are then encountered. (Figure 18.34 from Valentine JR, Wind GG. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:501.)

Peroneal Artery Exposure

Medial Exposure

Medial exposure of the peroneal artery is easily accomplished in its most proximal portion through the identical approach used for exposure of the TP trunk, as previously described. The artery is easily identified at the bifurcation of the TP trunk, and dissection continues along the anterior surface of the artery deep to the location of the posterior tibial artery and vein. The peroneal artery can also be exposed in its middle and distal portion through medial incision by detaching the soleus muscle from the tibia, as previously described. In general, a more lengthy incision should be used than is generally required for the posterior tibial artery due to the deep location of the peroneal artery, especially in individuals with large calf muscles. Once the posterior tibial neurovascular bundle has been identified, dissection is deepened either anterior or posterior to the posterior tibial structures (Fig. 56.12). Deepening the dissection anterior to the posterior tibial neurovascular bundle is probably the more traditional approach. This dissection can occasionally be quite tedious if there are numerous venous connections between the posterior tibial and peroneal veins. As one approaches the peroneal artery posterior to the posterior tibial neurovascular bundle there are fewer veins, but care must be taken to avoid injury to the peroneal nerve, which must also be retracted superiorly. Both approaches are useful in the authors' experience. The peroneal artery is first located by palpating the medial side of the fibula in the depths of the dissection. A continuous-wave

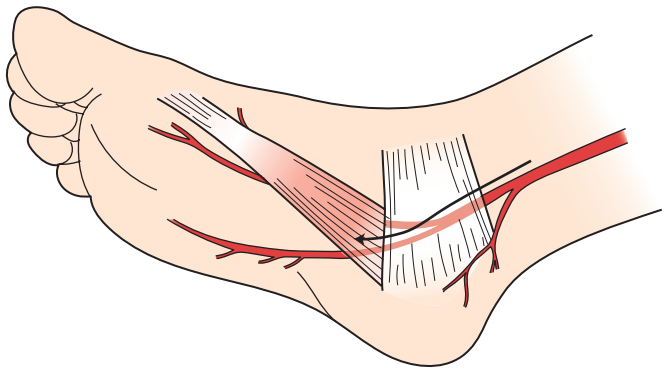


Figure 56.11 The distal posterior tibial artery is exposed through an incision posterior to the tibia and anterior to the Achilles tendon. After dividing the fascia, the posterior tibial artery and vein are identified in an investing layer of fatty tissue. (Figure 85 from Rutherford RB. *Atlas of Vascular Surgery: Basic Techniques and Exposure*. Philadelphia: WB Saunders; 1993:166.)

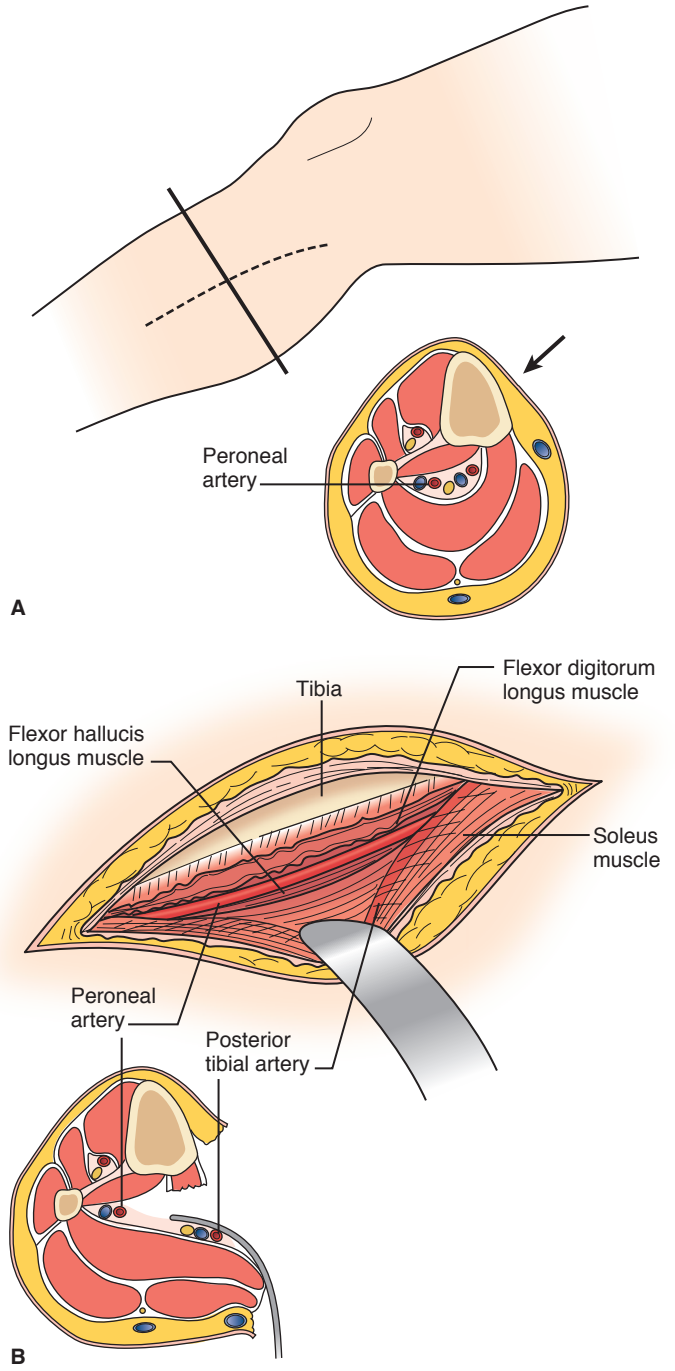


Figure 56.12 The proximal and mid-peroneal artery can be exposed through a medial incision as previously described for the posterior tibial artery. The posterior tibial neurovascular bundle is identified, and the dissection is performed anterior or posterior to the posterior tibial vessels and peroneal nerve. The peroneal artery is located deep in the incision in close proximity to the medial side of the fibula, which is a useful landmark. ([B] Figure 18.46 from Valentine JR, Wind GG. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:513.)

Doppler probe can be used to identify the location of the artery more precisely. The peroneal vascular structures are often covered by muscular fibers of the flexor hallucis muscle, which may have to be divided to expose the artery and vein. Unfortunately the vein is often encountered first and the artery is generally found behind the vein from this approach, which involves multiple small crossing venous branches. These must also be divided to expose the artery. Self-retaining retractors are a must during this exposure. The peroneal artery is often heavily calcified, which can make the creation of an anastomosis most challenging, particularly in its midportion in heavily muscled individuals. Tourniquet control can be very useful in this circumstance.

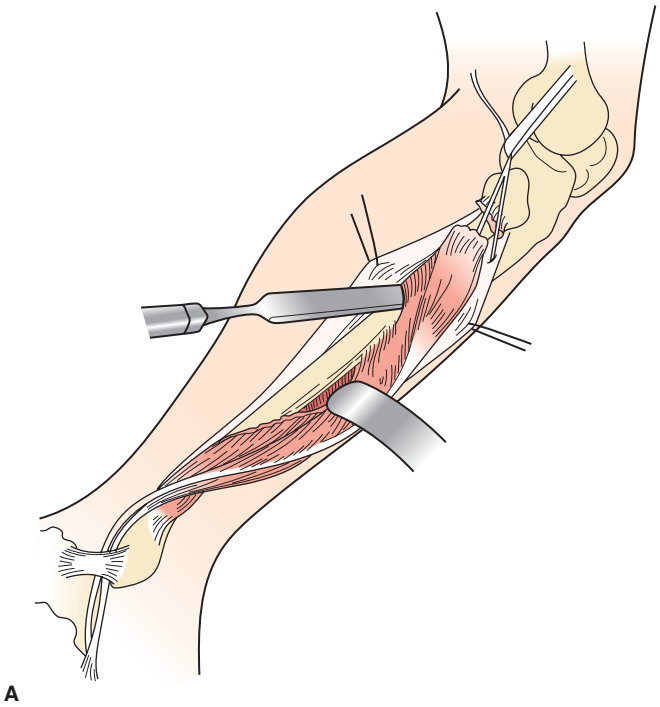
Lateral Exposure

Many vascular surgeons prefer to approach the peroneal artery from the lateral side of the calf to avoid the often difficult and challenging dissection required from the medial approach. A longitudinal incision is placed directly over the fibula. Once the fibula has been exposed, a periosteal elevator is used to free its muscular attachments on all surfaces. Careful dissection is important in freeing posterior attachments to the fibula to avoid injury to the underlying peroneal vein. Once the appropriate length of fibula has been dissected free of soft tissue, it can be divided with a rib shear or double-action bone cutter. Some authors recommend drilling small holes in the fibula to avoid shattering it. Alternatively, a small oscillating power saw can be used (authors' preference). Once the bone segment has been removed, the underlying fascia is incised longitudinally. The artery is then encountered superficial to the vein and dissected free with minimal difficulty (Fig. 56.13). This approach is particularly useful when exposing the peroneal artery in the distal half of the lower leg. Grafts can be tunneled subcutaneously and laterally as previously described for the anterior tibial artery or medially through the rent in the interosseous membrane created by removal of the fibula.

EXPOSURE OF THE ARTERIES OF THE FOOT

Bypass to the arteries of the foot is frequently used for limb salvage in patients with diabetes mellitus. Exposure of the pedal arteries is generally straightforward due to their superficial location. However, their small caliber, often being calcified, and requiring long venous conduits, can make for a challenging procedure that is lengthy, tedious, and unforgiving. Fortunately when these procedures are performed well, the rates of graft patency and limb salvage are comparable to more proximal reconstructions.[11] Although both the dorsalis pedis and posterior tibial arteries and their branches are suitable targets for bypass, in the authors' experience the dorsalis pedis arterial segment is more commonly spared of significant disease. Unlike the tibial and peroneal arteries, the vessels of the foot taper significantly as they run their course. Consequently it is advantageous to place the anastomosis as proximal as possible on the target artery. The dorsalis pedis and inframalleolar posterior tibial artery segments are connected through anastomoses of the tarsal and plantar arches of the distal foot. Successful bypass to either will often result in the healing of lesions even in angiosomes typically supplied by the other artery.

The anterior tibial (AT) artery runs along the lateral border of the extensor hallucis longus muscle and passes beneath the



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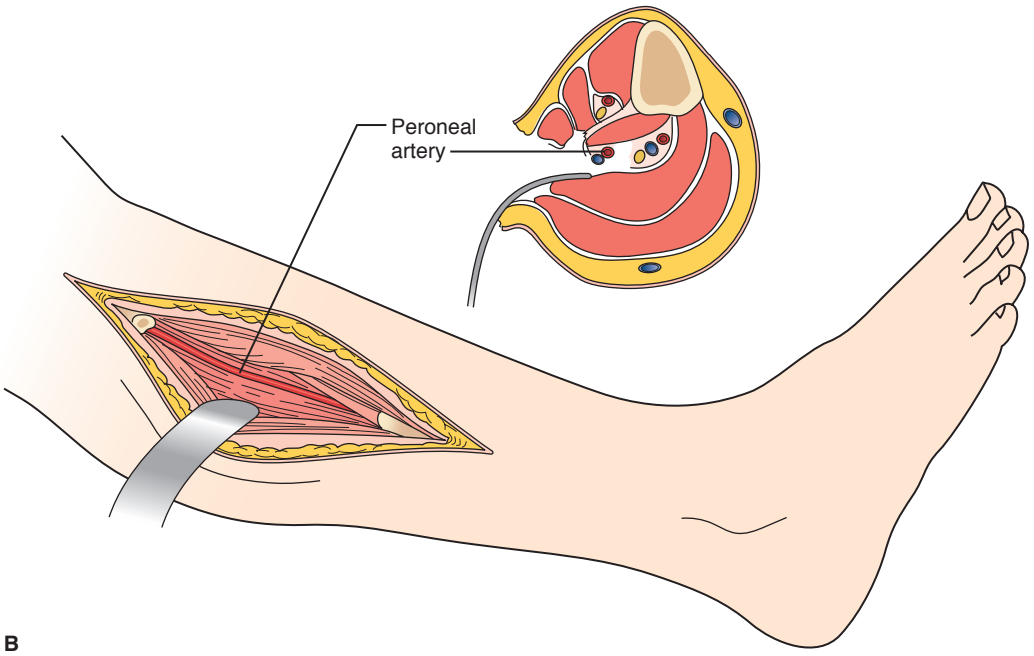

B

Figure 56.13 The lateral approach to the peroneal artery is especially useful in the distal half of the lower leg. (A) The incision is made directly over the fibula, and the muscular attachments are divided on all sides using a periosteal elevator. (B) A segment of fibula is removed, and the underlying fascia is incised to reveal the peroneal artery and vein. (Figures 18.48 and 18.49 from Valentine JR, Wind GG. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:515 and 516.)

inferior extensor retinaculum to become the dorsalis pedis artery, which runs parallel and immediately lateral to the extensor hallucis longus tendon between the first and second metatarsals. It gives off a deep plantar branch between the heads of the first interosseous muscles, connecting with the lateral plantar branch of the posterior tibial artery and forming the plantar arterial arch. The posterior tibial artery is found between the flexor digitorum longus and the flexor hallucis longus muscles and enters the foot after coursing beneath the flexor retinaculum. It travels in a neurovascular bundle with the tibial nerve and accompanying veins. It subsequently divides into medial and lateral plantar arteries, terminating in the anastomotic loop created by the tarsal and plantar arches, as previously described.

Exposure of the Dorsalis Pedis Artery

The dorsalis pedis (DP) artery is found on the dorsum of the foot as the continuation of the AT artery once it crosses under the inferior extensor retinaculum of the ankle.[12] The foot should be supported in a relaxed position with the operating table in reverse Trendelenburg position. Very small Weitlander retractors are very useful. Both good lighting and the use of magnification with surgical loupes are essential. A longitudinal incision should be placed directly over the DP just distal to the retinaculum. When the DP has an audible Doppler signal, its precise course can be marked on the foot prior to making the incision. When no signal is present, the incision should be placed parallel and immediately lateral to the extensor hallucis longus tendon. The location of the artery can also be mapped by duplex ultrasound when preoperative vein mapping is performed. This allows direct access to the artery without creating skins flaps. The dorsal branch of the peroneal nerve is often encountered and can be retracted or divided with no consequence. The artery and its corresponding vein lie under a layer of deep fascia and are often palpable and visible. The length of the DP is variable; it bifurcates into the medial and lateral tarsal arteries, which should both be preserved. Small side branches are always present and should also be preserved. If the artery is heavily calcified, the segment under the retinaculum is often found to be softer due to flexion of the ankle; it is a good place for proximal control.

Inframalleolar Posterior Tibial and Plantar Artery Exposure

The patient's knee should be slightly flexed with the foot elevated on towels or a pad behind the lateral malleolus. This will widen the space between the calcaneus and the medial malleolus, aiding in exposure. A curvilinear skin incision is made between the medial malleolus and the calcaneus, deepening the tissue down to the flexor retinaculum. Marking the course of the artery with a Doppler prior to making an incision is helpful. An investing layer of fat is encountered that occasionally contains small veins; these should be divided and ligated. The artery is invariably calcified and easily palpable beneath the deep fascia, which is incised to expose the distal PT, which is bound by the flexor digitorum longus superiorly and the flexor hallucis inferiorly. The artery is dissected distally until its bifurcation into the medial and lateral plantar arteries. Crossing veins are often present. The calcaneal branch of the PT should always be preserved. The abductor hallucis is then divided for additional exposure of the lateral plantar artery.[13,14]

EXPOSURE FOR OBTURATOR BYPASS

The obturator bypass is most commonly used to treat a severe arterial infection involving the CFA.[15,16] The inflow artery is typically the common or external iliac artery, which is exposed through a retroperitoneal approach. The obturator foramen is exposed through this same retroperitoneal approach. The dissection is performed medial to external iliac vein and posterior to the pubic ramus. The obturator internus muscle is then bluntly dissected to reveal the obturator membrane. Grafts should be tunneled through the anterior medial portion of the membrane to avoid injury to the obturator artery and nerve, which pass through its posterior lateral portion.

The distal target of the obturator bypass is the popliteal or distal SFA. The tunnel between the inflow and target arteries is made in the medial compartment of the thigh in the space between the adductor longus and brevis muscles anteriorly and the adductor magnus muscle posteriorly, which leads directly to the obturator foramen. The SFA is easily identified and controlled in the plane of the tunnel anterior to the adductor magnus muscle (Fig. 56.14). If the popliteal artery is the target, the graft must be either tunneled through the adductor hiatus or brought around the adductor tendon. The proximal and distal anastomoses are then performed in the standard fashion. After completion of the bypass, the surgical incisions are closed and excluded before the groin is explored to remove any infected prosthetic or native material in order to prevent contamination of the obturator bypass.

EXPOSURE OF THE LOWER EXTREMITY VEINS

Great Saphenous Vein

Anatomy

The great saphenous vein arises from the medial aspect of the dorsal pedal venous arch and ascends anterior to the medial malleolus, crossing the tibia at the junction of the distal and middle third of the calf to pass posteromedial to femoral condyle at the knee. The vein then ascends medially in the thigh, remaining parallel to the medial edge of the sartorius muscle. It then perforates the deep fascia and joins the common femoral vein approximately 4 cm below the inguinal ligament. The saphenous nerve lies anterior to the great saphenous vein in the calf and may be injured by procedures extended into the calf. The great saphenous vein usually lies directly on the muscular fascia in the saphenous compartment, a subcompartment of the superficial compartment that is bordered superficially by the saphenous fascia and deeply by the muscular fascia. This compartment is readily visualized in the thigh with ultrasound.

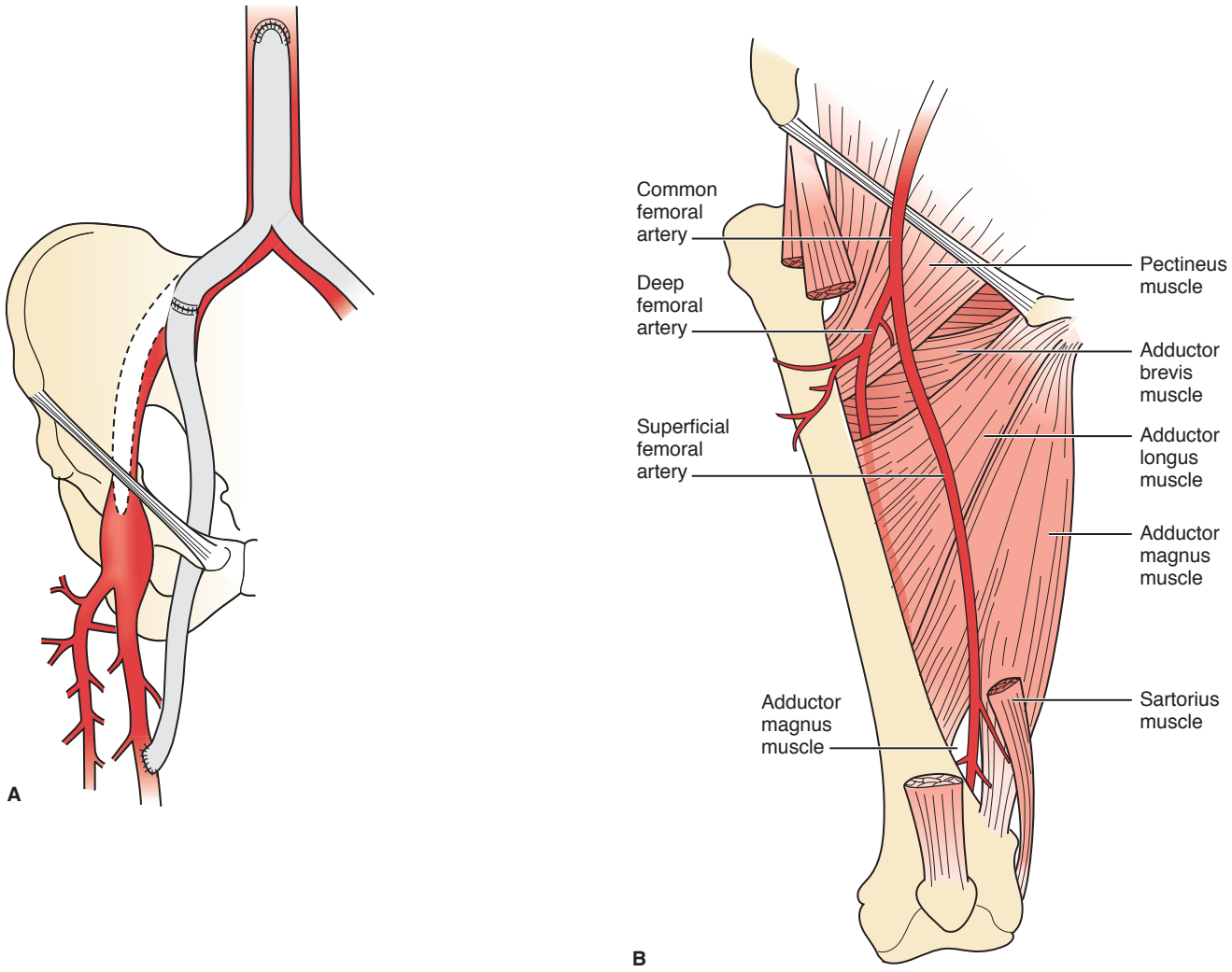

Figure 56.14 (A) The obturator bypass is tunneled through the obturator foramen via a retroperitoneal approach. Dissection is performed medial to the external iliac vein and posterior to the pubic ramus. The obturator foramen is identified by bluntly dissecting the obturator internus muscle. The tunnel is made through the anterior medial portion of the membrane to avoid the obturator artery and nerve. (B) The tunnel through the obturator foramen leads into the medial compartment of the thigh anterior to the adductor magnus muscle, where the superficial femoral artery is easily identified. ([A] Figure 35.3 from Chaikof EL, Cambria RP. *Atlas of Vascular Surgery and Endovascular Therapy: Anatomy and Technique*. Philadelphia: Elsevier Saunders; 2014:431. [B] Figure 16.8 from Valentine JR, Wind GG. *Anatomic Exposures in Vascular Surgery*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003:418.)

Exposure of the Great Saphenous Vein

If the upper portion of the great saphenous vein is to be used for bypass, the vein harvest typically begins in the groin. A 30- to 45-degree oblique incision is made starting at the femoral pulse at the groin crease. Preoperative evaluation of the saphenous vein with duplex ultrasonography and skin marking of its location may help in better placing the incision and avoiding large skin flaps, especially in overweight patients. It may also help to identify any issues with the quality of the vein preoperatively. The skin is incised sharply and the subcutaneous tissue is divided with electrocautery. The skin incision can be performed with either a continuous technique or using skip incisions based on the surgeon's preference. Comparison of vein harvest techniques using skip incisions versus continuous incisions from the Vascular Quality Initiative shows no difference in the rates of surgical site infection or in graft patency at 1 year.[17] Once the vein has been identified, the anterior aspect is dissected sharply with a Metzenbaum scissors and the subcutaneous tissue is undermined distally over the vein. The skin and subcutaneous tissue are then divided over an instrument superior to the vein. This process is continued until sufficient length of the great saphenous vein is exposed. The authors prefer a modified no-touch technique to remove the vein. The vein is first encircled with a vessel loop to apply gentle countertraction as sharp dissection at a slight distance from the adventitia is used to separate it from adjacent tissues. The vein is not grasped with forceps to minimize the potential for injury to the intima. Branches are ligated with silk

ties. The vein is not removed until all arterial dissections and tunnels are completed. The distal vein is divided first and gently dilated with a mixture of heparinized saline and papaverine instilled with an olive-tip needle to distend the vein gently and identify any untied branches. The proximal aspect of the vein is then clamped at the saphenofemoral junction, often with a cuff of femoral vein, which makes large hood when the vein is used in nonreversed fashion (our most common configuration). Valve lysis is done with a Mills valvulotome under direct imaging with an angioscope. If the vein from the lower leg is to be used, the incision is made just anterior to the medial malleolus and the dissection is continued proximally as described earlier.

SMALL SAPHENOUS VEIN

Anatomy

The small saphenous vein arises from the dorsal pedal arch and ascends posterolaterally from behind the lateral malleolus to a variable termination in the popliteal vein. The small saphenous vein usually has 7 to 10 valves, which are closely spaced along its length. The sural nerve ascends immediately lateral to the vein, beneath the muscular fascia prior to its junction with the popliteal vein. Approximately 75% of small saphenous veins join the popliteal vein, while as many as 25% ascend more proximally into the thigh, with no connection to the popliteal vein.[18] Recognition of this anatomic variant is important in harvesting the vein for bypass. The proximal extension of the small saphenous vein, often referred to as the vein of Giacomini,[19] may ascend in the posterior thigh to communicate with the great saphenous vein through the circumflex vein of the posterior thigh.

Exposure of the Small Saphenous Vein

The small saphenous vein harvest is begun in the lower leg with a vertical incision just posterior to the lateral malleolus. The authors will typically use ultrasound preoperatively just prior to the procedure to mark the location of the vein and facilitate its identification. Dissection of the vein is performed with the modified no-touch technique, as outlined previously. The distal vein is clamped and divided, and the vein is distended as described. The saphenopopliteal junction is then clamped and oversewn and the vein is prepared in a reversed or nonreversed fashion per surgeon preference.

FEMORAL VEIN OF THE THIGH

Anatomy

The femoral vein of the thigh (referred to as the *femoral vein* in the following section) is an excellent conduit for arterial reconstruction. Due to its sturdy structure and large caliber, it is most commonly used for reconstruction after removal of infected prosthetic grafts of the abdominal aorta or iliac and common femoral arteries. It may also be used in venous reconstruction procedures. The deep venous system of the leg is made up of the paired tibial and peroneal veins, the popliteal vein, the femoral vein of the thigh, the deep femoral vein, and the common femoral vein.[1] After passing through the adductor canal, the popliteal vein becomes the femoral vein, lying posterior and lateral to the artery. The vein is generally large in caliber and quite sturdy, making an excellent conduit where a larger-caliber graft than the typical saphenous vein is required. Harvesting of the femoral vein can be a tedious exercise in some patients owing to its typical location somewhat posterior to the SFA and the multiple crossing branches of the SFA that are usually encountered. The femoral vein and the deep femoral vein join together to form the common femoral vein approximately 4 to 12 cm below the inguinal ligament. The deep femoral vein is a critical collateral pathway that must be preserved in harvesting the femoral vein to avoid the significant lower leg edema which would occur if it were removed.

Harvest Technique

The patient is positioned with a bump under the knee to facilitate external rotation at the hip with a flexed knee. A longitudinal incision is then made in the thigh along the border of the sartorius muscle. The sartorius muscle is then reflected laterally and the fascia overlying the abductors is incised to expose the SFA and femoral vein. Branches of the SFA are often encountered which may cross over the femoral vein and can be divided. Distal SFA branches are best preserved if the popliteal artery is occluded, as these are important collaterals around the knee. Branches of the femoral vein are relatively large and should be either doubly ligated or suture-ligated to avoid bleeding when pressurized with arterial blood flow. Proximally, the junction of the femoral vein and deep femoral vein should always be fully exposed. When removing the femoral vein of the thigh, it is critical to preserve the deep femoral vein to prevent severe leg swelling. The femoral vein should be transected at its junction with the common femoral vein and the resulting defect closed with a running continuous polypropylene suture in a manner to both preserve the inflow of the deep femoral vein while not leaving a proximal stump of the femoral vein, which may result in thrombus formation. The distal end of the remaining vein should be suture-ligated or oversewn. The harvested femoral vein can then be used in a reversed orientation or the valves can be cut with a valvulotome to facilitate its use in a nonreversed orientation. The fascia is then reapproximated using a running technique followed by the subcutaneous tissue and the skin.[20]

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Rutherford RB. *Atlas of Vascular Surgery*. Philadelphia: W.B. Saunders; 1993.

This classic atlas takes a "how to do it" approach to the surgical exposures used throughout the circulatory system in vascular surgery. The text is written in Dr. Rutherford's typically clear and concise style and contains many personal observations based on his enormous clinical experience. The illustrations are well drawn and accurate, including many highly useful cross-sectional depictions of the anatomic relationships between the blood vessels and adjacent structures in the lower extremity.

Valentine JR, Wind GG. Anatomic Exposures in Vascular Surgery. 2nd ed.

Created by an expert vascular surgeon and anatomist, this well-written text contains a level of anatomic detail not often seen in surgical atlases and provides a unique perspective on the surgical anatomy of the lower extremity circulation. The late Charles Rob said it best in his Foreword: "The illustrations are the strong part of this excellent book." They are beautifully done with a three-dimensional quality that depicts the anatomy from the perspective of the surgeon. It should be required reading for all vascular surgical trainees.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 57

Upper Extremity Vascular Exposure

KARL A. ILLIG

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INTRODUCTION

Vascular surgeons who treat thoracic outlet syndrome and perform arteriovenous (AV) access obviously regularly operate in the upper extremities, but expeditious and safe upper extremity exposure is required for the treatment of trauma, complex aortic endograft repair of aortic diseases, and many other conditions.

For purposes of planning exposure, it is convenient to divide the relevant upper extremity vessels into three zones (Fig. 57.1). The intrathoracic zone contains the aortic arch, innominate artery, subclavian arteries on both sides, innominate veins, and superior vena cava. The importance of this classification is that exposure, although straightforward, requires more time than in the limb. The sternum must be divided or the thorax opened. Therefore in trauma cases, because it takes more time to expose the arteries, planning ahead and perhaps a more conservative and safer approach for proximal control should be considered. For venous reconstruction, although usually less emergent, somewhat complex exposure strategies are likewise needed. The next zone is essentially the thoracic outlet, extending from the base of the neck to the axilla, which contains the subclavian, proximal vertebral, and proximal axillary arteries and veins. This area contains critical nerves, which must be preserved, and the clavicle and to a lesser extent deltoid muscle can block access to certain parts of the vessels. Finally, the third zone is the arm itself, extending from the axilla to the fingers. Vascular exposure in the arm is usually much more straightforward, especially if the operative field is sufficiently distal so that a tourniquet may be used.

EXPOSURE OF ARTERIES WITHIN THE THORAX

In patients with normal anatomy, the first branch of the aortic arch after the coronary arteries is the innominate artery, which then bifurcates into the right subclavian and right common carotid arteries. Approximately 13% of patients have a "bovine arch," somewhat inaccurately but commonly used to describe the situation where the left common carotid artery arises from the innominate itself or a common ostium; in most patients the left common carotid artery is the next separate branch from the arch, followed by the left subclavian artery. There are two critical variants. The first is an aberrant right subclavian artery. This situation, occurring in up to 2% of patients, is variable but most typically creates a situation where the innominate artery simply becomes the right common carotid artery, and the right subclavian artery arises as the last branch (usually from the descending aorta, now on the left side), passing behind the esophagus to supply the right arm. Although often asymptomatic, this abnormal artery is sometimes associated with aneurysmal degeneration (diverticulum of Kommerell) and/or can produce dysphagia via a mass effect (dysphagia lusoria). A second important variant is origination of the left vertebral artery from the aortic arch, occurring in 2% to 5% of patients. Although this should specifically be identified ahead of time if direct intervention on this vessel is planned, its major significance lies in planning thoracic endovascular aneurysm repair, to avoid covering this vessel inadvertently.[1,2]

Abstract

Safe and expeditious exposure of the upper extremity vascular system requires a thorough knowledge of the relevant anatomy. Exposure proximally is more difficult than in the periphery, for two reasons: First, the bony thorax restricts and slows exposure, most relevant in traumatic situations. Second, there are several nerves intimately involved with the vessels proximally which should be preserved for best outcomes. This chapter describes exposures from the aortic arch to the wrist, and provides helpful details for safe and efficient surgery.

Keywords

brachiocephalic vessels
thoracic outlet
upper extremity anatomy

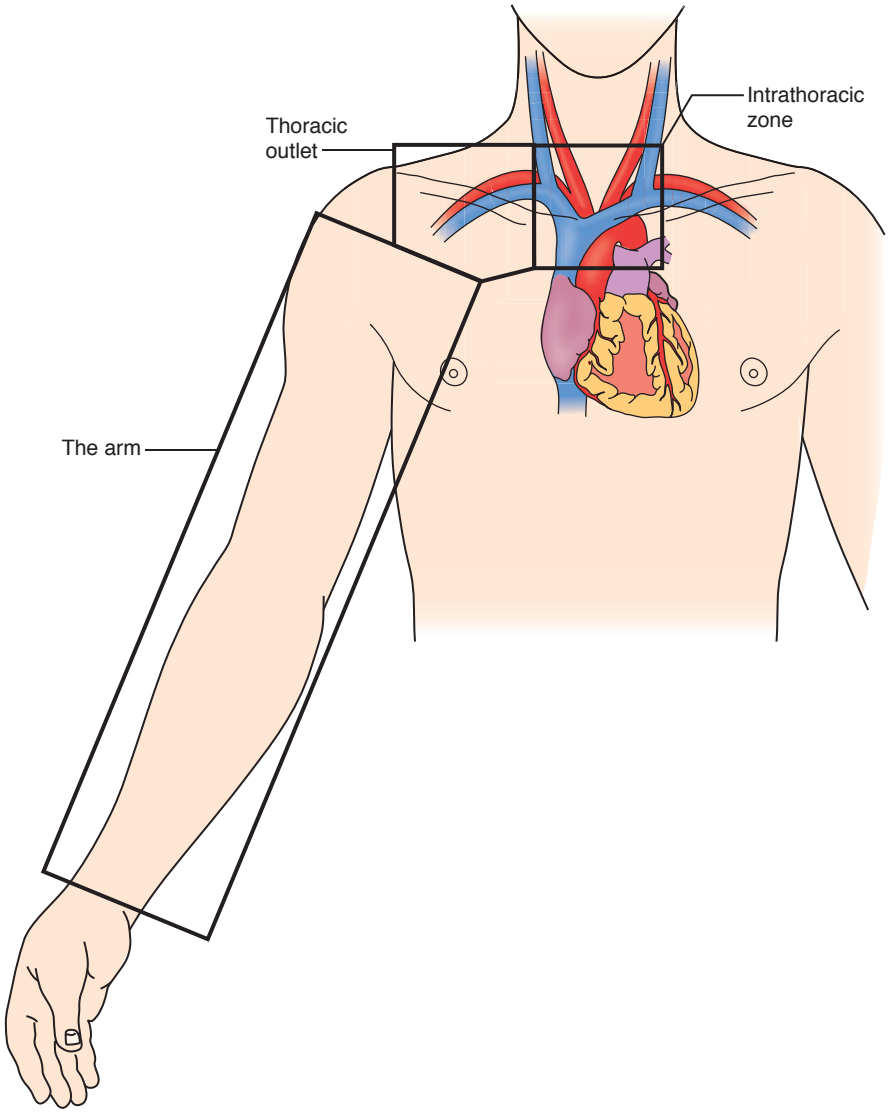

Figure 57.1 The chest and arms (right-side shown) illustrating the three general zones described. The intrathoracic vessels almost always require bony division, hence more thorough preplanning. The vessels in the thoracic outlet are easier to expose, but technical challenges exist. Finally, the vessels of the arm are relatively straightforward to expose.

As described previously, especially with regard to trauma, control of intrathoracic vessels takes more time than elsewhere, and thus a slightly more conservative approach may be considered. Exposure of most extremity vessel injuries directly is straightforward because proximal control is not difficult, although if a supraclavicular injury occurs that is constrained, proximal control may not be possible at the site of injury itself. Although endovascular approaches can be used, surgical control will take much longer than in the arm itself. The implication of this is that if there is any question that control may be needed within the thorax (again, classically an injury to the subclavian artery with a supraclavicular hematoma), it is prudent to obtain this control first, before the injury is approached directly.

Exposure of the arch and proximal great vessels is required for debranching, aortosubclavian and carotid bypass for atherosclerosis or Takayasu arteritis, or occasionally complex AV access and in some trauma cases. In general, exposure of the innominate, proximal right subclavian, and proximal left carotid arteries should always be performed by means of median sternotomy. The proximal left subclavian artery can be reached via median sternotomy, although not quickly, so if such exposure is needed urgently an anterolateral third interspace thoracotomy is the preferred approach.

Innominate, Right Subclavian, and Left Common Carotid Arteries, and Proximal Left Subclavian Artery in an Elective Situation

Median sternotomy provides superb exposure to these vessels, as well as to the ascending aorta. If the aorta does not need to be used, the sternotomy can be limited to the third interspace (Fig. 57.2). Following sternotomy, the anatomy will be very well delineated. The left innominate vein is superficial and should be preserved but can be sacrificed in an emergency. Two nerves are critical to protect. The right recurrent laryngeal nerve loops around the right subclavian artery just as it arises from

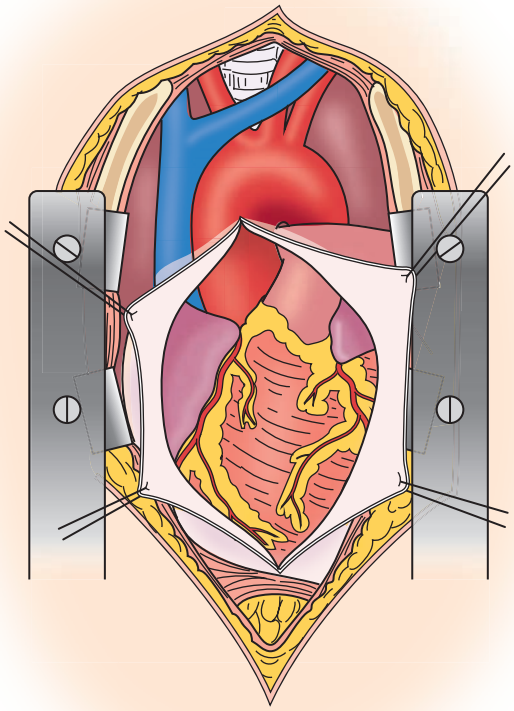

Figure 57.2 Open median sternotomy with arch vessel exposure.

the innominate artery, and the phrenic nerve passes behind the jugular and right innominate vein and anterior to the right subclavian artery and anterolateral to the innominate artery. Both should be easy to identify, but both can be in jeopardy if indiscriminate circumferential dissection of the vessels is carried out without caution.

After teasing away fatty tissue and mobilization and retraction of the overlying veins, this approach yields ideal exposure to the orifice of the innominate and left common carotid arteries, the proximal portions of these arteries themselves, and, by extending the incision onto either side of the neck or the right supraclavicular area, the rest of both common carotid arteries and the right subclavian artery into the thoracic outlet, respectively (Fig. 57.3). Exposure of the subclavian arteries will be limited by the sternocleidomastoid muscles (which can be partially divided, but ideally not fully transected) and anterior scalene muscle which can be fully divided (see later), but the vertebral arteries usually arise proximal to this and this approach can be excellent for proximal vertebral exposure (see Chapter 98). Finally, with further dissection, the proximal portion of the left subclavian artery (and left vertebral artery, if normal) can be reached through this incision. Again, caution should be taken with regard to the left recurrent laryngeal nerve; after looping around the aorta in the region of the ligamentum arteriosum, it ascends anterior to the arteries and can be within the surgical field.

Left Subclavian Artery, Emergent

In emergent situations (trauma with active bleeding) a more immediate need for proximal control may be present. In this situation an anterolateral limited third space thoracotomy, with the patient supine, allows expeditious proximal left subclavian artery control (Fig. 57.4). This approach usually does not permit extensive repair or other work in this area, but once bleeding has been controlled, definitive wide exposure can be obtained. When third space sternotomy and a supraclavicular incision is combined with the thoracotomy, this is termed a "trap-door" exposure (Fig. 57.5).

EXPOSURE OF VEINS WITHIN THE THORAX

Traumatic venous injuries are very often associated with concomitant arterial injury, and the previously described exposure concepts apply.

Exposure of the superior vena cava requires formal sternotomy. However, other techniques can be used for exposure of the central (medial) portion of the subclavian vein as it joins the jugular vein and/or the innominate veins on either side and are useful adjuncts in the treatment of venous thoracic outlet syndrome. The venous thoracic outlet is essentially the junction of the clavicle and sternum anteriorly, with the subclavius muscle and tendon and the ligamentous structures attaching the two bones playing a major role in venous obstruction (see Chapter 123). Over time these structures, especially in those who are muscular and/or participate in activities with arms overhead, can chronically injure the vein in this location. The decision to reconstruct this area is complex and exposure is critical. The injury to the vein is usually fairly central, and it is sometimes difficult to get centrally enough (defined as normal endothelium) from an infraclavicular approach. Molina has described an excellent technique for exposure of either innominate vein to the level of the cava.[3] The patient is supine, and the first rib has been resected using either an infraclavicular or paraclavicular approach. At this point a first interspace median sternotomy is performed (Fig. 57.6A). After the deeper tissues have been incised, the entire sternoclavicular complex (leaving the sternoclavicular junction intact) is then rotated upward, which provides superb visualization of this area. Finally, after the operation is completed, the sternal fragment is reattached to the main portion of the bone, using two sternal wires oriented at right angles to each other (see Fig. 57.6B).

Finally, although technically not a vein, the right atrial appendage can be used as outflow for complex venous occlusive disease (including patients with threatened AV access). This can be accessed fairly easily by means of a limited anterior third interspace thoracotomy (with the patient supine). The pericardial sac must be entered, but then the appendage is immediately accessible and easily clampable with a Satinsky-type clamp.[4]

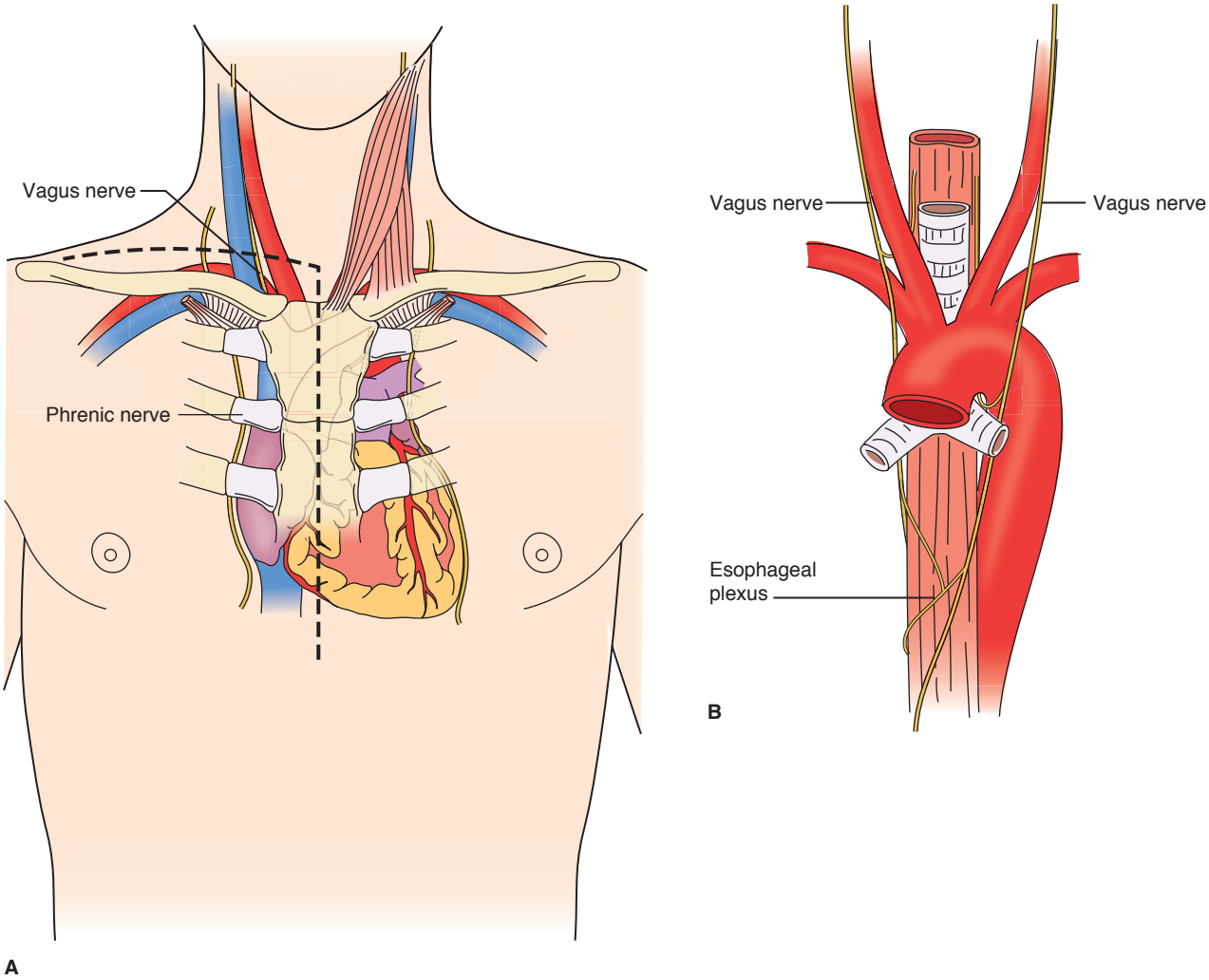

Figure 57.3 Median sternotomy extended to the (right) side, for better exposure of the innominate vessels, proximal subclavian artery and vein, and jugular vein. The sternocleidomastoid muscle can be divided in an emergency but is probably better left intact if possible (A). Note that the phrenic and vagus nerves both pass anterior to the arteries and posterior to the veins; both should be preserved (B).

EXPOSURE OF VESSELS WITHIN THE THORACIC OUTLET

The thoracic outlet broadly includes the neurovascular area from the scalene triangle to the axilla. This chapter will consider arterial exposures from the point at which they pass beyond the sternum to the deltoid to lie within this area. Barring anomalies, the anatomy is symmetric on each side, making descriptions easier.

As described previously, exposure of the vessels from the arch to the supraclavicular fossa, including the proximal vertebral arteries, is best performed by means of limited sternotomy and supraclavicular extension of the incisions. Direct access to the subclavian arteries will be limited by the sternocleidomastoid muscle medially and the anterior scalene muscle deep to it, the latter forming the anterior border of the scalene triangle. Through this triangle run the brachial plexus and subclavian artery, with the artery passing over the top of the first rib (the base of the triangle) (Fig. 57.7).

Subclavian Arteries

De novo exposure in this area can most easily be performed by means of a supraclavicular incision (however, it should again be stressed that in traumatic situations when a supraclavicular hematoma [or suspected subclavian artery injury] is present, strong consideration should be made of conservative, proximal control as described previously). Such a supraclavicular incision can essentially be placed anywhere; we use a convenient skin crease for best cosmetic results. This approach, in addition to being used for carotid-subclavian bypass, is also commonly used for treatment of neurogenic and arterial thoracic outlet syndrome and has been very well described by Thompson (see Chapters 121 and 122).[5] After division of the platysma and clavicular head of the sternocleidomastoid muscle, there is a

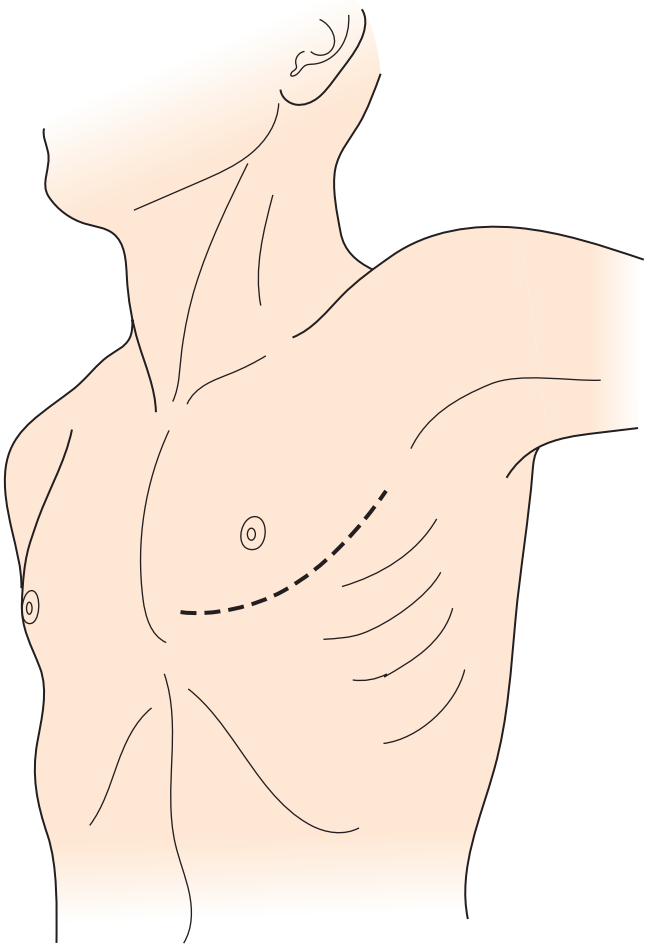

Figure 57.4 Left third interspace thoracotomy is ideal for emergent exposure of the proximal left subclavian artery when a patient is in the supine position. Be aware that the vagus nerve is anterior to the proximal portion of the artery and, after looping around the aorta near the ligamentum arteriosum, the recurrent laryngeal posterior (not shown).

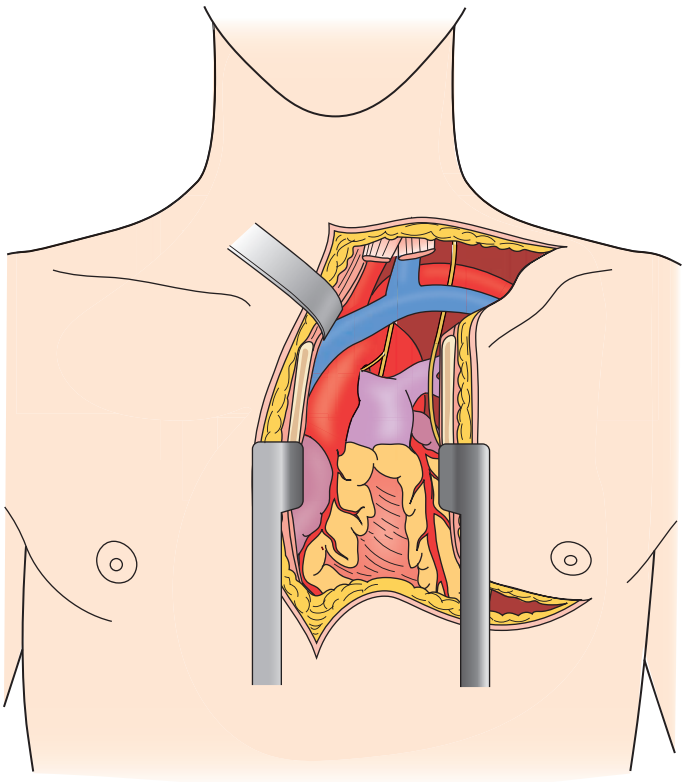

Figure 57.5 By adding median sternotomy and extending the incision to the left, the anterior thoracotomy is converted to a "trap-door" extension, nicely exposing the proximal left-sided great vessels. The sternocleidomastoid is divided in this figure.

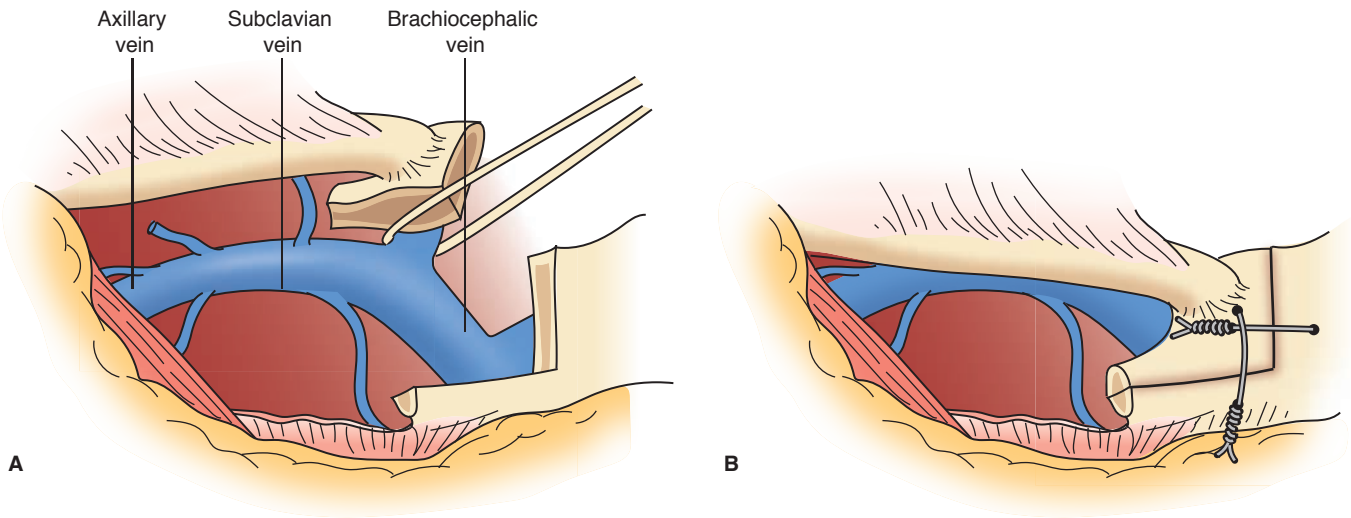

Figure 57.6 After anterior first rib resection, a first interspace sternotomy can be performed, leaving the sternoclavicular joint intact. (A) Initial exposure obtained by rotating this complex upward. (B) Repair using two perpendicularly oriented sternal wires. (From Molina JE. A new surgical approach to the subclavian and innominate veins. *J Vasc Surg*. 1998;27:576-581.)

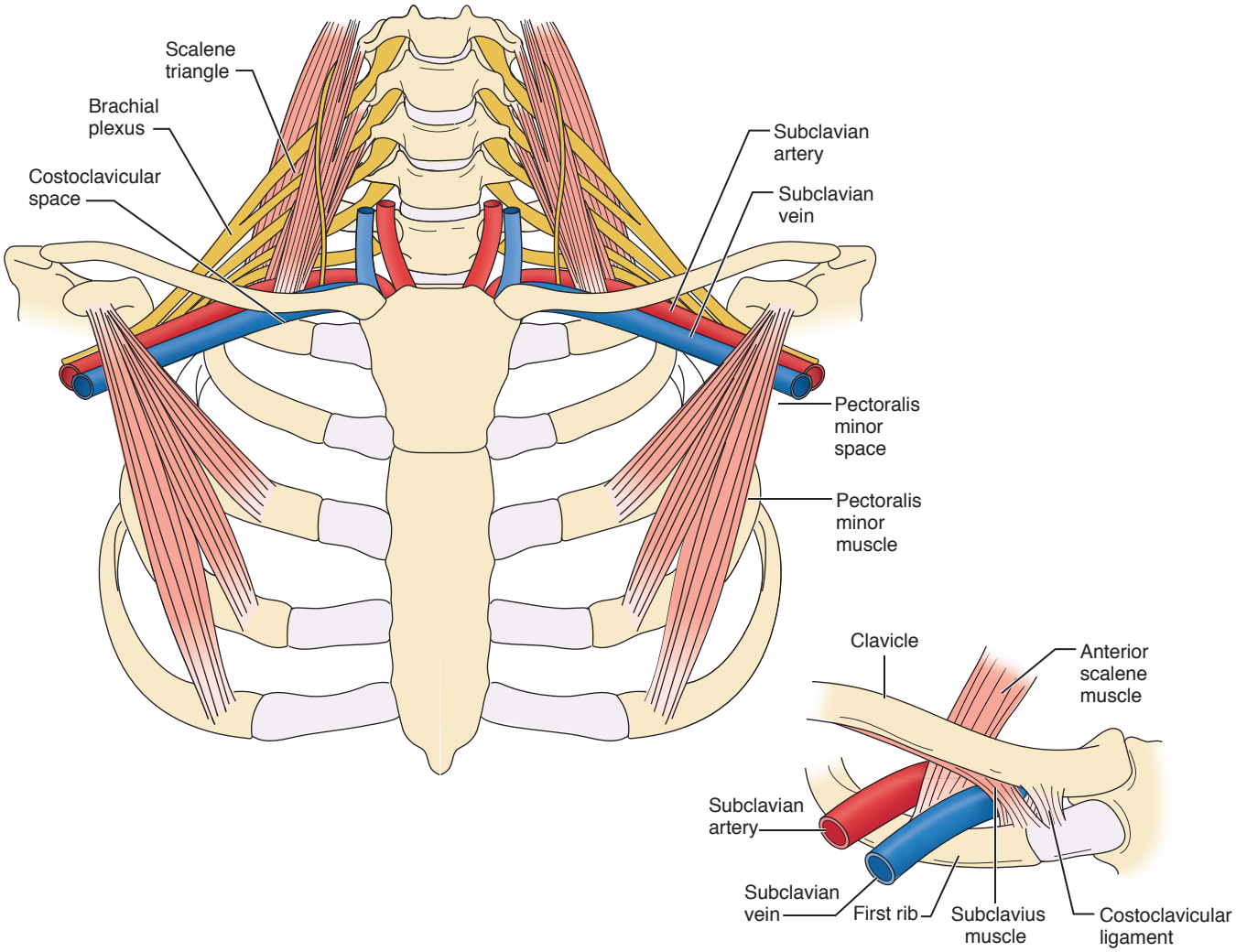

Figure 57.7 The Vessels and Nerves of the Thoracic Outlet. (A) Subclavian artery from its takeoff from the innominate to the pectoralis minor. The vertebral artery, internal mammary artery, and thyrocervical trunk arise proximal to the anterior scalene muscle; the latter two can be sacrificed. The phrenic nerve (and vagus nerve medially) runs anterior to the muscle (and thus artery) but behind the vein; this should not be sacrificed. (B) The anteromedial aspect of the thoracic outlet on the right side showing the subclavian vein running past the junction of the first rib and sternum, potentially compressed by the subclavius muscle, subclavius tendon, and fibrotic costoclavicular ligament.

fat pad of varying thickness, containing the omohyoid muscle. This should be divided and the fat pad teased superiorly or laterally. At this point the anterior scalene muscle will be exposed medially, with the phrenic nerve running in its characteristic (and unique) lateral to medial direction (Fig. 57.8). It is very important to identify and protect this nerve; complete injury can result in significant disability even for sedentary people. If it is not immediately visible, it should be looked for superficially directly anterior to the muscle or medially. If it is still not found, dissection of the muscle should be slow and careful because it may be intramuscular. Note that it is not uncommon to have bifid or duplicated nerves. The nerve can also be identified by first dissecting free the upper nerve roots (C5 and C6), then following them until the nerve is found.

Full division of the anterior scalene muscle is advised if carotid subclavian bypass is to be performed. Not all clinicians do this, and although we believe no data exist, essentially all failures we have treated are in patients whose muscle has been left intact (affecting both length and angles of the resultant bypass). This muscle should be divided as close as possible to the first rib then subtotally removed after the phrenic nerve is identified and protected; in theory, this prevents reattachment and scarring. After this is performed, the entire subclavian artery from beneath the sternocleidomastoid to the rib is nicely exposed. The vertebral arteries are more medial than one would expect. They generally lie beneath the SCM itself and can be reached by retracting this muscle. It should be noted that the clavicular head of the SCM can and may be sacrificed without consequence; in extenuating circumstances the entire muscle can be divided for full exposure from the sternum to the deltoid.

The subclavian arteries technically become the axillary arteries as they cross over the lateral border of the first ribs but obviously

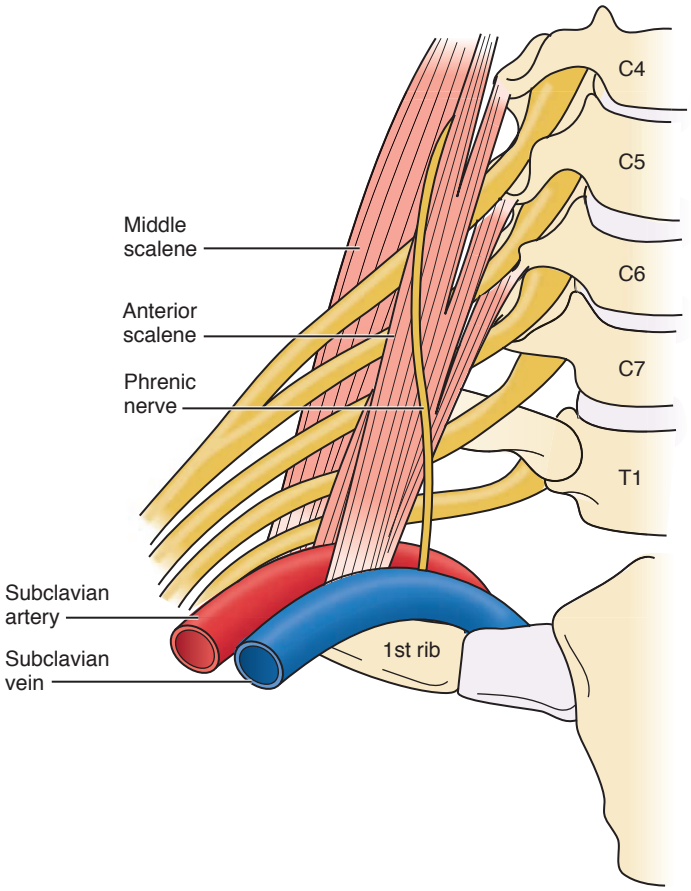

Figure 57.8 Anterior scalene muscle (right side) with phrenic nerve running lateral to medial as it descends (the only nerve in the body to do so).

structurally are the same vessel. They arch over the first rib then pass beneath the clavicle, cephalad to the vein. The area underneath the clavicle itself is difficult to approach, although claviculectomy is very well tolerated[6] and will afford excellent and expeditious exposure of both artery and vein. The axillary artery is easily accessible inferior to the clavicle, although it lies cephalad to the vein and is not always immediately visible (Fig. 57.9). The optimal approach to vessels in this area depends upon the indication. If the problem is a subclavian/axillary artery aneurysm (usually secondary to a bony abnormality: arterial thoracic outlet syndrome), a paraclavicular approach with control of the subclavian artery above the clavicle and axillary artery below, as described, allows bypass with a wide-open tunnel after the cervical rib, Roos band, and/or first rib have been resected. Conversely, if the lesion needs to be addressed directly, the clavicle can be resected with minimal morbidity. For axillary artery exposure inferior to the clavicle for an axillofemoral bypass, most advocate exposure as medially as possible (first part of the axillary artery), with tunneling of the graft deep to the pectoralis minor muscle and a very gradually diverging end-to-side anastomosis, to reduce the risk of axillary pullout syndrome. Again, the pectoralis minor muscle can be resected with impunity to expose the second part of the artery, and, if arterial inflow for an AV graft is needed, this allows excellent exposure.

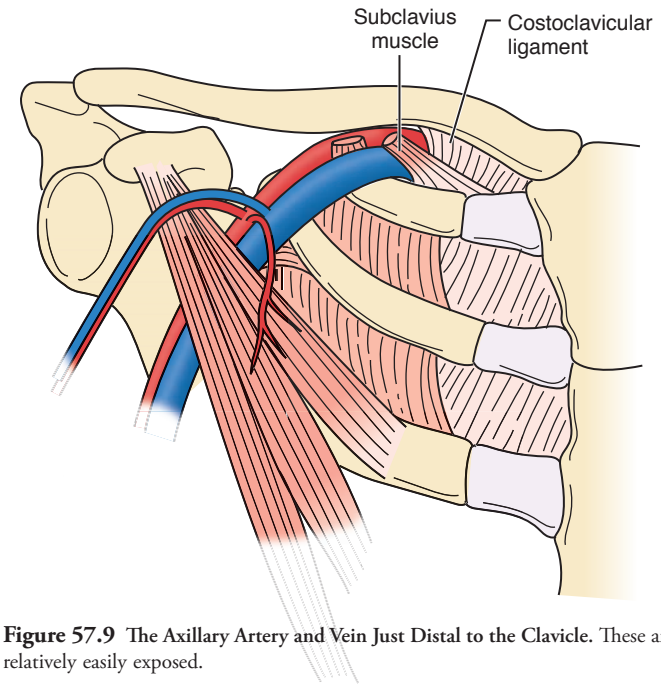

Figure 57.9 **The Axillary Artery and Vein Just Distal to the Clavicle.** These are relatively easily exposed.

Subclavian Veins

The veins lie inferior (caudal) and superficial to the arteries and are most often exposed for treatment of venous TOS. Although supraclavicular exposure is occasionally used, in the vast majority of cases the veins are very difficult to adequately expose from this direction. In addition, they obviously continue inferior to the clavicle as they move laterally, so we strongly advise an infraclavicular approach, usually combined with rib resection if venous TOS is the indication. The patient is supine, so imaging (for lysis, venoplasty, or AV access intervention) can easily be combined with surgery. An incision is made over the usually palpable first rib, extending to varying lengths laterally as the specific indication requires. The upper fibers of the pectoralis major are separated or divided, exposing a lateral fat pad. After this is retracted or resected, the inferior border of the rib can be identified and developed, although it is futile to explore the cephalomedial border at this point. We then identify the vein lateral to the rib and follow it medially; if a bulky subclavius muscle is present, it is resected off the clavicle, again moving laterally to medially. At this point the fibrotic tissue medially, made up to varying degrees of subclavius tendon and costoclavicular ligament, will be very obvious. Rather than incising this only, we advocate full resection from clavicle to rib (Fig. 57.10). At this point the cephalomedial border is exposed and can be developed to the level of the anterior scalene muscle. This muscle is then divided, and the mid- to posterior rib then developed by reflecting the fibers of the middle scalene muscle off of it. The rib is divided as posterior as possible and anteriorly within the cartilaginous segment and removed, after which a rongeur is used to pare back any bony or cartilaginous tissue impinging upon the vein. The vein can be freed at this point. There is often a fibrotic external cicatrix which, when removed, leaves behind surprisingly normal venous adventitia. If more proximal

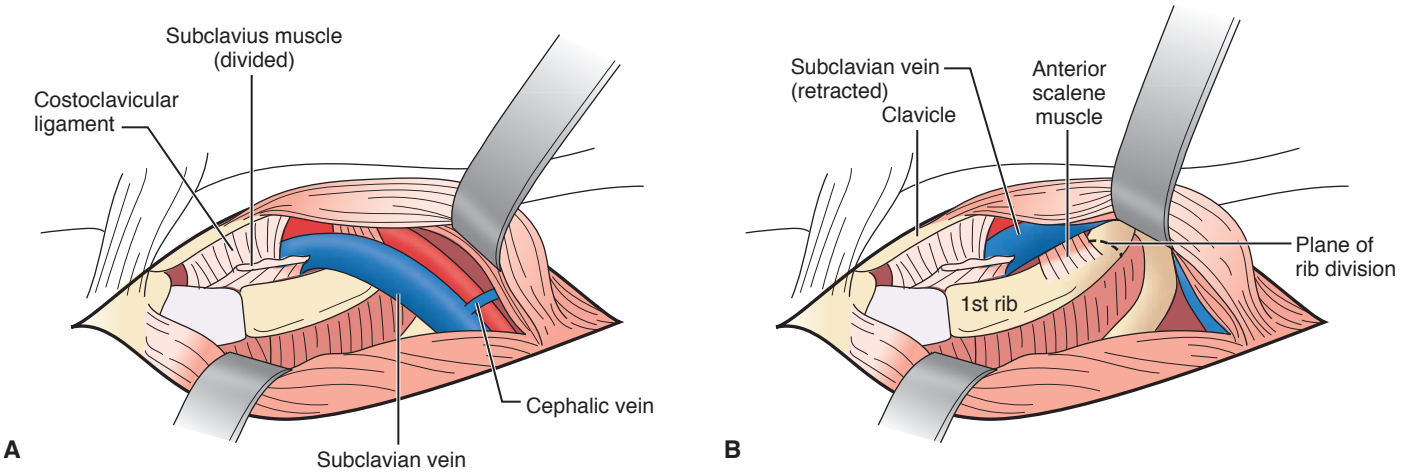

Figure 57.10 Infraclavicular exposure of the subclavian vein, most often used for treatment of venous thoracic outlet syndrome. (A) The intercostal muscle has been incised, exposing the anterior/inferior border of the first rib, and the subclavius muscle (laterally) and tendon (medially) and medial costoclavicular ligamentous structures exposed. The vein has been exposed laterally by resecting fatty tissue and then followed medially, at which point, all nonbony structures medially are resected. (B) The vein is then elevated upward; the anterior scalene muscle is exposed and divided. The phrenic nerve is well medial at this point and not in the surgical field, the medial border of the rib exposed, and the rib divided several centimeters deep to the vein.

exposure is needed, sternoclavicular rotation as, described previously (see Fig. 57.6), can be used; distal exposure requires division of soft tissue only and is relatively trivial.

Ultimately, exposure of the axillary vessels is limited laterally by the deltoid muscle. In an emergency this can obviously been excised, but other than in trauma, there is essentially no indication for exposure of the artery in the area deep to the deltoid itself.

EXPOSURE OF THE ARM VESSELS

Exposure of the vessels in the arm is relatively straightforward. Traumatic injuries can usually be approached directly by an experienced vascular or trauma surgeon. Even if hemorrhage is unroofed, direct pressure is usually trivial, and a tourniquet can be placed without problems.

The brachial artery in the upper arm is most commonly used as inflow for an upper arm AV graft or as inflow for distal revascularization interval ligation (DRIL), whereas the vein is commonly exposed for the venous anastomosis of an upper arm AV graft (see Chapter 175). Parenthetically, although some have described DRIL as being performed with a short bypass component, there is no evidence to support this and solid hemodynamic evidence exists to support as long a segment of interposed native artery as possible,[7] hence the recommendation for exposure as proximally as possible. A longitudinal incision is made in the upper arm distal to the deltoid muscle, and the neurovascular bundle is located just below (medial to) the biceps. The artery is usually deep to the vein (variably paired at this level) and nerve, but exposure is straightforward (Fig. 57.11). Although the median nerve must obviously be preserved, the superficial nerves in this area, some quite large, are all sensory and patients do not typically have significant symptoms after division. Of note, unlike in the leg, the deep brachial vein can

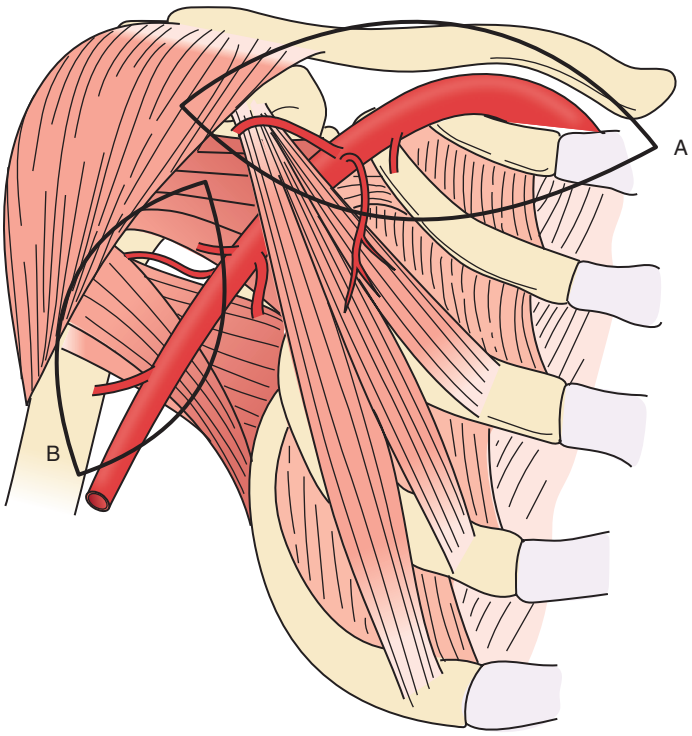

Figure 57.11 Exposure of the Axillary Artery. (A) Between the clavicle and pectoralis minor. (B) Distal to the pectoralis minor. Note that this muscle can be divided with impunity.

be sacrificed without problems; this can be helpful to increase length and eliminate problems caused by tethering at the swing point of a transposed brachiobasilic AV fistula.

More distally, the brachial artery at the antecubital fossa is obviously the most commonly exposed upper extremity artery; it serves as the inflow vessel for approximately 80% of upper

extremity AV access cases, as well as the access vessel for upper extremity imaging and intervention for many thoracic cases. For brachiocephalic fistula creation, a transverse incision is best. It is tempting to stay slightly proximal to the antecubital crease to avoid bending the vein, but as exposure moves proximally the cephalic vein is located more laterally, increasing the distance between the vein and the artery. The author finds that an incision slightly distal to the crease allows the best fistula to be created. In addition to the cephalic vein itself lying close to the artery, various anatomic variants (antecubital vein, perforating veins) can most easily be used for access. A longitudinal incision is most convenient if the antecubital fossa is not crossed; if so, a transverse or "lazy-S" incision will reduce the risk of stricture. The longitudinal incision also provides excellent exposure of the proximal radial artery just distal to its takeoff from the brachial artery. Constructing the AV anastomosis at this level may decrease the likelihood of developing a steal syndrome. Like many superficial arteries, an overlying tendinous band (the bicipital aponeurosis) tends to protect it. The artery is easily palpable; dividing the fibrotic tissue very easily exposes it (Fig. 57.12). Finally, although venous exposure in this area is relatively straightforward, knowledge of which vein is exposed is important for successful AV access. The cephalic vein can be used itself, or the variably located antecubital vein or deep perforating veins can be used to lengthen a brachiocephalic fistula. Similarly, if a first-stage (nontransposed) brachiobasilic fistula is to be constructed, usually a branch traveling into the antecubital fossa can be found. If this branch is not present or usable, the true basilic vein in this location is quite medial.

The artery just distal to this is commonly exposed for the distal anastomosis of a DRIL. The benefit of this operation is to fully perfuse the forearm (distal revascularization) while eliminating all retrograde flow into the fistula (interval ligation); it is thus critical to ensure that the brachial artery itself (above the bifurcation) is ligated. We prefer a longitudinal incision just distal to the takeoff of the AV fistula; formal landmarks are sparse, but the artery should be accessible with minimal exploration (Fig. 57.13). If the artery is not immediately localizable, occlusion of the fistula with localization by palpation or a Doppler probe can help. Once the artery is exposed, attention should be paid to ensure that the brachial artery itself (proximal to the bifurcation) is ligated (the anastomosis can be performed to any site on the vessels as long as continuity between the radial and ulnar arteries is maintained).

The radial artery and cephalic vein are most commonly exposed at the wrist for creation of a radiocephalic fistula. Most prefer a longitudinal incision; the pulse is followed to the artery (which lies between the flexor carpi radialis and brachioradialis tendons). No special precautions are followed, other than preservation of the radial sensory nerve; division or injury of this nerve leads to a surprising amount of disability. The cephalic vein is likewise easy to expose, although usually the lateral branch, "deep" with regard to this exposure, is best to use (Fig. 57.14). There is evidence that decreasing manipulation of this vessel improves early AV access patency, but extensive manipulation allows the vein to lie without tension at the "swing point"

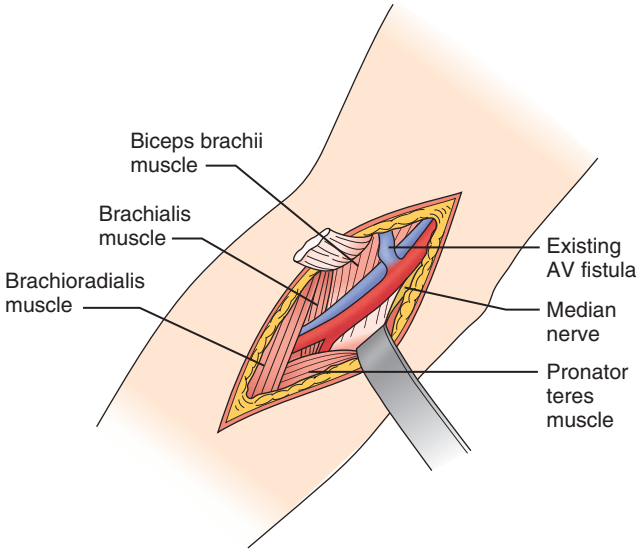

Figure 57.13 Exposure of the brachial artery distal to the antecubital fossa for distal revascularization interval ligation (DRIL) or embolectomy. In both cases the ulnar and radial artery takeoffs should be exposed and controlled. *AV*, Arteriovenous.

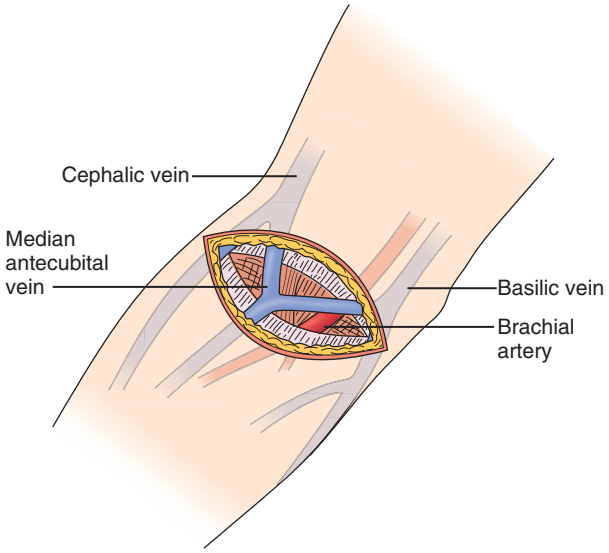

Figure 57.12 Exposure of the brachial artery and vein(s) at the antecubital fossa.

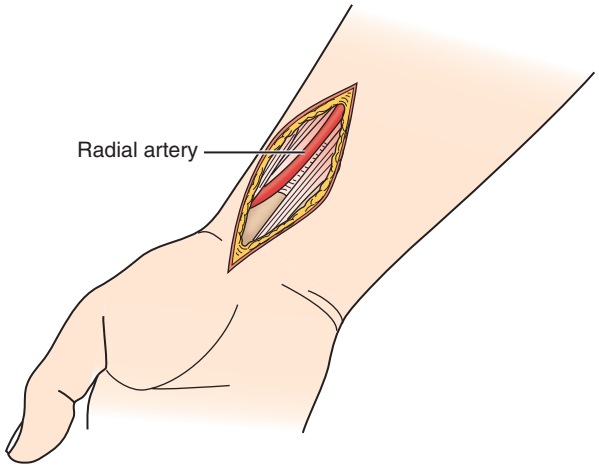

Figure 57.14 Exposure of the radial artery at the wrist.

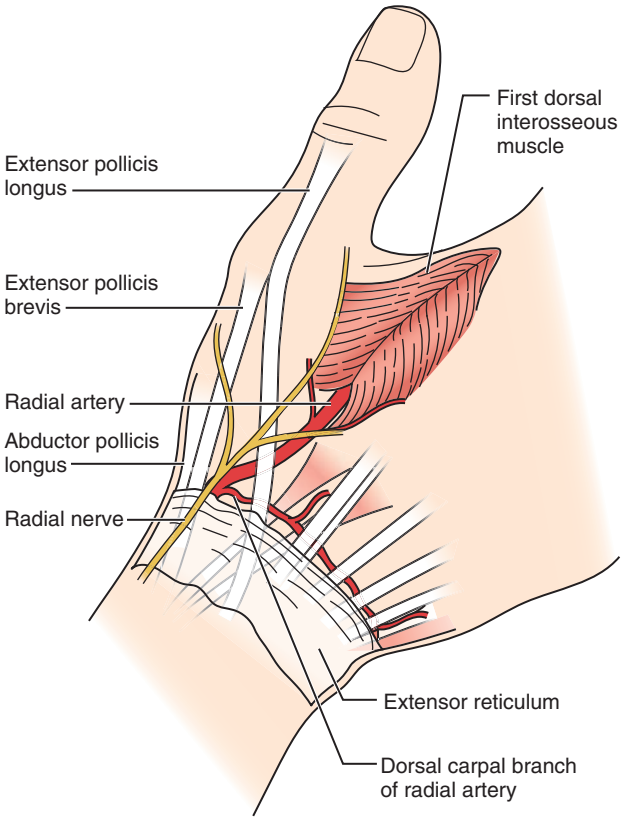

Figure 57.15 Exposure of the radial artery just medial to the extensor pollicis longus tendon for a snuff-box fistula.

where it transitions from "loose" to fixed by tissue. The radial artery can be exposed in the anatomic snuff-box quite easily for a snuff-box fistula, and is quite large in this area (Fig. 57.15).

The ulnar artery is very seldom exposed. Most avoid using this for access because it is the dominant artery to the hand. It is unclear whether this attitude is supported by evidence, but if exposure is needed, the pulse can simply be followed to the artery.

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CHAPTER 58

Spinal Operative Exposure

JEFFREY L. BALLARD and GREGORY D. CARLSON

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Anterior lumbar interbody fusion (ALIF) was first described by Carpenter[1] in 1932 and promoted by Hogson and Stock[2] in 1956 for definitive treatment of more anteriorly oriented spine pathology and to avoid posterior element injury. The originally described procedure, which required significant operative exposure and was considered to be quite invasive, has undergone a number of modifications that have minimized the extent of required surgical exposure. These surgical modifications have made the anterior approach to the lumbosacral (ALIF) as well as the thoracic (anterior thoracic interbody fusion [ATIF]) spine a widely accepted technique for spinal arthrodesis or for diskectomy/decompression.

Anterior spine exposure for interbody fusion, performed with the patient in either supine or lateral decubitus position depending upon disk level(s) of interest, is usually combined with supplemental posterior fixation with the patient prone to increase the rate of complete spinal fusion. A number of different implants are used to effect anterior interbody fusion (AIF); however, description of them is beyond the scope of this chapter. Advantages of AIF from the orthopedic perspective include preservation of posterior elements, decreased incidence of nerve injury, and avoidance of epidural scarring.[3] From the vascular surgeon's perspective, the key to successful AIF is to provide the spine surgeon with adequate vertebra side-to-side surgical exposure so that diskectomy, decompression, and partial corpectomy (if needed) can be safely performed and so that implants can be accurately inserted on the basis of the disk space midpoint.

AIF for lumbosacral (LS) spine pathology was originally performed through an open retroperitoneal exposure with a large incision, extensive tissue manipulation, and significant patient morbidity.[3] The retroperitoneal approach for ALIF takes advantage of the potential space between the peritoneal contents and kidney and the quadratus lumbar and psoas muscles to afford excellent anterior lumbosacral spine exposure. Other surgical approaches, such as mini-open retroperitoneal, endoscopic retroperitoneal, and endoscopic lateral transpsoas, have also been used to capitalize on the retroperitoneal plane of dissection but to minimize surgical morbidity without compromising anterior spine exposure.[3-18] Laparoscopic transperitoneal spine exposure also has it proponents.[6,8,9,11] However, all the previously mentioned surgical approaches eventually necessitate dissection and mobilization of the thoracic aorta, abdominal aorta, and/or iliac arteries with accompanying major venous structures depending on the disk level(s) of interest.

Notwithstanding the potential for major arterial or venous injury that could occur during anterior spine exposure, there is also the potential for significant injury to other vulnerable structures that are encountered during routine cases.[4] Recognition

Abstract

The chapter begins with a brief historical review anterior lumbar and thoracolumbar interbody fusion. Key issues related to clinical assessment and potential surgical risk factors are discussed as well as patient risk assessment. Diagnostic evaluation from a vascular surgeon's perspective is reviewed including noninvasive and invasive testing. Surgical treatment, indications and contraindications of surgery and relevant anatomy are then fully explored. Operative planning and options with description of various spine level exposures is detailed. Surgical results (early and late) and potential complications of surgery are examined with a brief discussion of postoperative management and follow up. Finally, special anatomical and pathological considerations such as re-do spine exposure and calcified arterial anatomy are reviewed.

Keywords

Anterior Retroperitoneal
Lumbar
Lumbosacral
Thoracolumbar
Interbody Fusion

of these possible complications has been the impetus for most centers of excellence to develop a two-team (vascular surgery plus either orthopedic surgery or neurosurgery) approach to minimize morbidity and to maximize optimal operative exposure for reconstructive spinal surgery. This chapter explores anterior spine exposure from a vascular surgeon's perspective.

CLINICAL PRESENTATION, DIAGNOSTIC EVALUATION, AND RISK ASSESSMENT

In contrast to the characteristic patient with atherosclerotic disease that a vascular surgeon encounters, the patient needing anterior spine exposure is often younger, has few to no risk factors for peripheral arterial disease (PAD), and, not infrequently, may be overweight due to inactivity. The patient often has associated radiculopathy, a long-standing pain syndrome that may be managed by many different specialists, and many have had a traumatic work-related injury. In short, the typical patient requiring AIF presents with a number of complicating issues that are not necessarily related to PAD.

Lumbosacral spine exposure involves extensive mobilization of major arteries within the abdomen/pelvis as well as their accompanying major veins; therefore, a history of claudication or any abnormality in the peripheral pulse findings should be first evaluated by noninvasive testing. Occasionally, further invasive testing such as arteriography and/or computed tomography is required for severe aortoiliac occlusive disease or aortic aneurysmal disease. Significant aortoiliac artery calcification can be problematic regarding placement of retractors and increases the potential risk of arterial injury or dissection. Extent of arterial calcification can be evaluated with plain radiographs or computed tomography if this diagnosis is suggested by noninvasive testing. The bottom line here is to have an accurate assessment of peripheral pulses prior to surgery because temporary vessel occlusion is part and parcel of mini-open retroperitoneal anterior spine exposure.

Besides a thorough peripheral pulse examination, it is wise to examine the patient's thorax, abdomen, and flank for signs of previous chest or abdominal procedures, the presence of which may influence subsequent incision placement. For instance, the lower lumbosacral spine can be well exposed via a right retroperitoneal approach if the procedure is a "redo" or, if the adjacent proximal or distal disk level will now be exposed, or if there has been prior abdominal surgery with incisions in the left upper or lower quadrant. In our experience, patients undergoing ALIF (particularly in younger individuals) are often focused on incision position and length; therefore, it is prudent to discuss the proposed incision prior to surgery because omission of this minor detail can be very problematic for both surgeon and patient in the postoperative period. Incision length may need to be extended to facilitate adequate spine exposure if there is significant calcific atherosclerotic disease or when the patient has a large body habitus.

Fortunately, the overwhelming majority of patients needing anterior spine exposure are relatively healthy and do not require any other preoperative testing except as mentioned previously. However, older patients may need preoperative cardiac stress testing or pulmonary function studies, particularly if the procedure requires thoracic spine exposure. Needless to say, it is paramount to thoroughly discuss possible complications of surgery with the patient, including but not limited to major artery/vein injury, bowel or ureter injury, deep venous thrombosis, wound infection/seroma, nerve injury, and erectile dysfunction (usually retrograde ejaculation as opposed to impotence) due to disruption of the intermesenteric nerve plexus and superior hypogastric nerve plexus, which course over the left common iliac artery origin.[4] Lastly, it is wise to note that there is often significant anterior spinal scarring with an increased incidence of complications if the procedure is done in the setting of diskitis, previous posterior laminectomy, or if the exposure is one disk level proximal or distal to one that has been previously exposed.

SURGICAL TREATMENT

It is beyond the scope of this chapter to discuss the indications for and contraindications to ALIF and ATIF from an orthopedic perspective, and in this clinical setting, the vascular surgeon must rely upon the expertise of the orthopedic colleague to ensure that surgical indications are sound. Rarely have we advised against surgery after a thorough orthopedic and vascular preoperative assessment except in the occasional case of a grossly morbidly obese patient. In these unusual cases, the risks of surgery far exceed the benefits until significant weight loss has been addressed. Nonetheless, we do have significant experience with successful AIF even in patients with body mass index (BMI) higher than 30.

Operative Planning and Surgical Exposure Options

In the majority of procedures, the disk space(s) of operative interest is exposed by dissection and mobilization of the overlying vessels from left to right across the midline via a left thoracotomy for thoracic spine procedures or via the left retroperitoneal space for lumbosacral spine procedures. No single approach lends itself to all circumstances; therefore, it is wise to become comfortable with the relationship of the target disk level(s) to overlying skin and bony structures such as ribs, costal margin, and anterior superior iliac spine, because the appropriately placed incision will minimize soft tissue dissection and extent of vessel mobilization. Palpation of pedal pulses before and after the procedure is also prudent because temporary arterial occlusion often accompanies disk exposure and spinal instrumentation.

Once the disk level or levels of interest are fully exposed, we have found it wise to remain present in the operating room to assist the orthopedic surgeon with diskectomy, decompression, and spinal fusion. Major vascular injuries may occur when sharp curettes, rongeurs, and drill bits are being used. Prompt, potentially life-saving, vessel repair can be performed only if the vascular surgeon remains close at hand. Finally, and particularly in teaching institutions, thoracic and retroperitoneal

exposure of major arterial and venous structures provides an excellent opportunity for vascular surgery residents to obtain open surgical training and to learn how to safely and effectively manipulate blood vessels.

Thoracic Spine Exposure

Thoracic spine exposure requires the least amount of vessel dissection because the interbody implants are designed to be placed from a more lateral position, unlike lumbosacral spine exposures, in which the implants are usually positioned from a true anterior approach. Therefore a mini-open left or, occasionally, right, thoracotomy with the lung deflated is normally employed for procedures that are limited to the thoracic spine. Very proximal thoracic spine procedures that involve disk pathology from T1 to T3 are usually approached posteriorly except in unusual circumstances that may require medial clavicleculectomy or mini-sternotomy. A limited right thoracotomy facilitates spine access and exposure from T3 to T6, and a limited left thoracotomy is usually utilized for procedures that involve disk pathology from T7 to T12, although one can also obtain spine exposure through the L2 vertebra from a low thoracotomy approach if needed.

Thoracolumbar (T12-L2), lumbar (L2-L5), and lumbosacral (L5-S1) spine exposures necessitate more extensive mobilization of major abdominal and pelvic vessels and risk injury to other vital structures within the operative field.[4] Various surgical approaches including mini-open retroperitoneal, laparoscopic transperitoneal, endoscopic retroperitoneal, and endoscopic lateral transpsoas have been used for ALIF to minimize vessel dissection and surgical morbidity without compromising anterior spine exposure.[4-18] No matter the approach, the key advantages of anterior spine exposure are direct access to and superb visualization of the intervertebral disk level of surgical interest.

Lumbosacral Spine Exposure

The surgical approach for ALIF can pass either through the abdominal cavity or outside the peritoneal contents in an extraperitoneal plane of dissection (see Chapter 54).

Transperitoneal Exposure

Transperitoneal lumbosacral spine exposure requires extensive mobilization of the midgut and hindgut out of the operative field. This can be a demanding exercise, particularly in obese patients or in those who have dense adhesions as a result of a prior abdominal procedure or inflammatory process. Furthermore, the transperitoneal approach is associated with prolonged postoperative ileus, third-space fluid sequestration, and an increased risk of retrograde ejaculation in male patients.[6,12-15] Sasso et al.[15] found a tenfold higher risk of retrograde ejaculation when they compared transperitoneal with retroperitoneal L4 to S1 spine exposure. Mini-open anterior retroperitoneal lumbosacral spine exposure has advantages similar to those that have been described for retroperitoneal aortoiliac vascular procedures.[19] This is particularly true in regard to length of hospital stay, postoperative ileus, and other perioperative complications.

Transperitoneal Laparoscopic Exposure

Transperitoneal laparoscopic interbody spine fusion has been evaluated as a method to minimize open surgical morbidity and potential abdominal wall complications.[6,8,9,16] Katkhouda et al.[16] compared the safety and efficacy of the laparoscopic approach for single- and multilevel degenerative disk procedures. Twenty-four consecutive laparoscopic transperitoneal interbody lumbar fusions were evaluated prospectively (18 single-level procedures were compared with 6 multilevel procedures). Results of the laparoscopic multilevel procedures were further compared with those of 12 mini-open multilevel operations. Twenty of 24 procedures were completed laparoscopically. Four procedures were converted to open procedures to control bleeding from an iliac vein laceration in three patients and a mesenteric tear in the fourth. Overall results were decidedly worse for multilevel laparoscopic procedures than those in the matched open group.

Another prospective, nonrandomized study directly compared laparoscopic with open mini-anterior L4 to L5 retroperitoneal lumbar interbody fusion in 50 consecutive patients.[8] Twenty-five patients underwent anterior laparoscopic interbody fusion, and 25 had open mini-ALIF. There was no statistical difference in operating time, blood loss, or length of hospital stay between the two groups for single-level fusions. However, laparoscopic procedures took 25 minutes longer ($P = 0.035$) than open procedures for multilevel fusions. The rate of complications was significantly higher in the laparoscopic group (20% vs. 4%), and in 16% of patients undergoing laparoscopic surgery, there was inadequate spine exposure. Other writers have commented that the perceived advantages of a laparoscopic approach have not been realized in clinical practice and that variability in vascular anatomy significantly limits its applicability.[6-9] Finally, the endoscopic lateral transpsoas approach does minimize vessel dissection, but has increased risk of groin/thigh numbness and pain from manipulation of the genitofemoral nerve coursing along the psoas muscle.[5]

Anterior Retroperitoneal Exposure

Despite a working knowledge of laparoscopic techniques, we continue to favor open mini-ALIF via anterior retroperitoneal lumbosacral spine exposure, if possible, for the following reasons. Our current experience demonstrates few overall complications for this approach in comparison with other spine exposure techniques.[18] Single-level or multilevel disk exposure can be performed in an expeditious manner with minimal intraoperative complications. Vital structures can be thoroughly mobilized out of harm's way to facilitate complete diskectomy and, in theory, better interbody fusion. Finally, the surgical approaches described in the following paragraphs facilitate the spine surgeon's need to have direct anterior access to the lumbosacral spine.

Relevant Surgical Anatomy

Thoracic Spine Exposure

Patient positioning for exposure of the thoracic spine is similar to the position that is often used for open thoracoabdominal

aortic aneurysm repair (see Chapter 53).[20] After central venous and radial arterial line placement and dual-lumen endotracheal intubation, the patient is placed in a true right or left lateral decubitus position. A beanbag device, or anterior/posterior padded bolster, is helpful to support the patient's position on the operating table. The free upper extremity can be passed across the upper chest and supported on a cushioned Mayo stand. Care should be taken to ensure that padding of the lower extremities is appropriate and that there is no external pressure on the feet or that the feet are severely plantar-flexed. Transcranial motor evoked potential (TCMEP) monitoring and somatosensory evoked potential (SSEP) monitoring of the posterior tibial nerve, with the ulnar nerve as control, is used for all of our spine procedures.

The rib interspace to be entered after the lung is deflated depends primarily on the extent of thoracic spine that is to be exposed, and there is no need to divide the costal margin in the vast majority of cases. In general, the best operating exposure for the spine surgeon is afforded by entering the chest two intercostal levels proximal to the disk level of interest. We often remove the lower rib to facilitate access at multiple disk levels and then morselize the rib for use as bone graft during the procedure. However, removal of the rib facilitates spine visualization at the potential cost of increased postoperative pain, which can be relieved with a multilevel intercostal block. Intraoperative fluoroscopy is vital to identify the appropriate disk space(s) and to limit the extent of surgical dissection. For proximal thoracic spine exposure via a right thoracotomy, incision of the parietal pleura along the lateral aspect of the thoracic vertebra and limited division of ipsilateral intercostal arteries/veins facilitates exposure of the disk space(s) as needed. Venous tributaries coursing into the azygos vein should be divided as needed to prevent injury and troublesome bleeding. These maneuvers are generally all that is needed for proximal thoracic spine exposure, and it is a rare circumstance that one would encounter the esophagus or the vagus nerve, which courses parallel and medial to the azygos vein in the proximal chest.

From the left side, for mid-to-distal thoracic spine exposure, the approach is similar to that already described, except that the descending thoracic aorta is encountered as one dissects across the anterior surface of the thoracic vertebra and disk space. After limited division of ipsilateral intercostal arteries/veins, the descending thoracic aorta can be retracted medially with Omni-Tract (Integra Lifesciences, Minneapolis, Minnesota) renal vein retractors to minimize the risk of arterial injury. Preservation of the blood supply to the spinal cord is critical; therefore, it is wise to ligate intercostal arteries close to the aorta to preserve potential collateral vessels. Brockstein et al. [21] have stressed the importance of the arteria radicularis magna (artery of Adamkiewicz) in providing circulation to the anterior spinal artery. This vessel is a branch of either a distal intercostal or a proximal lumbar artery. It has been identified as proximal as T5 and as distal as L4.[21] However, the artery generally arises between the T8 and L1 vertebral levels. Therefore it is unwise to ligate any large intercostal or proximal lumbar artery unless it is absolutely necessary to do so for adequate disk space exposure. Finally, the diaphragm can be divided in a limited fashion just lateral to its central tendinous portion to extend the dissection distally to facilitate exposure through the L1 to L2 disk space. Alternatively, these disk spaces can be exposed from the chest by "hooking" the central tendinous portion of the diaphragm with a renal vein retractor, pulling caudad, and performing very limited dissection of the diaphragmatic attachments to the proximal lumbar vertebral bodies.

T12 to L2 Exposure

For thoracolumbar (T12-L2) spine exposure, the patient is placed in the right lateral decubitus position on the operating table with the kidney rest at waist level. If needed, the kidney rest can be elevated and the operating table gently flexed to open the space between the left anterior superior iliac spine and the costal margin. The free left upper extremity is positioned as described earlier. A limited flank incision is made over the anterior extent of the 12th rib. This step decreases the chance of injury to the main trunk of the intercostal nerve within the 11th intercostal space.[20] Abdominal/flank muscle fibers should be split in their respective orientations as opposed to transected. Resection of the 12th rib facilitates safe entry into the retroperitoneal space, as well as an extraperitoneal plane of dissection. Alternatively, this limited thoracolumbar spine exposure can be obtained through the 10th or 11th intercostal space as mentioned previously, with dissection just lateral to the central tendinous portion of the diaphragm, rather than inferior to the diaphragm as described here.

Extraperitoneal entry into the upper left retroperitoneal space exposes Gerota's fascia with contained left kidney as well as the spleen, which can then be rotated inferomedially off the diaphragm and proximal psoas muscle. This maneuver facilitates exposure of the left diaphragmatic crus, which will be divided to reveal the underlying vertebra and abdominal aorta. Once again, limited ligation and division of intercostal/lumbar arteries as needed should be performed to preserve spinal blood flow. The Omni-Tract retraction system (Integra Lifesciences), with its multiple and varied blades, is critical for maintaining this exposure. The previously mentioned thoracolumbar spine exposure can also be performed from a right flank approach, requires mobilization of the right lobe of the liver and, in some cases, the vena cava. We have also performed limited thoracolumbar spine exposure via a left upper quadrant paramedian incision, which affords the spine surgeon superb anterior spine exposure.

L2 to S1 Exposure

More distal lumbosacral spine exposures (typically from L2 to S1) are usually performed with the patient supine and via small oblique or longitudinal left (occasionally right) paramedian incisions. The preoperative lateral lumbar spine radiograph can be useful to determine appropriate position of the incision for optimal disk space exposure. The relationship of the palpable iliac wing, which is easily visualized on the lateral radiograph, with the lower lumbar disk levels, provides an excellent landmark to determine incision placement. Oblique/transverse incisions that are centered over (or just between) the target disk(s) are useful for one- or two-level disk exposures, and longitudinal

paramedian incisions facilitate multilevel disk exposure. Electromyography in addition to somatosensory-evoked potential monitoring is used for these cases. A reduction in somatosensory-evoked potential amplitude may signal diminished blood flow and ischemia to the affected limb.

In either orientation, the incision is carried through the anterior layer of the rectus sheath to expose the rectus abdominis muscle. The muscle belly is dissected medially away from the medial aspect of the rectus sheath and retracted laterally to expose the posterior layer of the rectus sheath and/or the transversalis fascia. There is no transection of muscle fibers, so the incidence of muscle laxity or abdominal wall bulge is minimized. The posterior rectus sheath/transversalis fascia is incised to develop an extraperitoneal plane of dissection. Rotation of the peritoneal contents from left inferolateral to right superomedial opens the left lower retroperitoneal space and exposes the major arteries and veins that overlie the distal lumbosacral spine. For higher levels of thoracolumbar spine exposure (T12-L1), we typically utilize a retronephric, extraperitoneal plane of dissection by rotating the kidney and left ureter, as well as the peritoneal contents, medially off the psoas muscle. However, we have found that in most patients, particularly the morbidly obese patient, it is often easier to obtain proximal (L1-L3) lumbar spine exposure if the dissection plane to the anterior spine is developed between the left colon and Gerota's fascia, leaving the left kidney and ureter in place. In this circumstance, care must be taken to protect the left ureter, which will remain in situ and lateral to the spine. It is also important not to injure the very vascular tissue that is medial to the kidney hilum and adjacent to the adrenal gland. Occasionally, the spleen also requires medial mobilization away from the psoas muscle and diaphragm to facilitate some extended thoracolumbar spine exposures.

The maneuvers described previously, depending on their extent, facilitate exposure of the entire abdominal aorta and left common iliac artery with accompanying left common iliac vein (Fig. 58.1). Mobilization of these vessels from left to right across the midline is usually required to anteriorly expose the spine and disk space from side to side. The left ureter is generally swept medially with the posterior peritoneum out of harm's way; however, if the ureter appears to be under too much stretch and at risk for injury, it should be gently dissected away from the medially rotated posterior peritoneum. The ipsilateral vas deferens and testicular/ovarian vessels are gently dissected away from the posterior peritoneum to maintain their normal anatomic positions, and occasionally, division of the round ligament in women facilitates medial rotation of the peritoneal contents and exposure of the distal lumbosacral spine. The vestigial ipsilateral umbilical artery that courses into the internal iliac artery can be divided with impunity. Finally, and particularly in males, a concerted effort is made to protect the condensation of nerve elements (intermesenteric nerve plexus and superior hypogastric nerve plexus) that course over the left common iliac artery origin (Figs. 58.2 and 58.3). The use of bipolar cautery in this area for any small paraspinal and periarterial bleeders also helps decrease inadvertent nerve injury.

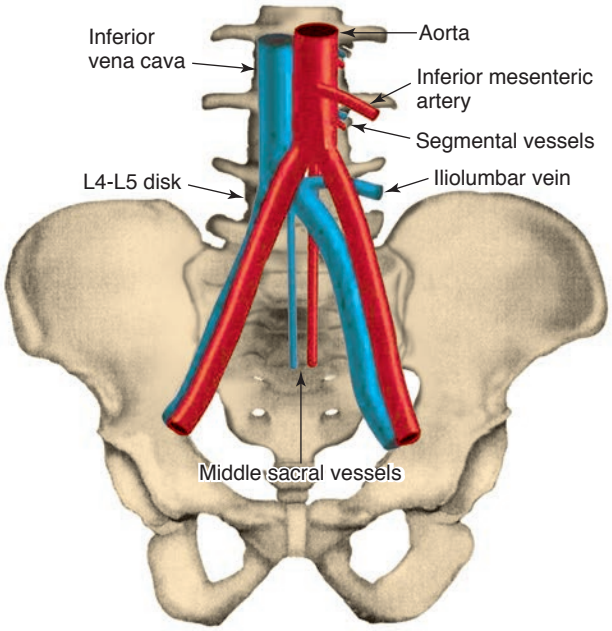

Figure 58.1 Arterial and venous anatomy that is typical for lumbosacral spine exposure. Note that in this case the L4 to L5 disk is just above the aortic and caval bifurcation.

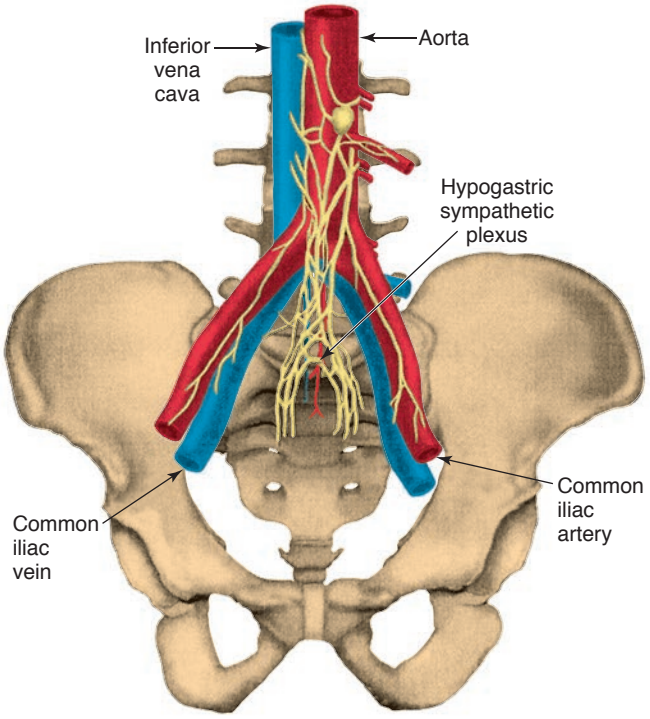

Figure 58.2 Relationship of the infrarenal sympathetic nerves to the aorta and iliac arteries.

L4 to L5 and L5 to S1 Exposures

Exposure of the L5 to S1 disk space is relatively straightforward compared with other levels, because once the rectosigmoid bowel is swept across the midline from left to right, the disk space is readily exposed between the left common iliac vein and the

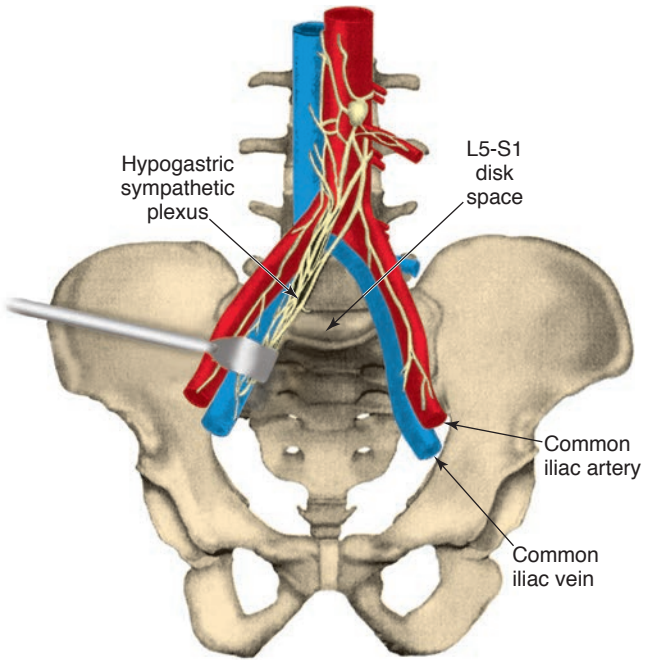

Figure 58.3 To approach the L5 to S1 disk and to protect the sympathetic nerves, it is wise to begin dissection along the medial aspect of the left common iliac vein and then to retract the soft tissue overlying the disk toward the right common iliac artery.

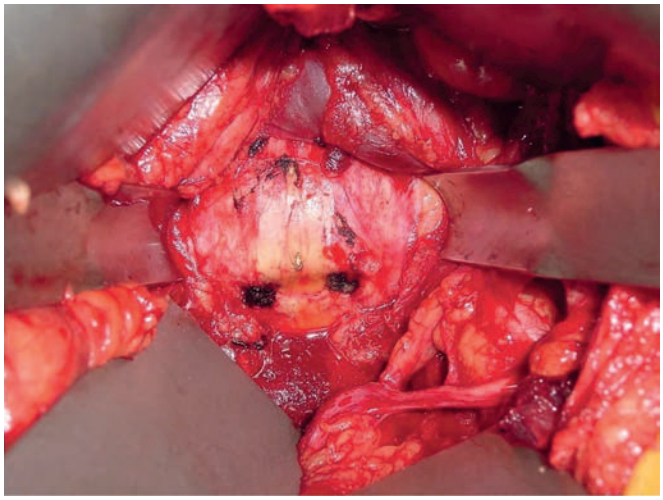

Figure 58.4 Intraoperative photo of the exposed L5 to S1 disk. Note the positioning of the Omni-Tract renal vein retractors (Integra Lifesciences, Minneapolis, Minnesota) as described in the text.

right common iliac artery after division of the middle sacral artery and vein (Figs. 58.4 and 58.5; see also Fig. 58.3). Various incisions can be used for this single-level exposure, including left lower quadrant oblique, transverse, and, occasionally, midline. We rarely utilize a midline approach, thereby avoiding transperitoneal exposure of the peritoneal contents.

Exposure of the L4 to L5 disk space can be technically demanding, particularly if there is significant spondylolisthesis at this disk level because the "tethered" left common iliac vein stretches and flattens out across the lower edge of the disk space, inviting inadvertent injury. L4 to L5 disk space exposure should always be accompanied by division of the iliolumbar

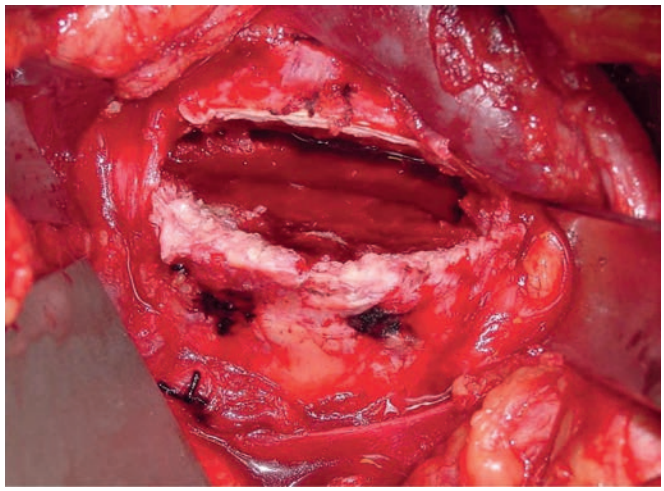

Figure 58.5 Intraoperative photo following diskectomy at the L5 to S1 disk level; subsequent insertion of allograft bone or a synthetic prosthesis to promote spine fusion completes the procedure.

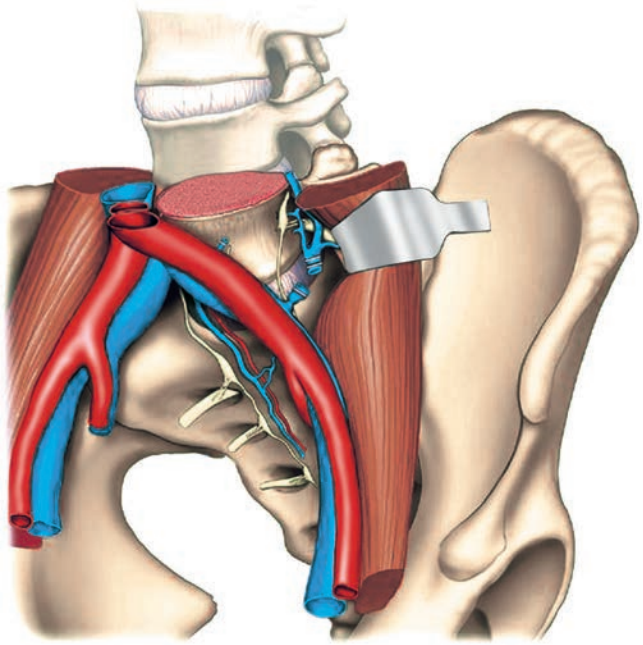

Figure 58.6 Division of the iliolumbar vein (or veins) is key for safe exposure of midlumbar and lumbosacral disk levels.

vein(s), which course toward the posterolateral aspect of the left common iliac vein (Fig. 58.6). Failure to divide this vein can result in a significant tear at this venous junction with bleeding that can be difficult to control. In other more proximal procedures, appropriate disk level exposure requires meticulous left-to-right dissection and mobilization of some portion of the abdominal aorta. Additional dissection of the common iliac arteries and/or iliac veins may also be required to fully expose the natural width of the desired disk space(s). Lumbar arteries and unnamed venous tributaries should be individually ligated and divided to facilitate the spine exposure. One particular advantage of this left-to-right dissection/mobilization plane is that the vena cava remains well protected throughout the procedure.

Exposure of More Than One Disk Space

Although tempting in some cases, it is unwise to perform diskectomy and spinal instrumentation at multiple disk levels simultaneously if this extended exposure occludes the aorta/common iliac artery or risks significant damage to the confluence of the common iliac veins and the vena cava. This is particularly true when the L4 to L5 disk space is involved, because there can be significant variability in the arterial and venous anatomy. On the other hand, in patients with nondiseased, tortuous iliac arteries, we can often simultaneously expose and operate upon multiple disk spaces from L1 to L5 with well-positioned retractors. The retractors are then repositioned to expose the L5 to S1 disk space if diskectomy/decompression is also required at this disk level.

Fig. 58.7 depicts the usual scenario in which the disk is exposed following left-to-right mobilization of the aorta and left common iliac artery across the anterior spine. However, the left common iliac artery and vein occasionally need to be separated and retracted away from each other to fully expose the disk space without prolonged arterial occlusion or arterial injury (Fig. 58.8). Figs. 58.9 and 58.10 depict other, less common dissections we have used to expose the L4 to L5 disk space, in the patient with a high aortic bifurcation, for instance. These alternate dissection schemes are particularly helpful for redo anterior procedures, in which the major overlying arteries and iliac veins may be densely adherent to the anterior surface of the spine, or in dissection being performed after previous posterior lumbosacral spine surgery, in which we have typically encountered significant scarring of the anterior spine surface.

Right-Sided Exposure

Spine exposures performed from a right-sided mini-open retroperitoneal approach necessitate mobilization of the vena cava and, to some extent, the right common iliac vein for lower lumbosacral spine procedures. Medical retraction of the vena cava all the way across the anterior surface of the spine often occludes the vessel and may result in significantly decreased preload, which is not well tolerated in elderly patients. Therefore and depending on arterial/venous anatomy, the disk space(s) may be better exposed by dissecting between the vena cava and abdominal aorta. This alternative causes less compression of each vessel with lateral retraction away from the midline.

Self-Retaining Retractors

Self-retaining renal vein retractors (Omni-Tract Surgical) are typically employed to maintain each exposed disk space and to protect the adjacent vessels/peritoneal contents. These particular retractors are slightly angled backward at their tips, and this angled portion can usually be positioned to hug the disk space laterally, thus protecting encroaching vital structures from

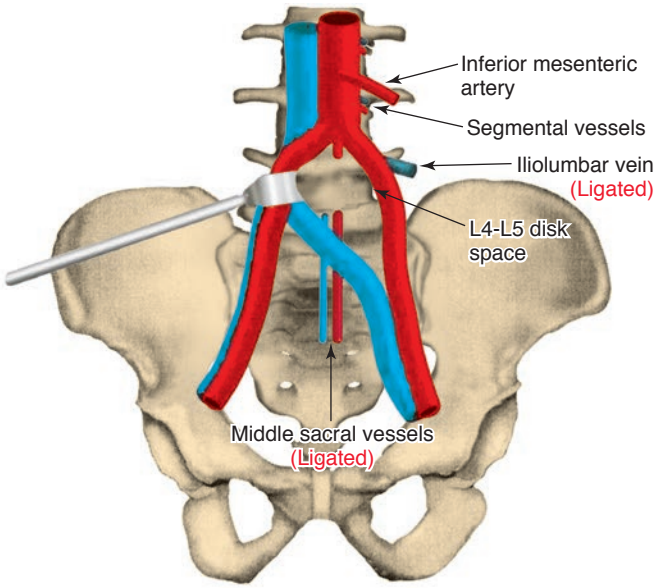

Figure 58.8 L4 to L5 disk exposure between the left iliac artery and vein.

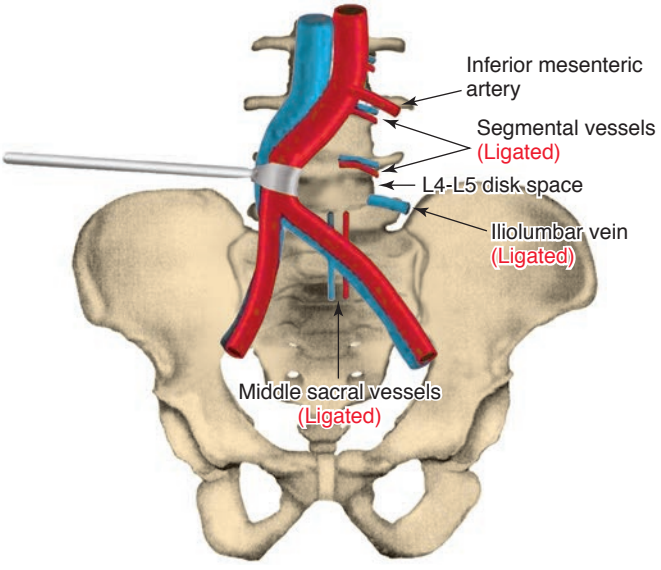

Figure 58.7 L4 to L5 disk exposure when aortic and caval bifurcations are distal to the disk level.

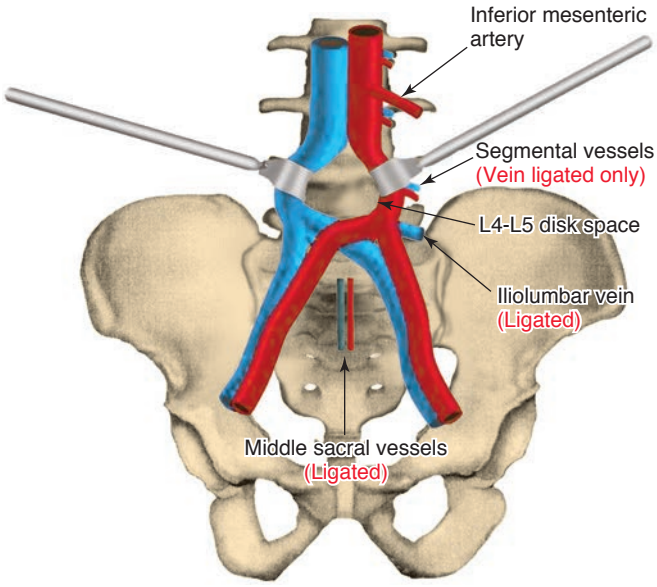

Figure 58.9 L4 to L5 disk exposure between the aorta and the vena cava.

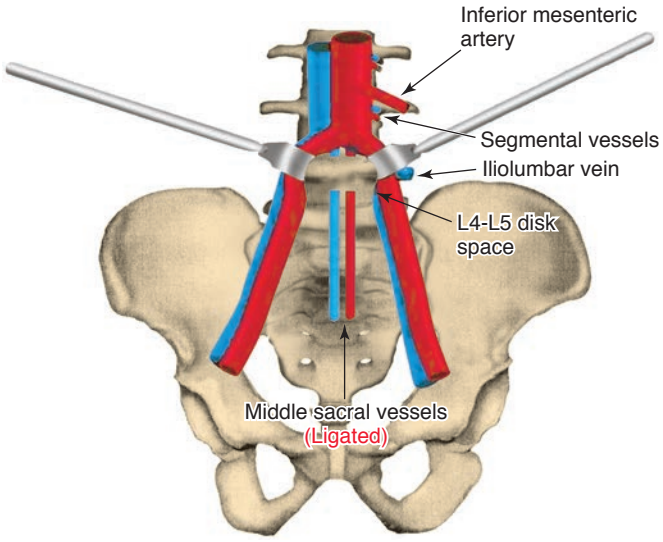

Figure 58.10 L4 to L5 disk exposure when aortic and vena caval bifurcations are proximal to the disk level.

the disk space and giving the spine surgeon just enough room to operate even in very large patients (see Fig. 58.6). These retractors should be placed with care to avoid excessive traction on the mobilized structures and should be positioned just medial to the sympathetic chains that course along the lateral aspects of the vertebra, to protect them from inadvertent injury. It is wise for the vascular surgeon to assist the spine surgeon with diskectomy, decompression, partial corpectomy (if needed), and spinal fusion to ensure swift recognition and repair of inadvertent injury to a vital structure.

Meticulous hemostasis is achieved throughout the operative site after ALIF, and we typically spray a fibrin sealant (Evicel, Ethicon US, LLC.) over each operative disk site to effect complete hemostasis and in theory, to decrease adhesions over the anterior spine surface.[18,22] The peritoneal contents are rotated back into place after confirming a palpable pulse in each common iliac artery. The wound should be closed in anatomic layers and we routinely close skin in a subcuticular manner. A one-inch Steri-Strip applied longitudinally for the length of the incision completes the closure. Pedal pulses are confirmed to be unchanged from preoperative before the patient transfers to the recovery room.

Special Considerations

Redo anterior spine exposure and calcified arterial anatomy deserve special mention as either situation increases the risk of vital structure injury.

Repeat Procedures

"Redo" procedures are often associated with significant scarring of the anterior spine from the previous procedures, which results in very adherent vessels and ureteral fixation. This is particularly true for explantation of artificial disks, which occasionally become displaced or have component failure. Alternative spine access strategies are often employed for these potentially complicated procedures.[18,23,24] In any event, it is wise to prepare for dissection difficulties and potential bleeding. Arteriorrhaphy or venorrhaphy with pledgetted nonabsorbable polypropylene (Prolene) suture is recommended because the vessels tend to be friable when re-dissected off the anterior spine surface. Large venous rents are best controlled with a side-biting vascular clamp, because it may not be possible to completely occlude the vein proximal and distal to the injury site without risking further injury. On rare occasions, transection (or even segmental resection) of the overlying iliac artery may be required to adequately expose a major pelvic venous injury. Standard arterial reconstruction techniques can be used after ensuring an intact vein repair or vein ligation as the case dictates.

Calcified Arteries

Calcified arteries present a unique problem because of the retraction required to expose the disk space. Even pliable vessels are frequently retracted at rather acute angles to limit dissection, but also to afford complete disk space exposure. Therefore the risk of arterial injury/dissection increases significantly when the vessel is heavily calcified. The best way to avoid injury to a calcified vessel is to mobilize more length of the artery proximal and distal to the disk level(s) of interest, even if doing so requires extension of the incision and/or more mobilization of adjacent structures. We have rarely encountered significant arterial injury during ALIF, but would not hesitate to perform appropriate arterial reconstruction as needed, as opposed to risking acute arterial occlusion by applying multiple blindly directed sutures and pledgets to an injured vessel.

SURGICAL RESULTS AND COMPLICATIONS

In our experience, the mini-open thoracic and retroperitoneal approaches described herein are associated with rare intraoperative complications and few perioperative or long-term complications. Tables 58.1 and 58.2 detail intraoperative and perioperative vascular and nonvascular complications associated with various surgical approaches that are used for ALIF.

In our first reported review of ALIF cases, there were two (2.8%) intraoperative complications—a single small bowel enterotomy and an iliac vein laceration, both of which were repaired primarily.[4] No patient or surgical variable was predictive of an intraoperative complication. The two complications occurred during partial corpectomy and spinal instrumentation, not during the spine exposure. Postoperative complications occurred in seven patients (9.7%). They included erectile dysfunction (two patients), transient unilateral lower extremity paresis (one patient), acute acalculous cholecystitis (one patient), femoral vein thrombosis (one patient), pneumonia (one patient), and acute myocardial infarction (one patient). There were no genitourinary or other major vascular injuries. The overall perioperative complication rate with utilization of the two-team approach described above was 12.5%.

Postoperative complications were more common in patients who presented with a history of coronary artery disease or who were older than 50 years at the time of surgery. In addition,

TABLE 58.1 Intraoperative and Perioperative Vascular Complications Associated With Anterior Spine Exposure

Study	Surgical Approach (No. of Patients)	Intraoperative Complications (No.)	Perioperative Complications (No.)
Bianchi et al.[4]	Mini-open retroperitoneal (72)	Major vein injury (1)	Deep vein thrombosis (DVT) (1)
Bergey et al.[5]	Endoscopic lateral (21)	None	None
Kleeman et al.[6]	Laparoscopic (139)	Major vein injury (2) Arterial embolus (2)	DVT (3)
Gumbs et al.[7]	Mini-open retroperitoneal (64)	Major vein injury (2) Ureter injury (1)	None
Zdeblick and David[8]	Laparoscopic (25) Mini-open retroperitoneal (25)	Major vein injury (1) None	DVT (1) None
Kaiser et al.[9]	Laparoscopic (47) Mini-open retroperitoneal (51)	Major vein injury (1) Major vein injury (2)	None None
Brau[23]	Mini-open retroperitoneal (684)	Major arterial injury (6) Major vein injury (6)	DVT (7)
Ballard et al.[18]	Retroperitoneal/thoracic (617)	Major vein injury (3) Major arterial injury (1)	DVT (12) Lymphedema (3)

TABLE 58.2 Intraoperative and Perioperative Nonvascular Complications Associated With Anterior Spine Exposure

Study	Surgical Approach (No. of Patients)	Intraoperative Complications (No.)	Perioperative Complications (No.)
Bianchi et al.[4]	Mini-open retroperitoneal (72)	Small bowel injury (1)	Erectile dysfunction (2) Lower extremity paresis (1) Cholecystitis (1) Pneumonia (1) Myocardial infarction (1)
Bergey et al.[5]	Endoscopic lateral (21)	Conversion to open (1)	Groin/thigh paresthesias (6) Psoas hematoma (1)
Kleeman et al.[6]	Laparoscopic (139)	Bowel injury (2) Bladder injury (2)	Erectile dysfunction (11) Ileus (1) Positioning pain (2)
Gumbs et al.[7]	Mini-open retroperitoneal (64)	Scarring/case aborted (2)	Persistent fever (8) Spinal headache (2) Colitis (1)
Zdeblick and David[8]	Laparoscopic (25) Mini-open retroperitoneal (25)	Ureter injury (1) None	Erectile dysfunction (1) Retroperitoneal hematoma (1)
Kaiser et al.[9]	Laparoscopic (47) Mini-open retroperitoneal (51)	Bladder injury (1) Conversion to open (2) Dural tear (1)	Urinary tract infection (UTI) (1) New radiculopathy (1) Ileus (1) Retroperitoneal hematoma (1) UTI (1) Wound infection (1) Worse radiculopathy (1)
Brau[23]	Mini-open retroperitoneal (684)	None	Erectile dysfunction (1) Ileus (4) Wound infection (3) Wound hernia (2) Compartment syndrome (2) Myocardial infarction (1) Death (1)
Ballard et al.[18]	Retroperitoneal/thoracic (617)	None	Wound infection (19) Seroma/hematoma (12) Readmission (49)

increased operative blood loss and an extended paramedian incision were also associated with a higher risk of perioperative complications.[4] These positive predictors were not entirely surprising in light of the magnitude of the surgical procedure. This was particularly true in patients undergoing exposure of multiple disk levels, in whom significantly more surgical dissection and major vessel mobilization were required.

Another report also utilizing a two-team approach (urology and orthopedics) for anterior spine exposure demonstrated a perioperative complication rate of 10.6%.[14] The reported complications were specific to the actual exposure, and the preferred incision was left paramedian. These complications included one death from widely metastatic lung cancer (spine fusion was attempted for palliation of an unstable spine), two occurrences of prolonged ileus, two occurrences of retrograde ejaculation, one episode of symptomatic femoral vein thrombosis, and one episode of *Clostridium difficile* colitis. There were no major vascular injuries, and consistent with our experience, there were no genitourinary injuries or anterior wound infections.

However, in one report, neurosurgeons reported that 24 perioperative complications occurred in 23 patients (38.3%) from a retrospective review of 60 patients undergoing anterior lumbar interbody fusion over a 2-year period.[13] Experienced general or vascular surgeons performed the spine exposures through a left paramedian or oblique infraumbilical skin incision. The complication list included sympathetic nerve dysfunction (six patients), vascular injury (four patients), somatic neural injury (three patients), sexual dysfunction (three patients), prolonged ileus (three patients), wound dehiscence (two patients), deep vein thrombosis (one patient), pancreatitis (one patient), and bowel injury (one patient). The incidence of complications was not related to age, previous abdominal or spinal surgery, or number of exposed disk levels (all P values >.1).[13] The investigators in this review commented that the complication rate did not seem to represent a learning-curve effect, because the rate was the same during both year-long study periods.[13] They did appropriately point out that it is paramount for the surgeon who is performing the spine exposure to have a keen awareness of the potential complications so that patients can be properly counseled and asked for informed consent prior to surgery.[13] Interestingly, and as in our first published review, there was no correlation between previous posterior spine fusion and perioperative complications—yet we know from experience that procedures in patients with posterior spine infusion are some of the most difficult to perform because dense scarring of the anterior spine surface complicates vessel dissection and mobilization.

Our latest ALIF and ATIF experience involved 617 consecutive patients with mean age of 56 years (16% >69 years).[18] Mean BMI was 29.27; 39% were considered obese, with BMI values greater than 30. One disk level was exposed in 36% of cases, two in 43%, and three or more in 21%. Six percent of patients had prior anterior spine exposure, 42% had previous posterior laminectomy and/or diskectomy, and 3% required disk re-exposure to remove hardware or an artificial disk. There was one major arterial dissection and three major venous injuries. Other complications were extensive deep vein thrombosis (DVT) (2%), debilitating lymphedema (0.5%), wound seroma/hematoma requiring treatment (2%), wound infection (3%), and hospital readmission within 60 days (8%). Multilevel (>2 levels) disk exposure was associated with a significantly increased rate of lymphedema, posterior lumbar wound infection, and hospital readmission. In patients with BMI values greater than 30, there were statistically significantly higher rates of postoperative DVT, posterior lumbar wound infection, and hospital readmission within 60 days.

This review demonstrated that the overall incidence of major vessel and nonvessel injury complications associated with anterior thoracolumbar spine exposure was low. Redo anterior spine exposure as well as redo disk exposure procedures, including those that require hardware removal, can be performed safely. However, multi-disk level exposure was associated with an increased incidence of lymphedema, posterior lumbar wound infection, and hospital readmission within 60 days. ALIF and ATIF in patients with BMI values greater than 30 should be approached with caution because of the significantly higher rates of DVT, posterior lumbar wound infection, and hospital readmission within 60 days in such patients.

POSTOPERATIVE MANAGEMENT AND FOLLOW-UP

Postoperative management is relatively straightforward and primarily is focused on initial rehabilitation for the spine. The retroperitoneal approach for ALIF facilitates early return of normal bowel function and minimizes pulmonary problems.[4,18,19] Paramedian and flank incisions are generally well-tolerated, and subcuticular wound closure minimizes postoperative wound care. Intercostal nerve block is often helpful to improve lung excursion, cough, and deep breathing for the patient undergoing thoracic spine exposure. This maneuver has little downside regarding the risk for pneumothorax because there is already an ipsilateral chest tube in place. Also, such a block enables patient activity to be rapidly progressed during the early postoperative period, so most patients can be discharged to home in 4 or 5 days. Transversus abdominis plane (TAP) block is another, relatively new, regional anesthetic technique that can be used to block sensation to the anterior abdominal wall and decrease postoperative pain after ALIF.[25] Our initial experience with this technique has been encouraging from the perspective of increasing patient mobility as well as decreasing postoperative pain and number of in-patient hospital days.

From the vascular surgeon perspective, the majority of the work associated with spine exposure is immediately preoperative, involving discussion of the surgical approach and potential complications, and intraoperative, to give the spine surgeon unobstructed anterior exposure of the spine. In our practice, intensive postoperative follow-up is usually conducted on an as-needed basis, because there are few to no long-term vascular problems requiring continued care, except in the occasional patient in whom DVT, severe lymphedema, or a chronic wound problem develops.

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59 CHAPTER

Technique: Open Surgical

ANTON N. SIDAWY and RICHARD F. NEVILLE

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The management of vascular disease has undergone a major evolution. A decade ago, whenever vascular intervention was deemed necessary, open vascular surgery was the norm. However, with advances in catheter-based technology, endovascular therapy is now the first option in most clinical situations. Endovascular intervention is less invasive, and patient recovery is rapid. The limitations of endovascular therapy are related to specific anatomic considerations and questions of durability.

Open vascular surgery traditionally offered the "gold standard" with respect to durability and efficacy. However, it was associated with the typical morbidity and mortality of all open surgical procedures. These drawbacks included complications of general anesthesia (when used), the physiologic changes of clamping and unclamping major vessels, the significant intraoperative blood loss and fluid shifts in vascular procedures, and the impact of various types of skin, abdominal, and thoracic incisions.

With the goal of decreasing the morbidity of vascular interventions, the shift toward endovascular procedures is well justified. When an endovascular intervention is anatomically challenging, hybrid procedures that combine open vascular

surgery and endovascular techniques can be used to modify the anatomy so that endovascular intervention is possible. For example, a bypass to the common iliac artery or aorta may be constructed to allow the safe passage of a large stent-graft for endovascular thoracic aortic aneurysm repair in a patient with a small or occluded iliac artery. Similarly, debranching procedures, such as iliorenal and iliomesenteric bypasses, in patients with suprarenal aortic aneurysms or carotid-subclavian and carotid-carotid bypasses in patients with thoracic aortic aneurysms can provide a landing zone during the endovascular treatment of a thoracoabdominal or thoracic aortic aneurysm.

Despite advances in endovascular technology and the increase in the number of endovascular interventions, open vascular reconstructions will continue to play a significant role in the management of patients with vascular disease for the foreseeable future.

BASIC PRINCIPLES

The key elements of a successful open vascular reconstruction are choosing the right procedure and vascular exposure and then executing the selected procedure correctly. Appropriate choices for the source of inflow, the target for outflow, and the proper conduit, if needed, are critical for the success of any revascularization. This success also requires the appropriate instruments, graft, and suture materials. In addition, open vascular procedures should be performed under excellent lighting aided by magnifying loupes in select cases. For the operating surgeon, maintaining good ergonomic position during the reconstruction is essential to prevent significant work-related discomfort in the neck, shoulders, or back.

Vascular Instruments and Retractors

A vascular instrument tray typically includes vascular clamps, needle holders, forceps, scissors, and various retractors. Depending on the size of the vessel and the location of the surgical reconstruction, the instruments used will vary.

Clamps

Vascular clamps typically have jaws with rows of fine interdigitating serrations that allow clamping of the vessel without slippage or significant crush injury. Although vascular clamps are considered atraumatic, a vascular clamp applied inappropriately can cause significant intimal damage or may tear the artery if placed over a plaque in an inappropriate manner. Even in a soft, minimally diseased artery, a clamp applied with excessive force can damage the arterial wall and intima.

In general, clamps can be divided into those used for large, medium, or small vessels. They vary in shape and angulation to fit into specific anatomic locations, and they can be used as fully or partially occluding clamps. Clamps with special soft plastic inserts (e.g., Fogarty soft jaw) are also available to allow the clamping of prosthetic grafts without damaging the graft material. Types of vascular clamps and their suggested uses are outlined in Table 59.1. For smaller vessels and branches, various sizes of bulldog clamps or intracranial aneurysm clips,

TABLE 59.1 Vascular Clamps and Target Vessels

Clamp Type	Vessel
Totally Occluding	
DeBakey aortic aneurysm clamp (side-to-side apposition of aortic wall)	Supraceliac, infrarenal aorta
DeBakey-Bahnson aortic aneurysm clamp	Infrarenal aorta
Howard-DeBakey aortic aneurysm clamp with reverse curve shafts (side-to-side apposition of aortic wall)	Infrarenal aorta
Fogarty aortic clamp (side-to-side apposition of aortic wall)	Infrarenal aorta; aortic grafts, calcified aorta
DeBakey aortic aneurysm clamp (apposition of anterior and posterior walls together)	Infrarenal aorta
Lambert-Kay aortic clamp (apposition of anterior and posterior walls together)	Infrarenal aorta
Wylie hypogastric clamp	Iliac arteries, especially hypogastric arteries
DeBakey peripheral vascular clamp (angled handle)	Iliac arteries
DeBakey peripheral vascular clamp (angled jaw, 45 degrees)	Iliac and common carotid arteries
Henley subclavian clamp	Subclavian and common femoral arteries
Partially Occluding (Side-Biting)	
Lemole-Strong aortic clamp	Aorta; aortic grafts
Satinsky clamp	Aorta, vena cava
Cooley anastomosis clamp	Aorta; aortic grafts
Cooley-Derra clamp	Graft limbs
Cooley pediatric clamp	Common femoral artery, saphenofemoral junction
Self-Compressing (No Applicator Required)	
Gregory carotid "soft" bulldog	Small vessels
Potts bulldog—straight and angled jaw	Small vessels
DeBakey bulldog	Small vessels
Dietrich bulldog	Small vessels
Self-Compressing (Applicator Required)	
Yasargil aneurysm clip	Small vessels and branches
Heifitz clip	Small vessels and branches
Kleinert-Kutz clip—straight, angled, curved	Microvascular anastomoses
Louisville microvessel approximator	Microvascular anastomoses

Adapted from Hoballah JJ. *Vascular Reconstructions: Anatomy, Exposures, and Techniques*. New York: Springer-Verlag; 2000.

such as the Yasargil or Heifitz clips, are available (see e-Figs. 59.1–59.12).

Needle Holders, Forceps, and Scissors

Needle holders of various lengths and shapes are available. The choice of needle holder is often dictated by the size of the needle used. A Mayo-Hegar needle holder is typically used with large needles, and Castroviejo needle holders are typically used with small, fine vascular needles (see e-Fig. 59.13).

The forceps used during vascular procedures typically have very fine, noncrushing jaws, exemplified by the DeBakey forceps. However, similar to vascular clamps, vascular forceps can crush a vessel wall if they are not used appropriately and delicately. Fine-tip ring forceps or Jarrell forceps are very useful during the construction of vein bypasses to infrapopliteal vessels. Metzenbaum and Church scissors are used for the dissection of blood vessels. Stevens tenotomy scissors with sharp tips are used for dissecting tibial vessels. Special Potts scissors with various angulations are used to enlarge and shape arteriotomies and venotomies. Right-angle clamps with various tip sizes are used to encircle blood vessels and branches (see e-Figs. 59.14–59.19).

Retractor Systems

Retractors can be self-retaining or handheld. Self-retaining retractors should be used whenever possible. The Omni-Flex vascular retractor (Omni-Tract Surgical, St. Paul, Minnesota) is frequently used for open aortic surgery, whether transabdominal or retroperitoneal (see e-Fig. 59.20). This retractor system consists of a wishbone that attaches to a post mounted on the operating room table rail, and it typically offers a selection of blades with different depths, widths, and shapes that can be clamped to the wishbone. Shallow, wide blades are typically used to retract the abdominal walls, whereas deeper splanchnic blades may be used to retract the splenic flexure and other parts of the colon. A wide, fence-shaped blade is typically used to retract the small bowel during aortic dissection, and a narrow, deep blade may be used to retract the left renal vein cephalad. This retractor system is useful during thoracoabdominal aortic aneurysm repair. Modifications of this retractor have also been designed for inguinal, carotid, and spine exposures.

Another self-retaining abdominal retractor is the Bookwalter retractor (Codman Johnson & Johnson, Raynham, Massachusetts; see e-Fig. 59.21). This retractor is often used when conducting abdominal aortic replacement through mini-laparotomy incisions. The retracting blades in the Bookwalter retractor attach to an oval metal ring placed around the abdominal incision instead of a wishbone.

Several single-instrument self-retaining retractors are available for neck and extremity procedures (see e-Figs. 59.22–59.24). The Weitlaner retractor is commonly used for inguinal and popliteal incisions. The Adson cerebellar retractor is angled such that it can also be very useful in groin and below knee exposure. In obese patients with significant inguinal pannus, a Miskimon retractor can be especially useful because of its deeper and wider blades, which provide a larger retracting area. Spring retractors are extremely useful when conducting infrageniculate vessel exposure because they tend to occupy little space. The Gelpi retractor is typically helpful when conducting a first rib resection through a transaxillary approach for thoracic outlet obstruction.

Vascular Sutures and Grafts

Sutures

Nonabsorbable sutures are used for vascular anastomoses and repairs. These sutures typically provide the tensile strength necessary to juxtapose and secure the vessels together until healing is completed. When prosthetic conduits are used in vascular reconstruction, the tensile strength provided by the sutures is needed indefinitely to maintain vascular integrity. Currently, monofilament sutures are most commonly used for vascular reconstructions, although some surgeons still prefer braided polyester multifilament sutures. Vascular sutures are usually double-armed with a needle on each end to allow continuous suturing in both directions from the initial knot.

Commonly used monofilament sutures include polypropylene, polybutester, and polytetrafluoroethylene (PTFE). Polypropylene sutures (Prolene, Ethicon Inc., Somerville, New Jersey; Surgipro and Surgilene, Covidien, Mansfield, Massachusetts) are made of a monofilament strand of synthetic linear polyolefin. These sutures tend to maintain their tensile strength over time. They have little friction and excellent handling characteristics. They are widely popular and are probably the most commonly used suture material in vascular reconstructions. Polybutester is another type of monofilament suture made of a copolymer of polyglycol terephthalate and polytrimethylene terephthalate coated with polytribolate to reduce drag and improve tissue passage. PTFE sutures were developed to minimize the needle hole bleeding that is often seen when polypropylene sutures are used with PTFE grafts or patches. They are designed so that there is minimal difference in the diameters of the needle and the suture. They have excellent handling characteristics, with a low tissue friction and low drag coefficient. The needle and suture sizes vary, depending on the vessel. Suggestions are provided in Table 59.2.

Grafts

Selection of a graft type is an integral part of any vascular reconstruction. Polyester grafts of different shapes and structures are available to replace the thoracic aorta. Polyester and PTFE grafts are available as conduits for the abdominal aorta and infrainguinal vessels. Autogenous vein grafts are favored in many small arterial reconstructions. These grafts are discussed in detail in Chapters 92, 93, and Chapter 94.

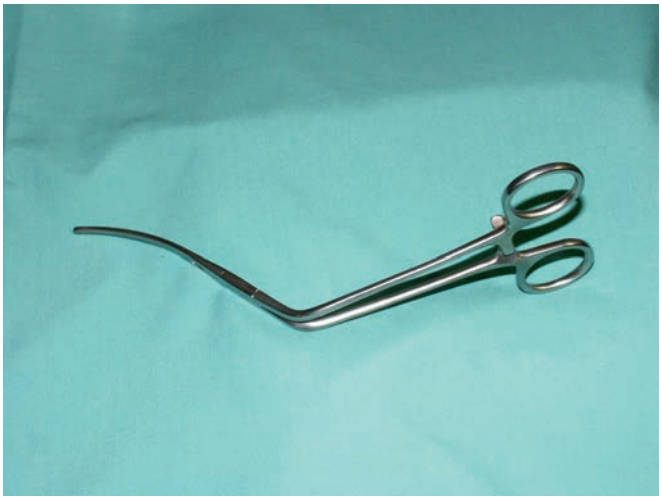
BASIC VASCULAR TECHNIQUES

Open vascular surgery is conducted using the general principles of blood vessel exposure with proximal and distal control, along with the basic techniques of vascular reconstruction. These basic vascular techniques include thromboembolectomy, endarterectomy, creation and closure of an arteriotomy, and construction of bypasses or in-line graft replacement using end-to-side or end-to-end anastomoses.

e-Figure 59.1 DeBakey-Bahnson aortic aneurysm clamp.

e-Figure 59.2 Fogarty aortic clamp.

e-Figure 59.3 Lambert-Kay aortic clamp.



e-Figure 59.4 Wylie hypogastric clamp.

e-Figure 59.5 DeBakey peripheral vascular clamp (angled handle).

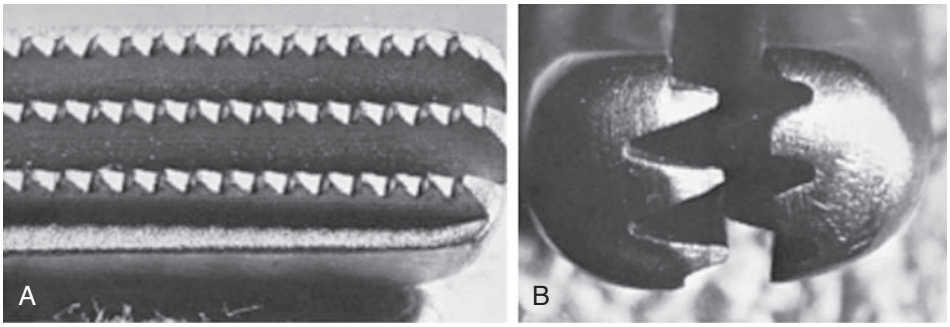
e-Figure 59.6 Henly subclavian clamp.

e-Figure 59.7 Lemole-Strong aortic clamp.

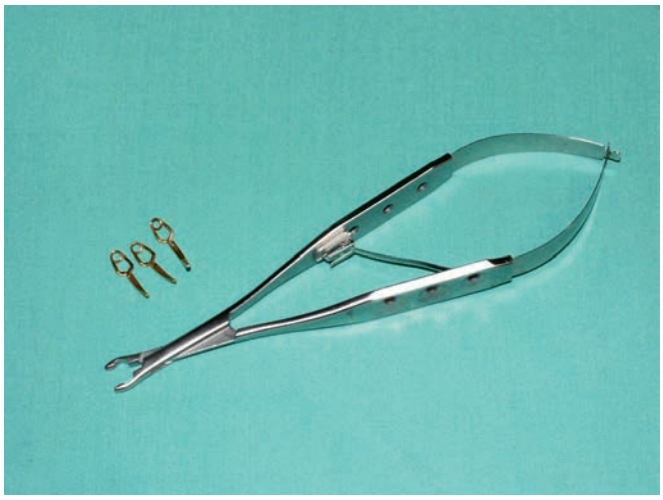
e-Figure 59.8 Satinsky clamp.

e-Figure 59.9 Cooley pediatric clamp.

e-Figure 59.10 Jaw of Fogarty clamp.

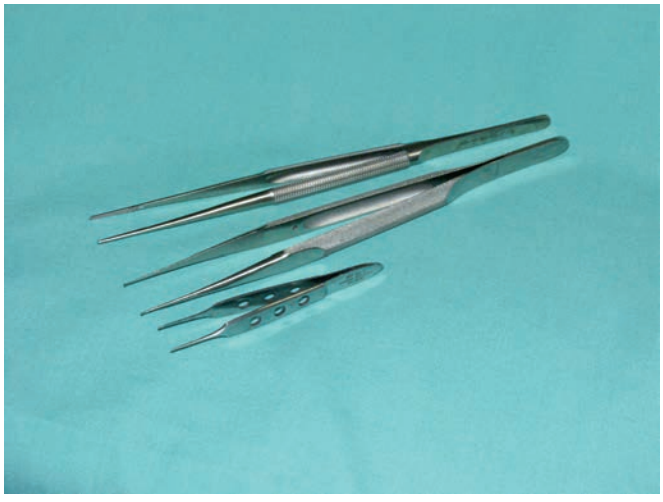


e-Figure 59.11 (A and B) Jaw of DeBakey vascular clamp.

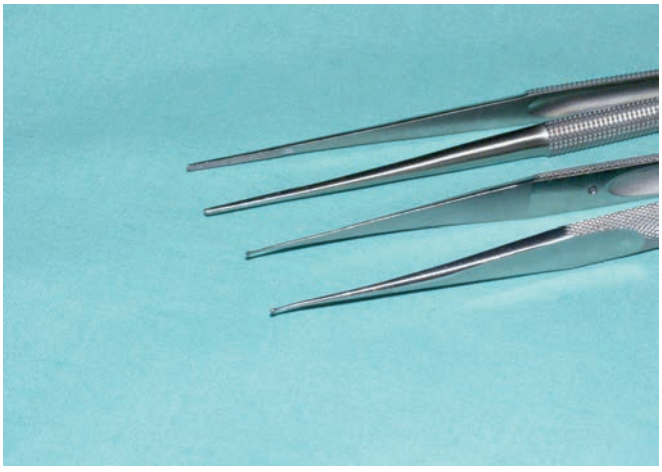


e-Figure 59.12 Yasargil aneurysm clips with clip applicator.

e-Figure 59.13 *Bottom to top,* Castroviejo, Ryder, and Mayo-Hegar needle holders.

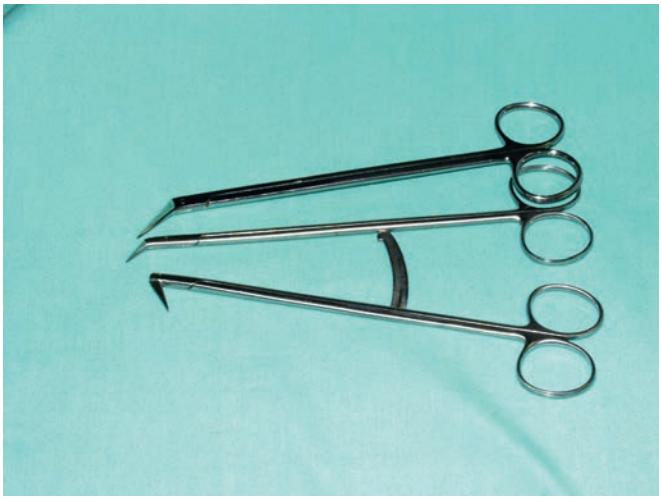


e-Figure 59.14 *Bottom to top,* Bishop-Harmon forceps, microsuture ring-tip forceps, and fine DeBakey forceps.



e-Figure 59.15 *Top to bottom,* Tips of DeBakey and ring-tip forceps.

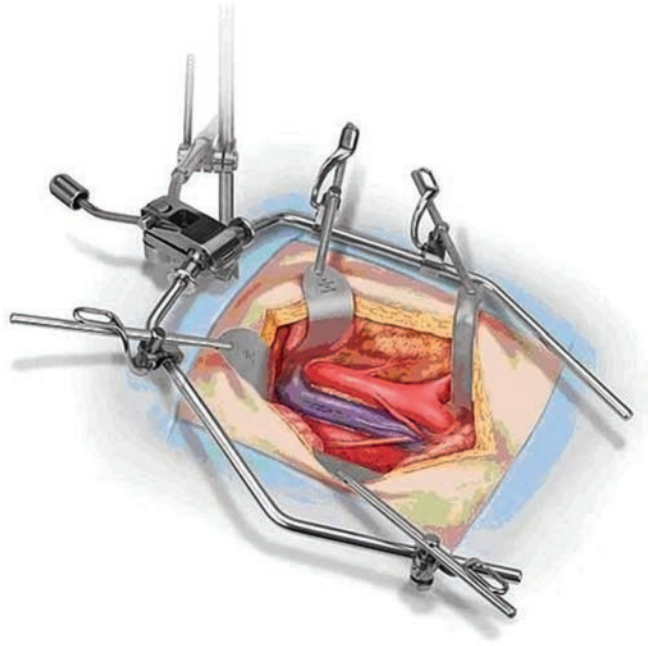
e-Figure 59.16 *Top to bottom,* Church and Metzenbaum scissors.



e-Figure 59.17 Potts scissors.

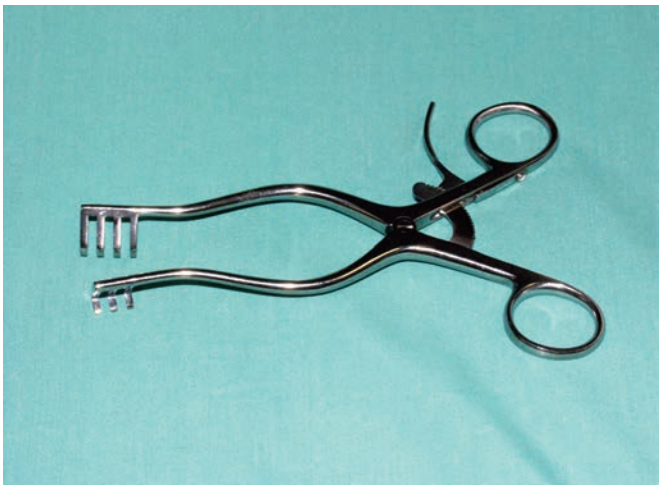
e-Figure 59.18 Castroviejo scissors.

e-Figure 59.19 Right-angle clamps.



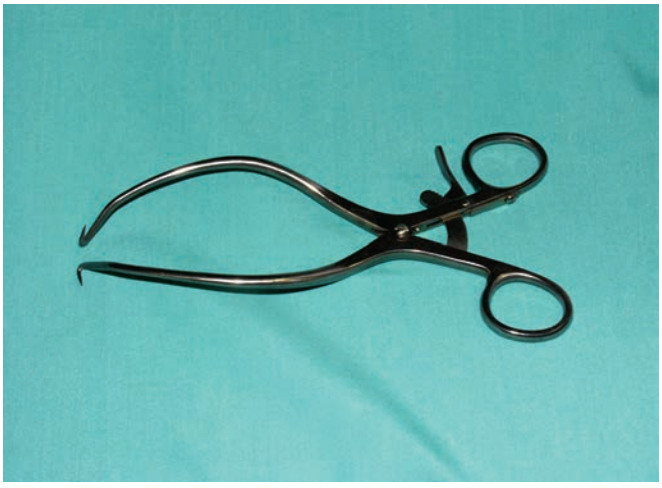
e-Figure 59.20 Omni-Tract retractor.

e-Figure 59.21 Bookwalter retractor.



e-Figure 59.22 Weitlaner retractor.

e-Figure 59.23 Miskimon retractor.



e-Figure 59.24 Gelpi retractor.

TABLE 59.2 Suggested Needle Sizes

Vessel Size[a]	NEEDLE BRAND AND SIZE			
	Ethicon	USSC	Davis and Geck	Gore-Tex
Small (calcified tibial)	CC	DV-1	CV-311/ DTE-10	PT-9
Small (tibial, internal carotid)	BV-1	CV-1	CV-310/ TE-10, 11	TT-9
Small (tibial)	BV	CV	CV-309/ TE-9	TT-12
Medium (common carotid, femoral, popliteal)	C-1	CV-11	CV-301/TE-1	TT-13
Large (common iliac)	RB-1	CV-23	CV-331/T31	TH-18
Large (aorta)	V7	V-20	DV-305/T-5	TH-26
Large (posterior wall of aorta)	MH	V26	CV-C00/T-10	TH-35

[a]For arterial anastomoses, the following suture and needle sizes are recommended: 2-0 or 3-0, aorta; 4-0, iliac arteries; 5-0, axillary, common carotid, common femoral, and superficial femoral arteries; 5-0 or 6-0, internal carotid, popliteal, and brachial arteries; 7-0 or 8-0, tibial and inframalleolar arteries.
Adapted from Hoballah JJ. *Vascular Reconstructions: Anatomy, Exposures, and Techniques*. New York: Springer-Verlag; 2000.

Vascular Exposure and Dissection

An exhaustive discussion of specific vascular exposures is beyond the scope of this chapter; these are addressed in greater detail in procedure-specific chapters. Several excellent resources are also available that describe the vascular anatomy and the variety of exposures available to the vascular surgeon.[1-4]

Initial Vessel Exposure

The basic concept of vascular exposure and dissection is to approach and expose the vessels by the most direct and shortest route possible. Selection of the surgical approach and incision should take into consideration the possibility that the operation may become more complex than originally anticipated, and that surgical control and reconstruction may occur at a more proximal or distal location. Anatomic landmarks, location of the pulse, or a combination of the two is typically used to guide placement of the initial skin incision. In most cases, the vascular structures can be exposed by dissection between existing muscle bellies. If dissection requires extensive muscle transection, the approach to the vascular structures should be reconsidered.

Following incision, proper handling of the skin and soft tissue overlying the vessels is essential to prevent significant wound complications. Lymphatics are typically ligated and divided to avoid lymphorrhea and lymphocele. Use of electrocautery through lymph nodes should be avoided to prevent significant lymph leak or the need to excise lymph nodes, leaving dead space in the wound.

Once the vascular sheath is identified and incised, the adventitia is held and retracted in one direction, and dissection is carried out in the tissue adjacent to the edge of the blood vessel wall. By staying close to the adventitia, the dissection can be maintained in the correct areolar anatomic plane, and the vessel can be circumferentially dissected and encircled with a Silastic loop or umbilical tape (Dow Corning Corporation, Midland, Michigan). The basic surgical technique of traction with countertraction is essential in vascular exposure. Traction on a vessel loop is often used to retract a vessel during dissection or mobilization. Gentle tension on the vessel loop is recommended to prevent injury to the intima.

"Redo" Vessel Exposure

"Redo" vascular exposure poses a unique challenge, given the fibrous obliteration of the normal anatomic vascular planes. When the surgeon is faced with a "redo" operation, sharp dissection with a No. 15 knife blade may allow better management of the scar tissue than scissor dissection, and it may allow the surgeon to stay in the appropriate dissection plane. An inadvertent arteriotomy caused by a small blade may be easier to repair than arterial disruption caused by dissecting scissors. The most common vessel that requires "redo" exposure is the common femoral artery, and the approach to this vessel is illustrative of "redo" vessel exposure in general.

The principle of dissecting from known to unknown can be useful in preventing branch vessel injury during reexposure and to obtain proximal control outside of the scarred area to aid in vascular control, should an inadvertent injury occur. A significant concern with a "redo" femoral artery exposure is injuring the profunda femoris artery. Consequently, the superficial femoral artery is exposed in the most distal part of the incision, where minimal scarring exists. The dissection is then carried along the medial aspect of the superficial femoral artery and progresses proximally. Typically, the common femoral vein is identified during the process, revealing a safe dissection plane. Once the inguinal ligament is reached, the common femoral artery is encircled with a loop. The direction of the dissection is then reversed and continued back distally toward the superficial femoral artery. The area of size transition between the common and superficial femoral arteries exposes the location of the profunda femoris artery. At that level, dissection from the medial and posterior aspect of the common femoral artery identifies a plane that has not been violated and allows dissection of the profunda femoris artery from underneath the common femoral artery. The profunda femoris artery is controlled at its origin by passing a vessel loop underneath the superficial femoral artery and then retrieving it just proximal to the common femoral bifurcation. In cases of extensive scarring, the profunda femoral branch can be controlled with a balloon occlusion catheter after common femoral arteriotomy, to avoid potential injury during profunda dissection.

Anticoagulation

Before interrupting blood flow, the patient must be adequately anticoagulated. Unfractionated heparin at 75 to 100 U/kg is typically administered intravenously, approximately 5 minutes before blood flow interruption. We recommend that the

anticoagulation be monitored by measuring the activated clotting time (ACT), aiming for a value of more than 250 seconds.

Distal limb ischemia following aortic reconstruction or other types of vascular procedures is a dreaded complication and is often attributed to distal embolization. However, an important factor in this complication is unrecognized suboptimal anticoagulation. Hence it is important to maintain adequate anticoagulation throughout the period of blood flow interruption by re-dosing with heparin when necessary, using the ACT for guidance. In patients with known heparin-induced thrombocytopenia, anticoagulation may be achieved with intravenous thrombin inhibitors such as argatroban (see Chapter 35).

Blood Vessel Control

Blood vessel control can be achieved using vascular clamping, balloon occlusion, vessel loops, pneumatic tourniquet, Rumel tourniquet, or internal occluders.

Vascular Clamping

Ideally, vascular clamps should be applied to a disease-free segment of the artery. Palpating the artery against a right-angle clamp can help determine the presence and extent of atherosclerotic plaque, which is often in a posterior location and not appreciated by only palpating the anterior aspect of the artery. In the presence of significant plaque, the artery should be dissected more proximally to identify a less diseased site for clamping. This situation is often encountered when clamping the common femoral artery, where plaque often extends to the level of the inguinal ligament. Further dissection proximal to the external iliac circumflex and inferior epigastric branches, however, usually reveals an external iliac artery that is soft and free of disease. If clamping is necessary across an area of diseased artery, the clamp should be applied in a manner that opposes the soft part of the artery against the plaque without causing plaque fracture or vessel tear.

Occasionally the plaque burden and calcification are so extensive that the only option is to identify a more proximal location for safe clamp placement. One example is supraceliac aortic control through the lesser sac, when clamping in the infrarenal or suprarenal location is not possible because of extensive calcification or scarring from previous surgery or an inflammatory process.

Balloon Occlusion

If the plaque is circumferential or occupies more than 50% of the circumference, vascular clamps can fracture the plaque or tear the wall, and may not provide vascular control. This can be managed by occluding the artery from within using a compliant balloon occlusion catheter, such as the Fogarty catheter normally used to perform embolectomy, or a noncompliant balloon catheter used for angioplasty. There are also several compliant occlusion balloons that can be used to occlude the aorta during ruptured aneurysm repair, including Reliant (Medtronic, Minneapolis, Minnesota), Coda (Cook, Bloomington, Indiana), and Equalizer (Boston Scientific, Natick, Massachusetts). Balloon occlusion can be used to control the external iliac artery in the presence of extensive calcification that extends beyond the most proximal part of the exposure. It is also useful for controlling the right common iliac artery during a left retroperitoneal abdominal aortic aneurysm repair, the profunda femoris artery during repair of a pseudoaneurysm of a femoral anastomosis, or the renal or visceral vessels during a thoracoabdominal aortic aneurysm repair.

Vessel Loops

Vessel loops are ideal for controlling small- to medium-sized vessels, such as the profunda femoris or popliteal arteries and arterial branches. Silastic vessel loops can be traumatic, however, if excessive tension is applied to them. A double loop, or Potts technique, can be helpful in the use of vessel loops by minimizing the tension required to obtain vascular control of small- or medium-sized arteries. Further, excessive tension on Silastic vessel loops for simultaneous proximal and distal control of a vessel may make an anastomosis or repair more difficult to construct. One way to avoid excessive tension on the artery in two opposing directions is to apply a vessel loop on the proximal side of the artery and a small Yasargil aneurysm clamp or bulldog clamp on the distal end of the artery (Fig. 59.25).

Pneumatic Tourniquet

A pneumatic tourniquet can be used for vascular control in the extremities and is ideal for infrapopliteal reconstructions. It allows for minimal exposure, dissection, and handling of the arteries, and may decrease the risk of spasm or injury caused by clamping of the tibial vessels. The tourniquet can be placed around the thigh or below the knee; usually a soft roll is applied first, followed by the tourniquet. The leg is elevated, and an Esmarch compression wrap is used to wrap the leg from the foot in a cephalad direction expelling the venous blood from the leg. The tourniquet is then inflated to a pressure of about 250 or 100 mm Hg above systolic pressure. It is essential to make sure the graft is well aligned and to mark the graft orientation before inflating the tourniquet. Bleeding occasionally occurs

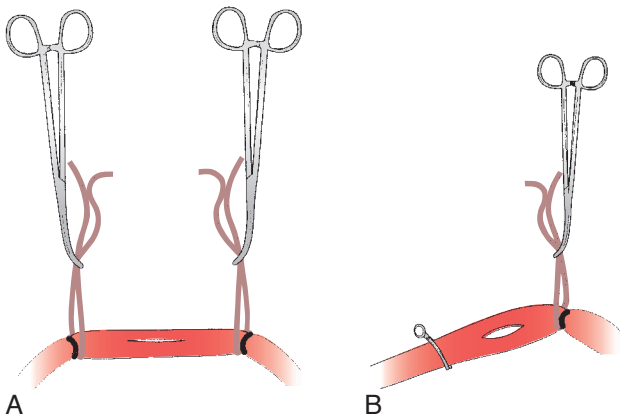


Figure 59.25 A vessel loop on the proximal side of the artery and a small Yasargil aneurysm clamp or bulldog clamp on the distal side of the artery can minimize tension on the anastomosis. (A) Pulling on both loops can result in tension on the arteriotomy. (B) Tension on the anastomosis is minimized when one loop is pulled and the other replaced with a bulldog clamp.

despite the tourniquet, and this can sometimes be controlled by increasing the pressure in the tourniquet. An additional clamp on the profunda femoris artery can also help control persistent bleeding. Sometimes calcified and incompressible arteries at the tourniquet site prevent this technique from completely controlling bleeding at the distal arteriotomy.

Other Techniques

Rumel tourniquets can be used for vascular control, but they can cause arterial wall damage in the presence of significant plaque. The Rumel tourniquet may be most useful during an endovascular aortic aneurysm procedure when there is a large sheath in an artery and persistent bleeding from the arteriotomy around the sheath. Cinching the sheath with a Rumel tourniquet at that level can control the bleeding. Pediatric Rumel tourniquets are useful to atraumatically secure carotid intraluminal shunts to control blood leak around the shunt, keeping blood flow to the brain while carotid endarterectomy is being performed.

When dealing with tibial vessels, direct clamping of the arteries should be avoided to prevent intimal injury or spasm. The use of internal coronary artery occluders in this setting can be useful to achieve vessel control. Florester internal vessel plastic tip occluders (Biovascular, St. Paul, Minnesota) are available in various sizes. However, the surgeon must be comfortable using such occluders, and oversizing should be avoided to prevent intimal damage during insertion.

THROMBECTOMY AND THROMBOEMBOLECTOMY

Basic Considerations

Thrombectomy and thromboembolectomy must be mastered by every vascular surgeon because the need to perform these procedures is inevitable. Even the most successfully performed open or endovascular procedure can be complicated by a distal embolic or a thrombotic event. Although numerous techniques are available to achieve pharmacologic or mechanical thrombectomy, the need for balloon thrombectomy cannot be completely avoided. Balloon thrombectomy allows the removal, inspection, and pathologic examination of the occlusive clot and restores blood flow expeditiously.

A vessel may become acutely occluded because of a thrombotic or embolic process. Thrombosis frequently occurs proximally and distally to the embolus because of the stagnant flow—hence the term *thromboembolectomy*. Balloon embolectomy is often paired with thrombectomy to remove the thrombus. Several issues need to be addressed during the performance of a thromboembolectomy procedure, including the location and shape of the arteriotomy used to extract the thrombus, selection of the thrombectomy catheter, and performance of the procedure with minimal blood loss and injury to the arterial system. In addition, steering the catheter into the appropriate location and extracting all the offending thrombi are essential to the success of the procedure.

Thromboembolectomy Catheters

A wide variety of thromboembolectomy catheters are available (see e-Figs. 59.26 and 59.27). The standard ones are balloon catheters that vary in size, length, and maximal balloon inflation. These catheters are typically available in sizes from 2 to 7F. Saline solution is used to inflate the balloon, except for the 2F balloon, which requires air insufflation for easy deflation. The diameter of the fully inflated balloon is 4 mm for the 2F catheter, 5 mm for the 3F, 9 mm for the 4F, 11 mm for the 5F, 13 mm for the 6F, and 14 mm for the 7F.

Size 2F catheters are typically used for very small pedal or hand vessels. The most commonly used catheters are 3 to 5F catheters. A 3F Fogarty catheter is typically used for tibial vessels. A 4F Fogarty catheter is used for vessels the size of the superficial femoral and popliteal arteries; it can also be used for external iliac arteries. A 5F Fogarty catheter is typically used for external iliac or common iliac arteries. Size 6F and size 7F catheters can be used for thrombectomy of an aortic femoral graft or a saddle aortic embolus. A venous thrombectomy catheter with a large, lower pressure balloon is also available.

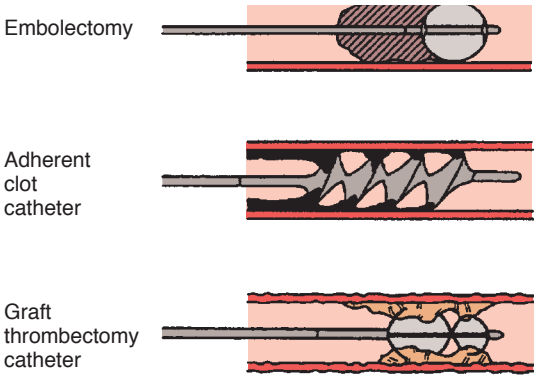
Standard balloons are made of latex; however, latex-free embolectomy catheters are available for patients with latex allergies. In addition, balloon catheters that can be introduced over guide wires for fluoroscopically assisted thromboembolectomy are also available in sizes 3, 4, 5.5, 6, and 7F.

Special catheters have been devised for adherent clots. The Fogarty adherent clot catheter (Edwards Life Sciences, Irvine, California) features a spiral-shaped, latex-covered stainless steel cable that assumes a corkscrew shape when retracted, thus expanding the surface area to entrap fibrous material. It is marketed for adherent clots resistant to removal by standard elastomeric balloons in both native arteries and synthetic grafts. The Fogarty graft thrombectomy catheter (Edwards Life Sciences) is designed to remove tough thrombus from synthetic grafts; it has a flexible wire coil at the distal end and expands when retracted to form a double-helix ring that acts as stripper, forming a plane between the graft and the adherent material. This catheter is not intended for native vessels and is marketed for use in PTFE dialysis grafts and aortobifemoral grafts (see e-Fig. 59.28).

Technique

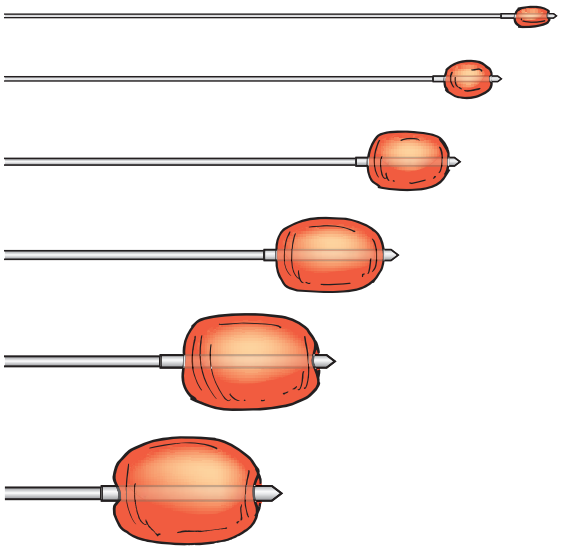
Arteriotomy Location and Shape

The balloon embolectomy catheter is designed to extract thrombi from a site remote from the clot's location. The arteriotomy for clot extraction can be performed in a location proximal or distal to the embolic or thrombotic process. Site selection depends on the ease of exposure, anticipated location of the thrombus, and ease of arteriotomy closure. In patients with acute lower extremity ischemia, the common femoral artery is an ideal site for clot extraction. A patient with an aortic saddle embolus or a popliteal embolus can be managed by thromboembolectomy through the common femoral artery. The common femoral artery and its bifurcation are easy to expose, and closure of the arteriotomy is easily accomplished in this relatively large artery. Further, the procedure can be performed under local anesthesia.



e-Figure 59.26 Thromboembolectomy catheters.

e-Figure 59.27 Thromboembolectomy catheters—diagram.



e-Figure 59.28 Fogarty catheters.

If thromboembolectomy proves to be inadequate, a site closer to the location of the thrombus may be required. Before performing the thrombectomy, it is important to ensure that the patient is adequately anticoagulated.

The selection of a transverse versus longitudinal arteriotomy for catheter access is influenced by the size of the vessel, the cause of the embolus or thrombus, and the presence of plaque in the vessel. A transverse arteriotomy is usually simpler to close and may be preferred when dealing with an embolic process. When the occlusive pathology is due to an atherosclerotic and thrombotic process, or when significant arterial plaque is present, a longitudinal arteriotomy should be used. In such a situation, it is not uncommon for an emergency bypass to become necessary, and the longitudinal arteriotomy can be incorporated into one of the anastomoses. If a bypass is deemed unnecessary, a patch is usually needed to close the longitudinal arteriotomy to avoid significant narrowing of the vessel lumen. Transverse arteriotomy can be easily closed with interrupted sutures to avoid purse-stringing and narrowing of the lumen of the artery at the site.

Minimizing Blood Loss

During the process of establishing inflow, a balloon catheter is passed proximally for an estimated distance, inflated, and withdrawn through the arteriotomy (Fig. 59.29). As the balloon exits the arteriotomy, the surgeon typically allows brief but unrestricted bleeding to flush any debris or thrombi that may still be present in the proximal part of the vessel or the graft. This step can be repeated once or twice to ensure there are no remnants of clot in the artery. A significant amount of blood can be lost in this process. This can be decreased by applying Silastic double-looped vessel tape around the artery and pulling on the loop while the catheter is being advanced proximally or distally. One technique can be used to avoid excessive blood loss; balloon thrombectomy can be repeated to clean up the artery while leaving the most proximal portion of the clot intact holding blood flow. Then, in the final pass, that proximal portion is removed, allowing a vigorous jet of blood to flush the artery for a brief period with a limited amount of blood loss.

When performing thromboembolectomy of a prosthetic bypass or the limb of an aortobifemoral bypass, vessel loops are not adequate to control bleeding. The surgeon can often control bleeding manually by squeezing the arterial wall between the index finger and thumb with one hand and withdrawing the inflated catheter with the other hand. Depending on the anatomy and the presence of scarring, bleeding may be excessive if finger control is used while passing the Fogarty catheter through the proximal artery. In such situations, use of a Fogarty soft-jaw clamp is recommended (Fig. 59.30). The soft jaws are intended to appose the blood vessel walls just enough to prevent bleeding and still allow the thromboembolectomy catheter to be advanced or withdrawn. The jaws are then opened as the inflated thromboembolectomy catheter is being withdrawn. The clamp is reapplied once the balloon catheter is pulled out of the vessel and vigorous blood flushing has occurred.

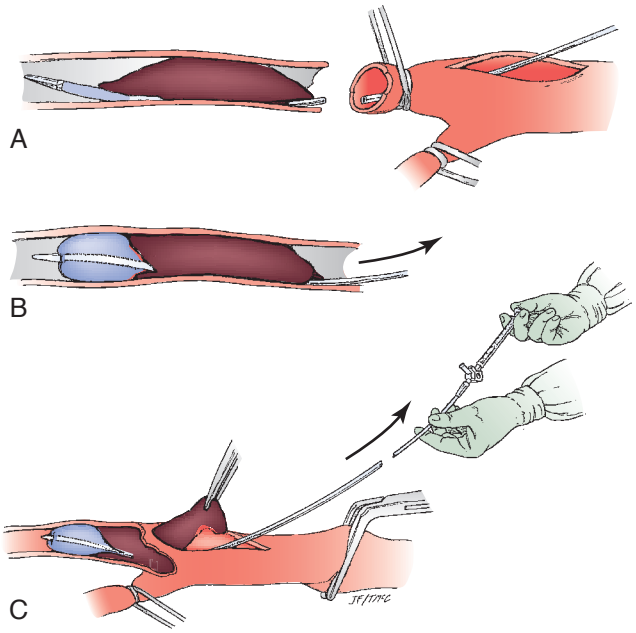


Figure 59.29 A balloon thromboembolectomy catheter is passed proximally for an estimated distance (A), inflated (B), and withdrawn through the arteriotomy, with bleeding controlled by double-looped Silastic tape (C).

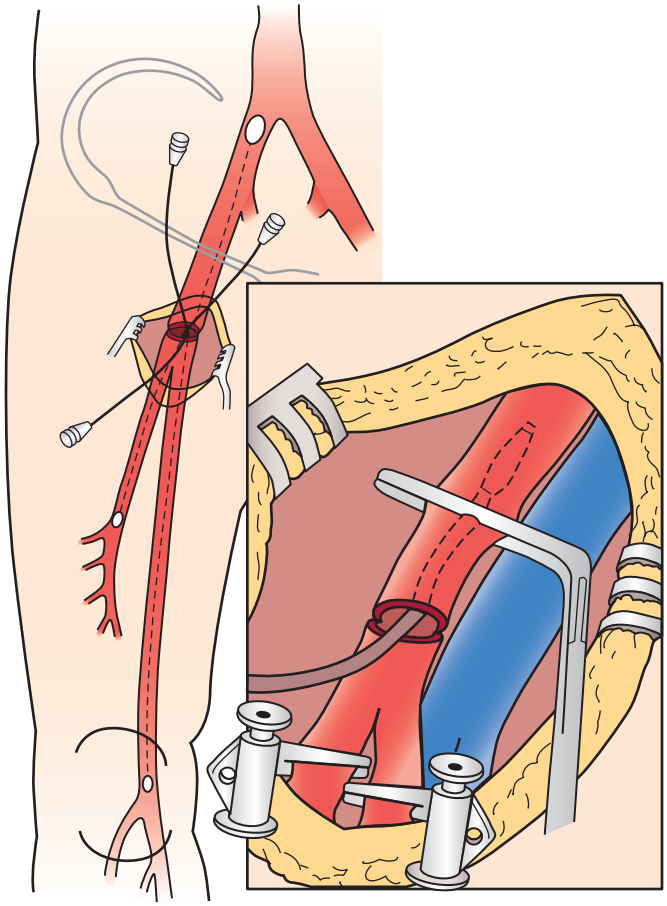


Figure 59.30 The Fogarty soft-jaw clamp may be able to appose the blood vessel walls just enough to prevent bleeding and still allow manipulation of the thromboembolectomy catheter.

Minimizing Vascular Injury

Significant vascular injury can occur from thromboembolectomy and inappropriate manipulation of the balloon catheter. Vascular injury can occur from inadvertent placement of the balloon tip or from excessive inflation of the balloon itself. Injury can also occur during insertion, advancement, or withdrawal of the thromboembolectomy catheter. During insertion, it is important to ensure that the catheter is being advanced intraluminally. It can inadvertently pass in a subintimal plane, and inflation and withdrawal of the catheter in that situation can cause arterial dissection or disruption. Injury is also possible because the procedure is commonly performed blindly or without fluoroscopic control. Hence it is very important to perform the procedure gently and be cognizant of any resistance during passage of the catheter. If the catheter does not advance freely, it may pass into a side branch or abut a curve in the artery. Further forceful advancement can result in either perforation or penetration into the subintimal plane.

Another cause of injury is overinflation of the balloon catheter and its withdrawal; this can result in significant shearing of the intima, with intimal disruption and damage. This technique has long been used to experimentally induce intimal damage or to harvest endothelial cells in animal models. Balloon overinflation can also result in rupture of the vessel or pseudoaneurysm formation.

To minimize vascular injury during balloon thromboembolectomy, several steps are necessary. Selection of an appropriately sized thromboembolectomy catheter is a must. Before inserting a thromboembolectomy catheter, it is important to test the balloon, visualize its size, and get a feel for its inflation. It is a good practice to limit the fluid used in the syringe to inflate the balloon to the minimum amount needed for full inflation. This protects against overinflation of the balloon when it is in the vessel. Another helpful maneuver is to externally measure the distance from the arteriotomy to the location of the thrombus. This helps determine whether the catheter has reached its desired destination. In addition, it may help limit unnecessary pushing of the catheter beyond the thrombus.

Once the catheter has reached its maximal advancement or the desired location, the balloon is gently inflated while the catheter is slowly withdrawn until tactile friction is sensed by the surgeon. At that point, the balloon should not be further inflated. The catheter is then retrieved, maintaining the same amount of friction and tension. The balloon may have to be further inflated as the catheter is being pulled into a more proximal location, where the artery's caliber may increase. The inflation, deflation, and withdrawal of the balloon should be a dynamic and variable process to accommodate changes in vessel caliber.

Fluoroscopy-Guided Thromboembolectomy

To achieve successful thromboembolectomy, the catheter should be advanced to the desired location distal to the occluding thrombus and then used to retrieve the thrombus. Once no more thrombus can be retrieved, the arteriotomy can be closed, especially if distal vessel backbleeding is present. However, the presence of adequate backbleeding does not ensure complete thromboembolectomy. A significant intraluminal thrombus burden may still exist despite multiple balloon passes and the presence of generous backbleeding. This is especially true when performing thromboembolectomy of the infrapopliteal vessels. The catheter may repeatedly pass into the peroneal artery, while significant thrombus remains in the anterior and posterior tibial arteries.

To avoid leaving behind clinically significant thrombus, the reperfused limb or organ is carefully examined following arteriotomy closure. An angiogram may be obtained if the reperfusion does not appear satisfactory. It may also be obtained before closing the arteriotomy to assess the completeness of the thromboembolectomy. Another option is to perform the thromboembolectomy procedure under fluoroscopic guidance.[5] Fluoroscopy can be used from the start of the procedure, or it can be used selectively to retrieve thrombi that cannot be extracted with non-image-guided thromboembolectomy.

Thromboembolectomy under fluoroscopic guidance can be educational even for a seasoned vascular surgeon. The balloon is first tested under fluoroscopy to appreciate its shape when inflated and deflated, and an angiogram through the arteriotomy can be performed before passing the Fogarty catheter. This may allow a better understanding of the anatomy and the location of the thrombus. Visualizing the catheter as it travels down the leg provides significant information about its location and course. When the balloon is inflated under fluoroscopy, the surgeon can appreciate the degree of inflation required. To best image the balloon, it should be inflated using contrast material diluted to 25%. Overinflation can be avoided, and inadvertent positioning of the catheter into a side branch before balloon inflation can be detected and corrected. Further, if the catheter passes through an area of stenosis, a change in the shape of the inflated catheter indicates the location of the stenosis.

When performing an infrapopliteal thromboembolectomy, the catheter can be directed into the desired tibial vessel by bending its tip and rotating it into the desired location. One approach is to use two balloon catheters; one is inflated at the origin of the tibioperoneal trunk, forcing the second one toward the anterior tibial artery (Fig. 59.31). Another technique is to use a 7 or 8F multipurpose guiding catheter, and park the catheter tip at the level of the popliteal trifurcation. The balloon catheter is introduced through the guiding catheter, and using the curve of the guiding catheter, the balloon catheter is directed into the desired location. The balloon is inflated and withdrawn together with the guiding catheter.

Another approach is to use over-the-wire balloon embolectomy catheters. Standard endovascular techniques are used to introduce a wire into the desired vessel, followed by advancement of the thromboembolectomy balloon over the wire. The 5.5F catheter can be advanced over a 0.035-inch wire; the 3F catheter, which is typically the size needed for tibial vessels, is passed over a 0.018-inch wire. The process of withdrawing the catheter over the wire may be frustrating, because often the wire is dislodged and pulled at the same time as the catheter.

The main drawback of thromboembolectomy under fluoroscopic guidance is the inconvenience of using fluoroscopy,

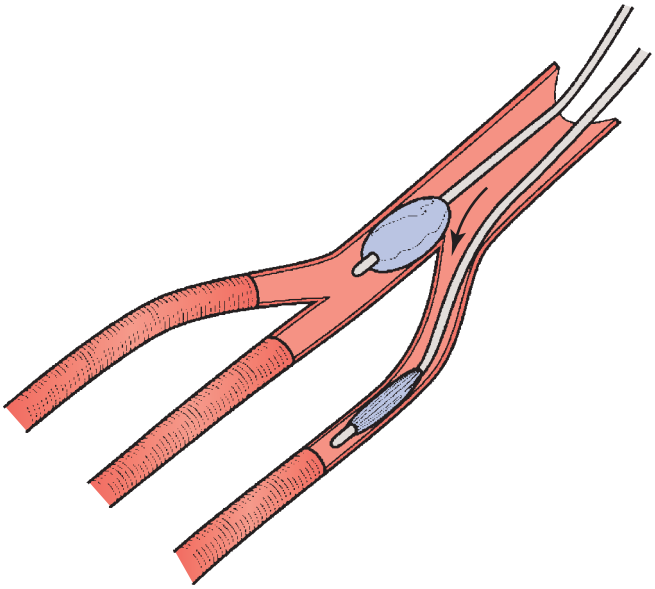


Figure 59.31 One approach to guide the thromboembolectomy catheter into the anterior tibial artery is to use two balloon catheters, inflating one at the origin of the tibioperoneal trunk and thus forcing the second one toward the anterior tibial artery.

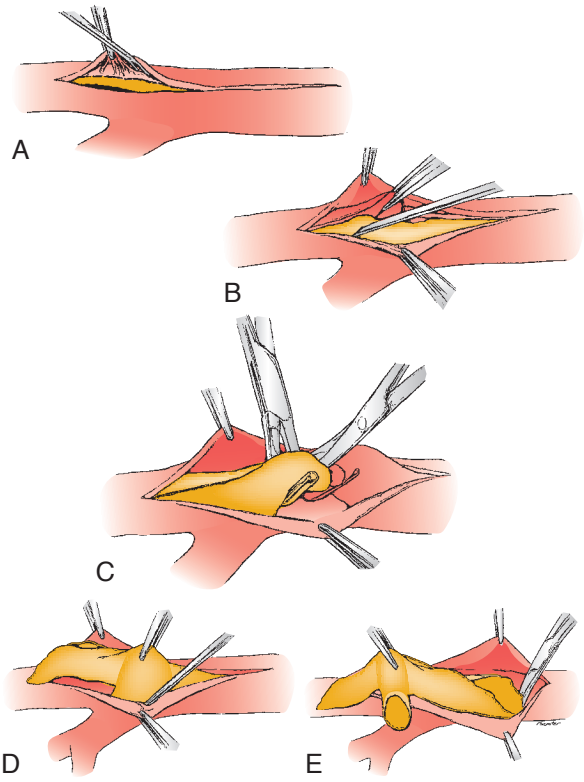


Figure 59.32 (A–E) In the open endarterectomy technique, the vessel is opened longitudinally at the site of disease. The plaque is then separated from the vessel wall in the direction of the arteriotomy and removed.

especially if skilled radiology technicians are unavailable. However, the advantages of fluoroscopy are significant: it allows the performance of a controlled thromboembolectomy, and it allows the opportunity for endovascular intervention when appropriate, such as balloon angioplasty and stenting of a dialysis graft venous stenosis, distal anastomosis of a femoropopliteal bypass, or occlusive iliac pathology.

Thromboembolectomy in Specific Conditions

The approaches to thromboembolectomy in specific vessels and for specific conditions, such as infrainguinal ischemia, aortic saddle embolus, visceral ischemia, graft occlusion, and iliofemoral venous thrombosis, are available in Appendixes e59.1 and e59.2.

ENDARTERECTOMY

Endarterectomy is a basic vascular procedure that should be mastered by every vascular surgeon.

Basic Considerations

This procedure involves the removal of atherosclerotic plaques that compromise the arterial lumen. It can be performed as the sole therapeutic procedure or in combination with bypass or even an endovascular intervention. For example, carotid endarterectomy may be the sole intervention for occlusive disease at the carotid bifurcation and is one of the most commonly performed open vascular procedures. Similarly, endarterectomy of the common femoral and profunda femoris arteries may be the sole procedure to treat lower extremity occlusive disease. However, endarterectomy of the common femoral and profunda femoris arteries can also be included in the construction of the femoral anastomosis of an aortobifemoral bypass to ensure a nonobstructed outflow into the profunda femoris artery. Great care should be taken to achieve a smooth transition at the endpoint of the endarterectomy plane in the direction of arterial flow. "Tacking sutures" can be considered to secure such an endpoint. Endarterectomy can also be incorporated into the construction of the proximal anastomosis of an infrainguinal bypass. Similarly, a common femoral endarterectomy can be performed while the common femoral artery is used as an access to perform an endovascular repair of an abdominal aortic aneurysm. Endarterectomy usually results in removal of the thickened intima and inner media, leaving behind the outer part of the media and the adventitia. It should not be performed in an aneurysmal artery because the remaining adventitial layer is too weak and degenerated to withhold suturing or arterial pressure. Several methods of endarterectomy have been described. These include open, semiclosed, eversion, orificial, and extraction endarterectomy.

Open Endarterectomy

In the open endarterectomy technique, the artery is opened longitudinally at the site of disease. The plaque is then separated from the artery wall in the direction of the arteriotomy and removed (Fig. 59.32). The arteriotomy can be closed primarily or with a patch. Being in the right anatomic vessel wall plane is essential to performing an adequate endarterectomy. This

can be accomplished by holding the edge of the adventitia with a forceps and pulling it away from the plaque. A plane is then developed between the plaque and the media or adventitia. Using the Freer elevator, the outer media and adventitia is typically pushed away from the plaque. The endarterectomy plane is developed on each side of the vessel wall and advanced posteriorly until it becomes circumferential. When dissecting in the appropriate plane, the dissecting instrument meets little resistance. It is very important to stay in the same plane if the endarterectomy is approached from both sides of an artery to meet the same point posteriorly for a clean endarterectomy specimen. Proximally, when a normal part of the wall is reached, either the plaque "feathers out" or it is transected flush with the arterial wall without leaving a significant protruding edge.

Completion of the distal endpoint of the endarterectomy can be challenging. Often the plaque clearly ends as a tongue into a normal soft artery. In this case, the endarterectomy plane is moved to a more superficial level, allowing the plaque to feather out from the wall. This provides a desirable flat distal endpoint, with a very smooth transition from the endarterectomized to the nonendarterectomized surface. On other occasions, the plaque may extend farther distally, with no visible end. In that situation, transection of the plaque in the least diseased segment is necessary, which results in a shelf between the endarterectomized and nonendarterectomized surface of the wall. Suture tacking of the intima and plaque to the adventitia is necessary to avoid plaque lifting, dissection, or thrombosis upon vessel reperfusion. To place a tacking suture, one end of the suture is placed in the remaining plaque, 1 mm distal to the endpoint, and the other end is placed at the junction of the endarterectomy and the endarterectomized surface (Fig. 59.33). Multiple sutures are often required to adequately tack the plaque edge to the arterial wall. If the proximal endarterectomy plaque does not feather out and needs to be transected, the same tacking technique can be used. Some believe that tacking the proximal end is not necessary because the direction of blood flow does not lift or dissect the flap. However, if the proximal plaque is thick and protrudes into the lumen, it may warrant proximal tacking sutures.

Inspection of the completed endarterectomized luminal surface may reveal loose circular fibers in the media and other debris that can be peeled away in a circumferential manner. It is essential to create a debris-free surface area at the endarterectomy site before vessel closure and reperfusion. The endarterectomized surface can be very thrombogenic; this can be alleviated by the administration of antiplatelet agents before the procedure.

Semiclosed Endarterectomy

The semiclosed endarterectomy was designed to avoid opening the artery longitudinally for the full extent of disease and thus circumvent a long arteriotomy closure. Typically, the artery is opened in a proximal and a distal location. The plaque is first dissected and transected at the proximal level; then it is cored out as a cylinder from the intervening segment with special ringed intraarterial strippers, transected again at the level of the distal arteriotomy, and removed (Fig. 59.34). With this technique, closure of what would have been a long arteriotomy is replaced by closure of two small arteriotomies, one proximally and one distally.

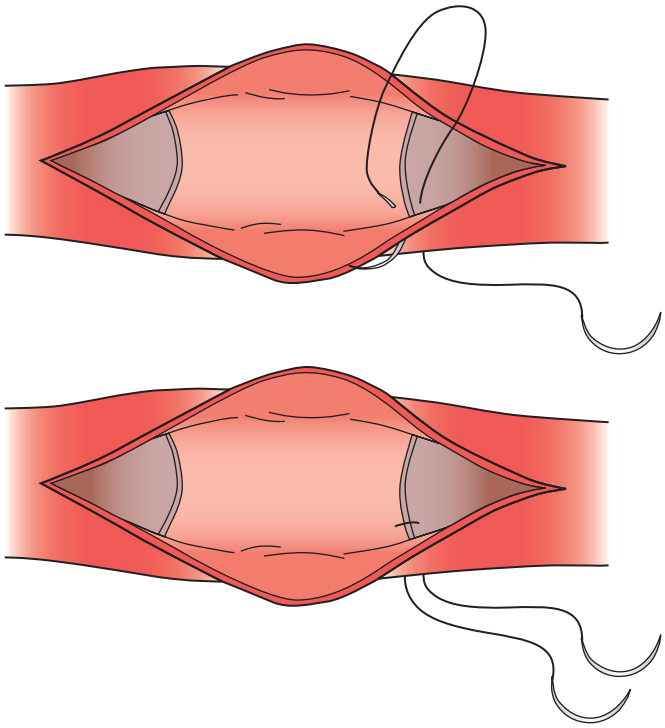


Figure 59.33 Endarterectomy plaque is tacked using multiple interrupted sutures, with one end of the suture placed 1 mm distal to the endpoint and the other end placed at the junction of the endarterectomy and the endarterectomized surface.

In one modification of the semiclosed technique, only one incision is made in the artery. The plaque is crushed manually or with the help of a clamp at the other end, eliminating the need for the second arterial incision, which is usually used to transect the plaque. Moll ring cutters allow sharp transection of the plaque from the remote site (Fig. 59.35)—hence the term *remote endarterectomy*. The disadvantage of this technique is the unpredictability of the endpoint. To address this concern, angioplasty with stent deployment can be performed to secure the distal endpoint. During this portion of the procedure, intravascular ultrasound is helpful to make certain that guide wires and therapeutic devices are intraluminally positioned. This technique has been successfully used in the external iliac and superficial femoral arteries.

Eversion Endarterectomy

In the eversion technique, the artery is transected, and the vessel wall is everted. The outer layer of the blood vessel, which includes the adventitia and part of the media, is held with forceps and gently lifted away from the plaque. The plaque core is developed circumferentially and held firmly with the forceps. As the plaque is being extracted from the artery, the adventitia is retracted backward, and the artery is pushed forward from within, causing the plaque to protrude and be separated from the outer arterial media and adventitia (Fig. 59.36). It is

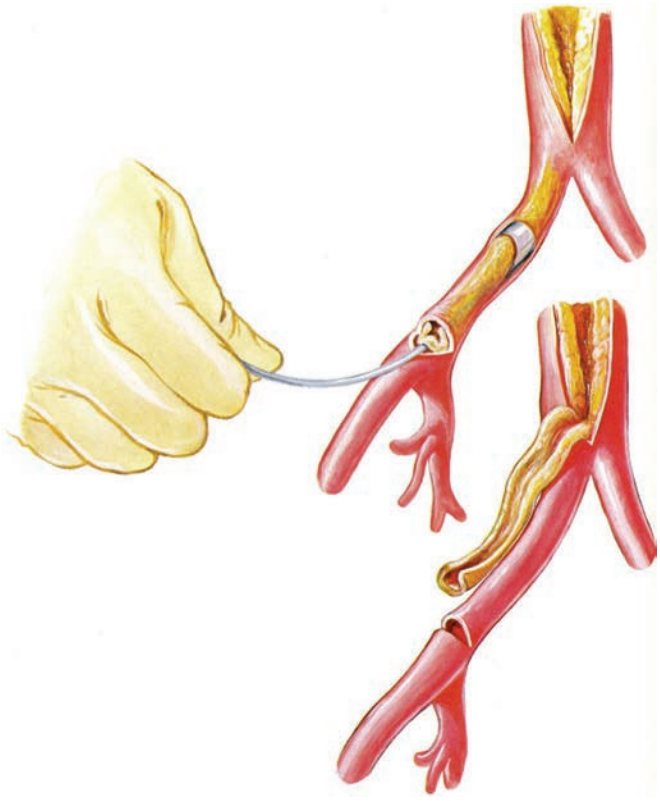


Figure 59.34 Plaque is cored out as a cylinder from the intervening segment, with the help of special ringed intraarterial strippers.

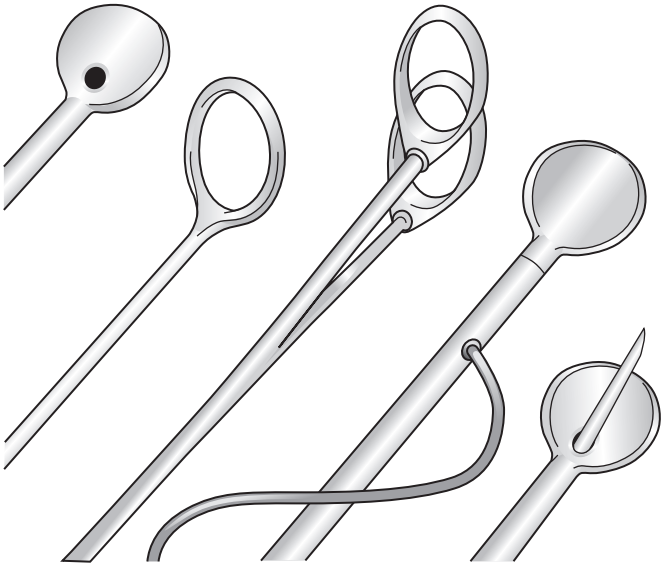


Figure 59.35 Moll ring cutters, spatula, and reentry needle system.

then transected when an appropriate endpoint is reached. This technique requires mobilization of a good segment of the proximal artery to allow eversion.

Orificial and Extraction Endarterectomy

Orificial endarterectomy is a modification of the eversion technique used to treat occlusive disease at the orifice of an

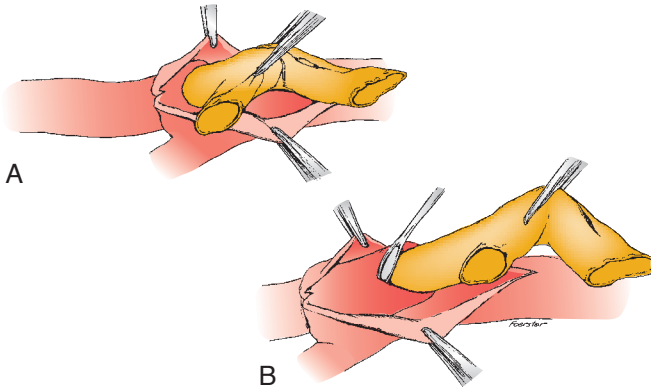


Figure 59.36 (A and B) As the plaque is being pulled out of the artery, the adventitia is retracted backward and the artery is pushed forward from within, causing the plaque to protrude and allowing it to be extracted from the artery.

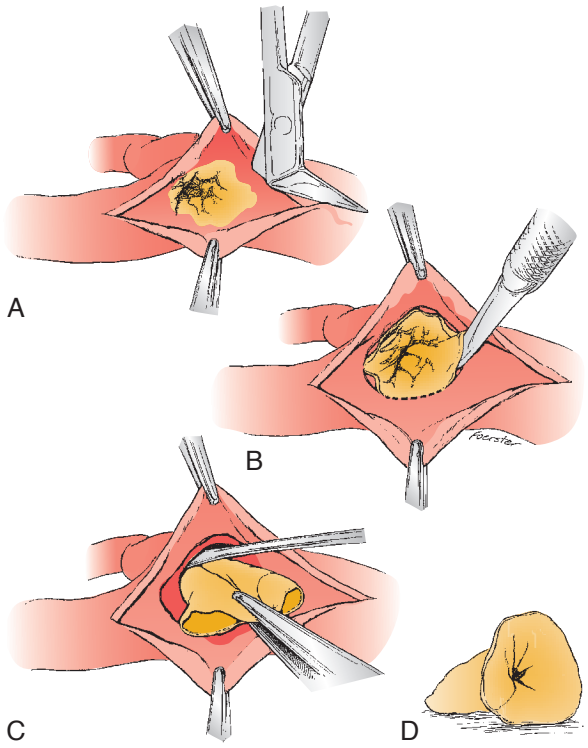


Figure 59.37 (A–D) Orificial endarterectomy is a modification of the eversion technique used to treat occlusive disease at the orifice of an artery.

artery. Typically the orifice of the artery has been exposed through the lumen of the vessel (Fig. 59.37). The plaque is extruded from the orifice by pushing the artery distal to the plaque toward the orifice in an everting manner.

In extraction endarterectomy, a clamp is introduced into the orifice and used to grab the distal plaque or plaque remnant and extract it from the lumen. Generally this technique is applicable only if the plaque ends a short distance beyond the orifice. Furthermore, because the endpoint is not under direct vision, it must be carefully assessed intraoperatively to ensure that a distal flap is not created after restoring blood flow. This is an especially important technique for establishing perfusion to the profunda femoris artery during femoral

thromboendarterectomy. However, if the plaque extends further into the profunda, the endarterectomy needs to be done under direct inspection by extending the incision onto the profunda, and then patching this artery. If the endarterectomy of the common femoral artery needs to be extended to the superficial and profunda femoris arteries, the adjacent walls of both arteries can be sutured together using a running suture to create a common channel, which is then patched. This technique of "syndactylization" can be used in any location where two adjacent branches need to be endarterectomized to avoid patching two arteries separately.

Endarterectomy in Specific Conditions

For approaches to endarterectomy in specific vessels and for specific conditions, such as carotid, arch, visceral, aortoiliac, and infrainguinal disease, see Appendixes e59.1 and e59.2.

ARTERIOTOMY CLOSURE

An arteriotomy can be closed either primarily or with a patch. The choice of a closure method depends on various factors, including the size of the artery, the direction and shape of the arteriotomy, and the degree of atherosclerotic involvement of the artery.

Primary Closure

Primary closure of an arteriotomy is a simple method that can be performed expeditiously. Most transverse arteriotomies in nondiseased arteries can be closed primarily. This can even be done in smaller arteries measuring 2 mm in diameter, such as a radial or posterior tibial artery. Similarly, primary closure can be performed in longitudinal incisions if the vessel is not diseased and has a diameter greater than 5 mm. A typical example is closure of a longitudinal arteriotomy in the common carotid artery or common femoral artery. Some narrowing of the lumen can be expected to occur with primary closure. Such narrowing should be minimal when the arteriotomy is transverse, but it can be significant if smaller arteries (<5 mm) are closed longitudinally.

Primary closure is most expeditiously performed using a continuous running suture technique (Fig. 59.38). A basic concept in the placement of arterial sutures during closure is to include all layers of the vessel wall. Adventitial fibers should be trimmed and not allowed to protrude into the lumen because they can be thrombogenic. The needle is preferentially introduced from the intimal side of the vessel toward the adventitial side, "inside to outside." In the presence of atherosclerotic plaque, a needle introduced from the adventitial side can push the plaque away from the arterial wall and create a site for dissection or thrombus formation.

In the continuous suture technique, the needle is introduced from the adventitial surface of one wall and then from the intimal surface of the opposite wall. For the reasons already cited, it is important that the arterial wall at the incision site and site of closure be free of plaque. Thus primary closure with

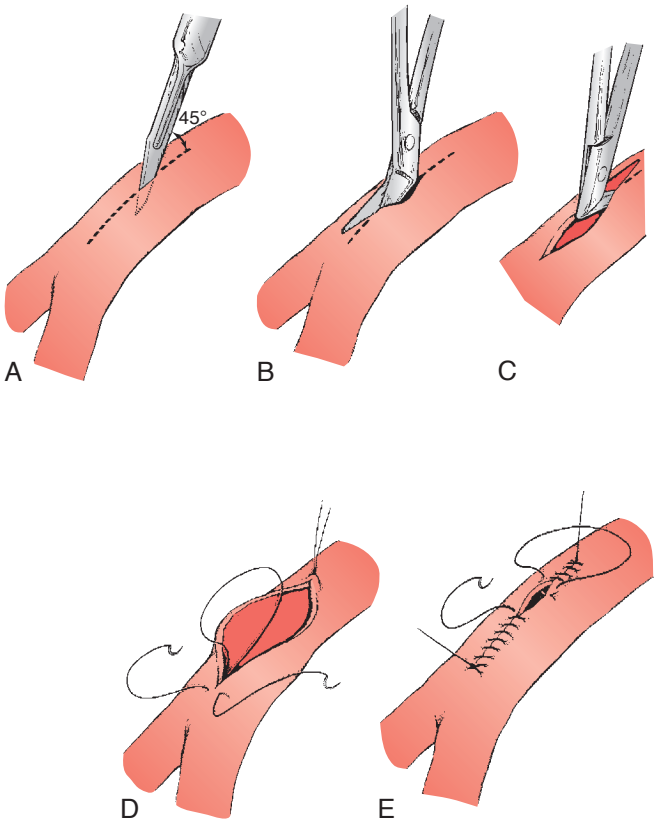


Figure 59.38 (A–E) Primary closure is performed most expeditiously using a continuous running suture technique.

a continuous suture is most suitable in disease-free arteries, endarterectomized vessels, prosthetic bypasses, or veins. The bites should be evenly placed throughout the length of the suture line, and the depth and advancement should be carefully monitored. Bites placed too deep can result in focal narrowing of the lumen.

In the presence of atherosclerotic plaque at the arteriotomy site, primary closure may still be possible; however, an interrupted suture technique is preferable. When closing transverse arteriotomies, interrupted sutures can be placed individually and then tied after all are placed, to allow better visualization of each suture placement (Fig. 59.39). This allows placement of all the sutures, with the needle being introduced from the intimal side and exiting from the adventitial side of the vessel. In addition, the interrupted closure technique is useful in preventing narrowing during the closure of transverse arteriotomies in small arteries.

Patch Closure

When primary closure is expected to cause significant luminal narrowing of an arteriotomy, patch closure should be performed. There are also data to support patch closure to improve the results of carotid endarterectomy. Several technical and nontechnical factors may play a role in the decision to perform patch closure. Technical factors include an artery less than 5 mm in diameter, the presence of significant atherosclerotic plaque

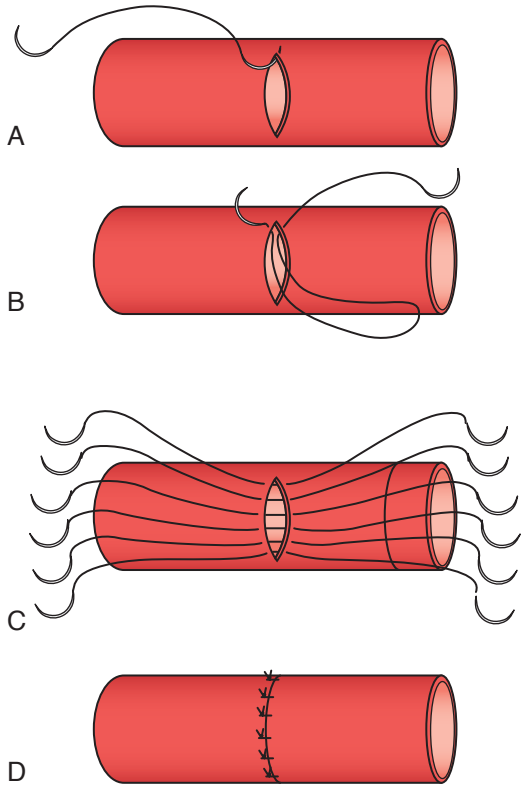


Figure 59.39 (A–D) An interrupted suture technique is preferable in the presence of significant plaque.

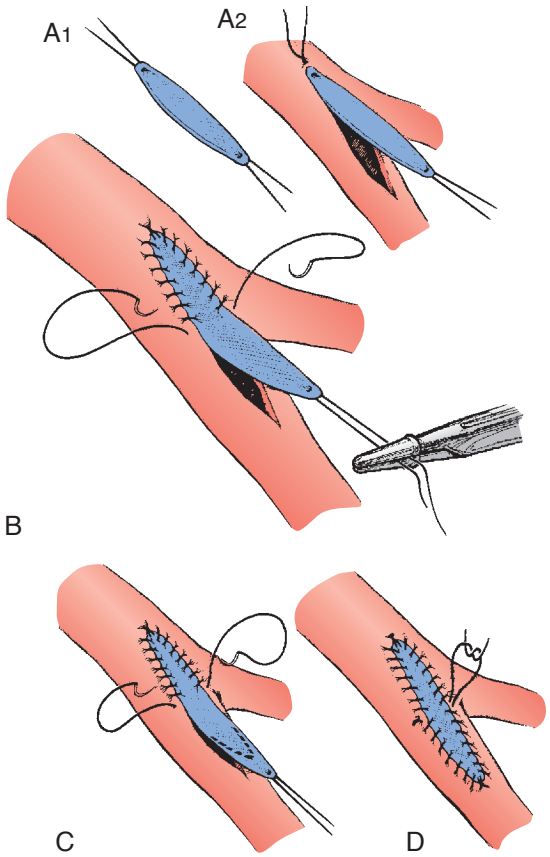


Figure 59.40 (A–D) The simplest technique is to place one suture on each apex of the patch and run both sutures on each side of the patch.

at an arteriotomy site, a jagged arteriotomy, or a very tortuous artery. Furthermore, if there is loss of area in the vessel wall or lumen narrowing pathology that cannot be excised, such as neointimal hyperplasia, closure with a patch is indicated. Nontechnical factors include risk factors that predispose to restenosis, such as hyperlipidemia, heavy smoking, female gender, and a history of recurrent stenosis. The advantage of patch closure is that it allows the needle to be introduced constantly from the intimal aspect of the arterial wall. This eliminates the possibility of pushing a plaque fragment into the arterial lumen and precipitating thrombosis or dissection. Patch closure also allows adequate arterial purchase in the patch and in the artery without compromising the lumen; taking large bites of the artery has the theoretical advantage of controlling the formation of future pseudoaneurysms. Nevertheless, the bites should be placed carefully, with matching depth and even advancement. Otherwise, undesirable lumen narrowing may occur.

When performing patch closure, the width of the patch should be selected to accommodate the vessel size. An overly wide patch can result in excessive redundancy in the arterial patch lumen and act as a nidus for thrombus formation.

Several techniques can be used for closure of a patch. The simplest technique is to place one suture on each apex of the patch and run both sutures on each side of the patch (Fig. 59.40). Alternatively, when suturing in a deep location, the patch can be closed using a parachute technique. In a parachute closure, suturing is started at the apex or a few bites off the apex without tying of the suture (Fig. 59.41). Suturing

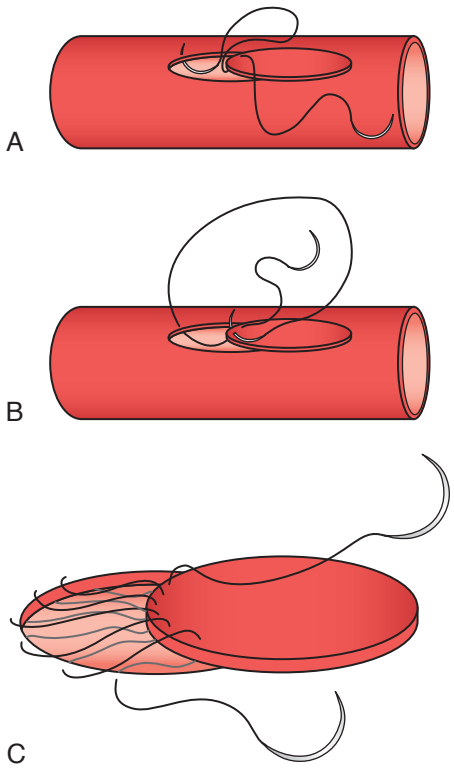


Figure 59.41 (A–C) In a parachute closure, the suturing can be started at the apex or a few bites off the apex without tying of the suture.

is continued until approximately three or more bites are placed on both sides of the center of the apex. The patch is then pulled down while intermittent tension is applied to the suture line. When the suture line is pulled, it is helpful to wet the suture with saline solution; be sure that it is clean from dried blood, and wiggle it back and forth from both ends while pulling the patch with a forceps, keeping the suture between the patch and the arterial apex under slight tension.

Closure of a Transected Vessel

The method used to close a transected vessel depends on its size and intraluminal pressure. Small arterial and venous branches are typically controlled by simple ligature with nonabsorbable suture material or the use of metal clips. Vessels with diameters ranging from 3 to 5 mm are usually controlled by suture ligatures, especially if the vessel is short. Larger vessels are typically closed with a running nonabsorbable suture. If the vessel has a low intraluminal pressure, such as in a large transected vein or the distal end of a transected artery, an over-and-over continuous running suture is usually sufficient to secure hemostasis. However, if the vessel is the proximal end of a transected artery, a single row of continuous sutures may not be adequate. This is especially true when closing an aortic stump after the removal of an infected aortic prosthesis. In such situations, two rows of sutures are preferred to secure hemostasis. The first row is usually constructed using horizontal mattress sutures, which can be placed using a continuous or an interrupted technique. The second layer is typically a continuous over-and-over running suture. The proximal row is meant to decrease the pressure and tension on the distal suture line (Fig. 59.42).

REPLACEMENT AND BYPASS PROCEDURES

Vascular replacement or bypass procedures are typically performed to manage occlusive disease or to replace aneurysmal or injured vessels. A variety of anastomotic techniques are employed in these procedures. The technique selected depends on the procedure, the vascular pathology, and the anatomic location of the operative field. Considerations for bypass anatomy include adequate inflow, outflow, and choice of conduit.

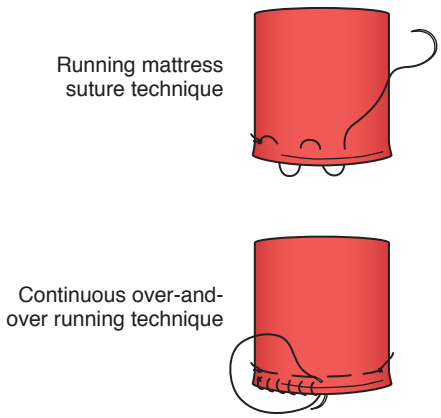


Figure 59.42 The *top panel* shows a running mattress suture technique. The *bottom panel* shows a continuous over-and-over running technique.

Basic Considerations

When creating a bypass to treat lower extremity occlusive disease, the reconstruction should be performed with preservation of the existing circulation. As a result, the proximal and distal anastomoses are typically performed in an end-to-side manner. Such a configuration allows the maintenance of antegrade flow in the native vessel at the level of the proximal anastomosis. Ideally, the distal anastomosis is placed in a disease-free segment of the vessel distal to the occlusive pathology. An end-to-side configuration at the distal anastomosis allows the maintenance of retrograde flow through all patent branches (Fig. 59.43).

Occasionally, disease in the artery requires the creation of an anastomosis with an end-to-end configuration. When treating aneurysmal disease, the aneurysm is typically replaced by interposing a new conduit using end-to-end anastomoses. Aneurysmal pathology is sometimes treated by an end-to-side bypass proximal and distal to the aneurysm and ligation of the aneurysm, as is done for popliteal artery aneurysms.

End-to-Side Anastomosis

An important step in constructing an end-to-side anastomosis is to align the vessels without a twist or kink. Anastomotic failure is more likely to be caused by technical imperfections than by the dimensions of the anastomosis.[6] The anastomosis should be prepared, such that the posterior incision in the conduit is parallel to its long axis; otherwise, a buckle effect may develop at the anastomosis. The ideal arteriotomy length is poorly defined and is influenced by the bypass diameter. Some recommend that the length be twice the bypass diameter.[3] Others recommend an arteriotomy greater than 2 cm.[7,8] In coronary artery vein bypass, a short arteriotomy (4 to 6 mm) is usually recommended.[9] Most often, an arteriotomy measuring 1.2 to 2 times the graft diameter is created. The end of the conduit is transected, and then a slit matching the arteriotomy length is made in its posterior aspect. This allows spatulation of the conduit end to minimize narrowing at the anastomosis. An arteriotomy shorter than 1.2 times the diameter of the conduit results in the bypass's joining the artery at an unfavorably sharp angle. An arteriotomy that is too long requires more time for construction, with no proven additional benefits. An

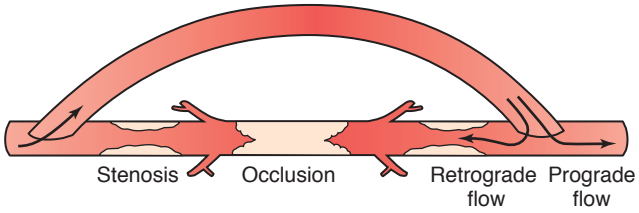


Figure 59.43 End-to-side configuration at the distal anastomosis allows the maintenance of retrograde flow through patent branches.

end-to-side anastomosis can be performed using an anchor or parachute technique.

Anchor Technique

In the anchor technique, the anastomosis is constructed by first placing a suture at the heel of the conduit and the arteriotomy. The suture is tied, thus stabilizing and anchoring the conduit at the heel of the anastomosis. Suturing is continued on one side of the heel to the toe, and then halfway down the other side of the anastomosis. The anastomosis is completed by suturing the other end of the heel suture until it meets the previously placed suture (Fig. 59.44). An alternative is to start another suture at the apex and run it in a continuous manner on both sides of the apex toward the heel to complete the anastomosis, tying the suture on both sides about the middle of the arteriotomy.

There are numerous other variations of the end-to-side anastomosis. The anchoring sutures placed at the apex or the heel can be either simple or mattress sutures. However, in small vessels, mattress sutures at the apex or the heel may cause narrowing of the lumen. Another option is to place interrupted sutures at the apical part of the anastomosis (instead of a continuous suture line). The theoretical advantages of this variation include allowing the anastomosis to stretch and expand with arterial pulsations and not be limited by the length of the continuous suture line. Further, the needle tip in a running suture can become blunted from repetitive piercing, especially of calcified vessels.

The anchor technique is ideal for superficial vessels and larger arteries. The anchoring sutures facilitate traction and countertraction during the anastomotic procedure.

Parachute Technique

In the parachute variation of the end-to-side anastomosis, the sutures at the heel and the apex are not initially pulled down or tied. Suturing is started a few millimeters from the center of the heel. The conduit is typically held with forceps a few centimeters from the arteriotomy. This allows the placement of sutures in deep areas without the conduit obscuring or interfering with suture placement. First, several bites are placed in the conduit and the arteriotomy until the challenging part of the anastomosis is completed. This usually requires a total of three sutures on each side of the center of the heel. Tension is then applied on both ends of the suture, and the bypass is slowly pulled toward the anastomosis, achieving a tight suture line (Fig. 59.45). It is important to avoid excessive, continuous pulling on the suture line during this step, because it could result in tearing of the arterial wall. As described previously, when using the parachute technique in patch closure of an arteriotomy, wetting the suture and wiggling its ends back and forth help in tightening the suture without injuring the arterial wall or breaking the suture line.

The parachute technique is especially useful if the vessels are small or in a deep location where visualization of the first few bites at the apex and heel may be suboptimal. Variations in the parachute technique relate to the site where the suture is started: it can be started exactly at the center of the heel or a few bites off-center. The technique of starting a few bites off-center can be challenging to learn. However, with experience, it may become the surgeon's preferred method of performing an end-to-side anastomosis.

End-to-End Anastomosis

An end-to-end anastomosis is typically performed for replacement of an arterial segment, such as an aneurysmal artery or a vessel that has been transected by trauma. An end-to-end anastomosis is also constructed when a composite bypass is needed or when preservation of retrograde or antegrade flow is not essential.

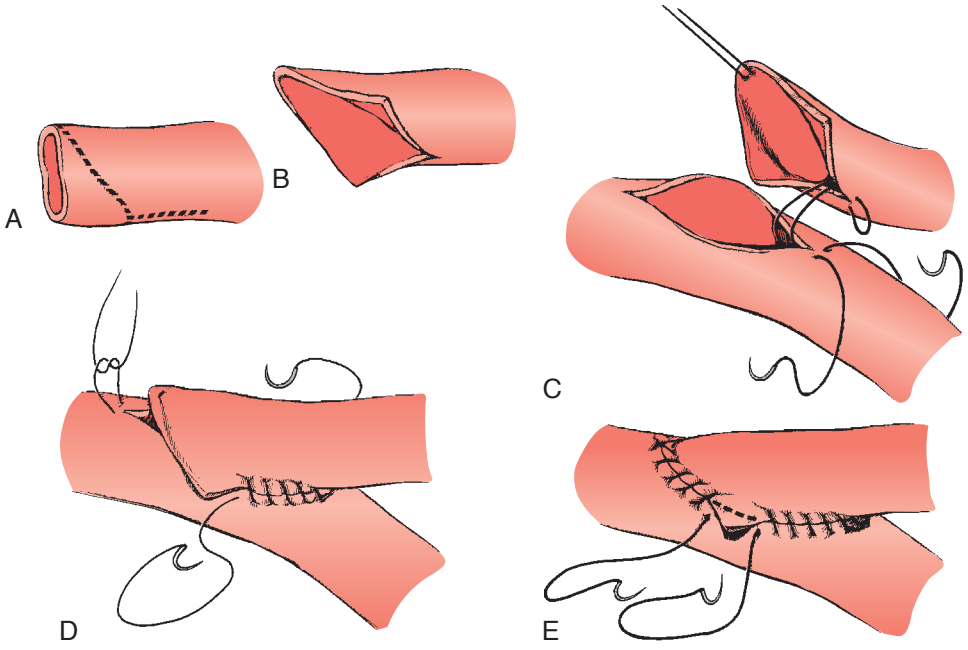


Figure 59.44 (A–E) End-to-side anastomosis anchor technique.

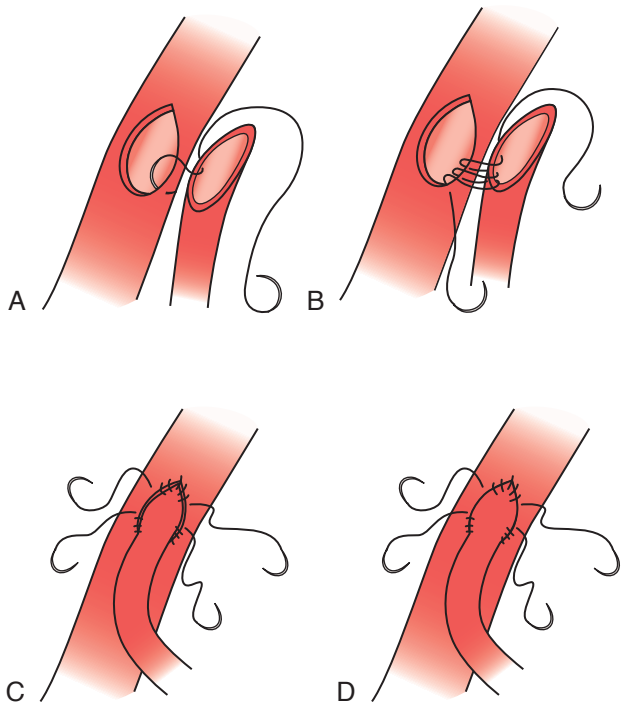


Figure 59.45 (A–D) Parachute technique—another variation of the end-to-side anastomosis.

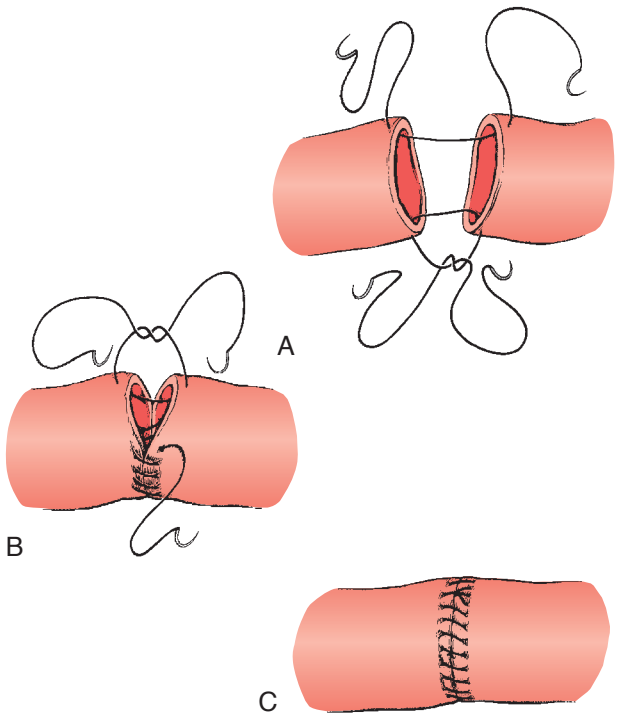


Figure 59.46 (A–C) End-to-end anastomosis in large, movable vessels. The vessels are then flipped 180 degrees, placing the posterior wall in an anterior location for completion of the anastomosis.

The technique varies, depending on the size of the vessels and their mobility. When constructing an end-to-end anastomosis between two large vessels of comparable diameters, the transection of the vessels and the anastomotic suture line are usually in a plane perpendicular to the long axis of the vessel. If both segments are freely movable, a number of techniques have been developed to simplify suturing in a forward manner, maintaining the most favorable angle for suture placement.

One technique involves placing two diametrically opposed sutures in an anterior and posterior part of the vessel. The sutures are tied, and the anterior part of the anastomosis is constructed first. The vessels are then flipped 180 degrees, placing the posterior wall in an anterior location for completion of the anastomosis (Fig. 59.46). This technique is a modification of the triangulation method first described by Carrell. In the triangulation technique, the anastomosis is divided into three parts rather than two parts, anterior and posterior (Fig. 59.47).

When the segments are not freely movable, such as when constructing an anastomosis for aortic aneurysmal disease, the back wall is sutured first, with a continuous suture using a parachute or an anchor technique, based on the depth of the anastomosis and the surgeon's preference (Fig. 59.48). When the back wall is left intact, suturing involves placing a double-layer bite in the posterior wall of the aorta. It is essential to take deep bites; shallow bites may miss the adventitia and do not provide the strength necessary to hold the aortic anastomosis.

When constructing an end-to-end anastomosis between two small vessels, it is essential to spatulate the anastomosis to avoid compromising the lumen. Thus both segments are transected in an oblique manner, and the incision is extended posteriorly.

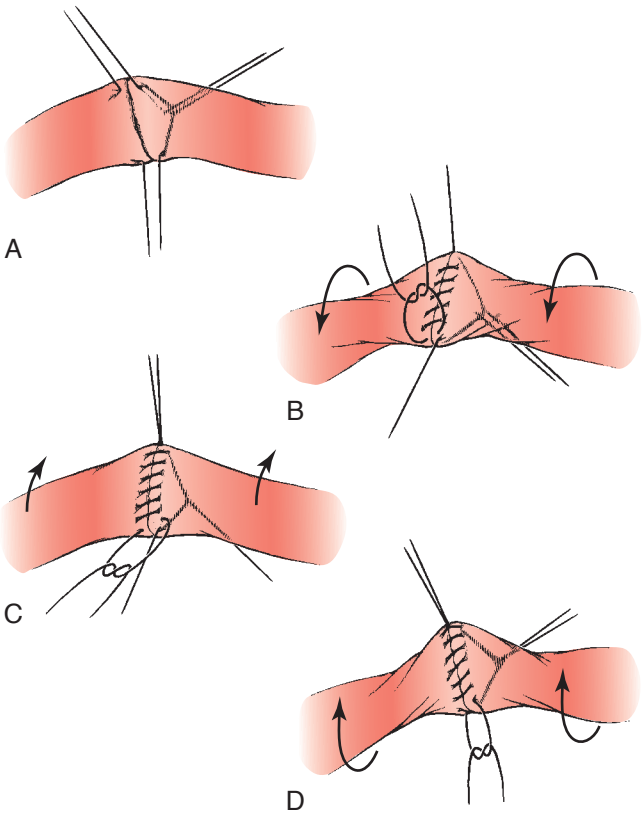


Figure 59.47 (A–D) End-to-end anastomosis using the triangulation method.

An anchoring suture is started at the center of the heel and continued on each side of it (Fig. 59.49). The suturing may be continued around the apex. Alternatively, another suture is started at the apex and continued on both sides of the apex toward the heel to complete the anastomosis. The reason why small vessels should be spatulated when they are to be sutured end to end is a matter of geometry. If the anastomosis is done in a perpendicular fashion to the length of the vessel, it will be a perfect circle with all the bites located in the same plane, which can be narrowed if some bites are too deep. A spatulated anastomosis will produce an oblong shape with the bites in different planes, which makes it more forgiving if some are too deep.

Side-to-Side Anastomosis

A side-to-side anastomosis is rarely performed. It can be used, however, to create a side-to-side radiocephalic arteriovenous fistula for chronic hemodialysis or a side-to-side arteriovenous fistula distal to an infrainguinal prosthetic bypass as an adjunctive procedure to improve graft patency by decreasing outflow resistance.[10] A side-to-side configuration can also be used in the construction of a second anastomosis in a sequential bypass for limb revascularization. To perform a side-to-side anastomosis, the vessels need to be dissected and mobilized so they lie adjacent to each other with minimal tension. The anastomosis is created by longitudinal arteriotomy or venotomy where the walls come in direct contact. The posterior wall of the anastomosis is typically constructed first. The anastomosis is usually 6 to 10 mm long.

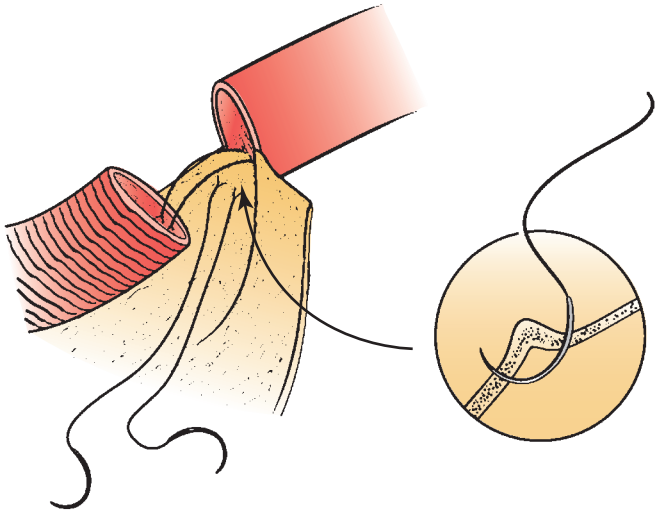


Figure 59.48 When the segments are not freely movable, such as when constructing an anastomosis for aortic aneurysmal disease, the back wall is sutured first with a continuous suture. It is essential to take deep bites because shallow bites may tear.

Adjunctive Techniques for Infrainguinal Bypass Anastomosis

T-Junction

A useful technique to facilitate the construction of an anastomosis in infrainguinal vein bypass is the T-junction technique (Fig. 59.50). In this method, a side branch in the vein is identified. The vein is transected 5 to 10 mm from the branch and then slit along the posterior wall in a fashion to incorporate the side branch in the anastomosis. The shape of that segment of vein looks like a "T." This can be used at the proximal or distal anastomosis and is helpful in minimizing sharp angulation of the bypass and narrowing at the heel of the anastomosis.

Saphenofemoral Junction Vein Cuff

When constructing a greater saphenous vein bypass, the vein can be transected at the saphenofemoral junction with a 1-mm rim of femoral vein (Fig. 59.51). This technique provides a large venous hood for construction of the anastomosis, especially if the artery is thickened and the vein is relatively small.

Venous Cuffs and Patches for Prosthetic Grafts

Several different anastomotic configurations have been described in an attempt to improve bypass results by the interposition of venous tissue between the prosthetic graft and the recipient

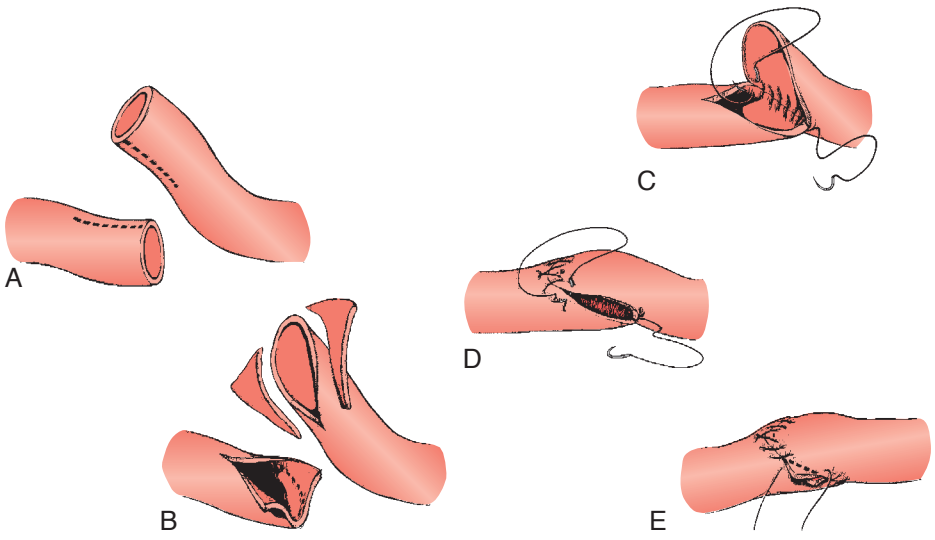


Figure 59.49 (A–E) Spatulated end-to-end anastomosis between two small vessels.

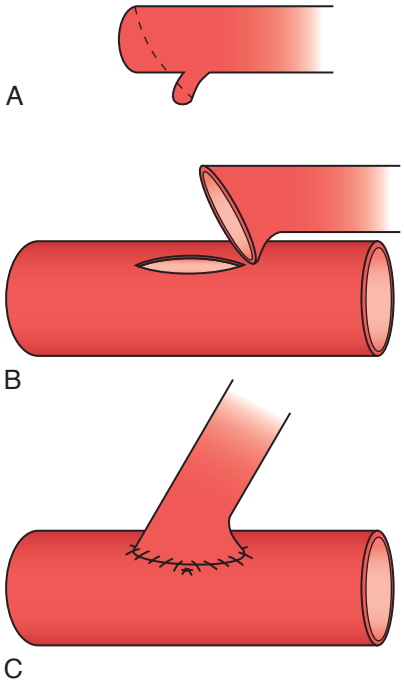


Figure 59.50 (A–C) T-junction technique.

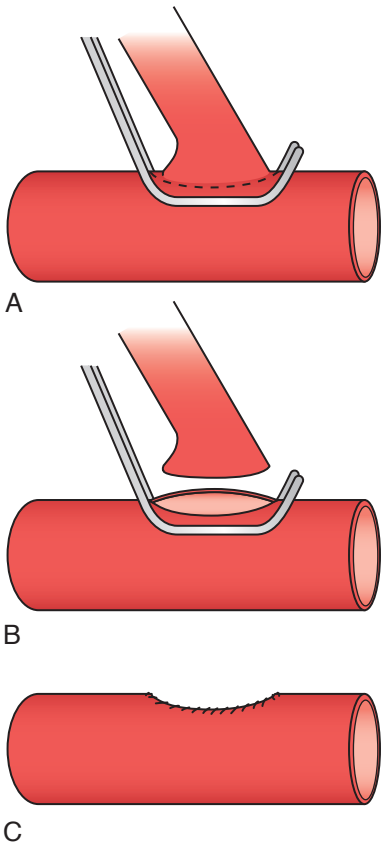


Figure 59.51 (A–C) Saphenofemoral junction technique.

artery, especially to tibial artery targets. Each configuration has certain advantages and disadvantages, both real and potential.

The Miller vein cuff involves the longitudinal opening of a segment of vein and a running suture line to secure the edge of the vein to the arteriotomy. The two cut ends of the vein

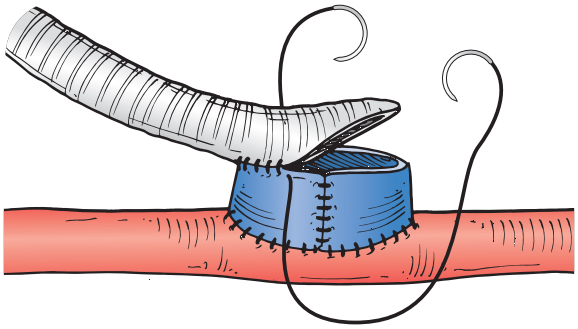


Figure 59.52 Venous cuff at the distal anastomosis of prosthetic grafts.

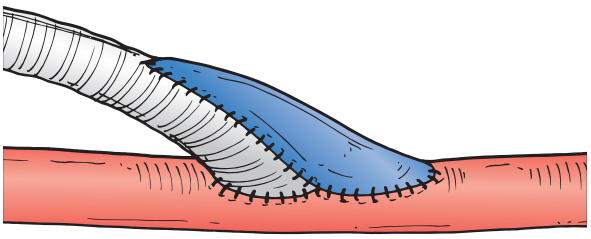


Figure 59.53 Taylor patch.

are then sutured together to construct an oval venous cuff. The prosthetic graft is then sutured directly to the oval vein cuff (Fig. 59.52).[10] However, several potential disadvantages have been recognized in association with the Miller cuff technique. Significant turbulence has been noted due to the deep anastomotic reservoir and the difficulty of achieving a proper angle between the graft and recipient artery. This results in increased turbulence and shear stress at the distal anastomosis. These hemodynamic factors may help to explain the immediate and early graft failures reported in Miller's initial series. In addition, the oval formation of the Miller cuff is difficult to maintain in tight anatomic spaces, such as those involved in very distal bypasses to the dorsalis pedis artery of the forefoot and the plantaris pedis branches of the posterior tibial artery. This feature is especially problematic in the diabetic population where pedal bypass may be required.

The Taylor patch technique requires a long arteriotomy (3 to 4 cm) so that the patch can be constructed longer than the diameter of the prosthetic conduit (Fig. 59.53).[11] A U-shaped slit approximately 1 cm in length is made on the underside of the graft, with minimal angulation to ensure that the graft lays almost parallel to the artery. The heel of the graft is then sutured directly to the proximal portion of the arteriotomy with the suture line continued along each side of the arteriotomy. The anterior surface of the graft is then incised parallel to the arteriotomy to a point 2 cm proximal to the heel of the anastomosis. A vein patch varying from 5 to 6 cm is used to close this elliptical defect. The patch begins distally on the artery with interrupted sutures and is completed proximally onto the PTFE with a running suture. However, there are theoretical and practical disadvantages to the Taylor patch technique. The arterial intima is directly exposed to prosthetic graft material for the proximal portion of the anastomosis, thereby losing the advantage of the venous endothelium for half the anastomosis.

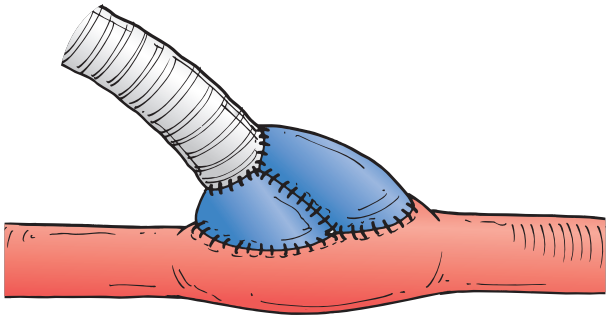


Figure 59.54 Saint Mary's boot

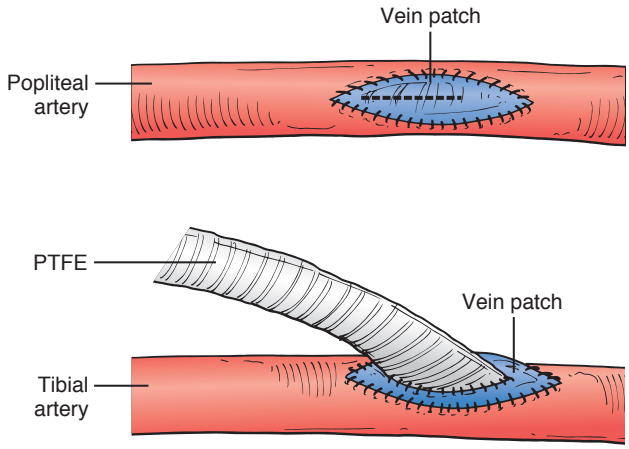


Figure 59.55 Distal vein patch. *PTFE*, Polytetrafluoroethylene.

There is also a point of possible anastomotic constriction where three suture lines converge between the artery, graft, and vein patch. Finally, a significant length of vein must be available to accomplish the anastomosis using the Taylor patch technique.

The Saint Mary's boot technique utilizes a similar arteriotomy and venous harvest as the Miller cuff; however, the corner of the venous segment is sutured to the apex of the arteriotomy to form the anastomotic toe (Fig. 59.54).[12] The remainder of the venous-arterial anastomosis is formed in a similar fashion to the Miller cuff; however, the redundant vein is excised obliquely and sutured to the longitudinal edge. Next, a segment of the posterior collar is incised to increase the size of the anastomosis between the graft and vein collar. Overall, the Saint Mary's boot maintains a fully compliant venous collar, avoids any direct contact between the artery and graft, and maintains the hemodynamic advantages of the Taylor patch. Its main drawback is the technical difficulty of its construction.

This distal vein patch bypass utilizes a technique familiar to all vascular surgeons and requires a shorter arteriotomy, thereby decreasing the amount of venous tissue required for the procedure (Fig. 59.55).[13] A 2- to 3-cm segment of tissue for the patch is suitable and can include saphenous vein remnants, arm vein harvested under local anesthesia, superficial femoral vein, or a segment of occluded superficial femoral artery that is opened and endarterectomized. The venous segment is gently dilated with heparinized saline and opened longitudinally, with valve

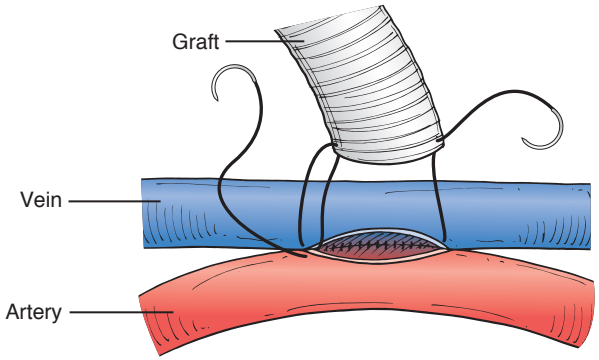


Figure 59.56 Distal arteriovenous fistula.

remnants excised. A 2- to 3-cm arteriotomy is then performed in the target artery, and the venous segment is cut to the appropriate length and width in preparation for the patch. In most cases, the width is left unaltered to allow for a generous patch to permit bulging of the patch under arterial flow to have a functional result similar to that of a vein cuff. The patch is sewn to the artery using 7-0 Prolene monofilament suture in a parachute technique. After the patch is sewn in place, a longitudinal venotomy is made in the proximal two-thirds of the patch, and the graft is sutured to the vein patch using 6-0 Prolene suture. The anastomosis is constructed to maintain a rim of venous tissue interposed between the graft and the entire circumference of the arterial wall. Because the venotomy is made in the proximal two-thirds of the patch, only venous tissue is interposed at the toe of the anastomosis.

Distal Anastomotic Arteriovenous Fistula

The addition of an arteriovenous fistula at the distal anastomosis has also been used to improve graft performance, especially when arterial runoff is poor. Dardik et al.[14] used human umbilical vein grafts and added a common ostium distal arteriovenous fistula to decrease the thrombosis rate by reduction of outflow resistance (Fig. 59.56). When there is no venous conduit and poor arterial runoff, an arteriovenous fistula can be added to the distal anastomosis of a distal vein patch bypass.[15] This modification has been performed in patients with no vein available and severely disadvantaged arterial runoff on the preoperative arteriogram. The target tibial artery is opened longitudinally with a venotomy in the corresponding tibial vein. The opposing walls of the artery and vein are sutured together to create a common ostium connection. The vein patch is then sutured to the common ostium created by this fistulous connection. An anastomosis is then constructed between the vein patch and the PTFE as described in the distal vein patch bypass configuration.

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APPENDIX e59.1

Technical Considerations for Thromboembolectomy in Specific Conditions

Although thromboembolectomy is a basic vascular surgical procedure used in various parts of the vascular tree, special techniques have been designed to achieve complete thromboembolectomy in specific conditions.

Infrainguinal Thromboembolectomy

If the thrombus is likely to involve the profunda and superficial femoral arteries, the arteriotomy can be placed half a centimeter proximal to the common femoral artery bifurcation. This simplifies steering of the catheter into the profunda and superficial femoral arteries. If the thrombus is known to be at the popliteal level and farther distally, with sparing of the profunda femoris artery, the arteriotomy can be performed in the superficial femoral artery while maintaining flow into the profunda femoris artery. Maintaining flow into the profunda femoris artery allows some perfusion to the limb while thrombectomy is being performed. It also helps backbleeding from the distal end once the thrombus is removed. During infrapopliteal thromboembolectomy, if the catheter cannot be passed into the tibial vessels despite fluoroscopic maneuvers, exposure of the popliteal artery below the knee, the anterior tibial origin, and the tibioperoneal trunk may be necessary to introduce the balloon catheter in the desired location. Rarely, exposure of the vessels at the ankle may be necessary to achieve complete thromboembolectomy. Occasionally, in very challenging situations, thrombus, cholesterol, or atherosclerotic debris may be packed into the vessels distally. The adjunctive use of intraoperative lytic therapy may improve the chance of successful thromboembolectomy with an irretrievable clot. A thrombolytic agent, such as tissue plasminogen activator 0.02 to 0.1 mg/kg/h, whereas non–weight-based doses generally range from 0.25 to 1.0 mg/h, even though higher doses have been reported, the lowest effective dose has not been determined. Following thromboembolectomy, the luminal area may be very thrombogenic. In addition to maintaining anticoagulation, the administration of intravenous antiplatelet agents, such as dextran 40 at a dose of 25 mL/h, may be useful in the perioperative period to prevent re-thrombosis due to hypercoagulability. Further, it is important to evaluate the patient following thromboembolectomy for any reperfusion injury problems, including compartmental hypertension. A low threshold for performing a fasciotomy should be maintained. All thrombi should be inspected and examined after retrieval. Occasionally, the thrombus may be related to a tumor elsewhere in the body, such as atrial myxoma, and pathologic examination may be necessary.

Aortic Saddle Embolus

In this situation, both groins should be exposed. First, thromboembolectomy is performed on one side. Inflating a balloon catheter at the level of the common iliac artery origin may be useful to avoid further inadvertent showering of thrombi into the revascularized limb while thromboembolectomy is being performed on the other limb. Embolization into the hypogastric artery while the balloon catheter is being withdrawn from the aorta to the femoral incision remains a hard-to-prevent problem. Hypogastric artery thrombectomy under fluoroscopic guidance using an over-the-wire balloon may be attempted to address this condition.

Occluded Bypass

When performing thromboembolectomy of an occluded bypass, the procedure may have to be modified, based on whether the graft is a vein or a prosthetic bypass and whether the occlusion has occurred after a recent or old revascularization. Bypass occlusion following recent revascularization is frequently due to a technical error. The incision in the bypass is usually made at the site where the technical problem is suspected to be, to allow its correction after thromboembolectomy. An incision at the level of the proximal anastomosis, and another one at the level of the distal anastomosis may be necessary to extract the clot if the bypass is a reversed vein, due to the difficulty of trying to negotiate a balloon catheter across the valves. When faced with a graft occlusion following an established prosthetic revascularization, one option is to expose the body of the bypass in the most accessible location and perform thromboembolectomy through a transverse incision. This is followed by an intraoperative angiogram to clarify whether additional intervention is necessary. Dissection of the proximal or distal anastomosis through scarred tissue may be inevitable to achieve complete clot extraction.

Iliofemoral Venous Thromboembolectomy

Thromboembolectomy is not limited to the arterial system. In the rare event of a venous thromboembolectomy required to manage a patient with phlegmasia and diffuse iliofemoral venous thrombosis, the thrombi from the distal leg may not be retrievable with a balloon catheter. After performance of a thrombectomy of the proximal iliofemoral venous segment, the clots in the lower extremity can be extracted from the venotomy site by elevating the leg and applying an Esmarch bandage, thus squeezing and milking the thrombi out of the leg and thigh. Insertion of a caval filter before performing the iliofemoral thrombectomy is often recommended to prevent major pulmonary emboli during the procedure.

APPENDIX e59.2

Technical Considerations for Endarterectomy at Specific Anatomic Locations

The decision to perform an endarterectomy depends on the location and distribution of the atherosclerotic disease pattern and the experience of the surgeon. When the arteries are medium to large (>5 mm diameter) and the atherosclerotic disease process is localized, an endarterectomy is very attractive.

Carotid Bifurcation Disease

Carotid endarterectomy can be performed using different techniques. Traditionally it has been performed using a longitudinal incision starting in the common carotid and extending

into the internal carotid past the disease process. The plaque in the common and internal carotid arteries is shelled out using an open endarterectomy technique, and the plaque in the external carotid artery is typically removed using an eversion orificial technique. The arteriotomy is closed either primarily or with a patch; practice patterns vary, with some surgeons routinely patching and others patching selectively. Another eversion technique has been developed to avoid the issue of patch closure. This technique involves transecting the internal carotid artery at its bifurcation, conducting an eversion endarterectomy, and then reconnecting the internal carotid back to its original location. This technique is expeditious and avoids the use of a patch, but it cannot be performed for recurrent carotid disease. Other factors that may limit the use of eversion endarterectomy include extensive disease in the common carotid artery and the surgeon's comfort level with the technique. Eversion endarterectomy of the internal carotid is possible despite the presence of significant common carotid plaque. After transection of the internal carotid artery, a longitudinal incision is performed in the common carotid artery. The common carotid plaque is removed, followed by closure of the common carotid arteriotomy in a continuous running fashion to the level where the internal carotid was transected.

Aortic Arch Vessels

Endovascular therapies provide attractive options for dealing with occlusive disease at the origin of the aortic arch vessels; infrequently, open surgery may still be recommended. The plaque typically originates in the aortic arch and spills into the origin of the arch vessels. Performing an endarterectomy at that level can be hazardous, and the location and extension of the plaque may not allow safe aortic clamping. Further, closure of the endarterectomy site can be challenging, with a very thinned out aorta. Thus endarterectomy of the origin of the arch vessels has been abandoned in most centers. Many surgeons have replaced this technique with bypass to the involved vessel originating from a nondiseased ascending aorta; this allows safe, partial cross-clamping for construction of the proximal anastomosis.

Abdominal Aorta and Its Branches

In the abdominal aorta, atherosclerotic disease of the mesenteric circulation and renal arteries can be managed by endarterectomy.

Visceral Endarterectomy

Very few centers have solid experience with endarterectomy of the celiac and mesenteric vessels, and these procedures have typically been replaced by aortoceliac and aortomesenteric bypasses, either from an antegrade approach, with the bypass originating from the supraceliac aorta, or from a retrograde approach, with the bypass originating from the infrarenal aorta or iliac arteries. Surgeons who perform endarterectomy of the celiac and mesenteric vessels frequently do so via a retroperitoneal approach. The procedure can also be performed with a transabdominal approach and medial visceral rotation. One of the challenges of this procedure is closure of the endarterectomy site. The aortic wall may appear very thin, and often felt pledgets are necessary to re-enforce the suture lines to allow them to withstand the aortic pressure. Another limiting factor is that the plaque may extend distally in the superior mesenteric artery and may not feather out in a desirable manner. As a result, an additional longitudinal incision may be needed distally in the superior mesenteric artery; this is closed using a patch once all the plaque is removed and the endpoints are tacked.

Renal Endarterectomy

The renal arteries are well suited to endarterectomy procedures, and several techniques have been described. Typically, clamping at the suprarenal or preferably in the supramesenteric location is necessary to allow for a safe endarterectomy. The plaque in the renal artery is typically removed using an eversion technique. One technique for treating bilateral renal disease involves performing a transverse incision in the aorta at the level of the renal arteries. The incision is extended into each renal artery through its respective orifice. The plaque is removed, and the arteriotomy is closed with a patch. This procedure requires a long cross-clamping time and may be very challenging. Another technique is to transect the aorta 1 to 2 cm distal to the origin of the renal arteries. The aortic stump is then lifted upward, and an eversion endarterectomy of the renal arteries and the aortic plaque at that level is performed. This allows the expeditious placement of an aortic graft in the infrarenal position or placement of a clamp in the infrarenal position and construction of a bypass below the renal arteries.

Aortoiliac Endarterectomy

Endarterectomy has also been used to treat aortoiliac occlusive disease. Typically, the aorta is cross-clamped in the infrarenal location, and a longitudinal incision is made in the infrarenal aorta, which allows for plaque removal. Plaques in the common and external iliac arteries are removed using a semiclosed endarterectomy technique. Additional incisions are typically performed at the level of the iliac bifurcation to allow completion and inspection of the endpoint. The main factor limiting the use of this technique is the distal extension of plaque, which may extend all the way down to the femoral bifurcation and the origin of the profunda femoris artery. When such extensive pathology is encountered, this technique may be undesirable and can easily be replaced with an aortobifemoral bypass, with the distal anastomosis connected to the femoral bifurcation or profunda femoris artery.

Infrainguinal Vessels

Atherosclerotic plaques in the common femoral artery extending into the femoral bifurcation and profunda femoris arteries are also amenable to endarterectomy procedures. This can be done in conjunction with construction of the distal anastomosis of an aortobifemoral bypass or as a separate procedure if inflow from the external iliac artery is adequate. One option is to extend the arteriotomy distally into the profunda femoris artery and perform an open endarterectomy. A modification involves making the incision in the common femoral artery, with possible extension into the superficial femoral artery, and then performing

an eversion endarterectomy of the profunda femoris artery. Selection of the reconstruction technique is influenced by the occlusive pathology and the ability to provide maximal revascularization. Attempts to treat the superficial femoral and popliteal arteries with closed and open endarterectomy have not gained popularity because of the extensive dissection required and the poor patency rates. However, interest in superficial femoral artery endarterectomy has been resurrected with the re-introduction of Moll ring cutters. This technique permits a remote endarterectomy under fluoroscopic guidance. Endovascular techniques allow for better handling of the endpoint. Using catheter-based technology, a wire is navigated into the lumen distal to the endpoint, and stents or stent-grafts can be deployed at the endpoint to provide a smooth transition between endarterectomized and nonendarterectomized segments. The value of this technique has yet to be proven, but it represents another option in the vascular surgeon's armamentarium. It may allow use of the popliteal artery as an inflow for constructing a popliteal-to-tibial bypass when a long segment of vein is not available. Endarterectomy has no role in the infrageniculate vessels.

60 CHAPTER

Endovascular Diagnostic Technique

SAPAN S. DESAI and KIM J. HODGSON

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INTRODUCTION

Mastery of endovascular technique is a cornerstone of the modern practice of vascular surgery. Vascular surgeons must be facile with a variety of instruments and techniques used for endovascular access, selective vessel catheterization, image acquisition, and postprocessing, as well as with techniques to mitigate complications that can occur. Access to complete endovascular diagnostic procedures can occur in a variety of arteries and veins located throughout the body. Proper selection of needles, wires, and catheters permits the safe conduct of these procedures. The purpose of this chapter is to familiarize the reader with these tools and techniques for diagnostic purposes. Interventional techniques will be discussed in Chapter 61.

VASCULAR ACCESS

Choice of Site

Most endovascular diagnostic procedures are performed through percutaneous access, the attainment of which being the initial step of the procedure. While recently the use of radial or pedal

artery access has become more popular, the far and away most common access site, arterial or venous, is in the common femoral location, with axillary/brachial access being a distant second in popularity. The key factors that must be considered in choosing a site for access include (1) appropriateness for the procedure being completed, (2) ability to obtain hemostasis once the procedure is completed, (3) ability to safely convert to an open procedure if there is a complication, and (4) ensuring that cannulation of that site will have minimal adverse effects on the tissue being supplied by the access vessel.

Appropriateness of access relates to utilizing a vessel appropriately sized for the catheters or devices intended, an access location that permits subsequent catheterization of the vessels of interest, and an access site that can be readily sealed, either by manual compression or with a closure device. For example, diagnostic angiography of the aorta, iliac arteries, and their subsequent outflow to the legs is most commonly performed via common femoral artery (CFA) access. An alternate site could include the brachial artery if both groins are hostile or there is a known occlusion of both common femoral arteries. If performing diagnostic imaging of the subclavian artery for thoracic outlet syndrome, either a retrograde approach using the brachial artery or an antegrade approach using CFA access can be obtained. In the former case, a wire and catheter are advanced into the proximal subclavian artery and diagnostic imaging completed. In the latter case, a wire and catheter are advanced from the CFA, through the external and common iliac arteries, up the aorta and to the aortic arch.

The ability to obtain hemostasis is critical for the safe completion of diagnostic procedures and one of the reasons that the CFA is such a preferred access site. While there are a variety of devices that can assist with hemostasis, termed *closure devices*, they cannot be used when there is significant calcification of the vessel, in small diameter vessels, or at least in intended fashion, for access sizes exceeding 8 French. Hemostasis is most commonly achieved through manual compression, which is facilitated in the common femoral region by the femoral head posterior to the artery, against which pressure can be exerted. The brachial artery can similarly be compressed against the humerus, but its mobility renders compression less effective and more challenging. Failure to obtain satisfactory compression, and thereby hemostasis, can lead to the development of a pseudoaneurysm or hematoma, potentially requiring operative drainage and repair.

The ability to convert to an open procedure is an important consideration for vascular access. In the event of sudden loss of access such as a sheath being inadvertently pulled out, or failure of hemostasis after intentional sheath removal, converting to an open procedure may be necessary to repair the defect in the vessel. Emergency conversion to an open procedure is facilitated by ready access to the underlying vessel. For example, converting a percutaneous CFA puncture to an open repair involves doing a relatively straightforward groin cut down. On the other hand, percutaneously accessing the subclavian artery is almost never done, as it could involve complex supraclavicular incisions or even a thoracotomy to obtain hemostasis.

Ensuring that occlusion of flow by the access sheath has minimal adverse effects on the tissue supplied by the vessel is another important consideration. Given the relatively small diameters of diagnostic catheters, this is rarely an issue for purely diagnostic angiography, but it must be remembered that blood flow to the distal tissues can be affected by indwelling catheters. While tissue beds such as the extremities are relatively resistant to the ischemic effects of cessation of flow for some time, thrombosis can more easily occur with sluggish flow. Although we would not routinely heparinize a patient undergoing a purely diagnostic procedure, we would give that greater consideration in situations of reduced flow. Furthermore, the cannulation of smaller vessels, such as the posterior tibial artery, has increased the risk of vessel trauma, dissection, and at least transient occlusion of flow.

The principles of venous access are generally similar to those of their arterial counterparts, but the diminished pressure present in the venous circulation allows for easier postprocedure hemostasis and fewer bleeding complications. Even so, the most common venous access sites mirror those typically used on the arterial side, with common femoral venous access being the most common. Another common venous access site is the internal jugular vein (IJV), as this is the optimal access for vena cava filter retrieval. As with arterial access, when planning access to the venous circulation for diagnostic purposes, it is prudent to consider any possible interventions that might be undertaken in the same setting. As such, while a diagnostic venogram in a patient being considered for thrombolysis could be performed from either the ipsilateral or contralateral femoral access, this would not provide a good approach for any subsequent intervention, so a small saphenous or popliteal venous access would usually be more appropriate.

Adjuncts to Obtain Access

The desired "sweet spot" to access the CFA is as it courses along the medial aspect of the femoral head, between the inguinal ligament cephalad and its bifurcation into the profunda femoris and superficial femoral arteries. While obesity makes anatomic landmarks for the inguinal ligament notoriously inaccurate, the desired puncture zone typically corresponds to the middle of the femoral head in the cranial-caudal dimension. This landmark is routinely imaged prior to attempting access. Percutaneous access can be achieved guided by one or more of three modalities: (1) manual palpation of the pulse, (2) radiographic guidance, and (3) ultrasound guidance. Regardless of which type of guidance is elected, the classic Seldinger technique is employed, initially gaining access with a needle, holding that access with a guidewire, and finally positioning a sheath into the access vessel over the guidewire.

Manual Palpation

Manual palpation of the pulse typically involves having two fingers on the pulse—one proximal and one distal and spread out by a few centimeters. Ideally, the vessel will travel in a straight line between the two fingers and the access needle inserted directly between the two fingers into the artery. This approach works well when the pulse is readily palpable and the appropriate bony landmarks are easily identified. However, in patients with significant peripheral artery disease, morbid obesity,

or other factors, the use of fluoroscopy or ultrasound can greatly improve the ease of access.

Fluoroscopy

Radiologic guidance involves the use of fluoroscopy to visualize the relevant bony landmarks described previously and their relationship to the position of the needle.[1] This is most commonly needed in situations where a pulse is either absent, or not able to be appreciated due to overlying scarring. It only provides two-dimensional guidance, but that is often all that is needed. While the radiographic relationships of the access vessel are important to understand and recognize, ultrasound-guided puncture has largely replaced its use in the pulseless or otherwise hostile groin. A variation of radiographic guidance occurs when a guidewire is being advanced into the intended site of access from some other access point, allowing radiographically guided access by directing the needle toward the guidewire.

Ultrasound

While color flow Duplex scanners can certainly aid in the identification of the intended access vessels, it is primarily the grayscale characteristics that are utilized to identify vessels and guide their puncture. Ultrasound guidance allows direct visualization of the vascular structures along with the surrounding anatomy. When seeking to cannulate the CFA, the inguinal ligament and femoral bifurcation can be clearly visualized, along with the common femoral vein (CFV) and femoral nerve. Insonation while advancing the access needle will allow the operator to visualize the needle as it compresses and passes through various tissues, and eventually indenting the artery as it pushes against the wall. This technique also allows small corrections in angle and approach, and facility with this method can allow rapid and safe percutaneous access.[2,3] The technique can be cumbersome, however, especially in patients with a large panniculus, and it is helpful to have an assistant ready to advance the entry guidewire once vessel puncture has been achieved.

Access Location Options

The most commonly used site for arterial access is the CFA, followed by the brachial artery and radial artery when a smaller caliber device can be used and femoral access is disadvantageous. Popliteal and tibial artery access can be used for lower extremity interventions, but are rarely the first choice of access and would not be considered for diagnostic purposes only. The same applies to other alternate sites of access such as the carotid, subclavian, axillary, and iliac arteries. While all of these vessels can serve as "access vessels" for endovascular procedures, the associated complexity and greater risk of complications render them largely reserved for specific vascular anatomy and pathology undergoing endovascular treatment, as adequate diagnostic imaging can usually be obtained through alternative modalities.

Common Femoral Artery

The CFA is the continuation of the external iliac artery as it crosses under the inguinal ligament, typically correlating with the origins of the superficial epigastric and circumflex iliac arterial branches. Existing for only 5 to 8 cm on average, the CFA then bifurcates into the superficial and deep femoral arteries. The CFA courses immediately medial to the femoral nerve, and lateral to the CFV. It overlies the medial aspect of the femoral head. The inguinal ligament is a useful landmark that can be identified using surface anatomy, but it is critical to recognize that in today's population of patients, its location has no correlation to the groin crease. However, radiographic landmarks can reveal the inguinal ligament, being attached to the anterior superior iliac spine laterally and the pubic tubercle medially. Identification of these bony landmarks will determine the location of the superior-most extent of the access site (Fig. 60.1).

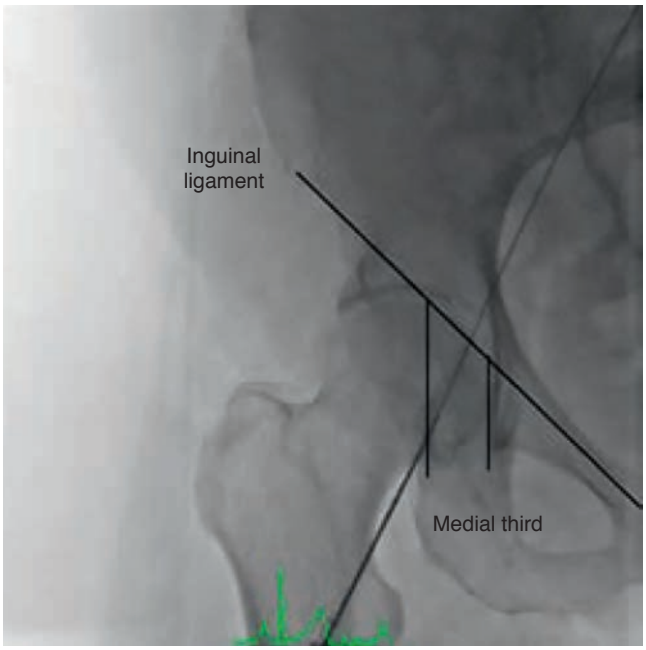

Figure 60.1 Anatomy of the femoral artery with the inguinal ligament and femoral head delineated. The common femoral artery lies over the medial one-third of the femoral head. A wire is located within the femoral artery in this x-ray image.

The CFA is an ideal choice for cannulation, as it meets the four criteria for choosing a site discussed previously and allows one to complete a wide variety of procedures. The large caliber of the CFA permits devices as large as 26F to be used, and the use of suture-based closure devices can permit successful completion of these procedures entirely through percutaneous means. Retrograde CFA access involves obtaining access over the femoral head, just above the femoral bifurcation but below the inguinal ligament with the needle pointing cranially. This permits the insertion of guidewires and subsequently catheters through the iliac system and up into the aorta, thus permitting diagnostic imaging of virtually any arterial bed in the body. Punctures occurring cephalad to the inguinal ligament may be difficult to seal, with or without a closure device, resulting in life-threatening retroperitoneal hematoma, while a too distal puncture increases the risk of an AV fistula from the profunda femoris artery or plaque dissection of the proximal superficial femoral artery (SFA).

In certain circumstances, antegrade CFA access may be desired, again most likely for interventional rather than diagnostic purposes. Antegrade access has the advantage of working in a single plane for distal extremity procedures, and the increased torque and force that can be generated for distal extremity interventional procedures may be well suited for this approach when no other proximal imaging is necessary. However, antegrade access into the CFA is a more complex endeavor than retrograde access. As the needle must still enter the CFA well above the bifurcation, this requires having a steep downward angle. In obese patients with a large pannus, this can be facilitated by having an assistant retract the pannus while obtaining access. Ultrasound-guided access can facilitate proper placement of the access site with care taken not to be too close to the bifurcation. Entering close to the bifurcation will make it difficult to selectively cannulate the SFA, as the downward angle of entry will make the wire and catheter more prone to entering the deep femoral artery.

Popliteal Artery

The popliteal artery is the continuation of the SFA as it exits Hunter's canal in the distal medial thigh. It travels behind the knee and divides into the anterior tibial artery and tibioperoneal trunk, which subsequently divides into the peroneal artery and posterior tibial artery (together, the so-called trifurcation). The popliteal artery is flanked on each side by the duplicated popliteal vein and can be accessed medially either above or below the knee, or posteriorly using a prone position.

While not commonly used for diagnostic purposes, the retrograde access of the popliteal artery in either a supine or prone position is helpful when attempting to cross and reenter an occlusion of the SFA. Ultrasound guidance is extremely helpful in identifying its location and distinguishing it from the popliteal veins. Hemostasis in this location can be difficult, as effective compression in the fatty popliteal space is challenging and there is nothing to compress the artery against.

Tibial Artery

Access to the anterior tibial, posterior tibial, or peroneal arteries is not commonly done for diagnostic purposes. However, as an adjunctive access to recanalize severe tibial disease, it has shown some utility. The cannulation of these vessels is commonly performed using micropuncture access (discussed later) assisted by ultrasound guidance. Small sheaths and soft wires are typically used to reduce the risk of vessel trauma.

The anterior tibial artery is located in the anterior compartment of the leg and dorsal surface of the foot, where it continues as the dorsalis pedis artery. It is this superficial location that is easiest to access and also the most straightforward to obtain hemostasis. The posterior tibial artery is located in the deep posterior compartment of the leg and is palpable near the ankle. This relatively superficial location is also amenable to percutaneous access and can be compressed readily for hemostasis. The peroneal artery is located in the deep posterior compartment of the leg and generally travels between the tibia and fibula; thus it is rarely used for percutaneous access due to the difficulty in reaching this vessel.

Iliac Artery

Iliac artery access at either the common iliac artery or external iliac artery is typically achieved using an open surgical approach. Percutaneous methods for accessing these vessels are contraindicated due to the inability to provide compression and because of the surrounding structures that can be injured. Furthermore, the only reason to access in this location would be for an intervention with a relatively large delivery system, in which case a conduit sewn end-to-side to the iliac artery can then be used to introduce large bore sheaths and devices.[4] Given the larger delivery systems of TEVAR and TAVR devices, common iliac artery conduits are more commonly employed during these procedures.

Axillary Artery

Cannulation of the axillary artery is typically done in the intramuscular groove between the triceps and coracobrachialis muscle with the upper arm in abduction and flexion. This permits ultrasound-guided access and subsequent hemostasis by compression against the humerus. Care must be taken to ensure satisfactory hemostasis as bleeding into the axillary sheath can create a compartment syndrome for the median nerve. As the caliber change between the axillary artery and brachial artery is minimal, most practitioners will use the more accessible brachial artery if upper extremity access is desired.[5]

Brachial Artery

The brachial artery is palpable just over the olecranon process when the arm is supinated. Ultrasound-guided access is often used in conjunction with a micropuncture needle to facilitate safe entry into the vessel.[6] Delineating the bifurcation of the brachial artery is important prior to attempting access, so that entry into the largest portion of the vessel is achieved. 6F sheaths can be used safely in most patients. Similar to axillary artery access, care should be taken to ensure satisfactory hemostasis due to the risk of median nerve compression from a hematoma. Brachial artery access is often used for coronary revascularization procedures, dialysis access imaging, treating diseases related to the subclavian artery such as occlusions or pseudoaneurysms, procedures on the celiac or mesenteric vessels, and occasionally when doing EVAR or FEVAR procedures.

Radial Artery

The radial artery is readily palpable in the distal extremity over the radius, and thus can be cannulated with ease, with or without using ultrasound guidance. Subsequent hemostasis is relatively straightforward through compression against the radius. As most patients are ulnar-dominant, the rare situation in which the radial artery is lost due to vessel trauma may have a minimal downstream effect on perfusion of the hand. The radial artery

can accommodate sheaths between 4F and 6F, thus facilitating endovascular procedures that are using a 0.014" or 0.018" platform (discussed later). Radial artery access is often used for coronary procedures and also for diagnostic purposes related to dialysis access.

Common Carotid Artery

Common carotid artery access is rarely done for purely diagnostic purposes due to the risk of cerebral ischemia and the difficulty with obtaining hemostasis. If cerebrovascular diagnostic imaging is needed, most practitioners will use CFA access with long guiding catheters or sheaths (discussed later) to achieve cannulation of the carotid artery.

Common Femoral Vein

Venous access differs from arterial access in several important ways. First, the pressure is significantly less, and while this can make hemostasis easier, it can also make access more difficult, as there will be less radial force keeping a vessel open against the force of the needle attempting to pierce the vein wall. While veins are capacitance vessels and can be quite large, they cannot stretch as much as arteries and are therefore prone to tearing if too large of a sheath or device is used. The final important consideration is that while a simple access needle can be used to access arteries and confirm vessel entry, a syringe may be needed for venous cannulation. This serves two purposes: first, the plunger can be pulled back to generate a vacuum and confirm proper entry into the vein, and second, inadvertent entry of air into the venous system (air embolism) is avoided. This is particularly important when accessing a vein located above the heart, such as the IJV with the patient's head up, where a negative venous pressure may exist and facilitate the entry of air into the system with potentially fatal consequences.

The CFV is commonly used for access when completing diagnostic procedures in the vena cava or its branches, such as the ovarian and internal iliac veins for pelvic congestion syndrome. The CFV is located medial to the CFA and can be compressed over the femoral head. Ultrasound guidance is often used for access to avoid injury to the CFA and to also avoid going through the back wall of the CFV during cannulation. This access readily allows catheterization of the contralateral extremity venous system, though navigating against the valves can require patience.

Popliteal Vein

The popliteal vein is accessed with the patient in the prone position. This paired structure flanks the popliteal artery, and either vein can be used for access. Ultrasound is used for guidance, which is particularly important when cannulating this vessel to diagnose and treat deep vein thrombosis of the extremity veins, as the access location itself may be thrombosed, rendering blood return via the needle meager or nonexistent. Ultrasound visualization of the puncture and guidewire passage can be very helpful in this situation.

Saphenous Vein

Both the great and small saphenous veins are often cannulated for diagnostic and therapeutic purposes when treating patients for extremity deep vein thrombosis or for chronic venous insufficiency secondary to venous reflux disease. Ultrasound guidance may or may not be necessary for access, but both the great and small saphenous vein will typically accommodate at least a 6F sheath. The proximal small saphenous vein is a commonly utilized access point for thrombolysis of femoral deep vein thrombosis, as it generally feeds directly into the popliteal vein.

Cephalic/Basilic Vein

An arm vein is sometimes accessed for dialysis and vein mapping. The superficial location of the cephalic vein makes it amenable to straightforward cannulation using a butterfly intravenous line if only vein mapping is desired, although most vein mapping is typically done by ultrasound guidance. Ultrasound-guided cannulation of the cephalic or basilic veins can be accomplished with introduction of a sheath if larger bore access is desired.

Internal Jugular Vein

The IJV is lateral to the carotid artery and can be accessed preferably using ultrasound guidance to prevent inadvertent injury to the common carotid artery. Access between the sternal and clavicular heads of the sternocleidomastoid is typically achieved, and relatively large sheaths can be used in this vessel. Access to the IJV is often used when inserting a central line or tunneled and nontunneled hemodialysis catheters. This is also a common site for retrieving IVC filters.

Subclavian Vein

The subclavian vein is not commonly accessed for diagnostic or therapeutic purposes other than the placement of a central line. It is a discouraged site for dialysis catheters due to subsequent stenosis. Although ultrasound guidance is recommended for femoral and internal jugular access, its value in subclavian vein puncture remains debatable due to poor visualization of the subclavian vein from the acoustic shadows of the overlying clavicle. Newer ultrasound probes such as the microconvex pediatric probe have been described to allow cannulation of the subclavian vein under real-time ultrasonography and avoiding trauma to the subclavian artery. Evaluation of pathologies such as venous thoracic outlet syndrome or central vein occlusion would more ideally be accomplished through cannulation of the cephalic or basilic veins.

Access Technique

Access Needles

Both single-wall and double-wall puncture needles are available. Double-wall needles are a blunt-tipped hollow needle with an

inner beveled stylet. Historically, when used in the femoral location, these needles were inserted through both the anterior and posterior wall until contact with the bone was made; the stylet is removed completely, followed by slow withdrawal of the hollow needle until blood return occurs. These needles cause unnecessary trauma to the posterior wall and are no longer used for standard femoral artery cannulation. However, a similar needle is often used for translumbar aortic cannulation of endoleaks, withdrawing the stylet once the aneurysm sack has been penetrated so that further needle advancement cannot puncture the endograft.

Single-wall puncture needles are almost universally used for percutaneous access. The larger 18-gauge needle permits passage of a 0.035-inch guide wire, while the smaller 21-gauge needle permits passage of an 0.018-inch guide wire.

Micropuncture Needle Technique

The micropuncture technique is commonly used for vascular access in a variety of sites. The vessel is identified using manual palpation, fluoroscopy, or ultrasound guidance. A 21-gauge needle is then inserted at a 30- to 45-degree angle such that it pierces the artery wall at the site of visualization. Ideally, ultrasound guidance is used to visualize this entry, as it will permit small corrections in angle and approach as the needle approaches the artery. Once the needle enters the vessel wall, blood return should be evident. When cannulating arteries, the flow is often pulsatile and red; when cannulating veins, a syringe should be used to draw back the darker red venous blood and also to prevent the passage of air into the vascular system.

Once successfully accessed, a 0.018” floppy tip guide wire is inserted into the vessel. Fluoroscopy can be used to confirm successful passage into the vessel. The 21-gauge needle is then removed from over the wire, followed by placement of a 4F introducer sheath. The passage should be without tension as the 0.018” wire is prone to bending from excess torque, leading to loss of access. If difficulty is encountered, a small rotating motion on the introducer sheath can be used to facilitate passage through scar tissue or a thick arterial wall; alternatively, sharp 4F introducer sheaths are now available that can be used to cut through dense tissue.

The inner cannula of the 4F introducer sheath is removed along with the 0.018” guide wire, thus permitting passage of a 0.035” guidewire. This is typically a J-tip wire for atraumatic passage. Nonetheless, fluoroscopy is used to confirm proper passage of the wire to ensure that inadvertent cannulation of a side branch or a dissection plane has not occurred. Manual pressure is held above and below the 4F introducer sheath and it is removed while keeping the 0.035” wire in place. A 5F or 6F by 10 cm long sheath can now be inserted over the 0.035” wire for definitive vascular access. The side port of the sheath is opened, blood return confirmed along with removal of any air in the system, and then flushed with heparinized saline to prevent thrombosis. Throughout all of these sheath exchanges, positive control over the wire is maintained to prevent losing the wire inside the vascular system, or losing access while pulling out the sheath.

Standard Needle Technique

For easily palpable femoral pulses in otherwise uncomplicated anatomy, many practitioners will go straight to an 18-gauge needle and 0.035” J-tip wire instead of using the micropuncture technique. The technique is similar to the micropuncture technique, except there is no exchange of a 4F introducer sheath to the larger 5F or 6F sheath, saving a little time and expense. The primary advantage of the larger initial access is seen in scarred groins, deep vessels, or when accessing Dacron grafts, all being situations where tracking the 4Fr sheath over the less supportive 0.018” guidewire can be problematic.

TECHNIQUE FOR CATHETERIZATION

Guidewires

Once needle puncture is obtained, a guidewire is then passed into the arterial system to maintain the access while the needle is removed and a sheath advanced over the guidewire, to stay resident in the access vessel. The standard entry wire is a 0.035” J-tipped moveable core steel guidewire designed for atraumatic passage up the iliac system. Fluoroscopic observation of the guidewire passage ensures the safest possible passage and also can give clues about underlying pathology. It is critical that hydrophilic-coated guidewires not be used as the initial entry guidewire as the hydrophilic coating is known to shear off and embolize when moved in and out of an entry needle.

Once sheath access is secured, a vast array of guidewires can be utilized to assist in catheter placement for diagnostic imaging. Among the variables are the tips of these wires, which vary in their geometry and flexibility. While guidewire tips are typically soft and floppy so as to be minimally traumatic, the shaft of the guidewire can be quite stiff, to allow tracking of relatively large and stiff devices. These types of guidewires, however, are more the domain of endovascular interventions and will not be discussed further here. Proper wire selection is essential, as choosing a very stiff wire could lead to perforation of a vessel, while a very soft, flexible wire may not provide adequate support to allow for the intended positioning of a catheter.

Guidewires generally come in two size categories—the larger 0.035″/0.038″ wires and the smaller 0.014″/0.018″ wires. Other sizes are made, but they are generally device-specific and rarely used by vascular surgeons. Wires are available in a variety of lengths, typically from 120 to 360 cm. Longer length wires, often referred to as “exchange length” wires, are used when introducing a very long catheter or device remotely from the site of access, but these longer wires require careful attention to ensure that they do not get contaminated by falling off the working table or hitting other objects. Wires can be very stiff (such as steel core wires), or very flexible (such as nitinol wires). Some wires have Teflon or hydrophilic coatings to reduce the friction of their passage, and that of devices passed over them. The stiffness and flexibility of a wire is determined by the construction of the outer spring coil and core wire.

The tip of the wire is also very important. Many wires have a soft, floppy tip that will reduce the risk of vessel trauma.

These are compliant wires, but the drawback of an overly floppy tip is that it cannot be used to cannulate side branches or make turns in a tortuous vessel. Other wires may have a stiffer construction at the tip with a slightly angled bend. These wires can permit navigation of tortuous vessels and cannulation of side branches by manipulating the wire and rotating it along its longitudinal axis. Finally, J-tip wires are ideal for rapidly cannulating vessels and doing sheath exchanges, as the rounded bend will reduce the risk of creating a dissection plane or inadvertently cannulating a side branch.

Sheaths

Sheaths are used for maintaining vascular access and serve as a portal through which any variety of wires, catheters, or devices are passed. Sheaths have a side port that permits aspiration or administration of fluids, and come in a variety of lengths and calibers (Fig. 60.2). The inside caliber of a sheath is measured by French size, where 1F = 0.013″ = 0.33 mm (Box 60.1). Thus a 5F sheath will accommodate catheters and devices up to 0.065″ (5F). Sheaths typically vary in size from 4F to 11F, but much larger sheaths are available to accommodate devices such as endografts (Fig. 60.3). Sheaths have a hemostatic valve on the end that maintains hemostasis whether wires and catheters are indwelling or absent. Braided sheaths may be used when cannulating a vessel through dense tissue or making sharp turns that can lead to kinking of the sheath. Similar to some guidewires, radiopaque markers may be present that can facilitate identifying the end of a sheath or making measurements.

Sheaths come in a variety of lengths, ranging from 5 to 100 cm. For diagnostic purposes, the most commonly used length of sheath will be the standard 10 cm sheath, as any more remote contrast injection will be through a catheter, not the sheath. Short sheaths are helpful when the working distance is very small, such as for dialysis access. Longer sheaths are important when working remotely from the site of access, such as the SFA contralateral to the access or the carotid arteries from a CFA access. Typically a 45-cm sheath will suffice when working on the contralateral iliac system or beyond, and a 90 cm sheath is helpful when intervening on the carotid arteries. Similarly, a 90-cm sheath is helpful when working on the mesenteric vessels from a brachial artery access. While longer sheaths create nice working platforms, it must be remembered that any length of sheath protruding from the body is simply going to mean that longer devices and guidewires will be needed, so the sheath should be no longer than necessary to allow adequate imaging during the intended intervention.

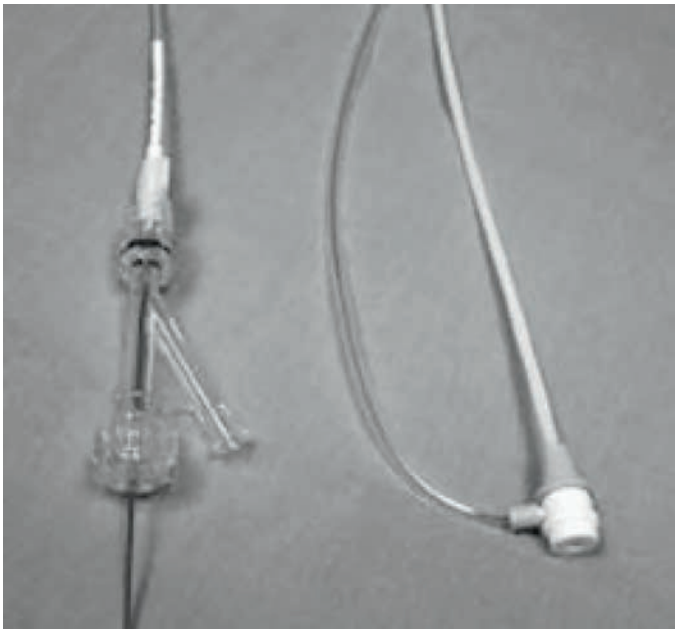

Figure 60.2 Y adapter on a guiding catheter *(left)* and hemostatic valve of a sheath *(right)*.

BOX 60.1 Conversion Between Gauge, French, Imperial, and Metric Units

18 gauge = 0.040 inches = 1.024 mm
21 gauge = 0.028 inches = 0.723 mm
1 millimeter = 3 French = 0.039 inches
3 millimeters = 9 French = 0.118 inches

Diagnostic Catheters

Diagnostic catheters are the vehicles used to deliver the radiographic contrast agent to the area of interest. Diagnostic catheters come in a range of sizes, lengths, and tip configurations (Table 60.1). Some catheters have radiopaque markers at uniform intervals along their length to assist with performing measurements, while others have hydrophilic coatings to facilitate their

Figure 60.3 Color-coded sheath caliber identification.

TABLE 60.1 Commonly Used Diagnostic Catheters

Vessel	Catheter Shape	Catheter Name
Contralateral iliac	Self-forming Manual-forming	Cobra 2, pigtail, Omni flush Simmons 1 or 2
Renal, mesenteric	Self-forming Manual-forming	Renal double curve, Cobra 2, SOS Omni Simmons 1 or 2
Axillary, brachial	Self-forming	Kumpe, Cobra 2
Subclavian, carotid	Self-forming Manual-forming	Headhunter H1, Vitek Simmons 1 or 2

TABLE 60.2 Endovascular Device Size Conventions

Device	Measurement Standard	Unit
Entry needle	Outer diameter	Gauge
Guide wire	Outer diameter	Inch
Sheath	Inner diameter	French
Diagnostic catheter	Outer diameter	French
Guide catheter	Outer diameter	French

TABLE 60.3 Names of Catheter by Type

Catheter Type	Name
Flush catheter	Pigtail, tennis racket, Omni flush, Contra 2
Single curve	Kumpe, vertebral, angled glide, Bernstein, multipurpose A and B
Double curve	Cobra (C1, C2, C3), Headhunter, renal double curve, rim
Reverse curve	SOS, visceral selective (VS1, VS2, VS3), Simmons, Sidewinder (1, 2, 3, 4), Vitek
Crossing catheter	Quick-cross, TrailBlazer, WildCat, CX1, CrossCath, Minnie, Seeker

advancement through long and tortuous pathways. Braided catheter construction renders the catheter more torque responsive and kink resistant. The caliber of diagnostic catheters is measured by their outer diameter; thus a 5F catheter has an outer diameter of 0.065″ and will fit inside a 5F sheath (which is measured by its inner diameter; Table 60.2). Most diagnostic catheters used by vascular surgeons are between 2F and 6F in size; the 2F and 3F catheters, referred to as microcatheters, are used primarily to deliver embolization coils to small distant targets. Diagnostic catheters can be grouped into nonselective selective and crossing catheters (Table 60.3).

Nonselective Catheters

Nonselective catheters are used to inject a high volume of contrast into relatively large blood vessels, typically using power injection, such as when performing aortography or vena cavography. As with all catheters, removal of the guidewire allows the catheter to take its shape, which, for these catheters, is typically some variation of circle. To reduce the "jet effect" of power injection through a simple end hole, and to facilitate contrast dispersal, these catheters also have multiple side holes along the terminal 15 mm (Fig. 60.4). In some situations, some nonselective catheters can be used to cannulate side branches or the contralateral iliac arteries when using contralateral femoral access (see the "Applications" section later in this chapter).

Selective Catheters

Selective catheters are so termed because they have a shape that facilitates their engagement in the orifice of a branch vessel, either for the injection of contrast or the subsequent passage of a guidewire. With but a few exceptions, selective catheters

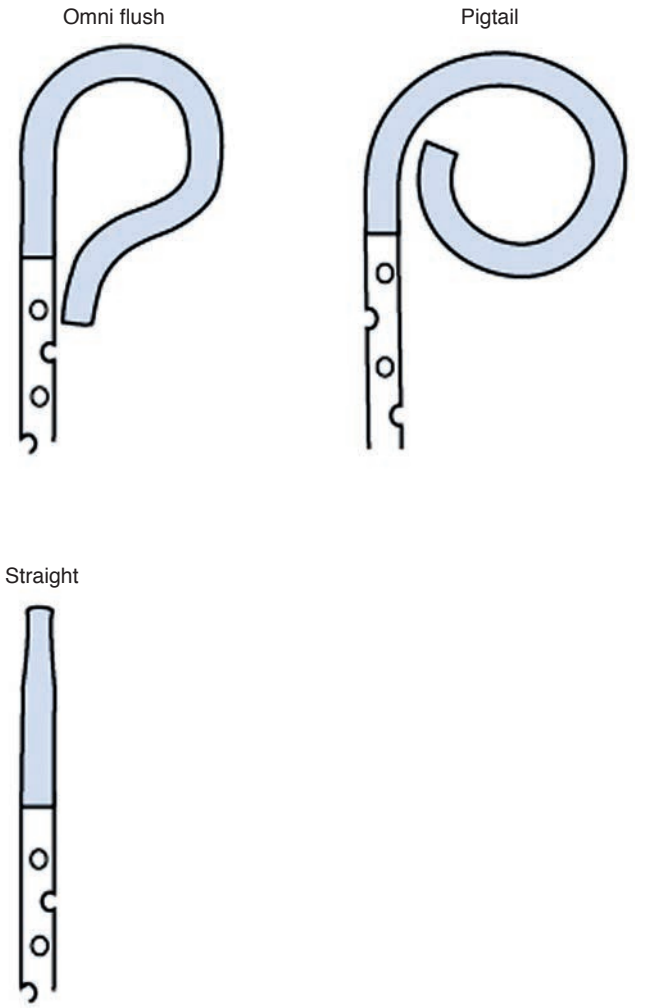

Figure 60.4 Nonselective diagnostic catheters with multiple side holes. (Courtesy of AngioDynamics, Queensbury, New York.)

have an end hole only, with no side holes, and thus should not be used for high pressure administration of contrast, as the resulting fluid jet could be traumatic to vessels. Selective catheters have a variety of shapes and curves that permit selective cannulation of side branches. Generally, selective catheters are divided into single-curved, double-curved, and reverse-curved configurations (Fig. 60.5).

A single-curved catheter is ideal for cannulating a side branch vessel that comes off at less than a 45-degree angle from the aorta. For example, a Kumpe single-curve catheter can be used to cannulate the common iliac artery when using brachial artery access. Double-curved catheters have angles up to 90 degrees and are more suitable for side branches that come off more acutely from the aorta. For example, a renal double-curve (RDC) catheter may be useful for cannulating a renal artery when using femoral access. Finally, reverse-curve catheters typically have a 180-degree curve in the catheter with the tip flaring off at an angle. These catheters are used to cannulate vessels that come off steeply, especially in curved blood vessels such as the aortic arch. For example, a Simmons 2 reverse-curve catheter can be used to cannulate the branches of the aortic arch when using femoral or brachial access. Reverse-curve catheters are

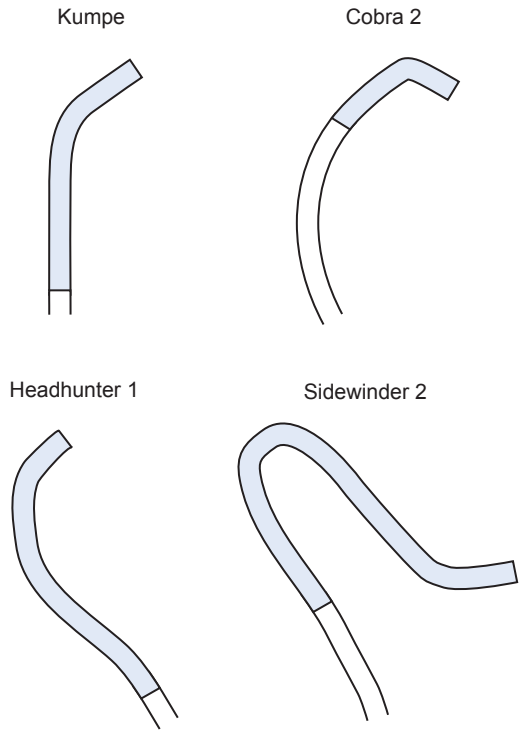

Figure 60.5 Selective diagnostic catheters. (Courtesy of AngioDynamics, Queensbury, New York.)

more difficult to work with, as their unique geometry requires the user to recreate the curves, also known as "forming the catheter," within the blood vessel after the guidewire is removed. The side arm of the catheter is available in varying lengths, depending on the depth of engagement desired, but the longer it is, the less responsive the tip will be to catheter manipulation.

Crossing Catheters

While most commonly used during interventional procedures, crossing catheters, in combination with guidewires, can be used to cross occluded or highly stenotic vessels. Crossing catheters are low profile, relatively stiff catheters with tapered tips that facilitate their passage through a tight stenosis or occlusion. They are available in both small-wire (0.014-0.018") and standard wire (0.035") versions, as well as with angled tips.

Guiding Catheters

Though not really diagnostic catheters, for the sake of completeness and to clarify often misquoted terminology, guiding catheters will be briefly reviewed. When confronted with the need to work remotely from the site of access, it becomes essential to have a sturdy platform through which to do wire and device exchanges and to be able to inject contrast that will opacify the site of intervention while the intervention is underway. There are two approaches for doing this, depending on the specific anatomy—one is to use a very long sheath, and the other is to use a guiding catheter. Guiding catheters are essentially sheaths that come in a variety of tip shapes. They have the advantage of coming in a variety of lengths and shapes to permit selective cannulation of a vessel, similar to that of a selective diagnostic catheter. Guide catheters are distinguished from diagnostic catheters in that their diameter typically remains constant throughout the length of the catheter, thus permitting insertion of a variety of smaller catheters (such as microcatheters), wires, and devices.

Techniques for using these catheters are described later in the "Applications" section.

Closure Devices

There are two primary methods of achieving hemostasis once a procedure is completed. Simple manual compression is effective in the majority of cases, particularly for small puncture sites (4F-8F). Care must be taken to avoid completely occluding the vessel as this can lead to thrombosis. At the same time, insufficient pressure will lead to a hematoma and contribute to the formation of a pseudoaneurysm. Depending on the extent of anticoagulation, the puncture size, and the patient's blood pressure, compression is commonly held between 5 and 20 minutes. The patient's body habitus can compromise effective compression, as can inadequate anesthesia. Compression time, either in the angio suite or in a recovery area, has to be figured into turnover time for the room and ultimate efficiency of practice. Furthermore, most patients have 6 hours of mandated bedrest, which also has to be figured into procedural costs.

To address patient complaints about the traditional 6 hours of bedrest, as well as facilitate patient throughput, a variety of "closure devices" have been developed which in some way or another seal the access hole, minimizing the need for compression and significantly shortening the bedrest period to less than 2 hours. These devices range from an extravascular plug to a suture-based technique for closure. The Angio-Seal device (St. Jude Medical, St. Paul, Minnesota) works by placing an intraarterial absorbable anchor against an externally placed collagen sponge; these are sandwiched together. This device works well on arteries that are at least 5 mm in size and free of significant calcification, and can be used to close puncture sites up to 8F.[7] The Mynx device (AccessClosure, Santa Clara, California) uses a polyethylene glycol polymer to close the tissue track over the puncture site, thereby providing hemostasis for puncture sizes up to 6F.[8] The ProGlide device (Abbott Vascular, Santa Clara, California) uses a single polypropylene stitch to suture close arteriotomy sites up to 6F.[9] Some practitioners have used this device off-label to close much larger puncture sites by placing two ProGlide devices through a single puncture site, thus allowing a totally percutaneous method for doing a TEVAR or EVAR procedure.[10] A variety of other closure devices are available. Closure devices increase the risk of groin infection and leg ischemia but decrease the time needed to achieve hemostasis.[9]

The decision to use a closure device on a given access site should be individualized to the patient's anatomy, clinical circumstances, and likelihood of benefit. Hospital inpatients who will be on bedrest anyway may have little to gain by the potential for early ambulation and discharge. Similarly, for

closure devices to recoup their cost, angio suite throughput really does have to increase and patients do truly have to be discharged sooner. If these can be achieved, however, and complication rates kept at a minimum, closure devices can recover their expense in briefer observation stays and enhanced patient satisfaction.

Applications

Theoretically, diagnostic angiography can be performed in any vascular territory, as long as one can safely position a catheter upstream of the area of interest and infuse sufficient contrast to adequately visualize it. And while there are many similarities to the technique of angiographic evaluation of the different vascular territories, variables such as vessel size, flow rates, cannulation pathway, and downstream organ sensitivity will invariably influence the choice of catheter and infusion technique to be used.

Abdominal Aortography

A standard diagnostic abdominal aortogram typically involves initial imaging in the AP orientation from L1 cephalad to as far distal as the image intensifier size permits, using power injection through a multiside hole flush catheter positioned in the region of the renal arteries (L2). Ideally, using a 48-cm flat panel detector with the patient elevated off the x-ray tube, you can expect to image to at least the mid-external iliac arteries. The catheter is then repositioned into the infrarenal aorta and the table repositioned so that the lesser trochanters are at the caudad-most aspect of the image. Two subsequent power injection runs are obtained in LAO and RAO orientations to splay out the iliac and femoral bifurcations, where stenoses often occur. These images will also ensure proper sheath placement and suitability for subsequent use of a closure device. A standard aortogram usually uses 15 mL of 50% contrast per second for a total of 30 mL of contrast ("15 for 30") at a pressure of 800 mm Hg. Longer catheters can be used if doing imaging of the thoracic aorta, and a catheter with regular 1 cm markings (i.e., "marker pig") can be used for distance calibration and making measurements, particularly relevant for aortic endografting.

Extremity Angiography

Most commonly, aortoiliac evaluation will be followed by unilateral or bilateral extremity imaging. Simultaneous bilateral imaging can be obtained using power injection of contrast into the infrarenal aorta and segmental bilateral extremity imaging, body habitus permitting. Alternatively, more advanced angiographic suites have bolus chase capabilities that allow for continuous bilateral DSA imaging from the aorta to the toes following a single injection of 80 mL of contrast over 8 seconds into the infrarenal aorta. While acquisition of imaging from nonselective catheterization may be more expeditious, image quality can be compromised by differential limb perfusion, less flexible radiographic projections, and contrast dilution. Furthermore, inadequate opacification or delineation of pathology can be problematic, since repeating a bolus chase run involves a substantial increase in contrast administered.

The best quality of imaging occurs with more selective catheterization of the tree of vessels of interest. Having evaluated the abdominal aorta and iliac systems and ascertained the safety of crossover catheterization, a catheter is positioned in the distal contralateral external iliac artery for subsequent imaging down the leg. A variety of catheter shapes can be utilized to effect this contralateral positioning, ranging from the pigtail catheter used for flush aortography to shapes specifically designed to navigate over the aortic bifurcation. Once the contralateral common iliac artery is hooked, the wire is gently advanced into the CFA, followed by the catheter (Fig. 60.6). Extremity imaging can now be completed, typically in the 30 to 45 degrees° ipsilateral anterior oblique projection, so as to splay out the trifurcation vessels and open up the tibia-fibula window. A variety of alternative selective diagnostic catheters are available to facilitate crossing over the aortic bifurcation and selecting other vessels (Fig. 60.7A and B). Extremity angiography on the side of arterial access is typically performed via simple sheath injection of contrast into the ipsilateral iliac system.

While many operators prefer hand injection angiographic runs, once the catheter is in position, a power injector can be used to complete the imaging, with care being taken to reduce injection rates and pressures commensurate to the vessel size and circumstances. An advantage of power injection is the ability for the operator and team to be sheltered from radiation, controlling contrast injection remotely during the angiographic runs. The primary disadvantage is the inability to vary the contrast concentration throughout the course of the evaluation, as can easily be done with hand injection using a manifold setup, as well as vary contrast infusion rates in real time.

Renal/Mesenteric Angiography

In many situations, the combination of preoperative imaging and the diagnostic aortogram is sufficient to make the diagnosis of renal artery stenosis, and selective angiography is unnecessary unless intervention is planned, in which case a guiding catheter would typically next be deployed. However, in cases where the desired anatomic information is not evident from the flush aortogram and selective angiography is elected, it is important to remember that most atherosclerotic disease of the renal and mesenteric vessels occurs near their origins off of the aorta. As such, the ideal diagnostic catheter shape to demonstrate the disease would be one curved and sized to sit softly against the aortic wall with slight downward angulation. Ideally, the catheter curve selected would be oversized enough relative to the aorta to lightly engage the vessel origin when pulled across it, without being so aggressive a curve that the catheter tip pops in, uncontrollably crossing any orificial disease. For diagnostic purposes, a RDC catheter (see Fig. 60.7C) is a commonly elected shape. In our practice, angiographic imaging is performed via hand injection of an already connected manifold system. While power injection imaging can be performed, catheter dislodgement is more likely, and it is more difficult to guide catheter placement with puffs of contrast.

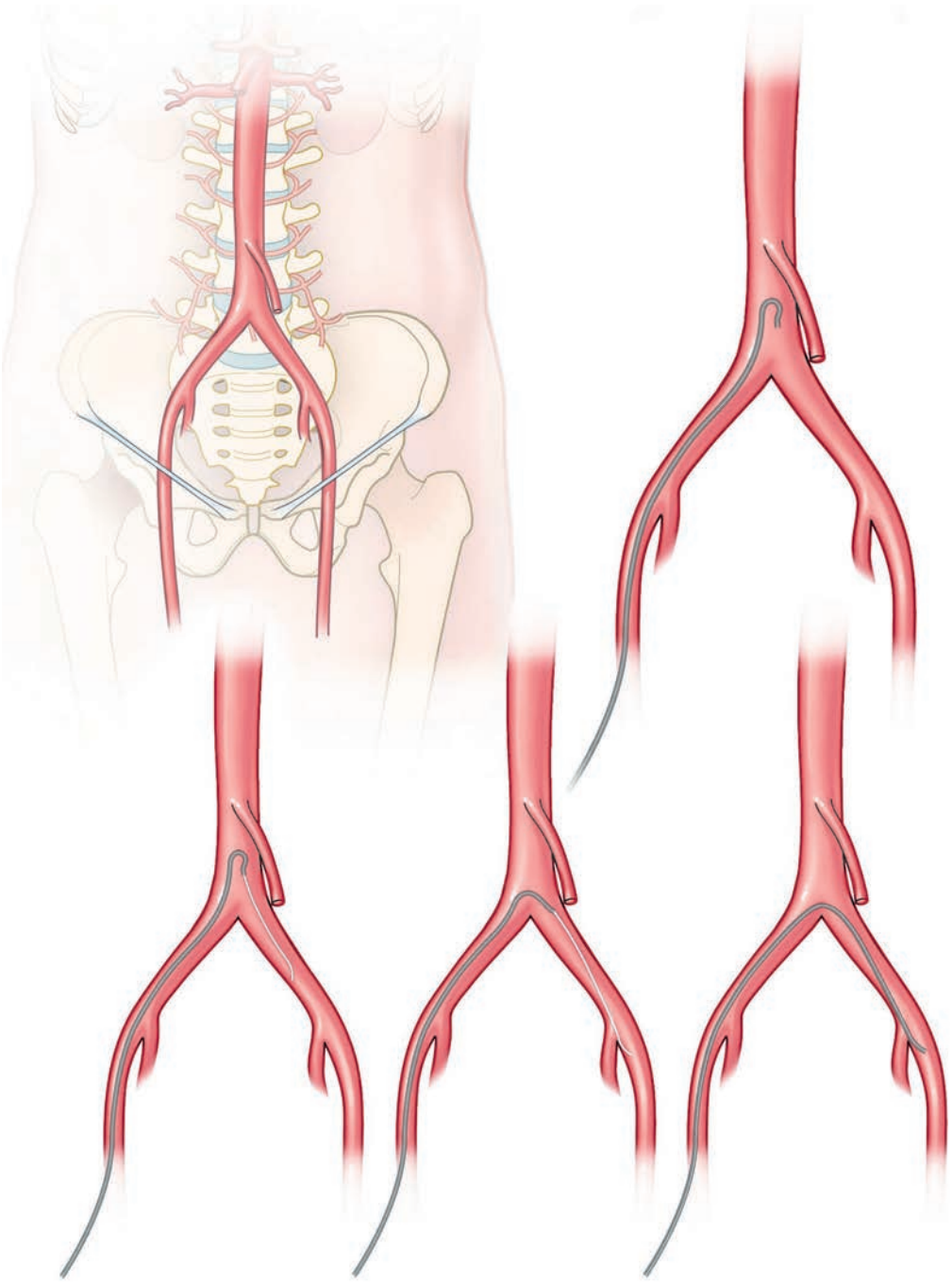

Figure 60.6 Crossing the aortic bifurcation to enter the contralateral iliac artery using an Omni flush catheter and soft angled wire.

As with renal artery disease, most mesenteric disease occurs proximally in the vessel. While AP aortography would still typically be performed to evaluate the entire abdominal aorta and possible mesenteric collaterals, evaluation of the celiac axis and superior mesenteric artery (SMA) will require a lateral projection, along with which often comes diminished image quality due to extra tissue to penetrate. Even more so than with renal arteries, the celiac and SMA can be sloped acutely caudally, sometimes to the extent that it complicates catheterization from femoral access. While rarely necessary for purely diagnostic purposes, the degree of angulation may favor a brachial approach for any necessary intervention. Without the U-turn required by a femoral access, catheters and guidewires should be more easily steered and devices should track better.

Carotid Angiography

Carotid angiography should begin with nonselective arch aortography performed through a multi-side-hole catheter using power injection. While in some situations all of the desired information can be obtained nonselectively, frequently requiring multiple runs in different projections, most commonly selective angiography will be desired, and the primary purpose of arch

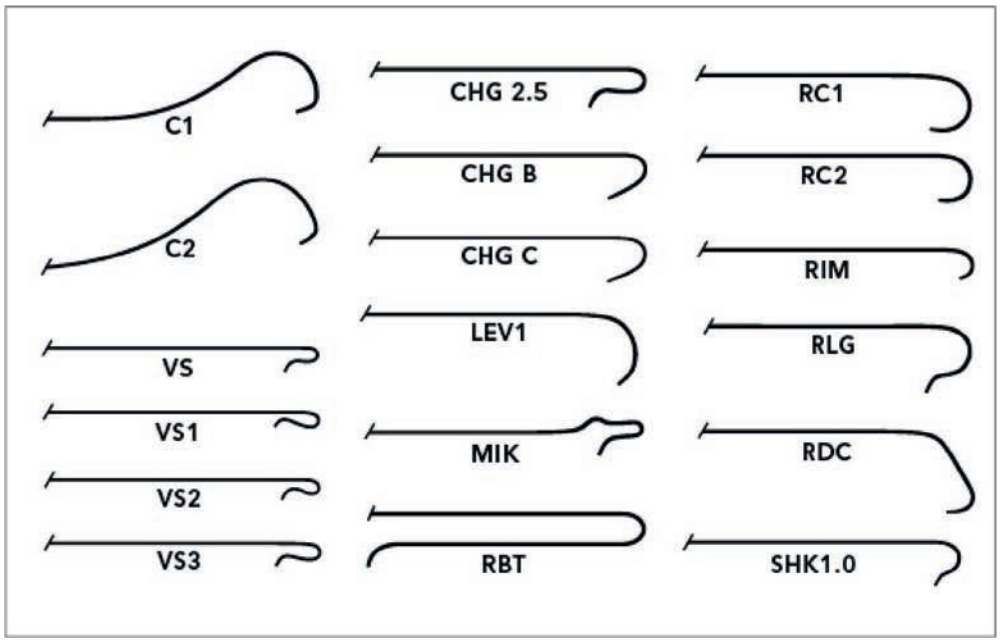

Figure 60.7 Common multipurpose catheters. (Courtesy Cook Medical, Bloomington, Indiana.)

aortography is to determine that it is safe to attempt to select the various brachiocephalic vessels and to help guide the performance thereof. The anatomic feature that complicates selective carotid angiography pertains to the origin of the parent arteries, which are typically proximal enough on the aortic arch that their cannulation requires a U-turn. Two catheterization options are generally available: a forward selecting catheter, usually combined with a guidewire, or a reverse-curved catheter, which will need to be reformed once the guidewire is removed. A commonly used reverse curve catheter, a Simmons 2, is advanced into the proximal aortic arch over a wire (see Fig. 60.7D). The tip is reformed either at the aortic root or by hooking the left subclavian artery or brachiocephalic trunk (Fig. 60.8). The catheter can now be slowly pulled back to selectively cannulate either the brachiocephalic trunk or left common carotid artery. If selective right common carotid access is desired and the innominate artery is long, a Simmons 2 catheter will likely be required. Alternatively, if less side-arm length is needed, a Simmons 1 catheter will be more responsive and easier to negotiate into the left common carotid artery. There are self-forming reverse curve catheters, such as the VTK (see Fig. 60.7D), that negate the need to be manipulated into shape, but their side-arm length, and therefore depth of vessel penetration, is limited.

Once the common carotid artery is cannulated, filming can be performed with either hand-injection of contrast or, if the catheter position is stable, with power injection. Only 4 mL of 50% contrast per second for a total of 6 mL is used at a pressure of 200 mm Hg. The complexity of carotid angiography increases if type II and type III arches, in which the aortic arch branches come off earlier on the curve of the arch, and a more steeply curved catheter may be necessary. At all times, careful manipulation of the wires and catheters in this region is required to prevent embolization from an atheromatous aortic wall, again underscoring the need for an initial arch angiogram to allow appreciation of arch and proximal branch vessel disease prior to attempting to catheterize through it.

Fistulography

Fistulography is typically performed via direct access into the fistula or graft in a location that allows for complete inflow and outflow imaging. These are relatively large-caliber, high-flow vessels that are readily palpable and usually easily accessed. Ultrasound guidance is helpful if the cannulation site cannot be readily palpated, as may be the case with a failing access or one failing to mature. For diagnostic purposes, a simple angiocath or 4Fr dilator are often all that is necessary, with conversion to sheath access if a lesion suitable for endovascular treatment is demonstrated. While outflow imaging is straightforward, demonstration of the aspects of the fistula upstream of the site of access may be facilitated by manual compression of the outflow track or placement of a temporary tourniquet such as a large Penrose drain. If a lesion to be treated is encountered, a shorter than standard sheath (6 cm instead of 11 cm) is often used, due to the close working distances involved.

Pelvic Congestion Syndrome Venography

Cannulating most veins for diagnostic imaging is similar to that described for their arterial counterparts. Pelvic congestion syndrome presents several unique challenges for imaging. Ultrasound-guided access into the CFV is obtained and a diagnostic venogram completed through the sheath using 10 mL of 50% contrast injected by hand. The renal vein orifices can often be visualized on vena cavography as an area of lower opacification, or contrast washout from contrast-free blood entering from the kidney. A suitably shaped catheter such as a

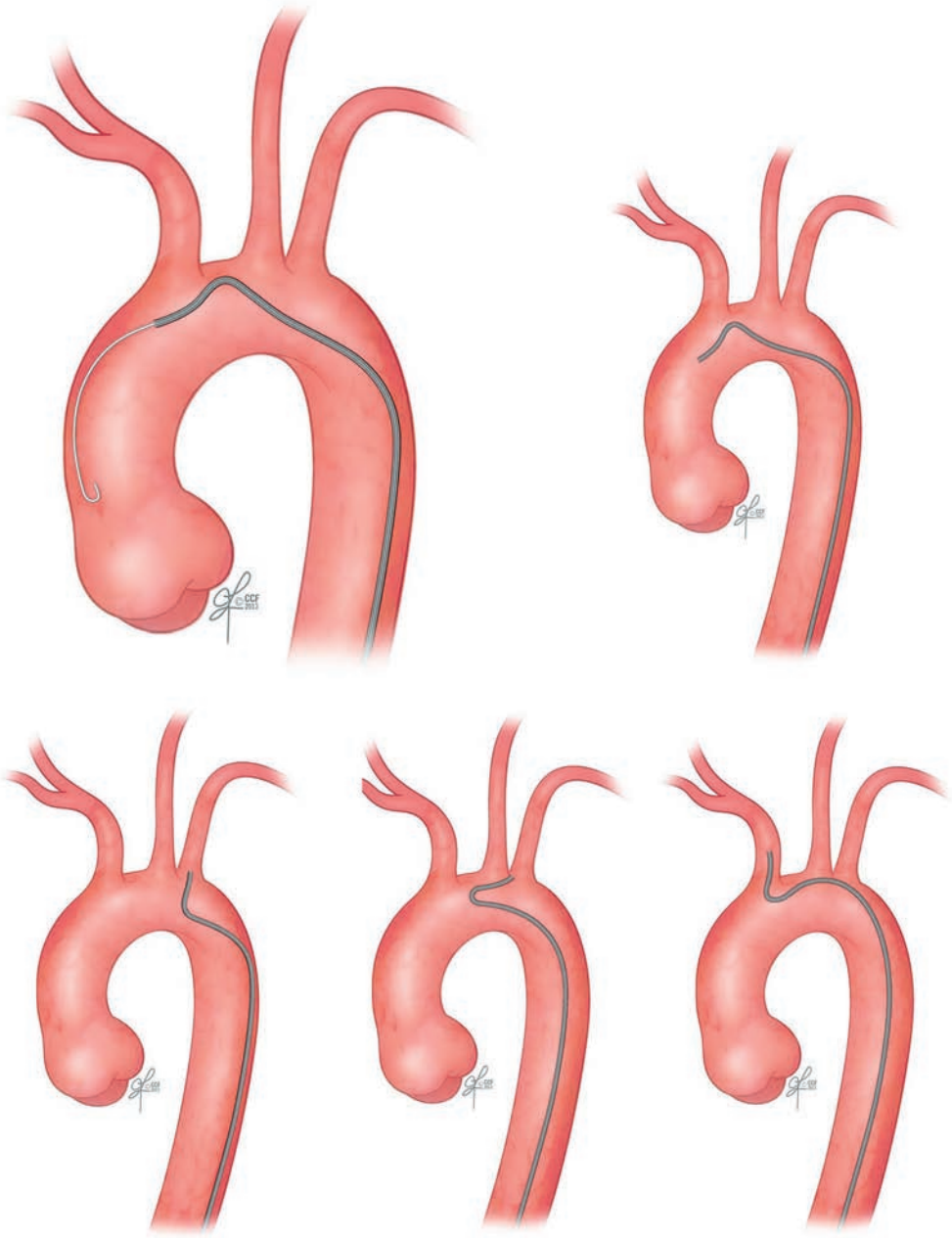

Figure 60.8 Technique for forming a Simmons 2 catheter with the aortic arch and selective cannulization of an arch branch.

RDC catheter is used in combination with a guidewire, if necessary, to cannulate the proximal ovarian vein. Filming is generally performed with hand injection of contrast under low pressure, so as not to traumatize the veins. If necessary, a more distal catheter position can be pursued to enhance opacification of the pelvic venous network. If an intervention is elected a distal catheter position will be required, usually mandating use of a microcatheter (0.022″) to navigate the tortuosity atraumatically. The typical setup in this situation is a guiding catheter in the renal vein, inside of which is a 4Fr hydrophilic catheter into the ovarian vein, inside of which is the microcatheter through which embolization coils or other materials are injected.

While the right ovarian vein can sometimes be accessed directly from the IVC, the acute angle can be problematic, and so the more common approach is via access the right ovarian vein via the contralateral internal iliac vein.

COMPLICATIONS

Access Site

These are the most common areas for complication following endovascular diagnostic procedures. Poential complications and their incidence include clinically significant hematoma (3%),

thrombosis (2%), bleeding (1%), traumatic arteriovenous fistula (0.9%), and pseudoaneurysm (0.6%).[11] There is some evidence that the incidence of these complications can be reduced through the use of either ultrasound or fluoroscopic guidance.[11-13] The incidence of these complications increases in patients who are obese, have diseased access vessels, required large sheath sizes, and who were on anticoagulation.[11-13]

While the majority of postcatheterization hematomas are clinically insignificant, failure to obtain puncture site hemostasis can result in significant local and systemic sequelae. Of greatest risk to the patient is retroperitoneal hemorrhage from an access site cephalad to the inguinal ligament. Punctures in this location are difficult to compress manually, and closure devices are both contraindicated and ineffective. If hemostasis cannot be achieved through simple manual pressure, reversal of anticoagulation may be helpful. Continuing bleeding should be managed with conversion to open technique and direct vessel repair, though endovascular treatment with peripheral endografting is a potential option, as is temporary endovascular balloon control as an adjunctive technique while open exposure is obtained.

The more common access site complication is a hematoma and/or false aneurysm in the groin. Many of these will resolve spontaneously, and therefore their diagnosis alone is no longer an indication for repair. When persistent, enlarging, or symptomatic, most access site false aneurysms these days are treated by simple ultrasound guided thrombin injection. If the hematoma is large and compromising the viability of the overlying skin, or otherwise unsuitable for thrombin injection, open surgical repair with hematoma drainage is indicated.

Access-related arteriovenous fistulae tend to occur with more distal punctures, often of the profunda femoris artery itself, with fistulization to the adjacent or crossing veins. This location is difficult to compress after sheath removal, which may play a role in formation of the fistula. While many are asymptomatic and will close spontaneously, persistent AV fistulae should undergo repair, most commonly through open surgery. Preoperative angiography can be helpful in revealing what should be expected and, in the uncommon scenario, allow for any endovascular treatment deemed suitable.

Catheter- or Guidewire–Related

Catheter- or guidewire-related complications are secondary to damage to the vessel wall from their passage or manipulation, such as the creation of a perforation or dissection, with or without embolization. Observation of wire and catheter advancement under fluoroscopy helps avoid these complications. Similarly, appropriate selection of wires and catheters can also minimize the risk of dissection, perforation, and embolization. Perhaps most important is that the catheter, in its natural shape, is not excessively larger than the diameter of the vessel that it is in, lest the tip inflict trauma on the vessel wall. Perforation of a vessel can be minimized by rigorous control over wires and catheters, particularly relevant when dealing with terminal vascular territories like the renal artery or mesenteric circulation, where excessively deep guidewire penetration can easily lead to perforation. Lastly, the super-stiff variety of guidewires have a rather abrupt transition from the floppy to the stiff areas and, consequently, do not lead out well. These are rarely used for diagnostic purposes, but when used are best positioned initially through a catheter to minimize vessel wall trauma. Dissections, if clinically relevant, can be treated with either bare metal or covered stents, while perforations and AV fistulae are best treated with endografting. Catheter-guidewire induced embolization, often secondary to dissection, is typically microembolic and therefore not amendable to angiographic detection or aspiration. Larger emboli, especially those that occur during thrombolysis, may be extracted or lysed through standard endovascular techniques.

Systemic

Systemic complications associated with endovascular diagnostic procedures are related to the use of iodinated contrast, anticoagulation, and radiation. While there are several protocols available that help identify a patient's upper contrast limit, the best option is to routinely use the lowest dose of contrast possible. This can be facilitated by diluting the contrast, titrating contrast administration to real-time visualization, and by selective catheterization of the territory of interest. In patients with chronic kidney disease, CO_2 can be a useful adjunct when performing arterial imaging procedures below the diaphragm. Similarly, following the principles of ALARA (as low as reasonably achievable) for radiation exposure will help prevent tissue damage from excess x-rays.

Anticoagulation with heparin is associated with a 0.2% incidence of heparin-induced thrombocytopenia (HIT). Severe HIT can lead to the formation of extensive thrombosis and cardiovascular collapse. Prompt recognition, removal of heparin from all sources, and conversion to another anticoagulation agent such as argatroban is necessary.

CONCLUSION

Endovascular diagnostic procedures are relatively safe when used properly. Adjuncts such as ultrasound-guidance and proper wire and catheter selection can decrease the incidence of complications. This valuable diagnostic and therapeutic tool is a mainstay of vascular surgery and mastery of the variety of wires, catheters, and sheaths important for the safe and effective practice of vascular surgery.

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CHAPTER 61

Endovascular Therapeutic Technique

KOJI MAEDA and TAKAO OHKI

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INTRODUCTION

Endovascular treatment has currently replaced open surgical procedures as the first-line treatment for many vascular diseases. The durability of endovascular treatment options should be evaluated in comparison with open surgical options during preoperative planning. This chapter reviews the basic principles, the devices, and techniques of endovascular therapy, including indications, limitations, pitfalls, and complications.

BALLOON ANGIOPLASTY

The first percutaneous treatment for peripheral artery disease (PAD) was performed in 1964, when Dotter and Judkins described a transluminal technique using progressively larger dilators in the lower extremities.[1] The balloon catheter, well-known today, was developed to dilate arterial stenotic lesions with flexible polyvinylchloride (PVC) balloons by Gruntzig and Hopff.[2] The mechanism of balloon dilation for stenotic lesions is a blunt dehiscence effect leading to fracture and separation of the arterial media from the intima, with stretching of the media and adventitia. Percutaneous intraluminal angioplasty (PTA) has disadvantages affected by the lesion type. Treatment of severely stenotic lesions and those with dense calcification may result in elastic recoil and/or flow limiting dissection after PTA, and stents are often utilized to overcome such complications. In addition, new technologies such as drug-coated balloons (DCBs) are expected to provide equivalent performance to stents without leaving foreign bodies prone to fracture. However, if the lesion can be treated with PTA alone, it is most cost-effective. In order to maximize the outcome of PTA, one must choose the appropriate balloon for a given lesion. An understanding of the characteristics, behaviors, and techniques of balloon angioplasty is essential.

Balloon Catheter Types

Balloon catheters for PAD are classified into two types: over-the-wire (OTW) and single-operator exchange (SOE) system. In OTW technology, the wire passes through the entire catheter, providing good support and high pushability compared with SOE system. In addition, this technology allows for guidewire exchange when a lesion is difficult to cross. The length of the shaft for OTW balloons ranges from 80 to 150 cm. If a long shaft, such as a 130- or 150-cm shaft, is selected to treat a lesion, a wire of 260 cm or longer is needed to treat the lesion.

In the SOE systems, often referred to as " monorail" or "rapid exchange" (Rx), the wire enters from the distal tip of the catheter and exits from a side hole in the catheter, 20 to 25 cm proximal to the balloon. The SOE balloons, which are generally used in coronary interventions, are supported by a 0.014-inch or 0.018-inch guidewire system. In PAD, these balloons are utilized for below-the-knee lesions, where vessel diameters are much smaller than above-knee lesions. Since an SOE catheter shaft does not have a wire through the lumen, SOE balloons can be inserted, delivered, or exchanged by a single operator who can hold the wire close to the insertion point. Thus, an exchange length wire is not necessary for SOE systems, which can use a wire of any length, shortening the procedural time. When compared to the OTW system, the SOE has generally a lower profile at the expense of less pushability and trackability In addition, it does not allow for exchanging the wire without a transfer catheter or the use of a long sheath or guiding catheter.

Balloon Characteristics

Balloon Compliance

Balloon compliance represents the degree of the expansive ability of the balloon, which is determined by the function of pressure and diameter. Currently available balloons for PAD are usually made of plastic polymer with varying degrees of compliance. The inflated pressure affecting compliance ranges from a stated nominal pressure to a rated burst pressure in each balloon. Nominal pressure is defined as the pressure at which the balloon expands to its determined diameter and length, and ranges generally from 3 to 10 atmospheres (atm). Rated burst pressure (RBP) is the pressure at which less than 1% of tested balloons will burst and beyond which the probability of rupture increases. RBP typically ranges from 6 to 16 atm. Mean burst pressure, defined as the pressure at which 50% of balloons will rupture, is commonly higher than the RBP and ranges from 10 to 27 atm. Regarding compliance, two types of balloons are mainly used: compliant and noncompliant.

Compliant balloons are usually made of polyolefin copolymer and polyethylene. These balloons, including semicompliant balloons, are superior in trackability and are suitable for lesions

in a curved portion of a vessel. Although they produce less vascular damage because of gentle dilation, high-pressure inflation can result in a doggie bone effect that may damage the normal vessel proximal and distal to the lesion. Thus, a compliant balloon is not suitable for severe calcific lesions. However, one advantage of a compliant balloon is that a single balloon may be adapted to various vessel diameters.

Noncompliant balloons are referred to as high-pressure balloons or low compliance balloons. Most noncompliant balloons are composed of polyethylene terephthalate or nylon reinforced polyurethane. These materials improve the radial force of the balloon and allow for high-pressure expansion. Thus, noncompliant balloons, which are constructed to maintain their designed shape and size under high pressure, have a higher RBP compared with compliant balloons. Noncompliant balloons, preferred by most interventional specialists, exert more recoil force when used for severe calcific lesions or following insufficient expansion during postdilation following stent deployment.

Profile and Balloon Ability

Profile is usually expressed in French (Fr.) size and is determined by the cross-sectional area and diameter of the balloon and shaft. A smaller profile is better than a larger profile in terms of deliverability to the lesion and the ability to cross severely stenotic lesions. Most peripheral balloons are deliverable via a 4- to 6-Fr. compatible sheath. The balloon tip is designed to make a smooth transition and to minimize crossing profile. Balloons of 0.014- or 0.018-inch wire systems have a smaller profile compared to the 0.035-inch systems.

The performances of balloons are determined by trackability, pushability, and crossability. Trackability is the ability of the catheter to follow the guidewire without loss of wire position. Balloons with better trackability advance better in tortuous vessels. Pushability is the ability to transmit force along the length of balloon catheter to the target lesion. Hydrophilic, hydrophobic, silicone, or other surface coatings on balloon catheters, as well as balloon stiffness, determine their pushability. Generally, balloons of 0.035-inch systems have higher pushability compared with the 0.014- or 0.018-inch systems. Balloon catheters with OTW systems also have higher pushability compared with similar SOE systems. Crossability is the ability to cross the stenotic lesion. Balloon shapes that are commonly used for the peripheral arteries, including tip features and low-friction surfaces, allow for smooth passage to the target vessels. Torque transmitting performance and kink resistance of the balloon catheter are also important.

Specialty Balloons

PTA is carried out by fracturing the plaque and irregularly dissociating the intima or media of the vessel and therefore often results in dissection and recoil, particularly in severely stenotic and calcified lesions where uneven overpressures are applied. Therefore, specialty balloons have been developed for specific purposes to improve PTA outcomes and to reduce the occurrence of recoil, dissection, and restenosis.

Cutting Balloons

A cutting balloon is a specialized device made of a series of 3 or 4 microsurgical blades (artherotomes) mounted longitudinally along the surface of a standard PTA balloon (Fig. 61.1). A cutting balloon was initially introduced as an angiography device for percutaneous coronary intervention by Barath et al.[3] Previously, only small size (less than 4 mm) balloons were available. However, there are now balloons with a larger diameter (8 mm) that are currently utilized for peripheral lesions. Peripheral cutting balloons (PCBs) require a 0.014- or 0.018-inch guidewire system with a 6- to 7-Fr. sheath. More specifically, small diameter PCBs are supported by a 0.014-inch guidewire system and either an OTW or SOE system, but large diameter PCBs are only used with a 0.018-inch guidewire system with an OTW system. PCB length is typically 1.5 to 2.0 cm. Peripheral lesions that are suitable for the treatment with a PCB are mainly short lesions involving venous graft stenosis following bypass, bifurcation stenosis, no-stenting zone (such as common femoral or popliteal artery), and in-stent restenosis (ISR), as opposed to areas that require primary treatment of occlusive disease. The midterm results of PCBs versus conventional PTA (noncompliant balloons) for the treatment of short lesion of femoropopliteal artery stenosis was reported in a retrospective study by Antonio et al.[4] A total of 142 short occlusive lesions under 3.0 cm were

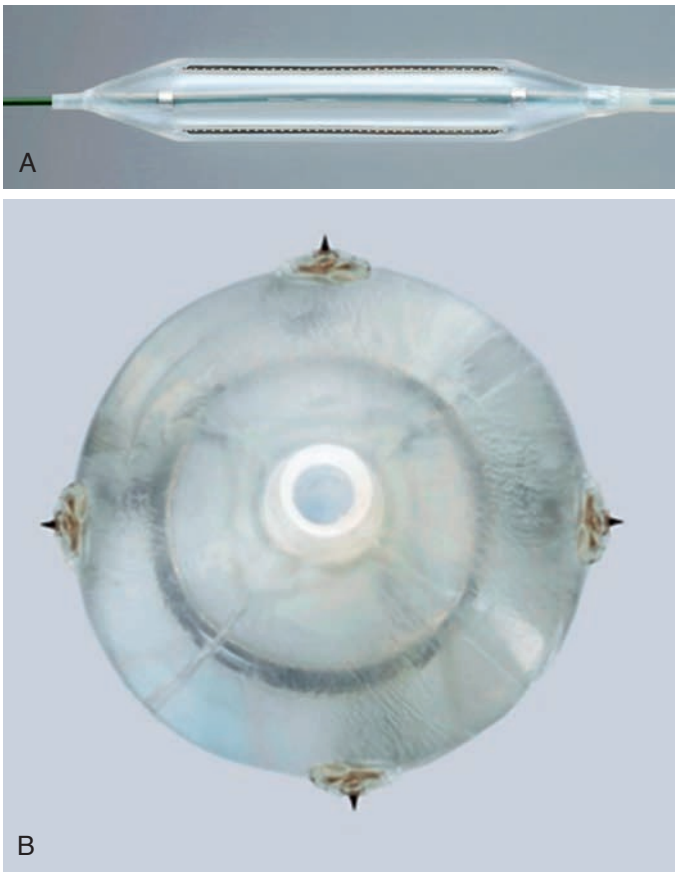

Figure 61.1 Peripheral cutting balloon (Boston Scientific, Natick, Massachusetts), (A) is seen from the side and (B) is from the top of the balloon.

treated in 84 consecutive patients. Forty patients underwent conventional PTA balloon (46 limbs, 67 stenotic lesions) and the remainder were treated with PCBs (44 limbs, 75 stenoses). Target lesions were located in the superficial femoral artery (SFA) in 91 limbs and the popliteal artery of 51 limbs. The primary endpoint was the 24-month patency rate of the treated lesions, and secondary endpoints were the estimation of complications after surgery and the 6- or 12-month patency rates. Technical success was 100%. Baseline reference vessel diameters and postprocedural minimum lumen diameters for the PTA group and PCB group did not show a significant difference. The primary patency rates of the PTA at 6-, 12-, 24-months were 91.0%, 83.1%, and 66.6%, respectively. In the PCB group, the primary patency rates at 6-, 12-, 24-months were 93.2% ($P < .001$ vs. PTA at same period), 90.4% ($P < .001$), and 79.7% ($P < .001$), respectively. Additionally, in 4 (6%) of 67 lesions of PTA, a self-expanding stent was required due to a flow-limiting dissection, but no recoil, dissection, or arterial tears requiring stents were observed in PCBs. There were no adverse events, deaths, or amputation in the two groups. Reintervention rates were 20% in the conventional PTA group and 9% in PCB group ($P < .001$). In another study of 128 patients undergoing treatment of infrainguinal lesions, the primary patency rate following treatment with PCB was 82.1% at 1 and 2 years. In patients with critical limb ischemia (CLI), the primary patency rates at 1 and 2 years were 64.4% and 51.9%, respectively.[5]

PCBs have also been used for hyperplastic stenosis in hemodialysis arteriovenous fistulae. In a review of several randomized trials, the patency of the target lesion at 6 months was significantly higher in the PCB group compared to the control group (conventional balloon dilatation), implying greater freedom from restenosis without a significant increase in the complication rate.[6] Considering the results of these studies, PCBs are recommended for the treatment of short stenotic or occlusive lesions in the femoropopliteal artery, or hemodialysis arteriovenous fistulae, achieving better patency compared to conventional noncompliant balloons.

Cryoplasty

Cryoplasty is a type of balloon angioplasty that uses cooling and pressure to dilate the plaque and vessel wall. This system was expected to reduce dissection and therefore avoid stenting and also reduce restenosis. When the balloon reaches the target lesion, liquid nitrous oxide inflates the balloon and exposes approximately 500 μm of lesion with cooling to 14°F (−10°C), which may induce an inflammatory response in the plaque, temporarily reduce the elasticity of the intima, and reduce smooth muscle cell proliferation by cell apoptosis. In a review of seven randomized controlled trials including 478 patients with iliac, infrainguinal, femoropopliteal, and popliteal lesions treated by cryoplasty or conventional angioplasty, target lesion patency and restenosis rates calculated at various periods in two primary cryoplasty trials demonstrated no statistical difference between the treatment groups. Adjunctive cryoplasty, which was performed for ISR of SFA lesions, was associated with improvements of patency only at 6-month (OR 5.37, 95% CI; 1.09 to 26.49). The authors concluded that the efficacy of cryoplasty over conventional angioplasty could not be proven.[7] Since the effectiveness of cryoplasty is not apparent and there are additional costs ($1700) compared to conventional PTA, the value and role of cryoplasty for the treatment of PAD is limited if nonexistent.

Focal Pressure Balloon

Focal balloons were designed to reduce dissection and restenosis. The AngioSculpt (AngioScore, Fremont, California) and VascuTrak 2 (Bard Peripheral Vascular, Tempe, Arizona) balloons are designed to exhibit focal pressure to the lesions. The AngioSculpt balloon is composed of nitinol wires placed in spiral struts along the surface of a standard semicompliant balloon. The 1-year outcomes of treatment for CLI by the AngioSculpt balloon were reported by Bosiers et al.[8] Thirty-six complex infrapopliteal atherosclerotic lesions, ranging from 6 to 100 mm, were treated in 31 patients. The primary patency and limb salvage rates at a 1-year period were 61.0% and 86.3%, respectively. Eleven patients (35.5%) required stents secondary to dissection or suboptimal angioplasty. The authors concluded that the AngioSculpt balloon catheter was effective and safe for patients with CLI. The VascuTrak 2 balloon catheter has two wires located along the longitudinal axis of the balloon to provide focal pressure, which is estimated to be approximately 50 to 400 times greater than a conventional balloon. Although there is no solid evidence supporting the VascuTrak 2, some authors have reported effective outcomes utilizing this balloon to treat infrapopliteal disease with a 100% delivery rate and only 20% of patients requiring stents as a bail-out.[9]

Drug Coated Balloon

Intimal hyperplasia occurs due to an inflammatory reaction following vascular damage from stenting or balloon expansion. Drug-eluting stents (DES) were developed in 1999 to achieve local administration of an agent capable of inhibiting intimal hyperplasia without systemic side effects. The Cypher stent (Cordis Corporation, Fremont, California), which was developed for the treatment of coronary artery disease, releases Sirolimus, a macrolide antibiotic which also has a potent immunosuppressive drug that controls intimal hyperplasia. Subsequently, the TAXUS stent (Boston Scientific, Natick, Massachusetts), which is coated with Paclitaxel, was developed as a second generation DES. These stents could provide greater durability and reduce restenosis; however, they did not prolong life-expectancy or decrease cardiac events compared to coronary bypass in the SYNTAX trial.[10] Moreover, dual antiplatelet drug therapy (DAPT) was required 3 to 6 months after stent placement, because of an increased risk of subacute thrombosis (SAT) without DAPT following DES deployment.

DCB adopted the DES technology for the treatment of femoropopliteal or below-the-knee (BTK) lesions. Multicenter clinical RCTs of DCBs have been performed. The LEVANT 1 trial, a single-blinded design comparing DCB and noncoated balloons in Europe, evaluated the safety and efficacy of the Lutonix DCB (Bard Peripheral Vascular, Tempe, Arizona) for the treatment of femoropopliteal lesions.[11] The Lutonix DCB

is coated with a low dose of Paclitaxel (2 μg/mm^2) as an antiproliferative drug and is available in diameters of 5 to 6 mm and lengths of 60 to 100 mm. A total of 101 patients who had femoropopliteal atherosclerotic disease with Rutherford class 2 to 5 were enrolled in this trial. The primary outcome was angiographic late lumen loss at 6 months, and the secondary outcome included major adverse events (MAEs), functional outcomes, and pharmacokinetics. Operators were instructed to insert the DCB beyond the margins of the predilation site and to inflate the balloon for over 30 seconds in order to transfer the drug to the lesion. Stenting as a bail-out procedure was permitted in either group for flow-limiting dissections. In this trial, the procedural success rates were 100% in the DCB group and 99% in the uncoated balloon group, respectively. The primary outcome of 6-month angiographic late lumen loss was significantly lower in the DCB group than in the uncoated group by intention-to-treat analysis (0.46 ± 1.13 mm vs. 1.09 ± 1.07 mm, $P = .016$). The primary patency rates were 72% in the DCB group versus 49% in the noncoated group at 6 months, and 67% in the DCB group versus 55% in the noncoated group at 12 months, respectively, which was based on freedom from target lesion revascularization (TLR), and restenosis on angiography at 6 months, and peak systolic velocity ratio (PSVR) ≧2.5 at 12 or 24 months. The MAEs, including death, thrombosis, amputation, and reintervention rate, were 39% in the DCB group compared with 46% in the uncoated balloon group ($P = .045$). This trial suggested that DCB balloons are efficacious for the treatment of PAD in femoropopliteal lesions. Consequently, LEVANT 2, a global, prospective, single-blinded randomized trial, was conducted comparing Lutonix DCB with standard PTA.[12] In this trial, 476 patients with symptomatic intermittent claudication or rest pain were randomly assigned in a 2:1 ratio to undergo angioplasty using DCB or the standard balloon for the treatment of femoropopliteal arterial disease. The primary endpoint was the primary patency of the target lesion at 12 months, defined as freedom from binary restenosis or TLR. Freedom from perioperative death from any cause and freedom at 12 months from limb-related death, amputation, or reintervention were also evaluated. The overall mean lesion length was 62.8 ± 41.0 mm, and the total treated length was 107.8 ± 47.8 mm. No statistical difference was observed between the DCB group and the standard PTA group in terms of procedural success (88.9% vs. 86.8%). Stent placement was more prevalent in the standard PTA group (2.5% in the DCB group, 6.9% in the standard PTA group, $P = .02$). The primary patency rate (primary endpoint) of the DCB group was superior to the standard PTA group (65.2% vs. 52.6%, $P = .02$). Additionally, the proportion of patients free from death or free from limb-related death at 12 months, amputation, or reintervention was 83.9% in the DCB group versus 79.0% in the standard PTA group, with no statistical difference. As a result, the authors concluded that the Lutonix DCB was effective and safe for the treatment of femoropopliteal arterial disease due to superior patency and fewer complications compared to standard PTA in the short term.

Initially favorable outcomes have been presented for several DCB trials, but long-term patency and safety remain unclear. Therefore, further long-term follow-up will be required to decide whether DCB therapy is appropriate for the treatment of complex stenotic lesions or occlusive lesions in infrainguinal PAD or dialysis access venous stenoses.

On a technical note, predilation with the appropriately sized balloon is first performed followed by using the DCB to deliver the Paclitaxel.

STENTS

The term "stent" originated from Charles R. Stent, a British dentist, who developed an apparatus to make dental molds. Thereafter, a mold embedded inner lumen came to be known as a stent. Stenting for vascular lesions is currently widespread as a method to reduce the incidence of restenosis or address balloon PTA failure due to elastic recoil or dissection. In 1964, Charles Dotter, who performed the first PTA, initially reported laboratory experience with a long-term patency of coil spring endoarterial tube grafts in canine popliteal arteries.[13] This was the first report of transluminal metallic stent placement. The nitinol stent, which accounts for the majority of the currently available stents, consists of an alloy of nickel and titanium and was not used until 1983.[14,15] In 1985, Palmaz et al.[16] introduced the first balloon-expanding stent which was approved for peripheral vascular use by the US Food and Drug Administration (FDA). The patency of the Palmaz-Schatz stent compared to PTA was demonstrated in several trials.[17,18] Currently, many available stents have been developed (Table 61.1) and evaluated in clinical studies.

Stent Types

Stents are classified as balloon-expanding (BES) and self-expanding stents, and also either as bare metal or covered stents. Most bare metal stents are composed of stainless steel, nitinol, cobalt chrome, or various metal alloys, whereas covered stents (stent grafts or endografts) are composed of stent with woven, expanded polytetrafluoroethylene (PTFE), polyurethane, or silicon. Stent characteristics, including flexibility, radial strength, kink resistance, and biocompatibility, vary depending on their material and design and may affect the ultimate patency of the stent.

Balloon-Expanding Stents

The first commercially available balloon-expanding bare metal stent is the Palmaz stent. The efficacy of this stent has been validated in clinical trials.[19-21] Balloon-expanding stents are slotted metal tubes that are mounted, or "crimped," onto a balloon suited to the diameter of the target vessel. The balloon is inflated to deploy the stent and secure it to the vessel wall. At first, the proximal and distal ends of the stent are expanded into a "doggie bone" shape and subsequently the middle portion of the stent is expanded. These stents are typically rigid in order to provide resistance against elastic recoil, but they may become irreversibly deformed when subjected to an external compression force. Thus, these stents are suitable for vessels that are not prone to external compression. Other advantages

TABLE 61.1 Variation of Available Stents

	Company	Introducer Sheath (Fr.)	Diameter (mm)	Length (mm)	Endohole (Inch)
Iliac					
Self-Expanding					
Absolute	Abbott	6	6-10	20-100	0.035
E-Luminexx	Bard	6	7-12	20-100	0.035
Wallstent	Boston Scientific	6	6-10	18-69	0.035
Zilver	COOK	6	6-10	20-80	0.035
EverFlex	Medtronic	6	6-8	20-120	0.035
S.M.A.R.T	Cordis	6	6-10	20-100	0.035
Epic	Boston Scientific	6	6-12	20-120	0.035
Balloon-Expanding					
Omnilink Elite	Abbot	6, 7	6-10	12-59	0.035
Express LD	Boston Scientific	6, 7	6-10	17-57	0.035
Palmaz	Cordis	6, 7	4-8	10-29	0.035
Assurant	Medtronic	6	6-10	20-60	0.035
SFA					
Self-Expanding					
LifeStent	Bard	6	5-7	20-170	0.035
Misago Rx	Terumo	6	6-8	40-150	0.035
S.M.A.R.T	Cordis	6	6-8	20-100	0.035
Innova	Boston Scientifics	6	5-8	20-200	0.035
EverFlex	Medtronic	6	6-8	20-200	0.035
Supera	Abbott 6		4.0-6.5 20-100		0.018
Drug-Eluting					
Zilver PTX	COOK	6	6-8	40-120	0.035
StentGraft					
Viabahn	Gore & Associates	6-12	5-13	25-250	0.014/0.018
Flair	Bard	9	6-9	30-70	0.035
Fluency	Bard	8-10	6-13.5	40-120	0.035

of balloon-expanding stents are the ability to place them precisely, and that they tend to be more radiopaque than self-expanding stents. Therefore, BES are advantageous for calcific ostial lesions involving the renal, mesenteric, iliac, subclavian, or brachiocephalic arteries. They are contraindicated for vessels prone to external compression including the internal carotid and superficial femoral artery. Balloon-expanding stents may foreshorten if stents are overdistended beyond their intended diameter. Furthermore, most stents composed of a stainless alloy cause artifacts (signal loss) with magnetic resonance imaging (MRI).

Although most balloon-expanding stents are made from stainless steel, newer balloon-expanding stents are composed of cobalt-chromium. Cobalt-chromium stents are stronger than stainless steel stents, and provide greater radial force with a lower crossing profile and with enhanced flexibility.

Self-Expanding Stents

Self-expanding stents are typically composed of nitinol, a nickel-titanium alloy which provides flexibility and shape-memory. Due to the elastic properties of nitinol, stents with a diameter greater than the target reference vessel are selected so that they exert an outward expansible force, resulting in appropriate vessel wall apposition. The diameter of the lesion treated with a self-expanding stent is the result of interference between the recoil of the lesion and the radial expansion force of the stent. In addition, self-expanding stents are more flexible than balloon-expanding stents, which provides greater trackability, allows for the navigation of tortuous vessels, and offers resistance to fracture. As a result of their elastic property, diameter sizing of the stent is more forgiving than balloon-expanding stents and generally apposes well to the vessel with

less chance of vessel perforation. In addition, because nitinol is a nonferromagnetic metal, it is less likely to cause artifact on MRI.

The radial strength, flexibility, and, most importantly, the maneuver of deployment differ by manufacturers. Regarding deployment of a self-expanding stent, most stents are stored in the delivery sheath, and they are deployed from the distal end to the proximal end of the stent by unsheathing. Once deployed, most self-expanding stents cannot be restored or repositioned, with exception of the Wallstent (Boston Scientific, Natick, Massachusetts), which can be sheathed and repositioned many times. With the exception of the Misago stent (Terumo, Somerset, New Jersey), self-expanding stent platforms are OTW systems.

Self-expanding stents are classified as open-cell or closed-cell design. An open-cell stent is a cylindrical shaped structure of stacked serrated metal. The current stents, such as S.M.A.R.T (Cordis Corporation, Fremont, California), Misago (Terumo, Somerset, New Jersey), EPIC (Boston Scientific Corporation, Natick, Massachusetts), Lifestent (Bard Peripheral Vascular, Tempe, Arizona), and E-Luminexx (Bard Peripheral Vascular, Tempe, Arizona), are composed of an open-cell configuration for the body of the stent and a closed-cell configuration for the stent edge. Although the open-cell structure has high flexibility, it is more susceptible to deformation, bending (strut), and could possibly create nonuniform radial force to the target vessel. In addition, due to the large cell size, it is prone to plaque protrusion through the strut. However, the open-cell design allows for better tracking through tortuous vessels. In contrast, in a closed-cell design, all edges and vertices of the stent cells constituting the mesh are shared with an adjacent cell; thus, it is advantageous for lesions at risk for embolization because the stent mesh is very fine. Disadvantages of the closed-cell stent include the fact that it is less flexible, less deliverable, and less conformable to a tortuous vessel compared to an open-cell stent.

Stent Grafts

Balloon-Expanding Stent Grafts

There are two balloon-expanding stents grafts available for use: the i-Cast (Atrium Medical Corporation, Hudson, New Hampshire) and Jostent (Abbott Vascular Inc., Redwood, California). The i-Cast (Advanta V12) is made of 316L stainless steel stent struts encased by PTFE fabric. The stent graft can be expanded beyond the stated stent diameter, although at the cost of stent foreshortening. All stent grafts of i-Cast (<10 mm) require 0.035-inch guidewire and 6- to 7-Fr. sheaths, depending on the diameter. This stent graft is approved by the FDA for the treatment of tracheobronchial strictures but not for PAD. However, it has been used in off-label fashion for various vascular beds such as the iliac or renal artery, for occlusive lesions as well as for perforation after PTA or stenting, ISR, and branch reconstruction for fenestrated endovascular treatment of thoracoabdominal aortic aneurysms. An advantage of the i-Cast stent is that it has the lowest profile. However, as with the balloon-expanding bare metal stent, the device is not suitable for severely tortuous vessels or for lesions that are subject to structural changes due to the rigidity of the stent. The improvement of patency using an i-Cast stent for the treatment of occlusive lesions has been demonstrated, although data are limited.[22]

The Jostent is made of a central layer of PTFE sandwiched between two 316L stainless steel stents. It is commercially approved for use as a bail-out for coronary perforation and is delivered by 0.014-inch guidewires through a 5 Fr. sheath. The superiority of this stent graft was not demonstrated in a study comparing Jostent and a bare metal stent in the treatment of aortocoronary saphenous vein grafts stenosis.[23] Additionally, since restenosis rates with this stent graft are relatively high, its use is largely limited for bail-out of vessel perforation during interventional procedures.

Self-Expanding Stent Grafts

Self-expanding stent grafts are used for various applications. There are three main devices, including the Viabahn (W.L. Gore Associates, Flagstaff, Arizona), Fluency (Bard Peripheral Vascular, Tempe, Arizona), and Flair (Bard Peripheral Vascular, Tempe, Arizona). The Viabahn endoprosthesis consists of heparin-bonded PTFE attached to a nitinol stent. The technology for surface heparin coating was adapted from the Propaten prosthesis (W.L. Gore Associates, Flagstaff, Arizona), which was designed to improve bypass patency. The superior properties of this stent graft, which are significantly different from other endografts, include high flexibility and proven extended patency in the treatment of femoropopliteal disease. The Viabahn endoprosthesis is composed of a single-wire nitinol stent frame without longitudinal connections. The stent frame is attached to the PTFE graft material with a thin film. These two proprietary design features allow for high flexibility. The VIPER trial, a prospective, single-arm, and non-RCT study, was conducted to evaluate primary patency at 12 months or performance of the device for the treatment of long SFA occlusive disease.[24] The overall primary patency was 73%, and notably, patency was not significantly different for the lesion length between over 20 cm and under 20 cm (70% vs. 75%). Furthermore, this trial demonstrated the safety of the Viabahn endoprosthesis, as there were no major adverse events at 1 year in a clinical device-related study. Subsequently, the VIASTAR trial, a randomized, prospective, single-blind, multicenter study, compared the Viabahn endoprosthesis and conventional bare metal stents in 141 patients with symptomatic SFA lesion (Rutherford stage 2 to 5).[25-26] At 24 months, the overall primary patency rates of Viabahn and bare metal stent were 63.1% versus 40.0%, respectively ($P = .004$). The patency rates of the Viabahn at 24 months for lesions ≧20 cm was higher than that of bare metal stents (65.2% vs. 26.7%; $P = .004$). Freedom from bypass surgery and TLR and secondary patency were comparable between the two groups. Restenotic lesion after deployment of the Viabahn are usually focal and limited to both edges of the graft, in contrast to restenosis occurring after bare metal stent that usually develops diffusely throughout the stent. The Viabahn endoprosthesis requires 0.018-inch wires and 6- to 7-Fr. sheaths, depending on the diameter of the device, and the available length ranges from 2.5 to 25 cm. The Viabahn is deployed by

withdrawing the rip cord and is similar to that of the Excluder stent graft (W.L. Gore Associates, Flagstaff, Arizona).

The Flair endograft, like the Viabahn, is composed of a nitinol stent and PTFE fabric. This graft is utilized in hemodialysis patients for the treatment of arteriovenous graft anastomotic stenosis. A tip of the graft has either straight or flared shape. Each graft has demonstrated improved patency compared with the standard PTA. The required delivery sheath is 9 Fr. and is supported by an 0.035-inch wire.

The Fluency stent is approved by the FDA only for biliary application and its vascular use is off-label. This stent graft is made of a nitinol stent based on the design of the Luminexx stent and encapsulated by PTFE along its length except for 2 mm at either end where the stent is flared. Its crossing profile is 9-Fr. sheath compatible. The Fluency is supported by 0.035-inch wires, and the deployment method is similar to other self-expanding bare metal stents in which the stent is deployed by withdrawing the covering sheath. The Fluency is often used for endovascular reconstruction of arch branches or visceral branches during t-Branch or a-Branch (COOK Medical, Bloomington, Indiana) procedures.

Drug-Eluting Stents

Stents have been associated with improved patency for the treatment of PAD compared to conventional balloon angioplasty. However, the incidence of ISR and stent thrombosis due to intimal proliferation became apparent when treating long lesions with multiple stents. In order to overcome this issue, the drug-eluting stent (DES), loaded with agents such as Paclitaxel and Sirolimus, usually using polymers, was initially developed for the coronary artery. The DES has been shown to dramatically improve the patency and ISR rates in the treatment of coronary stenosis.[27,28] Subsequently, the coronary DES technology was applied to the femoropopliteal segment. Sirolimus-eluting stent based on the S.M.A.R.T stent (Cordis Corporation, Fremont, California) was the first peripheral DES and was compared to a bare metal S.M.A.R.T stent in the prospective randomized SIROCCO I and II trials.[29,30] However, the restenosis rates at 24 months were not reduced and this program was terminated (22.9% in sirolimus-eluting S.M.A.R.T stent vs. 21.1% in bare metal S.M.A.R.T stent). The Dynalink stent (Abbott Vascular Inc., Redwood, California), which is an everolimus-eluting stent (unpublished), also failed to show superiority at 12 months compared with historical controls of the STRIDES trial.

The Zilver PTX stent (COOK Medical, Bloomington, Indiana) is a unique DES since it does not utilize a polymer to load the Paclitaxel. The sustained patency and freedom from TLR of the Zilver PTX stent was proven in a landmark multinational RCT with 479 patients, comparing primary Zilver stents with PTA with/without standard stents for the treatment of femoropopliteal (above-the-knee) lesions.[31] In this trial, patients with symptomatic PAD underwent primary DES or standard PTA. When PTA patients suffered from flow-limiting dissection and required placement of a stent, a secondary randomization was performed between bare metal stent and Zilver PTX. The primary patency rates at 12 months for the Zilver DES and PTA were 83.1% and 32.8%, respectively ($P < .001$). In addition, the secondary randomization showed that the primary patency rate of the DESs was superior to the patency rate of the bare metal stent group at 12 months (89.9% vs. 73.0%; $P = .01$). More recently, the sustained superiority of the Zilver PTX stent has been demonstrated up to 5 years.[32] At present, a new DES called the Eluvia stent (Boston Scientific, Natick, Massachusetts) that utilizes a polymer and Paclitaxel based on the Innova stent was developed for SFA lesions. Although not published, the primary patency of this DES platform at 12 months was 96.1% in patients with femoropopliteal disease. Currently, a single-blind RCT comparing Eluvia versus Zilver PTX is scheduled to enroll in the IMPERIAL global study.

Multilayer Stents

Multilayer Flow Modulator (MFM) stent is designed to exclude peripheral or visceral aneurysms while maintaining branch vessel flow. MFM is a three-dimensional braided tube composed of multilayer wire without any covering prostheses. The Cardiatis MFM (Cardiatis, Isnes, Belgium) was approved in Europe in 2009. The first case report detailing implantation in a human was for a patient with a renal artery aneurysm involving a branch of the renal artery.[33] The efficacy of the Cardiatis MFM for the treatment of peripheral and visceral aneurysms was evaluated in an Italian multicenter trial.[34] The primary patency at 1 year was 86.9%, and the cumulative side branch patency was 96.1%. Complete thromboses of aneurysms were achieved in 93.3%, and no aneurysmal rupture was identified. MFM is currently being investigated for the treatment of aortic dissection or as a supplement to endovascular aortic repair.

Bioabsorbable Stents

Bioabsorbable stents that were initially developed for coronary intervention are being applied to the peripheral arterial beds. The first coronary absorbable stent implanted in a human was the Igaki-Tamai stent (Igaki Medical Planning Company, Kyoto, Japan), which is made of poly-L-lactic acid (PLLA) and constitutes a helical coil with a straight bridge configuration. The efficacy of Igaki-Tamai stents was shown in several studies.[35-36] Biodegradable polymers including polyglycolic acid and polycaprolactone, or copolymers such as poly (D-, L-lactide/glycoide), as well as metallic alloys such as magnesium and iron, have been used for absorbable stents. In the peripheral regions, Peeters et al. described preliminary results of an absorbable stent for the treatment of BTK arterial disease in patients with CLI.[37] The Biotronik absorbable metal stents (Biotronik, Berlin, Germany) were implanted in 20 patients enrolled in this study. This stent is a tubular, slotted, balloon-expanding stent sculpted from layers of a single tube of biodegradable alloy containing over 90% magnesium and rare-earth elements. At the 3-month follow-up, the primary clinical patency rate was achieved in 89.5%, and there were no major amputations. However, in the INSIGHT study,[38] a prospective multicenter RCT, superior patency of absorbable stents could not be shown (32% in the absorbable stent vs. 58% in the standard PTA). In addition, a RCT,[39] comparing endarterectomy with absorbable stent

implantation for common femoral occlusive lesions, has also demonstrated less favorable results including primary patency at 1 year (80% in the absorbable stent vs. 100% in the endarterectomy). Considering these results, this technology and development of self-expanding absorbable stents seems to require further research and deployment.

ATHERECTOMY DEVICES (DEBULKING TECHNOLOGIES)

Stenting has improved the short- and mid-term primary patency rates in most stenotic or occlusive lesions and has been widely adopted. However, stenting has several shortcomings including ISR and stent fractures. Percutaneous atherectomy debulking devices were developed to overcome these stent limitations. Since debulking procedures ideally achieve a successful outcome without the need for stenting, it is especially useful for lesions where a stent should be avoided, such as the common femoral artery or popliteal artery behind the knee joint. Currently there are three different types of atherectomy devices including directional (excisional), rotational, and laser atherectomy.

Directional

The SilverHawk and TurboHawk Plaque Excision System (eV3 Inc., Plymouth, Minnesota) were approved by the FDA as directional atherectomy devices. These devices consist of a carbide cutting blade with a variable height and a plunger used to pack the atheroma into the nose cone (Fig. 61.2). The cutting blade rotates at a speed up to 8000 revolutions per minute (rpm), and shaves atherosclerotic material from the luminal portion of arterial wall. The cutting blade of the TurboHawk is designed for treating severe calcification. The devices are composed of a monorail catheter with a 0.014-inch compatible wire system, and the recommended sheath size is 6 to 8 Fr. They can be used in many cases without the need for balloons or stents.

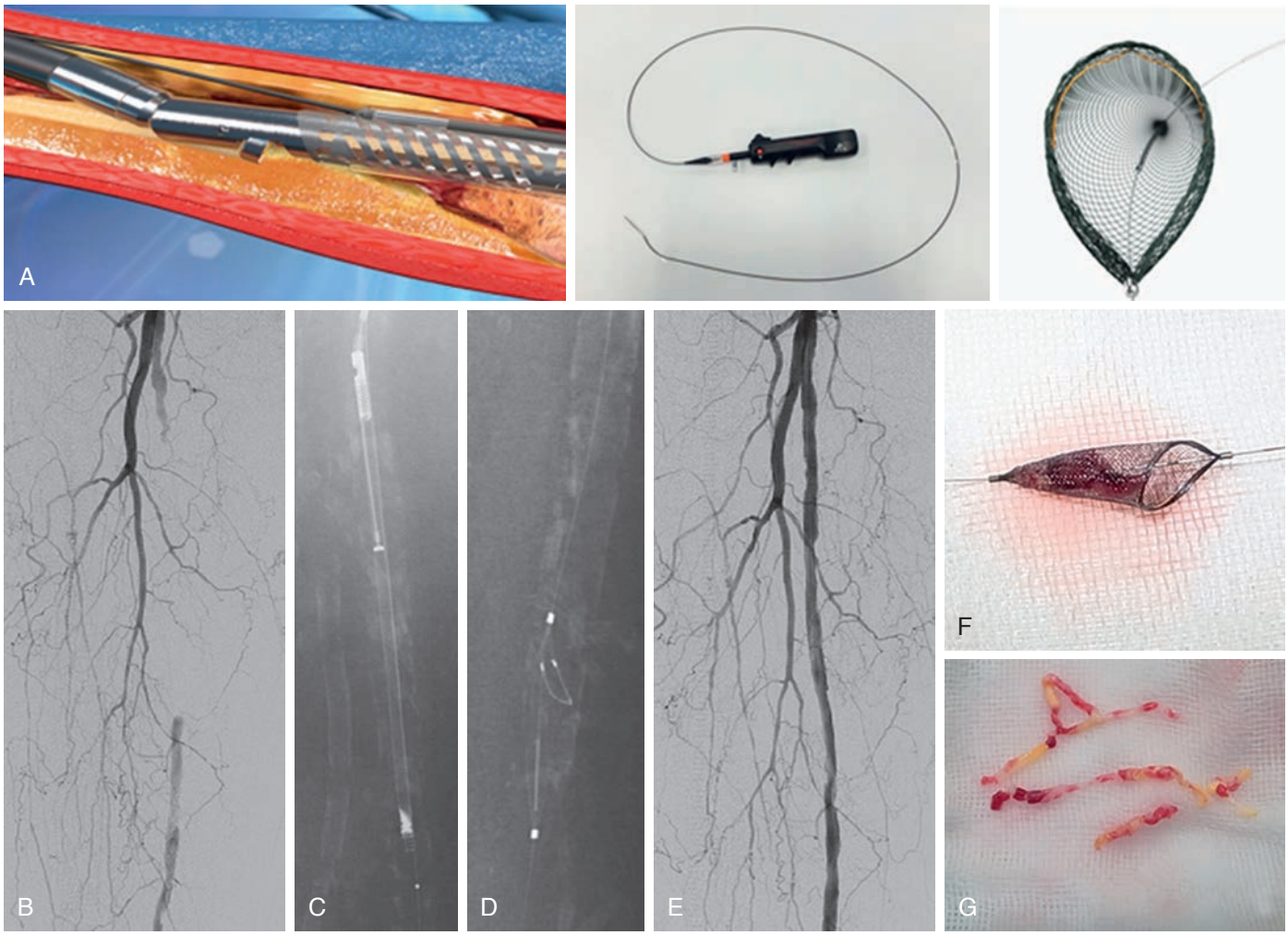

Figure 61.2 (A) TurboHawk atherectomy system (eV3 Inc., Plymouth, Minnesota). (B) Preintervention angiography showing a superficial artery occlusion. (C and D) The plaque is shaved off by the TurboHawk device with a Spider FX located distally to prevent embolization. (E) Completion angiography showing an improvement in vessel flow without distal embolization. (F and G) The shaved plaque captured by the nose cone of the TurboHawk and the filter of Spider FX.

The DEFINITIVE Ca^{++} study[40] demonstrated that the SilverHawk and TurboHawk atherectomy devices coupled with distal embolic protection (Spider FX; eV3 Inc., Plymouth, Minnesota) were safe and effective for the treatment of moderate to severe calcified lesions in the femoropopliteal arteries. The primary endpoint (≤50% residual diameter stenosis) was achieved in 92.0%, and the 30-day freedom from major adverse event rate was 93.1%. Additionally, the DEFINITIVE LE trial,[41] a prospective multicenter trial, and DEFINITIVE Ca^{++} enrolled 800 subjects suffering from claudication or CLI with an infrainguinal lesion up to 20 cm. in length. The primary patency at 12 months was 78%, and the rate of freedom from major unplanned amputation in CLI subjects was 95%.

Rotational

Rotational atherectomy involves inserting a small drill into the artery to fracture a plaque and to create a smooth lumen in the vessel. A high-speed rotating metallic burr abrades the calcified plaque into millions of microscopic particulates, of which 95% are less than 5 microns in size, which is smaller than red blood cells. The burr design is the most important aspect of the mechanism. The currently available rotablator system consists of an elliptical, nickel-plated, bass burr which is coated with 2000 to 3000 microscopic diamond crystals on the leading edge, while rotating at a speed of 160,000 to 180,000 rpm.

The Pathway Jetstream (Pathway Medical Technologies, Inc., Redmond, Washington) is also a rotational atherectomy device equipped with an infusion port of fluid and an aspiration port for removal of the plaque and debris, and this device can be used for both thrombectomy and rotational atherectomy by the same catheter. The system is advanced over a 0.014-inch wire at a maximum rate of 1 mm/s to avoid significant drops in rotational speeds. In a multicenter Pathway trial[42] including 172 patients, device success was 99%, and major adverse events occurred in 1%. The TLR was 26% at 12 months. The device was also evaluated in a prospective cohort study of 29 patients with femoropopliteal ISR lesions.[43] Acute success rate (≤30% residual narrowing with no serious adverse events) was achieved in 91%, and TLR at 6 months and 12 months occurred in 14% and 41%, respectively.

Orbital

Orbital atherectomy is used to reduce the atheroma burden to change the vessel compliance, while decreasing vessel wall trauma. The Diamondback 360 degree Orbital Atherectomy System (Cardiovascular System Inc., St. Paul, Minnesota) provides a versatile solution for removal of peripheral plaque. This device consists of an orbiting diamond-coated crown mounted on the end of a drive shaft. The device can be delivered through a 4 Fr. sheath along a 0.014-inch guidewire. Similar to rotational atherectomy devices, the orbital atherectomy devices reduce the plaque debris to a size small enough to minimize the potential for distal embolization. The CONFIRM series,[44] a prospective multicenter registry, was created to evaluate the performance of orbital atherectomy for PAD of the lower extremities. Plaque removal was most effective in severely calcified lesions and lowest for soft plaque. The overall plaque burden was reduced by more than 50% on follow-up angiogram after atherectomy. In another study,[45] the procedural success of orbital atherectomy combined with balloon angioplasty was 93.1% and for balloon angioplasty alone was 82.4%. The estimated freedom from TLR was 93.3%.

Laser

Advances in laser catheter design and recanalization techniques have resulted in improved outcomes for the treatment of complex PAD. The excimer laser, using a 308-nm wavelength, allows laser light to ablate the plaque and thrombus. The plaque is ablated on direct contact alone, minimizing surrounding thermal injury. In a prospective study of 35 patients, the CVX-300 Excimer Laser system (Spectranetics, Colorado Springs, Colorado) was evaluated as a first-line endovascular treatment for CLI. The clinical success, defined as restored direct arterial flow to the foot, was achieved in 88.2%.[46] The estimated patency rates were 96.6% at 12 months and 82.7% at 24 months, respectively, and limb salvage at 24 months was 94%. Recently, a RCT[47] was conducted across 40 US centers to assess the excimer laser plus PTA versus PTA alone for patients with ISR. The freedom from TLR of the laser plus PTA and PTA alone at 6 months was 73.5% and 51.8%, respectively, and 30-day major adverse event rates for the laser plus PTA were also significantly lower than for PTA alone (5.8% vs. 20.5%).

THROMBOEMBOLECTOMY

Over the years, the Fogarty catheter and other products have been developed to remove thrombi in arterial or venous circulation.[48] New innovations made it possible to perform totally percutaneous thromboembolectomy and has been applied to coronary, peripheral arterial thromboses disease, deep vein thrombosis (DVT) including pulmonary thrombosis, and cerebrovascular regions. Despite its efficacy, catheter-directed thrombolysis (CDT) has potential risks such as cerebrovascular hemorrhage, major bleeding, embolization, and recurrence of thrombosis.[49-51] In order to reduce these risks, several thrombectomy devices such as rheolytic or rotational thrombectomy devices have been developed including aspiration, rheolytic, rotational, and ultrasound enhanced platforms.

Aspiration

The simplest procedure to perform thrombectomy is to aspirate the thrombus with a large catheter or sheath. Currently available aspiration devices are the Export (Medtronic Inc., Minneapolis, Minnesota), PriorityOne (Terumo, Somerset, New Jersey), and Pronto (Vascular Solution Inc., Minneapolis, Minnesota). These aspiration devices are designed as monorail type and are 0.014-inch wire compatible. The Export catheter has a separate lumen for the wire and the aspiration port to maximize aspiration capability, while the PriorityOne catheter has guidewire-style stylet technology. With such devices, the risk of distal embolization due to crushing of the clot remains. Hence, thrombolytic drugs may

be used in combination with aspiration devices. These catheters seem to be well suited for small vessel diameters (<6 mm), and are less effective for a large thrombus burden.

Rheolytic

Rheolytic thrombectomy is a procedure in which a jet of saline is ejected from the tip of a catheter and is used to dissolve the thrombus by creating a "Venturi" effect. The Angiojet catheter (Possis Medical, Minneapolis, Minnesota) is such a hydrodynamic device, and provides a high speed saline jet which travels backward to create a low-pressure zone causing a vacuum effect. This vacuum removes thrombus material, which is then aspirated back into the exhaust lumen of the catheter. In the PEARL registry, a total of 238 patients with acute limb ischemia (ALI) undergoing Angiojet catheter were enrolled.[52] Procedural success was achieved in 83%. Amputation-free rate and freedom from mortality rate at 12 months were estimated to be 81%, and 91%, respectively. Additionally, the device also can be used for DVT and potentially reduce the need for additional CDT. Furthermore, the Angiojet catheter provided comparable outcomes for the treatment of thrombosed hemodialysis graft compared to surgical thrombectomy.[53]

Although complications such as acute myocardial infarction and renal insufficiency have been reported with the use of these devices, the outcomes appear to be superior to thrombectomy compared with simple aspiration devices in several clinical studies.

Rotational

Rotational thrombectomy devices remove the thrombus by rotating the tip of the catheter. The Rotarex (Straub Medical, Wangs, Switzerland) consists of three individual components which can be assembled in a few minutes. This device was evaluated in patients with acute or subacute ischemia due to femoropopliteal bypass occlusion.[54] A total of 22 patients were enrolled, and the technical success rate was 82%. There were no reinterventions at the 6-month follow-up.

The Trellis infusion catheter (Bacchus Vascular, Santa Clara, California) is a hybrid device that combines the delivery of thrombolytic drugs with a thrombus aspiration system. It is composed of proximal and distal balloons and the drug and the debris are trapped between the two balloons. Gupta and colleagues[55] evaluated the Trellis in 24 patients with ALI. More than 90% of vessels had a complete or substantial response. There was one in-hospital death due to severe limb ischemia with extensive occlusion of an axillo-femoral graft, but the amputation rate at 30 days was 0%.

Ultrasound Enhanced

The EkoSonic endovascular system (EKOS, Bothell, Washington) consists of three components, including an intelligent drug delivery catheter, a removal microsonic device, and a reusable EkoSonic control unit. In the SEATTLE II study,[56] including 150 patients with massive or submassive pulmonary embolism, the mean right-ventricular to left-ventricular diameter ratio and mean pulmonary artery systolic pressure were reduced 48 hours after the procedure. Moderate to severe bleeding after procedure occurred in 15 patients (10%). The authors concluded that this procedure has the potential to improve outcomes of the treatment of PE in high-risk patients.

Other Devices

Solitaire stent retriever (Medtronic, Minneapolis, Minnesota) is a new device for mechanical thrombectomy combining the ability to restore blood flow, administer medical therapy, and retrieve the clot. This device is not indicated for peripheral lesions, but is used for cerebrovascular lesions in the treatment of acute ischemic cerebral infarction. The safety and efficacy have been demonstrated in several RCTs.[57,58] In the periphery in a case report, although it represents off-label use, the Solitaire allowed the removal of a BTK thrombus after aspiration thrombectomy had failed.[57,58]

Trevo Xp (Stryker Neurovascular, Fremont, California) is also a stent retriever device, and is the first fully visible device that allows the operator to view placement or strut behavior. In an open-label trial comparing Trevo versus Merci retrievers for revascularization,[59] the stroke score significantly improved in the patients in the Trevo group.

Indigo System (Penumbra Inc., Alameda, California), which became commercially available in 2014, is expected to be a useful device for managing thromboembolic disease in the peripheral circulation, including visceral and upper-extremity lesions, although solid data is not yet available.

INTRALUMINAL DEVICES TO CROSS CHRONIC TOTAL OCCLUSIONS

Endovascular treatment of chronic total occlusion (CTO) is technically challenging and often results in prolonged procedure time and increased patient exposure to contrast agents and radiation. When endovascular treatment is attempted in patients with CTO, the inability to pass a guidewire across the lesion is the leading cause of technical failure. CTO typically involves a plaque or segment of poorly organized thrombus with fibrotic or calcified cap at both the cranial and caudal end. CTO may be generally refractory to crossing with conventional guidewires because of the fact that insufficient axial force is generated to achieve crossing of the lesion. This section describes ancillary devices for recanalization via the true lumen.

Crosser

The Crosser (Bard Peripheral Vascular, Tempe, Arizona) catheter is a high-frequency mechanical recanalization device designed for recanalization of CTO in a peripheral artery. The device is composed of an electronic generator, foot switch, transducer, FlowMate Injector (optional), and a catheter. The catheter is connected to the generator through the high-frequency transducer. When the system is activated, the catheter engages inelastic materials selectively. The elastic materials such as the vessel wall absorb the impact of the device, resulting in a reduced risk of

perforation. In the PATRIOT trial,[60] 85 patients with a previous or concurrent failed attempt to cross a CTO lesion using conventional guidewire techniques were enrolled, the CTO was crossed using the Crosser and the guidewire was successfully advanced into the distal true lumen in 83.5% of the patients, and freedom from perforation was achieved in 98.8% of the patients.

TruePath

The TruePath (Boston Scientific Corporation, Natick, Massachusetts) catheter features a rotating diamond-coated tip that is designed to pass the occluded lesions and facilitate the placement of conventional guidewires for the treatment of PAD. Once the lesion is crossed, the wire is advanced into the distal true lumen beyond the occlusion, as with the Crosser system. The TruePath system requires no capital equipment and is available with an optional extension wire to facilitate catheter exchange and increase the working length up to 300 cm. In the treatment of infrainguinal CTO lesions[61] with the TruePath, the technical success rate was 77%, although some cases required the use of a re-entry device. Clinically driven target vessel recanalization rate at 6 months was only 8% with no periprocedural complications.

Frontrunner XP

The Frontrunner XP (Cordis Corporation, Fremont, California) catheter is a disposable catheter consisting of an articulating, distal tip assembly manually actuated by a proximal rocker handle. The system is specially designed for facilitating placement of guidewire safely across the CTO lesion by steering the distal tip of the device to the occlusion site, and then remotely activating the tip to facilitate blunt microdissection of the plaque. In a retrospective study, 26 patients with TASC D femoropopliteal CTO lesions were treated with the Frontrunner after guidewire failure.[62] The overall technical success was achieved in 88.2%, and no major complications were observed.

RE-ENTRY DEVICES

Outback LTD Re-Entry System

The Outback LTD (Cordis Corporation, Fremont, California) is a re-entry device designed to penetrate the intimal flap and redirect the guidewire from the subintimal plane to the true lumen. It consists of a single lumen compatible with a 0.014-inch guidewire and is deliverable via a 6-Fr. sheath. A 22-gauge controllable curved nitinol needle (cannula) is located at the distal end of the catheter and is used to penetrate the intimal flap. Once the guidewire has crossed the lesion via a subintimal route but failed to return to the distal lumen, the Outback LTD catheter is inserted over this wire. The tip of the catheter is advanced to the distal end of the lesion and adjacent to the true lumen. The needle can then be advanced to penetrate the intima to redirect the guidewire into the true lumen. Correct positioning and direction of the nitinol cannula toward the true lumen is made possible by radiopaque markers located at the tip of the catheter.

Gandini and colleagues[63] evaluated the Outback LTD in a RCT in patients with TASC-DSFA CTO lesions. Subintimal angioplasty was performed in all patients (26 patients in both Outback and manual re-entry groups). Technical success was achieved in all patients. However, 15 patients who underwent a manual re-entry technique experienced extension of the dissection 5 cm beyond the distal end of the CTO. Furthermore, three cases required a bidirectional approach in order to achieve crossing the wire. Procedural time and fluoroscopic time were both shorter for the Outback group.

Pioneer Catheter

The Pioneer (Volcano Corporation, San Diego, California) utilizes intravascular ultrasound (IVUS) for visualization. This device is deliverable via a 6-Fr. sheath and is 0.014-inch wire compatible. The IVUS attached to the device allows for real-time imaging that shows not only the catheter position in the dissection plane, but the intimal flap and the true lumen on the other side of the flap. The adjustable 24-gauge needle is then advanced to penetrate the intimal flap and the guidewire can then be redirected toward the true lumen.

Enteer Catheter

The Enteer system (Covidien, Plymouth, Minnesota) consists of a catheter and guidewire, which is compatible with a 0.014- or 0.018-inch wire. This device involves a flat balloon with a side exit lumen for the catheter in the middle of the balloon. Inflation of the balloon in a subintimal plane provides the orientation of the exit point of the catheter toward the true lumen. A stiff 0.014-inch wire is then advanced from the side hole in order to penetrate the intimal flap and to achieve true lumen re-entry. The advantage of this device is low cost, but the penetrating ability of the Enteer is less compared with the needle-tipped device.

OffRoad Catheter

The OffRoad re-entry system (Boston Scientific, Natick, Massachusetts) is composed of a balloon catheter combined with needle-tipped hypotube (Fig. 61.3). The laser-cut stainless-steel hypotube with a straight needle tip is advanced out of the balloon catheter end to penetrate the intimal lumen or calcified plaque to achieve true lumen re-entry. The balloon catheter is 0.035-inch wire-compatible and is delivered through a 6-Fr.

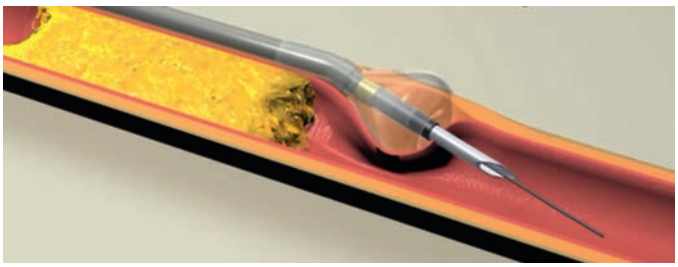

Figure 61.3 The OffRoad re-entry system (Boston Scientific, Natick, Massachusetts).

sheath. The needle can be advanced toward the desirable true lumen owing to inflation of the balloon in the subintimal plane.

In the Re-ROUTE trial, a total 92 patients with CTO lesions of femoropopliteal artery were assigned in a prospective and a single-arm study.[64] The technical success was 84.8%. At 30-day postprocedure, 75% of the patients experienced an improvement of at least one category in the Rutherford classification. The major device-related adverse event rate at 30 days was 3.3%, which was below the pre-specified trial goals.

EMBOLIZATION DEVICES AND AGENTS

Endovascular embolization is a minimally invasive procedure to treat various vascular conditions such as bleeding, small aneurysms, fistulas, or endoleaks following endovascular aortic aneurysm repair (EVAR) (see Chapter 72). The devices for embolization are categorized as mechanical (coils and vascular plugs; Table 61.2), particulates (polyvinyl alcohol, gelatin microspheres), and liquid agents (absolute ethanol and n-butyl cyanoacrylate [NBCA]).

Vascular Coils

In 1975, Gianturco and colleagues[65] described a novel occlusive device designed to allow transcatheter delivery, consisting of a metal coil attached with cotton threads. Thereafter, the Gianturco coil (COOK Medical, Bloomington, Indiana), which is composed of a stainless steel spring guidewire with the inner mandrel removed, became commercially available in 1976. Currently there are a number of coils with various designs. The vascular coil is classified as fibered and nonfibered coil, and pushable and detachable, based on deployment method. Generally, fibered coils are superior in their ability to embolize the vessel and induce thrombosis compared with nonfibered coils. However, nonfibered coils can also treat aneurysms although they may utilize more coils. These coils allow not only precise control and placement especially for the treatment of the tortuous anatomy, but also provide the capability to reposition if necessary. Most current materials consist of Inconel or platinum. These coils are accommodated to MRI, but the platinum coils tend to produce a strong halation on computed tomography (CT) examination. The coils ranging from 0.014- to 0.052-inch sizes are available. Coils have to be selectively used with respect to the lesions or pathologies, and approximately 20% larger coils compared with reference vessels (20% oversize) is recommended for framing. Although the diameter and the length of coils are different depending on the type, the available diameter ranges from 1 to 32 mm and the length ranges from 0.5 to 60 cm.

Vascular Plugs

Embolization of a large vessel, including left subclavian artery or internal iliac artery, to prevent a type 2 endoleak during EVAR is being performed with increasing frequency. However, coil embolization is often time-consuming and micro-platinum coils are costly. The Amplatzer Vascular Plug (St. Jude Medical, St. Paul, Minnesota), composed of 144 nitinol wire-mesh technology, allows full cross-section coverage of the target vessel and facilitates precise deployment with a single device. The plug has the ability to be recaptured and repositioned similar to the detachable coils. There are four types of plugs designed to treat various anatomies. Amplatzer Vascular Plugs I and II are commonly used to occlude large vessels including the subclavian or hypogastric artery. These plugs are compatible with 4- to 6-Fr. sheaths or 6- to 8-Fr. guiding catheters, depending on device size. The device diameters range from 3 to 22 mm, while the length ranges from 6 to 18 mm. Amplatzer Vascular Plug IV is deliverable through a 0.038-inch diagnostic catheter eliminating the need for exchanges, and is used for relatively small-diameter vessels.

TABLE 61.2 The Characteristics of Coil and Vascular Plug

Coil and Plug		Characteristic
Pushable		
0.035-inch	Tornado (COOK)	Platinum, Fibered, Vortex shape
	MReye (COOK)	Inconel, Fibered, Spinal shape
0.018-inch	Tornado (COOK)	Platinum, Fibered, Vortex shape
	Diamond (Boston Scientific)	Platinum, Fibered, Diamond shape
	Trufill (Codman)	Platinum, Fibered, Complex shape
Detachable		
0.035-inch	Flipper (COOK)	Inconel, Fibered, Screw type, Spiral shape
	Interlock (Boston Scientific)	Platinum, Fibered, Lock system, Spinal shape
0.018-inch >	GDC (Stryker)	Platinum, Nonfibered, Electrical, Complex shape
	Fibere vortex GDC (Stryker)	Platinum, Fibered, Electrical, Vortex shape
	Target (Stryker)	Platinum, Nonfibered, Electrical, Complex shape
	Interlock (Boston Scientific)	Platinum, Fibered, Lock system, Spiral shape
	Cashmere (Codman)	Platinum, Nonfibered, Hydraulic, Complex shape
	Matrix 2 (Boston Scientific)	Platinum, Nonfibered, Polyglycolic/polylactic acid polymer coated, Electrical, Complex shape
	Cerecyte (Micrus)	Platinum, Nonfibered, Polyglycol acid loaded, Electrical, Complex shape
	Azur (TERUMO)	Platinum, Nonfibered, Hydrogel polymer coated, Electrical, Spiral shape
Plug		
	Amplazer vascular plug	Nitinol, Screw type, Self-expanding

Liquid Embolic Agents

Liquid embolic agents are commonly used to treat persistent endoleaks after endovascular aneurysm repair or for arteriovenous malformations. These agents lack radiopacity and tend to penetrate deeper into the vasculature, resulting in difficulty controlling the distribution and thus may result in nontarget embolization.

Cyanoacrylate

NBCA is one of the most commonly used substances in vascular beds. NBCA is polymerized by mixing the blood that contains the ion, and is often mixed with lipiodol to ensure visibility and polymerization time adjustment. A microcatheter is required to inject NBCA to the target vessel. Although this agent is effective for the treatment of arterial bleeding, pseudoaneurysm, persistent type 2 endoleaks, or malformation unsuitable for coil embolization, attention should be paid to prevent the "stuck" phenomenon involving occlusion or transection of the microcatheter, or adhesion of the vessel wall and catheter.

Fibrin Sealant

In surgical hemorrhage or tissue sealing, fibrin sealant is commonly used. Fibrin glue is composed of two solutions of fibrinogen and thrombin. Usually, it is used for the treatment of persistent type 2 endoleaks in addition to type 1 endoleaks.[66,67] Fibrin sealant has also been used to effectively treat pseudoaneurysm or trauma-related hemorrhage. However, such uses are off-label. In addition, fibrin liquid injection is difficult to control and can result in unintended site embolization.

Ethylene Vinyl Alcohol

Onyx is nonadhesive polymer composed of ethylene vinyl alcohol dissolved in dimethyl sulfoxide (DMSO). This agent gradually solidifies once it comes in contact with blood. Therefore, unlike NBCA, it can be injected through a long tube and over time under fluoroscopic guidance. However, because DMSO dissolves the catheter material, it requires using an adaptable microcatheter. The FDA approved Onyx in 2005 for the treatment of arteriovenous malformations, but it has been used for the treatment of peripheral AVMs as well as for graft-related endoleaks. Bosiere et al.[68] described the efficacy of Onyx for the treatment of persistent type 2 endoleaks after EVAR. Technical success was achieved in 92% of the patients, and the extravasation of Onyx out of the aneurysmal sac into the vena cava occurred in one patient. The aneurysm sacs remained stable or decreased in diameter during follow-up after Onyx injection. Each liquid agent carries the risk of nontarget embolization.

VASCULAR CLOSURE DEVICES

Vascular access site complications are one of the important and most frequent causes of morbidity following endovascular therapy. Manual compression is still the gold standard method for obtaining hemostasis at the access site. However, manual compression is time-consuming and carries certain failure rate. In addition, with the introduction of newer interventional devices with large profile, there was a need to develop a better method to obtain hemostasis. The ideal vascular closure device (VCD) is able to achieve secure hemostasis without any complications. In the RCT trial (ISAR-CLOSURE trial),[69] 4524 patients undergoing coronary angiography with a 6-Fr. sheath via the common femoral artery were enrolled. Patients were randomized in a 1:1:1 ratio between two closure devices and manual compression. The primary outcome was the incidence of vascular site complications, including major bleeding, infection, leg ischemia, and the need for surgical repair or endovascular treatment. The study found that the access site–related complications were identified in 6.9% assigned to the VCD groups and 7.9% assigned to the manual compression group, confirming the noninferiority of VCDs. Additionally, the multicenter PEVAR trial[70] enrolled 151 patients undergoing aneurysm repair in a 2:1 ratio comparing percutaneous VCD and open femoral exposure. The primary endpoints were defined as procedural technical success, absence of major adverse events, and incidence of access-related complications. Similar to the ISAR-CLOSURE trial, noninferiority was demonstrated in VCD compared with standard open femoral exposure.

Extravascular Plug

Angio-Seal

The Angio-seal (St. Jude Medical, St. Paul, Minnesota) device exerts hemostatic effect by sandwiching the arteriotomy with a bioabsorbable anchor connected with sutures and a collagen sponge that dissolve within 60 to 90 days. The device is compatible with 5- to 8-Fr. sheaths (5, 6 Fr. are applied to 0.035-inch wire, while 7, 8 Fr. are 0.038-inch). In brief, the device sheath is exchanged with the procedural sheath, confirming the proper location by withdrawing and reinserting the device until blood flow resumes. The inner core (locator) and wire are removed, leaving the device's outer sheath in place. The body of Angio-seal is then inserted into the outer sheath. The anchor is released into the vessel by fully connecting the body and the outer sheath. The body and sheath are pulled back until the colored compaction marker is revealed as a guide. The effectiveness of this device has been reported in several studies.[71-73]

Exoseal

Exoseal (Cordis Corporation, Fremont, California) is a percutaneous closure device, based on a bioabsorbable polyglycolic acid plug to achieve hemostasis. The device is compatible with 5- to 7-Fr. sheaths. A small plug is stored in the distal end of the device and is fully absorbable within 60 to 90 days. This unique system involves a marker band, bleed-back indicator, and an indicator window. For deployment, appropriate Exoseal is inserted in the procedural sheath, advancing to the level of the black marker band. The combination of the procedural sheath and the Exoseal is then pulled out until back flow from bleed-black indicator is encountered. Then the sheath and the Exoseal are retracted further until the blood flow becomes slow. When flow from the black-back indicator is interrupted, and when the indicator window to changes to "all black," the plug is deployed just outside and adjacent to the vessel wall.

In the ECLIPSE trial,[74] including 401 patients undergoing diagnostic or interventional procedures with a 6-Fr. sheath, the use of this device significantly reduced time to ambulation compared to manual compression.

FISH (Femoral Introducer Sheath and Hemostasis)

FISH (Morris Innovative, Bloomington, Indiana) utilizes a bioabsorbable extracellular matrix of porcine small intestinal submucosa. The plug is remodeled into native arterial wall tissue and absorbed in 30 days. The device comes in a 5- to 8-Fr. version. In a RCT,[75] 191 patients were randomized to the FISH devices and 106 patients to manual compression. The mean time to hemostasis and ambulation were superior in the FISH group compared to manual compression. Major access-related bleeding requiring transfusion occurred in one patient. In the FISH group, there were five minor adverse events; three access-site hematomas, and two pseudoaneurysms that were treated with thrombin injection.

Mynx

The Mynx (AccessClosure, Mountain View, California) utilizes a polyethylene glycol sealant that is deployed outside the artery while a small balloon inflates the arteriotomy site to create temporary hemostasis within the artery. The device is compatible with 5- to 7-Fr. sheaths, and the sealant is absorbed in 30 days. Among 766 patients undergoing a cerebral angiogram or intervention using the Mynx device,[76] procedural success was achieved in 92%, and device-related complications occurred in 2.5% of the patients.

Suture-Based Devices

ProGlide

The ProGlide (Abbott Vascular Inc., Redwood, California) is a suture-based device that deploys a suture on either side of the arterial wall at the arteriotomy site, mimicking open surgical closure. The polypropylene sutures are pulled together outside the body, resulting in closure of the arteriotomy site. Since it is a mechanical closure, there are theoretically no limitations to re-access or the administration of antiplatelet and anticoagulant. The ProGlide can track over a standard 0.035-inch (or smaller) wire and accommodate 5- to 21-Fr. arteriotomies, but with a larger than 8-Fr. sheath, at least two devices are required to close the arteriotomy. Therefore, the device facilitates EVAR as well as transcatheter aortic valve implantation through percutaneous femoral access. In such cases, the ProGlide is deployed prior to the insertion of the large bore devices and is often referred as Perclose technique.

Prostar XL

The Prostar XL (Abbott Vascular Inc., Redwood, California) is designed for large bore device closures. It also utilizes a polyester suture to close the arteriotomy site. The device has two polyester sutures and four nitinol needles, is deliverable over a 0.038-inch (or smaller) guidewire, and is indicated for 8.5- to 10-Fr. closure. Similar to the ProGlide device, a vascular access can also be maintained throughout deployment, and the device can be used for EVAR or transcatheter aortic valve implantation.

ENDOVASCULAR THERAPEUTIC TECHNIQUES

Percutaneous Transluminal Balloon Angioplasty

Puncture and Approach to the Lesion

Puncture is the most basic and important procedure for the percutaneous treatment of PAD in terms of reducing postoperative complications, including bleeding or pseudoaneurysm formation. Selection of the most appropriate puncture site should take into account the location and extent of the target lesions. The common femoral artery (CFA) is the most common puncture site in endovascular treatment. However, the location of the CFA bifurcation differs in each patient. If the CFA bifurcation is located cranially, there may be a risk of high puncture, resulting in difficulty in compressing the access site after the procedure, which may lead to retroperitoneal hemorrhage. If there is severe calcification of the CFA, the puncture may cause dissection or arterial occlusion. In such cases, one should consider utilizing the contralateral CFA, brachial artery, radial artery, or SFA. Prior to puncturing the artery with the needle, sufficient local anesthesia should be administered subcutaneously and also around the femoral sheath. As most endovascular interventionists are right-hand dominant, generally, the needle is held and advanced to the puncture site with the right hand, while palpation of the pulse of the target artery is performed with the left hand. In addition to palpation, ultrasound and/or fluoroscopic guidance is helpful in difficult cases. Retrograde contralateral or ipsilateral approaches are commonly used for the treatment of various lesions, involving aortic, visceral, and iliac arteries. However, when treating the BTK lesion, an ipsilateral antegrade CFA approach may be selected due to the limited length of various catheters and balloons and better pushability. Bidirectional approaches (see below) via popliteal or tibial artery are often effective for the treatment of SFA or BTK CTO lesion. A retrograde brachial or radial artery approach is often preferred for the treatment of celiac or superior mesenteric artery disease because the angle between aorta and visceral branches is sharp.

When arterial access is obtained, a sheath is inserted into the vessel over the guidewire using the Seldinger technique. The guidewire should be advanced under fluoroscopic guidance to avoid accidental cannulation of the side branches. Most of the currently available endovascular devices, including guidewires, catheters, balloons, or stents, allow for delivery through a 6-Fr. sheath. It is important to choose an adequate sheath in order to avoid sheath-related complications. The diagnostic catheter is then deliverable via a sheath. It is important to place the image intensifier or the detector panel at the appropriate cranial-caudal and oblique angle to obtain a good image and outcome (see Chapter 60). Additionally, to achieve maximal support and

effective visualization with contrast, the sheath or catheter should be placed as close to the target lesion as possible. Systemic heparinization is desired once the decision is made to treat the lesion. Typically, 50 to 100 U/kg of heparin is administered via a venous bolus infusion, and the activated clotting time (ACT) is maintained at approximately 200 to 300 seconds during the endovascular procedure. For cerebrovascular intervention, the ACT should be maintained at above 250 seconds to prevent thrombus formation and brain infarction.

Lesion Crossing

Although there is no single standard technique, the most important principle is to pass the wire through the lesion via the true lumen. However, the techniques vary based on the location, degree of stenosis, presence or absence of CTO, or nature of the plaque. Due to the innovation of guidewires with hydrophilic coating, supportive devices, and new techniques, a stenotic lesion can be crossed almost in every case. A 0.035-inch hydrophilic wire is the wire of choice and has the ability to penetrate through hard plaques, although the wire tends to follow the path of least resistance which is the subintimal space. A 0.014- or 0.018-inch guidewire may be a better choice for highly stenotic or CTO lesions and if used along with support microcatheters, including the CXI (COOK Medical, Bloomington, Indiana), the Quick-Cross (Spectranetics, Colorado Springs, Colorado), or the TrailBlazer (Covidien, Plymouth, Minnesota), the chances of lesion crossing through the true lumen may increase. Intraluminal devices, as previously described, or ultrasound-guided techniques are also useful for passing through the true lumen. Furthermore, if the wire is inserted into the subintimal plane, it is possible to come back toward the true lumen by utilizing a reentry device. Additionally, the IVUS is a useful device to identify whether the wire is in the true lumen or not. Once the lesion is crossed and the wire enters the distal true lumen, as indicated by back bleeding, contrast injection via the catheter is performed to confirm that the wire is intraluminal.

Balloon Selection

A balloon is typically chosen based on the diameter of the reference vessel and the length of the lesion. Available balloons for various lesions are shown in Table 61.3. Currently balloons are available up to 30 cm in length and can be used to treat long segments of the SFA or BTK lesions with a single inflation. Most interventionists first verify the ease of expansion and stiffness of the lesion using an undersized-diameter balloon, and then upsize to an appropriately sized diameter balloon. In a severely calcified lesion, a conservative dilation balloon may be required to avoid rupture of the artery. The measurement of the reference vessel diameter is important to choose an appropriate balloon. Measurement with digital subtraction software, preoperative CT, IVUS, catheters with graduated markers, or using a predilation balloon as a reference are also useful for selecting the appropriate balloon size. Balloon shafts come in 80 cm to 150 cm. The shorter 80-cm shaft is suitable for the treatment of visceral, iliac, and proximal contralateral SFA lesions when approached from the CFA. Conversely, cerebral, contralateral popliteal, and BTK interventions via the CFA approach or visceral and iliac interventions via the brachial artery require a longer shaft.

TABLE 61.3 Commercially Available Balloon Size for Specific Artery

Lesion Location	Balloon Diameter (mm)	Balloon Length (cm)
Internal carotid artery	4-6	2
Common carotid artery	6-8	2-4
Vertebral artery	3-5	2
Subclavian artery	6-10	2
Axial artery	5-7	2-5
Brachial artery	2-4	2
Aorta	10-20	2-4
Celiac artery	5-8	2-4
Superior mesenteric artery	5-8	2-4
Renal artery	5-7	2-4
Common iliac artery	6-10	2-4
External iliac artery	6-8	2-10
Superficial femoral artery	5-7	2-15
Popliteal artery	4-6	2-4
Tibial artery	2-3	2-300

Balloon Placement

Contrast is injected though the sheath or catheter to accurately identify the lesion just before the balloon is placed. If difficulty is encountered during balloon passage due to severe stenosis or tortuosity of the access vessel, it may be necessary to exchange the wire for a stiffer wire, advance the sheath or guide catheter closer to the target lesion, or switch to a lower profile balloon or one with greater pushability.

Balloon Inflation and Completion Angiography

Preparation of the balloon is an important maneuver to avoid air embolization in the case of balloon rupture and visualization of the balloon under fluoroscopic guidance. The guidewire lumen of the balloon catheter is flushed with heparinized saline solution in the OTW balloon, and the guidewire lumen of SOE balloons should also be flushed from the distal end hole. The balloon is prepped by replacing preexisting air inside balloon with 25% to 50% strength contrast.

The balloon should be positioned so that the most severe stenotic lesion aligns with the center of the balloon. When inflated, the diluted contrast, commonly a 1 : 1 ratio of contrast agent and saline solution (undiluted contrast is typically used for 4-mm balloons or smaller), is used to inflate the balloon with the inflation device, and the balloon shape should be monitored with the fluoroscope in real time, confirming capture of the lesion during inflation. Additionally, based on a reference screen or by marking the reference vessel diameter on the screen, the operators need to avoid excessive overexpansion beyond the reference vessel diameter. Inflation of the balloon is typically

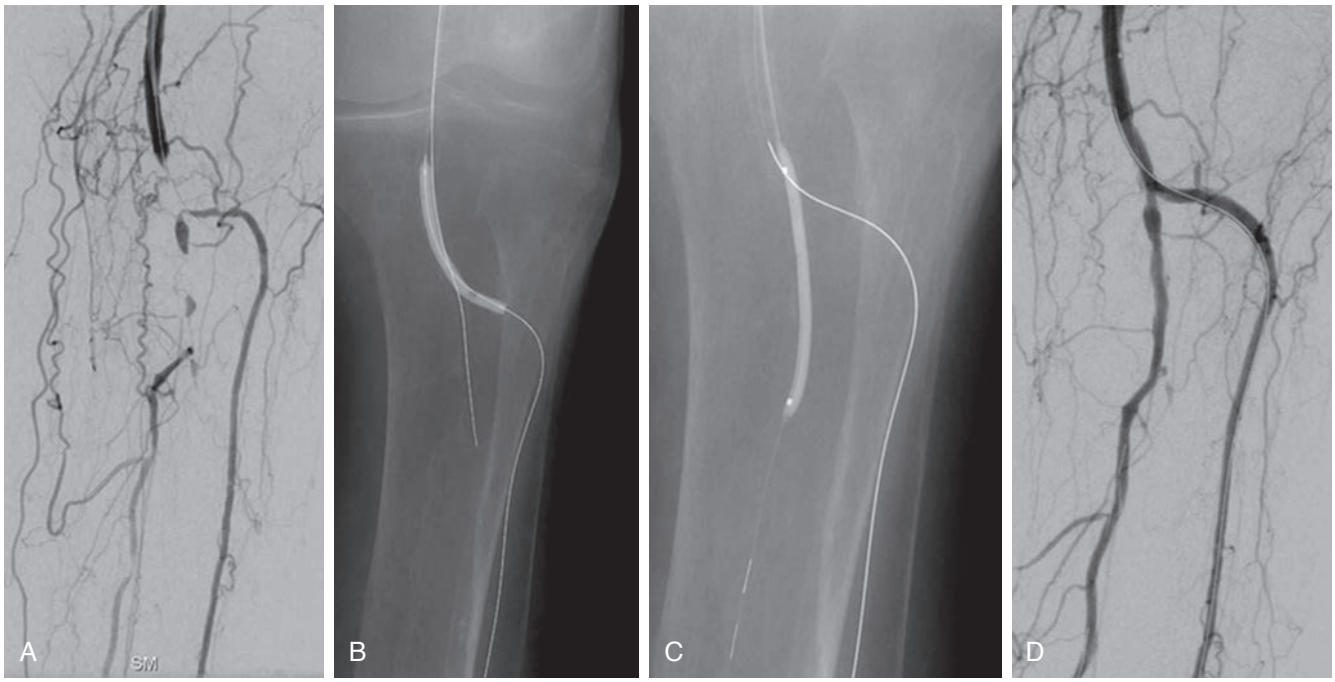

Figure 61.4 (A) Initial angiography shows a complex occlusive lesion of the below-the-knee arteries. (B and C) The wire is inserted to prevent an occlusion by a plaque shift. (D) Completion angiography shows an improvement in run-off.

performed for 30 to 60 seconds. Then, the balloon is deflated and inflated again for the same amount of time. While deflating, the balloon catheter should not be retracted into the sheath immediately since the remaining wings of the balloon may be caught by the tip of the sheath. It should be noted that there is a risk of vessel rupture when a patient complains of the severe pain during dilation of the balloon. The most important thing is to maintain guidewire position across the dilated lesion in case additional treatment is required. After the balloon catheter is removed, completion angiography is performed to evaluate the results of PTA.

Double Wire Technique

If cannulation of the target vessel cannot be accomplished with the wire, or the risk of nearby vessel occlusion due to plaque shift is anticipated, a double wire technique may be an effective option. For example, when cannulation of the SFA is attempted, the wire would be advanced first into the DFA, without entering the SFA. In this case, the sheath is inserted into the DFA first, and subsequently, the sheath is withdrawn to the bifurcation of the SFA and the DFA, maintaining the position of the DFA guidewire. A second thin wire is then inserted to cannulate the SFA. This technique has been applied to other lesions, such as renal interventions, and is known as nontouch isolation technique. For bifurcational lesions, the lesions are cannulated by two wires and the kissing balloon technique is used to prevent occlusion from plaque shift (Fig. 61.4).

Angiosome Concept

Most CLI lesions extend to the BTK area. According to the BASIL trial,[77] patients with a life-expectancy of less than 2 years

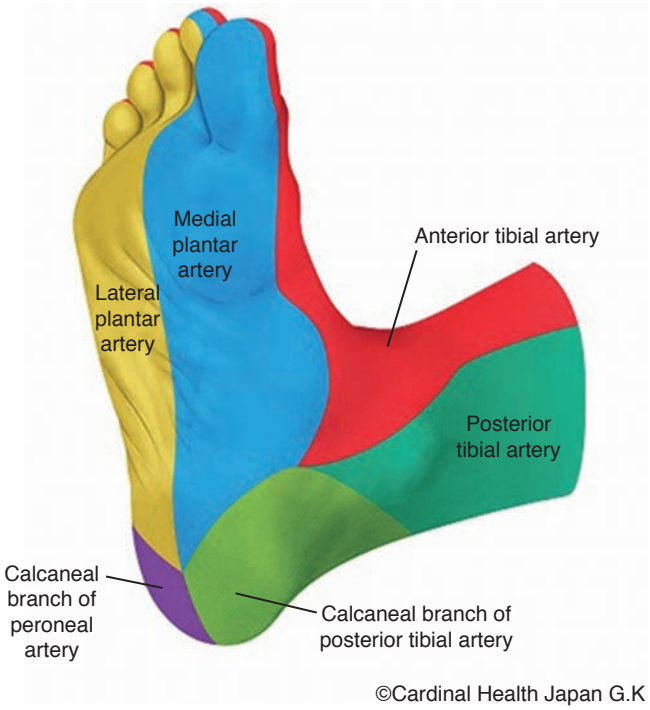

Figure 61.5 Angiosome concept.

are best treated with endovascular therapy. Taylor and Palmer[78] introduced the angiosome concept in 1987 (Fig. 61.5), which categorizes the limb into three vascular territories supplied by source arteries and has been clinically helpful in endovascular treatment. The six angiosomes of the ankle and foot are divided by the blood supply of the anterior tibial, posterior tibial, and

peroneal artery. For example, when treating gangrene of the great toe, it is most effective to revascularize the anterior tibial artery based on the angiosome concept. However, this concept has limitations in that angiosome varies among patients.

Dissection Grade

Arterial dissection often occurs after PTA, and may require a stent placement. Dissections after the PTA are classified into six grades:

Grade A is a small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material. *Grade B* is a filling defect parallel to the lumen of the vessel disappearing with the passage of contrast material. *Grade C* is a dissection protruding inside the lumen of the vessel persisting after passage of contrast material. *Grade D* is a spiral-shaped filling defect with delayed run-off of the contrast material in the distal vessel. *Grade E* is a persistent luminal filling defect with delayed antegrade flow. Grade F is a filling defect accompanied by total occlusion. Stenting is typically required with Grade C to F dissections.

Subintimal Angioplasty

The first subintimal angioplasty for an occlusive femoropopliteal artery was reported by Bolia and colleagues in 1989.[79] Subintimal angioplasty has become widespread to overcome long occlusive segments. With this technique, a guidewire is intentionally inserted into the subintimal plane to create a new track. The tip of a hydrophilic guidewire is formed into a loop shape above the level of the occlusive lesion. The wire is then advanced with a support catheter along the subintimal plane until the occlusive lesion is passed. The wire and catheter will naturally re-enter to the true lumen distal to the occlusion where the intimal flap is thin and is broken by the wire loop. The resistance of the guidewire in the subintimal plane disappears once it reenters into the true lumen. Recanalization of the true lumen is confirmed by injecting contrast from the tip of the catheter or by IVUS. The recanalization segment is then dilated with an appropriately sized balloon. Typically, stenting is not required with this technique, and it should only be used in cases of flow-limiting dissection or severe elastic recoil. Subintimal angioplasty is technically successful in approximately 80%, and limb salvage is achieved in over 80%, with primary patency at 12 months of 60% to 70%,[80] although subintimal angioplasty fails in approximately 20% of the patients. The most common reason for failure is inability to re-enter the true lumen. Re-entry devices were developed to overcome such failures.

CART

If re-entry into the true lumen is not possible and if re-entry devices are not available, the controlled antegrade and retrograde subintimal tracking (CART) technique may be useful. CART technique utilizes a bidirectional approach, in which the two wires are simultaneously inserted via antegrade and retrograde access. For example, in an SFA CTO lesion, the wire is first passed into the subintimal plane in a prograde manner. If it is impossible to redirect the wire into the true lumen, then a retrograde wire is inserted from a site distal to the lesions, including the distal SFA, tibial, or pedal artery, to approach the target lesion. The distal, prograde wire is also placed into subintimal space using directional catheters until both wires cross each other within the subintimal space. Then, PTA balloons are inserted over each wire and placed next to each other. By inflating both balloons, the intimal flap or the septum separating the two balloons will be broken, allowing the antegrade wire to enter the subintimal plane that eventually leads to the distal true lumen. PTA and stenting should be performed in the same manner as described earlier (Fig. 61.6).

STENTING

Indications

In treating iliac lesions, the primary patency for primary stenting at 5 years was superior to selective stenting. This difference was significant in complex lesions categorized as TASC C or D lesions.[81] Selective stenting or provisional stenting is performed as a bail-out procedure including dissection, residual stenosis, presence of residual pressure gradient, and acute occlusion following the PTA.

Dissection

Some degree of dissection commonly occurs following PTA. Angiography and IVUS are useful for the assessment of dissection. If the contrast flow is impeded by the flow-limiting dissection, or if a false channel is created, a stent should be placed. Extension of the dissection into the disease-free segment beyond the target lesion also requires stenting.

Residual Stenosis

Residual stenosis is typically defined as over 30% stenosis of the lesion by angiographic measurement following PTA. In such cases, repeat PTA with a longer inflation time or additional stenting should be considered.

Pressure Gradient

A systolic pressure gradient that exceeds 10 mm Hg across the lesion after PTA usually requires repeat PTA or stent placement.

Acute Occlusion

If acute occlusion is encountered during endovascular therapy, placement of a stent is usually necessary. If acute occlusion occurred in a lesion in the so-called no stent zone including CFA, popliteal artery, or BTK lesions, justification whether stent placement or not is controversial. Therefore, it is best to perform interventions of such lesions where surgical backup is available.

In-Stent Restenosis

Recurrent stenosis after stenting is referred to as in-stent restenosis (ISR) and is usually caused by intimal hyperplasia. Although

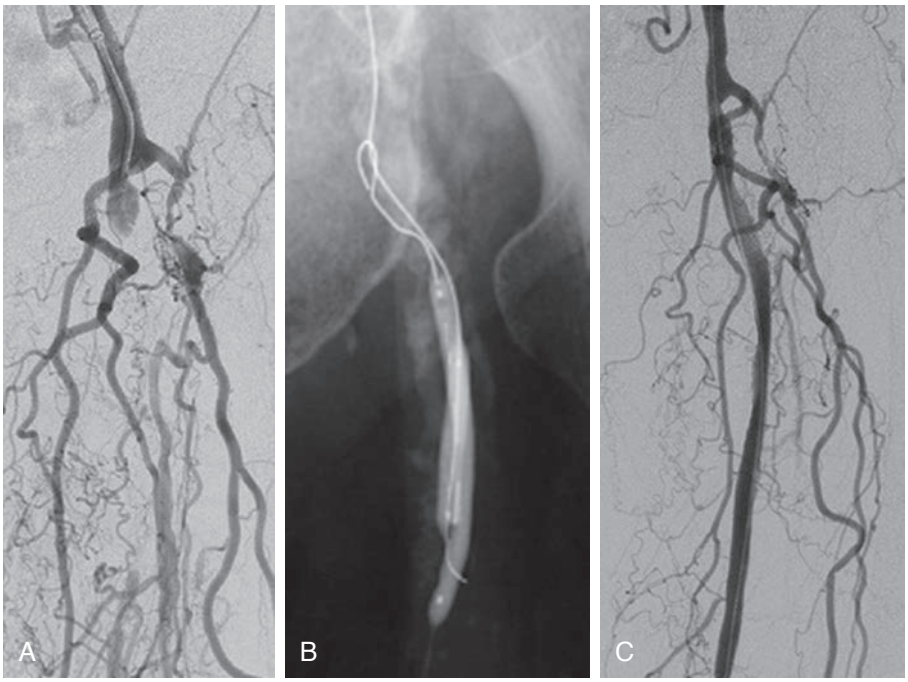

Figure 61.6 (A) Initial angiography shows an occlusive lesion of the proximal superficial femoral artery. (B) Two wires and balloons are inserted via both antegrade femoral artery and retrograde distal superficial femoral artery access sites (CART technique). (C) Completion angiography.

various treatments have been performed, including cutting balloon, atherectomy, stenting, and covered stent placement, due to absence of good quality data, it is difficult to make solid recommendations.

Stent Fracture

Stent strut fractures are commonly categorized into five types. *Type 0* means that there are no strut fractures. *Type I* is a single strut fracture only. *Type II* involves multiple single strut fractures that can occur at different sites. *Type III* involves multiple strut fractures resulting in complete transection of the stent, without displacement of the stent segments. Finally, *type IV* involves multiple strut fractures resulting in displacement of segments of the stent, including spiral fractures.

Stent Selections

The pros and cons of using a balloon-expanding stent versus a self-expanding stent are outlined in Table 61.4. Short or focal lesions are optimally treated with balloon-expanding stents because balloon-expanding stents can be placed with accuracy, expanded further using a larger balloon, and have high radial force which may be necessary to treat a calcified lesion. The balloon-expanding stents are often selected to treat ostial lesions of the visceral or aortoiliac artery since these lesions require accurate placement of the stent and since plaques are often calcified. When treating orificial common iliac lesion, a "kissing stent" technique may be necessary to prevent obstruction of the contralateral artery from plaque shift. In contrast, the self-expanding stents, which have the flexibility and kink resistance, are suitable for long and tortuous lesions along with superficial arteries that are subjected to external compression. Self-expanding stents are typically used for internal carotid, external iliac, SFA, and dissections secondary to stent graft insertion.

TABLE 61.4 The Characteristic of Balloon-Expanding and Self-Expanding Stents

	Balloon-Expanding Stent	Self-Expanding Stent
Pros	Precise deployment High radial force Further expansion with larger balloons Radiopaque	Flexibility Long length Kink resistance Ability to clamp
Cons	Rigid Short length Prone to fracture Less kink resistance	Low radial force Less precise deployment Insufficient radiopacity
Indications	Ostial lesions Focal lesions Calcified lesions Resistant lesions	Superficial lesions Long lesions Tortuous vessels Dissections

Technique of Balloon-Expanding Stents

The stent size is selected based on the reference vessel diameter. Although the stent diameter is typically selected to be 5% to 10% oversized compared to the reference vessel, it should also be determined based on the nature of the lesion including degree of calcification or thrombus. An adequately sized long sheath or guiding sheath is selected to pass the lesion. In order to prevent dislodgment of the balloon-mounted stent, the lesion should be adequately predilated and the tip of the long sheath should be advanced beyond the lesion using a dilator of the sheath or the PTA balloon to act as a dilator. After insertion of the sheath, the wire is advanced under fluoroscopic guidance. Once beyond the lesion, contrast is injected from the sheath

or IVUS interrogation is performed to confirm that the wire is located in the true lumen. The location of the lesion is then marked, and the sheath is advanced using the dilator or the balloon until it crosses the lesion. In severe stenotic or CTO lesions, an undersized predilation balloon is often used to facilitate insertion of the stent and is also useful in selecting the appropriately sized stent. A stent is then passed through the sheath across the lesion. After additional contrast is injected through the sheath to confirm proper stent location, the sheath is withdrawn to expose the stent. Then, the balloon is inflated to expand the stent with adequate pressure under fluoroscopic monitoring. During inflation, a "doggie bone" shape, with the proximal and distal ends of the balloon expanding, initially confirms that the stent has not dislodged. If a stent is not mounted properly on the balloon, then it should be exchanged with a new stent. A completion angiogram is performed to check for residual stenosis and adequate stent apposition. IVUS may be useful where visualization with fluoroscope is difficult. The wire purchase must be maintained until the procedure has been completed. Balloon-expanding stents can be further dilated to a certain extent with a larger balloon if necessary.

Technique of Self-Expanding Stents

The best features of self-expanding stent are the flexibility and the long length. The selected stent should be 1 to 2 mm larger than the reference vessel because the stent cannot be expanded beyond the stated diameter. As with balloon-expanding stents, after the wire is across the lesion, predilation is performed. Unlike the balloon-expanding stent, the introducer sheath is not always required to cross the lesion since self-expanding stents are stored in a covering sheath and there is no risk of stent dislodgement. The stent is deployed by withdrawing the covering sheath. Fluoroscopic guidance is necessary during deployment because most self-expanding stents tend to "jump" forward as they are unsheathed. Self-expanding stents cannot be resheathed once deployed, with the exception of the Wallstent (Boston Scientific, Natick, Massachusetts). After stent placement, postdilation with appropriate diameter and length is required.

The Viabahn (W.L. Gore & Associates, Flagstaff, Arizona), a newer endograft for SFA lesions, has been indicated for the treatment of long lesions due to better results. In VIASTAR trial, as previously described, the primary patency of this endoprosthesis was superior to bare metal stents even if the lesion exceeded 20 cm. The Viabahn may become an alternative for bypass surgery for the patients with serious comorbidities and long, complex lesions.

HYBRID THERAPIES

A hybrid approach utilizing both endovascular and surgical repair has currently gained wide acceptance, and includes debranching techniques, bypass or endarterectomy with stent placement, or application of an "elephant trunk" with endografts following arch replacement. In the periphery, an iliac lesion with a CFA occlusion is often best treated with an iliac stent and CFA endarterectomy (Fig. 61.7). The long term patency of the hybrid repair has been demonstrated to be comparable to open surgical repair.[82,83] Patients undergoing hybrid therapy for TASC C/D lesions experienced a shorter intensive care unit (ICU) stay and hospital stay than open surgery. The authors recommended that hybrid therapy should be performed for a high surgical risk patient regardless of TASC classification. Although stenting may be acceptable treatment for complex iliac lesions, it remains controversial whether TASC C/D infrainguinal lesions should be treated by endovascular therapy.

EMBOLIZATION

Technique of Coil Embolization

In order to minimize the risks and maximize the efficacy of coil embolization, it is best to position both the wire and the catheter as close to the target vessel as possible. Catheters with various shapes are useful for cannulating the target vessel, and the microcatheter which can be inserted into a diagnostic catheter enables it to reach target vessels that 4-Fr. catheters cannot reach due to tortuosity and distance of the access vessel. Once the catheter is cannulated selectively, a coil, plug, or liquid embolization can be performed.

Coil embolization is currently widely used for the treatment of peripheral and cerebral vascular diseases. In the periphery, coils are typically used for the treatment of a visceral aneurysm, prevention of type II endoleaks during stent graft procedure, or treatment of persistent endoleaks after stent graft placement. Coil embolization for a saccular aneurysm with a narrow neck requires packing, which commonly consists of three steps: "Framing," "Filling," and "Finishing" (Fig. 61.8A). The coil for the purpose of framing is typically oversized by approximately 20% of the target diameter. Equal size to the aneurysm or undersized coils is then deployed to fill and thrombose the aneurysm. An additional, smaller coil may be inserted into the remaining free space to finish the coiling.

Stent-Assisted Coil Embolization

Stent-assisted coil embolization is an effective technique for treating a wide-neck aneurysm and to protect the parent vessel. First, a bare metal stent with 10% to 20% oversize is placed in the parent vessel across the neck of the aneurysm. A microcatheter is then delivered into the aneurysm through the stent strut. The coils of adequate size are then used to pack into the aneurysm. This technique allows for safe embolization since the stent protects the parent vessel from protruding coils (see Fig. 61.8B-F). Both pushable and detachable coils are currently available. Detachable coils allow one to reposition the coil multiple times, thereby resulting in precise deployment. However, they are more expensive and also usually create a strong artifact on CT scans. The pushable coil cannot be repositioned and precise sizing and deployment can be challenging especially if the landing zone is short.

Coil Embolization for Type II Endoleak

Persistent type II endoleaks are usually treated by embolization with coils or embolic agents. The complex connections

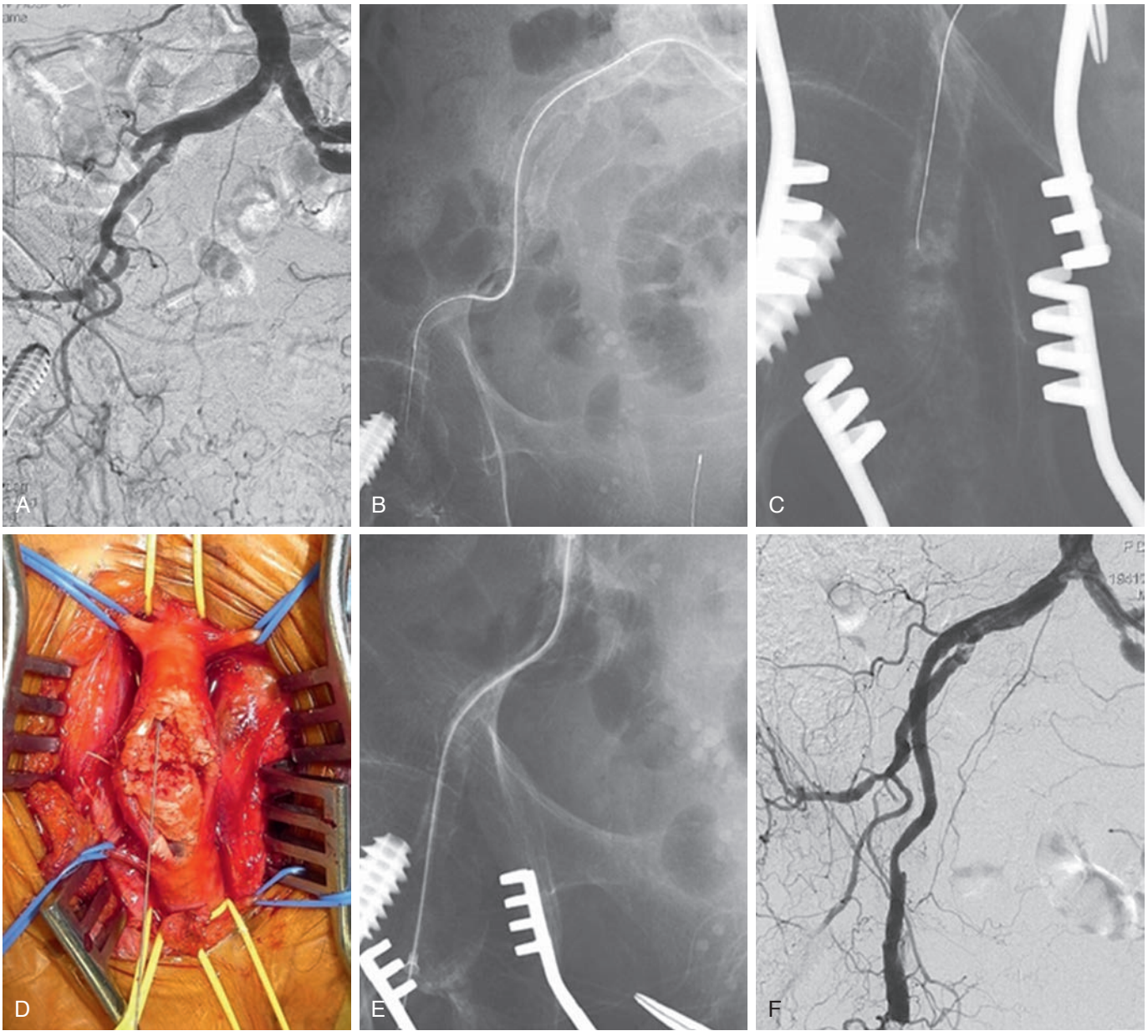

Figure 61.7 Hybrid Treatment. (A-C) The wire is inserted via the contralateral femoral artery to treat the iliac occlusion. When the wire reaches the common femoral artery, the wire is stabilized at that position. (D) Endarterectomy is performed for the common femoral occlusion and the wire is caught. (E) The new sheath is inserted via the common femoral artery following endarterectomy to make a "pull-through" wire. (F) The iliac stent is deployed.

of the inflow and outflow vessel in many persistent type II endoleaks are one of the reasons these endoleaks are difficult to treat. Even if some inflow and outflow lumbar arteries are successfully embolized, some type II endoleaks will not resolve since there are remaining feeding arteries. There are two strategies to treat type II endoleak following endovascular aortic repair: transarterial approach and translumbar approach. Although it is unclear which approach is better, the most important principle in the treatment of type II endoleaks is to embolize the nidus of endoleak within the aneurysm sac and interrupt the communications between multiple inflow and outflow vessels.

Technique of Vascular Plugs

A vascular plug allows precise and secure deployment. It is increasingly used for the treatment or prevention of type II endoleaks during stent graft procedures. Embolization of the left subclavian artery during endovascular thoracic aneurysm repair or embolization of the internal iliac artery during endovascular aneurysm repair to prevent of type II endoleak are ideal indications for the vascular plug. When deploying a vascular plug, the tip of the corresponding sheath must be inserted beyond the intended deployment site. The plug, in the folded state, is then advanced to the target location through the sheath and

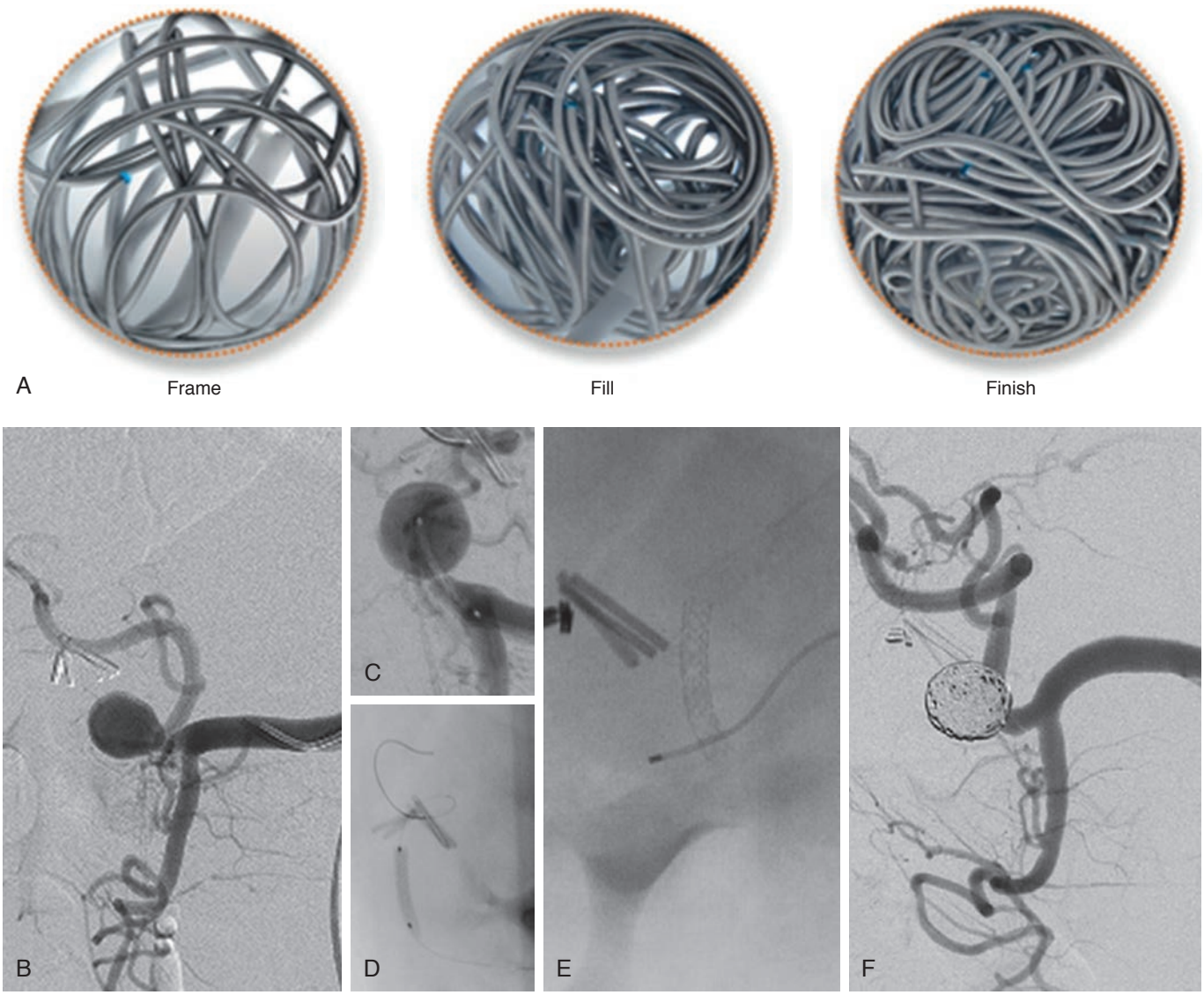

Figure 61.8 (A) Basic technique for embolization packing with coils. (B) Initial angiography shows a common hepatic artery aneurysm near the branch of the gastroduodenal artery. (C-E) A coronary stent is inserted to maintain hepatic vessel flow, and a microcatheter is inserted into the aneurysm via a stent strut. (F) Completion angiography following coil embolization.

by unsheathing the plug, is deployed and can be detached from the wire. The advantage of the plug includes secure and accurate occlusion of the vessel and may be more cost-effective than using multiple detachable coils. The fact that it requires a 5- to 6-Fr. sheath to be intubated across the target vessel could be traumatic in certain conditions or even impossible to use. In such situations, coil embolization that can be performed in an atraumatic fashion should be selected.

When performing embolization in the subclavian artery during thoracic endovascular repair, it is important to deploy the coils or plug proximal to the vertebral artery. When done in the internal iliac artery, it is best to deploy it proximal to the iliolumbar artery to maintain the distal collateral circulation to minimize complication.

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62 CHAPTER

Laparoscopic and Robotic Aortic Surgery

JEAN-BAPTISTE RICCO and FABIEN THAVEAU

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INTRODUCTION

As in other surgical specialties, minimally invasive laparoscopic techniques have evolved progressively in vascular surgery with a number of reports describing laparoscopic aortic repair for occlusive and aneurysmal disease.[1-3] There are no large randomized trials to support laparoscopic aortic repair over open or endovascular surgery for abdominal aortic aneurysm (AAA) or aortoiliac occlusive disease (AIOD). The lack of trained vascular surgeons with the skills to perform laparoscopic aortic repair and the improved outcomes after aortoiliac stenting and endovascular aneurysm repair (EVAR) have led some to question the need for laparoscopic aortic repair, although there is a subset of patients who will benefit from a potentially less invasive alternative to open repair when EVAR or iliac stenting are not in their best interests. In this setting, laparoscopic aortic surgery may also be considered as a cost-effective option.

Here we describe the current laparoscopic techniques used for aortic reconstruction, including hand- and robot-assisted laparoscopic surgery, their results, and the conditions required to master these procedures.

TOTAL LAPAROSCOPIC AORTIC SURGERY

The following four approaches have been described to perform total laparoscopic aortic bypass:

- Retrocolic prerenal transperitoneal approach
- Retrocolic retrorenal transperitoneal approach

Abstract

This chapter describes and evaluates the results of different laparoscopic techniques used to treat aortic disease, including (1) total laparoscopic aortic surgery, (2) laparoscopy-assisted procedures including hand-assisted laparoscopic surgery, and (3) robot-assisted laparoscopic surgery, with their current indications.

Results of these techniques are analyzed in a systematic review of the clinical series published with complete information concerning operative time, clamping time, conversion rate, length of hospital stay, morbidity, and mortality.

Heterogeneity of the studies and selection of the patients made comparison with current open or endovascular surgery difficult. Analysis of these series shows that laparoscopic aortic surgery can be performed safely provided that patient selection is adjusted to the surgeon's experience and conversion is liberally performed. The future of this technique in comparison with endovascular surgery is still unknown, and it is now time for multicenter randomized trials to demonstrate the potential benefit of this type of surgery

Keywords

laparoscopy
laparoscopic aortic surgery
laparoscopic aortic bypass
robotics
robotic aortic surgery

- Combined transperitoneal and retroperitoneal approach
- Retroperitoneal approach

Retrocolic Prerenal Transperitoneal Approach for Aortoiliac Occlusive Lesions

The transperitoneal procedure described by Dion et al.[4] and simplified by Coggia et al.[2] involves exposure of the aorta by a left prerenal colon dissection. The patient is placed in the dorsal decubitus position with an inflatable pillow under the left flank. The left arm remains free and the right arm is placed on an armrest. The lower extremities are flexed at 30 degrees and attached parallel to each other. Two supports must be placed on the right side of the thorax and flank in order to stabilize the patient when the table is titled to the right (at 45 degrees) and the pillow is inflated (to 35 degrees). After these maneuvers (i.e., tilting and inflation), the patient is in the complete right lateral decubitus position (Fig. 62.1). It is possible to move the patient from the right lateral decubitus position, used during exposure of the aorta, to the dorsal decubitus position for exposure of the femoral arteries, simply by tilting the operating table.

The operating surgeon and first assistant stand in front of the patient's abdomen and the second assistant stands opposite the operating surgeon. A pneumoperitoneum is insufflated up to 14 mm Hg through a Veress needle inserted in the left hypochondrium. A 45-degree endoscope is positioned on the left anterior axillary line below the costal margin. Five trocars are introduced under visual control after establishing a pneumoperitoneum. Two operating ports are placed 6 to 7 cm apart on the left transrectal line parallel to the midline (port no. 2 for scissors and needle holder and port no. 3 for fenestrated forceps). Two trocars for the first assistant are introduced in the left iliac fossa and on the midline 5 cm from the pubis (port no. 4 for suction catheter and port no. 5 for fenestrated forceps followed by the distal clamp). The last trocar (port no. 1) is positioned on the midline 2 cm below the xiphoid process for the proximal aortic clamp (Fig. 62.2).

The left laterocolic approach involves left colic dissection to achieve prerenal exposure of the aorta. The table is tilted as far as possible to the right (i.e., 45 degrees) and the pillow is inflated to enhance the right lateral decubitus position by 30 degrees. The Toldt fascia is incised from the left colic angle to the mesosigmoid to allow complete dissection of the left mesocolon. After identification of the genital vein, prerenal dissection is continued to the left renal vein. Because the patient is in the right lateral decubitus position, the small bowel and left mesocolon drop to the right side of the abdomen (Fig. 62.3). The mesocolon is then attached to the abdominal wall with transparietal sutures to form an apron providing stable exposure of the aorta.[4]

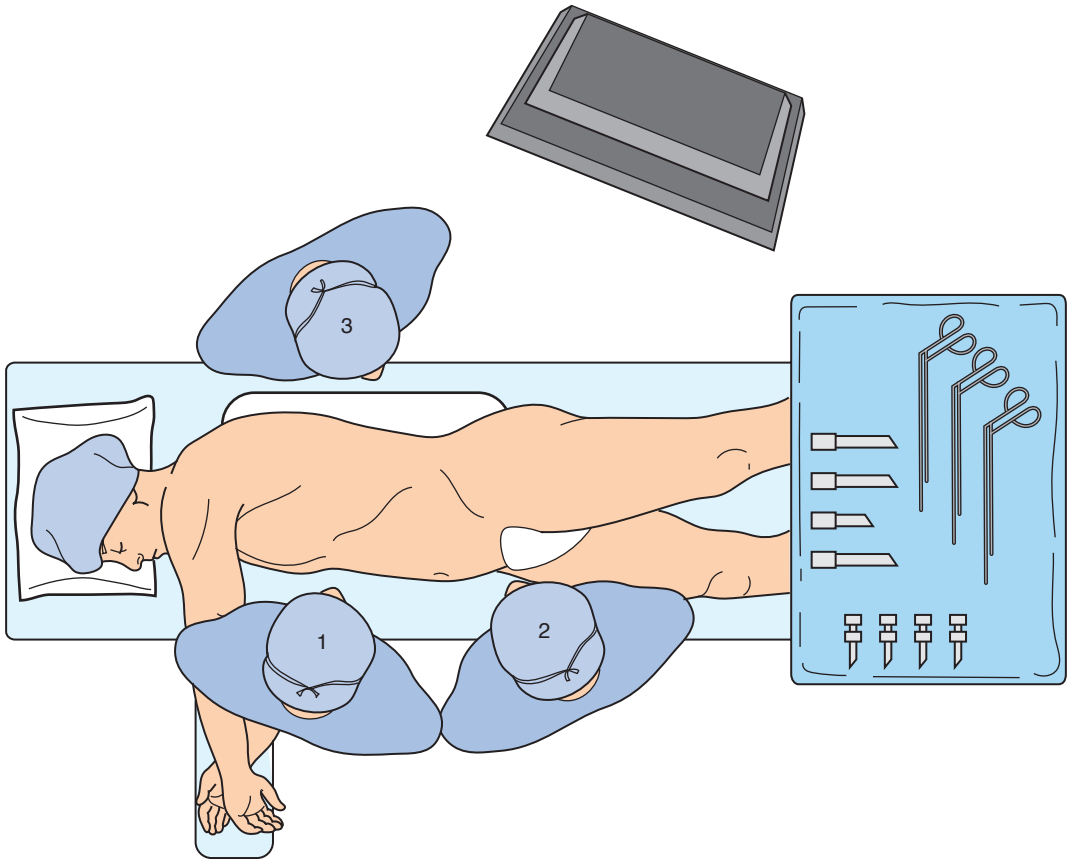

Figure 62.1 Patient in right lateral decubitus position for a total laparoscopic retrocolic transperitoneal approach. *1*, Operating surgeon; *2*, first assistant; *3*, second assistant.

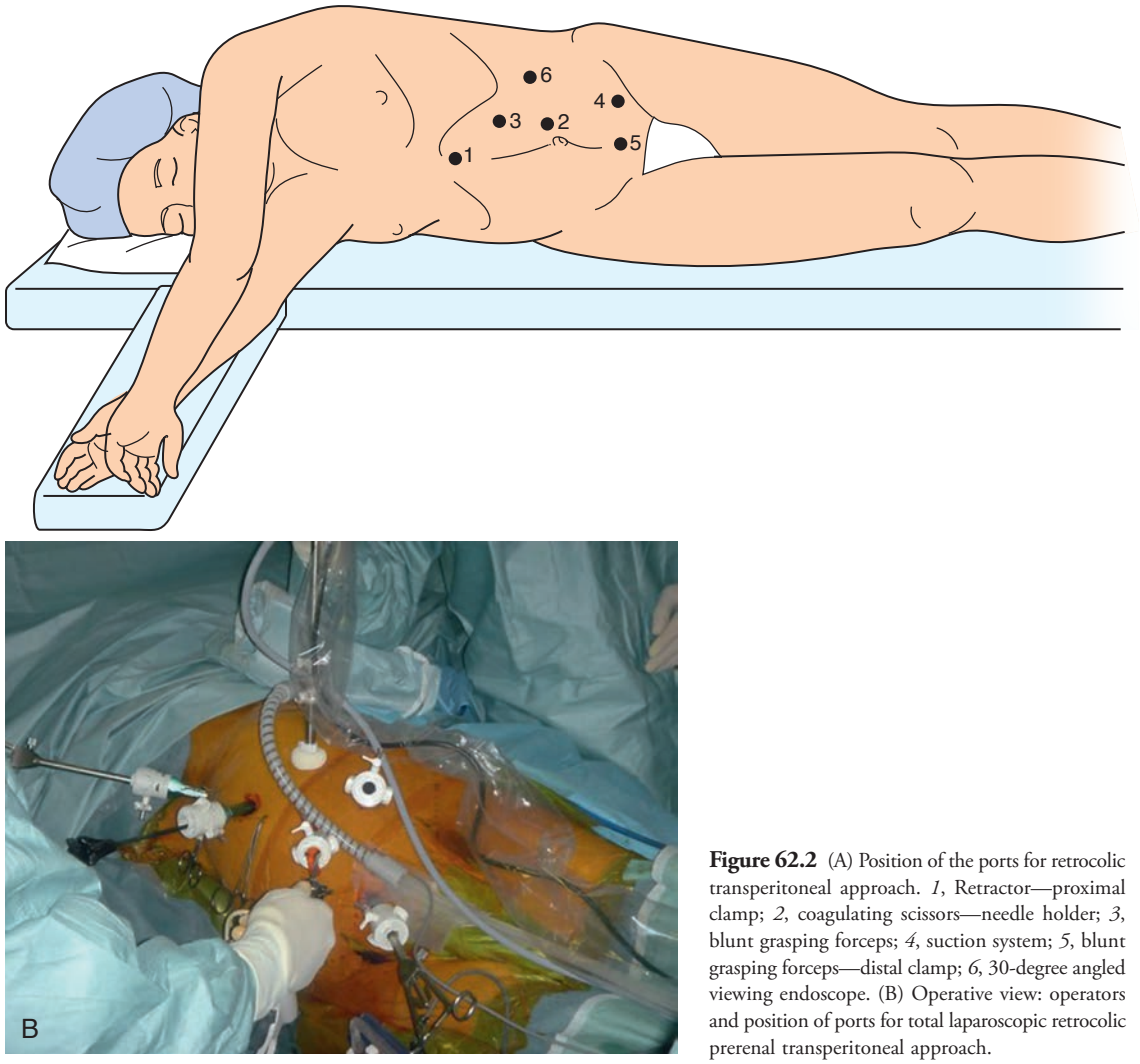

Figure 62.2 (A) Position of the ports for retrocolic transperitoneal approach. *1*, Retractor—proximal clamp; *2*, coagulating scissors—needle holder; *3*, blunt grasping forceps; *4*, suction system; *5*, blunt grasping forceps—distal clamp; *6*, 30-degree angled viewing endoscope. (B) Operative view: operators and position of ports for total laparoscopic retrocolic prerenal transperitoneal approach.

In case of extensive infrarenal aortic calcifications, mobilization of the renal vein is necessary to expose the juxtarenal aorta (Fig. 62.4). Dissection is then extended to the common iliac arteries.

For exposure of the femoral arteries, the table is rotated to the left and the pillow deflated. After conventional femoral exposure, the table is again tilted to the right to allow introduction of the bifurcated prosthesis through one of the ports. The right branch of the prosthesis is tunneled in the anatomical position before making the proximal anastomosis. The extremity of the left branch is ligated and left in the abdomen.

Aortic clamping is performed with laparoscopic clamps introduced through ports no. 1 and no. 5, which stabilize the left colon during completion of the proximal anastomosis. Anastomosis between the aorta and prosthetic graft is made by two running sutures using 3/0 or 4/0 polypropylene. Suturing is performed using an 18-cm polypropylene 3/0 suture with one end previously sutured to a pledget to avoid having to tie the first knot (Figs. 62.5 and 62.6). In case of an end-to-end aortic anastomosis, closure of the infrarenal aorta is accomplished with a double running polypropylene 3/0 suture. A technical alternative may be the use of an automatic stapler without cutting knife (Endopath ETS-Flex45, Ethicon , Somerville, New Jersey) to safely close the distal aortic stump. This alternative saves time on laparoscopic suturing but, to be effective, requires a moderately calcified aortic wall.

The left branch of the prosthesis is then tunneled with the help of an aortic clamp introduced through the left groin. The tip of the clamp is located under laparoscopic control and routed behind the left ureter. Femoral anastomoses are performed conventionally on a patient in dorsal decubitus position. After removing the clamp, the surgeon decreases the gas pressure to 6 mm Hg to check the hemostasis of the aortic anastomosis and reveal any venous bleeding hidden by the high-pressure pneumoperitoneum. The mesocolon is then repositioned under laparoscopic control to separate the graft from the bowel. This retrocolic prerenal approach achieves an adequate aortic exposure and provides a large operating space. The small bowel falls to the right part of the abdomen by positioning the patient in a right lateral decubitus position with the left mesocolon acting as a peritoneal apron.

Retrocolic Retrorenal Transperitoneal Approach

The retrocolic prerenal transperitoneal approach is used in most standard cases. However, in very thin patients, where dissection of the Toldt fascia is impossible, or in patients with previous left kidney or colon surgery or for suprarenal aortic clamping, a transperitoneal left retrorenal approach is preferred.[5] In this case, the dissection is conducted by elevating the left colon and the left kidney with section of the renoazygos lumbar vein to achieve a right medial visceral rotation.

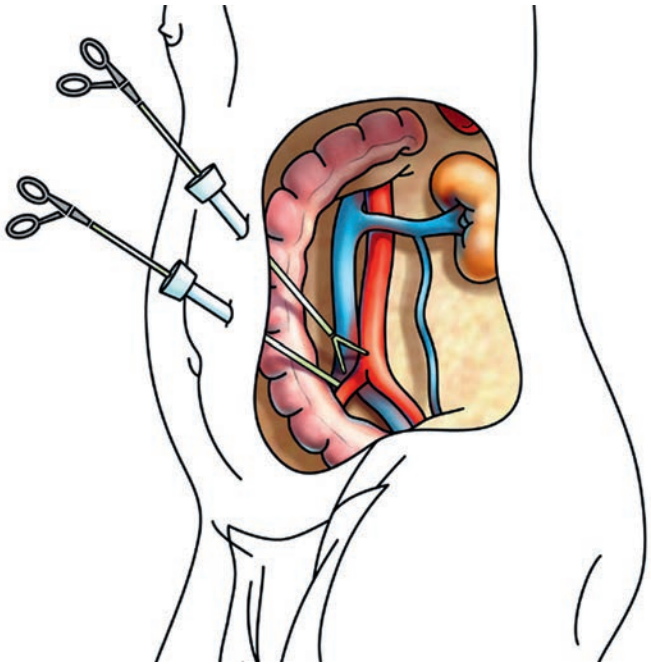

Figure 62.3 Aortic exposure through a left retrocolic prerenal approach. The patient is in right lateral decubitus. The intestinal loops collect on the right side of the abdomen, with the mesocolon forming an apron. This technique provides a stable exposure of the aorta.

Specificity for Abdominal Aortic Aneurysm

The retrocolic retrorenal transperitoneal approach is used most often for total laparoscopic aortic aneurysm repair, particularly in patients with a juxtarenal AAA.[5] After the aorta is clamped, a stitch is placed into the aneurysm's wall and pulled out through the abdominal wall to maintain the aneurysmal sac open. The right iliac clamping is performed through an infraumbilical trocar and left iliac clamping through another trocar inserted in the left iliac fossa. A bulldog clamp serves to occlude the inferior mesenteric artery. Mural thrombus is removed in a

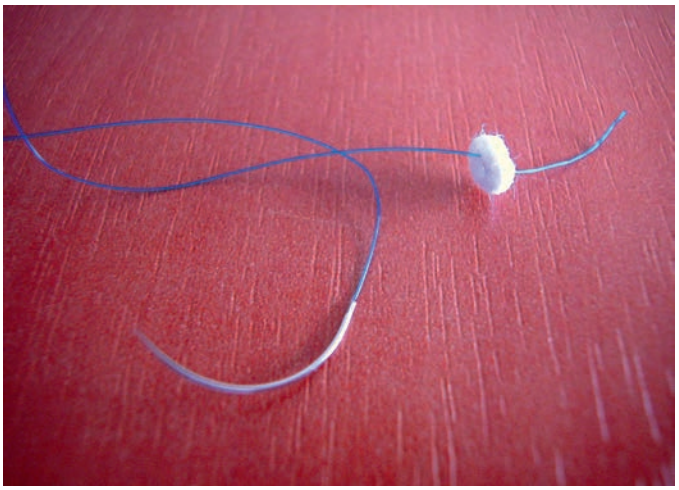

Figure 62.5 Aortic anastomosis performed with a prepared 18-cm polypropylene 3/0 suture with one end sutured to a pledget to avoid having to tie the first knot.

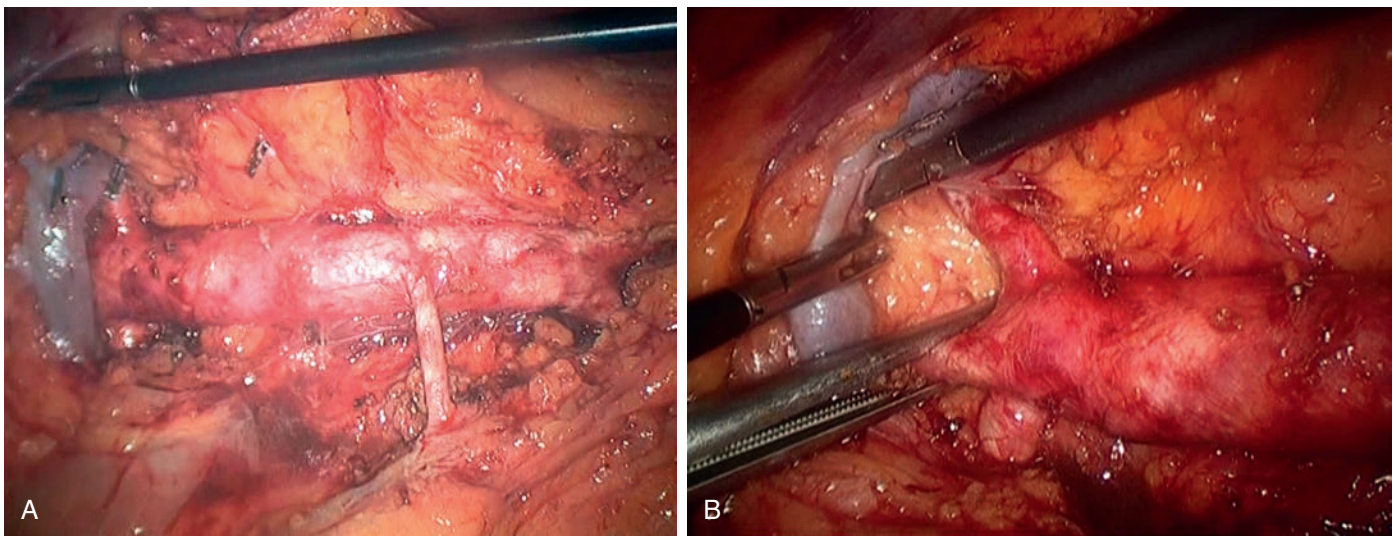

Figure 62.4 (A) Complete exposure of the aorta, iliac arteries, and inferior mesenteric artery through a left retrocolic prerenal approach. (B) Cross clamping of the suprarenal aorta for extensive occlusive disease and calcification of the infrarenal aorta (same approach).

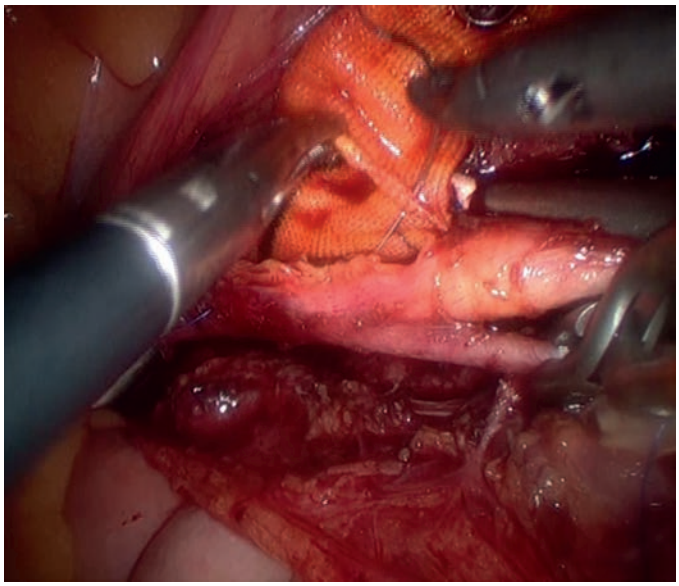

Figure 62.6 End-to-side totally laparoscopic aortic anastomosis with a 3/0 polypropylene running suture using curved jaws and axial handle needle holder.

container. Lumbar arteries are controlled with 3/0 polypropylene stitches as described in the Creech technique or by external hemoclips or staples. Anastomoses are performed as previously described.[6]

Combined Transperitoneal and Retroperitoneal Approach

This approach was first described by Dion.[7] The main feature of the technique is the creation of a peritoneal apron that retains the intestinal loops without reducing the size of the operating cavity. A 10-mm trocar is introduced at the level of the umbilicus to establish the pneumoperitoneum at a pressure of 12 mm Hg. The patient is then placed in the Trendelenburg position at 10 degrees with the table tilted to the right. As initially described by Dion, the technique involves two distinct retroperitoneal and transperitoneal maneuvers for dissection of the left parietal peritoneum and attachment to the wall by three transparietal sutures to form a peritoneal apron. The procedure begins with an incision of the left parietal peritoneum about 8 cm anterolateral to the Toldt fascia. Dissection is followed in front of the kidney up to the renal vein. The infrarenal aorta proximal to the inferior mesenteric artery is then dissected. The surgeon moves to the patient's left side to complete the procedure. The apron is then attached to the wall to keep the bowel out of the operating field. As previously described, this technique was subsequently simplified by Coggia.[8]

Retroperitoneal Approach

This laparoscopy-assisted technique with a short laparotomy to facilitate the aortic anastomosis was first described by Said et al.[9] and developed by Edoga et al.[10] for AAA repair. The patient is placed in a right lateral decubitus position as for the retrocolic transperitoneal approach. The viewing endoscope is introduced through a 15-mm incision above and medial to the iliac crest using the open retroperitoneoscopic technique with a prior hand dissection of the retroperitoneal space. This dissection should be extended up to the midline to avoid peritoneal tears. Although rarely used, the retroperitoneal procedure is a suitable alternative when the transperitoneal procedure is contraindicated in patients with hostile abdomen and peritoneal adhesions or when a complete exposure of the left common iliac artery is needed.[11] The main advantage of the retroperitoneal route is to exclude the visceral organs from the operative field, albeit at the expense of a smaller working space the risk of peritoneal tears. One reason that this surgical approach is rarely used for aortoiliac procedures is diffusion of the gas through the peritoneum, thus creating a "passive" pneumoperitoneum, which progressively replaces the pneumoretroperitoneum and reduces the working space.

HAND-ASSISTED LAPAROSCOPIC AORTIC SURGERY

Hand-assisted laparoscopic surgery (HALS), which enables the surgeon to introduce his nondominant hand through a special port while maintaining the pneumoperitoneum, has been routinely used by some authors for aortic occlusive lesions or AAA repair.[12-15] The patient is placed in the supine position. A midline incision of 7 to 8 cm is performed to allow placement of the port-site device. Through this port, the hand of the surgeon is introduced into the abdominal cavity without any carbon dioxide loss. The incision site is carefully selected to gain vision of the assumed anastomotic sites. A 10-mm trocar is then placed along the midline below the umbilicus with introduction of a 30-degree laparoscopic optic and for carbon dioxide insufflation to create a pneumoperitoneum of 12 mm Hg. At that point, with the nondominant hand, the surgeon pushes away the bowel loops to the right by tilting the operating table to the right and in the Trendelenburg position. A trocar is then introduced lateral to the border of the left rectus abdominis muscle for dissection of the infrarenal aorta and another trocar is inserted lateral to the border of the right rectus abdominis muscle. After laparoscopic dissection of the aorta, the abdominal cavity is deflated and the special port-site device removed, the bowel being left in place in the right abdomen with the aid of laparoscopic sponges. The incision is kept open with an autostatic retractor. The proximal anastomosis between the aorta and the graft is performed under direct vision with conventional instruments. If a distal anastomosis on the external iliac is planned, an oblique suprainguinal incision is done to expose the artery. HALS has proven in many studies to be a reliable technique to overcome the technical challenge of total laparoscopy aortic surgery, mainly the performance of vascular anastomoses. It may have increased the feasibility and reproducibility of this type of surgery, but its invasiveness compared with total laparoscopic aortic repair is a drawback.

TOTALLY ROBOTIC AORTIC AND ROBOT-ASSISTED PROCEDURES

The robot may be used in laparoscopy-assisted procedures as well as in total laparoscopic surgery.[16] Its usefulness becomes more evident when suturing the aortic anastomosis because robotic arms support five degrees of freedom. Optimal placements of the robot's arms are usually in ports located on the left axillary line.[17-21] The use of robots in vascular surgery is thought to result in a better surgical performance by overcoming the long learning curve of vascular suturing. But the system also has some disadvantages, including its complexity and high cost. The robot may be used in laparoscopy-assisted procedures as well as in total laparoscopic surgery.[16]

With more than 3000 Da Vinci robots (Intuitive Surgical, Sunnyval, California) in use around the world, robotic surgery has become unavoidable in the surgical field.[22]

Robotic aortic surgery takes the fundamentals of laparoscopic surgery.

The initial uses of robots have focused on the performance of anastomoses[23] and arterial reconstructions, but the system is now increasingly used for completing the entire intervention, from the incision to aortic reconstruction.[24]

Totally Robotic Aortic Surgery

The da Vinci surgical system is composed of three main parts, one patient-side cart with four articulated arms, one instrument tower with video command, and the surgeon's work station with the operating console. The fundamental difference between laparoscopic and robotic techniques is that the latter provides the surgeon with a surgical theater similar to that of open surgery. Indeed, with the robot, the surgeon uses his or her hands in the same manner as in open surgery. In addition, it provides seven degrees of freedom for the tips of the robotic instruments (Endo-Wrist technology), following rotational movements of the hands and wrists. Added to a three-dimensional-like vision, these characteristics explain why there is a faster learning curve with the robot.

Patient placement is similar to that described for total laparoscopic techniques. Only the placement of the trocars requires a different strategy.

With the patient under general anesthesia, an 80-degree rotation of the patient is obtained by adding a 45-degree right tilt to the table and placing a 35-degree inflated Pelvic Tilt pillow (O.R. Comfort, Branchburg, New Jersey) under the patient's left flank. One support is placed on the right side of the thorax, leaving the area below the xyphoid free for placement of a proximal aortic clamp trocar. The second trocar is placed facing the right hip, leaving the surgical approach of the right groin free in case aortobifemoral reconstruction should be required. Both lower limbs are maintained in line with the body; only the right leg is attached to the table; the left leg is flexed to 30 degrees to avoid any psoas elongation. In the cases involving aneurysm repair, the patient is immediately installed on the operating table as well and the robot is docked. In the case of aortobifemoral reconstruction for occlusive disease, the patient is first placed in the dorsal position to achieve femoral exposure and then rotated on the right side.

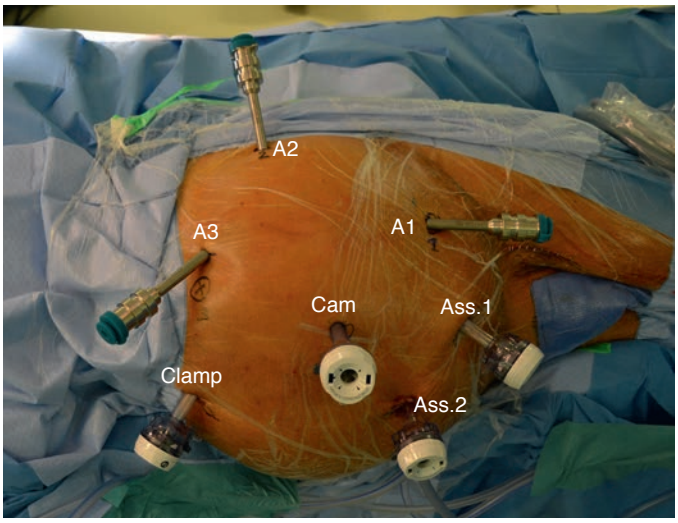

Figure 62.7 Placement of trocars for robotic aortoiliac surgery. *Clamp*, A 12-mm laparoscopic trocar placed just below the xyphoid, on the abdominal median line, is used by a surgeon's assistant during the surgical approach and dissection of the aorta and for the proximal laparoscopic clamp; *Ass.1*, 12-mm laparoscopic trocar placed up to the pubic symphysis, used by a surgeon's assistant during the surgical approach and dissection of the aorta and for the distal laparoscopic clamp; *Ass.2*, 12-mm laparoscopic trocar at the umbilicus, introduced by open technique, used for the creation of the peritoneum and for surgical assistance; *A1*, 9-mm robotic trocar docked on the articulated robotic arm 1, inserted close to the left iliac spine shifted 5 cm below, used by the right hand of the surgeon; *A2*, 9-mm robotic trocar docked on the articulated robotic arm 2, inserted close to the robotic trocar of the arm 3, shifted to the patient back, used by the left hand of the surgeon alternatively with the arm 3; *A3*, 9 mm robotic trocar docked on the articulated robotic arm 3, inserted close to the left costal margin, on the left axillary line, used by the left hand of the surgeon; *Cam*, 12-mm laparoscopic trocar inserted on a slightly lower line left pararectal, midway between trocars A1 and A2 with triangulation and docked on the robotic camera arm.

A pneumoperitoneum of 14 mm Hg is performed by an open technique at the umbilicus using a 12-mm trocar that will be used later by an assistant. Two other 12-mm trocars are inserted respectively below the xyphoid and above the pubic symphysis, using as assistant or for proximal and distal clamping of the abdominal aorta (Fig. 62.7).

As opposed to basic laparoscopy, the main problem encountered with the robot is the external conflict between the articulated arms. For this reason, robotic trocars of three main arms, right and left surgeon's hand, and camera are placed on the left axillary line and spaced as far as possible from each other. The right arm (arm 1) is close to the left iliac spine, shifted 5 cm below, and the left arm (arm 3) is close to the left costal margin. The camera trocar (camera arm) is placed midway between the remaining two trocars on a slightly lower line left pararectal. With the S and Si models, which are most used, placement of the robot is decided by the placement of the camera articulated arm. The last articulated arm (arm 2) is placed when a last trocar is used close to the trocar of arm 3, shifted to the patient's back. One 5-mm trocar can be added

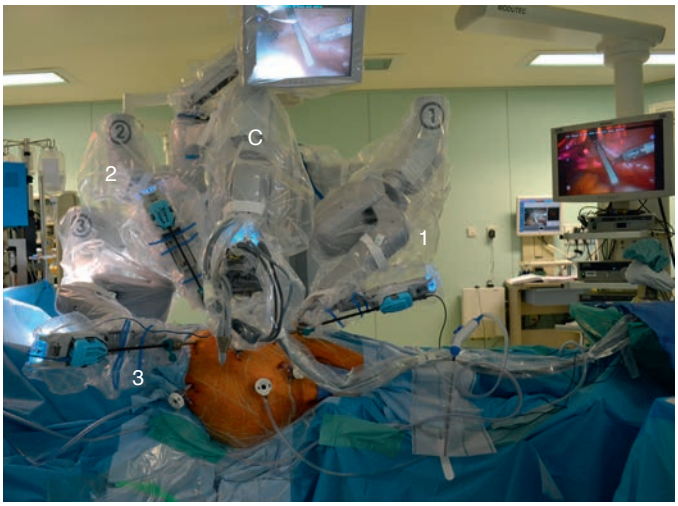

Figure 62.8 Side-docking method for robotic aortoiliac surgery. The robot is docked from the left side of the patient at an approximately 90-degree angle to the central axis of the table. *1*, articulated robotic arm 1, used by the left hand of the surgeon; *2 and 3*, articulated robotic arms 2 and 3 are used alternatively by the right hand of the surgeon; *C*, camera articulated robotic arm, with a 0- or 30-degree endoscope providing three-dimensional vision and used by both of the surgeon's hands independently of the operative robotic arms.

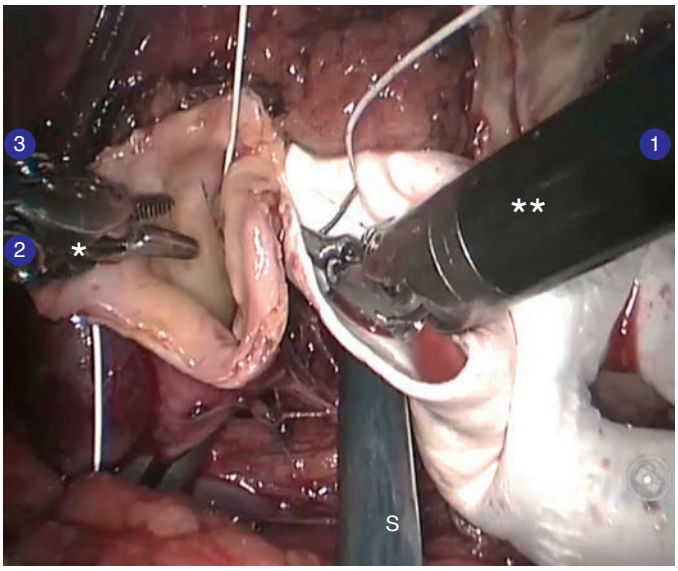

Figure 62.9 Robotic proximal anastomosis for abdominal aortic aneurysm repair with a polytetrafluoroethylene bifurcated graft. * Left robotic needle holder, used by the surgeon's left hand; ** Right robotic needle holder, used by the surgeon's right hand; *S*, Laparoscopic surgical suction.

between the proximal clamp trocar and the umbilicus on the median line.

The patient-side cart is docked from the patient's left side, placed at 90 degrees relative to the central axis of the operating table (Fig. 62.8). The assistant and operative nurse face the patient and, the surgeon works from the operating console at a remote place. The main dissection is done with a monopolar scissors on the right arm (arm 1) and a bipolar fenestrated forceps on left arm (arm 3). Another arm can be used as a robotic assistant with a second fenestrated forceps (arm 2). Most of the time, a 0-degree endoscope is used with the camera (camera arm), but a 30-degree endoscope may also be used, especially for obese patients with difficult exposure due to the intraperitoneal fat.

With total robotic technique, both retrocolic prerenal and retrocolic retrorenal dissections are achieved using the same principles as the total laparoscopic technique described earlier. However, there are some striking differences between the two techniques that give an advantage to the robot in performing aortic surgery. Because of the stable three-dimensional vision and capability of the instrument's movements in a close and deep space, the robot pushes the limits of laparoscopic dissection. The suprarenal aorta, origin of the superior mesenteric artery, origin of the right renal artery, and left renal artery are dissected. This offers the opportunity of temporary suprarenal aortic clamping for extensive aortic occlusive disease close to the renal arteries or for an aneurysm with a short aortic neck. Similarly, the right iliac bifurcation can be easily reached and dissected to perform the distal anastomosis in case of an aortoiliac aneurysm.

The retrocolic retrorenal approach is mostly performed for occlusive disease, and the retrocolic prerenal approach is preferred in the case of AAA repair. In this case, after clamping the proximal neck of the aneurysm, the lumbar arteries are clipped, helping to mobilize the aneurysmal sac with a fenestrated grasp (arm 2) without any risk of distal embolization. The distal aorta is clamped by a laparoscopic clamp through the distal trocar, and common iliac arteries are clamped selectively by removable bulldog clamps. In case of severe calcifications of the iliac arteries, transparietal aortoiliac clamps may be used instead of these ineffective bulldogs.

Aortic and iliac anastomoses are carried out with 3/0 or 4/0 Gore-Tex suture, which provides more strength than polypropylene. Robotic suturing with the help of a shorter learning curve provides better dexterity and pushes the limit of laparoscopic suturing. Proximal and distal aortic anastomoses are carried out with a unique running suture 25 cm long, blocked at one end by a pledget (Fig. 62.9). The same technique is applied for iliac anastomoses, with a 15-cm running suture. One challenge during robotic suturing is to judge the degree of tension needed on the suture line, as the tactile sensation cannot be transmitted to the hands of the surgeon from the robotic arms and is developed with experience.

Robot-Assisted Aortic Surgery

Some surgical teams have decided to use the robot only to perform one part of the aortic surgery with minilaparotomy for graft implantation.[24] In other cases, the robot is installed after completion of aortic exposure with a classic laparoscopic technique[19,21] and used only to perform arterial sutures. The robot makes it possible to facilitate the achievement of the suture while reducing its completion time and thereby the clamping time.[25]

PUBLISHED SERIES

Clinical studies eligible for inclusion in this chapter were identified by a thorough search of the PubMed database from 1995 to 2016. The present authors worked independently using the following key words: *laparoscopy, laparoscopic, endoscopy, aortic aneurysm, aortic occlusive disease, robot,* and *robotic*. In addition, we checked the references of relevant reviews. From 378 articles, we excluded those with fewer than five patients. Only studies with complete data on operative time, clamping time, length of hospital stay, morbidity, mortality, and conversion were selected. In case of duplicate material, the larger of the studies or the study with the best-documented data was included for analysis. Consequently 48 studies were found to be eligible, with 24 reporting total laparoscopic aortic surgery (TLAS), 14 reporting HALS and minilaparotomy-assisted laparoscopic surgery, and 10 reporting robot-assisted laparoscopic aortic surgery.

Total Laparoscopic Aortic Procedures

Total laparoscopic aortic procedures for AIOD were analyzed in 16 studies,[26-40] regrouping 932 patients (Table 62.1). Total laparoscopic procedures for AAA were reported in nine studies[3,5,10,28,34,41-44] regrouping 410 patients (Table 62.2).

Hand-Assisted and Laparotomy-Assisted Laparoscopic Surgery

Hand- or minilaparotomy-assisted laparoscopic aortic procedures for AIOD (Table 62.3) and AAA (Table 62.4) were reported in 14 studies[3,14,15,45-55] regrouping 860 patients.

Robot-Assisted Laparoscopic Surgery

Robot-assisted laparoscopic aortic procedures were analyzed in 11 studies[18,21,23-25,56-58] regrouping 525 patients (Table 62.5).

Robot-Assisted Laparoscopy

Results of robot-assisted aortic laparoscopy were analyzed separately with regard to the specificity of robotic technologies, with the first two cases published in 2002 by Wisselink et al.[58a] As shown in Table 62.5, results obtained from these studies showed that the robotic system was effective in performing aortic anastomoses with the surgeon operating from a console away from the operating table. Comparison of the performance of robot-assisted and standard laparoscopic surgery revealed the superiority of the former, with shorter suturing and clamping times. Only one comparative study of TLAS and robot-assisted procedures[28] demonstrated advantages in the time taken to complete the aortic anastomosis, 40.8 ± 4.1 minutes for robot-assisted procedures versus 52.7 ± 9.0 for total laparoscopic procedures ($P < .05$), although the procedure time was increased because of the robot setup time.

PERIOPERATIVE OUTCOMES

Operative Time

Total operative times, excluding robot-assisted aortic laparoscopy, varied widely from 199 minutes to 391 minutes (Table 62.6). HALS had the shortest median operating time but with a wide range of values (149 to 350 minutes).

TABLE 62.1 Total Laparoscopic Surgery for Aortic Occlusive Disease

Authors	Year	Patients	Operative Time (Minutes)	Clamping Time (Minutes)	Hospital Stay (Days)	Mortality	Conversion
Barbera[26]	1998	24	250	70	7	0/24	4/24
Dion[27]	2004	51	290	99	5	1/51	5/51
Coggia[2]	2004	93	240	68	7	4/93	2/93
Olinde[29]	2005	22	267	90	4	1/22	2/22
Lin[30]	2005	68	199	85	6	1/68	3/68
Rouers[31]	2005	30	244	66	5	0/30	6/30
Remy[32]	2005	21	240	60	7	0/21	1/21
Dooner[33]	2006	13	390	45	7	0/13	3/13
Cau[34]	2006	72	216	57	8	0/72	2/72
Fourneau[35]	2008	50	328	69	5	0/50	11/50
Di Centa[36]	2008	150	260	81	7	4/150	5/150
Tiek[37]	2012	14	273	48	4	0/12	0/12
Segers[38,a]	2014	12	265	0	6	0/12	0/12
Ghammad[39]	2015	173	205	50	7	4/173	21/173
Lecot[40]	2016	87	327	NR	6	1/87	18/87
Ricco[44]	2016	52	250	50	6	2/52	7/52

[a]Clampless and sutureless aortic anastomosis using a covered stent graft, no aortic clamping; median time for aortoprosthetic connection was 60 seconds.
Sixteen studies (932 patients) of total laparoscopic surgery for aortic occlusive disease.
Operative time, clamping times, and length of stay in the hospital are presented as median values. *NR*, Value not reported.

TABLE 62.2 Total Laparoscopic Aortic Aneurysm Repair

Author	Year	Patients	Operative Time (Minutes)	Clamping Time (Minutes)	Hospital Stay (Days)	Mortality	Conversion
Edoga[10]	1998	22	391	146	6	2/22	2/22
Kolvenbach[3]	2006	131	265	95	5	4/131	6/37
Coggia[28]	2004	30	290	78	9	2/30	2/30
Coggia[41]	2005	30	255	80	9	1/30	1/30
Cau[34]	2006	23	251	101	6	1/23	7/23
Coggia[5]	2008	13	260	77	10	0/13	0/13
Javerliat[42]	2013	99	210	81	6	0/99	5/99
Coscas[43]	2014	31	289	75	13	3/31	3/31
Ricco[44]	2016	31	273	110	8	1/31	9/31

Nine studies (410 patients) with total laparoscopic aortic repair for abdominal aortic aneurysm.
Operative time, clamping times, and length of stay in the hospital are presented as median values. *NR*, Value not reported.
Coggia[5] reported this series of juxtarenal aortic aneurysms.
Javerliat,[40] from the Coggia group, reported a subgroup of laparoscopic aortic aneurysm repair in patients with standard surgical risk.
Coscas,[43] from Coggia group, reported a subgroup of laparoscopic aortic aneurysm repair in octogenarians with anatomic criteria amenable to endovascular aneurysm repair.

TABLE 62.3 Hand and Minilaparotomy-Assisted Laparoscopic Surgery for Aortic Occlusive Disease

	Year	*N*	Operative Time (Minutes)	Clamping Time (Minutes)	Hospital Stay (Days)	Mortality	Conversion
Lacroix[45]	1999	10	350	NR	7	0/10	1/10
Alimi[46]	2004	58	238	54	8	2/58	1/58
Kolvenbach[47]	2000	41	149	36	4	1/41	3/41
Silva[48]	2002	18	191	44	7	0/18	1/18
Wijtenburg[49]	2003	25	180	37	7	1/25	2/25
Debing[50]	2003	13	230	29	6	0/13	1/13
Fourneau[51]	2005	46	208	28	6	2/46	1/46

Seven studies (211 patients) with hand-assisted or minilaparotomy-assisted procedures.
Operative time, clamping times, and length of stay in the hospital are presented as median values. *NR*, Value not reported.

TABLE 62.4 Hand and Minilaparotomy-Assisted Laparoscopic Aortic Aneurysm Repair

Author	Year	Patients	Operative Time (Minutes)	Clamping Time (Minutes)	Hospital Stay (Days)	Mortality	Conversion
Kline[52]	1998	20	245	NR	6	0/20	2/20
Castronuovo[15]	2000	60	462	112	6	3/60	3/60
Alimi[53]	2003	14	195	NR	4	1/14	1/14
Kolvenbach[3]	2006	215	175	55	7	4/215	11/215
Ferrari[14]	2009	188	231	25	4	0/188	0/188
Ferrari[14,a]	2009	51	220	28	4	0/51	0/51
Veroux[54]	2010	50	178	NR	4	0/50	NR
Howard[55]	2015	51	330	90	5	1/51	—

[a]Ferrari[14] reported a subgroup of laparoscopy-assisted surgery cases for juxtarenal aortic aneurysm.
Eight studies (649 patients) with hand-assisted or minilaparotomy-assisted procedures.
Operative time, clamping times, and length of stay in the hospital are presented as median values. *NR*, Value not reported.

TABLE 62.5 Robot-Assisted Laparoscopic Aortic Surgery

Author	Year	Patients	Robot	Operative Time (Minutes)	Clamping Time (Minutes)	Hospital Stay (Days)	Mortality (30-Day)	Conversion
Aneurysm Repair								
Kolvenbach[56]	2004	10	Zeus	242	96	7	0/10	2/10
Stádler[24]	2009	17	da Vinci	215	76	5	0/17	1/17
Lin[57,a]	2012	6	da Vinci	396	86	7	0/20	1/6
Stádler[21]	2016	61	da Vinci	253	93	7	1/61	8/61
Aortic Occlusive Disease								
Desgranges[25]	2004	5	da Vinci	188	75	8	0/5	1/5
Nio[18]	2005	8	Zeus	405	111	7	1/8	2/8
Diks[23]	2007	17	Zeus + da Vinci	365	86	4	1/17	3/17
Stádler[56]	2009	115	da Vinci	215	40	5	0/130	2/115
Novotný[58]	2011	40	da Vinci	295	60	NR	0/40	2/40
Lin[57,a]	2012	12	da Vinci	493	86	7	0/20	0/12
Stádler[21]	2016	224	da Vinci	194	37	5	0/224	2/224

[a]In the series of Lin,[57] total robotic aortic surgery was performed in three patients with aortoiliac occlusive disease (AOID); robot-assisted with a minilaparotomy was performed in all patients with abdominal aortic aneurysms and in nine remaining patients with AOID.
Eleven studies (525 patients) of robot-assisted laparoscopic aortic surgery.
Operative time, clamping time of the aorta, and length of stay in the hospital are presented as median values. *NR*, Value not reported.

TABLE 62.6 Main Data for Eligible Series of Laparoscopic Aortic Surgery

	TLAS (AIOD)	TLAS (AAA)	HALS (AIOD)	HALS (AAA)	ROBOT (AIOD)	ROBOT (AAA)
Patients	932	410	211	649	421	94
Operative time (min)	(199-390)	(210-391)	(149-350)	(175-330)	(188-405)	(215-396)
Clamping time (min)	(45-99)	(75-146)	(28-54)	(25-112)	(37-111)	(76-96)
Hospital stay (days)	(4-8)	(5-13)	(4-8)	(4-7)	(4-8)	(5-7)
Conversion	85 (9.1%)	35 (8.5%)	10 (4.7%)	17 (2.6%)	12 (2.8%)	12 (12.7%)
Death	18 (1.9%)	14 (3.4%)	6 (2.8%)	9 (1.4%)	2 (0.4%)	1 (1.1%)

Operative time, clamping time (aortic), and length of stay in the hospital are presented in each category as median values of the series with the shorter and the longer time periods.
AAA, Aortic abdominal aneurysm; *AIOD*, aortoiliac occlusive disease; *HALS*, hand or minilaparotomy-assisted laparoscopic aortic surgery; *ROBOT*, robot-assisted laparoscopic aortic surgery; *TLAS*, total laparoscopic aortic surgery.

Clamping Time

Aortic clamping extended from 28 minutes with HALS for AIOD to 146 minutes with TLAS for AAA, with a wide range of values for the same pathology and also for the same technique within different centers (see Table 62.6).

Conversion to Open Surgery

Conversion to open surgical repair with TLAS for AIOD was 9.1% (95% CI, 7.4–11.1) and 8.5% (95% CI, 6.1–11.6) in patients with AAA ($P = .75$). Rate of conversion was significantly higher with TLAS than with HALS or minilaparotomy-assisted laparoscopy for AIOD (9.1% versus 4.7%, $P = .03$) and also for AAA (8.5% versus 2.6%, $P = .001$), respectively. Reasons for conversion were multiple, including calcified aorta, bleeding from the lumbar veins or from the aortic anastomosis, and self-imposed operative time or aortic-clamping time limits.[30,32,35]

A significant number of specific complications occurred during laparoscopic aortic procedures, including bleeding lumbar veins that quickly retract behind the spine, retroperitoneal hematoma due to extended laparoscopic dissection, ureteral lesion in relation to dissection, and acute occlusion of the prosthetic graft in some patients due to a long aortic clamping time or inadequate tunneling of the graft.

Mortality

The 30-day postoperative mortality rate was 1.8 % (95% CI, 1.4-2.4) for the whole series ($n = 2717$). Postoperative mortality

among patients with an AAA treated by TLAS (3.4%, 95% CI, 2.1-5.3) was significantly higher than that of patients treated by HALS (1.4%, 95% CI, 0.7-2.6, $P = .03$).

Morbidity

Hemorrhage ($n = 34$) and transient renal insufficiency ($n = 27$) were the most frequently reported operative and postoperative complications occurring during the first 30 days after the procedure. Other complications were lower limb ischemia ($n = 13$), ischemic colitis ($n = 7$), thrombosis of the prosthesis ($n = 12$), and myocardial infarction ($n = 14$). These complications occurred more often after TLAS for AAA. However, many of the studies do not define their complications, and these data should be viewed with caution.

Hospital Stay

In all 48 studies, median hospital stay varied from 4 to 13 days regardless of the laparoscopic technique used (see Table 62.6).

SUMMARY

Almost all surgical specialties— gastrointestinal surgery, gynecology, and urology— incorporated laparoscopic techniques many years ago. Although several studies have demonstrated the feasibility of laparoscopy in aortic surgery,[4,33,59] vascular surgeons have been slow to adopt laparoscopic aortic techniques. One of the reasons is that the best way to begin doing laparoscopic aortic surgery is in dealing with aortic occlusive disease. However, even for common iliac artery occlusion, traditional bypasses have been replaced by stenting with a low morbidity and excellent results. Therefore aortoiliac bypasses are now reserved for complex aortoiliac occlusion or endovascular failure. This reduces the case load and increases the technical challenge of laparoscopic procedures.

The basic concept of laparoscopic aortic surgery is to combine the excellent and durable results observed after conventional open arterial repair with the advantages of a less invasive laparoscopic approach. For most authors, initial laparoscopic procedures were performed with HALS or with the assistance of a minilaparotomy through which the aortic anastomosis was performed under direct vision. Following this initial experience, some authors have developed total laparoscopic aortic procedures to enhance the major advantage of minimally invasive surgery with easier and faster recovery.

After the pioneering efforts of Dion et al.,[27,60] the key to total laparoscopic technique for aortoiliac disease was presented by Coggia et al.[8] who described the transperitoneal left retrocolic approach of the abdominal aorta. This technique with a patient in the right lateral decubitus position provides a large work space, allowing dissection of the abdominal aorta and completion of the aortic anastomosis.

Total laparoscopic bypass is safely performed by a few centers of expertise for complex AIOD or infrarenal aortic aneurysm.[61] Despite these encouraging results, the importance of prior training to obtain the required level of expertise to perform laparoscopic aortic anastomoses has been emphasized,[35,46] with the option of assisted laparoscopy to lessen the risk of totally laparoscopic aortic anastomosis.[45,46,51] Because of these technical challenges and the associated steep learning curve, no large randomized controlled trials have been done so far to prove the benefit of laparoscopic aortic surgery as compared with open or endovascular techniques. We observed in these series a trend toward decreased pulmonary complications as compared with open surgery; this could be related to avoidance of large abdominal incision and reduced pain. However, data from these series showed that even for well-trained surgeons, operative time and aortic clamping time were longer than usually observed during open aortic surgery. Specific operative difficulties were observed particularly with TLAS in treating aortic aneurysmal disease, leading to a high rate of conversion not seen with HALS or other laparoscopy-assisted techniques (see Table 62.6). Among all series, median blood loss was comparable to outcomes reported for open aortic surgery. Extreme blood loss was observed in some patients with AAA or with AIOD and a severely calcified aorta. Infrarenal circumferential aortic calcifications are not a contraindication for TLAS if suprarenal clamping is possible through a left transperitoneal retrorenal approach.

Concerning AAA repair, one small randomized trial with a 12-month follow-up[54] concluded that HALS could be a less invasive alternative for sexually active males who are unsuitable for EVAR. Coggia et al.[5] reported a prospective cohort study of 148 patients undergoing TLAS for juxtarenal AAA repair with no mortality and low morbidity. However, limitations of this study included strict patient selection before TLAS was considered; therefore, it may not be truly applicable to the general population. Ricco et al.[44] published the results of a cohort of 228 consecutive cases using propensity score matching to compare the outcomes after open and TLAS for aortic surgery through a composite primary end point of pertinent adverse events (AEs). Logistic regression analysis of the groups adjusted for propensity score showed that only two variables, TLAS (OR 4.50; $P = .01$) and coronary artery disease (OR 4.67; $P = .02$) were independently related to the occurrence of an AE during the postoperative period. In this study, the occurrence of AEs during follow-up was analyzed using the Cox model and TLAS (HR 4.40; $P = .02$) and coronary artery disease (HR 2.70; $P = .02$) were independently associated with the occurrence of an AE during follow-up. In this series, the small number of patients prevented a separate analysis with regard to AAA and AIOD. This study suggests that even with a well-trained team, TLAS increases the risk of AEs observed in the course of aortic surgery.

To overcome these technical difficulties, robotic systems have been recommended to facilitate advanced laparoscopic techniques, such as suturing, knot-tying, and the performance of aortic anastomoses. Laparoscopy creates a closed space in two-dimensional vision with a dissociation between eye-hand coordination; the robotic technology can compensate for these restrictions. We have identified eight studies of robot-assisted laparoscopic aortic surgery (see Table 62.6). The conversion rate ranged from 2.8% for AIOD to 12.7% for AAA with technical problems related to the robotic system and bleeding

from the lumbar arteries. Despite these limitations, robotic assistance goes beyond the making of aortic anastomoses; robotic techniques allow greater visualization and facilitate aortic dissection. There are several limitations to robotics in laparoscopic aortic surgery, the most obvious being the high cost of the system. In addition, the setup of the system may be time-consuming before the staff is fully trained. The robotic learning curve seems to be quicker and easier than that of laparoscopic surgery for developing the technical skills needed to perform an aortic anastomoses.[62] In addition, the postoperative length of stay ranges from 4 to 13 days in most series, with the majority being 6 days or greater, which is comparable to that with open aortic surgery and much longer than that with any endovascular procedure. Furthermore, endovascular procedures can be performed under regional or even local anesthesia, whereas the laparoscopic and robot-assisted procedures require general anesthesia. Therefore the development of robot-assisted aortic laparoscopy has not yet been widely adopted and experience is restricted to only a few centers worldwide.

CONCLUSIONS

Our review shows that laparoscopic aortic surgery can be performed safely with low mortality and morbidity provided that patient selection is adjusted to experience and conversion liberally performed. The future of this technique is still unknown; it is now time for multicenter randomized trials to demonstrate the potential benefit of laparoscopic aortic surgery for aortic occlusive and aneurysmal disease not amenable to an endovascular treatment.

SELECTED KEY REFERENCES

Coggia M, Javerliat I, Di Centa I, et al. Total laparoscopic bypass for aortoiliac occlusive lesions: 93-case experience. *J Vasc Surg*. 2004;40(5):899–906.

The authors describe a new technique of total laparoscopic bypass surgery to treat aortoiliac occlusive lesions with 93 total laparoscopic bypass procedures for TASC grade C or D aortoiliac occlusive lesions. The authors used a transperitoneal left retrocolic or retrorenal approach to the infrarenal abdominal aorta. Median operative time was 240 minutes (range, 150-450 minutes). Median aortic clamping time measured to unclamping of the first prosthetic limb was 67.5 minutes (range, 30-135 minutes). Median hospital stay was 7 days (range, 2-57 days). The authors demonstrated the feasibility of total laparoscopic aortic bypass in patients with TASC C and D aortoiliac occlusive lesions.

Dion YM, Katkhouda N, Rouleau C, Aucoin A. Laparoscopy-assisted aortobifemoral bypass. *Surg Laparosc Endosc*. 1993;3(5):425–429.

A seminal paper. The authors described the first case of laparoscopy-assisted aortobifemoral bypass. The patient's postoperative period was uncomplicated; the patient had minimal pain that allowed for a quick return to ambulation. This procedure appeared to be of interest for some patients with aortoiliac disease.

Lecot F, Sabbe T, Houthoofd S, Daenens K, Fourneau I. Long-term results of totally laparoscopic aortobifemoral bypass. *Eur J Vasc Endovasc Surg*. Elsevier Ltd; 2016;52(5):581–587.

Other papers have described safety and short-term outcomes of totally laparoscopic aortofemoral bypass, but this study estimates the long-term patency of this procedure for the first time. An estimate of long-term patency is a crucial parameter for weighing options for treatment of severe aortoiliac occlusive disease.

Lucereau B, Thaveau F, Lejay A, et al. Learning curve of robotic-assisted anastomosis: shorter than the laparoscopic technique? An educational study. *Ann Vasc Surg*. 2016;33:39–44.

The da Vinci robot could theoretically minimize the technical challenge of laparoscopic surgery. The aim of this study was to compare the learning curves of performing vascular anastomoses on an expanded polytetrafluoroethylene (ePTFE) abdominal aortic graft as model by trainees with no experience in using laparoscopic versus robotic techniques. The trainees were randomly assigned to the laparoscopic or robotic groups. Minimally invasive laparoscopic technique training demonstrates a learning curve to perform vascular anastomoses. The robotic learning curve seems to be quicker than that of laparoscopic surgery. The robot allowed faster, more accurate, and easier learning of technical skills on the first anastomoses. The authors conclude that robotics may offer the opportunity for surgeons to more easily acquire skills to perform laparoscopic aortic anastomosis and may provide better reproducibility.

Nio D, Diks J, Bemelman WA, Wisselink W, Legemate DA. Laparoscopic vascular surgery: a systematic review. *Eur J Vasc Endovasc Surg*. 2007;33(3):263–271.

The objective of this early systematic review was to evaluate the results of clinical studies on laparoscopic surgery for aortoiliac disease. Thirty studies were identified. These were all descriptive and included nine comparative studies. Operative times varied widely, the shortest being for hand-assisted procedures and the longest for totally laparoscopic procedures.

The conversion rate varied from less than 5% up to 16% in smaller series. The mortality rate was approximately 5%.

This systematic review has shown that the observational, noncomparative character and selection bias of most published series are their major limitations. More data are required to define the value of laparoscopic vascular surgery in comparison with endovascular and open surgery.

Ricco JB, Cau J, Biancari F, et al. Outcome after open and laparoscopic aortic surgery in matched cohorts using propensity score matching. *Eur J Vasc Endovasc Surg*. Elsevier; 2016;52(2):179–188.

This propensity score-matched cohort suggests that even in a well-trained laparoscopic surgical group, a total laparoscopic approach increases the risk of adverse events observed in the course of aortic surgery. This negative result contrasts with those reported in most observational studies, probably because the propensity score avoids the heterogeneity of the previous studies published on this subject and limits the confounding and selection biases.

Stádler P, Dvorácek L, Vitásek P, Matous P. Robot assisted aortic and non-aortic vascular operations. *Eur J Vasc Endovasc Surg*. Elsevier; 2016;52(1):22–28.

This study evaluates the results of a large experience with 310 robot-assisted vascular procedures. The authors demonstrate that robotic systems provide a real opportunity for minimally invasive surgery in the field of vascular surgery. The authors have shown that robotic systems remove fundamental disadvantages of laparoscopy and suggest the possibility of expanding robot-assisted laparoscopic surgery in this area.

A complete reference list can be found online at www.expertconsult.com.

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63 CHAPTER

Autogenous Grafts

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Despite ongoing attempts to develop prosthetic or bioengineered materials for bypass grafting in the lower extremities, autologous vein graft remains the conduit of choice for infrainguinal revascularization. Though it was sporadically used for repair of popliteal aneurysms in the early 20th century, the first report of the routine use of autogenous vein for the treatment of occlusive arterial disease was provided in 1944 by Dos Santos, who used segments of vein as patch material after superficial femoral artery endarterectomy.[1] This was followed several years later by the report of Kunlin, who described the use of reversed saphenous vein grafts for the treatment of focal lesions within the superficial femoral artery.[2] Based on these initial reports, expanded use of the saphenous vein for both endarterectomy and grafting was attempted, but creation of the anastomoses with the standard surgical techniques of the day proved difficult. With long-term patency negatively influenced by a high rate of anastomotic stricture and an inability to replicate the promising results of Kunlin, the majority of practitioners in the 1940s and 1950s used arterial homografts or the newly developed prosthetic grafts for infrainguinal arterial reconstruction. Reinvigorating the use of autogenous vein, however, was a small group of surgeons who traveled to Europe to observe Kunlin's vein grafting procedures.[3] Characterized by a spatulated end-to-side anastomosis using a small-caliber running silk suture, these meticulous techniques

Abstract

Autogenous vein remains the conduit of choice for bypass grafting, with great saphenous vein proving to be the most durable. Alternate conduits, such as arm vein, femoral vein, or small saphenous vein are viable options, but are notably compromised. Significant effort has been expended in trying to optimize the technique and conditions of vein harvest, with a use of a gentle-touch technique, storage in isotonic buffered crystalloid, and avoidance of over-distention emerging as the most important aspects of this procedure. Placement of the graft in a reversed, non-reversed, or in situ configuration are all viable options, with no clear patency benefit among these options. Angiography, duplex scanning, and angioscopy are the most widely used intra-operative techniques to evaluate for technical issues prior to completing the procedure. Post-operatively, duplex scanning is widely accepted as the test for of choice to identify the failing vein graft, although definitive clinical evidence to support this practice is lacking.

Keywords

Autologous vein
harvest techniques
duplex scan
intimal hyperplasia

allowed Linton, Darling, and others to duplicate the reported success with autogenous vein grafting.[4]

In the 1960s, wider interest in the use of autogenous vein was fueled by the observation that acceptable long-term patency of prosthetic bypass grafts could be achieved only with distal anastomoses placed in the above-knee position.[5] Treatment of critical limb ischemia in patients with compromised outflow via femorotibial bypass was a natural extension for autogenous vein grafting, with the first published report by Dale in 1963.[6] Although initial published reports of the use of saphenous vein for tibial bypass grafts suggested it to be notably inferior to femoropopliteal grafts,[7,8] further refinements in the techniques have proved the durability of tibial as well as inframalleolar bypass grafting with autologous vein.[9] Along with these technical improvements in the 1980s came increasing experience with alternative autogenous vein sources (i.e., arm, small saphenous, and femoral veins),[10] thereby expanding the potential for autogenous tissue reconstruction to 95% of patients undergoing infrainguinal bypass.[11]

HISTOLOGY

Analogous to other vascular structures, veins are composed of three layers—the tunicae intima, media, and adventitia (Fig. 63.1). The intima consists of a continuous monolayer of cuboidal endothelial cells supported by a subendothelial layer of loose connective tissue. In contrast to the arterial endothelium, where cells are tightly packed and highly aligned in the direction of flow, venous endothelial cells are cuboidal with poorly developed interendothelial tight junctions.[12,13] The resulting enhanced permeability to blood solutes, in conjunction with the underlying physiologic differences between arterial and venous endothelium, is thought to be among the underlying mechanisms for the accelerated intimal hyperplasia characteristic of vein grafts.[14] The intima is separated from the media by a poorly developed internal elastic lamina with large fenestrae that allow diffusion of substances into the wall. The media is composed of vascular smooth muscle cells and extracellular matrix, with type I collagen being the dominant component of this layer. Unlike arteries, which function in a pulsatile pressure environment and correspondingly have high elastin content, veins are exposed to small excursions in pressure and demonstrate only sparse elastin fragments. Transposition of a vein into the arterial circulation induces a marked increase in intraluminal wall tension that greatly exceeds the dynamic range of the elastic elements and therefore leads to a rigid graft with substantial compliance mismatch in comparison to the adjacent artery.[15]

External to a poorly developed external elastic lamina is the adventitia, a loose connection of extracellular matrix with a sparse vasa vasorum. Though traditionally thought to have limited influence on biologic function of the vein, evolving evidence suggests that remodeling of an implanted vein graft is very much dependent on adaptation within the adventitia. Recruitment of myofibroblasts, production of cytokines, and the influx of inflammatory cells into the adventitia are thought to have an important influence on the biology of the early vein graft.

Superficial extremity veins are prone to the development of a range of pathologies such as varicose degeneration, thrombosis with luminal recanalization, and phlebitis with intramural calcification. Limitations in available autogenous conduit frequently require these "compromised" vein segments to be included as a conduit in a revascularization procedure. Histologic evaluation of harvested vein segments, coupled with long-term clinical follow-up, has demonstrated that grafts with low endothelial cell coverage, stenosis of the lumen, and thick walls are at an increased risk for early graft failure.[16] Grafts with subendothelial spindle-shaped cells, which demonstrate a proliferative smooth muscle phenotype on electron microscopic examination, and calcification within the wall at the time of graft implantation are notably prone to the development of aggressive hyperplastic lesions.[17] Unfortunately, preoperative ultrasound is unable to reliably identify many of these abnormalities.[18]

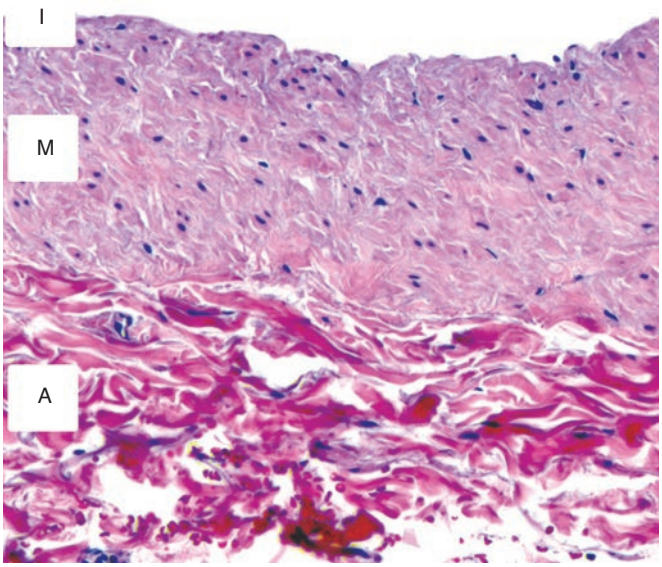


Figure 63.1 Cross-sectional histology of the normal saphenous vein. The intima *(I)* is composed of a single layer of endothelial cells and a thin basement membrane. The media *(M)* consists of smooth muscle cells surrounded by a tightly packed extracellular matrix. The adventitia *(A)* is a loose network of collagen-dominated extracellular matrix with sporadic inflammatory cells and fibroblasts.

ANATOMY

Lower Extremity Veins

The veins of the lower extremities are classified into three general groups: the deep, superficial, and perforating systems. The deep veins are encompassed by thick fascia and are contained within the muscular compartment of the leg. Superficial veins are bounded deeply by the muscular fascia and superficially by the dermis. Short veins piercing through the fascia and running between the superficial and deep systems are the perforating veins. Increasing interest in accurate description of the venous structures in the leg and confusion between the clinical and anatomic terminology used in naming them have prompted a review and standardization of the nomenclature. The following

descriptions are based on this consensus terminology,[19,20] with reference to the older nomenclature as appropriate.

The *great saphenous vein* (formerly called the greater or long saphenous vein) begins just anterior to the medial malleolus, crosses the tibia, traverses medial to the knee, and ascends in the medial-posterior aspect of the thigh to the groin. Duplicated systems within the great saphenous vein are relatively common and occur at a 25% and 8% incidence in the calf and thigh, respectively.[21] The *accessory great saphenous veins* run parallel to the main trunk within the thigh and leg, in an anterior or posterior location. Although these veins are at times mistaken for the great saphenous vein during surgical exposure, they are usually of inadequate diameter for use in bypass grafting. The saphenous veins, but not their tributaries, are covered by a fibrous sheath termed the *saphenous fascia*. Less well developed than the deep fascia, this fascia, in combination with the deeper muscular fascia, forms a subcompartment that extends along the length of the lower extremity. Recognition of this fascia can be useful in localizing the great saphenous vein during surgical dissection. In the proximal portion of the thigh, the great saphenous vein receives one or two large tributaries from the anterior or posterior accessory great saphenous vein (or both) and enters the fossa ovalis approximately 4 cm inferior and lateral to the pubic tubercle, where it joins with the superficial circumflex iliac, superficial epigastric, and external pudendal veins to create the *confluence of superficial inguinal veins* (formerly called the saphenofemoral junction) on the anterior surface of the *common femoral vein*.

The *small saphenous vein* (formerly called the lesser or short saphenous vein) ascends lateral to the Achilles tendon in the calf. It runs in the subcutaneous adipose tissue in the lower two-thirds of the calf, pierces the muscular fascia, and courses between the medial and lateral heads of the gastrocnemius. The small saphenous vein usually joins the popliteal vein in the popliteal fossa about 5 cm proximal to the knee crease. Rarely, the small saphenous vein ends high, either emptying into the femoral vein or running superficially to the posteromedial aspect of the thigh to join the great saphenous vein.

Particularly useful in arterial reconstructions within infected fields, the *femoral vein* (formerly called the superficial femoral vein) has increasingly become a potential source of autogenous conduit. The femoral vein originates from the popliteal vein at the upper margin of the popliteal fossa and courses in the femoral canal. The femoral vein is lateral to the femoral artery in the distal part of the thigh but crosses under and runs medial to the femoral artery in the proximal portion of the leg before joining the *deep femoral (profunda femoris) veins* approximately 9 cm below the inguinal ligament. During the harvest of the femoral-popliteal vein segment for use as an autogenous graft, preservation of the junction of the profunda femoris vein with the common femoral vein is critical for maintaining adequate venous outflow from the limb.[22,23]

Upper Extremity Veins

Veins of the upper extremity are also divided into superficial and deep groups, although direction of flow from superficial to deep is not as distinct as in the lower extremity. The *cephalic vein*, which originates on the posterolateral aspect of the wrist, gradually swings across the lateral portion of the forearm, ascends lateral to the biceps muscle into the deltopectoral groove, and passes through the clavipectoral fascia to join the axillary vein. The *basilic vein* swings across the posteromedial side of the forearm, passes lateral to the antecubital fossa, and ascends medially in the arm, where it joins the *brachial veins* to become the *axillary vein*. The *median cubital vein* starts at the apex of the antecubital fossa as a branch of the cephalic vein and ascends medially to enter the basilic vein.

Approximately 10 cm proximal to the antecubital fossa, the basilic vein passes through the deep fascia to reside along the medial side of the brachial artery. Harvest of the basilic vein proximal to this location requires longitudinal division of this fascia and ligation of multiple communicating branches coursing between the basilic and brachial veins. During this portion of the dissection, the medial cutaneous nerve of the forearm is often first identified as it travels anterior to the basilic vein. Injury to this nerve can lead to paresthesias along the medial portion of the forearm.

VEIN GRAFT PREPARATION

Preoperative Vein Mapping

As surgeons have increased the complexity of lower extremity reconstruction and become more aggressive with repeat revascularization after graft failure, assessment of available autogenous conduit has evolved into an essential component of preoperative planning. Initial attempts to evaluate available conduit centered around the use of routine preoperative saphenous venography, with information obtained from these studies influencing the operative approach in up to 30% of patients.[24] Although useful in defining the anatomy and dimensions of the greater saphenous system, broad application of this technique was limited by its requirement for percutaneous access, frequent underestimation of conduit diameter, and the small but worrisome risks of nephrotoxicity or chemically induced thrombophlebitis.

With refinements in ultrasound instrumentation and the increasing availability of skilled technologists, investigations into the merits of B-mode imaging for preoperative conduit evaluation were initiated.[25-28] By providing the ability to determine vein size and quality in a physiologic environment and facilitate operative exposure, duplex vein mapping generated significant enthusiasm. Early reports were mixed, however, with concern that duplicate saphenous systems were frequently not identified and diameters measured on B-mode imaging were not representative of in vivo graft geometries.[25] Although the former issue has essentially been solved by increased experience of vascular technologists and an understanding of anatomic variants, difficulties with direct correlation of preoperative mapping and graft size remain. Among the important issues in minimizing this variability is the development of a standard preoperative evaluation protocol.

Warming the examination room, placing warmed blankets on the extremities, and using prewarmed ultrasonic gel

minimize peripheral venous vasoconstriction. Imaging with a high-frequency probe (≥8 MHz) provides maximum resolution with 0.3-mm point-to-point discrimination. Veins are assessed in cross-section to evaluate compressibility, wall thickening, and the presence of intraluminal echoes, and sites of thrombus, intraluminal webs, and sclerotic walls are noted. Vein wall abnormalities have been described in 12% of potential conduits, with preoperative duplex evaluation correctly identifying 62% of these diseased segments.[29] To assess the great saphenous vein, patients are placed in a modified reversed Trendelenburg position and images collected for measurement of lumen diameter at six locations along the length of the limb. Evaluation of the small saphenous vein is performed with the patient in a prone position and the diameter measured at three locations within the calf. If either of the saphenous veins is of good quality but inadequate size, the patient is placed in a standing position and diameter measurements are repeated. Alternatively, a tourniquet may be placed on the proximal part of the thigh to facilitate this reassessment. For segments identified to be of adequate size and quality for bypass grafting, the overlying skin is marked with indelible ink. Routine evaluation of the femoral vein may also be warranted, depending on local clinical practice. In addition to lumen diameter, examination should include a thorough assessment for deep venous thrombosis and valvular incompetence. Use of standardized reference zones facilitates the reporting of relevant information, with zones 2, 3, and 4 corresponding to the proximal, middle, and distal portions of the thigh and zones 5, 6, and 7 corresponding to the proximal, middle, and distal portions of the calf, respectively.[30] Evaluation of the upper extremity cephalic and basilic veins should follow a similar protocol. An upper arm tourniquet may be used selectively or routinely to facilitate these measurements. Reference zones have also been established for the upper extremity, where zones 3, 4, and 5 correspond to the proximal, middle, and distal portions of the arm and zones 6, 7, and 8 correspond to the proximal, middle, and distal portions of the forearm, respectively.[30] Measurements of upper extremity vein diameter seem even more variable than those of the lower extremity. Although the underlying etiology is open to speculation, this variability should be recognized, and repeat testing of borderline upper extremity veins may prove valuable in preoperative planning.

Despite multiple attempts to define acceptable conduit size, no clear consensus has emerged. Smaller-diameter veins have repeatedly been shown to negatively influence long-term patency,[31,32] and a minimum suitable diameter ranging between 2.0 and 3.0 mm has been proposed.[33] Among the confounding issues is the variable effect of the mapping technique on approaching an accurate in vivo graft diameter. These variations are nonlinear and in part dependent on the initial size of the conduit; whereas a 2.5-mm vein increases 27% in diameter when placed in the arterial circulation, a 6-mm vein increases only 8%.[27] In the absence of a universally accepted vein mapping protocol, absolute delineation of a minimum acceptable vein size is problematic, and development of size criteria within an institutional practice is most appropriate.

Vein Handling Considerations

Research over the last decade has uncovered the importance of the endothelium in vascular injury and repair. Previously thought to be a passive monolayer with predominantly barrier functions, endothelial cells have been identified as central mediators in the maintenance of vascular homeostasis. Advanced by the work of Ross and his development of the response-to-injury hypothesis,[34-36] loss of endothelial integrity induces platelet deposition and elaboration of growth factors. Coupled with recruitment of inflammatory mediators, these growth factors stimulate smooth muscle proliferation and matrix deposition, which lead to the formation of an occlusive arterial lesion. Analogous mechanisms are thought to be fundamental in the pathologic remodeling of vein grafts, with early endothelial injury among the initiating events in the development of intimal hyperplasia.[37] Accordingly, maintenance of an intact endothelial monolayer during vein graft harvest is thought to provide improved long-term patency of autogenous vein grafts. Work by LoGerfo[38] and others[39] in a canine model supports this contention by demonstrating that smooth muscle cells are maintained in a contractile (nonproliferative) phenotype and that leukocyte infiltration is reduced when endothelial injury is avoided. Analogous work by Conte's group confirmed that the surgical manipulation of human vein segments results in a significant increase in monocyte adhesion.[40] However, direct evidence linking improved endothelial integrity to a reduction in intimal hyperplasia, enhanced outward remodeling, or improved patency is lacking. Nonetheless, significant indirect evidence supports the concept that endothelial preservation minimizes the early biologic perturbations within vein grafts, and therefore harvest techniques aimed at reducing endothelial dysfunction seem reasonable.

Dissection

Precise, atraumatic dissection and minimal direct manipulation of the vein via a "no-touch" technique have been demonstrated to reduce endothelial damage during harvest (Fig. 63.2).[41-44] Though somewhat a misnomer, the "no-touch" technique involves limited handling of the vein without direct application of forceps or vascular clamps. Major branches are ligated away from the wall to avoid narrowing of the lumen and promote outward remodeling after implantation. Opinions regarding the importance of maintaining continuity of the vein during dissection versus early ligation for intermittent infusion of isotonic fluids are mixed. Despite not being studied in a directed manner, continued continuity of vein has been shown to reduce the formation of small thrombi on the wall, and cannulation and division of the distal vein promote the direct application of antithrombotic and smooth muscle relaxants directly into the lumen. Although limited vein graft handling is universally considered an important component of promoting both short- and long-term graft patency, this concept is challenged by the nearly identical clinical outcomes for reversed, nonreversed, and in situ vein grafting techniques.[45,46] If limiting vein manipulation is a dominant factor, one might intuitively expect improved outcomes with in situ grafting, where direct vein manipulation can be essentially eliminated, and compromised outcomes with

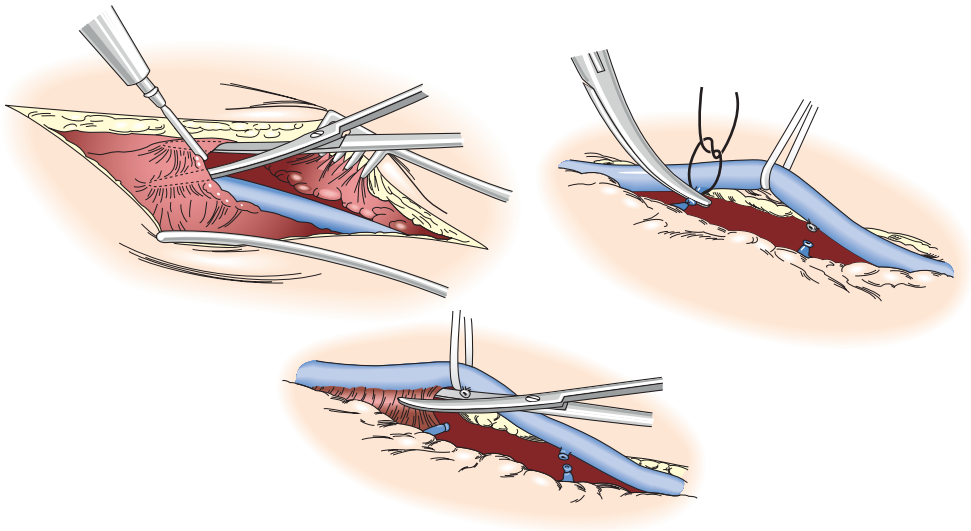


Figure 63.2 "No-touch" technique used in the harvest of autogenous vein. To minimize spasm, papaverine (120 mg/L) is injected into the periadventitial plane before surgical exposure. Side branches are identified and ligated several millimeters away from the wall to prevent luminal narrowing after implantation and outward remodeling of the vein graft. Using a Silastic vessel loop to control the vein without direct manipulation with surgical instruments, the periadventitial tissues are divided and the vein is excised.

nonreversed/excised grafts, which require complete mobilization with valvulotomy. The absence of such differences suggests that careful dissection of the vein is prudent, but absent extensive injury, it is of only modest importance to final outcomes.

Though not examined in the setting of peripheral vein grafts, saphenous vein encased by a thick pedicle of surrounding adipose tissue has been used for coronary bypass grafting with promising results. Morphologic and physiologic studies have confirmed reduced endothelial injury and increased expression of endothelial nitric oxide synthase when compared with the standard technique for vein harvest.[47,48] Prospective randomized clinical testing has demonstrated improved short- and long-term patency with use of the pedicle harvest technique, with 90% versus 76% patency rates at 8.5 years for pedicle versus standard grafts.[49,50] Although this technique may not be applicable to the long-segment grafts required for lower extremity revascularization, it is interesting to speculate on the underlying mechanisms for these improved outcomes, which could include decreased endothelial injury, maintenance of an intact vasa vasorum, or the potential delivery of biologic mediators from the surrounding periadventitial tissue.

Distention Pressure

Cannulation of the vein is required before implantation to evaluate the potential diameter of the graft, assess for leaks, and identify adventitial bands compromising the lumen. Use of a standard small-volume syringe can produce intraluminal pressure in excess of 700 mm Hg.[51] A number of investigations have examined the effect of distention pressure on endothelial integrity and almost uniformly have observed that pressure in excess of 100 mm Hg causes patchy endothelial denudation and that pressure in excess of 500 mm Hg leads to disruption of the underlying media.[52-54] The intrinsic biomechanical properties of the graft are negatively impacted, with a resultant decrease in wall compliance secondary to disruption of the elastic elements within the wall.[55] Biologic function is also influenced, with distention injury initiating an increase in *c-fos* expression, an upstream regulator of platelet-derived growth factor production.[56] Among the few studies to contradict this observation is the work of LoGerfo et al.,[54] who observed no significant injury up to a distention pressure of 500 mm Hg and speculated that their aggressive use of papaverine prevented vasospasm and minimized the effect of overdistention. Nevertheless, a variety of pressure-sensing devices have been developed to allow the surgeon to monitor or control distention pressure. Ranging from syringes with intrinsic pressure transducers to reservoir inflation bulbs that generate a fixed pressure, these devices have undergone only sporadic testing and have never been accepted into widespread clinical use.

Irrigating Solution

An array of irrigating solutions ranging from crystalloids to colloids to autogenous blood has been used during vein harvest. Among the first and still the mostly widely used solutions are the isotonic crystalloids normal saline (pH 5.5, 308 mOsm), lactated Ringer's (pH 6.5, 273 mOsm), and Plasma-Lyte (pH 7.4, 292 mOsm). Although the extent of injury and the magnitude of biochemical perturbations with these solutions are variable and depend on confounding variables such as temperature and the use of pharmacologic adjuncts, the bulk of the literature would suggest that unbuffered, isotonic crystalloid solutions are most damaging to the endothelium.[39,42,51,57] Simple buffered and modified crystalloid solutions (such as tissue culture and whole-organ preservation media) have been investigated and have demonstrated reductions in endothelial denudation and improvements in both cell viability and contractility when compared with an unbuffered saline perfusate.[54,58-61] While buffered crystalloid solutions (e.g., Plasma-Lyte) are readily accessible, the expense and limited availability of complex, modified solutions have limited their widespread adoption into clinical practice. The available literature regarding the efficacy of autologous blood is conflicting. Despite some concern for fibrin deposition, predominantly at higher temperatures, storage in heparinized autologous blood is among the best options for maintaining endothelial confluence.[39,42,51] Published reports, however, are not unanimous, with several suggesting equivalent results when using standard crystalloid solutions with pharmacologic

adjuncts.[60,62] Coupled with more recent studies that demonstrate reduced smooth muscle cell injury and enhanced endothelial relaxation when comparing normal saline against autogenous blood, buffered crystalloid has emerged as the best option for short-term storage of excised vein.[63]

Temperature

Focusing on maintaining endothelial integrity, LoGerfo et al. put forward the concept that warmer perfusate temperatures during active dissection would prevent vasospasm, whereas storage of the graft and minimization of metabolic insult would be best accomplished at a much cooler temperature.[54] Supporting this hypothesis, they demonstrated that infusion of 37°C perfusate during active vein harvest and storage of the distended vein at 4°C minimized the extent of endothelial damage. Notably the influence of this dual-temperature approach was most prominent in saline-treated grafts. Subsequent investigations using a single-temperature approach also favored perfusion with a 4°C irrigation solution,[39,54,57] with blood preferred over saline because of the mural edema associated with cold saline infusion.[42]

Although initial studies focused on endothelial morphology as the primary endpoint, further work in the field diversified to examine the effect of solution temperature on biologic activity of the vein graft wall. Nitric oxide–mediated vasodilation is greatly impaired after storage at 4°C, with room-temperature blood and Plasma-Lyte demonstrating little deterioration when compared with control veins tested immediately after harvest.[64] Analogous studies examining endothelial prostacyclin production and functional thrombomodulin activity support the use of room-temperature perfusates as the best option for preserving metabolic activity.[65,66]

With conflicting experimental evidence, delineation of the most favorable storage temperature is difficult, and reasonable arguments for either cold- or room-temperature treatments can be crafted. Although no definitive recommendation can be proposed, the increased effort required to supply and maintain cold perfusate in the operating suite has prompted most clinicians to favor the use of room-temperature solutions.

Pharmacologic Adjuncts

Unfractionated heparin has universally been included in most vein harvest solutions. Aimed at reducing fibrin deposition and the formation of microthrombi, doses ranging from 4 to 10 U/mL are typically used.[39,57,67]

Prevention of vasospasm is widely identified as being critical in maintaining an intact endothelium, and the use of pharmacologic agents to facilitate this goal may be the most important component of the vein harvest regimen. The most widely studied vasodilator for this purpose is papaverine. Although its exact mechanism of action is unclear, papaverine appears to induce smooth muscle cell relaxation through inhibition of phosphodiesterase and an increase in intracellular cyclic adenosine monophosphate levels. Percutaneous injection of papaverine (120 mg/L) along the outside of the vein before skin incision has been described as an important step to minimize spasm,[67,68] although this can prove challenging in all but the thinnest patients. Application of papaverine along periadventitial tissues and within the lumen perfusate is more easily accomplished and continued throughout vein harvest. Though not rigorously studied as an independent variable, most regimens containing papaverine have shown reduced endothelial injury in comparison to controls.[39,54,57,62]

Other vasodilators have been examined, and a combination of glyceryl trinitrate (8.3 mg/L) and verapamil (16.7 mg/L) appears to be particularly beneficial.[69] In direct comparison to papaverine, glyceryl trinitrate/verapamil demonstrated notable improvement in endothelial coverage.

Even though extensive research has been conducted in this area, no consensus has been reached regarding the optimal techniques for vein graft harvest, with each variable demonstrating unique advantages and shortcomings. Box 63.1 provides a practical summary protocol for the preparation of autogenous vein conduit. The relative importance of these variables is in part illustrated by the work of Adcock et al., who examined the combined benefits of papaverine, autologous blood, and limited pressurization in maintaining endothelial integrity.[39] Even though this combined regimen achieved a significant reduction in endothelial loss at the time of implantation, 71% of the endothelial cells exhibited morphologic abnormalities by the second postoperative day (vs. 92% for the "standard" regimen). More recent work by Brophy et al. expanded on these observations, identifying the application of blue marker dye to the adventitial surface for the purpose of tracking graft orientation during tunneling, over-distension, and storage in a nonbuffered isotonic crystalloid solution as critical factors that accentuate the hyperplastic response.[59,63,70-73] Avoiding these factors improved vasomotor function and limited the widespread metabolic decompensation associated with vein graft preparation.[58]

Although the majority of published regimens have sought to optimize variables to maintain an intact endothelial monolayer or reduce smooth muscle cell injury at the time of implantation,

BOX 63.1 Recommended Vein Graft Harvest Protocol

Handling

- Precise atraumatic technique
- Ligation of tributaries away from the wall
- Lysis of adventitial bands
- Minimization of time from vein excision to implantation

Solution

- Buffered isotonic crystalloid (e.g., Plasma-Lyte)

Temperature

- No definitive recommendation

Distention

- Maximum pressure of 100-150 mm Hg

Pharmacologic Adjuncts

- Heparin (4000–10,000 U/L)
- Papaverine (120 mg/L) or glyceryl trinitrate (8.3 mg/L)/verapamil (16.7 mg/L)

few reports have challenged their techniques to extended exposure in an in vivo environment. Among the clinical investigations in this area was the PREVENT IV trial, which sought to evaluate the efficacy of an E2F decoy in improving coronary vein graft patency.[74] Within the context of this study, three back table storage solutions (unbuffered saline, buffered saline, and blood) were used in a nonrandomized fashion. Given the caveat of potential confounding covariates, the use of buffered saline (compared with either unbuffered saline or blood) yielded a 30% reduction in the vein graft failure rate at 1 year.

Minimally Invasive Vein Harvest

Among the significant complications associated with a single continuous incision for lower extremity vein harvest are wound infection and dehiscence, observed in up to 40% of patients.[75] Minimally invasive approaches to saphenous vein harvest have been developed to reduce incisional length and diminish the attendant morbidity. Early investigations of this technique were initiated without specialized instrumentation but used a series of small, sequential incisions overlying the vein. The use of such "skip incisions" significantly improved primary wound healing, with wound complications developing in 28% of patients with a continuous incision, as opposed to 9.6% of patients in the "skip incision" group.[76] Over the past 2 decades the concept has evolved with the marriage of endoscopic visualization and specialized instrumentation to facilitate minimally invasive vein harvest. Several different devices have been developed for this purpose, all using three small incisions to access the vein and ligate side branches. Used predominantly for harvesting of vein for coronary bypass surgery, prospective randomized human trials have demonstrated significant reductions in wound morbidity when compared with single-incision saphenectomy.[77-79] Increased manipulation of the vein is inherent with this approach and raises concern about increased endothelial damage and accelerated graft failure. Blinded morphologic examination of harvested human vein specimens[80,81] and clinical outcome studies[79] have demonstrated no significant differences in vein injury or graft patency. Universally noted throughout these reports is the steep learning curve that accompanies endoscopic saphenous vein harvest, with many centers identifying a core group of practitioners who focus on this aspect of the procedure. Although performance of these studies at large-volume medical centers can provide insight into the optimum outcomes with this approach, extrapolation to lower volume centers may not be as promising.

Probably related to the long segments of vein required for lower extremity bypass and the prolonged learning curve inherent in this approach, endoscopic vein harvest for peripheral revascularization has not been uniformly embraced. A small number of centers have championed its use, with mixed results. With no randomized trials comparing single-incision with endoscopic saphenous vein harvest for peripheral bypass, experiences have predominantly been reported through case series with retrospective controls.[82-88] These reports generally support the observations in the cardiac literature and suggest that endoscopic harvest offers reduced wound complications with no notable deterioration in short- and long-term graft patency. Not all reports have been favorable, however, with several investigative teams detailing inferior patency rates with little improvement in wound complications after endoscopic vein harvest.[88,89] Compilation across centers, within the context of the Vascular Quality Initiative database and a meta-analysis of 18 published studies, has underscored this observation, where the primary patency was reduced in patients undergoing endoscopic harvest (vs. either continuous or skip incision techniques) with no associated improvement in the incidence of surgical site infection.[90,91]

Among the important conclusions in these studies is the significant learning curve inherent in this technique, with an estimated 40- to 50-patient experience required to become fully competent in harvesting the more difficult below-knee saphenous vein.[92,93] It is noteworthy that the center reporting inferior results performed an average of only one endoscopic harvest per month, probably an insufficient volume to master this technique. Concerns about increased cost of the procedure secondary to additional equipment expenses are relatively unfounded, with these costs more than offset by decreased length of stay during the primary admission and a reduction in the number of readmissions for wound complications.[86]

AUTOGENOUS VEIN GRAFT CONFIGURATIONS

In the preoperative planning stage before open lower extremity revascularization, the surgeon is faced with a number of variables concerning the suitability of various inflow and outflow arteries and the length and quality of the available conduit. Invariably, because of some discordance among the available options, assessment of the potential risks and benefits for each choice is required. Preoperative arteriography and duplex vein mapping provide the baseline data through which primary and secondary operative plans are developed. Direct operative assessment of the intended proximal and distal anastomotic sites and the quality of the autogenous conduit may initiate reevaluation and modification of the intended plan during the course of the operation. A summary of the various factors that influence this decision is provided in Table 63.1.

The conduit of choice is the ipsilateral great saphenous vein, with the contralateral saphenous vein being an appropriate secondary option. To preserve the great saphenous vein in the contralateral limb for future revascularization procedures, some surgeons have advocated the use of alternative conduit as a secondary option.[94] Studies examining this issue are in general agreement that in the absence of advanced ischemia (disabling claudication, rest pain, or tissue loss), use of the contralateral saphenous vein is recommended over alternative conduit because of its length, superior performance, and minimal risk to the donor limb.[95-97] Independent risk factors predictive of the need for future vascular intervention in the contralateral limb include age younger than 70 years, diabetes, coronary artery disease, and an ankle-brachial index (ABI) of less than 0.7. In patients demonstrating three out of these four risk factors, the potential for requiring contralateral revascularization within the next 5 years ranges from 25% to 43%, and the use of alternative

TABLE 63.1 Vein Graft Configurations—Preoperative Planning

Configuration	Advantages	Disadvantages
Reversed	Intraluminal manipulation and valve lysis not required Option for anatomic or nonanatomic tunnel placement	Potential size mismatch at the anastomoses Hemodynamic effect of intact valves Intact valves can complicate graft thrombectomy
Nonreversed	Improved vein-to-artery size match at the anastomoses Option for anatomic or nonanatomic tunnel placement	Intraluminal manipulation and valve lysis required
In situ	Facilitates the use of limited skin incisions Reduced manipulation of the vein with the potential benefit of less traumatic injury Improved vein-to-artery size match at the anastomoses Subcutaneous position assists in operative graft revision	Not an option when using alternative autogenous conduit (arm vein, small saphenous vein) Intraluminal manipulation and valve lysis required Subcutaneous position presents an increased risk for graft exposure with wound infection Construction of the proximal anastomosis may be dictated by length of the proximal saphenous vein

conduit over the contralateral saphenous vein may be a reasonable consideration in this select population.[98]

The approach of using the "best" available autogenous conduit has been advocated[99]; this practice is used routinely by most vascular surgeons. Although vein segments with chronic phlebitis, calcification, or organized intraluminal thrombus are prone to accelerated failure and should be excluded from use,[16,17] the other characteristics that define the "best" vein have been an active area of investigation. Even though single-segment saphenous vein has universally been identified as the most durable conduit, an array of single-institution, retrospective studies has attempted to define the effect of such characteristics as vein diameter, graft type, and orientation on long-term patency.[11,31,100-104] Though useful in framing this question, the most comprehensive examination of this issue can be obtained from the prospective, multiinstitutional PREVENT III (Project of Ex-vivo Vein Graft Engineering via Transfection) database.[32,105] Examining conduit diameter and using veins greater than 3.5 mm as the reference standard, this trial found that grafts ranging from 3.0 to 3.5 mm had a 1.5-fold risk for primary failure. Grafts smaller than 3.0 mm in diameter had a 2.4-fold higher risk for primary failure and a 37% loss of secondary patency at 1 year. In terms of graft type, composite veins had a 1.5-fold increase and arm veins a 1.6-fold increase in primary failure when compared with single-segment great saphenous vein. Graft orientation did not influence patency, with reversed and nonreversed configurations demonstrating equivalent patency rates. As these data demonstrate, deviation from using an adequately sized single-segment saphenous vein carries increased risk for failure, and understanding the magnitude of these risks is critical in operative planning and maximizing the potential for a durable outcome.

Reversed Vein Grafts

Excision of the vein with orientation in a reversed configuration while maintaining antegrade flow through intact valves offers the most straightforward method for vein graft implantation and is suitable for most clinical situations. Difficulty may arise when significant tapering of the saphenous vein in the distal part of the limb creates a size mismatch between the artery and vein graft at both the proximal and distal anastomoses. The proximal vein graft appears to be a common site for luminal narrowing and vein graft failure, and use of small-diameter conduit at this location may accentuate this problem.[106] The size mismatch can be most problematic, however, when performing a tibial or pedal artery anastomosis. A fourfold to fivefold difference in diameters may be encountered, and tailoring the proximal great saphenous vein into a suitable anastomotic configuration can be challenging in these situations.

Examination of normal venous physiology has demonstrated that complete effacement of the valves does not occur during periods of prograde flow. In the low-flow, nonpulsatile hemodynamic environment that characterizes the superficial venous system, the mild to moderate stenosis created by these partially open valves does not translate into a significant loss of pressure or impediment to flow. After implantation into the arterial system, the hemodynamic significance of the valves becomes more pronounced. Though not significantly narrowing the lumen during peak systole, a transition to turbulence with localized regions of stasis is noted within the valves.[107] Lysis of these valves leads to a 15% decrease in hydrodynamic resistance and a 15% to 30% increase in graft flow rates.[108-110] Intact valves have not been proved to adversely influence the long-term patency of reversed vein grafts, but based on these observations, routine valve lysis within these antegrade flow grafts has been proposed.

Less well studied is the biologic effect of the hemodynamic microenvironment within the valve regions, which serve as a nidus for the development of a hyperplastic lesion and focal graft narrowing. Strandness et al. prospectively evaluated the long-term remodeling of these valves in reversed saphenous vein grafts.[111,112] Ten percent of the valves were associated with greater than 50% stenosis, but only 2.5% progressed to a critical stenosis requiring operative intervention; these valves accounted for 17% of the total graft revisions within the 18-month follow-up period. Notably, valve morphology was dynamic, with 60% of the hemodynamically significant valve lesions showing regression to less than 20% stenosis in a mean period of 3 months.

Nonreversed Vein Grafts

Challenges in constructing a reversed-configuration vein graft include significant proximal-to-distal tapering of a vein and the resulting size mismatch at the proximal or distal anastomoses (or both). Although the use of an in situ grafting technique can be one solution to this issue, the combination of complete excision of the vein, lysis of the valves, and orientation in a nonreversed configuration offers an alternative technique. Despite the fact that initial attempts with this approach suggested results inferior to the in situ method, these early efforts were probably compromised by the use of an eversion valvulectomy technique and extensive injury to the vein wall.[113] With subsequent refinements in the approach to valve lysis, nonreversed vein grafts have proved as durable as other available techniques.[114-117]

Although nonreversed vein grafts inherently require increased manipulation with the potential for injury during valve lysis, this shortcoming is theoretically offset by the improved hemodynamics offered by this approach. After valve lysis, nonreversed grafts offer a 20% improvement in flow rates over nonlysed, reversed conduits.[109] This hemodynamic effect is most pronounced in smaller diameter vein grafts ranging from 2.0 to 2.5 mm, where the leaflets from intact valves encompass 45% of the luminal cross-sectional area.[108]

In Situ Vein Grafts

The concept of using the great saphenous vein as a graft with mobilization of only the proximal and distal segments while maintaining the interval region within its subcutaneous bed was initially suggested by Rob's group in 1959.[118] Interested in the potential hemodynamic advantages offered by removal of the valves and retrograde perfusion of the conduit, Rob believed the procedure to be too time-consuming for routine application. Hall, a visiting fellow from Norway, became intrigued by this approach, refined the techniques for routine clinical application, and published the first report of the in situ vein graft technique in 1962.[119] His version of the procedure, requiring valve excision by opening the vein at multiple locations along the graft, was tedious, required significant technical expertise, and failed to gain widespread acceptance. The development of efficient instrumentation for valve lysis provided the opportunity to reduce vein manipulation and maintain an intact vasa vasorum and fueled renewed enthusiasm for the in situ approach. Initial reports of this approach, championed by Leather et al.,[120] suggested improved patency over excised vein grafts.[121] These early analyses are compromised by the use of historical controls, however, and contemporary comparisons of in situ versus reversed or nonreversed grafts fail to demonstrate significant differences in long-term outcomes.[46,116,122]

Preparation of the saphenous vein for use in situ as an arterial bypass entails (1) mobilization of the proximal and distal segments for construction of the anastomoses, (2) removal of the valvular obstructions to arterial flow, and (3) interruption of the venous side branches to prevent the formation of arteriovenous fistulae. The objective is to accomplish these tasks in the most expeditious manner while minimizing traumatic injury to the vein.

Proximal and Distal Anastomoses

The common femoral artery serves as the most common source of inflow for infrainguinal revascularization, and the relative position of this artery and the confluence of the superficial inguinal veins dictates construction of the proximal anastomosis. Mobilization of the proximal great saphenous vein is accomplished by secure ligation of the superficial branches, placement of a side-biting vascular clamp across the common femoral vein, transection of the great saphenous vein flush with the wall, and repair of the femoral vein with running nonabsorbable suture. Lysis of the most proximal great saphenous valve can be difficult with standard valvulotomes, but localized eversion of this segment permits excision of the valve under direct vision. Intrinsic atherosclerotic disease in the common femoral artery may dictate more proximal placement of the anastomosis. Additional proximal vein length can be obtained by harvesting a segment of the superficial epigastric vein and extending the venotomy proximally along the posterior surface of this vein to provide an autologous patch for repair of proximal common femoral artery disease. Care should be taken to minimize longitudinal stretching of the graft, which can accelerate the development of intimal hyperplasia.[123] Extensive common femoral or profunda femoris origin disease (or both) may necessitate endarterectomy with patch angioplasty or graft replacement of the common femoral artery. In the absence of significant proximal artery occlusive disease, defined as greater than a 50% reduction in lumen diameter, the superficial femoral, profunda femoris, or popliteal artery can be considered for placement of the proximal anastomosis.[124]

The posterior tibial, peroneal, and dorsalis pedis arteries provide the most straightforward options for placement of the distal anastomosis. Although the below-knee popliteal artery can also be used, fashioning the anastomosis can be problematic because of the nearly 90-degree angle that is formed between the graft and artery. With most hemodynamic analyses detailing an increase in flow separation and activation of proliferative metabolic pathways with right-angle anastomoses, grafts configured to this segment of the popliteal artery may benefit from excision and placement in an anatomic tunnel. Distal anastomoses to the above-knee popliteal artery do not offer the same constraints on their configuration; however, after mobilization of the proximal and distal graft, the segment that remains in situ can be quite short and of limited benefit.

Valve Lysis

Although limited transverse venotomies were used in initial development of the in situ bypass graft, this approach to render the valves incompetent has given way to less invasive techniques. Valvulotomes have undergone a variety of revisions over the last several decades, and the current generation of devices can be classified into three categories—the modified Mills valvulotome, the adjustable valvulotome, and the fixed valvulotome (Fig. 63.3).

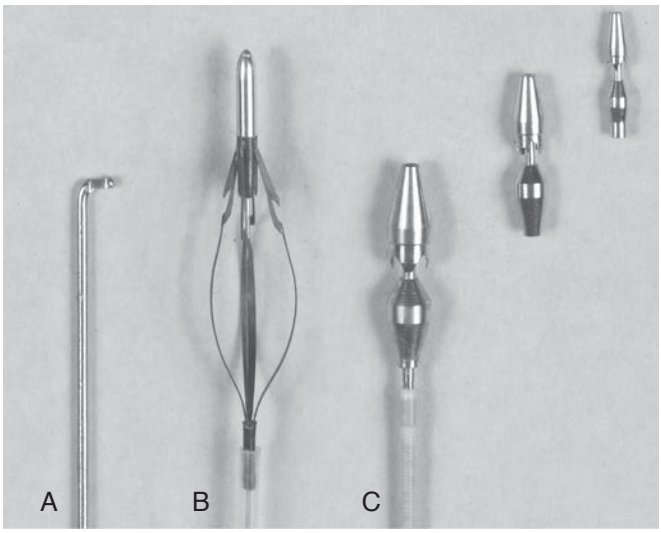


Figure 63.3 Valvulotomes. (A) Modified Mills. (B) LeMaitre adjustable. (C) Uresil fixed with 2-, 3-, and 4-mm cutting heads.

The modified Mills valvulotome (see Fig. 63.3A) was initially described in 1976 for application to coronary artery bypass surgery.[125] With limited modification, this device was rapidly adopted for use in peripheral vascular surgery. Introduced into a side branch or the distal end of the vein, the device is advanced through the valve leaflets (Fig. 63.4). The proximal vein graft is distended by arterial inflow or manual infusion to induce valve closure, and the valvulotome is slowly withdrawn until the reverse cutting blade engages the valve leaflet. The tip of the valvulotome is maneuvered toward the center of the lumen, and a short burst of inferior traction is applied to transect the valve.

Popularized by LeMaitre et al., the expandable valvulotome offers four cutting blades encompassed within a self-centering series of wire hoops (see Fig. 63.3B).[126] With the blades encased in a protective sheath, the device is advanced to the proximal end of the vein graft. The vein is distended, the cutting system deployed, and the device slowly withdrawn. Because of the mobility of the wire hoops, the position of the cutting blades is self-adjusting to accommodate vein diameters between 1.8 and 6 mm.

Fixed-diameter valvulotomes were developed from the original work of Hall, in which a blunt-tipped vein stripper was passed proximally to distally through the graft to avulse the valve leaflets and render them incompetent.[127] The addition of cutting blades and detachable heads of varying size led to the current generation of devices (see Fig. 63.3C).[128] A 2-, 3-, or 4-mm head is secured to a flexible shaft and reintroduced into the lumen of the vein. As with the other devices, the proximal vein is distended and the valves are lysed with a rapid burst of inferior traction.

Visualization studies after the application of valvulotomes report that complete disruption occurs in approximately 70% to 95% of the treated valve leaflets.[129,130] Proximal segments of the vein, where the size mismatch is most pronounced, are most likely to demonstrate only partial valve disruption; thus careful attention to this region seems warranted.[129] Limited

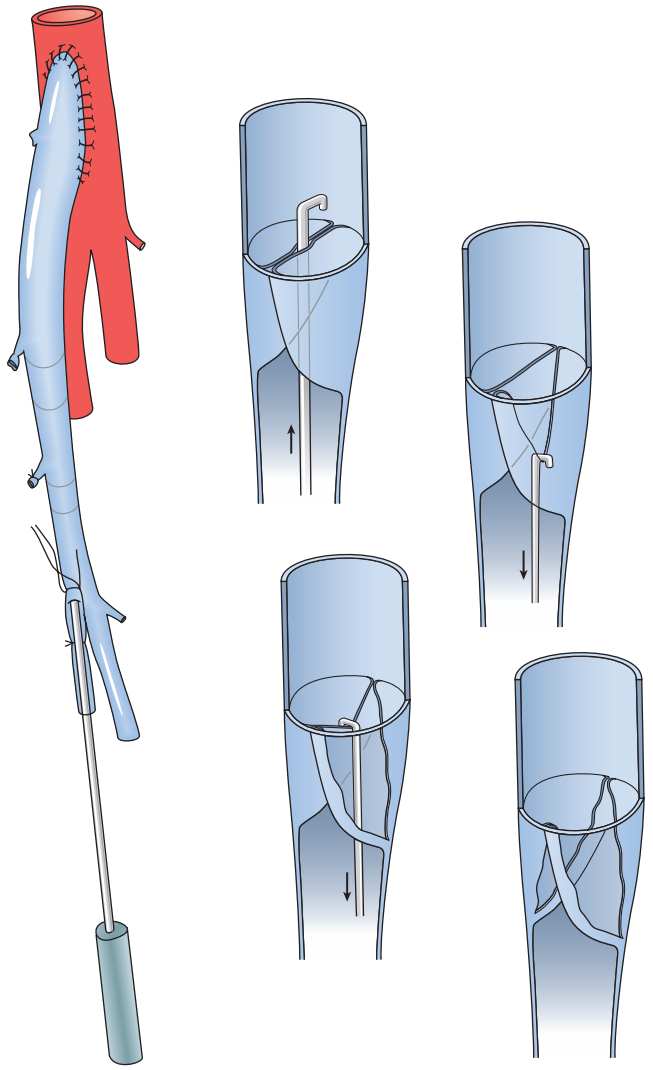


Figure 63.4 Valve lysis using the modified Mills valvulotome. The valvulotome is inserted into a long side branch and advanced into the proximal vein. Competent valves within the graft are maintained in closed position by arterial inflow pressure, and the valvulotome is withdrawn until resistance is encountered. After ensuring that the instrument has not engaged a side branch, a short burst of inferior traction is delivered and the valve leaflet transected. Short advancement and 180-degree rotation of the valvulotome permit division of the opposite valve in analogous fashion.

data providing a direct comparison among the types are available, with one study suggesting incomplete valve lysis to be more common with expandable valvulotomes[130] and another suggesting no differences among the groups.[131] A prospective randomized trial comparing clinical outcomes for fixed and expandable devices failed to show any difference in short-term patency.[131]

Intraoperative angiography, duplex scanning, and angioscopy have been proposed as suitable adjuncts to evaluate the completeness of valve lysis during in situ bypass grafting. Angiography and duplex scanning are relatively insensitive modalities for identifying retained valves and detect only about 20% of such valves; angioscopy is much more sensitive.[132] Used for either direct visualization during valve lysis or graft surveillance, angioscopy is successful, with a sensitivity of identifying retained

valve cusps approaching 100%. The clinical implications of identifying these valve abnormalities are uncertain, and several studies suggest no long-term improvement in graft patency with the routine use of angioscopy.[133,134] Potentially the most notable benefit from routine angioscopy may be the identification of significant preexisting venous disease. Veins with preexisting pathology have a high rate of early graft failure, and intraoperative recognition of these compromised vein segments may be the most important role for prebypass angioscopy.[76,135] Angioscopy may also be especially important in the evaluation of arm vein conduits because of their documented increased frequency of intrinsic vein abnormalities (see the "Arm Vein and Composite Grafts" section later in this chapter).

Side Branch Ligation

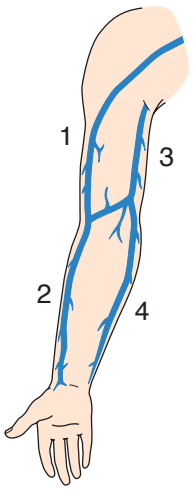
Without the need to mobilize the vein from its subcutaneous bed, multiple options are available for treatment of the venous side branches. The standard approach would be complete exposure of the great saphenous vein with a single continuous incision that extends the length of the leg. Although this open approach simplifies side branch ligation and valve lysis; it has been associated with a wound complication rate in excess of 40% in some reported series.[75,136] These complications are of even more significance because of the superficial location of the in situ bypass. Even though extended rehospitalization and operative débridement may be required, these wounds can usually be managed without loss of graft patency.

Noninvasive identification of the major side branches offers the opportunity for a limited-incision or semiclosed in situ technique. Intraoperative venography and duplex scanning are two readily available options for this task, but these methods can be surprisingly inaccurate and fail to recognize almost 50% of the side branches.[132] Using the angioscope to identify the orifice and transcutaneous illumination to guide the location of the skin incision has proved somewhat more successful, with detection of approximately two-thirds of patent side branches.[132,136] Commensurate with the smaller size of the incisions, these approaches offer notable improvement in wound complication rates.[133,136] Graft patency rates are relatively unaffected by the operative approach, but an increased incidence of persistent arteriovenous fistulae has been documented with most semiclosed techniques. Studies examining persistent fistulae have generally recommended their ligation; however, such an aggressive approach has been called into question. Conservative management of these fistulae results in spontaneous closure in a third of cases, with eventual revision for reduced distal graft velocity in a third, and a third remaining stable without intervention.[137,138]

Arm Vein and Composite Grafts

The ipsilateral great saphenous vein is clearly the most desired conduit, but reports suggest that it is absent in up to 45% of patients requiring infrainguinal revascularization.[139] Use of single-segment or composite arm grafts provides an important alternative in such challenging patients. The most extensive experience with arm vein bypass is detailed through a series of reports from the Beth Israel Deaconess Hospital.[94,103,140] Preoperative duplex evaluation of the upper extremity veins is critical in the operative planning for patients with inadequate or previously harvested ipsilateral saphenous vein. A summary of the advantages and disadvantages of available arm vein conduits, along with an estimate of their relative frequency of use, is provided in Fig. 63.5.[94]

To take advantage of the larger veins in the upper part of the arm, the basilic-cephalic loop graft has been proposed.[141,142] Using the median cubital vein as the connecting segment, the cephalic and basilic veins are harvested in a continuous loop from the antecubital fossa to their termination in the axillary vein. With the larger basilic vein serving as the proximal vein



Upper extremity vein segment	Frequency of use	Comment
1. Cephalic vein (arm)	70%	Uniform diameter 4-6 mm Implant reversed due to thin walls for lysis Can be harvested within the deltopectoral groove
2. Cephalic vein (forearm)	45%	Intraluminal webs and phlebitis common Wall thickness adequate for valve lysis
3. Basilic vein (arm)	50%	Significant diameter change along the length Valve lysis difficult due to large proximal diameter Located subfascial in its proximal portion
4. Basilic vein (forearm)	2%	Smallest caliber of the upper extremity veins Posterior position minimizes previous iatrogenic injury

Figure 63.5 Superficial upper extremity veins available for use in bypass grafting, including individual considerations and relative frequency of their use. (Hölzenbein TJ, Pomposelli FB Jr, Miller A, Contreras MA, Gibbons GW, Campbell DR, Freeman DV, LoGerfo FW. Results of a policy with arm veins used as the first alternative to an unavailable ipsilateral greater saphenous vein for infrainguinal bypass. *J Vasc Surg.* 1996;23(1):130–140.)

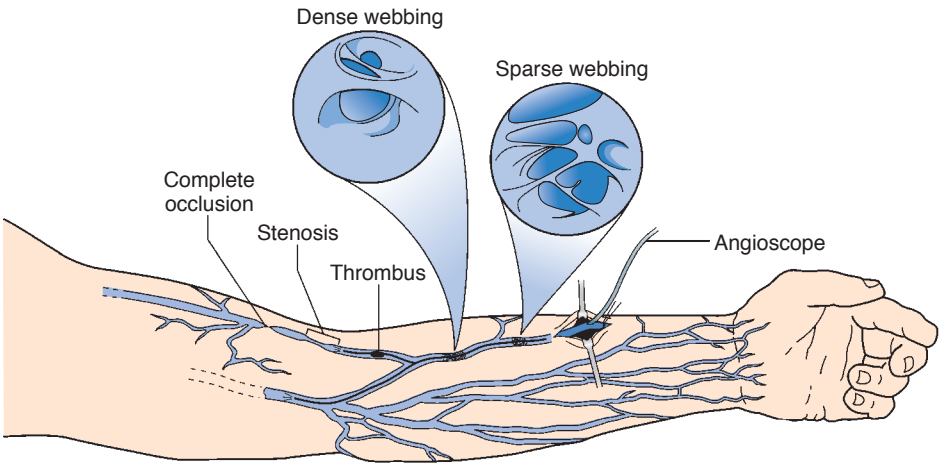


Figure 63.6 Iatrogenic injury to upper extremity veins leading to stenosis or segmental occlusion is common. Although preoperative duplex vein mapping can be helpful, intraoperative angioscopy offers the potential for precise localization of these compromised areas.

graft, a valvulotome is introduced into a midgraft side branch to facilitate lysis of valves in the basilic and median cubital segments. The cephalic vein segment, which tends to be thin-walled and troublesome for valve lysis, is maintained in a reversed configuration and used for the distal anastomosis.

Similar to the approach when using lower extremity veins, single-segment arm vein is preferable. Through extensive use of the median antecubital vein as a bridge, success can be achieved in up to 80% of cases requiring the use of arm vein.[94] Limiting this effort, however, is the inherent iatrogenic injury that occurs from repeated cannulation (Fig. 63.6). Veins that are most superficial and anatomically accessible, such as the forearm cephalic and median antecubital, are most frequently damaged, with 30% to 50% of these veins demonstrating a variety of pathologies.[143] Angioscopic evaluation of the quality of the arm vein and identification of compromised segments are thus fundamental to achieving long-term patency in these grafts. Minor abnormalities such as sparse webbing or an adherent thrombus can be successfully treated by endoluminal repair to restore a widely patent lumen. Other pathologies such as dense webbing or focal stenosis may require local repair with vein patch angioplasty. Marked abnormalities such as sclerosis with long-segment stenosis or occlusion cannot be repaired locally and require resection of the abnormal segment. Using such a treatment strategy, 25% of arm veins required local repair and 16% required resection, with no difference in long-term patency when compared with a good-quality arm vein that required no intervention.[94] In the subset of grafts in which a segment of suboptimal-quality vein was used, failure within 6 months of implantation was common.

Small Saphenous Vein Grafts

Although lacking the length offered by the great saphenous vein, the small saphenous vein can be a useful source of autogenous conduit in the vein-limited patient. Arising from tributaries lateral to the calcaneus and terminating in the popliteal fossa, this conduit is predominantly used in combination with other vein segments in a composite configuration. Preoperative duplex evaluation is critical to evaluate adequacy, with a lumen diameter of 3.0 mm considered suitable for grafting. Small saphenous vein is usually the third choice of autogenous vein (behind great saphenous and arm vein) because of the inherent difficulties in surgical exposure and harvest. While initial reports described use of a medial leg incision with development of a subfascial plane along the enveloping fascia of the superficial posterior compartment,[144] most surgeons currently use a posterior leg incision for surgical exposure of this conduit.[145-148] Short, unilateral segments of vein can be harvested with the patient in the traditional supine position by elevating the leg, with the surgeon positioned inferior to the extremity. However, extensive unilateral or bilateral harvests are best accomplished using an initial prone position, in which the veins are excised, wounds closed, and the patient rotated into a supine position for completion of the procedure. In an attempt to use the posterior leg veins as a single conduit for femorotibial bypasses, the Giacomini vein can be harvested in continuity with the small saphenous vein.[149] Although this extension of the small saphenous vein into the thigh is present in approximately two-thirds of individuals, details regarding the size distribution for this conduit and intermediate to long-term patency have not been reported.

Patients with isolated tibial artery occlusive disease may be candidates for in situ bypass using the small saphenous vein. Employing a posterior approach for exposure of the proximal and distal anastomotic sites, popliteal-crural bypasses to each of the three tibial arteries can be performed. Cumulative 1- and 3-year primary patency for these grafts is 75% and 60%, respectively,[147,148] approximating the same results observed with in situ grafting using the great saphenous vein. However, the durability of small saphenous vein used in composite grafting is notably inferior, with 1- and 3-year primary patency of 50% and 35%, respectively.[148]

Femoral-Popliteal Vein Grafts

Although primarily used for intraabdominal vascular reconstructions in most current day treatment algorithms, the

femoral-popliteal vein was initially investigated as the potential conduit of choice for lower extremity bypass procedures.[150-153] With promising results demonstrated in a retrospective review of their clinical practice, Schulman et al. initiated a prospective, randomized trial comparing autogenous femoral-popliteal vein to saphenous vein as the preferred conduit for infrainguinal bypass.[153] Based on a total enrollment approaching 100 patients, no significant differences in 5-year primary patency (55%) and limb salvage rates (70%) were observed. Thirty-day mortality and early postoperative complications were also similar in both groups. Follow-up examination to evaluate the long-term sequelae of deep vein harvest demonstrated chronic calf swelling and an obstructive pattern on venous plethysmography, but no significant increase in stasis dermatitis or venous ulceration.[154] Although no objective differences were observed between the femoral-popliteal and saphenous vein groups, the authors concluded that the increased complexity associated with femoral vein harvest made the saphenous vein the preferred conduit for lower extremity revascularization. Nonetheless, these data support the use of femoral-popliteal vein as a viable source of alternative conduit in select patients.

Superficial Femoral Artery Grafts

Patency of an occluded segment of excised superficial femoral artery can be restored via an eversion endarterectomy, providing an autogenous conduit up to 25 cm in length that is suitable for short interposition or composite grafting.[155] Although conceptually these conduits were thought to be useful in the salvage of patients with prosthetic graft infection, rupture of the anastomosis was observed in 75% of those grafts placed in an infected field.[156] When used in combination with an autogenous vein, patency rates for these composite grafts have demonstrated marginal 1-year primary patency rates (60%).[156,157] Frequently the mechanism of failure for these conduits was acute thrombosis in the absence of a stenotic lesion, which is different from what is usually seen in autogenous vein grafts.[157]

Hypogastric Artery Grafts

Facilitated by the rich collateral network in the pelvis, the hypogastric artery offers an available source of autogenous conduit for short segment, intraabdominal reconstructions. With a cascade of associated branches, this graft offers the ability to create several distal anastomoses from the primary graft, an advantageous configuration for use in complex aortorenal bypass procedures.[158] Although used sporadically in the adult population,[159,160] this segment of artery is the conduit of choice for renovascular reconstructions in the pediatric population.[161,162] Autogenous vein grafts, because of the propensity for late aneurysmal dilation in children, are rarely used for pediatric aortorenal bypass procedures. Although no detailed analysis of hypogastric artery patency has been performed, anecdotal experience across multiple centers support that a normal autograft placed without technical error should provide lifelong patency.[158-162]

ETIOLOGY OF VEIN GRAFT FAILURE

Technical Factors

Traditionally, graft occlusions within 30 days of implantation have been thought to be related to technical factors that could potentially have been corrected at the time of graft placement. Although flow-limiting lesions within the bypass graft are a clear component of these failures, estimated at about 20%,[163] the events leading to graft thrombus are clearly more complex. Similar to the etiology of venous thrombosis, Virchow's classic triad is probably at the intersection of early graft failure. Not uncommon is the scenario in which early graft failure prompts reexploration, which fails to identify any clear underlying cause.[163] Endothelial injury related to manipulation of the graft, hypercoagulability in the early postoperative period, and reduced graft flow because of inflow, outflow, or graft stenosis are factors that contribute to these early failures.

With insufficient time for formation of significant intimal hyperplasia, graft failures within 30 days are thought to be technical if they are associated with one of four categories: inadequate inflow, inadequate outflow, extrinsic lesions, and intrinsic lesions.[164] Inadequate inflow may be secondary to an unrecognized lesion in the proximal arteries or inflow graft. More common is the scenario in which the importance of the proximal lesion is underestimated, only to have its hemodynamic significance unmasked after placement of the distal graft. The resulting increase in flow leads to an accentuated drop in pressure across the lesion and converts a previously innocuous lesion into one that now has important hemodynamic implications. Cardiovascular compromise, such as systemic hypotension or a low cardiac output state (e.g., cardiogenic shock), can also be the cause of inflow-related graft failure.

Inadequate outflow as a result of extensive, preexisting tibial and inframalleolar occlusive disease is an established risk factor for early graft failure; patients demonstrating the most severe disease have a 10-fold increased risk for 30-day graft thrombosis.[165,166] Vasospasm of the target artery is a less well-studied but possible contributor to early postoperative outflow compromise. Though difficult to quantify and monitor postoperatively, a subset of patients demonstrate severe luminal narrowing and delayed reperfusion despite minimal atherosclerotic disease in the distal artery (Fig. 63.7).

Extrinsic causes of early graft failure include extrinsic compression because of tunneling errors or hematomas that may compromise graft flow. Other extrinsic causes of graft failure, such as hypercoagulability, are systemic. Alterations in the coagulation system are detectable in more than 25% of patients undergoing lower extremity revascularization.[167] Although some studies have suggested that 10% of early graft failures are primarily related to an identified hypercoagulable state,[163] the contribution of transient abnormalities in coagulation is unclear and perhaps underestimated.

Intrinsic vein graft defects include focal, flow-limiting lesions such as a retained valve leaflet, an intimal flap, or inappropriate placement of anastomotic sutures. Limitations in flow can result from the use of an undersized conduit, with vein grafts less

Figure 63.7 Intraoperative digital subtraction arteriogram of a vein bypass graft to the distal anterior tibial artery. Severe distal spasm of the outflow artery *(arrow)* has led to diminished diastolic flow in the graft.

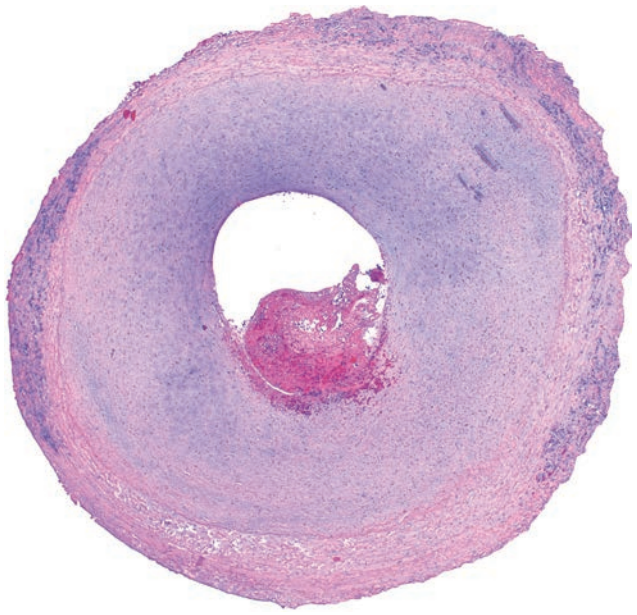


Figure 63.8 Cross-sectional histologic image of an 8-month-old vein graft demonstrating severe intimal hyperplasia. Adherent thrombus is present within the severely compromised lumen.

than 3.0 mm in diameter being at significant risk for early failure.[166] Independent of luminal narrowing, intrinsic vein graft defects, such as sclerosis and calcification, also contribute to graft thrombosis.[17]

Recent data from the multi-institutional PREVENT III trial have detailed a 5% incidence of thrombosis or reexploration within 30 days of graft implantation.[105] Whereas endovascular management of these early graft occlusions is of limited value, open surgical revision provides a reasonable opportunity for durable graft salvage, with a 90% 1-year patency rate reported after successful exploration and revision.[168]

Intimal Hyperplasia and Pathologic Remodeling

Surgical manipulation of the vein combined with the acute exposure to elevated shear and tensile forces elicits a complex series of biologic events in the vein wall that begins immediately on implantation. Analogous to the events that occur in generalized wound healing, repair of the damaged vein graft is initiated by the local synthesis of a wide variety of cytokines and growth factors. Chemokines induce the recruitment of neutrophils and mononuclear cells, which further amplifies these pathways. Activated by these chemoattractants and mitogens, smooth muscle cells begin to dedifferentiate from a contractile to a synthetic phenotype and replicate within the media. By tracing the gradient of chemokines, liberated smooth muscle cells migrate from the media to the intima, where continued proliferation and abundant matrix deposition are stimulated. Progressive thickening of the intima leads to narrowing of the lumen, a reduction in graft flow, and intraluminal thrombosis (Fig. 63.8).

Despite the relative uniformity of the surgical trauma and hemodynamic insult, vein graft lesions demonstrate a strong tendency to be focal rather than diffuse.[169] With a peak incidence at 4 to 12 months after implantation, 30% to 45% of autogenous grafts will fail or require revision secondary to significant narrowing of the lumen.[105,170] Stenotic lesions are more likely to be associated with the proximal or distal anastomosis (53% incidence) but occur not infrequently in the midbody of the graft (30% incidence).[106] It has been postulated that these midgraft lesions are associated with valve leaflets; detailed evaluation of this issue demonstrated substantial remodeling within valve sites, but progression to high-grade stenosis was rare and accounted for less than 20% of the intrinsic graft lesions requiring repair.[112] Despite such general observations, the underlying biologic mechanisms for development of this segmental pattern of intimal hyperplasia remain poorly understood. Although the local flow environment plays a significant role, physical forces in isolation fail to explain these observations. More likely, critical lesion development occurs at the intersection of localized trauma, ongoing hemodynamic stress, and an altered ability for local repair after injury.

Although much of the emphasis in vein graft pathology has focused on intimal hyperplasia, graft morphology is actually dictated by the balance between outward expansion and wall thickening. As Glagov et al. demonstrated, the normal vascular adaptive response is an increase in overall wall circumference to compensate for luminal narrowing in the presence of a developing occlusive lesion.[171] In response to hemodynamic and biochemical stimuli, smooth muscle cells degrade and reorganize the rigid matrix structure of the wall to facilitate these changes. Examination of early vein graft morphology

demonstrated a 20% increase in diameter within the first month after implantation; failure of this outward remodeling has been correlated with subsequent graft failure.[172] Inflammatory pathways appear to further modulate this shear-mediated adaptive response, thus providing potential mechanistic insight into the heterogeneity that is observed clinically.[173]

Graft Atherosclerosis

Although the peak incidence of vein graft failure occurs within the first year, delayed progression of intrinsic lesions leads to a 4% annual loss of graft patency in the 2- to 10-year time frame.[9,170] Because studies have focused predominantly on the mechanisms of early graft failure, insight into the pathology of delayed lesion development in peripheral vein grafts is limited. Much of our understanding of late graft failure is derived from coronary bypass grafts examined at the time of autopsy. Replacement of the fibrotic wall with lipid-laden macrophages and intramural calcification is common.[174-176] Degeneration of the vein graft wall with intramural thrombus formation, characteristic of ruptured atherosclerotic plaque, is also frequently observed.[177,178] Supporting these observations is the clinical impact of lipid-lowering therapy on coronary artery graft patency, where reductions in total serum cholesterol significantly enhance vein graft durability.[179-181]

With few relevant animal models, examination of these events in peripheral bypass grafts has been relegated to the analysis of sporadic samples obtained at the time of graft revision. The initial report published by Szilagyi et al. in 1973 identified atherosclerotic changes in 8 of 21 grafts ranging in age from 8 to 96 months.[169] These observations are supported by Walton et al., who described apolipoprotein B deposits, ulceration, calcification, and aneurysm formation in the majority of failed grafts that had been implanted for more than 2 years.[182] More recent reports, however, present a more variable picture and predominantly describe a fibrocellular hyperplastic intima with rare atherosclerotic degeneration as the cause of late failure.[183] Although investigators have speculated that modulation of early intimal hyperplasia will have an impact on cholesterol-driven atherogenesis and provide an avenue to improve graft patency, this view remains speculative with limited data to support it.[184,185]

Autogenous Graft Modifications to Improve Durability

For the last two decades, the prevailing concept in vein graft biology was that the initial stages of adaptation were critical in defining the long-term future of the conduit. Specifically, it has been hypothesized that inhibition of the early wave of smooth muscle cell proliferation would mitigate the development of stenotic lesions months to years following implantation.[186] Emanating from this strategy, edifoligide emerged as the most promising approach to improve vein graft durability. The regulation of cell cycle kinetics and DNA replication are under the control of the E2F pathway, and the double-stranded oligodeoxynucleotide edifoligide was designed to bind and inactivate the E2F family of transcription factors. Applied to the harvested vein, this therapeutic agent was developed to inhibit the burst of smooth muscle cell proliferation that is initiated in the first several days following implantation.

Based on successful preclinical studies in a rabbit vein graft model, human phase I and II clinical studies examining edifoligide were initiated.[187-189] Demonstrating safety and a suggestion of possible efficacy,[190,191] two phase III clinical trials (PREVENT III and IV) were undertaken to investigate the use of edifoligide in infrainguinal and coronary artery revascularization. Following randomization of 4400 patients, treatment with edifoligide was demonstrated to have no influence on vein bypass graft durability.[192,193] Although these were landmark trials in their attempts to directly modulate the biology of an implanted vein graft, the lack of a significant clinical effect has led to a reassessment of the fundamental paradigms in the field and the current wave of investigative research.

- *Delivery vehicles*—Founded in the concept that mitigation of the early vein graft response to injury prevents unchecked intimal hyperplasia, the PREVENT trials used a naked oligonucleotide approach to inhibit E2F binding to the promoter sites. The lack of clinical efficacy has brought into question such approaches using a single, ex vivo application of a therapeutic agent at the time of graft implantation. A more sustained but still transient delivery method, such as that offered by adenovirus, or the stable integration of a biologic modifier into the genome, using adeno-associated virus or lentivirus, may be more effective strategies for achieving a durable clinical outcome.[194,195]
- *Biologic processes*—Interrupting E2F binding, along with the transition from G1 to S phase within smooth muscle cells, was thought to be the critical event in improving vein graft survival. Although the conceptual model that smooth muscle cell proliferation leads to intimal hyperplasia and results in luminal narrowing and graft thrombosis is attractive in its simplicity, vein graft injury and repair occurs via a coordinated series of overlapping events.[196] Endothelial damage and recovery, local thrombosis, smooth muscle cell apoptosis, and matrix deposition are all components of the adaptive process. Accentuating or inhibiting one or more of these parallel events may be required.
- *Molecular targets*—Genomic analyses following vein graft implantation have failed to identify a single target that dominates the adaptive process.[197] Instead, the enhancement or repression of various biologic processes occurs via the broad modulation of the entire set of integrated pathways.[198] Central mediators offer the best opportunity for successful modifications, and this is supported by the recent investigations in the association between single nucleotide polymorphisms in the cyclin-dependent kinase inhibitor 1B (p27Kip1) gene and vein graft patency.[199] Influencing cell cycle progression at G1, this inhibitor protein acts as a gatekeeper to modulate cell division. While promising for further investigation, it is likely that a multitarget approach at specific times during the adaptation process is required for a robust and durable impact on vein graft morphology. An alternate approach is to develop a response system that adapts to the local biology of the environment. This concept is the

foundation for use of autogenous cells, which, when placed in a perivascular position, modify the signaling milieu to positively impact the local biology of the vein graft wall. Such approaches have been examined in early phase human trials and are moving toward phase III testing.

PREVENTION OF VEIN GRAFT FAILURE

Intraoperative Evaluation

Despite improvements in surgical technique, 5% of autogenous vein grafts fail within 30 days of implantation.[105] Retained valve leaflets, abnormal twists or kinks, intimal flaps, other unrecognized obstructive lesions, and technical defects at the time of graft placement are estimated to account for between 15% and 25% of early failures.[200,201] The initial technical adequacy of an infrainguinal bypass graft can be judged intraoperatively by the external appearance of the bypass and anastomoses and by the restoration of distal pulses and perfusion. Continuous wave Doppler is a useful intraoperative adjunct that permits evaluation of anastomoses and areas of concern within the body of the graft for localized increases in the audible sound frequency. Though adequate for gross defects, a more detailed assessment to ensure technical success and to optimize short- and intermediate-term graft patency has been advocated. Recent investigations report a 15% intraoperative graft revision rate for abnormalities identified on secondary imaging.[202] Although it is unclear to what extent these irregularities increase the risk for graft failure, the significant morbidity resulting from early reintervention for graft failure supports an aggressive approach to intraoperative repair.[203]

Angiography

Contrast-enhanced angiography remains the diagnostic standard for arterial anatomic imaging and is the most widely used method for intraoperative vein graft assessment. Facilitated by the increasing availability of high-quality intraoperative angiographic equipment, this technique provides the current standard for determination of technical adequacy of a bypass graft. Though particularly useful for identifying a kink or twist in the graft, a patent side branch or branch ligature stenosis, and distal arterial disease requiring sequential bypass,[204] angiography has several notable shortcomings. Limited by a single projection plane and the dense opacification provided by iodinated contrast material, retained valve leaflets and intraluminal webs can be difficult to identify, with one study reporting failure rates approaching 80%.[132] Particularly troublesome is the angiographic evaluation of the distal anastomosis and delineation of a structural abnormality versus spasm in the outflow artery (see Fig. 63.7). Significant spasm occurs in approximately 50% of tibial and pedal artery bypasses, but it is of no clinical consequence in the large majority of cases.[205,206] Routine intraluminal injection of papaverine hydrochloride (30-60 mg in 1-2 mL of 0.9% saline) into the vein graft before performing completion angiography has been advocated to alleviate vasospasm.[207]

With these technical limitations, the use of a standard evaluation algorithm (consisting of visual inspection, palpation, and interrogation with continuous wave Doppler) with selective arteriography has been proposed. Mills et al. noted that these simpler techniques failed to identify 80% of the vein graft and outflow abnormalities that were detected by completion angiography and required revision.[208] Focusing on 1-year patency as the primary endpoint, other investigators examining this issue arrived at the opposite conclusion and stated that the additional expense of routine arteriography outweighs its benefit.[209] In the latter retrospective review, where no difference in graft patency was observed in association with routine or selective angiography, patient enrollment was modest and statistical analysis insufficiently powered to allow firm conclusions. Completion angiography provides useful anatomic information, especially with regard to the status of the outflow arteries; its major weakness is that it fails to provide any hemodynamic assessment.

Flow Rate Measurements

Non-imaging-based modalities such as measurement of blood flow rates have been advocated as useful adjuncts in the intraoperative evaluation of vein grafts. Based on the assumption that flow-limiting stenoses could be detected by reductions in flow, investigators identified 80 mL/min as the critical threshold below which there was a high probability of a technical problem within the reconstruction and for which further evaluation with angiography was suggested.[210] Although of interest, this approach has largely been supplanted by duplex imaging. The use of intraoperative flow measurements has also been described as an independent predictor of graft patency. Despite being unreliable in identifying grafts at risk for early (<30 day) failure,[211] extensive literature confirms the importance of graft flow rates in determining intermediate- and long-term patency.[212-214] Not surprisingly, flow rates demonstrate high correlation with the angiographic runoff score[165] and can serve as a surrogate for this well-established risk factor with limited direct application to intraoperative decision-making. More quantitative assessments of graft hemodynamics, such as the resistive index and longitudinal impedance, have also been proposed.[215,216] Similar to flow rate measurements, these parameters have prognostic significance but little utility in therapeutic decision-making.

Duplex Scanning

After angiography, duplex scanning has developed into the next most commonly used intraoperative method for evaluation of vein grafts. Duplex uses B-mode imaging and velocity spectrum analysis to detect lesions and grade lesion severity, thus providing both anatomic and hemodynamic assessment. Initially described by Bandyk et al. for the assessment of in situ bypass grafts,[217] duplex scanning proved effective in the identification of competent valve leaflets, anastomotic narrowing, arteriovenous fistulae, hemodynamic stenosis caused by small-caliber conduit, and the intraoperative formation of fibrin-platelet aggregates. With evolving diagnostic criteria, duplex scanning was initially thought to be too sensitive and best suited for use as a screening tool in combination with selective arteriography to better define

suspect areas. Subsequent refinements in both instrumentation and interpretation have yielded improved accuracy, with multiple studies supporting the replacement of intraoperative angiography with duplex scanning.[218-220] Although the published literature has been unequivocal regarding the value of intraoperative duplex, application has been limited predominantly to centers of excellence where sufficient skilled vascular technologists are available to support these efforts.

A standardized procedure for intraoperative duplex graft scanning has been proposed by Johnson et al.[202] Before scanning, papaverine (30-60 mg) is injected into the distal vein graft segment with a 27-gauge needle. Using a linear-array 7- to 15-MHz transducer (for superficial grafts) or 5-MHz transducer (for tunneled grafts), velocity spectra along the distal anastomosis and outflow artery are recorded while maintaining a 60-degree Doppler angle. The entire length of the graft is then scanned in a distal to proximal direction to evaluate color-flow images and velocity spectra for retained valves and residual arteriovenous fistulae (if applicable). Evaluation is completed with scanning of the proximal anastomosis and inflow artery. Diagnostic criteria for elevated velocities and an appropriate management algorithm are presented in Table 63.2. In one center using this protocol, a normal intraoperative duplex scan has been associated with a reduction in 90-day graft thrombosis to 0.4%.[221]

A significant advantage of this technique is its ability to detect low-flow bypass grafts, defined as an average peak systolic velocity (PSV) of less than 45 cm/s (see Table 63.2). Subsequent analysis of these low-flow grafts has identified two clinical subgroups based on the presence or absence of diastolic flow. The majority of grafts with high peripheral vascular resistance and absent diastolic flow failed within 6 months of implantation,[222] and surgical revision consisting of either a sequential graft to an alternative target or placement of an arteriovenous fistula has been advocated to salvage these threatened grafts. Low-flow grafts with low peripheral vascular resistance (characterized by antegrade flow throughout the pulse cycle) were at intermediate risk of failure (30% failure rate at 6 months) and may benefit from postoperative anticoagulation.[202]

Angioscopy

Angioscopy provides an alternative image-based modality for intraoperative assessment of vein grafts. Not only does it assist in preparation of the conduit by allowing accurate and complete valvulotomy, detecting unsuspected intraluminal pathology, and assisting in the selection of optimal-quality vein segments for composite grafting, it also provides a tool for assessment of technical errors at completion of the procedure. However, successful application of angioscopy requires an investment in new instrumentation and a commitment to overcome its inherent learning curve. Several groups have examined the potential benefits of completion angioscopy, with a generalized consensus that angioscopy is significantly more sensitive in identifying intraluminal abnormalities than either angiography[223,224] or duplex scanning.[132] The most informative study to date, conducted by Miller et al., was a 250-patient prospective randomized evaluation of angioscopy versus angiography.[225] Intraluminal abnormalities were identified in a fifth of the enrolled grafts, with 75% of them determined to be of sufficient severity to prompt surgical correction. Intraoperative revisions were fourfold more likely to be performed after angioscopic evaluation and led to a 50% reduction in 30-day graft failure (3% after angioscopy vs. 6% after angiography). Although this difference did not reach statistical significance, it suggested that some improvement in early graft patency may be obtained with the use of completion angioscopy and aggressive intraoperative revision of any abnormalities identified. Not examined in this trial were the potential intermediate- and long-term benefits in graft patency afforded by this approach, which may

TABLE 63.2 Intraoperative Duplex Monitoring—Diagnostic Criteria and Management Options

Category	PSV (cm/s)	V_r	Interpretation and Intraoperative Management
Stenotic Lesion			
Normal/minimal	<125	1.0-2.0	Normal flow pattern; no further evaluation
Moderate	125-180	2.0-3.0	Residual flow abnormality; rescan after 5 min with papaverine flow augmentation; consider arteriography
Severe	>180, with spectral broadening	2.5-5.0	Significant abnormality, repair defect; if not repaired, perform arteriography to verify normal bypass graft segment
High-grade	>300	>5.0	Critical lesion, typically associated with a pulse pressure deficit and low graft flow
Low-Flow Graft			
Low flow, low PVR	<40	—	Consider systemic anticoagulation Caveats: large-caliber veins may have low peak systolic flow velocities; reversed veins to pedal outflow arteries may also have low distal graft flow velocities
Low flow, high PVR	<40	—	Consider an adjunctive procedure to increase graft flow (distal arteriovenous fistula, jump/sequential graft to an alternative target)

PSV, Peak systolic velocity; *PVR*, peripheral vascular resistance—low (antegrade flow throughout the pulse cycle) or high (antegrade flow only during systole with minimal diastolic flow); V_r, velocity ratio ($PSV_{at\ lesion}/PSV_{proximal}$).

Modified from Johnson BL, Bandyk DF, Back MR, et al. Intraoperative duplex monitoring of infrainguinal vein bypass procedures. *J Vasc Surg*. 2000;31:678–690.

have been even more pronounced than the effects on early patency.

Postoperative Surveillance

Physical Examination and Physiologic Assessment

As initially established by the seminal work of Szilagyi et al.[169] and reinforced by multiple other studies, it is now known that autogenous grafts develop segmental foci of luminal narrowing that lead to reductions in flow and precipitate thrombosis. Attempts to salvage thrombosed grafts outside of the early postoperative period have largely been unsuccessful, with 30% 1-year patency rates after thrombectomy.[226] These observations contributed to the concept of routine graft surveillance, or periodic evaluation to identify grafts with evolving lesions before the development of thrombosis. Resulting from a combination of intimal hyperplasia and pathologic (inward) remodeling, these lesions have a peak incidence within the first 12 months, with 30% becoming hemodynamically significant within this 1-year time frame.[106,227] These observations form the basis for graft surveillance protocols in which frequent evaluations are recommended during the first 12 to 18 months after implantation.

Clinical protocols for graft surveillance focus on physical examination with physiologic assessment of distal perfusion. Patient histories are elicited to detect new onset of claudication or ischemic pain at rest, and physical examination is performed to identify notable changes in the lower extremity pulse. The ABI is used as the quantitative measure of perfusion, with a reduction of greater than 0.15 being considered significant. Changes in any of these parameters should prompt further evaluation to identify the lesion or lesions that have precipitated the hemodynamic deterioration. To improve the sensitivity of physiologic testing, pulse volume recording with a transfer function index protocol has been proposed.[228] Pulse volume recordings are collected from upper extremity (inflow) and ankle (outflow) cuffs and subjected to a Fourier transform algorithm to produce discrete spectra for review. Direct comparison of the frequency response curves provides a numeric value that can be used to identify at-risk grafts. Proof-of-concept testing of this device has suggested accuracy equivalent to that of duplex scanning, but this approach has failed to gain acceptance outside the research arena.

Duplex Scanning

With the recognition that clinical surveillance parameters were insensitive until the lumen was severely compromised,[208,229] duplex scanning was identified as a method for earlier detection of these developing lesions. After an initial focus on reductions in PSV and the absence of diastolic flow,[230,231] changes in velocity along the length of the graft were recognized as a more useful approach for lesion localization.[232,233] Though not generated through a formal series of receiver operating characteristic curves, a duplex classification has evolved to correlate PSV and the velocity ratio (V_r) with the approximate degrees of vein graft stenosis (Table 63.3).[234] Complicating management of vein graft stenosis is the dynamic remodeling that occurs in 12 to 18 months after implantation, during which the appearance and subsequent regression of focal regions of luminal narrowing are frequently observed.[112,235] Retrospective reviews correlating duplex-derived hemodynamic data with lesion morphology suggested a PSV of 300 cm/s (or a V_r of 4.0) to be the critical threshold above which lesion regression was relatively unlikely (Fig. 63.9).[236,237] Intermediate stenoses (200 cm/s < PSV < 300 cm/s; $2 < V_r < 4$) are notably dynamic, with 20% to 30% of these lesions demonstrating significant regression within 2 years. Complicating these retrospective analyses, however, was the preexisting bias that high-grade stenoses mandate intervention, so the natural history of these high-grade lesions has been incompletely defined. Although the number of grafts with

TABLE 63.3 Postoperative Duplex Monitoring—Diagnostic Criteria and Management Options

Category	PSV (cm/s)	V_r	Waveform Characteristics	Management
Stenotic Lesion				
Less 20% stenosis (normal)	<150	<1.5	Absent or mild spectral broadening in systole	Rescan in 6 months
20%-50% stenosis (mild)	>150	1.5-2.0	Spectral broadening throughout systole with no change in waveform	Rescan in 6 months
50%-75% stenosis (moderate)	>180	>2.5	Severe spectral broadening in systole with reversed-flow components	Rescan in 4-6 weeks; if lesion does not progress during two cycles of testing, increase scan interval to 3 months
Greater than 75% stenosis (severe)	>300	>3.5	Severe lumen reduction with a "flow jet"; damped distal velocity waveform	Recommend repair (urgent if average PSV < 45 cm/s or change in ABI > 0.15)
Low-Flow Graft				
Low flow	<40	—		Angiography and repair of a non–flow-limiting stenosis should be considered

ABI, Ankle-brachial index; *PSV*, peak systolic velocity; *V_r*, velocity ratio ($PSV_{at\ lesion}/PSV_{proximal}$).

Modified from Bandyk DF. Infrainguinal vein bypass graft surveillance: how to do it, when to intervene, and is it cost-effective? *J Am Coll Surg*. 2002;194(1 Suppl): S40–S50.

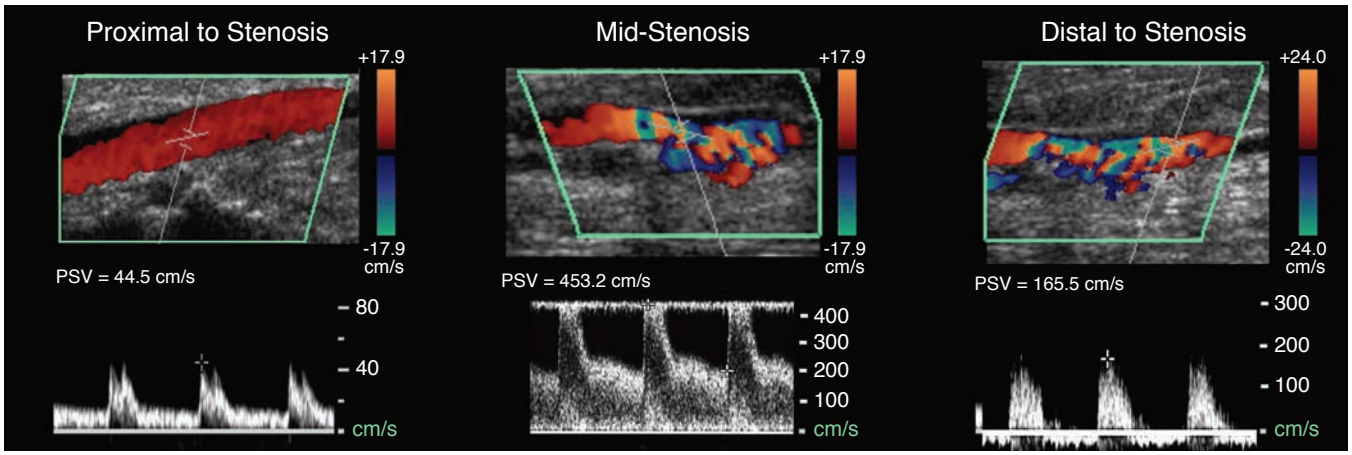


Figure 63.9 Postoperative duplex scan of a vein graft demonstrating markedly elevated peak systolic velocity and spectral broadening within an area of stenosis. Distal to the lesion, disordered flow is evident on color-flow imaging, and a significant reduction in diastolic velocity is observed.

high-grade stenoses that did not undergo elective revision is relatively small, the risk of occlusion of these unrepaired grafts appears to be in excess of 75%.[231,237] Predominantly based on these observations, an algorithm for the management of postoperative vein graft stenosis has been proposed,[234] with the key elements of this approach outlined in Table 63.3. Of particular concern are grafts with a PSV of greater than 300 cm/s and a change in the ABI of greater than 0.15 or significant dampening of the distal waveforms. These findings are generally thought to be preocclusive lesions, and initiation of systemic anticoagulation with prompt repair is indicated.

In parallel with these observational studies, multiple single-institution cohort studies have clarified the role of duplex surveillance in improving patient outcomes. Results from these studies are in general agreement and demonstrate an approximate 15% improvement in graft patency rates with routine duplex evaluation versus clinical follow-up alone.[238-240] Recommendations for the frequency of vein graft surveillance have been proposed and focus on the intermediate period (1-18 months), when lesion remodeling is most active. After an intraoperative or early postoperative scan to identify technical problems, outpatient duplex evaluations at 1, 3, 6, 12, and 18 months and annually thereafter are recommended. The development of moderate stenosis or the need for vein graft revision would prompt closer follow-up, with interval scans at approximately 6 weeks until lesion stabilization or regression is confirmed.

The economic benefits of a graft surveillance program have been investigated by a number of investigators, who have focused on major amputation as the dominant outcome variable.[241,242] Duplex scan surveillance was the least expensive ($2823) and resulted in the fewest major amputations (17 per 1000 patients examined) when compared with clinical follow-up alone ($5072 and 77 amputations per 1000 patients).[241] With the recognition that 90% of lesions that will require revision between 1 and 18 months will demonstrate some element of flow abnormality within 4 weeks,[243] investigators have questioned the need for continued aggressive surveillance after normal 1- and 3-month graft scans.[244] Longer-term follow-up has clarified this issue; one study reported that 30% of the flow abnormalities that ultimately required revision were not observed until after 6 months.[245] Annual examination to evaluate for graft atherosclerosis or aneurysmal degeneration and progression of native inflow-outflow arterial disease therefore seems warranted.

In an attempt to derive the potential benefit of routine surveillance while mitigating the expense, investigators have developed a risk prediction model for the development of stenotic lesions in the postoperative period. Combining the results of a 1-month duplex scan, location of the distal anastomosis, and a patient's smoking and diabetes status, patients are assigned to a relative risk category and a recommended protocol for postoperative surveillance.[246-248] While intriguing in its concept, the lack of prospective, multiinstitutional databases have limited its validation and potential application to clinical care.

Although the large array of cohort studies presents compelling data to support a routine duplex surveillance program, consensus on this issue is not uniform. Three randomized prospective trials were performed to evaluate vein graft surveillance and reached variable conclusions regarding its benefits. The first and smallest of these studies, published by Lundell et al. in 1995, randomized 156 patients after vein bypass grafts to either intense duplex surveillance or intermittent clinical follow-up.[249] Although major amputation was not explored as an endpoint, implementation of an intensive duplex protocol provided a 25% absolute improvement in both primary-assisted and secondary graft patency rates at 3 years. Among the confounding factors in this trial, however, was their use of frequent (every 3 months) follow-up in the duplex group but only annual follow-up in the clinical group. Consequently, a definitive conclusion on the value of duplex scanning versus more frequent clinical follow-up could not be obtained. The second trial randomized 342 patients between duplex and clinical surveillance and demonstrated no difference in graft patency or limb salvage at 1 year.[250] Though methodologically sound, the duration of follow-up was probably insufficient to realize the full benefit of serial duplex evaluation. The largest trial, in which 594 patients were randomized to a duplex or clinical protocol, demonstrated no difference in

major amputation or graft patency at 18 months.[251] Despite the use of a prospective randomized methodology, significant concern has been raised in regard to the validity of these findings.[252,253] Use of nonstandard duplex criteria resulting in an aggressive treatment approach to intermediate stenoses, delay in randomization until 4 to 6 weeks postoperatively (reducing the early benefit of duplex examination), and the short follow-up time were among the major issues that were raised.

Despite these potential methodologic flaws in the randomized trials, the available literature presents two diametrically opposing views on the relative value of a duplex surveillance program. Multiple cohort studies have exhaustively detailed the natural history of vein graft lesions and the perceived benefits of early detection and repair of high-grade lesions, yet all lack an appropriate control group. In contrast, the randomized trials suggest little benefit of duplex surveillance, but such generalization may be limited by notable methodologic flaws. Faced with this dilemma, the 2007 Inter-Society Consensus for the Management of Peripheral Arterial Disease came forth with a grade C recommendation supporting clinical surveillance only, with a focus on history taking for new symptoms, complete vascular examination of the extremity, and resting and postexercise ABI at 6-month intervals for a minimum of 2 years.[254] The consensus statement notes that the previous recommendation for routine duplex scanning after autogenous lower extremity bypass has not yet proved cost effective. Nevertheless, most surgeons continue a program of vein graft surveillance and remain skeptical of these negative findings.

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CHAPTER 64

Prosthetic Grafts (Heparin-Bonded and Spiral Grafts)

AHMED KAYSSI and RICHARD F. NEVILLE

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INTRODUCTION

Arthur Voorhees and colleagues first described the use of a prosthetic graft to bridge arterial defects in 1952.[1] Since then, numerous advances have been made in fabric technologies, and a large variety of prosthetic grafts are currently available on the market. Currently, vascular surgeons use prosthetic grafts for several different indications, including aortic aneurysm repair, arterial bypass in the upper and lower extremities, and dialysis access creation.

Prosthetic grafts can play an important role in the management of vascular disease for those patients who do not have adequate autogenous conduit. Although surgical bypass with autogenous vein has a well-established record with documented long-term patency rates, a growing proportion of patients needing bypass surgery lack suitable venous conduit.[2,3] Reasons for this include previous harvesting of the veins for coronary artery bypass or prior lower extremity procedures, small vein caliber, active infection at the vein harvest site, and vein varicosities or thrombosis.

The advent of endovascular technology has resulted in a corresponding reduction in the number of surgical bypasses performed in vascular patients, with a concomitant increase in the complexity of patients that do require bypass, such as the scenario of failed endovascular intervention.[4] As such, lower extremity bypass with a prosthetic conduit continues to serve as a therapeutic choice in the revascularization of patients with limb ischemia.

Abstract

Arthur Voorhees and colleagues first described the use of a prosthetic graft to bridge arterial defects in 1952.[1] Since then, numerous advances have been made in fabric technologies, and a large variety of prosthetic grafts are currently available on the market. Currently, vascular surgeons use prosthetic grafts for several different indications, including aortic aneurysm repair, arterial bypass in the upper and lower extremities, and dialysis access creation.

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Keywords

bypass
graft
prosthetic
adjuncts

BASIC PRINCIPLES

Materials

The ideal prosthetic conduit would be impermeable, compliant, biocompatible, durable, easy to sterilize, facile to implant, available in different sizes, resistant to thrombosis and infection, and cost-effective. Properties such as surface electronegativity, graft porosity, endothelial seeding, and heparin bonding have all been considered to improve graft function. Electronegativity on the graft surface plays a role in the inhibition of platelet aggregation with theoretic enhancement of this property by carbon-coating of the luminal graft surface. Graft porosity has not been shown to significantly affect graft thrombosis, but may be implicated in tissue ingrowth. Currently the most commonly used prosthetic materials are Dacron and expanded polytetrafluoroethylene (ePTFE), although there are several commercially available graft materials (Table 64.1).

TABLE 64.1 Selected Commercially Available Vascular Grafts in the United States

Material Type	Company	Product	Description
Standard			
ePTFE	Angiotech/Edwards Life Sciences (Irvine, California)	Lifespan	Re-enforced
	Atrium Medical Corporation (Hudson, New Hampshire)	Advanta VXT	Softwrap technology
		Advanta SST	Trilaminate, allows pulsation
		Advanta VS	60/20-μm through-pore design
		Flixene	Laminated with biomaterial film
	Bard Peripheral Vascular, Inc. (Tempe, Arizona)	Impra CenterFlex	Unmodified
	Boston Scientific (Natick, Massachusetts)	Exxcel Soft Vascular Graft	Unmodified
	B. Braun (Melsungen, Germany)	VascuGraft	Unmodified
	Vascutek, Ltd. (Renfrewshire, United Kingdom)	Maxiflo Ultrathin	Thin wall, external ePTFE wrap
		Maxiflo Wrap	Regular wall, external ePTFE wrap
	W.L. Gore & Associates Inc. (Flagstaff, Arizona)	Gore-Tex	Unmodified
		Gore-Tex Stretch	Stretch
		Gore Intering	Unibody, intrawall radially supported
Dacron	Braun	Protegraft	Knitted, double velour
	InterVascular, Inc. (Mahwah, New Jersey)	InterGard Ultrathin	Unmodified
	Vascutek, Ltd.	VP1200K	Unmodified
Sealed			
ePTFE	Vascutek, Ltd.	SealPTFE Ultrathin	Gelatin sealed, thin wall
		SealPTFE Wrap	Gelatin sealed, regular wall
		Taperflo	Gelatin sealed, tapered
Dacron	Atrium Medical Corporation	Ultramax	Knitted, gelatin sealed, double velour
	Bard Peripheral Vascular, Inc.	Vasculour II	Knitted, albumin sealed
	Boston Scientific	Hemashield Gold Microvel	Knitted, collagen sealed, double velour
		Hemashield Platinum	Woven, collagen sealed
	B. Braun	UniGraft	Woven, gelatin sealed, single/double velour
	InterVascular, Inc.	InterGard Woven	Woven, collagen coated
		InterGard Knitted	Knitted, collagen coated
	Vascutek, Ltd.	Gelseal	Knitted, gelatin sealed
		Gelsoft	Knitted, gelatin sealed
		Gelsoft Plus	Köper knitted, gelatin sealed
Heparin Modified			
ePTFE	W.L. Gore & Associates, Inc.	Propaten	Carmeda bioactive heparin coating
Dacron	InterVascular, Inc.	InterGard Heparin	Knitted, collagen coated

Continued

TABLE 64.1 Selected Commercially Available Vascular Grafts in the United States—cont'd

Material Type	Company	Product	Description
Carbon Modified			
ePTFE	Bard Peripheral Vascular, Inc.	Impra Carboflo	Carbon coated
		Distaflo	Preformed cuff at distal end
		Dynaflo	Preformed cuff at distal end
Silver Modified			
Dacron	B. Braun	SilverGraft	Antibacterial
	InterVascular, Inc.	InterGard Silver	Antibacterial
Others			
Collagen based	Artegraft (North Brunswick, New Jersey)	Artegraft	Cross-linked bovine carotid artery
Polyurethane	Bard Peripheral Vascular, Inc.	Vectra	Self-bonded, trilayer Thoralon design for hemodialysis vascular access

ePTFE, Expanded polytetrafluoroethylene.

Dacron

British chemists Whinfield and Dickinson developed the polyester fabric Dacron in 1941, and it is one of the oldest continuously used fabrics on the market.[5,6] Dacron grafts can be knitted or woven, and can also be reinforced by external rings for support (Fig. 64.1). Knitted grafts have the advantage of better compliance, but have larger pores that tend to leak and require preclotting. As such, modern versions of knitted Dacron grafts are coated with albumin to prevent leakage from such pores.[7] Dacron is a highly resilient fabric that is estimated to last more than 30 years, but these grafts are at a higher risk of dilation compared with other graft materials.[8] It is currently used primarily as a large-diameter graft in aortic and lower-extremity bypass surgery.

Expanded Polytetrafluoroethylene

ePTFE was described by Matsumoto and colleagues from Japan in 1973.[9] It is configured on a mandrel process with a nodal-fibril porous configuration with carefully constructed internodal distances to optimize function and healing properties. ePTFE grafts are available in several configurations: thin walled, ringed, and precuffed (Fig. 64.2). The precuffed configuration was an attempt to optimize graft hemodynamics, but this has been difficult to confirm.[10] The graft is produced by extruding a low porosity tube, producing a graft that is compliant, easy to suture, and does not need to be preclotted, in contrast to knitted Dacron grafts.[11]

Polypropylene and Polyurethane

Developed in the early 1990s, the early experience with the use of this hydrocarbon material was promising. Polypropylene's high tensile strength and relative inertness gave it an advantage over other prosthetic materials.[12] It also had a long history of successful use in suture and hernia mesh. Polyurethane grafts are produced by the reaction of isocyanates with an alcohol group.[5] The main advantage of polyurethane is high elasticity, but this material demonstrates poor biostability and loss of compliance after implantation limiting widespread clinical use.[6]

Composite Grafts and Allografts

The successful implementation of prosthetic grafts has triggered the development of novel materials such as composite grafts—biologic materials using human umbilical vein or ovine collagen.[13] While this type of material has yet to be used for lower extremity bypass, the conduit has been used in a hemodialysis access.[14,15]

Cryopreserved Vein and Human Umbilical Vein Grafts

Cryopreserved vein and human umbilical veins are alternative conduits that were first utilized in the 1960s. Cryopreserved grafts are relatively expensive compared with other prosthetic conduits and have a greater incidence of aneurysmal degeneration and thrombosis from late rejection. The current data from multiple centers reported a 30% to 58% patency rate at 1 year using cryopreserved veins for infrapopliteal bypass, which are inferior to autologous conduits and heparin-bonded ePTFE grafts.[16-18] However, given the biologic nature of the material, this graft may have value in bypasses that traverse infected fields in the absence of any autogenous conduit options, even as a temporizing procedure.

CLINICAL APPLICATIONS

Peripheral Bypass Grafts

Numerous studies have been carried out to compare Dacron and ePTFE grafts for lower-extremity bypasses. Rychlik and colleagues published a meta-analysis in 2014 that reviewed 91 publications and assessed 1192 patients who underwent above-knee femoro-popliteal bypass using Dacron versus ePTFE.[19] The authors reported similar 10-year primary patency between the grafts at up to 10 years, and no difference in the incidence of amputation, morbidity, or mortality between the patient

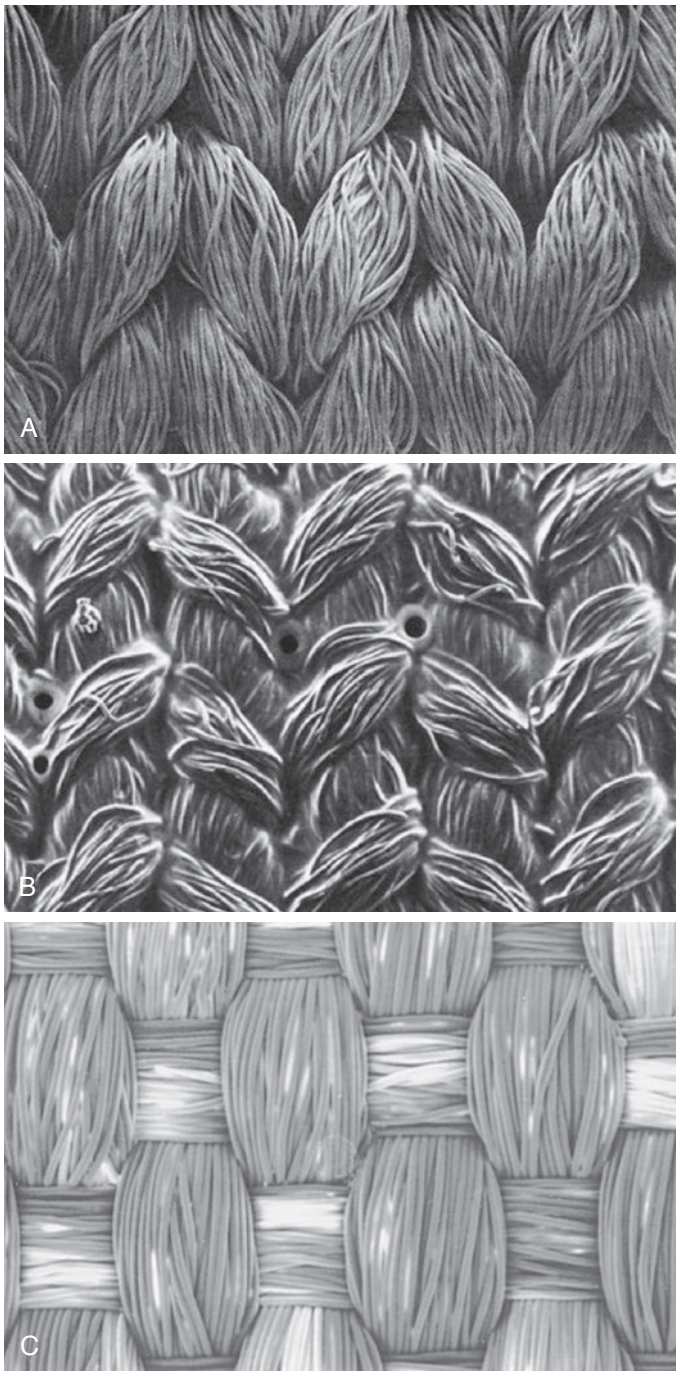


Figure 64.1 Dacron Structure. Scanning electron microscopy of typical yarn configurations in Dacron grafts. (A) DeBakey standard-knit Dacron vascular prosthesis (original magnification ×37). (B) Vascutek Gelsoft Köper knitted prosthesis sealed with gelatin (×40). (C) Woven Dacron (×50).

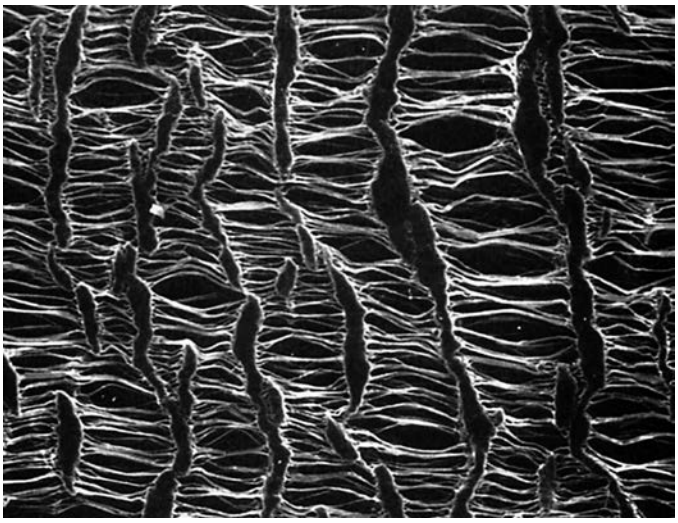


Figure 64.2 Polytetrafluoroethylene Structure. Scanning electron microscopy of node-fibril structure in expanded polytetrafluoroethylene grafts (original magnification ×500).

populations. A Cochrane review published in 2010 found that vein grafts were superior to prosthetic grafts, but that long-term outcomes using Dacron or standard ePTFE in the lower extremities were similar.[20] The inherent thrombogenicity of available polymeric materials and stimulation of hyperplasia, especially at the anastomosis, eventually leads to graft failure, whether a synthetic conduit is used for lower extremity revascularization or for arteriovenous (AV) hemodialysis access. A study of 4 mm lower extremity polypropylene grafts implanted in dogs by Greisler and colleagues from Illinois reported a 16-month patency of 81%, compared with 69% and 20% for Dacron and ePTFE, respectively.[12] Due to susceptibility to oxidation, however, polypropylene is only used as part of multicomponent grafts that render the polypropylene inert.[5] The use of human umbilical vein grafts has been impeded by aneurismal degeneration of the graft material. This complication has been addressed with recent modifications of the graft design, resulting in 61% patency at 36 months.[21] However, these grafts have also met with limited success when used for tibial bypass.[22] In a large National Surgical Quality Improvement Program (NSQIP) database, human umbilical vein composite grafts had a higher 30-day failure rate of 15.4%, compared with 10.5% in PTFE grafts and 7.5% in GSV conduits.[23]

Hemodialysis Access

The Fistula First Initiative has resulted in an increase of AV fistula use from 24% to 52% between 2000 and 2008. In that time frame, graft use decreased from 58% to 22%, and catheter use increased from 17% to 26%.[24] Prosthetic grafts for AV access can be indicated in patients with failed AV fistulas and lack of venous conduit. The most commonly used grafts are constructed from ePTFE, with early-access grafts having the advantage of earlier use and decreased need for catheter access.[25,26] Advantages of prosthetic AV grafts include ease of placement, shorter time from operation to utilization, and a potentially large surface area for cannulation. Grafts fail because of restenosis from intimal hyperplasia at the venous anastomosis as well as thrombosis and infection, which occur at higher rates compared with AV fistulas.[27,28]

Other Locations

Prosthetic grafts can deliver excellent long-term patency for visceral and renal arterial reconstruction because of the short

length that is required, high flow arterial beds, and the absence of extrinsic mechanical compression. Large-caliber venous reconstruction of the inferior or superior vena cava and the iliofemoral, jugular, and portal veins, including portosystemic shunts, can be performed with externally supported ePTFE grafts.[29-36]

Strategies for Improving Prosthetic Graft Patency

Autogenous vein remains the acknowledged ideal conduit for distal bypass, but there is a growing group of patients that either lack vein for bypass or have a disadvantaged vein as a conduit. This scenario has been identified for those veins with a diameter less than 3 mm, grafts of spliced vein segments, or a nonsaphenous venous conduit. Morbidity from vein harvest is also not insignificant, especially when greater saphenous vein is not available and construction of an autogenous conduit requires harvesting several segments, especially arm and lesser saphenous vein. Operative time can also be increased compared with bypass with a prosthetic conduit through two limited incisions. Improvement in outcome with prosthetic grafts may create an option for patients who lack autogenous material or have disadvantaged vein.

However, initial clinical outcomes with prosthetic grafts were severely suboptimal, with 1-year patency rates varying between 20% and 50%, with 3-year patency in 12% to 40%.[2,37-39] The results with prosthetic grafts were especially poor for tibial bypass. A comparison of venous and prosthetic conduits for infrapopliteal bypasses demonstrated a markedly inferior 2-year patency for prosthetic bypass to tibial arteries.[40] Thus efforts to improve outcomes for prosthetic grafts have focused on a reduction in the incidence of graft thrombogenicity and myointimal hyperplasia, venous adjuncts at the anastomosis, heparin bonding to the luminal surface, and the addition of a distal AV fistula.[41]

Vein Patches and Cuffs

Anastomotic techniques have been utilized to improve prosthetic graft performance. These efforts include interposition of venous tissue at the distal anastomosis. The Miller cuff involved interposition of autogenous vein at the distal anastomosis (Fig. 64.3A and B).[42] Miller reported on 114 infra-inguinal procedures using this vein cuff technique with a patency rate of 72% noted at 18 months.[42] However, several disadvantages have been recognized with this configuration, including significant turbulence at the anastomotic reservoir and difficulty in achieving an adequate angle between the graft and recipient artery. These factors might explain the immediate and early graft failures reported in Miller's initial series.

Subsequently, Taylor described a technique to address several of these concerns in which a composite of the prosthetic graft and a vein patch are anastomosed to the target artery (Fig. 64.4A and B). Reporting on 256 grafts with 83 tibial bypasses, Taylor and colleagues' 1-, 3-, and 5-year patency rates were 74%, 58%, and 54%, respectively.[43] However, using this technique, the tibial artery is directly exposed to PTFE graft material for the proximal half of the anastomosis, thereby losing the advantage of venous endothelium for half the anastomosis. There can also be a point of anastomotic constriction where the three suture lines converge between the artery, ePTFE, and vein patch. Finally, a significant length of vein must be available to accomplish the anastomosis using the Taylor technique. In addition, there can be difficulty in placement at the inframalleolar position due to space constraints.

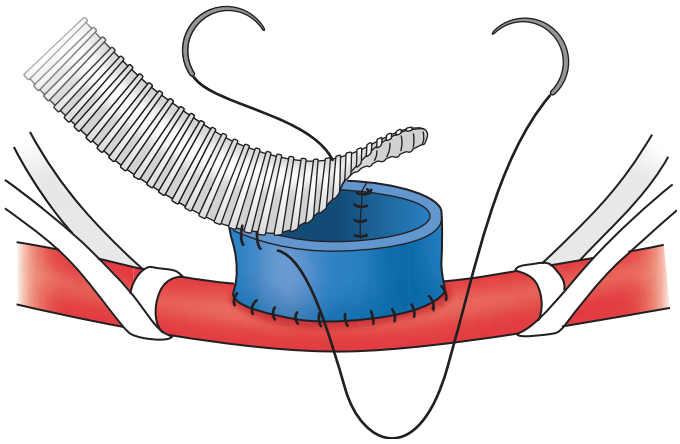


Figure 64.3 The Miller Cuff Technique. A venous cuff is interposed between a prosthetic graft and the target artery. (From Fischer's Mastery of Surgery, 7th ed., 2018; Kayssi A, Lee K, Neville RF. Section IX: Vascular Surgery, 198;1-8 Lippincott, Williams and Wilkins, Philadelphia, PA.)

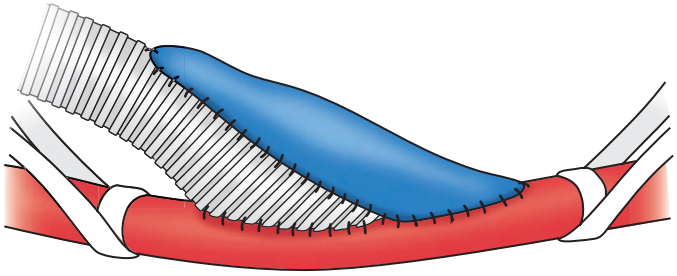


Figure 64.4 The Taylor Patch Technique. The graft is partially sutured onto the target artery, and a vein patch is used to suture the rest of the graft onto the artery and increase the anastomotic surface area. (From Fischer's Mastery of Surgery, 7th ed., 2018; Kayssi A, Lee K, Neville RF. Section IX: Vascular Surgery, 198;1-8 Lippincott, Williams and Wilkins, Philadelphia, PA.)

Several authors have studied clinical results and compared these techniques. Pappas and colleagues reported improved patency for prosthetic bypasses with the Miller cuff as compared with historic controls with standard ePTFE.[44] A prospective, randomized trial utilizing ePTFE grafts with and without a Miller vein cuff was reported by Stonebridge, who did not demonstrate a statistically significant benefit for the vein cuff technique in tibial bypasses, although there was a trend toward improved patency at 24 months.[45] Kreienberg compared grafts using ePTFE with a vein cuff versus composite saphenous vein grafts, and reported a similar primary patency at 2 years of 49% for the vein cuff patients versus 44% for the composite vein patients, with secondary patency rates somewhat better for the composite vein group.[46] The Albany group compared all bypasses with spliced vein segments to ePTFE and a Miller

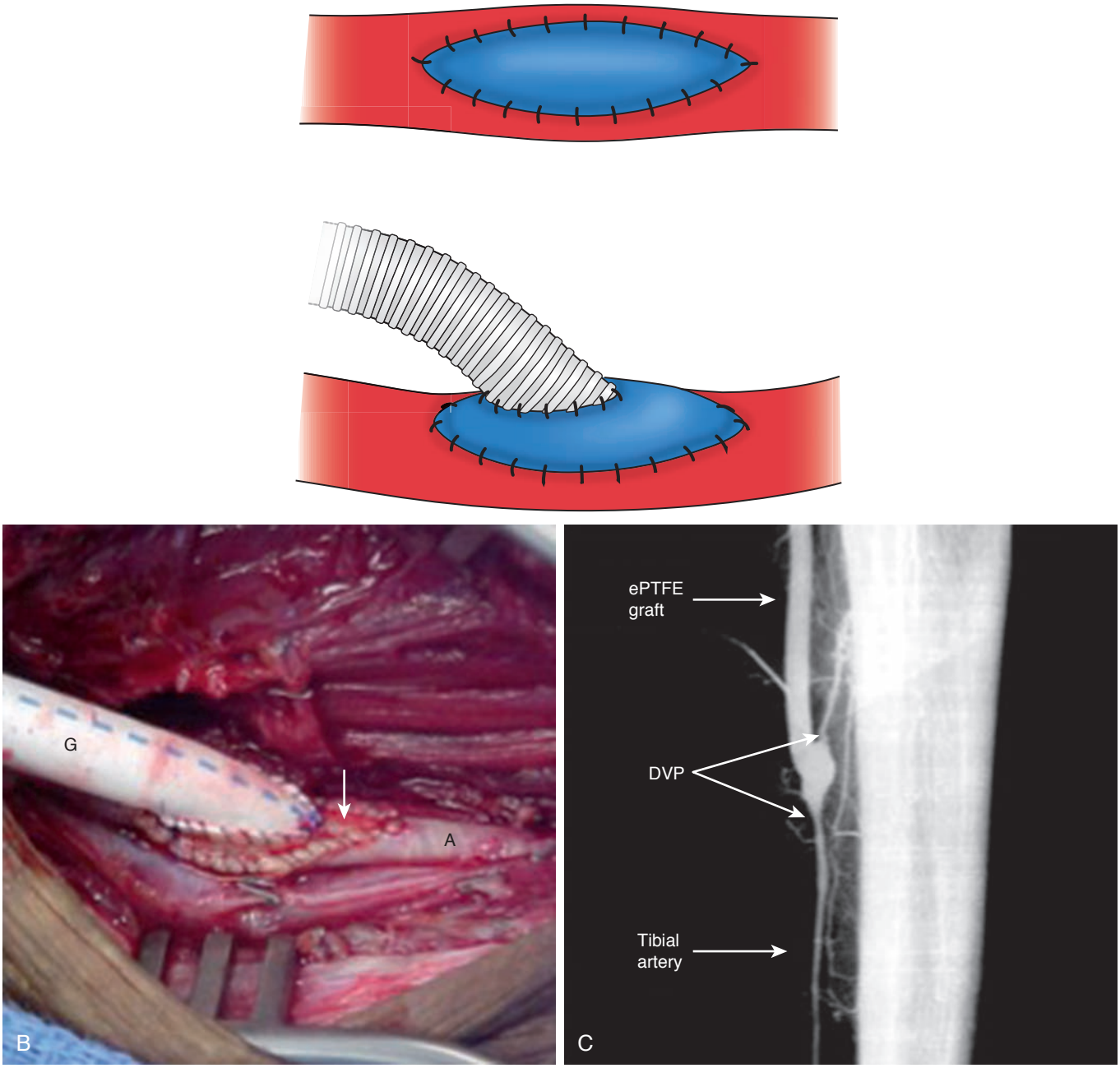


Figure 64.5 Distal Vein Patch (DVP) Technique. The distal arterial target is patched with a vein, and a prosthetic graft is sutured onto the proximal 2/3 of the patch. (A) Schematic of the DVP technique. (B) Intraoperative image of a completed DVP anastomosis. (C) Completion arteriogram after DVP bypass. *ePTFE*, Expanded polytetrafluoroethylene. (Source: [A] Fisher's Mastery of Surgery.)

vein cuff.[47] The primary patency was better with the vein bypasses, although 25% of the spliced vein procedures required secondary revision to obtain these results. In addition, spliced vein procedures involved increased operative time, longer hospital stays, greater intraoperative blood loss, and greater perioperative morbidity.

The distal vein patch (DVP) technique was developed to take advantage of standard techniques known to all vascular surgeons with the potential benefit of a venous adjunct at the distal anastomosis of the prosthetic graft. While prior procedures were somewhat complex, involving multiple intricate suture lines while requiring a significant length of vein, the DVP technique incorporates ease of technique, with maintenance of the proposed advantages leading to improved outcomes for prosthetic grafts (Fig. 64.5A to C). The initial series of tibial artery bypasses using DVP for patients with limb-threatening ischemia was reported in 1997.[48] The DVP technique resulted in improved 4-year patency (62%) and limb salvage (79%) in

TABLE 64.2 Data Regarding Primary Patency and Limb Preservation in an Extended Cohort of Distal Vein Patch Bypass With Long-Term Follow-Up

Series	N	BK Popliteal Versus Tibial	1	2	3	4	5
Miller Cuff							
Miller, 1984	114			72 (18 m)			
Raptis, 1995		BK popliteal 100%			57		
Stonebridge, 1997	96	BK popliteal 100%	80	52			
Kansal, 1999	56	BK popliteal 47% Tibial 53%	62	54	30		
Stonebridge, 2000	89	Tibial 100%	50	32			
Panneton, 2004	44	BK popliteal 21% Tibial 79%	62	44			
Griffiths, 2004		BK popliteal 100%			45		
Oderich, 2005		BK popliteal 35% Tibial 65%	78		54		
Lauterbach, 2005	105	BK popliteal 38% Tibial 62%	79	75	64		
Taylor Patch							
Taylor, 1992	86	BK popliteal	88		77		65
	83	Tibial	74		58		54
Yeung, 2001	44		71	71			
St. Mary's Boot							
Tyrell, 1991	30		40				
Kreienberg, 2000	59	BK popliteal 12% Tibial 88%		45	38		
Kreienberg, 2002	20	BK popliteal 20% Tibial 80%		49			
Distal Vein Patch							
Neville, 2001	80	Tibial 100%	82	77	69	62	
Flis, 2001	86	BK popliteal Tibial					53 vs. 29
Bellosta, 2005	22	Tibial 100%				62 (secondary)	
Neville, 2012 (current)	270	BK popliteal 6% Tibial 94%	79	75	65	51	

Comparative table including data gleaned from articles that reported results on specific data points with the Miller cuff, Taylor patch, St. Mary's boot, and distal vein patch. Data may have been collected in the context of a trial involving other techniques, and only data that could be gleaned from the publication regarding vein interposition techniques were used. While not a statistical comparison, this is as near a comparison of like-kind data as possible.
Source: Neville RF, Lidsky M, Capone A, et al. An expanded series of distal bypass using the distal vein patch technique to improve prosthetic graft performance in critical limb ischemia. *Eur J Vasc Endovasc Surg.* 2012;44:177-182.

a group of patients without adequate saphenous vein conduit options.[49] Since that report, the DVP technique has been used to perform more than 400 cases representing 23% of the authors' total tibial experience during that period. A report of this larger cohort resulted in 50% primary patency at 4 years (Table 64.2).[50] Secondary patency through thrombectomy and revision of the distal anastomosis can be obtained under local anesthesia. Prosthetic grafts often fail due to hyperplasia at the suture line between the graft and recipient artery, resulting in thrombosis of the recipient artery. When the DVP bypasses fail, the recipient artery rarely occludes because the hyperplastic response occurs primarily between the vein patch and ePTFE material, leaving the native artery patent and available for revision. This allowed reestablishment of graft patency by thrombectomy with revision of the distal anastomosis by extension of the patch (Fig. 64.6).

The advantages of a venous adjunct at the distal anastomosis derive from both biologic and mechanical factors. Venous endothelium may confer a beneficial effect through fibrinolytic and antiplatelet activity, although these effects remain unproven. The mechanical factors of shear stress and compliance mismatch have also been implicated in prosthetic graft failure. Theoretically, vein interposed between a stiff prosthetic graft and a more

pliable artery would minimize the expansibility mismatch created with pulsatile flow and thus decrease mechanical injury at the anastomosis. Anastomotic geometry may be altered by the presence of vein at the distal anastomosis, thereby positively effecting turbulence and shear forces that play a role in the hyperplastic process. The DVP anastomosis configuration results in a small vortex of turbulent flow at the heel and a more streamlined flow pattern at the toe (Fig. 64.7A and B).[10] Finally, it is possible that venous tissue simply enlarges the distal anastomosis so that the formation of hyperplasia must encroach on a wider lumen before becoming clinically significant. The venous tissue is also technically easier to suture to small, calcified tibial arteries, as the secondary suture line between the PTFE and vein is more technically appealing.

Heparin-Bonded Grafts

The bonding of heparin on the inner surface of a prosthetic conduit has been used in an attempt to reduce graft thrombosis and hyperplasia.[10] End-point covalent bonding of heparin to the luminal surface of the graft maintains the bioactivity of the heparin molecule.[51] This process reduces platelet adherence, acute thrombosis, and anastomotic intimal hyperplasia in canine and primate models.[52] Heparin bonding using the Carmeda bioactive surface technology (CBAS, Carmeda, Upplands Vasby, Sweden) allows binding of the heparin molecule to the luminal surface of ePTFE grafts while maintaining the morphology of the heparin molecule and hence its bioactivity. This process leads to a reduction in platelet deposition on the graft surface in animal and human models. Heparin bonding also reduces thrombus formation on the surface of the graft, with a subsequent decrease in graft thrombogenicity in acute and chronic models. A reduction in myointimal hyperplasia at the anastomotic site has been demonstrated with heparin-bonded biomaterial surfaces. Decreased platelet adherence, thrombus formation, and inhibition of myointimal hyperplasia could be hypothesized to decrease both early and late graft failure.

Initial clinical experience with heparin-bonded grafts was encouraging as compared to historical results with standard prosthetic grafts. Walluschek reported 80% 1-year patency for below-knee bypasses.[53] Furthermore, Bosiers reported primary and secondary 1-year patency rates of 82% and 97%, respectively, with little difference between popliteal and tibial bypasses.[54] A multicentered randomized-controlled trial of heparin-bonded Dacron versus ePTFE for femoropopliteal bypass reported greater patency rates with Dacron than with ePTFE at 3 years, but the advantage was not sustained at 5 years.[55] This was a small study of primarily above-knee bypasses that limits its generalizability to the infrapopliteal vascular beds. In regard to tibial bypass, recent data implies that heparin-bonded ePTFE grafts may be statistically noninferior to venous conduit although autogenous vein remains the ideal conduit for lower extremity bypass.[50,56-59] Comparison of primary patency and amputation rates achieved for tibial bypass with heparin-bonded ePTFE and great saphenous vein support the dictum that an intact, quality vein remains the preferred conduit for distal bypass (Fig. 64.8). However, the results with heparin-bonded ePTFE indicate that this conduit is an acceptable alternative choice when a quality, intact great saphenous vein is unavailable for tibial bypass.

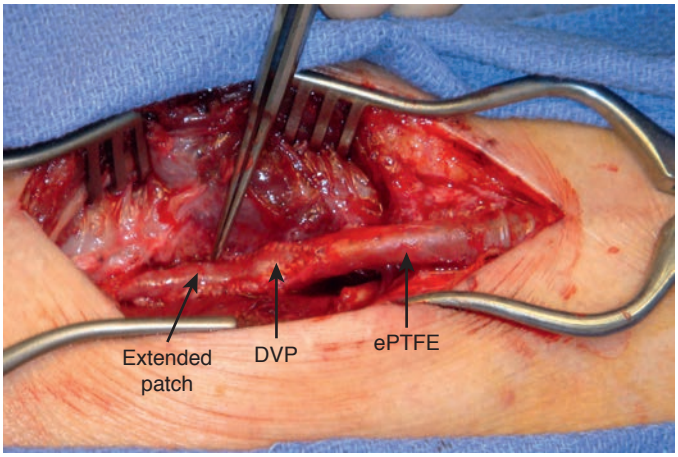


Figure 64.6 Distal Vein Patch (DVP) Revision. Revision of a DVP graft with opening of the graft hood, thrombectomy, and extension of the patch across the toe of the prior anastomosis onto the target artery. *ePTFE*, Expanded polytetrafluoroethylene.

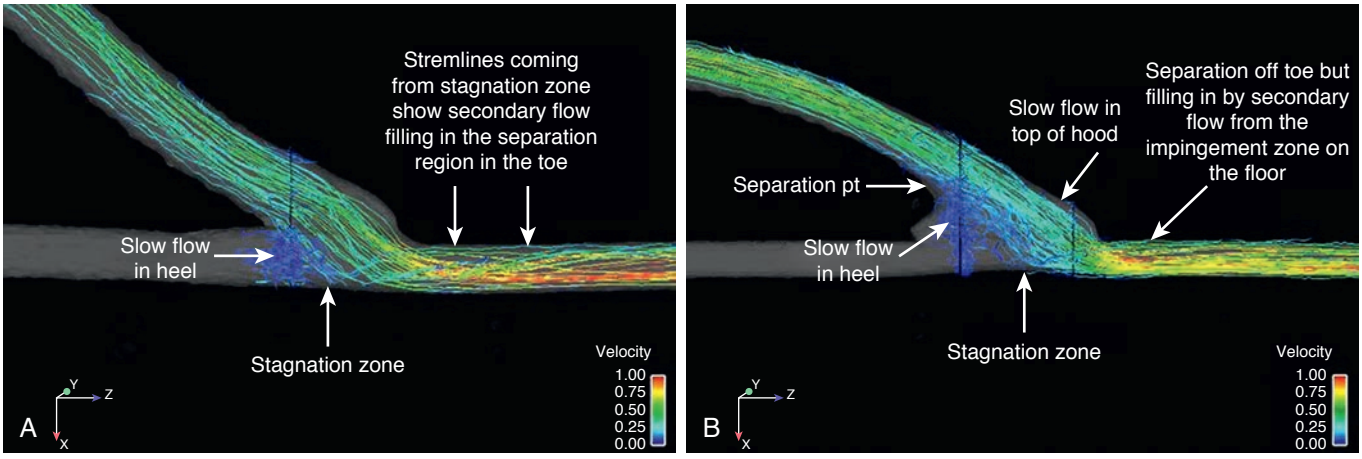
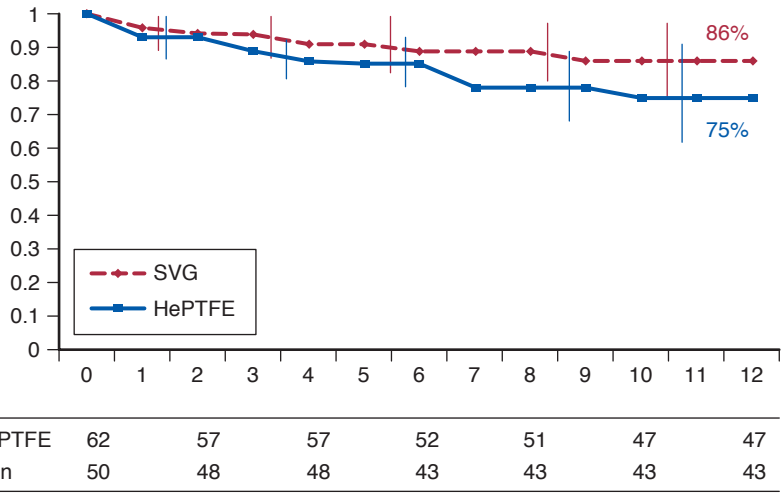


Figure 64.7 Graft Hemodynamics. Magnetic resonance velocimetry images analyzing anastomotic hemodynamics. (A) Distal vein patch anastomosis. (B) Precuffed polytetrafluoroethylene anastomosis.



HePTFE	62	57	57	52	51	47	47
Vein	50	48	48	43	43	43	43

Figure 64.8 Vein Bypass Versus Distal Vein Patch (DVP). Primary patency of tibial bypass using heparin-bonded expanded polytetrafluoroethylene (HePTFE) conduit with a DVP compared to great saphenous vein bypass. Kaplan Meier survival curves for primary patency over 12 months by graft type. (Source: Neville RF, Capone A, Amdur R, et al. A comparison of tibial artery bypass performed with heparin Bonded ePTFE and greater saphenous vein to treat critical limb ischemia. *J Vasc Surg.* 2012;56(4):1008-1014.)

Heparin-induced thrombocytopenia is a potential concern with implantation of heparin-bonded grafts. This phenomenon has been described in few case reports of patients undergoing lower-extremity bypass grafts despite the larger number of implants performed worldwide.[60-63] However, platelet counts were improving prior to graft explantation in cases where covalently bonded grafts were used, as compared with older grafts that used ionic interaction with the graft surface, leading to subsequent release of the heparin into the bloodstream.[64] Furthermore, a study of covalently bonded grafts found no increase in the systemic markers of hemostasis in vivo, and no antibodies against heparin were detected up to 6 weeks after implantation.[65]

Spiral Laminar Flow Grafts

Stonebridge and colleagues have reported that physiologic flow in blood vessels may not be laminar in the conventional sense, but a spiral laminar pattern of blood flow.[66] It was hypothesized that inducing such a spiral laminar flow pattern in prosthetic grafts may result in an inhibition of formation of neointimal hyperplasia and stabilize flow patterns through stenotic areas. Conceptually, a reduction of the laterally directed forces on the vessel wall, thereby improving shear forces, as well as reducing the expression of adhesion molecules, would inhibit the formation of neointimal hyperplasia.[67,68] A spiral laminar flow graft was developed (Vascular Flow Technologies, Dundee, United Kingdom; Fig. 64.9). Stonebridge and colleagues reported primary patency rates of 86%, 81%, and 81% (12, 24, and 30 months) for above-the-knee bypasses and 73%, 57%, and 57% for below-the-knee bypasses, respectively.[69] To date, there are no published randomized controlled trials comparing the efficacy of spiral laminar flow grafts with ePTFE or Dacron grafts.

Distal Arteriovenous Fistula

When the target artery outflow of a distal bypass is compromised, the addition of an AV fistula at the distal anastomosis has been used to increase the chances of bypass success. Dardik used a common ostium AV fistula in an attempt to decrease graft thrombosis by reduction of outflow resistance.[21] Ascer and colleagues described a technique involving construction of an AV fistula between the target tibial artery and corresponding tibial vein with a ePTFE bypass to the involved vein.[70] Reported patency rates with this technique were 62% at 36 months, despite a fistula thrombosis rate of 37%. A prospective, randomized trial compared distal bypasses using ePTFE with a Miller vein cuff with and without an AV fistula demonstrated that the fistula conferred no benefit, but the authors did not stratify patients based on arterial runoff.[71]

The addition of a common ostium AV fistula to the distal anastomosis of a DVP bypass has also been described. This modification has been performed in patients with no vein available and severely disadvantaged arterial runoff. The target tibial artery is opened longitudinally and a venotomy is created in the corresponding tibial vein (Fig. 64.10). The vein patch is then sutured to the common ostium created by this fistulous connection. An anastomosis is then constructed between the vein patch and the ePTFE, as described in the DVP bypass configuration (Fig. 64.11). Theoretically, the distal AV fistula decreases outflow resistance, reduces overload on a fixed arterial circuit, and increases flow velocity in the graft above the critical thrombotic threshold to improve graft function and decrease the incidence of thrombosis with bypass in the setting of disadvantaged runoff. Results using this technique have been reported and resulted in a 62% primary patency and 57% limb salvage rate at 24 months in a series of patients who would otherwise have undergone primary amputation.[72]

Adjunct Medical Therapies

The role of adjunct medical therapy in improving prosthetic graft patency has been debated, and there is no clear, consistent data to suggest an ideal adjunct medical therapy to improve prosthetic graft function. A Dutch multicenter randomized study compared 2690 patients who underwent infra-inguinal bypass both using vein or prosthetic grafts and randomly assigned patients to aspirin versus warfarin therapy. Overall data did not show any advantage of one therapy over another, but when separated into prosthetic conduit versus vein, the prosthetic group had better results with aspirin alone, whereas the vein

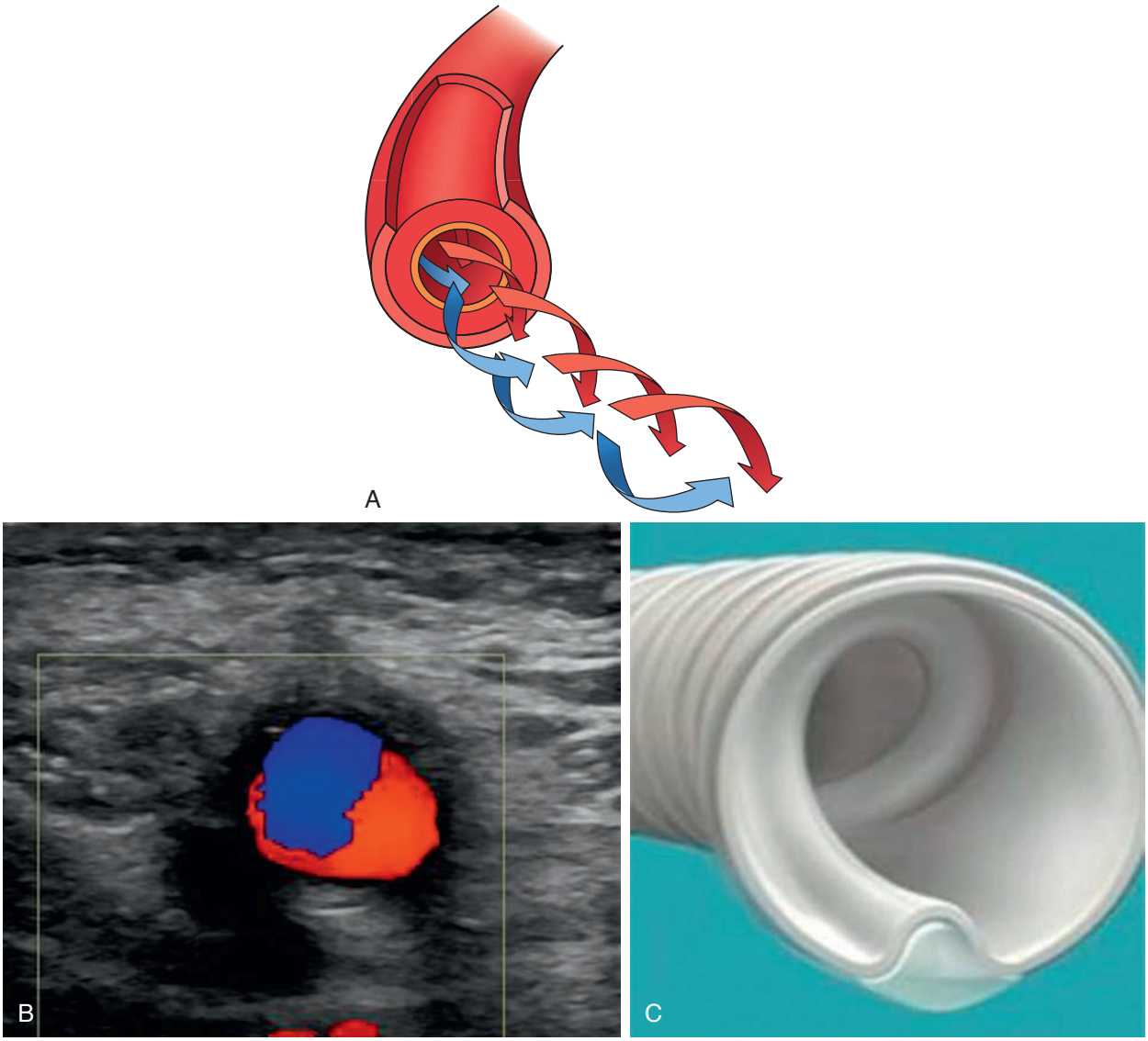


Figure 64.9 Spiral Laminar Flow. (A) Schematic of the concept of spiral laminar flow in a vessel. (B) Duplex ultrasound image of common femoral artery flow consistent with spiral laminar flow physiology. (C) Prosthetic graft constructed to reproduce a spiral laminar flow pattern.

group had better results with warfarin alone.[73] The Boston Veterans Affairs Hospital Prospective Study compared dual therapy (aspirin and warfarin) versus aspirin alone, and showed no difference in overall patency between the two groups. The dual therapy seemed to show benefit for smaller (6 mm) prosthetic grafts. However, there was a twofold increase in major hemorrhagic complications and a higher mortality rate.[74] Finally, the Clopidogrel and Acetyl Salicylic Acid in Bypass Surgery for Peripheral ARterial Disease (CASPAR) trial looked at the efficacy of dual therapy with clopidogrel and aspirin versus aspirin alone in distal bypasses. Dual therapy did not appear to reduce the occlusion rates in venous bypasses. However, in a subgroup of patients with prosthetic grafts, such dual antiplatelet therapy reduced the relative risk of graft occlusion by 35% without any deleterious side effects or major hemorrhagic event.[75] Bedenis and colleagues published a Cochrane Review on the role of antiplatelet medications in preventing postoperative thrombosis after lower extremity bypass, and similarly reported an improved graft patency with aspirin for up to 12 months in patients with prosthetic grafts.[76] The role of direct thrombin inhibitors and factor Xa inhibitors for peripheral bypass graft has not been adequately explored in literature. Some attempts have also been made to develop novel agents to prevent intimal hyperplasia in order to improve graft patency. So far, however, no new agents have been shown to have successfully achieved this goal.[77]

Graft Surveillance

Despite technological advances leading to improved performance of prosthetic conduits, graft failure continues to occur either perioperatively to "technical error" or after a prolonged period due to development of myointimal hyperplasia or acceleration

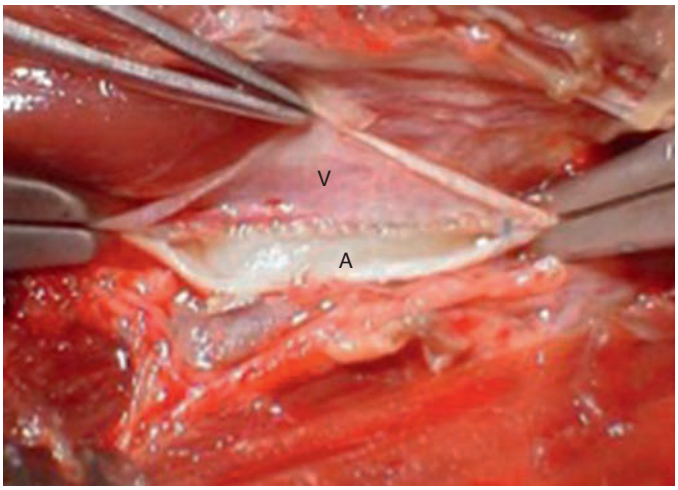


Figure 64.10 **"Patchula" Technique.** The target tibial artery and corresponding tibial vein are opened longitudinally and a common ostium is created with an onlay patch.

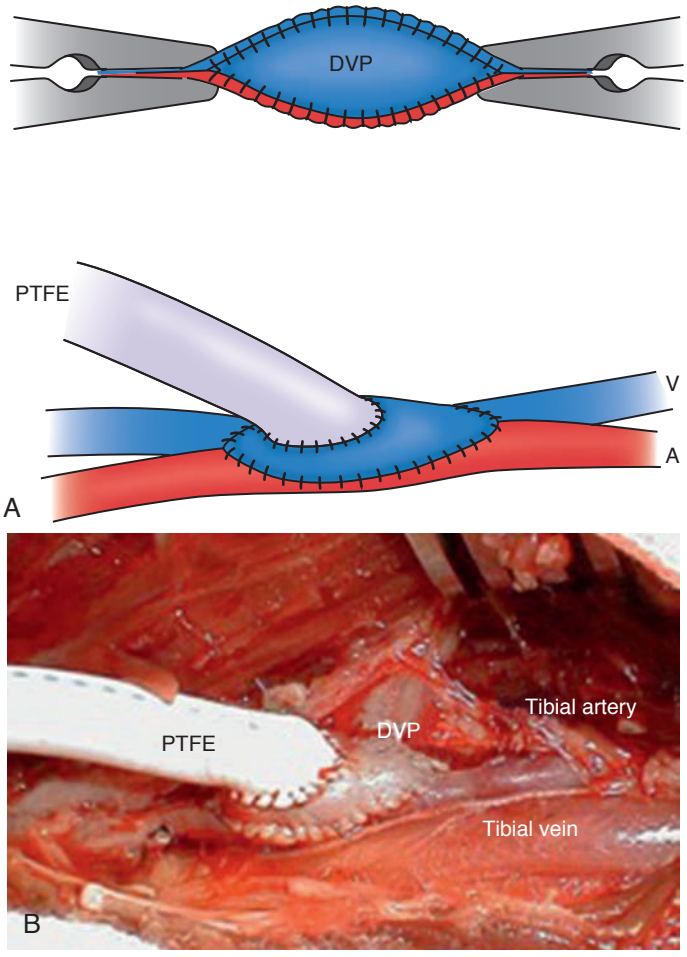


Figure 64.11 **"Patchula" Technique.** A distal vein patch (DVP) bypass is constructed using the patch over the common ostium in the usual manner. This creates a DVP bypass with concomitant anastomotic arteriovenous fistula. *PTFE*, Polytetrafluoroethylene.

of atherosclerosis in the proximal or distal arterial bed.[50,78] As such, it is important to detect the failing graft prior to thrombosis because the management and treatment of such grafts is often more complex than procedures required prior to graft occlusion. Early identification of these patients allows for a more tailored medical therapy that may improve outcome in the future. The addition of warfarin, though not without its side effects, has been shown to have benefit in patients with low velocity grafts.[79] Close surveillance also allows for early endovascular intervention, which may assist in maintaining patency for a longer period of time. A Dutch study, using aggressive surveillance and endovascular intervention, was able to achieve a near 90% patency rate for infra-inguinal bypasses at 2 years.[80] A failing graft can often be managed with endovascular techniques or more simplified surgical procedures such as local revision with patch angioplasty, resulting in enhanced secondary patency and enhanced limb preservation. Therefore graft surveillance programs have been incorporated in most vascular surgical practices to detect failing grafts and intervene early enough to improve graft function and secondary patency rates.

Graft surveillance involves clinical evaluation for recurrent or new symptoms of limb ischemia, as well as an examination of pulses and an ankle brachial index.[81] However, clinical assessment alone does not always identify significant stenoses that threaten graft function, especially in patients initially treated for critical limb ischemia. Therefore vascular laboratory imaging has been added to surveillance protocols as a noninvasive assessment of graft function. While the overall benefit of graft surveillance has not been well documented for prosthetic grafts, regular interval duplex ultrasound studies obtained at 3, 6, and 12 months postoperatively and then annually have been employed in many practices to identify threatened bypasses before they occlude.

Numerous authors have attempted to define the Doppler ultrasound criteria that should prompt further workup and potential repair of a "failing" graft. Bandyck has suggested that a peak systolic velocity exceeding 300 cm/s on Doppler ultrasound and a peak systolic velocity ratio across the stenosis exceeding 3.5 correlates with more than 70% stenosis in a graft.[82] Another study by Brumberg and colleagues demonstrated that mid-graft peak velocity of 45 cm/s or less was predictive of graft failure.[83] Sanchez and colleagues reported a series looking at surveillance in order to detect failing ePTFE grafts.[84] These authors reported on a 12-year experience with more than 90 ePTFE grafts and surmised that ultrasound surveillance was useful despite the observation that the progression of proximal and distal arterial disease was the primary cause of ePTFE graft failure in the series. These authors concluded that frequent graft surveillance may allow for the detection of hemodynamically threatening lesions prior to graft thrombosis and enhance long-term graft patency and function as the 5-year patency and limb preservation rate for treating "failing" ePTFE grafts was substantially improved over that for ePTFE grafts that have gone on to occlude. A smaller study from Sweden randomized 156 patients between clinical surveillance and surveillance that included Duplex ultrasound evaluation. Although only 40 of

the grafts in the trial were ePTFE grafts, the authors noted improved assisted primary and secondary patency in the group with regular Duplex ultrasound surveillance.[85] More recently, a combined experience from Boston and the Netherlands found ultrasound surveillance to be effective in leading to a reduction in amputation and cost.[86]

LIMITATIONS AND RISKS

Graft Failure Modes

The failure of prosthetic conduits can be classified as early, midterm, or late. Early failures that occur in the first month after surgery are commonly due to technical problems during surgery and the presence of underlying thrombophilia. Technical problems encompass more than procedural and suturing issues, such as poor/limited choice of inflow or outflow targets, or other operational related difficulties. Midterm graft occlusions occur between 6 and 24 months after surgery and are usually due to myointimal hyperplasia at an anastomosis. The interaction among blood, host artery, and graft initiates a complex set of biochemical and cellular responses that ultimately limit implant function. Finally, late graft thrombosis occurs several years after implantation and is frequently secondary to the progression of proximal or distal atherosclerotic disease.

The Blood-Material Interface

Prosthetic grafts with blood-compatible materials attempt to minimize activation of the body's prothrombotic and hyperplastic responses. The full spectrum of this response includes a combination of lipids, proteins, and cells that act in concert to provide localized amplification. A series of negative feedback mechanisms control the propagation and termination of these responses. The inability of current prosthetic materials to replicate these complex systems plays a role in graft failure.

Cellular Interaction and the Coagulation Cascade

When blood encounters an artificial surface, adsorption of proteins activates the complement and coagulation cascades. Activation of the complement system may contribute to surface-induced thrombosis through platelet activation, as well as monocyte and neutrophil infiltration, which also have been implicated in the development of myointimal hyperplasia.[87] Discussion of the coagulation system is beyond the scope of this chapter, but binding of plasma factor XII to prosthetic surface results in a conformational change that yields an activated form, XIIa, which catalyzes this cascade.[88,89] Blood flow modulates this process by controlling the rate at which coagulation proteins and activated factors are delivered to or removed from the graft surface. Locally disturbed flow or turbulence at an anastomosis creates recirculation regions that stimulate coagulation factors. Platelets are the major cellular component of the thrombotic response and are involved in both complement-mediated and T-cell–mediated immune responses.[90] Increased levels of platelet-generated thromboxane continue to be observed 1 year after graft implantation in animals, and clinical studies have revealed persistent platelet deposition on Dacron grafts for at least several months.[91-94] Antiplatelet agents can reduce platelet deposition onto prosthetic grafts.[95,96] Despite their role in the phagocytosis of foreign material and bacteria, neutrophils recruited to a biomaterial surface do not protect against infection.[97] Activated macrophages express tumor necrosis factor-α as well as growth factors that may stimulate smooth muscle cell (SMC) proliferation and contribute to intimal hyperplasia.[98,99]

Migration of endothelial cells from the peri-anastomotic area results in the formation of a neointima extending no more than a few centimeters from the anastomosis with little coverage of the midportion of the graft. However, scattered islands of endothelial cells have been observed far from the anastomotic regions due to transmural ingrowth of microvessels from perigraft tissue or adherence of blood-borne endothelial progenitor cells (EPCs).[100-106] Endothelial cells that grow onto prosthetic graft surfaces often display a procoagulant phenotype and promote rather than hinder graft thrombosis. Activated endothelial cells may increase growth factor production and thereby encourage SMC proliferation.

Graft Complications

Complications after placement of a prosthetic graft include bleeding, infection, occlusion, seroma formation, pseudoaneurysm, and rarely steal phenomenon secondary to inadequate proximal blood flow. A detailed discussion of all graft-related complications is beyond the scope of this chapter, but the two most important complications, graft thrombosis and infection, are briefly outlined as follows.

Graft Thrombosis

As previously discussed, implanted prosthetic grafts can develop myointimal hyperplasia and eventually thrombose, leading to graft occlusion. When myointimal hyperplasia results in the development of a hemodynamically significant stenosis prior to graft thrombosis, the bypass is referred to as a "failing graft," with diminished function.[107] Flow in a "failing graft" is hemodynamically compromised, but may not result in clinical signs or symptoms of diminished flow. Revision of failed grafts often requires a more complex procedure with increased morbidity and mortality as compared with an intervention to maintain assisted primary patency. Therefore routine surveillance is often performed to monitor graft function prior to total occlusion.

When graft failure does occur, the result is often a return of the patient's original symptoms or a significant increase symptom severity. Prosthetic graft occlusion might also lead to significant morbidity. Thrombosis of bypasses performed for intermittent claudication can lead to limb threatening ischemia and possible limb loss.[108] The treatment of lower extremity prosthetic bypass graft occlusion is tailored to the patient and guided by the clinical presentation and patient's anatomy. A patient with an occluded graft but no concurrent signs of critical limb ischemia, such as rest pain, night pain, or tissue loss, would benefit from a trial of thrombolysis to both restore flow within the graft and unmask any underlying stenotic lesions that would be amenable to endovascular or open surgical treatment. Conversely, a patient with critical limb ischemia or a

chronically occluded graft should undergo operative exploration for an open thrombectomy or creation of a new bypass.

Since its introduction in the 1970s as a technique to restore occluded arteries, thrombolysis is now a commonly used modality for treating occluded arteries, veins, and prosthetic grafts.[109] Thrombolysis can be administered systemically or as part of a catheter-directed or mechanical approach using specialized catheters. However, there are numerous contraindications to this treatment approach, including recent surgery, hemorrhagic strokes, bleeding disorders, and a nonviable limb.[110] Several retrospective studies have described an early technical success of 48% to 90% and a limb-salvage rate of 56% to 82% with thrombolysis.[111-117] The Surgery or Thrombolysis for the Ischemic Lower-Extremity (STILE) trial and the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial investigators assessed thrombolysis versus thrombectomy for limb ischemia, and reported that thrombolysis was superior to surgical thrombectomy in patients with fewer than 2 weeks of symptom duration, whereas surgical thrombectomy was superior to thrombolysis when symptoms lasted for 2 weeks or longer.[118,119]

Patients with more than 2 weeks of symptom duration should be considered for operative intervention and placement of a new bypass graft if feasible. Conversely, patients with acute (fewer than 2 weeks' duration) prosthetic graft occlusions and no evidence of critical limb ischemia can be considered for a trial of thrombolysis, but can also undergo a new bypass graft especially if there is a suitable outflow target vessel and an adequate length of autogenous conduit is available.[120]

Graft Infection

Prosthetic graft infection occurs in 1% to 6% of patients undergoing lower-extremity bypass and 0.5% to 2% of patients undergoing abdominal aortic repair.[121,122] These infections are associated with considerable morbidity, including amputation rates of 10% to 70%, and mortality rates up to 20%.[123,124] The most common causative organisms are *Staphylococcus* species, *Staphylococcus aureus* and *Staphylococcus epidermidis*.[122,125] The origin of the graft infection is often microorganisms seeded at the time of the operation, or postoperatively through wound complications, adjacent infections, or a bloodstream infection from a distant source. Predictors of prosthetic graft infection include reoperative bypass, female gender, diabetes, and active infection at the time of bypass.[126] There is no evidence that a particular type of graft material, such as Dacron or ePTFE, is more predisposed to infections compared with other materials.[127]

The diagnosis and management of graft infections is guided by the patient's clinical status and the type and extent of the infection. Patients typically present with fever and malaise, with or without a wound infection and purulent discharge. Elderly, malnourished, and frail patients may not mount an adequate inflammatory response to indicate an active infection. Patients with suspected graft infections should have blood cultures, and if applicable, cultures should be sent. Patients should then be started on broad-spectrum antibiotics that are reviewed when the culture results and antibiotic sensitivities are reported. Imaging should be obtained in the workup of patients with a suspected graft infection. Acceptable modalities include computed tomography (CT) angiography, ultrasonography, magnetic resonance imaging, Gallium scanning, and rarely labeled white blood cell scanning. Radiologic findings suggestive of graft infection include perigraft air, fluid or soft-tissue attenuation, and pseudoaneurysm formation.[128]

There are several treatment strategies for graft infections, depending on the patient's status and the type of infective organism. Graft preservation is sometimes possible in patients with limited infections and no signs of sepsis or extensive graft involvement with sparing of the anastomosios.[129] Grafts that are infected with *Pseudomonas* and methicillin-resistant *Staphylococcus aureus* (MRSA) are particularly virulent organisms that require removal of the infected graft.[121,130] In patients with graft thrombosis and clinical evidence of adequate collateralization, graft excision alone might be sufficient. In patients who require revascularization of the excised graft segment, an in situ graft can be placed or an extra-anatomic bypass might be created. Conduit options include autogenous, cryopreserved, and rifampin-soaked prosthetic grafts. The graft excision and replacement may be done concurrently or in a staged manner, depending on the patient's clinical status.

If patients are known to be MRSA-positive, then a decolonization strategy should be pursued prior to the surgery whenever possible. Moreover, given the devastating complications associated with prosthetic graft infections, some have advocated for regular pre-operative screening and, when detected, decolonization of MRSA. Lee and colleagues analyzed the economic impact of screening all vascular surgery patients prior to a vascular surgical procedure, and demonstrated that testing and decolonizing patients for MRSA may be cost-effective.[131]

FUTURE ADVANCES

Despite substantial advancements in prosthetic graft technologies and their associated clinical outcomes, current grafts are still inferior to autogenous vein grafts. As such, the quest continues for a durable prosthetic conduit that is resistant to intimal hyperplasia and infection while providing patients with long-term patency. Bioengineered human acellular vessels have emerged as a promising technology. These conduits are constructed from banked human vascular SMCs cultured on a biodegradable polymer. A process of decellularization then removes viable tissue elements, leaving an intact conduit with preservation of mechanical properties. A recently published trial utilized this conduit for dialysis access at six centers in the United States and Poland.[132] Trial endpoints were freedom from adverse events (immune reaction, pseudoaneurysm, infection) and patency rates. The acellular vessel was implanted into 60 patients with mean follow-up of 16 months. These bioengineered conduits demonstrated no dilation and minimal post cannulation bleeding with 6-month primary patency of 63% (primary assisted patency 73%, secondary patency 97%). Thrombosis at 12 months resulted in a 28% primary patency (primary assisted patency, secondary patency 89%). The rate of reintervention was similar to reported rates with ePTFE, including 16 venous anastomotic revisions showing no demonstrable reduction in

anastomotic hyperplasia. There were, however, no reports of systemic immune reaction or excessive inflammatory response. Although cannulation-related pseudoaneurysms were noted in some patients, no true aneurysmal degeneration of the vessels occurred. Although patency rates were acceptable, there was not an obvious improvement over prosthetic graft results, and patency was not as good as that with AV fistula construction. However, the potential benefits and significant scientific efforts surrounding this conduit support further testing and a larger controlled clinical study.

Another future avenue for improving prosthetic conduit outcomes includes the use of remote monitoring of graft function to detect early hemodynamic changes prior to graft failure. As noted previously, prosthetic grafts fail due to myointimal hyperplastic stenosis and thrombosis. Graft surveillance is used to monitor function; however, graft failure can occur between these episodic examinations. An innovative micro sensor with wireless, microchip technology may allow automated surveillance with assessment of graft function using a cloud-based algorithm. In vitro flow data has demonstrated the ability of the device to determine factors related to prosthetic graft function under varied hemodynamic flow conditions. Wireless signal acquisition using Bluetooth technology allows remote data analysis reflecting graft flow parameters through changes in microsensor voltage and frequency. Waveform analysis was applied to construct an algorithm using proprietary software, thereby determining parameters for graft flow characteristics as well as determination of degree of stenosis and location of stenosis. Subsequent in vivo experiments have confirmed the ability of the system to generate signal acquisition through skin and soft tissue under biologic conditions.[133] This automated system shows promise to deliver real-time data that can be analyzed by cloud-based algorithms alerting the clinician of a change in graft function or development of stenosis for further diagnostic study or intervention prior to graft failure.

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The selected references represent a spectrum of publications from classic historical work to the latest technical innovations in regards to prosthetic graft utilization for lower extremity revascularization.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 65

Biologic Grafts

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In the field of vascular surgery, the use of surgical bypass is fundamental to the treatment of a wide variety of arterial and venous disorders. In turn, the technical conduct and success of surgical bypass are directly dependent on the conduit used. The ideal conduit should be readily available, easy to handle, resistant to thrombosis and infection, durable, inexpensive, and should have characteristics similar to the vessel that it is replacing.

Although the perfect conduit does not exist, autogenous blood vessels are closest to the ideal. Autogenous arterial conduits, such as the internal mammary, radial, and gastroepiploic arteries, have been used with great success in the coronary circulation.[1-3] The internal iliac and radial arteries have been used in the visceral vascular bed,[4,5] and the superficial temporal artery has been used for extracranial-intracranial bypass.[6] Unfortunately, short conduit length and invasive harvest have limited the use of autogenous arterial grafts to a relatively small number of clinical scenarios.

Autogenous vein has been the preferred conduit for infrainguinal bypass because long lengths of vein can be harvested, removal is inconsequential, and harvest complexity is minimal.[7] Autogenous veins have been used for the bypass of upper extremity,[8] carotid,[9] coronary,[1] and visceral[10] arterial beds. They have also been preferentially used in the construction of arteriovenous fistulae (AVFs) for hemodialysis.[11]

Although autogenous vascular grafts perform well, there are multiple clinical situations in which these conduits are inadequate, unavailable, or improperly matched to the recipient vascular bed. These unmet demands led to the development of artificial grafts. Although multiple materials have been tried, polyethylene terephthalate (Dacron, DuPont, Wilmington, Delaware) and polytetrafluoroethylene (PTFE) have emerged as the standard materials for prosthetic vascular grafts. These grafts have been used with excellent success for the bypass of large vessels, such as the aorta and iliac arteries,[12] and medium-sized vessels, such as the subclavian artery.[9] Prosthetic grafts have also been used extensively for dialysis access[11] and with mixed results for infrainguinal revascularization.[13] Dacron and PTFE grafts offer "off-the-shelf" availability and a variety of sizes to permit replacement of even the largest vessels. In general, however, they cannot be used in infected fields, and compared with autogenous conduits, are at increased risk for infection,

Abstract

Certain circumstances cause limitations for the use of autogenous and prosthetic grafts, and other potential conduits are often needed in clinical practice. Extensive research has led to the development of numerous biologic grafts, which are useful under different clinical scenarios. Although they are still not the ideal conduits, these biologic grafts have become an important part of the armamentarium available to vascular surgeons.

Keywords

biografts
cryopreserved saphenous vein
human umbilical vein graft
arterial allograft
tissue-engineered grafts

structural deterioration, and occlusion. Although patency rates are acceptable for aortoiliac reconstruction because of high flow rates and low outflow resistance, bypass to smaller targets, such as the tibial arteries, is associated with low graft patency.

Limitations of autogenous and prosthetic grafts have fueled exploration for other potential conduits, and this investigative effort has led to the evaluation of biologic grafts for bypass. Biologic grafts, or biografts, are bypass conduits made of nonautogenous biologic vessels modified for use in clinical practice. Allografts or homografts refer to arteries or veins that are transplanted from one individual to another within the same species. Xenografts or heterografts are vessels transplanted from an individual of one species to an individual of another species.

Carrel[4] was first to experiment with fresh allografts and xenografts in dogs during the first decade of the 20th century. The first recorded human use of allografts, obtained from casualties, occurred during World War I.[14] In 1948, Gross et al.[15] described the first clinical series of fresh arterial allografts, and less than a decade later, Linton[16] published his series of fresh venous allografts. Various methods of allograft cryopreservation were developed in the 1950s,[16] refined in the 1970s,[17,18] and finally standardized and commercialized in the late 1980s.[19] In parallel, enzymatically treated and tanned bovine carotid artery (BCA) xenografts were evaluated and first described in a clinical setting in 1966.[20] Application of similar techniques to human vessels led to development of the human umbilical vein (HUV) graft by Dardik and Dardik in 1976.[21]

Theoretically, biografts promise to be the optimal vascular conduit. They can potentially offer "off-the-shelf" availability, a wide variety of sizes, excellent handling characteristics, and patency rates similar to those of autogenous vessels. These attractive features prompted scientific investigation and clinical use of these conduits that has spanned the course of almost a century. Although this collective experience with an assortment of biografts in a variety of clinical settings led to specific clinical indications for their use, biologic grafts have failed to become the "Holy Grail" of vascular surgery.

GRAFT PROPERTIES

Fresh Vascular Allografts

Fresh arterial and venous allografts have been studied in animal experiments.[22-24] In one canine model, fresh venous allografts had a patency rate of 69% at 20 months. Pathologic analysis of explanted veins revealed intimal proliferation, medial inflammation, medial degeneration, and periadventitial fibrosis.[23] In another canine venous allograft experiment, dogs that were immunosuppressed with azathioprine demonstrated slightly better graft patency than those that were not.[24] Conversely, in a murine model, fresh venous allografts implanted in rats had excellent patency rates and minimal intimal thickening on histologic analysis.[24]

In humans, fresh venous allografts used for infrainguinal bypass had a failure rate of 55% in one series, which failed grafts either occluded or became aneurysmal. Patency rates of allografts appeared to be higher in patients whose grafts were harvested from blood types that were ABO compatible donors.[25] In another study, fresh arterial allografts placed in the aortic position were noted to be highly immunogenic, with evidence of both a humoral and cellular immune response.[26] These animal and human data suggest that fresh vessel allografts initiate a host immune response. Furthermore, the patency of these grafts appears to vary among species.

Aside from their immunogenicity, the use of fresh vascular allografts in the clinical setting has been hampered by logistic factors. Scarce availability of fresh arteries and veins and a need to successfully store such vessels for future use have led to the development of a number of preservation and modification techniques. These techniques can be divided into those that involve preservation without a planned significant change in graft integrity and those in which the graft is intentionally chemically altered. Cryopreservation is the most common example of the preservation technique, whereas proteolytic enzymatic digestion and dialdehyde starch tanning are examples of the modification technique. In addition to creating a conduit that would be more readily available, it is hoped that these techniques will inhibit the host immune response and thereby increase graft patency.[27]

Over the past century, multiple vessel preservation techniques have been tested. Grafts were stored in a number of solutions, including nutrient broths,[15] glycerol,[28] and plasminate.[29] A variety of storage temperatures ranging from room temperature to −70°C were tried.[17,28] Finally, a number of adjunctive sterilization techniques, including ethyl dioxide and irradiation, were attempted.[17] Early techniques focused on preservation without much regard to viability of the vascular tissue. Initial results with preserved vascular grafts were inconsistent, probably because significant cellular and structural damage occurred in many of these vessels and made them nonviable.[25,30]

Cryopreserved Allografts

Methods of Preparation

There is evidence that cryopreservation can result in significant cellular damage unless appropriate precautions are taken.[31] During the cryopreservation process, the extracellular matrix freezes at a higher temperature than cellular cytoplasm. This leads to a vapor pressure gradient between the intracellular and extracellular components. When cooling occurs slowly, this gradient can result in cellular dehydration, whereas rapid cooling can lead to plasma membrane rupture. Work with cell suspensions, such as blood and semen, has revealed that certain substances, when added during the freezing process, can significantly improve cell viability.[32] These substances, called cryoprotectants, include dimethylsulfoxide and glycerol. Their mechanism of action is to enter cellular cytoplasm and decrease the vapor pressure gradient that exists between the intracellular and extracellular components.[19]

Over the last 20 years, cryopreservation techniques have been optimized and commercialized. Important variables inherent in modern cryopreservation processes include the type and amount of cryoprotectant used, freezing rate, storage temperature,

duration of storage, and additives used.[19] The most common cryoprotectant in use today is dimethylsulfoxide at 10% to 20% dilution. The freezing rate varies among protocols, and there is some evidence that rapid freezing at 5°C/sec may work best. Storage temperature may vary from −102°C to −196°C. The duration of cryopreservation may also be important, and longer duration has been shown to have an adverse influence on vessel wall morphology but not on graft patency in one animal model.[33] Finally, there is evidence that the addition of certain additives such as chondroitin sulfate to the storage solution enhances vein viability and function.[34]

Histology and Physiology

Cryopreserved arteries and veins are affected by both cryopreservation and immune rejection, and a large body of research has been performed to define and dissect these processes from one another.

Cryopreservation has effects on the mechanical properties, histology, and physiology of the treated vessel. Elasticity and compliance of a vessel are important mechanical characteristics that affect its performance as a conduit. Changes in these properties lead to an increased difference in compliance between the conduit and host vessel, which can adversely affect graft patency. In vitro models comparing the mechanical properties of cryopreserved and freshly harvested arteries and veins reveal that cryopreservation does not significantly affect elasticity, contractility, compliance, and the mechanical buffering function of the treated vessel.[18,35,36]

Cryopreservation of blood vessels leads to changes in the intima, media, and adventitia. Although appropriate cryopreservation does not affect the gross morphology of the endothelial layer, histologic changes such as focal microvillous projection, cytoplasmic vacuolization, nuclear prominence, and interruption of tight junctions have been visualized.[33,37] These changes increase with the duration of cryopreservation[33,37] and lead to partial endothelial cell loss.[37-39] Endothelial loss is significant when the cryopreserved graft is exposed to arterial flow. Although autogenous grafts reestablish an endothelial layer, only minimal re-endothelialization is observed in allografts.[19,29] Because of a compromise in intimal integrity, cryopreserved grafts accumulate low-density lipoprotein cholesterol at an accelerated rate as measured in an ex-vivo organ perfusion system.[40]

Endothelial vasodilatory function, as measured by response to acetylcholine, thrombin, and calcium ionophore, appears to be retained, but it is somewhat diminished with cryopreservation.[41] With regard to coagulation homeostasis, although cryopreservation of vein grafts is not associated with increased platelet deposition,[41] it does cause decreased thrombomodulin activity.[38] Fibrinolytic activity appears to be similar in both fresh and cryopreserved canine jugular veins, but this activity may be adversely affected by the duration of cryopreservation.[37]

The medial layer of cryopreserved vascular grafts appears to have grossly normal smooth muscle cells, although slight lysis and minimal mitochondrial edema were observed in a rabbit model. In that model, implantation of autologous veins into an arterial circuit led to the preservation of both smooth muscle cells and the elastic lamina. The smooth muscle cells displayed a synthetic, rather than a contractile, phenotype characterized by dilatation of the endoplasmic reticulum.[33] Despite these findings, collagen synthesis in cryopreserved veins was diminished in a canine model.[39] Smooth muscle cells in cryopreserved canine saphenous autografts were noted to have a diminished relaxation response to nitric oxide,[41] although contraction induced by norepinephrine, potassium chloride, and serotonin was unaltered.[19]

Immunology

Allogeneic implantation of cryopreserved vessels leads to a different histologic and physiologic picture than that seen with cryopreserved autologous grafts. These observed changes are caused by immune mechanisms. Endothelial loss, encountered when an allograft is exposed to arterial flow, is not appreciably reversed, and exposed subendothelial elements are noted on electron microscopy.[19,29] In addition, smooth muscle cell viability is lost,[23,42] severe medial fibrosis and disruption of elastic fibers occur,[23,29,42] and medial necrosis has been described.[43] Significant lymphocytic infiltration of the media and adventitia has also been observed.[29] However, these alterations in vessel wall biology are not routinely observed with autologous conduits.[43]

Although it is well known that transplanted allograft and xenograft organs elicit an immune response, it was initially believed that the host-mediated immune response of transplanted vessel allografts was minor[44,45] and could be successfully blunted by the cryopreservation process.[27] Recent literature, however, suggests that vascular allografts do trigger a significant immune response.[19,26] Endothelial cells present surface antigens that stimulate a cell-mediated immune response[46] against the donor graft and an immunoglobulin-G-mediated humoral immune response to donor-specific antigens has been described.[26,47] Transplanted canine venous allografts, but not autografts, demonstrated extensive medial fibrosis and lymphocytic infiltration consistent with immunologic rejection.[48] In a human model, the analysis of 22 explanted cryopreserved saphenous vein (CSV) allografts revealed moderate to severe intimal, medial, and adventitial inflammatory infiltrates. Immunohistochemical analysis demonstrated an abundance of activated T lymphocytes containing cytotoxic granules.[49] In another experiment, cryopreservation did not alter antigenic expression and the immunologic response of a murine host to allograft transplantation in a number of studies.[50,51] Chronic immunologic rejection clearly plays a role in allograft biology and appears to be responsible for both diminished patency of cryopreserved vascular grafts and the predilection of these grafts to aneurysmal degeneration.[43]

A number of investigators hypothesized that manipulating the host immune response to vascular allografts may attenuate immune rejection and improve graft patency. Matching of ABO blood groups was suggested by Ochsner et al.[25] who noted improved patency of allografts transplanted to ABO-matched patients. In animal models, immunosuppression with cyclosporine has been demonstrated to diminish immunologic rejection of aortic[43] and venous allografts.[52] Azathioprine has likewise been shown to decrease the effects of rejection in venous allografts.[24]

Based on these findings, attempts were made to improve the results of allograft use in humans by modulating the host immune response. Carpenter and Tomaszewski[53] performed a prospective, randomized trial of 40 CSV allografts implanted in patients treated with low-dose azathioprine, but they failed to show a significant improvement in graft patency at 1 year. Azathioprine immunosuppression, however, was associated with a decreased presence of T-lymphocyte cytotoxic granules in that study.[49] In another small human trial, a combination of low-dose cyclosporine, azathioprine, prednisone, warfarin, aspirin, and vasodilators was used in patients who underwent CSV bypass. Grafts treated with this immunosuppressive regimen demonstrated increased patency rates. This regimen, however, was associated with an increased incidence of complications and graft aneurysmal degeneration.[54] In one series of patients with prosthetic aortic infection, 10 of 30 patients who underwent aortic allograft replacement were concomitantly treated with cyclosporine. Although the measured humoral immune response was blunted in patients who received cyclosporine, no differences in graft patency or graft complication rates were appreciated.[26] In contrast, Randon et al.[55] contended that a low-dose cyclosporine immunosuppressive regimen for lower extremity bypass using CSV was effective at reducing the risk of rejection while facilitating host cell repopulation of biograft endothelium.

Furthermore, an immunologic response evoked by a cryopreserved allograft can induce allosensitization, which may interfere with future organ transplantation. This mostly affects the use of cryopreserved femoral vein (CFV) allografts in hemodialysis access. A case-matched series of 20 patients who underwent creation of hemodialysis access with this graft demonstrated host allosensitization in all patients as measured by the panel-reactive antibody assay.[56] Allosensitization, however, did not occur when the CFV graft was processed to remove cellular elements.[57] Diminution of the immune response by removal of antigenic epitopes has led to multiple attempts to structurally modify biologic grafts.

Structurally Modified Biologic Grafts

In parallel with the development of cryopreservation techniques, further research was conducted to modify blood vessels so that an acceptable vascular substitute could be developed. The goal was to transform a harvested blood vessel into a durable nonimmunogenic graft that could be easily produced and stored. During early experiments in the 1950s, animal arteries were modified by enzymatic digestion of the musculoelastic portion of the vessel wall with ficin, a proteolytic enzyme isolated from figs, to remove immunologically reactive proteins. The resultant collagenous vascular skeleton was strengthened by collagen cross-linking through subsequent tanning with dialdehyde starch.[20,58] This modified graft was then sterilized and stored in a 1% propylene oxide-50% ethanol solution.[20]

In the earliest experiments, modified BCA grafts were implanted as xenografts first in dogs and then in patients with symptomatic lower extremity occlusive disease. Although no graft ruptures had occurred at 3 years of follow-up, early neointimal hyperplasia and diminished patency were observed.[20] An unacceptable late rate of graft infection and aneurysmal degeneration led to a change to glutaraldehyde-based tanning protocols.[58,59]

Bovine mesenteric veins (BMVs) have also been modified by a patented process of glutaraldehyde cross-linking and sterilized by γ radiation.[60] Both BCAs and BMVs have been used as xenografts in several clinical applications.

HUV is a modified biologic conduit that was first evaluated in baboons[21] in the early 1970s and subsequently used in humans[21,61] in 1975. Umbilical vessels are uniform in caliber, valveless, and branchless. The umbilical vein was removed from the umbilical cord by a variety of techniques, including enzymatic digestion and mechanical stripping. After a rinsing process with a cold isotonic solution, this vein was tanned with glutaraldehyde. Polyester fiber mesh was then sutured in place about the length and outside circumference of the graft for added support.[21]

Although thrombosis and aneurysm formation were common in early experiments, tanning and external support modifications significantly reduced these complications. Increased adherence of platelets to the luminal surface of these grafts has been observed in a canine model.[62] Histologic analysis of modified HUV grafts explanted from baboons revealed an early neutrophil and late macrophage response in the vicinity of the surrounding polyester mesh. The inner collagen layer appeared thickened and dense but was free of significant inflammation.[21] The reduced immunogenicity of this graft was hypothesized to be secondary to pretreatment with glutaraldehyde, which was thought to bind to graft histocompatibility antigen sites and thereby shielded them from the host immune response.[63]

Other Grafts

The search for an ideal blood vessel substitute led to the investigation of a number of nonconventional biologic grafts in animal models. Vascular prostheses fashioned from pericardium[64] and small intestinal mucosa[65] have been evaluated, and chemically modified human[66] and bovine[67] ureters have been used as vascular conduits with some success. Modified bovine ureters have also been used clinically with acceptable patency rates in femoral to popliteal bypass in one small Australian series.[68] In addition, a small randomized trial claimed clinical equivalence between bovine ureters and PTFE used for hemodialysis access in patients with no vein options.[69] More recently, tissue engineered vascular conduits have been developed with the hopes of providing new dependable options for challenging situations.[70]

CLINICAL USE IN PERIPHERAL VASCULAR SURGERY

Indication

Biologic grafts have been used in modern peripheral vascular surgery mostly in three distinct clinical settings: extremity bypass in the absence of suitable autogenous conduit, arteriovenous (AV) access for hemodialysis, and replacement of infected prosthetic grafts.

Extremity Bypass

Acute or chronic ischemia of an extremity is caused by a number of conditions, including atherosclerosis, trauma, embolization, and in-situ thrombosis. Treatment of extremity ischemia involves revascularization by endovascular or surgical techniques. During infrainguinal surgical bypass, autogenous great saphenous vein has proven to be the preferred conduit for infrainguinal revascularization.[71,72] When the autogenous great saphenous vein is not available, alternative autogenous conduits, such as an arm vein,[73] the small saphenous vein,[74] and the composite autogenous vein,[75] have been used with good results. The ever-increasing age and complexity of patients with infrainguinal arterial occlusive disease has brought about increasingly frequent clinical scenarios in which the autogenous vein is not available, and an alternative conduit must be found. Although prosthetic grafts have been used with moderate success above the knee, they have been disappointing when used for infrageniculate bypass.[76,77] Distal modification of prosthetic grafts with a vein cuff or distal AVF may improve patency rates,[78-80] but it is more cumbersome.

Given the absence of reliable conduit options for infrageniculate bypass when a suitable autogenous vein is lacking, the feasibility of biologic grafts has been evaluated. In this setting, CSV allografts,[81] cryopreserved femoro-popliteal artery (CFA) allografts,[42] HUV grafts,[82] BCA xenografts,[58] and BMV xenografts[83] have been used with varying degrees of success.

Arteriovenous Access

End-stage renal disease is a significant public health problem in the United States; its prevalence is increasing steadily, and it is forecasted that by the year 2030 more than 2 million patients will be undergoing hemodialysis.[84,85] Long-term hemodialysis is best performed through a surgically created AVF that connects the arterial and venous circulations via a conduit. The ideal AV conduit carries high flow for efficient dialysis, is superficial enough for easy access, is sufficiently durable to withstand multiple cannulations, allows rapid sealing of cannulation sites, and is resistant to infection, stenosis, and thrombosis. A mature, native vein AVF comes closest to the ideal, and its use is strongly encouraged.[11] Unfortunately, many individuals lack suitable veins for native AVF construction because of small vein size, previous access procedures, or vein harvest for peripheral or coronary bypass. Furthermore, up to 60% of native AVFs fail to mature and therefore cannot be used successfully.[86,87] Although prosthetic AV grafts are widely used, they have lower patency rates, require more frequent revision, and are at higher risk than vein AVFs for infection.[88] The search for optimal hemodialysis access in patients who are not candidates for a native vein AVF has led to the use of biologic grafts. CFV allografts,[89] BCA xenografts,[90] bovine ureter xenografts,[69] and BMV xenografts[60] have been used in a variety of settings with variable results.

Replacement of Infected Prosthetic Grafts

Prosthetic graft infection, particularly when the aorta is involved, is one of the most dreaded complications in vascular surgery and is associated with high morbidity and mortality.[91] Treatment of an infected aortic prosthesis includes excision of the infected segment and extraanatomic prosthetic bypass[91] or reconstruction with an antibiotic-soaked or antibiotic-bonded prosthetic graft,[92] femoral vein,[93] or aortic allograft.[94] In addition, extraanatomic bypass and aortic ligation are associated with long operative times, risk of remote infection, bypass thrombosis, and aortic stump rupture.[91,95] Antibiotic-soaked prosthetic grafts may work well for infections caused by relatively indolent *Staphylococcus epidermidis*, but they are much less effective against more virulent organisms.[92] Finally, use of the femoral vein for aortic reconstruction is tedious and associated with harvest-related complications.[93]

Cryopreserved aortic allografts offer "off-the-shelf" availability, good handling properties, and the potential for expeditious in-situ repair. Cryopreserved aortic allografts were more resistant than prosthetic grafts to *S. epidermidis* infection in a canine model.[96] Resistance of vascular allografts to infection has led to the wide use of arterial allografts to treat aortoiliac infection,[97] CFV allografts to treat infection involving prosthetic AV grafts,[98] and CSV allografts to replace infected infrainguinal prosthetic bypass grafts.[99]

Biologic Graft Preparation

Cryopreserved Allografts

A number of tissue banks and commercial companies prepare, store, and supply cryopreserved blood vessels. Despite similarities in conduit preparation, many have proprietary cryopreservation protocols.[100] The great saphenous vein, femoral vein, and arterial segments are harvested from multiorgan donors who are screened for an array of viral, bacterial, and fungal infections. Branches are suture ligated, and the allografts are sized with calibrated dilators. They are tested for presence of pathogens, rinsed in an antibiotic solution, placed in a proprietary cryoprotectant solution, and stored in the vapor phase of liquid nitrogen at −110°C to −196°C. Allografts are shipped and stored in a solution of dimethylsulfoxide at −96°C until needed. The vein, but not artery, is usually matched for ABO/Rh compatibility with the recipient to decrease the risk of rejection. At the start of the procedure, the allograft is rapidly thawed by submersion in a warm water bath at 37°C to 42°C for 20 minutes, and after rinsing in a series of solutions provided by the manufacturer, it is ready for use.

CSV allografts are available in a number of lengths and diameters. Most commonly, the vein measures 3 to 5 mm in diameter. These grafts look, feel, and handle like the autogenous saphenous vein. During an infrainguinal bypass, the allograft is usually reversed and placed in a superficial tunnel for easy access.[81] Postoperative surveillance was not considered useful in one large series.[81]

CFV allografts are usually less than 25 cm in length and have a diameter between 5 and 7 mm, and they have most commonly been used in hemodialysis in the setting of prosthetic AV graft infection. When used for dialysis access, this allograft is appropriately reversed and tapered to a 5 mm diameter at the arterial anastomosis to decrease the incidence of ischemic steal syndrome.[89] It is allowed to mature for 3 to 4 weeks before

it is accessed for hemodialysis. Revision of these grafts is very difficult because of their thin wall and surrounding fibrosis.[98]

Arterial allografts have most frequently been used for aortic replacement in the setting of primary or prosthetic aortic infection. Given this clinical setting and the need to replace a large artery such as the aorta, these allografts must withstand particularly hostile conditions. Technical modifications for the use of these allografts have been developed, including vigilance in following thawing instructions, use of appropriately long grafts, and construction of tension-free anastomoses, taking great care that suture ligation of branches is performed with polypropylene sutures that include the graft wall along with the branches. Aggressive excision of infected tissue and wound drainage is required, and other adjuncts include circumferential anastomotic reinforcement with allograft strips, use of gentamicin-impregnated fibrin glue, and coverage of the graft with viable tissue, such as a pedicled omental or muscle flap.[94,101]

Structurally Modified Allografts

The HUV graft (Fig. 65.1) is shipped and stored in 50% ethanol and provided on a glass mandril. It is irrigated up to 10 times with a low-molecular-weight dextran-containing solution and rinsed with a high-concentration heparin solution (10,000 U/L). This graft does not tolerate traction or the application of standard vascular clamps. To avoid injury, it needs to be passed through a metal or plastic conduit during tunneling and preferably controlled with a tourniquet. To decrease the risk of pseudoaneurysm formation during suturing, both the vein and the Dacron mesh need to be incorporated into the suture line. Finally, infusion of low-molecular-weight dextran has been recommended in the early postoperative period by the manufacturer to decrease the risk of early thrombosis.

Manufacturing of the umbilical vein graft by Synovis Life Technologies, Inc. (St. Paul, Minnesota) stopped in May 2005 in compliance with new US Food and Drug Administration (FDA) guidelines governing combination tissue–medical devices.[102] To date, a next-generation HUV graft that will fulfill FDA regulations is not yet available, although developers are actively seeking corporate industry support for such a venture (Herbert Dardik, personal communication, April 13, 2016).

Figure 65.1 Human umbilical vein graft. (Courtesy Herbert Dardik.)

The BCA graft (Fig. 65.2) is supplied in a specially designed tube containing a proprietary solution of 1% propylene oxide in 40% aqueous ethyl alcohol. It is naturally compliant, soft, and relatively easy to use. It is presently available in 6-, 7-, and 8-mm diameters and 15- to 50-cm lengths (Artegraft; Artegraft, Inc., New Brunswick, New Jersey). The BMV graft (Fig. 65.3) is shipped in a sterile saline solution and is available in 6-mm diameters and 10- to 40-cm lengths (ProCol Vascular Bioprosthesis, Hancock Jaffe Laboratories, Irvine, California). This graft is compliant and handles much like a saphenous vein.[60] Both xenografts require a series of rinsing steps in the operating room before use.

CLINICAL OUTCOMES

Cryopreserved Saphenous Vein Allografts

Numerous reports on the utility of CSV allografts for infrainguinal revascularization have been published (Table 65.1).[53-55,69,70,81,87,103-161] However, this literature has confounding factors that may affect

Figure 65.2 Bovine carotid artery graft. (Courtesy Artegraft, Inc., North Brunswick, New Jersey.)

Figure 65.3 Bovine mesenteric vein graft. (Courtesy ProCol Vascular Bioprosthesis, Hancock Jaffe Laboratories, Irvine, California.)

TABLE 65.1 Summary of Published Cryopreserved Saphenous Vein Allograft Series Containing More Than 20 Grafts

Series	Number of Grafts	Primary Patency at 1 Year (%)	Secondary Patency at 1 Year (%)	2-Year Limb Salvage (%)
Farber et al.[81]	240	30	NR	71
Martin et al.[108]	115	37	40	66[a]
Randon et al.[55]	108	56	73	70[b]
Chang et al.[104]	81	27	NR	43[b]
Harris et al.[105]	80	36.8	NR	62[b]
Bannazadeh et al.[160]	66	19	42	73[c]
Hartranft et al.[103]	60	53	NR	70[b]
Shah et al.[109]	43	66	NR	NR
Carpenter and Tomaszewski[53]	40	13	NR	42[c]
Walker et al.[110]	39	28	46	67[a]
Buckley et al.[111]	26	87	NR	80
Harris et al.[106]	25	NR	36	74[c]
Leseche et al.[107]	25	NR	52	78

[a]At last follow-up.
[b]At 3 years.
[c]At 12 months.
NR, Not reported.

the interpretation of outcomes. CSV has been distributed by a number of vendors who use similar, but not identical, cryopreservation techniques. There is significant variability pertaining to patients, location of the proximal and distal anastomoses, use of anticoagulation, and use of immunosuppressive agents. The majority of these reports are retrospective, and the two largest studies contain 115[104] and 240[80] grafts. One of the more recently published reports spanned a 15-year period of implantation.[55] Four prospective studies have been published, but they include small numbers of patients.[53,54,81,107]

Graft Patency

Although use of CSV allografts has been reported in a number of settings, these grafts are generally used for the treatment of limb-threatening ischemia.[81,108] The primary patency rate of CSV grafts has been noted to be relatively low in most retrospective series (see Table 65.1).[81,105-111] The largest case series reported a 30% primary patency rate at 1 year,[81] which is similar to the 37% primary patency rate noted in the second largest series.[108] Although Buckley et al.[111] published an impressive 87% primary patency rate in their prospective study of 26 patients, Carpenter and Tomaszewski[53] found a dismal 13% primary patency rate in their prospectively monitored patient cohort. Randon et al.[55] showed slightly better than average patency and limb salvage rates in CSV recipients treated with low-dose cyclosporine, and Chang et al.[104] reported that CSV performed better in patients with rest pain compared to tissue loss when evaluating amputation-free survival, particularly in those who could be anticoagulated with warfarin.

Secondary procedures on failing or failed grafts generally seem to yield little gain. Primary-assisted and secondary patency of CSV grafts were not significantly higher than primary patency in the two largest allograft series.[81,108] Once the graft failed, it was abandoned, and secondary grafting was performed when indicated.[81] Other authors, however, almost doubled their secondary patency rates by adopting an aggressive posture toward allograft thrombectomy and revision.[110,161]

Multiple patient and procedural variables were evaluated for their influence on allograft patency. In the largest published series, multivariate analysis identified that diabetes negatively affected graft patency. Age, gender, hypertension, smoking, renal dysfunction, indication for surgery, history of bypass grafting, and site of distal anastomosis did not have an effect.[81] A recent series likewise noted a negative effect of diabetes on graft patency,[160] although others found no significant effect.[108,110] Two separate investigations found that secondary and composite allograft reconstructions adversely affected graft patency.[109,161] Lastly, in a recent study, statin use was noted to improve graft patency.[55]

Role of Anticoagulation and Immunosuppression

A number of studies have evaluated the effect of anticoagulation on allograft patency. Aspirin and warfarin, alone or in combination, did not improve graft patency in most series.[53,81,106,108,109] Although Chang et al.[104] identified a benefit to anticoagulation with warfarin in terms of limb salvage, this benefit was most pronounced in patients with rest pain and not tissue loss. Buckley et al.[111], however, reported an impressive 87% primary patency rate in their prospective cohort of 26 patients who were treated with an intensive anticoagulation protocol consisting of preoperative aspirin, perioperative low-dose heparin and dextran, and postoperative warfarin, aspirin, and dipyridamole. Of note, 42% of grafts in that series underwent distal anastomotic modification with either vein cuffs or AVFs. A limitation of most retrospective studies is that the precise level of therapeutic anticoagulation was not rigorously followed for each individual patient. The true effect of an anticoagulation protocol on allograft patency awaits a prospective randomized study that will closely monitor the adequacy of postoperative oral warfarin therapy.

Immunosuppressive regimens have been evaluated clinically. In a prospective randomized trial of 40 grafts in patients treated with low-dose azathioprine, Carpenter and Tomaszewski[53] failed to show a significant improvement in graft patency at 1 year. In contrast, Randon et al.[55] declared their low-dose cyclosporine immunosuppressive regimen to be effective at reducing the risk of graft rejection and thrombosis, and reported minimal side effects. Although immunosuppressive protocols may be effective, potentially serious side effects of therapy may not justify routine use in this patient population.[54]

Limb Salvage

Despite discouraging graft patency, use of CSV allografts has been associated with acceptable limb salvage rates (see

Table 65.1). In the largest published series, a 71% 2-year limb salvage rate was achieved,[81] whereas Randon et al.[55] reported a 5-year limb salvage rate of 64%. The discrepancy between graft patency and limb salvage can be explained, in part, by secondary bypass procedures performed after primary graft failure. Others have reported that repetitive bypass grafting significantly extends limb salvage.[112] Another possibility is that the saphenous allografts remained patent long enough to enable healing of lower extremity ulceration in a large proportion of patients. The ulcers may not have recurred despite graft failure.[81,107,108] Unfortunately, this hypothesis can be proven only in a trial in which ulcer healing is prospectively monitored, along with limb salvage.

Of the various clinical factors that could potentially influence limb salvage, multivariate analysis found the site of distal anastomosis to be significant.[81] Patients who underwent allograft bypass to the popliteal artery had better limb salvage than did those who underwent tibial bypass. Martin et al.[108] found patient age to be inversely related to limb salvage.

Aneurysmal Degeneration

CSV allografts that remain open for a prolonged period are prone to aneurysmal degeneration,[4,81,108] which is probably related to the immune response by the recipient against the graft. The true incidence of allograft aneurysm formation cannot be accurately determined because the majority of these grafts occlude long before a clinically detectable aneurysm can develop. In one series, aneurysmal degeneration developed in nine grafts, for a 2-year aneurysm incidence of 44%.[81] Martin et al.[108] reported a 25% aneurysm formation rate at 2.5 years. The development of aneurysms in allografts necessitates close surveillance of those few patients whose graft remains open for a prolonged period. Because allograft aneurysm rupture has been reported,[54,81] preemptive graft revision is recommended.

Summary and Indications for Use

Although CSV allografts look, feel, and handle like an autogenous vein, they are far from being the "Holy Grail" of conduits for infrainguinal reconstruction. Their poor patency rates are worsened by several risk factors, including diabetes, previous bypass, and composite reconstruction. Postoperative anticoagulation has not significantly improved graft patency,[81] although some authors believe that an intensive peri- and postoperative anticoagulation regimen has merit.[111] Given the immunologic mechanism of graft failure, it is unlikely that anticoagulation alone is sufficient to prevent graft occlusion. Grafts that stay open for extended periods, perhaps as a result of chance matching of important immunologic loci, are prone to aneurysmal degeneration. Finally, CSV allografts are expensive, costing approximately $9000 to $11,000 (in 2016 dollars) depending on the length of the graft.

Given published clinical data, many authors conclude that the use of CSV allografts should be limited.[54,81,105,107,108] Nevertheless, these grafts clearly have a place in the armamentarium of the modern vascular surgeon. Because they have been reported to be relatively resistant to graft infection,[99] they have an advantage when revascularization needs to be performed in an infected field. They also have an advantage when distal bypass needs to be extended onto the foot because closure of the wound is considerably easier than if a prosthetic graft is used. Finally, CSV allografts typically remain patent long enough to allow healing of an ischemic ulcer or minor amputation. The final piece of evidence supporting the continued role of this graft is persistent demand for the product by the vascular surgery community, as evidenced by the number of grafts that continue to be sold.

Cryopreserved Femoral Vein Allografts

Femoral vein allografts have been used for hemodialysis access in the setting of prosthetic AV graft infection, multiple graft failures, or compromised venous outflow sites. In one series of 48 allografts, 1-year primary and secondary patency rates of 49% and 75%, respectively, were achieved. No allograft infection or aneurysmal degeneration was noted.[89] In another series of 45 allografts, a cumulative 1-year patency rate of 68% was reported. Although no infection was noted during follow-up, two pseudoaneurysms required repair.[114] Madden et al.[115] compared the outcomes of 90 femoral allografts with 100 concurrent PTFE AV grafts and noted similar patency rates. No infections were seen in the allograft group, whereas 10% of the PTFE AV grafts became infected. In 18% of the allografts, however, aneurysmal degeneration developed.[115] In a prospective, randomized trial between CFV and PTFE grafts (suspended by the FDA after enrollment of 27 patients into each group), need for fistulography and aneurysmal degeneration was higher in the CFV cohort.[162] Others found that the use of CFV for AV access was associated with a 55% rate of infection, which was particularly common in thigh grafts. Allograft rupture occurred in 46% of infected grafts.[116]

CFV allografts do not have a primary role in hemodialysis access. They may have a secondary role in the setting of infected prosthetic access in a patient with limited reconstructive options. Because of allosensitization, they should not be used in patients who are candidates for future kidney transplantation,[56] although de-cellularized femoral vein allografts appear be safer in that regard.[57] Symptomatic pseudoaneurysms may develop in these allografts and should elicit a low threshold for repair. Finally, CFV placement in the thigh should be avoided.

Cryopreserved Arterial Allografts

Although most experience with arterial allografts has been gained with aortic replacement in the setting of prosthetic graft infection, CFAs have been used for infrainguinal revascularization. Cryopreserved femoropopliteal arterial allografts used for infrageniculate revascularization had a primary patency rate of 51% at 17 months of follow-up in one series of 17 bypasses[42] and 61% at 1 year of follow-up in a more recent series of 35 bypasses.[163] Because of short conduit length, a composite bypass was necessary in 53% of cases. Another series of 35 allografts reported a 39% primary patency and 59% secondary patency rate at 18 months of follow-up, and two grafts required replacement as a result of aneurysmal degeneration.[117] A 5-year primary patency rate of 16% was achieved in a retrospective multicenter

trial of 165 fresh and cryopreserved arterial allografts.[118] A more recent study compared 39 peripheral reconstructions using CFAs with 35 non-CFA bypasses including extraanatomically tunneled prosthetic grafts, autogenous veins, and endarterectomized superficial femoral artery grafts performed in the setting of infection. Total graft-related morbidity was 18% in the CFA group and 57% in the non-CFA group.[163] In this study, mortality at 18 months of follow-up was high in both groups: 31% in the CFA group and 43% in the non-CFA group.[163] These results suggest that in lower extremity bypass, cryopreserved arterial allografts have low patency rates, are predisposed to aneurysmal degeneration, do not offer any significant advantage over the use of saphenous vein allografts, and have the additional potential drawback of the need to connect two or more arterial segments together to create a conduit of sufficient length.

Arterial allografts have been used extensively for the management of primary and prosthetic aortic infection. To this end, fresh aortic allografts stored for less than 1 month at 4°C have been used with some success.[94,119,120] An Italian study of 44 patients treated with 13 fresh and 31 cryopreserved aortic allografts did not find a difference in patient outcomes.[119] A French study of 179 patients treated with 111 fresh and 68 cryopreserved grafts, however, did note long-term differences in graft behavior: fresh allografts were associated with allograft rupture and an increased incidence of late graft-related complications.[94]

There are eight published studies using more than 40 grafts that provide information about the outcomes of cryopreserved aortic allografts for the treatment of aortic infection (Table 65.2). Most of these represent multi-institutional registries with relatively short follow-up periods.[97,121,122,164] Although many patients had polymicrobial aortic infections, staphylococcal species were the most common organisms cultured.[97,101,119,122-124] As expected, perioperative mortality rates were high and ranged between 5% and 36%. Factors associated with increased mortality included emergent or urgent surgery and the presence of an aortoenteric fistula.[101,122] Aortic allograft repair in patients with aortoenteric fistulae was associated with prohibitive long-term mortality rates of 80% in one recent series[165] and 83% in an older series.[122]

As expected, these patients had very high perioperative complication rates ranging between 18% and 55%. Allograft rupture was seen in the immediate postoperative period and up to 4 years of follow-up,[101] and this devastating complication occurred in 2% to 14% of cases and was associated with high mortality. Allograft aneurysmal dilatation also was noted to occur in as many as 8% of patients in one series.[122] Graft stenosis and thrombosis were more often associated with grafts extending to the iliac or femoral arteries.[94] Amputation rates ranged between 1% and 14%. Despite these sobering statistics, 87% and 60% of patients were free of aortic and iliofemoral complications or interventions, respectively, at 7 years in one large single-institution series.[94] Furthermore, the largest study of cryopreserved aortoiliac allografts indicates that this modality allows aortic reconstruction in the setting of infection or those at high risk of infection, with lower early and long-term morbidity and mortality than previously reported.[164]

Aortic infection is one of the gravest conditions in peripheral vascular surgery. Therefore, allograft performance needs to be viewed against the results of other treatment options for the management of infected aortic grafts. Graft excision with extraanatomic bypass was associated with a 30-day mortality of 13% and an amputation rate of 10%.[91] Similarly, in-situ aortic graft replacement with a rifampicin-bonded prosthetic graft had a perioperative mortality rate of 18%.[92] Although cryopreserved aortic allografts clearly have a place in the

TABLE 65.2 Summary of Published Cryopreserved Aortic Allograft Series Containing More Than 40 Grafts

Series	Total Number of Grafts	Number of Aortic Grafts	Follow-up (Months)	30-Day Mortality (%)	Number with Perioperative Major Complications (%)	Number of Allograft Ruptures (%)	Amputation Rate (%)	Number of Graft Thromboses (%)	Graft Dilatation (%)
Harlander-Locke et al.[164]	220	220	30[a]	20 (9)	53 (24)	8 (4)	NR	9 (4)	6 (3)
Bisdas et al.[124]	110	57	36[b]	5 (9)	10 (18)	0	NR	1 (2)	1 (2)
Verhelst et al.[122]	90	66	36[a]	16 (17)	40 (44)	12 (13)	1 (1)	8 (9)	7 (8)
Kieffer et al.[94]	68	68	34[a]	9 (13)[c]	31 (45)	1 (2)	0	2 (3)	NR
Noel et al.[121]	56	56	5.3[a]	7 (13)	28 (55)	8 (14)	3 (5)	5 (9)	1 (2)
McCready et al.[165]	51	43	46[a]	11 (26)	11 (26)	0	NR	NR	NR
Vogt et al.[101]	49	49	27[a]	3 (6)	10 (20)	5 (10)	NR	NR	NR
Zhou et al.[97]	42	42	12.5[a]	7 (17)	21 (50)	0	6 (14)	1 (6)	0

[a]Mean follow-up.
[b]Median follow-up.
[c]In-hospital mortality.
NR, Not reported.

management of prosthetic aortic graft infection, their precise role has yet to be clearly defined. They are associated with allograft dilatation and rupture, probably because of the previously discussed immunologic mechanisms.[19,23,29,42,43] Graft surveillance protocols have yet to be standardized and validated. Although the use of current immunosuppressive regimens in these very ill patients is not practical, the development of more focused immunosuppressive therapy in the future may better define the role of aortic allografts in the armamentarium of vascular surgeons.

Human Umbilical Vein Grafts

Patency and Limb Salvage

The first large clinical experience with the use of HUV grafts was reported in 1988 by Dardik and Dardik,[82] which had 907 lower limb bypass procedures performed in 799 limbs of 715 patients. The 5-year primary-assisted patency rates were 57% and 32% for femoropopliteal and femorotibial bypasses, respectively. The 5-year limb salvage rate ranged between 70% and 80%. Fifty-seven percent of the grafts exhibited aneurysmal dilatation at a mean follow-up of 5 years. In 1989, ownership and manufacture of the HUV graft changed hands, and in an attempt to address the issue of time-dependent graft degradation, efforts were made to improve the graft manufacturing process. Improved cross-linking with glutaraldehyde and upgraded quality control procedures, including time, temperature, and pressure determinants during manufacture, led to the development of a second-generation graft that was resistant to aneurysmal degeneration.[102] In parallel, Dardik et al.[80] attempted to improve the patency of femorotibial HUV grafts by using adjunctive distal AVFs. These investigators published an updated experience with 283 second-generation HUV grafts in 2002. The 5-year primary patency rates for this graft were 60% and 50% for below-knee popliteal and tibial bypass, respectively; and 5-year limb salvage rates were 80% and 65% for below-knee popliteal and tibial bypass, respectively. No graft aneurysmal degeneration was noted on duplex surveillance of these grafts.[125]

Neufang et al. published three series of patients treated with the HUV graft for popliteal bypass,[126] composite bypass,[127] and composite sequential bypass.[128,166] Two hundred eleven patients treated by HUV femoropopliteal bypass had 5-year primary and secondary patency rates of 54% and 76%, respectively, but reported complications included early graft thrombosis in 17% and aneurysmal degeneration in 7%. This group did not use adjunctive distal AVFs, but they did recommend an aggressive anticoagulation protocol with peri- and postoperative aspirin and clopidogrel, early postoperative heparin, and long-term warfarin to keep the international normalized ratio at 2.5.[126]

Fifty-four patients with critical limb ischemia treated by a HUV–autologous vein composite bypass to tibial targets had 4-year primary patency, secondary patency, and limb salvage rates of 53%, 67%, and 88%, respectively. Patients who did not undergo anticoagulation had a significantly higher incidence of early graft thrombosis.[127] HUV–autologous vein composite sequential femoral-tibial bypasses demonstrated lower long-term patency rates.[128,166] Patency and limb salvage results in the most recent (and largest) studies using HUV grafts are listed in Table 65.3.[82,125,126,129-132]

Comparison of Human Umbilical Vein With Other Grafts

A number of studies compared the utility of HUV grafts with other conduits for infrainguinal revascularization. Cranley and Hafner[133] reported a 3-year cumulative patency rate of 74% for umbilical vein grafts, 41% for PTFE grafts, and 76% for saphenous vein grafts when used for bypass to the popliteal artery in the setting of critical limb ischemia. HUV patency was comparable to PTFE graft patency when tibial targets were evaluated (31% vs. 35%, respectively). A small Scandinavian multicenter, prospective randomized trial compared outcomes of HUV grafts with PTFE for below-knee femoropopliteal bypass, and the 4-year primary-assisted patency rate was 42% for umbilical vein grafts versus 22% for PTFE grafts.[134] The New England Society for Vascular Surgery Registry revealed HUV to have improved 5-year patency rates in comparison to

TABLE 65.3 Life-Table Analyses of Patency and Limb Salvage With Human Umbilical Vein Grafts

Series	Year	Number of Grafts Implanted	Aneurysm Formation (%)	Popliteal Bypass Patency (%)	Crural Bypass Patency (%)
Dardik et al.[82]	1988	907	57	57	33
Batt et al.[129]	1990	105	6	—	29[a]
Sommeling et al.[131]	1990	227	37	55/57 (BK/AK)	19
Sato et al.[130]	1995	111	NR	—	61
Johnson et al.[132]	2000	261	1	49	—
Dardik et al.[125]	2002	283	0	56	43
Neufang et al.[126]	2007	211	7	54	—

[a]At 3 years.

AK, Above knee; *BK*, below knee; *NR*, not reported.

PTFE grafts for bypass to the below-knee popliteal artery (45% vs. 20%, respectively).[135]

Another small, prospective randomized trial evaluated the outcomes of first-generation HUV grafts and PTFE grafts in above-knee femoropopliteal bypass. At 6 years, the primary patency rate of HUV was significantly higher than that of PTFE grafts (71.4% vs. 38.7%, respectively). Thirty percent of HUV grafts demonstrated aneurysmal dilatation.[136] The largest randomized trial of HUV grafts was a Veterans Administration–sponsored trial in the United States in which the outcomes of HUV, saphenous vein, and PTFE grafts were evaluated in 752 patients who underwent above-knee femoropopliteal bypass. At 5 years, primary-assisted patency rates were 73%, 53%, and 39% for saphenous, umbilical vein, and PTFE grafts, respectively. Although HUV grafts outperformed PTFE grafts, they were associated with a higher incidence of early graft thrombosis and amputation.[132] This study prompted the manufacturer of this graft to recommend low-molecular-weight dextran in the postoperative period. Some investigators routinely recommend antiplatelet agents, postoperative heparin, and long-term warfarin therapy.[125,126]

Aside from thrombosis, umbilical vein grafts are associated with a number of complications, including infection, stenosis, dissection, and pseudoaneurysm. These complications vary between the first- and second-generation HUV grafts.[125] Although HUV grafts have demonstrated adequate outcomes and improved patency rates compared with PTFE grafts, they have never made it into the mainstream of vascular practice. Many factors, including perceived handling difficulty, complexity of adjunctive distal AVF creation, and industry bias, partially account for this observation. Nevertheless, vascular surgeons must be aware of the HUV graft and its unique complexities and complications given the likelihood of encountering a patient with this type of bypass in clinical practice. Currently, the HUV graft is not commercially available.

Bovine Carotid Artery Xenografts

The BCA xenograft was first used for dialysis access by Chinitz et al.[137] who found that the graft tolerated frequent cannulation and maintained flow sufficient for successful hemodialysis. Patency rates of this graft range from 21% to 86% at 1 year and 45% to 76% at 2 years.[167,141] With the advent of PTFE and its use in hemodialysis access in the mid-1970s, multiple studies comparing BCA xenografts with PTFE grafts have been published (Table 65.4).[55,69,70,87,103,104,138,139,159-168] A prospective, controlled, randomized trial of 140 BCA and PTFE AV grafts found no significant differences in patency and complication rates.[145] Other studies, however, including a recently published small randomized trial, revealed PTFE grafts to have superior patency rates.[138,140,143,168] BCA xenografts are associated with higher infection[138,140] and aneurysmal degeneration[138,143] rates than PTFE AV grafts. A 9% to 20% infection rate[138,140,147] and a 1% to 8% aneurysmal degeneration rate[138,141,143,147] have been observed.

Although BCA xenografts elicit a dense desmoplastic reaction, they are predisposed to aneurysmal degeneration, which is exacerbated by repeated cannulation during hemodialysis. They are prone to infection, and when it occurs, they are very difficult to excise because of intense inflammation and the fragile nature of the graft.[143] Finally, they are more expensive than PTFE grafts. These issues have limited widespread use of this graft for hemodialysis access.[146]

There have been a few published series on the use of different BCA xenografts for infrainguinal revascularization. In one series, 30% of the grafts underwent degeneration within 4 months of insertion.[148] A study of 112 grafts used for femoropopliteal bypass yielded a 1-year primary patency rate of 90%.[149] Another study of 58 grafts used for above-knee femoropopliteal bypass yielded a 56% 5-year primary-assisted patency rate. No graft infections or aneurysmal degeneration was noted.[58] Short available lengths, wide availability of PTFE, and concern about graft degeneration have dampened enthusiasm for the use of BCA xenografts in lower extremity bypass.

TABLE 65.4 Published Reports Comparing the Cumulative Patency of Bovine Carotid Artery and Expanded Polytetrafluoroethylene Grafts

Series	Year	Grafts (n)	CUMULATIVE PATENCY (%) 6 Months	12 Months	24 Months
Kaplan et al.[142]	1976	BCA (16) ePTFE (15)	NR NR	NR NR	NR NR
Butler et al.[141]	1977	BCA (103) ePTFE (184)	94 85	83 75	76 74
Tellis et al.[143]	1979	BCA (71) ePTFE (66)	NR NR	33[a] 62[a]	NR NR
Lilly et al.[144]	1980	BCA (113) ePTFE (83)	NR NR	73 84	NR NR
Anderson et al.[140]	1980	BCA (76) ePTFE (100)	NR NR	70[a] 87[a]	45[a] 73[a]
Sabanayagam et al.[138]	1980	BCA (402) ePTFE (225)	57[a] 94[a]	21[a] 91[a]	NR NR
Hurt et al.[145]	1983	BCA (62) ePTFE (78)	NR NR	84 65	72 63
Anderson et al.[139]	2005	BCA (245) ePTFE (446)	NR NR	86 82	NR NR
Kennealey et al.[168]	2011	BCA (26) ePTFE (27)	NR NR	61[a] 21[a]	41[a] 14[a]

[a]Significant difference between conduits.
BCA, Bovine carotid artery; *ePTFE*, expanded polytetrafluoroethylene; *NR*, not reported.
Adapted from Scott EC, Glickman MH. Conduits for hemodialysis access. *Semin Vasc Surg*. 2007;20(158).

Bovine Mesenteric Vein Xenografts

BMV xenografts have been successfully used for hemodialysis access. In one series of 50 grafts placed in 49 patients who had an average of 3.6 previous AVFs, a primary patency rate of 62% was noted at 30 months. Four infections but no aneurysmal

degeneration developed.[150] In one prospective, multicenter registry, 183 patients with previously failed synthetic grafts were treated with a BMV hemodialysis access. Outcomes were compared with a concomitant nonrandomized group of patients who received PTFE grafts. One-year primary and secondary BMV patency rates were 36% and 66%, respectively. Although primary rates were similar to those of PTFE AV grafts, secondary rates were significantly higher for bovine xenografts. Graft infection was less common in the BMV xenograft group, and the pseudoaneurysm formation rate was similar to that seen with PTFE grafts. However, significant dilatation occurred in six grafts.[60] In another recent series of 62 BMV grafts used for hemodialysis access, 30% primary and 58% secondary patency rates were reported. Thirteen infections occurred, and six (10%) grafts required surgical excision. Significant graft dilatation was noted in two patients.[151]

BMV xenografts appear to have acceptable patency rates that are similar to those seen with PTFE grafts. Although data are limited, these grafts do not appear to be any more predisposed than PTFE grafts to infection or pseudoaneurysm formation. The significance of the dilatation that occurs in some of these grafts is not yet clear. More research will be required before the role of this graft for hemodialysis access is more precisely defined.

BMV xenografts have been used for infrainguinal revascularization. In one small trial involving six patients, all grafts failed within 4 months.[83] In another trial of 32 patients with critical limb ischemia, a 16% primary patency rate was noted at 1 month. Most of the occlusions occurred within 1 day of the operation.[152] Given these results, this conduit cannot be recommended for infrainguinal bypass.

Tissue-Engineered Vascular Grafts

Spurred by repeated failures of commercially available xenografts and allografts, numerous researchers started to focus on tissue engineering as a tool to improve functionality of current biologic grafts. These new graft concepts aim to utilize the patient's own cells grown on a variety of supportive scaffolds. Such grafts hold promise to eliminate immunogenicity and propensity for infection that have plagued many biologic grafts. A number of researchers have experimented with different scaffold systems and have created both in vitro and animal models for such grafts.[55,69,70,87,103,104,153-169] Despite these trends, the optimal tissue-engineered vascular graft has yet to be identified.

Cytograft Tissue Engineering, Inc. (Novato, California) has been actively involved in this line of research and has incorporated their novel sheet-based tissue engineering scaffold into the creation of the Lifeline vascular graft for use in humans.[159] Sheets of living fibroblasts grown from cells extracted from patient biopsy samples (skin and superficial veins) are wrapped around a stainless steel mandrel and allowed to fuse in culture during a 10-week maturation phase.[103] Seven days before surgery, the lumen of the new vessel is seeded with autologous endothelial cells and preconditioned to both flow and pressure; the total production time for these grafts ranges between 6 and 9 months (mean 7.5 months).[104] In the first study of its kind, 10 patients in need of hemodialysis were implanted with their own autologous Lifeline grafts. The primary patency of these grafts was 78% and 60% at 1 and 6 months, respectively.[104] There was one graft aneurysm, one graft dilatation, and one immediate graft thrombosis that required replacement with a PTFE graft. The remaining eligible patients continued to undergo successful dialysis through their grafts, with only one intervention required to maintain patency at short-term follow-up. To circumvent the prolonged time period required to create these unique and personalized grafts, the manufacturer has begun experimenting with an "off-the-shelf" version of their Lifeline graft for hemodialysis and has followed three patients for up to 11 months.[55]

CorMatrix Cardiovascular, Inc. (Roswell, Georgia) has been developing innovative biomaterial devices that restore the native tissues of a patient with no foreign material left behind. Their extracellular matrix material acts as a scaffold into which the patient's own cells migrate and integrate to stimulate natural wound healing mechanisms and form permanent tissue. DuBose et al.[69] conducted a prospective study of CorMatrix for AVF aneurysm repair in 15 patients and were able to avoid prosthetic grafts and hemodialysis catheters; cannulation of repaired segments was allowed after 6 weeks.

Future Directions

Biologic grafts differ from one another in composition and method of preparation. They are useful in a number of clinical scenarios and have earned a place in the armamentarium of modern vascular surgeons. They have not, however, delivered on the expectations that many early vascular surgeons had for these conduits. Despite an enormous amount of basic and clinical investigation they have failed to become the ideal conduit. The search for such a conduit is still progressing.

Significant research is currently being conducted in an attempt to create a biologic nonimmunogenic graft, mainly through improvements using vascular tissue engineering. It is still conceivable that in the future a biologic graft with little or no immunogenicity and characteristics similar to that of a normal artery or vein can be developed, in an acceptable period of time and without prohibitive cost.

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A complete reference list can be found online at www.expertconsult.com.

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66 CHAPTER

Bioengineered Vascular Grafts

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BASIC PRINCIPLES

The use of endovascular techniques to manage vascular disease has become increasingly widespread; however, surgical repair or replacement of diseased blood vessels remains a mainstay of modern vascular surgery. This includes a wide variety of procedures, including aortic reconstruction for aneurysmal disease, bypass of occlusive atherosclerotic lesions, vascular trauma, oncologic vascular reconstruction, and creation of durable arteriovenous access for hemodialysis. All of these procedures require implantation of a vascular conduit to replace diseased vessels or to augment normal anatomy. When available, autogenous blood vessels are generally the conduit of choice.[1] This is limited because individuals have a finite number of available vessels to be used for reconstruction and options may be limited due to concomitant disease of the desired vessels. Wound complications and infection from vessel harvest sites remain a vexing problem. Devitalization of the vessel during surgical excision prematurely injures the conduit and may contribute to poor performance or failure. Even in the best of conditions, autogenous venous tissue eventually remodels in high-resistance arterial or high-flow arteriovenous circuits in a manner that more closely resembles a hyperplastic injury response than the more desirable development of a vessel-like structure with functional adventitial, medial, and intimal layers. Synthetic alternatives provide additional options when autologous conduit is not available, but these grafts pose a clear disadvantage to host tissue in terms of patency, compliance, infection, and durability.

Despite their widespread adoption, none of these options reliably provide the desired long-term functionality and durability inherent to native vascular tissue. Indeed the development of an ideal arterial substitute has been referred to as the "Holy Grail" of vascular surgery.[2] Such a conduit would need to be designed to have a low immunogenic profile and an antithrombotic blood-contacting surface. It would have long-term patency approximating that of autogenous tissue and a resistance to the infectious complications seen with synthetic materials. It would need to combine durability, both for maintaining suture strength and resistance to subsequent mechanical stresses, with a capacity

Abstract

The development of a bioengineered vascular conduit has been a major focus of research within vascular surgery since the inception of the field in the early 20th century. Despite considerable investment of effort and resources the goal of an implantable, non-immunogenic, and mechanically durable vessel remained unfulfilled nearly a century later. In recent years, advances in tissue engineering have led to the development of several promising products that have the potential to revolutionize the field of vascular surgery.

This chapter provides an overview of the historical progress towards developing a bioengineered blood vessel and a detailed description of products in usage now, currently undergoing testing, and potential future directions of this research.

Keywords

Vascular graft
autologous
allogenic
xenogenic
tissue engineered graft
tissue-engineering
arteriovenous graft
arteriovenous access

to remodel into a functional tissue and to respond to physiologic stimuli. Lastly, it would need to be cost effective and ready to use "off the shelf."[3,4] Although the search for this ideal conduit remains ongoing, dramatic advancements have been made, particularly in the past two decades, due to developments in the field of tissue engineering.

In this chapter, we will review a brief history on the field of bioengineered grafts, highlight important advances in the field, provide an update on current clinical activity, and look to the future of bioengineered vascular conduit.

Initial History

The origin of vascular surgery is frequently traced back to the development of the triangulated vascular anastomosis in the early 20th century by Alexis Carrel.[5] Although venous interposition grafts had been used for trauma and aneurysmal disease, it was not until 1948 that saphenous vein was used successfully as a bypass graft for atherosclerotic vascular disease.[6] Shortly thereafter in the 1960s the field of nephrology was revolutionized when Michael Brescia and James Cimino developed the radiocephalic arteriovenous fistula as an alternative to the Scribner shunt.[7,8] Even as this early work defining the role for autogenous materials in vascular surgery was being done, there were pioneering investigations into the use of synthetic materials as vascular conduits. In the 1950s Michael DeBakey, Denton Cooley, and colleagues reported the use of Dacron grafts for aortic reconstruction.[9] By the 1970s polytetrafluoroethylene (PTFE) and expanded PTFE (ePTFE) were being used as replacements for small arteries and as hemodialysis access.[10,11]

In light of this history of autogenous and synthetic vascular conduits, it is somewhat surprising that the first investigations into the use of bioengineered blood vessels were conducted in the 1940s, when Robert Gross and colleagues experimented with aortic transplantation in dogs.[12] This work demonstrated that, although preservation of graft vessels by freezing alone carried unacceptable rates of thrombosis and hemorrhage, biologic modification of donor aortas by storage in a nutrient solution at temperatures slightly above freezing resulted in long-term patency even after several weeks of extracorporeal storage. The successes of those experiments led to the successful translation of these techniques to human tissue. Cadaveric human arteries were successfully treated and used both for aortic reconstruction in pediatric patients with aortic coarctation and as shunt material in patients with tetralogy of Fallot. This type of tissue preservation strategy, although successful, was quite volatile and required significant improvement to produce a therapy that was reliable and readily available.

Intact Isolated Blood Vessels

The earliest examples of bioengineered blood vessels, stemming from the work done by Gross, were intact blood vessels isolated from either animals (xenogeneic grafts) or later from humans (allogeneic grafts).[13] Although the structure of intact isolated blood vessels comes from donor cells, they can be considered bioengineered grafts because they undergo an extensive process to biologically modify the tissue so that it can be implanted without producing an immune-mediated response. A common way to prepare xenogeneic grafts for use is by treating the tissue with a chemical decellularization process and then fixation of the remaining collagen, connective tissue proteins, and cells with glutaraldehyde to reduce antigenicity. This technique fixes or "tans" the tissue, cross-linking proteins to prevent an immunogenic reaction. Unfortunately, variations in xenogeneic graft fixation may lead to the potential for aneurismal degradation, because some have reported a possible mechanism of host degeneration of medial layer if it is not fixed completely.[14] Although the use of isolated intact blood vessels was first reported in the 1960s, there are several grafts currently commercially available.

Artegraft

Rosenberg and colleagues can be credited with the successful translation of enzyme treatment of bovine arteries and then chemically fixing the vessels to preclinical and clinical models. In this early work, bovine arteries were stripped of most of their parenchymal proteins and subjected to "decellularization" by controlled enzyme action, leaving a tubular prosthesis composed mostly of collagen.[15] The first clinical application of this technology was reported in 1966, when a conduit made from collagen matrix of a bovine carotid artery treated with enzymatic removal of the musculoelastic portion of the vessel was used for lower extremity bypass.[13] These processes were refined, and the bovine carotid artery graft technology ultimately was developed by Artegraft (North Brunswick, New Jersey). In 1970 these xenogeneic grafts were FDA approved for use as conduit for dialysis access, and the graft is also currently approved for peripheral arterial bypass and as an arterial patch.

Procol

Decades after the introduction of bovine carotid artery xenografts, Hancock Jaffe Laboratories, Inc. (Irvine, California) developed a method to treat bovine mesenteric veins with a decellularization process, followed by fixation with glutaraldehyde cross-linking and gamma radiation.[16] The muscle content of the bovine mesenteric vein, as well as its relatively high content of elastin, provided a theoretical advantage of improved vessel compliance and thus decreased rate of venous stenosis. This xenograft technology, Procol (now LeMaitre Vascular, Inc., Burlington, Massachusetts) was FDA approved in 2003 for vascular access in patients who have failed at least one prosthetic access graft.

CryoVein

Efforts to develop vascular homografts from either cadavers or living donors extended beyond the work done by Gross in the 1940s. Although the work of Ochsner and colleagues in the 1970s demonstrated the superiority of venous homografts to arterial homografts, due to the dependence of arteries on the *vasa vasorum*, the techniques used for fixation and decellularization of xenogeneic grafts did not translate to allogeneic grafts.[17] Ultimately a combination of cryopreservation and fixation with either glutaraldehyde or dialdehyde improved upon early results

in terms of vein integrity and tissue handling; however, long-term patency remained a significant concern with allogeneic grafts through the remainder of the 20th century.[18,19] Subsequent improvements in cryopreservation and tissue fixation led to the development of the CryoVein graft by CryoLife (Kennesaw, Georgia). This product is currently approved for both hemodialysis access and as a peripheral bypass conduit.

Luminal Modification (Biohybrids)

The endothelium is a dynamic environment, not simply an inert blood-contacting surface. The endothelium and particularly vascular endothelial cells (ECs) play a central role in regulating cardiovascular physiology. ECs regulate vascular tone and thus modulate hemodynamics. In addition to providing an antithrombotic surface for blood flow under normal conditions, ECs control platelet activation and adhesion, as well as the adhesion and migration of both leukocytes and vascular smooth muscle cells (VSMCs) in response to pathologic stimuli.[20] The benefits of an intact and functional endothelium are clear. The clear benefits of an intact and functional endothelium led several investigators to develop "biohybrid" grafts by modifying the luminal surfaces of conduits to recreate the physiologic function of the native endothelium.

The concept of transplanting autogenous ECs into grafts emerged in the late 1970s. This can be done as either a single stage or two-stage method. In one-stage methods, ECs are both harvested and seeded at the time of surgery. In contrast, two-stage methods require seeding of the recipient graft with ECs via serial passaging in a bioreactor and incubation for several weeks prior to implant.[21] Later investigators were able to improve cell retention, as well as cell growth structure and adaption, by exposing the EC-treated conduit in vitro to hydrostatic pressure, laminar shear stresses, and circumferential and longitudinal stretching.[22,23] Indeed, some suggest that shear stresses from prolonged laminar flow (as opposed to turbulent flow) play a crucial role in the signal transduction, gene expression, cell proliferation, and cell survival of both ECs and VSMCs. This is hypothesized to reduce the incidence of both thrombotic complications and the development of atherosclerotic lesions in vivo.[24-26]

Tissue-Engineered Vascular Grafts

Tissue-engineered vascular grafts (TEVGs) are cellular or tissue-based vascular conduits designed to have any synthetic components degrade over time with progressive replacement by autogenous tissues, resulting in a functional blood vessel with an intact endothelium and a capacity to respond appropriately to physiologic stimuli. This technology has been made possible only recently by groundbreaking advances in the field of tissue engineering, although it truly represents the extension of half a century of continuous exploration and improvement.

TEVGs may be classified by the method used to construct the conduit. At present, there are three main categories of TEVGs: grafts created in vivo by "bioreactors," scaffold-based TEVGs, and sheet-based TEVGs.

Grafts Created in vivo ("Bioreactors")

One of the earliest methods used to generate TEVGs leverages the ability of a host's body to generate a foreign body reaction when a cylindrical mandrel or inert tubing is inserted into the body. The result of this is formation of connective tissue around the foreign body, which can be isolated and used as vascular conduit. This process is usually described as using the host's body as a "bioreactor."

The first descriptions of the bioreactor technique come from the late 1960s, when Charles Sparks and colleagues implanted a prosthetic tube into the subcutaneous tissues of subjects. This tube was composed of an inner cylindrical steel mandrel and an outer Dacron graft. After 5 to 12 weeks the tube was explanted and both the mandrel and Dacron layers were removed and the tube of fibrocollagenous materials that formed in the interval was implanted for use as a vascular conduit.[27,28] Although this technique was used in several human patients in the late 1960s and early 1970s, it was not widely adopted, due to poor patency, aneurysmal degeneration, and the prolonged incubation period.[28,29] Several decades later a modification of Sparks' techniques was reported by Julie Campbell and colleagues.[30,31] This entailed placement of Silastic tubing into the peritoneal cavities of rats, rabbits, and dogs. The resulting host response produced a structure with an inner layer of collagen, a middle layer of myofibroblasts, and an outer layer of mesothelium. After removal of the synthetic material, the tube could be turned inside out thus producing a conduit lined entirely with mesothelium. Histologic examination demonstrated that the myofibroblasts in the graft were derived of a bone marrow origin.[32] Although the conduits were relatively successful in animal models, this technique was not successfully translated to humans, largely owing to the need for a prolonged incubation period of several weeks and the requirement for an additional surgical procedure.

To eliminate the need for an incubation period within the intended recipient, Ketharanathan and colleagues experimented with the use of sheep as a bioreactor for grafts to be inserted in humans. Silicone tubes were implanted beneath the subcutaneous layer of adult sheep. Upon explantation 12 weeks later, the tubes were covered with ovine collagen.[33,34] The collagen tubes were then fixed in a glutaraldehyde solution, rinsed in a buffered saline, and then stored in 50% alcohol at room temperature. Early results in dogs were extremely positive, with the ability to comply with arterial pressures and resist degradation for up to 3 years.[35] This initial design was later augmented by the incorporation of a polyester mesh over the tube to improved burst strength and reduce the risk of aneurysmal degeneration.

Eventually Bio Nova (North Melbourne, Australia) used this technology to produce Omniflow, a glutaraldehyde-tanned ovine collagen tube grown around a Dacron mesh template in a sheep bioreactor.[36] These grafts were first approved for use as a hemodialysis access in Australia, Germany, and Canada. An improved version of the original Omniflow device, the Omniflow II (now LeMaitre Vascular, Inc.), was released in 1990.[37] Subsequent studies have demonstrated primary and secondary patency rates approaching that of an arteriovenous fistula, with

reported secondary patency at 2 years of 75%, as well as a lower infection rate than ePTFE.[38]

More recently, Rothuizen and colleagues have rekindled work on creating TEVGs by foreign body response. This group has successfully modulated the histologic composition and architecture of the fibrocellular capsule produced by the foreign body reaction by using templates with different physiochemical properties.[39,40] Following early work using polymer rods in rats, the investigators have more recently used a large animal porcine carotid interposition model. Their early results demonstrate acceptable patency and acceptable mechanical and physiologic characteristics, as well as positive vascular remodeling of the graft post implant.[41]

Scaffold Based

Weinberg and Bell are credited with the creation of the first TEVG prototype. They developed a process using bovine aortic tissue to create the TEVGs that took approximately 4 to 6 weeks. First a rigid scaffold was created in vitro by casting a culture medium of collagen and smooth muscle cells and molding around an annular mold. This mixture was dehydrated over the course of a few days to form a rigid lattice before a Dacron mesh sleeve was slipped over the lattice to improve the TEVG integrity. Adventitial fibroblasts were then cast around the collagen/Dacron structure and allowed to cure for 2 weeks. The tube was then slipped off the mandrel and seeded with ECs over the course of 1 week.[42] The result was a TEVG with three distinct layers of vascular cells with physical and biosynthetic function. Although the inner aspect of the conduit was successfully lined with endothelium, the surrounding synthetic conduit was still subject to many familiar problems, including infection and stenosis. Others attempted to improve upon this initial design by surrounding the inner cell lining with stronger biologic materials; however, none of these solutions were able to combine adequate strength to resist high pressure and degradation with sufficient compliance comparable with native vessels.[43,44]

Biodegradable Scaffolds

Early work on the development and use of bioabsorbable polymers as a scaffold for cell transplantation and tissue engineering can be attributed to Joseph Vacanti and Robert Langer. Their investigation into cell transplantation and experimentation with various polymers as tissue scaffolds had far-reaching effects on hepatic, cartilage, and bone tissue bioengineering.[45-50] By the mid-1990s considerable progress had been made toward the development of tubular structures composed of biodegradable polymer scaffolds.[51,52] The initial foray into the cardiovascular system came when Christopher Breur and Toshiharu Shin'oka developed autologous lamb heart leaflets on a polyglycolic acid (PGA) scaffold.[53,54] PGA is the same polymer that has been used commercially for biodegradable surgical sutures for decades (i.e., Vicryl, Ethicon, Somerville, New Jersey).

As techniques to develop tubular structures improved, this technology was translated to clinical applications. In 2001 Shin'oka and colleagues reported the first successful application of a TEVG produced in vitro with autologous bone marrow cells (BMCs) on a biodegradable scaffold composed of L-lactide and E-caprolactone reinforced with a PGA woven fabric.[55] A pediatric patient with a single ventricle and pulmonary atresia underwent a pulmonary artery reconstruction after the patient's ECs were used to seed the conduit prior to surgical implant. After this initial success, this method was applied to two other successful cases, followed by clinical success in 22 more patients.[56] This approach provides the potential benefit of producing a tissue graft that may continue to grow with a young child, thereby minimizing the need for re-interventions. Ultimately, although this TEVG was acceptable for the low-pressure system, it was not structurally robust enough to be used under systemic arterial pressure. One point of concern was that PGA, a foreign material, may generate an inflammatory reaction that could weaken the integrity of the graft.[57]

Further improvements came as Langer and Laura Niklason focused on improving the integrity of the bioengineered vessels to withstand systemic arterial pressures.[58] A comparison of autologous bovine vessels grown under pulsatile conditions mimicking systemic pressure demonstrated improved vessel integrity and strength relative to vessels grown without exposure to pulsatile flow.[59,60] When examined histologically, vessels exposed to radial strain and pulsatility demonstrated improved SMC deposition, alignment, and orientation, as well as increase extracellular byproducts. VSMCs in these vessels also exhibited contractile reactivity to chemical stimuli. This work yielded the strongest bioengineered vessels created to that point with the support of a biodegradable matrix. Burst strengths were greater than 2000 mm Hg, and suture retention strengths were recorded as high as 90 g; these represented the strongest bioengineered vessels to that point.

Following the validation of the structural integrity and mechanical durability of this conduit, attention turned to the challenge of developing an appropriate decellularization process to eliminate antigenic materials.[61] Although several decellularization processes have previously been outlined, none of these had been successfully applied to bioengineered tissues. Ultimately a protocol described in 1995 was found to adequately treat the conduit without unacceptably compromising the compliance and mechanical properties of the graft.[62] Importantly these experiments led these investigators to hypothesize that bioengineered vessels may not require reseeding of the vessels with host cells prior to implant, owing to the migration of host cells, such as VSMCs, into the conduit extracellular matrix.

These findings were successfully translated into several large animal models including canine, porcine, and Old World primates. In 2011 Dahl et al. (now as Humactye, Inc., Morrisville, North Carolina) reported success in a translational model of TEVGs created from allogeneic dog cells to be used in the canine models and from allogeneic human aortic cells in the Old World primate baboon models, combining decellularized technology and biodegradable scaffolds.[63] This species of primate was chosen to provide a genetic phylum that was the most similar to humans, which could allow non–cross-linked human matrix–containing bioengineered vessels to be implanted without immunosuppression. Canine vessels were reendothelialized with autologous cells prior to implant, but the human vessels were not.

For primate experiments, allogeneic smooth muscle cells from human donors were grown on biodegradable PGA mesh scaffolds, positioned over a Silastic mandrel. The PGA mesh degraded slowly as the vessels grew in vitro over the course of 8 to 12 weeks. A final decellularization process using a series of detergents and hypertonic solution rinses rendered the vessels acellular and free from antigenic material—a human acellular vessel (HAV).[63] As Table 66.1 shows, this model is robust enough for arterial pressure, with burst strength in vitro of between 2651 and 3337 mm Hg while retaining compliance between saphenous vein and internal mammary artery. The Humacyte HAV has been implanted in primates in a model for dialysis access, with 88% patency when measured at various time points between 1 month and 6 months. Fig. 66.1 shows the graft in situ in a nonhuman primate with angiography demonstrating graft patency. Fig. 66.2 shows histology of the graft, with the decellularized allogeneic tube composed of collagen, fibronectin, and vitronectin and containing only minimal residual PGA.

Xenogeneic Tissue Scaffolds

An alternative approach to that taken by Vacanti, Langer, Niklason, and their colleagues is to use xenogeneic tissue as the scaffold for a bioengineered vessel. The benefits of this method are that animal tissue is readily available and their vessels have

TABLE 66.1 Suture Strength, Burst Pressure, and Compliance for Tissue-Engineered Vascular Grafts: Human Internal Mammary Artery and Saphenous Vein Parameters Provided for Comparison

	Suture Strength (g)	Burst Pressure (mm Hg)	% Compliance Per 100 mm Hg
Human Saphenous Vein[88]	196 ± 29	1,599	0.7-1.5
Human Internal Mammary Artery[88]	138 ± 50	3,196	11.5 ± 3.9
ePTFE[97]		28,391	1.6 ± 0.2
Omniflow II[36]	>400	[a]1,688	3.1 ± 1.3
Humacyte TEVG[63]	178 ± 11	3,337	3.3 ± 0.8
Lifeline[88]	152 ± 50	3,523	3.4-8.8 (at 6 months)

Values when available are mean (M) ± standard deviation (SD).
[a]Omniflow II withstood 1688 mm Hg, which is equivalent of human saphenous vein, but additional pressures were not reported.
ePTFE, Expanded polytetrafluoroethylene; *TEVG*, tissue-engineered vascular graft.

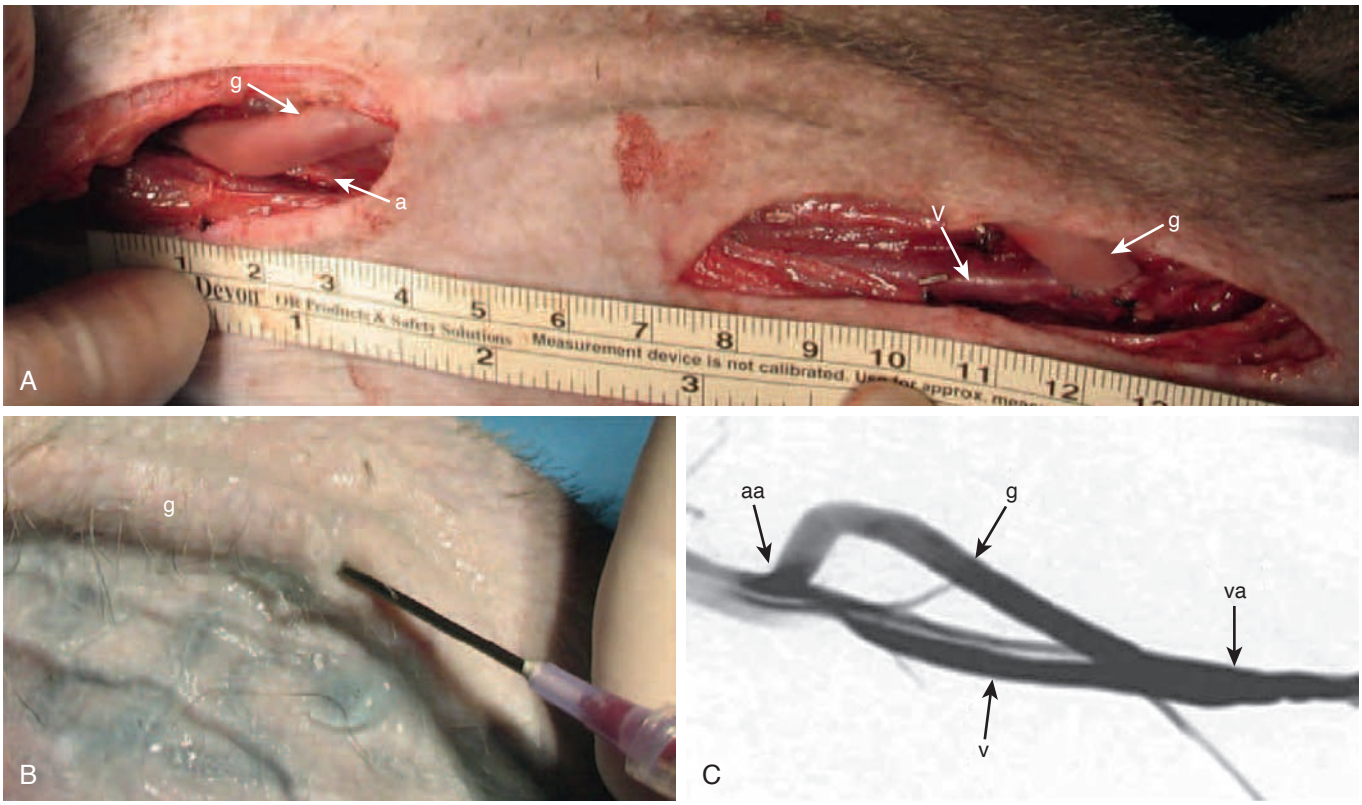

Figure 66.1 Images of Decellularized Allogeneic Graft in Preclinical Trial (Humacyte, Morrisville, NC). (A) Human cell-derived 6-mm grafts *(g)* were implanted between the axillary artery *(a)* and the brachial vein *(v)* in a baboon model. (B) Arteriovenous grafts *(g)* were first accessed with 16-gauge needles at 4 weeks after implant. (C) A representative angiogram of the graft demonstrates that the graft was patent *(g)*. The arterial anastomosis *(aa)*, venous anastomosis *(va)*, and brachial vein *(v)* are shown. (Reproduced with permission from Dahl SL, Kypson AP, Lawson JH, et al. Readily available tissue-engineered vascular grafts. *Sci Transl Med*. 2011;3(68):68ra9.)

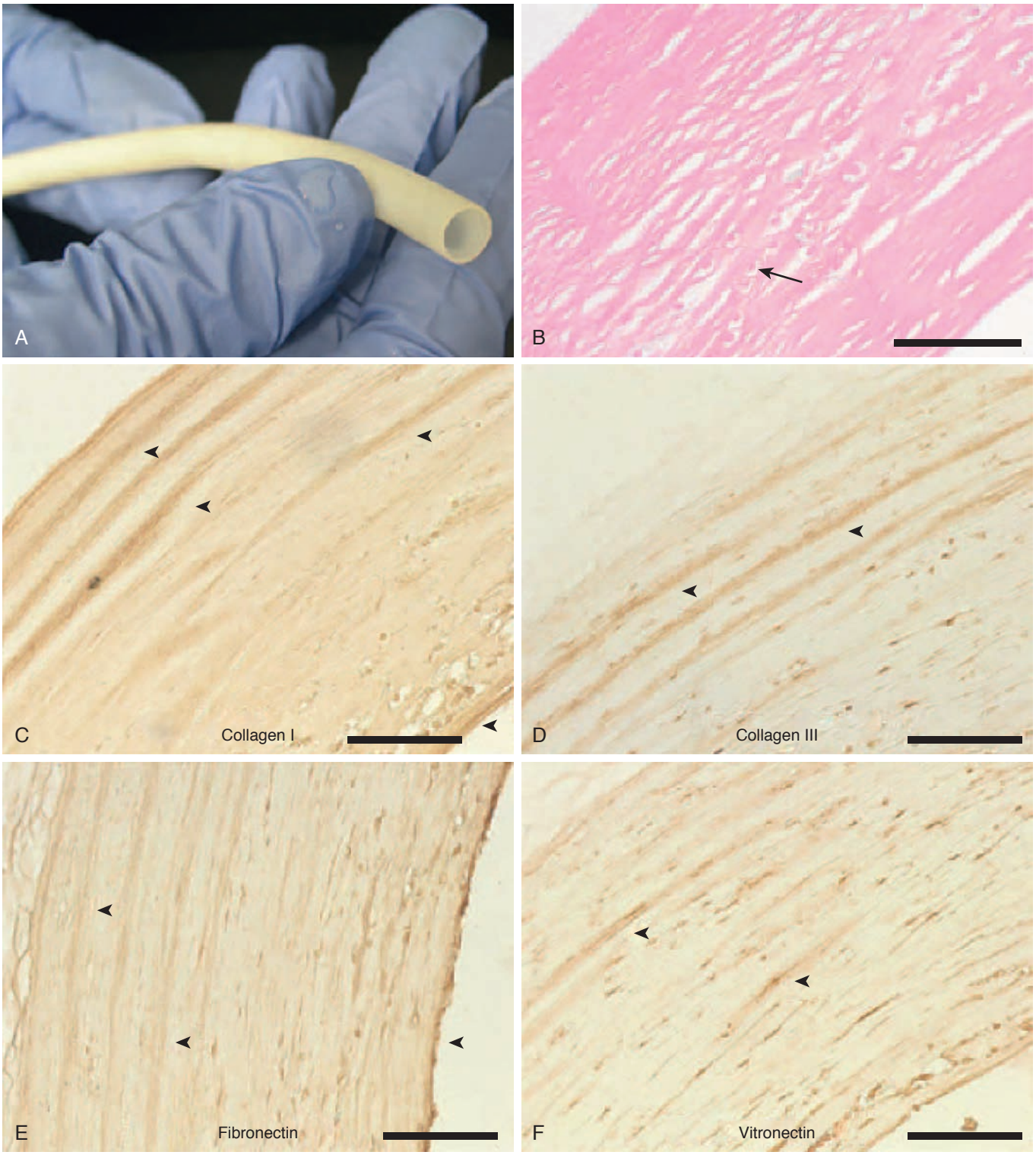

Figure 66.2 **Histologic Analysis of Decellularized Allogeneic Graft Before Implant (Humacyte, Morrisville, NC).** (A) A 6-mm-diameter graft before implant. (B) Representative histology—no cells in H&E-stained sections (*arrow* points to residual polyglycolic acid), and the porous structure typical of decellularized tissue-engineered vascular grafts (TEVGs). (C-F) Decellularized TEVGs stain strongly and diffusely for collagen type I (C) and also stain for organized (D) collagen type III, (E) fibronectin, and (F) vitronectin. Areas staining positive for extracellular matrix proteins are noted with *open arrowheads*. Note that DAB staining masks the porous structure in (C-F). Scale bars, 100 μm. (Reproduced with permission from Dahl SL, Kypson AP, Lawson JH, et al. Readily available tissue-engineered vascular grafts. *Sci Transl Med*. 2011;3(68):68–69.)

a supportive extracellular matrix premanufactured and, with adequate decellularized, their connective tissue matrix could be used as a scaffold for human EC seeding. In 2000 Augustinus Bader and colleagues reported the first such "humanization" of a xenogenic vessel. Porcine aortas were enzymatically decellularized before being seeded sequentially with human ECs and myofibroblasts were isolated from human great saphenous vein. The result was a porcine extracellular matrix, now fully endothelialized with human ECs and a myofibroblast media.[64] This work was expanded upon by Jörg Heine and colleagues, ultimately demonstrating that these "humanized" xenogeneic vessels regained vasomotor contractility and function.[65]

Human Tissue Scaffolds

Analogous to the method generating "humanized" xenogeneic grafts is the work done by Michael Olausson and his group in Sweden. This group performed the first and only procedure using a bioengineered vessel that they created from a decellularized human donor iliac vein.[66] This was done for a pediatric patient with thrombocytopenic purpura with extrahepatic portal vein thrombosis. With no autogenous options for conduit available, and with a family extremely resistant to the immunosuppressive medications required for transplantation, it was decided that a bioengineered vessel would be most suitable. The donor vessel decellularization process was similar to that described, and ECs and VSMCs differentiated and isolated from the recipient BMCs were seeded to the luminal surface of the decellularized human vessel scaffold over the course of 1 week.

Tissue-Engineered Sheets

The last subcategory of TEVGs is sheet-based grafts, which are cells grown in culture to create a sheet of cells that can then be formed into a tubular structure by wrapping the sheet repeatedly around a mandrel. Initial work with this methodology by Nicholas L'Heureux and colleagues was limited by the same difficulties with structural integrity that had previously limited Weinberg and Bell.[67] However, by 1998 this group had created a completely biologic tissue-engineered human blood vessel with sufficient burst strength and suture retention to be used in humans.[68] This relied upon a novel sheet-based manufacturing process. In brief, human umbilical vein ECs and VSMCs were isolated. VSMCs and fibroblasts were cultured in flasks to form sheets of cells and corresponding extracellular matrix. A fibroblast sheet was wrapped around a mandrel and dehydrated. A subsequent sheet-layer of SMCs, followed by fibroblasts, were wrapped around the initial dehydrated scaffold, and finally the luminal surface of the conduit was seeded with ECs. The total duration of this manufacturing process is approximately 4 to 6 months. Overall, if cell expansion time is factored in, this process requires approximately 4 to 6 months to complete.

In preclinical studies, L'Heureux and colleagues were able to demonstrate positive results with placement of human-derived xenografts in rodent, canine, and nonhuman primate models.[69] The group (Cytograft, Novato, California) demonstrated that these bioengineered vessels had structural integrity for human use and entered clinical trials and developed the Lifeline.[70,71] Indeed the tubular structure was capable of burst pressures greater than 3500 mm Hg, greater than that needed to support arterial pressure, with vessel compliance between that of saphenous vein and internal mammary artery (Table 66.2).

Cytograft has subsequently experimented with use of frozen, devitalized autologous vessels which allow autologous tissue biopsies to be taken far in advance of when the need for a vessel is anticipated. The vessel can then be manufactured, a process that takes 6 to 7 months, and stored safely at −80° C until it is needed. The vessel requires just 2 weeks of lead time to thaw and seed the lumen with ECs prior to implant. In the first case report of this device the vessel maintained patency and high flow rates up to the time of publication (8 weeks).[72] An alternative attempt to improve production efficiency has been the use of decellularized allogeneic tissue from healthy donors. Production of these vessels occurs as described previously up to the point of EC seeding, which is deferred. The vessel is dehydrated and frozen to −80° C until needed. Results from a case series of three patients, demonstrated acceptable results without any rise in either immunologic or inflammatory blood markers following implantation.[70]

CLINICAL EXPERIENCE

Intact Isolated Blood Vessels

The first significant clinical experience with intact isolated blood vessels came in 1970 after FDA approval of Artegraft. As a hemodialysis vascular access, patency rates have been similar to ePTFE.[73,74] However there have been reports of the medial layer of the bovine artery developing calcifications which have in some cases resulted in structural degradation and aneurysmal degeneration.[75] Although early experience with the bovine mesenteric vein xenograft Procol reported improved patency over ePTFE for dialysis access, with primary patency at 2 years of 70%, these findings did not translate to improved outcomes in infrainguinal reconstruction.[76-78] Indeed despite the positive performance of this product in terms of patency and decreased infection, Procol has not gained widespread clinical adoption.

CryoVein is currently approved for use as a conduit for both hemodialysis access and for peripheral bypass. Patency for CryoVein used as primary conduit for dialysis access was reported to have comparable but decreased patency when compared with ePTFE.[79] Due to the presumed resistance of CryoVein to infection relative to synthetic materials, some report using this as a salvage option for localized prosthetic graft infection.[80,81] Importantly other investigators report no decrease in infectious complications, at least not when these are used as thigh grafts.[82] In addition, despite treatment to remove blood type proteins and reduce immunogenicity, these grafts carry concerns about blood type compatibility and elevating panel-reactive antibodies in patients on the kidney transplant waiting list.

Biohybrids

The first clinical application of the luminal modification process was reported in 1978. Malcolm Herring and colleagues used ECs harvested from superficial veins to seed the luminal surface

TABLE 66.2 Comparison of the Preparation, Patency Rates, Complications, and Availability Between Isolated Vessels and Tissue-Engineered Vascular Tubes

	Preparation	Patency (Primary)	Patency (Secondary)	Complication Rate	Availability
Isolated Vessels					
Artegraft[98,99]	Bovine carotid artery treated with glutaraldehyde	87% (87/100) at 18 months 60.5%—12 months (16/26)	n/a 60.1%—12 months (16/26)	3% (1/26) thrombosis	Off the shelf
Procol[16,77]	Bovine mesenteric vein treated with glutaraldehyde	80%—12 months 70%—24 months (*n* = 25) 35.6% at 12 months (*N* = 183)	65.6% at 12 months 60.3% at 24 months (*N* = 183)	0.77 thromboses/year	Off the shelf
CryoVein (CryoLife)[79]	Cryopreserved human saphenous vein	60%—6 months 30%—12 months (*N* = 93)	82%—12 months 63%—24 months	18% aneurysmal 12% thromboses	Off the shelf
Tissue-Engineered Vascular Tubes					
Omniflow II[36,100,101]	Ovine collagen + polyester mesh grown in sheep, treated with glutaraldehyde	68% (*N* = 110) at 4 years[36] 77% at 1 year, 58% at 2 years, 48% at 3 years, 34% at 4 years (*N* = 47)[101]	78% (*N* = 110) at 4 years[100]	Aneurysm 0.96%, infection 1.92%[101]	Off the shelf
Humacyte[63]	Decellularized allogeneic cells grown on PGA scaffold (dissolved prior to implantation in subhuman primates)	88% (7/8) at 3-6 months	n/a	(1/8)-thrombosis at 3 months	Off the shelf
Lifeline (Cytograft)[71]	Autologous fibroblasts in sheets, seeded with ECs	78% at 1 month (7/9)	60% at 6 months (5/8)	22% (2/9) dilated 11% (1/9) aneurysm	24 weeks
Allogeneic sheet-based (Cytograft)[102]	Decellularized allogeneic cells in sheets	100% at 1-7 months (*N* = 3)	n/a	None reported	Off the shelf

Current technologies available on the market are listed by name; others by best descriptor available based on preparation.
ECs, Endothelial cells; *EPCs*, endothelial progenitor cells; *PGA*, polyglycolic acid; *SMCs*, smooth muscle cells.

of a Dacron graft at the time of a peripheral bypass.[83] Unfortunately, subsequent trials using this technique failed to reproduce the promising outcomes seen in early reports.[84,85] In later decades investigators were able to improve upon this early methodology by extracting ECs from fat, omentum, and other tissues rich in ECs to improve cell density and performance in preclinical models.[20,21,86]

An alternative to seeding vascular grafts with differentiated ECs is to use endothelial progenitor cells.[20] In the 1990s Noishiki and colleagues seeded BMCs harvested from dogs onto ePTFE grafts, which resulted in fully endothelialized grafts with superior patency to nonseeded ePTFE grafts at 6 months.[87] Ultimately, despite these and other advances, investigation into biohybrid grafts has declined in favor of fully TEVGs.

Tissue-Engineered Vascular Grafts

The earliest clinical experiences with totally autologous grafts on biodegradable scaffold were reported in 2001 after Shin'oka performed a reconstruction of the pulmonary artery of a pediatric patient using autologous BMCs seeded onto a PGA-reinforced L-lactide and E-caprolactone.[55] Although this technique was subsequently replicated, the limited mechanical strength of this material prevented use in the adult systemic circulation.[56]

Cytograft—Tissue-Engineered Vascular Grafts for Hemodialysis Vascular Access

In the mid-2000s L'Heureux and McAllister formed the company Cytograft. Between 2004 and 2007 the company conducted their first phase I/II clinical trial using the Lifeline sheet-based TEVG as hemodialysis access conduit in patients with end-stage renal disease.[69,71] This was the first clinical trial using autologous cells to create a patient-specific bioengineered vessel and the first human use of TEVG in the high-pressure systemic arterial circulation. Fig. 66.3 shows a Lifeline TEVG implanted in human subject. Fig. 66.4 shows a histologic cross-section of the graft demonstrating the sheet-like structure of the TEVG.

Even though the Lifeline is composed of human cells, which should have minimal immune reaction, investigators noted an early failure rate of approximately 30% within 90 days. This was ultimately attributed to the use of bovine proteins used during early vessel production, which generated an immune

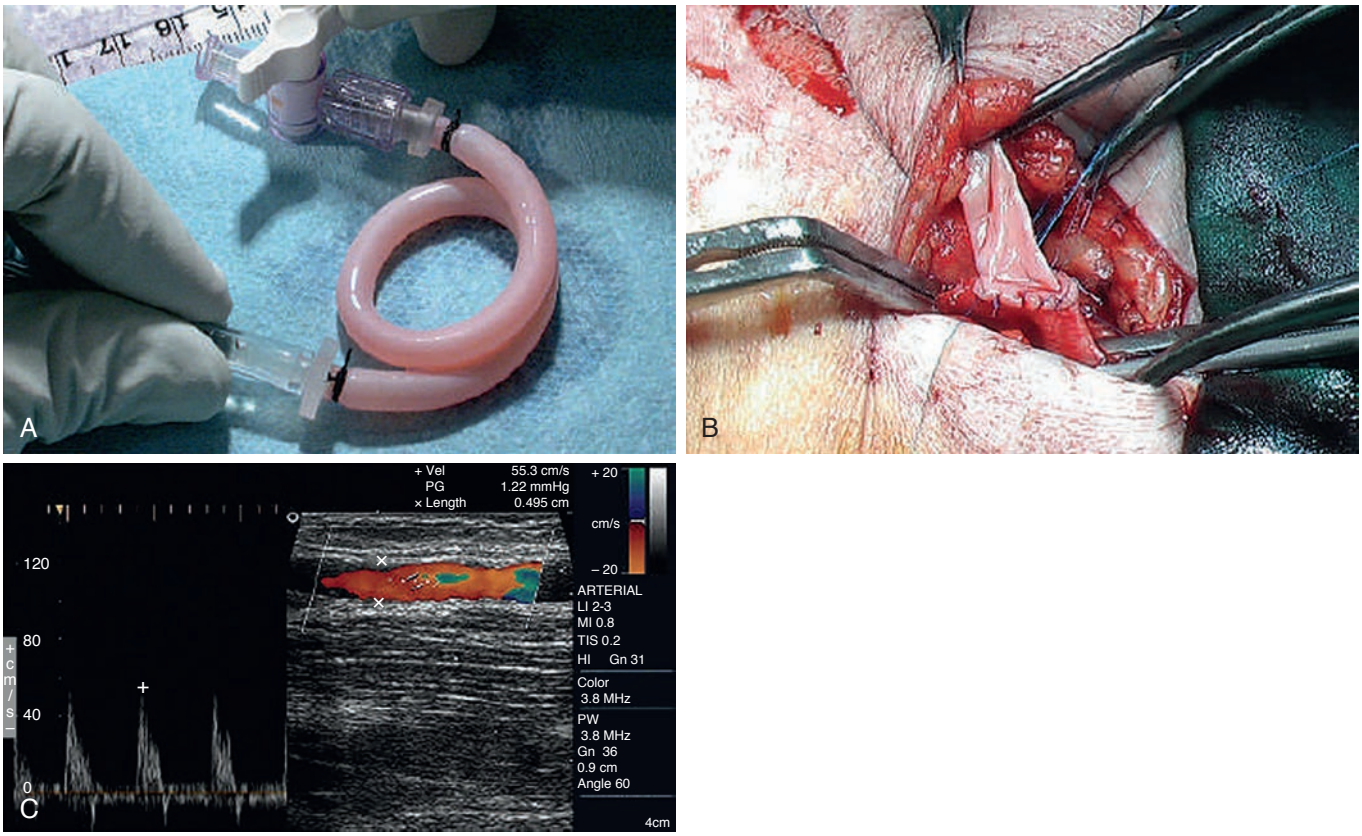

Figure 66.3 Images of a Sheet-based Graft (Lifeline, Cytovein, Novato, CA). (A) An autologous graft was implanted in a human recipient as an arteriovenous shunt between the humeral artery and the axillary vein. (B) The tissue-engineered blood vessel during implantation. (C) On duplex at 6 months the graft maintains high flow without signs of restenosis or aneurysm. (Reproduced with permission from Konig G, McAllister TN, Dusserre N. Mechanical properties of completely autologous human tissue engineered blood vessels compared to human saphenous vein and mammary artery. *Biomaterials*. 2009;30(8):1542–1550.)

reaction that was not seen in subsequent productions. Despite these successful clinical applications, the Lifeline is not available as a truly off-the-shelf conduit because the manufacturing process requires autologous cell culture over 24 weeks. Decellularized allogeneic grafts and devitalized, frozen grafts may expand the use of this vessel; however, further investigation is needed to define the long-term results with these modified devices.[88]

Olausson—Decellularized Human Donor Vessel Scaffold

The 2012 use of a decellularized human iliac vein for bypass of an extrahepatic portal vein thrombosis in a pediatric patient remains the only reported use of a TEVG derived from a fully decellularized intact human blood vessel.[66] The direct application of this technique to further clinical practice is limited both by the availability of suitable donor tissue and by the need for prolonged seeding of the conduit with recipient cells.

Humacyte, Inc.—Tissue-Engineered Vascular Grafts for Hemodialysis Vascular Access and Peripheral Arterial Bypass

Following successful preclinical work in baboons with decellularized, allogeneic human bioengineered vessels, Humacyte entered into its first phase I/II clinical trial in December 2012 using the HAV as a conduit for hemodialysis access. This study was conducted as two single-arm trials in the United States and Poland. The vessel was implanted into the arms of 60 patients with ESRD who were not candidates for AVF creation, and subjects were followed for a period of 24 months. Overall, the acellular vessel was tolerated well by all subjects without evidence for immune response to the HAV, as evidenced by no significant change in a panel of reactive antibodies. The incidence of HAV infection in the phase II AV access studies was extremely low. Only one vessel became infected during more than 82 patient-years of follow-up. Mean follow-up was 16 months, and there were no reports of spontaneous aneurysmal dilation or postcannulation bleeding. At 6 months, 63% of patients had primary patency, 73% had primary assisted patency, and 97% had secondary patency. At 12 months, 28% had primary patency, 38% had primary assisted patency, and 89% had secondary patency. Histology from isolated HAV explants (see Fig. 66.1) during surgical interventions revealed evidence of host VSMC and EC infiltration into the walls of the vessel, essentially rendering the bioengineered vessel a new living tissue in the recipient host.[89]

In May of 2016 the company commenced the first-ever phase III clinical trial for a bioengineered implantable tissue. This clinical trial is a multinational, double armed, randomized

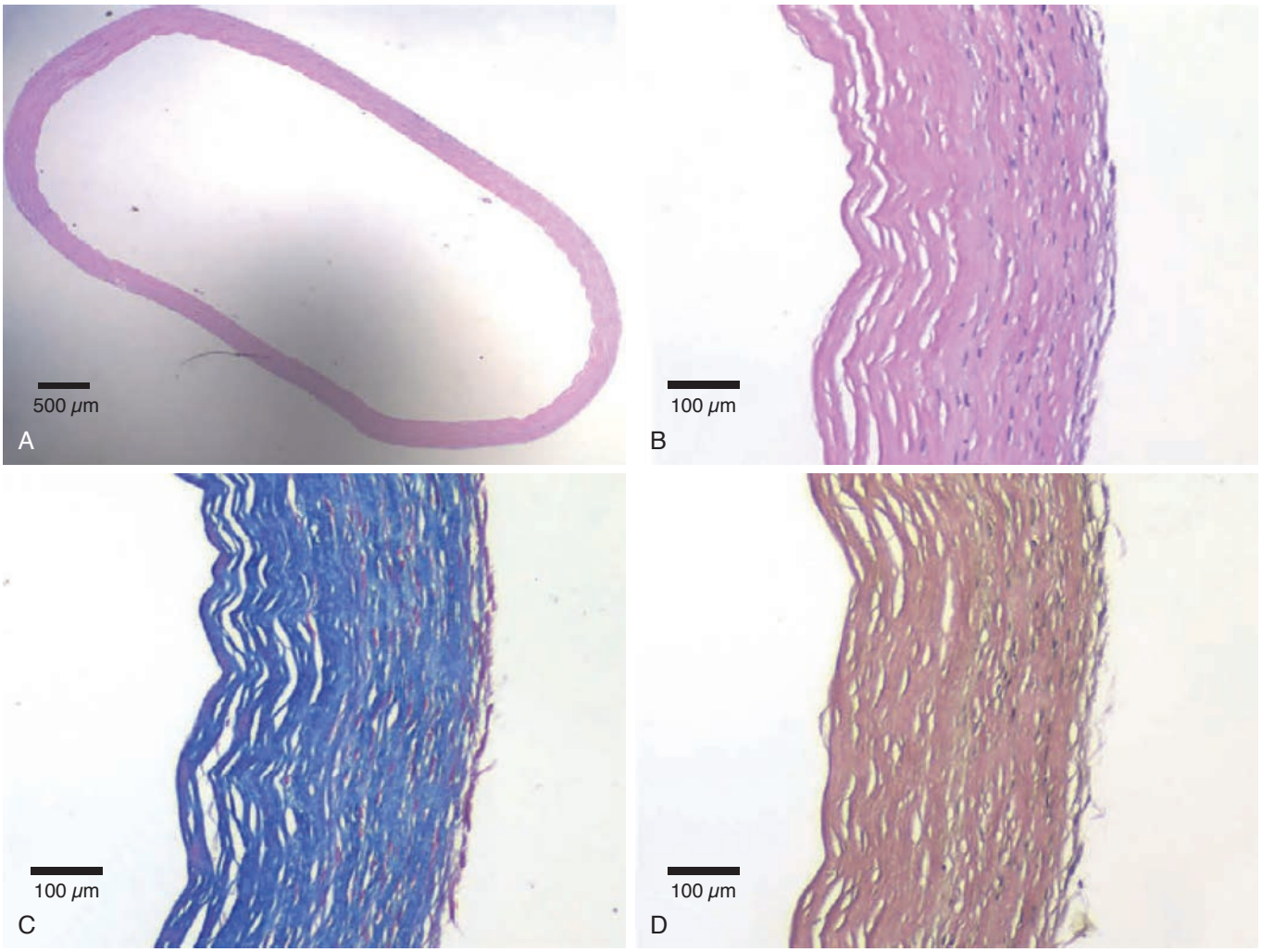

Figure 66.4 Histologic Analysis of a Sheet-based Graft (Lifeline, Cytovein, Novato, CA). (A) H&E stain of the graft at 2× original magnification. (B) H&E stain of the graft at 10× original magnification. (C) Masson trichrome stain at 10× original magnification, which stains collagen *blue*. (D) Verhoeff-van Gieson stain at 10× original magnification, which stains collagen *red* and elastin *black*. (Reproduced with permission from Konig G, McAllister TN, Dusserre N. Mechanical properties of completely autologous human tissue engineered blood vessels compared to human saphenous vein and mammary artery. *Biomaterials*. 2009;30(8):1542–1550.)

clinical trial to compare the HAV with the current standard of ePTFE for patients not suitable for creation of an AVF. The primary endpoint is secondary patency at 2 years, and the goal for total enrollment is 350 patients.

Humacyte has competed a phase II study in Poland using the HAV as a bypass conduit for above-knee superficial femoral artery occlusion, and the company has recently commenced a similar trial in the United States. Both studies are single armed and safety focused, with a goal to enroll a total of 40 patients (20 in the United States, 20 in Poland). Results from these studies have yet to be published.

To date, clinical experience indicates that the HAV remains mechanically strong over implantation periods of more than 45 months, with no evidence of dilation. During more than 150 patient-years of follow-up across the three phase II studies (ESRD and PAD), only one case of infection of the HAV material itself has been reported. The serious adverse event profile has been typical of that expected in the dialysis and PAD populations. Secondary patency of the HAVs is substantially higher than the historical data for both ePTFE and AVF (accounting for nonmaturation). No evidence of immunogenicity of the HAV has been found, and the HAV remains mechanically robust even after repeated puncture for hemodialysis. The HAV in the decellularized form has a shelf life of at least 6 months according to tests, but there is ongoing work to extend that window to 12 to 18 months.

LIMITATIONS AND RISKS

Despite rapid progress in the development of durable bioengineered vascular grafts, each of the products and technologies presented in this chapter have limitations. Use of intact isolated blood vessels continues to raise concern for decreased patency and durability. Biohybrids have fallen out of favor due to the

difficulty of harvesting and seeding ECs, as well as the potential need for a two-stage surgery. Although early clinical experience with fully TEVGs has shown promising results, large-scale clinical trials remain ongoing. Thus both cost effectiveness and long-term outcomes remain incompletely understood.

FUTURE ADVANCES

Three-dimensional (3D) printing is a rapidly evolving technology that holds significant promise for the future of bioengineered blood vessels. This process, in which the repetitive deposition of materials layer by layer is used to generate complex 3D structures, has been adapted to produce biologic and biocompatible materials in a process known as "bioprinting."[90] Using a combination of cells and biologic polymers as "bio-ink" this has already been used to produce in-vitro models of blood vessels lined with ECs, and this may ultimately overcome some of the limits of existing methods for bioengineered vessel production.[91-93]

Another technology that is being investigated for its potential applications for bioengineered blood vessels is electrospinning. This is an established technology in which an electrical field is used to guide the deposition of polymers onto a grounded platform. A source material (which can be chemicals, biopolymers, nanoparticles, or cells) is "sprayed" onto this platform, with an electrical charge guiding the orientation of the resulting structure.[94] This can be used to produce either tubular structures or flat sheets and provides the potential benefit of producing improved scaffolds that more accurately reproduce the triple-layered structure of human blood vessels. In addition, co-spinning of multiple substrates may result in improved strength and compliance of conduits relative to existing methods.[95,96]

The field of bioengineered vascular tissues spans a period of more than 50 years. In this time, we have benefited from the brilliant and diligent works of several teams from around the world. The processes of developing conduit for use as blood vessel replacements have progressed at an astonishing rate. Early work to use autologous conduit gave way to later processes attempting to decellularizing these vessels and ultimately the creation of entirely TEVGs.

Tissue-engineering technologies have now advanced to the degree that the manufacturing of an allogeneic, readily available, biomimicking vascular tube is feasible. There is now evidence to support that strong, nonimmunogenic, human-derived vessels are well received by the recipient host and may even become a living tissue within the patient who requires blood vessel replacement. Cost, scale, manufacturing, biocompatibility, thrombogenicity, and durability remain important questions on the horizon for this innovative technology. Continued careful, safety- and efficacy-focused clinical trials with progression to long-term, randomized clinical studies will be necessary to eventually validate this promising technology in hopes that it may one day provide a benefit to the millions of patients in need.

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CHAPTER 67

Nonaortic Stents and Stent Grafts

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Endovascular therapy has changed the landscape of vascular surgical practice. A major thrust into catheter-based therapy was initiated in 1999 with the US Food and Drug Administration (FDA) approval of endografts for aneurysmorrhaphy. As this important technique became ubiquitous, surgeons began to utilize stents in other vascular beds both for initial therapy and as secondary treatment after failed vascular grafts. Endovascular therapy with stents is now utilized throughout the vascular system, including arteries and veins ranging from the intracranial circulation to the tibial arteries.

As the use of endovascular stents has undergone more critical study, it has become evident that various vascular beds react differently to stent placement.[1-3] Furthermore, angioplasty and stenting alter the biology of the treated vessel, a finding that has implications for both short-term and long-term results. The nature of the lesion, as well as the vascular bed to be treated, dictate specific nuances that guide the surgeon in choosing an appropriate stent.

This chapter focuses on factors that relate to the choice of stents and stent grafts for endovascular intervention in nonaortic vascular beds. The indications for stent use in conjunction with balloon angioplasty as well as the interaction between vessel and stent are reviewed. The multiple factors that influence the optimal stent choice in a given circumstance are considered, including device characteristics relating to the mechanics of stent deployment, cell design, precision, treatment length, deliverability, and adjunctive stent designs that may affect therapy.

HISTORICAL BACKGROUND

Isolated dilation of vessels using dilation catheters was first introduced in 1964 by Dotter et al.[4] This technique was refined in the 1970s by Gruentzig et al,[5] who used smaller catheters with attached balloons that could be delivered through the vascular tree from a remote location. Balloon angioplasty became a popular technique in the 1980s but remained inferior to surgical reconstruction because of the high acute occlusion rate and intermediate restenosis rate. Acute technical failure occurred as a result of elastic recoil, vasospasm, plaque rupture, or dissection. Recurrent stenosis, caused by an intense hyperplastic response, was commonly seen within the first 2 years after intervention. In the initial series of coronary angioplasty, interval restenosis occurred in 30% to 50% of treated lesions.[6-8] Likewise, angiographic failure of isolated angioplasty in the renal, iliac, and femoropopliteal arteries occurred in up to 26%,[9,10] 32%,[1] and 50%,[11,12] of cases, respectively.

Abstract

Implants within the hemodynamic milieu of the vascular system undergo unique stress/strain relationships. The choice of stent composition and stent type—balloon expandable, self expanding, covered, non-covered, etc—have profound affect on long term patency and integrity. The failure modes of endovascular stent placement are related to both mechanical stress and biologic response of the host to the implant. Mitigation of mechanical failure can be achieved through proper selection of stent based upon vessel location, mobility, and external compression. Similarly, several novel strategies seek to limit the neo-initimal response and promote long term success with stenting. This chapter focuses on the construct of various stent types and reviews the mechanical advantage posed by them. In addition, we will review novel therapies to influence long term success.

Keywords

stent
stent-graft
neo-intimal hyperplasia
nitinol
drug-elution
plaque morphology

Stenting was introduced to improve results of angioplasty by ensuring an adequate lumen, maintaining flow, and reducing embolic load. Achieving optimal luminal diameter lessens the impact of in-stent neointimal formation. However, paradoxically, the stent itself has inherent properties that alter the development of normal vascular intimal formation and can lead to maladaptive remodeling through direct intimal damage related to the procedure and the interaction between the arterial wall and the stent itself.

STENT-VESSEL INTERACTION

Vessel Injury

The degree of intimal response to stent placement has been linked directly to the extent of vessel injury. Sullivan et al[13] used an experimental stent with beveled struts to demonstrate this negative remodeling effect in vivo, utilizing a swine model. This experimental stent was designed to violate the internal elastic lamina. In comparison with Palmaz stents deployed in control animals, the experimental stent was associated with significantly greater neointimal formation. Furthermore, the extent of vessel injury demonstrated a linear effect on the absolute neointimal formation.

In addition, an inflammatory response to stent placement has been demonstrated histologically. In an early autopsy series, Farb et al[14] demonstrated inflammatory cell infiltration in the area of the vessel directly adjacent to the stent struts. The absolute number of inflammatory cells present was significantly increased when stent struts violated the internal lamina and penetrated into the lipid core of the plaque. Subsequent analysis demonstrated that inflammatory mediators were present more than 6 months after implantation. Another study showed that, in addition to the effect of the stent itself, bacterial contaminants introduced to the vessel wall during stent delivery also play a role in neointimal formation.[15]

Fluid Dynamics

Endovascular stents also alter the fluid dynamics of the stented segment. The most widely studied impact of stent placement on flow and negative remodeling is the creation of areas of low (<5 dyne/cm^2) wall shear stress (WSS). Alteration in WSS occurs both as a result of a change in luminal diameter of the treated vessel and secondary to the presence of the stent itself. In a computational flow model, LaDisa et al[16,17] demonstrated several characteristics of stent placement that create a low shear stress environment. The factor that led to the most significant increase in the proportion of vessel wall exposed to a low shear environment was overdistention of the stented segment. Although some degree of stent oversizing is necessary for appropriate apposition of the stent to the vessel wall, LaDisa's group demonstrated a 13-fold increase in the total native vessel exposed to low WSS with 20% stent oversizing over that with 10% oversizing. The low WSS can subsequently lead to greater neointimal hyperplasia and recurrent stenosis. This finding is validated clinically because most surgeons aim for a 10% oversizing when stenting infrainguinal occlusive lesions.

Strut Characteristics

The tolerances for stent construction are very strict, and minimal alteration of the strut height can have a significant impact on shear stress and neointimal formation. Intuitively, the area of the vessel wall adjacent to the stent struts has the greatest potential for negative remodeling. Eddy currents created as blood flows over the stent struts lead to regions of low shear. This effect results in a proportional change in shear stress with alterations of strut thickness. The formation of neointima in such areas of low shear stress has been reproduced in several models, and the thickness of the resultant neointima correlates with strut coverage, configuration, and thickness.[18-20] Sprague et al[21] demonstrated that positive remodeling, as measured by endothelial cell migration, is hampered in low WSS environments. In normal shear models, migration of endothelial cells increased 2.5-fold within 1 week after implantation of steel struts onto the endothelial surface. However, in stented models with low shear, this migration was delayed up to several months.[22] The clinical effect of these findings was demonstrated by the angiographic restenosis rates of two nearly identical coronary stents that differed only by stent heights of 50 μm and 140 μm. The stent with the lower-profile design had less restenosis.[23]

Stent Composition

The material composition of the stent also plays a role in neointimal formation. The most common bare metal stent components are stainless steel, nitinol (nickel and titanium alloy), cobalt chromium alloy, and tantalum. Although the actual mechanism of vessel injury from stent components is unclear, corrosive products from alloys have been found within sections of vessel wall. In addition, hypersensitivity of some patients to certain metals has been observed.[24] Palmaz et al.[25] demonstrated that galvanic currents are created within stented arteries and lead to corrosion and subsequent vessel injury.

STENT TYPES AND CHARACTERISTICS

Each stent has intrinsic properties that determine whether or not it is suitable for any given lesion.[25-31] On the basis of the biologic interaction between vessel and stent, an ideal stent would be easy to deliver through a small-caliber sheath, be readily visible on fluoroscopy, conform to the vessel upon deployment, prevent acute procedural failure, provide long-term resistance to negative remodeling, and be fracture-resistant.

Generally, stents are divided into two groups according to their construction and mode of deployment—self-expanding (SE) versus balloon-expandable (BE) (Table 67.1).

Important Characteristics

In a comparison of SE and BE stents, the major characteristics that determine suitability are radial force, flexibility, and precision of deployment. Both SE and BE stents can be covered with polytetrafluoroethylene or polyester, and such stent grafts combine the advantages of a stent with those of a graft.

TABLE 67.1 Comparison of Balloon-Expandable and Self-Expanding Stents Based on Intrinsic Characteristics and Clinical Use

Characteristic	Balloon Expandable	Self-Expanding
Radial force	High	Low
Flexibility	Low	High
Requires delivery sheath	Yes	No
Radiopacity	High	Variable
Oversizing recommended	No	Yes
Treats lesions with variable diameter	No	Yes
Resistant to external compression/bending	No	Yes

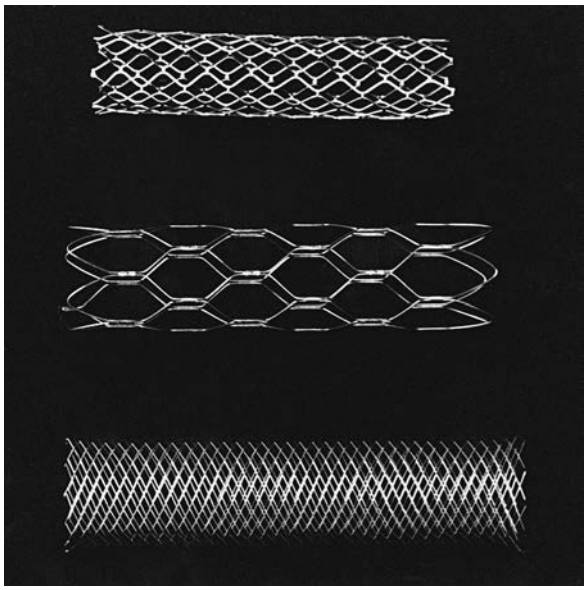

Figure 67.1 Comparison of stents. From top to bottom are the balloon-expandable Palmaz stent, the self-expanding nitinol Symphony stent, and the self-expanding stainless steel Wallstent.

Radial force is defined as the force required to produce a 50% reduction in the luminal diameter of the stent. The radial force of the stent maintains its apposition to the vessel wall and tacks down intimal flaps that may obstruct flow. It also provides the support to resist immediate vessel recoil and acute occlusion. This outward force may lead to a better technical result than that of balloon angioplasty alone. As the stent is incorporated into the vessel, the radial force resists deformation and negative remodeling to maintain luminal diameter over time.

Ultimately, radial force is a product of both stent design and composition. The original Palmaz stent has a stainless steel slotted/diamond design. The slotted configuration allows the stent to maintain a low profile for loading on the balloon. Once expanded, the slots become diamonds, resisting further conformational change and providing a high radial force. The Wallstent (Boston Scientific, Natick, MA, USA) also has a diamond configuration, but is designed to change lengths with its diameter. Therefore, its radial force is related to both its design and the degree of endothelialization within the artery. As the stent becomes more securely anchored, it resists shortening and actually leads to increased radial force. Various BE and SE stents are shown in Fig. 67.1.

Conversely, nitinol stents rely on the inherent nature of their metallic composition to provide resistance to deformation. The nitinol alloy assumes a predetermined configuration at a desired temperature. At low temperatures, the alloy exists in the martensite state (metallurgic property of shape-memory alloys in which the crystalline structure of the alloy is elongated or asymmetric at cooler temperatures), which is flexible and aids both mounting on the catheter shaft and deliverability. At higher temperatures, the alloy adopts a crystalline austenite state (metallurgic property of shape memory alloys in which the crystalline structure is symmetric) which makes the stent rigid, thereby providing more radial force.

Flexibility is determined by the same properties that govern radial force. BE stents require a force to change conformation. Thus these stents are less able to maneuver through tortuous vessels. BE stents are susceptible to deformation in mobile arteries because the torque required to maneuver them may enact a conformational change in the stent. In contrast, the nitinol stent, while in the martensite state, can be easily deformed and, therefore, is more suitable for arterial anatomy, which requires significant maneuverability to reach the target lesion. Interestingly, nitinol may change states not only in the setting of temperature change, but also in response to external compression. Such qualities afford nitinol stents improved flexibility in mobile arteries after implantation. Such is not the case for BE stents (Fig. 67.2).

Radiopacity is a consideration important in stent deployment. The material used in stent construction is a major determinant of radiopacity. Stainless steel is more visible than nitinol; thus BE stents are, generally, more visible on radiographic imaging than SE stents. Improved visibility leading to increased accuracy of deployment must be considered in the choice of the appropriate stent for a given indication (Fig. 67.3).

Cell Size: Open and Closed Cells

Stent cell size should be considered in the selection of the best stent for a given clinical situation. *Cell size* refers to the area outlined by connected metallic components within a stent. Stents with a large cell size are labeled "open cell" stents, and those with a small cell size are termed "closed cell" stents. The cell size of a stent and the connection of the metallic wires to each other may influence performance.

A closed cell stent has consistent interconnection of all stent wires throughout its length. This consistency provides a fixed area of interstices within the stent and uniform coverage of the vessel wall. Such construction decreases the free cell area, and may trap fractured plaque at the time of deployment, limiting distal embolization. However, this configuration makes a stent less flexible and conformable. Considering the previously

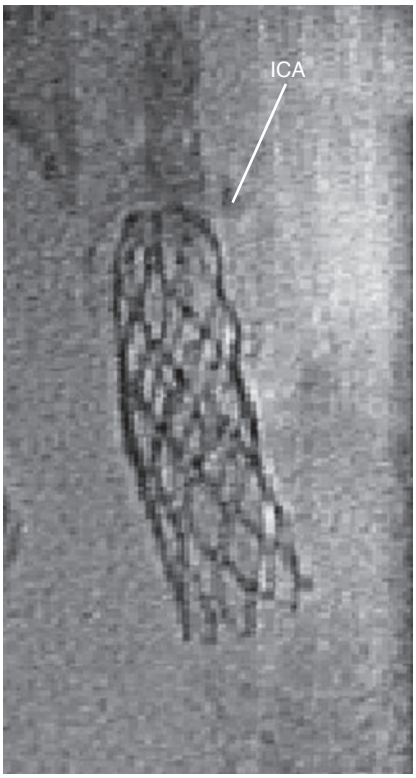

Figure 67.2 This balloon-expandable stent in the cervical portion of the carotid artery is deformed at the distal endpoint where the carotid artery is mobile and susceptible to external compression.

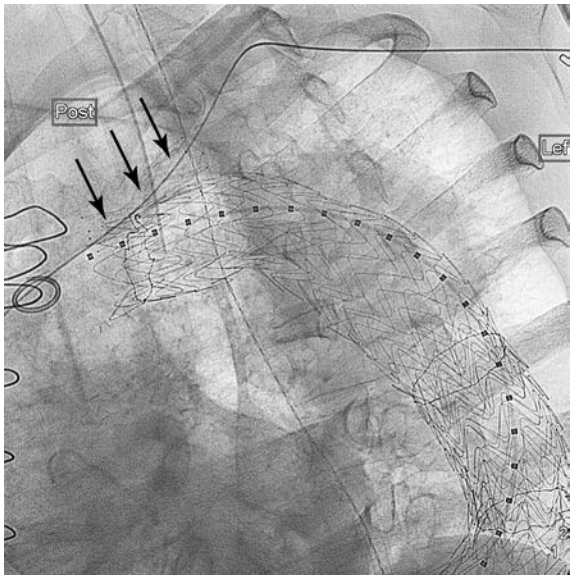

Figure 67.3 A flexible nitinol stent is placed across the subclavian artery origin *(arrow)* to maintain patency when a thoracic endograft has covered the ostium.

mentioned advantage of the SE stent, the closed cell stent may have more difficulty matching the tortuosity and change in luminal diameter across a vessel length.

Conversely, in open cell stents, the wires are not interconnected throughout the entire stent. This feature allows for a greater range of movement between the stent components and leads to added flexibility and conformability. It also results in significantly more vessel wall exposure between stent struts and greater potential for debris to embolize during deployment or balloon dilatation. Free cell area can vary from 1.08 mm^2 in the smallest closed cell stent to 11.48 mm^2 in the largest open cell stent.[26]

The efficacy of cell design to lower embolic phenomena during stenting has yet to be determined. Stent cell size has received the most attention in the treatment of carotid lesions but may also have implications at other sites. Hart et al[32] demonstrated a significant reduction in rates of stroke, transient ischemic attack, and death when closed cell stents were compared with open cell stents in a series of 701 carotid stents. The odds ratio was most significant in treatment of symptomatic lesions. A larger study combining patients from 10 European centers demonstrated no significant difference, even in symptomatic lesions, between the two stent designs.[27] Because closed cell stents are less flexible, a bias may exist to use them in straighter, less complicated lesions. Ultimately, the use of an open or closed cell stent remains the prerogative of the clinician because there is no convincing evidence of the superiority of one over the other. The operator should seek ideal stent characteristics based on both the nature of the lesion and its location.

Balloon-Expandable Stents

BE stents are optimal in clinical scenarios where high radial force and precise deployment are imperative. Unfortunately, the characteristics of BE stents may also limit deliverability to target lesions. Because they are mounted on balloons, BE stents are at risk for dislodgement both during transit to their target and while crossing the lesion. For this reason, it is recommended that a BE stent be delivered through a guiding catheter, or sheath, over a stiff guide wire. The guiding sheath should be advanced beyond the target lesion before the stent is delivered to the deployment site. Once the stent is positioned at the lesion, the sheath is retracted to allow for stent deployment. The BE stent is deployed as the balloon is inflated to nominal pressure. The balloon is designed to inflate at both ends simultaneously, so as to prevent a forward slippage ("watermelon seeding") of the stent off the balloon before complete deployment.

The BE stent achieves a size corresponding to the degree to which the balloon is expanded. Because this stent is deployed by expansion, vigorous oversizing of the stent in relation to the vessel is not recommended. However, one advantage of the BE stent is that it can be further distended to a larger diameter if optimal vessel apposition is not obtained. Of note, aggressive oversizing of the stent with a larger balloon will foreshorten the stent and weaken its struts, leading to increased risk of stent failure.

Innate characteristics of BE stents, including minimal displacement with deployment, make them ideal for treating difficult lesions in which precise placement is paramount. Thus, BE stents are widely used to treat ostial lesions of aortic branch vessels, such as renal, common iliac, and subclavian arteries, where the lesions are anatomically fixed and thus have little potential for stent deformation with movement. In addition, plaque at bifurcations tend to be more calcific and prone to

dissection. In our experience, deployment of "kissing" BE stents in such lesions results in a lower incidence of dissection than balloon angioplasty alone.

The construction of the BE stent also accounts for its major limitations. When the segment being treated transitions across a branch point from a larger into a smaller artery, the high radial force across arteries that have different radii make a BE stent inappropriate; examples of such branch points include the iliac and carotid bifurcations. In these settings, the rigid size constraints of the BE stent may not allow for adequate apposition to the entire treated segment. Furthermore, these transitions are frequently mobile and may lead to stent deformation. Additionally, the higher profile needed to deliver both stent and balloon may necessitate predilation for delivery of the stent to the desired location. In certain situations, such as treatment of renal and carotid stenoses, the consequences of embolization are severe. Predilation should be considered with small balloons to improve subsequent stent deliverability and to prevent embolism or dissection. Embolic protection devices can also be considered in territories at risk of embolic complications. Finally, a BE stent may fracture or retain a new conformation when stressed by outside forces. This risk of deformation affects the decision to use a BE stent across the inguinal ligament or joints. In these positions, the risk of stent compression with fracture and subsequent vessel occlusion is increased. Care must also be taken when one is operating on an artery treated with a BE stent. Clamping of such an artery may lead to a permanent conformational change or stent fracture that may require redilatation or surgical removal of the stent.

Self-Expanding Stents

SE stents are better suited for tortuous lesions or those traversing vessels of variable diameters. These stents are more flexible than BE stents (Fig. 67.4). Therefore, they can be delivered through vessels that create more torque within the catheter. To maintain the stent in its constrained form during transit to the lesion, the stent is covered by an outer sheath on the mounting catheter. When this sheath is withdrawn, the stent is allowed to take its natural shape. As such, SE stents do not require that guiding catheters or sheaths be advanced beyond the target lesion. Actual deployment of an SE stent requires sequential removal of the constraining sheath from the distal end of the catheter to its proximal end. During this maneuver, the stent can either inadvertently jump forward or be retracted by the operator. This potential jumping forward of the stent can lead to maldeployment and must be considered by the operator prior to final deployment maneuvers.

Another factor to consider in the use of an SE stent is the need for adequate oversizing. As mentioned previously, flow dynamic models demonstrate optimal shear environments at a 10% oversizing. Nevertheless, it is essential to choose a stent that opposes the vessel wall on deployment because an SE stent cannot be overdilated. In the instance in which an SE stent is undersized for a given vessel, a second, larger-diameter stent can be deployed within the initial stent to aid with stent fixation. A BE stent is the preferred choice in this circumstance because its increased radial force can overcome the nominal diameter of the SE stent.

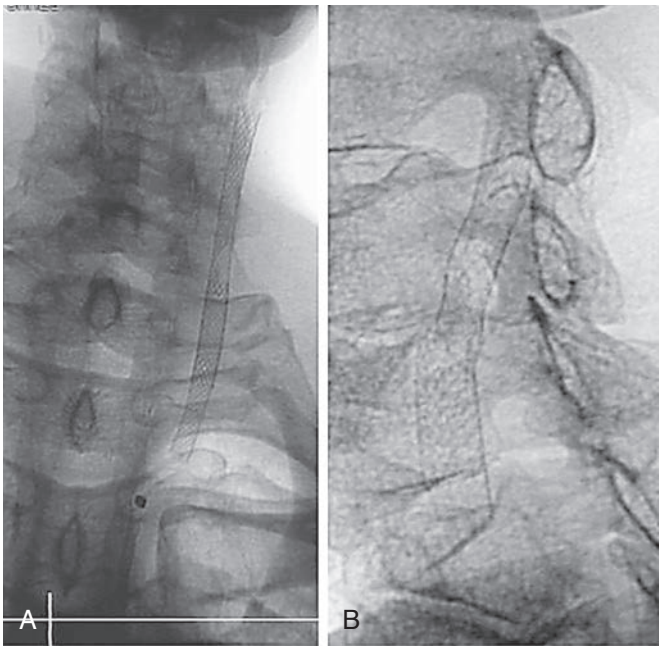

Figure 67.4 Plain radiographs of a stainless steel self-expanding stent **(A)** and a nitinol self-expanding stent **(B)** show the improved visibility of the stainless steel stent.

Because SE stents have less radial force and, conversely, improved elasticity, they are ideal for lesions that cross tortuous vessels, joints, or vessel branches. Common locations where SE stents are used include the carotid bifurcation and the transition zone from the common to the external iliac artery. SE stents are used preferentially in infrainguinal arteries because they can accommodate movement within the limb with less likelihood of fracture and subsequent failure.

Stent Grafts (Covered Stents)

Stent grafts, or covered stents, have expanded the use of endovascular technology beyond their contribution to the treatment of aortic aneurysms. A covered stent may be considered the ultimate closed cell stent, with the inherent applications and limitations of complete coverage of the treatment area. Stent grafts can be organized on the basis of graft material and deployment characteristics. Polyester (e.g., Wallgraft [Boston Scientific]) and polytetrafluoroethylene stent grafts (e.g., VIABAHN [W.L. Gore, Flagstaff, Arizona], iCAST [Atrium USA, Hudson, NH], Jostent [Abbott, Abbot Park, Illinois], Fluency [Bard Peripheral Vascular, Inc., Tempe, Arizona]) are currently available. Some stent grafts are balloon-expandable (e.g., iCAST) whereas others are self-expanding (e.g.,VIABAHN, Jostent, Wallgraft). This stent-graft variety is further complicated by different deployment mechanisms and delivery characteristics that affect clinical utility. Even within the SE category, deployment can be distal to proximal (Jostent, Wallgraft) or proximal to distal (VIABAHN). This variability allows stent grafts to be utilized in a wide variety of lesions.

Stent grafts provide the inherent advantage of continuous exclusion of the vessel wall from luminal flow. Historically, this feature allows complete exclusion of vessel defects, such as aneurysm, arteriovenous fistula (AV), pseudoaneurysm, embologenic plaque, and frank perforation. Several case reports have demonstrated the utility of stent grafts in acute vascular trauma. True aneurysms of peripheral arteries, such as popliteal or visceral artery aneurysms, are also amenable to treatment with covered stents.[33] Stent grafts have been deployed into the subclavian artery to treat aneurysmal degeneration, although special care should be taken to rule out an associated outlet syndrome in those patients who may require further surgical cervical or first rib excision.[30]

Stent grafts can be utilized to "trap" debris within the treated lesion. This approach, in theory, lessens the risk of embolization during inflation. The embolic source can be trapped by inflation of a BE stent graft, or an SE stent graft can be deployed followed by post-deployment molding. Embolization has been shown in both ex vivo and in vivo models of angioplasty in several arterial beds.[31,34,35] Therefore, the use of stent grafts may prove to be an effective treatment of renal, iliac, or subclavian lesions, in which embolization may add significant morbidity. However, the covered stent may have limited use in certain locations because it will exclude any branch points or collateral vessels covered by the stent during placement.

Another potential use for stent grafts is to treat long lesions of the superficial femoral artery (SFA). In this position, the covered stent provides protection from embolization during deployment and theoretically provides a barrier to smooth muscle cell migration and neointimal growth within the treated segment. The SFA often has a large plaque burden that can hasten failure of a bare metal stent due to an aggressive neointimal response and ingrowth by medial smooth muscle cells (Fig. 67.5). In a randomized comparison, Kedora et al[36] demonstrated equivalent rates of patency and limb salvage in a stent graft and a prosthetic bypass for various lesions in the above-knee position, treating various Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) lesions with comparable runoff. However, a rigorous, randomized trial has not compared stent-graft placement with popliteal bypass from femoral to above the knee using a vein conduit. A drawback of stent graft use is the potential of exclusion of important branches or collaterals. When the stent graft is deployed, collaterals may be covered within the treated segment; therefore, subsequent stent thrombosis may lead to worse limb ischemia than in the original limb before treatment.

Figure 67.5 Angiographic image of dense neointimal reaction through the interstices of a stent that was placed in a superficial femoral artery 12 months earlier.

SELECTION OF STENT

After consideration of the various stent characteristics, the selection of an appropriate stent depends on plaque morphology, external forces, anatomic location, and branch locations. Foremost, the stent must treat the primary lesion.

Plaque Morphology

If there is concern about microembolization of debris with stent deployment, a covered stent or closed-cell stent should be used. Procedural and early postprocedural embolization associated with carotid stenting can have important clinical sequelae (Fig. 67.6). Additional data about plaque morphology may help predict which lesions are more likely to embolize through the interstices of the stent. Some researchers have used ultrasound technology to evaluate a gray-scale median to determine the embolization potential of a specific carotid plaque.[37] Magnetic resonance or computed tomographic imaging may also provide morphologic plaque information about lipid content that can help the clinician choose a stent type.[38]

Additionally, if stenting is indicated in the setting of possible fresh thrombus, one should consider selecting a covered stent. Although it may be difficult to differentiate a stenotic plaque from an organized thrombus, clinical or angiographic evidence of distal embolization in the lower extremity should raise concern about a proximal iliac, femoral, or popliteal lesion that is unstable and prone to repeated embolization during manipulation. In addition, an evaluation of the size and filling of collaterals at the level of occlusion may indicate a chronic rather than acute process. If a covered stent cannot be used, one should consider various embolization protection methods, such as filter wires, reversal of flow devices, and open arterial exposure, to flush debris away from the distal vascular bed.

External Forces

After assessment of the luminal surface of the artery and its lesion-specific pathology, the clinician must also consider the potential external forces that may affect the stent in its designated location within the proposed arterial or venous circulation. Extrinsic forces on the origins of supra-aortic trunks are often

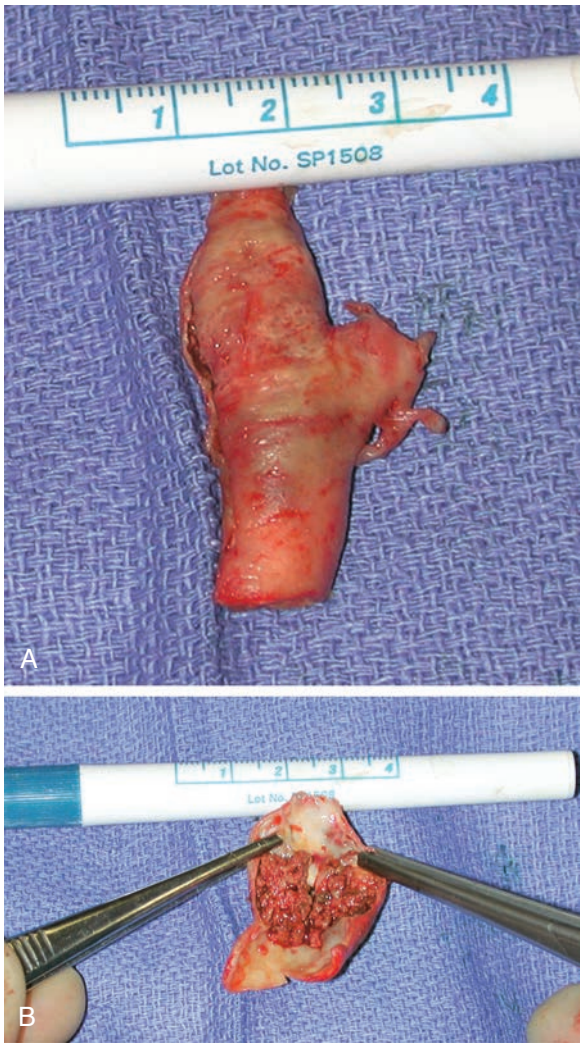

Figure 67.6 **(A** and **B)** Photographs of an endarterectomized carotid plaque that had embolized and caused symptoms. This type of plaque is thought to be a greater risk for periprocedural embolization when an open cell stent is used to cover the stenosis.

minimal, but the extrathoracic carotid or subclavian arteries can be subject to significant compressive forces from the surrounding musculoskeleton. Examples include compression of the subclavian artery by a cervical rib, or an axillary artery altered by a hypertrophic pectoralis muscle or axillary manipulation. A potentially catastrophic example includes compression or possible thrombosis of a carotid stent from aggressive rotation or external pressure on the neck, resulting in decreased cerebral perfusion or stroke (see Fig. 91.2). Because of these concerns, SE stents are often chosen for these more mobile areas given their greater resistance to external forces.

Anatomic Location

The **celiac artery** origin can be compressed by the median arcuate ligament. In our practice, treatment of this defect most often requires open surgical or laparoscopic division of the arcuate ligament followed by endovascular or open reconstruction of the celiac lesion.

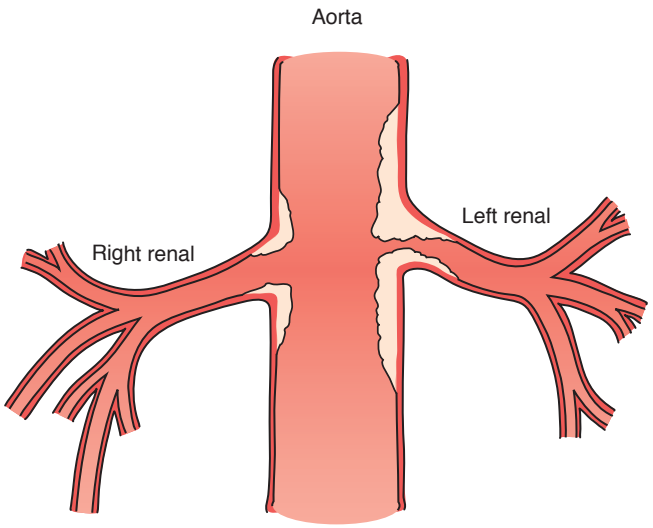

Figure 67.7 The atherosclerotic plaque of a renal artery stenosis actually originates in the aortic wall as the line drawing depicts. This type of plaque is susceptible to elastic recoil with angioplasty alone, and is often better treated with a balloon-expandable stent that protrudes slightly into the aortic lumen to maintain an improved luminal flow.

In atherosclerotic lesions involving the celiac artery, BE stents are commonly used and are associated with good patency. Although access can be gained by either the brachial or femoral approach, the brachial approach is preferred because it allows for easier cannulation of the celiac artery. Careful angiographic evaluation in multiple planes is warranted to ensure exact deployment of the stent short of the main division of the celiac artery.

Superior mesenteric artery and renal ostial stenoses are typically treated with BE stents because disease affecting these ostia is typically associated with extensive atherosclerotic plaque in the aortic wall (Fig. 67.7). An adequate landing zone before the middle colic and inferior pancreaticoduodenal arteries must exist to avoid occlusion of these important branches. A covered BE stent may provide better embolic protection than a bare metal stent. There are some preliminary reports that covered stents may have more resistance to restenosis than bare metal stents in the mesenteric circulation.[39] Covered stents in mesenteric and renal arteries are commonly used as adjuncts in complex endovascular thoracoabdominal aneurysm repair with good patency.

SE stents may be superior for nonorificial lesions, particularly those associated with dissection. A covered SE stent can be ideal in nonatherosclerotic pathologies, such as pseudoaneurysms associated with pancreatitis. More distal lesions of the mesenteric and renal circulations often can be treated with balloon angioplasty alone because of the high flow and small caliber of these vascular beds.

The **left common iliac vein** is another anatomic location where stents are often used to treat compression from the right common iliac artery (May-Thurner syndrome). Although most patients are asymptomatic, edema or deep venous thrombosis (DVT) may result (see Chapter 62). After lytic therapy for DVT, the underlying stenosis/compression may be exposed,

leading to an indication for treatment. Most clinicians recommend utilizing an oversized SE stent in this anatomic location to provide the appropriate radial force and avoid stent migration. BE stents are more likely to cause perforation and are relatively contraindicated in venous disease.

The **distal abdominal aorta and the iliac arteries** are prone to extensive plaque formation that can cause ischemic symptoms. Treating a proximal common iliac stenosis often requires a "kissing stent" technique, in which stents are placed concurrently in both common iliac arteries to prevent the shift of the aortic bifurcation plaque into the contralateral lumen. The two stents are deployed simultaneously, matching their position in the distal aorta and proximal iliac arteries. Although both stent types are used in the proximal iliac arteries, the BE type are more often used for short lesions and the SE type for longer lesions that traverse the change in artery caliber past the iliac bifurcation. Lesions in the external iliac artery are usually treated by SE stents because of the usual tortuosity of the artery. Occasionally, the more distal segment of the external iliac can be better treated with a precisely placed, short BE stent to avoid excessive material load in this smaller artery. Plaque characteristics that suggest a high risk of embolization would favor treatment with a closed cell or covered stent in the iliac arteries. Primary patency of endovascular repair falls short of open revascularization for complex aortoiliac pathology, but secondary patency rates are favorable.[40] Published clinical series are showing promise for the use of covered SE stents in the distal external iliac arteries extending into the common femoral arteries.[41,42] Fewer fractures are noted with these stents in other vascular beds, such as the popliteal. The covered construction theoretically would make a stent fracture less relevant because the graft would prevent the stent from injuring the underlying vessel wall. Stent grafts in this position also can be sewn directly, allowing for a femoral patch angioplasty or interposition graft in the femoral artery, if needed, to obtain adequate outflow.

For the **infrainguinal arteries,** SE stents are utilized preferentially with a few exceptions. Stents in the common femoral arteries are generally contraindicated for two reasons. First, the stent could cover the origin of the profunda femoris artery and compromise flow into this vital artery. Although arteries often remain patent after they have been "jailed" (e.g., hypogastric artery, external carotid artery), the extent of disease in the common femoral artery and the potential consequences of occluding the profunda femoris have a more serious effect on the long-term salvage of the leg. Second, the common femoral artery remains a major access point for vascular procedures throughout the body, and a stent in this position may adversely affect subsequent access through that artery. In addition, the common femoral artery is easily accessible surgically, and repair or endarterectomy of the vessel can be performed with minimal risk.

Stenting of the infrainguinal arteries for occlusive disease is indicated for the failure of primary angioplasty. YaJun et al[43] demonstrated in a meta-analysis that acute results are better with adjunctive stenting, but long-term patency is no different.

Dialysis outflow tracts are prone to treatment failure owing to the unique hemodynamic environment created by AVFs or AV grafts (AVGs). Stent-supported revascularization of the axillo-subclavian veins and cephalic arch have been proven to improve access salvage over that with angioplasty alone.[44] Because central stenosis often occurs in areas of significant mobility, careful evaluation for the contribution of thoracic outlet compression should be made before deployment of a stent. Given these considerations, a large SE stent is recommended. The failure mode in these situations relates to neointimal hyperplasia, so the use of a stent graft is not unreasonable. It is preferred in cases of venous disruption from high-pressure angioplasty. However, no significant data has demonstrated a benefit of covered over uncovered stents in treating central stenoses.

Much like venous anastomotic complications, the hemodynamics of the cephalic arch results in a common failure mode of cephalic vein-based access. Initial experience with bare metal stenting demonstrated a high incidence of recurrence. SE covered stents have been shown to be superior to bare metal stents in the treatment of these lesions.[45] (Care must be taken to avoid encroachment of the stent into the axillary vein.)

The venous anastomosis is the most common failure site of prosthetic arteriovenous grafts.[46] The use of covered stents has been especially promising in treating these lesions. In a randomized trial, Haskal et al[47] demonstrated the superiority of stent grafts over angioplasty alone for the treatment of venous anastomotic stenosis. Covered stents change the hemodynamics of these anastomoses to a functional end-to-end anastomosis, and retard the neointimal hyperplastic response. Stent grafts in dialysis access commonly fail secondary to thrombosis. However, secondary patency of these grafts is promising, and they appear to be an appropriate first-line of therapy in venous anastomotic complications of AV grafts.

Branch Location

Once the external forces that may affect stent choice have been reviewed, the clinician must also consider the extent of the disease relative to branch points of the artery. When a plaque radiographically appears at the origin of a vessel, histologically it will extend into the "parent" artery (Fig. 67.8). For example, an ostial renal artery stenosis may appear isolated to the renal artery on subtraction angiography when, in fact, the majority

Figure 67.8 This endarterectomized specimen shows the extent of the plaque that originates in the aortic wall but affects flow through the branched vessel.

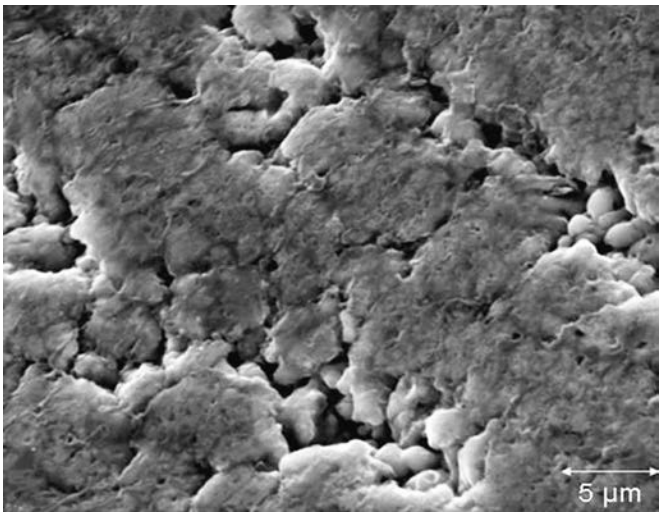

Figure 67.9 Scanning electron microscopy of nitinol stent that had been deployed in an iliac artery. The stent occluded and the patient ultimately required aortobifemoral bypass. (Photo courtesy Dr. Britta Brott.)

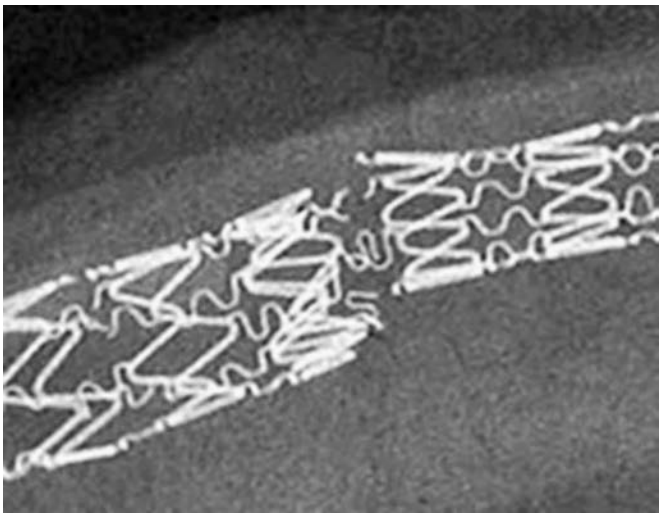

Figure 67.10 Two overlapping coronary stents placed at a tortuous portion in the coronary artery created a stress point that led to stent fracture and recurrent stenosis. (Photo courtesy Dr. Britta Brott.)

of the plaque is in the wall of the aorta (Fig. 67.9). This extensive plaque requires a high radial force stent with accurate deployment, and therefore the BE stent works best in this scenario. The BE stent is typically deployed with a small portion extending into the aorta to fully address the aortic portion of the plaque.

FAILURE MODES

Although stents are designed to maintain patency of the treated vessel, the presence of a foreign material in the arterial bed may actually lead to failure through neointimal hyperplasia and vessel restenosis or thrombosis. Studies have demonstrated that acute inflammatory changes occur with the disruption of the endothelial surface. After the acute phase, the arterial wall continues to react through a remodeling process, which includes acute and chronic changes with a smooth muscle response that can be seen as neointimal hyperplasia.[14] This chronic inflammatory change can actually lead to an obstructing lesion that creates a recurrent stenosis or in situ thrombosis.

Stents are designed of various metallic components that have long, but finite, lifespans under the mechanical stress of the cardiac cycle. Stent fracture or failure may be related to metallic corrosion, which may, in turn, be related to the local vascular environment, external forces, and interaction of other intravascular material.[48-52] Fig. 67.9 shows surface corrosion of an iliac stent that ultimately failed and was removed during the course of an aortobifemoral bypass. The figure shows pitting corrosion that may have contributed to device failure, recurrent stenosis, and eventual iliac artery thrombosis. In a common clinical scenario, when two overlapping stents are placed, the materials of the two stents can be additive in the corrosive process. Fig. 67.10 shows two overlapping stents in the coronary circulation that ultimately fractured, likely as a result of galvanic corrosion between the stents. In this patient, a recurrent stenosis developed at an angulated area of a coronary vein graft.

Long (>200 cm) SE stents are now available. The use of an appropriate-length stent to avoid overlap may lead to fewer fracture-induced occlusions. In addition, overlap within tortuous segments seems to be especially prone to failure.[53] Strategies to decrease occlusion within stented segments include the use of drug-eluting stents in overlapped segments[54] and telescoping of a covered stent inside a bare stent. The graft material theoretically inhibits the corrosive effect of metal-on-metal interaction.

Stents can also release ions into the local vascular environment that can adversely affect the treated lesion. Both stainless steel and nitinol stents have been shown to release cytotoxic agents that may contribute to smooth muscle necrosis, affecting the response of the artery to such a stent.[55,56]

Drug-Eluting Technology for Neointimal Failure

Many modalities have been investigated to control the hyperplastic response to an arterial implant. Specifically, stents have become a conduit to deliver medication to the local vascular environment in an effort to limit this response to injury. Three chemotherapeutic agents have been attached to BE stents for utilization in the coronary arteries: paclitaxel, sirolimus, and everolimus. These agents have been shown to aggressively inhibit the neointimal response and thereby improve patency rates. Paradoxically, drug-eluting stents (DESs) have created a new late-failure mode of delayed stent thrombosis, due to the lack of endothelialization and minimal incorporation into the associated vessel wall. The exposed raw surface of the stent carries a risk of stent thrombosis as high as 4% after 1 year.[57] When evaluating the use of DESs in the peripheral circulation, one must consider that late stent thrombosis of the femoral artery carries a significantly different risk from that of a coronary artery.

Initial clinical trials of DESs in the SFA did not demonstrate better patency than with bare metal stents. The Sirolimus-Coated Cordis Self-Expandable Stent (SIROCCO) trial compared the results of a drug-eluting SE stent and a bare metal SE stent, and found near-equivalent restenosis rates: 22.9% in for the DES and 22.1% for the bare metal SE stent at 2 years.[58] A

prospective industry-sponsored trial of a nonpolymer, paclitaxel-coated SFA stent (Zilver PTX, Cook Medical, Bloomington, Indiana) has shown more promising results. The main arm of the study demonstrated noninferiority of the DES to primary angioplasty, although these data may be unreliable because of an overly high primary failure rate of percutaneous transluminal angioplasty. More interestingly, a separate arm directly compared bare metal stents to DESs in patients with failed percutaneous transluminal angioplasty and showed statistically significant better patency with DESs at 1 year.[59] Enthusiasm for DES-supported intervention in the SFA on the basis of these results is hampered by the large number of short lesions and the high percentage of patients with claudication (90%) enrolled in the trial. Subsequent analysis from 12-month results for patients with *de novo* TASC II C & D lesions treated with Zilver PTX stents showed results similar to those of open surgical bypass (77% primary patency rate), fueling the argument for continued investigation into long-term efficacy.[60]

The PReventing Amputations using Drug eluting StEnts (PaRADISE) trial attempted to quantify the impact of DES technology on patients at greatest risk of amputation.[61] In this noncontrolled prospective study of DESs in tibial intervention, the major amputation rate was 6% at 3 years in patients presenting with critical limb ischemia. Maintenance of limb salvage required a re-intervention rate of 36% at a mean of less than 1 year, but overall survival, renal failure, and limb salvage rates were better than those in historical controls.

Treatment of in-Stent Restenosis

As primary endovascular interventions have become increasingly common for the management of *de novo* femoropopliteal stenoses, strategies for maintaining patency have also become of utmost importance. The long-term interaction between stent and vessel over time can lead to the development of late stenosis or occlusion, chiefly through the mechanism of neointimal hyperplasia. Various mechanisms have been proposed for the management of in-stent stenosis, including repeat PTA, stenting, atherectomy, and angioplasty or stenting with drug-coated technology. The EXCITE ISR Trial (EXClemer Laster Randomized Control Study for Treatment of FemoropopliTEal In-Stent Restenosis) demonstrated superiority of laser atherectomy with PTA compared with PTA alone in patients with in-stent stenosis following the prior placement of bare nitinol stents, for both TLR and 30-day MAEs.[62] The FAIR (Femoral Artery In-Stent Restenosis) Trial examined the effect of drug-coated balloon angioplasty for SFA in-stent restenosis, in comparison with conventional PTA alone. The results of this investigation showed a lower rate of recurrent restenosis at both 6- and 12-month intervals following intervention with a drug-coated balloon (DCB) compared with conventional PTA.[63] Building off known data regarding utility of drug eluting stents for coronary in-stent stenosis, data from the Zilver PTX Global Registry showed favorable results for the treatment of femoropopliteal in-stent restenosis with implantation of the Zilver PTX stent, with 6- and 12-month primary patency rates of 96% and 79%, respectively.[64] The Viabahn-covered stent also demonstrated superiority over PTA at 1- and 2-year primary patency in the RELINE trial.[65] Interestingly, the lesion lengths treated were nearly double in the RELINE trial compared to trials of drug coated technology indicating that stent graft treatment is likely the modality of choice in complex restenotic lesions of the SFA.

NEW DEVELOPMENTS

Absorbable Stents

The long-term interaction between stent and vessel can result in late stenosis and occlusion. One approach to mitigate this effect is to create stents composed of biodegradable material. Bioabsorbable stents theoretically provide scaffolding for healing of the vessel before they are eventually absorbed. Although lower extremity data are sparse, absorbable stents in the coronary arteries have shown a 30% mass reduction of neointimal hyperplasia at 12 months, and 60% reduction at 18 months.[66] Tamai et al[67] reported the use of a poly-L-lactic acid (PLLA) bioabsorbable stent in the coronary arteries of 15 patients with a restenosis rate of 10.5% at 6 months. Even with imaging at 4 years, these investigators found some hyperplasia related to the local stent reaction, but there were no late stent thromboses in these patients.[68]

The clinical effect of this expected degradation may lead to some late events, such as embolization with resulting small vessel ischemia. However, this clinical phenomenon has not been well documented. After the initial reports of success with the PLLA stent, Ormiston et al[66] reported the success of attaching everolimus to the PLLA stent to obtain the benefit of a medicated stent that reduces the intimal response while potentially removing the nidus for late stent thrombosis. These investigators found a decreased neointimal response and reduced cardiac event rate (3.3%) in a series of 30 patients.

The bulk of the data regarding the use of bioabsorbable stents in the peripheral circulation examine their efficacy in the femoral segments, with only a small number evaluating their utility in the infrapopliteal circulation. Substantive conclusions regarding efficacy relative to standard therapies are limited, due to the small sample size and heterogeneity in the study designs, but initial 30-day results in the femoral segment appear promising; however, longer term examination of data regarding 6-month data demonstrated patency that decreased as low as 60%.[69] The AMS INSIGHT trial compared infrapopliteal PTA versus PTA and stenting with bioabsorbable stents. These data showed no difference in initial 30 day outcomes of amputation or death, but the stenting group showed a worse 6-month primary patency than PTA alone.[69] Ultimately, the currently studied bioabsorbable scaffolds demonstrate safety and technical success in implantation without long-term clinical success in the infra-inguinal circulation; however, future research may improve this by combining various drug technologies to the scaffolds.[70]

Drug Delivery Without Stenting

Success in the use of drug delivery technology in the SFA has led to examination of this in the smaller crural vessels. Due to

the unique extrinsic compartment forces and smaller diameter, several institutions examined use of DCB without stenting the tibial vessels. Initial enthusiasm for DCB in the tibials has been tempered by the results of two larger multicenter, randomized trials (BIOLUX P-II and IN.PACT DEEP) demonstrating equivalent and inferior results, respectively, with the use of DCB compared to PTA alone.[71] Although there has been a fairly wide body of evidence to promote the utility of DCB technology in the femoropopliteal arterial segments, further information is needed to elucidate the differences in behavior between that and the below-knee vessels.

FUTURE DEVELOPMENTS

The progressive miniaturization of revascularization technology remains a consistent goal for clinicians treating vascular disease. Considering that open surgery has been refined over the last 50 years, the endovascular era is still relatively young. Simple dilation of diseased vessels has had limited clinical success, thus leading to intensive efforts to improve those results with intravascular devices, such as stents, and with antiproliferative medications. As with any new technology, new problems have been created. The alteration of hemodynamic variables, such as vessel compliance and shear stress, continues to limit the patency of endovascular intervention. Fortunately, this alteration appears to come at the cost of repeat interventions rather than limb loss. Stents have improved some of these catheter-based treatments, but further modifications are necessary to provide more effective therapy for the patient with vascular disease.

Looking forward, the modification of existing technology, such as bioabsorbable scaffolds, DCB, or novel treatments for occlusive disease, will likely focus on the elimination of stents, and their inherent limitations, completely. The combined use of debulking with drug technology is already being utilized in clinical practice, but has not been studied in a systemized fashion. Similarly, the introduction of stem technology or genetically engineered constructs, such as viruses to modulate the neointimal response, may render stenting obsolete.[72]

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LaDisa JF Jr, Olson LE, Guler I, et al. Stent design properties and deployment ratio influence indexes of wall shear stress: a three-dimensional computational fluid dynamics investigation within a normal artery. *J Appl Physiol*. 2004;97(1):424–430, discussion 416.

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68 CHAPTER

Novel and Evolving Aortic Endovascular Devices

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INTRODUCTION

The paradigm change in the management of aortic disease started in the late 20th century with minimally invasive techniques and endovascular devices has continued largely unabated to the present day. With advances in both technique and technology, the number of patients who are candidates for these endovascular approaches has increased, while the complications associated with the procedure has continued to decrease.[1] Whether it is superior to open surgery, patient expectations for a short hospital stay and smaller incisions has made endovascular aortic surgery the de facto standard of care.

The management of thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA) has evolved greatly over the past 20 years. With approximately 45,000 AAA repairs per year in the United States, over 90% were repaired using open means at the turn of the century. Today, the situation is reversed and over 90% are repaired using endovascular (endovascular aneurysm repair [EVAR]) means.[1] A similar transformation has occurred for TAA over the past decade due to the advent of thoracic endovascular aneurysm repair (TEVAR) devices.[2]

The success of these endovascular devices is dependent on suitable anatomy for endograft sealing without essential branch vessel compromise. Failure to meet the instructions for use (IFU) neck lengths and angles is associated with an increased rate of complications, such as endoleak, device failure, device migration, conversion to open, and aneurysm rupture.[3] To address patients with aneurysms outside standard IFUs for neck length, branched and fenestrated endovascular devices have been used with increasing success for both juxtarenal and suprarenal AAAs.[4] On the thoracic aortic side, a similar revolution is on the horizon for zone 0 and 1 TAA due to the advent of branched TEVAR devices (Fig. 68.1).

This chapter reviews the current state of the art and upcoming technology for the treatment of aortic disease, including aneurysms, dissection, trauma, and other pathologies.

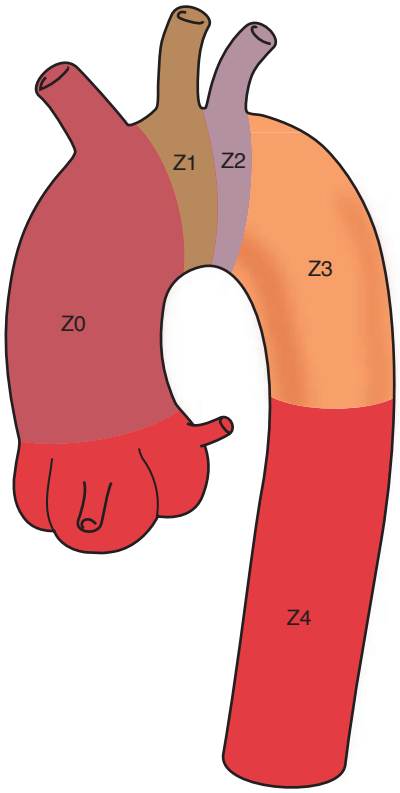

Figure 68.1 The zones of the thoracic aorta. (Courtesy Cheung AT, Weiss SJ. Diseases of the aorta. In: Oxorn DC, ed. *Intraoperative Echocardiography*. Philadelphia: Saunders; 2012:161–182.)

THORACIC AORTA

Current Practice

Aneurysms of the thoracic aorta have traditionally been amenable to endovascular repair if they are in zone 3 or 4 and have at least 2 cm of neck length. Achieving adequate proximal apposition may necessitate landing the TEVAR device across the left subclavian artery, thus entering zone 2. In an elective situation, this is often preceded by a carotid-subclavian bypass or subclavian to carotid transposition; in emergency situations, pre-TEVAR extraanatomic bypass grafting is required primarily for patients who have a LIMA-LAD graft, a left vertebral artery that terminates as an end artery (PICA syndrome), and preexisting left arm arterial disease.[5]

Open Repair

Open repair of thoracic aortic aneurysms has a variable morbidity and mortality depending upon how much of the arch and proximal aorta is replaced, and complications increase if a concomitant root replacement is also completed.[6] A median sternotomy is required along with cardiopulmonary bypass, and each of which have significant morbidity for the patient. Prior to the development of TEVAR, this was the only surgical option available for the patient with any type of thoracic arch aneurysm. With the advent of TEVAR, only patients with a zone 0 or 1 TAA remain the predominant candidates for open repair, and this landscape is changing rapidly.[5]

Standard Thoracic Endovascular Aneurysm Repair

The standard IFU for completing a TEVAR requires the thoracic aorta to be within a certain size threshold, a length, and quality of proximal and distal landing zone to provide adequate sealing, and satisfactory iliac or femoral access to permit passage of the device. Typically, a native aortic diameter between 16 and 42 mm is necessary with 2 cm long sealing zones. The minimum size requirements for iliac or femoral delivery vary by the size of the device, but they range between 5 and 9.8 mm. Iliac access vessels that are too small to permit delivery system passage may necessitate either a retroperitoneal "transplant" incision or a laparotomy to place a conduit onto the aorta or one of the common iliac arteries so that a TEVAR device can be inserted.

Ideally, the requisite 2 cm of the landing zone would be achievable without coverage of either the left carotid or subclavian arteries or the celiac artery. However, when left subclavian artery coverage is required to effectively exclude a TAA, the combination of a carotid-subclavian bypass with elective coverage of the left subclavian artery has been shown to be safe.[5] Similarly, coverage of the celiac artery, when the superior and inferior mesenteric arteries are patent, has been shown to be associated with a reasonably low rate of complications.[5,7] Despite these modifications, patients with more extensive aneurysms who require more aggressive coverage of arch or abdominal aortic branches presently need to undergo either a hybrid open endovascular procedure or chimney grafting in addition to the TEVAR.

Hybrid Procedure

Hybrid operations are options for patients whose anatomy does not meet standard IFU. For example, in a patient who will require coverage of both the left subclavian and left common carotid arteries (zone I TEVAR), a right common carotid to left common carotid artery bypass, followed by a left common carotid artery to left subclavian artery bypass can be completed prior to coverage by a TEVAR device.[8,9] An alternative approach is to do a subclavian-subclavian bypass, followed by a left subclavian artery to left common carotid artery bypass (Fig. 68.2). For patients with even more proximal disease who require coverage of all of the aortic arch branches (zone 0 TEVAR), two solutions have been used. One is a hybrid approach that begins with a de novo bypass from the proximal ascending aorta to the left subclavian artery, followed by the extraanatomic bypass described above.[10] This approach requires a median sternotomy but offers a less invasive repair option than standard open surgical repair, as cardiopulmonary bypass is not required. A second approach for zone zero TEVAR uses a chimney technique (parallel endografts) to maintain flow to the innominate artery, deploying it from the right brachial approach with simultaneous deployment of a TEVAR device.[11]

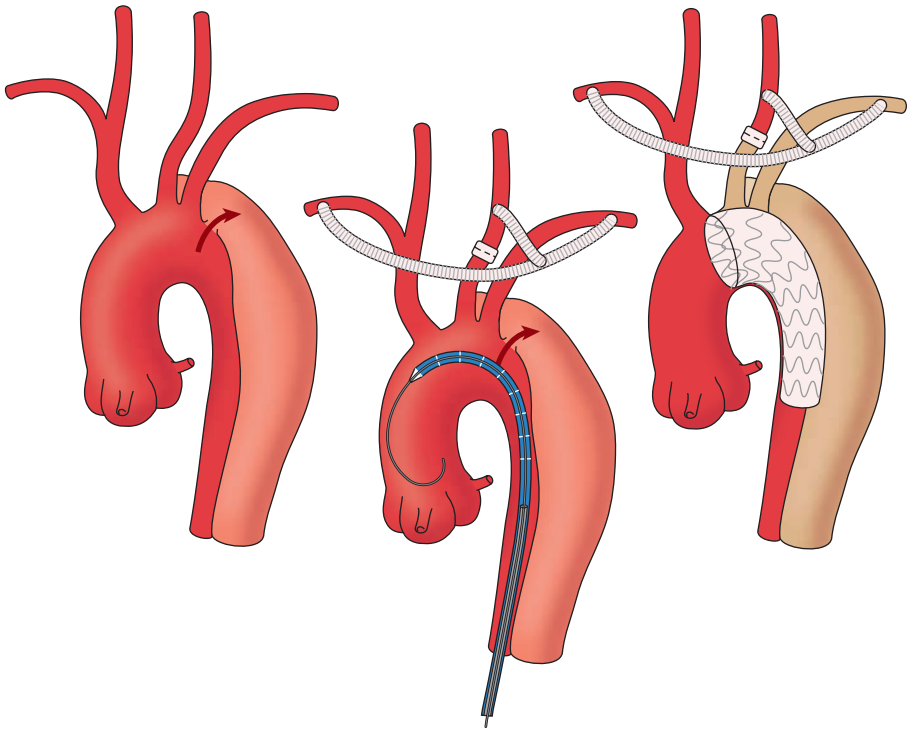

Figure 68.2 Zone I thoracic endovascular aneurysm repair with right-to-left subclavian bypass and left common carotid to left subclavian artery bypass. (Courtesy Kuratani T. Best surgical option for arch extension of type B dissection: the endovascular approach. *Ann Cardiothorac Surg*. 2014;3:292–299. doi:10.3978/j.issn.2225-319X.2014.04.04)

Chimney Technique

The chimney technique mentioned previously is associated with several major pitfalls. First, it relies on two cylindrical grafts being sandwiched together, and the inevitable gutters between them can be the source of an endoleak. The limited length of ascending aorta available for endograft deployment translates into relatively short gutters, further increasing the risk of endoleaks. On the distal end, the length of innominate artery available for endograft sealing prior to its bifurcation into the right subclavian, and right common carotid arteries can be inadequate for obtaining a seal and may necessitate another sandwich graft configuration, further increasing the complexity, risk, and potential failure modes. The second major pitfall is collapse of the innominate branch by the much larger TEVAR device, leading to loss of flow in the sole branch providing perfusion of the brain, a complication with usually fatal consequences. For these reasons, the use of a chimney technique to facilitate a zone 0 TEVAR should be used sparingly and only in the most infirm patient who would not tolerate a hybrid repair.[12]

Fenestrated Technique

An alternative method for revascularizing the branches of the aortic arch without resorting to extraanatomic bypass or chimney is to use laser fenestration to create holes in the endograft followed by balloon dilation and stent-graft placement to reestablish flow. Three-vessel fenestration can be completed to cover the entire aortic arch. The major pitfalls of this technique are that if the hole in the endograft does not line up with the ostium of the vessel, trauma to the aortic arch can occur through use of the laser, and modification of the endograft in this manner can lead to type II endoleaks.[13]

Laser fenestration involves placing a wire and catheter combination directly against the fabric of an endovascular device. The catheter is removed and a laser is then placed over the wire. Rotational angiography may be completed to ensure that the laser is directly apposed to the stent graft. The laser is activated for a short time, often just seconds, followed by advancement of the wire through the new hole in the stent graft. A balloon dilation is then completed, followed by deployment of a stent graft to ensure patency into the branch vessel.

Branched Endografts

There are two major endografts being tested that have a side-branch attached to a TEVAR endograft.[14] The Gore conformable thoracic aorta graft (C-TAG) branch endoprosthesis (W.L. Gore & Associates, Flagstaff, Arizona) and Medtronic Valiant Mona LSA thoracic graft system (Medtronic, Minneapolis, Minnesota) both offer a single side-branch that can be used to revascularize the left subclavian artery without the need for a carotid-subclavian bypass.

The Gore TAG thoracic branch endoprosthesis is similar to the existing C-TAG device but has been modified to have greater resistance to the tremendous forces within the aortic arch. The enhanced conformability further improves device deployment within angulated and curved aortic arches. The new branched endograft has three components: the first is an aortic component that is delivered over a stiff wire (Fig. 68.3). A side branch wire is precannulated through an internal docking portal and both wires

Figure 68.3 Gore thoracic aorta graft thoracic branch endoprosthesis device with side branch. (Courtesy W.L. Gore & Associates.)

are used to place the aortic component in the proper location within the arch. The aortic component is deployed and a side branch introducer sheath used to deliver a side branch device through the internal docking port over the side branch wire. The side branch device is then deployed, and both this and the aortic component are balloon molded to the arch (Fig. 68.4). Both proximal and distal aortic extension can then be completed using a variety of devices to ensure satisfactory coverage.

The Medtronic Valiant Mona LSA stent graft system is similar to the Gore device, but instead of having an internal docking port, there is a flexible external cuff that is used for placing the left subclavian artery stent graft.

A third novel device is being developed to permit zone 0 TEVARs and differs in construction compared to the Gore and Medtronic devices. Called the Relay Plus double branch arch system (Bolton Medical, Sunrise, Florida), this device builds upon the Relay Plus stent graft to have two parallel tunnels that can be separately cannulated and used to revascularize the innominate and left common carotid artery (Fig. 68.5). A left carotid-subclavian bypass would still be necessary with this graft. Cook Medical has developed a somewhat similar device known as the Zenith arch branched graft (Cook Medical, Canton, Illinois) that has two side branches that are used to cannulate the innominate and left common carotid artery. This graft is notable for having four trigger wires to sequentially deploy and stabilize the graft.[15]

ABDOMINAL AORTA

Current Practice

EVAR has become the standard of care for the treatment of AAAs with favorable anatomy for well over a decade. In patients who

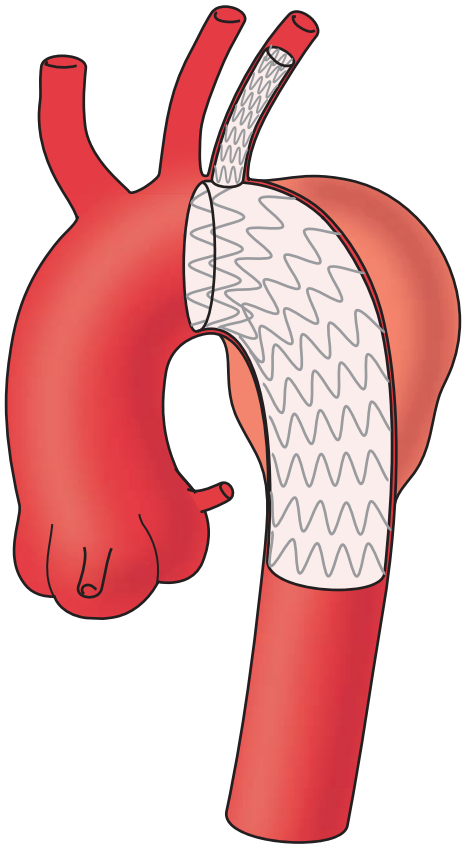

Figure 68.4 Gore thoracic aorta graft thoracic branch endoprosthesis device with side branch in a zone 2 configuration within the thoracic aorta. (Courtesy W.L. Gore & Associates.)

Figure 68.5 Bolton Medical double branch arch system. (Courtesy Bolton Medical, Sunrise, Florida.)

do not meet the anatomic criteria to undergo a standard, "on-label" EVAR, there are a variety of supplementary endovascular techniques available to exclude the aneurysm. These options have variable durability and include the chimney technique, P- and T-branched EVAR, fenestrated EVAR (FEVAR), hybrid techniques, and open repair.

Standard Endovascular

Commonly used EVAR devices are reviewed elsewhere in this textbook. Generally speaking, EVAR devices require a proximal neck diameter between 19 and 32 mm, a proximal neck length of at least 1.0 to 1.5 cm with less than 60-degree angulation, a distal landing zone of at least 1.5 cm, iliac artery diameters between 8 and 25 mm, and satisfactory iliac or femoral access to deploy the device. In contemporary practice, however, there has been significant deviation from the IFUs with corresponding increases in EVAR failures. Newer devices to the market now allow the treatment of patients with greater than 60% neck angulation, eliminating one of the more common reasons for "off-label" EVAR. The remaining major limitation of the standard EVAR technique is that juxtarenal or pararenal aneurysms cannot be treated using this method without covering the renal arteries, mandating adjunctive measures to maintain renal perfusion such as the chimney technique.

Chimney Endovascular

The chimney technique is similar to that described above for chimney TEVAR repair. Up to a four-vessel chimney can be constructed with complete coverage of the celiac, superior mesenteric, and right and left renal arteries. This technique requires independent four-vessel cannulation using axillary or brachial artery access and deployment of the EVAR device while simultaneously deploying the appropriate visceral stent graft. Complete exclusion of the aneurysm can be obtained while maintaining flow to the visceral segments. While this is an effective treatment in patients for whom a branched or fenestrated device is not available and who are not otherwise candidates for open repair, its major limitations are the potential for endoleak around the multiple gutters between the visceral stent grafts and the aortic endograft, migration of one of more visceral stent grafts, kinking leading to loss of flow to the viscera, and endograft migration from poor proximal fixation.[16,17] Of note, there are several series that have demonstrated equivalency of this technique to fenestrated endografts.[17]

Hybrid Technique

A hybrid technique has been used at some centers with increasing success and this technique is primarily reserved for thoracoabdominal aortic aneurysms (TAAA). The first portion of the procedure is a visceral debranching in which bypasses to the celiac, SMA, and/or renal arteries are performed. This is done using either the supraceliac aorta or a common iliac artery for inflow to the bypass. The choice of inflow is based on the extent of coverage expected with subsequent endografting. With the viscera supplied by remote bypasses, a subsequent EVAR can be performed, usually staged, that completely excludes the aneurysm. The advantage of this technique is that a complete reconstruction of the abdominal aorta can be avoided and partial-occlusion clamping of the aorta, if used as the inflow source, is less physiologically stressful than complete aortic clamping. Outcomes have been mixed with a greater than expected morbidity and mortality rate at some centers, potentially due to patient selection.[18]

Open Repair

Open repair of TAAA is performed with variable frequency across the American landscape, tending to be more concentrated in a handful of centers. And for good reason, high-volume centers that include distal aortic perfusion, moderate hypothermia, and spinal cord protection have been demonstrated to have the best outcomes.[19,20] Nonetheless, the magnitude of the operation cannot be minimized. Open repair requires cardiopulmonary bypass, a long thoracoabdominal incision, and replacement of the affected portion of the aorta along with its branches, the end organs of which invariably suffer some degree of ischemic injury. And while high-volume centers and practitioners have had excellent outcomes, those surgeons and centers less familiar with the challenges of these patients may not. Given the impracticality of regionalized treatment at this time, less invasive alternatives continue to be pursued. The strategies involved range from fenestrated and branched endografts to multilayer stents and, most recently, to endovascular aneurysm sealing (EVAS).

Fenestrated Endografts

Fenestrated endografts (FEVAR) have one or more fenestrations in their proximal aspect that permit deployment in the visceral aorta, as high as needed for secure attachment and seal, with flow to the visceral aortic branches being through bridging stent grafts. FEVAR endografts are custom constructed to each patient's specific vascular anatomy and geometry and, therefore, require several weeks of lead time. "One size fits many" FEVAR endografts have not yet been successfully developed. Scallops can be integrated into the design to permit a visceral branch to "peek out" over the top of the endograft, extending proximal attachment without the more complicated deployment of a fenestration. Over 1500 fenestrated grafts have been deployed since 2011 with an overall 98% technical success rate, 2% perioperative mortality rate, and 1% spinal cord ischemia (SCI) rate.[21,22]

Commercially available endografts include the Cook Medical Zenith fenestrated AAA device (Fig. 68.6) and the Anaconda Fenestrated device (available in Europe only). With multiple fenestrations that permit maintained perfusion of visceral branches, each endograft is customized to the patient based off a high-resolution CT scan. Fenestrated endografting has outcomes that are similar to open repair of type IV TAAA.[23,24] Laser fenestration of existing endografts has also been done by some investigators, although this technique is less commonly done now that there is a commercially available product.

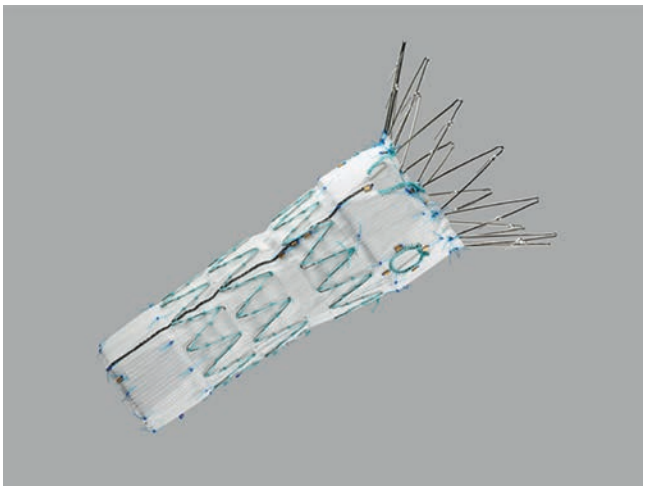

Figure 68.6 Cook Medical Zenith fenestrated endovascular graft. (Courtesy Cook Medical, Canton, Illinois.)

IFU for the Cook device include a nonaneurysmal infrarenal neck of 4 mm, proximal aortic neck diameter between 19 and 31 mm, neck angulation of less than 45 degrees, at least a 3-cm distal landing zone, and satisfactory iliac and femoral vessels for device introduction. More specific limitations regarding the placement of fenestrations and scallops exist, but they are beyond the scope of this chapter. The complexity of measuring for and manufacturing FEVAR endografts translates into a 4 to 6 weeks delay in treatment. Furthermore, this customization is labor intensive, costly, and can be quite inflexible with even minor degrees of malalignment. Hoping to eliminate these inflexibilities, effort has been exerted to develop branched endografts that offer a flexible platform that may allow an off-the-shelf solution to treating TAAA.

Branched Endografts

There are two types of branched endografts, termed P-branch and T-branch endografts. P-branch endografts are essentially fenestrated endografts designed so that the fenestrations emanate from a "turret" or outpouching of the endograft, creating a sort of pivoting fenestration that is more adaptable to a range of anatomic configurations (Fig. 68.7). T-branch endografts have tapered stent graft "sockets" for the visceral vessels connected to a Z-stent configuration endograft. In the ultimate four-branch version, the ability to maintain perfusion to all four visceral vessels permits full coverage for EVAR treatment of TAAA (Fig. 68.8).

The advantage of T-branch endografts over standard fenestrated endografts is that the risk of a type III endoleak from a component disconnection is significantly lower since the visceral endograft telescopes into the receiving socket of the aortic endograft with much greater component contact than what is available in a P-branch device or standard fenestrated endograft. The primary drawback of the T-branch devices is their delivery system size, 20 French for the Cook system with 8 mm celiac and SMA cuffs, and 6 mm renal artery cuffs. Theoretically, this design should have high utility in a variety of anatomic configurations due to the relative flexibility of the T-branches, especially when compared to the rigorous measurement and planning required for FEVAR.

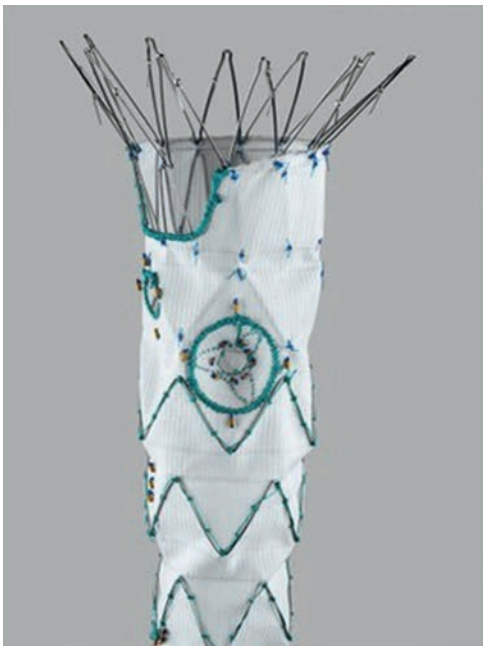

Figure 68.7 Cook Medical P-branch abdominal aortic aneurysms stent graft. (Courtesy Cook Medical, Canton, Illinois.)

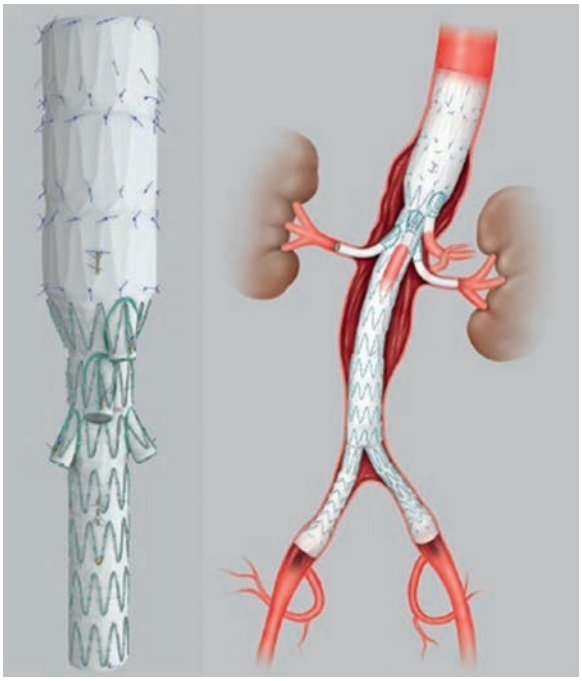

Figure 68.8 Cook Medical T-branch abdominal aortic aneurysms stent graft. (Courtesy Cook Medical, Canton, Illinois.)

P-branch devices have a pivot fenestration for the renal arteries and SMA and a scallop for the celiac artery. The configuration is such that two versions of this off-the-shelf device are suitable for almost 75% of all juxtarenal and pararenal AAA variations.[25] These P-branch devices differ from standard fenestrated

endografts in that a custom tailored solution for a patient's anatomy is not necessary, obviating the 4 to 6 weeks waiting time and allowing immediate repair. This same flexibility facilitates deployment of all of the components and mitigates errors in measurement or visceral vessel orientation.

There are other devices in development to treat TAAA. The Gore Excluder TAAA branch endograft is a T-branch device similar to the Cook device, and it differs somewhat in having renal artery branches that are oriented more cranially and is based on their Excluder platform. The precise orientation of the renal artery branches is debatable—some type IV TAAA have renal artery branches that are oriented more caudally than the standard anatomy, in which these branches tend to come off at a right angle to the aorta.

A modular graft being developed by Medtronic based off their Valiant platform is also being developed in a T-branch configuration. Similar to the Gore device, the main body is deployed via femoral access, and each of the four visceral branches catheterized and stented from the brachial artery.

Multilayer Endografts

A unique design for an AAA endograft has been developed by Cardiatis (Isnes, Belgium). This type of stent uses a multilayer flow modulator through multiple layers of a braided alloy to direct the majority of the blood flow within the reshaped lumen, leading to a pressure drop of over 90% within the aneurysm sac (Fig. 68.9).[26] Good outcomes have been seen with both infrarenal AAA and type B dissections. Other devices using a similar configuration have been successfully used in TAAA.[27] Additional studies using this novel design need to be completed to assess its long-term outcomes and overall patency.

Endovascular Aneurysm Sealing

The latest concept in endoluminal AAA repair to undergo a US-FDA clinical trial is the Nellix EVAS system (Endologix, Inc., Irvine, California), which uses a four-step system to fill aneurysm sacs with a polymer after bridging them with endograft limbs, conceptually preventing type 2 endoleaks by sac filling. The procedure begins with advancement of 17 French catheters, followed by aligning and expanding the stent grafts, filling the aneurysm sac to 180 mm Hg of pressure and confirming a satisfactory seal, and finally filling that space with a polymer. Anatomic requirements are similar to other aortic endografts and include a proximal neck diameter between 18 and 32 mm, a neck length of at least 10 mm, and less than 60 degrees of neck angulation. The luminal diameter of the sac should be less than 6 cm, and while satisfactory iliac artery diameters are necessary for access, no minimum iliac landing zone is required.[28]

Figure 68.9 Cardiatis multilayer braided stent. (Courtesy Cardiatis, Isnes, Belgium.)

In 150 patients who have had this procedure completed as part of a US-FDA clinical trial, 100% technical success has been achieved. The average time to implantation is 30 minutes for a total procedure time of about 88 minutes. On average, the volume of polymer needed to fill the aneurysm sac is 75 mL (29-215 mL range). Complications are similar to that seen with traditional EVAR devices, with an all-cause mortality of 0.7% at 30 days, and major adverse events occurring in about 2.7% of patients at 30 days. One-year all-cause mortality has been reported at 4.0% with a major adverse event rate of 6.7%.[28,29] Secondary interventions have been necessary in 3.7% of patients, and sac expansion was noted in two patients (1.5%). At 1 year, the only endoleaks that were noted included one patient (0.8%) with a type IB endoleak and three patients (2.3%) with a type II endoleak. Overall, these results are similar to that reported by other manufacturers of EVAR devices but with a lower rate of endoleaks and secondary interventions. Freedom from sac enlargement is similar to that reported by other manufacturers.[29]

FUTURE DIRECTIONS

While there have been numerous advances in endograft technology leading to an increase in patients who are candidates for this minimally invasive approach, the concept of total endovascular aortic treatment remains a work in progress. The new generation of thoracic devices seeks to avoid having to perform subclavian revascularization when completing a zone 2 TEVAR. It is likely that we will be seeing this generation of single-branched TEVAR devices being implanted as a zone 1 device with the branch used to revascularize the left common carotid artery followed by a carotid-subclavian bypass. There will undoubtedly be investigators who also use it to revascularize the innominate artery as part of a zone 0 TEVAR followed by a subclavian-subclavian bypass and left common carotid to subclavian bypass, thus obviating any need for a median sternotomy or chimney approach. Multi-branched TEVAR devices will not be far behind.

Regarding AAA and TAAA, we have seen a shift from custom-made devices individualized to a particular patient's anatomy to off-the-shelf designs that are suitable for a majority of patients. T-branch devices in particular offer tremendous flexibility in a safe, proven durable platform that is suitable for the repair of a variety of TAAAs. Not only do these advanced designs expand the population of patients that can be treated, but their deployment flexibility expands the population of vascular surgeons willing and able to embrace this new technology.

While devices continue to improve, one of the most significant problems that remains to be solved is that of SCI, because the rate of SCI remains between 1% and 8% when completing complex endovascular TAAA repairs.[28-32] The rate of SCI appears to be related to the extent of coverage and how much is covered

in a single setting. The use of staged procedures and adjuncts for spinal cord protection have decreased the rate of SCI. Cerebrospinal fluid drainage, preventing hypotension, neuromonitoring via motor and somatosensory evoked potentials, and ensuring flow within the internal iliac arteries are all strategies that can help reduce the incidence of this complication.[32,33] Advances in patient management to avoid this devastating complication are continuing in multiple novel areas, such as the use of dedicated institutional protocols, leukotrienes, and an "open branch" technique to permit some flow into the aneurysm sac after the initial stage, followed by completion coverage by a stent graft at a later date.[33-35]

CONCLUSION

Technology continues to advance rapidly in this area with improving morbidity and mortality for patients with complex aortic pathology. While each particular approach has advantages and disadvantages, altogether there has been an expansion in indications for minimally invasive aneurysm repair. Continuing advances in spinal cord protection seek to decrease the incidence of this devastating complication.

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69 CHAPTER

Arterial Aneurysms: Etiology, Epidemiology, and Natural History

PETER F. LAWRENCE and DAVID A. RIGBERG

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GENERAL CONSIDERATIONS

The term *aneurysm* describes dilatation of any blood vessel. Arterial aneurysms located extracranially occur throughout the body but are most prevalent in the infrarenal aorta (abdominal aortic aneurysm [AAA]). These aneurysms represent the primary cause of the significant death and morbidity attributed to arterial aneurysm disease. In the United States, AAA were directly responsible for approximately 9900 deaths in 2014, and approximately 120,000 AAA procedures were performed to prevent subsequent rupture.[1-3] The incidence of aneurysms increases with age, but aneurysmal disease can occur in any decade of life. These lesions may be the result of several degenerative processes, including inflammatory, infectious, genetic, and traumatic conditions. Although aortic aneurysms can cause a variety of clinical conditions, such as embolism, compression on adjacent organs, and fistulas, the primary danger from aortic aneurysms is rupture with uncontrolled hemorrhage, leading to death. Nonaortic aneurysms may also rupture, but they more often embolize, thrombose, or compress surrounding structures, and they rarely rupture into an open space where blood loss is catastrophic.

The risk of rupture of any aneurysm is related to both the absolute size of the aneurysm and its size relative to the normal diameter of the inflow and outflow artery from which it arises. A variety of other factors, including location, etiology, growth rate, and aneurysm morphology (i.e., fusiform vs. saccular) can also be critical in assessing aneurysm risk.

Abstract

The term aneurysm describes dilatation of any blood vessel. These can occur throughout the body, and can present risks of rupture, embolism, thrombosis and other complications. Such lesions are categorized based on their size, involved artery, morphology and etiology. The specific artery involved often plays the leading role in the risk of aneurysm-related complications. For example, abdominal aortic aneurysms are associated with rupture and life-threatening hemorrhage, while popliteal artery aneurysms are associated with embolization, thrombosis and acute limb-threatening ischemia. Aneurysms can also be associated with underlying conditions that predispose to formation of multiple lesions. This phenomenon is seen in the association between aortic aneurysms and popliteal aneurysms, the multiple aneurysms seen in some connective tissue disorders and with cystic medial degeneration. This chapter introduces all of these topics.

Keywords

aneurysm
pseudo-aneurysm
degenerative aneurysm
inflammatory aneurysm

HISTORICAL PERSPECTIVE

The presence of arterial calcification and atherosclerotic change has been documented in Egyptian mummies from 3500 years ago. The Ebers Papyrus (c.2000 BC) clearly identifies an arterial aneurysm, recommending, "Treat it with a knife and burn it with a fire so that it bleeds not too much."[4] Antyllus repaired aneurysms of the extremities with proximal and distal ligation, followed by packing of the aneurysm sac.[5] Few advances occurred during the next 1000 years; John Hunter ushered in the era of modern vascular surgery, based on a more scientific understanding of anatomy and physiology. He studied the collateral circulation resulting from the occlusion of arteries, and in 1785 successfully ligated the superficial femoral artery to treat a popliteal aneurysm. The patient did well and maintained function of his lower extremity.[6]

Rudolph Matas (1860–1957) made numerous contributions to the field of vascular and arterial reconstruction. In 1888, he was the first to perform endo-aneurysmorrhaphy in the treatment of a brachial artery aneurysm. This procedure augmented the principle of proximal and distal ligation by Hunter, using evacuation of the aneurysm sac and ligation of tributaries from within the sac while preserving important collaterals, and remains an important principle in the era of modern vascular surgery.[7,8] In 1923, Matas performed the first successful aortic ligation; the patient survived 18 months before succumbing to tuberculosis.[9] Little progress was made during the next two decades; Bigger's summary of surgical therapy for aortic aneurysms at the 1940 annual meeting of the American Surgical Association probably represented the consensus of the era: "Judging from the literature, only a small number of surgeons have felt that direct surgical attack upon aneurysms of the abdominal aorta was justifiable, and it must be admitted that the results obtained by surgical intervention have been discouraging."[10]

The modern era of aneurysm therapy was ushered in by Charles Dubost in 1951, with the first successful replacement of the aorta with an aortic homograft. The introduction of Vinyon N cloth in the construction of aortic prostheses by Voorhees, Jaretski, and Blakemore[11] addressed the poor availability of existing aortic homografts and initiated the era of prosthetic vascular reconstruction.* The eventual introduction of polyester, championed by DeBakey, and the introduction of new knitting machine technologies to make seamless grafts of multiple sizes and shapes led to a wider availability of materials and ultimately the diffusion of surgical techniques for repairing aneurysms.[12] Further refinements in surgical, anesthetic, and critical care, in the setting of increasing surgical volume, defined the ensuing decades until the 1990s, when many surgical series documented perioperative mortality for open aortic aneurysm repair below 5%, with some at 1% or lower.

The era of endovascular, or transcatheter, repair of aortic and other peripheral aneurysms was made a clinical reality in 1991 by Juan Parodi, when he used available balloon-expandable stents in combination with standard polyester grafts to create a device that could be delivered from the femoral artery to the abdominal aorta, where it was deployed and effectively excluded an infrarenal aortic aneurysm. Today there are numerous endografts available for use, and current estimates are that more than 70% of all aortic aneurysm treatment is performed with endograft technology. More recently approved devices and off-label combinations of various other endovascular devices have been increasingly used where critical branches are present, leading to the technical ability to repair virtually any aneurysm, from the aortic valve to the popliteal and brachial artery.

Historically, aneurysms of the upper and lower extremity arteries were the first to be treated, and the development of those techniques dates into antiquity. Modern approaches to peripheral aneurysm and nonaortic intraabdominal aneurysm (e.g., splenic, renal) repair typically uses techniques to bypass critical vessels following proximal and distal ligation of the aneurysm; their development has paralleled the techniques used for arterial bypass performed for occlusive disease. As with aortic aneurysms, a variety of endovascular techniques for treating peripheral aneurysms have been introduced during the last 20 years. Embolization techniques have also been selectively used for the treatment of saccular visceral artery aneurysms and other aneurysms providing blood supply to noncritical organs, or where good collateral circulation exists.

ANEURYSM CLASSIFICATION

Size Definitions

The size required to describe an artery as aneurysmal has been defined as "a permanent localized (i.e., focal) dilatation of an artery having at least a 50% increase in diameter compared with the expected normal diameter of the artery in question" by the Ad Hoc Committee on Reporting Standards of the Society for Vascular Surgery in 1991.[13]

Aortic

Magnetic resonance imaging of 70-year-old men and women in Sweden determined aneurysmal size and ratio to normal based on a two-standard deviation variance from normal diameters in the ascending and descending thoracic aorta, supraceliac aorta, and infrarenal aorta (Tables 69.1 and 69.2). Other definitions for infrarenal aortic aneurysms have used a 3.0-cm threshold for definition across all adults, or a 50% increase relative to an adjacent normal-appearing segment. Women generally have smaller aortic diameters than men; this becomes clinically relevant when determining the size threshold for intervention for aortic aneurysms in both sexes.

*Large samples of Vinyon N were made available for research following World War II. The material was manufactured to make parachutes for an invasion of Japan, which was cancelled following the atomic bombings of Hiroshima and Nagasaki and Japan's subsequent surrender. Interestingly, polytetrafluoroethylene (PTFE) was used to help contain uranium hexafluoride, a toxic byproduct of atomic bomb production during the Manhattan Project. (Foundation CH, Plunkett RJ, 2013 [cited 2013 April 25]. Available from: <http://www.chemheritage.org/discover/online-resources/chemistry-in-history/themes/petrochemistry-and-synthetic-polymers/synthetic-polymers/plunkett.aspx>.)

TABLE 69.1 Normal Mean Aortic Diameter in 70-Year-Old Men and Women

	MEN			WOMEN			
Aortic Segment	N	Mean Diameter (cm)	SD	N	Mean Diameter (cm)	SD	*P*[a]
Ascending	116	4.0	0.4	104	3.4	0.4	<.001
Descending	116	3.2	0.3	114	2.8	0.3	<.001
Supraceliac	115	3.0	0.3	113	2.7	0.3	<.001
Suprarenal	116	2.8	0.3	114	2.7	0.3	.004
Infrarenal	117	2.4	0.5	114	2.2	0.3	<.001
Bifurcation	113	2.3	0.3	112	2.0	0.2	<.001

[a]Independent sample *t* test.
SD, Standard deviation.
From Wanhainen A, Themudo R, Ahlström H, et al. Thoracic and abdominal aortic dimension in 70-year-old men and women: a population-based whole-body MRI study. *J Vasc Surg*. 2008;47:504-512.

TABLE 69.2 Definition of Aneurysm at Various Aortic Segments: Size and Ratio to Normal

	MEN		WOMEN	
Aortic Segment	Diameter (cm)	Ratio to Normal	Diameter (cm)	Ratio to Normal
Ascending	4.7	1.8	4.2	1.7
Descending	3.7	1.5	3.3	1.3
Infrarenal	3.0	1.1	2.7	1.0

From Wanhainen A, Themudo R, Ahlström H, et al. Thoracic and abdominal aortic dimension in 70-year-old men and women: a population-based whole-body MRI study. *J Vasc Surg*. 2008;47:504-512.

TABLE 69.3 Normal Diameters of Peripheral Arteries

	Normal Diameter (cm)
Celiac	0.5
Superior mesenteric	0.6
Common femoral	0.8
Popliteal	0.9
Tibial	0.3

Modified from Johnston KW, Rutherford RB, Tilson MD, et al. Subcommittee on Reporting Standards for Arterial Aneurysms, Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery and North American Chapter, International Society for Cardiovascular Surgery: Suggested standards for reporting on arterial aneurysms. *J Vasc Surg*. 1991;13:452-458.

Peripheral

Iliac, popliteal, and femoral aneurysms follow aortic aneurysms in the hierarchy of prevalence and are often coexistent with aortic aneurysms. Aneurysms throughout the rest of the peripheral vascular system, although usually degenerative in nature, may also be related to other pathologic processes, such as arteritis, infection, and connective tissue disorders. The "normal" diameters of a variety of peripheral arteries, as determined from imaging studies, are listed in Table 69.3. Irrespective of the ratio of an aneurysm to its normal arterial diameter, the physical forces of wall tension are dictated by the absolute radius rather than by any ratio to a standardized normal size.

True Versus False Aneurysms

The distinction of true or false aneurysms (usually termed pseudoaneurysms) is dependent on whether the lesion represents a dilatation of the entire vascular wall (i.e., true aneurysm) or is a locally contained hematoma resulting from disruption of the vessel (i.e., pseudoaneurysm). In pseudoaneurysms, the "wall" of the pseudoaneurysm is connective tissue formed in reaction to the contained hematoma. This distinction usually does not affect decisions regarding the necessity of intervention, since progressive enlargement and its consequences are indications for intervention in both aneurysm types. However, certain types of pseudoaneurysms may have an increased tendency toward rupture. Many peripheral pseudoaneurysms are the result of trauma, which is often iatrogenic during peripheral arterial access required for imaging or therapy (Fig. 69.1). These pseudoaneurysms often have a "neck" or narrow conduit between the affected artery and the main pseudoaneurysm cavity. When this morphology exists, therapy directed at inducing aneurysm thrombosis is often effective in treating the aneurysm.

Another frequent cause of pseudoaneurysms is the loss of anastomotic integrity at the site of a prior surgical anastomosis. These peri-anastomotic pseudoaneurysms represent actual dehiscence of the original suture line from the graft to the vessel (Fig. 69.2). Endovascular techniques have greatly simplified the repair of these lesions in many cases.

Location and Extent

Aneurysms are classified by their location (e.g., aortic, splenic) and their extent. *Ectasia* refers to an intermediate stage of enlargement, when an artery is abnormally large, but less than 50% greater than normal, whereas *arteriomegaly* refers to diffuse, continuous enlargement of multiple arterial segments, dilated

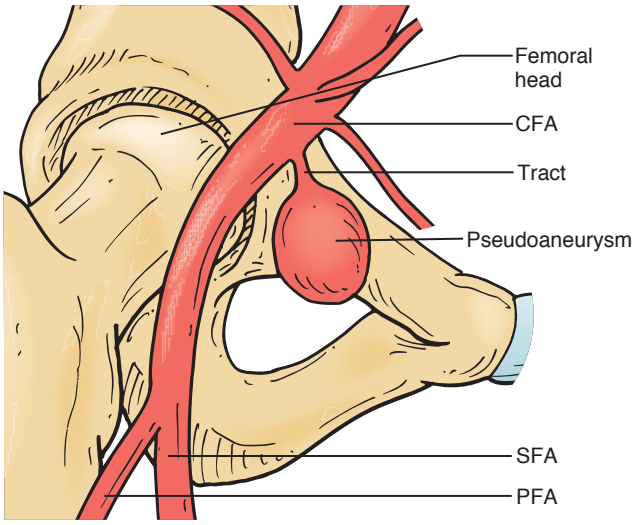

Figure 69.1 Iatrogenic femoral false aneurysm or pseudoaneurysm after percutaneous femoral arterial puncture. *CFA,* Common femoral artery; *PFA,* profunda femoris artery; *SFA,* superficial femoral artery. (From Kronzon I. Diagnosis and treatment of iatrogenic femoral artery pseudoaneurysm: a review. *J Am Soc Echocardiogr.* 1997;10:236-245.)

to greater than 50% of normal. Arteriomegaly is a descriptive term, rather than representative of a specific diagnosis, and likely constitutes part of a not yet clearly defined genetic syndrome of arterial degeneration. Both arterial ectasia and arteriomegaly are associated with an increased risk for aneurysm disease in first-degree relatives of affected patients.[14] The term *aneurysmosis* is often used to describe multiple aneurysms in several anatomic locations, or the combination of aneurysmal degeneration in the setting of arteriomegaly.[15]

Morphology

The shape of aneurysms is typically described as fusiform or saccular. Fusiform aneurysms represent a generalized increase in the entire diameter of the affected vessel, while saccular aneurysms are more localized and often eccentric in shape. Some saccular aneurysms are eccentric defects arising from a focal ulcer or weakness in the arterial wall, often because of trauma or infection (Fig. 69.3). In general, pseudoaneurysms are more likely to have saccular morphology, while true degenerative aneurysms are more likely to have a fusiform configuration.

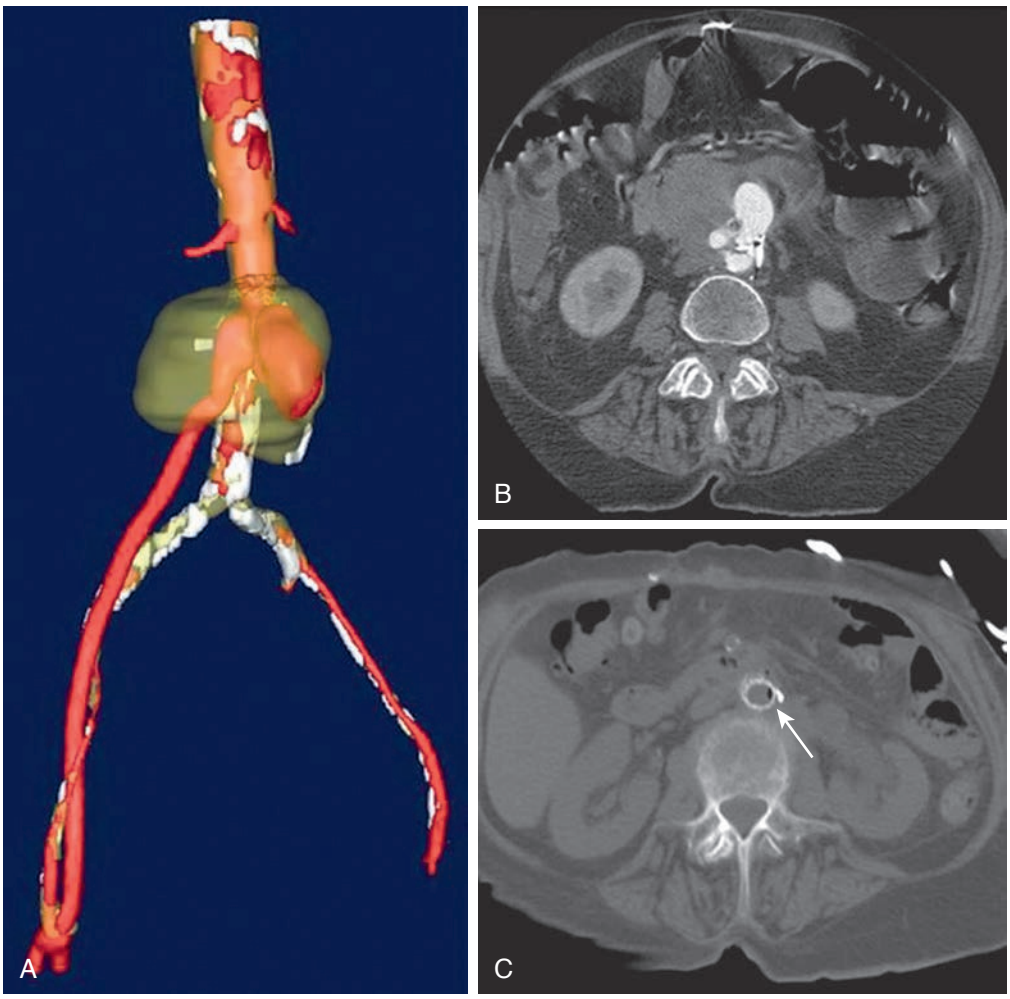

Figure 69.2 Three-dimensional reconstruction (A) and axial computed tomography imaging (B, C) of a proximal infected anastomotic pseudoaneurysm in an aortofemoral bypass graft. *Arrow* shows gas formed by infecting bacteria. (From Lew WK, Rowe VL, Cunningham MJ, Weaver FA. Endovascular management of mycotic aortic aneurysms and associated aortoaerodigestive fistulas. *Ann Vasc Surg.* 2009;23:81-89.)

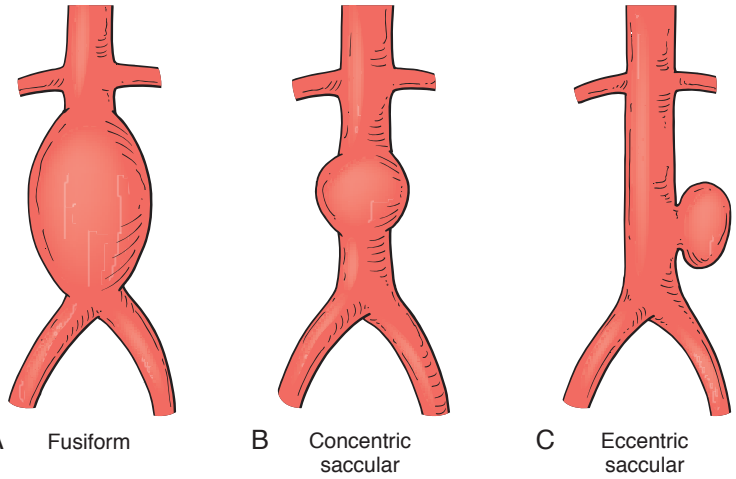

Figure 69.3 Fusiform and saccular (concentric or eccentric) aneurysm morphology.

Most peripheral arterial aneurysms are associated with atherosclerotic degeneration of the entire wall, which usually results in a fusiform or concentric saccular morphology. Eccentric saccular morphology is typical of renal aneurysms and intracranial or cerebral aneurysms but is less common in noncerebral locations, except for the kidney. However, most pseudoaneurysms do have an eccentric saccular shape. Whereas fusiform and concentric saccular aneurysms result from a generalized weakening of the entire circumference of the affected vessel, saccular aneurysms result from a focal weakness that may be due to an intrinsic abnormality or an extrinsic process causing focal arterial damage. Intrinsic causes associated with saccular aneurysms generally involve a focal "tear" or partial disruption of the arterial wall at that location. Penetrating atherosclerotic ulcers and intramural hematomas are examples of focal tears in the aortic wall that fail to completely propagate down the wall in the medial layers, resulting in frank aortic dissection, and have a morphology consistent with eccentric saccular aneurysms. These entities have become more recognized in the past decade with respect to their presentation, prognosis, and treatment, particularly as relatively straightforward endovascular techniques are often effective therapies for these lesions.[16,17] The risk of rupture is better characterized for fusiform or saccular shapes but is less well understood for eccentric saccular aneurysms. Saccular aneurysm morphology and associated symptoms are often used as factors in advising intervention at a diameter less than that for fusiform aneurysms, and many saccular aneurysms are easier to treat with endovascular techniques because of their focal nature. However, definitive data suggesting that saccular aneurysms are more prone to rupture versus fusiform lesions of the same size are lacking. Symptoms, size, growth rate, and amenability to repair are often significant factors in the decision to repair or to observe these unusual lesions.

Etiology

Degenerative

The terms *degenerative* and *atherosclerotic* are often used to describe the most common type of aneurysms. Some authors prefer the term *degenerative* to *atherosclerotic* in describing the common form of aneurysm to avoid the unproven causative relationship between aneurysms and typical atherosclerosis. The relationship of atherosclerosis to aneurysm formation is complex, but both aneurysms and obstructive manifestations are often found in the same patient cohort, with either the aneurysmal or obstructive manifestation predominating. Specific factors associated with degenerative aneurysms include the presence of abnormal levels of metalloproteinases in the media of aneurysm specimens.[18,19] In addition, there is evidence for a deficit of antiproteolytic enzymes that inhibit metalloproteinases—specifically the tissue inhibitor of metalloproteinase-1.[20] The intensity and duration of cigarette smoking by patients affected with aneurysm disease is the most significant risk factor for the development of these degenerative aneurysms[21] and represents the most attractive target for risk reduction.

Inflammatory

The term *inflammatory* refers to an aneurysm with an exaggerated inflammatory component, which often incites a fibrotic reaction around the aneurysm. The infrarenal abdominal aorta is most often affected by this inflammatory process and has the appearance on axial imaging of a thick inflammatory so-called rind around the exterior of the affected vessel, which may or may not envelope adjacent structures. Inflammatory infrarenal aortic aneurysms may be associated with ureteral obstruction as the process envelops the ureters in the retroperitoneal space (Fig. 69.4).

Efforts to determine a genetic susceptibility for inflammatory aneurysm formation have yielded only similarities, rather than differences, in the genetic background of patients with degenerative versus inflammatory aneurysms.[22] Detailed studies of the cellular infiltrate and cytokine profiles documented in patients with inflammatory aneurysms may eventually lead to a better understanding of this challenging and enigmatic disease state.[23] The primary surgical challenge associated with these lesions is the difficulty of dissecting surrounding structures safely during the open repair of these lesions. The complications associated with traditional open surgery for inflammatory aortic aneurysms have included duodenal perforation and ureteral injury. Endovascular repair of inflammatory aneurysms has been reported

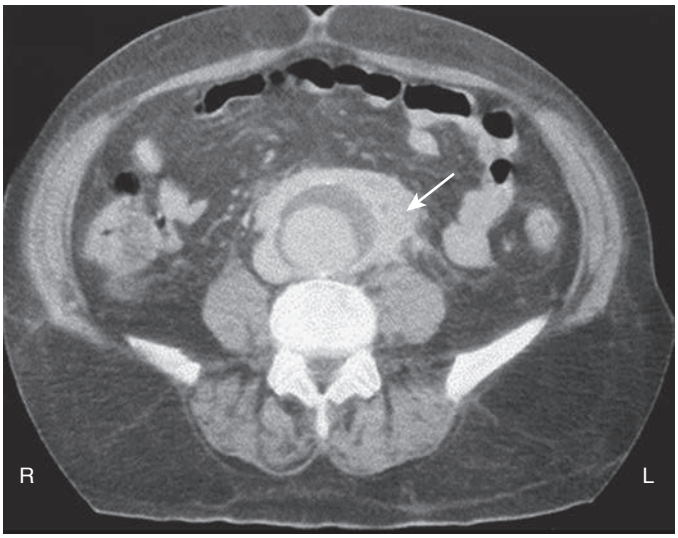

Figure 69.4 Typical appearance of inflammatory aortic aneurysm on computed tomography with thick peri-aortic fibrotic process. (From Speziale F, Barigia E, Grossi R, et al. Inflammatory aneurysms of the abdominal aorta involving the ureters: is combined treatment really necessary? *J Urol.* 2001;165:27-31.)

to result in regression of the peri-aneurysmal inflammation and fibrosis.[24]

Takayasu arteritis, giant cell arteritis, polyarteritis nodosa, Behçet disease, Cogan syndrome, and cystic medial necrosis represent other inflammatory arterial conditions that are associated with aneurysmal degeneration. The location and severity of these aneurysms are related to the specific diagnosis and the ability to control the primary process with medical therapy (see Chapter 137).

Aneurysms Associated With Arterial Dissection

Spontaneous arterial dissection occurs most often in the aorta, but can also occur in peripheral arterial locations. Arterial dissection describes a spontaneous tear of the intima of an artery and the subsequent propagation of that tear along the anatomic plane within the media (see Chapter 81). The failure of the initial intimal tear to propagate may result in a penetrating aortic ulcer or intramural hematoma, as discussed earlier. Arterial pressure and acute arterial distention as the result of mural delamination are the driving forces behind the propagation of the dissection. The most common clinical symptomatic presentation of this process is thoracic aortic dissection in either the ascending or descending portion, or both. The structural integrity of arteries is dependent on the integrity of their composite (three-layer) structure. The primary morbidities associated with arterial dissection are acute occlusive symptoms and subsequent aneurysmal degeneration. Aneurysmal degeneration resulting from dissection can take the form of acute distention and rupture, or a less severe acute dilatation followed by progressive dilatation over time, similar to that seen with degenerative aneurysms. Chronic aneurysms due to dissection are generally treated by the same guidelines for size, growth, and symptoms that are used for the management of degenerative aneurysms.

Traumatic

Aneurysms that result from trauma are pseudoaneurysms, due to perforation of an artery that results in local containment of hemorrhage rather than uncontrolled bleeding. The location of these aneurysms parallels the location and incidence of trauma (see Chapters 181 to 184).

Developmental and Congenital Anomalies

Aneurysms associated with anomalous arterial and cardiac structures are not uncommon but are highly variable, depending on the nature of the primary structural defect. These lesions are usually further representations of the embryologic defect that resulted in the primary arterial or cardiac anomaly. One such embryologic arterial anomaly is the persistent sciatic artery. More than 40% of these patients will develop aneurysmal degeneration. Kommerell diverticulum is another form of aneurysmal degeneration related to a developmental anomaly, located at the origin of an aberrant right subclavian artery. Aneurysm development in this location can intensify the esophageal obstruction associated with an aberrant right subclavian artery (*dysphasgia lusoria*).[23] Congenital AAAs have also been reported in young patients, such as those with tuberous sclerosis, but without other known connective tissue disorders, and are thought to represent a congenital defect in the aorta itself.[25] Although it is not strictly a genetic disorder, aortic aneurysm increases in incidence from approximately 5% in the general population to approximately 20% to 30% in male siblings of an aneurysm patient, suggesting a significant familial linkage.[26]

Infectious

Aneurysms may result from primary infection of the arterial wall, which can occur due to hematogenous seeding or the extension of an adjacent infectious process that then envelops and primarily infects the arterial tissue externally (Fig. 69.5). Most primary infected arterial aneurysms, as opposed to secondary infection of a preexisting aneurysm, have an eccentric saccular shape, and all such aneurysms should be evaluated for an infectious etiology. A wide variety of organisms, including many strains of bacteria[27] and fungi (e.g., *Candida, Aspergillus*), tuberculosis, and syphilis have been documented to be causative. Infected aneurysms can occur in essentially any vessel, and their incidence is increased in patients with a history of illicit drug injection/abuse and in patient populations that are severely immunosuppressed (e.g., transplant recipients, oncology patients, patients infected with human immunodeficiency virus, and patients with acquired immunodeficiency syndrome).[28]

Repair of infected aneurysms is difficult because prosthetic material is usually contraindicated and there are limited durable autogenous substitutes available. In addition, the open approach to these lesions is made more challenging by the inflammatory response to the infected structure, making tissues friable and tissue planes difficult to define. Surgical repair utilizing antibiotic-impregnated prosthetics, cryopreserved allografts, and primary endovascular stent-grafting in these cases remains controversial (see Chapter 144).

Figure 69.5 An infected aortic eccentric saccular aneurysm. (From Macedo TA, Stanson AW, Oderich GS, et al. Infected aortic aneurysms: imaging findings. *Radiology*. 2004;231:250-257.)

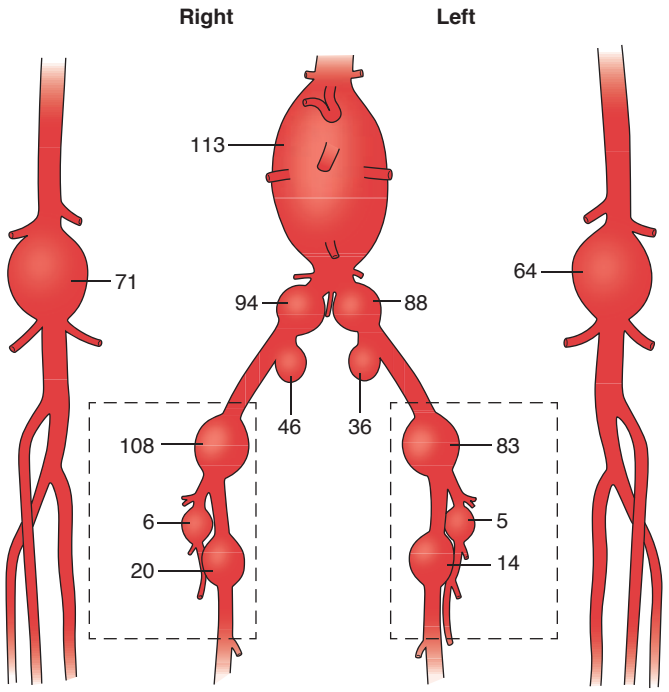

Figure 69.6 The locations and distribution are shown of degenerative femoral artery aneurysms (FAAs; *dotted boxes*) and additional synchronous and metachronous aneurysms. Forty-seven patients (26%) had bilateral degenerative FAAs. (From Lawrence PF, Hartlander-Locke MP, Oderich GS, et al. The current management of isolated degenerative femoral artery aneurysms is too aggressive for their natural history. *J Vasc Surg*. 2014;59(2):343-349.)

Specific Arteries

Arterial aneurysms occur throughout the vasculature from a wide variety of causes. Their prognosis and therapy are largely dependent on their anatomic location. Aneurysms located in circulatory beds that have robust collateral circuits can often be embolized or excluded from the circulation by ligation or other means without concomitant vascular reconstruction. Aneurysms in critical locations of the circulatory system require replacement of that arterial segment with an adequate substitute, in the form of an autogenous or prosthetic graft.

Aortic

Aneurysms occur throughout the length of the aorta, with a majority occurring in the infrarenal segment. Aneurysms occurring in the ascending aorta are typically degenerative or the sequela of prior aortic dissection; the aortic arch and descending aorta are similarly affected in their predilection for aneurysmal disease. Isolated thoracic aortic aneurysms were found in 0.9% of autopsies in Sweden[29] and represent 3% of aortic aneurysm repairs in the United States.[30] The infrarenal location is by far the most common for aortic aneurysms, and AAAs are at least nine times more common than thoracic aneurysms.[31] Approximately 1.7% of women and 5% of men older than 65 years have an infrarenal aortic diameter greater than 3 cm, and the incidence of aortic aneurysm increases by about 6% for each decade after that age.[32] Aneurysms involving segments of the thoracic and abdominal aorta, thoracoabdominal aneurysms, are less frequent than either isolated thoracic or isolated AAAs, but represent some of the most formidable challenges for repair in vascular surgery.

Iliac

Aneurysms are most frequently found in the common iliac artery, often in the presence of a concomitant infrarenal aortic aneurysm. A review of patients with iliac aneurysms in 1994 revealed that only 11% presented without a concomitant aortic aneurysm.[30] Internal iliac aneurysms are the next most frequent lesion in this circulatory bed. Although internal iliac aneurysms are often found in association with common iliac aneurysms, these lesions more commonly occur in isolation. Isolated internal iliac artery aneurysms present with rupture in 40% of patients and are associated with a 31% mortality rate.[33] Isolated internal iliac aneurysms are less frequently diagnosed when asymptomatic and are more difficult to control surgically when ruptured; these are two potential reasons for the elevated rates of rupture and death from lesions in this location. External iliac aneurysms are rare and usually associated with traumatic lesions or other nondegenerative causes.

Femoral

The incidence of true aneurysms of the femoral artery is relatively low, likely on the order of 5/10,000 patients.[34] Nevertheless, true degenerative femoral artery aneurysms do occur, and a recent study suggests that these lesions typically do not cause complications unless they are greater than 3.5 cm or contain thrombus.[35] These aneurysms are frequently bilateral (26%), and 88% of patients have a synchronous aneurysm at another site (see Chapter 83; Fig. 69.6).

Femoral pseudoaneurysms most commonly result as a complication of percutaneous femoral access or disruption of prior surgical bypass anastomoses. The most serious and high-risk femoral aneurysms are infected pseudoaneurysms from illicit injection drug abuse.[36] These lesions can be challenging to repair and are often not easily amenable to endovascular techniques.

Popliteal

The most common peripheral arterial aneurysm, popliteal aneurysm, occurs in approximately 1% of men aged 65 to 80 years.[37] Popliteal aneurysms are frequently bilateral and often occur concomitantly with aortic aneurysms,[34] making investigations for their presence an important part of the examination and workup of any patient with an AAA. As opposed to aortic aneurysms, the primary morbidity associated with popliteal aneurysms is acute thrombosis or embolization with resulting limb ischemia and potential limb loss, rather than rupture and hemorrhage.[38]

Visceral

There are different estimates of the prevalence of aneurysms occurring in the trunk or branches of the celiac and superior mesenteric arteries; a reasonable estimate is that these occur in approximately 1% of the population, based on postmortem series.[39] Splenic artery aneurysms lag behind only the aortoiliac segment as the second most common aneurysmal lesion in the abdominal cavity, and account for approximately 60% of all visceral or splanchnic aneurysms.[39] Splenic aneurysms occur more frequently in women and are also associated with portal hypertension. Pregnancy is a specific risk factor for rupture. Many visceral aneurysms can be managed with endovascular techniques including endografting or embolization. In the case of splenic artery aneurysms involving the hilum, laparoscopic splenectomy can also be performed (see Chapter 85).

Renal

The renal circulatory bed is characterized by its low resistance and high flow characteristics, and this profuse flow is an explanation for the location and frequency of renal aneurysms. Aneurysms involving the renal circulatory bed occur in approximately 0.1% of the population.[40] Renal artery aneurysms are often saccular rather than fusiform, and when associated with a disease concomitant condition, it is most often fibromuscular dysplasia. Renal aneurysms can also result from the full spectrum of associated aneurysmal causes, including connective tissue disorders, arteritides, trauma, and spontaneous dissection (see Chapter 128). The morbid sequelae of renal artery aneurysms include thrombotic and embolic events, poorly controlled hypertension, and rupture. Whereas the overall rates of rupture are rare, the risk of rupture is particularly elevated in the third trimester of pregnancy, with resulting maternal and fetal mortality rates of 70% and 100%, respectively.[41] Current recommendations for repair include size greater than 2 to 3 cm, lesions occurring in women of child-bearing age, refractory hypertension, flank pain, and hematuria. The size criteria for intervention are not based on rigorous data, and this may represent too aggressive an approach in some patient populations.[42] Both endovascular and open surgical reconstruction play a role in the treatment of these lesions.

Cerebrovascular

Whereas intracranial aneurysms are relatively common and represent a major area of therapeutic activity for neurosurgeons and interventional neuroradiologists, the extracranial cerebral arteries are rarely affected by aneurysmal degeneration. The few aneurysms that do occur in the carotid are in the internal, common, and external segments in order of decreasing frequency. Dissection, which may occur after trauma, can lead to late aneurysmal degeneration in both the internal carotid and vertebral artery territories (see Chapter 94).[43]

Upper Extremity

Subclavian artery aneurysms can result from the repetitive trauma associated with thoracic outlet syndrome.[44] Iatrogenic brachial pseudoaneurysms as a consequence of percutaneous arterial access are the only other upper extremity aneurysms that occur with any significant frequency (see Chapter 84).

MULTIPLE ANEURYSMS

Aortic

The fact that patients with a diagnosis of an infrarenal aortic aneurysm are more often found to have a concurrent thoracic aortic aneurysm or popliteal aneurysm has been known for many years. Crawford noted that more than 50% of patients with thoracic aneurysms also had abdominal aneurysms and that 12% of patients with abdominal aneurysms had thoracic aneurysms.[45] Gloviczki et al.[46] characterized their experience managing patients with multiple aneurysms during a 2-decade period in 1990, noting that this group represented only 3.4% of all aneurysm procedures performed at the Mayo Clinic during this period (Fig. 69.7). Patients with connective tissue disorders or other systemic conditions that predispose to aneurysmal degeneration obviously have a significantly higher prevalence of multiple aneurysms and recurrent aneurysm disease. These patients must be monitored closely throughout their lives for the development of aneurysms in both typical and atypical locations.

Peripheral

Popliteal aneurysm is the most frequently occurring peripheral aneurysm and is the most common aneurysm to be bilateral; synchronous and metachronous aneurysms in other sites are also common. Galland reviewed a 17-year experience with popliteal aneurysms and noted that 59% of the patients had bilateral aneurysms and 49% had coexisting AAAs.[47] Other peripheral aneurysms can occur in multiple locations, but their prevalence is far less, so they do not typically warrant a heightened suspicion for synchronous aneurysmal disease, as in the case of popliteal and infrarenal aortic aneurysms.

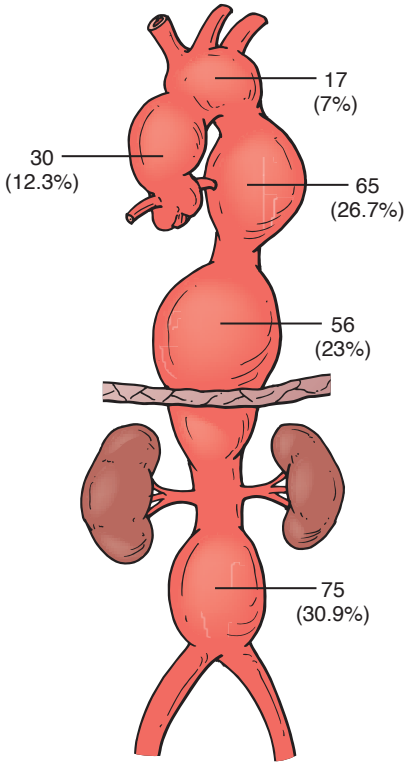

Figure 69.7 Incidence and location of 243 aneurysms in 102 patients with multiple aortic aneurysms. (From Gloviczki P, Pairolero P, Welch T, et al. Multiple aortic aneurysms: the results of surgical management. *J Vasc Surg*. 1990;11:19-27.)

Familial

Patients with a family history of aneurysm disease have a 30% increased risk of having an aneurysm, although the specific genetic explanation for this susceptibility has not been elucidated.[48] This is true for AAAs discovered outside the context of a diagnosed congenital disorder or connective tissue disorder. Although it is not completely understood, this is the most common familial risk factor for aneurysm disease and warrants screening of siblings and children of affected patients.

Connective Tissue Disorders

Connective tissue disorders are primary causes of familial aneurysmal disease and require careful genetic characterization and counseling. As the technology to completely delineate a single individual's genetic code becomes a clinical reality, this area of diagnosis and management is very likely to see significant changes in the coming years. Conditions with familial inheritance of aneurysmal disease include Ehlers-Danlos, Marfan, and Loeys-Dietz syndromes, and a variety of less common connective tissue defects (see Chapter 140).

Cystic Medial Degeneration

A familial pattern of thoracic aortic aneurysm has been termed *familial thoracic aortic aneurysm syndrome*. Whereas no overt connective tissue disorder has been recognized in these patients, they do share the characteristic of cystic medial degeneration.[49] The presence of a bicuspid aortic valve has been associated with a high incidence of ascending aortic aneurysm, and cystic medial degeneration has been proved by tissue biopsy in 75% of these patients.[50] Turner syndrome is also associated with ascending aortic aneurysm, aortic dissection, and bicuspid aortic valve.[51]

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The most recent comprehensive clinical practice guidelines for patients with abdominal aortic aneurysm.

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A comprehensive description of the history and evolution of aortic surgery. Important information regarding early approaches with rigid tubes, sutureless anastomoses, and a variety of other techniques that ultimately gave way to fabric prostheses and sutured anastomoses.

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CHAPTER 70

Aortoiliac Aneurysms: Evaluation, Decision Making, and Medical Management

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HISTORY

Since aneurysms of the aorta were first described in ancient Egyptian scrolls dating to 1550 BC, advances in the understanding of the anatomy, pathophysiology, epidemiology, and natural history of this entity have driven improvements in care.[1-3] During the era in which Galen produced the first detailed anatomic plates of abdominal aortic aneurysms (AAAs), Antyllus attempted treatment through ligation of these vessels, with poor results. In the 14th century, medical knowledge of aneurysms again advanced, as Vesalius used cadaveric dissections to help refine anatomic descriptions. Also in the late 14th century, Pare and Morgagni independently noted the development of aneurysms in prostitutes and correctly attributed them to syphilis.[3-5] The 20th century marked a period of rapid advances in the open surgical management of aortic aneurysms by proximal ligation or obliteration (Cooper, 1817; Matas, 1888), extra-arterial wrapping (Poppe, 1946), and direct reconstruction with autologous (Carrel, 1948; Dubost, 1951) or synthetic (Voorhees, 1952) material.[6-8] DeBakey and Cooley continued to advance the techniques of open aortic aneurysm repair.[9] Operative intervention techniques remained fairly static until the development of catheter-based intervention by Parodi, who performed the first endovascular stenting of an infrarenal aortic aneurysm in 1990.[10,11] Since the U.S. Food and Drug Administration (FDA) approved the first stent grafts for use in repair of infrarenal aortic aneurysms in 1999, endovascular techniques have overtaken traditional open repair as the most common approach to the elective management of this condition.

DEFINITIONS

A true arterial aneurysm is defined as an increase to 1.5 times the normal arterial diameter with involvement of all three anatomic layers. In the infrarenal abdominal aorta, an aneurysm is traditionally defined as a diameter greater than 3 cm or more than 50% larger than a normal proximal segment measured in either anteroposterior or transverse dimension in a plane

perpendicular to the longitudinal axis of the aorta. Although anatomic studies have identified a median-range diameter of 2.2- to 2.3-cm for the infrarenal aorta in 70-year-old Caucasian subjects, population studies have also identified variations in mean diameter at various levels of the aorta based on patient sex and race. This has led to the suggestion that truly evidence-driven guidelines may ultimately recommend different criteria for defining aneurysms and size thresholds for intervention by sex and race at each anatomic level.[12] The authors of the Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group concluded that variations in average aortic size based on age, sex, race, and body size (weight, body mass index [BMI] or BSA) were not of great enough magnitude to justify departing from the standard definition given previously.[13] Although pseudoaneurysms and penetrating aortic ulcers may also result in focal increases in arterial diameter, these entities differ in pathophysiology and are not evaluated by the same criteria as the more typical degenerative aneurysm.

EPIDEMIOLOGY

Although aneurysms may occur along the length of the aorta from the root through the bifurcation, the infrarenal aorta is the most commonly reported location, representing approximately 30% of aortic aneurysms.[14] Inferences regarding the affected patient cohorts, incidence, and prevalence of AAAs are drawn from autopsy and screening studies designed to target groups thought to be at increased risk for aneurysm, primarily based on age or sex (Table 70.1). These studies suggest a prevalence of aneurysms 4 cm or larger in approximately 1% of men between the ages of 55 and 64 years. This prevalence increases with advancing age by 2% to 4% per decade.[15,16] It has also been consistently demonstrated that AAAs occur with greater frequency in men,[14,17-19] smokers, and those with a family history of aortic aneurysm.

There is a direct correlation between the incidence of AAAs and the duration of smoking history[18] as well as decreased aneurysm growth rates in association with duration of smoking cessation. Although family history is reported in a small proportion of those with AAAs, it is a strong positive risk factor.[18] Additional risk factors with less strong associations include atherosclerotic disease, history of myocardial infarction, peripheral vascular disease, and hypertension.[19,26] Negative risk factors include female sex, African American race, and diabetes.[18,26]

Aneurysm incidence increases with age, peaking later in women than in men, although most screening studies have been conducted in primarily Caucasian populations. The Veterans Affairs Aneurysm Detection and Management (ADAM) study was a multicenter randomized trial study that documented that 99% of those with AAAs 4 cm or larger in diameter were male and 94% were white.[17]

Associated Aneurysms

The involvement of adjacent arterial segments is not uncommon in infrarenal AAAs, with 5% to 15% extending to the juxta- or suprarenal aorta and 10% to 25%[25] involving the iliac arteries. Synchronous lesions of the thoracic aorta (12%)[27] and femoral or popliteal artery (14% among male patients)[21] are also common. Popliteal artery aneurysms (PAAs) are the most common true peripheral artery aneurysms. The occurrence of PAAs in the general population is approximately 1%.[28] Risk factors for PAAs include age, male sex, presence of other arterial aneurysms, history of smoking, family history, cardiac disease, hypertension, and atherosclerotic disease. Careful evaluation for the presence of these lesions in patients with known AAAs is indicated, particularly given the potential for limb loss associated with undetected aneurysms of the popliteal artery.[22] Conversely, AAAs have been reported in 62% of patients with popliteal artery aneurysms and 85% of those with femoral artery aneurysms (see Chapter 83).[29,30]

Iliac artery aneurysms occur most frequently in the common iliac artery (CIA) (70%), typically in conjunction with an AAA. The largest published series of common iliac artery aneurysms (CIAAs) reports that 86% of patients with CIA aneurysms presented with concurrent or previously treated AAAs. Isolated aneurysms of the CIA are relatively infrequent (6.4% of patients), although approximately one-quarter of these are bilateral. Isolated aneurysms of the internal iliac artery (IAAA) are quite rare and thought to occur in conjunction with AAAs in less than 2% of cases. IAAAs are bilateral in 10.9% of cases. The defined size of an IAA is any vessel 1.5 times the diameter of the normal

TABLE 70.1 Prevalence of Abdominal Aortic Aneurysm by Age and Gender

Study Location	Lederle, USA[20]	Chichester, UK[21]	Viborg, Denmark[22]	Western Australia[23]	MASS UK[24]	Rotterdam, Netherlands[25]	Tromso, Norway[15]
N	73,451	15,775	12,628	41,000	67,800	5,419	6,386
Gender	Men and women	Men and women	Men	Men	Men	Men and women	Men and women
Age (years)	50–79	65–80	65–73	65–79	65–74	>55	55–74
Sampling dates	1992–1995	1988–1990	1994–1998	1996–1998	1997–1999	1994–1995	1994–1995
Date published	1997	1995	2002	2004	2002	1995	2001
Aneurysm prevalence	1.4% (1.4% in men, 0.2% in women)	4.0% (7.6% in men, 1.3% in women)	4.0%	7.2%	4.9%	4.1% men, 0.7% women	8.9% men, 2.2% women

vessel or a diameter greater than 1.85 in males and greater than 1.5 in females.[31] The prevalence of IAAs in patients with clinically relevant AAAs is anywhere from 15% to 40%. A retrospective study showed that 86% of patients who were diagnosed with an IAA had a corresponding AAA.[32] Risk factors for IIAs are thought to mirror those of other aneurysms. Although most IAAs are degenerative in nature, injury from penetrating trauma or iatrogenic injury from operative intervention in the area of the iliac arteries may also play a role in their development. There is also an association of IAAs with vasculitides, such as Behçet disease, fibromuscular dysplasia, Takayasu arteritis and connective tissue disorders. There have been reports of mycotic IAAs, but these are very rare.[33,34]

The natural history of iliac artery aneurysms, particularly those occurring in isolation, is less well understood but deserves special mention. The Mayo Clinic group reported a median expansion rate in CIAAs of 0.29 cm per year and reported no ruptures at less than 3.8 cm.[35] A recent review of the literature on IAAAs noted that these aneurysms are quite large when they initially present, likely due to an anatomic location that precludes detection on physical examination unless the aneurysm impinges on surrounding anatomic structures sufficiently to produce symptoms associated with the compression of nerves or urogenital/colorectal structures. Asymptomatic aneurysms, discovered by physical examination or incidentally through imaging, averaged 5.1 cm in diameter, whereas nonruptured and ruptured symptomatic aneurysms averaged 7.6 and 8.3 cm, respectively.[36]

Rupture Risk

Maximal AAA diameter is the standard basis for predicting rupture risk, with larger diameters associated with increasing risk of rupture (Table 70.2). The UK Small Aneurysm Trial reported an annual rupture rate of 2.2%, with most occurring in patients with an AAA diameter of 5 to 5.5 cm. This study also found that the risk of rupture was independently associated with female sex, larger initial AAA diameter, smoking, lower FEV_1, and higher mean blood pressure. Risk of rupture was not independently associated with age, BMI, serum cholesterol, or the ankle/brachial index. This study documented that females have a threefold increase in rupture risk compared with males with similar aortic diameters. Risk of rupture declined when hypertension was controlled or with smoking cessation.[37]

There are other features of AAAs in addition to diameter that correlate with increased risk of rupture. Saccular aneurysm morphology appears to portend an increased risk of rupture compared with fusiform aneurysms.[38] Certain imaging characteristics on CTA can also indicate an increased risk of rupture, including the presence of a dissection, mural thrombus, or a dissection of the peripheral calcification of the aneurysm sac.[39] The UK morphology of ruptured AAA study reported that the most likely site of rupture is in the middle third of the aneurysm at the point of greatest diameter.[40]

In discussing the natural history of AAAs, growth rate must be considered. This is challenging to assess on a consistent basis and depends on the imaging modality used for surveillance. In considering ultrasound-based assessment, it has been well documented that there is significant variability in diameter size depending on the ultrasonographer.[41] A Canadian study specifically showed that this variability is decreased when a measured change in diameter is greater than 0.78 cm.[42] Current practice guidelines indicate intervention based on AAA growth when the rate of expansion is greater than or equal to 10 mm in a 12-month period.[43]

TABLE 70.2 Twelve-Month Risk of Rupture Based on Abdominal Aortic Aneurysm Diameter

AAA Diameter (cm)	Rupture Risk (%)
3.0–3.9	0.3
4.0–4.9	0.5–1.5
5.0–5.9	1–11
6.0–6.9	11–22
>7	>30

AAA, Abdominal aortic aneurysms.

PATHOPHYSIOLOGY

The descending thoracic and abdominal aortas are formed through embryonic fusion of the paired dorsal aortas, which communicate with the developing heart via the aortic arches. The wall of the mature aorta is composed of three layers: the intima, with its single layer of endothelial cells; the media, made up of smooth muscle cells within a structural protein matrix; and the adventitia, a tough layer of collagen fiber and fibroblasts.

The embryologic process appears to give rise to regional heterogeneity in different parts of the aorta, with variation in the response of neural crest–derived smooth muscle cells of the thoracic aorta versus mesoderm-derived smooth muscle cells in the abdominal aorta. This regional variation clearly affects the secretion of and susceptibility to various cytokines and growth factors thought to be implicated in aneurysm development. This heterogeneity is also reflected in the tissue characteristics of the aortic media within different anatomic segments. In the thoracic aorta, the media contains 55 to 60 lamellar units, with adventitial vasa vasora penetrating the vascular zone of the outer layers, whereas there are 28 to 32 lamellar units in the abdominal aortic media. This makes the abdominal aorta relatively avascular compared with the more proximal aorta, relying more on the transintimal diffusion of oxygen and nutrients.[44]

Aneurysm formation has been associated with the inflammatory degeneration of the connective tissue matrix and smooth muscle cells of the aortic media and, less commonly, with inherited or sporadic defects of these components (Table 70.3). The accumulation of intraluminal thrombus (ILT), which has been described as "a biologically active neo-tissue," is associated with aneurysm progression. It is proposed that this effect is

TABLE 70.3 Connective Tissue Syndromes Associated With Abdominal Aortic Aneurysms

Syndrome	Gene	Defect	Inheritance Pattern
Marfan syndrome	FBN1	Defect in Fibrillin-1	Autosomal dominant pattern
Loeys-Dietz syndrome	*TGFBR1* gene mutations cause type I, *TGFBR2* gene mutations cause type II, *SMAD3* gene mutations cause type III, *TGFB2* gene mutations cause type IV, and *TGFB3* gene mutations cause type V	Overactive TGF-β pathway	Autosomal dominant pattern
Ehlers-Danlos vascular type (formerly type IV)	COL3A1	Defect in collagen type III	Autosomal dominant pattern
Familial abdominal aortic aneurysm[45-47]	Not specifically identified	ECM Defect in DAB2 interacting protein (DAB2IP) Defect in low-density receptor-related protein (LRP1)	Unknown

AAA, Abdominal aortic aneurysms; *ECM*, extracellular matrix; *TGF*, transforming growth factor.

mediated through a cascade of platelet activation ultimately leading to increased oxidative stress and proteolytic injury. The thrombus itself is laminated, progressing from an initial luminal layer with fresh thrombus and cross-linked fibrin to an outer layer in contact with the aortic wall, the latter being characterized by advanced fibrinolysis. At this level, plasmin serves to activate matrix metalloproteinases (MMPs) and TGF-β and participates directly in matrix protein degeneration. Oxidative injury may occur through enhanced oxidase activity or inhibition of antioxidants, both of which have been observed in human AAA tissue. Within ILT, the process of hemagglutination releases pro-oxidant free hemoglobin. The importance of the biologic activity of the ILT is underscored by the observation that increased thrombus burden is associated with an increased AAA growth rate even though wall stress modeling suggests modest reductions in local aortic wall stress with locally increased thrombus load. Wall thinning, medial loss of smooth muscle cells, elastin degradation, and adventitial inflammation have all been associated with the presence of ILT (Fig. 70.1). It has been suggested that the impact of thrombus burden may also be associated with aortic wall hypoxia.[44]

Although much attention has been focused on medial degeneration, marked changes in the adventitia have also been observed in AAAs. Inflammation—in the form of extensive periaortic and adventitial infiltration by lymphocytes, macrophages, and mast cells—is noted histologically. Adventitial degeneration is also characterized by extensive fibrosis. This fibrosis, driven by macrophage/TGF-β–mediated fibroblast proliferation and activation, may provide some degree of protection from rupture, but it may also be associated with pathologic retroperitoneal fibrosis, with adherence to and injury of adjacent retroperitoneal structures. Neoangiogenesis, typically limited to the adventitia and outer media, is also observed in AAAs.

Frank bacterial infection of the aortic wall is clearly associated with the development of mycotic aneurysms. It has been proposed that bacterial colonization of either the aortic wall or ILT may contribute to AAA formation and progression either directly or indirectly through alteration of the immunologic milieu. *Chlamydia pneumoniae* and oral flora, such as *Porphyromonas gingivalis* and *Streptococcus mutans*, have been identified in AAA tissue either through culture or isolation of bacterial DNA in tissue specimens.

DIAGNOSIS

History

Patients with AAAs are typically asymptomatic. Those who are symptomatic and previously undiagnosed often present with diffuse nonspecific abdominal and/or lower back pain. This pain is usually described as unique and different from their standard chronic abdominal or lower back pain. Patients may also state that they can feel pulsations in their abdomen. Those who are thin may state that they can see a pulsatile mass in their abdomen. Certainly there is a high probability that these patients have as part of their medical history hypertension, atherosclerotic disease, and tobacco usage.

Physical Examination

An AAA may be detected on physical examination as a palpable pulsatile (expansile) mass, most commonly supraumbilical and in the midline. The location, however, may be variable, as aortic tortuosity can result in a lateral and/or infraumbilical location. The sensitivity of physical examination depends on the aneurysm's size and the patient's habitus. Owing to the previously mentioned high probability of concomitant femoral artery aneurysms and PAAs, these areas should also undergo examination.

Ultrasound

The detection and characterization of aneurysms is greatly aided by modern imaging techniques. Ultrasound (US) examination has been demonstrated to afford excellent sensitivity and

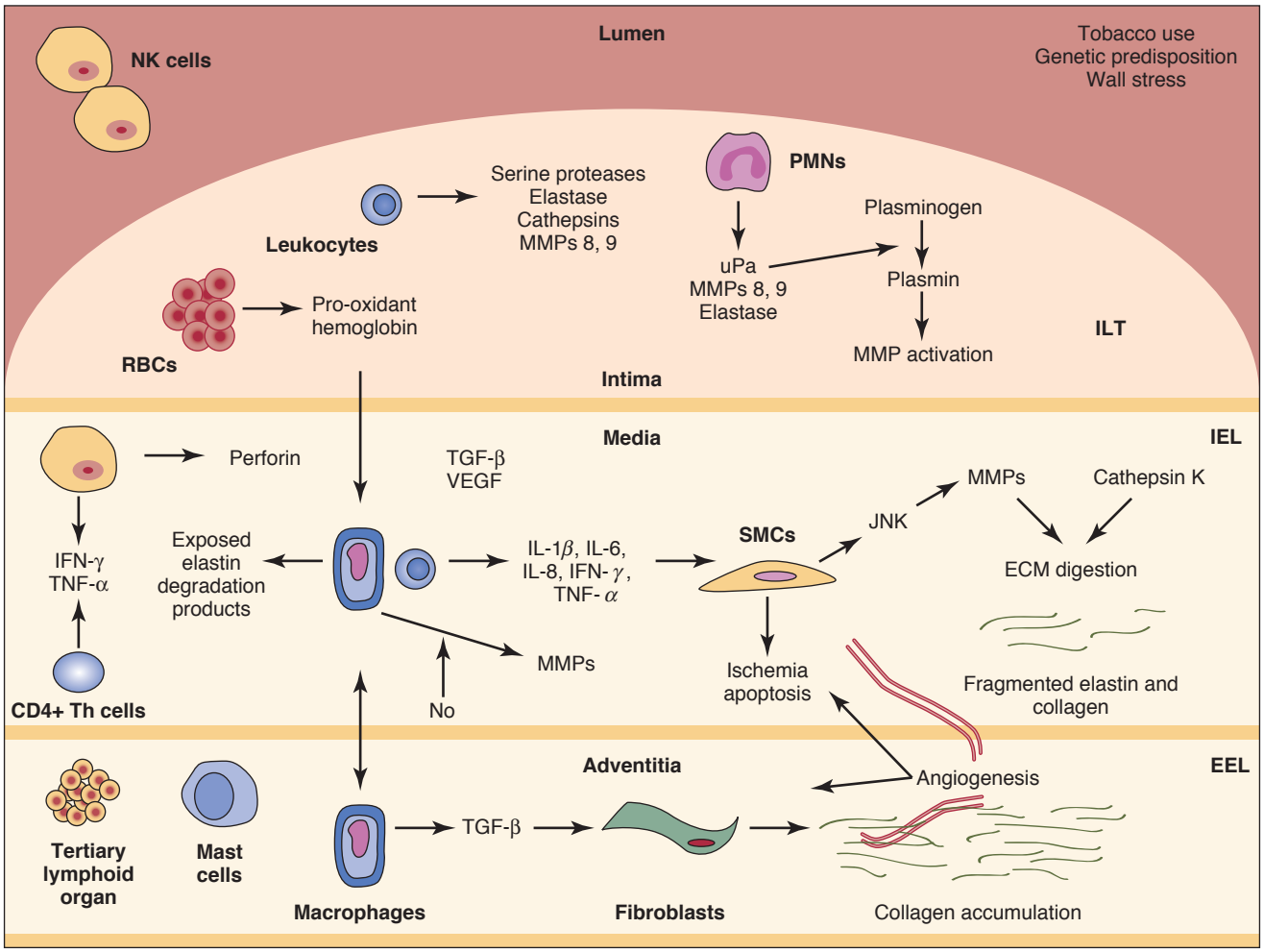

Figure 70.1 Schematic diagram demonstrating the complexity of abdominal aortic aneurysm pathogenesis.[41] *ECM*, Extracellular matrix; *EEL*, external elastic lamina; *IEL*, internal elastic lamina; *IFN-γ*, interferon-γ; *IL*, interleukin; *ILT*, intraluminal thrombus; *JNK*, c-Jun N-terminal kinase; *MMP*, matrix metalloproteinase; *NK*, natural killer cell; *NO*, nitric oxide; *PMN*, polymorphonuclear cell; *RBC*, red blood cell; *SMC*, smooth muscle cell; *TGF-β*, transforming growth factor-β; *Th*, T-helper cell; *TNF-α*, tumor necrosis factor-α; *uPa*, urokinase-type plasminogen activator; *VEGF*, vascular endothelial growth factor. (English SJ, Upchurch GR Jr. Pathogenesis of abdominal aortic aneurysms. In: Stanley JC, Veith FJ, Wakefield TW, eds. *Current Therapy in Vascular and Endovascular Surgery*. 5th ed. Philadelphia, PA: Elsevier; 2014:203-206, with permission).

specificity (Fig. 70.2). US may be limited by patient habitus or bowel gas, but, importantly, it avoids the complications associated with more invasive testing, radiation, and exposure to a contrast medium. US is an excellent choice for screening and evaluation of diameter. It must also be noted that US is not an ideal method for detecting rupture, as it is unable to image all portions of the aortic wall. In addition, in the nonfasting emergently examined patient, ideal image acquisition may be precluded. It has been estimated that US may fail to detect up to 50% of aneurysm ruptures.

Computed Tomography

Computed tomography (CT) provides excellent imaging of AAAs, with greater reproducibility of diameter measurements than US. CT, particularly with the adjunctive use of iodinated contrast to perform a CT angiogram (CTA), provides a wealth of anatomic information, including defects in vessel calcification,

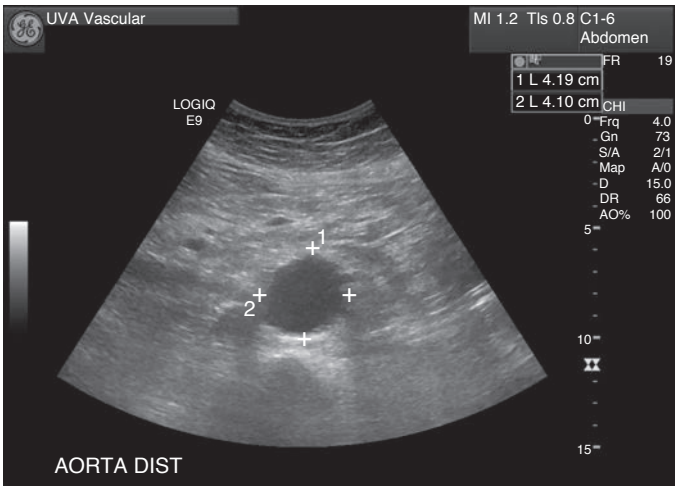

Figure 70.2 Ultrasound of the abdominal aorta documents an abdominal aortic aneurysm noted with maximal measurement of 4.19 by 4.10 cm in the anteroposterior and transverse dimensions.

Figure 70.3 Computed tomographic angiogram of the abdomen and pelvis shows an infrarenal abdominal aortic aneurysm measuring approximately 5.6 by 6.5 cm with extensive mural thrombus along the right lateral posterior aspect.

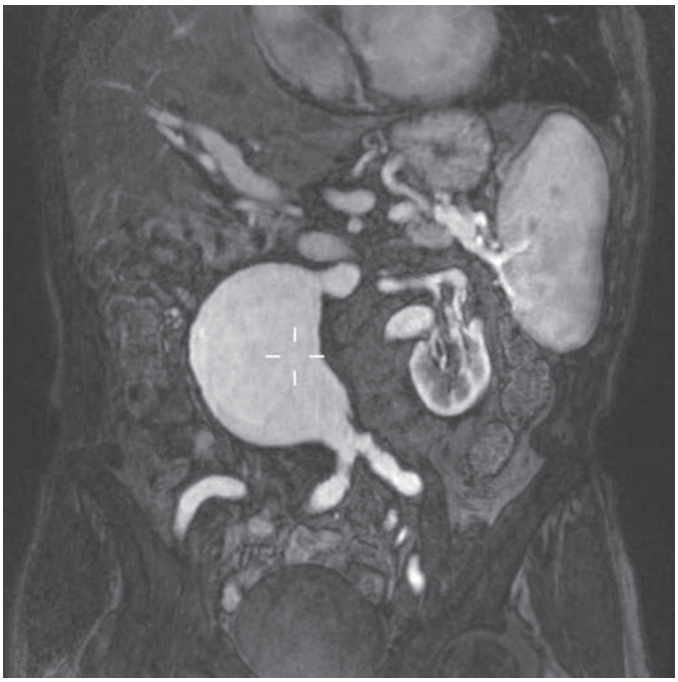

Figure 70.4 Magnetic resonance (MR) angiogram of the abdomen and pelvis performed on a 3 Tesla MR scanner with contrast. Imaging shows an infrarenal abdominal aortic aneurysm measuring 7.8 by 7.8 cm.

thrombus, and concurrent arterial occlusive disease. CTA also permits invaluable multiplanar and three-dimensional reconstruction and analysis for operative planning (Fig. 70.3). Drawbacks associated with CTA include substantial exposure to radiation, particularly in the setting of serial examinations, and the use of iodinated contrast media is problematic in a population with a high incidence of associated kidney disease (see Chapter 27).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are, like CT, quite sensitive in the detection of AAAs (Fig. 70.4). Unlike CT, MRI does not demonstrate aortic wall calcification, which may be quite important in operative planning. Although the study does not require the use of iodinated contrast, MRA utilizes gadolinium, which has been associated with the development of nephrogenic systemic fibrosis in patients with a low GFR. The availability of MRI may also be limited by the presence of incompatible metallic implants or foreign bodies. However, the ability to acquire dynamic images throughout the cardiac cycle may ultimately prove clinically useful (see Chapter 28).[44]

Angiography

Due to its invasive nature, contrast angiography is not the preferred method for screening or surveillance for AAAs. Typically, per the imaging guidelines developed by the American College of Radiology, it is reserved for cases where further detailed characterization of an aneurysm is required or for intervention, as in the case of preoperative embolization of an accessory renal artery prior to endovascular aneurysm repair.[48]

SCREENING AND SURVEILLANCE RECOMMENDATIONS

Guidelines for screening and surveillance for AAAs have been developed and promulgated by a variety of sources from various professional organizations and national healthcare entities. These guidelines are based on several key population-based screening studies. Their final recommendations are informed by a range of considerations, including the quality of evidence, the characteristics of the screening modality, and cost.[49]

There is controversy around the selection of specific populations for initial screening, including several issues such as the age at which screening should be performed, the influence of additional risk factors—such as smoking and family history for AAA on screening recommendations—as well as the appropriateness of screening for women (Table 70.4).

The screening of women with additional risk factors for aneurysm remains particularly controversial.[51] There is evidence of a strong association between smoking and AAA formation in women. Although mortality data suggest that the gender differences in aneurysm-related mortality narrow with advancing age as aneurysm prevalence rises in women, the overall benefit of screening has been questioned, considering poorer postintervention outcomes in women.[55] The paucity of population-based data on women is problematic, particularly to the extent that this complicates the demonstration of cost-effectiveness.

TABLE 70.4 Screening and Surveillance Recommendations

Year	Organization	Initial Screening	Referral for Treatment	Surveillance	Repeat Screening
2010	European Society for Vascular Surgery[49,50]	• Men should be screened with a single US at age 65 • Population screening of older female smokers does not reduce incidence of rupture	• Men should be considered for intervention when maximal diameter reaches 5.5 cm		
2009	Society for Vascular Surgery[51]	• One-time US screening for men aged ≥65 • Screening recommended for first-degree relatives of patients with AAA	• Smoking cessation is recommended to reduce risk of AAA growth and rupture • Elective repair is recommended for patients with a fusiform AAAs ≥5.5 cm in maximal diameter		
2007	National Screening Committee (UK)[50]	• US screening available for all men aged ≥65			
2007	Canadian Society for Vascular Surgery[52]	• All men aged from 65 to 75 to be screened • Individual selective screening for those at high risk: women aged > 65 with high risk secondary to smoking, cerebrovascular disease, and family history • Men aged < 65 with positive family history			
2005	American College of Cardiology/American Heart Association[53]	• Screening for men aged ≥65 • Screening for women aged 60–85 with a family history of AAA	Intervention is not recommended for asymptomatic infrarenal or juxtarenal AAAs if they measure less than 5.0 cm in diameter in men or < 4.5 cm in diameter in women	Patients with infrarenal or juxtarenal AAAs measuring 4–5.4 cm in diameter should be monitored by ultrasound or computed tomographic scans every 6–12 months to detect expansion	
2004	Society for Vascular Surgery/American Association for Vascular Surgery/ Society for Vascular Medicine and Biology[54]	• Screening for all men aged 60–85 • Screening for women aged 60–85 with a family history of AAA			

AAA, Abdominal aortic aneurysm.

Controversy also inevitably attends the suggestion that screening not be offered to other subgroups in whom racial or ethnic background is apparently associated with decreased aneurysm incidence.

Recommendations regarding the follow-up and rescreening of patients with initial aortic diameters less than 3 cm is controversial, particularly in considering cost-effectiveness. The incidence of AAAs exceeding 4 cm following "negative" initial screening is lower than that after initial screening, but both the ADAM trial and others have demonstrated that a subset of patients deemed "normal" at a first screening will go on to develop aneurysms susceptible to rupture.[19,26]

Payer policies regarding reimbursement do not precisely track any of the recommendations. Medicare, for instance, because of the Screening Abdominal Aortic Aneurysms Very Efficiently (SAAAVE) act, reflects an intermediate approach in offering a screening benefit for men with a personal smoking history and men *or* women with a family history of AAAs as part of a "Welcome to Medicare Physical Examination." This benefit was initially available only during the first 12 months of enrollment. This benefit was subsequently expanded in 2011, under the Patient Protection and Affordable Care Act (ACA), to an annual wellness visit that is free to Medicare beneficiaries. Early evaluation suggests that the uptake rate has remained low

(approximately 10% of eligible Medicare beneficiaries) in the early years of the program.

MEDICAL THERAPY

Medical Management

The current approach to the medical management of infrarenal aortic aneurysms focuses mainly on small aneurysms. Although multiple agents—including statins, angiotensin converting enzyme (ACE) inhibitors, β-blockers, and antibiotics including tetracycline and doxycycline—have been shown in animal models to slow aneurysm progression, effectiveness has not been clearly demonstrated in humans. Targeted mechanisms for potential medical management include the inhibition of immune function, dyslipidemia, hypertension, connective tissue degradation, oxidative stress, and vascular smooth muscle degradation.

It has also been proposed that increasing aortic blood flow through exercise may slow the growth of aortic aneurysms. However, this has not been proven in human modeling. It has been shown that patients with small aneurysms tolerated exercise programs well for the 3 years of the study. Concurrently, this same study showed that there was no significant increase in the size of AAAs during that time period.[56]

Beta blockers have been shown in animal models to be effective in stopping the expansion of AAAs.[57,58] Some earlier small randomized human trials supported this claim. However, more recently conducted large randomized controlled trials did not find a significant reduction in growth of AAAs in patients on beta-blocker therapy.[59,60]

Other antihypertensive medications have also been studied to determine their effectiveness in inhibiting AAA growth.[61-64] ACE inhibitors were reviewed with initial reports from small, retrospective studies resulting in positive effects in helping slow the growth of small aneurysms.[65] Again, further investigation in larger retrospective studies refuted these early claims and showed no demonstrable effect.[66,67] In fact, the UK small aneurysm trial indicated an increase in the growth rate of aneurysms in patients taking ACE inhibitors.[68] Although ACE inhibitors themselves have not been shown to significantly affect aneurysm growth, overall control of hypertension and initiation of statin therapy have a positive effect on the perioperative risk of those who will later undergo operative intervention.

Doxycycline has been the subject of many trials, as it inhibits the activity of multiple MMPs. Although doxycycline has been shown to be effective in multiple animal models,[69-72] this finding has not yet translated into humans. A decrease in inflammation with doxycycline was found but no change in aneurysm growth rate was noted as compared with placebo.[73,74]

Statin therapy has also been shown in animal models to slow the expansion of AAAs, but once again it has not clearly been shown to be effective by any randomized controlled trials in humans.[75-77] The UK Heart Protection Study showed that the requirement for AAA repair was unaffected by statin therapy. This same trial, however, showed a relative reduction of 22% in major adverse cardiovascular events.[78]

The use of antiplatelet agents to reduce thrombus burden has been proposed as a mechanism to slow aneurysm expansion. In rat models, antiplatelet agents were shown to reduce AAA expansion.[79,80] However, no randomized control trials have shown direct correlation of reduction of AAA expansion with the use of antiplatelet therapy in humans. In summary, to date, there is no definitive evidence to suggest any specific medical management strategy slows the growth rate of AAAs.

INDICATIONS FOR INTERVENTION

In general, the size criterion for elective repair is 5.5 cm for men and 5 cm for women or a 12-month growth rate of equal to or greater than 10 mm in both sexes. Both the UK small aneurysm trial and the ADAM trial documented that surveillance of aneurysms between 4 and 5.5 cm is safe with compliant patients. However, in the ADAM trial, over 80% of patients with aneurysms between 5 and 5.4 cm underwent eventual repair. Additionally, over 60% of patients initially assigned to the surveillance groups in both trials eventually underwent repair. With 10-year follow-up in the UK small aneurysm trial, this percentage increased to 74%. Additional indications for elective or early intervention included saccular aneurysms, dissection of mural thrombus, or fracture of saccular calcification. It has been shown that elective repair of asymptomatic AAAs less than 5.5 cm in diameter provides no survival benefit as compared with surveillance and elective repair once the AAA has reached traditional size criteria.[81]

For those patients who are symptomatic or have suffered rupture, there is no specific size criterion for repair. For patients who can tolerate repair, whether endovascular or open, intervention should be offered. An algorithm for determining when to intervene is described (Fig. 70.5).

The difficulty in the overall consideration of operative intervention is that early intervention in certain patients may be beneficial, especially when operative risk is less than rupture risk and/or potential mortality due to rupture. Factors that impact aortic rupture risk include the initial maximal aneurysm diameter, rate of growth, and morphology. One should also consider elective operative mortality risk, life expectancy, and patient preference before proceeding with AAA repair.

A secondary consideration is the decision to pursue open versus endovascular intervention. It has been shown that long-term mortality is equivalent at approximately the 2-year mark whether open or endovascular repair is performed. However, endovascular intervention offers clearly reduced early morbidity and mortality, particularly in patients with significant comorbidities. Schermerhorn and colleagues argue that early intervention may be cost-effective in younger patients with larger aneurysm diameters.[82]

Risk Calculator

With increasing sophistication of outcomes research, including the establishment of high-quality prospective registries, risk calculators have been developed enabling more patient-specific determination of risk when operative intervention is under

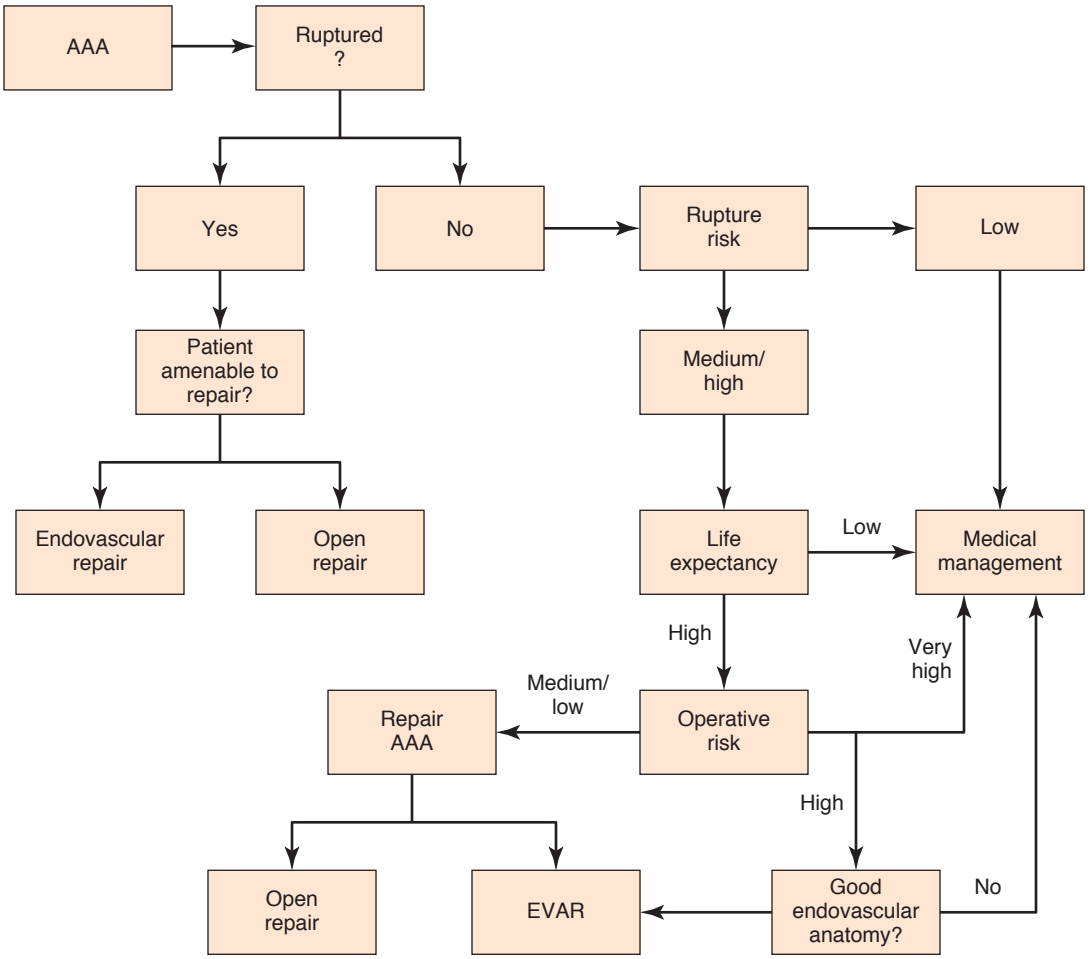

Figure 70.5 A simple algorithm for the management of patients with abdominal aortic aneurysms (AAAs). *EVAR*, Endovascular aneurysm repair.

consideration. The provision of more risk-specific information for patients with particular comorbidities is quickly becoming the standard of care, and it is recommended by the centers for Medicare and Medicaid as a discussion point during the informed consent process. Risk calculators are easily found on the Internet and are available in downloadable applications for a tablet or mobile phone. Berteges et al. reported the Vascular Study Group of New England (VSGNE) risk index specifically for patients undergoing carotid endarterectomy, lower extremity bypass, and endovascular or open repair of infrarenal AAAs.[83] As compared with previously used risk calculators, this one, explicitly derived for particular vascular interventions, was better at predicting the actual rates of postoperative cardiac events. As compared with previously used risk calculators, it was found that risk calculators that were not vascular-specific clearly underestimated the number of postoperative cardiac events in these patient cohorts.[84] The Society of Vascular Surgery provides online access to this risk calculator for intervention-specific events. For open AAA repair, the calculator considers the following patient and procedural variables: serum creatinine, the presence of chronic obstructive pulmonary disease, the anticipated level of distal anastomosis, planned proximal aortic clamp position, BMI, race, previous coronary artery bypass graft or percutaneous coronary intervention, results of patient's stress test within past 2 years, history of congestive heart failure, and age.

FUTURE DIRECTIONS

Endograft technology continues to evolve to improve outcomes and broaden current indications for use. Similarly, advances in our understanding of the molecular pathophysiology of aneurysm formation, growth, and rupture will drive the next round of advances in diagnosis and therapy. Better characterization of the serologic profile during aneurysm growth and particularly around the time of rupture may yield opportunities to develop biomarker screening for existing aneurysms and for evidence of active progression and impending rupture. As an example, future care of the AAA patient may involve measurement of circulating plasma levels of peptides associated with collagen and elastin degeneration during proteolysis of the extracellular matrix (ECM).[85]

Imaging interpretation and technology may also help with advancements in dealing with AAAs. At its most basic level, this may simply reflect the incorporation of observed characteristics of aneurysms into the interpretation of existing imaging

technology to provide the clinician parameters for consideration beyond simple maximal aneurysm diameter and gross morphology. Disruption of the ILT by fresh hemorrhage, yielding a "crescent sign" on CT or three-dimensional ultrasonographic imaging, may be used to suggest impending rupture. As calcification of the external media has been observed to be protective against growth, improved characterization of the degree and properties of observed calcification may also be used to inform imaging interpretation and individual patient risk. Better definition of the characteristics of aortic ILT and wall inflammation may also lead to the assessment of inflammatory cell activity using MRI, scintigraphy, or radionucleotide scans.

The most ambitious goal, however, remains the translation of the growing body of knowledge regarding the biologic mechanisms of aneurysm formation, growth, and rupture into effective medical therapy. Beneficiaries of these advances will include patients with small aneurysms as well as those with larger aneurysms who are medically ineligible for repair. Promising current targets include: 1) interruption of the inflammatory cascade leading to the degeneration of medial smooth muscle and ECM through MMPs 2, 8, and 9 as well as inflammatory cytokines, including TNFs and interleukins IL1β, IL-4, IL-6, and IL-8; 2) suppressing neoangiogenesis, which characterizes adventitial changes; and 3) minimizing the oxidative injury associated with ILT.

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CHAPTER 71

Abdominal Aortic Aneurysms: Open Surgical Treatment

EDWARD Y. WOO and SCOTT M. DAMRAUER

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Open abdominal aortic aneurysm (AAA) repair, initially described in 1952 by Dubost et al., has undergone continuous evolution and refinement.[1] Current outcomes with elective open repair are excellent, with perioperative mortality rates between 1% and 7% depending on center volume and surgeon experience.[2-4] Notably, a contemporary meta-analysis of the randomized trials of endovascular aneurysm repair (EVAR) demonstrated a 3.3% 30-day mortality among the combined 1342 patients repaired via the open technique.[5] This is concordant with a 4% mortality reported for the highest volume centers in an administrative database study using the National Inpatient Sample (NIS),[2] although single-institution case series and carefully controlled registry studies have reported even better results.[3,6]

Since its introduction in the early 1990s, EVAR has dramatically transformed the management of AAA, with significant reductions in the number of open aneurysm repairs performed over time in both the Medicare database[7-10] and the NIS.[11] In

addition, high-quality randomized controlled studies have demonstrated better short- and medium-term outcomes, and equivalent long-term outcomes, with EVAR, as compared with open repair.[12-15] This has propelled EVAR to become the primary mode of therapy for the majority of patients with AAA, with open repair reserved for those with increasingly complex anatomies or coexisting disease processes that prohibit them from an endovascular repair.[16-18] Nonetheless, open AAA repair remains a cornerstone of vascular surgery.

INDICATION FOR OPEN REPAIR

Anatomy

In the current era of endovascular therapy, open repair tends to be reserved for patients who cannot undergo EVAR. Despite the advances in device design, there remain a number of anatomic constraints that mandate open repair (Fig. 71.1).[19] No aortic neck or a hostile aortic neck is the leading indication for open

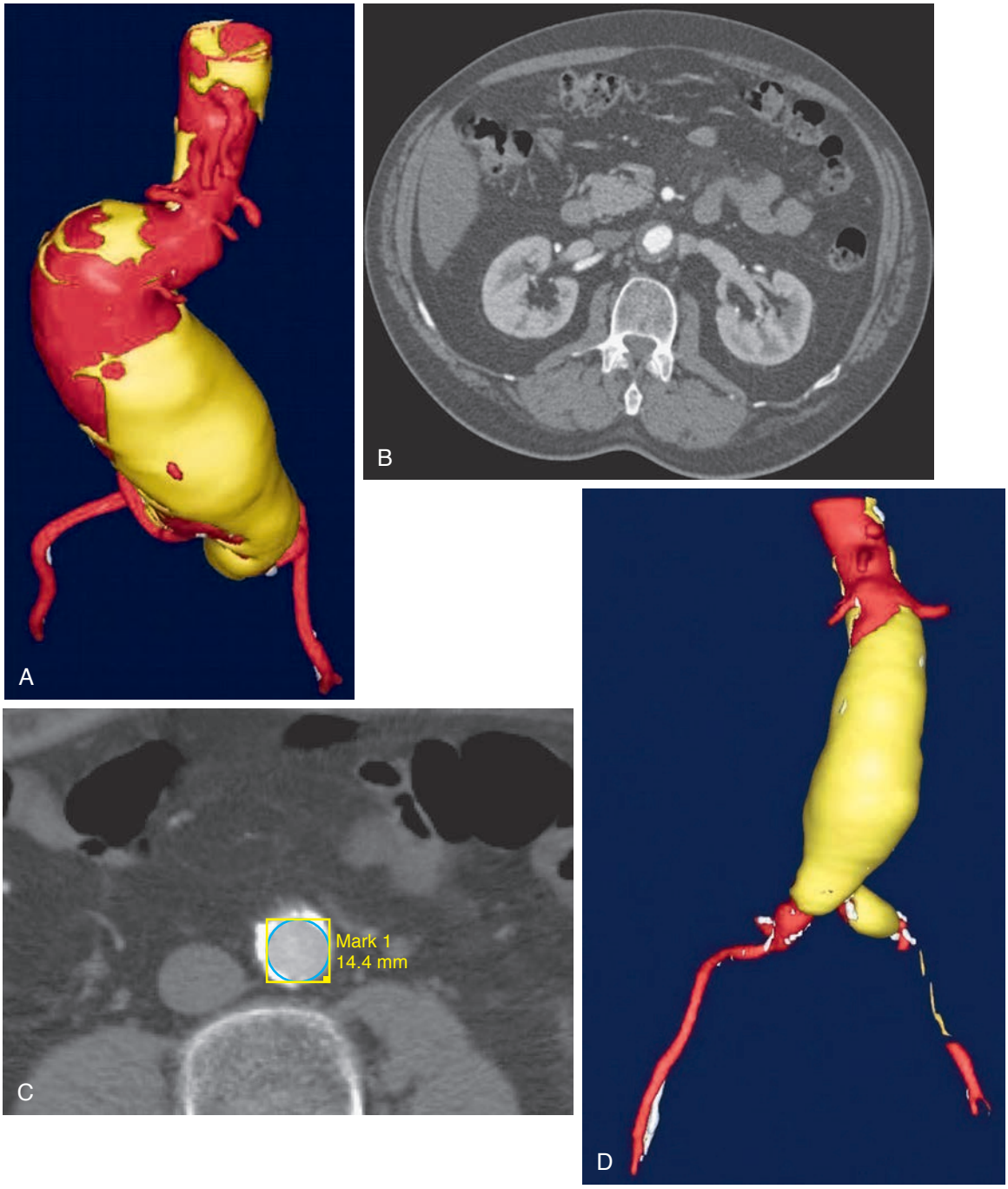

Figure 71.1 Axial images and three-dimensional computed tomographic angiography reconstructions demonstrating challenging aneurysm anatomy including a short, angled neck (A), circumferential thrombus (B), narrow calcified distal aorta (C), and bilateral common iliac artery aneurysms and left external iliac artery occlusion (D).

repair.[18] Proximal aortic necks that are short, angled, trapezoidal, have a high burden of thrombus, or are heavily calcified can compromise seal.[20-22] These patients are often better served with open repairs.

Anatomic constraints in the distal aorta and iliac arteries can also be preferentially treated with open aneurysm repair.[23] Likewise, iliac artery occlusive disease, especially chronic total occlusion, can mandate open repair for reasons pertaining to both access and treatment. Concomitant common or external iliac artery aneurysms may also represent indications for open repair, especially in situations in which internal iliac artery patency needs to be preserved, such as in claudicants and patients at risk for colonic, pelvic, and spinal cord ischemia (SCI).[24] None of these cases provide an absolute indication for open repair, especially with the introduction of newer devices such as branched endografts for the iliac arteries.

Endovascular Aneurysm Repair Conversion

Failure of a previous endograft due to migration or recalcitrant endoleak that is unable to be resolved via endovascular means requires open aneurysm repair. Due to the fibrosis and inflammation caused by the endograft, these operations can be significantly more complex than de novo AAA repair, and are associated with increased operative time, length of stay, and mortality.[25,26] Unless the EVAR explant is being performed for infectious indications, the endograft does not have to be completely removed, and in fact, it may be more expeditious to leave intact parts of the graft in situ. A recent series of 22 partial explants demonstrated no complications related to residual device components with 26 months of follow-up.[27]

Infection

Infection either of the native aorta or of a previous open or endovascular repair requires an open operation for definitive therapy. Endovascular salvage has been described, but this would be considered more of a palliative alternative or temporary bridge to open repair.[28,29] In cases of an infected prior aortic graft, excision of all prosthetic material and extra-anatomic reconstruction has long been the gold standard, but recent data suggest that the use of an aortic homograft[30] or rifampin-soaked Dacron may be equally efficacious in treating the infection.[31-33]

Additional Circumstances

A number of special circumstances can also influence the decision to proceed with open aneurysm repair. The presence of a horseshoe kidney with multiple renal and isthmus arteries originating from the aorta and iliac arteries[34] is best served with open repair so that these vessels will not be excluded.[35] Likewise, patients in which the patency of the inferior mesenteric artery (IMA) needs to be maintained, such as those with bilateral hypogastric artery occlusion, SMA stenosis/occlusion, or previous colectomy, may require open aneurysm repair as well.

PREOPERATIVE ASSESSMENT AND PLANNING

Careful patient selection and preparation is critical to obtaining excellent outcomes. Because of the physiologic derangements that occur as a result of the hemodynamic stress of an aortic cross-clamp, a detailed understanding of the patient's cardiac, pulmonary, and renal function is necessary to determine who is a candidate for open repair. In patients with a history of significant recent weight loss, nutritional parameters may be predictive of perioperative complications. Similarly, in patients with a history of liver disease and cirrhosis, appropriately tailored preoperative studies should be considered. Other subsets of patients require special consideration, such as those with a history of cerebrovascular or Parkinson disease. In these individuals with diminished physiologic reserve or compromised baseline functional status, it must be determined whether the patient's current and anticipated postoperative quality of life are sufficient to merit proceeding with an elective operation. This is especially pertinent in the very elderly, in which case postoperative complications may condemn the patient to long-term skilled nursing care and permanent loss of independent functional status.

Preoperative Imaging

Computed Tomography

Although CT angiography (CTA) with three-dimensional reconstructions, which allows for accurate anatomic measurements of a vessel's true cross-sectional diameter and center-line length (Fig. 71.2), is invaluable for EVAR,[36-39] it is also helpful for planning open repair. CTA visualizes aneurysm angulation, arterial tortuosity, arterial wall calcification, and intravascular thrombus (Fig. 71.3), which is useful for planning the best approach and clamp sites. A detailed view of the proximal aneurysm neck allows the involvement of the visceral aortic segment to be accurately determined (Fig. 71.4).[40,41] From this, the need for a suprarenal or supraceliac clamp site can be anticipated and potential clamp sites examined for the presence of heavy or circumferential calcification or thrombus. Concomitant occlusive disease of the visceral vessels and aortoiliac segment is also readily apparent on CTA, allowing decisions regarding the need for endarterectomy or complex reconstruction to be made preoperatively.[42-44]

CTA also provides valuable information about the venous and visceral anatomy that might alter the operative plan—the presence of a retroaortic or circumferential renal vein. Likewise, multiple renal arteries or a horseshoe kidney can affect both clamp site selection and arterial reconstruction. Appropriate visualization of the distal anatomy is also important. Concomitant stenotic, occlusive, or aneurysmal disease will influence the site of distal reconstruction, as well as the need for additional procedures. For example, additional graft limbs may be needed to preserve IMA or hypogastric flow. In addition, severe stenotic or occlusive disease can be bypassed at the time of the reconstruction.

Figure 71.2 Three-dimensional computed tomography reconstructions allow for accurate, inline measurement of aortic lengths and true cross-sectional diameter.

Finally, the rate of incidental findings on CTs obtained for AAA is not inconsequential,[45,46] and in certain circumstances, such as the diagnosis of an advanced malignancy, may take precedence over aneurysm repair.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) may also be used for preoperative planning. It has been shown to be just as accurate as CT in the determination of aneurysm size and extent, as well as in the evaluation of concomitant occlusive disease.[47-49] In patients with inflammatory aneurysms, it may offer more information regarding the extent of the inflammatory process.[50] MRA, however, does not offer information on the extent of calcification and sometimes can overestimate stenotic disease. Our preference, and that of most institutions, is to use CT.

OPERATIVE TECHNIQUE

There are two widely practiced approaches to open aneurysm repair: transperitoneal and retroperitoneal. Various other methods (beyond the scope of this chapter) have been described, including minilaparotomy,[51-54] laparoscopic,[55-59] and robotic approaches (see Chapter 62).[60-62]

Selecting the Approach

Because the goal of any approach is to obtain adequate exposure of the affected aortic segment, both transabdominal and retroperitoneal approaches will be technically equivalent in many situations. Under these circumstances, selection of approach should be determined by surgeon preference and familiarity.

Some situations, however, would be best treated with one technique over another. The transperitoneal approach offers rapid access to the infrarenal aorta with little need for complex patient positioning and is ideal for use in emergencies. In addition, for surgeons unfamiliar with the retroperitoneal approach, the transperitoneal offers a more comfortable approach to the aorta. As compared with the retroperitoneal approach, it also offers better, but not exclusive, access to the right renal artery and the right internal and external iliac arteries, as well as the femoral arteries. It is, however, more difficult to expose the visceral aortic segment from this approach.

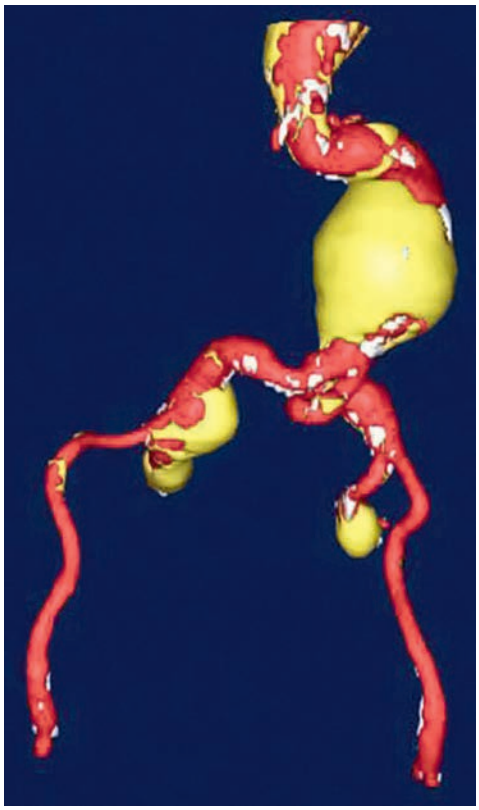

Figure 71.3 Three-dimensional computed tomography reconstruction showing an abdominal aortic aneurysm with tortuous proximal aorta and tortuous bilateral iliac artery aneurysms.

Figure 71.4 Axial computed tomographic angiography image showing visceral involvement in a type IV thoracoabdominal aortic aneurysm.

The retroperitoneal approach, usually via a left 10th interspace incision, allows for superior exposure of the visceral and supraceliac aorta as well as the left renal artery. This is useful in managing patients with pararenal aortic aneurysms and type IV thoracoabdominal aortic aneurysms. In addition, in patients who have undergone previous abdominal operations, it avoids the risk of "redo laparotomy" and eliminates the difficulties posed by intraabdominal adhesions. It may also offer advantages in obese patients by allowing the abdominal contents to fall away from the surgical field.[63,64] Although exposure of the right internal and external iliac artery can be more difficult from this approach, it can still be performed with appropriate careful dissection.

A number of both retrospective cohort and randomized trials have compared the outcomes of patients undergoing aneurysm repair using transperitoneal and retroperitoneal approaches. Depending on the study, retroperitoneal repair has been associated with significantly decreased postoperative fluid requirements, pulmonary edema, pneumonia, respiratory failure, postoperative ileus, shorter length of intensive care unit and overall hospital stays, shorter time to full recovery, and less costs.[64-67] Other studies have disputed this, showing equivalency between the two procedures regarding these variables.[63,68]

TRANSPERITONEAL REPAIR

Exposure (See Chapter 54)

The patient is positioned supine on the operating table with the arms abducted, and the abdomen is prepped and draped from the nipples to the knees. A midline incision is made. The omentum and transverse colon are retracted cephalad, and the small bowel is packed in the right hemiabdomen. A self-retaining retractor, such as the Bookwalter (Codman and Shurtleff, Inc., Raynham, Massachusetts) or Omni (Omni-Tract, St. Paul, Minnesota) retractor, greatly facilitates exposure and should be set up at this point.

To expose the aorta, the ligament of Treitz is divided, the third and fourth portions of the duodenum are reflected to the patient's right, and the periaortic lymphatic and connective tissue is ligated and divided (Fig. 71.5). Care must be taken to avoid injury to the inferior mesenteric vein; this structure can, however, be divided to facilitate exposure. The incision in the posterior peritoneum is then continued caudally in this plane to expose the entire infrarenal aorta. Although starting to the left of the aorta at the ligament of Treitz, the incision in the posterior peritoneum should course to the right of the aortic midline to prevent injury to the IMA, sigmoid mesentery, and autonomic nervous plexus at the bifurcation (Fig. 71.6). In cases in which a tube graft will be used and the distal anastomosis will be to the aorta itself, the dissection does not need to proceed beyond what is necessary to obtain distal control at the level of the bilateral proximal common iliac arteries.

Pararenal Aorta

A growing proportion of patients who require open aneurysm repairs have aneurysms with short or no infrarenal neck.[16] These juxtarenal aneurysms require the placement of a suprarenal clamp, which necessitates additional proximal aortic exposure. To do so, the posterior peritoneum is opened cephalad to the level of the renal veins. Note should be made as to location of the left renal vein on the preoperative CT scan. If it is anterior, as in most cases, it can be mobilized to gain more proximal

aortic exposure by dividing the gonadal, adrenal, and lumbar branches (Fig. 71.7A). Alternatively, it can be divided safely, albeit with an increased risk of postoperative renal insufficiency.[69-71] The decision to divide the left renal vein needs to be made before it is aggressively mobilized, because once it is divided, the gonadal, adrenal, and lumbar branches must be preserved in order to maintain adequate venous drainage; to facilitate this and maximize exposure, this should be done as close to the inferior vena cava as possible (see Fig. 71.7B). If a retroaortic or circumferential left renal vein is present, care must be taken during placement of the proximal clamp because the tips of the clamp can injure the vein.

Supraceliac Aorta

The supraceliac aorta is exposed by dividing the lesser omentum or gastrohepatic ligament. The aorta is identified by palpation, and the overlying fibers of the right crus of the diaphragm are divided with electrocautery. Mobilization of the left lobe of the liver by dividing the left triangular and coronary ligaments, as well as the falciform ligament, can assist with exposure but is often not necessary. In addition, the presence of a nasogastric tube helps identify the esophagus and thereby protect it from inadvertent injury. The esophagus is typically retracted to the left. The aorta can be dissected anteriorly down to the level of

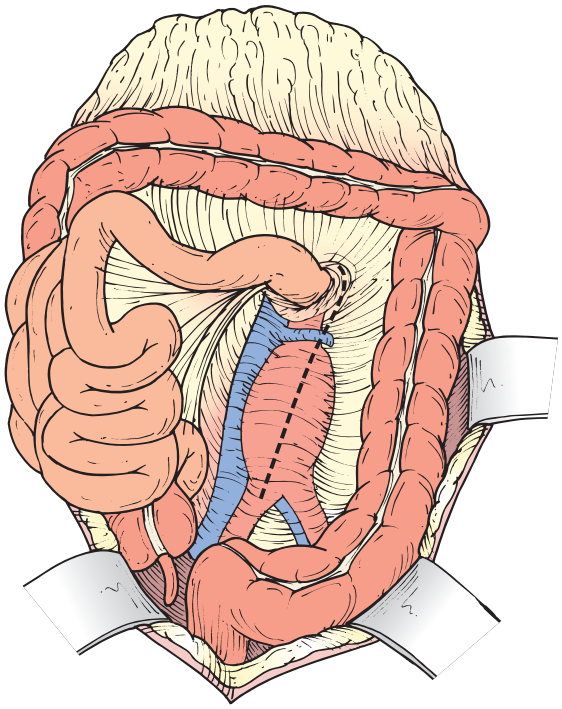

Figure 71.5 The aorta is exposed by incising the overlying posterior peritoneum.

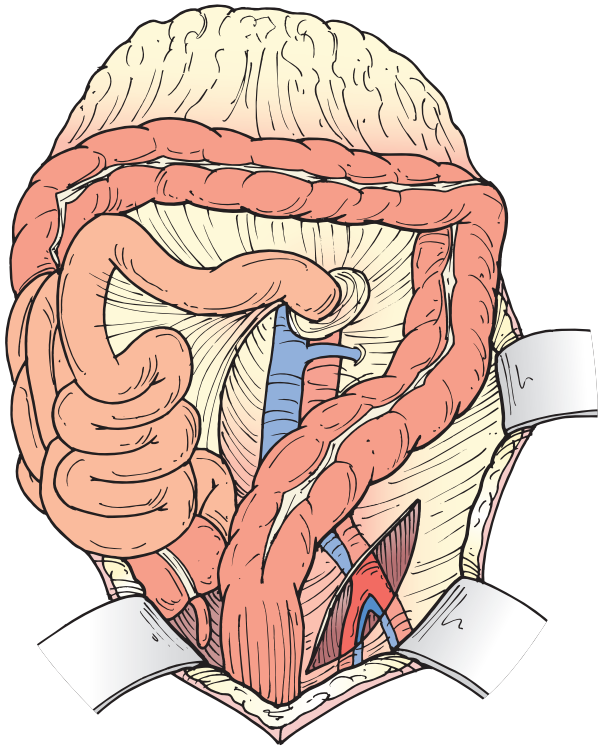

Figure 71.6 The left iliac artery can be accessed by mobilizing the sigmoid colon medially and incising the posterior peritoneum at its base.

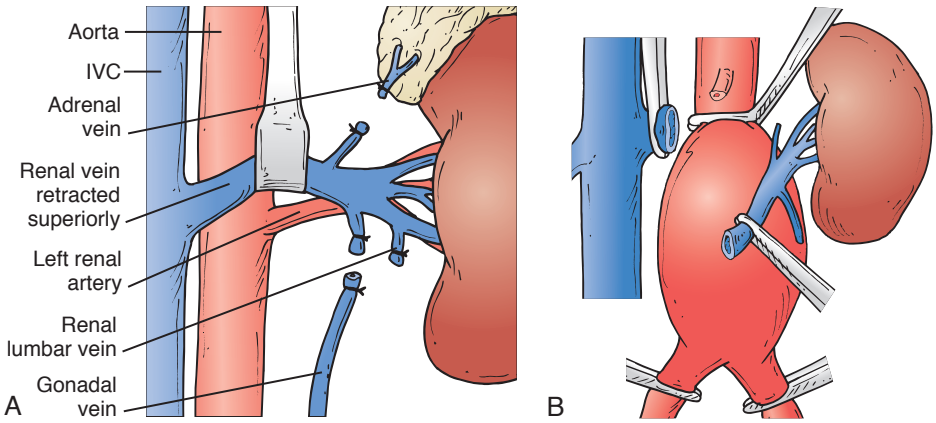

Figure 71.7 The renal vein can be mobilized by dividing it side branches (A) or simply divided close to the inferior vena cava (IVC) (B).

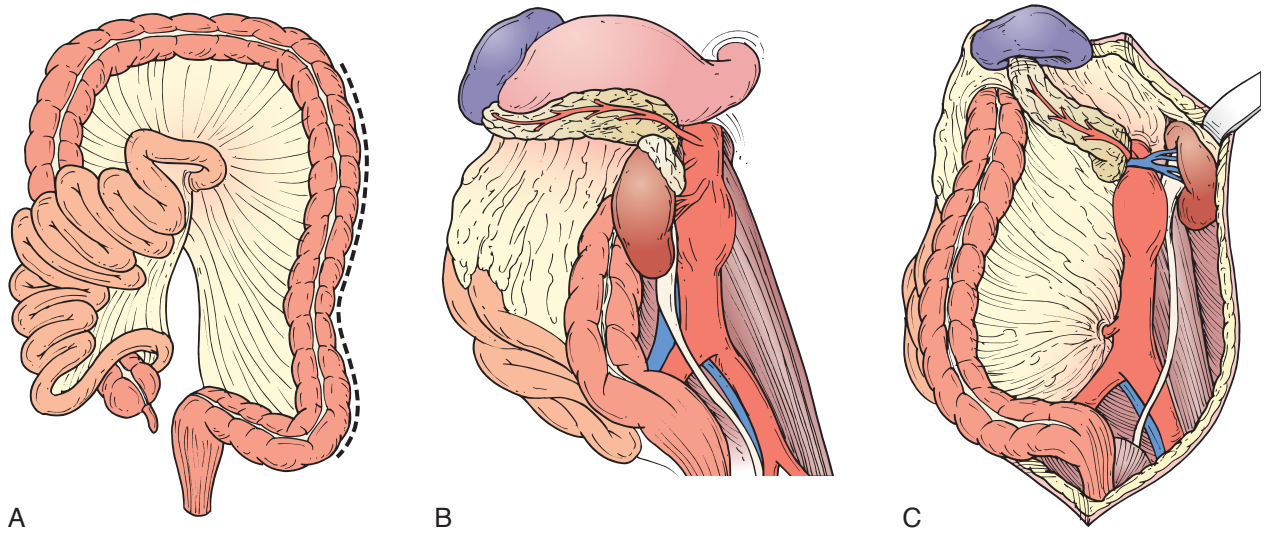

Figure 71.8 When using the transperitoneal approach, a left medial visceral rotation facilitates access to the visceral segment of the aorta. The peritoneum is incised along the line of Toldt (A) and the left colon, pancreas, and spleen are mobilized medially. The kidney can be mobilized en bloc (B) or left in the renal fossa (C).

the celiac axis, although care must be taken to avoid injury to the pancreas as one proceeds caudally.

Medial Visceral Rotation

Suprarenal aneurysms are best approached using a retroperitoneal exposure. Despite this, the complete visceral segment of the aorta can be accessed transperitoneally using a left medial visceral rotation (Fig. 71.8). The left colon is mobilized by incising the posterior peritoneum just lateral to the line of Toldt. This incision is then carried cephalad through the phrenicocolic ligament and then medially toward the aortic hiatus along the underside of the diaphragm. The plane separating the posterior aspect of Gerota's fascial and posterior abdominal wall is developed, allowing the colon, pancreas, spleen, and left kidney to be reflected medially. As the kidney is mobilized, the left renal lumbar vein should be identified and ligated to prevent avulsion. Alternatively, the kidney can be left in the renal fossa; this requires dividing the linorenal and linophrenic ligaments and developing a plane between the anterior surface of Gerota's fascia and the posterior surface of the colonic mesentery and pancreas (see Fig. 71.8C).

Arterial Reconstruction

Once the appropriate aortic segments are exposed, the proximal and distal clamp sites are identified. Encircling the vessels with Silastic vessel loops or cloth umbilical tape is not necessary and increases the risk of injury to posterior structures, especially the iliac veins. Only enough exposure to apply a clamp is needed. Care must be taken to avoid injuring or avulsing closely related venous structures. The patient is systemically heparinized, and the aorta and iliac arteries are clamped. Distal clamps are usually applied first to prevent any thrombus from embolizing to the legs during application of the proximal clamp. The aneurysm is opened via a longitudinal aortotomy, which transitions to a

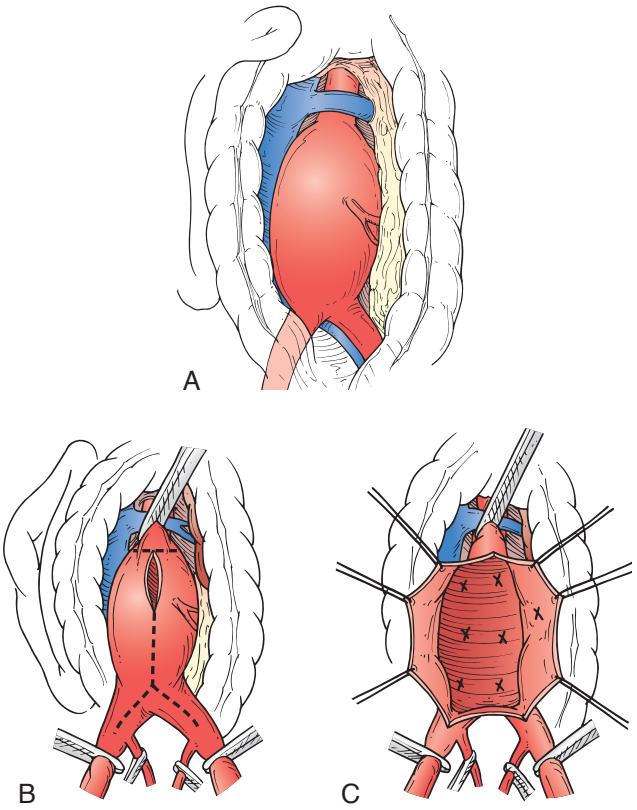

Figure 71.9 The aneurysm (A) is opened with a T-shaped (B) incision. Aortic retention sutures (C) can be used to help facilitate exposure.

T-shaped incision at the proximal and distal ends to allow for the graft anastomosis (Fig. 71.9). The proximal anastomotic site is cleared of thrombus and calcium, and an end-to-end anastomosis is performed using a running polypropylene suture. The use of aortic retention sutures or a self-retaining retractor

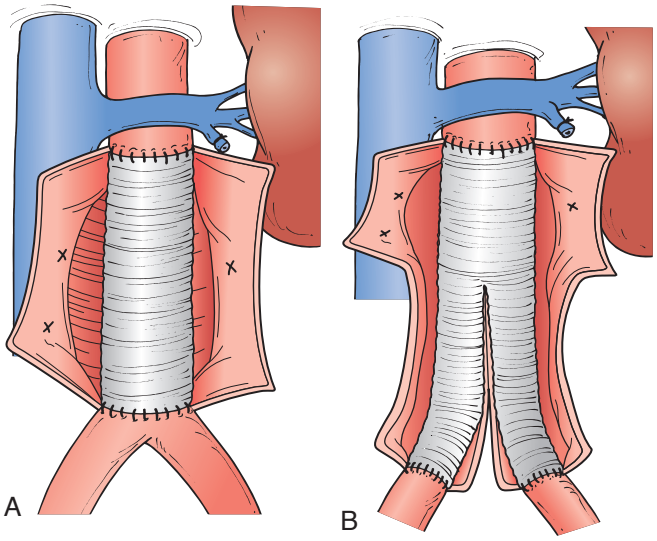

Figure 71.10 Completed repair with either a tube graft (A) or a bifurcated graft (B).

placed in the aneurysm sac helps facilitate exposure. Thrombus is then cleared from the remainder of the aneurysm sac, and back-bleeding lumbar vessels are controlled. The distal reconstruction is performed in a similar fashion (Fig. 71.10), allowing for forward flushing of the graft and back bleeding of the distal vessel before completing the anastomosis.

Closure

After hemostasis has been obtained, the aneurysm sac is closed over the graft using a running absorbable suture. The posterior peritoneum is likewise closed (Fig. 71.11). Both of these maneuvers help exclude the bowel from the retroperitoneal and prevent contact between the bowel and the graft. If the sac or retroperitoneum is unable to be approximated over the graft, the omentum can be brought down to cover the graft. It is critical to obtain separation of the graft from the bowels to prevent future aortoenteric fistulization. The intestines are then returned to their normal anatomic position, and the anterior abdominal wall closed according to surgeon preference.

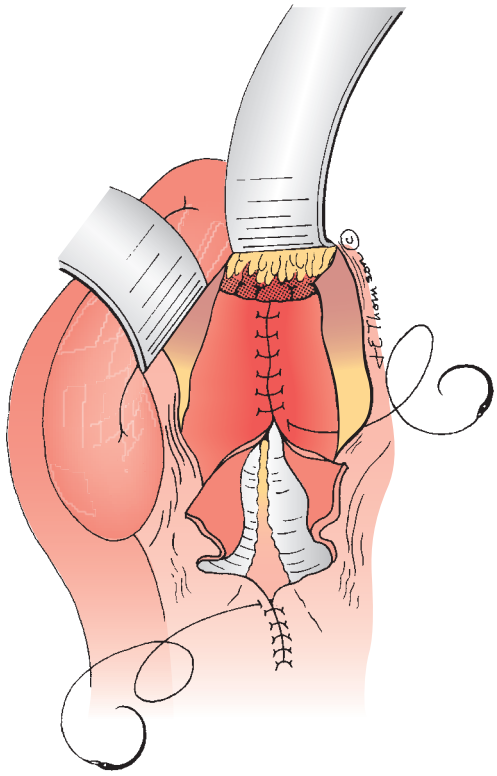

Figure 71.11 The aneurysm sac and posterior peritoneum are closed over the graft.

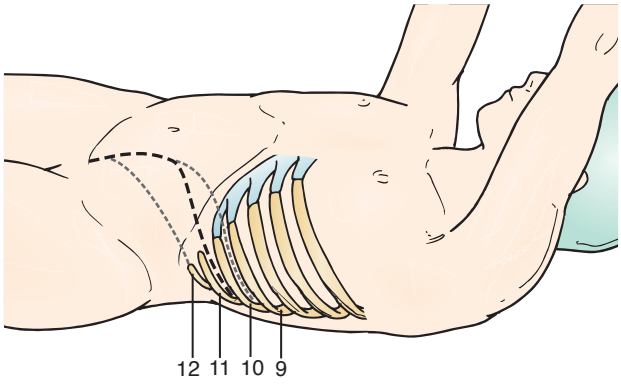

Figure 71.12 Incision *(heavy line)* for retroperitoneal aortic exposure. Alternate incisions are shown in *gray*.

RETROPERITONEAL REPAIR

Exposure

The patient is placed in right lateral decubitus position with the break in the table centered at the iliac crest. The table is maximally flexed and then leveled. A surgical beanbag positioner is used to help secure the patient in this position. Care must be taken to appropriately pad and protect the right axilla. The chest and abdomen and left groin are prepped and draped in the standard fashion. Access to the right groin can be obtained, if needed, by flexing the hips posteriorly.

The incision starts in the 10th intercostal space at the posterior axillary line; this can be varied depending on the proximal extent of the aneurysm (Fig. 71.12). It is carried onto the abdomen, where it runs lateral and parallel to the lateral boarder of the left rectus muscle and terminates below the umbilicus at a level determined by the distal extent of the intended arterial reconstruction. The skin and subcutaneous tissues are divided to expose the anterior fascia of the external oblique. The external oblique, internal oblique, and transversus abdominis muscles are sequentially opened over a short distance using a combination of blunt dissection and electrocautery. Care must be taken not to violate the peritoneum. The peritoneum is then blindly freed from the abdominal wall and diaphragm using careful blunt digital dissection. This permits the abdominal cavity to be opened to the level of the diaphragm. Exposure can be

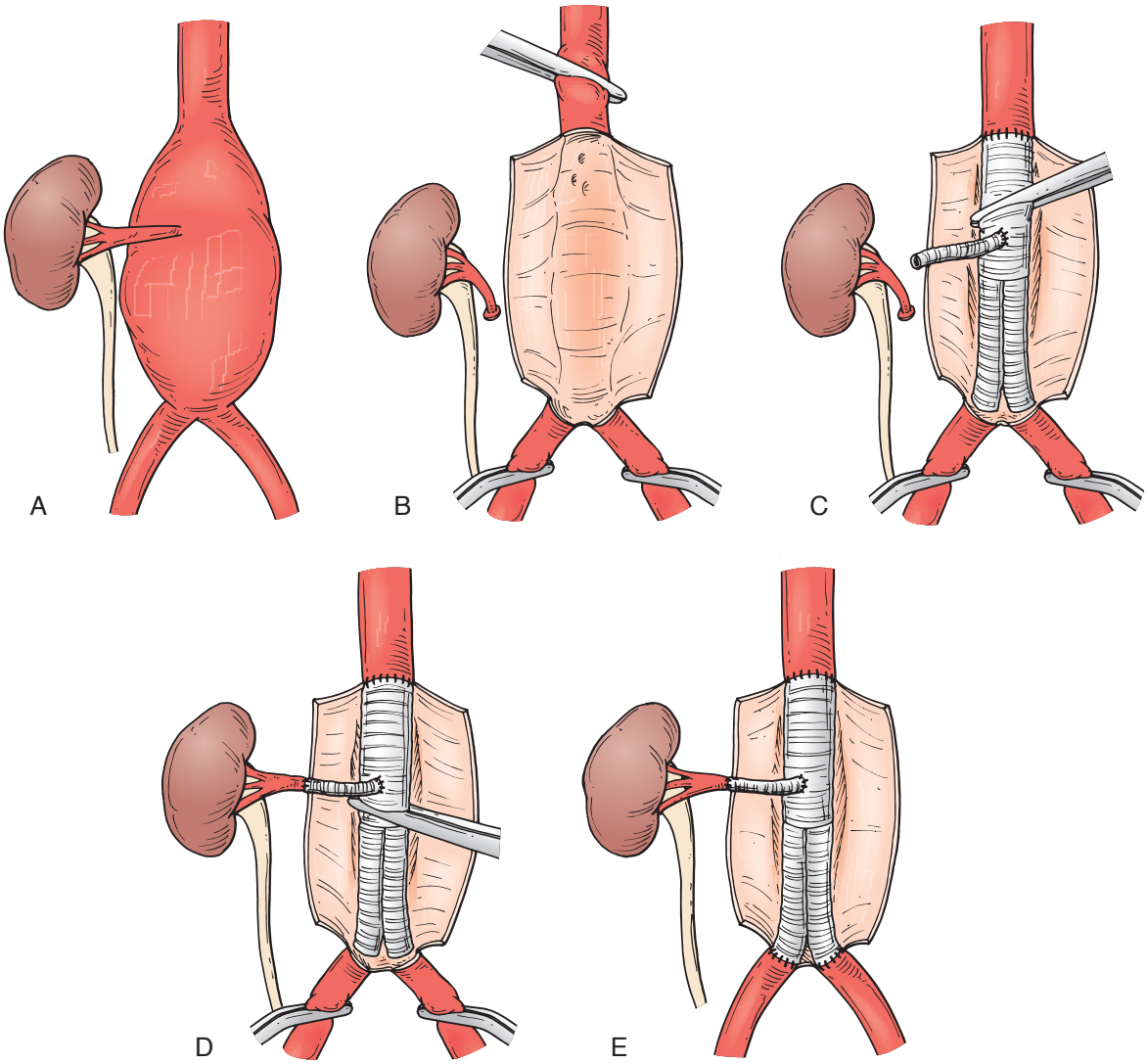

Figure 71.13 Beveled anastomosis with left renal bypass for a type IV thoracoabdominal aortic aneurysm. The aorta is clamped and opened with a T-shaped incision and the left renal artery is detached (A, B). The proximal anastomosis is beveled into the visceral segment and right renal artery, and the clamp is then advanced distal to the anastomosis (C). The left renal artery is bypassed with a presewn side arm from the graft (D). The distal anastomoses are completed and the clamp removed (E).

increased by entering the chest through the 10th intercostal space contiguous with the abdominal portion of the incision by dividing 2 to 3 cm of the diaphragm. The left psoas muscle is identified, and the peritoneal and retroperitoneal contents are swept anteromedially throughout the length of the wound, as well as off the inferior surface of the diaphragm. This exposes the entire intraabdominal aorta (Fig. 71.13A). At this stage, the left ureter should be identified and protected, because it runs anterior to the aorta and left common iliac artery. By staying on a plane directly anterior to the iliac arteries, the right ureter can also be identified and protected. A Bookwalter or Omni retractor can now be put in place to assist with exposure. If the patient has a posterior left renal vein, it may be advisable to not mobilize the kidney during the aortic exposure and to leave it in place in the retroperitoneum. Alternatively, it can be divided for exposure as long as the gonadal branch is preserved.

Supraceliac Aorta

To gain better access to the visceral segment of the aorta and obtain a supraceliac clamp site, the left crus of the diaphragm is divided. A suitable spot for clamping is identified, and the aorta is bluntly dissected along its anterior and posterior surfaces; care must be taken to avoid avulsing any lumbar arteries or veins that run posteriorly. Again, it is unnecessary to attempt to fully encircle the aorta or iliac arteries; this risks esophageal, caval, or iliac vein injury. The left renal artery is identified and dissected back to its origin so that it is not injured during the

opening of the aorta. Lumbar branches of the left renal vein are also identified, ligated, and divided to prevent avulsion.

Arterial Reconstruction

The use of a retroperitoneal incision is ideal for reconstruction of suprarenal and type IV thoracoabdominal aortic aneurysms, given the exposure it provides. After heparinization and supraceliac cross-clamping, the aneurysm is opened with a longitudinal aortotomy up to the level of normal proximal aorta, whereupon the aortotomy is transitioned into a T-shaped incision; it is important to have previously identified the origin of the left renal artery and to have divided the renal lumbar veins to avoid injuring these structures during this maneuver (see Fig. 71.13B). The left renal artery is freed from the aortic wall with a small cuff of surrounding aorta and retracted out of the immediate field.

Once the proximal extent of the aneurysm has been opened, the celiac, SMA, and right renal arteries are identified from the inside the aorta. Any significant stenosis detected on preoperative CTA, or at the time of operation, can be treated with either endarterectomy or a balloon-mounted stent deployed through the open aorta.[72] The proximal extent of the graft is beveled to incorporate the celiac, SMA, and right renal arteries, and the proximal anastomosis is completed using a running polypropylene suture (see Fig. 71.13C). The proximal graft is clamped, and the supraceliac cross-clamp is removed to allow perfusion of the viscera and right kidney (see Fig. 71.13D). The left kidney is now revascularized by bypass with a sidearm from the graft. If a bypass is to be performed, a hybrid stent graft can be fashioned as a sidearm from the main graft before aortic cross-clamping in order to reduce left renal ischemia time and to facilitate the anastomosis (Fig. 71.14). Once the anastomosis to the left renal artery is complete, the aortic cross-clamp can be shifted distally on the graft to allow for complete renal perfusion (see Fig. 71.13E). Minimizing ischemic time to this area is paramount; thus proper conduct of the operation and attention to technique is critical.

At this point the aneurysm sac is cleared of thrombus, and back-bleeding lumbar arteries are oversewn. By leaving the thrombus in situ until this point, visceral and renal ischemic time is reduced, because time is not wasted controlling bleeding with a supraceliac clamp in place. Moreover, the thrombus acts to obstruct the back-bleeding vessels and minimize blood loss. Distal reconstruction proceeds in a manner similar to that of the transabdominal approach.

Closure

After obtaining hemostasis, the self-retaining retractor system is removed and the peritoneal sac is returned to its normal anatomic configuration. Because the peritoneum has not been violated, the graft remains separate from the peritoneal contents, and the aneurysm sac does not need to be closed at the conclusion of the repair. Any rents in the peritoneum, however, should be closed; this can be accomplished with running absorbable suture. The flex is taken out of the operating table to remove tension on the wound during closure and the flank incision is closed in multiple layers. The ribs and diaphragm can be incorporated into the closure of the transversus abdominis and internal oblique muscles in a single layer of running absorbable suture. Great care must be taken to avoid inadvertent colonic injury during closure. The external oblique, with its associated fascia, is closed over this in an interrupted manner because it provides the strength for the closure.

ANATOMIC CONSIDERATIONS

A number of anatomic situations exist that can complicate open aneurysm repair and require additional planning to address. Fortunately, the vast majority of these should be detected on the preoperative CTA and plans can be made to address them in a proactive manner.

Management of the Inferior Mesenteric Artery

Note should be made on the preoperative CTA as to the patency of the IMA. If it is thrombosed, then it is of no further consideration. On the contrary, if there is significant SMA disease, bilateral hypogastric artery occlusions, a large IMA, or prior colectomy, IMA preservation may be indicated. This can be accomplished either by reimplantation of the IMA into the graft using a small cuff of surrounding aorta or in an end-to-end fashion from a sidearm attached to the body of the graft. This

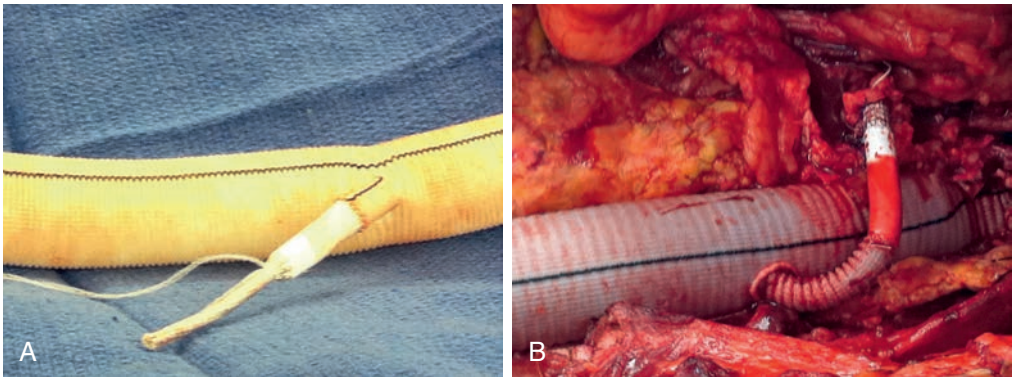

Figure 71.14 The left renal artery is revascularized with a hybrid stent graft sewn to sidearm from the aortic graft. Before (A) and after (B) graft anastomoses are performed.

is easily performed from both the transperitoneal and retroperitoneal approaches.

Renal Abnormalities

The presence of renal anomalies, such as a horseshoe kidney, pancake kidney, and crossed-fused renal ectopia, complicates open aneurysm repair. A renal perfusion scan can also be of assistance in this setting in helping to determine the functionality and contribution of not only each kidney but each portion of the respective kidneys. This is then helpful to determine what, if any, tissue can be sacrificed. Management is difficult because these situations pose technical challenges with respect to both exposure and revascularization, and longer aortic cross-clamp times have been reported.[73]

Venous Abnormalities

Based on surgical and radiologic studies, significant venous abnormalities of the renal veins and IVC are present in between 1% and 10% of the population, respectively.[74-77] The most common abnormalities include retroaortic left renal vein, circumaortic left renal vein, left-sided IVC, and duplicated IVC; accessory left renal veins and preaortic confluence of the iliac veins have also been described. These abnormalities can pose significant challenges with regard to aortic exposure and can complicate the operation.[77-79]

INTRAOPERATIVE MANAGEMENT

Management of Aortic Clamping

The dramatic effect of aortic cross-clamping on the patient's physiology must be managed in real time by the anesthesia team. Effort must be directed at maintaining adequate blood pressure and perfusion while avoiding excessive hypertension. Care must be taken to optimize preload and afterload to minimize the effects of cross-clamping on myocardial oxygen demand. Mean arterial pressure must also be reduced before application of the cross-clamp. This must all be done in a way that anticipates the ultimate need to remove the aortic cross-clamp and the ensuing hypotension. Accordingly, clear and direct communication between the surgeon and anesthesiologist is crucial around the time of the application and removal of the cross-clamp, so that the physiology can be managed appropriately. We typically give the anesthesiologist a prediction of the approximate duration of cross-clamping before beginning and then provide a several-minute warning before removal. A dedicated anesthesia team for these procedures likely results in the best outcomes.

Renal Protection

A number of agents have been purported to offer renal protection during aortic cross-clamping, including furosemide, mannitol, dopamine, and acetylcysteine; these benefits have not been borne out in clinical experience, and these interventions are not without risk and adverse effects.[80-83] Fenoldopam, a selective dopamine receptor antagonist, was thought to hold promise for renal protection based on its ability to augment renal blood flow in normotensive human volunteers,[84] as well as the results of two small studies on patients undergoing aortic surgery.[85,86] Unfortunately, a meta-analysis of the use of fenoldopam in cardiac surgery patients demonstrated that although it did reduce the rate of acute kidney injury, it had no effect on the need for renal replacement therapy.[87]

Renal perfusion with cold hyperosmolar crystalloid, histidine-tryptophan-ketoglutarate (HTK) solution, or saline with mannitol and methylprednisolone, resulting in renal hypothermia, has been reported by many groups to improve renal outcomes following the repair of juxtarenal aneurysms that require suprarenal aortic clamping and type IV thoracoabdominal aortic aneurysms.[88-93] However, this may be somewhat cumbersome to perform. In addition, establishing the perfusion circuit and performing the anastomosis around the perfusion cannulas can lead to increased overall ischemic time. It should be added, however, that other groups have obtained similarly excellent results without using intraoperative adjuncts and focusing on minimizing aortic cross-clamp time.[94,95] Ultimately, reducing ischemic times to the kidneys likely has the greatest beneficial effects on renal protection. Maneuvers such as beveling the proximal anastomosis to include the right renal artery and quickly reimplanting the left renal artery are useful in this regard.

POSTOPERATIVE COMPLICATIONS

Early Complications

Perioperative adverse events are not uncommon following open aneurysm repair.[6] Lifeline registry data of patients who underwent open repair of nonruptured infrarenal aortic aneurysms in the setting of randomized device trials demonstrated a 71% overall, 26% serious, and 11% major adverse event rates in the perioperative period. Moreover, data from single centers, the National Surgical Quality Improvement Program (NSQIP), and the Vascular Study Group of New England (VSGNE) suggest that as procedure complexity increases, the rate of overall complication does also.[96,97] It is clear that perioperative care has a direct effect on the incidence and outcome of these potentially devastating occurrences, and advances in intraoperative and postoperative care have been credited with improving aneurysm outcome over time.[63] In addition, the daily involvement of a critical care physician[98] and a high nurse-to-patient ratio[99] have been shown to significantly improve outcomes.

Myocardial Ischemia (See Chapter 42)

As previously described, aortic cross-clamping results in significant hemodynamic perturbations and creates increased demand on the heart. When combined with the baseline cardiac risk factors of patients undergoing aneurysm repair, this results in an increased rate of perioperative cardiac complications. With appropriate preoperative imaging, perioperative myocardial events can be reduced. Nevertheless, perioperative myocardial infarction still occurs in up to 10% of patients in the perioperative period.[100] The use of perioperative beta blockade for patients undergoing major noncardiac surgery has been shown to reduce

cardiovascular events and in-hospital mortality in both extremely large retrospective population studies[101] and in prospective randomized trials.[102,103] A smaller observational trial focused on patients undergoing AAA repair similarly showed that the administration of beta blockers was associated with significant reductions in in-hospital mortality.[104]

Respiratory Failure (See Chapter 43)

The decision to extubate the patient upon completion of the operation depends on the complexity of the procedure and the difficulty of the operation. In general, with more complex repairs that require higher proximal aortic control, leaving the patient intubated may be advisable. Patients often require ongoing fluid resuscitation for 12 to 36 hours because of the hemodynamic perturbations associated with proximal clamping. Once this is over and the patient has demonstrated hemodynamic stability with no evidence of ongoing bleeding, it is safe to proceed with extubation using standard criteria. Despite relative success in avoiding prolonged intubation, however, pulmonary complications still remain, with postoperative pneumonia occurring in up to 17% of patients.[100] Although very few patients progress to needing a tracheostomy, postoperative pulmonary complications of any form have been associated with reduced long-term survival.[105]

Renal Failure (See Chapter 44)

Patients undergoing open repair of AAAs are at significant risk of developing renal complications. Rates of postoperative renal insufficiency in the Medicare population approach 10%, albeit with only a 0.5% need for renal replacement therapy.[100] A meta-analysis of patients undergoing open elective pararenal aortic aneurysm repair demonstrated postoperative renal insufficiency in 15% to 20% of the patients, but dialysis-dependent renal failure in only 3.5%.[106] Close attention to volume status and the liberal use of intravenous fluids and colloid throughout the perioperative period are key in preventing recurrent episodes of renal ischemia and reversing the deleterious effects of aortic cross-clamping.

Colonic Ischemia

Ligation of the IMA, failure to revascularize the hypogastric arteries, preexisting iliofemoral occlusive disease, SMA stenosis, as well as atheroembolism, retractor injury, and previous colonic resection, can all contribute to colonic ischemia, which has a clinical incidence 0.2% to 6% following open aneurysm repair.[6,107-110] It is interesting to note that the rate of subclinical disease is much higher; surveillance studies following aortic surgery demonstrate rates of endoscopically evident disease approaching 13%, with histologically evident disease present in 30% of patients.[109,111,112]

The presence of early postoperative diarrhea, melena, hematochezia, or rectorrhagia mandates further interventions aimed at definitive diagnosis of the condition. In multiple large studies, the presence of bloody bowel movements is the primary presenting symptom.[108,109] Flexible sigmoidoscopy or colonoscopy can be done quickly and with little risk. In large series, intestinal ischemia is associated with a 25% to 55% mortality rate that can reach up to 90% when a bowel resection for infarction is required.[108,109] Accordingly, all patients should be aggressively resuscitated and started on broad-spectrum intravenous antibiotics targeting intestinal flora. Patients with disease limited to the mucosa, or limited to the mucosa and muscularis mucosae without evidence of systemic derangement, can be managed expectantly, whereas those with involvement of the muscularis mucosae and evidence of organ failure or those with full thickness ischemia require emergent exploratory laparotomy and bowel resection.[113] Ultimately, the extent of ischemia may be difficult to determine; in case of doubt, an exploratory laparotomy or laparoscopy may be the best way to make the diagnosis. A negative exploration is preferable to a missed full-thickness diagnosis and perforation.

Lower Extremity Ischemia

Patients undergoing open aneurysm repair are at increased risk for acute lower extremity ischemia. Distal perfusion should be checked before emerging from anesthesia and before leaving the operating room because the loss of lower extremity pulses or other evidence of limb ischemia in the immediate postoperative period suggests technical anastomotic complications, clamp injury, acute thrombosis, or acute embolic disease, all of which require intervention to resolve. Meticulous technique is important in performing the anastomosis, especially when sewing to diseased vessels. Care must be taken in selecting clamp sites to prevent atheroemboli or vessel injury. To prevent thrombotic complications, adequate systemic anticoagulation must be maintained and can be monitored using point-of-care measurement of the activated clotting time (ACT); heparin should be redosed accordingly. In addition, the graft itself should be clamped in a manner to minimize standing columns of blood in prosthetic surfaces, and all anastomoses should be adequately forward- and back-bled before completion.

Spinal Cord Ischemia

SCI following open AAA repair is an extremely rare event. Reported rates in the literature are generally less than 1%, even for suprarenal aortic aneurysm repairs,[96,105] but rates can be higher when patients undergoing extent IV (see Chapter 77) thoracoabdominal aortic aneurysm repair are included.[114-117] The extent of proximal coverage of the aorta appears to be the biggest risk factor; however, other considerations such as previous thoracic aortic procedures, aortic cross-clamp location and time, patency of the internal iliac arteries, and profound intraoperative or postoperative hypotension all likely play a role.[116,118]

Venous Thrombosis

Because of the use of systemic anticoagulation, lower extremity deep venous thrombosis (DVT) and pulmonary embolism (PE) are clinically rare events after aortic surgery[96,100,119]; in a recent study using NSQIP data from 2005 to 2009 that consisted of 3967 open AAA repairs, there was a 0.3% rate of

clinically diagnosed VTE at 30-days.[120] However, when routine surveillance with lower extremity duplex ultrasonography is performed, VTE can be detected at a rate of up to 8%, even in the setting of mechanical and chemical prophylaxis. The Society for Vascular Surgery guidelines in 2009 recommend prophylaxis consisting of intermittent pneumatic compression and early ambulation to all patients undergoing AAA repair, with the addition of chemoprophylaxis for those at high risk, including patients with prior VTE, BMI greater than 25, limited mobility, malignancy, or a hypercoagulable state.[121] In regard to PE, this complication is uncommon, occurring at a rate of 1.4%.[122]

OUTCOMES

Early Mortality

Historically in the 5% to 8% range, early mortality in large database, multi-institutional, and population-based studies now approaches 3% (Table 71.1).[67,100,120,123-141] Similar results of an overall mortality rate of 3.5% are obtained when examining the open arms of the major randomized controlled trials for EVAR (Table 71.2).[12,14,142,143] In fact, a meta-analysis of 30 peer-reviewed series, each with greater than 100 patients, also demonstrated an overall mortality of 3.2%.[144] Notably, this is in keeping with the reports of outcomes from large-volume centers of excellence.[105,145,146]

As endovascular devices have become more versatile and outcomes more durable, the aneurysms that remain for open repair have become increasingly complex. This has been manifest in an increasing percentage of patients who require suprarenal and supraceliac aortic cross-clamps and who have concomitant aortoiliac occlusive disease.[16,17,147] Despite the increased case complexity, the mortality rates within the series were unchanged, or in some cases even reduced, over the time studied, and in all cases outcomes were equal to or better than those reported earlier.

When the findings of major contemporary series of juxtarenal and suprarenal AAAs and extent IV thoracoabdominal aortic aneurysms are examined (Table 71.3),[90,92,95,105,114-117,148-152] it is

TABLE 71.2 Results From Open Aneurysm Repair Arms of Major Randomized Endovascular Aneurysm Repair Trials

Trial	Publication Year	Open-Arm Participants	Mortality
DREAM	2004	174	4.6%
OVER	2009	437	3.0%
EVAR-1	2010	626	4.3%
ACE	2011	149	1.3%
Combined Results		1386	3.5%

TABLE 71.1 Early Mortality in Population-Based and Database-Derived Series

Series	Study Period	Number of Patients	Mortality	Data Source
Bradbury et al.	1976-1996	842	7.5%	Royal Edinburgh Infirmary Database
Heller et al.	1979-1999	358,521	5.6%	National (US) Hospital Discharge Survey
Johnston et al.	1986	666	4.8%	Canadian Society of Vascular Surgery
Lawrence et al.	1990-1994	32,389	8.4%	National (US) Hospital Discharge Survey
Galland	1990-1995	2,680	4.8%	British Joint Vascular Research Group
Dardik	1990-1995	2,335	3.5%	Maryland Heath Service Cost Review
Akkersdijk et al.	1990	1,289	6.8%	Dutch National Medical Registration
Kazmers et al.	1991-1993	3,687	4.9%	(US) Veterans Affairs Medical Centers
Bush et al.	1991-2008	14,232	4.4%	US NSQIP-VA
Huber et al.	2001	4,607	3.8%	National (US) Inpatient Sample
Huber et al.	1994-1996	16,450	4.2%	National (US) Inpatient Sample
Rigberg et al.	1995-1999	9,778	3.8%	California Statewide
Dimick et al.	1996-1997	7,980	3.8%	National (US) Inpatient Sample
Anderson et al.	2000-2002	3,064	3.9%	New York (US) Statewide
Schermerhorn et al.	2001-2004	22,830	4.8%	Medicare (US) Beneficiaries
Schwarze et al.	2001-2006	75,222	3.0%	National (US) Inpatient Sample
Teixiera et al.	2003-2014	3,530	2.7%	Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI)
Davenport and Xenos	2005-2009	3,967	3.4%	US NSQIP
de la Motte et al.	2007-2010	1,176	3.3%	Danish nationwide cohort
Hicks et al.	2007-2011	34,535	3.8%	Medicare (US) Beneficiaries
Grant et al.	2008-2010	48,593	4.7%	UK National Vascular Database

TABLE 71.3 Major Contemporary Abdominal Aortic and Type IV Thoracoabdominal Aortic Aneurysm Series by Clamp Location

	Year	Patients	Early Mortality	Long-Term Survival
Suprarenal Clamp				
Chong et al.[a]	2009	171	1.8%	67.7% at 5 years
Landry et al.[a]	2009	82	6.1%	NR
Knott et al.[a]	2008	126	0.8%	63.8% at 5 years
Chiesa et al.	2006	85	3.5%	NR
Nathan et al.	2011	97	3.4%	69.1% at 5 years
Tsai et al.[a]	2012	199	2.5%	74% at 5 years
Supraceliac Clamp				
Martin et al.	2000	57	1.8%	NR
Martin et al.[b]	2000	53	11.0%	NR
Coselli et al.[b]	2002, 2007	329	3.60%	65.3% at 5 years
Chiesa et al.	2006	34	2.9%	NR
Kieffer et al.[b]	2008	171	13.4%	NR
Richards et al.[ab]	2010	53	6.0%	78% at 3 years
Nathan et al.	2011	108	5.4%	52.9% at 5 years
Nathan et al.[b]	2011	83	5.6%	50% at 5 years
Patel et al.[b]	2011	179	2.8%	62% at 5 years

[a]Elective.
[b]Type IV TAAA.
NR, Not reported.
Modified from Nathan DP, Brinster CJ, Jackson BM, et al. Predictors of decreased short- and long-term survival following open abdominal aortic aneurysm repair. *J Vasc Surg*. 2011;54:1237–1243.

clear that their outcomes come close to those listed for infrarenal aortic aneurysm repair in Tables 71.1 and 71.2. Despite the fact that clamp position has been shown to affect overall outcomes in a number of studies,[152,153] it is clear from these series that excellent, durable results can be attained even with more complex aneurysm repairs. What is most interesting is that in multiple instances the same group achieved nearly equivalent outcomes with both pararenal aortic aneurysm repairs and type IV thoracoabdominal aortic aneurysms. Several studies have demonstrated superb outcomes with both complex pararenal[105] and type IV thoracoabdominal aortic aneurysm repair,[95] with perioperative (30-day) mortality rates of 4.4% and 5.6%, respectively, and 2.5% and 2.8%, respectively.[90] A recent paper using data from the VSGNE demonstrated a 30-day mortality of 3.6% for complicated AAA repair (pararenal and type IV thoracoabdominal aortic aneurysms) as compared with 1.2% for routine AAA repairs ($P = .002$) in a series of 443 elective cases.[97]

Postoperative Surveillance

Patients who undergo open aortic aneurysm repair should be followed closely after discharge until it is clear that they are free from procedure-related complications, at which point they can be transitioned to standard follow-up. The aorta should be imaged with at least duplex ultrasound to ensure that there is no progressive aortic dilation. In keeping with current Society for Vascular Surgery guidelines, patients should undergo surveillance imaging every 5 years[121]—more often if there is reason for clinical concern. It may be appropriate to obtain CT scans that include the chest, as well as the abdomen and pelvis, given the high rate of metachronous thoracic and iliac aneurysms in this population. In addition, close attention should be paid to the popliteal arteries on physical examination.

SPECIAL CIRCUMSTANCES

Open Conversion After Endovascular Aneurysm Repair

Open AAA repair for a failed endograft is a complex undertaking. Because of the suprarenal fixation present on many grafts, the aorta must be clamped in the supraceliac segment in these situations, even if the reconstruction is going to be infrarenally. Furthermore, the endograft can induce fibrosis and inflammation in the surrounding tissue, making the dissection quite difficult. If the graft is being explanted for infectious reasons, then all prosthetic material needs to be removed. Otherwise, some of the device parts can be left intact to make the procedure easier.[27] In some situations, the suprarenal stent can be left and the fabric divided just under it, allowing for a proximal anastomosis to include this and the aorta. Distally, if the limbs extend to

the external iliac arteries, they may be difficult to remove and leaving them in place is often better. In order to avoid clamping the limbs in the iliac arteries, we typically apply the proximal clamp, open the aneurysm, and then clamp the endograft main body to obtain distal control. The proximal anastomosis is then performed, and the limbs can either be sequentially removed with clamping of the iliac arteries or be sewn to the graft with balloon control or clamping of the more distal nonstented vessel. It is important to recognize that the lumbar branches and the IMA were never surgically occluded at the time of the original endovascular repair and may need to be oversewn.

Outcomes of EVAR conversion reflect the procedural complexity. Reported mortality rates for late conversion among contemporary series range from 0% to 22%.[154-157] In a study of 300 EVAR conversions and 7188 open repairs from the NSQIP, EVAR conversion was associated with significantly longer operative time (275 ± 124 vs. 232 ± 99, $P < .001$), increased rates of complications (58% vs. 47%, $P < .001$), and increased mortality (10% vs. 4.2%, $P < .001$), as compared with open repair.[26] A recent meta-review of the literature suggests that the overall mortality among 593 elective conversions across more than 26 centers was 3.2%,[158] and two of the more recent reports specifically stand out for both their size and outcomes.[25,159] Kelso et al. describe removing 44 endografts at a mean of 33 months following implantation.[159] The most common indication was endoleak with aneurysm growth. Of these patients, 78% had a suprarenal or supraceliac aortic cross-clamp, and 85% of the devices were completely removed. Overall mortality was 19%. Our group subsequently reported a series of 21 patients with nearly identical results.[25] Clamp times, estimated blood loss, and length of stay were all increased; however, no mortality occurred in our series.

Inflammatory Aneurysms

Inflammatory aneurysms are marked by a thickened aortic wall, fibrosis of the adjacent retroperitoneum, and dense adherence of adjacent structures to the aorta.[160] Although all aneurysms have some element of associated inflammation, this degree of local inflammatory response is rare. Inflammatory aneurysms account for 5% of all aortic aneurysms and are especially challenging to manage.[161] Multiple theories exist as to the etiology of inflammatory aneurysms, including an exaggerated variation of the normal inflammatory response, chronic subacute rupture, and a variant form of retroperitoneal fibrosis leading to the characteristic inflammatory rind.[162,163] Of note, stent grafting has been shown to promote the resolution of the perianeurysmal inflammatory response, similar to that of open repair.[164] This suggests that the aneurysm itself is driving the inflammatory process.

Indications for repair are based on standard criteria for aneurysm intervention. Although the inflammation is frequently limited to the infrarenal segment, the dense adherence of local structures, including ureters, duodenum, and small bowel, to the inflamed aneurysm frequently requires suprarenal or supraceliac aortic control to avoid injuring the viscera.[50,165-167] Utilization of the retroperitoneal approach helps minimize these injuries by reducing the need to dissect away adjacent structures to reach the aorta.[168,169] In fact, the aneurysm sac should be entered early after obtaining distant control of the aorta, and little to no attempt should be made to dissect away adjacent structures.[170] As a result, the aortic anatomy can often be identified from the inside of the aorta. The ureters are frequently involved in the inflammatory process as well, and the use of ureteral stents helps decompress the kidneys as well as protect the ureters during dissection.[165,166,170]

The use of prednisone has been shown to diminish the retroperitoneal fibrosis associated with inflammatory aneurysms.[171] Its use, however, is limited to those patients with ongoing inflammation following surgical treatment of the aneurysm.

Infected Abdominal Aortic Aneurysms

Infected AAAs are a rare occurrence, with a prevalence between 0.65% and 1.5% of all aortic aneurysms.[32,33,172] The most common etiologies include primary infection of the native aorta leading to rapid development of an infected aneurysm or infection of a preexisting aortic aneurysm by either local spread or as a result of bacteremia.[172,173] Staphylococcus, streptococcus, salmonella, and *Escherichia coli* together represent the vast majority of the pathogens, with a recent trend toward staphylococcal and salmonella infections having the greatest prevalence. Despite this, the increasing prevalence of immunocompromised hosts, as well as more sensitive culture methodologies, has broadened the spectrum of pathogens that have been isolated from infected aortic aneurysms, and it should be cautioned that any bacterial or fungal infection can result in an infected aortic aneurysm.[174]

Diagnosis is confirmed by a combination of patient history, laboratory investigations including blood cultures and measurement of inflammatory markers, and CT imaging. Classic imaging findings include periaortic soft tissue mass, stranding or fluid, as well as signs of destruction of surrounding tissues such as the kidney or vertebral column; in addition, infected aneurysms tended to be saccular with a lobulated morphology rather than fusiform.[175] Between 47% and 73% of patients have a contained or free rupture.[33,174,176,177]

Treatment consists of aggressive intravenous antibiotics targeted at the offending organism followed by prompt surgical repair, the key principle of which is the débridement of all infected tissue. Both extraanatomic bypass and in situ reconstructive techniques have been described, and most studies demonstrate equal short-term mortality.[33,172,176,177] More recently, endovascular techniques have been used as a bridge to definitive therapy or as destination therapy in patients unable to tolerate an open procedure.[178] Mortality rates for infected aortic aneurysms range from 5% to 36% in most series, although it is much higher among patients who present with rupture.[33,176,177,179] Uncontrolled sepsis has been identified as a common cause of postoperative death,[180] and the failure to control sepsis preoperatively has been shown to be a risk factor for early mortality.[181] The presence of aortic rupture, the extent of periaortic infection, and the virulence of the infecting organism have all been identified as additional risk factors for poor outcomes.[33,172]

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CHAPTER 72

Aortoiliac Aneurysms: Endovascular Treatment

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Endovascular abdominal aortic aneurysm (AAA) repair was initially described by Volodos in 1986,[1] and later Juan Parodi published his experience with retrograde deployment through the femoral arteries of a stent-anchored, Dacron-prosthetic graft that would act to depressurize the aneurysm sac and thus reduce the risk of aneurysm rupture.[2] From there, the era of endovascular aneurysm repair (EVAR) was born. This chapter focuses on the outcomes of EVAR and their comparison with open surgical repair outcomes. The technique of EVAR is discussed in detail in Chapter 73.

GRAFT TYPES

The initial aortic endografts were constructed by suturing a balloon-expandable or self-expanding stent to a standard Dacron tube graft. These early grafts were tubular or "aorto-aortic" in design.[137] In 1993 the unibody bifurcated aorto-bi-iliac stent was developed[3] and the modular bifurcated design quickly followed.[4] Regulatory approval for the abdominal aortic stent-graft occurred in 1996 in Europe and subsequently in the United States in 1999. Although the timeline (Table 72.1) suggests

Abstract

This chapter provides an expansive overview of the endovascular treatment of aortic and iliac artery aneurysms. It reviews the literature comparing endovascular and open aneurysm repair, and provides an overview of current approved infrarenal aortic devices as well as approved and in trial iliac branch devices. Additional techniques including encroachment and snorkel/chimney management of the renal arteries are also discussed.

Keywords

endovascular aortic aneurysm repair
endovascular iliac artery aneurysm repair
iliac branch device

TABLE 72.1 Timeline for Endovascular Aneurysm Repair Development

Regulatory Approval (Europe)	
1996	AneuRx
1997	Excluder
1998	Talent
1999	Zenith
2001	Aorfix
2005	Anaconda
2010	Ovation
2010	Zenith Low Profile
2011	Fortevo Endograft (Aptus)
2011	Incraft
2012	Nellix
2012	Endurant II
Regulatory Approval (United States)	
1999	AneuRx
2002	Excluder
2003	Zenith
2004	New fabric for AneuRx
2004	New fabric for Excluder
2008	Talent
2010	Endurant
2011	AFX
2012	Endurant II
2013	Ovation
2015	Aorfix
Randomized Studies (Start Date)	
1999	EVAR-1, EVAR-2, and DREAM
2001	OVER

EVAR, Endovascular aneurysm repair; *OVER*, open versus endovascular repair.

that the development and advancement of EVAR were part of a natural evolutionary process of technology, notable problems occurred along the way. The Guidant Ancure device (Indianapolis, Indiana), which was approved in 1999, was recalled in 2001 due to delivery system failures.[5] Follow-up of procedures using the Ancure device also revealed attachment site hook fractures and iliac limb stenoses and occlusions attributed to the graft limbs being unsupported by stents.[6,7] The lessons learned from the Ancure experience led to the development of subsequent stent-graft systems having fully supported main body and limbs.

The original AneuRx graft (Medtronic, Minneapolis, Minnesota), although well received because of its ease of deployment and smaller profile, was plagued with a higher migration rate.[8-10] Subsequent modifications and iterations have improved on early results, making the device less rigid and the fabric more robust. The Vanguard endograft (Boston Scientific, Natick, Massachusetts) was prone to fabric tears caused by fatigue erosion of the stents against the material, resulting in fabric perforation.[11] This observation appropriately influenced the design of future stent grafts and led to the secure suturing of stents to the fabric to prevent excessive motion over time. The initial Excluder graft (WL Gore, Flagstaff, Arizona) had a propensity for type IV endoleak due to the porosity of the fabric. Subsequent development of a low-porosity fabric resulted in an improvement in the rate of aneurysm sac shrinkage and marked reduction in the incidence of sac expansion due to endotension.[12] The Talent LPS graft exhibited stent spring fractures and longitudinal C-bar breaks. Chemical etching and medial placement of the longitudinal bar proved to prevent stent fatigue and reduced the overall failure rate.[13] Since it became commercially available, the Zenith stent graft has undergone few fundamental iterative changes, although it is now a more flexible design with delivery system enhancements. In fact, much of the long-term data regarding EVAR available to date come from studies with a large representation of Zenith stent grafts (DREAM, EVAR-1, EUROSTAR).

The modern version of stent-graft design is a bifurcated graft, most commonly using a modular system to allow for the most flexibility with regard to patient anatomy. Currently, six FDA-approved infrarenal endografts are commercially available for the treatment of infrarenal AAAs (Fig. 72.1 and Table 72.2). Most current stent-graft designs have favored suprarenal stents (Zenith-Cook Medical, Bloomington, Indiana; AFX-Endologix, Irvine, California; Endurant-Medtronic; Ovation-Trivascular, Santa Rosa, California) to inhibit downward migration and the development of type I endoleak and endograft failure. In addition, the Zenith, Endurant, Excluder, Aorfix (Lombard Medical Inc., Irvine, California) and Ovation stents have barbs to provide active, rather than passive, fixation. Ovation stents also have unique polymer-filled sealing rings to create an enhanced seal at the aortic neck and endolegs. The AFX device is the only one that touts passive fixation, whereby the flow divider of the stent-graft sits directly on the aortic bifurcation. The C3 delivery system for the Gore Excluder graft is a recent iteration of the device which allows for the ability to reposition the graft through the use of a constraining dial which allows for proximal trunk reconstraining and reopening, a feature that may be particularly beneficial in tortuous proximal necks. The Aorfix stent graft is the only FDA-approved device indicated for the treatment of angulated necks of up to 90 degrees. Recent technologic advances have focused on addressing suboptimal anatomy, in particular, of the infrarenal neck.

Percutaneous Technique

With the advent of smaller delivery systems, percutaneous technique has been used, decreasing the morbidity of the procedure even further. The most common vascular closure device used for percutaneous EVAR is the Perclose Proglide (Abbott, Abbott Park, Illinois) which consists of a pretied Prolene suture, and can accommodate a 5- to 8-French arteriotomy with one suture and an 8.5- to 21-French arteriotomy with two sutures (Fig. 72.2). For arteriotomies greater than 8 French in size, the "preclose technique" is required. The vast diameters

Figure 72.1 (A) Cook Zenith stent graft. (B) Lombard Medical Aorfix stent graft. (C) Medtronic Endurant stent graft. (D) Gore Excluder stent graft. (E) Endologix AFX stent graft. (F) Trivascular Ovation stent graft.

treatable with the Perclose Proglide make it a popular choice in performing percutaneous EVAR. The predictors for failure of the technique include small access vessel diameter and anterior wall calcification,[1] thus the role of ultrasound-guided access when contemplating the use of vascular closure devices is crucial. There is a learning curve with these devices, but given the high technical success rates observed in recent series,[2-5] as well as the decreased complication rate and hospital length of stay,[6] it is clear that given appropriate anatomy, percutaneous EVAR is a useful technique.

RANDOMIZED TRIALS OF ENDOVASCULAR ANEURYSM REPAIR VERSUS OPEN REPAIR

Perioperative Outcome

EVAR-1 was a randomized prospective U.K. study including 1082 patients that compared EVAR with open AAA repair in patients who were fit enough to undergo open surgical repair

TABLE 72.2 Device Characteristics of Current Stent Grafts

Device Name	Company	Configura-tion	Max Device Diameter	Minimum Device Diameter	Fabric	Metal	Active Fixation	Anatomic Fixation
Zenith	Cook	Trimodular	36	22	Woven Polyester	Stainless Steel	Suprarenal stent with barbs	
Aorfix	Lombard Medical	Bimodular	31	24	Woven Polyester	Nitinol	Hooks	
Endurant	Medtronic	Bimodular	36	23	Woven Polyester	Nitinol	Suprarenal stent with barbs	
Excluder	Gore	Bimodular	35	23	ePTFE	Nitinol	Infrarenal barbs	
AFX	Endologix	Unibody	(cuff) 34	22	ePTFE	Cobalt Chromium	Suprarenal Deployment at aortic bifurcation	Deployment at aortic bifurcation
Ovation	Trivascular	Trimodular	34	20	ePTFE	Nitinol	Suprarenal stent with barbs and infrarenal sealing rings	

ePTFE, Expanded polytetrafl uoroethylene.

from 1999 to 2003.[14] The 30-day mortality rate was reduced in the EVAR group (1.7% vs. 4.7%), although secondary interventions were more common in the EVAR group (9.8% vs. 5.8%). The DREAM trial was a multicenter randomized trial (enrolling from 2000 to 2003) that compared open repair with EVAR in 345 patients,[15] with a reduction in operative mortality in EVAR patients (1.2% vs. 4.6%) and a combined rate of operative and mortality (4.7% vs. 9.8%), with the majority of complications accounted for by pulmonary issues. The Open Versus Endovascular Repair (OVER) trial including 881 patients from 42 Veterans Affairs centers randomized to either EVAR or open repair[16] demonstrated that perioperative mortality was improved in the EVAR group (0.5% vs. 3.0%), yet no difference was seen in mortality at 2 years (7.0% vs. 9.8%). The Anevrisme de l'aorte abdominal: Chirurgie versus Endoprosthese trial compared EVAR with open surgical repair in low- to moderate-risk patients. In-hospital mortality and the incidence of postoperative complications were not statistically different. In addition, with a median follow-up of 3 years, no difference was observed in survival or the incidence of major events.[17]

Long-Term Outcome

A comparison between current stent grafts and those that are off the market reveals a striking difference regarding rates of migration, rupture, conversion, and re-intervention.[18,19] Survival analysis from EVAR-1 demonstrated no difference in all-cause mortality at 6 years, although only 24% of patients survived until the end of the study period. The initial survival benefit of EVAR was lost within 2 years of repair, secondary to a higher death rate from cardiovascular causes among those patients who had undergone EVAR.[20] The rate of graft-related complications and need for re-interventions was significant at 4 years, likely accounting for the higher aneurysm-related death rate in the EVAR group. The rates of aneurysm-related death converged at 6 years in these two groups. The 2-year follow-up study from the DREAM trial showed similar results with a reduction in aneurysm-related mortality in the EVAR group compared with the open surgery group (2.1% vs. 5.7%), which was not reflected in overall mortality.[21] Mortality from cardiovascular causes in the EVAR group again contributed to the equalization of survival between groups at 2 years. As expected, the need for re-intervention was higher in the EVAR group and was 3 times that of the open group in the first 9 months after randomization. At 6-years follow-up, secondary interventions were again higher in the EVAR group: 30% versus 19.1%. The cumulative 6-year survival in the two groups was similar, at 69.9% for the open group and 68.9% for the EVAR group.[22] The OVER trial 2-year results revealed that, although the perioperative advantage of EVAR was still realized at 3 years, survival was similar between groups beyond this time.[23]

Although the results from the EVAR-1, DREAM, and OVER trials rather conclusively demonstrate the improved perioperative morbidity and mortality profile of EVAR compared with open aortic aneurysm repair, concerns remain over the long-term durability and survival benefit of EVAR.[139] Although device modifications and improvements in design have led to a decrease in device failure, the 6-year follow-up data from the U.K. EVAR-1 trial indicated no differences in overall or aneurysm-related mortality compared with open repair in the long term. Furthermore, EVAR was associated with a higher rate of interventions and was costlier.[20] Data from large registries such as EUROSTAR have estimated a re-intervention rate of 5% per year and a continued rupture rate of 1% per year despite EVAR.[24,25] The success of EVAR is highly dependent on the patient's anatomic suitability for the procedure. Factors that determine anatomic suitability include neck diameter, neck length, and angulation. In EVAR-1, 54% of patients were anatomically suitable for EVAR, but this percentage ranged

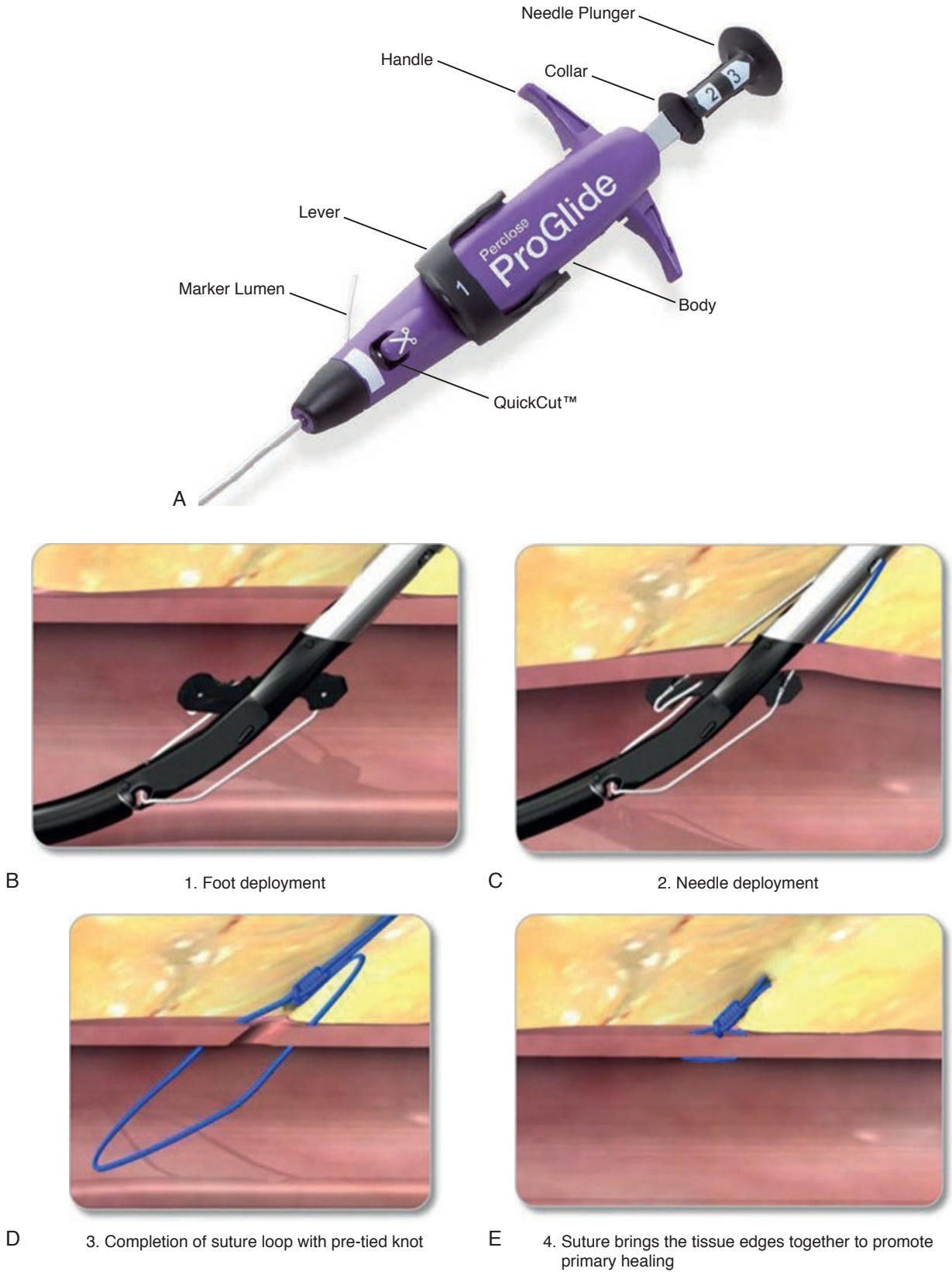

Figure 72.2 (A) Perclose device with components labeled. (B) The foot of the Perclose is deployed within the vessel. (C) The foot is brought up against the anterior wall of the vessel and the needles are deployed. (D) Schematic of suture loop with pretied knot. (E) Pretied knot is cinched down. (From Abbott Proglide Instructions for Use.)

from 6% to 100% across institutions. This wide variation in defining anatomic suitability was underscored in a U.S.-based study of 10,228 patients who underwent EVAR from 1999 and 2008 and had preoperative and postoperative CT assessment using the three-dimensional reconstruction company, M2s (Lebanon, NH).[7] Only 42% of patients met the most stringent criteria for instructions for use, whereas 69% met a more liberal definition of instructions for use. Most sobering, the 5-year rate of sac enlargement after EVAR was 41%. This paper showed the high rate with which EVAR technology was being applied to nonideal anatomy, as well as resultant continued sac enlargement after endovascular repair. Furthermore, long-term follow-up of EVAR patients has been inconsistent, a cause for concern given the not infrequent need for secondary interventions in the mid to long term. A study of 19,962 Medicare beneficiaries undergoing EVAR from 2001 to 2008 showed that 50% of patients were lost to annual imaging follow-up at 5 years after surgery.[8]

Population-Based Results

In general, institutional series results are reported by academic centers with a high level of expertise and controlled, prospective, multicenter studies reflect the beneficial effects of rigorous patient and investigator selection. Therefore statewide and nationwide audits may provide a more accurate clinical picture, although procedure-specific information may be sparse because the study is usually based on administrative data. Studies of this kind have confirmed the short-term advantages of EVAR over open AAA repair.[26,27] In an analysis of Medicare data from 2001 to 2004, in which one can assume that most of the repairs in this study were performed with AneuRx stent grafts because little else was available until 2003, the overall perioperative mortality rate was 1.2% for EVAR and 4.8% for propensity score–matched open surgical controls.[28] However, late survival was similar between the two groups, although the survival curves did not converge until after 3 years. By 4 years the EVAR group had more aneurysm ruptures, as well as a higher re-intervention rate. In contrast, a higher rate of laparotomy-associated complications was seen in the open repair group. This was further examined in a study of late survival with re-interventions and readmission after open and EVAR.[29] Re-intervention and readmissions were more frequent after EVAR than after open repair (7.56 vs. 6.96/100 person-years), but the majority of these re-interventions were minor endovascular interventions. Notably, rupture was five times more common after EVAR compared with open repair, but with a relatively low rate overall. In the open repair group, as expected, laparotomy-associated re-interventions were more common and were associated with a mortality rate of 12.2%. The study concluded that survival was negatively impacted by re-intervention or readmission after EVAR or open surgery, which contributed to the loss of survival benefit of EVAR over time. The late failures of EVAR are consistent with the known failure modes of the AneuRx stent graft.[30,31] In contrast, a more recent study of Medicare beneficiaries from 2003 to 2007 showed that open repair was associated with an increased risk of all-cause mortality and AAA-related mortality over a follow-up period of 5.7 years.[32] The initial increased 30-day mortality associated with open repair was sustained during the entire follow-up period.

Meta-Analysis

A large segment of the available data on EVAR, consisting of 161 papers and 278,862 patients, was examined in a recent meta-analysis.[33] The relatively high overall mortality rate (3.3%) in the combined series reflects the influence of poor early results. These authors used a technique of meta-regression to weigh the effects of different studies over time and assess temporal changes in outcome. The data show striking heterogeneity, some of which is attributable to the effects of changing technique and device design. Both mortality rate and endoleak rate showed steady improvement between 1992 and 2002. Based on the regression line, the perioperative mortality rate was estimated to have fallen to approximately 1.4% in 2002, which is very close to the rates seen in the Lifeline, EVAR-1, and DREAM studies discussed previously.

ENDOVASCULAR ANEURYSM REPAIR COMPARED WITH MEDICAL MANAGEMENT

The question of whether EVAR is better than medical management in high-risk patients was addressed by the EVAR-2 trial, in which 338 patients who were unfit for an open repair were randomized to either EVAR or medical management.[34] The aneurysm-related mortality and all-cause mortality rates were no different between groups. The 30-day mortality rate for EVAR was 9%, although 3.6% of these deaths were from rupture while awaiting EVAR, because the median time to intervention was 57 days. Furthermore, 25% of patients assigned to medical management eventually underwent EVAR either because of patient preference or surgeon preference, with a strikingly low mortality rate. Given the number of AAA ruptures in the EVAR group while awaiting surgery, as well as crossover of the medically treated patients to the treatment group, it is perhaps not surprising that no difference was seen in aneurysm-related or overall mortality between groups at 4 years. Despite its shortcomings, EVAR-2 correctly underscores the fact that very-high-risk patients may not benefit from AAA repair because they often die from other causes before a benefit can be realized. However, it appears that EVAR can be performed safely by experienced surgeons in carefully selected high-risk patients.

Other studies provide data on performing EVAR in high-risk patients.[35-37] Data from the Department of Veterans Affairs National Surgical Quality Improvement Program on high-risk veterans undergoing EVAR showed a 30-day mortality rate of 3.4% and a 1-year mortality rate of 9.5%, which was significantly reduced compared with open repair (5.2% and 12.4%, respectively).[37] A subset analysis of high-risk patients from five industry-sponsored FDA trials showed a perioperative mortality rate of 2.9%. Both studies had open surgical controls, which suggests that the relatively improved survival percentages may have been due to a "healthier" high-risk cohort. The Veterans

Affairs large aneurysm study, which was an observational study of surgically unfit patients, showed a 1-year rupture rate of 9.4% for aneurysms measuring 5.5 to 5.9 cm, 10.2% for aneurysms 6.0 to 6.9 cm, and 32.5% for aneurysms measuring 7.0 cm or greater.[38] Thus very large AAAs even in high-risk patients may benefit from EVAR, but often such AAAs are not anatomically suited for EVAR.

ENDOVASCULAR ANEURYSM REPAIR IN RUPTURED ABDOMINAL AORTIC ANEURYSMS

EVAR has been shown to be a successful, less morbid approach of ruptured aneurysms compared with open repair in select patients and in the setting of an appropriate endovascular infrastructure to accommodate emergent performance of the procedure. In an early single-institution study describing the use of a multidisciplinary protocol including involvement by emergency department physicians, anesthesiologists, and operating room staff, as well as radiology technicians, the authors reported a 95.2% technical success rate and a perioperative mortality rate of 18%, attributed to multisystem organ failure and abdominal compartment syndrome.[9] In a follow-up study from the same institution, EVAR patients had a significantly lower 30-day mortality compared with the open group (24.2% vs. 44.2%, $P < .005$) and an improved 5-year survival rate (37% vs. 26% $P < .005$).[10] However, these results were again balanced by the need for re-intervention in the EVAR group in up to 23% of cases. In another institutional study which used propensity score matching to compare EVAR versus open repair for ruptured AAAs, there was no difference in perioperative mortality (22% vs. 32%, $P = .40$) or 3-year survival rates (42% vs. 47%, $P = .66$), but there was a higher rate of tracheostomy, renal failure, and myocardial infarction in the open group.[11] In a Dutch study of patients with suspected aortic aneurysm rupture who were suitable for either endovascular or open repair, the intraoperative, 30-day and 6-month survival after EVAR was 4%, 20%, and 28% compared with 6%, 45%, and 54% in the open group, respectively. Thus, in patients with anatomy amenable for EVAR, there was a 25% perioperative mortality reduction with EVAR which persisted to 6 months of follow-up.[12] It is clear that in patients who are suitable candidates for EVAR and at institutions where endovascular stents of varying sizes are available for emergent use, as well as in the setting of having well-trained operating room staff, EVAR for ruptured aneurysms is associated with a high technical success rate and lower perioperative morbidity and mortality rate compared with open repair.

COMPARISON OF DIFFERENT STENT GRAFTS

There is a dearth of data to allow appropriate comparison among different EVAR devices, due to lack of large numbers and lack of long-term follow-up. From the EUROSTAR data,[36] the AneuRx and Talent stent grafts had the highest rates or migration, endoleak (types I and III), and conversion. The Zenith stent graft, although having the highest rate of aneurysm sac shrinkage and lowest rate of migration, had the highest rates of limb occlusion. The Excluder stent graft had the lowest rate of limb occlusion. There are limitations to the EUROSTAR Registry—including voluntary, not mandatory, enrollment—which likely introduce bias. The Lifeline Registry consists of data from patients collected under four multiinstitutional investigational device exemption clinical trials for FDA approval with mandatory 5-year follow-up.[39] Unfortunately, the only device-specific information was for the Ancure device, which is no longer commercially available. No data are available on Zenith stent grafts. Resch et al. devised a method to evaluate the amount of longitudinal traction required to disrupt endograft fixation to cadaveric aortas, with a sutured anastomosis used as a comparison.[40] Although a force of 150 newtons was needed to disrupt a surgical anastomosis, all endografts required much less traction for dislodgment. The Zenith required the most force to be exerted (24 N), followed by the Ancure (12.5 N), Vanguard (9.0 N), and Talent (4.5 N). A similar study by Malina et al. showed that barbs and hooks increased the fixation 10-fold, whereas radial force had no impact.[41] The migration rate appears to be lowest for stent grafts that offer proximal active fixation.

COMPLICATIONS OF ENDOVASCULAR ANEURYSM REPAIR

Endoleak

An endoleak is defined as persistent blood flow in the aneurysm sac following stent grafting. Endoleaks are categorized into five different types, which differ in etiology as well as treatment (Fig. 72.3).[42-48]

Type I

Type I endoleak is defined as persistent blood flow into the sac either from around the graft proximally (type IA) or distally (type IB). When recognized in the operating room, type I endoleaks are typically addressed by performing proximal device extension and/or bare metal stent deployment to buttress radial support in the neck, with or without renal artery snorkel/encroachment techniques to preserve renal artery blood flow.[49] The Aptus EndoStapling System (Heli-FX, Aortic Securement System, Sunnyvale, California), which uses screws to secure the stent graft to the aortic wall, may also be used to enhance the proximal seal. If the main body or trunk of the prior stent graft is too short for the deployment of a proximal extension, an aorto-uniiliac device may be used, necessitating a femoral-femoral artery bypass and embolization of the contralateral proximal iliac artery with an occlusion device. The patency rate of femoral to femoral artery bypass done with aorto-uniiliac stent grafting for treatment of aortic aneurysmal disease is high, with a primary patency at 54 months of 90.9% and assisted primary and secondary patency rates of 97.7% and

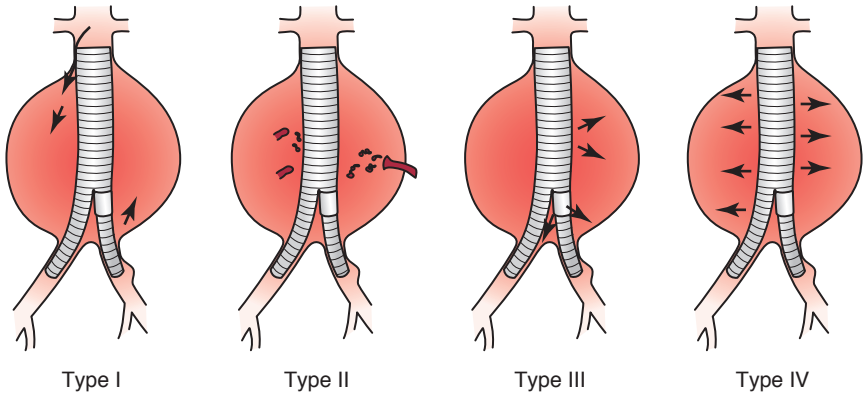

Figure 72.3 A type I endoleak (periprosthetic) occurs at the proximal or distal attachment zones (or at both). A type II endoleak is caused by retrograde flow from patent lumbar or inferior mesenteric arteries. A type III endoleak arises from a defect in the graft fabric, an inadequate seal, or disconnection of modular graft components. A type IV endoleak is due to graft fabric porosity, which often results in a generalized mild blush of contrast material within the aneurysm sac. (From White GH, May J, Waugh RC, et al. Type III and type IV endoleak: toward a complete definition of blood flow in the sac after endoluminal AAA repair. *J Endovasc Surg*. 1998;5:305-309.)

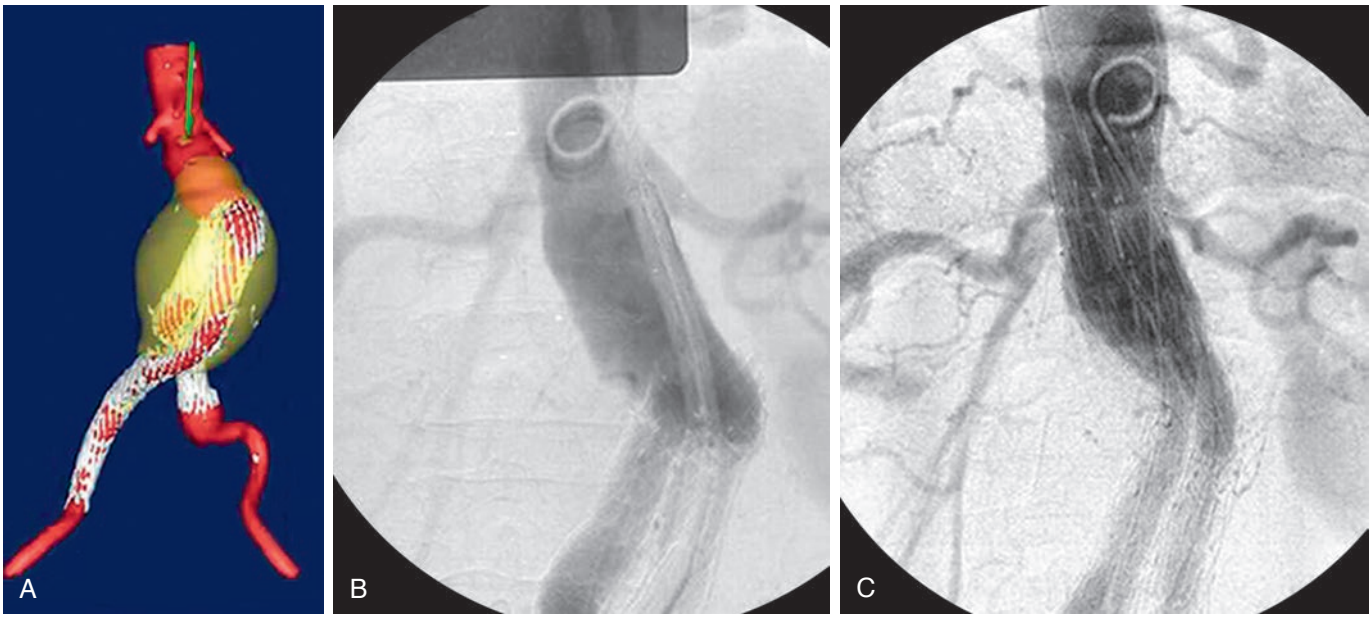

Figure 72.4 (A and B) Example of delayed type I endoleak secondary to graft migration. (C) Treatment consisted of proximal extension with a Zenith extender cuff.

100% at 66 months.[50] When type I endoleak is detected late, it is typically secondary to caudad migration of the stent graft or continued dilatation of the neck. A proximal extension may be deployed to achieve a proximal seal (Fig. 72.4). If type I endoleak continues after proximal stent-graft extension or bare metal stent placement, embolization with glue and or coils has been shown to be a useful adjunct in treating persistent type I endoleak in a small series.[51] A fenestrated graft may also be used to extend the seal zone to the juxtarenal and suprarenal aorta (see Chapter 80). Another described maneuver to treat proximal type I endoleak includes the aortic wrap method with a 12-mm Hemashield patch secured around the aortic neck.[52] Distal common iliac artery dilatation with type IB endoleak is retreated with hypogastric artery occlusion and extension to the external iliac artery or by use of a branched iliac device (Zenith or Gore). If the previously described maneuvers are not successful in fixing the endoleak, operative explant of the stent graft is necessary because of the high risk of rupture associated with type I endoleak.

Type II

Type II endoleak is defined as persistent sac filling from back-bleeding side branches (i.e., the inferior mesenteric artery, lumbar arteries, or middle sacral artery). Postoperative CT scans show type II endoleak in 10% to 20% of patients following EVAR.[42-44,53] In comparison with type I and type III endoleaks, type II endoleaks have a relatively benign course, with as many as 80% resolving spontaneously within 6 to 12 months of

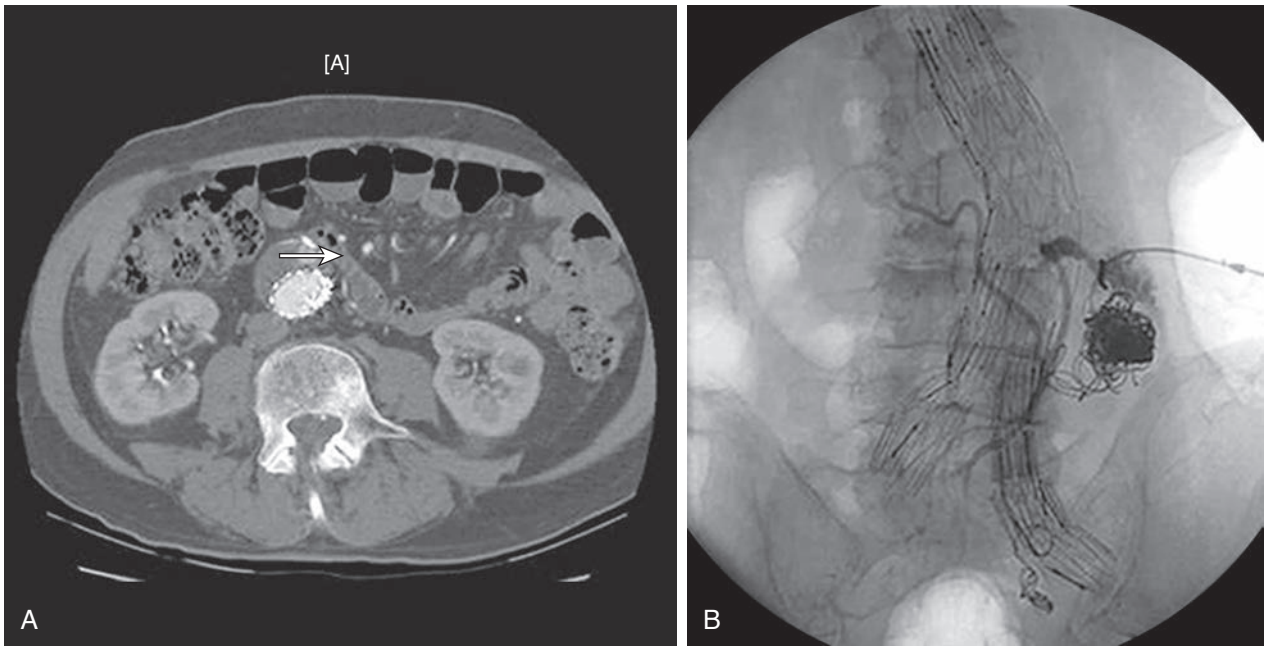

Figure 72.5 (A) A type II endoleak is visible on computed tomographic angiography. (B) A translumbar approach was used to deliver coils into the origin of the inferior mesenteric artery.

stent-graft repair.[18] Furthermore, the risk of aneurysm rupture due to a type II endoleak is small. Multivariate analysis of the EUROSTAR data showed no association between type II endoleak and risk of aneurysm rupture or need for surgical conversion.[44] A recent meta-analysis likewise demonstrated the rarity of aneurysm rupture with isolated type II endoleak.[54] Therefore typically type II endoleaks are not treated unless aneurysm sac enlargement is documented. Persistent type II endoleaks are usually associated with a large endoleak cavity,[55] flow between inflow and outflow arteries,[56] and large patent inferior mesenteric and lumbar arteries.[57] Embolization can be performed using coils or N-butyl cyanoacrylate glue. The transarterial approach can be undertaken to embolize the inferior mesenteric artery through the superior mesenteric artery via the marginal artery of Drummond. Another technique involves catheterizing the sac via the femoral artery by advancing the wire and catheter in between the iliac limb and the iliac artery into the AAA.[58] The translumbar approach uses direct aneurysm sac puncture technique (Fig. 72.5). Regardless of the approach, type II endoleaks physiologically behave like AV malformations, and embolization of the nidus of the endoleak, including the inflow and outflow vessels, is the optimal approach. Retroperitoneal endoscopic ligation of the lumbar arteries has also been described.[59] If the previous interventions fail to be successful, operative explant or direct ligation of the backbleeding vessel via sacotomy is required.

Type III

A type III endoleak results from fabric erosion or a leak between stent-graft components. Only modular grafts are at risk for component separation, but all devices are at risk for graft failure. Rates of type III endoleak range from 0% to 1.5%.[44,60] Type III endoleak from fabric erosion is effectively treated with stent-graft relining or bridging of components to effectively seal the defect (Fig. 72.6). Component separation is likewise treated with relining. In cases in which the device pieces are particularly separated in space due to excessive tortuosity, obtaining wire access through both components may be challenging, and transbrachial access with a snare may be useful in this situation. Plain radiographs are often more sensitive for detecting impending component separation because they offer a more global overview of the framework of the stent graft. While in the operating room, arteriography with the pigtail catheter in the main body of the stent graft and below the proximal fixation site can help to distinguish a type I from a type III endoleak.

Type IV

Type IV endoleaks are related to porosity of the graft fabric, occur less frequently with current-generation stent grafts, and are noted within 30 days of graft implantation. They usually resolve after graft interstices thrombose. No treatment is usually required because they are short-lived and resolve on their own. However, high graft porosity, as demonstrated by the earlier-generation Excluder graft, can lead to sac growth in the absence of demonstrable endoleak.[12]

Type V

Type V endoleak, or "endotension," is defined as elevated sac aneurysm pressure without a demonstrable endoleak. It is generally believed that the etiology is an undetected endoleak or transmission of systemic pressure through thrombus. Endotension is typically detected as continued sac enlargement on CT scan but can also be detected by direct aneurysm sac pressure sensors (Cardiomems, Atlanta, Georgia). Relining with proximal and/or distal extension may be initially performed. If this is

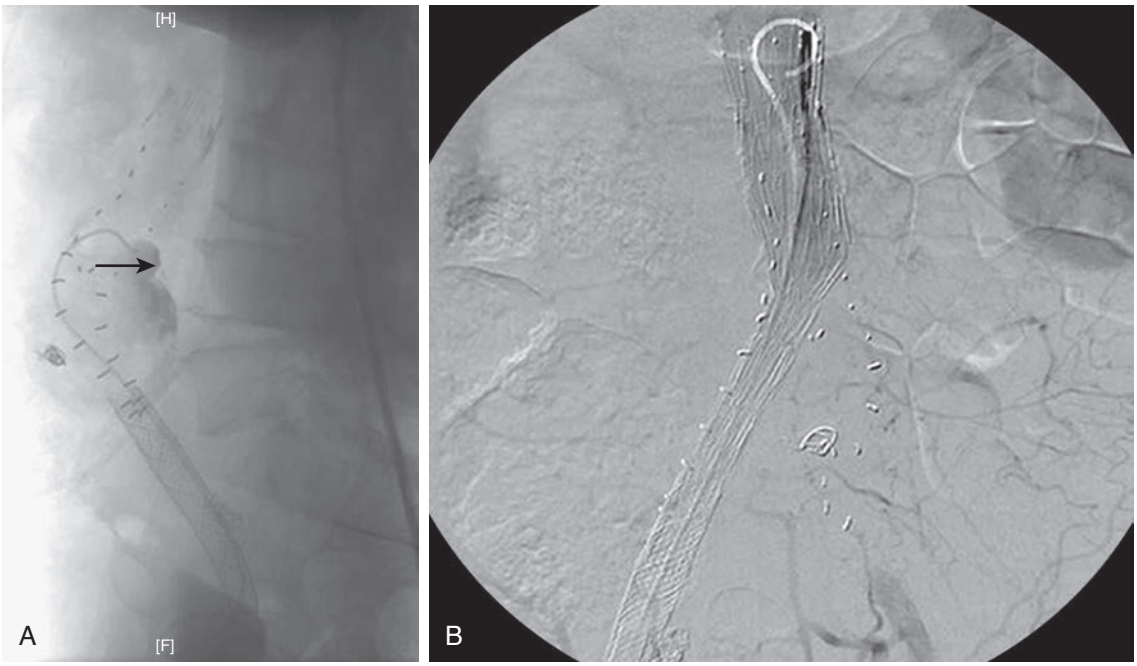

Figure 72.6 (A) A patient who had undergone an endovascular aneurysm repair 4 years previously with the Ancure device. His left limb was chronically occluded, which was causing claudication symptoms. Computed tomography scan additionally revealed continued aneurysm sac enlargement. A lateral projection arteriogram demonstrated erosion of the stent graft in the posterior portion of its main body *(arrow)*. (B) Aortouniiliac stent graft was deployed to reline the original repair followed by femoral-to-femoral artery bypass to revascularize the contralateral limb.

not successful, operative explant is necessary in the setting of continued AAA enlargement.

Endoleak Detection

Contrast-enhanced CT scan is the "gold standard" for detection of endoleaks unenhanced, early, and delayed phases. The unenhanced scan shows mural calcium, which can be distinguished from contrast on subsequent series. Types I and III endoleaks are detected on arterial phase images, whereas type II endoleaks are detected on delayed phase images. The location of the endoleak may give an indicator as to its origin. For example, a ventrally oriented leak is likely to be emanating from the inferior mesenteric artery, whereas a dorsally oriented endoleak is more likely to supplied by the iliolumbar arteries.[46] If the endoleak is not demonstrated on three-dimensionally reconstructed CT images, arteriography is warranted. Alternative imaging modalities include magnetic resonance imaging (MRI)[61,62] and duplex ultrasound.[63-65] MRI is an expensive imaging modality, and caution must be used with stainless-steel devices such as the Cook Zenith stent grafts.[66] In addition, the earlier proposed benefit of use in patients with renal insufficiency has been overturned in light of the increased incidence of nephrogenic systemic fibrosis with gadolinium exposure in patients with a glomerular filtration rate less than 30.[67] Duplex ultrasound does not require contrast administration and is not associated with radiation exposure, but its success depends greatly on the technologist and it can be challenged by patient factors such as morbid obesity or presence of bowel gas. A recent meta-analysis revealed a pooled sensitivity of 0.83 and a pooled specificity of 1.00 for duplex ultrasound detection of type I and type III endoleaks.[68] Data from a relatively large study revealed that, although duplex ultrasound yielded only a sensitivity of 67% compared with CT scan, no type I endoleaks or endoleaks requiring intervention were missed.[64]

Migration

Migration refers to caudal movement of the stent graft, which may lead to loss of proximal fixation and result in type IA endoleak. Cephalad migration of iliac limbs occurs less frequently, and rarely a stent graft can migrate proximally to encroach on the renal arteries. The tendency toward caudal migration increases with angulation of the neck,[69] decreased neck length, neck thrombus, and large diameter of the neck.[70] In the multicenter AneuRx trial, 8.4% patients experienced migration of their stent grafts, with initial low deployment of the device and short fixation length found to be significant predictors.[71] Postprocedural causes for stent-graft migration include aortic neck dilatation, sac shrinkage with concomitant sac shortening, and displacement of the stent graft from external compression.[52,72,73] The most important planning strategy is adherence to the instructions for use, as much as possible. Preprocedurally, a proximal neck fixation length of 15 mm is typically recommended, although some data suggest that as little as 10 mm may be effective in providing a seal, at least in the short term.[74,75] In addition, avoiding angulation greater than 60 degrees between the infrarenal neck and the longitudinal axis of the aortic aneurysm is associated with less migration. In a particularly angulated

patient, a more flexible stent graft should be chosen. The Aorfix stent graft (Lombard Medical Inc.) is the only stent graft approved for neck angulation of up to 90 degrees. In a flow model study comparing the Aorfix stent graft with other manufactured stent grafts of less flexible design, the endoleak rate in angulated necks was lower in the Aorfix-treated patients.[76] Midterm results from a European multicenter study on the Aorfix also revealed acceptable results, although longer-term follow-up is needed.[77]

To avoid migration in patients with short and angulated necks, several manufacturers have modified their original devices to make them more flexible. In addition, the Zenith and the Excluder also offer active fixation with the use of barbs, which are an integral part of the device and become embedded in the aortic wall. The AFX stent graft (Endologix) provides passive fixation via its "anatomic" seating on the aortic bifurcation. It is designed to allow for aortic extensions to be added proximally, which is ideal in the presence of a highly angulated neck. The Aorfix stent graft has proximal clips for active fixation of the device to the aortic wall. Its fish-mouth design also enhances the length of seal available at the neck. In addition, because of its unique ring stent design, it is very flexible and resistant to kink. The Aptus EndoStapling System helps to fix the proximal aspect of the main body to the aortic wall. The Anaconda (Vascutek, TERUMO Cardiovascular Systems Corp, Ann Arbor, Michigan) is another device undergoing clinical trials in the United States. In addition to its unique flexibility, the Anaconda allows for repositioning after graft deployment, allowing for optimum graft placement.[78]

Graft Limb Occlusion

Stent-graft limb occlusion occurs after 3% to 7% of procedures over a 9-month to 4-year period,[79,80] usually within the first 6 months following EVAR; it is more frequent in patients who have aortoiliac occlusive disease, a small distal aorta (<14 mm), or tortuous iliacs or in those who require external iliac artery landing. Earlier-generation stent grafts with unsupported limbs were at greatest risk for limb kinking.[6,81,82,140] However, newer stent grafts are protected from graft limb kinking by more limb support. In a review of 460 patients, current-generation stent grafts were associated with a graft limb occlusion rate of 4.3% compared with 18.7% in first-generation devices.[80] Data on the Endurant graft revealed a graft limb occlusion rate of 4.0% at 1.7 years.[83] More recent data comparing limb occlusion in patients undergoing elective EVAR with the standard Zenith flex stent graft versus the low profile stent graft showed that despite more challenging iliac artery anatomy in the low profile group, the 24-month rates of freedom from limb occlusion were no different (92% vs. 95% respectively, $P = .293$). During the conduct of the operation, it is important at the completion of the endovascular stent-graft repair to remove stiff wires before performing the completion arteriogram. This provides the ability to detect any occult kinks that may be straightened by the presence of a stiff wire.[81] Most patients with limb occlusion present with either buttock, thigh, and/or calf claudication; rest pain is infrequently encountered.[80] Usually the limb can be recanalized with either thrombolysis or surgical thrombectomy techniques, with adjunctive iliac stenting as needed. When a kink is identified and treated with a stent, patency rates are quite high. Arteriography with oblique orientation can be helpful in providing views to identify the problem. In addition, intravascular ultrasound (IVUS) and measurement of pullback pressures may help identify graft infolding, which may not be appreciated on arteriography.[84] In those patients in whom the limb cannot be reopened, femoral-femoral bypass or axillofemoral bypass is performed to revascularize the affected leg.

Renal Artery Occlusion

Renal artery occlusion occurs either from inadvertent stent-graft coverage of the renal artery origins or from embolization. Stent-graft coverage most often occurs procedurally; delayed upward migration of the stent graft after EVAR is uncommon.[85] During the procedure, under systemic heparinization, graft impingement on the renal artery orifice may not be readily apparent. Often the graft fabric of stent grafts extends 2 mm above the radiopaque markers (e.g., Zenith); thus the radiopaque stent struts must be placed to ensure that the fabric does not cover the renal artery origin. Appropriate positioning of the C-arm to avoid parallax and to ensure that the origin of the renal artery is appreciated is paramount. When detected in the operating room, rescue renal stenting can be attempted via the femoral or brachial approach to preserve renal artery flow. When detected late, open hepatorenal or splenorenal bypass may be required.[86] In a single-institution study investigating suprarenal versus infrarenal fixation, suprarenal fixation did not cause a decrease in renal function or increase the need for dialysis.[87] Embolization to the renal arteries can be a cause of early or delayed renal insufficiency. This is especially true if thrombus is present in the area of aortic fixation. A recent study showed that the presence of thrombus in the neck in combination with suprarenal fixation was associated with an increase in thromboembolic complications.[88]

Neck Dilatation

The juxtarenal portion of the aorta is not as prone to dilatation as is the infrarenal aorta, but this region can dilate following EVAR,[89] resulting in migration and/or type I endoleak and risk of rupture.[9] In a study of 230 patients, the predictors for neck dilatation were large AAA diameter, large aortic neck size, and circumferential neck thrombus.[90] It is interesting to note that no difference was found between stent grafts with infrarenal or suprarenal attachment. Indeed, a study evaluating the neck following endovascular and open repair found similar increases in neck diameter over time, suggesting that the dilatation is a sign of progression of disease rather than the radial force of a stent graft that is larger than the aortic neck.[91] However, generous oversizing of the stent graft should be avoided because greater than 30% oversizing with the Zenith stent graft was associated with a higher migration and aneurysm expansion risk.[92] Excessive device oversizing also contributed to neck dilatation with the AneuRx graft.[93]

Stent-Graft Infection

Infection of the aortic stent graft is a rare event, with small case series reporting an incidence of 0.2% to 0.7%.[94] Development of aorto-enteric fistula has also been described. In the largest case series to date, nine patients presented with infected EVAR at a tertiary referral center.[95] All patients underwent complete explants of the stent graft—five patients with preemptive extra-anatomic revascularization (axillary-femoral to femoral artery bypass), the other four patients by in-situ reconstruction with Rifampin-soaked polyester. Seven of the patients survived to discharge, and the mean follow-up of the surviving patients was 11 months. In this series the presence of a concomitant aortoenteric fistula was particularly virulent. Two of the three patients with aortoenteric fistula died before discharge. Although stent-graft infection is generally considered a highly morbid condition with mortality rates estimated at 36%,[96] the findings from this study suggest that explantation of infected grafts can be performed with an acceptable mortality rate. Additional data suggest that conservative management may be possible. Data from a retrospective study of TEVAR and EVAR graft infections showed an overall mortality of 25% but no difference in outcome in those patients treated with antibiotics alone versus those who underwent surgical explantation. Although the numbers are small and the authors acknowledge the possibility of a type II error, this study does suggest that a subset of patients may be best treated with antibiotic therapy alone.[97] Indeed, the patients treated conservatively either had no microorganisms isolated or predominantly *Staphylococcus* and *Streptococcus* species grown in their blood cultures.

Pelvic Ischemia

Pelvic ischemia can manifest itself as buttock claudication, buttock necrosis, spinal cord ischemia, colorectal ischemia, and erectile dysfunction.[98-100] The incidence after EVAR varies in the literature, but pelvic ischemia occurs frequently, and the complications should be discussed with the patient during the consenting process. It typically occurs as a consequence of occlusion of one or both internal iliac arteries in the presence of a common iliac or internal artery aneurysm. In a study that also included data from 18 papers detailing internal iliac artery embolization before EVAR, buttock claudication occurred in 55% of patients overall, with 52% occurring in unilateral embolization and 63% occurring in bilateral embolizations.[99] Staging the bilateral internal iliac artery embolizations by at least 1 week appears to decrease the risk of ischemic complications.[13–15] Erectile dysfunction occurred in 17% overall, with 17% occurring after unilateral and 24% occurring after bilateral embolizations. Other studies similarly found that bilateral embolization was associated with an increase in pelvic ischemic complications.[100] Furthermore, when bilateral profunda femoral arteries are diseased, these complications tend to be most severe. Although relatively common initially, buttock claudication appears to improve in most patients. In a study in which bilateral internal iliac arteries were occluded, buttock claudication occurred in 31% of patients but persisted beyond 1 year in only one-third of those patients.[101] In addition, multiple studies have shown that embolization of the internal iliac artery proximal to its bifurcation is associated with a lower incidence of buttock claudication than if more distal branches are occluded, because this allows more pelvic collateral flow via internal iliac branches.[101,102] Colonic ischemia is relatively rare following internal iliac artery embolization and EVAR, with an incidence of 1.7% in one series.[103] Spinal cord ischemia is also a rare complication following internal iliac artery occlusion and EVAR. In a small series that examined the incidence of complications following bilateral internal iliac artery embolization before EVAR, the incidence was 3% and was characterized as paraparesis.[101]

Stent-Graft Fatigue

The aortic stent graft is under constant mechanical stress during the cardiac cycle, which can cause fracture of barbs and stent struts. With the exception of the original Zenith stent (stainless steel), most stent grafts are composed of nitinol, which is an ideal material given its flexibility and conformability. However, nitinol can be associated with surface irregularities, which serve as foci for stress and strain and can predispose to wire fracture. This problem has been lessened with electropolishing chemical etching techniques. Strut and stent fractures have been reported in multiple older-generation devices, including the Ancure,[104,138] Vanguard,[105] and Lifepath.[106] Strut failure, barb separation, and stent breakage have also been described with current-generation devices.[107,108] Not all stent failures require intervention; enough redundancy exists in the number of barbs and stents per ring that all stents do not need to be intact for appropriate fixation and support to occur. Barb separation or disruption associated with migration and endoleak formation or stent fracture associated with graft disruption must be treated as outlined earlier for type I endoleak and type III endoleak, respectively.

FOLLOW-UP

Postoperative follow-up is important for ensuring continued success of EVAR. Postoperative surveillance allows the detection of endoleaks, aneurysm sac expansion, stent fracture, limb kinking, and material fatigue.

Computed Tomography Scans and Ultrasound

Initial protocols were adopted from early FDA-sponsored pivotal trials, which recommended CT scans at 1-, 6-, and 12-month intervals and annually thereafter.[109] The frequent use of CT scanning has raised concerns related to the added cost of these studies, as well as cumulative radiation exposure[110,111] and use of nephrotoxic agents. Although ultrasound/duplex avoids radiation exposure and the use of contrast, concerns have been raised in the past regarding its variable sensitivity in detecting endoleaks.[65] The utility of ultrasound is also limited in obese patients or those presenting with substantial bowel gas. Based on recent reports, some investigators have proposed that follow-up with duplex as the sole imaging modality is appropriate, provided no endoleak or sac enlargement is documented on

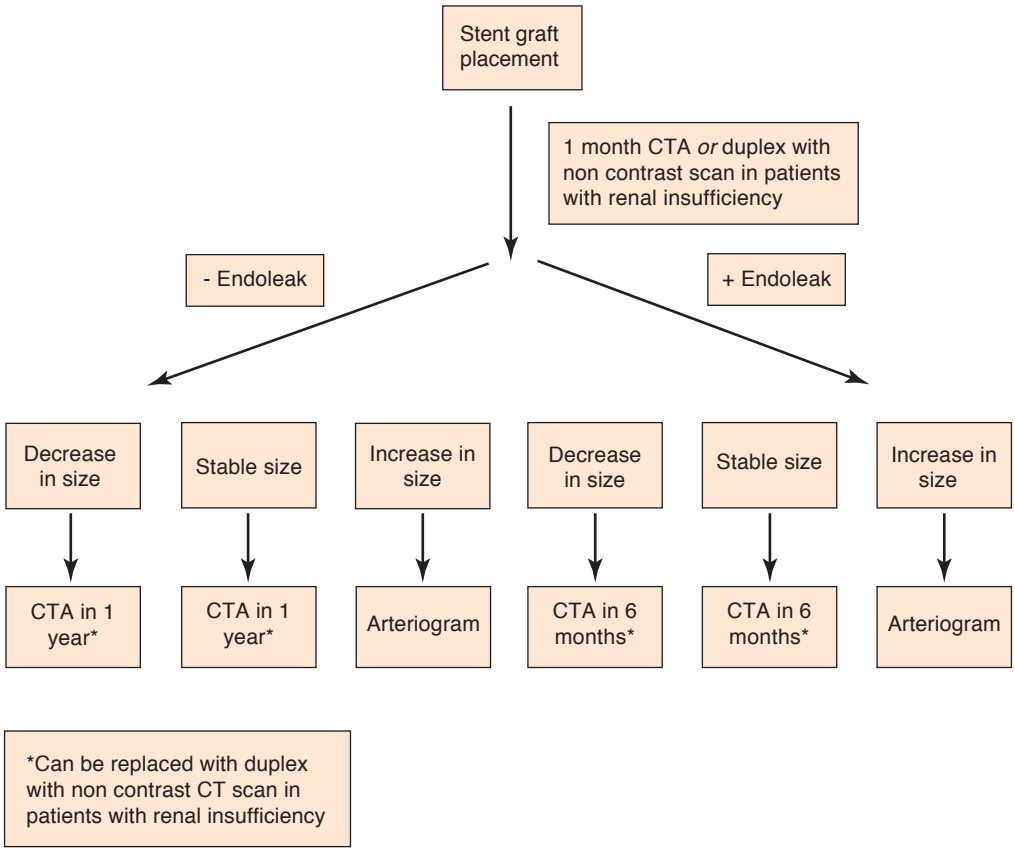

Figure 72.7 Surveillance strategy following endovascular aneurysm repair. *CTA*, Computed tomographic angiography.

the first annual CT scan.[112] A significant increase in sac size or a newly diagnosed endoleak would then prompt CT imaging.[113] Omitting the 6-month scan has also been recommended, if CT imaging at 1 month does not identify an endoleak.[112,114] These protocols have been shown to be safe, with minimal risk of clinical adverse event.[115] The Society for Vascular Surgery practice guidelines currently recommend contrast-enhanced CT scanning at 1 and 12 months during the first year after EVAR.[109] Detection of an endoleak at 1 month would prompt another CT scan at 6 months to evaluate the need for intervention. If neither endoleak nor aneurysm expansion is detected during the first year after EVAR, subsequent duplex follow-up may be a reasonable alternative. In patients with renal insufficiency, duplex ultrasound in combination with a noncontrast CT scan is an alternative surveillance strategy (Fig. 72.7). Although the risk of endoleak declines with each negative surveillance CT scan, new endoleaks have been identified as late as 7 years following EVAR,[116] underscoring the importance of lifelong surveillance.

Sac Pressure Measurement

Sac pressure measurement has also been recommended as an alternative method to image-based follow-up.[117,118] One such device, CardioMEMS (Cardiomems Inc.) uses a $30 \times 5 \times 1.5$ mm sensor that contains no battery and is powered externally with radiofrequency energy. This wireless implantable pressure-sensing device is placed in the aneurysm sac at the time of EVAR. The pressure measurements obtained from these sensors have been shown to correlate well with transcatheter pressure measurements from the sac, with a sensitivity of 0.94 and a specificity of 0.80 for detecting type I or III endoleaks.[118] Sac pressures have been shown to decrease in shrinking aneurysms and in patients who have undergone successful coil embolization of type II endoleaks.[119]

Re-intervention Rates

The long-term (>20-year) outcome of stent grafts has not yet been established, and multiple reports of the midterm results of EVAR using various devices cite a not insignificant need for secondary intervention. From the EVAR-1 and EVAR-2 trials the secondary intervention rates were 7.0% for the Zenith and 9.4% for the Talent grafts at approximately 4 years of follow-up.[120] In the 5-year follow-up study of patients who underwent Zenith stent-graft repair as part of the pivotal trial, the cumulative risk of conversion, limb occlusion, migration greater than 10 mm, or component separation was 3% or less at 5 years. The cumulative risk of late endoleak was 12% to 15%, accounting for most of secondary interventions and underscoring the importance of continued surveillance long term.[121] The effect of re-interventions and readmissions following EVAR versus open aneurysm repair was also examined in Medicare beneficiaries (Fig. 72.8).[29] Survival was found to be negatively

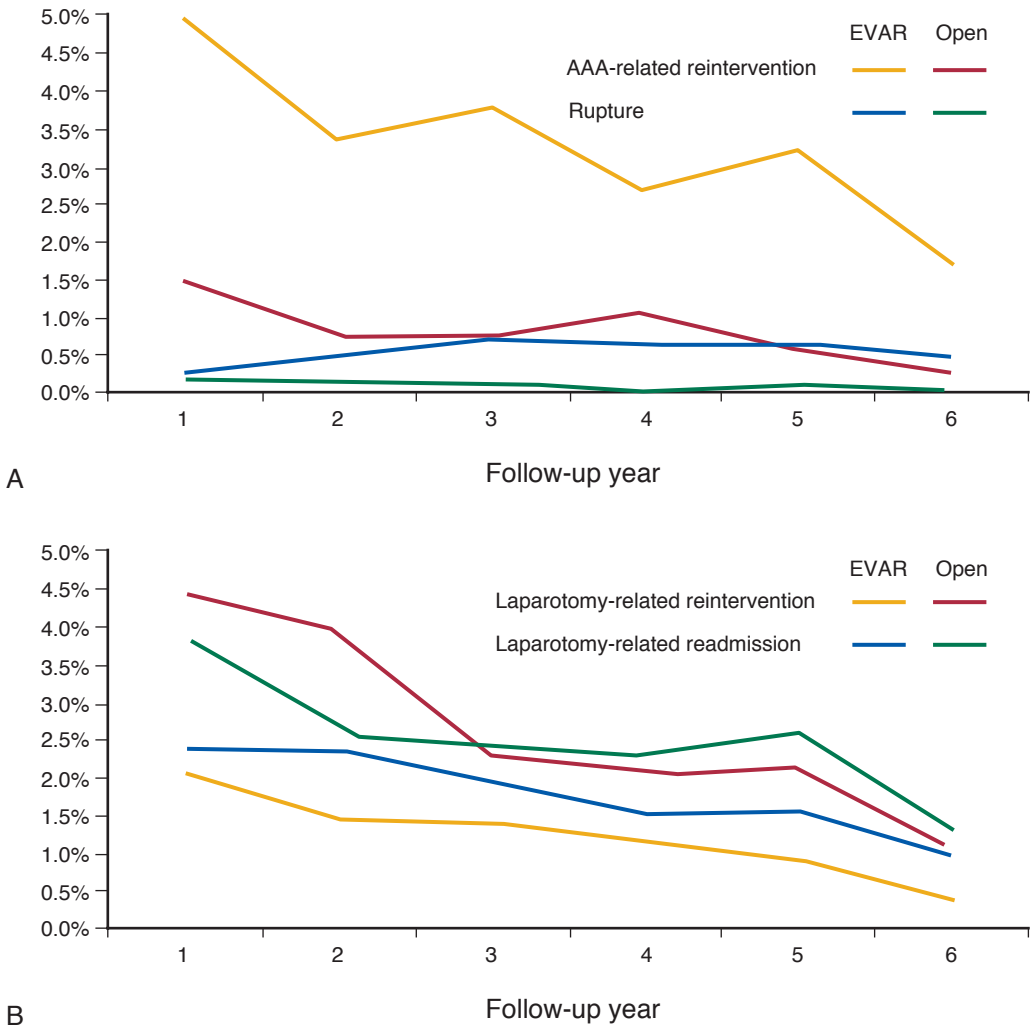

Figure 72.8 Re-interventions for Medicare beneficiaries undergoing endovascular aneurysm repair (EVAR) or open repair. (A) Abdominal aortic aneurysm (AAA)-related re-interventions and AAA rupture. (B) Laparotomy-related re-interventions and readmissions. (From Giles KA, Landon BE, Cotterill P, et al. Thirty-day mortality and late survival with reinterventions and readmissions after open and endovascular aortic aneurysm repair in Medicare beneficiaries. *Vasc Surg*. 2011;53(1):6-12, 13.)

affected by readmission or re-intervention in both groups. However, the majority of secondary interventions were minor in nature, with a relatively low 30-day mortality. In contrast, laparotomy-related re-interventions were more common in the open repair group and were associated with a relatively high mortality. The authors point out that, although the cumulative effect of re-interventions and higher rate of rupture following EVAR contribute to the equalization of survival benefit, the surviving patients in the EVAR group are likely sicker than those in the open repair arm.

ENDOVASCULAR REPAIR OF THE JUXTARENAL AORTA

For some patients with a proximal infrarenal neck length less than 10 to 15 mm (the traditional desired neck length for EVAR), partial renal artery coverage with adjunctive renal artery stenting can be performed.[49]

Encroachment Technique

This technique is used when partial renal artery coverage is needed to achieve a seal (Fig. 72.9A). The aortic stent graft is deployed in the usual fashion, with careful attention paid to the relationship between the top of the stent-graft fabric and the lowest renal artery. The optimal degree of angulation and rotation for visualizing the takeoff of the renal artery is then determined. Catheter and wire access of the renal artery can usually be obtained transfemorally. If a device with a suprarenal stent is used, care is taken to access the base of the triangular stent rather than in between the triangular stents. The authors use a combination of a Rosen wire (Cook Medical) and a guide catheter system to serve as a platform for performing

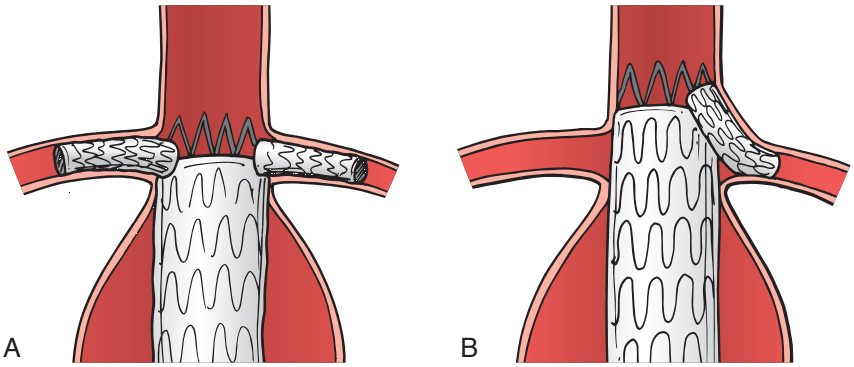

Figure 72.9 (A) The encroachment bilateral renal stenting technique. (B) The snorkel technique. (From Chaikof E, Cambria R. *Atlas of Vascular Surgery and Endovascular Therapy.* Philadelphia: Elsevier; 2012.)

the renal stent. Balloon-expandable stents are favored in this location because the increased radial force is essential to push the superior margin of the stent graft inferiorly to preserve renal artery flow.

Snorkel Technique

This technique is used when complete coverage of the renal artery origin is required to achieve a seal (see Fig. 72.9B). Transbrachial access is key because the snorkel maneuver is often used when more extensive coverage of the renal artery is required, and the stent is required to run alongside the stent graft before entering the orifice of the artery. The authors use a combination of a Rosen wire and a long Destination sheath (Terumo, Somerset, New Jersey) as our platform. The renal stent comes to lie entirely outside the aortic stent graft, parallel to it, until it enters the renal artery orifice. A covered stent is preferred for this purpose. The length of the renal stent is usually longer because of the distance along the aortic stent graft, which needs to be traversed before reaching the origin of the renal artery. It is important to maintain balloon support of the renal stent while ballooning the aortic graft, because compression of the stent can occur with this maneuver.

Results

Using either the encroachment or snorkel technique, a case series showed that sealing of the aneurysm was possible (no type I endoleak at 1-month follow-up) with a primary assisted patency of renal artery stents of 100% at a median follow-up of 12.5 months.[49] Another case series examined the efficacy of snorkel for repair of juxtarenal aneurysms.[122] In this study, 56 snorkel stents were placed in the renals alone or in the renals in combination with the mesenteric vessels. Technical success was 98.2% for snorkel placement, with 98.2% patency over a mean follow-up of 10.7 months. The 30-day mortality rate was 7.1%, with a 25% early endoleak rate, which was distributed among types I, II, and III. Another meta-analysis summarized the results from 15 case series of snorkel or chimney grafts in which 77.4% of patients underwent a concomitant EVAR.[123] Primary technical success was achieved in all patients, but a 14.0% type I endoleak rate occurred, over half of which required treatment. The primary patency was 97.8% at a mean follow-up of 9 months, and the 30-day in-hospital mortality rate was 4.3%.

ENDOVASCULAR REPAIR OF COMMON ILIAC AND INTERNAL ILIAC ARTERY ANEURYSMS

Common Iliac Artery Aneurysms

Current stent-graft technology allows treatment of iliac artery aneurysms with a seal zone diameter of up to 25 mm at the common iliac artery bifurcation.[124,125] The largest iliac limb diameter is 28 mm, provided by the Endurant endograft (Medtronic Inc.). When the diameter of the seal zone is greater than 25 mm or the aneurysmal disease extends into the external iliac artery, the endograft can be extended into the external iliac artery, with coil embolization or plug occlusion (Amplatzer vascular plug, St. Jude Medical, Inc., St. Paul, Minnesota) of the proximal internal iliac artery to prevent a type II endoleak.[126] To preserve internal iliac artery flow, an external to internal iliac artery bypass can be performed with proximal ligation of the internal iliac artery to effectively "move" the iliac bifurcation more distally. In one series of 22 patients, all bypasses remained patent at a mean follow-up of 15 months, with only mild buttock claudication occurring in two patients ipsilateral to the site of coil embolization.[127] Another series showed similar excellent internal iliac bypass patency rates of 91%, as well as freedom from ischemic symptoms.[128] Using the iliac-branched device (IBD) designed by Cook (Cook Medical) (Fig. 72.10A-C and 72.11), in a single-institution study of 46 patients, IBD side-branch patency was 87% at 5 years.[129] In another series with 100 patients, internal iliac artery patency was 91.4% at 5 years.[130] However, initial results from the trial in the United States revealed a stent fracture in the connecting stent, causing a type III endoleak, which has been treated with relining. The recently FDA-approved Gore Excluder Iliac Branch Prosthesis in the United States has the potential to achieve a more stable seal in those with ectatic iliac arteries, as well as preservation of important pelvic collaterals to decrease the likelihood of buttock claudication as well as reduce the complications of spinal cord ischemia should further aortic repair be required (Fig. 72.12). In a study of 10 patients evaluating the safety and

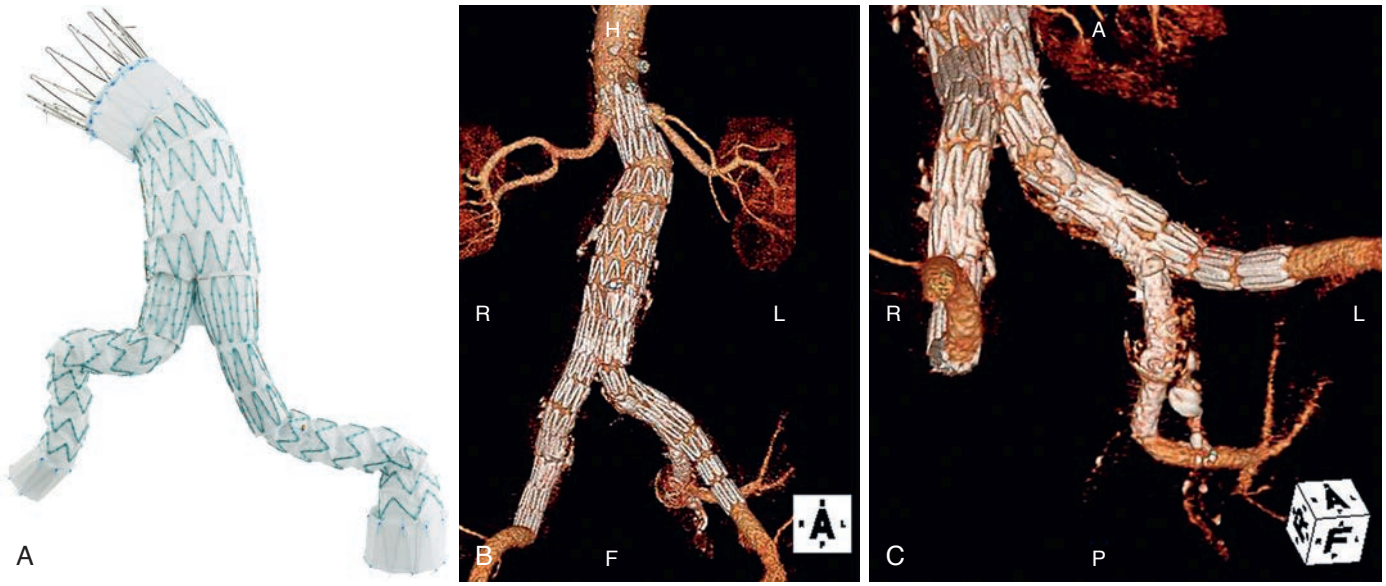

Figure 72.10 Zenith Iliac Branch Graft. (A) Picture of iliac branch graft (Cook Medical, Bloomington, Indiana). (B) Computed tomographic angiography (CTA) of aortic stent graft and iliac branch graft. (C) CTA of iliac branch graft.

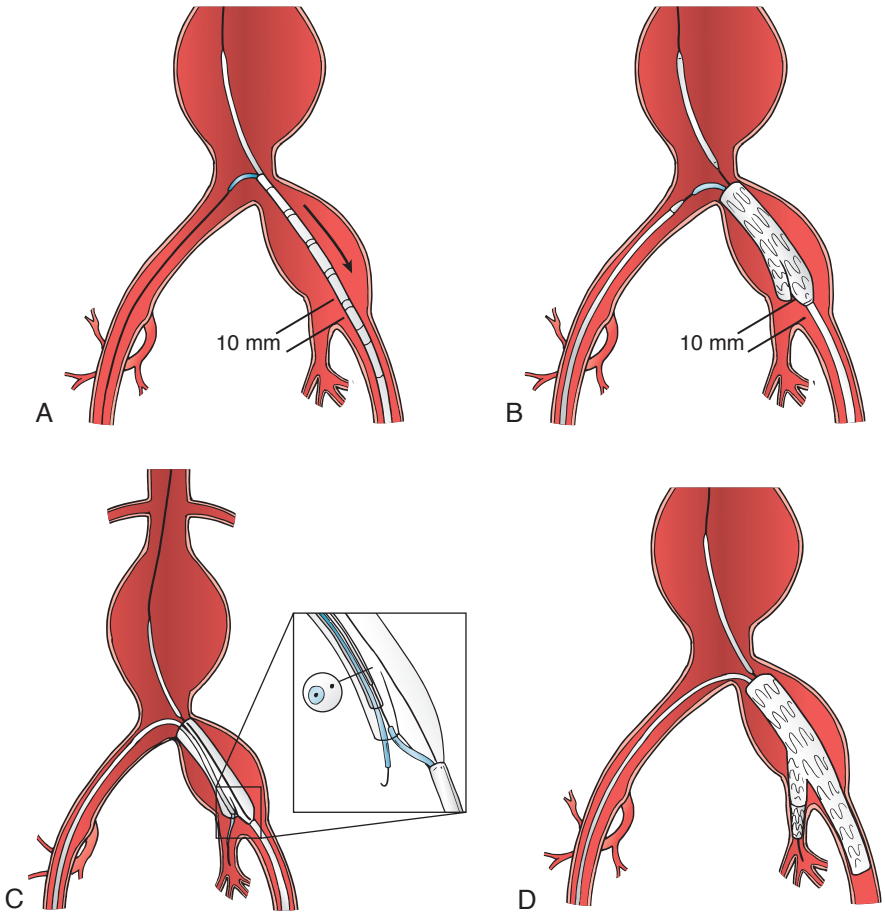

Figure 72.11 (A) The guide wire is passed through the curved catheter and snared from the contralateral groin. (B) The iliac-branched device (IBD) is partially deployed, and the sheath is advanced from the contralateral groin into the side branch of the IBD. (C) The wire is advanced into the internal iliac artery. (D) Following stiff-wire exchange, the covered stents are deployed after fully unsheathing the IBD. (From Serracino-Inglott F, Bray AE, Myers P. Endovascular abdominal aortic aneurysm repair in patients with common iliac artery aneurysms: initial experience with the Zenith bifurcated iliac side branch device. *J Vasc Surg*. 2007;46:211-217.)

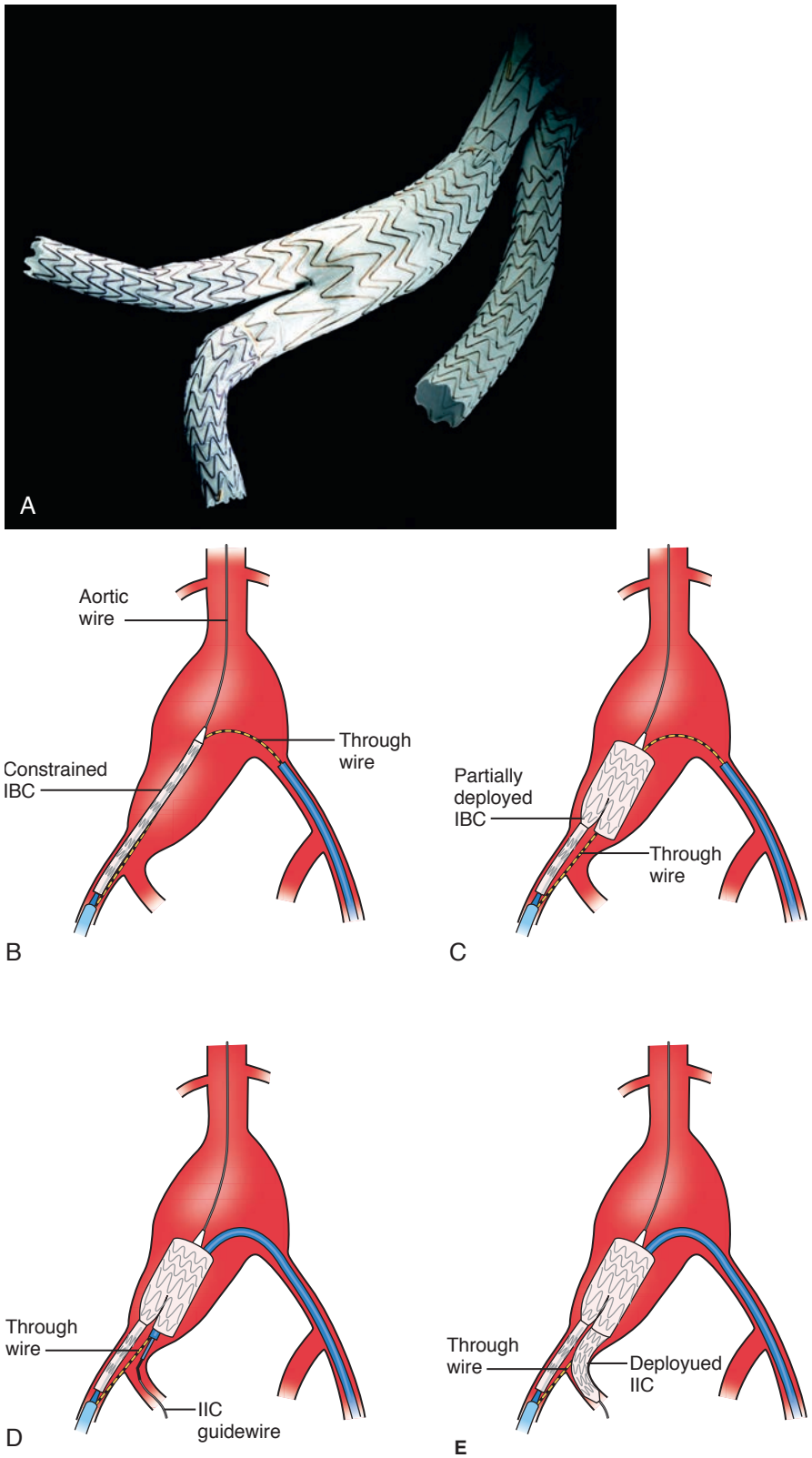

Figure 72.12 (A) Gore Iliac Branch Component. (B) Aortic wire, Constrained iliac branch component (IBC), Through wire. The guide wire is passed through the sheath and snared from the contralateral groin. (C) Partially deployed IBC, Through wire. The aortic wire is passed through the IBC and the through wire is passed through the branch and the IBC is advanced into common iliac artery and partially deployed. (D) Through guide wire, Internal iliac component (IIC) guide wire. The wire is advanced into the internal iliac artery. (E) Through wire, Deployed internal iliac component. The internal iliac stent is deployed. (From Gore Iliac Branch Endoprosthesis IFU.)

short-term efficacy of this device in the treatment of iliac artery aneurysms, there was a 100% technical success rate, with 100% branch patency at 1 month and 90% branch patency at 6 months (see Chapter 75).[16]

Internal Iliac Artery Aneurysms

Internal iliac artery aneurysms are typically managed with endovascular coiling/plug occlusion with stent-graft coverage of the origin, although an iliac branch device solution could be considered if anatomy is suitable. If the proximal landing zone is compromised, a chimney/snorkel can be deployed extending into either the common or external iliac artery,[131] or the "sandwich technique" may be used (Fig. 72.13).[141] A hybrid technique has also been described. An aorto-uniiliac endograft with a femoral-to-femoral artery bypass can be performed with a covered stent deployed from the contralateral external to the internal iliac artery in a "reverse U" fashion (Fig. 72.14).[132]

COST OF ENDOVASCULAR ANEURYSM REPAIR

The in-hospital cost of EVAR is approximately $20,000 in the United States.[133] In an Australian study comparing the cost of endovascular with open repair, operative costs were significantly higher in the endovascular group and were attributed entirely to the cost of the endograft. In addition, although overall length of stay and ICU stay were shorter in the endovascular group, total hospital costs were still greater in the EVAR group.[134] Because of the need for continued surveillance, the average cost for follow-up (median was 1 year) was also significantly greater in the EVAR group, which increased over time. The data from the EVAR-1 study likewise showed that EVAR was more costly than open repair.[135] In a study investigating the cost of long-term surveillance and secondary procedures, the cumulative cost at 5 years was $11,351.[133] The cost was significantly higher if the

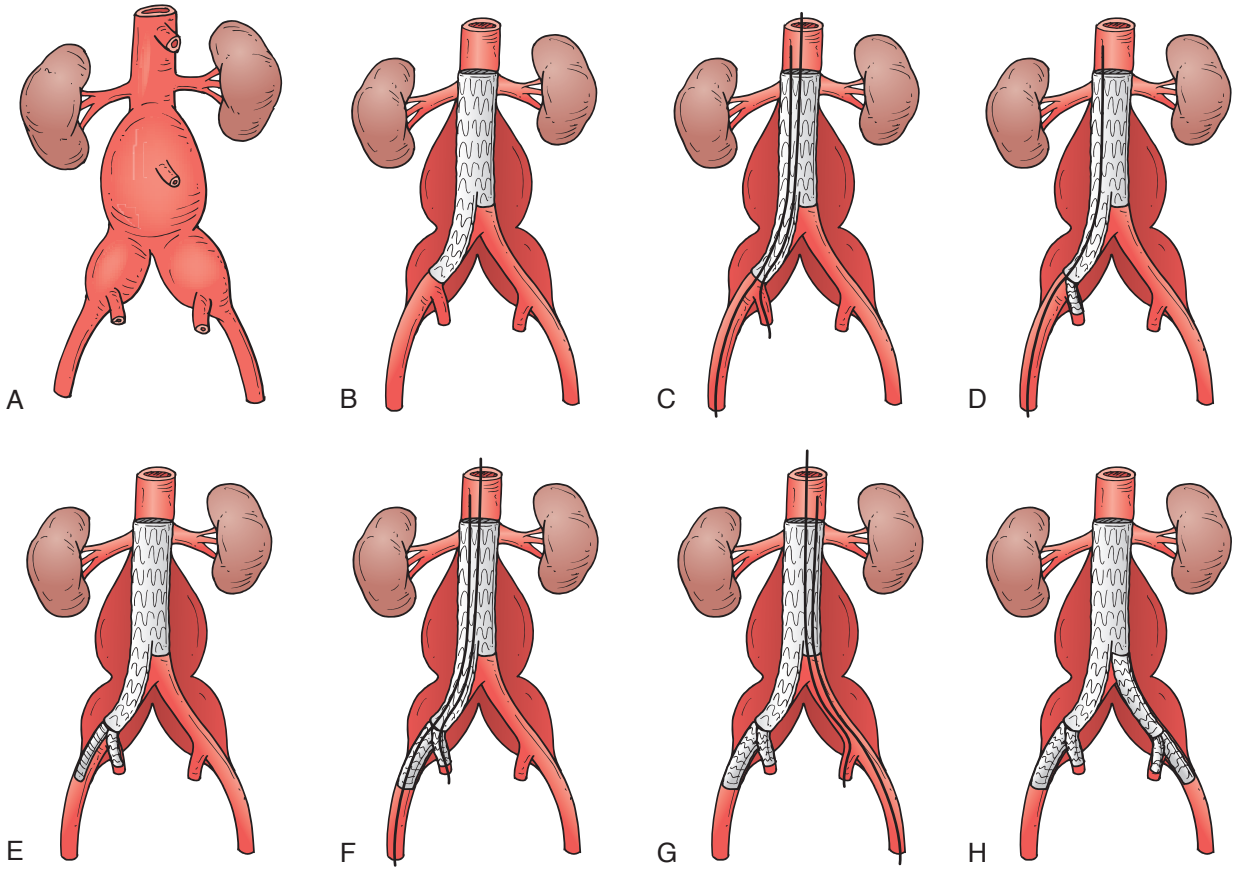

Figure 72.13 (A) Aortoiliac aneurysm extending to the internal iliac artery (IIA). (B) Deploy the main body of the bifurcated stent graft. (C) Cannulate the ipsilateral IIA using left brachial access. (D) Deploy the covered stent inside the nondiseased IIA with 5-cm overlapping into the iliac limb extension. (E) Position the iliac limb extension with the proximal end distal to the IIA stent. (E) Deploy the iliac limb extension and then the internal iliac artery stent. (G) For bilateral sandwich repair, deploy the contralateral iliac limb stent graft, then cannulate the remaining IIA, using left brachial access. (H) Deploy the iliac limb extension followed by the internal iliac artery stent. (From Lobato AC, Camacho-Lobato L. The sandwich technique to treat complex aortoiliac or isolated iliac aneurysms: results of midterm follow-up. *J Vasc Surg*. 2013;57:28S.)

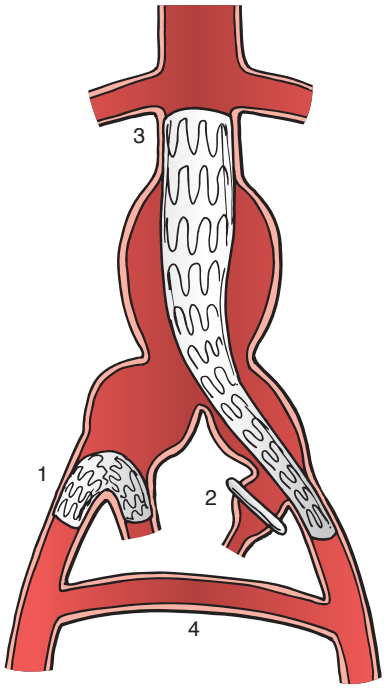

Figure 72.14 Diagram of external-to-internal iliac artery stent *(1)* and contralateral internal iliac artery occlusion *(2)*. Aortouniiliac device *(3)* and femoral-femoral artery bypass *(4)*. (From Ghosh J, Murray D, Paravastu S, et al. Contemporary management of aorto-iliac aneurysms in the endovascular era. *Eur J Vasc Endovasc Surg*. 2009;37:184.)

patient required a secondary intervention ($31,696 compared with $3668). The 5-year cost for patients with endoleak was $26,739 compared with $5706 for those without endoleak. In the OVER trial,[136] although the operative costs were significantly higher in the EVAR group, the shortened length of stay led to a decreased overall hospital cost for EVAR ($37,068 vs. $42,970). However, by 2 years, this difference in cost was no longer statistically significant. In addition, the probability of EVAR being less costly and more effective was 71% for life-years and 51% for quality-adjusted life years (QALYs). Recently, a cost-utility model based on a meta-analysis of patients treated with EVAR or open repair of ruptured aneurysms was performed. EVAR was less costly compared with open repair ($26,133 vs. $28, 395).[17] The mean QALY was higher for EVAR compared with open repair (3.09 vs. 2.49). EVAR was thus cost effective compared with open repair at a threshold of $30,000 to $45,000/QALY.

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A complete reference list can be found online at www.expertconsult.com.

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73 CHAPTER

Endovascular Aneurysm Repair Techniques

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Abstract

Endovascular aortic aneurysm repair is currently the mainstay of treatment for the elective repair of anatomically suitable aortic aneurysms. Appropriate repair requires in depth knowledge of the types of stent-grafts available, including their configurations, sizes, methods of "sealing" and physical properties. Successful treatment also requires precise preoperative measuring techniques, as well as extensive knowledge of vascular access techniques, stent graft deployment techniques and troubleshooting, the appropriate use of adjunctive procedures when warranted, and the management of intraoperative troublshooting and complications, including endoleaks. These areas are reviewed in the current chapter.

Keywords

Endovascular aortic aneurysm repair
aortic stent grafts
EVAR
endoleaks

CHARACTERISTICS OF ABDOMINAL AORTIC STENT GRAFTS

Current commercially available systems have a wide variety of configurations that can treat the majority of infrarenal aortoiliac aneurysms. Various options exist for stent-graft fixation, sealing, patency, sizing, and durable exclusion of aortic aneurysms. Radiopacity, deployment precision, ease of use, and sheath size and flexibility are additionally important characteristics. Current commercially available infrarenal endografts and their respective U.S. Food and Drug Administration (FDA) approval dates can be seen in Table 73.1.

Fixation

An essential feature of all stent grafts is a method of fixation to inhibit distal migration from the seal zone after deployment. Aortic blood flow delivers constant caudad force against the proximal end of a stent-graft. In tortuous anatomy, augmented vector forces increase the risk of component separation and even cranial migration of the distal components. Aortic remodeling after endovascular aneurysm repair (EVAR) can also result in morphologic changes and cause stent graft component separation. These factors increase endograft susceptibility to distal migration, kinking, and limb thrombosis over time.

Positive Fixation, Column Support, and Friction

Multiple endograft features are designed to prevent graft migration and consequent complications. *Positive fixation* describes the use of metal hooks, barbs, anchors, or supplemental staples to attach the graft to the aortic wall and prevent migration. In endografts with stents that run the full length of the device, *column support* helps maintain the position of the cranial end of the device in place by straddling the aortic bifurcation for buttressed stability. The outward radial force of the stents themselves creates *friction* with the vessel wall that can reduce migration. However, increased risks of long-term migration in earlier devices without active fixation (AneuRx) have led to near universal incorporation of active fixation in current endograft designs. Some devices have polyester fuzz or other prosthetic material that induces a fibrotic reaction in the aortic neck that aids in graft fixation, and several devices include a combination of these characteristics.

TABLE 73.1 Current Commercially-Available FDA-Approved Infrarenal Aortic Stent Graft Devices

Device	Manufacturer	FDA Approval Date	Implants Worldwide (Approx.)
Excluder	Gore	2002	250,000
Zenith Flex	Cook Medical	2003	150,000
Endurant	Medtronic	2010	200,000
AFX	Endologix	2011	80,000
Ovation	Trivascular	2011	8,500
Aorfix	Lombard	2013	4,000

FDA, U.S. Food and Drug Administration.

Infrarenal Versus Suprarenal Fixation

Infrarenal fixation describes active sealing at the proximal most aspect of the endograft in the infrarenal aortic neck. Endografts with suprarenal fixation employ a bare-metal stent that is separated from the sealing component of the infrarenal neck portion of the stent-graft, extending the fixation component into the pararenal and suprarenal aorta. The suprarenal aortic neck is typically more resistant to late dilation, and long-term fixation with this suprarenal fixation may be improved. If open conversion and complete graft explantation become necessary, removal of endografts with suprarenal fixation requires a comparatively more complex surgical approach.

Sealing

Almost any endograft will seal in an aortic aneurysm with an ideal straight, cylindrical, 15-mm-long neck without thrombus or calcification. Seal zone adjuncts include covered flares that expand beyond the nominal diameter of the main graft, polyester fuzz, sealing cuffs, and off-label stent utilization. The basic stent pattern of the seal zone of the device has a large impact on both sealing and conformability, which are critical factors for treating angulated necks. The scallop depth of the graft material at the cranial margin of the device also determines the effective required seal zone of the device.

Iliac Limbs

The unsupported limbs of early EVAR devices were often plagued by limb occlusion, which prompted frequent off-label use of stents within the originally unsupported limbs. Late fabric erosion with subsequent type III endoleak and aneurysm enlargement or rupture is one complication of this approach that illustrates a late pitfall of off-label use without adequate evidence of safety and effectiveness. Although most current fully supported endograft limbs provide excellent long-term patency, there is sufficient space between stents or stent rings in some devices to allow potential limb kinking, compression, and occlusion. Concomitant iliac arterial injury during EVAR, heavy circumferential distal aortic or iliac calcification, severe iliac tortuosity, and excessive graft limb oversizing are additional factors that may lead to limb occlusion.

Sizing

EVAR stent-grafts come in a wide range of aortic diameters, iliac limb diameters, and graft lengths that are labeled for varying arterial diameters and angulations. The complexity of case planning varies with each system because of differences in sizing windows, techniques, tapering zones, and usable seal zones.

Graft Material

The polyester or polytetrafluoroethylene (PTFE) graft material is similar to that used for open surgical repair. In contrast to open grafts, which become incorporated in fibrous retroperitoneal tissue, stent-grafts are suspended in the thrombus and may develop transudates or microfenestrations that do not close. The graft material may abrade with constant wear against metallic stent components or may be subject to weave deformation by attachment sutures. Sutures themselves may wear or break, causing subsequent increased abrasion. Some stent-grafts are sutured only at the ends of the stent, whereas others use a composite bonding process without sutures.

Radiopacity

Stent components are visible with high-quality fluoroscopic equipment, but some EVAR procedures are performed with portable C-arms, and visualization in these conditions may be difficult in heavy patients. Delivery systems and stent-grafts have additional radiopaque markers to facilitate rotational orientation, deployment, and gate cannulation. Such markers vary with each graft, and not all are positioned in the same position with respect to the graft's fabric edge, which is not itself radiopaque. Some markers are circumferential, whereas others are positioned intermittently around the circumference of the device.

Deployment Precision and Ease of Use

Deployment components vary in flexibility, trackability, valve function, outer diameter of the ipsilateral and contralateral sheaths, number of times that a large sheath must be inserted, and deployment precision. The labeling, torque responsiveness, need for exchange-length wires, difficulty in cannulation of a contralateral gate or snaring a contralateral wire, and other attributes all contribute to the relative complexity of the deployment sequence with each respective graft. Ease of use is thus only one aspect of a deployment system's performance.

Graft Selection and Primary Device Characteristics

Detailed knowledge of sizing, deployment techniques, failure modes, expected outcomes, and reintervention techniques is essential to provide a durable endovascular result. There are a few anatomic situations in which one particular device may be preferred, although even in these situations a surgeon with mastery of a single specific device could probably make that device work for even challenging cases (Fig. 73.1). Difficult iliac anatomy can often be treated with smaller systems or those featuring deployment systems with a higher degree of flexibility and trackability. Short lengths from the lowest renal artery to the aortic bifurcation can be better treated with some devices. Severely angulated, short aortic necks are not well treated with any approved system except the Aorfix, but more flexible investigational devices and off-label aortic stents can potentially overcome challenging proximal necks. Less angulated short necks may be addressed with branched or fenestrated devices or snorkel or chimney adjuncts (see Chapter 80).

Endograft Configurations

Bifurcated endografts are currently utilized in greater than 95% of EVAR cases. These are either modular (Endurant, Excluder, Trivascular, Zenith, Aorfix) or unibody (AFX—Endologix). In the infrarenal position, tube endografts are now utilized only for focal saccular aneurysms or penetrating ulcers that have sufficient normal distal aorta for a dependable seal. While there are no commercially available devices for this indication, off-label use of "stacked" aortic cuffs, larger iliac components, or small diameter thoracic extensions can be utilized for this purpose. Aorto-uni-iliac endografts (ReNu, Endurant) can be utilized in conjunction with a contralateral iliac occlusion device and a femoral-femoral bypass. The relative indications for use of this configuration are listed in Box 73.1. Branched and fenestrated endografts and chimney or snorkel grafts can be utilized in juxta/pararenal aneurysms and TAAA, where there is inadequate normal aorta to achieve a durable seal adjacent to a critical side branch.

Preoperative Sizing and Planning

Precise sizing and preoperative planning are essential for successful initial and long-term outcome after EVAR.

Preoperative Imaging

Computed Tomography Arteriography

Computed tomography arteriography (CTA) is the cornerstone of preoperative imaging for EVAR. The maximum recommended slice diameter is 2.5 mm for standard devices, while sizing for fenestrated or branched devices requires ≤1 mm cuts. Intravenous contrast should be routine unless the patient has severe renal insufficiency. The axial, coronal, sagittal, and three-dimensional (3D) reconstructions (Fig. 73.2A) should all be reviewed. Postprocessing software allows further image interrogation by generating centerline reconstructions, which aid in precise length and diameter measurements. Access to dedicated workstations that allow postprocessing and manipulation of images is ideal. Alternatively, such image processing is available by third parties. Standard digital subtraction arteriography (DSA) has little utility in the preoperative evaluation for EVAR and should not be routinely employed.

Patients with significant renal insufficiency present challenges in preoperative imaging prior to EVAR. Frequently, noncontrast computed tomography (CT) scanning provides enough anatomic information to proceed with standard EVAR. Diameter and length measurements can be made from such a study, and if the anatomy appears uncomplicated and there is no clinical suspicion of associated occlusive disease, it may be reasonable to proceed. Potentially important anatomic information can be missed, however, including: (1) the presence of laminated thrombus in the aortic neck, (2) patency of important side branches such as the hypogastric arteries, and (3) potential occlusive disease in the common or external iliac arteries.

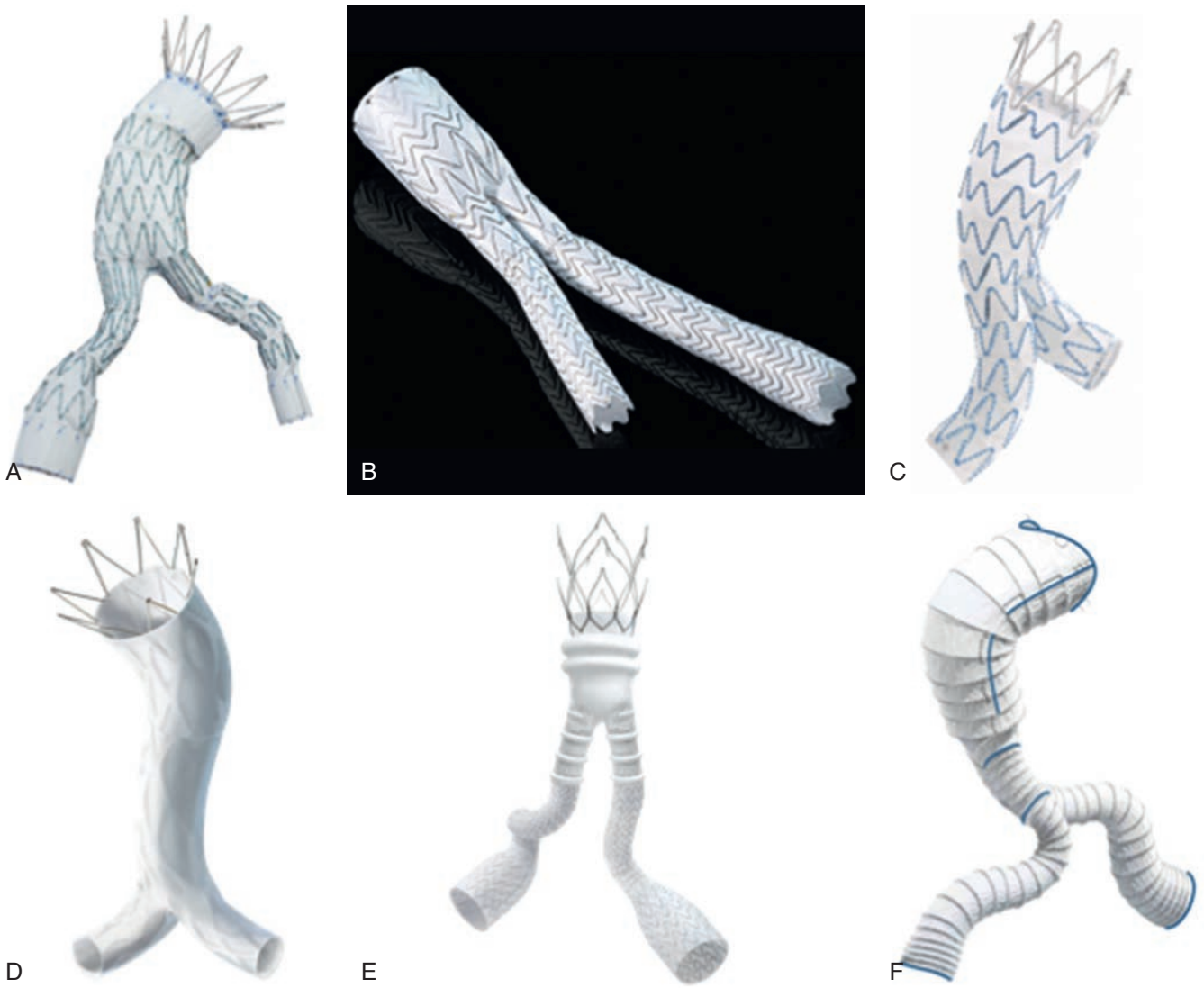

Figure 73.1 Commercially Available Endografts. A, Cook Zenith Flex; B, Gore Excluder; C, Medtronic Endurant IIs; D, Endologix AFX; E, Trivascular Ovation; F, Lombard Aorfix.

BOX 73.1 Relative Indications for Aorto-Uni-Iliac Endograft Configuration

- Very small (<15 mm) terminal aorta (which would not accommodate a bifurcated device)
- Severe unilateral iliac occlusive disease
- Secondary treatment of migration of a short-body endograft

Significant calcification in the iliac arteries, particularly the external iliacs, should make the operator suspicious that associated occlusive disease may be present.

Alternative Imaging

In the patient with severe renal insufficiency who needs further delineation of pertinent anatomy prior to EVAR, intravascular ultrasound (IVUS) can be used to size the aortic and iliac seal zones, evaluate for potential aortic neck eccentric thrombus, and interrogate the external iliacs for potential occlusive disease. Direct angiographic imaging can be obtained using CO_2 as the contrast agent with relatively good visualization.

Endograft Sizing

Aortic Neck Diameter

Measurement of the aortic neck diameter should be taken proximally at the level of the lowest renal artery and extend 15 mm caudal in 5 mm increments. These measurements should be made from the *minor axis* of axial cuts, or ideally from reformatted slices that allow a plane perpendicular to the centerline. The key here is not to overestimate diameter based on oblique CTA cuts of the tortuous aortic neck. Using electronic calipers, these measurements are generally made from adventitia to adventitia to size the aortic neck for most devices. Intima-to-intima measurements were used in the U.S. pivotal studies of the Excluder endograft (W.L. Gore) and are recommended for use with this device.

Endografts should be oversized 10% to 20% in comparison to the aortic neck. In practical terms, this usually translates

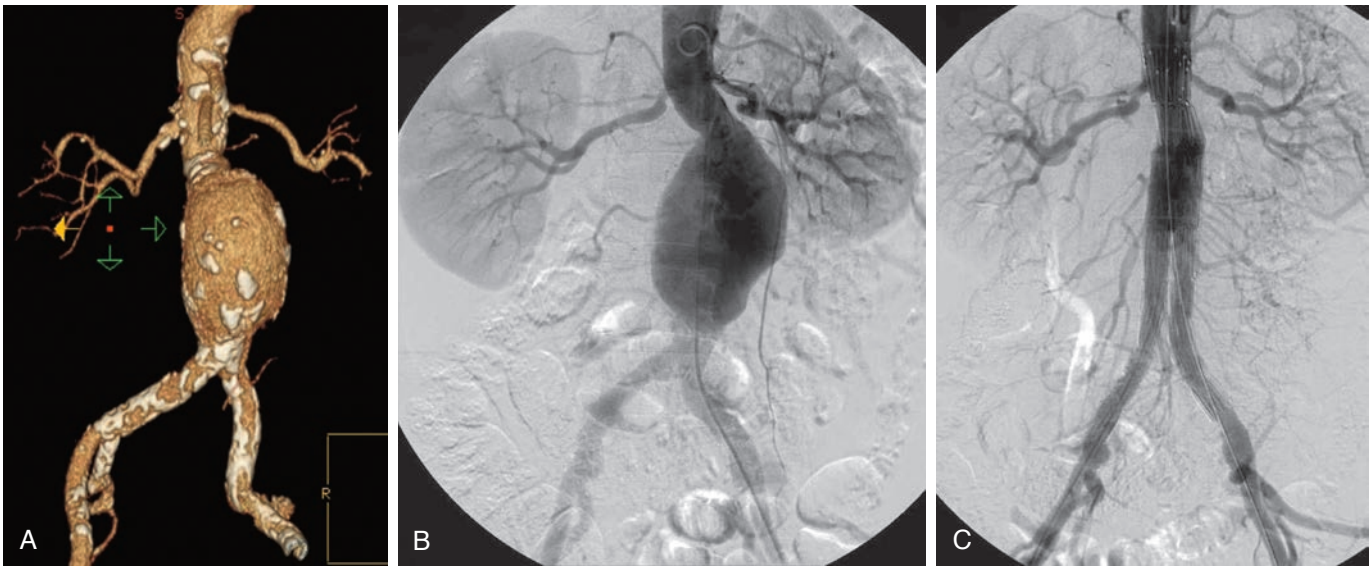

Figure 73.2 (A) Computed tomographic angiography reconstruction of a 6.3-cm abdominal aortic aneurysm (AAA). (B) Angiogram demonstrating the same AAA. (C) Immediate postendovascular aneurysm repair angiogram demonstrating exclusion of the AAA without endoleak.

TABLE 73.2 Specific Notable Characteristics of Current Commercially-Available Infrarenal Aortic Stent Graft Devices, Including Their Graft and Stent Material Design, the Sizes of Aneurysms Appropriate for Treatment With Each Respective Device, The Delivery System Profile, Proximal Fixation Level, and Other Unique Features.

Device	Graft Material	Stent Material	Treatable Aortic Neck Range (mm)	Treatable Iliac Artery Range (mm)	Delivery System Profile Main Body/ Limb (Fr)	Proximal Fixation	Unique Features
Excluder	ePTFE	Nitinol	19-29	8-25	16-20/12-15	Infrarenal	Repositionable proximal delivery system allows multiple attempts to achieve accurate proximal landing
Zenith Flex	Woven Polyester	Stainless Steel	18-32	7.5-20	21/14-16	Suprarenal	Partial proximal repositioning; shortened z-stents of main body and limbs inhibit migration and kinking
Endurant II	Woven Polyester	Nitinol	19-32	8-25	18/14-16	Suprarenal	Three piece system allows flexible *in situ* length sizing, approved to treat 10 mm proximal neck length
AFX	ePTFE	Cobalt Chromium Alloy	18-32	10-23	19/9	Infrarenal or Suprarenal	Unibody component provides anatomic fixation on aortic bifurcation
Ovation	ePTFE	Nitinol	16-30	8-25	14-15/12-15	Suprarenal	Smallest delivery sheath profile (14 Fr OD), proximal sealing ring expanded with polymer *in vivo*
Aorfix	Woven Polyester	Nitinol	19-29	9-19	22/20	Infrarenal	Ability to treat aortic necks with 60°-90° angulation

ePTFE, Expanded polytetrafluoroethylene.

into an endograft diameter that is 3 to 4 mm larger than the aortic neck. Currently, EVAR devices range from diameters of 18 to 36 mm and can accommodate aortic diameters of 16 to 32 mm (Table 73.2).

If there is not full apposition of the endograft to the aortic wall, the risk of a type IA endoleak is substantial. The risks of excessive oversizing are less obvious, however. Bench testing has demonstrated that oversizing greater than 20% creates pleats in the fabric (Fig. 73.3). This pleating of the fabric may contribute to an increased risk of a type IA endoleak and decreased fixation regardless of the endograft used.

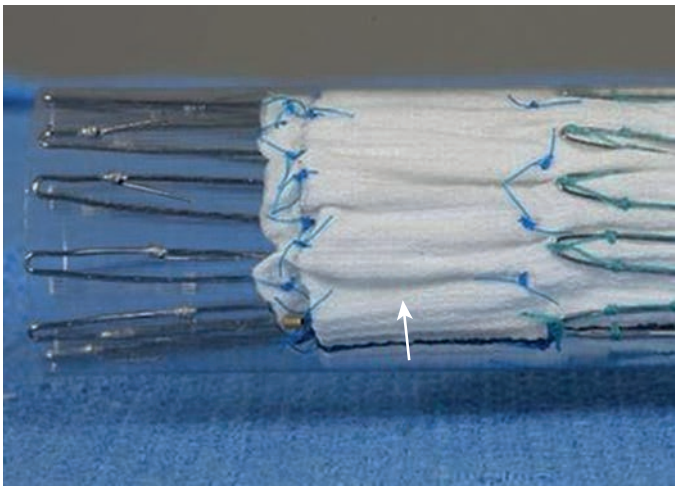

Figure 73.3 Oversizing causes pleating of the fabric *(arrow)*. This is a 28-mm Zenith endograft in a 22-mm tube (27% oversize). Such pleating increases the risk of type I endoleak and migration.

Sizing the Conical Aortic Neck

Patients with conical necks, meaning those with more than a 2 to 3 mm change in neck diameter over the first 15 mm length of aortic neck length, pose an interesting sizing conundrum. In a patient with an aortic neck diameter of 20 mm at the renal arteries that dilates to 24 mm at a position 15 mm caudal, sizing to the larger diameter would suggest the use of a 28 mm endograft. However, this would correspond to a proximal oversizing of 40%. Conversely, sizing to the smaller diameter, such as a 24 mm endograft in a 20 mm neck, would result in inadequate oversizing in a larger area caudally. In these situations, it is prudent to "split the difference," so as to give at least a minimum 10% oversizing in the larger segment and a less than 30% oversizing in the smaller segment. If the degree of size mismatch does not allow such sizing, for example in a situation where there is more than a 3 to 4 mm conical change in first 15 mm of neck, EVAR is not advisable.

Length Measurements

Accurate length measurement between proximal and distal landing zones is critical in selecting the correct endograft components. For EVAR cases, counting the axial cuts is accurate when calculating the distance between the lowest renal artery and the aortic bifurcation in the absence of significant tortuosity or aortic neck angulation. Axial measurements will underestimate the length between the aortic bifurcation and the hypogastric arteries, especially with tortuous vessels. Conversely, length measurements based on centerline calculations with EVAR will occasionally *over*estimate the true length needed.

Situations that typically require longer iliac limbs than the measurements suggest including the presence of extreme iliac tortuosity, when utilizing "balleting" of iliac limbs (Endurant and Excluder, Fig. 73.4) and when extension of the limbs to the external iliac arteries is necessary. In these anatomic circumstances, it is wise to choose a longer length, when in doubt.

Figure 73.4 "Balleting" of iliac limbs. This technique can facilitate cannulation of the contralateral gate of short-bodied modular endografts. A longer iliac limb is frequently required.

Modular devices with variable body lengths, such as the Cook Zenith system, give additional flexibility in sizing by allowing adjustment of the amount of overlap between the components. With this device, the contralateral iliac gate is ideally positioned 1 to 2 cm from the aortic bifurcation. Unlike the iliac components, when there is doubt about the correct main body length, the shorter length should generally be chosen. Other scenarios that would call for a shorter body length include patients with a narrow (<20 mm) distal aortic neck or those with an eccentric calcific "reef" in the terminal aorta. In these instances, after opening the ipsilateral limb, there may be inadequate room for the contralateral gate to open, making cannulation difficult. Of note, the Medtronic Endurant IIs, approved by the FDA in 2014, aims to address and simplify the main body and limb length issues. This stent graft features the shortest available ipsilateral and contralateral main body covered length at 103 and 80 mm, respectively. All main body limb diameters are fixed, allowing any limb to be used on either side. Limb length can therefore be determined during the procedure.

Iliac Diameters

Limbs for the iliac arteries should be sized 10% to 20% greater than their respective minor axis diameter. For non-ectatic iliac arteries, this generally translates into an iliac limb diameter 1 to 3 mm larger than the native vessel. Particular care should

be made to correctly size the iliac limb if extension to the external iliac is required. Excessive oversizing in this scenario may increase the risk of limb thrombosis. When extending to the external iliac artery, the limb should ideally land proximal to or greater than 15 mm distal to points of major angulation in order to avoid kinking and possible limb thrombosis. At least 2 to 3 cm length of distal seal is recommended in patients with large or tortuous common iliac aneurysms that may undergo significant conformational changes as the aneurysm remodels.

Patient Selection

The major anatomic factor in predicting suitability for EVAR is the character of the aortic neck, including the length, diameter, angulation, and shape of the neck. The instructions for use (IFU) of most current devices suggest a minimum neck length of 10 to 5 mm and angulation of less than 45 to 60 degrees. An exception to the limitations on neck angulation is found with the Aorfix device (Lombard), which is FDA approved for aortic neck angles ≤90 degrees. Considering proper oversizing and available endograft sizes, aortic neck diameters up to 32 mm can be accommodated. The shape of the neck is also important in both immediate and long-term success.

The ideal native anatomic configuration is a parallel aortic neck without eccentric laminated thrombus or heavy calcification. Patients with irregularly shaped necks will have a greater risk of inadequate seal and subsequent endoleak. In addition to patients with conical and reverse conical necks, the occasional patient will have a localized posterior bulge in the neck, the so-called double-bubble, which can compromise the seal zone.

While a patient with a single adverse aortic anatomic variable can frequently be treated effectively, those patients who have aortic necks with multiple compromising anatomic features are more problematic. Although highly angulated necks are associated with inferior outcomes, if the neck length is greater than 2 cm and the shape is parallel, the patient may be a reasonable EVAR candidate. Patients with neck lengths of 10 to 15 mm can frequently attain a good initial outcome in the absence of other anatomic compromise. However, the risk of late neck degeneration and a subsequent type IA endoleak may be increased, particularly in the setting of a larger aortic neck diameter or significant angulation. All devices will have compromised outcomes if the anatomic constraints are profoundly exceeded. Patients with aortic necks less than 10 mm in length should be considered for open surgical repair, fenestrated EVAR, or EVAR with adjunctive endovascular techniques.

ANESTHESIA, ACCESS, AND IMAGING

Anesthesia

The choice of anesthetic technique can be tailored to the patient's comorbidities and body habitus. In all situations, it is ideal to control the patient's respirations, either by vocal instruction or by control with the ventilator. Although general anesthesia is used commonly with percutaneous access, the use of local infiltration and intravenous sedation is possible and may be preferred in some clinical scenarios such as rupture. When utilizing open vascular access, a regional (spinal or epidural) or general anesthetic is favored by most operators. In a patient who may need an ilio-femoral conduit, general anesthesia is clearly the appropriate choice.

Vascular Access

Access to the femoral vessels can be achieved in an open surgical or percutaneous fashion.

Percutaneous Access

The popularity of percutaneous access for EVAR and thoracic endovascular aortic repair (TEVAR) has increased over the last 10 years. A recent systematic review of percutaneous access for EVAR cites the potential for a shorter procedure time, less postoperative pain, and a lowered risk of wound complications. A 2016 meta-analysis of three randomized controlled trials and 18 observational studies reported that percutaneous access for EVAR was associated with a significantly lower frequency of groin infection and lymphocele, and with a shorter procedure time and hospital length of stay compared with open surgical access. In addition, percutaneous access did not increase the risk of hematoma, pseudoaneurysm, or arterial thrombosis or dissection. Disadvantages of percutaneous access for EVAR include increased hospital cost and the occasional need for urgent conversion to open repair, which can be quite cumbersome. Percutaneous access is possible for sheath sizes up to 24 Fr. The reported success rates for percutaneous closure of ≥18 to 20 Fr sheath is 78% to 95%, increasing to 95% to 99% with sheaths 12 to 16 Fr. Of note, a substantial learning curve for the percutaneous technique has been observed. Given the 5% to 10% rate of failure in closure of larger arteriotomies with percutaneous access, the immediate availability of surgical expertise for operative exploration is essential. Box 73.2 lists the relative contraindications for this procedure. Preoperative imaging should be closely scrutinized for anatomic information regarding the common femoral artery, including its diameter, associated occlusive disease, particularly anterior calcification, and the location of the femoral bifurcation relative to the femoral head and inguinal ligament.

The percutaneous technique employs off-label use of suture-mediated closure devices in a "preclose" fashion. The common femoral artery is ideally accessed 1 to 2 cm proximal to its bifurcation but below the inguinal ligament. Some operators

BOX 73.2 Relative Contraindications to Percutaneous Access for Endovascular Aneurysm Repair

- Severely scarred groin
- High femoral bifurcation
- Need for frequent introducer sheath changes
- Significant proximal iliac occlusive disease
- Small iliofemoral arteries
- Anterior calcific femoral disease

routinely employ a micropuncture set with a 21-gauge needle and 3 Fr introducer rather than a standard 18-gauge needle. Routine use of ultrasound guidance in the transverse plane is highly recommended to increase the accuracy of arterial access. Verification of appropriate wire entry location should be routine. This is done through a small retrograde arteriogram with the appropriate ipsilateral oblique angulation of the image intensifier to better define the SFA and profunda femoris origins.

A 0.035-inch guidewire is then advanced into the aorta and a 6- or 7-Fr sheath placed. A 10- to 15-mm incision in the skin is made around the sheath. The sheath is then removed, and the wire track is aggressively dilated with a hemostat, down to the level of the artery. This is an important step to ensure that the Proglide knots will not "catch" on subcutaneous tissue and prevent hemostasis at the end of the procedure. The "preclose" technique may be performed with either a single 10 Fr Prostar or with two 6 Fr Proglide (Abbott Vascular) devices. Utilizing the Proglide devices, the first device is deployed with a 30-degree medial rotation. Maintaining wire access, the second device is deployed with a 30-degree lateral rotation. These devices place a single monofilament suture proximal and distal to the puncture site. The sutures are exteriorized and then tagged for later use when the delivery device is removed. An 8- to 10-Fr sheath is then replaced for hemostasis. Alternatively, a single 10 Fr Prostar device may be used. Some operators have suggested the routine use of serial "coons" dilators to predilate the tract and the arteriotomy after the preclose sutures have been placed but prior to delivery of the sheath for endograft delivery. This maneuver may decrease the chance of the "lip" of the dilator/sheath interface catching on the subcutaneous tissue or the arteriotomy itself.

After completion of the EVAR, the delivery sheath is removed while retaining guidewire access. Prior to sheath removal, the sutures are irrigated with heparinized saline to remove any clotted blood. We have also found that gentle traction of the blue suture prior to using the knot pusher will help "seat" the knot closer to the vessel. Hemostasis is maintained with manual compression until the preformed knots (Proglide) are cinched down with the knot-pusher. After hemostasis is confirmed, the guidewire is removed, and manual compression is reapplied. Reversal of the heparin with protamine is suggested at this time. If there is pulsatile bleeding after the two Proglide sutures are tied, a third Proglide can be placed over the existing wire and deployed. If there is continued pulsatile bleeding, an open surgical repair should be performed. Replacement of an appropriate sized dilator over the existing wire facilitates this exposure by providing a nonhemorrhagic field.

Open Surgical Access

With open access, either a vertical or oblique skin incision can be utilized. The advantages of a vertical incision include the ease of gaining additional exposure of the iliac and femoral vessels. Postoperative wound problems can be minimized by keeping the incision above the femoral crease, which is possible in most patients. The oblique skin exposure is favored by many operators because wound problems may be less frequent. This technique of open exposure may be particularly useful in the morbidly obese patient. If the angle into the femoral vessel is too acute, a small counterincision can be made inferior to the skin incision to facilitate sheath insertion.

Iliac Occlusive Disease

The iliac vessels should be carefully studied preoperatively with CTA so any potential difficulties in access can be anticipated. Focal iliac occlusive disease can be treated with balloon angioplasty immediately prior to endograft insertion. Bare metal stents should not be placed initially, however, as the large sheath for the endograft would need to be advanced through them, increasing the possibility of stent migration or arterial injury. If an iliac lesion warrants stent placement and is not covered by the distal extent of the endograft, the additional stent can be placed at the completion of the EVAR.

Hydrophilic "coons" dilators can be effective in dilating longer segments of occlusive disease, and may also alert the operator to potential issues with device tracking. These dilators should only be placed over very stiff wires to avoid wire kinking and arterial trauma. However, sometimes a larger sheath can be negotiated into the aorta with significant pressure, only to have catastrophic bleeding from iliac disruption upon removal of the sheath or with repeated exchanges. In addition, maintenance of wire access across a diseased, narrowed, or angulated segment during device and sheath removal is essential to allow potential endovascular salvage of life-threatening arterial injury. Confirmatory angiography after device or sheath removal is recommended.

There are other potential endovascular approaches to obtaining access in the setting of small iliac arteries. It is possible to create an "internal endoconduit" by placing a covered stent in the external iliac vessel, which is then aggressively angioplastied to the required diameter of 9 to 12 mm. The covered stent will protect against the extensive dissection and/or free rupture of the native vessel which can be caused by aggressive angioplasty. Clearly, there must be a sufficient proximal and distal seal zone for the covered stent. From a practical point of view, however, such ideal landing zones are not routinely present. Prudent patient selection is critical. While these techniques have been anecdotally reported with successful outcomes, larger series are needed to establish the safety of these adjunct access procedures prior to broader utilization. Recently a balloon-expandable sheath has become available to help in accessing smaller iliac arteries (SoloPath, Onset Medical Corp, Irvine, California). This sheath is delivered in an 11.5 to 15 Fr size and then dilated by an integrated balloon to sizes from 17 to 24 Fr.

Iliac Conduit Placement

The potential use of a surgically placed conduit should be in the "toolbox" of all operators performing endovascular aortic aneurysm repair. The need for a conduit is currently unusual, particularly with the introduction of lower profile devices. Nevertheless, patients with diffused calcified and very small external iliac arteries need a conduit in many circumstances. If the operator is concerned about access in this situation, serious consideration should be given to performing a surgical conduit without even trying to access the iliac artery. Visual inspection of the common femoral and terminal external iliac artery with open exposure can aid decision making in equivocal cases.

An iliac conduit is performed through a right or left low retroperitoneal incision. We favor a standard end to side anastomosis at the level of the distal common iliac artery. A 10-mm prosthetic conduit (Dacron or PTFE) will accommodate the largest needed sheath. The conduit should be tunneled under the inguinal ligament through a femoral counterincision. The distal end of the conduit is then clamped to the drapes and accessed in the usual fashion. After the EVAR is completed, most operators elect to anastomose the distal end of the conduit to the common femoral artery in an end-to-side fashion. Alternately, the conduit can be removed, leaving a small "stump" on the common iliac artery.

Imaging

Equipment

High-quality fluoroscopy and angiographic equipment is essential to successful EVAR. A contemporary fixed-imaging unit as part of a "hybrid" odds ratio (OR) room is increasingly utilized in many institutions. The performance of fenestrated or branched EVAR mandates this level of imaging. Portable C-arm fluoroscopy with a modern unit is acceptable for standard EVAR but cannot provide the versatility and imaging capabilities of fixed units.

Gantry Positioning

The precision of proximal endograft deployment with EVAR is considerably enhanced by adjusting the gantry of the fluoroscope to be perpendicular to the axis of the aortic neck. A large percentage of infrarenal aortic necks have a modest amount of anterior angulation, which should be adjusted for by adding an appropriate amount of cranial tilt to the fluoroscopy unit. The amount needed can be estimated by the preoperative CTA. The majority of infrarenal aortic necks have 5 to 15 degrees of cranial angulation, but this increase to as much as 30 to 40 degrees in highly angulated necks. Adjusting the left/right obliquity is also helpful in precisely locating the origin of the lowest renal artery. The left renal artery typically comes off the aorta slightly posterior to the centerline, while the right renal most commonly originates somewhat anterior to the centerline. An appropriate amount of left anterior oblique (LAO) will give the proper orientation to the renal arteries in most cases. Frequently, this translates to approximately 10 to 20 degrees of LAO. These adjustments are particularly important in patients with short or angulated aortic necks.

EVAR DEPLOYMENT

Wire Placement

After bilateral open or percutaneous femoral access is achieved, a floppy J-wire should be placed in the proximal thoracic aorta and exchanged over a catheter for a stiff guidewire (Lunderquist, Amplatz Super Stiff, or Meier). Failure to routinely visualize the location of these stiff wires in the aortic arch increases the risk of inadvertent cannulation of an arch vessel, aortic or branch vessel trauma, plaque disruption and stroke. After the stiff wire is placed, the distal end of the wire should be marked on the operative drape so that a stable position is ensured throughout the procedure. Through the contralateral femoral access, a pigtail catheter is then placed just above the renal arteries, which is usually between the L1 and L2 vertebral bodies. If there is concern about iliac occlusive disease, an angiogram should be taken at the aortic bifurcation and the occlusive disease treated as detailed previously. If there is uncertainty regarding the correct main body length to select, an aortogram with a 1 cm graded marker catheter can be performed to confirm the distance between the lowest renal artery and the ipsilateral hypogastric artery origin. Otherwise, arteriography should not be performed until the undeployed main component is advanced into the pararenal aorta. Particularly in patients with significant iliac or aortic neck tortuosity, placement of the undeployed endograft in the pararenal aorta may alter the relative position of the renal arteries as the aorta accommodates to the hardware over a stiff wire, making preinsertion arteriography inaccurate.

Delivery of the Main Device

The contralateral gate or limb of the main device should be appropriately oriented by fluoroscopic evaluation prior to insertion. This orientation should be rechecked as the device is being advanced and during any rotational adjustments made while the device is advancing to eliminate friction associated iliac injury. In addition, attempts to rotate the device statically may not translate to the entire device, particularly in tortuous or small iliac arteries. Failure to follow these principles can cause a relative twist and misdeployment of the endograft

If the endograft is not advancing smoothly, the first step is to change to an extra stiff guidewire such as a Lunderquist. Using this wire and current trackable endografts, it is uncommon to fail to deliver the endograft to the desired location. Rarely, external manipulation of the distal aortoiliac segment may be beneficial. An assistant stabilizes the aorta from the contralateral side of main device placement by placing a hand on the lateral edge of the aneurysm, thus helping reduce any additional induced tortuosity created by advancement of the endograft. Finally, one should reconfirm that unexpected occlusive disease is not contributing to the inability to advance the endograft. If these maneuvers are not successful, use of a "buddy wire" should be considered. A second extra stiff wire can be placed through the iliac helping to further straighten the tortuous segment.

Proximal Endograft Deployment

After the main device is placed in the pararenal aorta and the contralateral gate/limb position is satisfactory, the gantry position of the fluoroscopy unit is adjusted with the appropriate amount of cranial and oblique angulation as detailed previously. A magnified view should be utilized, with the lowest renal artery in the center of the screen and proximal graft marker position verified to minimize parallax errors. Using a power contrast injector, a short-burst injection using a high rate to small volume ratio will allow good visualization of the renal arteries with a small amount of contrast. A 20 cc/s injection rate with a total of 7 to 15 cc of contrast is usually sufficient, depending on the equipment and patient's body habitus. It is essential to visualize

both renal arteries. If the lowest renal artery is not close to the center of the image, the table or fluoroscopy unit should be adjusted, and the image repeated.

With devices that are designed for a slow step-wise deployment (Endurant, Excluder, Zenith), initial deployment should begin approximately 1 cm above the intended target position. The endograft should then slowly be pulled down until the proximal extent of the device fabric sits immediately below the lowest renal artery. After the initial proximal deployment, the gantry position may be adjusted further to ensure a perfectly perpendicular alignment with the aortic neck. The anterior and posterior aspects of the endograft should appear superimposed if the gantry position is parallel to the aortic neck. If they do not, the degree of cranial tilt can be adjusted, and the arteriogram repeated. The goal is to place the endograft within 2 mm of the caudal edge of the lowest renal artery orifice. Maximal overlap of the graft within the aortic neck will increase the seal zone and reduce the likelihood of a type IA endoleak and late migration.

After the proximal landing zone of the endograft is established, deployment of the endograft continues until the contralateral gate is deployed. Many operators will then recheck the position of the endograft relative to the renal arteries at this time. Deployment of a bare suprarenal stent is now generally performed with devices that have this feature. After deployment of the bare suprarenal stent, no further movement of the main device is possible. An exception to this principle is found with the C3 Excluder endograft (W.L. Gore), which has no suprarenal stent and can be reconstrained and repositioned if the initial position is not ideal.

Accessory Renal Artery Management

In patients with normal renal function, it is generally safe to cover such an accessory renal artery with the endograft. Embolization of the vessel prior to coverage is not generally performed. Patients with significantly impaired renal function pose a more difficult situation. Further reduction in a patient's renal function by coverage of an accessory renal artery is far from ideal. However, alternate approaches, including a fenestrated endograft or open surgical repair, have markedly elevated morbidity and mortality in the patient with significant renal insufficiency.

Contralateral Gate Cannulation

For modular devices, the next step is cannulation of the contralateral iliac gate. This step is obviated if a unibody device such as the AFX Endologix is utilized. Retrograde cannulation of the gate should be possible in greater than 95% of cases. Several "pearls" will facilitate this maneuver. Perhaps the most important step is planning appropriate gate orientation for favorable cannulation. Deployment of the gate in a slightly anterolateral position will usually compliment the angle of the iliacs and allow straightforward access. With short body devices such as the Endurant and Excluder, it is sometimes easier rotate the contralateral gate ipsilateral to the main limb, thus crossing or "balleting" the limbs. This maneuver is particularly helpful if the angle of the proximal common iliac artery is splayed laterally, there is a large aortic sac, or the anterior-posterior diameter of the aortic bifurcation is significantly less than the left-right diameter. With a long body device such as Zenith, the contralateral gate should be within 1 to 2 cm of the iliac artery, and thus balleting the iliac limbs is inadvisable. In cases where one common iliac has significantly more lateral angulation than the other, placing the main device in the *more* tortuous side will facilitate the contralateral gate cannulation.

Several maneuvers will speed cannulation of the gate:

1. After retrieving the pigtail or other angiographic catheter, avoid pulling the wire back into the iliac artery. If there is severe tortuosity or a narrow distal aortic neck it can occasionally be challenging to regain access to the aneurysm sac.
2. Choose a steerable angled wire such as an angled Glidewire and an appropriately angled catheter such as a DAV/Bernstein or Vanchie 4.
3. Position the contralateral sheath (8 Fr × 25 cm or similar) at the bifurcation just proximal to the respective common iliac orifice for increased catheter support.
4. Oblique the fluoroscopic views to maximally "open" the gate. Using both the catheter and wire to steer, attempt to place the wire into the gate. If the wire first appears to be in the appropriate orientation with the gate but ultimately is not, then the operator knows that the wire is either anterior or posterior. In such a case, by changing the obliquity of the fluoroscopic image with the wire in place, it will then become clear whether anterior or posterior deflection is needed. If the wire is seen to transiently engage the gate fabric but not cannulate successfully, subtle, controlled movements of the catheter tip to slightly change the angle of the wire should follow until the gate is accessed. Occasionally a different-shaped catheter will facilitate cannulation.

Confirmation of proper gate cannulation is essential and can be done with angiography or by spinning the pigtail catheter in the area of the aortic neck. Some operators utilize a 12- or 14-mm balloon inflated in the gate while the gantry is rotated to confirm appropriate positioning. Failure to routinely confirm the wire position can result in deployment of the limb outside of the gate.

Rarely the contralateral gate cannot be cannulated in a retrograde fashion despite utilization of the above maneuvers. Failure to cannulate is usually the result of the gate not opening adequately because of a small (<20 mm) distal aortic neck, an eccentric calcific distal aortic "reef" (long body devices) or extreme tortuosity (short body devices). In such situations, the gate should be cannulated in an antegrade fashion, usually via brachial access. Once a wire is negotiated through the gate in an antegrade fashion from above, it is snared in the respective iliac artery and withdrawn through the corresponding femoral access sheath. Then, over a catheter, the wire can be exchanged for typical retrograde deployment. An alternate method of antegrade cannulation is to approach the gate by going "up-and-over" the flow divider with an appropriately shaped catheter, such as a Simmons 1, or SOS. However, our experience has been that the anatomic issues that made retrograde cannulation impossible also make this approach problematic and frequently unsuccessful. Recently

available steerable sheaths do provide better support and can allow for easier "up and over" antegrade catheterization.

If all attempts at gate cannulation are unsuccessful, the final bailout technique is conversion of the bifurcated device into an aorto-uni-iliac configuration. This maneuver should be needed in less than 1% of cases. With the Zenith device, this is accomplished with a specifically made converter endograft that is deployed within the main body, excluding the contralateral gate. A similar configuration can be accomplished with other modular devices by either the use of stacked aortic/iliac cuffs, an aortounibody graft, or deploying a second main body device within the existing main body device with the contralateral gate oriented 180 degrees opposite the existing contralateral gate. After conversion to such a configuration, an occluder must be placed in the contralateral common iliac artery, and limb perfusion reestablished with a femoral-femoral bypass.

Limb Deployment

Once contralateral gate cannulation is confirmed, the distal landing zone in the iliac artery is established with a retrograde arteriogram shot through the previously placed iliac sheath. The image intensifier should be positioned with complimentary, contralateral obliquity to best visualize the takeoff of the respective hypogastric artery; this is typically 20 degrees LAO for the right iliac and RAO for the left iliac. Appropriate angulation should be determined during evaluation of the preoperative images and reconstructions. If the required length of the limb is in question, a marker catheter can be placed over the wire. Ideally, more iliac overlap is preferred over less. The absolute minimum overlap into the iliac artery (common or external) is 2 cm in a patient with nontortuous vessels and a less than 6 cm AAA. Patients with larger AAA and/or tortuous anatomy should receive longer iliac coverage, if possible. These patients may have greater conformational changes as the AAA sac thromboses and shrinks in the postoperative period, putting increased axial strain on the device components. This scenario can produce migration of the iliac limb with a subsequent type IB endoleak, graft kinking, and limb thrombosis, or component separation.

In patients with extremely tortuous iliac arteries, landing the distal end of the device within 1 centimeter of an acute angle should be avoided. Any kinking or stenosis of the endograft limbs should be aggressively angioplastied, usually with a compliant balloon (Coda, Reliant). If any significant residual stenosis persists, one should consider the placement of a self-expanding stent within the endograft. Occasionally a narrow distal aortic neck compresses both iliac limbs. Use of simultaneous, conventional, noncompliant angioplasty balloons will usually resolve this issue. If there is significant recoil, the use of bilateral balloon-expandable stents in this location should be considered.

A compliant molding balloon (Coda, Reliant, P50) may be utilized at the aortic neck, iliac gates, and distal iliac limb to optimize seal (Fig. 73.5). It is important not to overinflate this balloon outside the proximal or distal aspect of the endograft. Rupture of the pararenal aorta and iliac arteries has been reported after overly aggressive inflation of these compliant balloons.

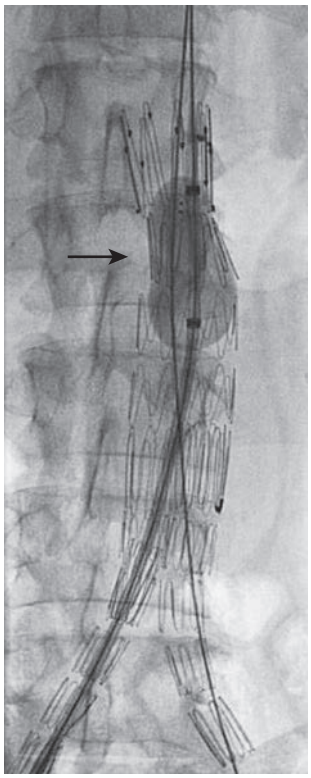

Figure 73.5 Use of a compliant molding balloon (Coda) on the aortic neck to optimize the seal *(arrow)*.

Completion Arteriography

After endograft placement is completed, a completion arteriogram is performed through an angiographic catheter placed in the pararenal aorta (see Fig. 73.2C). Use of a power injector with an injection rate of 15 cc/s and a total contrast volume of 30 cc is recommended. Because the large sheath size of devices will frequently reduce iliac flow, these should be routinely aspirated with 20 cc syringes during the injection. Image acquisition should continue for a minimum of 5 sec after the contrast in the iliac arteries has washed out to allow visualization of late type II endoleaks. The completion arteriogram should be systematically and carefully studied in the following manner:

1. Confirm patency of the renal and hypogastric arteries.
2. Assess the precision of the proximal and distal endograft landing zone apposition. The proximal extent of the endograft should be ideally within 2 mm of the lowest renal artery. If this distance is considerably greater, and the residual seal zone is less than 10 to 15 mm, placement of an aortic cuff should be considered, even in the absence of a type IA endoleak. Likewise, iliac extensions should be placed if there is inadequate overlap with the iliac artery or if a type IB endoleak persists after balloon dilation.
3. Evaluate for unsuspected occlusive external iliac disease. If significant tortuosity in the iliac vessels exists, the stiff wires in place for the endograft deployment should be exchanged for flexible wires prior to the final arteriogram. Stiff wires will occasionally cause the tortuous iliac artery to "accordion," giving the radiographic appearance of severe stenosis

(Fig. 73.6). These pseudo-lesions will disappear with removal of the stiff wire. True occlusive lesions should be treated accordingly.

4. Assess for endoleak.

EVAR TROUBLESHOOTING

Type I and III Endoleaks

Every effort should be made to definitively treat any initial type I or III endoleak prior to leaving the endovascular suite. Type II endoleaks should be observed, as the large majority will spontaneously resolve without intervention. In general, the early appearance of endoleak after contrast injection almost always signifies a type I or III endoleak, whereas late-appearing endoleaks are more commonly type II. However, even late contrast seen in the sac adjacent to the proximal or distal seal zones is worrisome for a type I endoleak and should be aggressively interrogated. Additional magnified views with differing obliquities may be helpful in establishing the presumptive type of endoleak.

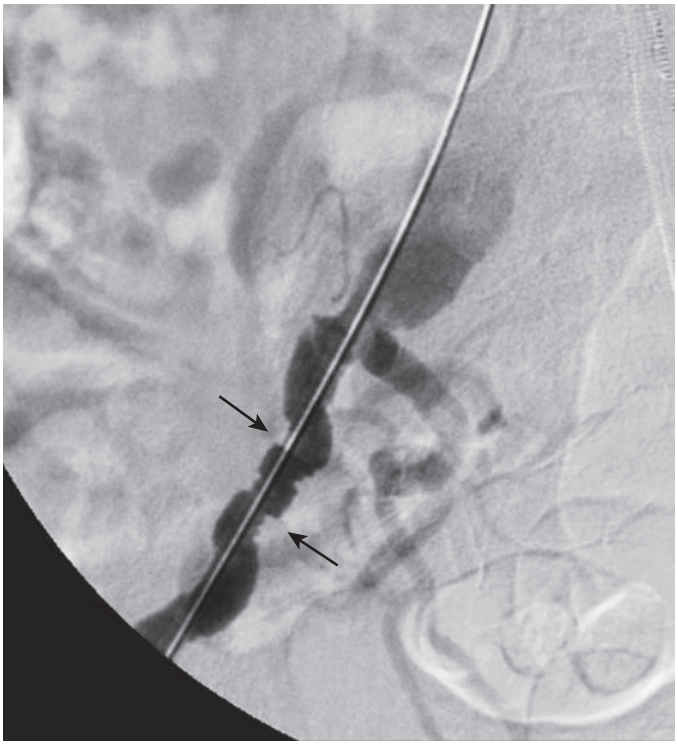

Figure 73.6 "Pseudolesion" of the external iliac artery *(arrows)*. This is caused by placement of a super-stiff wire in a tortuous vessel, causing it to "accordion" around the wire. Removal of the stiff wire corrects the stenosis without adjunctive measures.

Aortic Cuffs

Initial type IA endoleak treatment is predicated on the proximity of the endograft to the lowest renal artery. If this distance is less than 3 mm, the seal zone should be angioplastied with a compliant molding balloon. If the distance is greater than 5 mm, placement of a proximal aortic cuff followed by compliant balloon angioplasty should be performed.

Giant Palmaz Stent Placement

If a type IA endoleak persists despite the above maneuvers, placement of a giant Palmaz stent should be considered (Fig. 73.7). A 4010 or 5010 Palmaz stent is hand mounted on an appropriately sized valvuloplasty balloon (Braun Z-Med) in a slightly asymmetric fashion such that more of the proximal extent of the balloon will inflate first. The existing main body delivery sheath, or comparable sized sheath, is then advanced beyond the intended deployment zone. The Palmaz stent is then carefully delivered through the sheath with continuous fluoroscopic observation to confirm the position of stent on the balloon. One should be aware that the stent will foreshorten significantly as it is expanded. While it is 5 cm in length at 10 mm of expansion, it shortens to approximately 3.8 at 28 mm of expansion. To prevent the stent from "watermelon seeding" and potentially misdeploying during balloon inflation, the distal two-thirds of the stent is constrained in the delivery sheath while the initial balloon deployment is performed (Fig. 73.8). Because the stent is slightly asymmetrically mounted, no movement should occur. After the proximal portion of the stent is expanded, the sheath in carefully retracted and the remainder of the stent is deployed. In most cases, use of a compliant molding balloon is needed

Figure 73.7 (A) Short aortic neck immediately before endovascular aneurysm repair. (B) Type IA endoleak *(arrow)* after initial endograft placement and molding balloon angioplasty. (C) Resolution of the type IA endoleak after placement of a 5010 "giant" Palmaz stent (*arrows*, proximal and distal extent).

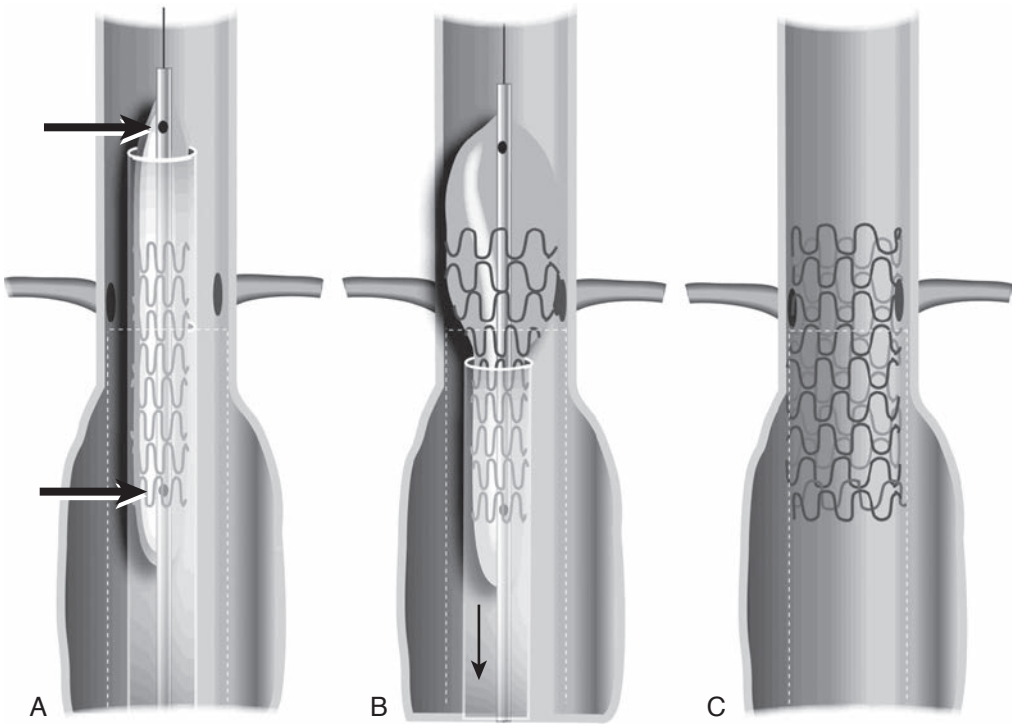

Figure 73.8 Sequence of the modified deployment technique of a "giant" Palmaz stent in the perirenal aorta for repair of a type IA endoleak. The *white dotted lines* represent the previously placed endograft for endovascular aneurysm repair. Details of the endograft have been omitted to enhance the clarity of the giant Palmaz stent device. (A) The stent (Palmaz 3010, 4010, or 5010) is hand-crimped off-center on a valvuloplasty balloon *(arrows)*. The balloon-mounted stent is then positioned at the intended area of deployment through the sheath under fluoroscopic guidance. (B) The sheath is partially retracted, and the balloon is inflated, deploying the proximal (cranial) portion of the stent. The off-center mounting of the stent ensures that it will not "watermelon-seed" craniad; the sheath prevents caudad displacement. (C) Fully deployed stent. (Redrawn from Kim JM, et al. A technique for increased accuracy in the placement of giant Palmaz stents for treatment of type I endoleaks following EVAR. *J Vasc Surg.* 2008; 48:755-777.)

after removal of the valvuloplasty balloon to optimize apposition of the Palmaz stent to the endograft.

Endo-Anchors

Another option for treatment of a type IA endoleak is the use of a device that "staples" or "anchors" the stent graft to the aortic neck to achieve better apposition. There are several devices currently on or coming to the market, led by the Heli-FX EndoAnchor system (Aptus Endosystems), which received FDA approval in 2011. It consists of two devices used in concert: a16-F outer-diameter deflectable sheath, the Heli-FX Guide, and an electromechanical, motorized delivery device, the Heli- FX Applier, which implants the actual EndoAnchor. The anchor itself is a metallic alloy, helical screw implant with an atraumatic tip that is 4.5 mm in length, 3 mm in diameter, and made of a round wire that measures 0.5 mm in diameter. A minimum of four anchors are recommended for aortic necks up to 29 mm in diameter, and at least six anchors are required for larger necks. A tapered point and "crossbar" allow penetration through calcified tissue but prevent penetration through the adventitia of the aortic wall.

Type IB endoleaks should be initially treated with repeat angioplasty at the distal seal zone. If this is not successful, extension of the limb with an appropriately sized cuff of limb should be performed. Type III endoleaks should almost always resolve with angioplasty, assuming the correct amount of overlap was achieved, and the limb was sized appropriately. If the overlap between components is not adequate, one should place a bridging iliac component.

Renal Artery

Inadvertent partial or complete coverage of a renal artery by the endograft should be a rare occurrence, but knowledge of "bailout" strategies can prove invaluable. It may be possible to caudally displace the endograft by pulling on a wire that has been placed over the flow divider, snared, and brought out the contralateral femoral artery sheath. Alternately, a large compliant balloon can be inflated just above the flow divider and caudal pressure applied. These maneuvers should be utilized with extreme caution to avoid aortic injury. Placement of a balloon-expandable stent in the respective renal artery can restore flow in most cases, and this is the preferred treatment strategy. Depending on the percentage of renal ostium covered and the amount of caudal angulation of the renal artery, a brachial approach can facilitate this maneuver, especially if suprarenal endograft fixation was utilized. If none of these endovascular options is successful, extraanatomic bypass via an iliorenal or

hepatorenal approach is possible. As a last resort, acute open conversion could be considered.

The management of the incidentally discovered renal artery stenosis should follow the same indications as that of isolated renal artery disease. Generally it is best to treat the renal artery stenosis after EVAR. This sequential treatment may be done at the same setting or in a staged manner. The rationale for this approach is that theoretical dislodgement or crushing of the renal stent could occur during manipulation and deployment of the aortic endograft. These concerns are more pronounced when using devices that are commonly deployed slightly above the renal arteries and then moved caudally into their final positions (Endurant, Zenith). An exception to this rule is the patient with either severe renal insufficiency due to renal artery stenosis or severe hypertension that increases the perioperative risk of EVAR. In such circumstances, staged treatment of the renal artery stenosis prior to EVAR is indicated.

Iliac Artery

External Iliac Extensions

Ectatic common iliac arteries up to 2 cm in diameter are suitable landing zones for the iliac limbs of an aortic endograft. However, common iliac arteries greater than 2 cm generally necessitate extension of the endograft to the external iliac artery to ensure adequate distal sealing. When extending to the external iliac artery, one should be particularly mindful of excessive oversizing, as this can predispose to limb thrombosis or type IB endoleak. There is frequently significant iliac tortuosity in these cases, which makes accurate length measurement difficult.

Hypogastric Artery

Embolization

The most frequently utilized approach is embolization of the proximal hypogastric artery to eliminate the possibility of a type II endoleak (see Chapter 72). Coverage of the hypogastric artery without embolization has been described and may be an appropriate choice in some situations. Although rare, the theoretical limitation of such a strategy is a persistent type II endoleak from the internal iliac artery that contributes to aneurysm growth.

Preservation

Preservation of flow to the hypogastric artery can be achieved either with the use of a branched endograft, the placement of a covered stent from the hypogastric artery into the ipsilateral external artery combined with a contralateral aorto-uni-iliac endograft and a femoral-femoral bypass, or a short open bypass or transposition from the external artery (see Chapter 72).

Management of Late Type II Endoleaks

Indication

Type II endoleaks associated with AAA sac growth of ≥5 mm should generally be treated. However, there is no level 1 or 2 evidence supporting a specific threshold for intervention of type II endoleaks. Embolization of the inferior mesenteric artery (IMA) prior to EVAR has been performed in an attempt to decrease late endoleak, but these interventions have not demonstrated aggregate late benefit.

Diagnosis

A high quality thin-cut CTA can reveal the source(s) of type II endoleak in many cases. Frequently, continuity between patent lumbar vessels and/or the IMA and the AAA sac is evident with contrast opacification. However, detailed angiography is generally recommended to confirm the etiology of the endoleak prior to treatment. In addition, the possibility of occult type I or type III endoleaks as the etiology for sac expansion should be eliminated. In a recent series of treatment for type II endoleak, more than 20% of patients were found to have an occult type I or III endoleak. After the proximal and distal seal zones and component connections are interrogated, selective arteriography of the superior mesenteric artery (SMA) and hypogastric arteries may be needed to identify the source of the type II endoleak.

Treatment

Box 73.3 lists the various options for treatment of type II endoleaks. A central tenet to successful treatment of type II endoleaks is occlusion of the offending branch vessel as centrally as possible—ideally at its takeoff from the aneurysm sac. Embolization of a more peripheral feeding branch has a high failure rate, as new collateral pathways frequently maintain flow into the IMA or relevant lumbar vessel.

Endoleaks from the IMA are most commonly managed by transarterial coil embolization. This is performed by accessing the middle colic artery via the SMA, providing retrograde access to the proximal IMA through the arc of Riolan or marginal mesenteric artery. A hydrophilic 0.014 wire and 3 Fr supporting microcatheter should be advanced to the ostial IMA, and microcoils deployed in the first ~1 cm of the vessel to avoid flow disruption to the middle sacral artery and other colorectal collaterals.

Alternatively, direct antegrade access to the IMA can be achieved from within the aneurysm sac by several methods. Occasionally it is possible to obtain access to the sac by placing a hydrophilic wire in retrograde fashion between the endograft limb and the native iliac artery, giving direct transarterial access. Translumbar puncture of the AAA sac (frequently using CT or

BOX 73.3 Treatment Options for Type II Endoleak

Coil or Glue Embolization
Transarterial
- Via branch vessel
- Behind graft limb

Translumbar
Transcaval
Laparoscopic Ima Clipping
Open Surgical
- Ligation of lumbars or IMA
- Open conversion

IMA, Inferior mesenteric artery.

fluoroscopic guidance) is the most popular route for antegrade access to branch vessels. Finally, transcaval access to the AAA sac has been described.

Endoleaks from patent lumbar vessels can be treated with transarterial coil embolization, typically via hypogastric artery branches, using a microcatheter system. However, it is sometimes difficult to advance the microcatheter to the ostium of the lumbar vessel because of native vessel tortuosity. Translumbar access to the AAA sac for embolization with glue or coils facilitates this process and is favored by some operators for the treatment of lumbar endoleaks. The use of glue from this approach may allow simultaneous occlusion of multiple branch vessels. Endovascular treatment of type II endoleaks has a relatively high failure rate, with a 20% need for reintervention and a freedom from AAA sac growth of only 43% at 5 years.

Finally, open approaches to treatment of type II endoleaks are possible, but usually reserved for repeated endovascular failure and concomitant sac growth. The IMA can be ligated laparoscopically; because proximal control of the vessel is required with this approach, advanced laparoscopic skills are needed. Direct ligation of lumbar vessels via a laparotomy is possible, but seldom utilized.

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CHAPTER 74

Ruptured Aortoiliac Aneurysms and Their Management

THOMAS F. LINDSAY

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Rupture of an abdominal aortic aneurysm (RAAA) remains a lethal condition despite advances in all aspects of care.[1,2] RAAA repair has a 5-fold to 10-fold higher mortality[3] compared with elective repair.[4] Despite advances in perioperative management and service centralization, open RAAA survival rates have only marginally improved. A shift to REVAR techniques has improved outcomes, with reductions in mortality noted in population and randomized data.[4-12] A major decline in RAAA incidence is evident in the United States and Europe.[9,13-15]

TERMINOLOGY AND HISTORY

Definitions

RAAA is an abdominal aortic aneurysm (AAA) with extraluminal blood on computed tomography (CT) or noted clinically at the time of surgery. A contained rupture refers to blood outside the aneurysm sac confined to the retroperitoneal space. A free rupture refers to bleeding directly into the peritoneal cavity. A symptomatic, nonruptured AAA is one with back pain or tenderness over the aorta on deep palpation but with an intact aneurysm on CT and at surgery. The pain is thought to be secondary to acute expansion of the wall, intramural hemorrhage, wall degeneration, or bleeding into the thrombus and is considered a prelude to rupture. Symptomatic aneurysms are not associated with hypotension; however, the prognosis is much better than that of RAAAs (but worse than after elective repair).[16] Symptomatic aneurysms require rapid diagnosis and urgent management to prevent rupture; however, inclusion within RAAAs data can artificially improve outcome data.[17]

History of Ruptured Abdominal Aortic Aneurysm Repair

The first successful reconstruction for RAAA was by Henry Bahnson with a homograft in 1953.[18] By 1954 Cooley and DeBakey had treated six RAAA patients, with a 50% survival rate.[19] Just as elective open aneurysm reconstruction was rapidly applied to ruptures, so too was endovascular aneurysm repair (EVAR), with Hopkinson reporting the first REVAR in England in 1994.[20]

EPIDEMIOLOGY

Declining Incidence

The true incidences of RAAA have historically been difficult to quantify. In the 1950s a diagnosis of RAAA was made on clinical grounds (or at autopsy), without CT or other abdominal imaging, and missed those who died out of hospital, because deaths were attributed to another cause. The incidence of RAAA was thought to be increasing based on a Swedish population study in which the incidence almost doubled between 1971 and 2004.[21] The incidence of RAAA in men increased threefold despite more elective repairs.[22] In 2011 a decline in the incidence of ruptured (and intact) AAA began to be reported in most Western populations. In Australian men the number of deaths from RAAAs fell by 38% between 1999 and 2006[23]; in New Zealand the decline was 53%.[24] A review of population-based mortality in England and Wales from 1979 to 2009 showed a steady increase in deaths from RAAAs, especially in men, until 1996, then deaths declined.[3] In Medicare beneficiaries from 1995 to 2008, AAA-related deaths halved, with the greatest decline seen in patients older than 80 years.[14] Data from the Centers for Disease Control and Prevention reported that in 1999–2014 deaths from RAAA dropped across all ages and in both sexes (Fig. 74.1). RAAA deaths have declined by 33% for men and women together.[25] Deaths are more frequent in men compared with women and the peak age for females was older than for men. Confounding information from a detailed prospective analysis of acute AAA in Oxfordshire, United Kingdom demonstrated the rates of symptomatic and ruptured AAA were 30% to 40% higher than the local and national coding data, but the rates have fallen in the younger age groups over the past 2 decades.[26]

Population screening has been shown to reduce AAA-related deaths,[27] but the decline in mortality due to RAAA began before widespread population screening. EVAR may have led to more elective AAA repairs in older and less fit patients, thereby reducing the at-risk population for RAAA.[28] The biggest reduction in absolute numbers of RAAA has come from a decline in the prevalence of intact AAA identified in the Swedish (1.7%[29]) and UK screening programs, where the detection rate is only 1.7%, less than the 4% detection rate expected.[30] This has been attributed to decreased levels of smoking and improved control of cardiovascular risk factors.[26,28,31,32]

Overall Mortality of Ruptured Abdominal Aortic Aneurysm Repair

Two population-based series of RAAA mortality rates were 89% and 86% for RAAAs.[6,33] In 2006 a population-based Swedish study[21] with a high autopsy rate reported that the early mortality rate (death in the community or during hospitalization) was 74% and that in 2004, only 48% underwent repair.

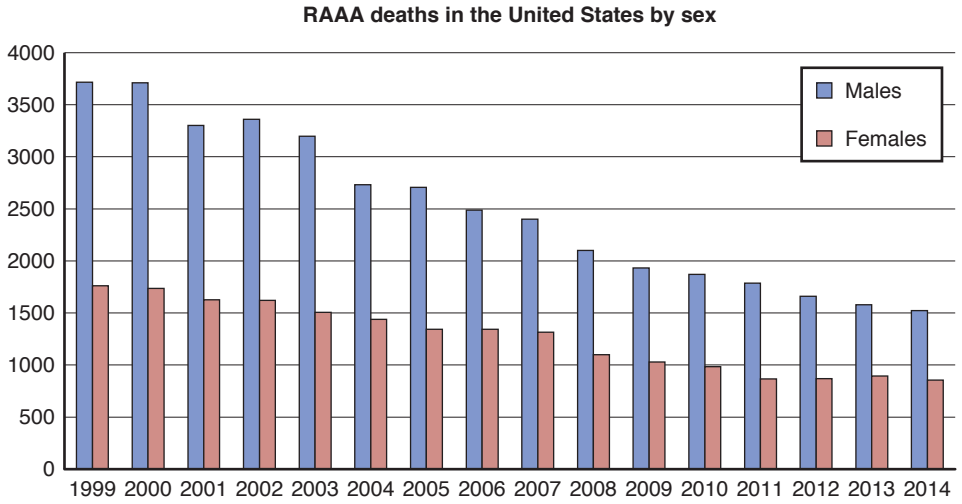

Figure 74.1 Ruptured abdominal aortic aneurysm *(RAAA)* death rates per 100,000 population between 1999 and 2014 in United States for men and women between the ages of 55 and 94 years. (From Centers for Disease Control and Prevention, National Center for Health Statistics: Compressed Mortality File 1999-2009. CDC WONDER online database, compiled from Compressed Mortality File 1999-2009, Series 20, No. 2O, 2012. http://wonder.cdc.gov/cmf-icd10.html.)

The Danish national registry (1994–2008) noted operative mortality decreased from 51% to 42%, attributed to centralization of services and better prehospital care. Data from the Vascunet (from nine national and regional registries) of outcomes for RAAA repairs in 7040 patients noted a mortality rate of 31.6%, with the rate declining by 4.2% between 2005 and 2009 attributed to EVAR.[34] Comparison of English and American databases from 2005 to 2010 noted that intervention for RAAA was offered to 80% in the United States (21% EVAR) versus only 58% in England (8.5% EVAR). Postintervention mortality was similar at 41.6% and 41.8%, respectively.[10]

The high postoperative mortality rates after aortic rupture are related to a high incidence of myocardial infarction, colon ischemia, renal failure, and multiple organ failure (MOF). The synergistic effect of the total body ischemia caused by hemorrhagic shock and the lower torso ischemia that occurs during repair, followed by reperfusion secondary to resuscitation and aortic unclamping, has been proposed to explain the high incidence of MOF and mortality after repair is supported by data from both animal and human clinical studies.[35,36] EVAR for RAAAs may reduce the ischemic insult by minimizing lower torso ischemia induced by aortic clamping. RAAAs anatomically suitable for EVAR have the lowest mortality and complication rates.[37,38]

PATHOPHYSIOLOGY OF AORTIC RUPTURE

Aneurysm rupture represents failure of the aortic wall to bear the load or tension of the blood pressure. In-vitro testing has demonstrated that the aneurysmal aortic wall is weaker than the normal structure: aneurysmal aortic wall 65 N/cm^2 versus 121 N/cm^2 for normal aortic wall.[39,40] Laplace's law (tension is proportional to radius times pressure) relates wall tension to pressure and emphasizes the importance of aneurysm size but does not account for complex geometry of individual AAAs.

Abdominal Aortic Aneurysm Shape and Finite Element Analysis

Finite element analysis has been applied to AAAs to estimate regional variations in peak wall stress (PWS) for many small segments of the entire aortic wall using CT scan data and provides a visual representation of PWS variability. Early 3D representations of PWS noted that the posterior wall of the aorta had higher values corresponding to sites where clinical observations and autopsy studies document the rupture sites.[41,42] Initial studies assumed that AAAs had uniform wall thickness and material isotropy (uniform strength in all orientations), but studies[42-45] show there are localized "hot spots" of matrix metalloproteinase (MMP) activity that could cause focal weakening of the aneurysm and rupture at relatively low levels of intraluminal pressure. Newer models include growth and remodeling theory that allows evolving wall thickness, stiffness, regional heterogeneity, and fluid-structure interactions within the aneurysm sac to be analyzed.[46,47] A study of CT scans of patients who subsequently ruptured compared with diameter-matched controls, ruptures had higher peak wall rupture risk (PWRR) at equivalent diameters but no difference in PWS or intraluminal thrombus volume (Fig. 74.2). These findings provide some justification for prediction of individual risk of AAA rupture from conventional CT.[48]

Role of Aortic Thrombus

In 1965 Martin surmised that as an aneurysm develops, it becomes lined with thrombus, which weakens it by interfering with nutrition of that wall segment.[49] Schurink et al.[50] confirmed that intraluminal thrombus does not reduce pressure near the

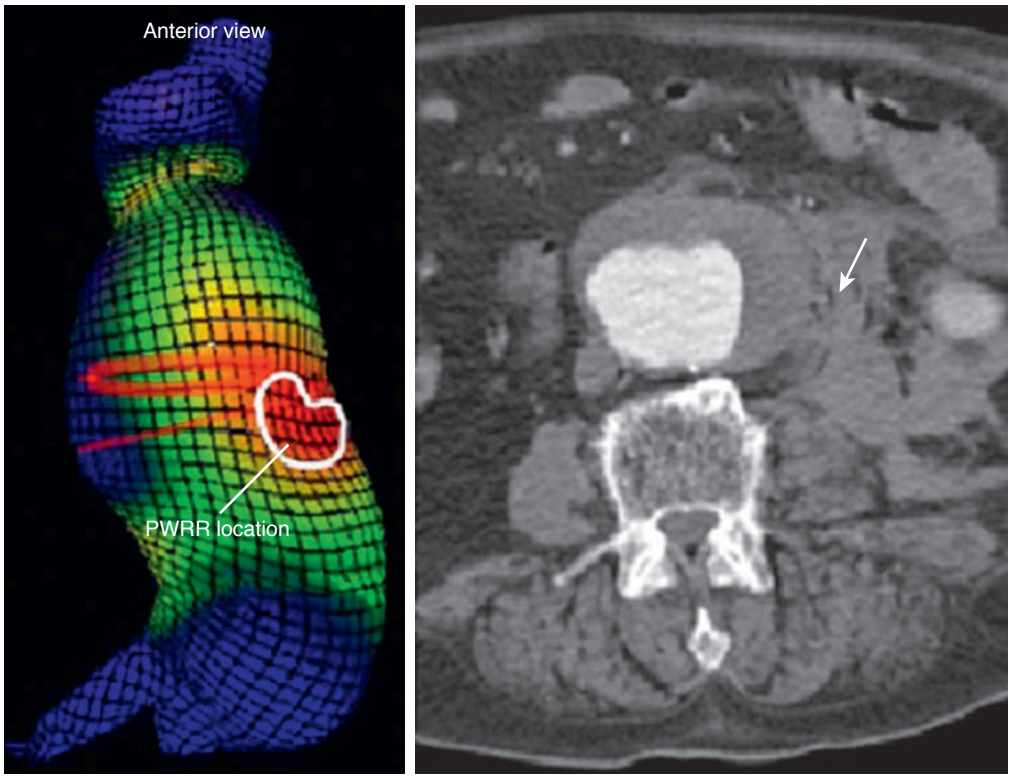

Figure 74.2 Peak wall rupture risk *(PWRR)* predicts subsequent indefinite rupture site. Finite element analysis (FEA, *left*) of patient 5 indicates PWRR location on the left lateral region within the aneurysm wall. Rupture occurred (image on the *right*) 154 days after FEA computation, and a left lateral periaortic hematoma *(white arrow)* was detected.

aneurysm wall, using a pressure transducer during open AAA repair. Vorp et al.[51] noted localized hypoxia in regions of thicker thrombus leading to localized wall neovascularization, inflammation, and regional wall thinning. Hypoxia also affects the function of vascular smooth muscle cells, causing them to secrete more collagenase than in normoxic conditions, with less elastin and collagen production.

An autopsy study of patients who died of infrarenal RAAAs noted that 80% of ruptures occurred at the site of mural thrombus.[52] CT studies of patients admitted with rupture showed that most occurred through the thrombus or at its edge. Others argue that ruptures are caused by fissures in the intraluminal thrombus, due to proteolytic enzymes on the luminal surface of the clot.[53] A Dutch report[54] in 2013, although accepting a role for fissure formation, confirmed that intraluminal thrombus thickness was associated with vascular smooth muscle cell apoptosis (or cell death), elastin degradation, and high levels of matrix metalloproteinase 2 and correlated with aneurysm rupture. PET-CT with ^{18}F-fluorodeoxyglucose has not be predictive of rupture.[9,55]

CLINICAL FEATURES

Signs and Symptoms

The classic presentation of RAAA includes the triad of acute-onset abdominal/back pain, hypotension, and a pulsatile abdominal mass. Severe and unremitting back pain is caused by rupture of the aneurysm into the retroperitoneal lumbar space. The pain may radiate to the back, testes, inguinal canal, or rectum and possibly hip due to psoas irritation. On examination, the patient is frequently pale, diaphoretic, and hypotensive with a tender, pulsatile abdominal mass. Flank ecchymosis is a late sign.

Differential Diagnosis

In patients older than 50 years with hypotension and/or syncope, consideration of RAAA is critical. The differential diagnosis may include renal colic, diverticulitis, pancreatitis, gastrointestinal hemorrhage, myocardial infarction, and perforated ulcer. Although the signs and symptoms of RAAA can be clear-cut, recognition in the early stages can be difficult. Presentation can range from sudden onset with hypotension and collapse to slowly increasing pain over a few days as the AAA wall has gradually stretched and then torn. In this age group, chronic back problems are common; there may be a tendency to ascribe symptoms to exacerbation of long-standing back problems.

Among those subsequently diagnosed with an RAAA, only 23% had a definitive and immediate diagnosis of RAAA made by the first examining physician.[56,57] The rate of incorrect diagnosis ranges from 16% to 60%.[58] The most common misdiagnoses were renal colic, perforated viscus, diverticulitis, gastrointestinal hemorrhage, and ischemic bowel. The initial manifestation of renal colic occurs infrequently in patients older than 60 years. The classic triad was present in only 9% of the

misdiagnosed group compared with 34% of the correctly diagnosed group. The presence of a pulsatile mass was identified in 72% of those correctly diagnosed but in only 26% of the misdiagnosed patients. Furthermore, the use of ultrasound in older studies was reported as being consistent with rupture in only 51% of cases.[59]

Rare presentations include rupture into an adjacent structure, such as an acute gastrointestinal bleed due to a primary aortoduodenal fistula or an aortocaval fistula that presents as a pulsatile abdominal mass, loud machinery-like bruit, or thrill with elevated jugular venous pressure associated with new-onset acute congestive heart failure.

Diagnostic Evaluation

Plain Radiographs

Although the use of plain radiography is currently rare, a retrospective review of plain films of patients with RAAAs showed evidence of the diagnosis on 90% of the films.[60] Enlargement of a calcified aortic wall beyond normal limits was seen in 65%, and loss of a psoas shadow from retroperitoneal hemorrhage was identified in 75%.

Ultrasound

Bedside ultrasound in the emergency department by trained emergency physicians has led to its use in cases of suspected RAAA. FAST (focused assessment with sonography in trauma) ultrasound protocols can rapidly identify fluid collections and direct further trauma care.[59,61] When ultrasound is used in patients with back pain, abdominal pain, or other indication of AAA, it can identify aortic aneurysms with high sensitivity, specificity, and positive and negative predictive values.[62,63] No large prospective studies have been conducted, although with appropriate training the use of ultrasound to quickly assess patients for the presence of AAA is likely beneficial as it directs rapid investigation and therapy. It is not sufficiently accurate to exclude rupture.[62,64]

Computed Tomography

The most accurate method for diagnosis of RAAA is CT, which also provides important associated information. A non–contrast-enhanced CT scan can identify retroperitoneal hemorrhage associated with RAAA and important anatomic information (Fig. 74.3A and B). However, CT scanning with contrast enhancement is ideal to plan RAAA either open surgical repair (OSR) or EVAR. Proper timing of contrast injection reduces the volume required, lessening its renal impact. Patients leaving the ER department for CT if RAAA is in the differential should be accompanied and monitored for acute deterioration.

If evidence of retroperitoneal blood with an AAA is used as the "gold standard" for diagnosis of RAAA on CT, it is 77% sensitive and 100% specific in a retrospective series.[65] Its positive predictive value was 100%, and its negative predictive value was 89%.[66] The level of agreement of the diagnosis of RAAA based on CT scanning was only moderate in five observers, whereas agreement on suitability for EVAR was only fair in vascular surgeons and radiologists experienced in EVAR from the Amsterdam Acute Aneurysm study.[67] Intraobserver agreement on rupture and suitability for EVAR was higher than interobserver agreement.

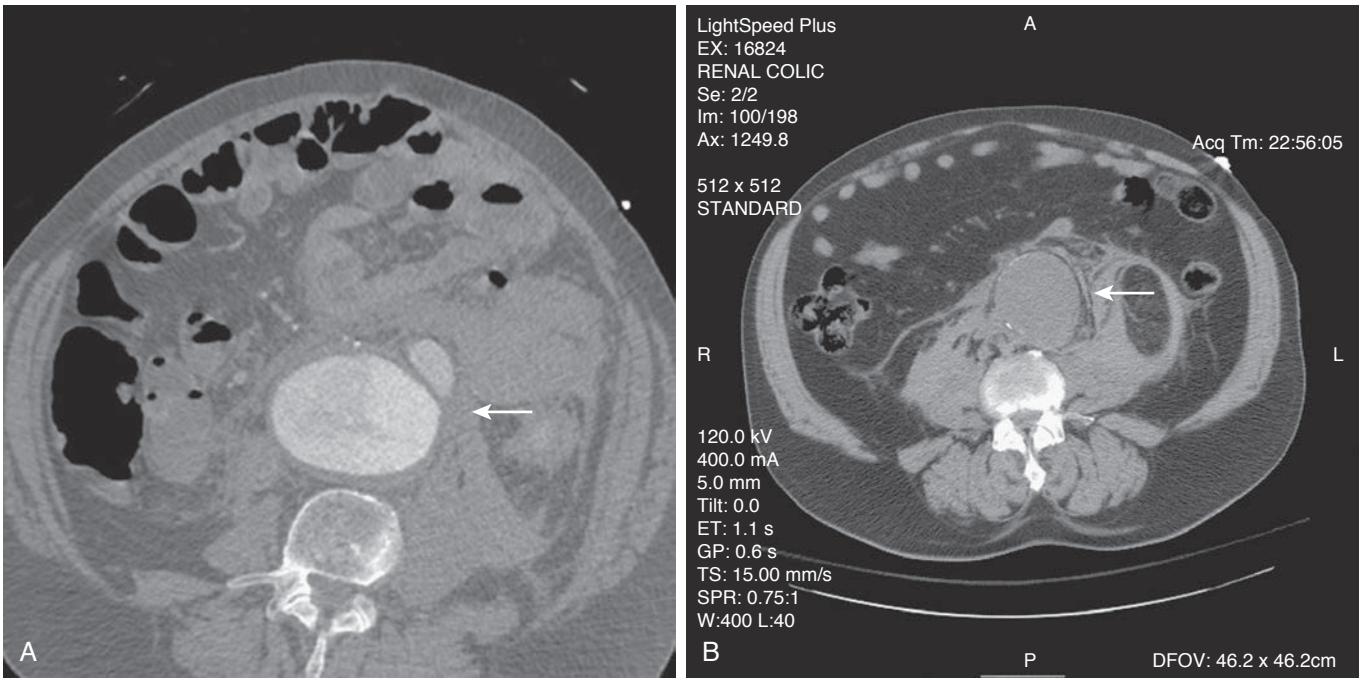

Figure 74.3 (A) Frank rupture of an infrarenal abdominal aortic aneurysm with contained extravasation *(arrow)*. (B) Computed tomography scan of a ruptured abdominal aortic aneurysm. Note the pattern of stranding of blood into the tissues *(arrow)*. No contrast material was used, and the scan was performed for the diagnosis of renal colic.

Is There Time for a Computed Tomography Scan in Ruptured Abdominal Aortic Aneurysm?

Prospective and retrospective studies have examined the delay between the initial manifestation of RAAA and the time to death to determine whether sufficient time exists to perform a CT scan and to evaluate patients' suitability for EVAR. The time to death for conservatively managed patients (due to age or comorbidities) from onset of symptoms to death was a median of 16 hours.[68] Only 13% died within 2 hours of hospital admission, suggesting that sufficient time exists for most patients to undergo CT scanning and evaluation for EVAR. A small number of patients in both the UK RAAA randomized trial (Immediate Management of the Patient with Rupture: Open Versus Endovascular Repair [IMPROVE]) and the Amsterdam Acute Aneurysm study were too unstable for CT scanning and required immediate transfer to the operating room.[69] Prospective data from the IMPROVE trial demonstrated that 90% to 97% of patients had a CT scan prior to intervention and the time to arrival at the operating room was 25 minutes shorter in the EVAR group versus OSR despite the requirement for a contrast-enhanced CT scan.[70] Thus, for the majority of patients who are stable on arrival at a center where definitive care will be carried out, a prompt CT scan does not adversely affect mortality.[68,71] A protocol for priority management of RAAA may significantly shorten the time to definitive therapy despite the CT scan requirement.[72,73]

INITIAL MANAGEMENT STRATEGIES

Patient Triage and Transfer to Appropriate Institutions

RAAA is a surgical emergency, and when the diagnosis is being considered, immediate vascular surgery consultation is critical. Rural hospitals without vascular surgery expertise tend to face a higher burden of RAAA patients and more commonly do not offer any intervention.[74,75] Patient transfer increases the time of arrival from the initial hospital to the operating room, although most studies demonstrate that patients who are transferred do not have a higher mortality but in fact have lower mortality as noted in the US National Inpatient data.[72,74] Furthermore, high-volume regional centers, teaching centers, and high bed capacity hospitals have significantly lower mortality for RAAA patients.[10,74,76]

Permissive Hypotension

Preoperative resuscitation of RAAA patients with hypotension must be judicious.[70,77-81] Large volumes of intravenous fluids raise blood pressure, causing further hemorrhage by overcoming the tamponade, result in hemodilution, coagulopathy, hypothermia, and acidosis, and further deterioration.[82] Protocols that restrict aggressive fluid resuscitation in hypotensive trauma patients with hemorrhagic shock improve survival so that permissive hypotension for RAAA patients is recommended. Fluid resuscitation should be sufficient to maintain consciousness, minimize organ ischemia, prevent ST depression, and maintain a systolic pressures of 70 to 80 mm Hg, although some have suggested lower BP targets.[78,83] Contemporary algorithms for management of RAAA patients include permissive hypotensive resuscitation.[82] Aggressive volume resuscitation before proximal aortic control is a predictor of increased postoperative mortality.[77,80] The IMPROVE trial demonstrated that those with the lowest BP had the highest mortality and increasing SBP to greater than 70 mm Hg was beneficial.[70] Observational studies also suggest that increased fluid administration prior to aortic control increased mortality.[83] Implementation of a controlled hypotension strategy in a regional ambulance service for patients with hypotension, in which only 27% had a final diagnosis of RAAA, demonstrated the overall risk of harm was low.[77] Evidence regarding resuscitation with blood versus crystalloids is limited; if blood is available, it should accompany the patient during transfer and can be given to maintain consciousness.

Protocol-Based Approach

EVAR for RAAA now requires a preoperative contrast CT scan (Fig. 74.4). EVAR obstacles are anatomic suitability, availability of staff and equipment at all hours, feasibility of treating hemodynamically stable and unstable patients, and ability of the care team to manage unexpected scenarios under emergent circumstances. One key factor is awareness among the emergency department staff of the diagnosis of RAAA and early notification of the on-call vascular surgeon/team.[73,84,85] A fine cut, low contrast volume CT scan to assess neck diameter, angulation, and iliac size is of critical importance.[85] Hemodynamically unstable patients can be directly transferred to the operating room without a preoperative CT scan for balloon control with either an EVAR or conversion to OSR as needed.[84] The initial emergency room evaluation must include a blood crossmatch.

Anatomic Suitability of Ruptured Abdominal Aortic Aneurysms for Endovascular Aneurysm Repair

The proportion of RAAA patients suitable for EVAR varied from 47% to 67% in two meta-analyses.[86,87] RAAAs have larger infrarenal aortic diameters and shorter neck lengths, which impact the percentage suitable for EVAR.[88,89] The success of EVAR on RAAA outcomes has been examined in patients with favorable versus unfavorable aortic neck morphology.[86,87,90,91] Data from the IMPROVE trial demonstrated that shorter neck lengths were associated with higher mortality in both open and EVAR patients.[92] For every 15-mm increase in neck length the mortality dropped by approximately 20%. A longer neck in RAAA facilitated both open (with an easier clamp site) and EVAR (improved proximal seal). The relationship between neck length and outcome may be a key variable that explains the discrepancy in RAAA outcomes between population-based data and randomized trials.[92]

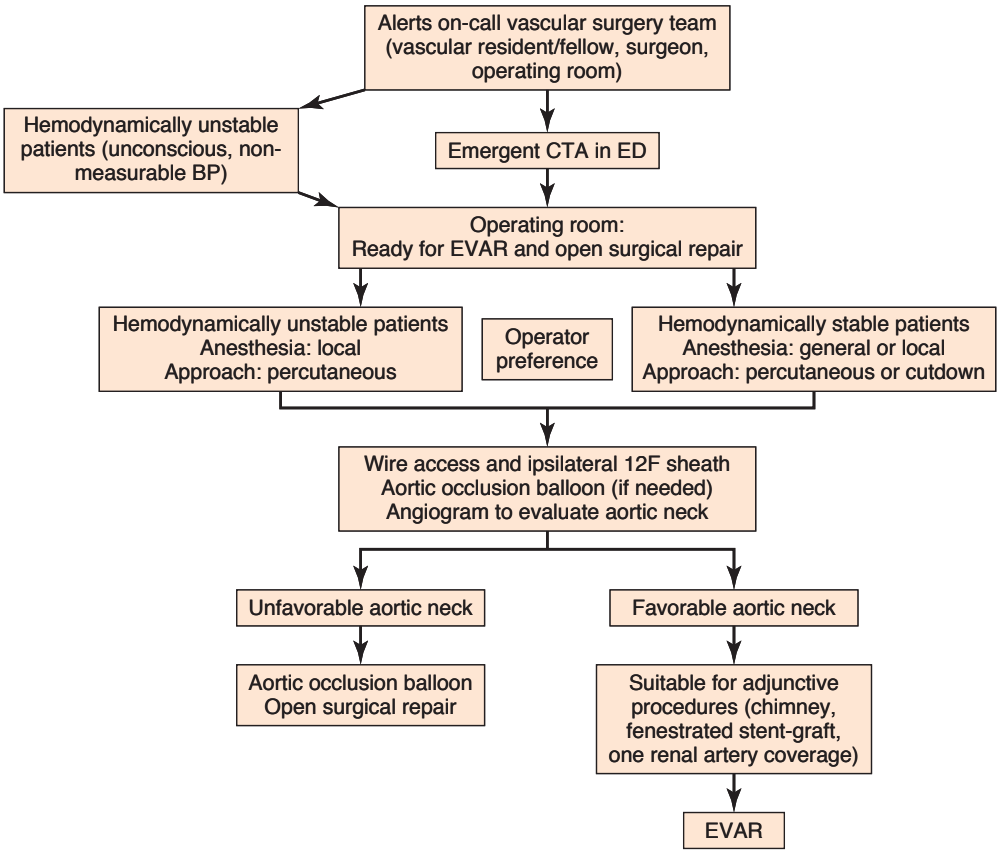

Figure 74.4 Albany Vascular Group standardized protocol for endovascular aneurysm repair (EVAR) of ruptured abdominal aortic aneurysms. *BP*, Blood pressure; *CTA*, computed tomography angiography; *ED*, emergency department. (From Mehta M. Endovascular aneurysm repair for ruptured abdominal aortic aneurysm: the Albany Vascular Group approach. *J Vasc Surg*. 2010;52:1706–1712.)

Operative Preparation and Setup

The operating room should be equipped for EVAR and OSR. Anesthesia, nursing, and technical personnel can simultaneously and rapidly prepare the patient for intervention. Large-bore access, insertion of an arterial line, and placement of a Foley catheter can be done simultaneously. The patient is prepared and draped (including one brachial artery site) awake for both EVAR and open conversion. Local anesthesia can be infiltrated and ultrasound used to obtain percutaneous access for balloon control, then EVAR or open repair can proceed with agents designed to have minimal effect on blood pressure.

OPERATIVE STRATEGIES: ENDOVASCULAR REPAIR

EVAR has become the preferred method of therapy for RAAA repair for those with suitable anatomy.[93] At institutions with infrastructure for both EVAR and OSR for RAAA, by 2012 most RAAA patients (>70%) undergo EVAR in the United States.[8] OSR is generally reserved for those who are anatomically unsuitable for EVAR, for institutions that do not have the infrastructure to provide emergent EVAR, or when EVAR fails to seal the AAA.

Initial Management Technique

Arterial Access and Aortic Occlusion Balloon

After local anesthesia percutaneous access (preferred) or femoral artery cutdown (if required) is performed, ipsilateral access is obtained with exchange to place a stiff wire for device delivery. A large sheath (12F-16F × 45-cm length) in the ipsilateral femoral artery is placed over the stiff wire and advanced above the renal vessels, a compliant aortic occlusion balloon is deployed in hemodynamically unstable patients, into the supraceliac abdominal aorta under fluoroscopic guidance, and partially or fully inflated as needed (Fig. 74.5).[84,94,95] A retrospective review of a single-center experience of unstable RAAAs comparing open conventional cross-clamp and balloon occlusion demonstrated that balloon occlusion reduced intraoperative mortality to 19% from 34%; however, 30-day and in-hospital mortality rates were not significantly different (69% vs. 77%).[96]

Choice of Anesthesia and Approach

A key benefit of local anesthesia with conscious sedation is maintenance of "sympathetic tone" in the hemodynamically compromised patients. In hemodynamically unstable patients with weak or absent femoral pulses, this can be difficult and should be aided by ultrasound-guided femoral access and a micropuncture technique. The advantages of local anesthesia

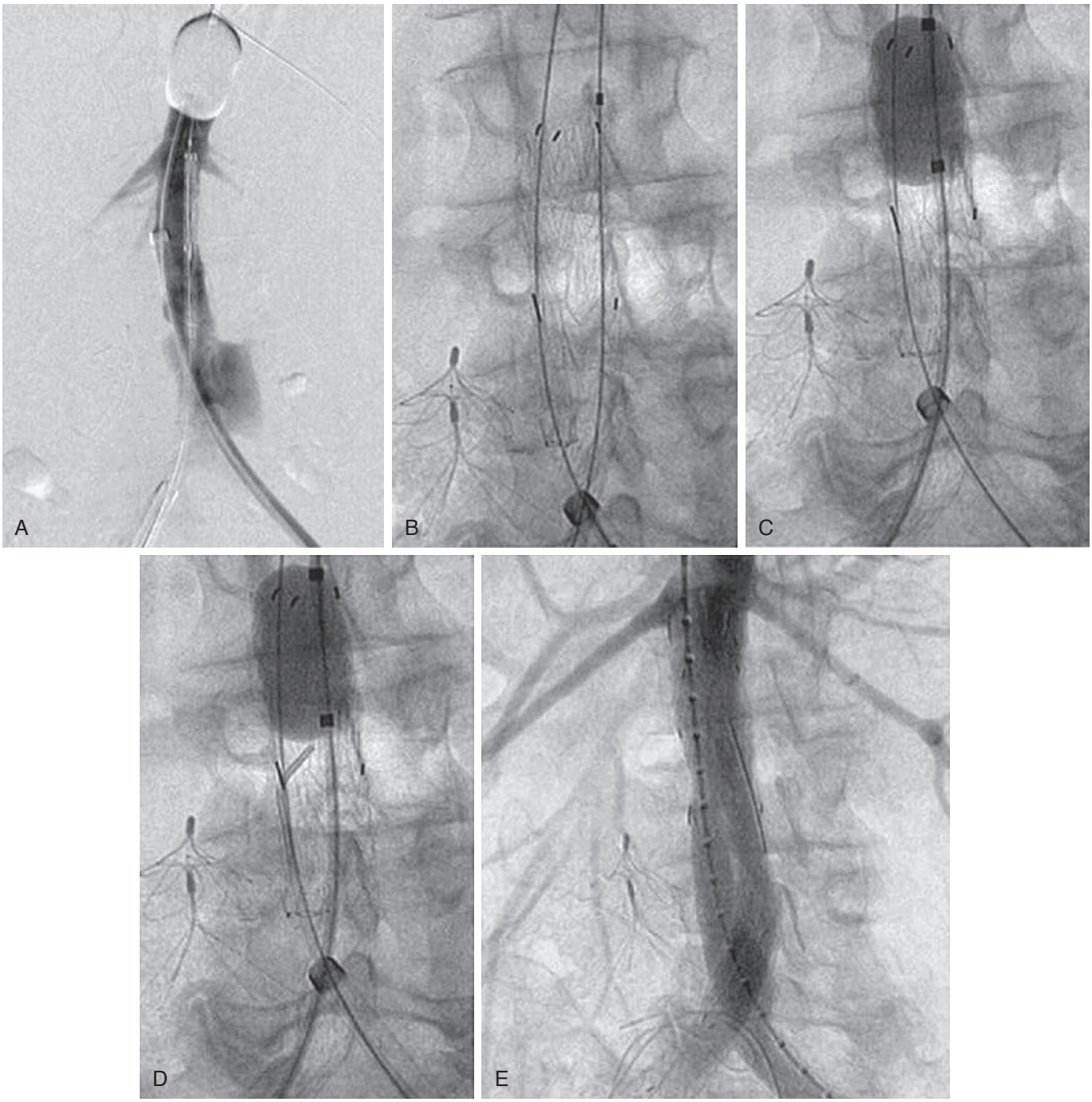

Figure 74.5 Managing the Aortic Occlusion Balloon During Stent-Graft Deployment. (A) The inflated suprarenal aortic occlusion balloon is advanced through the left femoral approach, the stent-graft main body is advanced through the right femoral approach, and arteriography is performed through the left femoral sheath supporting the occlusion balloon. (B) The aortic occlusion balloon is deflated and retracted from the aortic neck, and the stent-graft main body is subsequently deployed. This avoids trapping of the compliant aortic occlusion balloon between the aortic neck and the stent-graft. (C) In hemodynamically unstable patients the occlusion balloon can be redirected into the aortic neck from the side ipsilateral to the stent-graft main body and reinflated at the infrarenal aortic neck within the stent-graft main body before contralateral gate cannulation. (D) After the occlusion balloon is reinflated in the stent-graft main body in hemodynamically unstable patients, the contralateral stent-graft gate can be cannulated, and contralateral stent-graft extensions are placed as needed. (E) After contralateral iliac extension and ruptured abdominal aortic aneurysm exclusion, the occlusion balloon can be removed, as shown in the completion arteriogram. (Mehta M. Endovascular aneurysm repair for ruptured abdominal aortic aneurysm: the Albany Vascular Group approach. *J Vasc Surg*. 2010;52:1706–1712.)

must be balanced by the potential difficulties with the incoherent and uncooperative patients.[73,70] In hemodynamically unstable patients, starting the procedure under local anesthesia, then conversion to general anesthesia after RAAA exclusion, can be required for sheath removal and femoral repair.[97] Local anesthesia for EVAR in the IMPROVE trial greatly reduced the 30-day mortality compared with general anesthesia (adjusted OR of 0.27).[70]

Bifurcated Versus Aorto-Uni-Iliac Stent-Grafts for Ruptured Abdominal Aortic Aneurysm

Choice of stent-graft is determined by the patient's aorto-iliac morphology. An aorto-uni-iliac stent-graft for RAAA can be an advantage if there is inability to access the contralateral gate expeditiously or significant unilateral occlusive disease or tortuosity. Use of aorto-uni-iliac devices for EVAR of RAAA has similar outcomes to bifurcated stent-grafts.[98,99] Maintaining pelvic perfusion with at least one internal iliac artery patent is advantageous.

Conversion to Open Surgical Repair

When OSR or conversion is needed, the aortic occlusion balloon is invaluable to maintain hemodynamic stability. During laparotomy, it is crucial to maintain the position of the aortic occlusion balloon and its delivery sheath to prevent prolapse into the AAA. For conversion after stent-graft deployment, a tailored approach is suggested. For a IA leak, the suprarenal stent can be left in place to avoid aortic tearing. For IB endoleaks, sewing an interposition graft to an endograft body is possible.

OPERATIVE STRATEGIES: OPEN SURGICAL REPAIR

Transperitoneal Approach

This widely advocated approach allows safe, rapid, and effective proximal aortic control at the supraceliac, suprarenal, or infrarenal aorta and distal control of the iliac or even femoral vessels (see Chapter 54).[78,100] The supraceliac aorta can be exposed as shown in Fig. 74.6. Supraceliac clamping is preferred compared with the aortic compression devices, which provide only incomplete and imperfect control. After supraceliac clamping, the infrarenal aortic neck is dissected and the clamp may be repositioned to the infrarenal aortic neck before or after the proximal anastomosis is completed, trying to minimize visceral ischemic time. Supraceliac clamping induces ischemic injuries to the liver, bowel, and kidneys, which, in addition to the injury induced by hemorrhagic shock, may contribute to the development of postoperative MOF.[35,101] Supraceliac unclamping requires coordination with the anesthesia team to avoid sudden hypotension. Supraceliac control is beneficial for uncontrolled hemorrhage when immediate aortic control is needed, and it helps to avoid the renal and inferior mesenteric vein injuries that occur with blind retroperitoneal dissection in the face of large bleeding retroperitoneal hematoma.

For RAAA with clear evidence of suprarenal extension identified on CT, a thoracoabdominal incision allows rapid access to the aorta just above the diaphragm. A medial visceral rotation is then carried out to expose the visceral aorta, and standard elective techniques are used to reconstruct the visceral vessels and the aorta.

Retroperitoneal Approach

This approach is suggested to expedite supraceliac exposure and control and is safe when performed by those fascicle with its elective use.[102,103] It is particularly useful in patients with challenging body habitus or hostile abdominal situations.

Operative Technique

After proximal control is achieved in open repair, allowing the anesthesia team time for resuscitation, before the blood loss associated with aneurysm sac opening occurs. Controlling the IMA and iliacs can limit this. Once the aneurysm is opened, balloon iliac occlusion, if required, and lumbar suture ligation are rapidly accomplished. With supraceliac aortic control, bleeding from the proximal visceral arteries will require continuous suction during construction of the proximal anastomosis, preferably with a cell saver. Systemic heparin is generally avoided during RAAA repair, although it can be administered in a lower than usual dose just prior to clamp application. Alternatively, heparinized saline can be administered directly into the iliac arteries through occlusion balloons in an attempt to reduce distal thrombosis. Aggressive retrograde flushing of the iliac artery before distal anastomosis completion to remove any soft clot, particularly in nonheparinized patients, is important. Aortic repair is most rapidly accomplished with a tube graft. If bifurcated grafts are required, the easier of the two iliac (or femoral in ABF grafts) anastomoses is repaired first to reduce lower torso ischemic time. Maintaining perfusion of one internal iliac artery is optimal to reduce pelvic and colon ischemia.

Aortocaval Fistula

Continuous venous bleeding into the aortic open aneurysm sac after proximal and distal control have been achieved suggests an aortocaval fistula. Direct digital pressure or the use of sponge sticks above and below the fistula is recommended. Suture of the fistula from within the aneurysm is recommended to avoid further additional venous injury, with care to avoid an air or aortic debris embolus during the repair.

Autotransfusion

The use of red cell salvage with a cell saver device has proven beneficial in reducing mortality in RAAA patients undergoing OSR.[104] Red cell salvage reduces blood transfusions, morbidity, and mortality.[105] A retrospective review demonstrated that a ratio of autotransfusion/PRBC of greater than or equal to 1 was associated with lower mortality for open repair; however, liberal use of fresh frozen plasma did not decrease mortality.[106]

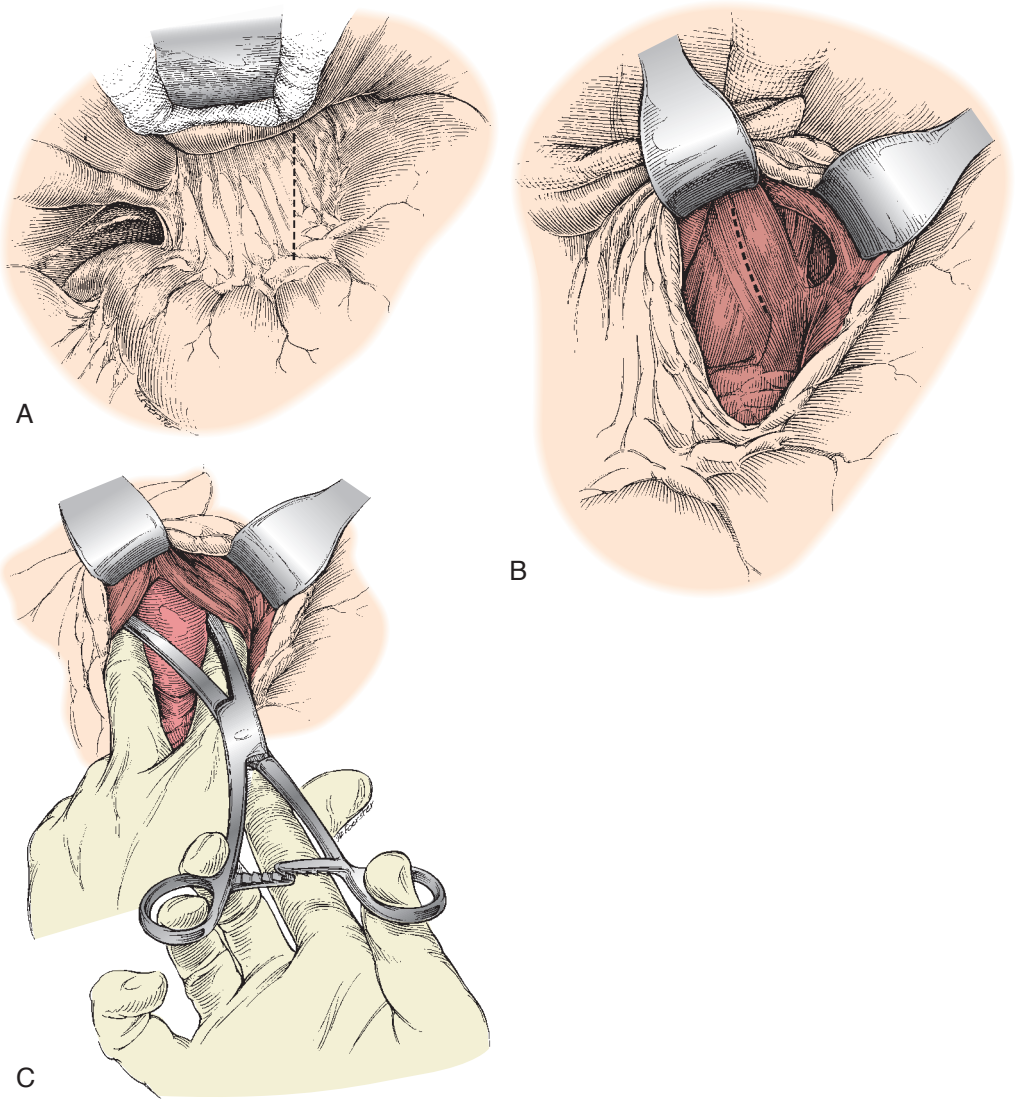

Figure 74.6 Exposure of the Supraceliac Aorta. (A and B) Initially, the lesser sac needs to be opened to allow opening of the diaphragmatic crura. (C) Blunt dissection of the aorta then allows a clamp to be placed over the two fingers that are exposing the aorta. (From Rutherford RB. *Atlas of Vascular Surgery: Basic Techniques and Exposures.* Philadelphia: WB Saunders; 1993:188–189.)

Hypothermia

Hypothermia increases surgical bleeding, wound infections, and cardiac events and is significantly associated with RAAA mortality.[104,107] Current recommendations for hypothermic patients include the use of warmed anesthetic gases, intravenous fluids, and the use of forced-air warming devices.

Anatomic Abnormalities

Variant arterial, venous and renal anatomy can greatly complicate OSR of RAAA; however, the preoperative CT scan can identify these abnormalities and allow planning. Arterial and venous injuries increase the mortality rate in RAAA repairs. Intraoperative finding of an inflammatory aneurysm may require suprarenal or supra celiac control with repair from within the aneurysm without duodenal dissection.

Venous Abnormalities

The most common venous abnormalities encountered include a retroaortic renal vein (1%-3%), circumaortic renal vein (0.5%-1.5%), left-sided vena cava (0.15%-0.5%), and duplicated inferior vena cava (0.4%-3%).[108] Retroaortic renal vein injury can be managed by more proximal clamp application, division of the aorta with anterior aortic retraction, and vein ligation. A left-sided vena cava or duplicated inferior vena cava that crosses in front of the aorta at the level of the renal vein can complicate proximal aortic clamp application. If elevation and mobilization fail to allow sufficient access for repair, temporary division and reanastomosis may be required.

Renal Abnormalities

A horseshoe kidney discovered on preoperative CT scanning prior to RAAA repair can present technical challenges for both

EVAR and OSR. Adjunctive measures for renal protection may include systemic mannitol (3-5 mL/kg), renal cooling, and arterial revascularization using an island with the arterial supply.[109]

Abdominal Closure

Primary abdominal closure is most common. In 25% to 30% of patients the abdomen cannot be closed primarily without significant tension secondary to swollen bowel, tissue edema, and retroperitoneal hematoma.[110] Patients who have severe preoperative anemia, prolonged shock, preoperative cardiac arrest, massive resuscitation, profound hypothermia, and severe acidosis may benefit from closure with mesh sewn to the fascia. Early mesh closure prevents abdominal compartment syndrome (ACS) and appears to reduce the incidence of MOF and may reduce mortality in comparison with patients who eventually returned to the operating room for decompressive laparotomy and delayed mesh closure.[110] Vacuum-assisted closure systems are available but have not been proven in RAAA patients but offer advantages in terms of high abdominal closure rates with a low incidence of complications in selected patients.[110,111]

COMPLICATIONS OF RUPTURED ABDOMINAL AORTIC ANEURYSM REPAIR

Local Complications

After OSR and EVAR, postoperative bleeding related to coagulopathy occurs in 12% to 14% of patients.[112] Limb ischemia can be related to in-situ graft limb thrombosis or distal thromboembolism. EVAR complications include access site bleeding and thrombosis ranging from 7% to 10%.[8]

Colonic Ischemia

Colonic ischemia is a potential lethal consequence of any AAA repair. Prospective sigmoidoscopy studies noted an ischemic colitis incidence of 38% after OSR and 23% after EVAR of RAAA ranging from patchy mucosal necrosis (grade I), to mucosal and muscularis involvement (grade II), to transmural necrosis, gangrene, and perforation (grade III).[113-115] If colonic ischemia is suspected during the postoperative period, sigmoidoscopy or colonoscopy to visualize the area is diagnostic. A prospective analysis of RAAA patients who survived 24 hours demonstrated a 26% incidence of grades I and II ischemia and 10% grade III changes.[113] Only 11% of grade I or grade II changes progressed to grade III in 48 hours. Grade III changes have extensive sigmoid and rectal necrosis and a mortality rate of 55% despite aggressive surgical management. Factors determining the degree of colonic ischemia after RAAA repair include the degree and duration of hypotension, patency of the inferior mesenteric artery, and collateral supply between the superior mesenteric, inferior mesenteric, and internal iliac arteries. At the conclusion of OSR, careful bowel examination with Doppler evaluation of the mesenteric vessels should be routinely performed and reimplantation of the inferior mesenteric artery considered. The incidence of ischemic colitis differs with the type of repair: 4% for tube grafts, 2.7% for aorto-iliac grafts versus 22% for an aortobifemoral graft. Colonic ischemia is also prevalent after EVAR of RAAA. After EVAR, prospective flexible sigmoidoscopy done 24 hours postoperatively noted a 22% incidence of ischemic changes, with 5% having segmental necrosis.[114,115] No blood test parameter was sufficiently discriminative to assist reliably in the diagnosis of colonic ischemia so that a high index of suspicion and routine sigmoidoscopy for all RAAA patients has been suggested.[115]

Assessment for Abdominal Compartment Syndrome

RAAA repair is a common cause of ACS. ACS is defined as an acute and rapid elevation in intraabdominal pressure of more than 20 mm Hg that is associated with cardiovascular, pulmonary, renal, and splanchnic organ dysfunction. Postoperative oozing and tissue edema contribute to the increase intraabdominal pressure. Clinical findings include a tense distended abdomen, progressive respiratory failure (elevated peak inspiratory pressures, decreased tidal volume, and elevated PCO_2), diminished cardiac output, and oliguria.[116,117] Intraabdominal hypertension is graded on the basis of bladder pressures.[117] Decompression laparotomy is recommended for intraabdominal hypertension greater than 25 mm Hg (grade III and grade IV).[116,117] Bladder pressure is measured with 50 to 100 mL of instilled bladder fluid and zeroed at the pubic symphysis.

ACS after EVAR of RAAA increases mortality and is associated with use of an aortic occlusion balloon, massive blood transfusions, coagulopathy, and hemodynamic instability.[117-119] A meta-analysis of ACS in RAAA demonstrated an incidence of 8% for all RAAAs and 21% after EVAR with a suggested management algorithm (Fig. 74.7).[120] ACS requires prompt recognition and decompression laparotomy. Proactive abdominal decompression by percutaneous intra peritoneal blood removal or retroperitoneal hematoma evacuation after EVAR of RAAA has been successful.[119]

Spinal Ischemia

Paraplegia and paraparesis are rare complications after RAAA repair with a risk for OSR of 1.2% compared with 0.5% to 11.5% for EVAR.[121,122] Factors associated with spinal cord ischemic complications include interruption of the pelvic blood supply, prolonged aortic cross-clamping, preoperative and intraoperative hypotension, and embolization. Early recognition with CSF drainage and pelvic revascularization are the main therapies.

Systemic Complications

Cardiac Complications (See Chapter 42)

Myocardial infarction, arrhythmias, cardiac arrest, and congestive heart failure increase mortality after RAAA.[112] Myocardial infarction develops secondary to the increased demand placed on the heart in the setting of preexisting coronary artery disease. Preexisting coronary artery disease has been shown to increase

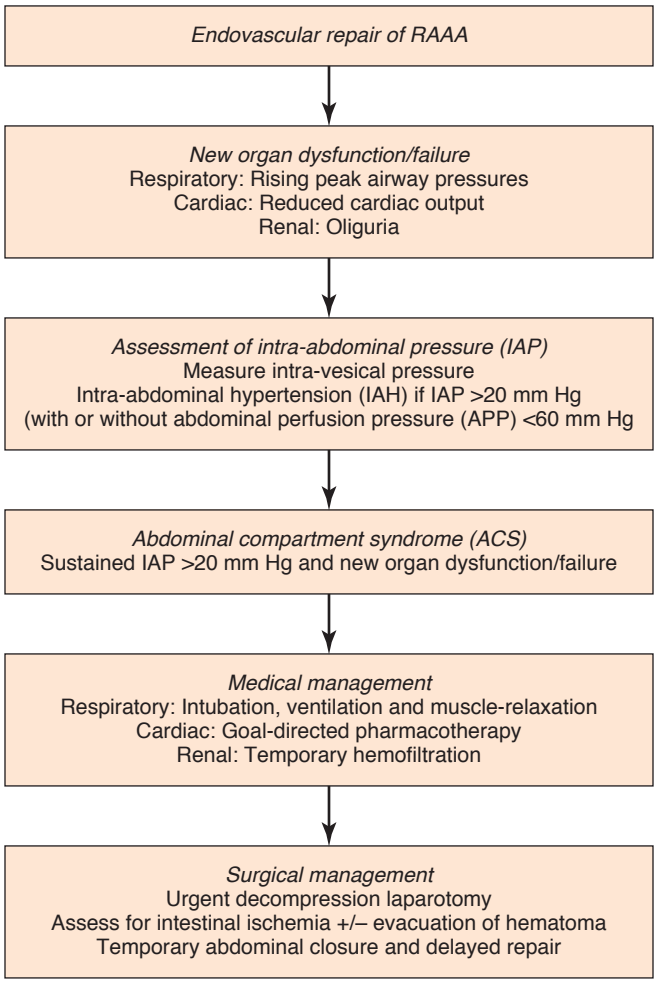

Figure 74.7 Algorithm for escalation of management of abdominal compartment syndrome (ACS) after endovascular repair of ruptured abdominal aortic aneurysms (RAAAs). (From Karkos CD, et al. A systematic review and meta-analysis of abdominal compartment syndrome after endovascular repair of ruptured abdominal aortic aneurysms. *J Vasc Surg.* 2014;59(3):829–842.)

the risk for MI and death after OSR of RAAA but not after EVAR.[8] Cardiac arrest occurs in up to 20% of patients, with a mortality of 81% to 100%. Myocardial infarction develops in 15% to 20% of patients, with a mortality rate of 17% to 66%; arrhythmias and congestive heart failure develop in nearly 20% of patients, with a mortality approaching 40%.[8,37,112] EVAR for RAAA has not been demonstrated to reduce the number of cardiac complications.[37] Postoperative measurement of cardiac-specific troponin has been shown to be elevated in up to 55% of RAAA patients. An elevated troponin and EKG changes were associated with significantly higher rates of CHF, cardiogenic shock, and in-hospital mortality (56.3% vs. 29.3%).[123] Elevation of troponin alone irrespective of the EKG changes was associated with an elevated mortality rate of 40.3% versus 14.1%.

Respiratory Failure (See Chapter 43)

Respiratory failure, pneumonia, and pulmonary complications develop in 36% to 41% of patients after OSR of RAAA and are predicted by preexisting chronic obstructive pulmonary disease (COPD).[37,124] Administration of large volumes of fluid and blood products, long cross-clamp times and COPD predisposes to the development of respiratory failure. Pneumonia, respiratory complications, and the need for tracheostomy are significantly lower after EVAR compared with OSR (28.5% vs. 35.9%, 4.6% vs. 9.9%, respectively; $P < .001$ for both).[37,124] Lung dysfunction is significantly reduced by EVAR.

Renal Dysfunction (See Chapter 44)

Renal dysfunction after RAAA predicts mortality.[37,112] Although the incidence of renal dysfunction after elective AAA repair is low, RAAA patients have an incidence of 26% to 45%.[37] In RAAA patients who require dialysis (incidence 11%-40%), the mortality rate is between 76% and 89%.[112,125] Renal dysfunction has been found to be increased in those with suprarenal cross-clamping, longer duration of cross-clamping, preexisting renal insufficiency, shock, and increased age.[124-127] The US National Inpatient Sample (NIS) noted significantly less acute renal failure (ARF) for EVAR (12.1%) compared with 19.6% in OSR.[74] In Medicare patients, EVAR was associated with 33.4% incidence of ARF despite contrast administration versus 45.4% for OSR.

Liver Failure

Hepatic failure is a late event after RAAA and described as hypoxic hepatic injury.[128] Increased metabolic demands, hematoma reabsorption, and unrecognized preexisting hepatic dysfunction are risk factors and are associated with pulmonary, cardiac, and gastrointestinal dysfunction with a mortality rate of 83%.[128,129]

Multisystem Organ Failure

The development of MOF depends upon the magnitude, number, and timing of inflammatory insults. Clinical RAAA data suggest that suprarenal clamp location, duration of clamping, and development of ACS are associated with higher rates of MOF and death.[118,126] The incidence of MOF was noted to be 3.8% after elective AAA repair, 38% after urgent AAA repair, and 64% after OSR of RAAA.[127] MOF after RAAA repair occurs more frequently after OSR than after EVAR and has mortality rates of 64% to 93%.[101,129,130]

The two-hit hypothesis of RAAA (hemorrhagic shock and ischemia secondary to temporary aortic clamping) initiating MOF may account for the persistently elevated mortality in the patients undergoing RAAA repair.[36,131-133] In a model of RAAA, individual insults of hemorrhagic shock alone or aortic clamping alone were insufficient to result in the development of systemic organ injury. However, combining the insults resulted in a synergistic effect with systemic organ injury that resembled MOF.[131-133] Hemorrhagic shock causes cardiac contractile dysfunction after resuscitation which further reduces tissue perfusion.[134] RAAA patients have neutrophils that are primed to respond to ex-vivo stimulation on arrival to the ER and with further significant elevations in neutrophil oxidative burst postoperatively.[135] A significant relationship between the level of neutrophil oxidative bursts and the level of tissue oxidative

injury products was identified. Both laboratory model and human subject data suggest that RAAA is a two-hit model of injury which may explain why the mortality after RAAA repair has failed to drop dramatically despite advances in perioperative management.

OUTCOMES OF RUPTURED ABDOMINAL AORTIC ANEURYSM REPAIR

Results of RAAA repair by OSR and EVAR are published from single-center series, national registries, randomized trials, and a meta-analysis of the randomized trials.[136-155] Major differences in outcomes exist between large registry data and the randomized trials. Large data sets (US National Discharge database, the NIS, and the US Medicare database) demonstrate a significant in-hospital and/or 30-day mortality benefit of EVAR over open repair, between 13% and 14%.[10,37,74] A major bias that cannot be addressed in observational data sets is that those with longer necks and anatomy suitable for EVAR are more likely to undergo EVAR. Those with shorter, angulated necks and unfavorable EVAR anatomy are relegated to OSR, which are technically more challenging to repair, likely adding to the mortality rate. The randomized trials had different randomization strategies, criteria, and outcome measures. The Amsterdam Trial (AJAX) randomized patients after a CT scan that demonstrated a rupture and patients eligible for either therapy.[146] The ECAR (French) randomized RAAA patients after a CT scan confirming both rupture and anatomy suitable for EVAR and a systolic BP of greater than 80 mm Hg.[124] IMPROVE randomized the largest number of patients (with more women) with a clinical diagnosis of RAAA, before a CT scan; thus not all patients had a RAAA and not all randomized to the EVAR cohort had suitable anatomy for EVAR, leading to crossovers.[147]

Observational Ruptured Abdominal Aortic Aneurysm Study Outcomes

US Medicare data of repaired RAAAs between 2001 and 2008 were propensity matched for baseline demographics, coexisting conditions, admission source, and hospital volume of RAAA repair to assess short- and long-term mortality, complications, and re-interventions, but differences in hemodynamic stability and anatomic suitability for EVAR are not accounted for in this comparison of EVAR and OSR outcomes.[37] EVAR mortality of 33.8% versus 47.7% for OSR, and all ages derived significant benefit. Complications were lower in the EVAR group, including pneumonia, ARF, respiratory failure but not MI, venous thromboembolism, or the incidence of hemodialysis. Surgical complications were significantly lower with EVAR except wound hematomas, LOS was 7 versus 14 days for survivors and discharge to home was 22% higher for EVAR. A significant long-term benefit for EVAR was seen in all ages which persisted for more than 4 years. Laparotomy-related complications were less after EVAR, but EVARs did have higher open surgical and endovascular AAA-related re-interventions. The important trends over the study period were: increased EVAR use 6% to 31%; EVAR mortality dropped from 46% to 27%; OSR mortality dropped from 44.7% to 40%; and the percentage of unrepaired RAAAs declined.

The NIS RAAA data (21,206 patients: 2005–2009) noted that EVAR was performed with higher percentages in teaching versus urban versus rural hospitals and nonoperative therapy was highest in rural hospitals.[74] After age 80, the rate of OSR dropped and the rate of no therapy increased. EVAR patients were older, with more CHF, CAD, DM, and renal disease. Univariate and multivariate analysis showed they were less likely to die (OR = 0.54) and had fewer postoperative complications with an EVAR repair (OR = 0.51).

A retrospective RAAA analysis (2005–2010) compared the UK Hospital Episode Statistics of 11,799 cases with 23,828 cases from the NIS. The percentage undergoing any type of repair was 58.4% in the United Kingdom versus 80.4% in the United States, OSR percentage was higher in the United Kingdom 91.5% versus 79.1%, but in the United Kingdom open repair mortality rates were significantly lower; however, EVAR mortality rates were significantly better in the United States. The postintervention mortality was not different (41.8% vs. 41.7%). UK survivors had longer LOS but were more commonly discharged to usual residence, whereas in the United States discharge to a skilled nursing facility was most common. In both countries the overall mortality, postintervention mortality, and rates of mortality after open and EVAR were significantly lower in teaching hospitals versus nonteaching hospitals. After adjustment for age, sex, comorbidity, and hospital size the predictors of mortality were weekend admission versus weekday, interhospital transfer, and treatment outside a teaching institution. In the United Kingdom after risk adjustment, noncorrective therapy was more common on a weekend or when treatment was delivered outside a teaching hospital. US predictors of mortality were weekend admission and treatment outside a teaching hospital. Significant difference in the incidence of noncorrective therapy accounts for the major differences in overall outcomes, although the significant outcome differences between weekday versus weekend therapy need to be addressed. The treatment and outcome differences based on hospital size and teaching status have important implications for improving population-based mortality for RAAA patients.

Randomized Ruptured Abdominal Aortic Aneurysm Trials

A pilot prospective randomized trial that evaluated 103 patients identified 32 who were stable enough to be randomized and CT scanned and were also fit for OSR between 2002 and 2004.[72] The mortality of EVAR and OSR were both 53%. However, it demonstrated the feasibility of randomized trials for RAAA.

The Amsterdam multicenter randomized RAAA trial (AJAX) evaluated mortality and severe complications as its primary endpoints between 2004 and 2011.[146] Of the 520 patients enrolled, 395 (76%) were evaluated by CT scan, 240 (61%) were excluded due to unfavorable EVAR anatomy, and 39 (10%)

were excluded due to unfit for open, logistics, severe hemodynamic instability after CTA, and surgical refusal. The remaining 116 (22%) patients deemed EVAR suitable by CT and clinically suitable for OSR were randomized to EVAR (57) or OSR (59). EVAR mortality was 21% versus OSR mortality of 25%. Death and severe complications at 30 days occurred in 42% of EVAR versus 47% after OSR of RAAA ($P > .05$), with OSR mortality much lower than expected. Renal insufficiency was significantly reduced after EVAR.

The IMPROVE trial randomized patients with a clinically diagnosed RAAAs prior to a CT scan.[147] The pragmatic design meant that, in each group, some symptomatic AAAs were randomized, some patients did not undergo repair and treatment crossovers occurred. Analysis was done on an intention-to-treat basis comparing endovascular-first to open surgical–first strategies. The 30-day mortality was 35.4% in EVAR versus 37.4% for OSR. Women had a significant mortality benefit from EVAR (37% to 57%; $P = .02$). The average aneurysm size was greater than 8 cm, and core lab review of all CT scans suggested 64% of RAAAs were suitable for EVAR. Older patients and those with a Hardman index of two or more did better with EVAR versus OSR, although these did not reach statistical significance. All of those who had EVAR from both treatment assignment groups had a 30-day mortality of 25% versus 38% for those who had OSR. Important secondary outcomes included shorter ICU stay for the EVAR group and higher rate of discharge to directly to home 94% versus 77% OSR; however, overall costs were not different at 30 days.

ECAR (Endovasculaire vs. Chirurgie dans les Anévrysmes Rompus) randomized hemodynamically stable RAAA patients, eligible for both therapies with a proven RAAA.[124] The 30-day and 1-year mortalities were not different (30% EVAR vs. 35% OSR at 1 year). EVAR benefits were lower total respiratory support time, reduced pulmonary complications, total blood transfusions, and duration of ICU stay.

Meta-Analysis of Ruptured Abdominal Aortic Aneurysm Randomized Trials

The pooled mortality in the three randomized trials demonstrated a nonsignificant mortality difference at 1 year of 38.5% for EVAR versus 42.8% for open repair. Data for re-interventions could not be subject to meta-analysis.[155] When the analysis was redone including only those anatomically suitable for EVAR from the IMPROVE trial, the results were unchanged. The benefits of EVAR were shorter LOS, fewer pulmonary and renal complications, and lower costs. There was a significant mortality benefit for women from EVAR.[11]

Why have randomized trials failed to demonstrate the mortality benefits seen in large observational studies?[156] First, observational studies of discharge databases frequently do not contain hemodynamic stability data or neck length. A meta-analysis of more than 80,000 patients demonstrated that EVAR had better outcomes compared with OSR in RAAA. However, when hemodynamic stability was accounted for, the results of OSR and EVAR were equivalent.[157] Second, a reanalysis of neck length of RAAAs demonstrated that aneurysm neck length was inversely associated with mortality.[70]

IMPROVE at 3 Years

At 3 years the EVAR strategy in IMPROVE was clearly superior, EVAR mortality was 42% versus OSR 54%.[93] Average LOS was 14.4 days for EVAR versus 20.5 days for OSR, with more EVARs cases discharged directly to home.[11] EVAR was the more cost-effective strategy and delivers more QALYs. IMPROVE data demonstrated that aneurysm neck length was inversely associated with overall mortality for both EVAR and for open repair and there was a significant relationship between lowest recorded BP and survival; every 10-mm Hg increase in systolic BP improved survival odds by 13%.[70] Use of local anesthesia for EVAR had a fourfold adjusted survival benefit.

Preoperative Predictors of Mortality

Many RAAA scoring systems assess preoperative variables to predict postoperative outcomes before repair, including the Hardman index, Glasgow Aneurysm Score, V- and RAAA-POSSUM, Edinburgh Ruptured Aneurysm Score, Vancouver score, the VSGNE RAAA risk score, and Neural network scores.[158-160] None definitively predicts outcomes with sufficient accuracy to deny RAAA repair. Variables associated with a reduction in survival after OSR of RAAA include loss of consciousness, preoperative cardiac arrest, preexisting congestive heart failure, preexisting renal insufficiency, advanced age, female gender, nonwhite race, and high APACHE II score.[a] Variables most commonly associated with death after RAAA include hypotension, advanced age, ischemic heart disease, cardiac arrest, low hemoglobin level, and preexisting renal insufficiency.[158] Women with RAAA tend to be 2 to 3 years older, have smaller AAA size, are offered repair less frequently, and have a higher mortality.[8,168,169] The VSGNE RAAA score identified the following independent predictors of death: age 76 years or older, (OR = 5.3), preoperative cardiac arrest (OR = 4.3), loss of consciousness (OR = 2.6), and suprarenal clamp (OR = 2.4).[163] The potential advantage of artificial neural network calculations to assist in predicting RAAA mortality could be the ability to combine age with other categorical risk factors not assigned a specific weight and the flexibility of the model to evolve as additional information is added.[161] This AI approach offers promise for real time estimates of mortality.

Postoperative Estimates of Survival

At the conclusion of RAAA repair, the surgeon can review the key variables to give the family an estimate of the expected outcome. Table 74.1 combines the preoperative and intraoperative variables that were significant in a prospective analysis of early survival using a logistic regression model based on prospective data of OSR for RAAA patients.[112] Predictive variables (univariate analysis) associated with increased mortality were preinduction systolic BP, preoperative serum creatinine, intraoperative urine output, site of the cross-clamp, and duration of cross-clamping. Intraoperative variables included the site of the aortic clamp, the volume of blood administered, and the intraoperative urine output. When all preoperative, intraoperative, and postoperative

[a]References 10, 112, 125, 127, 160, and 161-167.

TABLE 74.1 Logistic Regression Model Showing the Interaction of Significant Preoperative and Intraoperative Variables That Predict Early Survival After Repair of Ruptured Abdominal Aortic Aneurysms

CREATININE LEVEL			Intraoperative Urine Output (mL)	Probability of Survival (%)
mg/dL	µmol/L	Clamp Site		
≤1.3	≤115	Infrarenal	≥200	90
≤1.3	≤115	Infrarenal	1-199	76
>1.3	>115	Infrarenal	≥200	71
≤1.3	≤115	Suprarenal	≥200	65
≤1.3	≤115	Infrarenal	0	52
>1.3	>115	Infrarenal	1-199	46
≤1.3	≤115	Suprarenal	1-199	39
>1.3	>115	Suprarenal	≥200	33
>1.3	>115	Infrarenal	0	23
≤1.3	≤115	Suprarenal	0	18
>1.3	>115	Suprarenal	1-199	15
>1.3	>115	Suprarenal	0	6

Modified from Johnston KW. Ruptured abdominal aortic aneurysm: six-year follow-up results of a multicenter prospective study. Canadian Society for Vascular Surgery Aneurysm Study Group. *J Vasc Surg.* 1994;19:888–900.

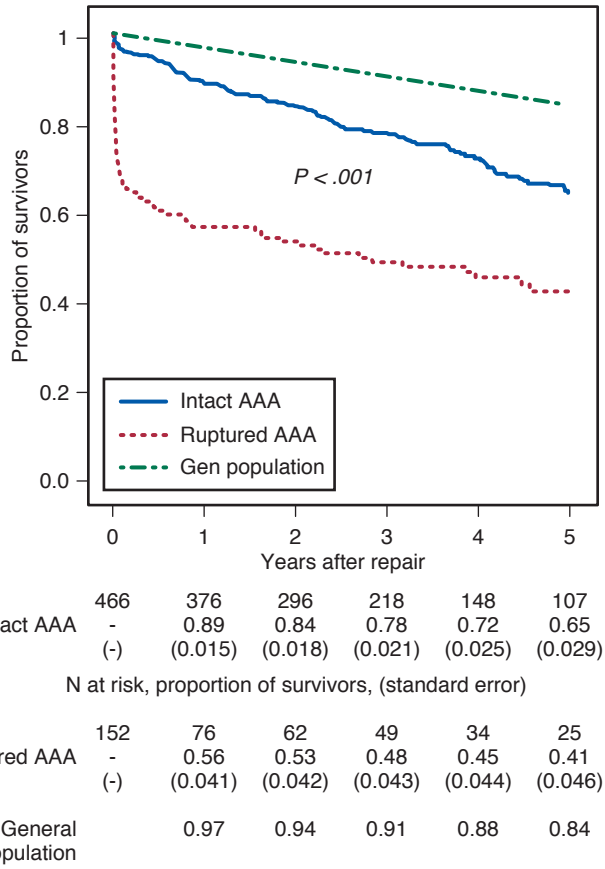

Figure 74.8 Kaplan-Meier survival estimates after abdominal aortic aneurysms (AAA) repair compared with an age-and-gender matched general population.

variables were included, early survival was predicted by site of the aortic cross-clamp and occurrence of myocardial infarction, respiratory failure, kidney damage, and coagulopathy. Dialysis has a dramatic impact on survival, even when no other complications are present. The development of two complications also has a dramatic impact on mortality, especially if one is a rise in creatinine concentration or dialysis requirement.

Predictors of Late Survival

Three studies assessed late survival after OSR of an RAAA compared with elective OSR: US Veterans Affairs (VA) data, the Mayo Clinic, and the Canadian aneurysm study.[112,167,170] The 5-year RAAA survival data were remarkable similar for those alive 30 days postoperatively: Canadian aneurysm study data was RAAA 53% versus 71% elective; US VA data 5-year survival rate was 54% RAAA versus 69% elective[170]; and Mayo Clinic study was RAAA 64% and 74% elective AAA repair.[167] Variables associated with late mortality were lower intraoperative urine output, respiratory failure, and myocardial infarction. The VA study also identified increasing age, illness severity, patient complexity, rupture, and aortic graft complications as being independently associated with late mortality.[170] Long-term survival has been assessed in the United States, United Kingdom, Sweden, and the Netherlands at 5 years and ranges between 38.6% in the United Kingdom and 50% in the United States.[162,164,171] There are significant differences between countries in 5-year survival for RAAA patients which is related to the early 30- to 90-day mortality. The most common causes of long-term mortality were cardiovascular death (35% of cases) and cancer (29%, lung cancer most common followed by GI cancer). The early mortality of the rupture accounts for the largest drop in the RAAA patient's survival (Fig. 74.8).[164]

RAAA long-term outcomes from VQI noted an increasing usage of EVAR in the cohort over time, and the unadjusted in-hospital mortality was 23% for EVAR versus 35% for OSR.[162] After adjusting for confounding variables, EVAR did not independently demonstrate a lower 1- or 5-year mortality rate; however, in a US Medicare cohort, EVAR was associated with improved survival (Fig. 74.9).[37] Primary predictors of 1- and 5-year mortality were patient comorbidities (home oxygen, dialysis, cerebrovascular disease, and ejection fraction <50%) and the indices of shock on admission (SBP <90, loss of consciousness, cardiac arrest).[162]

Late Re-Interventions

In the IMPROVE trial at 3 years a 28% re-intervention rate was noted in each group related to the aneurysm, and most of which occurred in the initial 3 months postoperatively.

Rupture After Endovascular Aneurysm Repair

None of the currently available stent-grafts is completely effective in preventing aneurysm rupture after EVAR.[154] A meta-analysis of late re-intervention for repeat RAAA following EVAR for RAAA demonstrated that the rate is similar to elective EVAR:

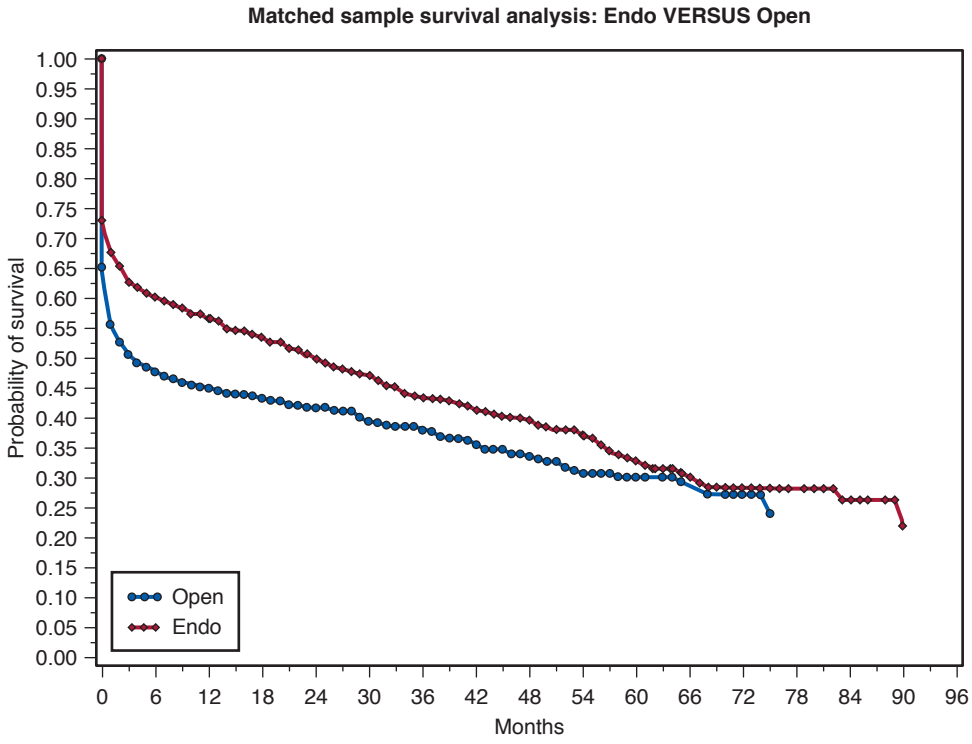

Figure 74.9 Probability of survival in propensity-matched data from Medicare beneficiaries age 67 or older admitted with a primary discharge diagnosis of ruptured abdominal aortic aneurysm between 2001 and 2008. (From Raghavan ML, Vorp DA, Federle MP, et al. Wall stress distribution on three-dimensionally reconstructed models of human abdominal aortic aneurysm. *J Vasc Surg.* 2000;31:760–769.)

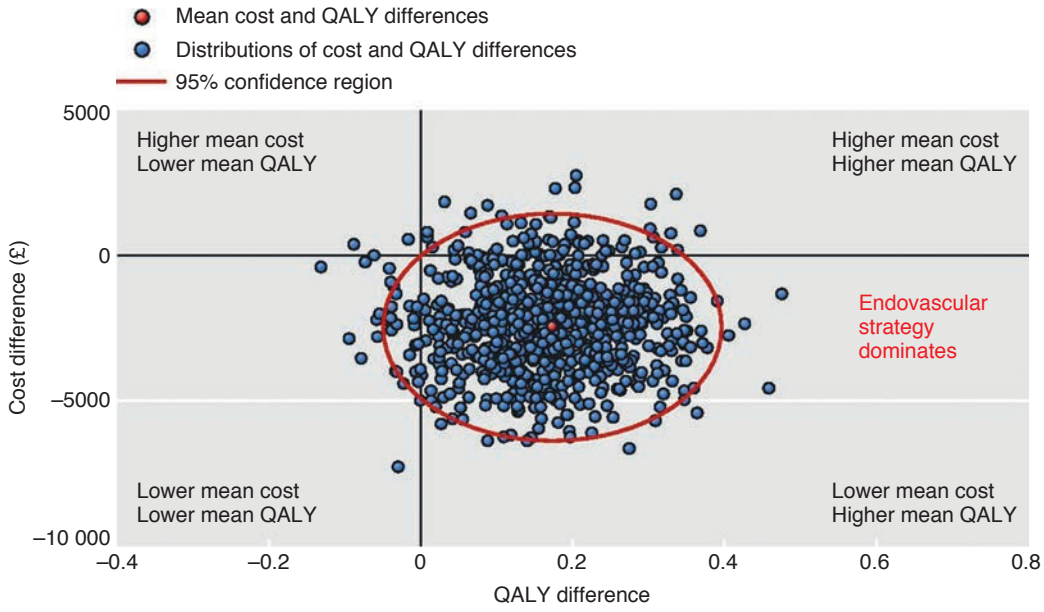

Figure 74.10 Uncertainty in mean cost (£) and quality-adjusted life year (QALY) differences and their joint distribution for endovascular strategy versus open repair for all 613 patients.

1.4% at 28 months and most common etiology is a type 1 endoleak.[155] Of those who ruptured after EVAR, 46.8% underwent intervention to treat the endoleak. Careful follow-up of RAAA EVAR patients is required, especially those who have had intervention for endoleaks.[172]

QUALITY OF LIFE

Quality of life (QoL) after RAAA repair has been assessed with several different instruments.[157,173,174] The overall SF-36 scores compared favorably with those of the age- and sex-matched general population. Hospital survivors had 8.5 quality-adjusted life years, but physical functioning was significantly lower in RAAA repair survivors than in age- and sex-adjusted population controls. Major postoperative complications did not reduce the QoL in RAAA survivors. IMPROVE prospectively measured differences in QoL between EVAR and OSR survivors at 3 and 12 months. Mean utility scores were significantly higher for the EVAR group at 3 months but were not significant at 1 year. When mean cost was plotted versus quality-adjusted life year differences, EVAR for RAAA delivered the best quality for the lowest costs (Fig. 74.10). The more rapid recovery from EVAR

was likely reflected in these early differences which dissipated over time. Therefore an aggressive approach to RAAA repair is justified as patients derive significant survival with good QoL following successful repair.

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This study highlights the importance of appropriate volume resuscitation in patients with RAAA and its impact on patient survival.

IMPROVE Trial Investigators. Comparative clinical effectiveness and cost effectiveness of endovascular strategy v open repair for ruptured abdominal aortic aneurysm: three-year results of the IMPROVE randomised trial. *BMJ*. 2017;359:j4859.

Excellent data on RAAA patients randomized to OSR vs. EVAR at 3 years

Johnston KW. Ruptured abdominal aortic aneurysm: six-year follow-up results of a multicenter prospective study. Canadian Society for Vascular Surgery Aneurysm Study Group. *J Vasc Surg*. 1994;19:888–900.

This landmark study, one of the largest prospective OSR RAAA registries, highlights 6-year actuarial survival rates and determines the predictive variables that are associated with survival of patients.

Powell JT, et al. Endovascular or open repair strategy for ruptured abdominal aortic aneurysm: 30 day outcomes from IMPROVE randomised trial. *BMJ*. 2014;348:f7661.

Thirty-day mortality results for the largest randomized RAAA trial of OSR vs. EVAR

Powell JT, et al. Observations from the IMPROVE trial concerning the clinical care of patients with ruptured abdominal aortic aneurysm. *Br J Surg*. 2014;101(3):216–224.

Detailed analysis of EVAR vs. OSR in the largest randomized trial with a rich data set

Sweeting MJ, et al. Ruptured aneurysm trials: the importance of longer-term outcomes and meta-analysis for 1-year mortality. *Eur J Vasc Endovasc Surg*. 2015;50(3):297–302.

This meta-analysis of three randomized RAAA EVAR vs. open repair trials results at 1 year.

A complete reference list can be found online at www.expertconsult.com.

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75 CHAPTER

Isolated Iliac Artery Aneurysms and Their Management

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INTRODUCTION

Iliac artery aneurysms (IAAs) commonly occur concurrently with other more proximal arterial aneurysms. As a distinct entity, IAAs were initially described by Valentine Mott in 1827, and later by Halstead in 1912.[1-3] In contrast to generalized aortoiliac aneurysms, isolated iliac aneurysms are much less frequently recognized, and are prevalent in ≤ 2% of the general population.[4,5] Aneurysmal degeneration typically involves the common iliac (70%-90%) and internal iliac (10%-30%) arteries, or both of these segments contiguously; external iliac artery (EIA) involvement is extremely rare.[1,6] Bilateral common IAAs are present in at least 50% of affected patients.[7]

Iliac arteries are defined as aneurysmal when their diameter is 1.5 times greater than the "normal" or expected diameter. On physical examination, isolated asymptomatic iliac aneurysms are difficult to identify, mainly due to their anatomical location deep within the pelvis. Most commonly, IAAs are identified during abdominal aortic aneurysm (AAA) screening studies, or recognized as incidental findings on abdominal and pelvic computed tomography (CT) imaging obtained for other purposes. When they do become symptomatic and rupture; however, isolated IAAs are associated with a high rate of mortality, frequently due to late or missed diagnosis.[4,6] Moreover, emergent open IAA repair in the setting of rupture portends relatively high morbidity and mortality rates due to uncontrolled hemorrhage. Iliac aneurysms carry the potential for severe complications if not managed appropriately.

The type of operative repair depends largely on patient anatomy, clinical stability, and the presence and severity of concomitant AAAs. Like the experience with AAA repair, isolated IAA management has evolved toward an endovascular first approach over the past decade. The availability of dedicated iliac devices, including multiple branching or "bell-bottom" stents, has steadily improved the feasibility, ease, and durability of endovascular repair.

PATHOGENESIS

The mechanisms relevant to IAA formation are multifactorial and involve an altered balance between proteolytic degradation of the extracellular matrix, mechanical integrity, inflammation, and an impaired arterial remodeling process, in the setting of specific at-risk genetic polymorphisms and environmental exposures (see Chapter 70).[8,9] Ferreira and colleagues demonstrated that hypertension and cigarette smoking were prevalent in patients with iliac aneurysms.[10] Other less common etiologies include previous trauma, iatrogenic injury, arteritis, connective

tissue disorders, and infections. Historically, syphilis and tuberculosis were frequently associated with mycotic IAAs, but *Salmonella, Staphylococcus, Klebsiella,* and *Candida* species are more commonly reported today.[2,7,11,12]

It remains unclear as to why the anatomical distribution of IAA tends to involve only the common and internal iliac segments, as opposed to the EIA. A developmental etiology has been proposed. Developmental factors encountered during embryogenesis involve signaling pathways that influence the fate of cell lineages and response to factors implicated in aneurysm formation. It has been demonstrated that different parts of the normal and aneurysmal adult aorta appear to have distinct DNA expression profiles, which may explain the site specificity and prevalence of various aneurysm phenotypes.[12,13] This genetic heterogeneity of endothelial and smooth muscle cells, in conjunction with systemic and physiologic exposures, alter the structural integrity of a vessel to enable aneurysmal degeneration. Tilson[14] and others have speculated that the EIA is resistant to aneurysm formation because of the distinct embryonic lineage of its vascular smooth muscle cells as compared to the aneurysm-prone common and internal iliac arteries.[12,14] Immunobiological characteristics suggest phenotypical differences between the internal and external iliac arteries, emphasizing the concept that normal and disordered embryogenesis can influence the propensity of an artery to aneurysmal disease.[12,14,15]

NATURAL HISTORY

There is a paucity of level I evidence available regarding the true prevalence, natural history, and rupture potential of IAAs.[9] Retrospective surgical case series provide most of the basis of our understanding of this condition. In a series of 715 common IAAs in 558 patients, 65% had bilateral IAAs.[16] Another series of 198 patients undergoing repair of 323 IAAs had a demographic profile similar to the previous study.[17] In both series, the rate of diameter enlargement for IAAs under surveillance varied based on the baseline diameter present at the time of diagnosis; for IAA ≤ 3 cm, expansion rates averaged 0.05 to 0.15 cm/year, whereas aneurysms greater than 3 cm enlarged 0.26 to 0.29 cm per year; no differences in growth rates were noted between isolated IAAs and those present in patients with concomitant AAA.[11,17]

IAAs are reportedly associated with a high propensity for rupture. Although asymptomatic initially, they are difficult to recognize on physical examination, enlarge slowly over time, and are often first identified at the time of rupture.[18] According to Bacharach and associates, as many as 33% of IAAs have ruptured at the time of initial presentation, an event associated with significant mortality.[11] The mortality from emergent repair for rupture in reports from the last 20 years is approximately 28% (range from 0% to 60%) as compared to a reported 5% mortality for elective IAA repair (range from 0% to 50%).[9] The mean size of ruptured IAAs varies in reports from 6 to 6.8 cm.[19]

Kato and associates reported 11 cases of unusual isolated external iliac artery aneurysms (EIAAs). According to their review, there were four (36%) ruptured EIAAs and one (9%) symptomatic EIAA associated with peripheral embolization. All ruptured EIAAs were greater than 4 cm in diameter.[20]

Dix and associates performed a literature review of internal iliac artery aneurysms (IIAAs) and identified 94 cases; the initial presentation was associated with rupture in 40%. Mortality in this group was 31%, with a median aneurysm size at presentation of 7.7 cm (range, 2-13 cm). [21] From a recent retrospective study across 28 vascular centers, Laine and associates[22] reviewed 63 IIAA patients who were all surgically treated. Regarding anatomical distribution, isolated IIAAs were uncommon (30%); they were more typically present concurrent with aortic and/or common iliac aneurysms. Only one IIAA rupture occurred at less than 3 cm in diameter, and four occurred at less than 4 cm (6.3% of all ruptures). Patients were treated with both open (73%) and endovascular techniques (27%); the outcomes include a 30-day postoperative mortality of 12.7% and a 1-year Kaplan-Meier survival estimate of 74.5% (standard error, 5.7%).[22] Overall, literature on isolated IIAAs remain sporadic and consist largely of case reports.

Thus, natural history studies suggest that IAAs smaller than 3.8 cm to 4 cm in diameter are not frequently associated with rupture,[21,22] supporting a generally accepted threshold of 3 cm to 3.5 cm for elective repair of asymptomatic IAAs (indications may vary between common iliac and IIAAs). These recommendations vary based on anatomical location and complexity, rate of enlargement, presence of symptoms, and concomitant comorbid conditions. Symptomatic IAAs should be expeditiously repaired upon presentation at any diameter.

PRESENTATION

The size and location of the aneurysm may foretell the clinical presentation of the IAA. Their anatomic location and proximity to adjacent pelvic structures including bowel, bladder, the urinary collecting system, nerve roots, and pelvic veins can obscure the diagnosis in the absence of a perceptible mass.[1] Vague lower abdominal pain often results from compression or impingement of these neighboring structures. Patients may also complain of intermittent claudication or lower extremity pain secondary to embolic arterial occlusion, lower extremity paresis, sciatic neuralgia, lumbosacral pain, ureteral obstruction, tenesmus, or even constipation.[11]

Sudden abdominal, groin, or flank pain associated with hemorrhagic shock likely indicates rupture. Although IAA rupture may initially be contained in the retroperitoneum, uncontrolled exsanguination typically leads to irreversible shock. Delays in diagnosis contribute significantly to reported mortality, with or without emergent intervention.

In rare instances, an IAA can elicit thromboembolic symptoms and peripheral arterial insufficiency. In the era preceding the current nearly ubiquitous use of cross-sectional imaging in the assessment of vascular compromise, Richardson and associates noted that IAAs were often recognized only after observed ipsilateral limb ischemic changes precipitated the need for angiographic evaluation.[1] In a reported observational cohort study, Nachbur and associates retrospectively identified four cases where intermittent claudication was a result of thrombotic

stenosis or occlusion caused by an iliac aneurysm.[23] Distal embolization was the clinical presentation of IAA disease in one patient (9%) of 16 symptomatic aneurysm IAA patients identified in a single institution over 6 years.[10]

DIAGNOSIS

As noted previously, physical examination frequently fails to identify even large IAAs.[18] Imaging modalities provide needed sensitivity and specificity for both diagnosis and anatomical information crucial to surgical planning. Ultrasound represents the primary diagnostic and screening tool, especially in asymptomatic patients. Limitations involve user variability and presence of other organs and structures. CT and magnetic resonance (MR) angiography imaging provide far more extensive detail of aortoiliac anatomy, and improve diagnostic accuracy in challenging circumstances.[24] However, the expense and risks of these techniques should be factored into the overall approach to the individual patient.[9]

Precise operative planning requires high-resolution, high-fidelity imaging, and in most circumstances, CT arteriography is optimal for this purpose. Using a combination of axial imaging and 3-D postprocessing, evaluation includes locations, diameters, and length of proximal and distal landing zones for endovascular grafting, information regarding iliac artery tortuosity and angulation, the presence and severity of associated occlusive disease, ipsilateral and contralateral internal iliac artery patency, the status of the ipsilateral deep femoral artery, and concomitant abdominal or thoracic aortic pathology.[25]

MANAGEMENT

Iliac aneurysms are targeted for repair as they enlarge or become symptomatic. Based on retrospective reviews and consensus statements, current recommendations favor elective repair for asymptomatic IAAs ≥ 3.5 cm in diameter in healthy patients.[9] Early and extensive application of CT imaging in the assessment of patients with abdominal pain has substantially reduced the historically high morbidity associated with delays in diagnosis of ruptured IAAs, but rupture of previously unrecognized IAA still occurs, often presenting serious surgical management challenges.[21]

Asymptomatic IAAs less than 3 cm in diameter are best managed with serial surveillance imaging studies. In fact, general abdominal ultrasound screening for aortoiliac aneurysms is recommended by the US Preventive Services Task Force (USPSTF) for men aged 65 to 74 years who have ever smoked.[24,26] The strong association between smoking and aortic aneurysm was described by Hammond and Horn in 1958.[25,27] A systematic review that included this and other large studies relating smoking behavior to subsequent mortality showed that the relationship between smoking and aortic aneurysm was several times stronger than the relationship between smoking and occlusive vascular disease.[25,27,28] Notably, other documented characteristics have been shown to influence AAA and IAA growth or rupture rates: smokers and nondiabetics have higher growth rates, and smoking, older age, and higher blood pressure increase rupture risk.[26-28] In general, smoking cessation may reduce the rate of aneurysm expansion, as has been demonstrated in early AAA disease.[26] Depending on concomitant patient medical comorbidities, a conservative approach to some IAAs may be most appropriate for even symptomatic patients.[29] Santilli and associates correlated IAA expansion rates with baseline diameter; aneurysms less than 3 cm in diameter expanded at 1 mm annually, whereas IAAs between 3 cm and 4 cm in diameter expanded 2.6 mm/year.[17] Interestingly, these rates were similar across all types of IAA, whether isolated or multiple.

Operative Approaches and Techniques

Due to the relatively inaccessible location of iliac aneurysms (situated deep in the pelvis), the presence of densely adherent pelvic veins, and the frequent cooccurrence of calcific occlusive disease, conventional surgical repair is challenging and fraught with risk of significant hemorrhage.[30] Using standard open operative techniques, modern retractor systems, and patience; however, repair of isolated iliac aneurysms provides excellent long-term results and is generally well tolerated by good-risk patients.

The primary goal of surgical intervention is to maintain distal perfusion while preventing further aneurysmal degeneration and rupture.[18] The iliac artery may be best approached from a midline, retroperitoneal, or transplant-type incision, depending on the extent of the aneurysm, the presence of unilateral or bilateral disease, and surgeon preference and experience. In general, large aneurysms that produce compressive symptoms require adequate exposure to effectively open and repair the aneurysm via standard endoaneurysmorrhaphy techniques. If an adequate portion of proximal common iliac artery is nonaneurysmal, common IAAs can be replaced with a prosthetic interposition graft. When the entire common iliac artery is aneurysmal, however, control must obtained on the aorta itself and the proximal graft needs to be anastomosed directly to the aorta; this usually requires transperitoneal or full retroperitoneal exposure (see Chapters 54 and 71).

The quality of the artery will dictate the amount of exposure required for proximal vascular control. In terms of the distal extent, the graft can almost always be sewn to the bifurcation of the external and internal iliac arteries, thus preserving pelvic flow. In rare circumstances, with significant splaying of the external and internal iliac arteries or aneurysmal extension into the internal iliac artery, the distal extent of the graft must be sewn to more normal, distal arteries.

Direct open repair of the common iliac artery also maintains collateral flow to the pelvis via the lumbar arteries and the inferior mesenteric artery, thus reducing the risk of postoperative colonic or pelvic ischemia.[31] As in the case of open AAA repair, resection of the aneurysm sac is not advised, because this increases the risk of bleeding and injury to adjacent adherent structures such as the iliac veins and the inferior vena cava. Preoperative placement of ureteral stents can reduce the risk of ureteral injury, particularly in advanced and inflammatory aneurysms.

Maintenance of antegrade internal iliac artery flow is essential for optimal outcomes, particularly in younger patients or those

with contralateral internal iliac artery compromise or occlusion. Loss of internal iliac artery perfusion can lead to buttock claudication, impotence, and more rarely, colonic ischemia, gluteal necrosis, and spinal cord ischemia.[32-37] In situations when both internal iliac arteries are affected, or if both internal iliac arteries are aneurysmal, it is advisable to use bypass grafting of at least one internal iliac artery to preserve antegrade flow.[7] In their clinical experience with open repair of 715 iliac aneurysms in 438 patients, Huang and associates advised reimplantation of the inferior mesenteric artery to the aortic graft if both internal iliac arteries were occluded; however, even adherence to that algorithm resulted in ischemic colitis in two patients.[16] When aneurysmal disease is limited to a single common iliac artery, the ipsilateral internal iliac may be ligated without significant ischemic consequences. This strategy has other limitations, however, including a relatively high likelihood of progressive enlargement of residual IIAAs distal to the ligature site. These may continue to be pressurized by retrograde branch artery flow, resulting in progressive enlargement, compressive symptoms, and a continued risk for late rupture.[38-40]

Ultimately, iliac artery aneurysmorrhaphy, in experienced hands, provides a durable repair with excellent outcomes. Mortality rates for elective procedures range from 0% to 5%, depending on the comorbidity profile and anatomic considerations.[9,16,41,42] The overall incidence of perioperative complications ranges up to 22% including lower extremity ischemia from distal embolization or stenosis; visceral and pelvic wall ischemia from disruption of hypogastric flow; aneurysm reperfusion and rupture; arterioenteric fistula formation; graft infection; and ureteral, neural, and venous injuries.[1,9,28] Both early and late graft-specific complications are rare, and primary patency at 5 years approaches 100%.[16,42]

Endovascular Repair of Common Iliac Artery Aneurysms

Treatment of concomitant aortoiliac aneurysmal disease has been preferentially endovascular since the advent of later-generation bifurcated AAA grafts.[43] Continued advancement of these technologies has shifted isolated IAA management to an endovascular-first approach as well. Endovascular IAA management reduces length of hospitalization, operative blood loss, the need for invasive monitoring and intensive care unit care postoperatively, and perioperative complications.[44] In a study of 33,161 patients with isolated IAA, derived from the National Inpatient Sample Database from 1988 to 2011, Buck and colleagues observed that the total number of aneurysm repairs increased from 28 to 71 per 10 million US population following the introduction of endovascular AAA and IAA treatment methodologies ($P < .001$).[45] This analysis demonstrated that the number of annual endovascular iliac aneurysm repairs surpassed the number of open repairs in 2003. Moreover, death from rupture or repair of isolated IAAs decreased from 4.4 to 2.3 per 10 million US population ($P < .001$) over a similar time period, although technical issues alone do not likely completely account for this improvement (see Chapter 72 and Chapter 73).[24]

The primary goal of endovascular intervention is similar to that of open repair: exclude the aneurysm sac from the circulation, thereby minimizing risk for further expansion and rupture. Anatomic considerations that influence endovascular treatment strategies include: (1) the presence and quality of proximal and distal landing zones (e.g., location and length of nonaneurysmal inflow and outflow arteries), (2) the presence of concomitant internal iliac artery involvement, (3) the presence of bilateral or unilateral iliac disease, and (4) the presence or absence of concomitant aortic aneurysm.[19] Melas and colleagues proposed a revised common IAA classification system based on the proximal and distal extent of the lesion, providing a framework for treatment selection.[46,47] Anatomic considerations are paramount in endovascular management considerations (Table 75.1).

Using standard techniques and devices, endovascular repair of isolated common IAAs requires approximately 2 cm of proximal and distal landing zone (Fig. 75.1). Lack of a proximal landing zone necessitates extension into the abdominal aorta to achieve seal. In this situation, depending on the extent of aneurysmal involvement, a bifurcated aortic endograft is generally the most appropriate choice. Current "on label" applications allow for endovascular management of common iliac bifurcation disease up to 25 mm in diameter, including the use of flared or bell-bottom iliac limbs. Although an initial seal may be obtained with these devices, durability may be suspect based on the inherently diseased nature of the landing zones. Agu and associates identified late aneurysmal degeneration at the distal iliac landing zone following endovascular repair in 2.4% of patients with up to 9 years of follow-up.[48] Similarly, in a retrospective review,[49] bell-bottom iliac limbs placed concomitantly with AAA endografts were associated with subsequent dilation of common IAAs in 35.3% of cases; endoleak and reoperation rates were 17.6% and 15.7%, respectively. Over a 4-year period, the average increase in arterial dilation was 16% in the first year, 29% in the second year, 57% in the third year, and 95% from the fourth year.[49] Although simple to use and generally considered to be a safe alternative to preserve pelvic blood flow, long-term outcomes for the durability of this method remain questionable.[50]

When the distal seal zone diameter is greater than 25 mm, or aneurysmal degeneration extends into the proximal internal iliac artery, the seal zone may be extended into the EIA; coil embolization or plug occlusion (Amplatzer vascular plug, St. Jude Medical, Inc., St. Paul, Minnesota) of the proximal internal iliac artery is generally employed to prevent retrograde flow into the common iliac aneurysm.[51] Because coil embolization of the internal iliac artery can be technically challenging, these adjuncts may be associated with increased operative time, contrast use, radiation time, and cost.[52]

As an alternative, straightforward stent graft coverage of the internal iliac artery orifice without embolization can extend the distal sealing zone of the repair without significant complications. Papazoglou et al.[52] reported on their series of 137 patients undergoing endovascular aneurysm repair. Patients were treated with simple stent graft coverage across the internal iliac artery ($n = 112$) or stented with concomitant internal iliac artery coil embolization ($n = 25$). Overall, there was no difference in

TABLE 75.1 Classification Scheme for Endovascular Treatment of Isolated Iliac Artery Aneurysms

Aneurysm Type	LANDING ZONES		Internal Iliac Artery Configuration	Endovascular Techniques
	Proximal	Distal		
A	CIA	CIA		Direct aneurysm exclusion with covered stents within proximal and distal fixation zones (balloon-expandable or self-expandable)
B1	CIA	IIA	IIA diameter < 15 mm	**Anatomical with IIA preservation** Iliac side-branch device **Extraanatomical with IIA preservation** 1. Placement of AUI in contralateral nonaneurysmal CIA with a femorofemoral bypass and endograft deployment from ipsilateral EIA to ipsilateral IIA 2. Placement of bifurcated endograft with ipsilateral extension to EIA, ipsilateral retroperitoneal open surgical ligation of IIA, bypass grafting from ipsilateral distal EIA to the ipsilateral IIA 3. Placement of bifurcated endograft with an ipsilateral iliac limb extension toward the ipsilateral IIA and adjunctive femorofemoral bypass and distal EIA ligation **Sacrificing IIA** Exclusion with coverage or embolization of IIA and placement of covered stent across CIA aneurysm to EIA
	CIA	IIA	At least 20 mm of nonaneurysmal tissue within IIA	
B2			Aneurysm extends into IIA IIA diameter < 15 mm Insufficient length of IIA (< 20 mm)	
C	Aorta	CIA		**Anatomic with IIA preservation** Placement of bifurcated endograft with the ipsilateral iliac limb extending to the distal CIA landing zone **Extraanatomic with IIA preservation** 1. Placement of AUI into contralateral nonaneurysmal CIA with femorofemoral bypass and endograft extending from the ipsilateral EIA to the ipsilateral IIA 2. Placement of AUI into contralateral nonaneurysmal CIA with femorofemoral bypass and occlusion of distal CIA before bifurcation
D1	Aorta	IIA	IIA diameter < 15 mm	**Anatomic with IIA preservation** 1. Iliac side-branch device 2. Double barrel graft technique using a bifurcated device **Extraanatomical with IIA preservation** 1. Placement of AUI into contralateral nonaneurysmal CIA with femorofemoral bypass and endograft extending from ipsilateral EIA to the ipsilateral IIA 2. Placement of bifurcated endograft with an ipsilateral iliac limb extension toward the ipsilateral IIA and adjunctive femorofemoral bypass and distal EIA ligation **Sacrificing IIA** 1. Exclusion of aneurysm with placement of bifurcated endograft with ipsilateral extension to the ipsilateral EIA and ipsilateral IIA embolization
D2	Aorta	IIA	At least 20 mm of nonaneurysmal tissue within IIA Aneurysm extends into IIA IIA diameter < 15 mm Insufficient length of IIA (< 20 mm)	

"Landing Zone: Aorta" signifies no proximal landing zone of 1.5 cm in the common iliac artery, i.e., the CIA aneurysm extends to or within 1.5 cm of the aortic bifurcation

AUI, Aortouniiliac endograft; *CIA*, common iliac artery; *EIA*, external iliac artery; *IIA*, internal iliac artery.

Modified from Melas N, Saratzis A, Dixon H, et al. Isolated common iliac artery aneurysms: a revised classification to assist endovascular repair. *J Endovasc Ther*. 2011;18(5):697–715 and Uberoi R, Tsetis D, Shrivastava V, et al. Standard of practice for the interventional management of isolated iliac artery aneurysms. Subcommittee on Reporting Standards for Arterial Aneurysms of The Society for Vascular Surgery. *Cardiovasc Intervent Radiol*. 2011;34(1):3–13.

incidence of postoperative buttock claudication between the two groups (13.4% for stenting alone, 12% for stenting with coil embolization, $P = .852$). In fact, after 4 years, there were no differences in cumulative survival or the rates of secondary interventions between the two groups. In another similar series of 32 patients, Stokmans et al.[53] reported that endovascular coverage of the internal iliac artery did not result in severe symptoms of pelvic ischemia and had a low rate of secondary reinterventions. The incidence of buttock claudication (22.6%) was within the range reported in previous studies on sole internal iliac artery coverage, and compared favorably to the incidence reported in the majority of studies on coil embolization.[53] Covering the internal iliac artery without coil embolization may thus provide a safe alternative approach for some patients. However, failure to adequately seal the internal iliac artery in the process of common iliac artery endografting may lead to long-term procedural failure secondary to persistent retrograde endoleak arising from the patent internal iliac artery. Furthermore, once the internal iliac artery origin is covered, future percutaneous access is likely precluded, requiring open conversion or CT-guided transpsoas access directly to the internal iliac artery for later definitive management of aneurysm expansion.

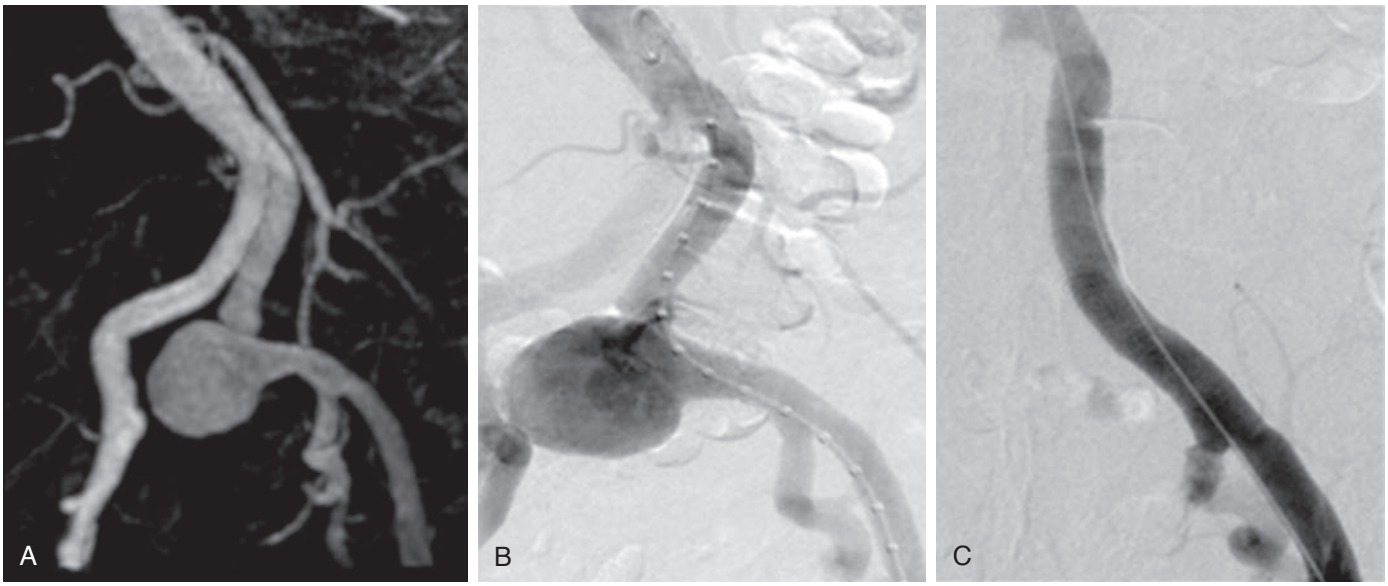

Figure 75.1 (A) Magnetic resonance imaging (MRI) of isolated 3.8 cm × 3.5 cm left common iliac aneurysm that was incidentally discovered. (B) Endovascular repair with sizing catheter placed ipsilateral. Angiogram demonstrating proximal and distal landing zones and iliac bifurcation. (C) Approximately two covered stents deployed to seal and exclude aneurysm while preserving internal iliac artery.

In patients with contralateral internal iliac artery occlusion or bilateral common IAAs, or those who are otherwise perceived to be at high risk for spinal cord ischemia, it is essential to preserve internal iliac artery flow. Typically, few patients experience prolonged or permanently debilitating symptoms following unilateral occlusion, and if bilateral internal iliac artery occlusion is deemed necessary, staged intervention to allow collateral flow development and close patient monitoring to detect symptom development is warranted. As an alternative to uni- or bilateral internal iliac artery occlusion, an external-to-internal iliac artery bypass may be performed in conjunction with proximal internal iliac artery ligation to effectively "move" the iliac bifurcation more distally. Iliopoulos and colleagues examined the collateral arterial supply to the hypogastric arterial bed.[54] Using staged, sequential internal and external iliac artery occlusion techniques while measuring corresponding stump pressures, Iliopoulos et al. demonstrated that the ipsilateral external iliac and femoral arterial systems actually provide more collateral internal iliac artery flow than does the contralateral internal iliac artery system. These findings emphasize the importance of maximizing ipsilateral external iliac and femoral arterial inflow to compensate for an ipsilateral internal iliac artery occlusion and to minimize the risks for resulting pelvic ischemia. In one series of 22 patients, Hosaka and associates assessed the impact of performing endovascular aortoiliac stent-grafting with concomitant unilateral internal iliac artery embolization and contralateral external-to-internal iliac artery bypass grafting, with both endograft limbs extended into the EIAs for distal seal.[55] After following their patients for approximately 15.7 ± 7.8 months, all bypasses (100%) remained patent without graft-related complications. Although there were no cases of sac enlargement or development of type I endoleaks, persistent mild buttock claudication occurred in two patients (9%) ipsilateral to the site of coil embolization.[55] Another series showed similar excellent internal iliac bypass patency rates of 91% and freedom from ischemic symptoms at 36 months.[56] It is important to avoid embolization of the distal hypogastric branches to further decrease the risk of pelvic ischemic complications.

Endovascular Repair of Internal Iliac Artery Aneurysms

Because of the multiple branches emanating from the internal iliac artery, preservation of flow in the presence of an IIAA is challenging. Maintaining pelvic perfusion helps to avoid any potential ischemic complications of internal iliac artery occlusion, including buttock claudication; vasculogenic impotence; and perineal, vesicular, colonic, rectal, or spinal cord ischemia.[57] In a series of 103 patients, Yano and associates[58] elaborately quantified the clinical presentation of pelvic ischemia after intentional internal iliac artery occlusion during endovascular aortoiliac aneurysm repair. The authors developed the following criteria based on the severity of clinical symptoms: class 0, no symptoms; class I, nonlimiting claudication with exercise; class II, new onset impotence, with or without moderate to severe buttock pain, leading to physical limitation with exercise; class III, buttock rest pain, colonic ischemia, or both. From their results, following internal iliac artery occlusion, pelvic symptoms developed in 22 patients (21%) with 12 patients categorized in class I, 9 patients in class II, and 1 patient in class III. Furthermore, the authors commented on two unique preoperative angiographic findings that they identified in 16 patients (16%) who ultimately developed chronic pelvic claudication: (1) stenosis of the remaining internal iliac artery origin greater than 70% with nonopacification of more than three of the six typical internal iliac artery branches (63%); and (2) small-caliber,

diseased or absent medial and lateral femoral circumflex arteries ipsilateral to the side of the internal iliac artery occlusion (25%).[58] These findings emphasize the importance of preoperative evaluation of the pelvic circulation to aid in the safe planning of internal iliac artery embolization and identification of the need for revascularization procedures.

In general, direct stent graft repair is possible provided proximal and distal landing zones are present within the aneurysmal internal iliac artery. This may require landing the stent in the largest distal branch available following coil embolization of smaller branches feeding into the aneurysm sac. If the proximal landing zone is compromised, a "chimney" type graft can extend into the common or EIA,[59] or the "sandwich" technique may be employed.[60] In the latter technique, the covered self-expanding stent within the internal iliac artery lies side by side with the iliac limb extender within the common iliac limb. This technique is the most successful and durable endovascular option to preserve internal iliac artery flow because it involves stenting into normal-sized arteries while excluding flow to the aneurysm itself. Alternatively, Wu and associates described the crossover chimney technique, which consists of delivering the chimney graft across the aortic bifurcation outside the bifurcated stent graft to provide retrograde flow to the internal iliac artery in endovascular repair of iliac or aortoiliac aneurysms.[61,62] Their midterm results were promising, with 100% initial technical success of internal iliac preservation without intraoperative endoleak. The crossover graft primary patency was 92.8% over a mean of 14.3 months (range 6-21 months).[61] Another hybrid approach employs an aortouniiliac endograft with femoral-to-femoral artery bypass along with a covered stent that is deployed retrograde from the "target" (distal) EIA into the ipsilateral internal iliac artery in a reverse U-shaped configuration (see Fig. 72.14).[63] Experience has demonstrated, however, that it is difficult to maintain position and patency in the "U" endograft, which tends to dislodge or kink over time. Due to these durability concerns, and the need for adjunctive open femoral-femoral bypass, this procedure has not gained widespread acceptance.

The W.L. Gore & Associates, Inc. (Flagstaff, Arizona) Gore Excluder Iliac Branch Endoprosthesis (IBE) device recently gained Food and Drug Administration approval in the United States. As of 2017, this is the only device with an on-label indication for endovascular management of common iliac aneurysms. The IBE device is composed of an iliac branch and a precannulated internal iliac component. At 16 French, the delivery system allows for repositioning and cannulation of the internal iliac vessels without need for brachial or axillary access. In their retrospective case series of 10 patients, Millon and associates[64] described a technical success of 100% in deployment of all components, and no intraoperative adverse events or endoleaks. They followed their patients up to 6 months and reported one internal iliac component occlusion. In a larger series spanning multiple centers using the IBE, Ellozy and associates[65] demonstrated 95.1% internal iliac limb patency, 95.2% technical success, and no type I or type II endoleaks or device migration at 6-month follow-up. Moreover, data from the IBE 12-04 US pivotal trial (28 centers) and Global Registry for Endovascular Aortic Treatment (GREAT registry, 14 centers) revealed 100% freedom from new buttock claudication symptoms at 6 months.[65] Across all centers, use of the device was associated with 90% iliac branch patency over 2 years. Although gaining favorable usage, further long-term results are needed to fully evaluate the longer-term durability of this and other similar devices.

Purpose-specific iliac branch devices (IBD) designed by Cook (Cook Medical, Bloomington, Indiana) have been implanted in patients outside of the United States since 2006 (see Fig. 72.1A–F). The delivery system for this device comes with a preloaded curved catheter, which simplifies cannulation of the internal iliac artery from the contralateral groin. The IBD is positioned over a stiff wire in typical fashion. Wire passage through the curved catheter is snared from the contralateral femoral artery. Following stiff wire exchange and partial deployment of the IBD, a sheath is then introduced from the contralateral femoral artery into the internal iliac artery branch. A covered bridging stent is then deployed after fully unsheathing the IBD (see Fig. 72.11). Depending on the anatomy, the standard bifurcated iliac stent configuration comes with a modular side-arm branch that can be short (~14 mm) and straight, or helical and elongated, to provide a longer sealing zone. The application of this device preserves internal iliac arterial flow and can also be used for complicated cases of concomitant common and internal IAAs.

In a case series study of 27 patients, Chowdhury and his associates demonstrated that these procedures achieved a primary patency rate of 100%, a cumulative patency rate of 94.1%, and a 12-month patient mortality rate of 3.7% with low rates of reintervention and no device-related adverse complications.[66] From a single institution study of 46 patients, Cook IBD side-branch patency was 87% at 5 years.[67] In another series with 100 patients, internal iliac artery patency was 91.4% at 5 years, and cumulative IBD side-branch patency was 87% at 60 months with 11% hypogastric side-branch occlusions occurring within the first year.[68] Extracting data from nine series reporting the use of the Cook IBD in 196 patients, Karthikesalingam et al.[69] noted that early technical success was between 85% and 100%. The review also revealed a collective 12% postoperative IBD limb occlusion rate; half of the patients with IBD limb occlusion developed buttock claudication. The reported rate of combined type I or III endoleak was only 1.5%, and the reintervention rate across all series was 6%.

More recently Simonte et al.[70] reported their long-term experience with the Cook IBD used in 149 patients over a 10-year period. Initial technical success was 97.5%; however perioperative procedure failure occurred in seven patients, four during surgery and three within 30 days of the index procedure. In follow-up, freedom from IBD reintervention was 91.8% at 9 years and hypogastric patency was 90.4% at 10 years. Interestingly, the presence of ipsilateral hypogastric aneurysm ($P = .031$) and initial IBD use during the early "learning curve" period of the study ($P = .006$) were predictive of early failure on multivariate analysis.[70] Having the distal seal landing zone in the hypogastric artery was also predictive of endoleak in a reported series from the Cleveland Clinic. Reporting on 138 IBDs used in 130 patients, estimated patency at 5 years was

81.8% and freedom from IBD-related endoleak was 96% at 5 years; all endoleaks were due to loss of the distal sealing in the hypogastric artery.[71] Finally, in their 5-year experience, Parlani and associates[68] also demonstrated that the presence of a hypogastric aneurysm was the only significant predictor of reintervention, with a hazard ratio of 5.9 (95% confidence interval 1.57–22.08; $P = .008$). Based upon their reported experience, the authors now tend to avoid short distal necks, with more extensive distal landing into the gluteal artery in case of extensive hypogastric aneurysmal involvement.[68,70]

Although designed to be user friendly, both the Gore IBE and Cook IBD prostheses are less adaptable to complex anatomy, thus limiting their wider applicability especially when adhering to the instructions for use (IFU). Based on the current criteria for IBD use, up to 52% of patients may not be suitable for these devices.[72] Pearce and associates[73] conducted a study from two centers and noted that by strictly complying with the manufacturer's IFU, only 35% (35/99) of patients with IAAs treated over the past decade at those institutions would have been suitable for treatment with the IBD or IBE device while remaining strictly within the IFU. In their analysis, only 18.2% and 25.3% of patients fit the stringent inclusion criteria for the Cook and Gore iliac branch devices, respectively.[73] The most common reason for exclusion for either device is the diameter of the internal iliac artery precluding an appropriate landing zone.

In a single-center study, Della Schiava and associates[74] compared the in vivo anatomical conformability of the branched stent grafts (13 Gore IBE vs. 9 Cook IBD) when used in aortoiliac aneurysm repair. Because the branched stent grafts rely on both the external and internal iliac axes, they are subjected to high tortuosity constraints that generate stiffness along the axes of repair, resulting in gradual shortening of the covered lengths.[74] This applied stress, in a setting of marked iliac tortuosity, can potentiate type Ib endoleaks, graft limb plication, and limb thromboses.[74-77] After applying centerline software to compute and compare the index of tortuosity along the iliac axis, the authors noted that the IBD stent graft more significantly modified the length and tortuosity of the iliac axis following implantation. The implantation of an IBD causes a shortening of the total iliac length of 20.56 mm on average versus only 9.77 mm for IBE stent grafts ($P \leq .02$).[74] The postoperative lengths along the internal iliac axis were not affected by either stent. Within anatomical constraints, this finding appears to favor the use of the more conformable Gore IBE in cases of severe iliac tortuosity to minimize postoperative complications associated with stent malposition (type 1b or 3 endoleaks) or branch occlusion (pelvic ischemia). Although the early results associated with both these devices are promising, additional information regarding long-term outcomes are still required.

CONCLUSIONS

Isolated iliac aneurysms are uncommon lesions, usually recognized incidentally during imaging procedures indicated for other reasons. Symptomatic or large iliac aneurysms greater than 3 cm in diameter can be electively repaired safely with open or endovascular techniques. Surgical objectives are to repair and exclude the aneurysm with reconstruction or preservation of the internal iliac artery to minimize pelvic ischemia. Endovascular repair, with its associated reduced incidence of in-hospital morbidity and mortality along with reduced length of stay, has gained favor over open repair as the initial approach of choice for patients with suitable anatomy. Successful endovascular repair is highly dependent on precise, preoperative high-resolution cross-sectional imaging for detailed case planning.

Short- and midterm outcomes for complete endovascular repair using new stent graft devices that maintain flow to both the external and internal iliac artery are promising, with acceptable initial technical success rates and durability as compared to techniques involving unilateral or bilateral internal iliac artery occlusion. Nevertheless, in situations where internal iliac artery patency is essential and a complex anatomy is not amenable to these devices, open surgical repair may be the preferred modality. Knowledge of all current devices and techniques allows for predictably excellent outcomes for almost any patient, regardless of anatomic limitations, when these are applied in a creative and innovative fashion.

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CHAPTER 76

Thoracic and Thoracoabdominal Aortic Aneurysms: Etiology, Epidemiology, Natural History, Medical Management, and Decision Making

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INTRODUCTION

Aortic diseases, including aortic aneurysms, are the 12th leading cause of death in the United States.[1] Although abdominal aortic aneurysms (AAAs) and ascending aortic aneurysms are more common, descending thoracic aortic aneurysms (TAAs) and thoracoabdominal aortic aneurysms (TAAAs) are not rare, with an estimated incidence of 5.9 cases per 100,000 person-years.[2] A study by Clouse and others suggests that the incidence is increasing.[3] During the last 5 years, the mortality for nonruptured and ruptured TAAs in the US population aged 55 and older ranges from only 0.1 to 2.8 and 0.2 to 3.2 per 100,000, respectively, and increases with age. TAA repair is associated with a high morbidity and mortality. Although aortic aneurysms may affect the ascending aorta and aortic arch, the focus of this chapter is on descending TAAs and TAAAs, which can occur from the left subclavian artery to the aortic bifurcation.

Thoracic aortic pathology is very complex and may be related to a variety of histopathologic conditions. Most TAAs and TAAAs are secondary to either medial degeneration or aortic dissection. Medial degeneration is characterized by disruption and loss of elastic fibers and increased deposition of proteoglycans. Many other thoracic aortic pathologies, including the acute aortic syndromes (aortic dissection, intramural hematoma, and penetrating aortic ulcers) and various forms of vasculitis (giant cell arteritis, Takayasu arteritis, and Behçet disease), can induce TAAAs. Although isolated abdominal aortic aneurysms were once called atherosclerotic, TAAs associated with frank atherosclerosis are much rarer. Other histopathologies associated with the thoracic aorta include coarctations, various brachiocephalic anomalies (e.g., aberrant right subclavian arteries), and tumors. Disastrous complications of TAA include pulmonary and enteric fistulas.

This chapter is intended to provide an overview of thoracic aortic disease in order to help these patients' caregivers make the decisions involved in dealing with these pathologies. Importantly, guidelines for the diagnosis and management of patients with thoracic aortic disease have recently been published,[4] and contemporary reviews on the management of TAA and TAAA are also available.[5-7]

THE THORACIC AORTA: ANATOMY AND EPIDEMIOLOGY OF TAA AND TAAA

Although the techniques of open and endovascular TAA and TAAA repair are discussed in more detail in Chapters 77-80, this chapter provides a description of the normal anatomy, as well the many and varied pathologies that are associated with TAA.

Definition

TAAAs are localized dilatations in the thoracic and abdominal aorta secondary to weakening and subsequent expansion of the aortic wall. A TAAA by definition is a dilatation at least 1.5 times its normal value.[8] It is critically important to define these anatomic aortic sizes (Table 76.1) to help identify pathologic aortic growth, because TAAA diameter is the strongest predictor of rupture, with a reported mean aortic diameter of ruptured TAAAs of 6.1 cm.[9] When all aneurysms of the thoracic aorta are considered, those of the ascending aorta are the most common (40%), followed by those of the descending thoracic aorta (35%), aortic arch (15%), and thoracoabdominal aorta (10%).[10]

Normal and Pathologic Aortic Size

The normal thoracic aortic is divided into four parts: the aortic root, the ascending aorta, the aortic arch, and the descending thoracic aorta.[4] The normal thoracic aortic wall is composed of three layers, similar to all blood vessels, which include the intima, media, and adventitia. The aorta normally enlarges as it progresses from the aortic root to the terminal aorta.[10] In addition, gender, age, and body surface area influence aortic diameter (Table 76.2). Even after adjusting for age and body surface area, mean aortic size is significantly smaller, usually 2 to 3 mm, in women than in men.[11-14] Body surface area is reported to be a better predictor of aortic diameter than height or weight.[14] The annual increase in TAAA cross-sectional diameter is highly variable, with reported increases of 1.9 to 3.4 mm/year.[15] Importantly, the growth rates of TAAAs are not predictable or linear. However, there is consensus that TAAAs, similar to

TABLE 76.1 Normal Aortic Diameter and Length by Segment, as Well as Percentage of Aortic Aneurysm Total Represented by Each Aortic Segment[2,9]

Aortic Segment	Mean Aortic Diameter (cm)	Mean Aortic Length (cm)	Percentage of Aneurysms
Ascending	3	5	40
Aortic arch	2.5-3.5	4	15
Descending thoracic	2.0-2.3	NR	35
Thoracoabdominal	1.7-2.6[a]	NR	10

NR, Not reported.
[a]Average 2 mm larger in males than in females.

TABLE 76.2 Normal Adult Thoracic Aortic Diameters by Gender[4]

Aortic Segment and Gender	Range of Reported Mean (cm)	Modality of Assessment
Mid-descending (female)	2.45-2.64	CT
Mid-descending (male)	2.39-2.98	CT
Diaphragmatic (female)	2.40-2.44	CT
Diaphragmatic (male)	2.43-2.68	CT

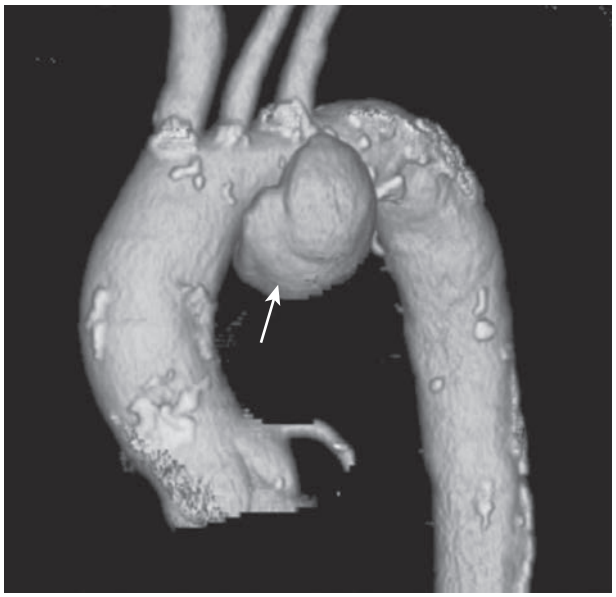

Figure 76.1 Saccular, mycotic thoracoabdominal aortic aneurysm. The patient had bacteremia and was found to have a distal aortic arch/proximal descending thoracic aortic saccular aneurysm *(arrow)*.

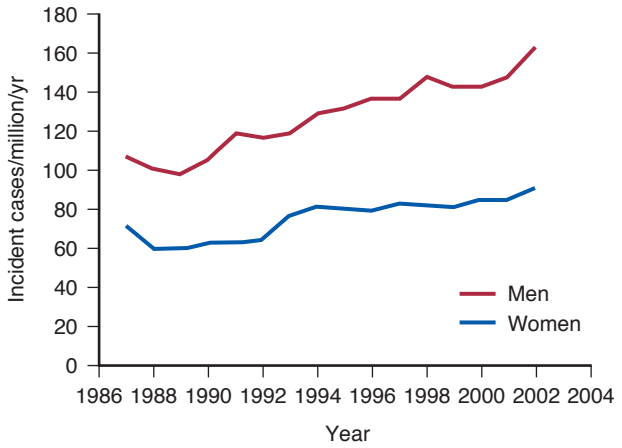

Figure 76.2 Increasing incidence of thoracoabdominal aortic aneurysms and dissection in the Swedish population (men and women), 1987 to 2002 (cases per million). (Used with permission from Olsson C, Thelin S, Stahle E, et al. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. *Circulation*. 2006;114:2611–2618.)

AAAs, have growth rates that accelerate as they enlarge.[16] For example, TAAAs larger than 5 cm expand at a rate of 0.79 cm/year, whereas TAAAs less than 5 cm experience growth rates of 0.17 cm/year.[15] Dapunt and associates have documented that patients with ruptured TAAAs experienced growth rates of 0.7 cm/year.[9] Additionally, the distal aorta manifests more rapid growth than the more proximal segments.[15]

The terms *saccular* and *fusiform* should also be defined for TAAAs, because the morphology of an aneurysm will often dictate treatment options as well as pointing to specific causes (i.e., mycotic aneurysms are often saccular and at high risk for rupture).[17] Most TAAAs are fusiform aneurysms, which involve a chronic uniform dilatation involving the whole circumference of the aorta. In contrast, saccular aneurysms often represent an eccentric dilatation of the aorta (Fig. 76.1). The size at which eccentric saccular aneurysms should be repaired has not been well studied; however, most would concur that a lower threshold is an acceptable indication for repair.

Incidence/Prevalence

Clouse and coauthors have documented that the incidence of TAAAs in the United States is 10.4 cases per 100,000.[3] Olsson examined the prevalence of TAAA in a large contemporary population. All subjects with thoracic aortic dissections or aneurysms from 1987 to 2002 were identified in the Swedish National Healthcare Registry. Of 14,229 individuals with thoracic aortic disease, the diagnosis was made in 11,039 (78%) before death. The incidence of thoracic aortic disease rose by 52% in men and 28% in women to reach 16.3 and 9.1 per 100,000 per year, respectively. The authors concluded that the prevalence and incidence of thoracic aortic disease were higher than previously reported and were increasing (Fig. 76.2).[18] The increasing prevalence of TAAAs has been attributed to a number of factors, including improved imaging techniques, an aging population, and increased patient and physician awareness.[19]

Population Affected

TAAAs are primarily a disease of the elderly. The average age of patients with TAAAs is 65 years, with a male-female ratio of 1.7 : 1[2]; in contrast, in patients with AAAs whose mean age is 75 years, the male-female ratio is 6 : 1.[20] TAAAs clearly have a genetic component, since more than 20% of patients will have a first-degree relative affected by aneurysm disease.[21-23]

Risk Factors for Disease and Rupture

Many risk factors that are common in patients with AAAs, including hypertension, smoking, and atherosclerosis in other arteries, are also common in patients with TAAAs.[2,24-26] Systemic hypertension—in particular elevated diastolic blood pressure greater than 100 mm Hg—has been associated with aortic growth and rupture.[9,27] Although TAAAs are most often described as degenerative, up to 20% are the sequelae of chronic aortic dissection.[28]

Although patients with chronic dissection do not seem to be at risk of more rapid aneurysm expansion than those with purely degenerative aneurysms,[15] dilatation of the outer wall of the false lumen necessitates late aortic repair in up to 40% of patients irrespective of initial medical or surgical treatment of the dissection.[28] Durham and colleagues reviewed their experience of 200 patients serially followed by axial imaging after acute uncomplicated type B dissection. They found that at a mean time to intervention of 27 months, 28% of patients required aortic reconstruction for aneurysm degeneration, typically open TAAA repair. The only factor predictive of aortic growth was an initial aortic diameter greater than 3.5 cm, while

false lumen thrombosis prior to discharge was protective against aortic growth.[29] Given that nearly all of the operated patients ultimately underwent open TAAA, early intervention with thoracic endovascular aortic repair (TEVAR) to cover the entry tear in selected high-risk patients may induce positive aortic remodeling and avoid the morbidity associated with open aortic reconstruction. This should be an area of inquiry for future investigations.

Multiple genetic syndromes, including, most commonly, Marfan syndrome, have been associated with TAAs and dissections. The vascular manifestations of Marfan syndrome invariably involve aortic root dilation, progressive root and ascending aortic aneurysmal degeneration, and potentially aortic dissection of variable extent.[30] The extent of dissection predicts the need of future intervention on the distal aorta, but there is no consensus on appropriate management of the aortic arch.[31] Reoperation is common in Marfan syndrome, it has occurred in 20% of patients at a mean of 5 years from the index operation, with most of these requiring multiple reoperations.[32]

Familial aggregation studies have shown that between 11% and 19% of patients referred for TAA or dissection repair have a first-degree relative with a TAA or dissection.[21,24,25] Patients with a strong family history of TAA tend to present at a younger age than those without a positive history, yet at an older age than those with connective tissue disease. This disease appears to be inherited in an autosomal dominant fashion with variable expression.[33] Mapping studies have shown that there is significant genetic heterogeneity in these patients with familial thoracic aortic aneurysm and dissection (TAAD). Causative genes for TAAD2 (due to TGFBR2 mutation), 16p (due to MYH11 gene), and TAAD4 (due to ACTA2 gene) have been identified, suggesting that mutations to the basic aortic wall building blocks of actin and myosin are responsible for these syndromes.[23,34,35]

Even among patients with Marfan syndrome, in whom mutations in fibrillin-1 (*FBN1*) are the culprit genetic defects, the pathogenesis is more complicated than previously thought. Homology between *FBN1* and transforming growth factor beta (TGF-β) binding proteins and the insufficiency of impaired elastogenesis alone to provoke aneurysmal aortic degeneration suggest a complex interplay between multiple factors and perhaps a central role for TGF-β signally.[36] Further studies have suggested that rare copy-number variants disrupt genes responsible for smooth muscle cell adhesion and contraction in patients with both sporadic and familial TAA disease.[37] The genetic implications of TAAs and dissections are the subject of many contemporary reviews.[36,38,39]

Because most patients with TAAAs are asymptomatic, treatment is aimed at preventing rupture. Natural history studies of TAAAs are rarer than those of isolated infrarenal AAAs, likely related to their much less frequent occurrence. In addition, studies on TAAAs often include patients with both acute and chronic aortic dissection, which serves to complicate natural history analyses. Initial studies from the 1970s by Pressler and McNamara documented that approximately 40% of patients who did not undergo surgical repair died of TAAA rupture, whereas 32% died of other cardiovascular diseases. Mean survival was less than 3 years. During the extended period of observation, more than 90% of patients sustained aortic rupture, with 68% of ruptures occurring more than 1 month after the diagnosis.[40,41]

The 5-year survival rate for patients with 6.0-cm TAAAs is 54%, with a risk for rupture of 3.7%/year and a risk for death of 12%/year. Median survival in patients with untreated TAAAs, at only 3.3 years, is poor.[42] In a natural history study by Crawford and DeNatale of patients who were not candidates for surgery, the survival rate was just 24% at 2 years, with over half the deaths related to aneurysm rupture. Chronic obstructive pulmonary disease (COPD) was noted in 80% of the subgroup with rupture.[43] Similar studies in patients with small infrarenal AAAs have confirmed COPD as a significant risk factor for rupture.[44] Cambria and others followed a series of 57 patients with TAAAs who were not considered operative candidates. In addition to COPD, the authors found an association ($P = .06$) between rupture and chronic renal failure.[45] In a study by Griepp and colleagues, 165 patients with TAAAs were monitored after being assigned nonoperative status. Twenty percent of patients eventually suffered rupture. Important risk factors for rupture included older age, COPD, uncharacteristic continued pain, and aortic diameter. Patients with aortic dissection ruptured at smaller aortic diameters than did those with degenerative aneurysms.[46]

Maximal aortic dimension has emerged as the most reliable predictor of future aortic dissection or rupture. Those with aortic diameters less than 50 mm experienced estimated annual event rates (rupture or dissection) of less than 1%, as compared with 2.7% to 8.1% and 37.5% to 62.5% among those maximal diameters of 50 to 60 and greater than 60 mm, respectively.[47] Dapunt and coworkers documented that TAAAs greater than 8 cm have an 80% risk for rupture within 1 year of diagnosis.[9] However, the size at which TAAAs rupture is unpredictable. Similar to AAAs, it appears that aneurysm growth rates play a role. The average expansion rate of a TAAA is approximately 0.10 to 0.42 cm/year.[42,48-50] Coady and associates suggested that expansion by more than 1 cm/year signals impending rupture.[48] Juvonen and colleagues examined 114 patients with TAAAs in detail.[51] Multivariate analysis suggested that increasing age, pain (even atypical), COPD, descending thoracic aortic diameter, and abdominal aortic diameter were predictive of rupture (Table 76.3).

TABLE 76.3 Risk Factors for Thoracoabdominal Aortic Aneurysm Rupture[51]

Risk Factor	Odds Ratio	*P*-Value
Age	2.6[a]	0.02
Pain	2.3	0.04
COPD	3.6	0.004
Descending aortic diameter	1.9[b]	0.003
Abdominal aortic diameter	1.5	0.05

[a]Per decade of age.
[b]Per centimeter of diameter increase.
COPD, chronic obstructive pulmonary disease.

PATHOGENESIS

The development of a TAAA is a multifactorial event that involves a complex interaction of genetic factors, cellular imbalance, and altered hemodynamic factors.[52] The increased incidence of TAAAs in patients with Marfan syndrome and other connective tissue disorders inherited in a Mendelian manner, as well as the familial inheritance of nonsyndromic TAADs typically inherited in an autosomal dominant fashion with marked variability in the age of onset and decreased penetrance, suggests a varying genetic role along different segments of the aorta.[23,33-35] As alluded to previously, even in Marfan syndrome, the mechanisms behind aortic aneurysm degeneration are more complex than previously appreciated. More recent studies have suggested that genetic variation in extracellular matrix (ECM) actin and myosin may contribute to the development of TAAAs.[53,54] Wang and coauthors examined genetic signatures in the peripheral blood of patients with TAAAs (n = 58) and control patients (n = 36). This study documented a number of gene families that were different between the two groups, including those involved in the cell cycle, DNA metabolism, glycolysis, interferon-γ signaling, and transcription factors. The authors concluded that analysis of peripheral blood to determine expression signatures may help to identify patients with TAAAs with high accuracy.[55]

TAAA formation, therefore, is a complicated, dynamic process involving both extracellular and cellular processes, similar to other aneurysms (see Chapter 69). Once initiated through a combination of the aforementioned factors, inflammation and pathologic remodeling of the ECM occur. A large body of evidence suggests that ECM degradation by matrix metalloproteinases (MMPs) exceeds matrix production and repair during aneurysm formation. It is important to emphasize that there are significant differences in the composition of the aortic wall as one progresses from the ascending aorta to the iliac bifurcation. Andreotti and colleagues documented that the ascending aorta has a greater concentration of elastin and is therefore more compliant than the descending aorta. This alteration in elastin concentration leads to a progressive decrease in the elastin-collagen ratio as the aorta progresses from the ascending aorta to the abdominal aorta.[56] The media also becomes thinner as one progresses from proximal to distal along the aorta.[57]

A number of recent studies have documented the overexpression and increased activity of various ECM proteinases, specifically the MMPs, in human TAAAs.[58] These proteolytic enzymes, which have been more extensively studied in AAAs, are clearly critical as well during the formation of TAAAs. Sinha and coworkers documented asymmetric production of MMP9 in the expanding human TAAA wall, which correlated with increased numbers of macrophages.[59] In contrast, MMP2 was documented to be increased in the wall of the TAAA that was preserved, in particular, at the point where smooth muscle cells were more abundant and the wall was preserved. Ikonomidis and associates studied the role of MMPs in a murine model of TAAAs.[58] These authors documented that MMP9 gene deletion attenuated TAA formation despite increases in MMP2 activity. They concluded that interactions between MMP9 and MMP2 are necessary to facilitate TAAA progression. Recent studies by Ikonomidis and others have documented altered membrane type-1 matrix metalloproteinase and tissue inhibitor of metalloproteinase2 (TIMP2 an inhibitor of MMPs), in the murine TAA model.[60] Further studies by Johnston, Pope and others have also suggested a critical role for IL-1β and IL-6 in TAA based on animal studies.[61,62]

Aortic Wall Histology

The histology of TAAAs is most closely associated with medial degeneration, formerly known as cystic medial necrosis (Fig. 76.3). Medial degeneration is characterized by fragmentation and loss of elastic fibers, loss of smooth muscle cells, and collections of interstitial collagenous tissue, basophilic ground substance, and proteoglycans.[63,64] Although medial degeneration is considered part of the normal aging process, it is accelerated by certain clinical conditions such as hypertension and atherosclerosis.[65] Given the relatively widespread process along the thoracic aorta, medial degeneration is most closely associated with the development of fusiform aneurysms. Genetic abnormalities, such as Marfan syndrome, also accelerate aortic medial degeneration.[66] Although TAAAs were originally described as noninflammatory, recent studies have shown that infiltration of leukocytes contributes to the formation and development of TAAAs. The significant difference in the epidemiology and histology of TAAAs and AAAs suggests distinct causes.

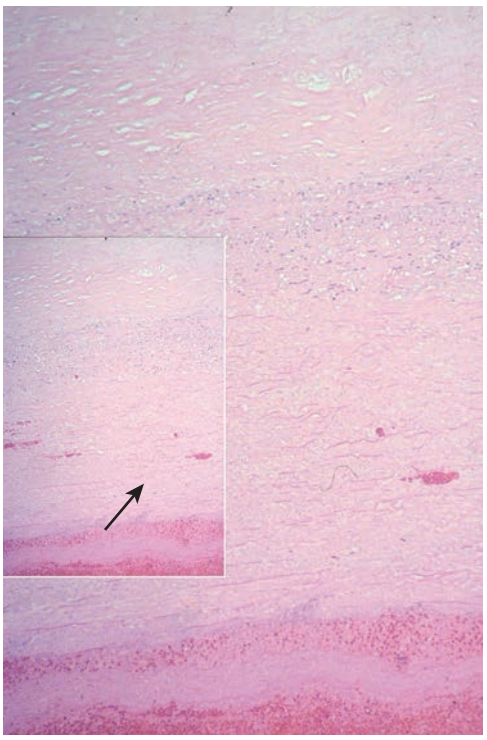

Figure 76.3 Documentation of medial degeneration and fragmented elastin (see *insert*, *arrow*) by histology (hematoxylin and eosin, 100×) of an aortic section in a patient with a thoracoabdominal aortic aneurysm. (Courtesy of Dr. David Williams.)

ETIOLOGY

Eighty percent of TAAAs are secondary to medial degeneration, with approximately 15% to 20% caused by aortic dissection (Table 76.4) (see Chapter 81). Patients with TAAAs secondary to aortic dissection are typically younger and involve more extensive aortic segments than do degenerative aneurysms.[67] The aorta in patients with Marfan syndrome is particularly prone to aortic dissection and subsequent TAAA formation.[68] Both systemic autoimmune disorders, such as Takayasu arteritis, and chronic nonspecific aortitis can destroy the aortic media with progressive aneurysm formation. Aneurysms associated with arteritis are more commonly seen in women than are degenerative aneurysms. Aneurysms of the upper thoracic aorta can also be secondary to congenital aortic coarctations, either in unrepaired coarctations or after repair.[69-71]

TAAAs may also form secondary to infection. Although saccular aneurysms have been described as mycotic, these aneurysms are most often bacterial and occur because of hematogenous spread of emboli laden with bacteria. Infected TAAAs usually arise as a result of seeding of atherosclerotic plaque in the aorta, the development of a focal inflammatory process in the aortic wall, and ultimately the formation of a false aneurysm. Infected TAAAs present many challenging dilemmas. The goal of therapy is to debulk the infection and restore arterial continuity. For years this has involved in situ repair with its attendant lifetime risk of reinfection. Recent reports of treatment of infected TAAAs with endovascular prostheses are beginning to accumulate.[73,74] The endovascular approach can be utilized as either definitive management or as a bridge to stabilize an ill patient to eventual open operation. An endovascular approach, if durable, may definitively circumvent the challenges posed by open aortic reconstruction in an infected field (Fig. 76.4).

TABLE 76.4 Etiology of Thoracoabdominal Aortic Aneurysms and the Relative Percentage Contributing to Disease[72]

- Degenerative (associated with atherosclerosis) (80%)
- Dissections (15%-20%)
- Connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz syndrome)
- Infection (2%)
- Mycotic aneurysms (*Salmonella, Haemophilus influenzae, Staphylococcus* sp.)
- Syphilis
- Tuberculosis
- Aortitis (2%)
- Takayasu disease
- Nonspecific variety of giant cell aortitis
- Rheumatoid aortitis
- Ankylosing spondylitis
- Reiter syndrome
- Relapsing polychondritis
- Postoperative pseudoaneurysms (<1%)
- Associated with unrepaired and repaired aortic coarctations
- Traumatic (<1%)

ANATOMIC CLASSIFICATION

Evaluation of a patient with a TAAA, as well as the technical performance of either open or endovascular repair, is closely

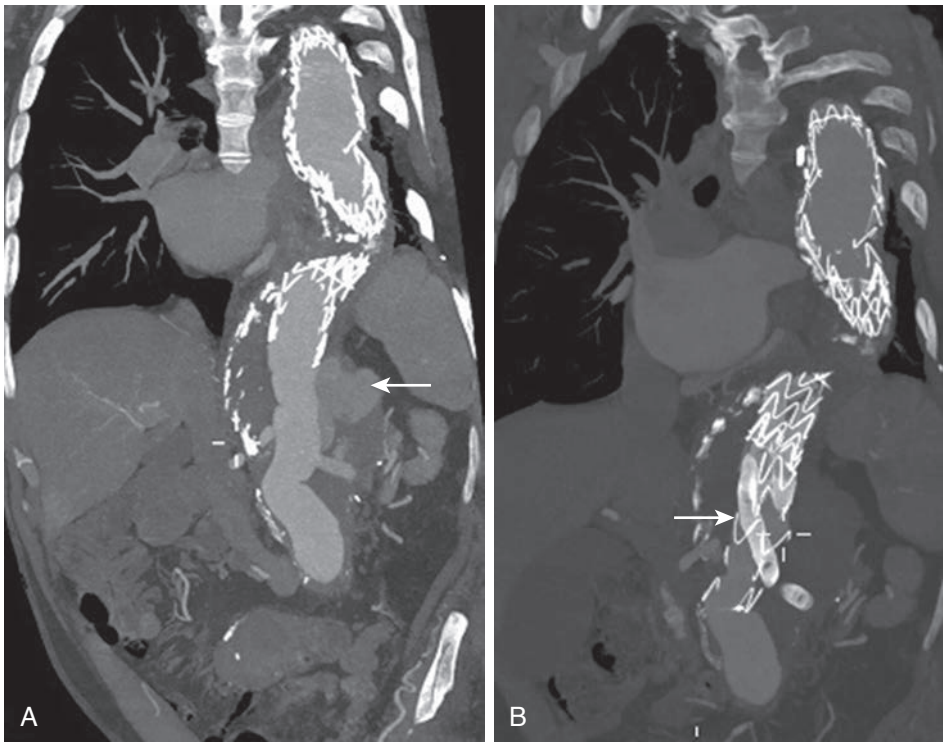

Figure 76.4 Patient with Marfan syndrome—who had previously undergone open thoracic aortic aneurysm repair, open thoracoabdominal aneurysm repair through redo thoracoabdominal approach, and thoracic endovascular aortic aneurysm repair—who presented with para-anastomotic pseudoaneurysm (A, *arrow*) and was successfully treated with a snorkeled exclusion of his pseudoaneurysm (B, *arrow marks* the celiac trunk snorkel).

aligned with the Crawford classification (Fig. 76.5).[72,75-77] Classification of TAAAs also has important therapeutic implications for the operation to be performed as well as the risk for specific complications. Type I TAAAs account for approximately 25% of all TAAAs. They involve the entire descending thoracic aorta and extend only to the upper abdominal aorta. Type II TAAAs (approximately 30% of TAAAs) involve the entire descending thoracic aorta and most of or the entire abdominal aorta (Fig. 76.6A). Type III TAAAs (<25%) involve variable lengths of the descending thoracic aorta and extend into the abdominal aorta (see Fig. 76.6B). Type IV TAAAs (<25%) are limited to the abdominal aorta, including the visceral and renal arteries.

CLINICAL FINDINGS

History and Physical Examination

Most patients with TAAAs have no symptoms attributable to their disease at the time of diagnosis.[26,41,72] The diagnosis is therefore often made when evaluating the patient for unrelated

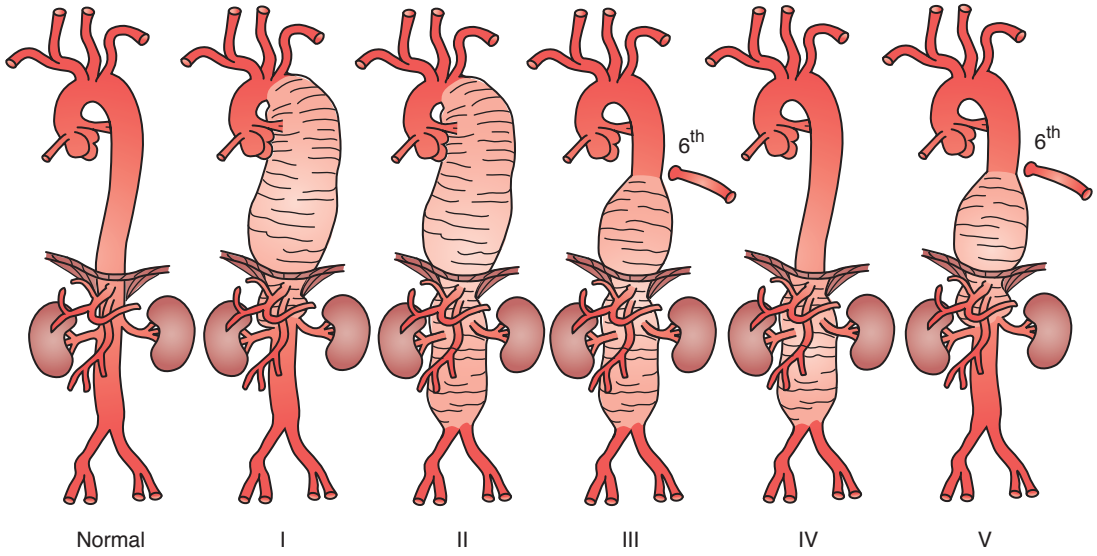

Figure 76.5 Crawford classification of thoracoabdominal aortic aneurysms. Type I, distal to the left subclavian artery to above the renal arteries. Type II, distal to the left subclavian artery to below the renal arteries. Type III, from the sixth intercostal space to the renal arteries. Type IV, entire abdominal aorta. Type V, below the sixth intercostal space to just above the renal arteries.

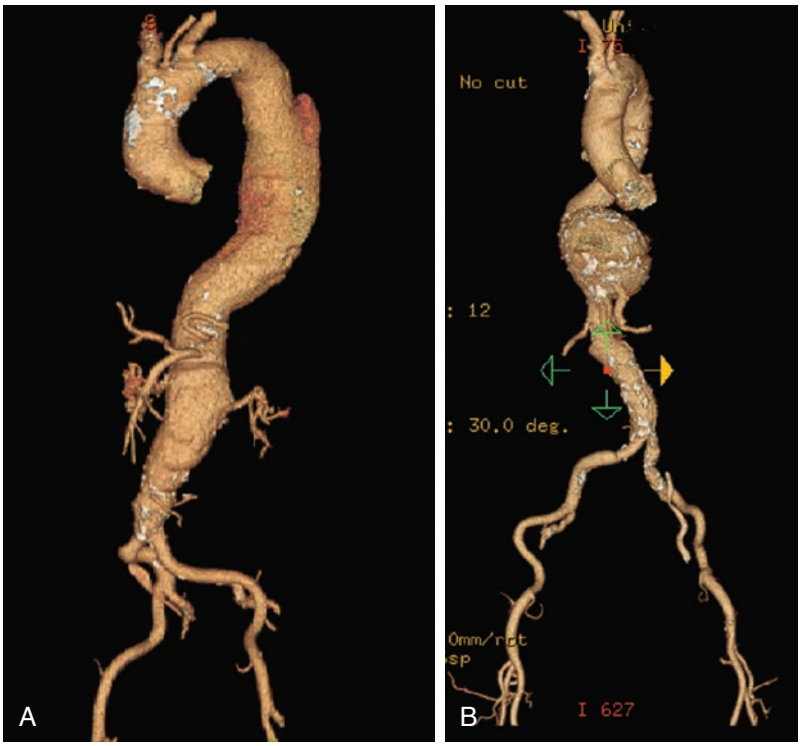

Figure 76.6 Three-dimensional computed tomography angiogram of a type II thoracoabdominal aortic aneurysm (TAAA) (A) with associated dissection and a type III saccular TAAA (B).

TABLE 76.5 Recommendations for Physical Examination of the Patient Presenting With Thoracic Aortic Aneurysm

Class/Level of Evidence	Recommendation
I/C	Perform a focused physical examination evaluating • Perfusion differentials in the upper and lower extremities • Evidence of visceral ischemia • Focal neurologic deficits • Murmur of aortic regurgitation • Evaluation for bruits • Findings compatible with possible cardiac tamponade

conditions. Although most patients with TAAAs are asymptomatic, Panneton and Hollier documented that 57% of patients with degenerative TAAAs will have symptoms before rupture.[72] The recent American Heart Association (AHA) guideline for thoracic aortic disease includes recommendations regarding the history and physical examination for the general approach to the patient with suspected thoracic aortic disease (Table 76.5).[4] The authors have suggested based on Class I, Level C evidence, that "the clinician should perform a focused physical examination, including a careful and complete search for arterial perfusion differentials in both upper and lower extremities, evidence of visceral ischemia, focal neurologic deficits, a murmur of aortic regurgitation, bruits, and findings compatible with possible cardiac tamponade."[78-80]

The most common initial symptom in patients with TAAAs is vague pain, which can occur in the chest, back, flank, or abdomen. The differential diagnosis in a patient with a symptomatic TAAA therefore includes angina, aortic dissection, and degenerative disease of the spine. The chronic pain associated with TAAAs may easily be dismissed in patients with TAAAs before the diagnosis of a TAAA has been made. Typical of most aneurysms that are enlarging, pain may increase in severity dramatically. Juvonen and coworkers suggested that the back pain associated with a TAAA can indeed be chronic and have a different pattern and implication than noted with AAAs, in which the back pain is more often acute and suggests impending rupture.[51]

Symptoms may also occur in patients with TAAAs from compression of the thoracic aorta by structures in the thoracic cavity. Hoarseness can develop in patients with TAAAs as a result of stretching or compression of the left recurrent laryngeal nerve (Fig. 76.7). Tracheal deviation, persistent cough, or other respiratory symptoms may also be present.[40,81] Dysphagia is an uncommon, nonspecific complaint due to compression of the aneurysm by the esophagus.[82] Sudden and catastrophic hemoptysis or hematemesis may occur as a result of erosion of the TAAA into the bronchial and pulmonary space or the esophagus, respectively.

Patients with TAAAs may rarely have neurologic deficits, including paraplegia. This is much more common in those with

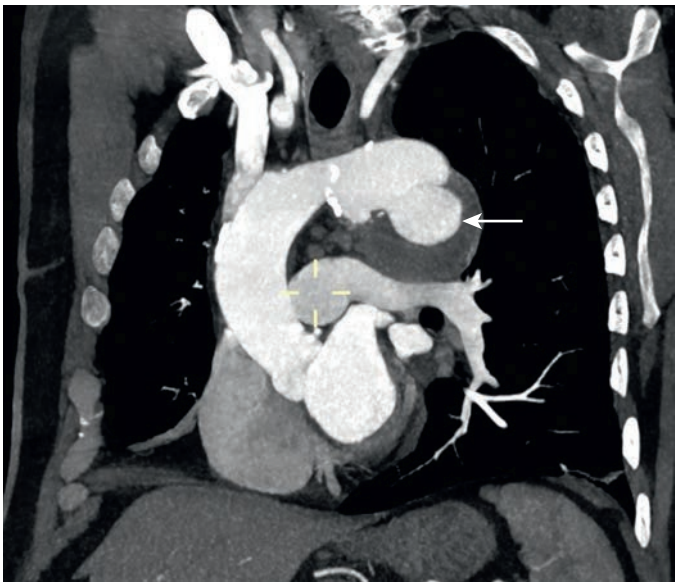

Figure 76.7 Patient who presented with new-onset hoarseness and voice weakness following previous endovascular abdominal aortic aneurysm repair. The patient was found to have a saccular thoracic aortic aneurysm *(arrow)*, ultimately requiring arch reconstruction with elephant trunk and subsequent thoracic endovascular aneurysm repair.

aortic dissection. Embolization to the visceral and renal arteries and arteries of the lower extremities has been reported.[83] Patients with an abdominal component of their aneurysm may have gastrointestinal hemorrhage, aortoenteric fistulas, or a functional obstruction of the small bowel secondary to compression of the duodenum. Most patients with symptoms have TAAAs that have attained a diameter greater than 5 cm.

On examination of a patient with TAAA there are generally no obvious physical findings in the chest area unless tracheal deviation is present.[84] Patients with an abdominal component of their TAAA may have a pulsatile abdominal mass similar to that seen in patients with pure AAAs. It is important to note that no controlled or blinded study has been performed that reproducibly stratifies patients with TAAAs into groups that predict poor outcomes.[4] The critical issue is to identify those patients who are acutely ill from their thoracic aortic disease and to triage them accordingly.

Synchronous Aneurysm Risk

Studies examining the natural history of patients with TAAAs indicate that between 20% and 30% will also have an AAA.[40,85] In a series of 1500 patients, Crawford and Cohen documented that 13% harbored aneurysms in other segments.[86] This appears to be true when examining patients who undergo TAAA repair as well, where as many as a third of patients will have undergone previous aortic repair.[87] Most commonly patients with TAAAs have undergone previous infrarenal AAA repair. Synchronous proximal ascending and arch aneurysms are noted in 6% to 13% of patients with TAAAs.[72] Even after repair, at least 10% of patients with TAAAs will require subsequent aneurysm repair in noncontiguous aortic segments.[88] Patients with Marfan

syndrome appear to be at high risk for this type of manifestation. Among patients with Marfan syndrome who had undergone cardiac surgery—over an average of 5 years following initial operation—20% required reoperation, with 37% of reoperations performed on the thoracic or thoracoabdominal aorta.[32] In Marfan patients presenting with type A dissection, 27% eventually required reoperation on the thoracoabdominal aorta, and this was three times more common in DeBakey I compared with DeBakey II dissections.[31] As discussed in subsequent chapters, there is clearly an increasing trend toward treating complex arch aneurysms and TAAAs with sequential open and endovascular therapies.[89-91]

DIAGNOSTIC EVALUATION

Imaging

Accurate and precise determination of the anatomy of a patient with a TAAA is mandatory in determining both the need for and the details of operative repair as well as the prescribed follow-up in patients with TAAAs who have not reached a diameter threshold for repair. Recommendations for aortic imaging techniques to determine the presence of progression of thoracic aortic disease have been modified and summarized (Table 76.6). Cross-sectional imaging, mainly by computed tomography (CT), is the primary method to visualize the thoracic and abdominal aorta for determining aneurysm diameter and extent. Because most TAAAs are small when discovered, serial imaging is required; however, level A and B evidence regarding the timing of surveillance is lacking. Serial imaging is typically performed at 6- to 12-month intervals, but it varies depending on the initial diameter and extent of the aneurysm.

Chest X-Ray

A chest radiograph (Fig. 76.8) or plain films of the abdomen in patients with TAAA may suggest an enlarged thoracic aorta secondary to a calcified aortic wall. Indirect findings suggestive of TAAA on chest radiography include a widened mediastinum, enlargement of the aortic knob, tracheal deviation, or left main stem bronchus displacement. Although chest x-rays are part of the routine preoperative workup of every patient considered for TAAA repair, they are inadequate to definitely exclude the presence or absence of thoracic aortic disease. A study of data pooled from 10 studies suggests that the predictive sensitivity of a widened mediastinum or an abnormal aortic contour associated with thoracic aortic disease is 64% and 71%, respectively.[92] In contrast, a prospective study of over 200 patients with thoracic aortic pathology documented a specificity of 86% for chest x-ray.[93]

Computed Tomography

Multidetector CT (MDCT) scanning with three-dimensional reconstruction capability is now the "gold standard" for evaluating the aorta in patients with TAAAs, rendering a diagnosis and establishing the extent and maximal dimensions of the aneurysm. New-generation MDCT scans have been shown to

TABLE 76.6 Recommendation for Aortic Imaging to Determine the Presence and Progression of Descending Thoracic Aortic Disease[4]

Class/Level of Evidence	Recommendation
I/C	Measurements of aortic diameter should be taken at reproducible landmarks, perpendicular to the axis of blood flow, and report in clear and consistent format. For measurements taken by CTA or MRA, the external diameter should be measured perpendicular to the axis of blood flow. Abnormalities of aortic morphology should be recognized and reported separately even when aortic diameters are within normal limits. The finding of aortic dissection, aneurysm, or trauma with or without aortic rupture should be immediately communicated to the referring physician. Techniques to minimize episodic and cumulative radiation exposure should be utilized whenever possible.
IIa/C	If clinical information is available, it can be useful to relate aortic diameter to the patient's age and body size.

CTA, computed tomography angiography; *MRA*, magnetic resonance angiography.

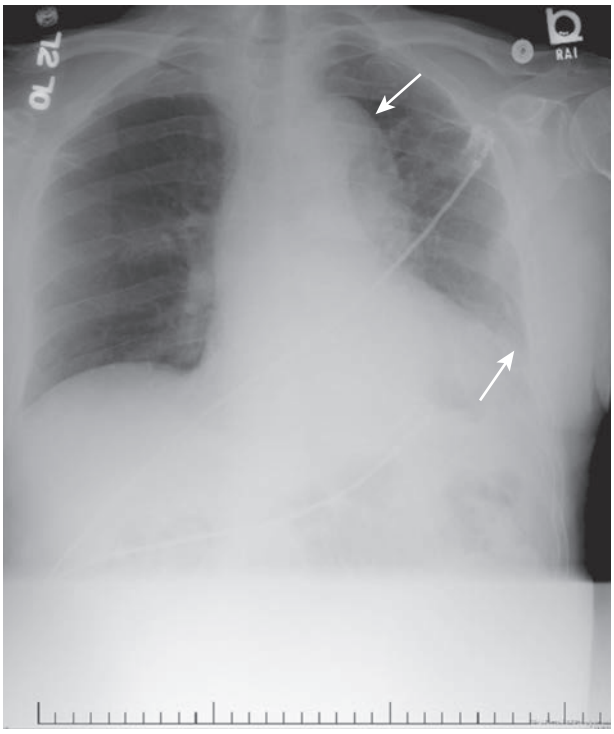

Figure 76.8 Chest radiograph in the posteroanterior projection documenting a rim of calcification outlining the dilated thoracic aorta *(top arrow)* as well as a left-sided pleural effusion *(bottom arrow)* in a patient with a ruptured thoracoabdominal aortic aneurysm.

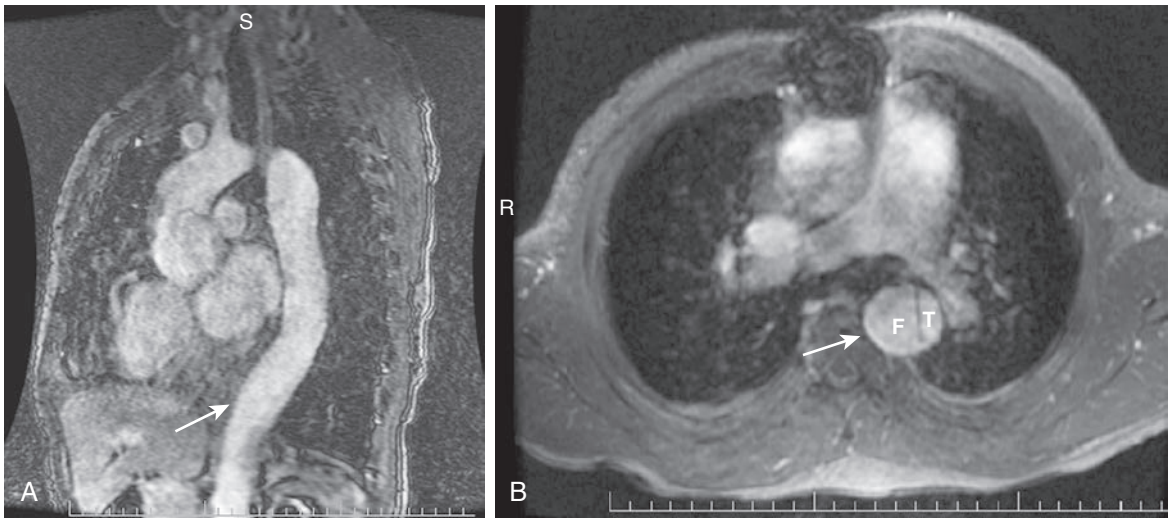

Figure 76.9 Magnetic resonance angiography (MRA) of a thoracoabdominal aortic aneurysm (TAAA). (A) Sagittal MRA view with gadolinium enhancement in a patient with a type B aortic dissection and subsequent TAAA formation. The *arrow* denotes an area of maximal aneurysmal dilatation. (B) Axial cut at same level *(arrow)* documenting the true (T) and false (F) lumen of dissection.

have sensitivities and specificities of well over 95%.[94-97] Post-acquisition image processing can generate sagittal, coronal, and oblique images as well as three-dimensional renderings that can be used to determine whether a patient is a candidate for a stent or graft.[98] A general assessment of other organs in the chest, abdomen, and pelvis is also obtained with MDCT, which allows the detection of other pathology, including cancer, that might affect patient management and surgical planning.[99,100] In patients with renal insufficiency, MDCT without iodinated contrast agents can be useful to determine TAAA size or extent but will not provide accurate data regarding the atherosclerotic burden of branch vessels or the presence of a dissection. It is our general impression, supported by the medical literature, that given the standard use of small boluses of low-osmolar contrast material in performing CT angiography (CTA), contrast-related acute renal failure after CTA is, in fact, rare and, when it does occur, mild.[101]

CTA also importantly allows other essential information to be obtained, as from the assessment of occlusive disease in branch vessels including the vertebral, subclavian, and hypogastric arteries, all essential contributors to the spinal collateral network. In addition, CTA documents the patency of important intercostal arteries that might be reimplanted into the aortic graft if extensive open TAAA repair is being considered. CTA further documents the presence of thrombus, inflammatory changes, dissection, and retroperitoneal blood suggestive of a ruptured aneurysm. The relative advantages of CT scanning over magnetic resonance imaging (MRI) include its better spatial resolution, reduced cost, rapidity of acquisition (thereby decreasing patient claustrophobia, anxiety, and image motion artifact), applicability to patients with previously implanted ferromagnetic devices, and wide availability.

A word of caution is needed regarding CTA and the timing of TAAA repair. Because of the nephrotoxicity of iodinated contrast agents, in the elective surgery and endovascular therapy setting, repair is best delayed for at least 24 hours after CTA, especially in patients with chronic renal insufficiency. The administration of *N*-acetylcysteine and intravenous hydration are current strategies used to limit contrast-induced nephropathy.[102,103] If the latter complication does occur, elective repairs should be delayed until renal function returns to baseline.

Magnetic Resonance Imaging and Magnetic Resonance Angiography

MRI/MR angiography (MRA) can be considered when evaluating patients with TAAAs, especially those with renal insufficiency, because it avoids the use of iodinated contrast material (Fig. 76.9). MRA has also been used to map the spinal cord circulation before TAAA repair.[104,105] Although MRI is believed to provide better contrast resolution, its spatial resolution is poorer than that of MDCT. Initially there was enthusiastic support for using MRI/MRA to identify the patency of visceral and renal vessels in patients with TAAAs.[106] However, recent concerns over the use of gadolinium in patients with renal insufficiency has made the use of MRA less attractive in those with aortic aneurysms.[107] MRI/MRA is also technically limited in that thrombus and calcium are not prominently displayed. In addition, the increased time required to acquire the images, the associated claustrophobia, the increased cost, and interference from metallic implants make MRA of limited use in the diagnostic evaluation of TAAAs.

Arteriography

Although in the past aortography was routinely performed as part of the preoperative evaluation of patients with TAAAs to define the extent and location of the aneurysm, angiography is currently considered obsolete except for special situations, such as attempting to map the spinal cord circulation. Williams and coworkers used angiography to identify the spinal artery of Adamkiewicz, or the great radicular artery. By knowing in

advance of TAAA repair which intercostal artery was providing this important branch, they sought to enable prompt and focused revascularization while also preventing paraplegia.[108] Indications for angiography also include the evaluation of branch anatomy in a patient with a TAAA and occlusive disease in the cerebrovascular, visceral, renal, or iliac beds when it is important to limit the use of iodinated contrast material in patients with chronic renal failure. Selective angiography using dilute contrast or CO_2 might also be used to treat patients with occlusive disease before TAAA repair, even though few specific studies documenting this approach have been performed.

Laboratory Testing

At present, there are no available biomarkers to suggest the presence of a TAAA. Initial research in patients with acute aortic dissections has focused on a number of proteins, including lipoprotein (a), S-100B, and calponin.[109-111] Touat and others have suggested that platelet activation and thrombin generation occur in patients with large dilated ascending aortic aneurysms, particularly in areas of mucoid degeneration.[112] Recent reviews suggest that although there are currently no clinical serologic screening tests for TAAA, there are multiple promising targets for investigation.[113,114] One recent study examined plasma and aortic tissue markers in patients with and without bicuspid aortic valves undergoing aortic valve or ascending aortic repair. The investigators demonstrated differential expression of microRNA and MMP subtypes between those patients with bicuspid and tricuspid aortic valves. This suggests that familial and degenerative aortic disease may be distinguished by a relatively simple blood test, although these tests are not yet clinically available.[115] Standard laboratory testing, including a complete blood count with platelets, coagulation studies, and determination of blood urea nitrogen and creatinine levels, is routine before TAAA repair. Reports have suggested that the rare patient with a TAAA may have low-grade disseminated intravascular coagulation based on consumptive coagulopathy from the aneurysm.[116]

MEDICAL THERAPY

It is important to acknowledge that there is no level A or B evidence comparing modern medical therapy (aspirin, beta blocker, statin, angiotensin-converting enzyme inhibitor [ACE-I] or angiotensin receptor blocker [ARB], smoking cessation medications) with open or endovascular TAAA repair. In addition, most of the literature on which we base our medical management of patients with TAAAs is extrapolated from literature on patients with ascending aortic aneurysms or aortic dissections.[117-120] In general, nonoperative management consists of strict blood pressure control with beta blockade and an ACE-I or ARB, cessation of smoking, and periodic imaging to monitor the size of the TAAA. There are guidelines that are helpful in the management and preoperative preparation of patients with AAAs but not specifically for patients with TAAAs. In addition, reports focused on medical therapies to limit or slow the growth of TAAAs are few. The AHA Guidelines suggest that "stringent control of hypertension, lipid profile optimization, smoking cessation, and other atherosclerotic risk-reductions should be instituted for small aneurysms not requiring surgery, as well as for patients who are not considered to be surgical or stent graft candidates."[4] The medical management of TAAA has recently been reviewed and is further detailed in the following text.[121,122]

Antihypertensive Medication

Recent guidelines suggest that antihypertensive therapy should be administered to patients with TAAAs; it should be titrated to a goal blood pressure of 140/90 in patients without diabetes and 130/80 in patients with diabetes or chronic renal failure.[4] It has been recommended that, unless contraindicated, patients with Marfan syndrome and aortic aneurysms be given beta blockers to reduce the rate of aortic dilatation. A Class IIa recommendation has been made that in those with TAAs, blood pressure should be reduced with beta blockers, an ACE-I, or anARB to the lowest point the patient can tolerate without adverse effects.

Beta Blockers

Wheat and Palmer are credited with documenting that decreasing the force of myocardial contraction (dP/dt) slows aortic growth and may prevent TAAA rupture secondary to aortic dissection; however, it does not apply to degenerative TAAAs.[123] This observation is the basis for prescribing β-adrenergic blocking agents as first-line antihypertensive therapy for patients with TAAAs. Shores and colleagues used propranolol over a 10-year period and showed a significant reduction in growth of the aortic root, aortic events, and mortality in patients with Marfan syndrome.[124] Results in animal models of AAA have not translated into beneficial effects of slowing AAA growth in humans.[125,126] It is therefore not clear that beta blockers retard aortic growth in patients with degenerative TAAAs. Nevertheless, the safety and efficacy of beta blockers in preventing death secondary to myocardial infarction are well documented; therefore they should be prescribed, or, if already prescribed, continued in the perioperative setting.

Angiotensin-Converting Enzyme Inhibitors or Receptor Blockers

There is increasing evidence that oxidative stress plays an important role in the development of degenerative TAAs. Ejiri and associates documented a role for the renin-angiotensin system in the pathogenesis of TAAAs. Human thoracic aneurysmal ($n = 40$) and nonaneurysmal (control, $n = 39$) aortic sections were examined, and the results documented markedly increased in situ production of reactive oxygen species throughout the TAAA wall. Multiple regression analysis revealed that medical treatment with angiotensin II type 1 receptor blockers suppressed expression of reactive oxygen species in TAAA.[127] A study by Moltzer and others specifically focusing on TAAs also suggests that angiotensin II type 1 (AT_1) receptor blockers, and not ACE or renin inhibitors, should be preferred treatment for patients with TAAs.[128] Multiple lines of evidence now suggest that the mechanism of action of ACE-I, and particularly the ARB losartan, on the attenuation of aneurysm growth is

modulation of TGF-β–mediated signaling.[121,122] It remains to be seen whether this is an ARB class effect or if one particular ARB is more effective than others at preventing aneurysm growth.

It should be noted that the evidence for the use of ARB in preventing aneurysm growth is strongest among patients with Marfan syndrome. However, this finding should not be surprising given the new evidence, discussed previously, of the pivotal role of TGF-β signaling in the pathogenesis of that disease. But even in this patient population, the data are somewhat contradictory. In a large randomized trial comparing losartan to atenolol (considered standard therapy), Lacro and colleagues demonstrated no difference in efficacy between the two drugs in preventing aortic root dilatation among young Marfan patients.[129] Similarly, a smaller randomized study comparing losartan to atenolol in group of patients with a broader age range found no difference in aortic root dilatation or adverse aortic events.[130] Yang et al. demonstrated the ability of losartan, in combination with the MMP inhibitor doxycycline, to normalize MMP and TGF-β expression profiles and thereby maintain aortic structural integrity and decrease aortic degeneration in a mouse model of Marfan syndrome.[131] In a study comprising nearly 600 Marfan patients, den Hartog and colleagues demonstrated that ARB use is associated with a 70% reduction in the incidence of subsequent type B aortic dissection compared with patients not taking ARB. Given our understanding of TAAA development following aortic dissection, this study suggests that ARBs have the potential to alter, at least in Marfan patients, the natural history of the disease.[132]

Statins

A well-studied class of drugs with important cholesterol-lowering properties is the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. HMG-CoA reductase inhibitors, also known as statins, in addition to lowering cholesterol, also have pleiotropic effects that inhibit inflammation.[133,134] Specific to TAAAs, recent studies in human TAAAs have shown a role for p22phox-based reduced nicotinamide adenine dinucleotide/reduced nicotinamide adenine dinucleotide phosphate (NADH/NADPH) oxidase in the pathogenesis of TAAAs. This study suggests that statins might have inhibitory effects on the formation of TAAAs via the suppression of NADH/NADPH oxidase.[127]

Although data examining TAAA growth in humans are limited, Schouten and associates documented that statins inhibit the growth of AAAs.[135] A recent propensity score matched retrospective review investigated the effect of statins on patients with dilated ascending aortas. The investigators found a significant decrease in further aortic degeneration as well as a composite of death, dissection, rupture, and need for repair among patients receiving statins.[136] As mentioned earlier, the structural anatomy and the pathophysiology of aortic degeneration in different aortic segments varies. Extrapolating the benefit of statins to other thoracic aortic pathology is thus speculative. Another retrospective review of patients with aortic aneurysms stratified by statin use demonstrated a reduction in rates of aneurysm-related events (dissection, rupture, or death) and need for operation among patients taking compared to those not taking statins.[137] Other investigators have suggested that statins are effective in lowering mortality after endovascular AAA repair but not after TAAA repair.[138] These authors concluded that this variable response to statins, again, indirectly supports the concept of a distinct pathogenesis of AAAs and TAAAs. Nonetheless, most patients with TAAAs have other indications for statin therapy.

Smoking Cessation

Patients who smoke or who have COPD are at increased risk for the development of TAAAs. TAAAs also grow faster and rupture more often in smokers.[9,51] Cannon and Read suggested that this was secondary to increased elastolytic activity.[139] Based on the AAA literature, few would argue that patients who smoke are at risk for the development of TAAAs.[140,141] These studies suggest that active pursuit of cessation of cigarette smoking is an important adjunct in those under observation with a TAAA. Yet, similar to statin usage, no randomized or prospective trials have ever shown that smoking cessation will slow thoracic aortic growth.

SELECTION OF TREATMENT

The decision as to when to operate on a patient with a TAAA involves assessment of the likelihood of aortic rupture versus the operative risk of the individual patient.[142] It is unclear at present what the impact of thoracic endovascular aortic repair (TEVAR) will be, with its attendant lower short-term mortality and morbidity, on decision making regarding what aortic diameter should serve as a threshold for TAAA repair. Two major factors, the patient's physiologic reserve and vascular anatomy, play a significant role in determining whether a patient is best suited for open repair or an endovascular approach.[143] Recent guidelines specifically tailored for when and how to repair TAA and TAAA have been issued (Table 76.7).[4]

Size Criteria

Size criteria for TAAA repair are not as clearly defined as for infrarenal AAAs because there are no level A or B scientific data regarding the timing of operative intervention.[144,145] This issue is further complicated by the observation that degenerative TAAAs are often not uniform in size and involve aortic segments of varying diameters and morphology. In addition, it is important to recognize the impact of body size on aortic size. Adjustment for body surface area or height must be incorporated into decision making about the threshold for repair and risk for rupture.[146] For the average older man (1.7-1.8 m in height), the normal proximal descending aorta is 2.8 cm, the mid-descending aorta is 2.7 cm, and the distal descending aorta is 2.6 cm. The authors suggested that the accepted size indications for TAAA repair, independent of etiology, might be a diameter of 5.2 to 5.6 cm or twice the diameter of the normal contiguous aorta, depending on the aortic segment being repaired. Algorithms suggest that

TABLE 76.7 Recommendation for Thoracic and Thoracoabdominal Aortic Aneurysm Repair[4]

Class/Level of Evidence	Recommendation
I/B	For patients with chronic dissection, particularly if associated with a connective tissue disorder but without significant comorbid disease and a descending thoracic aortic diameter exceeding 5.5 cm, open repair is recommended. For patients with degenerative or traumatic aneurysms of the descending thoracic aorta exceeding 5.5 cm, saccular aneurysms, or postoperative pseudoaneurysms, endovascular stent grafting should strongly considered when feasible. For patients with thoracoabdominal aneurysm and with end-organ ischemia or significant stenosis from atherosclerotic visceral artery disease an additional revascularization procedure is recommended.
I/C	For patients with thoracoabdominal aneurysms in whom endovascular stent graft options are limited and surgical morbidity is elevated, elective surgery is recommended if the aortic diameter exceeds 6.0 cm, or less if a connective tissue disorder, such as Marfan or Loeys-Dietz is present.

0.6 cm can be added to or subtracted from these figures for individuals taller than 1.8 or shorter than 1.5 m.[75,147] Others have suggested that repair of TAAAs should be considered in patients with aortas twice the size of a normal continuous segment or approximately 6 cm in diameter.[84]

Based on natural history studies documenting an extremely high risk for rupture and death if a TAAA is left untreated, all patients with TAAAs should be considered for repair.[40,46,148] The natural history of ruptured TAAAs was first studied extensively by Crawford and colleagues.[149] In a series of more than 100 ruptured TAAAs, the authors noted that 80% of ruptures occurred in patients with aneurysms that were less than 10 cm in diameter. The presence of an aortic dissection portended rupture at smaller diameters, with a reported 13% of ruptures occurring in aneurysms smaller than 6 cm. Rupture occurred in the thoracic and abdominal cavity with approximately equal frequency. They concluded by suggesting that because elective surgery was associated with a 92% survival rate, TAAA repair should be considered before rupture when aneurysms are 5 cm or larger in good-risk patients, in patients with symptomatic aneurysms, and in most patients with larger aneurysms.

In a large Scandinavian autopsy series, Juvonen and colleagues suggested that 6 cm should be the threshold for open TAAA repair.[51] More recently, Elefteriades suggested that the size criteria for surgical TAAA intervention should be greater than 6.5 cm. The author believe that this threshold should be lowered for patients with connective tissue disorders, in whom repair should be offered when the aneurysm attains a diameter of 6.0 cm.[150] A positive family history for aortic rupture or dissection might also serve to lower the threshold for repair. Coady and coauthors suggested that in asymptomatic TAAA patients who are monitored longitudinally, there are "hinge points" that demarcate highly dangerous aortic thresholds.[48] For the descending thoracic aorta, the hinge point is 7 cm, where a 43% risk for rupture is encountered. This suggests a "conservative" criterion of 6.5 cm for surgical intervention in TAAAs.

Because multiple studies have suggested increased mortality and morbidity—particularly spinal cord ischemia (SCI)—for types I, II and III TAAAs, perhaps a higher threshold for repair (6 cm) should be used in these patients. In contrast, patients with less extensive aneurysms, such as type IV TAAAs, might be better served to undergo repair at a diameter of 5.5 cm. Although patients with symptoms should undergo TAAA repair even if their aneurysm has not attained a certain threshold size, the threshold for repair should be tailored to the individual surgeon and institutional results. In our practice, for most patients we utilize a threshold for repair of 6 cm, and this threshold has not changed with the advent of TEVAR.

PREOPERATIVE EVALUATION

The physiologic stress on a patient undergoing open TAAA repair is unparalleled, and it is to be emphasized that the preoperative evaluation detailed herein will probably differ substantially as a function of the mode of operative repair. The initial evaluation of a patient with a TAAA begins with a thorough history and physical examination focusing on the patient's cardiac, pulmonary, and renal function. Imaging studies are reviewed to determine the operative plan. Standard preoperative laboratory testing, electrocardiography (ECG), and chest radiography should be performed. Guidelines for perioperative evaluation prior to repair of open surgical and endovascular thoracic aortic repairs have been created (Table 76.8).[4] Patterson and colleagues developed an externally validated risk-stratification model for patients undergoing elective TEVAR comprising six easily obtainable variables (Table 76.9). The authors stress that while the decision to offer repair to a particular patient must be individualized, the risk model can lead to a more informed discussion with the patient.[151]

Cardiac

The presence of coronary artery disease varies based on the aortic pathology being treated. Because the typical patient undergoing TAAA repair is elderly, compared with a patient with a connective tissue disorder with a dissection, impaired myocardial function and the presence of atherosclerotic disease of the coronary arteries are common in patients undergoing aneurysm repair.[153,154] In landmark studies in patients before undergoing AAA repair, Hertzer and colleagues documented that 42% had significant coronary artery disease in the setting of ischemic cardiac symptoms. Importantly, 19% of the patients who were symptom-free also had significant coronary artery disease. Given the high prevalence of coronary artery disease combined with the stress of this operation, cardiac disease is

TABLE 76.8 Recommendations for Preoperative Evaluation for Patients Undergoing TAA Repair[4]

Class/Level of Evidence	Recommendation
I/C	In preparation for surgery, imaging studies adequate to establish the extent of disease and the potential limits of the planned procedure are recommended. Patients with thoracic aortic disease requiring a surgical or catheter-based intervention who have symptoms or other findings of myocardial ischemia should undergo additional studies to determine the presence of significant coronary artery disease (CAD). Patients with unstable coronary syndromes and significant CAD should undergo revascularization prior to or at the time of thoracic aortic surgery or endovascular intervention with percutaneous coronary intervention or concomitant coronary artery bypass surgery.
IIa/C	Additional testing is reasonable to quantify the patient's comorbid states and develop a risk profile. These may include pulmonary function tests, cardiac catheterization, aortography, 24-hour Holter monitoring, noninvasive carotid screening, brain imaging, and neurocognitive testing.
IIb/B	For patients who are to undergo surgery or endovascular intervention for descending thoracic aneurysm and who have clinically stable but significant (flow limiting) CAD, the benefits of coronary revascularization are not well established.

TABLE 76.9 Risk Factors Predictive of Perioperative Mortality Following Thoracic Endovascular Aneurysm Repair[152]

Risk Factor	Hazards Ratio	*P* Value
Age	1.04[a]	<0.001
Renal insufficiency	1.68	0.002
History of stroke	1.58	0.011
Placement of >2 devices	1.46	0.018
Maximal aneurysm diameter	1.02[b]	0.01

[a]Per year of age.
[b]Per millimeter of diameter increase.
All-cause mortality score = 0.0398 × (age) + 0.516 × (renal insufficiency) + 0.46 × (previous history of cerebrovascular disease) + 0.352 × (prior tobacco use) + 0.376 × (number of devices > 2) + 0.016 × (maximum aneurysm diameter).
Categorical variable expressed as "1" if present, "0" if absent.

the leading cause of mortality after open TAAA repair,[72,76] including 49% of early deaths and one third of late deaths. Therefore, before TAAA repair, all patients should undergo extensive evaluation of their coronary arteries and heart valves.

The preoperative ECG in a hypertensive patient with a degenerative TAAA may suggest left ventricular hypertrophy. There may also be evidence of ischemic heart disease. Although noninvasive stress testing can often predict areas of reversible ischemia and may be useful in an asymptomatic patient, the use of coronary angiography in patients with suspected atherosclerotic coronary disease (e.g., angina, low ejection fraction, previous coronary artery bypass grafting [CABG]) may be indicated (see Chapter 42).

In the elective setting, coronary artery revascularization may be indicated. If the patient undergoes coronary stenting, clopidogrel is used for a minimum of 6 weeks, which will delay TAAA repair. The use of drug-eluting coronary stents typically requires lifelong clopidogrel use. In addition, if the patient is to undergo CABG, use of the left internal mammary artery is discouraged, primarily because it serves as an important collateral to the spinal cord as well as the chest wall.

Echocardiography, most often transesophageal echocardiography (TEE), is helpful in demonstrating left ventricular function and concomitant valvular abnormalities. TEE is also useful in evaluating the ascending and descending thoracic aorta. There are many advantages to TEE over other modalities, including the ability to perform it in the emergency room or operating room. It can also be safely used in patients with renal insufficiency to assess ascending and descending thoracic aortic size as well as the presence of dissection. However, TEE may not be widely available in the emergency setting and is operator-dependent.

Recent authoritative guidelines reflect the uncertain value of extensive preoperative cardiac evaluation in patients undergoing TEVAR in the presence of stable coronary disease, even if this workup prompts percutaneous or surgical cardiac revascularization. Bub and colleagues reviewed their experience involving 395 high-risk patients undergoing complex endovascular thoracoabdominal and juxtarenal aneurysm repairs. Overall, 7% of patients suffered a myocardial infarction, and 30-day cardiac-related mortality was only 2%. Of the total, 73% and 65% of patients underwent preoperative stress testing and echocardiography, respectively. Among the 85% of patients who had a negative stress test, 6% suffered a postoperative myocardial infarction, similar to the 7% of those with a positive test. The majority of the patients with positive stress tests were managed either medically after cardiac catheterization or were cleared by their cardiologists with no further testing. Only 30% of patients ultimately underwent percutaneous coronary intervention, and one quarter of them suffered a postoperative myocardial infarction.[155]

Another similar study stratified perioperative cardiac outcomes following TEVAR by extent of cardiac evaluation. Of 352 stable patients, 95% underwent only resting ECG or TTE and then proceeded to operation. Only 5% required additional cardiology evaluation and 1% underwent coronary angiography or revascularization. Those patients with more risk factors were more likely to undergo a more extensive workup. In this population,

only 2.4% of patients suffered a postoperative myocardial infarction, all in patients evaluated solely with ECG or TTE; this was a relationship found not to be statistically significant.[156] Taken together, these studies call into question the utility of routine extensive preoperative cardiac evaluation even among high-risk patients undergoing endovascular repair.

Pulmonary

Pulmonary complications after open TAAA repair are common, with the incidence of COPD estimated to be between 30% and 40%. COPD is also associated with increased perioperative mortality after TAAA repair.[76,157] Pulmonary function tests and arterial blood gas analysis are performed routinely. Preoperative maneuvers to improve pulmonary function before TAAA repair include immediate cessation of smoking, use of appropriate bronchodilators, and rarely the administration of preoperative steroids when an acute exacerbation of reactive airway disease occurs. Patients can also be placed on an exercise program to improve lung capacity and be required to lose weight if obesity accompanies their lung disease. In a study of patients with COPD undergoing elective open AAA repair, fewer prescribed inhalers, lower hematocrit, renal insufficiency, and coronary artery disease were associated with unfavorable outcomes.[158] Preservation of the left recurrent laryngeal and phrenic nerves is an important adjunct to decrease the incidence of pulmonary complications in these patients.

Renal

Review of a large series of patients undergoing open TAAA repair suggested that the rate of renal failure postoperatively ranges from 5% to 40%, with an attendant mortality rate as high as 70%.[159-162] Acute renal failure also predicts increased nonrenal complications postoperatively, including respiratory failure. Second only to aortic rupture, chronic renal insufficiency is the strongest predictor of perioperative acute renal failure and mortality after TAAA repair (Fig. 76.10).[152,163] Therefore evaluation of renal function before TAAA repair, whether open or endovascular, is imperative.[152] A full 15% of patients with TAAAs will have some degree of chronic renal insufficiency as defined by a creatinine level of 1.8 mg/dL (159 µmol/L) or greater.[24]

Preoperative renal insufficiency is such a strong predictor of poor outcome after type II to type V TAAA repair that it has been suggested to be a relative contraindication to proceed with repair. Huynh and coworkers documented that calculation of the glomerular filtration rate is a better predictor of outcome after TAAA repair than serum creatinine.[164] Cross-sectional imaging will aid the surgeon in evaluating diminutive kidney size and the often associated renovascular atherosclerotic disease. If physiologic testing is required, duplex ultrasonography will provide information regarding the severity of ostial atherosclerotic disease, based on velocities, as well as parenchymal function, based on resistive indices. In performing TAAA repair in patients with renal failure, it is imperative that severe renal artery occlusive disease be treated intraoperatively by endarterectomy, stenting, or bypass grafting with the expectation that renal function will not worsen.[165,166] Stenting before TAAA repair to theoretically improve renal function has been reported.[167]

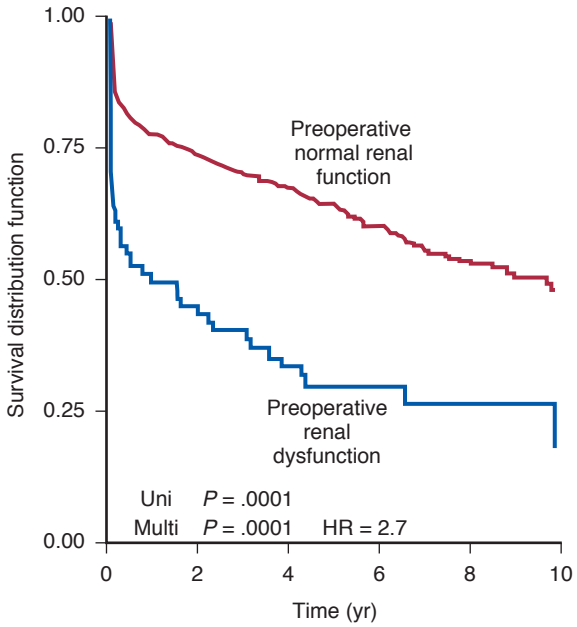

Figure 76.10 Ten-year actuarial survival for patients undergoing thoracoabdominal aortic aneurysm repair with and without preoperative renal failure. *HR,* Hazard ratio.

Preoperative intravenous hydration, as well as avoidance of nephrotoxic agents such as iodinated contrast material, is indicated. Although national trends have moved away from admitting patients preoperatively to the hospital, this group of patients, especially if their visceral arteries are to be bypassed, should probably still be admitted to the hospital and undergo both bowel preparation and intravenous hydration. The rationale for this strategy is reduction in the risk for bacterial translocation, especially in the setting of visceral ischemia during placement of a synthetic graft at the time of TAAA repair.[168]

Functional Status

The preoperative functional status of patients undergoing TAAA is critical in evaluating risk. Hua and coworkers, using the National Surgical Quality Improvement Program database in patients undergoing AAA repair, suggest that "poor functional status" predicts mortality.[169] Although TAAA repair has been shown to improve survival, Zierer and coauthors, in a recent report, examined the late functional status and quality of life of asymptomatic patients undergoing elective repair.[170] Over a 5-year period, 110 asymptomatic patients underwent elective thoracic aortic replacement for ascending, descending, or thoracoabdominal aneurysms. Functional status, physical and psychological quality of life, and survival were assessed. The results documented that return to normal activity levels was independent of age and procedure. At a mean of 35 months, psychological quality of life was similar between the various surgical groups, but physical quality of life was lower after

thoracoabdominal than after ascending or descending aneurysm repair (P <.02). Importantly, age did not affect physical quality of life, and, interestingly, older patients had improved psychological quality of life. The overall survival rate was 70% at 4 years and was lower for thoracoabdominal than for ascending or descending aneurysms (P <.002). The authors suggested that advanced age does not impair return to normal functional status and that patients with asymptomatic thoracic aneurysms thus should not be denied elective replacement based on age alone, because functional recovery is not significantly impaired.[171]

Patients considered for TAA repair are often old and frail, with multiple medical comorbidities. In these circumstances, there may be reluctance to offer repair with the expectation that the elderly patient is unlikely to accrue much benefit from intervention. Rango and colleagues reviewed their TEVAR experience in treating patients with aortic pathology isolated to the descending thoracic aorta and found that although, overall, patients aged 75 years and older were at four times the mortality risk of younger patients, most of the mortality difference stemmed from the fact that aged patients underwent surgery in the setting of an emergency or rupture. Elective outcomes were similar among older and younger patients. Furthermore, older patients survived on average 54 months after their repairs, with 57% and 84% 3-year overall and aneurysm-related survival. As noted in the study by Zierer et al., the authors argue that elective treatment should not be withheld based on age criteria alone and, in fact, elderly patients might be better served by aggressive elective intervention as opposed to emergency intervention for rupture.[172]

Although most of these studies have focused on perioperative functional status, Rigberg and colleagues documented that late (1-year) survival was poor after open TAAA repair and decreased with patient age.[173] Another study by Crawford and coworkers also investigated late (5-year) functional status after open TAAA repair. These authors concluded that permanent loss of functional capacity occurs only rarely in survivors of TAAA repair, but they also noted the difficulty in obtaining appropriate controls for studies such as this.[174]

Addressing quality-of-life issues between open aortic repair and TEVAR, Dick and associates performed a post hoc analysis of a prospectively collected (between January 2001 and December 2005) consecutive series of 136 patients with surgical diseases of the descending aorta. Endpoints included perioperative and late mortality rates as well as long-term quality of life as assessed by the Short Form Health Survey and Hospital Anxiety and Depression Score questionnaires. The study documented no differences in perioperative mortality rates (9% for open repair versus 8% for TEVAR, P = .254). Cumulative long-term mortality rates were similar in both cohorts. Overall quality-of-life scores were 93 (63-110) for open repair and 83 (60-112) for TEVAR and were not significantly different. Anxiety and depression scores were not increased after open surgery. The authors suggest that both TEVAR and open aortic repair provide excellent long-term results in the treatment of thoracic aortic disease and thus provide little aid in helping us counsel patients on which type of repair they should seek.[171]

OTHER PATHOLOGIES ASSOCIATED WITH THE THORACIC AORTA

Aberrant Right Subclavian Artery

Although multiple and various brachiocephalic congenital abnormalities have been described, the most common variant is an aberrant right subclavian artery. This anomaly is associated with the right subclavian artery taking a course posterior to the esophagus. As many as 80% of individuals with this anomaly will develop dysphagia (*dysphagia lusoria*) as the artery grows larger with the patient's growth.[4] The artery itself, as it enlarges, develops a Kommerell diverticulum. This artery will often become aneurysmal and is associated with thoracic aortic dissections and aneurysms. Although initial treatment of this condition was surgical resection of the proximal right subclavian artery and replacement of it and the abnormal section of the descending thoracic aorta with a graft, reports describe a hybrid approach in managing the aberrant right subclavian, where a bypass from the right common carotid artery to the distal right subclavian artery is performed with ligation of the right subclavian artery proximal to the vertebral artery. This is followed by stent grafting of the abnormal descending thoracic aorta.[175] It must be added that it is imperative that prior to covering the origin of the right subclavian artery, coil embolization of side branches off the aberrant subclavian artery be performed. Often, to achieve proximal seal, the origin of the left subclavian artery must also be excluded, which then requires left carotid subclavian bypass or transposition.

Coarctation of the Aorta

Coarctation of the aorta is relatively common congenital abnormality occurring in approximately 40 to 50 of 100,000 live births.[4] On physical examination, patients may have a disparate exam between their upper extremity and lower extremity pulses. Although this finding is most often managed soon after birth or in childhood by nonvascular surgeons, some patients may present later with resultant heart failure, refractory hypertension, or diminished pulses. It is important to diagnose and treat this pathology because, if left untreated, it is uniformly fatal. Surgical options depend on the location of the coarctation, but coarctation discovered in the thoracoabdominal aorta is typically managed by patch aortoplasty or thoracoabdominal bypass.[176,177] Congenital stenoses of the renal and mesenteric arteries are also commonly seen in these patients and can be managed concurrently in the same surgical setting.[178-180]

Vascular surgeons may be called on to help manage previously repaired coarctations in the descending aorta that present later in life with patch pseudoaneurysms. The use of both uncovered and covered stents have been described and appear to be effective. A recent review by the Cochrane Group concludes that there is insufficient evidence with regard to the best treatment for coarctation of the thoracic aorta. The authors suggested a randomized, controlled trial was needed.[181]

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77 CHAPTER

Thoracic and Thoracoabdominal Aneurysms: Open Surgical Treatment

CHARLES W. ACHER and MARTHA WYNN

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The surgical repair of descending thoracic aorta (DTA) and especially thoracoabdominal aortic aneurysms (TAAA) remains one of the major challenges in vascular surgery because of the technical demands of the surgery, which may require reattaching brachiocephalic, visceral, renal, and intercostal arteries (ICA) to a synthetic graft or aortic homograft, as well as the physiologic stress of the surgery, which can result in stroke, renal failure, cardiac or pulmonary failure, and paraplegia leading to significant disability, decline in quality of life, and death. The first successes in treating thoracic aortic disease were by Crawford, Gross, and Etheridge. The difficulty of thoracic aortic surgery was documented early in aortic surgical history by Adams' 1954 landmark paper on paraplegia causation and risk in thoracic aortic surgery, where he described the anatomy of spinal cord blood flow and the high mortality and paralysis risk of 25% in attempts at just thoracic aortic repair. Ten years later, DeBakey reported 50% mortality in his first small series of TAAA repair.[1,2]

The modern era of surgical treatment of TAAA began with E. Stanley Crawford, who in his first published series in 1974, reported significant reductions in mortality and paraplegia rates accomplished without assisted circulation (AC-cardiopulmonary bypass).[3] With his lifetime experience of over 1500 TAAA, achieving an overall mortality of 8% and paralysis risk of 16%, Stanley Crawford set the standard for a generation of surgeons.[4]

Despite improved outcomes reported from major centers in the modern era with mortality and paraplegia rates <7% in elective operations,[5] high mortality and morbidity continue to occur as demonstrated in two administrative database studies that documented 20% or higher elective mortality and equally high paraplegia rates in smaller lower volume centers attempting treatment of these challenging complex aneurysms.[6,7] In this chapter, we explore how the different pathologies encountered affect surgical approach and treatment indications, the mechanics

Abstract

The fundamental principles of open thoracoabdominal aneurysm repair have remained remarkably stable with controlled hypothermia, spinal fluid drainage and optimized mean arterial pressure and cardiac function as the primary interventions to minimize paraplegia risk from surgical repair regardless of the technique of repair. These interventions along with neurochemical protection and the addition of staging of repair of the most extensive aneurysms when possible have reduced paralysis risk by 85% to 90% when applied stringently and reduced mortality by 50%. With the advent of thoracic endovascular repair, staging in patients with aortic aneurysm and dissection requires newer anastomotic techniques to sew surgical aortic grafts to endografts, making it possible to convert a more difficult Crawford type 2 repair to a type 3 or 4 repair, which is less stressful on the elderly patient; and the combined treatment options has significantly changed the way surgeons approach open repair. However, open thoracoabdominal aneurysm repair remains a very complex and high-risk surgery that requires equally experienced anesthesia, surgical, and intensive care teams working in concert to optimize probability of successful treatment.

Keywords

Thoracoabdominal
Aortic aneurysm
Open aneurysm repair
hybrid aneurysm repair

of repair, and how experienced centers have been able to reduce morbidity and mortality of open surgical repair. To understand paraplegia and mortality risk more comprehensively, we explore how observed/expected (O/E) ratios are calculated for paraplegia from a predictive model that was previously published using clinical factors (extent of aortic replacement and clinical acuity and dissection) to compensate for differing populations in clinical reports.[8] Data from our own experience from treating over 1000 patients and a database of over 15,000 patients from published reports are also described.

PATHOLOGY

Aneurysm causation and pathologic classification are discussed in Chapter 76. It is important, however, for the surgeon to understand the pathology involved in an individual patient, because it can affect technical considerations in thoracoabdominal aneurysm repair.

DEGENERATIVE

Degenerative aneurysms are the most common TAAA, usually occurring in older patients who have atherosclerosis and smoked. The pathogenesis is complex and associated with the inflammation of atherosclerosis and the individual's response to injury through matrix metalloproteinases and collagen remodeling of the aorta.[9–14] Degenerative aneurysms are more likely calcified to varying degrees and may have a damaged and poorly functioning intimal surface covered with debris from plaque and old thrombus, as well as plaque stenosis or occlusion of branch vessels, which makes repair and revascularization more difficult. These older atherosclerotic patients may also have significant cardiac, pulmonary, and renal comorbidities, as well as the infirmities of advanced age, significantly increasing treatment risk. Although not common, the inflammatory response in degenerative aneurysms can be so severe that they fall into a category called "inflammatory aneurysms" in which the periaortic structures, such as branch vessels, ureters, bowels, or mediastinal structures are encased in a dense retroperitoneal fibrosis that makes surgery especially difficult.[15,16]

INHERITABLE

The known heritable pathologies such as Marfan, Ehlers-Danlos, and Loeys-Deitz syndromes[17–20] are defined by known genetic mutations that create abnormalities in elastin and collagen and TGF Beta receptors that weaken the aortic wall leading to aortic aneurysms and dissections that usually occur in younger patients. It is also increasingly apparent that similar mutations account for familial aneurysms and other noncategorized patients predisposed to aneurysms and aortic dissection (Fig. 77.1).[21–25] The quality of the aortic tissue the surgeon is required to work with may vary within a group depending on the severity of the structural defect and differences between pathologic groups with Ehlers-Danlos and Loeys-Deitz patients having more fragile aortas than Marfan patients.[26,27] These differences may require different surgical techniques with less traumatic vascular clamps, using hypothermic circulatory arrest (HCA) to avoid clamping, or the use of aortic wall reinforcement with felt pledgets or strips to secure the suture line because of tissue fragility. In some patients, for example, some severe types of Ehlers-Danlos syndrome, surgical repair may not be a viable option (see Chapter 10).[28,29]

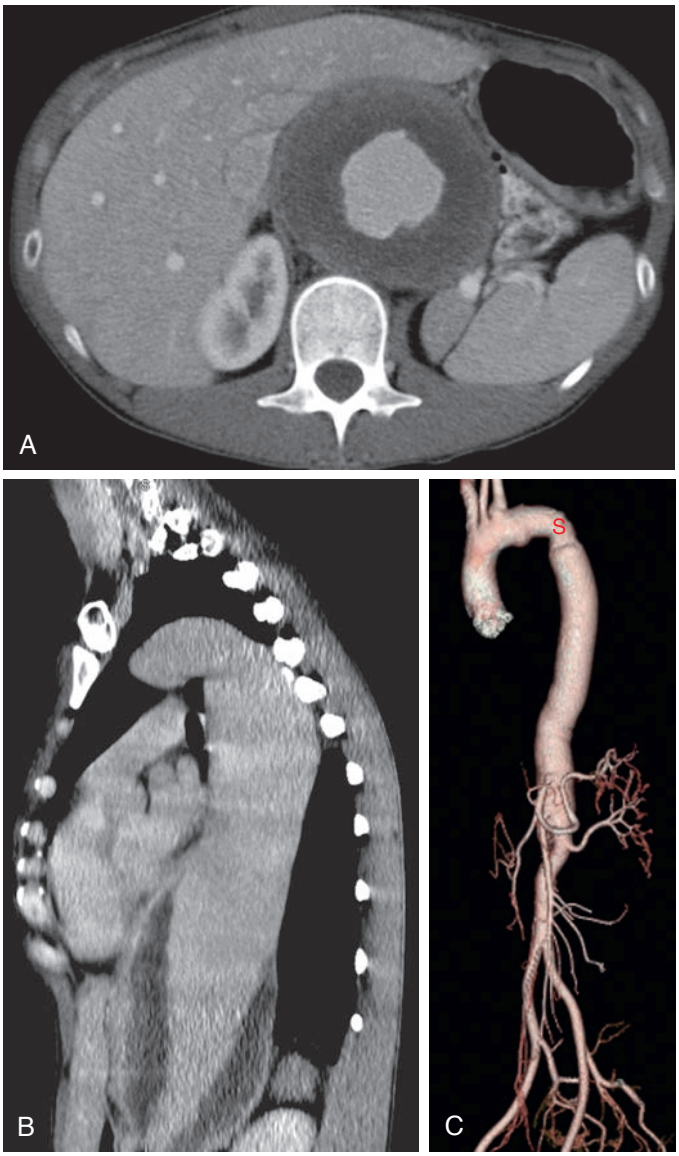


Figure 77.1 (A and B) A very large thoracoabdominal aneurysm in a 32-year-old woman (5′4″, 110 lbs) with no family history or stigmata of Marfan, Loeys-Deitz, or Ehlers-Danlos syndromes and no elevated inflammatory markers. Presented with vague chest pain and fatigue. At repair (C) the proximal neck was wrapped with a Dacron sleeve to prevent future expansion. Patients like this are undefined genetically but obviously have some molecular defect, which more than likely will be defined within the next decade from research efforts such as the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC).

TRAUMA, MYCOTIC, VASCULITIS

Clinical presentation also poses significant challenges for the surgeon as in trauma with multiple injuries or mycotic aortitis

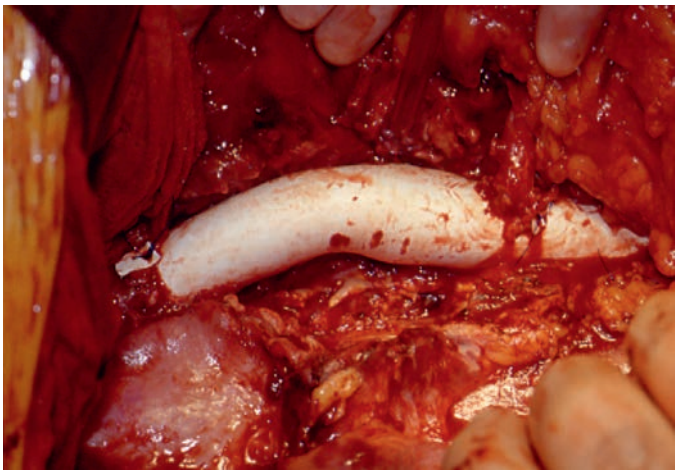


Figure 77.2 The fundamental principle in mycotic thoracoabdominal aneurysm is radical debridement of all infected aortic and periaortic tissue as seen here in a patient who developed a mycotic thoracoabdominal aneurysm from an *Escherichia coli* urinary tract infection and required debridement of the distal third of the thoracic and all the abdominal aorta with in situ aortic reconstruction using a Teflon graft.

where treatment requires radical aortic and periaortic debridement with *in situ* repair (Fig. 77.2) or aortic oversewing with extra-anatomic bypass in desperate situations.[30]

Thoracoabdominal aneurysm associated with the vasculitis of rheumatoid diseases (ankylosing spondylitis)[31–33] or the vasculitis of Takayasu disease, lupus erythematosus, or giant cell arteritis, which although uncommon, they may have associated branch vessel occlusive disease and cardiac and pulmonary involvement that can complicate repair.[34–36]

ANATOMIC CLASSIFICATION

Aneurysms of the thoracoabdominal aorta are classified anatomically (see Chapter 76) primarily by extent of aortic involvement, which is associated with the surgical complexity of repair. Crawford type 2 have the greatest paralysis risk followed by Crawford types 1, 3, 4, and thoracic aortic aneurysms (TAA), which are confined to the distal arch and DTA and have the lowest paralysis risk from surgery.[37]

Aortic dissections have a different classification based on origin and extent of the dissection and the need for immediate surgery (Stanford A) and those historically treated medically with antihypertensives which originate in the distal arch or more commonly in the DTA at or near the ligamentum arteriosum and left subclavian artery (Stanford B) (see Chapter 76). These classifications capture most but not all of the variation seen clinically and in general indicate increased risk of stroke and paralysis associated with repair.[38–40]

INDICATIONS FOR SURGICAL TREATMENT

The primary indication for treatment of aortic aneurysms is rupture risk, which is generally considered to correlate with aortic diameter in accordance with Laplace's law. A larger aneurysm and thinner wall increases the likelihood of rupture, which usually results in death. Some TAAA become very large (>10 cm) before rupture and invariably have thick walls that allow such unusual size before structural failure occurs. However, there is considerable variation in TAAA diameter at the time of rupture or other acute event (dissection, plaque hemorrhage), which in our experience averages 8.2 ± 2.8 cm (median 7.4 cm) with only 13% of all ruptures occurring below 6 cm and rarely below 5.5 cm.

Griepp, Elefteriades, and others have performed extensive research on the natural history of thoracic aneurysms.[41–47] These natural history studies indicate that beside diameter and pain, age, the presence of chronic obstructive pulmonary disease (COPD) or renal insufficiency, the extent of the aneurysm, and the expansion rate of the aneurysm are independent risk factors for rupture.[48–55] The growth rate for DTA (0.42 cm per year) found by Hirose was the same as the growth rate for AAA found in the ADAM trial.[56,57]

The dilemma in TAAA repair, because of the significantly greater surgical risk than infrarenal AAA repair, is if and then when to treat. Most aortic surgeons put the threshold for risk benefit at about 6 cm from natural history information weighed against surgical risk and long-term survival.[42,46,48,58–61] It is known from these observational studies that 40% to 50% of patients die of other causes before rupture, making the decision for aneurysm treatment much more complex than just natural history, physics, and molecular biology. Furthermore, individual patients have differing treatment and rupture risks related to pathology, age, comorbidities, and personal preference.

Other indications, such as occlusive or aneurysmal disease of branch vessels (mesenteric or renal ischemia, brachiocephalic, visceral, or iliac aneurysms), may lead to treatment of smaller TAAAs. Similarly, acute events of aortic plaque rupture, mycotic aortitis, trauma, renal failure from obstructive uropathy in inflammatory aneurysms, or malperfusion in acute dissection may require aortic repair or bypass with little aneurysmal dilatation. Some patients have significant aneurysm enlargement in the ascending aorta and arch in addition to the thoracoabdominal aorta that requires staged repair, which presents unique technical challenges. In addition to all these factors, new dilemmas are created because of new and advancing endovascular technologies that may require surgical rescue because of failure or surgery to treat aneurysm progression above or below previously placed endografts. The surgeon may also decide to stage or combine open and endograft repair for ascending arch and descending aneurysm repair (see Chapters 78-80).

PATIENT EVALUATION

The decision to treat begins with and is clarified by evaluation of cardiac, pulmonary, renal, and overall vitality factors to establish patient fitness for elective surgery (see Chapter 32). This evaluation is expensive and time consuming for patients and families, but it is important when discussing operative risk.

IMAGING

Aortic and branch vessel imaging primarily with magnetic resonance imaging (MRI) and computed axial tomographic angiography (CTA) is important for identifying extent of pathology for preoperative planning (see Chapters 27 and 28). The improved resolution and quality of imaging that has occurred over the last 15 years allows identification of patent ICA of interest, detailed understanding of complex dissection anatomy, and plaque morphology. A newer and exciting imaging technique is four-dimensional MRA. With this MRI technique, detailed anatomy and flow dynamics such as velocities, flow rates, wall stress, and pressure gradients can be measured noninvasively, which increases our clinical understanding of the effects of treatment, as well as the complex flow and stress dynamics in aneurysms and aortic dissection.[62–64]

INFORMED CONSENT

Informed consent for complex high-risk surgeries for life-threatening diseases is a difficult and nuanced process that should give the patient a realistic understanding of what you face as the surgeon and what they face as the patient, which must include the worst case scenario along with the best if the patient is to make a decision consistent with his goals in treatment.[65–67] Especially because of the risks of paraplegia, stroke, and renal failure in addition to possible ventilator dependence in marginal patients facing DTA or TAAA surgery, the consent conversation has to be a realistic discussion of probability and uncertainty surrounding surgery and what life will be like if the surgical effort fails to return the patient to his preoperative functional status. The older the patient the more selective both surgeon and patient should be about treatment.

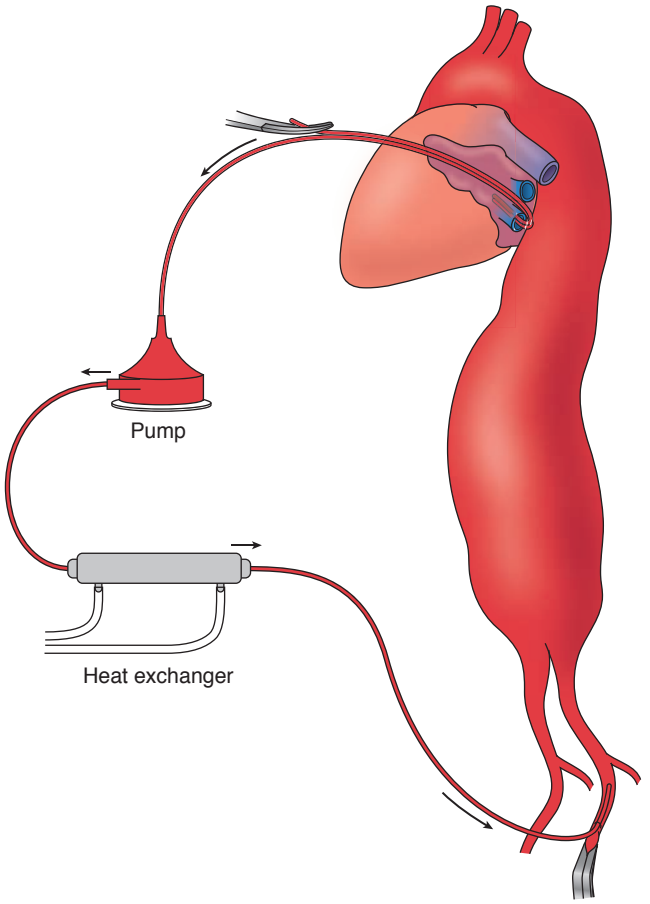


Figure 77.3 Left heart bypass is the most commonly used technique of assisted circulation and is dependent on the lungs for oxygenation and the heart as the primary pump. The circuit is from the left atrium via direct cannulation or through the pulmonary vein to a centrifugal pump back into the arterial circulation (the femoral artery most commonly).

SURGICAL REPAIR

Once the decision for surgery has been made, the surgeon and anesthesiologist must develop and execute the plan for repair. That plan depends on anatomy and pathology that can vary greatly between patients, requiring the surgeon and anesthesiologist to adapt. In addition to patient variation, surgeons may favor different surgical approaches ranging from simple cross clamp (Crawford technique) with adjunctive measures to protect the kidneys and spinal cord, assisted circulation-AC (atrial femoral or femoral femoral bypass), or HCA.

Extracorporeal Circulation

AC is usually atrial-femoral (partial heart bypass) with oxygenated blood coming from a left atrial or left pulmonary vein cannula to a centrifugal pump that feeds a femoral artery cannula that can retrograde perfuse the pelvic and visceral arteries during proximal repair (Fig. 77.3). The bypass flow rate is adjustable, so proximal and distal arterial perfusion pressures can be maintained and is an effective technique to off load the heart, reducing cardiac strain with very proximal aortic clamping. This technique is dependent on the heart and lungs for oxygenation and cerebral circulation but does not require full systemic heparinization. HCA requires complete cardiopulmonary bypass with arterial perfusion cannulas in the femoral artery or ascending aorta and venous return through a femoral vein cannula that usually extends to the right atrial level and superior vena cava and is placed with guidewire and transesophageal echocardiography to confirm location. A left ventricular sump drain is required to prevent cardiac dilatation and pulmonary congestion during cardiopulmonary bypass. Patients are cooled to 16 to 18°C, and then circulation is arrested during the proximal anastomosis after which cerebral perfusion is resumed through a side arm on the aortic graft while the remaining aorta is reconstructed. HCA is a complex procedure because of longer pump runs and coagulopathy with bleeding made worse by the large surface area of a thoracoabdominal incision. Profound hypothermia provides excellent organ protection during aortic reconstruction; however, because of its complexity, this technique is used the least.

Other Perfusion Techniques

Distal aortic perfusion and selective perfusion of the mesenteric arteries can be achieved without pump devices. The Gott shunt

and external axillofemoral artery bypass have been used as a passive bypass circuit for repair of DTA and TAAA.[68,69] Cambria describes an in-line mesenteric shunt technique that restores pulsatile flow to the mesenteric circulation within 25 minutes, even in the absence of distal aortic perfusion. This technique is used in combination with renal artery perfusion with 4°C renal preservation solution.[70] Cambria, however, has abandoned epidural cooling because of poor results. Each technique has advantages and disadvantages.

Our approach is to simplify the surgery as much as possible but vary the surgical technique depending on anatomy and pathology. Therefore, most of the time we use Crawford's technique of simple cross clamping with adjuncts (hypothermia, spinal fluid drainage, steroids, endorphin receptor antagonists, and optimizing perfusion pressure and cardiac function) that Crawford did not use to protect the spinal cord, kidneys, and other organs.[71] When anatomy dictates (no place to proximally clamp the aorta or occasionally in acute dissection) we use HCA. Our surgical approach is based on experimental studies of the effects of aortic occlusion and preservation of spinal cord, renal, and other organ function. This chapter demonstrates experimentally how validated protective adjuncts work regardless of surgical technique and that equal results can be obtained with all techniques if experimentally demonstrated protective principles are followed.

ANESTHESIA

The anesthesia for TAAA repair is complex, requiring multisystem monitoring and control. Arterial lines in the upper (radial artery) and lower (femoral artery) extremities, pulmonary artery catheter for monitoring cardiodynamics (cardiac index [CI], central venous pressure, pulmonary artery pressures), and transesophageal echo to evaluate ventricular function and valve function are used to optimize mean arterial pressure and cardiac function. Electroencephalogram (EEG) monitors central nervous system activity because barbiturates are used to reduce oxygen demand[72] prior to and during aortic occlusion. Blood and nasopharyngeal temperature are monitored, because these correlate with spinal fluid and brain temperature. Coagulation parameters, blood chemistries, and arterial blood gases are closely monitored throughout surgery. A 16 French Medtronic lumbar spinal drain is fluoroscopically placed in most patients to monitor and control spinal fluid pressure (SFP) by draining spinal fluid to improve spinal cord blood flow during aortic occlusion.[73] The anesthesiologist uses vasoactive medications to control arterial pressure and maximize cardiac function. Arterial dilators such as nitroprusside and hydralazine are avoided because of their experimentally demonstrated stealing effect on spinal cord blood flow.[74] Infusing sodium bicarbonate (0.05 meq/kg per min) while the aorta is occluded above the renal arteries prevents systemic acidemia. Our group administers methylprednisolone after induction and naloxone (1 μg/kg per hour) is infused during and after the procedure.[75,76] Mannitol is given before and during aortic occlusion and after renal reperfusion. When one lung ventilation is required in extensive proximal aortic replacement, we use an Arndt endobronchial blocker, bronchoscopically placed using a guidewire,[77] which we think is easier and safer than a double lumen endotracheal tube. This technique provides excellent lung isolation without the need to change endotracheal tubes at the end of surgery. Moderate systemic hypothermia (31-34°C) is used to prolong spinal cord and organ ischemic tolerance. Aggressive blood component replacement is important to prevent coagulopathy.

During the surgical exposure, the anesthesiologist cools the patient (34°C or lower) with a cold operating room and intravenous (IV) fluids. As the time for aortic clamping approaches, our anesthesiologists drain enough spinal fluid to achieve a SFP less than 6 mm Hg during aortic occlusion. Timing this requires close communication between the surgeon and anesthesiologist. If assisted circulation (cardiopulmonary bypass, circulatory arrest, or atrial femoral bypass) is used, we complete the exposure dissection before cannulation and heparinization to minimize bleeding. These assisted circulation patients require additional exposure, depending on surgeon preference for cannulation of the femoral artery and vein, left ventricle apex, ascending aorta, left atrium, or pulmonary veins

During surgical reconstruction, the anesthesiologist assures the patient is volume resuscitated with blood reclaimed from the high-speed cell saver, red blood cells, and fresh frozen plasma to replace coagulation factors from blood loss. The anesthesiologist's goal is to optimize tissue oxygen delivery, intravascular volume, cardiac function, and arterial perfusion pressure (MAP >90 mm Hg), in addition to keeping the SFP low without draining excessive fluid. Unless the anesthesiologist is aggressive and proactive in managing cardiac function, fluid resuscitation, and preventing coagulopathy, hypovolemia, and hypotension, the patient will have increased risk of coagulopathy, paraplegia, renal failure, cardiac ischemia, and death. The anesthesiologist is as important as the surgeon in the success of these complicated aortic reconstructions.

When surgery is done using assisted circulation, the anesthetic management must adjust primarily to prevent the proximal relative hypotension associated with left heart bypass that puts the spinal cord at increased risk because of reduced perfusion pressure to the collateral circulation. This negative effect is exacerbated if hypothermia is not used. To maintain proximal and distal MAP greater than 90 mm Hg while on partial bypass requires aggressive volume replacement, inotropes, and vasopressors. This is even true in hypothermic arrest where the very potent spinal cord protective effects of profound hypothermia can be undone during rewarming if a low MAP is allowed and the patient is made normothermic.

PATIENT POSITIONING

For a thoracoabdominal incision, the patient is positioned in a lateral decubitus position with the left side up. The shoulders are usually vertical, but the pelvis is tilted so the left femoral artery and vein can be easily accessed for aortofemoral bypass, arterial line, or cannulation if left heart bypass is planned. Extreme pelvic tilting can expose the right groin for access to those vessels (Fig. 77.4A). We use an Olympic Vac-Pak patient

positioner (beanbag) with inner gel pad to secure the patient in this position.

SURGICAL EXPOSURE

The level of the incision is determined by what portion of the aorta is to be replaced (see Fig. 77.4B; Chapter 53). An aneurysm confined to the DTA may only require a thoracotomy in the 4th, 5th, 6th, or 7th intercostal space depending on the extent of aortic involvement. A Crawford type 3 or 4 replacement allows extraperitoneal exposure via the 8th or 9th intercostal space, but a Crawford type 1 or 2 requires incision at the 5th or 6th intercostal space with intraabdominal exposure with the spleen, colon, and left kidney mobilized medially off the retroperitoneal space. Posterior "shingling" of the ribs is usually done with the higher costal incisions to minimize rib fracture with the rib spreader (see Figs. 77.4C, D and 77.5A). In such cases, the diaphragm is incised through the aortic hiatus, which allows compete exposure of the descending thoracic and abdominal aorta with its visceral branches, and the iliac arteries if necessary (see Figs. 77.5B, C and 77.6A, C). Some surgeons spare the central diaphragm and some use two incisions, a higher thoracotomy and a lower thoracoabdominal extraperitoneal incision, believing that this reduces pulmonary morbidity, but this approach obscures the anatomy making surgical repair more difficult with only a modest decrease in prolonged ventilation (36% vs. 48%) without any demonstrable decrease in mortality.[78]

If the patient has had previous aortic or thoracic surgery, the exposure can be more difficult because of periaortic scaring, inflammation, and adhesions, especially lung adhesions to the parietal pleura, which can be very tedious to take down and can result in lung injury with bleeding or air leaks. We usually dissect and expose the celiac, superior mesenteric, and left renal arteries, but if the aneurysm is very large or is inflammatory, the mesenteric exposure may be too difficult and is avoided. In the case of associated mesenteric ischemia, the superior

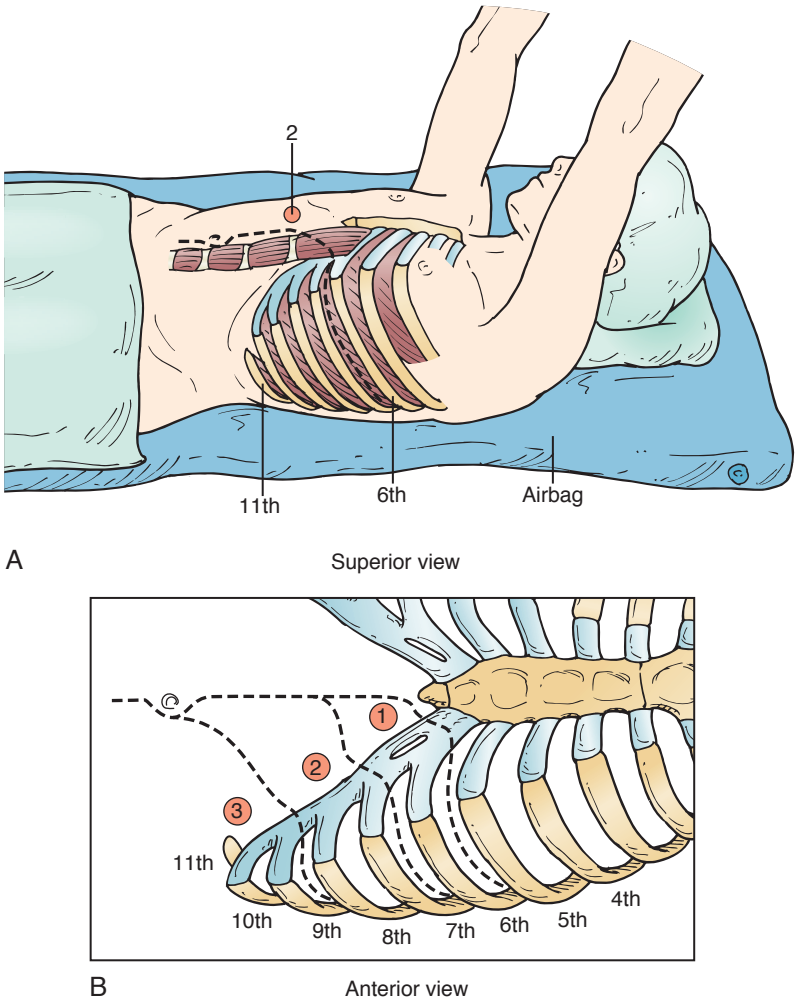


Figure 77.4 (A and B) The lower the interspace of the incision the lower the risk of pulmonary complications so the lowest incision is chosen that allows aortic repair. Aneurysms at the arch level usually require a 5th interspace incision, whereas type 3 and 4 aneurysms can be repaired with an incision in the 8th or 9th interspace, with extraperitoneal exposure. In older patients and in patients with elevated body mass index, in addition to cutting the costochondral junction, the ribs are cut posteriorly to create a controlled cut instead of a fracture.

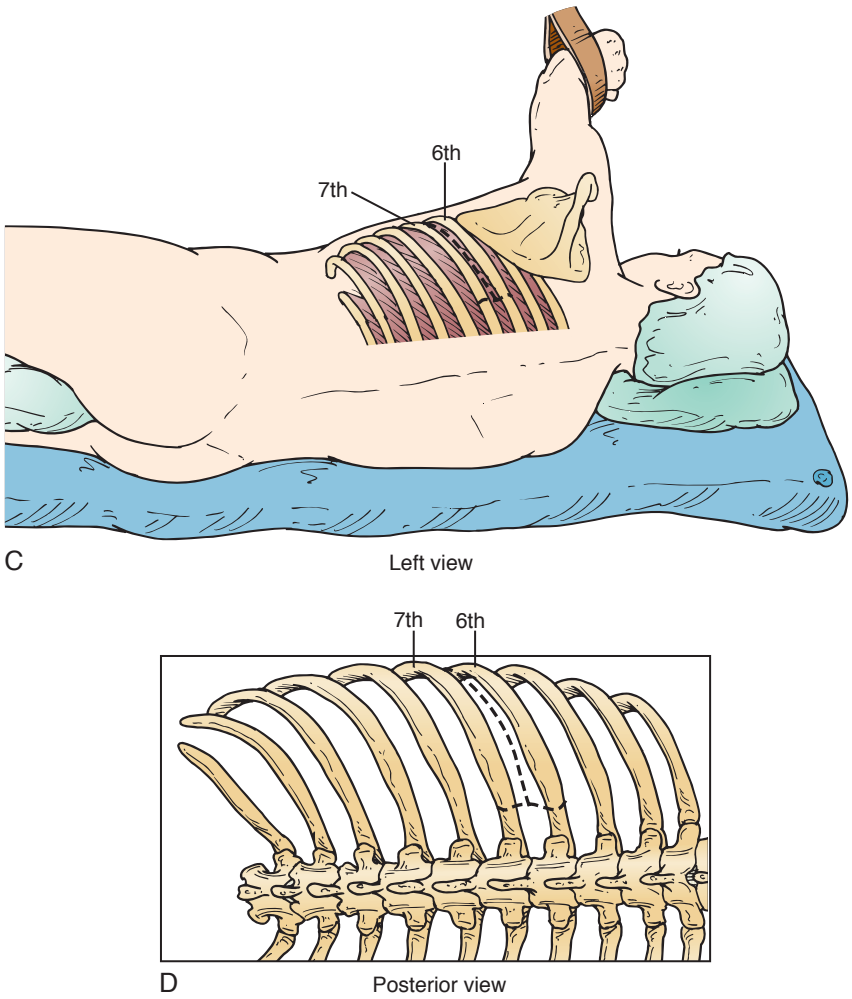


Figure 77.4, cont'd **(C and D)** As much of the latissimus dorsi and serratus anterior is preserved as possible by incising them lower than the interspace to be opened.

mesenteric artery (SMA) can be exposed more completely if necessary by dissecting anterior to the kidney between the peritoneal sac and Gerota's fascia. Occasionally, the left renal vein is retro-aortic, requiring the surgeon to work around it and/or divide it for re-anastomosis after aneurysm repair (see Fig. 77.6B).

The extent of exposure of the arch vessels depends on where the proximal aortic clamp is placed and requires avoidance of injury to the phrenic nerve and the vagus, and its recurrent branch because injury to these nerves increases the risk of pulmonary complications. Patients should be informed preoperatively about recurrent nerve injury and the resulting vocal cord dysfunction, which cannot always be avoided and occurs in about 10% of patients where the proximal anastomosis is at or proximal to the left subclavian artery. Also at this level, the ligamentum arteriosum is usually divided for more complete arch exposure. Occasionally in emergencies with a large mediastinal or arch hematoma or in the case of a very large proximal aorta, the pericardium is opened to obtain easier access to the proximal arch for aortic control. Patients with aneurysms from chronic dissections or with anomalous arch anatomy present special challenges and operative planning. The patient in Fig. 77.7A is an example of difficult arch anatomy because of an aneurysmal aberrant right subclavian artery in a dissected arch. Only after a right carotid subclavian transposition, which was staged a month before his TAAA repair, could the arch be safely crossclamped and the aneurysm be repaired (see Fig. 77.7B).

The left iliac artery is easily seen and exposed, but the right may require dividing the inferior mesenteric artery (IMA) at its origin to mobilize the distal aorta for better access to the right iliac artery. If the IMA is patent and large, it may be important for colonic perfusion and require reattachment, although this is uncommon. The ureters, especially the left, are vulnerable to injury in inflammatory aortas or redo surgery and in such cases, ureteral stents can be placed prior to surgery so the ureters can be identified more easily. It is important to take the time to get complete enough anatomic exposure in anticipation of problems that might develop (such as a need for a more proximal clamp or more distal exposure) so that if the need arises, further dissection is not necessary after aortic occlusion.

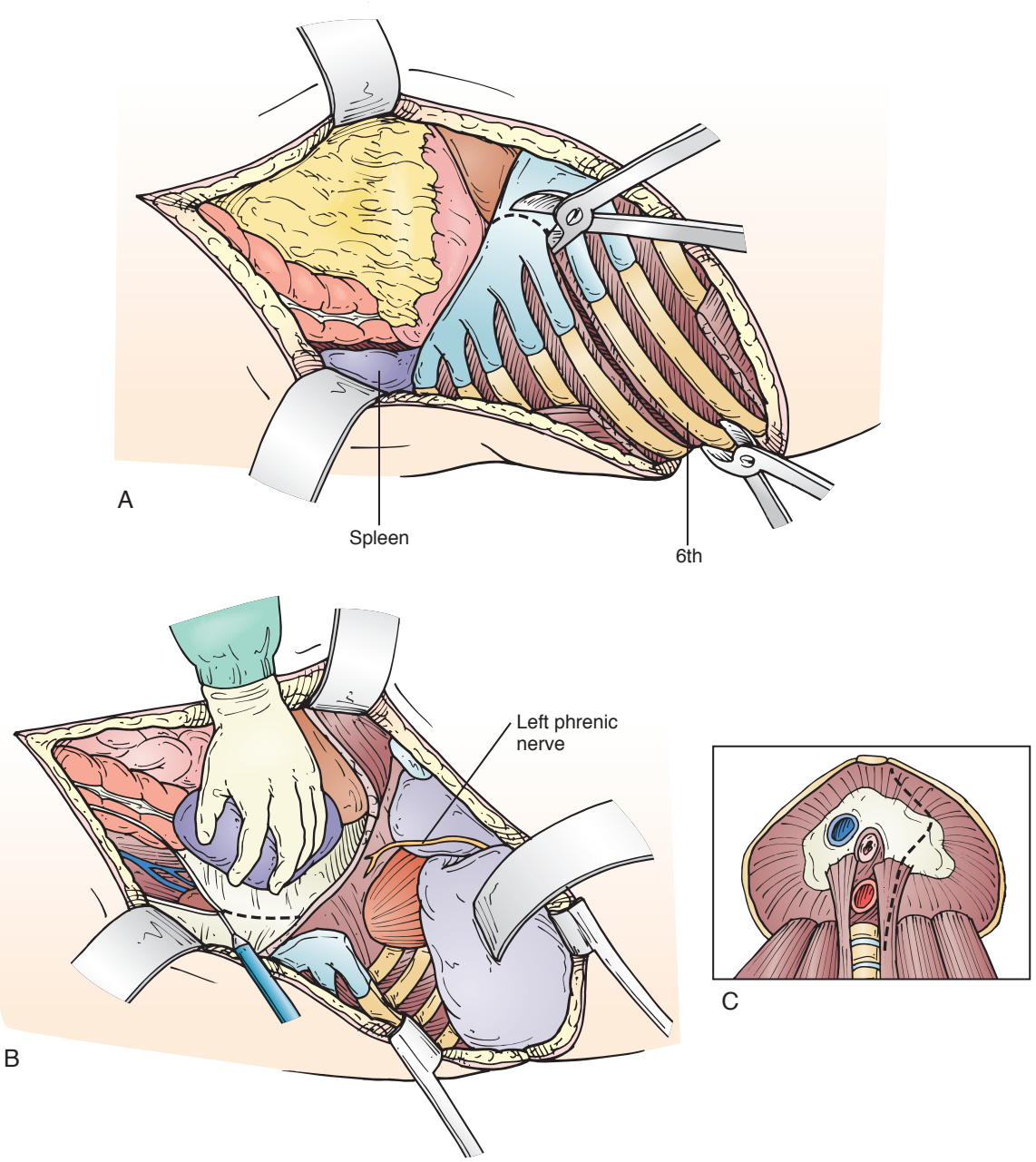


Figure 77.5 **(A-C)** After incising the diaphragm down to the peritoneal reflection, the spleen, pancreas, colon, and left kidney are mobilized off the retroperitoneum. It is important to not dissect into the psoas fascia but open Gerota's fascia posteriorly closer to the midline so the retroperitoneal periaortic space can be easily seen and exposed. Occasionally, dissection is also anterior to the left kidney to gain access to more of the superior mesenteric artery.

ANEURYSM REPAIR

Initial Clamping

With the simple crossclamp surgical technique, heparin flush (1000 units/L) is used on the field. Systemic heparin is used if patients have previous aortic grafts or if clamping is proximal to the subclavian or carotid arteries and then the dose is small (3000-5000 units). In patients with AC (partial bypass) heparin requirements are reduced, and ACTs are monitored. With complete heart bypass (hypothermic arrest) total systemic heparinization is required (400 units/kg).

Once the exposure is complete and the systolic pressure is <100 mm Hg, temperature <34°C, SFP <6 mm Hg and barbiturate burst suppression is initiated, the aorta is crossclamped and the aneurysm is opened for repair. Mean arterial pressure is kept at greater than 100 mm Hg while the aorta is clamped. If there are many open ICA and/or assisted circulation is used, a distal or distal sequential clamp technique is used to avoid what can be exsanguinating back bleeding from open intercostal and lumbar arteries. In aneurysms of just the DTA, we usually do not re-attach ICA; but in TAAA patients before or after opening the aneurysm, the ICA chosen for reimplantation by preoperative MRA and/or patency and location at surgery are temporarily

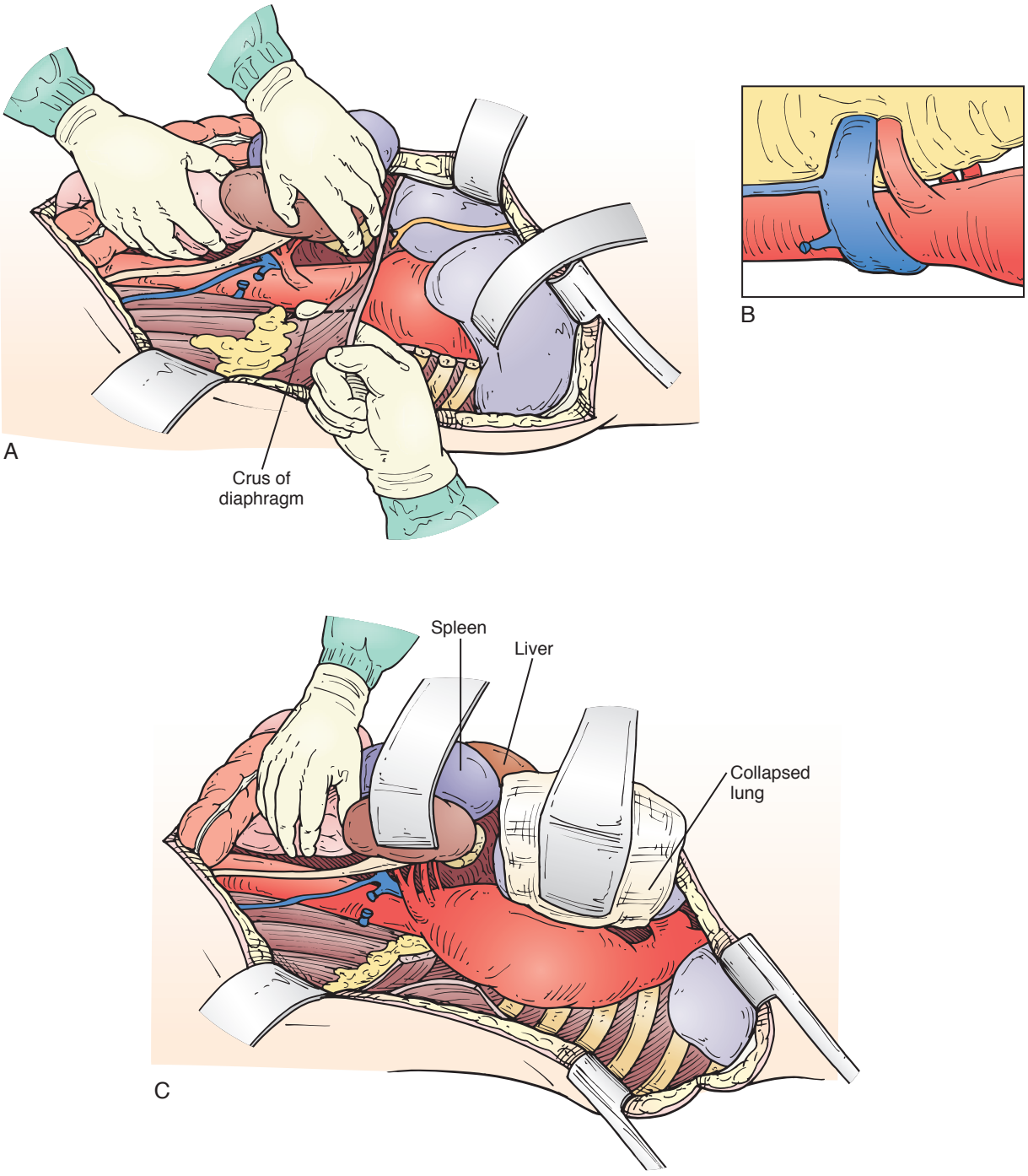


Figure 77.6 **(A)** After mobilizing renal and visceral structures off the retroperitoneal space, the diaphragm is incised through the aortic hiatus, the inferior pulmonary ligament is divided with cautery, and the periaortic lymph tissue is divided exposing the thoracoabdominal aorta. **(C)** We usually dissect the first few centimeters of the left renal and visceral arteries. Occasionally, a retroperitoneal left renal vein is encountered **(B)** which we preserve by dividing between two straight DeBakey vascular clamps and then sewing it back together after the arterial reconstruction is done.

occluded using micro bulldog clamps (usually 2-4 arteries between T8 and L2), and the remaining intercostal and lumbar vessels are quickly oversewn to minimize blood loss and maximize collateral perfusion pressure. Similarly, Fogarty balloon catheters are used to occlude the visceral and renal arteries. At this point, the renal artery orifices are exposed, and each kidney is cooled with 300 to 400 mL of cold (4°C) renal perfusion solution (12.5 g of mannitol and 1000 units of heparin/L of lactated Ringers). This gives hypothermic renal protection and further lowers the body temperature to 31 to 32°C to enhance spinal cord and end organ ischemic tolerance. This sudden volume infusion increases SFP, which may require more drainage to keep the SFP low.

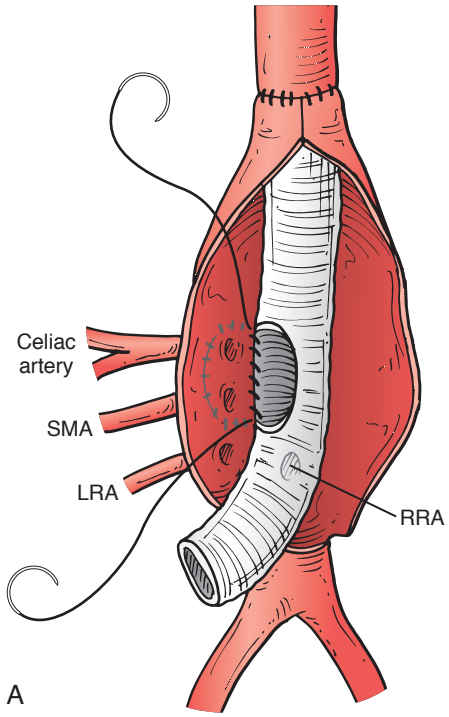
Figure 77.7 Marfan patient with an 8-cm Crawford type 2 aneurysm from a chronic dissection from an acute type A dissection presents additional challenges because of an aneurysmal aberrant right subclavian artery shown from the posterior view (A). Right carotid subclavian transposition was done prior to TAAA repair to fix the subclavian aneurysm and secure the arch for crossclamp and TAAA repair (B). Even though the dissection runs through the arch, it is not aneurysmal and is suitable for clamping and suturing a graft with felt reinforcement.

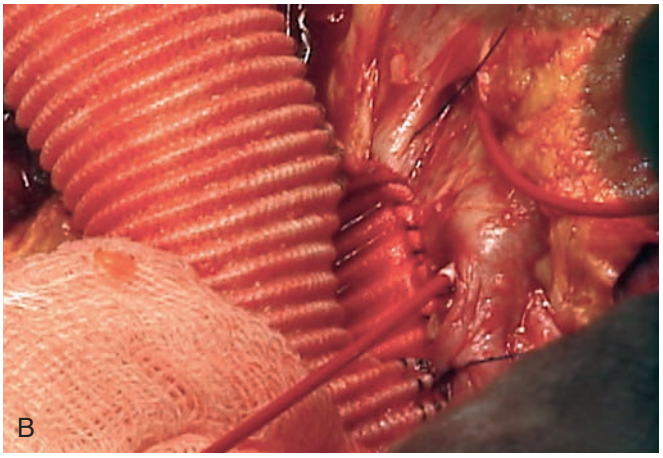
Proximal Anastomosis

After completing this portion of the operation, the proximal graft aortic anastomosis is performed using 2-0 Prolene on a large CT1 needle most of the time. Depending on the tissue integrity (dissection, calcium requiring aortic endarterectomy, or just a fragile thin aortic wall), a finer suture or needle (3-0 suture or SH needle) and/or felt strips or pledgets may be used to reinforce the anastomosis. An important technical point is that all anastomosis should be done so the aorta is not repeatedly crossclamped to repair leaks. This requires a little more time but makes for a faster less traumatic anastomosis. After completing the proximal anastomosis, the patient is put in Trendelenburg, and the anastomotic integrity is tested by placing a vascular clamp on the graft after flushing (to remove air and thrombus that can cause a stroke via the arch vessels) and removing the proximal clamp. If there is a leak requiring attention, we will usually repair this with a pledgeted stitch without reclamping the aorta.

Visceral-Renal Reattachment

The next stage of the repair is visceral and renal artery reattachment, which is usually done with a Carrel patch directly to the aortic graft (Fig. 77.8A-C). The patch configuration is





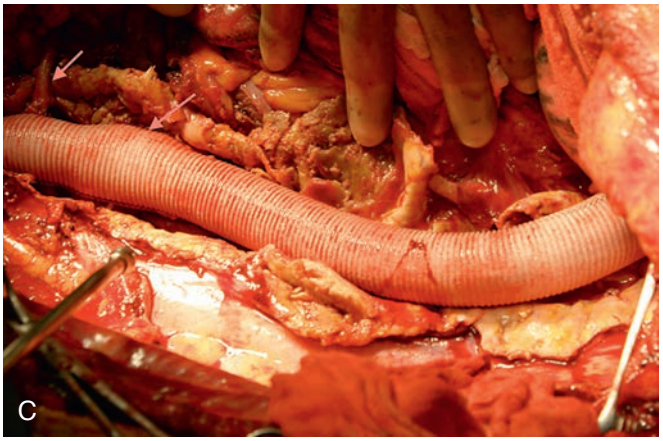


Figure 77.8 (A) When attaching visceral and renal arteries to the graft, it is important to keep the Carrel patch as narrow (small) as possible so patch aneurysms do not form. Spacing between the vessels determines patch configuration, and if the vessels are too far apart, they are attached individually. (B) Photo of sewing a visceral patch comprising the celiac and SMA with their balloon catheters in place. These are removed after establishing blood flow to that portion of the aorta. (C) is the completed graft within the aneurysm sac with arrows to the visceral patch and left renal artery. *LRA,* Left renal artery; *RRA,* right renal artery; *SMA,* superior mesenteric artery.

determined by the spacing of the vessels and the most common configuration is the celiac, SMA, and right renal in one patch and the left renal artery attached separately. Another common grouping is the celiac and SMA in one patch and both renal arteries attached separately. The Carrel patch is kept as narrow as possible to avoid patch aneurysms, but if the vessels are spaced too far apart, they are attached individually to avoid a large visceral patch that is prone to aneurysm dilatation over time. There is a tendency by inexperienced surgeons to sew all the visceral vessels on one patch or create a too large proximal bevel and this more often than not leads to problems later.[79] In our experience, by using the above principles for visceral patch reconstruction, we avoid patch aneurysms. However, individual bypass grafts to the visceral arteries is another strategy that has been advocated with the Coselli branched graft specifically designed for this,[80] especially in patients with connective tissue disorders such as Marfan syndrome, because patch aneurysms are more prevalent in patients with connective tissue disease. In about a third of patients, an endarterectomy of some or all the renal and visceral vessels is required (Fig. 77.9A, B) because of calcified plaque with or without stenosis. If the renal or visceral artery has been previously stented, the stent is usually removed with the endarterectomy plaque. Some surgeons prefer bypass or direct stenting rather than endarterectomy because of possible flap dissection beyond the endarterectomy endpoint, which can require additional exposure and artery repair to avoid occlusion. However, the superior long-term patency of a properly endarterectomized artery is why we prefer endarterectomy. A bypass to a renal or visceral vessel may be necessary, however, if the endarterectomy fails or if the artery is aneurysmal or too distant from the graft surface for easy no tension reattachment. In patients with dissections, the dissection flap may extend some distance into a visceral or renal artery, which can create a possible flap occlusion with re-attachment. In most cases, the flap can be excised to create a common channel for re-attachment, but stenting the true lumen directly has also been proposed as an effective technique.[81]

After completing the visceral and renal reattachment, the patient again is put in the Trendelenburg position with flushing of the graft and then reestablishing blood flow to the visceral and renal arteries (by removing the Fogarty occlusion balloons). Intravenous Indigo Carmine is then given to document when urine is produced after renal reperfusion. The visceral and renal flow is evaluated with vessel palpation and a handheld Doppler to confirm normal blood flow. If there is a concern regarding patency, intraoperative duplex is used to interrogate the arteries in question. In our experience, the average time for the proximal anastomosis and reestablishing renal blood flow is 47 minutes, but it is not unusual to exceed one hour. If renal ischemia time is longer, the kidneys are flushed again with the cold renal perfusion solution.

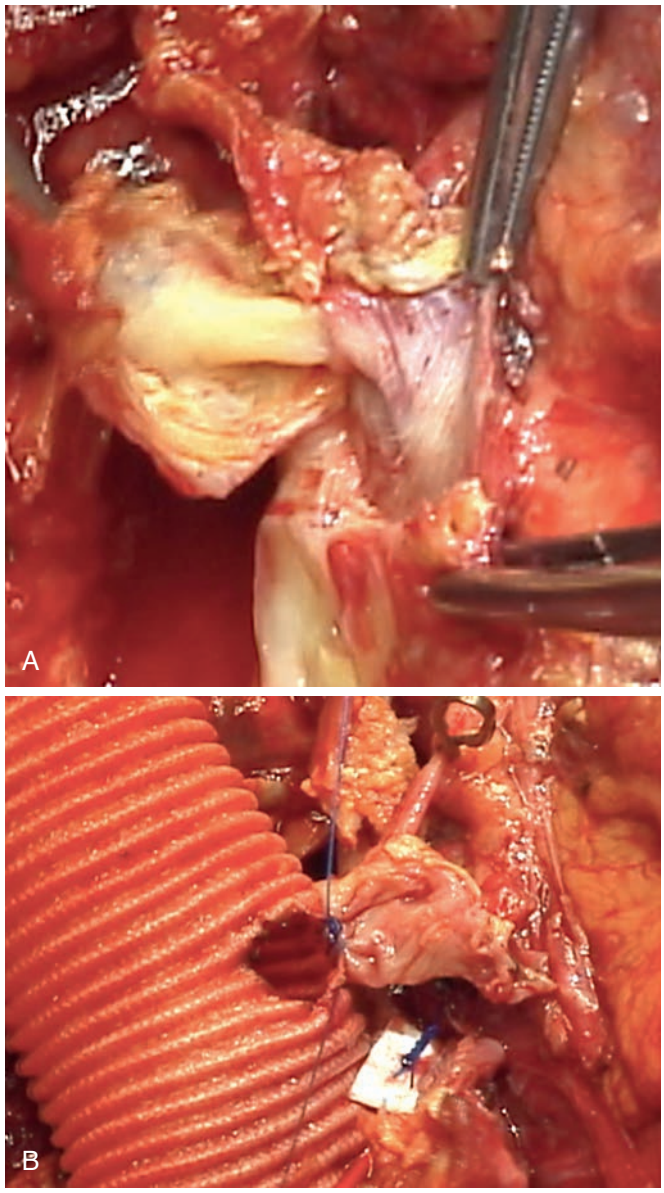


Figure 77.9 Approximately 35% of patients require a visceral and/or renal endarterectomy because of occlusive disease or a very calcified aorta or vessel orifice. This is a sequence of renal endarterectomy (A), which is attached directly to aortic graft (B).

Distal Anastomosis

After completing the visceral reattachment, the aortic graft is sutured to the distal aorta, usually at the iliac bifurcation, and after confirming there is no thrombus by back bleeding the iliac arteries and flushing the graft, the anastomosis is completed and blood flow opened to the iliac arteries. If the iliac arteries are aneurysmal and need repair, a bifurcated aortic graft is sutured to the proximal graft and the distal anastomosis is sutured to the iliac arteries or to a previously placed aortic graft in patients who have had a previous aortic surgery (infrarenal aneurysm, aortofemoral graft) or endovascular repair

Reimplanting Intercostal Arteries

It is only after finishing the aortic reconstruction that we reattach 2 to 4 ICA, which we have previously selected and preserved. This is done by side biting the aortic graft and reattaching the ICA using a button technique we have previously reported

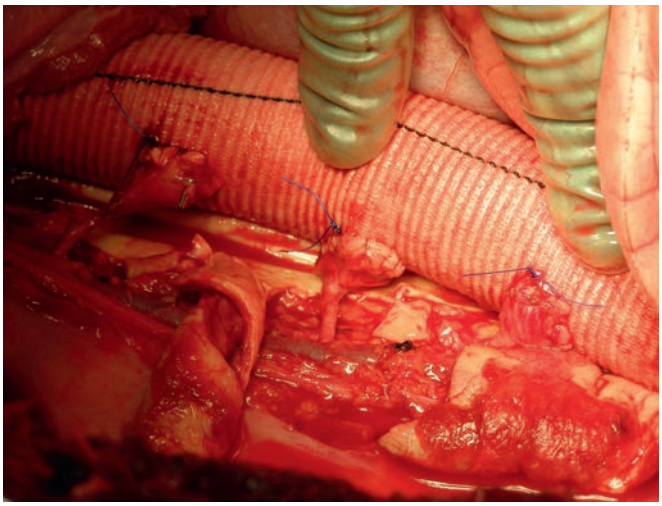


Figure 77.10 In the most extensive aneurysms with many open intercostal arteries we re-attach intercostal arteries identified with preoperative spinal artery MR angiography or by patency and location between T8 and L2 at surgery, as shown in this operative photo.

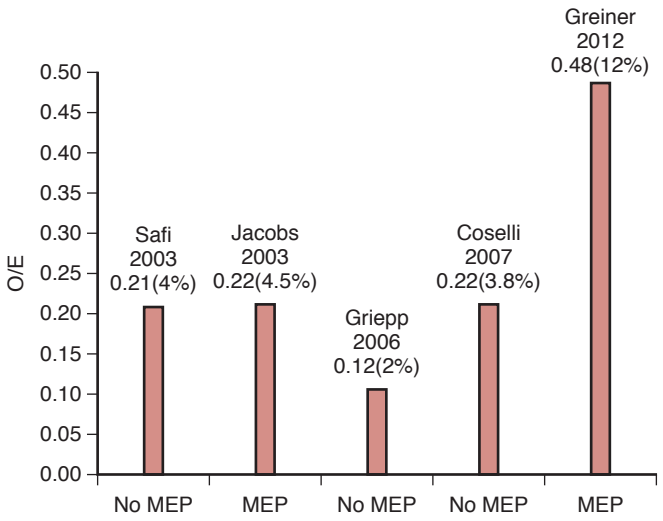


Figure 77.11 Motor evoked potentials have given us a good understanding of the relationship of mean arterial pressure to spinal cord perfusion, but the use of motor evoked potentials *(MEPs)* to select intercostals for reimplantation has not decreased the incidence of paraplegia, as indicated by comparing multiple reports with and without MEPs, which have similar observed/expected *(O/E)* ratios for paraplegia. Griepp used MEPs, but their use did not lead to intercostal re-implantation (therefore, we labeled him as no MEP); but in his and others' experience, MEP loss was reversed by raising arterial pressure.

(Fig. 77.10).[82] Although there are a variety of intercostal re-attachment techniques published, in our opinion, only those with in line flow have reasonable patency rates, while end on bypass grafts fail most often because of low flow. However, it should be acknowledged there is no good data on re-implanted intercostal patency rates.

Some surgeons use motor evoked potentials (MEPs) or somatosensory evoked potentials (SSEPs) or both to select intercostals for reimplantation, but there is little evidence that using MEPs is any more successful than other selection criteria, although MEPs may be helpful to monitor adequacy of arterial perfusion pressure.[83–87] In addition, evoked potential monitoring requires assisted circulation to prevent MEP loss due to peripheral nerve ischemia that occurs with a simple cross clamp surgical technique (and in EVAR and TEVAR with occlusive sheaths in the iliac arteries). Loss of MEPs from peripheral nerve ischemic fatigue interferes with the ability to monitor MEP changes caused by spinal cord ischemia. In addition, use of assisted circulation simply to monitor evoked potentials complicates the surgery without providing any demonstrated reduction in paralysis risk (Fig. 77.11). We re-attach ICA only in the most extensive aneurysms to reduce the risk of delayed paraplegia and sequence reattachment at the end of aortic reconstruction so organ, pelvic, and lower extremity ischemia are not prolonged. The goal is to complete the surgery in 3 to 5 hours with as little blood loss as possible using good surgical technique. Longer operations make it more difficult for the anesthesiologist to keep the patient stable.

IMPACT OF ENDOVASCULAR TREATMENT

The introduction of thoracic endovascular aortic repair (TEVAR) has added additional dimensions to open surgery by creating treatment options not previously available in treating aortic dissection, thoracic and thoracoabdominal aneurysm, and traumatic injury[88–91] In elderly patients, TEVAR has replaced open surgery and medical management for most problems confined to the DTA (see Chapter 79). However, in younger patients with longer life expectancy, TEVAR is practiced with greater restraint (the exception is traumatic aortic transection) because of perceived durability issues. There are several situations where open DTA/TAAA repair and TEVAR complement each other.

Aneurysm formation proximal to a previous open TAAA repair or staging thoracoabdominal repair with TEVAR followed by TAAA repair are examples of TEVAR's complementary potential, which may decrease treatment risk (Fig. 77.12A, B).[92] Suturing a Dacron graft to a thoracic endograft may require a modified felt technique because of size mismatch (see Fig. 77.12C). In aortic dissection, TEVAR may greatly simplify treatment in patients who eventually need surgical repair by converting a Crawford type 2 repair to a type 4 repair (Fig. 77.13A-C). Another patient we treated required open TAAA repair after a failed EVAR. Follow-up CTA revealed a retrograde thoracic dissection with a contained rupture that was treated with a TEVAR (Fig. 77.14A-C).

As indicated previously, in the modern era, aneurysms confined to the DTA are usually treated with endografts if suitable landing zones are present or can be created. For open DTA repair, the same principles apply as we have discussed for TAAA repair except that the incision is usually limited to a thoracotomy; although in aneurysm extending to the celiac artery, the costochondral margin may be cut or a thoracoabdominal incision is performed to get adequate exposure for the distal anastomosis. In DTA repair, ICAs are not reattached,

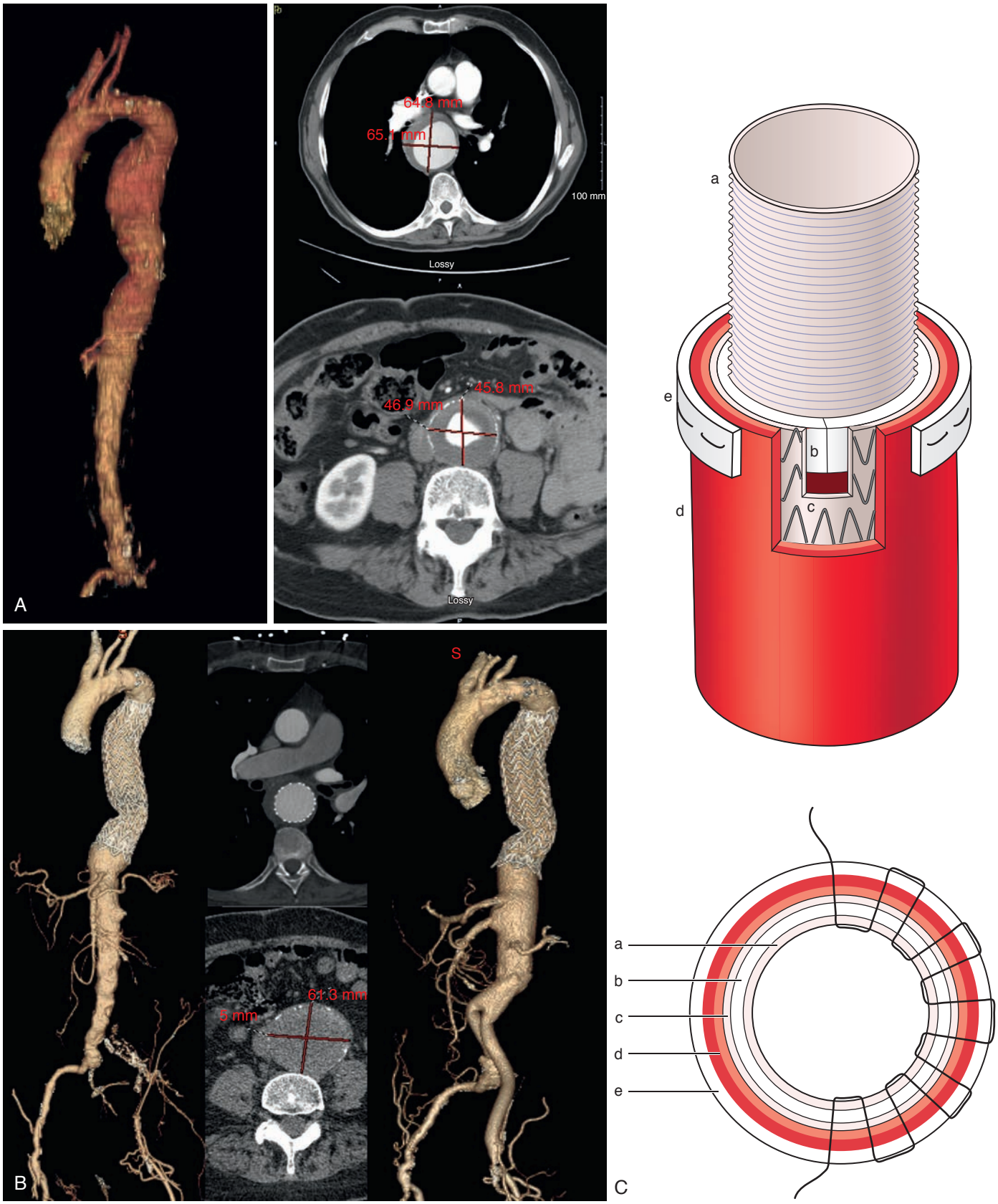


Figure 77.12 Staged repair when possible may reduce operative morbidity by allowing a lower better tolerated thoracoabdominal incision as in this patient who had the thoracic portion of a type 2 thoracoabdominal aneurysm repaired with TEVAR (A), followed 2 years later with a Type 4 TAAA repair of the remaining aneurysmal aorta with suture to the previous TEVAR (B) and avoided a higher risk Type 2 TAAA repair. (C). Sewing a Dacron graft to an endograft may require a double felt technique because of size mismatch when endografts are large diameter. In closer matched grafts, just an outer felt strip is necessary, but the aortic wall should be included with the endograft anastomosis. *a* is Dacron, *b* is inner felt strip, *c* thoracic endograft, *d* aortic wall, *e* outer felt strip and horizontal mattress suture.

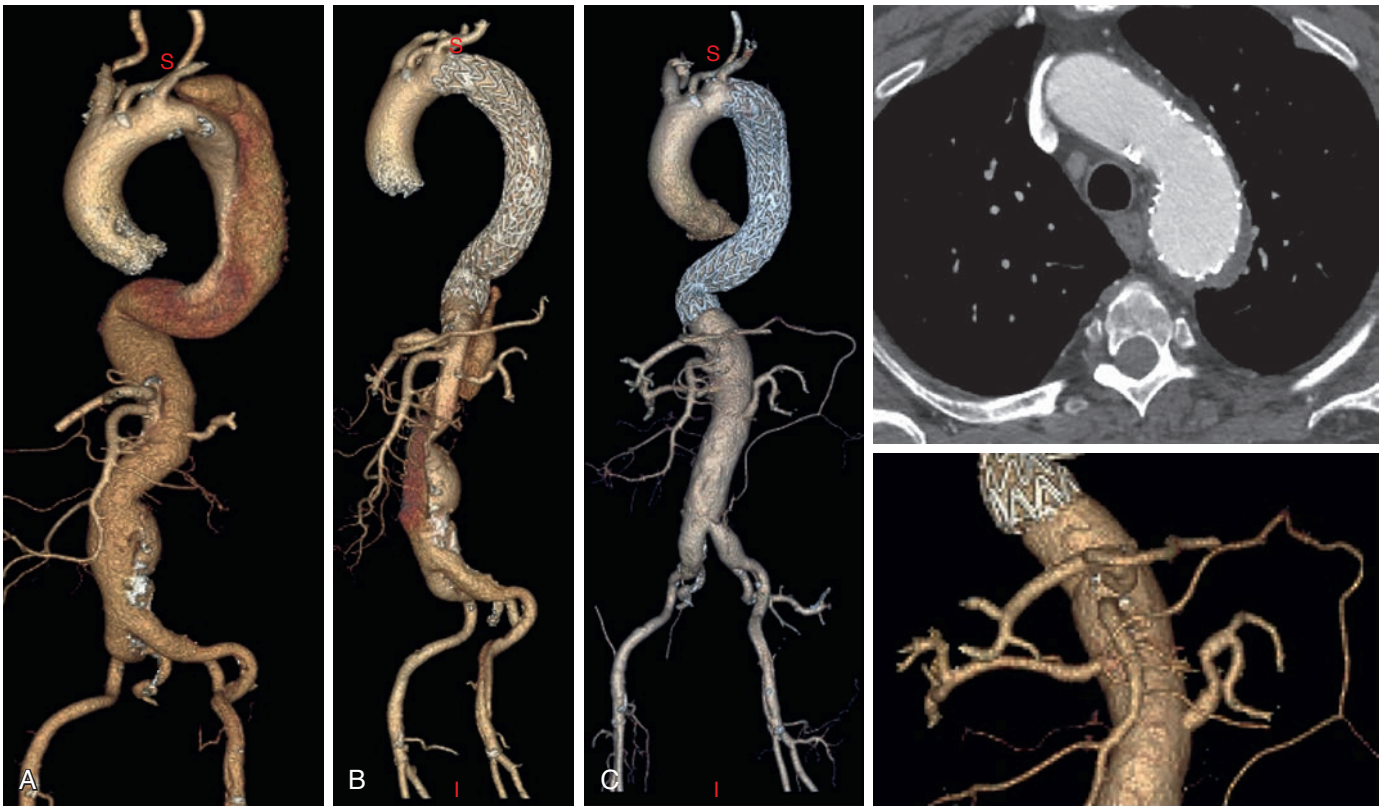


Figure 77.13 (A) An example of complete treatment of a rapidly expanding type B aortic dissection with (B) TEVAR and remodeling of the thoracic aorta. (C) Followed 9 months later with type 4 TAAA repair sutured to the thoracic endograft converting the need for type 2 subacute repair to an elective type 4 repair of a type B aortic dissection.

and direct renal perfusion cannot be done; however, we do use the other adjuncts of spinal fluid drainage (SFD) including hypothermia, steroids, mannitol, and naloxone without AC.

POSTOPERATIVE CARE

After open TAAA repair, patients are managed in the Intensive Care Unit (ICU) for 2 to 4 days depending on clinical progress. They are ventilated until adequately awake and able to breathe without assistance. This may be a few hours after repair of a Crawford type 4 aneurysm or 2 days after a Crawford type 2 aneurysm if there are no complications. Because patients are intentionally hypothermic to reduce metabolism and oxygen demand, we let them rewarm gradually with no attempt at rapid rewarming with Bair Huggers or other heating devises. Patients have continuous spinal fluid drainage to keep SFP below 6 mm Hg until they are awake enough to determine if spinal cord function is normal. After the patient can lift legs, SFP is monitored, but spinal fluid is not drained unless weakness develops. Cardiac function and hemodynamics are optimized with adequate volume replacement and inotropic support. Mean arterial pressure is kept above 90 mm Hg for the first 48 hours to maximize collateral perfusion of the spinal cord, while fresh frozen plasma and naloxone infusions are continued for 48 hours. Because of its negative effects following spinal cord ischemia, we do not use morphine for analgesia and prefer Fentanyl both intra- and postoperatively.[93] Propofol is used for sedation rather than benzodiazepines, because we want the patients to awaken easily for neurologic evaluation and weaning from the ventilator.

Delayed paralysis can occur after TAAA surgery. Delayed weakness is treated by increasing the mean arterial pressure and CI, draining spinal fluid, and restarting neuroprotective medications. In our experience, delayed deficits can sometimes be reversed if interventions are undertaken immediately. However, patients that cannot establish adequate collateral circulation to the spinal cord after surgery remain vulnerable to paralysis if spinal cord oxygen delivery is compromised by decreased cardiac function, hypotension, hypoxemia, or anemia.

OUTCOMES

Study of surgical outcomes has gone beyond operative and perioperative mortality and morbidity to include functional recovery and quality of life measures from the patient's perspective.

SPINAL CORD ISCHEMIA

Since the 1940s, spinal cord ischemia leading to paraplegia or paraparesis has been the most unpredictable and feared complication of thoracic aortic repair. Adams' landmark paper linked

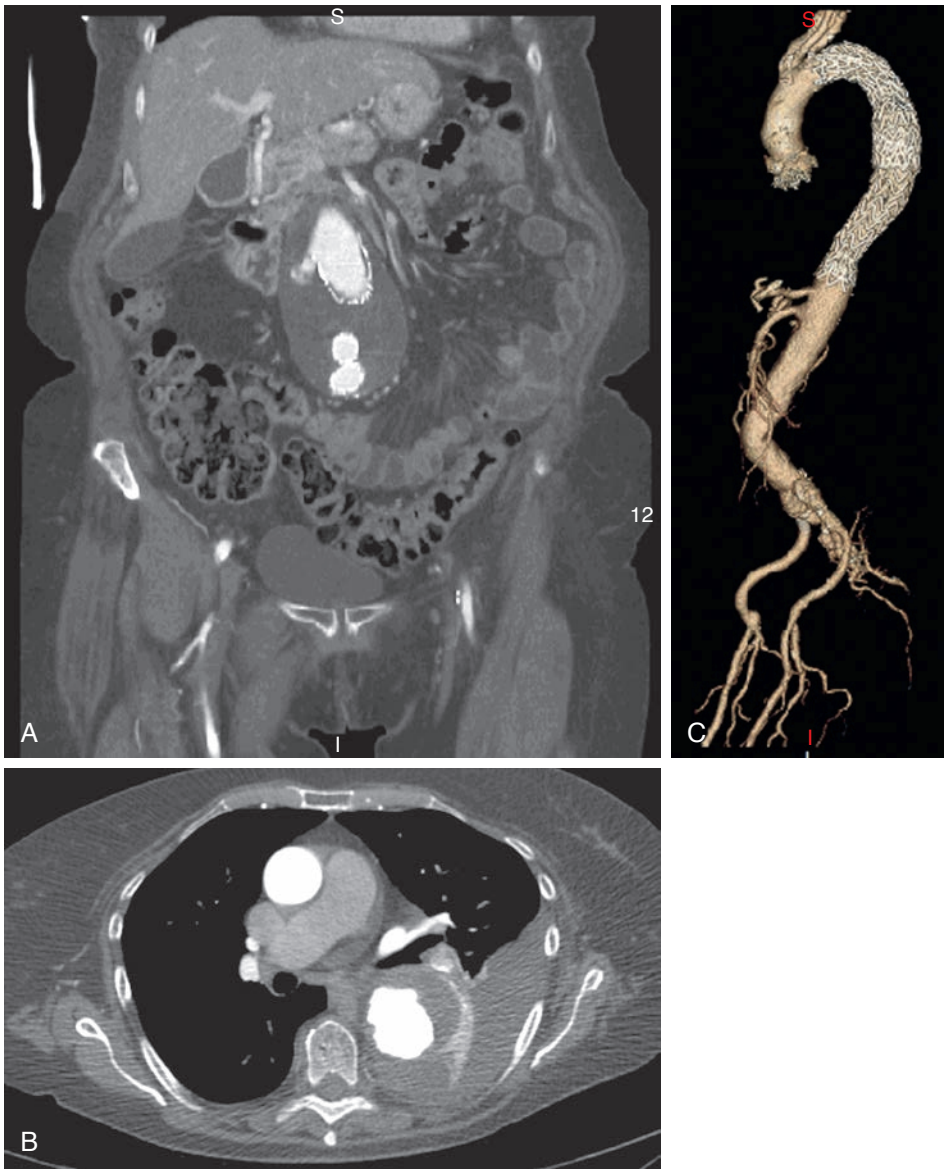


Figure 77.14 This patient required a C4 thoracoabdominal repair to rescue a failed EVAR that was sitting in the middle of a 7-cm aneurysm (A). To our surprise, at her follow-up CT, angiogram 4 months after repair her entire descending thoracic aorta was aneurysmal from a presumed retrograde dissection, which we believe was caused by the aortic clamp at her thoracoabdominal repair (B). We successfully treated this rather threatening appearing new aneurysm with pleural effusions with a TEVAR (C).

the anatomic variations of spinal cord arterial anatomy to neurologic complications of aortic surgery.[1] Adams's paper identified the Greater Radicular Artery (arising from the artery of Adamkiewicz between T8 and L2 spinal levels in 85% of humans) as most important, because it supplied an especially vulnerable region of the spinal cord in the lower thoracic aorta where there were fewer feeding radicular arteries and the anterior spinal artery is smaller. Even though the anterior spinal artery is continuous, the ascending portion from the greater radicular artery (GRA) is small with high resistance to blood flow and retrograde perfusion from aortic shunts and cardiopulmonary bypass. There are also muscular cushions associated with this ascending ASA that implies possible neurochemical factors that may potentiate spinal cord ischemia.[94–96] The decline in spinal cord blood flow and paraplegia risk with aortic occlusion is proportional to the number of open ICA in the length of aorta replaced, which varies depending on the pathology. On average, half the intercostals are occluded from the disease process with even more chronically occluded in degenerative aneurysms.[97] This patient data obviously shows that the pruning of ICA by the disease process leads to auto collateralization that reduces spinal cord ischemic risk associated with aortic replacement. Surgeons have focused primarily on an anatomic paradigm of paraplegia prevention for the last 60 years by attempting to identify and reattach critical ICA. This effort has failed to prevent paralysis because, as experimental and clinical studies have demonstrated, spinal cord circulation during and after aortic occlusion and aneurysm repair is via collateral arteries, such

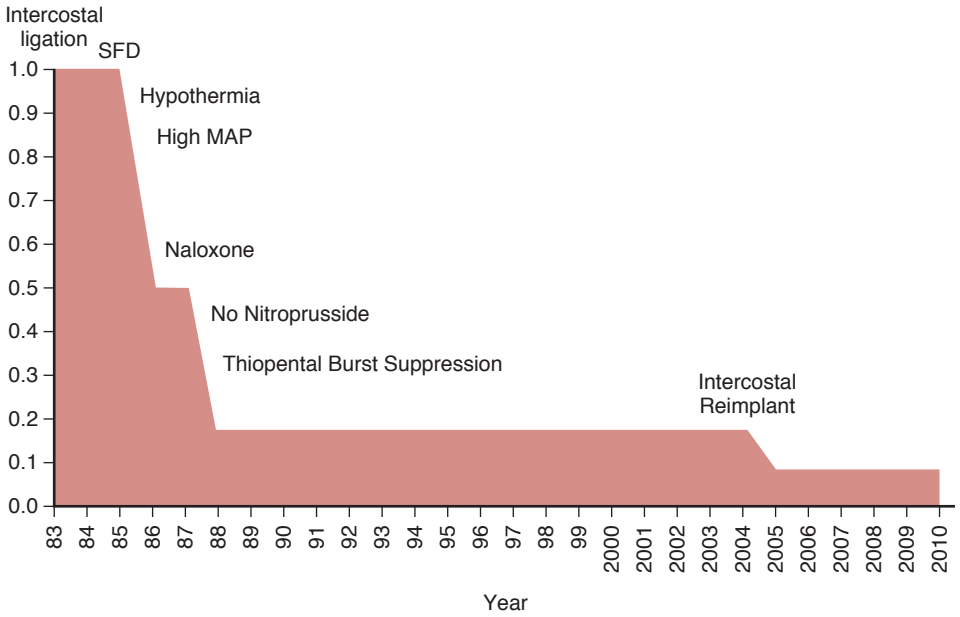


Figure 77.15 By applying the experimentally validated spinal cord protection strategies of hypothermia, spinal fluid drainage *(SFD)*, neurochemical protection (naloxone, barbiturates, steroids), and optimizing arterial pressure (MAP >90 to 100) and cardiac function, we reduced paraplegia incidence by 80% to 85% without assisted circulation or intercostal replantation. Replanting intercostals had a modest effect in the highest risk aneurysms (O/E declined from 0.34-0.18 in C2 aneurysms) by reducing delayed paraplegia, supporting the concept that the most important factors relate to prolonging cord ischemic tolerance, and maximizing the collateral perfusion as it recovers.

that manipulation of physiologic factors that impact the perfusion pressure in the collateral network, tissue oxygen delivery, and ischemic tolerance of the spinal cord are more effective at preserving spinal cord function.[98] Thus, even though the cause of spinal cord ischemia is anatomic, the most important neuroprotective strategies in our opinion are physiologic.

Physiologic Spinal Protection

The most elegant and insightful research into how the collateral circulation responds to interruption of direct intercostal and lumbar artery blood flow has been done by Etz and Greipp who described the coaxial collateral network concept.[99] In an experimental pig model, they found that the more acutely obstructed ICA increases the decline in collateral network pressure. More importantly, they found that spinal cord blood flow and recovery of collateral perfusion pressure occurs quite rapidly to 40% of pre-occlusion values within 24 hours and to 80% within 72 hours even with no open ICA. The most important experimental factors for optimizing this collateral perfusion network and protecting the spinal cord until collateral recovery occurs are as follows: hypothermia; spinal fluid drainage to keep SFP low, high arterial perfusion pressure (MAP), maintaining tissue oxygen delivery (avoid anemia and hypoxia, maintain cardiac index-CI); and neurochemical protection (naloxone, steroids, and barbiturates).[72,73,75,100–107] Elevated levels of excitatory amino acid neurotransmitters, which are reduced by naloxone, have also been implicated in exacerbating injury in spinal cord ischemia. In addition, it is important to avoid stealing effects of arterial vasodilators such as nitroprusside.[108] Applying these experimentally validated principles and interventions, we reduced our paralysis incidence by 82% to 85% with O/E ratios going from 1 to 0.15 to 0.18 without assisted circulation or intercostal re-implantation (Fig. 77.15).[8,109]

Expected Paralysis Model

To study paraplegia outcomes more comprehensively, we developed a mathematical model for calculating expected paraplegia based on the extent of aortic replacement and clinical presentation (acute, dissection) based on Crawford's results of TAAA surgery done without neuroprotective adjuncts (where C1, C2, C3, C4, and TAA indicates the number of those aneurysms):

$$E = [0.1C1 + 0.2C2 + 0.05C3 + 0.02C4 + 0.01TAA] + [0.3(\text{acute} + \text{dissection})]$$

The model was validated with over 5000 patients and accounted for over 98% of the variability in paraplegia between clinical reports (Fig. 77.16A).[5,8] The model calculates O/E ratios for paraplegia and can be used to analyze clinical outcomes traditionally expressed as percent paralysis, which is misleading because it does not account for clinical variations in patient populations regarding extent of aneurysm and acuity. We have now modeled over 15,000 patients from clinical reports in the last 25 years, and it is evident that paraplegia rates have declined significantly (about 75%, see Fig. 77.16B), which published reports show that the decline can be divided into two eras with most of this decline occurring since 1997 (Era 2 of the modern era). The transition from Era 1 to 2 marks a change away from Adams's anatomic paradigm to the more physiologic

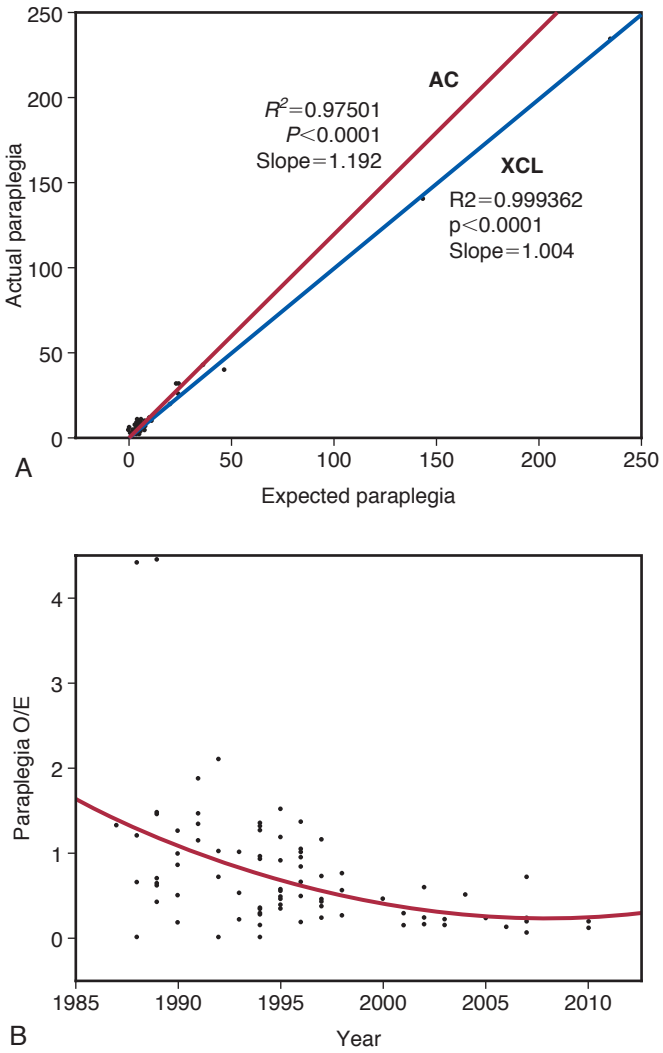


Figure 77.16 The paraplegia risk model accurately predicts ($R^2 > 0.97$) paraplegia risk when no effective spinal cord protection strategies are used and shows that assisted circulation *(AC)* and Crawford's simple crossclamp technique *(XCL)* have similar paralysis risk, which is consistent with experimental data. Using this model to calculate O/E ratios allows for a much more accurate understanding of the effects of protective strategies than using percent paralysis, which does not account for variation in a population of known clinical factors that affect paralysis risk. This modeling allows populations and techniques to be normalized for comparison.

TABLE 77.1 In Multivariate Modeling of Our Patients Cardiac Index Was More Important Than Age in Protection From Paraplegia While Extent of Replacement (Crawford Type C2), Dissection and Acute Presentation Were Associated With Increased Paralysis Risk

Variable	Odds Ratio	*P*-Value
Cardiac index	0.556/unit	.0038
Dissection	5.26	.0001
C2	6.35	<.0001
Acute	2.24	.0378
Age	1.035/year	.0763

TABLE 77.2 Younger Patients Have Less Risk for Paralysis and Mortality but in a Multivariate Model Age Is Less Significant Than Cardiac Index (Table 77.1), Which May Indicate That Better Cardiac Function Is Important in Collateral Perfusion Dynamics

Group	No. of Patients	O/E Ratio	% Paralysis	% Mortality
<60 years	153	0.06	1.4	0.7
>60 years	617	0.28	5.7	8.9

neuroprotective interventions of spinal fluid drainage, hypothermia, increased MAP, and neurochemical protection based on the experimental literature. The experimental literature also failed to validate assisted circulation when used alone to prevent paralysis in primates, pigs, and dogs, because perfusion of the abdominal aorta and iliac arteries did not improve blood flow to the lower thoracic spinal cord.[110–112] Other factors such as epidural analgesia and neuraxial narcotics may increase paralysis risk.[113–115] The extent of replacement (Crawford type) and dissection are proportional to open ICA at risk. In addition, physiologic instability (hypotension and anemia) of acute processes (rupture, dissection, infection, trauma, and underlying cardiac and pulmonary disease) are all important in the predictive model and explain why the model accounts for so much of the variation in clinical reports. However, also significant in multivariate analysis is cardiac function (Table 77.1). CI declines with age and statistically is more important than age.[116,117] Cardiac function fits with the collateral circulation concept by associating a stronger pump with more effective collateral perfusion and may explain one of the reasons older patients have increased paralysis risk [O/E 0.06, 1.4% <60 years; O/E 0.28, 5.7% >60 years] (Table 77.2).[5]

Impact of Physiologic Protection Measures

The experimental observations are consistent with our own experience and the analysis of clinical outcomes in over 5000 patients where assisted circulation and simple cross clamping without protective adjuncts both had the same O/E ratios of about 1 (Fig. 77.17A). However, if spinal fluid drainage is added to both techniques, the O/E ratios decline on average to between 0.4 to 0.5, and if we model the results from Era 2 when hypothermia and increased MAP were added by most surgeons to spinal fluid drainage, the O/E ratios declined further to a mean of about 0.25 (see Fig. 77.17A).[118]

From this analysis, if spinal fluid drainage, hypothermia, perfusion pressures (MAP), and, in our experience, neurochemical protection are optimized, outcomes are independent of technique of repair (simple cross clamp, assisted circulation, or hypothermic arrest) and O/E ratios are equivalent. It is also apparent that the variation (range) of O/E ratios within techniques reflects

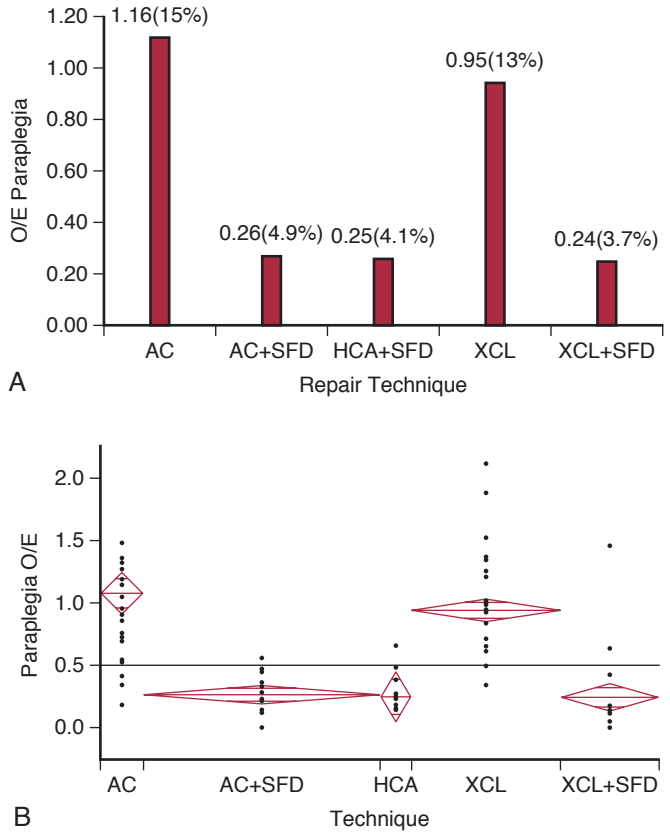


Figure 77.17 (A and B) It is evident that the reason paraplegia rates have declined is the clinical application of spinal cord protective strategies that have demonstrated experimentally to be effective, such as spinal fluid drainage, hypothermia, high perfusion pressure, neurochemical protection and measures that enhance cord oxygen supply-demand balance. These interventions are effective regardless of technique of repair *(AC, HCA, XCL)*. However, there is also variation within technique (B), which we think is a reflection of the stringency (effectiveness) of application of the protective strategies. This variation in application may also explain the very poor outcomes in smaller centers that do not have the resources or experience to apply these principles of spinal cord protection consistently. *AC,* assisted circulation; *HCA,* hypothermic circulatory arrest; *SFD,* spinal fluid drainage; *XCL,* Crawford's simple crossclamp technique.

the aggressiveness of applying effective spinal cord protective strategies (see Fig. 77.17B). This effectiveness issue is demonstrated by two randomized trials of spinal fluid drainage separated by a decade from the same institution. Crawford's early study, showing no benefit from spinal fluid drainage, did not control SFP, but just withdrew 50 mL of spinal fluid while maintaining normothermia and using nitroprusside. Coselli's later study controlled SFP, used hypothermia, and increased MAP, and demonstrated a significant protective effect from SFD with O/E ratios declining to 0.22.[119,120]

Evoked Potential Measurement and Intercostal Reimplantation

SSEPs and MEPs used by some surgeons to identify critical ICA have added greatly to our clinical understanding of the role of arterial perfusion pressure and intercostal artery reimplantation in spinal cord protection. Greipp and Jacobs have shown that intraoperative spinal cord ischemia reflected by loss of MEPS after aortic occlusion is reversed in most patients just by raising the MAP to 100 mm Hg and observing the return of MEP's.[85,121,122] However, they came to opposite conclusions about intercostal reimplantation with Greipp's studies (O/E 0.14) demonstrating no necessity or benefit to reimplanting intercostals, while Jacobs (O/E 0.25) found that using MEPs is necessary to select which intercostals to implant. To study this issue, in 2005 for the first time, we started reimplanting intercostals that we identified by MRA or by patency and location (85% GRAs arise between T8 and L2), primarily to reduce delayed paraplegia occurring from hypotensive events post repair (sepsis, MI, bleeding, dialysis, drugs). Our O/E ratios declined modestly from 0.18 to 0.11 for all patients, and this effect was most noticeable in the most extensive C2 aneurysms where O/E declined from 0.34 to 0.18.[123] From our experience and Greipp's, it is apparent that intercostal reimplantation is not the most important factor in paralysis prevention but may play a role in the most extensive aneurysms.

Descending Thoracic Aneurysms

These same spinal cord protection principles apply to open DTA repair. Even though modern series of open DTA are limited in number because of TEVAR, Safi and Coselli published their results of a large series of DTA with comparable results. Coselli compared Crawford's simple crossclamp technique (XCL) (2.3% paraplegia) and AC (4% paraplegia) in 387 (4% mortality) patients with no statistical difference in paralysis risk and Safi 2.3% (O/E 0.9) paralysis (8% mortality) in 300 patients most treated with AC + SFD.[124,125] This compares with our own experience in 166 (0.6% paraplegia, O/E 0.11, 7% mortality [1.6% elective, 9% acute]) XCL + SFD open DTA patients.

PULMONARY COMPLICATIONS

The most common complications following open TAAA repair is pulmonary, with prolonged ventilation, pneumonia, or respiratory failure occurring in up to 27% of patients. As many as 8% to 10% require tracheostomy, and half of those patients die from respiratory failure. This high pulmonary risk is because 80% of patients are active or former smokers, and 40% of patients have varying degrees of COPD limiting their pulmonary function and reserve.[126–128] These factors are exacerbated by age, osteoporosis, chronic renal disease, and congestive heart failure, which all are associated with loss of strength and loss of respiratory muscle strength, producing reduced maximum inspiratory and expiratory pressures (MIP, MEP) and reduced endurance (MVV). This loss of pulmonary muscle strength is associated with mortality in the elderly.[129–137] The incision itself reduces lung function postoperatively: after simple thoracotomy, it takes 10 to 15 days for FEV1, MIP, and MEP and 15 to 30 days for FVC to return to baseline.[138] The higher the interspace level of the thoracoabdominal incision the more difficult weaning from ventilator support will be. With incisions in the 8th interspace and below, patients are usually extubated within a few hours, but patients with 5th interspace thoracoabdominal incisions for extensive Crawford type 2 aneurysms may be

ventilator dependent for 2 to 4 days even without complications. Routine use of continuous positive airway pressure (CPAP) and adequate pain control may improve lung function and shorten intubation after surgery.[138] It is very evident to most surgeons who treat TAAA that postoperative pulmonary problems are a major harbinger of prolonged hospitalization and increase the effect of age on mortality risk. The effects of age and chronic disease on respiratory and skeletal muscle strength may be the most important underlying factors in survival and functional recovery. This suggests that preoperative strengthening regimens may improve strength and functional capacity and possibly reduce mortality risk.

MORTALITY

Mortality in our database (15,000 patients from 86 published reports in the last 25 years) averaged 9.3% (95% confidence 8.1-10.4, median 9.9%, range 4.1-37.2). Since many reports do not separate elective and acute operations, for better comparison of mortality between reports, we developed a mortality model that accounted for 86% of the variation between published reports:

$$\text{Expected Mortality} = [\text{acute} + \text{predicted paraplegia}] \times 0.38$$

This model was predictive with $R^2 = 0.86$, $P < .0001$. The mean O/E ratio was 1.00 ($P < .0001$, 95% confidence 0.842-1.168, median 1.07 range 0.22-7.61).[5] The model quantifies what we inherently know from experience, which is that patients with acute pathology (rupture, dissection, mycotic aortitis, acute plaque hemorrhage, trauma) or who develop paraplegia account for most of the mortality and that these patients die because they have a fatal event such as myocardial infarction or stroke or do not have the reserve functional capacity (pulmonary, cardiac, renal) or physical strength to survive as is the case in many patients with respiratory failure. Operative or postoperative bleeding can cause shock leading to multiorgan failure and death. Acute patients are at increased risk not only from unstable clinical conditions but also because they have not been screened for renal, pulmonary, coronary, or valve disease that could be corrected or optimized to reduce operative risk or exclude them from treatment, because operative risk was unacceptably high. These factors are reflected in the effect of age on mortality from our own data. For elective surgery, the operative mortality was 0.0 for patients less than 60 years of age and increased with each decade to 5.7% for patients 80 years or older who were highly selected. However, for acute patients, the mortality increased from 1.6% for <60 years to 42.9% for >80 years. In patients older than 80 presenting acutely with creatinine >2.0, the mortality was 67% (Table 77.3). As with paraplegia, the operative mortality in published reports has declined significantly ($P < .0001$) in the last 25 years from an Era 1 O/E mean of 1.46 (11.34%, 95% confidence 1.2285-1.6930) to 0.72 (7.99%, 95% confidence 0.534-0.903) in Era 2.[5] Because paraplegia has such a high mortality risk (27% overall, 45% for >70 years, 100% >80 years of age), its decline accounts for almost half (43%) of this improvement in mortality (Table 77.4). The causes of the remaining decline are much harder to determine but may be related to better centralization of care in larger referral centers in Era 2 with the average number of patients in reports increasing from 114 to 384. Patient selection may also play a role, although there is no data on this.

TABLE 77.3 Mortality by Decade in 771 or Our Patients Surgically Treated for Thoracoabdominal and Thoracic Aortic Aneurysms. Acute Patients Were Defined as Having Rupture, Contained Rupture, Acute Dissection, Mycotic Aortitis, Trauma, Plaque or Intramural Hemorrhage

Age by Decade	% Elective Mort	% Acute Mort	No.
<60	0.0	1.56	153
60-70	1.78	14.67	244
70-80	4.00	24.27	311
>80	5.13	41.94	70

TABLE 77.4 Mortality O/E and % by Technique of Repair for Over 15,000 Patients Analyzed From 86 Clinical Reports

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Mortality O/E Ratio					
Means for One-way ANOVA					
AC	1324	1.57	0.29477	0.98092	2.1562
AC+SFD	6685	0.95703	0.13118	0.69552	1.2185
HCA+SFD	823	0.95349	0.37388	0.20817	1.6988
XCL	4967	1.28981	0.15219	0.98642	1.5932
XCL+SFD	2455	0.45217	0.21647	0.02064	0.8837
% Mortality					
Means for One-way ANOVA					
AC	1324	10.3927	2.1667	6.0735	14.712
AC+SFD	6685	9.4242	0.9643	7.5020	11.346
HCA+SFD	823	8.5053	2.7482	3.0270	13.984
XCL	4967	10.7711	1.1187	8.5411	13.001
XCL+SFD	2455	5.9063	1.5912	2.7343	9.078

RENAL FUNCTION

Poor renal function is associated with more complications, paraplegia, and mortality risk in most clinical reports, because it reflects a less robust patient with more advanced cardiac and pulmonary co-morbidities and less physical strength and reserve to survive such a physical assault. Postoperative dialysis–dependent renal failure is associated with a 50% to 60% mortality risk and preserving renal function and avoiding dialysis reduces mortality risk and improves long-term survival. Age and baseline renal function are the most important mortality risk factors in

most clinical reports. Normothermic renal perfusion in complete or partial cardiopulmonary bypass has not been effective in reducing renal failure, with permanent dialysis dependent renal failure rates up to 15%, because normothermia does not prolong ischemic tolerance, and hypotensive renal perfusion is inadequate especially for perfusing kidneys with any glomerular sclerosis.[139–141] Perfusing at higher pressures with moderate or deep hypothermia (hypothermic arrest or cold renal perfusion decreasing renal temperature to <20°C during occlusion), however, appears to provide effective renal protection with dialysis rates of 3% or less in most reports whether cold blood or crystalloid is used.[142–145] These results are consistent with our renal protection strategy of rapidly flushing each kidney with 300 to 400 mL of 4°C renal perfusion solution, which along with a 30% renal artery revascularization rate (endarterectomy or bypass), has resulted in 3.2% postoperative dialysis (80% of which are in acute patients) but only 0.8% permanent dialysis with most patients recovering baseline renal function within 14 days.[146]

EFFECT OF SURGICAL TECHNIQUE ON MORBIDITY

We have demonstrated with data from the experimental literature, published reports, and our own experience that a more complete understanding of the mechanisms of injury and protection in aortic surgery can lead to improved results. This effort requires a team approach using anesthetic, surgical, and ICU protocols that are evidence based and data driven. One of the controversies concerning TAAA repair is which technique to use: AC + SFD, XCL + SFD, or HCA. Some surgeons have strongly held opinions about the best method, but as the data tells us, equivalent results are attainable with each approach if experimentally supported principles are followed. However, patient physiology or anatomy may dictate the technique such as AC if the patient cannot tolerate one lung anesthesia, the cardiac strain of proximal cross clamping, or HCA if there is no place for a proximal aortic clamp. The different techniques each have strengths and weaknesses. XCL + SFD is surgically simpler with fewer steps associated with cannulating, it is easier to avoid hypotension, does not require heparinization, and results in faster surgery but is a more difficult anesthetic because of left heart strain and hypertension from very proximal aortic clamping. AC + SFD reduces cardiac strain but is associated with hypotensive perfusion, more bleeding because of heparinization, and is more complicated because of cannulating and decannulating for bypass. However, many cardiac surgeons use this technique. HCA is the most complicated technique and takes the most time, because HCA is such an extreme state, requiring long cooling and rewarming times, which means longer time on cardiopulmonary bypass and is associated with more bleeding because of coagulopathy, extreme systemic hypothermia, and total heparinization. However, profound hypothermia provides excellent organ protection from the ischemia of aortic occlusion.

We have examined the different methods of repair by quantifying total morbidity, which we define as observed number paralyzed + number of deaths divided by the expected (calculated from our models) to give an overall morbidity O/E ratio. Our analysis shows that total morbidity was comparable between techniques but showed a significant decline from Era 1 to Era 2 in all categories (Table 77.5).

TABLE 77.5 Total Morbidity O/E Is Sum of Paralysis and Death/Expected Sum Calculated From the Mortality and Paraplegia Predictive Models. This Ratio Is a Way of Evaluating the Overall Effectiveness and Risk by Procedure Technique. There Was No Statistical Difference Between Techniques but There Was Between Eras. The Primary Driver of Reduced Morbidity Was Reduction in Paraplegia Incidence but Centralization of Care Into Larger Centers May Also Play a Role.

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Means for One-way ANOVA for Morbidity O/E by ERA					
ERA 1&2 Morbidity O/E (P = .0001)					
ERA 1	6693	1.12241	0.08909	0.94493	1.2999
ERA 2	8803	0.41659	0.07768	0.26183	0.5713
ERA 1 Morbidity O/E by Technique of Repair (P = .2823)					
AC	1215	1.42994	0.17514	1.078	1.7817
AC+SFD	569	0.88577	0.25593	0.372	1.3998
HCA	297	0.77945	0.35425	0.068	1.4910
XCL	4244	1.10978	0.09371	0.922	1.2980
XCL+SFD	336	0.48416	0.33305	-0.185	1.1531
ERA 2 Morbidity O/E by Technique of Repair (P = .0674)					
AC+SFD	6116	0.466853	0.03542	0.39212	0.5416
HCA+SFD	526	0.319093	0.12079	0.06426	0.5739
XCL+SFD	2119	0.299920	0.06018	0.17295	0.4269

LONG-TERM SURVIVAL AND QUALITY OF LIFE

There have only been a few studies of long-term survival after TAAA repair and even fewer on quality of life measures.[147–149] These data show that there is mortality within the first year after surgery from COPD, paraplegia, and renal failure, but after one year, although survival is lower, it more closely matches age matched expected survival with 69% to 78% survival at one year and 45% to 68% survival at five years, depending on the mean age of the patients in the study; however, females over 70 had significantly worse long term survival than males. After the first year, the quality of life scores was similar to age matched populations, but there was a marked difference in stamina in the older TAAA patients. The conclusion from these studies is that approximately 80% of patients return to

preoperative quality of life, but if there is dialysis or paraplegia or both, quality and length of life is severely reduced.

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This report is a modern experience with open thoracoabdominal aneurysm repair in 823 patients and demonstrates consistent improved spinal cord injury rates of 5%(O/E 0.21) using SFD and moderate hypothermia compared to Crawford's 16%(O/E 1.0) from the same institution two decades earlier.

Svensson LG, Crawford ES, Hess KR, Coselli JS, Safi HJ. Experience with 1509 patients undergoing thoracoabdominal aortic operations. *J Vasc Surg*. 1993;17(2):357–368, discussion 68-70.

This paper summarizes E. Stanley Crawford's experience as the dominant influence in thoracoabdominal aortic surgery in the world in ERA 1 and included the authors (Coselli, Svensson and Safi) who have had such an important influence in the improvement in results in ERA 2.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 78

Thoracic and Thoracoabdominal Aneurysms: Endovascular Treatment

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Since the US Food and Drug Administration (FDA) approved the first thoracic endovascular aortic repair (TEVAR) in 2005, its use has rapidly increased.[1,2] In a relatively short period of time, TEVAR for descending thoracic aortic aneurysms (DTAAs) and various other aortic pathology has not only become the preferred treatment method but also the standard of care. For many reasons, mainstream TEVAR technology has advanced at a rapid pace since the release of the first commercially available endograft. Investigational work continues through a combination of clinical trials, industry-sponsored research, physician-driven device modifications, and investigational device exemptions. The penultimate goal of in-line branch vessel preservation during repair of complex thoracoabdominal aortic aneurysms (TAAAs) appears to be technically feasible, efficacious, and durable.[3,4,5-9] In contrast to EVAR, most clinical TEVAR data originate from industry-sponsored, nonrandomized comparisons with open

Abstract

Thoracic aortic aneurysms (TAAs) are a relatively uncommon disease process which occurs more frequently in older individuals. There is an equal gender distribution, and various pathologies are associated with TAA. There are few signs or symptoms of TAAs. The natural course of TAA is one of progressive aortic expansion, which may be associated with an increased risk of life-threatening aneurysm rupture if not treated in a timely manner. Conventional treatment options are medical management for smaller aneurysms and open surgical repair, which includes replacing the diseased aortic segment with a prosthetic graft; unfortunately the latter is associated with a higher than desired rate of intraoperative and postoperative adverse events. Thoracic aortic endovascular repair (TEVAR) is an alternative approach for treating thoracic aneurysms, which appears to have a lower morbidity and mortality compared with open repair. Long-term data from industry-sponsored TEVAR studies are available and comparative analyses have been completed which have validated the use of TEVAR in a variety of thoracic aortic pathology. Advancing TEVAR technology using branches and fenestration to treat thoracoabdominal aortic aneurysms has shown immense promise but has yet to be approved for use in the United States.

Keywords

thoracoabdominal aortic aneurysms
descending thoracic aortic aneurysms
thoracic aortic disease
fenestrated and branched endovascular aneurysm repair
multibranched thoracoabdominal aortic stent grafts
thoracic endovascular aortic repair (TEVAR)

repair of DTAAs, as well as from single-center experiences or registry data that combine different pathologic processes and indications. Nonetheless, TEVAR has emerged as an attractive option for the treatment of a wide range of thoracic aortic pathology.

Indications

Thoracic aortic disease remains one of the leading causes of death in the United States[10] and accounts for more than 11,000 deaths annually, with estimated incidence of 5.6 to 10.4 cases per 100,000.[11-13] Based on epidemiologic data, the increase appears to be multifactorial in nature and includes an aging population, along with improved educational awareness of patients and healthcare providers.[14,15] Indications to treat thoracic aneurysms depend on various factors, including aneurysm diameter, rate of growth, anatomic location, presence of symptoms, and general medical condition of the patient (see Chapter 76). Similar criteria should be rigorously applied for both open and endovascular repair: diameter ≥5.5 to 6.0 cm with saccular morphology, rapidly expanding aneurysms, symptomatic aneurysms, and rupture. The main considerations supporting TEVAR over open repair are based on physician experience, patient anatomy, and underlying comorbidities. There are select situations in which repair at a smaller diameter may be considered including nonsaccular aneurysms, symptomatic or ruptured, and those associated with connective tissue disorders.

Anatomically, if considering TEVAR, there should be suitable landing zones (≥20 mm) proximal and distal to allow adequate seal and exclusion of the aneurysm, as well as appropriately sized arterial access to deliver the stent-graft. Anatomy is not the only parameter in treatment planning; age and risk assessment play a significant role in selecting the appropriate treatment. Societal guidelines have recognized the absence of high-quality data to support the increasing use of TEVAR. The Society for Thoracic Surgeons Endovascular Task Force has emphasized an individualized approach.[16,17] A Cochrane review confirmed that clinical equipoise exists between TEVAR and open repair of thoracic aortic aneurysms (TAAs) due the paucity of supporting data.[18,19]

In the presence of suitable anatomy, TEVAR appears to be an acceptable first choice for most, based on its lower morbidity and mortality. However, enthusiasm for TEVAR should be tempered by the paucity of follow-up data and requirement for lifelong follow-up. Consideration should be given to open repair in younger patients with longer life expectancies and apparent low risk for open repair. For higher-risk individuals the decision is straightforward because clinical results favor an endovascular approach. Long-term data may eventually support a more liberal use of TEVAR in lower-risk individuals, particularly in light of the demonstrated significant perioperative reduction in risk with TEVAR (see later).[11] In the absence of high-level evidence comparing the results of open repair and TEVAR, some investigators advocate TEVAR only when the predicted operative risk is less than the risk associated with conventional open repair.[12]

In the patients without "ideal" TEVAR anatomy, the risk/benefit assessment becomes more challenging to equate. Many aneurysms impinge on major arterial branches that may need to be covered for adequate seal. In these situations the safety of branch sacrifice must be balanced against continued observation and open repair. The alternatives would be use of snorkel technique, fenestrated/branched endograft, and surgical bypass, which maintain perfusion while extending the seal zone. The incremental risks of planned branch occlusion should be carefully evaluated when considering TEVAR; presumably this option would be appropriate in a select situation (high risk with large aneurysm). This category encompasses those with cardiac or pulmonary comorbidities that preclude safe open repair or "high-risk" anatomic conditions. The durability of TEVAR can be compromised by treating aortic pathology outside of the IFU, this includes large diameter necks, angulated aortic segments, and circumferential thrombus lining the seal zones. Significant angulation of the arch (>60 degrees) adjacent to the proximal portion of the aneurysm increases the difficulty of device tracking and may compromise seal. TEVAR should be performed with caution in patients with life-threatening allergies to intravenous contrast or to nickel or stainless steel and in those who cannot be monitored reliably.

APPROVED DEVICES FOR THORACIC ENDOVASCULAR AORTIC REPAIR

The pace of development of commercially available TEVAR devices has lagged behind that of EVAR devices, presumably because of lower incidence of DTAA, larger device profiles, challenging hemodynamic forces of the thoracic aorta, and proximity to the great vessels. Despite these hurdles, steady progress has been made, with several new or modified thoracic devices released (see Chapter 79). Five commercially available devices (Table 78.1) have completed regulatory trials and are approved for use in the United States.

Gore Conformable Thoracic Aortic Graft Device

The Gore thoracic aortic graft (TAG) endoprosthesis (W.L. Gore and Associates, Flagstaff, Arizona) was the first thoracic endograft approved in the United States. The Conformable TAG (C-TAG) endoprosthesis is a third-generation device that was approved January 2012. The device conforms to the aortic wall, which improves aortic wall apposition and minimizes the risk of proximal bird-beaking. The C-TAG device is constructed with an expanded polytetrafluoroethylene (ePTFE) tube reinforced with ePTFE/fluorinated ethylene propylene film and an external nickel-titanium (nitinol) self-expanding stent affixed to the graft (Fig. 78.1). This device uniquely deploys from the middle of the graft outward, a design characteristic intended to prevent windsock effect at the proximal fixation. A circumferential PTFE sealing cuff is located on each flared end. Device lengths, diameters, and delivery profile are documented in Table 78.1. Based on the IFU the C-TAG is designed to be oversized 7% to 22%.

TABLE 78.1 US Food and Drug Administration–Approved Thoracic Aortic Endovascular Repair Devices

	Device Diameters (mm)	Lengths (cm)	Delivery Profile (F)	Tapered Component	FDA Approval
Gore C-TAG	21-45	10, 15, 20	ID- 18, 20, 22, 24	yes	2012
Medtronic Valiant	22-46	10.7-22.4	OD- 22, 24, 25	yes	2014
Cook TX2 with Pro-Form	28-42	Proximal 12-21.6 Distal 13.6-20.7	ID- 20, 22	yes	2008
Cook Zenith Alpha	24-46	Proximal 10.5-23.3 Distal 14.2-21.1	ID- 16, 18, 20	yes	2015
Bolton Relay Plus	22-46	10, 15, 20, 25	OD- 22, 23, 24, 25, 26	no	2012

ID, Inner diameter; *OD,* outer diameter.

Figure 78.1 Gore Conformable C-TAG thoracic endoprosthesis.

Figure 78.2 Medtronic Valiant stent-graft.

Medtronic Valiant Captivia Device

In January 2014 the Valiant thoracic stent graft (Medtronic, Santa Rosa, California) was approved for use in the United States. It is a modified Talent endograft without the longitudinal connecting bar and has been widely implanted outside of the United States. The device is composed of a monofilament woven polyester graft attached to sinusoidal nitinol springs that are placed on the outside of the graft. The modular design consists of an eight-peaked bare metal proximal FreeFlo configuration that evenly distributes radial force across the proximal aortic neck (Fig. 78.2). Valiant has a wide assortment of diameters and lengths, with both closed web and open FreeFlo stents available (see Table 78.1). Oversizing 10% to 20% in relation to the native aorta is recommended.

Cook TX2 With Pro-Form

The Cook TX2 (Cook Medical, Bloomington, Indianapolis) was approved for commercial use in 2008 and is a two-piece modular graft consisting of woven Dacron fabric sewn to self-expanding stainless steel Z-stents. The Pro-Form modification uses a trigger-wire release mechanism that improves proximal conformity and wall apposition. During device deployment, the proximal stent remains in a trifold configuration, which improves deployment accuracy and avoids a windsock effect. Unique to this device, the metal stents are located on the inside of the graft in the sealing zone but outside on the remainder (Fig. 78.3). Active fixation is provided by barbs on both ends; these barbs are intended to prevent migration and component separation. Device sizes and lengths are located in Table 78.1.

Cook Zenith Alpha

In September 2015 the Cook Zenith Alpha (Cook Medical) received FDA premarket approval. This lower profile device (18 or 20 F) addresses most access limitations. The two-piece modular graft consists of external nitinol stents and woven polyester fabric sewn together. Similar to the TX2, the Alpha uses active fixation. Gold radiopaque markers near the ends of the device improve visualization (Fig. 78.4) and a wide range of sizes and lengths are available (Table 78.1).

Bolton Relay

The Bolton Relay Thoracic Stent-Graft with Plus Delivery System (Bolton Medical, Sunrise, Florida) is a one-piece endograft made of woven polyester fabric sewn to self-expanding polished nitinol stents. Longitudinal support is provided by a curved nitinol support strut that aids aortic conformability. The device was

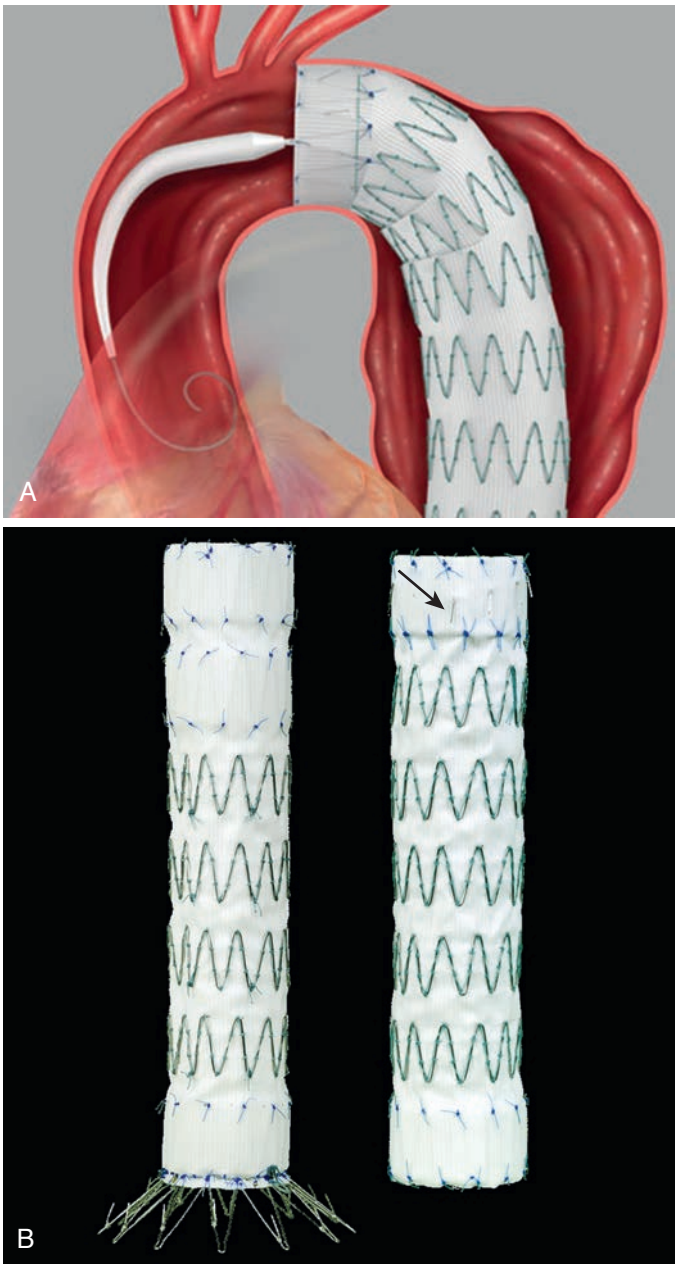

Figure 78.3 **A,** Schematic of Cook TX2 endograft with Pro-Form modification for improved proximal conformity and wall apposition. **B,** Cook TX2 device. Note the caudally oriented barbs intended to provide active fixation *(right, arrow)* at the proximal attachment site. On the left, the intended distal component of the intended two-piece construct has a distal bare metal stent to prevent migration.

approved in September 2012. The transport delivery system consists of a hydrophilic braided outer coaxial sheath, flexible secondary sheath with a through lumen that facilitates device advancement and precise endograft deployment. Active proximal fixation is provided by bare stents on the Relay plus device and nonbare stent (NBS) configurations are also available. The device is available in straight and tapered designs and oversizing of 10% to 15% is recommended. A wide range of diameters and lengths are available (Table 78.1; Fig. 78.5).

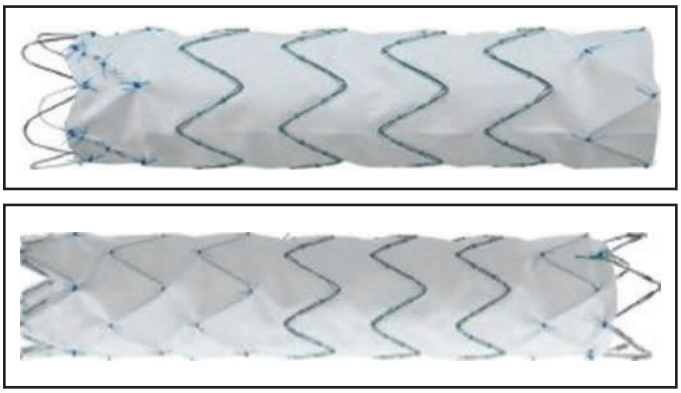

Figure 78.4 Cook Zenith Alpha lower-profile thoracic endograft.

Figure 78.5 Bolton Relay Plus and Relay NBS devices. (add new image) Note the proximal bare stents on the Relay plus device.

PLANNINGTHORACIC ENDOVASCULAR AORTIC REPAIR FOR THORACIC ANEURYSMS

Relevant Anatomy

Careful assessment of anatomy and meticulous preoperative planning are essential for successful TEVAR. Although anatomic requirements can be device specific, adequate arterial access and sealing zones are essential for all. Several anatomic features, when present, may facilitate TEVAR success or render it very difficult.

Aorto-Iliac Anatomy

Most procedures use common femoral artery access. Vessel calcification, small lumen diameter, and tortuosity can have a profound impact on the procedure. The right iliac artery is typically favored for device access, whereas the contralateral side is reserved for diagnostic catheters. An ideal access vessel should be ≥7 mm in diameter to accommodate larger delivery sheaths. The proximal external iliac typically has the smallest diameter and is prone to calcified plaque, which can restrict device insertion. This is a particular problem in women, whose

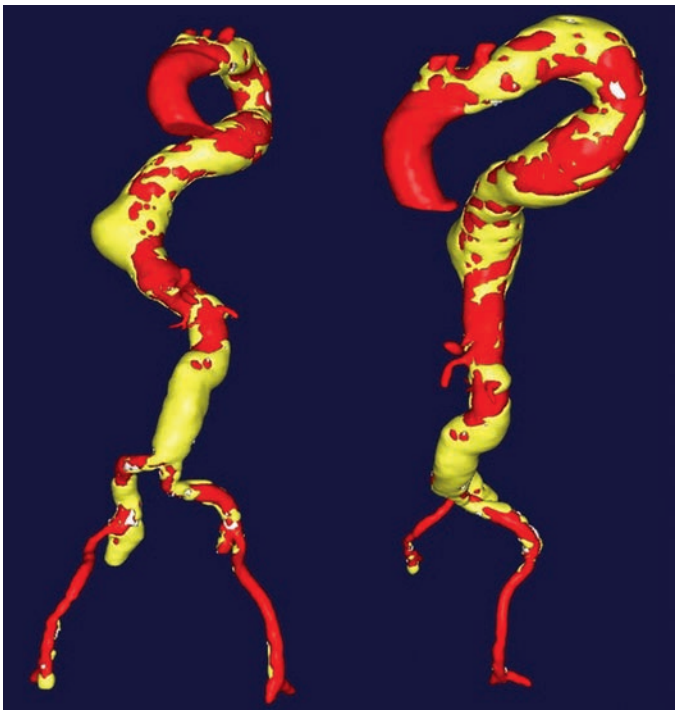

Figure 78.6 Three-dimensional reconstruction of the entire aorto-iliac tree demonstrating tortuosity at the level of the aortic arch, descending thoracic aorta, abdominal aorta, and iliac arteries.

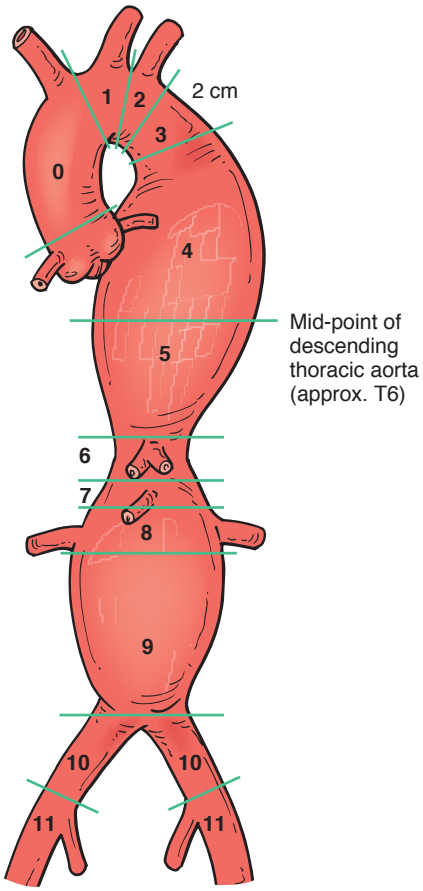

Figure 78.7 Eleven landing zones for thoracic aorta interventions.

iliofemoral arteries tend to be smaller.[14] Prior TEVAR studies required an iliac conduit in up to 15% of patients.[20] If the narrowest segment of the iliac is less than the expected diameter required for the planned device, access may be shifted proximal to the common iliac artery. Rarely, the entire iliac system is hostile and consideration should be given to alternative access techniques (crack and pave) or direct aortic access. An alternative approach for dealing with unfavorable iliac anatomy is the use of an internal endoconduit.[21] A 10- or 12-mm covered stent is deployed across the diseased iliac segment and aggressively inflated, which creates a controlled vessel rupture. The dilated 10-mm graft will allow sheath sizes up to 22 F, and 12-mm grafts up to 24 F. Planned embolization of the internal iliac artery may be needed if the occlusive disease is adjacent to the internal iliac artery. The use of hydrophilic sheaths and lower profile devices (Cook Alpha) should decrease the need for adjunctive techniques.

The abdominal aorta rarely presents an anatomic hindrance to device delivery, but tortuosity of the thoracic aorta can be challenging in the presence of aneurysmal disease because it frequently is associated with thoracic aortic elongation and exaggeration of normal curvatures. As illustrated in Fig. 78.6, this is particularly relevant in a large descending thoracic aorta when cephalocaudal elongation causes exaggeration of the posterior-anterior course of the aorta as it enters the aortic hiatus. This tortuosity, if combined with increased angulation at the transition from the arch to the proximal descending aorta may result in difficulty with device tracking due to bending of the delivery sheath at multiple flexion points as it negotiates the severely angulated regions.

Aortic Sealing Zones

Adequate TEVAR fixation in the proximal and distal landing zones is essential for durable performance. TEVAR reporting standards were published by the Society for Vascular Surgery (SVS) and 11 landing zones described for thoracic aortic disease (Fig. 78.7).[16] This anatomic standardization aids in determining procedural risk and complexity in relation to the site of fixation and length of aortic coverage. Several publications have shown that the frequency of neurologic events correlates with location of the proximal landing zone.[18,22] The proximal attachment zones define the proximal edge of the TEVAR device in relation to branch vessels: zone 0: proximal to the innominate artery; zone 1: proximal to left common carotid artery (CCA); zone 2: proximal to origin of the left subclavian artery (SCA); zone 3: proximal descending thoracic aorta (<2 cm from left SCA); zone 4: 2 cm distal to SCA extending to proximal half descending thoracic aorta (T6 vertebral body); zone 5: distal half descending thoracic aorta to celiac artery; zone 6: celiac artery to top of superior mesenteric artery (SMA); zone 7: SMA to suprarenal aorta; zone 8: perirenal aorta; zone 9: infrarenal aorta; zone 10: common iliac arteries; zone 11: external iliac arteries.

Atherosclerotic aneurysms typically are not limited to one focal area, and the degenerative process usually involves apparently normal adjacent aorta. This is important in selection of landing zones and device length. Although 2 to 3 cm is

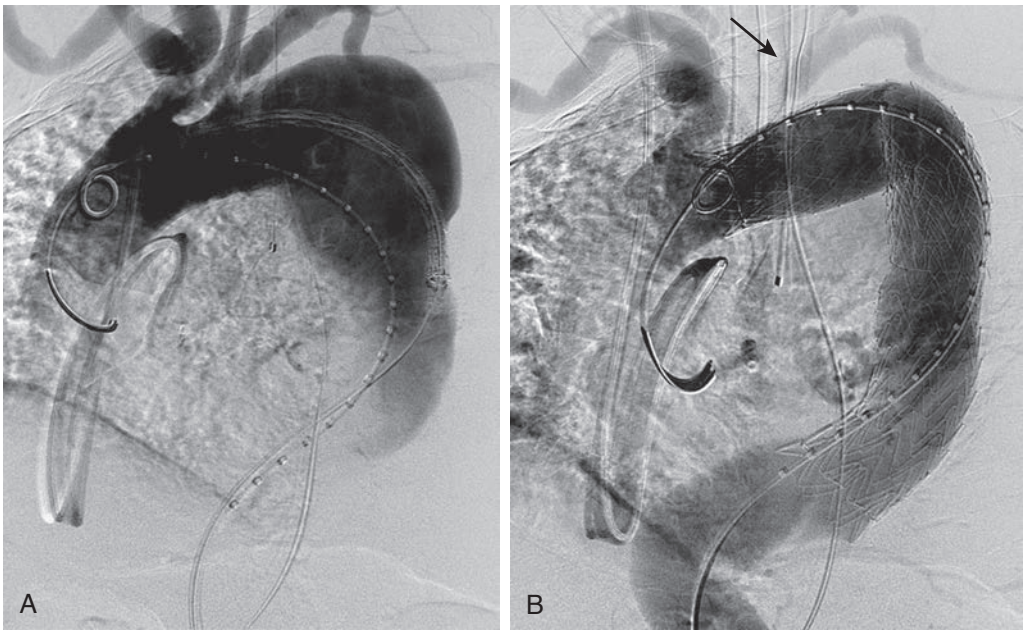

Figure 78.8 **(A)** Operative thoracic aortography demonstrating a large thoracic aortic aneurysm. Note the parallel proximal and distal landing zones. **(B)** Completion aortography showing the thoracic endograft deployed proximal to the left subclavian artery with exclusion of the aneurysm. Note the retrograde filling of the left subclavian artery without endoleak *(arrow)*.

considered adequate for most devices, a longer seal zone may be preferable in angulations to decrease the occurrence of endoleaks and migration and protect from late aneurysmal degeneration. The urge to cover longer aortic segments should be tempered by the increased risk for spinal cord ischemia. If anatomically feasible, the landing zone should ideally be parallel in configuration, distal to the left SCA, and proximal to the celiac artery (Fig. 78.8). Sealing in curved portions of the aorta, generally near the left SCA, presents added complexity. The longitudinal stiffness of the device can limit device apposition to the inner curve. The minimum sealing length in these regions should focus on the inner curvature rather than to the outer curve. The proximity of the sealing zones to major branches should be carefully evaluated to avoid branch vessel occlusion. If indicated, a surgical bypass should be considered to maintain patency of the branch vessel or a chimney/snorkel technique used to preserve in-line flow.

Operative Planning and Options

Imaging

Preoperative imaging studies delineate morphologic features of the aneurysm, branch vessel anatomy, and quality of access vessels. Computed tomographic angiography (CTA) is capable of providing all necessary anatomic information (see Chapter 27). A 128-slice computed tomography (CT) scanner provides high definition and very fast scan acquisition times. It provides three-dimensional volume rendering capability and maximum intensity projections, along with sagittal and coronal reconstructions. Imaging software such as M2S (M2S, West Lebanon, New Hampshire), Vitrea (Vital Images, Minnetonka, Minnesota), and Aquarius (TeraRecon, San Mateo, California) offer additional tools, such as reconstructions orthogonal to line of flow and virtual grafts to aid in procedure planning. When patients are unable to undergo CTA, gated magnetic resonance angiography (MRA) should be considered.

The preoperative CTA needs to include the aortic arch, chest, abdomen, and pelvis with and without contrast enhancement to adequately evaluate the quality of the native vessels. Tortuosity is best delineated by three-dimensional reconstructions. Qualitative evaluation of arch disease (i.e., atheromatous burden), as well as location of vertebral arteries, is critically important when landing in zones 0, 1, or 2. Assessment of pelvic perfusion is essential for evaluating risk of spinal cord ischemia, especially in patients who have undergone prior aortic repair, or in anticipation of long aortic segment coverage.

Sizing

Accurate measurements of access vessels and sealing zones are critically important for determining appropriate graft sizes. Excessive oversizing may cause graft infolding, poor seal due to gutter formation, and possible aortic neck degeneration from excessive radial force. Aortic diameters are best measured on orthogonal reconstructions, especially in areas of tortuosity and angulation. If reconstructions are not available, the short axis is a reasonable estimate of the true diameter.[23] Neck diameters between the proximal and distal sealing zones can vary, which may lead to inaccurate sizing. Appropriate aortic length measurements are necessary to calculate device lengths. This can be difficult because the thoracic aorta moves posterior lateral in the proximal portion and anterior medial near the diaphragm. The presence of an aneurysm exacerbates this tortuosity. A centerline flow measurement from a three-dimensional reconstruction provides the best length estimate, although this can still underestimate endograft length because the devices follow the greater curvature, especially in large aneurysms.

Identification of Landing Zones

The lack of adequate landing zones both proximally and distally is not infrequently encountered. Extension into zone 2 to achieve adequate seal proximally was required by more than 20% of patients in some regulatory trials.[20] Although coverage of the left SCA is generally well tolerated because of a rich collateral network,[24-29] routine exclusion should be discouraged because both experimental and clinical evidence suggests that not all patients can tolerate the occlusion safely.[29-31] The left SCA is an important vessel for perfusion of both the spinal cord and the brain via the left vertebral artery.[32] It provides blood flow to the spinal cord through the internal mammary and anterior intercostal branches.[33] The decision to preserve or cover the left SCA has undergone a substantial paradigm shift. Although early-generation cases underwent a left carotid–subclavian bypass or transposition, later reports of safe coverage resulted in indiscriminate coverage of the left SCA.[24-28] Current data support and guidelines recommend preserving left SCA flow due to the risk of brainstem stroke and spinal cord and arm ischemia.[34,35] A dominant left vertebral artery is present in greater than 60% of patients, which coincides with an absent or atretic right vertebral artery. Intuitively, these findings place patients at increased risks for posterior circulation infarct. Intentional left SCA coverage without revascularization significantly increases the overall risk of stroke, especially for the posterior circulation (5.5% vs. 1.2%).[36,37] Coverage without revascularization has been linked to an increased risk for spinal cord ischemia in a review of EUROSTAR (European Collaborators on Stent/Graft Techniques for Aortic Aneurysm Repair) registry data.[35] On multivariate analysis, left SCA coverage without revascularization was an independent predictor of spinal cord ischemia, with an odds ratio of 3.49.

When reconstruction is undesirable, careful preoperative imaging should be performed to assess the patency of the right vertebral artery connecting to the basilar artery and circle of Willis, to identify patients unable to tolerate left SCA occlusion. Mandatory left SCA revascularization is imperative in the presence of a dominant left vertebral artery, left internal mammary to coronary artery bypass, presence of left arm hemodialysis access, aberrant right SCA, hypoplastic or absent right vertebral artery, termination of left vertebral artery in the posterior inferior cerebellar artery, occluded internal iliac arteries, or anomalous origin of the left vertebral artery from the arch.[29,34,38,39] Revascularization should also be considered when an elevated risk for paraplegia exists with extensive coverage of the thoracic aorta combined with previous infrarenal aortic replacement. Delayed revascularization can be performed in cases of arm ischemia without untoward effects.[34,39] Revascularization by either left CCA to left SCA bypass or SCA transposition can be performed. Transposition eliminates one source of type II endoleaks; technically it can be more challenging and less desirable in situations where the left SCA is aneurysmal or displaced by the **descending thoracic aorta.** Preservation of a posteriorly located vertebral artery can be difficult, and for this reason most surgeons prefer carotid-to-subclavian bypasses (see Chapter 118) combined with ligation or embolization of the proximal left SCA. The updated SVS practice guidelines recommend routine left SCA revascularization be performed prior to TEVAR in elective situations.[38]

Debranching of the Arch Vessels

Several alternative treatment options have emerged to maintain branch vessel perfusion during TEVAR in zones 0 to 2; these include hybrid procedures with in situ fenestration, extra-anatomic bypasses, endovascular debranching with chimney techniques, and open aortic debranching. The goals of each technique are to extend the proximal landing zone, maintain branch vessel perfusion, lower the risk of a type Ia endoleak, and decrease procedure related adverse events. Thoracic aneurysms juxtaposed to the left CCA can be technically challenging. If coverage of the left carotid artery is necessary, several options are available to maintain carotid perfusion. More frequently an extra-anatomic carotid-carotid bypass is performed. This requires bilateral common carotid exposure through oblique neck incisions and tunneling a ringed 6- or 8-mm PTFE graft retroesophageal. Caution should be taken because larger grafts may compress the esophagus and cause dysphagia. Carotid bypasses have been found to be durable (3-year primary patency rate of 88%).[40] In select situations when inflow from the right CCA is inadequate and the patient is high risk for open arch reconstruction, sequential extra-anatomic bypasses should be considered. This would involve performing a series of bypasses originating from the left common femoral to the left axillary artery then from the left SCA to left CCA. The length and number of bypasses creates concern when defining patency rates.[41] Endovascular debranching techniques for the left CCA have been described.[42] Exposure of the left CCA allows retrograde access into the aortic arch and the creation of a left carotid to SCA bypass if needed. TEVAR deployment from the femoral and retrograde CCA covered stent placement extending into the arch is performed (chimney technique).[43] The covered stent is deployed to the same level as the TEVAR. Limited results have shown this technique to be an acceptable option for high-risk patients.

Thoracic aneurysms encroaching on the innominate artery are the most challenging to manage. Hybrid endovascular repair options are described. Involvement of zones 0 and 1 are often managed with an open arch debranching originating from the proximal ascending aorta (Fig. 78.9). Through a median sternotomy, a bifurcated prosthetic graft is sewn to the ascending aorta, the innominate artery, and the left CCA. A TEVAR can then be inserted and deployed.[44] Andersen proposed an algorithmic approach to the management of aortic arch disease. This technique was found to be successful but did carry a higher than expected rate of type A dissection and 30-day mortality (14.9%).[45]

Management of the Celiac Artery

If the distal landing zone is inadequate, the surgeon faces a similar situation as the left SCA. Adequate collateral circulation between the celiac axis and SMA is expected via the gastroduodenal and pancreaticoduodenal arcades, their presence helps to determine if the celiac can be covered.[46] Vaddineni et al.[47] reported seven

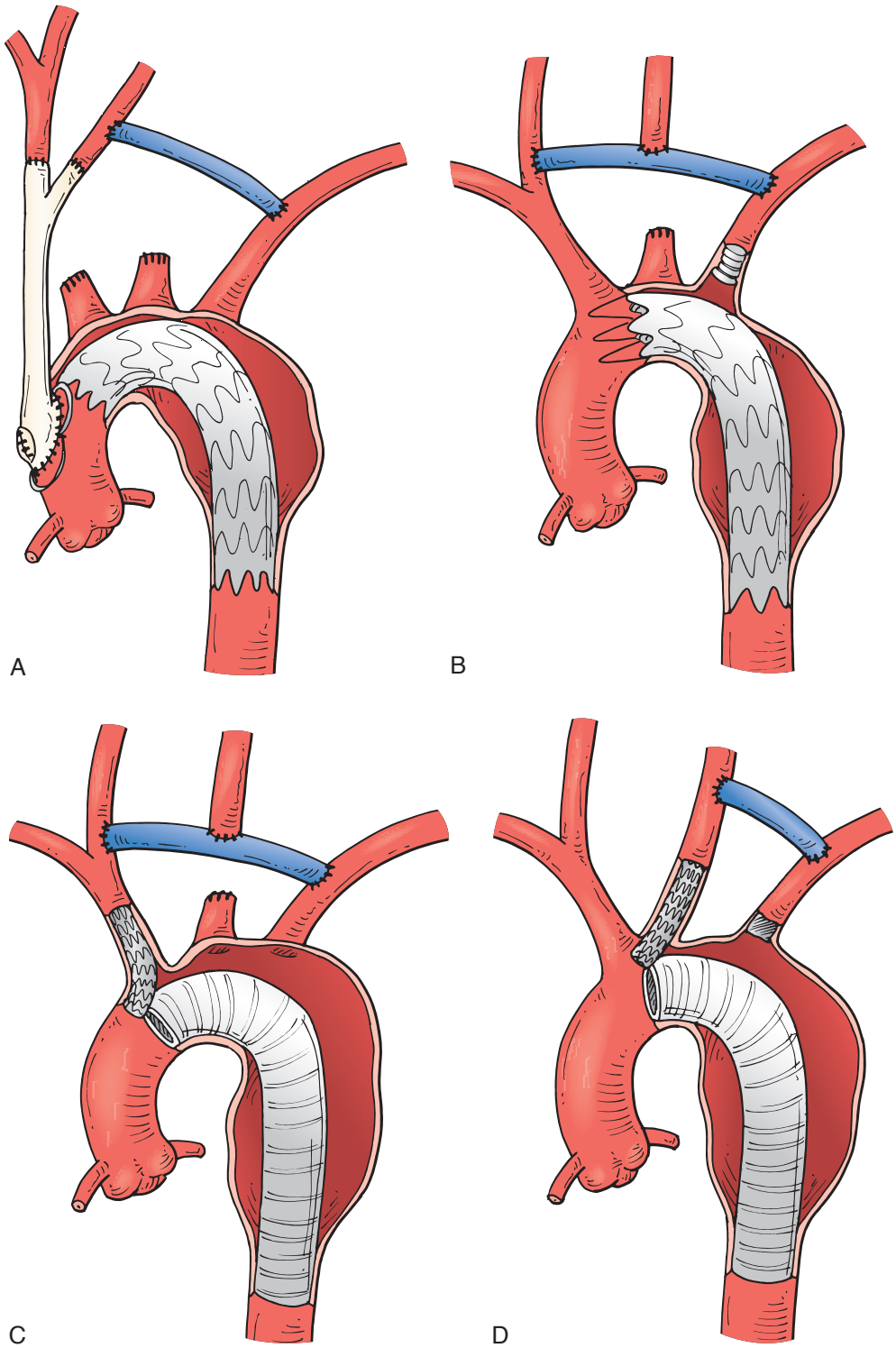

Figure 78.9 **(A)** Zone 0 hybrid arch debranching with thoracic aortic endovascular repair. **(B)** Zone 1 hybrid arch repair. **(C)** Right to left carotid-carotid bypass and left subclavian bypass to extend the proximal landing zone. **(D)** Zone 1 endodebranching.

such cases without mesenteric or spinal ischemic complications. If the collateral network is inadequate, consideration to preserving the celiac should be undertaken. Mehta et al. published a series of 31 patients undergoing TEVAR with celiac interruption. Postoperative mesenteric ischemic complications occurred in 6%, and another 6% sustained paraplegia. He concluded that celiac coverage was relatively safe in the presence of prominent SMA-celiac collaterals.[48] Outcomes of 18 patients with celiac coverage during TEVAR were published by Rose in 2015 and had similar results. Consistent with these studies, a review of the worldwide data reported a low rate (6% to 8%) of foregut ischemia associated with celiac coverage.[49,50] Use of periscope

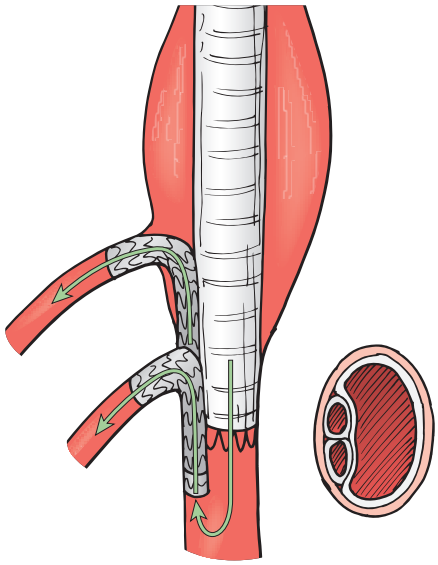

Figure 78.10 Thoracic aortic endovascular repair with downward periscope graft in the celiac artery and superior mesenteric artery.

grafts is an acceptable option in situations when celiac preservation is necessary and open revascularization unfavorable (Fig. 78.10). This technique has proved useful as a means of preserving or rescuing branch vessels in TEVAR seal zones. A self-expanding covered stent is inserted into the celiac artery via femoral access, and the TEVAR is deployed in the standard manner. Reinforcement of the self-expanding celiac stent may be necessary because of the steep downward angle created by the TEVAR.[43]

Adjunctive Measures for Neuroprotection

TEVAR is not without risk for spinal ischemia; there is consensus that patients with long-segment descending thoracic aortic coverage and antecedent or concomitant abdominal aortic grafting are at particular risk. In such circumstances, adjuncts are used, albeit without firm evidence. Such techniques have been evaluated mostly during open repair of TAAA. (For a more detailed discussion, the reader is referred to Chapter 77). Most centers selectively use cerebral spinal fluid (CSF) drainage in patients who are at an increased risk for spinal cord ischemia. The spinal drain is inserted preoperatively and maintained for 48 to 72 hours while CSF pressure is kept ≤10 cm H_2O. The advantages of selective drain use relate to an obligatory intensive care unit admission and hemorrhagic complications associated with catheter placement (0% to 3%).[49] CSF drainage has also been shown to effectively reverse delayed-onset paraplegia after TEVAR and should liberally be used if spinal cord ischemia is suspected.[51] Besides the anatomic features noted earlier, hemodynamic stability plays a crucial role in spinal cord ischemia because the underlying pathology appears to be poor collateral flow and decreased perfusion. Low intraoperative mean arterial blood pressure (less than 70 mm Hg) has been linked to spinal cord ischemia.[51] Except for the short time required for endograft deployment, when a relatively low blood pressure may be desired, an elevated pressure is preferred intraoperatively. Similar to open aneurysm repair, postoperative hypotension can precipitate spinal cord ischemia. The importance of the artery of Adamkiewicz, which is usually located between T8 and L2, has been debated extensively but has not clearly been linked to spinal cord ischemia. The EUROSTAR review found an association between T10 coverage and spinal cord ischemia; 40% of patients with spinal cord ischemia exhibited T10 occlusion, and only 18% did not suffer periprocedural paraplegia or paraparesis.[35] However, the association was not present on multivariate regression analysis. Accordingly, no recommendation can be made to avoid covering the T10 region.

Operative Technique

After the optimal site for device entry has been determined, the ipsilateral common femoral artery is exposed or can be accessed percutaneously.[52] The contralateral femoral artery or brachial may be accessed for placement of a marker catheter. Once access is established, a stiff wire is advanced into the ascending aorta. It is helpful to mark the back end of the wire on the table to detect any unintentional movements. When a conduit is needed, it is constructed through a small retroperitoneal incision in the ipsilateral lower quadrant. A 10-mm Dacron graft is anastomosed to the common iliac artery in an end-to-side fashion; this large-diameter conduit accommodates larger sheaths. The conduit can be accessed through the same incision or can be brought out through an incision in the lower abdomen or groin. Inserting the sheath through the graft wall rather than the open end provides better sheath stability during manipulations and decreases blood loss. At the end of the procedure, the conduit can be ligated or converted to an iliofemoral bypass if indicated. Iliac tortuosity can generally be addressed with stiff wires and hydrophilic delivery sheaths. On occasion, excessive tortuosity of the external iliac may require more proximal common iliac access. Aortography is performed through the marker catheter in a left anterior oblique projection (30 to 60 degree). The preoperative CT imaging should define the optimal angle. For visualization of the distal landing zone, especially near the celiac axis, a lateral projection is ideal. The angiogram locates branch vessels and can confirm the estimated length of endograft. Prophylactic placement of a guide wire or catheter in the celiac axis or SMA can be useful. In the event that imprecise deployment results in encroachment on the celiac axis or SMA, the wire provides ready access to the vessel for possible stent placement. Similarly, the left SCA can be accessed via the left brachial artery and provide access should restoration of flow be required. Once the landing zones are determined, the endograft is introduced under fluoroscopic guidance. The device is advanced past the target region and drawn back to eliminate any stored energy. Application of steady antegrade pressure on the wire keeps it positioned against the outer aortic curvature for accurate device deployment.

Acute angles in the descending thoracic aorta may render device tracking difficult. Various strategies, such as buddy wires, long sheaths, and distal graft deployment first, may be used to negotiate these areas. If these techniques fail, a body floss brachiofemoral wire may improve device tracking and delivery. When more than one device is needed, the smaller device should be deployed first. If both devices are the same diameter, strategies to create a longer overlap zone (7.5 to 10 cm) should be planned.

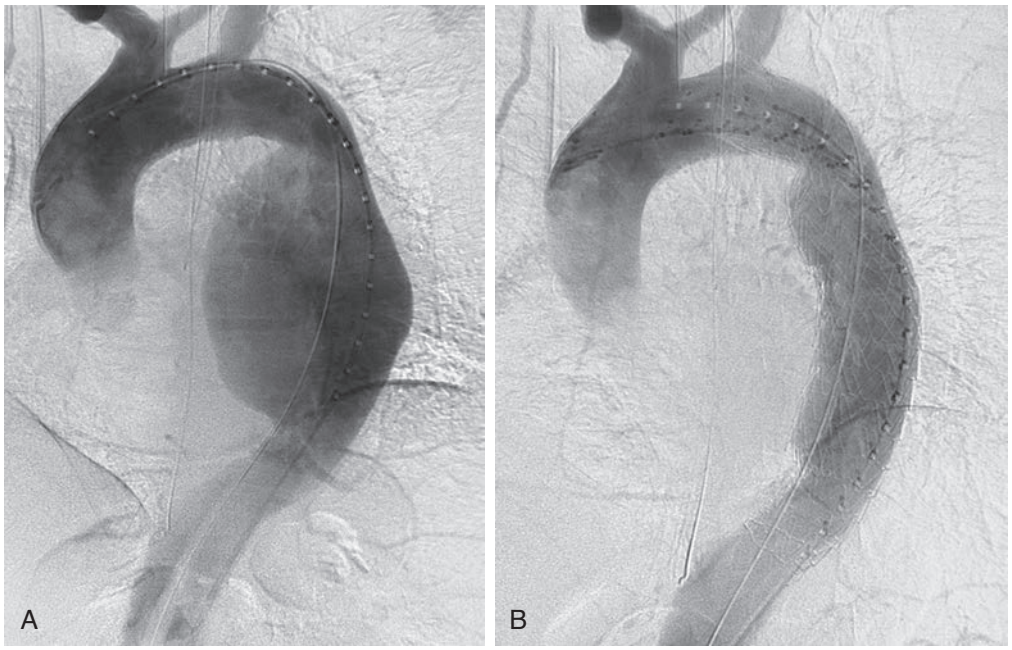

Figure 78.11 **(A)** Intraoperative angiogram showing a large fusiform descending thoracic arotic aneurysm. **(B)** Two TAG stent grafts are deployed to exclude the aneurysm.

When more than two devices are required, ideally the proximal and distal landing zones should be treated and the third (largest) device bridges the gap between the first two components. For large proximal aortic aneurysms, deploying the distal endograft first may be preferable because it stabilizes the proximal endograft which improves deployment accuracy. All techniques benefit from temporary reduction of mean arterial pressure, which decreases the windsock effect that may result in distal endograft migration. Infrequently, adenosine-induced cardiac asystole or rapid cardiac pacing may be necessary. Completion angiography confirms accurate stent graft placement, as well as the absence of endoleaks (Fig. 78.11). Types I and III endoleaks should be addressed by additional balloon inflation or insertion of extension pieces. Care should be exercised during sheath removal because iatrogenic iliac artery injuries are often recognized at this stage. Iliofemoral angiography after the sheath has been pulled into the distal external iliac artery aids in evaluating vessel integrity. Maintaining wire access is of paramount importance; balloon control and endovascular repair with covered stents can be lifesaving.[53]

Postoperative Management

If a spinal drain is present, CSF pressures should be maintained at ≤10 cm H_2O. If the patient is awake and neurologically intact, the drain can be clamped and removed the following day. Maintaining a modestly elevated mean arterial pressure (≥80 mm Hg) is an important adjunct; acceptance of an even higher pressure limit should be used if a neurologic deficit is detected. After TEVAR, neurologic assessments should occur at 1-hour intervals for the first 6 hours and thereafter every 2 hours. If a neurologic change occurs, patients are transferred to the intensive care unit and mean arterial pressure pharmacologically increased to greater than 100 mm Hg and a spinal drain inserted. If neurologic symptoms resolve, pharmacologic support to maintain a mean arterial pressure greater than 80 to 100 mm Hg is continued at the physician's discretion. If no improvement is seen within 4 to 6 hours, magnetic resonance imaging is performed to evaluate for spinal cord infarction.

Follow-Up

Recommended follow-up at 1 month and 1 year includes a CT scan of the chest with and without contrast enhancement, preferably with delayed imaging to detect subtle endoleaks. Thereafter annual CT scans are recommended for life. MRA can be used with most grafts, and the frequency of surveillance imaging is undergoing critical appraisal to reduce radiation exposure, cost, and patient inconvenience.

Results

The feasibility of TEVAR for descending thoracic aortic pathology is firmly established; however, indications for intervention are poorly defined due to a paucity of data. Despite a large body of literature published in the past 10 years, randomized trials have not adequately compared TEVAR with open surgery. The availability of long-term results is mostly limited to industry sponsored studies, and what exists fails to reflect device evolution and maturation of general learning curves. Most single-center and registry reports include a combination of anatomic locations, diverse pathology, and various stent-graft types along with varying degrees of urgency, all of which makes comparison of results difficult. These concerns were recognized by the SVS, which published reporting standards for TEVAR in 2010, and an updated set of guidelines reflective of current TEVAR practice

TABLE 78.2 US Food and Drug Administration Pivotal Trial Results

	# Enrolled	Spinal Cord Ischemia	30-Day Mortality	1-Year Endoleak Rate	Technical Success	Freedom From Aneurysm-Related Mortality
Gore TAG	140	2.8%	2.1%	3.9%	98%	97% at 3 years
Cook TX2 Starz Trial	160	5.6%	1.9%	3.9%	98.8%	94.1% at 5 years
Medtronic Talent Valor Trial	195	8.7%	2.1%	12.2%	99.5%	96.9% at 1 year

is in preparation. In addition to the SVS guidelines, there exists an expert consensus document published and supported by the Society of Thoracic Surgery. This publication describes criteria for intervention and defines optimal therapy based on data collected from earlier generation endografts. Similar shortcomings are common in the open surgical literature on the topic and prevent accurate comparisons of mortality and morbidity between the two modalities. This is exaggerated by the typically low-risk patients in surgical series; most patients undergoing TEVAR are usually in a higher risk category.

Technical Results

Three pivotal trials (Table 78.2) of the approved endografts (Gore, Medtronic, and Cook) have provided the best insight on TEVAR safety and efficacy primarily due to rigid follow-up of a uniform, well-defined population of good-risk surgical candidates undergoing elective operation. However, definitions, procedures, and inclusion criteria were not uniform among the studies, thus limiting direct study comparisons. In general, technical success is defined as delivery of the device to the intended location with satisfactory exclusion of the aneurysm and no type I or II endoleaks, and clinical success is defined as the outcomes of aneurysm-related deaths, rupture, endoleaks, and re-intervention. The demographics and early results are remarkably similar in all three trials. Male gender predominated, accounting for greater than 60% of patients. The average age at intervention was 71 years and average aneurysm diameter greater than 6 cm in all but one trial. With minor differences, demographic parameters, as well as risk factors, were in general well matched and successful TEVAR completion rates were expectedly high (≥98%). All technical failures were access related despite a high incidence of conduit use (9.4% to 21%), averaging nearly one in seven patients. Most of the conduits were to the common iliac artery and a few to the aorta. The number of devices implanted depended on the length of the **pathology**, the length of the available devices, and the tapering requirements of each device. Even with long nontapered devices, 56% of patients required more than one component. Although the VALOR trial did not report this statistic, the shortest aneurysm treated was 8 cm, and because of the minimum landing zones of 4 cm and the longest device length available, essentially all cases required more than one piece (average 2.7 per case). Extending into zone 2 for obtaining a proximal seal was not uncommon; it was performed in up to 20% of cases, and the VALOR trial reported deployment into zones 1 or 2 in 33% of cases.

Perioperative Outcomes

The early experience with first- and second-generation endograft devices in higher-risk individuals was associated with a high early mortality rate (9% to 12%) but did document TEVAR feasibility.[54,55] Recent trials report a 30-day mortality of 1% to 2%, which is significantly less than the 7% mortality of open surgical repair. Two TEVAR studies (Gore CTAG and Cook Zenith Alpha) using next-generation endografts confirmed these results with low 30-day mortality rates (0% to 1.5%) in a combined cohort of 176 patients.[56,57] Operative mortality, which includes all in-hospital deaths beyond 30 days, impacted the open surgical group far more than TEVAR (2% vs. 12% TAG study, 1.9% vs. 5.7% STARZ trial, and 2.1% vs. 7.9% VALOR trial).[20,58-60] Summarizing and applying statistical analysis to the data, it can be stated that TEVAR compares favorably with open repair with respect to operative mortality. In conglomerate, the three comparative clinical trials included 495 patients treated by TEVAR for anatomically suitable DTAA and 353 patients managed by open surgery; notably, these procedures mostly were performed in academic medical centers of excellence. Operative mortality for TEVAR was 2% compared with 8.5% for open repair ($P < .001$). However, with more liberal application of this technology, the European registry reported higher elective 30-day mortality (5.3%), but this included arch aneurysms. In a meta-analysis of 17 studies, Walsh et al.[61] found a significant reduction in mortality and major neurologic complication rates with TEVAR. Similar findings were consistent in a meta-analysis of 42 nonrandomized studies published in 2010 by Cheng et al. However, beyond 1-year the existing evidence suggests clinical equipoise when comparing TEVAR with open surgical repair.[62]

Late Results

Although many reports provide early and midterm results, the only long-term (5-year) data available originate from the Zenith TX2, Gore TAG, and Medtronic Valiant Studies.[11,54,55,63-71] One-year outcomes did reinforce the advantage of TEVAR in aneurysm-related survival, which averaged 95% across the trials, significantly better than the 89% for the combined open surgical repair. All three trials reported late TEVAR benefits continued for at least 5 years, noting that the early difference reflected the perioperative period with few if any late aneurysm-related mortalities in either group.[11,58,69-71] However, all-cause late survival showed minimal differences between open and endovascular modalities beyond 1 year, which not surprisingly mirrored the

findings of randomized **EVAR** trials.[11,63,67] At 5 years, overall survival rates in the Gore TEVAR and open groups (68% and 67%), and in the Cook TEVAR study (62.9% and 62.8%), indicated similar late effectiveness and sustained protection from aneurysm-related mortality for both procedures.[11] However, late outcomes are not as encouraging in high-risk populations. For example, in a series from Stanford (103 patients, 60 of whom were deemed inoperable) 5-year survival was only 31% compared with 78% for those who were open surgical candidates. This brings to question the appropriateness of any treatment in asymptomatic high-risk patients.[54]

Complications

Complications of TEVAR, like those of all endovascular procedures, can be divided into a general category common to all operative interventions and a procedure-specific category. General complications are not well detailed, and the FDA trials focused on combined trial-specific safety endpoints, which made individual complication rates difficult to determine. At any rate the incidence of major or serious adverse events strongly favors TEVAR over open repair in the three regulatory trials that compared similar metrics. As expected in a population with advanced age and atherosclerotic disease, cardiopulmonary complications dominated the early morbidity, although frequency and severity were less than open repair.[58,68] For example, the STARZ trial reported a cardiovascular complication rate of 15.6% (TEVAR) and 44.3% (open repair) with an identical incidence of pulmonary complications (15.6% vs. 44.3%).[58] The incidence of major or serious adverse events and other secondary measures, such as blood loss and hospital stay, were strongly in favor of TEVAR.

Vascular Complications

Vascular complications due to large sheaths in atherosclerotic arteries were relatively high in the early TAG trial (14%). They were reduced significantly (6%) in the follow-up confirmatory trial of the modified TAG device, which reflects a collective learning experience for TEVAR.[20] The spreading awareness of vascular access issues resulted in a reduction of vascular complications (5% to 7%) in recent reports.[20,59,72] The high incidence in the STARZ trial was not an indication of a higher complication rate because it was a difference in the definition of vascular events, which was more inclusive than other studies. Serious iliac artery injuries, a subset of vascular complications ranging from a tear to complete avulsion during sheath withdrawal (Fig. 78.12), are less common nowadays but remain potentially life-threatening. The prophylactic use of iliac conduits and endoconduits should be encouraged to avoid these injuries. The Cook Zenith Alpha endograft has addressed the universal need for a lower-profile TEVAR device. One-year data published by Illig et al. included 110 patients with technical success achieved in 98%, and no iliac conduits were used. However, severe iliac occlusive disease prevented two patients from receiving the endograft; these findings suggest that, despite a presumed expanded applicability of lower-profile devices, proper patient selection remains of utmost importance.

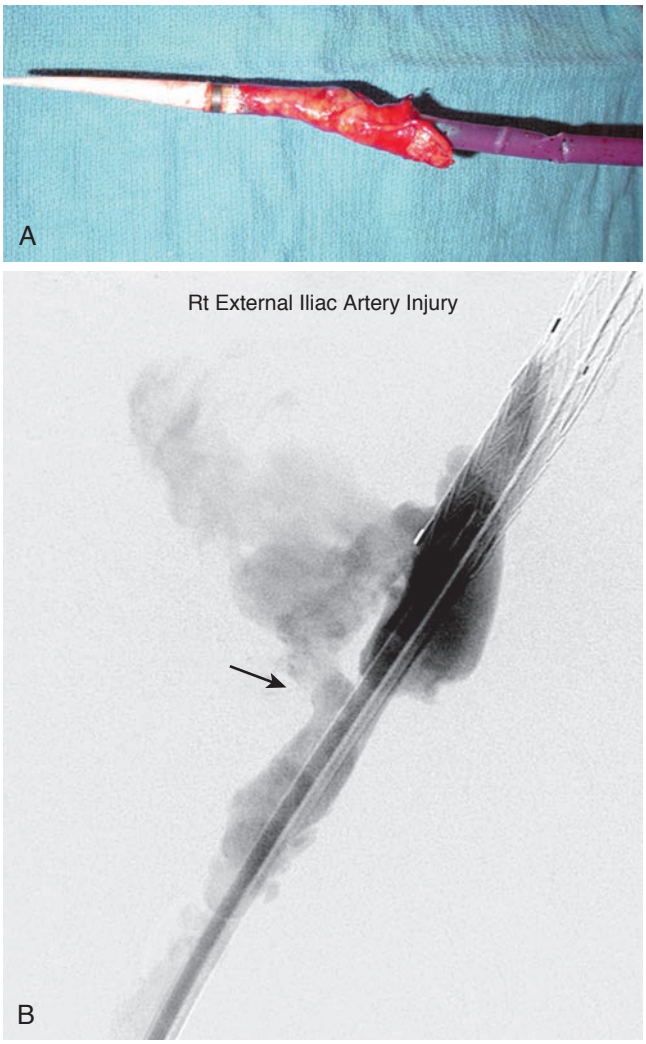

Figure 78.12 **(A)** Torn segment of an external iliac artery on the delivery system. **(B)** Angiography illustrating the injury *(arrow)*. The stent-graft in the iliac artery is from previously performed endovascular abdominal aortic aneurysm repair.

Neurologic Complications

Neurologic complications can be devastating after DTAA repair. Although stroke receives less attention than spinal cord ischemia, it is not uncommon and occurs at similar rates during open and endovascular repair (3% to 7%).[20,34,35,58,59] Deployment of the endograft proximal to the left CCA shows a strong association with perioperative stroke, probably secondary to manipulation of the arch with catheters, wires, balloons, and stent-grafts.[14,20,27] In the TAG study, stroke occurred in 14% of patients during zone 2 deployments versus 1% when TEVAR was placed distal to the left SCA.[73] Only the Zenith TX2 study reported dissonant results, with all four strokes occurring in patients that had a TEVAR placed distal to the left SCA.[58] This finding is difficult to explain but may relate to deployment of the TX2 device, which often started more proximal to eliminate tension and was adjusted to its final position. The importance of technique; limit aortic manipulations, meticulous cleansing of guide wires and catheters, and limited use of molding balloons cannot be

overemphasized enough to minimize the stroke risk. Independent predictors of stroke in the EUROSTAR registry included female sex and prolonged procedure time (>160 minutes).[35]

The TAG study showed a marked reduction in paraplegia and paraparesis in comparison with open repair (3% vs. 14%). The advantage of spinal cord protection with TEVAR was evident in all three FDA trials compared with open controls (6.2% vs. 13%; $P < .007$). The high incidence of spinal cord ischemia in the control group has been criticized by aortic centers of excellence, which report lower paraplegia rates (2.5% to 3%) associated with open DTAA repair.[74,75] The difference may represent the retrospective analysis of these reports, exclusion of high-risk patients with anastomoses in the distal arch requiring hypothermic arrest, variable use of neuroprotective adjuncts, and most notably lack of reporting of paraparesis as part of these series. Stone et al.[76] reported a spinal cord ischemia rate of 8.6% in a recent open repair cohort when paraparesis was included. If only devastating permanent paraplegia is considered, TEVAR (1.6% vs. 5.1%; $P < .0037$) is still favored. The reduced incidence of spinal cord ischemia with TEVAR may be related to avoidance of aortic clamping and reduced hemodynamic disturbances at the spinal cord level because of lack of blood loss from intercostal back bleeding.[77,78]

Several factors have been linked to spinal cord ischemia after TEVAR: concomitant or previous infrarenal aortic repair,* extensive thoracic aortic coverage,† renal insufficiency,[35,84] intraoperative hypotension (systolic blood pressure <80 mmHg),[80,51] and coverage of the hypogastric artery and left SCA.[34,35,78,86] Some of these risk factors are beyond the clinician's control, but many (coverage of the left SCA and hypogastric artery) can often be avoided by modifying the operative plan. The EUROSTAR data showed that left SCA coverage without revascularization was independently associated with spinal cord ischemia.[35] Recent reports suggest that left SCA revascularization should be performed more frequently than was previously recognized for either left upper extremity ischemia[39] or spinal cord protection.[34,35] Lumbar and pelvic collaterals account for 25% of spinal cord perfusion,[87] and thus compromised hypogastric flow contributes to spinal cord ischemia.[67] For that reason, preservation of the internal iliac and staged repair of synchronous aneurysms to allow time for collateral maturation are advocated.[51,81] In addition to preservation of left SCA and pelvic collateral flow, a strategy should be implemented to prevent SCI. Acher et al. used an aggressive intraoperative and postoperative neuroprotective intervention to reduce SCI associated with TEVAR.[88] Strategies to increase cord perfusion and reduce metabolism and oxygen demand were combined on 155 patients. The protocol included patient management by cardiac anesthesiologists, intraoperative hypothermia (34° C), intraoperative naloxone, mannitol and steroids, avoidance of arterial vasodilators, goal-directed blood pressure therapy (MAP 90 to 100 mm Hg), maintaining hemoglobin ≥10 g/dL and spinal drain. The mean thoracic aortic coverage was 25 cm, 81.1% had greater than 12 cm of coverage, and 49% had complete coverage from the left SCA to the celiac artery. In hospital mortality (1.9%), stroke (1.3%), and SCI (0.65%) rates were acceptable. Thus, based on the published data, intraoperative protective measures rather than rescue measures are strongly recommended.

*References 14, 35, 64, 67, 73, 79, 80-82.
†References 27, 35, 55, 65, 68, 72, 81, 83.

Endoleaks

Early endoleak rates at 30-day follow-up were inexplicably high in the VALOR trial (26%) but far lower in the TAG trial (3.6%), STARZ study (4.8%), and EUROSTAR registry. This appears to be a definition issue because all endoleaks observed at any time before 30 days were included in the VALOR report, whereas only endoleaks at the 30-day follow-up were included in the other studies. At 1 year, endoleaks were present in 4% of patients (TAG and TX2) and 12.2% (Talent). In long-term follow-up of the TAG study, between 4% and 8% of patients had endoleaks at each time interval out to 5 years.[11,58,59] Long-term STARZ follow-up revealed a low annual endoleak rate (2% to 7%), which decreased in years 3 through 5. The endoleak incidence was consistently higher in the VALOR study (12% to 17%), and similar to the TX2 study the majority of endoleaks were defined as type II.[69-71] The incidence of endoleaks has decreased with device improvement.[9] The distribution of endoleak type was variable; the TAG study reported more type I and III endoleaks, whereas the other studies found a larger number of type II endoleaks. This again is likely a reporting issue because the TAG study relied on investigator reports, whereas the other trials used a core lab. Endoleaks were in general less common than in comparable EVAR series, with more type I and III endoleaks and fewer type II which accounted for most but not all re-interventions.[89,90]

Sac Enlargement

Aneurysm sac shrinkage is a surrogate marker for successful repair of all aneurysms, including DTAA (Fig. 78.13). Sac enlargement rates greater than 5 mm are encountered frequently with TEVAR and have been reported in 7% to 14% of patients at 1 year. The TAG pivotal trial reported late results in a longitudinal cohort: 5-year sac enlargement was 20%, and shrinkage was observed in 50%.[11] These rates may or may not apply to other grafts because the ePTFE material in the TAG study graft was somewhat porous, with a sac behavior resembling that of the original Gore Excluder.[91] Through 5-year follow-up, 84.6% of Talent patients had sac shrinkage or no change. Similar to Talent, the aneurysm sac decreased in size or remained the same in greater than 90% of Cook TX2 cases through 5 years. The TAG endograft was modified to a less porous ePTFE material and has shown a lower incidence (14%) of sac enlargement at 3 years.

Migration, Device Integrity, and Rupture

Late endograft migration has been reported in 0% to 30% of patients, can occur at either end, and was more frequently seen with early generation devices.[83,81,92,93] The current devices clearly possess lower migration rates (0.7% to 3.9%). At 5 years, the TAG trial showed no late migrations (>10 mm) by investigator reporting.[11] Illustrating the variability in data sources, a core

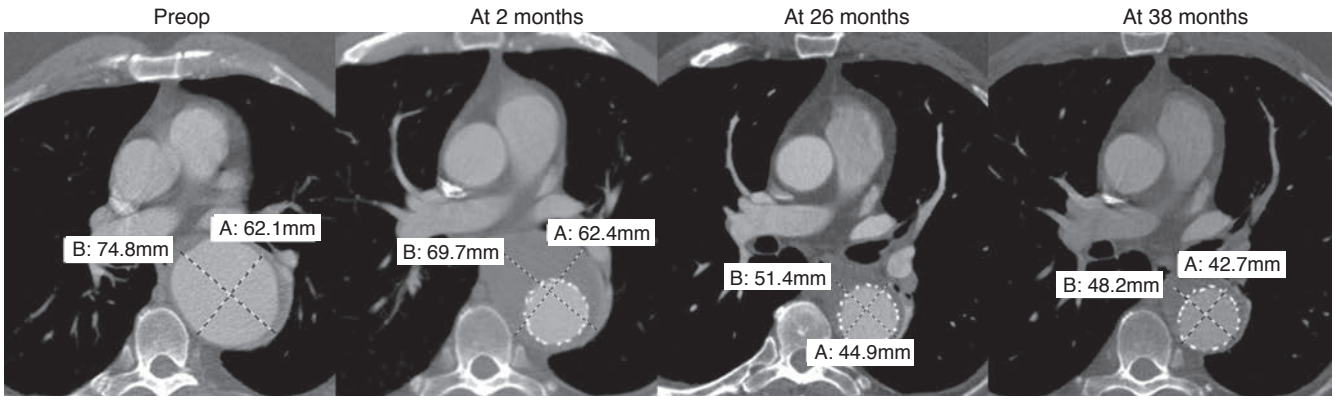

Figure 78.13 Serial follow-up computed tomography scans after thoracic endovascular aortic repair showing progressive sac shrinkage over a time course of 38 months.

laboratory evaluation of a limited number of patients from the same study reported 97% freedom from migration at 12 months, 87% at 24 months, and 83% at 3 years.[94] None of the migrations were clinically significant except for one associated with an arch aneurysm. Migration (>10 mm) was noted on both ends of the devices in the TX2 trial which reported 12 migrations (2 cranial, 9 caudal, 1 cranial and caudal) through 5 years. Retrospective analysis revealed that inadequate aortic neck anatomy was at fault.[69] Site-reported stent-graft migration was infrequently seen with the Talent device at 5 years (1% to 1.8%). None were associated with endoleaks, sac expansion, or required intervention.[70] A very low incidence of device migration was found in the RELAY registry, which had one migration at 24 months.[95]

Re-Interventions

Re-interventions are defined as procedures performed as a consequence of the initial endograft procedure. Early re-interventions were reported in 2.1% (pivotal TAG cohort) during the first year but in 10.7% in the Talent study. Most re-interventions for endoleaks used an endovascular approach. Interesting, STARZ-TX2 re-intervention rates through 1 year were similar between the two groups (4.4% TEVAR vs. 5.7% open surgery). Contrasting to this, long-term TAG study data showed TEVAR re-intervention rates were slightly higher (3.6% vs. 2.1%). Two TAG patients underwent surgical conversion, one for aorto-esophageal fistula and the second for device migration. Both interventions occurred during the first year of follow-up. Three patients had five additional endovascular interventions for endoleaks. Secondary procedures of any kind during the 5-year follow-up were reported in 15% of TAG patients and 32% of open repair. Although most TAG re-interventions were endoleak related, those following open aortic repair were wound complications, tracheostomy, and gastrointestinal tract–related problems. This high rate of secondary re-intervention performed in the open surgical group is contrary to conventional wisdom.[11,76] No TEVAR conversions occurred in the STARZ study, four open conversions were required in VALOR, and only two in RESTORE; indications for open conversion were similar to the Gore study.[95,69,70]

HYBRID ENDOVASCULAR REPAIR FOR THORACOABDOMINAL ANEURYSMS

For patients with inadequate landing zones above the visceral vessels or with extension of aneurysmal disease into the visceral aortic segment, TEVAR can still be performed. This is accomplished by relocating the visceral aortic branches with a bypass procedure originating from distal inflow sites (common iliac arteries or the infrarenal aorta). Exclusion of the TAAA with TEVAR or EVAR devices then follows. This hybrid endovascular technique has the theoretical advantage of replacing a thoracoabdominal exposure for a midline celiotomy, avoiding division of the diaphragm and aortic clamping, along with reducing visceral ischemia time. Intuitively, complication rates are presumed to be lower than those of open thoracoabdominal repair on the basis of the decreased physiologic stress of operating in one visceral cavity rather than in two.

Experience and long-term results are limited with this procedure, and indications and contraindications are poorly defined. The hybrid approach is considered for patients with TAAA who meet standard criteria for repair, but whose limited physiologic reserve prohibit an open repair, and complex anatomy precludes standard TEVAR. Hybrid repair of TAAA remains an extensive operation with high potential for postoperative complications. The most appropriate indication is a patient with significant pulmonary compromise but adequate cardiac and renal function. Indeed, advanced chronic obstructive pulmonary disease (COPD) commonly presents a management dilemma because of the threat of major pulmonary morbidity with open surgery, yet the presence of such COPD is a well-established risk factor for TAAA expansion and rupture (see Chapter 76).[96] Some surgeons find it preferable in all patients because it provides a better safety profile for extensive TAAA.[97] Poor cardiac function, end-stage renal disease requiring hemodialysis, lack of healthy distal aorta or iliac artery, and insufficient landing zones are relative contraindications. Limited data suggest there is little benefit in patients with type IV TAAA, unless associated with a visceral patch aneurysm or severe COPD.

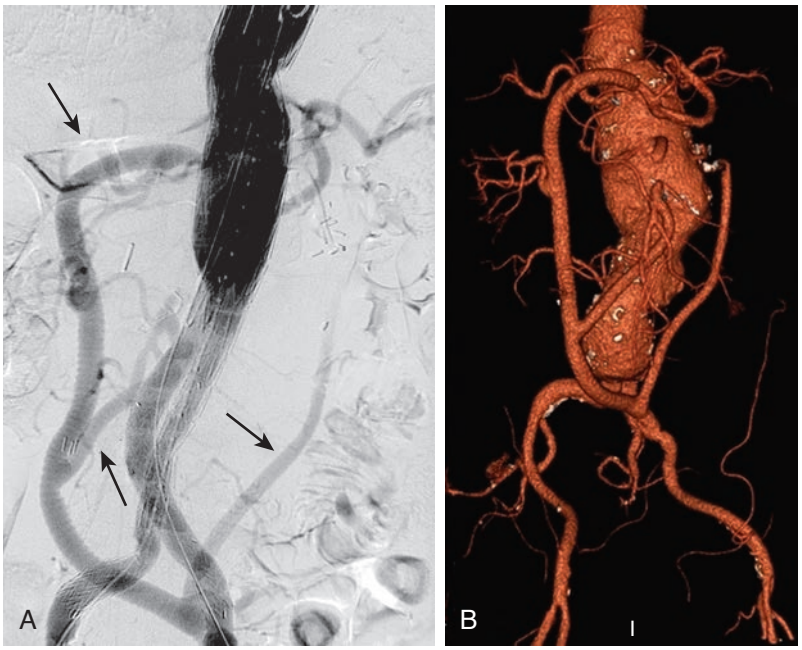

Figure 78.14 **(A)** A thoracic endograft is deployed into a bifurcated abdominal endograft. Retrograde bypass grafts originating from the distal common iliac artery to the celiac axis *(top arrow)*, the right renal artery *(bottom left arrow)*, and the left renal artery *(bottom right arrow)* are illustrated. **(B)** Three-dimensional reconstruction of a postoperative computed tomography scan.

The presence of landing zones and other anatomic requirements remain similar to those for TEVAR. As previously mentioned, a suitable inflow source for the bypass and adequate target vessels are necessary. Multiple renal arteries, severe occlusive disease of the aortoiliac segments, and severe calcification and/or tortuosity make this approach challenging. Access for endograft delivery can be facilitated by direct access through the iliac or aorta if part of the same procedure. In circumstances in which the surgeon chooses a staged procedure, a conduit can be tunneled to the femoral region and temporarily buried; it can be retrieved and used to introduce the endograft.

Additional planning for a hybrid procedure centers around the arteries to bypass and choice of inflow, which is based on patient anatomy and extent of the aneurysm. Previous infrarenal aortic repair or type IV TAAA repair presents a technical benefit in that the existing graft provides not only a secure landing zone but also a safe clamp and anastomotic site for inflow. If the aneurysmal disease extends to the distal aorta and no landing zone exists, a distal iliac is chosen for the inflow source and a standard EVAR device used (Fig. 78.14). If anatomy allows, an isolated infrarenal AAA repair with either a tube or bifurcated surgical graft may be performed first, from which retrograde bypasses to the visceral and renal arteries are constructed, followed by TEVAR. When inflow is derived from an iliac artery, the contralateral femoral artery is preferred for device access to avoid compromising blood flow through the bypasses. Alternatively, a side limb may be sewn onto the bypass graft itself and used as a conduit.

Standard inframesocolic aortic exposure provides adequate access and visualization of the visceral vessel origins. The iliac arteries are exposed if they are intended to be the inflow source. A variety of reconstruction configurations may be used; standard bifurcated Dacron grafts are frequently used with 6- or 7-mm limbs sewn to the recipient vessels. The hepatic bypass is usually routed retrogastric and anastomosed end to side to the common hepatic artery. To avoid kinking, the lengths of all grafts are predetermined under arterial pressure and visceral grafts routed in a "lazy C" fashion. The proximal end of the recipient vessels should be ligated to prevent type II endoleaks and the grafts are covered with an omental flap to minimize the risk of graft-enteric erosion. After revascularization of the visceral and renal arteries, endovascular exclusion of the TAAA is carried out.

The literature is limited, mostly because of small numbers, patient selection criteria, different levels of acuity, and various lengths of coverage. Reported technical success, defined as aneurysm exclusion without type I or III endoleak, ranges from 77% to 100%. Black reported a series of 29 patients with Crawford type I, II, and III aortic aneurysms, and mortality rates improved from 31% to 13%, there were no documented cases of spinal cord ischemia, and branch vessel patency was 98% at 8 months.[98] In another series, procedural time ranged from 239 to 368 minutes, and blood loss averaged 2 L.[99] Mean hospital length of stay was 26 to 27 days in the two largest series, with a median 9 day intensive care unit length of stay.[97,100] In a study that used a staged approach, the mean length of stay after TEVAR was 12 days.[93] However, it is important to recognize that mean organ ischemic time was considerably less (15 to 20 minutes) compared with open TAAA repair.[97,100] Data on intermediate-term outcomes suggest acceptable results. Chiesa et al.[99] reported no aneurysm-related or procedure-related complications with a median follow-up of 15 months. Zhou et al.[101] noted no late aneurysm-related mortality, whereas Resch et al.[102] reported two late aneurysm-related deaths in 13 patients. Two systematic literature reviews have been published. Moulakakis et al.[103] reviewed 19 publications that included 507 patients. A single-stage procedure was used in 55% of patients, and the 30-day mortality was 13%. Graft patency was 96% at 35 months; however, follow-up included only 22% of the total group. Irreversible spinal cord ischemia occurred in 4.5% of patients. Bakoyiannis et al.[104] reviewed 108 patients from 15

reports between 1999 and 2008. The technical success rate was 92%, and 30-day mortality 10%. Spinal cord ischemia occurred in 3% of patients, and 97% of branch grafts were patent at 10 months. The North American Complex Abdominal Aortic Debranching registry included 208 patients from 14 academic centers in North America. The 30-day mortality rate was 14% for all patients, 16% for TAAAs, and 9% for pararenal aneurysms. Mortality was directly associated with severity of comorbidities as determined by SVS clinical scores. Independent predictors of mortality were three-vessel revascularization, coronary artery disease, congestive heart failure, high SVS score, and chronic kidney disease. The mean length of stay was 21 days, and patient survival at 1 year was 77%.[105] Despite a perceived theoretical advantage, hybrid visceral debranching is associated with relatively high morbidity and mortality rates. The incidence of complications ranges widely from 19% to 59%.[100,106] Graft thrombosis is not uncommon (11% and 6.4%) and may result in end-organ ischemia.[100,106]

INVESTIGATIONAL DEVICES FOR THORACOABDOMINAL AORTIC ANEURYSMS

As endovascular technology continues to advance, a wide range of patients with thoracic and thoracoabdominal aortic pathology will benefit from device modifications that accommodate landing zones in the arch or perivisceral aorta while maintaining branch vessel perfusion. Building on basic platforms of TEVAR and EVAR, devices have been created to treat more extensive aortic pathology involving the branch vessels. Endovascular therapy of TAAA is rapidly evolving, and current midterm data strongly support its application. Specifics about each device and the complex techniques for device implantation are beyond the scope of this chapter (see Chapter 79). However, it is important to recognize the advancements and future benefits of these investigational devices. In 2001, Chuter et al. successfully implanted the first branched aortic endograft for treatment of a TAAAs (Fig. 78.15).[107] Fourteen years later, numerous reports have shown a high technical success (95% to 96%) combined with low 30-day mortality (7.8%).[108,109] Cook Medical was the first to develop a thoracic branch endograft and currently has two device options: off-the-shelf t-Branch device with four downward facing external cuffs and a custom-made device (CMD). Both devices have been implanted with very favorable results. These devices are available only in the United States under physician-sponsored IDE studies. Three other device manufacturers are in the process of developing commercially available off-the-shelf or custom-made multibranch endografts at the time of this writing. The Gore Excluder thoracoabdominal branch device is an off-the-shelf four-vessel branch device. Two design options are available: one has four downward facing cuffs and the other possesses two upward renal cuffs and two downward mesenteric branches. A US feasibility study was recently completed, and preliminary data are favorable. Medtronic is developing a modular branched endograft based on the Valiant and Endurant platforms for treatment of TAAA. Currently, this device is being investigated in a physician-sponsored IDE.

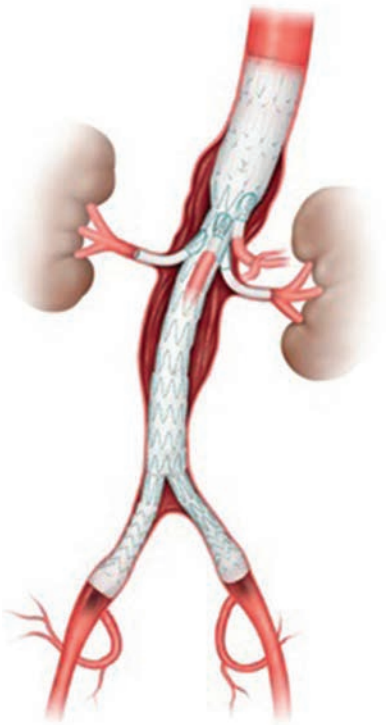

Figure 78.15 Cook Medical t-Branch device

Ferrer et al. investigated outcomes of TAAA patients treated with endovascular repair or open surgical repair from 2007 to 2014.[110] In this prospective database, 341 patients were compared using a propensity score matching. It was determined that patients undergoing endovascular repair had an early benefit in regard to the composite end point of mortality and paraplegia. However, no significant differences were found in spinal cord ischemia or renal insufficiency rates at 30 days and in survival. Midterm outcomes comparing Cook custom branch stent-graft (CSG) and standard off-the-shelf branch stent-graft (SSG) were reported by Fernandez. Fifty-five patients underwent repair using SSG and 83 with CSG. All stent grafts were deployed as intended, no open conversions were needed, and no differences were noted at all primary end points. However, it was recognized that use of SSGs for TAAA and pararenal AAA resulted in shorter wait times for surgery. Both devices were shown to be safe, effective, and durable. Additional supporting data from the Cleveland Clinic have shown that treatment of type II and III TAAA with fenestrated or branched endografts is a promising treatment option. Data from 354 patients from 2004 to 2013 were collected from a physician-sponsored investigational device exemption trial. A 96% technical success rate of 1305 fenestrations and branches were reported, type I or II endoleaks were rare (2.8%), permanent spinal cord ischemia occurred in 4%, and 7.6% of branches required re-intervention. At 36 months, secondary branch patency was 96% and freedom from aneurysm-related mortality was 91%. It was concluded that technical success and branch vessel patency are very good but re-interventions are not unexpected.

INVESTIGATIONAL DEVICES FOR AORTIC ARCH

Endovascular branched stent graft repair of aortic arch pathology is an alternative to complex debranching and/or open surgical repair. The development of conformable and adaptable arch devices specifically designed for deployment in zones 0, 1, and 2 are currently under investigation. Five endograft devices are being investigated: Medtronic Valiant Mona LSA, Gore TAG thoracic branch endoprosthesis, Cook Medical Zenith arch branched device, Endospan Nexus aortic arch system, and the Bolton Medical Ascending Thoracic device. Each of these devices eliminates the need for open surgical revascularization while extending the proximal landing zone. Similarities between the devices include the use of a through and through wire, precannulated side branches to facilitate device alignment and flexible bridging stents. The Cook Zenith is an off-the-shelf device with two branches and seals in the ascending aorta. Early data (38 patients) show an acceptable technical success of 84.2%. A follow-up study (27 patients) had improved technical success (100%), no 30-day deaths, and 11.1% stroke rate.[111,112] The Gore TAG branch endoprosthesis was created to land in zones 0 to 2 and is intended to eliminate the need for LSA debranching (Fig. 78.16). A preliminary feasibility (22 patients) study was published in 2016. Primary end points were met, including successful device delivery and patency of the side branches in 100%; there were no strokes or deaths at 30 days.[113] Results of the Valiant Mona LSA early feasibility study were just as favorable: technical success in nine patients was 100%, no endoleaks required secondary interventions, four minor nondisabling strokes occurred, and all branches remained patent.[114]

Figure 78.16 Gore TAG branch endoprosthesis

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This study reports on outcome data comparing TEVAR and open repair of thoracic aortic aneurysms.

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A complete reference list can be found online at www.expertconsult.com.

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79 CHAPTER

Thoracic and Thoracoabdominal Aneurysms: Aortic Stent Grafts and Techniques of Thoracic Endovascular Aortic Repair

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Abstract

Reduced early mortality and simplicity of implantation have made thoracic endovascular aortic repair (TEVAR) the first-line approach for thoracic aortic aneurysm repair in suitable anatomy. This chapter summarizes the literature available on guidelines for thoracic endovascular repair, characteristics of thoracic devices, proper planning of the operative strategy, technical aspects of implantation, the main results, and complications.

Keywords

TEVAR
sizing
spinal cord ischemia
endoleak
ruptured thoracic aneurysm

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INTRODUCTION

Morbidity and mortality remain high after open repair of thoracic aneurysm, so many high-risk patients are regularly excluded.[1] Stent graft placement first performed in abdominal aortic aneurysms has now been extended to thoracic endovascular aneurysms (thoracic endovascular aortic repair, or TEVAR). Reduced early mortality favors TEVAR as the first-line approach for thoracic aortic aneurysm repair with suitable anatomy.

INDICATIONS

Guidelines

Improvements in thoracic imaging and the availability of TEVAR have resulted in an increase in repairs of thoracic aneurysms, especially among patients older than 75 years. The 2010 American consensus guidelines establish that "for patients with degenerative or traumatic aneurysms of the descending thoracic aorta exceeding 5.5 cm, saccular aneurysms, or postoperative pseudoaneurysms, endovascular stent grafting should be strongly considered when feasible" (Level of Evidence: B).[2] The European guidelines state that "In patients with asymptomatic thoracic aortic aneurysm, TEVAR is indicated when the maximum diameter of the aneurysm exceeds 5.5 cm or if rapid expansion (>5 mm in 6 months) occurs." However, they also report that "comorbidities and patient age must be considered, and it may be appropriate to set a larger aortic diameter threshold in patients with increased operative risk" (Table 79.1).[3] There is inadequate evidence to support surveillance or TEVAR in patients with small aneurysms, and a reluctance to offer TEVAR to octogenarians and women, highlighting the need for stronger evidence in specific diameter thresholds.

Thoracic Endovascular Aortic Repair Versus Open Repair

The potential advantages of TEVAR compared with open surgical treatment include reduced procedure time and length of both critical care and hospital stay, avoiding thoracotomy and aortic

TABLE 79.1 Summary of Main Societies Guidelines

Guideline	Threshold for TEVAR	Provisos	Surveillance Imaging
STS[1] 2008	5.5 cm or twice the diameter of the normal contiguous aorta	Saccular aneurysm: width of 2 cm or total aortic size of 5 cm	/
American guidelines[2] 2010	5.5 cm	Endovascular stent grafting should be strongly considered when feasible	Annual basis if stable in size on the first follow-up. Every 2-3 years for relatively small stable aneurysms, especially in older patients
European guidelines[3] 2012	5.5 cm or rapid expansion (.5 mm in 6 months)	Larger diameter threshold should be considered in patients with increased operative risk due to comorbidities and age Saccular aneurysms: TEVAR may be justified at a diameter <5.5 cm	/
ESC[4] 2014	5.5 cm	>6 cm for open repair	<45 mm: annual imaging >45 to <55: imaging every 6 months unless stability confirmed by serial imaging
CCS[5] 2014	/	>6.5 cm for open repair or >0.5 cm/year increase in diameter	6-12 months after diagnosis, then every 6 or 12 months depending on aortic size and rate of change Intervals may be increased in patients with stable dimensions

CCS, Canadian Cardiovascular Society; *ESC*, European Society of Cardiology; *STS*, Society of Thoracic Surgeon; *TEVAR*, thoracic endovascular aortic repair.

cross-clamping, with potential reduction of renal failure and cardiopulmonary complications. Although several studies suggest that TEVAR is associated with early benefits compared with open repair, long-term benefits remain less clear.

In a study of 19 patients who underwent TEVAR between 1999 and 2000 compared with a historical cohort of 10 patients who underwent open repair, TEVAR was associated with a shorter operative time and hospital and ICU stay.[6] In a multicenter comparative trial including 140 patients who underwent TEVAR using the GORE TAG Thoracic Endograft between 1999 and 2001, at 30 days there was a significantly lower incidence of spinal cord ischemia (SCI; 3% vs. 14%), respiratory failure (4% vs. 20%), and renal insufficiency (1% vs. 13%) in the TEVAR group, and a significantly shorter hospital and ICU stay. However, at 2 years there were three reinterventions in the TEVAR group, none among the open repairs, and no difference in overall mortality.[7]

In the Nationwide Inpatient Sample (NIS) database, between 1998 and 2007 there were 8967 thoracic aneurysm repairs, including 8% TEVAR and 92% open procedures. On multivariate analysis, mortality in patients undergoing TEVAR was reduced by 46%, as well as postoperative neurologic, cardiac, and respiratory complications.[8] Using Medicare claims from 1998 to 2007, Goodney et al. reported a lower perioperative mortality with TEVAR, but a worse long-term mortality, suggesting that higher-risk patients were offered TEVAR, and the necessity to identify candidates unlikely to benefit from repair.[9]

Finally, a meta-analysis of 42 studies including 5888 patients suggested a reduced all-cause mortality at 30 days and paraplegia, as well as reduced cardiac complications, transfusions, reoperation for bleeding, renal dysfunction, pneumonia, and length of stay for TEVAR compared with open surgery, despite older patients. However, there was no significant difference in stroke, myocardial infarction, aortic reinterventions, and mortality beyond 1 year.[10]

DEVICES

History

Endovascular thoracic aneurysm repair was first described by Dake in 1994 in a cohort of 13 patients who had descending thoracic aneurysm disease. These early stent grafts were custom-designed for each patient, with a combination of Gianturco Z-stents and polyester fabric. The metallic framework was covered with Dacron graft (Meadox Medicals, Oakland, New Jersey) attached to the stent by interrupted 5-0 polypropylene sutures.[11] Stent-graft technology has evolved to standardize production and delivery systems that allow for more precise placement, with multiple manufacturers, and by 2005 there were several approved stent grafts commercially available. First-generation devices suffered initial drawbacks of large sheath size and rigidity, potential modular disconnection, decreased fabric integrity, and graft porosity. Technical refinements have led to second-generation devices with smaller, more flexible, and more accurate delivery systems, improved conformability, less porosity, and a greater variety of sizing options.

First Generation

GORE TAG thoracic endoprosthesis (W.L. Gore, Flagstaff, Arizona). This is the first thoracic stent graft commercially available in the United States, approved by the Food and Drug Administration in 2005 based on a multicenter, nonrandomized prospective trial comparing results of stent graft repair of thoracic aortic aneurysm (TAA) with those of open surgical repair in low-risk patients. TAG expands from the middle of the stent graft and progresses toward the ends to avoid the windsock effect and reduce device migration.[12]

Talent thoracic graft (Medtronic Vascular, Santa Rosa, California). The Talent stent graft with CoilTrac delivery system is the second-generation Medtronic stent graft introduced in 1999 offering an improved deployment. It is a polyester graft fabric sewn to a self-expanding nickel-titanium wire frame and a proximal bare spring. This device was used in the VALOR high-risk clinical trial for Food and Drug Administration (FDA) approval.[13]

Cook Zenith TX1 and TX2 thoracic endovascular grafts (Cook Inc, Bloomington, Indiana). These devices, commercially available in Australia since 2001, in Europe and Canada since 2004, and in the United States since 2008, are founded on the platform of the Zenith abdominal aortic stent graft. The TX1 design is a one-piece system with proximal and distal fixation, and the TX2 is a two-piece system, with proximal barbs oriented caudally and distal barbs cranially to reduce migration. This graft was later modified with the addition of ProForm, which allows improved conformability to the arch and limits the "bird-beak" effect.[14]

EndoFit Stent Graft (LeMaitre Vascular, Burlington, Massachusetts). This device is composed of self-expanding nitinol stents encapsulated in two layers of polytetrafluoroethylene (PTFE) fabric using a thermal process, available with or without an external fixation on the proximal end and in a tapered version. The sutureless design eliminates the potential for graft material tearing.

Modern Devices

Improvements in device and delivery system design include a decrease in caliber and improved conformability. Newer-generation stent grafts use a tip-capture mechanism to stabilize the proximal part, avoiding the windsock effect (downstream dislodgement of the partially deployed stent graft) and allowing for more accurate deployment.

Conformable TAG (W.L. Gore). This device provides a wider range of diameters and is designed to improve treatment of small-diameter, tortuous, and tapered aortic anatomy compared to the TAG stent graft.

Low-profile Zenith Alpha Thoracic Endoprosthesis (Cook Medical, Bloomington, Indiana). This latest generation graft has been designed to facilitate precise deployment, especially when the proximal landing zone is in the arch, with encouraging early clinical outcomes.[15]

Valiant thoracic device (Medtronic, Oakbrook, Illinois). First introduced in Europe in 2005 and available in the United

States since 2008, its design has been modified compared to the Talent stent graft to enhance conformability and distribution of radial force. The delivery system has also been improved to allow tip capture and more controlled deployment.[16]

Relay (Bolton Medical, Sunrise, Florida). This polyester/nitinol graft has a longitudinal nitinol bar for support and comes with either covered or bare metal proximal graft configuration. It is available in straight or tapered configurations.

Custom-made proximal scalloped Relay Plus stent grafts (ABS Bolton Medical, Barcelona, Spain). This graft consists of a self-positioning system using a curved nitinol catheter along the length of the stent graft to allow the placement of the scallop systematically on the upper side of the aortic arch. The distal marker of the scallop is used to align the stent graft with the targeted supraaortic vessel.[17]

E-vita thoracic 3G (JOTEC GmbH, Hechingen, Germany). This device, not available in the United States, is a low-profile flexible third-generation stent graft that may also be part of a frozen elephant trunk repair using a graft combining a conventional vascular graft and an attached endovascular stent graft.[18]

TAArget Thoracic Stent Graft (LeMaitre Vascular). Introduced in 2008 to replace the EndoFit stent graft, it offers a new Tortuous Tracker Delivery System for more precise deployment and a new, optional uniform top stent design for improved external fixation.[19]

TECHNIQUE

Training

The implantation of thoracic stent grafts requires advanced endovascular skills, attention to both the process of implantation and specific bail-out techniques needed to rescue unintended events, but also attention to planning and sizing prior to implantation. The impact of training during residency and operative experience on clinical and hospital outcomes after TEVAR was assessed in a 3-year review of thoracic repairs in the NIS. Among 2531 procedures, vascular surgeons with more experience than other specialties had the lowest morbidity rate (stroke and cardiac event) and lower mortality.[20] Rehearsal of the TEVAR procedure on an endovascular simulator has also been associated with reduction of overall procedure and fluoroscopy time, and subjective measure of technical success.[21] However, operative mortality after TEVAR is not significantly different in high- (≥8 cases/year) compared to low- (<8) volume hospitals,[22] and has also been demonstrated during aneurysm repair for rupture,[23] contrary to open repair where results are closely correlated to hospital volume.

Sizing

High-quality (≤1 mm) computed tomography angiography (CTA) extending from the supraaortic vessels to the common femoral arteries, is recommended for the correct sizing of the thoracic stent graft (see Chapter 27). Use of postprocessing software that can facilitate curved planar reconstruction provides information about the sealing zones, coverage length, tortuosity and angulation of the aorta, involvement of the arch side branches, intraluminal thrombus and wall calcification, and iliac access.

Aortic diameter and length should be assessed by semiautomatic centerline reconstruction, which provides the least variable and fast diameter measurements in TEVAR patients with the same accuracy as the reference standard multiplanar reformations.[24] For most device platforms, the length of the sealing zones should be at least 2 cm and ideally larger, with a good wall apposition throughout without thrombus or dissection, and with a consistent diameter (parallel walled aorta). The maximum aortic diameter recommended is usually 38 mm, with clearly hostile neck above 42 mm. When multiple stent grafts are used, a minimum of 30 mm of overlap is required to prevent modular disjunction.

In a review of the M2S database including 899 patients who underwent TEVAR between 2004 and 2013, there was a higher sac expansion rate (>5 mm) at 3 years when the proximal or distal sealing zone was more than 38 mm in diameter or less than 20 mm in length, which reinforces the hostile neck as a predictor of advanced disease. At 5 years, 60.9% of patients were free from sac expansion, with significant influence of sealing zone morphologic features.[25] The authors advise a maximum diameter of 38 mm and length of 20 mm, clinical judgment, and postoperative imaging surveillance.

In addition to anatomic assessment, 10% to 20% oversizing at the proximal landing zone is recommended, and some authors use 10% to 15% oversizing for degenerative aneurysms to reduce the risk of retrograde aortic dissection and stent-graft collapse.[26] In the case of a proximal landing zone in a previous Dacron graft, a longer length (4-5 cm) and more aggressive oversizing is recommended to avoid type Ia endoleaks.[27] Applications are available to facilitate sizing.[28]

Access

The size of the delivery system remains an important challenge with significant coexisting occlusive arterial disease. Assessing vessel diameter, tortuosity, and calcification to avoid iliac rupture or aborting the procedure requires a dedicated 3D workstation.

Several techniques have been described to deal with poor iliac access. Balloon angioplasty or dilation angioplasty in limited stenoses of the iliac arteries is the first and earliest step. The use of a brachiofemoral through-and-through guidewire may allow graft insertion in highly tortuous arteries, but does not overcome the challenge of occlusive disease. Retroperitoneal access is used in cases of marginal common femoral arteries, or when external iliac arteries are highly tortuous with excess length to pull on the artery and straighten the vessel. In the case of small external iliac diameter, retroperitoneal access also allows a direct puncture of the common iliac artery to insert the graft,[29] or more commonly to perform an iliac conduit. The conduit usually consists of a 10-mm Dacron graft sutured to the common iliac, and used to insert the stent graft. Once the endovascular procedure is completed, the conduit is either

oversewn or anastomosed distally.[30] The last alternative is the "paving and cracking" technique, consisting of deploying a 10-mm or 13-mm self-expandable covered stent in the common and external iliac artery ("paving") and opening the access with a 10- to 12-mm balloon ("cracking"), through a femoral access.[31]

Management of Proximal or Distal Short Neck

Management of the proximal landing zone remains challenging in cases of short proximal neck or severe angulation of the arch. In these cases, if coverage of the left subclavian is not sufficient to deal with compromised proximal sealing, then development of alternative techniques, such as hybrid repair with debranching, chimneys, fenestrations and branches, or scallop should be considered.

In instances of planned left subclavian artery (LSA) coverage, the SVS suggests a routine preoperative LSA revascularization (GRADE 2, level C); strongly recommends revascularization when the perfusion to critical organs is compromised (GRADE 1, level C); and suggests an individualized approach in cases of life-threatening acute aortic syndrome, based on anatomy, urgency, and availability of surgical expertise (GRADE 2, level C).[32] Studies have reported a higher incidence of stroke among patients with LSA coverage (11% vs. 3%[33] or 25% vs. 2%[34]) and of upper extremity ischemia (15% vs. 0%[34]). Moreover, the LSA is one of the collateral beds for spinal cord network perfusion, and its preservation is of main importance to reduce neurovascular complications during extensive TAAA repairs. However, a systematic review pooling 5 studies and 1161 patients failed to demonstrate any significant reduction in neurovascular complications or mortality rate with LSA systematic revascularization. Future randomized trials are needed to elucidate the role of routine or selective revascularization in these cases.[35]

In every case of LSA coverage, the origin has to be occluded to avoid type II endoleak and secondary rupture.[36] This may be performed by coil embolization from the ipsilateral brachial artery after TEVAR deployment, or by occlusion plug positioning from femoral access before TEVAR insertion or from the left arm after TEVAR.

A proximal scallop may increase the proximal landing zone in the inner curvature of the arch without compromising the patency of supraaortic trunks. Although a scallop does not improve the distance for sealing, it may improve the conformability of the stent to the steepest portion of the arch and thus promote a better overall position of the graft. A few single-center series reported early and midterm experience with a Bolton device with 100% technical success, no proximal endoleaks, and acceptable rates of stroke and 30-day mortality.[17,37] However, longer-term outcome data is required. Newer off-the-shelf branched devices for the LSA are also currently under investigation.

In the case of a short distal landing zone, several alternatives have been described: a hybrid procedure with TEVAR and open bypass to the celiac artery, a custom-made stent graft with distal scallop or fenestration, and intentional celiac trunk coverage after confirmation of adequate collateral supply to the upper gastrointestinal tract. This latter alternative has been described with an intact superior mesenteric artery and gastroduodenal artery providing collateral flow to the celiac with a complication rate of 6% of mesenteric ischemia, 6% SCI, and 6% mortality in a series of 31 patients).[38] Preoperative angiography has to be performed through the superior mesenteric artery with temporary balloon occlusion of the celiac artery.

Perioperative Consideration

The advanced age and multiple comorbidities of patients with thoracic aortic aneurysms render these patients susceptible to a number of postoperative complications.

Preoperative Cardiac Workup

Recommendations for cardiac workup are generalized across all vascular disease (see Chapters 32 and 42). However, it has been suggested that a resting transthoracic ECHO and electrocardiogram should be performed, with subsequent invasive studies (exercise/pharmacologic stress testing, or coronary angiography) only if initial screening reveals cardiovascular abnormalities.[39] In addition, the frequent concurrence of bicuspid aortic valve with proximal aortic aneurysms suggests that echocardiography to assess structural valve disease may also have benefit.[40] There are data suggesting that the incidence of cardiac adverse events may be reduced with endovascular techniques compared with open surgery in abdominal aortic repairs.[41]

Antibiotic Prophylaxis

Intravenous antibiotics should be given prior to TEVAR to reduce the incidence of graft infection[42] including broad-spectrum coverage such as cefazolin 1000 mg intravenously or amoxicillin-clavulanic acid 1200 mg intravenously.

Implantation

Procedure

The procedure is generally performed under general anesthesia to allow respiratory control and more precise imaging. Ipsilateral femoral access is gained with open or percutaneous femoral artery exposure. An additional access for pigtail catheter placement is obtained percutaneously with a short 4 or 5 Fr sheath from the contralateral groin or from brachial artery access. From the ipsilateral access, a floppy guidewire is positioned into the ascending aorta and then replaced with a stiff 0.035-inch wire. Prior to surgery, the proximal and distal target landmarks are chosen: a supraaortic trunk or the celiac or superior mesenteric artery, are most common. Over the stiff wire, the stent graft is inserted to the approximate level, and then imaging is performed. The pigtail catheter is placed at the level of the aortic arch and the C-arm angulation is optimized to visualize the target vessel. A first acquisition is then performed with power injection of contrast during respiratory cessation. The stent graft is deployed gradually after ensuring controlled moderate hypotension (≤100 mm Hg systolic) to avoid downstream displacement due to the windsock effect. In the early experience, rapid pacing or other techniques to decrease cardiac output were performed to improve accuracy of deployment, but this is no longer mandatory when using advanced-generation devices.

During deployment, respiratory cessation and repeated angiographies are performed to adjust the position of the stent graft to the optimal landing zone. Once the stent graft is partially deployed, only distal traction is possible (no advancement to a more proximal position), and even that is not advised with devices with barbs because of possible damage to the intima. The "jailed" pigtail catheter is withdrawn over a standard 0.035-inch guidewire under fluoroscopic vision. Once the stent graft is deployed, the delivery system is used to advance the sheath inside the graft to provide further support to the aortic occlusion balloon that is used in the sealing zone. Completion angiography is performed to assess for endoleak. Then the large sheath is withdrawn, leaving a stiff wire access in place until the hemodynamic stability of the patient is confirmed. At this point, the heparin is reversed before manual compression of the percutaneous access or closure of the arteriotomies.

Optimal C-Arm Angulation

A preoperative assessment of the ideal C-arm angulation should be performed on a dedicated 3D workstation to save time and radiation exposure, particularly in angulated views.[43] Moreover, it has been reported that at 20 degrees from optimal C-arm angulation, there is a 25% loss of available sealing zone (6.2 ± 2.3 mm), which may have an impact on successful seal and fixation.[44]

Staged Procedure

Any associated procedure (supraaortic trunk debranching or conduit) should be performed as a first stage to minimize blood loss and hemodynamic instability during the TEVAR.[45,46]

Fusion Imaging

Fusion imaging, which reduces contrast volume and radiation dose, should be considered.[47] The mask usually requires manual realignment after a first acquisition to be accurate enough to deploy the stent graft,[48] and reflects preoperative aortic shape, which may change once a stiff device is placed.

Radiation Exposure to Staff and Patient

The estimated dose received by the first operator during TEVAR is 0.06 ± 0.05 mSv, significantly correlated to procedural dose area product, iodinated contrast volume, and left anterior C-arm projections greater than 60 degrees (but weak correlation with fluoroscopy time).[49] As an average of the radiation exposure to the patient, the dose area product during TEVAR is reported to be 20 (11.4-30.0) Gy.cm^2 when performed on a mobile C-arm,[50] and 24.7 (22.0-28.7) Gy.cm^2 in an hybrid room (see Chapter 24).[51]

COMPLICATIONS

Intraoperative Complications

Iliac Rupture

The tortuosity and degree of calcification can impact the risk of iliac rupture as much as vessel diameter. Maintaining stiff wire access after the withdrawal of the large sheaths to assess hemodynamic stability before losing wire access can facilitate urgent endovascular rescue if an iliac artery is injured. In case of iliac disruption, the stiff wire access has to be maintained across the rupture for occlusion balloon placement and vessel control, while disruption is addressed through an endovascular or an open approach.[52]

Failure to Deliver the Device

In addition to rupture risk, severe iliac and aortic calcification, angulation, tortuosity, and small iliac diameter less than 8 mm, are predictive of deployment failure.[53] A meticulous analysis of iliac and aortic access on a dedicated workstation is mandatory to anticipate this complication. The presence of previous aortic repair, either open or endovascular, may also impede delivery of the device. Having low-caliber options available and using through-and-through access can sometimes overcome these challenges.

Device Distal or Proximal Device Migration

Device migration is more common when only one device is used, and the rate has been reported at 8.5% (3.6% of distal migration and 4.9% of supraaortic trunk covering) with a significant association with the use of a TAG or C-Tag device (Gore Medical, Flagstaff, Arizona).[26] The use of two devices allows for intercomponent movement, taking stress off of the sealing zones. Recent reports of the use of endostaples show some promise.[54] Care must be taken with aggressive proximal ballooning to avoid retrograde type A aortic dissection (RTAD). If a device migrates proximally, and a supraaortic trunk is covered, several rescue techniques have been described, including manual balloon traction, parallel stent placement (chimney or stenting of the target vessel), open conversion, or surveillance.

Perioperative Complications

Postimplantation Syndrome

Fever and elevated inflammatory markers with pleural effusion in the immediate postoperative period may be related to endothelial activation from the stent graft and aneurysm thrombosis. This syndrome is benign and does not require any medication with an otherwise negative infectious workup.[55,56] However it is imperative that this be a diagnosis of exclusion.

Spinal Cord Ischemia

SCI remains the most devastating complication after thoracic or thoracoabdominal repair. Its rate has not declined with the use of endovascular technology and ranges from 2% to 10% after TEVAR (3.89% in a review of 4936 patients).[57]

Pathophysiology

SCI is caused by ischemic injury and cellular damage secondary to reduction in proximal, medial, and distal direct and collateral arterial blood flow to the spinal cord. This risk is directly correlated with the location and extent of aortic coverage, as with the quality of the spinal cord network. In addition to the artery of Adamkiewicz, it is now understood that spinal cord circulation

is part of a continuous network that includes the intercostal, lumbar, subclavian, and hypogastric arteries, which provide flow to the anterior spinal artery. Common risk factors associated with SCI include aneurysm extent (number of segmental arteries compromised), location (aneurysms affecting the lumbar region have less robust collateralization), and perioperative hypotension.[58] Additionally, there is a risk of embolization from aortic atheromatous lesions.

NEUROPROTECTIVE STRATEGIES

Increasing Tolerance to Ischemia

Pharmacologic Neuroprotection

- ***Intrathecal papaverine:*** In vivo studies in nonhuman primates revealed that intrathecal papaverine injection prevented paraplegia through a mechanism of enhanced vasodilation and blood flow augmentation into the anterior spinal artery[59] and preservation of myelin integrity.[60] A prospectively randomized trial including open thoracic and thoracoabdominal repairs concluded that intrathecal papaverine injection in addition to modern neuroprotective adjuncts considerably diminished the occurrence of spinal cord injury.[61] Since then, it has been employed during endovascular thoracic or thoracic aneurysm repair, but results have not been published yet.[62]
- ***Additional measures***: Because steroids stabilize neuronal cell membranes damaged during ischemia and naloxone reduces the release of excitatory neurotransmitters that exacerbate injury in animal models of ischemia,[63-65] some surgeons administer naloxone (1 mg/kg/h intraoperatively and for 48 hours postoperatively), intraoperative mannitol (12.5 g), and steroids (30 mg/kg up to 2 g methylprednisolone) as an adjunct to other modern neuroprotective measures.[45]

Ischemic Preconditioning by Staged Repair

This strategy is based on the remodeling that occurs after the loss of elements of the collateral supply.[66] Whenever possible with a temporary landing zone, the completion of the repair in two temporally separate procedures allows maximizing collateralization and reducing SCI.[67]

Intraoperative Hypothermia (34°C)

Experimentally, hypothermia reduces the metabolism and oxygen requirement in nervous tissue and prolongs ischemic tolerance and reduces cell swelling after transient ischemia and injury. Similar to the experience with open repair of thoracic aneurysms, some surgeons use intraoperative hypothermia (34°C) with natural warming as an adjunct for spinal cord protection to reduce SCI in TEVAR.[45]

Augmenting Spinal Cord Perfusion

Deliberate Hypertension

The maintenance of a high mean arterial pressure (MAP) intra- and postoperatively is important, with a goal of 90 to 100 mmHg of MAP. Pharmacologic vasodilators may need to be held.

Cerebrospinal Fluid Drainage

Reducing intrathecal pressure improves spinal cord perfusion. A meta-analysis of open thoracic and thoracoabdominal aneurysm repairs demonstrated a decrease in SCI by nearly half using cerebrospinal fluid (CSF) drainage.[68] However in TEVAR, a recent meta-analysis of 46 studies comprising 4936 patients failed to demonstrate a benefit of routine prophylactic drain placement compared to selective use.[57] An alternative to preoperative prophylactic insertion is to wake up the patient even temporarily at the end of the operation to evaluate the neurologic status, and insert the CSF drain only if SCI occurs. Somatosensory evoked potential monitoring may also be used to initiate the drainage in case of intraoperative change. The lumbar drain is usually maintained for 48 hours postoperatively at 10 cmH_2O with coverage with a third-generation cephalosporin for a better CSF penetrance.[69] Monitoring and drainage by an automated system is described but has been associated with a higher rate of complications.[70]

Preservation of the Collateral Network Supplying the Spinal Cord

Every effort should be made to preserve direct perfusion (intercostal and lumbar arteries) and inflow of the alternate routes (left subclavian and internal iliac arteries) to the spinal cord.[62] Simultaneous closure of at least two supplying vascular territories (intercostal and left subclavian or internal iliac for instance) was highly correlated with development of SCI, especially if associated with hypotension.[71]

Maximize Oxygen Delivery

There is a consensus to maintain hemoglobin greater than 10 g/dL and oxygen saturation greater than 95% during and after surgery. Additionally, Maurel et al. described transfusion of 15 mL/kg of fresh frozen plasma and at least one pool of platelets after extensive aneurysm repair, with therapeutic targets of prothrombin time greater than 50%, plasma fibrinogen greater than 2 g/L, and greater than 100 G/L platelets.[46] Endovascular exclusion is associated with blood sequestration between the aneurysmal aortic wall and the stent graft, and results in an acute consumption of coagulation factors and platelets that seems to correlate with the amount of aneurysm thrombosis.[72] These coagulation disorders may induce severe bleeding and need to be corrected.

Recently, a novel approach to enhance collateralization consists of a selective segmental artery coil embolization as a first stage procedure before TEVAR (MISACE). More clinical work is needed before recommendation can be made.[73]

Complications Related to Cerebrospinal Fluid Drainage

Although CSF drainage improves outcomes, it may convey risks, including catheter fracture; postdural puncture headache; neuraxial hematoma; intracranial hemorrhage including subdural, cerebellar, subarachnoid, intraventricular and intraparenchymal hematomas; and meningitis.[74,75] Recovering the patient in a

unit familiar with CSF drainage and supervised by experienced individuals is imperative.

In patients who experience headache after catheter removal, the first line of treatment is bed rest, hydration, and occasionally caffeine administration. If the patient does not improve within 24 hours, an epidural blood patch should be considered. In a review of 504 patients who underwent TEVAR with preoperative CSF, Youngblood et al. reported a 12.7% complication rate, including headache (9.7%), catheter fracture (0.2%), intracranial bleeding (2.8%), and subdural hematoma (1.9%) associated with a mortality rate of 14.3%. The clinical presentation of an intracranial hemorrhage after CSF drainage varies from severe headache and confusion to coma, motor deficit, or respiratory arrest,[75] but the patient may also be asymptomatic with only bloody spinal fluid that can be managed by immediately stopping drainage and correcting coagulopathy.[76]

Cerebral Infarction/Stroke

Stroke remains a major risk after TEVAR with an incidence of 2.3% to 8.2%, and is usually related to embolization. This has most frequently been associated with acute dissections,[26] the atheroma burden of the aortic arch, and a more proximal landing zone.[77] Risk factors also include hypertension, chronic renal failure, known cerebrovascular disease, increased aortic coverage (from LSA to computed tomography [CT]),[78] female gender, longer surgery duration, and occlusion of the LSA.[79] One high-volume center reported a 3.9% rate of perioperative stroke and multivariate analysis–identified risk factors of a history of ischemic heart disease or cerebral infarction, "shaggy aorta," the use of a pull-through wire, and intraoperative blood loss of greater than 800 mL.[80] Treatment should be focused on preventing secondary injury by providing supportive care (avoidance of hypoxia, hypercarbia, hyperglycemia, fever, and adequate airway maintenance), decreasing the risk of hemorrhagic conversion, minimizing cerebral edema, improving perfusion to the ischemic penumbra, and the treatment of acute complications.[81] An imaging study has also reported a high-incidence, silent, per-procedural embolization, with new foci of restricted diffusion on cerebral magnetic resonance imaging (MRI) in more than 60% of TEVAR patients free of neurologic deficit.[82]

Retrograde Type A Aortic Dissection

RTAD occurs in less than 2% of cases, is usually secondary to aortic wall damage, and is associated with high mortality up to 42% in several large series.[83-85] More than two-thirds of RTAD occurs within the perioperative period, but late presentations are also reported (up to 1050 days after procedure), including 25% asymptomatic presentations that underline the importance of lifelong surveillance of TEVAR. It mainly occurs after treatment of type B dissection and especially acute presentations, but also after thoracic aneurysm repair. It has been described with all commercially available stent grafts, regardless of the presence of a proximal bare stent. The MOTHER registry of 1010 patients identified several risk factors, including oversizing 24.4% versus 14.1% without oversizing;[83] post-ballooning; more proximal landing zone (from 6.8% risk in zone 0 to 1.3% in zone 3/4); manipulation of guidewire and sheaths; and progression of the underlying disease. RTAD carries a similar morbidity and mortality rate to de novo type A aortic dissection, so that emergent surgical repair is mandatory. Usually the repair should include a stent graft for the distal anastomosis, involving an aortic arch repair or a reverse frozen elephant trunk technique.[85]

Acute Kidney Injury

This complication is often multifactorial and may be related to preoperative dysfunction, exposure to iodinated contrast, involvement of the renal arteries in the aneurysm, renal macro/micro embolization, a high degree of inflammatory response, and prolonged procedure. Its management remains largely supportive, with hydration and adequate MAP, avoidance of nephrotoxic agents, and dialysis or continuous renal replacement therapy in case of refractory hypervolemia, hyperkalemia, or hyperphosphatemia.[81] The rate of post-TEVAR acute kidney injury has been reported as high as 17%, but with dialysis in less than 1% of cases.[86] Preoperative chronic renal failure has also been strongly associated with late complication and death.[78]

Cardiovascular Complications

Perioperative myocardial infarction is often related to ischemia and management includes hemodynamic stability, glucose control, and adequate oxygenation with consideration of coronary angiography.[81]

Thoracic Endovascular Aortic Repair Collapse

Collapse of a thoracic stent usually occurs where there is lack of apposition of the graft through the circumference of the first stent, causing a type 1 endoleak. This devastating complication is very rare using more flexible second-generation stent grafts. The few cases reported have occurred in young patients with traumatic transection with the underlying mechanism related to small aortic diameter and oversizing or tight arch curvature.[87]

Late Complications

Long-term results after TEVAR are affected by specific complications, such as late aortic ruptures and endoleaks, especially in patients with more challenging anatomy as part of a hybrid repair. Progression of aortic disease may affect the integrity of either the proximal or distal sealing zone, which is more common if small, contiguous aneurysms are present at the time of the index procedure. The rate of secondary procedures after TEVAR for aneurysms is estimated between 10% and 15%, and lack of operator experience may play a role in the development of complications.[88]

Endoleak

This is the main cause of procedural late failure, with an incidence ranging from 3% to 10% with current devices.[89] Similar to abdominal endovascular repair, major endoleak (type I or III) inducing reperfusion of the aneurysm sac is strongly associated with the risk of aneurysm rupture and requires repair. **Type I endoleak** is the main cause of late reinterventions mainly related

to degeneration of the landing zones over time. Distal migration related to stent-graft undersizing or progression of aortic disease may also be responsible. Reinterventions consist of proximal or distal extension of the main stent graft in association with hybrid debranching if necessary, and ultimately open conversion.[90] **Type III endoleak** is usually related to inadequate overlap between components and requires an additional component to bridge the defect with sufficient overlap (three stents). This may develop over time as the graft adjusts to the curvature of the descending thoracic aorta and intercomponent movement occurs. Conversely, **type II endoleak** coming from intercostal arteries may resolve spontaneously. In the setting of sac enlargement, embolization may be required, but it does not occur as frequently as in the infrarenal territory.

Device Migration, Component Separation, and Device Integrity Failure

These complications are linked to late failure and must be identified with high-quality imaging and 3D reconstruction surveillance and addressed before endoleak or rupture occurs. The definition of stent graft migration is a caudal or cranial movement of the stent graft with respect to the native vasculature of more than 10 mm or any distance that results in clinical sequelae or prompting a secondary intervention. Methods have been described to standardize imaging analysis during follow-up.[91]

Stent Graft Infections

The incidence of this complication is 0.2% to 5%. The patient may present with unexplained fever or sepsis. CTA findings suggestive of stent-graft infection include aortic-wall thickening, perigraft soft tissue greater than 5 mm between an adjacent organ and the stent graft, fluid collection, perigraft air (>6 weeks after surgery) or increasing amount of air on serial imaging examinations, adjacent soft-tissue stranding, abscess formation, and graft thrombosis or expansion.[92] Fistulization with either the airway or upper digestive tract can be both a cause and an effect of this process. It requires the complete removal of the infected stent graft and the wrapping of the replacement graft with pedicled omentum, in association with optimum antibiotic treatment. The Vascular Low-Frequency Disease Consortium reported 26 infected TEVARs at a mean of 22 months postoperatively. The clinical presentation included pain (66%), fever (66%), and fistula (27%). Five patients were managed medically and four of them died at a mean of 56 days. The other patients underwent in situ aortic replacement with cryoallograft, a neoaortoiliac system, or an antibiotic-soaked prosthetic. Thirty-day mortality was 11%. Prosthetic graft replacement was associated with higher reinfection and graft-related complications and decreased survival compared with autogenous reconstruction.[93] Medical management with antibiotics alone is not a durable option and only offered as a palliative option or bridging procedure for severely ill patients.[94]

Aorto-Esophageal/-Bronchial Fistulae

The European Registry of Endovascular Aortic Repair Complications (EuREC) estimated a 0.6% incidence of aorto-bronchial or aorto-pulmonary fistula and 1.5% of aorto-esophageal fistula, commonly associated with graft infection. The underlining mechanism is thought to be related to the external compression that the stent graft exerts on nearby structures, with endoleak playing a crucial role. This complication is encountered within 1 to 16 months after TEVAR, presenting as either hematemesis (massive or intermittent) or fever with elevated inflammation markers. CT may help to identify abnormalities in the descending aorta or secondary changes of the adjacent organs but extravasation is rarely seen.[92] Aggressive radical treatment, combining bronchial or pulmonary parenchymal repair or esophagectomy in combination with stent graft removal and aortic reconstruction, appears to be the most durable treatment strategy. A conservative approach resulted in 100% 1-year mortality.[95,96]

IMAGING SURVEILLANCE

Long-term surveillance is indicated after TEVAR, but there is little evidence to support annual surveillance for every patient. CTA is the most common imaging modality used, but is associated with radiation exposure, contrast-induced nephropathy, and cost. Indeed, assuming a preoperative CTA, the procedure, and three CTAs in the first year and yearly thereafter, Zoli et al. reported an estimated overall exposure of 89 mSv at 1 year and 161 mSv at 5 years. At 2 years of follow-up, these doses exceed the threshold of 100 mSv associated with a lifetime risk increase in radiation-induced leukemia and solid-tumor cancer greater than 2.7%.[97] MRI can be used for nitinol-based stent graft surveillance as an alternative to avoid radiation exposure. However, it lacks the ability to visualize metallic stent struts and should be supplemented by chest x-ray to assess metallic skeleton integrity. MRI is not compatible with stainless steel stent grafts due to large artifact.[98] A tailored approach to each patient, with closer monitoring for patients at risk of late stent graft failure has been proposed, as well as alternative imaging like noncontrast CT (maximum aneurysm diameter), plain radiography (integrity of the device and migration); intravascular ultrasound (endoleaks), intrasac pressure measurements, and magnetic resonance angiography.[99] Because late stent graft failure up to 10 years after the procedure is reported, there is no threshold for device-related complications and more long-term experience is needed to define optimal long-term surveillance.[100]

OUTCOMES

Reporting standards published in 2010 define primary and secondary outcomes, technical and clinical success, and how to report death and complications.[101]

Short- and Long-term Results After Thoracic Endovascular Aortic Repair (see Table 79.1)

In a systematic review and meta-analysis combining the results of 11 studies including 673 patients with thoracic aneurysms undergoing TEVAR published in 2016,[102] the technical success rate was 91% with access complications requiring repair in 9.1% of cases. Survival at 30 days, 1 year, 2 years, and 3 years was 96.0%, 80.3%, 77.3%, and 74.0%, respectively. The rate

of SCI was 3.2% (1.4% permanent) and stroke was 2.7%. Type Ia endoleaks occurred in 7.3%, type II in 2%, and type III in 1.2%. At 3 years, 90.3% of patients were free of reintervention. Aneurysm-related deaths occurred in 3.2% of patients. In a recent single-center 15-year experience including 223 patients (24 ruptures) undergoing TEVAR from 1998 to 2013, estimated survival rates were 73.6%, 58.2%, and 58.2%, at 1, 3, and 5 years, respectively.[26] In a series of 371 patients undergoing secondary procedures for thoracic stent graft complications (endoleaks [7.5%], organ malperfusion [2.4%], aorto-esophageal or bronchial fistulae [2.4%], stent graft infections [1.1%], aneurysm progression [0.8%], RTAD [0.5%] and aortic regurgitation [0.3%]), 15.1% required secondary open (44.6%) or endovascular (55.4%) procedures. In-hospital mortality was 16% after endovascular and 4% after open surgery (4%), with a cumulative rate of 80.4%, 73.5%, and 69.3% at 6 months, 1 year, and 3 years respectively. The main complications included stroke, SCI, renal failure, respiratory failure, organ malperfusion, and sepsis.[103]

Risk Stratification Scores

A preoperative all-cause mortality risk-stratification system using the formula 0.0398×(age)+0.516×(renal → insufficiency) + 0.46×(previous → cerebrovascular disease)+0.352×(prior tobacco use)+0.376×(number of devices >2)+0.016×(maximum aneurysm diameter), classified patients as low-, medium-, or high-risk groups, with a predicted survival at 5 years of 80%, 60%, and 40%, respectively.[104] The ATOM score has also been proposed to predict operative mortality among 2000 patients. Significant factors associated with operative mortality were age of 70 or more years, body mass index less than 30 kg/m^2, chronic obstructive pulmonary disease requiring total functional assistance, blood urea nitrogen greater than 25 mg/dL, white blood cell count greater than 12,000 cells/mL, emergency operation, left subclavian artery coverage, thoracoabdominal extension, and mesenteric debranching. Low- (ATOM < 5), moderate- (ATOM 5-9), and high- (ATOM ≥ 10) risk categories correlated with 1.3%, 6.6%, and 24% operative mortality, respectively.[105] Finally, a preoperative prediction score of SCI after TEVAR has been proposed, based on age, aortic coverage length, chronic obstructive pulmonary disease, chronic renal insufficiency, and hypertension.[106]

RUPTURED DESCENDING THORACIC AORTIC ANEURYSM

Ruptured descending thoracic aortic aneurysms (RTAAs) account for approximately 30% of all thoracic aortic ruptures and TEVAR is now considered as the first line option. In a 2010 review including 224 patients, the 30-day rates of mortality were 19% versus 33%, myocardial infarction 3.5% versus 11.1%, stroke 4.1% versus 10.2%, and paraplegia 3.1% versus 5.5% after TEVAR and open repair, respectively.[107] Jonker et al. reported 32% mortality, 24% strokes, and 40% pulmonary complication among patients older than 75 years, compared to 13%, 1.5%, and 9%, respectively, for younger patients. Thirty-day mortality was 40% among those older than 80.[108]

Five studies that compared the results of TEVAR after elective (n = 151) and urgent procedures (n = 77) demonstrated a 30-day mortality of 17.1% versus 1.8%, respectively.[102] This may be related to the rupture itself and an increased risk of device-related complication. Indeed, for an emergency procedure, the physician may have a restricted choice of device sizes, and inadequate sizing may occur due to hypovolemic shock or poor-quality imaging. Therefore, the durability of the repair has to be carefully checked by postoperative CTA surveillance. Device-related complications after TEVAR for RTAA include type Ia endoleak, perforation of the aortic wall by the bare portion of the stent graft, and infection.[107]

There is no recommendation concerning whether RTAA should be performed under local, regional, or general anesthesia. The overall intraoperative anesthetic goals should be focused on establishing a stable hemodynamic environment and maintaining good cardiac function and adequate blood flow to the spinal cord and abdominal vital organs.[109]

The use of proactive spinal cord protection protocols could lead to a decreased rate of paraplegia. In any case, every attempt should be made at the end of the procedure to obtain a neurologic assessment of the spinal cord and employ adequate treatment of SCI if necessary.

CONNECTIVE TISSUE DISORDERS

The Society of Thoracic Surgeons Endovascular Surgery Task Force stated that "stent grafting in patients with Marfan syndrome or any other known connective tissue disorder is not recommended [because] there is limited information regarding the impact of persistent radial forces of a stent graft in the abnormal and weak aorta."[1] The European Society stated that "TEVAR is not recommended in patients with connective tissue disease except as a bail-out procedure or bridge to definitive open surgical therapy, or as a procedure following prior aortic repair when both landing zones lie within previously sited prosthetic grafts."[5] The Canadian Cardiovascular Society reserves TEVAR in this population for patients in a complex repeat surgical setting or judged to have prohibitive open surgical risk, or as a life-saving bridge to a definite open repair in cases of severe bleeding or malperfusion.[110] Therefore, open surgery remains the treatment of choice. The role of TEVAR in these patients is unknown related to securing a device with radial force in a fragile aorta with potential long-term aortic dilation and subsequent endoleak or rupture.[111-113] Moreover, a higher risk of RTAD has been described in this population.[84] Further study is needed to refine the indications for endovascular surgery in the setting of genetic aortopathy (see Chapter 140).

METHODS FOR FAILURE TO RESCUE

Endovascular Rescue

Most secondary endovascular procedures for type I endoleak consist of additional TEVAR implantation in case of adequate

sealing zone (more than 2 cm), or in association with vessel debranching.[103] Alternatively, a custom-made device with branches or fenestrations may be used to maintain target vessel patency while achieving sealing, or snorkel/chimney techniques. In case of type II endoleak, coil embolization may be necessary in the setting of aneurysm growth (more than 5 mm).

Open Conversion

The incidence of open repair after TEVAR is estimated in large series (>300 patients) to range from 0.4% to 7.9%. Open conversion after TEVAR is classified as full extraction, partial extraction, or full salvage of the stent graft. The main reasons for open conversion are elective (type I endoleak, aortic fistula, endograft infection, device collapse or migration, continued expansion of the aneurysm sac) or emergent (rupture, RTAD, malperfusion, endograft infection). Open conversion for endoleak repair is the most common indication and is associated with the use of TEVAR outside of the IFU (shorter landing zone). It is indicated when associated with aneurysm growth after endovascular rescue. Hypothermic circulatory arrest is necessary when the graft impinges on the supraaortic trunks. Partial explantation is a useful strategy without infection when the stent graft is well incorporated and has not been associated with an adverse event during follow-up.[88]

In a recent series including 30 cases of late open conversion at an average time of 57 months after TEVAR due to progression of distal aortic disease (30%), stent graft infection/fistulization (33.3%), retrograde dissection (20%), endoleak (10%), and device migration (6.7%), the perioperative mortality rate was 16.6% (20% and 33% among the subgroups of infection and retrograde dissection, respectively). In most cases the proximal portion of the stent graft was left in place.[114]

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 80

Fenestrated and Branched Endograft Treatment of Juxtarenal, Paravisceral, Thoracoabdominal, and Aortic Arch Aneurysms

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Abstract

The goal of fenestrated and branched endovascular aneurysm repair (F/BEVAR) is to reduce the morbidity and mortality associated with complex aortic pathology. First described in 1999, F/BEVAR has been reported to treat juxtarenal, paravisceral, thoracoabdominal, and arch aneurysms. The need to maintain perfusion to aortic branch vessels had previously prevented the ability to repair these aneurysms via a total endovascular approach. A variety of techniques have been utilized to maintain patency of aortic branch arteries and these will be described in detail. In addition to advances in device design and availability, advances in patient selection, case planning, and intraprocedural imaging have supplemented the utilization of this technology and improved outcomes. Although Level I evidence for the efficacy of fenestrated and branched repair of thoracic and thoracoabdominal aneurysms in comparison to open repair does not yet exist, a growing body of literature has demonstrated high technical feasibility with excellent short-term outcomes. Encouraging midterm data has emerged, although, as with standard endovascular aneurysm repair, the need for re-intervention remains a concern. Long-term durability has not yet been established. Utilization of this technology is increasing worldwide which raises practice, training, and regulatory issues that will need ongoing attention.

Keywords

fenestrated and branched endovascular repair
branch graft
physician – modified endograft
complex endovascular aneurysm repair
custom made endografts

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HISTORY OF FENESTRATED AND BRANCHED ENDOVASCULAR AORTIC ANEURYSM REPAIR

Fenestrated and branched endovascular aortic aneurysm repair (F/BEVAR) uses customized, patient-specific, endovascular devices with potential to significantly reduce morbidity and mortality associated with open repair of complex aortic pathology. The first publications describing F/BEVAR were reported in 1999 and involved the treatment of short-neck infrarenal abdominal aortic aneurysms (AAAs), using fenestrations for the renal arteries to extend the effective seal zone into the pararenal aortic segment.[1,2] Over the past two decades, the use of F/BEVAR has steadily increased.[3] In the early experience, uncovered stents were used to bridge fenestrations in the aortic endograft to target arteries to maintain target artery patency and aid in endograft alignment. Subsequently, covered stent-grafts have become preferred due to their superior ability to supplement aortic seal at the fenestration site and to improve long-term branch patency. Stented fenestrations are suboptimal for anatomic conditions in which the aortic diameter at the level of the target branch artery is significantly larger than the diameter of the aortic endograft.[4,5] In these cases, side arm branches sewn to the aortic endograft have emerged as an alternative approach to stented fenestrations. Side arm branches can be attached to the aortic endograft in an orientation that is proximal (antegrade) or distal (retrograde) to the level of the target branch artery origin. These side arm branches are then bridged to the target branch artery with a stent-graft as fenestrations are bridged to target branch arteries. Consensus has not emerged regarding the superiority of branches versus fenestrations, and most high-volume users would agree that there is a role for both methods of including target arteries into a complex endovascular repair.

Since its inception, F/BEVAR has been primarily performed in large-volume tertiary care centers. This reflects not only the complexity of the technology, but also the investigational nature of these devices. In the United States, F/BEVAR was initially confined to centers with access to company-manufactured devices through industry-sponsored clinical trials or to centers with an FDA-approved physician-sponsored investigational device exemption (PS-IDE) to study physician-modified devices and/or custom-made devices (CMDs). However, since FDA approval of the Zenith Fenestrated Device (Cook Medical, Bloomington, Indiana) in 2012, fenestrated technology has been made more broadly available for its application to short-neck and juxtarenal AAA in the United States.[6] Additional off-the-shelf devices for TAAA and aortic arch aneurysms are currently in or entering clinical trials in the United States.[7–13]

DEFINITIONS

Techniques for Incorporating Branch Vessels

It is important to differentiate the nomenclature used for F/BEVAR from two other common approaches to aortic branches during endovascular aortic aneurysm repair, "debranching" and "parallel stent-grafting." The term "debranching" refers to the use of open surgical bypass to an aortic branch artery from a location proximal or distal to the intended placement of the aortic endograft. In "parallel stent-grafting," grafts are aligned alongside the primary aortic endograft in a variety of configurations (chimney, snorkel, periscope, sandwich graft) to allow blood flow to aortic branches which are otherwise covered by the aortic endograft. Blood flow to the parallel grafts can originate from the aorta or iliac arteries either above or below covered portion of the aorta.

Standard definitions and terminology for F/BEVAR have been defined in the SVS TEVAR reporting standards document (Fig. 80.1).[14] A scallop refers to a semicircle cut-out of the endograft fabric involving the proximal or distal edge of the endograft which allows filling of an aortic branch. Scallops can vary in width and depth. A fenestration indicates the presence of an opening in the endograft fabric which allows perfusion of an aortic branch vessel which would otherwise be covered. They can vary in diameter in both the major and minor axis. If stents (or stent-grafts) are placed through the fenestration into the target vessel, this is described as a stented fenestration. Even when this stent-graft is not required to achieve a seal, the term "stented fenestration" is still used. A branch is a cylindrical tube of fabric, which may be placed either internally or externally on the aortic endograft; branches may have varying lengths and orientations. Its origin can be located on the endograft proximal or distal to the origin of the target vessel. Just as with a fenestration, a stent-graft is required to bridge the branch to

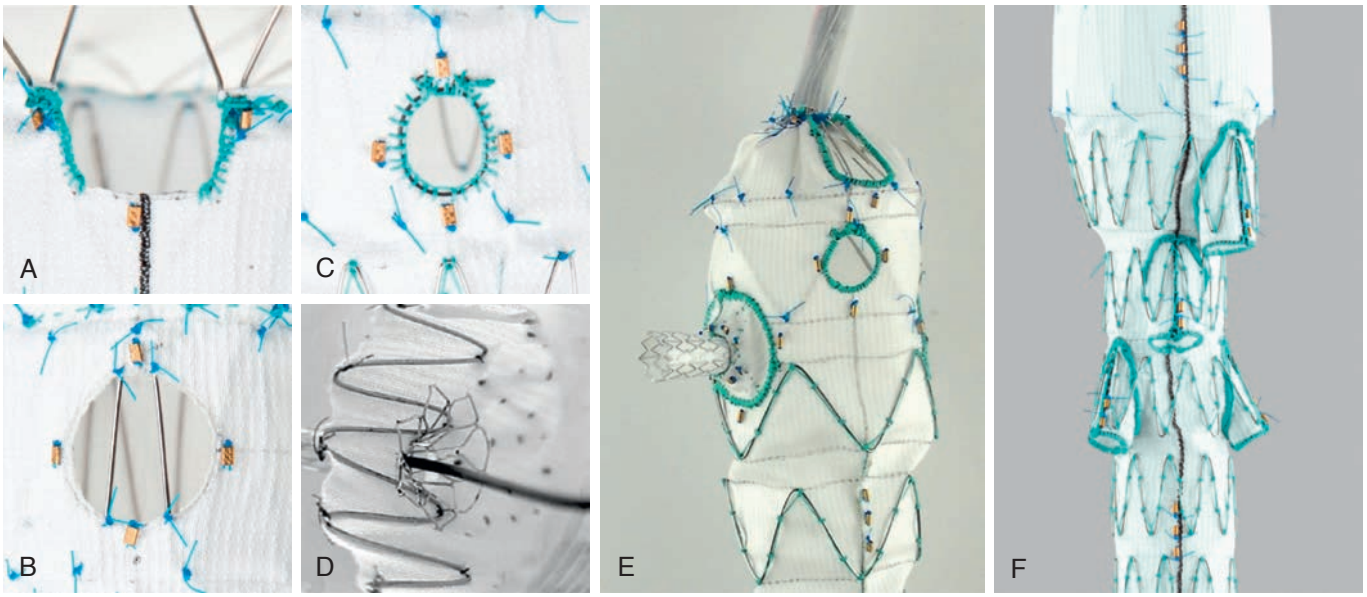

Figure 80.1 Illustrations of (A) scallop, (B) fenestration, (C) reinforced fenestration which is more suitable for stenting or fenestrated branches. (D) Stented fenestration, (E) fenestrated branch, and (F) side arm branch, as defined by the SVS TEVAR Reporting Standards.

the target artery origin to maintain target artery perfusion and to prevent flow into the aneurysm sac.

Device Availability

As previously alluded to, F/BEVAR devices can be obtained in a variety of ways. These are generally grouped into physician-modified endografts (PMEGs), custom-ordered patient-specific devices (CMDs), or off-the-shelf designs which have been tested to be applicable to a variety of anatomic configurations. There are a number of pros and cons associated with each type.

Physician Modified Endografts

In this approach the physician deploys a standard endograft on the back table under sterile conditions and creates modifications by hand to accommodate branch vessels at locations specific to the patient's anatomy based on preoperative imaging (Fig. 80.2). The modified endograft is then resheathed for insertion and deployment in the patient. The rationale for such an approach is twofold: (1) many institutions do not have access to CMDs and, (2) in urgent or emergent situations, there may not be time to wait the 6 to 8 weeks typically required for the manufacturing of a CMD.

Numerous reports have described techniques for modifying nearly all of the devices that are presently commercially available.[15–17] PMEGs have been used for the treatment of short-neck infrarenal to large extent thoracoabdominal aneurysms. Expertise and experience in planning and executing graft modification, as well as the implantation itself, is crucial. Although the planning techniques for PMEGs are similar to those for CMDs, PMEGs do not have standard measurement forms or manufacturer support. There are also some design

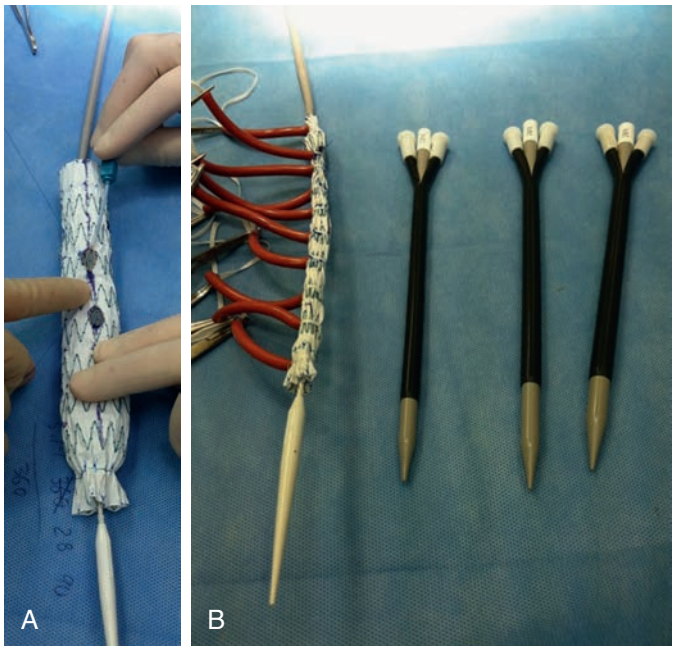

Figure 80.2 Physician-Modified Endovascular Graft. Commercially available device modified by the implanting surgeon with fenestrations on an operating room back table (A). The modified device is then reconstrained, and using a set of serial dilators, resheathed into the delivery system for implantation (B).

aspects (such as aggressive tapering) that cannot be achieved with commercially available endografts. Physician modification thus requires a much more detailed knowledge of devices and deployment mechanisms, and acceptance of some design limitations. It is imperative to note the serious responsibility assumed by the implanting physician, particularly if the procedure is not performed in the context of an investigational device exemption study.[18]

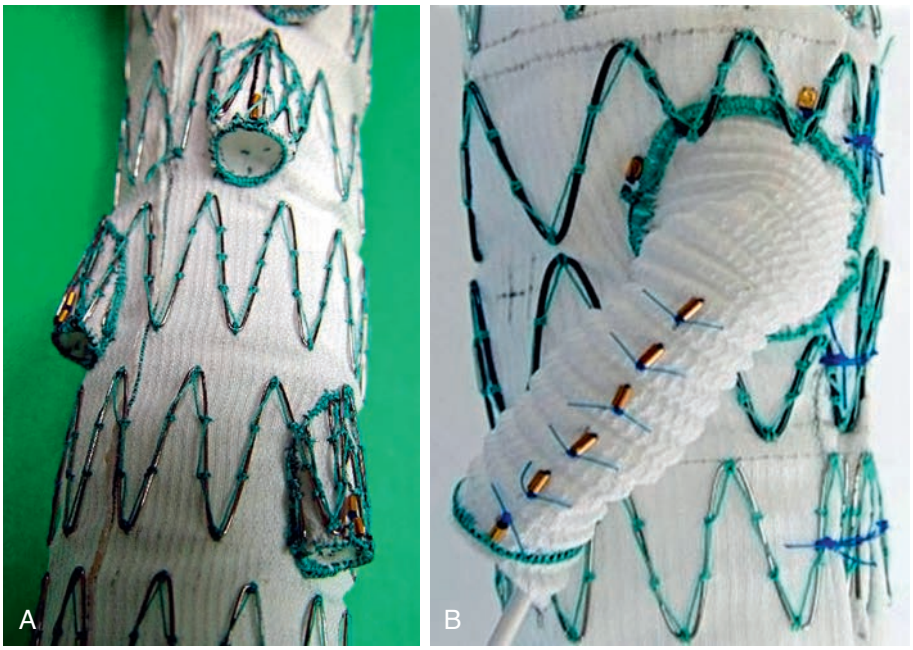

Figure 80.3 Visceral artery branched devices, showing both straight cuffs (A) and helical branches (B).

Company-Manufactured Custom-Made Devices

The majority of the experience accumulated to date with F/BEVAR is through the use of CMDs based off of the TX2 and Zenith platforms (Cook Medical). These devices can include any combination of fenestrations and/or branches. Branches have varied in configuration but have generally involved straight axial cuffs, directional cuffs, and helical limbs (Fig. 80.3). Often the device is "preloaded," whereby a catheter and wire is threaded through the delivery system and then through the fenestration and/or branch (Fig. 80.4). Preloaded catheters/wires can be used to facilitate F/BEVAR in one of two ways: (1) snared from above to facilitate target artery cannulation from the brachial or axillary approach or (2) loaded from below to guide a sheath through the transfemoral ipsilateral delivery system and out the fenestration (Fig. 80.5). Although these CMDs are commercially available throughout much of the world, they have limited availability in the United States. To date, other than the FDA-approved Zenith Fenestrated Device (Cook Medical), all CMDs that have been implanted in the United States have been done so as part of an industry-sponsored clinical trial or at a center with an ongoing PS-IDE trial.[16,19–22]

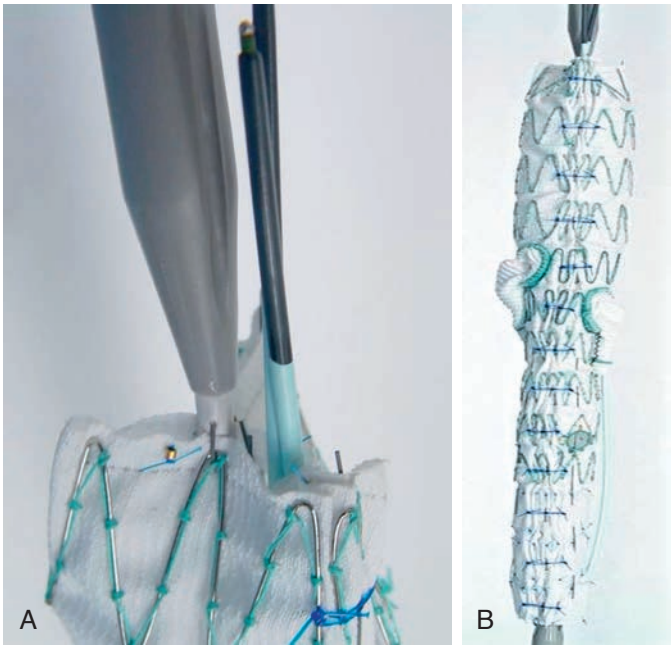

Figure 80.4 (A and B) A preloaded, two-branch, two-fenestration device. In this device the preloaded catheters and wires are threaded through the visceral branches, with a proximal exit as depicted in B. This design facilitates cannulation of the branches during the operation.

Company-Manufactured Off-the-Shelf Devices

Off-the-shelf devices have been developed to overcome the limitations of custom-made CMDs requiring several weeks of manufacturing time. Off-the-shelf designs take advantage of the fact that branch vessel anatomy varies within a defined range for the majority of patients.[23–26] Pivoting fenestrations and downgoing axial side branches have both been used to create different off-the-shelf devices applicable to different types of aneurysms. There are currently three different off-the-shelf F/BEVAR devices in trial in the United States: Cook "p-Branch" (Cook Medical), "t-Branch" (Cook Medical), and Gore Excluder Thoracoabdominal Multibranch Endoprosthesis (W.L. Gore and Associates, Inc., Flagstaff, Arizona). Each of these designs is specifically engineered to allow for more degrees of freedom for cannulation of target vessels within a set range of positions. While these devices are more versatile than custom-made CMDs, off-the-shelf designs are not able to accommodate all extremes of anatomy.

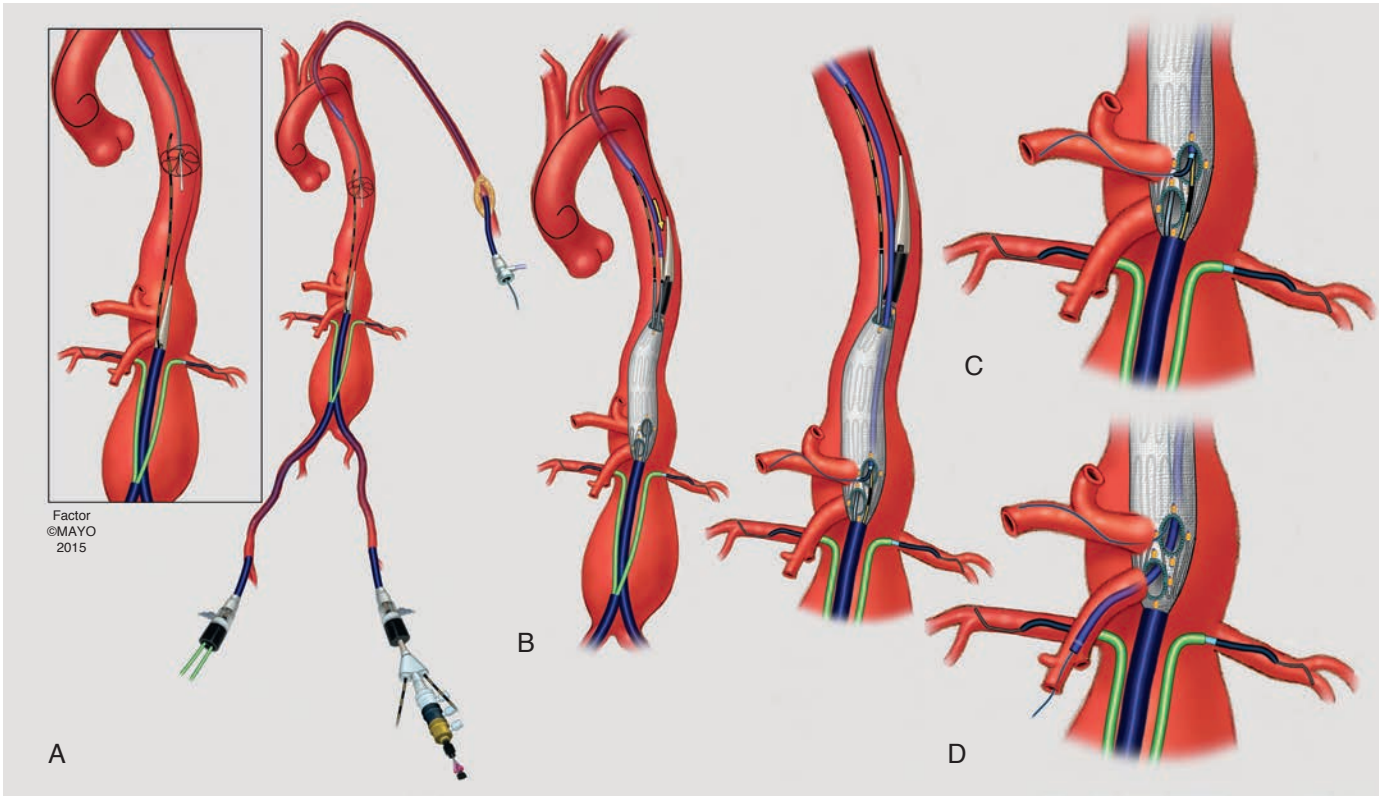

Figure 80.5 Demonstration of the Use of Preloaded Catheters During Fenestrated and Branched Endovascular Aortic Aneurysm Repair. Preloaded catheters are loaded through the graft and ipsilateral device delivery system in the left groin and emerge through the top of the endograft. The catheters are snared from a left axillary approach (A). After unsheathing of the proximal endograft, catheters and sheaths can be advanced from the axillary artery over wires placed through the preloaded sheaths, which have been threaded through the fenestrations for the celiac artery and superior mesenteric artery (B). After sheaths have been advanced from above through the graft fenestrations, wire and catheter selection of the branch arteries is performed (C). Sheaths are subsequently advanced over wires through the graft fenestrations and into the branch vessels which will allow placement of covered stents into the branch vessels after deployment of the aortic endograft (D). (Figures courtesy of Gustavo Oderich, MD, Division of Vascular and Endovascular Surgery, Mayo Clinic, Rochester, MN.)

OVERVIEW OF CURRENT DEVICES BASED ON ANEURYSM LOCATION AND EXTENT

Juxtarenal Abdominal Aortic Aneurysm

The commercially available Zenith Fenestrated Endovascular Graft (Cook Medical) also known as the "Z-Fen" device, is intended to treat "short-neck" infrarenal and juxtarenal AAA and is the only fenestrated device currently FDA-approved (Fig. 80.6). The proximal main body graft is a tube graft which utilizes a combination of fenestrations and/or a scallop to accommodate the superior mesenteric artery (SMA) and renal arteries; these are custom-made to the patient's specific anatomy. The most common graft design employs either a scallop or a large fenestration for the SMA and two small fenestrations for the renal arteries. There are several restrictions on how scallops and/or fenestrations can be placed due to specific engineering constraints. As a result, not all branch vessel anatomy can be accommodated. The proximal main body is deployed with the fenestrations appropriately aligned with their target arteries. After deployment of the proximal main body device, the fenestrations and branch arteries are selected from inside the proximal main body endograft and sheaths are advanced into the target arteries to allow deployment of bridging stent grafts. The proximal main body is subsequently mated to a distal bifurcated endograft which can be designed to extend into the ipsilateral iliac artery or from which standard iliac limbs can be extended bilaterally.

Pararenal Abdominal Aortic Aneurysm

There are currently no commercially available devices intended available in the United States to treat pararenal AAAs. The Cook "p-Branch" (Cook Medical) device, so named for the ability of the renal fenestrations to "pivot," is currently in clinical trial within the United States. This is an off-the-shelf device which incorporates fenestrations for the SMA and bilateral renal arteries and a scallop for the celiac artery, thereby allowing more proximal extension of the aortic endograft seal zone in comparison to the "Z-Fen" device. As an off-the-shelf device, it is currently manufactured in two configurations which, in combination, are anticipated to accommodate the aortic branch anatomy in approximately 70% of pararenal aneurysms.[26] There

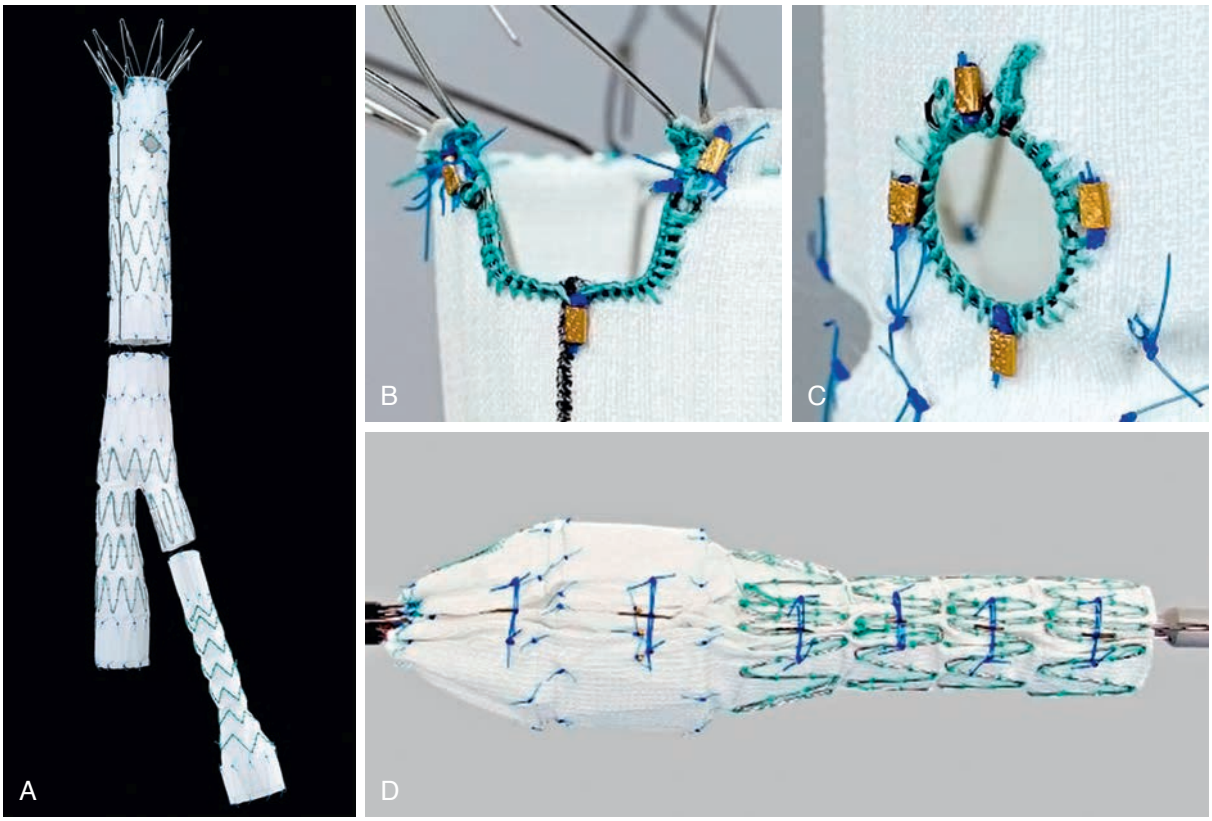

Figure 80.6 **The Zenith Abdominal Aortic Aneurysm Fenestrated System (Cook Medical, Inc., Bloomington, Indiana).** (A) The device is a modular bifurcated device. (B) Nitinol-reinforced scallop with three gold radiopaque markers. (C) The fenestrations are reinforced with nitinol rings and radiopaque gold markers to aid with orientation of the graft during deployment. (D) Constraining ties which reduce the diameter of the proximal main body help to allow rotation of the graft which is necessary to achieve alignment.

are two notable features of this device (Fig. 80.7). First, the renal fenestrations are created within a pocket of redundant fabric which can "pivot" and thereby allow selection of the renal artery and extension with a stent graft into the renal artery in a myriad of directions. Second, the proximal main body of the "p-Branch" device has preloaded wires and catheters specifically designed to cannulate the renal arteries without the need to select via contralateral femoral access. Both aspects of this graft are designed to facilitate selection of the renal arteries. After proximal main body deployment and target vessel selection and stent graft placement, the remaining graft deployment proceeds similarly to the "Z-Fen" device.

Thoracoabdominal Aortic Aneurysms

There are currently no commercially available devices intended to treat thoracoabdominal aortic aneurysms (TAAA) in the United States. As a result, options for the F/BEVAR of TAAA are limited to PMEG or custom-made patient specific (CMDs) available through an industry-sponsored clinical trial or physician-sponsored IDE study.

Custom Made Devices

CMDs can be custom-manufactured to include any combination of fenestrations and/or branches. On average, these devices require 6 to 10 weeks of time for manufacturing. These devices are available with standard fabric and stainless steel stents that require delivery systems ranging from 22 to 26 French or with low-profile fabric and nitinol stents that require delivery systems ranging from 18 to 22 French. As mentioned previously, a diverse array of preloaded wires and/or catheters can be incorporated into the endograft design to ease target artery cannulation from either below or above.

Thoracic Branch or "t-Branch" (Cook Medical)

Based upon the experience with custom-made CMDs, Thoracic Branch or "t-Branch" (Cook Medical) is an off-the-shelf device based on the Cook TX2 platform which uses four downgoing axial branches sewn to the thoracic component which allow extension of stent grafts into the visceral vessels (Fig. 80.8). The thoracic endograft is mated with a standard modular infrarenal bifurcated graft distally and can be extended proximally with a thoracic endograft. This device, available in Europe, is scheduled to enter a clinical trial in the United States in the near future.

Gore Excluder Thoracoabdominal Multibranch Endoprosthesis (W.L. Gore and Associates)

The Thoracoabdominal Multibranch Endoprosthesis, or "TAMBE" graft, is an off-the-shelf device designed for the

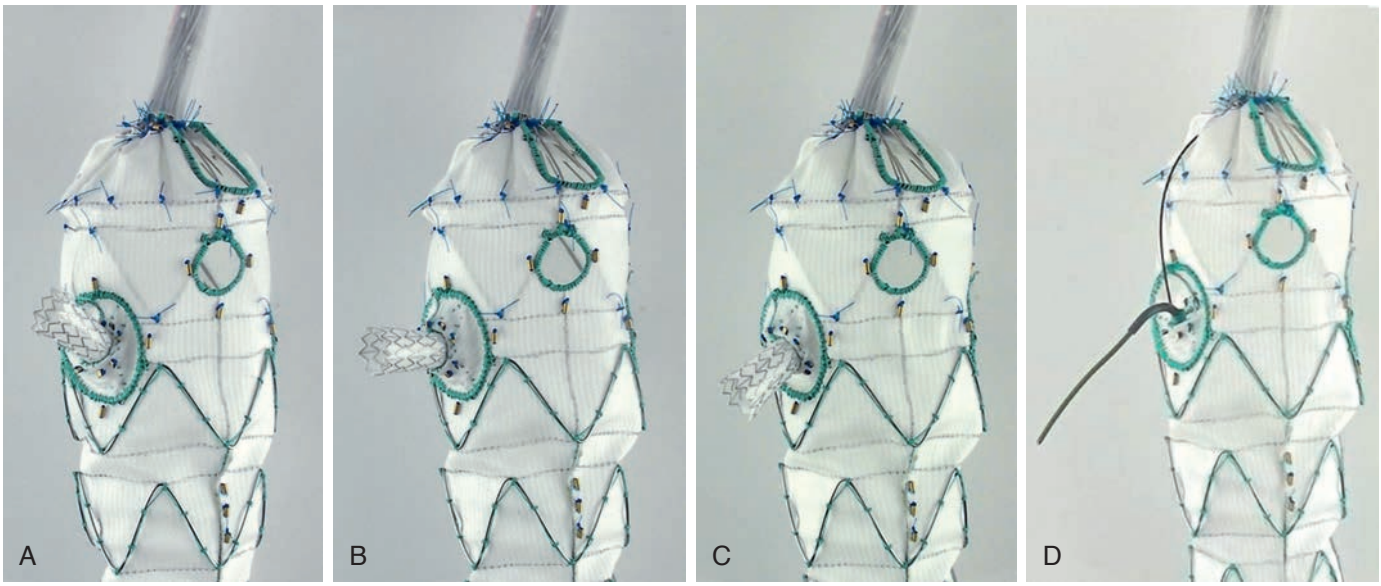

Figure 80.7 The off-the-shelf Zenith Pararenal Endovascular Graft (Cook Medical, Inc., Bloomington, Indiana), currently known as "p-Branch," has a standard configuration consisting of a celiac scallop, a superior mesenteric artery fenestration, and "directional" fenestrations to accommodate most renal arteries with fenestrated branches. (A). This allows stenting of the renal arteries through the renal pivot in a variety of orientations while still attached to a flexible "directional" reinforced fenestration (A-C). Pre-loaded wires and catheters in the renal pivot intended to select the renal arteries (D).

Figure 80.8 The Thoracic Branched ("t-Branch") device (Cook Medical, Inc., Bloomington, Indiana), an off-the-shelf endograft system designed for repaired of thoracoabdominal aortic aneurysms.

treatment of aneurysms involving the visceral segment (Fig. 80.9). The graft has two downgoing internal branches for the celiac artery and SMA into which stent grafts are placed to bridge the gap from the device to these target arteries. There are two separate configurations for the internal renal branches through which stent grafts are placed into the renal arteries. Both renal branches are perfused in an antegrade fashion in one configuration and in a retrograde fashion in the other. Feasibility testing has been performed, and this device is scheduled to enter clinical trial in the United States at the time of writing of this chapter.

Aortic Arch

Encouraging early results using F/BEVAR devices for aneurysms involving the visceral segment has inspired extension of this technology to treat aneurysms of the transverse and descending aortic arch with involvement of the great vessels. Challenges unique to the aortic arch include greater vessel flow, pulsation and rotation within the cardiac cycle and with respiration, greater tortuosity and angulation of the arch and great vessel ostia, longer distance to the target vessels, the proximity of the aortic valve and coronary arteries, and lower cerebral tolerance to transient ischemia and embolism.[27] Given these challenges, experience has dictated that aortic arch pathology appears better suited for treatment with branched endografts rather than fenestrations. While misalignment of fenestrations results in severe neurologic complications, precise alignment of branched grafts is not as critical as long as the branch grafts can be successfully extended into the great vessels.

To date, the majority of the experience in total endovascular repair of aortic arch lesions has been gained outside of the United

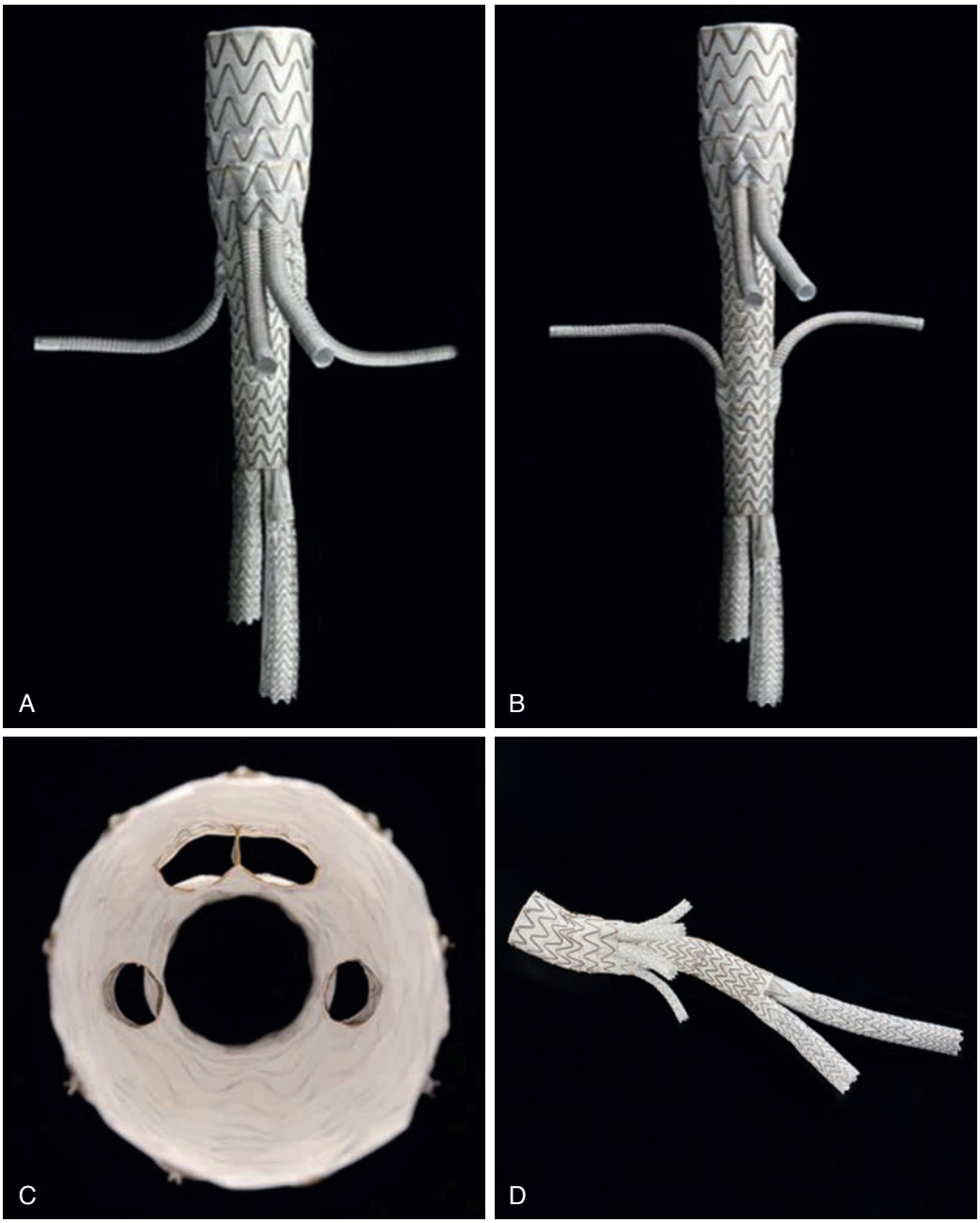

Figure 80.9 The Thoracoabdominal Multibranched Endoprosthesis ("TAMBE" device, Gore Medical, Flagstaff, Arizona), an off-the-shelf endograft system designed for the repair of thoracoabdominal aortic aneurysms. The device has configurations with both antegrade (A) and retrograde (B) orientation of branches for the renal arteries. The visceral arteries are accessed via internal portals in the main body of device (C), through which Viabahn stent-grafts are extended into the target arteries (D).

States. Inoue established the technical feasibility of branched endovascular repair of arch aneurysms with the first published experience in 1999.[28] The high stroke and mortality rate seen in this experience was thought to be due to the use of branches which protruded external to the aortic graft and required extensive manipulation in the arch during cannulation of target vessels.[29] Chuter et al. reported the first use of a modular branched endograft for arch repair in 2003. This design required full arch debranching based on the right common carotid artery followed by delivery of the proximal bifurcated ascending graft via the right common carotid artery. One limb of the ascending graft was extended into the innominate artery while the other served as a gate for mating with the distal tube endograft component which was delivered via the femoral artery.[30] Ultimately, the large sheath size in the carotid artery hindered the broad application of this technique.[29] Fenestrated custom-made endografts have also been used to repair arch aneurysms. The largest cohort study comes from Japan with a precurved endograft with preloaded catheters placed through the fenestrations. This graft came to be known as the Najuta graft, a device with 19

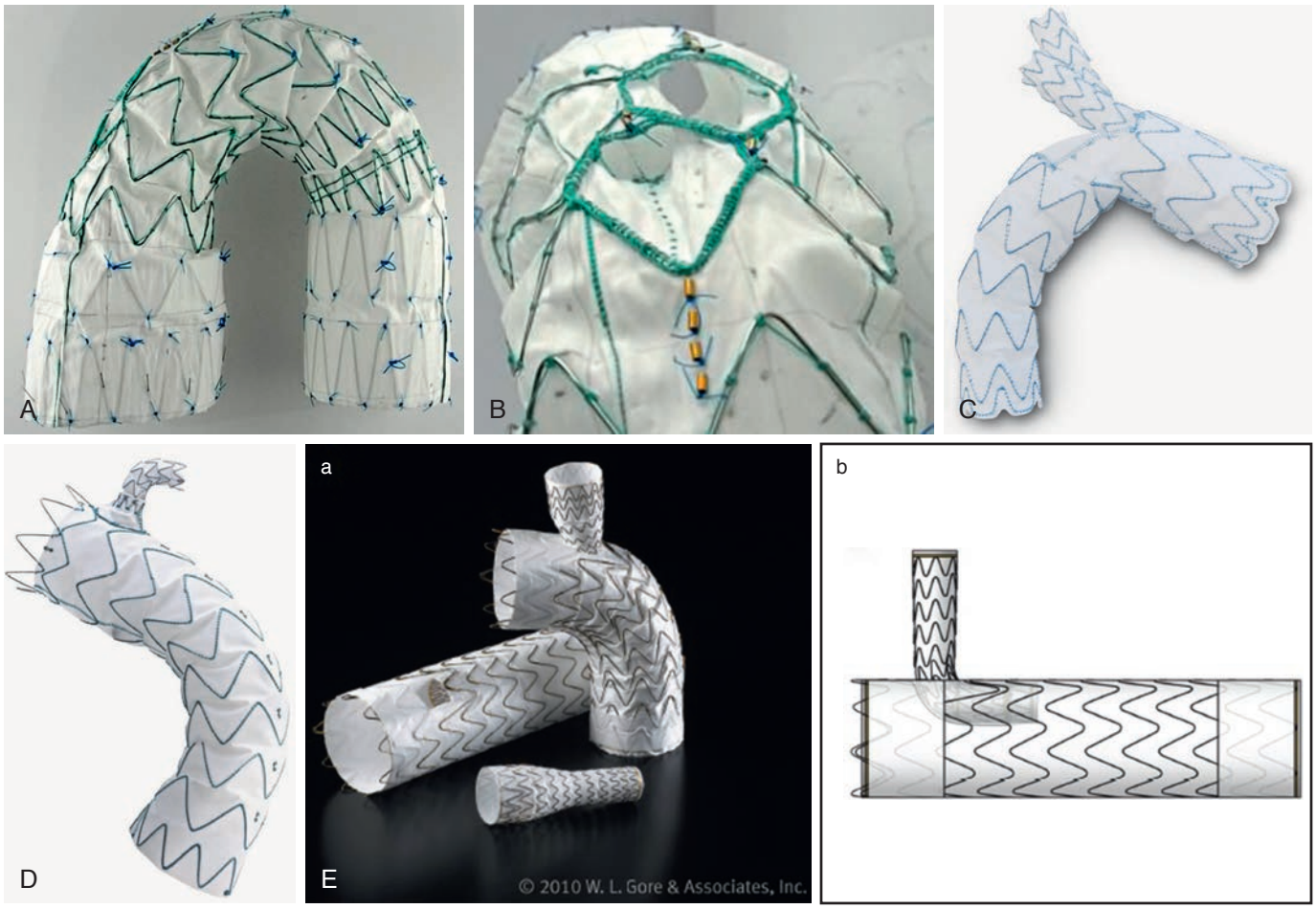

Figure 80.10 Branched Devices for the Aortic Arch. Cook Arch Branch Device (Cook Medical, Inc., Bloomington, Indiana). The device designed based on Cook TX2 (A) and includes two inner branches placed on the outer curvature of the device (B). The double branch Relay NBS PLUS for aortic arch (C: Bolton Medical, Inc., Barcelona, Spain), The Valiant Mona LSA stent graft system (D: Medtronic, Inc., Minneapolis, Minnesota). The TAG Thoracic Branch Endoprosthesis (W.L. Gore & Associates, Flagstaff, Arizona) aortic component and side branch as well as schematic showing side branch in retrograde inner portal (E).

types of three-dimensional (3D) stent skeletons and 8 types of graft fenestrations for arch vessels.[31] From 2010 to 2012, 383 patients were repaired with this device with low morbidity, including a 1.8% stroke rate, and low 30-day mortality (1.6%).

Despite these encouraging early results, the technical challenges associated with arch repair and the desire for immediately available off-the shelf grafts has driven the development of the four arch branch devices which are now the most commonly used worldwide. The use of aortic arch branched grafts for repair of thoracic aneurysms remains in its relative infancy because there are currently no FDA-approved devices for use in the United States. Current grafts are in clinical trials in the United States or Europe or available within physician-sponsored IDE trials (Fig. 80.10).

Cook Arch Branch Device

The current configuration of the Cook custom-made arch device has two internal branches intended for zone 0 deployment. The largest proximal device diameter is 46 mm. A key component of the delivery system is a precurved introducer and sheath. In addition, the outer curvature of the device is attached to the inner cannula with a spiral wire, which aids in orienting the internal branches along the outer curvature of the arch. After graft deployment, there is ongoing arch perfusion through the open branches. After surgical access from above (right carotid artery or right axillary artery; left carotid artery or left axillary artery in the setting of a left carotid subclavian bypass), the internal branches are catheterized and bridging stents deployed from the internal branch into the respective target vessels. Traditional open left subclavian revascularization is generally performed to maintain antegrade perfusion through the left vertebral artery. This graft has the largest worldwide experience, with greater than 200 implants reported.[32]

Relay NBS Plus for Aortic Arch (Bolton Medical, Barcelona, Spain)

This device, based on the Relay NBS platform, is custom-made outside of the United States and is not currently available in

the United States. Proximal diameters range from 32 to 48 mm, and distal diameters range from 22 to 48 mm. Customized tapering of the graft up to 16 mm can be achieved and device lengths vary from 255 to 270 mm, which allows the endograft to span the length of the arch with a single device. A dual sheath design is meant to improve conformability along the inner curve of the arch, and a precurved nitinol hypo tube aids in orientation of the branches along the outer curve. The most current iteration of device includes two 12-mm internal "tunnels," which are oriented such that the anterior tunnel is optimally bridged to the left carotid artery and the posterior tunnel bridged to the innominate artery. The tunnels open into a single large aperture which is meant to direct guide wires into the tunnels from a femoral approach. Dedicated bridging stent grafts are part of the system, with distal diameters ranging from 8 to 20 mm to accommodate the majority of innominate and carotid artery sizes. The results of 40 implantations have been reported.[8,33,34]

Valiant Mona LSA Stent Graft System (Medtronic, Inc., Minneapolis, Minnesota)

The Mona LSA device is a single-branch device designed for zone 2 deployment, although it can also be used in more proximal landing zones assuming any covered arch vessel can be revascularized with open debranching as necessary. This endograft is based on the Valiant thoracic graft platform, with proximal diameters ranging from 30 to 46 mm and distal diameters ranging from 22 to 46 mm. Grafts are 150 mm in length and have a maximum taper of 4 mm over the length of the graft. The branch is a modified fenestration with a short inverted funnel that is intended to engage the origin of the arch vessel. A preloaded catheter is threaded through the fenestration. A guide wire passed through the catheter within the delivery system is snared from access via direct exposure of the arch vessel and the "through-and-through" wire used to orient the fenestration at the origin of the target vessel. The system offers dedicated bridging stent-grafts between 10 and 14 mm in diameter that can be delivered through the arch vessel and flared within the wide mouth of the fenestration. The cuff can pivot, allowing for as much as 20 to 30 degrees of malalignment between the cuff and the subclavian artery. Nine patients were successfully treated in an early feasibility study, and the device is now being evaluated in a feasibility trial at seven sites in the United States.

TAG Thoracic Branch Endoprosthesis (W.L. Gore and Associates)

The Gore device for use in the aortic arch (Gore TBE) is based on the conformable Thoracic Aortic Graft (C-TAG) platform. The device is intended for either zone 0, 1, or 2 deployment, with a caudally oriented internal branch. The device is currently available with proximal diameters ranging from 26 to 45 mm and lengths of 100 or 150 mm. The delivery system has a preloaded catheter threaded through the branch which allows snaring of a guide wire from either upper extremity or left carotid access. A "through-and-through" guide wire is used to orient the device during deployment. A series of bridging stents are available which are delivered and deployed via the femoral artery into the arch vessel. The Gore TBE device has completed a multicenter feasibility trial, and a pivotal trial is currently enrolling patients.

CASE PLANNING AND SIZING

Detailed and accurate planning is absolutely crucial to successfully executing F/BEVAR. Due to the variety of anatomic factors that impact device delivery, deployment, and target artery cannulation, the procedural planning is highly complex and requires a substantial knowledge base. Planning includes not only thorough review of sophisticated imaging and precise measuring, but also sound decision making on the type of device (diameters, lengths, tapering, fabric type, etc.), the type of target artery preservation method (scallop, branch, fenestration), and strategy for cannulation (preloaded systems, ipsilateral or contralateral transfemoral access, access from above, etc.). The physician must also give consideration to the influence that iliac access will have on the ability to deploy the device, manipulate the device superiorly and inferiorly, rotate the device, and the optimal sequence of intraoperative steps for deployment. Although a comprehensive review of all planning details and design decisions is beyond the scope of this chapter, several key considerations are outlined later.

Preoperative Imaging

Aortic imaging with high-resolution computed tomographic angiography (CTA) and 3D reconstruction should be obtained in all patients without strict contraindication to moderate doses of contrast agent. In cases of advanced renal dysfunction, strong consideration should be given to the appropriateness of complex endovascular repair if progression to renal replacement therapy is not acceptable to the patient. The CTA should be reconstructed at slices of 1 mm or less to offer the best possible resolution. If the aortic arch is involved, the CTA should be obtained with electrocardiography gating to provide clear images of the mobile ascending aorta and aortic arch. CTA is the cross-sectional imaging modality of choice because magnetic resonance angiography (MRA) has approximately half the resolution of CTA and does not demonstrate calcification as clearly.[35] In addition, dedicated postprocessing software which can manipulate the Digital Imaging and Communications in Medicine (DICOM) data in three dimensions is crucial to procedural planning. Such software allows for curved planar reformatting and the creation of an aortic centerline of flow; this allows for all measurements to be made perpendicular to the center line of flow and thereby adjusts for angulation and movement of the aorta in three dimensions. Measurements orthogonal to the centerline of flow provides the basis for assessing the location of aortic branches, both in terms of their cranial—caudal position off of the aorta as well as the "clock face" orientation of their origins from the aortic circumference (Fig. 80.11). These measurements are required for both off-the-shelf and custom-made devices. In the case of custom-made devices, F/BEVAR device is designed

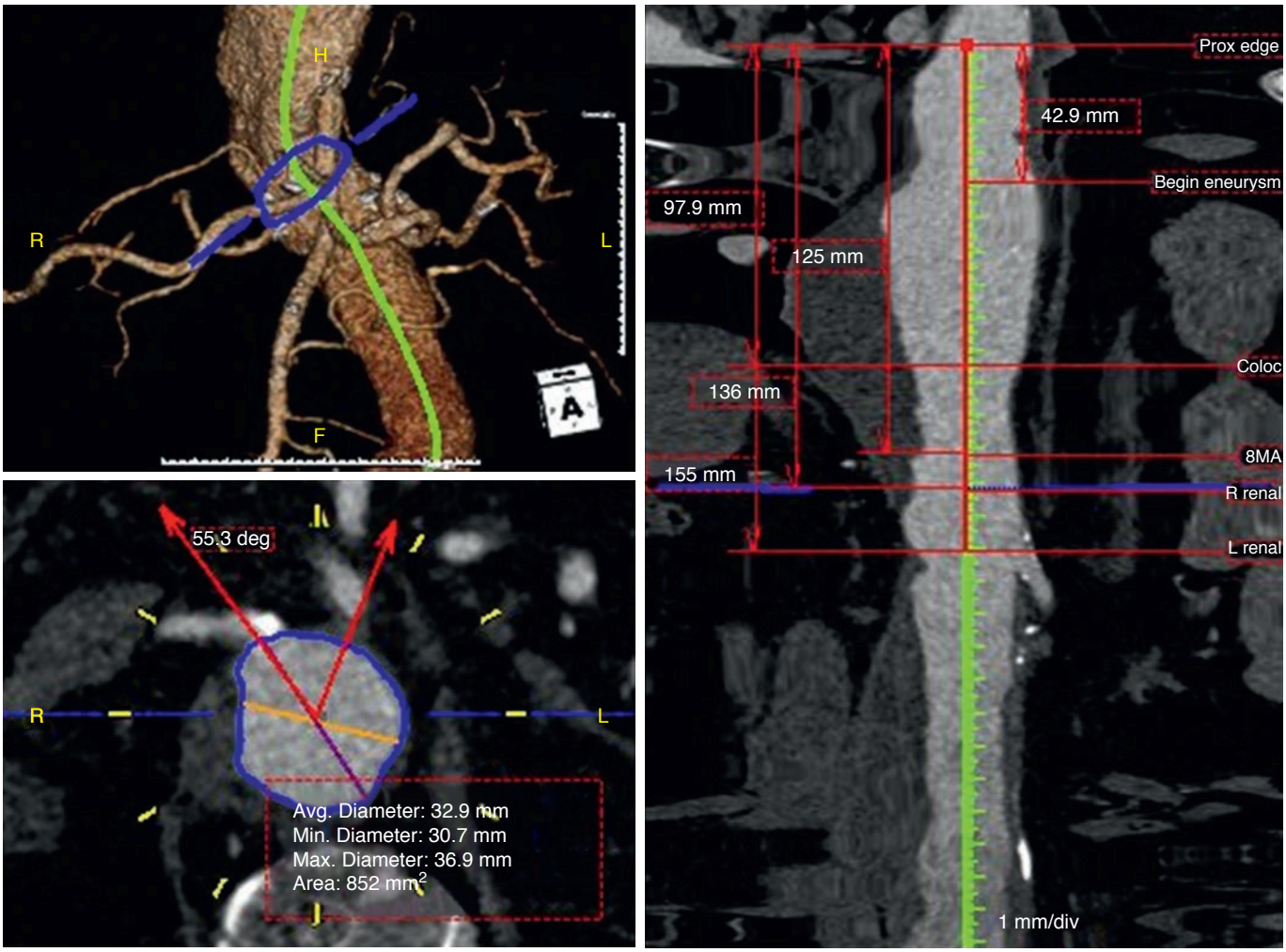

Figure 80.11 The use of dedicated postprocessing software to create centerline of flow and precisely assess location of aortic branches to design and fenestrated and branched endograft.

to match the precise location of aortic branches that will be incorporated into the repair. The person performing the graft implantation should also perform the preoperative measurement and planning because this leads to greater understanding of anatomy which impacts the execution of the procedure, aids in troubleshooting, and provides insight about the short- and long-term risks of the procedure.

Anatomic Considerations for Fenestrated and Branched Repair

Proximal Seal Zone

Choice of the proximal seal zone is one of the most important decisions when planning F/BEVAR. Seal should be achieved in a relatively straight segment of aorta which is cylindrical with parallel walls and without significant mural thrombus or calcification. Degenerated or unhealthy aorta is vulnerable to subsequent aneurysmal degeneration which can destabilize proximal seal and jeopardize the integrity of the repair. One important principle for F/BEVAR is that adequate proximal seal should not be compromised in favor of incorporating fewer aortic branches into the repair. In contrast to infrarenal endografts, where seal lengths as short as 10 to 15 mm may be adequate, seal lengths of 20 to 40 mm are often sought for F/BEVAR. The availability of F/BEVAR devices which can accommodate four visceral vessels often allows for a healthy segment of the thoracic aorta to be chosen as the proximal seal zone. In addition, as with many infrarenal endografts, F/BEVAR endografts often use active fixation (e.g., barbs) in the proximal seal stents.

Aortic Angulation, Calcification, and Mural Thrombus

Significant angulation in the aorta adjacent to the visceral or aortic arch branches can complicate F/BEVAR. Branch location along the aortic centerline and "clock position" along the aortic circumference are more difficult to determine in angulated segments. In addition, angulation often leads to less predictable deployment of the fenestrated or branched portion of the endograft which can lead to misalignment of fenestrations/branches with their target arteries and subsequent challenges, decreasing the success rate of target artery cannulation. In general, for branched paravisceral AAA or TAAA repair, angulation should be limited to less than 45 degrees between the distal thoracic

aorta and the visceral aorta, the suprarenal aorta to infrarenal aorta, and the infrarenal aorta to the iliac artery.

In addition, the degree of aortic calcification and mural thrombus should be evaluated during preoperative planning because they pertain to risk of embolization intraoperatively. F/BEVAR requires stiff wire access across the aortic arch into the ascending aorta to have a stable platform for advancing devices. In addition, compared with standard infrarenal endovascular aneurysm repair, F/BEVAR requires significant rotational movement of the endograft to achieve appropriate branch vessel alignment. Unfavorable vessel characteristics in the arch and proximal descending thoracic aorta greatly increase the risk of stroke. Similarly, vessel calcification, thrombus, and atheroma ("shaggy aorta") in the distal aorta increase the risk of lower extremity embolism.

Branch Vessel Characteristics

The characteristics of the arch branch vessels, celiac artery, SMA, and renal arteries influence the choice of fenestrations or branches and impact the ability to successfully execute F/BEVAR. Branch arteries which are small or highly stenotic at their origin may be difficult to cannulate through a fenestration or branch. In addition, branch arteries which are small and highly tortuous in the proximal segments are more difficult to traverse with wires and catheters. This may prevent advancement of a stable wire/catheter/sheath platform that is necessary to bridge the fenestration or branch to the target artery with a stent graft. All of these anatomic challenges increase the chance that the branch vessel will not be successfully stented. This can lead either to loss of perfusion to the vessel or to an endoleak with perfusion of the aneurysm sac. In addition, branch vessels that are excessively small may have diminished long-term patency.

Access Vessels

F/BEVAR generally requires slightly larger iliac access vessels than standard infrarenal endovascular repair. The "Z-Fen" and "p-Branch" devices are typically loaded in a 22-French delivery system. Although CMDs for F/BEVAR for the thoracoabdominal aorta formerly required 22- to 26-French delivery systems, recent material changes have allowed the devices to be downsized to 18 to 20 French. In addition, the contralateral iliac artery must often accommodate a 20- to 24-French sheath because this sheath size is required to accommodate the multiple 6- to 7-French sheaths used to extend stent grafts into multiple fenestrations. The use of upper extremity access for extension into the visceral arteries and the use of ipsilateral preloaded sheaths can minimize the sheath size required in the contralateral iliac artery. Therefore the iliac arteries must generally be approximately 7 mm in diameter and free of obstructing plaque. In addition, iliac artery tortuosity must be considered during planning because delivering F/BEVAR devices through tortuous anatomy can lead to "stored torque" in the delivery system which can greatly complicate alignment of fenestrations/branches with target vessels. Just as with infrarenal EVAR, in many instances, inadequate access vessels can be overcome with use of aortic or iliac conduits and endoconduits.

Finally, stent-grafting the visceral vessels via downgoing branches must be performed from above using brachial access or axillary access. At a minimum, these arteries must accommodate a 7- to 12-French sheath. When multiple sheaths are required, an 8- to 10-mm axillary conduit can be sewn to the axillary artery, although this is not always necessary. The choice of left or right axillary artery is at the discretion of the physician, with pros and cons to each.

Sequence of Intraoperative Steps and Staging of Repair

Although minimally invasive, complex F/BEVAR is an extensive operation, with several steps necessary in the majority of cases. From the surgeon's perspective, performance of all stages in one procedure is generally technically feasible. However, the duration for which large sheaths may be in the femoral arteries, risking lower extremity ischemia and contributing to spinal cord ischemia, is an important consideration. Various techniques have been described to mitigate this duration of lower extremity ischemia. For example, femoral sheaths can be removed, restoring lower extremity perfusion, prior to cannulating branches from an axillary or brachial approach.[22] In addition, Voerhaven and colleagues have described using purse strings in the femoral arteries to allow for temporary sheath removal to allow for perfusion to the lower extremities.[36] Finally, Resch and colleagues have described connecting an antegrade sheath in the superficial femoral artery to maintain lower extremity perfusion throughout.[37]

Although the length of proximal seal should not be compromised to decrease length of coverage, there is a balance that must be struck between optimal seal length and the risk of spinal cord ischemia. In cases where extensive aortic coverage is required, or prior aortic surgery has increased the risk of spinal cord ischemia, consideration should be given to a staged approach to repair.[38,39] For example, in the case of an extensive TAAA, the thoracic endograft and left carotid-subclavian bypass can be performed first, separated in time by greater than 2 weeks, from the F/BEVAR portion of the procedure incorporating the visceral segment. Other techniques to minimize the risk of spinal cord ischemia intraoperatively are discussed later.

PATIENT SELECTION AND PREOPERATIVE EVALUATION

Patient Longevity

Patients with juxtarenal, pararenal, and TAAA require careful medical evaluation prior to offering F/BEVAR, with careful consideration of overall life expectancy. Currently, in the United States, these repairs are offered within the context of clinical trials, which generally require that patients have been deemed medically unfit for open repair. As with infrarenal AAAs, the anticipated risk of rupture based on aneurysm size must be balanced against the patient's expected longevity and risk of perioperative complications. There are no data

to suggest that availability of this technology and increasing experience with its use should lower the size threshold used for aneurysm repair.

Preoperative Evaluation

Renal Evaluation

There is a high prevalence of renal dysfunction in patients with TAAA, with up to 45% of patients in some series having a glomerular filtration rate less than 60 mL/min per 1.73 m^2.[40,41] Just as with open repair of TAAA, preoperative renal dysfunction has been associated with perioperative morbidity and mortality with endovascular aneurysm repair.[40,42] In addition, evaluation of baseline renal function helps to guide the timing of preoperative and postoperative CTA and determines if intravenous fluid hydration is required before and after CT scans and the operation itself. Furthermore, in cases of baseline renal dysfunction, an operative strategy that minimizes the use of iodinated contrast becomes increasingly important.

Cardiac Evaluation

In spite of the fact that TAAAs appear to be associated with coronary atherosclerosis, there is currently no clear guideline as to the appropriate extent of cardiac evaluation and intervention that should be performed prior to F/BEVAR. In an analysis by Bub et al., the incidence of atrial fibrillation, ventricular arrhythmia, and 30-day cardiac death were 9%, 3%, and 2%, respectively, after complex endovascular aortic repair.[43] In the absence of specific data in this area, most experts would support preoperative cardiac testing according to current guidelines for moderate to high-risk vascular procedures. It is worth noting that for cases in which rapid ventricular pacing or adenosine are to be used for device deployment in the proximal aorta or aortic arch, coronary blood supply must be sufficient to recover from the intentional induction of asystole, and therefore a thorough pre-procedural investigation of coronary blood supply is recommended.[44]

Pulmonary Evaluation

Chronic obstructive pulmonary disease (COPD) is highly associated with TAAAs. Although pulmonary failure is the most common postoperative complication of open TAAA repair, occurring in 10% to 45% of patients, it is reported to occur in only 9% of fenestrated and branched repairs for extensive TAAA.[41,45,46] In one series of 905 patients undergoing endovascular repair of AAA and TAAAs, the incidence of COPD was 32%. There was no difference in perioperative aneurysm-related outcomes or 30-day survival between patients with and without COPD.[47] However, the severity of COPD was highly associated with diminished long-term survival. In a scoring system proposed by Mastracci et al. for high-risk patients undergoing F/BEVAR, the presence of COPD and the need for supplemental home oxygen at baseline were strong negative predictors of long-term survival.[48] There are no clear guidelines for pulmonary function testing before F/BEVAR, although the presence of COPD and its severity should be considered when weighing the overall risk/benefit ratio of any TAAA repair and determining whether open or fenestrated/branched repair is preferable.

Evaluation of Spinal Cord Circulation

Although there is no single method which accurately predicts which patients will suffer spinal cord ischemia after F/BEVAR, special attention should be paid to risk factors that increase the risk of paraplegia. Just as with open TAAA repair, the most significant factor associated with the development of spinal cord ischemia is the extent of aortic coverage with repair.[41,49] However, a prior distal aortic operation or compromised internal iliac artery or vertebral artery flow are also important risk factors for spinal cord ischemia. Collateral networks for spinal cord perfusion are thought to be increasingly important as the extent of endovascular coverage increases.[50] Based on preoperative CTA or MRI/MRA of the spinal cord, intercostal arteries and lumbar arteries should be carefully noted; coverage of these should be limited whenever feasible while still ensuring durable aneurysm exclusion. As mentioned previously, evidence also suggests that coverage of the thoracic aorta should occur in a staged fashion, whenever possible, to improve the recovery of collateral circulation and decrease the risk of spinal cord ischemia.[38,51] In the case of concomitant iliac aneurysms, efforts should be made to preserve flow into both, or at least one, of the internal iliac arteries through the use of iliac artery branch devices or with an external-internal iliac artery bypass.

When repair involves the aortic arch, CTA should be used to assess the entirety of the great vessels. In addition, duplex ultrasonography should be performed to assess the status of the carotid and vertebral arteries, including presence of any occlusive disease and direction of flow.

OPERATIVE TECHNIQUE

Anesthesia

Most authors report the use of general anesthesia due to the duration of the procedures and the necessity to control patient breathing to allow precise imaging and accurate device deployment. Arterial lines are placed routinely for continuous blood pressure monitoring, with consideration to the potential use of right or left brachial or axillary artery for imaging and/or branch artery cannulation. Either large-bore peripheral intravenous lines or central venous catheters are placed to allow appropriate resuscitation if needed. Lumbar spinal drainage catheters are routinely placed in any patient at high risk of development of spinal cord ischemia, including type II and type III TAAAs and those with other risk factors for spinal ischemia. The anesthesiologist must also be prepared to dose anticoagulation and maintain an activated clotting time of at least 300 seconds. This is critical due to the duration of time that large sheaths may be positioned in the femoral arteries or in branch arteries off of the aorta.

Intraoperative Imaging

A "hybrid" operating room with high-quality fixed imaging is invaluable for the performance of F/BEVAR. Although possible to perform F/BEVAR with mobile imaging equipment, it is not recommended. An imaging gantry capable of a full

180-degree rotation around the patient is crucial to obtaining the necessary oblique and lateral views to visualize the origins of aortic branches and their corresponding fenestrations and branches. The need for appropriate equipment to minimize radiation exposure cannot be overemphasized because these procedures often require relatively long fluoroscopy times.[52,53] Fluoroscopy time and radiation dose can be minimized by planning in advance the appropriate imaging gantry angles and bony landmarks which will allow accurate device deployment and fenestration and branch orientation.

Although not an absolute requirement to conduct F/BEVAR, the use of fusion imaging has been reported to reduce contrast volume and radiation dose in comparison to deployment based on standard and/or digital subtraction angiography (see Chapter 27 and Chapter 31).[54–56] With this technique, a preoperative CTA is "fused" with a noncontrast 2D or 3D x-ray obtained immediately before operation based on alignment of bony landmarks. This fusion is registered to the patient's position on the x-ray table so that it is preserved with any movement of the gantry or the table. The end result is a 3D overlay of the aorta, iliac arteries, and branch arteries superimposed on the 2D x-ray image of the patient on the table. This overlay facilitates alignment of the endograft with the patient's anatomy and increases the ease of target vessel cannulation (Fig. 80.12). An alternative to using the overlay of the entire arterial tree is to place markers at the origins of target arteries or other important locations (Fig. 80.13).

It should be noted that aortic anatomy, including the position of branch vessels, can change with the insertion of stiff wires which often straighten tortuous arteries. For this reason, fusion imaging should be supplemented with injections of small amounts of contrast to ensure appropriate identification of branch vessels. Alternatively, preselection of aortic branches to guide endograft deployment is a reliable technique that can be performed with little or no contrast and allows for subtle adjustment of the overlay.

Technical Skills and Resources

Surgeons performing F/BEVAR should have advanced skills in procedure planning and endovascular techniques involving the aorta and branch arteries. To date, in the United States the majority of F/BEVAR repairs have been performed in a limited number of tertiary care centers in the context of industry-sponsored or physician-sponsored IDE studies. With FDA approval of the "Z-Fen" device (Cook Medical) in 2012, fenestrated technology has become more widespread. The requisite experience in endovascular intervention and aortic endografting necessary to optimally execute F/BEVAR has not been specifically defined. Cook Medical has a process by which operators are approved to order "Z-Fen" devices based on case experience and completion of device training. The planning, wire and catheter skills, and the ability to execute a 3D repair using 2D imaging guidance are well above and beyond those required for standard EVAR or TEVAR.

Device Delivery and Deployment

All F/BEVAR procedures begin with access of the femoral arteries by either open or percutaneous technique. When necessary for

Figure 80.12 Use of three-dimensional fusion overlay to identify location of aortic branched to guide fenestrated and branched endograft placement.

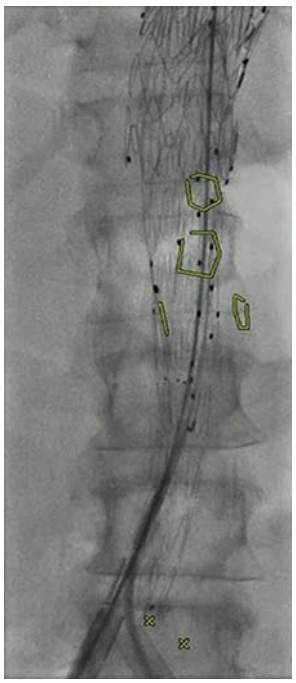

Figure 80.13 Use of markers placed at origin of branch vessels based upon fusion of preoperative computed tomography angiography with a noncontrast two- or three-dimensional x-ray obtained at operation. Markers guide alignment of radiopaque markers at graft fenestrations.

downgoing branches or for fenestrations intended to be cannulated from above, brachial or axillary artery access is performed at case outset before heparinization. As mentioned previously, F/BEVAR devices may be designed with catheters or wires that are "preloaded," facilitating selective catheterization of the fenestration/branch and target artery. There are a number of different options for preloading—wires versus catheters, direction of the wire load relative to the endograft fabric—which are beyond the scope of this chapter.

Nonpreloaded Devices

These devices, such as the Zenith Fenestrated graft, require bilateral femoral access. The contralateral iliac artery is accessed first and a 20- to 24-French sheath is placed over a stiff guide wire into the infrarenal aorta. The hemostatic valve of the sheath can be punctured multiple times to allow for placement of smaller sheath/catheter combinations for cannulation of branch arteries. When fusion imaging is not used as the sole basis for graft orientation, catheters and wires may be placed into the branch vessels to serve as markers for orientation of the device during deployment. The F/BEVAR device is then prepared and oriented extracorporeally prior to insertion. This is a critical step to ensure that the device is deployed with the fenestrations/branches oriented properly.

The device is introduced into the aorta over a stiff wire, such as a double-curved Lunderquist wire, situated in the ascending aorta. The device is then unsheathed slowly, with careful attention paid to the orientation of the fenestrations relative to the target branches (Fig. 80.14). In general, deployment of the device such that fenestrations and branches rest slightly proximal to target artery origins is advantageous for selection and stenting.

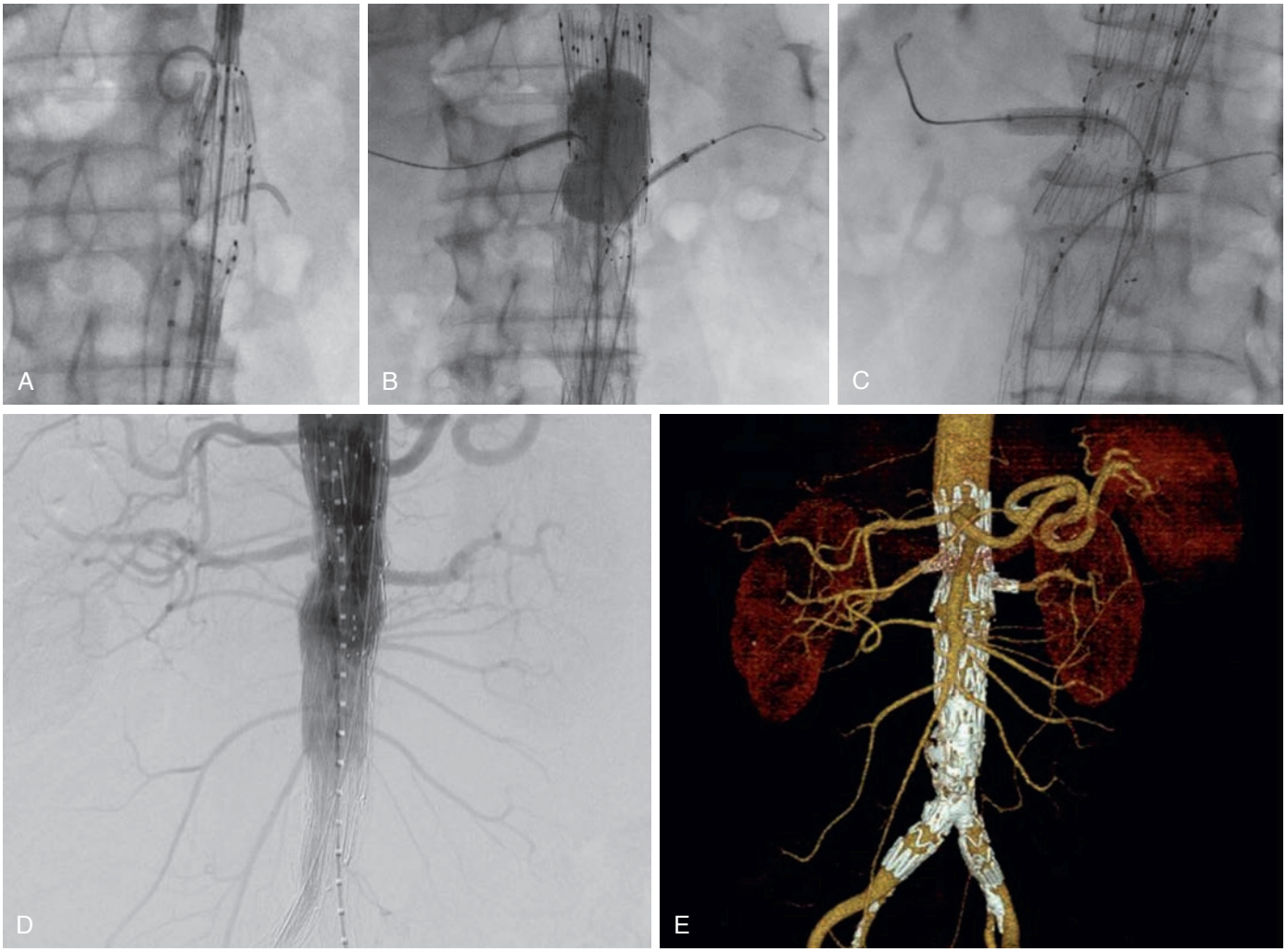

Figure 80.14 Deployment Sequence of the Proximal Portion of a Fenestrated Endograft. Alignment of fenestrated endograft according to location of renal artery origins marked by external selective catheters (A). After sheaths are placed through fenestrations into branch vessels for delivery of covered stents into renal arteries, the graft is molded in proximal seal zone with a noncompliant balloon (B). Deployment of covered stents through both renal fenestrations with appropriate fabric overlap and apposition at the fenestrations (C). Completion angiogram demonstrates aneurysm exclusion with no endoleak and excellent perfusion of superior mesenteric artery and bilateral renal arteries (D). Follow-up computed tomography angiography reveals patency of visceral vessels and aneurysm exclusion (E).

Small adjustments in orientation can be made during and after initial unsheathing, whereas the constraining, diameter-reducing ties remain in place.

Cannulation of target vessels occurs via the contralateral sheath. The distal end of the fenestrated main body device is selected and the wire/catheter is confirmed to be within the endograft. A 6- or 7-French guiding sheath is then delivered into proximity of the target fenestration. Wires and selective catheters are used to select the graft fenestrations followed by the corresponding target arteries; proper catheter selection is key because the catheter alone is typically used to select the fenestration. A selective angiogram confirms proper location. Using exchange catheters, moderately stiff wires such as a Rosen wire are placed into the branch vessels and 6- to 8-French sheaths are then advanced securely into the target vessels (see Fig. 80.14). The stent grafts are then delivered into place, just beyond the tip of the guiding sheath, but not deployed at this stage.

Trigger wires of the fenestrated device, including those which release diameter-constraining ties and the top cap, if present, are then removed. The top cap is then deployed to release the top bare stent (if one is present), and the entire delivery system is removed. Although wire access to the branch vessels is maintained, consideration should be given to whether or not molding of the proximal sealing stents with a compliant balloon is desired to promote apposition of the graft to the aorta (see Fig. 80.14). In contrast to infrarenal endovascular repair, this step may not be necessary, given the longer lengths of seal typically used. Placement of covered stents, usually 6 to 7 mm in diameter, into the target arteries is then performed. It is important to ensure that the image intensifier is oriented perpendicular to each fenestration so that the covered stent is deployed with 3 to 4 mm of fabric overlapping the fenestration into the aortic endograft. The proximal aspect of each covered stent is then flared, or "trumpeted," with a 10-mm balloon to maximize apposition to the endograft fabric (see Fig. 80.14). The distal bifurcated main body graft is then advanced with appropriate overlap into the proximal main body device and unsheathed to the level of the contralateral gate above the aortic bifurcation. Branch vessel access is removed before distal main body deployment. The contralateral iliac limb and then the ipsilateral iliac limb, if necessary, are extended as in standard EVAR.

Preloaded Fenestrations

The deployment sequence is simplified with preloaded fenestrated devices such as the Cook "p-Branch" device, as well as the majority of custom-made CMDs because the fenestration is already selected with the preloaded wire/catheter. With the p-Branch device, after unsheathing the proximal fenestrated portion of the device, the renal arteries are selected through a sheath that is advanced through the delivery system and out the fenestration over a preloaded wire. This obviates the step of needing to get a catheter from inside the endograft to track outside of the fenestration because the sheath is already delivered outside of the fenestration over the preloaded wire. Furthermore, because these target arteries are cannulated through the ipsilateral delivery system, a much smaller diameter sheath can be used in the contralateral femoral artery. After renal artery selection and exchange for a stiffer working wire, the remainder of the main body device is deployed and stenting of the renal arteries proceeds as described previously.

Preloaded Branches

Branched devices that incorporate the SMA and celiac artery into the repair can also be designed with preloaded wires in a diverse host of configurations. One possible configuration includes wires that travel through the delivery system ipsilateral handle, outside of the endograft distally, then enter the branch at its distal aspect, and run within the endograft proximally to exit the endograft at the proximal fabric edge. These wires are snared via upper extremity access (typically necessitating the use of a long 12-French sheath) to achieve through-and-through access from the femoral artery to the brachial or axillary artery. The device is unsheathed in the desired position. If fenestrations are used for the renal arteries, they are cannulated from the femoral arteries as described previously. The visceral segment device is then mated with a bifurcated device in the infrarenal aorta. Perfusion can be restored to the legs at this time with removal of the transfemoral sheaths and attention can be turned to completing the visceral artery branches from access above.

Repeated access of the 12-French brachial or axillary sheath permits delivery of long guiding sheaths over the preloaded wires and out the visceral branches of the graft. Via these sheaths, the visceral arteries are selected and stent grafts are used to bridge the branches to the target arteries (Fig. 80.15).

Aortic Arch Branched Devices

Given the variability of the devices currently in use, a comprehensive and detailed description of device deployment is not possible within the context of this chapter. In most cases, one or more supraaortic trunks is cannulated to access the fenestration(s) and/or branch(es) of the thoracic device (Fig. 80.16). In most cases, open surgical exposure is needed to allow the delivery of appropriate diameter stent grafts which mate with the aortic branch. In general, the arch device is advanced and deployed over a stiff wire that has been placed in the left ventricle. Most experienced practitioners use rapid venous pacing or temporary balloon occlusion of the IVC to decrease the cardiac output during deployment.[27,57] In many instances a preloaded wire is snared to allow through-and-through access from the femoral artery through the supraaortic branch. In addition to facilitating cannulation of the branch, the preloaded wire aids in alignment of the aortic stent-graft during deployment, which is critical to mitigate the challenges associated with the curvature of the arch.

OUTCOMES OF FENESTRATED AND BRANCHED REPAIR

Given the relative infancy of F/BEVAR, the majority of reported outcomes are from small- to moderate-sized single institution

Figure 80.15 Extension of stent grafts into visceral arteries during repair of thoracoabdominal aneurysm with four-vessel branched graft (A). Completion imaging shows flow into all visceral branches and no evidence of endoleak (B).

or multiinstitution series. Level I evidence regarding its efficacy does not exist, and there have been no prospective randomized controlled trials comparing F/BEVAR with open repair. To date, the majority of evidence regarding F/BEVAR has been reported in patients deemed unfit for open repair, making these cohorts not appropriate for comparison to historical cohorts of open repair. Furthermore, the majority of published reports include a heterogeneous mix of patients with varying aneurysm extents and complexities of repair. As experience increases, it will be advantageous to report outcomes according to aneurysm extent to facilitate more granular comparisons with alternative treatment strategies.

Juxtarenal, Pararenal, and Type IV Thoracoabdominal Aortic Aneurysm

Early Outcomes

Excellent technical success and low morbidity and mortality of complex endovascular repair for juxtarenal and pararenal AAA have been reported in prospective clinical trials, institutional reports, and clinical registry data.[58–68] Oderich et al. reported 100% technical success and 1.5% 30-day mortality in 67 patients repaired within the U.S. Zenith Fenestrated AAA Endovascular Graft Trial. There were no renal artery occlusions at 30 days, and no patients had a rise in serum creatinine to a level greater than 2 mg/dL within 30 days. In this cohort, 4.5% of patients developed mesenteric ischemia. Mean hospital length of stay was 3.3 ± 2.1 days.[19] Single institution series have reported slightly higher morbidity and mortality but still encouraging results. In a systematic review and meta-analysis of 14 studies with greater than 10 patients, published between 2005 and 2012, Rao et al. reported a pooled perioperative mortality of 4.1%.[48,59–62,65,66,69–76] Major complications, including cardiac events, pulmonary infections, ischemic colitis, and wound complications, occurred in 15.7% of patients after complex endovascular repair of juxtarenal AAAs. Postoperative renal insufficiency was reported in 11.4% and permanent hemodialysis reported in 1.9% in studies reporting these outcomes.[76]

Midterm Outcomes and Branch Durability

The limited existing data demonstrate promising midterm outcomes, although secondary interventions are not uncommon. Among 67 patients enrolled in the U.S. Zenith Fenestrated AAA Endovascular Graft Trial, there were no aneurysm ruptures or conversions to open repair at a mean follow-up of 37 ± 17 months. Five-year estimated survival was 91% ± 4%, and freedom from major adverse events was 79% ± 6%. In this group of patients, 15 (22%) required secondary interventions, primarily for renal artery stenosis/occlusion. Primary and secondary patency of targeted renal arteries was 81% ± 5% and 97% ± 2% with 91% ± 5% freedom from deterioration of renal function.[19] Among nine institutional series reporting results of complex endovascular repair for juxtarenal aneurysms, the pooled secondary graft related re-intervention rate during follow-up (2–120 months) was 12.7%.[76]

Data regarding long-term mortality remains limited. Rao et al. reported the pooled results from five series reporting long-term follow-up which demonstrated overall estimated Kaplan-Meier survival of 93%, 74%, and 55% at 1, 3, and 5 years, respectively.[48,60,62,69,75,76] Mastracci et al. reported an aortic-related mortality of only 2% at 8 years in patients undergoing fenestrated repair of juxtarenal and type IV TAAA. However, overall survival of these patients was only 20% at 8 years, presumably reflecting the high rate of significant comorbidities in this population.

Thoracoabdominal Aortic Aneurysms

Early Outcomes

Repair of thoracoabdominal aortic aneurysms with F/BEVAR has also been reported with encouraging results since the first significant series was reported by Greenberg and colleagues in 2008. Data from 11 series of F/BEVAR endografts, including 4406 patients, showed a combined perioperative mortality of 3.7% (95% CI 2.02–5.3, SE = 0.008) with individual series estimates ranging from 1.6% to 25%.[21,22,77–84] The risk of

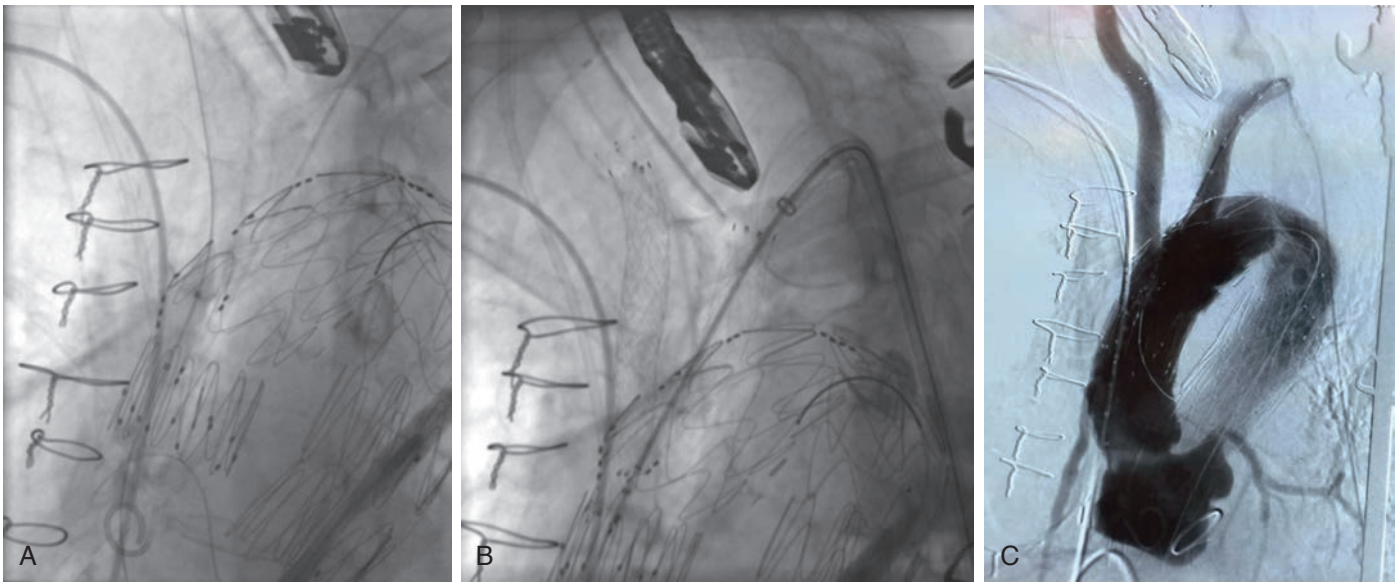

Figure 80.16 Branch Graft Repair of Aortic Arch Aneurysm. The graft is deployed to align internal branches for the supraaortic trunks with external marker wires (A). After cannulation of the branches, stent grafts are extended into supraaortic vessels (B). Completion imaging demonstrated filling of supraaortic branches and aneurysm exclusion (C).

perioperative renal dysfunction and spinal cord injury are 16% (95% CI 8.42–23.7, SE = 0.039) and 2.5% (95% CI 0.5–4.5, SE = 0.10), respectively. In 2016 Eagleton et al. reported on 354 high-risk patients with type II and type III TAAA repaired with F/BEVAR in a physician-sponsored IDEW trial.[41] These authors reported successful stenting in 96% of 1305 implanted fenestrations/branches, with type I or type III endoleak seen in 2.8% of patients on completion aortography. Perioperative mortality was 7% and 3.5% for type II and type III TAAA, respectively. Permanent spinal cord ischemia and renal failure requiring hemodialysis were reported in 4% and 2.8% of patients, respectively.

Midterm Outcomes and Branch Durability

Midterm data after fenestrated/branched endovascular repair of TAAAs are limited, and long-term data are lacking. The limited data suggest that rates of re-intervention are significant but that aneurysm-related mortality remains low.[85] Excellent long-term durability of branches in F/BEVAR has been reported in select centers. Mastracci et al. reported 30-day, 1-year, and 5-year freedom from branch intervention of 98% (95% CI, 96%–99%), 94% (95% CI, 92%–96%), and 84% (95% CI, 78%–90%) after F/BEVAR in 650 patients involving 1679 total branches at a mean follow-up of 3 ± 2.3 years. In this series, only three patients (0.5%) died from branch stent complications.[5] Eagleton et al. reported Kaplan-Meier estimated freedom from secondary intervention of 54% (95% CI, 0.47–0.61) at 36 months after F/BEVAR of type II and type III TAAAs. In 354 patients with a mean follow-up of 22 ± 19 months, secondary procedures were required in 129 (36.3%) patients, including 67 (18.9%) for an endoleak. Only 27 patients required re-intervention to maintain branch vessel patency and primary patency was greater than 92% for renal and mesenteric arteries at 36 months. Aneurysm-related death was rare, with a freedom from aneurysm-related death of 91% (95% CI, 0.80–0.95) at 36 months. However, freedom from all-cause mortality was significantly lower at 57% (95% CI, 0.50–0.63) at 36 months, reflecting the high rate of significant comorbidities in these patients.

Aortic Arch Aneurysms

Outcomes of total endovascular arch repair with branched endografts are limited to small series of selected patients repaired in centers of excellence. The majority of reports include only short-term follow-up, although limited results out to 1 year have been reported. F/BEVAR of arch aneurysms is technically feasible with acceptable short-term morbidity and mortality in patients deemed too high risk for open repair. Haulon et al. reported the world experience with aortic arch repair using an endograft with two inner branches for the supraaortic trunks in 38 patients.[86] The 30-day mortality rate was 13.2% (95% CI, 2.2–24.2), and technical success was obtained in 32 patients (84.2% [95% CI, 72.4–95.9]). Early cerebrovascular complications were diagnosed in six patients (15.8% [95% CI, 4.0–27.6]), including four transient ischemic attacks, one stroke, and one subarachnoid hemorrhage. Four patients required early secondary procedures (10.5% [95% CI, 0.7–20.3]). Over a median follow-up of 12 months (range, 6–12 months), no aneurysm-related deaths were detected. Spear et al. later reported on 27 patients who underwent branched repair with inclusion of the innominate artery and left common carotid artery in all patients.[87] Technical success was 100%, and 30-day mortality was 0%. Early neurologic events included two major strokes (7.4%), one minor stroke (3.7%), and two transient spinal cord ischemia events with full recovery (7.4%). Four patients (14.8%) underwent early (<30 day) re-interventions. Finally, in an analysis of fenestrated and branched endovascular repair of aortic arch

lesions in 29 patients using the Cook custom-made platform, both fenestrated and branched designs were technically feasible with promising results, although there was a trend towards improved results with branched grafts.[57] Reporting of midterm and long-term outcomes is necessary to demonstrate the efficacy and durability of fenestrated and branched arch repair.

SURVEILLANCE RECOMMENDATIONS AFTER FENESTRATED AND BRANCHED REPAIR

The need for secondary interventions to maximize durability of F/BEVAR emphasizes the importance of an aggressive surveillance protocol. Patients should undergo both CTA and duplex ultrasonography of incorporated target vessels prior to leaving the hospital after repair or at a 1-month follow-up visit. Most practitioners use CTA and duplex exam as complementary modalities. CT scans provide a baseline aneurysm sac diameter and also provide important information about the integrity of branched stents. Mastracci et al. have proposed a classification of endoleaks of branched devices to reflect the different modes of failure that have been observed on aggressive and detailed postoperative imaging (Fig. 80.17).[5] Duplex ultrasonography likewise provides important information about stenoses of branch vessels. Ultrasound criteria for renal stent stenoses have been proposed based on comparison with CTA and conventional angiography but have not been widely validated (Table 80.1).[88] Most practitioners repeat surveillance imaging at 6 and 12 months after repair and annually thereafter, although analysis of specific surveillance protocols has not been published in the literature.

The longer procedure times and the need for surveillance imaging as well as secondary interventions have increased concern about the total radiation burden involved in F/BEVAR.[89] Perini and colleagues have demonstrated in a single center study that contrast-enhanced ultrasound (CEUS) is as accurate as CTA in endoleak detection, aneurysm diameter measurement, and evaluation of target vessels after complex endovascular repair of juxtarenal aneurysms.[90] Currently, CEUS is not available in the United States due to lack of FDA-approved contrast agents. In patients who have not received implants composed of stainless steel, contrast-enhanced MRA and noncontrast MR can be used to evaluate for the presence of endoleaks and monitor aneurysm sac size.[91] To our knowledge, data are not yet available regarding the application of these techniques to F/BEVAR grafts after more extensive endovascular TAAA repair and future study is needed. The goal of surveillance is to allow timely and aggressive re-intervention to maintain stability of the repair and target artery patency.

TABLE 80.1 Revised Ultrasound Criteria for the Detection and Grading of Renal Artery Stent Stenosis and Occlusion in Patients With Fenestrated or Branched Endografts

Renal Stent Stenosis	Revised Ultrasound Criteria	Computed Tomography Criteria
<60%	PSV 57-280 cm/s	As visualized from centerline of flow and curved planar reconstructions
60%-90%	PSV > 280 cm/s and/or RAR > 4.5	As visualized from centerline of flow and curved planar reconstructions
Occlusion	No flow seen in renal artery stent *OR* PSV < 1.2 (or RAR cannot be determined because proximal renal artery not visualized)	Lack of contrast enhancement through the lumen of the stent on center line and curved planar reconstruction and marked difference in renal parenchymal opacification in three-dimensional reconstructions

PSV, Peak systolic velocity; *RAR,* renal artery/aorta ratio.

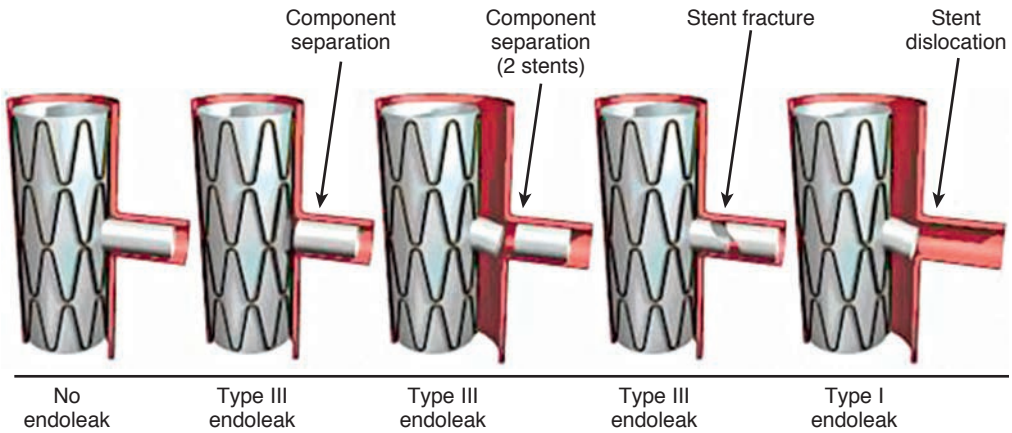

Figure 80.17 Newly proposed classification of endoleaks of branched devices *(top)*; type of endoleak shown across *bottom*. (From Mastracci TM, Greenberg RK, Eagleton MJ, Hernandez AV. Durability of branches in branched and fenestrated endografts. *J Vasc Surg.* 2013;57:926-933.)

PRACTICE AND REGULATORY ISSUES

The enthusiasm for F/BEVAR of juxtarenal and pararenal AAA, TAAA, and arch aneurysms has grown steadily over the past decade. The lack of commercially available devices to treat these aneurysms has led to the desire to modify currently FDA-approved commercially available abdominal and thoracic aortic endografts to accommodate aortic branch vessels and other anatomic variations. The Society for Vascular Surgery (SVS) issued an advisory statement on the clinical use of PMEGs, emphasizing that serial planned use of PMEGs requires both Institutional Review Board (IRB) approval as well as IDE approval from the FDA.[92] In the United States, approved access to F/BEVAR devices is limited to investigators and hospitals participating in either industry-sponsored or physician-sponsored IDE clinical trials. The SVS statement endorses the physician's discretion to recommend compassionate use of any treatment in an emergency if it is judged to be in the patient's best interests, including off-label use of PMEGs. Compassionate use requires IRB approval and may require FDA or manufacturer approval in some instances.

Despite the steadily growing experience with F/BEVAR endografts, it is necessary to recognize that the overwhelming majority of evidence to date has been provided by surgeons and institutions with interest and resources dedicated to these techniques. It appears that dedicated training in centers of excellence is of great value before undertaking fenestrated and branched repairs.[20] Furthermore, both cumulative case experience and adoption of technological advancements appear to be of critical importance to achieve acceptable results with increasingly complex repairs.[93,94]

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CHAPTER 81

Aortic Dissection: Epidemiology, Pathophysiology, Clinical Presentation, and Medical and Surgical Management

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Acute aortic dissection is the most common catastrophic event affecting the aorta, with an incidence exceeding that of ruptured abdominal aortic aneurysm. Without treatment, the majority of patients with aortic dissections will die within 3 months of presentation, and few survive the chronic phase more than 5 years due to aneurysmal degeneration and rupture of the outer wall of the false lumen.[1,2] Despite improvements in both medical and surgical therapeutic options, overall mortality associated with acute dissection remains significant. In a population-based epidemiologic study by Clouse et al., 38% of aortic dissections were diagnosed at autopsy.[3] This substantial mortality rate in undiagnosed patients underscores the importance of early

diagnosis and initiation of appropriate therapy. Indeed, Khan et al. predicted that the mortality of acute dissection (type A and B) left untreated will exceed 22.7% within 6 hours, 50% within 24 hours, and 68% within the first week.[4] Death due to an acute dissection of the ascending thoracic aorta is usually secondary to the central cardio-aortic complications of aortic rupture into the pericardium, acute aortic regurgitation, and coronary ostia compromise,[5,6] while patients with descending thoracic aortic dissections are more likely to die from end organ compromise due to obstruction of visceral or extremity vessels in the acute phase of the disease.[7,8]

Over the last decade, there has been a fundamental shift in the way we approach acute type B aortic dissections. Contributions from multicenter collaborations such as The International Registry of Acute Aortic Dissection (IRAD), the Investigation of Stent Grafts in Aortic Dissection (INSTEAD) trial, and large single institution series have cast doubt on the ability of medical therapy alone to effectively treat acute type B aortic dissections, and it is clear that there is a subset of uncomplicated patients who will benefit from early intervention with a thoracic endovascular aortic repair (TEVAR).[9-11]

In this chapter, we review the classification, pathologic anatomy, clinical presentation, diagnostic, and treatment modalities for acute aortic dissection, with emphasis on the role of the vascular/endovascular surgeon. While a thorough understanding of all components of acute dissection seems requisite for those who propose to treat aortic dissection, the technical principles of graft replacement of the ascending aorta, typically performed by cardiac surgeons, is not detailed. Since open graft replacement for treatment of descending aortic dissection is rarely indicated, it is anticipated that the vascular/endovascular surgeon will become the primary operator in the care of patients with acute dissection of the descending aorta and the complications of peripheral vascular compromise. Finally, treatment of the principal late complication of acute aortic dissection—the development of thoracoabdominal aneurysms—is considered in other chapters (see Chapters 77 and 78).

CLASSIFICATION

Aortic dissections are classified according to the anatomic location of the entry tear and the time between onset of symptoms and patient presentation.

Temporal

A dissection has traditionally been considered acute within the first 2 weeks after the initial onset of symptoms. While such designation appears arbitrary, it is based on autopsy studies showing that 74% of patients who die from aortic dissections do so in the first 14 days.[12] The period from 2 weeks to 90 days after initial presentation is now considered the subacute phase. During this period, the risk of death decreases but the dissection flap remains pliable such that this is the best time to consider performing elective TEVAR coverage of the proximal entry tear.[13] Finally, after 90 days, the dissection is considered chronic as the flap becomes stiff and fibrotic and the aorta begins to positively or negatively remodel. Indeed, such temporal classification combined with the anatomic location of the entry tear (discussed later) should be used to determine intervention.

Anatomic

Anatomically, aortic dissection is classified based on the location of the intimal tear and the extent of aorta involved in the dissection. There are two classification schemes used to describe aortic dissections. The original, proposed by DeBakey in 1965, delineates both the origin of the entry tear and the extent of the descending aortic dissection.[14] The scheme (Fig. 81.1) uses the following classification:

- Type I: Dissection originates in the ascending aorta, extends through the aortic arch, and continues into the descending aorta and/or abdominal aorta for a varying distance.
- Type II: Dissection originates in and is confined to the ascending aorta.
- Type IIIa: Dissection originates in the descending aorta and is limited to same.
- Type IIIb: Dissection involves descending and variable extents of the abdominal aorta.

The Stanford Classification was described by Daily in 1970[15] and simplified the anatomic classification according to the origin of the entry tear alone. A Stanford type A dissection originates in the ascending aorta, and therefore encompasses DeBakey type I and II dissections, while a Stanford type B dissection originates in the descending aorta distal to the origin of the left subclavian artery (DeBakey type IIIa, IIIb, Fig. 81.1).

Because the origin of the entry tear is the key predictor of early outcomes, most patients are now stratified into Stanford type A or B at the time of presentation in order to direct initial therapy. However, neither the Stanford nor the Debakey classification systems address patients whose entry tear originates in the aortic arch between the innominate and left subclavian arteries. The classic Stanford type A dissection is confined to the ascending thoracic aorta, and most cardiac surgeons consider any dissection that originates distal to the innominate artery to be Stanford type B. This is driven by the fact that prompt graft replacement of the ascending aorta is the appropriate treatment for most type A dissections because of the high risk of lethal cardio-aortic complications (principally aortic rupture or myocardial ischemia from extension into the coronary arteries). Alternatively, the classic Stanford type B dissection is confined to the descending thoracic aorta, and vascular surgeons consider any dissection that originates proximal to the left subclavian artery to be type A and the purview of cardiac surgery, because open intervention would require circulatory arrest and placing a stent graft proximal to the left common carotid artery requires surgical debranching or access to investigational branched and fenestrated devices.

EPIDEMIOLOGY

Recent population-based studies have estimated the incidence of acute aortic dissection to range from 2.9 to 3.5 per 100,000 person-years.[3,16] Factors that predispose one to develop aortic

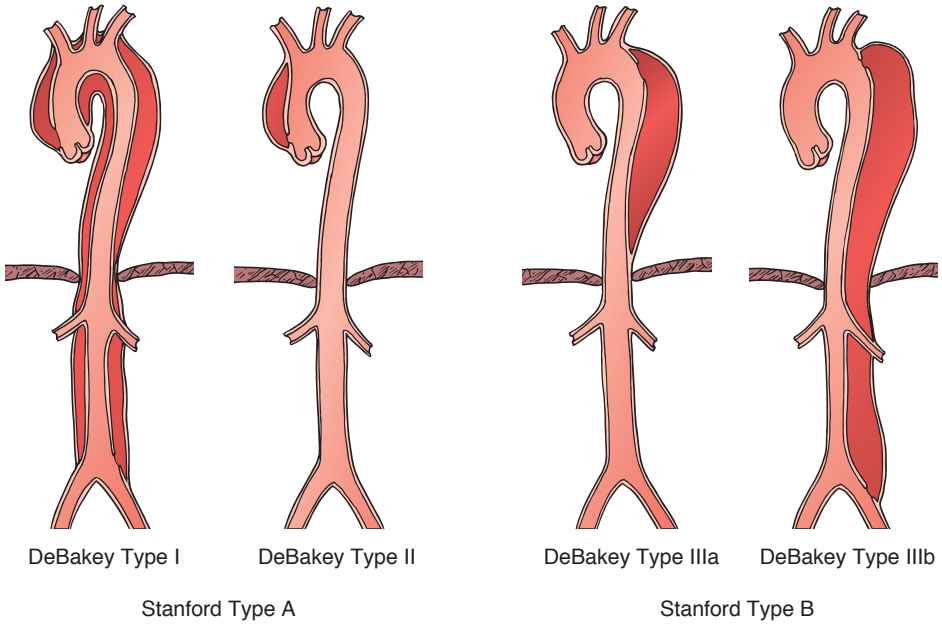


Figure 81.1 Acute aortic dissection can be classified by the original DeBakey system based on location of proximal tear and distal extent of the dissection flap, or the Stanford system that uses location of proximal tear alone.

TABLE 81.1 Demographic and Clinical Features of Combined Mgh and IRAD Experience With Acute Aortic Dissection

Variable	MGH (%)[7]	IRAD (%)[37]	Total (%)
Patients	512	1078	1590
Age (mean)	62 years	62.4 years	
Male	347 (67.8%)	732 (67.9%)	1079 (67.9%)
Type A	278 (54%)	674 (62.6%)	952 (60%)
Hypertension	361 (70.5%)	755 (71.8)	1116 (70.2%)
VC/pulse deficit	159 (31%)	259 (27.7%)	418 (26.3%)

IRAD, International Registry of Acute Aortic Dissection; *VC,* vascular complication.

dissection include age, hypertension, and structural abnormalities of the aortic wall.[4,17] Men are more frequently affected, with a male/female ratio of 4:1 reported by IRAD.[18] In our cumulative experience, type A dissections account for 60% of cases, and this is consistent with the IRAD data, wherein 62.5% of 1417 patients presented with a type A dissection.[11] The incidence of type A dissection peaks between 50 and 60 years, while type B dissections occur more frequently between 60 and 70 years of age.[17] Hypertension is prevalent and was present in 70% of patients in the IRAD database (Table 81.1).[18]

Risk Factors for Dissection

Cardiovascular Conditions

Acute aortic dissections tend to demonstrate chronobiologic patterns of occurrence.[19] The onset of dissection occurs most frequently in the morning hours between 6 a.m. and 12 p.m., and more often in the winter (28%) than the summer (20%), independent of endogenous climate.[19,20] Aortic wall structural abnormalities and the presence of a bicuspid aortic valve with or without its accompanying aortic root dilation are well-established risk factors for ascending aortic dissections. Indeed, the presence of a bicuspid aortic valve has been documented in 7% to 14% of all aortic dissections.[17,21] Other aortic diseases, such as coarctation of the aorta, annuloaortic ectasia, chromosomal abnormalities (Turner syndrome and Noonan syndrome), aortic arch hypoplasia, and hereditary conditions (Marfan syndrome and Ehlers-Danlos syndrome), are also risk factors for the development of acute aortic dissection.[22] Marfan syndrome accounts for 50% of cases of acute aortic dissection in patients less than 40 years of age.[18]

Pregnancy

Pregnancy is associated with a fourfold increased risk of aortic dissection and rupture when compared with nonpregnant women of child bearing age.[23] However, it still remains rare, as the incidence of aortic complications is 5.5 per million pregnant women.[23] Preeclampsia with resultant hypertension is the most common etiology of peripartum aortic dissection, but pregnant women with Marfan syndrome are also at high risk, and the presence of a dilated aortic root (>4 cm) is the best predictor of dissection in the pregnant patient with Marfan syndrome.[24] The most common site of aortic dissection in young (<40 years) patients is the ascending aorta involving the sinuses of Valsalva or the sinotubular junction, while type A dissections in older patients are more likely to originate higher in the ascending aorta.[18]

Cocaine Abuse

Cocaine ingestion, a rare cause of acute aortic dissection in otherwise healthy individuals, has an incidence as high as 37% in an urban setting, but was present in 1.7% of the IRAD population.[18,25-27] The typical patient with a cocaine induced dissection is a young (average age 47 years), male (86%) smoker (92%) with a history of hypertension (82%) and no particular trend toward dissection type (type A 52% vs. type B 48%).[25-27]

One possible mechanism is related to catecholamine release, which causes a triad of profound hypertension, vasoconstriction, and increased cardiac output. This creates a dramatic, acute increase in ventricular contraction (shearing) force (dP/dt) on the aortic wall.[25,28]

PATHOLOGIC ANATOMY OF ACUTE AORTIC DISSECTION

Intimal Tear

The process of aortic dissection is dynamic and can occur anywhere along the course of the aorta, resulting in a wide spectrum of clinical manifestations. The pathognomonic lesion is one of an intimal tear followed by blood surging either antegrade (typically) or retrograde (depending on the hemodynamic gradient between the true and false lumens), and cleaving the intima and media layers of the aortic wall longitudinally for a variable distance.[4,29] The typical tear is transverse, not circumferential, and the intimomedial layer can be cleaved both longitudinally and circumferentially.[4] The adventitia-bound blood-filled space created between the dissected layers of the aortic wall becomes the false lumen. Fenestrations (connections between the true and false lumens) occur within the intimal flap downstream, usually at branch vessel ostia, which are cleaved by the dissection process: these serve as sites of reentry of blood flow into the true lumen (fenestrations), thus maintaining false lumen patency. The presence of an "intimal flap," representing the intimomedial septum between the true and false lumen, is the most characteristic pathology in acute aortic dissection. The origin of the intimal flap/tear is in the ascending aorta in 65%, the descending aorta in 25%, and in the arch and abdominal aorta in 10% of patients.[17] In the descending aorta, the intimal tear typically originates within a few centimeters of the left subclavian artery, because this segment of the aorta is subject to the greatest dP/dt pressure fluctuations.[12,30,31] In the usual pattern of a Stanford type B dissection, the cleavage plane will progress with the distal false lumen on the left posterolateral aspect of the aorta (80% of patients); the celiac, SMA, and right renal arteries typically emanate from the true lumen; and the left renal artery arises from the false lumen.[12] It is to be emphasized, however, that variations in this pattern are frequently encountered.

Cystic Medial Necrosis

One pathologic process that is associated with an increased risk of aortic dissection is medial degeneration of the aortic wall (cystic medial necrosis) that diminishes the structural integrity of the aortic layers.[31,32] The central lesion appears to be deterioration of medial collagen and elastin fibers through elastolysis; this is considered to be a factor in most cases of aortic dissection.[33] In particular, classic cystic medial necrosis appears to be an essential feature of several hereditary conditions, such as Ehlers-Danlos syndrome and Marfan disease.[22] Yet, specific connective tissue diseases account for only 10% to 15% of all acute aortic dissections.[17] Even in "normals," in which dissections occur without any antecedent diagnosis of a specific underlying contributing disease, the degree of medial degeneration still tends to be greater than expected as part of normal aging. The exact cause of this medial degeneration remains unclear, but advanced age and hypertension appear to be the most important factors.[19,33,34]

PATHOGENESIS OF MALPERFUSION SYNDROMES

Malperfusion syndrome occurs when there is end organ ischemia secondary to aortic branch compromise from the dissecting process. This can involve one or more vascular beds simultaneously, with early symptoms often subtle and of varying severity over the hours and days after initial symptom onset. Consistent over several series, aortic branch compromise is present in up to 31% of patients with acute aortic dissection,[8,35-37] with progression to the malperfusion syndrome correlating with early mortality.[7,8,37] Any aortic branch can be affected, and as intuitively suspected, the morbid clinical events will vary as a function of the vascular territory involved. Mesenteric involvement is associated with intestinal infarction, whereas subclavian and/or lower extremity occlusive events are often well-tolerated.

Mechanism

Identifying the mechanisms of branch compromise is a critical step in formulating effective treatment plans. The anatomic and physiologic variables underpinning any compromised vascular bed include (1) the percentage of aortic circumference dissected, (2) the presence of a distal re-entrant focus in the false lumen or true lumen outflow, and (3) the topography of branch ostia to the true versus false lumen.[5] In the minutes after an aortic dissection is initiated, the true lumen (representing the remnant of the original aortic lumen) collapses to a variable degree, and the false lumen expands.[38] The adventitia-bound outer wall of the false lumen must expand to a larger diameter in order to accommodate the same wall tension at a given blood pressure, as governed by the law of LaPlace. In contrast, the true lumen, which contains the majority of the elastic components of the aortic wall, undergoes radial elastic collapse.[38] Therefore the degree to which the true lumen recoils and the false lumen expands (i.e., their respective cross-sectional area) is dependent on the percentage of the total aortic circumference involved with the dissection. In the presence of a deep proximal tear and the absence of distal fenestrations, the mean false lumen pressure increases leading to compression of the true lumen (Fig. 81.2).[39] A compressed true lumen will lead to impaired perfusion of distal structures and should increase the index of suspicion for visceral and renal ischemia.

Two mechanisms for aortic branch vessel compromise have been identified, and each has specific treatment implications in the management of malperfusion syndromes, as originally described by Williams et al.[38] In *dynamic obstruction*, the compressed true lumen is unable to provide adequate volume

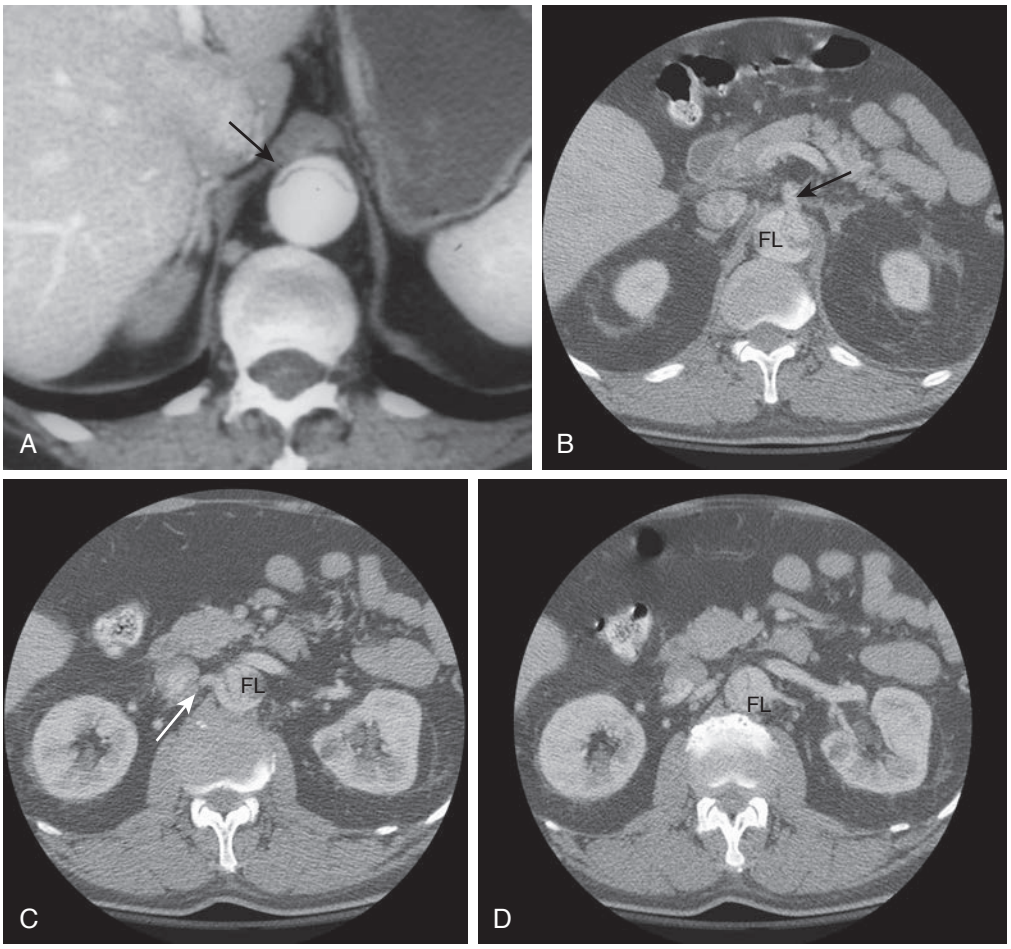


Figure 81.2 Computed Tomography Angiogram Findings of Acute Aortic Dissection. **(A)** Axial image of aortic dissection with compressed true lumen *(black arrow)*. **(B)** Axial image of aortic dissection with SMA arising from the true lumen *(black arrow)*. **(C)** Axial image of aortic dissection with right renal artery *(red arrow)* arising from the compressed true lumen. **(D)** Axial image of aortic dissection with left renal artery originating from the false lumen *(FL)*.

flow, or the dissection flap may prolapse into the vessel ostium, which remains anatomically intact (Fig. 81.3). This is the more common mechanism of branch compromise and is responsible at least in part for some 80% of malperfusion syndromes.[40] The severity of the true lumen collapse and the degree of aortic-level ostial vessel occlusion is determined by the circumference of the dissected aorta, cardiac output, blood pressure, heart rate, and the peripheral resistance of the outflow vessel.[41] Pulse deficits based on dynamic obstruction may wax and wane over time, due to the variability of the aforementioned factors.[5,42] In *static obstruction*, malperfusion is caused by the dissecting process extending into the branch vessel proper, narrowing it to a variable degree.[40] The false lumen is highly thrombogenic as a result of the exposed adventitial and medial layers, and thrombus formation may occur in the blind end of the dissection.[43] If this enters and constricts the ostia of a branch vessel, organ injury can occur by thrombosis or hypoperfusion of the involved vessel. This obstruction is unlikely to resolve with restoration of aortic true lumen flow alone, and some manipulation of the vessel itself (e.g., stent or bypass graft) will typically be required (see Fig. 81.3).

CLINICAL PRESENTATION

Pain

The most common presenting symptom of acute aortic dissection is pain (located in the back, abdomen, or chest), reported in more than 93% of patients, with 85% specifying an abrupt onset.[17,44] While the pain is typically described as anterior in location in type A dissections, for type B dissections, pain is more often experienced in the back (78% vs. 64%, respectively).[17,21] Pain has been localized to the abdomen in up to 21% of patients with type A and 43% of patients with type B dissections.[17] In such patients, a high index of suspicion for mesenteric vascular compromise is warranted. Typically the pain is severe, causing the patient to seek medical attention within minutes to hours of onset, and has been described as "the worst ever" by nearly 90% of patients.[17] The control of pain with antihypertensive therapy is a mainstay of the early management of acute aortic dissection, and the recurrence of pain implies failure of medical therapy, warranting repeat imaging to direct therapy. However, in the absence of clinical or radiographic

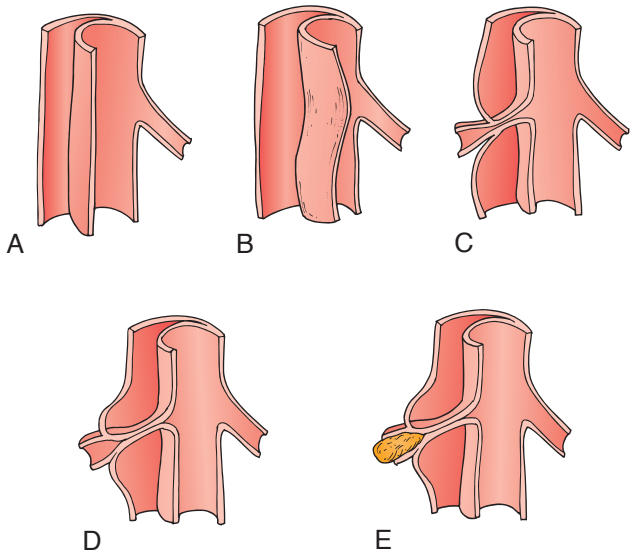


Figure 81.3 Mechanisms of Aortic Branch Obstruction in Acute Dissection. (**A** and **B**) In dynamic obstruction, the septum may prolapse into the vessel ostium during the cardiac cycle, and the compressed true lumen flow is inadequate to perfuse branch vessel ostia which remain anatomically intact. (**C-E**) Near complete circumferential dissection with static obstruction—the cleavage plane of the dissection extends into the ostium and compromises inflow. Thrombosis beyond the compromised ostia may further worsen perfusion.

signs of patho-anatomic changes, medical therapy remains an appropriate management of most patients with early recurrent pain after type B dissection.[45]

Hypertension

On initial physical examination, hypertension is present in 70% of type B dissections, but only in 25% to 35% of type A dissections. The presence of hypotension complicating a type B dissection is rare (<5% of patients), but may be present in 25% of dissections that involve the ascending aorta, potentially as a result of aortic valve disruption or cardiac tamponade.[17] The malperfusion of brachiocephalic vessels by the dissection may falsely depress brachial cuff pressures.[46] Hypertension that is refractory to medical management is common in type B dissections, occurring in 64% patients.[47]

Syncope/Neurologic Symptoms

Syncope may complicate the presentation of acute aortic dissection in 5% to 10% of patients, and its presence often indicates the development of cardiac tamponade or involvement of the brachiocephalic vessels.[48] Patients presenting with syncope have a higher rate of severe complications (tamponade, stroke, death), but in half of the patients, this is not the cause of their loss of consciousness. The mechanisms underlying this fact may be related to other pathophysiologic perturbations, such as vasovagal events or direct stretching of baroreceptors in the aortic wall.[49,50] Spinal cord ischemia from the interruption of intercostal vessels occurs in 2% to 10% of type B dissection.[51] Direct compression of peripheral nerves is rare but can present as paresthesias (lumbar plexopathy), hoarseness (recurrent laryngeal nerve), or Horner syndrome (compression of sympathetic ganglion).[52-54]

Peripheral Vascular Complications

Peripheral vascular complications are common and occur in 30% to 50% patients in whom the aortic arch and/or the thoracoabdominal aorta is involved.[8,35,36] Cambria et al. detailed the distribution of branch vessel compromise and found that brachiocephalic trunk was involved in 14% of patients, the common carotid arteries in 21%, left subclavian in 14%, and ileofemoral arteries in 35%.[8] Patients presenting with pulse deficits more often have neurologic deficits, coma, and hypotension, and a deficit of the carotid artery pulse strongly correlates with fatal stroke.[7] In this population, mortality is clearly linked to the number of pulse deficits at the time of presentation. Indeed, within the first 24 hours, 9.4% of patients with no deficits died, 15.8% of patients with one or two deficits died, and 35.3% of patients with three or more deficits died.[55]

DIAGNOSTIC EVALUATION

In the United States, 4.6 million patients present to the emergency department with acute chest pain annually.[56] The majority of these patients do not have an aortic dissection, and it would be inefficient, unrealistic, and costly to obtain axial imaging on all patients with acute chest pain, as this would yield an 85% false positive rate.[57] However, aortic dissection often affects younger patients (in their 50s) and thus is not readily apparent. Indeed, physicians correctly suspect the entity in only 15% to 43% of presentations, as aortic dissection is often identified as an incidental finding during the evaluation of another pathologic process.[16,58] Historically, retrograde aortography was considered the reference standard in the evaluation of acute aortic dissection. However, the improvement of other techniques, such as contrast computed tomographic angiography (CTA), transesophageal echocardiography (TEE), and magnetic resonance imaging (MRI), has shifted the role of aortography from diagnostic to adjunctive during endovascular management. While the choice of diagnostic modality may be predicated on local availability/practice patterns, certain essentials exist. First, the diagnosis of acute aortic dissection must be confirmed or refuted. Second, the extent of the dissection, the potential involvement of branch vessels, and the presence of immediate life-threatening complications such as tamponade should be provided.

Imaging

Plain Radiography

Plain chest radiography is often the first imaging study obtained during the workup of acute chest pain, but the findings of aortic dissection on chest radiography are nonspecific and never diagnostic. These include widening of the cardiac or aortic silhouette, displacement of aortic calcifications, and effusions.[17,21] Widening of the mediastinum is the most common finding, while displaced aortic calcifications are usually seen with type A dissections.[17] Pleural effusions occur most frequently in patients

with type B dissections and are usually secondary to an inflammatory reaction of the mediastinal pleura.[59] Because these findings are not diagnostic, additional imaging is required.

Computed Tomographic Angiography

CT scanning is readily available, noninvasive, and has a reported sensitivity of 83% to 95% and specificity of 87% to 100% for the diagnosis of acute aortic dissection.[60-62] The chief limitation of imaging is the ascending aorta, where the sensitivity may drop to less than 80%, but this is readily overcome by the addition of TEE.[46] A helical CT dissection protocol will give excellent aortic imaging of the true and false lumens, approximate entry tear sites, and aid in planning intervention. In most cases, the true lumen may be localized by its continuity with an undissected segment of the aorta, and in the descending thoracic aorta, the false lumen is larger than the true lumen in more than 90% of cases.[63]

The orientation and mobility of the dissection flap can be assessed with CTA and if the dissection flap is concave toward the false lumen, a true lumen pressure deficit can be predicted with a 91% sensitivity and 72% specificity.[43] The dissection flap is more often noted to be in a curved orientation (63% of cases) in the acute phase the flap was flat in 75% of cases of chronic dissection.[63] As displayed in Fig. 81.2, a slitlike compressed true lumen is perhaps the key radiographic finding, which should substantially raise the index of suspicion for renal, visceral, or lower extremity malperfusion syndrome.

Echocardiography

The sensitivity and specificity of transthoracic echocardiography (TTE) range from 35% to 80% and 40% to 95%, respectively.[64,65] The chief limitation of TTE imaging is the anatomic blind spot in the distal ascending aorta and arch, secondary to the air-filled trachea and left main stem bronchus, and inability to document dissection extension beyond the diaphragm.[66,67] TEE overcomes the limitations of surface echocardiography and has a sensitivity that is as high as 98%, with a specificity that ranges from 63% to 96%.[68-70] Advantages of TEE include wide availability, ease of use, and bedside capability. Indeed, TEE possesses the ability to detect entry tear sites, false lumen flow/thrombus, involvement of the arch or coronary arteries, degrees of aortic valvular regurgitation, and pericardial effusions. In addition, TEE can be particularly useful in delineating dissection and relevant surgical pathology in the ascending aorta and, therefore, is chiefly applied in this territory.[71] Moreover, in the unstable patient with a suspected acute dissection in the ascending aorta, TEE may be performed in the operating room to expedite diagnosis and definitive therapy.

Magnetic Resonance Imaging

MRI has an overall sensitivity and specificity for diagnosis of aortic dissection in the range of 95% to 100%.[72-74] MRI can detect the site of the entry tear, the extent of the dissection, potential branch vessel involvement, and differential true versus false lumen flow. The overall sensitivity and specificity for diagnosis of branch vessel involvement is 90% and 96%, respectively.[75] The chief limitations of MRI include lack of immediate availability, long examination times, and lack of monitoring for critically ill patients.

TREATMENT OF TYPE B DISSECTION

Optimal treatment of acute type B dissection included timely diagnosis, prompt control of blood pressure, and early recognition of the malperfusion syndrome. In type B dissections, the catastrophic complication of rupture is uncommon, except in those patients who present with advanced false lumen dilation or the equivalent of aneurysm formation at the aortic entry site.[5] A complication-specific approach involving open surgical and endovascular options to treat malperfusion syndromes remains the standard of care and is reviewed as follows. Open graft replacement of the aortic entry tear has been shown to be inferior to medical therapy in patients with uncomplicated type B dissections and is not recommended.[44] However, recent natural history data of medically managed uncomplicated patients suggests that there is a subset of patients who are likely to benefit from elective TEVAR in the subacute period after symptom onset.

Medical Treatment

Medical management in an intensive care unit is the initial therapy for virtually all patients with the tentative diagnosis of aortic dissection. The goal is to reduce the hemodynamic forces that have initiated and propagated the intimal tear and cleavage of the aortic wall. This involves reducing the systolic blood pressure and dP/dT, which should in turn stabilize the extent of the dissection, reduce intimal flap mobility, and relieve the forces predisposing the dissected aorta to rupture or compromise of branch vessels.[76] Intravenous antihypertensive therapy should be started in all patients in whom acute aortic dissection is suspected, with the exception of those with hypotension.[76] For those patients with hypotension in the setting of acute dissection, an expeditious evaluation for tamponade is warranted, but percutaneous pericardiocentesis as a temporizing measure is not advised, as it often accelerates bleeding or shock.[77] In contemporary practice, a combination of a beta-blocker and vasodilator is standard medical therapy. The beta-blocker should be initiated before the direct vasodilator (i.e., sodium nitroprusside); otherwise, reflex sympathetic stimulation from direct vasodilation will cause catecholamine release, and resultant increases in dP/dT, contrary to the desired effect.

Patients should be placed in the intensive care unit during the acute period with continuous blood pressure monitoring via an intraarterial catheter, telemetry monitoring of cardiac rhythms, and hemodynamic surveillance. Once the patient's blood pressure has been controlled to a systolic of 100 to 120 mm Hg (or mean of 60 to 70 mm Hg) and their pain has resolved, they can be transitioned to oral antihypertensives. These patients need to be closely monitored, even after the blood pressure is under control. Durham et al. reported the natural history of patients with uncomplicated type B aortic dissections who were initially medically managed and found that 12% became complicated within the acute follow-up period (<15 days), with

an early mortality of 5%.[9] It is important that patients who are managed medically are followed with serial surveillance imaging with contrast CTA. The first should be obtained prior to discharge from the initial hospitalization, and then at 6-month intervals. Once a dissection has been stable for two scans, follow-up imaging can be obtained on a yearly basis.[78]

The 30-day mortality with medical management of uncomplicated type B dissection is 10% and compares favorably with the near 30% mortality associated with open repair in the acute setting.[79] In addition, multiple studies have shown a 1-year survival of 72% to 90% with medical therapy of type B dissection alone.[80-83] However, the late consequence of medical therapy is aneurysmal degeneration of the false lumen outer wall that can occur in up to 40% of patients despite medical therapy.[14] The natural history study of Durham et al. included 298 patients with medically managed type B dissections and found that 58% of patients failed medical therapy either through the need for aortic intervention (29%) or death (38%) over an average follow-up of 4.3 years.[9] The indication for intervention was aneurysmal degeneration in 66% of the patients and the average time to aneurysm repair was 2.3 years from the initial presentation.[9] Indeed, with long-term serial CT imaging, only 51% of the patients are free from aortic growth at 5 years.[84]

Open Surgical Repair of Descending Aortic Dissection

Threatened or actual rupture at the aortic intimal tear in the proximal descending aorta with no identifiable proximal seal zone remains, in our view, the only indication for acute open graft replacement in distal dissection. Unless an extensive aneurysm is present, resection should be confined to the proximal descending aorta, as mortality and spinal cord ischemia risk increase dramatically with extensive aortic replacement in the setting of an acute dissection.[85] The mortality rate for the open repair of acute type B aortic dissection has ranged from 6% to 69% in several large series.[86-90] The IRAD review of 476 patients with type B dissection showed that 82 (17.2%) were treated surgically with descending aortic replacement (70%), partial arch replacement (21%) or total arch replacement (8%) with an in-hospital mortality of 29%.[89] In addition, a recent series of patients undergoing graft replacement of the descending aorta for acute type B dissections reported spinal cord ischemic complications in 32% of patients.[85]

Endovascular Treatment of Aortic Dissection

Goals of Treatment

Stent-graft coverage of the aortic entry tear provides the means to accomplish the intuitively logical short- and long-term goals of sealing the proximal entry tear and inducing false lumen thrombosis, which has the potential to reduce the risk of late aneurysm degeneration.[91] This approach was initially used only in patients with complicated type B dissections to correct malperfusion syndrome and treat impending rupture, but the promotion of aortic remodeling has promise for all patients with type B dissections.[92-94] When indicated, the goals of TEVAR for acute type B dissection include coverage of the proximal entry tear, expansion of the true lumen with restoration of flow to the visceral vessels, and obliteration of false lumen flow with subsequent complete thrombosis (Fig. 81.4). When these components of therapy are successfully achieved, aortic remodeling should occur with subsequent prevention of future aneurysmal degeneration of the outer wall of the false lumen.

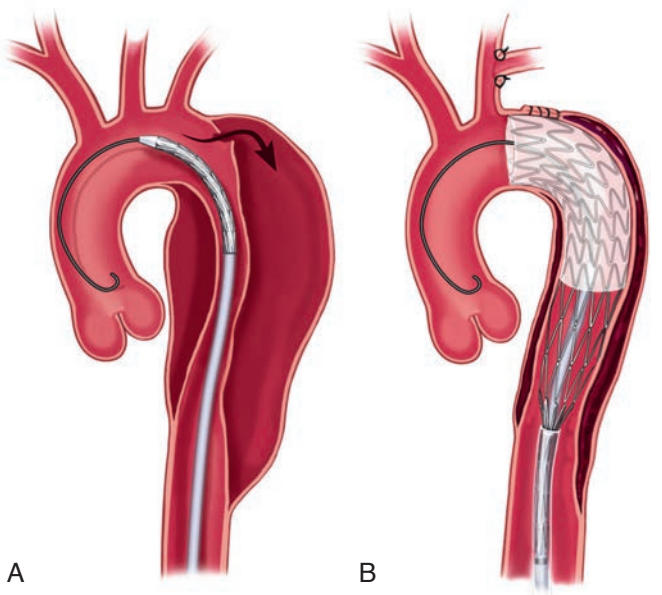


Figure 81.4 Stent graft deployment to cover the proximal entry tear with the goal of inducing false lumen thrombosis and true lumen reexpansion. The latter should also alleviate "downstream" branch compromise caused by dynamic obstruction mechanisms. False lumen thrombosis in the thoracic aorta should, in theory, minimize subsequent aneurysmal expansion of the outer wall of the false lumen. **(A)** Type B aortic dissection with undeployed stent graft advanced to the level of the left common carotid artery. **(B)** Stent graft deployed across the proximal entry tear to induce false lumen thrombosis.

False Lumen Thrombosis

In the natural history of medically managed type B dissections, continued patency of the false lumen is an independent risk factor for aneurysmal degeneration and dissection related adverse events.[84,95] During the first 4 to 7 years after acute aortic dissection managed medically, aneurysmal degeneration of the false lumen in the thoracic aorta may develop in 14% to 40% of patients treated with medical therapy alone.[17,83,96] Indeed, Sueyoshi et al. showed that a patent false lumen will enlarge 3.3 mm/year even in stable, uncomplicated cases,[97] and Tsai et al. showed that partial thrombosis of the false lumen is an independent predictor of postdischarge mortality (patent 13.7%, partial thrombosis 31.6%, complete thrombosis 22.6%).[98] Thus the concept of inducing false lumen thrombosis by sealing the aortic tear with an aortic endograft has the potential to both reduce early and late complications of type B dissection (Fig. 81.5).

Technical Details

There are particular technical points of stent-graft repair of aortic dissection that deserve emphasis (see Chapters 78 and 79). First,

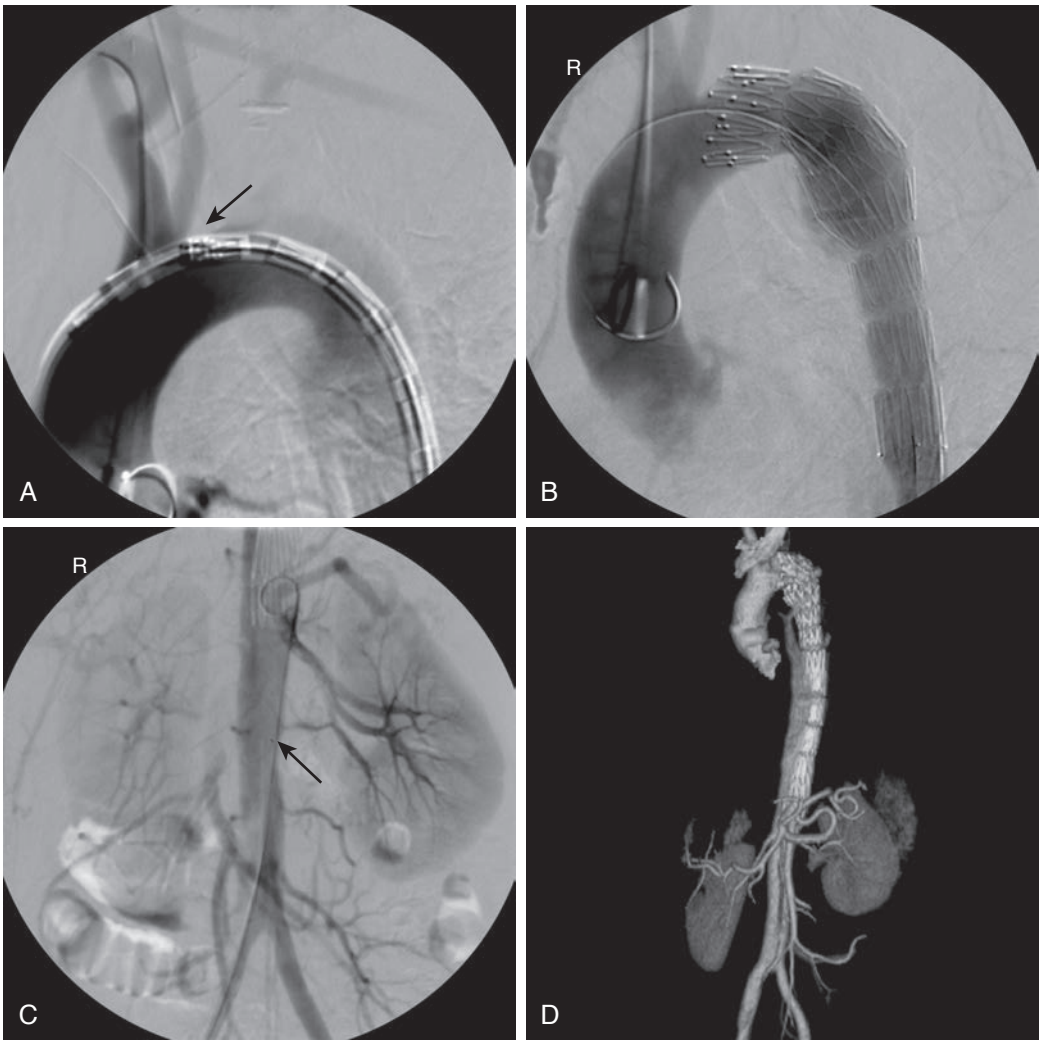


Figure 81.5 Endovascular Repair of Acute Type B Aortic Dissection. (A) Thoracic aortography showing stent graft in descending thoracic aorta. The proximal portion of the graft *(black arrow)* is placed at the level of the left common carotid artery, covering the left subclavian artery in order to obtain proximal seal in normal aorta. **(B)** Thoracic aortography showing stent graft deployed with obliteration of the proximal false lumen. **(C)** Abdominal aortography after proximal stent grafting showing true lumen expansion *(black arrow)* with persistent false lumen flow. **(D)** Three-dimensional aortic reconstruction after endovascular repair showing obliteration of false lumen in the thoracic aorta, persistent flow in the abdominal aorta, expansion of the true lumen, and perfusion to all visceral vessels.

the placement of uncovered stents over the entry tear within the proximal true aortic lumen is ill-advised, and the entry tear should be sealed by a stent graft.[99] If a patient is to be considered a candidate for stent-graft treatment, the location of the entry tear and proper recognition of the proximal zone of fixation is fundamental to the procedural success. Once selected, stent-graft repair of acute aortic dissection should be performed in an operating room with adequate fluoroscopic imaging. True lumen access should be obtained from either a brachial or a femoral approach; typically, since the tear in type B dissection is distal to the left subclavian artery, rapid true lumen access is easily obtained through a right transbrachial approach. Proper true lumen position should then be confirmed using intravascular ultrasound (IVUS), which is also useful for confirming the relationship of branch vessels to the dissection flap (Fig. 81.6). It is ideal to have at least 2 cm of normal aorta proximal to the entry tear for the proximal seal zone in order to prevent retrograde dissection into the ascending aorta. This usually requires coverage of the origin of the left subclavian artery and sealing to the level of the left common carotid artery. We generally limit the length of aorta covered to decrease the risk of paraplegia and use IVUS to assess true lumen expansion and flap mobility after each intervention is performed. Finally, we rarely, if ever, balloon the proximal seal zone in patients with acute dissections.

Outcomes

Short-term results with endovascular therapy for symptomatic acute type B dissection have been promising. Fattori et al. reported on 1129 patients with type B dissections from the IRAD database, of whom 24% were treated with TEVAR. There was 10% in-hospital mortality after TEVAR, which was similar to medical therapy in patients with uncomplicated dissections.[100] There have

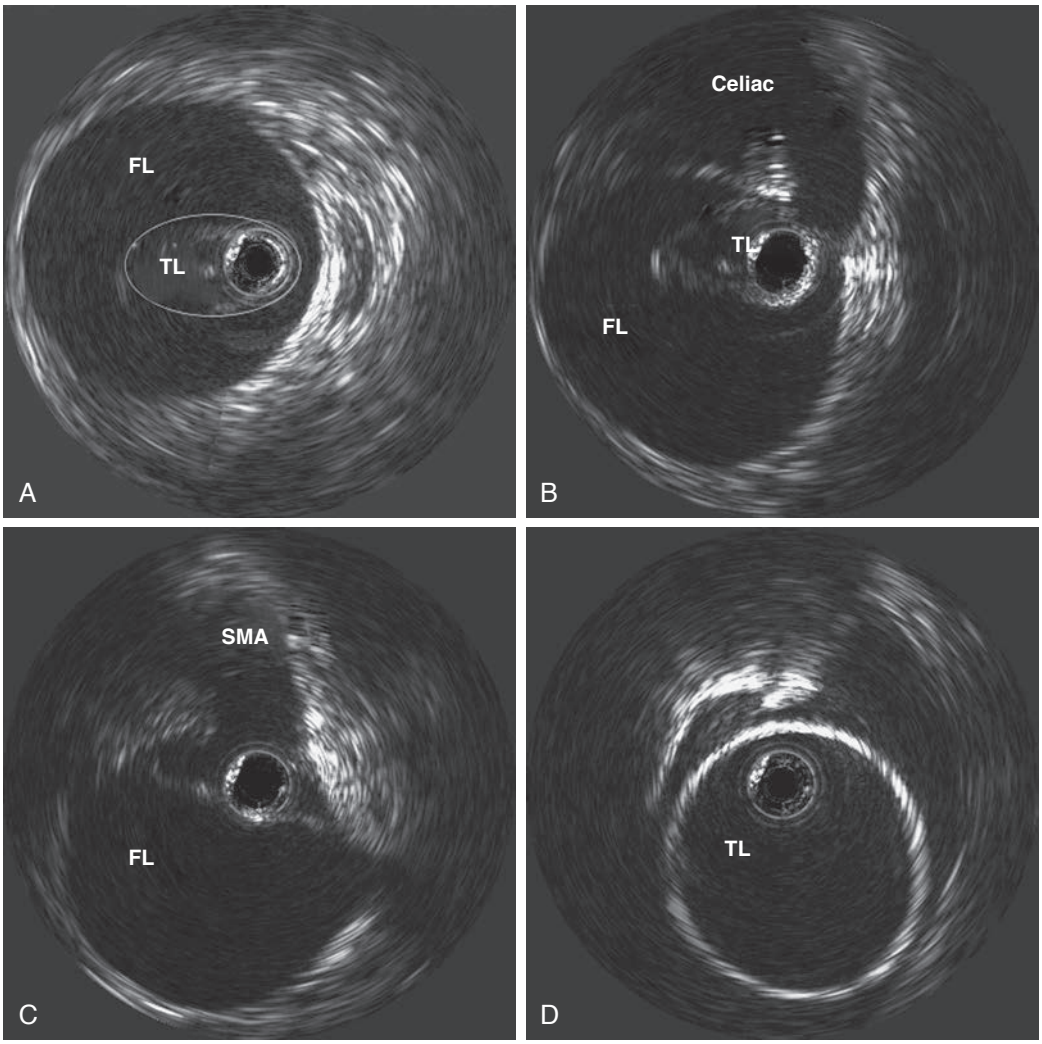


Figure 81.6 Intravascular Ultrasound (IVUS) of Acute Aortic Dissection. **(A)** IVUS of acute type B dissection with "floating" true lumen *(TL)* that is enhanced by the circle. **(B)** IVUS of acute type B dissection at the level of the celiac artery that originates from the compressed TL. **(C)** IVUS of acute type B dissection at the level of the SMA which originates from the compressed TL. **(D)** IVUS of expanded TL after endovascular repair of acute type B dissection. *FL,* False lumen.

been multiple prospective industry-sponsored trials of endovascular stent graft repair of acute type B dissections. The Gore TAG 08-01 study included 50 patients with acute, complicated type B dissections who were treated with TEVAR. The 30-day all-cause mortality in this high-risk population was 8%, with no paraplegia, but the stroke rate was 18%.[93] The Study of Thoracic Aortic Type B Dissection using Endoluminal Repair (STABLE) included 40 patients with type B dissection and reported a 30-day mortality of 5%, with a stroke rate of 7.5% and paraplegia rate of 2.5%.[101] Finally, in an attempt to establish performance goals for future prospective trials, the Society for Vascular Surgery Outcomes Committee reported the results of TEVAR in 85 patients with acute, complicated type B dissections from five centers with single-center Individual Device Exemption (IDE) studies. They established a 30-day mortality of 10.6%, with a stroke rate of 9.4% and paraplegia rate of 9.4%.[101]

The long-term anatomic benefit of TEVAR in patients with acute type B dissection is predicated upon the promotion of false lumen thrombosis and subsequent positive remodeling of the aorta, as evidenced by stabilization of the overall aortic diameter, expansion of the true lumen, and obliteration of the false lumen. Conrad et al. showed positive remodeling at 1 year across the stented segment in 33 patients treated for acute complicated dissection, with 90% of patients maintaining at least partial false lumen thrombosis. This remodeling persisted at 5 years along the stented portion of the aorta in 84% of patients.[94] Lombardi et al. looked at aortic remodeling in 86 patients enrolled in the STABLE trial. With 2 years of follow-up, 74% of patients had a stable or shrinking thoracic aortic segment around the graft.[102]

Treatment of Malperfusion Syndrome

Malperfusion syndromes may complicate the initial presentation of acute aortic dissection in 25% to 40% of patients.[8,103,104] Current indications for aortic fenestration or branch vessel

stenting are dependent upon the anatomic extent of the dissection as determined by CT scanning.[104]

Endovascular Treatment

In the initial endovascular management of the patient with an acute aortic dissection complicated by malperfusion, true and false lumen access must be obtained. IVUS should be performed from the ascending aorta to the iliac vessels in order to define the relationship of the dissection flap to the visceral and renal arteries.[105-107] Angiography can often be limited to hand injections of selected branch arteries to prove that the catheter/wire is beyond the dissection in "normal" artery. Power injection in the true lumen of the dissected aorta may give the false impression of adequate perfusion to branch vessels compromised by dynamic obstruction. All aortic branches should be visualized before intervention, as changes in flap mobility due to relief of obstruction in any single vessel may alter perfusion in other aortic side branches. If compromise of any aortic branch vessel is identified by the dissection, wire access into the distal true lumen of the vessel should be secured. In general, placement of stents in a potentially compromised aortic branch should precede aortic fenestration, as fenestration may unpredictably alter aortic flow and make it extremely difficult to regain endovascular access to compromised vessels.[104]

Percutaneous Fenestration

Fenestration of the intimal flap may be performed by several techniques using the combination of ultrasound and fluoroscopy. Most commonly, fenestration is performed from the smaller (usually true lumen) to the larger false lumen. There is usually a natural fenestration that occurs at the level of the left renal artery or other branch vessel that is being perfused by the false lumen. This fenestration can be identified and selected with the aid of IVUS. If no natural fenestration is identified, a needle, or the back end of a .014 wire, can be used to create a fenestration close to the compromised aortic branch. After the needle and a stiff wire are advanced from the true to the false lumen, a 5 F catheter is advanced into the alternate lumen. Confirmation of the position across the membrane is performed by contrast injection. Subsequently, an angioplasty balloon of at least 12 to 15 mm in diameter and 20 to 40 mm in length is used to create a fenestration tear (Fig. 81.7). A stent can be placed across the fenestration to ensure equal flow on both sides. Patel et al. analyzed 69 patients with malperfusion syndrome treated with endovascular fenestration and found a reasonable 17% 30-day mortality (five from false lumen rupture). The long-term durability was good, with nine patients requiring aortic resection over a 72-month follow-up period.

Open Surgical Treatment

Since dynamic obstruction at the aortic level is the most common mechanism of malperfusion syndromes, surgical fenestration has been the most commonly applied open procedure (Fig. 81.8).[5] The fundamental technique of surgical fenestration is wide resection of the dissected septum to relieve aortic obstruction by equalizing flow between the true and false lumens. It is important to consider whether aortic clamping and the fenestration will be confined to the infrarenal aorta. It may be desirable to extend the septectomy into the visceral segment, permitting direct inspection/repair of the ostia of the mesenteric and renal vessels.[108] Experience has demonstrated that the duration of supraceliac clamping can be limited to the 20-minute range, with repositioning of the clamp to an infrarenal location following closure of the visceral segment aortotomy. Interposition of a short segment polyester graft in the infrarenal aorta facilitates reconstruction of the aortic layers at the distal anastomosis with the double-layer Teflon felt technique. Such an approach permits direct repair of a static obstruction—that is, where the branch vessel itself is dissected. This can be accomplished by circumferential suture of the vessel intima to the aortic wall at the ostia. Since continuous exposure of the visceral segment is desirable in surgical treatment of malperfusion syndrome, we prefer left flank approaches for this procedure (see Chapter 53). Depending on body habitus, an eighth or ninth interspace thoracoabdominal approach is used to allow for complete infradiaphragmatic aortic exposure and transperitoneal inspection of the viscera, with palpation of the superior mesenteric artery pulse caudal to the mesocolon. At a median follow-up of 19

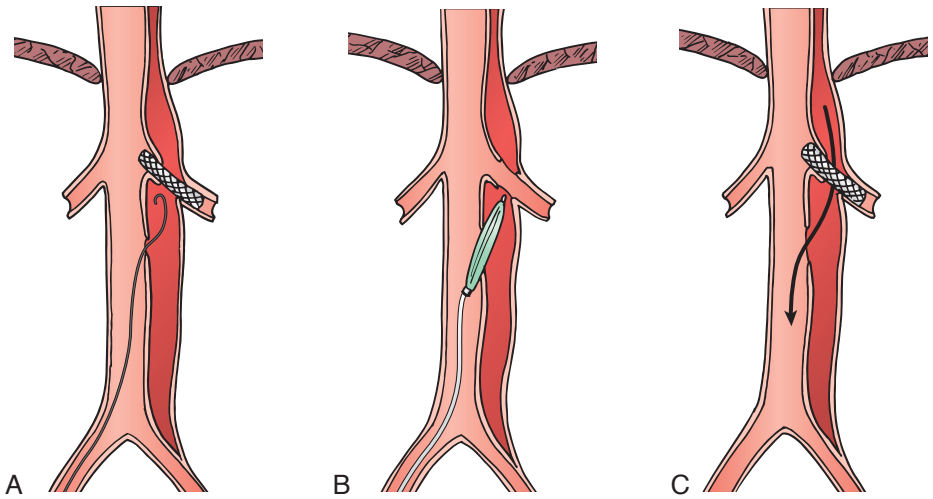


Figure 81.7 Cartoon Depiction of Endovascular Fenestration. **(A)** The left renal artery (coming off the false lumen) made to originate from the true lumen. This requires stenting using either a covered or bare metal stent. **(B)** A balloon is then used to enlarge natural fenestrations in the dissection flap. **(C)** A stent can be used to keep this fenestration open.

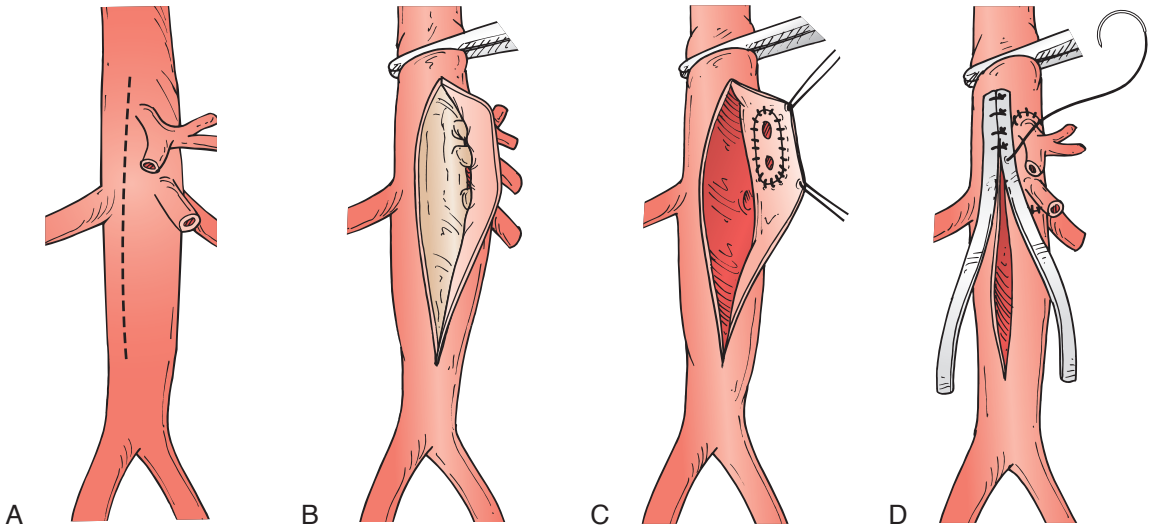


Figure 81.8 Technique of Surgical Abdominal Aortic Fenestration. **(A)** Dissection involving the visceral segment of the aorta. **(B)** If static obstruction of the renal or visceral vessels is suspected based on axial imaging studies, the fenestration can be carried onto the visceral aortic segment. The left kidney has been swept anteriorly, and note the left renal artery is perfused from the false lumen. The septum is incised to expose the origins of the celiac/SMA/right renal artery perfused via the true lumen. **(C)** Direct suture repair of the vessel ostium may be required, herein shown at the left renal origin whose orifice abuts the circumferential terminus of the dissection. **(D)** After septectomy in the visceral segment, the outer aortic wall is closed over Teflon felt and the clamp is moved to the infrarenal aorta, which is most conveniently reconstructed with a tube graft.

months, no significant aortic dilation occurred with such aortic tailoring as a surgical technique.[108]

A report from the Mayo Clinic provides perspective on both the infrequent need for and the durability of surgical fenestration.[109] From their database of 857 patients with a diagnosis of aortic dissection, only 14 (1.6%) patients underwent surgical fenestration during the study period. Recently, the IRAD data reported open fenestration in nine patients with malperfusion, and all survived with successful restoration of visceral flow.[17]

NATURAL HISTORY AND FOLLOW-UP

The primary late complication of aortic dissection is aneurysmal dilation of the outer wall of the false lumen; of patients surviving acute dissection, 25% to 50% will progress to have aneurysmal dilation of the dissected aorta despite medical management.[9,110,111] In most clinical series of thoracoabdominal aneurysms, some 20% of cases are the sequelae of chronic dissection, for which conventional open repair is typically the only treatment option in contemporary practice.[112] Indeed, in our own series of medically managed type B dissections, only 51% of patients were free from aortic growth at 5 years, and almost 30% of patients required intervention for aneurysmal degeneration of the aorta, most of which were open thoracoabdominal aneurysm repairs.[84] A variety of technical and anatomic considerations indicate that stent graft repair of aneurysms of chronic dissection etiology remains a major challenge.[113] Factors that appear to have a significant impact on chronic aneurysm development after dissection include poorly controlled hypertension, and anatomic factors such as a maximal aortic diameter of ≥4 cm in the acute phase, continued patency of the false lumen, a proximal entry tear ≥10 mm, and a partially thrombosed distal false lumen (Fig. 81.9).[114] It is these patients who will likely benefit from elective coverage of the entry tear with a TEVAR during the subacute phase. Finally, some 10% to 20% of those with dissection will subsequently experience late rupture of the aneurysm,[114] and conventional surgical repair of such lesions is considerably more complex than with degenerative aneurysms.

Long-Term Survival

The INSTEAD trial is a prospective, randomized, multicenter trial performed in Europe that compared stent grafting to medical therapy for the treatment of subacute and chronic uncomplicated type B aortic dissection.[81] The study randomized 140 patients to medical versus stent graft therapy. The investigators found no difference in survival between the two cohorts at 2 years, but this served as a break point between the groups, as the 5-year survival was superior in the TEVAR cohort.[10] Recent data from IRAD examined 1129 consecutive patients with acute type B dissection, of whom 24.4% were treated with an early TEVAR. Similar to the INSTEAD trial, there was no difference in early survival between the two cohorts, but at 5 years, it was significantly higher in patients who had undergone TEVAR (84.5% vs. 71%, $P = .018$).[100] Finally, Durham et al. looked at the natural history of 298 patients with acute type B dissection that were initially managed medically, and reported the 6-year survival in patients who eventually required aortic intervention

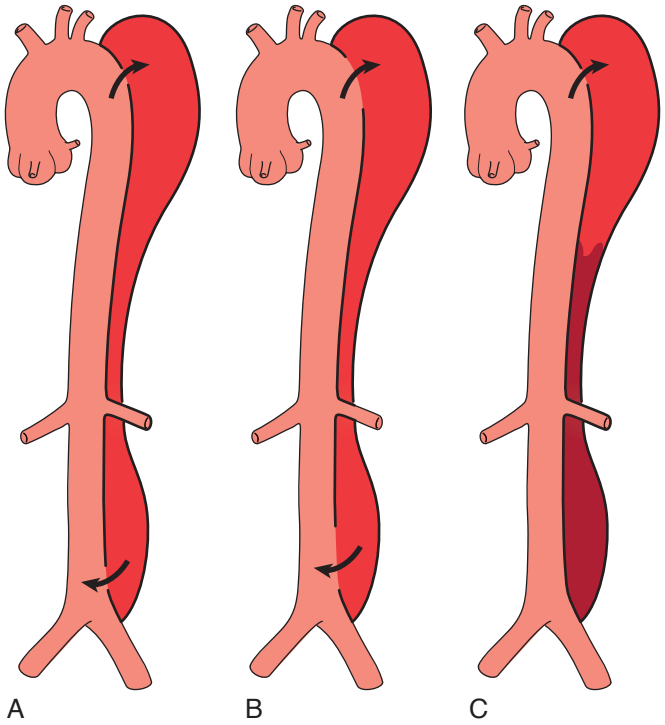
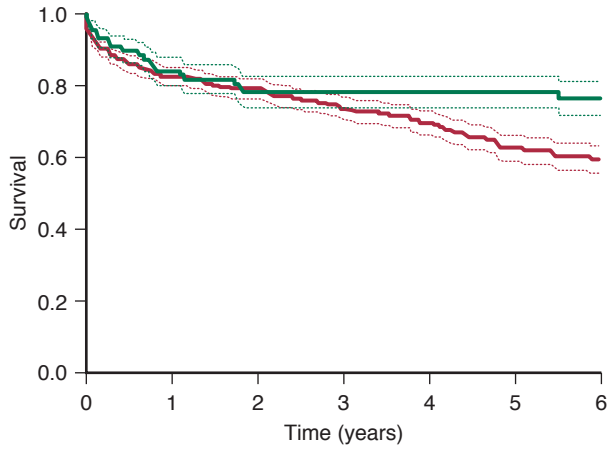


Figure 81.9 Anatomic predictors of aneurysmal degeneration in medically managed type B dissections include **(A)** A descending thoracic aorta that measures greater than 4 cm at the time of presentation. **(B)** Proximal entry tear that measures greater than 10 mm. **(C)** Partially thrombosed false lumen where the outflow fenestrations have thrombosed but proximal flow persists.



Intervention:							
At risk:	87	73	68	65	59	53	43
Survival:	100.0	83.9	78.2	78.2	78.2	78.2	76.4
SE (+/–):	0.0	3.9	4.4	4.4	4.4	4.4	4.7
Medically managed:							
At risk:	211	174	167	136	108	82	65
Survival:	100.0	82.5	79.2	73.6	68.9	62.6	59.3
SE (+/–):	0.0	2.6	2.8	3.1	3.3	3.6	3.8

Figure 81.10 Kaplan Meier curve for survival of 298 patients with uncomplicated acute type B dissection from the time of presentation. The cohorts are stratified by those undergoing intervention *(green)* and those continuing on medically therapy *(red)* ($P = .018$). *SE,* Standard error.

was significantly higher than those who were treated with medical therapy alone (76.4% vs. 59.3%, $P = .018$) (Fig. 81.10). Although the exact mechanism for this survival advantage is unknown, there is a clear trend that favors TEVAR over medical therapy over time that begins after 2 years.[9]

Late Therapy

Aneurysms that are the sequelae of chronic dissection tend to be more extensive and occur in younger patients compared with degenerative aneurysms. Treatment with effective beta-blockade is an essential feature of long-term therapy and follow-up. The rationale of such therapy is based on the recognition that patients with aortic dissection have a systemic illness that places their entire aorta at risk for further dissection, aneurysm, or rupture. Guidelines recommend progressive upward titration of beta-blockade to achieve a blood pressure less than 125/80 mm Hg in usual patients and less than 120 in those with Marfan syndrome. In addition, aggressive beta-blockade has been shown to retard the growth of the aortic root in Marfan's syndrome patients and may have a similar effect on the thoracoabdominal aorta.[115] Serial imaging is the cornerstone of long-term follow-up, and axial imaging modalities should encompass the entire aorta. While in the developmental stages at present, branched stent-graft technologies will likely have an important role in the future management of patients with aneurysms of chronic dissection etiology (see Chapter 80).[116]

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A complete reference list can be found online at www.expertconsult.com.

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82 CHAPTER

Penetrating Aortic Ulcers

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INTRODUCTION

The penetrating aortic ulcer (PAU), when present, indicates a severely diseased aorta. Although first described as an incidental component of dissecting aneurysms in 1934, PAU was not clearly defined as an aortic pathology until 1986.[1,2] PAUs are the rarest subset of the acute aortic syndrome (AAS), which comprises aortic dissection (AD), intramural hematoma (IMH), and PAU, affecting between 2% and 3% of the population.[3-5] Most of the principles of PAU management have been established through 20+ years of retrospective case series. Currently, PAUs are better defined, easily identified on imaging, and treatment strategies for symptomatic and concerning lesions have been shown to improve outcomes.

PATHOPHYSIOLOGY

A PAU is a focal ulcerative lesion that develops in the region of an atheromatous plaque that penetrates the internal elastic lamina of the vascular wall. Sheenan was the first to describe PAU, but it was not described as a distinct lesion distinguished from other aortic pathologies until Stanson's report in 1986.[1,6] Often, PAUs occur in an area of significant atheroma, but not all PAU are associated with atherosclerosis. Only 53% of PAU identified on imaging were associated with atherosclerotic lesions.[7] Regardless of the etiology of the PAU, the pathology commonly resolves with treatment such as after endovascular stenting, with most PAUs found to regress on follow-up imaging. Unfortunately, getting tissue to determine a true histologic diagnosis of PAU is infrequent, since so many of these lesions are treated with conservative medical management or endovascular therapy.

The diagnosis of a PAU in most cases is made based on radiologic appearance. Imaging shows a localized, contrast material-filled, craterlike, outpouching of the endoluminal border with discontinuity of the internal elastic lamina into the aortic wall. Distinct from AD, there is an absence of an intimal flap or double-barreled true and false lumen.

Macrophages are frequently present in the vascular media of a PAU, and similar inflammatory markers are expressed in both PAU and IMH, including matrix metalloproteinases. Both etiologies of AAS have apoptosis and medial layer, specifically *vaso vasorum,* degeneration.[8] Up to 80% of PAU may have an associated IMH within the medial layer of the aortic wall.[9] If an IMH is associated with the PAU, the hematoma is often focal without much extension. PAU with IMH, as compared to isolated PAU, may have behave differently and eventually may progress to an AD.[10] PAU with IMH is also more difficult to treat in endovascular fashion.[11,12]

Traumatic injuries to the aortic wall are not contributory to the development of PAU. PAU do not necessarily occur more commonly in patients with genetic mutations associated with AD, such as Marfan syndrome, cystic media necrosis, or seronegative spondyloarthropathies. Ulcers can be circumferential or longitudinal lesions. Unlike AD, PAUs do not necessarily occur at points of maximal hydraulic stress, such as the right lateral wall of the ascending aorta or at the ligamentum arteriosum of the descending aorta.[13]

PAUs, despite a similar appearance, are separate entities from pseudoaneurysms, saccular, and mycotic aneurysms. However,

Abstract

Penetrating aortic ulcers (PAUs) are important lesions of which vascular surgeons should be aware. With the aging population and improvements in vascular imaging, their observed frequency will likely increase. The presence of a bland PAU in an asymptomatic patient is not necessarily predictive of an evolving vascular pathology. However, those patients presenting with symptoms associated with a PAU or other associated aortic pathologies in addition to a PAU are at increased risk for poor outcomes, even after intervention. The onset of endovascular stent-grafting has provided patients with PAU, who would have not been eligible for open repair, an opportunity for therapeutic intervention.

Keywords

penetrating aortic ulcer
PAU
aortic ulcer
acute aortic syndrome
intramural hematoma
IMH
aortic dissection
saccular aneurysm
pseudoaneurysm

PAUs can degenerate into pseudoaneurysms and saccular aneurysms with adventitial expansion beyond the original borders of the aortic wall. Saccular aneurysm degeneration with associated PAU occurred in nearly a quarter of abdominal and thoracic PAUs.[14] Mycotic aneurysms can also have an ulcerated appearance on imaging; however, there is an associated systemic response (fevers, leukocytosis, tachypnea, or tachycardia). Characteristic radiographic findings of a mycotic aneurysm include the appearance of surrounding phlegm with stranding on imaging representing infected fluid or tissue. Patients presenting with such symptoms or radiographic findings should have blood cultures drawn, broad spectrum antibiotics started, and definitive surgical repair if appropriate.[15]

INCIDENCE

Of those patients diagnosed with AAS, only 2% to 8% have PAU with the majority of these lesions found in the descending thoracic aorta.[13,16] ADs are much more common compared with PAUs. In 120 patients undergoing transesophageal echocardiograms to assess suspected AAS, only 2.5% of the population was found to have PAU, whereas 37.5% of patients had an AD identified.[17] In 684 consecutive aortograms performed for suspected AD, the occurrence of PAU was noted to be similar at 2.3%.[6] However, others have reported a higher incidence. In a retrospective review of 198 patients with the initial diagnosis of AD, Coady et al. noted the incidence of PAU to be 7.6%.[13]

PAU can be identified in the presence of other AAS pathologies or they can be solitary. They can be symptomatic or incidentally identified on imaging. The percentage of patients with a symptomatic PAU as opposed to those with an asymptomatic PAU incidentally discovered is unknown, making their true incidence difficult to determine. As more frequent high-resolution, cross-sectional imaging is performed, their incidence is likely to increase.

PAUs are most frequently found in elderly male patients compared to other AAS etiologies, and the majority of patients with PAUs are in their 7th and 8th decade of life.[11,13,18-22] Patients with PAUs are considerably older than those with other aortic pathologies, with the exception of aortic aneurysms, and are generally a decade older than patients with ADs.[9,23] The mean age at PAU diagnosis is 71.9 ± 6.1 years, which is considerably older than the mean age of patients with an AD (63 years).[24,25] Gender dispersion is two-thirds male and one-third female, which is similar to AD.[24,25] Female patients with PAU in some reviews were noted to have worse outcomes compared with their male counterparts.[23] However, survival after treatment with TEVAR for females with PAU was no different from males at 1 and 5 years.[26]

As with IMH and AD, patients with PAUs almost universally have a concurrent medical history of hypertension with case series quoting a hypertension incidence of 92%. Unlike IMH and AD, patients with PAU generally are infirm with multiple serious comorbidities. Other common comorbidities include smoking history, coronary artery disease, and chronic obstructive pulmonary disease.[20-22,24,27-29] Multiple studies suggest the smoking incidence in patients with PAU is between 60% and 80%.[9,19-21,23,27,30] Other vascular pathologies are frequently identified in PAU patients. For example, approximately 50% will have a concomitant aneurysm that may or may not be near the identified PAU. Aneurysms identified are most frequently located in the abdominal aorta.[31-33] Peripheral arterial disease is also notable with a third of abdominal aortic PAU patients so diagnosed.[31]

PAU can occur anywhere along the aorta, iliac, and femoral arteries, but the most common location is in the descending thoracic aorta. PAUs in the ascending aorta and aortic arch are infrequent.[9,13,34] In a retrospective review assessing a single center experience treating PAU over 11 years, PAU distribution was as follows: 17% aortic arch, 68% descending thoracic aorta, and 14% thoracoabdominal aorta (Fig. 82.1).[35] PAU found

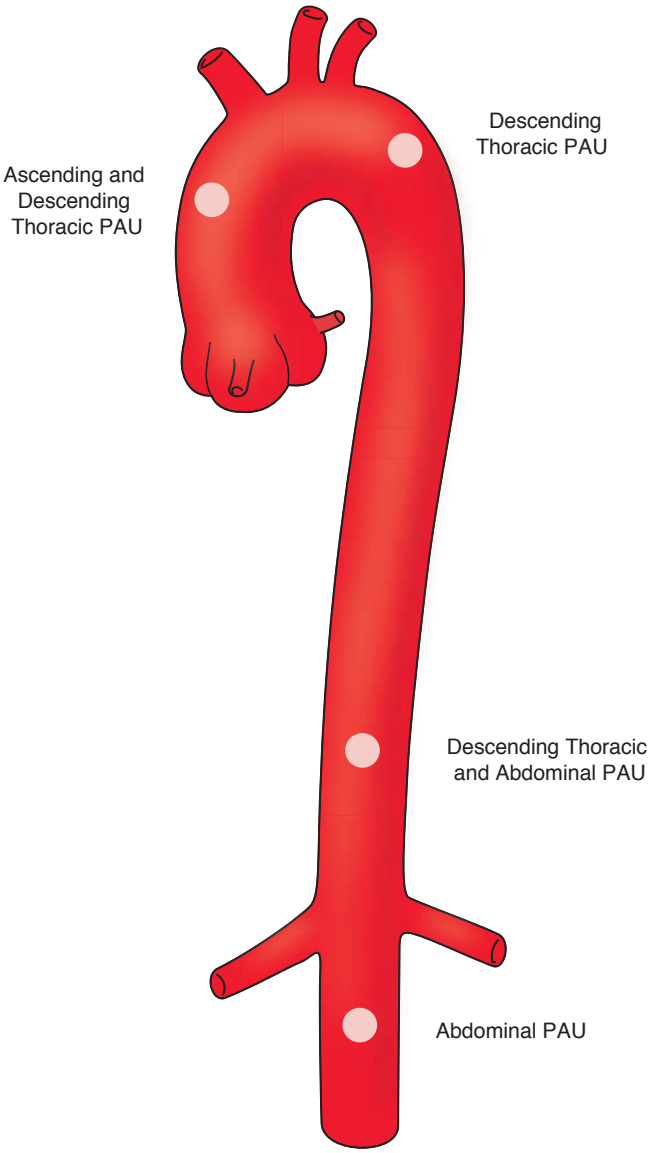

Figure 82.1 Distribution of Penetrating Aortic Ulcer *(PAU)* Along the Aorta and Associated Common Symptoms. Ascending and descending thoracic PAU: 47% chest pain, 40% midscapular pain. Coady et al.[13]; **Descending thoracic PAU:** 100% pain, 38% back pain, 14% chest pain, 9.5% abdominal pain, 14% combined chest and abdominal pain. Brinster et al.[20]; **Descending thoracic and abdominal PAU:** 22% chest pain, 45% back pain, 22% combined chest and back pain, 11% abdominal pain. Dalainas et al.[21]; **Abdominal PAU**: 46% lumbar pain, 11% lower limb ischemia 4% shock. Batt et al.[27]

along the infrarenal aorta and distally are more atypical with less than 4% of patients being affected.[18,27] The frequency of abdominal PAUs is 0.48% and the frequency of iliac and femoral PAU is 0.3% for all patients undergoing computed tomography angiography (CTA) of the abdomen and pelvis,[28,31] and multiple PAUs are identified in 17% to 22% of patients.[19]

CLINICAL PRESENTATION

Symptoms associated with PAUs can be quite variable, and they can present similar to acute coronary syndrome with chest pain and shortness of breath. If the ascending aorta is involved, the affected patient can have anterior chest, neck, and jaw pain. PAU can also present with symptoms similar to AD with sudden onset of tearing or ripping back pain. Upper back, mid-scapular, and abdominal pain is frequently present if the arch or descending aorta is involved, and presentation can be as subtle as isolated dyspnea or mild abdominal pain or as dramatic as hemodynamic instability with frank bleeding from the oropharynx. A few reports of patients with hemoptysis and hematemesis from ruptured PAU with associated bronchial tree or esophageal fistula are described.[36-38]

PAUs can be completely asymptomatic, and the true incidence of these silent PAUs is dependent upon imaging performed for other indications. Thoracic PAUs most commonly present with chest, back, or abdominal pain; and most are symptomatic. In a recent meta-analysis of multiple studies treating thoracic PAUs, as a whole, only 9% of patients were asymptomatic at initial presentation.[24] Generally, more than 75% present with acutely worsening pain for less than 2 weeks.[7,20] PAUs in the abdominal aorta can also have an insidious presentation with a history of chronic lower back or intermittent abdominal pain. Not infrequently, patients with abdominal PAU are completely asymptomatic. All 53 patients identified with PAU along the abdominal aorta were asymptomatic in a recent retrospective review.[31]

Ruptures associated with PAUs are also variable. While a rupture is not necessarily predictable, it is almost uniformly and immediately lethal if not treated expeditiously, and rupture associated with PAU is more common than rupture associated with AD. In symptomatic patients with PAU, 9% to 44% were found to have an aortic rupture.[6,9,11,16,18-23,30] Patel et al. noted that 41% of the patients evaluated with a PAU of the descending thoracic aorta presented emergently with rupture. Similarly, Stanson et al. recognized the rate of rupture associated with a PAU to be around 44%.[6] Unlike descending thoracic PAUs, abdominal PAUs are thought to be responsible for only 1% to 5% of all aortic ruptures.[18]

When assessing for AAS in the symptomatic patient, there are often physical findings that distinguish patients with a PAU from those with AD. The differences generally occur in the cardiovascular exam and neurologic assessment. Patients with PAU seldom have aortic valve regurgitation, which is frequently observed in patients with type A AD, and peripheral pulses are typically equivalent in bilateral upper and lower extremities in patients with PAU, whereas pulses may not be equivalent in patients with AD, especially in those with lower extremity malperfusion. Moreover, patients with AD may also present with neurologic deficits, mesenteric malperfusion, and renal failure, which are not typically found in patients even with symptomatic PAU.

Generally, patients with PAUs have large aortic diameters at the time of diagnosis. Geisbusch et al. found the aortic diameter in 48 patients with PAU to be a mean of 5.0 ± 1.7 cm (range 2.7-10.5),[19] and multiple groups have noted an association between PAU and abdominal aortic aneurysms (AAA). Both patients with thoracic and abdominal PAU are likely to have AAA (Fig. 82.2).[13,31] Coady et al. found concomitant AAA in 6 of 15 patients (40%) with PAU. Stanson et al. and Kazerooni et al. found 38% and 75% of patients with a PAU to have an associated aortic aneurysm.[6,39] The incidence of AAA associated with PAU is higher as compared to the AAA associated with

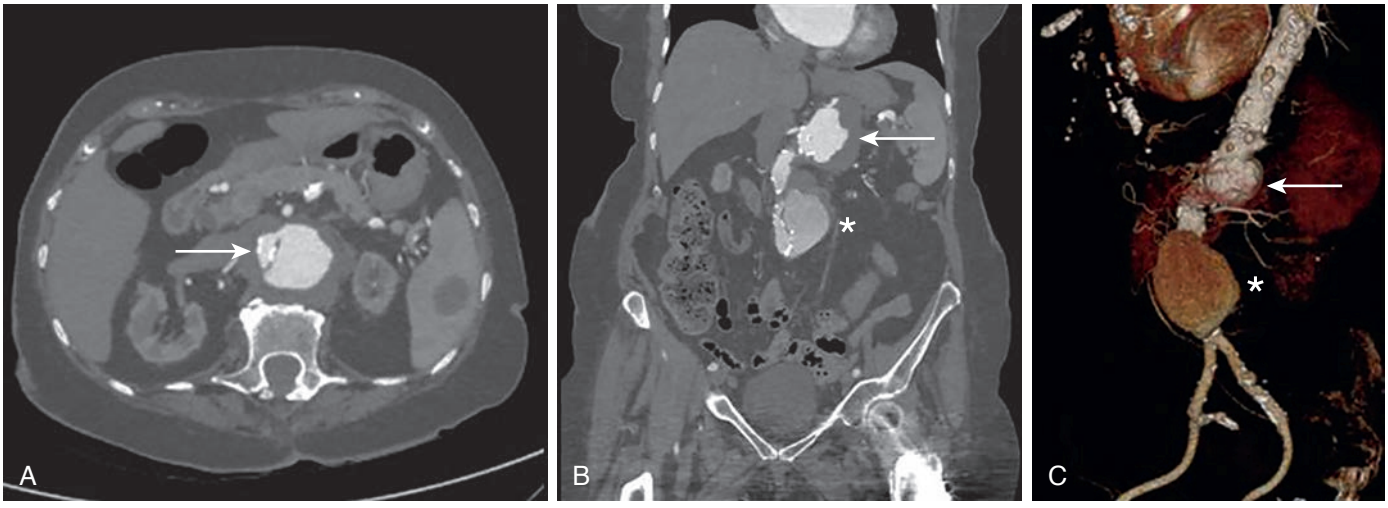

Figure 82.2 Penetrating Aortic Ulcer (PAU) of the Descending Thoracic Aorta and Infrarenal Abdominal Aortic Aneurysm. (A) Sagittal images of the PAU *(arrow)*, (B) coronal images of PAU *(arrow)* and infrarenal aortic aneurysm *(asterisk)*, (C) three-dimensional construction showing left lateral projection with the PAU *(arrow)* protruding and infrarenal aortic aneurysm *(*)* below.

type A and B dissections (9% and 31%, respectively).[13] These findings suggest the pathophysiologic process of PAU formation is similar or related to AAA formation.

Symptomatic PAU frequently will often have pulmonary complications, and respiratory complications can be aggravated especially if other vascular pathologies (IMH, AD and rupture) are present. Pleural effusions are found in conjunction with 10% to 44% of PAU.[9,20,30,39] An enlarging hemothorax is also a notable finding associated with 9.5% of PAU. These respiratory findings suggest an acute presentation of a PAU and impending rupture necessitating urgent treatment, whether or not the patient presents with pain.[20]

PAUs may also present with embolization of atheromatous particles resulting in ischemia or even distal infarction.[18] If no cardiac origin is determined to be the source for the lower extremity embolism, a search for an aortic etiology, particularly a PAU, should be pursued with CTA of the chest, abdomen, and pelvis. Abdominal PAUs, in contrast to thoracic PAUs, are more likely to cause embolization and distal ischemia.[6,31,40,41]

OTHER AORTIC PATHOLOGIES ASSOCIATED WITH PENETRATING AORTIC ULCER

IMH are not universally associated with PAU, but the two aortic pathologies are frequently found together. The frequency of IMH with PAU is reported to be 22% to 94%.[7,9,11,13,21,39,42] The surrounding aortic wall near a PAU is typically thickened with intimal calcification and is often inwardly displaced. Chronic atherosclerosis in the affected area leads to fibrosis in the vascular media preventing hematoma propagation. The mean longitudinal extension of an IMH found with a PAU is limited and was noted to be approximately 2.8 cm.[21] Cho et al. found that more than 85% of IMH diagnosed with PAU spontaneously thrombosed after 1 year.[9] Patel et al. suggest that patients with a PAU and an associated IMH require urgent or emergent intervention due to an increased risk of rupture.[11] In this study, of the 11 patients with concurrent IMH and PAU, seven patients (64%) developed AD or a new intimal tear during hospitalization.

Mortality associated with IMH and PAU was considerably higher compared to isolated IMH. Thirty-six percent of the patients with an IMH and PAU died during the follow up period, while only 8% of patients with a solitary IMH died.[42] This study implies that IMH found in the presence of a coexisting PAU might be associated with worse outcomes, as PAUs found in conjunction with IMH might be the cause of newly developed dissections with intimal tear and aortic rupture. In patients with an isolated PAU compared to those patients with IMH and PAU, there was no difference in age, prevalence of comorbidities, presentation with rupture, and extent of repair performed.[11] Importantly, no difference in overall patient survival between those presenting with an IMH and PAU compared to PAU alone was noted.[11] However, IMH presence with PAU was associated with a higher risk of endovascular treatment failure treatment compared to isolated PAU. Treatment failure was defined as the additional need for open repair, endovascular re-intervention, aortic rupture, or aortic-related death.[11] The optimal treatment time is still debated for patients presenting with both PAU and IMH, and allowing for IMH resolution prior to endovascular intervention especially might be of value.[11]

PAU presenting with an AD is not uncommon. The frequency of PAU with thoracic AD is reported between 11% and 20%.[7,43] Often a thicker calcified, static flap is affiliated with the tear.[44] Like IMH found in association with PAU, the AD with PAU are typically shorter in length as compared to a classic AD. When studied in conjunction with AD, patients with PAU are more likely to suffer aortic rupture than patients with AD alone (AD + PAU, 40% versus type A AD alone 7.0% and type B AD alone 3.6%).[13] The survival trend of AD in association with a PAU is worse as compared to solitary AD because of increased rupture potential.[13]

DIAGNOSTIC IMAGING

CTA imaging has now become the standard imaging of PAU. CTA can accurately visualize PAU-associated vascular pathology, including aortic wall enhancement, thrombosed IMH external to the calcified intima, contrast extravasation through the ulceration, the absence of a double lumen, a thrombosed pseudoaneurysm, and transmural rupture.[43]

In addition to evaluating for other adjacent aortic pathologies, PAUs are assessed for ulcer dimensions. These include the maximum width of the entry defect from the lumen, the maximum depth from the lumen to the aortic wall, and the maximum length of the intramural component of the ulcer itself (Fig. 82.3). Cho et al. reviewed CTA imaging of 105 patients with PAUs. Three quarters of the patients were symptomatic upon presentation. All three PAU dimensions measured, width, depth, and length, were found to be significantly greater in the symptomatic patients as compared to asymptomatic patients.[9]

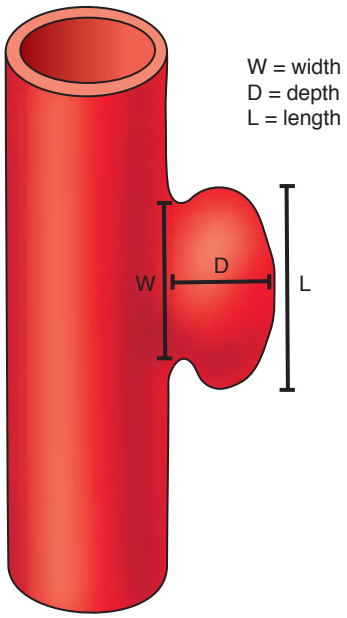

Figure 82.3 Penetrating Aortic Ulcer Dimensions Measured.

The greatest disadvantage of CTA is the requirement for iodinated contrast and radiation exposure. Another limitation of CTA imaging is that if intimal calcification associated with the PAU is not present, intraluminal thrombus and IMH can be difficult to distinguish.[44] Imaging techniques used to identify PAU generally demonstrate an outpouching of the aortic wall with the presence of jagged edges surrounded by extensive aortic atheroma. The starting point for a PAU is distinct, whereas the starting point for an AD can be difficult to determine.

Alone, magnetic resonance angiography (MRA) might not be as sensitive for detecting PAU. MRA is of little value in the identification of aortic wall calcification, and Yucel et al. reported that MRA identified six of seven PAU as compared to aortography.[44] However, MRA is useful as adjunctive imaging and may even be superior to aortography at identifying complicating features. MRA shows the PAU as a craterlike ulceration in the absence of an intimal flap or false lumen, and the aortic wall appears thickened with high intensity signals on T1 and T2 weighted images when the PAU was complicated by an acute IMH. An obvious advantage of MRA is that no iodinated contrast is required and that images may be acquired using time of flight sequences. Unfortunately, the high cost of MRA, the long time needed for evaluation, the difficulty monitoring unstable patients, and the limitation for patients with metal implants still limits its use.

Other imaging modalities useful for evaluating PAU include transesophageal echocardiography (TEE). With TEE, PAUs appear as crater-like ulcers with ragged edges in the presence of extensive atheroma without an intimal flap or false lumen. When an IMH is present in conjunction with a PAU, the IMH will appear echolucent with mottled thickening of the aortic wall and inward displacement of intimal calcification. When a PAU is identified, the benefit of TEE is the ability to simultaneously evaluate cardiac function and identify regional wall motion abnormalities. The results are operator dependent relying on the ability to obtain accurate images and the interpreter's read of the imaging acquired.

TREATMENT

The goal of intervention for symptomatic PAU, as well as those with concerning features, should be to prevent aortic rupture and progression to AD. Incidentally discovered PAU, depending on location and appearance, might not require intervention and might be best followed with repeat imaging and conservative measures including treatment of hypertension and hyperlipidemia if present. Tittle et al. found progression of aortic diameter to be 0.2 cm/year in the presence of a PAU and suggested annual imaging surveillance.[29] Harris et al. found that approximately one-third of patients with PAU progressed to form a saccular or fusiform aneurysm.[44]

Conservative management is preferred in patients presenting with an isolated PAU without associated symptoms or if symptoms are well controlled with antihypertensive medications. Patients with PAU should have strict blood pressure control with beta blockade or vasodilators. Cho et al. presented a retrospective series of 105 patients with conservatively treated PAU over a 1- to 7-year period. Medical management in this study was associated with a significantly lower early mortality rate compared to open surgical repair and were 4% and 21%, respectively.[9] Conservative treatment with antihypertensive therapy in this study showed one-third of patients required intervention for progression of PAU to aneurysms, dissection, or perforation over a 25-year period.[9]

Some research has yielded better results associated with the conservative management of PAU. Hussain et al. found few if any patients treated with conservative management progressed to aneurysm formation or rupture. In this study, patients with thoracic PAU were followed for 30 months, and none required surgical intervention. Within 6 months of diagnosis, all patients were symptom-free, and imaging showed that 80% of patients had a resolution of their PAU with no signs of progression to aneurysm or rupture.[43]

Treatment should be pursued for all symptomatic PAU to prevent possible rupture and should incorporate both blood pressure control and operative intervention. Other PAU treatment indications include recurrent or refractory pain and signs of impending or contained rupture. Rapidly growing aortic ulcers, periaortic hematoma, hemothorax, and pleural effusions are all signs of impending PAU rupture. PAUs presenting with symptoms are more malignant, and urgent operative intervention is warranted.[16] The median time between admission and endovascular repair for patients who failed conservative management for their PAU was 2 days (range 1-4 days).[21] In addition, Geisbusch et al. advocated PAU repair, specifically with endovascular intervention in their study, within 48 hours of symptom onset.[28]

Radiologic characteristics of PAU more likely to rupture in asymptomatic patients have also been identified. Patients with aortic diameters greater than 60 mm adjacent to the PAU, PAU diameter greater than 20 mm, and PAU depth greater than 20 mm should be referred for repair.[14,16,45,46] Prognosis for the PAU is correlated with size, with most believing that PAU with larger diameters and depths require earlier intervention. It is important to note however that PAU adjacent to normal diameter aorta have been known to rupture. Continued observation with repeat imaging for asymptomatic PAU that develop concerning features and patient education regarding the symptoms that might be attributed to impending rupture are important.

PAU should be repaired if there are signs of progression (accelerated growth) or impending vascular compromise. These signs include an expanding IMH, an evolving AD, distal embolization, or hemodynamic instability. Failure of medical management to control pain or blood pressure is another indication for surgical repair.

The use of fludeoxyglucose-positron emission tomography/CT is being investigated for the assessment of aortic lesion inflammation. Associated inflammation is thought to be a marker for aortic wall instability.[47] These findings in combination with PAU imaging characteristics might prove valuable in determining which PAU should be intervened upon and appropriate timing. Interestingly, D-dimer levels in patients with PAU are not as elevated as compared to other AAS etiologies (AD and IMH), suggesting that PAU might not always have associated

inflammation.[48] Janosi et al. did find that both biomarkers, d-dimer and troponin, were significantly elevated in symptomatic PAU patients as compared to asymptomatic PAU patients ($P = .016$ and $P = .04$, respectively).[35]

OPERATIVE REPAIR

Some of the larger studies describing their results treating patients with PAU are listed in Table 82.1. Historically, PAUs were treated with open aortic repair. In 1959, Shumacker and King were the first to perform successful open operative repair of a ruptured PAU in the descending thoracic aorta.[49] Open surgical repair for all aortic pathologies, including PAU, has improved greatly in recent years (see Chapter 77). Studies from specialized aortic surgery centers have demonstrated 30-day mortality rates for all open aortic surgery as low as 6%.[45] However, the subset of patients affected by PAU is an elderly group of patients with multiple comorbidities. Therefore, operative mortality for PAU

TABLE 82.1 Representative Case Series Describing the Treatment of Patients With PAU

First Author	Year	Number Treated	PAU Location	Repair Type
Murgo et al.	1998	4	Thoracic	TEVAR
Brittenden et al.	1999	2	Thoracic	TEVAR
Czermack et al.	2002	2	Thoracic	TEVAR
Kos et al.	2002	10	Thoracic	TEVAR
Schoder et al.	2002	4	Thoracic	TEVAR
Haulon et al.	2002	2	Thoracic	TEVAR
Nienaber et al.	2002	15	Thoracic	TEVAR
Krohg-Sorensen et al.	2003	2	Thoracic	TEVAR
Fattori et al.	2003	6	Thoracic	TEVAR
Demers et al.	2004	26	Thoracic	TEVAR
Destrieux-Garnier et al.	2004	5	Thoracic	TEVAR
Melissano et al.	2005	2	Thoracic	TEVAR
Batt et al.	2005	8	Infrarenal	Open tube graft or aortobifemoral repair, EVAR
Brinster et al.	2006	21	Thoracic	TEVAR
Pauls et al.	2007	12	Thoracic	TEVAR
Attia et al.	2007	3	Thoracic	TEVAR
Dalainas et al.	2007	18	Thoracic-16 and infrarenal-2	TEVAR and EVAR
Pifaretti et al.	2007	13	Abdominal	EVAR
Botta et al.	2008	19	Thoracic	TEVAR
Geisbusch et al.	2008	48	Thoracic-46 and infrarenal-2	Hybrid procedures, TEVAR, TEVAR and EVAR
Gottardi et al.	2008	27	Thoracic	TEVAR
D'Souza et al.	2009	13	Thoracic	TEVAR
Eggebrecht et al.	2009	22	Thoracic	TEVAR
Patel et al.	2010	37	Thoracic	TEVAR
Hyhlik-Durr et al.	2010	20	Abdominal	EVAR
Czerny et al.	2011	72	Thoracic	TEVAR
Tumelero et al.	2011	2	Thoracic	TEVAR
Mestres et al.	2012	22	Thoracic	TEVAR
Palombo et al.	2012	16	Aortic arch-2, thoracic-11, abdominal aorta-3	Hybrid procedures, EVAR
Sato et al.	2012	4	Infrarenal	Open tube graft
Georgiadis et al.	2013	19	Abdominal	EVAR
Taher et al.	2016	12	Pararenal	Hybrid procedures, chimney and fenestrated EVAR
Gifford et al.	2016	Immediate-20, delayed-13	Thoracic-28 and abdominal-29	Open, EVAR and TEVAR

EVAR, Endovascular aneurysm repair; *PUA*, penetrating aortic ulcer; *TEVAR*, thoracic endovascular aortic repair.

patients undergoing open repair has ranged between 5% and 21%.[9,50-52] One of the few advantages of open surgical repair is that it allows for a histologic diagnosis.

Disadvantages of open surgical repair include operative duration under general anesthesia, a large incision, clamping and unclamping the aorta, possible cardiopulmonary bypass, and an extended hospital stay with potential frequent post-procedural complications.

ENDOVASCULAR REPAIR

Endovascular management of PAU has largely become the operative treatment of choice. Nonetheless, no randomized study has been performed confirming the superiority of open or endovascular repair for PAU. In addition, no difference in late survival has been noted between patients with thoracic PAU undergoing open repair as compared to endovascular repair suggesting noninferiority.[12]

While the anatomic features of the PAU will ultimately dictate the appropriate intervention, generally, patients affected by PAU are not ideal candidates for open repair because of advanced age, poor functional status, and multiple comorbidities. PAUs, because of their focal, segmental nature, are an ideal lesion to be treated with stent-grafting. Multiple groups have shown that endovascular repair of PAU associated with symptoms or concerning features such as associated pseudoaneurysm, and rupture is a feasible option for treatment. Endovascular repair, specifically thoracic endovascular aortic repair (TEVAR), for descending thoracic PAU has proven safe and efficacious (Table 82.2).[11] TEVAR for PAU has been demonstrated to be at least as effective as traditional open surgical repair or a hybrid procedure. Multiple groups have reported their results with TEVAR for PAUs, and in a meta-analysis of these studies with over 300 PAU treated with TEVAR, the overall reported technical success was 98.3%.[24] Clinical success of endovascular stenting ranges from 76% to 100%.[11,18-20,22-24,30]

There are many appealing features of endovascular repair as compared to open repair for the treatment of PAU. The less invasive nature with small incisions or percutaneous approach is desirable as compared to a large thoracotomy or abdominal incision. Mean operative time with endovascular stent-graft placement is decreased compared to open repair.[18,20,53] In addition, hospital length of stay is less with endovascular stent placement for PAU with multiple studies reporting a mean hospital stay after endovascular repair ranging from 4 to 8 days.[18,20,53]

Limitations of endovascular repair include adjacent aneurysm, PAU in proximity to the branch or mesenteric vessels, steep aortic angulation, heavy burden of atherosclerotic disease in the associated area, inadequate working length (insufficient landing zones), and other proximal aortic pathology. Sufficient landing zones remain important for successful PAU exclusion and as close to 20 mm proximal and distal to the PAU of healthy aorta is the goal for endovascular exclusion.

Most studies suggest that only a 5% to 10% maximum oversizing should be performed.[11,21] Aggressive attempts to dilate the landing zones for stent grafts are usually not indicated in the presence of PAU.[54] Balloon dilation should only be done in areas of stent-graft overlap, and dilation around the region of PAU should not done to avoid device erosion into the aortic wall.[54] Hybrid approaches, including preoperative aortic debranching, carotid to subclavian bypass, mesenteric debranching/bypass, or snorkeling techniques, have been reported prior to PAU endovascular repair. Interestingly, Patel et al. reported aortic arch repair to be protective on multivariate analysis with regard to late aortic outcomes associated with TEVAR repair of thoracic PAU. While the study lacked sufficient numbers of patients treated to yield statistical significance, the researchers hypothesized that the aorta associated with proximal and mid-descending thoracic PAU without prior arch repair is subject to propagating retrograde dissection, aneurysm formation, and rupture. Their suggestion was for more extensive coverage with multiple centimeters above and beyond the PAU to be treated.[11]

Postprocedural imaging usually with CTA should demonstrate lesion regression or thrombosis. Clinical symptoms associated with PAU should resolve in most cases after endovascular treatment. In a retrospective review of 14 symptomatic patients

TABLE 82.2 Comparison of Studies Reporting Endovascular Treatment of Thoracic PAU

	n	Average Age	Follow Up (Months)	Technical Success (%)	30-Day Mortality (%)	Overall Mortality (%)	Endoleaks (%)
Demers et al., 2004	26	70	51	92	12	30	4
Brinster et al., 2006	21	73	14	100	0	5	0
Eggebrecht et al., 2006	22	69	27	96	0	18	5
Piffaretti et al., 2007	11	73	15	100	0	10	0
Geibusch et al., 2008	48	70	31	94	6	39	23
Gottardi et al., 2008	27	66	42	100	11	15	7
Botta et al., 2008	19	72	22	95	11	21	16
Patel et al., 2009	37	72	37	100	5	38	24

PUA, Penetrating aortic ulcer.

undergoing TEVAR for thoracic PAU, all patients treated had their preoperative pain relieved after endovascular stent-graft placement.[20]

The mortality associated with the procedure is still considerable despite the less invasive nature of the procedure, and the mortalities were most likely due to the comorbidity of the patient population treated. Thirty-day mortality overall was 4.8% and has ranged between 0% and 26%.[11,18-20,22,23,30,53] Some groups have reported higher in-hospital mortalities, although their treated populations included patients with PAU complicated with AD and other aneurysmal disease.[19] Not surprisingly, PAU patients who were asymptomatic at presentation had a lower in-hospital mortality rate than symptomatic patients (0% vs. 23%, respectively).[19] By univariate analysis, Patel et al. found older age correlated with early mortality.[11]

Mid- and long-term follow-up statistics are limited for PAU patients treated with TEVAR, and the data does show that long-term survival is limited by patient comorbidity and not by PAU disease progression after stent-graft placement. D'Annoville et al. found after a mean follow-up of 17.7 months (range 1-52 months), all-cause mortality was 22.9% (71 of 310).[24] In a separate study assessing long term results, median survival was 89.8 months and 7-year actuarial survival was 84.4% ± 10.2% with operative status, elective versus urgent or emergent at the time of presentation, being an independent risk factor for late all-cause mortality (OR 14.7, $P = .007$).[11]

Other factors found to correlate with late mortality in patients following endovascular treatment of PAU included history of congestive heart failure, perioperative stroke, or need for dialysis.[12] In a meta-analysis of PAU treated with TEVAR, overall aortic-related mortality after treatment was 4.1% (13 of 310) with individual studies reporting a range of aortic-related mortality rates between 1.3% and 15.3%.[11,23,24,55-61]

COMPLICATIONS ASSOCIATED WITH REPAIR

The same complications associated with any aortic surgery can occur after both open and endovascular PAU repair. Some of the most common perioperative complications include myocardial infarction, cerebrovascular accidents, pulmonary complications, renal failure, sepsis, and multi-organ failure. Most of the data available to evaluate complication frequency is obtained from the multiple case series reporting TEVAR for thoracic PAU repair. While the aforementioned complications are not common, they can be devastating. D'Annoville et al. quoted an early (<30 days post) morbidity incidence of 36.4% (113 of 310)[24] and noted that the incidences of postoperative sepsis, multiorgan failure, renal failure, and pulmonary complication in patients undergoing TEVAR repair of PAU were 1.2% (2 of 157), 2.3% (6 of 261), 4% (9 of 221), and 4.7% (9 of 189), respectively.[24] Out of 21 studies reporting post-operative coronary complications, only one patient reviewed suffered a myocardial infarction. Twenty-seven studies reported a post-operative stroke rate of 2.4% (7 of 287).[24]

Spinal ischemia with associated paraplegia among thoracic PAU patients undergoing TEVAR occurred in 2.9% of cases, but reversed in eight of nine patients with cerebrospinal fluid drainage.[24] Only 25% of patients with thoracic PAU treated with TEVAR underwent preventative cerebrospinal drainage. Given the focal nature of most PAU and the urgency for treatment, cerebrospinal drainage is not uniformly recommended.

Complications after TEVAR repair for PAU specific to the stent-graft include endoleaks, access complications, peripheral embolization, stent migration, stent fragmentation, infection, and PAU progression. The most common complication specifically related to TEVAR repair of thoracic PAU is access complications with a reported rate of 16% (26 of 161).[24] Endoleaks can be observed at the time of treatment or noted with follow up imaging. Proximity to aortic arch branches, mesenteric, and renal vessels increases their probability of endoleaks. The number of stent-graft pieces used to cover the PAU also increases their likelihood. Early endoleaks were observed in 19% of patients with thoracoabdominal PAU included in the study by Geisbusch et al. However, this study included PAU found in conjunction with multiple other aortic pathologies including AD, associated aneurysms, and aortic fistulas.[19] Others describe a less frequent rate of endoleaks. D'Annoville et al. identified endoleaks in 8% of cases (25 of 310).[24] In this large meta-analysis, type I ($n = 9$), II ($n = 10$), and III or IV ($n = 6$) endoleaks were observed. During follow-up, new endoleak and ulcer recurrence were observed in 5.4% and 4.5%, respectively, requiring a new aortic endovascular procedure in 50% ($n = 10$).[24] Dalainas et al. demonstrated a 5.5% rate of endoleak after endovascular repair of both thoracic and infrarenal PAU. The only endoleak experienced in this study was associated with covering a pseudoaneurysm found in association with a PAU at the time of presentation.[21]

Several predictors of treatment failure have been identified. As with rupture risk, Demers et al. identified increased aortic diameter adjacent to the PAU as a risk factor for treatment failure.[23] PAU in the presence of other aortic pathology is also a risk for treatment failure. PAUs have also been described complicating aneurysm repair. Some groups have elected to treat PAU with coil embolization in addition to stent-graft repair with the intention of eliminating the risk of type I endoleak, but only a handful of case reports describe such treatment. Patients presenting with PAU and associated IMH were more likely to have treatment failure defined as the need for open or endovascular aortic re-intervention, aortic rupture, or aortic-related death.[11,12] Finally, late mortality correlated with urgent or emergent endovascular repair.[11]

SUMMARY

Despite being rare compared to the other AAS pathologies, PAUs are important aortic lesions. With the aging population and improvements in vascular imaging, their observed frequency will likely increase; and the presence of a bland PAU in an asymptomatic patient is not necessarily predictive of an evolving vascular pathology. However, those presenting with symptoms and other associated aortic pathologies in addition to a PAU

are at increased risk for poor outcomes, even after intervention. The onset of endovascular stent-grafting has provided patients with PAU, whom would have not been eligible for open repair, which is an opportunity for therapeutic intervention. Endovascular repair has also become the preferred treatment for PAU.

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Cho KR, Stanson AW, Potter DD, Cherry KJ, Schaff HV, Sundt TM. Penetrating atherosclerotic ulcer of the descending thoracic aorta and arch. *J Thorac Cardiovasc Surg*. 2004;127:1393–1399.

This is a retrospective review of 105 patients followed with thoracic PAU over 25 years. The article includes separate discussion regarding PAU diagnosed with and without an associated intramural hematoma.

Coady MA, Rizzo JA, Hammond GL, Pierce JG, Kopf GS, Elefteriades JA. Penetrating ulcer of the thoracic aorta: what is it? How do we recognize it? How do we manage it? *J Vasc Surg*. 1998;27:1006–1015.

Retrospective review of PAU patients wrongly characterized as having an AD. The article includes a thorough discussion regarding PAU radiologic characteristics. The paper highlights the diagnosis of PAU as an etiology distinct from aortic dissection.

D'Annoville T, Ozdemir BA, Alric P, Marty-Ane CH, Canaud L. Thoracic endovascular aortic repair for penetrating aortic ulcer: literature review. *Ann Thorac Surg*. 2016;101:2272–2278.

This publication includes an extensive literature review of TEVAR repair for PAU.

D'Souza S, Duncan A, Aguila F, et al. TEVAR for non-aneurysmal thoracic aortic pathology. *Catheter Cardiovasc Interv*. 2009;74:783–786.

Harris JA, Bis KG, Glover JL, Bendick PJ, Shetty A, Brown OW. Penetrating atherosclerotic ulcers of the aorta. *J Vasc Surg*. 1994;19:90–98.

This publication had a detailed discussion of the natural history and complications associated with PAU.

Nathan DP, Boonn W, Lai E, et al. Presentation, complications, and natural history of penetrating atherosclerotic ulcer disease. *J Vasc Surg*. 2012;55:10–15.

This is a large single center experience reviewing 388 patients with PAU. The publication includes an excellent discussion of the literature regarding PAU.

Patel HJ, Williams DM, Upchurch GR Jr, Dasika NL, Deeb GM. The challenge of associated intramural hematoma with endovascular repair for penetrating ulcers of the descending thoracic aorta. *J Vasc Surg*. 2010;51:829–835.

This is a retrospective review of a single center's experience treating descending PAU endovascularly with TEVAR. There is a separate discussion regarding the co-existence of intramural hematoma with PAU.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 83

Lower Extremity Aneurysms

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Aneurysms occurring in the arteries of the lower extremity are second in frequency only to aneurysms of the infrarenal aorta and iliac arteries. Historically, lower extremity aneurysms were typically mycotic, syphilitic, or traumatic in origin. However, most aneurysms in the femoral, popliteal, and tibial arteries are currently either degenerative aneurysms or posttraumatic pseudoaneurysms related to catheterization or instrumentation. True aneurysms occur far more commonly in men than in women, at a ratio of 30:1.[1,2] Furthermore, true aneurysms of the femoral or popliteal arteries are often associated with aortic aneurysms and aneurysms in the contralateral lower extremity. The association with aortic aneurysms ranges from 50% to 90% for femoral aneurysms,[2-6] from approximately 30% to 50% for popliteal aneurysms, and as high as 70% for bilateral popliteal aneurysms.[1,2,7,8] Bilaterality is also common, occurring in approximately 25% to 50% of femoral aneurysms and 50% to 70% of popliteal aneurysms.[2-4,7,9] Conversely, up to 14% of men with aortic aneurysms have been found to have femoral or popliteal aneurysms, but this combination is a rare finding in women.[6] Additional imaging, such as duplex ultrasound (DUS), may therefore be indicated to evaluate for concomitant aneurysmal disease when an aortic or lower extremity aneurysm is diagnosed.

Aneurysms in the lower extremity are of clinical significance because of their potential to cause limb-threatening ischemia. More rarely, such aneurysms can rupture, particularly false aneurysms of the common femoral artery. Treatment is preferable when they are asymptomatic—hence the importance of detection and a thorough knowledge of the association with other aneurysms. Symptomatic true aneurysms have a much higher incidence of limb loss because of the prevalence of embolization of thrombus from within the aneurysm sac to more distal arteries. Clinicians must always consider embolization from an aneurysm when evaluating lower extremity ischemia and when planning

interventions. There have been significant changes in the treatment of lower extremity aneurysms, along with additional treatment options, including various endovascular therapies.

FEMORAL ARTERY ANEURYSMS

Femoral artery aneurysms occur primarily in the common femoral artery and less commonly in the profunda femoris and superficial femoral arteries. The common femoral artery (CFA) can be the site of true aneurysms and of pseudoaneurysms related to prior instrumentation or previous revascularization procedures. True aneurysms are less common and are often associated with popliteal artery and aortic aneurysms.[10] In any artery, an aneurysm is defined as a focal, fusiform dilation of the artery to 1.5 times the normal diameter of the adjacent segment of artery.[11] The normal size of a CFA in men is approximately 1.0 and 0.8 cm in women.[12] Repair has been considered clinically indicated for aneurysms more than 2.5 cm in diameter, but data from 2014 has 3.5 cm as an indicated diameter for repair.[13,14]

Pseudoaneurysm of the CFA usually appears as a saccular outpouching of the vessel and has a narrow neck representing a defect in the vessel wall due to instrumentation. The pseudoaneurysm is actually a rim of fibrous tissue containing thrombus and arterial flow in continuity with a defect in the CFA. Iatrogenic pseudoaneurysms are addressed separately from true aneurysms.

True Aneurysms

Epidemiology

In a large study of true aneurysms of the femoral arteries, 57% were in the CFA, 26% in the superficial femoral artery (SFA), and 17% in the profunda femoral artery (PFA); 26% were bilateral and 48% were associated with additional aneurysms.[10] They are found predominantly in older men (70 years or older) and are associated with smoking and hypertension.[3] The majority are degenerative, but they have also been reported with atriomegaly and other conditions such as Behçet disease, Parkes Weber syndrome, and Wegener granulomatosis.[15-20]

In addition, a recent study on true aneurysms in the femoral arteries by Lawrence et al., in which eight institutions pooled data in the Vascular Low Frequency Disease Consortium, showed similar results, with a higher percentage (81%) in the CFA, and lower percentage (14%, 5%) in the SFA and PFA, respectively,.[13]

Clinical Presentation and Diagnosis

Isolated true femoral aneurysms are asymptomatic in 30% to 40% of patients, and are often found on physical examination or DUS scan. Another 30% to 40% cause localized pain and tenderness or compressive symptoms, resulting in neuropathic pain or leg edema. The most common presentation in up to 65% of cases is lower extremity ischemia, including claudication or critical ischemia resulting from embolization.[2,3,10] Rupture is a rare occurrence—occurring in approximately 4% of cases.[21]

Duplex ultrasound is the modality of choice for diagnosis and assessment of femoral artery aneurysms. It is cost-effective and accurate. Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) can also be used and may be of additional value in the planning of endovascular repair and when specific measurements are needed to identify normal artery proximal and distal to the identified aneurysm. CTA and MRA can also be useful to look for additional aneurysms such as aortic, iliac artery, contralateral femoral artery, and popliteal artery aneurysms (PAAs).

Indications for Treatment

All symptomatic femoral aneurysms should be treated to prevent embolization, thrombosis, worsening of local compressive symptoms, and rupture. Although the natural history of asymptomatic femoral artery aneurysms is unclear, it had previously been suggested that the repair of asymptomatic femoral aneurysms more than 2.5 cm diameter is indicated in "good-risk" patients.[14] This suggestion is based on one of the largest reported series of 172 femoral aneurysms in 100 patients; 40 were asymptomatic, and 105 small (<2.5 cm) aneurysms were managed nonoperatively.[2] In the more recent study by Lawrence et al., it was noted that acute complications such as ischemia or rupture did not occur in patients with asymptomatic femoral artery aneurysms less than or equal to 3.5 cm. The size threshold for elective repair may be reduced in the presence of intraluminal thrombus.[3] Smaller asymptomatic aneurysms can be managed with observation by duplex scan and do not require intervention unless they expand or become symptomatic.[13]

Surgical Treatment

Treatment of CFA true aneurysms usually consists of open repair, in which the aneurysm is excluded with an interposition graft. To prevent injury to surrounding structures that may be adherent to it, the aneurysm sac is usually not resected. The preferred graft material is synthetic—either polytetrafluoroethylene (PTFE) or Dacron.[3,10,14] The prosthetic grafts are better size matches and have equivalent or better patency rates than vein grafts in this positon.[3] Preoperative assessment of the aorta and the iliac, superficial femoral, and popliteal arteries should be performed to detect additional aneurysmal disease. In both elective procedures and emergency procedures for rupture, open repair can be achieved with minimal morbidity and excellent long-term patency.[3,10,14] Proximal control can usually be achieved with a clamp on the distal external iliac artery or proximal CFA via a longitudinal groin incision. In cases of large aneurysms, proximal control can be achieved with balloon occlusion placed via the contralateral femoral approach. If this is not possible, a suprainguinal retroperitoneal exposure of the external iliac artery may rarely be required to obtain proximal control of a large, proximal CFA aneurysm.

An aneurysm confined to the CFA can be treated with a short interposition graft (Fig. 83.1). An aneurysm extending into the PFA or SFA requires more complex reconstruction with an interposition graft from the proximal CFA to the PFA

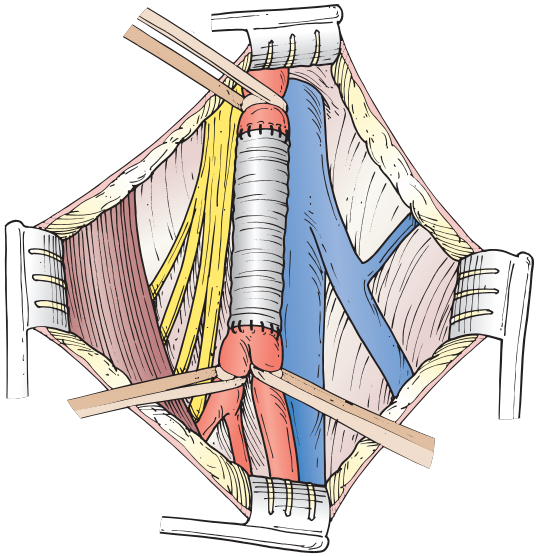

Figure 83.1 Surgical repair of an aneurysm confined to the common femoral artery can be accomplished with a simple interposition graft. (From Ouriel K, Rutherford RB, eds. *Atlas of Vascular Surgery: Operative Procedure.* Philadelphia: WB Saunders; 1998.)

or SFA, and a jump graft to the other femoral branch (Fig. 83.2). It is important to preserve flow to the PFA to prevent future severe ischemia.[14]

Endovascular Treatment

Endovascular treatment of CFA aneurysms has largely been limited to emergency situations or performed as part of a hybrid approach with an open surgical procedure. Bakoyiannis et al.[22] described such a procedure using a stent-graft to exclude a distal external iliac artery aneurysm and a traditional Dacron graft for the femoral portion of a large aneurysm extending from the distal external iliac artery into the common femoral artery. Percutaneous endovascular treatment of a ruptured femoral artery aneurysm has also been described.[21] Contralateral femoral access is often required in these cases for delivery of the stent-graft. However, caution should be used in the consideration of placement of a stent-graft in the CFA, particularly when it crosses the inguinal ligament, because of possible stent fracture or dislodgement in this location.

Endovascular techniques can be used as adjuncts to open procedures. For example, proximal control can be obtained via a balloon placed under fluoroscopic guidance through the opened aneurysm sac in standard surgery,[23] or percutaneously via the contralateral CFA when necessary.

Pseudoaneurysms

Pseudoaneurysms in the CFA occur most commonly from iatrogenic causes such as instrumentation for cardiac or peripheral catheterization and after open reconstructions.[14,24] Iatrogenic false aneurysms can be treated with open surgery or ultrasound-guided therapy, or with observation alone if they are small in diameter. Pseudoaneurysms may also occur as a result of infection

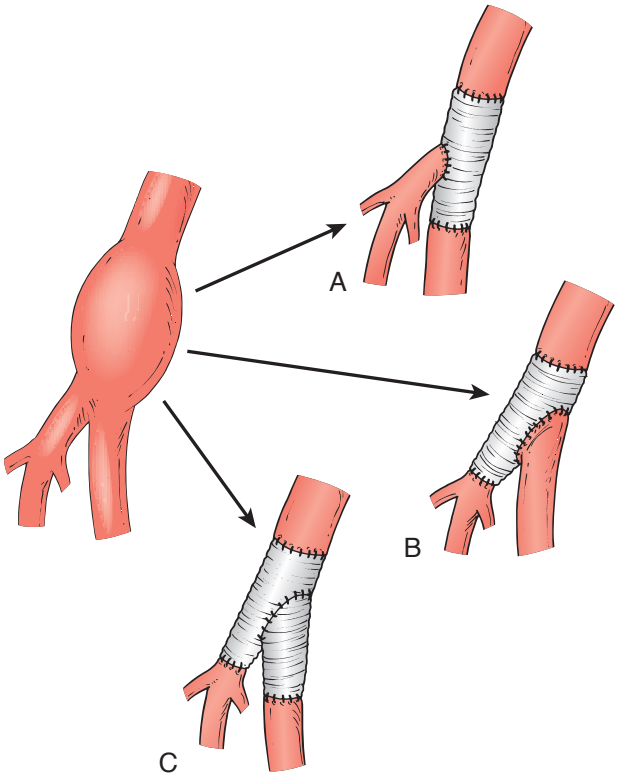

Figure 83.2 Surgical reconstruction of a femoral artery aneurysm extending beyond the common femoral artery bifurcation can be performed with different configurations, depending on local anatomy. The interposition graft can be placed between the common femoral and either the superficial femoral artery (A) or the profunda femoris artery (B) with reimplantation of the other branch into the side of the graft. (C) If the origin of the artery to be implanted is diseased or not long enough, a short interposition graft can be used. (From O'Hara P. Treatment of femoral and popliteal artery aneurysms. In: Zelenock GB, Huber TS, Messina LM, et al., eds. *Mastery of Vascular and Endovascular Surgery.* Philadelphia: Lippincott Williams & Wilkins; 2006.)

that causes focal erosion of the arterial wall, usually from external sources such as contaminated needles used during intravascular substance abuse. The management of infected pseudoaneurysms is difficult and requires ligation either alone or with extraanatomic bypass.[25] Infected aneurysms are discussed in detail in Chapter 47. Management of anastomotic pseudoaneurysms is discussed in Chapter 48.

Clinical Findings and Natural History

The most common clinical manifestation of a femoral pseudoaneurysm is a painful pulsating mass in the groin, usually with an associated hematoma. Femoral bruits are heard frequently, and if an arteriovenous fistula is present, the bruit has a characteristic continuous to-and-fro quality. Patients may also complain of femoral neuropathic pain, paresis of hip flexion, or edema from compression of adjacent structures. Progressive enlargement can result in overlying skin ischemia and necrosis. In our experience, distal embolization or limb ischemia is rare. Rupture can lead to cardiovascular collapse and death from hemorrhagic shock and is a surgical emergency.[26] Significant bleeding can occur without overt clinical findings if the initial

puncture is in the external iliac artery or through the inguinal ligament, and results in occult bleeding into the retroperitoneal space.

Aneurysm size and the presence of anticoagulation determine which pseudoaneurysms require treatment. Most aneurysms less than 2 or 3 cm in diameter undergo spontaneous thrombosis and may be safely observed with periodic DUS examinations. Continued anticoagulation therapy greatly decreases the likelihood of spontaneous closure of such a pseudoaneurysm.[27,28] In one prospective series, 18 pseudoaneurysms were identified after 1838 femoral catheterizations over an 8-month period (0.98% incidence). Aneurysms that were less than 1.8 cm in diameter and causing no symptoms were observed. Surgical repair was carried out if the aneurysms enlarged by 100% or did not close within 2 months. Of the 16 that were managed expectantly, half underwent spontaneous thrombosis and the other half required repair. Although the difference did not reach statistical significance, the likelihood of spontaneous closure was lower for aneurysms more than 1.8 cm in diameter, and no aneurysm closed spontaneously in the presence of continued anticoagulation, regardless of size.[29]

Diagnosis

Duplex ultrasound is the preferred imaging method. The sensitivity and specificity of DUS for femoral false aneurysms are 94% and 97%, respectively.[30] Duplex ultrasound also provides important information on diameter, morphology, and anatomy of the neck and location of the femoral artery defect. On B-mode imaging, an aneurysm appears as a characteristic echolucent mass adjacent to the femoral artery and a channel, usually narrow, with arterial flow into the mass (Fig. 83.3).

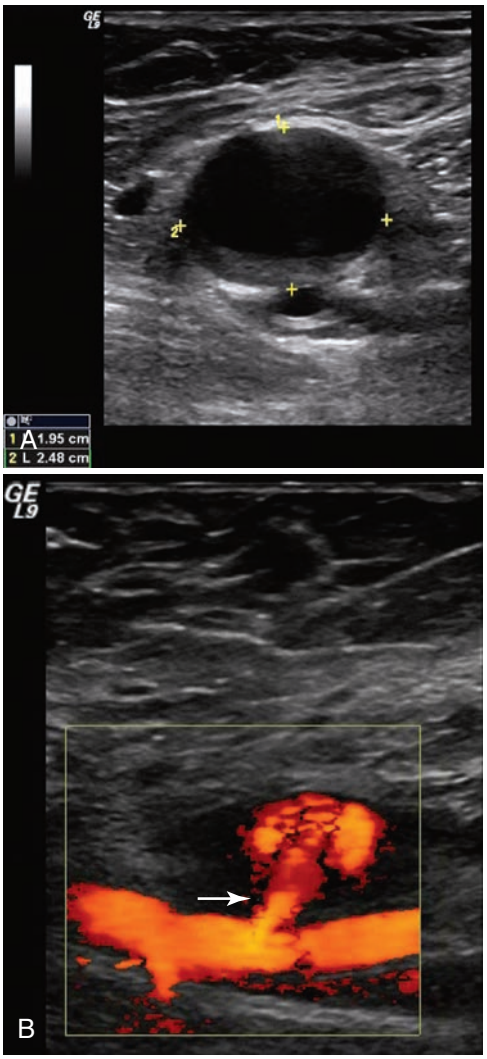

Figure 83.3 (A) Duplex ultrasound of a femoral false aneurysm in B mode demonstrating a large echolucent mass anterior to the femoral artery. The *cursor* marks the dimensions of the aneurysm cavity. (B) Color-flow imaging demonstrating blood entering the aneurysm sac via a relatively long channel or "neck" *(arrow)*, arising from the femoral artery.

Treatment

Ultrasound-Guided Compression

Compression of false aneurysms to induce thrombosis was proposed as a less invasive alternative to surgery in 1991.[31] Duplex ultrasound is used to locate the aneurysm, and suitable pressure is applied with the transducer to stop flow within the aneurysm cavity while maintaining flow in the adjacent femoral artery. Excessive pressure can result in femoral artery thrombosis.[32] Compression is maintained for 10 to 20 minutes, after which time flow is reassessed. If flow persists, the procedure is repeated one or more times until flow within the aneurysm cavity is noted to have stopped. The patient is kept on bed rest for 6 hours, being reevaluated with DUS at 24 and 48 hours after the procedure to rule out recurrence. If the procedure is performed in the outpatient setting, the patient may be discharged home after the initial 6 hours.

Success rates for ultrasound-guided compression (UGC) range from 66% to 86%, with required compression times averaging 30 to 44 minutes.[31-33] Recurrence has been reported in 4% of cases.[32] The presence of anticoagulation greatly reduces the likelihood of success to less than 40%.[32-34] UGC is contraindicated in patients with ischemic skin changes or infection, and when the puncture site originates above the inguinal ligament. Moreover, UGC is not usually possible in patients with severe pain and very large hematomas. Imaging and compression are technically more difficult in obese patients, thus decreasing the likelihood of success. Aneurysm rupture, femoral vein thrombosis, limb ischemia from femoral arterial thrombosis, and hypotension from vasovagal events are all potential complications that have occurred in 2% to 4% of cases.[32,33,35]

From a practical standpoint, UGC has the disadvantage of being time-consuming and placing demands on the vascular laboratory, time, equipment, and personnel. Operator and patient fatigue and management of the often significant pain that patients experience during compression are common problems.[36] The use of mechanical compression devices can obviate some of these issues, but requires a cooperative and immobile patient and repeated reevaluation during compression.[37] Such devices offer little advantage and have not generally been widely accepted.

Ultrasound-Guided Thrombin Injection

Angiographically directed thrombin injection via percutaneous access into the aneurysm cavity to induce immediate thrombosis was first described by Cope et al.[38] more than 20 years ago. Kang et al.[39] modified the technique by performing direct percutaneous aneurysm puncture under duplex ultrasound guidance. Thrombin directly converts fibrinogen to fibrin, thereby leading to immediate clot formation and "short-circuiting" the upstream mechanism of the coagulation cascade, where heparin and warfarin interact. Consequently, thrombin injection is effective even in patients receiving anticoagulation. Bovine and human thrombin are commercially available in powder form that is reconstituted in normal saline immediately before use.

Ultrasound-guided thrombin injection (UGTI) is quick, simple, and relatively painless. Duplex ultrasound is used to identify the aneurysm cavity. After infiltration with local anesthetic, the cavity is punctured with either a 22-gauge catheter or a 25-gauge hypodermic needle. Spinal needles can be used for deeper aneurysms. Identification of the needle or catheter within the aneurysm sac is a critical step (Fig. 83.4) and can be facilitated with the use of a commercially available echodense needle.[40-42] The needle is filled with thrombin, which when inserted causes a small clot to form at the needle tip that is readily visualized on ultrasound.[39] Once proper positioning of the needle is confirmed, thrombin (1000 IU/mL) is injected slowly through a 3-mL syringe for a period of about 10 to 15 seconds, until flow within the cavity ceases. In our experience and that of others, a dose of approximately 1000 units of thrombin is required to induce thrombosis. It is important to inject slowly and to stop immediately once thrombosis has occurred to minimize the chance of thrombin entering the circulation. A second injection is sometimes required.[39] Patients are given bed rest for 1 hour. Duplex ultrasound is repeated 24 hours later to confirm permanent thrombosis of the aneurysm. UGTI has a success rate of 96% to 100%.[40,43-45] Second injections of thrombin are necessary in up to 7% of cases to achieve complete thrombosis.[45]

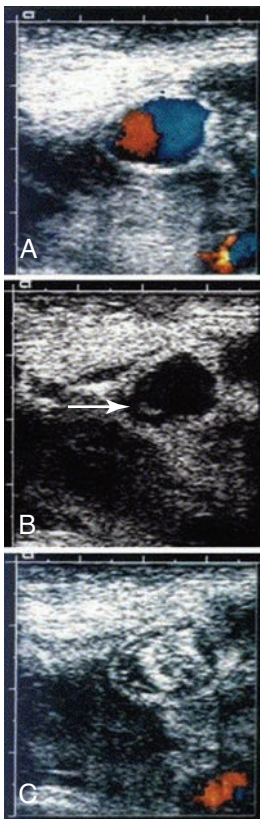

Figure 83.4 Duplex Ultrasound of a Femoral Pseudoaneurysm. (A) Color-flow image demonstrating typical swirling flow in the pseudoaneurysm cavity. (B) Image taken 18 seconds later with color flow turned off shows the tip of a 22-gauge needle in the left lower portion of the pseudoaneurysm *(arrow).* After placement of the needle, color flow is turned back on and thrombin is injected. (C) Color-flow image demonstrating that the pseudoaneurysm cavity is completely filled with echogenic thrombus. (From Kang SS, Labropoulos N, Mansour MA, Baker WH. Percutaneous ultrasound guided thrombin injection: a new method for treating postcatheterization femoral pseudoaneurysms. *J Vasc Surg.* 1998; 27:1032-1038.)

Most writers prefer to use UGTI to treat pseudoaneurysms and to use UGC only in patients in whom thrombin products are contraindicated. Contraindications to bovine thrombin include known allergy, infection, and pregnancy. A relative contraindication to UGTI is a short, wide channel or "neck" of flow into the pseudoaneurysm. In these cases there can be a higher incidence of embolization of thrombus into the CFA with thrombin injection. An update of a Cochrane review compared multiple no-surgical treatments, including ultrasound-guided compression, blind compression, and ultrasound-guided thrombin injections. Compression was effective in achieving pseudoaneurysm thrombosis. Ultrasound-guided application did not confer an additional benefit. Percutaneous thrombin injection was more effective than a single session of ultrasound-guided compression within individual randomized controlled trials.[46]

Open Surgical Repair

Open surgical repair is usually reserved for ruptured pseudoaneurysms, failures of or contraindications to UGC or UGTI, overlying skin ischemia, or pseudoaneurysms associated with an arteriovenous fistula. Direct repair with polypropylene sutures or patch angioplasty is an effective method of repair (Fig. 83.5). However, complications are not infrequent, with wound complications in up to 4% to 8% of cases and an associated mortality rate of 2.9% related to the underlying cardiac disease for which the catheterizations are often performed.[46,47] In high-risk cases, open repair can be performed with local anesthesia and the use of balloon occlusion for proximal control of the external iliac artery. If there is extensive damage to the femoral arterial wall, patch angioplasty with autologous or synthetic tissue may be required. Autologous tissue is preferred, because pseudoaneurysms may be associated with latent infections.

Superficial Femoral Artery Aneurysms

Isolated aneurysms of the SFA are rare and considerably less common than those of the common femoral artery. They more commonly manifest as proximal extensions of popliteal artery aneurysms. An extensive review of all language literature by Leon et al.[48] identified 61 reported cases of isolated SFA

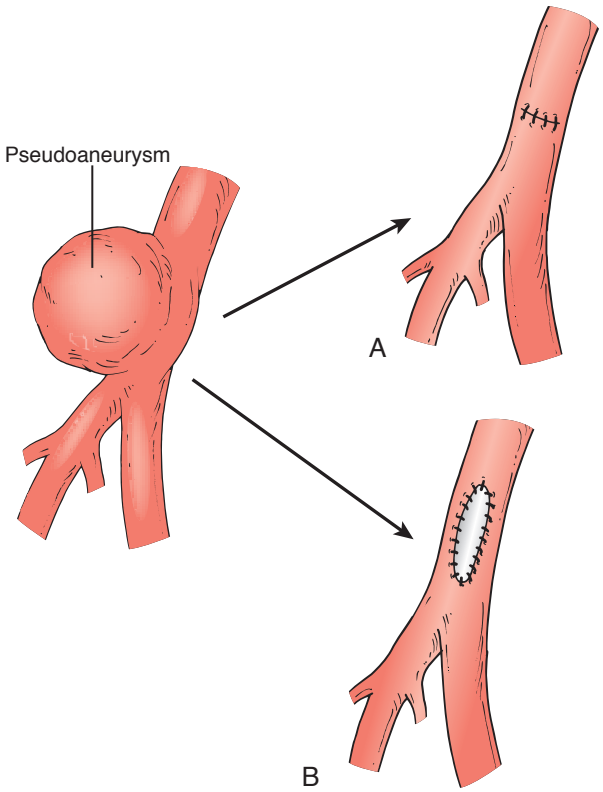

Figure 83.5 Surgical Repair of a Femoral Artery False Aneurysm. After proximal and distal control is obtained, the sac is opened and the arterial defect exposed. Repair can be accomplished in most cases by direct suture repair (A), although patch angioplasty may occasionally be required (B). (From O'Hara P. Treatment of femoral and popliteal artery aneurysms. In: Zelenock GB, Huber TS, Messina LM, et al., eds. *Mastery of Vascular and Endovascular Surgery.* Philadelphia: Lippincott Williams & Wilkins; 2006.)

aneurysms. They occurred most commonly in elderly men (87%), with an average age of 75.7 years. Most were located in the middle third of the artery and were large at presentation, with a mean diameter of 8.4 cm at diagnosis. Such a large size is likely related to the deep anatomic location of the distal SFA, which precludes early detection. The most common mode of manifestation was a pulsatile tender thigh mass (59%) associated with localized pain. Rupture was more common manifestation (42%) than distal ischemia (13%), and repair most commonly consisted of interposition graft or exclusion with bypass. Limb salvage rate is reported at greater than 90%. Endovascular repair was reported in three cases in this review.[48]

Because of the rare nature of this entity, the natural history is not well known, and no specific aneurysm diameter has been identified at which the incidence of complications increases. SFA aneurysms of 2.5 cm or more in diameter, particularly those that are known to have grown over time, are usually repaired. Duplex ultrasound scan is an accurate imaging modality for following smaller asymptomatic aneurysms.

Prior to surgical treatment, arteriography is performed to evaluate the inflow and outflow vessels. Either saphenous vein or prosthetic graft can be used. Prosthetic grafts work well in the groin or thigh and can usually be matched to the diameter of the artery. Vein grafts are preferred for any reconstruction crossing the knee joint, which may be necessary with distal occlusive disease or if the aneurysm is being treated in conjunction with a PAA. Exposure is obtained in either the groin or midthigh or at both sites, depending on the extent of the aneurysm. The surgical approach is nearly identical to that for popliteal aneurysm repair. Focal aneurysms are treated by opening of the sac, evacuation of thrombus, and creation of an end-to-end interposition graft. For more extensive aneurysms, proximal and distal ligation can be performed, followed by placement of a bypass graft. Although long-term follow-up is not available, Rigdon et al.[49] reported a limb salvage rate of 94% with no deaths, whereas Jarrett et al.[50] reported successful bypass in 11 cases with no mortality. Two patients underwent primary amputation for unsalvageable ischemia at initial evaluation.

Perini et al. retrospectively reviewed surgical outcomes in multiple centers over a 10-year period for patients treated for isolated superficial femoral artery aneurysms and noted 5-year survival, limb salvage, and graft patency rates of 62%, 88%, and 85%, respectively. Mean follow-up was 41 months.[51]

Although endovascular repair has been reported in only a few instances of isolated SFA aneurysms, it is likely that percutaneous repair will become more prevalent as the profile of devices is reduced and they are easier to deploy. However, long-term data on the effectiveness of this treatment method are not available at this time.

Profunda Femoral Artery Aneurysms

Degenerative aneurysms of the PFA are extremely rare, representing less than 3% of all femoral artery aneurysms (Fig. 83.6). Most cases are unilateral, although bilateral aneurysms have also been reported.[52] Synchronous aneurysms are common and occur in up to 70% of cases, with popliteal aneurysms being the most common.[53,54] They can manifest as either rupture or limb-threatening ischemia from distal embolization of thrombus, particularly if there is concomitant SFA occlusive disease. Like SFA aneurysms, PFA aneurysms are often of large size at presentation because of their deep anatomic location.[55] Repair is always recommended because of the high rate of complications and unknown natural history of asymptomatic PFA aneurysms.

Surgical repair is carried out through a vertical groin incision. In most cases, aneurysmectomy within an interposition graft of either saphenous vein or prosthetic material is preferred. In the construction of interposition grafts, large branches of the profunda femoral artery should be preserved whenever possible. Dissection is usually started at the CFA bifurcation and extends inferiorly and slightly laterally over the course of the deep femoral artery. The SFA is retracted medially, and as the dissection extends more distally, the sartorius and rectus femoris muscles are reflected laterally. Larger crossing branches of the deep femoral vein are encountered and must be carefully divided and suture-ligated. Branches of the femoral nerve are also encountered and must be preserved and protected from injury by self-retaining retractors or cautery. Gentle dissection is necessary to avoid troublesome venous injury. Proximal control is usually obtained at the level of the CFA, although in instances of rupture with massive hematoma in the groin, control of the distal external iliac artery may be necessary. Distal arterial control can be

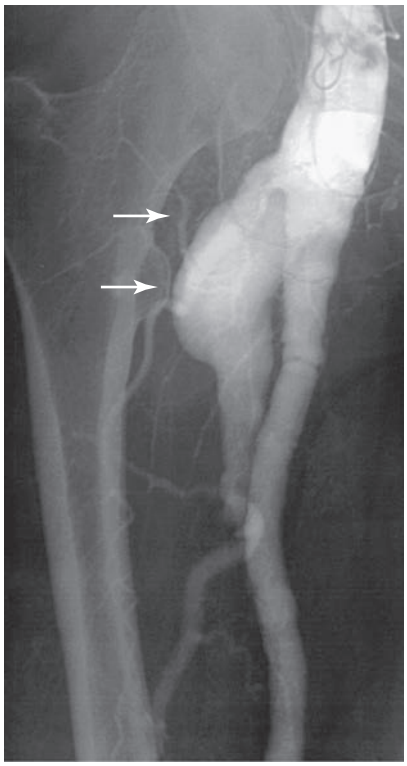

Figure 83.6 Arteriogram of a large symptomatic aneurysm of the profunda femoris artery *(arrows)*. The aneurysm originates at the origin of the profunda femoris artery, and there is ectasia in the common femoral and superficial femoral arteries.

accomplished with silicon rubber vessel loops or balloon catheter occlusion.

Although graft replacement is generally preferred, simple ligation may be a reasonable treatment for aneurysms confined to the distal branches of the deep femoral artery.[56] Proximal PFA ligation may also be reasonable in patients with rupture, especially when the SFA is patent; however, such ligation may put the patient at risk for future limb ischemia and amputation.[54] In highly selected cases of aneurysms involving distal branches of the PFA, embolization may be a reasonable nonsurgical alternative.[57,58]

Endovascular management of PFA aneurysms has been reported. Stent-grafts have been used to treat three cases of PFA pseudoaneurysms after instrumentation or penetrating trauma, with good short-term results.[59] This approach may be effective in stable patients without major compressive symptoms. Coil embolization has also been shown to be successful treatment, particularly if the aneurysm involves distal branches of the main PFA.[58] Embolization of the main PFA has been reported via a contralateral approach and may be a useful alternative if the SFA is patent.[60]

PERSISTENT SCIATIC ARTERY ANEURYSM

Persistent sciatic artery (PSA) is a rare vascular anomaly present in 0.01% to 0.05% of the population. Embryonic blood flow in the lower extremities is provided by the sciatic artery originating from the umbilical artery. As the external iliac artery system develops by gestational month 3, the sciatic artery regresses and becomes a small part of the inferior gluteal artery. When it fails to regress, the remnant is called a *persistent sciatic artery*.

It is prone to aneurysmal degeneration, potentially leading to distal ischemia, sciatic neuropathy, and rupture. When present, most PSAs involve the dominant limb arteries of the lower extremity, with aneurysm formation occurring in up to 40% of cases. The femoral artery is often hypoplastic. The patient with PSA aneurysm may present with an enlarged buttock mass, with local compressive symptoms and distal ischemia. An interposition graft is the preferred method of repair.[61] Because of potential damage to the adjacent sciatic nerve, exposure and surgical dissection of the aneurysm are not recommended.

Endovascular stent placement has been reported as an effective method of repair for PSA aneurysm, provided that there are no significant associated compressive symptoms.[62] Embolization of a ruptured PSA aneurysm with Amplatzer plugs (St. Jude Medical Inc., St. Paul, Minnesota) in a hemodynamically unstable patient has also been reported. This maneuver successfully controlled the hemorrhage but was complicated by footdrop, likely secondary to sciatic nerve ischemia and a buttock abscess.[63]

POPLITEAL ARTERY ANEURYSMS

The popliteal artery, a continuation of the superficial femoral artery in the thigh, extends from the adductor canal to the origin of the anterior tibial artery below the knee. The definition of what constitutes a popliteal artery aneurysm varies in the contemporary literature. The normal diameter of the popliteal artery varies with the size and gender of the patient, ranging from approximately 0.5 to 1.1 cm.[11,64] Anatomic studies have now shown that the popliteal artery itself differs in diameter from proximal to distal, with the proximal portion more closely approximating the diameter of the SFA and the distal popliteal artery tending to be smaller.[65] Most PAAs appear to occur in the proximal part or midportion of the artery. According to 1991 suggested standards, an aneurysm may be considered to be present if the total enlargement is 1.5 times the diameter of a normal adjacent segment of artery.[11] Other writers consider a diameter of 1.5 cm or greater in the "average" patient to be an aneurysm, although in clinical practice most surgeons use 2 cm as the threshold diameter.

Epidemiology

PAAs are rather rare in the general population, although they are the most common peripheral artery aneurysms, accounting for at least 70% of them.[66] PAAs are found almost exclusively in men. One study of hospitalized patients identified the incidence of femoral or popliteal artery aneurysms to be 7.4 per 100,000 men and only 1.0 per 100,000 women.[66] Another study that screened more than 1000 men between the ages of 65 and 80 years in the United Kingdom revealed a prevalence

of only about 1%.[67] About 50% of patients have bilateral PAAs, and 30% to 50% of patients may have an associated abdominal aortic aneurysm (AAA).[7,68] On the contrary, less than 15% of all patients with AAAs have coexisting PAAs.[6] In patients treated for isolated popliteal aneurysms, the likelihood of development of another aneurysm at a remote site over a 10-year period is estimated to be as high as 50%, thus mandating careful scrutiny of all patients upon initial encounter and lifelong surveillance after treatment.[69]

Pathogenesis

With the exclusion of trauma and rare congenital disorders, the majority of PAAs are considered to be true aneurysms, involving all layers of the arterial wall. Many writers in the past regarded PAAs as atherosclerotic, but most PAAs are degenerative. Jacob et al.[70] identified disruption and fragmentation of the elastic lamellae in the walls of PAA specimens in comparison with normal popliteal arteries. In addition, they identified decreased numbers of vascular smooth muscle cells in the walls and an increased expression of molecules linked to apoptosis. A significantly greater number of $CD68^+$ macrophages and $CD3^+$ T cells in the media of the PAA wall specimens were detected than in normal arteries. The researchers attribute the aneurysm formation to a loss of the mechanical integrity of the popliteal artery wall and the altered balance between the production and degradation of the vascular wall constituents.[70]

The anatomic location of the popliteal artery at a high flexion point and the encountered repetitive stresses of the artery in this location may be additional causative factors for PAAs.

Natural History

The mean growth rate for PAAs is 1.5 mm/year for PAAs smaller than 20 mm, 3 mm/year for PAAs 20 to 30 mm, and 3.7 mm/year for those larger than 30 mm.[71] Hypertension is the most common risk factor associated with increased PAA growth. In contrast to AAAs, PAAs rarely rupture, with a reported incidence of only 2.5%. In patients in whom rupture occurs, there is a very high rate of limb loss.[72] When PAAs are symptomatic, they more typically manifest as acute or chronic ischemia due to distal embolization or thrombosis. Although it may be difficult to determine the actual percentage of patients with PAAs who become symptomatic over time, several series of observed patients report a high incidence of thromboembolic complications. Szilagyi et al.[73] reported that over a 5-year period, only 32% of observed (nonoperated) patients with PAA remained without lower extremity complications. Dawson et al.[69] reviewed 71 PAAs, 25 of which were initially treated nonsurgically. Complications developed in 12 of the 21 asymptomatic popliteal aneurysms (57%) and in two of the four symptomatic aneurysms (50%). The probability of development of complications increased with time to 74% within 5 years. Lowell et al.[74] identified the presence of aneurysmal thrombus and poor distal runoff as risk factors for ischemic complications among asymptomatic PAAs.

Clinical Findings

Although a PAA may be found incidentally, more than half of patients with the lesions typically have symptoms at initial presentation.[75-78] Lower extremity ischemia is the most common presenting symptom. The ischemia is usually secondary to embolization or thrombosis, and patient symptoms can range from being essentially none or minimal claudication to acute limb-threatening ischemia. Patients may present with chronic ischemic symptoms similar to those of atherosclerotic occlusive disease when chronic emboli occlude the outflow vessels and collaterals develop prior to thrombosis of a PAA. It is not uncommon for patients to have occlusion of multiple tibial vessels secondary to chronic emboli. The patient with chronic symptoms and a nonpulsatile popliteal mass should be evaluated for a thrombosed PAA.

Less frequently, patients present with compressive symptoms, which may include vein (leg swelling, deep venous thrombosis) or nerve compression as a result of the mass effect associated with large aneurysms. Rupture is an unusual complication that occurs at a rate of 0% to 7% in published series,[1] with an average of about 2%. Patients with rupture most commonly are seen initially with severe swelling and pain in the popliteal space and distal limb edema. Approximately 14% have an associated popliteal vein thrombosis. Hemorrhagic shock is rare, probably because of containment of the hematoma by the small confines of the popliteal space.

Diagnosis

Ideally the diagnosis of PAA should be made before the onset of limb-threatening complications. The outcomes of surgical treatment are best in asymptomatic patients and progressively worse in those with either chronic ischemic symptoms or advanced acute limb ischemia.[7] The diagnosis of PAA is suspected any time a prominent or widened popliteal artery pulse is felt on physical examination, which is especially true if it can be easily felt with one hand. A PAA is more likely to be found in men with known AAA, femoral artery aneurysm, or contralateral PAA. Therefore special attention should be given to detecting possible PAAs in these patients. Likewise, a prominent popliteal pulse with gangrene of the ipsilateral foot in a nondiabetic man should trigger the diagnosis of possible PAA. A nonpulsating popliteal mass in a patient with ischemic symptoms should lead one to suspect a possible thrombosed PAA. Physical examination has, however, been proven unreliable, with both false-positive and false-negative results.[79]

Imaging

The main imaging modalities used for the diagnosis of PAA are DUS, CTA, and MRA. Occasionally a PAA can be seen on a plain radiograph as a radiopaque, calcified, enlarged aneurysm perimeter. Digital subtraction angiography (DSA) may identify a PAA, but its results can be misleading because of nonvisualization of mural thrombus or an overlooked thrombosed PAA. Although not a good first diagnostic test,

DSA can be very useful for planning of revascularization once the diagnosis is confirmed. Duplex ultrasound has the advantage that neither ionizing radiation nor contrast agents are required. It can be accurate in detecting PAA, thrombus burden, and patency of outflow vessels.[80,81] Duplex ultrasound is also useful in detecting PAAs when DSA reveals an occluded popliteal artery and PAA is suspected.

CTA is a very useful and accurate imaging modality for the diagnosis and evaluation of PAAs. Disadvantages include the use of ionizing radiation and intravenous contrast agent, which limits its use in patients with renal insufficiency and severe contrast allergy. CTA can accurately demonstrate the size, thrombus burden, and inflow and outflow vessels. It can also be extremely helpful in the planning of either open or endovascular repair of a PAA.

In addition to not utilizing radiation, MRA is a very accurate imaging modality for PAA. Its use is limited to patients without pacemakers and somewhat limited to those with advanced renal failure. MRA can give good information on the inflow and outflow vessels, as well as the thrombus burden, as long as the cross-sectional images are evaluated.

DSA is used in conjunction with the aforementioned radiologic examinations to determine inflow and outflow vessel patency and for operative planning. It is the "gold standard" for determining the status of the outflow vessels. In most institutions, CTA and MRA, particularly with three-dimensional reconstructions, may provide very accurate information about the runoff vessels. However, if there is any question about the outflow or distal perfusion, DSA should be obtained prior to any intervention.

Indications for Treatment

Although it is generally accepted that all symptomatic PAAs and those 2.0 cm or more in diameter should be considered for treatment in medically suitable candidates, some controversy exists. Treating asymptomatic patients with PAAs 2.0 cm or larger may be justified, given the associated 30% to 40% risk for development of acute ischemic complications and the subsequent high risk of limb loss.[1,73,82,83] Some writers suggest that all popliteal aneurysms should be repaired once found, regardless of size, because of the high complication and limb loss rates.[83-85] Ascher et al.[83] suggested, in a review of 34 popliteal aneurysms, that a higher incidence of embolic and thrombotic complications may be associated with smaller PAAs, although only two in their series were less than 2 cm in diameter. Those who advocate repairing all PAAs, regardless of size and before limb-threatening symptoms develop, quote high limb salvage and patency rates and low operative mortality for smaller, asymptomatic aneurysms.[8,74,78] Critical limb ischemia prior to intervention is associated with an up to three or four times higher perioperative mortality and considerably higher rates of limb loss.[75-77]

Other writers advocate that some asymptomatic PAAs can be safely observed.[86-89] Galland et al.[88] evaluated 95 popliteal PAAs. Of those that were asymptomatic, less than 3 cm, and without distortion, none became thrombosed. The presence of thrombus in a PAA, however, appears to increase the incidence of the development of symptoms and may raise expansion rates.[74,90]

The decision to treat a patient with a PAA must be individualized, with careful weighing of the risks and benefits of treating and observing. Treatment should generally be offered to the medically fit patient who has a symptomatic PAA or whose PAA is asymptomatic but is at least 2.0 to 2.5 cm in diameter and contains thrombus. In older patients with multiple comorbidities, observation of even a larger aneurysm may be warranted. Extensive thrombus or asymptomatic occlusion of tibial vessels may be indications for intervention. Chronically thrombosed PAAs associated with lifestyle-limiting claudication or limb-threatening ischemia may also need revascularization.

Elective Treatment

Once the decision has been made to treat the patient with a PAA, the preoperative evaluation involves ensuring that the patient's medical status is optimized and determining the operative approach. If indicated, beta blockers should be considered and statins should be added, ideally at least 1 month prior to the procedure.[91] The patient should be taking aspirin or some other antiplatelet agent.

Planning for surgery and deciding to proceed with an endovascular, open, or hybrid approach depends on the patient's anatomy, age, and comorbidities. The patient's arterial system should be imaged from the abdominal aorta down to the pedal vessels. If the preoperative imaging is not of sufficient quality, an angiogram should be performed. Options for elective repair of PAAs include an endovascular approach (purely percutaneous or hybrid with exposure of the femoral artery) utilizing an intraluminal stent-graft and an open approach utilizing an arterial bypass. It should be stated here that although endovascular repair of PAAs is being widely performed and reported on, no devices have been approved yet by the US Food and Drug Administration (FDA) for this particular procedure. Endovascular repair of PAAs is therefore considered an off-label use of a stent-graft.

Endovascular and Hybrid Treatment

Endovascular treatment has the benefit of not requiring general or regional anesthesia, and therefore the theoretical advantage of decreasing cardiac risk. The procedure can be performed either via either a percutaneous puncture or a small cutdown to expose either the SFA or CFA. If a cutdown is to be performed, SFA exposure is preferred because it is an easy dissection, the artery is usually fairly large in patients with PAAs, and direct access avoids the extra step of directing a wire into the vessel from the CFA. Anatomic selection criteria for endovascular repair of PAAs include a normal proximal and distal segment (landing zones) of at least 2 cm (without a large discrepancy in size between proximal and distal landing zones), lack of extensive vessel tortuosity, and an aneurysm that is not extremely large (which would make a stent-graft prone to kinking and displacement). Patients who frequently flex their knees to more

than 90 degrees, such as carpenters or people who garden, are usually excluded from endovascular repair of a PAA owing to the risk of stent deformation and thrombosis. In addition, if antiplatelet therapy is contraindicated, an endovascular approach is not recommended.

All patients are given a loading dose of clopidogrel and then maintenance doses, an approach that has been shown to be a predictor of success after endovascular PAA repair.[92] If there is no contraindication to the drug's prolonged use, clopidogrel is prescribed indefinitely. A minimum of 4 to 6 weeks of dual antiplatelet therapy is recommended in all cases. Unless there is a known hypercoagulable state, anticoagulation with warfarin is not routinely used. Patients with single-vessel outflow have been shown to have a statistically significantly higher stent-graft thrombosis rate than patients with two- or three-vessel outflow.[93] However, at present there are no data demonstrating improved patency in this subset of patients with the addition of warfarin therapy.

Procedure

For an endovascular approach, the Viabahn endoprosthesis (W.L Gore & Associates, Newark, Delaware) has been useful. It is made of polytetrafluoroethylene (PTFE) with a nitinol exoskeleton. The Viabahn is approved by the US Food and Drug Administration for treating arterial occlusive disease. The device is usually oversized to about 10% to 15% more than the internal diameter of the popliteal vessel above and below the aneurysm. Oversizing the graft much more than 15% is not recommended. Graft infolding and operative occlusion related to oversizing, requiring conversion to an open femoral-to-popliteal bypass, have been reported.[94] The vessel measurements can be based on preoperative imaging and checked with the intraoperative angiogram. Because the profile of the device has decreased, up to an 8-mm graft can be delivered via a 7-Fr sheath using an 0.018-inch guide wire. Therefore, in most cases, percutaneous common femoral artery access via an ipsilateral prograde or contralateral retrograde approach (over the iliac bifurcation) can be used. If a larger sheath is required (9- to 13-mm device requires a 9- to 12-Fr sheath and 0.035-inch guide-wire system) or if direct vessel exposure is desired, the superficial femoral artery can be easily exposed with the use of local anesthesia.

Once vascular access is obtained and the appropriate sheath is placed, an angiogram is performed. The proximal and distal landing zones as well as the runoff vessels are confirmed. The patient is systemically heparinized to an activated clotting time (ACT) exceeding 250 seconds. The PAA can then be carefully crossed, and the correct devices can be chosen on the basis of preoperative imaging and the intraoperative angiogram. A maximum of 1 mm of size differential between grafts is suggested if more than one stent-graft is required because of a discrepancy in proximal and distal landing zones. It is preferable to avoid landing the distal end of the graft at the bend of the popliteal artery, which is usually a few centimeters above the actual knee joint and can be located by performing an angiogram with the knee bent (Fig. 83.7).

Figure 83.7 Arteriogram With Knee Bent. *Arrow* points to the actual bend in the artery a few centimeters above the knee joint.

Some advocate routinely extending the stent-graft to the P3 segment of the popliteal artery to avoid having the distal end of the graft in a mobile segment of the popliteal artery.

The stent-grafts are deployed from small to large if more than one is needed, preferably starting most distally. Usually at least 2 or 3 cm of normal artery on either side of the aneurysm are preferable for landing zones. If more than one graft is required, minimum 2- to 3-cm overlap between stent-grafts is preferred. Each stent-graft is always molded with a balloon about the size of the graft. The balloon is inflated inside the stent-graft, and not in native artery, to avoid arterial dissection. A completion angiogram is performed, and runoff is assessed. An angiogram is performed again with the knee bent (Fig. 83.8). If the stent-graft ends on the bend of the popliteal artery, it is usually extended. The access site is either repaired open or through an access closure device, or direct manual pressure is held on the puncture site for 20 to 30 minutes after the activated clotting time is normalized (Box 83.1).

Open Treatment

The primary objective of the treatment of PAAs is to exclude them from the circulation while maintaining distal perfusion. In 1785 John Hunter ligated the popliteal artery of a coachman with a large popliteal aneurysm in the canal that now bears his name. Hunter correctly postulated that collateral circulation would maintain the viability of the limb.[95] In the modern era, arterial bypass with ligation or interposition grafting has replaced simple ligation and remains the gold standard for treatment.

As with any lower extremity arterial reconstruction, proper treatment requires careful planning and starts with a comprehensive arteriogram of the entire extremity from the groin to

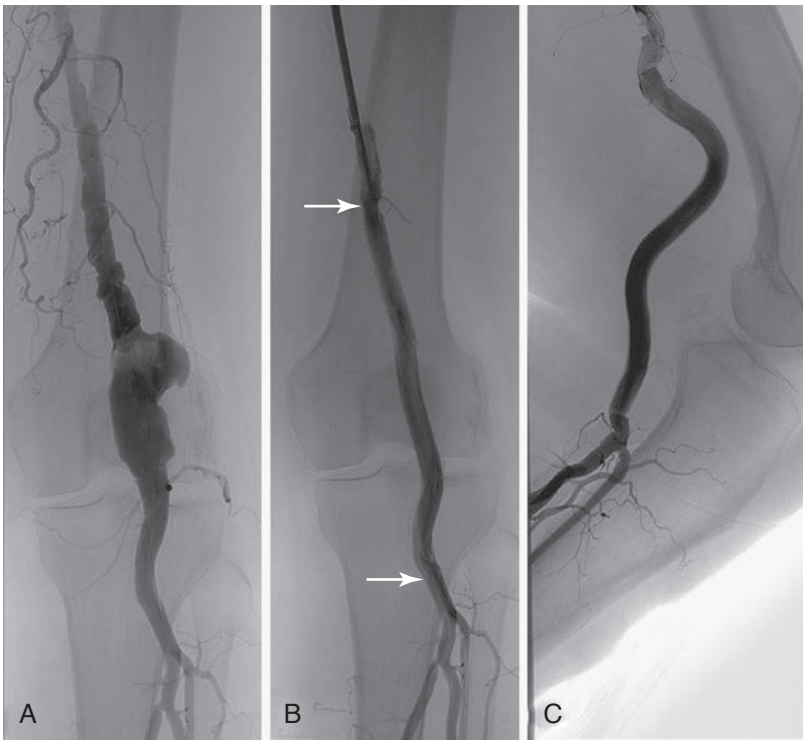

Figure 83.8 Endovascular Repair of a Popliteal Artery Aneurysm. (A) Initial arteriogram demonstrating that the aneurysm involves most of the above-knee popliteal artery. The below-knee popliteal artery is normal and will be the distal attachment site for the stent-graft, which necessitates crossing the knee joint with the device. (B) Completion arteriogram through the introducer sheath showing the stent-graft in place across the knee joint *(arrows).* (C) A lateral projection with the knee flexed 90 degrees demonstrates that the point of maximal flexion is actually proximal to the joint and does not result in kinking of the graft. Minimal bending and some posterior deflection of the graft are evident at the level of the articular surface of the joint (see text).

BOX 83.1 Steps in Deployment of an Endograft for a Popliteal Aneurysm

1. Pretreat with clopidogrel.
2. Perform femoral puncture with a delivery of an appropriately sized delivery sheath either via a contralateral approach over the bifurcation or via an ipsilateral approach into the superficial femoral artery. Ipsilateral superficial femoral artery cutdown may also be performed with direct puncture of the ipsilateral superficial femoral artery.
3. Heparinize to an activated clotting time of more than 250 seconds.
4. Cross the aneurysm into the distal popliteal artery or tibial vessels with a 0.035- or 0.018-inch wire, depending on the instructions for use of the device. Create a road map angiogram.
5. Deploy the graft from the distal to the proximal landing zone and overlap with additional grafts as needed. Post-dilate the entirety of the graft to "iron out" any kinks or stenoses.
6. Perform a completion angiogram to evaluate for endoleak and preservation of runoff without embolization. In addition, an angiogram with the knee in extreme flexion should be performed to identify potential areas of kinking. A fluoroscopic image should be saved as a baseline for assessing the structural integrity of the graft.
7. Prescribe clopidogrel to be taken postoperatively indefinitely.

the toes. Alternatively, this information can be obtained with MRA or spiral CTA, as previously described. Duplex ultrasound is used for screening and diagnosis and has a limited role in terms of anatomic imaging for bypass, although it is very useful for vein mapping in preparation for bypass. The information obtained from contrast-enhanced angiography or MRA is used to determine the location of the proximal and distal anastomotic sites. MRA and CTA can also provide information about the size, shape, and extent of the aneurysm, which is helpful in determining whether to use a medial or posterior approach. Small or fusiform aneurysms are best approached medially and treated with conventional bypass and aneurysm ligation. For a large, saccular aneurysm, particularly one with symptoms attributable to compression of adjacent structures, direct exposure from the posterior approach with interposition grafting from within the sac is preferable, unless the aneurysm extends too far proximally. The posterior approach is also advantageous for decompressing an aneurysm that has continued to enlarge after bypass and ligation because of backfilling from geniculate branches.

Medial Approach

For the medial approach, the patient is positioned supine and the saphenous vein is exposed as the first step, starting in the groin, midthigh, or ankle, depending on the procedure. Once the vein has been mobilized and harvested, the same incision can be used to expose the popliteal artery above and below the knee joint in a fashion identical to that used for femoropopliteal bypass. Similarly the same incision can be used to expose the posterior tibial and peroneal arteries. For the anterior tibial and pedal arteries, or if a lateral approach is planned for the distal peroneal artery, separate incisions are required. Arterial exposure of the above-knee or below-knee popliteal artery can be difficult with large aneurysms or in the presence of atriomegaly. Compression of the popliteal veins can lead to venous engorgement and venous hypertension. Extensive kinking, tortuosity, and lateral displacement, especially of the distal popliteal artery, can occasionally make exposure challenging. In cases of atriomegaly, even the inflow and outflow arteries may be unusually large,

making their separation from the adjacent structures more difficult. Vessels are isolated with conventional silicone rubber vessel loops. In most cases a tunnel is then created from the above-knee to the below-knee popliteal space between the heads of the gastrocnemius muscle. This maneuver may be difficult in patients with large popliteal aneurysms filling most of the popliteal space. Decompression of the aneurysm sac and endoaneurysmorrhaphy may be required before tunneling can be performed safely. The patient is administered intravenous heparin at a dose of 80 to 100 units/kg or at a dose to prolong the activated clotting time to 250 to 300 seconds.

Arterial bypass is performed in standard fashion with either an end-to-side or an end-to-end anastomosis. There is frequently a size discrepancy between the vein graft and the popliteal arteries, especially above the knee, thus making the end-to-side technique preferable. Either reversed or nonreversed vein grafts can be used, depending on surgeon preference and experience. In bypasses extending from the CFA to a distal tibial vessel, in situ bypass is an alternative. For occluded aneurysms, the procedure is conducted like any other lower extremity arterial bypass. If the aneurysm is patent, ligation must be performed in conjunction with the bypass procedure. The inflow and outflow arteries to the aneurysm sac should be ligated as close to the aneurysm as possible. In focal aneurysms confined to the proximal and mid popliteal artery, the aneurysm is ligated just distal to the proximal anastomosis and just proximal to the distal arterial anastomosis. If an in situ bypass to a more distal target is performed, separate exposure of the two points of ligation is required. The aneurysm should always be ligated both proximally and distally as close to the sac as possible to promote aneurysm thrombosis and decrease the likelihood of continued expansion from collateral filling. Jones et al.[96] demonstrated that proximal ligature alone or ligature of the inflow and outflow arteries performed remotely from the aneurysm sac increases the likelihood of continued aneurysm expansion.[96] Completion arteriography, angioscopy, or DUS is performed before closure.

The medial approach is the preferred technique for most popliteal aneurysm repairs and the only logical option for bypass grafts that must extend to the distal tibial or pedal vessels. The medial approach has the advantages of being familiar to all vascular surgeons and providing easy access to the entire great saphenous vein. Virtually all of the procedure is performed at some distance from the aneurysm, thus reducing the likelihood of operative injury to structures adherent to the surface of the popliteal aneurysm. The principal disadvantage of the medial approach is that it is generally used in conjunction with aneurysm ligation but without decompression. Numerous studies have shown that even with proximal and distal ligation, as many as 30% of aneurysms do not ultimately undergo thrombosis and may continue to enlarge if collateral blood flow into the aneurysm sac persists, in a situation analogous to that of a type II endoleak with endovascular aneurysm repair.[96-98] Continued expansion can result in pain, compression symptoms, and even rupture.[99] To avoid this problem, most writers are proponents of opening all but the smallest popliteal aneurysms in order to suture-ligate back-bleeding side branches. This can usually be done from the above-knee or below-knee popliteal space. A thigh tourniquet can decrease bleeding from collaterals once the aneurysm sac is opened.[7] In some cases it may be necessary to divide the tendon of the medial head of the gastrocnemius muscle to facilitate access to the popliteal aneurysm. After decompression the tendon can be reattached with a heavy-gauge monofilament suture. In our experience, this procedure rarely leads to disability.

Posterior Approach

The posterior approach is preferred for large aneurysms that are confined to the popliteal space and are causing symptoms from compression, or for those that have caused distortion and displacement of the normal anatomy as a result of tortuosity, elongation, and kinking. This is also an appropriate approach for a smaller aneurysm, but it is not applicable for aneurysms that extend proximally beyond the popliteal space.

The patient is placed prone. An S-shaped incision is made with the superior end starting on the medial side of the thigh to expose the proximal popliteal artery and great saphenous vein. The incision extends laterally across the flexion crease of the knee and ends on the lateral aspects of the proximal part of the calf, directly over the proximal small saphenous vein (Fig. 83.9). If the small saphenous vein is of adequate size for bypass, the incision can be continued for harvest of the vein. Alternatively, the great saphenous vein can be harvested relatively easily from the thigh with the patient prone. Preoperative vein mapping should always be performed before popliteal aneurysm repair to ensure that the vein is adequate in caliber or quality and to avoid unnecessary extension of the incision if it is not.

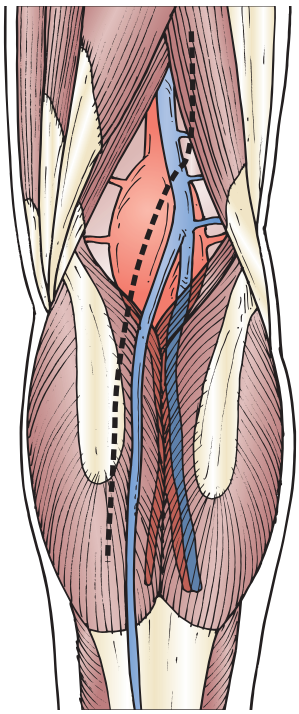

Figure 83.9 Placement of a "lazy S" incision for the posterior approach to a popliteal artery aneurysm. (From Ouriel K, Rutherford RB, eds. *Atlas of Vascular Surgery: Operative Procedure,* Philadelphia: WB Saunders; 1998.)

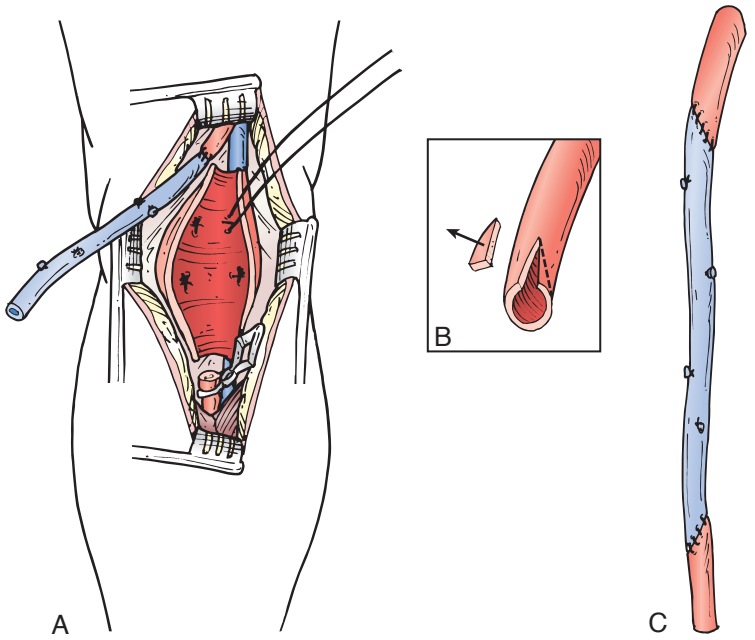

Figure 83.10 Posterior Approach. The aneurysm is opened, thrombus is removed, and the geniculate vessels are ligated, a procedure analogous to aortic aneurysm repair **(A).** A spatulated interposition bypass graft is then used to reconstruct the popliteal artery **(B,C).**

The proximal popliteal artery is identified by palpation distal to the adductor canal and exposed by separation of the semimembranosus and semitendinosus muscles located medially from the long head of the biceps femoris located laterally. Circumferential control is obtained with silicone rubber vessel loops. Dissection is continued distally on the anterior surface of the aneurysm sac to avoid injury to the tibial and peroneal nerves, which may be encountered coursing lateral and slightly posterior to the aneurysm. The distal popliteal artery is identified and circumferentially controlled. If exposure of the tibioperoneal trunk or proximal tibial vessels is required, access from this approach is possible, although the medial approach is preferable if tibial bypass is required.

After the administration of intravenous heparin, proximal and distal control is obtained and the aneurysm sac is opened. Thrombus is removed, and back-bleeding geniculate collaterals are oversewn from within, analogous to the approach used for aortic aneurysms. Circulation can be restored by either bypass or an interposition graft. If an interposition vein graft is planned, the graft can be beveled to facilitate end-to-end anastomosis to the transected popliteal artery (Fig. 83.10). Alternatively, a standard end-to-side bypass can be performed and is preferable when there is a significant size discrepancy between the popliteal artery and the bypass graft, which commonly occurs when vein conduit is used. For interposition prosthetic grafts, an end-to-end anastomosis can be created from within the aneurysm sac by application of the graft inclusion technique used for abdominal aortic aneurysm repair. This approach has the advantage of requiring less dissection of the popliteal artery. Some surgeons prefer the routine use of prosthetic conduits for the posterior approach because the diameter of the graft can be more closely matched to the diameter of the popliteal artery and the complications associated with vein harvest are avoided. Excellent short-term results with prosthetic popliteal bypass have been reported in some series, especially when outflow is good.[100]

Urgent/Emergent Repair

Approximately 30% of patients with popliteal aneurysms have acute ischemic symptoms at initial evaluation.[101] In patients who present with acute occlusion or symptomatic embolization, there is a high rate of limb loss.[75-77] In an acutely symptomatic PAA patient without motor or sensory deficits, preoperative imaging can be very useful. The patient should be admitted to the hospital and systemically heparinized. Either CTA or MRA can be used to evaluate the perfusion of the affected extremity and the outflow vessels. If the diagnosis of PAA is already made, angiography can be used in place of either of these tests; it can give additional information about the status of the runoff vessels. DSA is still considered the gold standard for evaluation of the outflow vessels. A treatment strategy can be formulated on the basis of the symptoms and the preoperative imaging. If there are no motor or sensory deficits, treatment can be delayed to allow for imaging and preoperative planning. The patient with neurosensory deficits should be taken directly to the operating room, ideally a hybrid operating room/angiosuite.

Open Approach

In a patient with a viable limb and no symptoms of sensory or motor dysfunction, intravenous heparin can be administrated to stabilize him or her. Arteriography and surgery are performed during the same admission. If the aneurysm is fully occluded and a patent distal outflow vessel is identified on arteriography, a vein bypass to the patent outflow vessel is performed as described previously. If no outflow vessel is identified and the patient's limb is not immediately threatened, intraarterial thrombolysis is started with the objective of restoring flow to potential outflow target vessels (see Endovascular Treatment—Thrombolysis).

In cases in which the patient's limb is immediately in jeopardy because of sensory and motor dysfunction, and there is no time

for thrombolysis, surgery should be performed immediately. If no outflow vessel was identified on the arteriogram, thromboembolectomy of the distal popliteal or tibial vessels (or both) should be attempted. Embolectomy or thrombectomy of the popliteal artery is relatively straightforward and best approached from the below-knee popliteal artery. For embolectomy of individual tibial arteries, blind passage of embolectomy catheters from the popliteal artery usually fails and is ill-advised. The region of the trifurcation of the popliteal artery should be exposed to gain access to all three arteries. A No. 2 Fogarty balloon embolectomy catheter can then be passed into each of the three tibial vessels. This must be done with utmost care to avoid potential intimal injury, perforation, and rupture. Alternatively, tibial vessels can be exposed at the ankle, and retrograde passage of Fogarty catheters attempted.[102] Bypass grafts can then be extended to this level via the same arteriotomy, or a vein patch angioplasty of the distal arteriotomy can be performed with bypass to the more proximal portion of the artery. Intraarterial thrombolysis in conjunction with bypass and embolectomy to further clear residual thrombus from the outflow vessels has been described in some cases.[103,104] After bypass, patients may exhibit signs of reperfusion injury, including rhabdomyolysis, and may require fasciotomy.

Endovascular Treatment—Thrombolysis

When studied with angiography, 25% to 45% of acutely ischemic patients have thrombosis of the aneurysm with either no visible runoff vessel or with severely compromised runoff thought to be unsuitable for bypass because of embolization. In these challenging cases, pre-bypass catheter-directed intra-arterial thrombolysis has been shown to be effective in improving the likelihood of limb. Considerable judgment is required to determine whether a patient is a suitable candidate for thrombolysis, and the need to delay surgery for 12 to 24 hours for the performance of thrombolysis must be taken into account. Moreover, the potential risk of serious or life-threatening bleeding complications must be considered, and it may vary from patient to patient. Ultimately the decision to perform thrombolysis must be individualized according to patient factors and clinical circumstances.

Traditional lysis is usually performed via a 6-Fr sheath placed in the contralateral CFA, over the bifurcation, and into the affected leg. One of the best predictors of success after lytic therapy is easy traversal of the thrombus. A 5-Fr lytic catheter can be placed in the thrombosed popliteal artery, and a lytic wire advanced through the lytic catheter into one of the tibial outflow vessels. Direct intraarterial lytic therapy can be begun with tissue plasminogen activator (t-PA) or other thrombolytic agent at equivalent doses. The patient is placed in a monitored setting (intensive care or postanesthesia care unit) during the infusion for careful monitoring. The infusion rate is typically 2 mg/h of t-PA or less, administered via the catheter and wire combined. Five hundred units of heparin are given via the 6F sheath to prevent thrombosis around the catheter. The t-PA is diluted to 25 mg in 500 mL to ensure sufficient volume via the catheters (20 mL/h = 1 mg/h). Partial thromboplastic time (PTT) and fibrinogen are checked every 3 to 4 hours. The PTT should be less than therapeutic to prevent bleeding complications (PTT < 50 seconds). As long as the fibrinogen level is above 200 mg/dL, lytic therapy is continued. If it drops below 200 mg/dL, the dose is halved and the drip is withheld until the fibrinogen drops below 150 mg/dL.

Angiography is performed again within 6 to 18 hours or earlier if required. On the basis of the angiographic findings and clinical scenario, either a bypass can be performed if a target vessel opens, lytic therapy can be continued, or the patient can undergo an attempt at urgent thrombectomy/bypass if the leg is acutely threatened. Alternatively, if the thrombus lyses and anatomy permits (as described earlier), and there is more than one outflow vessel, an endovascular stent-graft can be placed as previously described. As already mentioned, patients with PAAs and single-vessel outflows who are treated with endovascular stent-grafts have inferior patency rates.[93] A rheolytic percutaneous thrombectomy catheter may also be used to spray t-PA (10 mg t-PA in 100 mL) directly using the power-pulse spray technique into thrombus, and the catheter can then help to debulk the thrombus prior to initiation of a lytic drip as described.

Results

Several series have demonstrated the value of preoperative thrombolysis started at the time of diagnostic arteriography for improving outflow before bypass in 29% to 45% of patients with acute ischemia.[7,101,105-107] Marty et al.[108] found that thrombolysis restored one- or two-vessel runoff in 77% of cases and predicted short- and long-term limb salvage, whereas failure of thrombolysis resulted in the need for amputation. In the series by Aulivola et al.,[101] 13 patients had acute ischemia. In the emergency group, the cumulative primary and secondary patency rates were 85% and 100% at 1 and 5 years, respectively. In the four patients who underwent thrombolysis, none required amputation. Tibial or pedal arteries were the outflow artery in 57% of the bypasses performed in the emergency group. In another series from the Mayo Clinic, of the 74 patients with an acute manifestation, 38 underwent thrombolysis, 24 preoperatively and 14 during surgery.[7] Thirty-day results were 94% primary patency and 91% limb salvage for patients who underwent lysis, and 87% primary patency and 92% limb salvage for those who did not. Preoperative thrombolysis appeared to reduce the amputation rate from 96% to 69% in the group of patients presenting with severe critical limb ischemia.

The largest report on thrombolysis for popliteal aneurysms comes from the Swedish Vascular Registry, which included treatment of 717 limbs for popliteal artery aneurysms over a 15-year period.[103,109] Acute ischemia was present in 235 limbs, 100 of which (43%) were treated by preoperative thrombolysis, whereas 135 other limbs went directly to surgery. In the immediate surgery group, 32 limbs underwent intraoperative thrombolysis. On the basis of review of preoperative and postoperative arteriograms, thrombolysis significantly improved runoff in 87% of limbs and remained unchanged in 13%, all of which ultimately required amputation.

Intraarterial thrombolysis can uncover outflow target arteries suitable for bypass, thereby improving the chance of limb salvage.

However, the decision to use thrombolysis in cases of critical ischemia is never straightforward and must be individualized to the specific clinical situation. If surgeons do not possess the requisite endovascular skills and expertise to perform it themselves, they must have the immediate support of a committed interventionalist. The importance of adhering to the principles of treatment of acute limb ischemia must be remembered; most important is that any patient in whom the use of thrombolysis is being considered must be able to withstand another 12 to 18 hours of ischemia. It should never be used in marginally viable or nonviable limbs or in patients with specific contraindications to its use.

Hybrid Approach

It is not uncommon for a combination of the aforementioned endovascular and open techniques to be used for emergency cases, which should ideally be performed in a hybrid operating room with optimal angiographic equipment and operative capability. Open thrombectomy can be performed via the below-knee popliteal artery if intraoperative lysis is not successful or the patient's symptoms would not allow for the time that it takes for the lytic therapy to work. Likewise, if open thrombectomy is not successful, intraoperative lytic therapy and pharmacomechanical thrombectomy can be attempted.

If distal tibial thrombus remains after open thrombectomy and the below-knee popliteal artery is patent, a below-knee bypass can be performed. A 4-Fr sheath is placed percutaneously and then into the bypass graft. A lytic wire can be advanced into the tibial outflow vessel for further lytic therapy.

A 1 mg of t-PA diluted in 10 cc therapy may be injected as a pulse spray in the vessel and then continued at a low dose. Alternatively the t-PA is just started without a pulse spray dose, keeping the dose fairly low (0.5 to 1 mg/h) to avoid bleeding from surgical sites.

The t-PA dose is kept fairly low in this circumstance because bleeding can be encountered from the surgical sites. The patient is taken back to the operating room for a second angiogram and removal of the catheter/repair of the graft.

Results: Open Versus Endovascular Repair

The results of both open repair and endovascular repair of PAAs are somewhat dependent on the severity of the patient's symptoms upon presentation, with the most symptomatic having the worst outcomes.[75-77]

Pulli et al.[106] give support to this assumption in their review of 159 PAAs in 137 patients treated surgically. Asymptomatic limbs had significantly better results than symptomatic ones in terms of limb salvage (93% vs. 80%) and primary patency (87% vs. 52%). Patients who presented with critical limb ischemia had a low 5-year limb salvage rate—only 59%. Likewise, Huang et al.[7] reported on 289 patients with PAAs treated with open repair with a mean follow-up of 4.2 years. They divided the patients into three groups: group 1 consisted of 144 (40%) patients with asymptomatic limbs, group 2 of 140 patients (39%) with chronic symptoms, and group 3 of 74 patients (21%) with acute ischemia. Early mortality was 1% (3/358), all in group 3 (4% [3/74]). All six early amputations (8%) were also in group 3. In addition, six out of seven patients with perioperative myocardial infarctions were in group 3 (8%). Overall, 5-year primary and secondary patency rates were 76% and 87%, respectively. The overall 5-year limb salvage rate was 97% (85% in group 3).

Endovascular repair of PAAs overall has been shown to be relatively safe with patency rates approaching those of open repair in patients who have appropriate anatomy. We earlier reported on the endovascular treatment of PAA on 26 limbs in 21 patients.[93] Primary and secondary patency rates were both 91% at 1 year and 86% and 91%, respectively at 2 years. Single-vessel runoff was the only significant predictor of graft failure. Mohan et al.[110] reviewed 35 PAAs treated with stent-grafts. They found 3-year primary and secondary patency rates to be 75% and 83%, respectively. In a review of 73 PAAs treated with stent-grafts, a follow-up report by Tielliu et al.[111] after their original study found 5-year primary and secondary patency rates of 70% and 76%, respectively. When analyzing the later cases, they found that with more experience and the addition of clopidogrel, the 5-year primary patency increased to 80%. Jung et al.[112] performed a retrospective review of 15 PAAs treated with stent-grafts that had long-term follow-up (mean, 54 months). Primary and secondary patency rates were 85% and 100%, respectively. Two patients experienced endoleaks, which were successfully treated with additional stent-grafts. Both amputation-free survival and overall survival were 86% by Kaplan-Meier analysis.

Antonello et al.[113] reported one of the first prospective randomized trials comparing open and endovascular PAA repair. This trial, however, included only 30 patients, 15 in each group. These investigators did not find a statistically significant difference in patency or limb salvage rates, with a follow-up period of up to 4 years. As would be expected, they did find a statistically significant decrease in operative time and length of stay in the hospital for the endovascular group. Lovegrove et al.,[114] in a meta-analysis comparing open with endovascular repair of PAAs, reported similar results with no significant difference in long-term patency rates; however, patients who underwent endovascular repair were more likely to have graft thrombosis and reintervention at 30 days than those who had open repair. They also reported significantly shorter lengths of hospital stay and shorter operative times with endovascular repair.

A retrospective review by Curi et al.[115] of 56 PAA repairs, in which open and endovascular treatments were compared, demonstrated no significant difference in primary patency, secondary patency, or survival rates between the two treatment groups (Fig. 83.11). All urgent cases, however, were treated with open repair, and endoleaks developed in 20% of the patients undergoing endovascular repair.

Lastly, a 2015 consecutive cohort of patients undergoing either open or endovascular repair of PAAs was retrospectively reviewed by Leake et al.[116] They reviewed 186 PAAs (110 open and 76 endovascular). Open repair was associated with a longer hospital stay (5.8d vs. 1.6d; $P < .001$) and increased 30-day complication rate (22% vs. 6%; $P < .001$). While open repair is associated with a better 3-year primary patency rate (88.3%

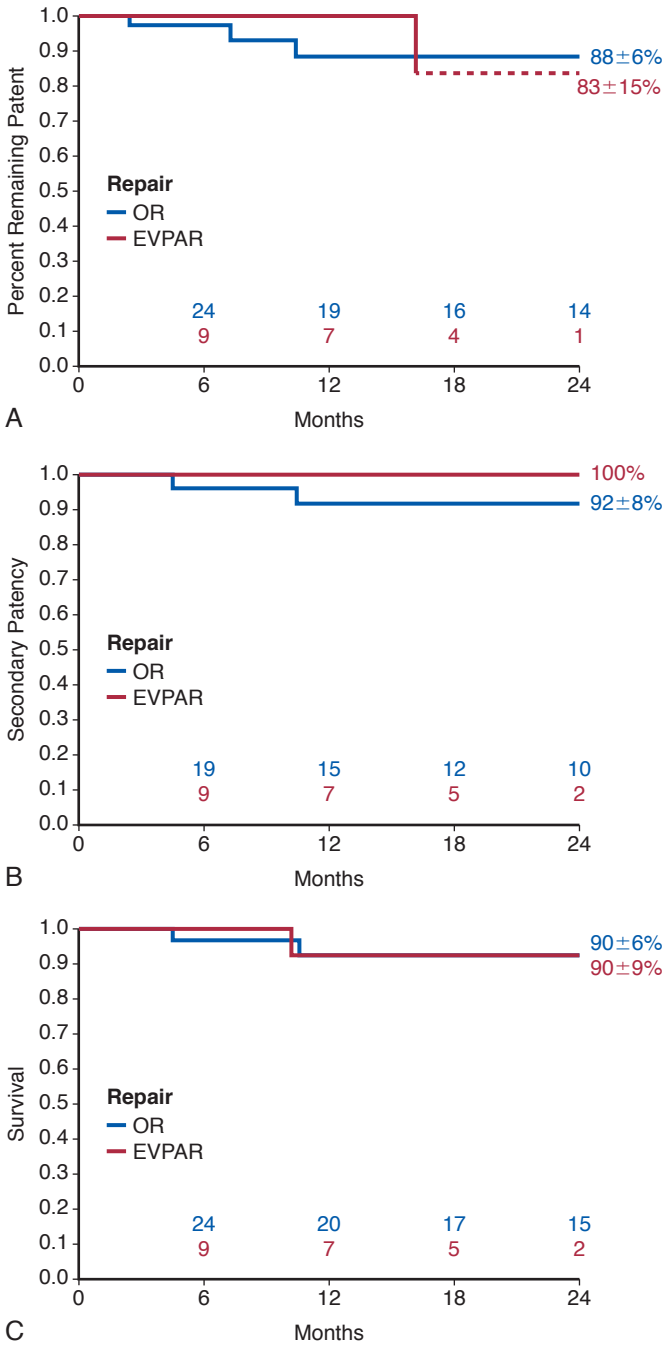

Figure 83.11 Rates of primary patency (A) and secondary patency (B) and survival (C) after open repair *(OR)* versus endovascular repair *(EVPAR)* of popliteal artery aneurysms and Kaplan-Meier analysis of patient survival after undergoing open repair versus endovascular repair of popliteal artery aneurysms. (From Curi MA, Geraghty PJ, Merino OA, et al. Mid-term outcomes of endovascular popliteal artery aneurysm repair. *J Vasc Surg.* 2007;45:505-510.)

vs. 69.8%; P = .03), there was no difference in secondary patency or amputation rates.[116]

CONCLUSION

Although PAA is a relatively uncommon disease, its presence has the potential to put the limb at risk. Once suspected, it should be fully evaluated. PAAs that are larger than 2 to 2.5 cm

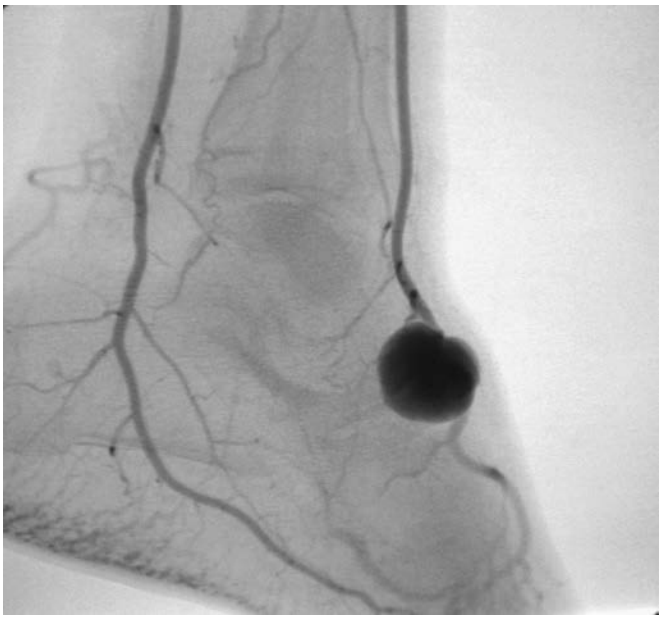

Figure 83.12 Aneurysm of the dorsalis pedis artery without prior trauma manifested as a pulsatile mass on the dorsum of the foot. It was treated with excision and ligation. Arterial flow to the foot was maintained by the patent posterior tibial artery and intact pedal arch.

and symptomatic in any way should be considered for repair in medically fit patients. Although endovascular repair of PAAs has been shown to decrease length of hospital stay and operative morbidity, data are somewhat varied as to its durability in comparison with open repair. In addition, endovascular devices for PAA repair are yet to be approved by the US Food and Drug Administration. On the basis of current literature, endovascular repair in general should be reserved for patients who have good anatomy (as described earlier), who do not frequently bend their knees more than 90 degrees, and who can take clopidogrel for a minimum of 4 to 6 weeks. The decision to perform open or endovascular repair should be individualized and should involve a clear discussion between the treating physician and the patient.

TIBIAL ARTERY AND PEDAL ARTERY ANEURYSMS

True aneurysms of the tibial and pedal arteries are rare, and their description in the literature has been limited primarily to case reports.[117-119] They most commonly occur in the setting of penetrating trauma, fractures, or iatrogenic injury during orthopedic surgery or peripheral interventions.[120] In addition, they can occur as a result of thromboembolectomy of the tibial vessels with balloon catheters.[121] Symptomatic aneurysms should be repaired with autologous vein bypass grafts if there is distal ischemia.[117,119] If other tibial arteries are patent, treatment with simple ligation will suffice (Fig. 83.12). Coil embolization has been reported as an effective treatment of tibial artery aneurysms, and observation with spontaneous thrombosis of small pseudoaneurysms has also been described.[122,123]

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84 CHAPTER

Upper Extremity Aneurysms

M. SHADMAN BAIG and CARLOS H. TIMARAN

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Upper extremity aneurysms are uncommon relative to other peripheral arterial aneurysms.[1] Arch vessel aneurysms, the most frequent type of upper extremity aneurysm, can lead to life-threatening exsanguination as a result of rupture, as well as numerous other complications, including stroke, local nerve compression (leading to hoarseness or brachial plexus palsy), and dysphagia from esophageal compression in cases of an aberrant right subclavian artery (ARSA) aneurysm, localized pain, or limb ischemia. More distally located upper extremity aneurysms are manifested almost exclusively by thromboembolic complications of the hand and digits.

The earliest reported attempts at surgical correction of arch vessel aneurysms were common carotid aneurysm ligations by Astley Cooper in 1805 and 1808,[2] followed by ligation of the innominate artery by Valentine Mott in 1818 for the treatment of a subclavian artery aneurysm.[2,3] Mott's patient expired within 1 month as a result of hemorrhage from the necrotic aneurysm. The first successful treatment of a subclavian artery

Abstract

Arch vessel aneurysms are the most frequent type of upper extremity aneurysms that may result in rupture or other complications, including stroke, local nerve compression, dysphagia from esophageal compression or limb ischemia. More distally located upper extremity aneurysms are manifested almost exclusively by distal thromboembolic complications. True subclavian aneurysms are usually degenerative and are the most common type of arch vessel aneurysm.

Aneurysmal degeneration of the aberrant right subclavian artery usually affect adults older than age 50 years. The majority of these require intervention, owing either to symptoms or to the risk of rupture. Degenerative aneurysmal changes may occur in up to 60% of patients in the proximal portion of the aberrant subclavian artery, a condition known as Kommerell's diverticulum.

Axillary artery aneurysms are rare and usually caused by blunt or penetrating trauma. Aneurysms of the brachial artery are primarily false aneurysms secondary to repetitive trauma, or iatrogenic complications. More recently, brachial artery aneurysms associated to the creation of arteriovenous access for hemodialysis have increasingly been reported.

Although open repair has been the main treatment modality of upper extremity aneurysms, endovascular therapies are increasingly been used alone or as hybrid repairs. Early results demonstrate safety and effectiveness of these therapies as well as decreased periprocedural morbidity and mortality. Long-term outcomes and the need for surveillance and secondary interventions remain to be established and warrant further investigations.

Keywords

upper extremity aneurysms
arch vessel aneurysm
subclavian artery aneurysm
innominate artery aneurysm
aberrant right subclaviar artery aneurysm
Kommerell's diverticulum
axillary artery aneurysm
brachial artery aneurysm

aneurysm was achieved in 1864 by Smyth in New Orleans, who ligated the right common carotid and innominate artery.[4] The aneurysm recurred and ruptured 10 years later. Halsted was the first to combine ligation successfully with resection of a subclavian artery aneurysm in 1892 at the Johns Hopkins Hospital.[5] In 1913 Matas reported 225 cases of aneurysms treated by endoaneurysmorrhaphy, and seven of these were subclavian aneurysms.[6]

ARCH VESSEL ANEURYSMS

Epidemiology and Etiology

Innominate, common carotid, and subclavian artery aneurysms usually arise from degenerative disease. In a series of 74 patients with arch vessel aneurysms, Cury et al. reported that 63% were degenerative in nature with the vast majority in men older than 60 years.[7] Less commonly, these aneurysms can also result from trauma, fibromuscular dysplasia, syphilis, cystic medial necrosis, vasculitis, invasion of the vessel wall by contiguous tuberculous lymphadenitis, and idiopathic congenital causes. Although only 1% of all peripheral arterial aneurysms involve the subclavian and innominate arteries, 30% to 50% of patients with nonspecific, degenerative arch vessel aneurysms have aortoiliac or other peripheral aneurysms.[8,9] Patients presenting with these aneurysms should therefore be evaluated thoroughly for concurrent aneurysms.

Aneurysms of the distal subclavian artery, frequently with extension into the first portion of the axillary artery, are usually associated with a thoracic outlet obstruction, cervical rib, and other bony abnormalities that result in arterial compression and poststenotic dilation. This specific type of aneurysm is discussed in Chapter 122.

Subclavian Artery Aneurysms

True subclavian aneurysms, typically seen in older adult patients, are usually degenerative and are the most common type of arch vessel aneurysm, accounting for 50% of the cases in the two largest series reported.[7,10] Pairolero et al.[8] reported the treatment of 31 patients with subclavian artery aneurysms treated over a 20-year period. True degenerative aneurysms were repaired in 12 patients, traumatic pseudoaneurysm in 10, and aneurysms secondary to thoracic outlet obstruction in 6. McCollum et al.[9] also reported their 25-year experience with subclavian artery aneurysm repairs, which included 15 patients, more than half of whom had true degenerative aneurysms. More recently, Naz et al.[11] reported their series of 10 patients of whom five were traumatic in origin, four were related to thoracic outlet syndrome, and only one was degenerative. Pseudoaneurysms frequently occur as a result of blunt and penetrating trauma. Iatrogenic injury from inadvertent cannulation of the subclavian artery with pseudoaneurysm formation is uncommon but increasing in frequency due to subclavian vein catheterization for various indications.[12,13] Although many small-caliber (<7 F) misplaced catheters can be removed and simple compression applied, removal of larger catheters, such as those used for hemodialysis, can lead to significant hemorrhage or pseudoaneurysm formation because of an inability to compress the puncture site beneath the clavicle. Recent reports have described the successful use of endovascular techniques to repair arterial injuries occurring during central venous access using endografts or percutaneous closure devices.[12,14-17]

Innominate Artery Aneurysms

True aneurysms of the innominate artery are rare, representing 2% to 5% of cases of arch vessel aneurysms. Bower et al.[10] reported their 40-year experience, which included only four patients with true aneurysms of the innominate artery among 73 patients treated surgically for brachiocephalic aneurysms. Similarly, in the series reported by Cury et al.,[7] 2 out of 74 surgically treated supraaortic aneurysms were of the innominate artery. As is the case with subclavian artery aneurysms, iatrogenic pseudoaneurysms after inadvertent arterial puncture during central venous access have recently been reported.[18] The largest series of innominate aneurysm repair is by Kieffer et al.,[19] in which they found six degenerative aneurysms among 27 patients with innominate artery aneurysms. Other etiologies included mycotic, dissecting, and connective tissue disorders, extension of arch aneurysms, and traumatic and iatrogenic pseudoaneurysms. Because of the devastating consequences of untreated innominate artery aneurysms, Bower et al.[10] have recommended operative treatment of all symptomatic and asymptomatic affected patients fit for surgical repair to avoid the natural history that inevitably leads to rupture or thromboembolism.

Common Carotid Artery Aneurysms

True aneurysms of the common carotid arteries are very rare. In fact, pseudoaneurysms of the carotid arteries are considerably more frequent and usually result from complications of carotid reconstructions, blunt or penetrating trauma, carotid dissections, or infection.[20,21] The vast majority of the true aneurysms of the carotid arteries are degenerative[22]; other less frequent causes include fibromuscular dysplasia, Marfan syndrome, Behçet disease, and Takayasu arteritis.[20,23] Bilateral common carotid artery aneurysms are extremely unusual, generally associated with Takayasu arteritis or Cogan syndrome.[24,25] Carotid bifurcation and internal carotid artery aneurysms are discussed in Chapter 94.

Clinical Presentation

Symptoms

Given the prevalence of imaging in modern medical practice, most arch vessel aneurysms are discovered incidentally and only 25% demonstrate symptoms at the time of diagnosis.[8] Presenting symptoms include (1) chest, neck, and shoulder pain from acute expansion or rupture; (2) upper extremity acute and chronic ischemic symptoms from thromboembolism; (3) upper extremity pain and neurologic dysfunction from brachial plexus compression; (4) hoarseness from compression of the right recurrent laryngeal nerve; (5) respiratory insufficiency from tracheal compression; (6) transient ischemic attacks and stroke

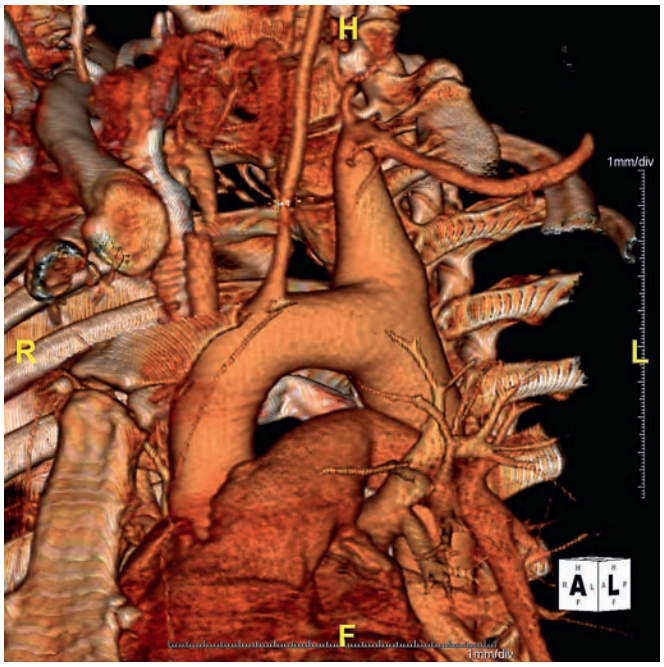

Figure 84.1 Three-dimensional computed tomography reconstruction of an aortic arch demonstrating an isolated aneurysm of the proximal left subclavian artery involving the aortic origin.

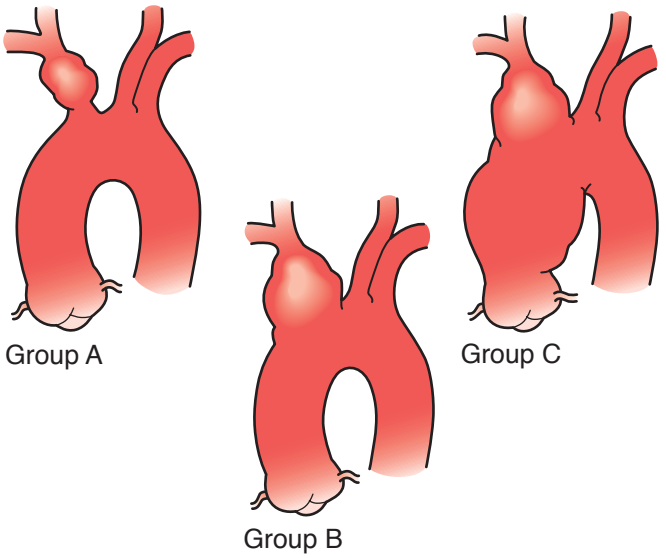

Figure 84.2 Classification of aneurysms of the innominate artery according to extent of involvement. (A) *Group A*, no involvement of origin of the innominate artery. (B) *Group B*, involvement of origin of the innominate artery but not of aorta. (C) *Group C*, involvement of innominate artery and aorta. (From Kieffer E, Chiche L, Koskas F, et al. Aneurysms of the innominate artery: surgical treatment of 27 patients, *J Vasc Surg*. 2001;2:222.)

from thromboembolism in the vertebral and carotid circulations; (7) dysphagia from esophageal compression in cases of aberrant right subclavian artery; and (8) hemoptysis from erosion into the apex of the lung. Tracheobronchial or esophageal fistulization from contiguous arch vessel aneurysms can also occur. In the case of iatrogenic pseudoaneurysms, clinical presentation includes a pulsatile mass, airway or nerve compression, chest pain, upper limb ischemia, or hemodynamic instability.[26]

Signs

Patients without symptoms may be diagnosed through imaging studies for unrelated conditions (Fig. 84.1). In cases of subclavian artery aneurysms, patients may note the presence of a supraclavicular pulsatile mass. However, most asymptomatic pulsatile masses in this area represent tortuous and elongated common carotid and subclavian arteries and not necessarily aneurysmal degeneration. Other physical signs may include (1) a supraclavicular bruit, (2) absent or diminished pulses in the upper extremity, (3) normal pulses with signs of microembolization ("blue finger" syndrome), (4) sensory and motor signs of brachial plexus compression, (5) vocal cord paralysis, and (6) Horner syndrome resulting from compression of the stellate ganglion and other contributions to the cervical sympathetic chain at the base of the neck.[27]

Imaging

Plain films of the chest may reveal a superior mediastinal mass that may suggest the presence of a neoplasm. Ultrasonography, MR, or CT imaging establishes the diagnosis. Conventional arch and upper extremity angiography, or MR or CT angiography (CTA) are important to delineate the extent of the aneurysm, to assess the sites of vascular occlusion in cases complicated by thromboembolism, to note the competency of the contralateral vertebral circulation if the ipsilateral vertebral artery originates from an aneurysmal vessel, and to assess anatomic suitability for endovascular repair. These points are essential in planning appropriate management (i.e., surgical reconstruction or endovascular repair).

Open Surgical Repair

Contemporary surgical repair of arch vessel aneurysms involves resection or endoaneurysmorrhaphy and reestablishment of arterial continuity with an end-to-end anastomosis (for very small aneurysms) or, more commonly, an interposition arterial prosthetic graft. Although proximal and distal ligation of arch vessel aneurysms occasionally has been successful in the past, ligation without direct or extraanatomic reconstruction generally should not be performed because ischemic symptoms develop in 25% of cases so treated.[8]

Innominate Artery Aneurysms

An anatomic classification of the extent of the aneurysm has been proposed by Kieffer et al.[19] to guide the surgical repair of aneurysms of the innominate artery (Fig. 84.2). Type A is confined to the innominate artery distal to its origin. Type B is the most common and involves the innominate artery and its origin, whereas type C involves both the innominate artery and the ascending aorta. The innominate and proximal right subclavian arteries are usually exposed through a median sternotomy extended into the right neck. Proximal control of the innominate is obtained at the aortic arch. The right subclavian and right common carotid arteries are exposed and dissected for distal control. The aneurysm is resected, and reconstruction with a prosthetic graft is usually performed. For type A and B

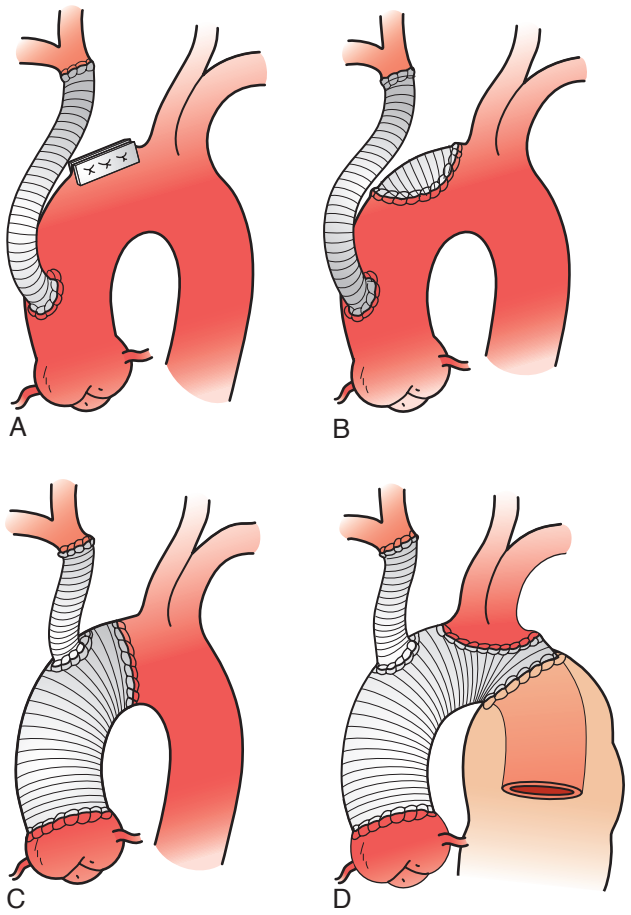

Figure 84.3 Techniques used for treatment of aneurysms of the innominate artery. (A) Lateral suture of aorta. (B) Patch angioplasty of aorta. (C) Replacement of ascending aorta. (D) Replacement of ascending aorta and transverse aortic arch in association with distal elephant trunk prosthesis. (From Kieffer E, Chiche L, Koskas F, et al. Aneurysms of the innominate artery: surgical treatment of 27 patients, *J Vasc Surg*. 2001;2:222.)

aneurysms, the proximal graft anastomosis is usually performed to the native ascending aorta proximal to the innominate origin. The graft is then anastomosed to the uninvolved distal innominate artery (Fig. 84.3). The origin of the innominate artery is oversewn with a running suture, or patch angioplasty of the aorta may occasionally be required. For lesions extending into the origins of the right subclavian or common carotid artery, a bifurcated graft can be used, or a branch graft to the subclavian artery can be sewn onto the graft going into the common carotid artery. The bifurcated configuration may sometimes be prone to compression or kinking when the sternum is closed, so caution should be taken to perform the proximal anastomosis in the lateral aspect of the ascending aorta. In cases of a bovine arch, additional graft reconstruction of the left common carotid artery may be necessary. Type C innominate artery aneurysms usually require aortic arch and innominate artery prosthetic graft replacement using cardiopulmonary bypass and hypothermic circulatory arrest.

Subclavian Artery Aneurysms

Subclavian artery aneurysms can be divided into proximal, typically degenerative, or distal, usually related to thoracic outlet syndrome. For proximal right subclavian aneurysms, median sternotomy with extension into the supraclavicular fossa is usually necessary to gain adequate exposure for proximal control. Supraclavicular and infraclavicular incisions may be used to mobilize the proximal and distal subclavian artery. Resection of the clavicle also offers excellent exposure of the subclavian artery. Partial medial clavicular resection is rarely necessary, although it may be helpful for proximal subclavian artery exposure when median sternotomy is not feasible. The supraclavicular incision is extended medially, and the fascia and periosteum are incised. The origins of the sternocleidomastoid and pectoralis major muscles are reflected subperiosteally, the first superiorly and the second inferiorly. The medial third of the clavicle is disarticulated and subperiosteally resected with care to avoid injury to the subclavian vein. In cases of proximal left subclavian aneurysms a left thoracotomy combined with supraclavicular exposure may be necessary.

Extraanatomic reconstruction combined with proximal and distal aneurysm ligation has also been described in unusual circumstances.[28] For aneurysms involving the midsubclavian artery and the distal subclavian artery, a supraclavicular incision often gives adequate exposure and may be complemented by an infraclavicular incision for distal control. Alternatively, proximal and distal control may be obtained endovascularly using balloon occlusion catheters placed angiographically. Division or resection of the midportion of the clavicle may be necessary to gain additional exposure; if so, the clavicle may be reconstructed at the completion of the operation. If the aneurysm involves the origin of the vertebral artery, reconstruction by reimplantation or other means is appropriate, particularly if this is the dominant vertebral artery or for cases in which the contralateral vertebral artery is hypoplastic or diseased.

Results

Aneurysm resection with graft replacement is durable and yields excellent long-term results. In one of the largest reported series, normal upper extremity circulation was maintained and there were no procedure-related complications during a mean follow-up of 9.2 years.[8] Although open repair frequently results in durable and excellent long-term outcomes, considerable associated morbidity and mortality has been reported. In-hospital mortality could be as high as 11% according to a report of open repair of innominate artery aneurysms, in which 18% of patients required prolonged ventilation.[19] Because many patients with true aneurysms are unfit for open repair because of their advanced age and multiple comorbidities, careful patient selection is mandatory to improve outcomes. Relative contraindications to open repair also include severely compromised pulmonary function, prior sternotomy or left thoracotomy, and hemodynamic instability secondary to multiple trauma.

Endovascular Repair

Endovascular repair is an attractive option for patients unfit for open repair because it is associated with lower morbidity and mortality. Many reports of endovascular repair of arch vessel aneurysms, particularly those involving the innominate

and the subclavian artery, have been published in recent years.[26,29-34] This has led to treatment of better-risk patients with appropriate anatomy, to avoid the morbidity of open surgery. Aneurysms secondary to connective tissue disorders may also be more suitable for endovascular repair to avoid direct resection and anastomoses to diseased vessels, although long-term outcomes are not known.[35]

Anatomic Considerations

The proximal portion and midportion of the subclavian artery are most amenable to endovascular treatment. However, several anatomic limitations exist. It is unusual for true subclavian or innominate aneurysms to have adequate proximal and distal landing zones. Also, coverage of branch vessels, such as the right carotid, vertebral arteries, and left internal mammary when it has been used for coronary bypass, may not be feasible. Endografts crossing the first rib may be subject to extrinsic compression. The distal subclavian artery is located between the clavicle and the first rib, and endografts in this location are subject to compression, deformation, and fracture.[35-38] Another potential complication of endograft placement in the right subclavian artery is stroke from embolic debris dislodged into the right common carotid artery.[35] The vertebral artery origin is vulnerable on both sides and may be covered during stent-graft deployment. This usually is well tolerated when the contralateral vertebral artery is patent and of adequate size. However, posterior circulation stroke may occur when the contralateral vertebral artery is highly stenotic, hypoplastic, or occluded. In this circumstance, the ipsilateral vertebral artery should be revascularized by end-to-side anastomosis to the common carotid artery or other means. Whenever the origin of the vertebral artery is involved by the aneurysm, coil embolization of the ipsilateral vertebral artery is desirable to prevent future branch vessel endoleaks.

Technique

Endovascular repair of subclavian or innominate artery aneurysms is usually performed through a transbrachial or transfemoral approach. A transaxillary approach has occasionally been necessary.[39] Both balloon-mounted and self-expandable endografts have been used off label for endovascular repair of arch vessel aneurysms.[40] The most frequently used endografts include the Wallgraft (Boston Scientific, Natick, Massachusetts), Viabahn (W.L. Gore & Assoc, Flagstaff, Arizona), or Fluency (C.R. Bard, Inc, Murray Hill, New Jersey).[41] Most contemporary endografts usually require 7 to 9 F delivery sheaths, depending on endograft diameter. However, larger endografts, such as those required for endovascular repair of innominate artery aneurysms, require still larger introducer sheaths, usually 11 or 12 F. The more flexible Viabahn endograft may be more suitable in cases of considerable arterial tortuosity. Lower-profile devices, such as the balloon-mounted iCast endograft (Atrium Medical, Hudson, New Hampshire), which is currently available up to 10 mm in diameter, can be delivered through a 7-F sheath. Of note, the largest iCast endograft can potentially be dilated up to 14 mm in diameter. Because of discrepancy in proximal and distal landing zone diameters, a combination of endografts of different sizes may be necessary. Furthermore, given the rigidity of balloon-mounted endografts, these may be used for accurate proximal deployment at the level of the ostium of the vessel and combined with more flexible distal self-expanding endografts. A novel approach is the use of multilayer stents to cause aneurysm thrombosis while maintaining flow through branch vessels.[42] Although technically feasible, mid- and long-term results of these techniques have yet to be reported to accept them as valid alternatives for the treatment of aneurysms.

Hybrid Operations

In this minimally invasive approach, embolization with coils or a vascular plug of a proximal subclavian artery aneurysm (not involving the origin) is combined with subclavian artery transposition or carotid-subclavian bypass, avoiding placement of an endograft.[43] Complete exclusion of the subclavian aneurysm is facilitated by ligation of the subclavian artery proximal to the distal anastomosis of the carotid-subclavian bypass. These procedures can be staged or combined in an operating room equipped with high-resolution imaging equipment. As with endograft placement, care must be taken to preserve the vertebral artery, if the contralateral vertebral artery is inadequate, and the left internal mammary when it has been or is anticipated that will be used for coronary bypass.

Off-label use of iliac limb endografts has been reported for the exclusion of right subclavian as well as innominate artery aneurysms combined with carotid-subclavian or carotid-axillary bypass (Fig. 84.4).[44-46] This technique introduces the endograft into the innominate artery in a retrograde fashion using the carotid-subclavian bypass limb as a conduit before anastomosis to the subclavian artery. Cerebral embolization is a risk and may be minimized by occluding antegrade carotid flow during endoprosthesis introduction and deployment.[44]

With the introduction of endografts specific for endovascular treatment of thoracic aortic aneurysms, hybrid procedures have become feasible for more proximal aneurysm of the great vessels extending into the aortic arch. In these procedures, exclusion of the orifice of aneurysmal arch vessels is combined with thoracic endovascular aortic aneurysm repair and extraanatomic arch vessel revascularization (i.e., carotid-carotid, subclavian transposition, and carotid-subclavian bypass).[34,47]

Results

Because of the low incidence of arch vessel aneurysms, only small case series and case reports are available to assess outcomes of endovascular treatment of these aneurysms. For nonatherosclerotic aneurysms such as those due to connective tissue disorders,[40,48] Takayasu arteritis,[45] or infections such as HIV,[46] only case reports are available and reveal acceptable outcomes. However, there is an inherent bias in case reports because successful outcomes are primarily published. Thus the long-term durability of endovascular therapy, particularly endografts, in arch vessels is unknown. Short-term patency for subclavian stent-grafts ranges from 83% to 100% over a mean follow-up of 7 to 29 months.[33,36,37,49] Endograft compression, deformation, and fracture and stenosis from intimal hyperplasia have been reported and may limit the applicability of endovascular repair

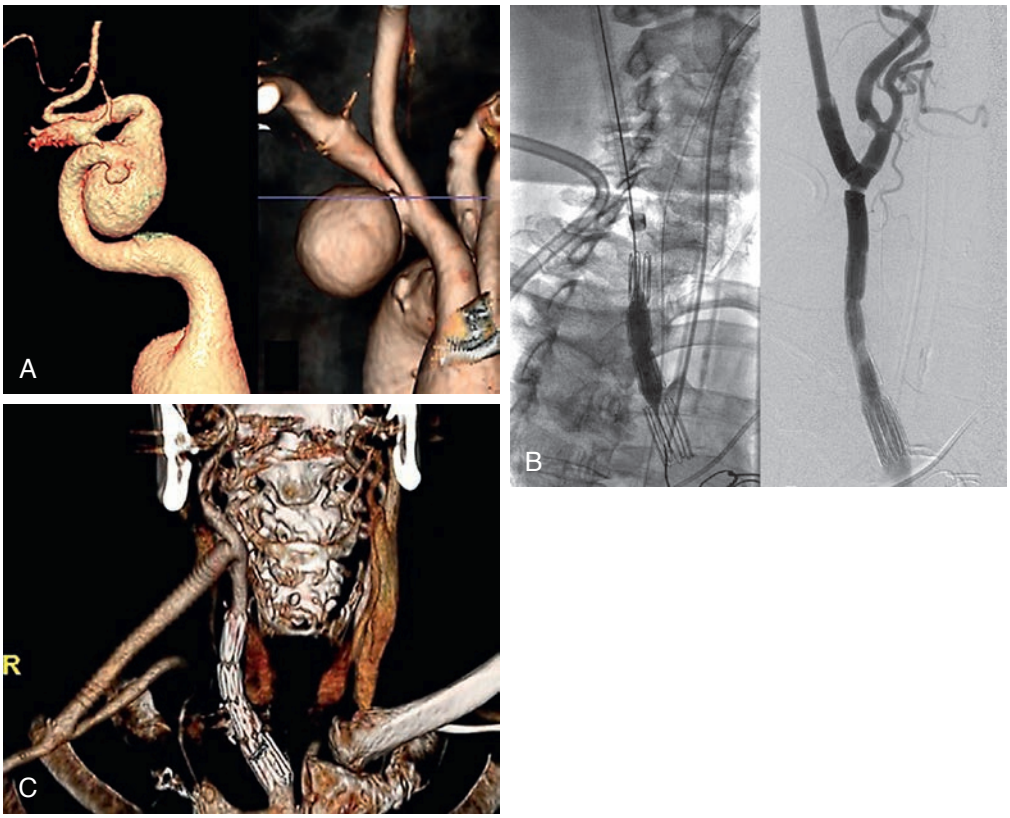

Figure 84.4 (A) Three-dimensional computed tomography (CT) volume rendering of right subclavian artery aneurysm. (B) Deployment of iliac extender limb via a right carotid conduit placed for bypass to the right axillary artery after exclusion of right subclavian artery aneurysm. (C) Follow-up CT angiography of the excluded aneurysm and patent carotid-axillary bypass. (From Bruen KJ, Feezor RJ, Lee WA. Hybrid management of proximal right subclavian artery aneurysms, *J Vasc Surg*. 2011;53:528.)

in this location.[49-51] Bruen et al.[44] reported a case series of four patients with right subclavian aneurysms treated with carotid-axillary bypass and retrograde placement of iliac limb endografts across the innominate bifurcation into the common carotid artery. Mean follow-up time was 232 days (range, 50-564) with 100% patency of the endograft limbs and bypass grafts. No endoleaks were found on follow-up scans. Two of the four patients suffered a minor stroke. Cury et al.[7] reported on the experience at the Cleveland Clinic in treating supraaortic vessel aneurysms that included 11 patients treated endovascularly. Eight of these aneurysms were of the subclavian artery. In this series, one death occurred in the endovascular group, with no endoleaks and no sac enlargement in the follow-up period. Patency rates were not reported. In the series of Andersen et al.,[34] outcomes of 13 hybrid or completely endovascular repairs of intrathoracic subclavian artery aneurysms were reported. All patients underwent repair with thoracic aortic stent-graft placement with (10/13) or without (3/13) revascularization. One death (7.7%) occurred within 30 days after urgent zone 0 hybrid arch repair for an aberrant subclavian artery-esophageal fistula. One incidence of stroke was reported. In a recent series of 26 extracranial carotid aneurysms, three were treated with covered stents.[52] At a mean follow-up of 33 months (range, 23-47 months), all carotid stent-grafts remain patent. In a systematic review of 113 studies including 224 patients undergoing endovascular repair of extracranial carotid artery aneurysms, Li et al.[53] reported a procedure success of 93%, with in-hospital mortality of 4%. Periprocedural stroke rate was 1.8%, with a postprocedural endoleak rate of 8%. At a mean follow-up of 15 months, stent-graft patency was 93%. Late surgical conversion and re-intervention rates were 2.4% and 4.7%, respectively. In a series of four patients reported by Zehm et al.[54] who underwent endovascular repair of subclavian artery aneurysms, all stent-grafts remained patent at a mean follow-up of 38 months. Re-interventions were required in two patients, including coil embolization and additional stent-grafting. Although these case series are small, they provide encouraging results for continued advancement of endovascular therapy for these complex lesions.

ANEURYSM OF ABERRANT SUBCLAVIAN ARTERY AND KOMMERELL DIVERTICULUM

Anatomy

Aberrant Subclavian Artery

An aberrant right subclavian artery arising from the proximal portion of the descending thoracic aorta is the most common congenital anomaly of the aortic arch, occurring in 0.5% to 1% of the population.[55] It was first described in 1735 at autopsy

Figure 84.5 Anterior (A) and posterior (B) three-dimensional computed tomography angiography views of the aortic arch reveal that the anomalous right subclavian artery *(arrowheads)* originates both distal and posterior/inferior on the arch relative to the left subclavian origin.

by Hunauld. In 1794 Bayford described "dysphagia lusoria," a difficulty in swallowing caused by impingement of the aberrant vessel on the esophagus. The anomalous right subclavian artery originates distal to the left subclavian origin, typically posterior and inferior on the arch, and in 80% of cases crosses the midline between the esophagus and the spine (Fig. 84.5). Less commonly, it crosses the midline between the esophagus and trachea or anterior to the trachea. In individuals with a right-sided aortic arch, an aberrant left subclavian artery may originate distal to the origin of the right subclavian, and this may also become aneurysmal. During embryologic development, the left fourth arch becomes part of the aortic arch and the right fourth arch becomes the root of the right subclavian artery. An aberrant right subclavian artery occurs when the right fourth aortic arch and right dorsal aorta involute cranial to the seventh intersegmental artery. Most patients with this anomaly are asymptomatic, and the aberrant subclavian artery is of no clinical consequence. A nonrecurrent right laryngeal nerve is associated with this anomaly.

Aberrant Subclavian Artery Aneurysm

Aneurysmal degeneration of the aberrant right subclavian artery is encountered most frequently in adults of either sex older than 50 years. The majority of these require intervention, owing either to symptoms or to the risk of rupture. Clear size criteria have not been established due to the rarity of this finding, although Cina et al. have proposed repair of aneurysms larger than 3 cm in size in good-risk patients.[56] Mean size of the aneurysm is greater than 4 cm, according to a multicenter registry.[57]

Kommerell Diverticulum

Degenerative aneurysmal changes may occur in up to 60% of patients in the proximal portion of the aberrant subclavian artery.[58] This condition has been termed Kommerell diverticulum after Kommerell, who in 1936 described a diverticulum of the aorta at the origin of the anomalous subclavian artery.[55] McCallen and Schaff[59] first called attention to the clinical significance of aneurysmal change in an anomalous right subclavian artery in a report of 1956. The largest experience to date with this condition was reported by Kieffer et al.,[60] who surgically treated 33 adults with aberrant subclavian arteries, 17 of whom had a Kommerell diverticulum or aneurysmal change of the thoracic aorta at the origin of the aberrant subclavian artery.

Clinical Presentation

Aberrant Right Subclavian Artery

A classification system based on clinical presentation and anatomy has been proposed for aberrant subclavian arteries (Fig. 84.6).[60] Nonaneurysmal aberrant right subclavian artery may result in dysphagia and symptomatic arterial occlusive disease (groups 1 and 2). According to Kieffer et al.,[60] 11 of 33 patients without aneurysmal degeneration presented with dysphagia, whereas five developed upper right limb ischemia because of either arterial occlusive disease or embolism originating from the nonaneurysmal aberrant right subclavian artery. More recently, Stone et al.[61] reported 24 patients diagnosed with an aberrant right subclavian artery over a period of 6 years in the Mayo Clinic health system. Sixteen (66%) were asymptomatic at the time of presentation, and eight presented with various symptoms of dysphagia, upper extremity ischemia, or findings of aneurysmal degeneration. Intervention was performed in 10 patients. Fourteen patients were observed with no complications or aneurysmal degeneration over a mean follow-up period of 38 months.

Aberrant Subclavian Artery Aneurysm

Although patients with aneurysms of an aberrant right subclavian artery are sometimes diagnosed incidentally, they usually present with dysphagia from esophageal compression, dyspnea and coughing from tracheal compression, chest pain from expansion or rupture, or symptoms of right upper extremity ischemia secondary to thromboembolism. Patients may also present emergently with aneurysm rupture or dissection. According to a multicenter registry,[57] 14% of patients presented with rupture. Cina et al.[56] reported that 53% of patients in their series presented with either rupture or dissection. Aneurysm rupture in these cases seems to be unrelated to the size of the aneurysm. Many reported cases were in asymptomatic patients whose

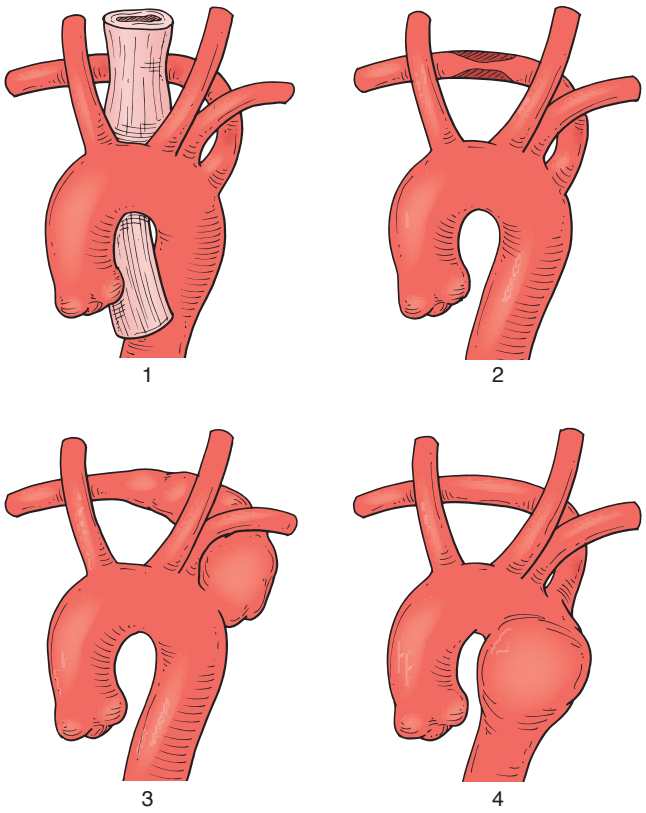

Figure 84.6 Classification system for aberrant subclavian artery as proposed by Kiefer et al.[60] *Group 1*, Nonaneurysmal aberrant right subclavian artery (ARSA) causing compressive symptoms. *Group 2*, Occlusive disease of a nonaneurysmal ARSA. *Group 3*, Aneurysmal dilation of the ARSA without aortic involvement. *Group 4*, Aneurysmal ARSA with aortic involvement. (From Kieffer E, Bahnini A, Koskas F. Aberrant subclavian artery: surgical treatment in thirty-three adult patients. *J Vasc Surg*. 1994;19:100–9.)

aneurysm was found on chest radiography and interpreted as a superior mediastinal mass. Chest CT can detect this condition noninvasively, but CT or digital subtraction angiography is necessary to plan surgical treatment or endovascular repair (Fig. 84.7). Approximately one-fifth of reported patients with this anomaly have an associated abdominal aortic aneurysm.[55]

Treatment

Conservative management is appropriate for asymptomatic patients without a Kommerell diverticulum.[61] No specific surveillance or follow-up protocol exists for these patients, but the presence of symptoms or aneurysmal degeneration should prompt treatment.

Surgical Treatment

Aberrant Right Subclavian Artery

Open repair is usually performed through a supraclavicular incision. The aberrant right subclavian artery is divided after dissecting it to the left of the esophagus via a right supraclavicular incision. The distal end of the subclavian is then transposed and anastomosed end-to-side to the right common carotid artery.

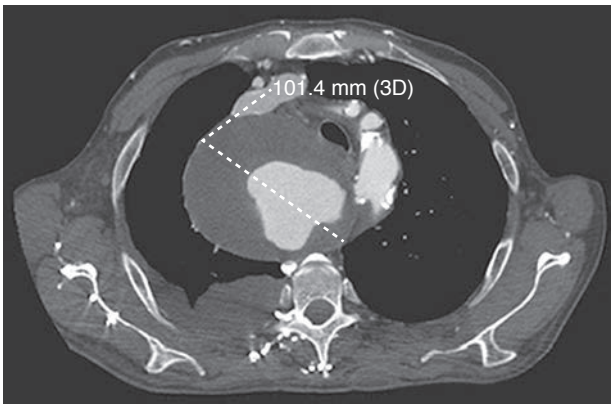

Figure 84.7 Contrast enhanced axial computed tomography scan at the level of the aortic arch. A large aneurysm of the aberrant right subclavian artery is demonstrated passing posterior to the trachea and esophagus. (From Ilijevski N, Nenezic D, Popov P, et al. Images in vascular medicine: giant aneurysm of the aberrant right subclavian artery, *Vasc Med*. 2011;16:157–158.)

Ligation to the left of the esophagus relieves local pressure symptoms. This approach is satisfactory when the more proximal aberrant subclavian is not aneurysmal.[62,63]

Aberrant Subclavian Artery Aneurysm

Because of the propensity of these aneurysms to cause symptoms—and because of the possibility of lethal rupture—resection or exclusion of the aneurysmal artery with vascular reconstruction of the subclavian artery is recommended. Multiple procedures and reconstructions for open repair of these aneurysms have been described. The best approach depends on the anatomic characteristics of the lesion, patient fitness, and acuity of presentation. In the elective setting, open repair consists of staged extraanatomic bypass to reconstruct the aberrant subclavian artery, followed by thoracotomy to oversew the origin of the Kommerell diverticulum. Simple side-biting clamp exclusion may be possible, although interposition graft resection of the aorta itself may be necessary in up to 30% of patients with aortic involvement.[60] Considerations for the procedure are similar to those for open repair of a degenerative proximal left subclavian aneurysm. This repair may be accomplished via a right or left posterolateral thoracotomy (depending on the position of the aortic arch) or a median sternotomy.[55,60,64,65] The subclavian artery is reconstructed by interposition arterial grafting in which the proximal anastomosis may be performed to the ascending aorta. Alternatively, a left posterolateral thoracotomy for proximal resection of the aneurysm coupled with a right supraclavicular incision for reconstruction of the subclavian artery by end-to-side anastomosis to the right common carotid artery has been described.[66] A staged approach with right carotid-subclavian bypass or transposition (end-subclavian to side-carotid) preceding left thoracotomy and aneurysm resection with oversewing of the origin from the aortic arch is attractive because the risk of cerebral and right upper extremity embolization is minimized. Extraanatomic reconstruction of the right subclavian artery also has been described. Because it is necessary to resect the aneurysmal vessel near its origin from the aorta, the modified extrathoracic approach alone, described

for treatment of dysphagia lusoria with nonaneurysmal aberrant subclavian vessels, would not be effective.

Endovascular-Hybrid Treatment

Open repair may be associated with high rates of neurologic complications and mortality, particularly in patients unfit for open major vascular reconstructions. Because the thoracotomy and aortic clamping are the most morbid portions of open repair, which has a reported mortality up to 30%,[60] the combination of aortic endografting and extraanatomic bypass is a particularly appealing combination for treatment of this condition. In addition, open repair may be contraindicated after previous thoracotomy. As the preferred treatment has evolved to an endovascular approach, significant improvement has occurred in perioperative outcomes, with no affection of late outcomes according to a recent review.[67]

Hybrid Approach

Endovascular occlusion of a symptomatic aberrant right subclavian artery, with or without aneurysm, using thoracic aortic endografts combined with distal ligation is an alternative to open repair. Hybrid repair is currently the most frequent treatment method according to a recent multicenter registry.[57] Because exposure to the proximal aberrant right subclavian artery is limited through a cervical approach—and to avoid leaving a stump that may evolve into an aneurysm, a hybrid approach to the proximal end of the artery may be used as an alternative. For this purpose an occlusion device may be placed in antegrade or retrograde fashion at the origin of the aberrant right subclavian artery (Fig. 84.8).[68] The antegrade approach may be preferable to have better control of the deployment and to avoid embolization of the occluder into the aortic arch, which may occur when a retrograde approach is used.

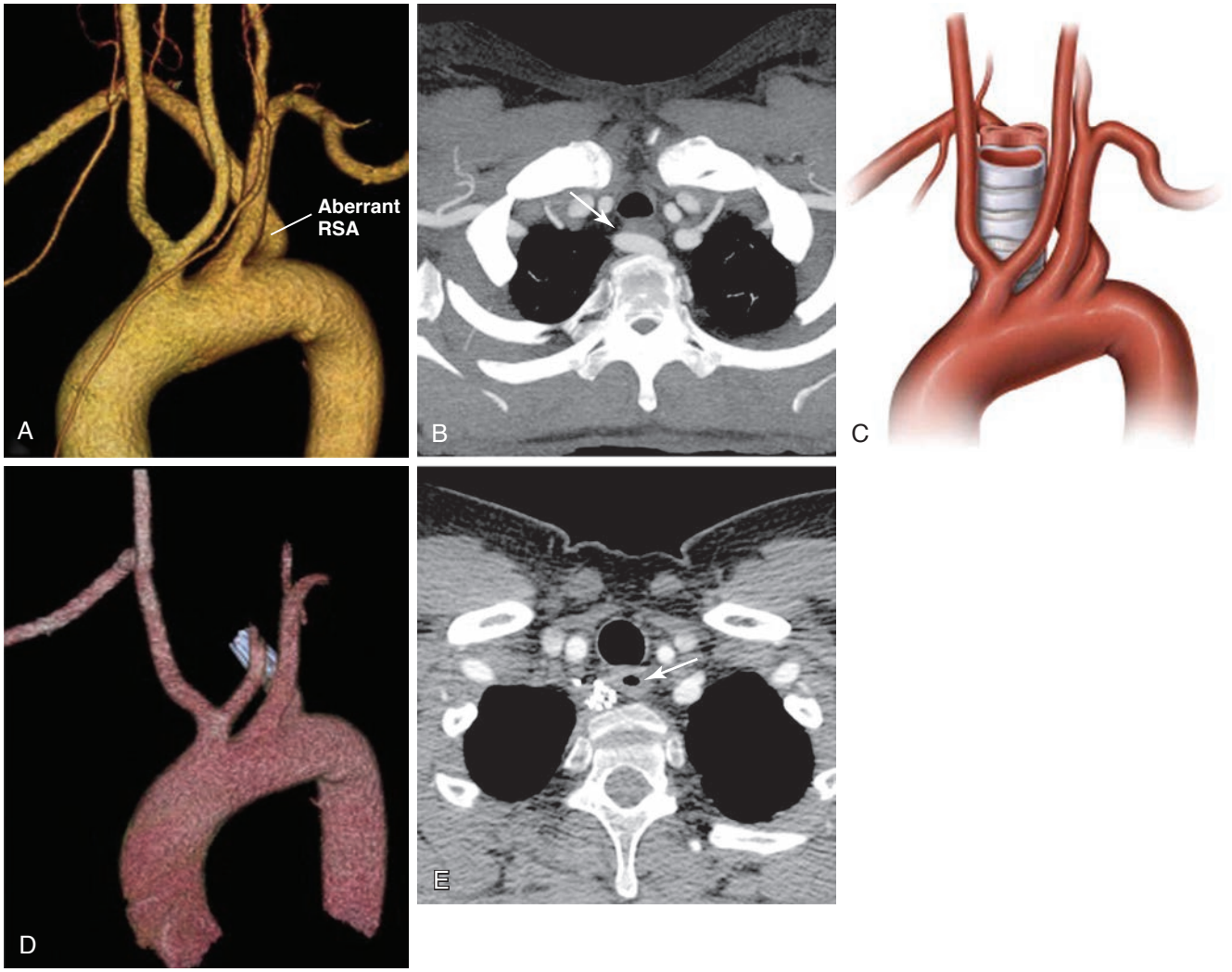

Figure 84.8 (A) Three-dimensional computed tomography angiography (CTA) shows the aberrant right subclavian artery arising from the distal arch and running posterior. (B) A CT scan axial image shows aberrant right subclavian artery compressing the esophagus through a posterior course. (C) Illustration of the aberrant origin and course of the right subclavian artery. (D) Postoperative CTA shows the right carotid-subclavian bypass and occlusive device within the aberrant subclavian artery. (E) Postoperative CT scan axial image at same level as in the preoperative CT shows decompression of the esophagus. (From Shennib H, Diethrich EB. Novel approaches for the treatment of the aberrant right subclavian artery and its aneurysms, *J Vasc Surg*. 2008;47:1066.)

A thoracic endograft can effectively exclude antegrade flow into an ARSA aneurysm (Fig. 84.9).[69-71] However, with current devices, endovascular repair alone is insufficient for treatment of most lesions. Thoracic aortic endografting usually needs to be combined with revascularization of one or both subclavian arteries (Fig. 84.10). In the majority of cases the orifices of the aberrant right and left subclavian arteries are situated at the same level or in close proximity. To effectively occlude the origin of the aberrant vessel with a thoracic endograft, its placement usually requires exclusion of both subclavian arteries.[70] Although single subclavian artery coverage may be feasible during thoracic aortic endografting, bilateral occlusion is not recommended because subclavian steal syndrome or upper limb ischemia may occur, as well as spinal ischemia or stroke.[72] To reduce these complications, bilateral subclavian transposition or carotid-subclavian bypass procedures may need to be performed before endovascular treatment.[73] In some cases the left common carotid artery can also arise from the aortic arch in very close proximity to the origins of the left subclavian and aberrant right subclavian artery. Transposition and revascularization of two or three arch vessels to provide an adequate neck for thoracic endografting may be necessary.[69]

The combination of endovascular and subclavian revascularization procedures significantly reduces morbidity and mortality of the repair of these aneurysms and, if effective and durable, could become standard treatment. Midterm results reveal a 36-month survival of 90% with two late endoleaks (one type I and one type II) among 24 patients with ARSA aneurysms.[57] However, long-term outcomes of such therapy are not established and, more important, it remains unclear whether covering the aortic origin of the aneurysm using an aortic endograft can effectively relieve compressive symptoms of the diverticulum and prevent rupture.

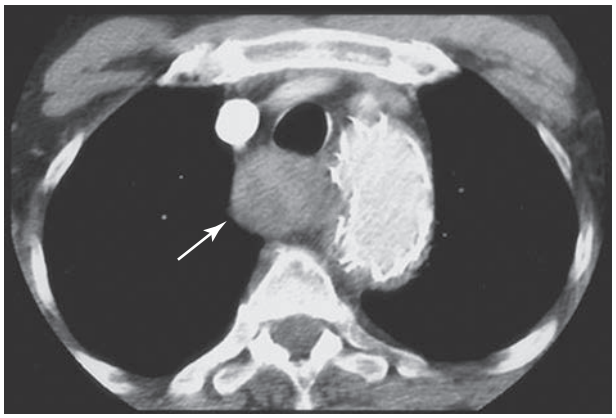

Figure 84.9 Contrast-enhanced computed tomography performed 6 weeks following endovascular repair, demonstrating thrombosed right subclavian artery aneurysm *(arrow)*. (From Munneke GJ, Loosemore TM, Belli AM, et al. Aneurysm of an aberrant right subclavian artery successfully excluded by a thoracic aortic stent graft with supra-aortic bypass of three arch vessels, *Cardiovasc Intervent Radiol.* 2005;5:653.)

Endovascular Approach

Total endovascular repair of aberrant subclavian artery aneurysms may be feasible using chimney or branched stent-grafts. A chimney graft repair was reported in one case in which open debranching was not considered feasible because of prior cardiac transplantation and comorbidities. A type III endoleak occurred postoperatively from the gutters left between the stent-grafts, which is a limitation afflicting these type of repairs.[74] Other endovascular techniques for the treatment of ARSA aneurysm have been described. Davidian et al.[31] reported a case in which the aneurysm exclusion was performed by intraluminal placement of an endograft confined to the aberrant vessel. A similar approach has been used to seal the entry site of an aortic dissection originating from an aberrant right subclavian artery.[71] In this case the dissection involved the aortic arch and the distal aorta. A Wallgraft endograft was deployed in the aberrant right subclavian artery to seal the main intimal tear. Alternatively, Hoppe et al.[75] chose to occlude an aberrant subclavian artery

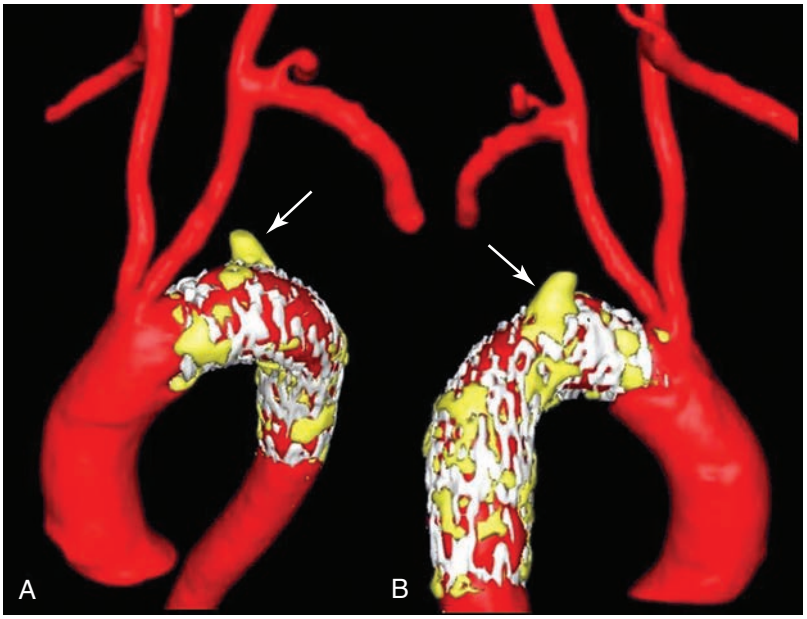

Figure 84.10 Anterior (A) and posterior (B) three-dimensional computed tomography angiography views after thoracic aortic endografting combined with revascularization of one or both subclavian arteries and exclusion of the proximal left subclavian artery *(arrows)*.

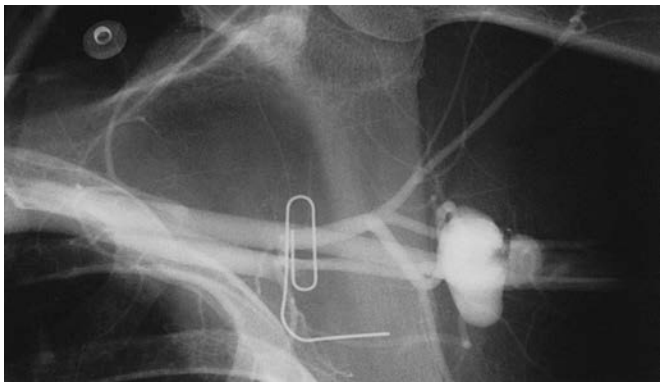

Figure 84.11 Pseudoaneurysm of the axillary artery as a result of a stab injury.

aneurysm with two Amplatzer septal occluders (AGA Medical, Golden Valley, Minnesota) at the proximal and distal ends of the aneurysm, preserving antegrade flow in the left common carotid, subclavian, and vertebral arteries while excluding the aneurysm. The eventual need for revascularization of the right upper extremity could be assessed after the procedure.

AXILLARY ARTERY ANEURYSMS

Etiology and Pathology

Axillary artery aneurysms are rare and usually caused by blunt or penetrating trauma (Fig. 84.11).[76] Congenital axillary aneurysms have infrequently been reported.[77,78] Most posttraumatic axillary artery aneurysms occur typically in young men involved in athletic activities that are associated with repetitious, forceful extension of the upper extremity.[79,80] The mechanism of injury is probably related to the repeated abduction and external rotation of the upper extremity with downward displacement of the humeral head. The repeated compression of the axillary artery can lead to intimal damage, thrombosis, and aneurysm formation. Posttraumatic axillary artery aneurysms have been primarily reported in baseball pitchers, but such aneurysms should be suspected in any athlete with signs and symptoms suggestive of digital ischemia.

Pseudoaneurysms

Pseudoaneurysms of the axillary artery usually occur with penetrating trauma, but they also may occur with blunt trauma in the form of humeral fractures and anterior dislocation of the shoulder.[81,82] These aneurysms often present late as chronic false aneurysms because diagnosis is delayed. Given the excellent collateral circulation in this area, distal perfusion may be adequate despite extensive axillary artery injury. However, these aneurysms can lead to serious and permanent neurologic disability because of hemorrhage into the axillary sheath and compression of the brachial plexus.

Arteriography should be considered in all cases of significant penetrating trauma to the shoulder or arm, blunt trauma with abnormal pulse examination, and blunt trauma with normal pulse examination, but brachial plexus palsy, because the likelihood of concomitant vascular injury is high in these cases. Duplex ultrasonography also may allow accurate diagnosis. Digital, CT, or MR angiography should be performed in patients with blunt trauma to the shoulder or axilla with a normal neurovascular examination initially but with signs of brachial plexus neuropathy on follow-up. The presence of an expanding chronic pseudoaneurysm should be suspected in such cases.

Crutch-induced blunt trauma producing aneurysmal dilation of the axillary artery usually occurs in older patients. These were first described by Rob and Standeven[83] in 1956. Pathologic examination of these aneurysms reveals markedly thickened walls and wrinkled, roughened intima. Instead of the typical changes of degenerative aneurysms, severe fragmentation of medial elastic fibers and marked periadventitial fibrosis are present, suggesting chronic trauma.[84] Thrombus, usually loosely adherent to the damaged intima, may become dislodged by further trauma from crutches and is the source of acute, chronic, or repetitive emboli. In many cases the aneurysm thromboses completely when symptoms begin. The most common presenting complaints relate to upper extremity ischemia, and these aneurysms should be suspected when a patient who has been using crutches for a prolonged period presents with an absent brachial pulse.

Treatment

Open Surgery

Surgical treatment of axillary artery aneurysms is straightforward and involves resection of the aneurysm and interposition vein grafting. The brachial plexus and surrounding vascular structures should be protected during dissection of the aneurysm. Prosthetic reconstruction of the axillary artery may be performed when adequate vein conduits are not available. Autogenous vein grafts in upper extremity reconstructions are preferred because of improved patency rates with these conduits.[85] Occasionally, an adjacent segment of the axillary or brachial vein has been used to reconstruct the artery. However, this vein is extremely thin walled and may itself become aneurysmal with time (Fig. 84.12). For this reason a segment of saphenous vein is the conduit of choice. Perioperative morbidity is usually minimal. Long-term results are excellent, with 100% graft patency in one report with a mean follow-up period of 3.2 years.[86] Presenting symptoms usually resolve, except for paralysis.

Endovascular Treatment

Endovascular repair of axillary artery aneurysms and pseudoaneurysms has been reported (Fig. 84.13).[87,88] In most cases, endograft placement is sufficient to obtain complete exclusion of the aneurysm cavity. Occasionally, embolization with microcoils of avulsed branch vessel to isolate the sac and prevent retrograde endoleak may be required.[89] However, case series of endovascular treatment are small, with limited follow-up. DuBose et al.[41] conducted a review of the literature, describing a total of 160 patients undergoing management of axillosubclavian arterial injuries by endovascular techniques. Pseudoaneurysm formation was present in 77 of these cases. Technical success was 97%; however, significant variability occurred in the reported follow-up period, ranging from hospital discharge to 70 months.

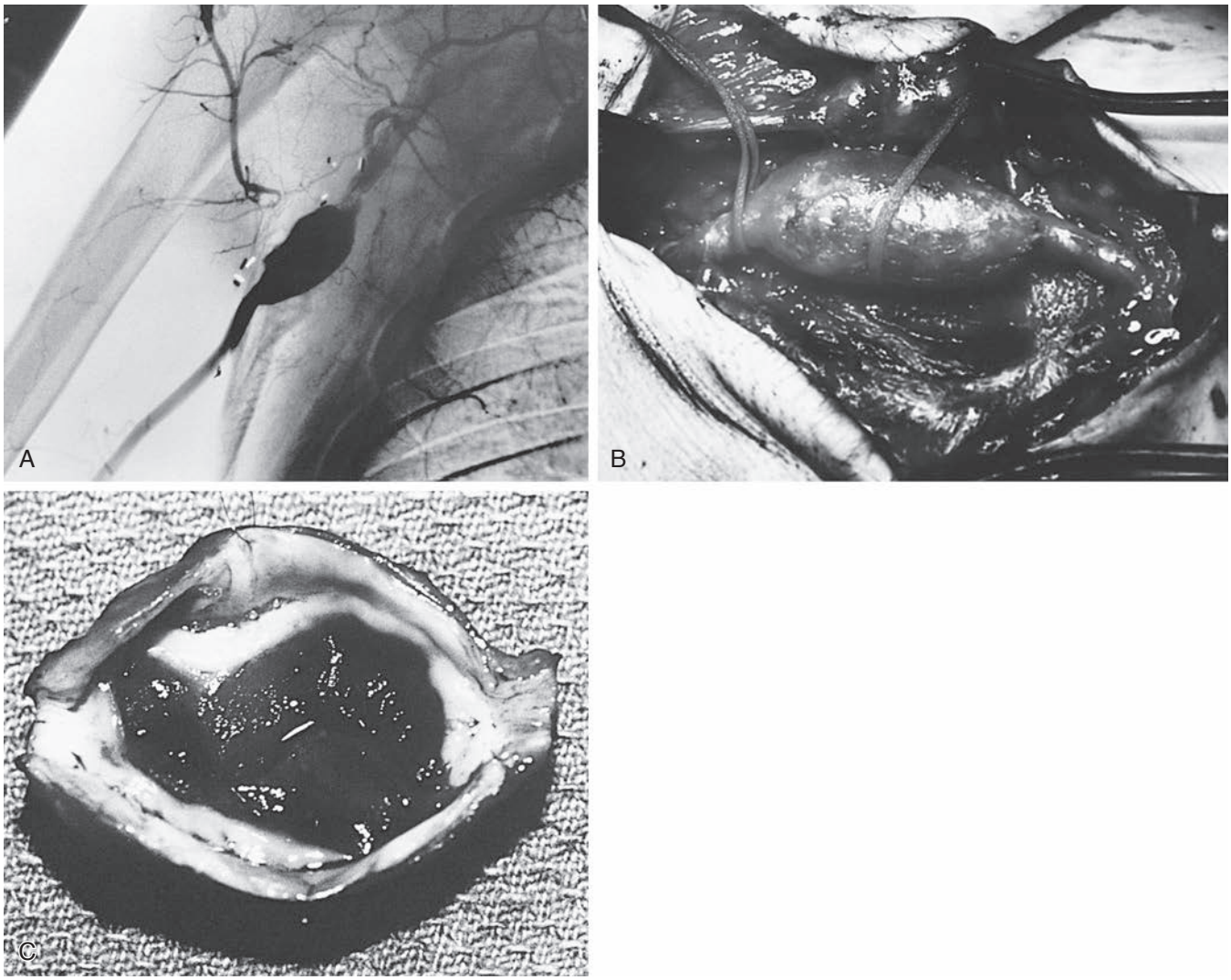

Figure 84.12 (A) Aneurysmal dilation of an interposition brachial vein graft used to reconstruct the axillary artery at the time of penetrating trauma 4 years previously. (B) Operative dissection of the aneurysmal interposition brachial vein graft. (C) Mural thrombus lining the aneurysmal interposition brachial vein graft.

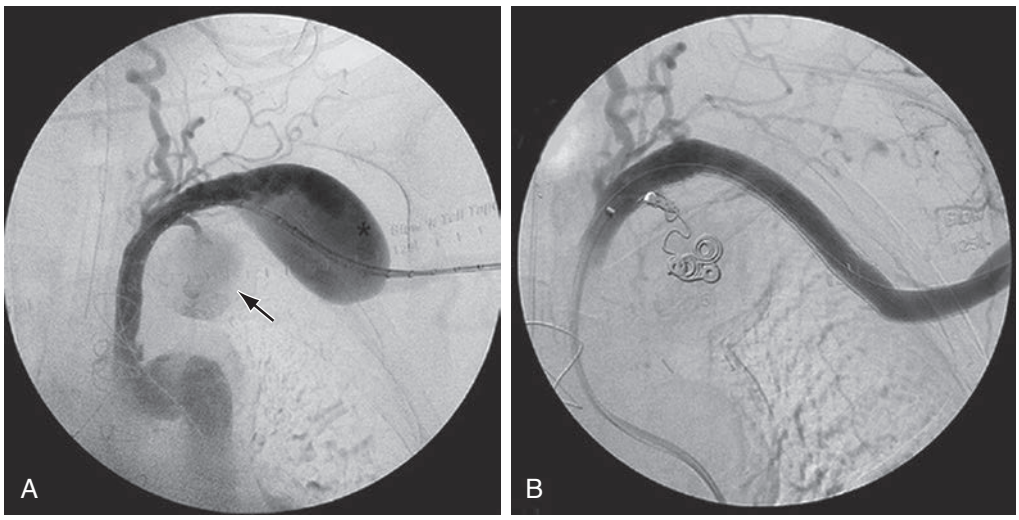

Figure 84.13 (A) Arteriography demonstrating a 6-cm axillary artery and internal mammary artery aneurysm *(arrow)* in a patient with Marfan syndrome. (B) Successful treatment with coil embolization of the LIMA and placement of msultiple stent-grafts for exclusion of the axillary aneurysm. (From Rose JF, Lucas LC, Bui TD, et al. Endovascular treatment of ruptured axillary and large internal mammary artery aneurysms in a patient with Marfan syndrome, *J Vasc Surg*. 2011;53:478.)

Overall patency during the follow-up period was reported at 84.4%. These reports provide encouraging results for endovascular treatment of these life-threatening injuries, and endovascular repair of axillary aneurysms and pseudoaneurysms should be considered an alternative to surgical treatment in patients with major comorbidities and high surgical risk.

BRACHIAL ARTERY ANEURYSMS

Etiology

Aneurysms of the brachial artery are primarily false aneurysms secondary to repetitive trauma, or iatrogenic complications. More recently, brachial artery aneurysms associated to the creation of arteriovenous access for hemodialysis have increasingly been reported. Occupational and recreational activities have also been implicated. However, in many instances, no specific cause can be identified, and these aneurysms are classified as idiopathic.[90] Matas was the first to recognize a traumatic aneurysm of the brachial artery; the patient was a young laborer, and the aneurysm was repaired with Matas's classical endoaneurysmorrhaphy technique.[87] Repetitive blunt trauma can lead to aneurysm formation by compression of the arterial wall and contusion of the arterial media. Penetrating trauma can also cause partial arterial wall laceration and pseudoaneurysm formation. Intravenous drug abuse is currently a frequent cause of infected pseudoaneurysms in the antecubital fossa.[91] Similarly, frequent arterial catheterization contributes to increased incidence of false-aneurysm formation.[92] Arteriovenous access creation can lead to aneurysmal degeneration of donor arteries as well.[93] Other uncommon causes of true aneurysms of the brachial artery include congenital connective tissue abnormalities, such as those found in association with type IV Ehlers-Danlos syndrome,[94] Kawasaki syndrome,[95] Buerger disease,[96] Kaposi sarcoma,[97] cystic adventitial disease,[98] and dissection.

Clinical Evaluation

Most patients with brachial artery aneurysms present with symptoms of median nerve compression or local pain given the close proximity of the two structures. Other symptoms include hand and digital ischemia as a result of thrombosis of the aneurysm and/or distal embolization. Diagnosis of brachial artery aneurysm can be made on physical examination. The presence of an obvious pulsatile mass is also frequently recognized by patients. Duplex ultrasonography can establish the diagnosis. However, upper extremity arteriography is usually necessary to delineate the extent of the aneurysm, to assess the sites of vascular occlusion in cases complicated by thromboembolism, and to determine whether anatomic variants are present that might affect reconstruction. Simple iatrogenic brachial artery false aneurysms can usually be repaired without the need for angiography.

Treatment

Although brachial artery aneurysms have been safely followed nonoperatively, it is impossible to predict which aneurysms are more likely to become symptomatic and lead to complications. Because of the high incidence of symptoms and complications and the minimal morbidity associated with operative treatment, aneurysm repair should be offered to all patients.

Open Surgical Treatment

Open surgical repair, the preferred method of treatment, can be performed under local, regional, or general anesthesia. It usually consists of resection with either patch or interposition vein grafting, resection and primary anastomoses, or, in the case of iatrogenic false aneurysms, simple suture repair. Chemla et al.[93] reported on the outcomes of 13 brachial artery aneurysm repairs, which were associated with arteriovenous fistula creation. Seven patients underwent simple resection with end-to-end anastomosis, and six required interposition grafting with autologous vein conduits. Patency at a mean follow-up of 16 months was 100%.

Endovascular Treatment

Although few reports have described the use of endografts for repair of traumatic brachial artery injuries, only two case reports have described their use in the treatment of brachial artery aneurysms. In one case a mycotic brachial pseudoaneurysm developed secondary to a methicillin-resistant *Staphylococcus aureus* (MRSA) wound infection that occurred after an emergency brachial artery bypass grafting using greater saphenous vein.[99] This pseudoaneurysm was successfully treated with an endograft and antibiotics. In a second case a brachial artery aneurysm was treated with an endograft in a patient who had sustained a gunshot wound to the left arm.[100] This patient had a complex open humerus fracture and brachial plexus injury, initially treated with wound débridement, skin grafting, external fixation, and physical therapy. Two months after the initial injury, the patient developed acute left arm pain and a pulsatile mass in the upper arm. Arteriography demonstrated near total transaction of the proximal left brachial artery. The origin of the pseudoaneurysm was successfully excluded with an endograft.

Iatrogenic Injury

Presentation

Brachial artery pseudoaneurysms secondary to access injuries during peripheral angiography, cardiac catheterization, or endovascular interventions are common indications for upper extremity arterial repairs.[101] However, brachial artery thrombosis is more frequent; it occurs in 1% to 7% of cases.[102,103] Although percutaneous brachial access for peripheral and cardiac angiography or interventions has largely replaced brachial artery cutdown, the frequency of brachial artery pseudoaneurysm formation continues to be low (0.3% in one large series)[102] and not different from pseudoaneurysm rates for the femoral artery approach.[101] Distal (near antecubital) access of the brachial artery is recommended because the artery is less mobile and easier to puncture here than more proximally; furthermore, improved compression against the distal humerus is possible here. The presence of a pseudoaneurysm may be suggested by a mass at the puncture site, evidence of distal occlusion or

embolization, or neurologic complications related to compression. Diagnosis can usually be made with duplex ultrasonography.

Treatment

Nonoperative treatment of brachial artery pseudoaneurysms can be considered when they are small and asymptomatic and likely to thrombose spontaneously. However, in most instances, symptomatic iatrogenic brachial artery pseudoaneurysms should be surgically repaired under local or regional anesthesia because it is difficult to predict which ones will continue to expand and require more difficult later repair. Direct suture repair with evacuation of the hematoma is usually sufficient. Although reported, thrombin injection of pseudoaneurysms of the brachial artery may be considered less favorable because the superficial location of the vessel is usually associated with pseudoaneurysms with relatively short necks.[104,105] If thrombin injection is deemed appropriate, small-gauge needles and lesser amounts of thrombin than those typically used in the femoral artery may be injected in the brachial artery pseudoaneurysm using duplex ultrasound guidance.

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85 CHAPTER

Splanchnic Artery Aneurysms

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Splanchnic artery aneurysms represent a rare pathology that mandates awareness due to their potentially lethal clinical course. These lesions were described more than 200 years ago, and initial case reports consisted mostly of emergent interventions for rupture.[1] Diagnosis in these cases was often made postmortem. The first reported successful operative repair was performed by Kehr in 1903; it consisted of ligation of a proper hepatic artery aneurysm (HAA).[1] This was followed many years later in 1951 by Paul, who described ligation and revascularization of a traumatic HAA,[1] and in 1953 by Debakey and Cooley, who described their repair of a mycotic superior mesenteric artery (SMA) aneurysm.[2] Since that time, evidence has been steadily accumulating in the vascular literature, and the natural history of these aneurysms is becoming better understood. Additionally, the advent of

Abstract

Splanchnic artery aneurysms are defined as aneurysms involving the celiac, superior mesenteric, and inferior mesenteric arteries as well as their associated branches. These aneurysms are incompletely understood given the rare nature of the disease, however remain an important topic for which vascular specialists need to be familiar. This chapter provides an overview of the diagnosis and general treatment principles regarding splanchnic artery aneurysms followed by more in depth review of specific splanchnic artery aneurysms.

Keywords

Splanchnic artery aneurysm
pseudoaneurysm
splenic artery aneurysm
Hepatic artery aneurysm
Superior mesenteric artery aneurysm
Celiac artery aneurysm
rupture diagnosis
diagnosis
surgical management
endovascular management

modern technologic advances—including improved imaging modalities along with complex endovascular techniques—has revolutionized the management of these often lethal entities. This chapter reviews the previous experience as documented in the literature and attempts to establish management guidelines for the various types of splanchnic artery aneurysms.

INCIDENCE AND ETIOLOGY

Traditionally an aneurysm is defined as a dilation or enlargement of an artery more than 1.5 to 2 times its normal diameter.[3] Splanchnic (or visceral) artery aneurysms include those affecting the celiac artery, SMA, inferior mesenteric artery, and their branches. Aortic and renal artery aneurysms are excluded in this categorization despite the fact that they encompass approximately 95% of all intra-abdominal aneurysms.[4] Nearly one-third of patients with a splanchnic artery aneurysm will have an associated aortic, renal, iliac, lower extremity, or cerebral artery aneurysm, signifying the importance of screening these individuals. The overall incidence in the adult population is estimated to range from 0.1% to 2%,[5-9] which, based on autopsy review, increases to 10% in the elder population.[10] Splenic artery aneurysms (SAAs) encompass the majority (60%); followed by HAAs, 20%; superior mesenteric artery aneurysms (SMAAs) 6%; celiac artery aneurysms (CAAs), 4%; gastric artery aneurysms (GAAs), 4%; jejunal, ileal, and colic artery aneurysms (4%); pancreaticoduodenal artery aneurysms (PDAAs), 2%; gastroduodenal artery aneurysms (GDAAs), 1.5%; and inferior mesenteric artery aneurysms (IMAAs), less than 1%.[11-13]

The etiology of splanchnic artery aneurysms differs from that of true aneurysms and pseudoaneurysms. Causes of true splanchnic aneurysm formation include atherosclerosis, medial degeneration, collagen vascular diseases, and fibromuscular dysplasia.[14] Other factors—such as multiparity, portal hypertension, and posttransplant status—have been implicated in true SAA formation,[15-17] and celiac artery occlusive disease has been implicated in true GDAA and PDAA formation.[18] Splanchnic pseudoaneurysms result from infectious or inflammatory conditions, vasculitis, surgery/iatrogenic intervention, and trauma.[12,14,19-23] Furthermore, evidence suggests that pseudoaneurysms display relatively rapid growth soon after the initial insult, such that treatment strategies should focus on early intervention regardless of size.[24]

However, aneurysmal morphology can impact treatment options and the application of endovascular therapies.

Special Considerations for Associated Conditions

Rare medical conditions such as von Recklinghausen disease, Ehlers-Danlos syndrome, periarteritis nodosa, and Behçet disease have been implicated in the development of splanchnic aneurysms. Reported case series have demonstrated the association of multiple splanchnic aneurysms with systemic arteritis, endocarditis with septic emboli, connective tissue disorders, and even excessive use of acetaminophen.[25]

GENERAL TREATMENT PRINCIPLES

Advances in endovascular therapies have caused a paradigm shift in the management of splanchnic artery aneurysms. These aneurysms can be managed by a variety of methods including open surgery, laparoscopic surgery, endovascular techniques, or any combination of these modalities.[26-28] A prior review including 27 published case series of splanchnic artery aneurysms concluded that there is no consensus dictating indications for treatment or specific treatment options.[29] Expert opinion indicates that this is guided by patient and aneurysmal characteristics. Patient age, gender, and comorbidities in conjunction with aneurysmal size, anatomic location, and collateral circulation should dictate optimal management strategies.

Elective Repair

The elective treatment of splanchnic artery aneurysms allows for complete evaluation and imaging with ultrasound, CT, MRI, or a combination of these.[30] Diagnostic angiography is usually combined with percutaneous intervention. A thorough evaluation of the patient should address any history of trauma, pancreatitis, or any other infectious/inflammatory process to ascertain etiology and risk of rupture. Past surgical intervention or hepatobiliary instrumentation, current pregnancy status, history of pregnancies, and risk factors associated with atherosclerosis are also pertinent. Patients undergoing SAA embolization or ligation may be at risk for splenic loss and should receive pneumococcal, meningococcal, and *Haemophilus influenzae* type b vaccinations.[31] A recent literature review noted the benefits of endovascular treatment options in the elective setting, particularly in poor surgical candidates and patients with a hostile abdomen.[32]

Emergent Repair

Ruptured splanchnic artery aneurysms represent a true surgical emergency, and patients should be expeditiously transferred to the operating room for exploratory laparotomy in the setting of hemodynamic collapse. Often, the preoperative diagnosis is ruptured abdominal aortic aneurysm and exploration leads to the actual ruptured artery. Ligation of the splanchnic aneurysm can be performed with or without vascular reconstruction. Patients presenting with ruptured SAAs are most often treated with concomitant splenectomy. Given the extensive collateralization of the viscera, vascular reconstruction is rarely needed in the emergent treatment of proximal HAAs, PDAs, and GAAs.[33,34] When mesenteric arterial aneurysms are ligated, small bowel affected by ischemia may require resection. Arterial reconstruction may be necessary for ruptured SMAAs and CAAs. Endovascular management of ruptured splanchnic artery aneurysms has been reported as a feasible option but should be used selectively.[35,36]

Observation

Most large case series involving the management of splanchnic artery aneurysms have included an observational cohort, with encouraging results.[15,23,24,34,37-40] The majority of observational

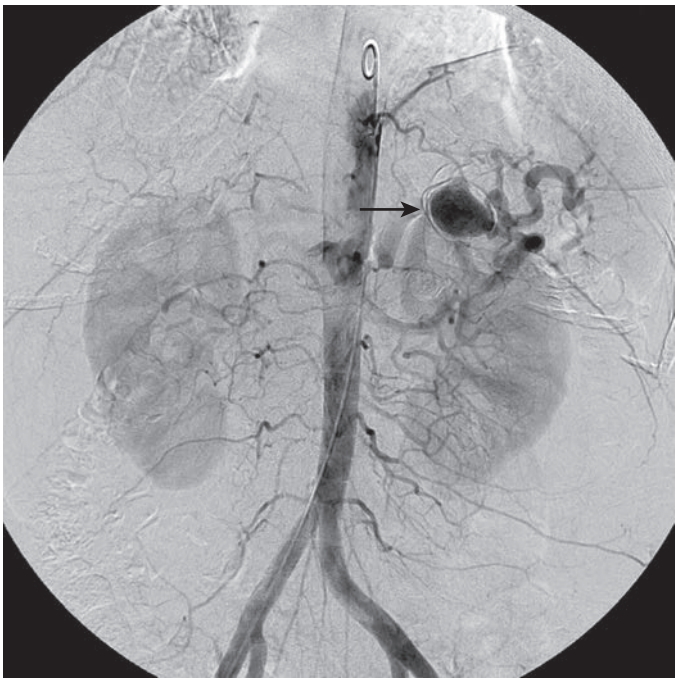

Figure 85.1 A 2.7-cm splenic artery aneurysm *(arrow)* is visualized during an abdominal angiogram. A calcified shell covers the aneurysm sac, with flow maintained to the end organ.

cases involve the splenic artery. General guidelines state that SAAs less than 2 cm in size that are asymptomatic and show little to no growth can be safely observed and monitored with serial imaging. Women who are either pregnant or of childbearing age should have any SAA treated regardless of size.[41] There is no firm evidence to show that aneurysmal calcification protects against growth or rupture, but calcified SAAs (Fig. 85.1) may be associated with smaller size at initial diagnosis.[38] Most series advocate for all pseudoaneurysms to be treated irrespective of size or location owing to their rapid growth rate and propensity to rupture.[22,42] There is also evidence to support intervention in all SMAAs, GDAAs, and PDAAs because of their high rupture rate and the associated mortality.[18,43]

SURGICAL AND ENDOVASCULAR TECHNIQUES

Open Repair

Treatment of splanchnic artery aneurysms with open surgery has been established as a safe and durable standard. An open surgical approach allows for direct visualization of end organs and concomitant diseases processes, including pancreatic pseudocysts or abscesses; thus this approach is useful in determining the need for arterial reconstruction. Expeditious ligation of both the proximal and distal branches is generally performed without reconstruction in the case of frank rupture and hemodynamic collapse and during elective cases if adequate collateralization to end organs is present.[44] The spleen has a rich blood supply from the short gastric arteries and pancreaticoduodenal arcade, which usually allow the splenic artery to be sacrificed without major consequence. The celiac axis and common hepatic artery can also be ligated if there is sufficient collateralization from the gastroduodenal and pancreaticoduodenal arteries and the portal vein is patent. Vein grafts should be used preferentially in cases of suspected infection or bowel ischemia.

Arterial ligation is the procedure of choice in the setting of free rupture.

Endovascular Therapy

The immediate benefits associated with endovascular intervention include a shorter hospital stay, the use of local/conscious sedation, lower cost, and faster recovery. Patients with comorbidities prohibitive to open surgical management, including intra-abdominal malignancy and previous surgery, can also benefit from minimally invasive techniques.[45] Drawbacks to endovascular repair include the risk of access-related injury, contrast toxicity, end-organ embolization, a relatively higher rate of failure compared with open surgery, and the need for prolonged postembolization imaging surveillance. Treatment by means of endovascular intervention can be achieved through several different modalities often in combination, including deployment of coils and glue, injection of particles or Gelfoam, placement of covered stents or flow-diverting stents (FDSs), and injection of thrombin or ethyl alcohol.[7,14,24,37,46-51] Results of the endovascular treatment of 48 consecutive patients—(60% men, mean age 58) with 20 splanchnic artery aneurysms and 28 splanchnic artery pseudoaneurysms—have been reported.[24] The endovascular treatment of visceral artery aneurysms was technically successful in 98% of 48 these procedures, comprising 20 splenic arteries, 12 hepatic arteries, 1 SMA, 3 celiac axis arteries, 2 pancreaticoduodenal arteries, 2 left gastric arteries, 7 gastroduodenal arteries, and 1 middle colic artery. Coil embolization was used for aneurysm exclusion in 96% of the cases, and *N*-butyl-2-cyanoacrylate (glue) was used selectively in 19%. The 30-day mortality was 8.3%, with all perioperative deaths occurring in patients who required urgent or emergent intervention in the setting of hemodynamic instability. Complete exclusion of flow within the aneurysmal sac occurred in the 97% interventions with follow-up imaging, with postembolization syndrome (PES) developing in three patients (6%) after splenic artery embolization. Another report detailed the endovascular treatment results of 185 splanchnic artery aneurysms encountered over 10 years in three distinct geographies.[48] Thirty-four percent of the aneurysms were located in the splenic artery, followed by 30% in the hepatic artery. Initial intervention was successful 98% of the time. Coiling was used alone in 75% of the cases and in combination with at least one other technique in 11% of cases. Thirty-day aneurysm-related mortality was low at 3.4%, and all involved death due to bleeding.

Embolization

Ablation of splanchnic artery aneurysms through endovascular intervention can be accomplished with nitinol coils, cyanoacrylate glue, thrombin, and even ethyl alcohol.[51-55] A unique characteristic of cryanoacrylate glue is that the rate of glue

polymerization can be altered for precision targeting using ethiodized oil dilution in different ratios. A 3-Fr microcatheter is useful for intervention in the distal aspect of an arterial aneurysm before selective embolization material is deployed.[24] Both true aneurysms and pseudoaneurysms of the splanchnic circulation can be managed with embolization. Endovascular exclusion to both inflow and outflow can be achieved by placement of coils first distally, in the sac, and then proximally to the sac (Fig. 85.2). For aneurysms supplied by terminal branches, the sac can be directly injected or coiled.[56]

Covered Stents

In selected cases, a covered self-expanding stent may be placed to maintain flow within a vessel (Fig. 85.3). This technique is often limited by relatively large, rigid delivery devices that are not ideal for navigating secondary and tertiary visceral branches.

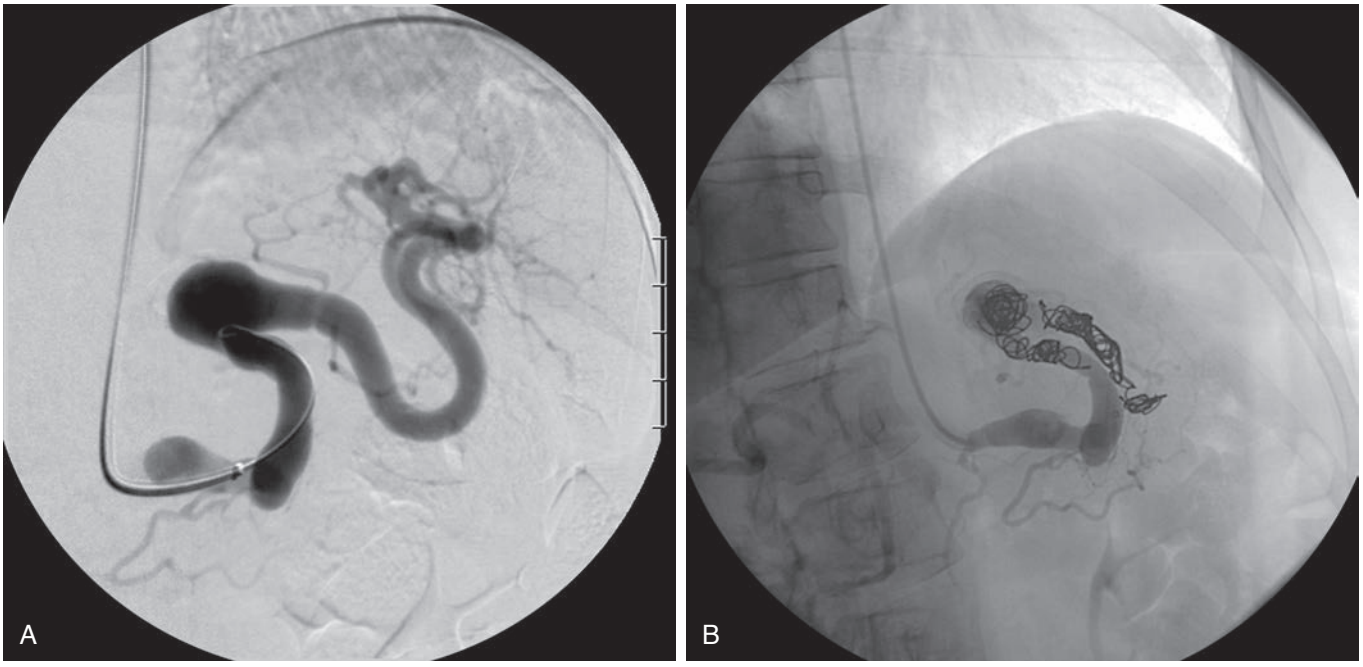

Figure 85.2 **A,** Angiogram of a 2-cm splenic artery aneurysm prior to intervention. **B,** Post intervention angiogram. Aneurysm ablated with nitinol coils. Occlusion of both inflow and outflow to the sac is achieved.

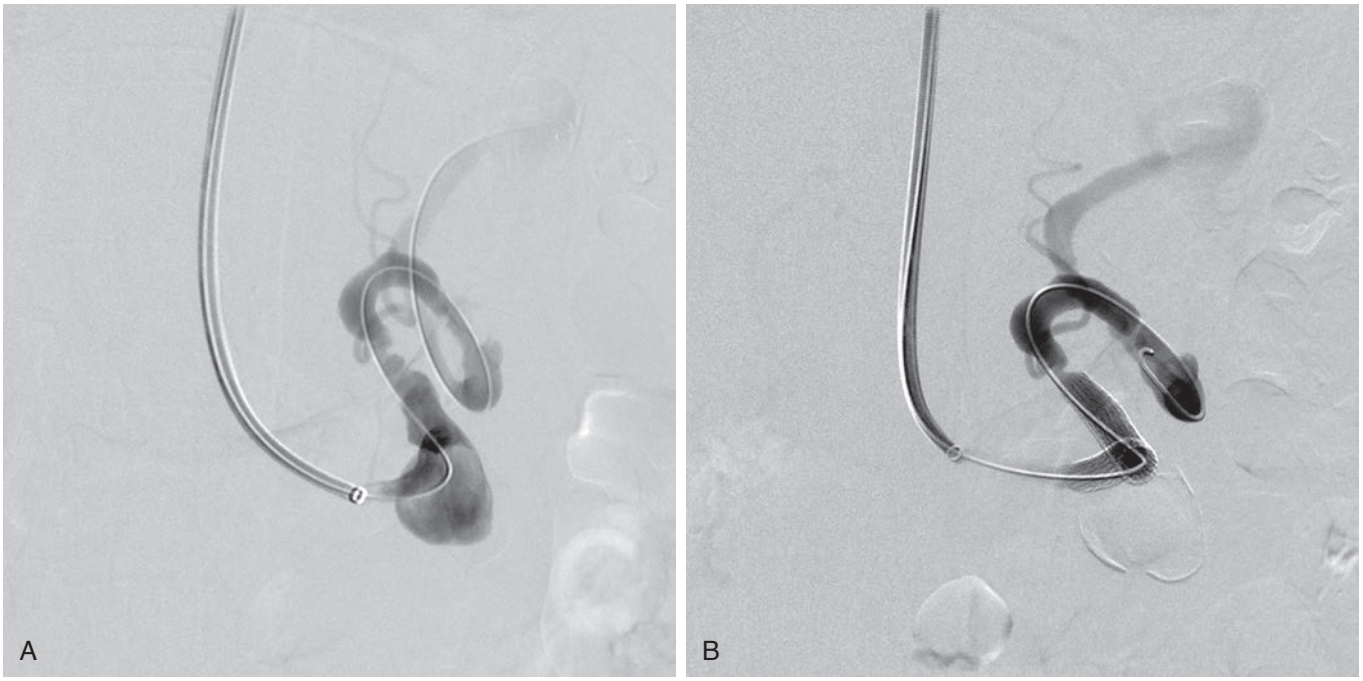

Figure 85.3 **A,** Angiogram of a 2-cm splenic artery aneurysm prior to intervention. **B,** Post intervention angiogram. Aneurysm excluded with covered stent. Post deployment imaging demonstrates intact flow to end organ.

Covered stents also risk occluding flow into side branches of the target vessel.[57-61]

Follow-up imaging is not limited by artifact from radiopaque coils or glue, and this notable advantage of covered stent placement over embolization has allowed for accurate documentation and surveillance of aneurysm sac growth or shrinkage.[62]

Flow-Diverting Stents

FDSs, sometimes referred to as multilayer stents, are specially designed to reduce flow velocity in the aneurysmal sac while promoting thrombosis and maintaining flow within the main artery and any branch vessels. The FDSs were originally developed for the endovascular treatment of intracranial aneurysms. By 2010, this technology had been used to treat over 2500 intracranial aneurysms.[63] Initial case reports demonstrated success in multiple peripheral and splanchnic vascular vessels.[64-69] A prospective, multicenter study of FDS use in 19 splanchnic artery aneurysms recently reported encouraging results of freedom from rupture, patency of the stents and vessel branches, aneurysmal thrombosis, sac shrinkage, and low morbidity and mortality.[70] Widespread use of these modalities should be tempered, however, until more experience regarding efficacy becomes available.

SPECIFIC SPLANCHNIC ANEURYSMS

Splenic Artery Aneurysms

Epidemiology

SAAs have been established as the most common of the splanchnic artery aneurysms, accounting for nearly 60% of reported splanchnic aneurysms. Like any splanchnic artery aneurysm, their clinical significance is related to the potential for rupture. The most accurate calculated incidence in the general population is most often cited as 0.78%, which is based on a review of incidentally noted SAAs seen on nonselective angiography.[71] One general autopsy study cited the overall incidence to be 0.01%,[72] with incidence increasing to 10.4% in an elder population autopsy series.[10] In contrast to other arterial aneurysms, SAAs disproportionately affect females at a ratio of 4 : 1 over males.[44,73] Although incidence increases markedly in the elder population, they occur at a younger age compared with other splanchnic aneurysms.[71,73]

Most SAAs are close to 2 cm in diameter when initially noted. Reports of SAAs associated with symptoms and/or with rupture average closer to 3 cm at presentation.[15,38,74] The majority of these aneurysms have saccular morphology and are located more commonly in the mid- or distal splenic artery and its bifurcations.[73,75] The rare phenomenon of a "giant" SAA greater than 10 cm in diameter has been encountered in the literature and seems to be found more often in men.[76]

Etiology

The underlying pathologic processes in the development of most SAAs are related to atherosclerosis, arterial fibrodysplasia, and arteritis.[23,71] Associated risk factors include female gender, multiparity, and portal hypertension.[17,73] Several reports have established an association between multiparity and SAA development,[15,74] but the precise interactions of hormonal influence, fibromuscular dysplasia, and wall stress are not yet fully understood.[35,77] Some series have noted that nearly 50% of females with more than six pregnancies had been diagnosed with an SAA.[75,78] Yet another noted that 80% of females with SAAs had averaged 4.5 pregnancies.[74] Still, the utility of screening women for SAAs who are either pregnant or of childbearing age has been proven to be unwarranted in one recent study.[79]

The association between SAAs and portal hypertension has been documented, especially in patients undergoing orthotopic liver transplantation.[11] Evaluations of patients with known portal hypertension or cirrhosis have shown a likely incidence of SAA incidence ranging from 10% to 20%,[80] with one study reporting an incidence as high as 50%.[16] Notable etiologies of splenic artery pseudoaneurysm formation include blunt trauma, infection, and pancreatitis.[22] Pseudoaneurysm formation associated with pancreatitis has been attributed to digestion of the splenic artery by pancreatic enzymes.[81] Hemosuccus pancreaticus is a rare cause of upper chronic and intermittent gastrointestinal hemorrhage, usually due to the rupture of a visceral aneurysm into the main pancreatic duct. Splenic artery pseudoaneurysm formation associated with chronic pancreatitis represents the leading cause of hemosuccus pancreaticus and presents as a challenging clinical scenario.[82]

Clinical Presentation

Prior to the introduction of modern imaging techniques and their abundant use in everyday practice, it was estimated that more than 10% of SAAs were ruptured at the time of diagnosis.[73,78] Most current case series report that SAAs are incidental findings noted on imaging performed for unrelated symptoms. Incidental diagnosis can often be presumptive, based on circular calcified shadows or "signet rings" seen in the left upper quadrant of an abdominal roentgenogram.[83] In cases not associated with pregnancy, SAAs have a relatively low rupture rate of less than 2%.[84] Most patients with otherwise asymptomatic SAAs will have benign physical examinations. Hemodynamic collapse secondary to rupture is most often accompanied by acute left-sided abdominal pain. The patient will typically present in extremis as a result of free intraperitoneal rupture and shock.[72] On occasion the initial rupture may be contained in the lesser sac. This "double rupture" phenomenon, which occurs after initial tamponade of splenic artery hemorrhage into the lesser sac, can occur in up to 25% of ruptured SAA cases and can sometimes precede free rupture into the retroperitoneum by as long as 4 days.[21,83,85,86] Mortality reports associated with ruptured SAAs range from 10% to 25%.[15,83,75] Pregnancy is a significant contributing risk factor and may be associated with as many as half of all ruptures.[73,87] Significant maternal and fetal mortality has been documented to be close to 75% for pregnant women and about 95% for the fetus.[88,89] Rupture occurs almost exclusively in the third trimester; to date there have been only three reported cases of first-trimester rupture in the literature.[90] Although the prevalence of SAAs in pregnancy is thought to be low, at only 0.1% in one series,[79] their clinical importance is highlighted by the thought that over

50% of these aneurysms rupture during pregnancy[73,87] Portal hypertension is an additional significant risk factor for rupture, as it was associated with nearly 20% of all SAA ruptures.[74] A recent review of the English and French literature found only 613 reported cases of splenic rupture without risk factors or previously diagnosed disease.[91] The most common associated diseases with these patients were infectious in nature, followed by hematologic and nonhematologic neoplasms.

Treatment

All patients who present with a ruptured SAA should undergo immediate and definitive treatment. Additionally, any patient who has symptoms attributed to a nonruptured SAA should undergo intervention. Women who are pregnant or are of childbearing age should undergo treatment as well. Most advocate for the treatment of any splenic artery pseudoaneurysm regardless of size or symptoms owing to their propensity to rupture. In the absence of these scenarios, the threshold for intervention is based mainly on size of the aneurysm and/or rate of growth. Consensus in the literature has generally established the indications for treatment to include those aneurysms greater than 2 cm in diameter.

A large review reported from the Mayo Clinic involved 217 patients with SAAs. Of these patients, 168 underwent nonoperative management for a mean period of 75 months.[15] The mean size in the nonoperative group was 2.1 cm, with a range from 0.8 to 5 cm in diameter. About half of these aneurysms were monitored with serial imaging, of which only 10% were noted to have growth averaging 0.06 cm per year. No rupture or other complications related to the SAAs occurred and only 3 of the original 168 required intervention due to aneurysmal growth. Similar results were reported by Lakin et al. in reviewing the Cleveland Clinic experience of 128 SAAs managed over a 15-year period.[38] The observational cohort of 66 SAAs had a mean diameter of 1.7 cm at presentation with a range from 0.8 to 4.2 cm. Serial imaging was available for 94% of the aneurysms, and these patients received an average of 2.5 CT scans over 4.6 follow-up years. The average growth rate was a nominal 0.2 mm per year over 3.1 follow-up years. There were again no ruptures or other complications attributed to the aneurysms in the observed group. More recently, Corey et al. reported the experience from Massachusetts General Hospital, which included 95 patients with SAAs, 59 of which underwent nonoperative management.[18] These investigators found that only 10.5% of aneurysms less than 2.5 cm in diameter grew over an average surveillance period of 31 months.

Open Surgical Repair

Options include complete resection with splenectomy, proximal and distal ligation of the aneurysm, or ligation with arterial reconstruction. To visualize the splenic artery, dissection proceeds with mobilization of the splenocolic ligament. The splenic flexure is then mobilized away from the retroperitoneum and abdominal wall. Splenectomy is not uniformly needed, since the short gastric vessels will adequately perfuse the organ after splenic artery ligation. Splenectomy is preferred for lesions adjacent to the splenic hilum or those involving the intrasplenic branches within the parenchyma.

The long-term results of open surgical repair for SAAs show a high survival and low complication rate, confirming the durability of the surgical approach. Marone reported a series of 34 SAAs treated with elective open surgical repair in which survival at 1 and 5 years was 100% and 92%, respectively.[40] In the Mayo Clinic series, 49 patients underwent surgical intervention; 39 of these procedures were elective. Operative mortality was 20% in the ruptured group and 5.1% in the elective group. Complications were low for the nonruptured group, with no reported recurrence over a mean follow-up of 70 months. More recently, a meta-analysis by Hogendoorn et al. reported the results of 1321 patients with true SAAs; 511 of these patients were managed with open techniques, 385 with endovascular techniques, and 425 nonoperatively.[92] This study found that open surgical management was associated with fewer long-term complications and reinterventions as compared with endovascular management. Endovascular management brought improved short-term results in this study—namely, lower perioperative mortality—but the open management group contained more instances of ruptured SAAs, which could account for this difference. In the setting of splenectomy, it is important to remember to administer splenectomy vaccinations to reduce the risk of overwhelming postsplenectomy infection.

Endovascular Therapy

Endovascular techniques have emerged as an effective option in the management of SAAs. Treatment usually includes coil embolization, the use of cyanoacrylate glue, stenting, or a combination of both. The Cleveland Clinic series reported the outcomes of 49 SAAs treated with endovascular intervention.[38] Coil embolization was performed in 45 cases, of which 11 had glue used adjunctively. There was a 96% technical success rate in the initial procedure, with secondary intervention ultimately achieving desired results when needed. Complications included a femoral access site hematoma requiring operative drainage and two brachial artery access site injuries. Splenic abscess was noted in three patients, which required reintervention.

PES occurred in an additional five patients. PES is a known complication of SAA embolization, and infarcts are common events; however, they generally resolve without sequelae.[93] Other selected series have reported similar success rates in the endovascular management of SAAs, ranging from 90% to 100%.[24,49,94,95] Covered stent repair is thought to be ideal for exclusion of the aneurysm and preservation of the splenic artery and in theory will not lead to PES.[96] The use of covered stents in treating SAAs remains limited to proximal lesions, and their use has not been as widespread as endovascular ablation. One of the main limitations is getting adequate wire support to advance the covered stent through the tortuous splenic artery, especially in the case of distal aneurysms. Multilayered stents have also been used sporadically.

Hepatic Artery Aneurysms

Epidemiology

HAAs were first described by Wilson in 1809, with the first successful ligation being reported in 1903.[97] The hepatic artery is the

second most common location of splanchnic aneurysm formation and is believed to represent approximately 20% of these lesions. The true incidence is not known, but it is estimated to be less than 0.4% in the general population.[98] Approximately 75% to 80% of these aneurysms are located along the extrahepatic vasculature, with the remainder involving the intraparenchymal and/or extraparenchymal liver space (20%); in rare cases (<5%) they may be located exclusively within the liver. Along the extrahepatic vasculature, 63% are found in the common hepatic artery, 28% in the right hepatic artery, 5% in the left hepatic artery, and 4% in both the left and right hepatic arteries (Fig. 85.4).[39,99] The male-to-female ratio is 3 to 2, with reported rates of rupture ranging from 20% to 80%.[39] Unlike SAAs, these lesions have no known association with pregnancy in either incidence or rupture rate. The age of presentation is closer to a mean of 60 years old if trauma etiologies are excluded.[8] Notably, HAA incidence appears to be on the rise with increasing use of hepatobiliary instrumentation and manipulation.[100-102] In some recent series, HAAs were actually the most frequently reported aneurysms encountered.[12,103] Half of these were pseudoaneurysms located within the parenchyma of the liver, which underscores the increasing incidence of an iatrogenic etiology for hepatic pseudoaneurysms. Mycotic etiology, once seen frequently in patients with a history of endocarditis, has decreased with the widespread availability of antibiotics.

Etiology

As with SAAs, atherosclerosis is the leading cause of HAA formation, accounting for approximately 30% of cases.[98] In a Mayo Clinic series of 36 true HAAs, the most commonly associated comorbidity was hypertension, occurring in 72% of patients.[39] Arterial dysplasia, medial degeneration, trauma, polyarteritis nodosa, and biliary diseases have also been implicated in the formation of HAAs. Percutaneous and endoscopic procedures will undoubtedly contribute an ever-increasing source of HAA formation.[99] Concomitant aneurysms of other splanchnic vasculature are seen with HAAs in nearly one-third of cases; in one series, 20% also had a SAA. Nonsplanchnic aneurysms are also seen in nearly 40% of patients with HAAs.[8,39] A recent review of the Mayo Clinic experience found that, among patients who ultimately underwent intervention for a HAA, 63% had synchronous aneurysms, which most commonly involved the aorta.[104]

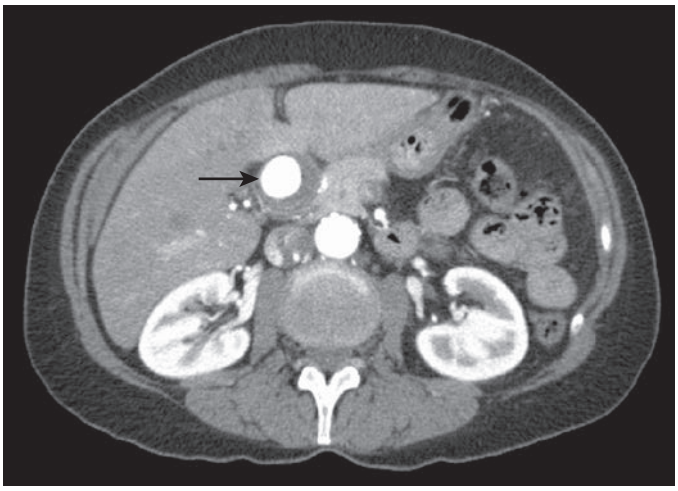

Figure 85.4 This abdominal computed tomography scan of a 61-year-old female shows an incidentally noted 2.5-cm proper hepatic artery aneurysm *(arrow)*. The patient underwent excision and repair with a reversed greater saphenous vein bypass graft from the common hepatic artery to both the right and left hepatic arteries.

Clinical Presentation

The majority of HAAs are identified incidentally on cross-sectional imaging or abdominal ultrasound.[105] Abdominal discomfort and back pain are vague symptoms that may be caused by rapidly expanding aneurysms. In the setting of true HAAs, rupture risk approaches 25% for larger aneurysms.[78] Rupture into the peritoneal cavity or hepatobiliary tract can be seen with equal frequency. Quincke's triad of hemobilia, jaundice, and right-upper-quadrant pain can be seen when rupture into the bile ducts occurs.[106] HAA with erosion into the stomach is a rare but serious cause of upper and lower gastrointestinal bleeding.[107]

Mortality rates associated with rupture are high, ranging from 20% to 70%.[21,39,108,109] Risk factors associated with rupture remain poorly defined, and there are currently no studies correlating HAA size with the likelihood of rupture.[110] In the Mayo Clinic case series, 22 patients with HAAs averaging 2.3 cm in diameter were managed nonoperatively for a mean of 68 months.[39] No aneurysm-related complications were reported. Aneurysmal growth was identified in 27% of patients, with the greatest being 0.8 cm over 34 months.

It is important to distinguish between true and false HAAs as this may prove to be one of the most important prognostic factors when planning management. The Cleveland Clinic experience found that pseudoaneurysms of the hepatic artery were more likely to be symptomatic versus true aneurysms and more often required urgent intervention.[24] Consistent with trends over the past two decades, nearly all (11/12) of the HAAs in this series were pseudoaneurysms. Most of the splanchnic pseudoaneurysms in the series presented with gastrointestinal bleeding or hemobilia, such that 92% of these patients required urgent intervention. Based on their experience, the authors concluded that all splanchnic artery pseudoaneurysms should be treated regardless of size due to their higher risk for rupture.

Treatment

General guidelines for intervention include the treatment of any symptomatic aneurysm, pseudoaneurysm, and aneurysms greater than 2 cm in diameter in appropriate surgical candidates. Patients presenting with multiple HAAs should also be treated regardless of size. HAAs presenting in patients with PAN or other inflammatory conditions are also considered at increased risk for rupture and should be repaired regardless of size.[111] True aneurysms of the hepatic artery have been safely observed, particularly in the case of smaller aneurysms. Similar to the Mayo Clinic experience, Corey et al. reported their surveillance of 18 patients with HAAs (average diameter 17.8 ± 6.9 mm) and found no instance of increased aneurysmal growth with a mean follow up of 28 months.[18]

HAAs are accessible via a right subcostal or midline laparotomy incision. The proper hepatic artery can be visualized in the gastrohepatic omentum. The use of intraoperative ultrasound may assist in identifying the aneurysm.

Open Surgical Repair

Techniques include aneurysmorrhaphy with or without patch angioplasty, ligation with or without bypass using autologous vein or graft, and, if needed, hepatic resection.[39,104] Common HAAs can be treated with simple ligation or endovascular embolization if the GDA is patent, since it provides sufficient collateral flow in most patients. HAAs distal to the GDA can be treated by arterial reconstruction or other methods to restore blood flow to the end organ if the revascularization is straightforward. Aneurysms located within the parenchyma may be treated with resection, ligation, or embolization.[102] If the hepatic artery is ligated, an increase in the oxygen content of the portal vein blood as it passes through splanchnic arteriovenous shunting occurs.[112] Therefore hepatic artery ligation should never be performed in the presence of cirrhosis or any other condition where liver function is compromised. If the proper or right hepatic artery is ligated, the gallbladder is at risk for necrosis and cholecystectomy should be performed simultaneously.[113] Embolization techniques are ideally suited for lesions located within the hepatic parenchyma. These lesions are not only relatively difficult to access with open surgery but also often require parenchymal resection or hepatic lobectomy. However, patients undergoing embolization should be watched carefully for hepatic parenchymal necrosis, which may require operative intervention or drainage.

Special consideration must be made for the association of hepatic artery pseudoaneurysm formation after liver transplantation. Although the incidence is relatively low, ranging from 0.3% to 2% after liver transplantation, this represents a severalfold increase relative to the general population.[114] Liver transplant patients who develop hepatic artery pseudoaneurysms usually present with intra-abdominal or gastrointestinal bleeding within 2 months of transplantation. In many cases, there is evidence of intra-abdominal infection, and bile-containing drainage often precedes the rupture of these pseudoaneurysms.

Endovascular Repair

Treatment results of HAAs have shown endovascular intervention to be a safe and effective method of repair in limited series.[100] Endovascular coil embolization was the predominant therapeutic strategy. Tulsyan et al. reported on 11 hepatic artery pseudoaneurysms and 1 true hepatic aneurysm.[24] Two patients required a second intervention; they were both successfully managed with an additional ablation procedure. No liver infarctions, hepatic insufficiency, or intestinal ischemia attributable to aneurysm ablation occurred in the cohort. Sachdev and colleagues reported similar success in their series of 11 HAAs treated with endovascular intervention.[95] An endovascular approach predominated in the treatment of hepatic artery pseudoaneurysms, whereas true aneurysms involving the extrahepatic circulation were more likely to be treated by an open surgical approach.

Superior Mesenteric Artery Aneurysms

Epidemiology

Aneurysms of the SMA represent approximately 6% of all splanchnic artery aneurysms. Traditionally they were thought to affect men and women equally, with most patients presenting over the age of 50.[84] Recent studies, however, have shown a more male predisposition and, particularly in the setting of mycotic SMAAs, a wide range in age among those affected.[18,115] Incidence based on autopsy studies is reportedly 1 in 12,000 to 1 in 19,000.[116] They occur almost exclusively along the first 5 cm of the artery (Fig. 85.5). In addition to hemorrhagic shock in the case of rupture, SMAAs place a majority of the intestine at risk for ischemic complications. Because of these potentially devastating consequences, timely diagnosis and treatment of SMAAs is essential for the optimization of outcomes.[117]

Etiology

Unlike other aneurysms found in the viscera, the most common etiology of SMAAs continues to be infection.[118,119] Mycotic etiologies account for 60% of all SMAAs, and many patients have a history of bacterial endocarditis and the use of intravenous drugs. The SMA may be more vulnerable to mycotic aneurysm formation owing to the size and orientation of its base in relation to the aorta; however, this predisposition is not completely understood. Other conditions related to true SMAA formation include atherosclerosis, connective tissue disease, PAN, and pancreatitis with trauma implicated in the development of SMA pseudoaneurysms.[43,117,120]

Clinical Presentation

Nonruptured SMAAs are more likely to cause symptoms compared with other splanchnic artery aneurysms, and history of vague colicky pain, intestinal angina, weight loss, or other symptoms may be elicited in 70% to 90% of such patients. Like HAAs, SMAAs are associated with a significant rate of

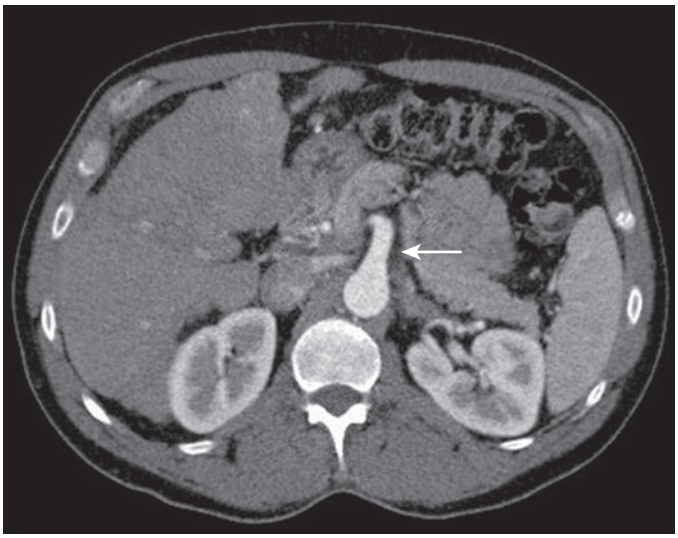

Figure 85.5 A 49-year-old male with a history of hepatitis B received a preoperative computed tomography scan of a 1.7-cm superior mesenteric artery aneurysm *(arrow)*. The aneurysm was treated with a reversed greater saphenous vein bypass.

rupture. One series of 52 patients with SMAAs cited the most frequent symptoms to be abdominal pain, nausea, vomiting, and gastrointestinal bleeding.[12,117] A recent meta-analysis by Kordzadeh and colleagues reviewed the contemporary literature involving mycotic SMAAs. They reviewed 38 cases from 1944 to 2015 and found the most common presenting symptoms to include abdominal pain (65%), pyrexia (60%), malaise (26%), weight loss (23%), and nausea/vomiting (20%). Additionally, the most common pathogens were *Streptococcus* (47%) and *Staphylococcus* (28%). Ruptures rates for all SMAAs ranged from 38% to 50%, with an associated mortality of 30% to 90%.[43,117,121] The high mortality rates are likely attributed to the result of free rupture into the peritoneal cavity, with accompanying intestinal ischemia.

Spontaneous isolated dissection of the SMA is a clinically rare disease that can be associated with aneurysmal dilation. Clinical findings range from incidental discovery on CT scans to frank bowel ischemia or aneurysm rupture.[122]

Treatment

Previously, due to the high risk for rupture and its associated mortality, repair of any SMAA was advocated regardless of size or symptomatology.[117] More recently, evidence has suggested that observation of small (<2.5 cm) aneurysms may be a safe alternative, especially in patients at poor surgical risk.[18,43] All pseudoaneurysms and those with a mycotic etiology should be repaired, as these show a greater potential for rupture and subsequent mortality. SMAAs can be treated surgically with aneurysmectomy, arterial reconstruction, and rarely simple ligation. It is important to take into account that SMAAs have a predilection for a mycotic or inflammatory etiology rather than being caused by fibrodysplasia or atherosclerosis. The predisposition for mycotic or inflammatory etiologies may serve as a contraindication for polytetrafluoroethylene (PTFE) or Dacron bypass grafts.

Open surgical treatment is performed via a midline or retroperitoneal approach. The SMAA can be identified by ultrasound or palpation. Dissection is continued proximally and distally until there is normal-caliber vessel. The proximal dissection may extend underneath the renal vein, and if necessary the adrenal vein can be ligated. It is essential to confirm the presence or absence of a replaced or aberrant right hepatic artery branch, which is one of the most commonly encountered variants in the splanchnic circulation. SMAA surgical repair carries a relatively high mortality of close to 15%.[117]

Endovascular therapies provide an additional therapeutic option to high-risk candidates in whom open surgery may not be feasible. Reports of endovascular management of SMAAs describe the use of coil embolization and stent grafts.[7,24,43,95,123] Endovascular therapy is particularly useful in patients with a hostile abdomen and medical comorbidities.[46]

Celiac Artery Aneurysms

Epidemiology

Celiac aneurysms represent approximately 4% of all splanchnic aneurysms, with little over 100 cases reported in the literature.[11,124] True prevalence based on autopsy review is about 1 in 8000.[125] They are found concomitantly with other splanchnic artery aneurysms 40% of the time and with abdominal aortic aneurysms in 20% of cases.[5,126] Atherosclerosis is associated with the majority of these aneurysms, with an infectious etiology implicated in 20% of cases. The majority are discovered in male patients in their fifth or sixth decade of life.[18,44,127]

Etiology

A literature review of 108 CAAs revealed an interesting trend in CAA pathogenesis.[128] Among 60 CAAs encountered before 1950, a total of 40% were infectious (usually syphilis), 7% were traumatic, and 52% were of undetermined cause. Most of these were also symptomatic. The majority presented with rupture, and 95% were diagnosed at postmortem examination. Atherosclerosis and/or medial degeneration of the arterial wall are the most common causes of contemporary CAAs. Additionally, median arcuate ligament syndrome has been implicated in the formation of CAAs.[129] Most aneurysms in the contemporary group were either asymptomatic or accompanied by vague abdominal pain. Additionally, only 13% of these aneurysms presented with rupture. CAAs have also been reported to develop as a result of iatrogenic intervention or spontaneous isolated dissection of the celiac artery.[130] Patients with spontaneous dissections are predominantly male and younger than 50 years. Mortality can be high if dissection extends to the hepatic artery and warrants immediate operative or endovascular treatment. Conservative treatment can be justified in patients with isolated celiac dissection without bowel ischemia or hemorrhage.[131] There is also a reported association with anomalous origins of the right and left hepatic arteries, a common celiacomesenteric trunk, and other anomalous mesenteric vasculature.[132-134]

Clinical Presentation

CAAs remain noteworthy due to the high mortality rates associated with rupture. Historically, mortality after rupture approached 100%.[135] Modern series report rupture rates ranging from 10% to 20%, with a mortality of 50%.[75,127,128] There are no established aneurysm characteristics or patient comorbidities that may predict rupture risk. Size at presentation, aneurysm etiology, and aneurysm calcification do not appear to influence the propensity to rupture.[127] Patients may present with a history of vague colicky abdominal pain or intestinal angina.[136] Acute abdominal pain and hemorrhagic shock are frequently encountered in cases of rupture. Patients experiencing biliary obstruction may also present with gastrointestinal bleeding and jaundice. The "double rupture" phenomenon seen in SAAs is reported in nearly 25% of ruptured CAAs.[33]

Treatment

Given the reported mortality rates associated with rupture of 50% and higher,[12,75] previous consensus suggested treating any CAA encountered regardless of size unless patient comorbidities prevented intervention. Corey et al. recently described their experience with 78 patients with CAAs, of whom 71 were managed with surveillance. Only 3 (5%) of those patients' aneurysms were noted to grow in size during an average

44-month surveillance time and none ruptured. A size criterion of greater than 2.5 cm for repair was advocated as a result of these findings.[18] Additionally, the Mayo Clinic reported the outcomes of 18 CAAs.[127] The patients observed in this series ($n = 8$) were considered to pose too high a risk for intervention and were followed with serial imaging. The only reported rupture occurred in a patient with a 2.5-cm CAA 5 years after initial presentation, with no other complication or aneurysmal growth reported in the remaining observed patients. The authors concluded that observation of CAAs can be a reasonable option if comorbidities preclude operative repair. However, the use of endovascular intervention for treating CAAs has been shown to be effective and may be an appropriate option for patients otherwise considered at high risk for surgery.[137]

Before the incorporation of endovascular intervention into modern practice, open surgical repair was the only option for the treatment of CAAs. Surgical options include ligation with or without reconstruction, aneurysmectomy, and aneurysmorrhaphy.[44,128,138] The need for arterial reconstruction depends largely on aneurysmal location and the adequacy of mesenteric collateralization. Ligation alone has been reported to be performed in one-third of cases, but this option is avoided in patients with liver disease.[12,128] A transabdominal approach is used to access the celiac axis. A prosthetic conduit or saphenous vein graft may be used in cases where simple ligation cannot be performed alone.[127] Intestinal viability should be assessed, and patients will need to be monitored for evidence of bowel, liver, or splenic ischemia in the postoperative course. A review of the modern literature demonstrated that operative therapy was successfully undertaken in 91% of 43 patients during the contemporary era, including eight in the author's series.[128] Endovascular intervention has been used with increasing success, incorporating coil or glue embolization, percutaneous thrombin or ethanol injection, and stent grafting.[63,136,137,139-142]

OTHER RARE SPLANCHNIC ANEURYSMS

Gastric/Gastroepiploic Aneurysms

Etiology

GAAs and gastroepiploic artery aneurysms (GEAAs) together represent less than 4% of all splanchnic artery aneurysms. The etiology of GAAs and GEAAs has been attributed to atherosclerosis in 30% of cases, trauma in 25%, and infection in 15%, but their true natural history is poorly defined.[143] Comorbid conditions include peptic ulcer disease, vasculitis, and pancreatitis.[34,75] There is a reported male predominance, with initial presentation in the sixth or seventh decade of life.[144] The majority of these aneurysms are located along the left or right gastric artery, whereas aneurysms along the greater curvature of the stomach are encountered much less frequently, at a reported ratio of 1 : 10.[145]

Clinical Presentation

Over 90% of reported GEAAs are ruptured on initial presentation, resulting in hemorrhage into the peritoneum. They usually present with mild epigastric pain, hemoperitoneum, and hemorrhagic shock requiring some form of intervention.

Treatment

Mortality rates for patients presenting with ruptured GAAs and GEAAs are near 70%.[75] Any GEAA or GAA discovered before rupture should be repaired. Emergent or ruptured cases are usually managed with open laparotomy. Open surgical repair includes either aneurysmectomy or exclusion. Simultaneous revascularization to maintain arterial inflow is generally not required. If proximal embolization is performed alone, the aneurysm may recruit a new vascular supply in a retrograde manner, hence the importance of simultaneous distal and proximal embolization.[146]

Pancreaticoduodenal and Gastroduodenal Artery Aneurysms

Etiology

PDAAs, GDAAs, and any aneurysms of their branches are extremely rare entities representing 2% and 1.5% of all splanchnic artery aneurysms, respectively. Since Ferguson's original description of a superior pancreaticoduodenal aneurysm in 1895, there has yet to be a definitive study evaluating the natural history of these lesions or a description of a preferred method of treatment.[147] Roughly 100 cases of PDAAs (Fig. 85.6) are described in the literature, most as single case reports.[148] Consistent with other splanchnic artery aneurysms, distinguishing between true and pseudoaneurysms is clinically significant due to varying etiologies and prognoses. GDA and PDA pseudoaneurysms are almost always associated with pancreatic pathology, celiac occlusion or stenosis, or abdominal trauma, including iatrogenic injury from percutaneous and laparoscopic interventions.[149,150] The male-to-female predominance is 4 to 1, with the average age of presentation in the sixth decade of life. This disproportionate

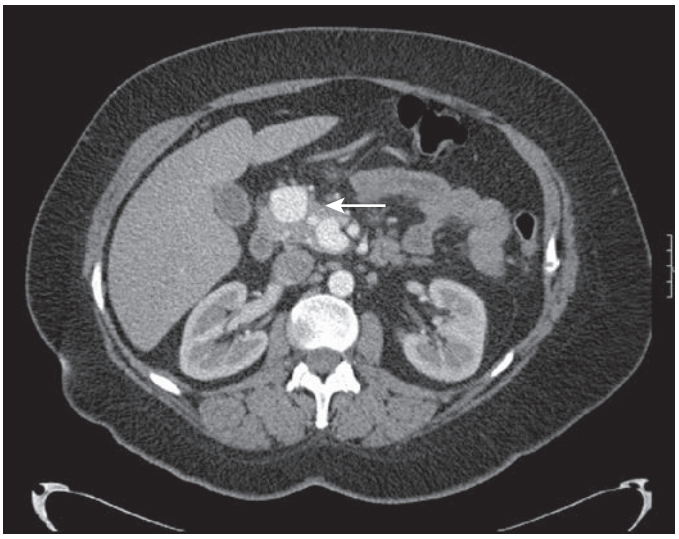

Figure 85.6 A 45-year-old female presented with abdominal pain and pancreatitis. A computed tomography scan revealed two aneurysms in the pancreatic head *(arrow)* that originated from branches of the superior mesenteric and celiac arteries.

ratio in relatively younger men may reflect alcoholic pancreatitis leading to pseudoaneurysm formation in the PDA or GDA.[151]

Clinical Presentation

Although the majority of patients have clinical findings, symptoms arising from PDAAs and GDAAs are most often vague and include epigastric abdominal pain, which may radiate to the back (Fig. 85.7). Other symptoms may include gastrointestinal bleeding, hypotension, emesis, diarrhea, and jaundice.[147] The gastrointestinal or biliary tract is the site of rupture in 65% of cases, whereas rupture into the retroperitoneal space occurs in 35% of cases.[152,153] In one series, 75% of PDAAs presented as rupture, with 50% mortality.[50] Another recent series reported 62% of PDAAs initially diagnosed at the time of rupture, with a 21% mortality rate.[148]

Treatment

There is no correlation between size and rupture risk of PDAAs and GDAAs. Diagnosis of these rare aneurysms mandate timely intervention given the high rate of rupture and mortality.[12] General consensus favors treatment of these lesions regardless of size.[148] Patients presenting with rupture have reported mortality rates of 30% to 40% even with intervention.[154] Ligation of the aneurysm and a partial pancreatectomy or pancreaticoduodenectomy may have to be performed.[148,155]

Endovascular techniques offer an excellent option in treating lesions that would otherwise be surgically challenging to access. Successful treatment requires ablation or exclusion of the aneurysmal sac from the circulation. Coil embolization techniques are generally preferred for these aneurysms, and limited case reports have reported promising success rates.[14,24,45] A large series reported a 78% success rate with coil embolization of 32 cases.[156] Reported complications included rupture and reperfusion of the sac. Percutaneous transabdominal thrombin injection of these aneurysms has also been described.[157]

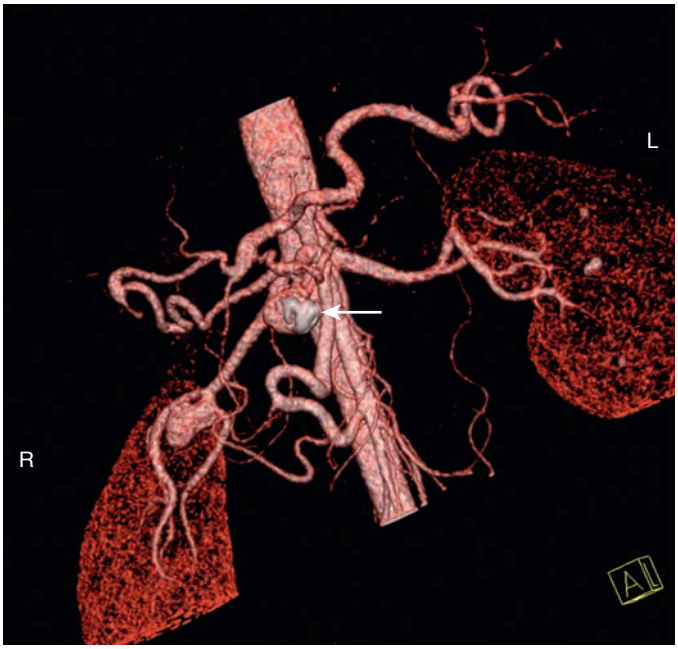

Figure 85.7 A computed tomography scan to evaluate a 44-year-old male with a history of nephrolithiasis revealed an aneurysm involving his right renal artery as well as a 2-cm aneurysm involving his gastroduodenal artery.

Inferior Mesenteric, Jejunal, Ileal, and Colic Artery Aneurysms

Etiology

Aneurysms of the inferior mesenteric and colic arteries are extremely rare, usually anecdotally reported in the literature, and have no clear treatment modalities beyond lifesaving intervention in the setting of free rupture. Most reported lesions are small (<1 cm) compared with other splanchnic aneurysms.[44,121,158] Literature review and large case series estimate that inferior mesenteric branch aneurysms comprise less than 2% of all reported splanchnic artery aneurysms.[12,44,159] The etiologies of these aneurysms remain poorly defined, with inflammation and infection associated with one-third of the cases. A large series from the Mayo Clinic reported eight patients with these mesenteric branch aneurysms, adding that most of these had a significant smoking history and used alcohol.[15] Two of the three females reported a history of multiple pregnancies, but no true relationship with multiparity and these aneurysms has been established. A recent literature review showed a male-to-female predominance of nearly 5 to 1.[160] There is also an association with inferior mesenteric branch aneurysm formation and stenosis or occlusion of the SMA and celiac trunk.[161]

Clinical Presentation

Mesenteric branch artery aneurysms are usually symptomatic and often ruptured at the time of presentation, and emergent operations are performed for lifesaving intervention. When rupture occurs, the mortality has been reported to be close to 20%.[12] Abdominal pain and hypovolemic shock are seen in approximately 85% of cases. In one series, 50% of patients presented with symptoms, whereas the other aneurysms were found incidentally.[15] Diagnosis can be made with cross-sectional imaging. As with other ruptured splanchnic aneurysms, diagnosis is often made at the time of laparotomy.

Treatment

Inferior mesenteric, jejunal, ileal, and colic artery aneurysms can rupture freely into the peritoneal cavity or into adjacent intestinal segments, causing gastrointestinal hemorrhage. Most reported cases of rupture involve an aneurysm less than 1 cm in size; therefore, any such lesion encountered should be treated.[15,44,121] Preoperative arteriography can aid in identification of the lesion and operative planning.[160,162] Open surgical treatment usually involves aneurysmectomy, particularly in the setting of IMAAs or ligation. Cases of endovascular treatment have been limited due to the scarcity of these lesions. Treatment results have generally been favorable, with few reported technical failures.[15,163] Successful treatment with endovascular intervention has been reported in the setting of rupture.[164]

Visceral Venous Aneurysms

Aneurysms of the visceral veins are an extremely rare and seldom encountered in the clinical setting. A recent meta-analysis of the English and French literature identified 93 reports wherein 176 patients with 198 visceral venous aneurysms were described.[165] Aneurysms are usually located at the main portal vein, the junction of the superior mesenteric and splenic veins, or the hepatic hilus.[166,167] Thrombosis, adjacent organ compression, and rupture are rare complications. The majority of these lesions can be followed with serial imaging. Open aneurysmorrhaphy or aneurysmectomy is indicated for symptomatic cases, thrombosis, adjacent organ compression, or rupture. Cases involving aneurysms of the splenic vein often require concomitant splenectomy and distal pancreatectomy. The role for endovascular intervention remains undefined.

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86 CHAPTER

Cerebrovascular Disease: Epidemiology and Natural History

CARON B. ROCKMAN and THOMAS S. MALDONADO

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BACKGROUND

Until fairly recently, stroke was largely believed to be a result solely of intracranial pathology. Indeed, in the seventh edition of his textbook published in 1909 and entitled *The Principles and Practice of Medicine*, William Osler attributed stroke mainly to intracranial hemorrhage or vasospasm and made no mention of carotid or vertebral artery occlusive disease.[1] Yet the relationship between extracranial carotid disease and stroke had been surmised previously as early as 1875, when Gowers reported on a patient with carotid occlusion, left visual loss, and right hemiplegia.[2] Subsequently, in 1905, Chiari studied 400

Abstract

Stroke is among the major causes of mortality and disability worldwide. The relationship of extracranial cerebrovascular disease to ischemic stroke has been clearly demonstrated. In particular, atherosclerotic occlusive disease of the carotid artery is considered to be one of the key treatable causes of ischemic stroke, and thus the role of the vascular surgeon in stroke prevention is critical. In this chapter, we provide an overview of the risk factors, epidemiology and natural history of both stroke and carotid artery occlusive disease, with an emphasis on those factors which influence the decision to treat carotid artery stenosis with either medical therapy or surgical or endovascular intervention.

Keywords

stroke
carotid artery stenosis
cerebrovascular disease
carotid endarterectomy
transient ischemic attack

consecutive autopsies and discovered thrombus superimposed on carotid artery atherosclerotic plaque in seven patients, four of whom had suffered embolic strokes.[3] This important observation likely represented the first pathophysiologic description linking carotid plaque atheroembolism to ischemic stroke. Perhaps the greatest breakthrough in the study of the mechanism of cerebrovascular disease was Fisher's publication of clinicoanatomic correlations on occlusion of the carotid arteries in 1951 and 1954.[4,5] He describes the atherosclerotic plaque as the culprit lesion in carotid artery disease and importantly notes that the distal internal carotid artery (ICA) is usually free of disease, raising the possibility of surgical bypass to a healthy target vessel. Fisher's prediction of surgical treatment for carotid atherosclerosis was soon realized. In 1954, Eastcott, Pickering, and Rob reported on the first successful carotid surgery for occlusive disease, in which the carotid bifurcation was resected and in-line flow restored via a common carotid-to-ICA anastomosis.[6] The first successful carotid endarterectomy (CEA) was performed by DeBakey in 1953 and reported along with a 19-year symptom-free follow-up in 1975.[7,8]

The precise role of this operation in the treatment of cerebrovascular disease remained controversial until the early 1990s, when several randomized clinical trials clearly demonstrated not only its safety and effectiveness but also its superiority to contemporaneous medical treatment in both symptomatic as well as certain asymptomatic patients.[9-13]

STROKE—BACKGROUND/INTRODUCTION

Stroke, or cerebral infarction, is the acute development of a focal neurologic deficit caused by disruption of the blood supply to an area of the brain. Strokes can be ischemic, due to occlusion of a blood vessel or other causes of malperfusion, or hemorrhagic, due to rupture of a blood vessel. Hemorrhagic strokes include both intracerebral hemorrhage, which is bleeding within the brain parenchyma, and subarachnoid hemorrhage, which is bleeding in the subarachnoid space.[14] The majority of strokes in the United States, approximately 87%, are in fact ischemic in etiology.[14] Extracranial cerebrovascular disease consisting of atherosclerotic occlusive disease of the carotid artery is considered to be one of the key preventable cause of ischemic stroke, along with atrial fibrillation and hypertension.

Stroke

Stroke is defined as an acute neurologic dysfunction of vascular etiology with corresponding signs and symptoms lasting more than 24 hours and resulting from infarction of focal areas of the brain. Ischemic stroke related to the carotid artery can present with sudden contralateral sensorimotor loss, speech deficit, and ipsilateral monocular blindness. In a transient ischemic attack (TIA), the ischemic parenchyma recovers and returns function to baseline. The full clinical impact of a stroke is often not apparent for up to 2 weeks, as the ischemic penumbra either recovers or succumbs to infarction. Although supportive care and rehabilitation following stroke allow for some or significant recovery in many patients, many deficits are long-lasting if not permanent as the cerebral parenchyma is irrevocably lost.

Cost of Caring for Stroke Patients

The estimated total direct and indirect cost of stroke in the United States in 2013 was $33.9 billion.[15,16] The direct costs of $18.8 billion included hospital outpatient or office provider visits, hospital inpatient stays, emergency department visits, medicines, and home healthcare.[15,17] Between 2012 and 2030 total direct medical stroke-related costs are projected to triple, from $71.6 billion to $184.1 billion, with the majority of the increase arising from patients between the ages of 65 to 79 years.[18] The total cost of stroke from 2005 to 2050 is projected to be approximately $1.52 trillion for non-Hispanic white patients, $313 billion for Hispanic patients, and $379 billion for black patients.[15,19]

Treatment of Acute Stroke

The acute treatment of ischemic stroke is generally and historically supportive and medical. The role of urgent surgical (CEA) or endovascular treatment of acute ischemic stroke related to carotid artery occlusive disease is controversial and its indications uncertain. In several recent studies, improved functional outcome in stroke patients who received endovascular intervention in conjunction with thrombolysis within a defined period of symptom onset was noted.[20-22] Although urgent thrombolytic therapy in combination with adjunctive endovascular therapy within several hours after an ischemic stroke is an attractive and important option, its widespread application may be limited from a practical and logistical point of view. Therefore the principal strategy against cerebrovascular disease and its role in causing ischemic stroke remains primary stroke prevention.

STROKE—PREVALENCE/INCIDENCE

Stroke Prevalence

Stroke is among the major causes of mortality and disability worldwide; it is estimated that in 2013 the prevalence of stroke was 25.7 million, with 10.3 million people experiencing a first stroke.[23] Stroke causes 5.5 million deaths and over 44 million disabilities every year.[24] In the United States alone, a stroke occurs approximately every 40 seconds; this translates into about 2160 strokes each day. Each year, approximately 800,000 Americans suffer a stroke.[14] The overall stroke prevalence or proportion of the population affected by stroke relative to the population as a whole in the United States during the years 2005 to 2008 was approximately 3.0%. The prevalence of additional but clinically silent cerebral infarction is estimated to range from 6% to 28%.[15,25-27] Projections show that by 2030, an additional 3.4 million people will have had a stroke, a 20.5% increase in prevalence from 2012.[16,18]

The prevalence of stroke varies with the population studied and is related to age, ethnicity, sex, and risk-factor profile (Figs. 86.1 and 86.2).[15] The prevalence of ischemic stroke increases with age in both men and women. In the United States, the prevalence of stroke varies by race and ethnicity; it is 6% among American Indian/Alaska Native populations, 4.0% among blacks, 2.6% among Hispanics, 2.3% among whites, and 1.6% among Asians.[28]

Stroke Incidence

Each year in the United States approximately 800,000 people experience a new or recurrent stroke[15]; approximately 185,000 of these are recurrent strokes.[15] Although women have a lower age-adjusted stroke incidence than men, women have a higher lifetime risk of stroke than men because of their longer life expectancy.[15,29,30] African Americans have a risk of first-ever stroke twice that of whites (Fig. 86.3).[15,29] Data from the Framingham Heart Study indicate that the age-adjusted incidence of clinical stroke per 1000 person-years in 1950 to 1977, 1978 to 1989, and 1990 to 2004 was 7.6, 6.2, and 5.3 in men and 6.2, 5.8, and 5.1 in women, respectively.[29] Analysis of data from the Framingham Study additionally suggests that stroke incidence is declining over time in this largely white cohort.[31] Unfortunately a similar decline was not noted in African Americans.

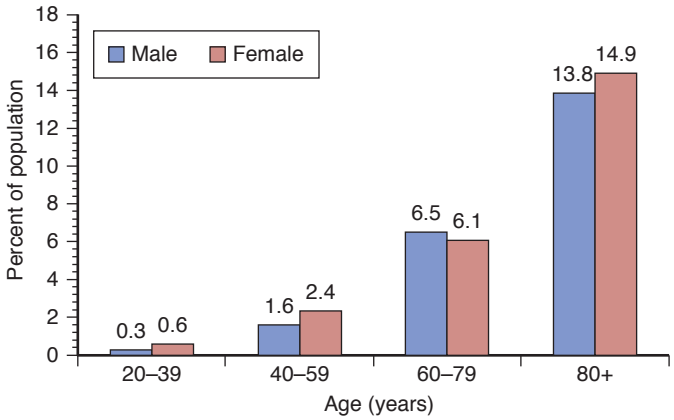


Figure 86.1 Prevalence of stroke by age and sex (National Health and Nutrition Examination Survey: 2011-2014). (From Benjamin EJ, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146-e603. *Used with permission.*)

DECLINING PREVALENCE/INCIDENCE OF STROKE

Possible Decreasing Prevalence and Incidence of Stroke

In December 2010, the Centers for Disease Control and Prevention announced that stroke had become the fourth leading cause of death in the United States, down from the third place ranking it had held for decades.[32,33] Currently stroke is felt to be the fifth leading cause of death when considered separately from other cardiovascular diseases.[16] Several additional population-based studies have tracked stroke incidence during recent decades.[34] Rothwell et al. reported a decrease in stroke incidence of nearly 40% between the 1980s and the year 2002 in the United Kingdom.[35] In an additional report from the American Heart Association, the lifetime risk of stroke in a 65-year-old male decreased from 19.5% 50 years ago to 14.5% in 2013.[36,37] In the United States, the Framingham cohort and the Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) also found that the incidence of stroke has been

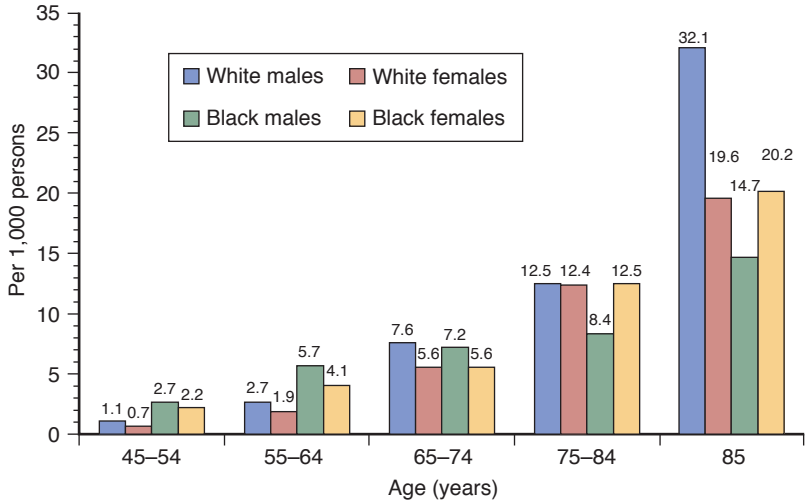


Figure 86.2 Annual incidence of first cerebral infarction by age, sex, and race (Greater Cincinnati/Northern Kentucky Stroke Study: 1999). Rates for black men and women 45 to 54 years of age and for black men 75 years of age and above are considered unreliable. *GCNKSS*, Greater Cincinnati/Northern Kentucky Stroke Study. (From Unpublished data from the Greater Cincinnati/Northern Kentucky Stroke Study; From Benjamin EJ, et al. Heart disease and stroke statistics; 2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146-e603. *Used with permission.*)

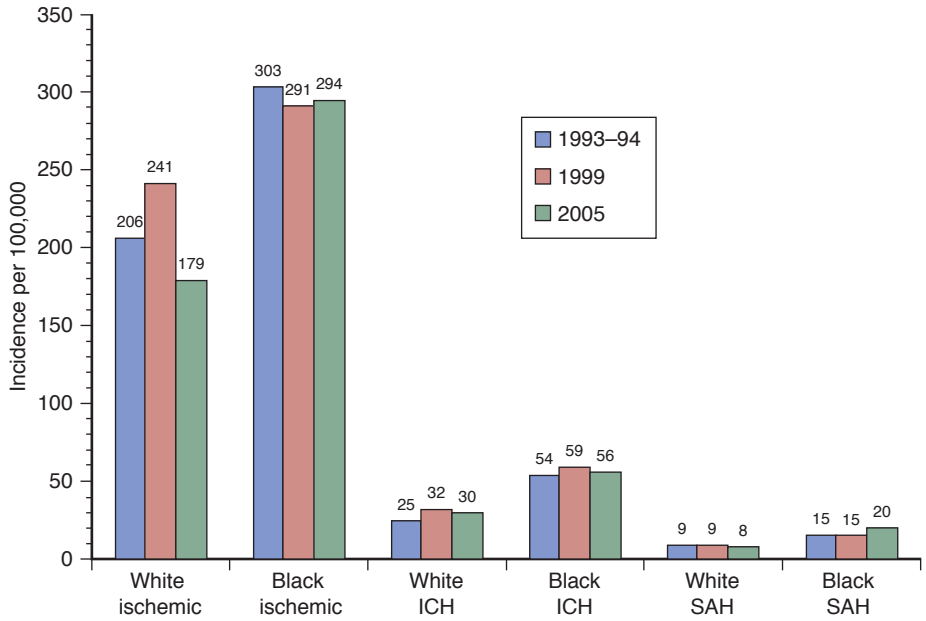


Figure 86.3 Annual age-adjusted incidence of first-ever stroke by race. *ICH*, Intracerebral haemorrhage; *SAH*, subarachnoid haemorrhage. (From Benjamin EJ, et al. Heart disease and stroke statistics; 2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146-e603. *Used with permission.*)

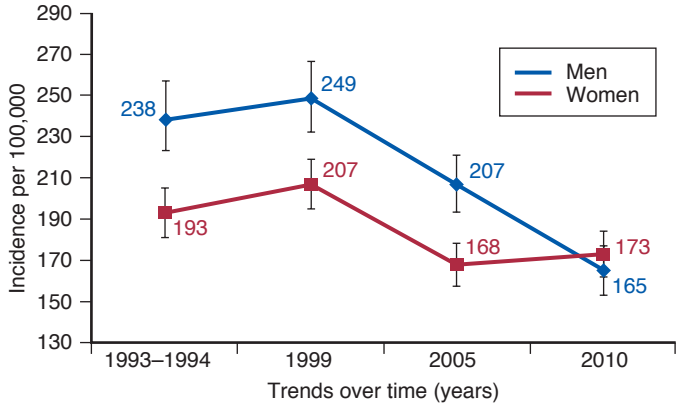


Figure 86.4 Ischemic stroke incidence rates and trends over time by sex. Incidence rates and 95% confidence intervals. Incidence rates were adjusted by age and race. (From Madsen TE, et al. Sex-specific stroke incidence over time in the Greater Cincinnati/Northern Kentucky Stroke Study. *Neurology*. 2017;89:990-996. *Used with permission.*)

declining over the past 50 years (Fig. 86.4).[29,34] In contrast to the prior reports, the Minnesota Stroke Study noted that the incidence of stroke appeared to be stable in both men and women between the years 1990 and 2000.[38]

In 2012, Koton et al. reported on trends in stroke incidence and mortality in the United States from 1987 to 2011.[39] This report from the Atherosclerosis Risk in Communities Study (ARIC) was a prospective cohort study of 14,357 participants. Stroke was ultimately diagnosed in 1051 of 14,357 participants (7%). Stroke incidence was strongly related to older age, male sex, black race, hypertension, diabetes, coronary heart disease, and current smoking. It was negatively associated with the use of cholesterol-lowering medications. Stroke incidence decreased over time in both white and black subjects. The decrease in age-adjusted incidence was evident in participants aged 65 years and older but not in younger subjects. The decrease in incidence was similar by sex. Additionally, mortality after stroke was noted to decrease over time. The authors conclude that there was a demonstrable decrease in stroke incidence and mortality rates in the United States during this time period. The decrease varied across age groups but was similar across sex and race.[39]

A review article by Zhang et al. in 2012 noted that the prevalence of stroke reported in the United States by the Centers for Disease Control (CDC) Behavioral Risk Factor Surveillance System in the years 2005 and 2008 was equivalent at 2.6%.[40] After a comprehensive review of multiple population-based studies, it was not possible to prove or disprove whether the prevalence of stroke may be decreasing. However, it was felt that there was abundant evidence that the *mortality* attributable to acute stroke is decreasing, likely related to improvements in acute stroke treatment.[40] It was furthermore noted that an increase in the burden of stroke due to the aging populations of both the United States and European countries was still to be expected.

Finally, more recent data from GCNKSS reported in 2017 showed that decreases in stroke incidence over time have been driven primarily by a decrease in ischemic stroke in men as opposed to women. In contrast to their reports from prior study periods, stroke incidence rates were noted to be similar by sex in 2010.[41]

Effect of Improved Medical Therapy on the Reduced Incidence of Stroke

The possible effect of improved modern medical therapy on the decreased incidence of stroke has received great attention

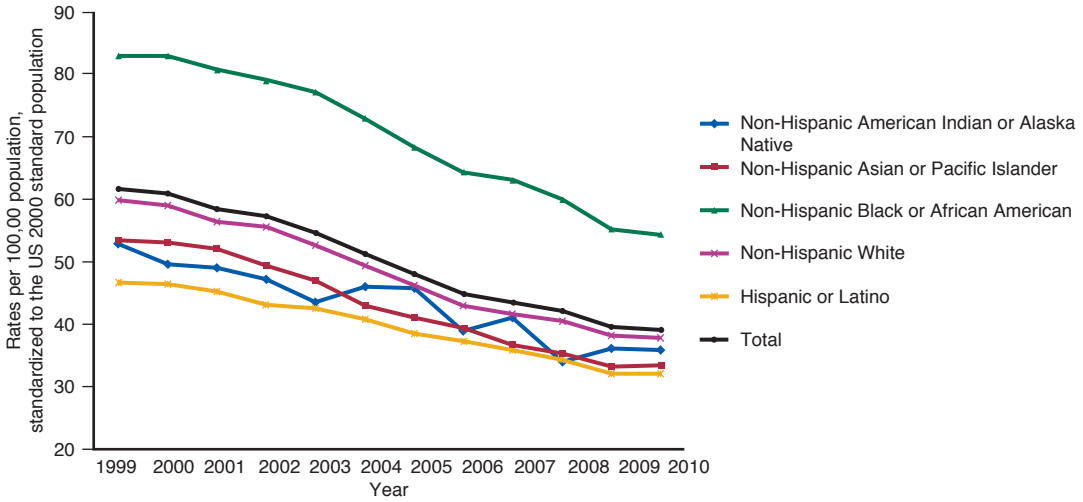


Figure 86.5 Age-adjusted death rates for cerebrovascular disease by race and by year. United States 1999–2010. (From Lackland D, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:315-353.)

in the recent literature and has resulted in challenges to the role of CEA for asymptomatic patients. Previous randomized trials have demonstrated a clear benefit of surgical therapy with CEA over contemporaneous medical therapy regarding stroke prevention in both asymptomatic and previously symptomatic patients with severe extracranial ICA stenosis.[11,13,42] Some recent analyses have additionally reported that the annual risk of stroke even in patients with known asymptomatic ICA stenosis is lower than that reported in the CEA trials, presumably due to improved medical therapy.[43,44] Nevertheless it remains clear that asymptomatic ICA stenosis continues to cause a significant number of strokes.[45] Data from the GCNKSS have resulted in conservative estimates that about 41,000 strokes may be attributed to previously asymptomatic extracranial ICA stenosis annually in the United States.[45] The increased usage of cholesterol-lowering medications is often cited as the likely reason behind the decreased incidence of stroke.

The epidemiologic association between elevated cholesterol levels and stroke is inconsistent and somewhat controversial.[46] Despite this, treatment with statins has generally shown stroke reduction, as also reflected in the report of a meta-analysis of more than 90,000 patients.[47] It should be noted that many of the studies included in this meta-analysis involved secondary as opposed to primary stroke prevention. Nevertheless the relative reduction in stroke risk was found to be 21%. Statins have also been demonstrated to be associated with a reduction in stroke incidence in a variety of specific patient populations, including those with known coronary artery disease,[48] hypercholesterolemia,[48] normocholesterolemia,[48] elderly patients,[48] and diabetics.[49] Statins have also been demonstrated to consistently reduce carotid intima-media thickness (CIMT).[50] A recent meta-analysis including over 113,000 patients has shown that the use of statin therapy at stroke onset is associated with improved late outcome, including both rates of functional independence and survival.[51] Although data regarding the utility of statin medications for the primary prevention of stroke is less conclusive than for secondary prevention, current guidelines do in fact recommend statins for the prevention of first stroke in high-risk patients, including those with LDL levels greater than 4.1 and for males older than age 45 and females older than age 55 with the following risk factors: a positive family history, smoking, hypertension, or left ventricular hypertrophy.[46] However, it is unclear what exact role and effect statins have in patients with known severe carotid occlusive disease with regard to stroke prevention (see Chapter 13).

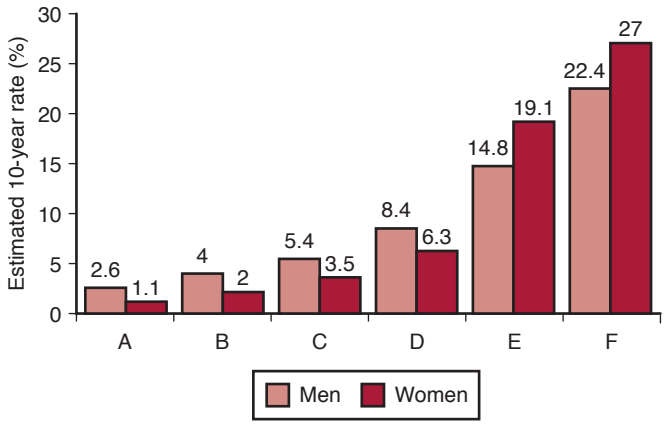
In a recent report authored by Writing Group Members on behalf of the American Heart Association's Stroke Council, a clear decline in stroke mortality is noted (Fig. 86.5).[52] The authors feel that this reduction is mainly due to the treatment of hypertension as opposed antilipid therapy. The authors note that epidemiologic studies have shown that elevated blood pressure is the most important determinant of the risk of stroke.[52] They also believe that improved treatment of hypertension is likely the most important factor that has contributed to the decline in stroke mortality (see Chapter 14).

ISCHEMIC STROKE—EPIDEMIOLOGY

Risk Factors for Stroke

Stroke prevention strategies should ideally be focused on high-risk populations. The risk factors for ischemic stroke include many of the risk factors for generalized atherosclerosis, as listed further on and shown in Fig. 86.6.[14,15,53] In addition to these risk factors for ischemic stroke, prior TIA and carotid artery atherosclerosis represent obvious major clinical risk factors for future ischemic stroke. The following factors have been clearly shown to be related to the risk of stroke in the general population:

Sex: The estimate 10-year stroke risk in adults 55 years of age and older differs by sex and the increasing presence of multiple risk factors.[16] Ischemic stroke is in general more prevalent in men than in women.[54] However, women tend to account for a higher percentage of stroke mortalities; this is likely because of their greater longevity.[14]



	A	B	C	D	E	F
Systolic BP	95–105	130–148	130–148	130–148	130–148	130–148
Diabetes	No	No	No	Yes	Yes	Yes
Cigarettes	No	No	No	Yes	Yes	Yes
Prior A Fib	No	No	No	No	Yes	Yes
Prior CVD	No	No	No	No	No	Yes

Figure 86.6 Estimated 10-year stroke risk in adults 55 years of age according to levels of various risk factors. *AF*, Atrial fibrillation; *BP*, blood pressure; *CVD*, cardiovascular disease. (From Benjamin EJ, et al. Heart disease and stroke statistics; 2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146-e603. *Used with permission.*)

Age: Increasing age is a major risk factor for ischemic stroke. For each decade after 55 years of age, the risk of stroke approximately doubles.[55]

Race: Blacks and Hispanics have a risk of first-ever stroke that is approximately twice that of whites.[56] Blacks may have a lower prevalence of carotid artery disease than whites, and it is hypothesized that the increased stroke rate among black patients is more likely related to hypertension and intracranial disease.[57]

Hypertension: Hypertension is a significant risk factor for both ischemic stroke and intracranial hemorrhage.[16] Appropriate treatment of blood pressure in hypertensive patients is associated with a significant reduction in the risk of ischemic stroke; patients with a blood pressure less than 120/80 have half the lifetime risk of stroke than subjects with hypertension.[15,58] So-called intensive blood pressure control as opposed to standard treatment has also resulted in a significantly lower risk of stroke.[59] Strict blood pressure control can also reduce the risk of recurrent stroke.[60]

Family history: A parental history of stroke, TIA, or myocardial infarction is associated with a 1.4- to 3.3-fold increased risk for stroke.[61]

Atrial fibrillation: Patients with atrial fibrillation have a three- to fivefold increased risk of cardioembolic ischemic stroke.[62]

Cigarette smoking: Current cigarette smokers have a two to four times increased risk of stroke as compared with nonsmokers or those who have quit for more than 10 years.[15,63,64] Discontinuation of smoking reduces future stroke risk in multiple demographic patient categories.[65]

Hypercholesterolemia: Trials specific to ischemic stroke have demonstrated that there may be a 25% increased risk of ischemic stroke with each 38.7 mg/dL increase in total cholesterol levels.[66] However, not all trials have consistently demonstrated a correlation between hypercholesterolemia and ischemic stroke.[14] An association between total cholesterol levels and ischemic stroke has been found in some studies but has not been confirmed in others.[16]

Physical activity: Increased leisure-time physical activity is protective against stroke across race, sex, and age, and related to the level of intensity and the duration of activity.[67] In the REGARDS study, participants who reported physical activity less than four times a week had a 20% increase in stroke risk as compared with those who exercised more than four times a week. However, it is possible that this is related to the fact that physical activity also improves traditional risk factors such as diabetes and obesity.[16,68]

Diabetes: Diabetes is a risk factor for ischemic stroke at all ages, but the most significant risk increase appears to occur among patients less than 65 years of age.[16] Diabetes mellitus nearly doubles the risk of stroke among persons with diabetes as compared with others who have normal glucose levels.[69] The effect of diabetes on stroke risk appears to be more significant in women than in men.[70] Intensive glucose control did not appear to result in reduced stroke risk as compared with conventional glucose control (see Chapter 12).[71]

Diet: A protective relationship between fruit and vegetable consumption and decreased ischemic stroke risk has been reported.[72] A Mediterranean-style diet higher in the consumption of nuts and olive oil has been shown to be associated with a reduced risk of stroke.[73]

Obesity: Obesity is a specific risk factor for ischemic stroke in both men and women.[74,75] There is an additional association between abdominal obesity and ischemic stroke in men.[76]

Alcohol: There is a reported increased risk of ischemic stroke with "irregular" drinking, including heavy and binge drinking.[77] However, moderate drinking may be associated with a decreased risk of ischemic stroke.[78]

Renal insufficiency: Mild to moderate renal insufficiency is an independent predictor of ischemic stroke in both asymptomatic patients and patients with peripheral arterial disease.[79-81]

The INTERSTROKE Study, in 2010, reported a case-control study of 2337 ischemic stroke cases in 22 countries worldwide. Patients with an acute first stroke were compared with controls with no history of stroke and were matched for both age and sex.[53] The authors found that five factors accounted for more than 80% of the global risk of all ischemic strokes: hypertension, current smoking, abdominal obesity, poor diet, and physical inactivity.[53] Hypertension was the most important risk factor for all stroke subtypes.[53,82]

ISCHEMIC STROKE—NATURAL HISTORY

Because carotid artery interventions are performed to prevent future stroke, it is essential to understand the natural history

of carotid disease, stroke, and TIA in order to properly assess the risks and benefits of potential intervention.

Outcome of Stroke

Following an ischemic stroke, the risk for recurrent ischemic stroke is 2% at 7 days, 4% at 30 days, 12% at 1 year, and 29% at 5 years.[83] The risk of death after an initial ischemic stroke is 7% at 7 days, 14% at 30 days, 27% at 1 year, and 53% at 5 years (Fig. 86.7).[83] Somebody in the United States dies every 4 minutes from a stroke,[15,84] and strokes accounts for 1 out of every 18 deaths.[15,84] When considered separately from other cardiovascular diseases, stroke currently ranks fifth among all causes of death, behind heart disease, cancer, and chronic lower respiratory disease.[15,84] As previously discussed, stroke mortality rates appear to be decreasing; from 1998 to 2008 the actual number of stroke deaths declined by 19.4%.[15,85]

Stroke is the leading cause of serious long-term disability in the United States.[15,86] Among ischemic stroke survivors who were 65 years of age or older, the following disabilities were observed at 6 months after a stroke: 50% had hemiparesis, 30% were unable to walk without assistance, 26% were dependent in activities of daily living, 19% had aphasia, 35% had depressive symptoms, and 26% were institutionalized.[15,87] A contemporary perspective on the impact of stroke is available from the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) data[88]; even though few of the strokes related to either CEA or carotid artery angioplasty and stenting carotid artery stenosis (CAS) were major in extent, the estimated 4-year mortality after stroke was 21.1%, compared with 11.6% for those without stroke, including those who had undergone carotid revascularization. The adjusted risk of death at 4 years was higher after periprocedural stroke (hazard ratio, 2.78).

Stroke may also be associated with long-term cognitive decline.[89] Although it is obvious that acute stroke may be responsible for acute changes in cognition, it has also been demonstrated that acute stroke is additionally associated with accelerated and persistent cognitive decline over 6 years.

Recurrent Stroke Following an Initial Event

Patients who have had an initial stroke are additionally at greatly increased risk for subsequent events. Based upon a population cohort study of more than 10,000 patients discharged from hospitalization with a diagnosis of stroke, the rates of recurrent stroke were 1.8% at 1 month, 5% at 6 months, 8% at 1 year, and 18.1% at 4 years.[90] This information is particularly relevant in considering the timing of carotid intervention in appropriate patients following an initial nondisabling stroke so as to most successfully prevent a subsequent cerebrovascular event. Recurrent stroke is associated with a greater number of baseline risk factors and with large artery occlusive disease as opposed to other causes of stroke (Fig. 86.8).[91,92]

In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), medically randomized patients with symptomatic carotid artery disease (stroke or TIA) and high-grade carotid stenosis had an ipsilateral stroke rate of 26% over 2 years.[13] Major or fatal ipsilateral stroke occurred in 13.1% of patients. In the 32-day period following randomization of medically treated symptomatic patients, 3.3% experienced stroke or death.

Stroke Mortality

Stroke accounts for approximately 1 of every 20 deaths in the United States.[16] Data from the ARIC study revealed that all-cause mortality rate after a stroke was 10.5% at 30 days, 21.2% at 1 year, 39.8% at 5 years, and 58.4% at 24 years.[39] A CDC report found that among Medicare beneficiaries, the 30-day mortality following a stroke varied by age and ranged from

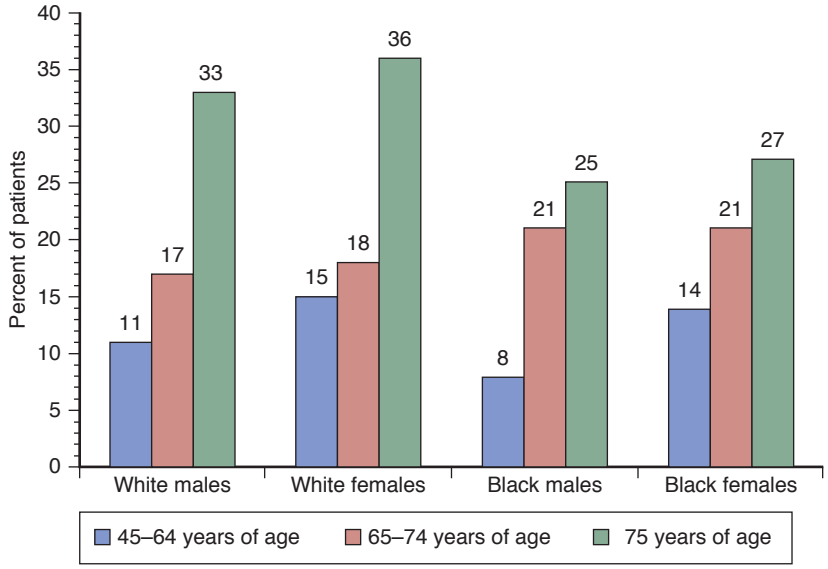
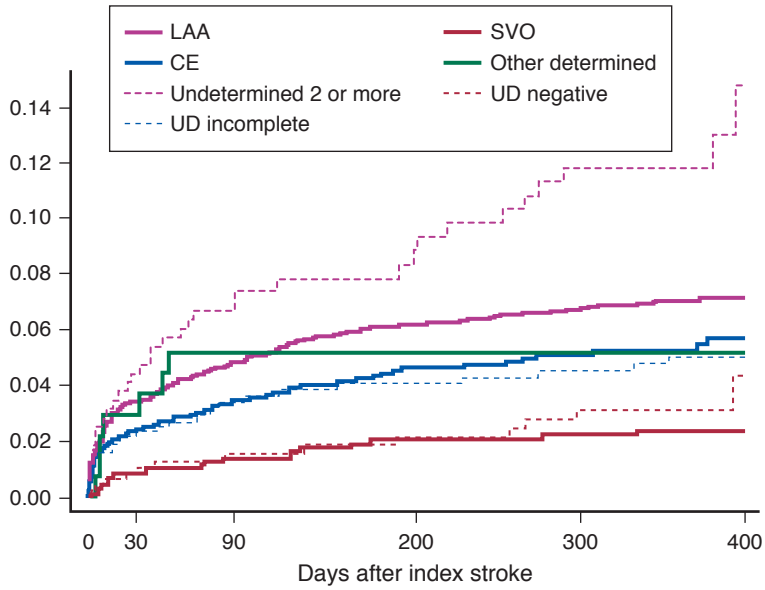


Figure 86.7 Probability of death within 1 year after first stroke. (From Benjamin EJ, et al. Heart disease and stroke statistics; 2017 update: a report from the American Heart Association. *Circulation*. 2017;135:e146-e603. *Used with permission.*)



Number at risk						
LAA	2,531	2,404	2,225	1,706	1,689	402
SVO	963	942	876	669	666	150
CE	1,500	1,411	1,265	933	918	228
Other determined	136	130	120	96	95	17
Undetermined 2 or more	319	297	261	185	178	37
UD negative	457	445	404	315	311	61
UD incomplete	691	636	583	407	404	107

Figure 86.8 Kaplan-Meier survival curves comparing risk of recurrent stroke according to stroke subtype. *CE,* Cardioembolism; *LAA,* large artery atherosclerosis; *SVO,* small vessel occlusion; *UD,* undetermined cause. (From Ko Y, et al. MRI-based algorithm for acute ischemic stroke subtype classification. *J Stroke*. 2014;16:161-172. *Used with permission.*)

9% in patients 65 to 74 years of age to 23% in those over 85 years of age.[93]

TRANSIENT ISCHEMIC ATTACK—BACKGROUND/INTRODUCTION

A TIA, often referred to as a "ministroke," is a neurologic event that presents with stroke-like symptoms less than 24 hours in duration. In fact, the vast majority of these symptoms last for only a few minutes. A TIA should be considered a warning sign for future stroke, as approximately 30% of patients who have had a TIA go on to suffer a stroke within 5 years.[94] Unlike a stroke, where flow is permanently interrupted, resulting in infarction, TIA symptoms are short-lived and resolve upon restoration of flow to the brain, returning the patient to neurologic baseline. Yet it is important to note that a TIA is a clinical diagnosis; although neurologic baseline is restored within 24 hours, cell death may have occurred nonetheless. Indeed, brain computed tomography performed on 284 patients presenting with clinical TIA and without previous clinical stroke revealed demonstrable infarction in 24% of patients.[95]

Symptoms of TIA or stroke resulting from carotid disease are related to the cerebral vascular territory affected. The carotid artery supplies the anterior circulation; thus carotid disease can result in symptoms associated with injury to brain parenchyma of the anterior cerebral artery or middle cerebral artery distribution. Motor symptoms can range from mild hemiparesis to complete hemiparalysis contralateral to the affected hemisphere. Likewise, sensory deficits may consist of mild numbness or complete paresthesia of the contralateral extremities. Language loss (dysarthria, dysphasia, or aphasia) can occur when the dominant hemisphere is affected. Amaurosis fugax (transient monocular blindness or field cuts), resulting from emboli to the retinal artery via the ophthalmic artery, is considered to be the classic symptom of TIA related to carotid artery lesions. Unlike thromboemboli of cardiac origin, carotid emboli tend to present with TIAs rather than stroke. Moreover, TIAs of carotid artery origin tend to occur in the same vascular territory, whereas TIAs of cardioembolic origin are more haphazard in location and symptomatology.[96,97]

TRANSIENT ISCHEMIC ATTACK—PREVALENCE

Like the epidemiology of stroke, the incidence of TIA increases with age and varies by sex and race/ethnicity.[16] Approximately 15% of all strokes are heralded by a TIA.[98] Patients who have had a TIA have a significant risk of subsequent stroke in the short term: among a cohort of patients seen in an emergency room with a TIA, 11% experienced a subsequent stroke within

90 days, and 5% experienced a subsequent stroke within 2 days.[99] This finding and other supportive data are relevant to the recommendations for the timing of carotid intervention in appropriate patients following an initial TIA so as to prevent a subsequent episode of frank or completed clinical infarction. The estimated incidence of self-reported or physician-diagnosed TIA in the United States is approximately 2.3%, but the true incidence is likely higher.[15,99] Additionally, the true prevalence of TIAs may actually be higher than reported because many patients who may experience subtle neurologic symptoms do not report them to a healthcare provider.[16]

TRANSIENT ISCHEMIC ATTACK—NATURAL HISTORY

The most important consideration in patients who have experienced a TIA is their future relevant stroke risk. The presence and diagnosis of a TIA, if found in the setting of ipsilateral and appropriate severity of carotid artery disease, offers the practitioner the opportunity to intervene to prevent subsequent stroke.

Independent predictors of subsequent stroke following a TIA included age greater than 60 years, diabetes mellitus, the presence of focal symptoms, and TIAs that lasted longer than 10 minutes.[15,99] Individuals who experience a TIA and survive the initial high-risk period have a 10-year stroke risk of about 19%.[15,100] Two meta-analyses of TIA patients reported that the short-term risk of stroke following TIA was a similar: 3% to 10% at 2 days, and 9% to 17% at 90 days.[98,101] Approximately one-third of episodes characterized as a TIA according to the clinical definition would probably be considered cerebral infarctions on the basis of diffusion-weighted magnetic resonance imaging (MRI) findings.[15,102,103] Because of the substantial risk of ischemic stroke following a TIA, patients with transient focal hemispheric symptoms should be expediently evaluated for the presence of significant carotid artery disease.

Patients with TIA are also at risk for disability as well as long-term morbidity and mortality.[104] In 2017, Edwards et al. reported that among more than 25,000 patients who were initially stable after a TIA or stroke, both clinical groups were at significant risk for recurrent stroke. Although patients who initially had a stroke were the higher-risk group, even 31.5% of TIA patients specifically experienced an adverse event within 5 years.

EXTRACRANIAL CAROTID ARTERY ATHEROSCLEROSIS—BACKGROUND

Pathophysiology

Most acute coronary syndromes are caused by thrombus formation in moderately stenotic coronary arteries at the site of a ruptured or eroded fibrous cap.[105,106] Atherosclerotic plaque in the carotid artery causes a substantial proportion of ischemic strokes, but the mechanisms are less well understood than those of acute coronary thrombosis.[105] Carotid artery plaque can cause TIA or stroke by two mechanisms: embolization and hypoperfusion. Due to the abundant collateral circulation in the brain, global cerebral hypoperfusion is rare; it occurs only in patients with severe multivessel occlusive disease in both the carotid and vertebral artery territories. Atheroembolization of debris originating from carotid artery plaque and traveling to the brain is felt to be the predominant cause of both TIA and ischemic stroke related to carotid artery disease. Evidence for the role of embolization comes from the early reports of Hollenhorst, who found embolic debris in the retinal vessels of patients with transient monocular blindness.[107] The severity of carotid artery stenosis is strongly associated with stroke risk in symptomatic patients.[10,105,108] Currently it is the most important predictor of benefit from carotid artery intervention.[109] However, other factors predictive of stroke clearly exist, including an ulcerated appearance present on carotid arteriography or duplex ultrasonography, which is also a strong independent risk factor for acute stroke.[105,110,111]

The degree of carotid artery stenosis is a critical factor involved in identifying patients at increased risk of future ischemic stroke; in fact, however, most asymptomatic patients with moderate degrees of carotid artery stenosis are at relatively low risk for future stroke. On the other hand, only 15% of ischemic strokes are preceded by a warning TIA. Therefore waiting for stenosis to become symptomatic fails to prevent most strokes caused by carotid artery disease.[112] Hence there is a critical need to improve the selection of asymptomatic patients for carotid intervention so as to improve the potential effectiveness of treatment in stroke prevention.[113] With this goal in mind, there has been a great deal of focus on identifying other characteristics of both the patient and the carotid plaque itself that would be distinguishable on imaging studies and allow the clinician to identify patients at increased risk for ischemic stroke who would most benefit from vascular intervention. The term "vulnerable" plaque is often used to denote unstable plaques, or plaques prone to complications, including embolization and subsequent stroke.

The Vulnerable Plaque and Patients at Increased Risk for Ischemic Stroke

A strong attempt has been made to identify patients with carotid disease at increased risk for stroke by combining both morphologic plaque features and clinical patient characteristics. The Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group attempted to determine the cerebrovascular risk stratification potential of baseline degree of stenosis, clinical features, and ultrasonic plaque characteristics in patients with asymptomatic carotid artery stenosis.[79] This was a prospective cohort study involving 1121 patients with 50% to 99% asymptomatic ICA stenosis who were followed for 6 to 96 months. The authors found that the following characteristics were associated with increased risk for ipsilateral cerebral or retinal ischemic events: severity of stenosis, age, systolic blood pressure, increased creatinine, smoking history of more than 10 pack-years, history of contralateral TIA or stroke, low

TABLE 86.1 Estimated Percent Risk of Ipsilateral Ischemic Cerebral Stroke Within 5 Years Based Upon Degree of Stenosis, History of Symptoms, and Plaque Characteristics

Degree of Stenosis	History of Contralateral TIA or Stroke	DWAs Present	Plaque Area (mm^2)	GSM		
				>30	15–30	<15
83% to 99% NASCET	Present	Yes	>80	20.3%[a]	52.8%[a]	[b]
			40–80	13.8%	35.8%	70%[a]
			<40	7.8%[a]	20.1%[a]	[b]
		No	>80	13.3%[a]	34.5%[a]	[b]
			40–80	9%[a]	[b]	45.7%[a]
			<40	5.1%[a]	13.1%[a]	25.7%[a]
	Absent	Yes	>80	7.7%[a]	20%	39.1%[a]
			40–80	5.2%	13.5%	26.5%
			<40	2.9%	7.6%	14.9%[a]
		No	>80	5%[a]	13%[a]	25.5%[a]
			40–80	3.4%[a]	[a]	17.3%
			<40	1.9%	5%	9.7%[a]

[a]Covariate combination, which occurred less than five times in observed data.
[b]Covariate combination, which did not occur in observed data,
DWAs, Discrete white areas; *GSM*, gray scale median; *NASCET*, North American Symptomatic Carotid Endarterectomy Trial; *TIA*, transient ischemic attack.
Modified from Nicolaides AN, et al. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg*. 2014;52:1486-1496. *Used with permission.*

gray-scale median, increased plaque area, and the absence of discrete white areas without acoustic shadowing. Combinations of these characteristics could stratify patients into different levels of risk for stroke (Table 86.1). Of 923 patients with 70% or greater stenosis, the predicted cumulative 5-year stroke risk was less than 5% in 495, 5% to 9.9% in 202, 10% to 19.9% in 142, and 20% or more in 84. The authors concluded that cerebrovascular risk stratification related to carotid artery disease is possible using a combination of clinical and ultrasonic plaque features. In a more recent update from the ACSRS group,[114] the authors expounded on their previous work and noted that the size of a juxtaluminal black hypoechoic area in ultrasound images of asymptomatic carotid artery plaques is linearly related to the risk of future stroke and is an additional factor that can be utilized to predict the risk of future ipsilateral ischemic stroke (see Chapter 87).

Transcranial Doppler Detection of Microembolization

Since thromboembolization is generally regarded as the mechanism of ischemic stroke in patients with carotid bifurcation atherosclerosis, the detection of subclinical embolization may help to identify patients at high risk of future stroke.[113] Transcranial Doppler (TCD) testing involves the detection of microembolism in the MCA using TCD insonation; the detection of high-intensity transient signals ("HITS") is felt to represent microemboli to the brain. HITS are detectable only in the presence of an embolic source, are undetectable days after CEA, and are absent in controls without carotid stenosis, suggesting a relationship between carotid atherosclerotic plaque and microembolization.[113] HITS frequency rises with increasing stenosis, and an increased rate of HITS is associated with plaque ulceration; this emphasizes the likely association between HITS and plaque instability.[113] Thus the concept of HITS represents an attractive option for stratifying patients with carotid artery disease who may be at increased risk for future stroke.

The Asymptomatic Carotid Emboli Study (ACES) attempted to investigate whether detection of embolic signals by use of TCD could predict stroke risk in patients with asymptomatic carotid stenosis.[112] This was a prospective observational study including patients with carotid stenosis of at least 70% who were followed for at least 2 years. The primary endpoint was ipsilateral stroke or TIA. The study included 267 patients; embolic signals were present in 77 patients at baseline. The hazard ratio for stroke or TIA was 2.54 as compared with patients without embolic signals at baseline. The hazard ratio for ipsilateral stroke alone was 5.57. The absolute annual risk of ipsilateral stroke or TIA was 7.13% in patients with embolic signals and 3.04% in those without; for stroke alone the annual risk was 3.62% in patients with signals and 0.7% in those without.[112] The authors concluded that detection of asymptomatic embolization on TCD can be used to identify patients with asymptomatic carotid stenosis who are at higher risk of stroke and TIA and who might benefit from carotid intervention. Similarly, Spence et al. studied 319 patients with carotid artery stenosis of 60% or more who had been asymptomatic for at least 18 months.[115] Of these, 32 patients or 10% had emboli

signals at baseline examination. Patients with embolic signals were more likely to have a stroke within 1 year (15.6% vs. 1%).

Unfortunately TCD may not represent a practical screening tool on a widespread scale in view of its having a time consuming nature, there is no reliable automated emboli detection system, and a small proportion (10%) of subjects lack a cranial acoustic window needed for TCD.[113]

Types of Strokes and Relationship of Stroke to Carotid Artery Atherosclerosis

There are five general categories of ischemic stroke, according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification: cardioembolic strokes, large vessel disease strokes, strokes due to small vessel disease, strokes related to unusual causes, and strokes of undetermined etiology.[116] The TOAST classification is based on clinical and radiologic findings as well as additional investigations such as duplex ultrasonography, electrocardiography (ECG) analysis, echocardiography, and blood tests. Clinical studies on stroke subtype fail to identify a definitive cause of stroke in at least 25% to 39% of patients.[117] Traditionally it has been estimated that large vessel disease caused stroke in 50% of cases.[117] Recent studies, however, have shown that small vessel disease is more frequent and large vessel disease less frequent than previously estimated.[118]

In the Rochester Epidemiology Project, 442 patients with a first ischemic stroke from 1985 through 1989 were evaluated. Four major categories were identified: large vessel cervical or intracranial (16.7%), cardioembolic (29.9%), lacunar (16.3%), and strokes of uncertain cause (37.1%). Therefore the large vessel cervical etiology comprised approximately 16% of all ischemic strokes and 27% of strokes with determined causes. Interestingly, patients with large vessel strokes had the highest rates of recurrent stroke at 30 days (18.5%).[119]

In an additional study, patients with first-ever or recurrent ischemic stroke in the greater Cincinnati area were identified during the year 2005.[45] This report comprised 2204 ischemic strokes, including 365 (16.6%) of the large vessel subtype. Carotid artery stenosis was associated with 8% of all ischemic strokes, while ICA occlusion was associated with an additional 3.5%. The annual rate of first-ever and recurrent stroke attributed to the extracranial carotid artery was 13.4 per 100,000 persons. Based on this analysis, it was conservatively estimated that about 41,000 strokes per year in the United States may be attributed to extracranial ICA stenosis alone (without considering additional strokes related to complete carotid artery occlusion).[45]

Most prior studies on this topic have examined patients who have sustained strokes, and tried to ascertain the etiology of the cerebrovascular event. An additional study took an alternative approach by following a group of patients with known unilateral asymptomatic carotid artery stenosis and analyzed the types of strokes that occurred in such patients.[120] The risk of stroke at 5 years in 1820 patients increased with the severity of stenosis; it reached 3.2% annually among the 216 patients with 60% to 99% stenosis. Among this cohort, however, the 5-year risk of a stroke in the territory of a large artery was 9.9%, that of lacunar stroke was 6%, and that of cardioembolic stroke was 2.1%. Risk factors for large artery stroke included silent brain infarction, a history of diabetes, and a higher degree of stenosis. The study concluded therefore that 45% of strokes in patients with asymptomatic stenosis of 60% to 99% are attributable to either lacunar strokes or cardioembolism and are not a direct result of large artery disease.

Racial differences have been noted in stroke subtypes.[121] Of ischemic stroke patients, large vessel strokes were felt to account for 10% in black patients and 12% in white patients. However, stroke cause was felt to be undetermined in approximately 50% of both racial groups. Only 60% of patients in both racial groups underwent a carotid duplex examination, and only 3% to 5% underwent a cerebral angiogram.

Based on these and other studies and in consideration of the fact that most studies on this topic fail to determine with certainty the etiology of ischemic stroke in a high percentage of cases, most experts in this field feel that at least 20% of ischemic strokes are likely related to extracranial carotid artery atherosclerosis.

EXTRACRANIAL CAROTID ARTERY ATHEROSCLEROSIS—EPIDEMIOLOGY

Prevalence of Carotid Artery Disease

As with atherosclerosis in other vascular territories, cerebrovascular disease, particularly in the extracranial carotid artery, is relatively prevalent in the general population In the Tromso Study involving nearly 7000 adults aged 25 to 84 years, ICA stenosis was detected in 3.8% of men and 2.7% of women. The prevalence increased with age, total cholesterol, systolic blood pressure, and cigarette use.[122] In another population-based study of older healthy patients aged 60 to 79 years, the prevalence of ICA stenosis found by duplex examination was 10.5% in men and 5.5% in women.[123] Despite the increased risk of carotid artery disease in known patient populations, the actual role of screening in asymptomatic patients remains controversial.

In a screening program of asymptomatic patients in the United States for treatable causes of ischemic stroke, 610 patients were evaluated. Unilateral or bilateral ICA stenosis of 50% or greater was detected in 66 patients (10.8%). The finding of occult ICA stenosis was more frequent than that of new hypertension (2.6%) or new atrial fibrillation (0.5%); therefore, ICA stenosis was the most frequently detected treatable cause of ischemic stroke. Patients with known hypertension were significantly more likely to have CA stenosis (12.7% vs. 7.8%) than were patients with heart disease (18.2% vs. 8%). Patients with both risk factors were significantly more likely to have CA stenosis than were patients without either risk factor (22.1% vs. 8.5%; $P < .0001$).[124]

A meta-analysis of nearly 24,000 subjects accumulated from large population studies reported in 2010 noted the overall prevalence of moderate-range carotid stenosis varied from 0.2% in men under 50 years of age to 7.5% in men over 80 years of age. The prevalence was lower in women. The following variables were predictive of both moderate and severe carotid stenosis

in the populations: age, sex, a history of vascular disease, systolic and diastolic blood pressure, total cholesterol/high density lipoprotein (HDL) ratio, diabetes, and current smoking.[125]

In recent analyses of another database comprising nearly 3.5 million patients in the United States who underwent voluntary screening for vascular disease, 3.9% were found to have ICA stenosis.[57,126-129] Independent risk factors for ICA stenosis included advanced age, smoking, peripheral arterial disease, hypertension, coronary artery disease, diabetes, hypercholesterolemia, and abdominal aortic aneurysm. Exercise and the consumption of fruit, vegetables, and nuts were noted to have a modest protective effect.[130] Women had a 3.4% prevalence of ICA stenosis of 50% or more, whereas males had a 4.2% prevalence.[57] Prevalence increased dramatically with age (Fig. 86.9). It was also noted that the prevalence of ICA stenosis varied significantly by race: Native American subjects had the highest prevalence of ICA stenosis across all age ranges and in both sexes, while Caucasian subjects had the second highest prevalence of ICA stenosis across most age ranges and in both sexes (Figs. 86.10 and 86.11). African American males and Asian females appeared to have the lowest prevalence. In all races, increasing age was the most significant risk factor for carotid stenosis. Additional risk factors included smoking history, diabetes, hypertension, and hypercholesterolemia.[57] It has been previously noted that African American patients may have a lower relative risk of severe carotid artery disease and that the increased stroke rate in this population is likely due to small vessel disease and hypertension.[57]

The prevalence of carotid artery stenosis was noted to be significantly increased in subjects with lower extremity peripheral arterial disease, and in diabetics (Fig. 86.12). Increasing severity of peripheral arterial disease as quantified by the ABI was significantly associated with an increasing prevalence of carotid artery stenosis.[127] In this large population-based study, higher levels of physical activity were independently associated with lower odds of carotid artery stenosis.[129] Age remains a critical factor; after adjustment for sex, race, body mass index (BMI), family history, smoking, diabetes, hypertension, hypercholesterolemia, and physical activity, the odds of carotid artery stenosis increased with every decade of life (odds ratio, 1.8).[128]

A report from Berger et al. analyzed modifiable risk factors and their relationship with carotid artery stenosis.[126] Risk factors included hypertension, hypercholesterolemia, smoking, diabetes, and sedentary lifestyle. The multivariate adjusted prevalence of carotid artery stenosis with 0 to 5 risk factors was, respectively, 1.41%, 2.36%, 3.72%, 5.73%, 8.48%, and 11.58% (Fig. 86.13). Results were similar in men and women. For every additional modifiable risk factor that was present, the multivariate-adjusted

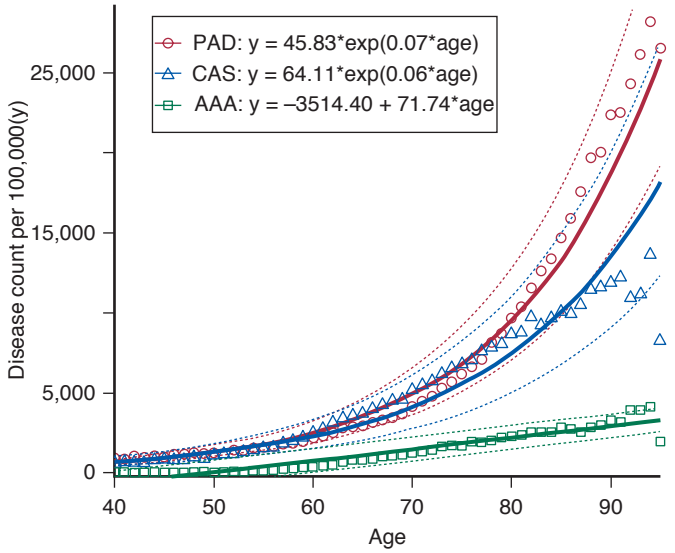


Figure 86.9 Prevalence of peripheral artery disease (PAD), carotid artery stenosis (CAS), and abdominal aortic aneurysm (AAA) by age. (From Savji N, et al. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. *J Am Coll Cardiol*. 2013;61:1736-1743. *Used with permission.*)

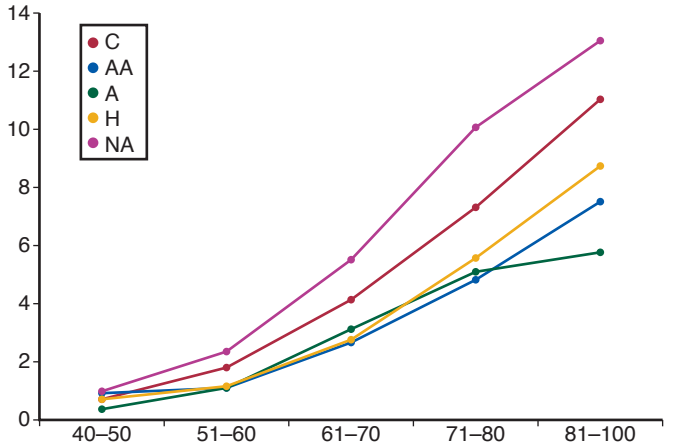


Figure 86.10 Relationship between race, carotid artery stenosis, and age in male subjects. *A,* Asian; *AA,* African American; *C,* Caucasian; *H,* Hispanic; *NA,* Native American. (From Rockman CB, et al. The prevalence of carotid artery stenosis varies significantly by race. *J Vasc Surg*. 2013;57(2):327-337. *Used with permission.*)

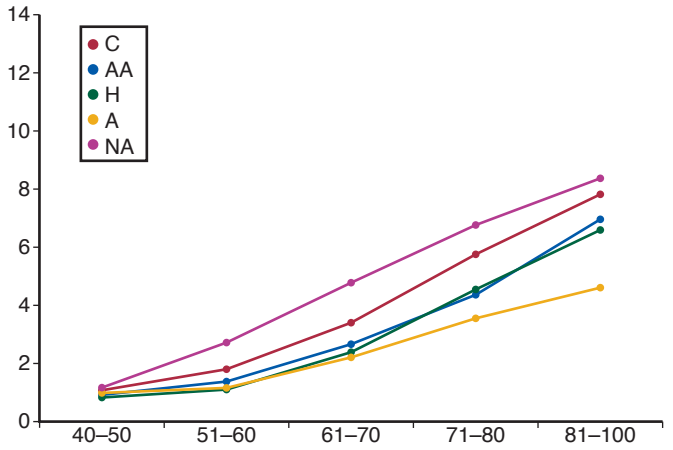


Figure 86.11 Relationship between race, carotid artery stenosis, and age in female subjects. *A,* Asian; *AA,* African American; *C,* Caucasian; *H,* Hispanic; *NA,* Native American. (From Rockman CB, et al. The prevalence of carotid artery stenosis varies significantly by race. *J Vasc Surg*. 2013;57(2):327-337. *Used with permission.*)

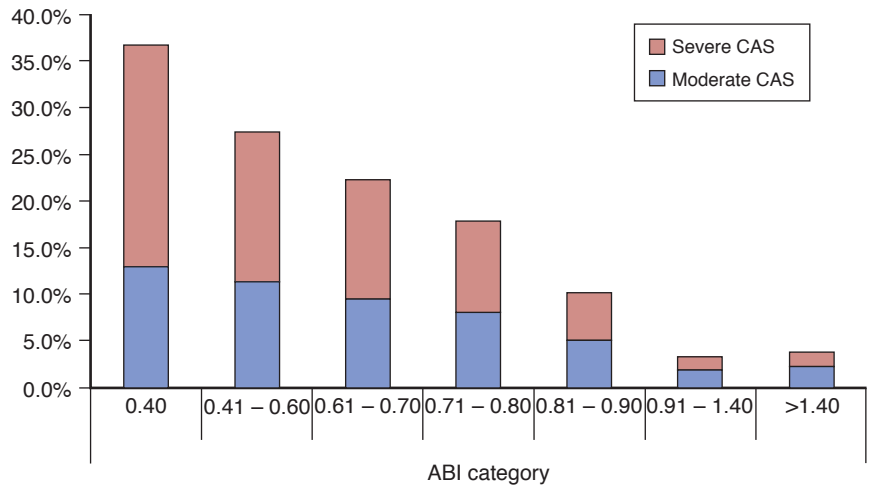


Figure 86.12 Frequency of moderate and severe carotid artery stenosis by the severity of peripheral arterial disease. *ABI,* Ankle-brachial index; *CAS,* carotid artery stenosis;. (From Razzouk L, et al. Co-existence of vascular disease in different arterial beds: peripheral artery disease and carotid artery stenosis—Data from life line screening. *Atherosclerosis*. 2015;241:687-691. *Used with permission.*)

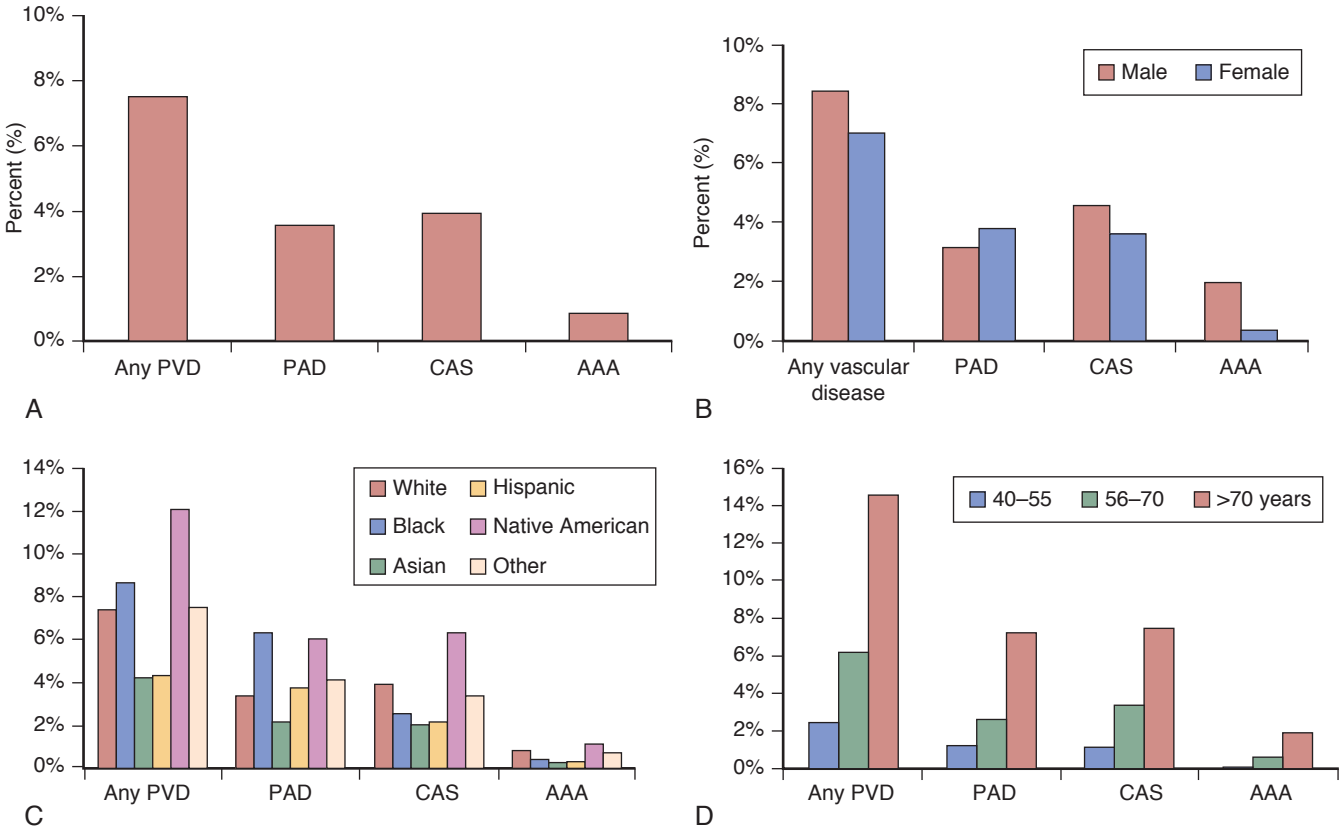


Figure 86.13 Prevalence of carotid artery stenosis overall and stratified by sex, race/ethnicity, and age. (A) Overall prevalence. (B) Stratification by sex. (C) Stratification by race/ethnicity. (D) Stratification by age. *AAA,* Abdominal aortic aneurysm; *CAS,* carotid artery stenosis; *PVD,* peripheral vascular disease; *PAD,* peripheral artery disease. (From Berger JS, et al. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg*. 2013;58:673-681 e1. *Used with permission.*)

odds of having carotid disease increased significantly (odds ratio, 1.57) (Figs. 86.13 and 86.14).

In comparing medical to endovascular or surgical treatment of carotid artery disease, it is essential to understand how the treatment of risk factors might affect the natural history of the condition. In patients with ICA stenosis, the treatment of risk factors—including hypertension, diabetes, lipid disorders, as well as lifestyle modifications, particularly smoking cessation—is of utmost importance.[131,132] Medical therapy of ICA stenosis includes treatment of hypertension with target BP of less than

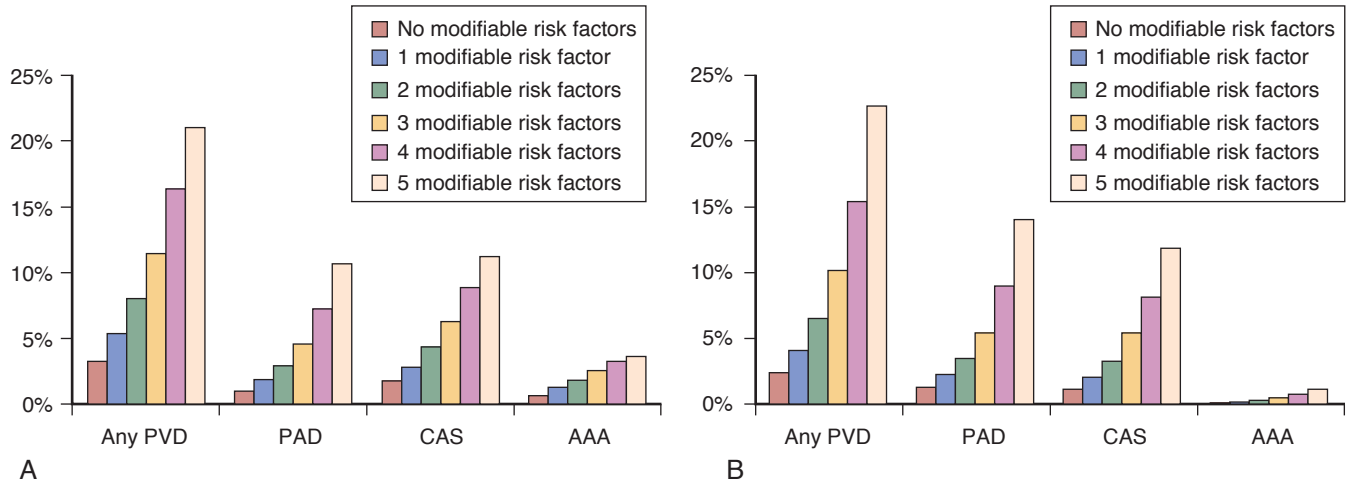


Figure 86.14 Prevalence of vascular disease according to the aggregate burden of modifiable risk factors in (A) men and (B) women. Risk factors included hypertension, hypercholesterolemia, smoking, diabetes, and sedentary lifestyle. *AAA,* Abdominal aortic aneurysm; *CAS,* carotid artery stenosis; *PVD,* peripheral vascular disease; *PAD,* peripheral artery disease. (From Berger JS, et al. Modifiable risk factor burden and the prevalence of peripheral artery disease in different vascular territories. *J Vasc Surg.* 2013;58:673-681 e1. *Used with permission.*)

140/90 and statins with a goal of decreasing LDL to less than 100, triglyceride less than 150, and increasing HDL to more than 40. Statins lower stroke risk by approximately 30%, and likely work by improving plaque stabilization.[133] Antiplatelet therapy in the form of aspirin or clopidogrel is also recommended for all patients with asymptomatic ICA stenosis.[134] Some studies have reported that the combination of aspirin and clopidogrel may be more effective than aspirin alone, but larger trials have not confirmed the benefit of adding clopidogrel (see Chapter 89).[135]

EXTRACRANIAL CAROTID ARTERY ATHEROSCLEROSIS—NATURAL HISTORY

Whether carotid artery disease remains a significant cause of ischemic stroke, and whether optimal medical therapy can decrease this risk to the same degree as proven carotid revascularization procedures is currently a matter of significant controversy. Although mortality rates from stroke have declined globally in the past two decades, the absolute numbers of people affected has risen and the costs of caring for stroke survivors are increasing.[23,136]

When a patient has already experienced an initial TIA or nondisabling stroke in the carotid territory, there is little disagreement that prompt intervention on an appropriate carotid lesion is warranted to decrease the otherwise extremely high risk of a subsequent infarction. These recommendations are based on the relatively undisputed known high risk of subsequent stroke in these patient categories, as discussed previously. The debate is ongoing in the case of asymptomatic carotid atherosclerosis in patients who have never experienced cerebrovascular symptoms. Challenges to the role of CEA in the treatment of asymptomatic carotid stenosis supported by level I data generally fall into two categories: (1) the view that modern optimal medical therapy may allow better stroke protection, obviating the need for CEA (or CAS), and (2) the argument that the degree of stenosis alone is a poor surrogate for vulnerable plaque and does not allow the accurate prediction of patients at high risk for stroke.[137]

Carotid intervention should only be undertaken in asymptomatic patients who are at a high lifetime risk of stroke. In addition to age, sex, the degree of stenosis, medical comorbidities, and life expectancy, relevant factors include the severity of the stenosis,[136,138] progression of stenosis,[136,139] evidence of infarction on brain imaging,[140] and plaque imaging characteristics.[79]

A consistent rate of stroke risk of approximately 2% per year in patients with high-grade asymptomatic stenosis was reported in ACAS, NASCET, and ACST. Although the ACAS study results have been criticized as obsolete in the current era of improved medical management of atherosclerosis, in the later years of ACST 80% of patients in fact were on statins.[11,13,42,120] Additionally, the Reduction of Atherothrombosis for Continued Health Registry (REACH) states that carotid stenosis of 70% or more was associated with a significantly increased stroke risk despite the fact that more than two-thirds of subjects were on statin medications.[141]

Progression of carotid stenosis has been shown to be a significant predictor of stroke risk in multiple natural history studies.[142-144] In a follow-up study from the ACSRS group, 1121 patients with asymptomatic carotid stenosis of 50% to 99% were analyzed with a mean follow-up period of 4 years (Figs. 86.15 and 86.16).[145] Progression occurred in 19.8% of patients. Independent predictors of progression included male sex, high creatinine, not taking lipid-lowering medications, low grade of stenosis, and increased plaque area. A total of 130 first ipsilateral cerebral of retinal events occurred, including 59 strokes. Forty strokes (67.8%) occurred in patients whose stenosis was not changed and 19 strokes (32.2%) occurred in those with progression. For patients with baseline 70% to 99% stenosis

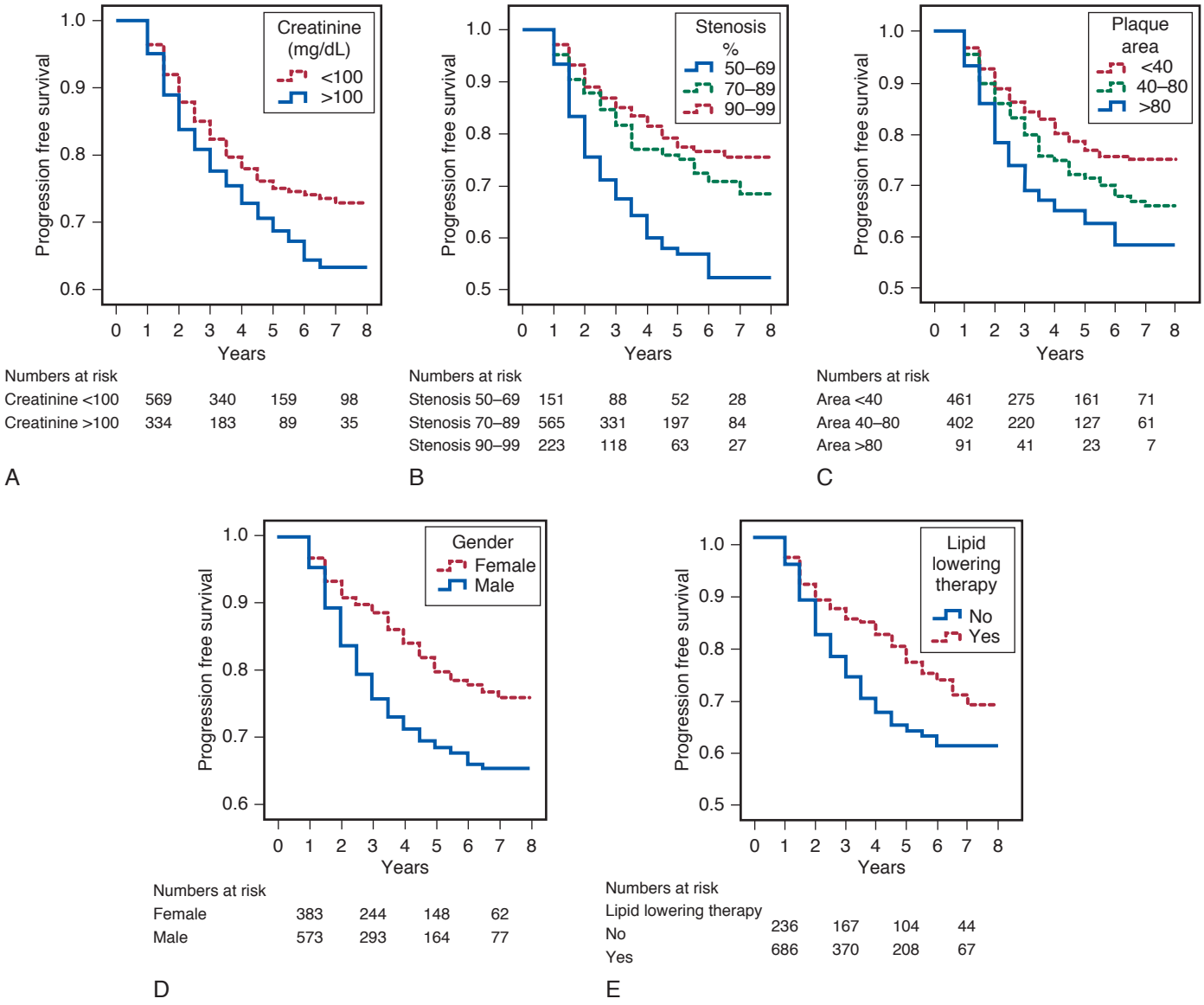


Figure 86.15 Predictors of progression of asymptomatic carotid stenosis; progression-free survival. Effect of significant factors, including (A) creatinine, (B) ipsilateral stenosis, (C) plaque area, (D) gender, and (E) lipid-lowering therapy. (From Kakkos SK, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. *J Vasc Surg.* 2014;59:956-967 e1. *Used with permission.*)

and in the absence of progression ($n = 349$), the 8-year cumulative ipsilateral ischemic stroke rate was 12%. In the presence of progression, it was 21% ($n = 77$).

Another report comprised 126 arteries with severe stenosis in patients who were treated medically.[137] Of this cohort, including 86% taking a statin medication with a mean follow-up period of 63 months, ipsilateral neurologic symptoms developed related to 25% of the arteries (Fig. 86.17). Of these events, 14 (45%) were strokes and 17 (55%) were TIAs or retinal events. Of this cohort of patients who initially were not considered for carotid artery intervention or were refused, 33% ultimately underwent carotid revascularization during the follow-up period.

Conrad et al. reported a study including 900 arteries in 794 patients with moderate stenosis.[36] Optimal medical therapy included aspirin and a statin with documented LDL levels less than 100 mg/dL. Mean follow-up was 3.6 years. The 5-year freedom from progression to severe stenosis was 61.2% ± 2.6%, with no benefit seen from optimal medical therapy (Fig. 86.18, Table 86.2). Plaque progression occurred in 262 arteries, and 36 (13.7%) of these developed symptoms. Average time to plaque progression was 32 months. Of this cohort, 90 patients (11.3%) developed ipsilateral neurologic symptoms during follow-up; 58% of these were strokes. Average time to symptom onset was 36 months. A total of 36 (40%) symptomatic patients also showed plaque progression, but the remaining 60% developed symptoms with a stable moderate stenosis. Five-year freedom from symptoms was 88.4%, with no benefit seen with OMT. Overall the authors concluded that current medial therapy was unable to halt the progression from moderate to severe stenosis or the development of symptoms in 45% of the cohort.

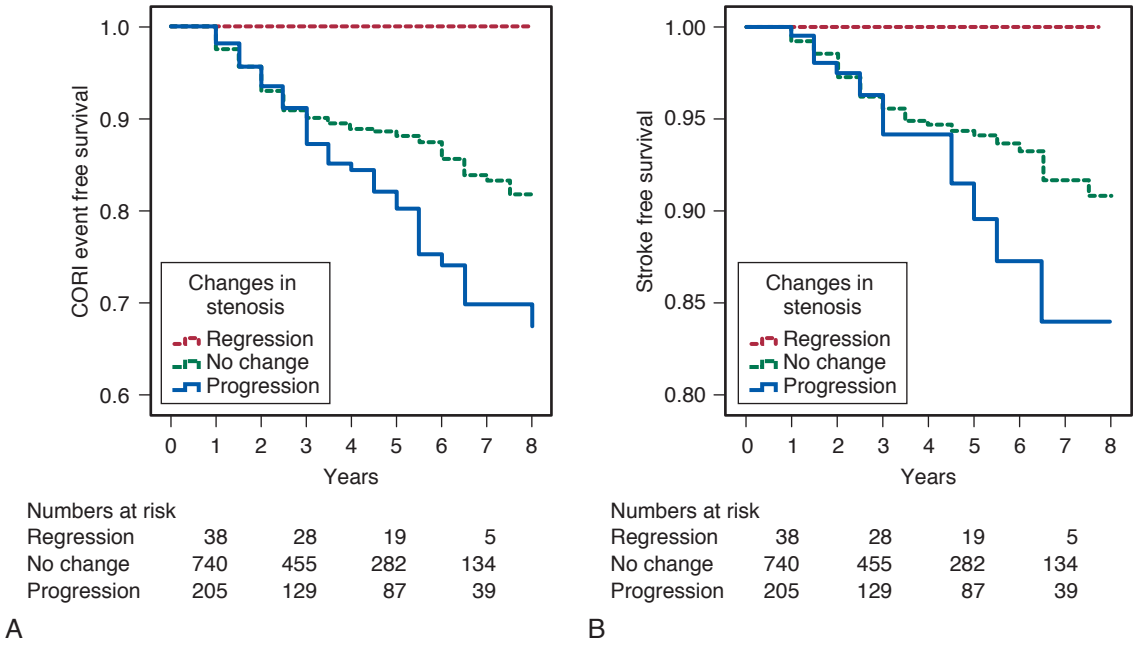


Figure 86.16 (A) Effects of changes in stenosis on ipsilateral cerebrovascular or retinal ischemic events (CORI). (B) Effect of changes in stenosis on ipsilateral hemispheric stroke. (From Kakkos SK, et al. Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis. *J Vasc Surg*. 2014;59:956-967 e1. *Used with permission.*)

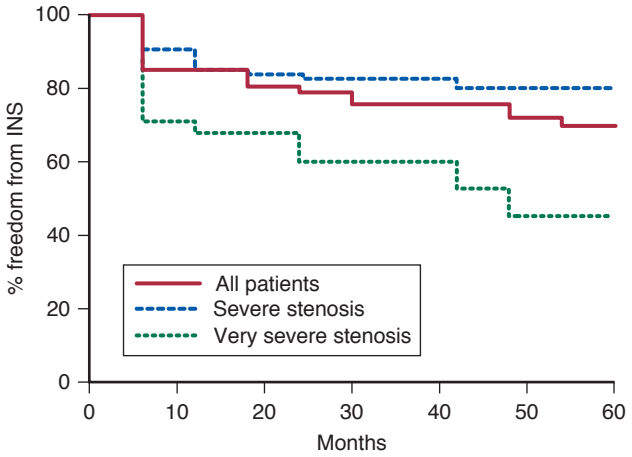


Figure 86.17 Kaplan-Meier curves of freedom from ipsilateral neurologic symptoms (INS) in the entire cohort and stratified according to lesion severity. (From Conrad MF, et al. The natural history of asymptomatic severe carotid artery stenosis. *J Vasc Surg*. 2014;60:1218-1225. *Used with permission.*)

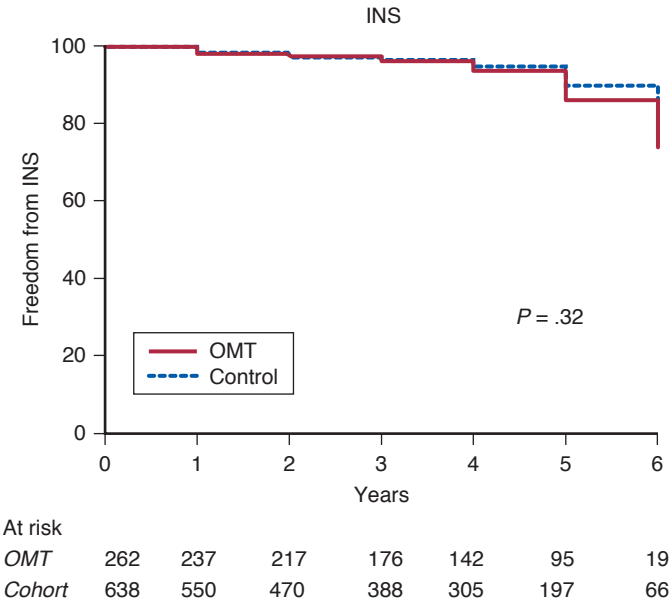


Figure 86.18 Kaplan-Meier curve of freedom from ipsilateral neurologic symptoms stratified by optimal medical therapy. *INS,* Ipsilateral neurologic symptoms; *OMT,* optimal medical therapy. (From Conrad MF, et al. Progression of asymptomatic carotid stenosis despite optimal medical therapy. *J Vasc Surg*. 2013;58:128-35 e1. *Used with permission.*)

Patients with significant carotid atherosclerosis are also at increased risk for cardiovascular disease and death. In the Tromso study, a cohort of 248 individuals with greater than 35% carotid stenosis was shown to have a 3.5 times higher risk of death from any cause as compared with patients with no carotid disease, even when other risk factors were controlled for. Most deaths were from cardiovascular causes.[146] In another large systematic review of 12 studies involving more than 4000 patients with greater than 50% stenosis, there was an average cardiac mortality of 2.9% per year.[147]

Most recently Zhang et al. studied the relationship between asymptomatic carotid artery stenosis and the development of cardiovascular disease (Fig. 86.19), including 1376 subjects over 55 years of age.[148] After adjustment for demographics and risk factors, the odds ratios for the risk of cardiovascular disease for those with minimal carotid disease, nonstenotic carotid plaque, and stenotic plaque was 0.8, 2.0, and 3.1, respectively, as compared with patients without significant carotid artery

TABLE 86.2 Multivariate Models of Outcomes

Predictor	HR	CI	*P* Value
Predictors of Death			
Age[a]	1.1	1.04–1.09	<.0001
Contralateral occlusion	1.9	1.1–3.3	.017
CAD	2.1	1.4–3.1	.0003
COPD	1.8	1.3–2.4	.0003
CKD	2.4	1.4–4.1	.0018
Plavix	1.7	1.2–2.3	.0026
Aspirin	0.6	0.39–0.83	.0033
Predictors of Plaque Progression			
CKD	2.1	1.2–3.7	.009
Aspirin	1.9	1.2–3.0	.01
CCB	1.4	1.1–1.8	.007
Predictors of INS			
Diabetes	2.3	1.5–3.6	.0002
Warfarin	1.9	1.2–2.9	.009
Statins (protective)	0.37	0.22–0.65	.0005

[a]Age was included in the model as a continuous variable.
CAD, Coronary artery disease; *CCB*, calcium channel blocker; *CI*, confidence interval; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *HR*, hazard ratio; *INS*, ipsilateral neurologic symptoms.
From Conrad MF, et al. Progression of asymptomatic carotid stenosis despite optimal medical therapy. *J Vasc Surg*. 2013;58:128-135 e1. *Used with permission.*

stenosis During a mean follow-up 62 months, 136 new strokes occurred in this cohort.

ADDITIONAL TOPICS

Vertebrobasilar Insufficiency

Vertebral artery origin stenosis may cause as many as 20% of posterior circulation ischemic strokes.[149] Additionally, symptoms may be caused by occlusion or stenosis of the subclavian artery proximal to the origin of the vertebral artery, causing the classic "subclavian steal" syndrome (see Chapters 98 and 99). Vertebrobasilar ischemia can result from embolic, thrombotic, or low-flow hemodynamic mechanisms.[150] The indications for surgical or endovascular treatment of vertebral artery disease are not as clearly defined as are those for carotid artery occlusive disease.

Vertebrobasilar insufficiency (VBI) results in ischemia to the posterior circulation of the brain, vascular territories supplied by the paired vertebral and common basilar artery (brain stem, cerebellum, thalamus, and occipital cortex). Posterior circulation TIAs and strokes represent approximately 20% of all TIAs and strokes.[149] Vertebral artery insufficiency can result from occlusive disease that interrupts flow to the posterior circulation or from hemodynamic mechanisms resulting in hypoperfusion. The most common causes of VBI include large artery atherosclerosis, emboli, penetrating small artery disease, and arterial dissection.[151]

The subclavian steal phenomenon is perhaps the best example of VBI resulting from hypoperfusion. Proximal subclavian artery stenosis or occlusion and associated retrograde ipsilateral vertebral flow can result in a collection of symptoms including arm pain with exertion as well as posterior cerebral neurologic symptoms, most commonly dizziness or vertigo. Sensorimotor deficits are extremely rare in subclavian steal syndrome and usually indicate the presence of concomitant carotid occlusive disease.

Atherosclerotic lesions usually occur at the vertebral artery origins and present with transient ischemia due to hypoperfusion of the brain stem and cerebellum, resulting in dizziness, difficulty focusing visually, and loss of balance. Thromboembolic events can also result in vertebrobasilar ischemia. Large emboli often involve the intracranial vertebral arteries, resulting in cerebellar infarction, or the distal basilar artery, affecting the upper cerebellum, brain stem, and territories of the posterior cerebral arteries. Cerebellar infarction usually presents with vertigo, vomiting, blurred vision, and difficulty walking.

Global Cerebral Ischemia

Global ischemia or systemic hypoperfusion represents only a small fraction of all ischemic strokes from carotid occlusive disease. Patients presenting with global ischemia often present unconscious to an emergency room or with symptoms resembling near syncope.[152] Neurologic symptoms can be varied and are usually attributable to decreased perfusion of watershed territories in the cerebral circulation. Decreased visual acuity, cognitive difficulties, bilateral upper extremity weakness, and symptoms of VBI are possible.[153] This can be a result of prolonged cardiogenic shock, dysrhythmias, or cardiac arrest, and treatment should initially focus on correcting cardiac failure and improving perfusion pressure to the brain.

Symptoms may be asymmetric in cases where hypoperfusion is isolated to a territory distal to a severe extracranial stenosis if inadequate collateral flow exists. Such patients may benefit most from treatment of proximal flow-limiting lesions and have been shown to fare better than those with more global hypoperfusion.[154]

Lacunar Infarcts

Lacunar infarcts are typically defined as small subcortical infarcts that result from presumed occlusion of a single penetrating artery of the brain.[155] These arteries are thought to be so small that they cannot be readily imaged in vivo, so these lesions are presumed to be ischemic in etiology. Typical risk factors for lacunar infarcts include increasing age, male gender, hypertension, diabetes, and smoking.[155] Lacunar infarcts represent roughly 20% of all ischemic strokes[156] and consist of small (1- to 2-cm) subcortical defects often located in the internal capsule or basal ganglia, areas supplied by the lenticulostriate vessels (small proximal branches of the intracranial carotid). The typical presentation can include pure motor hemiparesis, pure sensory syndrome, sensorimotor syndrome, ataxic hemiparesis, and dysarthria–clumsy hand syndrome.[157,158] Therefore from a clinical perspective lacunar infarcts can easily mimic carotid artery–related

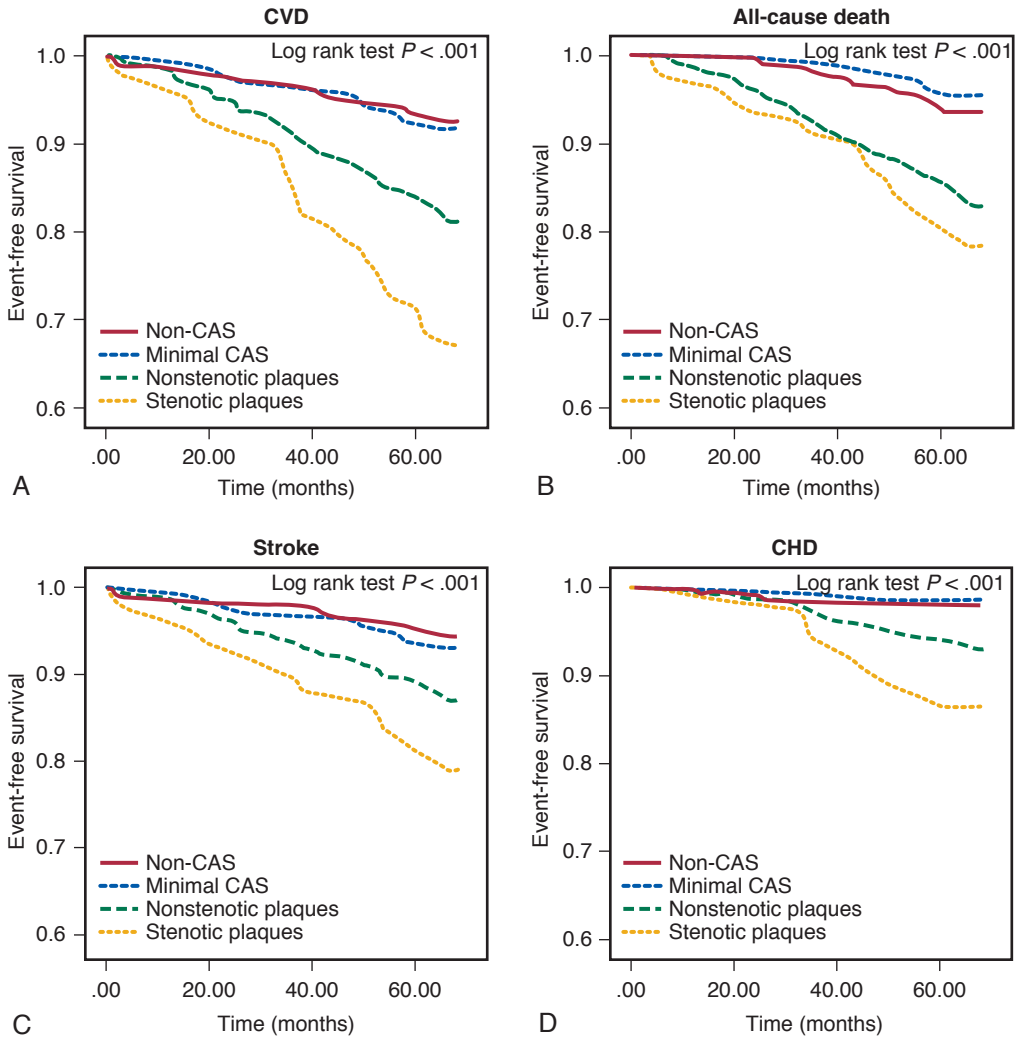


Figure 86.19 Kaplan-Meier curves for cardiovascular disease (all-cause death, stroke, and coronary heart disease) in participants according to the degree of carotid atherosclerosis. (A) *CVD*, cardiovascular disease. (B) All-cause death. (C) Stroke. (D) *CHD*, coronary heart disease. *CAS*, Carotid artery stenosis. (From Zhang Y, et al. Carotid artery plaques, carotid intima-media thickness, and risk of cardiovascular events and all-cause death in older adults: A 5-year prospective, community-based study. *Angiology*. 2018;69:120-129. *Used with permission.*)

ischemic events. Lacunar infarcts may be present in as many as 23% of persons over 65 years of age and remain asymptomatic or silent in up to 89% of patients.[159]

The association between atherosclerotic extracranial lesions and lacunar infarcts is controversial. Most believe that such infarcts are a result of small-vessel disease deep in the brain resulting from long-standing hypertension and/or diabetes unrelated to carotid occlusive disease.[160] This is consistent with the variable pattern of distribution for lacunar infarcts. They can occur alone or in groups and are often present in both hemispheres. Recent studies, however, show that ICA stenosis (>70%) was found more commonly on the side of lacunar infarction and may be associated with large vessel disease in up to one-third of patients.[161,162] This would lend support to the theory that embolization from carotid atherosclerosis to the lenticulostriate vessels may contribute to lacunar infarction in some cases.

Cognitive Decline

Although stroke is a well-established cause of dementia, the relationship between carotid stenosis itself and cognitive impairment is less clear. A systematic review of the literature found 18 studies examining cognitive function in patients with carotid stenosis who had not yet undergone surgery. Of these, 14 studies found deficits in patients with both symptomatic and asymptomatic lesions and 4 showed no cognitive impairment.[163] Cognitive function is rarely considered in evaluating or treating carotid stenosis. Moreover, patients with carotid occlusive disease share many of the known conventional risk factors for dementia (hypertension, diabetes, dyslipidemia, and smoking). Thus carotid stenosis may be a direct cause of cognitive impairment or serve simply as a marker of intracerebral or generalized atherosclerosis.[164,165] Asymptomatic carotid stenosis may logically result in cognitive impairment by causing cerebral infarction. However,

it is less clear if the asymptomatic carotid lesion represents an independent risk factor for cognitive decline. Silent brain infarcts may prove to be a link between carotid stenosis and cognitive impairment. Lacunar infarcts, known to be associated with vascular dementia, may also be more prevalent in patients with ipsilateral carotid stenosis, as discussed earlier.[166]

Atheroembolization and hypoperfusion represent two proposed mechanisms by which carotid stenosis could result in cognitive decline.[167] Thus asymptomatic carotid stenosis may in theory contribute to cognitive impairment via microembolization even in the absence of radiographic evidence of brain injury (i.e., lacunar infarcts or silent stroke). Cerebral hypoperfusion has also been implicated in the onset of clinical dementia.[168] Although critical carotid stenosis may contribute to global ischemia to varying degrees, there is a paucity of data correlating degree of carotid stenosis with cognitive decline.[169]

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CHAPTER 87

Cerebrovascular Disease: The Unstable Carotid Plaque

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MECHANISM OF STROKE IN CAROTID ATHEROSCLEROSIS

Autopsy studies in the early 1950s confirmed the association between atherosclerotic plaques in the carotid artery bifurcation and stroke. The vast majority of strokes from carotid artery plaques are from focal ischemic brain injury. Flow restriction from luminal encroachment can occur in extremely tight stenoses in the presence of inadequate cross-collateralization across brain hemispheres, and some strokes in patients with carotid stenosis are indeed attributable to hypoperfusion.[1] Most strokes, however, do not occur in watershed areas of the brain. Further support for plaque disruption with embolic infarction as the mechanism is that microemboli are detectable in the middle cerebral artery of several patients with symptomatic carotid stenosis.[2] Carotid plaque disruption with embolic cerebral infarction, rather than hemodynamic compromise from luminal narrowing, is therefore the primary contributor in the pathogenesis of stroke in patients with carotid atherosclerotic stenosis.[3]

STABLE VERSUS UNSTABLE CAROTID PLAQUES

In the Asymptomatic Carotid Atherosclerosis Study (ACAS), a majority (89%) of patients in the medical treatment alone arm remained stroke-free over 5 years.[4] The Asymptomatic Carotid Surgery Trial (ACST) also confirmed that plaques in most patients with high grade carotid artery stenosis did not develop a stroke.[5] In these and other studies, a small proportion of asymptomatic patients did, however, harbor plaques that progressed to disruption and caused cerebral infarction and stroke. This suggests that carotid atherosclerotic plaques exist as two distinct types: a majority are those that remain quiescent, and a smaller proportion are "unstable" and vulnerable to disruption, leading to atheroembolization and brain infarction. The percent diameter reduction in the carotid artery lumen is the most readily measured feature of the disease and currently used as a marker for identifying plaques that may be vulnerable to disruption. Increasing degrees of stenosis, however, have not

Abstract

It is likely that several mechanisms contribute to carotid plaque disruption with consequent cerebral infarction. Morphologic changes occurring within the plaque in combination with biomechanical forces acting on the plaque influence vulnerability to disruption. Conversely, plaques may also stabilize, leading to a phenotype-reversal to a normal-risk plaque, depending on their surrounding milieu. Duplex ultrasonography and magnetic resonance imaging can quantify morphologic features (lipid-rich necrotic cores and intraplaque hemorrhage) implicated in plaque vulnerability. Computational fluid dynamics and speckle tracking allow for mapping of biomechanical forces on the plaque (wall shear stress, plaque wall stress and plaque strain).

Keywords

Carotid
atherosclerosis
plaque
lipid core
fibrous cap
stress
strain

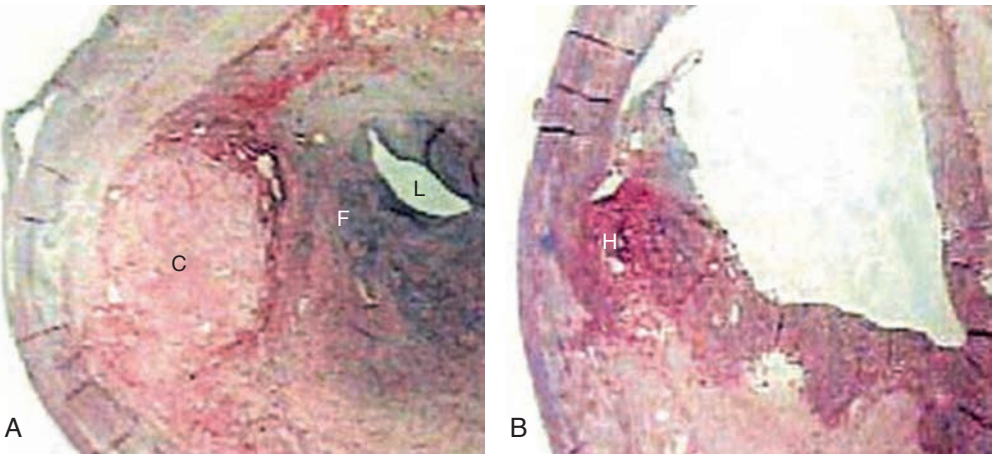

Figure 87.1 (A) Asymptomatic carotid plaque. Note the small and deep seated lipid-rich necrotic core, marked "C". The lumen is marked "L" and fibrous cap is marked "F." (B) Symptomatic carotid plaque. Note the fibrous cap disruption, intraplaque hemorrhage marked "H", and exposure of the underlying lipid-rich necrotic core. (Adapted from Lal BK, Hobson 2nd RW, Pappas PJ, et al. Pixel distribution analysis of B-mode ultrasound scan images predicts histologic features of atherosclerotic carotid plaques. *J Vasc Surg*. 2002;35(6):1210-1217.)

been consistently associated with a correspondingly increased risk for stroke in asymptomatic patients.[6] Neither ACAS nor ACST showed a correlation between degree of stenosis and stroke-risk. The degree of stenosis is therefore not an adequately sensitive or specific marker for determining plaque instability and stroke-risk.

HISTOMORPHOLOGY OF THE UNSTABLE CAROTID PLAQUE

Carotid bifurcation plaques are representative of atherosclerosis at other locations in the vascular tree. Our understanding of plaque histology comes largely from studies of the coronary arteries and the aorta, substantiated subsequently with studies of the carotid arteries. Histologic evaluation of explanted human arteries indicates that atherosclerotic lesions originate as "early" forms (types I, II, and III). Plaques start as fatty streaks, found as early as at 6 months of life. Over time, they coalesce into lipid cores.[7] A fibroatheroma develops next as fibrous tissue accumulates over the core and forms a fibrous cap.[8] Some plaques then continue to progress to "later" or more advanced forms (types IV, V, and VI), with a growing lipid rich necrotic core (LRNC), developing intraplaque hemorrhage (IPH) and demonstrating thinning of their fibrous cap.[9] The Oxford plaque study reviewed histology on 526 carotid plaques explanted post-carotid endarterectomy and found that these histomorphologic features were associated with plaques that had recently caused neurologic symptoms (transient ischemic attacks and stroke).[10] Our group[11,12] and others have identified these features in plaques from patients presenting with neurologic symptoms (large LRNCs,[13] located close to the flow lumen,[14] IPH,[15] fibrous cap disruption, and luminal surface ulceration[16]; Fig. 87.1). A review of 31 histologic studies with 4447 explanted carotid plaques indicated a strong association between IPH and ischemic neurologic symptoms.[17] Conversely, smooth homogeneous fibrous plaques tend to be clinically stable and less prone to atheroembolization.[9]

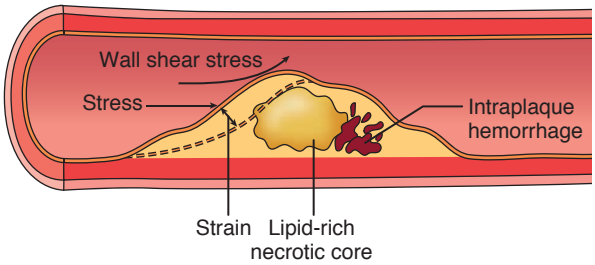

Figure 87.2 Morphologic and biomechanical correlates of carotid plaque vulnerability. See the text for a description of individual terms.

BIOMECHANICS OF THE UNSTABLE CAROTID PLAQUE

Not all plaques with unstable histologic features cause symptoms. Approximately 50% of asymptomatic patients with carotid stenosis have identifiable IPH or fibrous cap rupture,[18] yet only approximately 2% of asymptomatic patients develop a neurologic event at 1 year.[4,5] Therefore morphology alone has limited ability to identify unstable carotid plaques and predict future strokes (Fig. 87.2).[19] Furthermore, the histomorphology of plaques is not static, and plaques may transition from one morphologic type to another, in response to biological influences such as inflammation and oxidative stress. These biological processes are in turn potentially influenced by mechanically induced signaling. Mechanical forces can alter several aspects of vascular biology. Short-term elevations in arterial wall shear stress (WSS), the result of frictional force on the luminal surface exerted by flowing blood, can activate endothelial cell signaling and induce nitric oxide and prostacyclin production with consequent vasodilation. Long-term elevations in blood flow–related forces

such as WSS impact endothelial function, wall permeability, plaque formation, vessel wall remodeling, plaque progression, and changes in plaque composition to a more vulnerable phenotype.[20] For instance, endothelial cells may modify the balance between extracellular matrix synthesis versus degradation in the fibrous cap by metalloproteinases secreted by infiltrating macrophages in response to WSS.[21] Acting over time, these changes can create conditions suitable for disruption.

In addition, blood pressure–induced forces (e.g., plaque wall stress, PWS) can exceed the plaque's material strength, leading to disruption.[13,22] PWS was higher in disrupted coronary artery plaques from 12 randomly selected patients who died from acute myocardial infarction (MI), compared with plaques from 12 patients who died of noncoronary causes.[23] ApoE−/− mice and rabbits with inheritable hyperlipidemia develop some "unstable plaque" histologic features that do not rupture on their own. When these models are subjected to additional hemodynamic or mechanical stresses, disruption can be induced.[24,25]

Repetitive deformation of plaques from cardiac cycle-induced motion can result in excessive plaque strain and tissue fatigue that may also contribute to disruption.[26] Due to its high temporal resolution, duplex ultrasonography (DUS) is well suited for imaging plaque motion, deformation, and resulting plaque strain during the cardiac cycle. Ultrasonography has identified asymmetric discordant motion with high strain patterns in carotid plaques from symptomatic patients compared to asymptomatic plaques.[27]

NONINVASIVE IDENTIFICATION OF THE UNSTABLE CAROTID PLAQUE

Carotid plaque disruption likely results from a combination of biological and histomorphologic changes within the plaque occurring in the context of biomechanical forces acting on it. Noninvasive plaque characterization can assist in several aspects of the management of carotid occlusive disease. It could help stratify asymptomatic patients for treatment; serial assessments could track response to potentially "plaque stabilizing" pharmacotherapy, and it may guide appropriate stent designs (e.g., open vs. closed cell). The challenge is to develop imaging techniques that can reveal this level of structural detail. Several noninvasive imaging approaches can assist in identifying histomorphologic (e.g., large LRNC, IPH) and biomechanical (WSS, plaque strain) markers for patients at risk for plaque disruption.

Ultrasonography is cost-effective and safe for serial testing. The morphologic appearance of carotid plaques was first quantified in two-dimensional B-mode images. The first generation of three-dimensional ultrasound transducers that reduce operator-dependence and variability are now clinically available. Ultrasonography provides additional physiologic information enabling measurement of disruptive forces acting on the plaque. Magnetic resonance imaging (MRI) is a sensitive and specific method for determining plaque histomorphology, biomechanical forces, and metabolic activity. Computed tomography angiography (CTA) is at present not as accurate in delineating plaque composition. It is, however, useful for identifying the luminal surface.[28]

TWO-DIMENSIONAL B-MODE IMAGING

B-mode (brightness mode or 2D mode) imaging displays anatomic wall features that range from primarily hyper- or hypoechoic, to heterogeneous in echogenicity. Since different tissues reflect ultrasound to varying degrees, the first histologic interpretation of the B-mode appearance of carotid plaques was a subjective visual classification (Gray-Weale): pure hypoechoic (type I), hypoechoic with small hyperechoic areas (type II), hyperechoic with small hypoechoic areas (type III), and hyperechoic (type IV).[29] Type I and type II plaques occurred commonly in patients with neurologic symptoms.

The Gray-Weale classification is subject to observer variability, both during image acquisition and during image-interpretation. Nicolaides and his group subsequently introduced standardization in image acquisition and normalization of image brightness. The plaque was then outlined, and the median brightness of all the pixels in a single longitudinal image of the plaque was measured and expressed as a Grayscale Median value (GSM).[30] In 1121 patients with 50% or greater carotid stenosis followed for 6 to 96 months, the longitudinal plaque area (hazard ratio [HR] 1.92, confidence interval [CI] 1.50 to 2.46) and a GSM ≤40 (HR 0.09, CI 0.04 to 0.17) were predictors for future stroke.[31]

Histologic studies show that the necrotic core of a symptomatic plaque is located closer to the luminal surface than in asymptomatic plaques.[32] On B-mode imaging this necrotic core appears hypoechoic and has been named the Juxtaluminal Black Area (JBA). In the Asymptomatic Carotid Stenosis and Risk of Stroke trial (1121 patients), a JBA of 8 to 10 mm^2 represented an annual risk of stroke of 3.2%, while JBAs greater than 10 mm^2 were associated with a stroke rate of 5.0%.[33]

ULTRASONOGRAPHIC VIRTUAL HISTOLOGY

Different tissues reflect ultrasound differentially, resulting in B-mode images with variable brightness or pixel intensities. Using this principle, we identified the echogenicity of key histologic components of atherosclerotic plaques (calcium, fibromuscular tissue, LRNC, and IPH). These pixel intensity ranges were mapped in normalized longitudinal images of carotid plaques (pixel distribution analysis, PDA) to measure the virtual histology (DUS-VH) of individual tissues and the architectural features (lipid core size and location) of the plaques.[11] Eighteen symptomatic plaques demonstrated larger quantities of IPH ($P < .001$) and LRNC ($P = .002$), and LRNCs located closer to the flow lumen ($P = .01$), while 27 asymptomatic plaques demonstrated larger amounts of calcium ($P < .001$).[12] The PDA approach provides quantification of carotid plaque histomorphology using simple and readily available B-mode ultrasound technology.

THREE-DIMENSIONAL ULTRASONOGRAPHY

Plaques progress along the vessel 2.4 times faster than they thicken.[34] Therefore methods that capture both longitudinal and circumferential growth (area and volume) are more sensitive than methods limited to thickness measurements (diameter-reducing stenosis). The 5-year risk of stroke, MI, and vascular death was 19% for plaques with a longitudinal-sectional area of 1.2 to 6.7 cm^2 compared with 6% for areas of 0 to 0.1 cm^2. Similarly, progression of total carotid plaque volume predicted cardiovascular events (stroke, vascular death, TIA, or MI) in 349 patients with carotid stenosis.[35] Three-dimensional (3D) ultrasonography involves collating a series of 2D cross-sectional slices in a computer and reconstructing them into a 3D volume. It reduces the operator variability inherent in traditional 2D imaging. It requires a special 3D transducer with a motorized linear array transducer that moves within a housing to capture a series of 2D image-frames. The operator's hand and patient's head must be steadied to prevent movement artifacts. It takes less than a second to acquire a complete volume, which minimizes artifact from cardiac and respiratory movements.

We have developed a standardized postprocessing protocol for 3D plaque quantification.[36] The lumen-intima boundary defining the plaque surface, and the outer wall boundary defining the outer surface of the plaque, are segmented in each image. The region between these two boundaries is the vessel wall containing plaque. The stacked 2D images are collated to develop volume-rendered reconstructions that reproducibly quantify total plaque volume (Fig. 87.3). While 2D imaging detected changes of 19% or more in the carotid plaque area between two scans on a patient (minimum detectable change), 3D imaging could detect changes as small as 12.9% in plaque volume when two different technologists performed the test, and 4.5% or more for the same technologist.[36] Our semiautomatic postprocessing algorithm is comparable to manual segmentation in accuracy and takes 10 to 15 minutes to complete (Fig. 87.4). It reliably detects plaque volume changes as low as 4% to 6% with 95% confidence.[37] These developments are bringing 3D quantification of carotid plaques closer to the clinical environment. Another advantage of 3D imaging is an improved ability to evaluate the plaque surface. In 313 patients with asymptomatic carotid plaques, an ulcer volume ≥5 mm^3 was associated with a higher combined rate of stroke, TIA, MI, death, and revascularization ($P = .017$).[38] In another study, patients with three or more ulcers detected by 3D ultrasonography were more likely to have a stroke or death during 3 years of follow-up (18% vs. 2%).[39]

CONTRAST ENHANCED ULTRASONOGRAPHY

Contrast enhanced ultrasonography (CEUS) has traditionally been used in cardiac echocardiography, and its use is now being explored in carotid ultrasonography.[40] It uses standard B-mode imaging after administration of an intravenous ultrasonographic contrast agent. This improves the delineation of structures where the contrast can reach. The contrast consists of 1 to 10 micron microbubbles of an inert gas usually stabilized by a phospholipid shell. These microbubbles stay in the vascular system for a few minutes and then are eliminated by the respiratory tract. Ultrasound contrast is not nephrotoxic and does not require radiation, and complications are uncommon.

In CEUS of the carotid artery, the plaque and intima-media complex appear hypoechoic, while the carotid lumen and adventitia appear enhanced. It improves visualization of luminal irregularities, thereby improving the detection of ulcerated plaques.[41,42] One potentially important characteristic of unstable carotid plaques is increased neovascularization, identified on CEUS as increased enhancement within the plaque.[43] Histologic analysis confirms that plaques with enhancement have more neovascularization. Such plaques have increased microembolic signals and neovascularization could be a marker of carotid plaque instability and increased risk for future stroke.[44] After the administration of ultrasound contrast, some carotid plaques remain enhanced for up to 30 minutes postinjection. Contrast microbubbles are ingested by monocytes and become adherent to inflamed endothelium, thereby retaining the contrast for a longer time period.[45] Increased presence of inflammatory cells may predispose the plaque to early rupture;[46] therefore, late phase enhancement may be a marker for plaque instability. Late phase enhancement offers an opportunity to develop novel contrast agents that will generate "molecular images" of the carotid plaque. Microbubbles tagged with monocytes or antibodies would then concentrate in areas of inflammation or other target proteins within or on the carotid plaque such as receptors to P-selectin and VCAM-1 to target inflammation, or VEGF-1 to target neo-vascularization.[47]

PLAQUE STRAIN MEASUREMENT

The motion of carotid plaques and its associated arterial wall can be complex and may play a role in plaque rupture.[48] Carotid plaques with increased mobility or with asymmetric discordant motion may have an increased risk for disruption. Ultrasound elastography or strain imaging visualizes and quantifies the deformation that tissues undergo in response to a force. Elastography has been utilized to differentiate normal from abnormal tissue in the thyroid, liver, breasts, prostate, and lymph nodes.[49] Measurement of carotid plaque deformation has been challenging due to the small target size and its mobility during the cardiac and respiratory cycles. Recently introduced optical tracking techniques allow quantification of the direction, extent, and rate of movement of individual pixels within a plaque image through the cardiac cycle.[50]

Displacement of plaques can occur along the length of the artery due to blood flow or radially due to pulsatile expansion of the artery. Therefore data must be acquired in two planes. Studies using radiofrequency ultrasound protocols have found that increased strain patterns correlated with high-risk histomorphologic features.[51] We have developed a B-mode protocol for strain measurement that is suitable for clinical vascular

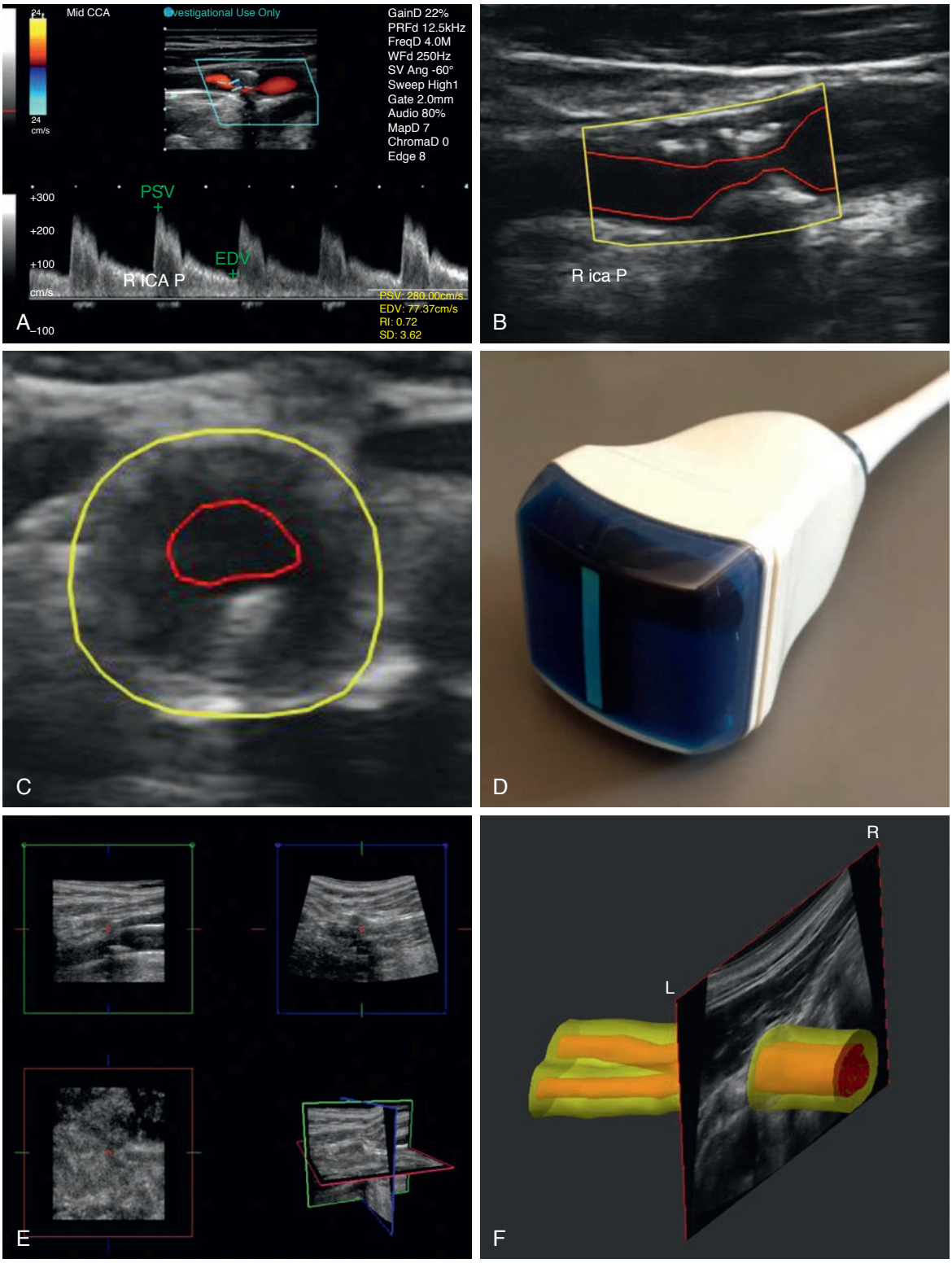

Figure 87.3 Duplex Ultrasound Imaging for Plaque Morphometry. (A) Standard Doppler measurements to localize the plaque and measure peak systolic and end-diastolic velocities to estimate the percentage of stenosis. (B) Best longitudinal view as determined by the sonographer. The luminal *(red line)* and adventitial *(yellow line)* boundaries identify the plaque area in the longitudinal section. (C) Cross-sectional image at the region with tightest stenosis, with the luminal and adventitial boundaries outlined to measure the plaque cross-sectional area. (D) The 4DL14-5/38 US transducer (Ultrasonix, Richmond, British Columbia, Canada) used for volume acquisition. (E) Different slices of the acquired three-dimensional (3D) volume. (F) Reconstructed volume generated after segmentation of the plaque within the arterial wall. (Adapted from AlMuhanna K, Hossain MM, Zhao L, et al. Carotid plaque morphometric assessment with three-dimensional ultrasound imaging. *J Vasc Surg*. 2015;61(3):690-697.)

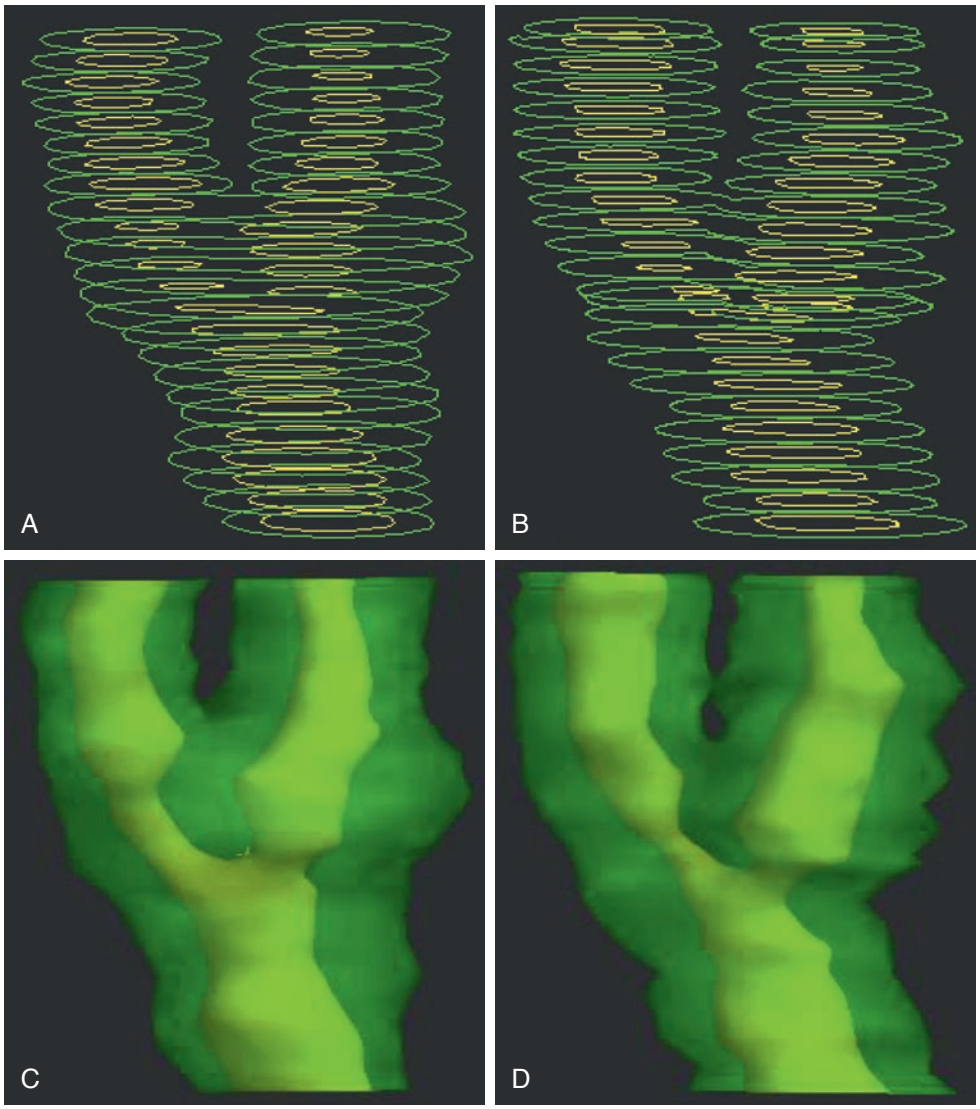

Figure 87.4 Three-dimensional (3D) carotid artery bifurcation plaque volumes rendered from the outlined contours for (A and C) manual and (B and D) semiautomatic segmentation. (A and B) Segmented contours in individual slices of a volume and (C and D) the 3D volume reconstruction based on the contours in A and B. (Adapted from Khan AA, Koudelka C, Goldstein C, et al. Semiautomatic quantification of carotid plaque volume with three-dimensional ultrasound imaging. *J Vasc Surg*. 2017;65(5):1407-1417.)

laboratories. Thirty-six percent of plaques in 25 asymptomatic patients demonstrated high strain and high heterogeneity in displacement patterns (Fig. 87.5). These plaques were hypoechoic (mean GSM 19), indicating that softer plaques had higher and more variable strain rates.[52] Whether these findings translate into high stroke risk will need to be evaluated in larger longitudinal studies; one of which (CREST-Imaging) is being conducted within the context of the CREST-2 trial.[53]

INTRAVASCULAR ULTRASOUND

Information about morphologic characteristics of a carotid plaque may be important at the time of carotid intervention. For example, endovascular instrumentation of a soft plaque could provoke embolization, or a stiff calcified plaque could prevent stent expansion during carotid artery stenting (CAS). Periprocedural stroke is more frequent with CAS; therefore, every attempt should be made to reduce embolization during stenting.

Intravascular ultrasound (IVUS) is used in the coronary arteries to obtain useful information on plaques. As with DUS-VH, IVUS uses the intensity and frequency of reflected ultrasound to provide a map of the constituent histologic components of the plaque. Carotid plaque IVUS-VH correlates with histology (accuracy of 72.4% for calcified fibroatheroma and of 99.4% for thin-cap fibroatheroma).[54] In this study, plaque fragments were identified more frequently in filter devices during CAS for plaques with larger LRNCs. In another study, IVUS-identified calcification in the carotid artery predicted microembolization during CAS.[55] IVUS has not been used routinely in the carotid arteries, and its role is not well established. It is an invasive procedure, and its utility must be weighed against the risks of inducing a stroke from passing the ultrasound catheter across the lesion.

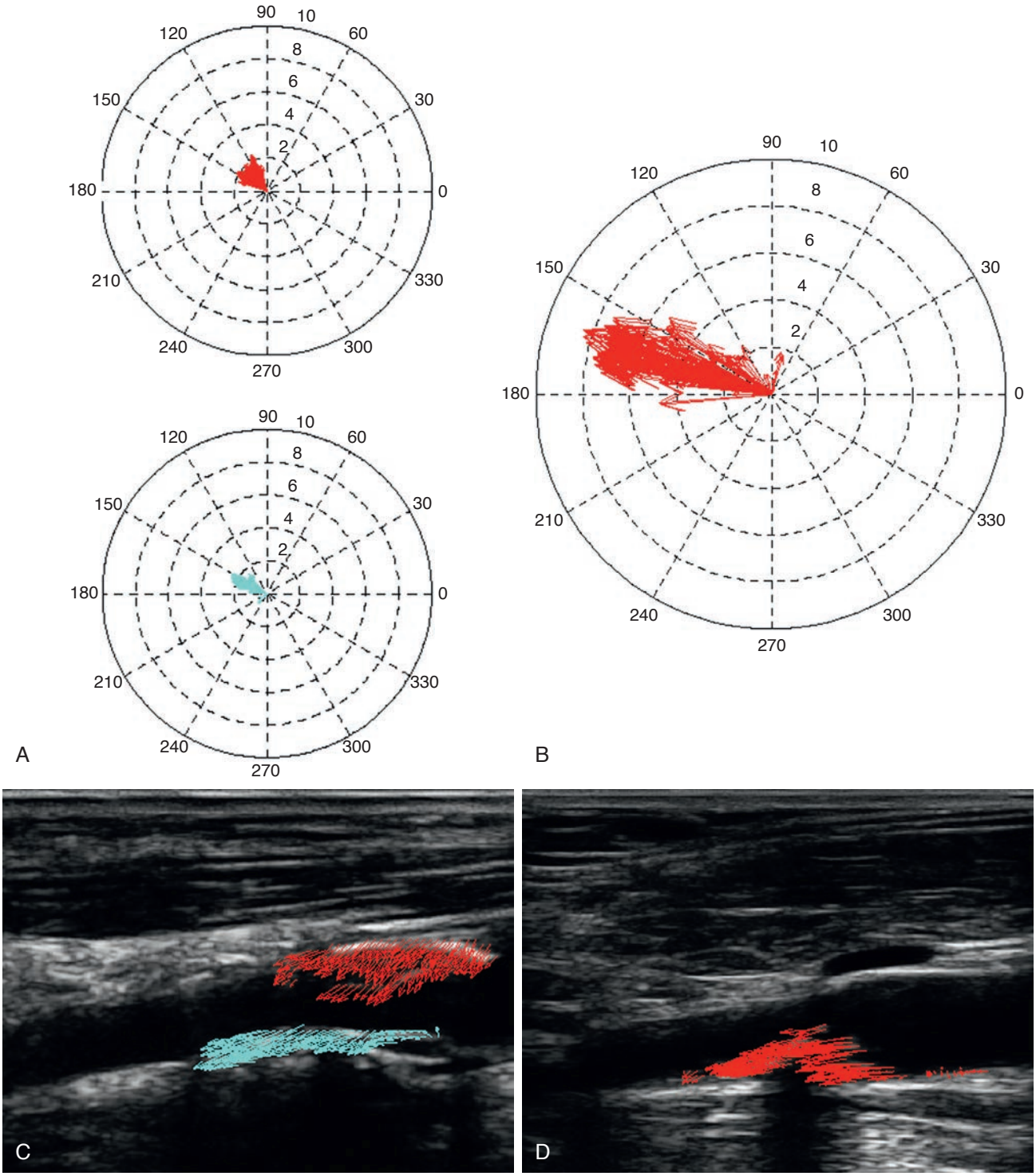

Figure 87.5 Speckle tracking-based displacement fields from B-mode cine-loops of two carotid plaques. (A and B) Compass plots representing displacement fields for the plaque regions in two different patients. The length of the arrows represents the magnitude of plaque displacement, and the angle of arrows represents the angular orientation of displacement. (C and D) Quiver plots showing the displacement vectors superimposed on B-mode images of the plaque regions. (Adapted from Khan AA, Sikdar S, Hatsukami T, et al. Noninvasive characterization of carotid plaque strain. *J Vasc Surg.* 2017;65(6):1653-1663.)

MAGNETIC RESONANCE IMAGING FOR HISTOMORPHOLOGY

In vivo carotid plaque MR imaging has been extensively validated against histology.[56-58] MRI identifies large LRNC, IPH, and luminal surface ulceration accurately and with good reproducibility.[59,60] Traditionally, long duration scanning protocols using customized carotid coils and large magnets were required to produce high-resolution images with sufficient tissue detail.[61] Such protocols were not readily translatable to the clinical environment. However, advances in 3D-MRI protocols have reduced scan times and now permit differentiation of disrupted versus intact carotid plaques or detection of IPH and LRNC on clinical scanners using standard commercial coils.[62] Clinical contrast-enhanced MR angiography and vessel wall imaging improves quantification of the LRNC and delineation of the luminal surface to identify ulceration.[63] Gupta et al. compared studies utilizing multisequence carotid coil-dependent protocols versus those using a single sequence with standard commercially available neck coils.[64] Using either technique, IPH correlated with risk for TIA or stroke (HR 4.40 and 5.04 for multisequence versus standard imaging protocols).

Histologic studies indicate that enlarging LRNCs, presence of IPH, and fibrous cap thinning or ulceration are precursors of plaque disruption, and could serve as imaging markers of stroke risk. Studies utilizing MRI have detected a higher prevalence of these features in patients with symptomatic carotid plaques.[64,65] The presence of IPH on MRI has also been associated with the risk for future neurologic events.[64,65] Conversely the absence of IPH portends a benign clinical course.[66] Plaques with a large lipid core are at a high risk for disruption.[67] In addition, MRI-detected luminal surface ulceration has also been associated with increased stroke risk.[68] Small prospective studies[69] and meta-analyses[64,65] demonstrate an elevated risk of developing neurologic symptoms in the presence of IPH (HR 3.66 to 5.86), large LRNC (HR 2.41 to 5.74), and thin or ruptured fibrous cap (HR 4.54 to 6.30). While these are compelling findings, they need to be substantiated in large prospective longitudinal studies with objective adjudication of stroke endpoints. One such study (CREST-Imaging) is being conducted within the CREST-2 cohort of patients.[53]

COMBINED MAGNETIC RESONANCE IMAGING AND ULTRASONOGRAPHY FOR BIOMECHANICS

Direct in vivo measurement of WSS in patient carotid bifurcations is difficult to obtain. However, provided that the luminal geometry from MRI and the entrance and exit flow waveforms from DUS are obtained, patient-specific computational fluid dynamics (CFD) models can be constructed.[70] These models yield the velocity, pressure, and WSS fields at all points along the vessel wall. Using this approach, patients with 60% or greater carotid stenosis had a higher mean WSS (>100 dynes/cm^2) compared with those with normal or minimal stenosis (mean <60 dynes/cm^2).[70] Ten patients with carotid plaques underwent MRI-based WSS measurement across the cardiac cycle.[71] WSS was higher in subjects with IPH or with large LRNC compared with those without. Similarly, MRI of 12 carotid arteries underwent fluid structure interaction modeling to compute PWS. Ulcerated plaques had higher plaque wall stress (PWS, 247 vs. 108 kPa, $P < .0016$) and WSS (39 vs. 14 dynes/cm^2, $P < .001$) compared with nonulcerated plaques.[22] In another study, PWS was 11% higher ($P = .0003$) and WSS was 30% higher ($P = .0002$) in plaque regions with IPH compared with IPH-free regions.[72] This indicates possible links between biomechanical forces on the plaque (high WSS and PWS), and plaque histomorphology features associated with adverse neurologic outcomes (ulceration and IPH). The heterogeneity in populations studied and analytic techniques utilized, the small sample sizes, and paucity of serial assessments for these studies precludes firm conclusions on the relationship.

SUMMARY

The estimation of degree of stenosis based on Doppler velocity measurements is the most well established role of ultrasonography in the diagnostic workup of carotid artery atherosclerotic disease. There is, however, a clinical imperative to obtain additional information on the plaque. Characteristics of the plaque such as volume, LRNC size, and location, surface ulceration, IPH, as well as hemodynamic effects around the plaque have been associated with an increased risk of stroke. 2D B-mode imaging with GSM analysis, ultrasonographic VH using PDA, and additional analyses of the image texture provide improved information about plaque composition and architecture. Recently introduced 3D imaging technology offers an excellent opportunity to reduce observer-dependence and to sample the entire plaque for volumetric and surface assessments. CEUS has improved the definition of the plaque luminal surface and of neovascularization. It has the potential to allow targeted visualization of plaque inflammation with molecular imaging. While IVUS has found limited adoption in the carotid artery, it may have the potential to assist in planning endovascular procedures. MRI provides consistent and reliable identification and quantification of IPH, LRNC, and thin fibrous caps. Clinical scanners are improving rapidly and afford excellent resolution. Ultrasonography and MRI also offer an opportunity to quantify biomechanical forces acting on the plaque. Adequately powered prospective longitudinal studies are underway to definitively establish the role of noninvasive risk stratification of carotid plaques in clinical practice.

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88 CHAPTER

Cerebrovascular Disease: Diagnostic Evaluation

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DUPLEX ULTRASOUND

Indications

Carotid Artery Disease

In 2006,[1] a UK Health Technology Assessment (HTA) meta-analysis of the accuracy of noninvasive imaging (but not multidetector computed tomography [CT] angiography [MDCTA]) concluded that while contrast enhanced magnetic resonance angiography (CEMRA) was the most accurate (Table 88.1), its "clinical effectiveness" was limited by accessibility, availability, and delays. HTA concluded that duplex ultrasound (DU) remained the "first line" imaging modality for identifying patients with 70% to 99% internal carotid artery (ICA) stenoses because of (1) low cost, (2) the higher number of strokes likely to be prevented in the long-term (because patients are scheduled more rapidly for surgery), (3) robustness in sensitivity analyses, and (4) its ability to match the needs of current surgery (i.e., patients were selected for surgery through attendance at "single visit clinics" incorporating DU imaging with a low probability of the surgeon encountering unexpected findings at operation that might otherwise compromise patient safety).[1]

The HTA[2] did, however, highlight concerns about DU accuracy for diagnosing 50% to 69% stenoses (see Table 88.1). Because the benefit conferred by carotid endarterectomy (CEA) in patients with 50% to 69% stenoses falls significantly with delays to surgery, HTA recommended that if 4 weeks or more had elapsed after the index event, corroborative imaging (CEMRA/MDCTA) should be performed to confirm stenosis severity. If, however, DU was performed within 4 weeks of the index event, the HTA felt it reasonable to proceed to CEA based on DU alone, as the number of strokes prevented through rapidly performed surgery exceeded the potential risk to patients with less than 50% stenoses undergoing inappropriate surgery.

Consensus ultrasound criteria for diagnosing carotid stenosis severity[3] are summarized in Table 88.2. These have been validated by AbuRahma et al.,[4] who concluded that the criteria could accurately diagnose a greater than 70% stenosis. However, the accuracy for diagnosing a 50% to 69% stenosis would be improved by changing the peak systolic velocity (PSV) range from 125 to 230 cm/s to 140 to less than 230 cm/s.[4]

TABLE 88.1 Results of a Meta-Analysis of the Accuracy of Noninvasive Imaging for All Stenosis Groups and Imaging Modalities

Stenosis Group	Imaging	Sensitivity (95% CI)	Specificity (95% CI)
70%-99% (0.77-0.89)	US	0.89 (0.85-0.92)	0.84
(0.91-0.97)	CTA	0.77 (0.68-0.84)	0.95
(0.76-0.90)	MRA	0.88 (0.82-0.92)	0.84
(0.89-0.96)	CEMRA	0.94 (0.88-0.97)	0.93
50%-69% (0.87-0.94)	US	0.36 (0.25-0.49)	0.91
(0.63-0.89)	CTA	0.67 (0.30-0.90)	0.79
(0.78-0.97)	MRA	0.37 (0.26-0.49)	0.91
(0.93-0.99)	CEMRA	0.77 (0.59-0.89)	0.97
0%-49%, 100% (0.62-0.95)	US	0.83 (0.73-0.90)	0.84
(0.74-0.98)	CTA	0.81 (0.70-0.88)	0.91
(0.76-0.95)	MRA	0.81 (0.70-0.88)	0.88
(0.90-0.99)	CEMRA	0.96 (0.90-0.99)	0.96

CEMRA, Contrast enhanced magnetic resonance angiography; *CTA*, computed tomography angiography; *MRA*, magnetic resonance angiography; *US*, ultrasound.

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Vertebrobasilar Disease

Extracranial DU offers limited information about flow dynamics in the vertebral arteries (VAs), and nothing about the basilar system. It is not always possible to image VA origins and only those sections running between the transverse processes can be imaged distally. Accordingly, if a patient presents with suspected

TABLE 88.2 Consensus Panel Gray-Scale and Doppler Ultrasound Criteria for Diagnosis of Internal Carotid Artery Stenosis

Degree of Stenosis (%)	PRIMARY PARAMETERS		ADDITIONAL PARAMETERS	
	ICA PSV (cm/s)	Plaque Estimate (%)[a]	ICA/CCA PSV (ratio)	ICA EDV (cm/s)
Normal	<125	None	<2.0	<40
<50	<125	<50	<2.0	<40
50-69	125-230	≥50	2.0-4.0	40-100
>70 but less than near occlusion	>230	≥50	>4.0	>100
Near occlusion	High, low or undetectable	Visible	Variable	Variable
Total occlusion	Undetectable	Visible, no detectable lumen	Not applicable	Not applicable

[a]Plaque estimate (diameter reduction) with gray-scale and color Doppler US.
CCA, Common carotid artery; *EDV*, end-diastolic velocity; *ICA*, internal carotid artery; *PSV*, peak systolic velocity.
Reproduced from Grant EG, Benson CB, Moneta GL, et al. Carotid artery stenosis: gray-scale and doppler US diagnosis—Society of Radiologists in Ultrasound Consensus Conference. *Radiology*. 2003;229:340–346.

vertebrobasilar symptoms, DU assessment can exclude co-existent carotid disease, but diagnostic imaging with MRA/MDCTA remains mandatory. DU is, however, useful for demonstrating complete/partial VA flow reversal, suggesting proximal subclavian or innominate artery disease.

Role in Screening

While the Society for Vascular Surgery advocates carotid screening in patients aged greater than 55 years with cardiovascular risk factors, the 2014 US Preventive Services Task Force continues to recommend against this.[5] For those committed to screening, DU is the first-line modality. Portable DU machines are available, but there is little data regarding accuracy. Users of portable machines are, therefore, advised to undertake a corroborative DU study in an accredited vascular laboratory (or use MDCTA/CEMRA) should a greater than 50% stenosis be suspected. DU remains the preferred screening modality prior to coronary artery bypass graft (CABG) surgery. Screening all CABG patients is not cost-effective (2% yield for 80%-99% stenoses),[6] but the yield increases in selected patients (left mainstem disease, carotid bruit, previous stroke/TIA). Any patient being considered for CABG using internal mammary artery (IMA) and who has weak/absent radial pulses should undergo DU assessment of the subclavian, innominate, and VAs. Where inflow disease or VA flow reversal is suspected, further imaging (MDCTA/CEMRA) is essential, and the cardiac surgeon should be warned that unless corrected, use of the ipsilateral IMA (as a conduit) could cause postoperative coronary steal syndrome (Fig. 88.1).

Role in Trauma

Duplex offers a screening/surveillance role in patients with zone II carotid injuries (between cricoid cartilage and angle of mandible), especially intimal irregularities or small false aneurysms treated conservatively. DU is, however, less reliable in zone I injuries (clavicle to cricoid cartilage) or zone III injuries (angle of mandible to skull base).

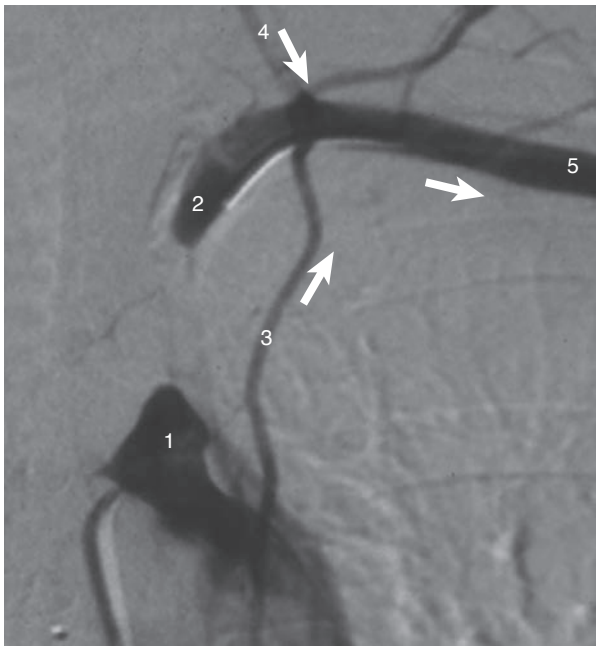

Figure 88.1 Intraarterial digital subtraction arteriography in a patient with coronary steal syndrome that had previously undergone coronary artery bypass graft using the left internal mammary artery as a conduit. There is occlusion of the proximal left subclavian artery (1), which refills distally (2, 5) via reversed flow in the left vertebral (4) and internal mammary artery (3). It was treated successfully by angioplasty.

Evaluation of Carotid Body/Glomus Vagale Tumors (See Chapter 95)

Because of their vascularity, DU is ideal for diagnosing carotid body (CBT) or glomus vagale tumors (GVTs). Given the availability of DU, it is unwise to biopsy a "lymph node" in the jugulodigastric region without first undertaking a DU. Once suspected, MDCTA/MRA should be performed to exclude

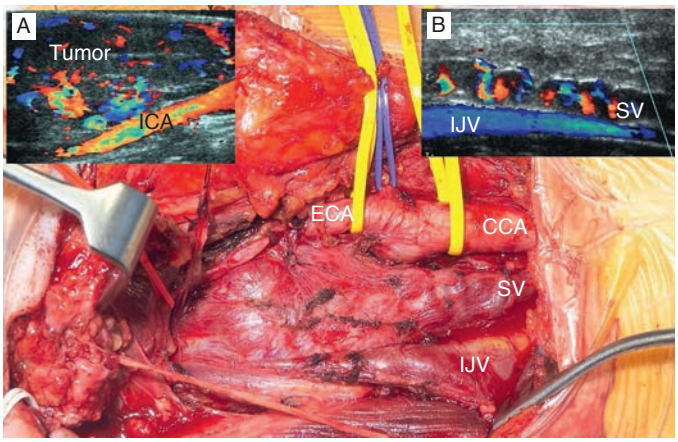

Figure 88.2 Glomus vagale tumor (GVT, *main picture*). This does not splay the bifurcation but displaces the distal internal carotid artery (ICA) (*duplex image*, A). Occasionally, preoperative ultrasound features can suggest that this is a GVT and not a carotid body tumor. Note the serpiginous feeding vessels extending down the vagus nerve (SV: main picture and duplex ultrasound scan [B]). These are separate from the common carotid artery (CCA) and internal jugular vein (IJV). *ECA*, External carotid artery.

bilateral lesions (5%) and to image the upper and lateral extent of the lesion. Large, distally placed lesions require a totally different operative strategy, which must be anticipated preoperatively (temporomandibular subluxation cannot be performed once the operation is underway). Duplex can also warn the surgeon that a GVT might be present (Fig. 88.2), enabling the patient to be counseled about vagus nerve division (hoarseness, swallowing difficulties). CBTs cause splaying of the carotid bifurcation. GVTs do not splay the bifurcation, but they do tend to cause displacement of the distal ICA (see Fig. 88.2). In addition, GVTs tend to have vascular serpiginous feeding vessels tracking down the proximal vagus nerve. These usually lie separately from the bifurcation, internal jugular vein, and common carotid artery (CCA).

Role in the Planning of Carotid Endarterectomy and Carotid Artery Stenting

Up to 95% of CEAs are undertaken on the basis of DU, and there is no evidence that reliance on DU compromises safety or operability,[1] provided certain caveats are met: First, the vascular laboratory should be accredited and have validated criteria for measuring stenosis severity. Second, European vascular units must be absolutely clear which measurement method is being used (NASCET/ECST) (see Chapter 21). Evidence suggests that there may be confusion.[7] Third is awareness of DU findings that suggest tandem inflow/outflow problems or subocclusion. In each situation, corroborative imaging is mandated (MDCTA, CEMRA).

In practice, one of the most frequent pathologic lesions to be missed with DU is the coiled distal ICA (see Chapter 96). In most situations, coils do not cause problems to the surgeon, but they can be a cause of shunt failure (hemodynamic stroke) should the distal shunt tip occlude against the distal loop and not be recognized. DU is useful in diagnosing unusual causes of cerebral symptoms, such as ICA "stump syndrome" (Fig. 88.3). In this rare condition, a "vault" at the origin of an occluded ICA stump (identifiable on DU) acts as a reservoir for fresh thrombus formation that can embolize up the external carotid artery (ECA) and into the brain via retrograde flow through the supra- and infraorbital vessels.

By contrast, carotid artery stenting (CAS) cannot be planned using DU alone. Table 88.3 details anatomic and morphologic features that are associated with difficulties in performing CAS or which influence choice of cerebral protection device (CPD) or stent. For example, choice of CPD will depend upon ECA patency, integrity of the circle of Willis (COW), and whether there is a straight, nontortuous distal ICA. Stent selection will depend upon vessel tortuosity and plaque friability. DU can demonstrate (1) the presence of an appropriate ipsilateral stenosis, (2) ECA patency, (3) extent of contralateral disease, (4) tortuosity at the bifurcation, (5) it can advise on plaque morphology, and (6) warn that there may be coexistent inflow and outflow problems. However, DU cannot provide information regarding (1) type of aortic arch, (2) extent of calcification at the great vessel origins, (3) proximal CCA tortuosity, (4) whether there is an adequate distal landing zone for a filter CPD, or (4) COW status. If the COW is not intact, CAS practitioners tend not to deploy the flow reversal type of CPD. This type of information can only be provided by MDCTA or CEMRA. However, reliance on additional imaging will introduce delays in planning the management of symptomatic patients. If delays are likely, patients may be better treated by CEA.

Evaluating Plaque Morphology

In the Asymptomatic Carotid Surgery Trial (ACST), the subjective Gray-Weale classification (Table 88.4) was unable to predict outcome in medically treated asymptomatic patients,[8] but the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study showed that provided computerized "image normalization" was undertaken, 94% of strokes destined to occur in a cohort of 1008 asymptomatic patients with 50% to 99% stenoses had Type 1 to 3 plaques (see Table 88.4).[9-12]

The ability to identify "higher-risk for stroke" patients with asymptomatic carotid disease is important, as it is believed that up to 95% of interventions in asymptomatic patients are ultimately unnecessary.[13] The weakness of DU plaque morphology studies (in the past) has been a lack of objectivity, but this has been addressed by developing a number of computerized plaque analyses including the Gray-Scale Median (GSM) and measurement of overall plaque area and juxta-luminal black area (JBA).[11,12] High-resolution B-mode images are combined with a quantitative computer assisted measurement of plaque echogenicity. The GSM is a numerical measure representing average echogenicity of the plaque (low values are observed in predominantly echolucent plaques, while high values are seen in more sclerotic lesions). ACSRS[11,12] observed that asymptomatic patients with a 60% to 99% stenosis and an overall plaque area less than 40 mm^1 had a 1.0% annual risk of stroke, increasing to 1.4% (40-80 $mm)^1$ and 4.6% for plaque area greater than 80 mm.[1] Asymptomatic patients with a JBA less than 4 mm^1 had a 0.4% annual risk of ipsilateral stroke, increasing to 1.4%

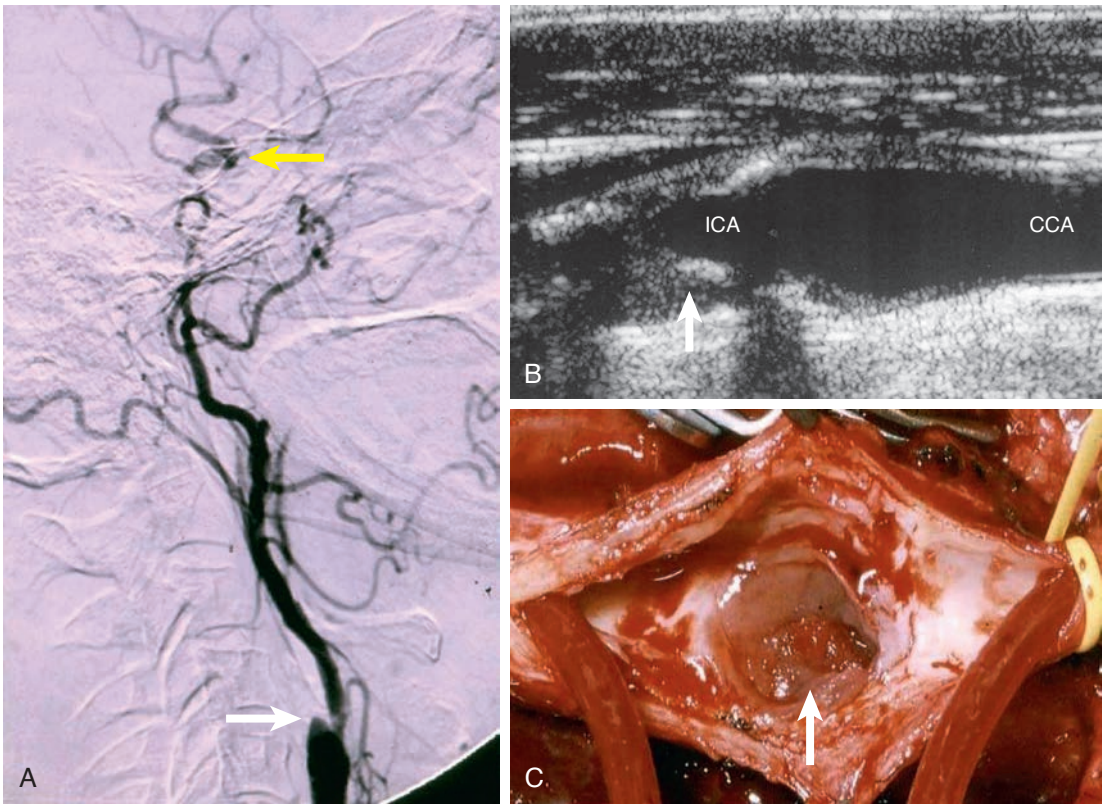

Figure 88.3 Internal carotid artery (ICA) stump syndrome. (A) Selective intraarterial digital subtraction arteriography with delayed imaging confirms the presence of an occluded ICA with a small stump *(white arrow)*. The external carotid artery (ECA) is an important source of collateral flow because there is refilling of the distal ipsilateral carotid syphon *(yellow arrow)*. (B) B-mode ultrasound image of the ICA stump in this patient *(arrow)*. (C) Operative image with a shunt inserted between the common carotid artery (CCA) and the ECA. Note the extensive fresh thrombus within the ICA stump *(arrow)*.

(4-8 mm),[1] 3.2% (8-10 mm),[1] and 5.0% for JBAs greater than 10 mm.[1] In addition, the presence of ≥3 carotid plaque ulcers on high-resolution three-dimensional (3D) DU in asymptomatic patients was associated with a significantly higher annual risk of late ipsilateral stroke (6%) compared to 0.6% in patients with 0 to 2 micro-ulcers.[14]

In recently symptomatic patients, Salem reported that the presence of a large lipid core on DU and a GSM less than 25 were predictive of a significantly increased risk of recurrent neurologic events in the 48- to 72-hour time period before undergoing expedited CEA.[15] The same group performed a logistic regression analysis of computerized plaque DU features in 126 patients prior to undergoing CEA (with blinded histologic assessment) and showed that the combination of a plaque area greater than 95 mm^1 and a JBA greater than 6 mm^1 was 90% predictive of there being an unstable carotid plaque following ex-vivo histologic examination.[16]

Perioperative Roles

DU should be repeated prior to CEA if greater than 4 weeks have elapsed since the initial DU. This ensures the ICA has not occluded (i.e., CEA is unnecessary), it is also the final opportunity to warn of distal disease extension (last chance to consider temporomandibular subluxation or alternative exposure techniques), and it fulfills an important internal validation role. Intraoperative DU enables completion assessment following flow restoration through (1) residual filling defects (luminal thrombus), (2) undue turbulence, and (3) evidence of intimal flaps/residual stenoses (see Chapter 91). Evidence from the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study suggested that a GSM ≤25 was associated with a 7.1% stroke rate after CAS compared with 1.5% in patients whose plaque had a GSM greater than 25.[17]

Postoperative Roles

Because of its versatility, DU is invaluable in guiding the management of postoperative neurologic deficits. These often occur when other imaging modalities are unavailable and DU can be brought to the patient's bedside. Air in the deep tissues can interfere with insonation early after surgery, but it is usually possible to exclude thrombosis. Diagnosing the exact cause of the deficit can be difficult, and the role of DU is enhanced if combined with transcranial Doppler ultrasound (TCD).

The role of serial DU surveillance after CEA/CAS remains controversial. As with screening, this is rarely undertaken in the United Kingdom and Scandinavia, but this is common practice in North America, Australasia, and mainland Europe. On a practical note, those who offer DU surveillance after CAS

TABLE 88.3 Anatomic and Morphologic Features Associated With Adverse Outcomes After Carotid Artery Stenting or That Might Influence the Choice of Protection Device or Stent and Relationship With Imaging Modalities

		US	CEMRA	MDCTA	IADSA
Aortic arch	Ulceration	X	+	++	++
	Excessive calcification	X	X	++	+
	Bovine arch variants	X	++	++	++
	Type III arch	X	++	++	++
Great vessels	Ulceration	X	+	++	+
	Tortuosity/kinking	X	++	++	++
	Excessive calcification	X	X	++	+
	Anatomical anomalies	X	+	++	+
	Severe inflow stenosis	X	+	++	++
Common carotid	Diffuse disease	+	++	++	++
	Coiling/kinking	+	++	++	++
	Excessive calcification	+	X	++	+
Carotid bifurcation	Excessive calcification	X	X	++	+
	Angulation	++	++	++	++
Ipsilateral ECA	Occlusion/severe stenosis	++	++	++	++
Ipsilateral ICA	Excessive calcification	X	X	++	+
	Distal tortuosity/coiling	X	++	++	++
	plaque characterization	++	++	+	X
	Fresh thrombus	+	+	+	X
	Preocclusive stenosis	++	++	++	++
	Long lesion (>3 cm)	+	+	++	++
Contralateral ICA	stenosis >50%	++	++	++	++
Incomplete circle of Willis		X	++	++	+

X, Not really suited for imaging; *+*, basic information provided; *++*, highly suitable for imaging; *CEMRA*, contrast enhanced magnetic resonance angiography; *ECA*, external carotid artery; *ICA*, internal carotid artery; *IADSA*, intraarterial digital subtraction angiography; *MDCTA*, multidetector computed tomography angiography; *US*, ultrasound.

TABLE 88.4 Plaque Characterization Using Duplex Ultrasound

Gray Weale	Classification[8]	Nicolaides	Classification[9,11,12]
Type 1	Echolucent	Type 1	Uniformly echolucent Bright echoes occupy <15% of plaque
Type 2	Predominantly echolucent	Type 2	Mainly echolucent Bright echoes occupy 15%-50% of plaque
Type 3	Predominantly echogenic	Type 3	Mainly echogenic Bright echoes occupy 50%-85% of plaque
Type 4	Echogenic	Type 4	Uniformly echogenic Bright echoes occupy >85% of plaque
		Type 5	Calcified cap (>15% of cap) with acoustic shadow

must be aware that stents change the physical properties of the carotid artery so that different diagnostic criteria are required.[18]

DU is also useful in warning about the possibility of late prosthetic patch infection (Fig. 88.4). DU is the first line investigation in patients returning with pulsatile neck swellings, discharging sinus tracts, or neck pain, and the recognition of patch "corrugation" may precede clinical diagnosis of patch infection by up to a year (i.e., recognition of this phenomenon can alert the surgeon to the possibility of patch infection and start antibiotics early).[19] Duplex DU can also identify "leaks" into false aneurysms (see Fig. 88.4).

Contraindications

There are no contraindications to DU, but it should only be undertaken by an operator who has been adequately trained.

Accuracy and Limitations

The most important determinant is the experience and skill of the operator. Second is awareness of the wide array of stenosis thresholds being used in individual centers (>50%, >60%, >70%) and the spectrum of PSV and velocity ratios being used

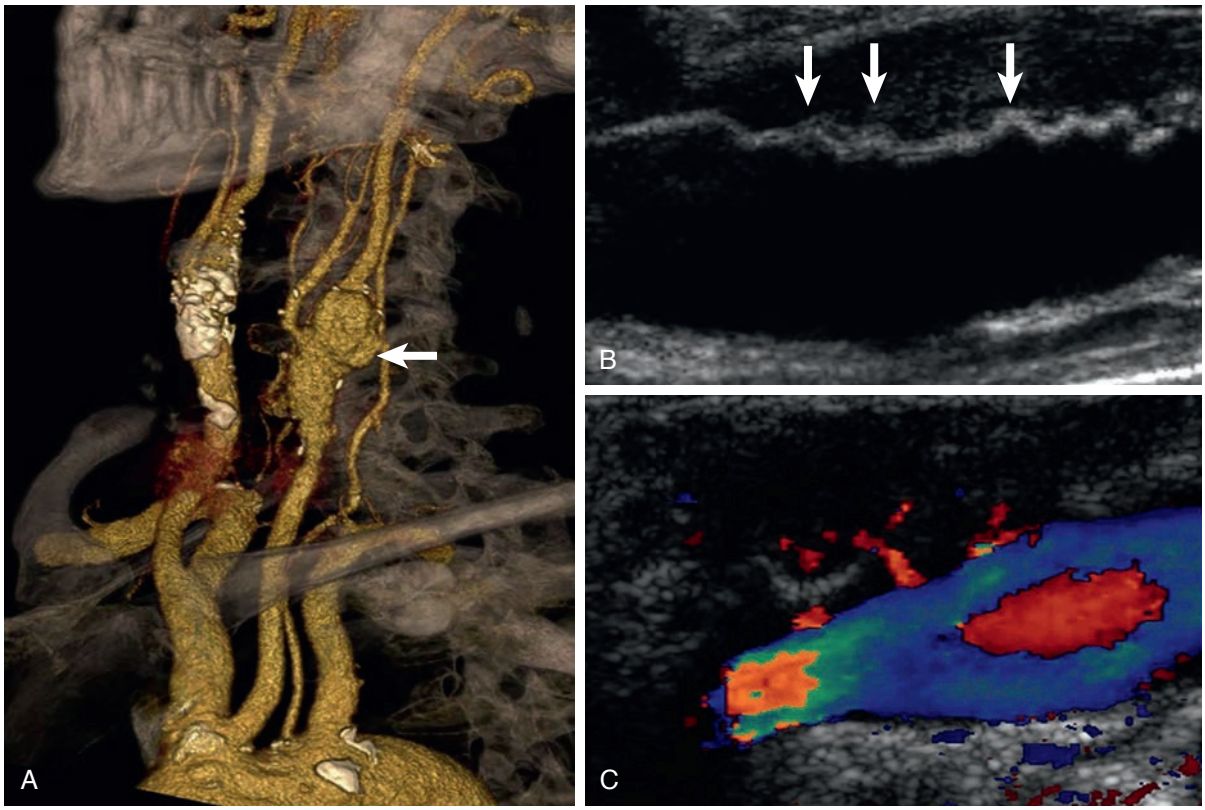

Figure 88.4 Prosthetic patch infection 15 years after CEA. Multidetector computed tomography angiography (A) shows a false aneurysm *(arrow)* at the left carotid bifurcation. (B) Corrugation of the polyester patch on B-mode ultrasound imaging *(arrows)*. (C) Color duplex ultrasound showing jets of blood into a false aneurysm secondary to patch infection (not the same patient as in A or B).

to diagnose stenosis subgroups. This uncertainty has been reduced by publication of North American DU consensus criteria.[3] Third most important is knowing whether the operator is using ECST or NASCET measurement criteria. UK experience suggests that many vascular laboratories remain unsure.[7] Interestingly, the North American consensus document provides no advice for grading the large carotid bulb that contains large amounts of atherothrombotic material. This could score 0% using the NASCET measurement method (i.e., no need for CEA) but 70% stenosis using the ECST method (i.e., CEA justified). This anomaly has been addressed in the UK carotid stenosis guidelines.[20] Fourth are those situations where caution should be exercised when interpreting DU findings. These include (1) the inability to image above the plaque, (2) dampened waveforms in the proximal CCA suggesting inflow stenosis, (3) high resistance flow in the distal ICA suggesting a distal tandem lesion, (4) in the presence of a contralateral occlusion or very severe stenosis, since PSV velocities may be increased in the contralateral ICA (due to hyperemic collateralization), leading to overestimating the degree of ipsilateral stenosis based on PSV measurement, (5) excessive calcification (which prevents accurate velocity measurement due to acoustic shadowing), and (6) suspicion of subocclusion.

The diagnosis and management of subocclusion has aroused considerable controversy. Previously considered to be a marker of increased stroke risk, the Carotid Endarterectomy Trialists Collaboration observed that chronic subocclusion (a severe ICA stenosis that does not open into a normal-caliber lumen) is not a high-risk predictor for stroke and that CEA does not confer long-term benefit.[21] An important exception to this rule, however, is when DU is performed in the first 7 to 14 days after onset of symptoms. Here it is not uncommon for the DU technician to report a very narrow lumen extending up into the neck, with no apparent opening out into a normal-caliber lumen. Previously, this would have been diagnosed as a "subocclusion," but the critical difference is that there are high peak systolic and end-diastolic velocities across the stenosis. In chronic subocclusions, there are very low peak systolic velocities (<20 cm/s) with no diastolic flow. In the hyperacute situation, corroborative CTA/MRA imaging is mandatory and will usually confirm that the stenosis opens out into a normal lumen (i.e., revascularization is appropriate). In short, no one should be "labeled" as having a subocclusion in the hyperacute period after onset of symptoms without corroborative imaging.

MAGNETIC RESONANCE IMAGING/MAGNETIC RESONANCE ANGIOGRAPHY

Indications

MR angiography has been available since 1996, but only following the introduction of CEMRA has it become a legitimate

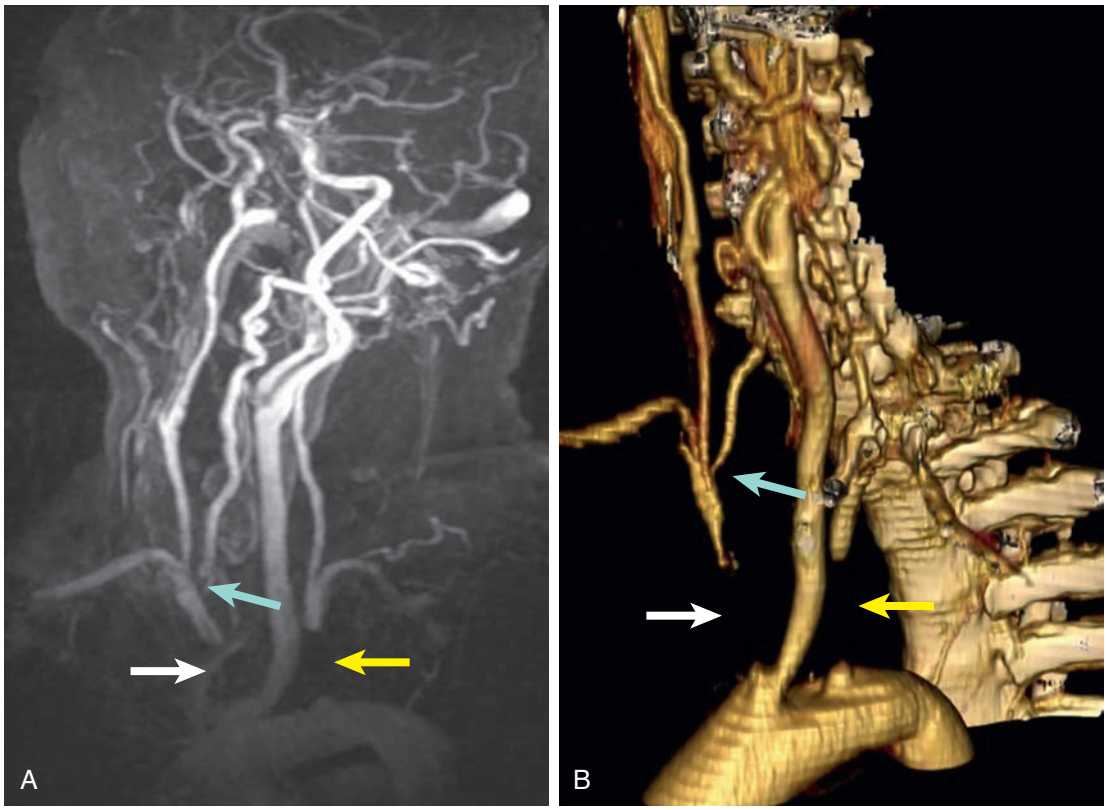

Figure 88.5 Sixty-year-old female with a vertebrobasilar stroke and recurring unsteadiness of gait imaged by contrast-enhanced magnetic resonance angiography (CEMRA; A) and multidetector computed tomographic angiography (MDCTA; B). There is complete occlusion of the innominate artery *(white arrow)* and left subclavian artery *(yellow arrow)*. The right vertebral artery has a stenosis at its origin *(blue arrow)*. CEMRA and MDCTA have shown identical features, but MDCTA is easier to interpret because of venous contamination in the CEMRA image.

rival to angiography for the title of "gold standard" (see Chapter 28). Its main advantage is the avoidance of exposure to radiation. Because of the way magnetic resonance imaging (MRI) images are acquired, bony structures are not present on the resultant image, thus avoiding the need for complicated postprocessing. However, adjacent soft tissue structures are not well visualized unless unsubtracted or additional MRI imaging is performed, and calcium within a plaque is not well defined.

Carotid Disease

MRA has assumed an increasingly important role in the evaluation of patients with carotid artery disease. Table 88.1 summarizes sensitivity analyses from the HTA systematic review for time of flight (TOF) MRA and CEMRA. Sensitivity and specificity for diagnosing a 70% to 99% stenosis with TOF MRA is identical to that for DU and similarly poor for diagnosing 50% to 69% stenoses. Two-dimensional TOF MRA provides strong vascular signals, even when flow is low (useful for differentiating occlusion from "subocclusion"), while 3D TOF MRA offers better spatial resolution for measuring stenosis severity and enabling assessment of flow directionality in steal phenomena. However, to minimize acquisition times and artifacts (flow related, motion and boundary), the field of view must be restricted. Accordingly, while it is possible to image both carotid bifurcations simultaneously, two further acquisitions are required to image the aortic arch/great vessels and the COW using TOF. This limits overall versatility and accessibility and means that TOF-MRA for the most part offers little in addition to DU.

CEMRA uses the paramagnetic agent Gadolinium and (compared to TOF-MRA) images are obtained more rapidly. CEMRA incurs fewer flow related artifacts and provides a much greater field of view that enables high-resolution imaging from the aortic arch (Fig. 88.5) up to the COW while retaining the ability to evaluate flow directionality. The HTA meta-analysis (see Table 88.1) concluded that CEMRA was the best (noninvasive) imaging modality (although MDCTA was not evaluated), and it has superseded TOF-MRA.[2] Another advantage of CEMRA is that it can be combined with MR brain imaging, although this requires an additional period of data acquisition. The recent use of blood-pool contrast agents facilitates high-resolution image acquisition by allowing equilibrium phase imaging, thereby increasing the temporal window.

There is evidence that the presence of infarction on CT/MR can identify patients at increased risk of suffering an early recurrent stroke in the early time period after presenting with a TIA or minor stroke (Table 88.5). The ABCD^2 score is a clinically based scoring system that predicts the 48-hour and 7-day risk of stroke based on A: age, B: blood pressure, C: clinical presentation, D: duration of symptoms, and D: diabetes.[22]

The maximum score is 7, and the risk of recurrent stroke increases as the score increases (see Table 88.5). The table shows that the presence of acute infarction on CT/MR in a patient with a recent TIA or minor stroke should warn the surgeon of an increased risk of early recurrent stroke, prompting expedited CEA. Interestingly; where no infarction was present on CT/MRI; a high ABCD[2] score no longer predicts an increased risk of recurrent stroke.[23]

TABLE 88.5 Early Risk of Stroke After Presenting With a TIA Stratified for the ABCD2 Score and Presence/Absence of an Infarction on Computed Tomography/Magnetic Resonance Imaging

	Stroke Risk at 48 Hours	Stroke Risk at 7 Days
ABCD2 score 0-3[22]	1.0%	1.2%
ABCD2 score 4-5[22]	4.1%	5.9%
ABCD2 score 6-7[22]	8.1%	11.7%
Infarction on CT/MRI + ABCD2 score 0-3[23]		2.3%
Infarction on CT/MRI + ABCD2 score 4-5[23]		8.9%
Infarction on CT/MRI + ABCD2 score 6-7[23]		15.0%
No infarction on CT/MRI + ABCD2 score 0-3[23]		0.2%
No infarction on CT/MRI + ABCD2 score 4-5[23]		1.4%
No infarction on CT/MRI + ABCD2 score 6-7[23]		3.3%

CT, Computed tomography; *MRI*, magnetic resonance imaging.

Role in Vertebrobasilar Disease

One of the advantages of TOF-MRA and CEMRA is that they can provide information regarding flow directionality. This is useful in evaluating steal phenomena (subclavian, coronary). Both, however, are limited by artifact at the VA origins due to vessel tortuosity, respiratory motion, and cardiac pulsation. In practice, MDCTA is probably the preferred (noninvasive) investigation for evaluating patients with suspected vertebrobasilar symptoms.

Role in Screening

MRA has no role as a screening modality. It is simply not cost-effective.

Role in the Evaluation of Trauma

MRI/MRA studies are seldom undertaken in trauma patients. This is because of scanner location (relative to the emergency department or operating room), prolonged acquisition times, and poor access to an unstable patient for monitoring.

Role in the Evaluation of Carotid Body/Glomus Tumors

MR and CEMRA provide basic information, which is useful for planning surgical management and for excluding contralateral lesions (Fig. 88.6). MDCTA is probably the best imaging modality in this situation, largely because of the high-resolution axial images that detail the full extent of the lesion and its relationship to adjacent bony structures. However, while MR is limited by the fact that there are no "bony landmarks" retained

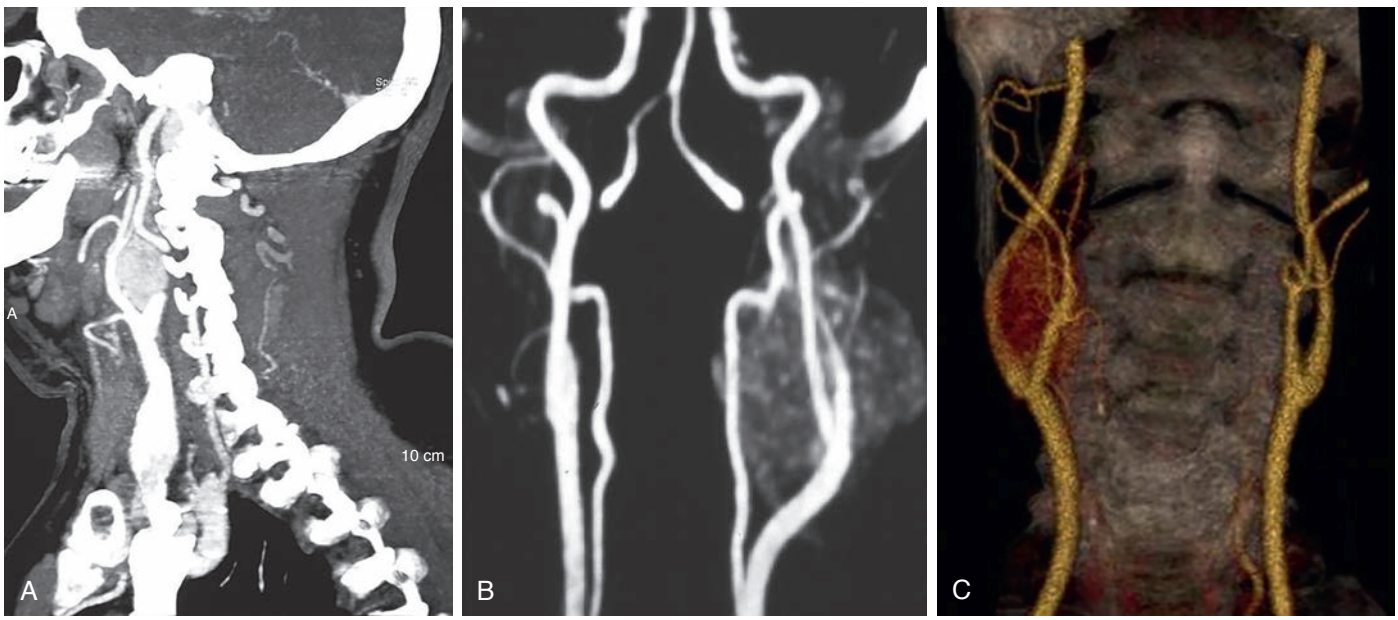

Figure 88.6 Carotid body tumor. (A) Multidetector computed tomographic angiography (MDCTA) maximum intensity projection (MIP) image. (B) Contrast-enhanced magnetic resonance angiography MIP image. (C) MDCTA volume rendition image.

on the image, it does provide excellent soft tissue contrast resolution that may be helpful when evaluating intracranial extension of lesions.

Role in the Planning of Carotid Endarterectomy and Carotid Artery Stenting

Surgeons who regularly perform CEA based on DU alone will be unlikely to find any additional role for CEMRA and little or no use for TOF-MRA. If DU studies are nondiagnostic, MDCTA is probably preferable to CEMRA. However, CAS requires much more imaging information during the planning process than CEA (see Table 88.2; Chapter 92) Accordingly, the choice between CEMRA, MDCTA, and DSA for planning CAS will reflect resources, clinician preferences, and local expertise. CEMRA is preferable to conventional spiral CT, while MDCTA is accepted to be superior because of its versatility and ability to combine anatomical imaging with the identification of calcification, vessel tortuosity, and vascular anomalies in addition to being able to perform functional brain imaging during one period of data acquisition.

CEMRA can identify vessel anomalies, but if arteries are occluded, they can sometimes be missed because of the way images are acquired. The main limitation of CEMRA is its inability to display calcification. Documenting extent of calcification in the arch and origins of the great vessels is not a major problem for CEA, but with increasing age, the arch and great vessels become more tortuous and calcified. This makes CAS more challenging (especially for less experienced practitioners)[24] and are associated with increased procedural risks. A further problem with CEMRA is the tendency for multiple vessels to be included in the final image (some venous). This can lead to difficulties in overall image interpretation without reference to the source dataset or without time consuming postprocessing to "tidy up" the final images (see Fig. 88.5).

Role in Evaluating Plaque Morphology

There is growing interest in the role of MR for evaluating subtle changes in carotid plaque morphology that might help identify a subgroup of patients who may be at higher (or lower) risk of suffering a stroke if left untreated (see Chapter 87). MR is probably the best modality for visualizing the fibrous cap and lipid core,[25] while inflammatory molecules within the plaque can be imaged using MR Spectroscopy (still very much a research tool). Newer contrast agents that facilitate prolonged imaging now permit higher resolution without compromising the signal to noise ratio. This allows greater accuracy in the depiction of ulcers or subtle plaque surface irregularities.[26]

Considerable interest has focused on the ability of MR to diagnose intraplaque hemorrhage (IPH), which is thought by many to be one of the most important predictors of increased stroke risk. In a series of themed projects, Altaf showed that an MR diagnosis of IPH in recently symptomatic patients was associated with (1) increased spontaneous embolization, (2) increased embolization during initial dissection during CEA, (3) an increased prevalence of white matter hyperintense lesions (leukariosis), and (4) a much higher risk of ipsilateral recurrent stroke/TIA in symptomatic patients with 70% to 99% stenoses awaiting CEA and in recently symptomatic patients with 30% to 69% stenoses managed medically.[27-30] It has also been shown that 78% of acutely symptomatic patients with AHA type VI plaques (intraplaque hemorrhage, fibrous cap rupture, mural thrombus) diagnosed using MRI had an average of seven new ischemic lesions on diffusion weighted imaging.[31]

In terms of predicting late stroke, Hosseini et al. pooled data from three prospective data sets involving 179 patients with recently symptomatic 50% to 99% ICA stenoses who underwent high resolution MRI imaging within 6 weeks of symptom onset.[32] Two-thirds had evidence of MRI diagnosed IPH at baseline. During follow-up (1 day to 9 years), 62/179 patients (35%) suffered recurrent TIA/stroke and 57 (92%) had IPH on the baseline MRI scan. The cumulative 5-year risk of "any recurrent neurologic event" was 85% in patients with an MRI diagnosis of IPH compared with 13% in non-IPH patients.[32]

One of the key imaging goals is to identify "high risk for stroke" asymptomatic patients. A few studies have now evaluated MR plaque features in asymptomatic patients, although most are restricted to patients with less severe carotid stenoses (50%-79%). Takaya observed that asymptomatic patients with MR evidence of a thinned or ruptured fibrous cap, large lipid core, or intraplaque hemorrhage faced a higher risk of late ipsilateral stroke than those without these features.[33] Similarly, Singh showed that 6/36 asymptomatic patients (17%) with MR evidence of intraplaque hemorrhage suffered an ipsilateral stroke during follow-up compared with 0/62 that did not exhibit this MR feature.[34]

Perioperative Roles

There is no role for MR in the perioperative setting.

Postoperative Roles

MR/MRA does not have a role in the investigation of patients suffering a neurologic deficit after CEA/CAS. The exception might be the rare patient suffering a suspected hyperperfusion syndrome stroke where CT imaging suggests that there is an evolving ischemic infarct (usually in the posterior circulation). Perfusion MR imaging will usually demonstrate that this area of "infarcted" brain tissue is normally perfused and that the area of low attenuation on CT represents vasogenic as opposed to cytotoxic edema.[35] New hyperintense white matter lesions (attributed to microembolization) have been well documented in the early period after CEA (and particularly after CAS).[36] To date, there is no evidence that these lesions predispose toward declining cognitive function in the long term, but they have been shown to be a marker for an increased risk of recurrent stroke or TIA in the long term.[37] Finally, CEMRA has no role in surveillance after CEA/CAS. This is partly because it will never be cost-effective and because of difficulties imaging near the metallic stents used in CAS.

Contraindications

Contraindications include (1) selected metallic implants (pacemakers, defibrillators, stents, joint replacements), (2)

claustrophobia, and (3) obesity. Caution should be exercised in patients with chronic renal impairment, as they are more likely to develop nephrogenic systemic fibrosis following Gadolinium exposure.[38]

Accuracy and Limitations in Clinical Practice

Diagnostic accuracy is related to technology and expertise, and 2D and 3D-TOF MRA are limited by a tendency to overestimate stenosis severity and need multiple data acquisitions to image the inflow and outflow vessels accurately and artifact (motion, flow related). These are less of an issue with CEMRA, although the same contraindications apply. The inability to image calcification makes it less attractive for working up patients for CAS, while lower spatial resolution can lead to difficulties in identifying subtle tandem lesions. Anomalous vessels that have occluded may not be apparent on CEMRA. In practice, however, the main limitation of MRI is lack of availability and the need for specific sequences and hardware to enable dedicated plaque imaging.

POSITRON EMISSION TOMOGRAPHY-COMPUTED TOMOGRAPHY (See Chapter 29)

Indications

Carotid Artery Disease

Positron emission tomography-computed tomography (PET-CT) has no role in the work-up of patients for CEA/CAS. However, because it can measure cerebral blood flow and oxygen extraction fraction, PET is the "gold standard" for evaluating the hemodynamic effect of extracranial disease, particularly autoregulatory failure and impaired cerebral vascular reserve (CVR).[39] However, in patients with a recently symptomatic extracranial ICA occlusion and evidence of impaired CVR on PET, patients randomized to extracranial-intracranial bypass had no reduction in ipsilateral stroke rates at 2 years compared to patients randomized to medical therapy.[40]

In contrast, a recent meta-analysis suggests that the presence of impaired CVR in asymptomatic patients may serve as a predictor of increased late stroke risk if treated medically (OR 3.9 [95% CI 2.0-7.5]).[41] However, while this could become a novel role for PET in the future, it is likely that more accessible and less technologically complicated imaging strategies will assume this function.

Role in Evaluating Plaque Morphology

PET scanners offer good spatial resolution (2 mm), and many are combined with a CT scan to allow tomographic radionuclide imaging (with anatomic correlation). F^{18} Fluorodeoxyglucose (FDG), like glucose, is transported into cells where its metabolites accumulate at a rate proportional to glycolysis. The accelerated metabolism associated with inflammatory cells raises the possibility that a number of cellular processes can be targeted within the carotid plaque (inflammation, macrophages, apoptosis, angiogenesis, protease enzyme function). The ability to link metabolic activity with biomarkers and plaque imaging could have important implications in the future (patient selection, monitoring drug therapy), especially in diagnosing an unstable plaque in high-risk patients. Marnane et al. undertook FDG-PET studies in recently symptomatic patients and observed that an FDG standardized uptake value of 2.14 had a 98% specificity and a 31% sensitivity for predicting late recurrent stroke, with 83% of all patients suffering a recurrent stroke having an FDG standardized uptake value greater than this threshold.[42]

Other Roles

PET-CT has no role in the evaluation of vertebrobasilar disease, screening, the evaluation of trauma, perioperative management, or in the evaluation of carotid body/glomus tumors.

Accuracy and Limitations in Clinical Practice

While becoming more commonplace in Oncology Units, CT-PET for carotid disease is currently limited by inaccessibility, high cost, and lack of relevance to clinical practice.

COMPUTED TOMOGRAPHY ANGIOGRAPHY

Indications

Carotid Artery Disease

CTA is less likely to overestimate stenosis severity, compared with MRA. Since the HTA meta-analysis in 2006, 64, 256 and 320 section MDCTA have now been developed and are widely available. MDCTA has revolutionized the role of CTA because it is (1) extremely fast (5 seconds to perform scan from aortic arch to COW) (Fig. 88.7), (2) it is cheaper than CEMRA, (3) it offers submillimeter spatial resolution (0.3 mm spatial resolution compared with 0.8 mm for CEMRA and 0.2 mm for DSA), (4) it has sophisticated imaging workstations that enable the production of high-quality 2D and 3D reformatted images from the aortic arch to COW, which are easy to interpret (see Fig. 88.5), (5) it offers faster processing times, (6) it can visualize soft tissue, bone, and vessel at the same time, (7) it can rapidly demonstrate vascular anomalies, even if occluded (Fig. 88.8), and (8) it is able to provide data regarding the extent of vessel calcification, especially in the aortic arch (Fig. 88.9). Because of these characteristics, it is now possible to define extra- and intracranial vascular anatomy in combination with brain imaging during one period of data acquisition. By utilizing rapid advances in software and hardware, combined with bolus tracking, imaging can be achieved with a lower radiation dose and with reduced contrast.

Vertebrobasilar Disease

Imaging the VAs has always presented a challenge (see Fig. 88.7). The VA has a tortuous course, a thick bony covering, adjacent veins, and a large variation in normal vessel caliber,

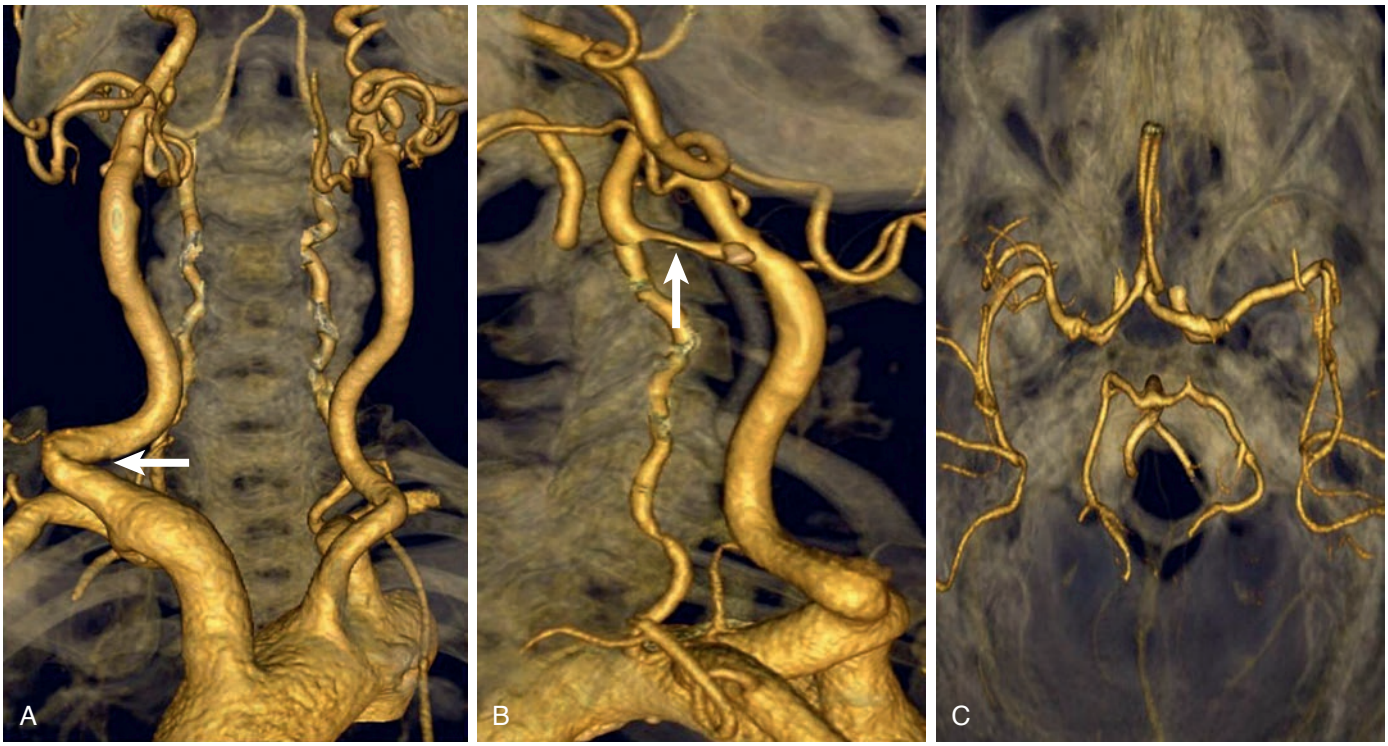

Figure 88.7 Multidetector computed tomographic angiography of the aortic arch and great vessels (A), carotid and vertebral arteries (B), and circle of Willis (C). This scan took 10 seconds to acquire. Note the acutely angled right common carotid artery (CCA; A, *arrow*), which would pose a significant challenge to safe passage of a wire and sheath for carotid artery stenting. The left CCA is less angulated and would not pose such a problem. A severe, relatively smooth stenosis is seen in the internal carotid artery (B, *arrow*).

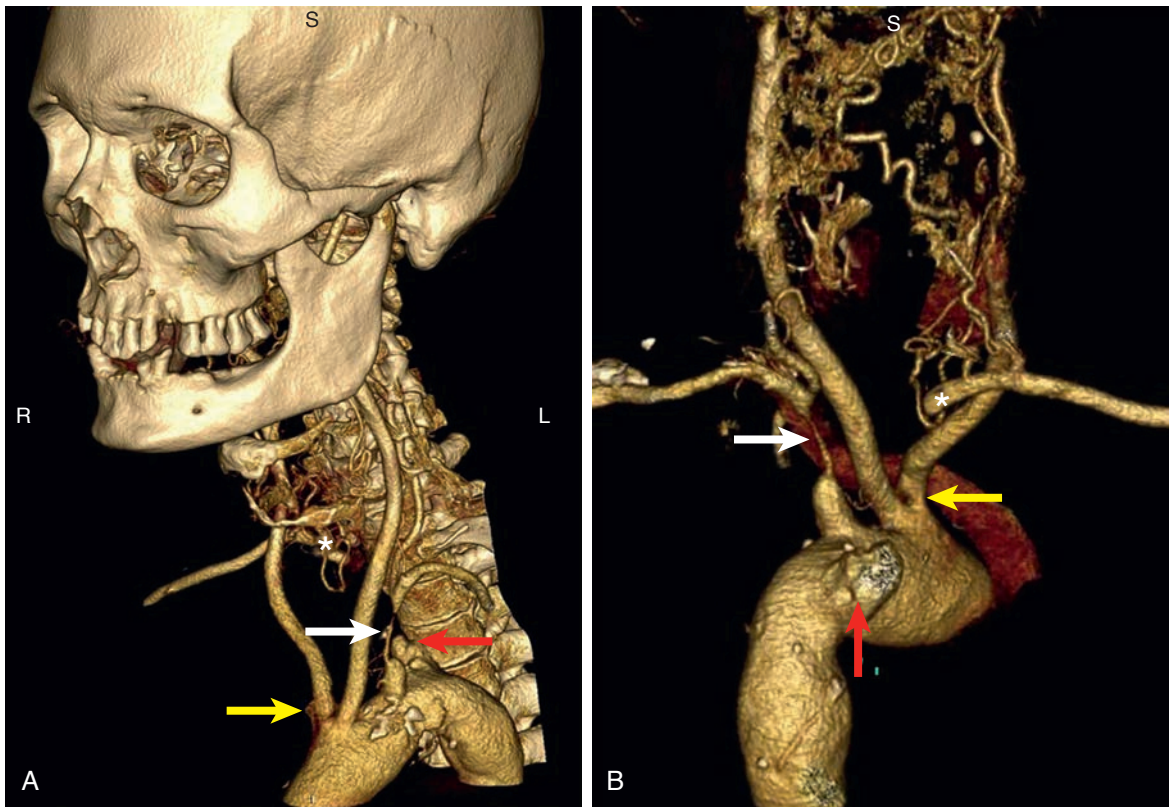

Figure 88.8 Multidetector computed tomographic angiography showing an unexpected anomaly of the great vessels of the aortic arch. (A) Arch viewed from its anterior aspect. (B) Arch viewed from its posterior aspect. Both common carotid arteries arise from a joint origin *(yellow arrow)*, and there is a long, severe stenosis of the proximal left subclavian artery *(white arrow)*. The right subclavian artery arises from an aberrant position and is occluded just beyond its origin *(red arrow)* with refilling distally *(asterisk)*. The *red arrow* marks the "diverticulum of Kommerl."

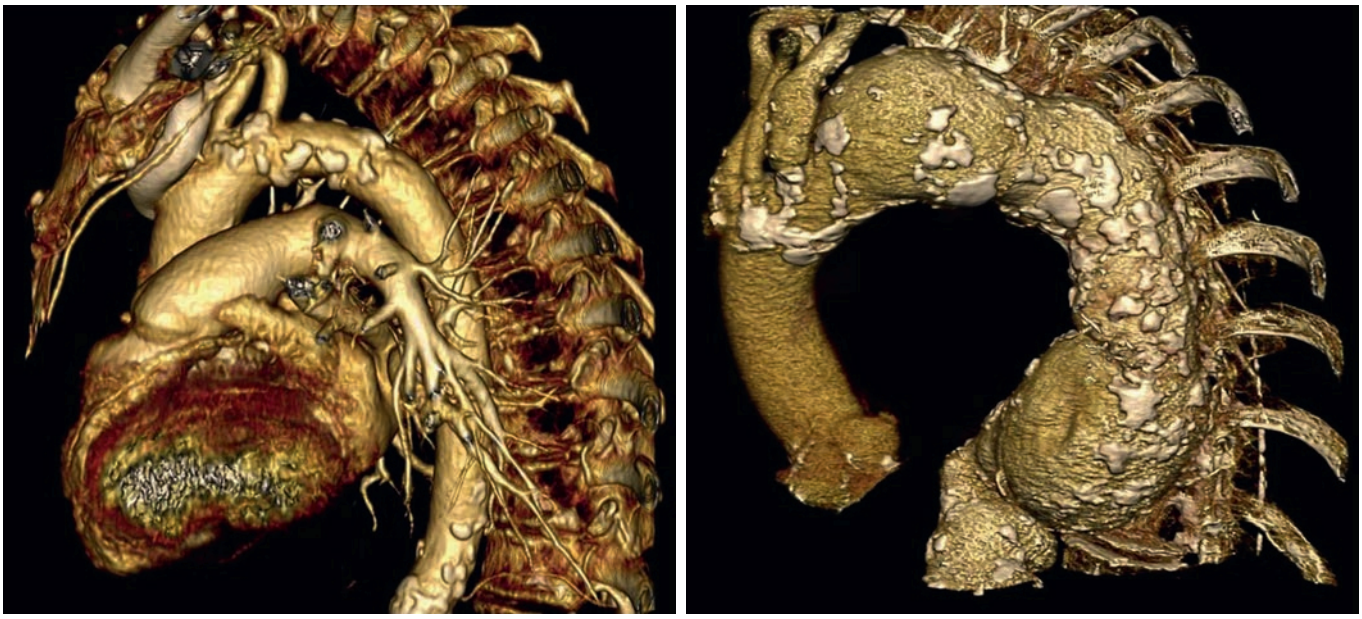

Figure 88.9 Volume rendition multidetector computed tomographic angiography showing calcification in the thoracic aorta, aortic arch, and origins of the great vessels.

and it is not unusual to find that one is hypoplastic. MDCTA provides better images of the extra- and intracranial vertebrobasilar system than CEMRA. An important advantage of MDCTA is that it retains bony landmarks (see Fig. 88.7) and vessel coverings (which can then be "virtually dissected off" as required). Automated subtraction enables easier evaluation of the VAs (and the internal carotid arteries) as they pass through bony structures. In this technique, a low dose scan is obtained immediately prior to the contrast angiogram. The two scans are coregistered and bone and calcified structures from the low dose mask image are automatically subtracted from the post-contrast images, leaving the vessels and soft tissues behind.[43] Vessel tortuosity is easily demonstrated, and there is no problem with artifact at the VA origins. MDCTA cannot, however, provide information regarding flow directionality.

Role in Screening

There is no role for CTA as a screening tool, as it is not cost-effective and it would be unethical to expose patients to the radiation involved.

Role in the Evaluation of Trauma

MDCTA has an important role, because it can rapidly provide anatomical vascular images from the arch to COW, together with bony, soft tissue, and functional brain imaging during a single scan, even in a ventilated patient. CT angiography and venography of neck structures are easily incorporated into trauma whole body CT scan protocols for comprehensive vascular assessment.

Role in the Evaluation of Carotid Body/Glomus Tumors

Due to its better spatial resolution and easy interpretation, MDCTA is the optimal imaging modality for evaluating tumor circulation (see Fig. 88.6), tumor extent, whether it is bilateral, and the relationship between tumor and adjacent soft-tissue structures. This information is usually more than enough to plan a safe surgical resection and can be relied upon to warn when a high or difficult dissection might be encountered (i.e., enabling the surgeon to plan for temporomandibular subluxation as required).

Role in the Planning of Carotid Endarterectomy and Carotid Artery Stenting

Most CEAs can be performed without CTA. However, if there is evidence of inflow/outflow disease or excessive calcification on DU, MDCTA can reliably provide the additional information to plan management. MDCTA is currently the optimal non-invasive imaging modality for planning CAS (see Table 88.2). This is partly because of the production of easily interpretable 3D images from aortic arch to COW (see Fig. 88.7) and because of the ease of demonstrating vessel tortuosity (see Fig. 88.7), abnormalities of the COW (see Fig. 88.7), patterns of calcification in the aortic arch (see Fig. 88.9), and status of the great vessel origins (see Fig. 88.5). Unlike CEMRA, MDCTA is unaffected by occluded anomalous vessels arising from the arch (see Fig. 88.8). Procedural risks after CAS increase with age, and this is probably related to progressive calcification/tortuosity of the arch and great vessels. This can lead to difficulties in accessing the carotid arteries with guidewires and sheaths (see Fig. 88.9). While many of the adverse features detailed in Table 88.2 may not "deter" the experienced interventionist, they should help the less experienced operator (on his/her learning curve) to identify unsuitable or suboptimal cases for CAS.

In a preceding section (see Table 88.4), the presence of infarction on CT/MR was predictive of an increased risk of stroke in the first few days after onset of TIA or minor stroke symptoms,[23] irrespective of the ABCD^2 score. This should alert the surgeon

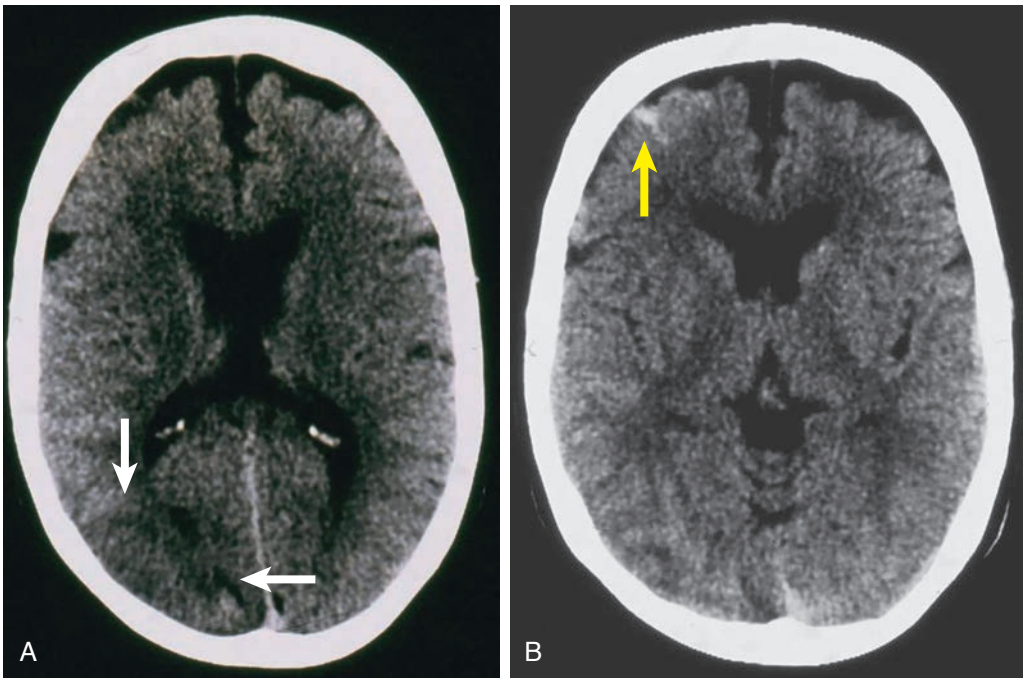

Figure 88.10 Computed tomography (CT) scan in a patient who underwent right carotid endarterectomy and was seen 5 days later with seizures, hypertension, and left-sided weakness. The CT scan revealed an area of white matter edema in the right posterior circulation (A, *arrows*) and a focal petechial hemorrhage in the right frontal region (B, *arrow*). White matter edema in the posterior circulation is not an uncommon finding in this syndrome and is often mistaken for an evolving infarct. (Reproduced with permission from Naylor AR, Evans J, Thompson MM, et al. Seizures after carotid endarterectomy: hyperperfusion, dysautoregulation or hypertensive encephalopathy? *Eur J Vasc Endovasc Surg.* 2003;26(39).)

of the need to consider expedited CEA. In addition, ACSRS has reported that the presence of "silent" infarction on CT (in asymptomatic patients with 50%-99% stenoses) was associated with an increased annual risk of stroke on medical therapy (3.6%) compared to 1.0% in patients with no infarction.[44]

Role in Evaluating Plaque Morphology

The available evidence suggests that MR is better than CT at visualizing thrombus, the fibrous cap, and its rupture (largely because MRI is better than CT at differentiating soft tissues structures), but MDCTA may be better at identifying plaque ulcers.[45] Intraplaque hemorrhage (provided it is >1 mm in diameter) can be visualized indirectly on MDCTA, but it is not as reliable as MR. In addition, MDCTA can measure carotid artery wall thickness (CAWT) with a thicker (>1 mm) CAWT being associated with an increased risk of stroke.[46]

Perioperative Roles

There is no role for CTA in the intraoperative management of patients with cerebral vascular disease.

Postoperative Roles

MDCTA has an important role in the evaluation of patients suffering a neurologic deficit after CEA/CAS. In the first 12 hours, the likelihood of intracranial hemorrhage (ICH) is remote. Accordingly, the patient should be considered for reexploration, and this should not be delayed to perform a CT scan (in most circumstances). However, because MDCTA can be performed rapidly, it may be useful in selected cases of early postoperative neurologic deficit, especially if a completion DU or DSA was normal and intracranial embolism is suspected. After 12 hours, there is an increased likelihood that the stroke was due to ICH or the hyperperfusion syndrome. In this situation, it is important to avoid an unnecessary (and potentially dangerous) return to the operating room. An emergency CT scan will exclude ICH but may demonstrate features associated with the hyperperfusion syndrome (Fig. 88.10). In the latter situation, middle cerebral artery velocities are generally elevated (usually in association with hypertension), and it is not unusual for the CT scan to display areas of low-attenuation (usually in the posterior fossa) that are often misinterpreted as evolving infarction.[35] DWMRI studies have shown that the white matter edema seen in the hyperperfusion syndrome on CT is vasogenic (if it was an evolving infarct, it would be cytotoxic), while perfusion studies show no loss of blood supply.[46] Why the hyperperfusion syndrome causes vasogenic edema predominantly in the posterior circulation has never been adequately explained.

Once ICH and hyperperfusion syndrome have been excluded, the possibility remains that the neurologic deficit was thromboembolic (see section on Transcranial Doppler/Duplex). Duplex imaging of the carotid bifurcation can be difficult to interpret in the early postoperative period (air in deeper tissues, edema, overlying hemostatic gauze), and it may not be possible to exclude an intraluminal filling defect. In this situation, MDCTA will quickly provide high quality images of the extracranial circulation, which will not unduly delay the patient from

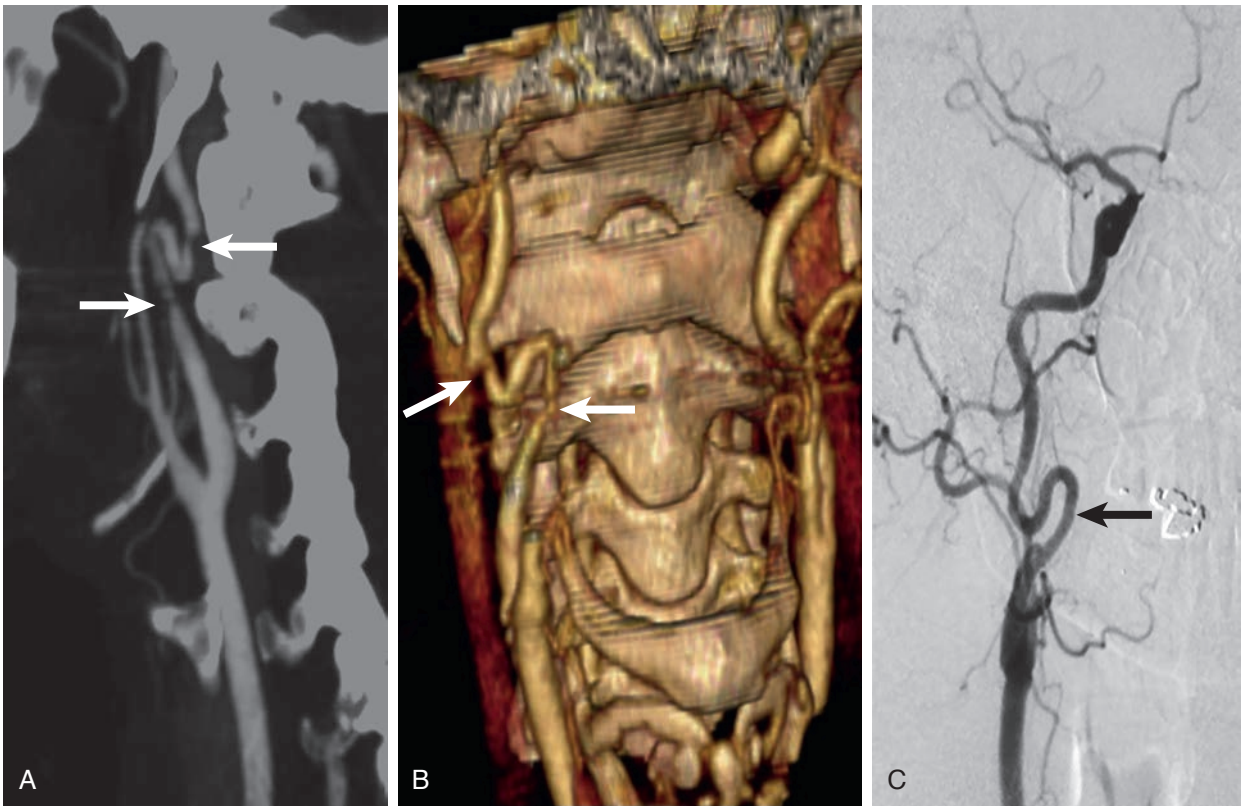

Figure 88.11 Image processing in patients with distal internal carotid artery (ICA) loops can lead to the creation of artifacts that can be interpreted as clinically important stenoses. (A) Multidetector computed tomographic angiography (MDCTA) maximum intensity projection; note the normal bifurcation and a distal looped ICA with apparent inflow and outflow stenoses (*arrows*). (B) Three-dimensional MDCTA in the same patient suggesting that the stenoses were real (*arrows*). (C) Selective intraarterial digital subtraction arteriography showing the looped ICA *(arrow)* but no stenoses. The "stenoses" identified on A and B were caused during image processing.

returning to surgery if necessary. Finally, MDCTA does not have a routine role in serial surveillance after CEA and CAS. This is better achieved using DU.

Contraindications

A history of allergy or reaction to iodinated contrast agents may be a contraindication to CTA, although in milder cases, parenteral steroid therapy may allow safe test completion. Caution must be exercised in patients with impaired renal function who require intravenous hydration beforehand.

Limitations in Practice

MDCTA has superseded previous CT technologies and is becoming the "new" gold standard. Notwithstanding, MDCTA is limited by the need for intravenous contrast, a risk of contrast-related nephropathy (hence the occasional need for hydration), not being able to provide information on flow directionality, and the exposure to radiation. Newer CT scanners, however, have automatic exposure control systems that continuously modulate the x-ray tube (based on patient size and tissue density) enabling potential reductions in radiation dose. Finally, there are occasional situations where MDCTA (and CEMRA) cannot reliably provide accurate and diagnostic imaging information in selected complex patients, especially those with tandem syphon disease or stenoses within coiled segments of the ICA (Fig. 88.11). In these cases, high quality selective carotid DSA imaging remains the "gold standard" (see later).

DIGITAL SUBTRACTION ANGIOGRAPHY

Indications

Conventional catheter angiography was previously the "gold standard" prior to surgery (see Chapter 25). Used in four out of five randomized trials comparing CEA with best medical therapy, its easily interpreted images found favor among surgeons and neurologists. However, the performance of angiography is not without potential risks. In the Asymptomatic Carotid Atherosclerosis Study (ACAS),[47] angiographic related stroke accounted for 50% of the procedural risk after CEA. In a review of complications following 23,416 carotid angiograms,[48] groin hematomas occurred after 4% of procedures, while 2.6% of patients suffered a transient or permanent neurologic deficit. The prevalence of anaphylaxis was 0.03%, while death complicated

0.06% of all carotid angiograms. The risk of suffering a neurologic deficit after catheter angiography was significantly higher in patients with carotid atherosclerosis (hazard ratio 2.5 [95% CI 1.9-3.3]) and in patients with frequent TIAs (hazard ratio 1.7 [95% CI 1.3-2.1]). The prevalence of TIA following angiography in 7614 patients with atherosclerotic carotid disease was 3.2%, while minor strokes occurred in 0.6% and permanent strokes occurred in 0.2%. Angiography-related neurologic deficits have significantly declined with time (reflecting better case selection and improved technology and techniques) from 3.8% in 1988 to 0.6% in 2003.

Carotid Artery Disease

There is no role for routine catheter angiography in modern cerebrovascular practice. However, there are still situations where intraarterial digital subtraction angiography (IADSA) can provide valuable diagnostic information (see Fig. 88.11). Improvements in CEMRA and (especially) MDCTA mean that it is rarely necessary to undertake IADSA to look at the origins of the great vessels (see Figs. 88.5 and 88.8). Similarly, MDCTA can reliably image patients with heavily calcified plaques in the arch or great vessel origins (see Fig. 88.9). However, CEMRA and MDCTA can provide misleading information in patients with severe distal ICA disease (Fig. 88.12) and in patients where there is marked coiling of the ICA in the upper reaches of the neck (see Fig. 88.11). In the former, slow flow through a tiny lumen can be missed. In the latter, unless extreme care is taken with image processing (i.e., ensuring that the axial measurements are in a true perpendicular cross-sectional plane), it is possible that an artifact introduced during image processing can lead to the surgeon or interventionist being persuaded that significant carotid disease exists. Advances in automated bone removal techniques, as described above, or using dual source CT scans, may be useful in such circumstances.[43]

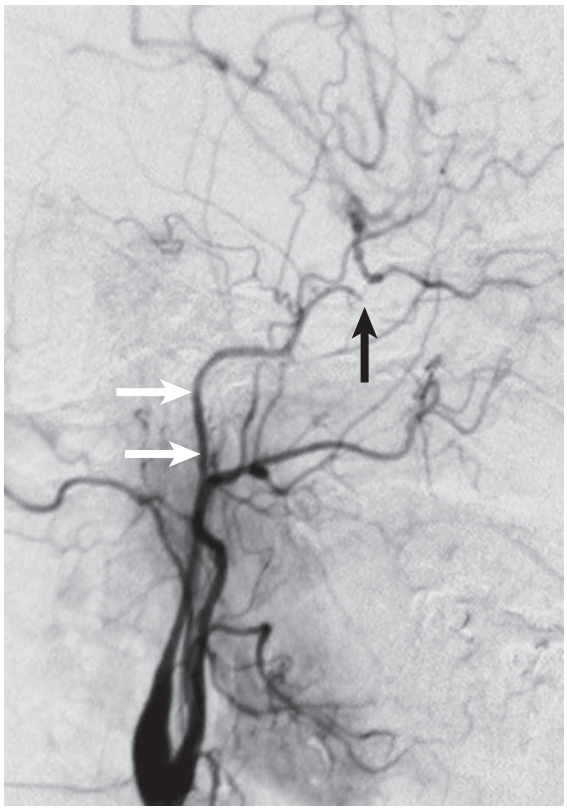

Figure 88.12 Selective intraarterial digital subtraction arteriography (IADSA) in a 38-year-old woman with stroke (middle cerebral territory infarct on computed tomography scan). Duplex ultrasound showed slow, high-resistance flow in the carotid artery but a normal bifurcation. Contrast-enhanced magnetic resonance angiography suggested a subocclusion but could not image the distal internal carotid artery (ICA). This delayed IADSA image shows a normal-caliber carotid bifurcation with a narrow-caliber ICA in its midsection (*white arrows* where flow was extremely slow). In the very distal ICA *(black arrow)*, vessel diameter dwindles toward complete occlusion. The images are probably consistent with acute dissection and compression of the true lumen by thrombus in the false lumen.

Vertebrobasilar Disease

There is no role for IADSA in the routine investigation of patients with suspected vertebrobasilar disease.

Role in Screening

There is no role for IADSA as a screening tool in vertebrobasilar disease.

Role in Trauma

Angiography was previously the first-line imaging modality in patients with a suspected extracranial arterial injury. This role has, however, been superseded by MDCTA, which can perform a diagnostic study from arch to COW in 5 seconds. However, IADSA remains an important secondary option in situations where image quality is compromised or difficult to interpret. Furthermore, angiography retains the unique distinction of allowing one to proceed with endovascular interventions (coil/balloon occlusion, insertion of a covered stent).

Role in the Evaluation of Carotid Body/Glomus Vagale Tumors

There is no role for IADSA in the routine evaluation of patients being considered for resection of CBTs and GVTs. It provides no information on the overall extent or operability of the lesion. However, preoperative embolization of ECA feeding vessels is considered by some to reduce perioperative bleeding (Fig. 88.13), while insertion of a covered stent into the ECA can significantly reduce bleeding in patients with very large tumors.[49]

Role in the Planning of Carotid Endarterectomy/Carotid Artery Stenting

Most centers now perform the majority of CEAs without preoperative IADSA and without compromising patient safety, and the surgeon rarely encounters operative scenarios that cannot be addressed.[1] In reality, the safe performance of CEA does not depend on preoperative imaging of inflow or distal vessels (unless the DU scan suggests an abnormal flow pattern) and there is no evidence that imaging the intracranial circulation alters outcome.

In contrast, some CAS practitioners have been reluctant to dispense with diagnostic IADSA (usually an arch angiogram) as part of the routine work-up of their patients. Advocates of this strategy must, however, remember that the need for a diagnostic angiogram (in place or in addition to CEMRA/MDCTA) will inevitably delay treatment and so potentially

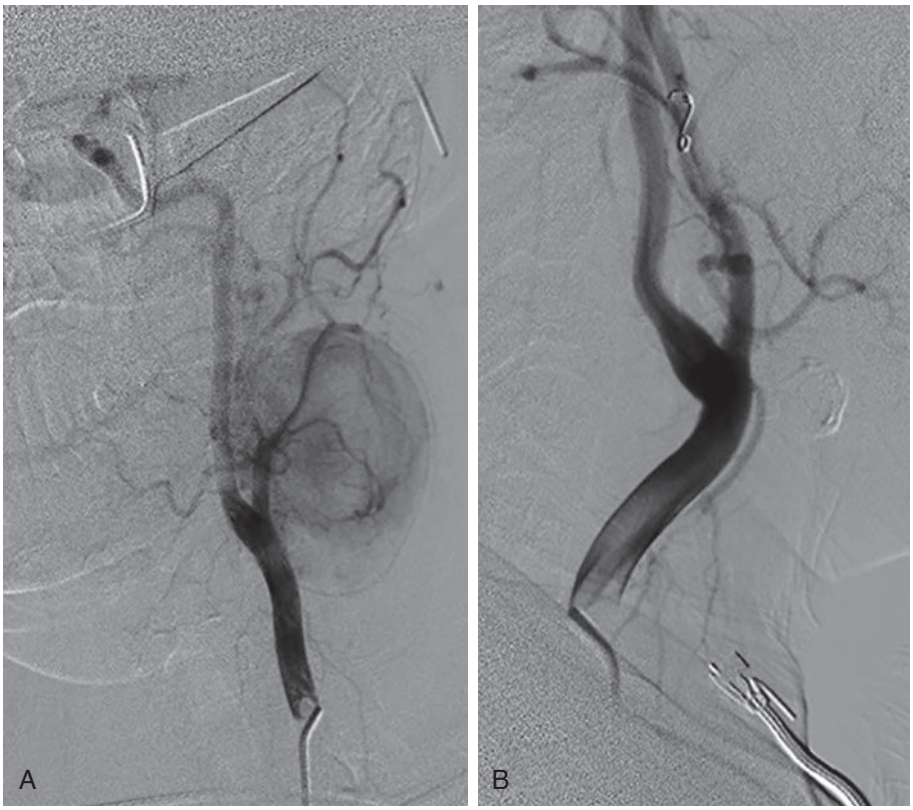

Figure 88.13 (A) Preoperative intraarterial digital subtraction arteriography of carotid vessels in a patient with a large carotid body tumor. Most of the tumor circulation is derived from external carotid artery (ECA) branches. (B) All major feeding ECA branches have been coiled. The patient went direct from the Angio suite to the operating theater for an uneventful tumor resection.

reduce the overall effectiveness of CAS in recently symptomatic patients while also exposing the patient to two catheterization procedures. The advent of CEMRA and (especially) MDCTA with the drive towards expedited treatment in symptomatic patients has probably rendered this practice obsolete. In practical terms, this could mean that a patient may be worked very rare occasions up for CAS solely based on CEMRA/MDCTA only to have the procedure abandoned following the diagnostic IADSA that immediately precedes the planned CAS procedure. In reality, this is unlikely to happen due to excellent preinterventional imaging and planning.

Role in Evaluating Plaque Morphology

DSA has no role in evaluating plaque morphology other than demonstrating that surface irregularity and angiography are not particularly good at identifying intraluminal thrombus.[50] Although NASCET and ECST showed that plaque irregularity (using angiography) was associated with an increased risk of stroke in medically treated patients, as well as an increased risk of major cardiac events during follow-up,[50] there is no evidence to justify IADSA for plaque morphology evaluation.

Perioperative Roles

Intraoperative completion angiography can identify technical errors (intimal flaps, luminal thrombus, residual stenoses) following flow restoration, but it has been superseded by color DU imaging (facilitated by dedicated "L"-shaped probes) or angioscopy. Completion angiography can be cumbersome; it requires the presence of a C-arm and radiology technician in the operating room and (for most patients) represents an unnecessary exposure to radiation.

On table angiography does, however, retain a useful diagnostic role in the rare patient who suffers a stroke due to carotid thrombosis or acute distal dissection in the early postoperative period after CEA/CAS. After CEA, the key to ensuring the best outcome is early reexploration (preferably within 1 hour). At reexploration, it is not uncommon to find a "pulse" in the ICA (suggesting to the unwary surgeon that the vessel is still patent). In this situation, it is important to avoid manipulation of the bifurcation, as this can precipitate major embolization. Despite the apparent "pulsation," it is not unusual for an angiogram to demonstrate complete occlusion. Angiography can also identify the very rare case of acute distal dissection that may follow shunt trauma. In the latter situation, the diagnostic angiogram can be followed by insertion of a stent/covered stent into the true lumen, while embolic occlusion of intracranial vessels can be treated by intraarterial, low dose thrombolysis, or catheter-directed embolus retrieval.

Thromboembolic stroke in the first few hours after CAS raises the possibility of in-stent thrombosis (Fig. 88.14). For a detailed discussion of CAS and prevention/ management of complications, please see Chapter 92.

Postoperative Roles

There is no role for IADSA in the serial surveillance of patients after CEA or CAS.

Contraindications

Previous allergic reaction to iodinated contrast media is a contraindication.

Figure 88.14 Selective intraarterial digital subtraction arteriography in a patient who had undergone uneventful carotid stenting of an extensive symptomatic plaque at the origin of the internal carotid artery. He was readmitted on day 5 with extensive hemiplegia. This image shows extensive in-stent thrombosis.

Accuracy and Limitations in Clinical Practice

IADSA now has a "supporting role" because of radiation exposure, delays to performing studies, and the risk of neurologic deficits. IADSA is also associated with a small risk of access complications (bleeding, dissection, thromboembolism) and contrast-induced nephropathy.

TRANSCRANIAL DOPPLER

Indications

Carotid Artery Disease

TCD can provide a simpler evaluation of the hemodynamic effect of a stenosis (compared to PET) by measuring the proportional increase in middle cerebral artery (MCA) velocity in response to intravenous administration of Acetazolamide (a cerebral vasodilator). TCD is, however, the only modality capable of diagnosing spontaneous in-vivo embolization. This is because the embolus reflects more back-scattered signal than red cells, and despite initial skepticism, there are now validated criteria for diagnosing embolization and for excluding artifacts.[51] Embolization is more commonly encountered in the MCA ipsilateral to a symptomatic carotid stenosis, and this is indicative of an unstable plaque. Recognition of this phenomenon should prompt the surgeon to undertake an expedited CEA, and although it seems intuitive that these patients might be suboptimal candidates for CAS, this has never been properly evaluated.

TCD diagnosed spontaneous embolization may, however, assume an increasingly important role in identifying a "high risk for stroke" cohort of patients with asymptomatic carotid disease. A meta-analysis of six observational studies (1144 patients with an asymptomatic 70%-99% stenosis) observed that the presence of a single embolic signal during one hour of TCD monitoring was associated with a near eightfold increase in stroke during follow-up (odds ratio 7.6 [95% CI 2.3-24.7]).[52] Interestingly, patients with Geroulakos type I/II plaques (see Table 88.3) and evidence of spontaneous embolization at baseline had an annual stroke rate of 8.9%, versus 0.8% in the remaining patients.[53]

Spontaneous embolization rates are significantly higher in recently symptomatic patients, especially in the hyperacute period, reflecting underlying plaque instability. In a study involving 123 recently symptomatic patients, 43% who underwent CEA within seven days of symptom onset had evidence of spontaneous embolization (preoperatively), decreasing to 22% in patients who underwent CEA 8 to 14 days after onset of symptoms and 16% in patients whose CEA was performed greater than 14 days after onset of symptoms. Interestingly, 23% of symptomatic patients with spontaneous embolization on their admission TCD went on to suffer recurrent neurologic events prior to surgery.[54] In terms of predicting 90 day rates of recurrent stroke, the presence of spontaneous embolization on TCD at baseline in symptomatic patients was associated with a threefold excess risk (OR 3.35 [95% CI 1.7-6.7]).[55]

Vertebrobasilar Disease

One practical role for TCD (in the vertebrobasilar circulation) involves patients who report isolated dizziness or vertigo following head movements. In the past, many were labeled as having suffered "vertebrobasilar TIAs" due to compression of the VAs within the transverse processes of the upper cervical vertebrae during neck movement. Subsequent research has shown this to be rarely the case. In a series of 46 "symptomatic" patients undergoing extracranial DU and intracranial TCD with the head rotated into provocative positions, not one patient exhibited flow reversal or flow reduction,[56] suggesting that most historical cases were probably misdiagnosed. In reality, most have inner ear pathologies.

Role in the Evaluation of Trauma

TCD has no proven role in the management of trauma other than being used to monitor the effect of intraoperative carotid ligation/endovascular balloon occlusion in an unconscious patient should reconstruction prove impossible or to determine whether any vessel injury is associated with distal embolization. During CEA, provided mean MCAV is greater than 15 cm/s, most will tolerate carotid ligation (balloon occlusion) without suffering a stroke.[57] Whether this velocity threshold also applies to head trauma patients has never been evaluated.

Intraoperative Monitoring

The main reason that monitoring and quality control assessment has failed to gain wider acceptance is a simple failure to ask the appropriate questions.[58] TCD warns of embolization

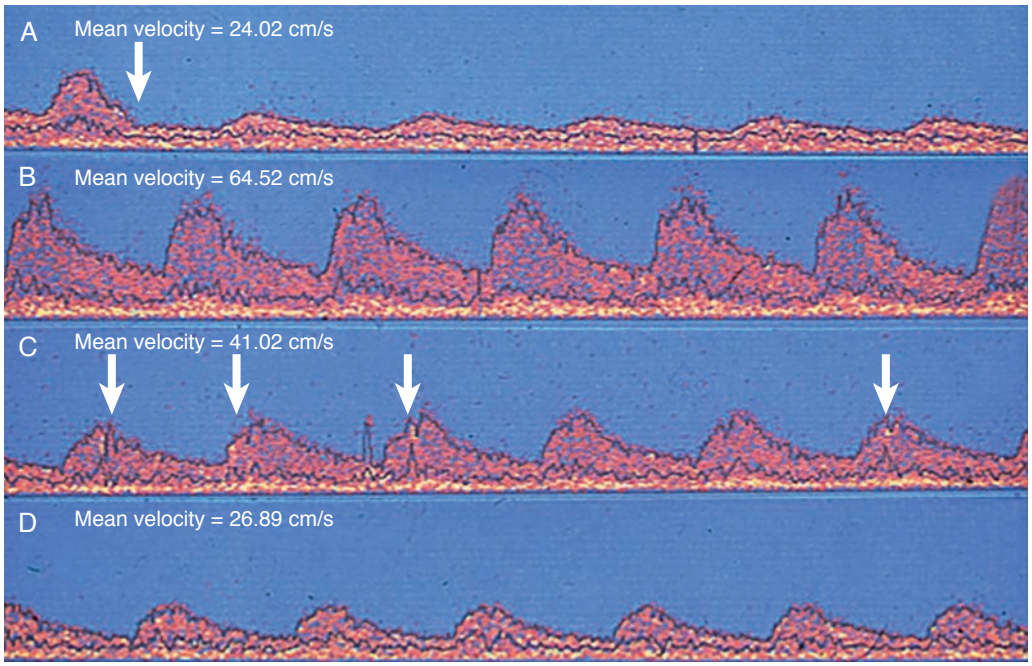

Figure 88.15 Transcranial diagnosis of a patient suffering an on-table carotid thrombosis. (A) Last cardiac cycle *(arrow)* before the carotid clamp is applied. After clamping, middle cerebral artery (MCA) velocity falls to 24.02 cm/s. (B) MCA waveform after restoration of flow (i.e., after endarterectomy). MCA velocity is now 64.52 cm/s. (C) Increasing embolization is detected within 12 minutes of restoration of flow *(arrows)* which is associated with a gradual decline in MCA velocity. (D) Within 23 minutes of restoration of flow, the internal carotid artery is occluded, as demonstrated by the fact that MCA velocity (26.89 cm/s) is now virtually identical to that noted during carotid clamping (A).

(enabling the surgeon to modify technique), but it cannot prevent stroke due to embolization of luminal thrombus following restoration of flow.

Accordingly, TCD has only four roles during CEA:[58](1) determining if there is spontaneous embolization during operative carotid exposure (i.e., warning the surgeon of an unstable plaque), (2) determining if the shunt is working (3% malfunction following insertion),[59] (3) determining if MCAV is greater than 15 cm/s (if not flow can be increased by pharmacological elevation of blood pressure), and (4) determining if this patient is one of the very rare ones destined to thrombose their ICA before the operation is completed (Fig. 88.15). At present, the role of TCD monitoring during CAS has not been clarified, but the potential to answer some of the questions posed above during CEA could also be relevant for CAS.

Role in Evaluating Postoperative Strokes

TCD has a useful (but unexploited) role in determining the cause of intra- and postoperative stroke. Intraoperative stroke mostly follows inadvertent technical error. Hemodynamic failure accounts for only 20% of intraoperative events, with the remainder being thromboembolic.[58] In a large, prospective audit, intraoperative stroke was virtually abolished using TCD and completion angioscopy.[58] Although intimal flaps were occasionally diagnosed on angioscopy, 5% of patients had retained luminal thrombus (despite venting and irrigation) that was derived from transected vasa vasorum.[58]

For those without the availability of angioscopy or other quality control methods, the patient wakening with a new neurologic deficit poses a considerable management dilemma. However, if TCD-derived MCA velocity is now the same as observed during carotid clamping, it is highly likely that the carotid artery has thrombosed (see Fig. 88.15). If MCA velocity is unchanged but with ongoing embolization, it is likely that there is an evolving thrombus within the endarterectomy zone. Both scenarios warrant immediate reoperation.

The etiology of postoperative stroke is multifactorial. After 24 hours have elapsed, most follow ICH or the hyperperfusion syndrome. Unfortunately, no TCD protocol has been developed to reliably anticipate and prevent either of these. In the first 24 hours after CEA, postoperative carotid thrombosis (POCT) remains the most frequent etiology of stroke.[58] Previously considered unpredictable, there is now growing evidence that it is probably related to patient mediated factors (e.g., increased platelet sensitivity to ADP) and may be preventable.

In the past, the Leicester Unit performed TCD monitoring for three hours after CEA.[57] The aim was to identify the 5% cohort of patients with high-rates of early postoperative embolization (who faced a 50% risk of progression onto thrombotic stroke) in whom to target incremental dose Dextran therapy.[58] However, a randomized trial subsequently showed that the addition of a single 75 mg dose of Clopidogrel the night before surgery (in addition to routine aspirin therapy) virtually abolished postoperative embolization. Routine postoperative TCD

monitoring ceased in 2009, all patients now receive dual antiplatelet therapy and none have suffered a postoperative thrombotic stroke.[58]

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Rothwell PM, Eliasziw M, Gutnikov SA, et al; for the Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915.

All of the individual patient data from NASCET, ECST, and the VA trial (>6000 patients) have been combined after remeasuring the degree of stenosis using the NASCET measurement method. This paper shows that delay to surgery significantly reduces the long-term benefit in terms of stroke reduction.

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89 CHAPTER

Cerebrovascular Disease: Decision Making Including Medical Therapy

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INTRODUCTION

Despite extensive clinical experience, including several prospective randomized trials comparing carotid endarterectomy (CEA) to "best" medical therapy (BMT), providing a large body of level 1 evidence, there is still controversy regarding the indications for carotid intervention for the prevention of stroke.

Clinical Implications of Carotid Stenosis and Goals of Therapy

Patients with evidence of extracranial carotid stenosis have an increased overall risk of cardiovascular events, including stroke. Therefore the identification of extracranial carotid stenosis should prompt a program of BMT, including control of hypertension, antiplatelet and statin therapy, as well as smoking cessation.[1] Approximately 20% of ischemic strokes are due to extracranial carotid stenosis, whereas only about 15% of strokes are preceded by a warning transient ischemic attack. An estimated 13 million Americans have evidence of silent cerebral infarction.[2] Therefore the identification of carotid stenosis in a patient provides an important opportunity to intervene with the goal of stroke prevention.

The most important initial step in clinical evaluation is the identification and accurate quantification of carotid bifurcation disease, expressed as the percent diameter stenosis. In a neurologically symptomatic patient, the presence of "significant" carotid bifurcation disease is a target for intervention, whereas its absence should prompt a search for another source of symptoms. In a neurologically asymptomatic patient, the presence of "significant" carotid bifurcation disease, as defined further on, should prompt the institution of BMT, patient education on the signs and symptoms of stroke, and consideration of carotid intervention. The most common and cost-effective method to identify carotid bifurcation stenosis is duplex ultrasound. This should be performed in all patients in whom extracranial cerebrovascular disease is suspected (see Chapter 21).

TREATMENT OPTIONS WHEN CAROTID BIFURCATION STENOSIS IS IDENTIFIED

When a patient is identified as manifesting neurologic symptoms or harboring moderate to severe carotid bifurcation stenosis, BMT should be instituted. Whether or not to add intervention to BMT will depend on balancing three factors:

1. The estimated risk of stroke in a particular circumstance (combination of clinical scenario and plaque phenotype)
2. Assessment of patient-specific benefit (functional capacity, life expectancy)
3. Intervention-specific risk (both procedure- and operator-related)

TABLE 89.1 Effect of Risk Reduction and Best Medical Therapy on Stroke and Cardiovascular Events

Treatment	Goal	Comments
Antiplatelet therapy	Either single or dual drug acceptable	Reduces both stroke rate and overall MACEs
Antihypertensive therapy	Decrease BP by 10 mm Hg systolic 5 mm Hg diastolic or to 140/90 mm Hg with 130/90 mm Hg for recent lacunar in hypertensive patients	Reduces stroke recurrence Treat all patients regardless of baseline BP, after first 24 h
Diabetes mellitus	Aim for $HgbA_{1c}$ <7	Reduce overall stroke rate, no benefit in tight control
Smoking cessation	Total abstinence	Reduces stroke and MACEs
Statin therapy	Reduce LDL by 50% or <70 mg/dL	Treat hyperlipidemia and normolipemic patients with H/O stroke, may be beneficial before CEA/CAS
Alcohol	Avoid excessive consumption	

BP, Blood pressure; *CAS*, carotid artery stenting; *CEA*, carotid endarterectomy; *$HgbA_{1c}$*, glycosylated hemoglobin; *H/O*, history of; *LDL*, low-density lipoprotein; *MACEs*, major adverse cardiovascular events.

BEST MEDICAL THERAPY

Risk-Factor Reduction and Medical Management

A variety of clinical conditions have been associated with increased stroke risk: hypertension, diabetes, hyperlipidemia, smoking, and alcoholism. Efforts to control these conditions have been shown to reduce stroke risk in large population studies. In addition, treatment with antiplatelet agents and the use of statins have been shown to reduce long-term stroke risk and also overall cardiovascular morbidity and mortality. The current data on BMT have recently been recapitulated in a set of guidelines from the American Heart Association (Table 89.1).[3]

Blood Pressure Control

Control of blood pressure has been shown to reduce the overall risk of stroke and recurrent stroke in a number of studies.[4,5] This beneficial effect is seen in both hypertensive patients and those whose baseline blood pressure falls within the accepted guidelines. The one exception to this occurs in the first 24 hours after an acute stroke, where aggressive reduction of blood pressure should be avoided in order to optimize cerebral perfusion pressure. Efforts to reduce blood pressure after the first 24 hours should be made in all patients after stroke.[3] There is no definitive

benefit of one class of antihypertensive agents over another for stroke reduction.

Diabetes Mellitus

Diabetes is an independent predictor of recurrent stroke, with an incidence of 9%.[6,7] The potential advantage of "tight" glucose control (HgbA1c <7) in stroke reduction has been addressed in two large trials: ACCORD[8] and ADVANCE.[9] In the ACCORD trial, 251 patients were randomized between "tight" glucose control (HgbA1c ≤6) and routine control (HgbA1C <7). No benefit in stroke reduction or overall reduction in the rates of adverse cardiovascular events was seen with tight control, and there was an increased mortality rate in the tight control group (HR 1.22, CI 1.01-1.46). The ADVANCE trial randomized 11,140 patients between targets for HgBA1C of ≤6.5 and ≤7 and demonstrated no difference in stroke, overall cardiovascular events, or overall mortality (unlike ACCORD). These trials conclude that there was no benefit from increasing glucose control for diabetics for stroke prevention to levels below the recommended levels of Hgb A1c <7%.[10]

Lipid Management

Elevated cholesterol has been shown to be related to increased risk of stroke.[11-13] Statins exert both a lipid-lowering and anti-inflammatory effect and have been shown to reduce the risk of subsequent neurologic events in neurologically symptomatic patients as well in patients following carotid intervention.[14-16] Meta-analyses of major trials using statins in patients with hyperlipidemia revealed a strong correlation between reduction of low-density lipoprotein C (LDL-C) and a reduced risk of stroke.[17,18] However, the patients in most of these trials also had a history of cardiovascular disease. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial[14] tested the efficacy of atorvastatin (80 mg) on reducing the risk of subsequent stroke and the overall cardiovascular event rate in patients with a history of stroke or transient ischemic attack (TIA) but no evidence of cardiac disease and moderate elevations of LDL-C (100-190). At 5 years there was an absolute risk reduction for subsequent stroke in the atorvastatin group from 13.1% to 11.2% (RR = 0.84, $P = .03$) and an absolute reduction in overall cardiovascular risk of 3.5% (RR = 0.8, $P = .002$). There was an increased risk of hemorrhagic stroke in the atorvastatin group, primarily in patients who presented initially with hemorrhagic stroke. The most significant reduction of events was seen in patients with the more significant reductions in LDL-C. Patients whose LDL-C was reduced by more than 50% had a RR of 0.63 (CI 0.49-0.81) for developing subsequent stroke, whereas those whose LDL-C was below 70 had a RR of 0.72 (CI 0.59-0.89) compared with control patients.

There are no compelling data on the use of statins in stroke patients with a normal lipid profile and no evidence of cardiovascular risk factors. It is worth noting that none of these large population-based studies stratified patients based on the type of stroke or the status of their carotid arteries. Thus the data from these studies cannot be directly extrapolated to the asymptomatic patient with known carotid bifurcation stenosis.

Behavioral Modification

Smoking and excessive alcohol consumption have both been associated with increased stroke risk. Every effort to encourage smoking cessation should be made, including the use of pharmacotherapy.[19,20] Alcohol seems to have a bimodal effect, with mild alcohol consumption (<2 drinks per day) associated with a reduced risk of stroke, but excessive alcohol consumption (>2 drinks per day) should be discouraged.[3] There are no data to support encouraging the consumption of alcohol for stroke prevention. There are also no data documenting a relationship between obesity and stroke risk.

Metabolic Syndrome

This syndrome is defined by the coexistence of three of the following five factors: increased waist circumference (>102 cm for males, >88 cm for females), triglycerides greater than 150 mg/dL, high-density lipoprotein C (HDL-C) below 50 for males and below 40 for females, fasting blood glucose above 100 mg/dL, and blood pressure (BP) above 135 systolic and above 85 diastolic.[21] Patients with metabolic syndrome are known to have increased insulin resistance and are at increased risk for adverse cardiovascular events. Although there is an association between metabolic syndrome and increased stroke risk, it has not been shown to be additive to the individual risk factors that make up the syndrome.

Antiplatelet Therapy

Several studies have demonstrated the benefit of aspirin in secondary stroke prevention and over a wide range of aspirin doses (50-1500 mg).[22] The gastrointestinal side effects of aspirin increase with increasing dosage. Therefore a low dose of aspirin, such as 81 to 325 mg/d, is generally recommended. There is some evidence that enteric-coated aspirin is more frequently associated with aspirin resistance[22]; therefore low-dose non–enteric coated aspirin may be preferred. Dipyridamole has been combined with aspirin for stroke reduction in patients with a history of stroke or TIA. The European Stroke Prevention Study (ESPS-1) showed a benefit from 325 mg aspirin daily plus 75 mg dipyridamole thrice daily over placebo ($P < .001$). ESPS-2[23] compared low-dose aspirin (25 mg twice daily), extended-release dipyridamole (200 mg/d), and a combination of the two drugs to placebo. Both aspirin ($P = .013$) and dipyridamole ($P = .039$) reduced the risk of subsequent neurologic events compared with placebo, and the combination therapy was superior to either drug alone for the reduction of stroke ($P = .006$). However, headache and gastrointestinal symptoms were more common with combination therapy, an observation also made in the PROFESS study,[24] which showed no benefit from the combination of aspirin and dipyridamole over clopidogrel alone.

Ticlopidine (250 mg twice daily) has been shown to be effective in preventing recurrent cardiovascular events including stroke in patients with a history of prior stroke[25] and is similar to aspirin in its effectiveness,[25,26] with a slightly lower bleeding profile. The side effects of neutropenia and rarely thrombotic thrombocytopenic purpura associated with ticlopidine have

limited its clinical use. Clopidogrel has emerged as an alternative antiplatelet agent; as noted earlier, it has been shown to be as effective as the combination of aspirin and dipyridamole for stroke prevention.[24] Clopidogrel was compared with aspirin in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial,[27] which included 19,000 patients and demonstrated an overall cardiovascular event rate of 5.32% in the clopidogrel group versus 5.83% in the aspirin group ($P = .043$). Whether this is clinically significant enough to justify the increased cost of clopidogrel is a matter of clinical judgment. The MATCH trial[28] randomized patients with recent stroke or TIA to clopidogrel or clopidogrel plus aspirin. There was no incremental benefit of adding aspirin to clopidogrel therapy, but there was a 1.3% absolute increase in bleeding risk with dual therapy. The CHARISMA trial[29] compared aspirin alone with aspirin plus clopidogrel and found no difference between monotherapy with aspirin and dual therapy (HR 0.93, $P = .22$). The role of DAPT in patients who do not have a recently placed intravascular stent remains unsettled.[30,31] DAPT has been shown to reduce stroke rate (HR 0.61) but also to increase the rate of reexploration for bleeding (HR 1.71) in patients who undergo CEA, although the absolute risks remain low for both conditions.[30,31] In summary, antiplatelet therapy in patients with stroke or other manifestations of cardiovascular disease is beneficial in reducing both stroke risk and overall cardiovascular morbidity. The benefit of combining antiplatelet agents is modest at best. Resistance to aspirin or other antiplatelet agents clearly exists in some patients, and failure of therapy should prompt a change in agents or tests for drug resistance.[32] Newer drugs such as prasurgel may have a role, especially in patients with drug resistance.[33]

In clinical practice most patients are placed on aspirin (81 or 325 mg daily) alone, clopidogrel (75 mg daily), or a combination of these drugs. Currently routine testing of efficacy is not recommended and drug resistance is investigated only when symptoms recur on standard therapy. Either monotherapy or dual antiplatelet therapy is acceptable for patients prior to CEA, whereas DAPT (ASA aspirin and clopidogrel) is indicated prior to carotid angioplasty and stenting (CAS).

ESTIMATING THE STROKE RISK IN A PARTICULAR CLINICAL SCENARIO

Patient Characteristics

Prior Neurologic Symptoms

The most important indicator of future stroke risk is the presence of recent (within 6 months) ipsilateral neurologic symptoms. The stroke risk in the medical arms of the two major symptomatic carotid trials[34-36] was much higher than that seen in the medical arms of the two major asymptomatic trials (Table 89.2).[37,38] Furthermore, the North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET) and European Carotid Surgery Trial (ECST) both demonstrated that stroke risk is highest within the first month after an initial neurologic event and then declines to approach that of an "asymptomatic" lesion by about 6 months.[39] The observed reduction in stroke risk as the initial event becomes more remote likely reflects "stabilization" or healing of the plaque over time either spontaneously or in response to medical therapy.

In symptomatic patients with high-grade (70%-99%) stenosis, the relationship of the stenosis to future stroke risk is so strong that a causal relationship can be assumed. However, in symptomatic patients with more moderate degrees of stenosis (50%-69%) the benefit of carotid intervention is not as great, implying that the relationship between the bifurcation lesion and stroke is not as clear. In these patients, therefore, other

TABLE 89.2 Results of Randomized Trials of Carotid Endarterectomy Versus Best Medical Therapy (NASCET, ECST, ACAS, ACST)

Study	Population Studied	Number of Patients	Stroke Rate BMT	Stroke Rate BMT+CEA	Study Conclusions
NASCET	Symptomatic patients with carotid stenosis ≥70%	649	26% (2 yr) 28% (5 yr)	9% (2 yr) 13% (5 yr)	CEA is beneficial for symptomatic patients with ≥70% carotid stenosis (P <.001)
NASCET	Symptomatic patients with carotid stenosis ≥50% to 69%	858	15% (2 yr) 22.2% (5 yr)	9% (2 yr) 15.7% (5 yr)	CEA is beneficial for symptomatic patients with ≥50% carotid stenosis ($P = .045$)
ECST	Symptomatic patients with carotid stenosis 80%-99% ECST (=60%-99% by NASCET)	1279	20.6% (3 yr)	6.8% (3 yr)	CEA is beneficial for symptomatic patients with 60% carotid stenosis (NASCET) (P <.0001)
ACAS	Asymptomatic patients with carotid stenosis ≥60%	1662	11% (5 yr)	5.1% (5 yr)	CEA is beneficial for asymptomatic patients with ≥60% cartoids stenosis ($P = .004$)
ACST	Asymptomatic patients with carotid stenosis ≥60%	3120	11.8% (5 yr)	6.4% (5 yr)	CEA is beneficial for asymptomatic patients with ≥60% cartoids stenosis (P ≥.0001)

ACAS, Asymptomatic carotid atherosclerosis study; *ACST,* asymptomatic carotid surgery trial; *BMT,* best medical therapy; *ECST,* European Carotid Surgery Trial; *NASCET,* North American Symptomatic Carotid Endarterectomy Trial Collaborators.

Halliday A, Harrison M, Hayter E, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial. *Lancet*. 2010; 376(9746):1074-1084.

potential sources of neurologic symptoms should be excluded before carotid intervention is undertaken. This includes a search for a cardiac source, interrogation of the intrathoracic and intracranial circulation, and brain imaging to evaluate both the presence of ipsilateral infarction (supporting carotid bifurcation intervention) and the existence of intracranial lesions (interdicting carotid bifurcation intervention).

Although ipsilateral neurologic symptoms are the strongest predictor of stroke risk, a history of stroke of any kind is also associated with increased risk of subsequent stroke. In the Asymptomatic Carotid Stenosis and the Risk of Stroke (ACSRS) study, any prior stroke or a prior contralateral TIA was an independent predictor of stroke risk in a patient with asymptomatic carotid stenosis.[40] Imparato observed that an individual patient tends to have the same type of plaque in both carotid arteries.[41] This implies that patients with prior symptomatic carotid plaque are more likely to have "vulnerable plaque" in the contralateral artery. It is clear that a totally asymptomatic patient and a patient with any prior neurologic events are not at equal risk of stroke.

Contralateral Carotid Occlusion

The presence of contralateral carotid occlusion (CCO) may be associated with increased stroke risk in patients with significant carotid stenosis. Although a post hoc analysis of patients in the ACAS study with contralateral carotid occlusion[42] demonstrated a decreased risk of stroke (3.5% at 5 years) in 168 patients from the medical arm of the trial, the explanation for this is unclear and this association has not been substantiated by other studies, including the Asymptomatic Carotid Surgery Trial (ACST).[38] AbuRahma et al.[43] followed 82 patients with greater than 60% stenosis and CCO and documented a combined neurologic event rate of 60%, including a stroke rate of 33% at a mean of 5 years follow-up, with events distributed between ipsilateral and contralateral arteries. In patients with contralateral carotid occlusion, the degree of intracranial collateral circulation is related to late stroke risk. The adequacy of collateral cerebral circulation can be measured by imaging collateral intracranial circulation or functional assessment of collateral flow by measuring cerebrovascular vasomotor reactivity. Several studies employing this technique have shown that patients with CCO and impaired collateral circulation are at an increased risk of late stroke, whereas CCO patients with relatively normal intracranial hemodynamics have a lower risk of late stroke.[44,45]

Evidence of Clinically Silent Emboli

Clinically silent cerebral infarction can be manifest in one of two ways: (1) evidence of prior ipsilateral cerebral infarction on computed tomography (CT) or magnetic resonance imaging (MRI) imaging of the brain or (2) detection of embolic material in the ipsilateral middle cerebral artery using transcranial Doppler (TCD) techniques.

Routine CT scans taken prior to operation in asymptomatic patients demonstrated an incidence of silent cortical infarction in up to 20% of cases.[46] Subsequent studies have correlated the presence of such infarcts with an increased risk of subsequent ipsilateral hemispheric symptoms.[47,48] A systematic review of 19 studies of TIA patients demonstrated that evidence of acute ischemic lesions on diffusion-weighted MRI was associated with an early increased risk of ischemic stroke.[49] A prospective cohort study of asymptomatic individuals has correlated the presence of microembolic "hits" detected by transcranial Doppler (TCD) with increased risk of subsequent clinical stroke.[50] A review of 58 articles investigating the impact of TCD microemboli on subsequent neurologic events was recently reported by Jayasooriya et al.[51] The duration of TCD monitoring ranged from 30 minutes to 8 hours, with the most common intervals being 30 or 60 minutes. Several of the studies used multiple monitoring sessions. The prevalence of microemboli was higher in patients with neurologic symptoms. Between 4% and 30% of neurologically asymptomatic patients had microemboli with a frequency of 0.35 to 4 embolic signal events per hour. There was an increased rate of subsequent stroke or TIA in patients with silent microemboli detected by TCD as compared with patients in whom no microemboli were identified (28% vs. 2% $P = .001$). The authors concluded that there is level 1 evidence for using TCD indications of microembolization as a risk stratification tool and that it might be used with other techniques such as sophisticated carotid plaque imaging to identify increased stroke risk associated with asymptomatic carotid stenosis. This technique is both patient- and operator-dependent.

Plaque Characteristics

Degree of Stenosis

In the major symptomatic trials as well as in natural history studies, the degree of stenosis was directly related to stroke risk. In NASCET, each decile of stenosis was correlated with an increase in stroke risk, and lesions from 70% to 99% were much more likely to progress to stroke on medical therapy than were lesions of 50% to 69% diameter stenosis, while lesions of less than 50% stenosis were unlikely to result in subsequent neurologic symptoms.[34,35] This finding of increasing stroke risk with an increasing diameter of stenosis was also demonstrated in the ECST trial.[36] In asymptomatic patients, no linear correlation between diameter of stenosis and increased stroke risk was seen in the medical arms of the ACAS trial[37] or in ACST.[38] There are a number of potential explanations for this seeming inconsistency. First, the use of duplex ultrasound to determine stenosis in the asymptomatic trials may not have permitted as accurate a distinction between degrees of stenosis as was possible in ECST and NASCET trials, which quantified stenosis angiographically. Second, the low number of events in the asymptomatic trials may have resulted in inadequate sample size to demonstrate a difference between patients with 60% to 79% stenosis and those with 80% to 99% stenosis. In the ACST study, the mean diameter reduction of the group with greater than 60% stenosis was 69%, suggesting that the lesions in the trial were not evenly distributed across deciles of stenosis but rather were weighted toward the in the 60% and 79% category.[38] It is likely that there were not enough "severe" (80% or greater) stenosis in the large asymptomatic

trials to estimate gradation in risk between deciles of stenosis. Natural history studies of asymptomatic plaques with stenosis ranging from minimal to severe confirm the increased risk of stroke associated with plaques with more severe stenosis.[52-54] In the larger and more detailed study of asymptomatic plaques (ASCRS) including 1121 asymptomatic plaques subjected to observation and BMT, Nicolaides et al. found a linear correlation between degree of stenosis as measured by the ECST method and stroke risk.[55] It is of interest to note that analysis of asymptomatic contralateral stenosis in the NASCET study did find a correlation between degree of stenosis and stroke risk.[48] The risk of "large artery" stroke ipsilateral to an asymptomatic 60% to 99% stenosis was 9.9% in addition to a 6.0% risk of lacunar stroke (many such cases are now thought to result from artery-to-artery emboli). The overall 5-year risk of stroke was higher in the 75%-94% stenosis category (18.5%) than it was in the 60%-74% (14.8%) or the 95%-99% (14.7%) groups. Although these patients are not identical to neurologically asymptomatic patients, such findings do confirm a relationship of angiographically determined stenosis and an increased risk of late stroke.

Since the diameter of most carotid arteries falls within range of a few millimeters, diameter of stenosis is in fact a surrogate measure of plaque size or volume. Plaque size has been correlated with plaque composition, larger plaques being less likely to be fibrotic and more likely to contain lipid, intraplaque hemorrhage with a necrotic core and inflammatory cells.[56] It is likely that diameter of stenosis is a surrogate measure for plaque size. Although stenosis is an important feature used to assess stroke risk, on a hierarchal basis it is not as important as the presence or absence of symptoms.

Plaque Progression

Plaque progression is associated with increased risk of subsequent stroke. The natural history studies noted earlier demonstrate that patients with plaques that progressed from less to more than 50% stenosis while under observation were at increased risk of stroke, and this was even more marked when the progression was to greater than 80% stenosis. Bertges et al., studying 1701 asymptomatic carotid arteries over a 9-year period, demonstrated that plaque progression increased the odds risk of subsequent stroke or TIA by 1.68 ($P < .001$).[57] More recently, Sabeti followed 1065 asymptomatic patients with carotid plaque for a mean of 3.2 years. They documented a correlation between carotid plaque progression and major adverse cardiovascular events (MACE) (OR 2.01, $P < .001$), stroke (OR 2.0, $P > .035$), and cardiovascular death (OR 1.75, $P = .039$).[58] It is likely that plaque progression is a manifestation of dynamic plaque events such as inflammation, intraplaque hemorrhage and/or rupture of the fibrous cap and consequent exposure of necrotic plaque elements to the flow lumen.

Plaque Character

Features associated with "vulnerable plaque" include plaque heterogeneity with increased echolucency, evidence of surface irregularity as manifest by ulcerations on angiography, a thin or disrupted fibrous cap with adjacent echolucent plaque area, and increased inflammatory infiltrate as seen on MRI or positron emission tomography (PET) scan (see Chapter 29). Moore et al. first described the relationship between surface irregularity (ulceration) and stroke risk more than four decades ago.[59] Asymptomatic lesions that were ulcerated had an annual stroke risk of up to 12%. Fisher et al., studying plaques from both the NASCET and ACS trials, found that ulceration was more common in symptomatic patients, as was the presence of thrombus.[60] The Oxford plaque study confirmed an association between ulceration and histologic plaque rupture, large lipid core, macrophage infiltration, and general evidence of inflammation.[61] More recent studies of plaque from patients with remote symptoms suggest that they have a higher incidence of unstable plaque characteristics than do patients who have never been symptomatic.[62]

The Nicolaides group has also used normalized duplex ultrasound to correlate plaque echolucency with the frequency of ipsilateral neurologic symptoms.[63-65] Plaque echogenicity has also been correlated with the amount of embolic material recovered after carotid stenting.[66] The ACSRS study[40] followed 1121 neurologically asymptomatic patients with known carotid plaque on ultrasound between 50% and 99% stenosis. Using a combination of clinical and anatomic risk factors, the investigators were able to identify patients at very low (<5%), low (5%-9.9%), moderate (10%-19.9%), and high (>20%) 5-year risk of stroke. The factors they found that were associated with an increased risk of stroke for patients with asymptomatic carotid stenosis included percent of stenosis, smoking history, renal insufficiency, prior contralateral events, plaque area, and plaque character (gray scale median and presence of "discrete white areas within the plaque"). At present, however, the most reliable imaging predictor of stroke risk remains the accurate measurement of diameter stenosis. Factors associated with increased stroke risk are enumerated in Table 89.3.

TABLE 89.3 Clinical Factors Associated With Increased Stroke Risk

Plaque Characteristics	Patient Characteristics
Diameter stenosis[a]	Neurologic symptoms
Plaque ulceration	H/O contralateral stroke[a]
Plaque progression	Contralateral carotid occlusion[a]
Echolucent plaque[a]	Renal insufficiency[a]
Plaque area[a]	Smoking[a]
Disrupted fibrous cap	Clinically silent emboli by TCD or MRI/CT
"Discrete white areas" within plaque[a]	
Active inflammation by MRI	

[a]See Nicolaides (Ref #40) for risk model.
CT, Computed tomography; *H/O*, history of; *MRI*, magnetic resonance imaging; *TCD*, transcranial Doppler.

Factors Influencing the Decision to Recommend Intervention

Life Expectancy

The patient's longevity plays an important role in considering intervention, particularly in the case of asymptomatic patients. In NASCET, ECST, and ACAS, only patients who had a life expectancy of 5 years were eligible for enrollment.[34-37] In the symptomatic studies,[34,35] patients in the medical arm with most recurrent events occurred within the first 1 to 3 months of the initial symptom. In the asymptomatic studies, the risk of stroke in the medical arms was considerably less: 11% in ACAS and 11. 8% ACST at 5 years.[37,38] These observations suggest that symptomatic patients with high-grade stenosis can be reasonably considered for intervention even when their life expectancy is only 2 to 3 years. However, asymptomatic patients should be expected to survive at least 3 to 5 years to derive significant benefit in stroke reduction from CEA. Of interest, long-term results from Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) indicate that patients in that trial had an estimated life expectancy approximating that of the population at large, indicating that patients in this trial were well selected for intervention.[67]

Age

There is a complex interaction of age with the decision to recommend intervention. NASCET, ECST, and ACAS excluded patients over the age of 80, whereas ACST permitted randomization up to age 91. However, the number of patients above age 80 in ACST was low, and reliable subgroup analysis of the effect of advanced age on outcomes was not possible.[38] There are data demonstrating that age itself is not associated with an increased risk of adverse events after CEA,[68-70] although age does seem to influence the outcomes after CAS.[70,71] Whereas the effect of age on the combined endpoints in CREST was reached at approximately age 70, the age at which stroke rates (as opposed to the composite endpoint) increased with CAS was 64 years.[71] Multiple other reports indicate that older patients are at significantly higher risk of stroke and to a lesser degree of death after CAS (see Chapter 92).[68,71-75]

Gender

Most of the major randomized trials have found a greater benefit from CEA in males as compared with females.[34-37,39] Female gender was associated with an overall increase in MACE (HR 1.98) in the ICSS trial.[76] Women generally have smaller carotid arteries than men and more often require patching after endarterectomy. There were no standard criteria for patching after CEA in any of the major carotid trials, and routine patching after CEA was not standard of care during the time those trials were performed. It is impossible, therefore, to know the effect inconsistent patching may have had on the postoperative results in the female cohort of these studies. NASCET[35,39] and ECST[36] both reported this gender-based difference, although CEA was still beneficial in women with 70% to 99% stenosis. ACAS did not find a benefit for CEA in women,[37] although the number of women enrolled in the trial was small. The ACST trial,[38] with almost double the enrollment of ACAS, found benefit from CEA in both men and women. Several recent population-based studies suggest that CAS may be associated with more complications than CEA in women.[77,78]

Functional Status

Functional status is an important element in decision making. The patient should have a baseline level of function sufficient that a further neurologic event would result in serious deterioration in functional or cognitive ability. Patients with dense hemispheric neurologic deficits are unlikely to benefit from further intervention. Similarly, intervention for patients who have evidence of mild to moderate dementia or limitation in functional ability should be undertaken only after very detailed and careful discussions with the patient, family, and another physician familiar with the patient. There is an argument that intervention in patients with mild to moderate disability can be justified in an attempt to maintain function, but these decisions are often complex, and an unbiased assessment of the patient's functional status and future course is imperative to avoid unnecessary intervention. Poor functional status—as reflected particularly in cardiac, renal, and pulmonary impairment—has been correlated with increased perioperative risk and a higher risk of adverse events during follow-up, thus limiting the effectiveness of operation for asymptomatic stenosis in this patient group.[79]

Cardiac Status

Recent studies have shown that CEA is associated with an increased risk of overall cardiac events, including subclinical infarction, compared with carotid stenting.[80-82] There is evidence that perioperative cardiac events are associated with late mortality.[83] Therefore it is important to evaluate the cardiac status of patients prior to recommending intervention. Predictors of adverse cardiac events include evidence of uncompensated congestive heart failure and of untreated significant coronary disease. In symptomatic patients with 70% to 99% stenosis cardiac risk may be established by clinical risk assessment alone. Stress testing is reserved for those with a history of active angina, new onset of EKG changes or new onset of congestive heart failure. In the asymptomatic patient, where benefits of surgery are less robust, a full cardiac workup, including evaluation for subclinical coronary ischemia, should be strongly considered. A recent analysis of data from CREST[84] indicates that the use of regional anesthesia for CEA was associated with a decreased risk of myocardial infarction (MI) compared with general anesthesia (1.8% vs. 3.4%). This rate was not significantly different from that reported in the CAS subgroup. Although this is a post hoc analysis, one might consider regional anesthesia for CEA in patients with a significant cardiac history. Attention to these details will optimize the results of intervention, whereas failure to consider them sufficiently may result in suboptimal outcomes as a result of intervening in "high risk" asymptomatic individuals, as was done in the SAPPHIRE trial.[81]

Pulmonary Disease

In general, pulmonary disease does not play a major role in morbidity after carotid intervention. Any active pulmonary disease should be stabilized before intervention is undertaken

and the effect of pulmonary disease on longevity should be considered.

Renal Insufficiency

Moderate to severe renal insufficiency reduces life expectancy and is associated with increased complication rates after both CEA and CAS.[85-89] Chronic kidney disease has also been associated with features of increased plaque instability on histologic examination as well as an increased incidence of cerebrovascular events prior to surgery.[90] Renal insufficiency was an independent risk factor for subsequent stroke in the ASCRS study.[40] Patients with chronic renal insufficiency have been excluded from the randomized trials; therefore, the natural history of asymptomatic carotid stenosis in this group of patients is unknown. As a consequence, although it is clear that intervention in these patients is associated with increased risk, no clear recommendations regarding the impact of renal insufficiency on decision for type of intervention can be made.

Contralateral Carotid Occlusion

NASCET identified increased perioperative stroke risk after CEA in patients with contralateral carotid occlusion from 5.8% to 14%.[48] However, a number of single-center studies have not confirmed this increased risk,[91-94] and a meta-analysis of the literature suggests a statistically significant but small (overall risk 2.4%-3.7%) increase in perioperative stroke rate in the face of a contralateral carotid occlusion following CEA.[95] Recently results of both CEA and CAS in patients with contralateral carotid occlusion were compared in patients entered into the Society for Vascular Surgery (SVS) Carotid Registry database.[96] This comparison demonstrated a small but statistically significant increased risk of stroke after CEA (3.15% vs. 1.06%) in the presence of carotid occlusion. The stroke risk in the CAS group was not affected by the presence of contralateral occlusion (2.1% vs. 2.3%). It is relevant that in the data from the SVS Carotid Registry, which included both symptomatic and asymptomatic patients, the overall stroke rate in all patients with a contralateral occlusion still fell within the AHA guidelines and did not statistically favor CAS or CEA (CEA 3.15%, CAS 2.13%, $P = .2$). As noted earlier, data on stroke risk in patients with contralateral occlusion treated with BMT alone are conflicting.

PATIENT-SPECIFIC FACTORS THAT INFLUENCE THE CHOICE OF THERAPY

Early application of CAS was focused on patients at "high risk" for CEA. With increasing clinical experience with CAS, it has become clear that there are also clinical scenarios where CAS is "high risk" (Table 89.4). Fortunately risk factors for CAS and CEA are, for the most part, different and these techniques can be considered complementary. Clearly, when a patient exhibits risk factors for both CAS and CEA, the need for intervention should be carefully considered, and BMT alone may be the best option.

TABLE 89.4 Factors Associated With Increased Stroke Risk From Carotid Endarterectomy and Carotid Artery Stent

Carotid Endarterectomy	Carotid Artery Stent
Poorly compensated cardiac ischemia/heart failure	Symptomatic lesion
Lesion above C2 or below clavicle	Age >70
Scarring from prior surgery or XRT	Vessel/arch tortuosity
Recurrent carotid stenosis	Adverse lesion characteristics: Length >15 mm Echolucent, irregular Tandem lesions Preocclusive lesion Circumferential calcification
Stoma in neck	

Presence of Neurologic Symptoms

The preponderance of data has shown that results with CAS are inferior to CEA in neurologically symptomatic patients.[97-100] This position is reflected in all of the societal guidelines published to date (see further on). A publication combining the results of the three large European trials comparing CEA and CAS in symptomatic patients suggest that the benefit of CEA over CAS (stroke rate 2.8% vs. 9.4% HR 3.4) is especially high in the first week after symptom onset.[101] This is particularly relevant, since most guidelines currently recommend early carotid intervention after stroke (see later text).

Hostile Neck

This is defined by neck anatomy with poor tissue planes or increased risk of postoperative infection. A history of prior radiation, stoma, or prior surgery alone does not in itself define a hostile neck; rather, it is the degree of local change in the tissues surrounding the carotid artery that is relevant. There are series reporting excellent results with CEA for recurrent carotid stenosis[102] and after cervical radiation.[103] However, it is generally accepted that cranial nerve injury is increased when CEA is performed for restenotic lesions, and this is likely also true with radiated fields. Increased wound complications following radiation and/or in the presence of a tracheotomy are well known. In general these conditions represent a relatively increased risk for CEA.

Lesions Outside the Area of the Cervical Carotid Artery

Lesions that are below the clavicle or above the level of the second cervical vertebra also present challenges for open surgical repair. These lesions are infrequently encountered in practice. High lesions, requiring mandibular subluxation or other maneuvers to increase surgical exposure, may result in an increased incidence of cranial nerve injury after CEA.[104] Although

tandem lesions involving the proximal common carotid artery and carotid bifurcation have been treated by CEA combined with retrograde stenting with good results,[105] they cannot be assumed to be equivalent to those of CEA alone. A recent analysis of the CREST data indicates that tandem lesions are associated with an increased risk of stroke after CAS.[106] Intervention in these lesions should be carefully considered, particularly in the asymptomatic patient.

Vessel Tortuosity

Tortuosity of the aortic arch, aortic arch atheroma, and tortuosity of the proximal carotid vessels all increase the difficulty of establishing a stable platform for CAS and increase the risk of embolization with CAS.[75,107] Some surgeons have tried to address this by transcervical CAS.[108] In a recent trial of transcervical stenting, Kwolek et al.[109] reported a stroke rate of 1.4% and a MACE rate of 3.5% in a cohort of 208 patients (20% symptomatic) from 18 centers. The relative role of transcervical CAS in relation to CEA and transcervical CAS remains to be defined. Tortuosity of the distal internal carotid artery may also present challenges for CAS,[75] so that proximal protection with flow reversal should be considered.[109,110]

Lesion Character

There are data suggesting that lipid-rich, echolucent lesions (i.e., "vulnerable plaque") are more likely to result in emboli after CAS than after CEA (see Chapter 88). In addition, lesions that are greater than 15 mm in length, preocclusive and highly calcified, or contain fresh thrombus have all been associated with worse outcomes after CAS.[75,106,111]

EVIDENCE-BASED SELECTION OF THERAPY

Best Medical Therapy Alone Versus Carotid Endarterectomy Plus Best Medical Therapy

Major trials have demonstrated a clear benefit of CEA for stroke risk reduction in symptomatic patients with stenosis of 50% to 99% as well as a less robust but still significant benefit in asymptomatic patients with a 60% or greater bifurcation stenosis (see Table 89.2).[34-38] Even a modest reduction in stroke risk can be "cost effective" given the cumulative cost of stroke.[112]

Maximizing the efficacy of CEA for asymptomatic stenosis requires both focusing intervention on patients with "stroke prone" lesions and limiting the complication rates. The ACST trial demonstrated that this net benefit of CEA in stroke prevention can be maintained over 10 years of follow-up even in those patients on maximal medical therapy at the time of intervention, indicating that BMT and CEA are complementary (Fig. 89.1).[113]

Improvements in medical therapy for conditions associated with an increased risk for stroke and the concurrent reduction in stroke risk has prompted a reexamination of CEA versus BMT alone in patients with asymptomatic carotid stenosis.[114-118]

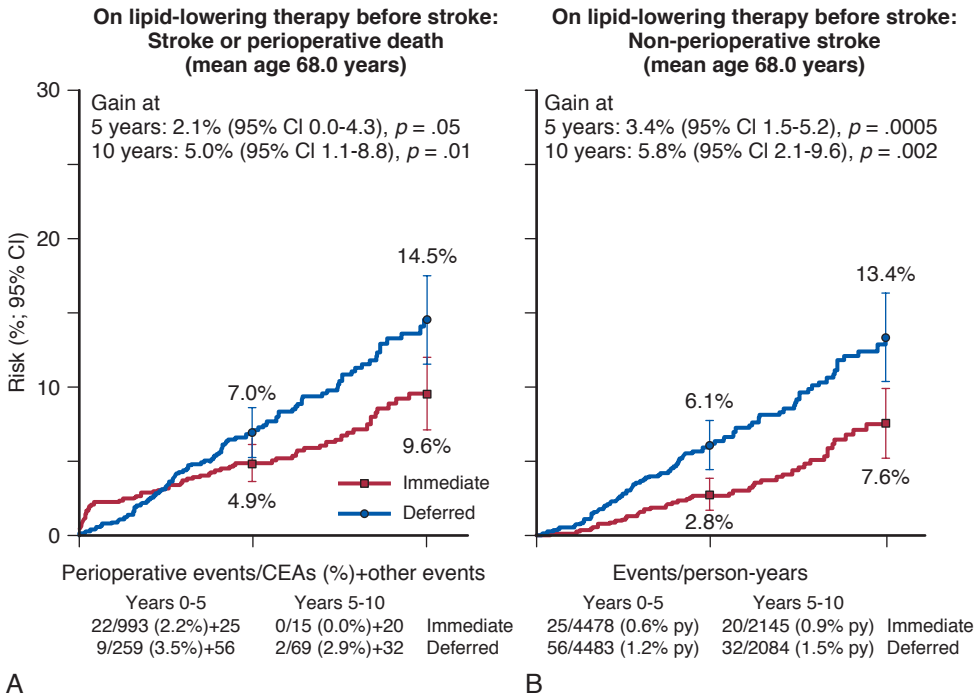

Figure 89.1 Plot of asymptomatic carotid surgery trial long-term results comparing immediate (CEA + BMT) with deferred (BMT alone) treatment strategies in patients who were on lipid-lowering and antiplatelet therapy at the time of randomization. (A) Stroke or perioperative death, (B) late stroke. *BMT*, Best medical therapy; *CEA*, carotid endarterectomy.

Proponents of BMT as sole therapy point to the small annual absolute risk reduction conferred by CEA in the asymptomatic randomized trials, which is similar to risk reduction seen in trials of BMT such as SPARCL.[14] However, it is important to note that trials of medical therapy in stroke prevention included large numbers of patients with a variety of mechanisms for stroke and no information as to the status of their carotid arteries. Since only 20% of all strokes are thought to be related to carotid stenosis, the results in these large medical trials of stroke prevention cannot be extrapolated to patients with known carotid bifurcation stenosis.

In an effort to address the efficacy of medical therapy in patients with known carotid stenosis, Abbott performed meta-analyses of 11 trials, including 3724 patients from 1985 to 2007 in which there were data available on the outcome of medical therapy alone in patients with greater than 50% carotid stenosis.[115] She concluded that the risk of stroke in patients with carotid stenosis had declined significantly over the time-interval studies and that it was now equal to or lower than the stroke risk of the surgical cohort in ACAS. This argument has achieved significant acceptance in the medical community, although the analysis is flawed in several respects. First, trials chosen for analysis were heterogeneous and included both completely asymptomatic patients (ACAS), asymptomatic contralateral stenosis in symptomatic patients (NASCET and ECST), and other small single-center studies. The degrees of stenosis varied from 50% to 100%, and the techniques to measure stenosis differed among studies. Some studies included patients with asymptomatic carotid occlusion, which is known to have a benign natural history. Second, these studies were given equal weight in the analysis to extrapolate a contemporary stroke risk regardless of their sample size. The two largest studies in this analysis, ACAS and ASCRS (comprising two-thirds of the total cohort) both concluded that there was a correlation between diameter of stenosis and stroke risk in patients treated with BMT alone. Third, the "contemporary" stroke risk estimated from these chronologically and methodologically heterogeneous data was compared with the results from ACAS, published 2 decades earlier. Finally, the most contemporary and largest trial comparing CEA plus BMT to BMT alone, ACST,[38] was inexplicably excluded from the analysis. Taken together, these concerns seriously undermine the validity of the conclusions drawn from these comparisons.

Considering only patients with stenosis greater than 70% for CEA, the impact of BMT alone is attenuated. The Oxford vascular study[114] identified a low stroke risk (0.7% annual event rate) in patients with stenosis of 50% to 70% but a 3% annual stroke rate in the 32 patients with greater than 70% stenosis, somewhat higher than seen in ACAS. In the SMART study,[117] of 2684 neurologically asymptomatic patients with arterial disease or diabetes, asymptomatic carotid stenosis of 50% or greater was seen in 221 patients (8%), 147 of whom had a stenosis of 70% to 99%. There was a relationship between degree of stenosis (50%-69% vs. 70%-99%) and the risk of ischemic stroke during the 3-year follow-up, although the numbers were too small to attain significance. The REACH registry documented a twofold increased risk of stroke in patients with asymptomatic carotid stenosis greater than 70% even though a preponderance of patients in the registry were treated with statins.[118] Sabeti et al. have documented plaque progression in nearly 10% of patients despite the fact that some 80% were on statin medications.[122] Finally, level 1 data comparing BMT with BMT plus CEA come from a subgroup analysis of the patients in the ACST trial[111] who received both antiplatelet agents and statins during follow-up documented a statistically significant benefit of CEA in addition to BMT in patients treated with statins and antiplatelet agents, all of whom had stenosis greater than 60% by NASCET criterion (see Fig. 89.1).

The case for BMT alone was bolstered by the results of the SAMMPRIS trial, comparing BMT with intracranial angioplasty for patients with symptomatic intracranial carotid stenosis.[120] The efficacy of BMT alone was much greater than expected and negated any benefit of endovascular intervention. Whether these rates can be implemented on a large scale and at what cost remains a subject for debate.[121]

At present the data do not support BMT as stand-alone therapy in patients with significant carotid stenosis who are good candidates for intervention and have a reasonable life expectancy. The long-term data from both CREST[67] and ACST[113] indicate that intervention performed with low perioperative complication rates can bring lasting protection against stroke with a low rate of restenosis. Further, these data indicate that patients who undergo carotid intervention are likely to live for many years after their procedure. The question of BMT as stand-alone therapy is currently being addressed in the CREST 2 trial[122]; however, data will not be forthcoming for a number of years.

Interventional Strategies: Carotid Angioplasty and Stenting Versus Carotid Endarterectomy

CAS and CEA have been compared in multiple prospective trials. Since 2011, multiple meta-analyses of these clinical trials, each including between 8 and 16 trials predominantly involving patients with neurologic symptoms, have reached similar conclusions (Table 89.5). In summary, the results are quite consistent, indicating a roughly 1.5- to twofold increase in periprocedural stroke and/or death for CAS as compared with CEA, most striking in symptomatic patients. There is a consistent reduction, approximately 55%, in the incidence of MI associated with CAS. In all reviews there was a benefit of CAS in terms of cranial nerve deficits. Differences in mortality, while slightly in favor of CEA, were not statistically different between CAS and CEA. When age-related analyses were performed, the significant differences between CAS and CEA in stroke and death were seen primarily in patients over the age of 70.[74,123-126] It is clear that contemporary data supports CEA over CAS in "normal risk" patients who are fit for surgery because of the consistently lower stroke risk associated with CEA.

The largest trial to date comparing CEA and CAS patients was the CREST study,[80] including 2500 normal-risk patients, 1182 with asymptomatic stenosis, to either CAS or CEA. Interventionalists in CREST were required to demonstrate competence and meet threshold outcomes before they were

TABLE 89.5 Summary of Published Meta-analyses Comparing Carotid Endarterectomy and Carotid Artery Stent

Reference ([a])	# Trials	# Pts	Stroke	Death	MI	S/D
Bonati[123]	16	7572	Favors CEA OR 1.81 (1.40-2.34)	No Diff OR 1.59 (0.94-2.70)	Favors CAS OR 0.44 (0.28-0.87)	Favors CEA OR 1.75 (1.29-1.31)
Liu[124]	13	7501	Favors CEAOR 1.87 (1.40-2.40)	No Diff OR 1.43 (0.85-2.40)	Favors CAS OR 0.43 (0.26-0.71)	Favors CEA OR 1.59 (1.30-1.93)
Economopoulos[126]	13	7477	Favors CEA OR 1.23 (1.23-1.91)	No Diff OR 1.49 (0.93-2.37)	Favors CAS OR 0.49	Favors CEA OR 1.54 (1.25-1.89)
Yavin[127]	12	6973	Favors CEA OR 1.72 (1.20-2.47)	No Diff OR 1.11 (0.56-2.18)	Favors CAS OR 0.47 (0.29-0.78)	
Bangalore[128]	13	7477	Favors CEA OR 1.31 (1.08-1.59)	Not Reported	Favors CAS or 0.45 (0.28-0.71)	Favors CEA OR 1.65 (1.34-2.02)
Guay[a125]	10	6950	Favors[a] CEA OR 0.50 (0.38-0.67)	No Diff OR 0.72 (0.42-1.24)	Favors CAS[a] OR 2.16 (1.32-3.54)	
Murad[49]			Favors CEA OR 1.45 (1.06-1.99	No Diff OR 1.40 (0.85-2.33)	Favors CAS OR 0.43 (0.26-0.71)	
Luebke[129]						Favors CEA Early: OR 1.69, $P = .002$ Late: OR 1.4, $P = .0014$
Vincent[130]	8	7081				Favors CEA Early: OR 1.49 Late: OR 1.36

[a]This analysis used CAS as the standard comparator, while others used CEA.

CAS, Carotid artery stent; *CEA*, carotid endarterectomy; *MI*, myocardial infarction; *OR*, odds ratio.

allowed to participate in the trials.[131] Dual antiplatelet therapy and embolic protection were required for all CAS patients. Therefore the CREST results represent the optimal results currently achievable for either CAS or CEA.[132] The CREST investigators found no significant difference in the composite MACE rate between CEA and CAS (6.8% CEA, 7.2% CAS). However, stroke occurred significantly less often in the CEA group, MI significantly less often in the CAS group, and death was slightly but not significantly less frequent, in patients who underwent CEA. Perioperative occurrence of stroke and MI were both associated with a reduction in long-term survival.[83,133] The reduction in survival was associated with the occurrence of either endpoint and was independent of which intervention was undertaken (i.e., CAS or CEA). A quality-of-life analysis of the CREST cohort did demonstrate that the occurrence of stroke had a greater impact on perceived quality of life than did MI, although this increased impact was lost at late follow-up.[134] Advancing age increased the risk of CAS and the benefit of CEA, with an inflection point at 64 years.[71] When analyzed by symptom status, reduction in stroke and/or death was significant in symptomatic patients (6.0% CAS vs. 3.2% CEA, OR 1.89, $P = .02$). Stroke and death rates were also reduced after CEA in asymptomatic patients (1.4% vs. 2.5% after CAS, OR 1.88), but this did not reach statistical significance.[100] Ten-year follow-up has been reported in 1607 of the 24,502 patients in CREST.[67] The primary composite endpoint was 11.8% in CAS and 9.9% in CEA, with total ipsilateral stroke rates of 6.9% in CAS and 5.6% in CEA. The late stroke and/or death rate favored CEA (HR 1.37, $P = .04$), driven primarily by the difference in perioperative events. The major long-term stroke rates were equivalent after both procedures (2.5%-2.7%), as were rates of restenosis (12.4% CAS and 9.7% CEA, $P =$ NS). There was no effect of initial symptom status on restenosis or late stroke risk. Of particular note was the average survival in patients aged 65 at the time of enrollment, estimated to be 18 years in men and 20 years in women. For patients aged 75 at the time of enrollment, estimated life expectancy was 10.8 years in men and 12.4 years in women.[67]

Recently the role of CAS in asymptomatic normal-risk patients was evaluated in the ACT1 trial.[135] As in CREST, the operators were vetted for experience with a lead-in phase, and a single closed cell stent along with distal embolic protection was used. The study was designed to recruit 1658 patients but stopped after 1453 because of slow enrollment. Based on these numbers, there was a 75% chance of establishing noninferiority (defined as an overall adverse event rate of 3% or less). There was no difference between CEA and CAS for MACE (3.8 ± 0.5% CAS, 3.4 ± 0.98% CEA), or perioperative stroke/death (2.9% CAS, 1.7% CEA, $P = .33$). There was also good durability, with freedom from ipsilateral stroke in both groups greater than 97% at 3 years and any stroke 94% at 5 years.

It is clear that the results of CAS, as demonstrated in CREST and ACT1, have improved over the last decade as a result of increasing technical experience, the development of new technologies, and better patient selection as well as avoiding clinical scenarios associated with increased risk. Proper patient selection is critical to achieving optimal results, especially in asymptomatic patients (see Table 89.4). Recent data document

as much as a fourfold variations in outcomes after CAS.[136] It has become apparent that outcomes are related to both operator experience and volume to a much greater extent than are those with CEA.[137] Optimal CAS results will require that the procedure be performed in centers of excellence with sufficient volumes and documented excellent outcomes.

SOCIETAL GUIDELINES REGARDING CAROTID REVASCULARIZATION AND STROKE PREVENTION

Several professional organizations have published evidence-based guidelines to help define the role of carotid intervention in stroke prevention.[138-141] All guidelines share the following recommendations:

1. Symptomatic patients with angiographic stenosis less than 50% and asymptomatic patients with stenosis less than 60% should not undergo intervention and should be treated by BMT.
2. The particulars of medical therapy include control of comorbid conditions, risk reduction with antiplatelet therapy, and with statins and beta blockers as indicated.
3. CEA is preferred over CAS in symptomatic patients with stenosis greater than 50% unless there are contraindications to CEA, such as uncompensated cardiac disease or local scarring, which increase the risk of cranial nerve complications. The greater the degree of stenosis, the stronger the indication for intervention.
4. In symptomatic patients with stenosis greater than 50% who are at high risk for CEA, CAS is preferred over BMT. The greater the degree of stenosis, the stronger the indication for intervention.
5. In patients with stroke or TIA, intervention should be performed within 2 weeks unless there are contraindications.
6. In good-risk patients with asymptomatic stenosis greater than 60%, CEA may be recommended in addition to BMT for the reduction of stroke risk as long as the combined stroke and death rate is less than 3%.
7. In asymptomatic patients at high risk for intervention, neither CAS nor CEA has proven superior to BMT.
8. Intervention is not indicated for patients with chronic total occlusion of the internal carotid artery or with severe disability that precludes the preservation of useful function.

The role played by CAS in stroke prevention is somewhat different in the various guidelines. The American College of Cardiology/American Heart Association (ACC/AHA)[138] and European Society for Cardiology[140] support a role for CAS *as an alternative* to CEA in symptomatic patients of normal risk and in asymptomatic patients provided that one can demonstrate sufficient institutional volume and document outcomes within AHA standards. In contrast, the SVS guidelines[139] and those of the Australasian College of Physicians[141] support CAS only symptomatic patients at high risk for CEA due to specific cardiac or anatomic characteristics and do not recommend CAS in asymptomatic patients. Their conclusions place greater emphasis on the reduction of stroke risk rather than MACE; accept the validity of the symptomatic stroke trials, particularly ICSS; and take the position that overall lowest stroke and death rates should be used to recommend a specific therapy.

The biggest difference in approach is to the asymptomatic patient. AHA guidelines suggest that "Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), while at the same time acknowledging that "its effectiveness compared to medical therapy alone in this situation is not well established."[138] The SVS guidelines, though supporting CEA in asymptomatic patients at normal risk, do not support CAS in asymptomatic patients except in centers that can demonstrate periprocedural stroke and death rates less than 3%.[139] In situations where this threshold cannot be met or life expectancy is less than 3 years, the SVS position favors medical management of the neurologically asymptomatic lesion due to the relatively benign natural history of asymptomatic carotid stenosis (Table 89.6).

TABLE 89.6 Summary of Societal Guidelines

	Symptomatic	Asymptomatic
AHA[138]	CEA for 50%-99% stenosis, CAS is recommended when CEA complication rates are high and CAS can be performed with complication rates of 4%-6%	CEA for 60%-99%, *CAS in selected pts, but its effectiveness is not well established.*
SVS[139]	CEA preferred in pts 50%-99%, CAS in hostile neck and severe uncorrectable cardiac conditions	CEA in good-risk pts with 60%-99% stenosis and 3- to 5-year life expectancy with complication rates >3%. Insufficient data to support CAS outside of trials, may be used by selected interventionalists with established complication rates <3%. High-risk pts should have BMT alone.
ESC[140]	CEA for 70%-99% stenosis, CAS for high surgical risk	CEA for 60%-99% stenosis with complications <3% and 5-year survival, CAS *as an alternative* in high-volume centers with complications <3%.
Australasian[141]	CEA for 50%-99%, CAS for pts at high surgical risk	CEA for 60%-99%, no evidence to support CAS, consider BMT as primary treatment.

BMT, Best medical therapy; *CAS*, carotid artery stent; *CEA*, carotid endarterectomy; ESC, European Society of Cardiology; *SVS*, Society for Vascular Surgery.

SELECTING THE APPROPRIATE THERAPY FOR THE APPROPRIATE PATIENT

Patients With Carotid Bifurcation Stenosis of Less Than 50%

Data from all symptomatic trials indicate that BMT alone is indicated for neurologically symptomatic patients with stenosis less than 50% (NASCET criterion). In neurologically asymptomatic patients with carotid stenosis less than 50% and no other manifestations of cardiovascular disease there is no clear support for BMT, as the data supporting pharmacotherapy for primary prevention are not robust. Patients found to have evidence of asymptomatic carotid plaque greater than 50% should be evaluated for evidence of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes, and smoking and these risk factors should be appropriately modified. Antiplatelet therapy with aspirin is likely beneficial in this patient group and poses no significant risk. There is some evidence to support statin therapy even in patients with a normal lipid profile.

Asymptomatic Patients With Carotid Bifurcation Stenosis of 70% to 99%

Although both ACAS and ACST demonstrated the efficacy of CEA at a threshold of 60% diameter stenosis, most surgeons prefer to reserve intervention for asymptomatic plaques with stenosis in the range of 70% to 99%. Adverse plaque characteristics (echolucency, ulceration, evidence of silent emboli) strengthen the indication for intervention. Even with severe stenosis and "high risk" asymptomatic plaque, the rate of subsequent neurologic events is low and careful patient selection and preparation is essential. Asymptomatic patients should be operated on if perioperative morbidity is minimal and they have at least a 3- to 5-year life expectancy. Patients should be thoroughly evaluated for cardiac comorbidity, including occult coronary ischemia, since this may affect not only their perioperative complication rate but also their long-term survival. Patients with multiple comorbidities and poor functional status have an increased rate of MACE at 1 year and are less likely to benefit from prophylactic endarterectomy.[142]

To date the available data support CEA as the intervention of choice in most circumstances. The results of CREST and ACT1 have not been achieved outside the limits of a controlled clinical trial; they represent "proof of concept" rather than justification for general application of the procedure in asymptomatic patients. CAS or CEA should be considered only in the asymptomatic lesion if there are no factors that increase periprocedural risk (see Table 89.4). Based on the increased complication rate of CAS seen in older patients, CAS cannot be recommended at this time for asymptomatic patients over the age of 80 (and perhaps over the age of 70) outside of a clinical trial. The goal for intervention in an asymptomatic patient should be a complication rate as close to zero as possible.

Symptomatic Patients With Carotid Bifurcation Stenosis 50% to 99%

Patients with symptoms of anterior or middle cerebral artery embolic stroke and an ipsilateral carotid bifurcation stenosis of greater than 50% should be considered for carotid intervention.[34-36] The more severe the stenosis, the greater the justification for intervention. Patients who have moderate (50%-69%) stenosis without adverse plaque features (described earlier) should be carefully evaluated to be sure that there is no other source of emboli such as the heart or great vessels or evidence of a culprit lesion in the intracranial circulation.

Data from randomized trials, including CREST,[80,98] indicate that CEA is preferred to CAS in symptomatic patients whose cardiac condition is stable or can be stabilized on the basis of reduced stroke risk. For symptomatic patients with a high likelihood of a major adverse event after CEA due to physiologic or anatomic factors, CAS by an experienced operator is preferred. In symptomatic patients with moderate stenosis who are at high risk for both CAS and CEA, consideration of plaque stabilization with maximal medical management is appropriate as first-line therapy, with intervention reserved for breakthrough symptoms.

Contralateral Carotid Occlusion

Patients with contralateral carotid occlusion are at increased risk from intervention after CEA. This increased risk is relatively mild and actually controversial.[91-96] However, the benefits of operation in a symptomatic patient should not contravene intervention. The natural history of an asymptomatic patient with contralateral occlusion is a matter of dispute. In the medical arm of the ACAS trial these patients exhibited a relatively benign postoperative course, with a 3.2% 5-year stroke rate—an observation not validated in any other study.[42] In the ACST[38] trial, patients with contralateral occlusion faced a similar long-term stroke risk as other asymptomatic patients and derived benefit from CEA. It appears that the modestly increased risk of intervention in the face of contralateral occlusion would support intervention in an otherwise good-risk patient. Based on the data from the SVS database,[96] it is likely that both CEA and CAS done by an experienced interventionalist would be equally effective in the face of contralateral occlusion.

Timing of Intervention After Acute Stroke

At the time of the NASCET and ECST trials, clinical practice was to defer CEA for 4 to 6 weeks after a stroke to allow for stabilization of the ischemic penumbra and prevent postoperative hemorrhagic transformation of a bland infarction. Data from the medical treatment arms of both these studies demonstrated that the highest risk of recurrent neurologic events was in the first 2 to 6 weeks after the incident event. These findings prompted reexamination of the 4- to 6-week delay of surgery. Several studies[143-149] have demonstrated that early endarterectomy after an acute neurologic event, including crescendo TIA and evolving stroke, could be performed with increased but acceptable

risk in patients with mild to moderate neurologic deficits and limited infarction on CT scan. Appropriate patients should have mild to moderate neurologic deficits as reflected in the NIH stroke scale, no evidence of cerebral hemorrhage, and less than 30% of the hemisphere involved in the stroke. Patients with more profound deficits are less likely to be improved by early intervention and more likely to suffer hemorrhagic transformation.

Despite this compelling evidence and recommendations from several guidelines,[138,139] compliance with recommendation for early intervention is poor in clinical practice.[150,151] Barriers to such early intervention include delays in the diagnosis and treatment of patients with TIA, delayed diagnosis of carotid stenosis in patients with stroke, and surgeon reluctance to operate on such patients in an urgent fashion. Early referral of patients to a stroke unit, with admission and in-hospital referral for surgery, has been proposed as a method to increase compliance with these guidelines.[148]

Unstable Neurologic Syndromes

Patients who present with unstable neurologic syndromes such as crescendo TIA or stroke in evolution (waxing and waning neurologic events) have either highly unstable plaque or compromised intracranial collateral circulation. A meta-analysis of the literature in from 1980 to 2008[152] confirmed an overall increased risk of postoperative stroke or death for both crescendo TIA (OR 5.6, $P < .0001$) and stroke in evolution (OR 5.5, $P > .001$) compared with neurologically stable patients who presented with stroke or TIA. Comparisons with the results of early medical management are unfortunately not readily available. A review of the literature suggests that properly selected patients can be stabilized and prepared for early endarterectomy with an expectation of good results.[152-154] Such patients should be managed by an experienced multidisciplinary team, including stroke neurologists and surgeons skilled in CEA, so as to optimize patients' preparation and selection. The role of CAS in the management of these patients is not established at present.

Recurrent Carotid Stenosis

Recurrent carotid stenosis occurs after both CAS and CEA with a similar incidence of between 8% and 12%.[67,155,156] Early recurrent stenosis after both CEA and CAS is generally a proliferative lesion (intimal hyperplasia) and the data suggest a relatively benign course. A number of reports indicate that patients who demonstrate recurrent stenosis after either CEA or CAS are more prone to restenosis after a secondary intervention.[155,156] These observations, along with the benign history of the lesion, should prompt careful consideration before either CAS or CEA is undertaken for an asymptomatic stenosis that recurs within 24 months of the initial intervention. In contrast, a stenosis that recurs late (>36 months) after CAS or CEA is more often the result of recurrent atherosclerotic disease and for this reason is more likely to be associated with new neurologic symptoms. The case for intervention in a symptomatic patient or one with a documented late recurrence is more robust. When intervention is contemplated for recurrent stenosis after CEA, CAS has been generally recommended over CEA. This is based on the increased risk of cranial nerve dysfunction seen with reoperation in a scarred neck. However, recurrent stenosis is not an absolute contraindication to CEA, and several series[102,103,157-159] reported good results with CEA for recurrent stenosis in carefully selected patients (see Chapter 92).

The decision to intervene in recurrent stenosis depends on many factors, including the symptomatic status of the patient, the nature and location of the collateral circulation, and the status of the neck and the degree to which it is viewed as "hostile" due to scarring, stoma, obesity, or expectations of difficulty with proximal or distal exposure. The fact that asymptomatic recurrent disease is usually benign and the propensity for second and third recurrences in these patients are important factors that should temper the enthusiasm for treating asymptomatic recurrent disease, especially if the remaining extracranial vessels are relatively normal.

Radiation-Induced Stenosis

Reports of small series[160,161] of patients demonstrate good results with either open surgery or CAS, with reduced rates of cranial nerve injury and wound infection after CAS and better durability of open carotid surgery, which may include interposition vein grafts (see Chapter 92). A meta-analysis of the literature including 533 patients revealed no difference between CAS and CEA in terms of stroke risk 3.9% versus 3.5% with a higher risk of cranial nerve injury with CEA and a higher risk of restenosis with CAS.[162] Because many of these lesions are asymptomatic and patients may have a limited life expectancy due to an underlying disease that requires radiation, a thoughtfully conservative approach should be taken, particularly in asymptomatic individuals.[163]

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Jayasooriya G, Thapar A, Shalhoub J, Davies AH. Silent cerebral events in asymptomatic carotid stenosis. *J Vasc Surg*. 2011;54:227–236.

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Kernan WB, Ovbiagele B, Black HR, et al. Guidelines of rhte Prevention of Stroke in Patients with Stroke and Transient Ischemic attack. A guidelines for Healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236.

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This article highlights factors that are associated with increased complication rates following CAS.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 90

Nonatherosclerotic Carotid Artery Disease and Its Management

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Although the majority of carotid artery disease encountered by the vascular specialist is primarily atherosclerotic, there are a number of nonatherosclerotic carotid artery pathologies with clinical implications as well. This chapter focuses on carotid stenosis after radiotherapy and recurrent carotid artery stenosis. Both disorders have pathologic features, natural histories, and clinical management considerations that are distinct from those of primary atherosclerotic disease.

More than 40,000 people in the United States were diagnosed with cancers of the oral cavity and pharynx in 2012, and nearly 75% of these patients are treated with radiation therapy. There were an estimated 9000 new cases of Hodgkin and 70,000 new cases of non-Hodgkin lymphoma diagnosed in the same year, with 30% and 18% of these patients, respectively, receiving radiation therapy.[1] Although breast cancer is the most common cancer diagnosis in women, only a small proportion of new cases (<1%) require radiation to the supraclavicular fossa. In all, an estimated 50,000 people underwent radiation therapy of the neck in 2012 in the United States. With a 25% incidence of carotid stenosis after radiotherapy and 6% incidence of restenosis after carotid endarterectomy (CEA), approximately 12,500 cases of radiation stenosis and 8500 cases of carotid restenosis can be expected annually in the United States alone.

CAROTID STENOSIS AFTER RADIOTHERAPY

Radiation damage to the carotid artery is associated with both asymptomatic and symptomatic stenosis. The mechanism involves

Abstract

Although the majority of carotid artery disease encountered by the vascular specialist is primary atherosclerotic, there are a number of nonatherosclerotic carotid artery pathologies with clinical implications as well. This chapter focuses on carotid stenosis after radiotherapy and recurrent carotid artery stenosis. The epidemiology, clinical decision making, treatment options, technical considerations, and outcome of the described approaches are discussed here.

Keywords

carotid restenosis
radiotherapy
carotid endarterectomy
carotid artery stent

direct damage to the artery and the acceleration of atherosclerosis. CEA and carotid artery stent (CAS) are well-studied treatments for postradiotherapy carotid stenosis. The clinical decision making, technical considerations, and outcomes of these modalities are discussed here.

Epidemiology

A number of case control studies have demonstrated an increased prevalence of carotid artery stenosis of 16% to 55% among patients who have undergone neck irradiation.[2] The association is observed even when studies are controlled for age and comorbidities,[3] and the effect is seen even in the very young. A study of 30 pediatric cancer survivors who underwent carotid duplex imaging on average 15 years after completion of radiation therapy compared to 30 age-, ethnicity-, and gender-matched controls found that those treated with neck irradiation were much more likely than controls to have plaque deposits in their carotid arteries (18% and 2%, respectively).[4] Neck irradiation has also been shown to be associated with an increased risk of cerebrovascular events, as high as 2.6% compared with 0.29% in matched controls (OR 9.0).[5] The stroke risk varies by pathology, with the relative risk of stroke highest for patients treated with radiation for head and neck cancers. For survivors of Hodgkin lymphoma, one-fifth of ischemic cerebrovascular events are attributable to significant carotid stenosis.[6] Irradiation of the supraclavicular fossa for breast cancer may be an exception. Although a small but statistically significant association between supraclavicular radiation for breast cancer and cerebrovascular events has been demonstrated in some studies,[7,8] other studies found no such association, including a large study of 5752 women from the Surveillance, Epidemiology, and End Results (SEER) Medicare database.[9]

A number of factors may be associated with the risk of developing carotid stenosis after neck irradiation, including older age, a history of smoking, heart disease, and treatment of malignancy without surgical resection; but the data are inconsistent regarding the effects of these factors.[10,11] The risk of developing carotid artery stenosis and associated cerebrovascular events has consistently been shown to increase with the passage of time after radiotherapy. A prospective cohort study of patients who received unilateral irradiation for head and neck cancers determined that carotid stenosis increased as the time after radiotherapy increased, but the difference in rate of stenosis compared with the contralateral side reached significant only 10 years or more after radiotherapy.[12] In a study of 367 patients with a history of irradiation for head and neck malignancy,[13] the relative risk for stroke was 10.1 after more than 10 years of follow-up, and the 15-year cumulative risk of stroke was 12%.

Pathogenesis

Radiation arteritis, though histologically similar to primary atherosclerosis, results from a distinct mechanism of arterial injury. The endothelial cell of both the artery proper and the vasa vasorum is the most radiosensitive mesenchymal cell within the radiotherapy field.[14] In the acute phase, radiation causes swelling, vacuolization, and vesicle formation within capillary endothelial cells. The acute changes are followed by platelet aggregation and fibrin deposition, which obstructs the capillary lumen and results in obliteration of the vasa vasorum. Focal necrosis and fibrosis of the media along with periadventitial fibrosis develop late as a result of this damage to the vasa vasorum, resulting in extrinsic compression and narrowing of the vessel lumen.[15,16] Nitric oxide and prostacyclin-mediated endothelium-dependent relaxation have been shown to be impaired in cervical arteries at 4 to 6 weeks after radiation, which may also contribute to the development of carotid artery stenosis.[17] Radiation-induced release of endothelium-derived growth factors is thought to be involved in the pathogenesis of both early vascular damage and late fibrosis.[18] Inflammation in irradiated arteries of the head and neck can be demonstrated even years after radiation treatment, with one study showing sustained activation of the transcription factor nuclear factor-kappa B, which results in alterations in the expression of adhesion molecules and cytokine production in the cervical arteries of irradiated patients an average of 7 years after radiation.[19]

Atherosclerosis is also accelerated by radiation, but the relationship between radiotherapy and atherosclerotic risk factors has not been elucidated. Macrophage foam cell formation is induced by radiation through activation of CD36 scavenger receptors[20]; in a mouse model, the atherosclerotic plaque of irradiated carotid arteries was macrophage-rich compared with that of nonirradiated mice, where the plaque demonstrated only minimal macrophage infiltration.[21] Histologic examination of carotid plaques after endarterectomy, however, suggests that radiation-induced carotid stenotic lesions are more stable than primary atherosclerotic plaques, with less infiltration of macrophages and a smaller lipid core (Fig. 90.1).[22]

Carotid artery intima-media thickness (CIMT), as measured by duplex ultrasound, has been shown to be directly associated with risk of stroke.[23] A significant increase in CIMT after neck irradiation has been demonstrated in multiple case-control studies.[24-29] Increased CIMT compared with controls is demonstrated in the early phase, within the first year after radiotherapy,[30] and persists as long as 50 years after treatment,[31] increasing in a linear manner with duration after radiotherapy when adjusted for age and gender.[32] Increases in CIMT are found with increasing doses of radiation.[33] There appears to be a threshold radiation dose for carotid artery injury,[34] with significantly increased CIMT demonstrated only at doses higher than 35 Gy.

Clinical Findings

History and Physical Examination

A detailed history should be taken to distinguish symptomatic from asymptomatic carotid stenosis. Symptomatic patients may present with amaurosis fugax, transient ischemic attack, or stroke. The physical exam should include inspection of the head and neck with attention to the location of scars from prior neck reconstruction, presence of patent or healed tracheostomy

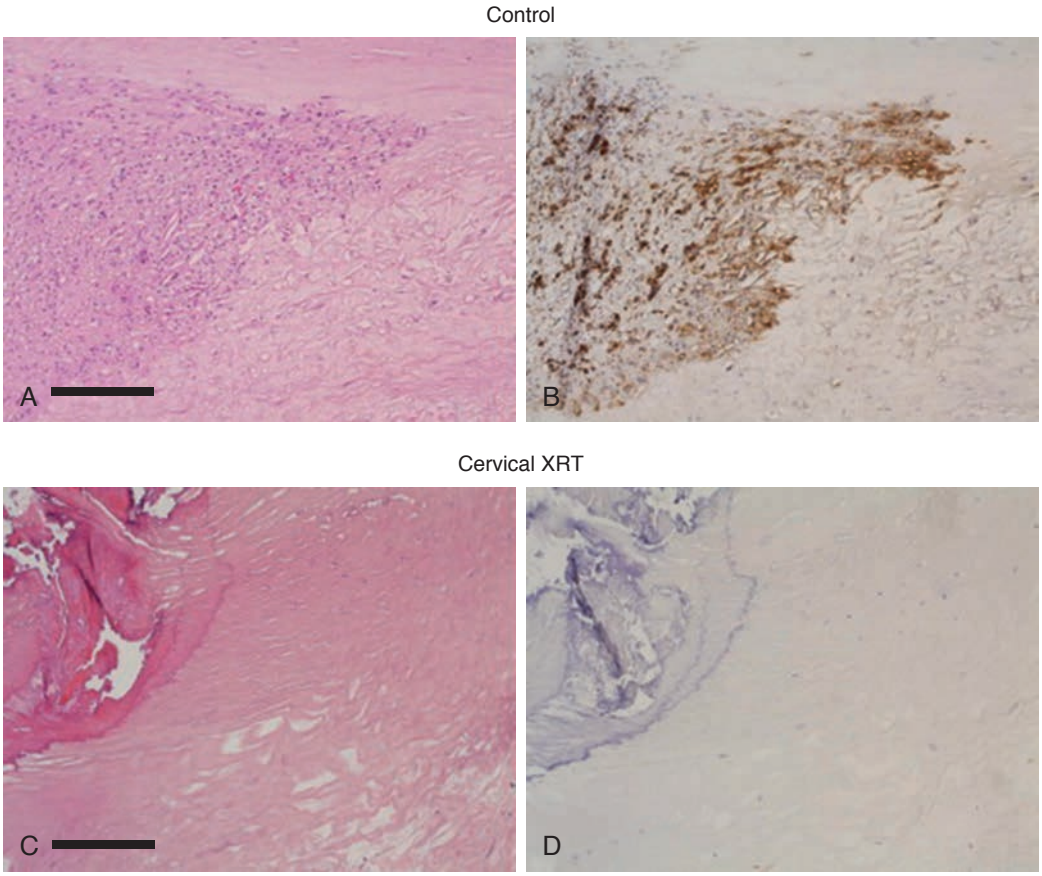

Figure 90.1 Carotid plaque histology of radiated and nonradiated patients' carotid endarterectomy specimens. (A) Hematoxylin and eosin staining showing macrophages *(left)* at the border of an atheroma *(right)*. (B) Immunohistochemical (CD68 immunostain) detection of macrophages *(brown)* in the same plaque as A. (C) Hematoxylin and eosin staining of postradiotherapy plaque. (D) Immunohistochemical (CD68 immunostain) with no macrophages present in the same plaque as C. (Reproduced from Fokkema M, den Hartog AG, van Lammeren GW, et al. Radiation-induced carotid stenotic lesions have a more stable phenotype than de novo atherosclerotic plaques. *Eur J Vasc Endovasc Surg*. 2012;43:646.)

sites, auscultation for carotid bruits, as well as a thorough pulse exam and neurologic exam.

Diagnostic Evaluation

Carotid duplex surveillance (CDS) may be indicated for patients after radiotherapy, but since radiation-induced stenosis rarely develops until 5 to 10 years after treatment, no consensus exists regarding when screening should begin.[35] CDS should be performed for all symptomatic patients. Any patient with a positive CDS should be further studied with MRA, CTA, or catheter-based contrast angiography; this is necessary to fully evaluate the lesion and for preoperative planning. Carotid stenosis following radiation presents in more diffuse and atypical locations than primary atherosclerotic carotid artery disease.[36] One study of patients with greater than 70% carotid artery disease by duplex compared the location of stenosis in 30 patients who had a history of neck radiation with that of 100 patients with typical atherosclerotic disease, and found that those who had undergone prior neck irradiation were significantly more likely to have severe disease in the common carotid artery and the distal internal carotid artery.[37] The unusual location of stenosis in irradiated patients was similarly found by Tallarita,[38] who characterized the location of stenosis in 60 patients undergoing intervention for postradiotherapy carotid stenosis. The common carotid artery was the site of stenosis in 16% of vessels and the distal internal carotid artery was involved diffusely in 38%. On angiography the radiation-induced lesion appears significantly longer than the primary atherosclerotic lesion, with the maximal area of stenosis in the irradiated carotid at the end of the stenotic lesion rather than the center of the lesion, as seen in atherosclerotic disease.[39]

Treatment

General Considerations

The decision to treat with medical, surgical, or endovascular intervention should be individualized. Multispecialty consensus guidelines for the selection of patients for carotid revascularization include recommendations for revascularization of symptomatic patients with greater than 50% stenosis by angiography and asymptomatic patients with greater than 70% stenosis if the periprocedural risk is low. Prior radiation therapy is identified

TABLE 90.1 Anatomic and Physiologic Factors Affecting Perioperative Morbidity With Carotid Intervention

Favors Carotid Endarterectomy	Favors Carotid Artery Stenting	Favors Medical Management
Age >70 years	Prior neck irradiation	Life expectancy <3 years
Severe aortic arch calcification	Prior radical neck dissection or laryngectomy	Asymptomatic patient with one of the following:
Type III arch	Patent tracheostomy	CHF with EF <30%
Carotid artery tortuosity	Prior carotid endarterectomy	Severe uncorrectable CAD
Circumferential heavy plaque calcification	History of cranial nerve injury	Oxygen-dependent COPD
Ulcerated/soft plaque on duplex	Proximal common carotid artery stenosis below clavicle	
Near-occlusive lesion	Distal internal carotid artery stenosis above C2	
Extensive (>15 mm) plaque	Symptomatic carotid stenosis with one of the following:	
	CHF with EF <30%	
	Severe uncorrectable CAD	
	Oxygen-dependent COPD	

CAD, Coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *EF*, ejection fraction.

as a high surgical risk category for which CAS may be preferred over surgical revascularization.[40] In asymptomatic patients, the more stable morphology of postradiation stenosis makes it appropriate to manage these patients medically and monitor the degree of stenosis for longer than recommended for the primary atherosclerotic plaque. Intervention should be delayed until at least 80% stenosis is demonstrated in the asymptomatic patient and should be planned only if periprocedural risk is low. Medical comorbidities, level of disability, life expectancy, physical exam, arch anatomy, and technical expertise of the practitioner should be considered (Table 90.1).

Carotid Stenting (See Chapter 92)

Carotid stenting is preferred for most symptomatic patients since it eliminates the risk of cranial nerve injury associated with dissection in the irradiated field. For patients with calcified type III arches (arch vessels arise proximal to the lesser curvature of the aortic arch) and near-occlusive or ulcerated plaque morphology, the risk of stroke from carotid stenting may outweigh the added risk of cranial nerve injury in the postradiotherapy CEA.

Carotid Endarterectomy (See Chapter 91)

CEA may also be preferred in young patients with minimal comorbidities even if they are anatomically appropriate candidates for CAS due to the higher rate of restenosis after carotid stent placement. In older patients or those with multiple comorbidities, CEA after radiotherapy should be reserved for those patients with anatomic factors that preclude stent placement.

Medical Management

No specific studies of the effect of atherosclerotic risk-factor modification on stroke risk in the postradiotherapy plaque have been performed; therefore, no specific recommendations for medical management of radiation-induced carotid injury exist. Antihypertensive treatment, smoking cessation interventions, statin medication (goal LDL 100 mg/dL), and glucose control (through diet, exercise, and glucose-lowering medications) are components of best medical management of carotid atherosclerosis and should be utilized for risk-factor modification in the postradiotherapy patient as well.[40]

Open Surgical Approach

Given the difficulty of dissection and thus potential prolonged operating time, general anesthesia is preferred. The groin should be prepped for possible greater saphenous vein harvest in any patient with a tracheostomy or previous extensive neck dissection. A longitudinal neck incision may be beneficial rather than a transverse incision, particularly when a prior ipsilateral neck dissection incision is present or when the lesion is diffuse or extends into the distal internal carotid, so that the incision may be lengthened to provide additional exposure (Fig. 90.2). The surgeon should anticipate a more tedious dissection, as normal tissue planes may be obliterated from prior neck dissection and/or radiation injury. Identification and preservation of the hypoglossal, vagus, and superior laryngeal nerves are essential. Careful attention to avoid injury to the marginal mandibular and glossopharyngeal nerves is of increased concern during high dissections of the internal carotid artery. Given the atypical lesions found in postradiation therapy patients, conventional is preferred to eversion endarterectomy, and may be more challenging than removing primary atherosclerotic plaque due to radiation-induced fibrosis that obliterates the endarterectomy plane. In most cases reconstruction (Fig. 90.3) is performed with patch angioplasty. An interposition graft with saphenous vein or prosthetic conduit may be necessary if the endarterectomy results in a vessel wall so attenuated that segmental resection is required or if the severity of radiation arteritis makes endarterectomy impossible.[41] In the setting of a patent tracheostomy, an autogenous vein patch or conduit is preferred to decrease subsequent risk of infection. Subclavian-to-carotid bypass grafting is an alternative approach if there is extensive involvement of

the common carotid artery.[42] If there has been previous extensive dissection leaving little soft tissue for coverage, a myocutaneous flap should be used to provide adequate closure (Fig. 90.4).[43] An elliptical skin and soft tissue flap is created in the ipsilateral inframammary region and the attachments of the pectoralis major are divided from the anterior chest wall, sternum, and clavicle so that the muscle can be rotated 180 degrees on its thoracoacromial pedicle. The myocutaneous flap is then advanced through the subcutaneous tunnel into the incision in the neck.[38]

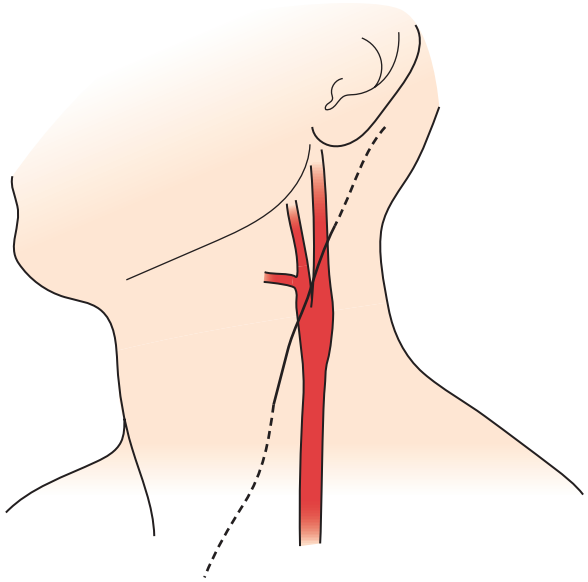

Figure 90.2 Typical carotid endarterectomy incision overlying carotid bulb *(solid line)*. Proximal and distal extension of incision for exposure of extensive plaque *(dashed line)*.

Endovascular Approach

The procedural steps are identical to those of primary atherosclerotic disease. The extensive nature of disease involvement may present a larger surface area for embolization. Evaluation of the embolic material captured in embolic protection filters demonstrates that filters from postradiotherapy patients have more numerous large particles per filter and larger mean particle size.[44] Long-segment angioplasty and the placement of additional stents may be necessary to attain procedural success but may also predispose to intimal hyperplasia and early recurrence.[45] A completion carotid and cerebral angiography should be performed after retrieval of the embolic protection device. Patients should be monitored postoperatively with neurologic assessment for 24 to 48 hours.

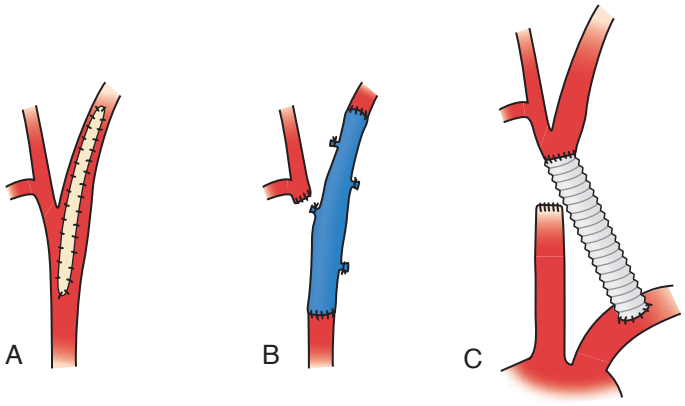

Figure 90.3 Reconstructive techniques for radiation-induced carotid stenosis. (A) Patch angioplasty. (B) Common carotid to internal carotid artery bypass with saphenous vein graft. (C) Subclavian to carotid artery bypass.

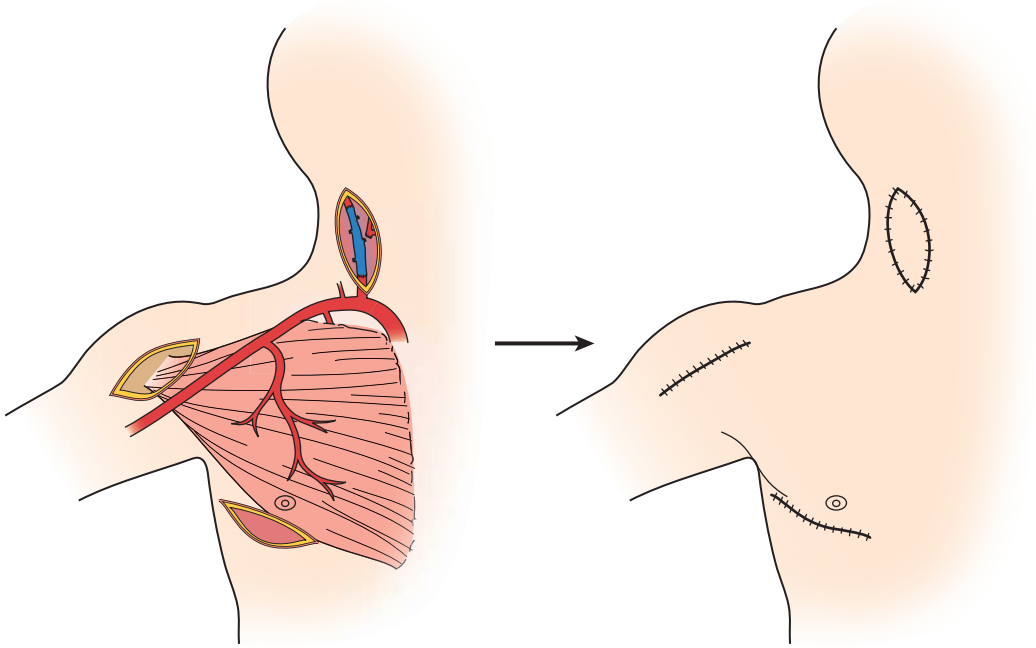

Figure 90.4 Pectoralis major myocutaneous flap.

Results

The outcomes after surgical revascularization and stent placement for carotid stenosis in postradiotherapy patients have been reported in a number of small studies over the last few decades.[38,41-60] These results are summarized in Table 90.2. A recent meta-analysis of these studies demonstrates that for patients undergoing surgical revascularization or stent placement, there was no significant difference in 30-day mortality or combined stroke and death rate. For symptomatic patients, the 30-day mortality rate was 2.6% and the combined stroke or death rate was 2.7% in the surgical group compared with carotid stenting, which was associated with a 5.1% mortality rate and 5.1% stroke and death rate at 30 days. For asymptomatic patients, the 30-day mortality rate was 0% and combined stroke and death rate was 1.1% after surgical revascularization and 1.4% and 2.3% after stent placement, respectively. The rate of permanent nerve palsy in the surgical revascularization group was low (0.6%). Restenosis of postradiotherapy carotid stenosis was more common after carotid stent placement (18%) than after surgical revascularization (10%).[61] Although 30-day outcomes of carotid stent placement for postradiotherapy stenosis are similar to those for atherosclerotic disease,[59] long-term patency rates of carotid stent placement in the irradiated neck are significantly lower than those for primary atherosclerotic disease.[53,62] A history of head and neck cancer as the indication for stent placement has been found to be an independent risk factor for in-stent restenosis after carotid angioplasty and stenting.[52]

Follow-Up

After CEA or CAS in the postradiotherapy patient, postoperative monitoring for the first 24 to 48 hours should include an initial inpatient neurologic exam. Following CEA, patients should be maintained on antiplatelet medication indefinitely. After CAS, dual-antiplatelet therapy should be continued for 6 weeks after the procedure followed by aspirin daily for life. Follow-up after CEA or CAS with physical examination and duplex is performed every 6 months during the first year and annually thereafter.

RECURRENT CAROTID STENOSIS

Epidemiology

Rates of restenosis range from 3% to 12% for CEA and 2% to 31% for CAS in these studies over 2 to 5 years, and they favor CEA (Table 90.3).[63-68] For patients with high-grade carotid restenosis (≥70% by duplex) the 5-year cumulative risk of cerebrovascular events including transient ischemic attack and stroke is 23%, with most events occurring within the first year.[65] A number of predictors of restenosis have been identified, including patient age, female gender, history of head and neck cancer, diabetes, history of smoking, dyslipidemia, residual stenosis after stent placement, and larger number of stents deployed.[52,65,67-69] Restenosis is five times more common after CEA with primary closure than if a patch is used (see Chapter 91).[70,71] No differences have been found for rates of in-stent restenosis after CAS between different carotid stents or embolic protection devices.[72]

Pathogenesis

Early restenosis after CEA or CAS can be attributed to intimal hyperplasia, whereas late stenosis represents recurrence of atherosclerotic disease. Histologic examination of restenotic plaques has demonstrated that early restenotic plaques (<5 years postendarterectomy) contain less calcification, more luminal thrombus, and a smaller lipid core compared with primary atherosclerotic plaques. The late recurrent stenotic plaques (>5 years) demonstrate marked macrophage infiltration, calcification, and a larger lipid core, making these lesions histologically indistinguishable from primary atherosclerosis.[73] The extent of inflammatory response has been associated with early restenosis after stent placement, with a postinterventional rise in leukocyte count and C-reactive protein associated with early restenosis (see Chapter 92).[74,75]

Clinical Findings

History and Physical

Pertinent history—including symptoms of cerebrovascular events, atherosclerotic risk factors, and medical comorbidities that pertain to surgical risk, including a history of cranial nerve injuries—should be elicited. The physical examination should include evaluation of the head and neck as well as vascular and neurologic examinations.

Diagnostic Evaluation

Duplex ultrasound should be performed every 6 months for patients with stenosis of 50% or more on postoperative duplex. The intimal hyperplasia observed in early restenosis appears homogeneous and echolucent on duplex, whereas the late atherosclerotic recurrences demonstrate heterogeneity with marked luminal irregularity.[76] Duplex criteria developed for grading primary atherosclerosis can be used for measuring restenosis, with similar sensitivity and specificity. However, a number of studies have suggested that velocity criteria developed for the native carotid artery may overestimate the degree of in-stent restenosis after CAS,[77-79] but no consensus criteria exist for the interpretation of carotid duplex for stents. Proposed criteria are listed in Table 90.4.

Carotid restenosis often involves the distal extent of the endarterectomy[80] or the proximal or distal extent of the stent. Therefore a CTA, MRA, or conventional angiogram should be obtained prior to intervention to determine the extent of the lesion. This will also help with decision making between an open or endovascular approach as well as preoperative planning for either approach.

Treatment

General Considerations

A history of previous CEA has been identified as posing a high surgical risk for which CAS is preferred over surgical

TABLE 90.2 Studies of Surgical Revascularization and Endovascular Stent Placement for Postradiotherapy Carotid Stenosis

Study, Year	Number of Patients	Age, Years Mean/Median (Range)	Years From Radiation to Treatment Mean (Range)	Number of Interventions	Stroke <30 Days	Death <30 Days	Stroke or Death <30 Days	Cranial Nerve Injury	Wound Complications	Hematoma
Surgical Revascularization										
Rockman, 1996[46]	10	67 (45–85)	16 (12–31)	14	1 (7%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)	0 (0%)
Kashyap, 1999[43]	24	62	17	26	0 (0%)	0 (0%)	0 (0%)	6 (23%)	2 (8%)	1 (4%)
Hassen–Khodja, 2000[47]	17	62 (49–77)	10 (3–42)	18	0 (0%)	0 (0%)	0 (0%)	2 (11%)	0 (0%)	1 (6%)
Friedell 2001[41]	10	70 (60–82)	14 (1–44)	11	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cazaban, 2003[48]	25	68	12 (3–32)	34	1 (3%)	1 (3%)	1 (3%)	4 (12%)	0 (0%)	0 (0%)
Leseche, 2003[42]	27	67 (48–84)	10 (3–42)	30	1 (3%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	2 (7%)
Tallarita, 2011[38]	27	67	21	36	1 (3%)	0 (0%)	1 (3%)	6 (17%)	3 (8%)	2 (6%)
Magne, 2012[49]	24	67 (45–82)	12 (1–41)	27	0 (0%)	0 (0%)	0 (0%)	5 (19%)	0 (0%)	NR
Carotid Artery Stenting										
Al-Mubarak, 2000[50]	14	61 (52–79)	13	15	1 (7%)	0 (0%)	1 (7%)	NA	NR	NR
Ting, 2004[45]	16	64	12 (3–25)	18	1 (6%)	0 (0%)	1 (6%)	NA	1 (6%)	NR
Harrod-Kim, 2005[51]	14	65 (52–79)	9 (1–23)	17	1 (7%)	0 (0%)	1 (7%)	NA	0 (0%)	1 (7%)
Skelly, 2006[52]	13	62 (49–87)	NR	17	1 (6%)	0 (0%)	1 (6%)	NA	0 (0%)	0 (0%)
Protack, 2007[53]	23	71	NR	23	2 (9%)	0 (0%)	2 (9%)	NA	0 (0%)	0 (0%)
Favre, 2008[54]	135	67 (43–88)	12	149	2 (1%)	0 (0%)	2 (1%)	NA	NR	4 (3%)
Henry, 2008[55]	14	71	NR	14	0 (0%)	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)
Sadek, 2009[56]	28	72	NR	28	0 (0%)	0 (0%)	0 (0%)	NA	NR	1 (4%)
Dorresteijn, 2010[57]	24	68	13	24	1 (4%)	2 (2%)	1 (4%)	NA	NR	NR
Eskandari, 2010[58]	49	67 (47–81)	NR	49	0 (0%)	0 (0%)	0 (0%)	NA	NR	2 (4%)
White, 2010[59]	119	67	NR	119	5 (4%)	2 (2%)	6 (5%)	NA	NR	NR
Tallarita, 2011[38]	33	67	6	37	2 (5%)	0 (0%)	2 (5%)	NA	0 (0%)	0 (0%)
Huang, 2013[60]	43	61	NR	47	4 (9%)	0 (0%)	4 (9%)	NA	0 (0%)	0 (0%)
Ravin, 2015[44]	43	69	NR	43	0 (0%)	0 (0%)	0 (0%)	NA	NR	3 (7%)

TABLE 90.3 Restenosis Rates Reported by Clinical Trials of Carotid Endarterectomy and Stenting

Trial (Year)	*N*	*N* CEA	*N* CAS	FU Duration	Stenosis	Rate of Stenosis CEA	Rate of Stenosis CAS	Risk Ratio (CI)
SPACE (2008)[63]	1214	601	613	2 years	≥70% by duplex	4.6%	11.1%	$P < .01$
SAPPHIRE (2008)[64]	260	117	143	3 years	≥50% with symptoms or ≥70% asymptomatic by angiogram	5.4%	2.4%	$P = .26$
CAVATAS (2009)[65]	413	213	200	5 years	≥70% by duplex	10.5%	30.7%	$P < .01$
CaRESS (2009)[66]	397	254	143	4 years	>50% with symptoms or ≥75% asymptomatic by duplex	5.9%	14.7%	$P = .01$
EVA-3S (2011)[67]	507	265	242	3 years	≥70% by duplex	2.8%	3.3%	Not significant
CREST (2012)[68]	2191	1105	1086	2 years	≥70% by duplex	6.3%	6.0%	$P = .58$

CAS, Carotid artery stenting; *CEA*, carotid endarterectomy; *CI*, confidence interval.

TABLE 90.4 Proposed Duplex Criteria for In-Stent Carotid Stenosis

Study (Year)	Degree of Stenosis	PSV (cm/s)	EDV (cm/s)	ICA/CCA
AbuRahma (2008)[77]	50%–79%	224–324	—	—
	≥80%	>325	—	—
Lal (2008)[78]	50%–79%	220–339	—	2.7–4.14
	≥80%	≥340	—	≥4.15
Zhou (2008)[79]	>70%	>300	>90	>4

CCA, Common carotid artery; *EDV*, end-diastolic velocity; *ICA*, internal carotid artery; *PSV*, peak systolic velocity.

revascularization. Patients with recurrent carotid stenosis greater than 50% who have cerebrovascular symptoms attributable to the stenosis should be revascularized unless life expectancy is low or the patient has high level of disability at baseline. The threshold for treatment for asymptomatic recurrent stenosis should be higher than for primary atherosclerosis in early lesions due to the characteristics of these plaques, continuing surveillance until the stenosis is greater than 80%,[76] but the decision should be individualized (see Table 90.1).

Carotid Stenting

The main benefit of CAS for treating both asymptomatic and symptomatic patients with recurrent stenosis following CEA or CAS is the ability to avoid a difficult redo dissection that puts the patient at risk for cranial nerve injury. Because these lesions originate from intimal hyperplasia, plaque embolization and perioperative stroke risk are lower than in the case of primary stenting. However, CAS may not be possible in patients with difficult type III arch anatomy, extensive calcifications, ulcerated plaque morphology, or damaged stents.

Redo Carotid Endarterectomy

In young patients with minimal comorbidities, even if, anatomically, they are candidates for carotid stenting, redo CEA may be preferred owing to the higher rate of restenosis after carotid stent placement (see Chapter 92). In older patients with more comorbidities, redo CEA should be reserved for those with anatomic factors precluding stent placement. Conversion to a CEA after CAS is rarely done; in general this is reserved for carotid stenting in patients who have damaged stents requiring removal.

Medical Management

As in primary atherosclerotic disease, antihypertensive treatment, smoking cessation intervention, statin medication, and glucose control should be utilized for risk-factor modification.

Reoperative Surgical Revascularization

General anesthesia is preferred for redo CEA given the possibility of extensive dissection and prolonged operating time. If possible the previous neck incision should be used. The exposure for redo CEA is often more challenging due to the disruption of normal tissue planes with postoperative scarring, which can make identification of anatomic structures, particularly cranial nerves, quite difficult. The vagus and hypoglossal nerves in particular may become adherent to the planes of previous dissection.[81] Retraction injury is most common, but transections must also be avoided. The most common site of recurrence is the endarterectomy site; however, stenosis may be observed at the proximal or distal extent of the previous arteriotomy or at the prior clamp site of the proximal common carotid artery. Intimal hyperplasia in early recurrent stenosis may make separation of the layers of arterial wall impossible, necessitating patch angioplasty without endarterectomy. Venous or prosthetic bypass is indicated for extensive disease in as many as one-third of patients.[82] The raw surface area of the reoperative field makes hemostasis of the wound bed more challenging. The risks of cranial nerve injury, hematoma formation, and wound complications are notably higher than expected for initial CEA.

Endovascular Management of Post-Endarterectomy Stenosis

CAS has been increasingly performed for carotid restenosis since the Centers for Medicare and Medicaid Services approved reimbursement for the procedure in patients with symptomatic restenosis after CEA.[83] The anatomic considerations and procedural steps are the same as in CAS for primary atherosclerotic disease. Anatomic variations such as severe calcifications, pathologic elongations of the carotid arteries, tortuosity or ectasia of the thoracic aorta, and acute angulation or anomalous origin of the left common carotid artery—which create difficult angles for tracking and sheath stabilization prior to stent deployment—may increase the risk of embolic events during CAS.[84] The risk of bradycardia during carotid angioplasty and stent placement is lower for patients who have previously undergone CEA.

Stenting Versus Endarterectomy for Restenosis After Carotid Endarterectomy

Two recent meta-analyses compare repeat CEA to stenting for recurrent carotid stenosis after CEA. The first, by Fokkema et al.,[85] included 13 studies and 1132 patients (CEA $N = 479$, CAS $N = 653$). The baseline characteristics of the two groups differed in that the redo CEA group was significantly younger, more likely to be symptomatic, and more likely to be current or past smokers, whereas the CAS group was significantly more likely to have hypertension and/or renal failure and to be taking antiplatelet therapy. After adjusting for confounders, there were no significant differences in the outcomes of stroke, death, or combined perioperative stroke or death between CEA and CAS (2.7% versus 2.3%, respectively). There were no differences in these outcomes between symptomatic and asymptomatic patients. Cranial nerve injury, bleeding, and wound infections were uncommon in the redo CEA group: 5.5%, 2.7%, and 0.2%, respectively. Technical failures and access-site complications were rare in the CAS group at 1.3% and 1.9%. Restenosis rates were available for 712 patients with a median follow-up of 13 months. The restenosis rate (≥70% stenosis) for redo CEA was 7.7% and for CAS 4%, which was not a statistically significant difference.

The second meta-analysis, by Tu,[86] included 4399 patients from 50 studies (CEA $N = 2292$, CAS $N = 2107$). There were no significant differences in the baseline characteristics or comorbidities between the patients who underwent CEA or CAS for recurrent stenosis after CEA, but the duration of follow-up was significantly longer for the redo CEA group (50 months) compared with that for the CAS group (24 months). There were no significant differences in rates of perioperative stroke between redo CEA and CAS or between treatment modalities within subgroups of symptomatic or asymptomatic patients. Cranial nerve injury was observed in 6% of the redo-CEA group, with more than 80% of the deficits resolved within 3 months. Significant differences were identified in rates of restenosis between redo CEA and CAS at 1 year (1.7% vs. 8.3%), 2 years (2.6% vs. 9.8%), and 5 years (4.4% vs. 13.5%).

Surgical Revascularization for In-Stent Restenosis

CEA with stent removal for in-stent restenosis may be necessary in cases of stent kinking, fracture, or erosion through the vessel wall. Control of the internal carotid artery distal to the stent can be challenging, and inflammation of the periarterial tissue makes identification and protection of nerves more difficult than with a standard CEA.[87,88]

Techniques of surgical exposure are discussed in Chapters 55 and 91. The length of the longitudinal arteriotomy will depend on the length of the implanted stent. The stent should be removed in toto, carefully, to avoid penetration through the thinned arterial wall.[89] The intimal endarterectomy should be continued until the proximal and distal resection planes are free from atherosclerotic debris. The distal internal carotid artery should be carefully inspected where the stent is removed since the artery may be very fragile in this area. Reconstruction may be performed with a venous or prosthetic patch. If the extent of the inflammatory response causes the stent to become adherent to the arterial wall, reconstructive options include internal to external carotid artery transposition, common to internal carotid artery bypass or subclavian to internal carotid artery bypass.[90] Results from 15 patients in a multicenter prospective registry indicate that surgical revascularization for in-stent carotid stenosis is safe and durable, with 1 perioperative stroke (7%), no mortalities, and no recurrent stenosis at 21-month follow-up.[91]

Endovascular Management of In-Stent Restenosis

Endovascular treatment strategies for carotid in-stent restenosis include percutaneous balloon angioplasty alone, cutting balloon angioplasty, and balloon angioplasty with stent placement.[72,92-94] Technical success can be achieved in most cases using these techniques.[72,92-94] Placement of an additional stent to resolve a distal in-stent stenosis may result in a kink or bend in the distal internal carotid artery and elicit a significant hyperplastic response.[95]

Follow-Up

Patients must be followed closely after reintervention since the rate of recurrent restenosis based on available published data is around 14%,[96] with some studies describing rates as high as 50%.[97] Recommendations are physical examination and duplex every 6 months during the first year and annually thereafter.

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CHAPTER 91

Carotid Endarterectomy

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Abstract

Carotid endarterectomy, introduced in the 1950s, has been the most frequently performed open vascular surgical procedure for many years. Several randomized prospective clinical trials have demonstrated the safety and efficacy of this procedure in the prevention of ischemic stroke in symptomatic and properly selected asymptomatic patients with significant carotid stenoses. The excellent perioperative results of this procedure reported in multicenter randomized clinical trials are being matched by the results reported in individual institutional series and in large population-based studies. Numerous studies have confirmed the long-term efficacy of carotid endarterectomy based in terms of stroke prevention and anatomic durability. This chapter outlines evidence to support the role of carotid endarterectomy as the gold standard procedure to treat patients with clinically significant carotid artery disease, the technical details of its performance, and its risks and long-term benefits.

Keywords

Carotid endarterectomy
stroke prevention

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First performed in the 1950s, carotid endarterectomy (CEA) experienced remarkable growth in the 1970s and 1980s after several studies demonstrated that carotid stenosis was an important risk factor for disabling stroke and death,[1-6] and a randomized multicenter trial published in 1969 showed that carotid surgery reduced the incidence of stroke from symptomatic carotid lesions.[7] However, other studies reported high complication rates, thus compromising the potential benefit of CEA.[8] However, randomized controlled trials (RCTs) performed in the 1990s definitively established the safety and efficacy of CEA and its superiority over the best medical management of patients with symptomatic and asymptomatic carotid disease.[9-12]

EPIDEMIOLOGY

Incidence

At least 750,000 strokes occur annually in the United States: approximately 15% are fatal, 15% to 20% are severely disabling, and another 15% to 20% of stroke patients who recover will experience a subsequent disabling stroke. At least 80% of these strokes are ischemic and atherosclerotic disease of the cervical carotid artery is responsible for 20% to 40% of ischemic strokes.[13]

Etiology

Strokes secondary to carotid artery stenosis are a consequence of atheroembolization, thromboembolism, or are secondary to a low flow state through the carotid artery.

INDICATIONS FOR CAROTID ENDARTERECTOMY

Based on the most recent evidence-based guidelines published by the Society for Vascular Surgery, CEA is recommended for most symptomatic patients with a 50% to 99% ICA stenosis. Further, CEA should be considered for patients with a 60% to 99% asymptomatic ICA stenosis if perioperative stroke and death rate is less than 3% and if the patient has at least a 3- to 5-year life expectancy. In the symptomatic patient with a 50% to 99% ICA stenosis, and either medical or anatomic contraindications to CEA, carotid artery stenting (CAS) should be considered (see Chapter 92). Medical therapy, rather than CEA or CAS, should be selected in symptomatic patients with a less than 50% (although there is some recent evidence suggesting that CEA may be indicated for rare symptomatic patients with <50% ICA stenoses [see below]) and for asymptomatic patients with a greater than 60% stenosis and surgical contraindications.[14]

PREOPERATIVE IMAGING

Duplex ultrasound in an accredited laboratory is the most appropriate first test to evaluate the patient with suspected carotid artery disease, with either CTA or MRA reserved for patients with suspected disease proximal or distal to the neck, when there are indeterminate duplex findings, or other confounding issues.[15-21] There is some evidence that CTA underestimates, and MRA overestimates, the degree of stenosis.[19] It is the practice in some centers to proceed to endarterectomy based on duplex findings alone.[14] Since the benefit of CEA is highly dependent on the degree of stenosis, others maintain that verification of duplex findings is essential before proceeding to operation.[22] Clearly, if the patient is found to have an intermediate stenosis and is asymptomatic, one should perform at least another noninvasive test to confirm this finding before recommending CEA. If there is discordance between these studies, one should either obtain a third noninvasive test or proceed to angiography.

PERIOPERATIVE MEDICAL MANAGEMENT

Risk stratification is important in determining the most appropriate preoperative cardiac work-up and perioperative management of the patient undergoing CEA (see Chapter 32). The American Heart Association's (AHA) perioperative guidelines classify CEA as an intermediate risk procedure.[23] The perioperative medical management of the patient undergoing CEA should include blood pressure control, and beta blocker, statin, and antiplatelet therapy.

Beta-Blockers

Based upon early small clinical trials, it was felt that all patients with vascular disease would benefit from perioperative beta-blockade. This recommendation has evolved based on several large trials, especially the pivotal POISE trial.[24] Perioperative

beta blockade, with a goal of achieving a maximum heart rate of 60 to 80 beats per minute, is recommended in the recent Society for Vascular Surgery carotid guidelines.[14]

Antiplatelet Therapy

Meta-analyses of antiplatelet therapy trials published by the UK Antithrombotic Trialist Group in 1994 and 2002 concluded that antiplatelet therapy significantly reduces the incidence of stroke in high-risk patients, with a resultant 25% reduction in strokes overall.[25,26] The majority of these studies included aspirin or aspirin plus another antiplatelet agent. Recent studies of clopidogrel provide evidence that perioperative embolization is decreased without an increase in bleeding complications or transfusion requirements after CEA. Other antiplatelet agents, such as ticlopidine and glycoprotein IIb/IIIa antagonists have not been specifically studied during CEA and generally have a higher risk profile than ASA or clopidogrel. Based on this evidence, it is possible to recommend either ASA or clopidogrel, or both, for use before and after CEA. Based upon the preponderance of evidence, the authors do not withhold aspirin and will continue clopidogrel if there is a clinical indication in the CEA patient.[14]

Heparin

Although the International Stroke Trial did not find any benefit of routine heparin administration for acute stroke because of increased numbers of hemorrhagic stroke and fatal extracranial bleeding,[27] a report from the Oregon Health Sciences University found that urgent crescendo TIAs could be controlled with intravenous heparin, thereby allowing CEA to be delayed in these patients.[28] Unfractionated heparin (UFH) is routinely used intraoperatively to prevent carotid thrombosis despite a lack of level I evidence to support this practice. The combination of aspirin and intraoperative heparin administration appears to be especially effective in preventing thrombosis.[29]

Protamine Administration

Numerous publications have examined whether reversing heparin with protamine during CEA is safe. In the GALA trial (General Anesthesia versus Local Anesthesia for carotid surgery), protamine was not found to be associated with stroke.[30] The preponderance of recent evidence suggests that protamine administration does not increase perioperative stroke risk, although the authors prefer not to use it routinely unless there is truly unusual bleeding.

Dextran

Dextran is a polysaccharide that inhibits platelet aggregation.[31] It has been used to control embolic episodes both preoperatively and postoperatively. British investigators in 1997 showed that a 6-hour dextran infusion effectively controlled postoperative embolic events as measured by transcranial Doppler (TCD), with a 0% stroke and mortality rate in a series of 100 patients.[32] We favor dextran infusion for 24 hours after CEA to control platelet aggregation on the endarterectomy site and potential microembolization.

Statins

The potential benefits of statins in patients with carotid artery disease are several-fold. A reduction in cholesterol levels with statins may be associated with plaque regression (see Chapter 29).[33-41] The Asymptomatic Carotid Artery Progression Study (ASAPS) demonstrated that lovastatin was associated with reduced carotid artery intima-media thickness and also a lower rate of combined cardiovascular events, although not the stroke rate.[42,43]

Numerous trials conducted over the past decade have demonstrated statin medications to be highly effective in primary and secondary stroke prevention.[44-48] Furthermore, it appears that the stroke prevention benefits of statins are related to the pleiotropic effects of statin medications rather than their cholesterol-lowering effects. In addition, several studies have demonstrated that statins are associated with a reduced rate of perioperative cardiac morbidity and overall mortality in patients undergoing major vascular surgical procedures.[49-52]

In a series of 1566 patients undergoing CEA at our Institution, statins were associated with a reduced 30-day incidence of stroke (1.2% vs. 4.5%, $P = .002$), TIA (1.5% vs. 3.6%, $P = .01$), and mortality (0.3% vs. 2.1%, $P = .002$).[53] A large administrative database analysis from Canada documented a significantly lower rate of perioperative stroke and death in symptomatic patients who were taking statin medications at the time of CEA.[54] Furthermore, LaMuraglia and coworkers reported that lipid-lowering agents were associated with significant protection against recurrent carotid stenosis or late anatomic failure after CEA.[55] The evidence seems clear that all patients undergoing CEA should be taking statin medications at the time of surgery and long-term.

OPERATIVE TECHNIQUE

Anesthesia

CEA may be performed under GA regional anesthesia (RA) with deep or superficial cervical block, and even under pure LA, with comparable lengths of stay. The majority of studies comparing the two techniques have reported improved perioperative cardiac stability with RA, but this does not necessarily result in a reduced incidence of myocardial infarction (MI).[56,57]

Disadvantages of RA include patient discomfort or anxiety, risk of seizure or allergic reaction, anxiety for the operating surgeon, and compromise of technique in a teaching setting. The main benefit of LA is that it facilitates efficient selective shunting if that is the surgeon's preference (see below).

Patient Positioning

A roll is placed behind the scapulae used in conjunction with a padded ring under the head to achieve some hyperextension of the neck without being overextended. If LA or RA is used,

a Mayo stand is placed over the patient's head to suspend the surgical drapes away from the patient's face to prevent sensations of claustrophobia. The patient is placed in the flexed position with the table rotated to expose the side of the neck to be operated on.

Skin Incision

One of two skin incisions may be used (Fig. 91.1). The standard incision is a longitudinal incision parallel to the medial border of the sternocleidomastoid muscle. The upper portion of the incision is angled posterior to the earlobe if cephalic exposure above the angle of the jaw is required. An alternative method is to place the incision in an appropriately located skin crease, usually 1 to 2 cm inferior to the angle of the jaw. If the incision is made too low, more cephalic exposure can be obtained by extending the skin crease incision posteriorly. If the incision is made too high, more caudal exposure can be obtained by extending the incision more anteriorly.

Carotid Exposure (see Chapter 55)

Manipulation of the carotid artery should be minimized because intraoperative embolization can result from careless handling. The external jugular vein lies deep to the platysma and is more commonly encountered with an oblique skin crease incision. The other structure located at this level is the greater auricular nerve; injury to this nerve leads to numbness of the earlobe. The carotid sheath is entered and the facial vein is identified crossing medially in the base of the wound and divided; sometimes it has an early bifurcation or trifurcation, and multiple branches need to be ligated. The jugular vein is then retracted laterally. The vagus nerve is identified at this point in the carotid sheath, usually located posteriorly between the jugular vein and carotid artery, although in a minority of patients it may lie anteriorly. The CCA is controlled circumferentially with an umbilical tape and a Rummel tourniquet. The ansa cervicalis nerve should be identified; it usually lies medial to the distal CCA and identifying this nerve facilitates safe dissection of the carotid bifurcation and avoids injury to the hypoglossal nerve, which crosses medially from a superior to an inferior location. The dissection should be continued along the posterior edge of this nerve. If one dissects along the anterior border of the ansa, it is possible to inadvertently transect the hypoglossal nerve in the crotch of the junction of these two nerves before the hypoglossal nerve is identified (Fig. 91.2).

The superior thyroid artery originating from the medial border of the carotid bifurcation or proximal ECA is controlled with a tie or plastic vessel loop. The ECA is controlled with a vessel loop. Finally, the ICA is exposed coming off the lateral side of the bifurcation and should be controlled distal to the plaque. In this location the artery has a typical bluish appearance because of translucency of the vessel. During dissection of the carotid bifurcation and its branches, one should avoid dissecting in the crotch of the carotid bifurcation to avoid injuring the carotid body to minimize hemodynamic instability and troublesome bleeding. If hemodynamic instability results, the carotid body can be gently injected with 1% lidocaine.

Before clamping, the patient is administered 70 to 100 U/kg of heparin, which is allowed to circulate for 3 minutes. The ICA is clamped first to prevent the embolization that can result when the CCA or ECA is clamped. Care should be taken to make sure that the ICA is clamped on a normal portion of the artery distal to the plaque.

If LA or intraoperative electroencephalography is used for selective shunting, a test clamp on the distal ICA should be applied for at least 3 minutes to check for changes in the neurologic examination or electroencephalographic (EEG) pattern. If such changes occur, the artery should be unclamped to allow reperfusion before reclamping and opening the carotid bifurcation; opening the bifurcation and placing a shunt may take 2 to 3 minutes and should not be performed while the brain is already ischemic. However, unclamping the ICA introduces the potential for embolization from disrupted plaque.

Figure 91.1 Longitudinal and transverse skin incisions for carotid endarterectomy.

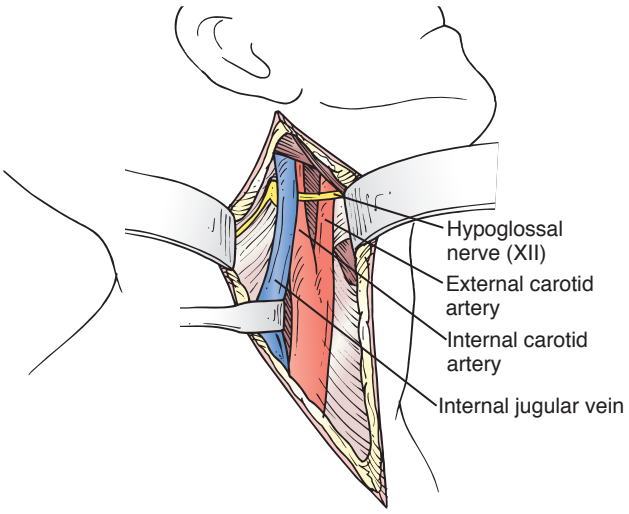

Figure 91.2 Operative field. Note the internal jugular vein mobilized posteriorly after ligation of the anterior facial branch and the hypoglossal nerve crossing the vessels superior to the bifurcation.

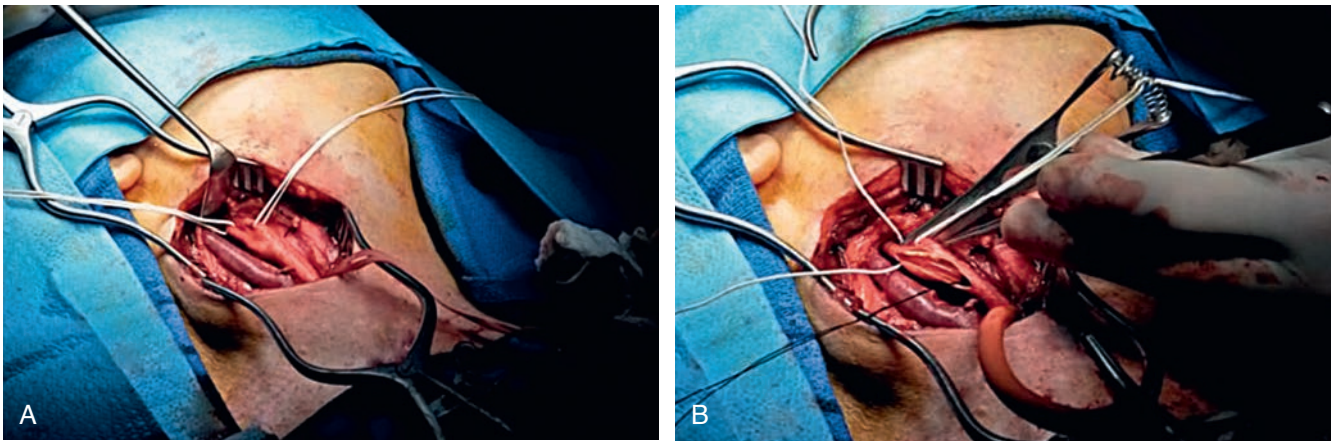

Figure 91.3 (A) Initial operative exposure with the Rumel tourniquet around the common carotid artery and the internal and external carotid arteries isolated with vessel loops. (B) The arteriotomy has been made and the shunt, with a silk suture attached, lies within the vessel.

If carotid stump pressure is to be measured, clamps are placed on the CCA and the ECA, and a needle connected to a pressure line is placed into the distal CCA below the carotid bifurcation. Both clamping the CCA and placing the needle into the artery introduce the potential for embolization.

Conventional Endarterectomy

The conventional technique for CEA consists of a vertical arteriotomy and closure usually by patch angioplasty. One should avoid making the incision too close to the flow divider at the ECA origin because this can distort the anatomy and make the closure more difficult (Fig. 91.3).

The endarterectomy is begun in the CCA in the plane between the media and the adventitia. The proximal endpoint in the distal CCA is established and the plaque is trimmed in that location in a beveled manner. The endarterectomy is continued into the orifice of the ECA, first with a Freer elevator and then with a fine clamp that is passed up into the ECA in the plane of the endarterectomy and spread to further mobilize the plaque away from the adventitia in the 6-, 9-, and 12-o'clock positions; it is usually hard to pass the clamp in this plane at the 3-o'clock position next to the flow divider. The vessel loop on the ECA is released transiently while the plaque is everted from within the ECA. The endpoint of the plaque is inspected; an ideal endpoint is gradually tapering and feathered (Fig. 91.4). In our practice, all loose bits of intima and media in the orifice of the ECA are removed to perform complete endarterectomy of the ECA, although others believe that endarterectomy of the ECA may be neglected without compromising results.[58]

A technically perfect endpoint in the ICA is critical. Occasionally special maneuvers may be required to expose the distal ICA to extent the arteriotomy to achieve an acceptable endpoint, as seen in Fig. 91.4. Tacking sutures at the distal endpoint should be avoided unless absolutely necessary; such suturing is problematic and associated with an increased perioperative stroke rate.[59] The endarterectomy is best ended by pulling the plaque transversely away from the artery with lateral traction. One should avoid pulling out or down on the plaque, which is more likely to result in a step-off that can be difficult to correct.

Figure 91.4 Carotid endarterectomy specimen. Note the smooth endpoints of the distal plaque from the external and internal (longer portion) arteries.

We believe that repairing the arteriotomy with a patch angioplasty represents the standard of care in contemporary practice (Fig. 91.5). A variety of patch materials are available, including autologous vein, polytetrafluoroethylene (PTFE), woven polyester (Dacron), and bovine pericardium, and no material appears to be clearly superior to another.

When the suture line is nearly completed, the CCA and ICA clamps are briefly sequentially released to flush air or debris (or both) out of the arteries. The carotid bifurcation is flushed vigorously with heparinized saline and inspected again for debris or intimal flaps before the arteriotomy is finally closed. Once again the clamp on the ICA is briefly released to fill the bifurcation with blood. It is then replaced while the clamps on the CCA and ECA are released so that any remaining air or debris will be flushed up the territory of the ECA rather than the ICA. At this point the ICA clamp is removed.

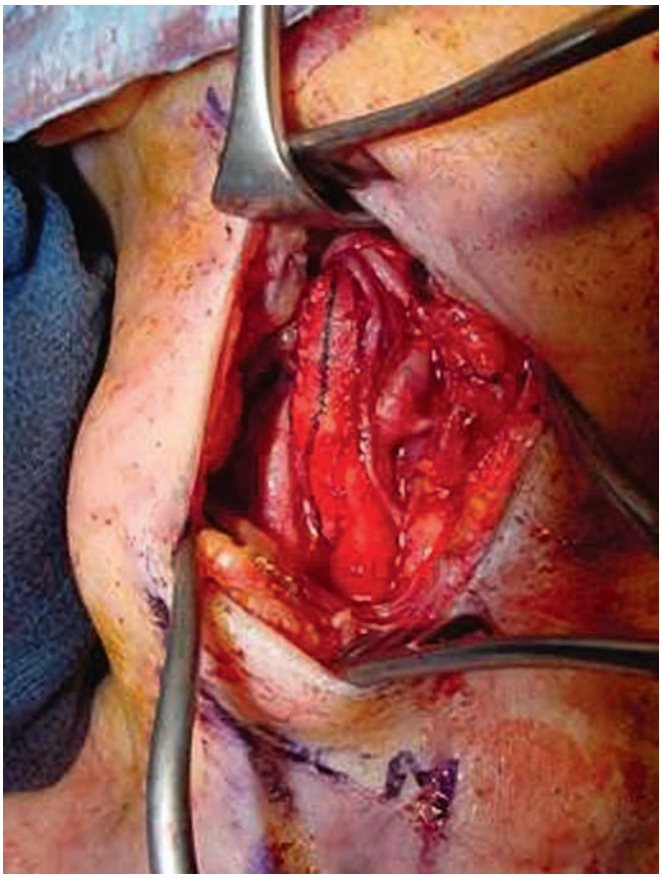

Figure 91.5 Patch closure of the arteriotomy for carotid endarterectomy. Dacron was used in this case. Note the ansa cervicalis coursing along the vessel, the vagus nerve posteriorly, and the hypoglossal nerve at the apex of the incision.

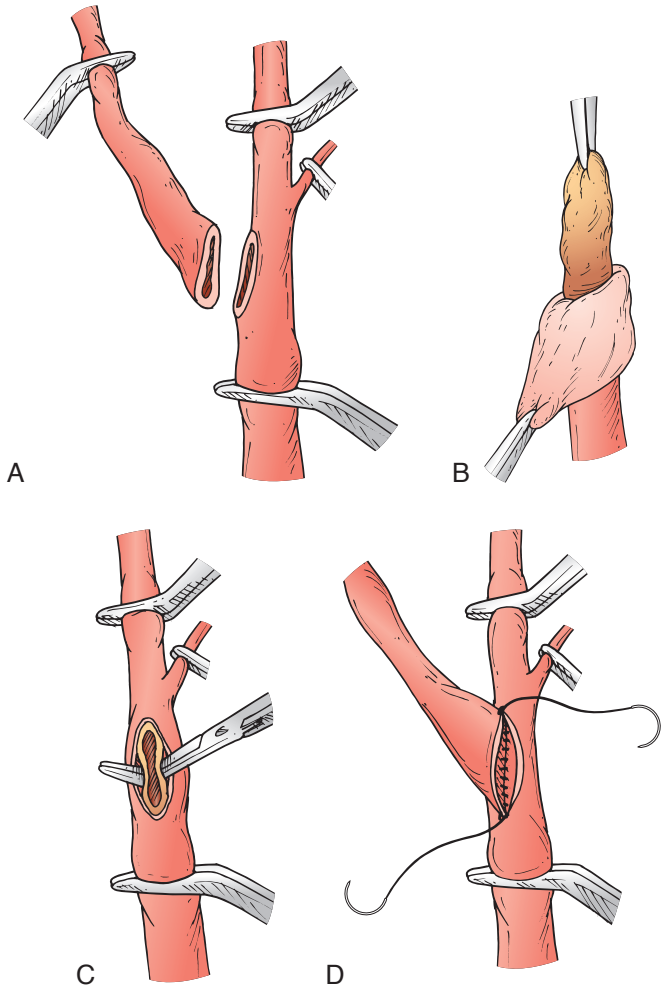

Figure 91.6 Eversion endarterectomy. (A) Internal carotid artery transected from the bifurcation. (B) Adventitia teased back off the internal carotid artery plaque. (C) Plaque endarterectomized from the common carotid and origin of the external carotid artery. (D) Reanastomosis of the internal carotid artery to the bifurcation. (Modified from Saratzis N, Saratzis A, Milaras S, et al. Eversion carotid endarterectomy illustrated: tips and tricks of the procedure. *Surg Rounds.* 2006;29(8):382-389. http://www.hcplive.com/general/publications/surgical-rounds/2006/2006-08)

Any bleeding from the suture line is addressed at this time. One should avoid re-clamping unless absolutely necessary to control bleeding at this stage and avoid the risk for formation of thrombus or a fibrin-platelet aggregate on the patch or endarterectomized vessel.

Eversion Endarterectomy

DeBakey originally described eversion endarterectomy with partial transection of the anterior portion of the carotid bifurcation.[2] Etheredge revised DeBakey's technique with complete transection of the bifurcation,[60] which allowed the origins of both the ICA and ECA to be everted for a longer distance. The endarterectomy is performed by mobilizing the entire circumference of the carotid adventitia off the plaque (described as a "circumcision" by Etheredge) and then everting the adventitia and mobilizing it upward while gentle caudad traction is applied to the plaque. This maneuver is performed distally into the orifices of the ICA and ECA and then proximally into the CCA. Once the endarterectomy is complete, the divided bifurcation is reunited with a simple end-to-end anastomosis.

Kieney and coworkers introduced a modification of eversion endarterectomy in 1985 in which the origin of the ICA is excised obliquely off the carotid bifurcation, and is inverted on its own, and endarterectomy of the CCA and ECA is performed through an arteriotomy in the side of the carotid bifurcation.[61] The ICA is reanastomosed to the carotid bifurcation primarily (Fig. 91.6).

Advantages of the eversion technique are that the anastomosis can be performed rapidly and it is not prone to restenosis, and therefore patching is not required. Disadvantages of this technique are that more extensive dissection is sometimes necessary to mobilize the vessels during the eversion; the procedure does not lend itself readily to shunting (although shunting is not precluded by this technique), and it can be difficult to visualize the endpoint in the ICA after the plaque has been removed. Therefore, in our opinion, a completion study should be performed with this technique, which is particularly effective for dealing with a redundant, coiled, or kinked ICA as the ICA can be pulled down and straightened and the redundant portion excised. The remaining portion of

the ICA is spatulated and reattached to the arteriotomy on the carotid bifurcation.

Comparison of Conventional and Eversion Carotid Endarterectomy

In EVEREST (EVERsion CEA vs. Standard Trial study), a randomized, prospective multicenter study including more than 1400 patients randomized to eversion or standard CEA, there were no statistically significant differences in outcomes between the two techniques, although a slightly higher incidence of perioperative complications was noted with eversion CEA and a slightly higher incidence of restenosis with standard CEA. While other studies have shown better outcomes with eversion CEA,[62,63] a large meta-analysis comparing eversion to conventional CEA found no significant differences in the rate of perioperative stroke or death (1.7% vs. 2.6%, odds ratio [OR] 0.44; 95% confidence interval [CI], 0.10-1.82), but did note that eversion endarterectomy was associated with a lower rate of restenosis during follow-up (2.5% vs. 5.2%, OR 0.48; 95% CI, 0.32-0.72).[64]

EXPOSURE FOR HIGH LESIONS

The carotid bifurcation can be located anywhere between the second and seventh cervical vertebrae, and a bifurcation located high in the neck poses technical challenges that can increase perioperative risk for stroke and cranial nerve injury. Ideally, one will recognize a high bifurcation on the preoperative imaging study. This is a potential advantage of CTA, in which bony anatomy is always included in the images. A conscious effort must be made to locate the bony anatomy with DSA if unsubtracted images are not provided with the study, but the anatomy can still be defined from subtracted images. Bony landmarks are never provided with carotid duplex imaging, but an astute vascular technologist will note a high bifurcation and should record it in the report.

Nasotracheal Intubation

The initial approach is to utilize nasotracheal intubation. With the patient's mouth closed, the vertical ramus of the mandible is displaced anteriorly 1 to 2 cm relative to its position when the mouth is open with an oral endotracheal tube. The additional few millimeters of exposure afforded by this maneuver will often be the difference in achieving a suitable endarterectomy endpoint in the distal ICA.

Division of the Digastric Muscle

The next step to enhance distal exposure is to divide the posterior belly of the digastric muscle. The hypoglossal nerve should be carefully identified and protected before the muscle is divided. Two other nerves that can be injured high in the neck are the spinal accessory nerve, which enters the tendinous portion of the sternocleidomastoid muscle usually in the upper third of the muscle, and the glossopharyngeal nerve, which lies deep to the digastric muscle.

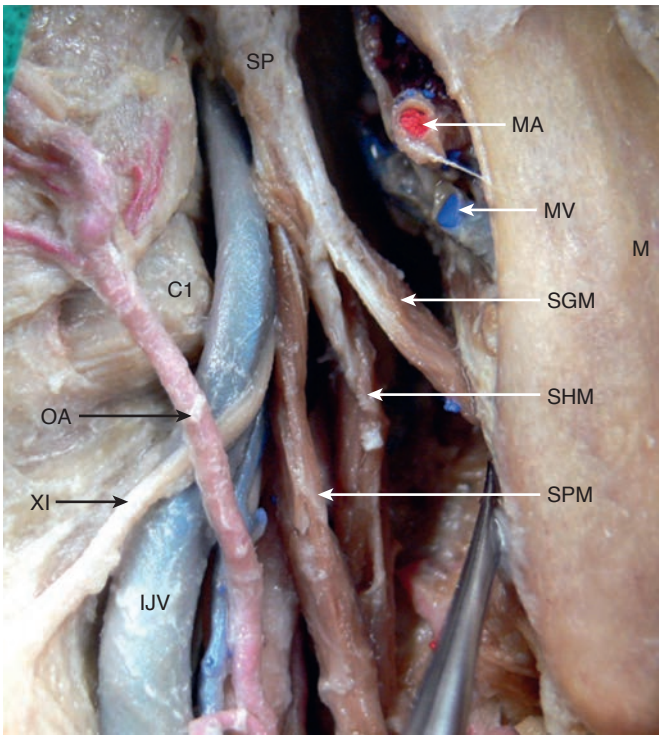

Figure 91.7 Anatomic relationships of the styloid process. *C1*, Transverse process of C1; *IJV*, internal jugular vein; *M*, mandible; *MA*, maxillary artery; *MV*, maxillary vein; *OA*, occipital artery; *SGM*, styloglossus muscle; *SHM*, stylohyoid muscle; *SP*, styloid process; *SPM*, stylopharyngeus muscle; *XI*, spinal accessory nerve. (Modified from Izci Y, Moftakhar R, Pyle M, et al. Retromandibular fossa approach to the high cervical internal carotid artery: an anatomic study. *Neurosurgery.* 2008; 62[5 Suppl 2]:ONS363-ONS369.)

Resection of the Styloid Process

The final maneuver that can be extremely effective in gaining cephalic exposure is resection of the styloid process (Fig. 91.7). After the posterior belly of the digastric muscle is divided, the insertions of the styloid apparatus: styloglossus, stylopharyngeus, and stylohyoid muscles on the styloid process are excised with a scalpel. The stylohyoid muscle can be found posterosuperior to the ECA and inserts into the posterior portion of the styloid process.[65] In addition, the occipital artery runs along the inferior border of the posterior belly of the digastric muscle. Identification and division of the occipital artery can prevent bleeding secondary to trauma caused by retraction (see Fig. 91.7). The styloid process is carefully resected with a rongeur.[66] This can extend the exposure of the ICA by an additional 4 to 5 mm. However, damage to the underlying facial nerve is a potential complication of styloidectomy.[67]

Anterior Subluxation of the Mandible

Two other options can be used to improve exposure of a high bifurcation, and both require preoperative planning and coordination with an oral or plastic surgeon (Fig. 91.8). These patients should all be nasotrachealy intubated. Anterior subluxation of the mandible was described for use in high carotid exposures in 1984. The authors describe their technique for subluxation

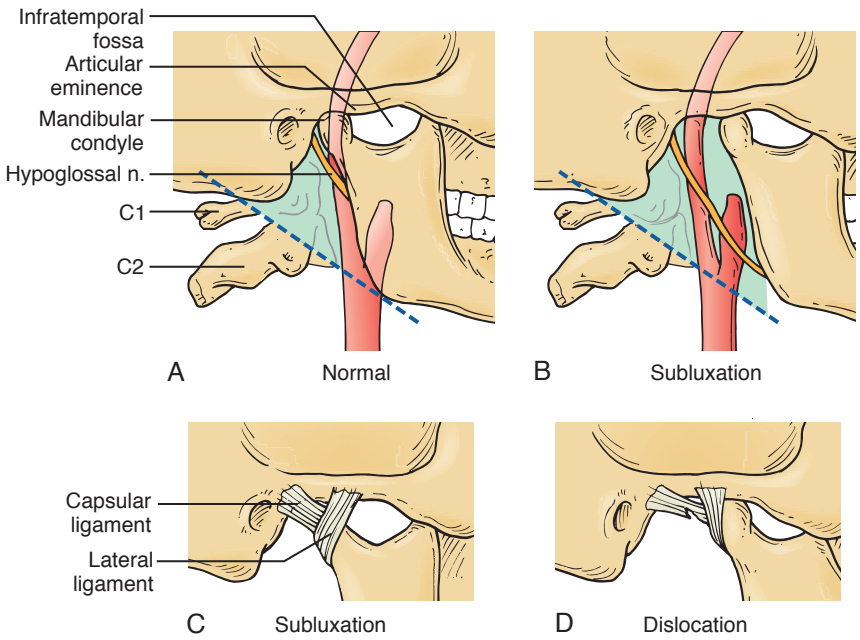

Figure 91.8 Mandibular subluxation/dislocation. (A) Normal bony anatomy with high carotid bifurcation. (B) The mandibular condyle is pulled forward onto the articular eminence, providing additional exposure when the subluxed mandible is fixed in place at this position. (C) Illustrates the desired position of the temporomandibular ligaments during subluxation. (D) Illustrates the potential undesired position of the temporomandibular ligaments from dislocation, which may cause a tear in the capsular ligament. (Modified from Simonian GT, Pappas PJ, Padberg FT, et al. Mandibular subluxation for distal internal carotid exposure: technical considerations. *J Vasc Surg.* 1999; 30:1116-1120. [ref. xvii].)

as an evolution from full mouth arch bars with circumdentate wiring to unilateral subluxation by circummandibular/transnasal wiring.[68] For patients with healthy dentition, anterior subluxation of the mandible can be accomplished by placing circumdental wires around the mandibular cuspid and bicuspid teeth on the side ipsilateral to the vascular lesion. Corresponding wires should be placed around the corresponding contralateral maxillary teeth. The mandible is then subluxed anteriorly and the wires are twisted together to hold the fixation. Patients with poor dentition can have arch bars placed prior to wiring to facilitate the placement of the wires.[69] An even more aggressive approach involves the use of a complete vertical osteotomy through the vertical ramus of the mandible and separation of the mandible to expose the ICA.

CEREBRAL PROTECTION AND MONITORING

Shunting

CEA may be performed with the routine nonuse of shunts,[70-72] routine shunting,[73-76] or selective shunting. Under GA, selective shunting may be determined by intraoperative measurement of carotid "stump pressure," intraoperative monitoring of the EEG or somatosensory evoked potentials (SSEP), measurement of MCA flow by TCD, and monitoring with cerebral oximetry. An alternative method is to perform CEA under RA, with shunt insertion if symptoms develop after the carotid artery is clamped. These adjuncts are designed to detect intraoperative cerebral ischemia, whereas TCD has the added advantage of detecting intraoperative emboli. Two commonly used shunts are the Pruitt-Inahara and Javid shunts. In a randomized trial the Pruitt shunt was less likely to maintain physiologic flow in the MCA, whereas the Javid shunt was associated with a higher incidence of cerebral embolism at declamping.[77]

Placing a shunt has the capacity only to prevent ischemic stroke, but it could actually increase the risk for embolic stroke if performed poorly. Intraoperative cerebral ischemia is a relatively uncommon cause of intraoperative stroke.[78-80] This would support the argument of the routine nonshunters who believe that cerebral ischemia is a rare cause of stroke and that shunting may do more harm than good (by causing embolic complications) so that even selective shunting is never justified. However, it is clear that cerebral ischemia can lead to perioperative stroke[81-83] and can be completely relieved by placement of a shunt. This should translate into the prevention of stroke in these patients if embolic complications related to shunt placement are minimized. In fact, there is evidence that the benefits of shunting outweigh the risks in these patients.[84-86]

A recent meta-analysis by AbuRahma, et al., including papers published from 1990 to 2010, found that the mean perioperative stroke rate for CEA with routine shunting was 1.4% and for routine nonshunting was 2%. For selective shunting, the stroke rate varied depending upon the method used for intraoperative monitoring. It ranged from 1.1% for cervical block anesthesia, 1.6% for EEG and carotid stump pressure, to 4.8% using TCD. The authors concluded that both routine and selective shunting are acceptable and should be employed at the surgeon's discretion.[87]

Stump Pressure

Measurement of carotid stump pressure was the first method used to predict intraoperative ischemia.[88] In patients with measured stump pressures lower than 50 mm Hg, Hays and colleagues noted a 50% neurologic event rate in those who were not shunted versus a 10% rate in those who were in a

series of 297 patients.[89] Kelly and coworkers measured stump pressure with concurrent EEG monitoring in 289 patients[90] and performed shunting only in those with evidence of ischemia by EEG criteria. They found that 6% of patients with stump pressure higher than 50 mm Hg had ischemia by EEG criteria. Stump pressure correlated well with EEG findings in patients with completed strokes but had a false-negative rate of 77% in patients with vertebral artery disease. In another report using EEG as a "gold standard," Harada and associates found that a stump pressure lower than 50 mm Hg had a positive predictive value of only 36%.[91] In this series, 11% of patients with ischemia by EEG criteria would not have received shunts and 64% of patients with a stump pressure lower than 50 would have received them unnecessarily by stump pressure criteria. Similarly, Brewster and coworkers found that 11 of 17 patients with ischemic EEG findings would not have been shunted by stump pressure criteria, and 7 of 63 would have unnecessary shunts.[92] Finocchi and colleagues used TCD to verify stump pressure and found that stump pressure did not correlate well with ischemia by TCD criteria in patients with postoperative deficits.[93] Clearly, even in the setting of what appears to be a satisfactorily high stump pressure, there may still be regions of the brain that are relatively hypoperfused.

Electroencephalographic and Somatosensory Evoked Potential Monitoring

Intraoperative EEG monitoring is the most widely used method of intraoperative cerebral monitoring.[94-97] Evidence suggests that electroencephalography is overly sensitive—positive in 10% to 40% of patients with unilateral carotid disease and positive in as many as 69% with bilateral carotid disease,[98,99] thereby overestimating the number of people who require shunts. Blume and coworkers observed postoperative strokes in only 9% of patients with abnormal EEG findings in whom shunts were not placed.[100] Furthermore, several series have documented neurologic events that occurred in the absence of EEG abnormality when shunting was not used.[95,101] Tempelhoff and associates found that 5 of 6 patients with postoperative deficits in a series of 103 patients showed EEG changes only late in the operation, when shunting was no longer feasible.[101]

Similarly, while there are multiple published studies on the use of SSEP suggesting that it is a useful adjunct to detect ischemia,[102-106] a meta-analysis of 15 studies, Wober and colleagues found that SSEP monitoring is not a reliable means of detecting ischemia and predicting neurologic outcome.[107]

Transcranial Doppler

TCD was introduced by Schneider and coworkers in 1988.[108] Visser and coauthors reported that with normal TCD findings one could safely avoid shunting in one third of patients, but that abnormal findings on TCD predicted ischemia by EEG criteria only 60% of the time.[109] TCD has the unique advantage of detecting microemboli intraoperatively, which may alert the surgeon to avoid further vessel manipulation and microembolization.[110,111] However, Belardi and associates also reported that TCD (as well as stump pressure) was not accurate in predicting cerebral ischemia.[112]

Awake Carotid Endarterectomy With Regional or Local Anesthesia

In view of these findings, performing CEA under RA is the most reliable method of predicting the need for selective shunting. Shunt rates of 5% to 15% are consistently lower than with other modalities.[112-119] In two recent prospective trials in which both stump pressure and EEG measurements were recorded before performing endarterectomy under RA, but in which the need to shunt was ultimately determined by neurologic changes, both EEG findings and stump pressure were found to inaccurately predict the need for shunting.[120,121] In a study by Calligaro and Dougherty published in 2005, a cost analysis found that RA saved more than $3000 per case by avoiding EEG measurements.[120]

Three studies have shown decreased length of stay with RA,[116,122,123] but in two of them the length of stay in the GA group was not reflective of modern practice, approximately 5 days.[116,123] There is no evidence in the literature that demonstrates the cost effectiveness of selective shunting versus routine shunting, and insufficient data to conclude that CEA performed under RA is associated with a lower rate of MI or neurologic complications.[117-124]

Routine Shunting

One risk of selective shunting is that neurologic events may be attributable to the shunt itself secondary to embolism or ischemia and may not occur with routine shunting. Specifically, selective shunting, regardless of the adjunct used, always involves a test clamp. In the case of stump pressure measurement, instrumenting the carotid artery with a needle introduces the added risk of embolism. When a test clamp is positive, there are two options. One is to unclamp the vessels and reperfuse the brain while preparations are made to shunt. This maneuver exposes the patient to the risk of embolization. The other option is to proceed with the endarterectomy and placement of a shunt. In this instance, the brain is ischemic when the test clamp becomes positive and is exposed to an additional period of ischemia while the shunt is being placed, whereas during routine shunting, shunt placement can usually be accomplished in 1 to 2 minutes after clamping before the brain becomes ischemic.[56,57,89,101,125]

The routine use of carotid shunts allows CEA to be performed in a consistent manner, which eliminates surgeon and patient anxiety, without the added cost or complexity of monitoring equipment. Studies consistently show that carotid shunting relieves the intracerebral ischemia caused by clamping, whether measured by neurologic status, EEG changes, MCA flow on TCD, or cerebral blood flow, and there is no convincing evidence that placement of a shunt increases embolic complications or causes arterial injury leading to more subacute or chronic complications. However, there is evidence that placing a shunt in the setting of severe ischemia decreases the stroke rate[126] and may limit ischemia-reperfusion injury. Further, Parrson and

associates have shown that carotid shunting diminishes the inflammatory response of ischemic brain injury, as demonstrated by the production of various inflammatory mediators.[125] This may be an important mechanism in the occurrence of delayed postoperative strokes, which can account for up to 70% of perioperative strokes.[79]

Several large series including nearly 7000 patients have documented a perioperative stroke rate of 1.0% to 1.6% with routine shunting.[73-76,127] In our practice, routine shunting is the preferred technique. Despite acceptable results in some individuals' hands, routine nonuse of shunts cannot be advocated in view of the abounding evidence that intraoperative ischemia can be a source of stroke that is preventable with shunts. Selective shunting based on stump pressure, TCD, or neurophysiologic monitoring does not accomplish the goal of improving results through decreased shunt use and only adds to the cost and complexity of the procedure. The only form of selective shunting that is truly reliable is that based on neurologic examination during RA.

ARTERIOTOMY CLOSURE

Considerable experience indicates that patch closure yields superior clinical and anatomic outcomes compared to primary arteriotomy closure.

Patch Material

Saphenous Vein Patches

Saphenous vein patching has been used extensively with good results. Complications specific to saphenous vein patching include wound complications at the harvest site, potential compromise of a valuable conduit for later bypass procedures, and the potentially devastating complication of patch rupture, which has been reported to occur in 0.5% to 4% of cases.[128-133] Because most of these were ankle veins, several investigators recommended harvesting the great saphenous vein (GSV) from above the knee. Lord and coworkers also noted that aneurysmal expansion of saphenous vein patches can occur in up to 17% patients.[134]

Archie and Green investigated the relationship of GSV diameter and rupture pressure and found that GSVs with diameters less than 3.5 mm were more prone to rupture.[135] Their group also noted that women were three times more likely to have a GSV measuring less than 3.5 mm. Applying this knowledge to their practice, Archie found that by using a GSV with a distended vein diameter of greater than 3.5 mm and maintaining a carotid bulb diameter of less than 13 mm, patch rupture was completely avoided in a series of 534 patients over an 8-year period.[136]

Synthetic Patches

Synthetic materials that are commonly used include PTFE, woven polyester (Dacron), and bovine pericardium.

Comparative Analyses

Pooled data from meta-analyses and large databases demonstrated no definitive clinical benefit of vein versus prosthetic patching. In a New York state database including 1972 CEAs performed at six regional hospitals, perioperative stroke was significantly more common with primary closure than with eversion or patching (5.6% vs. 2.2%, no difference between eversion and patching), as well as higher perioperative stroke rates and death with primary closure versus eversion or patching (6% vs. 2.5%). There were no differences in any outcomes between eversion and patching.[137] In a review of more than 10,000 CEAs performed in several states, the use of a patch—in particular a prosthetic patch—was a statistically significant indicator for improved outcomes.[138] Based on these findings, the U.S. Centers for Medicare and Medicaid Services adopted patching of conventional CEA as a physician quality measure for 2009.

After these studies were published, Al-Rawi and coworkers reported an RCT that included 328 patients in which primary closure was performed by a single surgeon using microvascular techniques. There were no statistically significant differences in outcomes, but a trend toward a higher combined stroke and death rate was noted in the patched group.[139] Therefore, primary closure with microvascular technique may be the only instance in which it might be justified, although the preponderance of evidence supports patch closure after conventional CEA.

In a randomized trial of 160 CEAs with either external jugular vein and PTFE patches, there was no difference in stroke-free survival at 12, 30, and 60 months, and no difference in recurrent stenosis rates, but there was a trend toward improved results with a vein patch.[140] In an RCT comparing bovine pericardium with Dacron in 95 CEAs performed in 92 patients, there was significantly less suture line bleeding with bovine pericardium than with Dacron (4% vs. 30%) and no difference in neurologic outcomes.[141] Another study compared saphenous vein and internal jugular vein with knitted Dacron in 275 CEAs and found no significant differences in perioperative morbidity, mortality, or early restenosis between any of these groups.[142] Another report studied internal jugular vein, GSV from the thigh, and knitted Dacron, and documented a higher death rate in the jugular vein group (8% vs. 0% with GSV and 1.1% with knitted Dacron), as well as a higher stroke rate that was not statistically significant (4% vs. 1.3% and 1.1%, respectively).[143] In another study of primary closure versus patching with GSV, jugular vein, and PTFE,[144] perioperative neurologic event rates were significantly higher with primary closure than with all patch methods. Event rates were slightly higher with jugular vein patches, and recurrent stenosis was also higher in this group than in the GSV or Dacron patch group and similar to primary closure. In a follow-up study 2 years later, primary closure had a higher incidence of restenosis and need for reoperation, especially in women who had smaller carotid arteries.[145] Finally, in a small RCT comparing Dacron with PTFE, a higher stroke rate with Dacron was largely due to perioperative thrombosis.[146] As a result of this trial the manufacturer of the Dacron patch re-engineered it, and this group found no difference in outcomes between the two patches.

Selective Patching

It has been suggested that carotid patching may not be necessary in all patients, and the technique does have some drawbacks,

such as longer operative time, greater potential for bleeding from longer suture lines, and increased cost. To avoid these pitfalls while preventing the increased morbidity associated with primary closure, some surgeons use a policy of selective patching. Golledge and associates studied selective patching based on intraoperative measurement of the outer diameter of the ICA and found that selective patching was safe in arteries measuring at least 6 mm.[147] Other work has clearly identified other risk factors for recurrent carotid stenosis and indications for selective patching, including female gender, elevated cholesterol level, and possibly cigarette smoking and hypertension[105] (see section on "Recurrent Carotid Stenosis," below).

COMPLETION STUDIES

A preventable cause of perioperative stroke is thromboembolism or carotid artery thrombosis resulting from technical imperfection. To minimize this risk, intraoperative completion studies have been used, including continuous wave Doppler, duplex ultrasound, and intraoperative angiography. Using continuous wave Doppler, an experienced operator can document vessel patency and a stenosis by the associated high-pitched audible signal. However, it is insensitive to small intimal flaps or more subtle stenoses, and its accuracy is operator dependent. Duplex ultrasound is a much more sensitive tool that provides detailed anatomic imaging, as well real-time physiologic information. However, this modality is also operator dependent. The authors have found completion duplex ultrasound to be particularly helpful in identifying plaque disruption secondary to clamp or Rommel tourniquet trauma in the proximal CCA as well as distal intimal flaps (Fig. 91.9). Intraoperative angiography has been considered the gold standard of completion studies. However, the quality of the information obtained from an angiogram may vary significantly depending on the technique used.

Results of Completion Studies

Several studies have demonstrated the utility of completion studies to identify technical defects, with subsequent improvement of results.[148,149] On the other hand, not all technical imperfections, such as minor intimal flaps and especially ECA lesions, will cause strokes. In addition, attempts to revise significant lesions can convey additional morbidity from repeat manipulation of the vessels and a further risk for ischemia, embolism, thrombosis, or bleeding. In the EVEREST trial, the only significant risk factor for a major defect was plaque extension greater than 2 cm into the ICA (OR 1.5; $P = .03$). One of the unanswered questions about completion studies is the extent of abnormality (either flap length or stenosis severity) that warrants intervention. Clearly, other workers have found no significant benefit in completion imaging.[150,151] However, if there is any doubt about the condition of the endpoint, a completion study should be obtained.

During eversion endarterectomy one may have only a fleeting glimpse of the endarterectomy endpoint before the artery retracts when the plaque separates from the artery, or none at all. Therefore, completion studies are more likely to be useful in this procedure.

PERIOPERATIVE STROKE MANAGEMENT

In a comprehensive study of the etiology of perioperative stroke associated with CEA, more than 20 mechanisms were delineated.[81] These mechanisms can be grouped in decreasing order of frequency as perioperative arterial thrombosis and embolization, cerebral ischemia during carotid clamping, and intracerebral hemorrhage. Perioperative carotid arterial thrombosis most often results from technical imperfection in performance of the operation, such as disruption of the intima during placement of the intraluminal shunt, residual intimal flaps or atheromatous disease, or residual luminal thrombus. Completion imaging studies, as described in the previous section, will help identify technical imperfections and can reduce the incidence of neurologic complications (see Fig. 91.9). Maximizing the chance for neurologic recovery is most dependent on early recognition of the deficit and immediate institution of proper therapy. Establishing the correct diagnosis is dependent on the time of

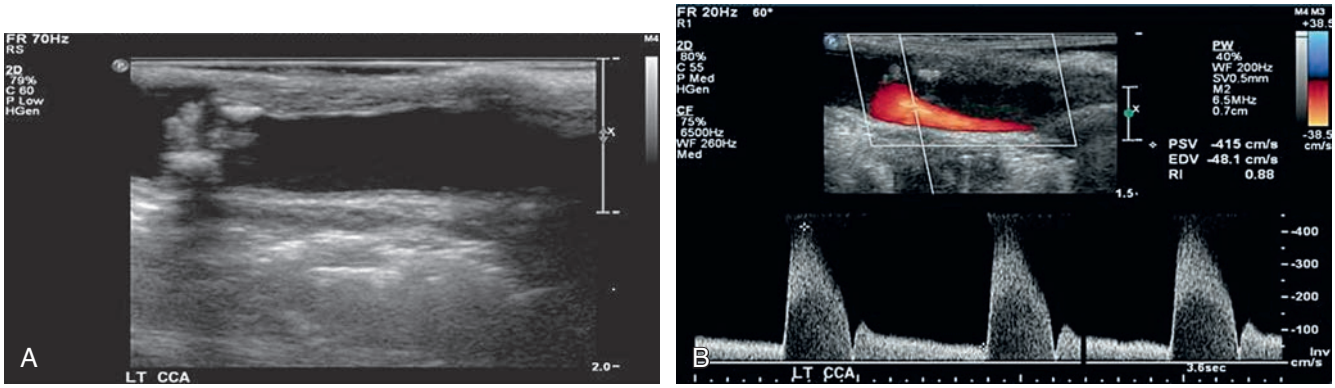

Figure 91.9 (A) Intraoperative completion carotid B mode image revealing significant plaque disruption in the proximal common carotid artery. (B) Note the markedly elevated flow velocities at the site of plaque disruption. The vessel was re-clamped and this site was endarterectomized.

onset of symptoms and is supported by selected noninvasive vascular laboratory or radiologic studies.

Intraoperative

A patient undergoing CEA under GA should be awakened in the operating room immediately after wound closure, and a neurologic examination performed. If a new focal central neurologic deficit is identified, the incision should be immediately opened, and the ICA is checked for flow with Doppler. If flow appears to be present, the surgeon should perform duplex ultrasonography or arteriography to identify a potential correctable etiology. Angiography should include intracranial imaging if no cause is found at the endarterectomy site because a distal embolus is potentially treatable by thrombolysis or extractable via microcatheter techniques. However, if the ICA does not have flow, or if a local defect is suspected, the endarterectomy must be re-explored. If there is acute thrombosis of the endarterectomy site, a meticulous search for a technical defect, such as a distal intimal ledge, should be carried out after careful thromboembolectomy. It is best not to clamp the distal ICA initially in the case of thrombosis and to extract the clot in the bulb and visible ICA so that backpressure may extrude any more distal ICA thrombus with the CCA clamped. If there is no back flow, a balloon catheter can be used, but care must be taken to prevent distention in the distal ICA to avoid causing a carotid artery–cavernous sinus fistula.[152] If there is a local flap, platelet accumulation, or other problem within the endarterectomy, it should be corrected. In the setting of re-exploration, great care must be taken if a shunt is reinserted to be sure that the distal endpoint is not injured and a flap created with insertion of the shunt.

At re-exploration, if the vessel is found to be patent without a local defect, the most likely cause is either ischemia during carotid clamping or, much more likely, intraoperative embolization. Despite careful technique, in a small minority of patients, excessive platelet deposition may occur acutely on the endarterectomy site and predispose to distal embolization or even acute thrombosis of the vessel. In this case, we favor resection of the endarterectomy segment and replacement with an interposition graft and preferentially a ringed 6 mm PTFE graft. Conversely, if the vessel appears normal at re-exploration, thus suggesting that the patient experienced either embolization during vessel dissection before clamping or ischemia during clamping, treatment is medical (namely, close attention to hemodynamic monitoring, oxygenation, and blood pressure stability postoperatively) or thrombolysis/microcatheter embolus extraction in institutions with such capability.

Postoperative

If the patient awakens neurologically intact in the operating room and then a new deficit develops in the recovery room or later postoperatively, the differential diagnosis is more complex. Initially, the patient should undergo Duplex ultrasound if it can be performed rapidly. If this testing indicates occlusion of the vessel or abnormal flow velocities suggestive of an intimal flap or other anatomic deficit, the patient should be immediately be taken to the operating room for re-exploration. Timing is crucial because most neurologic deficits are significantly reversible if flow is restored within 1 to 2 hours after vessel thrombosis. If the noninvasive studies are negative and thus suggest a patent vessel, head computed tomography (CT) should be performed immediately to rule out a cerebral hemorrhage. If negative, carotid angiography should be performed to identify any technical defect requiring revision at the operative site, or a possible intracerebral embolus.

The availability of intracerebral catheter-directed thrombolysis has provided another tool for neurologic salvage in a patient who experiences an embolic event associated with CEA. In addition, catheter-based thrombectomy of ICA and MCA emboli has been accomplished successfully in the setting of acute ischemic stroke and as "neurorescue" for carotid thrombosis complicating CAS.[153-160]

SURGICAL RESULTS

Considerable clinical experience reported over the last three decades indicates that CEA can be performed with low rates of perioperative complications, and that it substantially reduces the risk for subsequent stroke in patients with significant symptomatic as well as asymptomatic extracranial carotid atherosclerotic lesions.[161-166]

Randomized Trials

Symptomatic Disease

The National Institutes of Health (NIH)-funded North American Symptomatic Carotid Endarterectomy Trial (NASCET) included investigations of both high-grade (70%-99%) and moderate-grade (50%-69%) stenosis (Table 91.1). The 30-day mortality, disabling stroke, and nondisabling stroke rates were 1.1%, 0.9%, and 4.5%, respectively.[9,167] In the NASCET high-grade stenosis investigation, 659 patents with symptomatic ICA stenoses (70%-99%) were randomized to optimal medical management versus CEA and optimal medical management. At the 2-year follow-up, there was a highly significant reduction in ipsilateral stroke incidence (9% vs. 26%) in patients who underwent CEA.[9] This benefit became apparent within 3 months of randomization and has persisted through 8 years of follow-up.

In the moderate-stenosis limb of the investigation including 865 patients with 50% to 69% ICA stenoses, at 5 years of follow-up the ipsilateral stroke rate was 22.2% in medical patients and 16.7% in surgical patients ($P = .045$), and this benefit has persisted through 8 years of follow-up.[167]

Two recent randomized clinical trials comparing CEA to CAS have provided further evidence of the safety and efficacy of CEA. In the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), the 30-day stroke and death rate was 3.2% among symptomatic patients.[168] In the International Carotid Surgery Trial, the 30-day stroke, death, and MI rate was 5.2%.[169]

TABLE 91.1 Benefit of Carotid Endarterectomy: Randomized Trials

		PERIOPERATIVE		
Trial	Indication	CVA/ Death	Risk Reduction	*P*
NASCET	Sx: >70%	5.8%	16.5%/2 years	<.001
	Sx: 50%-69%	6.7%	10.1%/5 years	<.05
ECST	Sx: 70%-99%	7.5% 9.6%/3 years	<0.01	—
ACAS	Asx: >60%	2.3%	5.9%/5 years	= 00.004
ACST	Asx: >60%	3.1%	5.4%/5 years	<.0001

ACAS, Asymptomatic Carotid Atherosclerosis Study; *ACST*, Asymptomatic Carotid Surgery Trial; *Asx*, Asymptomatic; *ECST*, European Carotid Surgery Trial; *NASCET*, North American Symptomatic Carotid Endarterectomy Trial; *Sx*, symptomatic.
Source: References 9-12, 18, 19.

TABLE 91.2 Population Studies of Carotid Endarterectomy Outcomes

Source	Number of Patients	Years	% CVA/ Death
North Carolina[172]	1,973	1998-1993	2.9
New York[173]	9,308	1998-1999	4.0
Maryland[174]	23,237	1994-2003	1.3
California[174]	51,331	1999-2003	1.0
Connecticut[175]	7,089	1997-2002	2.8 (VA) 1.2 (non-VA)
VSGNE[182]	7,649	2003-2010	1.1
Georgia Medicare[176]	1,945	1993	3.7
NSQIP[296]	13,622	2003-2003	3.4
NSQIP[297]	13,316	2007-2008	2.0

CVA, Cerebrovascular accident; *NSQIP*, National Surgical Quality Improvement Project; *VA*, Veterans Administration hospitals; *VSGNE*, Vascular Study Group of New England.

Asymptomatic Disease

Management of asymptomatic carotid disease has recently become somewhat controversial because the long-term risk for stroke is not as high in asymptomatic when compared to symptomatic patients, and because the natural history of asymptomatic carotid disease may be improving due to improvements in medical therapy. In the NIH-funded Asymptomatic Carotid Atherosclerosis Study (ACAS), 1600 patients with greater than 60% asymptomatic stenosis were randomized to optimal medical management versus CEA and optimal medical management (Table 91.1). The 30-day stroke per death rate was 2.3% in the surgical cohort by intent-to-treat analysis. However, there were seven strokes and two deaths preoperatively, so the actual perioperative stroke rate was 1.3% and the mortality rate was 0.1%. At the 5-year follow-up, stroke and death rates were 5.1% in the CEA group and 11% in the medical management group ($P = .004$).[11]

The Asymptomatic Carotid Surgery Trial (ACST) was carried out in Europe, and was similar in design to ACAS, and randomized 3200 patients with greater than 60% asymptomatic ICA stenoses to best medical therapy versus CEA and best medical therapy. The 5-year stroke and death rates were 6.4% for CEA and 11.8% for medically managed patients ($P < .0001$; see Table 91.1).[11,170] In CREST, the 30-day stroke and death rate was 1.2% among asymptomatic patients who underwent CEA.[168]

Institutional Experience

Since publication of the NASCET, ACAS, and ACST results, the safety and efficacy of CEA have been confirmed in multiple individual institutional reports. For example, in a series 2236 CEAs performed between 1989 and 1999 at the Massachusetts General Hospital, the perioperative stroke and death rate was only 1.4%.[171] In a report of 1566 CEAs performed at the authors' institution from 1994 through 2004, the 30-day stroke and death rates were 2.5% and 0.8%, respectively.[53]

Population-Based Experience

In recent years several population-based analyses have demonstrated results of CEA in community practice comparable to the outcomes in tertiary referral centers and randomized trials (Table 91.2).[172-183]

COMPLICATIONS

Cardiac

MI is responsible for 25% to 50% of all perioperative deaths after CEA.[184-186] Furthermore, more late deaths are due to MI than to stroke or other causes.[184,185,187] At least 40% to 50% of patients who undergo CEA have symptomatic CAD.[25,26,188-191] In a prospective angiographic study, severe surgically correctable CAD was identified in 20% of patients about to undergo treatment of carotid disease.[192] However, operative mortality has declined significantly over the past 2 decades in large measure due to a significant reduction in the incidence of major cardiac complications reflecting improvements in screening, as well as perioperative medical management of this patient population (see Chapter 32).

Cranial Nerve Injury

Incidence

Cranial nerve dysfunction is the most common neurologic complication of CEA. The incidence of postoperative dysfunction of cranial nerves ranges from 5% to 20% in several series, and a variety of nerves may be affected (Table 91.3).[193-202] In the CREST trial, the incidence of cranial nerve injury was 4.7%.[168]

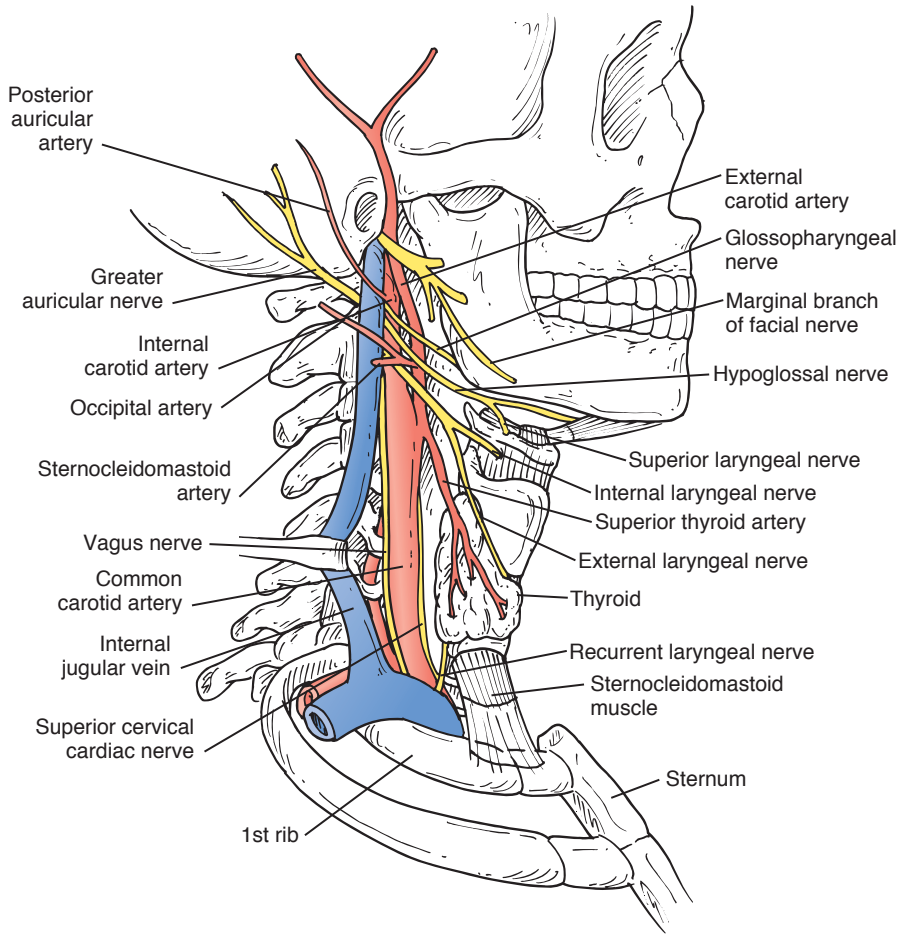

Figure 91.10 Relationship of the cranial nerves and their major branches to the common, internal, and external carotids in the neck. (Modified from Eisele DW, Smith RV, eds. *Complications in Head and Neck Surgery*, Philadelphia: Elsevier; 2009.)

TABLE 91.3 Incidence of Cranial Nerve Dysfunction Following Carotid Endarterectomy

Nerve	Reported Incidence (%)
Hypoglossal	4.4-17.5
Recurrent laryngeal	1.5-15
Superior laryngeal	1.8-4.5
Marginal mandibular	1.1-3.1
Glossopharyngeal	0.2-1.5
Spinal accessory	<1.0

Source: References 228, 232, 234-238, 241, 244.

Retrospective reviews may significantly underestimate the true incidence of cranial nerve dysfunction after CEA. In a prospective study of patients undergoing 450 CEA procedures and who also underwent postoperative otolaryngology examination, 72 cranial nerve injuries were identified in 60 (13%) patients. Approximately one third of the patients with documented deficits were asymptomatic and would have been missed by cursory clinical examination.[202] In the vast majority of cases, the clinical deficit is transient, with complete resolution noted within weeks to months after the procedure. In one prospective study, all injuries resolved within 5 months.[198] In another prospective study, almost all nerve deficits resolved within 12 months after CEA, although it was noted that two patients with recurrent laryngeal nerve dysfunction regained normal function at 20 and 50 months after CEA, respectively.[196] In the CREST trial, there was no significant adverse impact of cranial nerve injury on the patients' quality of life 1 year later.[168] In the ECST randomized prospective trial, it was noted that the risk for permanent nerve injury was 0.5%.[198] In another report, the incidence of permanent cranial nerve injury was only 1.1%.[196]

Anatomic and Clinical Considerations

Iatrogenic injury to the cranial nerves results from the close anatomic proximity of these structures to the carotid bifurcation (Fig. 91.10). Most deficits are due to direct blunt injury during dissection, stretch trauma from excessive retraction, electrocoagulation damage, inexact placement of ligatures, or pressure injury secondary to postoperative hematoma formation. Cranial nerve injury is much more likely during reoperative surgery because of excessive scar formation.[194] In one recent detailed analysis, the incidence of cranial nerve dysfunction correlated with the duration of surgery; there was a significantly higher incidence of nerve injury when the duration of CEA exceeded 2 hours.[198]

Hypoglossal Nerve

Hypoglossal nerve dysfunction, manifested by ipsilateral tongue weakness and deviation to the affected side with protrusion

and difficulty masticating, is the most frequent cranial nerve deficit documented in most reports (see Table 91.2). The structure descends from the hypoglossal canal (anterior condylar foramen) medial to the ICA and then courses lateral to the ECA, usually several centimeters distal to the carotid bifurcation, although in rare cases it may cross at the carotid bifurcation.[202] In this situation, if a patient has an unusually high carotid bifurcation or if atheromatous plaque extends well past the origin of the ICA, cephalad mobilization of the nerve is usually required for adequate operative exposure. In most cases mobilization can be accomplished safely without morbidity by division of the ansa hypoglossi. In other cases, division of tethering branches of the ECA or internal jugular vein is required, which increases the likelihood of transient injury. Although unilateral hypoglossal nerve injury is rarely serious, bilateral deficits have been associated with serious articulation and swallowing difficulty and upper airway obstruction requiring tracheotomy.[203] Therefore, it is important to assess the functional integrity of this nerve after CEA in a patient who is scheduled for early contralateral CEA.[197]

Vagus Nerve

The vagus nerve is easily identified within the carotid sheath posterior to the CCA, although in the occasional patient it may lie anterior to the carotid and be mistaken for the ansa hypoglossi. Therefore, before division of the latter structure, the vagus nerve should be clearly identified. The recurrent laryngeal branch usually originates from the vagus within the mediastinum, loops around the subclavian artery on the right or the aortic arch on the left side, and passes cephalad in the tracheoesophageal groove behind the strap muscles. In most cases, this nerve is not in close proximity to the operative field and is not likely to be directly injured. Typically, recurrent laryngeal nerve dysfunction results from vagus nerve trauma. In rare cases, the recurrent laryngeal nerve arises from the vagus at the level of the carotid bifurcation, the so-called nonrecurrent recurrent laryngeal nerve, and enters the larynx posterior to the CCA. Vagus or recurrent laryngeal nerve injury results in paralysis of the ipsilateral vocal cord in the paramedian position and is manifested as hoarseness and loss of an effective cough mechanism. In occasional patients, the vagus and hypoglossal nerves will be in apposition in the upper portion of the operative field, and no effort should be made to separate these structures to minimize the risk for injury. Patients who have previously undergone contralateral carotid, thyroid, or parathyroid surgery should have a careful examination of their vocal cords before CEA if there is any suggestion of recurrent laryngeal nerve injury because bilateral vocal cord paralysis may cause postoperative airway obstruction.

Superior Laryngeal Nerve

The superior laryngeal nerve originates from the vagus near the jugular foramen and passes obliquely to the larynx posterior to the ECA and ICA where it divides into internal and external branches. It is not usually visualized during routine dissection for CEA, and it may be injured by injudicious clamping of the ICA or ECA. Injury to the external branch of the superior laryngeal nerve primarily results in loss of tensioning of the ipsilateral vocal cord and may be manifested clinically by early fatigability of the voice and difficulty with voice modulation at the high registers. Conversely, injury to the internal branch may result in decreased sensation at the laryngeal inlet and mild swallowing difficulty.[196]

Facial Nerve: Marginal Mandibular Branch

Injury to the marginal mandibular branch of the facial nerve causes drooping of the ipsilateral lower lip. Although this may be cosmetically bothersome to the patient, it is of little functional significance. This nerve courses from the anterior border of the parotid gland between the platysma and deep cervical fascia across the masseter muscle and ramus of the mandible. It may be drawn into the operative field as the patient's head is turned to the opposite side and the chin is extended for exposure of the carotid bifurcation. Injury is usually due to excessive stretch from self-retaining retractors in a transverse cervical incision. When a longitudinal incision is used for CEA, angling the superior aspect of the incision posteriorly toward the mastoid process below the angle of the mandible will minimize the risk of injury to the nerve.[204]

Glossopharyngeal and Spinal Accessory Nerves

Injury to the glossopharyngeal and spinal accessory nerves is exceedingly uncommon during CEA because of their anatomic location at the upper extent of the operative field. However, in rare cases in which excessive mobilization or division of the digastric muscle is required for distal ICA exposure, either nerve may be encountered and traumatized. The glossopharyngeal nerve provides sensory and motor innervation to the larynx. Symptoms of glossopharyngeal nerve injury range from mild dysphasia to recurrent aspiration.[196,199]

The spinal accessory nerve exits the jugular foramen, runs posterior to the stylohyoid muscle, and enters the most cephalic extent of the sternocleidomastoid muscle. Injury is manifested as shoulder droop and pain, scapular winging, and difficulty abducting the shoulder because of weakness of the trapezius muscle.[196,200]

Cutaneous Sensory Nerves

Two important cutaneous sensory nerves that are not infrequently injured during the performance of CEA are the greater auricular and transverse cervical nerves. In one prospective study, the incidence of greater auricular and transverse cervical nerve injury was 60% and 69%, respectively, 1 week after CEA.[205] The greater auricular nerve courses along the most superior and the transverse cervical nerve along the most inferior area of the typical CEA longitudinal incision. Injury to the greater auricular nerve is manifested as numbness of the angle of the mandible and the lower part of the ear, and injury to the transverse cervical nerve is manifested as anesthesia of the anterior neck skin.

Hemodynamic Instability

Incidence and Etiology

If hypotension occurs after CEA, it usually does so within the first 2 hours after CEA, is generally associated with bradycardia,

and most likely results from disordered baroreceptor function.[206-208] Considerable evidence suggests that endarterectomy of fixed atheromatous plaque at the bifurcation, with its chronic dampening effect on pulse pressure, creates a heightened sensitivity of the baroreceptor mechanism that results in reduced central nervous system sympathetic activity with resultant hypotension or bradycardia, or both.[206,207,209,210] This reflex hypotension persists until the carotid sinus mechanism has been reset.[211]

Although perioperative hypertension is closely correlated with preoperative hypertension, its mechanism remains poorly understood. Baroreceptor dysfunction as a result of denervation of the carotid bulb is commonly assumed to be responsible, although there is considerable evidence to refute this hypothesis[208,212] and other mechanisms may be responsible, such as elevated cerebral norepinephrine or renin production.[213,214] In at least 80% of patients, this hypertensive response normalized within the first 24 hours, and in approximately 60% of patients it did so within the first 16 hours after surgery.[163]

Treatment

The episodic and generally unpredictable nature of post-CEA hypotension or hypertension is one of the more cogent reasons for observing the patient in a monitored unit after CEA, at least initially, with an indwelling radial artery catheter for systemic blood pressure monitoring. Hypotension should initially be treated by infusion of colloid solutions while a careful evaluation is conducted for any other causes of hypotension. Once normovolemia has been achieved, if hypotension persists, we favor supporting blood pressure with an intravenous infusion of phenylephrine (Neo-Synephrine), with the dosage adjusted to maintain systolic blood pressure within at least 20 mm Hg of the preoperative level. In almost all cases, the patient may be weaned from this vasoconstricting agent during the first postoperative day.

Conversely, postoperative hypertension is most effectively treated with intravenous sodium nitroprusside. Its effect is immediate, and it is quickly dissipated by stopping the infusion. The agent should be titrated to maintain systolic pressure within 20 mm Hg of the preoperative level. If myocardial ischemia is associated with these hypertensive episodes, intravenous nitroglycerin should also be administered. Most patients are able to resume their preoperative oral antihypertensive agents on the evening of surgery or within the next 12 hours, and this often obviates the need for further and more prolonged intravenous therapy.

Cerebral Hyperperfusion Syndrome

Cerebral hyperperfusion syndrome usually occurs several days after CEA and is often associated with severe hypertension. The reported incidence of cerebral hyperperfusion syndrome ranges from 0.4% to 7.7%.[215,216] This complication is now also being recognized after CAS procedures as well.[217,218] Symptoms include a migraine like headache progressing to seizures and, in its most severe manifestation, intracerebral hemorrhagic stroke. Though an infrequent complication of CEA and CAS, it is associated with a very high mortality rate that approaches 75% to 100% in some series.[219,220]

The cause of hyperperfusion syndrome appears to be increased regional cerebral blood flow secondary to disordered intracerebral autoregulation after relief of a high-grade carotid stenosis in the setting of severe contralateral carotid disease.[217] Systemic hypertension appears to be an important risk factor. Therefore, strict attention to postoperative blood pressure control is paramount, especially in a patient who undergoes CEA for a high-grade stenosis contralateral to complete ICA occlusion or severe stenosis. There may be some association with the use of anticoagulants and antiplatelet agents, but this evidence is speculative at best. If cerebral hemorrhage occurs, neurosurgical consultation is required to determine the necessity for craniotomy. One report noted that hyperperfusion syndrome can be predicted by a significant drop in pressure across the carotid stenosis and that it is related to temporary loss of cerebral autoregulation as evidenced by a transient increase in mean arterial velocity of the ipsilateral MCA after CEA.[221-223] Another study found that CEA performed less than 3 months after contralateral CEA was associated with a higher risk for hyperperfusion syndrome.[224]

Other Complications

Infections

CEA is rarely associated with infectious complications. Difficulty in primary healing is occasionally seen when this operation is performed in a previously irradiated field, but it is almost nonexistent in the absence of this complicating factor.[194] The reported incidence of wound infection, generally cellulitis, ranges from 0.09% to 0.15%.[225,226] Although the true incidence of patch infection has not been established, it appears to be extremely rare. In several studies, no cases of patch infection were documented.[226-228] However, in a recent systematic literature review, 14 publications were cited with a total of 77 cases of graft infection, including 0.25% to 0.5% for Dacron patches.[229] In another comprehensive review of the literature, 57 carotid pseudoaneurysms were identified, and 40 were associated with carotid patches. However, only four (10%) were infectious in etiology.[228]

Bleeding

Postoperative hemorrhage has a reported incidence of 0.7% to 3.0%.[189,209,230-232] Most cases result from diffuse capillary oozing secondary to the administration of heparin during the procedure and the concomitant administration of antiplatelet drugs. Though not systematically studied, at least anecdotally this degree of oozing appears to be greater in patients who are taking the antiplatelet agent clopidogrel at the time of surgery. Nevertheless, if there are indications for the administration of this agent, such as a recent coronary stent procedure or symptomatic carotid disease, we would not stop clopidogrel before surgery. In general, unless bleeding appears excessive at surgery, we do not favor reversal of the heparin effect with protamine sulfate at completion of the procedure, but this practice varies widely (see later).

If the neck incision has been closed over a suction drain, the acute onset of drainage of bright red blood postoperatively is suggestive of suture line disruption and is an indication for

urgent re-exploration. Similarly, the development of a hematoma in the neck, often caused by inadequate function of the drain, may compress the trachea and is an indication for re-exploration of the wound. More gradual development of a neck hematoma usually results from inadequate ligature of facial veins or other muscle arterioles or venules.[194]

Recurrent Carotid Stenosis

Recurrent carotid stenosis has been estimated to occur in 5% to 22% of patients, although only approximately 3% of these lesions were symptomatic.[55,233-236] In a meta-analysis of 55 reports, the overall incidence of recurrent carotid stenosis after CEA was 6% to 14%, which reflected an annual incidence of restenosis or occlusion of 1.5% to 4.5%.[237] In another analysis of the MEDLINE database, the rate of restenosis was 10% within the first year, 3% in the second, and 2% in the third year after CEA, thus suggesting that the rate of restenosis is clearly not a linear process biologically.[238] In CREST, at 2 years the rate of significant restenosis or occlusion was 6.3%.[239]

Recurrent stenoses develop more frequently in women, in patients who continue to smoke, and in hypercholesterolemic, diabetic, and hypertensive individuals.[234] It has also been suggested that intraoperative injury secondary to arterial clamping, insertion of an intraluminal shunt, or placement of tacking sutures within the vessel may also predispose to early myointimal hyperplastic lesions.[233] As noted earlier, there is compelling evidence that closure of the arteriotomy with a patch will reduce the incidence of recurrent stenosis.

Long-term follow-up of 950 CEAs performed at the Massachusetts General Hospital demonstrated that reintervention was required in 3.8% of patients with a cumulative follow-up of 4.5 years. There was no difference in restenosis rates between patients who underwent patch closure and eversion endarterectomy.[240] In another series that included 1150 patients, 98.8% were free of occlusion or restenosis greater than 70% at a mean follow-up of 74 months after CEA.[241] In the EVEREST trial, life-table estimates of the cumulative risk for restenosis at 4 years was not significantly different between eversion CEA and conventional CEA with patch closure.[242] Therefore, while there may be anatomic indications for performing an eversion CEA—or it may be surgeon preference—the consensus is that this technique is not associated with a significantly lower rate of restenosis.

Early recurrent stenosis usually develops within 2 years of CEA and typically results from intimal hyperplasia, an inflammatory response that produces a firm, rubbery plaque rich in fibroblasts and smooth muscle cells surrounded by dense accumulation of collagen and acid mucopolysaccharide, and it typically develops within the endarterectomy bed (see Chapter 5). Regression of these lesions is not uncommon and is observed in as many as one third or more of cases.[243,244] Therefore, one should have a very high threshold for reintervention for an early restenosis. Later restenoses typically have features of atheromatous plaque and are more widely distributed along the carotid artery. There are no prospective, randomized trials to support repeat CEA, but most available evidence supports treatment of symptomatic and very high grade asymptomatic recurrent stenoses.[233,245]

Repeat Carotid Endarterectomy

Scarring typically makes the carotid dissection more technically difficult, so a higher incidence of cranial nerve injury and hematoma has been reported.[246] In addition, the more extensive disease within the carotid artery may necessitate carotid artery replacement with an interposition graft. This is technically more difficult, may preclude shunting, and could be associated with longer periods of cerebral ischemia, possibly leading to higher perioperative stroke rates.[246] However, repeat endarterectomy is often possible, even after eversion endarterectomy.[247] Furthermore, with careful planning and technique, excellent results can be achieved in this situation as well, and reoperative CEA has been shown to be a very durable procedure. In one series, for example, at 48 months follow-up, 100% of patients were free of recurrent stenosis after repeat CEA.[248]

Carotid Artery Stenting Versus Repeat Carotid Endarterectomy

The increased technical difficulty and higher complication rate anticipated with repeat CEA has led some to advocate CAS as an alternative to CEA for recurrent stenosis. However, AbuRahma and coauthors reported lower perioperative stroke rates with repeat CEA than with CAS for recurrent stenosis[248] Repeat CEA on the other hand was associated with a much great incidence of cranial nerve injury (14% vs. 0%, $P < .0001$).[182]

SPECIAL CONSIDERATIONS

Combined Carotid Artery and Cardiac Disease

Significant carotid disease occurs in approximately 3% to 14% of patients undergoing cardiac surgery.[249] Between 1970 and 2000, Naylor and colleagues found that the risk for stroke after coronary artery bypass grafting (CABG) was 2% overall—less than 2% in patients without carotid disease, 3% in asymptomatic patients with unilateral 50% to 99% stenosis, 5% in those with bilateral 50% to 99% stenosis, and 7% to 11% in patients with carotid occlusion. However, the authors noted that 50% of CABG patients who experienced a stroke did not have significant carotid disease and that 60% of territorial infarctions on CT scan/autopsy could not be attributed to carotid disease alone. They estimated that CEA could prevent only about 40% to 50% of perioperative strokes in this patient population.[250] Nevertheless, carotid bifurcation disease is easily diagnosed and therefore at least one preventable cause of perioperative stroke in the cardiac surgical patient population.

Simultaneous Carotid Endarterectomy and Coronary Artery Bypass Grafting

One strategy pursued to reduce the risk of perioperative stroke is to perform simultaneous CEA and CABG. A prospective,

randomized trial performed at the Cleveland Clinic demonstrated a significantly lower stroke rate in patients undergoing combined CEA/CABG (2.8%) versus staged CABG followed by CEA (14%), although mortality was not significantly different. The stroke rate was much higher if CEA was performed early after CABG than at later intervals.[213]

Conversely, other studies have documented increased morbidity or no benefit from combined CEA/CABG.[251-253] Naylor and colleagues reviewed 97 published studies and found no significant difference in outcomes for staged and synchronous procedures.[253] Mortality was highest in patients undergoing synchronous CEA/CABG (4.6%; 95% CI, 4.1-5.2). Reverse staged procedures (CABG followed by CEA) were associated with the highest risk for ipsilateral stroke (5.8%) and any stroke (6.3%). Perioperative MI was lowest after the reverse staged procedure (0.9%) and highest in patients undergoing staged CEA-CABG (6.5%). The risk for death with or without any stroke was highest in patients undergoing synchronous CEA-CABG (8.7%) and lowest after staged CEA/CABG (6.1%). The risk of death/stroke or MI was 11.5% after synchronous procedures versus 10.2% after staged CEA and then CABG. In a related paper they found that the risk for death/stroke appeared to significantly diminish in studies published after 1993.[254] Patients with severe bilateral carotid disease or symptomatic stenoses were significantly more likely to suffer death or stroke (or both).[255] The communitywide outcomes of combined CEA/CABG in the Medicare population are inferior to those reported in many single-institution reviews.[256]

More recently, off-pump coronary artery bypass (OPCAB) has been introduced as an alternative method for coronary bypass, and outstanding results have been published on combined CEA/OPCAB, with combined stroke and mortality rates of 0% to 1.2%.[257,258]

In our institution, we prefer to stage CEA followed in 1 or 2 days with CABG in patients with significant carotid disease. These are typically patients with symptomatic significant ICA stenoses, or those with bilateral severe asymptomatic ICA stenoses. A combined CEA/CABG is reserved for patients with significant carotid artery disease and severe three-vessel or left main coronary disease and/or critical aortic stenosis.

Carotid Artery Stenting Before Coronary Artery Bypass Grafting

To date, the results of CAS followed by CBG have been conflicting, with some series demonstrating this strategy to be safer than combined CEA/CABG but other reports do not confirm this.[259-262]

Advanced Age

While the prevalence of stroke increases exponentially with advancing age, patients 80 years and older were excluded from NASCET and ACAS; therefore, it has been assumed that advanced age represents a high-risk factor for CEA and that such patients might thus be optimally treated by CAS. However, compelling evidence accumulated over the past 2 decades has confirmed the safety of CEA in elderly individuals. In a recent meta-analysis that included more than 20 institutional series and over 3000 elderly patients with a minimum age of 75 or 80 who underwent CEA, the perioperative stroke rate was 2.2% and the mortality rate was 1.5%.[263] In a population-based analysis of CEA in the state of Maryland from 1990 through 1995, we reported that the outcome in octogenarians was the same as in younger patient cohorts (perioperative stroke and death rate of 2.6%).[264] Considerable experience reported to date has confirmed the safety of CEA among the elderly and also excellent long-term survival and clinical results.[169,265-267]

Gender

There are conflicting reports with respect to the impact of gender on the outcome of CEA. In ACAS, for example, women received less benefit in terms of stroke prevention than did men, as they experienced more strokes in both the perioperative period and long-term follow-up.[11] However, other studies have shown no difference in outcomes between men and women.[268-270]

Race

There are conflicting results on the impact of race on CEA outcomes. In a national Medicare database analysis, between 1994 and 1999 African American patients experienced crude mortality rates higher than white patients in seven of the eight procedures, including CEA. The study suggests multiple reasons for this finding, including more frequent emergency operations and residence in low-income areas. Additionally, African Americans were more likely to receive care in lower volume hospitals and hospitals with overall higher mortality.[271] Likewise, a 2002 meta-analysis demonstrated a 40% greater likelihood of short-term death after CEA for African Americans than for whites undergoing CEA.[272] In our review of the Maryland state database, African American patients undergoing CEA had an increased incidence of in-hospital stroke, longer hospital stays, and higher hospital charges. This research noted that African American patients were more likely to undergo CEA in low-volume hospitals and were less likely to be treated by higher volume surgeons.[273]

Conversely, Horner and colleagues' review of the National Surgical Quality Improvement Project (NSQIP) data revealed similarly low stroke and death rates between African American and white patients in the VA system. In patients with TIA, though, Hispanic males experienced significantly worse outcomes in terms of stroke and death when compared with white patients.[274] An institutional review from Henry Ford Hospital revealed similar stroke and death rates between African American and white patients, as well as acceptable protection from ipsilateral stroke without racial variation. However, African American patients in this study did have a higher incidence of all strokes in the long term than did white cohorts.[275] In a study of the NIS from 2005 to 2008 including 347,450 CEAs, Hispanics were found to have the greatest risk of operative mortality ($P < .001$) and African Americans were found to have the highest stroke rate ($P = .02$). However, on multivariable analysis, Hispanic ethnicity remained an independent risk factor

for mortality after CEA whereas the increased risk of perioperative stroke in black patients was no longer significant.[183]

Symptomatic Disease With Less Than 50% Carotid Stenosis

There is no Level I evidence to support CEA for patients with less than 50% ICA stenoses. However, a growing body of evidence suggests that plaque morphology is an important predictor of subsequent neurologic events. For example, intraplaque hemorrhage has been shown to be associated with a high rate of recurrent ischemic events.[276,277] In one series of 25 patients with symptomatic low-grade carotid artery stenosis with intraplaque hemorrhage, there were 30 recurrent ischemic events (46% per patient per year).[276] At our institution, we have utilized contrast-enhanced duplex and contrast-enhanced MRA to identify plaque instability, including hemorrhage and ulceration, among symptomatic patients with less than 50% ICA stenoses, and have performed CEA with complete long-term symptomatic resolution (Fig. 91.11).[278] In addition, recent reports have identified carotid webs as another risk factor for ischemic stroke among patients with hemodynamically insignificant ICA stenoses. A carotid web is a thin membrane of tissue that typically extends from the posterior wall of the ICA into the lumen, which can be a nidus for thrombus formation and cerebral emboli, and is best seen on CTA imaging.[279-281]

External Carotid Endarterectomy

In the setting of ICA occlusion, atherosclerotic disease of the ipsilateral ECA can result in embolic stroke through the collateral pathways that exist between the external carotid and intracranial circulation.[282] There have been several small series of patients treated successfully for symptomatic ECA stenoses with ECA endarterectomy.[283-290] One large series the perioperative stroke rate varied from 0% to 10%[289,291] but was as high as 33% to 38% in patients with contralateral disease and previous stroke, or if ECA endarterectomy was combined with adjunctive procedures. On long-term follow-up with angiography or duplex ultrasonography, Rush and coworkers found that two thirds of ECAs closed primarily occluded or developed significant stenoses versus none with patch angioplasty.[292] In a review of 195 ECA endarterectomies and 23 ECA bypasses, the resolution of symptoms was seen in 83% of patients, with another 7% showing marked improvement. The perioperative mortality rate was 3%, mostly secondary to stroke, and the overall neurologic complication rate was 5%. A diseased contralateral carotid artery was associated with higher neurologic morbidity, whereas disease in the vertebral arteries had no impact on outcome. The best results were obtained when surgery was performed to relieve specific hemispheric or retinal symptoms as opposed to nonspecific neurologic complaints or previous stroke.[292] However, there is no evidence that ECA endarterectomy should be performed prophylactically for asymptomatic disease.

Impact of Radiation Therapy

Cervical irradiation is a known risk factor for carotid artery stenosis and cerebrovascular ischemic events. Carotid artery lesions secondary to irradiation therapy tend to occur at unusual locations, such as in the proximal or mid-common carotid artery. In addition to a predisposition to significant atherosclerotic disease, the effects of radiation include a fibrotic reaction and obliteration of normal tissue planes. This makes dissection and mobilization of the carotid vessels and identification of the cranial nerves more difficult. Although development of an appropriate endarterectomy plane may be more difficult than

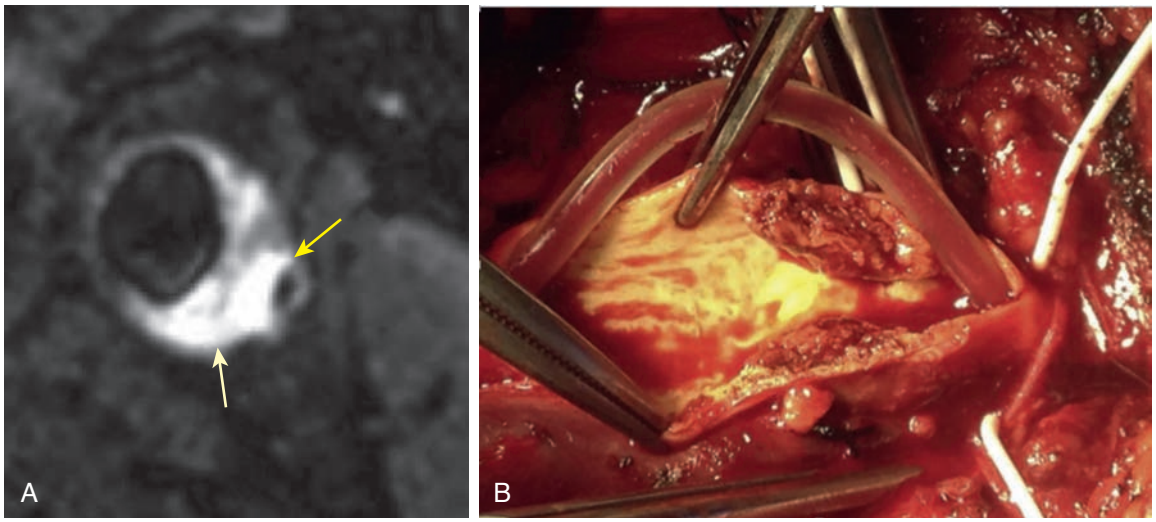

Figure 91.11 Axial reconstruction of three-dimensional high-resolution blood and calcium gradient-echo sequence of magnetic resonance imaging/magnetic resonance angiography in a 72-year-old man with a history of three right hemispheric cerebral vascular accidents. A routine duplex scan revealed a less than 50% right internal carotid artery stenosis but a contrast-enhanced duplex revealed hemorrhagic plaque. (A) The *dark yellow arrow* indicates calcification and *light yellow arrow* indicates hemorrhagic plaque. (B) The operative photograph demonstrates hemorrhagic plaque.

usual, in most cases conventional endarterectomy can be successfully carried out. In the uncommon case where conventional endarterectomy cannot be performed, the obstruction may be relieved simply by placement of a patch, or vessel resection and placement of an interposition graft with placement of the anastomoses outside of the radiated field. There also may be more potential for impairing wound healing in the patient with prior irradiation therapy. In the patient with particularly abnormal tissues, or if there is wound breakdown, closure with a muscle flap is an excellent option.

The reported clinical experience with CEA in this clinical scenario has been excellent, and appears superior to the results of CAS. Lesèche and associates published a series 30 cases from France, and also summarized 77 cases published by other authors.[293] The overall stroke and mortality rate for this entire cohort was 2%. Restenosis and recurrent stroke were not commonly encountered. The mean interval between cervical irradiation and CEA was 10 years. Bypasses from either the CCA or the subclavian artery were required to reconstruct the carotid artery in one third of their cases. In another early series including 26 cases, bypasses were rarely performed, although some patients required tissue flaps.[294] The mean time interval between irradiation and CEA in that series was even longer: 17 years. In a more recent series of 24 patients who underwent 27 carotid revascularization procedures, including 23 vein and 3 PTFE interposition bypass grafts, and one eversion endarterectomy from 1996 to 2004, there were no perioperative strokes or deaths, and only three patients experienced transient cranial nerve dysfunction.[295] Follow-up ranged from 6 to 120 months (mean, 28). There were 11 deaths—all unrelated to cerebrovascular disease. There were three (4.2%) strokes within the first 3 months of follow-up, with no additional strokes thereafter. A meta-analysis including 172 patients who underwent CEA and 361 who underwent CAS following neck irradiation, the periprocedural rates of stroke and TIA were 3.5% and 3.9% for CEA and CAS ($P = .77$), respectively. The rate of cranial nerve injury was 9.2% following CEA. The long-term rates of ≥50% restenosis or occlusion were 5.4 per 100 person-years and 2.8 per 100 person-years ($P = .003$) following CAS and CEA, respectively.[296] The long-term clinical outcome was also superior following CEA. Specifically, the rate of late strokes and TIAs was 4.9 per 100 person-years following CAS and 2.8 per 100 person-years following CEA ($P = .014$).

Hospital/Surgeon Volume

In contemporary practice, many have advocated regionalization of specialized care or high-risk procedures (or both) to higher volume centers and high-volume surgeons. A meta-analysis published in 2007 suggests that the CEA stroke and death rate is significantly lower in high-volume centers, with a critical volume threshold of 79 CEAs per year. Interestingly, this study demonstrated that patients undergoing operations performed by lower volume surgeons operating in higher volume centers also experienced lower stroke and death rates, thus suggesting that the hospital infrastructure and available resources rather than surgeon experience were more important in lowering complication rates.[297] Other population-based studies have shown similar trends of mortality being inversely proportional to volume. In California between 1982 and 1994, mortality rates decreased for CEA, and higher hospital volume was found to be an important determinant of outcome.[298]

Conversely, a retrospective review of CEAs performed in Oregon over a 2-year period examined the outcomes between two low-volume institutions (total of 156 CEAs) and one high-volume institution (404 CEAs). There was no significant difference in 30-day stroke and death rates between the low- and high-volume centers.[299] This was observed despite the fact that the low-volume centers had significantly older patients, more smokers, and fewer asymptomatic patients. This paper makes a legitimate point that an individual surgeon in a low-volume institution may perform more individual high-risk procedures than another individual surgeon at a higher volume center.

Ultimately, it is surgeons and not hospitals that perform surgery. Furthermore, the ideal break point to define a suitably "high-volume" caseload remains to be defined. Data published on CEA outcomes from institutional series, as well as large hospital and government databases, much of which has been summarized in this chapter, would suggest that vascular surgeons both individually and as a group have been tremendously successful in achieving published guidelines of a perioperative CVA/death rate ≤3% for asymptomatic and ≤6% for symptomatic CEA cases.[299] Therefore, CEA continues to be an effective treatment of carotid disease more than 60 years after it was introduced, and it is the treatment with which all future therapies must be compared.

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92 CHAPTER

Cerebrovascular Disease: Carotid Artery Stenting

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BACKGROUND

The concept of using endovascular therapy for the treatment of carotid artery stenosis was first proposed in 1977 by Mathias, who reported successful results of carotid artery angioplasty using adapted peripheral arterial angioplasty technology.[1,2] Balloon-expandable stents for the treatment of cerebrovascular disease were introduced 10 years later, when Marks et al. reported the successful deployment of carotid artery stents in two patients with aneurysms and stenosis of the distal cervical carotid artery.[3]

Abstract

With the increasing interest in carotid artery stenting (CAS) as a means to treat carotid artery stenosis, a number of randomized controlled trials (RCTs) comparing outcomes after CAS versus the "gold standard" of carotid endarterectomy (CEA) were designed. Herein, we provide an overview of the major RCTs investigating CAS. We also provide a summary of the current societal recommendations for CAS versus CEA, and summarize the major patient characteristics that must be considered when planning the procedure. Finally, we discuss major technical considerations for optimizing result, including use of an embolic protection device, access considerations, and perioperative medications.

Keywords

carotid artery stenting
carotid artery stenosis
cerebrovascular disease
embolic protection

This experience was subsequently adapted for the use of treating high-grade symptomatic carotid artery stenosis. However, the initial enthusiasm with the procedure was dampened by high perioperative stroke rates ranging from 6% to 9%.[4–8]

In 1990 Theron et al. published their technique of performing carotid angioplasty using cerebral protection to prevent brain embolism.[9] This led to the development of embolic protection devices (EPDs), which drastically reduced stroke rates and revitalized interest in the use of endovascular therapy for carotid artery stenosis.

LANDMARK CLINICAL TRIALS

With the increasing interest in carotid artery stenting (CAS) as a means to treat carotid artery stenosis, a number of randomized controlled trials (RCTs) comparing outcomes after CAS versus the "gold standard" of carotid endarterectomy (CEA) were designed (Table 92.1).

SAPPHIRE

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) is a multicenter, randomized, noninferiority US trial designed to compare CAS versus CEA for patients with greater than or equal to 50% asymptomatic or greater than or equal to 80% asymptomatic carotid artery stenosis, based on angiography.[10,11] Nearly all CAS patients (97%) underwent stenting with an EPD. The primary endpoint was a composite of death, stroke, or myocardial infarction (MI) within 30 days after the intervention or death

TABLE 92.1 Summary of Major Completed Randomized Controlled Trials Comparing Carotid Artery Stenting vs. Carotid Endarterectomy

Trial	Publication Date	Sample Size	Carotid Stenosis Criteria	Study Design	EDP Use for CAS	Primary Outcome	Results CAS vs. CEA	Conclusion
SAPPHIRE[10,11]	2004, 2008	334	≥50% symptomatic or ≥80% asymptomatic	Noninferiority RCT United States	97%	Composite death, stroke, MI within 30 days or ipsilateral stroke up to 1 year	1 year: 12.2% vs. 20.1% 3 years: 24.6% CAS vs. 26.9%	CAS noninferior to CEA
EVA-3S[7,12]	2006, 2008	527	>60% symptomatic carotid artery stenosis	Noninferiority RCT Europe	92%	Any stroke or death within 30 days	30 days: 9.6% vs. 3.9% 6 months: 11.7% vs. 6.1% 4 years: 11.1% vs. 6.2%	Worse periprocedrual stroke/death outcomes with CAS
SPACE[8,13]	2006, 2008	1,200	≥70% symptomatic carotid stenosis	Noninferiority RCT Europe	27%	Ipsilateral stroke or death within 30 days	30 days: 6.8% vs. 6.3% 2 years: 9.5% vs. 8.8%	Higher risk of periprocedural adverse events with CAS
ICSS[6,14]	2010, 2015	1,713	>50% symptomatic carotid artery stenosis	Noninferiority RCT Europe	72%	3-year fatal or disabling stroke in any territory	120 days: 8.5% vs. 5.2% 4.2 years: 6.4% vs. 6.5%	Long-term risk of disabling stroke is similar for CAS and CEA
CREST[15,16]	2010, 2016	2,502	Symptomatic or asymptomatic carotid artery stenosis ≥70% (ultrasound) or symptomatic ≥50% (angiography)	Noninferiority RCT North America	96%	Composite stroke, MI, or death within 30 days or ipsilateral stroke within 4 years	4 years: 7.2% vs. 6.8% 10 years: 11.8% vs. 9.9%	No significant long-term differences for CAS vs. CEA in composite endpoint or risk of stroke
ACT-I[19]	2016	1,453	>80% asymptomatic carotid stenosis	Noninferiority RCT United States	100%	Composite of death, stroke, or MI within 30 days or ipsilateral stroke within 1 year	30 days: 2.9% vs. 1.7% 1 year: 3.8% vs. 3.4%	CAS not inferior to CEA for

CAS/CEA, carotid artery stenting (CAS)/carotid endarterectomy (CEA); *CREST*, Carotid Revascularization Endarterectomy Versus Stenting Trial; *ICSS*, International Carotid Stenting Study (ICSS); *MI*, myocardial infarction; *RCT*, randomized controlled trials; *SAPPHIRE*, Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy; *SPACE*, The Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy.

or ipsilateral stroke between 31 days and 1 year. SAPPHIRE enrolled 334 patients total (167 in each group), and demonstrated that CAS was noninferior to CEA both at 1 year (12.2% CAS vs. 20.1% CEA; $P = .004$)[10] and 3 years (24.6% CAS vs. 26.9% CEA; $P = .71$)[11] postoperatively.

EVA-3S

The Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis (EVA-3S) trial is a multicenter, randomized, noninferiority French trial designed to compare CAS versus CEA for patients with greater than 60% symptomatic carotid artery stenosis, as diagnosed by either angiography or both duplex scanning and magnetic resonance angiography.[7,12] EPDs were used in 92% of stent patients. The primary endpoint was any stroke or death within 30 days of the procedure. EVA-3S enrolled 527 patients total (265 CAS and 262 CEA) but was stopped prematurely due to significantly worse stroke/death outcomes with CAS at both 30 days (9.6% CAS vs. 3.9% CEA; $P = .01$) and 6 months (11.7% CAS vs. 6.1% CEA; $P = .02$).[7] Of note, outcomes with CAS were much worse among patients without cerebral protection (7.9% with EDP vs. 25% without EDP; $P = .03$).[7] Follow-up out to 4 years demonstrated worse outcomes with CAS (11.1% CAS vs. 6.2% CEA; $P = .03$), but this was largely attributable to higher periprocedural stroke/death.[12] Based on this data, the authors concluded that CAS might be a reasonable alternative to CEA in patients with symptomatic carotid artery stenosis if the periprocedural risk of stenting can be minimized.[12] This trial was heavily criticized for unbalanced training requirements between both groups; although the vascular surgeon had to have performed at least 25 endarterectomies in the year before enrollment, the interventional physicians only had to have performed 12 carotid-stenting procedures or 35 supraaortic trunk stenting procedures, of which 5 were in the carotid artery.

SPACE

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial is a German multicenter, randomized, noninferiority trial designed to compare CAS versus CEA among patients with greater than or equal to 70% symptomatic carotid stenosis on duplex ultrasound.[8,13] In this trial, EDP was only used in 27% patients who underwent stenting. The primary endpoint was ipsilateral stroke or death between randomization and 30 days after treatment. SPACE enrolled 1200 patients total (605 CAS and 595 CEA) but was stopped prematurely due to cost issues and futility. The 30-day rate of stroke or death was 6.8% for CAS versus 6.3% for CEA ($P = .09$), which failed to meet criterion for noninferiority.[8] There were no differences in stroke rates comparing patients who underwent CAS with versus without EDP (7% in both groups at 30 days). After 2 years of follow-up, there were no significant differences in cumulative 30-day stroke/death and 2-year ipsilateral stroke between treatment groups (9.5% CAS vs. 8.8% CEA; $P = .62$), although recurrent stenosis greater than or equal to 70% was more common in the CAS group (10.7% CAS vs. 4.6% CEA; $P < .001$).[13] Similar to EVA-3S, the authors concluded that CAS could not be proven to be noninferior to CEA due to concerns over a higher risk of periprocedural adverse events with CAS.

ICSS

The International Carotid Stenting Study (ICSS) is a multicenter, randomized, British trial designed to compare CAS versus CEA for patients with greater than 50% symptomatic carotid artery stenosis based on angiography.[6,14] EPDs were used in 72% of cases. The primary endpoint was the 3-year rate of fatal or disabling stroke in any territory, but the authors also published an interim safety analysis comparing the 120-day rate of stroke, death, or procedural MI rate between groups. ICSS enrolled 1713 patients (855 CAS and 858 CEA). At 120 days, adverse outcomes were higher in the CAS group (8.5% CAS vs. 5.2% CEA; $P = .006$).[6] However, after a median of 4.2 years of follow-up, the risk of fatal or disabling stroke was similar between groups (6.4% CAS vs. 6.5% CEA; $P = .77$), leading the authors to conclude that the long-term functional outcomes and risk of disabling stroke are similar for CAS and CEA.[14]

CREST

The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) is the largest multicenter, randomized trial designed to compare outcomes for CAS versus CEA to date.[15,16] It is a North American trial sponsored by the National Institutes of Health and an industry partner that compared CAS versus CEA for patients with carotid artery stenosis greater than or equal to 70% for asymptomatic or asymptomatic patients (based on ultrasound criteria) or greater than or equal to 50% for symptomatic patients (based on angiographic North American Symptomatic Carotid Endarterectomy Trial criteria). The primary composite endpoint was stroke, MI, or death from any cause during the periprocedural period up to 30 days or any ipsilateral stroke within 4 years after randomization. EPDs were used in 96% of patients, and all surgeons and interventionalists involved in the trial were required to meet robust training and experience requirements.[17] CREST enrolled 2502 patients (1262 CAS and 1240 CEA). At a median follow-up of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary endpoint between groups (7.2% CAS vs. 6.8% CEA; $P = .51$).[15] However, CAS had a higher risk of periprocedural stroke (4.1% CAS vs. 2.3% CEA; $P = .01$), whereas CEA had a higher risk of periprocedural MI (1.1% CAS vs. 2.3% CEA; $P = .03$). Notably, the periprocedural risk of stroke/death was only significantly higher after CAS for symptomatic patients (6.0% CAS vs. 3.2% CEA; $P = .02$). The risk of restenosis following CAS versus CEA at 2 years was similar between groups (6.0% CAS vs. 6.3% CEA; $P = .58$).[18] CREST has the longest follow-up period of all CAS RCTs. After 10 years of follow-up, there were no significant differences between CAS versus CEA in either the composite primary endpoint (11.8% CAS vs. 9.9% CEA) or long-term ipsilateral stroke (6.9% CAS vs. 5.6% CEA).[16]

ACT-I

The Carotid Angioplasty and Stenting Versus Endarterectomy in Asymptomatic Subjects Who Are at Standard Risk for Carotid Endarterectomy With Significant Extracranial Carotid Stenotic Disease (ACT-I) trial is a randomized noninferiority trial designed to compare outcomes after CAS (with EDP) versus CEA among patients with severe asymptomatic carotid stenosis, were younger than 80 years, and were not considered to be at high risk for surgical complications.[19] The primary endpoint was a composite of death, stroke, or MI within 30 days or ipsilateral stroke within 1 year after the procedure. ACT-I was terminated early due to slow enrollment, with 1453 of a planned 1658 participants enrolled (88%). The rate of stroke or death within 30 days was 2.9% in the CAS group and 1.7% in the CEA group. The primary outcome was not significantly different between groups (3.8% CAS vs. 3.4% CEA; $P = .01$ for noninferiority). After 5 years the cumulative rate of stroke-free survival was 93.1% in the CAS group and 94.7% in the CEA group ($P = .44$). Based on these findings, the authors concluded that stenting was noninferior to endarterectomy for asymptomatic patients with severe carotid stenosis who were not at high risk for surgical complications.

CURRENT GUIDELINES

Because of the perceived higher periprocedural risk of stroke with CAS compared with CEA, based on results from the previously described RCTs, the current guidelines for use of CAS for treating carotid artery stenosis are limited. A consensus supports the use of CAS in symptomatic patients with high-grade stenoses who are deemed too high medical risk to undergo open surgery. There are also some data to support the use of CAS in a lower medical risk population of patients with higher anatomic risk factors for CEA such as restenosis or neck radiation.[20] The use for CAS for patients who are low or moderate risk without prior neck radiation or surgery, or those who have asymptomatic carotid artery disease, is less well supported. Many cite concerns about the long-term viability of CAS as a reason to use this technique judiciously. As such, societal guidelines around the appropriate use of CAS are cautious.

Symptomatic Carotid Artery Stenosis

Current guidelines are fairly consistent regarding the use of CAS in patients with symptomatic carotid artery stenosis. Based on available RCT data, in 2011 the American College of Cardiology/American Heart Association (ACC/AHA),[21] the Society for Vascular Surgery (SVS),[22] and the European Society of Cardiology (ESC)[23] each published guidelines for the use of CAS (Table 92.2). Each of these guidelines calls for CEA over CAS except in symptomatic patients who were deemed to be surgically unsuitable for CEA. In these cases, CAS is recommended for use only by experienced operators with a documented risk of death or stroke less than 6%.[24]

Similarly, the Centers for Medicare and Medicaid Services (CMS) support the use of CAS with embolic protection for patients with symptomatic carotid artery stenosis greater than or equal to 70% who are deemed to be high risk for CEA or patients with symptomatic carotid artery stenosis between 50% and 70% who are enrolled in CMS-approved clinical trial.[25] CMS also published a list of minimum standards pertaining to the evaluation, procedure, and follow-up of patients treated by CAS that are now required for an institution to be deemed eligible to perform the procedure.[25]

Asymptomatic Carotid Artery Stenosis

The use of CAS for patients with asymptomatic carotid artery stenosis is less clear (Table 92.3). Based on the ACT-I trial, it appears to be safe at least among patients with severe carotid artery stenosis.[19] Currently, ACC/AHA guidelines support the use of CAS in select patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by duplex ultrasound), but note that the evidence supporting CAS over best medical therapy (BMT) is not convincing.[21] The SVS also notes that there are insufficient data for the use of CAS over BMT in patients with asymptomatic carotid artery stenosis between 70% and 99% but does recognize that in experienced hands the risk of stroke with CAS may be equivalent to that of CEA.[22] In contrast, the ECS endorses the use of CAS as an alternative to CEA as long as the procedure is performed in a high-volume center with a documented death or stroke rate less than 3%.[23] CMS recognizes CAS only for patients with asymptomatic carotid artery stenosis greater than or equal to 80% who are enrolled in a CMS-approved clinical trial.[25]

PATIENT SELECTION

Based on the guidelines noted previously, it is clear that CAS is currently supported only for use in a group of highly select patients meeting appropriate diagnostic criteria. According to CMS criteria (Table 92.4),[25] all patients must have a diagnosis of high-grade carotid artery stenosis based on duplex ultrasound or carotid artery angiography; if the diagnosis is based on duplex findings, the degree of stenosis must be confirmed via angiography at the time of the procedure prior to stenting. Patients must also be symptomatic, as determined by a history of transient ischemic attacks with distinct focal neurologic dysfunction last <24 hours, a prior cerebrovascular incident resulting in a nondisabling stroke, and/or amaurosis fugax; and at high risk for open surgical intervention, as determined by the presence of either a significant medical comorbidity (see Table 92.4) or prior neck radiation therapy or a previous CEA. Other considerations when selecting a patient who might be appropriate for CAS are as follows.

Age

Given the less invasive nature of CAS over CEA, the use of carotid stents for treating elderly patients with carotid artery stenosis was initially considered one of the main indications of the procedure. Unexpectedly, data from a multitude of RCTs on CAS demonstrated that the opposite was true; the risk of

TABLE 92.2 Recommendations of the 2011 Carotid Guidelines for Patients With Symptomatic Carotid Artery Stenosis

Society	Recommendation	Strength
ACC/AHA[21]	CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6%.	Class I; level of evidence B
	Among patients with symptomatic severe stenosis (≥70%) in whom the stenosis is difficult to access surgically, medical conditions are present that greatly increase the risk for surgery, or when other specific circumstances exist, such as radiation-induced stenosis or restenosis after CEA, CAS may be considered.	Class IIb; level of evidence B
	CAS in the above setting is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4%–6%, similar to those observed in trials of CEA and CAS.	Class IIa; level of evidence B
SVS[22]	In most patients with carotid stenosis who are candidates for intervention, CEA is preferred to CAS for reduction of all-cause and periprocedural death.	Grade I; level of evidence B
	CAS is preferred over CEA in symptomatic patients with ≥50% stenosis and tracheal stoma, situations where local tissues are scarred and fibrotic from prior ipsilateral surgery or external beam radiotherapy, prior cranial nerve injury, and lesions that extend proximal to the clavicle or distal to the C2 vertebral body.	Grade II; level of evidence B
	CAS is preferred over CEA in symptomatic patients with ≥50% stenosis and severe uncorrectable coronary artery disease, congestive heart failure, or chronic obstructive pulmonary disease.	Grade II; level of evidence C
ESC[23]	In patients with symptomatic 70%-99% stenosis of the internal carotid artery, CEA is recommended for the prevention of recurrent stroke.	Class I; level of evidence A
	In symptomatic patients at high surgical risk requiring revascularization, CAS should be considered as an alternative to CEA.	Class IIa; level of evidence B
	In symptomatic patients requiring carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centers with documented death or stroke rate <6%.	Class IIb; level of evidence B

ACC/AHA, American College of Cardiology/American Heart Association; *CAS*, carotid artery stenting; *CEA*, carotid endarterectomy; *ESC*, European Society of Cardiology; *SVS*, Society for Vascular Surgery.
Adapted from Paraskevas KI, Mikhailidis DP, Veith FJ. Comparison of the five 2011 guidelines for the treatment of carotid stenosis. *J Vasc Surg*. 2012;55(5): 1504-1508.

TABLE 92.3 Recommendations of the 2011 Carotid Guidelines for Patients With Asymptomatic Carotid Artery Stenosis

Society	Recommendation	Strength
ACC/AHA[21]	Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.	Class IIb; level of evidence B
SVS[22]	Neurologically asymptomatic patients with ≥60% diameter stenosis should be considered for CEA for reduction of long-term risk of stroke, provided the patient has a 3- to 5-year life expectancy and perioperative stroke/death rates can be ≤3%.	Class I; level of evidence A
	There are insufficient data to recommend CAS as primary therapy for neurologically asymptomatic patients with 70%–99% diameter stenosis. In properly selected asymptomatic patients, CAS is equivalent to CEA in the hands of experienced interventionalists with a combined stroke and death rate <3%.	Grade II; level of evidence B
ESC[23]	In asymptomatic patients with carotid artery stenosis ≥60%, CEA should be considered as long as the perioperative stroke and death rate for procedures performed by the surgical team is <3% and the patient's life expectancy exceeds 5 years.	Class IIa; level of evidence A
	In asymptomatic patients with an indication for carotid revascularization, CAS may be considered as an alternative to CEA in high-volume centers with documented death or stroke rate <3%.	Class IIa; level of evidence B

ACC/AHA, American College of Cardiology/American Heart Association; *CAS*, carotid artery stenting; *CEA*, carotid endarterectomy; *ESC*, European Society of Cardiology; *SVS*, Society for Vascular Surgery.
Adapted from Paraskevas KI, Mikhailidis DP, Veith FJ. Comparison of the five 2011 guidelines for the treatment of carotid stenosis. *J Vasc Surg*. 2012;55(5): 1504-1508.

TABLE 92.4 Medicare Decision Summary for Carotid Artery Stenting[25]

CAS with embolic protection is reasonable and necessary for the following:
1. Patients who are at high risk for CEA and who also have symptomatic carotid artery stenosis ≥70%. Coverage is limited to procedures performed using US Food and Drug Administration (FDA)-approved carotid artery stenting systems and embolic protection devices.
2. Patients who are at high risk for CEA and have symptomatic carotid artery stenosis between 50% and 70%, in accordance with the Category B IDE clinical trials regulation, as a routine cost under the clinical trials policy, or in accordance with the National Coverage Determination on CAS post approval studies.
3. Patients who are at high risk for CEA and have asymptomatic carotid artery stenosis ≥80%, in accordance with the Category B IDE clinical trials regulation, as a routine cost under the clinical trials policy, or in accordance with the National Coverage Determination on CAS post approval studies.
Patients who are at high risk for CEA include those with any of the following:
Congestive heart failure class III/IV
Left ventricular ejection fraction <30%
Unstable angina
Contralateral carotid occlusion
Recent myocardial infarction
Previous CEA with recurrent stenosis
Prior radiation treatment to the neck
Other conditions that were used to determine patients at high risk for CEA in the prior carotid artery stenting trials and studies

CAS, Carotid artery stenting; *CEA*, carotid endarterectomy; *IDE*, Investigational Device Exemption.

an adverse event with CAS was significantly higher than that with CEA in older patients.[26-30]

In a post hoc analysis of data from the SPACE trial, ipsilateral stroke or death after CAS occurred in 2.7% of patients 68 years or younger versus 10.8% in patients older than 68 years, whereas outcomes after CEA were not significantly different.[26] Similarly, an analysis of CREST data examining the treatment-specific impact of age demonstrated the risk of adverse events (i.e., stroke, MI, or death) increased by 1.77 times per 10-year increment increase in age after CAS but was stable for CEA.[27] These findings are confirmed by a meta-analysis of 4754 patients enrolled in CREST and the Carotid Stenting Trialists' Collaboration trials, which demonstrated a significant pattern of increased periprocedural risk with increasing age in patients assigned to CAS versus CEA starting at 70 years and older ($P < .001$).[31]

Population database analyses examining the effects of age on adverse events after CAS and CEA report similar findings. Data from the SVS Vascular Registry demonstrated inferior 30-day composite outcomes in patients 65 years or older undergoing CAS, regardless of symptomatic status.[29] Data from the Nationwide Inpatient Sample demonstrated worse stroke rates and cardiac complications among patients 70 years or older who underwent CAS.[28]

A Cochrane Database Systemic Review from 2012 including 16 trials involving 7572 patients supported these findings; the overall risk of perioperative death or any stroke was significantly higher for CAS versus CEA among patients 70 years or older (OR 2.20, 95% confidence interval [CI] 1.47 to 3.29) but not significantly different for patients younger than 70 years (OR 1.16, 95% CI 0.80).[30] Taken together, these data suggest that CAS should be reserved for younger patients,[29] the age of which varies between 65 and 70 years, depending on the data source used.

Sex

There are well-described differences in outcomes between women versus men in both the cardiovascular and CEA literature.[32-34] However, the sex-specific effects on outcomes after CAS are less clear. A secondary analysis of data from the CREST trial suggested that the perioperative risk of an adverse event (i.e. stroke, MI, or death) was higher in women who underwent CAS versus those who underwent CEA (6.8% vs. 3.8%) but similar among men regardless of revascularization approach (4.3% vs. 4.9%).[33] These findings were largely attributable to an increased stroke rate in females underdoing CAS (5.5% vs. 2.2%).[33] In contrast, a meta-analysis of patients enrolled in the European Carotid Stenting Trialists Collaboration, which includes the EVA-3S, SPACE, and ICSS trials, demonstrated equivalent outcomes with CAS and CEA for both males and females.[35] A subsequent meta-analysis using data from both CREST and CSTS in combination with data from the CAVATAS trial supported the latter conclusion that sex had no real effect on the risks of either treatment.[36]

Interestingly, observational data evaluating the embolic debris captured in EPDs after CAS suggested that symptomatic women have a greater mean debris particle size compared with asymptomatic women, whereas the difference in debris size after carotid stenting is not statistically different between symptomatic versus asymptomatic men.[37] Accordingly, CREST data suggest that the main difference in stroke/death rates with CAS versus CEA occurred among symptomatic women (7.5% vs. 2.7% in CAS vs. CEA, respectively).[33] Although data on this topic from other RCTs are not convincingly worse for women compared with men, it should be noted that symptomatic women may have a different plaque morphology with greater embolic potential than their asymptomatic counterparts.

Hostile Neck

Patients with prior neck surgery or radiation should be considered for CAS to reduce risks of cranial nerve injury. Based on a systemic review of available literature through 2012, Kasivisvanathan et al. reported that CAS is technically feasible in postradiotherapy carotid stenosis and has a similar safety profile to that of nonirradiated necks when performed at a high-volume center.[38] Furthermore, in a meta-analysis of 27 articles reporting data on 533 patients with prior cervical irradiation undergoing carotid revascularization for carotid artery stenosis, Fokkema et al. demonstrated that the perioperative

risk of any cerebrovascular adverse event was similar for CAS versus CEA (3.9% vs. 3.5%) but the risk of cranial nerve injury was substantially higher after CEA (9.2% vs. 0%).[39] Societal guidelines now include the presence of neck scarring and fibrosis from prior ipsilateral surgery such as radical neck dissection or prior CEA or external beam radiotherapy as one indication for considering CAS over CEA.[21-23]

Combined Carotid and Coronary Artery Disease

Due to the systemic nature of atherosclerotic disease, the presence of combined significant carotid artery stenosis and coronary artery disease is common. CAS has been considered as a noninvasive option by which to treat patients with carotid artery stenosis just prior to coronary artery bypass grafting (CABG). In 2009 Naylor et al. published a meta-analysis of 11 studies reporting data on (predominantly asymptomatic) patients undergoing CAS plus CABG procedures and demonstrated a 30-day death/stroke/MI rate of 9.4%.[40] This risk was not significantly different for patients undergoing CAS within 48 hours of CABG versus those where CABG was delayed.

More recently Velissaris et al. reported results from a prospective nonrandomized study evaluating outcomes among 90 consecutive patients with carotid stenosis (≥60% in symptomatic patients and ≥70% in asymptomatic patients) who were treated using CAS under local anesthesia immediately before CABG.[41] In this series the 30-day death/stroke rate was only 2.2%. Similarly, Barrera et al. reported no deaths, strokes, or MI among 15 consecutive patients with severe asymptomatic carotid artery disease in need of urgent coronary revascularization who underwent synchronous CAS and urgent CABG.[42] Notably, EPDs were used in both of these two series cases.

Based on these data, it appears that CAS is at least equivalent if not safer than CEA for patients in need of combined carotid and coronary revascularization. CAS offers the benefit of being less invasive, to the point that it can be performed immediately prior to open heart surgery under local sedation, assuming that appropriate cerebrovascular protection is used. One question that remains is how to best manage patients' postoperative antiplatelet therapy, which is essential to preventing in-stent thrombosis and stroke (see section "Postoperative Medications: Antiplatelet Therapy," later) but may put patients at higher risk of intraoperative and/or postoperative hemorrhage following cardiac surgery.

Restenosis

Based on data from the CREST Trial, approximately 6% of patients undergoing CAS or CEA will demonstrate restenosis (i.e., reduction in diameter of the carotid artery by ≥70%) by 2 years postoperatively (see section "Complications: Restenosis," later).[18] Restenosis is associated with increased risk of stroke similar to native carotid artery stenosis. Preliminary data from the Vascular Quality Initiative suggest that CAS after prior CEA or CAS is safe, with an estimated 30-day risk of stroke of 1.4% (Arhuidese et al., in press). However, the clinical relevance of restenosis, as well as the associated risks of adverse events after CAS in patients with prior carotid revascularization, is currently unclear. At this time, we would recommend that only patients with severe restenosis should be considered for CAS using embolic protection performed by an expert at an institution with substantial CAS experience.

Contraindications

Absolute contraindications to CAS include the presence of a visible thrombus within the carotid lesion, active infection, and inability to gain vascular access. The presence of thrombus puts the patient at high risk for embolic stroke, and use of CAS should be aborted if noted prior to the procedure. Active infection confers a substantial risk of stent infection and should be avoided in all cases. Access difficulties can be minimized by using different approaches as indicated based on the patients' history, including femoral access, brachial access, or transcervical access (see section "Technique: Arterial Access," later). If none of these options are feasible, CEA should be considered over CAS.

Relative contraindications to CAS include older age (see section "Patient Selection: Age," earlier), the presence of a circumferential carotid plaque with severe calcification, severe carotid artery tortuosity (two 90-degree angles), near occlusion of the carotid artery (i.e., string sign), and an inability to deploy a cerebral protection device (see section "Technique: Embolic Protection Devices," later). The high rate of periprocedural stroke noted with CAS in the previously mentioned European RCTs is largely attributed to the variable use of EDPs in those studies. CREST, which used EDPs in 96% of cases, reported a 4.1% periprocedural stroke rate,[15] compared with notably higher rates in prior trials (6.8% stroke in SPACE[8] 8.65% stroke in ICSS,[6] and 9.6% stroke/death in EV-3S [7,12]), which implemented EDPs less frequently. As such, the use of EDPs is now considered standard of care in the deployment of a carotid stent.[25]

ANATOMIC CONSIDERATIONS

Several anatomic factors can influence outcomes after CAS. A comprehensive understanding of patient anatomy can help with appropriate selection and operative planning. Specifically, the presence of a type III aortic arch or an aortic arch with extensive wall irregularities or calcifications may benefit from transcarotid artery access for stent placement in an effort to avoid the maneuvering of wires and catheters in this area (see section "Arterial Access," later).

Aortic Arch Morphology

Aortic arch morphology can be classified into three different types depending on the position of the takeoff of the great vessels (Fig. 92.1). In type I aortic arches the great vessels arise at or above the same horizontal place as the outer curvature of the arch. In type II aortic arches the origin of the innominate artery lies between the horizontal plane of the inner and outer curve of the aortic arch. In type III aortic arches the innominate

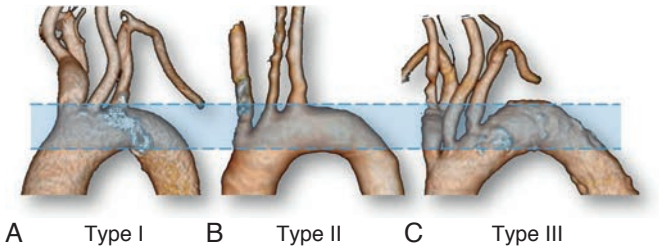

Figure 92.1 Aortic Arch Classification. (A) Type I: the great vessels arise above or in the same horizontal plane of the outer curvature of the arch. (B) Type II: the origin of the innominate artery lies between the horizontal planes of the outer and inner curvatures of the aortic arch. (C) Type III: the innominate artery lies below the horizontal plane of the inner curvature of the arch.

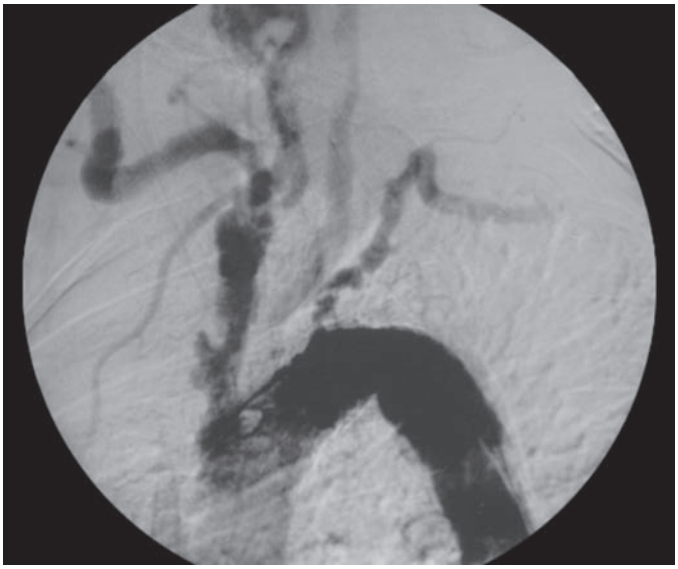

Figure 92.2 Severe Atherosclerosis and Calcification in Aortic Arch (Shaggy Aorta). The procedure should be terminated immediately; accessing the great vessel from a shaggy aortic arch should not be attempted due to potential catastrophic neurologic complications. Alternatively, a transcarotid approach will avoid the severe atheromatous arch.

artery lies below the horizontal plane of the inner curvature of the aortic arch. As the takeoff of the supraaortic vessels moves more inferiorly (i.e., type II and type III configurations), vessel selection and the manipulation of sheath, balloon, and stent delivery system become more difficult because the origin of the arteries becomes more oblique. Type III aortic arch morphologies are particularly challenging and can lead to a higher risk of embolic events due to repeated and/or prolonged wire and catheter manipulation leading to the disruption of aortic plaques.

Aortic arches with extensive aortic wall atheroma and irregularities (i.e., shaggy aorta) and those with severe calcification (eggshell aorta) may also increase the technical complexity of performing CAS and subsequently increase the patient's risk of stroke (Fig. 92.2). Shaggy aortas are composed of multiple atheromas that can break off upon contact with a wire or catheter, leading to atheroembolism to either the brain or the renal or visceral arteries. An eggshell aorta has poor compliance and thus is at risk for dissection or embolism that can similarly lead to devastating neurologic or visceral sequelae. The stiffness of an eggshell aorta can also make wire and catheter torqueability a challenge, leading to difficulty manipulating the stent delivery system into appropriate position within the target lesion.

Of note, bovine aortic arches, where two of the three great vessels share a common origin, are relatively common, occurring in approximately 27% of the population.[43] The most common type 2 form of this variant, the innominate artery and left common carotid artery (CCA) share a common origin. Somewhat less commonly, the common carotid branch takes off from the innominate artery. A "pure" bovine arch, where a common brachiocephalic trunk originates off the aortic arch and then branches into the right and left subclavian arteries and a single bicarotid trunk, is very rare. Although the bovine aortic arch variants are not necessarily contraindications for CAS, they should be noted when present because they may increase the difficulty of obtaining endovascular carotid access.

Carotid Artery Morphology

Carotid artery tortuosity and plaque burden can greatly affect the deliverability of both the EPD and the stent delivery system into the appropriate positions. Data from the EVA-3S trial suggests that the internal carotid artery (ICA)-CCA angulation of greater than or equal to 60 degrees increases the relative risk of death or stroke after CAS by 4.96 times (95% CI, 2.29 to 10.74).[44] ICAs that are particularly tortuous, especially distally, can cause difficulty positioning the EDP sufficiently far enough away from the lesion to allow for stent deployment. Internal carotids with severe angulation at the distal end of the stenotic lesion can cause flow limitations after the procedure due to significant changes in carotid morphology after stent deployment (Fig. 92.3). Tortuous vessels are also more prone to vasospasm at the end of the procedure.

Carotid arteries with circumferential plaque burdens and atheroma are noncompliant and thus can be difficult to access and can increase the risk of embolization during manipulation (Fig. 92.4). In addition, highly stenotic lesions with only a small area of flow (i.e., string sign; Fig. 92.5) may make stent delivery difficult and can result in inadequate stent expansion after deployment and subsequent early restenosis due to recoiling of the stenosis.

Plaque Morphology

Both qualitative and quantitative aspects of carotid artery plaque morphology play a role in determining post-CAS outcomes. Based on data from the EVA-3S trial, ICA stenoses greater than 10 mm in length are associated with a 2.36 (95% CI 1.28 to 3.38) increased risk of death or stroke after CAS.[44] Data from CREST show similar findings; in patients with longer lesion lengths (≥12.85 mm), the risk of CAS was significantly higher than CEA (OR 3.42; 95% CI, 1.19 to 9.78).[45]

Carotid plaque echolucency, as assessed by duplex ultrasonography, has also been shown to increase the risk of stroke in CAS.[46,47] Unfortunately, user variability with this technique results in poor reproducibility and reliability with these measurements, and as such plaque morphology characteristics are not standardly used for risk-stratifying patients undergoing CAS.[48]

Figure 92.3 Severe tortuosity in the ICA: double 90-degree bends increase the difficulty of EPD placement and reduce its effectiveness and can cause a significant kick after stent placement.

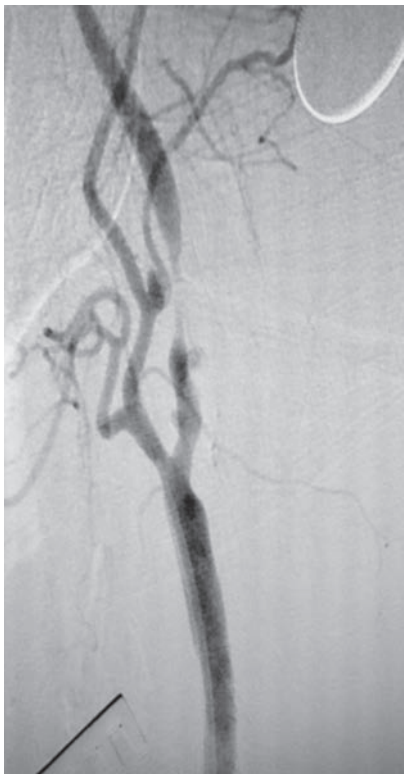

Figure 92.5 Carotid artery string sign: these complex lesions should not be stented.

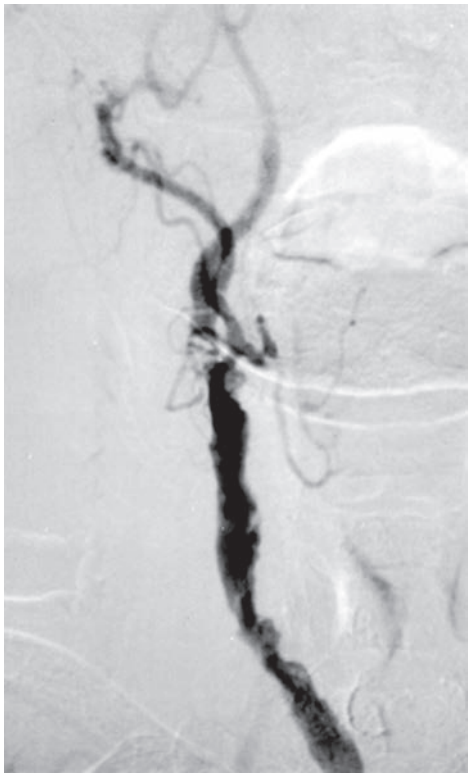

Figure 92.4 Severe plaque and atheroscleroma burdens increase the risk of neurologic complications during access of the common carotid artery. These lesions should not be treated with stenting.

Contralateral Carotid Artery Occlusion

The presence of contralateral carotid artery occlusion should not influence the decision to perform CAS. A subgroup analysis of 3137 patients undergoing CAS who were enrolled in a German Carotid Artery Stent registry (ALKK-CAS) demonstrated a low rate of periprocedural death or major strokes among patients with contralateral carotid occlusion versus those without (1.6% vs. 1.4%).[49] Separate retrospective reviews of in-hospital data from both Northwestern University and Emory University similarly demonstrated that both CAS and CEA can both be performed with good perioperative results and acceptable midterm (approximately 2 year) mortality in patients with carotid artery stenosis and contralateral carotid artery occlusion.[50,51] As such, current recommendations suggest that, although a preexisting contralateral carotid artery occlusion does not appear to adversely impact CAS outcomes, there are no data to suggest the use of CAS over CEA in this setting in the absence of other indications.

PREOPERATIVE CONSIDERATIONS

Preoperative Imaging

As mentioned previously, per CMS requirements, all patients require proof of diagnosis of carotid artery stenosis using angiography prior to stent placement.[25] In nonclinical trial patients, this can occur either preoperatively or intraoperatively,

as long as the patient has appropriate duplex ultrasound imaging to support a diagnosis of high-grade carotid artery stenosis. Duplex ultrasound allows for a comprehensive evaluation of extracranial anatomy and the hemodynamic significance of the CCA, ICA, and external carotid artery (ECA) lesions in most patients. In patients with extensive atherosclerotic disease in which duplex ultrasound findings are inconclusive or unclear, magnetic resonance imaging or computed tomographic angiography (CTA) may be helpful. Both of these imaging modalities allow for a more comprehensive assessment of carotid anatomy, as well as aortic arch morphology and carotid tortuosity. CTA specifically can be helpful in patients in whom carotid plaque morphology or extent is unclear and can be used to measure the diameter of the CCA and the ICA to allow for preoperative planning of stent sizing. Regardless of whether a preoperative CTA is obtained, the CCA and ICA diameters should be remeasured via angiography intraoperatively prior to definitive device selection.

Timing of Surgery

Data on the appropriate timing for surgery among patients with recent stroke who require carotid revascularization are conflicting. Patients who undergo urgent CEA within a week of TIA or minor (nondisabling) stroke do not have worse outcomes than patients who undergo delayed surgery, and thus the use of early carotid revascularization to prevent recurrent stroke is appealing in this population.[52] In contrast, data reporting outcomes after early CAS are inconsistent. An analysis of pooled dated from the EVA-3S, SPACE, and ICSS trials demonstrated that the risk of stroke or death with CAS compared with CEA was highest among patients treated within 7 days of symptoms.[53] The Carotid Acculink/Accunet Post-Approval Trial to Uncover Unanticipated or Rare Events (CAPTURE) registry also reported worse outcomes among patients undergoing CAS within 0 to 13 days of symptom onset, with an odds ratio of having 30-day complications of 2.52 (95% CI, 1.33 to 4.78).[54] In contrast, data from a prospective institutional registry has shown that 30-day stroke, MI, or death rates were similar for CAS performed early (≤4 weeks, 6%) and late (>4 weeks, 8%) after symptom onset.[55] These findings are supported by Groschel et al., who report equivalent outcomes with early versus late CAS based on a cohort of 320 patients from two centers in Germany.[56] Given the conflicting data, no firm conclusions can be made about the safety of CAS following recent stroke. However, given the poor outcomes associated with early CAS as reported by RCT data, use of early stenting in patients with recent cerebrovascular events should probably be approached with caution.

TECHNIQUE

General Principles of Stenting

The concept of CAS is based on the premise of dilating the carotid plaque that is responsible for the stenosis and preventing embolization or restenosis by scaffolding the ruptured, dilated plaque against the vessel wall with the stent. The exact techniques of achieving this outcome vary based on the user, but there are a number of general principles that have been shown to improve outcomes with this procedure and which should be considered standard of care. These include adequate periprocedural monitoring with frequent neurologic assessment, stable sheath access to the proximal CCA, use of EPDs, completion angiography, and perioperative antiplatelet therapy. In addition, the use of a hybrid operating suite with a high-resolution image intensifier, a large inventory of both endovascular and operative supplies, and a multidisciplinary approach to postoperative patient care can help to prevent poor outcomes before they occur.

Periprocedural Monitoring

Adequate hemodynamic monitoring in the operating room is essential to success during CAS. All patients should have continuous electrocardiographic, pulse oximetry, and intraarterial pressure monitoring throughout the procedure, the latter of which can be obtained via the side arm of the introducer sheath. Hypotension and hypertension and any changes in oxygenation or cardiac tracings should be treated immediately.

All procedures should be performed with the patient awake, using local anesthesia. This allows for continuous evaluation of neurologic function in the form of speech, alertness, and motor function, which can be monitored by asking the patient frequent questions and having him/her squeeze a plastic toy in the contralateral hand. If necessary, mild sedation may also be used but only to make the patient comfortable without altering level of consciousness because the awake neurologic exam is the cornerstone of periprocedural monitoring during CAS.

Adjunct methods of assessing neurologic status include continuous electroencephalogram (EEG) and/or transcranial Doppler (TCD). EEG can help to identify subclinical cerebrovascular changes that may aid in the early identification of a periprocedural stroke. However, the clinical utility of some of these changes is questionable and thus, as with CEA, EEG is not essential for performing CAS. Although TCD is purported to differentiate the size and composition of emboli during cerebroembolic events, the accuracy of this technology is inconsistent and thus its use during CAS is surgeon and center specific.[57]

Arterial Access

The most common access used for CAS is transfemoral. In a right-handed operator, retrograde right transfemoral access using a 6-F introducer allows for the easiest catheter manipulation. Left transfemoral access should be the second choice for access if the right groin is inaccessible due to severe peripheral arterial disease, prior interventions, or other reasons. Once the working sheath is in place, a full dose of heparin should be administered as with any endovascular procedure.

Transcarotid access may also be used successfully in patients with hostile groin or aortic arch anatomy (see section "Anatomic Considerations," earlier). Percutaneous transcervical carotid artery access can be obtained using ultrasound guidance, with

care taken to puncture the CCA at the base of the neck well below the carotid bifurcation to allow for a stable working platform.[58] Alternatively, access to the CCA can be obtained using a surgical cutdown. This allows for direct visualization of the CCA puncture site and may be the safest option. The Safety and Efficacy Study for Reverse Flow Used During Carotid Artery Stenting Procedure (**ROADSTER**) trial reported 30-day results of the ENROUTE neuroprotective system (Silk Road Medical Inc, Sunnyvale, California), which is deployed through direct common carotid cutdown access.[59] In this trial that enrolled 208 patients with symptomatic carotid artery stenosis greater than or equal to 50% stenosis and asymptomatic carotid artery stenosis greater than or equal to 70% stenosis, the overall stroke rate with transcarotid artery revascularization (TCAR) was 1.4%, which is lower than any prior prospective multicenter clinical trial of CAS. Based on these data, the authors conclude that direct TCAR with flow reversal may be a safe, less invasive alternative to CEA.[59,60] Based on the safety results of the **ROADSTER** trial, the US Food and Drug Administration approved use of the ENROUTE device for patients who qualify for CAS for both commercial and RCT purposes.[61]

Less commonly, transbrachial or transradial access may be used. In these cases a 6-F sheath should be used to access the artery using ultrasound guidance. Upper extremity access is indicated in patient who have either severe abdominal aortoiliac disease or shaggy or eggshell aortas and a hostile neck. Recently, a right transradial approach for patients with a bovine-type aortic arch or type III aortic arch morphology has been shown to be a safe and technically feasible approach to perform CAS for left and right carotid artery lesions, respectively.[62]

Target Lesion Access

For successful deployment of the carotid artery stent, stable sheath access in the CCA must be obtained. In patients with remote (i.e., trasfemoral, transbrachial, or transradial) arterial access, this can be achieved via two different platforms.

In a sheath-based platform a 6-F 90-cm Shuttle Select sheath (Cook, Inc. Indianapolis, Indiana) is placed in the descending aorta. A preshaped compatible 125-cm catheter (e.g., JB1, VTK, Headhunter, Simmons 1) is used to cannulate the CCA, and an exchange-length 0.035 guide wire is passed into the mid CCA. The catheter is advanced carefully over the wire and positioned a few centimeters below the carotid bifurcation. At this point the sheath is advanced into position over the catheter. This telescopic technique provides better support and fewer working maneuvers. However, due to a recent end of production of the 6-F compatible catheters, the size mismatch between the 6-F sheath and the 5-F catheter can increase the risk of the sheath scraping plaque off or dissecting the arterial wall as the catheter is advanced ("snowplowing"), which can result in embolization. Alternatively, the older technique of advancing a stiff glide wire into the ECA, followed by catheter withdrawal and dilator placement, can be used. The sheath and dilator are then advanced together into the mid CCA. This technique carries a number of risks, including crossing the carotid bifurcation unprotected with a stiff wire, the dilator crossing the plaque at the bifurcation, and the need for several exchanges and manipulations.

In a guiding catheter–based platform, the CCA is directly accessed with a preshaped 6- or 7-F guiding catheter (e.g., multipurpose curve, vertebral or reversed-angle Vitek catheter) that is left in place for the duration of the procedure. The benefit of this approach is that it minimizes the number of wire and catheter exchanges needed to get the system in place, making it ideal for patients with shaggy aortic arches. The disadvantage of this approach is that the platform can be easily dislodged from the CCA during stent advancement if it is not positioned far enough into the vessel. To avoid this from happening, a 0.014-inch coronary artery buddy wire can be placed into the ECA to assist with platform stabilization.

Angiography

As noted previously, adequate intraoperative carotid artery angiography should be obtained in all patients to assist with stent measurements and procedural planning prior to stent delivery. Once the working platform has been advanced into the CCA, an angiogram should be obtained through the guiding catheter or sheath using anteroposterior (AP) and lateral projection to try and minimize ICA and ECA overlap. If the carotid branches overlap with this approach, adjunct oblique views should be obtained to allow for complete visualization of the CCA, ICA, ECA, and intracranial carotid vessel distribution (Fig. 92.6). Occasionally, rotational angiography can help to detect the true degree of stenosis. Precerebral and postcerebral images can help to detect distal branch embolization.

Embolic Protection Devices

After carotid artery angiography is obtained, an EPD should be placed in the distal ICA for cerebral protection against intraoperative embolism. Data from the EVA-3S trial demonstrated a significant protective effect with EPDs against 30-day risk of stroke (7.5% with EPD vs. 25% without EPD; $P = .03$).[7] Although data from the SPACE trial did not support this finding,[63] a pooled analysis of 12,263 protected CAS patients and 11,198 unprotected CAS patients demonstrated a relative risk for stroke of 0.62 (95% CI 0.54 to 0.72) in favor of protected CAS.[64] The CREST trial mandated the use of EDP whenever feasible (95% of patients), and the ubiquitous use of cerebral protection is one of the reasons cited for the low number of adverse events reported in that study.[15] Accordingly, current clinical guidelines all support the use of EPDs during CAS,[21-23] and CMS mandates use of an EPD to qualify for reimbursement.[25]

Because of the current widespread use of EPDs with CAS, a number of different models have been developed. Each of the available EDPs is based on one of three conceptually different methods.

Filter-type EDPs are the most commonly used and are designed to allow antegrade cerebral flow throughout the entire CAS procedure (Fig. 92.7). The filter is passed across the carotid lesion over a wire and deployed distally in the ICA to capture

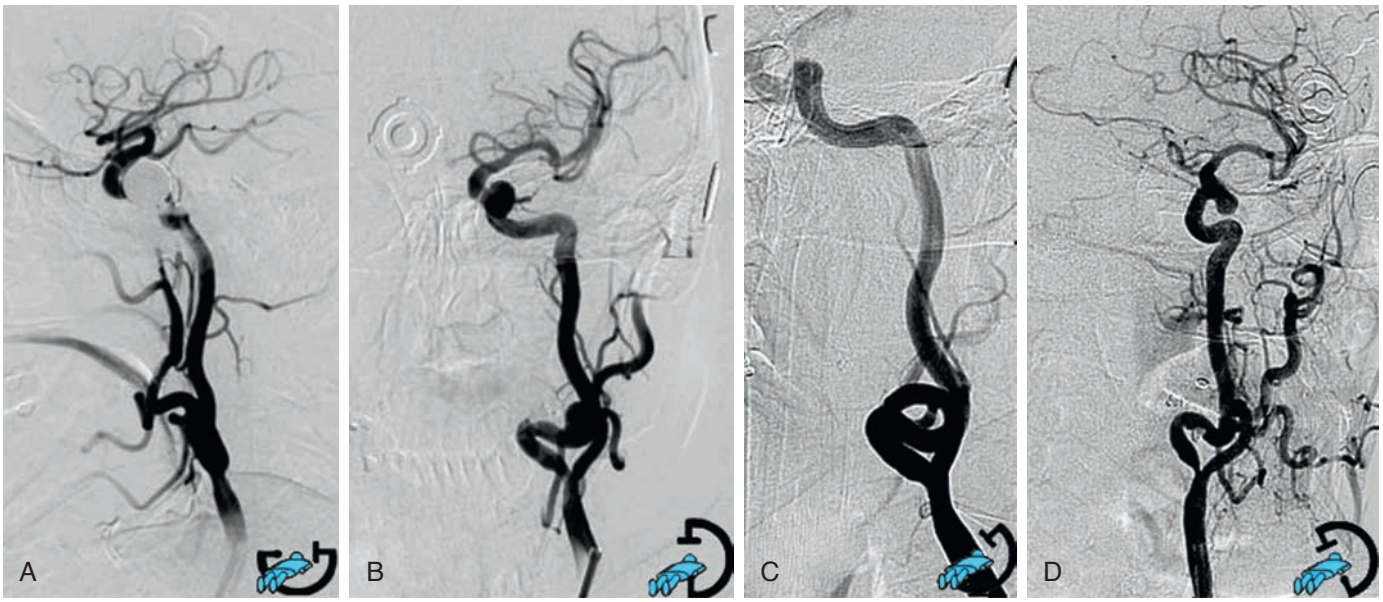

Figure 92.6 Standard projections showing mild to moderate stenosis. The projection selected with rotational angiography shows severe stenosis. (A) Laterolateral. (B) Anteroposterior. (C) Left anterior oblique. (D) Right anterior oblique.

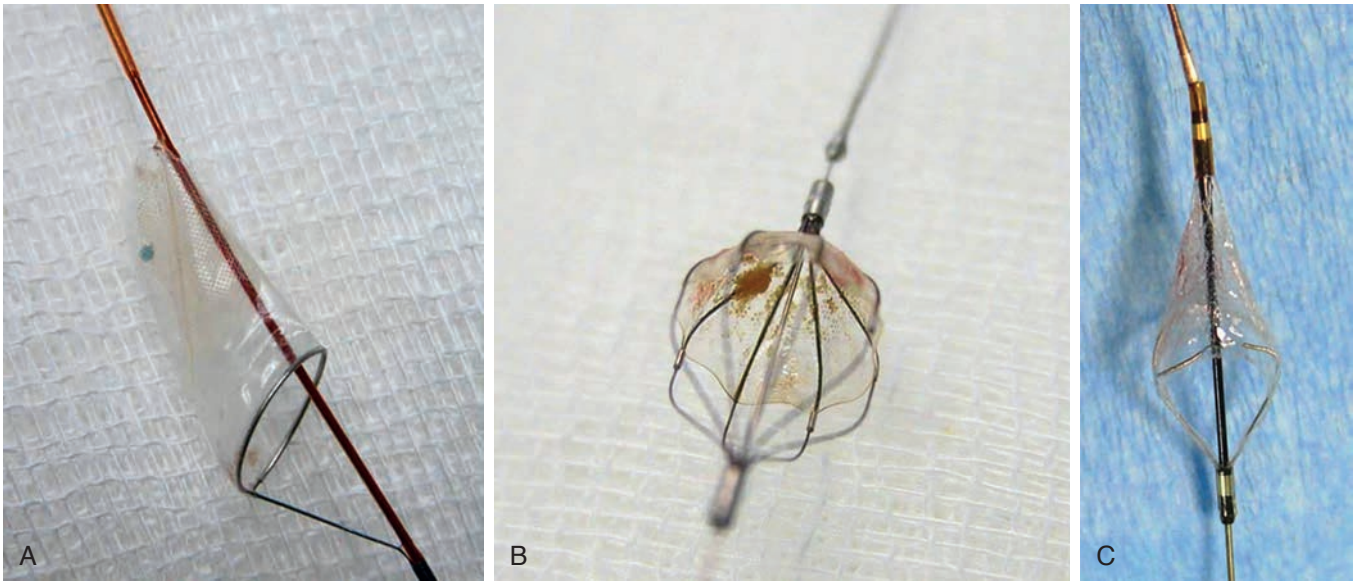

Figure 92.7 Filter-type embolic protection devices. Different types of filters containing debris after retrieval. (A) EPI FilterWire. (B) Angioguard. (C) Emboshield. ([A] Courtesy Boston Scientific, Natick, MA. [B] Courtesy Cordis, Somerville, NJ. [C] Courtesy Abbott Vascular, Redwood City, CA.)

any debris that may come loose during stenting. After the stent is successfully deployed, the filter is recaptured using a dedicated filter-retrieval system. The advantages of this EDP design are uninterrupted cerebral blood flow, continuous access to angiography throughout the procedure, and a low number of manipulations required within the carotid vessels. The main disadvantage is that the filter must be passed through the carotid lesion prior to deployment, which can be challenging in high-grade lesions and carried a risk of plaque dislodgement or rupture prior to filter deployment.

The distal occlusion balloon is the EDP that was originally used by Theron et al.[9] but which has been largely abandoned nowadays. With this device, a balloon is inflated in the distal ICA, preventing antegrade blood flow during the procedure. After stent deployment, the blood and any debris material are flushed and suctioned endovascularly, and then the balloon is deflated and removed. Like distal filter-type EDPs, this model requires passage of the carotid lesion prior to placement of embolic protection. There is also risk of incomplete evacuation of debris, and distal ICA vasospasm or damage as a result of

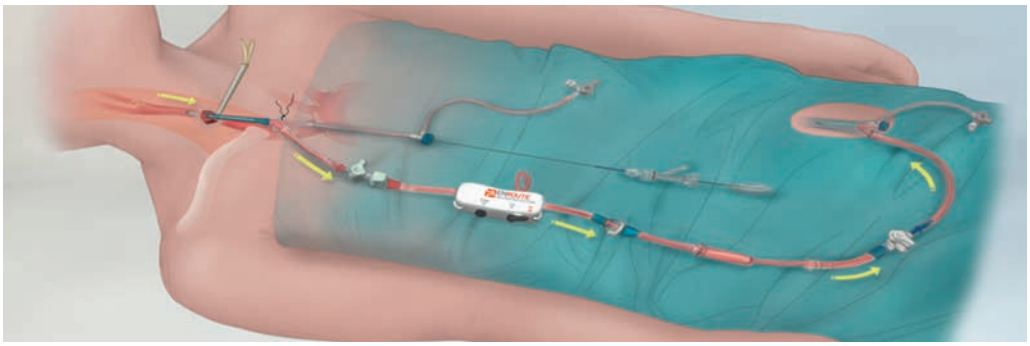

Figure 92.8 Transcarotid artery revascularization with cerebral flow reversal using the Enroute Neuroprotection System. In this system the arterial sheath placed in the common carotid artery via cutdown, and a low pressure venous sheath is placed in the femoral vein.

balloon deployment. Few patients are unable to tolerate occlusion with resulting neurologic changes that can mandate balloon deflation in the middle of the procedure.

Proximal protection EDPs provide protection against embolic events prior to crossing the lesion using either flow stasis or flow reversal. One proximal protection EDP, the Mo.Ma (Invatec, Roncadelle, Italy), deploys an occlusion balloon in the CCA and the ECA using a single delivery catheter. This causes flow stasis during stent deployment. Debris is aspirated after the stent is deployed using intermittent syringe aspiration through the introducer sheath, after which the distal occlusion balloon is deflated.[65] Flow reversal systems similarly employ the principles of CCA and ECA occlusion, but an external shunt containing a filter to capture any debris is placed between the long introducer sheath in the carotid artery and a shorter introducer in the femoral vein, allowing for continuous arteriovenous flow throughout the procedure.[66,67] The recent ENROUTE system for TCAR allows for effective cerebral flow reversal at low and high flow, avoiding the arch and ECA ballooning (Fig. 92.8). The main advantage to proximal protection EDPs is that they prevent the need for crossing the carotid lesion prior to obtaining cerebral protection. The main disadvantage is that a larger sheath is required to accommodate the EDP system (9 F for transfemoral access, 8 F for TCAR access) and the need for EDP device manipulation in close proximity to the target lesion. In addition, approximately 5% to 9% of patients will not tolerate flow stasis or reversal for prolonged periods of time; in these cases, short periods of balloon occlusion can be used to minimize neurologic intolerance and still maintain a degree of cerebrovascular protection during stent deployment.[68]

There is no obvious clinical advantage to one EDP design over another. In the Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting (PROFI) study, which is the only RCT designed to compare EDP approaches to date, proximal balloon occlusion was shown to have a lower incidence of silent new cerebral ischemic lesions on postoperative magnetic resonance imaging compared with filter protection (6.5% vs. 29%; $P = .05$), but there were no significant differences in the 30-day risk of major adverse cardiovascular and cerebral events (0% vs. 3.2%; $P =$ NS).[69] A small benefit with proximal protection EDPs over filter EDPs has similarly been shown in smaller nonrandomized trials,[70,71] but many of these studies have substantial industry influence. Currently, it is most important that surgeons practicing CAS use the EDP that they are most familiar with to minimize complications related to user error or excessive device manipulation.

Predilation

After the EDP is in place, a decision must be made as to whether the carotid lesion requires predilation prior to stent deployment. When the stenosis is severe, predilation with a small (2.5 to 4.0 mm) coronary artery balloon to 4 to 6 atm of pressure may assist in stent positioning and deployment. Rarely, predilation may be necessary to pass a filter-type EDP. In these cases a proximal protection EDP should be considered as an alternative in an effort to avoid dilation of the lesion without cerebral protection.

Stent Selection and Delivery

Carotid artery stents are self-expandable stents made of either stainless steel (a cobalt alloy) or nitinol (a nickel-titanium alloy). There are two main configurations of carotid artery stent construction. In closed cell stents, all of the stent struts are interconnected, whereas in open cell stents they are not. As a result, closed cell stents have a smaller free cell area and those provide better scaffolding of the vessel wall. In contrast, open cell stents more conformable or flexible.

Stent selection depends on the carotid anatomy and plaque characteristics of the lesion in question. For tortuous carotid arteries, flexible stents may be preferred to prevent kinking. In contrast, stents with better scaffolding may be preferable for plaques at risk of protruding through the stent struts and causing distal embolization. In general, nitinol stents have a higher radial force than stainless steel stents and may be more effective for highly calcified plaques with poor compliance. However, there are no definitive data to support the use of one self-expanding stent over another.[72-75]

The diameter of the stent to be placed should be based on angiographic measurements taken at the time of the procedure. Preoperative CTA can assist in this and may be helpful for ensuring the availability of appropriate stent inventory, but all measurements should be confirmed in real time. The diameter of the stent should be sized to the largest portion of the carotid artery, which is usually the distal CCA.

Once an appropriate stent has been selected, it should be deployed using road mapping or, alternatively, using vertebral bones as landmarks, depending on the surgeons' comfort with either technique. The stent should be placed across the carotid bifurcation because in most cases the carotid lesion extends to the carotid bulb. Of note, recent stents under clinical investigation use a cover mesh to cover the lesion.[76] This is particularly important because the principle of successful CAS is to stabilize the plaque with minimal manipulation of the lesion.

Postdilation

When CAS was first adapted for the treatment for the carotid artery stenosis, it was performed using the basic tenants of peripheral arterial interventions. To that end, balloon dilation of the lesion being treated was performed both prior to and after the stent was placed. The theory behind this practice was that prestenting balloon dilation disrupts the plaque causing the lesion and allows the stent to be placed, and poststenting ballooning allows for full expansion of the stent. However, an analysis using data from the Vascular Quality Initiative suggests that poststent balloon dilation may increase perioperative hemodynamic depression and stroke and death rates in patients undergoing CAS. Compared with prestent ballooning only, the prestent and post-stent ballooning technique was associated with a 2.1-odds increase in hemodynamic depression (95% CI 1.51 to 3.01) and 2.4-odds increase in perioperative stroke and death (95% CI 1.01 to 5.620).[77] Accordingly, continued artery stent expansion has been demonstrated by duplex up to 30 days after deployment even without post-stent ballooning.[78] Based on these data, we suggest that post-stent balloon dilation be reserved for lesions with severe residual stenosis after stent deployment.

Completion Angiography and Retrieval of Embolic Protection Device

After the stent is deployed, a completion angiogram should be performed with the EPD in place to evaluate for accuracy of stent positioning, residual stenosis, vasospasm at the distal stent endpoint, and filling defects inside the stent due to plaque protrusion. After the EDP is retrieved, a final angiogram capturing both the cervical and intracranial circulation should be obtained to evaluate all aspects of cerebral blood flow. Careful attention should be paid to the distal ICA, which may spasm after a filter-based EDP is removed. In these cases, waiting a few minutes usually allows for spasm resolution. Rarely, small volumes of nitroglycerin (100 to 200 μg) can be instilled through the guiding sheath into the CCA to assist in vasorelaxation if needed.

Access Hemostasis

Heparin reversal with protamine has not been shown to increase the risk of MI, stroke, pulmonary embolism, or death in a number of CEA studies.[79-81] It is the authors' preference to administer a small dose of protamine slowly to reverse half the heparin dose given during the case (based on 1 mg per 100 unit of intravenous heparin). This allows for adequate access hemostasis and may reduce the potential for intracranial hemorrhage (ICH) postoperatively. Access hemostasis should be obtained using percutaneous closure assist devices and/or manual pressure as with any endovascular procedure.

PERIOPERATIVE MEDICATIONS

Anticoagulation

As noted previously, all patients should be fully anticoagulated with unfractionated intravenous heparin (70 to 100 units/kg) once sheath access is obtained and before starting catheter manipulation within the aortic arch. Activated clotting times (ACTs) should be followed and should not exceed 300 seconds to prevent hemorrhagic stroke secondary to reperfusion following the procedure.

Atropine

Hypotension with bradycardia, or HD, may occur after balloon dilation in response to stretching of the carotid baroreceptors. This is particularly common in older patients with long, heavily calcified plaques.[82,83] Hemodynamic depression may be associated with an increased risk of adverse periprocedural events including stroke[82] and thus should be avoided whenever possible. To prevent hemodynamic depression, the senior author avoids post-stent ballooning and the resulting stretching of carotid baroreceptors. In patients who develop severe hypotension and bradycardia after balloon dilatation and/or stent deployment, aggressive volume expansion and intravenous atropine (0.4 to 1 mg) may be administrated. Less commonly, use of vasopressors, including intravenous phenylephrine (1 to 10 μg/kg per minute) or dopamine (5 to 15 μg/kg per minute) infusion, may be necessary.[21] Persistent hypotension after cardiac stenting can occur, lasting 24 to 48 hours postoperatively. Risk factors for persistent hypotension include distance from the carotid bifurcation to maximum stenotic lesion (≤10 mm), type of stenosis (eccentric), plaque morphologic features (echogenic), and calcification at carotid bifurcation.[84] In these cases, management generally involves pharmacologic support until the carotid baroreceptors adapt to the radial force of the stent and the resulting hemodynamic depression is resolved. There are reports of using transcutaneous temporary cardiac pacing in carotid stenting in patients who are deemed to be high risk for postoperative bradycardia (i.e., older patients, those taking beta blockers or digoxin, or who are bradycardia at baseline),[85,86] but this is rarely indicated.

Vasodilators

Intravenous vasodilators should be used throughout the procedure to maintain a systolic blood pressure less than 180 mm Hg to minimize risk of ICH.[21] As mentioned, small volumes of nitroglycerin (100 to 200 μg) may also be instilled through the guiding sheath into the CCA to assist in vasorelaxation in cases of persistent ICA spasm after EDP removal. However, both of these therapies should be used judiciously because excessive vasodilation in combination with hemodynamic depression after balloon dilation may exacerbate the prolonged hypotension that can be observed in some CAS patients postoperatively.

Beta Blockers

The use of beta blockers to improve outcomes after CAS is somewhat controversial. Although once considered universally cardioprotective, the initiation of perioperative beta blockers for major elective vascular surgery may not be advisable in some subgroups.[87,88] Recent data from the Vascular Quality Initiative suggest that preprocedural beta blocker use for more than 30 days was associated with a 34% reduction in the stroke/death risk compared with nonuse[89] and is associated with an increased risk of postprocedural hypotension.[89,90] Taken together, these data suggest that if beta blockers can be initiated well in advance of a planned intervention, they may have a role in CAS therapy. In contrast, the use of periprocedural beta blockers in beta-blocker naïve patients may carry an increased risk of perioperative cardiac morbidity.[88]

Antiplatelet Therapy

The use of dual antiplatelet therapy has not been shown to have a significant benefit for reducing stroke, MI, or death as a preventative treatment strategy among patients who are at high-risk atherothrombotic events.[91,92] However, data from coronary revascularization studies have demonstrated a protective benefit with clopidogrel and aspirin for patients undergoing percutaneous coronary intervention, particularly in high-risk populations.[93,94] Given that periprocedural stroke is the highest concern in CAS, current guidelines recommend dual-antiplatelet therapy with aspirin (81 to 325 mg daily) plus clopidogrel (75 mg daily) at least 4 days before and for a minimum of 30 days after surgery for those patients undergoing CAS.[21,23,95] For patients intolerant of clopidogrel, ticlopidine (250 mg twice daily) may be used instead.

Antithrombotic Therapy

The routine use of antithrombotic therapy after CAS is not indicated. In an RCT designed to compare dual antiplatelet therapy (aspirin plus clopidogrel) versus aspirin and 24-hour heparin for patients undergoing CAS, neurologic complications were significantly higher in the heparin group (25% vs. 0% with dual antiplatelet therapy), causing the trial to be terminated prematurely.[96] The use of systemic antithrombotic therapy with warfarin among patients with recent stroke has also not been shown to be beneficial compared with aspirin.[97] As such, antithrombotic therapy after CAS should be restricted to those patients who were on it preoperatively due to cardiac or thromboembolic indications. In this group, warfarin may be converted to low-molecular-weight heparin prior to the procedure.

Statins

All patients undergoing evaluation for CAS should be initiated on statin therapy preoperatively. In a meta-analysis of 12 retrospective and 3 prospective trials representing 223,010 patients, preoperative statin therapy was shown to be associated with a 59% reduction in risk of mortality after vascular surgery.[98] Statins have also been shown to be effective at reducing the risk of cardiovascular events in both women and men[99] and that the protective benefit likely occurs within a month of starting treatment.[100] Consistent with this notion, patients undergoing CAS who are on preprocedural statin therapy have been shown to have a lower incidence of stroke, MI, and death within 30 days surgery; based on a prospectively maintained intuitional database composed of 180 consecutive CAS patients, the incidence periprocedural cardiovascular events was shown to be significantly lower among statin users (4% with statin vs. 15% without).[101] These findings have been corroborated by a large retrospective review of 1,083 CAS patients that demonstrated a significantly lower incidence of perioperative stroke and death among those taking statins (1.5% statin vs. 4.0% no statin).[102] Although the optimal timing, dosing, and agents are unclear at this time, consensus guidelines suggest that all patients undergoing carotid revascularization should be initiated on statin therapy as early as possible.[103]

COMPLICATIONS

Technical Complications

Acute stent thrombosis is an emergency because it carries a substantial risk of clot propagation and subsequent thromboembolic stroke. It can be caused by stent misplacement, severe carotid artery recoiling due to annular calcification, or massive plaque protrusion through the stent struts. When acute thrombosis occurs, the procedure should be immediately converted to CEA. Rapid reestablishment of cerebral perfusion via endarterectomy is associated with a good neurologic outcome.[104]

Kinking may occur at the endpoints of the stent, especially when placed in vessels with severe tortuosity. Usually, this is visible on the completion angiogram. In these cases the patient can be observed if the kink is mild, as long as there is good antegrade blood flow, because carotid remodeling occurs up to 3 to 6 months postoperatively and may reduce or eliminate the kink over time.[105]

Carotid dissection can also be observed on completion angiogram and may be managed by observation, balloon

apposition of the stent (i.e., poststent dilation), or placement of an additional stent, depending on the location and extent of the dissection flap. If the dissection is flow-limiting, use of an additional stent is indicated.[95]

Neurologic Complications

Neurologic complications are the most common complications following CAS and include embolism, ICH, hyperperfusion, and neurocognitive effects.

Embolism is the most common and feared complication following CAS and is usually the result of an atherosclerotic plaque or catheter-generated thrombus. The diagnosis is usually made as a result of changes in the intraoperative neurologic exam; when this occurs, an angiogram should be obtained immediately to visualize the offending occlusion. Depending on the location of the embolus, potential neurorescue procedures include catheter-directed chemical thrombolysis with urokinase or recombinant tissue plasminogen activator, thrombus maceration, aspiration thrombectomy, snare removal, and glycoprotein IIb/IIIa receptor inhibitor administration. The results of each of these salvage therapies are variable, and embolus prevention remains the mainstay of CAS therapy, predominantly by use of EPDs.[106]

Intracranial hemorrhage is a rare complication of CAS but can have devastating consequences. In a review of CAS versus CEA using data from the Nationwide Inpatient Sample, CAS was found to be associated with a sixfold higher risk of ICH than CEA.[107] However, these finding have not been confirmed with RCTs. Data from the EVA-3S, SPACE, and CREST trials have all shown relatively equivalent risk of ICH after CAS versus CEA (<1%).[7,8,18] There is some suggestion from CREST that when ICH occurs after CAS they are more severe, which may be attributable to the use of dual antiplatelet therapy before and after this procedure.[18] Groups that have been recognized as being high risk for developing ICH after CAS include patients with symptomatic carotid stenosis and those with bilateral severe carotid stenosis with associated hypertension.[108]

Hyperperfusion is also a relatively uncommon complication of CAS, occurring in an estimated 1% to 2% of patients.[108,109] Hyperperfusion is diagnosed when a patient develops a neurologic change and CT imaging reveals ipsilateral cerebral edema without evidence of stroke.[109] Headaches or transient ischemic attacks are not included. Symptoms usually develop at a mean of 10 hours postoperatively and are more common in patients with hypertension or a recent history of transient ischemic attacks.[109] The risk of hyperperfusion syndrome is progression to ICH. The treatment is largely supportive, with a focus on blood pressure control.

Subclinical neurocognitive complications represent microembolic events after CAS that do not result in a clinical deficit. In a small prospective study including 82 patients, new brain lesions were identified by diffusion-weighted imaging in 71% of CAS patients, compared with only 4% of CEA patients.[110] Although not immediately symptomatic, the concern is that these microembolic events could lead to accelerated cognitive loss and premature senescence.[111] To date, existing data on this topic do not suggest that microembolic events after CAS result in worse long-term neurocognitive function. Data from ICSS demonstrate no differences in cognitive performance following CAS versus CEA.[112] Analyses of smaller institutional series support these findings, demonstrating no significant differences in cognitive function up to 6 months after CAS versus CEA despite a substantially higher rate of new ischemic lesions after CAS.[110,113] The longer-term effects of microembolic events that may occur with CAS remain to be seen.[114]

Cardiovascular Complications

The risk of periprocedural MI after CAS is consistently lower than that after CEA based on RCT data.[7,8,15] As such, CAS may be a good option for carotid revascularization in patients who are at high risk for having an adverse cardiac event with open surgery. Hemodynamic depression can occur (see section "Intraoperative Medications: Atropine," earlier), but this rarely results in ischemic events or alterations in blood pressure in the long term.[115,116]

Renal Dysfunction

The contrast load associated with CAS can cause contrast-induced nephropathy, particularly in patients who have baseline chronic renal insufficiency. This risk is equivalent to any generic endovascular procedure, and patients should be counseled accordingly. The total amount of contrast injected during the procedure should be minimized as much as possible and in most cases should not exceed 60 mL. Adequate fluid resuscitation is the cornerstone to avoiding acute kidney injury and should be managed with attention to the patients' other risk factors (i.e., congestive heart failure). Of note, patients with baseline chronic renal insufficiency are at risk of having higher major adverse events after CAS in general and should be approached with caution.[117]

Access Complications

As with any endovascular procedure, access complications, including hematoma formation, pseudoaneurysm, peripheral embolization, and access site infections, can occur. Of the 1262 patients in the CAS cohort of the CREST trial, there were 24 cases of major bleeding requiring blood transfusion and 12 cases of retroperitoneal major bleeding or femoral hematoma requiring revision.[15] Most access site complications resulting from CAS are self-limited and can frequently be managed expectantly. In our practice the use of duplex ultrasound to guide access, reversing anticoagulation at the end of the case, and the use of closure devices have all contributed to minimizing access site bleeding and pseudoaneurysm complications.

Stent Fracture

Stent fracture has been reported after CAS with an incidence of approximately 9%.[118] It has been reported to occur any time

from 0 to 37 months after surgery. In a review of 201 carotid stents in 10 case reports and 3 clinical studies, less than one-third of patients with stent fractures became symptomatic, but carotid artery restenosis occurred in 55% of cases.[118] The majority of these fractures were successfully treated by de novo stent placement, although balloon angioplasty, CEA, carotid bypass, and observation alone have also been reported.

Restenosis

One of the major concerns with CAS is that of long-term restenosis. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial reported a 10-year restenosis rate of 30.7% following an endovascular treatment approach to patients with caroti artery stenosis, compared with 11% in the CEA group.[119] However, the endovascular arm of CAVATAS used carotid stents in only 26% of the patients treated endovascularly; the remainder underwent balloon angioplasty alone.[120] More recent data from the CREST trial suggest a much lower incidence of restenosis following CAS; at 2 years postoperatively, carotid artery restenosis or occlusion occurred in 6.0% of CAS patients and 6.3% of CEA patients.[18] The longer-term risks of restenosis with CAS are unknown, but high-risk features include diabetes, female sex, and dyslipidemia.[18] Patients with carotid stenosis that is longer than 0.65 times the CCA diameter have also been shown to be at increased risk of restenosis following CAS.[121]

POSTOPERATIVE SURVEILLANCE

Duplex ultrasound should be performed in all CAS patients 3 to 6 weeks postoperatively.[122] This allows for the establishment of new baseline flow for the patient to be used in future comparisons, which is particularly important because the presence of stents have shown to alter duplex flow velocity measurements.[123] Although no definitive RCT data exist on this topic, currently repeat duplex surveillance is recommended 6 months after the initial postoperative study and then annually thereafter for all patients undergoing CAS.[122]

LONG-TERM OUTCOMES

Randomized Controlled Trials

Ten-year outcomes after CAS versus CEA were recently reported by the CREST trial investigators.[16] Among 2502 patients, 10-year postprocedural ipsilateral stroke rates were not significantly different between the CAS versus CEA group (6.9% CAS vs. 5.6% CEA). The incidence of periprocedural stroke, MI, or death and subsequent ipsilateral stroke also did not differ between groups. Similarly, 5-year outcomes were reported for the ACT-I trial, which demonstrated no significant differences between CAS versus CEA in the rates of non–procedure-related stroke, all stroke, and survival in patients with high-grade asymptomatic stenosis.[19] These trials represent the first data on long-term outcomes after CAS, and based on reported findings the results are encouraging.

Ongoing Trials

There are currently a number of trials that have recently closed or are still in progress that were designed to compare CAS versus CEA versus BMT for the treatment of asymptomatic carotid stenosis.[124]

The Stent-Protected Angioplasty Asymptomatic Carotid Stenosis Versus Endarterectomy 2 (**SPACE-2**) trial was recently designed to compare the superiority of BMT versus intervention (CAS or CEA), as well as the noninferiority of CAS versus CEA.[125] The primary outcome of the study is the cumulative rate of any stroke or death within 30 days plus ipsilateral ischemic stroke within 5 years of follow-up. SPACE-2 was recently closed prior to completion due to slow enrollment, but the data are expected to be part of a meta-analysis comparing BMT versus carotid revascularization for asymptomatic carotid stenosis.[124]

The Asymptomatic Carotid Surgery Trial-2 (**ACST-2**) was designed to compare CAS versus CEA for the prevention of stroke in patients with asymptomatic carotid artery stenosis.[126] The primary outcomes are 30-day MI, stroke and death, and 5-year stroke rates. ACST-2 currently open for randomization, with an expected enrollment of more than 5000 patients.

The European Carotid Surgery Trial 2 (**ECST 2**) is a randomized trial designed to compare BMT versus carotid revascularization (CAS or CEA) in patients with greater than or equal to 50% carotid artery stenosis.[127] In this trial, patients can either be asymptomatic or symptomatic with associated factors indicating intermediate or lower risk of ipsilateral stroke (5-year ipsilateral stroke risk of <20%). The primary outcome for ECST 2 is any stroke at any time plus nonstroke death within 30 days of intervention. The trial targets enrollment of 200 patients in the United Kingdom and is currently open for randomization.

The Carotid Revascularization for Primary Prevention of Stroke (**CREST-2**) trial is actually composed of two independent multicenter RCTs designed to compare BMT versus carotid revascularization in patients with asymptomatic high-grade (≥70%) carotid artery stenosis.[128] One trial will randomize patients to BMT versus CAS+BMT, and the second trial will randomize patients to BMT versus CEA+BMT. The primary outcome for CREST-2 is a composite outcome of stroke plus death within 44 days after randomization and ipsilateral stroke thereafter up to 4 years. The trial is currently active and estimates a total enrollment of 2480 patients.

Based on the safety results of the **ROADSTER** trial,[59] the Reverse Flow Used During Carotid Artery Stenting Procedure 2 (ROADSTER 2) trial is now underway. ROADSTER 2 is a postapproval, multicenter study designed to assess the efficacy of TCAR using the ENROUTE Transcarotid Neuroprotection and Stent System from Silk Road Medical (Silk Road Medical Inc, Sunnyvale, California).[129] The primary outcome of the study is rate of procedural success through 30 days following stent implant. ROADSTER 2 is aiming for a minimum enrollment of 600 patients with symptomatic carotid artery stenosis greater than or equal to 50% or asymptomatic carotid artery stenosis greater than or equal to 80% at up to 100 sites.

TABLE 92.5 Recommended Techniques to Reduce Periprocedural Adverse Events During Carotid Artery Stenting

Timing	Technique	Comment
Preoperative	Statin therapy	All patients undergoing carotid revascularization should be initiated on statin therapy as early as possible[103]
	Beta blocker therapy	Preprocedural beta blocker use for >30 days is associated with a reduction in periprocedural stroke/death risk compared to nonuse[89]
	Adequate imaging	Consider computed tomography angiography in patients with potential complex aortic or carotid anatomy to allow for better operative planning
Intraoperative	Frequent awake neurologic assessment	Allows for early detection of stroke
	Stable sheath access	Consider transcarotid artery revascularization in patients with challenging aortic anatomy to reduce stroke risk[59]
	Embolic protection devices	Consider proximal protection EDPs to reduce risk of embolic lesion caused by initial crossing of the lesion[69]
	Atropine	Intravenous atropine (0.4-1 mg) may be administrated before balloon inflation to suppress the hemodynamic response to stretching of carotid baroreceptors
	Appropriate stent sizing	The diameter of the stent should be sized to the largest portion of the carotid artery, which is usually the distal common carotid artery
		All sizing should be confirmed by intraoperative angiography even if preoperative computed tomography angiography is obtained
	Avoid post-stent dilation	Hemodynamic depression and perioperative stroke and death have been shown to be lower without post-stent dilation[77]
	Completion angiography	Confirm stent placement and check for distal internal carotid artery spasm
Postoperative	Antiplatelet therapy	Aspirin (81-325 mg daily) plus clopidogrel (75 mg daily) 4 days before and for a minimum of 30 days after carotid artery stenting is recommended[21,23,95]

CONCLUSIONS

The implementation of EPDs, continued development of newly designed stent options, use of dual antiplatelet therapy, and a better understanding of the appropriate criteria for use of a noninvasive approach to carotid revascularization have substantially improved outcomes with this procedure over time (Table 92.5). The long-term results of CAS remain to be established, especially with regard to stent patency, but 10-year data from the CREST trial appear promising.[16]

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Bonati LH, Dobson J, Featherstone RL, et al. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet*. 2015;385(9967):529–538.

The International Carotid Stenting Study (ICSS) is a multicenter, randomized, British trial designed to compare CAS versus CEA for patients with >50% symptomatic carotid artery stenosis. This paper describes the long-term outcomes of the study (median follow-up time 4.2 years), which demonstrated that the risk of fatal or disabling stroke was similar for CAS and CEA.

Brott TG, Hobson RW 2nd, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363(1):11–23.

This paper describes the original outcomes of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), which is the largest multicenter, randomized trial designed to compare outcomes for CAS versus CEA to date. At a median follow-up of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary composite endpoint (stroke, MI, or death from any cause during the periprocedural period up to 30 days or any ipsilateral stroke within 4 years after randomization) between groups. However, notably, the data from CREST demonstrated that CAS had a higher risk of periprocedural stroke, whereas CEA had a higher risk of periprocedural MI.

Brott TG, Howard G, Roubin GS, et al. Long-term results of stenting versus endarterectomy for carotid-artery stenosis. *N Engl J Med*. 2016;374(11):1021–1031.

This paper describes the long-term follow-up data from the CREST trial. After 10 years of follow-up, there were no significant differences between CAS versus CEA for the risk of periprocedural stroke, myocardial infarction, or death and subsequent ipsilateral stroke. The rate of postprocedural ipsilateral stroke also did not differ between groups.

Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol*. 2008;7(10):893–902.

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial is a German multicenter, randomized, noninferiority trial designed to compare CAS versus CEA among patients with ≥70% symptomatic carotid stenosis. This paper describes the 2-year follow-up outcomes for the study, which demonstrated no significant differences in cumulative 30-day stroke/death and 2-year ipsilateral

stroke between treatment groups. However, CAS failed to meet criterion for noninferiority compared with CEA at 30 days, and the study was stopped prematurely due to cost issues and futility.

Gurm HS, Yadav JS, Fayad P, et al. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2008;358(15):1572–1579.

This paper describes the 3-year results for the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, which is a multicenter, randomized, noninferiority US trial designed to compare CAS versus CEA for patients with ≥ 50% symptomatic or ≥ 80% asymptomatic carotid artery stenosis. SAPPHIRE enrolled 334 patients total (167 in each group) and demonstrated that CAS was noninferior to CEA both at 1 year and 3 years postoperatively.

Mas JL, Trinquart L, Leys D, et al. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol*. 2008;7(10):885–892.

The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial is a multicenter, randomized, noninferiority French trial designed to compare CAS versus CEA for patients with >60% symptomatic carotid artery stenosis. This paper describes the trial's 4-year follow-up, which demonstrated worse outcomes with CAS due to significantly higher rates periprocedural stroke/death.

Ricotta JJ, Aburahma A, Ascher E, et al. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg*. 2011;54(3):e1–e31.

This paper outlines the official Society for Vascular Surgery guidelines regarding use of CAS and CEA and patients with carotid artery stenosis. Based on available RCT data, these guidelines suggest that CAS be reserved for symptomatic patients with stenosis of 50%–99% at high risk for CEA for anatomic or medical reasons; CAS is not recommended for asymptomatic patients. For asymptomatic patients undergoing CEA, the perioperative risk of stroke and death must be <3% to ensure benefit for the patient. These guidelines are supported by similar guidelines published by the American College of Cardiology/American Heart Association and the European Society of Cardiology in the same year.

Rosenfield K, Matsumura JS, Chaturvedi S, et al. Randomized trial of stent versus surgery for asymptomatic carotid stenosis. *N Engl J Med*. 2016;374(11):1011–1020.

The Carotid Angioplasty and Stenting Versus Endarterectomy in Asymptomatic Subjects Who Are at Standard Risk for Carotid Endarterectomy With Significant Extracranial Carotid Stenotic Disease (ACT-I) trial is a randomized noninferiority trial designed to compare outcomes after CAS versus CEA among patients <80 years of age with severe asymptomatic carotid stenosis who were not considered to be at high risk for surgical complications. The primary outcome (composite of death, stroke, or MI within 30 days or ipsilateral stroke within 1 year) was not significantly different between groups, and after 5 years of follow-up the cumulative rate of stroke-free survival was similar for CAS and CEA.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 93

Cerebrovascular Disease: Carotid Artery Dissection

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Carotid artery dissection is a relatively uncommon entity that results from either traumatic injury or can be spontaneous without a clear etiology. This chapter summarizes the current state of knowledge about carotid dissection, with a focus on spontaneous dissection.

CAROTID ARTERY DISSECTION

Arterial dissection occurs when disruption of the intima allows blood to extravasate between layers of the vessel wall. The resulting intramural hematoma usually extends distally and can lead to acute stenosis or occlusion (Fig. 93.1) and later to aneurysmal change with an increased risk for thromboembolic events. Dissection of the carotid artery either is spontaneous or has a precipitating mechanical event (traumatic or iatrogenic). Although each type of dissection is relatively uncommon, both are important clinically because they can be a source of stroke and occur particularly in young people. Cervical carotid artery dissections are responsible for only 2% of all ischemic strokes but account for 10% to 20% of strokes in young and middle-aged patients.[1] Spontaneous and traumatic carotid dissections differ in their pathophysiology and will be reviewed separately.

Spontaneous Carotid Artery Dissection

Epidemiology

The overall incidence of clinically apparent spontaneous carotid dissection is reported to be between 1.7% and 2.6%.[2,3] Spontaneous cervical carotid artery dissection occurs most frequently in the third through the fifth decades of life, and the mean age at diagnosis is 45 years. There is no gender predilection for spontaneous dissection, but women are affected at an average of 5 years younger than men.[4,5]

Pathogenesis

Spontaneous dissection can occur in any artery but is more likely to occur in the extracranial carotid and vertebral arteries than in other vessels of similar size (see Chapter 97). These arterial segments are mobile and can potentially come into contact with the bony structures of the head and neck.[4] A history of antecedent minor trauma is often elicited in patients with "spontaneous dissection," but the significance of these events is unclear and the course is distinctly different from dissection caused by definite and severe trauma.[5] Chiropractic manipulation has been implicated as an etiology of "spontaneous"

Abstract

Carotid artery dissection is a relatively uncommon entity that results from either traumatic injury or can be spontaneous without a clear etiology. This chapter summarizes the current state of knowledge about carotid dissection, with a focus on spontaneous dissection. Etiology, natural history, and treatment options and outcomes are discussed.

Keywords

Carotid
Dissection

Figure 93.1 Dissection of the Cervical Segment of the Internal Carotid Artery. Note the elongated, narrowed, and tapered luminal stenosis *(solid arrows)*, a finding frequently seen in association with extracranial dissections. Another common feature of this entity, fairly abrupt reconstitution of the carotid lumen at the base of the skull *(open arrow)*, is also shown. (From Mokri M. Dissection of the cervical and cephalic arteries. In: Meyer FB, ed. *Sundt's Occlusive Cerebrovascular Disease*. Philadelphia, PA: WB Saunders; 1994:51.)

dissection of the carotid and vertebral arteries, but a true relationship is elusive because 25% of these patients also have connective tissue disorders and neck pain, which may or may not be related to the dissection.[4,6]

Atherosclerosis and other known risk factors for vascular disease such as smoking, diabetes, hypercholesterolemia, and oral contraceptive use are usually absent in patients with spontaneous dissection. These patients do have a higher incidence of hypertension, and a migraine disorder has also been shown to have an independent association with spontaneous dissection.[7,8] Spontaneous cervical carotid artery dissection occurs more frequently in the winter, and recent infection is present in up to 58% of patients. There is a preponderance of respiratory infections, but mechanical factors such as coughing, sneezing, and vomiting do not seem to be independent risk factors.[9] Winter peaks in hypertension and infection may contribute to seasonal variability.[10]

Underlying abnormalities of the vasculature have been implicated in spontaneous cervical carotid artery dissection, including fibromuscular dysplasia, Ehlers-Danlos syndrome, cystic medial necrosis, Marfan syndrome, autosomal dominant polycystic kidney disease, and osteogenesis imperfecta type I.[4] Associated vascular anomalies implicated in spontaneous dissection include arterial redundancy, intracranial aneurysms, aortic root dilatation, and increased arterial distensibility.[11] Familial occurrences of spontaneous carotid dissection are also described, which further supports the possibility of an inherited disorder,[8] but definitive proof is lacking.

Clinical Findings

The most common initial symptom in patients with spontaneous dissection of the carotid artery is headache, whereas "classic" patients have a partial Horner syndrome. Nausea occurs more often with vertebral dissections, and hemispheric symptoms more often with carotid dissections.[12] Patients with cervical carotid artery dissection also suffer from neck pain, amaurosis fugax, anisocoria, pulsatile tinnitus, and cranial nerve palsy.[4,12] Cranial nerves IX through XII and in particular the hypoglossal nerve are most commonly involved.[13]

The classic clinical description of patients with spontaneous carotid dissection is ipsilateral head or neck pain, ipsilateral partial Horner syndrome (also referred to as oculosympathetic palsy), and cerebral or retinal ischemia. Oculosympathetic palsy refers to miosis and ptosis caused by involvement of the sympathetic fibers accompanying the internal carotid artery but does not include the facial anhidrosis of Horner syndrome, which is mediated by sympathetic fibers running along the external carotid artery. The onset of cerebral or retinal ischemia can occur hours or days after the initial symptoms. The classic triad of symptoms is present in less than a third of patients with spontaneous carotid dissection, and the diagnosis must obviously be considered in patients with more subtle manifestations and isolated symptoms.[4]

Traumatic Carotid Artery Dissection

Epidemiology

The incidence of traumatic carotid artery dissection in all patients seeking medical care after blunt traumatic injury is 0.08%,[14] but it is higher in patients with specific patterns of injury.[15] After blunt head and neck trauma, the incidence of internal carotid dissection is 0.86%,[16] and patients with head and neck injury and an altered level of consciousness have a reported incidence of carotid injury of up to 3.2%.[17]

Improved imaging modalities and increased awareness of cervical carotid arterial injury may have contributed to an apparent rise in incidence over the past decade. It is suggested that cervical carotid artery dissection is underdiagnosed, and several groups have reported a much higher incidence than was previously noted when all patients with severe head and cervical spine injuries are screened.[17,18] Screening may have particular value in trauma patients because neurologic deficits can have a delayed manifestation or be attributed to associated injuries, and some data suggest that early anticoagulation in asymptomatic patients with blunt carotid injury detected by screening leads to improved neurologic outcome.[19,20]

Pathogenesis

Traumatic cervical carotid artery dissection can occur after blunt or penetrating trauma, and both direct and indirect forces

contribute to injury. The most common mechanism of injury is extreme cervical hyperextension or lateral hyperflexion associated with severe blunt head and neck trauma caused by a motor vehicle collision.[15,16]

Clinical Findings

Most series reporting patients who experienced traumatic dissection are small or retrospective, describe clinical manifestation that vary from exclusively asymptomatic patients to patients with lateralizing symptoms appearing after a latent period of 4 hours to 75 days, and combine outcomes for injury and dissection of all cervical vessels.[15,17,21] Head and neck pain, hemiparesis, hemiplegia, dysphasia, aphasia, Horner syndrome, lateralizing transient ischemic attack (TIA), and stroke have all been described as initial symptoms of traumatic cervical carotid artery dissection. Some advocate routine screening (ultrasonography) in all patients with head and neck trauma.[17,18] Mandatory diagnostic evaluation is advocated for active bleeding in the head and neck, expanding neck hematomas, cervical bruits in patients older than 50 years, imaging suggesting acute brain infarction, central or lateralizing neurologic deficits, Horner syndrome, head or neck pain, cervical spine fracture, Glasgow Coma Scale score less than 6, petrous bone fracture, diffuse axonal injury, basilar skull fracture, Le Fort II or III fracture, or any combination of these findings.[16,21]

Diagnostic Evaluation

Diagnostic modalities are the same for spontaneous and traumatic carotid artery dissection. Although ultrasound is readily available and thus commonly used as the initial test, four-vessel selective cerebral angiography remains the "gold standard." Angiography allows visualization of the arterial lumen and characterization of the lesion. An intimal flap or double lumen is pathognomonic for dissection. The internal carotid stenosis caused by dissection is usually irregular, originates 2 to 4 cm distal to the bulb, and has a long tapering stenosis that usually ends before the internal carotid artery enters the petrous portion of the temporal bone.[4,22] Occlusions are characteristically tapered and have a flamelike appearance (Fig. 93.2), whereas aneurysms, often a later development, are usually fusiform and most commonly occur in the distal subcranial segment, although more proximal saccular pseudoaneurysms are also seen (Fig. 93.3). Angiography carries a 1% to 2% risk of hematoma or pseudoaneurysm at the access site, a 1% to 2% risk of contrast-induced nephropathy, and a 1% risk of stroke,[23] but it may also provide opportunities for endovascular intervention or surgical planning.

Computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and ultrasound are increasingly used noninvasive alternatives for diagnosing and monitoring carotid artery dissection. CTA and MRA are particularly attractive for diagnosis because their resolution approaches that of conventional angiography in detecting direct signs of vascular injury, such as irregular vessel margins, filling defects, changes in caliber, extravasation of contrast material, and occlusion,[24] and they are superior to angiography for evaluation of intramural

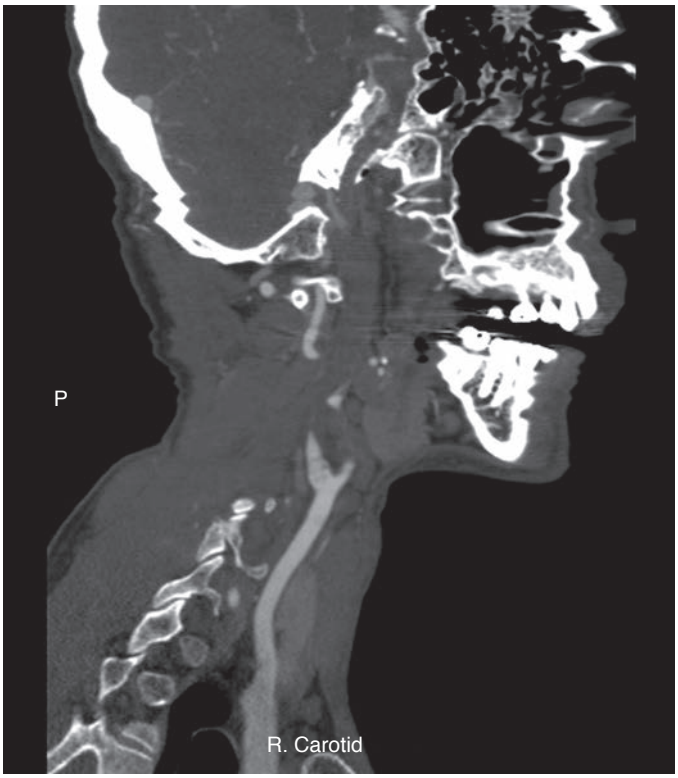

Figure 93.2 Computed tomographic angiography (centerline trace, right carotid artery) of a patient with a spontaneous dissection. Note the tapered occlusion with reconstitution near the skull base.

Figure 93.3 Angiogram showing residual stenosis and proximal pseudoaneurysm formation after traumatic carotid dissection.

hematoma and injury to surrounding structures. It should be noted that the initial results from two prospective studies in the trauma literature comparing CTA and MRA with angiography were disappointing and showed poor sensitivity and specificity.[25,26] CTA technology has improved, however, and more recent studies show 97.7% sensitivity and 100% specificity for 16-slice CTA in the diagnosis of blunt carotid and vertebral artery injuries.[27] These results suggest that CTA is a reliable, safe, fast, and cost-effective means of diagnosing cerebral artery dissections. Potential problems with CTA include artifact from metal (including projectiles) and bone, effective timing of the administration of contrast material, and the high doses of contrast material needed.

In addition to demonstrating the hyperintense crescent-shaped mural hematoma and eccentric flow typical of dissection, MRA shows a characteristic evolution of signal intensity over time and is the modality able to detect ischemic changes in the brain the earliest. Disadvantages of MRA are lack of availability, longer time required for imaging, and interference from extrinsic structures such as external fixation devices in trauma patients. Nephrogenic systemic fibrosis is a potential complication in patients with renal insufficiency who receive gadolinium for MRA.

Ultrasound does not evaluate the surrounding tissue or define the actual site of dissection as well as other noninvasive modalities do, but it does effectively detect resulting flow abnormalities. In experienced hands it is up to 95% sensitive in the diagnosis of carotid dissection when extracranial Doppler, transcranial Doppler, and duplex ultrasonography are appropriately combined.[28] Advantages of ultrasound are accessibility and convenience, which are particularly valuable in an acutely injured patient and for purposes of monitoring disease progression and resolution over time.

Natural History

Cerebral infarction is documented in 42% of spontaneous carotid dissections, and 58% of patients have persistent neurologic deficits.[12] Higher incidences of stroke appear in earlier reports,[13] and this may be the result of improved diagnosis and treatment.[4] More recently, studies of blunt traumatic carotid injury report mortality rates of up to 30% (in many cases related to associated injuries) and rates of permanent severe neurologic deficits of up to 20%.[19,20]

In patients with spontaneous dissection managed medically, the incidence of recurrent dissection is 0.3% to 1.4%, and recurrent dissection is more frequent in the first month and more common in patients with connective tissue disease or a family history of cervical carotid artery dissection. The annual risk of recurrent stroke ranges from 0.3% to 3.4%. Dissection is the most common cause of extracranial internal carotid aneurysm, but two-thirds of carotid aneurysms resolve, and complications related to aneurysm are rare.[29]

The prognosis is worse for traumatic carotid dissection. Patients with traumatic dissection are more likely to develop aneurysms and progress to occlusion, and are less likely to show improvement or resolution of aneurysms and stenoses than patients with spontaneous dissection.[30] The prognosis after stroke caused by dissection is worse than the prognosis after stroke caused by atherosclerosis. Dissection patients have more global middle cerebral artery involvement and severe clinical impairment.

A recent analysis of the Cervical Artery Dissection in Stroke Study (CADISS) trial evaluated the natural history of dissecting aneurysms and whether they are associated with an increased recurrent stroke risk, and whether the type of antithrombotic drugs (antiplatelets vs. anticoagulants) modifies the persistence or development of carotid aneurysms.[31] A total of 264 patients with extracranial cervical artery dissection were included from the CADISS, a multicenter prospective study that compared antiplatelet with anticoagulation therapy. Logistic regression was used to estimate age- and sex-adjusted odds ratios (ORs). The authors also conducted a systematic review of published studies assessing the natural history of dissecting aneurysms and stroke risk in patients with non-surgically-treated extracranial carotid dissection with a carotid aneurysm. A dissecting aneurysm was present in 24 of 264 patients at baseline. In 36 of 248 patients with follow-up neuroimaging at 3 months, 12 of the 24 baseline aneurysms persisted, and 24 new ones had developed. There was no association between treatment allocation (antiplatelets vs. anticoagulants) and whether an aneurysm at baseline persisted at follow-up or whether a new one developed. During 12 months of follow-up, stroke occurred in 1 of 48 patients with a dissecting aneurysm and in 7 of 216 patients without (age- and sex-adjusted OR 0.84; 95% confidence interval [CI] 0.10 to 7.31; $P = .88$). Published studies, mainly retrospective, showed a similarly low risk of stroke and no evidence of an increased stroke rate in patients with a dissecting carotid aneurysm. The authors concluded that the results of CADISS provide evidence suggesting that dissecting carotid aneurysms may have benign prognosis and therefore medical treatment should be considered.

Patients with strokes caused by dissection are younger with fewer vascular risk factors.[32] Although the overall functional prognosis in patients with stroke caused by dissection may be the same in young patients with stroke from other causes,[29] the overall implications of permanent impairment are greater because younger people are involved.

Treatment

Medical Therapy

Carotid artery dissection is thought to cause stroke as a result of ischemic stenosis or embolism from the site of the intimal tear. Microemboli have been detected acutely after dissection and correlate with the presence of stroke in patients with spontaneous and traumatic dissections.[33] Because of these factors, antithrombotic therapy has logically been the mainstay of medical treatment of carotid artery dissection. Concerns regarding anticoagulation include possible worsening of intramural bleeding at the site of dissection, bleeding from associated injuries in the case of trauma, and bleeding from unrelated sources. A

Cochrane Database Systematic Review in 2003 unfortunately found no randomized trials that compared antiplatelet drugs with anticoagulants or either type of agent with controls for the treatment of dissection. Although nonrandomized studies do not show a difference in mortality between patients receiving antiplatelet medications and patients receiving anticoagulation, the intracranial hemorrhage rate of anticoagulated patients is 0.5%, as opposed to 0% in those receiving antiplatelet medications alone.[34] An ongoing prospective trial is currently comparing antiplatelet therapy with anticoagulation for the treatment of acute cervical carotid artery dissection. The primary endpoint is ipsilateral stroke or death within 3 months of randomization, and secondary endpoints include any TIA or stroke, major bleeding, and residual stenosis.[35]

Despite the lack of level I evidence, most patients with spontaneous or traumatic dissection are treated with systemic heparin followed by warfarin for 3 to 6 months. Therapy after this is typically individualized and depends on vascular imaging.[33]

More recently, the CADISS trial was designed to be a prospective multicenter randomized-controlled trial in acute (within 7 days of onset) carotid and vertebral artery dissection. Intracerebral artery dissection was excluded. Patients were randomized to antiplatelet therapy (aspirin, dipyridamole, or clopidogrel alone or in dual combination) or anticoagulation therapy (heparin followed by warfarin aiming for an International Normalized Ratio [INR] in the range 2 to 3) for at least 3 months. The primary endpoint was ipsilateral stroke or death within 3 months of randomization, and secondary endpoints included any TIA or stroke, major bleeding, and residual stenosis.[23]

The results of the nonrandomized arm of the CADISS-NR trial, along with a meta-analysis of these results with previously published studies comparing the two therapeutic strategies were recently published. A total of 88 patients from 22 centers with extracranial carotid and vertebral dissection were recruited within 1 month of symptom onset.[24] At the primary endpoint of 3 months, three (5.08%) patients treated with antiplatelet had recurrent TIA, compared with none in the anticoagulation group. For meta-analysis, there were data from 40 nonrandomized studies including 1636 patients. There was no significant difference between the two treatments in recurrent stroke risk, or risk of death. These data suggested no superiority of anticoagulation or antiplatelet therapy in prevention of stoke after carotid and vertebral artery dissection.[36]

The results of the randomized trial showed similar findings. Two hundred and fifty participants (118 carotid, 132 vertebral) were enrolled, with a mean time to randomization of 3·65 days (SD 1·91). The major presenting symptoms were stroke or TIA (n = 224) and local symptoms (headache, neck pain, or Horner syndrome; n = 26). One hundred and twenty-six participants were assigned to antiplatelet treatment versus 124 to anticoagulant treatment. Overall, four (2%) of 250 patients had stroke recurrence (all ipsilateral). Stroke or death occurred in three (2%) of 126 patients versus one (1%) of 124 (OR 0.335, 95% CI 0.006 to 4.233; $P = .63$). There were no deaths, but one major bleeding (subarachnoid hemorrhage) in the anticoagulant group. Central review of imaging failed to confirm dissection in 52 patients. Preplanned per-protocol analysis excluding these patients showed stroke or death in three (3%) of 101 patients in the antiplatelet group versus one (1%) of 96 patients in the anticoagulant group (OR 0.346, 95% CI 0.006 to 4.390; $P = .66$).[37] The authors found no difference in efficacy of antiplatelet and anticoagulant drugs at preventing stroke and death in patients with symptomatic carotid and vertebral artery dissection, but stroke was rare in both groups, and much rarer than reported in some observational studies, questioning the clinical practice of using anticoagulation in patients with carotid dissection.

Surgical Treatment

Indications for surgical treatment of acute carotid artery dissection are fluctuating or deteriorating clinical neurologic symptoms despite medical treatment, compromised cerebral blood flow, contraindications to antithrombotic therapy, and a symptomatic or expanding aneurysm.[38-40] Indications for surgery after 6 months of medical treatment are persistent high-grade stenosis and a new or persistent aneurysm greater than twice the diameter of the normal internal carotid segment.[38] Aneurysms rarely (if ever) enlarge or rupture but may be a source of distal thromboembolization.[41] A cerebral embolus is an appropriate indication for repair, but there are no data regarding the need for repair in an asymptomatic patient with an aneurysm.

Exposure of the internal carotid artery for treatment of dissection is more difficult than exposure for atherosclerotic disease because lesions are more distal. Most dissections are superior to the bulb in the transition zone, where the artery becomes elastic rather than muscular. Distal exposure can require maneuvers that include division of the digastric muscle, mandibular subluxation, fracture of the styloid bone, and subtotal petrosectomy (see Chapter 91). Reports of distal balloon control in this setting could not be found, but it might be considered. Once exposure is obtained, surgical options include carotid ligation, interposition saphenous vein graft to a cervical or intracranial segment, and patch angioplasty. Ligation is considered safe, if necessary, in patients with systolic stump pressure greater than 70 mm Hg,[42] and the response to preoperative temporary balloon occlusion is also helpful in predicting whether ligation will be tolerated.

Postoperative complications are common after surgery for carotid dissection. In one group's experience, mortality was 2%, ipsilateral stroke occurred in 8%, 20% of reconstructions did not have primary patency at discharge, and 58% of patients experienced cranial nerve dysfunction (although 41% had a cranial nerve palsy preoperatively).[38] Another group reported a 9% rate of postoperative stroke and a high rate of cranial nerve palsy after high cervical exposure, but no sequelae at a mean follow-up of 6.2 years.[41] Most providers continue antithrombotic medication postoperatively if there are no contraindications, but confirmatory data do not exist.

Endovascular Therapy

Indications for endovascular intervention are essentially the same as for surgery. Given the morbidity and mortality associated

with open procedures, endovascular therapies for carotid dissection are increasingly being applied to treat the carotid dissection itself, or a resulting expanding aneurysm with the use of stents and/or other catheter based interventions. Two trials have compared intravenous thrombolysis and stent-assisted intraarterial thrombolysis for symptomatic middle cerebral artery occlusion secondary to carotid dissection. The larger series (N = 18) showed no difference between the groups at 3 months,[43] and the smaller series (N = 10) showed a better outcome at 3 months with endovascular treatment.[44] The authors of both papers agree that larger randomized controlled trials are needed.

Endovascular treatment is increasingly being applied to a number of acute cerebrovascular conditions, including stroke secondary to atherosclerosis or dissection,[45] carotid "blowout" syndrome, aneurysm, stenosis,[46] and arteriovenous fistulae.[47] Endovascular treatment of cervical carotid artery dissection is also being explored, and multiple case reports have documented encouraging outcomes.[48-50] An early small series from 1999 reported the results of carotid stents placed for four acutely symptomatic traumatic dissections and one spontaneous dissection.[51] There were no procedural complications, all patients improved clinically within the first 24 hours, and all remained well at follow-up. Another group reported placement of stents in seven patients with acute and chronic spontaneous carotid dissection. All patients exhibited improvement or resolution of symptoms, and the patency rate was 100% on follow-up imaging.[39] The only complication was an asymptomatic intraprocedural dissection (one patient died after heart transplantation 4 months after stent placement). All patients were pretreated for at least 4 days with clopidogrel and aspirin, received heparin intraoperatively, and took clopidogrel for at least 6 weeks postoperatively and aspirin indefinitely. All procedures were performed under local anesthesia without the use of cerebral protection devices. Equally favorable results have been reported for the treatment of traumatic dissection[40] and in series combining patients with traumatic and spontaneous dissection.[52]

Intraarterial or intravenous thrombolytic agents can also be used for the management of dissection associated with ischemic symptoms caused by thromboembolism, but data are still controversial. Excluding the contraindicated traumatic dissection, lytic therapy in spontaneous dissection can presumably increase the risk of expansion of the subintimal hematoma and subsequent dissecting aneurysm formation, vascular rupture, luminal narrowing, or even vessel occlusion, and can also increase the risk of subarachnoid bleeding. Yet there is no evidence to support these concerns. In a systematic review including studies on both intravenous and intraarterial thrombolysis in CeAD, the symptomatic intracranial hemorrhage rate was 3.1% with an overall mortality of 8.1%. The authors concluded that the outcome from thrombolysis for CeAD seems to be similar to that of other ischemic stroke causes. Most recently, the Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) multicenter study showed that thrombolysis was not associated with unfavorable outcomes or with an increased rate of symptomatic bleeding.[53,54]

Given the morbidity and mortality associated with open procedures, preliminary results describing endovascular treatment of carotid dissection seem promising.

Endovascular management strategies include stenting of the dissection with bare metal or covered stents, coiling of dissecting aneurysms, stent-assisted coiling, and embolization or occlusion of dissected vessels. Among these technical alternatives, bare metal stenting is the procedure of choice that will eventually restore the normal carotid contour (Fig. 93.4). A recent systematic review confirmed the safety and technical feasibility of stenting of carotid dissection in the setting of failed medical management, stroke, hemodynamic instability, or pseudoaneurysm formation. No distal protection devices were used in any of the studies reviewed. The technical success rate was 99%, with a 1.3% procedural complication rate. At a mean angiographic follow-up of 12.8 months, in-stent stenosis or occlusion was seen in 2% of patients.[55] While some authors report endovascular treatment for asymptomatic dissections, currently there is no evidence to support such a strategy, given the high rate of spontaneous clinical and angiographic resolution with medical management alone.[56]

Selection of Treatment

At present, there are no randomized trials comparing open and endovascular treatment of patients with acute or late sequelae of carotid dissection, and no clear indications regarding when either approach might be preferred. There is concern that endovascular interventions at the skull base could be compromised by bony resistance to stent deployment or bending and rotational forces at the point where the skull constrains the vessel. Although the results from recent endovascular series are promising, the case numbers are small and do not conclusively support endovascular intervention over open repair or medical management.

While the best treatment modality remains to be elucidated by large randomized trials, most patients can be safely treated with either anticoagulation or antiplatelet therapy and have good clinical and anatomic outcomes over long-term follow-up.

Surgical outcomes, including carotid ligation, have been inferior to conservative management with unacceptably high rates of stroke and cranial nerve injury.[57] Thus surgery should be limited to those cases with progression of symptoms in anatomically accessible lesions.

Endovascular interventions represent an attractive minimally invasive alternative, with potentially less cranial nerve injury compared with surgery. While recent data suggest that they are indeed safe,[58-61] they can pose potential hazards, including stroke and perforation in these thin-walled acutely dissected arteries, with unproven long-term benefit.

Thus larger series and longer-term follow-up are needed to determine whether such interventions provide low risk-to benefit ratio compared with conservative medical management alone.

Spontaneous carotid dissection seems to follow a relatively benign course and can be safely managed conservatively with short-term antiplatelet therapy. While invasive interventions are available, mainly in the form of endovascular interventions, the majority of patients are expected to make a full recovery with medical therapy alone.

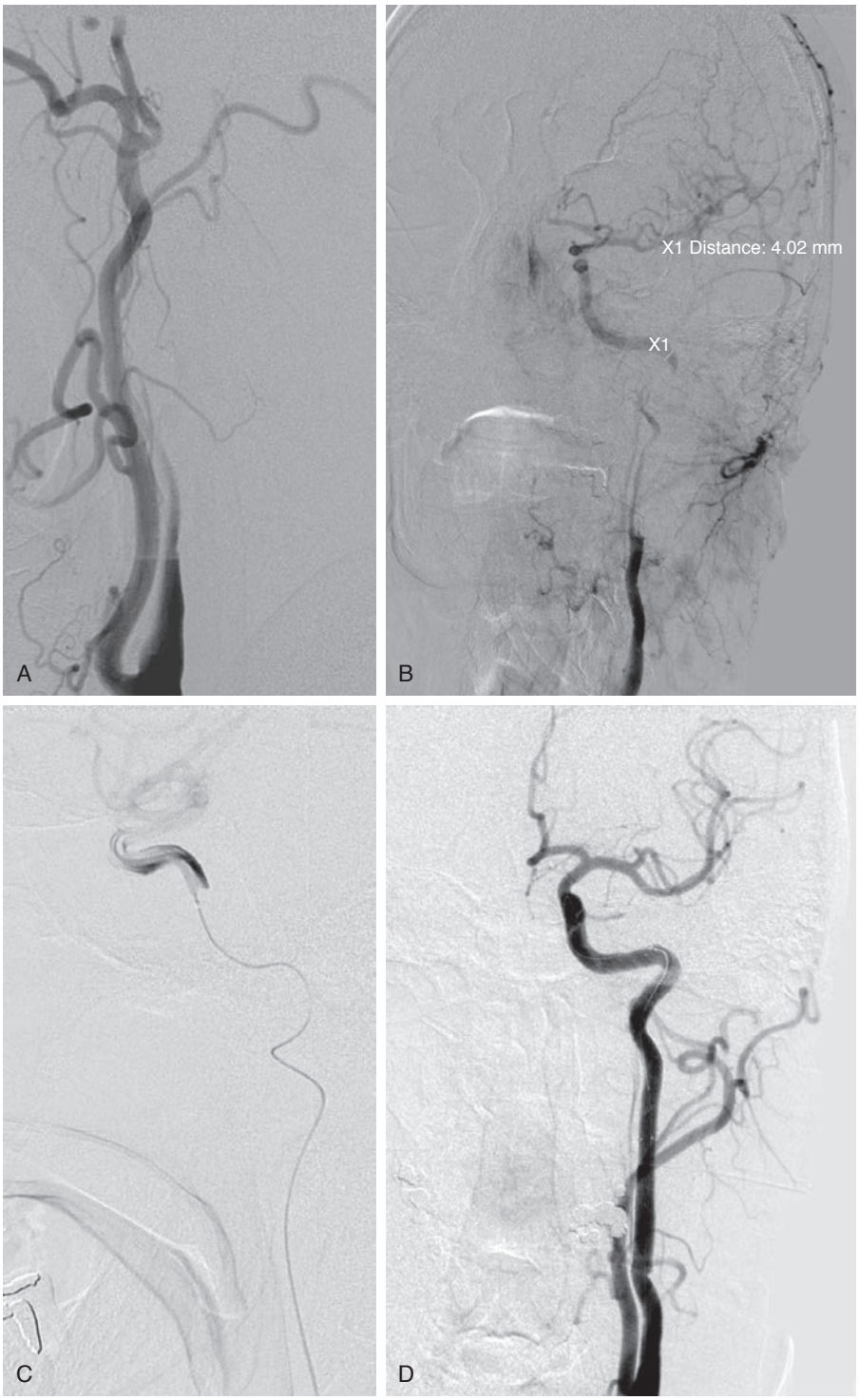

Figure 93.4 The patient is a 55-year-old male who presented with after left eye visual loss and right sided weakness. He was found on noninvasive imaging to have concern for an occlusion of the internal carotid artery likely secondary to dissection. He had a fluctuating neurological exam and this lesion was suspected to be flow-limiting. A) Selective injection through the guiding catheter positioned in the left common carotid artery demonstrates he flame-shaped tapering of the distal cervical carotid suggestive of a dissection at the skull base; B) Selective injection through the guiding catheter positioned in the left proximal internal carotid artery demonstrates occlusion but reconstitution of the supraclinoid carotid artery as well as middle cerebral artery and anterior cerebral artery branches; C) Using an 0.14" microwire and a microcatheter the occlusion has been traversed; D) Two overlapping 6mm self-expanding stents were deployed and the internal carotid artery intracranially as well as the anterior and middle cerebral artery branches fill well without evidence of branch vessel occlusion.

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CHAPTER 94

Carotid Artery Aneurysms

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Aneurysms of the extracranial carotid arteries can occur as a result of atherosclerotic degeneration, traumatic injury, dissection, local infection, or as a complication after carotid endarterectomy (CEA). Extracranial carotid artery aneurysm (ECAA) is an uncommon but important clinical entity. Carotid aneurysms are extremely rare in comparison with atherosclerotic occlusive disease of the same location. These aneurysms are also rare in comparison with aneurysms involving the *intracranial* carotid arteries and their branches. The reported incidence of incidental intracranial aneurysms discovered in autopsy studies ranges from 0.8% to 18%.[1,2] The incidence of ECAA is largely unknown, but repair represents only 1% to 1.5% of procedures performed for extracranial cerebrovascular disease at major referral centers.[3-5] The true incidence of ECAA is well less than 1% of all carotid diseases. This chapter updates the contemporary management of ECAAs, including both open surgery and the evolving experience with endovascular therapy.

DEFINITION

The normal carotid bifurcation is typically 40% greater in diameter than the more distal internal carotid artery (ICA). The accepted definition of most arterial aneurysms is "an artery having at least a 50% increase in diameter compared to the

Abstract

Extracranial carotid artery aneurysms (ECCA) are rarely entities, often occurring secondary to atherosclerosis, traumatic injury, intimal dissection with subsequent degeneration, infection, or post-endarterectomy. Both endovascular techniques as well as traditional open surgical resection have been described, albeit in small series due to the low incidence of this disease process.

Keywords

carotid aneurysm
carotid artery disease
carotid artery
internal carotid artery surgery
interposition graft
stents

expected normal diameter of the artery."[6] Given this definition, it does not require much dilation of the carotid bulb to reach this threshold, a fact that has led to disagreement about what constitutes an ECAA. De Jong et al.[7] proposed that ECAA be defined as bulb dilation greater than 200% of the diameter of the ICA or greater than 150% of the diameter of the common carotid artery. This strict definition is used in many of the contemporary reports of ECAA and is helpful, given the normal physiologic dilation of the carotid bulb.

HISTORICAL REVIEW

Sir Astley Cooper[8] is credited with the first unsuccessful and first successful operations for ECAA in London in 1806 and 1808, respectively. Ligation of the common carotid artery was the sole treatment. Winslow[9] reported an exhaustive review of 124 reported cases through 1925, including 82 patients treated by carotid ligation with a mortality rate of 28%. The first report of resection of a carotid aneurysm with primary anastomosis was described by Shea in 1955.[10] The first successful procedure of this type was performed by Dimitza in 1952.[11] When inadequate length of vessels precludes primary anastomosis, an interposition graft must be used. Beall et al.[12] performed the first prosthetic graft replacement for this lesion in 1959. By the 1970s, direct arterial reconstruction or autogenous vein grafting (or both) had supplanted carotid ligation. Endovascular techniques were first applied as a treatment strategy for ECAAs in the 1990s.

EPIDEMIOLOGY

Population Affected

The population affected and age at diagnosis are directly related to the cause of the aneurysm. The relative frequency of the various potential causes of ECAA has changed over the years. Syphilis, tuberculosis, middle ear, and tonsillar infections were the most common causes of carotid artery aneurysms before the advent of antibiotics. In Winslow's review, the majority of these early cases were pseudoaneurysms related to trauma or "erosions" from middle ear infections and tonsillitis, rather than true atherosclerotic aneurysms.[9] Therefore the majority of patients were between 20 and 40 years of age, and the surgical morbidity and mortality associated with treatment, were excessive. Although mycotic ECAAs were thought to be a problem of the past, a modern series reported from Durban, South Africa, found 22 patients presenting with ECAAs to have human immunodeficiency virus (HIV) and/or tuberculosis, suggesting that (mycotic) ECAAs are more commonly encountered in the immunocompromised patient population.[13]

In contemporary practice, atherosclerotic degeneration, dissection, trauma, and previous carotid surgery have supplanted infection as the most frequent causes of ECAA, so the age at initial evaluation tends to mirror that of patients with carotid occlusive disease (Table 94.1).[3,14-26] Increasing the use of antibiotics for head and neck infections has significantly reduced the incidence of mycotic arterial infections involving the carotid artery from local extension of a septic process. ECAAs have also occurred in patients who have undergone extensive surgery and radiation therapy for head and neck cancer.[27]

TABLE 94.1 Data From the 17 Largest Single-Center Experiences With Extracranial Carotid Artery Aneurysms Since 1950[a]

Cases of extracranial carotid artery aneurysm (ECAA):	
Number	649
Indications for treatment (% of ECAA cases):	
Atherosclerotic origin	36
Pseudoaneurysm	33
Trauma	13
Dissection	6
Fibromuscular dysplasia	7
Infection	2
Other	3
Bilateral aneurysms	5% of ECAA cases

[a]Data from references 11 through 23.
Adapted from El-Sabrout R, Cooley DA. Extracranial carotid artery aneurysms: Texas Heart Institute experience. *J Vasc Surg*. 2000;31:702-712.

Blunt trauma, dissection, and penetrating injury to the neck can result in a carotid pseudoaneurysm. Such lesions are typically encountered in a younger population. Pseudoaneurysms after CEA performed for occlusive disease usually affect individuals in their sixth or seventh decades of life.

True degenerative carotid aneurysms affect men twice as often as women,[17,28] and there does not seem to be a predilection for the right or left side. Most patients are older than 60 years, but true degenerative carotid artery aneurysms have also been reported in children.[29] There does not seem to be a specific racial distribution of true degenerative carotid aneurysms. Earlier reports suggested that the incidence of ECAAs coexisting with other aneurysmal disease ranged from 14% to 25%.[9,15] Most modern series, however, have not reported similar findings. There have been several reports of ECAAs in patients with connective tissue disorders, including Ehlers-Danlos syndrome, neurofibromatosis, and Behçet disease. It should be noted that in such patients, it is unwise to use autologous vein for arterial reconstruction because there has been late aneurysmal degeneration of the repairs using this conduit. Synthetic conduits to replace the ECAA appear to be the best option at this point in this patient population.

Incidence

A 1979 report of a search of the world's literature from 1687 to 1977 found only 853 ECAAs.[4,5] Pooled data from the 13 largest single-center series from 1960 to 1995 demonstrated 392 aneurysms involving the extracranial carotid arteries. Including only series that reported concurrent CEA volume during that same period, a total of 17,854 carotid procedures were performed, 276 of which were for ECAA, for a relative

incidence of 1.54%. The largest single-center series reported, that by El-Sabrout and Cooley[3] from the Texas Heart Institute, included 67 ECAAs treated between 1960 and 1995. During the same period, 7394 peripheral aneurysm and 4991 carotid operations were performed at the same institution. This 1.31% relative incidence is mirrored in several other published series.[16,30] These single-center series are from large referral centers, so the true incidence of ECAAs is probably less than 1% of all carotid disorders. Because these aneurysms are rare, it is impossible to define their true incidence or to determine whether their frequency is increasing. However, advances in vascular and soft tissue imaging have contributed to their greater recognition, especially in victims of trauma.[31]

PATHOGENESIS

Etiology

Degenerative/Atherosclerotic

Currently degenerative (or atherosclerotic) is the most frequently reported pathology associated with ECAAs (40% to 70% of cases). These are true aneurysms. The histologic features include disruption of the internal elastic lamina and thinning of the media. Although most true carotid aneurysms exhibit arteriosclerosis, it is considered a secondary event rather than a primary etiologic factor. Grossly, these aneurysms tend to be fusiform rather than saccular and are most commonly located at the bifurcation of the common carotid artery or the proximal ICA, where atherosclerotic plaque is common (Fig. 94.1). Atherosclerotic aneurysms that do not involve the carotid bifurcation are frequently saccular and occur in patients with severe arterial hypertension. Most bilateral, nontraumatic ECAAs are of the saccular type.

Posttraumatic Causes

Penetrating injuries involving the extracranial carotid arteries can have two important vascular sequelae: arteriovenous fistula and pseudoaneurysm formation. The incidence of carotid artery injury in civilian trauma series ranges from 12% to 17% of the total penetrating neck injuries. The internal jugular vein is most frequently involved in penetrating injuries of the neck. The common carotid artery is the most frequent site of arterial injury from penetrating trauma in this location. The incidence of pseudoaneurysm development after penetrating carotid injury is not known. Iatrogenic injury to the carotid artery during attempted placement of a catheter in the internal jugular vein is another frequent cause of carotid pseudoaneurysm.

Blunt cerebrovascular injury (BCVI) is rare, occurring in 0.18% to 2.7% of blunt trauma patients, and typically involves the distal ICA just below the skull base. Traumatic dissections can degenerate into persistent pseudoaneurysms, which can enlarge, embolize thrombus, or even rupture. Some authors advocate treatment of Grade 3 pseudoaneurysms that persist beyond a week.[32] Many of these patients have associated head injuries precluding antiplatelet therapy and anticoagulation initially. In the rare instances of enlarging or symptomatic pseudoaneurysm, the patients are typically diagnosed at a later time point from their original injury and can safely be treated with clopidogrel and treated intraprocedurally with heparin.

Post-Endarterectomy Aneurysms

CEA-related pseudoaneurysms are some of the most frequently reported aneurysms of the extracranial carotid arteries. El-Sabrout and Cooley[3] demonstrated that 57% of their 67 cases were a result of previous CEA. Zhou et al.,[26] in a later series from the Baylor College of Medicine, found post-CEA pseudoaneurysm

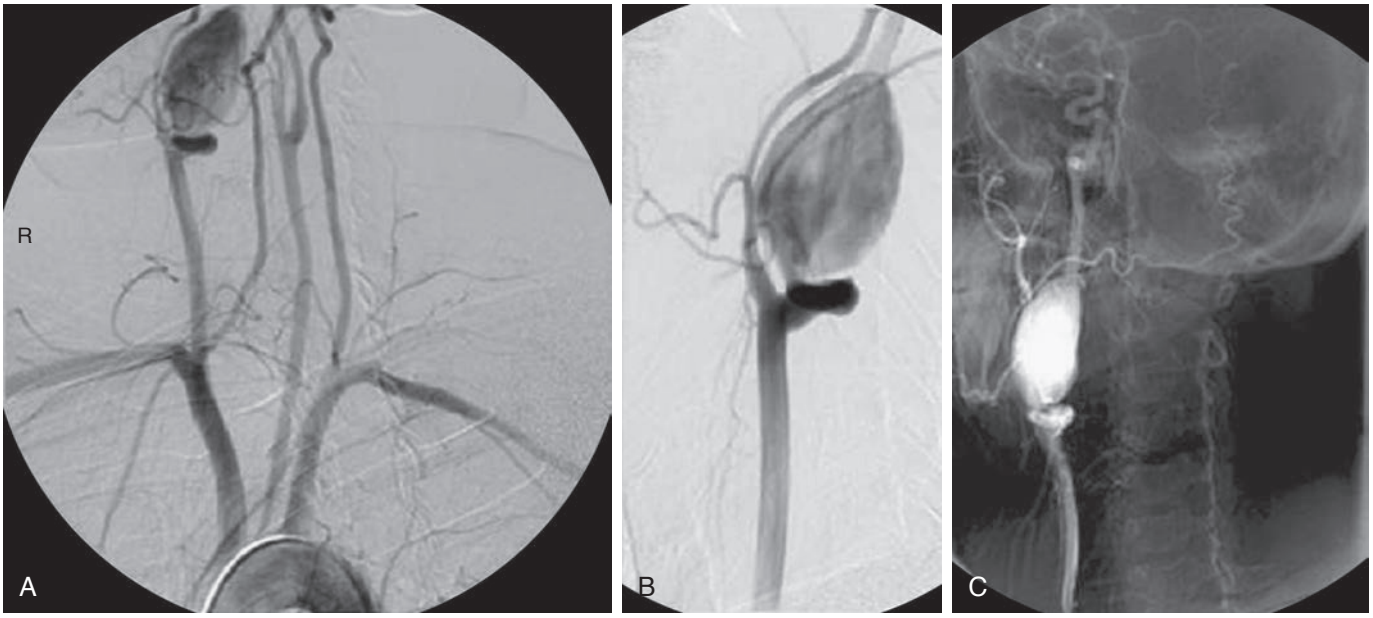

Figure 94.1 Arch (A) and right carotid (B and C) arteriograms showing a large extracranial carotid artery aneurysm involving the proximal internal carotid artery.

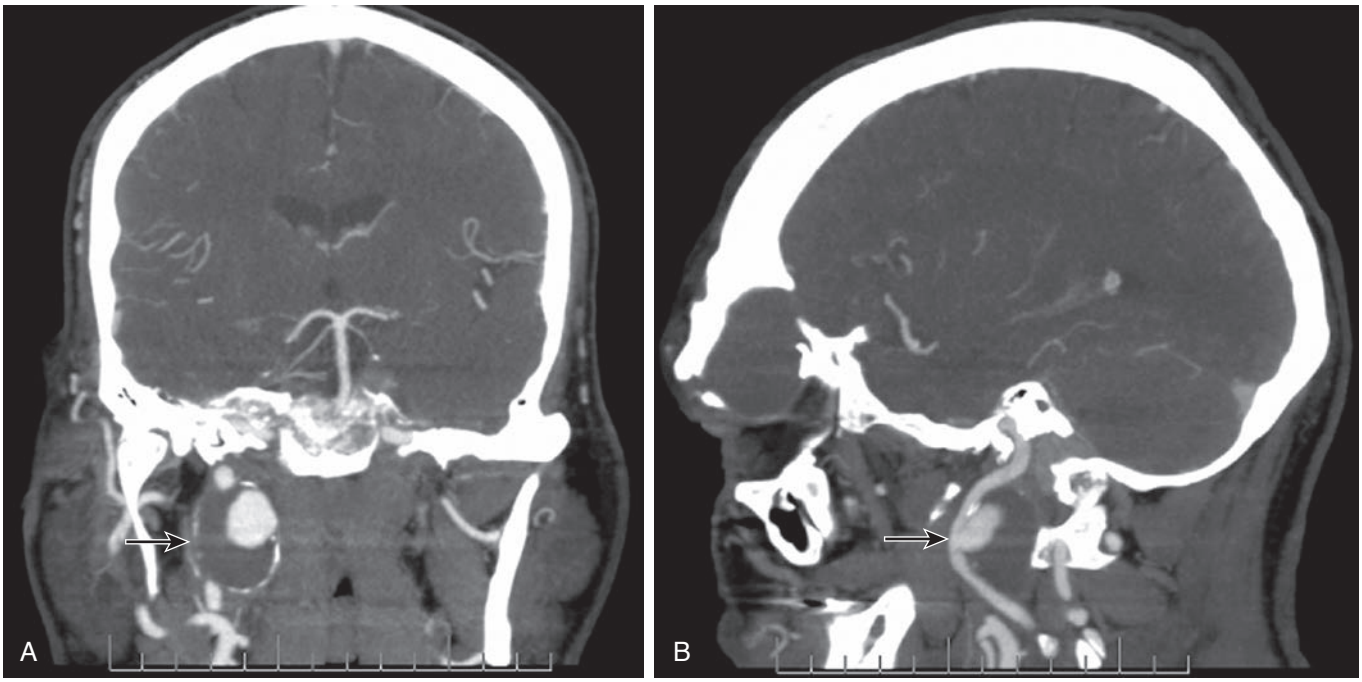

Figure 94.2 Anterior (A) and lateral (B) computed tomography arteriogram reconstructions of a 4-cm distal internal carotid artery aneurysm *(arrow)*. This aneurysm was treated with a covered stent graft with good result. (Courtesy Steven Oweida, MD, and John Parp Jones, MD.)

to be the principal etiology in 15 (36%) of 42 cases. The development of post-CEA pseudoaneurysm is related to either suture line failure or infection. Aneurysmal degeneration of saphenous vein patches has also been reported. El-Sabrout and Cooley[3] reported seven patients in whom the silk sutures (used for patch angioplasty before the advent of monofilament sutures) degenerated. Infectious complications were seen in a third of all post-CEA pseudoaneurysms. The patients typically have local signs and symptoms of infection, including pain and erythema at the operative site or draining neck sinuses. Infection of the synthetic patch is identified at the time of removal, with *Staphylococcus* species being the most commonly cultured causative organism (Figs. 94.2 and 94.3).

Arterial Dysplasia

Arterial dysplasia, usually a fibromuscular variant, was the most frequent pathologic cause of ECAAs reported in the series by Faggioli et al.[22] and also by several others.[30,33] However, this finding has not been the experience documented in most other reported large series. The arteries of patients with fibromuscular dysplasia typically display a beaded appearance (alternating stenotic webs and dilations). These dysplastic lesions may lead to ICA dissection and pseudoaneurysm formation.

Pathology

Although ECAAs are frequently associated with atherosclerotic pathologic changes, the pathologic process is much more complex. The rarity of primary carotid artery aneurysm in comparison with carotid occlusive disease makes it difficult to accept atherosclerosis as the sole cause. Histologic study of carotid artery aneurysms, however, does reveal many of the findings seen in atherosclerotic specimens: fragmentation of the elastic lamina, lipid-laden foam cells, extracellular accumulation of cholesterol, deposition of hemosiderin, degeneration of the media, and neoangiogenesis. Thinning of the media and fragmentation of the internal elastic lamina are also seen, as in aging arteries. Just as many authorities propose for abdominal aortic aneurysms, atherosclerosis is a coexisting finding but may not be the primary cause.[34,35]

CLINICAL FINDINGS

Physical Features/Symptoms

Pulsatile Mass

The symptoms of ECAAs vary according to their location, size, and etiology. The most common symptom is a usually painless pulsatile neck mass, which was the initial symptom in 93% of patients in the series reported by Zhou et al.[26] Tenderness and overlying erythema, especially if associated with fever, should raise suspicion for an infected aneurysm.

ICA aneurysm is occasionally recognized as a pulsating mass in the tonsillar fossa or pharynx with little or no manifestation of its presence externally in the neck. The classic analytic study by Shipley et al.[36] emphasized that aneurysms of the ICA are directed inward into the throat, whereas those of the common carotid artery are directed outward into the neck. The absence of cervical swelling in the former is attributed to the dense, deep cervical fascia and muscles attached to the styloid process anteriorly and the cervical vertebrae posteriorly, which crowd the gradually dilating aneurysm inward toward the tonsillar

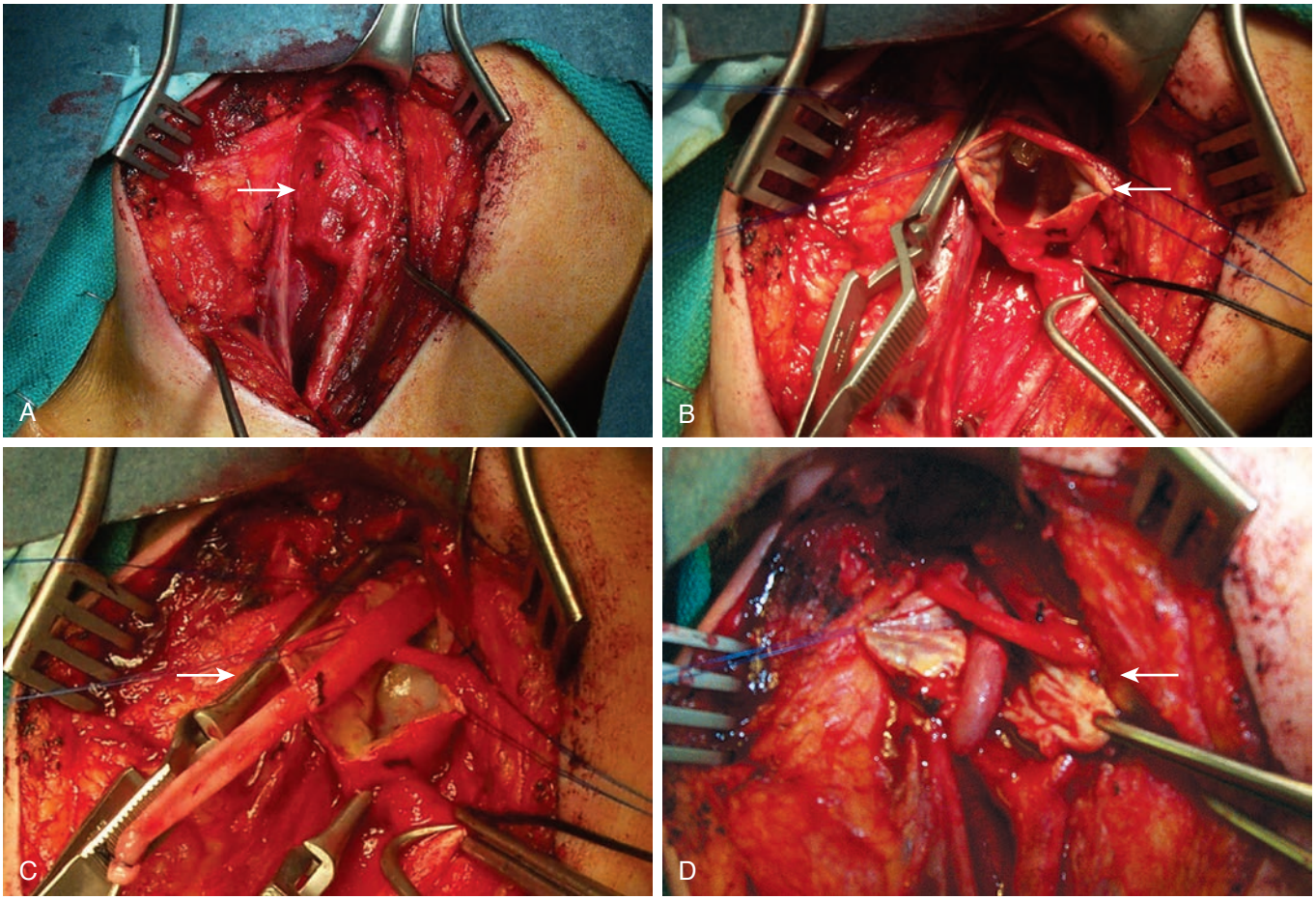

Figure 94.3 (A to D) Open repair of the extracranial carotid artery aneurysm seen in Fig. 94.1 via reversed–saphenous vein interposition.

fossa, where the thin superior pharyngeal constrictor muscle and mucous membrane offer only minimal resistance to inward protrusion.

Aneurysms that arise at or proximal to the carotid bifurcation are readily palpable and usually pose no diagnostic difficulty. Those arising from the ICA near the base of the skull can cause diagnostic problems. A chronic unilateral swelling of the posterior pharynx should raise the level of suspicion, especially when other physical signs are lacking, bizarre, or atypical. Otolaryngologists are often the first to see these lesions. A high index of suspicion usually leads to computed tomography angiography (CTA), magnetic resonance angiography (MRA), or catheter-based angiography, any of which is nearly always diagnostic when an aneurysm is present.

Neurologic Symptoms

Many series report hemispheric neurologic events as the initial symptom of carotid artery aneurysms. In the Texas Heart Institute series, 28 of the 65 patients (43%) had neurologic symptoms, including amaurosis fugax and transient ischemic attacks.[3] Three of the 28 patients suffered a stroke preoperatively. Zhou et al.[26] reported six patients (14%) with transient ischemic attack, stroke, or Horner syndrome. Most neurologic events are secondary to embolization of thrombotic material from within the aneurysm wall, but some could be potentially related to diminished flow and compression of the ICA from the mass effect of large aneurysms. Transient ischemic attacks appear to occur twice as often as completed strokes.[15,17,37]

Cranial Nerve Dysfunction

Distal ICA aneurysms are more frequently associated with cranial nerve dysfunction than are aneurysms located more proximally, but clearly nerve injury or compression can occur with large proximal carotid aneurysms as well. The ICA enters the cranium through the foramen lacerum and traverses the carotid canal in the petrous portion of the temporal bone. Accompanying the ICA are the sympathetic nerve fibers of the carotid plexus. Compression of these fibers can result in Horner syndrome. Aneurysms located more proximally can result in hoarseness from compression of the vagus or recurrent laryngeal nerve. Compression of the facial nerve can cause severe facial pain. Compression of the fifth (trigeminal) and sixth (abducens) cranial nerves has been reported as well.

Dysphagia

Occasionally, the mass of a large aneurysm can cause difficulty swallowing. Protrusion of the aneurysm into the pharyngeal constrictor muscles can produce the sensation of dysphagia, as

well as compression of the nerves involved in the swallowing mechanism. On occasion these aneurysms are discovered during evaluation for dysphagia.

Hemorrhage and Rupture

Fortunately, hemorrhage and rupture are now infrequent manifestations of carotid artery aneurysms. There have been descriptions of herald bleeds before massive rupture. When these aneurysms do rupture into the oropharynx, the bleeding is profound and death is usually due to suffocation and aspiration. Mycotic aneurysms are especially susceptible to rupture and bleeding.

Another group of patients at risk for the so-called carotid blowout syndrome[27] consists of those who have received extensive head and neck surgery and/or radiation therapy for head and neck cancer. Lesley et al.[27] reported their experience with 16 actual or impending carotid ruptures in 12 patients. Ten of these patients had undergone extensive treatment of head and neck cancer. Risk factors identified for the development of carotid blowout as a complication of treatment of head and neck cancer included thrombosis of the vasa vasorum secondary to wound infection, direct exposure and desiccation of the carotid artery, stripping of the carotid sheath, exposure of the artery to saliva, adjacent tissue necrosis, pharyngeal fistula formation, and previous irradiation.

Differential Diagnosis

The differential diagnosis for a pulsatile neck mass is extensive. The most common cause is a tortuous, kinked, or coiled carotid artery. Duplex ultrasound and occasionally CTA are required to help differentiate this finding from an ECAA. Other entities in the differential diagnosis include a prominent carotid bifurcation in a thin neck, cervical lymph nodes overlying the carotid bifurcation, carotid body tumors, glomus jugulare tumors, cervical metastatic disease, branchial cleft cysts, and cystic hygromas.

DIAGNOSTIC EVALUATION

Duplex ultrasound is the initial diagnostic imaging modality of choice for the evaluation of ECAAs emanating low enough in the neck to be evaluated by this modality. Aneurysms located high in the distal ICA, such as those related to blunt cervical carotid dissection, are notoriously missed by ultrasound. Such aneurysms require further imaging with CTA or MRA. MRA has the advantage of being able to distinguish old from recent thrombus, a differentiation that is particularly helpful in cases of carotid dissection. Knowledge of the strengths and weaknesses of the imaging modalities at one's institution should direct the next noninvasive imaging study chosen.

CTA has the benefit of visualizing the relationships of bony anatomic landmarks, which are critical in deciding whether a lesion is considered "surgically inaccessible" and requires an endovascular intervention (see Fig. 94.2A and B). MRA, when obtained in conjunction with head and brain imaging, provides indispensable information regarding the circle of Willis and collateral cerebral circulation. CTA can also provide similar intracranial imaging views, depending on the protocol utilized.

Catheter-based angiography was previously considered mandatory in the evaluation of ECAAs to obtain the detailed vascular anatomy information necessary to planning surgical treatment.[38] We currently find diagnostic arteriography is usually unnecessary, and reserve catheter-based angiography for endovascular interventions because of the potential stroke risk associated with this invasive diagnostic procedure.

The utility of diagnostic angiography in the current management of ECAAs involves the rare case in which open or endovascular arterial reconstruction are not considered to be feasible options, and carotid ligation may be necessary. Combined preprocedure noninvasive imaging of the circle of Willis anatomy and a balloon occlusion test of the ipsilateral ICA have been recommended before carotid ligation. The latter examination involves a period of occlusion with an end-hole balloon occlusion catheter in patients who are awake, anticoagulated, and at baseline blood pressure. The end-hole catheter also allows measurement of carotid artery "stump" pressure or back-pressure. A stump pressure greater than 50% of mean systemic pressure indicates adequate cerebral blood flow during the carotid balloon occlusion test.[39] Occlusion of the ICA is typically performed for 30 minutes, and the awake patient is assessed for neurologic changes. Blood pressure is also pharmacologically lowered to assess tolerance of hypotension. Several reports have detailed the inadequacy of the balloon occlusion test to accurately predict tolerance of carotid occlusion in 10% to 20% of patients.[40,41] In patients in whom ipsilateral hemispheric neurologic events developed after carotid occlusion, thromboembolic events secondary to disturbed flow were thought to be the cause. These reports stress the importance of anticoagulation with warfarin for 6 weeks to 3 months after carotid ligation.

NATURAL HISTORY

Based on prior case series demonstrating high risk of TIA, stroke, or rupture associated with nonoperative treatment, recommendations have been to intervene on essentially all carotid aneurysms once found.[9,15,17,18,26] As mentioned previously, the etiology of ECAAs has shifted from mycotic or traumatic to degenerative or postprocedural, with a more benign natural history. Furthermore, given our advances in medical therapy with statins, antiplatelet, and anticoagulation as well as improved imaging techniques, medical management in properly selected high-risk patients with small true aneurysms may prove to be a reasonable option. This was demonstrated in the Mayo Clinic study by Fankhauser et al., where 75/141 ECAAs over a 15-year period were treated nonoperatively. This series included 25 true aneurysms and 116 pseudoaneurysms. Medical management with antiplatelet therapy or anticoagulation as well as serial imaging occurred in 10 patients with true aneurysms and 65 patients with pseudoaneurysms. The size of the ECAA, as well as the age of the patient, symptomatic status, and comorbidities played a major role in the decision to pursue conservative treatment. True aneurysms undergoing observation had a mean diameter of 12.0 mm compared with 21.2 mm in those that were treated

with open surgery. Pseudoaneurysms treated medically had a diameter of 10.2 mm compared with 20.9 mm treated with open surgery and 14.5 mm undergoing endovascular intervention. During a mean follow-up of 77 months, none of these patients progressed to needing an intervention and none of them suffered death or major morbidity related to the ECAA. This is the largest series published to date and the first to demonstrate the safety of medical management in patients with small ECAAs. Clearly more research into proper patient selection based on size, presenting symptoms, etiology, associated comorbidities, aneurysm location, and associated thrombus morphology is needed to guide treatment decisions.

In cases of ECAA greater than 2 cm, any mycotic aneurysm, the presence of thrombus within the aneurysm, symptomatic aneurysm, or evidence of enlargement on serial imaging, operative intervention is warranted in the vast majority of cases. Serial observation of small, asymptomatic ECAA, especially in the elderly, is likely safe and justified.

TREATMENT

The primary objective in the treatment of such aneurysms is to prevent the permanent neurologic deficits that can arise from atheroembolism and thromboembolism. This objective is best accomplished by exclusion of the aneurysm from the arterial circulation and restoration of antegrade flow. The choice of therapy must be tailored to the individual and based on the location, size, and underlying cause of the aneurysm as well as the overall condition of the patient.

Open Surgical Approaches

Ligation

The subsequent development of modern reconstructive vascular techniques has eliminated ligation as a standard therapy for ECAAs. Ligation was performed in just 1 of the 65 patients with carotid aneurysms treated at the Texas Heart Institute over a 35-year period.[15] Ligation of the carotid artery may still be necessary in emergency situations of arterial rupture, especially if infection is the cause and the artery is deemed unreconstructable. If an elective carotid ligation is being considered, preoperative evaluation with the carotid balloon occlusion test and stump pressure measurement is necessary. Aneurysms involving the external carotid artery alone are typically ligated without reconstruction or significant sequelae.

It is recommended that patients undergoing carotid ligation be started on heparin therapy and then switched to warfarin anticoagulation for a period to prevent distal embolization because the ICA progressively fills with thrombus, with the risk of stump embolization. This approach is analogous to management of carotid artery trauma that might require ligation of the ICA. The duration of such anticoagulation is not standardized, but several groups have recommended a 2-week to 3-month course of therapy.[42,43]

Adjunctive Measures

Extracranial-to-intracranial (EC-IC) bypass, wrapping the aneurysm in fascia or mesh, and saphenous vein bypass through the aneurysm to the petrous portion of the carotid have all been described but largely abandoned due to failure to improve patient outcomes or decrease stroke risk.[44,45]

Resection and Reconstruction

Resection of the aneurysm with restoration of antegrade flow has been the conventional treatment of ECAAs in contemporary practice (see Fig. 94.3A–D). This surgical option is applicable to lesions involving the common carotid artery and proximal third of the ICA. Aneurysms involving distal portions of the ICA require further adjuncts to gain distal exposure and control.[30,46] Complete excision of large carotid aneurysms risks injury to the cranial nerves, including the facial, vagus, spinal accessory, hypoglossal, and glossopharyngeal nerves. The literature demonstrates cranial nerve injury rates between 4% and 20%. Similar dissection principles to CEA should be adhered to, with minimal aneurysm manipulation prior to vascular control, to decrease embolization risk.

Reconstruction Options

After resection of a carotid artery aneurysm, several reconstruction options are available. Small saccular aneurysms with narrow necks can be resected, and the artery closed primarily or with a patch. Mobilization of a tortuous carotid artery can frequently allow resection with primary end-to-end anastomosis. Autologous or prosthetic interposition grafts can be used with excellent results (Fig. 94.4). Autologous grafts are preferred if infectious etiology is suspected. A novel technique of using a Gore Hybrid graft was reported in 2014.[47] In this case report, the 6 mm nitinol stent portion was inserted into the distal ICA after resection of the ECAA; then a shunt was placed within the graft while the proximal anastomosis was performed.

In cases of true ECAA, it would seem intuitive to replace the entire aneurysmal segment to prevent the risk of further aneurysmal degeneration with partial excision. In the treatment of patch pseudoaneurysm following prior CEA, resection back to normal arterial wall plus redo patch angioplasty with autologous conduit when infection is a possibility is an acceptable alternative to interposition grafting.

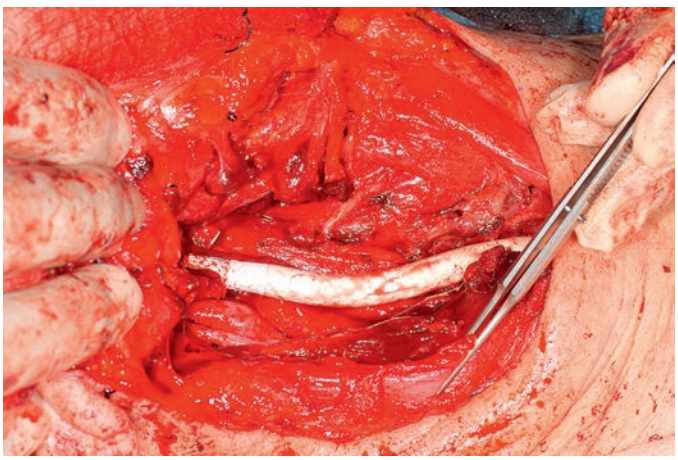

Figure 94.4 Treatment option of surgical exclusion with a prosthetic interposition graft for a large extracranial carotid artery aneurysm to prevent rupture and embolic sequelae.

Pseudoaneurysm Repair After Previous Carotid Endarterectomy

Patch angioplasty during CEA has become routine in an effort to decrease the restenosis rates seen after primary closure of the arteriotomy (see Chapter 91). Materials currently used for patch angioplasty include Dacron, polytetrafluoroethylene, and bovine pericardium. In current practice, patch pseudoaneurysm after CEA is more frequently related to infection than to degeneration of the patch. In one series, 28/141 ECAAs were pseudoaneurysms from prior CEA, 79% of whom had a Dacron patch. This trend was also seen in another large case series where 58% of pseudoaneurysms were related to Dacron patch use, and some of these used silk suture or were associated with infection.

Open Surgical Technique

Methods of cerebral monitoring and protection during carotid cross-clamping are the same as those used during conventional CEA and include electroencephalographic waveform analysis, selective shunting based on carotid stump pressure, and routine shunting. General anesthesia is usually recommended because of the difficult exposure and longer operative times for aneurysm repair than for CEA. As part of our usual practice, we routinely use shunting during CEA in patients under general anesthesia, although other authors may advocate selective shunting in these cases based upon cerebral monitoring.

Large aneurysms and aneurysms extending to the most distal ICA are technically challenging. Nasotracheal intubation should be used because it allows complete closure of the jaw which opens the space around the distal ICA. Several techniques can be used to improve distal operative exposure, including the ones described herein.

1. The first step in obtaining distal exposure should always be extension of the incision to curve in a posterior fashion behind the ear to the mastoid process.
2. Divide the ansa cervicalis to allow gentle retraction on the hypoglossal nerve.
3. Divide the posterior belly of the digastric muscle.
4. Divide the occipital artery and adjacent venous branches.
5. Divide the ascending pharyngeal artery.
6. Divide the sternocleidomastoid muscle from its mastoid attachment and elevate or resect the parotid gland. Careful dissection of the facial nerve and its branches is mandatory.
7. Remove the styloid process and its attached muscles.
8. Subluxate the mandible to increase the width of exposure at the skull base by approximately 1 cm. This maneuver is in general performed by an oral surgery team after nasotracheal intubation and prior to carotid exposure.
9. Drill and remove portions of the inferior surface of the petrous portion of the temporal bone. This process usually requires a multidisciplinary approach, including the participation of nonvascular surgeons with experience in skull base surgery.
10. Use of intraluminal balloons, usually as part of a shunt (e.g., the Pruitt-Inahara shunt), to control distal internal carotid back-bleeding can be a useful adjunct when distal control is difficult.

Once proximal and distal control is obtained, the decision must be made whether to perform complete aneurysm exclusion or partial resection. With a true atherosclerotic aneurysm, we typically replace the entire aneurysm with a saphenous vein interposition graft harvested from the groin. We typically use an endoaneurysmorrhaphy technique so that the cranial nerves are not injured during excision of the aneurysm wall. As with repair of abdominal aortic aneurysms, the sac of the aneurysm is used to cover the interposition graft. Use of a prosthetic graft in this situation has been reported. No large series have compared use of the two conduits, but a prosthetic graft is a reasonable alternative.

In situations of prosthetic patch pseudoaneurysm, El-Sabrout and Cooley[3] have reported good results with resection of the pseudoaneurysm back to normal arterial wall and repeat patch angioplasty. In such circumstances we would also recommend autologous material to patch the artery because infection is frequently encountered in this situation. Painter et al.[28] recommended the use of an in-line straight shunt, as opposed to the Javid type, during vein interposition to tailor the vein graft to the appropriate length so that kinking could be avoided. In such cases, the vein interposition graft is telescoped over a straight shunt. After the distal anastomosis is performed, the vein graft is pulled to length over the shunt and trimmed accordingly. The shunt is then removed just before completion of the proximal anastomosis, and flushing maneuvers are performed in the usual fashion. We routinely use intraoperative duplex ultrasound to evaluate carotid reconstructions.

Endovascular Therapy

Endovascular management of ECAAs offers the advantages of avoiding a potentially difficult dissection and eliminating the need for high cervical exposure, thus reducing the risk for cranial nerve injuries and other procedure-related complications. Although most cranial nerve dysfunction is temporary, the incidence of such injuries is significant, reaching 20% in some series.[26] Although rare, permanent significant cranial nerve injuries can be devastating.

Several endovascular techniques for the treatment of ECAAs have been reported, including bare-metal stents with and without trans-stent coiling (Fig. 94.5A and B),[48] placement of double stents,[49] autogenous vein graft–covered stents,[50] endovascular coil or balloon occlusion,[51] and placement of covered stent-grafts (Fig. 94.6).[52]

Percutaneous injection of thrombin under ultrasound guidance has become the treatment of choice for traumatic pseudoaneurysms of the common femoral artery. Holder et al.[53] reported successful thrombosis of a traumatic carotid pseudoaneurysm by endovascular balloon occlusion of the neck of the aneurysm followed by percutaneous injection of thrombin after inadvertent central venous catheter puncture. We have had no personal experience with this technique and have concerns about the risk for embolization once the balloon is deflated.

In 2006, the Baylor College of Medicine group reported their development in the treatment of such aneurysms, including 14 patients managed by endovascular means.[26] Stent-grafts were

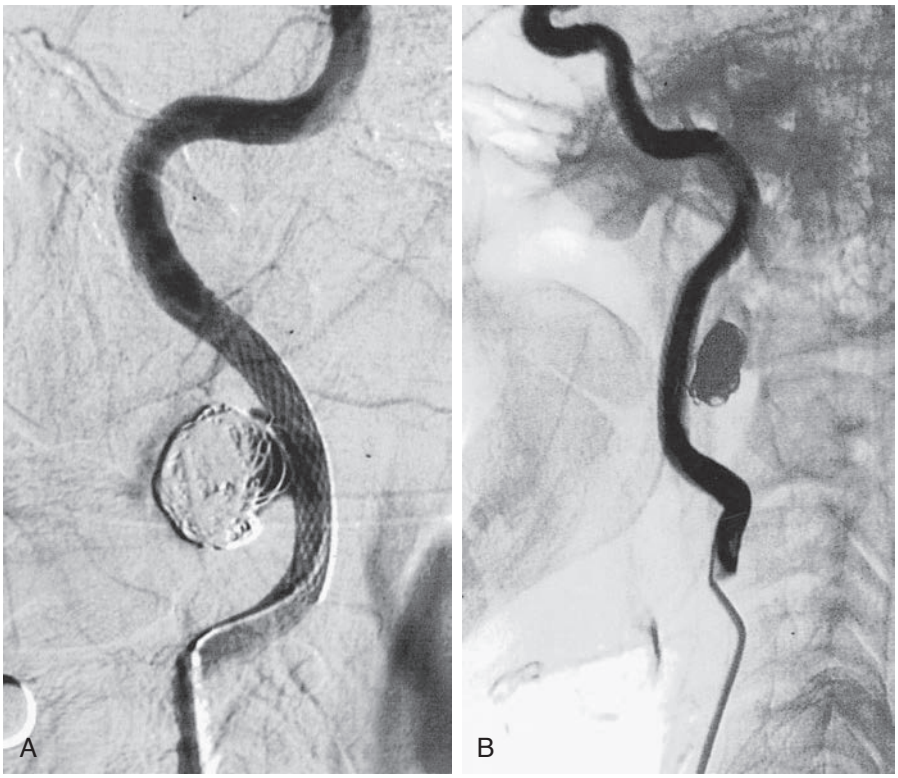

Figure 94.5 After placement of a self-expanding stent across the neck of the aneurysm, a microcatheter is used to introduce coils into the aneurysm sac. (A) Completion arteriogram documented a patent internal carotid artery (ICA) with aneurysm exclusion. (B) Arteriography after 5 months showed excellent flow through the ICA with exclusion of the pseudoaneurysm. (From Bush RL, Lin PH, Dodson TF, et al. Endoluminal stent placement and coil embolization for the management of carotid artery pseudoaneurysms. *J Endovasc Ther*. 2001;8:53–61.)

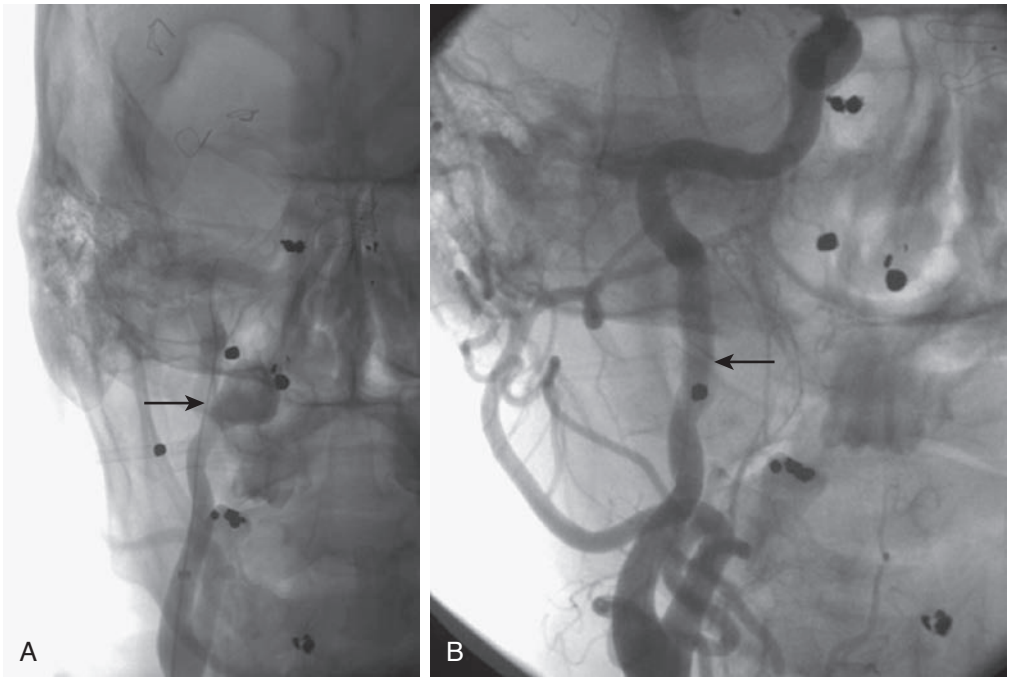

Figure 94.6 (A) Selective right carotid arteriogram revealing the distal right internal carotid artery aneurysm demonstrated in Fig. 94.2. (B) Placement of a 5-mm × 2.5-cm Gore Viabahn (W.L. Gore and Associates, Inc., Flagstaff, Arizona) covered stent-graft for treatment of the distal right internal carotid artery aneurysm seen in A and Fig. 94.4.

TABLE 94.2 Endovascular Management and Results From Recent Single-Center Studies

Author	Year	# of Patients	Techniques	Approach	Complications
Fankhauser et al.[56]	2015	18	CS, TSC, BO/CE	NS	None
Welleweerd et al.[57]	2015	7	BMS, CE,	Femoral, carotid	Transient CNI ×2
Zaghlool[60]	2014	1	CS	NS	None
Angiletta et al.[61]	2014	3	CS	femoral	None
Pan et al.[62]	2014	1	SWS	femoral	none
Pulli et al.[63]	2013	5	CS, BMS	NS	none
Du toit et al.[64]	2009	10	CS, BMS	femoral	CVA ×1, last occlusion ×1

BMS, Bare metal stent; *BO*, balloon occlusion test; *CE*, carotid embolization; *CS*, covered stent; *NS*, not specified; *SWS*, stent within a stent; *TSC*, trans-stent coil.

used in seven patients, carotid stenting with trans-stent coiling in six, and endovascular balloon occlusion in one. In most series of endovascular treatment of carotid artery aneurysms, a variety of endovascular therapies have been used, and thus the small numbers in each group have precluded any meaningful comparison of the various treatments.

We currently use a 6-Fr Flexor Shuttle Select Sheath (Cook Medical, Inc., Bloomington, Indiana) in the majority of carotid interventions performed from a femoral approach. If one is contemplating the use of a covered stent, such as the Gore Viabahn Endoprosthesis (W.L. Gore and Associates, Inc., Flagstaff, Arizona), larger sheaths may be needed (Table 94.2). We typically use a 0.014-inch wire to cross the aneurysm and have used a distal embolic protection device as long as there is reasonable length to land such a device above the aneurysm neck. In a circumstance of difficult transfemoral access, a cervical direct common carotid cutdown can be utilized.

Trans-Stent Coil Embolization

The technique of trans-stent coiling involves initially crossing the neck of a saccular aneurysm with a self-expanding stent. If a distal embolic protection device is deployed on the 0.014-inch wire, there is adequate room to introduce a second wire ("buddy wire") to track a 3-Fr RAPIDTRANSIT Microcatheter (Cordis Endovascular) into the aneurysm sac between the stent interstices. Coil embolization of the entire aneurysm sac is performed with detachable or platinum coils. The stent prevents migration of the coils into the distal carotid circulation.

Stent-Graft Coverage

In patients who have a fusiform aneurysm without a discrete neck, a stent-graft prosthesis is a better treatment option as long as there is adequate length of artery for proximal and distal sealing. How much proximal and distal seal zone is considered adequate, however, is unknown. Typically a larger introducer sheath is required for a stent-graft prosthesis. The stents are oversized to the artery per the instructions for use of the individual device. The stent-graft with the shortest length that will have adequate seal is chosen so that a distal kink is not created in the carotid artery. We angioplasty only within the stent graft and avoid angioplasty of the normal adjacent proximal and distal intima of the carotid artery.

Hori et al.[49] described a novel double-stent technique in which overlapping uncovered stents are placed within each other. The greater surface area coverage of the two stents is thought to increase the chance of immediate aneurysmal thrombosis through decreased flow into the sac. We have no personal experience with this technique but are concerned that if aneurysm sac flow is persistent, it may be impossible to track a catheter across the double latticework of stents to place coils if an additional procedure becomes necessary.

Selection of Treatment

The location and size of a carotid aneurysm also play a critical role in determining which therapy to offer. Large aneurysms and those involving the distal ICA, because of the difficult surgical exposure and significant morbidity, are probably best managed with endovascular techniques. On the other hand, the presence of unstable-appearing thrombus within an aneurysm or pseudoaneurysm or the occurrence of preoperative embolic symptoms may be considered a relative contraindication to endovascular repair. Aneurysms in very tortuous carotid arteries also present a relative contraindication to endovascular therapy because of the difficulty of stent tracking and conformability to the artery wall. In fact, many tortuous arteries lend themselves to aneurysm excision and primary end-to-end repair of the artery.

TREATMENT OUTCOME

Open Surgical Repair

Results vary widely depending on the type, size, and location of the aneurysm. Carotid ligation was previously associated with a 30% to 60% risk of stroke, and half of such patients died after stroke.[9,54,55] In a 2000 review of the 13 largest single-center series since 1950, El-Sabrout and Cooley[3] found that the combined stroke/death rate associated with carotid ligation had decreased to 12%. This change probably represents improvements in anesthetic technique and medical management as well as an understanding of the importance of anticoagulation after carotid ligation. Carotid ligation is reserved in current surgical practice for the unusual circumstance of an unreconstructable carotid artery.

In general, surgical reconstruction is associated with a combined stroke and mortality rate of about 10%.[3] Transient cranial nerve dysfunction occurs in about 20% of patients.[3] Pooled data reported by El-Sabrout and Cooley,[3] including 392 cases of ECAA, showed a combined stroke and death rate of 21% in those managed nonoperatively, 12% in those treated by carotid ligation, and 9% in those treated by surgical reconstruction (Table 94.3).[14-26]

Endovascular Therapy

The early results of endovascular repair of ECAAs appear favorable in comparison with those of open surgical repair. In a series of 141 ECAAs spanning 14 years, including 18 repaired using endovascular techniques for pseudoaneurysms, 4 covered stents, 11 uncovered stents with trans-stent coiling, and 3 carotid emoblizations were described, with no cranial nerve injury or strokes reported.[56]

In another series of 24 ECAAs in 19 patients, including 8 who underwent endovascular repair, one patient underwent coil embolization and 7 were treated with bare metal stents. Of note, three patients required open carotid exposure with manual straightening of the artery to deploy the stents from a common carotid puncture site due to tortuosity in the ICA. No strokes were described, but two patients did have transient cranial nerve palsies from traction during the open carotid exposure.[57]

Saatci et al.[58] reported using stent-grafts to treat 25 distal ICA pseudoaneurysms, the majority of which were posttraumatic. Endoleak, which occurred in two patients, resolved spontaneously in one and required the additional placement of a bare-metal stent in the other. Twenty-three aneurysms were immediately excluded from the circulation after stent-graft placement. No technical adverse events—vessel dissection, vessel perforation, or thromboembolism—occurred. No mortality or morbidity developed during or after the procedure or during the follow-up period. Follow-up angiography in 21 patients showed patent reconstruction of the ICA with no aneurysm recanalization. All symptoms resolved after treatment in patients who initially had mass effect complications.

In a report of 14 patients with traumatic pseudoaneurysms after BCVI, all patients with evidence of blunt carotid dissection underwent anticoagulation with heparin for 7 days, followed by repeat arteriography. Those with flow-limiting dissections or pseudoaneurysm formation were treated with self-expanding WALLSTENT endoprostheses (Boston Scientific Corporation, Natick, Massachusetts) and warfarin anticoagulation. In the follow-up period of 2.5 years, no strokes occurred and arteriography showed all lesions to have healed by 4 months.[32]

Zhou et al.[26] compared two different treatment periods: 22 cases all treated by open repair before 1995 and 20 cases treated after 1995. Of the 20 later cases, 14 were treated with endovascular therapy by a variety of techniques. During the second treatment period, hospital length of stay was significantly shorter, the rate of cranial nerve injury was diminished, and 30-day combined stroke/death rates were lower (14% vs. 5%, $P < .004$). No strokes occurred in the endovascular group at 30 days. At a mean follow-up of 4.6 years, 11 of 16 deaths were thought be related to cardiovascular causes, and continued aneurysm exclusion was confirmed in all patients.

Treatment of Carotid Blowout

Lesley et al.[27] reported a series of 16 carotid blowout events occurring in 12 patients, the majority of whom had undergone radiation therapy or surgery (or both) for head and neck cancer. All patients were deemed to be at high risk for cerebral ischemic complications because of a negative balloon occlusion test result or known incomplete circle of Willis. These patients were managed with a variety of stent devices and techniques. Adjunctive embolization of carotid pseudoaneurysms with platinum coils or acrylic glue was performed in five patients. Hemostasis was achieved in all cases, although one patient with traumatic carotid blowout and three patients with aggressive head and neck cancer–related carotid blowout syndrome required retreatment with endovascular therapy. Rates of recurrent carotid blowout were similar to those reported in other studies using percutaneous balloon occlusion. Overall, no treatment-related strokes or deaths occurred.

Li et al.[59] systematically reviewed all available published data of the endovascular treatment of ECAA during 1995 through 2010. There were 113 studies comprising 224 patients undergoing treatment for ECAA. Procedural success was 92.8%. Endoleaks occurred in 8.1%. The periprocedural stroke and death rates were 1.8% and 4.1%, respectively. The rate of cranial nerve injury was 0.5%. Follow-up of these patients averaged 15 months, and the stent patency rate was reported to be 93.2%. The investigators concluded that these intermediate results suggest that low complication and high success rates make endovascular treatment of ECAAs favorable. As with all meta-analyses, selection bias may contribute to the favorable results reported.

MEDICAL MANAGEMENT

Mycotic Aneurysms

Medical management of suspected or known mycotic carotid aneurysms involves the perioperative administration of antibiotics specific for the organism or organisms responsible. *Staphylococcus aureus* and *Staphylococcus epidermidis* are the most frequently encountered organisms. Gram-positive "coverage" with either vancomycin or linezolid is recommended until definitive culture and susceptibility results are available. *Escherichia coli*, *Klebsiella* species, *Corynebacterium* species, *Proteus mirabilis*, and *Yersinia enterocolitica* have also been reported. Therefore initial broad gram-negative coverage is warranted as well. Once the standards for treating vascular infection have been completed, including graft removal, autologous reconstruction, débridement of perigraft tissue, muscle flap coverage, and drainage, a course of parenteral antibiotics is recommended. There are no clinical trial data on which to base recommendations for the length of antibiotic therapy, but patients are typically treated with parenteral culture-specific antibiotics for 4 to 6 weeks followed by oral antibiotics for 3 to 6 months or for life.

TABLE 94.3 Management and Outcomes for the 14 Largest Single-Center Experiences With Extracranial Carotid Artery Aneurysms Since 1950

	LIGATION		NONOPERATIVE		SURGICAL MANAGEMENT						OUTCOME			
Series	Number of Cases	Stroke/ Death (%)	Number of Cases	Stroke/ Death (%)	Graft	Patch	EEA	Primary Closure	EC-IC	Other	Major Stroke	Death	Combined Results for Major Stroke and Death (%)	CN Cranial Nerve Dysfunction (%)
Bower et al.[14]	5	1 (20)	0	0	10	0	7	2	0	1	1	0	1 (5)	7 (35)
Welling et al.[15]	0	0	20	1 (5)	19	0	0	1	1	0	2	0	2 (9.5)	NS
McCollum et al.[16]	4	1 (25)	9	3 (33)	6	18	0	0	0	0	2	1	3 (12.5)	0
Zwolak et al.[17]	0	0	6	3 (50)	8	2	6	2	0	0	1	0	1 (5.6)	5 (22)
Rhodes et al.[18]	1	0	2	0	8	3	8	1	0	0	2	0	2 (10)	1 (5)
Pratschke et al.[19]	8	0	5	2 (40)	8	2	0	4	1	0	2	1	3 (20)	0
Krupski et al.[20]	4	1 (25)	1	0	5	6	5	0	0	0	2	0	2 (13)	6 (15)
El-Sabrout and Cooley[3]	1	0	1	0	9	39	10	1	0	6	4	1	6 (9)	4 (6)
Moreau et al.[21]	1	0	0	0	12	0	11	14	0	0	0	1	1 (3)	26 (66)
Faggioli et al.[22]	0	0	0	0	10	3	9	2	0	0	2	0	2 (8)	5 (21)
Sundt et al.[23]	3	0	0	0	7	0	5	0	4	1	1	0	1 (6)	5 (25)
Schievink et al.[24]	5	0	0	0	11	0	1	0	4	1	2	0	2 (12)	12 (55)
Pulli et al.[25]	0	0	0	0	10	6	4	1	0	0	3	0	3 (14)	2 (10)
Zhou et al.[26,a]	5	NS	0	0	17	6	0	0	0	14[a]	1	3	4 (9.5)	4 (9.5)
Totals	*37*	*3 (8.1)*	*44*	*9 (20)*	*140*	*85*	*66*	*28*	*10*	*23*	*25*	*7*	*33 (9.8)*	*77 (17.8)*

[a]Series included 14 patients who underwent endovascular treatment.

EC-IC, Extracranial-intracranial bypass; *EEA*, end-to-end anastomosis; *NS*, not specified.

SPECIAL CONSIDERATIONS

Pediatric Patients

Pourhassan et al.[29] reviewed their experience of ECAAs in children, including 27 case reports of ECAAs occurring in the pediatric population within the past 25 years. The usual initial symptom of carotid artery aneurysm in children is a pulsatile mass in the neck. The greater frequency of aneurysm rupture seen in children is probably a manifestation of the etiology. Traumatic and mycotic aneurysms seem to have the highest risk for rupture, and these causes represent the majority of cases occurring in childhood.

Given the higher rates of rupture seen in children, aggressive surgical intervention is warranted. As in adults, resection plus interposition grafting is the treatment of choice. In the pediatric population, resection of the aneurysm should be followed by interposition grafting with saphenous vein. An autologous conduit is recommended because of the infectious etiology in many cases. It also allows longitudinal growth of the vessels as the child ages.

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A complete reference list can be found online at www.expertconsult.com.

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95 CHAPTER

Carotid Body Tumors

WARREN B. CHOW, WESLEY S. MOORE, and GLENN M. LAMURAGLIA

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INTRODUCTION

The carotid body tumor, first described in 1743 by Von Haller, is the only known pathologic condition of the carotid body. The tumor is extremely rare. In 1971, only about 500 cases had been reported in the literature; this figure doubled to more than 1000 by the early 1980s. Due to the infrequency of this disorder, very little is known about its etiology, clinical, and biologic behavior, or its malignancy potential. In 1903, the first successful resection of a carotid body tumor was performed by Scudder in the United States. He was able to preserve the carotid artery and there were no significant complications. Despite over a century of literature describing surgical treatment, significant controversy remains surrounding the details in the management of carotid body tumors.

EPIDEMIOLOGY AND ETIOLOGY

The exact incidence is unknown. Although they may be discovered in patients of all ages, they are usually diagnosed in the third to fifth decades of life. Patients with family histories of carotid body tumors may present at an earlier age. Gender predominance has not been established.

Carotid body tumors may be classified as sporadic, familial, or hyperplastic. Sporadic is the most common form. Familial patterns may occur in up to 10% of cases with apparent autosomal dominant inheritance. In addition to lower age of presentation for familial cases, rates of bilateral tumors have been reported in up to 30% of cases, in contrast to bilateral disease in 2% to 20% of nonfamilial cases. Hyperplastic lesions, although not true neoplasms, are more prevalent in patients exposed to prolonged hypoxia, including those living at high altitudes and those suffering from chronic obstructive pulmonary disease or cyanotic heart disorders. This association has suggested chronic hypoxia as a potential etiology of carotid body tumors.

ANATOMY AND PHYSIOLOGY

The carotid body is the largest mass of chemoreceptor tissue in the body. It is located within the periadventitia of the posterior surface of the carotid bifurcation. The normal carotid body is ovoid in shape and approximately 5 mm in its longest dimension. It usually receives its blood supply through branches of the external carotid artery. Blood returns through tributaries of the lingual and laryngopharyngeal veins. The carotid body derives sensory innervation through small nerve fibers from the glossopharyngeal nerve.

The embryologic origins of the carotid body are both neural crest ectoderm and mesodermal tissue from the third branchial arch. The neural crest cells migrate in close association with autonomic ganglion cells; thus they are often referred to as

Abstract

Carotid body tumors are rare paragangliomas that arise from the chemoreceptive tissue located at the carotid bifurcation. Most carotid body tumors are benign; although, aggressive local invasion or malignant transformation have been observed. Carotid body tumors are typically discovered as asymptomatic neck masses. Diagnosis is confirmed with imaging studies, such as duplex ultrasound, computed tomography scanning, magnetic resonance imaging, and conventional angiography. Surgical resection is the recommended treatment for patients with acceptable perioperative risk.

Keywords

Carotid body tumor
Paraganglioma
Shamblin classification

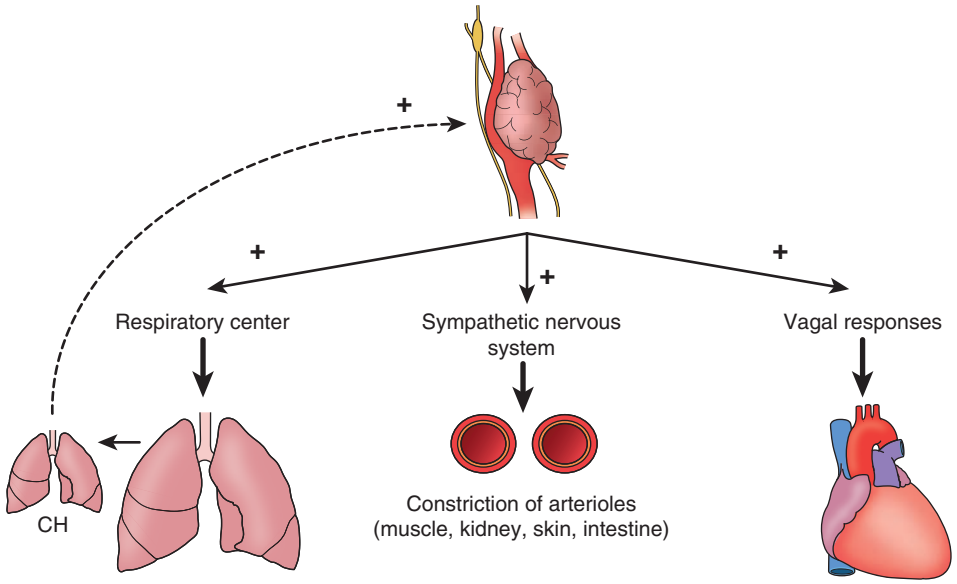

Figure 95.1 The carotid body tumor is stimulated by partial pressure of O_2, partial pressure of CO_2, and arterial pH. It sends signals to multiple body systems including cardiopulmonary centers that regulate breathing and blood pressure.

paraganglioma cells. These cells differentiate into the chemoreceptors, also known as type I glomus cells. The mesoderm forms the rich vascular stroma, made up of type II glomus cells, which support the chemoreceptor cells.

The carotid body is stimulated primarily by the partial pressure of O_2, and to a lesser degree the partial pressure of CO_2 and arterial pH. In response, the type I glomus cells release neurotransmitters that act on the receptors of afferent nerve fibers. Signals are carried through the glossopharyngeal nerve to the medulla oblongata, affecting a number of the body's systems (Fig. 95.1). Most notable are cardiopulmonary centers in the brain that regulate breathing and blood pressure. For example, hypoxia, hypercapnia, or acidosis can stimulate the carotid body, resulting in increases in respiratory rate, tidal volume, and blood pressure with vasoconstriction.

PATHOLOGY

Carotid body tumors are also known as carotid chemodectomas, carotid paragangliomas, and glomus tumors. They represent neoplastic growths of the chemoreceptive tissue. These tumors belong to the family of paragangliomas, which are neoplastic tumors that occur along the autonomic ganglion chain from the head to pelvis. Within the head and neck, carotid body tumors are the most common type. Other cervical paragangliomas include the glomus tympanicum, glomus vagale, and glomus jugulare (Fig. 95.2).

Macroscopically, carotid body tumors resemble normal carotid body tissue. They are reddish brown, rubbery, and well circumscribed, although they lack a true capsule. They are highly vascular, and can invade the adventitia of adjacent carotid vessels. As the tumors enlarge, they distort the carotid bifurcation and splay the internal and external carotid arteries, known as the "lyre sign" seen on angiography (Fig. 95.3). Frequently, large tumors will encase the external carotid artery, but they rarely wrap around the internal carotid artery, which is likely attributable to the blood supply from branches of the external carotid artery.

Microscopically, carotid body tumors tend to resemble normal carotid body architecture with a well-differentiated benign appearance. Only very rarely does histology demonstrate degenerative malignant characteristics, such as nuclear polymorphism, vascular invasion, increased mitotic activity, and necrosis. Malignant transformation cannot be predicted based on histologic findings. Advanced immunohistochemical studies have revealed that carotid body tumors can produce numerous neuroendocrine substances, often with granules rich in catecholamines seen in the cytoplasm. These tumors, in contrast to retroperitoneal paragangliomas, are usually nonfunctional and stain negative for chromaffin.

Most carotid body tumors are benign. Malignant transformation has been reported, but the exact incidence is unknown. In contrast to many other types of cancer, malignancy of carotid body tumors and other neuroendocrine tumors is based on clinical behavior instead of histology. Even benign tumors are capable of aggressive invasion into adjacent structures, as well as nodal and distal metastatic spread. Local growth may include adherence or encasement of neurologic and vascular structures, and even extension into the skull. Metastatic disease usually spreads into regional lymph nodes. If carotid body cells are found in lymph nodes biopsied during surgery, this is diagnostic for malignancy. Metastases have also been seen in the cerebellum, thyroid, brachial plexus, lungs, kidney, pancreas, bones, and breast.

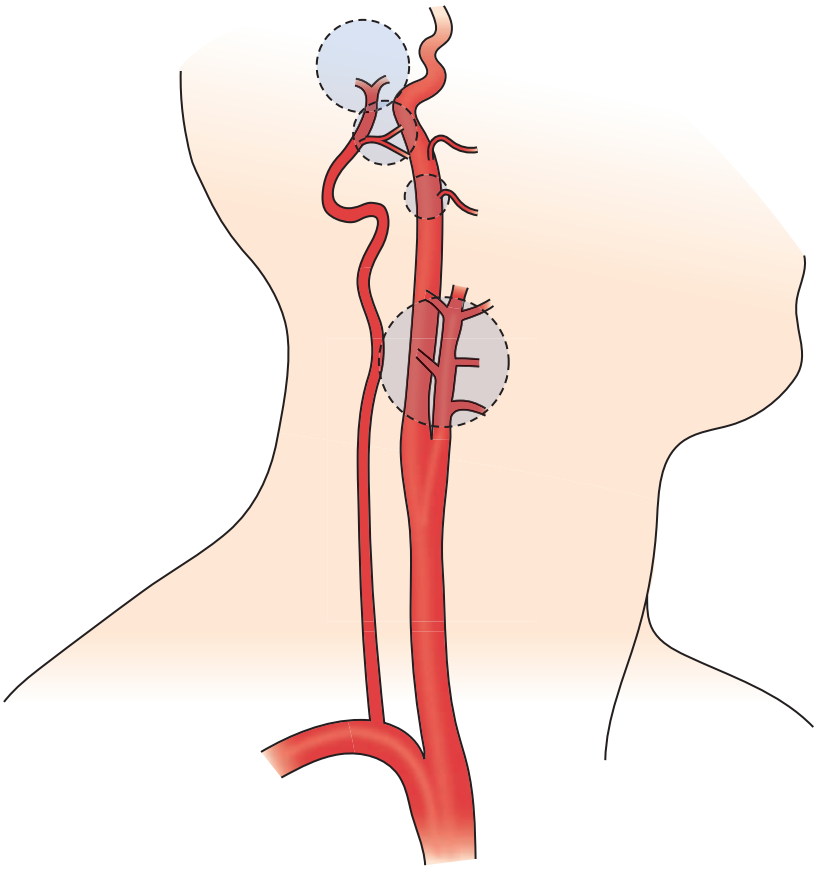

Figure 95.2 Carotid body tumors belong to the family of paragangliomas, which are neoplastic tumors that occur along the autonomic ganglion chain from the head to pelvis. Carotid body tumors are the most common of the cervical paragangliomas. Others include the glomus tympanicum, glomus vagale, and glomus jugulare. The circles represent the relative incidences of these cervical paragangliomas.

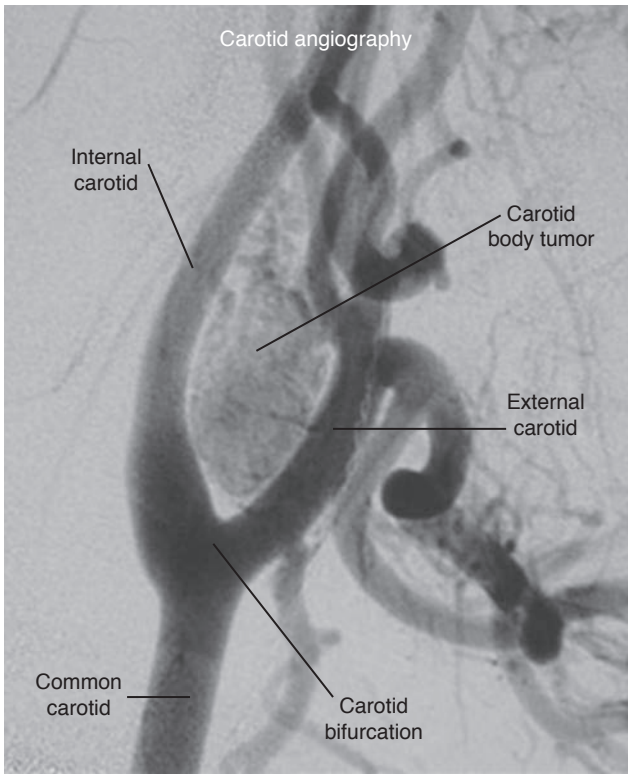

Figure 95.3 As carotid body tumors enlarge, they distort the carotid bifurcation and splay the internal and external carotid arteries, known as the "lyre sign" seen on angiography. Large tumors often encase the external carotid artery, but rarely wrap around the internal carotid artery.

CLINICAL PRESENTATION

Carotid body tumors most commonly present as asymptomatic neck masses located below the angle of mandible. On palpation, the lesions are firm, smooth, and lobulated, and are characteristically mobile laterally but fixed longitudinally due to their association with the carotid artery. Carotid pulsation may be transmitted through the mass, and approximately 30% to 40% of patients may have an audible bruit over the tumor. Very large carotid tumors may cause compression or local invasion, leading patients to present with nonspecific symptoms, such as localized tenderness, fullness, numbness, dysphagia, hoarseness, chronic cough, and tinnitus. Tumors rarely produce cranial nerve dysfunction, and if there is involvement, symptoms are typically associated with the vagal, hypoglossal, and cervical sympathetic nerves. Occasionally, Horner syndrome has been reported with this tumor. Patients may complain of dizziness, but lateralizing neurologic signs are uncommon.

Despite possessing apparatus to synthesize and secrete catecholamines and hormones, carotid body tumors are almost never functional. In extremely rare cases, tumors demonstrate neuroendocrine activity and patients may complain of headaches, dizziness, palpitations, tachycardia, arrhythmias, flushing, diaphoresis, and photophobia. Some cases have been reported of patients with hypertension that resolves after tumor resection, which may be caused by tumor-related catecholamine release.

These neoplasms tend to grow slowly over several years, although occasional cases of rapid growth have been reported.

Although the risk of malignancy is believed to be relatively low, these tumors do progress in size and become locally invasive. Patients may live many years without treatment; however, due to the morbidity and mortality associated with progressively enlarging tumors, the low but unpredictable risk of malignancy, and the ease of excising small tumors, most surgeons recommend early diagnosis and surgical resection.

DIAGNOSIS

The workup begins with a history and physical examination. The differential diagnosis for neck masses is broad, and includes congenital lesions (vascular malformations, branchial cleft cysts, hygromas), inflammatory disorders (chronic lymphadenitis, reactive lymphadenopathy), infection (viral, bacterial, and parasitic lymphadenopathy), benign lesions (lipomas, cysts, parotid, and salivary tumors), and malignancies (metastatic head and neck cancer, lymphoma). Other vascular lesions (carotid artery aneurysms, kinks, and coils) and cervical paragangliomas (glomus jugulare and glomus vagale) may also present as neck masses.

Radiographic imaging is a critically important modality in the diagnostic confirmation and preoperative evaluation. Conventional angiography was traditionally the gold standard, and provides excellent details about the overall size, extent, and vascularity of the lesion. It also shows variation in blood supply and encasement of carotid vessels, both of which can significantly affect operative planning. It can also identify synchronous and contralateral tumors, carotid atherosclerotic or ulcerative disease, and other anatomic variations (aneurysms, kinks, and coils). It can also identify intracranial vascular lesions that may affect management. Finally, angiography provides the opportunity for preoperative embolization (see below). Limitations of angiography include high costs, risk of access complications, wound complications (hematoma, dissection, pseudoaneurysm), distal embolization with stroke, and contrast problems (allergic reaction and renal failure).

Duplex ultrasound has emerged as the most important, noninvasive method for examining carotid body tumors. It subjects the patient to minimal discomfort and essentially no risk. Ultrasound can provide excellent anatomic detail, estimate tumor vascularity with color Doppler, and determine tumor size, vessel encasement, and atherosclerotic disease. Finally, compared to angiography, ultrasound is significantly less expensive. Its limitations include an inability to clearly visualize the proximal (chest) and distal extent (intracranial) of the carotid artery and the possible extent of the tumor. The level of detail is lower compared to angiography, and it may not be as sensitive for small lesions. Like other duplex studies, the reliability of carotid ultrasound is highly operator dependent.

Recently, computed tomography angiography (CTA) and magnetic resonance angiography (MRA) have supplanted conventional angiography. These methods are noninvasive but provide high levels of anatomic and vascular detail when duplex ultrasound is insufficient. CTA and MRA more clearly show the proximal and distal portions of the neck compared to duplex ultrasound and avoid the access/wound and embolic risks of conventional angiography. Both also have the advantage of 3D reconstruction. CTA has radiation exposure and contrast risks that are similar to conventional angiography, and MRA risks include nephrogenic systemic fibrosis associated with gadolinium contrast in patients with renal failure.

Due to the highly vascular nature of the carotid body tumor, percutaneous needle biopsy and incisional biopsies are *contraindicated*. Risks include hemorrhage, hematoma, pseudoaneurysm, and injury to adjacent neurovascular structures. Furthermore, the ability to confirm the diagnosis with high-quality imaging renders further diagnostic tests, including biopsy, unnecessary.

Shamblin and colleagues at the Mayo Clinic developed a classification system for carotid body tumors based on tumor extent and neurovascular involvement (Fig. 95.4). Group I tumors are smaller and can be dissected easily off the walls of the carotid arteries in the periadventitial plane. Group II tumors are larger, more adherent to the adventitia, and partially surround the carotid vessels. Group III tumors have more intimate adherence to the vessels and encase the internal and external carotid arteries. Modern imaging allows staging of carotid body tumors according to the Shamblin classification, and can assist in preoperative planning.

TREATMENT

Surgical resection is the mainstay of treatment for carotid body tumors. Although these lesions tend to be small and slow growing, they are best treated early for several reasons: smaller tumors are easier to remove; most tumors can become locally invasive; lesions may grow distally into the skull or involve cranial nerves, complicating resection; and these tumors may develop malignant behavior. In the absence of prohibitive comorbidities, perioperative risks, or limited life expectancy, patients with carotid body tumors should undergo surgical resection as soon as the diagnosis is made.

Radiation therapy is another treatment modality for carotid body tumors, although its use as a primary or adjunct therapy remains controversial due to conflicting studies and lack of long-term follow-up. Carotid body tumors are traditionally considered not radiosensitive, and radiation is used for suppression. Preoperative radiation may render surgery more difficult due to fibrosis. Radiation therapy is usually reserved for patients deemed poor operative candidates, and for bulky, unresectable, or recurrent tumors.

There are currently no effective chemotherapy treatments for carotid body tumors.

PREOPERATIVE PREPARATION

Planning should start with the evaluation of the patient's general medical condition, following current perioperative guidelines for vascular, and specifically carotid artery disease. Because the operation is elective, reasonable steps should be taken to optimize the patient's health and reduce their risk factors for perioperative adverse events.

Appropriate imaging should be performed to determine the tumor size and extent, and to identify other cervical

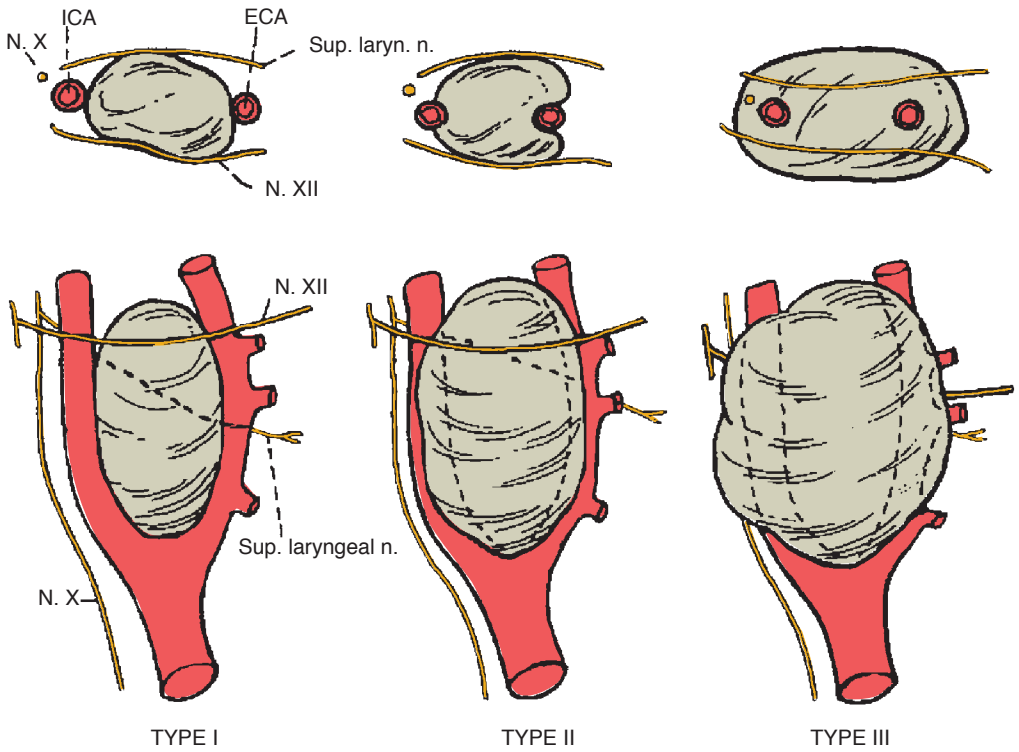

Figure 95.4 The Shamblin classification describes the staging of carotid body tumors and can assist in preoperative planning. Type I tumors are smaller and can be easily dissected from the walls of the carotid arteries in the periadventitial plane. Type II tumors are larger, more adherent to the adventitia, and partially surround the carotid vessels. Type III tumors have more intimate adherence to the vessels and encase the internal and external carotid arteries.

paragangliomas. Extension into the cranium and synchronous lesions can change operative planning. In addition, any existing cranial nerve involvement and neurologic deficits should be carefully and thoroughly documented. Although neuroendocrine activity from carotid body tumors is rare, if endocrine dysfunction or hormone imbalance is suspected, appropriate laboratory tests, including urinary catecholamines, should be ordered. Positive workup may also indicate an active synchronous lesions, such as adrenal pheochromocytomas. Medical and surgical treatment for these lesions should precede treatment for the carotid body tumor.

Preoperative embolization remains controversial. Some surgeons routinely perform embolization on Shamblin group II and III tumors. Carotid angiography is performed with selective catheterization of the ECA and embolization (Gelfoam or coils) of branch vessels feeding the tumor. Several studies demonstrate conflicting results regarding reduction in blood loss, surgical time, length of stay, and perioperative complications. The senior author does not advocate preoperative embolization. The disadvantages include the risk of inadvertent cerebral embolization and stroke. It also adds an additional invasive procedure with associated patient discomfort and increases the overall cost of care.

SURGICAL TECHNIQUE

Carotid body tumors are highly vascular lesions that carry a massive hemorrhage risk during resection. The lesions may also adhere to or envelop neurovascular structures, increasing the risk of complications. The surgeon must plan his or her operative approach according to the tumor characteristics, and attempts must be made to reduce blood loss and preserve vital structures.

Anesthesia for this operation could potentially be either cervical block or general anesthesia, as is the case for other carotid artery operations. However, resection of carotid body tumors usually requires more time than carotid endarterectomy and tends to be more invasive, particularly with large tumors. As a result, it is difficult to maintain patient comfort and compliance during a technically demanding operation that requires all of the surgical teams' attention to the operative field without the distraction that can occur with patient discomfort and restless movement. Therefore most surgeons prefer the more controlled setting of general anesthesia, with better airway management and reduced patient movement during the operation.

Cerebral monitoring and protection should be used for carotid body tumor resection due to potential or planned internal carotid artery occlusion or reconstruction. The choices are to use EEG monitoring or routine shunting of the internal carotid artery. Internal carotid artery back pressure is not an option due to the inability to clamp the external carotid artery due to tumor involvement. If continuous EEG monitoring shows ischemic changes with clamping of the carotid artery, a Pruitt-Inahara shunt can be inserted through an arteriotomy in the common carotid artery. The distal shunt is passed into the internal carotid artery and held in place by gentle inflation of the distal balloon. The proximal shunt is passed retrograde into the common carotid artery and can be held in place with the proximal balloon or a Rummel tourniquet. Some surgeons have advocated doing

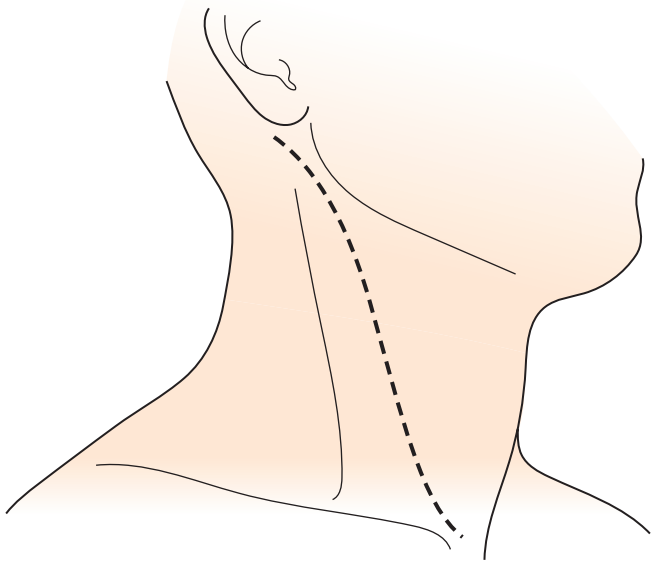

Figure 95.5 The skin incision for carotid body tumor resection is longitudinal along the anterior border of the sternocleidomastoid muscle. The incision should be centered over the carotid bifurcation.

this in all cases of carotid body tumor resection because the placement of the shunt effectively blocks inflow to the external carotid artery and may make tumor resection and hemostasis more effective.

POSITIONING AND EXPOSURE

The setup and dissection of carotid body tumors are similar to that of carotid endarterectomy (see Chapter 91). The patient is supine with the head rotated to the contralateral side. Depending on the patient's body habitus, a shoulder roll may be placed to extend the neck. The head of the table can be elevated 10 to 15 degrees to reduce venous pressures and incisional blood loss.

A longitudinal incision is made through the skin and subcutaneous tissues along the anterior border of the sternocleidomastoid muscle. The incision should be centered over the carotid bifurcation. If necessary, the incision can be extended proximally toward the sternal notch and distally toward the mastoid process (Fig. 95.5). Additional techniques for extended exposure include continuing the incision across the mastoid process behind the ear, detachment of the posterior belly of the digastric muscle from the mastoid process, division of the stylohyoid muscle with or without the styloid process, and subluxation or division of the mandible.

RESECTION OF TUMOR

The dissection continues along the anterior border of the sternocleidomastoid until the muscle can be reflected off the carotid sheath. If the parotid gland is encountered, it can be mobilized and reflected anteriorly. The carotid sheath should be opened along the anterior border of the jugular vein. The common facial vein typically joins the jugular vein near the level of the carotid bifurcation and is a useful landmark that can be divided. The jugular vein can be reflected laterally to expose the carotid arteries (Fig. 95.6). The surgeon should identify and protect the hypoglossal, vagus, and laryngeal nerves. These structures may be displaced by large tumors.

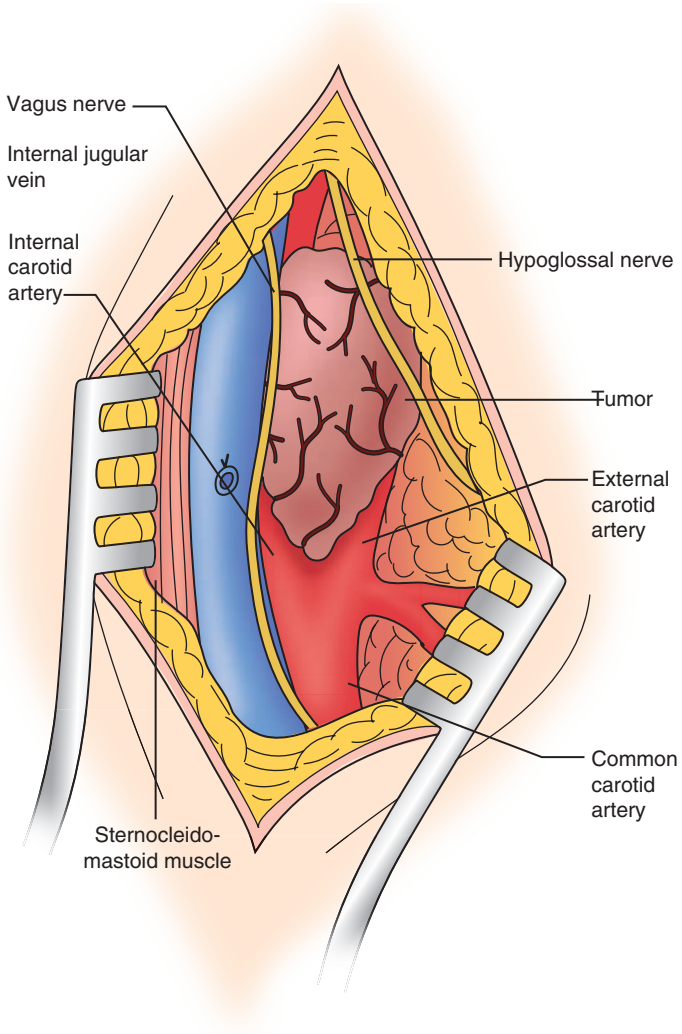

Figure 95.6 For the exposure of the carotid body tumor, the carotid sheath should be opened along the anterior border of the jugular vein. The common facial vein, which typically joins the jugular vein near the level of the carotid bifurcation, is divided to allow lateral reflection of the jugular vein. The hypoglossal, vagus, and laryngeal nerves are identified and protected. These structures may be displaced by large tumors.

The proximal common carotid artery should be circumferentially mobilized in the perivascular plane, with sufficient length obtained for possible bypass shunt (Fig. 95.7). At this point it is usually possible to see the vagus nerve. The dissection proceeds distally on the lateral aspect of the common carotid artery, in the perivascular plane, separating the artery from the vagus nerve, until a point at the upper end of the tumor mass where the internal carotid artery can be circumferentially mobilized. It is during this maneuver that the hypoglossal nerve may be encountered and must be carefully separated from the tumor mass and protected (Fig. 95.8).

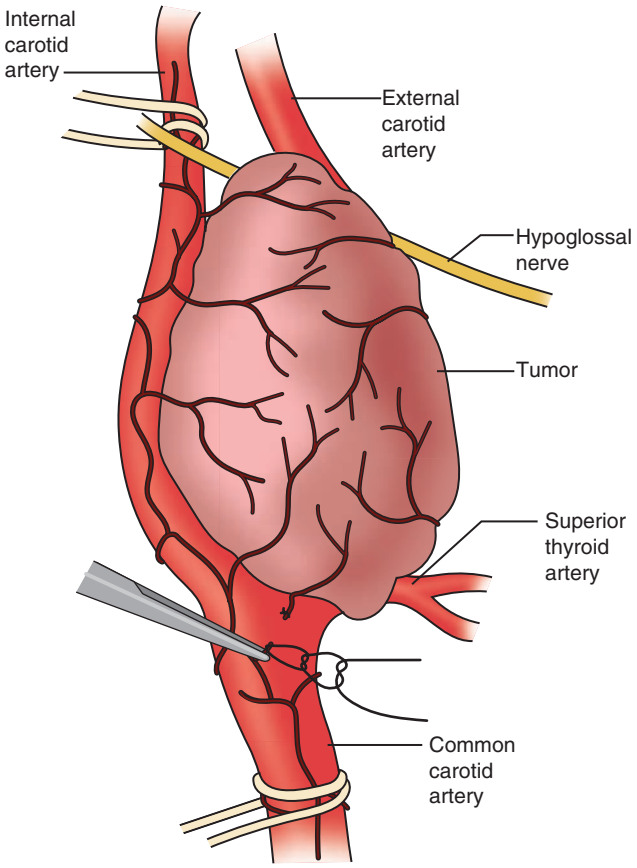

Figure 95.7 The common carotid artery is circumferentially mobilized in the perivascular plane to obtain proximal control of the artery. Dissection proceeds distally on the lateral aspect of the common carotid artery in the perivascular plane to a point beyond the tumor. The vagus nerve is separated from the artery and protected.

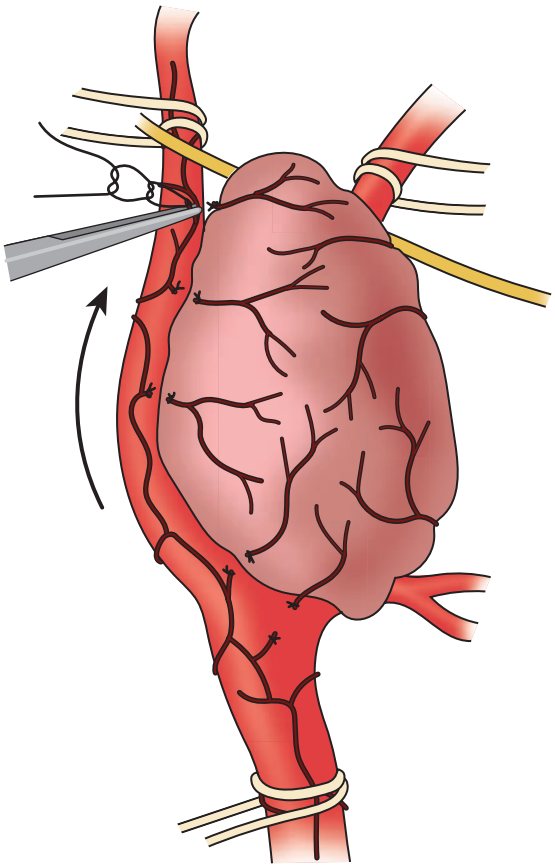

Figure 95.8 The internal and external carotid arteries are circumferentially mobilized for distal control. The hypoglossal nerve may be encountered during the dissection; it is separated from the artery and mass and protected.

Because carotid body tumors rarely encase the internal carotid artery, attempts are made to preserve it. The dissection is continued down the medial aspect of the internal carotid artery in the same perivascular plane, separating the tumor from the internal carotid artery to the bifurcation (Fig. 95.9). At this point, the external carotid artery can be circumferentially mobilized. For small tumors (Shamblin group I), the external carotid artery can be preserved. The dissection should stay on the tumor pseudocapsule; branches of the external carotid artery that supply the tumor can be divided and ligated with care to protect the hypoglossal nerve. Once the posterior, lateral, and medial aspects of the tumor are mobilized, the superior extent is divided between the ligature and the mass removed (Fig. 95.10).

For larger tumors that are adherent to the external carotid artery (Shamblin group II), the vessel can be divided at its origin, and the proximal stump is oversewn at the point where it was circumferentially mobilized. This maneuver is useful in reducing blood loss, and it provides a handle to rotate the tumor and aid in the dissection. The external carotid artery is resected en bloc with the tumor (Fig. 95.11).

For tumors that cannot be dissected from the bifurcation (Shamblin group III), the bifurcation and possibly the internal and external carotid arteries must be removed with the tumor. Vascular reconstruction for the internal carotid can be performed with a prosthetic or autologous vein interposition graft (Fig. 95.12). However, it is our preference to use a 6-mm PTFE graft, because long-term patency in this position is well documented as opposed to vein grafts. If a carotid shunt is required, the vascular reconstruction can be performed by passing the shunt through the graft and removing the shunt before the second anastomosis is completed. In addition, if clamping of the common or internal carotid arteries must be performed, the patient should receive systemic heparin. If the neoplasm adheres to or encases nerves, attempts should be made to preserve the nerves, even by splitting the tumor. If it is necessary to split the tumor to preserve a cranial nerve, use of bipolar forceps is helpful for hemostasis.

The wound is irrigated and meticulous hemostasis is obtained. The platysma is reapproximated, and the skin is closed with subcuticular sutures or skin staples. Drains are rarely needed, but if used, they can be placed beneath the platysma layer and brought out through the skin through a separate stab wound. A sterile dressing is placed.

POSTOPERATIVE CARE

A preliminary neurologic assessment should be performed when the patient awakens from anesthesia. The patient is brought to the

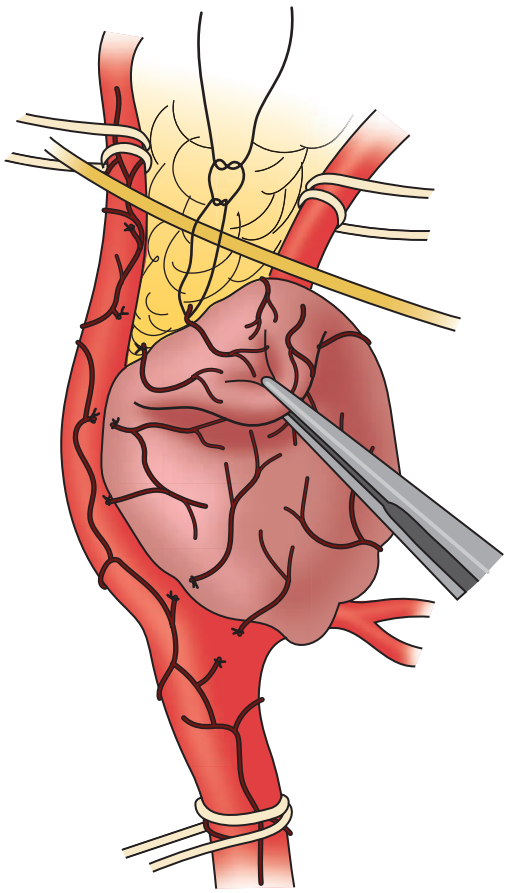

Figure 95.9 Dissection is continued along the medial aspect of the internal carotid artery in the same perivascular plane. The carotid body tumors rarely encase the internal carotid artery, and attempts should be made to separate and preserve the internal carotid artery.

recovery room where the blood pressure and neurologic function can be carefully monitored. The care team should be vigilant for neck hematomas, which can lead to an airway emergency, as well as stroke symptoms and evidence of cranial nerve injuries. If a drain is placed, it can be removed after 24 hours. Most patients are discharged 24 to 48 hours postoperatively.

Although recurrence is rare, patients should be followed closely after discharge.

RESULTS

In experienced hands, the perioperative mortality should be significantly less than 0.5%, and cerebrovascular, cranial nerve, or other minor complications occur very rarely. Particularly for tumors that appear and behave benignly, perioperative mortality and morbidity rates must be low. Other complications include hemorrhage and hematoma, especially when vascular control is inadequate. As described, several important cranial nerve structures lie within the tumor and dissection regions. Higher rates of nerve injury are seen with larger tumors. Most cranial nerve dysfunction is transient. Most complications are considered technically preventable, and adequate planning by the surgeon can greatly reduce the rates of adverse events.

CONCLUSIONS

- Carotid body tumors are rare neoplasms.
- Patients usually present with asymptomatic neck masses.
- Carotid body tumors are usually slow-growing, benign lesions, but may exhibit locally aggressive behavior. Malignant transformation is rare.

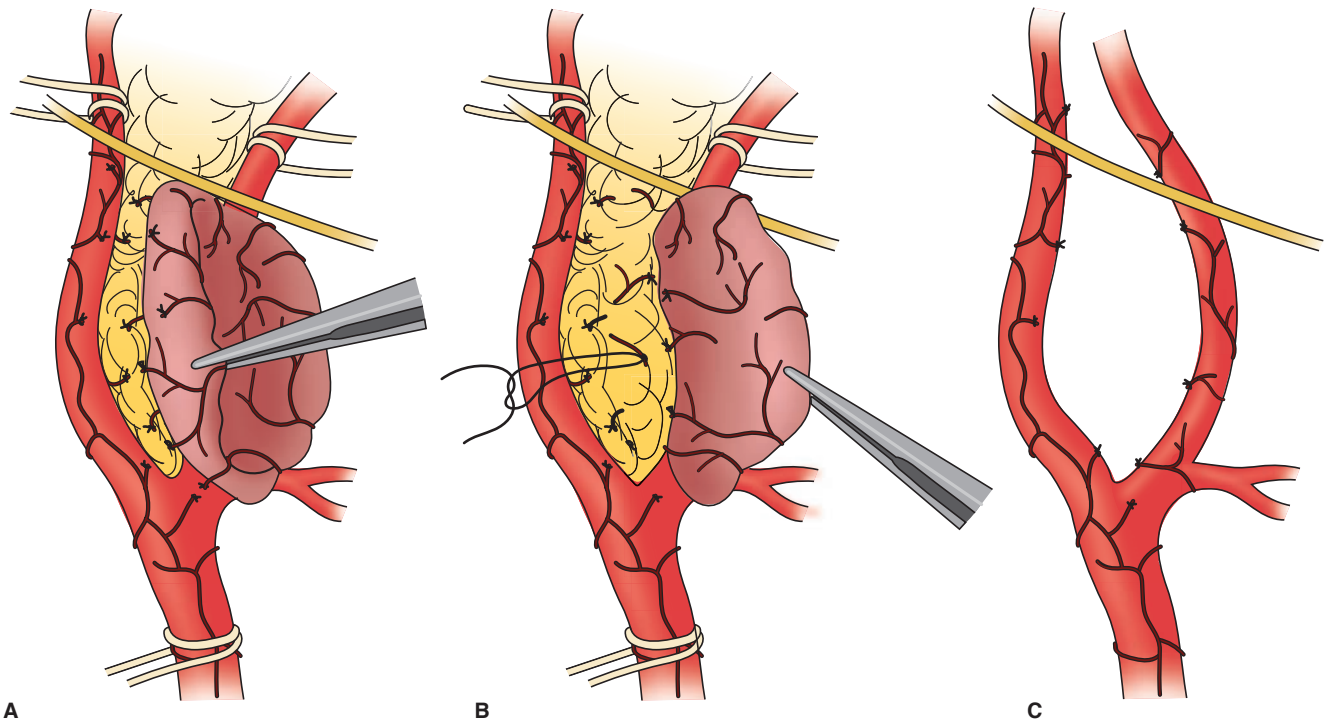

Figure 95.10 For small tumors (Shamblin group I), the external carotid artery can be preserved by mobilizing the carotid body tumor along the pseudocapsule (A). The blood supply to the tumor from branches of the external carotid artery can be divided and ligated (B).

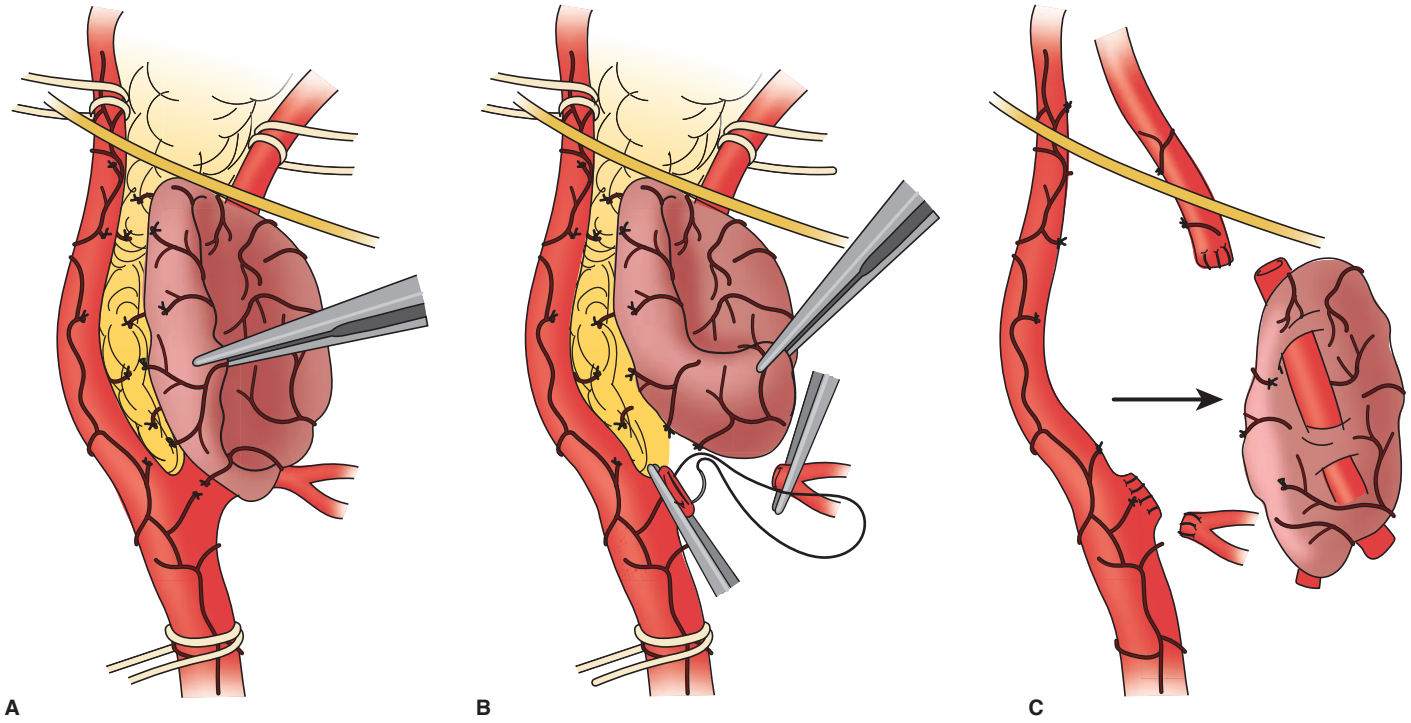

Figure 95.11 For larger tumors (Shamblin group II) that adhere to the external carotid artery, the vessel can be resected en bloc with the tumor. The carotid body tumor is mobilized from the internal carotid artery and carotid bifurcation (A). The external carotid artery is divided at its origin and the proximal stump oversewn (B). The tumor is then rotated to facilitate the remaining dissection. The distal external carotid artery and remaining branches are oversewn (C).

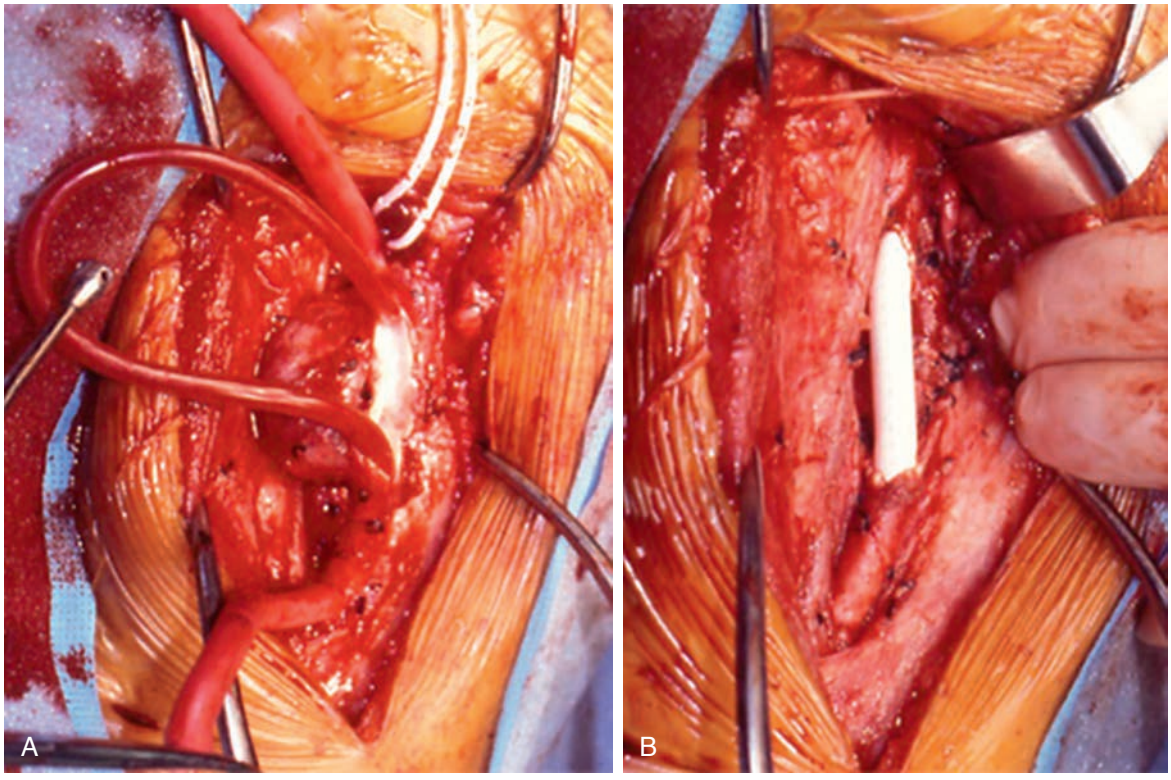

Figure 95.12 For tumors that involve the carotid artery bifurcation (Shamblin group III), the bifurcation and possibly the internal carotid artery, must be removed with the tumor (A). A carotid shunt may be required during the reconstruction. The internal carotid artery can be revascularized with a prosthetic or autologous vein interposition graft (B).

- Carotid body tumors are highly vascular structures.
- Imaging (conventional angiography, duplex ultrasound, CTA, and MRA) is the primary tool for diagnosis.
- Early complete surgical resection is the mainstay of treatment.
- In experienced hands with adequate operative planning, perioperative mortality and complication rates are very low.

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Describes work up of patients with carotid body tumors.

96 CHAPTER

Unusual Carotid Artery Conditions

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Atherosclerotic stenosis and occlusion of the extracranial vessels are the leading causes of the cerebrovascular diseases with which vascular surgeons have the most experience. There are several others disorders affecting carotid arteries and cerebral vessels that are underestimated and unacknowledged due to their rarity. For these uncommon pathologies, there is limited experience as well as few reports of best practices. This chapter addresses the clinical presentation and management of carotid sinus syndrome and carotid sinus hypersensitivity (CSS/CSH), Moyamoya disease, carotid artery kinks and coils, intracranial vascular stenosis, lacunar infarcts, cerebral vasculitis, and intracranial aneurysm with extracranial carotid stenosis.

BACKGROUND

There are several unusual diseases that affect the carotid arteries. These rare vascular conditions can cause disabling neurologic symptoms and deficits similar to atherosclerotic lesions (Box 96.1). This chapter discusses several of these rare cerebrovascular diseases including their presentations and risk factors as well as potential treatment modalities.

Abstract

There are many rare and unusual vascular diseases of the carotid artery; some occurring only in certain patient populations. Thus, physicians may not be familiar with their presentation or management. This chapter will review several carotid conditions, including epidemiology, clinical presentation, and available evidence for treatment.

Keywords

carotid artery
cerebrovascular disease
Carotid sinus syndrome
Moyamoya disease
carotid artery kink intracranial stenosis
lacunar infects
cerebral vasculitis
intracranial aneurysm

BOX 96.1 Common Nonatherosclerotic Causes of Cerebrovascular Symptoms

- Carotid kinking or coiling
- Carotid aneurysms
- Spontaneous dissection
- Posttraumatic dissection
- Fibromuscular dysplasia
- Radiation-induced arteritis
- Giant cell arteritis
- Takayasu arteritis
- Cardioarterial embolization

CAROTID SINUS SYNDROME/ CAROTID SINUS HYPERSENSITIVITY

Background and Epidemiology

Carotid sinus syndrome (CSS) was first reported over 200 years ago and is a relatively common finding. The carotid sinus is a high-pressure baroreceptor located at the carotid bifurcation. CSS is most often associated with the elderly patient population; hypersensitivity of the carotid sinus develops for unknown reasons. CSS presents with syncopal symptoms triggered by manipulation of the carotid sinus that occurs in daily life, resulting in a neurally mediated reflex bradycardia and hypotension. It is likely underdiagnosed, and common presenting symptoms include dizziness, falls, and syncope in the elderly patient population.[1,2] Carotid sinus hypersensitivity (CSH) is defined as bradycardia or hypotension due to carotid sinus massage or manipulation in patients without a clinical history of such symptoms.[3]

Epidemiology

The prevalence of CSS is highest among the elderly, even those without a history of symptoms. Generally the lifetime prevalence of syncope is 35% (95% CI 31% to 39%) in individuals from 35 to 60 years of age; it occurs more often in women than in men (41%, compared with 28%, respectively).[4] There are controversial findings regarding sex association, however. A study by Kerr et al. found that male sex was associated with CSH.[2] Another study by Volkmann et al. similarly found higher rates among men than among women (28% vs. 10% in asymptomatic patients and 48% vs. 34% in symptomatic patients, respectively).[5] A third study, by Kumar et al., supports these findings as well, with higher rates for men than for women (26.3% vs. 13.1%).[6] This wide distribution of the prevalence of CSS by sex is potentially due to variations in stimulation method, nonmodifiable patient characteristics, and the relevant diagnostic criteria utilized in each study.[7]

Classification

There are three main types of CSH. Cardioinhibitory carotid sinus hyperactivity (CICSH) is characterized by ventricular pauses greater than or equal to 3 seconds. Vasodepressor carotid sinus hyperactivity (VDCSH) displays blood pressure drops of at least 50 mm Hg without concomitant bradycardia. Finally, mixed CSH shows ventricular pauses of greater than or equal to 3 seconds along with a decrease in systolic blood pressure of at least 50 mm Hg on rhythm resumption. It is important to differentiate these classifications clinically as they dictate the approach to treatment; CICSH is a class 1 indication for cardiac pacing, whereas VDCSH typically requires pharmacologic treatment.[8,9]

Physiology and Pathophysiology

In normal physiology, sudden increases in arterial blood pressure result in expansion of the carotid arterial wall. Triggering of the carotid sinus receptor sends an afferent signal via the glossopharyngeal and vagus nerves to the brain stem and an efferent signal via the vagus nerve to the heart and blood vessels. This results in increased vagal activity and decreased sympathetic activity. Therefore increases in blood pressure cause compensatory vasodilation, bradycardia, and hypotension. Similarly, decreases in blood pressure decrease stretch in the carotid arterial wall and result in decreased afferent signals, resulting in a relative increase in sympathetic activity.[10]

The pathophysiology of the disease is poorly understood, but several models have been proposed. The first is that an abnormality in the central nervous system due to upregulation of postsynaptic alpha-2 adrenoceptors causes an exaggerated efferent response. However, testing with yohimbine (an alpha-2 antagonist) indicated no findings of baroreflex attenuation.[11,12] Another theory is that chronic terminal denervation of the sternocleidomastoid increases baroreflex sensitivity, but no definitive cause and effect relationship has been established in this case either.[13]

Presentation and Risk Factors

Common symptoms include dizziness (presyncope) or syncope of sudden onset, short duration, and quick recovery; this can occasionally be more prolonged if hypotension is severe.[8] Complications are most serious in the elderly who have falls (typically without loss of consciousness) and sustain resulting trauma. Both CICSH and VDCSH can induce falls.[14,15] Neurologic symptoms, which are rare and transient, include abnormal sensorium, vision changes, paresthesia, paresis, and cognitive dysfunction.[16] Risk factors include provocative maneuvers such as head turning, shaving, wearing tight neck collars, and age itself.[6,17-19]

Diagnosis and Workup

Proper diagnosis requires a thorough history to differentiate spontaneous from provocation-induced CSS.[1] Carotid sinus massage (CSM) should be conducted to determine if a hypersensitive response occurs. There is debate regarding whether the ability to spontaneously reproduce a response is required for diagnostic purposes. CSM is a safe and low-cost procedure

to stimulate the carotid sinus by the application of pressure, but descriptions of the technique vary by practitioner with respect to patient positioning and timing. CSM is contraindicated in patients with previous transient ischemic attacks, but the presence of a carotid murmur is not a contraindication.[3,7,20,21]

The technique serves to reproduce spontaneously occurring symptoms during 10-second sequential right and left massage[10] performed in both the supine and erect position under continuous heart rate and blood pressure monitoring.[21] Current guidelines from the European Society of Cardiology state that the upright position is preferred, and this is supported by data reported by Morillo (diagnostic accuracy of CSM increased by 38%).[1,22] The guidelines recommend continuous electrocardiography and noninvasive blood pressure monitoring as a 5- to 10-second massage is conducted at the anterior margin of the sternocleidomastoid at the cricoid cartilage level. If the test is negative, it can be repeated on the contralateral side after 1 to 2 minutes. If the test is positive, eliciting a cardioinhibitory response, atropine is administered, and repeat massage is performed to determine the degree of vasodepression. The differential diagnosis should include vasovagal syncope, given the potential for the coexistence of common conditions in elderly patients. Unlike CSS, vasovagal syncope is typically triggered by prolonged standing, strong emotion, and pain.[1]

Treatment

Nonpharmacologic treatment includes adequate fluid and salt intake as well as avoidance of physical counterpressure maneuvers.[23] If the patient is not responsive to these conservative measures, medical or surgical management should be considered. Regarding pharmacologic treatment, several drug trials have been conducted. In midodrine drug trials, the proportion of patients with syncopal complaints induced by CSM was lowered by midodrine treatment as compared with placebo (RR 0.13; 95% CI 0.02 to 0.82).[24] Selective serotonin reuptake inhibitors (SSRIs) and fludrocortisone have been shown to be effective, but atropine and propranolol did not prevent the vasodepressor response. Norepinephrine was shown to diminish the vasodepressor responses without a hypertension response, whereas ephedrine attenuated hypotensive responses. Isoproterenol and amphetamine did not have efficacy and the sympathomimetic side effects were dangerous in older patients who have high rates of systolic hypertension and coexisting coronary artery disease.[10]

Permanent pacemaker implantation is the treatment of choice if bradycardia occurs in CICSH.[25,26] Pacemakers can be atrial, ventricular, or designed for dual-chamber sensing and pacing. Indications for pacemaker placement include a clinical history of syncope, a positive response to CSM (asystole and bradycardia, indicating a severe reflex response), and syncope during CSM.[27] There is sparse evidence from randomized controlled trials but one study found that patients with syncope and CICSH respond to permanent pacing with a reduction in symptoms. There is conflicting evidence on whether or not pacing actually helps with unexplained falls.[28]

The current literature indicates that single-chamber atrial-based pacing should not be used as it has led to high rates of AV block.[29] A study by Brignole compared dual pacing and sensing, inhibitory and triggered (DDD) with ventricular pacing and sensing, inhibitory (VVI) and found no significant differences in follow-up for CSS.[30] However, another study by McIntosh et al. noted that CSM-induced syncope was higher in patients with VVI than those with DDI pacemakers (RR 5.50; 95% CI 1.33 to 22.73)[31] DDD pacing is currently accepted as better for symptom reduction, and the guidelines reflect this by noting that dual-chamber pacing is better than single-chamber pacing.[1]

Surgical or radiologic denervation of the carotid sinus, involving adventitial stripping, has been conducted for 60 years (Fig. 96.1). One study found that in 39 procedures on 27 individuals from 1980 to 2007, the procedure was relatively effective, safe, and could be considered as an alternative to pacemaker therapy.[32] Another study reporting data from 130 procedures indicated 85% effectiveness in preventing CSS, with low complication rates. Postoperative monitoring is required

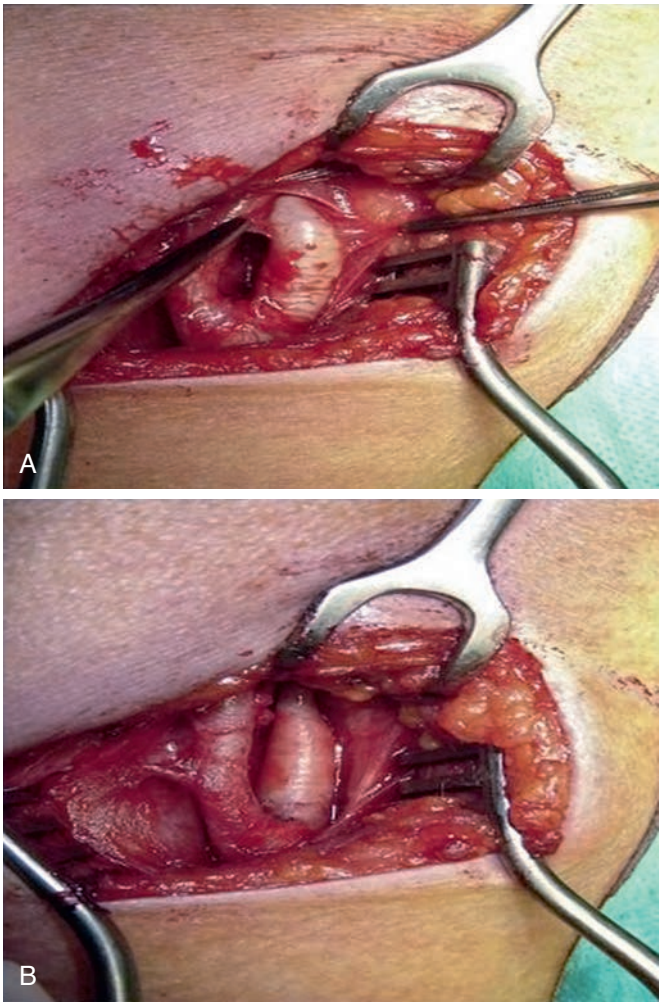

Figure 96.1 Operative Photographs Depicting Adventitial Stripping of the Left Carotid Artery. (A) The process of stripping with the forceps holding the nervous tissue. (B) The 3 cm of stripped proximal internal carotid artery after the procedure. (From Toorop RJ, Scheltinga MR, Huige MC, Moll FL. Clinical results of carotid denervation by adventitial stripping in carotid sinus syndrome. *Eur J Vasc Endovasc Surg*. 2010;39:146-152.)

due to transient alterations in blood pressure and heart rate.[33] A literature review following 28 patients undergoing carotid sinus denervation found that no patients experienced recurrent syncopal attacks or dizziness.[34] Therefore this is a potential therapy when pharmacotherapy is not effective.

MOYAMOYA DISEASE

Background and Epidemiology

Moyamoya disease (MMD) was first described by Suzuki and Takaku in 1969 and is now characterized as a chronic, idiopathic, progressive cerebrovascular disease presenting with internal carotid artery stenosis and occlusion.[35,36] The condition displays abnormal vascular networks at the brain base and is a common cause of stroke or transient ischemic attack; hemorrhages are possible as well (Fig. 96.2). It is most commonly seen in East Asian countries (i.e., Korea, Japan, China, Taiwan). Several large epidemiologic studies have been conducted in these regions[37-41] noting an incidence ranging from 3 to 14 in 100,000 and prevalence ranging from 0.35 to 2.3 in 100,000. These ranges are potentially due to improvements in diagnostic procedures. There is a bimodal age distribution to the disease, occurring in pediatric patients 5 to 15 years of age and adults in the third and fourth decades of life. Females are also more likely to have the disease than males. A US study found similar results, with a bimodal age distribution, increased prevalence in females, and higher prevalence in Asian American subpopulations.[42]

Presentation and Risk Factors

Pediatric MMD commonly presents with transitory repetitive cerebral ischemia, paroxysmal hemiplegia, paresthesia and facial paralysis, paroxysmal headaches, fine involuntary movements of the extremities, and progressive mental impairment.[35,43] In contrast, adult-onset MMD is characterized by sudden

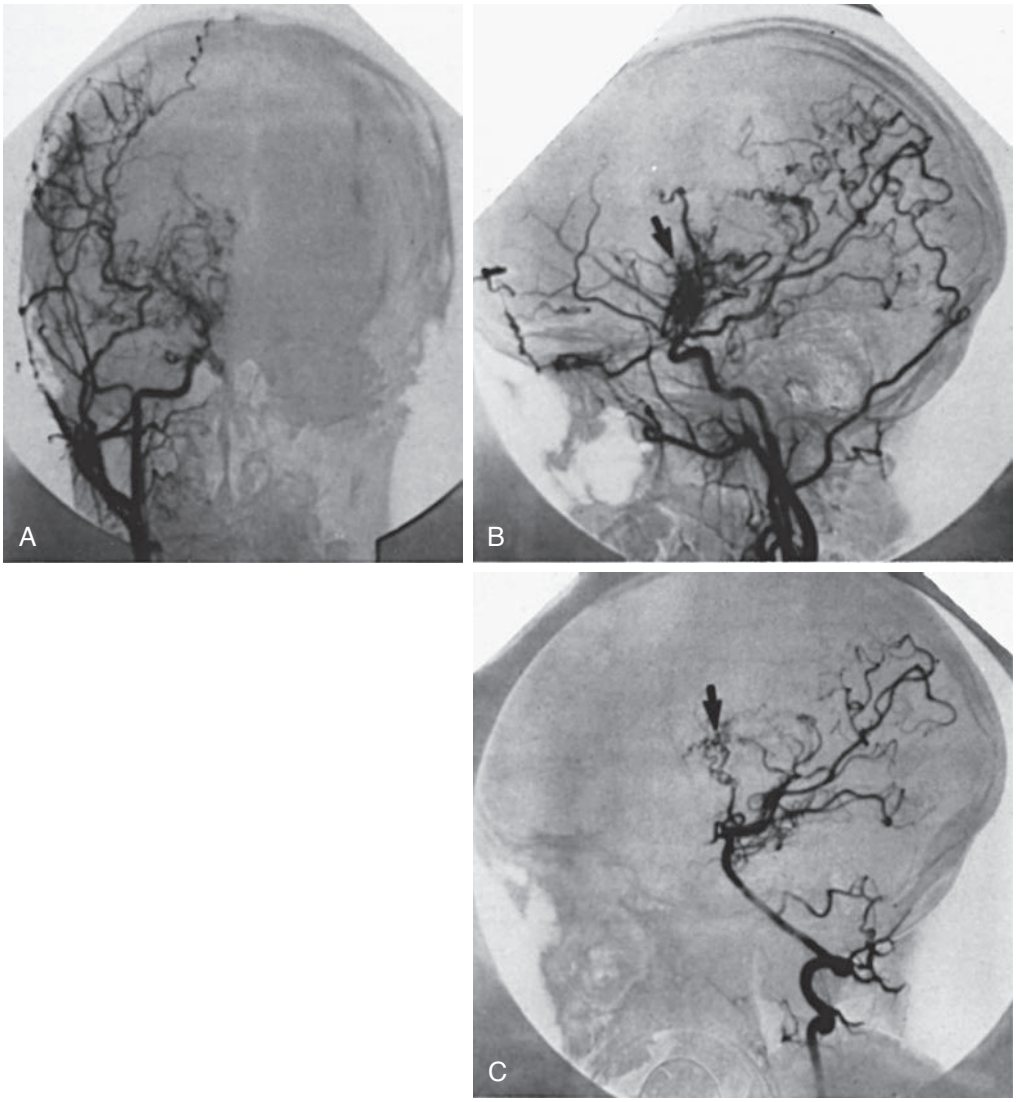

Figure 96.2 Cerebral Angiograms of a Patient With Moyamoya Disease. The collateral networks *(arrows)* around the sites of the occlusive disease. (A) Anterior and (B) lateral injections of the anterior circulation. (C) A selective angiogram of the vertebral and posterior circulation.

disturbances of consciousness, intracranial hemorrhage, bleeding into the ventricles, and subarachnoid hemorrhage.[43] Patients often present due to headache, dizziness, palpitations, syncope, or hyperventilation.[44] Risk factors include Japanese/East Asian heritage, female gender, family history, age, Graves disease, and genetic factors, as discussed in the following section.[38-41]

Pathology and Genetics

Epidemiologic data may point to a familial form of MMD, which constitutes 10% of cases.[45] The etiology of sporadic MMD is currently unknown, but many models have been proposed: infectious (viral and bacterial), autoimmune, protein abnormality, and genetic.[46] The genetic theory posits an autosomal dominant pattern of inheritance with low penetrance.[47] The following genetic loci are implicated: 3p24-26, 8q23, 6q25, 17q25, and 10q23.31.[48-52] The strongest candidate for gene susceptibility in patients of Asian descent with MMD is RNF213 from the 17q25-ter region.[53,54]

Pathophysiology

In MMD, progressive bilateral or unilateral stenosis of the internal carotid artery is seen, leading to thickening of the intima. Smooth muscle cell proliferation results in eventual arterial stenosis or occlusion; there is a notable lack of inflammation and atherosclerosis. Arterial stenosis due to fibrocellular thickening of the intima and occlusion due to smooth muscle cell accumulation occurs; ultimately potential thrombosis can result in regional cerebral hypoxia. As a result, collateralization by so-called Moyamoya vessels occurs; these vessels are characterized by a thin media, fibrin deposition in the vessel walls, fragmented elastic laminae, and an increased tendency to form microaneursyms. Neovascularization occurs due to the expression of HIF-1, VEGF, TFG-B, hepatocyte growth factor, and MMP.[46,55-58]

Histologically, the internal carotid artery shows concentric fibrocellular thickening of the intima, inducing vascular luminal stenosis, intimal elastic lamina undulation, a thickened layer of smooth muscle, and a lack of inflammation. Cerebrocortical microvascularization (an increase in microvascular density and diameter) is a potential compensatory mechanism for reduced blood flow or absent neovascularization prior to frank occlusion. However, MMD pediatric patients often show this neovascularization prior to hemodynamic impairment.[59]

Diagnosis and Workup

Based on recent changes in care management, there is no requirement for bilateral steno-occlusive changes in the internal carotid artery as a diagnostic criterion; instead, it can be a unilateral presentation leading to subsequent bilateral presentation.[60] Unilateral changes require diagnostic catheter angiography to assess for prominent basal collaterals. Bilateral changes can be evaluated with either catheter angiography or magnetic resonance imaging (MRI) studies. Angiography is very sensitive, although MRI can have decreased diagnostic sensitivity in early-stage Suzuki grading (stage 1) due to a lack of the characteristic vascular network. However, three-dimensional constructive interference in steady-state MRI and high-resolution MRI can both demonstrate constrictive remodeling in the affected segments and concentric enhancement of symptomatic segments; these techniques can therefore provide increased accuracy of diagnosis in the early stages of the disease.[61,62] Genetic testing should be considered as tests become more rapidly available and genetic associations are clarified.

Grading of MMD is done by the Suzuki and Takaku scales, with a six-stage evolutionary model indicating stepwise progression. However, the disease does not always present exactly in this order, so the clinical relevance of this scale has been debated.[35,63] The stages are as follows: (1) narrowing of the carotid fork, with no other abnormalities demonstrated; (2) initiation of Moyamoya vessels, where dilation of intracerebral main arteries is seen—the blood vessels are thick but no collateral circulation from the external carotid artery to the intracranial vessels has occurred; (3) the Moyamoya process intensifies, affecting the middle and anterior cerebral arteries; (4) the Moyamoya vessels are minimized, with occlusion of the internal carotid artery to the level of the posterior communicating artery junction; (5) further reduction of the Moyamoya vessels while the main internal carotid arteries disappear; and (6) the Moyamoya process disappears and the internal carotid artery is completely gone. The original Moyamoya vessels at the base of the brain are not visualized; only collateral circulation from external carotid artery or vertebral artery enters the intracranial region.

Treatment

There is an elevated risk of both ischemic and hemorrhagic stroke in asymptomatic patients.[64] Antiplatelet therapy is contraindicated in asymptomatic patients due to the risk of bleeding (50% of patients experience hemorrhage).[65] Therefore modifiable risk factors should be managed and lifestyle guidance provided to prevent recurrence of stroke. Hyperventilation can induce symptoms, so patients should avoid hot meals and strenuous exercise.[65] Furthermore, the patients should also start the following medical treatment plans: antihypertensive medication, lipid-lowering therapy, diabetic glycemic control, smoking cessation, weight reduction, and the elimination of oral contraceptive agents.[66,67]

Surgical management is indicated in individuals with symptomatic cerebral ischemia.[65] Pediatric cases tend to be more progressive, and this is another potential indication for surgical management.[68] The goal of revascularization is to allow normalized cerebral perfusion, and this treatment has been noted as the standard of care to prevent recurrent stroke. Furthermore, revascularization has been shown to reduce the risk of transient ischemic attacks (TIAs) and cerebral infarction, to improve activities of daily living, and to ameliorate overall brain function as tracked over time.[69]

Surgical techniques include direct bypass (surgical revascularization) and indirect bypass (pial synangiosis). Direct bypass is indicated under the following conditions: availability of a highly trained and experienced surgeon as well as the presence

of sufficient diameter in the superficial temporal artery and cortical arteries, given that later stages lead to cortical arterial shrinkage and vessel wall fragility. The donor artery is most often the superficial temporal artery, which is harvested and treated with papaverine to prevent vasospasm. The recipient artery is usually the middle cerebral artery, and Chater's point is used as a landmark in searching for a large cortical branch.[70]

Indirect bypass is typically a more expedient procedure with decreased operative times and a lower complication rate; it is also a technically less demanding procedure. In these cases, distal anastomoses are not directly performed to the intracerebral vasculature. However, indirect bypass may be difficult in pediatric patients as well as advanced-stage adult patients due to the reduced diameter of cortical arteries and longer neovascularization times. The most common types are encephalomyosynangiosis, where the deep temporal artery is the neovascularization supply, and encephaloduroateriosynangiosis, where the superficial temporal artery's parietal branch is harvested instead.[70]

Management and Prognosis

In the postoperative period, blood pressure should be carefully monitored and fluid balance should be assessed to prevent ischemic or hemorrhagic stroke. This is due the fact that postoperative neurologic sequelae are often caused by hyperperfusion syndrome, which involves increased blood flow in vessels that are unable to autoregulate.[71] Regarding the prognosis, Kim et al.[70] have reported the perioperative stroke rate after revascularization for ischemic MMD patients. They note that with conservative management, stroke rates are as high as 3.2% to 15% annually. In direct/combined revascularization in adults, there is a 0% to 1.6% rate annually, whereas in pediatric patients it is 0.2% annually (rate reported from an aggregate average of three studies). For indirect bypass, the stroke rates (0% to 14.3%) are higher than with direct revascularization. Specifically it was noted that pediatric patients have similar stroke rates with direct or indirect revascularization, whereas adults benefit more with direct revascularization.[72,73] The management of hemorrhagic MMD remains controversial.[70]

CAROTID ARTERY KINKS AND COILS

Background

The association between kinking and coiling of the internal carotid artery (ICA) and cerebrovascular insufficiency was first noted in 1951.[74] Coiling is defined as elongation and redundancy of the ICA resulting in an exaggerated S-shaped curvature or even in a circular configuration of the vessel (Fig. 96.3). Kinking is the angulation of one or more segments of the ICA associated with stenosis in the affected segment (Fig. 96.4). The degree of kinking has been defined as mild (>60 degrees), moderate (30 to 60 degrees), and severe (<30 degrees).[75] Unlike coiling, kinking is associated with clinically relevant stenosis that has led to neurologic symptoms in 4% to 20% of patients, even in the absence of atherosclerotic plaques at the carotid bifurcation[76]; kinking generally occurs in the proximal ICA.[77,78]

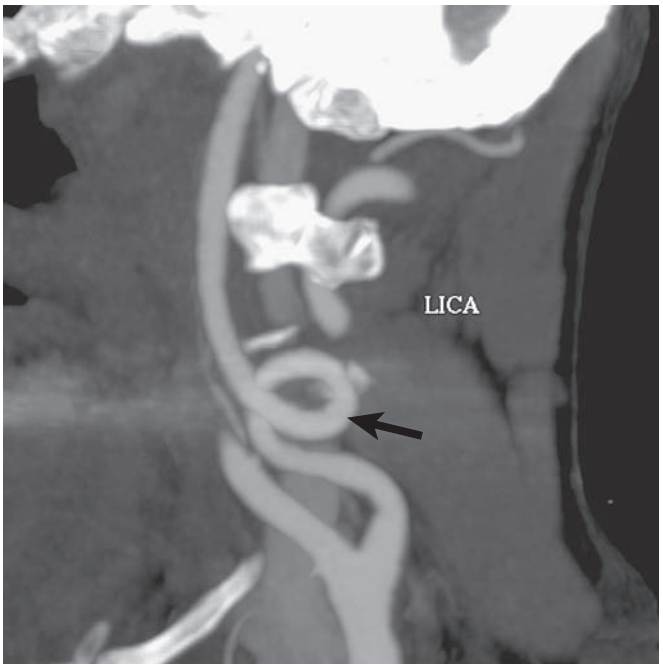

Figure 96.3 Computed axial tomography angiogram with sagittal reconstruction identifying a complete 360-degree coil of the internal carotid above the carotid bulb. *Arrow* indicates looping carotid artery resulting in "coil". *LICA,* Left internal carotid artery.

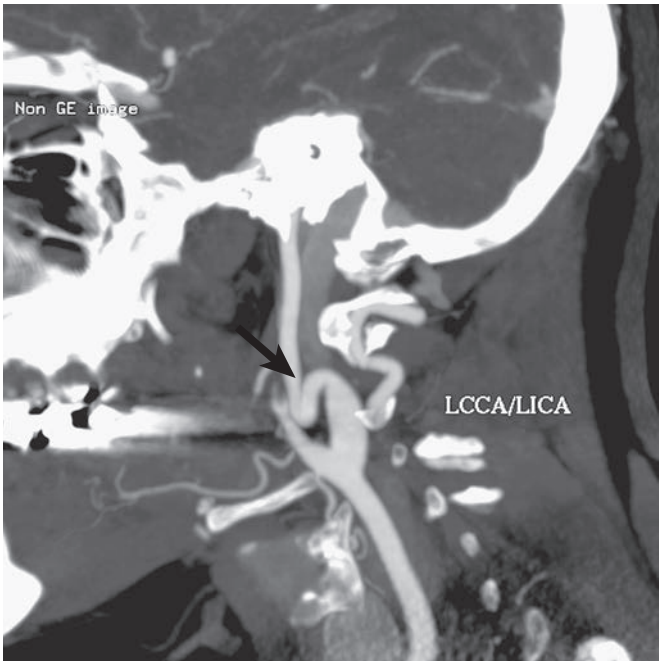

Figure 96.4 Computed axial tomography angiogram with sagittal reconstruction identifying two kinks that represent angulations of less than 90 degrees of the internal carotid just above the carotid bulb. *Arrow* indicates redundant carotid artery resulting in "kink". *LCCA,* Left common carotid artery; *LICA,* left internal carotid artery.

Epidemiology

The incidence of these carotid anomalies has been studied primarily in adults. Variations in incidence rates of internal carotid abnormalities are likely due to varying diagnostic

modalities. Arteriographic methods indicate that the incidence of these anomalies can range from 10% to 25% or even 43%.[75,78] A study by Togay-Isikay et al. using duplex ultrasound indicated a 24.6% rate. The overwhelming majority of patients with these carotid abnormalities were female (70.6%) and most were over 60 years of age. The most common abnormality noted was kinking (56%), followed by tortuosity (38%) and then coiling (6%).[79] Infantile carotid anomalies have also been reported, with associated symptoms. A study by Sarkari et al. identified nine infants with cerebrovascular disease and unilateral or bilateral looping or kinking.[80] Parrish and Byrne similarly reported five cases of infant hemiparesis and seizures in those with ICA kinking.[81]

Etiology and Clinical Presentation

There is controversy regarding the underlying cause of this condition, but two theories predominate.[82] The first describes an embryologic etiology: the internal carotid artery arises from the third aortic arch and dorsal aorta. In the embryo, the vessel is naturally coiled or kinked. The heart receding into the thorax during normal development causes arterial stretching and the disappearance of kinks. Therefore failure of this process might allow for persistence of the original coils or kinks. This could explain the kinking found in infants by Sarkari et al.[80] and Parrish and Byrne.[81] It is generally believed that coiling is associated with embryologic causes, whereas kinking is more likely to be linked to atherosclerosis or fibromuscular dysplasia.[83] These findings may explain the low rates of coiling with respect to kinking, as embryologic causes are less likely than the common risk factors that can lead to atherosclerosis. Other studies indicate the possibility that carotid coiling and kinking may be sequelae of prior carotid endarterectomy, age-related degeneration, normal deviation, or hypertension.[84-86]

Most patients are symptomatic later in life, and the symptoms demonstrated are caused by the vessel course deviations that result in hemodynamic changes.[82] Consequently embolism formation can eventually cause occlusion of intracerebral vessels. One study found that the hemodynamic conditions in a region of coil concavity are similar to those of aneurysms and can lead to endothelial denudation and the formation of embologenic material.[87] Several studies have also found that carotid kinking may be the source of cerebral emboli or that the kinked vessel may be temporarily occluded by rotation of the head and neck.[78,88,89] It should be noted that kinking of the ICA is more often associated with symptomatic cerebrovascular disease than is coiling. In this case, patients often present with hemispheric stroke or TIA. Physical findings vary and are based on where occlusion occurred in the cerebral vasculature.[90,91]

Treatment

Clinical evaluation can include carotid ultrasonography, duplex ultrasound scan of arteries supplying brain, CT with imaging of the brain, biplane carotid angiography, and multislice CT of the arteries to the brain. Medical treatment is limited to antiplatelet therapy (typically aspirin) to reduce platelet coagulation; however, this has been found to be significantly less effective than surgical correction of isolated carotid elongations with coiling or kinking.[92]

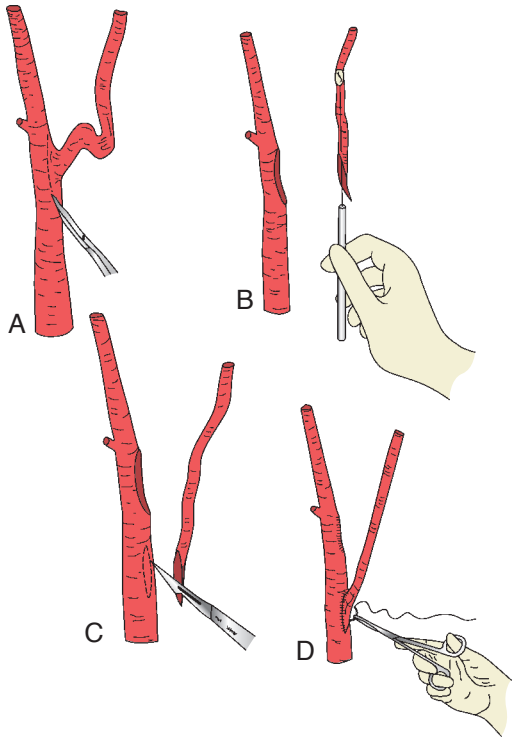

Figure 96.5 Management of a Highly Redundant Internal Carotid Artery. (A) Transection of the internal carotid artery from the bulb. (B) Transluminal dilation of any internal webs or fibrous bands. (C and D) Reimplantation of the internal carotid artery lower on the common carotid artery with repair of the original orifice. (From Ballotta E, Thiene G, Baracchini C, et al. Surgical vs medical treatment for isolated internal carotid artery elongation with coiling or kinking in asymptomatic patients: a prospective randomized clinical study. *J Vasc Surg*. 2005;42:838-846.)

With respect to surgical treatment, many small studies exist but few are randomized, and the anecdotal nature of existing data makes it challenging to draw firm conclusions with respect to the patient population at large. However, a randomized clinical study by Ballotta et al. in patients with symptomatic ICA coiling and kinking without atheromatous lesions demonstrated that surgical treatment was significantly better than antiplatelet therapy alone for the relief of neurologic symptoms and the prevention of ICA thromboses and stroke (Fig. 96.5).[92] Another study by Illuminati et al. indicated that operative correction of ICA elongation is safe and effective in patients with isolated stenotic kinking and hemispheric symptoms that persisted even with antiplatelet therapy.[93]

Simple kinking is an indication for shortening angioplasty. The ICA is sectioned at its site of origin on the common carotid artery and then the adhesions are released, followed by kink straightening. Next, proximal extension of the arteriotomy on the common carotid artery (CCA) is conducted, and then oblique transection at the base of the ICA. The distal arteriotomy on the ICA is elongated, and the ICA is reimplanted more proximally on the CCA. Distal dilation of the ICA should be performed if the lumen of the kinked artery does not return to normal after straightening.[93]

Double kinking should be addressed with resection of the diseased arterial segment and the distal ICA reconstructed either by transposition with side-to-end anastomosis onto the external carotid artery (ECA) or by interposition bypass grafting. The ICA is transposed to the ECA when the diameter of the ECA is suitable. In this case, the ICA is transected distal to the kinked segment and transposed onto the ECA using an end-to-side anastomosis. If transposition is not possible, bypass grafting should be performed using the greater saphenous vein as the bypass conduit; if it is unavailable, synthetic conduits may be considered.[93]

Management and Prognosis

In their study, Ballotta et al. found that the surgical treatment group experienced lower rates of TIAs, stroke, amaurosis fugax, deaths, carotid occlusion, and nonhemispheric symptoms than did the medically treated group; the follow-up period varied from 1 month to 10 years (median 5.9 years).[92] Illuminati et al. found that after 83 surgical procedures, there were no postoperative deaths and a postoperative stroke rate of 1%. At 5-year follow-up, primary patency of the carotid revascularizations was 89% ± 4%, and freedom from neurologic symptoms was 92% ± 4%.[93] Therefore surgical treatment conferred a significantly improved prognosis with minimal perioperative or postoperative side effects compared with medical management.

INTRACRANIAL VASCULAR STENOSIS

Background and Epidemiology

Intracranial arterial stenosis (ICAS) is defined as large intracranial arterial luminal narrowing. The etiology of the condition has not been entirely determined, but several causes are noted.[94] Primary atherosclerosis is the most common condition linked to ICAS, and emboli can be a source of stenosis as well. Other causes—such as arterial dissection, vasculitis, central nervous system infections, radiation, sickle cell disease, and Moyamoya disease—should be considered. ICAS is one of the most common causes of stroke worldwide and has been associated with an increased risk of recurrent stroke. The potential sequelae of this condition were relatively underappreciated until noted in brain biopsy studies, cerebral angiographic studies in racially mixed populations, and the extracranial-intracranial bypass trial.[95-98]

In the United States, ICAS causes approximately 100,000 strokes each year. Worldwide, 20 to 40 individuals per 100,000 are affected yearly.[99] The true burden of the condition might be considerably underappreciated. Several multiracial studies have focused on symptomatic individuals and have noted that the condition extensively affects Asians, accounting for 20% to 50% of strokes in Chinese, Korean, Thai, and Japanese populations. ICAS also accounts for approximately 5% to 10% of strokes in Caucasians, and 15% to 29% of TIAs in African Americans, Additional studies indicate that a large proportion of strokes in the Hispanic population are attributable to ICAS.[95,100-103]

These studies show that the lack of prevalence studies among asymptomatic patients in highly affected racial populations might explain the underestimation of the true burden of this condition on a global scale. Furthermore, genetic, environmental, and lifestyle influences likely play roles in the development of ICAS. Finally, it should be noted that subanalyses of the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study have demonstrated that women with symptomatic ICAS are at higher risk for recurrent stroke, leading to death.[104]

Pathophysiology and Risk Factors

Hypertension, smoking, and other risk factors culminate in endothelial injury and increased vascular permeability. Subsequent monocyte and lymphocyte adhesion to damaged endothelium causes white blood cell migration into the surrounding subendothelial tissue. Macrophage activation and cytokine and growth factor release induce smooth muscle cell migration and proliferation. Fibrous cap formation occurs next, covering the leukocyte, lipid, and necrotic mass; cap rupture leads to platelet aggregation and the formation of emboli. The vascular changes create turbulent flow, creating flow separation and oscillatory shear stress that propagates endothelial and arterial wall damage. Ultimately luminal stenosis and the generation of emboli result in ischemic stroke due to tissue hypoperfusion.[105]

Modifiable risk factors include hypertension, smoking, diabetes mellitus, and dyslipidemia.[106] Nonmodifiable risk factors include race, age, and a variety of genetic variations (angiotensin converting enzyme polymorphisms, increased plasma endostatin/vascular endothelial growth factor, plasma homocysteine levels, glutathione S-transferase omega-1 gene polymorphism).[103] Interestingly, Turan et al. noted that the location of intracranial stenosis varied based on the patient's risk factors and demographics; this implies some type of pathophysiologic difference among the typically affected intracranial arteries.[106]

Diagnosis

Catheter digital subtraction angiography is the gold standard due to its ability to quantify precisely the degree of intracranial luminal stenosis.[107] The benefits of the modality include excellent visualization of the intracranial vasculature; however, recent commentary has raised the question of whether it is actually superior to CTA with respect to visualization of the posterior circulation in low-flow conditions. The limitations include the high operator skill required and the fact that intra-arterial catheterization has led to increased morbidity and mortality.[108] Given these considerations, the modality is best used for in patients when considering endovascular intervention and not as a screening tool.

There is currently a shift toward the use of noninvasive or minimally invasive neuroimaging techniques, including transcranial Doppler (TCD) ultrasound, MRA, CTA, and high-resolution MRI owing to their noninvasive nature and reduced cost. However, limitations have been explored in the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial. This study found that both TCD and MRA can identify 50% to 99% intracranial stenosis noninvasively with a high negative predictive value (86% and 91%,

respectively). However, the positive predictive value was far lower (36% and 59%, respectively).[107] The conclusion from this study is that these modalities should be used in tandem with formal arteriography. The former two methods are better for screening purposes, but the latter should still be primarily employed for confirmatory diagnosis or intervention.

Treatment

Medical therapy for ICAS is limited to antiplatelet treatment; its use was first reported in the treatment of symptomatic ICAS in 1955.[109] Since then, a number of trials have been conducted to determine the efficacy of recurrent stroke prevention in symptomatic patients.

The Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis (WASID) trial in 2005, a double-blind randomized trial comparing the efficacy of aspirin versus warfarin, determined that there was no statistically significant benefit from warfarin over aspirin for stroke or death prevention in ICAS patients. It was noted that a high risk of recurrent stroke existed for patients on medical therapy alone.[110] The Clopidogrel plus Aspirin for Infarction Reduction (CLAIR) study in 2010 found that the combination therapy of clopidogrel and aspirin was more effective than aspirin alone in the reduction of microemboli formation (relative risk reduction of 42.4%).[111] The Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) study was conducted to compare the benefits of medical treatment with intracranial endovascular treatment. Medical management with aspirin and clopidogrel (followed by aspirin alone) was better than medical management plus angioplasty and stenting using the Wingspan stent system.[112] Of note in this study is the lower stroke recurrence rates in the medically treated group, which also highlighted the benefits of dual antiplatelet therapy compared with aspirin alone.

Despite the results of these studies, surgical and endovascular interventions have shown promise in the prevention of recurrent stroke. Medical management alone does not produce optimal results, as supported by the high rates of recurrent stroke risk in the WASID trial and the short-term ability of using dual antiplatelet therapy (considering the risk of hemorrhage).

Surgical treatment for ICAS was introduced in the 1960s and was popular until the EC/IC bypass study group demonstrated that extracranial-intracranial anastomosis was not efficacious in preventing stroke in carotid and middle cerebral arterial atherosclerotic disease as compared with aspirin therapy.[98]

Endovascular intervention has generated interest in the treatment of ICAS. In 2005, the US Food and Drug Administration (FDA) approved the Wingspan self-expanding nitinol stent designed for use in the cerebral vasculature in the treatment of ICAS. Initially, its use was limited to patients with greater than 50% stenosis, but in 2012, the usage was again further restricted to patients with 70% to 99% stenosis and recurrent stroke despite medical management. This change was linked to the following reported data. In 2007, a US multicenter study using the Wingspan stent system found that angioplasty and stenting for symptomatic ICAS had high technical success rates, with a pretreatment degree of stenosis of 74.6% improving to 43.5% after angioplasty and 27.2% after stenting. However, there was a 6.1% periprocedural rate of neurologic complications, 80% of which resulted in death within 30 days.[113] In 2008, the National Institutes of Health (NIH) Wingspan registry, which was limited to data from patients with 70% to 99% stenosis, found similar rates of technical success, with greater improvement of stenosis (82% to 20%).[114] These findings were the catalyst for the 2011 SAMMPRIS trial, which, as noted earlier, found that aggressive medical management was indeed still more effective than treatment with the Wingspan stent in reducing 30-day rates of stroke or death.[112] Nevertheless, as endovascular techniques continue to be refined, there is a possibility that endovascular treatment may confer greater benefits to patients than medical treatment, especially in the case of severe stenosis. Currently medical treatment remains the treatment of choice.

INTRACRANIAL ANEURYSM WITH EXTRACRANIAL CAROTID STENOSIS

Background and Epidemiology

Intracranial aneurysms are often asymptomatic and undetected (Fig. 96.6); when patients present, it is most often acutely with a subarachnoid hemorrhage.[115] Based on current guidelines, treatment of unruptured intracranial aneurysms should be via surgical clipping or endovascular coiling to prevent potential hemorrhage. The appropriate management when unruptured aneurysms exist concomitantly with extracranial carotid stenosis presents a more complex situation. Debate exists regarding the treatment approach for the conditions in tandem.

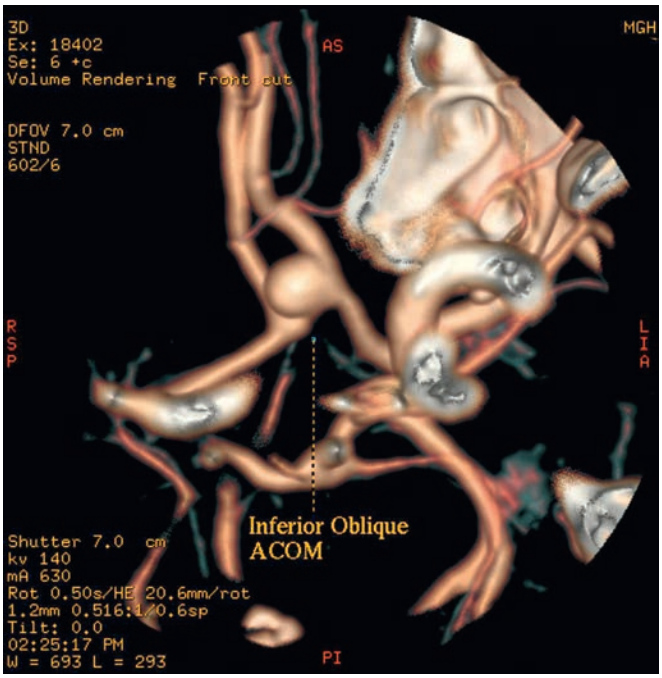

Figure 96.6 CTA reconstruction in the inferior oblique orientation of an intracranial aneurysm of the anterior communicating artery *(ACOM)*.

There is a low prevalence of carotid stenosis presenting with intracranial aneurysm (3.2% based on a literature review of 4251 patients), and most cases are diagnosed during imaging to assess the degree of stenosis in symptomatic carotid arteries.[116] Studies of the prevalence of intracranial aneurysms in healthy populations note the prevalence to be approximately 1.8%.[117] There are several reasons postulated as to why the incidence of ICA in patients with carotid stenosis may be increased as compared with the general population. Confounding factors among studies, such as age and sex, may account for rate disparities between healthy populations and those with carotid stenosis. The two conditions clearly do share several risk factors, including but not limited to age, hypertension, and tobacco use.[118]

Treatment and Management

The hemodynamic relationship between the conditions when they coexist underlies the continuing controversy regarding appropriate management. If one chooses to treat severe carotid stenosis prior to the ipsilateral intracranial aneurysm, several changes can occur within the cerebral vasculature. Given that carotid stenosis typically occurs progressively over a period of time, the intracranial vasculature can demonstrate compensatory vasodilation. With acute treatment and revascularization of the carotid artery, the subsequent increase in cerebral blood flow and pressurization can lead to shear stress on the aneurysm's wall, with resulting rupture.[119,120] This is one potential argument against addressing ipsilateral carotid stenosis first, especially in a multiprocedure treatment plan spaced across several weeks.

If aneurysm repair is conducted first with the patient under general anesthesia, there are also potential perioperative complications. These include hypoperfusion due to the ipsilateral carotid stenosis, which can lead to hypoxia and stroke. Additionally, endovascular access to the aneurysm itself may be challenging, and movement of the coiling device through the stenotic carotid plaque can lead to thromboembolic events.[121]

The following factors should be considered in considering treatment of patients with symptomatic carotid stenosis and asymptomatic intracranial aneurysm. In the literature, there is no conclusive evidence suggesting that all intracranial aneurysms must be treated.[115] Size and location are key factors involved in aneurysm risk and should be considered with an endovascular approach. Life expectancy is an important factor as well. One study noted that in patients with a remaining life expectancy that was less than 15 to 35 years or those who were aged 45 to 70, repair of aneurysms smaller than 7 mm in the anterior circulation conferred no significant benefit when considering surgical risk. The treatment of symptomatic carotid stenosis is appropriate based on current guidelines, but again, one should consider the potential intracranial hemodynamic changes that may incurred as a result when deciding on the appropriate approach to a particular patient.[122]

As noted earlier, there is no consensus on the treatment of choice in concomitant lesions. Recent studies discuss a variety of approaches to this clinical scenario. Single-stage endovascular treatment may be considered with stenting of the carotid stenosis performed prior to coiling of the aneurysm. The major concern with this approach is the loss of a potentially protective effect of carotid stenosis on an ipsilateral intracranial aneurysm, which could result in postoperative cerebral hyperperfusion.[121,123] However, one study indicates that close monitoring of blood pressure could reduce risks associated with sudden changes in cerebral blood flow.[124] At the same time, the risk of acute carotid stent thrombosis secondary to the trauma of subsequent catheter manipulation during secondary aneurysm treatment should be considered. Even with these potential complications, the benefits of single-stage treatment include reduced cost to the patient as well as reduced time of aneurysm exposure as well as increased perfusion after carotid revascularization. Furthermore, stenting before coiling facilitates aneurysmal access and decreases the risk of thromboembolism from stenotic plaque rupture.

The opposite sequence of treatment during endovascular management may also be considered. Endovascular coiling for aneurysm repair followed by carotid stent placement was conducted by Iwate et al. in a single elderly female patient.[125] The rationale for aneurysm coiling proport to stenting was based on the aneurysmal sac pressure being equivalent to mean systolic blood pressure. Therefore this procedure purported to decrease the risk of turbulence during proximal carotid stenosis treatment, which might cause the aneurysm to rupture; this is a potential choice in dealing with large aneurysms in locations of high shear stress. In this case report, both lesions underwent successful treatment over a 1-month period with no complications or stroke. Given that this occurred in an elderly female, a patient at higher risk for stroke complications, this may suggest support for staged endovascular treatment. It should be noted again that this procedure was successfully performed in only one patient and that operator experience and other unknown factors could have led to the favorable outcome.

Based on the current literature, no single treatment can be advocated above others. The benefits of aneurysm treatment versus carotid stenosis treatment must be balanced based on the degree of risk associated with each individual lesion as well as the patient profile.

CEREBRAL VASCULITIS

Background and Epidemiology

Vasculitis is blood vessel inflammation that occurs due to a heterogeneous set of etiologies. Due to the variety of patterns, classification systems focus on identifying the origin of pathology (immunologic, infectious, neoplastic, etc.), vessel size, presence of granulomas or vessel wall necrosis, and the involvement of peripheral or cerebral vessels. Vasculitis affecting the cerebral vessels is a rarer condition than systemic vasculitis, as evidenced by the annual incidence of 1 to 2 per million in the former compared with 39 per million in the latter.[126]

Presentation and Diagnosis

Cerebral vasculitis can be a mild to potentially life-threatening disease entity given the clinical and pathologic presentation,

which can be acute, subacute, chronic, or relapsing-remitting. Specific symptoms depend on the vessels affected and can include headaches, seizures, cranial nerve neuropathies, encephalopathy, ischemic stroke, intracranial hemorrhage, cognitive changes, and aseptic meningoencephalitis.[127] These features, along with lab testing, can aid in diagnosis. Diagnostic examinations include electroencephalography and cerebrospinal fluid (CSF) analysis (detecting pleocytosis and intrathecal immunoglobulin synthesis). Imaging studies including conventional digital subtraction angiography, MRA, and CTA are also critical to ascertain the degree of cerebral involvement. However, all of these studies remain secondary to histopathologic examination, which is the gold standard and is required for definitive diagnosis.[128]

Treatment

Vasculitides that may include the cranial arteries include Takayasu arteritis, Wegener granulomatosis, and temporal lesions. As with other central nervous system (CNS) vasculitides, ischemia may result in neurologic functional loss; this can be due to frank luminal obstruction or proinflammatory cytokines that result in increased coagulation on the endothelial surface. Generally the lesions are nongranulomatous in nature.[129] Patients of all ages can be affected, but the majority are between 40 and 60 years of age.[130] Potential therapies include the use of glucocorticoids, which are also used in other small, medium, and large cerebral vasculitides. However, in the case of systemic vasculitis with CNS involvement, revascularization procedures should be considered when extracranial arteries or proximal intracranial vessels are diseased.[131]

LACUNAR INFARCTS

Background

Lacunar infarcts were first described by Dechambre in 1838 in identifying subcortical regions of softening on brain autopsy.[132] They are currently defined as noncortical infarcts resulting from single penetrating branch occlusion of larger cerebral arteries; infarct diameters can range from 0.2 to 15 mm, with the size of lacunae potentially correlating to clinical features.[133] Risk factors for lacunar infarct are similar to those for ischemic stroke and include hypertension, cardiac disease, smoking, high levels of low-density lipoprotein cholesterol, and age.[134] These insults account for 20% of ischemic strokes and are mostly asymptomatic.[135] If symptomatic, the most common presentations are as follows: motor hemiparesis, aphasia, dysarthria, change in level of consciousness, mutism, and sensorimotor dysfunction.[134]

Pathophysiology

Lacunar infarcts most often affect the putamen, pallidum, pons, thalamus, internal capsule, corona radiate, and caudate nucleus. These are regions where the collateral circulation is typically limited. The pathophysiology for these infarcts is currently postulated as involving one of two potential mechanisms. The first posits that chronic hypertension or uncontrolled diabetes results in arterial media thickening due to fibrinoid deposition and smooth muscle hypertrophy, ultimately resulting in localized ischemia. The second notes that parental artery intimal plaques can result in penetrating artery obstruction. Both result in focal brain ischemia and edema due to blood-brain barrier damage.[136]

Diagnosis

The differential diagnosis should include intracranial hemorrhages, infections (syphilis and cysticercosis), tumors, cerebral vasculitis, and cardiac emboli. Imaging studies are often employed, with CT and MRI being the most common. The Stroke Data Bank found that CT scans identified only 35% of lesions in lacunar stroke patients, whereas MRI was found to identify at least one lacuna correlating with signs and symptoms in 73 patients out of 100.[137,138] However, a direct comparison between the sensitivity of CT versus MRI is not truly feasible between these studies given that CT is often performed sooner than MRI after symptom onset.

Treatment

Medical therapy is similar to other nonhemorrhagic stroke management, with current guidelines indicating administration of intravenous tissue plasminogen activator within 3 hours of stroke onset.[139] Preventative treatment should focus on attenuating medical conditions that contribute to increased stroke recurrence. Surgically, carotid endarterectomy is indicated for lacunar stroke, with patients with 70% stenosis or greater in the ipsilateral internal carotid artery achieving the most benefit. A relatively low perioperative risk of stroke and death has been reported (1.5% to 5.6%), but a higher number needed to treat (83 individuals) to prevent one stroke in 2 years has also been noted.[140]

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This large (n = 1377) multicenter randomized clinical trial evaluated the benefit of extracranial-intracranial anastomosis in preventing stroke in patients with symptomatic atherosclerotic disease in the carotid and middle cerebral arteries. There was no additional benefit of surgery over medical management.

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This meta-analysis of over 4000 patients with symptomatic internal carotid artery stenosis found a 1% incidence of intracranial aneurysms at a size associated with possible rupture, with women being at higher risk than men. This is a much higher incidence than in the general population, although the authors do not recommend routine screening for intracranial aneurysms in patients with ICA stenosis.

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97 CHAPTER

Vertebral Artery Dissection and Other Conditions

MARK MORASCH

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The vertebrobasilar system supplies blood to the brain stem, cerebellum, and occipital lobes via paired vertebral arteries. Posterior circulation ischemia is most often the result of the atherosclerotic process involving the vertebrobasilar arteries but may also the related to a number of other vasculidities. Although vertebrobasilar ischemia is less common than ischemic episodes related to internal carotid artery disease, approximately 25% of all ischemic strokes do occur in the distribution of the posterior brain circulation; these events should be diagnosed appropriately as they may be the result of a treatable vasculopathy. For patients who experience vertebrobasilar transient ischemic attacks, disease in the vertebral arteries portends a 22% to 35% risk of stroke over a 5-year period.[1-4] The mortality associated with a posterior circulation stroke is 20% to 30%, higher than that for an anterior circulation event.[5-7]

PATHOGENESIS AND ANATOMY

The surgical anatomy of the paired vertebral arteries has traditionally been divided into four segments: segment V1 includes the origin of the vertebral artery as it arises from the subclavian artery to the point at which it enters the C6 transverse process; segment V2 includes the segment of the artery buried deep within the intertransversarium muscle and the cervical transverse

Abstract

Interventional procedures for symptomatic vertebral artery disease should be considered in when appropriate lesions are encountered and in patients where medical therapy has failed. Open techniques for revascularization of the vertebral artery have proven clinical durability and acceptable surgical morbidity in experienced hands. Endoluminal techniques have yet to deliver on durability benchmarks set by open surgical revascularization. For each individual patient who suffers from medically refractive vertebrobasilar ischemia, practitioners must carefully balance the risks of surgery versus the limitations of endoluminal intervention before recommending intervention.

Keywords

Vertebral
Vertebrobasilar
Posterior brain circulation
Vertibrobasilar stroke

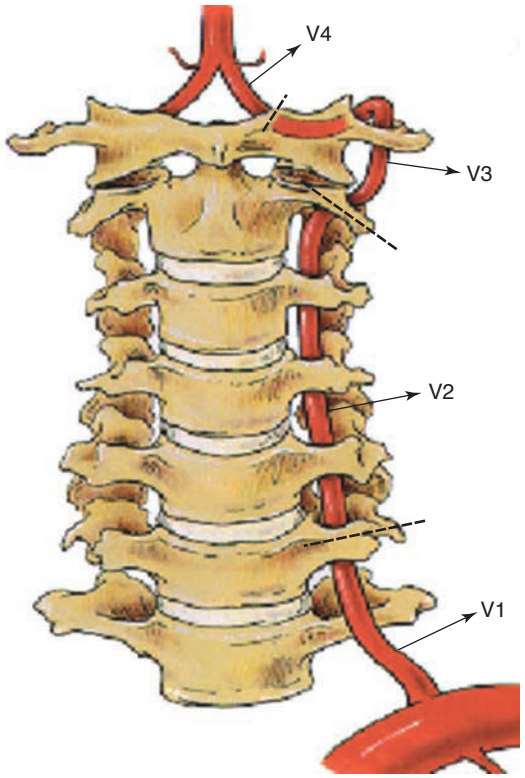

Figure 97.1 The four segments of the vertebral (V) artery. (From Berguer R. Surgical management of the vertebral artery. In: Moore WS, ed. *Surgery for Cerebrovascular Disease*, New York: Churchill Livingstone; 1986.)

processes of C6 to C2; segment V3 includes the segment of the vertebral artery that extends from the top of the transverse process of C2 to the atlanto-occipital membrane at the base of the skull; and segment V4 includes the intracranial, intradural portion of the vertebral artery beginning at the atlanto-occipital membrane and terminating as the two paired vertebral arteries that converge to form the basilar artery (Fig. 97.1).

Ischemia affecting the temporo-occipital areas of the cerebral hemispheres or segments of the brain stem and cerebellum characteristically produces bilateral symptoms. The classic symptoms of vertebrobasilar ischemia are dizziness, vertigo, drop attacks, diplopia, perioral numbness, alternating paresthesia, tinnitus, dysphasia, dysarthria, and ataxia. When patients have two or more of these symptoms, the likelihood of vertebrobasilar ischemia is high (Box 97.1).

Posterior circulation ischemia and strokes occur most commonly in relation to large-artery diseases (Table 97.1), with the vertebral artery being the most common large vessel with occlusive lesions that lead to stroke in this distribution (Table 97.2). The most common disease affecting the vertebral artery is atherosclerosis. Less common pathologic processes include dissection, trauma, fibromuscular dysplasia, Takayasu disease, osteophyte compression, aneurysms, and other arteritides.

Ischemic Mechanisms

In general, the ischemic mechanisms can be broken down into those that are hemodynamic and those that are embolic. In contrast to ischemia resulting from carotid artery occlusive disease, the low-flow hemodynamic mechanism of ischemia is better recognized and more frequent than the embolic one in the case of vertebral artery disease.

Low Flow

Patients with low-flow hemodynamic ischemia have transient symptoms in the cerebral territories supplied by the basilar artery because they lack appropriate inflow from the vertebral

BOX 97.1 Symptoms Associated With Vertebrobasilar Ischemia

Disequilibrium
Vertigo
Diplopia
Cortical blindness
Alternating paresthesia
Tinnitus
Dysphasia
Dysarthria
Quadriplegia
Drop attacks
Ataxia
Perioral numbness

TABLE 97.1 Mechanisms of Posterior Circulation Stroke or Transient Ischemic Attack in 407 Patients

Mechanism	Number (%)
Large-artery occlusive disease	132 (32)
Embolism—cardiac source	99 (24)
Embolism—arterial source	74 (18)
Penetrating artery disease	58 (14)
Vasospasm/migraine	10 (2)
Other causes	34 (8)

Modified from Caplan LR, Wityk RJ, Glass TA, et al. New England Medical Center Posterior Circulation registry. *Ann Neurol*. 2004;56:389.

TABLE 97.2 Frequency of Symptomatic Vascular Occlusive Lesions in 417 Patients

Lesion	Number
Innominate artery	2
Subclavian artery	5
Extracranial vertebral artery	131
Intracranial vertebral artery	132
Basilar artery	109
Posterior cerebral artery	38

Modified from Caplan LR, Wityk RJ, Glass TA, et al. New England Medical Center Posterior Circulation registry. *Ann Neurol*. 2004;56:389.

arteries and have inadequate compensation from the carotid artery territory. Hemodynamic symptoms occur as a result of transient end-organ (brain stem, cerebellum, occipital lobes) hypoperfusion and can be precipitated by postural changes or a transient reduction in cardiac output. Ischemia from hemodynamic mechanisms rarely results in tissue infarction. Rather, symptoms are short-lived, repetitive, and more of a nuisance than a danger. Some patients may be prone to traumatic injuries from loss of balance or consciousness, resulting in falls. For hemodynamic symptoms to occur in direct relation to the vertebrobasilar arteries, significant occlusive disease must be present in both paired vertebral vessels or in the basilar artery itself. In addition, compensatory contribution from the carotid circulation via the circle of Willis must be incomplete. Alternatively, hemodynamic ischemic symptoms may result from proximal subclavian artery occlusion and the syndrome of subclavian/vertebral artery steal.

Embolic

Embolic causes of vertebrobasilar ischemia are generally the result of microembolization from the heart or aortic arch or from the subclavian, vertebral, or the basilar artery. Approximately one-third of vertebrobasilar ischemic episodes are caused by distal embolization from plaque or mural lesions of the subclavian, vertebral, or basilar arteries (or any combination of these vessels).[8] Arterial-to-arterial emboli can arise from atherosclerotic lesions, intimal defects caused by extrinsic compression or repetitive trauma, and rarely fibromuscular dysplasia, aneurysms, or dissections. Although fewer patients suffer from embolic phenomena than from hemodynamic mechanisms, actual tissue infarction is most often the result of an embolic event. As compared with the hemodynamic mechanisms of ischemia, emboli are much more likely to cause fatal events or debilitating strokes. The importance of the embolic mechanism as a cause of vertebrobasilar symptoms has been emphasized in clinical and anatomicopathologic studies. This information has been derived from autopsy and magnetic resonance imaging (MRI) studies, which have identified small infarcts in the brain stem and cerebellum and shown their source, via arteriography, to be lesions in the subclavian or vertebral arteries. As opposed to patients with hemodynamic symptomatology, multiple and multifocal infarcts in the brain stem, cerebellum, and occasionally the posterior cerebral artery territory more often develop in patients with embolic ischemia.[9,10]

DISEASE DISTRIBUTION

V1 Segment

The most common atherosclerotic lesion of the vertebral artery is stenosis of its origin. The prevalence of such lesions is approximately 20% to 40% in patients with cerebrovascular disease.[8] The atherosclerotic lesions are usually smooth and fibrotic and have low embolic potential. Redundancy and kinks are also common in the V1 segment, but only very severe kinks associated with poststenotic dilatations can be responsible for hemodynamic symptoms.

V2 Segment

The most common pathology of the V2 segment is extrinsic compression by either bone or tendon. Compression can be caused by osteophytes,[11] the edges of the transverse foramina (Fig. 97.2), or the intervertebral joints. Rotation or extension

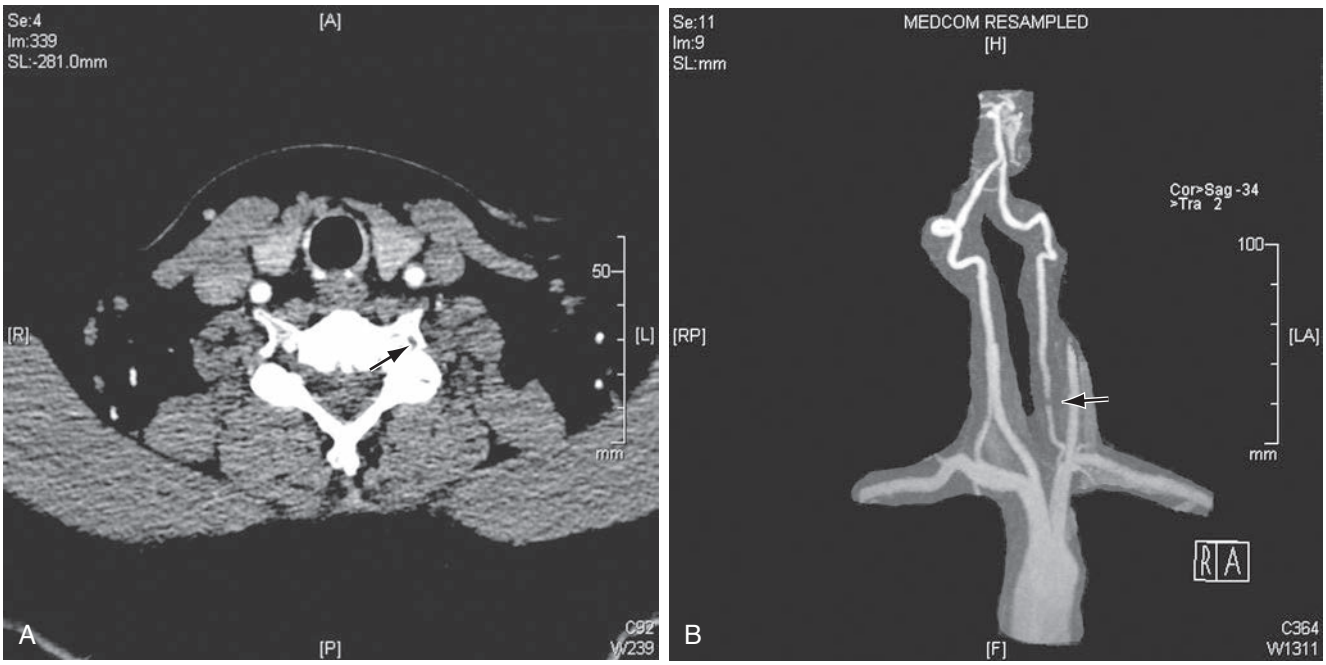

Figure 97.2 Computed tomography (CT) (A) and magnetic resonance angiography (MRA) (B) images demonstrating large osteophytes occluding the vertebral artery at C5.

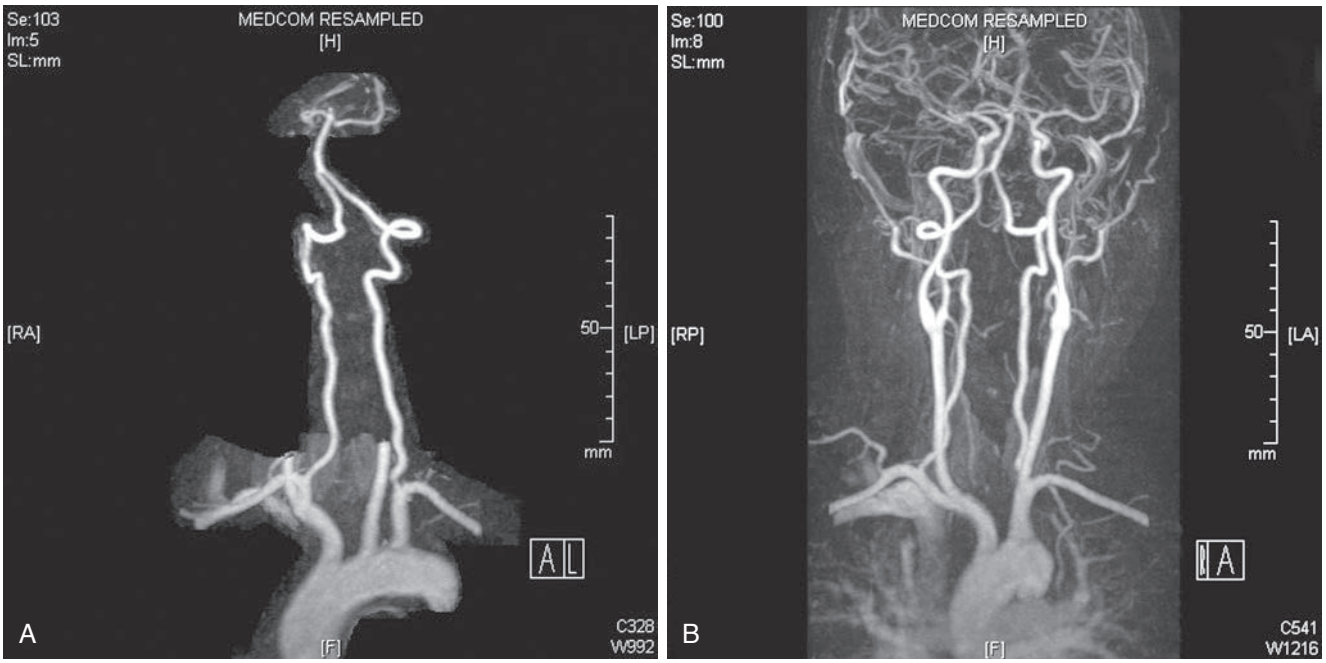

Figure 97.3 (A) Vertebral magnetic resonance angiography (MRA) (with the carotid image subtracted). (B) Arch and four-vessel MRA.

of the neck usually triggers compression of the vertebral artery in this segment. Extrinsic vertebral artery compression by musculotendinous structures is common in patients with an abnormally high level of entry into the transverse processes of the spine, usually C4 or C5, due to the sharp angulation resulting from the abnormal level of entry (Fig. 97.3).

The V2 segment is a frequent site for the development of traumatic or spontaneous arteriovenous fistulas. Fistulas occur in the V2 segment because fixation of the adventitia of the vertebral artery to the periosteum of the foramina makes the former vulnerable to luxation/subluxation injuries. The close proximity of the artery to its surrounding venous plexus results in an arteriovenous fistula when the artery and vein are damaged in continuity. The vertebral artery may tear completely or incompletely (dissection) as a consequence of stretch injury after brisk rotation or hyperextension of the neck.

Although most vertebral artery aneurysms occur intracranially, the V2 segment is the most common site of extracranial aneurysmal degeneration (Fig. 97.4). Two-thirds of all extracranial vertebral artery aneurysms involve the V2 segment, and most form as pseudoaneurysms secondary to trauma or dissection.[12] True degenerative extracranial vertebral artery aneurysms are rare, accounting for less than 1% of all vertebral artery lesions.[13] In one review, all patients with a true extracranial vertebral artery aneurysm had some form of connective tissue disorder.[12] Most extracranial vertebral aneurysms are asymptomatic and found incidentally. Some present with symptoms that can include a palpable neck mass, dizziness, headaches, and/or neurologic deficit from cerebral ischemia or nerve compression. Rupture is rare. Because the natural history is unknown, vertebral ligation with or without reconstruction is most often recommended for large extracranial vertebral aneurysms.[12]

Figure 97.4 V2 segment true aneurysm *(arrow)* in a patient with connective tissue disorder. Also note the left common right subclavian and right external carotid aneurysms.

In addition to aneurysms and fistulas, dissection, fibromuscular disease, arteritis, and embolizing atherosclerotic plaque can be identified in the V2 segment. Disease in the second segment of the vertebral artery can result in extracranial occlusion or stenotic lesions in the intraforaminal segment, which commonly give rise to emboli.

V3 Segment

The most common problems at the V3 level are related to trauma and arterial dissection; they include occlusive lesions, arteriovenous fistulas, and pseudoaneurysms. Extracranial

Figure 97.5 Intramural dissection of the vertebral artery at the V3 segment in a 40-year-old woman with Klippel-Feil syndrome and subluxation of the atlantoaxial joint.

Figure 97.6 Distal V2 segment pseudoaneurysm resulting from dissection.

vertebral artery dissection occurs most commonly in the V3 segment because the artery is most mobile in this location and therefore vulnerable to mechanical injury. The first two cervical vertebrae are the most mobile of the spine. Approximately 50% of neck rotation occurs between C1 and C2. The vertebral artery is redundant at this level to allow the arc of displacement of the transverse process of the atlas (80 degrees), to which the vertebral artery is attached. Clinically, extracranial vertebral dissection may present with severe occipitocervical neck pain with associated dizziness, vertigo, double vision, ataxia, and dysarthria.[14] Dissection may be associated with fibromuscular dysplasia; it can also occur in a normal artery after seemingly trivial trauma (Fig. 97.5). Vertebral artery dissection often follows hyperextension or rotation of the neck and has been associated with, among other activities, practicing yoga, painting a ceiling, coughing, vomiting, sneezing, and cervical chiropractic manipulation.[15,16] Vertebral dissection is rare, with an overall incidence of 1 per 100,000, but it is a significant cause of stroke in a young and otherwise healthy population.[17] In one study, 62% of dissections observed serially with angiography went on to heal with complete resolution.[18] The remaining dissections went on to vessel occlusion, remained stenotic, or developed pseudoaneurysmal dilation and/or AV fistulas (Fig. 97.6). One-half of the patients diagnosed with extracranial vertebral artery dissection will develop no neurologic symptoms, whereas 21% will experience mild neurologic sequelae, 25% will suffer moderate to severe deficits, and 4% will die.[19] Notably, there appears to be no relationship between recanalization rates and neurologic outcome.[20]

An arteriovenous fistula results from rupture of the wall of the vertebral artery into its surrounding venous plexus. In long-standing fistulas, the pulsatile mass formed by the fistula and its dilated venous channels is called an arteriovenous aneurysm.

The vertebral artery may be compressed in the pars atlantica of the third segment between the occipital ridge and the arch of the atlas. In these patients the symptoms of low-flow posterior circulatory systems are usually precipitated by head extension or rotation. The V3 segment is rarely affected by significant atherosclerosis.

When the vertebral artery is occluded proximally in the V1 or V2 segments, it usually reconstitutes at the V3 segment by forming collateral blood vessels from the external carotid via the occipital artery (Fig. 97.7) or collaterals from the ipsilateral subclavian artery via branches of the thyrocervical trunk (Fig. 97.8).[21] Because of this collateral network, the distal vertebral and basilar arteries usually remain patent despite a proximal vertebral artery occlusion. This anatomic finding is crucial for developing the appropriate surgical strategy.

V4 Segment

Similar to the V3 segment, the fourth segment (V4) is infrequently affected by atherosclerosis. This segment is also prone to arteriovenous fistula formation and aneurysmal degeneration. Advanced atherosclerotic disease of the basilar artery is generally a contraindication to the reconstruction of vertebral artery lesions.

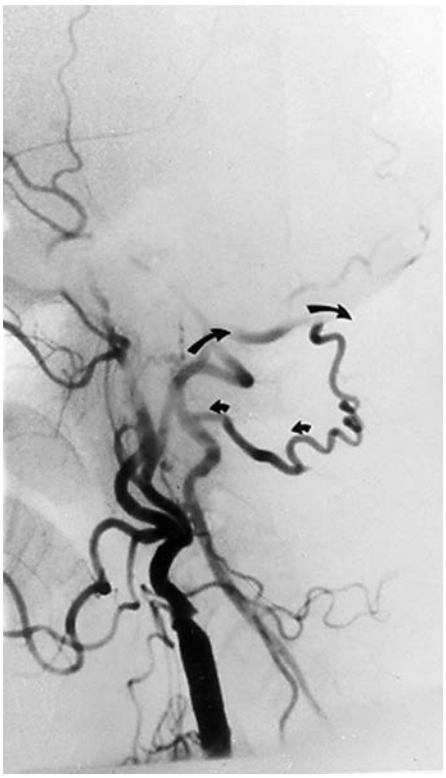

Figure 97.7 The distal vertebral and basilar arteries being fed by an occipital artery collateral in a patient with proximal vertebral artery occlusion.

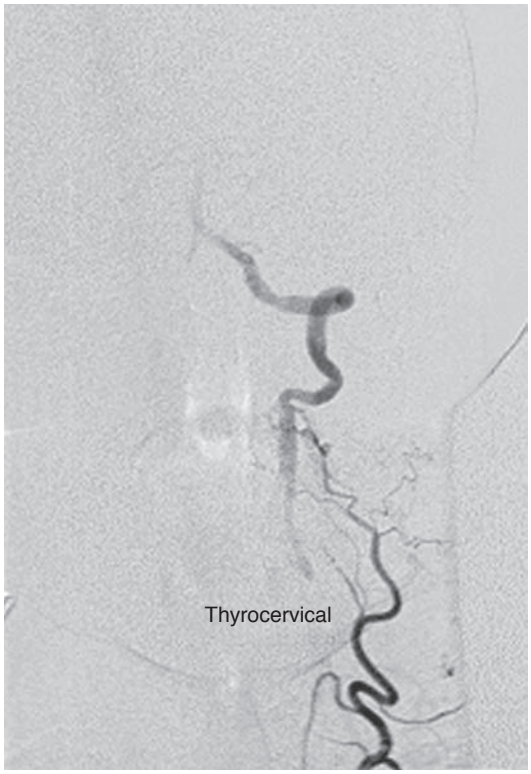

Figure 97.8 The distal vertebral and basilar arteries fed by a thyrocervical trunk collateral in a patient with proximal vertebral artery occlusion.

PATIENT SELECTION FOR VERTEBRAL ARTERY RECONSTRUCTION

Anatomic Considerations

The minimal anatomic requirement to justify vertebral artery reconstruction for hemodynamic symptoms would be greater than 60% diameter stenosis in both vertebral arteries if both are patent and complete or the same degree of stenosis in the dominant vertebral artery if the opposite artery is hypoplastic, ends in a posteroinferior cerebellar artery, or is occluded. A single normal vertebral artery is typically sufficient to adequately perfuse the basilar artery regardless of the patency status of the contralateral vertebral artery. Unlike carotid artery disease, the mere presence of vertebral artery stenoses in an asymptomatic patient would not be an indication for reconstruction because these patients are well perfused from the contralateral vertebral or the carotid circulation through the posterior communicating vessels.

Etiologic Considerations

Low Flow

For patients with hemodynamic symptoms, it is essential to rule out systemic causes of ischemia before advising evaluation of the vertebrobasilar arteries as the definitive etiology. In the later years of life, vertebral artery stenosis is a frequent arteriographic finding and dizziness in the elderly is a common complaint. The presence of both cannot necessarily be assumed to have a cause-effect relationship. The indication for intervention in patients with hemodynamic symptoms depends on the ability to demonstrate insufficient blood flow to the basilar artery. Other common systemic causes of hemodynamic ischemia, aside from vascular occlusion, include orthostatic hypotension, poorly regulated antihypertensive therapy, arrhythmias, heart failure, malfunction of pacemakers, and anemia.

Embolic

In contrast to individuals with low-flow states, patients who present with posterior circulation ischemia secondary to embolization from lesions in a vertebral or subclavian artery should be considered for medical or surgical treatment regardless of the status of the contralateral artery. Surgical or endoluminal intervention is warranted if medical treatment fails. Surgical intervention is not indicated in asymptomatic patients who present only with radiographic findings.

Patients who present with nonatherosclerotic lesions such as aneurysm, dissections, and fistulas may also be considered as potential candidates for vertebral artery reconstruction depending upon their presentation.

Differential Diagnosis

The identification of patients who could benefit from vertebral artery reconstruction begins with an accurate assessment of the symptom complex, followed by efforts to exclude other causes of the symptoms (Box 97.2). These other medical conditions

BOX 97.2 Routine Testing for the Potential Diagnosis of Vertebrobasilar Ischemia

Cardiology consultation
Echocardiography
Holter monitoring
Medication review
Serum electrolytes
Neurology consultation
Thyroid function tests
Audiology/ear, nose, throat evaluation
Magnetic resonance imaging

BOX 97.3 Nonvascular and Cardiac Conditions That Cause or Mimic Vertebrobasilar Ischemia

Cardiac arrhythmia
Pacemaker malfunction
Cardioemboli
Labyrinthine dysfunction
Tumors of the cerebellopontine angle
Use of antihypertensive medications
Cerebellar degeneration
Myxedema
Electrolyte imbalance
Hypoglycemia

commonly include inappropriate use of antihypertensive medications, cardiac arrhythmias, anemia, brain tumors, and benign vertiginous states. A thorough investigation consists of ruling out (1) inner ear pathology, (2) cardiac arrhythmias, (3) internal carotid artery stenosis/occlusion, and (4) inappropriate use of medications (Box 97.3).

The evaluation of patients with posterior circulation ischemia should include assessment of the precise circumstances associated with the development of symptoms. Any systemic mechanism that decreases the mean pressure of the basilar artery may be responsible for hemodynamic symptomatology, and affected individuals may or may not have concomitant vertebral artery stenosis or occlusion. Symptoms from orthostatic hypotension often appear upon standing in older individuals with poor sympathetic control of their venous tone. This causes excessive pooling of blood in the veins of the leg and resulting transient hypotension. A drop of 20 mm Hg in systolic pressure on rapid standing is a criterion for the diagnosis of orthostatic hypotension causing low flow in the vertebrobasilar system.

Because certain prescription medications can mimic vertebrobasilar ischemia, patient medications require thorough review. In fact, excessive use of antihypertensive medications is the most common etiology of posterior circulation symptoms and can also cause hemodynamic posterior circulation ischemia by decreasing perfusion pressure and inducing severe orthostatic hypotension.

A cardiac source is the second most common cause of brain stem ischemia, especially in older adults; a thorough evaluation should include 24-hour Holter monitoring for arrhythmias and echocardiography to assess heart valve function. Arrhythmias commonly cause symptoms as a result of decreased cardiac output. In addition, transesophageal echocardiography may be useful in patients with a suspected embolic mechanism of ischemia to rule out a cardiac source.

In some patients, the cause of the drop in mean arterial pressure can be corrected simply by readjusting their antihypertensive regimen, by the administration of antiarrhythmic drugs, or by inserting a cardiac pacemaker. In patients with a combination of orthostatic hypotension and occlusive lesions, the hemodynamic problem may not respond to medical treatment; in such cases only reconstruction of a diseased or occluded vertebral artery will render the patient asymptomatic in the presence of persistent oscillations in blood pressure.

Investigation must also be undertaken to exclude inner ear pathology, including rare tumors of the cerebellopontine angle. In addition, neurologic evaluation to rule out benign vertiginous states should be considered.

When patients present with a combination of anterior and posterior hemispheric symptoms, investigation of the great vessels and the carotid circulation is usually warranted. Significant great vessel or carotid occlusive lesions may warrant reconstruction to alleviate symptoms.

An important aspect of the history is identifying triggering events, such as positional or postural changes. This is followed by a thorough physical examination, which includes palpation, auscultation, pulse examination, and comparative arm blood pressures (recumbent and standing). Physical examination can alert the physician to the possibility of subclavian steal in patients with differences in brachial blood pressure greater than 25 mm Hg or with diminished or absent pulses in one arm. The diagnosis of reversal of vertebral artery flow can be made accurately by noninvasive indirect methods and demonstrated directly by duplex imaging of the reversal of flow in the vertebral artery (see Chapter 88).

Patients may relate their symptoms to turning or extending the head. These dynamic symptoms usually appear on turning the head to one side and are caused by extrinsic compression.[11] To differentiate this mechanism from dizziness or vertigo secondary to labyrinthine disorders that appear with head or body rotation, the patient should attempt to reproduce the symptoms by first turning the head *slowly* and then repeating the maneuver *briskly*, as in shaking the head from side to side. In labyrinthine disease, the sudden inertial changes caused by the latter (brisk) maneuver result in immediate symptoms and nystagmus. Conversely, with extrinsic vertebral artery compression, a short delay occurs before imbalance develops.

Diagnostic Testing

Once a suspicion of vertebrobasilar ischemia has been entertained, only a few diagnostic tests are available to clearly ascertain the vertebral anatomy.

Duplex Ultrasonography

Although duplex ultrasound is an excellent tool for detecting lesions in the carotid artery, it has significant limitations when

it is used to detect vertebral artery pathology. Direct visualization of the second portion of the vessel is difficult because of its intraosseous course through the transverse processes of C2 to C6. The usefulness of duplex ultrasound lies in its ability to confirm reversal of flow within the vertebral arteries and detect changes in flow velocity consistent with a proximal stenosis.[22] In addition, ultrasound imaging can diagnose pathology of the great vessels and confirm subclavian steal.

Computed Tomography and Magnetic Resonance Imaging

MRI is another modality that provides a safe, noninvasive, detailed evaluation of both the extracranial and intracranial vasculature as well as structures within the posterior fossa. Contrast-enhanced magnetic resonance angiography (MRA) with three-dimensional reconstruction and maximum image intensity techniques provides full imaging of the vessels, including the supra-aortic trunks and the carotid and vertebral arteries (see Fig. 97.3). MRA can also diagnose reversal of flow in the vertebral artery.

In contrast to traditional computed tomography (CT) scans, transaxial MRI can readily diagnose both acute and chronic posterior fossa infarcts. Brain stem infarctions are often missed by CT because they tend to be small and the resolution of CT in the brain stem is poor. In patients who are candidates for vertebral artery reconstruction, brain MRI is performed preoperatively to ascertain whether infarctions have taken place in the vertebrobasilar territory. Transaxial MRI is particularly important in patients suspected of having suffered embolic infarction in the distribution of the posterior circulation.

CT angiography can readily identify occlusive lesions and has the advantage of being able to demonstrate significant osteophytic lesions that may impinge on vertebral flow.

Arteriography

Despite the technologic advances in MRI and CT evaluation, selective subclavian and vertebral angiography remains the best imaging modality for the preoperative evaluation of patients with vertebrobasilar ischemia. Some surgeons still consider angiography mandatory before endovascular intervention or surgical reconstruction. Arteriographic investigation of vertebral artery pathology necessitates systematic positions and projections to evaluate the vertebrobasilar system from its origin to the top of the basilar artery. Such an evaluation begins with an arch view, which determines the presence or absence of a vertebral artery on each side. Angiography shows whether one vertebral artery is dominant (generally the left) and can clearly define aberrant vessel anatomy. The most common anomalous origin involves the left vertebral artery, which can originate from the aortic arch in 6% of patients. A much rarer variant involves the right vertebral artery, which can be seen to arise from the innominate or right common carotid artery. This anatomy usually occurs in patients with an aberrant retroesophageal right subclavian artery. Arch views must be obtained in at least two projections: right and left posterior oblique views. Usually these two projections will sufficiently display the first segment (V1) of the vessel from its subclavian origin up to the transverse process of C6. The most common site of disease, the vertebral artery origin, may not be well imaged with ultrasound or MRA and, in fact, can often be displayed only with oblique projections that are not part of the standard aortic arch evaluation. A vertebral origin stenosis may be missed in standard arch views because of superimposition of the subclavian artery over the first segment of the vertebral artery. Additional oblique projections may be needed to "throw off" the subclavian artery to obtain a clear view of the origin of the vertebral artery. The presence of poststenotic dilation in the first centimeter of the vertebral artery suggests that there may be a significant stenosis at its origin hidden by an overlying subclavian artery. Visualization of the second segment (V2) of the vertebral artery, from C6 to the top of the transverse process of C2, is accomplished in the oblique arch views in conjunction with selective subclavian injections. An effort should be made to attempt to angiographically identify the point of entry of the vertebral arteries into the transverse processes of the cervical spine. Whether a patient has an abnormally low entry at the level of C7 instead of C6 should be noted. This finding is associated with a short V1 segment of the artery. In this circumstance, the short extraosseous length can create challenges for reconstruction at the V1 level.

Patients with suspected vertebral artery compression should undergo dynamic angiography, which incorporates provocative positioning. Arteriography is required to demonstrate extrinsic dynamic compression of the vertebral artery. This is performed either with the patient sitting up, by means of bilateral brachial injections, or, if the transfemoral approach is used, with the patient supine in the Trendelenburg position with the head resting against a block. The reason for positioning the patient either sitting up or in a 25-degree Trendelenburg position is to mimic the effects of the weight of the head on the spine. With the patient standing, the weight of the head acting on the cervical spine changes its curvature and decreases the distance between C1 and C7. This longitudinal compression of the spine often enhances the extrinsic compression effects caused by osteophytic spurs. In these positions, intended to exert axial compression on the cervical vertebrae, the angiographer should obtain the specific rotation or extension of the head that provokes the symptoms. When the patient is rendered symptomatic, arteriographic injection should demonstrate the extrinsic compression that developed with the head in rotation or extension.[23] The vertebral artery may be normal in one position and occluded by extrinsic compression in the other (Fig. 97.9). Finally, delayed imaging should be performed to demonstrate reconstitution of the extracranial vertebral arteries through cervical collaterals. Delayed angiographic views are of the utmost importance in identifying a patent V3 segment, which can be exploited as a distal target for revascularization. Finally, the basilar artery should be seen clearly in a lateral projection. Subtracted views are needed to eliminate the temporal bone density in the lateral projection. In the Towne anteroposterior view, routinely used in neuroradiology, the basilar artery is foreshortened and therefore the resolution is poor.

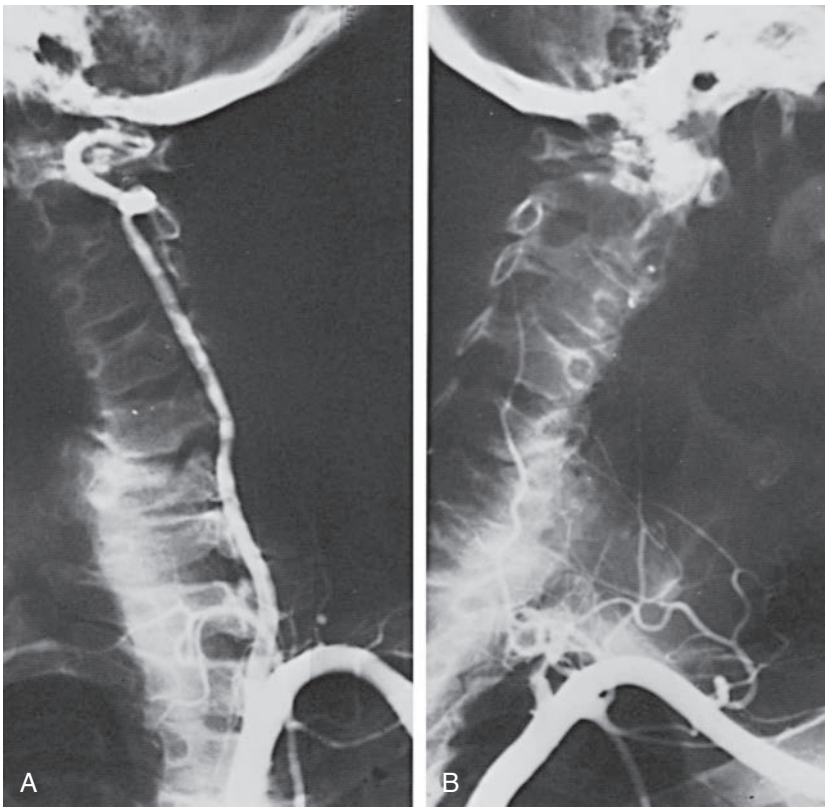

Figure 97.9 A patient with a single vertebral artery showing minimal extrinsic compression (A) when the neck is rotated to the right and occlusion (B) when the neck is rotated to the left. (From Berguer R. Surgical management of the vertebral artery. In: Moore WS, ed. *Surgery for Cerebrovascular Disease*. New York: Churchill Livingstone; 1986.)

VERTEBRAL ARTERY RECONSTRUCTIVE PROCEDURES

Accumulated experience has shown that with appropriate surgical intervention, predictable resolution of hemodynamic symptoms and cessation of embolic events can occur.

Disease Location

The location of disease will dictate the type of surgical reconstruction that is required. With rare exceptions, most reconstructions of the vertebral artery are performed to relieve an orificial stenosis (V1 segment) or stenoses, dissection, or occlusion of its intraspinal component (V2 and V3 segments).[24]

V1 Segment

Several operations have been described for treating ostial lesions in V1.[25,26] Transposition of the proximal vertebral artery onto the adjacent carotid artery is the most common reconstruction. Less commonly, a bypass using saphenous vein can be performed from either the common carotid artery or the adjacent subclavian artery.[27,28] Alternatively, a subclavian–vertebral artery endarterectomy can be performed, but this operation is fraught with technical challenges.

V2 Segment

Although the second segment of the vertebral artery is the site of a wide variety of pathologic conditions, the V2 segment is rarely accessed surgically due to its interosseous position. The most common indication for exposure of the V2 segment is hemorrhage, which, when untreatable endoluminally, is best managed by proximal and distal ligation of the artery. After complete V2 occlusion, patency of the distal extracranial segment is often maintained by collaterals from the external carotid or subclavian artery. Ligation (at the C1-C2 level) and bypass to the distal (V3 segment) vertebral artery may be indicated for embolizing V2 pathology.

V3 Segment

Reconstruction of the distal (V3 segment) vertebral artery is usually performed at the C1-C2 level. The technique most often used to reconstruct the distal vertebral artery includes saphenous vein bypass from the common carotid, subclavian, or proximal vertebral artery.[21,25] Alternatively, the radial artery can be used as a conduit in the absence of suitable vein. Transposition of the external carotid or hypertrophied occipital artery into the distal vertebral artery, as well as transposition of the distal vertebral artery into the side of the internal carotid artery, has also been described.

Suboccipital Segment

For more distal pathology, the vertebral artery can also be accessed surgically above the level of the transverse process of C1. Surgical exposure at the suboccipital segment requires resection of the C1 transverse process and part of its posterior arch. Reconstruction at this level is limited to saphenous vein bypass from the distal internal carotid artery. Bypasses above the level of C1

(suboccipital) are technically demanding and have been required in only 4% of cases of distal vertebral artery reconstruction.

Transposition of the Proximal Vertebral Artery Into the Common Carotid Artery

The approach to the proximal vertebral artery is the same as the approach for a subclavian-to-carotid transposition. The incision is placed transversely one fingerbreadth above the clavicle and directly over the two heads of the sternocleidomastoid muscle (Fig. 97.10). Subplatysmal skin flaps are created to provide adequate exposure. Dissection is carried down directly between the two bellies of the sternocleidomastoid, and the omohyoid muscle is divided. The internal jugular vein is retracted laterally and the carotid sheath entered. The carotid artery should be exposed proximally as far as possible, which is facilitated if the surgeon temporarily stands at the head of the patient and looks down into the mediastinum. The vagus nerve should be left with the common carotid to prevent traction injury from lateral displacement.

After the carotid artery has been mobilized, the sympathetic chain is identified running behind and parallel to it. On the left side, the thoracic duct is divided between ligatures. Accessory lymph ducts—often seen on the right side—are identified, ligated, and divided. The entire dissection is confined medial to the prescalene fat pad that covers the scalenus anticus muscle and phrenic nerve.

The vertebral vein is next identified emerging from the angle formed by the longus colli and scalenus anticus and overlying the vertebral artery and, at the bottom of the field, the subclavian artery. The vein is ligated in continuity and divided. Below the vertebral vein lies the vertebral artery. It is important to identify and avoid injury to the adjacent sympathetic chain. The vertebral artery is dissected superiorly to the tendon of the longus colli and inferiorly to its origin from the subclavian artery. The vertebral artery is freed from the sympathetic trunk resting on its anterior surface without damaging the trunk or the ganglionic rami. Preserving the sympathetic trunks and the stellate or intermediate ganglia resting on the artery usually requires freeing the vertebral artery from these structures, and after dividing its origin, the latter is transposed anterior to the sympathetics.

Once the artery is fully exposed, an appropriate site for reimplantation in the common carotid artery is selected. The patient is given heparin systemically. The distal portion of the V1 segment of the vertebral artery is clamped below the edge of the longus colli with a microclip placed vertically to indicate the orientation of the artery and to avoid axial twisting during its transposition. The proximal vertebral artery is closed by transfixion with 5-0 polypropylene suture immediately above the stenosis at its origin. The artery is divided at this level and

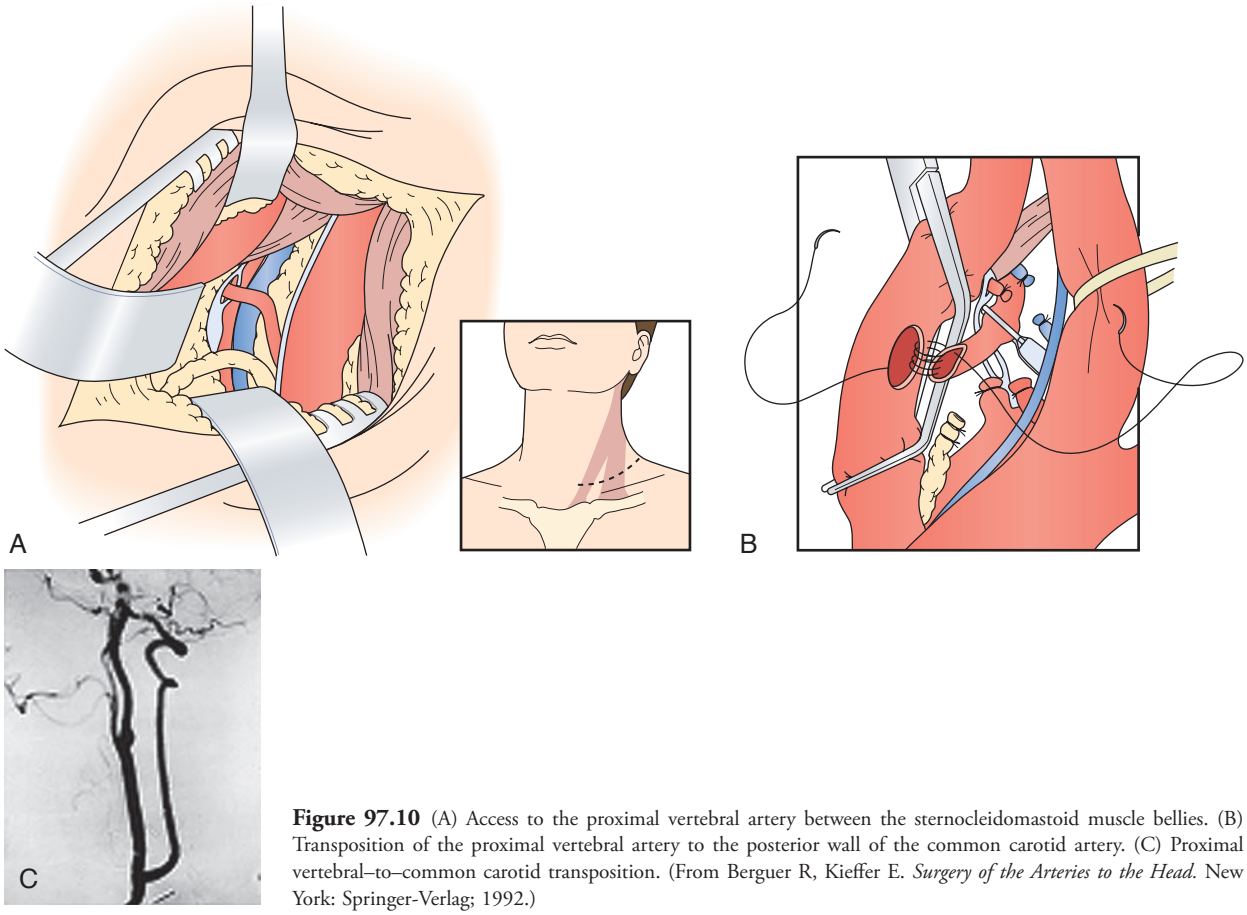

Figure 97.10 (A) Access to the proximal vertebral artery between the sternocleidomastoid muscle bellies. (B) Transposition of the proximal vertebral artery to the posterior wall of the common carotid artery. (C) Proximal vertebral–to–common carotid transposition. (From Berguer R, Kieffer E. *Surgery of the Arteries to the Head.* New York: Springer-Verlag; 1992.)

then brought to the common carotid artery, and its free end is spatulated for anastomosis.

The carotid artery is then cross-clamped. An elliptical 5- to 7-mm arteriotomy is created in the posterolateral wall of the common carotid artery with an aortic punch. The anastomosis is performed in open fashion with continuous 6-0 or 7-0 polypropylene suture while avoiding any tension on the vertebral artery, which tears easily. Before completion of the anastomosis standard flushing maneuvers are performed, and the suture is tied to reestablish flow (Fig. 97.10C).

When simultaneous carotid endarterectomy is planned, the vertebral artery is approached through the standard carotid incision extended inferiorly to the head of the clavicle. With this approach, the sternocleidomastoid muscle is lateral and the field is a bit narrower than when the vertebral artery is approached between the heads of the sternocleidomastoid. The remaining steps of the operation are performed as described previously.[29]

Distal Vertebral Artery Reconstruction

Common Carotid–Vertebral Artery Bypass

Reconstruction of the distal vertebral artery is generally done at the C1-C2 level. Rarely, the reconstruction is done between C1 and the base of the skull via a posterior approach. Although various techniques can be applied to revascularize the vertebral artery in its V3 segment (between the transverse processes of C1 and C2), the approach to the vertebral artery at this level is the same for all procedures.[21,30]

The incision is made anterior to the sternocleidomastoid muscle, the same as for a carotid operation, and is carried superiorly to immediately below the earlobe (Fig. 97.11). The dissection proceeds between the internal jugular vein and the anterior edge of the sternocleidomastoid to expose the spinal accessory nerve. The nerve is followed cranially as it crosses in front of the transverse process of C1, which can easily be felt by the operator's finger. The levator scapulae muscle is identified by removal of the fibrofatty tissue overlying it. With the anterior edge of the levator scapulae identified, the surgeon searches for the anterior ramus of C2. With the ramus as a guide, the levator scapulae is transected from its origin on the C1 transverse process (Fig. 97.12). The C2 ramus divides into three branches after crossing the vertebral artery. The artery runs below, in contact with the nerve and perpendicular to it. The surgeon cuts the ramus (Fig. 97.13) before its branching; underneath it, the vertebral artery can be identified. A small minority of patients may develop noticeable but self-limiting posterior scalp numbness as a result of cutting the ramus. The artery is freed from the surrounding veins with care, as venous bleeding is difficult to control at this level. Before encircling the artery with fine silicone vessel loops (Fig. 97.14), one must ensure that a branch from the occipital collateral artery does not enter the posterior aspect of the vertebral artery at this location. Tearing of this important collateral vessel complicates preparation of the distal vertebral artery. Once the vertebral artery has been encircled, the distal common carotid artery is dissected and prepared to receive a saphenous vein graft. There is

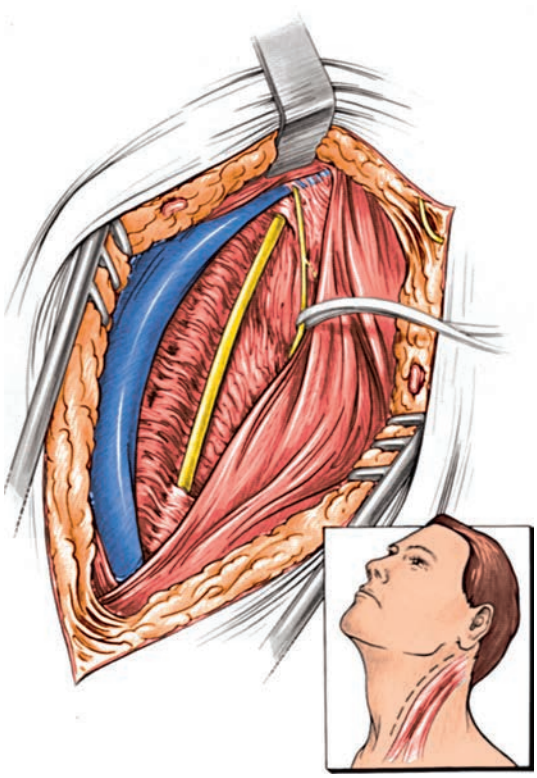

Figure 97.11 Retrojugular approach and isolation of the spinal accessory nerve. (From Berguer R, Kieffer E. *Surgery of the Arteries to the Head.* New York: Springer-Verlag; 1992.)

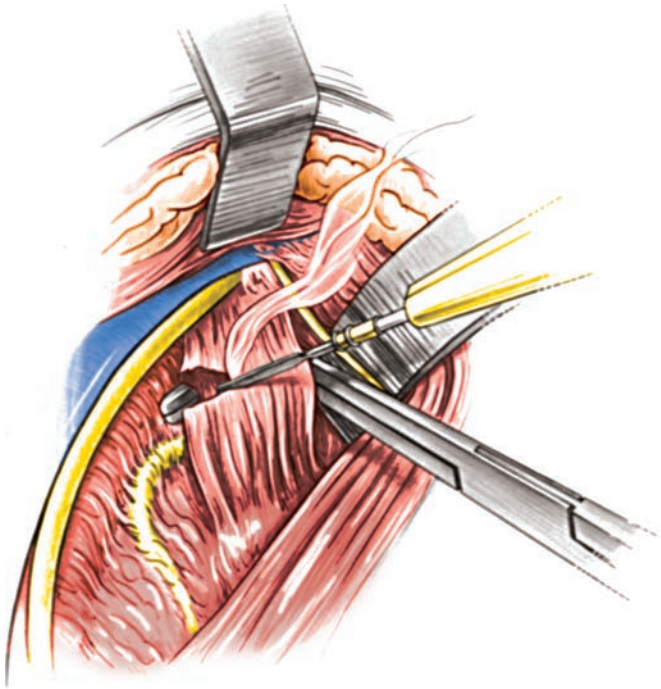

Figure 97.12 Dividing the levator scapulae over the C2 ramus. The vagus, internal jugular vein, and internal carotid artery are anterior to the muscle. (From Berguer R, Kieffer E. *Surgery of the Arteries to the Head.* New York: Springer-Verlag; 1992.)

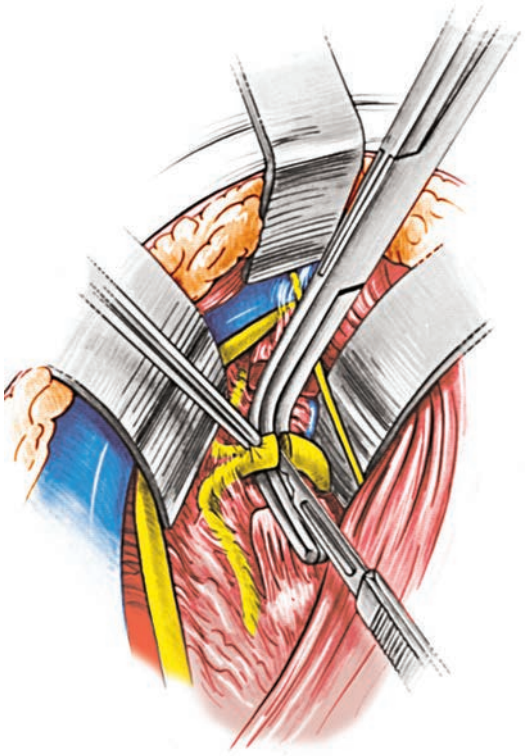

Figure 97.13 Dividing the anterior ramus of C2 to expose the underlying vertebral artery running perpendicular to the anterior ramus. (From Berguer R, Kieffer E. *Surgery of the Arteries to the Head.* New York: Springer-Verlag; 1992.)

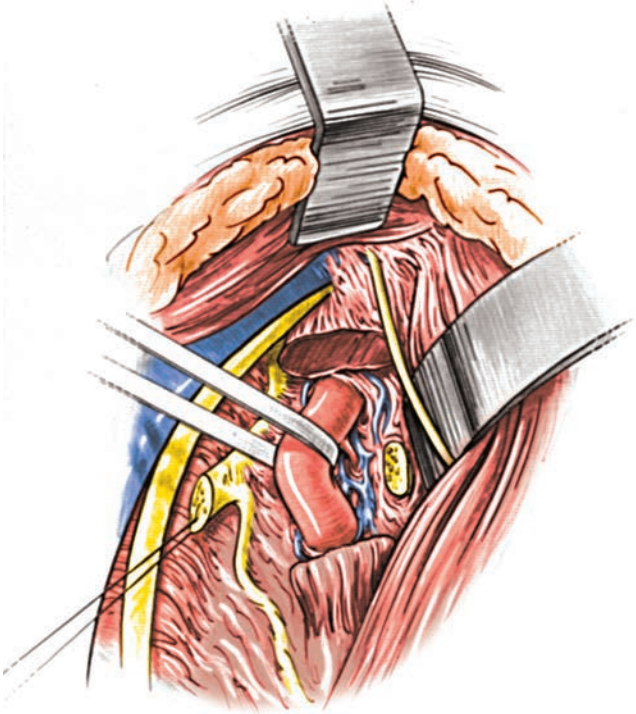

Figure 97.14 After the vertebral venous plexus is dissected away, the vertebral artery is slung with a polymeric silicone (Silastic) loop for clamping and anastomosis. (From Berguer R, Kieffer E. *Surgery of the Arteries to the Head.* New York: Springer-Verlag; 1992.)

no need to dissect the carotid bifurcation. The location selected for the proximal anastomosis of the saphenous vein graft on the common carotid artery should not be too close to the bifurcation, because cross-clamping at this level may fracture any underlying atheroma.

A saphenous vein graft or other suitable conduit of appropriate length is prepared. A valveless segment facilitates back bleeding of the vertebral artery after completion of the distal anastomosis. The patient is given intravenous heparin. The vertebral artery is elevated by gently pulling the loop and is occluded with a small J-clamp to isolate this segment for an end-to-side anastomosis. The vertebral artery is opened longitudinally with a coronary knife for a length adequate to accommodate the spatulated end of the vein graft. The end-to-side anastomosis is performed with continuous 7-0 polypropylene and fine needles. The distal anastomosis is assessed for backflow, and if satisfactory, a small clamp is placed in the vein graft proximal to the anastomosis and the J-clamp removed to restore flow through the vertebral artery.

The proximal end of the graft is passed beneath the jugular vein. The common carotid artery is then cross-clamped, an elliptical arteriotomy is made in its posterior wall with an aortic punch, and the proximal vein graft is anastomosed end to side to the common carotid artery with continuous 6-0 polypropylene. Before the anastomosis is completed, standard flushing maneuvers are performed, the suture is tied, and flow is reestablished. Next, the vertebral artery is occluded with a clip immediately below the anastomosis to functionally create an end-to-end configuration. In the absence of suitable common carotid artery, the ipsilateral subclavian artery can be used as a donor vessel.

Alternative Options for V3 Reconstruction

The distal vertebral artery may also be revascularized via the external carotid artery (ECA), either directly by means of transposition of the ECA to the distal vertebral artery or by anastomosis of the proximal end of a graft to the ECA (Fig. 97.15). Another method of revascularization of the distal vertebral artery is transposition of this vessel into the distal cervical internal carotid artery below the transverse process of C1. This technique is particularly applicable for patients with inadequate saphenous vein or those in whom the ECA cannot be used because of unsuitable anatomy or disease of the carotid bifurcation.

A small number of patients have disease that extends up to the level of C1 and require revascularization in the most distal segment of the extracranial vertebral artery.[31-33] To accomplish this, the vertebral artery must be exposed in its pars atlantica, where the artery runs parallel to the lamina of the atlas before entering the foramen magnum.

Posterior Suboccipital Vertebral Artery Bypass

For more distal pathology, the vertebral artery can also be accessed surgically above the level of the transverse process of C1. Surgical exposure at the suboccipital segment requires resection of the C1 transverse process and part of its posterior arch. Reconstruction at this level is limited to saphenous vein bypass from the distal internal carotid artery. Bypasses above the level of C1

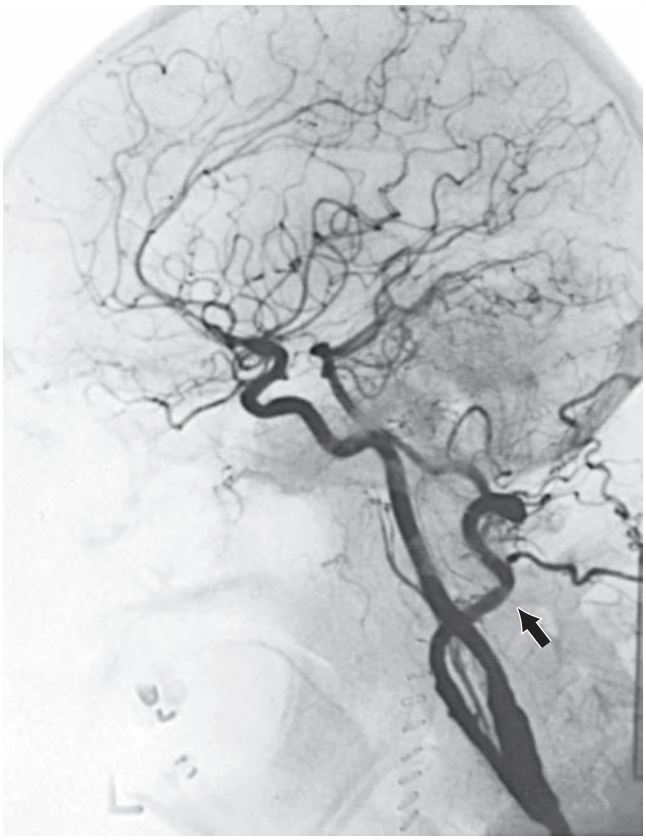

Figure 97.15 Arteriogram of a transposition of the external carotid artery to the distal vertebral artery. This patient had previously undergone internal carotid endarterectomy. (From Berguer R, Kieffer E. *Surgery of the Arteries to the Head.* New York: Springer-Verlag; 1992.)

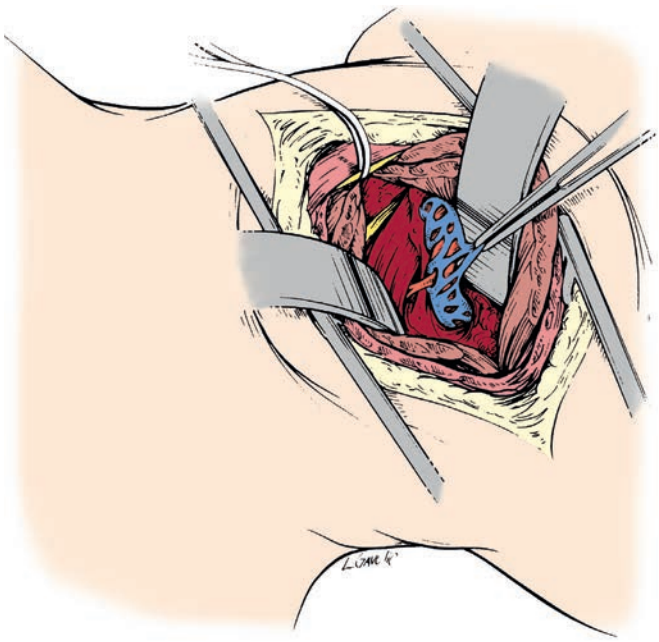

Figure 97.16 The pars atlantica of the distal vertebral artery exposed and surrounded by a dense venous plexus.

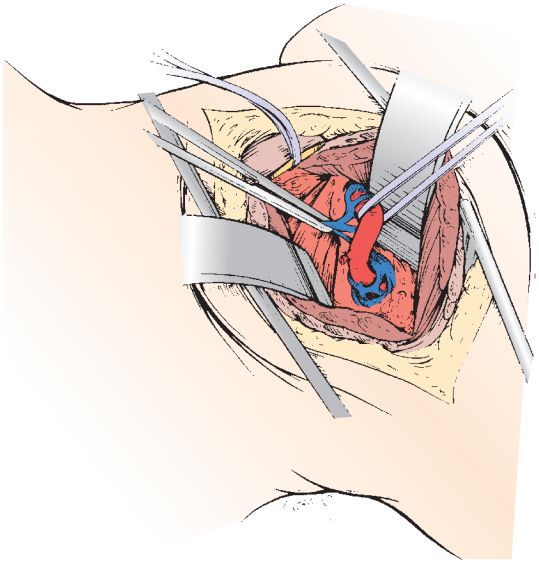

Figure 97.17 Exposure of the pars atlantica of the vertebral artery from its exit from the transverse foramen of C1 to its entrance into the dura mater.

(suboccipital) are technically demanding and have been required in only 4% of cases of distal vertebral artery reconstruction.

A small group of patients have disease up to the level of C1 and require revascularization in the last segment of the extracranial vertebral artery. To accomplish this, the vertebral artery must be exposed in its pars atlantica, where the artery runs parallel to the lamina of the atlas before entering the foramen magnum (Figs. 97.16 and 97.17).

OPERATIVE RESULTS

Perioperative Outcomes

Perioperative complication rates differ for proximal versus distal vertebral artery reconstruction. Perioperative complications that can follow any reconstruction include stroke, bleeding, thrombosis, and nerve injury. Intraoperative completion imaging with digital angiography is useful and should be considered for all types of vertebral artery reconstruction. Reparable technical flaws may be identified, and repair can prevent reconstruction failure.

Proximal Reconstructions

The technically easier proximal operations have been reported to have a combined stroke and death rate of 0.9%.[22] Among patients undergoing proximal operations in one report, no deaths or strokes occurred in those who underwent only a vertebral reconstruction. When the proximal vertebral artery reconstruction was combined with a carotid operation, the observed stroke and death rates increased to 5.7%.[22] Berguer et al.[22] reported four instances of immediate postoperative thrombosis (1.4%). Three of the four patients had vein grafts interposed between the vertebral artery and the common carotid because of a short V1 segment. The grafts kinked and thrombosed. Other complications that are particular to proximal reconstruction include vagus and recurrent laryngeal nerve palsy (2%), Horner's

syndrome (8.4%-28%), lymphocele (4%), and chylothorax (0.5%).

Distal Reconstructions

Operations on the distal vertebral artery carry higher stroke and death rates than do operations on the proximal vertebral artery. Distal reconstructions have a combined stroke and death rate of 3%.[34] The immediate graft thrombosis rate has been reported at 8%, and spinal accessory nerve injury occurs in 2% of patients.[35]

Long-Term Outcomes

Results after both proximal and distal vertebral artery reconstruction are generally equal to or better than those reported in series reviewing other forms of extracranial cerebrovascular reconstruction.[34,36] After proximal vertebral–to–common carotid transposition, patency rates at 5 and 10 years equal or exceed 95% and 91%, respectively. When selected appropriately, more than 80% of patients will have relief of their symptoms after proximal surgical reconstruction.[36]

For distal bypass reconstruction, patency rates of 87% and 82% should be expected at 5 and 10 years.[34,36] Seventy percent of patients undergoing distal vertebral artery reconstruction are dead at 5 years of follow-up, mostly from cardiac disease, whereas 97% of survivors are free of stroke at 5 years. Symptoms are expected to be cured in 71% of patients and improved in an additional 16%.[34,36]

Predictably, in patients treated for severe hemodynamic symptoms who also suffer from compensatory high blood pressure, appropriate reconstruction and reperfusion of the brain stem results in significant improvement in their hypertension.

ENDOVASCULAR THERAPY

Endovascular Treatment

In the last two decades, a growing number of case reports and small nonrandomized case series suggest that endovascular intervention in the posterior circulation may be safe and technically feasible.[37-48] Endovascular access to the vertebral artery is relatively straightforward. Patients are pretreated with dual-therapy aspirin and clopidogrel. The procedure can be performed under local anesthesia, enabling continuous neurologic monitoring of the patient. Most cases are performed from a femoral approach (93%), although transbrachial (3%) and transradial (5%) access have also been used (see Chapter 92).[49] The stenotic lesions are crossed and treated with 0.014- or 0.018-in. guidewires and small coronary-diameter balloons and stents. Procedures can be performed with or without the assistance of embolic protection, although vertebral arteries are usually too small to accommodate most distal protection devices. One large review found distal protection used in only 2% of cases.[49]

Periprocedural risks include access complications, distal embolization and stroke, arterial rupture, stent malposition and vessel thrombosis or dissection. Later, restenosis and stent fracture are not uncommon.

Overall, retrospective reviews suggest that endoluminal vertebral artery intervention is reasonably safe, although a selection bias exists. A 2005 Cochrane review identified 313 interventions for vertebral artery stenosis, with just over half using stent placement as part of the treatment. The technical success rate was 95%, and the 30-day stroke and death rate was 6.4%.[50] The Cochrane group concluded that although angioplasty with stenting for vertebral artery stenosis is technically feasible, evidence is currently insufficient to support its routine application.

A subset of 16 patients treated within the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS 2001) represents the only report of a randomized controlled trial comparing endoluminal therapy with best medical care for symptomatic vertebral stenosis. No 30-day strokes or deaths occurred in either group, although two of eight patients who underwent endoluminal therapy experienced transient ischemic symptoms. Furthermore, with a mean follow-up of 4.5 years, no posterior circulation strokes were noted in either group.

Despite high technical success rates, vertebral artery angioplasty alone, especially when used for the treatment of disease at the origin of the vessel, appears to have an unacceptably high rate of restenosis. Adjuvant stent placement seems to add to the clinical durability, although stents carry inherent morbidity of their own, such as malposition and potential stent fracture. In their series of 105 patients who underwent endovascular stenting for symptomatic vertebral artery disease, Jenkins et al. achieved 100% radiographic improvement (residual stenosis ≤30%). The authors reported an immediate (30-day) periprocedural risk of death of 1% and periprocedural complication rate of 4.8%. Complications included transient ischemic attack, flow-limiting dissection, hematoma, and access-site problems. At 1 year of follow-up, six patients had died and five had experienced a vertebrobasilar stroke; at approximately 2.5 years of follow-up, 70% of patients remained symptom-free, but 13% had restenosis requiring retreatment.[51]

In the Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) trial, 18 patients with extracranial vertebral artery disease underwent angioplasty and stenting. Technical success (determined as less than 50% residual stenosis following treatment) was achieved in 17 (94%) of the 18 patients. No periprocedural neurologic complications were observed. The investigators, however, reported 6-month restenosis rates of 50%. These recurrences were symptomatic in 39% of cases.[52]

A recent systematic review of the available literature noted a weighted mean technical success rate of 97%. The authors estimated the mean periprocedural stroke and death rate from combined angioplasty and stenting to be approximately 1.1%. Transient ischemic events occurred in 1.5% of patients. Recurrent symptoms occurred in 8% of patients within a reported follow-up range of 6 to 54 months, and greater than 50% restenosis developed in 23% of the subset of patients who underwent follow-up imaging.[49]

Late stent fracture with concomitant in-stent restenosis may be a problem plaguing endoluminal therapies that target lesions at the vertebral artery origin. Anatomically, the vertebral artery

takes origin from the subclavian artery at a near right angle. In addition, the first portion of the subclavian artery has relative mobility, whereas the vertebral artery becomes fixed as it passes into the transverse foramen of C6. This particular anatomy may create unique mechanical forces that make stent fracture more likely than it is for other parts of the body.

The use of drug-eluting stents to impede neointimal hyperplasia and prevent restenosis has been well established in the coronary arteries and may be beneficial in the treatment of vertebral disease.[53] Ogilvy et al. reported a series of patients with the longest follow-up thus far (21 months); for these patients, drug-eluting stents were used in stenosis of vertebral artery origin. The authors found that the incidence of in-stent restenosis (>50% diameter) decreased from 38% in patients who received non–drug-eluting stents to 17% in those who received drug-eluting stents.[54] Other reports also suggest decreased restenosis rates with drug-eluting stents; however, many of those studies have mean patient follow-up times of less than 1 year.[55,56] Treatment with drug-eluting stents requires long-term dual antiplatelet therapy. It remains unclear whether differing stent makeup will have a significant impact in the outcomes of patients who undergo interventions of the vertebral artery.

With the exception of the small subset of patients from CAVATAS 2001, only retrospective case series exist for endoluminal therapies for the treatment of vertebral artery disease, as with open surgical techniques. Currently no level I data support the routine application of angioplasty and stenting of the vertebral artery over best medical therapy. The multicenter, randomized Vertebral Artery Stenting Trial (VAST), which was designed to prospectively analyze the impact of percutaneous vertebral interventions over medical therapy for stenting of intracranial or extracranial vertebral artery stenosis was stopped due to regulatory requirements but after enroling 115 subjects the authors were able to conclude that stenting of symptomatic vertebral artery stenosis is associated with a major periprocedural vascular complication in about one in 20 patients and that the risk of recurrent vertebrobasilar stroke under best medical treatment alone was low, questioning the need for and feasibility of a phase 3 trial.[57]

CONCLUSION

Surgical or endovascular reconstruction of the vertebral artery is often a viable option and should be considered in symptomatic patients with appropriate atherosclerotic lesions or other vasculopathy in whom medical therapy has failed. Open techniques for revascularization of the vertebral artery have proven clinical durability and acceptable surgical morbidity in experienced hands. Endoluminal techniques, which have gained momentum over the past decade, have shown clinical feasibility but have yet to deliver on durability benchmarks set by open surgical revascularization. For each individual patient who suffers from medically refractive vertebrobasilar ischemia, practitioners must carefully balance the risks of surgery versus the limitations of endoluminal intervention before recommending intervention.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 98

Brachiocephalic Artery Disease and Its Surgical Treatment

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INTRODUCTION

The innominate, left common carotid, and left subclavian arteries originate at the transverse aortic arch and are collectively referred to as the supraaortic trunk or the brachiocephalic arteries. Brachiocephalic arterial occlusive disease can cause transient ischemic attacks, stroke, and upper extremity ischemia. The most common occlusive etiology is atherosclerosis. Other pathologies include arterial dissection (either extending from the aortic arch or in isolation), vasculitides, and radiation arteritis. Other entities affecting the brachiocephalic arteries include infection, trauma, and aneurysm. Revascularization options include endovascular techniques, extraanatomic bypass, and direct access via median sternotomy.

ANATOMIC VARIANTS

The most common configuration of the aortic arch is to have three distinct origins of the innominate, left common carotid, and left subclavian arteries. However, a variety of congenital alterations to the aortic arch exist (Table 98.1). Up to 20% of normal patients have the so-called "bovine arch" variation, where the left common carotid artery originates from a shared trunk with the innominate artery (Fig. 98.1). There is some evidence of association between anomalous brachiocephalic arteries and thoracic aortic disease requiring intervention.[1] Most commonly, the vertebral arteries originate from the subclavian arteries but the left vertebral artery occasionally originates directly from the aortic arch between the left common and

Abstract

Brachiocephalic artery disease can cause transient ischemic attacks, stroke, and upper extremity ischemia. The most common occlusive etiology is atherosclerosis. Other pathologies include arterial dissection, vasculitides, and radiation arteritis. In this chapter, we examine the various surgical treatments for brachiocephalic artery disease and report postoperative results. We first look at anatomic variants and the key indications for surgical intervention, highlighting the best diagnostic tools. We outline the different means for revascularization, including endovascular techniques, extraanatomic bypass, and direct access via median sternotomy. We report operative results, including those from Berguer and colleagues who reviewed 182 cervical reconstructions in 1999. They found that stroke, myocardial infarction, and mortality rates were 3.8%, 3%, and 0.5%, respectively. Five- and 10-year survival rates were 72% and 41%, with 5- and 10-year patency rates of 91% and 82%. In 2007, Byrne and colleagues reported a 5-year cumulative patency rate of 92% in 143 patients with cervical brachiocephalic artery revascularization. They had stroke, myocardial infarction, and mortality rates of 1.4%, 4.3%, and 0.7%, respectively. We conclude the chapter with our postoperative management protocols, which typically include discharge after 1 or 2 days and plan follow-up visits where we monitor graft patency by duplex ultrasound examination every 6 months for the first year and annually thereafter.

Keywords

Brachiocephalic artery disease
atherosclerosis
aortic arch

TABLE 98.1 Aortic Arch Anomalies

Arch Anomaly	Description	Prevalence (%)
Normal aortic arch configuration	Consists of three great vessels originating from the aortic arch. The first branch is the innominate artery, which branches into the right subclavian artery and right common carotid artery. The second branch is the left common carotid artery. The third branch is the left subclavian artery.	70-74
"Bovine aortic arch" subtype II	Left common carotid artery and innominate artery share a common origin. More common in African Americans (25%) versus whites (8%).	13-20
"Bovine aortic arch" subtype I	Left common carotid artery arises directly from the innominate artery, most often <1 cm from aortic arch. More common in African Americans (10%) versus whites (5%).	9
Aberrant left vertebral artery	Left vertebral artery arises from the aortic arch. The most common location is between the left common carotid and subclavian arteries.	2-6
Aberrant right subclavian artery	Right subclavian artery is the last branch of the aortic arch arising distal to the origin left subclavian artery. It courses posterior to the esophagus (80%), between the esophagus and trachea (15%), or anterior to the trachea or mainstem bronchus (5%).	0.5-2
Aberrant left subclavian artery	Left subclavian artery is the second branch of the aortic arch, arising before the left common carotid artery.	<0.5
Right aortic arch	Vessels originate in the following order: left common carotid, right common carotid, right subclavian artery, and left subclavian artery.	<0.1

left subclavian arteries. An aberrant right subclavian artery may originate distal and posterior to the left subclavian artery. In treating aortic arch pathology, it is critical to recognize these anomalies.

INDICATIONS FOR INTERVENTION IN OCCLUSIVE DISEASE

Brachiocephalic arterial occlusive disease can be unifocal, multifocal, single vessel, or multivessel. In the series of 282 transthoracic and transcervical brachiocephalic revascularizations reported by Berguer et al.,[2,3] there was a 40% incidence of multivessel disease. Repair is clearly indicated in symptomatic lesions, such as causing stroke, transient ischemic attacks, subclavian steal syndrome, upper limb ischemia, and other thromboembolic phenomena.

There is limited data regarding treatment of asymptomatic severe lesions defined as causing more than 75% stenosis.[2,4,5] With few exceptions, asymptomatic lesions of the subclavian arteries should be medically managed, regardless of severity. Invasive treatment of asymptomatic lesions involving the innominate or common carotid arteries is controversial and is based on extrapolation from carotid bifurcation studies. In general, the risks of open transthoracic surgical repair for asymptomatic occlusive lesions likely outweigh the benefits in most patients (Table 98.2). Reasonable exceptions to this include severe subclavian stenosis with patent internal mammary-coronary bypass, preservation of arteriovenous accesses, preservation of axillary artery-based peripheral bypass grafts, planned sternotomy and reconstruction of the aortic arch or other brachiocephalic artery lesions.

OTHER INDICATIONS FOR INTERVENTION

Infection

Infectious processes (including syphilis and tuberculosis) can lead to aneurysmal degeneration of the brachiocephalic arteries and, in particular, the subclavian artery. These are rare causes of proximal (intrathoracic) aneurysm. Aberrant right subclavian artery aneurysms (Kommerell diverticulum) can fistulize into the esophagus.[6,7] When diagnosed, infectious brachiocephalic aneurysms or pseudoaneurysms should be repaired, regardless of size. All patients should receive long-term systemic antibiotics. Depending on organism virulence and anatomy, treatment includes resection, debridement, and extraanatomic or in situ repair.

Trauma

Blunt traumatic injuries can lead to brachiocephalic pseudoaneurysm formation, especially involving the origin of the innominate artery.[8] Penetrating trauma may affect the brachiocephalic vessels in any location (Fig. 98.2). Urgent repair of traumatic brachiocephalic artery injury is indicated for patients with hemorrhage, critical extremity ischemia, and compression of vital structures. Minor asymptomatic injuries can be medically managed if patients can adhere to a surveillance program. Most asymptomatic, clinically occult injuries will remain stable or resolve.[9,10] Most strokes from blunt cerebrovascular injuries occur at the time of injury, or soon afterward. Few patients have recurrent stroke on medical management with anticoagulation

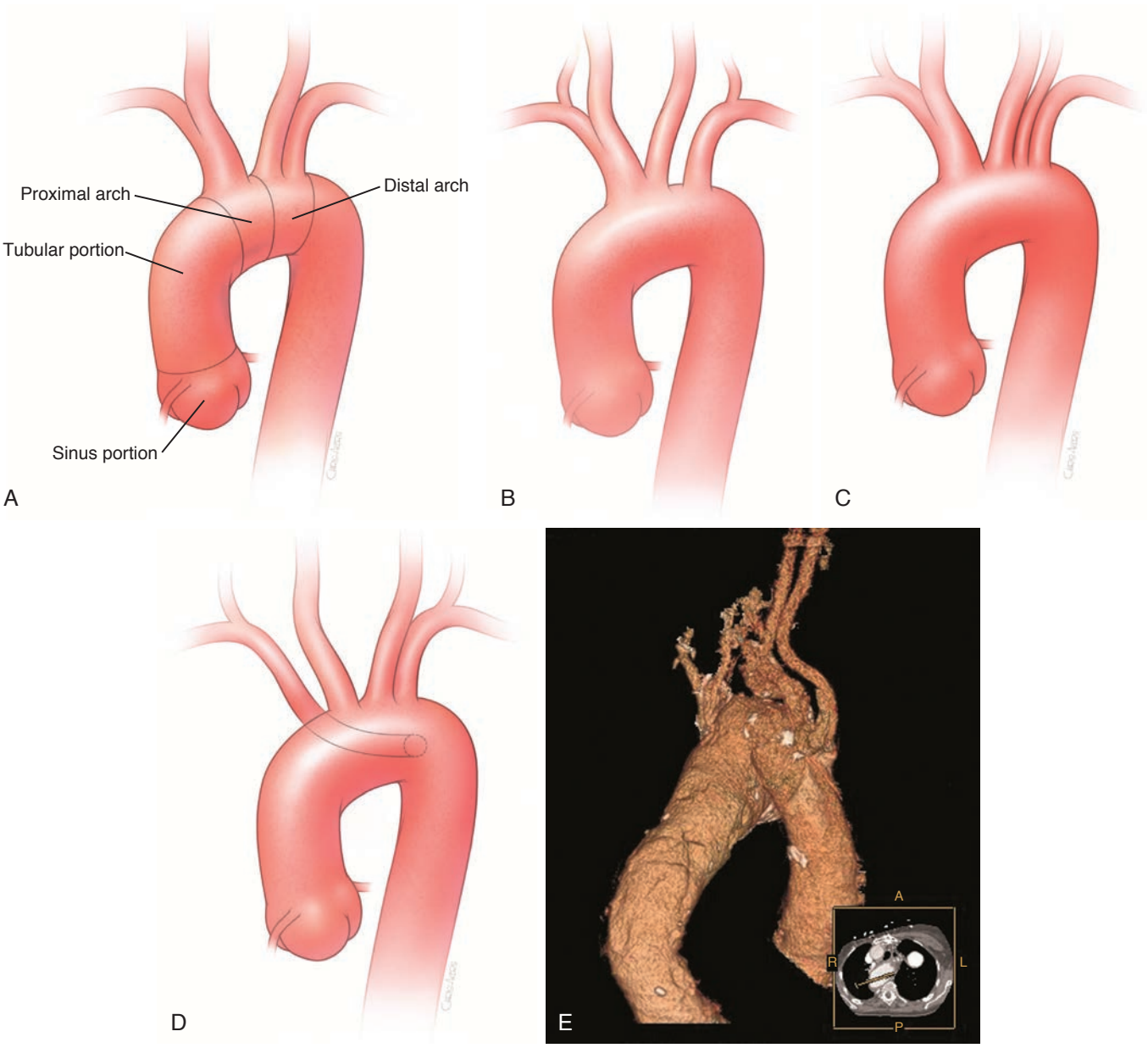

Figure 98.1 Normal and Variant Aortic Arch Anatomy. (A) The normal aortic arch configuration (70%-74% prevalence) consists of three great vessels originating from the arch of the aorta. The first branch is the innominate artery, which branches into the right subclavian artery and right common carotid artery. The second branch is the left common carotid artery. The third branch is the left subclavian artery. (B) The "bovine aortic arch" subtype II (13%-20% prevalence) consists of the left common carotid and innominate arteries sharing a common origin. This is more common among African Americans (25% vs. 8% of whites). In the "bovine aortic arch" subtype I, the left common carotid artery arises directly from the innominate artery, most often less than 1 cm from the aortic arch. It is also more common among African Americans (10% vs. 5% of whites 5%). (C) The aberrant left vertebral artery (2%-6% prevalence) arises directly from the aortic arch, most commonly between the left common carotid and subclavian arteries. (D) The aberrant right subclavian artery (0.5%-2% prevalence) occurs as the last branch of the aortic arch, arising distal to the origin of the left subclavian artery. It typically courses posterior to the esophagus (80%), between the esophagus and trachea (15%), or anterior to the trachea or mainstem bronchus (5%). The aberrant left subclavian artery occurs less frequently (<0.5% prevalence), and manifests as the second branch of the aortic arch, arising proximal to the left common carotid artery. (E) The right-sided aortic arch is a rare variant (<0.1% prevalence) whereby the arch vessels originate in the following order (proximal to distal): left common carotid, right common carotid, right subclavian artery, and left subclavian artery. The following represents a three-dimensional reconstruction of a contrast-enhanced computed tomography scan depicting a patient's right-sided aortic arch.

TABLE 98.2 Selected Transthoracic Revascularization Results

Series	Year	Number of Patients	RESULTS						
						Survival		Patency	
			Mortality	Stroke	MI	5-Year	10-Year	5-Year	10-Year
Crawford et al.	1962	122	13 (10.8[a])	NA	NA	NA	NA	NA	NA
Crawford et al.[25]	1983	43	4.7	6.9	NA	NA	NA	NA	NA
Kieffer et al.[26]	1995	135	5.2	2.9	1.5	77.5	51.9	98.4	96
Berguer et al.[2]	1998	100	8	8	3	87	81	94	88
Rhodes et al.[27]	2000	92	3	7	3	88	NA	80	NA
Uurto et al.[47]	2002	76	2.5	2.6	NA	84	72	95	91

[a]Incidence for bypass procedures alone.
MI, Myocardial infarction; *NA*, not available.

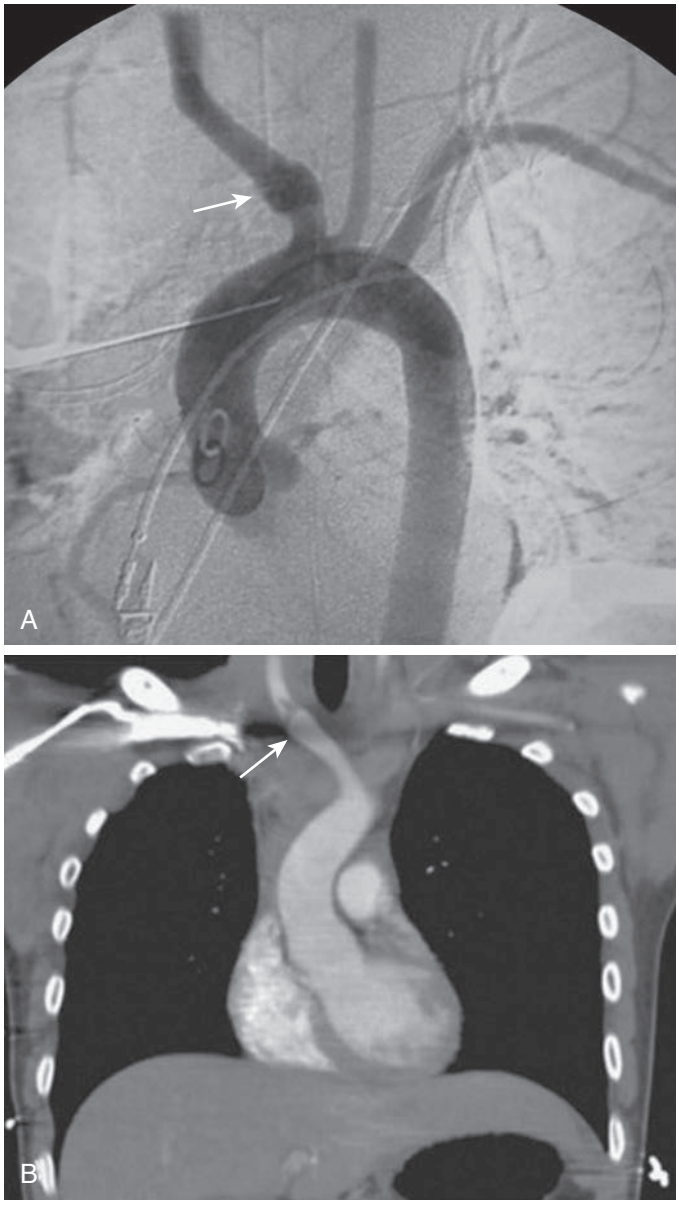

Figure 98.2 Blunt Traumatic Injury. (A) Aortogram demonstrating blunt traumatic injury *(arrow)* to the innominate artery. (B) CT scan demonstrating an intimal flap in the innominate artery after blunt traumatic injury *(arrow)*.

or antiplatelet therapy.[11-13] In follow-up, surgical repair should be limited to patients with new symptom onset; recurrent thromboembolic events, despite medical therapy; and enlarging or symptomatic pseudoaneurysms.

Dissection

Dissection of the brachiocephalic arteries occurs spontaneously or as an extension from the aortic arch. In patients with aortic dissection and extension into the common carotid arteries, nearly 19% of cases initially present with stroke. Even with aortic repair, the dissection of the carotid arteries usually persists. However, subsequent thromboembolic events are rare.[14] Medical management includes antithrombotic agents for 3 to 6 months, and is the initial treatment of choice. A recent randomized trial confirmed the low rate of recurrent stroke with either anticoagulant or antiplatelet agents.[15] Only patients with active hemorrhage, enlarging pseudoaneurysm, or recurrent thromboembolic events, despite medical therapy, are offered surgical or endovascular repair.

Arterial Thoracic Outlet Syndrome

Distal (extrathoracic) subclavian artery aneurysms are commonly related to a cervical rib that causes arterial thoracic outlet syndrome (Fig. 98.3) (see Chapter 122). The pathogenesis of the aneurysm is thought to be related to repetitive trauma to the artery at the level of the thoracic outlet.[16] Bony abnormalities, such as a cervical rib, are usually present. The clinical consequences of aneurysmal degeneration are usually related to distal thromboembolization causing arm claudication, rest pain, and digital ischemia. Most subclavian artery aneurysms are repaired at the time of thoracic outlet decompression. In experienced centers, the procedure is safe and provides excellent functional outcomes.[17]

Aneurysm

True, isolated, brachiocephalic artery aneurysms are rare in the absence of adjoining aortic arch aneurysm. Patients younger

Figure 98.3 Innominate and Subclavian Artery Aneurysms. Intraoperative photo representing distal right subclavian artery aneurysm *(white arrow)* in a patient with arterial thoracic outlet syndrome exposed via an infraclavicular incision. The patient's head is at the top, left corner; the feet are to the bottom, right corner.

than 50 years should be screened for genetic disorders, such as Loeys-Dietz and Marfan syndromes. Because of the risk of nerve compression and thromboembolic events, most brachiocephalic artery aneurysms should be repaired, regardless of size or presence of symptoms. Pairolero reported thromboembolism in 16% of axillary and subclavian artery aneurysms.[18] However, open repair is associated with significant mortality and morbidity. Kieffer and colleagues reported an 11% perioperative mortality after open repair of innominate artery aneurysm, although this also included ruptured and infected cases.[19] Patients had a heterogeneous etiology and most also had aortic aneurysm. In patients with high surgical risk, small asymptomatic aneurysms less than 2 cm in diameter, without intraluminal thrombus, may be observed. Proximal occlusion with cervical revascularization may be an option in some cases. Unfortunately, it is rare that the anatomy is suitable for endovascular repair. However, it may be a reasonable option in selected cases.[20]

DIAGNOSTIC EVALUATION

In addition to a comprehensive physical examination, careful assessment of the upper extremity pulses, and bilateral upper extremity blood pressure measurements, Duplex ultrasound examination may be of some utility in identifying flow reversal in the vertebral arteries and excluding significant disease in the extracranial carotid arteries. Axial imaging modalities, such as magnetic resonance imaging and computed tomography (CT) scans, provide excellent imaging of the aorta and great vessels. These imaging techniques have mostly replaced conventional aortography as a diagnostic tool. Body habitus, claustrophobia, and metallic implants may limit the use of these imaging techniques.

Transesophageal echocardiography (TEE) is another important diagnostic tool because of its ability to accurately identify atherosclerotic disease in the proximal ascending and descending portions of the thoracic aorta. Disadvantages of TEE are that accurate evaluation requires an experienced sonographer and that the patient needs conscious sedation during the procedure. If transthoracic revascularization is planned, the proximal ascending aorta should be devoid of any atheromatous plaque or dissection. If accurate preoperative or intraoperative TEE is not available, a handheld (epiaortic) ultrasound probe can be used intraoperatively, once the aorta is exposed, to assess for atheromatous plaque in the ascending aorta at the potential clamp site.

REVASCULARIZATION

Transthoracic revascularization is preferred for patients with multivessel disease and reasonable surgical risk. Proximal aneurysms and traumatic injuries are also best treated with a bypass from the ascending aorta to the involved brachiocephalic arteries (Fig. 98.4), especially when not anatomically suitable for endovascular repair. Infections involving the innominate and proximal common carotid arteries can be resected and revascularized via a median sternotomy. Adjunctive techniques, such as pedicled omental flaps, can easily be added with this approach.

Extraanatomic cervical revascularization is ideal for single-vessel subclavian disease or in high-risk patients. This approach is often combined with endovascular treatment of thoracic aortic aneurysms (see Chapter 78). Left subclavian-carotid transposition or carotid-subclavian bypass may be required for a suitable proximal landing zone for thoracic aortic endografts. A right-to-left carotid bypass can further extend the proximal landing zone to the level of the innominate artery. The recent introduction of branched aortic endografts will reduce the need for cervical brachiocephalic artery bypasses (see Chapter 80).

Transthoracic Revascularization

The ascending aorta and transverse aortic arch are approached through a median sternotomy. The procedure is initiated with a skin incision from just below the sternal notch. The incision can extend to the xiphoid process for complete sternotomy, if needed. A mini-sternotomy also allows for exposure of the ascending aorta and proximal brachiocephalic arteries. The mini-sternotomy incision extends from the sternal notch to the fourth intercostal space. Electrocautery is used to divide the soft tissues down to the sternum. The lateral sternum is exposed between the third and fourth ribs. A sternal saw is used to create the osteotomy and a sternal retractor is used to gently free the mediastinal structures from the undersurface of

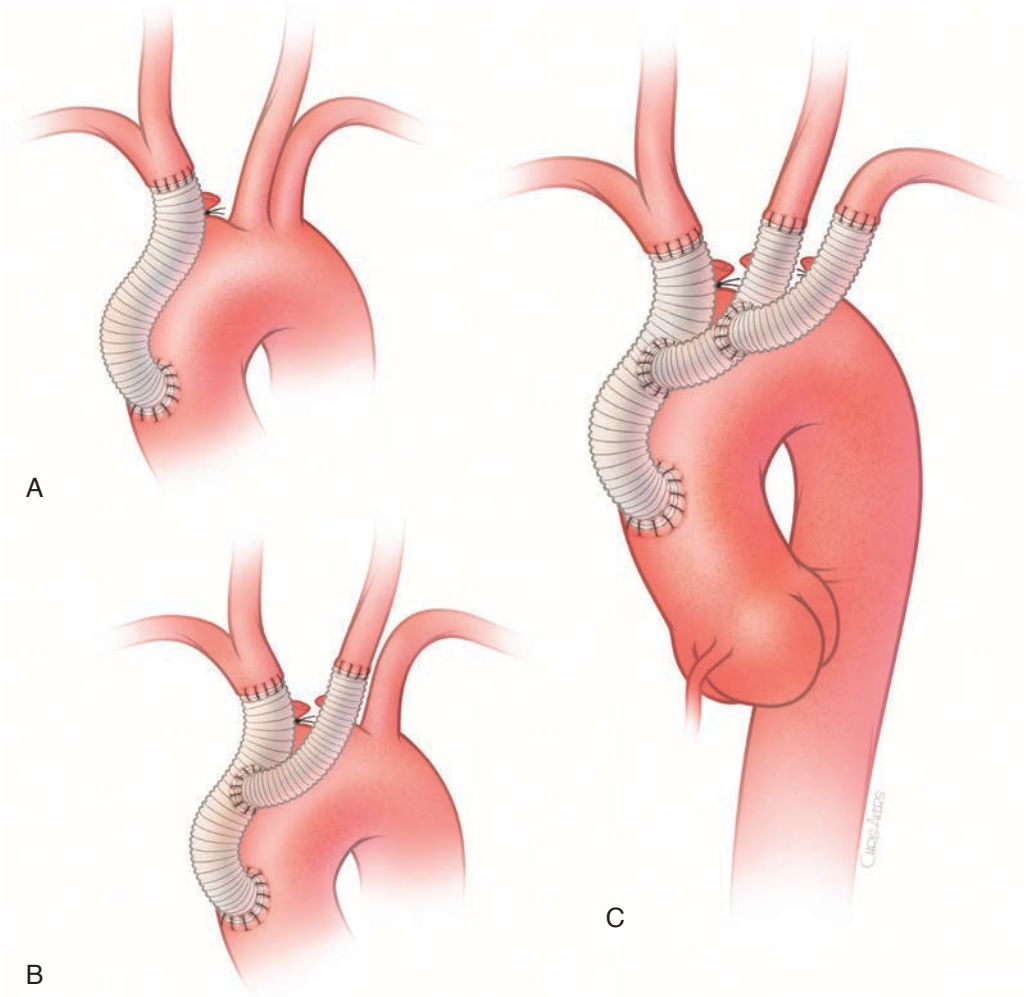

Figure 98.4 Technical Approach for Transthoracic Revascularization. (A) Creation of an aorto-innominate bypass. (B) Sidearm bypass graft to the left carotid artery. (C) Sidearm bypass graft to the left subclavian artery.

the bone. Incision of the superior portion of the pericardium exposes the heart and ascending aorta. Anatomic revascularization of the brachiocephalic arteries can be accomplished by endarterectomy or bypass.

Endarterectomy

Endarterectomy is an effective strategy for focal lesions involving the midsection of the proximal innominate or common carotid artery. When the atherosclerotic lesion is located at the orifice of the brachiocephalic trunk, the transverse arch is usually involved in this process. In this setting, endarterectomy can be fraught with the dangers of embolization, incomplete endarterectomy, and aortic dissection. Also, endarterectomy is not suitable for patients with disease involving a bovine arch variant because clamping of the innominate artery would cause ischemia to both cerebral hemispheres.

Bypass Grafts

Bypasses generally originate from the ascending aorta to the brachiocephalic arteries if the ascending aorta is free of atherosclerotic disease (see Fig. 98.4). The presence of atheroma can be confirmed by intraoperative TEE or epiaortic ultrasound. The patient is anticoagulated and a partial-occlusion clamp is applied. A 12- to 14-mm woven Dacron tube graft impregnated with collagen or gelatin is sewn to the ascending aorta in end-to-side fashion with 4-0 polypropylene suture. The partial-occlusion clamp is released with the patient in the Trendelenburg position, and a clamp is placed distally on the graft. The innominate artery is then transected distal to the diseased portion and the proximal stump is oversewn with 4-0 polypropylene suture. The distal anastomosis is completed in an end-to-end fashion with 4-0 or 5-0 polypropylene suture.

When the left common carotid or subclavian artery is involved, we avoid the use of a premade bifurcated graft, such as an aortoiliac or aortofemoral graft, because the volume of this graft near the proximal anastomosis creates difficulty in closing the sternotomy. We use a separate sidearm graft sewn to the innominate bypass graft in an end-to-side fashion with 4-0 polypropylene suture. This graft is then sewn end-to-end to the left common carotid artery with 5-0 polypropylene suture. If the left subclavian artery also has a proximal lesion, a separate bypass is constructed in a similar fashion. Exposure of the proximal left subclavian artery is facilitated by downward retraction on the ascending aorta and the transverse arch. After

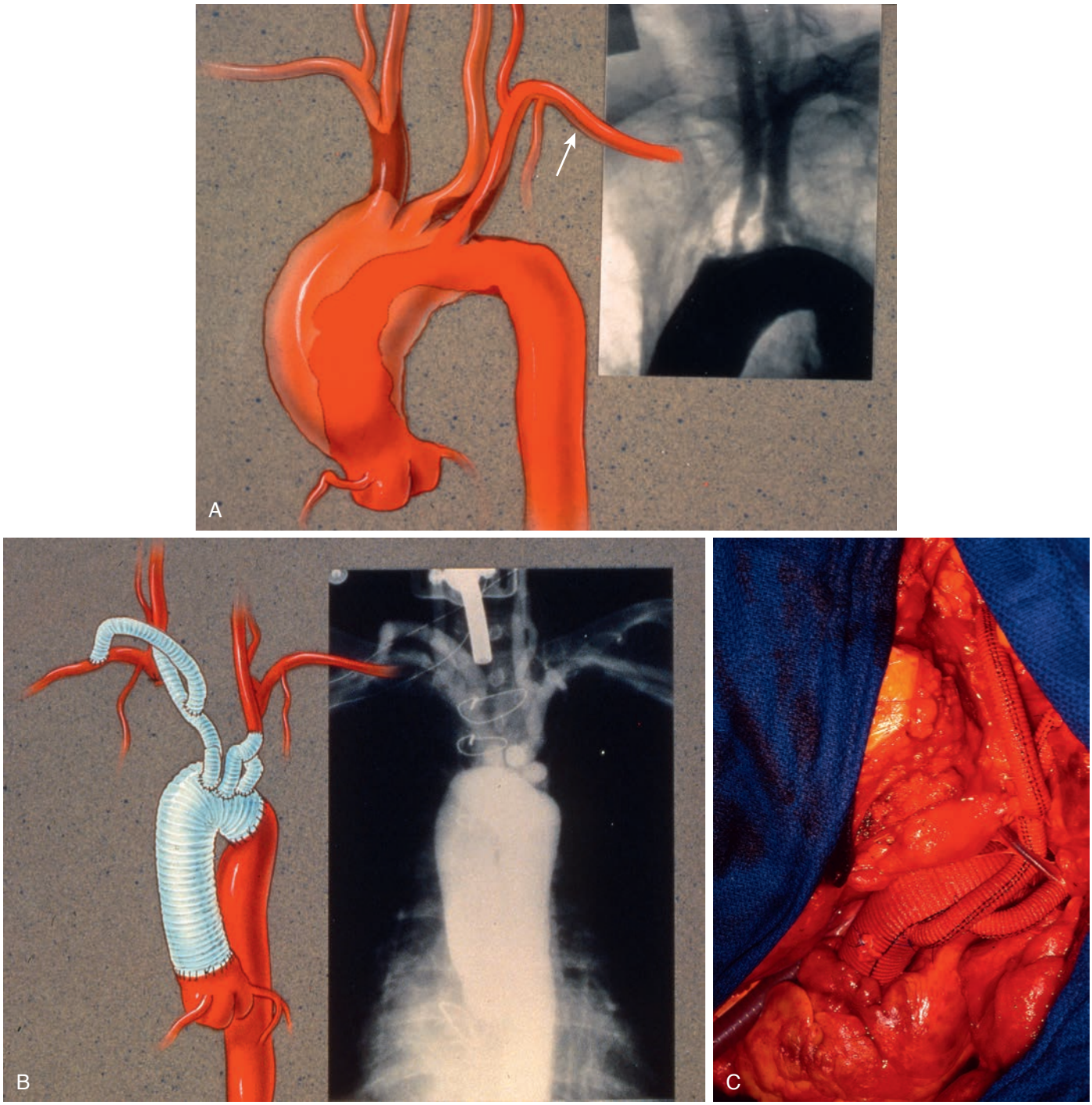

Figure 98.5 Total Aortic Arch Replacement. Replacement of ascending aorta and transverse aortic arch, with reconstruction of brachiocephalic arteries using a prefabricated branched graft. (A) Illustration and preoperative aortogram of patient with multivessel ascending aorta, arch, and brachiocephalic atherosclerosis, including left subclavian artery involvement *(white arrow)*. (B) Illustration and postoperative aortogram after replacement of the ascending aorta and aortic arch with individual bypasses to the brachiocephalic arteries. (C) Intraoperative photo representing the completed replacement of the ascending aorta and aortic arch with individual bypasses to the brachiocephalic arteries.

revascularization, anticoagulation is reversed and we insert 2 (32 or 36 Fr) chest tubes in the mediastinum for drainage.

Total Aortic Arch Replacement

Patients with severe atheromatous plaque involving the ascending and transverse aortic arch have a significant risk of stroke from atheroembolic debris with manipulation. We replace the ascending aorta with the transverse arch and reconstruct the brachiocephalic arteries with a prefabricated branched graft (Fig. 98.5). Our center has low mortality and neurologic morbidity in total arch replacement with use of retrograde cerebral perfusion, cardiopulmonary bypass, profound hypothermia, and circulatory

TABLE 98.3 Selected Results of Cervical Bypasses

			RESULTS						
						SURVIVAL		PATENCY	
Series	Year	Number of Patients	Mortality	Stroke	MI	5-Year	10-Year	5-Year	10-Year
Crawford et al.[25]	1983	99	1	2	NA	NA	NA	NA	NA
Salam et al.[48]	1994	41	0	0	0	NA	NA	73	NA
Berguer et al.[3]	1999	182	0.5	3.8	3	72	41	91	82
Byrne et al.[45]	2007	143	0.7	1.4	4.3	NA	NA	92	NA

MI, Myocardial infarction; *NA*, not available.

arrest.[21,22] Endovascular total aortic arch repair using brachiocephalic debranching and thoracic aortic endografting is an alternative approach.

Transthoracic Operative Results

DeBakey and colleagues performed the first aorto-innominate bypass in 1957.[23] Crawford and colleagues subsequently published results of direct brachiocephalic revascularization (combining endarterectomy and bypass) in 1962 and reported a 30-day mortality of 7.5%.[24] In 1983, the group updated their series and reported stroke and 30-day mortality rates of 6.9% and 4.7%, respectively.[25] Since that time, there have been several reports of excellent initial and long-term results after transthoracic revascularization of the brachiocephalic arteries (Table 98.3). Kieffer and colleagues reported 2.9% stroke, 1.5% myocardial infarction, and 5.2% mortality rates, with 5- and 10-year patency rates of 98.4% and 96%, respectively.[26] Rhodes and colleagues reported 7% stroke, 3% myocardial infarction, and 3% mortality rates, with a 5-year patency rate of 80%.[27] Berguer and colleagues reported 8% stroke, 3% myocardial infarction, and 8% mortality rates, with 5- and 10-year patency rates of 94% and 88%, respectively.[2] Nevertheless, despite outstanding long-term patency rates, the mortality and stroke rate is probably too high for treatment consideration in most asymptomatic patients.

Postoperative Management

In the immediate postoperative period, patients are observed in a monitored unit for the first 24 hours. Mediastinal drains are removed once the drainage is less than 200 mL/day. Patients are discharged with poststernotomy precautions, including not lifting more than 5 to 10 lb, avoiding upper extremity or chest weight-bearing exercises, and limiting arm abduction to less than 90 degrees for 6 weeks postoperatively. After the initial postoperative visit, we monitor patients with duplex ultrasound of the extracranial carotid system and the graft itself every 6 months for the first year and annually thereafter.

Extraanatomic Revascularization

Extraanatomic reconstructions are suitable for patients with single-vessel disease or patients in whom median sternotomy presents prohibitive risk. A bypass can be constructed between the carotid and subclavian, bilateral carotid, bilateral subclavian, or bilateral axillary arteries. The most common lesion is isolated proximal subclavian artery stenosis, and there are several options for revascularization.

Subclavian-Carotid Transposition

Subclavian-carotid transposition carries the advantage of avoiding prosthetic material and is performed with a single anastomosis. However, it requires more extensive dissection of the proximal subclavian artery and isolation of the vertebral and internal mammary artery origins (Fig. 98.6). The procedure is initiated via a transverse supraclavicular incision between the two heads of the sternocleidomastoid muscle. Platysmal flaps are created, with care taken to avoid injury to the external jugular vein. The omohyoid is divided and the common carotid artery is circumferentially dissected and mobilized. If a left-sided exposure is being performed, the thoracic duct is identified and ligated; accessory lymphatic channels on either side are also meticulously identified and ligated to avoid lymph leak. The internal jugular vein and vagus nerve are retracted laterally, and exposure of the subclavian artery and its proximal branches proceeds after division of the vertebral vein.

Once the vertebral internal mammary arteries and thyrocervical trunk are controlled, the patient is anticoagulated and the proximal subclavian artery is transected proximal to the origin of the vertebral artery. Absolute control must be maintained until the proximal stump can be oversewn because a transected stump lost in the thoracic cavity can be disastrous. For this reason, we place two pledgeted, 4-0 polypropylene sutures under the proximal subclavian clamp before transecting the artery. The sutures are tied, left long, and attached to a hemostat. If the clamp is accidentally released after transection, the sutures can be elevated, preventing the artery from retracting into the chest. Once the subclavian stump is ligated with running suture, the artery is released and allowed to fall back into the chest.

The common carotid artery is then clamped, and a longitudinal lateral arteriotomy is made. The free, transected subclavian artery is brought next to the common carotid artery. With proper mobilization, there is usually ample subclavian length for a tension-free anastomosis. An end-to-side anastomosis is created with 5-0 or 6-0 polypropylene suture. Because of the tight spaces and acute angles involved, a parachute technique can be used to facilitate the anastomosis. Shunting is cumbersome

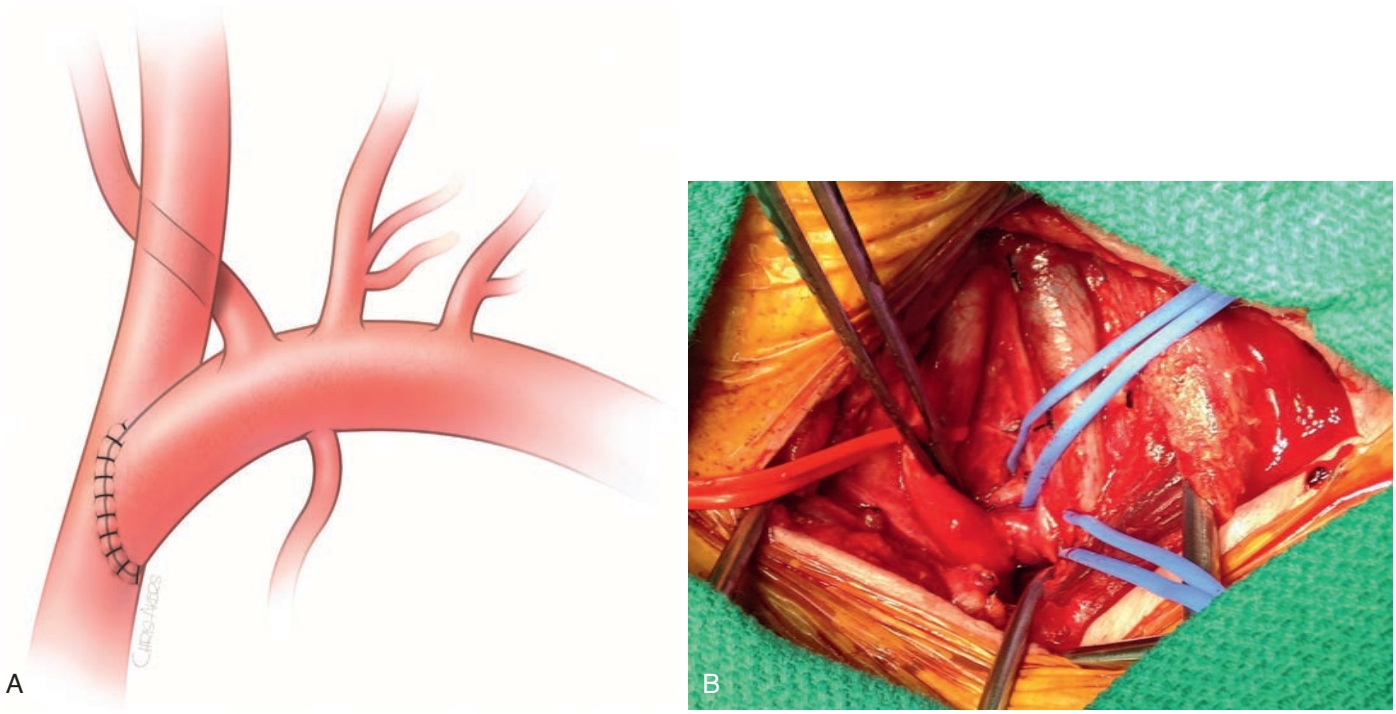

Figure 98.6 Subclavian-Carotid Transposition. (A) Illustration depicting left subclavian-carotid artery transposition using an end-to-side anastomosis. (B) Intraoperative photo depicting left subclavian-carotid artery transposition using an end-to-side anastomosis. The patient's head is at the top, right corner; the feet are to the left. The red vessel loop encircles the left common carotid artery.

and usually not necessary because collateral flow to the internal carotid is maintained from the external carotid artery. The incision is closed after reapproximation of the platysma.

Transposition is contraindicated in patients with an early origin of the vertebral artery and in patients with patent internal mammary-coronary artery bypass grafts. Care should be taken to preserve the vertebral artery whenever possible during transposition. In patients unable to tolerate temporary vertebral artery clamping, such as with contralateral vertebral artery occlusion, bypass may be preferred over transposition. This also applies in cases of aberrant termination of the vertebral artery into the posteroinferior cerebellar artery.

Most reports cite very low mortality and good midterm patency rates. Duran and colleagues reported results after 126 cases with no perioperative deaths and a 2.4% stroke rate.[28] Early thrombosis occurred in 4% with cumulative patency of 96% at mean follow-up of 54 months. Earlier results in 178 cases by Edwards and colleagues showed an early mortality rate of 2.2%, stroke in 1%, and patency of 99% over a mean follow-up of 46 months.[29] Several authors report improved patency, lower early thrombosis, and better hemodynamics with subclavian-carotid transposition compared to bypass. The difference in patency rates within single-center series are generally minor and not statistically significant.[30,31] However, a systematic review by Cina and colleagues analyzed 1027 cervical subclavian revascularizations (511 transpositions and 516 bypasses) and found that transpositions had lower early thrombosis ($P = .01$) and better midterm cumulative patency ($P < .0001$).[32] Cumulative patency was 99% over a mean follow-up of 61 ± 15 months.

Carotid-Subclavian Bypass

Carotid-subclavian bypass is a straightforward procedure with good results. It does not require extensive dissection of the proximal subclavian artery. However, a conduit (usually prosthetic) must be used (Fig. 98.7). A transverse supraclavicular incision extending lateral to the clavicular head of the sternocleidomastoid muscle provides exposure for both the carotid and subclavian arteries. The platysma is divided and the sternocleidomastoid is retracted medially. The jugular vein is dissected free and retracted to expose the common carotid artery, which is encircled and mobilized sufficiently to obtain proximal and distal control. The scalene fat pad is ligated medially and retracted laterally. Care must be taken to identify and protect the phrenic nerve.

The anterior scalene muscle is divided at its attachment on the first rib. Meticulous attention should be given to careful ligation of the thoracic duct and all its tributaries and to avoid trauma to the surrounding brachial plexus. The thyrocervical trunk can be divided for further mobilization of the subclavian artery. Sufficient length is obtained for control of the artery and space for an arteriotomy.

Prosthetic conduit appears to have superior patency over autologous conduit[32,33] and we typically use an 8-mm polytetrafluoroethylene (PTFE) or Dacron graft. The subclavian anastomosis is created first in an end-to-side fashion with 5-0 or 6-0 polypropylene suture. The graft is passed under the jugular vein, flushed, and cut to the appropriate length. Carotid clamps are then applied, and a clamp is

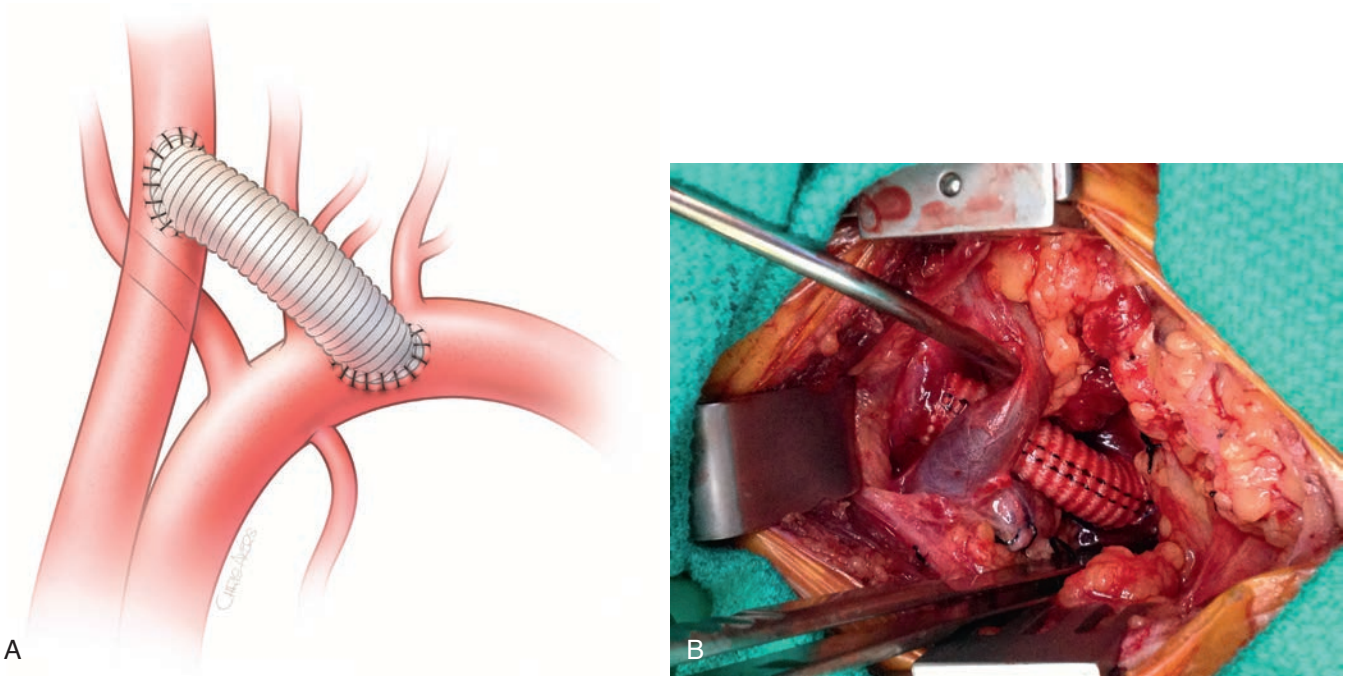

Figure 98.7 Carotid-Subclavian Bypass. (A) Illustration depicting a left carotid-subclavian artery bypass using an 8-mm woven Dacron graft configured with end-to-side anastomoses to both the common carotid and subclavian arteries. (B) Intraoperative photo depicting a left carotid-subclavian artery bypass using an 8-mm woven Dacron graft. The patient's head is at the top; the feet are to the bottom. The bypass graft courses under the jugular vein.

placed on the graft near the subclavian anastomosis. The carotid anastomosis is completed in an end-to-side fashion with 5-0 or 6-0 polypropylene suture. If the procedure is being performed for proximal common carotid artery disease involving ulcerated plaque, we transect the carotid artery distal to the plaque and perform an end-to-end anastomosis with the graft.

Most of the recent, larger series report perioperative mortality and stroke at less than 2%.[34-36] Takach and colleagues recently reported their results after 287 bypasses with 1% perioperative mortality, 2.1% stroke, but with 94% 5-year patency.[37] In a systematic review, vein grafts had lower patency compared to prosthetic grafts (P = .0006).[32] Cumulative patency using prosthetic bypass grafts was 86% over a mean follow-up of 58 ± 18 months.

Carotid-Carotid Bypass

Occasionally, no ipsilateral source artery is suitable for bypass. In these situations, the contralateral carotid artery can provide inflow for carotid or subclavian revascularization (Fig. 98.8). Bilateral exposure of the carotid artery is achieved through a longitudinal incision overlying the anterior border of the sternocleidomastoid muscle on each side. The carotid sheath is opened and the common carotid artery is dissected free bilaterally. The pharynx is identified medially, and blunt dissection is used to create a tunnel posterior to the pharynx and anterior to the prevertebral fascia. This retropharyngeal tunnel, as described by Berguer et al.,[38] eliminates the risk of skin erosion, enables transposition of the carotid artery, and places any graft safely away from possible future tracheostomy.

Once the tunnel is created, the inflow common carotid artery is clamped proximally and distally. A medial longitudinal arteriotomy is created, and a prosthetic graft is sewn end-to-side with 5-0 or 6-0 polypropylene suture. The graft is passed through the tunnel, the carotid clamps are released, and the graft is clamped. The target carotid artery is then clamped, and an end-to-side anastomosis with 5-0 or 6-0 polypropylene suture is performed. If the proximal plaque on the target carotid artery is at risk of distal thromboembolization, we transect the artery distal to the plaque. The proximal stump is oversewn, and an end-to-end anastomosis is performed with 5-0 or 6-0 polypropylene suture.

In one report, there was no perioperative mortality, 4.1% stroke, and a 3-year cumulative patency rate of 92% in 24 carotid-carotid bypass patients.[39] However, the reported stroke rates of 4% to 6%[38,39] are higher compared to subclavian or axillary-based bypasses. When performing total arch debranching, a carotid-carotid bypass is often combined with a carotid-subclavian bypass prior to zone 0 aortic endografting.[36,40]

Axilloaxillary and Subclavian-Subclavian Bypass

Another option to revascularize the subclavian artery is via axilloaxillary bypass (Fig. 98.9). The axillary artery is exposed bilaterally by transverse infraclavicular incisions along the lateral third of the clavicle. The pectoralis major is retracted between the muscle fibers, and the axillary artery is identified just inferior to the clavicle, posterior to the deep pectoral fascia. A

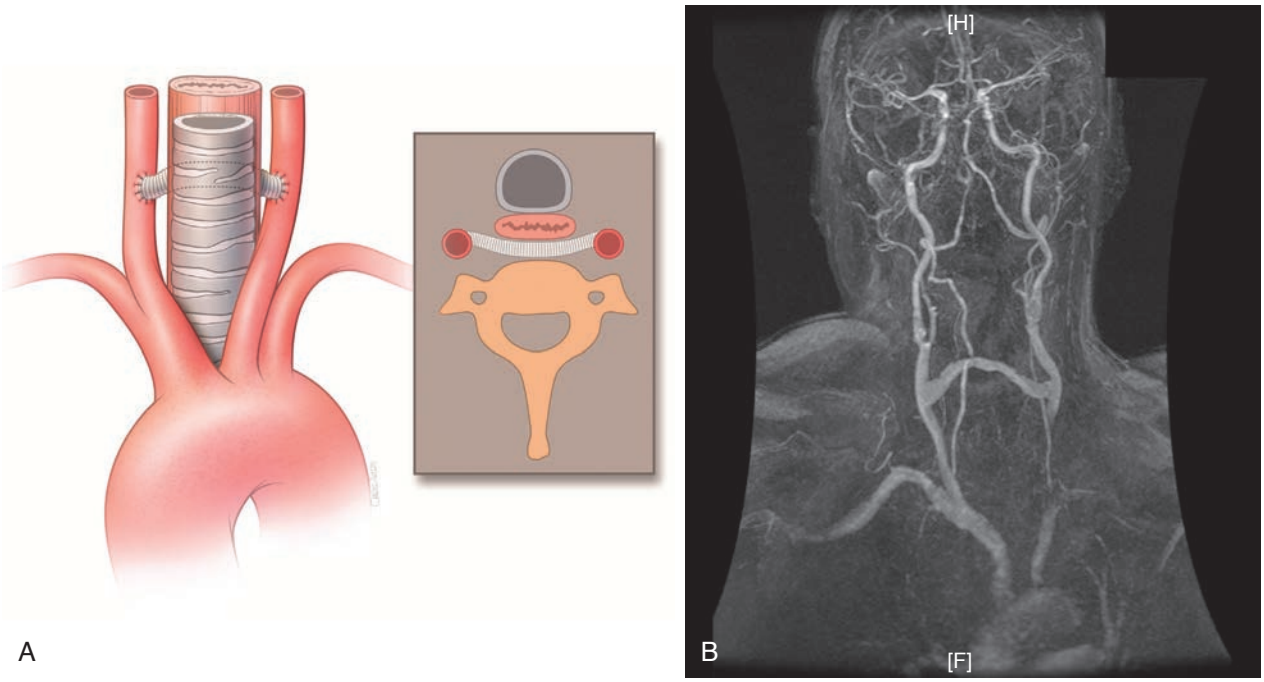

Figure 98.8 Carotid-Carotid Bypass. (A) Illustration depicting a right-to-left carotid-carotid artery bypass using an 8-mm ringed prosthetic graft configured with end-to-side anastomoses to both common carotid arteries. (B) Completion angiogram after carotid-carotid bypass.

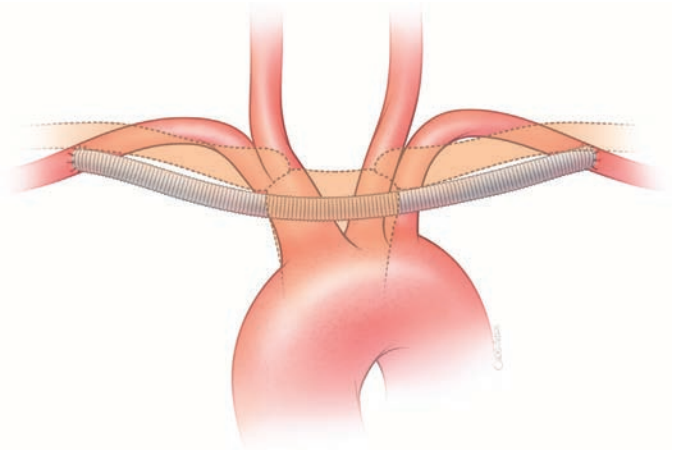

Figure 98.9 Axilloaxillary Bypass. Illustration depicting axilloaxillary artery bypass using an 8-mm ringed prosthetic graft configured with end-to-side anastomoses to both axillary arteries.

subcutaneous tunnel is created between the two arteries, and an end-to-side anastomosis with prosthetic graft is performed bilaterally. The axilloaxillary bypass can be used to maintain cerebral flow during total aortic arch debranching prior to zone 0 aortic endograft deployment.[41]

Although good results have been reported,[42,43] the potential risks of graft infection, skin erosion, and need for possible future sternotomy have limited widespread use of this technique. Aziz and colleagues summarized 16 studies with 426 patients.[36] The perioperative mortality was 0.5% with stroke in 1.1%. A cervical subclavian-subclavian bypass avoids tunneling across the chest.[44]

Carotid-Contralateral Subclavian Bypass

If the target vessel is the contralateral subclavian artery, exposure of the subclavian artery is performed as described earlier for subclavian transposition, and the graft is sewn end to end with 5-0 or 6-0 polypropylene suture. If transposition is contraindicated, the graft can be sutured end-to-side at a more distal location on the subclavian artery.

Operative Results

In general, perioperative mortality and stroke rates are lower with cervical revascularization compared to transthoracic reconstructions. Long-term patency rates are also slightly lower. Berguer and colleagues reviewed 182 cervical reconstructions in 1999.[3] Stroke, myocardial infarction, and mortality rates were 3.8%, 3%, and 0.5%, respectively. Five- and 10-year survival rates were 72% and 41%, with 5- and 10-year patency rates of 91% and 82%. In 2007, Byrne and colleagues reported a 5-year cumulative patency rate of 92% in 143 patients with cervical brachiocephalic artery revascularization.[45] They had stroke, myocardial infarction, and mortality rates of 1.4%, 4.3%, and 0.7%, respectively. Analysis of registry data comparing transthoracic and cervical revascularizations showed similarly low perioperative composite stroke, myocardial infarction, and death rates but a slightly higher complication rate in median sternotomy patients.[46]

Postoperative Management

The physiologic stress after extraanatomic revascularization is less than that after transthoracic revascularization. The primary postoperative concern is the presence of neurologic deficits in

patients in whom the carotid artery was clamped. All patients are observed in the operating room for gross motor function before transfer to the recovery room. Patients are usually discharged after 1 or 2 days. After the initial postoperative visit, graft patency is monitored by duplex ultrasound examination every 6 months for the first year and annually thereafter.

ACKNOWLEDGMENTS

We thank Troy Brown for editing and Chris Akers for illustrations.

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CHAPTER 99

Brachiocephalic Artery Disease and Its Endovascular Management

DANIEL G. CLAIR

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Although early treatment for this disease process involved open surgical reconstruction,[1,2] more recently endovascular therapy has assumed a more important role in the treatment of patients with brachiocephalic artery disease.[3-6] New developments in the technology available for interventional therapies and strategies for dealing with these complex lesions from an endovascular approach have improved risks and recovery times related to these procedures. For the experienced interventionalist, the risks remain low and the morbidity acceptable; however, the consequences of inadequate preparation and poor technique can be devastating.

PROCEDURE PLANNING

A great deal of the information on patients with occlusive disease of the arch vessels comes from reports of open surgical series.[7-10] A detailed understanding of the anatomy of the aortic arch along with knowledge regarding the positions of the vessel origins is a necessity for planning these procedures. The most common cause of arch vessel stenosis is atherosclerosis, but even this occurs relatively infrequently. In evaluations for carotid bifurcation occlusive disease, only 5% to 15% of patients are found to have concomitant disease in the arch vessels.[11-14] The prevalence in patients without cerebrovascular disease is lower, but it is not insignificant even in the general population, where it is found in approximately 1.5% to 2.0%. In patients with coronary artery disease, prevalence can be as high as 4% to 7%[15-18] and greater (up to 11%) in those with more significant coronary disease. The left subclavian artery is involved most often, followed by the innominate and left common carotid arteries, which are both affected approximately 30% of the time.[12,19] Less common causes of arch vessel disease include

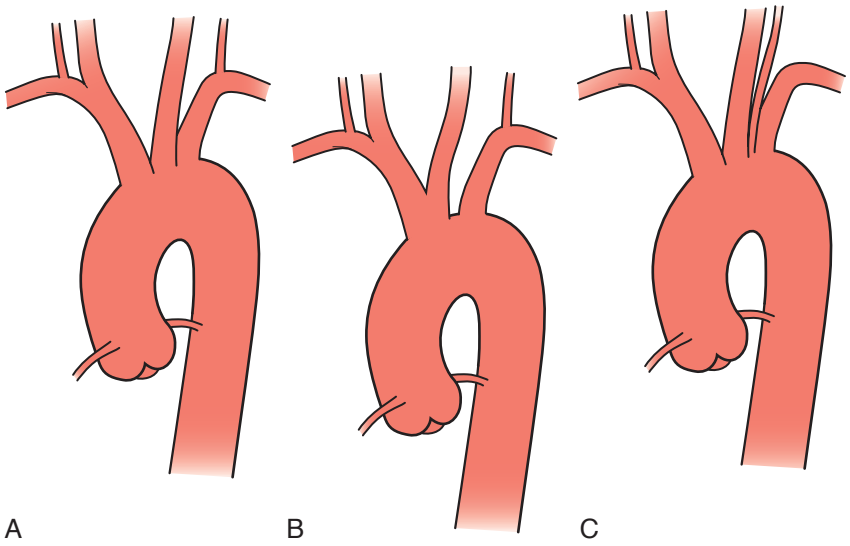

Figure 99.1 A more proximal origin of aortic arch branches, as shown here for a type III arch, makes catheter access to the arch vessels difficult. A, Normal aortic arch anatomy; B, "Bovine arch" anatomy with common origin of innominate and left common carotid artery; C, Aortic arch with vertebral artery origin between left common and left subclavian artery.

Takayasu arteritis, radiation-induced injury, aneurysm, and dissection.

IMAGING STUDIES

Duplex Ultrasound

Ultrasound imaging of the vessels of the aortic arch is often the initial imaging modality. The velocity information obtained can provide insight into the degree of stenosis, and often the visualization (or lack thereof) of calcification can provide information regarding the nature of the occlusive process.[20-22] However, the anatomic discrimination necessary to guide intervention can be obtained only with more detailed imaging.

Computed Tomography and Magnetic Resonance Angiography

The most commonly used methods for assessing the anatomy of the aortic arch are computed tomographic angiography (CTA) and magnetic resonance angiography (MRA), along with standard angiography. The axial imaging modalities have the obvious advantage of avoiding catheter manipulation within the aortic arch and its potential complications; they can detect both aneurysmal disease and mural atherosclerotic debris. These studies can also assess the extent of calcification at the origins of the vessels. When the imaging region includes the brain, they can define the intracranial circulation as well. In most instances the source images can be reformatted into three-dimensional models of the aortic arch and its branches to allow excellent visualization of the relevant anatomy. The information obtained from these studies can often allow complete procedural planning before conventional angiography is performed.

The normal anatomic makeup of the aortic arch involves three arch vessels: the innominate or brachiocephalic artery, which normally gives rise to the right subclavian and right common carotid arteries; the left common carotid artery; and the left subclavian artery. However, in up to 20% of individuals, the left common carotid artery originates from the innominate artery in a "bovine" configuration, thus leaving only two main trunks off the aortic arch (Fig. 99.1).[23] In as many as 6% of individuals, the left vertebral artery originates from the aortic arch directly, between the left common carotid and left subclavian arteries. Finally, aberrant origin of the subclavian arteries, with or without an associated Kommerell diverticulum (see Chapter 98) and/or a right-sided aortic arch, are best displayed on preprocedural axial imaging studies.

Arteriography

For most patients, procedural planning and determination of the degree of stenosis can be achieved with axial imaging alone; angiography is typically performed as part of the therapeutic intervention to treat identified disease. In performing catheter-directed imaging, care must be utilized, as disease of the arch vessels is often associated with disease of the aortic arch itself. Manipulations in this area provide the opportunity to dislodge plaque or debris, which can lead to emboli in the cerebrovascular or other circulatory beds. Flush aortography is normally performed with a pigtail or halo flush catheter to prevent high-pressure injections via a straight-end catheter, which can cause arch dissection. Imaging of the arch is best performed in a left anterior oblique projection to "open up" the arch on the imaging screen, while the flush catheter is best positioned proximal to the origin of the innominate artery. Frequently it is helpful to rotate the imaging acquisition arm with a wire in the catheter placed across the arch to allow optimization of the imaging plane for maximum visualization. Images obtained from aortography are used to help identify vessel origins, degree of vessel stenosis, and the type of catheter or guide that may be necessary to cannulate and image the individual arch vessels.

Angiographic imaging of the bifurcation of the innominate artery is best performed in a right anterior oblique projection of approximately 20 degrees with a selective catheter positioned in the proximal innominate artery. This orientation will often maximally separate the origins of the branches of the innominate

artery, allowing individual assessment of the right common carotid and subclavian artery origins and ideal visualization for treatment of either vessel.

Transesophageal Echocardiography

Transesophageal echocardiography can be used to image the aortic arch, but it has not often been used in planning arch interventions.[24] This imaging modality can provide real-time information regarding the presence and extent of dissection in this region and the mobility of atheromatous plaque near the arch vessel origins. Although it is not commonly used for interventional planning, transesophageal echocardiography can provide important information, especially in the setting of complex arch disease.

Anatomic Considerations

For interventions in this location, it is particularly important to understand the high-risk anatomic features, as missteps in performing these procedures can lead to terrible consequences for the patient. High- and low-risk lesion features are noted in Table 99.1. Axial imaging with either CT or MR can now provide a functional three-dimensional model of the relevant anatomy, which can allow the calculation of ideal imaging angles for viewing the aortic arch and the branch vessel origins as well as the ability to select the preferred catheter for vessel access preoperatively.

Normal arch anatomy with vessel origins at the peak of the arch offers the ideal situation for vessel access. In this scenario the left subclavian artery is often cannulated with ease and antegrade recanalization can be performed even in the setting of complete occlusion; forward pressure on the occlusion can be achieved with nearly a direct path of the catheter and sheath combination. In the most common variant of arch anatomy, with the left common carotid artery originating from the innominate artery, access to this same vessel can be challenging; in situations where the origins of these vessels have rotated around the arch such that they are located in the ascending aorta, it may be so challenging to access the vessels that either open surgical reconstruction or hybrid endovascular and/or open repair may be easier and safer and thus preferable to a completely endovascular approach.

TABLE 99.1 Favorable and Unfavorable Characteristics of Arch Vessel Disease

Favorable	Unfavorable
Stenosis	Occlusion
Concentric lesions	Eccentric lesions
Vessel origin at top of arch or distal	Vessel origin in ascending aorta
Absence of calcium	Heavy calcification
Nonulcerated plaque	Ulceration
Asymptomatic	Symptomatic
Nonostial lesions	Ostial lesion
	Plaque abutting vertebral artery origin

Disease Distribution

Knowledge of disease extent in the arch vessels is important before beginning the intervention. Occlusions of these vessels can be crossed and intervention successful; however, there is wide variability in the technical success rates in reported series of treatment of arch vessel occlusions, with reported failure rates ranging from 0% to 40%.[25-28] Knowledge of the anatomic relationships of the disease to other vessel origins is critical. For example, when intervening in the left subclavian artery, it is imperative to know the location of the origin of the left vertebral artery and its proximity to disease to avoid injury to the vessel, whether originating directly off the arch, near the subclavian origin, or at the normal anatomic position off the proximal subclavian artery. Additionally, it is essential to recognize that intervention in the origin of any arch vessel can have an impact on the orifice of closely located neighboring vessels. In all arch interventions, knowledge of the status and location of neighboring vessels allows planning to prepare for and mitigate risk of occluding or injuring closely located arch branches.

OPTIONS FOR ENDOVASCULAR THERAPY

Angioplasty

Initial descriptions of endovascular intervention in the supra-aortic trunks involved balloon angioplasty alone.[3-6,29-33] Initial success rates reported in these series varied from 80% to 95%, and recurrence rates were acceptable at 8% to 25% at 1 to 2 years. Initial failures were commonly related to an inability to pass the balloon itself across the lesion rather than an inability to gain wire access. Currently lower-profile balloons make this scenario an uncommon problem. A recent report has documented a technical failure rate of less than 10%,[34] with a meta-analysis showing technical success rates of 94% for stenosis and 64% for complete occlusions.[35] The use of angioplasty with selective stenting rather than primary stenting has been argued by some to be a reasonable alternative. A recent meta-analysis of series comparing angioplasty with selective stenting with primary stent placement revealed mean technical success rates for angioplasty and/or stent of 87% as compared with primary stenting, which was successful in 92% of reported cases.[36] Despite the improved initial success rate with primary stenting, midterm primary patency rates for angioplasty and/or selective stent and primary stent were similar at 89.9% and 88.7%, respectively, at 24 months. Similar patency rates were noted at later time periods as well (79.6% vs. 76.9%). From these data one can infer reasonable outcomes with angioplasty alone, with good initial success. Nevertheless, since the introduction of stents for treatment of this disease, the principal interventional therapy approach has become primary stent placement.

Medicated balloons have been utilized for the treatment of recurrent stenosis,[37] but the widespread use of this technology is difficult to justify without definitive outcome data.

Stents

Since the introduction of stents for treating arch vessel disease, this technology has been the mainstay of interventional therapy in this location.[26,38-43] These studies report technical success rates from 91% to 100%, with failures occurring only in patients with total occlusions. Follow-up in the larger of these series has demonstrated patency rates of 77% to 100% over an 18- to 24-month period. It remains unclear whether primary stenting of all arch vessel lesions is clearly beneficial, and some authors have suggested that a selective approach to stenting may be a better alternative.[44,45] The most common approach reported today involves the routine use of stents in treating these vessels. It appears that in treating occlusions or complex stenoses, primary stenting should be the preferred approach. There remains little information regarding the use of medicated stents for the treatment of supra-aortic trunk[46] occlusive disease.

Covered Stents

Covered stents for the treatment of arch vessel disease have been reported for conditions involving aneurysms and traumatic injury,[47-49] but no meaningful data are available on the use of these devices for the treatment of arch vessel occlusive disease. Reports document excellent acute success of these devices in the setting of trauma or aneurysm treatment and patency of the devices has been maintained; repeat interventions have occasionally been necessary for the treatment of either kinks or angulation within the prosthesis. It is conceivable that the use of covered stents for occlusive disease in this anatomic location may prove helpful in reducing the incidence of neointimal hyperplastic recurrent stenosis, but at present there is inadequate information to make a recommendation for their routine use in this setting.

PERIOPERATIVE MEDICAL MANAGEMENT

Antiplatelet Agent

There are few data regarding the use of antiplatelet therapies for specific intervention in the supra-aortic trunks. Recommendations are currently based on inference from the use of these agents in patients with peripheral and cerebrovascular disease and those requiring carotid bifurcation intervention (see Chapters 40 and 89). The benefit of the use of aspirin in patients with peripheral vascular disease is well documented, and it is recommended that all patients with peripheral or cerebrovascular disease be maintained on aspirin.[46] The routine use of aspirin is mandatory, and aspirin should be considered part of standard therapy for aortic arch interventions. The use of clopidogrel for the treatment of patients with atherosclerotic vascular disease has also been well documented; it provides a reduction in risk compared with aspirin use alone in this population.[50] The combination of this agent with aspirin for the treatment of symptomatic carotid disease is beneficial in reducing embolic episodes, as documented by transcranial Doppler examinations,[51] and the combination of aspirin and clopidogrel has shown benefit when used as the periprocedural antiplatelet regimen in carotid stenting.[52,53] The addition of glycoprotein IIb/IIIa inhibitors to the dual antiplatelet therapy has not been shown to reduce embolic events and may significantly increase intracranial hemorrhagic complications.[54-56] Based on this information, dual aspirin and clopidogrel therapy is recommended as the standard antiplatelet regimen for arch intervention.

Intraprocedural Heparin

Heparin is normally used as the intraoperative anticoagulant for intervention in the arch vessels, and there are no meaningful data assessing alternative anticoagulant strategies in this clinical setting.[57] The use of bivalirudin in carotid interventions has been reported,[58] and this approach may prove to be a safe alternative to the routine use of unfractionated heparin. Without additional data, however, the routine use of bivalirudin cannot be recommended. Currently heparin administration adequate to maintain activated clotting times of greater than 250 to 300 seconds is recommended, and reversal of the heparin with protamine after intervention is reasonable.

Technical Details

After angiography of the arch, selective catheterization must be performed to gain adequate imaging of the relevant arch vessels and allow intervention. In most instances, this is best achieved with a forward-facing catheter with minimal angulation. Options for this initial access include the vertebral (Cook, Inc., Bloomington, IN), Headhunter (Cook, Inc.), and angled Glide (Terumo, Tokyo, Japan) catheters. These less complex catheters allow simple access to the vessels, and if advancement of the catheter is necessary, it may be performed easily. When the angulation of the vessel origin mandates an increased angle on the catheter, alternatives include the C2 (Cook, Inc.), JR4 (Cordis, Mexico), and internal mammary (Boston Scientific, Mexico) catheters. The use of complex or reverse-curve catheters necessitates formation of the catheter within the aortic arch, which can increase the risk for embolic complications and may complicate access to these vessels. Nevertheless, use of these reverse-curve catheters may be essential because of the angulation of the vessel origin. Once selective access has been obtained, the vessel can be imaged and intervention can be performed.

One positive aspect of endovascular intervention in this vascular distribution is the potential for an alternative access site for treatment. Brachial access for intervention in the subclavian arteries and the innominate artery can provide an approach to treat an obstructive lesion that might otherwise prove impossible to revascularize from the femoral route. These

other access routes also provide alternative methods for imaging or the insertion of protective devices while attempting to intervene for the treatment of stenotic lesions.

Left Subclavian Artery Intervention

Many of the techniques described in this section are applicable to interventions in the other arch vessels and can be helpful to keep in one's armamentarium. Other arch vessels less frequently undergo intervention because they are less often affected by occlusive disease. However, because of the increased angulation noted at the origin of these vessels, these interventions can prove to be more challenging, especially when performed from a groin approach.

Of the three vessels, access to the left subclavian artery is usually the easiest to obtain. Often only a mildly angled catheter is required, and most interventions can be performed with a sheath rather than an angled guide catheter. Typically, after arch aortography with either a 4- or 5-Fr flush catheter, an exchange is made for a selective catheter. After accessing the origin of the vessel, a 0.035-in. Glidewire (Terumo Cardiovascular Systems, Ann Arbor, MI) is passed across the lesion into the distal vessel. If a stiff Glidewire is used, it can be left in place, and a long 6-Fr sheath can be advanced from the groin over this wire. If the Glidewire used has less support, wire exchange for either a Rosen (Infiniti Medical, Menlo Park, CA) or Storq (Cordis, Bridgewater, NJ) wire can be performed, and the sheath then advanced over this wire. The sheath is positioned at the origin of the vessel and just below the level of disease. The vessel origin and the area of disease are positioned within the center of the imaging field to minimize distortion from parallax. Predilation with a 4- to 6-mm angioplasty balloon allows accurate determination of size and will ensure free passage of the stent. Frequently this predilation is performed with a balloon that is longer than the lesion itself to allow fixation of the balloon at either end of the stenosis. The balloon diameter chosen for predilation should be slightly smaller than the vessel distally so that dissection of the distal vessel is not induced. In the case of proximal subclavian lesions, this will limit the potential for damage to the origin of the vertebral artery. This technique also allows imaging of the distal extent of the lesion to gauge the proximity of the vertebral and internal mammary artery origins, because preservation of these vessels is critical. The length and diameter of the stent selected should be sufficient to ensure that the lesion is covered fully and the vessel is expanded to its true size and not that of a poststenotic dilated segment. The stent should not extend beyond the origin of the vertebral artery. Ideally, for lesions located proximally in the vessel, the stent should additionally extend approximately 1 to 2 mm into the aortic lumen. If a balloon-expandable stent is undersized, it will allow further expansion by dilation with a larger diameter balloon. It is important to know the limits of expansion of the stent while still retaining the strut architecture, which provides adequate radial resistance to compression. After adequate dilation of the stent in the vessel, if the proximal extent of the stent has been positioned partially in the aorta, it is helpful to "flare" this end of the stent by dilating it with an oversized balloon. This will further open the origin of the vessel and reduce protrusion of the stent into the aortic lumen, which can be an impediment to future interventions in either the arch vessels or the coronary arteries.

In some situations, the interventionalist may choose to place the stent in "protected" fashion through the lesion. To do so, the sheath and dilator are passed through the lesion and the sheath remains within the lesion itself. Typically, for orificial disease, a balloon-expandable stent is positioned just at the origin of the vessel; if the stent has been placed in protected fashion, the sheath is withdrawn to expose the stent within the lesion. In using this approach, the interventionalist must ensure that the stent is positioned appropriately before complete withdrawal of the sheath. This positioning can be difficult to achieve; thus it is not often used as the principal approach.

Vertebral Artery Protection

When the lesion approaches the origin of the vertebral artery and does not directly involve the origin of the subclavian artery, it is important to "protect" the vertebral artery origin. This can be done in two ways. The first is to use a slightly larger sheath and insert a second wire into the origin of the vertebral artery. If there is concern that the origin of the vessel may need to be partially covered once the sheath is within the subclavian artery, the 0.035-in. wire can be exchanged for a 0.014-in. wire placed antegrade via the axillary artery. A second 0.014-in. wire can then be positioned in the vertebral artery. If a balloon-expandable stent is used in this region, it may be possible to place a 0.035-in. system over both wires and position the stent over both wires as well. This ensures that the origin of the vertebral artery will be protected. In this region, a self-expanding stent may be preferable because some vessel torsion and flexion will occur outside the thorax. The delivery system of a self-expanding stent will not allow proximate placement to the vertebral origin if the delivery system is inserted over both wires. Therefore the stent delivery system must be placed over the wire in the axillary artery. Placement of this system on the wire in the vertebral artery poses a significant risk of dissecting the origin of the vertebral artery.

It is imperative in this situation to be able to adequately visualize the vertebral origin as the stent is being deployed. For this reason, brachial access should be considered. Ultrasound guidance can be used to obtain micropuncture access to the brachial artery, which is cannulated in a retrograde direction with a 5-Fr sheath. A straight catheter can be positioned in the proximal vessel just beyond the vertebral origin, and retrograde imaging via this catheter will allow precise visualization of the origin and positioning of the stent. An additional degree of safety can be afforded if a longer sheath (30-45 cm) is inserted into the brachial artery and wire access into the vertebral artery is obtained via this access. This will allow continuous simultaneous angiographic imaging of the vertebral origin and protective wire access.

Embolic protection of the vertebral artery system during endovascular intervention has been described, but its routine use is not advocated. The baseline risk of embolic complications

with intervention in this region is very low; the risks of adverse events related to insertion of a protection device in this area remains undefined.[59] Complex lesions proximal to the origin of the vertebral artery pose an increased risk of posterior cerebral embolization; therefore, care should be taken in crossing and treating these lesions. In the setting of subclavian steal, it is clear that normalization of flow takes some time to occur, and there is inherent protection related to the preexisting reversed flow in the vertebral artery.[60]

Brachial Access

Retrograde brachial access can be important for traversing proximal occlusions in the left subclavian artery. With flush occlusion of the vessel origin, it can be impossible to position a catheter at the origin to allow traversal of the occlusion via aortic access. In certain difficult situations, through-and-through access may be necessary to ensure access across the lesion and adequate purchase within the vessel for delivery of the device. Access to the brachial artery is similarly obtained as noted earlier, and a long 5- or 6-Fr sheath is positioned in the vessel just distal to the extent of the occlusion. A Glidewire is used in conjunction with either a straight or mildly angled catheter to traverse the occlusion. It is important to ensure reentry into the aorta because it is relatively easy to enter a dissected plane within the aortic arch. Once it appears that the wire is traversing through the arch or the descending aorta, the catheter can be introduced, and the wire removed; blood should exit the catheter freely. In the absence of free flow of blood, the catheter can be assumed to be in a plane outside the vessel lumen; therefore a different path must be created for access into the aortic lumen. Once access into the aortic lumen has been obtained, treatment of the lesion can be completed from the brachial approach. In this situation, it is imperative that the stent be positioned 1 to 2 mm into the aorta, because this is almost certainly an ostial lesion. When positioning the stent, imaging can be difficult from the brachial sheath. In this situation, the groin access that has been obtained for arch aortography can be extremely helpful. The wire is positioned within the flush catheter around the aortic arch. This wire then creates a fluoroscopic marker for the aortic wall, so that the location of the subclavian artery origin can be identified. This technique can be used to assist in identifying the level of the origin of any of the arch vessels, but it is particularly helpful in performing a retrograde intervention.

Radial Access

Increasingly, the radial artery is being utilized for percutaneous coronary interventions. This approach has proven to decrease bleeding complications and diminish renal dysfunction.[61] Reports have demonstrated that the use of this access site as an alternative for the retrograde treatment of subclavian and innominate disease provides safe results, comparable wih those achieved via brachial access.[62,63] Particularly in situations where femoral and upper extremity access is being considered or utilized, transradial access can be considered as a reasonable alternative.

Innominate Artery Interventions

Interventions in the innominate artery expose the patient to a risk of embolization in both the carotid and vertebral distributions. Although the risk of embolization should be low, there are options to minimize the potential for embolization, including protection during intervention (see the section titled Carotid Protection, further on). However, in most circumstances innominate interventions completed from a retrograde femoral access do not use protection devices.

In treating innominate artery disease it is important to understand where the origins of the branches of this vessel are in relation to the disease process. Frequently, imaging of the vessel in the left anterior oblique projection will be needed to image the origin of the innominate artery from the aortic arch. Imaging of the vessel in the right anterior oblique projection will also be required to isolate the origins of the innominate branches. It may be necessary to add either caudad or cephalad angulation to the right anterior oblique projection to isolate the origins of these branches. However, it is imperative to ensure that the distal aspect of the stent placement be understood in relation to the bifurcation of the innominate artery

Access

The most challenging of the arch vessels to access from the groin, even in the normal arch configuration, the innominate artery may pose an additional challenge in the situation where the left common carotid artery originates from this vessel, as the left anterior cerebral circulation may be potentially exposed to embolic risk from vessel cannulation. One must also ensure that the origin of the left common carotid artery is not compromised by stent placement across the origin of the innominate artery. In some instances, it may be better to perform extra-anatomic revascularization of the left common carotid artery and then treat the innominate vessel as needed with an interventional approach. This option will avoid the possibility of "jailing" the left common carotid artery with stent placement.

Because the innominate artery often has the most difficult angulation off the aortic arch, it can be very challenging to engage its orifice adequately to allow interventional access. As with the left subclavian artery, access via the brachial artery on the right side can allow excellent interventional access and visualization of the distal aspect of the plaque. Access via a through-and-through technique can also be used by snaring the wire and bringing it through the alternative access site. In some instances it may be helpful to have a second access so that a protection device can be used to protect the right common carotid distribution. Normally, if access to the innominate origin from the groin has not been achieved easily within 15 to 20 minutes of initiating the attempt, brachial access should be used. Extensive attempts in patients with significant disease at the origin expose them to unnecessary risk when there is an easy alternative site for interventional access. In most situations, when the brachial approach is used, the distal brachial wire is left in the ascending aorta so that the angle of stent placement

is closer to the angle of blood flow within the proximal aorta and the innominate artery.

Carotid Protection

If there is concern about the need for protection in the carotid distribution and access from the groin has proved challenging, the wire from the arm can be snared and brought out through the femoral access. This will allow a catheter to be brought through the lesion from below and a guide to be positioned at the origin of the vessel. The through-and-through wire can be used to provide support, holding the guide in place, and a protection device can be placed from either the brachial or femoral approach to within the right carotid distribution; the lesion can then be treated from the groin. If the protection device has been placed from the groin, the intervention should be performed over the protection device's wire. This will allow capture and removal of the protection device through the stent rather than around it.

In most instances, however, there is a low risk of embolization, and the lesion can be treated using the simplest approach, without protection. As discussed earlier, when access from the arm is used, the femoral wire can be left around the arch to assist in identifying the origin of the arch vessel. Finally, many surgeons approach innominate lesions via a cervical common carotid cutdown, affording both simple access to the lesion and providing embolic protection by direct carotid clamping and flushing.

Innominate Branches

Disease in branches of the innominate artery usually occurs at the vessel origins; in many instances it will require a kissing-stent technique to avoid impingement of the origin of the other vessel (Fig. 99.2). This approach can be performed from single access in the groin but requires a larger sheath for the introduction of two-stent delivery systems. An alternative approach involves simultaneous access from the groin and arm to allow separate introduction of the devices. Wire access to the carotid artery is obtained through the groin, and the arm approach provides access through the subclavian artery. Simultaneous positioning of stents in the origin of each vessel can thus be achieved, and imaging from the sheaths in both locations allows excellent visualization of the proximal and distal aspects of the occlusive lesion. Simultaneous deployment of the stents allows preservation of the ostia of both vessels.

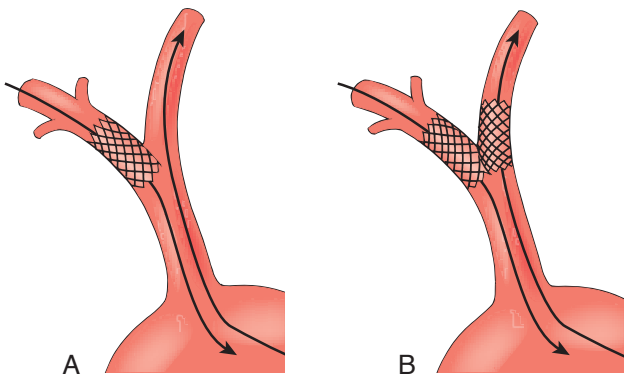

Figure 99.2 (A) Treatment of the right subclavian artery origin can result in "jailing" the origin of the right common carotid artery when the proximal end of the stent projects into the common carotid lumen, as shown. (B) Treatment of the innominate artery branch origins with a kissing-stent technique to preserve both origins.

Left Common Carotid Artery Interventions

Interventions in the left common carotid artery most commonly involve the origin of the vessel as it arises from the aortic arch, but intervention may also be necessary because of disease at the vessel origin as it arises from the innominate artery. When the vessel originates from the arch, the intervention is performed similarly to the previously described femoral approach to the left subclavian artery. Access to the vessel is obtained with the least angled catheter possible, and a decision is made regarding the use of either a guide catheter or sheath to deliver the stent. In some instances access to the origin of this vessel is tenuous because of its angle off the aorta; in this situation a "buddy wire" can be positioned in the external carotid artery distally to maintain the position of the guide or sheath at the origin of the vessel. A protection device is then advanced and deployed within the internal carotid artery. Intervention is performed over the protection device wire, which can subsequently be captured and removed. The buddy wire is removed last to ensure that the access sheath or guide remains stable throughout the treatment.

When access to the origin of this vessel proves challenging, the interventionalist must decide whether to attempt retrograde interventional access through open carotid artery exposure or to proceed to surgical revascularization. Several factors contribute to this decision, including the extent of disease in other arch vessels, in particular the left subclavian artery; the presence of significant disease in the ipsilateral carotid bifurcation, which may be addressed at the same time by simultaneous carotid endarterectomy (CEA) and retrograde intervention; and a history of operations or radiation therapy to the neck. When attempting intervention in this vessel, it is important to remember that changing to an alternative approach may be safer than persisting in attempting access in a very diseased arch.

Innominate and Left Common Carotid Interventions in Combination With Carotid Endarterectomy

As stated earlier, patients with cerebrovascular disease have a higher rate of brachiocephalic occlusive disease than the general population. It remains rare that both lesions will be significant enough to require treatment. This occurs in approximately 5% of patients who require carotid intervention.[64,65] In those who need both innominate or common carotid intervention in conjunction with internal carotid intervention, a hybrid approach has emerged as a safe and efficacious option. Clinical decision making as to whether a proximal intervention must be added

to a CEA is generally straightforward; only flow-reducing lesions need treatment, and with the proliferation of CTA and MRA, lesions at the arch vessels origins are commonly detected. One clinical clue is the presence of a palpable common carotid pulse in the neck, which implies that the proximal lesion is not flow-limiting; in addition, the duplex image of the cervical common carotid waveform will be blunted in proximal flow-reducing lesions. Finally, it is a simple maneuver to obtain an intraoperative intra-arterial pressure measurement to assess the hemodynamic significance (or lack thereof) of the proximal lesion.

Technique

The hybrid approach as described by Moore et al.[66] involves proceeding with surgical exposure of the carotid bifurcation and internal carotid in the standard fashion for endarterectomy. Once exposed, the internal carotid can be clamped above the level of disease to avoid cerebral embolization, and intervention on the common or innominate lesion is performed under that protection. Access is gained into the common carotid below the level of disease, and a hydrophilic wire is passed through the lesion. This is then exchanged for a stiff wire, and angioplasty and/or stenting conducted in the normal fashion. After the intervention has been performed, a clamp is placed on the common carotid above the stent but below the bifurcation disease. The artery is opened and any embolic debris is cleared with endarterectomy. An alternative option is to first perform the endarterectomy, which allows for avoidance of stagnant flow in a newly placed stent for any significant period of time.

Results

A recent meta-analysis of 13 studies, in which tandem lesions were treated in the fashion reported earlier, a technical success rate of 97% was achieved.[67] Stents were used in 61% of procedures, whereas the remainder underwent simple balloon angioplasty alone. Thirty-day mortality and stroke rates were 0.7% and 1.5%, respectively. These studies had a mean follow-up of 12 to 36 months. During this time, 10 of the 129 total patients developed restenosis of the proximal lesion, and 2 patients were found to have asymptomatic restenosis of the endarterectomy site. With regard to proximal restenosis, 70% of these patients did not have stents placed at the initial operation. Four of these patients were symptomatic, and a total of 7 underwent reintervention, including repeat angioplasty ($n = 4$) and bypass graft ($n = 3$). The favorable results seen so far in published series for this approach seem to indicate that it is both a reasonable and efficacious option, but further study is justified prior to widespread application. A more recent review of a large single-center series reported less optimistic outcomes.[68] These authors reported their experience with 23 patients undergoing combined endarterectomy with proximal intervention and noted dissection in the proximal intervention site in 3 patients, 2 of whom required additional stent placement and one of whom sustained stroke and death. There were two early strokes (9%) and one death (4%), along with five patients having restenosis (4 at the endarterectomy site and 1 at the proximal intervention site) at a mean follow-up of 30 months. These authors advised caution in utilizing this approach and, as noted previously, they advised that performance of this combined procedure should be limited to those with hemodynamically significant proximal stenosis.

RESULTS

Initial descriptions of endovascular treatment of arch vessel disease involved limited numbers of patients treated with angioplasty alone.[3,4,69,70] Since that time, however, extension of the experience of these and other authors has increased the information available regarding perioperative complications and longer-term outcomes.[24,71,72] These investigators have noted a low complication rate with reasonable initial success and acceptable long-term results. In these patients, stents were applied selectively.

The introduction of stents has markedly changed the interventional options available for treating lesions; they have more commonly been used as a primary method of treating occlusive lesions in this region. As primary stenting is the more commonly utilized technique, the initial technical results of reports of primary stenting are noted in Table 99.2**.** Complication rates in these series ranged from 0% to 20% with the majority consisting of access-related problems, including hematoma, pseudoaneurysm formation, and vessel thrombosis. Importantly, there were very few neurologic sequelae in these series, with two strokes occurring in a single series[42]; both occurred in patients undergoing combined endarterectomy and proximal branch intervention. In one of the larger series reported, Karpenko et al.[73] noted an incidence of TIA in 1 (0.8%) of patients with stenosis and 3 (2.5%) of patients with occlusion, and no strokes were identified. In an additional large study, the SCALLOP investigators[74] noted no TIA in patients with stenosis and two (1.2%) in patients with occlusion. Stroke rates were similar in both groups at 1.8%; however, in the SCALLOP registry, over 15% of patients had stents placed across the origin of the vertebral artery, a technique we would not recommend because of the neurologic risk, which would seem to be inherent in this approach. In most of these series, the incidence of death and neurologic morbidity was extremely low with no deaths noted in the two largest studies.

Rupture is a rare but recognized risk when using endovascular means to treat brachiocephalic occlusive disease. There are few reports on the incidence or management of brachiocephalic rupture. Options for management are similar to those in the event of rupture in other vessels during angioplasty and/or stenting.[76] This would typically include the use of balloon occlusion to immediately control the injury and treatment with covered stent placement to control hemorrhage.

Patency

From the reported series published to date, endovascular patency rates appear to be lower than those reported for surgical

TABLE 99.2 Technical Success Rates for Arch Vessel Interventions

Series	Year	No. of Patients (Lesions)	TECHNICAL SUCCESS	
			Stenosis	Occlusion
Rodriguez-Lopez et al.[38]	1999	69 (70)	55/58 (95)	15/15 (100)
Sullivan et al.[37]	1998	83 (87)	76/77 (99)	6/10 (60)
Al-Mubarak et al.[34]	1999	38 (38)	34/34 (100)	2/4 (50)
Bates et al.[33]	2004	91 (91)	83/83 (100)	6/8 (75)
Brountzos et al.[23]	2004	48 (49)	42/42 (100)	5/7 (71)
Peterson et al.[64]	2006	20 (20)	20/20 (100)	0
Tyagi et al.[65]	2008	10 (12)	12/12 (100)	0
Woo et al.[75]	2006	25 (27)	20/20 (100)	4/7 (57)
SCALLOP Registry[74]	2017	553 (560)	389/389 (100)	153/171 (89)
Karpenko et al.[73]	2017	245 (245)	122/125 (98)	110/120 (92)

TABLE 99.3 Patency Rates for Arch Vessel Interventions

Series	Patency Measure	PATENCY (%)				
		1 Year	2 Years	3 Years	4 Years	5 Years
De Vries et al.[62]	Duplex (>50%) and clinical symptoms	94	89	89	89	89
Przewlocki et al.[24]	Duplex (>50%), clinical symptoms, and arm pressure	88.5	83.6	N/A	N/A	77.2
Rodriguez-Lopez et al.[38]	Duplex (>50%)	92 100[a]	82 96[a]	73 90[a]		
Bates et al.[33]	Arm pressure	97	91	83	N/A	77
Bakken et al.[67]	Duplex (PSV ratio 3:1)	92	84	77		
Karpenko et al.	Duplex (>70%) and clinical symptoms				89.8 (stenosis) 87 (occlusion)	
SCALLOP registry	Duplex (>50%) and arm pressure	90.6 99.2[a]		83.4 98.2[a]		80.5 97.7[a]

[a]Secondary patency.

reconstruction in these vessels (Table 99.3). One-year patency rates vary from 88.5% to 97%, and 5-year patency rates vary from 77% to 89%. Importantly, recurrent stenosis can be treated by reintervention, with improvement in primary patency rates as noted by Rodriguez-Lopez et al.[43] and the SCALLOP registry investigators.[74] These investigators reported a 36-month secondary patency rate of 90%[38] and a 60-month secondary patency rate of 97.7%,[74] which is comparable to data from open surgical bypass series.

There are currently four retrospective studies that have compared the results of endovascular therapy for subclavian occlusive disease with outcomes from surgical reconstruction.[77-80] In the first of these studies, AbuRahma et al.[77] compared data on procedures performed over a 13-year period at a single institution. During this period, 121 patients underwent intervention with angioplasty and stenting for subclavian artery occlusive disease, whereas 51 patients underwent operative reconstruction via carotid-subclavian bypass grafting. The diagnosis of restenosis was based on the presence of an arm pressure differential together with appropriate duplex criteria. In the endovascular group, two completely occlusive lesions could not initially be crossed. Complication rates were 5.9% in the bypass group versus 14.9% in the endovascular group. Bypass complications included two phrenic nerve injuries, from which patients recovered within several months, and one nonfatal myocardial infarction. Endovascular complications included two distal embolic events treated by intervention, congestive heart failure, brachial artery thrombosis treated by thrombectomy, reperfusion arm edema, pseudoaneurysm, procedure-related dissection and/or thrombosis treated by thrombolysis and stenting, and 11 minor complications (8 hematomas not requiring transfusion, 2 cases of headache and/or syncope, and 1 superficial wound infection). Overall the patients treated via an endovascular approach experienced a major complication rate of 5.8%, which was very similar to the major complication rate of surgical bypass. Primary patency rates for bypass at 1, 3, and 5 years were 100%, 98%, and 96%, respectively, versus 93%, 78%, and 70%, respectively, for endovascular therapy.

Another report compared the outcomes of 114 patients who underwent 137 procedures for subclavian artery stenosis

treated by either primary stent placement (67 lesions) or carotid-subclavian bypass grafting (70 lesions).[78] Among lesions that underwent endovascular therapy, 62 were successfully treated. The five patients in whom endovascular attempts failed underwent bypass. Primary patency rates in the interventional patients were 78%, 72%, and 62%, respectively, at 1, 3, and 5 years, with assisted-primary patency rates at the same time points of 84%, 76%, and 76%. For patients who underwent surgical therapy, 1-, 3-, 5-, and 10-year patency rates were 95%, 92%, 90%, and 90%, respectively, and primary-assisted patency rates at the same time points were 97%, 97%, 95%, and 95%, respectively. There was no mortality in either group, and complication rates were similar: 20% in the open surgery group and 10% in the endovascular group. Furthermore, no cerebrovascular events occurred in either group.

In another study of 76 patients treated over a 20-year period at a single institution, 35 underwent surgical reconstruction with bypass and 41 had attempted angioplasty.[79] The surgical group had a total of four complications, including an early graft occlusion treated by thrombectomy, two brachial plexus neurapraxias that resolved fully, and one hematoma in the neck, with no perioperative neurologic events or deaths. The 5-year secondary patency rate in this group was 97%. In the endovascular group, there were eight failed attempts at treatment. Six of these failures occurred in the setting of total occlusions, and one failure occurred because of the development of a cerebellar infarct, at which point further interventional attempts were abandoned. There were four complications among these patients, including the one cerebellar infarct noted, two subclavian artery dissections requiring stenting, and one covered stent protruding into the aorta to an extent that necessitated surgical removal of the stent. The primary patency rate of successfully treated lesions was 82% at 4 years.

The most recent notable report[80] evaluated outcomes over a 20-year period in 252 patients who underwent balloon-expandable stent placement ($n = 148$) or extrathoracic bypass grafting ($n = 104$). Of the bypass patients, 71 underwent axilloaxillary bypass and 33 had carotid-subclavian bypass. There were no perioperative deaths and no permanent neurologic deficits in either group. The overall complication rates were 6.1% in the endovascular group and 9.6% in the surgical bypass group. Cumulative 1-, 3-, 5-, and 10-year primary (secondary) patency rates in the stent group were 91%, 78%, 67%, and 49% (95%, 91%, 86%, and 64%), whereas those same values in the bypass group were 99%, 97%, 95%, and 89% (99%, 99%, 98%, and 94%). The authors concluded that although both therapies were safe and effective, surgical bypass was a more durable solution for this entity. Importantly, for those patients with endovascular therapy failure, all were able to undergo surgical revascularization with a technical success rate of 100%.

It appears notable from these reports that long-term patency seems to be better with open surgical reconstruction than with endovascular therapy (see Chapter 98). However, the option of endovascular therapy remains reasonable because it offers extremely low risk at the time of intervention, rapid recovery, hospitalizations that are normally no longer than 1 to 2 days, early resumption of normal activities, and preservation of surgical options if needed.

Arch Intervention in Inflammatory Conditions

Interventional therapy for inflammatory diseases (e.g., Takayasu arteritis) of these vessels mandates an understanding of the nature of the inflammatory process (see Chapter 139). For stenosis of an arch vessel that is severe enough to cause symptoms, the inflammatory disease process must have been active for some time. In most cases, treatment with anti-inflammatory medications is aimed at reducing the inflammatory state and not at decreasing the amount of stenosis in the vessel. Because revascularization procedures in these disease states are hampered by cell overgrowth and neointimal hyperplasia, it is important to ensure that the patient's disease is quiescent before vascular reconstruction by any route. This should include normalization of inflammatory serum markers and improvement in systemic symptoms such as fevers and malaise. Nevertheless, occasionally cerebral ischemic symptoms develop that mandate acute attention to revascularization, even with an active inflammatory state. In this setting, reconstruction ideally with autogenous material carries the lowest risk of recurrence. Endovascular intervention in the setting of acute inflammation can be achieved, although immediate and long-term success rates appear lower than those achieved in patients with atherosclerotic disease, and recurrence rates are related to the degree of ongoing inflammation.[81] There is a suggestion that covered stents may be of some benefit in treating lesions in this scenario.[82]

Once the inflammatory state has diminished, the residual lesion in question should be assessed. Improved endovascular outcomes are obtained with the treatment of short focal stenoses. Stent placement appears to have a distinct advantage over angioplasty alone. For complex lesions, especially long occlusions, it appears that autogenous reconstruction via arch vessel transposition offers recurrence rates that are about half those of endovascular therapy. Little information is available regarding the use of either covered stents or medicated stents in this setting, but it would seem likely that they might play a more significant role in treating these problems in the future.

Long-Term Management

Long-term management of this patient population includes appropriate medical therapy to address the underlying atherosclerotic process to limit their overall risk for cardiovascular complications. This will involve appropriate medical therapy for their comorbid conditions, including hypertension, hyperlipidemia, and diabetes. Smoking cessation should be a major component of therapy aimed at reducing this risk as well (see Chapter 11).

Medical Therapy

Medical therapy for patients treated by stenting for arch vessel disease should include antiplatelet therapy, which should be initiated before any procedure, as noted earlier. The antiplatelet

therapy is continued for at least 1 month as a combination of both aspirin (325 mg) and clopidogrel (75 mg) with a transition normally to clopidogrel alone after 1 month. However, there are currently no data to objectively define the optimal time frame for continuing aggressive antiplatelet therapy.

Surveillance Protocol

After intervention in the arch distribution, it is important to maintain continued follow-up. These patients have a 15% to 25% risk for recurrent stenosis within the first 3 to 5 years, with about half of these recurrences being symptomatic. Follow-up should consist of an office evaluation with a history and physical examination including bilateral arm pressure determination. In addition, duplex assessment of the arch vessels should be done every 6 months for the first 18 to 24 months, with annual evaluation thereafter.

In some instances, duplex examination will be unable to assess the degree of stenosis within these vessels because of the difficulty encountered when trying to insonate at this depth behind the bony anatomy of the chest. In this situation, CTA can be helpful in assessing the degree of stenosis. Repeat evaluations are recommended at 6-month intervals for the first 2 years after intervention and then annually. This recommendation is based on the fact that recurrent stenosis in a number of the previously published studies appears to occur at significantly diminished frequency more than 2 years after interventional therapy.

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100 CHAPTER

Acute Limb Ischemia: Evaluation and Decision Making

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Acute ischemia of the limb represents one of the toughest challenges encountered by vascular specialists. The diagnosis and initial assessment are largely clinical, and diagnostic errors can result in a high price to the patient—amputation or even death. Amputation and death rates remain high despite intervention, which is in contrast to major advances in the treatment of many other vascular diseases. Acute ischemia is often an end-of-life condition that presents in a patient with multiple medical comorbidities. Therefore careful clinical assessment of the individual is as important as assessment of the limb. Unlike many other vascular conditions, there is no one definitive treatment; a variety of modalities are available, including anticoagulation, operative intervention, thrombolysis, and mechanical thrombectomy. Selection of the most appropriate intervention or combination of interventions can be critical to the eventual outcome.

ETIOLOGY AND PATHOLOGY

Acute ischemia is the result of a sudden deterioration in the arterial supply to the limb. Excluding trauma and iatrogenic causes, there are two main reasons for acute ischemia to occur: arterial embolism and thrombosis. The distinction between thrombosis and embolism is important in terms of diagnosis and prognosis, but it may not be crucial when deciding on the form of treatment.

Embolism

Embolism (from the Greek *embolos*, or "plug") is the result of material passing through the arterial tree and obstructing a peripheral artery. Usually the source of the embolus is the heart, and the material is mural thrombus that has accumulated and detached. The other main cause is atherosclerotic debris from a diseased proximal artery, often the thoracic aorta, in individuals with a heavy burden of atherosclerotic disease.

Once the embolus detaches, it passes easily through large arteries and lodges peripherally, usually at an arterial bifurcation, where vessels naturally narrow. Emboli can occlude any artery, but in the legs, the common femoral and popliteal arteries are commonly obstructed. Only large emboli, so-called saddle emboli, occlude the normal aortic bifurcation. In the upper extremity, the brachial artery bifurcation and the brachial artery at the takeoff of the profunda brachialis artery are frequent locations for emboli.

Embolic ischemia is usually catastrophic because it often occurs in otherwise normal arteries, without any established collaterals. Typically, the patient presents with an acute white leg, including a complete neurosensory deficit. Embolic occlusion is also progressive; the ischemia worsens as secondary thrombus forms both proximal and distal to the occlusion. The secondary thrombus is the plum-colored clot removed at embolectomy (Fig. 100.1). It is particularly important that this secondary thrombus be removed because it may be responsible for obstruction in smaller distal vessels. If the presentation is delayed, the secondary thrombus adheres to the arterial wall, making it particularly resistant to removal with an embolectomy catheter and less easily lysed by thrombolytic drugs.

Figure 100.1 Embolic Fragment in the Centre of the Image, With the Tail of Secondary Thrombus Shown Around It.

Cardiac Embolism

Atrial and Ventricular

Embolism may occur in patients with otherwise normal arteries, with the embolic material usually arising from the heart. Embolic material from the heart usually consists of platelet-rich thrombus. Often it is organized, giving it the characteristic white surface on removal at embolectomy. The most common cause is atrial fibrillation; thrombus forms in the left atrial appendage as a result of stasis due to incoordinate contractions of the atrium and ventricle.

Mural thrombus, as a result of acute myocardial injury due to infarction, is a particularly dangerous cause of embolism. The patient has not only an ischemic extremity but also a high-risk medical condition (Fig. 100.2). Left ventricular aneurysm is also a high-risk cause of embolism, because these patients have a low cardiac output as a result of the previous infarcts that caused the aneurysm.

In the past, cardiac valve disease was the main cause of arterial embolism, but advances in the management of these patients have virtually eliminated this as a cause.[1-3] Instead, many patients now have artificial heart valves, and those with prosthetic valves are usually anticoagulated. Embolism is rare in patients with porcine replacement heart valves.

Paradoxical

Paradoxical embolism occurs when a clot from the venous system, usually deep venous thrombosis, travels through a patent foramen

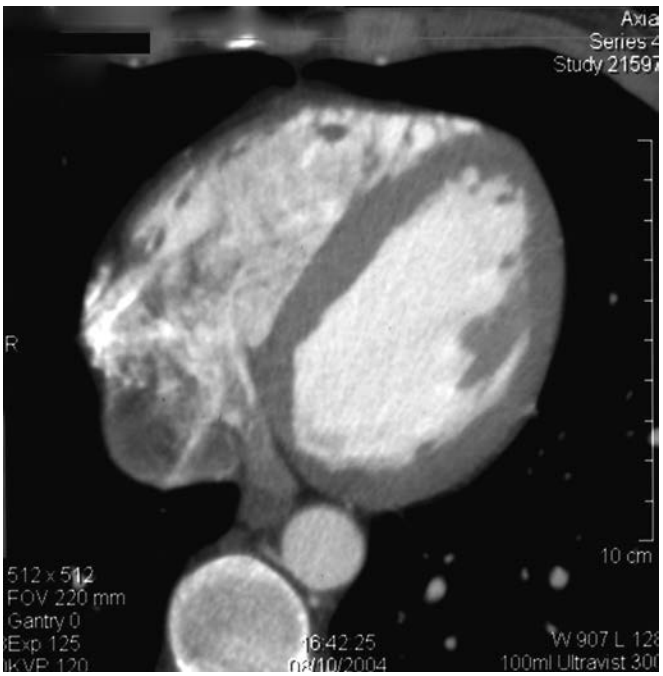

Figure 100.2 Computed Tomogram of the Heart Showing Mural Thrombus That Caused Brachial Embolus (Same Patient as in Fig. 100.9).

ovale into the arterial system. The clinical clue is acute arterial ischemia in a young patient with simultaneous deep venous thrombosis.[4]

Endocarditis

Bacterial endocarditis is an infrequent diagnosis since the introduction of widespread echocardiography and antibiotics. However, certain patient groups are at risk, including intravenous drug users, patients with indwelling arterial or venous lines, and those who are immunocompromised.

Cardiac Tumor

Atrial myxoma is a benign tumor of the left atrium that may fragment as it enlarges. Surgeons are advised to send the embolic material for histology if there is anything atypical about the material removed at embolectomy, or if the patient is young with no obvious reason for embolic disease.[5]

Noncardiac Embolism

Atheroembolism

Another source of embolism is the native arteries themselves. Particularly in patients with extensive atherosclerotic disease in major arteries such as the aortic arch or the descending thoracic aorta, fragments of plaque or adherent thrombus may detach and cause symptoms that mimic cardiac embolism (Fig. 100.3). The embolic material may consist entirely of platelet-rich thrombus, similar to embolism. More sinister are fragments of atheromatous plaque that detach (Fig. 100.4); these are more difficult to remove at embolectomy and may irreversibly occlude small distal vessels (see Chapter 164). Atheroembolism may occur spontaneously or may be precipitated by intraarterial manipulation of wires or catheters during cardiac or peripheral arterial interventions.

Aortic Mural Thrombi

Occasionally patients with hypercoagulable conditions develop an aortic mural thrombus in the absence of aortic pathology, which then embolizes to a limb. This should be suspected in a patient without atherosclerotic vascular disease and in whom

Figure 100.3 Ulcerated Aortic Atheroma at Autopsy.

Figure 100.4 Angiogram Showing Aortic Plaque (A) Causing Distal Popliteal Thromboembolism (B).

the cardiac evaluation is negative. Although the acutely ischemic limb may need urgent treatment, the underlying aortic pathology can often be treated simply by anticoagulation, with resolution of the thrombus.[6]

Thrombosis

Thrombosis results from blood clotting within an artery, which can be caused by progressive atherosclerotic obstruction, hypercoagulability, or arterial dissection.

Atherosclerotic Obstruction

Thrombotic occlusion is most commonly the result of progressive atherosclerotic narrowing in peripheral arteries of the leg. Once a stenosis becomes critical, platelet thrombus develops on the stenotic lesion, leading to an acute arterial occlusion. The clinical manifestations are seldom as dramatic as those of embolization, because the progressive process of atherosclerotic narrowing results in the development of robust collateral circulation. Patients with atherosclerosis deteriorate in a stepwise fashion, as thrombosis supervenes on an arterial stenosis. The resulting symptoms of ischemia (usually the acute onset of claudication) improve as collateral vessels expand. Critical ischemia is the end result when this process occurs at multiple levels. Acute stroke or myocardial infarction is the result of atherosclerotic plaque disruption, which may be confirmed by plaque inspection at carotid endarterectomy or autopsy.[7] In the extremities, it is not known whether plaque disruption is a cause of acute-on-chronic arterial thrombosis, because the offending plaque is rarely available for examination. It is possible, however, that the process of plaque disruption is the etiology in certain cases.

In patients with extensive atherosclerotic peripheral vascular disease, a reduction in cardiac output may produce acute limb ischemia by a global reduction in limb arterial perfusion. For example, if a patient with severe claudication develops complicated diverticulitis, the onset of shock may cause low cardiac output and result in acute critical limb ischemia in the absence of thrombosis. It is important to recognize this phenomenon because it is the underlying disease, not the leg, that needs urgent treatment.

Hypercoagulable States

In situ vessel thrombosis can also occur in the absence of atherosclerotic disease in states of hypercoagulability, low arterial flow, or hyperviscosity. These hypercoagulable states are associated predominantly with venous thrombosis, but thrombocythemia in particular can cause arterial occlusion, usually in small vessels. Malignant disease is also linked mainly to venous thrombosis, but several authors have observed an association with acute arterial ischemia.[8] It may be worth screening patients with acute leg ischemia without obvious atherosclerosis for an underlying malignancy. Because the vessel thrombosis is often a marker of advanced malignancy, the outcome in these patients is poor, despite active treatment.

Vascular surgeons occasionally encounter heparin-induced thrombocytopenia, in which a patient on heparin develops progressive vessel thrombosis with a falling platelet count. Other hypercoagulable conditions that may cause arterial thrombosis and result in acute limb ischemia are discussed in Chapter 38.

Vasospasm

Primary Raynaud disease rarely, if ever, causes acute ischemia. Secondary Raynaud's, due to underlying connective tissue disorder, can be acute and may present with digital ischemia. Open revascularization is seldom possible, and the key to a successful outcome is prompt diagnosis and treatment with intravenous or intraarterial infusion of a vasodilator or prostanoid. Digital ischemia can also follow intraarterial injection, most commonly as a result of inadvertent injection of illicit drugs. Ischemia may be profound and irreversible, particularly if particulate material is injected. Treatment consists of anticoagulation to prevent secondary thrombosis and infusion of thrombolytics, vasodilators, or prostanoids, as appropriate.

Aortic Dissection

Another condition that requires a high index of suspicion for diagnosis is aortic dissection, which may involve the aortic bifurcation and give the appearance of iliac artery thrombosis.[9] These patients typically have chest or back pain and may be hypertensive. Another clinical clue is renal failure if the dissection involves the renal arteries. Arterial dissection of other arteries supplying the lower extremity is uncommon but may follow trauma, or could be a sign of underlying fibrodysplasia.

Bypass Graft Occlusion

Another significant cause of acute limb ischemia is the occlusion of an existing patent bypass graft. Clearly the rate depends on how many bypass grafts exist in a community.[10,11] In areas that are well endowed with vascular services, patients frequently present emergently with graft thrombosis. In the United Kingdom, a national survey in 1996 reported that graft or angioplasty occlusion was responsible for 15% of acute limb ischemia.[12] The diagnosis is usually easy, and the cause is more likely to be thrombosis than embolism. Assessment and treatment are similar to that for native vessel ischemia, but decisions about treatment can be much more difficult because of the variety of options available (see Chapter 113).

CLINICAL PRESENTATION

The symptoms caused by vascular occlusion depend on the size of the artery occluded and whether collaterals have developed beforehand. Sudden occlusion of a proximal artery without existing collaterals leads to an acute white leg, whereas occlusion of the superficial femoral artery in the presence of well-established collaterals may be entirely asymptomatic. This is borne out by the number of individuals who are found to have occult femoropopliteal occlusive disease on population screening. Acute ischemia affects sensory nerves first; therefore loss of sensation is one of the earliest signs of acute leg ischemia. Motor nerves are affected next, causing muscle weakness; then skin and finally muscles are affected by the reduction in arterial perfusion. This is why muscle tenderness is one of the end-stage signs of acute leg ischemia. Once ischemia is established, the skin's initial

pallor becomes dusky blue as capillary venodilatation occurs. At this stage, pressure over the discolored skin leaves it white because the vessels are still empty (Fig. 100.5). The terminal stage of skin ischemia is caused by extravasation of blood owing to capillary disruption; digital pressure over the discolored skin produces no blush. At this stage, the skin is nonviable, and revascularization of necrotic tissue risks compartment syndrome and renal failure without salvaging the extremity (Fig. 100.6).

Historical series of patients with acute leg ischemia reveal a preponderance of embolic occlusion, usually secondary to valvular heart disease; however, this cause has essentially been eradicated owing to modern cardiovascular surgical expertise.[1-3] Today the usual cause of cardiac emboli is atrial fibrillation as a result of ischemic heart disease. This means that the affected population tends to be much older than it was 50 years ago, and patients often have established atherosclerotic disease of the arteries. This can produce the confusing picture of a patient with an embolus as well as peripheral arterial disease. Another effect is the gradual increase in the incidence of acute ischemia as the population ages.[13,14]

Figure 100.5 Acute Ischemia, Class IIb—Immediately Threatened.

Figure 100.6 Acute Ischemia, Class III—Irreversible.

CLINICAL ASSESSMENT

The initial assessment of acute critical ischemia involves an evaluation of both the limb and the patient as a whole.

History

The initial symptoms depend on the severity of ischemia and can range from incapacitating pain to the sudden onset of mild claudication. Obviously, the more severe the ischemia, the faster the patient seeks medical attention. Severe acute ischemia is usually obvious, with extreme pain and loss of sensation and power in the limb. Less severe ischemia can be difficult to diagnose and may be confused with musculoskeletal pain, sciatica, and other causes of limb discomfort. The duration of symptoms is the most important part of the history; in patients with severe ischemia, irreversible muscle necrosis occurs within 6 to 8 hours if the condition is untreated. Patients with an acute white leg require urgent intervention. The symptoms of sensory loss and muscle pain are also evidence of critical ischemia.

The history should include an attempt to define the cause of the ischemia. Historically, patients with emboli had valvular heart disease but no evidence of peripheral vascular disease or other atherosclerotic conditions; however, the presence of atherosclerosis no longer rules out embolism. Patients with acute-on-chronic thrombosis often give a history of prior intermittent claudication in the ipsilateral or contralateral leg. A full medical history is important because it may reveal other associated diseases such as diabetes mellitus. Risk factors for atherosclerotic disease should be sought, including smoking, hypertension, hyperlipidemia, and family history.

Physical Findings

Examination of the leg is used to define the severity of the ischemia and is therefore fundamental. The well-known rule of Ps—pain, pallor, paresis, pulse deficit, paresthesia, and perishing with cold—remains a good guide to both symptoms and signs. The color of the skin reflects its vascular supply. Marble-white skin is associated with acute total ischemia. Slow capillary refill is a sign that at least a small degree of distal flow is present and runoff vessels are probably patent. Sensation may be lost completely and the foot may be numb, but more often there is loss of fine touch and proprioception, which should be tested specifically. Muscle tenderness, particularly in the calf, is a sign of advanced ischemia. Acute ischemia is associated with the loss of peripheral pulses, which also helps define the level of the occlusion. Palpable normal pulses in the contralateral leg point toward embolism as the cause.

A full vascular examination reveals the level of the occlusion by the loss of arterial pulsation. A strong pulse can, however, mask an occlusion at that level because of the water-hammer effect. Other possible sources of embolization may become apparent, such as aortic or popliteal aneurysm or cardiac abnormalities such as atrial fibrillation. Patients with acute leg ischemia are often older adults with multiple comorbidities, and a full physical examination should be undertaken because

the final outcome may depend as much on associated conditions as on the severity of the leg ischemia.

Handheld Doppler examination is also a basic part of the examination. Pedal arterial signals may be absent or reduced. The presence of normal biphasic signals excludes the diagnosis. Soft monophasic signals are associated with patent distal vessels but proximal arterial occlusion. Absent Doppler signals in the ankle arteries is a poor prognostic sign. The arteries may be patent but with little flow, or they may be occluded with thrombus. In severe ischemia, ankle Doppler pressures are impossible to measure, partly owing to the lack of signal but also because of muscle tenderness. In less severe ischemia, an ankle pressure of 30 to 50 mm Hg can be expected, and an ankle-brachial index of about 0.3 is diagnostic of subcritical acute ischemia. Doppler can also be used to examine the extremity veins. In particular, a lack of a venous signal in the popliteal fossa suggests popliteal venous occlusion, which is a particularly poor prognostic sign in a patient with acute arterial ischemia.

CLASSIFICATION OF ACUTE LIMB ISCHEMIA

Acute limb ischemia used to be classified according to cause—thrombosis or embolism—because this had implications for treatment and prognosis. Patients with thrombosis tended to be younger but had a higher risk of major amputation. Patients with emboli tended to be older and had a higher risk of dying after treatment.[15,16] It has become clear that this is not a useful classification, because there is no way of proving definitively whether an occlusion is thrombus or embolus. A more valuable method of classification is based on the severity of the arterial ischemia, which is helpful in determining the urgency of intervention and has implications for outcome.[17,18]

The Society for Vascular Surgery and the International Society for Cardiovascular Surgery have published definitions of acute leg ischemia that are valuable for treatment and prognosis (Table 100.1).[19,20] These standards were modified in 2007 by a larger group—the Trans-Atlantic Inter-Society Consensus—which defined acute ischemia as any sudden decrease in limb perfusion causing a potential threat to limb viability.[21] They may be modified again in the future, but they have stood the test of time, and are unlikely to change significantly. The categories of ischemia are based on clinical findings and Doppler measurements, which can be performed at the bedside and are immediately available. In patients with class I ischemia (viable) or acute-onset claudication, intervention, particularly with thrombolysis, may be risky, and there is an argument for conservative treatment consisting of exercise and best medical therapy. In class III or irreversible ischemia, there is no indication to improve the blood supply, which may risk rhabdomyolysis, so the decision is between major amputation and conservative treatment.

Patients with class II ischemia require intervention, and the distinction between IIa (marginally threatened) and IIb (immediately threatened) is crucial. Any delay in treating the latter risks irreversible muscle necrosis, whereas in patients with IIa ischemia, there is time for investigation and semielective intervention. Class II ischemia encompasses the majority of patients with acute leg ischemia, and it may be helpful to think of class IIa as acute subcritical ischemia and class IIb as acute critical ischemia.[18] As outlined in Table 100.1, the three findings that best differentiate IIa from IIb ischemia are pain at rest, sensory loss, and muscle weakness.[21]

DIAGNOSIS

Following clinical assessment and classification, the anatomic location of the arterial occlusion can be diagnosed with a high degree of reliability.

Aortic Occlusion

The diagnosis of an aortic occlusion is usually obvious. Paralysis of the legs is often the presenting feature; patients are unwell, with mottled skin discoloration that often extends above the inguinal ligament onto the lower abdomen and no palpable

TABLE 100.1 Classification of Acute Limb Ischemia

Category	Description/Prognosis	FINDINGS		DOPPLER SIGNALS	
		Sensory Loss	Muscle Weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
II. Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III. Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

From Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.

extremity pulses. This is a particularly high-risk condition, and urgent treatment is indicated.[22] The kidneys are especially at risk, particularly if the aortic occlusion is due to an aortic dissection. The dissection or occlusion may already involve the renal arteries, in which case the patient presents in established renal failure. Successful revascularization restores the blood supply to a large muscle mass, and the effects of ischemia-reperfusion may cause further renal damage.

Iliac Occlusion

The findings are similar to those for aortic occlusion, but unilateral. The femoral pulse is lost on the affected side, and mottling usually extends to the inguinal level. Aortic dissection should be excluded if there is time for investigation or if symptoms are suggestive.

Femoropopliteal Occlusion

Femoropopliteal occlusion is the most common situation in those with acute leg ischemia. The severity of the ischemia depends on whether the profunda femoris remains patent. The symptoms are more severe if the profunda is involved. Although the femoral pulse may be strongly palpable (owing to the water-hammer effect), the artery may be occluded.

Popliteal and Infrapopliteal Occlusion

In popliteal and infrapopliteal occlusion, the calf muscles are ischemic with a palpable femoral pulse. In young patients, rare diagnoses include popliteal thrombosis due to muscular entrapment or cystic adventitial disease. The most sinister cause is popliteal aneurysm thrombosis or embolization. This diagnosis should be suspected if a generous popliteal pulse is palpable in either leg or there is a nonpulsatile mass in the popliteal fossa of the affected leg. The outcome of this condition is particularly poor, despite aggressive treatment.[23] Chronic embolization of thrombus from within the aneurysm gradually occludes the distal vessels and arterial outflow; the aneurysm then thromboses, leaving no distal arterial targets for revascularization. Tibial embolism is an infrequent diagnosis, because most emboli that produce symptoms are large and obstruct proximal arteries (Fig. 100.7). Very distal emboli can be challenging to treat because the embolectomy catheter is least effective in small distal vessels. Some authors recommend retrograde embolectomy of tibial emboli via pedal arteries.[24]

INVESTIGATION

Investigation may be valuable in confirming the clinical diagnosis and planning the appropriate treatment for patients with acute ischemia. However, when the ischemia is critical, there may be no time for investigation if direct operative intervention is required. It is possible to employ on-table angiography to assist in decision making in the operating room. In a modern vascular service, treatment in a hybrid operating theater with access to the full range of interventional and surgical procedures is optimal.

Figure 100.7 Distal Ischemia Due to Occlusion of Small Vessels (Acute Blue Toe Syndrome).

Time permitting, a number of methods can be used to definitively determine the site and nature of the arterial occlusion.

Computed Tomographic Angiography

New-generation computed tomography (CT) scanners acquire images at very high speed and are available in most emergency suites. CT angiography has thus become the investigation of choice for urgent investigation of acute arterial ischemia. Intravenous contrast injection with current CT technology provides images that are similar in quality to intraarterial arteriography. The images sometimes require manipulation to produce the best results, but this is an acquired skill of many young vascular specialists. These images are particularly good for aortoiliac occlusions but give adequate information to plan treatment of infrainguinal occlusions. One concern is that the contrast material may have a deleterious effect on renal function, so intravenous fluids should be considered for prehydration at this stage.

Ultrasound

Imaging with duplex ultrasonography is the mainstay of investigation for chronic arterial ischemia. It may not be available in all hospitals after hours, but it can be employed in cases of acute ischemia to define the level of the arterial occlusion and the patency of other vessels. Portable ultrasound machines may permit rapid, bedside imaging by vascular specialists trained in duplex imaging.

Transfemoral Arteriography

Arteriography was the mainstay of investigation for acute leg ischemia, but it is less accessible than CT angiography in many hospitals without a hybrid theater. Brachial puncture can be used in the absence of femoral pulses. The angiogram documents the level of occlusion and sometimes its nature. Thrombotic occlusion is likely if there are established collateral arteries and evidence of arterial atherosclerosis. Sometimes emboli can be

Figure 100.8 Angiogram Showing Popliteal Embolus. Note the Meniscal-Type Cutoff, With No Existing Collaterals.

seen in several vessels, establishing the diagnosis (Fig. 100.8). Angiography is the best choice when an endovascular solution to the arterial occlusion is likely, because thrombolysis, percutaneous thrombectomy, angioplasty, or stenting can be performed during the same operative session. Arteriography may not visualize all the distal vessels in the acute situation, because the lack of collaterals and associated spasm limit visualization. It may still be worth exploring distal vessels surgically when contemplating a distal bypass in this situation, although an alternative would be to consider intraarterial thrombolytic therapy (see Chapter 162).

Magnetic Resonance Angiography

Magnetic resonance angiography with gadolinium enhancement is less useful than either CT or ultrasound in the context of acute limb ischemia. It is often unavailable at off hours, takes time for images to be acquired, and is generally inconvenient for sick patients.

Echocardiography

Debate continues about the role of echocardiography. In practical terms, the investigation seldom alters management, because most patients are anticoagulated for life after successful treatment for acute ischemia. Some surgeons, however, regard the investigation as a vital part of the postoperative management. There are certainly some conditions that require echocardiography to make a diagnosis, such as valvular disease (including vegetations), septal defect, and cardiac tumor. Problems associated with the routine application of echocardiography include the variability in results between transthoracic and transesophageal techniques and among different technicians, the inability to visualize the left atrial appendage, the fact that failure to visualize the source of an embolus does not rule out its existence, and the test's lack of influence on overall management.[25] A pragmatic view would be that echocardiography is indicated in young patients, those in whom a cardiac diagnosis is suspected, and those in whom the results might affect decisions about long-term anticoagulation.[26]

INITIAL MANAGEMENT

Once the diagnosis of acute ischemia has been established and its severity classified, a number of immediate interventions are possible. These are discussed briefly here and addressed in greater detail in Chapter 162.

Anticoagulation

The threat to the limb escalates with secondary thrombosis of underperfused distal vessels, particularly in patients with emboli. Therefore, immediate anticoagulation with intravenous calcium heparin can stabilize the condition of the leg and prevent deterioration. Whereas low-molecular-weight heparin is a valuable therapy for many conditions, the potential for immediate reversal with protamine makes calcium heparin the drug of choice in this situation. Protocols using a weight-based bolus and infusion rates facilitate rapid therapeutic anticoagulation. If urgent operation is not undertaken, the infusion should be monitored using the activated partial thromboplastin time, aiming for a ratio of 2 to 3. It is vital not to assume that anticoagulation is being accomplished while heparin is being administered; there is a wide variation in response to the drug, and careful monitoring by protocol is needed.

Ancillary Supportive Measures

Other first-aid measures that are beneficial in patients with leg ischemia include the use of oxygen delivered by facemask. This has been shown to improve skin perfusion, even in the ischemic limb.[27] Patients with acute ischemia are often dehydrated and at risk of renal dysfunction, so an intravenous infusion of fluid and monitoring of urine output is appropriate. Many radiologic maneuvers involve the use of contrast agents that can damage the kidneys, and adequate renal perfusion is important. As part of the diagnostic workup, a full blood screen for blood urea nitrogen and a full blood count are indicated. In patients with recurrent thrombosis, a full thrombophilia screen should be performed at this stage, if indicated, because therapeutic anticoagulation renders these investigations inaccurate.[28,29] These tests are indicated in patients with a strong family history of arterial and venous thrombosis or those with recurrent disease.[30,31] Patients are often in severe pain, and adequate analgesia is important. Intramuscular opiates are contraindicated in a patient

who may receive thrombolysis, and patient-controlled intravenous analgesia is a good alternative.

TREATMENT

Options

Once the initial assessment is complete, a decision should be made about the intervention required and its timing. The following options are available: anticoagulation alone, operative intervention, and endovascular intervention via mechanical thrombectomy or thrombolysis.

Anticoagulation

Heparin anticoagulation has no direct thrombolytic effect; it is used to stabilize clot formation and prevent further secondary thrombosis. Use of anticoagulation alone as a treatment implies that the limb is likely to remain viable or that other therapeutic options are limited, perhaps by age or comorbidity. Before anticoagulants were available, treatment of acute leg ischemia was largely expectant, and historical series documented high morbidity and mortality rates, despite amputation. Heparin and then warfarin made an immediate impact after their introduction.[32,33] Anticoagulation for stable class I ischemia, followed several weeks later by intervention (usually endovascular) if collaterals do not become established, is safe and effective. Anticoagulation has been shown to improve results after embolectomy.[34] In class III irreversible ischemia, anticoagulation allows stabilization of the patient while his or her medical condition is improved, pending major amputation at a later date. Otherwise, anticoagulation may be a component, but does not constitute definitive treatment for acute leg ischemia.

Operative Intervention

After Fogarty et al. described the embolectomy catheter for the remote removal of a clot via a groin incision in 1963, surgery became the main treatment for acute leg ischemia.[35] Over the years, the pattern of disease has changed, and emboli now occur in patients with ischemic heart disease, often in association with peripheral vascular disease. Thus the embolectomy procedure has become more complicated, and the results are inferior in patients who may have an acute thrombosis.[36,37] Increasingly, surgical bypass techniques are required in this situation, and a modern vascular surgeon should be able to offer a full range of bypass and endovascular procedures to patients with acute leg ischemia in a specialized environment to achieve optimal outcomes.[38]

Endovascular Intervention

Endovascular interventions offer an expanding range of alternative treatments for acute limb ischemia. Options include mechanical thrombectomy with homemade (aspiration embolectomy) or commercially available custom-built devices. In expert hands, mechanical thrombectomy can yield good results in selected patients, particularly those with bypass graft occlusions. If unsuccessful, it can be followed promptly by surgical intervention or thrombolysis.[39]

Percutaneous thrombolysis is also an established intervention for all forms of acute arterial occlusion (see Chapter 36). A potential advantage of thrombolysis is that unlike surgical embolectomy, which simply removes the thrombus from the large arteries, thrombolysis lyses clot in both large and small arteries and arteriolar and capillary beds.[40]

Selection

The choice of intervention depends on the available expertise and the severity of the leg ischemia.[41] The most recent evidence summary[42] and a recent Cochrane review[43] found little difference in outcomes to guide treatment selection between surgery and thrombolysis. There is a suggestion that endovascular first treatment may be more expensive overall,[44] but even in modern series, open vascular reconstruction for acute limb ischemia carries a significant risk of major morbidity (20%) or limb loss (22%).[45] The management of other vascular emergencies such as ruptured abdominal aortic aneurysm benefits from treatment in a hybrid operating theater, where endovascular or surgical treatment can be individualized. Similarly, treatment of acute limb ischemia could benefit from this approach; early indications are that this flexible approach has the potential to reduce the morbidity of a dangerous condition.[46] UK hospital process data show an increasing burden of acute limb ischemia (bucking the downward trend of other cardiovascular diseases), but no increased use of endovascular treatments.[47] Clearly a sea change in attitude is required to take advantage of new facilities, and the skill set of a modern vascular specialist. The severity of ischemia, however, remains the fundamental factor affecting choice of intervention.

Acute Critical Ischemia

Patients with acute critical (class IIb) ischemia need urgent intervention. In institutions where vascular and endovascular services are limited, the choice may be restricted to surgical intervention. Where expertise is limited, consideration should be given to transferring the patient to an institution with a full range of vascular and endovascular services. This clinical setting has been shown to improve outcomes.[38]

If endovascular treatment is offered for acute critical ischemia, there should be no delay. Percutaneous thrombectomy is a valuable option in cases where expertise exists. Low-dose intraarterial thrombolysis is contraindicated because it usually takes 12 to 24 hours to be effective. Accelerated thrombolysis may be an option in experienced units, using either high-dose bolus infusion techniques[48] or pulse spray thrombolysis.[49] However, with these few exceptions, most patients with acute class IIb critical limb ischemia are best treated in the operating room. In the operating room or hybrid theater, numerous interventions are available, ranging from embolectomy to reconstruction to on-table angioplasty or thrombolysis.

Acute Subcritical Ischemia

The treatment of patients with stable (class IIa) acute ischemia should be individualized, given the number of options and the greater time available for deliberation. These decisions are often

best made by multidisciplinary teams reflecting local expertise. Obvious emboli may be treated most appropriately by embolectomy. With this exception, the primary alternative to surgery for class IIa ischemia is intraarterial thrombolysis, with or without adjunctive mechanical thrombectomy. There has been much debate about the advantages and disadvantages of thrombolysis versus a surgical approach, and a number of large randomized trials have compared the two modalities.[50] Premier vascular units are familiar with both surgery and thrombolysis, and can make treatment decisions on an individual basis.[51] If a good surgical option exists, it is probably best that this is undertaken in a fit patient. Many patients with acute leg ischemia are in poor general health and at high risk of complications following operative intervention, particularly if general anesthesia is required. Thrombolysis is particularly indicated when the surgical options are poor and the runoff vessels in the leg appear occluded. An early meta-analysis of the available trials suggested that thrombolysis was best for short-duration ischemia and bypass graft occlusions.[52]

In Gloucestershire, a clinical pathway has been used for the past two decades that requires urgent embolectomy or thrombectomy in a patient with the acute onset of ischemia (<24 hours), an obvious embolic source, class IIb ischemia, and normal pulses in the contralateral leg. All other patients with class IIb acute critical ischemia require consultation with a specialist vascular surgeon on admission. The remainder with subcritical (class IIa) ischemia are anticoagulated overnight and treated by a vascular specialist in daylight hours.[53]

PROGNOSIS

The medical state of a patient who presents with acute leg ischemia is a good prognostic index of survival.[54] In particular, patients with acute myocardial infarction or poor cardiac output have a high mortality rate.[55,56] Outcome can also be predicted from pretreatment POSSUM (Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity) physiology scores.[57] Despite active intervention, the outcome after treatment for acute limb ischemia is often poor. In some patients, limb ischemia is a manifestation of the end of life. Such agonal thrombosis may be recognized in the very elderly with multiple comorbidities, particularly in hospitalized patients,[58] and is an indication for palliative care rather than active intervention.[59] Another very high-risk group in whom palliation might be appropriate is patients with acute ischemia due to hypercoagulable blood as a consequence of advanced malignancy. Prognosis is dependent on cancer stage, which is usually advanced; most of these patients succumb from their cancer within 6 months, even if treated actively.

UPPER LIMB ISCHEMIA

A number of significant differences exist between acute ischemia of the arm and leg. Patients with acute arm ischemia tend to be, on average, about 4 years older than those with acute leg ischemia (mean age, 74). Arm ischemia seldom threatens the limb, and treatment decisions are less urgent.[60,61] The main reason for treating arm ischemia is to prevent late complications such as activity-induced arm fatigue and pain.[62] Most arm ischemia is due to cardiac embolism (Fig. 100.9); atherosclerosis is rare in upper limb arteries.

Patients often present with a cold feeling and numbness rather than pain in the arm. The diagnosis is clinical and can be confirmed by duplex imaging. The arm often improves after initial anticoagulation, and decisions about whether to perform embolectomy can be difficult. Up to 50% of patients have late symptoms of arm pain if untreated; consequently, if limb viability is in doubt, there should be a low threshold to perform embolectomy under local anesthesia.[62] A small number of patients present with class IIb critical ischemia and should undergo urgent surgical intervention.[61] Failed surgery in this situation risks ischemic contracture (Fig. 100.10) or even arm amputation on occasion. The threat to the arm is generally low, but up to 20% of patients with acute arm ischemia do not survive the acute event, usually owing to cardiac complications.[63] Like acute leg ischemia, the attrition rate after successful treatment is high; only 60% of patients survived 3 to 5 years in one typical series.[63]

Figure 100.9 Acute Arm Ischemia Due to Brachial Embolus of Cardiac Origin (Same Patient as in Fig. 100.2).

Figure 100.10 Failed Embolectomy with Wound Dehiscence Resulting in Ischemic Contracture.

Rare causes of arm emboli include thoracic outlet syndrome and proximal subclavian artery aneurysm. Arteriovenous fistulae for dialysis may also cause a number of complications, including thrombosis and aneurysm formation.

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CHAPTER 101

Acute Ischemia: Treatment

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Acute limb ischemia (ALI) results from a sudden decrease in limb perfusion that threatens limb viability and often requires urgent revascularization.[1] Historic rates of amputation and mortality range from 10% to 25%, emphasizing the need for prompt evaluation and treatment.[2,3] The initial evaluation and decision making in the management of ALI are discussed in detail in Chapter 100. This chapter focuses on percutaneous endovascular, open surgical, and hybrid treatment options for the management of acute arterial ischemia.

INITIAL MANAGEMENT

Once the diagnosis of acute ischemia has been established and its severity classified, a number of immediate interventions are critical to optimize patient outcomes.

Anticoagulation and Supportive Measures

Systemic anticoagulation with unfractionated heparin should be initiated to minimize the risk of further clot propagation and to prevent microvascular thrombosis of underperfused distal vessels. An initial weight-based bolus of 100 units/kg is appropriate for most patients, followed by an intravenous infusion of 1000 units/h. If urgent operation is not undertaken, the heparin dose should be titrated to maintain an activated partial thromboplastin time (aPTT) between 50 and 80 seconds or 2.0 to 3.0 times normal values. For those patients with a known heparin allergy, a direct thrombin inhibitor can be used and titrated to an aPTT of 50 to 80 seconds.

Other measures that may be beneficial in patients with ALI include intravenous hydration, supplemental oxygen, and intravenous analgesia. Patients with acute ischemia are often relatively volume depleted, and careful fluid resuscitation is necessary, with fluid administration titrated to urine output. The potential for myoglobinuria due to ischemia-reperfusion, combined with the use of contrast agents during diagnosis and treatment of ALI, increases the risk of acute renal insufficiency, which may be mitigated with appropriate fluid resuscitation.

Results of a full serum chemistry panel, including blood urea nitrogen and creatinine, complete blood count, and baseline coagulation studies, will guide further therapy. A baseline plasma creatine phosphokinase will be helpful to follow for evidence

Abstract

This chapter focuses on the initial treatment options for the management of acute arterial ischemia of the extremities.

Keywords

Acute Limb Ischemia
arterial thrombosis
revascularization

TABLE 101.1 Clinical Categories of Acute Limb Ischemia

Category	Description/Prognosis	FINDINGS		DOPPLER SIGNAL	
		Sensory Loss	Muscle Weakness	Arterial	Venous
I: Viable	Not immediately threatened	None	None	Audible	Audible
II: Threatened					
a. Marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Inaudible	Audible
b. Immediately	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	Inaudible	Audible
III: Irreversible	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

From Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26: 517-538.

of rhabdomyolysis after reperfusion of the extremity. In patients with recurrent thrombosis, a full hypercoagulability workup should be considered, including evaluation for a history of previous heparin exposure and the possibility of a thrombophilia due to heparin-induced thrombocytopenia.

TREATMENT SELECTION

Treatment for ALI depends largely on the extent of limb ischemia present clinically. Rutherford et al.[4] developed a classification of ALI that is helpful in determining the appropriate therapeutic intervention and overall prognosis (Table 101.1).

Class I ALI may require only medical therapy, such as anticoagulation. Revascularization, if contemplated, can be performed electively and can consist of either thrombolytic or open surgical intervention. Treatment selection depends on the duration of ALI, the location and cause of the occlusion, the presence or absence of underlying atherosclerotic occlusive disease, and the patient's overall medical condition.

Class II ALI requires a flexible approach to intervention. All patients with class II ALI require revascularization to preserve the functional integrity of the affected extremity. For patients with class IIa ischemia, immediate revascularization is not necessary. Consequently, either endovascular or surgical options may be considered. In the planning of therapy for a patient with class IIa ALI, the duration of symptoms is of prime importance. Percutaneous endovascular options are more effective in patients with ischemia of less than 2 weeks' duration, whereas ischemic symptoms of more than 2 weeks' duration are better served by surgical revascularization.[5] For a duration of symptoms less than 14 days, prospective studies comparing thrombolytic and surgical intervention favor the initial use of thrombolytic therapy, with surgical intervention reserved for those limbs that do not show response to lytic therapy. Because the ischemic insult in class IIa ALI is mild, therapy may be performed on an urgent, rather than emergency, basis.

More severe ALI (class IIb), manifested by both sensory and motor deficits, requires emergency revascularization. Because time is a factor, surgical revascularization has been preferred. However, advances in catheter-based thrombolytic delivery and percutaneous mechanical thrombectomy (PMT) devices have shortened the time to reperfusion. Consequently, these techniques are increasingly being used as first line therapy in patients with class IIb ALI. In addition, the availability of hybrid operating rooms has allowed physicians to perform diagnostic imaging, endovascular intervention, and open surgical revascularization in single settings as necessary.

Class III ALI manifests as a profound neurologic deficit (insensate, paretic limb), muscle rigidity, and the absence of arterial and venous Doppler ultrasound signals in the affected vascular bed. In patients with class III ALI, revascularization is usually futile and may have adverse systemic effects such as cardiac arrest due to acidosis and hyperkalemia, and primary amputation should be considered.

ENDOVASCULAR TREATMENT

Endovascular procedures offer less invasive revascularization strategies for sick or elderly patients with decreased morbidity and mortality. Currently available percutaneous endovascular procedures include catheter-directed thrombolysis (CDT), pharmacomechanical thrombolysis, catheter-directed thrombus aspiration, and PMT.[1,3] These techniques clear the occluding thrombus from a peripheral artery with a minimally invasive approach, restore blood flow to the extremity, and allow the identification of underlying lesions responsible for the occlusive event. Culprit lesions may then be addressed in a directed fashion with an endovascular procedure such as angioplasty, stenting, or atherectomy.

Catheter-Directed Thrombolysis

CDT has become the preferred treatment in many centers for the management of most viable or marginally threatened limbs (classes I and IIA) after recent occlusive events in native arteries and for thrombosed grafts and acutely occluded stents. One potential exception is cardioembolic events to either the brachial artery or the common femoral artery, which can be expeditiously removed with surgical embolectomy and use of local anesthesia, or to the aortic bifurcation, where expeditious revascularization

BOX 101.1 Contraindications to Pharmacologic Thrombolytic Agents

Absolute Contraindications

Active bleeding disorder
Gastrointestinal bleeding within 10 days
Cerebrovascular event within 6 months
Intracranial or spinal surgery within 3 months
Head injury within 3 months

Relative Contraindications

Major surgery or trauma within 10 days
Hypertension (systolic >180 mm Hg or diastolic >110 mm Hg)
Cardiopulmonary resuscitation within 10 days
Puncture of noncompresssible vessel
Intracranial tumor
Pregnancy
Diabetic hemorrhagic retinopathy
Recent eye surgery
Hepatic failure
Bacterial endocarditis

may be important to minimize risks from metabolic systemic complications. Of the previously used thrombolytic agents, streptokinase, urokinase and tissue plasminogen activators (tPAs), only tPAs are in active use in the United States. A complete discussion of the available pharmacologic lytic agents and their actions is provided in Chapter 41.

Peripheral thrombolytic therapy is administered through a catheter-directed approach to achieve regional thrombus dissolution with minimal systemic fibrinolysis. However, a moderate systemic proteolytic state often results from the use of thrombolytic agents, limiting their use to patients without contraindications to such a state (Box 101.1).[6-8]

Technique

Most physicians prefer a retrograde contralateral femoral approach when dealing with ALI. We routinely use a micropuncture needle to perform a single wall puncture of the common femoral artery and always use ultrasound guidance. Multiple attempts at blind puncture are discouraged due to the risk of access site hemorrhage during thrombolytic infusion. Antegrade ipsilateral femoral access carries a higher risk of hemorrhagic complications and increases the risk of wound infection if an open vascular procedure becomes necessary. Once access is obtained, a short 5 Fr sheath is introduced and diagnostic angiography is performed. A complete evaluation of the runoff vessels is obtained before an attempt is made to cross the occlusion with the sheath. This evaluation assists in the recognition of embolic events and identifies a potential target vessel for bypass in the event of failed thrombolytic therapy. We routinely place a 45- or 55-cm 6 Fr sheath over the aortic bifurcation into the contralateral femoral artery to provide support for crossing the occlusion and later intervention. A straight 4 Fr Glidecath catheter (Terumo Interventional Systems, Somerset, New Jersey) with a 0.035-inch angled Glidewire (Terumo Interventional Systems) and liberal fluoroscopic "road-mapping" techniques are used to cross the occlusion. A 0.035-inch QuickCross Support Catheter (Spectranetics Corporation, Colorado Springs, Colorado) may be useful for crossing the occlusion if more support is needed. An alternative is to use a smaller hydrophilic V-18 ControlWire guide wire (Boston Scientific Corporation, Natick, Massachusetts) to cross the occlusion. The "guide wire traversal test," the ease with which a guide wire is able to cross the occlusion, is a good predictor of technical success in CDT. However, one must take care to avoid intimal dissection in traversing the occlusion.[9]

In the treatment of a thrombosed bypass graft, multiple oblique angiographic views may be required to visualize the proximal stump of the graft. If a bypass graft cannot be entered from the native artery, ultrasound-guided direct puncture of the graft may be helpful. Open cutdown is required to remove the sheath and repair the graft once thrombolysis is complete. Direct graft puncture is also useful in treating thrombosed axillofemoral grafts. Two separate sheaths are placed directly into the midportion of the occluded graft, approximately 5 cm apart in crossing fashion so that the sheath tips are directed toward each other. Two separate thrombolysis catheters are then used to cross the occluded graft from opposite directions and treat the entire occluded graft segment.

After the occlusion has been crossed, a distal angiogram is performed to confirm the catheter location in the true lumen of the native vessel. A catheter exchange is performed to place a specifically designed, 0.035-inch compatible infusion catheter across the occluded segment. We prefer to use the Fountain Infusion Catheter (Merit Medical Systems, Inc., South Jordan, Utah), which is a 4 Fr catheter with a working length of 90 or 135 cm and infusion lengths of 5 to 50 cm (Fig. 101.1A and B).

Multiple side holes in this infusion catheter are designed to distribute the lytic agent throughout the thrombus. A ball-valve occlusion wire included with the catheter directs flow out the side holes and temporarily occludes the end of the catheter. The distal sidehole marker should be placed at the end of the thrombus, and the proximal side hole located just proximal to the thrombus origin. A list of various infusion catheter sizes and designs is shown in Table 101.2. Both low-dose and high-dose regimens can be used with recombinant tPA (rtPA) (Alteplase, Genentech, Inc., South San Francisco). The low-dose regimen prescribes a 1-mg bolus, followed by a continuous infusion of 0.5 to 1 mg/h. The infusion can run for 10 to 12 hours or overnight with another arteriogram performed the following day. Heparin is administered through the proximal side port of the 5 Fr sheath at 300 to 500 units/h to prevent perisheath thrombosis.

We currently use a high-dose tPA regimen for shorter periods. In our experience, this protocol has been very effective, with no increase in bleeding complications. This regimen involves delivering a 10-mg pulse-spray bolus of tPA over 5 minutes, followed by a continuous infusion at 0.05 mg/kg per hour with a maximum dose of 4 mg/h.[9-11] The high-dose infusion is continued for 6 hours before angiography is again performed. We routinely check the serum fibrinogen level every 4 hours and discontinue the infusion if the fibrinogen level drops to less than 100 mg/dL. If the thrombolytic agent is discontinued due to hypofibrinogenemia, it is usually best to remove the

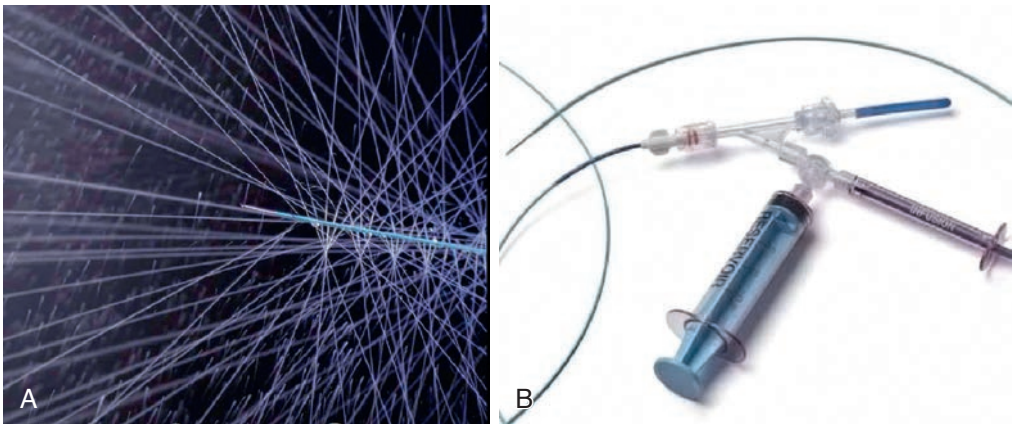

Figure 101.1 (A) Distal end of fountain infusion catheter (Merit Medical Systems, Inc., South Jordan, Utah), which has multiple side holes, with test infusion demonstrated. (B) Proximal end of the fountain catheter.

TABLE 101.2 Therapeutic Infusion Systems

Company Name	Product Name	Sheath Size (Fr)	Guide Wire (inch)	Working Length (cm)	Mode of Operation	U.S. FDA Indicated Use
AngioDynamics	Pulse Spray	3, 4, 5 (catheter size)	0.018, 0.035	45, 90, 135 (catheter length); 2, 5, 10, 20, 30, 40, 50 (infusion pattern working length)	Patented pressure response outlet technology and occluding ball wire provides even distribution of lytic	Intended for use in the administration of fluids, including thrombolytic agents and contrast media, into the peripheral vasculature
AngioDynamics	SpeedLyser Infusion System	5 (catheter size)	0.018	15, 20, 25 (catheter length); 10, 15, 20 (infusion pattern working length)	Patented pressure response	Intended for use in the outlet technology and administration of fluids, occluding system provides including thrombolytic agents even distribution of lytic and contrast media, into the peripheral vasculature
AngioDynamics	Unifuse Infusion Catheter	4, 5 (catheter size)	0.035	45, 90, 135 (catheter length); 2, 5, 10, 15, 20, 30, 40, 50 (infusion pattern working length)	Patented pressure response outlet technology and occluding ball wire provides even distribution of lytic	Intended for use in the administration of fluids, including thrombolytic agents and contrast media, into the peripheral vasculature
Medtronic	Cragg-McNamara Valved Infusion Catheter	4, 5	0.035, 0.038	40, 65, 100, 135	Catheters with radiopaque markers proximal and distal to the infusion segments; Cragg-MicroValve at the distal tip provides endhole occlusion	Indicated for use in the controlled selective infusion of physician-specific pharmacologic agents or radiopaque contrast media in the general vasculature
Medtronic	MicroMewi Infusion Catheter With Multiple Side Holes	2.9	0.018	150, 180	Catheters with radiopaque markers proximal and distal to the infusion segment; 5 and 10-cm infusion lengths for comprehensive infusion	Indicated for use in the controlled selective infusion of physician-specific pharmacologic agents or radiopaque contrast media in the general vasculature

Continued

TABLE 101.2 Therapeutic Infusion Systems—cont'd

Company Name	Product Name	Sheath Size (Fr)	Guide Wire (inch)	Working Length (cm)	Mode of Operation	U.S. FDA Indicated Use
Medtronic	ProStream Infusion Wire	—	0.035	145, 175	Constructed with an integral core wire, stainless steel coil, and an outer Teflon layer for placement without a separate guide wire	Indicated for use in the controlled selective infusion of physician-specific pharmacologic agents or radiopaque contrast media in the general vasculature
Merit Medical Systems, Inc.	Fountain Infusion Catheter With Squirt Fluid Dispensing System	4, 5	—	45, 90, 135	Fluid delivery system with consistent, forceful, pulsed injections for optimal thrombolysis procedures	Intended to administer infusions of various therapeutic solutions into the peripheral vasculature of a patient
Merit Medical Systems, Inc.	Fountain Occluding Wire	4, 5	—	45, 90, 135	Can be used for slow, continuous, or pulse infusion	Intended to administer infusions of various therapeutic solutions into the peripheral vasculature of a patient
Merit Medical Systems, Inc.	Mistique Infusion Catheter	5	0.035	45, 90, 135	Can be used for slow, continuous, or pulse infusion	Intended to administer infusions of various therapeutic solutions into the peripheral vasculature of a patient
ThermopeutiX, Inc.	TAPAS Targeted Adjustable Drug Delivery System	7	0.014	15-300 mm (adjustable)	Dual occlusive balloon technology to target, deliver, dwell, and aspirate any drug or therapeutic agent	Intended for use in peripheral arteries 1.8 mm or larger for infusion of diagnostic or therapeutic agents
Translational Research Institute	ND Infusion Catheter	6	0.014	135	Expandable balloon to control blood flow during infusion through a multilumen spray tip	Intended to isolate a specific vascular treatment region from blood flow while allowing infusion of physician-specified fluids into the target region

U.S. FDA, United States Food and Drug Administration.
Please see Table 2—Therapeutic Infusion Systems PDF from Endovascular Today 2017 Buyers Guide US Edition, https://evtoday.com/buyers-guide

thrombolytic catheter to prevent thrombosis around the catheter. All patients are kept nothing by mouth and at bed rest in a critical care setting so they can be observed for clinical or laboratory evidence of local or systemic bleeding.

Results

In the 1990s three multicenter randomized trials were published comparing thrombolysis with operation for arterial occlusion (Table 101.3).[12–14]

The first trial, the Rochester study, randomly assigned 114 patients with acute limb-threatening ischemia to thrombolysis with urokinase (57 patients) or to immediate operation (57 patients).[12] At 1 year the amputation-free survival rates were 75% and 52%, respectively, a statistically significant difference. A closer analysis revealed this finding to be the result of a higher mortality rate in the operative group caused by perioperative cardiopulmonary complications. It appeared that taking patients with severe limb ischemia directly to operation without the opportunity for preparation resulted in a high frequency of complications that culminated in death.

The second large multicenter evaluation was the Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial.[13] In this study 393 patients were randomly assigned to surgery or to thrombolysis with either rtPA or urokinase. Clinical outcomes for the rtPA and urokinase groups were similar, so the data were combined for an overall comparison of thrombolysis and surgery. Post hoc stratification of patients into two subgroups on the basis of duration of symptoms before enrollment (more or less than 14 days) showed that among patients with symptoms of longer duration, the surgical group had lower amputation rates

TABLE 101.3 Outcome of Patients Treated With Initial Thrombolytic Therapy or Primary Operation for Acute Limb Ischemia

			THROMBOLYTIC THERAPY		PRIMARY	
Series	Number of Patients	Period (Months)	Amputation (%)	Death (%)	Amputation (%)	Death (%)
University of Rochester[9]	114	12	18	16	18	42
STILE Trial[13]	393	6	12	6.5	11	8.5
TOPAS Trial-II[14]	544	12	15	20	13.1	17

STILE, Surgery versus thrombolysis for ischemia of the lower extremity; *TOPAS*, thrombolysis or peripheral arterial surgery.

than did the thrombolysis group at 6 months (3% vs. 12%). In contrast, among patients with symptoms of shorter duration, patients assigned to thrombolysis had lower amputation rates than surgical patients (11% vs. 30%).

The third multicenter trial to evaluate thrombolytic therapy was the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial.[14] Recombinant urokinase (rUK) therapy (4000 IU/min for 4 hours, followed by 2000 IU/min) was compared with primary operation in 544 patients with lower extremity native artery or bypass graft occlusions of 14 days' duration or less. There was no significant difference in amputation-free survival rates or mortality rates between the two groups at the time of discharge from the hospital. Likewise, the amputation-free survival rates 6 months after randomization were not significantly different: 71.8% in the rUK group and 74.8% in the operative group. At the end of 6 months, 31.5% of the patients in the rUK group had avoided amputation or death without the need for anything more than a percutaneous procedure. By contrast, 94.2% of the patients who had had primary operation underwent open surgery, a rate that was not unexpected owing to the design of the trial. The median length of hospitalization was 10 days in both treatment groups. Among the patients assigned to thrombolysis, those with occlusions in bypass grafts had better clinical outcomes, better rates of clot dissolution, and lower rates of major hemorrhagic complications than did those with native artery occlusions.

In patients with ALI, CDT leads to resolution of thrombus with satisfactory clinical results in 75% to 92% of patients.[1] The factors that portend a higher likelihood of success are: (1) recent graft occlusion (<14 days), (2) guide wire traversal of the occluded graft, (3) graft patency of at least 1 year prior to the thrombotic event, and (4) the presence of a remediable lesion that may be treated. Factors associated with a poor outcome after thrombolysis include diabetes, current smoking, and prosthetic graft material. The reported 24-month vessel patency rate after thrombolysis for native arterial occlusions was 79% if an underlying lesion was identified and treated compared with 9.8% when no lesion was identified. For bypass graft thrombotic events, post-thrombolysis graft patency rates are between 10% and 40% at 2 years, making a case for replacement of a failed graft, especially if an anatomic lesion is not identified as an etiology of graft thrombosis.

Suffice it to say that there is not a "one-size-fits-all" standard of care for the initial treatment of ALI. Successful treatment depends on experience, judgment, skill, and the willingness to modify treatment based on evolving clinical information.

Complications

Hemorrhagic complications are the primary cause of morbidity following CDT. In the TOPAS trial, major hemorrhagic complications occurred in 32 patients (12.5%) in the rUK group, compared with 14 patients (5.5%) in the surgery group.[14] Patient age, duration of infusion, and aPTT at baseline were unrelated to the risk of bleeding. Intracranial hemorrhage occurred in four patients in the rUK group (1.6%), one of whom died. There were no instances of intracranial hemorrhage in the surgery group. The risk of bleeding was significantly greater when therapeutic heparin was used. In 102 patients who received therapeutic heparin, bleeding occurred in 19 patients (19%). By contrast, of the 150 patients in whom therapeutic heparin was not used, bleeding occurred in only 13 (9%). These data are the basis for the use of low-dose heparin infusions via the sheath, rather than therapeutic heparin dosing, in current protocols. Other complications include compartment syndrome after reperfusion, in 5% to 25% of patients, and acute renal insufficiency in up to 20% of patients.

Although not widely reported, distal embolization during CDT is commonly observed in real world practice. Symptoms may worsen or a distal Doppler ultrasound signal may be lost during the initial phase of lytic infusion. This is often managed by continued treatment with the thrombolytic agent and pain medication. More significant distal embolization that does not resolve in a few hours requires immediate arteriography, with the occasional need to reposition the catheter to a more distal location. The use of glycoprotein IIb/IIa inhibitors has been proposed as a mechanism to reduce distal embolization but does not appear to improve outcomes and may increase the risk of hemorrhagic side effects.[15]

Pharmacomechanical Thrombectomy

Several of the mechanical clot removal devices are intended to be used in conjunction with thrombolytic agents. Ultrasound energy (EkoSonic Endovascular System, BTG Corporation, Bothell, Washington) or "power pulse injection" (AngioJet, Boston Scientific, Marlborough, Massachusetts) are used to accelerate the speed of thrombolysis. The resultant decrease in

the dose of lytic agents and duration of thrombolysis has the potential to minimize the bleeding risk associated with standard CDT and to shorten the time to reperfusion.

EKOS EkoSonic Endovascular System

The EKOS Catheter (EKOS Corporation/BTG, Bothell, Washington) uses ultrasound to facilitate clot penetration by the lytic agent, thereby accelerating thrombolysis. The device consists of a 5.2 Fr multiple-lumen drug delivery catheter and a coaxial ultrasound core wire. The active treatment zone of the catheter is available in lengths from 6 to 50 cm; catheter selection is based on the length of the occlusion.

After the thrombus has been crossed with a standard 0.035-inch guide wire, the drug delivery catheter is placed over the guide wire. The guide wire is exchanged for the ultrasound core wire, which contains a series of transducer elements (2.2 MHz, 0.45 W) spaced approximately 1 cm apart. In addition to the guide wire (ultrasound core) lumen, the back end of the catheter has two additional ports—one for infusion of the lytic agent and the other for infusion of normal saline as a coolant. The ultrasound energy is delivered via the core wire simultaneously with the infusion of lytic agent and coolant. The EkoSonic system's control unit monitors the temperature and alters the ultrasound power to prevent overheating. Theoretically, maximal ultrasound power is reached with complete thrombus dissolution because the free flow of blood and coolant prevents the thermocouples from overheating. The control unit displays a continuous graph of the power generated, which may help to determine when the patient needs to have a recheck angiogram.

In preclinical studies, thrombus exposed to ultrasound absorbed 48% more tPA in 1 hour, 84% more in 2 hours, and 89% more in 4 hours than did thrombus not exposed to ultrasound.[16] This phenomenon is thought to be secondary to thrombus deformation by the ultrasound waves, which exposes a greater surface area to the infused lytic agent. The pharmacomechanical approach using the EkoSonic system decreases the procedure time and the amount of lytic used while increasing the clinical success rate to 90% in some studies.[17,18]

AngioJet Thrombectomy System

The AngioJet Thrombectomy System (Boston Scientific, Marlborough, Massachusetts) has been approved by the U.S. Food and Drug Administration for use in the peripheral arterial circulation. Of the mechanical thrombectomy devices available, the AngioJet has the longest clinical history.[5,19] With use of "power pulse-spray" mode, tPA is actively injected into the thrombus, allowed to dwell there for a short time (5 to 20 minutes), and aspirated, along with liquefying the thrombus. The AngioJet system has three major components: the catheter, pump set, and drive unit. The pump set and drive unit are responsible for producing a controlled, high-velocity saline jet (350 to 450 km/h) that is redirected at the tip of a dual-lumen catheter back into the effluent lumen of the catheter. The inflow lumen is a low-profile stainless steel tube that forms a transverse loop at the distal end of the catheter and has multiple 25- to 50-µm-diameter orifices directed retrograde toward the inflow lumen. Saline solution from the pump drive unit is driven at 50 to 60 mL/min and 8000 to 10,000 pounds per square inch, resulting in a high-velocity jet at the catheter tip. The velocity of the saline jets produces an area of extremely low pressure (Venturi effect) that is exposed to the intraarterial lumen only at the catheter tip. Thrombus surrounding the catheter tip is fragmented[20] and rapidly evacuated through the effluent lumen in an isovolumic manner (fluid instilled equals fluid and blood removed). Embolization and hemolysis are known complications of this technique. In addition, the use of this device can lead to bradyarrhythmias and renal insufficiency related to hemolysis.[21]

Percutaneous Mechanical Thrombectomy Without Thrombolysis

PMT devices can be classified as hydrodynamic, rotational/mechanical, or aspiration thrombectomy catheters (Table 101.4).

Hydrodynamic Devices

Percutaneously delivered devices can remove thrombus from the peripheral arteries through the use of a stream of fluid and hydrodynamic forces to extract the thrombotic material from the lumen.[20,21-23] The AngioJet system as described previously uses a dedicated fluid delivery machine to achieve thrombus removal without the use of adjunctive TPA.

Rotational/Mechanical Devices

A variety of "brushes," rotating wires, and mechanical thrombectomy devices that fragment thrombus with or without aspirating the fragments have been designed to establish arterial recanalization. This class of devices includes the Cleaner rotational thrombectomy system (Argon Medical, Plano, Texas) and the Arrow-Trerotola thrombectomy device (Teleflex Inc., Morrisville, North Carolina).[24-27] Although these devices have gained a foothold in the treatment of dialysis access graft occlusion, clinicians have been reluctant to use them in native arteries for fear of injuring the vessel wall. The Cleaner system has also been used for treatment of iliac and IVC deep venous thrombosis. Another potential limitation of this class of device involves the risk of distal embolization of macroparticles of thrombus. Currently none of these devices is routinely used in the management of peripheral arterial disease. A new class of retrievable stent thrombectomy devices such as the Stryker Trevo (Stryker, Kalamazoo, Michigan), the Medtronic Solitaire (Medtronic, Minneapolis, Minnesota), and the Revive thrombectomy device (Codman Neuro/Johnson and Johnson, Raynham, Massachusetts) have proven to be very effective in the treatment of acute thrombotic stroke by removing acute thrombus from the intracranial circulation. However, these devices have not been tested extensively in the peripheral arterial system.[28,29]

Thrombus Aspiration Devices

Percutaneous aspiration thrombectomy involves moving a catheter over a wire while aspirating thrombus with a large

Text continued on p. 1337

TABLE 101.4 Mechanical Thrombectomy/Thrombolysis Devices for Acute Limb Ischemia

Company Name	Product Name	Sheath Size (F)	Guide Wire (inch)	Working Length (cm)	Mode of Operation	U.S. FDA Indicated Use
Argon Medical Devices, Inc.	Cleaner 15	7	—	65, 135	Battery-operated, handheld drive unit initiates the mechanical rotation of an atraumatic, wall-contacting, 15-mm sinusoidal vortex wire for effective thrombus maceration	Indicated for mechanical declotting and controlled and selective infusion of physician-specified fluids, including thrombolytics, in the peripheral vasculature; also indicated for mechanical declotting of native vessel dialysis fistulas and synthetic dialysis access grafts
Argon Medical Devices, Inc.	Cleaner XT	6	—	65, 135	Battery-operated, handheld drive unit initiates the mechanical rotation of an atraumatic, wall-contacting, 9-mm sinusoidal vortex wire for effective thrombus maceration	Indicated for mechanical declotting and controlled and selective infusion of physician-specified fluids, including thrombolytics, in the peripheral vasculature; also indicated for mechanical declotting of native vessel dialysis fistulas and synthetic dialysis access grafts
Boston Scientific Corporation	AngioJet Solent Dista Thrombectomy Catheter	4	0.014	145	High-velocity water jets enclosed in catheter use the Bernoulli principle for capture, microfragmentation, and removal	Breaking apart and removing thrombus from upper and lower extremity peripheral diameter and for use with the AngioJet Ultra Power Pulse Kit for the control and selective infusion of physician specified fluids, including thrombolytic agents, into the peripheral vascular system
Boston Scientific Corporation	AngioJet Solent Omni Thrombectomy Catheter	6	0.035	120	High-velocity water jets enclosed in catheter use the Bernoulli principle for capture, microfragmentation, and removal	Breaking apart and removing thrombus from upper and lower extremity peripheral arteries diameter, and for use with the AngioJet Ultra Power Pulse Kit for the control and selective infusion of physician specified fluids, including thrombolytic agents, into the peripheral vascular system
Boston Scientific Corporation	AngioJet Solent Proxi Thrombectomy Catheter	6	0.035	90	High-velocity water jets enclosed in catheter use the Bernoulli principle for capture, microfragmentation, and removal	Breaking apart and removing thrombus from upper and lower extremity peripheral arteries, upper extremity peripheral veins, iliofemoral and lower extremity peripheral veins and for use with the AngioJet Ultra Power Pulse Kit for the control and selective infusion of physician specified fluids, including thrombolytic agents, into the peripheral vascular system
Boston Scientific Corporation	AngioJet Solent ZelanteDVT Thrombectomy Catheter	8	0.035	105	High-velocity water jets enclosed in catheter use the Bernoulli principle for capture, microfragmentation, and removal	Breaking apart and removing thrombus from upper and lower extremity peripheral veins, and iliofemoral veins greater than 6 mm in diameter and for use with the AngioJet Ultra Power Pulse Kit for the control and selective infusion of physician specified fluids, including thrombolytic agents, into the peripheral vascular system
Codman Neuro (Johnson & Johnson)	Revive PV Peripheral Vascular Thrombectomy Device	5 or larger	—	205	Mechanical thrombectomy with aspiration	The nonsurgical removal of emboli and thrombi from peripheral blood vessels
Control Medical Technology	Aspire Mechanical Thrombectomy Drive Unit	—	—	—	Mechanical thrombectomy drive unit, continuous and/or pulsed mechanical thrombectomy	A high-performance thrombectomy pump and drive unit to improve thrombectomy performance

Continued

TABLE 101.4 Mechanical Thrombectomy/Thrombolysis Devices for Acute Limb Ischemia—cont'd

Company Name	Product Name	Sheath Size (F)	Guide Wire (inch)	Working Length (cm)	Mode of Operation	U.S. FDA Indicated Use
Ekos Corporation, a BTG International group company	EkoSonic Endovascular System	6	0.035	106 catheter length; treatment areas: 6, 12, 18, 24, 30, 40, 50; 135 catheter length; treatment areas: 12, 30, 40, 50	The treatment offers a minimally invasive system for the acceleration of thrombus dissolution; the ultrasonic core generates a localized acoustic field that targets the entire thrombus; this greatly accelerates lytic dispersion by driving the drug deeper into the clot and unwinding the fibrin to expose plasminogen receptor sites	Indicated for the ultrasound-facilitated, controlled, and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism; the controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature; and the infusion of solutions into the pulmonary arteries; Instructions for Use, including warnings, precautions, potential complications, and contraindications can be found at www.btg-im.com/ekos; Caution: Federal (USA) law restricts these devices to sale by or on the order of a physician
Medtronic	Mindframe Capture LP Revascularization Device 3 × 15, 3 × 23, 4 × 15, 4 × 23	Balloon guide (8, 9)	0.010	Capture push wire (178)	Compatible with a catheter in the 10/14 class. It is designed to navigate, access, and treat distal zone occlusions, and has distal and proximal markers for accurate positioning and a proprietary cell geometry that minimizes deformation and maximizes entrapment	Indicated for endovascular temporary use in patients with acute ischemic stroke and to restore blood flow in patients who are experiencing symptoms of an acute ischemic stroke caused by an embolus in a cerebral vessel
Medtronic	Solitaire 2 Revascularization Device 4 × 15, 4 × 20, 4 × 40, 6 × 20, 6 × 30	Balloon guide (8, 9)	0.014	Solitaire push wire (180)	Designed to restore blood flow in patients experiencing ischemic stroke due to large intracranial vessel occlusion and for use in the neurovasculature, such as the internal carotid artery, M1 and M2 segments of the middle cerebral artery, basilar, and the vertebral arteries	Indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received IV tPA; endovascular therapy with the device should be started within 6 hours of symptom onset; indicated to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischemic stroke within 8 hours of symptom onset; patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment
Medtronic	Solitaire Platinum Revascularization Device 4 × 20, 4 × 40, 6 × 20	Balloon guide (8, 9)	0.014	Solitaire push wire (180)	Designed to restore blood flow in patients experiencing ischemic stroke due to large intracranial vessel occlusion and for use in the neurovasculature, such as the internal carotid artery, M1 and M2 segments of the middle cerebral artery, basilar, and the vertebral arteries	Indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received IV tPA; endovascular therapy with the device should be started within 6 hours of symptom onset; indicated to restore blood flow by removing thrombus from a large intracranial vessel in patients experiencing ischemic stroke within 8 hours of symptom onset; patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment

Penumbra, Inc. (Neurovascular)	3D Revascularization Device	6 (long sheath [Neuron MAX])	0.020	200 (delivery wire; compatible with Velocity Delivery microcatheter [160 cm] and 3MAX Reperfusion catheter [153 cm])	Designed to successfully treat large vessel occlusion in combination with Ace Reperfusion catheters; the architecture provides maximum clot capture capability through four intraluminal chambers and is optimized for use with aspiration delivered by Ace catheters	Indicated for use in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease (within the internal carotid and middle cerebral [M1 and M2 segments] within 8 hours of symptom onset; patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment
Penumbra, Inc. (Neurovascular)	Penumbra System Reperfusion Catheter ACE, 5MAX, 4MAX, 3MAX, 026	6 (ACE and 5MAX require 8 Fr short sheath or 6 Fr long sheath)	0.014-0.016	Reperfusion catheter lengths 132, 139, 150, 153	Direct aspiration clot removal with ADAPT technique	Intended for use in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease within 8 hours of symptom onset
Penumbra, Inc. (Neurovascular)	Penumbra System Separator and Separator Flex 5MAX, 4MAX, 3MAX, 026	—	—	Separator and Separator Flex length 175-200	Separator-assisted clot debulking, if needed	Intended for use in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease within 8 hours of symptom onset
Penumbra, Inc.	Indigo System Separator	—	—	90-190	The Indigo Separator is (Peripheral Vascular)	SEPD, SEP8, SEP6, advanced and retracted SEP5 and SEP3 through the CAT
Penumbra, Inc. (Peripheral Vascular)	Indigo System Catheter CATD, CAT8, CAT6, CAT5, and CAT3	CATD (8 Fr Sheath), CAT8 (8 Fr sheath), CAT6, CAT5 (6 Fr sheath)	0.014-0.038	50-150	Separator-assisted mechanical extraction of thrombus/debris with constant vacuum aspiration. Available in a selection of sizes, the CAT family can provide access to distal peripheral vessels of the upper and lower extremities, including below the knee catheter at the proximal margin of the primary occlusion to facilitate clearing of the thrombus from the catheter tip Intended for the removal of fresh, soft emboli, and thrombi from vessels of the peripheral arterial and venous systems	Intended for the removal of fresh, soft emboli, and thrombi from vessels of the peripheral arterial and venous systems

Continued

TABLE 101.4 Mechanical Thrombectomy/Thrombolysis Devices for Acute Limb Ischemia—cont'd

Company Name	Product Name	Sheath Size (F)	Guide Wire (inch)	Working Length (cm)	Mode of Operation	U.S. FDA Indicated Use
Stryker	Trevo XP ProVue Retriever 3 × 20 mm, 4 × 20 mm, 4 × 30 mm, 6 × 25 mm	BGC (8, 9)	0.014	TrevoPro 18 microcatheter 150-cm effective length; Trevo XP delivery wire 180 cm	Mechanical thrombectomy; Trevo XP ProVue Retriever is the fourth-generation stent retriever; tubular with 360 degrees of large cells, Trevo XP is designed to integrate and capture clot; it is also fully visible under fluoroscopy to allow the physician visual placement and strut interaction with the clot	Indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received IV tPA; endovascular therapy with the device should start within 6 hours of symptom onset; intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset; patients who are ineligible for IV tPA or who fail IV tPA therapy are candidates for treatment
Teleflex	Arrow-Trerotola OTW		0.025	65, 120	Battery-operated PTD handheld unit rotates unique 9-mm fragmentation basket at 3,000 rpm, macerating clot to < 2 mm; basket can be deployed/withdrawn within catheter; deployed basket can be used to pull arterial plug Permits mechanical declotting of native arterio/venous fistula synthetic dialysis grafts in conjunction with the Arrow Rotator Drive Unit (PT-03000-R)	
Teleflex	Arrow-Trerotola PTD	5	—	65	Battery-operated handheld unit rotates unique 9-mm fragmentation basket at 3,000 rpm, macerating clot to < 2 mm; basket can be deployed/withdrawn within the catheter; deployed basket can be used to pull the arterial plug	Permits mechanical declotting of native arterio/venous fistula and synthetic dialysis grafts in conjunction with the Arrow Rotator Drive Unit (PT-03000-R)
Walk Vascular, LLC	Jeti	8	OTW: 0.010-0.038 or none	100	Internal saline jet just to break up and remove within the catheter tip thrombus and soft and aspiration emboli	

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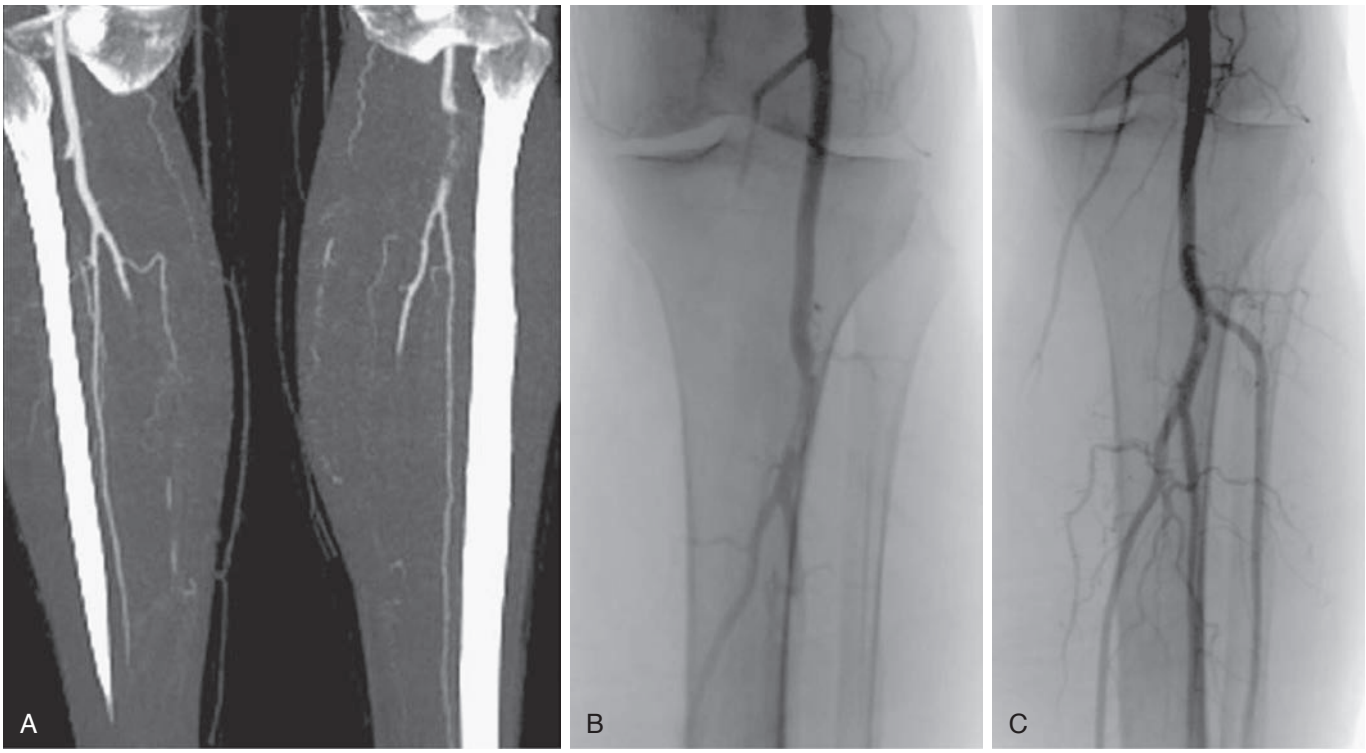

Figure 101.2 Preoperative computed tomography angiogram (A) and digital subtraction arteriogram (B) showing thrombus in the tibioperoneal trunk. (C) Completion arteriogram showing clearance of the thrombus after percutaneous aspiration.

syringe. This technique has been used more frequently in the coronary system to retrieve thrombus. The size of thrombus fragments that can be removed with this device is limited by the distal diameter of the catheter tip (Fig. 101.2).

This technique has been very useful when small amounts of fresh thrombus are identified in the distal circulation or to treat embolization after recent angioplasty, particularly when combined with the use of low-dose tPA. However, this technique has a low success rate when used as stand-alone therapy.[30] A list of currently available catheters and their sizes is provided in Table 101.5. More recently Penumbra, Inc. has developed a line of neurovascular aspiration catheters for the treatment of acute stroke and have now begun to promote a series of larger-diameter Indigo System catheters, which are designed to remove fresh peripheral thrombi.[31]

Results

The ability of percutaneous devices to rapidly restore arterial perfusion is an attractive addition to pharmacologic thrombolysis alone. In patients with significant ischemia that precludes the obligatory delay associated with pharmacologic thrombolysis, percutaneous thrombectomy devices may rapidly clear a channel through the occluded segment. Partial reperfusion of the extremity may provide enough improvement to allow complete removal of thrombus with thrombolytic infusions thereafter. Initial thrombus debulking may also significantly reduce the dose and duration of thrombolytic agents, thereby decreasing the risk of hemorrhagic complications associated with pharmacologic thrombolysis.[5,19,22,32,] Finally, the devices may be used as sole therapy in patients with contraindications to thrombolytic administration, such as those who have recently undergone major surgical procedures.

It appears unlikely that mechanical thrombectomy devices will completely eliminate the need for pharmacologic thrombolysis or open surgery.[19,22,31] In all but one clinical report,[23] a significant number of patients required adjunctive thrombolytic therapy for complete thrombus removal. However, the advantage of mechanical devices lies in the ability to rapidly debulk the thrombus (Fig. 101.3), significantly reducing the duration of ischemia and increasing the exposure of the residual thrombus and distal vessels to pharmacologic thrombolytic agents. The reductions in dose and in time needed to achieve complete thrombolysis may result in considerable cost savings and fewer bleeding complications.[14]

In patients with contraindications to pharmacologic thrombolysis and at high risk with open surgery, mechanical thrombectomy may represent the best therapeutic option. Braithwaite et al.[31] managed 15 patients with ALI due to infirmity or surgical or thrombolytic contraindications with anticoagulation alone, resulting in dismal 30-day limb salvage and mortality rates of 33% and 60%, respectively.

Kasirajan et al.[33] compared patients with ALI treated with the AngioJet catheter with historic controls treated with standard open surgical techniques. The 65 patients in the AngioJet group received stand-alone treatment ($n = 21$) or subsequent adjunctive pharmacologic thrombolysis ($n = 44$). They were compared with 79 patients who underwent open surgical revascularization. No difference was noted in the 1-month amputation rate (11%

TABLE 101.5 Thrombus Aspiration Devices

Company Name	Product Name	Type	Maximum Tip Diameter (mm)	Minimum Guide Catheter Size (Fr)	Catheter Length (cm)
Control Medical Technology	Aspire Max 5 Mechanical Thrombectomy System	5 Fr braided large-lumen OTW	1.65	6	55, 135
Control Medical Technology	Aspire Max 6 Mechanical Thrombectomy System	6 Fr braided large-lumen OTW	1.91	7	55, 135
Control Medical Technology	Aspire RX-LP6 Mechanical Thrombectomy System	Rapid-exchange low-profile system	1.7	6	136
Getinge	Xpress-Way RX Extraction Catheter	7 Fr, kink-resistant shaft design, hydrophilic coating, preloaded stylet, short guidewire lumen for improved deliverability and performance	1.52	7	140
Getinge	Xpress-Way RX Extraction Catheter	6 Fr, low-profile tip, resistant shaft design, hydrophilic coating, preloaded stylet, short guidewire lumen for improved deliverability and performance	1.35	6	140
Medtronic	Diver CE Aspiration Catheter	Low-profile, rapid-exchange, hydrophilic coating with and without side holes	1.58	6	145
Medtronic	Export AP Catheter	Full-wall variable hub to tip braiding; hydrophilic coating; short, soft tip	1.73	6	140
Medtronic	Export Catheter	Guide catheter braid technology	1.73, 1.98	6, 7	145
Medtronic	Export XT Catheter	Full-wall variable hub to tip braiding; hydrophilic coating; short, soft tip	1.73	6	140
Merit Medical Systems, Inc.	Asap Aspiration Catheter Kit	Manual aspiration catheter and kit	1.73	6	140 Catheter length (cm)
Spectranetics, a Philips company	QuickCat Extraction Catheter	Ideal for removal of fresh, soft emboli and thrombi from vessels in the arterial system	1.4	6	145
Teleflex	Pronto .035 Extraction Catheter	Large-vessel thrombus aspiration catheter; full-length braided shaft; patented Silva tip	3.25	10 (sheath)	115
Teleflex	Pronto LP 5 Fr Extraction Catheter	Low-profile; hydrophilic coating; patented Silva tip; delivery stylet; 5 Fr guide catheter compatibility	1.35	5	138
Teleflex	Pronto LP Extraction Catheter	Low-profile; hydrophilic coating; patented Silva tip; round, braided shaft; delivery stylet	1.35	6	140
Teleflex	Pronto V3 Extraction Catheter	Full-length braided shaft; hydrophilic coating; patented Silva tip; maximized extraction lumen and force	1.65	6	140
Teleflex	Pronto V4 Extraction Catheter	Embedded longitudinal wire; hydrophilic coating; patented Silva tip; maximized extraction lumen and force	1.64-2.2	6-8	138
Terumo Interventional Systems	Priority One Aspiration Catheter	Fully braided stainless steel shaft with guidewire-style stylet for better deliverability	1.65, 1.9	6, 7	140

U.S. FDA, United States Food and Drug Administration.

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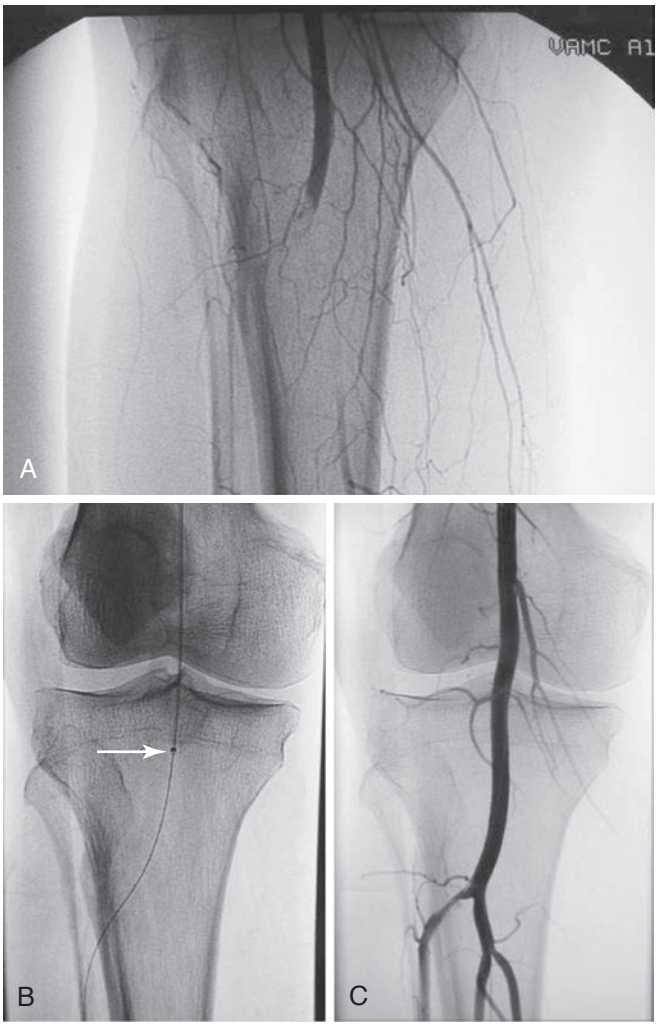

Figure 101.3 (A) Acute popliteal artery embolization. (B) AngioJet catheter advanced over a guide wire (Boston Scientific, Marlborough, Massachusetts) *(arrow)* used to aspirate the embolic debris. (C) Complete thrombus resolution following thrombectomy.

vs. 14%; $P = .57$); however, a lower rate of early mortality was observed in the AngioJet group (7.7% vs. 22%; $P = .037$). A lower rate of local ($P = .002$) and systemic ($P < .001$) complications was observed for the AngioJet treatment group.

The EKOS Infusion Catheter has also been investigated as an option for treating ALI. In a series of 25 patients presenting with ALI and undergoing treatment with the EKOS total clot removal was achieved in 22 (88%) after 16.9 hours (range, 5 to 24 hours) using a mean dosage of 17 mg (range, 5 to 25 mg) rtPA. In eight patients, total clot removal of the main lesion was achieved after 6 hours with 6 mg of rtPA.[6] A prospective randomized study comparing the EKOS system with standard CDT, the Dutch Randomized Trial (DUET), included 32 patients randomized to standard thrombolysis and 28 randomized to ultrasound-accelerated thrombolysis. Although the time to achieve complete lysis and the overall lytic dose were significantly less in the ultrasound-accelerated thrombolysis group, there was no difference in technical success, 30-day death or serious adverse events and no difference in 30-day patency.[34] Fig. 101.4 demonstrates a successful EKOS thrombolysis case.

Complications

With any mechanical thrombectomy device, there is always the possibility of inducing distal embolization as the device is passed through the thrombus. The use of distal filters typically used in the carotid circulation has been suggested as one possible solution but seem cumbersome and ineffective at this time. The efficacy of the thrombectomy devices are also limited by the diameter of the cylindrical "core" of thrombus that can be extracted with each pass of the catheter—a property dependent on the size of the device. A larger size device might remove more thrombus but would also increase the risk of trauma to the arterial wall. Thus the size limitation must be balanced by the convenience of placing the device through a relatively small-bore sheath, as well as by the greater safety associated with the use of a smaller device in the tibial vessels. Another limitation of current devices is the amount of potential red blood cell damage. Hemolysis with hemoglobinemia and hemoglobinuria can occur, especially with repeated passes of the device. Finally, volume overload can develop if one does not carefully monitor the volume of intravascular irrigation instilled. Despite these theoretical limitations, fluid overload and hemolysis have not proven to be problems in preliminary clinical trials.[20,22,32,35]

In vitro studies comparing endothelial denudation with the AngioJet and the Fogarty thrombectomy catheter have demonstrated significantly greater mean endothelial loss in vessels treated with the Fogarty balloon catheter (58.0% vs. 88.0%).[24] Particulate embolization was uncommon, and 99.83% of particles were smaller than 100 µm. Hemolysis equivalent to that resulting from lysis of 75 mL of blood was seen after a standard pump run, but no elevation in blood urea nitrogen or creatinine was noted.[24]

SURGICAL REVASCULARIZATION

Balloon catheter thrombectomy, first introduced by Fogarty et al.[36] in 1963, has been the cornerstone of therapy for the surgical management of ALI.[37] Severe ALI (class IIb), manifested by both sensory and motor deficits, requires urgent intervention, and surgical therapy has remained the treatment of choice. With the increasing availability of hybrid operating rooms, surgeons can now perform diagnostic imaging, endovascular intervention, open surgical revascularization, and hybrid procedures in single settings.

Techniques

Techniques for salvage of an ischemic limb include: (1) balloon catheter thrombectomy or embolectomy, (2) bypass procedures to direct blood flow beyond the occlusion, (3) endarterectomy with or without patch angioplasty, and (4) hybrid procedures combining open and endovascular techniques.

Balloon Catheter Thrombectomy or Embolectomy

Balloon thrombectomy is routinely used to deal with an embolic event or chronic graft thrombosis. The technique involves direct cutdown over either the common femoral artery or the brachial

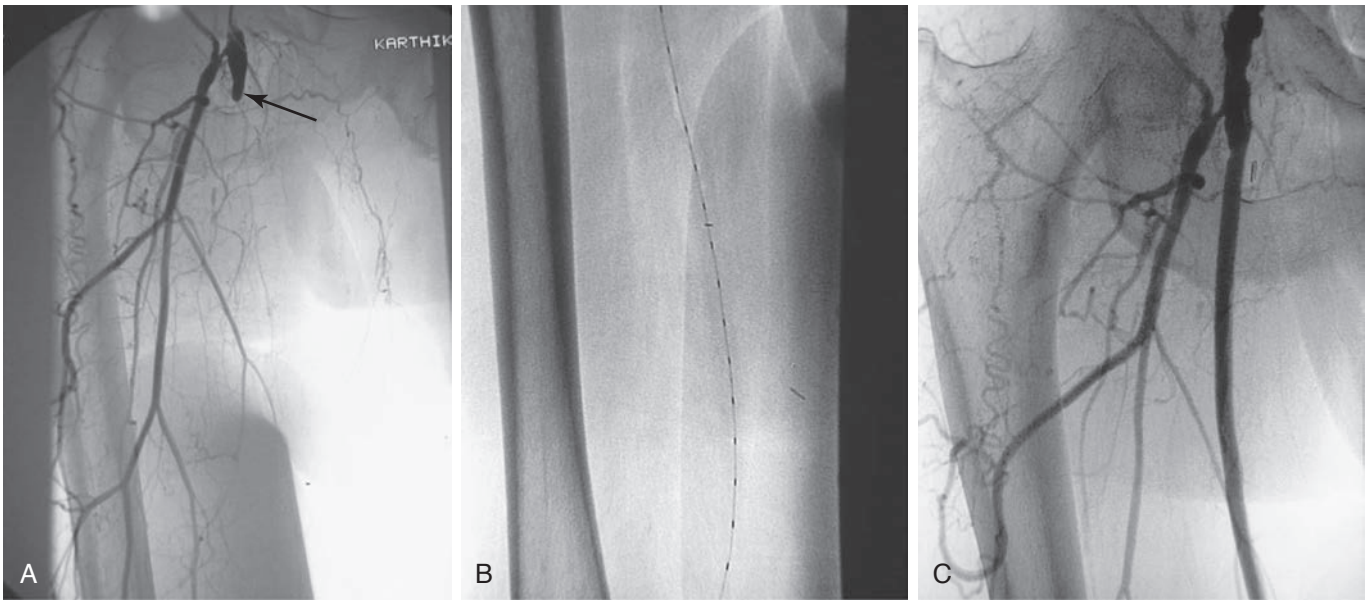

Figure 101.4 (A) Patient with a right femoropopliteal artery graft occlusion *(arrow)*. (B) EKOS ultrasound catheter (EKOS Corporation, Bothell, Washington) placed in the femoropopliteal graft. (C) After 8 hours of lytic infusion, complete thrombus resolution is noted.

artery with proximal and distal control of the major branches. A transverse arteriotomy is performed immediately proximal to the common femoral artery or brachial artery bifurcation to allow for direct visualization of the distal branches, with the ability to directly pass an appropriate-sized embolectomy catheter into those branches. A longitudinal arteriotomy is made when there is concern that endarterectomy with patch angioplasty closure will be required. Balloon embolectomy catheters are passed proximally and distally until no visible thrombus is removed and a pulse or backflow is established. Completion angiography is important to evaluate the effectiveness of thrombus removal. Over-the-wire embolectomy catheters may also be used to direct the embolectomy catheter into the tibial branches. Fig. 101.5 demonstrates the treatment of a patient with acute-on-chronic arterial ischemia who presented with a threatened limb. Initial attempts at open thrombectomy from a femoral approach failed, and subsequent attempts at over-the-wire embolectomy were also unsuccessful. Due to the chronic-appearing nature of the thrombus on angiogram, the decision was made to explore the below-knee popliteal artery directly. An arteriotomy at the popliteal artery and tibioperoneal trunk revealed chronic thrombus. Thromboendarterectomy of the tibioperoneal trunk was performed with patch angioplasty closure using bovine pericardium. A common femoral artery to tibioperoneal trunk bypass graft with reversed saphenous vein was then placed for limb salvage.

Bypass Procedures

Bypass procedures are more commonly performed in patients with known peripheral arterial disease or after failed open balloon thrombectomy. Proximal and distal targets are evaluated by intraprocedural arteriography. If the clinical scenario permits, a preoperative angiogram from a contralateral femoral approach provides the best guide to open intervention. The ideal bypass conduit is an ipsilateral single-segment saphenous vein of adequate caliber (>3 mm). Otherwise, the contralateral saphenous vein, arm veins, or lesser saphenous vein is preferred if below-knee revascularization is required. For above-knee revascularization, synthetic grafts can be used.

Endarterectomy

Endarterectomy is uncommonly used for limbs with ALI but may be performed for in situ occlusion of the common femoral artery. After arteriographic confirmation of occlusion of the common femoral artery, the target vessel is usually approached via a longitudinal groin incision. The common femoral, deep femoral, and proximal superficial femoral arteries should be adequately exposed and controlled. Atherosclerotic plaque often extends into the superficial femoral and profundal femoris orifices. Distal endpoints that extend into the superficial femoral or profundal femoris artery may require tacking sutures. To prevent narrowing of the common femoral artery, we use bovine pericardium for patch angioplasty closure of the femoral artery.

Results

Although improvements in open surgical technique have diminished the rate of limb loss associated with ALI, the mortality rate remains unacceptably high (Table 101.6).[5] In fact, patient survival has not changed dramatically since the report by Blaisdell et al.[38] more than 30 years ago, with mortality as high as 25%. The discordance between limb salvage and patient survival is explained by the specific factors controlling the two events. Death occurs as a result of medical comorbidities and the fragile baseline medical state of patients presenting with ALI, whereas limb loss is related to an unsuccessful revascularization procedure.

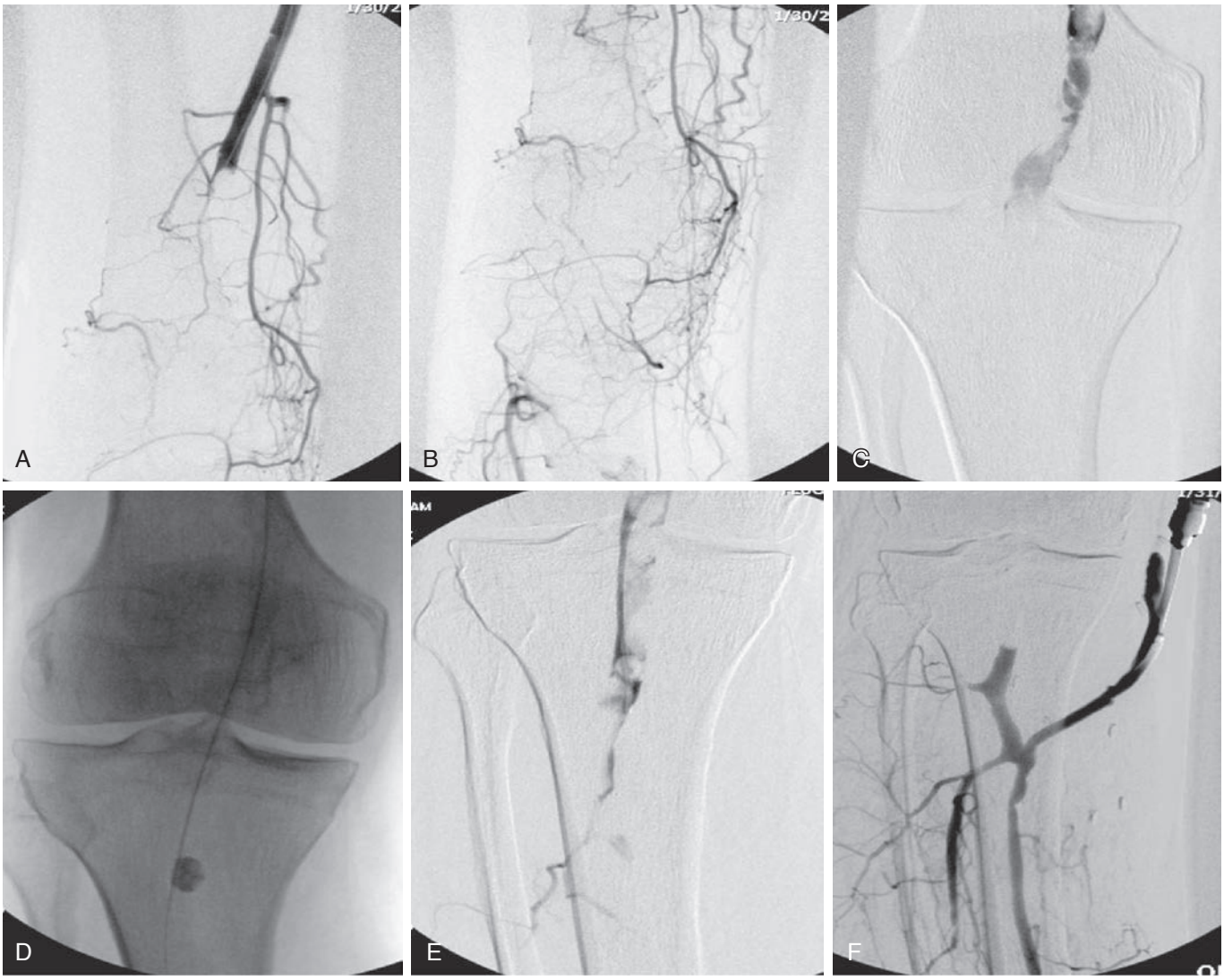

Figure 101.5 Thrombus is visualized at the superficial femoral artery (A) with occlusion of the popliteal artery (B). After embolectomy, residual thrombus was present (C). Over-the-wire thrombectomy was performed (D) with persistent popliteal artery thrombus (E). This finding necessitated a salvage bypass from the common femoral artery to the tibioperoneal trunk after endarterectomy and patch angioplasty of the distal target artery (F).

TABLE 101.6 Amputation, Mortality, and Long-Term Limb Salvage for Open Surgery for Acute Limb Ischemia

			RESULTS		
Series	Year	Number of Patients	Amputation (%)	Mortality (%)	Limb Salvage
Campbell et al.[6]	1998	474	16	22	Not reported
Nypaver et al.[7]	1998	71	7	10	62% at 1 year
Pemberton et al.[8]	1999	107	12	25	75% at 2 years

As such, the rate of amputation has diminished over the decades, presumably because of improvements in surgical technique. Unfortunately, the ability to rapidly restore arterial flow to the extremity with an operative procedure represents a significant insult to a medically compromised patient—one that all too frequently culminates in the patient's death.

SPECIAL CONSIDERATIONS

Myoglobinuria

Myoglobinuria is not uncommon after the treatment of ALI. It can be a significant problem in patients with preexisting renal

insufficiency and in patients who have received large volumes of iodinated contrast agents. Hemoglobinuria can be commonly seen after the use of some PMT devices such as the AngioJet, which cause lysis of red blood cells. Hemoglobinuria may also induce acute kidney injury. The incidence of hemoglobinuria with the AngioJet device appears to be correlated with treatment times exceeding 10 minutes and infusion volumes exceeding 300 mL. Patients with any of these risk factors are monitored for myoglobinuria, hemoglobinuria, and oliguria. A urine output of more than 100 mL/h is maintained. Alkalization of the urine is achieved by the addition of sodium bicarbonate to intravenous fluids. Acute renal failure may require temporary dialysis until the kidney function improves.

Fasciotomy

Compartment syndrome is most commonly seen in patients who have undergone open surgical revascularization and in those treated with PMT devices, owing to the speed of revascularization. Fasciotomy for compartment syndrome is less frequently required in patients undergoing CDT because of the more gradual resolution of ALI. Any patient with early motor changes (Rutherford class IIb or III) should undergo fasciotomy after open surgical revascularization or successful PMT. Further details regarding the diagnosis and treatment of compartment syndrome and indications for fasciotomy can be found in Chapter 102.

Pediatric Population

Currently, there are few studies relating to the management of ALI in the pediatric population, even though catheters are known to be responsible for more than 80% of venous-acquired and 90% of arterial-acquired thrombotic complications in children. Symptomatic secondary thromboembolic complications develop in approximately 2.4 per 1000 patients admitted to the neonatal intensive care unit, although asymptomatic catheter-related thrombi occur more frequently, on the basis of post mortem (3% to 59% of cases) and angiographic studies (10% to 90% of cases).[39]

The use of thrombectomy catheters, thrombolytics, and combinations of these approaches has been extensively reported in the adult literature. In the pediatric population, although rare reported cases exist, there are no studies supporting the use of these techniques. The writers of one report believe that a combination of CDT and percutaneous aspiration and/or mechanical thrombectomy, when feasible, may improve results in the treatment of ALI in children. Repeated interventions were necessary to improve results. In their five cases, the writers were able to resolve small proximal clots, but they were not able to reach distal clots if complete occlusions were present, especially in the absence of collateral circulation. On the basis of this limited report, it appears that aggressive management is warranted because tissue salvage was achieved in those five cases, even when initial gangrenous changes were present.[40]

UPPER LIMB ISCHEMIA

There are a number of significant differences between acute ischemia of the arm and that of the leg. Patients with acute arm ischemia tend to be, on average, approximately 4 years older than those with acute leg ischemia (mean age, 74 years). Arm ischemia is seldom limb threatening, and treatment decisions are usually less urgent.[41,42] The main reason for treating arm ischemia is to prevent late complications such as exercise-induced arm fatigue and pain.[43] Most arm ischemia is due to cardiac embolism. Rare causes of arm emboli include thoracic outlet syndrome and proximal subclavian artery aneurysm. Atherosclerosis is rare in upper limb arteries, and collateral vessels usually prevent ALI when atherosclerosis is present.

Patients with upper limb ischemia often present with a cold feeling and numbness, rather than pain in the arm. The diagnosis of ALI in the upper extremity is clinical and can be confirmed by duplex ultrasonography. The arm often improves after initial anticoagulation, and decisions about whether to perform embolectomy can be difficult. Up to 50% of patients have late symptoms of arm pain if untreated. Consequently, there should be a low threshold to undertake embolectomy if there is doubt about limb viability.[43] A small number of patients present with class IIb critical ischemia and require urgent surgical intervention.[42] In our practice these are often patients who have experienced arterial embolization due to a proximal subclavian artery aneurysm related to ongoing thoracic outlet syndrome. Failed surgery in this situation risks ischemic contracture or even arm amputation on occasion. The threat to the arm is generally low, but up to 20% of patients with acute arm ischemia do not survive the acute event, usually owing to cardiac complications.[44] As with acute leg ischemia, there is a high attrition rate after successful treatment; only 60% of patients survived 3 to 5 years in one typical series.[44]

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One of the first large, randomized trials comparing open surgery to CDT. Failure of CDT was thought to be primarily due to the duration of ischemia, and many patients were treated for chronic limb ischemia (6 months' duration) with this technique. Currently, most physicians limit the use of CDT for symptoms of less than 2 weeks' duration. Additionally, the dose of tPA used in the STILE study is rarely administered with a cautious approach to systemic anticoagulation.

Rutherford RB, Baker DJ, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517–538.

Establishes guidelines for reporting on limb ischemia to facilitate a more universal practice pattern.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 102

Compartment Syndrome and Its Management

J. GREGORY MODRALL

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INTRODUCTION

Compartment syndrome is a surgical emergency and a recognized complication of several conditions treated by vascular surgeons. Failure to arrive at a timely diagnosis increases the risk of short- and long-term morbidity, including limb loss or permanent disability. Conversely, appropriate recognition and management of a compartment syndrome will optimize the chances of a full recovery. This chapter will address the pathogenesis, diagnosis, and treatment of compartment syndrome of the lower leg and other less common anatomic sites. Abdominal compartment syndrome is discussed in Chapter 183.

Abstract

Compartment syndrome is a surgical emergency and a recognized complication of several conditions treated by vascular surgeons. Early recognition and prompt treatment are critical to minimizing the risk of severe morbidity, including limb loss.

Typical symptoms include pain with passive motion of the muscles traversing the compartment, paresis or paresthesias referable to the compartment, or a tense compartment. Compartment syndrome is a clinical diagnosis, but measurement of intracompartmental pressures (ICP) may aid in decision-making. The most appropriate ICP criteria are ICP minus mean blood pressure < 40 mm Hg or ICP minus diastolic blood pressure < 10 mm Hg. This chapter includes descriptions of the surgical technique for fasciotomy of the lower leg and other less common anatomic sites for compartment syndrome.

Keywords

Compartment syndrome
fasciotomy
intracompartmental pressure

PATHOGENESIS OF COMPARTMENT SYNDROME

Local Hemodynamics of Compartment Syndrome

The unifying feature of all compartment syndromes, regardless of etiology or anatomic location, is an increase in intracompartmental pressure (ICP) within an unyielding fascial envelope that impairs tissue perfusion.[1] The adverse consequence of elevated ICP on tissue perfusion may be understood by applying Poiseuille's law ($F = \pi r^4 \Delta P/8\eta L$) to capillary blood blow within a muscle compartment. In this equation, F represents capillary blood flow, r is the radius of the capillary to the fourth power, and ΔP is the pressure gradient from the precapillary arteriole to the postcapillary venule. Increasing ICP alters two variables in this equation, ΔP and R. As ICP rises, pressure is transmitted to the postcapillary venules, increasing the venous pressure and decreasing the arterial-venous pressure gradient (ΔP). Furthermore, increased ICP may collapse capillaries, decreasing their radius and further increasing resistance to flow.[1,2]

Compartment Pressures

Several theories exploring the role of ICP in the development of compartment syndrome have been proposed. The concept of a critical closing pressure was one of the earliest concepts, whereas more recent research suggests that the dynamic ICP threshold more accurately predicts which muscle compartments will develop compartment syndrome.

Critical Closing Pressure

Matsen suggested that there is a "critical closing pressure" above which capillaries collapse from transmural pressure and blood flow is arrested.[1] The pressure at which capillary blood flow ceases has been debated over the decades. Using vital microscopy to observe the response of isolated rat cremasteric muscle to increased external pressure, Hartsock found that a pressure gradient between the ICP and mean arterial pressure (MAP) of 25.5 ± 14 mm Hg arrested capillary blood flow. Hartsock saw no significant collapse of arterioles, capillaries, or venules.[3] This study and others disproved the "critical closing theory" proposed by Matsen, suggesting instead that the arterial-venous pressure gradient (ΔP) is the critical determinant of capillary blood flow.[1,3,4] This conclusion has direct implications for determining the threshold ICP that defines compartment syndrome.

Absolute Intracompartmental Pressure Threshold

Defining the threshold ICP that produces tissue injury and cell death is an important step in determining the pressure at which fasciotomy is advisable. Hargens found that an absolute ICP of 30 mm Hg for 8 hours universally produced muscle necrosis in normotensive dogs, whereas pressures less than 30 mm Hg produced no muscle necrosis.[5] Tissues differed in their susceptibility to increased ICPs. Early signs of endoneurial injury were observed at pressures of 30 mm Hg for 8 hours.[6,7] The differential susceptibility to injury between tissues may provide an explanation for those cases in which a delayed fasciotomy fails to restore full neurologic function despite viable muscle in the compartment.

Dynamic Intracompartmental Pressure Threshold

Defining compartment syndrome based on an absolute pressure threshold is appealing in its simplicity but ignores the role of arterial blood pressure in affecting compartmental blood flow. Changes in arterial pressure affect the arterial-venous pressure gradient (ΔP), altering compartment blood flow. Some authors have proposed defining compartment syndrome using a pressure threshold relative to MAP or diastolic pressure. Heppenstall found that healthy muscle in dogs developed evidence of tissue ischemia on[8] P-magnetic resonance spectroscopy when the difference between MAP and ICP (MAP – ICP) dropped below 30 mm Hg.[9] Injured muscle showed greater sensitivity to ischemia, as tissue ischemia became evident when the difference between MAP and ICP was less than 40 mm Hg ([MAP – ICP] < 40 mm Hg).

Heppenstall found that a dynamic pressure threshold (MAP – ICP) < 40 mm Hg, prevented unnecessary fasciotomy in a number of patients with absolute ICP exceeding 30 mm Hg.[9] Another study found that use of a dynamic ICP threshold of 30 mm Hg less than diastolic pressure prevented unnecessary fasciotomies in most patients.[10] Using the diastolic blood pressure as their reference point, Heckman observed a dramatic increase in tissue injury and necrosis when the difference between the diastolic blood pressure and ICP was less than 10 mm Hg in dogs.[11] These studies offer compelling evidence that a dynamic ICP threshold *relative to MAP or diastolic pressure* is more appropriate for selecting patients for fasciotomy.

CLINICAL ETIOLOGIES

Vascular Causes

ICP is elevated by conditions that either increase compartment volume or produce external compression on the compartment. The most common vascular etiologies for compartment syndrome are ischemia-reperfusion (IR) injury associated with acute ischemia, arterial and venous traumatic injuries, crush injuries, phlegmasia cerulea dolens, and hemorrhage within a compartment.

Ischemia-Reperfusion

The IR phenomenon, described in detail in Chapter 6, plays a central role in the pathogenesis of compartment syndrome due to acute ischemia and crush injury. IR increases compartment volume by causing muscle tissue injury, which leads to increased microvascular permeability with efflux of plasma proteins and progressive interstitial edema.[12] With reperfusion, oxygen radical generation exacerbates microvascular permeability and resulting interstitial edema.[12] Papalambros identified several risk factors for compartment syndrome after acute arterial ischemia, including prolonged ischemia time (>6 hours), young age, insufficient arterial collaterals, acute time course for arterial occlusion,

hypotension, and poor back-bleeding from the distal arterial tree at embolectomy.[13]

Trauma

Both arterial and venous trauma may produce compartment syndrome. Occlusive arterial injuries result in distal ischemia that initiates the IR phenomenon, whereas venous injuries may compromise venous outflow. The impact of compromised venous outflow is discussed next (Venous Outflow Obstruction). Fasciotomy rates vary according to the type of vascular injury, ranging from 29.5% for isolated arterial injuries, 15.2% for isolated venous injuries, and 31.6% for combined arterial and venous injuries. Injuries to the popliteal artery are notorious for a higher risk of compartment syndrome (61% incidence), compared with injuries above the knee (19% incidence).[14]

Venous Outflow Obstruction

Uncomplicated deep venous thrombosis (DVT) often increases ICP, depending on the extent of DVT.[15] Only when there is extensive, multilevel DVT with occlusion of venous collaterals is the venous outflow obstruction sufficient to increase ICP and produce compartment syndrome. With increased venous hypertension the arterial-venous pressure gradient (ΔP) is altered and capillary blood flow is impaired. With reduced capillary blood, muscle cell injury ensues, exacerbating tissue edema. This cycle continues until eventually the postcapillary venules thrombose and venous gangrene develops.

Hemorrhage

Hemorrhage may be a source of rapid increases in compartment pressure. Thigh compartment syndrome has been described as the presenting symptom for rupture of a popliteal artery aneurysm[16] or postoperative hemorrhage after joint replacement surgery in an anticoagulated patient.[17]

Nonvascular Etiologies

Fracture

Tibial or forearm fractures are the most common orthopedic causes of acute compartment syndrome. These fractures injure the surrounding muscles and cause bleeding within the compartment, elevating ICP. The incidence of compartment syndrome with fractures ranges from 1% to 29%.[10,18-20] The anterior compartment of the leg and the flexor compartment of the forearm are most prone to this phenomenon. Comminuted fractures are more likely to result in a compartment syndrome, owing to the greater energy absorbed in such injuries.[19]

Crush Injury

Crush injuries are another form of trauma that may cause compartment syndrome. Reported mechanisms include crushing by equipment at industrial sites or large building structures during earthquakes and blunt trauma due to assault.[21,22] Compartment syndrome after crush injury results from a combination of direct muscle injury and IR due to direct compartment pressure with underlying muscle ischemia and subsequent reperfusion upon removal of the external compressive force. Large-volume crystalloid resuscitation can exacerbate the increase in ICP.[21]

Iatrogenic

Iatrogenic causes of compartment syndrome include extravasation of large volumes of fluid within a muscle compartment, extravasation of caustic medications such as contrast agents, inadvertent arterial injections, and hemorrhage related to arterial or venous punctures in coagulopathic or anticoagulated patients.[23-25] Additional mechanisms include the compression injuries associated with prolonged intraoperative immobilization, as occurs in the dorsal lithotomy position, and cast immobilization for fractures.[26,27]

Secondary Compartment Syndrome

Rarely a compartment syndrome develops in a trauma patient without overt evidence of extremity trauma. This phenomenon has been termed "secondary compartment syndrome" and is believed to be a consequence of diffuse microvascular permeability due to trauma-induced systemic inflammatory response syndrome in concert with massive fluid resuscitation.[28]

CLINICAL PRESENTATION

History and Examination

The diagnosis of an acute compartment syndrome begins with a high index of suspicion. Symptoms of a compartment syndrome include pain that is disproportionate to the magnitude of the injury and paresthesias in the distal extremity.[8] The pain is typically not relieved by immobilization or reduction of fractures and responds poorly to analgesic medications. Paresthesias represent an early symptom of ischemia of the nerves traversing the muscle compartment in question.

On examination, the most common findings are a tense, swollen compartment with pain elicited by passive movement of the muscles in that compartment. A careful neurologic examination should document sensory and motor function distal to the compartment, focusing especially on the nerves that traverse the compartment at risk. For example, a compartment syndrome afflicting the anterior compartment of the lower leg may be accompanied by dysfunction of the deep peroneal nerve, causing numbness at the first dorsal webspace of the foot or inability to extend the great toe. Loss of two-point discrimination is a relatively sensitive indicator of developing compartment syndrome.[29] The overall sensitivity of exam findings for compartment syndrome is dubious. In a meta-analysis of compartment syndromes related to tibial fractures, Ulmer found that the sensitivity of clinical findings for diagnosing compartment syndrome is low (13% to 19%). The positive predictive value is equally low (11% to 15%), and the negative predictive value is high (97% to 98%). Ulmer concluded that the "clinical features of compartment syndrome are more useful in their absence in excluding the diagnosis."

Measurement of Compartment Pressures

Measurements of ICP are not required to ascertain the diagnosis of a compartment syndrome in most cases. Pressure measurement should be reserved for equivocal cases, unconscious patients, and pediatric patients in whom a compartment syndrome is suspected. In cases in which the diagnosis is apparent from history or examination, measuring ICP is superfluous and risks delaying definitive therapy.

Technique

Measuring ICP requires an instrument for measuring compartment pressures and a working knowledge of the muscle compartments. ICP has been measured using a host of techniques and instruments, including simple manometers, wick catheters, slit catheters, side-ported needles, and fiberoptic transducers. There are two components to each system: (1) a needle to access the compartment and (2) a pressure measurement system. The most commonly used ICP measuring systems are the arterial line manometer and handheld Stryker system. The arterial line manometer is ideally suited for use in the intensive care unit and operating room where pressure transducers and monitors are readily available. In the emergency room the handheld Stryker system is particularly convenient.

The choice of compartments for pressure measurement should be guided by clinical exam. The most symptomatic or turgid compartment should be interrogated first, remembering that the anterior compartment of the lower leg and the flexor compartment of the forearm are most prone to compartment syndrome. Ultimately it is advisable to obtain compartment pressures from all compartments at risk. If necessary, multiple readings may be obtained. ICP, MAP, and diastolic pressure should be recorded for the medical record. The pressure criteria that define a compartment syndrome will be discussed later in this section. A normal compartment pressure is ≤10 to 12 mm Hg.

Unusual Presentations for Compartment Syndrome

Compartment syndrome may affect any myofascial compartment. Although less common than the lower leg, compartment syndromes have been described in the upper extremity, hand, thigh, foot, and buttock. For any of these compartment syndromes, pain out of proportion to examination and swelling remain the hallmarks of their clinical presentation. In some cases, pain with passive motion may exacerbate the pain. The presence of neurologic symptoms is highly variable and is not required to secure the diagnosis.

Hand compartment syndromes are usually associated with crush injuries or fractures of the carpal bones. Hand compartment syndrome may affect any of the 10 compartments of the hand. The classic symptoms are pain and local paralysis at the intrinsic muscles.[30] Forearm compartment syndromes are typically associated with direct blows, crush injuries, or fractures.[31] Pain, swelling, and neurologic symptoms are the classic symptoms of increased ICP in the forearm, especially after trauma.[31]

Thigh compartment syndrome is usually caused by blunt trauma from motor vehicle accidents, contusion,[32] or crush injury.[21] Reperfusion injury rarely results in a compartment syndrome of the thigh. The anterior thigh compartment is most commonly involved and universally presents with pain on passive motion. Paresthesias and paralysis may also be present.[32]

Gluteal compartment syndrome has been associated with hypogastric artery ligation or embolization during aortic aneurysm repair, hip arthroplasty, and prolonged compression during operative procedures.[33-36] Gluteal compartment syndrome has been cited as a cause of rhabdomyolysis, renal failure, and sciatic nerve palsy.[33]

ADJUNCTIVE MEASURES

Prevention of Compartment Syndrome

A variety of adjuncts have been proposed to mitigate muscle swelling and prevent compartment syndrome. The most common approach has been pharmacologic therapy to blunt oxygen radical formation during reperfusion of an ischemic limb to minimize IR injury. Mannitol, allopurinol, superoxide dismutase, deferoxamine, thromboxane A_2, and melatonin have shown promise in reducing oxygen radical formation and ICP in animal models.[37-41] The use of these agents in humans has been limited to anecdotal reports.[42,43]

In cases of impending compartment syndrome, Mars[44] proposed a protocol of "first aid to hypoxic cells." Mars' protocol included: (1) maintaining normal blood pressure because hypotension reduces perfusion pressure; (2) removing any constricting bandages; (3) maintaining the limb at heart level (with no elevation) to avoid reducing the arterial-venous pressure gradient; and (4) supplemental oxygen to optimize oxygen saturation.

Prevention of Systemic Sequelae

Myonecrosis associated with compartment syndrome may liberate intracellular potassium, phosphate, myoglobin, and creatine phosphokinase (CPK). Treatments designed to prevent systemic sequelae of compartment syndrome are aimed at preventing further complications related to the electrolyte disturbances or myoglobinuria that result from extensive myonecrosis.

Hyperkalemia

Hyperkalemia with cardiac arrest has been described among patients with significant myonecrosis, especially among patients with crush injuries.[21,22] Aggressive pharmacologic interventions, even hemodialysis or continuous hemofiltration, may be required to control severe hyperkalemia.[45]

Myoglobinuria

Myoglobinuria exerts its nephrotoxic effects by inducing renal vasoconstriction, tubular cast formation, and direct heme protein–induced cytotoxicity.[45] The management of myoglobinuria includes aggressive crystalloid infusion, forced diuresis

with mannitol, and alkalinization of the urine with bicarbonate. The rationale for crystalloid and bicarbonate infusion is based on the observation that heme proteins have minimal nephrotoxicity in the absence of hypovolemia and aciduria.[45] Clinical data affirm that early resuscitation with crystalloid diminishes the risk of progression to acute renal failure.[21,22,45] The data in support of mannitol and bicarbonate are more circumstantial. In a review of 1771 patients with acute renal failure due to myoglobinuria, Brown and colleagues found no difference in the incidence of acute renal failure, need for dialysis, or mortality between patients receiving mannitol and bicarbonate, compared with those receiving crystalloid infusion alone.[46] Current recommendations for the management of myoglobinuria include hydration with a goal urine pH of greater than 6.5, despite the fact that the use of sodium bicarbonate has not been shown to be superior to saline diuresis.[47]

Myoglobin is poorly cleared by conventional dialysis membranes due to its relatively large molecular weight (17,000 Da), so hemodialysis is not a useful adjunct in preventing renal injury due to myoglobinuria, although continuous venovenous hemofiltration has shown promise in preliminary studies.[48] Renal replacement therapy is currently reserved for standard indications, including the management of severe hyperkalemia.[47]

FASCIOTOMY

Criteria for Fasciotomy

The decision to proceed to fasciotomy may be dictated on clinical grounds or by ICP measurements (Table 102.1).

Clinical Criteria

Clinical criteria for fasciotomy include a swollen, tense compartment, pain with passive motion of muscle groups traversing that compartment, and neurologic findings referable to the compartment. Not all of these criteria are required to proceed to fasciotomy. The presence of a turgid compartment with either of the other two criteria (pain with passive muscle movement, neurologic changes) is sufficient to warrant fasciotomy. Any neurologic finding referable to a tense compartment is an absolute indication for expeditious fasciotomy because nerve injury is ongoing. The presence of a tense compartment alone places the limb in an equivocal category for which fasciotomy or continued serial examinations are options. Patients who are obtunded or require other operations are poor candidates for serial examination, making fasciotomy the best option. If serial examinations are pursued, they must be performed by an experienced surgeon. In equivocal cases, ICP measurement may assist in decision-making.

An important consideration is the likely evolution of muscle swelling over the next several hours. In an equivocal case in which additional muscle swelling is inevitable, a "prophylactic" fasciotomy may be prudent. Scenarios in which prophylactic fasciotomy may be reasonable include acute ischemia exceeding 6 hours, especially if there is inadequate collateral flow, and combined arterial and venous traumatic injuries.[13,49-51]

TABLE 102.1 Indications for Fasciotomy

Absolute Indications	Potential Indications
• Tense compartment *plus either*: • Pain with passive motion of muscles traversing the same compartment *or* • Paresis or paresthesias referable to the same compartment • Tense compartment in a patient who cannot be examined serially due to obtundation or need for other operations • ICP minus mean blood pressure <40 mm Hg • ICP minus diastolic blood pressure <10 mm Hg	• Acute ischemia >6 h with few collaterals • Combined arterial and venous traumatic injuries • Phlegmasia cerulea dolens • Tense compartment after crush injury • Tense compartment after fracture

ICP, Intracompartmental pressures.

Intracompartmental Pressure Measurements

The threshold ICP for the diagnosis of compartment syndrome remains controversial, but the data favor the use of a dynamic ICP threshold related to MAP or diastolic pressure.[9,11,10] Fasciotomy is warranted if the difference between the ICP and MAP falls to less than 40 mm Hg or the difference in ICP and diastolic pressure is less than 10 mm Hg.

Contraindications to Fasciotomy

Fasciotomy is contraindicated when the extremity is nonviable, due to extensive traumatic or ischemic injury. Crush injuries, in particular, may result in life-threatening complications from reperfusion because of the magnitude of the electrolyte shifts that result from reperfusion of ischemic muscle after fasciotomy.[21]

TECHNIQUE OF FASCIOTOMY

Fasciotomy is the only known treatment for acute compartment syndrome. Performing an adequate fasciotomy is critical to complete decompression of a compartment syndrome. Poor technique may lead to incomplete decompression or injury to anatomic structures within the compartment. Technical details and relevant anatomy for fasciotomy are outlined in this section.

Lower Extremity Technique

Lower Leg

Anatomic Considerations

The lower leg is the most common site for compartment syndrome. The lower leg is subdivided into four anatomic compartments: anterior, lateral, superficial posterior, and deep posterior compartments. The most commonly injured nerve during a fasciotomy of the lower leg is the superficial peroneal nerve, which branches from the common peroneal nerve at or below the proximal fibular head and descends in the lateral compartment along the intermuscular septum separating the anterior and lateral compartments.[52]

Skin Incisions

The length of the skin incisions is critical to ensuring that complete decompression of the compartments is achieved. Jensen et al. found that 12% of subcutaneous fasciotomies, using minimal incisions, had incomplete decompression requiring reoperation to extend the skin incision.[8] Jensen and Sandermann hypothesized that the skin itself could prevent adequate decompression of the compartment syndrome. Cohen noted that a skin incision of 8 cm decreased the mean ICP in the anterior compartment of the lower leg from 48 to 25 mm Hg; however, one-third of patients had compartment pressures that remained elevated. Full decompression of all compartments of the lower leg required incisions 12 to 20 cm in length.[53] Some authors have advocated using limited incisions when the muscle swelling is expected to be minimal, reserving extensive open incisions for cases in which the muscle swelling is dramatic.[54] Unfortunately it is often difficult to predict the extent of postoperative swelling that will evolve postoperatively.

Double-Incision Technique

The double-incision technique (Fig. 102.1) for lower leg fasciotomy involves a generous longitudinal incision on the lateral aspect of the lower leg between the fibular shaft and the crest of the tibia. The incision is oriented directly over the intermuscular septum between the anterior and lateral compartments, approximately 4 cm lateral to the crest of the tibia. Skin flaps are then raised medially and laterally to expose the fascia of the anterior and lateral compartments. The intermuscular septum between these compartments must be identified clearly to ensure that both compartments are thoroughly decompressed. The anterior and lateral compartments are opened via separate, parallel 12 to 20 cm fascial incisions using Metzenbaum or Cooley scissors, taking care to sufficiently elevate the posterior blade of the scissors off of the muscle to avoid injury to the common, superficial, and deep peroneal nerves. These nerves are most at risk of injury near the fibular head, so it is advisable to terminate the proximal extent of these fascial incisions 4 to 5 cm distal to the fibular head. A second incision is placed on the medial aspect of the leg 1 to 2 cm posterior to the tibia for decompression of the two posterior compartments. The saphenous vein and nerve should be avoided in the subcutaneous tissue. The superficial posterior compartment is decompressed via a longitudinal incision along the gastrocnemius fascia. The deep posterior compartment is decompressed by dividing the attachments of the soleus muscle to the tibia, exposing the fascia overlying the tibialis posterior and flexor muscles of the foot. This fascia is then incised longitudinally, avoiding injury to the posterior tibial artery. The advantage of the two-incision technique is its relative simplicity, allowing rapid decompression of the four compartments of the lower leg.[55]

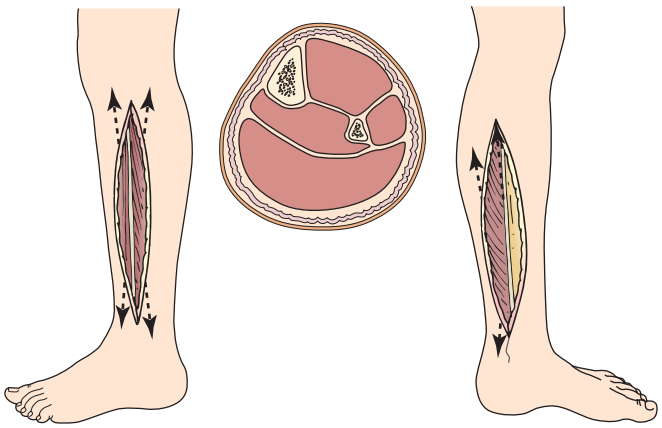

Figure 102.1 Double-incision fasciotomy of the lower leg.

Single-Incision Technique

The single-incision technique (Fig. 102.2) involves a lateral incision over the fibula from the fibular neck to 3 or 4 cm above the lateral malleolus.[56] A subcutaneous flap is developed in an anterior direction to access the anterior and lateral compartments. These compartments are decompressed using the same technique outlined previously for these compartments *(Double-Incision Technique)*. A posterior subcutaneous flap is developed to access the superficial posterior compartment for a longitudinal fascial incision. The interval between the lateral and superficial posterior compartments is exposed. The flexor hallucis longus muscle is identified and dissected off of the fibula in a subperiosteal plane. The peroneal vessels should be displaced posteriorly to avoid injury to these structures during the subperiosteal dissection. The fascial attachment of the posterior tibial muscle to the fibula is incision to open the deep posterior compartment. Most surgeons no longer perform a fibulectomy. The primary advantage of the one-incision approach is the ability to decompress all four compartments through a single-incision, but it is a relatively tedious approach to fasciotomy with a potential for injury to the peroneal artery and nerve. Most vascular surgeons now favor the double-incision technique.

Thigh

The thigh contains three compartments: anterior, posterior, and medial. The anterior compartment contains the sartorius and quadriceps muscles (rectus femoris, vastus lateralis, vastus intermedius, and vastus medialis). It receives its innervation from the femoral nerve. The posterior compartment contains the biceps femoris, semimembranous, and semitendinous muscles. The sciatic nerve innervates this compartment. The medial compartment contains the pectineus, obturator externus, gracilis, and adductor muscles (longus, brevis, magnus, and minimus). The obdurator nerve innervates the medial compartment.[57]

In most cases a single lateral incision may be used to decompress the posterior and anterior compartments (Fig. 102.3), whereas the medial compartment rarely requires decompression.[58] An incision is placed along the lateral thigh, beginning just distal to the intertrochanteric line and extending distally to the lateral epicondyle. The iliotibial band is exposed and incised longitudinally along the length of the skin incision to decompress the anterior compartment. The vastus lateralis is reflected medially to expose the lateral intermuscular septum. The intermuscular septum is incised over the length of the skin incision to release the posterior compartment. The medial compartment pressure

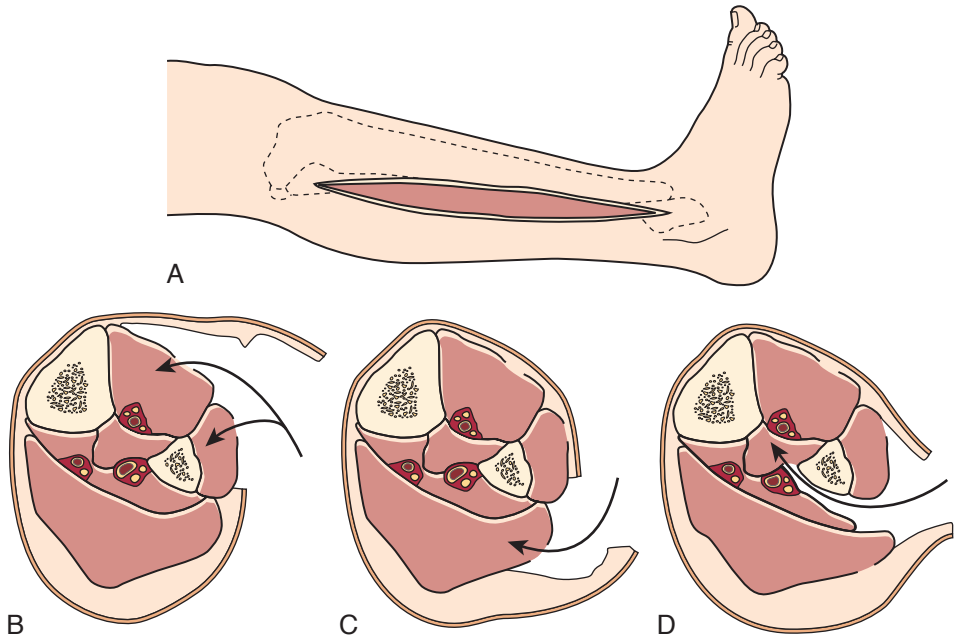

Figure 102.2 Single-incision fasciotomy of the lower leg. **A,** Lateral skin incision from the fibular neck to 3 to 4 cm proximal to the lateral malleolus. **B,** The skin is undermined anteriorly, and a fasciotomy of the anterior and lateral compartments is performed. **C,** The skin is undermined posteriorly, and a fasciotomy of the superficial posterior compartment is performed. **D,** An interval between the superficial posterior and lateral compartments is developed. The flexor hallucis longus muscle is dissected subperiosteally off the fibula and retracted posteromedially. The fascial attachment of the posterior tibial muscle to the fibula is incised to decompress the muscle. (From Davey JR, Rorabeck CH, Fowler PJ. The tibialis posterior muscle compartment: an unrecognized cause of exertional compartment syndrome. *Am J Sports Med* 12:391-397, 1984.)

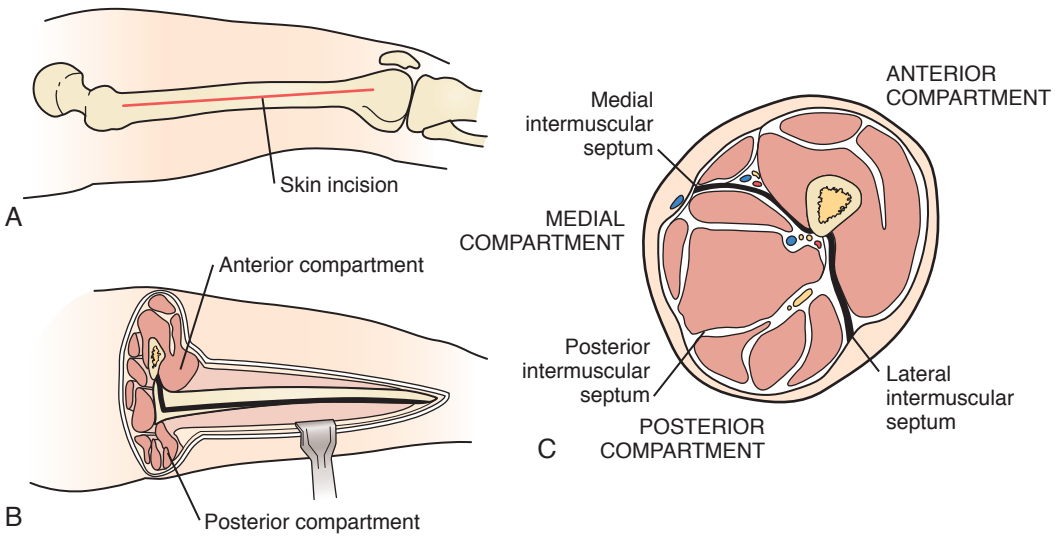

Figure 102.3 Fasciotomy of the thigh. **A,** The incision extends from the intertrochanteric line to the lateral epicondyle. **B,** The anterior compartment is opened by incising the fascia lata. The vastus lateralis is retracted medially to expose the lateral intermuscular septum, which is incised to decompress the posterior compartment. **C,** Thigh compartments and appropriate incision. (A and B, redrawn from Tarlow SD, Achterman CA, Hayhurst J, et al: Acute compartment syndrome in the thigh complicating fracture of the femur: a report of three cases, *J Bone Joint Surg Am* 68:1439, 1986.)

should be measured. Decompression of the medial compartment is rarely necessary, although a separate incision over the adductor muscle group will decompress this compartment.

Buttock

The buttock is composed of three major muscles, each with its own fascial compartment. There is no universally accepted standard incision for a buttock fasciotomy. However, a longitudinal incision is most frequently described in case series. Each of the muscle compartments requires decompression for a complete fasciotomy. Some authors have also recommended performing neurolysis of the sciatic nerve to prevent tension on the nerve from inflammatory adhesions.[59]

Foot

Currently, there is variability to the number of compartments ascribed to the foot. The most frequently named compartments are medial, lateral, superficial, and calcaneal compartments, with an additional compartment corresponding to each interosseous muscle.[60,61] Decompression of the foot is required infrequently and most commonly associated with crush injuries.[62] Two longitudinal dorsal incisions are fashioned. The first incision is oriented along the medial aspect of the second metatarsal, and the second incision is placed at the lateral margin of the fourth metatarsal bone. A separate incision is required to decompress the calcaneal compartment. Through these incisions, each of the muscle compartments can be incised, typically with fine scissors. Care must be taken to avoid the medial and lateral plantar neurovascular bundles that traverse the longitudinal axis of the foot.[62,63]

Upper Extremity

Forearm

The forearm is the most frequent site of compartment syndrome in the upper extremity. Within the forearm, there are volar (flexor, superficial, and deep), lateral (mobile wad), and the extensor (dorsal, superficial, and deep) compartments. The volar, or Henry, fasciotomy (Fig. 102.4) uses a single incision to decompress both the lateral and volar compartments.[29,64] A curvilinear incision begins proximal to the antecubital fossa, medial to the biceps tendon, crosses the antecubital crease, and extends to the radial side of the forearm where is extends distally along the medial border of the brachioradialis muscle. From the distal forearm the incision extends across the carpal tunnel along the thenar crease. The fascia overlying the superficial flexor compartment is incised along the entire length of skin incision. The radial nerve and brachioradialis muscle are retracted to the radial side of the forearm, and the flexor carpi radialis and radial artery are retracted to the ulnar side. The fascia overlying each of the muscles of the deep flexor compartment are incised to complete the volar fasciotomy. If the dorsal ICP is elevated, a long incision from the lateral epicondyle to the wrist is used to perform a fasciotomy between the extensor carpi radialis brevis and the extensor digitorum communis.[29] Carpal tunnel releases are controversial and may not be of benefit in isolated forearm compartment syndromes.[64]

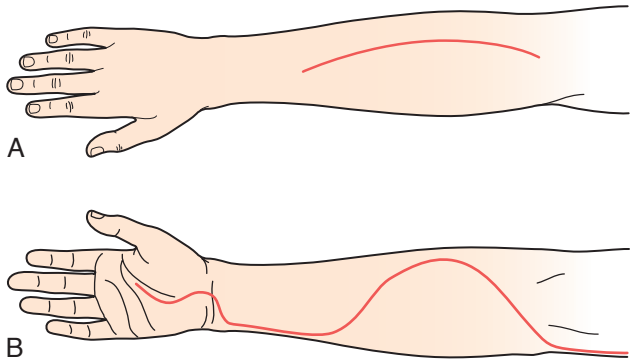

Figure 102.4 Fasciotomy of the volar forearm for severe Volkmann's contracture. **A,** Extensive opening of the fascia of the dorsum of the forearm for dorsal compartment syndromes. **B,** Incision used for anterior forearm compartment syndromes. The skin and underlying fascia are released completely throughout.

Hand

The hand is a rare location for compartment syndrome. There are 10 compartments of the hand: hypothenar, thenar, and adductor pollicis compartments; four dorsal interosseous compartments; and three volar interosseous compartments. The number of compartments in the hand complicates decision-making in performing a fasciotomy of the hand. The choice of fasciotomies for the hand should be tailored to symptoms.[23] All patients should have a carpal tunnel release, and most will require one to two dorsal interosseous fasciotomies. Many patients will also require thenar or hypothenar fasciotomy. All dorsal hand fasciotomies should be performed through longitudinal hand incisions.

FASCIOTOMY WOUND MANAGEMENT

Fasciotomy may solve the problem of increased ICP, but resulting wounds may be a source of considerable short- and long-term morbidity.[65,66] The goal of wound care early after fasciotomy is preventing further muscle injury or necrosis until muscle swelling subsides sufficiently to permit closure. When muscle viability is questionable, periodic saline dressings permit caregivers the opportunity to inspect and debride the wound at regular intervals. Vacuum-assisted closure (VAC) therapy is an alternative means of wound coverage, although the wound should be inspected at frequent intervals early after fasciotomy. After tissue viability is ensured and wound swelling has subsided, the priority shifts to wound closure.

Fasciotomy wound closure has been attained through a variety of approaches. The options include delayed primary closure, closure by secondary intention, gradual dermal apposition, split-thickness skin grafting (STSG), and myocutaneous flap coverage. Each of these approaches has a role, depending on the clinical circumstances. Delayed primary closure offers the simplicity of direct closure but should be reserved for those cases in which muscle swelling is minimal or nonexistent. Wiger found that 7 of 12 fasciotomy wounds had increased ICP

(>30 mm Hg) with attempted delayed primary closure on postoperative days 3 or 4, so early closure should be undertaken with caution.[67] Closure by secondary intention should be reserved for cases in which the patient is either medically or nutritionally ill-suited for any other option because this approach is the least expeditious in achieving wound closure. The addition of VAC therapy accelerates the process of closure by secondary intention and has been used with success for fasciotomy wounds.[68-70] To accelerate closure further, various forms of gradual dermal apposition have been advocated, including progressive closure with silastic vessel loops or cutaneous sutures placed at surgery or commercially available products.[71-75] Anecdotal reports have documented success with each approach.[72] Finally, several authors have proposed closure of fasciotomy wounds using STSG.[13,31,37,65,76] Myocutaneous flap coverage is generally reserved for coverage of neurovascular structures or exposed bone in a limb that remains functional. Early closure may decrease the rate of wound complications associated with closure by secondary intention and truncate the length of hospital stay.[13,65]

OUTCOMES

Early Outcomes

The mortality rate for patients undergoing calf fasciotomy ranges from 11% to 15%.[8,77,78] Major amputations are required in 5% to 21% of limbs.[8,77,78] Wound complications occur in 4% to 38% of patients.[65,66,77] Wound complications are more frequent if fasciotomy is delayed more than 6 hours (37%), compared with early fasciotomy (25%).[31,67,79] Renal failure is a rare complication after compartment syndrome, unless there is considerable myonecrosis.[45] Neurologic deficits occur in 7% to 36% of limbs[77,78,80] and are the most frequent early complications following a forearm fasciotomy.[31]

Late Outcomes

The late outcomes for fasciotomy are determined largely by the functional status of the patient at hospital discharge. Neurologic deficits or amputation in the early postoperative period are harbingers of long-term disability. Even in the subset of patients discharged without amputation or neurologic deficits, a fasciotomy predisposes the limb to future problems. Fitzgerald and colleagues noted at late follow-up that 77% of fasciotomy sites were associated with impaired sensation at the margins of the wound, 7% had tethered tendons, and 13% had recurrent ulcerations at the fasciotomy site.[81] Bermudez and colleagues[82] found that a significant proportion of patients (47%) had clinical evidence of chronic venous insufficiency after lower leg fasciotomy due to impaired calf muscle pump function. A small subset (7.5%) of patients will require late amputation (between 30 days and 1 year).[78,83]

Sequelae of Missed Compartment Syndrome

A delayed or missed compartment syndrome will have devastating consequences for the patient and the limb, increasing the risk of neurologic deficit, amputation, and renal failure. Sheridan and colleagues found that the overall complication rate increased dramatically if fasciotomy was delayed more than 12 hours (54%), compared with early fasciotomies (4.5%).[76] Nearly half of the patients with delayed fasciotomies required amputation and 92% had a significant neuropathy.[76] Not surprisingly, delay of fasciotomy for more than 36 hours almost invariably results in amputation. After 3 to 4 days, compartment syndrome is not indicated since the rate of infection and muscle necrosis is prohibitively high.

The classic late consequence of a missed compartment syndrome is a Volkmann contracture. In this state the ischemic muscle and nerve tissue are replaced by fibrosis, leaving the compartment firm, contracted, and dysfunctional.[84] Adjacent joints become stiff and immobile. Treatment consists of contracture and joint capsule release.[85] Orthopedic consultation for immediate- and long-term management is advisable.

CHRONIC EXERTIONAL COMPARTMENT SYNDROME

Clinical Presentation and Diagnosis

Chronic exertional compartment syndrome (CECS) is a syndrome of exercise-induced pain and tightness that usually affects the muscles of the lower leg, especially the anterior and lateral compartments, due to increased ICP and transient muscle ischemia.[86-88] The typical patient is a young (20- to 30-year-old), athletic patient who is a runner.[86] The syndrome is characterized by pain beginning 20 to 30 minutes after the onset of exercise, which abates with 15 to 30 minutes of rest. Paresthesias and muscle dysfunction often occur in the distribution of peripheral nerves traversing the compartment. Symptoms are bilateral in 82%. Physical examination often shows tenderness of the affected muscle compartment.

The differential diagnosis includes fascial hernias, medial tibial syndrome (for anterior compartment symptoms), and claudication due to popliteal entrapment syndrome (for calf symptoms). Although MRI and other tests may rule out other causes of leg pain, measurement of ICP is required to secure the diagnosis. Pedowitz and colleagues established pressure criteria for the diagnosis: (1) resting ICP >15 mm Hg; (2) ICP >30 mm Hg, 1 to 2 minutes after completion of exercise; or (3) ICP >20 mm Hg, 5 minutes after completion of exercise.[89] One or more of these criteria are sufficient for the diagnosis with the characteristic symptoms that are reproducible on exercise.

Fasciotomy for Chronic Exertional Compartment Syndrome

Treatment for CECS is either avoidance of the precipitating exercises or surgical decompression of the affected compartment. Avoidance is poorly accepted by athletic patients, so fasciotomy is typically the treatment of choice. The approach to compartment decompression for CECS differs from treating acute

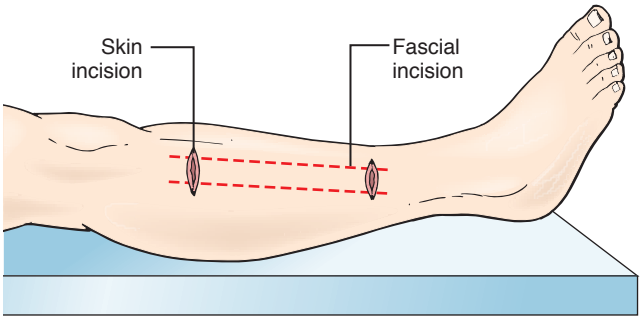

Figure 102.5 Fasciotomy of the anterior and lateral lower leg compartments for chronic exertional compartment syndrome.

compartment syndrome because only symptomatic compartments are decompressed. Both fasciotomy and fasciectomy have been proposed to decompress the symptomatic compartments. For subcutaneous fasciotomy (Fig. 102.5), two 2- to 4-cm transverse incisions are commonly used.[90] Both incisions are oriented over the intermuscular septum between the anterior and lateral compartments at the proximal and distal ends of the standard longitudinal fascial incisions of the anterior and lateral compartments. Two longitudinal fascial incisions are then performed between the two transverse skin incisions, akin to the fascial incisions used for a standard open fasciotomy (see *Double-Incision Technique*). For fasciectomy, a single longitudinal skin incision overlying the intermuscular septum between the anterior and lateral compartments is used. Two standard longitudinal fascial incisions are performed in the anterior and lateral compartments, followed by resection of a 2 × 6 cm ellipse of fascia. In his review of the treatment of 796 patients with CECS, Turnipseed advises fasciectomy as the treatment of choice in most cases of chronic compartment syndrome.[87]

Outcomes

Long-term results appear promising in case series, which describe significant reduction in pain at 2 years following anterior compartment fasciotomy in 83% of subjects.[90]

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 103

Atheromatous Embolization and Its Management

BAO-NGOC NGUYEN

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Atheromatous embolization is a poorly recognized and underdiagnosed multisystem disorder that is associated with high risk of all-cause and cardiovascular mortality.[1] There are a myriad of clinical manifestations that may occur across all specialties, making differential diagnoses broad and diagnosis difficult. In addition, atheromatous embolization is a confusing entity to many physicians because it is known by many different names: cholesterol embolization, cholesterol crystal embolization, blue toe syndrome, purple toe syndrome, atheroembolism, and pseudovasculitis. For the purposes of this chapter, these terms will be used interchangeably. After atheroembolism occurs, therapy involves three major strategies: treat the end organ that is undergoing embolization, prevent further embolization from occurring, and prevent future cardiovascular morbidity and mortality by risk factor modification. Therefore it is critical for clinicians to have a high index of suspicion and to recognize the clinical manifestations of this syndrome.

INCIDENCE

The prevalence of atheroembolism ranges from 0.18% to 2.4%, based on series of unselected autopsy studies.[2] However, in older patients with more severe atherosclerosis, the incidence is much higher, from 8.6% to 12.3%.[3,4] Autopsy studies performed in patients with known advanced atherosclerosis who have undergone cardiac or vascular surgical procedures before their deaths found 22% to 27% with evidence of atheroemboli.[5,6] Postmortem examination of patients who had abdominal aortic aneurysm resection found evidence of atheroembolism in 77% of this population.[7] In general, retrospective autopsy studies may overestimate the frequency of the disease because of the detection of subclinical cases and the selection bias inherent in obtaining information after necropsy. In contrast, clinically significant atheroembolic disease in clinical studies may be missed because of short-term follow-up. The prevalence of

atheroembolic disease in clinical studies has been estimated to be between 1% and 4%.[8-12] There are two factors that may be associated with either an increased prevalence of atheromatous embolization (the continuing increasing age of the population, and thus, more advanced atherosclerosis) or a decreased prevalence (better guide wires, catheters, and endovascular and surgical techniques). However, there have been no recent studies on current prevalence rates.

PATHOGENESIS

The first description of atheroembolism was published more than a century ago by the German pathologist, Panum. However, Flory[13] is credited for accurately describing the syndrome in 1945. Among 267 consecutive autopsies, he observed that the risk of atheroembolism is directly related to the severity of aortic atherosclerosis. There was no cholesterol crystal embolism when aortic ulceration was absent, 1.4% embolization with moderate aortic plaque erosion, and 12.8% with severe aortic plaque ulceration. The sources of atheroembolism are atherosclerotic plaques in large arteries such as the aorta, iliac, or carotid arteries which consist of a fibrous cap, under which are macrophages, necrotic debris, and cholesterol crystals. The vulnerable plaque, or the plaque at the highest risk of rupture, is the one with a thin fibrous cap surrounding a large lipid-rich core.[14] Plaque rupture caused by either spontaneous, traumatic, or iatrogenic maneuvers leads to embolization of cholesterol crystals, platelets, fibrin, and other detritus into arteries or arterioles and results in local mechanical obstruction, as well as an inflammatory reaction that contributes to end-organ ischemia and necrosis.[15]

Cholesterol crystals are white and rhomboidal or rectangular in shape. They can also be elongated, biconvex, and needle shaped, and range in size from 250 µm to less than 10 µm in diameter.[9] Because they are light in weight and hydrophobic, they pass quickly through blood vessels until they are stopped by arterial bifurcations, a narrowing of the vessel lumen, or when they reach the end of the arterial circulation.[9] Cholesterol crystals that lodge in the arterioles immediately incite an inflammatory response characterized by varying degrees of polymorphonuclear and eosinophilic infiltration.[9,13,16,17] By 2 to 4 weeks, a more chronic inflammatory infiltrate is seen where cholesterol crystals become embedded in multinucleated giant cells and smooth muscle cells.[16] Endothelial proliferation and fibrous tissue can be found surrounding the crystals, ultimately leading to luminal obliteration.[16,17] At 1 to 2 months, crystals may extrude out of the vessel lumen and be buried in the adventitia, or remain in the lumen, embedded within organized thrombus that may recanalize.[16] The crystals are resistant to breakdown by macrophages and have been shown to persist in tissue for up to 9 months.[18,19] Arterial lumina are eventually occluded by the accumulation of cells and fibrous material. These pathologic changes result in tissue effects distal to the cholesterol crystal emboli, including ischemia, and rarely, infarction, depending on the extent of organ involvement. This type of foreign body reaction is the reason it may take weeks to months for serum creatinine to rise in patients with atheroembolic renal disease and illustrates why renal function does not usually recover.[18,20-22]

RISK FACTORS

The major risk factor for atheromatous embolization is atherosclerosis of the thoracic and abdominal aorta.[23,24] Other risk factors include age (>60 years), coronary artery disease, peripheral arterial disease, and abdominal aortic aneurysms.[5,13,24] Patients with protruding mobile atheroma or aortic plaques greater than 4 mm in diameter have increased risk of embolic events.[25,26] Another feature that increases risk of atheroembolization is lack of plaque calcification.[24] It was hypothesized that the noncalcified plaques are probably lipid-laden plaques with a thin fibrous cap, which are unstable and prone to ulceration, rupture, and thrombosis.[27] Pedunculated, mobile plaques have also been associated with an increased risk of recurrent embolization (Table 103.1).[28-30]

Complex thoracic aortic plaques are not only valuable "markers" of severe widespread atherosclerosis[24,31] but also identify individuals at a high risk for cardiovascular disease such as peripheral arterial occlusive or coronary artery disease.[32] Although atheroembolism could occur spontaneously, precipitating factors are often invasive procedures that could potentially dislodge the plaques by mechanical trauma to the arterial wall either from endovascular intervention or from arterial clamping during cardiac/vascular surgeries.[8,33-37]

TABLE 103.1 Incidence of Events According to Plaque Thickness in the Aortic Arch Proximal to the Ostium of the Left Subclavian Artery

	RECURRENT BRAIN INFARCTION			ANY VASCULAR EVENT[a]		
Plaque Thickness (mm)	Person-Years of Follow-Up	Number of Events	Incidence Per 100 Person-Years of Follow-Up	Person-Years of Follow-Up	Number of Events	Incidence Per 100 Person-Years of Follow-Up
<1	359.3	10	2.8	354	21	5.9
1-3.9	312.6	11	3.5	308.2	28	9.1
≥4	92.4	11	11.9	88.4	23	26

[a]Includes brain infarction, myocardial infarction, peripheral embolism, and death from vascular causes.

From The French Study of Aortic Plaques in Stroke Group: Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. *N Engl J Med.* 1996;334:1216-1221.

Endovascular Procedures for Coronary and Peripheral Arterial Occlusive Disease

Endovascular intervention is now the most frequent precipitating cause of the atheromatous embolization syndrome.[20,21,38-40] Manipulation of the aorta with rigid catheters or guide wires and the force of contrast injection can cause mechanical trauma, consequently dislodging atheromatous material from the arterial wall.[41] Nevertheless, the most important factor determining risk remains the severity of the atherosclerotic disease in the aorta. The reported incidence of atheromatous embolization from cardiac catheterization is from 0.15% to 2%.[11,21] Clinically apparent cholesterol embolism, such as livedo pattern on the feet, blue toe syndrome, digital gangrene, or renal failure, was found in 1.4% of patients who underwent left heart catheterization.[42] As with coronary angiography, catheter manipulation of the aorta in endovascular procedures for noncoronary arterial occlusive disease is also a serious concern. Embolic protection devices used in both renal and carotid artery stenting procedures frequently retrieved visible atherosclerotic debris.[43-50] Although spontaneous cholesterol emboli occurred in only 4.3% of patients who did not undergo arteriography, those who had arteriography had up to 27% incidence of cholesterol embolization.[6]

Cardiac Surgery

Atheroembolization is a well-recognized complication of cardiac surgery and has profound medical and economic consequences. Doty et al.,[34] in a retrospective analysis of 18,402 patients who underwent cardiac surgery, found evidence of atheroembolism in 0.2% of patients at autopsy. The clinical presentation of atheroembolism in this study was broad and included five distinct organ systems: heart, central nervous system, gastrointestinal (GI) tract, kidneys, and the lower extremities. In 21% of these cases, death was directly attributable to atheroembolism.[34] Kolh et al.[51] documented a significant increase in intensive care unit stay, overall hospital stay, and total hospital cost in patients with documented atheroembolism after cardiac surgery.

Vascular Surgery

The effect of atheroembolism after major vascular surgery was first recognized by Thurlbeck et al. in 1957.[7] In their series, atheroembolism was present at autopsy in more than 75% of the patients who died after aortic aneurysm surgery. Atheromatous embolization was the cause of death or significantly contributed to mortality in nearly half of the patients in this series. Vascular surgery procedures may disrupt plaque when the vessel is manipulated, cross-clamped, or incised during surgery. Other vascular surgery procedures known to precipitate cholesterol embolization include aortoiliac and aortofemoral bypass, carotid endarterectomy, and renal artery revascularization.[11] In a retrospective series of 1011 patients who underwent infrarenal aortic surgery or infrainguinal surgery, the diagnosis of cholesterol embolization was 2.9%.[52] Due to the advent of better surgical techniques and an awareness of the risk of surgery precipitating atheromatous embolization, this complication has become much less common than reported in the older literature.[53]

Anticoagulation

An increased risk of cholesterol embolization with anticoagulation and clinical improvement when anticoagulation was removed has been reported in case reports for nearly half a century.[8,11] One hypothesis is that anticoagulation may prevent thrombus formation over unstable atherosclerotic plaque, thus allowing exposed cholesterol crystals to embolize. Another hypothesis is that these agents may initiate the disruption of a complex plaque by causing intraplaque hemorrhage.[54-57] Based on these small case series and case reports, some investigators have recommended that warfarin be discontinued, when feasible, in patients who have had an episode of cholesterol embolization for which no other precipitant can be identified.

However, the data are not entirely clear in assessing anticoagulation safety in patients with a large amount of aortic plaque. The assumption that anticoagulation precipitates cholesterol emboli syndrome was not confirmed by the SPAF-3 trial, in which patients with documented aortic plaque who were assigned to warfarin therapy had a low annual rate of cholesterol embolization (0.7% per patient-year; 95% confidence interval, 0.1% to 5.3%).[58] Likewise, there was no report of cholesterol embolization in warfarin-treated patients with aortic arch plaque in The French Study of Aortic Plaques in Stroke Group.[32] As a matter of fact, Dressler et al.[30] found that patients with mobile aortic atheroma who did not receive warfarin had a higher incidence of vascular events than those who received warfarin treatment (27% had strokes vs. 0%). Whether the use of anticoagulation is associated with a higher incidence of atheroemboli remains controversial, but anticoagulation has been advocated for patients with crescendo transient ischemic attacks (TIAs), a syndrome caused by atheromatous embolization to the eye or brain. The current literature suggests that it is safe to continue anticoagulation therapy in patients with a compelling reason to do so, such as those with atrial fibrillation or venous thromboembolism.

Thrombolysis

Atheromatous emboli have also been associated with thrombolytic therapy in case reports and small series,[37,59] but again this is controversial. Thrombolytic agents act by converting plasminogen to plasmin; plasmin directly degrades fibrin. Theoretically, any therapy that causes the thrombus to undergo lysis may leave atherosclerotic plaque uncovered, placing the patient at risk for embolization. In one small prospective study, no relationship between the administration of thrombolytic therapy and cholesterol emboli syndrome was found.[60]

CLINICAL FEATURES

Atheroembolism may not result in any apparently clinical symptoms but could also present with a myriad of symptoms, including cardiovascular catastrophes such as myocardial infarction, stroke, acute renal failure, mesenteric ischemia, or peripheral

BOX 103.1 Clinical Manifestations of Atheromatous Embolization

Skin
- Purple or blue toes
- Gangrenous digits
- Ischemic ulcerations
- Livedo reticularis
- Nodules

Renal
- Acute, subacute, and chronic renal failure
- Severe uncontrolled hypertension
- Renal infarction (rare)

Neurologic
- Transient ischemic attack
- Amaurosis fugax
- Stroke
- Altered mental status

Eye
- Hollenhorst plaque

Cardiac
- Myocardial infarction or ischemia

Gastrointestinal
- Abdominal pain
- Gastrointestinal bleeding
- Ischemic bowel
- Acute pancreatitis
- Liver function abnormalities
- Cholecystitis
- Splenic infarcts

Constitutional Symptoms/Signs
- Fever
- Weight loss
- Malaise
- Anorexia

Modified from Bartholomew JR, et al. Atheromatous embolization. In: Young JR, et al., eds. *Peripheral Vascular Diseases.* 2nd ed. St. Louis: C.V. Mosby; 1996.

arterial occlusive disease (Box 103.1).[61-63] In general, the organs affected by cholesterol embolism depend on the location of the embolic source. Atheroemboli from the ascending aorta and proximal aortic arch usually manifest with central nervous system or retinal pathology, whereas cholesterol crystal emboli originating from the descending thoracic or abdominal aortas affect the visceral organs and extremities. In general, bilateral lower extremity atheroembolism signifies a source proximal to the aortic bifurcation, whereas unilateral emboli may originate either proximally or in any artery distal to the aortic bifurcation. Patients with one or more large atheromatous plaques in the aorta may present with a catastrophic event, such as an acutely ischemic limb, or renal or mesenteric infarction.[38,64] Conversely, patients with microemboli may have milder localized signs or a clinical picture that suggests a systemic illness. There may be a temporal delay in clinical findings (especially for renal failure) after the inciting event of up to 8 weeks.[62]

Cutaneous Manifestations

Skin manifestations are among the most common clinical manifestations of atheroembolism, and the common cutaneous features are livedo reticularis and blue toes.[65,66] The appearance of cutaneous signs can be delayed, with 50% of patients in one series showing skin signs of atheroembolism more than 30 days after their procedure or other inciting event.[65]

Livedo Reticularis

Livedo reticularis is a blue-red mottling or discoloration of the skin that occurs in a netlike pattern, most commonly seen on the buttocks, thighs, or legs (Fig. 103.1A). A detailed skin examination performed in both the supine and upright posture is necessary because livedo reticularis has been shown to be more readily demonstrable in the upright position.[67] Livedo reticularis is caused by obstruction of small arteries, capillaries, or venules in the deep dermis.[11,21] When the skin is biopsied in patients with atheromatous embolization, cholesterol crystals may be seen in the dermal blood vessels. However, livedo reticularis is not pathognomonic of atheroemboli and has an extensive differential diagnosis including, but not limited to, other causes of intravascular obstruction (i.e., antiphospholipid antibody syndrome, cryoglobulinemia, endocarditis, left atrial myxoma), vasculitis, or be drug induced (i.e., quinidine, quinine, amantidine, catecholamines).[68] Furthermore, there are also physiologic (Cutis marmorata) and idiopathic (livedoid vasculitis) forms of livedo reticularis. Livedo can occur in young healthy women and appears to be related to abnormal sensitivity of the dermal blood vessels to cold (primary livedo reticularis). This livedo reticularis pattern usually disappears on rewarming. Patients who exhibit this should be reassured that there is no serious circulatory abnormality present.

Blue Toe Syndrome

In its classic presentation, the blue toe syndrome presents as the sudden appearance of a cool, cyanotic, and painful toe in the presence of palpable distal pulses (see Fig. 103.1B).[54-56,65] Discoloration may also be seen on the sole of the foot. The discoloration may be patchy (see Fig. 103.1A), and comparison of both feet shows that the distribution is not symmetric. These lesions may progress to ulceration, necrosis, and frank gangrene (see Fig. 103.1C).[11] Accessory lesions may be present on the lateral and posterior aspects of the heels, which later develop into linear fissures with skin edge gangrene and a dark, necrotic base.

Other Skin Manifestations

Other skin manifestations include splinter hemorrhages, petechiae, purpura, ulcers,[69] and raised nodules that appear as the result of subepidermal inflammation surrounding cholesterol crystals.[11,65] These nodules are painful, violaceous in appearance with a necrotic center, and may mimic a necrotizing vasculitis, such as polyarteritis nodosa or leukocytoclastic vasculitis. Ulceration of the penis and scrotum have also been described.[70]

Renal Involvement

The kidneys are the second most common target for cholesterol crystal embolization, due to the enormous amount of blood that flows through the kidney and the close proximity of the proximal renal arteries to the plaque-bearing abdominal aorta.[20-22] The incidence of clinically detectable atheroembolism amounted to at least 4% of all inpatients examined, representing approximately 5% to 10% of the acute renal failure patients encountered.[10] This condition is significantly underdiagnosed because of delayed presentation.[1,20,22] The cholesterol emboli cause occlusion of the medium-sized arterioles (150 to 200 μm in diameter) and glomerular capillaries resulting in mechanical ischemia at the onset, but they also produce an inflammatory

Figure 103.1 Examples of Cutaneous Manifestations of Atheroembolism. Characteristic appearance of the foot in a patient with atheromatous embolization (A). There is a patchy distribution of livedo reticularis on the lateral aspect, plantar surface, and heel of the right foot (note the purple second toe). Typical appearance of blue or purple toes that may occur in atheromatous embolization (B). More severe cases may progress to gangrene (C).

reaction within the arterioles. The inflammatory infiltration of PMNs, macrophages, and multinucleated giant cells leads to thickening and fibrosis of the arterioles resulting in glomerular sclerosis, tubular atrophy, and interstitial fibrosis.[20,62,71]

It is important to recognize several different clinical presentations (Fig. 103.2)[11,20-22] of this disease, especially the differences between acute tubular necrosis (ATN) (see Fig. 103.2A) and atheroembolic renal disease (see Fig. 103.2B–D). Marked renal impairment with acute onset is the easiest form of atheroembolic renal disease to recognize. It has the closest temporal relationship to the inciting event and is generally considered the consequence of massive embolization, often resulting in catastrophic consequences. The subacute form of atheroembolic renal disease, the most frequently observed, is more insidious in onset, occurring a few weeks after the inciting event. Renal impairment may worsen over weeks to months due to an inflammatory response and foreign body reaction, or the cyclic occurrence of cholesterol crystal embolic showers (see Fig. 103.2B). Under this circumstance, atheroembolic renal disease can be diagnosed only by performing a renal biopsy. Atheroembolic renal disease may also be present with chronic stable renal impairment (see Fig. 103.2C) in an asymptomatic patient. Clinical features tend to be similar to those of ischemic nephropathy and nephrosclerosis. Recovery of dialysis-dependent renal failure (see Fig. 103.2D) may occur in 21% to 39% of patients who initially require renal replacement therapy.[22] Atheroembolic renal disease is often associated with severe and poorly controlled hypertension due to ischemic atrophy of the renal parenchyma and activation of the renin-angiotensin-aldosterone system as glomerular filtration declines.[56,62,72,73] As a result, atheroembolic renal disease should be strongly considered in patients who present with resistant hypertension.[73,74]

The renal outcome for patients with atheroembolic renal disease is quite variable. In early reports the renal outcome was uniformly dismal, with progression over weeks or months to end-stage renal failure.[55,72] However, over the past decade, spontaneous recovery of renal function in patients with atheroembolic renal disease have appeared in the literature, even after variable periods of dialytic support.[8,75-77] The improvement in renal function may be related to reversal of inflammation,

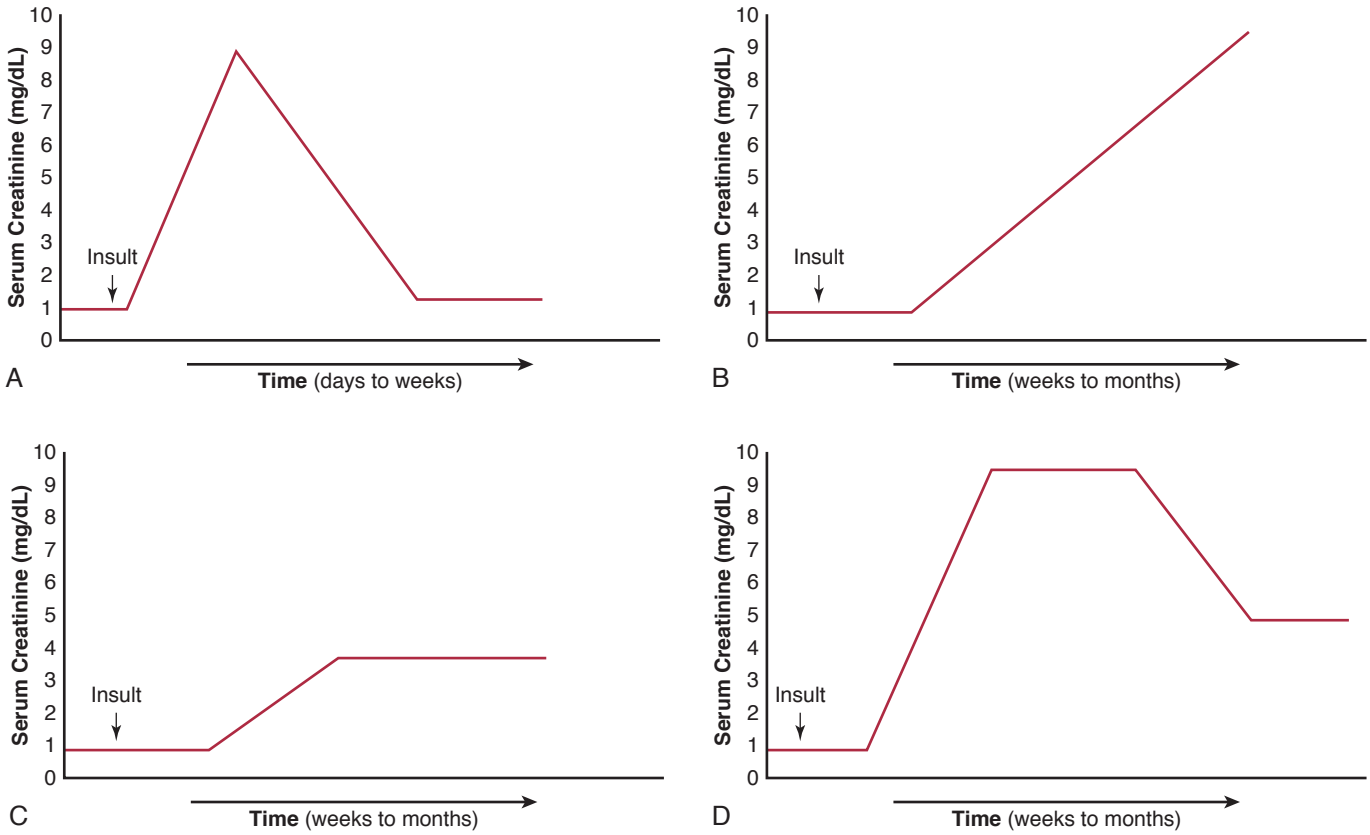

Figure 103.2 Patterns of Renal Failure in Patients With Acute Tubular Necrosis (ATN) and Atheroembolic Renal Disease. In ATN, the serum creatinine rises within 24 hours of the inciting event and progresses to a peak over a period of days to weeks. Under most circumstances, the creatinine slowly returns to normal or near normal (A). In atheroembolic renal disease, there is a delay of 1 week to several weeks from the inciting event until the creatinine begins to rise. This may progress to end-stage renal disease over a period of weeks to months (B). Another presentation of atheroembolic renal injury is also a delay from the inciting event, followed by a rise in the serum creatinine over a period of weeks to months eventually leveling out and leaving the patient with chronic stable renal disease (C). There have been an increasing number of reports in which the patient requires renal replacement therapy and after a period of time, the renal function improves to the point where the patient no longer requires dialysis (D). (From Bartholomew JR, et al. Atheromatous embolization. In: Young JR, et al., eds. *Peripheral Vascular Diseases*. 2nd ed. St. Louis: C.V. Mosby Co.; 1996:266.)

resolution of ATN in ischemic areas, and hypertrophy of surviving nephrons.[77] Despite these promising case reports, most patients with atheroembolic renal disease continue to have either advanced chronic renal insufficiency or progress to end-stage renal disease requiring dialytic support. In the large study by Scolari et al.,[21] of the 354 patients followed for an average of 2 years, 116 (32.7%) patients required dialysis therapy. Eighty-three patients remained on maintenance dialysis therapy, whereas 33 were able to discontinue dialysis. Five patients restarted dialysis within 2 to 6 months of stopping therapy. Cumulative renal survival probability was reduced by the presence of heart failure ($P < .001$), baseline chronic kidney disease categories ($P < .001$), age older than 70 years ($P < .039$), iatrogenic atheromatous embolization ($P < .001$), acute and/or subacute onset ($P < .001$), and leg ($P < .007$) or GI involvement ($P < .001$). Statin treatment was associated with protective effects both when already in place at the time of diagnosis and when initiated after diagnosis ($P < .001$). Multivariable analysis showed that the same factors plus diabetes were associated with a significant increased risk for end-stage renal disease.

Gastrointestinal Involvement

The GI tract is the third most common organ system involved according to autopsy findings, but it is frequently overlooked and rarely diagnosed premortem.[55,78,79] Sites of GI involvement include the colon, which is involved in up to 42% of cases, with the small bowel in 33%, and the stomach in 12%.[80] The preferential involvement of the GI tract is probably a result of its rich vascular supply. Other areas of digestive system involvement that have been reported include the pancreas, liver, gallbladder, and, less commonly, the spleen.[81] The pancreas and liver are frequent sites of cholesterol embolization, as indicated by autopsy reports, although clinically overt pancreatitis and hepatitis are an exceedingly rare presentation of cholesterol embolization.[81] In contrast, cholesterol embolization to the

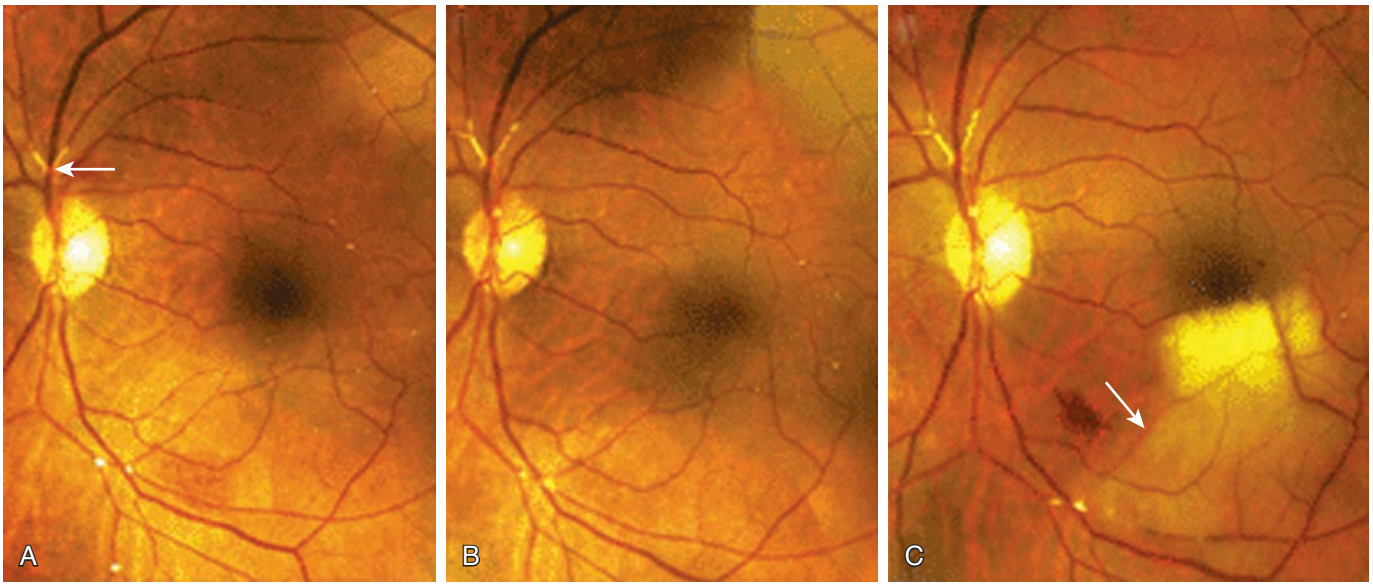

Figure 103.3 Examples of Hollenhorst Plaques. This 59-year-old man underwent stenting of the left internal carotid artery. Two months later, retinal examination of the left eye showed multiple, tiny refractile retinal arteriolar cholesterol emboli and a saddle embolus (A) superior to the optic nerve *(arrow)*. Repeated examination showed an increase in the number of cholesterol emboli (B). Four weeks later, a sudden, painless loss of the left superior visual field occurred. Examination revealed whitening in the inferior macular region (C) *(arrow)*, a finding that was consistent with an occlusion at the second major bifurcation of the inferior temporal branch of the retinal artery. (From Colucciello M. Images in clinical medicine. Retinal arteriolar cholesterol emboli. *N Engl J Med*. 2008;358:826.)

gallbladder, although even rarer, tends to be clinically significant when present, with a clinical presentation ranging from chronic acalculous cholecystitis to acute gangrenous cholecystitis.

The most common manifestations of GI tract involvement are abdominal pain, diarrhea, and GI bleeding. Abdominal pain may be caused by bowel ischemia with or without infarction, or by fibrous stricture with bowel obstruction as a consequence of tissue repair after repeated showers of atheroembolism.[11] The pathogenesis of diarrhea may be related to multiple mechanisms, including mucosal inflammation, accumulation of luminal blood, and malabsorption. GI bleeding is caused by superficial mucosal ulceration, erosions, and microinfarcts.[80]

The diagnosis of cholesterol embolism is rarely made by endoscopy alone because most endoscopic findings are nonspecific, including congestive or erythematous mucosa, erosions, ulcerations, necrosis, inflammatory polyps, or strictures.[2,8,80,81] Mucosal punch biopsies from the stomach, duodenum, or colon may be helpful in making the diagnosis occasionally, demonstrating the typical appearance of cholesterol crystals.[80]

The prognosis of patients with GI involvement tends to be poor; the overall death rate is high. Patients with GI involvement commonly have a multisystem cholesterol embolization syndrome. In a retrospective review of 10 patients with histologically proven cholesterol crystal emboli diagnosed by endoscopic GI biopsy, death due to atherosclerotic complications occurred in 5 patients (multisystem failure [3], stroke [1], and ruptured abdominal aortic aneurysm [1]) within 3 months after diagnosis. All of these patients also had cutaneous manifestations and end-stage renal disease.[80]

Central Nervous System and Eye Involvement

Cholesterol embolization commonly occurs in the brain and eye and causes significant morbidity and mortality.[2]

Retinal

The culprit atherosclerotic plaques are located in the ascending aorta, aortic arch, and/or carotid arteries.[82,83] Patients may develop visual disturbances such as amaurosis fugax or variable degrees of blindness caused by central or branch retinal artery occlusion.[9] Retinal cholesterol embolization is evident as yellow, highly refractile plaques (Hollenhorst plaques) at arterial bifurcations on ophthalmoscopic examination (Fig. 103.3).[9,84] From 2000 to 2005, 130 patients were analyzed with either Hollenhorst plaques or branch retinal artery occlusions.[85] This study found a low rate of significant extracranial carotid artery disease among these patients (<30% in 68%, 30% to 60% in 22%, and >60% in 8%). Only six patients underwent a carotid endarterectomy or received a stent. With a median follow-up of 22 months, no stroke or TIA occurred, and overall survival was 94% in this group of patients.[85] Among the 3654 survivors of the Blue Mountain Eye Study, the cumulative incidence of retinal emboli was only 2.9%.[86] The authors believed that this was an underestimation of the true incidence due to the transient nature of emboli and differential loss to follow-up. The same authors[87] assessed the relationship between retinal emboli and mortality in elderly patients. Of the 8384 patients with retinal photographs available, 2506 (30%) patients died over a 10- to 12-year period of time. The cumulative mortality was higher in patients with than without emboli (all-cause mortality: 56% versus 30%;

stroke-related mortality: 12% versus 4%; and cardiovascular mortality: 30% versus 16%).

Cerebral

Cerebral cholesterol embolism may be manifested as TIA, stroke, altered mental status, headache, dizziness, or organic brain syndrome.[8,82,88] In a retrospective review of 29 patients with autopsy-proven brain cholesterol emboli, encephalopathy was the predominant finding on neurologic examination.[89] This was most likely due to the diffuse and bihemispheric nature of cholesterol embolization. Involvement of the spinal cord artery, which can lead to lower extremity paralysis, has been rarely reported.[61] A case history that is composed of a procedure that involves the ascending thoracic aorta, acute renal failure, and encephalopathy in an elderly patient should raise the suspicion of cholesterol emboli to the brain. Radiologic studies can be helpful by showing multiple small ischemic lesions or border zone infarcts.

Other Areas

Cholesterol emboli can occur in virtually any organ. Cardiac manifestations include angina pectoris and myocardial infarction. The usual source in these circumstances is the aortic root or proximal coronary artery.[90] Pulmonary involvement has rarely been reported in the context of cholesterol embolism.[91,92] Hemoptysis and dyspnea are the most common respiratory symptoms described. The pathogenesis of pulmonary involvement in cholesterol embolism may be related to direct deposition of atheroemboli in the lungs[93] or de novo production of pulmonary lesions as a result of systemic inflammation associated with cholesterol embolism.[94] Atheromatous emboli have also been demonstrated in the spleen, bone marrow,[95] muscle, prostate, thyroid, and adrenal glands in autopsy studies.[2,54,55,72]

Nonspecific findings such as fever, weight loss, headaches, and myalgias have been reported and may suggest a multisystem illness (see Box 103.1).[8,75]

DIAGNOSIS

The diagnosis of cholesterol embolization syndrome remains a significant challenge for physicians. The symptoms and signs are nonspecific and diverse, which is why this disease is sometimes referred to as the "great masquerader."[12] For this reason, a high index of suspicion and a thorough understanding of the various clinical manifestations are needed to correctly make the diagnosis ante mortem. The diagnosis can often be made on clinical grounds alone, without histologic evaluation, in a patient who has a precipitating event, acute or subacute renal failure, difficult to control hypertension, and evidence of peripheral embolization.[8]

Laboratory Tests

Other than laboratory data that reflect specific organ injury such as elevations in serum levels of amylase, hepatic transaminases, blood urea nitrogen, creatinine, and creatinine phosphokinase which may be seen with involvement of the pancreas, liver, kidney, and muscles, respectively, there are no specific laboratory tests that are diagnostic of atheromatous embolization. Eosinophilia can be found in up to 80% of cases and is probably related to the generation of complement C5, which has chemotactic properties for eosinophils.[96] However, eosinophilia tends to be transient and short lived.[2,19] Laboratory markers of inflammation, including C-reactive protein, fibrinogen, and the erythrocyte sedimentation rate, have also been found to be elevated in many patients.[55] Other reported laboratory findings include leukocytosis, anemia, thrombocytopenia, and decreased complement levels.[54,55,97] Mild proteinuria, microhematuria, and hyaline or granular casts are the most common urinary findings in patients with confirmed cholesterol embolism.[55] Nephrotic range proteinuria, and eosinophiluria have also been reported less commonly.[18,98]

Imaging Modalities

Invasive vascular procedures requiring aortic instrumentation should be avoided as a diagnostic modality due to the potential risk for producing recurrent atheroembolism. Noninvasive imaging studies, such as multidetector CT angiography (Fig. 103.4), magnetic resonance angiography, and TEE (Fig. 103.5), can assist in confirming the diagnosis if a markedly irregular and shaggy aorta is demonstrated. It should be emphasized that these imaging modalities only demonstrate that the patient has significant underlying atherosclerosis but cannot discern whether the atherosclerotic lesions are responsible for the embolic events.

Histologic Findings

In the absence of obvious clinical clues, a definitive diagnosis may require a biopsy. The highest yield for histologic confirmation is in the skin in patients exhibiting livedo reticularis or in an affected organ, such as an amputated extremity in a patient with gangrenous toes, the kidney in a patient with new-onset renal failure, or in the GI tract in a patient with abdominal pain and GI bleeding. The cholesterol crystals dissolve in paraffin-fixed sections, leaving needlelike clefts (Fig. 103.6). Frozen or wet formalin-fixed sections reveal doubly refractile cholesterol crystals; with the Schultz histochemical stain, these crystals stain blue-green.[99]

DIFFERENTIAL DIAGNOSIS

Diseases that should be considered in the differential diagnosis include, but are not limited to, contrast nephropathy, ATN from ischemic injury, necrotizing vasculitis, leukocytoclastic vasculitis, thrombotic thrombocytopenic purpura, antiphospholipid antibody syndrome, and multiple myeloma. Thromboembolism from the heart or aneurysms, and other cardiac sources of emboli, such as an atrial myxoma, nonbacterial thrombotic endocarditis, and infective endocarditis,[100] should always be excluded.

No laboratory test uniformly helps in the diagnosis of atheroembolic disease. The peripheral blood eosinophilia, hypocomplementemia, elevated sedimentation rate, and increased

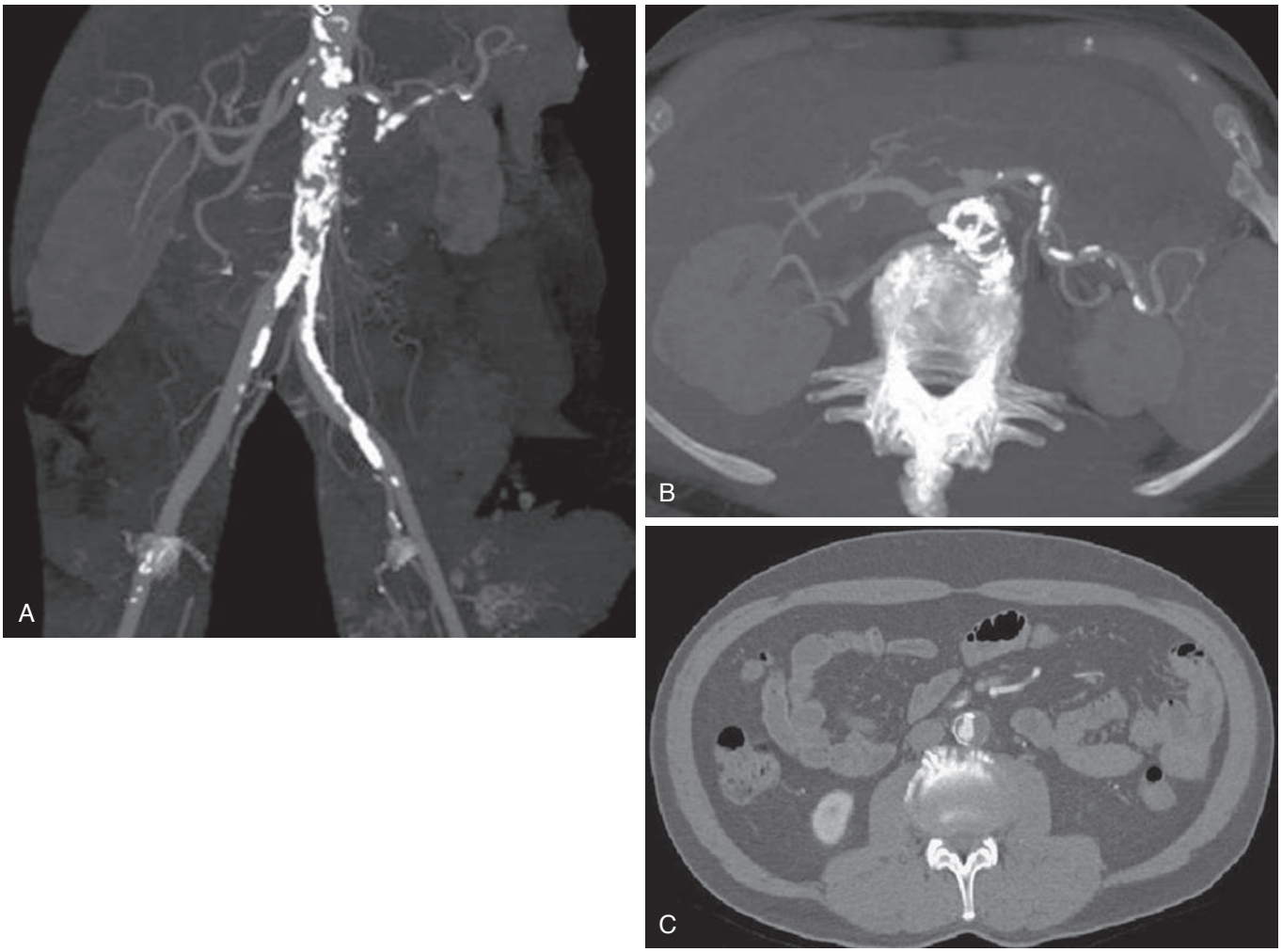

Figure 103.4 Multidetector computed tomography angiogram demonstrating marked calcified atherosclerotic disease in the infrarenal abdominal aorta in axial view (A) and reformatted view (B). Another example of infrarenal aorta with calcified plaque and extensive thrombus formation (C).

level of C-reactive protein seen in these patients are nonspecific findings that can also be found in patients with systemic or renal vasculitis.[101] Atheroembolic disease should be distinguished from vasculitis on the basis of other clinical findings and histology. The urine sediment in patients with atheroembolic renal disease is usually benign or shows only microhematuria. Rarely, eosinophiluria may be present.[102] In contrast, the urine sediment in patients with ATN often demonstrates pigmented casts (dirty brown casts) and renal tubular cells. Atheroembolic renal disease can further be differentiated from ATN or contrast nephropathy based on the time frame of renal impairment. In contrast nephropathy and ATN, renal failure occurs within 48 to 72 hours after the inciting event, whereas in patients with atheroembolic renal disease, the rise in creatinine is often delayed for 7 to 10 days.[20,21,61,62] In addition, full recovery of renal function is the rule for contrast nephropathy and ATN if the underlying precipitating factor is corrected, whereas it is the exception in atheroembolic renal disease.[11,62] However, there are examples of late recovery of renal function in patients with atheroemboli.[103] ATN is further characterized by normal blood pressure levels as opposed to the severe and refractory hypertension present in many patients with atheroembolic renal disease. The other previously listed disorders that may mimic cholesterol embolization due to their multisystem involvement should be excluded by appropriate diagnostic studies.

TREATMENT

Preventive Strategies

It is clear that the most effective strategy for the management of atheroemboli in vascular surgery is prevention. Imaging modalities such as MRI/MRA, TEE, or CTA are excellent techniques to screen for high-risk patients by detecting the presence of aortic atherosclerosis preoperatively. When a severely atherosclerotic aorta is visualized, alternative surgical procedures should be considered to minimize aortic manipulation. Utilization of long guide wire exchanges is recommended, and back bleeding from guiding catheters allows for removal of debris. Advancement and removal of catheters should occur over a

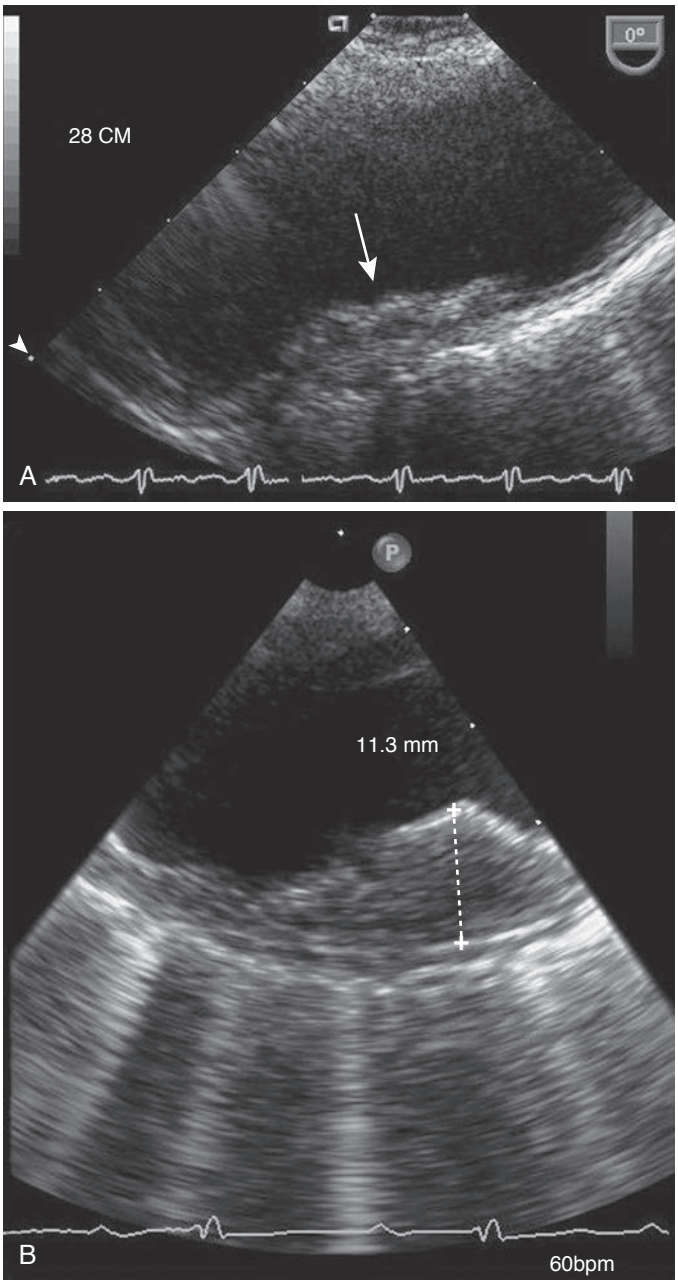

Figure 103.5 Transesophageal echocardiogram demonstrating a large atheroma in the aortic arch (A) *(arrowhead)* and in the descending thoracic aorta (B). The descending thoracic aorta plaque measured 11.3 mm.

guide wire to straighten the catheter and minimize contact with the aortic wall. Brachial and radial access may minimize embolization from the abdominal aorta but not from the ascending aorta or arch.

Several studies showed that distal protection devices used at the time of renal artery stenting were associated with less deterioration in renal function compared with stenting without the use of these devices (Fig. 103.7).[45-47] In a small prospective randomized trial, Cooper et al.[46] demonstrated that during renal artery stenting, the combination of distal embolic protection and the use of the glycoprotein IIb/IIIa inhibitor abciximab resulted in an improvement in renal function compared with the use

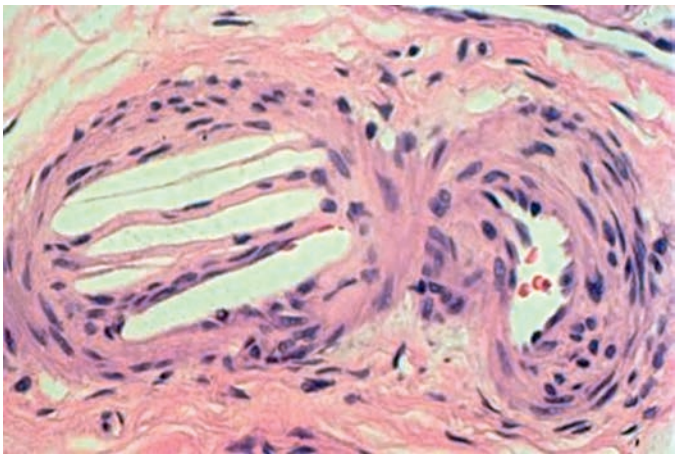

Figure 103.6 Typical Appearance of the Cholesterol Clefts in a Specimen from a Kidney Biopsy. The convex-shaped crystals within the small arterioles of the kidney dissolve during the fixation process leaving the ghosts *(left side)*, which is what is seen in the histopathology (hematoxylin and eosin stain, 200× original magnification). Note the three red blood cells in the arteriole *(right side)*.

of either of these modalities alone.[46] In addition, Paul et al.[104] showed that there is a much greater improvement in renal blood flow when a distal protection device was used during renal artery stent implantation compared with renal artery stenting without a distal protection device. Although distal protection devices are routinely used in carotid artery stenting, this is not the case in renal artery stenting. In the initial design of the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, a distal protection device was used in every patient who was randomized to stenting. However, due to slow recruitment, this requirement was dropped from the protocol and the decision was left up to the discretion of the interventionalist.[105]

Medical Therapy

After atheromatous embolization has occurred, therapy is mostly supportive. Avoiding further inciting events (such as aortic manipulation), good control of hypertension and heart failure, dialytic support, and adequate nutrition are the mainstays of treatment.[8,56] Symptomatic care of the end organ where the emboli are located and risk factor modification to prevent myocardial infarction, stroke, and the progression of atherosclerotic disease are important treatment goals.[61,106]

Pathologic descriptions of cholesterol embolism highlight the severe inflammatory reaction that contributes to vascular obstruction. Although the inflammatory process caused by cholesterol embolism may suggest a role for antiinflammatory agents,[19] the use of corticosteroids has had conflicting results. Dahlberg et al.,[57] in a report of two patients given prednisone (60 mg daily) or methylprednisolone (80 mg daily) for 5 days, found a rapid and dramatic improvement in the manifestations of peripheral embolization.[57] More recent case reports described improvement in renal function in patients with suspected atheroembolism when corticosteroid therapy was used.[107-112] Corticosteroid administration has also been shown to be helpful in relieving symptoms related to mesenteric ischemia, such as

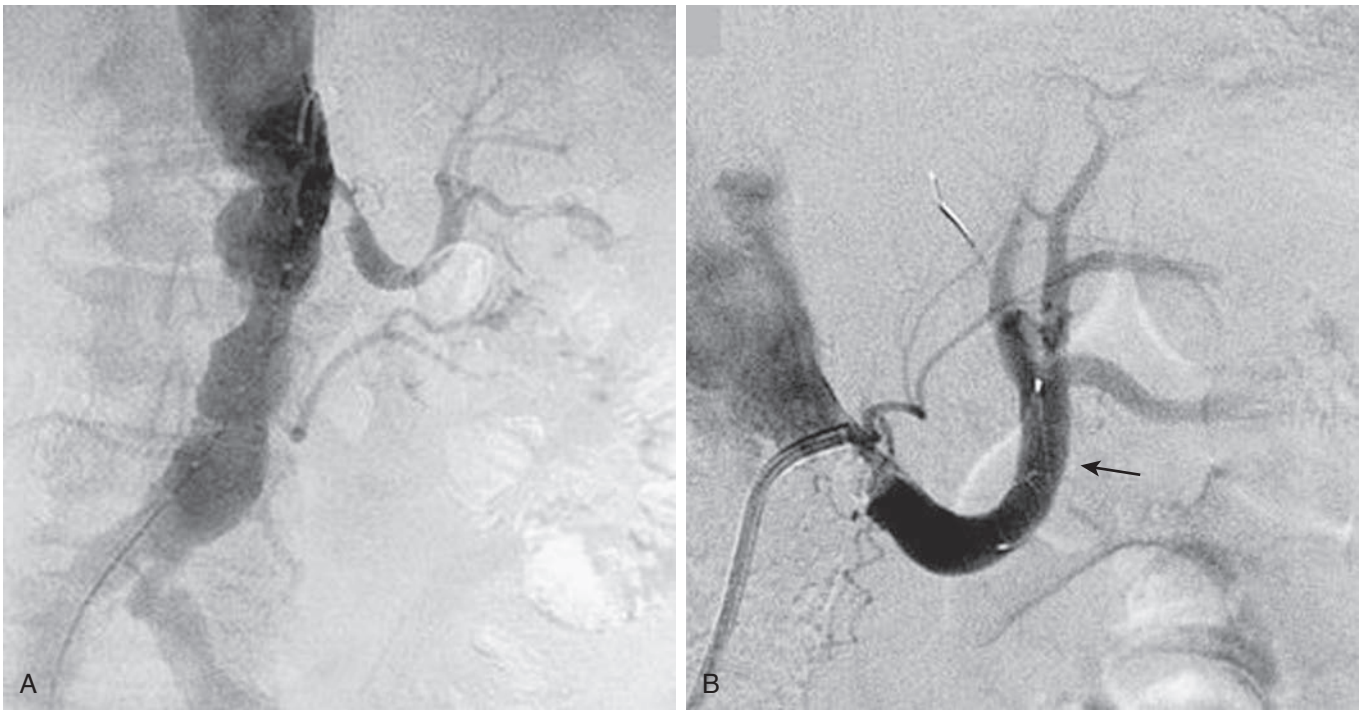

Figure 103.7 (A) Catheter-based angiogram demonstrating a severely atherosclerotic aorta with a severe stenosis of the left renal artery and an occluded right renal artery. A selective angiogram of the left renal artery shows the severity of stenosis (A). There was a 7-mm Spider embolic protection device *(arrow)* (ev3 Endovascular, Inc., Plymouth, Minnesota) placed before renal artery stenting (B).

abdominal pain and food intolerance, and for ischemic leg pain.[8] In contrast, in a series of 67 patients, of whom 18 were treated with corticosteroids, no survival benefit was attributed directly to this therapy.[8] Furthermore, in large retrospective series, Falanga et al.[65] found that corticosteroid use was associated with 100% mortality. Based upon the available literature, corticosteroid use cannot be recommended on a routine basis for this patient population, although some authorities have recommended corticosteroids in patients with multisystem atheroembolic disease.[22]

Statins have been reported to be beneficial in the treatment of livedo reticularis caused by cholesterol embolization[113] and for treatment of atheroembolic renal disease.[114] Furthermore, in a retrospective analysis of 519 patients with severe thoracic aortic plaque visualized on TEE, multivariate analysis showed that statin use was independently protective against recurrent embolic events ($P = .0001$).[115] The mechanism of the beneficial effects of statin therapy is most likely related to the plaque-stabilizing activity of these drugs.

Iloprost (Schering AG, France), a prostacyclin analogue, has been reported to be beneficial for treatment of atheromatous embolization. It is a potent vasodilator that inhibits platelet aggregation and also has cytoprotective properties. It has been used to treat pain at rest and nonhealing ulcers in patients with critical limb ischemia, as well as severe Raynaud phenomenon and thromboangiitis obliterans. In some reported individual cases or small series, patients who received iloprost infusions for ischemia of the distal extremities or kidneys reported a decrease in pain and improvement in their nongangrenous skin lesions, as well as renal function.[116-118]

Low-density lipoprotein (LDL) apheresis with or without the addition of steroids was shown to be effective in improving skin manifestations. Hasegawa et al.[119] showed that combining corticosteroids and LDL apheresis improved atheroembolism related to blue toe syndrome. The mechanism is unknown, although it was postulated to improve blood viscosity by removing large molecular weight substances and decreasing total and oxidized LDL, thus improving endothelial function and reducing circulating inflammatory cytokines and chemokines.[119]

Other forms of therapy that have been advocated include antiplatelet agents such as aspirin[54,55] and dipyridimole, low-molecular-weight dextran, intraarterial papavarine, and the use of platelet infusions to help stabilize the source of atheroemboli. However, no controlled trials have shown that any of these forms of therapy are of benefit. All patients should receive optimal risk factor modification with an antiplatelet agent (aspirin, clopidogrel, or both), a statin, and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocking agent, all of which have been found to improve mortality in patients with underlying atherosclerotic disease.[61,120-125]

Surgical and Endovascular Therapy

Surgical or endovascular treatment is a viable option when a source of cholesterol emboli can be identified, and the source

is surgically or endovascularly accessible. However, it is often difficult to identify which of the many atherosclerotic plaques is the culprit lesion.

Surgical Therapy

The aims of surgical therapy for atheroembolic disease are, first and foremost, the elimination of the embolic source, and second, arterial reconstruction of any hemodynamically significant proximal occlusive disease to encourage healing through improved end-arterial bed perfusion. Given the frequent instability of these lesions, surgical treatment has been perceived to be safer than endovascular approaches because the surgeon can clamp the artery proximal and distal to the lesion before manipulating the diseased vessel in an attempt to decrease the risk of recurrent embolization.[126] Thromboendarterectomy or resection and graft replacement have been the surgical approaches most commonly used.[127] Two prospective series reported favorable outcomes with vascular resection of atherosclerotic segments of large arteries identified as being the source of previous cholesterol crystal embolism.[128,129] However, when the suprarenal aorta was involved, greater mortality rates were observed, likely related to the risk for visceral and renal ischemia and/or atheroemboli.[128] Thus, according to some investigators, surgical elimination of the presumed source of cholesterol embolization should be reserved for patients with lower limb ischemia and an infrarenal source of embolization.[11] In patients who are too weak for a major surgical intervention, ligation of the external iliac arteries or common femoral arteries, followed by an extra anatomic bypass (e.g., axillobifemoral bypass) has been advocated.[127,130] The ligation prevents further embolization from reaching the legs, although embolization to the kidneys and intestines may still occur.

Finally, surgical treatment of thoracic aorta atherosclerosis may be considered. Surgical therapy cannot be recommended routinely for the asymptomatic patient because the risks inherent in such a complex procedure outweigh the benefits.[131] However, performing aortic arch endarterectomy or aortic resection along with the planned cardiac procedure, if severe atheromatous disease is discovered, has been addressed. Stern et al.[132] reported a large increase in intraoperative stroke and mortality when surgery was performed to limit the risk of stroke after cardiopulmonary bypass. At this time, in the absence of randomized controlled trials, surgical indications for aortic endarterectomy should be restricted to highly selected patients who have multiple and documented embolic events with a low operative risk, despite optimal medical treatment.[29]

Endovascular Therapy

There are a few reports of intraarterial treatment of embolizing lesions, including thrombolytic administration,[52,133] percutaneous atherectomy,[134,135] balloon angioplasty,[52,133] and stent implantation.[136,137] Intraarterial thrombolytic administration in isolation is controversial. By destroying the platelet-fibrin thrombus that covers the atheromatous ulcerated plaques, thrombolysis may allow for the liberation of the cholesterol crystals into the arterial circulation with consequent microembolization. There are no data currently on the adjunctive use of tissue plasminogen activator in treating lesions believed to be responsible for atheroembolic events.

In percutaneous transluminal angioplasty, the intima is fractured and remolded, which could increase the risk of distal embolization. However, anecdotal reports using this approach have shown symptomatic improvement in leg pain, reestablishment of peripheral pulses, and no evidence of recurrent embolization. Stent placement, in conjunction with angioplasty, may provide a protective scaffold to help secure these lesions. However, a potential risk of recurrent atheroembolism may exist due to either plaque dislodgement or extrusion of atheromatous material through stent interstices at the time of stent placement.

The possibility of procedural-related distal embolization due to stent placement was highlighted in a recent study by Ohki et al.[138] that demonstrated a significant risk of distal embolization secondary to intraarterial stent placement in an ex vivo carotid endarterectomy model. In contrast, Matchett et al.,[136] in a retrospective report of 15 patients treated with stent placement for blue toe syndrome, found no procedure-related embolization and only one recurrent embolization during follow-up. Renshaw et al.[139] reported successful angioplasty with stenting in eight patients with unilateral blue toe syndrome. Symptoms resolved in all eight patients over the ensuing month, and there were no recurrences with a mean follow-up of 18.5 months.[139]

The short-term results in studies using percutaneous atherectomy, in which the plaque is shaved off the wall of the vessel and removed through a collection device, are similar to those of patients undergoing percutaneous transluminal angioplasty or surgery.[134,135]

The availability of covered stent-grafts in recent years has raised their potential utility in the management of patients with distal atheroembolic lesions. Covered stents offer the added advantage of completely excluding the diseased segment, preventing the escape of thrombus or plaque debris. Kumins et al.[140] reported on the successful use of the Wallgraft endoprosthesis in two patients with distal microembolism from common iliac artery pathology.

Carroccio et al.[141] recently reported on endovascular stent-graft repair for abdominal aortic aneurysms in 16 patients with atheromatous embolization syndrome. The 30-day mortality was 0%, and the abdominal aortic aneurysms were successfully excluded in 88% of patients. Resolution of foot ischemia and prevention of further atheromatous embolization occurred in 89% of the patients still alive at 1 year. Six patients died during a mean follow-up of 26 months, further illustrating the very high mortality in this patient population.

Distal embolic protection devices, especially filters, were originally designed to minimize atheroembolism during percutaneous coronary or carotid interventions. An off-label use of these devices is to protect the outflow arteries from atheroembolism during peripheral interventions. It would not be cost effective to use distal embolic protection for all peripheral interventions, and the arterial diameters compatible with these devices are limited. Nonetheless, distal embolic protection may be a useful adjunct for endovascular treatment of lesions deemed to be a high risk for embolization during the procedure, especially

TABLE 103.2 Outcomes in Patients With Atheroembolic Renal Disease

Reference	*N*	Renal Failure Requiring Dialysis No. (%)	Recovery of Dialysis-Dependent Renal Failure No. (%)	Maintenance Dialysis (End of Follow-Up) No. (%)	1-Year Mortality No. (%)
Fine et al.[55]	221	62 (28)	13 (21)	0	179 (81)
Lye et al.[72]	129	52 (40)	13 (26)	0	83 (64)
Thadhani et al.[18]	52	23 (44)	7 (32)	0	45 (87)
Belenfant et al.[8]	67	41 (61)	16 (39)	23 (35)	9 (13)
Scolari et al.[21]	354	116 (33)	33 (28)	88 (25)	60 (17)

From Scolari F, Ravani P. Atheroembolic renal disease. *Lancet*. 2010;375:1650-1660.

in patients who have already experienced an atheroembolic event.

Because of the limited studies available in the literature regarding the role of endovascular therapy for atheromatous embolization, its clinical efficacy is difficult to compare with operative treatment strategies. Undoubtedly, further clinical evaluation is warranted to further validate endovascular therapy in the treatment of atheroembolism.

Pain Control

Pain control is a critical aspect of the management of peripheral cholesterol embolism. The degree of pain associated with lower extremity ischemic and necrotic lesions secondary to cholesterol embolism is generally severe and disproportionate to the extent of the tissue involved. Sympathectomy has received attention as a surgical measure for the palliation of atheroembolic lesions. Lee et al.[142] demonstrated that adjunctive sympathectomy resulted in improved healing of distal digital ischemic ulcers. Sympathectomy is easily performed during aortic procedures, or it can be achieved postoperatively through lumbar sympathetic block or laparoscopic techniques.

More recently, Ghilardi et al.[143] reported on two cases of inferior limb ischemia secondary to cholesterol embolism treated with the temporary surgical implantation of spinal cord stimulation devices. Spinal cord stimulation in this study was found to provide rapid and effective pain control in the reported cases and improvement in peripheral microcirculation manifested by the rapid resolution of the necrotic lesions within 4 to 6 weeks.[143] These surgical techniques may not only be an adjunct to direct surgical treatment of the offending arterial segment but also may be useful to control the pain of severe atheroembolic lower extremity lesions in patients who are not candidates for direct reconstruction of the embolic source. It is often helpful to ask a pain specialist to help in the management of the severe pain that may occur in these patients.

SUMMARY

Atheroembolism is a multisystem disease complicating advanced atherosclerosis. The clinical presentation varies from subtle to catastrophic manifestations. It is still often underrecognized and requires a high clinical suspicion to diagnose. The treatment is mainly supportive and risk factor modification to prevent further insults. Removal of the embolic sources is sometimes possible with surgical or endovascular intervention. In general, the prognosis of patients with atheroembolic disease is poor and most likely related to the severe and diffuse atherosclerosis that is present in this patient population. However, the course varies depending on type of clinical presentation. Patients with symptoms limited to an extremity tend to have a better prognosis compared with patients with disseminated cholesterol crystal embolization, particularly when there is evidence of visceral and renal involvement. The reported 1-year mortality in four different reports varied from 64% to 81% (Table 103.2).[18,55,57] Causes of death were multifactorial and included cardiac, central nervous system, and GI ischemia.

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CHAPTER 104

Lower Extremity Arterial Occlusive Disease: Epidemiology and Natural History

MICHAEL S. CONTE

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EPIDEMIOLOGY OF PERIPHERAL ARTERIAL DISEASE

Incidence and Prevalence

Peripheral arterial disease (PAD) is defined as chronic, atherosclerotic occlusive disease of the lower extremities. It has become a major global health problem, largely secondary to aging of the world's population, combined with the growing prevalence of risk factors such as diabetes, smoking, hypertension, and dyslipidemia. The increasing burden of PAD has resulted in mortality, morbidity, and escalating public health costs associated with care for the disease and its complications. Accurate information on PAD prevalence and incidence is limited because a large proportion of affected individuals have preclinical disease or atypical symptoms, and PAD screening (e.g., ankle-brachial index [ABI] testing) is not routinely used. As a result, epidemiologic data have been drawn from isolated community screening studies, data on symptomatic states such as intermittent claudication (IC), and by extrapolation from other measured diseases (e.g., diabetes) and events (amputation) with known relationship to underlying PAD.

Epidemiologic studies have estimated that more than 200 million individuals are currently affected by PAD worldwide.[1] This prevalence rate has increased by approximately 25% over the preceding decade. The growth of PAD is evident in both high-income countries (HICs) and low- and middle-income countries (LMICs), with LMICs and the Pacific Rim/Southeast Asia region specifically demonstrating higher rates of growth

Abstract

Peripheral arterial disease (PAD), defined as chronic occlusive disease of the lower extremities, is a major and growing health problem, estimated to affect more than 200 million individuals around the globe. Aging of the world's population, combined with diabetes, smoking, dyslipidemia, and hypertension are the critical risk factors and significant socio-economic disparities exist. Most individuals with PAD are asymptomatic, and the most common symptom is intermittent claudication (IC). A small minority (< 10%) develop chronic limb threatening ischemia (CLTI). Even in its asymptomatic stage PAD carries significant risk for reduced survival and major cardiovascular events, and is associated with progressive decline in function. Progression of disease from IC to CLTI may occur in up to 20% of patients, associated with similar risk factors but especially diabetes, smoking, and renal disease. Improved staging systems, such as the SVS Threatened Limb Classification System may allow for improved prognosis and evidence based treatment algorithms.

Keywords

peripheral arterial disease
claudication
chronic limb-threatening ischemia
epidemiology
risk factors

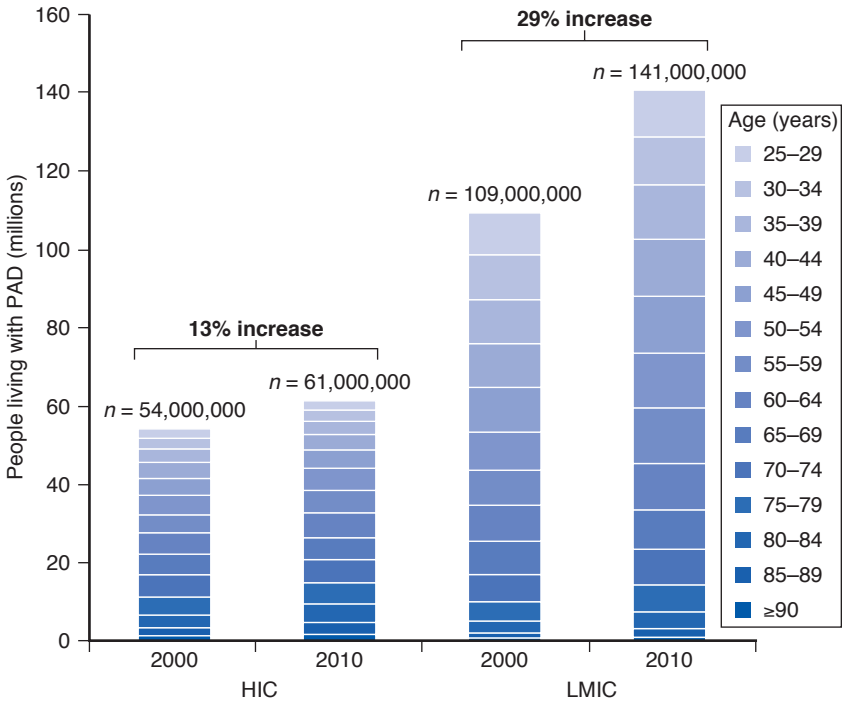

Figure 104.1 Estimated global prevalence of peripheral arterial disease *(PAD)* by age in high-income countries *(HICs)* and low- and middle-income countries *(LMICs)* in 2000 and 2010. (From Fowkes FG, Aboyans V, Fowkes FJ, et al. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol*. 2017;14(3):156–170.)

(Fig. 104.1). Sex- and age-related prevalence of PAD differs somewhat around the globe. In HIC, men and women appear approximately equally affected and the prevalence rises from less than 5% younger than age 50 to approximately 20% in individuals older than 80 years. In LMICs, age-specific rates appear higher in women compared with men. Many studies have demonstrated that women have lower ABI than do men, although the reasons for this observation are unclear and not readily explained by differences in established risk factors for atherosclerosis. Data on PAD are sparse from many areas of the world, and concerted public health efforts will be needed to develop more accurate models of incidence, prevalence, and outcomes. These efforts are justified by the economic impact of disability and health resource use that is engendered by PAD.

Data from the US population estimate that 8.5 million Americans are living with PAD.[2] There is a strong age-dependent increase in the United States, with a prevalence of greater than 20% in individuals older than 80 years (Fig. 104.2).[3] Nehler et al. estimated US incidence and prevalence of PAD over the years 2003 to 2008 using a broad capture of claims data from multiple insurers. including Medicare, Medical, and commercial plans.[4] They reported an annual incidence rate of 2.35% and an overall prevalence of 10.69% among the enrollees.

Estimates of the prevalence of IC and critical limb ischemia (CLI) are fraught with similar limitations and are likely to be systematically undervalued. Estimates of IC prevalence have been derived from community questionnaire studies and, for CLI, using administrative (billing) data on hospitalizations, procedures, and amputations. IC is estimated to affect up to 6% of individuals older than 65 years in Western countries.[5] It is recognized that many PAD patients describe atypical leg pain syndromes (non–calf pain or calf pain with nonclassic

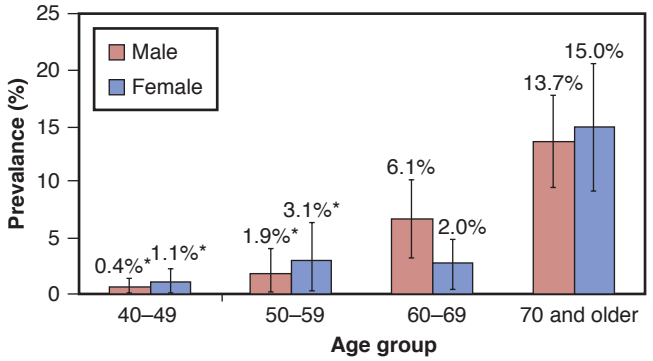

Figure 104.2 Estimated age-specific prevalence of PAD in the United States from the National Health and Nutrition Examination Survey 1999-2000. *Relative standard error > 30%. (From Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. *Circulation*. 2004; 110(6):738–743.)

descriptors) that are not accurately captured. Estimates of CLI incidence and prevalence have ranged from 0.02% to 0.35% and 1.2% to 2.35% across studies of disparate adult populations.[4,6,7]

Risk Factors

PAD is a chronic manifestation of systemic atherosclerosis in the arteries of the lower extremities. As such, it shares many risk factors with other clinical atherosclerotic conditions such as coronary artery disease (CAD) and cerebrovascular disease (CVD). However, differences in the profile of PAD, CAD, and CVD patients have been characterized, and the strength of association of specific risk factors varies across the clinical syndromes, as well as across anatomic patterns (Fig. 104.3).

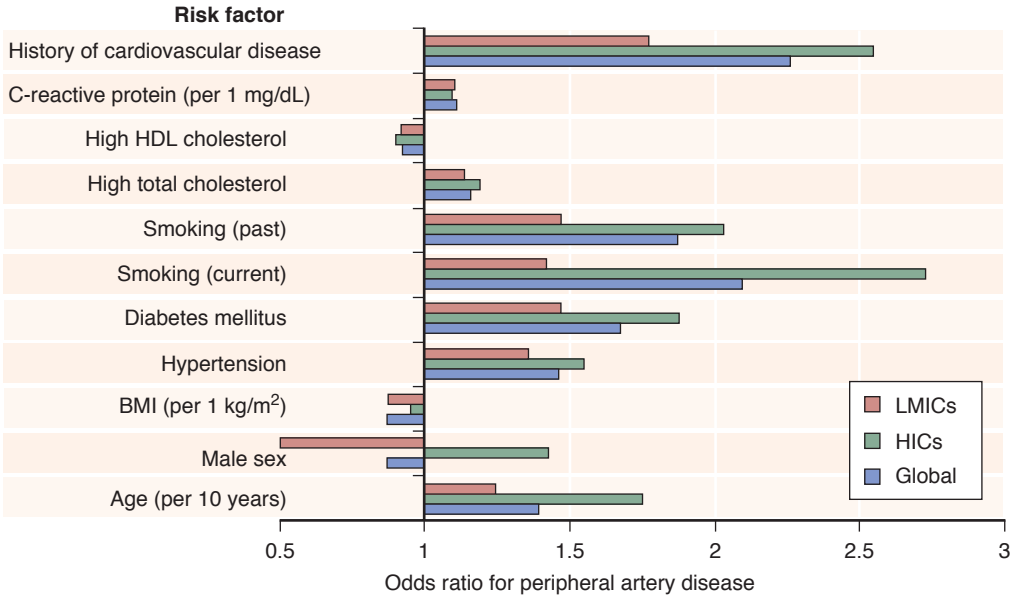

Figure 104.3 Risk factors for PAD across the globe, in both low- and middle-income and high-income countries (*LMICs* and *HICs*, respectively). *BMI,* Body mass index; *HDL,* high-density lipoprotein. (From Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol.* 2017;14(3):156-170.)

Demographics

Age is the strongest risk factor for PAD. The disease is rare in individuals younger than 40 years, rises in prevalence in the sixth to eighth decades, and may affect 25% or more of individuals 80 years and older.[3,8-11] As mentioned previously, sex-related differences in PAD appear to be different around the globe, although the prevalence of more advanced, symptomatic stages of disease is consistently higher in men.

Several studies have demonstrated higher rates of PAD and poorer outcomes for black populations in comparison with non-Hispanic or Hispanic white populations (Fig. 104.4).[2,3,12-15] Reasons remain unclear because this disparity is not accounted for based on an imbalance of traditional risk factors such as age, smoking, diabetes, or hyperlipidemia.

Smoking

Cigarette smoking is a strong and independent predictor of PAD across populations. Several studies have demonstrated odds ratios in the range of twofold to fourfold.[3,10,16] Secondhand smoke exposure appears to also carry increased risk for PAD, although data in this regard are limited.[17,18]

Diabetes

Diabetes has been strongly associated with PAD prevalence and severity. Odds ratios reported for diabetes are similar to those for smoking, in the range of twofold to fourfold.[3] This association is modified by age and the duration of diabetes, such that older individuals with more than a decade of diabetes are at highest risk. The combination of diabetes and smoking is most insidious, portending a high risk for PAD severity, amputation, and mortality. Multiple studies have demonstrated that long-term outcomes of PAD are adversely influenced by the presence of diabetes, including reduced survival and a fivefold increased rate of limb loss.[19]

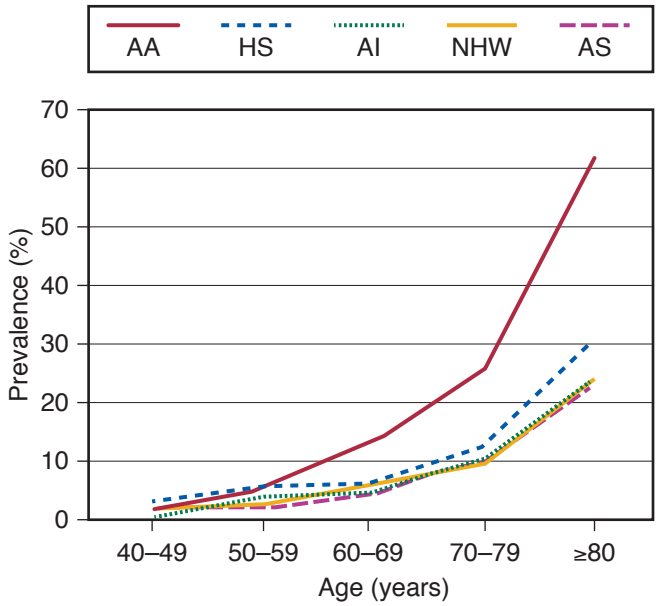

Figure 104.4 Estimated United States prevalence of PAD by age and ethnicity in (A) men and (B) women. *AI,* Aorto-iliac; (From Allison MA, Ho E, Denenberg JO, et al. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med.* 2007;32(4):328-333.)

Hypertension

Hypertension is common in the PAD population. The association is consistent across many epidemiologic studies, although less

strong than that seen with smoking and diabetes. Because age is a common risk factor for both, the independent association between hypertension and PAD appears weaker on multivariable analyses.

Dyslipidemia

Elevated total cholesterol (TC) and reduced high-density lipoprotein (HDL) levels have been associated with PAD in multiple studies. The ratio of TC/HDL was a strong predictor in both the San Diego population study[12] and the Physician's Health Study.[20] Some studies have demonstrated a link between elevated triglyceride levels and PAD.[21] The relationship between PAD and low-density lipoprotein (LDL) levels appears less consistent, and no target LDL values for therapy have been developed specific to PAD.

Obesity

Data specifically relating obesity to PAD are inconclusive. Some studies suggest a U-shaped relationship.[22,23] The distribution of body fat may be of greater relevance. Central obesity, more consistently linked to diabetes and to the "metabolic syndrome" (the cluster of central obesity, hypertension, elevated triglycerides, low HDL, elevated fasting blood glucose), appears of greater relevance to PAD than overall obesity.[24,25]

Inflammation

Elevated biomarkers of systemic inflammation have been consistently associated with atherosclerosis in general and PAD specifically. Plasma levels of C-reactive protein and fibrinogen have shown consistent associations with PAD.[3,26] Both of these biomarkers have also been associated with PAD severity and with adverse outcomes in symptomatic patients. Indeed, CLI patients appear to have the most pronounced proinflammatory phenotype across the spectrum of clinical atherosclerosis syndromes. Circulating cytokines such as interleukin-6 and adhesion molecules (soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1) are also elevated in PAD patients.[27] The predictive value and clinical utility of these markers, as well as other candidate biomarkers such as D-dimer, β2-macroglobulin, asymmetric dimethylarginine, and cystatin C, remain undefined.[28-30]

Homocysteine

Several studies have demonstrated a statistical relationship between elevated plasma levels of homocysteine and PAD.[31] However, the strength of the association is moderate when controlled for other risk factors.[20] In addition, homocysteine levels have not been clearly associated with progression or severity of PAD, and studies of folate supplementation (which reduces homocysteine) have shown no consistent effects on PAD.[31]

Socioeconomic Status

PAD has been associated with lower socioeconomic status, including lower levels of income and education.[32,33] These associations span race/ethnicity and are only partly explained by traditional risk factors such as smoking. A recent analysis from the Atherosclerosis Risk in Communities (ARIC) study demonstrated that household income, educational attainment, and area-level deprivation index were strong predictors of hospitalization for advanced PAD.[33] These findings were attenuated but not eliminated after controlling for age, sex, race, risk factors, and access to healthcare. Mechanisms may include psychological stress, health literacy, and nutrition.

ANATOMIC DISTRIBUTION OF DISEASE AND CLINICAL CORRELATIONS

A broad spectrum of anatomic lesion distribution and disease severity is encountered in the PAD population. Lower extremity arterial disease has been anatomically described by the levels (segments) affected—aorto-iliac (AI), femoropopliteal (FP), and tibiopedal (TBP). These descriptors are both clinically useful and tend to be associated with patterns of risk factors across the spectrum of disease presentation. For example, smokers have a high frequency of AI and FP disease, whereas diabetes is more typically associated with TBP and FP involvement. There is also a clear relationship between disease pattern and clinical presentation. Patients with IC typically present with AI and/or FP disease, often with a single segment involved. In contrast, severe limb ischemia (SLI) or CLI generally results from involvement of at least two arterial segments or severe TBP disease. This correlation is largely a reflection of the development of collateral pathways of blood flow circumventing single-level (especially proximal) occlusions.

Cohort studies including vascular imaging provide greater insight into anatomic distribution of lesions across subgroups of patients. Smoking tends to be more highly associated with AI and FP involvement, whereas diabetes is strongly linked to FP and TBP patterns of disease.[19,34-36] Diehm et al. examined angiograms from a series of 2659 patients who had undergone endovascular interventions for PAD. Proximal (AI) disease was associated with younger age, smoking, and male sex, whereas TBP disease was associated with diabetes and advanced age. Rueda et al. described patterns of disease among a cohort of 450 patients who had undergone angiography and revascularization for CLI at a single institution.[37] They found that more than half of such patients had occlusions in the popliteal or TBP segments, and another 30% had combined FP and TBP occlusions; these patterns were particularly common in patients with diabetes and/or end-stage renal disease (ESRD).

CLINICAL SYNDROMES OF PERIPHERAL ARTERIAL DISEASE, STAGING AND NATURAL HISTORY

Individuals afflicted with PAD may be grouped by clinical presentation, with the largest proportion being asymptomatic. Atypical leg symptoms, classic IC, and CLI signs or symptoms are frequent indications for referrals to vascular specialists for evaluation and treatment. We will consider each of these distinct subgroups and describe modes of presentation, staging, prognosis,

TABLE 104.1 Stages of Chronic Limb Ischemia

Fontaine Grade	Rutherford Category	Clinical Description	Objective Criteria
I	0	Asymptomatic	Normal treadmill or reactive hyperemia test
IIa[a]	1	Mild claudication	Completes treadmill exercise[b]; AP after exercise >50 mm Hg but at least 20 mm Hg lower than resting value
IIb[a]	2	Moderate claudication	Between categories 1 and 3
	3	Severe claudication	Cannot complete standard treadmill exercise[b]; AP after exercise <50 mm Hg
III[a]	4	Ischemic rest pain	Resting AP <30-50 mm Hg; ankle or metatarsal PVR flat or barely pulsatile; TP <30 mm Hg
IV	5	Minor tissue loss	Resting AP <50-70 mm Hg; ankle or metatarsal PVR flat or barely pulsatile; TP <40 mm Hg in nondiabetics, <50 mm Hg in diabetics; $tcPO_2$ <30 mm Hg
	6	Major tissue loss[c,d]	Same as Rutherford 5 (Fontaine IV)

[a]Grades II and III correspond to critical limb ischemia.
[b]Five minutes at 2 miles per hour on a 12% incline.
[c]Nonhealing ulcer or focal gangrene with diffuse pedal ischemia.
[d]Extending above transmetatarsal level, or foot no longer salvageable.
AP, Ankle pressure; *PVR*, pulse volume recording; *$tcPO_2$*, transcutaneous oxygen; *TP*, toe pressure.
From Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26(3):517–538; and Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg*. 2007;45:S34.

and key disease modifiers. The reader is referred to other chapters in the text for detailed discussion of diagnostic testing modalities, medical therapies, and use of vascular interventions.

Classification schemes for PAD have used clinical descriptors and associated objective measures (Table 104.1). The Fontaine and Rutherford systems have been widely adopted for this purpose. They have been useful for developing treatment algorithms and prognosis across the broad spectrum of PAD. However, recent efforts to improve staging of limb-threatening disease may provide greater predictive value for endpoints such as amputation and are discussed later.

Asymptomatic Disease

The majority of individuals with PAD detected by noninvasive testing are asymptomatic.[38] Reasons for the lack of symptoms may include lower severity/burden of disease, adequate collateral artery reserve, and limited levels of activity among older subjects or those with sedentary lifestyle or with other sources of disability.

Despite the lack of claudication or CLI symptoms, asymptomatic PAD carries significant cardiovascular risk and mortality and is associated with functional decline (Fig. 104.5). Criqui demonstrated that individuals with asymptomatic PAD had an overall 2.7-fold greater risk of mortality and a 5.6-fold greater risk of CAD related death.[39] Thus the importance of diagnosing PAD in asymptomatic individuals relates to counseling and treatment of associated atherosclerosis risk factors. Notably, mortality and CV risk are strongly associated with both reduced ABI and with elevated ABI (>1.4) consistent with vessel calcification.[40,41] These data demonstrate an important relationship between the severity of PAD as determined by objective testing and long-term mortality, independent of symptoms.

Work from McDermott has highlighted that individuals with asymptomatic PAD have significant physical impairments and tend to decline further over time, leading to increased sedentariness.[13,42,43] Manifestations included reductions in daily physical activity, walking velocity, and 6-minute walk distance. These findings have been correlated to reduced calf muscle mass, increased calf muscle fat content, and impaired peripheral nerve function in asymptomatic subjects. The reversibility of these muscle and nerve changes remains unknown.[44]

The risk of progression from asymptomatic PAD to symptomatic states is not well defined. A meta-analysis estimated that 7% (4%-11%) of asymptomatic patients deteriorate to IC over a 5-year period.[45]

Intermittent Claudication

IC is a clinical syndrome characterized by reproducible leg pain brought on by exercise and relieved by rest. Other causes of leg pain that must be considered in the differential diagnosis include neurogenic (e.g., spine disease), venous, joint, and other musculoskeletal disorders. Instruments such as the Rose and San Diego Claudication questionnaires have been used in clinical and epidemiologic studies to distinguish IC from other conditions.[46,47] In clinical practice a careful history, combined with a physical exam and simple noninvasive studies, readily establishes the diagnosis in the majority of patients. However, it is well recognized that atypical leg symptoms are common in PAD patients, including pain that may also occur while standing still or sitting and discomfort or fatigability with exercise that does not cause the individual to stop walking.

IC may affect proximal (buttock, hip, thigh) or distal (calf) muscles, although calf pain is by far the most common presentation. Symptom location reflects arterial disease proximal to that level. Thus AI disease frequently presents with proximal muscle symptoms (buttock, hip, or thigh), with or without associated

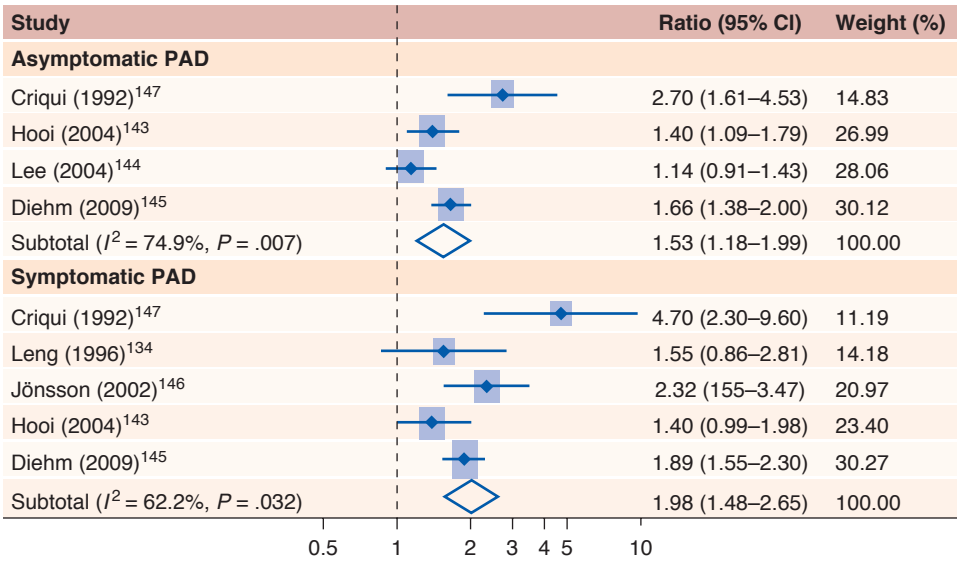

Figure 104.5 Estimated odds ratios for all-cause mortality for individuals with asymptomatic or symptomatic peripheral arterial disease *(PAD)*. (From Fowkes FG, Aboyans V, Fowkes FJ, McDermott MM, Sampson UK, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol*. 2017;14(3):156-170.)

calf pain, whereas FP disease will manifest as calf pain with exercise. An important corollary is that individuals with isolated infrapopliteal (TBP) disease frequently do not have claudication symptoms, although foot claudication in plantar muscles has been described.

Severity of IC is generally described in terms of the initial claudication distance, based on walking in daily life or on a treadmill test. Patients with severe IC are generally unable to complete a standard 5-minute treadmill protocol (2 mph, 12% incline). These individuals often describe symptom onset within minutes of walking that forces them to stop, producing significant disability and impaired QoL. Functional testing of patients with IC demonstrates a broad range of impairment in lower limb strength, balance, and associated loss of mobility. Moreover, functional decline over time in IC is significant and is associated with the severity of PAD (e.g., ABI), as well as other factors such as age, race, and socioeconomic status.[42,43,48]

Numerous studies have associated IC with long-term risk for cardiovascular events and mortality, highlighting the importance of diagnosis, medical therapy, and surveillance in these patients.[39,49,50] Over 5 years, approximately 20% of patients with IC experience a major CV event and mortality ranges between 10% and 15%, (see Fig. 104.5). Data from large registries have demonstrated that symptomatic PAD is strongly associated with CV events and mortality, even more strongly than isolated CAD or CVD.[51-53] Despite this natural history, undertreatment of patients with symptomatic PAD has been a consistent finding across studies comparing the use of antithrombotic and lipid-lowering medications across PAD, CAD, and CVD populations.[9,54] These studies and others indicate that the delivery of guideline-based medical care remains suboptimal for patients with all stages of PAD.

The limb prognosis for patients with IC is generally considered as benign; however, a significant minority of patients will progress in the degree of disability and severity of limb threat.[55,56] In a recent systematic review, 21% of IC patients experienced deterioration of limb status over a 5-year period.[45] Symptomatic deterioration is greatest within the first year after diagnosis. Risk of major amputation has been estimated at less than 1% per year across a number of studies, although accurate data are limited. Risk for progression from IC to SLI/CLI is associated with similar underlying factors as for baseline PAD, although diabetes and continued smoking appear of heightened significance.

Limb-Threatening Ischemia

The terms CLI and SLI have been defined clinically as an advanced stage of PAD in which pain at rest in the foot or tissue necrosis (gangrene or nonhealing ulceration) has occurred. These terms connote a severe impairment of limb perfusion insufficient to maintain baseline tissue requirements. Although this clinical presentation is easily distinguished from asymptomatic PAD and IC, it represents a very broad range of hemodynamic compromise and associated limb threat. As such, there remains ongoing debate as to its definition, the corresponding objective criteria, and the overall relevance of this terminology in current practice. More recent consensus efforts have suggested the alternative terminology of "chronic limb-threatening ischemia" (CLTI) to be more broadly inclusive of the full spectrum of ischemia and neuropathy that are seen in these patients.[57] This subtle change implies that absolute threshold values for perfusion deficits that are "critical" are not readily defined across the population at risk and may vary in relation to the degree of

tissue loss or infection that coexists in the individual patient and limb. In this chapter, we use the term CLI only when referencing studies in the literature that used the historical definition.

Historically, hemodynamic criteria associated with the definitions of CLI or SLI have differed for rest pain versus tissue loss and vary by technique used (e.g., ankle pressure [AP], toe pressure [AP], ankle or toe index, tissue oximetry). Typical values associated with ischemic rest pain are an absolute AP less than 40 to 50 mm Hg and TP less than 30 mm Hg. With tissue loss, these defining values are typically increased to AP less than 50 to 70 mm Hg and TP less than 40 to 50 mm Hg, respectively. In the Fontaine and Rutherford schemes, rest pain and tissue loss are assigned different stages and Rutherford further discriminates "minor" (Rutherford 5) from "major" (Rutherford 6) tissue loss. Of note, the definition of Rutherford 6 used in the literature has ranged from a nonsalvageable foot to necrosis extending anywhere proximal to the forefoot, leading to difficulty in analysis of treatment outcomes and prognosis of disease. All of these issues argue for a more consistent and comprehensive staging system for the threatened limb, as outlined later.

CLI affects a minority of individuals with PAD, variably estimated at between 1% and 10%. The prevalence of CLI has been estimated at 1.3% of an insured US adult population and 0.5% to 1.2% of Swedish adults older than 60 years.[4,7] A recent meta-analysis estimated the prevalence of CLI at 0.8%.[58] Risk factors for CLTI include all of those relevant for PAD, with a notably higher preponderance of diabetes and renal disease. Many of these patients do not relate an antecedent history of classic IC, presenting with rest pain or tissue loss as the initial clinical manifestation of PAD. This may relate to the anatomic distribution of disease (e.g., predominantly infrapopliteal involvement), coexistent peripheral neuropathy, reduced mobility from comorbid factors, or an acute inciting event such as trauma or foot infection. Careful examination of the limb and foot should evaluate for signs of ischemia, infection, skin breaks, and bony involvement and document the presence and quality of pulses and Doppler signals.

Numerous studies have documented the adverse systemic and limb prognosis associated with a diagnosis of CLI. These patients have a greater burden of coexistent CAD and CVD and are at high risk for major CV events, mortality, and amputation. A recent systematic review examined the natural history of CLI, summarizing data from 13 studies and 1527 patients who did not receive limb revascularization.[59] At 1 year, estimated mortality was 22% (12%-33%) and major amputation had occurred in 22% (2%-42%). However, these data are limited in generalizability because many patients with CLI undergo revascularization.

Given the high cardiovascular risk and its importance for clinical decision-making in CLI, multiple studies have sought to define prediction models for mortality and major amputation (Table 104.2).[60-66] Predictors have included advanced age (>75 or 80 years), renal failure, coronary heart disease, congestive heart failure, diabetes, CVD, tissue loss, body mass index, dementia, and functional status. Frailty is a recently identified functional measure that is also of clear importance in this population.[67,68] All of these tools have been developed retrospectively using data from cohorts who have undergone revascularization, thereby excluding those who were managed conservatively or treated by primary amputation. None have been prospectively tested across the full spectrum of CLI/CLTI patients presenting for evaluation and treatment.

Limb prognosis in this patient population has a broad range consistent with the spectrum of presentation from rest pain through minor and major tissue loss, with or without infection. The need for improved staging to better define amputation risk and to appropriately compare treatment outcomes led to the recent development of the Society for Vascular Surgery Lower

TABLE 104.2 Summary of Risk Prediction Models for Patients With Chronic Limb-Threatening Ischemia Who Have Undergone Revascularization

	Endpoints	Critical Factors	Reference
Taylor et al.	Mortality, ambulatory failure (median follow-up 2 years)	Age, race, ESRD, CAD, COPD, DM, dementia, baseline ambulatory status	Taylor et al.[65]
FINNVASC	Perioperative (30 day) mortality, limb loss	DM, CAD, gangrene, urgent operation	Biancari et al.[66]
PREVENT III	AFS (1 year)	ESRD, tissue loss, age >75, CAD, anemia	Schanzer et al.[60]
BASIL	Survival (2 years)	Age, CAD, smoking, tissue loss, BMI, Bollinger score, serum creatinine, ankle pressure (number measured and highest value), prior stroke/TIA	Bradbury et al.[61]
CRAB	Perioperative (30 day) mortality, morbidity	Age >75, prior amputation/revascularization, tissue loss, ESRD, recent MI/angina, emergency operation, functional dependence	Meltzer et al.[62]
Soga et al.	Survival (2 years)	Age, BMI, nonambulatory status, ESRD, cerebrovascular disease, tissue loss, left ventricular ejection fraction	Soga et al.[64]
VQI	AFS (1 year)	Age, tissue loss, DM, CHF, serum creatinine, ambulatory status, urgent operation, weight, bypass conduit used	Simons et al.[63]

AFS, amputation-free survival; *BMI,* body mass index; *CHF,* congestive heart failure;; *TIA,* transient ischemic attack.

Extremity Threatened Limb Classification System.[57] This system stratifies limb risk by grading three critical factors—Wound, Ischemia, and foot Infection ("WIfI")—similar to a "TNM" system for malignancy (Table 104.3). The staging system applies to all patients with rest pain or tissue loss, combined with objective evidence of PAD. Each of the three key factors is graded on a four-level scale, and the 64 combinations were assigned to four stages of clinical severity expected to correlate with amputation risk at 1 year. Multiple studies have been published demonstrating that WIfI staging is strongly associated with amputation and wound-healing outcomes.[69-72] These studies confirm that WIfI stage 1 is associated with very low amputation risk, whereas stages 3 and 4 are more likely to require revascularization and are at increased risk for limb loss. WIfI stage may also predict wound healing time[69,73] and has been correlated with costs of care.[74] Further efforts will be needed to prospectively

TABLE 104.3 Society for Vascular Surgery Threatened Limb Classification System (WIfI) and Relationship to Amputation Risk

Component	Score	Description		
W (Wound)	0	No ulcer (ischemic rest pain)		
	1	Small, shallow ulcer on distal leg or foot without gangrene		
	2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
	3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I (Ischemia)		ABI	Ankle pressure (mm Hg)	Toe pressure or $TcPO_2$
	0	≥0.80	>100	≥60
	1	0.60-0.79	70-100	40-59
	2	0.40-0.59	50-70	30-39
	3	<0.40	<50	<30
fI (foot Infection)	0	No symptoms/signs of infection		
	1	Local infection involving only skin and subcutaneous tissue		
	2	Local infection involving deeper than skin/subcutaneous tissue		
	3	Systemic inflammatory response syndrome		

SVS WIfI Clinical Limb Stage

Based on Estimated Risk of Amputation at 1 Year

	Ischemia – 0				Ischemia – 1			
W-0	1	1	2	3	1	2	3	4
W-1	1	1	2	3	1	2	3	4
W-2	2	2	3	4	3	3	4	4
W-3	3	3	4	4	4	4	4	4
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

	Ischemia – 2				Ischemia – 3			
W-0	2	2	3	4	2	3	3	4
W-1	2	3	4	4	3	3	4	4
W-2	3	4	4	4	4	4	4	4
W-3	4	4	4	4	4	4	4	4
	fI-0	fI-1	fI-2	fI-3	fI-0	fI-1	fI-2	fI-3

SVS WIfI Clinical Stage and 1-Year Rate of Major Amputations

Weighted Mean of Published Studies, N = 2779 Patients[a]

Clinical Stage 1	Very low risk	0.75%
Clinical Stage 2	Low risk	5.9%
Clinical Stage 3	Moderate risk	8.4%
Clinical Stage 4	High risk	25%
Clinical Stage 5 = Unsalvageable limb		

[a]Reference for composite data: Mills JL. The application of the society for vascular surgery wound, ischemia and foot infection (WIfI) classification to stratify amputation risk. *J Vasc Surg*. 2017;65:591-593.

Upper table demonstrates grading system for each component—wound, ischemia, foot infection. Bottom table summarizes their integration into four stages of limb threat and published data on outcomes.

Key: *fI,* foot infection; *I,* ischemia; *W,* wound.

ABI, Ankle-brachial index; *$tcPO_2$,* transcutaneous oxygen.

Adapted Aboyans V, Ricco JB, Bartelink MEL, et al. Eur Heart J. 2017 Aug 26. doi: 10.1093/eurheartj/ehx095. [Epub ahead of print] No abstract available. PMID:28886620

validate and refine this system using large population-based registries.

Screening for Peripheral Arterial Disease

The role of screening for PAD has been controversial. Given the strong association of PAD with mortality and CV events, some have advocated for ABI screening, which is noninvasive, simple, and inexpensive. However, the US Preventive Services Task Force found the evidence to support PAD screening as insufficient in terms of the balance of benefits and harms.[75] A recent systematic review concurred that the evidence to support PAD screening was lacking.[76] Current Society for Vascular Surgery guidelines recommend against population screening for PAD; however, they suggest that targeted screening may be reasonable among individuals at higher risk (e.g., age >70 years, diabetes) if it would improve risk stratification or influence medical therapy.[77] The 2016 AHA/ACC guidelines also recommend targeted ABI testing in asymptomatic individuals at increased risk for PAD, which they define as age older than 65 years, age 50 to 64 with risk factors for atherosclerosis or family history of PAD, age older than 50 with diabetes plus one additional risk factor, or any individual with established atherosclerosis in another vascular bed (e.g., coronary, cerebral).[78]

Surveillance of Peripheral Arterial Disease Patients With Established Disease

The benefit of surveillance for patients with asymptomatic PAD is unclear. However, patients and their primary providers should be made aware of the presence of the disease and the signs and symptoms of its advancement. Those with diabetes or history of CLTI should have regular foot examinations and be counseled on preventive foot care. Symptomatic patients with objectively determined PAD are typically followed long-term to monitor for symptomatic worsening or disease progression. Many patients with mild-moderate IC are treated with smoking cessation, optimal medical management, and exercise. Others with disabling symptoms may require revascularization. The current SVS guideline recommends that all patients with IC be followed annually to assess for compliance with medical and lifestyle management, as well as for evidence of progression, with clinical exam and noninvasive testing (ABI).[77] The AHA guideline concurs with the need for long-term clinical follow-up.[78] Patients with IC or CLI who have undergone revascularization are monitored more closely, including surveillance of the vascular reconstruction. Although level 1 evidence is lacking, multiple cohort studies and the aforementioned guidelines support a benefit for duplex ultrasound surveillance of vein bypass grafts to promote long-term patency. It is less clear if surveillance of prosthetic bypass grafts or endovascular interventions is beneficial, although it is commonly used in clinical practice. Assessment of lower extremity functional performance, new or recurrent symptoms, and a complete foot examination should be a component of semiannual or annual visits in all patients following vascular interventions.

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105 CHAPTER

Lower Extremity Arterial Disease: Medical Management and Decision Making

JESSICA P. SIMONS, WILLIAM P. ROBINSON, and ANDRES SCHANZER

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The management of lower extremity peripheral artery disease (PAD) represents one of the most challenging problems for the vascular specialist. Although its worldwide prevalence is unknown, it is estimated that 8 to 12 million Americans are affected by lower extremity PAD.[1,2] In an analysis of 2381 patients participating in the United States National Health and Nutrition Examination Survey, the prevalence of PAD was found to be 4.3% overall, progressively increasing with each decade of aging: 0.9% (40 to 49 years of age); 2.5% (ages of 50 to 59); 4.7% (ages of 60 to 69); and 14.5% (age >69).[3] The prevalence of PAD is expected to increase in the United States and worldwide as the population ages, cigarette smoking persists, and the epidemics of diabetes mellitus, hypertension, and obesity continue to grow.[2]

In accordance with the increasing prevalence of PAD, the number of lower extremity revascularization procedures has been increasing; among US Medicare beneficiaries, the number of revascularizations has increased from 357 to 581 per 100,000 between 1996 and 2006.[4] Decisions regarding the management of lower extremity PAD pose a unique challenge owing to the

Abstract

Decision making in lower extremity peripheral artery disease represents one of the most challenging and nuanced algorithms in vascular surgery. Optimal management is highly individualized, tailored to patient-specific goals, factoring in clinical presentation, anatomic pattern of disease, conduit availability, functional status, perioperative risk, and long-term survival. Medical management, principles of decision-making, and future directions for treatment of peripheral artery disease are discussed herein.

Keywords

peripheral artery disease
exercise therapy
lower extremity bypass
peripheral intervention
amputation-free survival
TASC II

complex interplay of factors that must be considered, including the underlying pathology and its natural history, anatomic defect, degree of ischemia, availability of conduit, comorbid conditions, functional status, ambulation potential, and suitability of anatomy for successful revascularization. Appropriate management of lower extremity PAD requires a firm understanding of these factors for good decision making.

Patients with lower extremity ischemia are typically divided into two groups—those with intermittent claudication and those with chronic limb-threatening ischemia (CLTI)—depending on symptoms at presentation. The term "chronic limb-threatening ischemia" is now preferred to describe the condition previously referred to as critical limb ischemia. Claudication and CLTI are managed differently because of major differences in their natural histories and expected clinical outcomes after treatment. In general, there is more consensus among clinicians regarding decision making for CLTI because the natural history of untreated CLTI more frequently leads to limb loss than does claudication. Appropriate decision making requires an understanding of the systemic nature of the disease. Patients with CLTI often have severe associated cardiovascular comorbidities and are generally older and in poorer health than those with claudication. Treatment must therefore be structured accordingly. In contrast, patients with claudication typically seek treatment for the relief of lifestyle-limiting pain with ambulation. These patients exhibit a more benign natural history with respect to limb loss, with amputation rates of 1% to 7% at 5 years and clinical deterioration of the limb in only 25%.[5-7] As with CLTI, claudication is a marker of significant systemic atherosclerosis, with associated cardiovascular mortality rates at 1, 5, and 10 years as high as 12%, 42%, and 65%, respectively.[5-7] All patients with PAD require medical management of their cardiovascular disease, and many also benefit from either endovascular or open revascularization, as discussed later.

MEDICAL MANAGEMENT

Because atherosclerosis is a systemic disease, the initial treatment of lower extremity PAD must include risk factor modification. PAD patients are at significantly increased risk for premature cardiovascular events, including myocardial infarction (MI), stroke, and death.[8,9] PAD is an important indirect marker for systemic atherosclerosis.[10] Any patient older than 40 years who is found to have an ankle-brachial index (ABI) of less than 0.90 has significant PAD, even in the absence of symptoms.[11] Interestingly, more than 50% of patients with an abnormal ABI fail to show typical symptoms of claudication or CLTI, owing to the coexistence of other major comorbidities, a condition sometimes referred to as "chronic subclinical lower extremity ischemia."[12] There is wide agreement that risk factor modification is indicated for any patient with lower extremity PAD, regardless of symptom presence or severity. Several guidelines have been published[13-17] regarding the use of screening for PAD, including a clinical practice guideline from the Society for Vascular Surgery (SVS) Lower Extremity Guidelines Writing Group.[18] The authors recommend accepted preventive strategies for systemic atherosclerosis and comprehensive tobacco cessation interventions, as well as education on signs and symptoms of progression of PAD to the symptomatic state. As a corollary, a systematic review of screening for PAD concluded that there was no evidence for revascularization in patients with asymptomatic PAD, although screening may help to identify a population in whom aggressive medical therapy may be warranted to prevent cardiovascular and cerebrovascular events.[19] The natural history of asymptomatic PAD is also not well studied. Unfortunately, there are currently no data available to accurately predict which patients will go on to develop symptoms in the future.

Risk Factor Modification

The risk factors associated with PAD are similar to those classically linked with coronary artery disease (CAD). Investigators from the Framingham Heart Study analyzing "factors of risk" for CAD were first to identify demographic and comorbid factors independently associated with systemic atherosclerosis.[20] Numerous reports since have confirmed that advanced age, tobacco use, diabetes, dyslipidemia, and hypertension are the primary risk factors associated with PAD (Fig. 105.1). More recent studies have identified non-Hispanic black race,[3,21] chronic renal insufficiency,[3,22] and elevated homocysteine levels[23,24] as additional factors. All patients with the diagnosis of PAD require appropriate risk factor modification, regardless of whether more aggressive therapy is also being contemplated. Risk factor modification is discussed in detail in Section 2: Atherosclerotic Risk Factors.

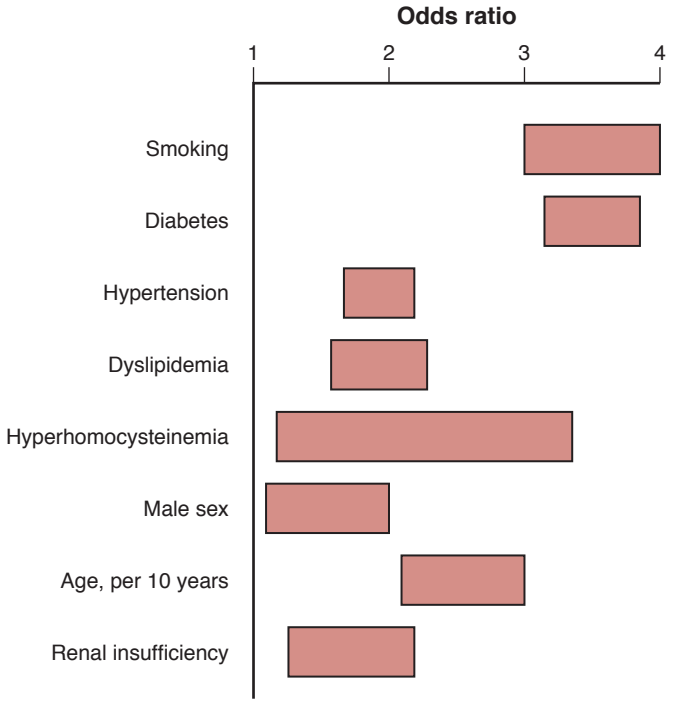

Figure 105.1 Odds ratios for risk factors for symptomatic peripheral artery disease. (Adapted from Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg.* 2007;45(Suppl S):S5-S61.)

Exercise Therapy for Claudication

Multiple reports have clearly demonstrated improvements in pain-free ambulation and overall walking performance with structured exercise training.[7,25-27] Data from more than 20 randomized trials have confirmed that exercise therapy is the best initial treatment of intermittent claudication.[27] The benefits of exercise extend beyond improvement in the symptoms of claudication. Regular aerobic exercise reduces cardiovascular risk by lowering cholesterol and blood pressure and by improving glycemic control. In most patients, claudication initiates a downward spiral of cardiovascular deconditioning that can result in an annual mortality rate as high as 12%.[27] Ambulation distance can decline at a rate of 8.4 m/year beginning with symptom onset.[28] This cycle can be halted and even reversed with exercise training. In a recent report from Japan, Sakamoto and colleagues showed that the implementation of structured exercise resulted in a 5-year cardiovascular event–free survival rate of 80.5% in patients with PAD, compared with 56.7% in untreated matched controls.[29]

The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines support supervised exercise for the treatment of intermittent claudication as a level IA recommendation.[15] The guidelines suggest that exercise training, in the form of walking, should be performed for a minimum of 30 to 45 minutes per session, 3 to 4 times per week, for a period not less than 12 weeks. During each session, the patient should be encouraged to walk until the limit of lower extremity pain tolerance is reached, followed by a short period of rest until pain relief is obtained, then a return to exercise. This cycle should be followed for the duration of the session. As the pain-free interval of ambulation increases, the level of exercise should be increased (Box 105.1).[25]

Although exercise therapy would appear easy to implement, effectiveness is often limited by poor patient compliance. Studies have shown the superiority of clinic-based exercise programs over home-based programs.[7] However, effective exercise training is not possible in up to 34% of patients because of comorbid medical conditions, and an additional 30% of patients simply refuse to participate in exercise training.[30] In addition, supervised exercise training programs are usually not covered by third-party insurance plans, although it may be in the near future by Medicare. Therefore, even though exercise therapy in motivated patients offers proven benefits, its effectiveness is applicable to only approximately one-third of patients presenting with intermittent claudication.

BOX 105.1 Key Components of a Structured Exercise Program for Claudication

Role of the Primary Clinician

- Establish the diagnosis of PAD using the ABI or other objective vascular laboratory evaluations.
- Determine that claudication is the major symptom limiting exercise.
- Discuss the risks and benefits of therapeutic alternatives, including pharmacologic, percutaneous, and surgical interventions.
- Initiate systemic atherosclerosis risk modification.
- Perform treadmill stress testing.
- Provide formal referral to a claudication exercise rehabilitation program.

Exercise Guidelines for Claudication[a]

- Include warm-up and cool-down periods of 5-10 min each.

Types of Exercise

- Treadmill or track walking is the most effective exercise for claudication.
- Resistance training may be beneficial for individuals with other forms of cardiovascular disease, and its use (as tolerated) for general fitness is complementary to but not a substitute for walking.

Intensity

- Initially, set the treadmill to a speed and grade that elicits claudication symptoms within 3-5 min.
- Patients walk at this workload until they experience claudication of moderate severity, at which point they take a brief rest period, either standing or sitting, to permit symptoms to resolve.

Duration

- The exercise-rest-exercise pattern should be repeated throughout the exercise session.
- The initial duration usually consists of 35 min of intermittent walking. This should be increased by 5 min each session until 50 min of intermittent walking can be accomplished.

Frequency

- Perform treadmill or track walking 3-5 times per week.

Role of Direct Supervision

- As walking ability improves, the exercise workload should be increased by modifying the treadmill grade or speed (or both) to ensure the stimulus of claudication pain during the workout.
- As walking ability improves, it is possible that cardiac signs and symptoms (e.g., dysrhythmia, angina, ST-segment depression) may appear. These events should prompt physician reevaluation.

ABI, Ankle-brachial index; *PAD,* peripheral artery disease.

[a]These general guidelines should be individualized and based on the results of treadmill stress testing and the patient's clinical status. A full discussion of the exercise precautions for persons with concomitant diseases can be found elsewhere for patients with diabetes (Ruderman N, Devlin JT, Schneider S, Kriska A. *Handbook of Exercise in Diabetes.* Alexandria, VA: American Diabetes Association; 2002), hypertension (*ACSM's Guidelines for Exercise Testing and Prescription.* In: Franklin BA, ed. Baltimore, MD: Lippincott, Williams & Wilkins; 2000), and coronary artery disease (*Guidelines for Cardiac Rehabilitation and Secondary Prevention/American Association of Cardiovascular and Pulmonary Rehabilitation.* Champaign, IL: Human Kinetics; 1999).

From Stewart KJ, Hiatt WR, Regensteiner JG, et al. Exercise training for claudication. *N Engl J Med.* 2002;347:1941-1951.

Pharmacologic Treatment of Claudication

Pharmacologic therapy for intermittent claudication has been the subject of intense research for more than 30 years. To date, only two drugs (pentoxifylline and cilostazol) have achieved FDA approval for the treatment of intermittent claudication in the United States. However, a number of other medications have been investigated, with varying degrees of evidence supporting their efficacy (Table 105.1). These include a number of drugs and supplements with various reported mechanisms of action such as changes in tissue metabolism (naftidrofuryl, levocarnitine), enhanced nitric oxide production (L-arginine), and vasodilatory effects (statins, buflomedil, prostaglandins, angiotensin-converting enzyme inhibitors, K-134).

Cilostazol

Cilostazol (Pletal) gained FDA approval in 1999 for the treatment of intermittent claudication. Oral administration of this phosphodiesterase III inhibitor increases cyclic adenosine monophosphate (cAMP) and results in a variety of physiologic effects, including the inhibition of smooth muscle cell contraction and platelet aggregation. Cilostazol is also thought to decrease smooth muscle cell proliferation, a process that has been implicated in coronary artery restenosis following percutaneous transluminal angioplasty.[31] Finally, cilostazol has a beneficial effect on plasma lipid concentrations, resulting in a decrease in serum triglycerides and an increase in HDL. Although the precise mechanism by which cilostazol improves the symptoms of intermittent claudication is unknown, it is likely a combination of these effects.

Several controlled clinical trials, including a meta-analysis, have confirmed the efficacy of cilostazol.[32,33,34] Results have shown increased maximal walking distances up to 50%, as well as significant improvements in health-related quality of life (QoL) measures.[33] There is also increasing evidence that cilostazol may modulate the synthesis of vascular endothelial growth factor (VEGF), potentially stimulating angiogenesis in patients with chronic lower extremity ischemia.[35]

The benefits of cilostazol in the treatment of intermittent claudication were compared with those of pentoxifylline in a randomized controlled trial performed by Dawson and associates.[32] They found that cilostazol therapy significantly increased maximal walking distance by 107 m (54% increase), compared with a 64-m improvement in the pentoxifylline group (30% increase). There was no difference in maximal walking distance improvement between the pentoxifylline and placebo groups. Regarding the durability of the effect, a recent pooled analysis of nine randomized controlled trials demonstrated a significant benefit in maximal walking distance compared with placebo at 6 months.[36]

Cilostazol has a moderate but notable adverse effect profile that includes headache, diarrhea, and gastrointestinal discomfort. Its use is contraindicated in patients with congestive heart failure, and high plasma drug levels may result when taken in combination with other medications metabolized by the liver via the cytochrome P-450 pathway.

The adverse effects of cilostazol can be minimized by initiating a progressive treatment regimen, starting at 50 mg/day for 1 week, increasing to 50 mg twice a day the following week, and finally achieving the standard dose of 100 mg twice a day in week 3. Of the pharmacologic agents used to treat claudication, cilostazol has the most data supporting its clinical use.

DECISION MAKING FOR REVASCULARIZATION

Patients with lower extremity PAD present with a wide spectrum of symptoms, ranging from asymptomatic, to only minor exertional leg pain, significant walking impairment, or even ulceration or gangrene. Therefore the first critical step in decision making for the treatment of PAD is to confirm that PAD is responsible for the patient's symptoms (see Chapter 18). In brief, noninvasive vascular laboratory testing is indicated for patients with a history consistent with vasculogenic claudication, rest pain/metatarsalgia, or tissue loss. Measurement of ABI is the most common PAD screening and diagnostic tool used. An ABI of ≤0.90 is highly sensitive and specific for the identification of PAD when compared with the "gold standard" of invasive arteriography (evidence of a hemodynamically significant peripheral arterial stenosis).[16] Complete physical examination will often disclose pulse deficits, but intact pulses at rest do not exclude hemodynamically significant PAD. After the symptom complex (either claudication or CLTI) is determined to be secondary to PAD, decision making depends on symptom severity and whether the symptoms are acute or chronic. The following discussion relates to chronic lower extremity ischemia; acute ischemia is discussed in Chapter 100.

Decision making regarding revascularization is based first on symptom status and a sophisticated understanding of the natural history of the patient's condition. Treatment strategies may thus be very different for patients with disabling claudication compared with those with CLTI because the risk of limb loss is dramatically different for the two conditions. Anatomic classification systems, such as the Trans-Atlantic Inter-Society Consensus (TASC) classification system, may assist in gauging the extent of angiographic disease. Although the TASC II classification system can be helpful in the revascularization decision-making process (i.e., endovascular or open), atherosclerotic burden as measured by arteriography is not the sole factor upon which treatment decisions should be made. Notably absent from the TASC classification system are any features relating to degree of ischemia, wounds, infection, functional status, and conduit availability, all of which are extremely important determinants of revascularization success. Clearly, angiographic anatomy alone cannot guide therapy.

Another critical element of decision making focuses on determining whether a patient will achieve meaningful benefit from a technically successful procedure. Technical success does not always equate directly with clinical success. As a result, it is important to assess baseline functional status, as well as the burden of comorbid conditions. Patients who are either bedbound at baseline or who have prohibitive medical risk may incur significantly more benefit from a treatment that differs from the TASC II recommendations (based on lesion type alone),

TABLE 105.1 Pharmacologic Treatment of Claudication

Drug	Mechanism of Action	Clinical Benefit	Adverse Effects	Current Clinical Role
Pentoxifylline	Methylxanthine derivative; improves oxygen delivery by enhancing red blood cell deformability; may inhibit platelet aggregation[34]	Improved PFWD and MWD over placebo[65,135,136]	May interfere with blood clotting, particularly when taken in combination with warfarin	FDA approved for use
Cilostazol	Phosphodiesterase III inhibitor; inhibits smooth muscle cell contraction and platelet aggregation	Improved MWD compared with pentoxifylline and placebo[135,137,138]	Headaches, diarrhea, GI discomfort; contraindicated in patients with history of congestive heart failure	FDA approved for use
Naftidrofuryl	Serotonin antagonist thought to improve aerobic metabolism	Improved PFWD; no improvement in MWD[139,140]	Minor GI, flatulence, abdominal discomfort	Widely available in Europe; not FDA approved
Levocarnitine	Carrier molecule involved in the transport of long-chain fatty acids; increases the availability of energy substrate for skeletal muscle metabolism	Improved PFWD and MWD compared with placebo[141]; no benefit was seen over exercise alone[142]	Flu-like symptoms	Available over the counter as a dietary supplement, not subject to FDA approval
HMG-CoA reductase inhibitors	Unknown; may alter vasomotor tone or stimulate angiogenesis[143]	Improved pain-free walking time; no improvement in maximal walking time compared with placebo[144]	Headache, abdominal pain, constipation; rarely, increased liver enzymes, cholestatic hepatitis, rhabdomyolysis	FDA approved for cardiovascular protection, not specifically for treatment of claudication
Buflomedil[145,146]	α_1 and α_2 antagonist, causing vasodilation; also inhibits platelet aggregation and enhances red blood cell deformability	Improved PFWD and MWD compared with placebo[147]	Lethal and nonlethal neurologic and cardiovascular adverse events have been reported[148]	Not FDA approved; studied in phase 2 trials
L-Arginine[149,150]	Amino acid precursor of endothelial-derived nitric oxide; indirectly modulates vasodilation of vascular smooth muscle	Improved MWD (with IV administration) compared with placebo[150]; no improvement over placebo when studied with oral formulation over 6 months[118]	GI distress[151]	Not FDA approved; studied in phase 2 trials
Prostaglandins: Prostaglandin E_1,[120] prostaglandin I_2,[152-154]	Vasodilatory effects; inhibit platelet aggregation	Prostaglandin E_1 improved MWD compared with placebo[120]; beraprost (prostaglandin I_2) has demonstrated conflicting results[152-154]	Headache, flushing, GI distress[119,120]	Not FDA approved; studied in phase 2 trials
Angiotensin-converting enzyme inhibitors	Vasodilation through reduction in angiotensin II, sympathetic inhibition, and improvement in endothelial function through preservation of bradykinin[52]	Ramipril improved pain-free walking time and maximal walking time over placebo[52]	Hypotension, headache, cough; rarely, hepatotoxicity, Stevens-Johnson syndrome, angioedema	FDA approved for cardiovascular protection, not specifically for treatment of claudication
K-134[155]	Novel phosphodiesterase III inhibitor; inhibits smooth muscle cell contraction and platelet aggregation	Primary analysis showed no benefit; mixed effects model showed both K-134 and cilostazol to improve peak walking time	Headache, nausea, diarrhea, tachycardia	Not FDA approved; studied in phase 2 trials

FDA, Food and Drug Administration; *GI,* gastrointestinal; *HMG-CoA,* hydroxy-3-methylglutaryl-coenzyme A; *MWD,* maximal walking distance; *PFWD,* pain-free walking distance.

to more appropriately balance the chances for functional limb salvage with the risks of periprocedural morbidity. Included in this evaluation is an assessment of the available conduit, should bypass be required. The challenge of decision making in PAD is accurately assessing each of these factors and synthesizing a plan that optimizes the likelihood of a favorable outcome for each individual patient.

Defining Treatment Success

Optimal treatment must ultimately be tailored to each patient. Although the general goal of any revascularization, whether for claudication or CLTI, is to increase the perfusion to the extremity as measured by physiologic testing, there are several other aspects that define treatment "success." These will not be the same for every patient with lower extremity PAD.

Limb- and Patient-Centered Outcomes

Traditional definitions of treatment success included technical outcomes such as graft/stent patency. However, graft patency may not correlate well with limb preservation; Simons et al. found that 10% of patients who underwent lower extremity bypass for CLTI failed to achieve clinical improvement despite having a patent graft at 1 year postoperatively.[37] Other outcome measures such as survival or amputation-free survival (AFS) have also been widely used. Some have questioned the appropriateness of these endpoints. In a critique of the Bypass Versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial,[38] Conte noted that lower extremity bypass is generally not offered as a life-saving therapy, and therefore survival is not an appropriate measure for comparisons between revascularization strategies.[39] In addition, Conte stressed the importance of limb- and patient-centered outcomes, such as freedom from re-intervention. This shift toward more patient-centered outcomes is reflected in the SVS objective performance goals (OPGs) (https://www.vascularweb.org/research/clinicalresearch/Pages/cli-objective-performance-goals.aspx). These guidelines were developed specifically for comparative evaluations of different treatments for CLTI,[40,41] but the endpoints chosen are key components of treatment success for PAD, namely major adverse limb events, which included both freedom from major amputation as well as from re-intervention. This novel approach shifts the focus of outcome measures from technical success rates such as primary and secondary patency to one that acknowledges a burden incurred by the patient with each intervention that is required to maintain that limb and function (Table 105.2).

Claudication

For patients with claudication, surgeon-defined, procedural endpoints may not accurately capture all relevant outcomes. Some have challenged the traditional approach to patients with claudication.[42,43] Given the more benign natural history with respect to limb loss, nonoperative therapy is traditionally recommended as the first line of treatment; limb loss is therefore not a logical measure of treatment success. Kalbaugh and colleagues, using the Short Form (36) Health Survey (SF-36), found that

TABLE 105.2 Chronic Limb-Threatening Ischemia Endpoint Definitions and Event Rates Reported by the Society for Vascular Surgery Working Group for the Development of Objective Performance Goals for Evaluating Catheter-Based Treatment[a]

Endpoint	Definition	Event Rate (%) (95% CI)
Safety Outcomes (30 Day)		
Major adverse cardiovascular event (MACE)	Myocardial infarction, stroke, or death (any cause).	6.2 (4.7-8.1)
Major adverse limb event (MALE)	Above-ankle amputation of the index limb or major re-intervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis).	6.1 (4.6-7.9)
Amputation	Above-ankle amputation of the index limb.	1.9 (1.1-3.1)
Efficacy Outcomes (1 Year; All Rates Are Freedom From Event)		
Perioperative death or MALE	Perioperative death (30 days), or any MALE	76.9 (74.0-79.9)
Amputation-free survival (AFS)	Above-ankle amputation of the index limb or death (any cause).	76.5 (73.7-79.5)
Re-intervention or amputation or stenosis (RAS)	Any re-intervention, above ankle amputation of the index limb, or stenosis	46.5 (42.3-51.2)
Re-intervention or amputation (RAO)	Any re-intervention or above ankle amputation of the index limb.	61.3 (58.0-64.9)
Limb salvage	Freedom from above-ankle amputation	88.9 (86.7-91.1)
Survival	Freedom from death (any cause)	85.7 (83.3-88.1)

[a]As reported by the Society for Vascular Surgery Working Group for the development of objective performance goals for evaluating catheter-based treatment.
CI, Confidence interval.
Data are pooled from prospective trials of vein bypass surgery in CLTI.
From Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *J Vasc Surg*. 2009;50:1462-1473.

reassurances about the benign natural history of their condition did little to alleviate patients' symptoms. Conversely, intervention for claudication improved QoL scores considerably. Improvements were similar to those found after coronary artery bypass surgery for angina and were half as beneficial as hip replacement surgery. In a more recent series, Taylor and coworkers reported significant symptomatic improvement after intervention for claudication in nearly 80% of treated patients.[44] Revascularization in this series was exceedingly safe, with no early amputations and a 99% limb salvage rate at 5 years.

Although it is accepted that revascularization is not appropriate in every case, there is clear evidence that QoL is improved by revascularization in many instances.[45-48] Indeed, the recent focus on patient-oriented endpoints has stimulated new research in the objective measurement of QoL for patients undergoing lower extremity revascularization. Various questionnaires have emerged as tools to measure QoL. Unfortunately, there is no consensus on the ideal questionnaire to use for the evaluation of patients with PAD. The two most commonly used surveys are the SF-36 and the Nottingham Health Profile.[49,50]

Chronic Limb-Threatening Ischemia

Taylor and colleagues recently studied 331 consecutive patients treated for Rutherford class 5 and 6 ischemia (tissue loss).[51] A bypass was deemed clinically successful if all four outcome criteria were met: (1) bypass patency until wound healing occurred, (2) limb salvage for at least 1 year, (3) maintenance of ambulatory status for at least 1 year, and (4) survival for at least 6 months. The authors found acceptable results when examining these components separately, including a graft patency rate of 72% and a limb salvage rate of 73% at 36 months. However, the clinical success rate, defined as the achievement of all four criteria, was only 44%. Furthermore, patients who presented with impaired ambulatory status, end-stage renal disease, gangrene, and infrainguinal disease (each independent statistical predictors) were especially prone to failure (Table 105.3).[51] Prospects for a successful outcome became progressively dismal as the number of independent negative predictors increased. Patients harboring two of these independent predictors of failure experienced approximately a 33% probability of success; those with three predictors, a 10% probability of success; and those with all four independent predictors of failure, less than a 5% probability of success. Similar studies using consensus definitions of success are needed to help guide decision-making regarding who should receive intervention and who should not.

TABLE 105.3 Probability of Failure After Bypass[a] When the Clinical Condition Is Present at Presentation

Predictor Variable	Probability of Failure (%)	Odds Ratio (95% CI)
Impaired ambulation	58	6.4 (2.9-14.4)
Infrainguinal disease	46	3.9 (1.6-9.8)
ESRD	35	2.5 (1.2-5.4)
Gangrene	34	2.4 (1.5-4.0)
Hyperlipidemia	11	0.6 (0.34-0.93)

[a]Defined as patent bypass until healed, limb salvage for 1 year, maintenance of ambulation for 1 year, and survival for 6 months.
CI, Confidence interval; *ESRD*, end-stage renal disease.
From Taylor SM, Cull, DL, Kalbaugh CA, et al. Critical analysis of clinical success after surgical bypass for lower extremity ischemic tissue loss using a standardized definition combining multiple parameters: a new paradigm of outcome assessment. *J Am Coll Surg*. 2007;204:831-839.

Treatment Guidelines According to Anatomic Disease Classification

Several classification systems have been developed that characterize PAD on the basis of anatomic descriptions of lesion type and location. The major goals have included standardization of reporting disease burden, development of methods to correlate disease burden with clinical severity, and development of recommendations for method of intervention. Although these classification schemes provide some value, they notably fail to capture major factors that determine the success of intervention.

Trans-Atlantic Inter-Society Consensus Classification

In January 2000 the TASC for the Management of Peripheral Arterial Disease published a document authored by a working group of representatives from 14 surgical vascular, cardiovascular, and radiologic societies.[52] An updated document (TASC II) was published in January 2007. These important works not only classified the lesions but also provided treatment recommendations according to lesion type. The TASC working group has classified anatomic patterns of disease involvement (types A through D) for both the aortoiliac (Fig. 105.2) and femoropopliteal (Fig. 105.3) segments, based on recommended treatment (endovascular versus open surgery). The TASC working group advocated endovascular treatment for TASC type A lesions and open surgical treatment for TASC type D lesions. For TASC type B and C lesions, the authors concluded that there was insufficient evidence to definitively recommend one modality over the other.[53]

Runoff Score

In 1986 the SVS and the International Society for Cardiovascular Surgery published reporting standards for lower extremity ischemia, which included the description of a runoff score to characterize the status of the outflow vessels distal to the distal anastomosis of a lower extremity revascularization procedure[54]; this was revised to the current version in 1997[55] to better incorporate the contribution of pedal vessels. The score values range from 0 to 10 (with 0 being completely patent, disease-free outflow) that is calculated based on the degree of occlusion and the relative contribution to outflow of each vessel. This formula translates into a description of the resistance in the outflow bed and therefore was designed to facilitate comparisons of expected bypass patencies. A simplified four-level version

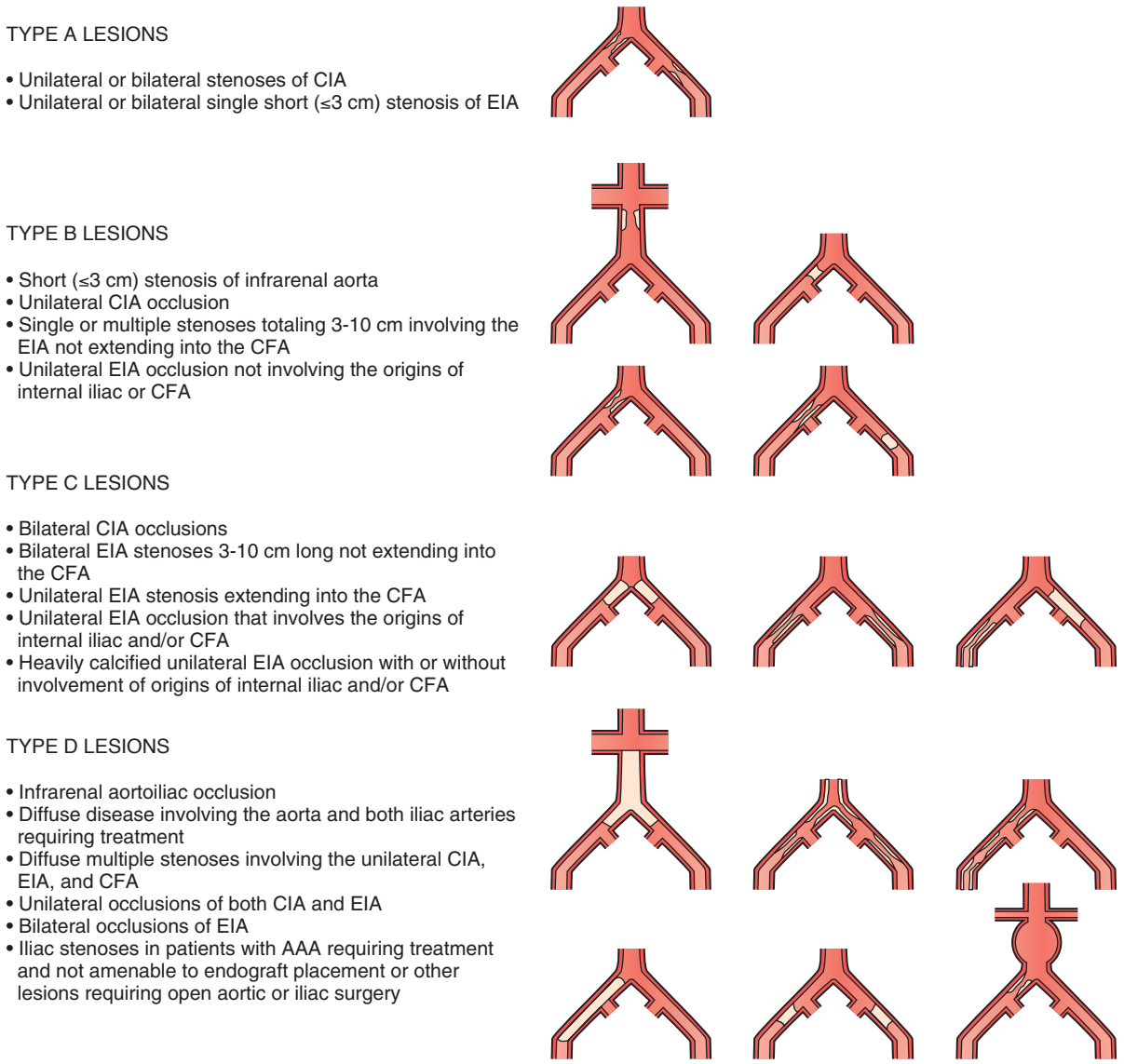

Figure 105.2 Trans-Atlantic Inter-Society Consensus classification of aortoiliac lesions. *AAA*, Abdominal aortic aneurysm; *CFA*, common femoral artery; *CIA*, common iliac artery; *EIA*, external iliac artery. (Redrawn from Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg*. 2007;45(Suppl S):S5-S61.)

(scores 0 to 3) is also described that applies the weighting units to the outflow in an all-or-none fashion based on the presence of any hemodynamically significant stenosis. The authors note explicitly that neither of these systems should be used to the exclusion of other systems, and do not offer these as a scheme for making treatment decisions.

TREATMENT GUIDELINES ACCORDING TO PRESENTATION

Claudication

Traditional treatment recommendations for intermittent claudication have balanced the risk of intervention against the natural history of the disease. It has long been appreciated that claudication is a marker for more serious potential manifestations of systemic atherosclerosis. With the goal of preserving life and limb, many experts agree that the best strategy is to initiate systemic medical therapy aimed at reducing cardiac morbidity. This strategy is based on the low relative risk of limb loss in patients with claudication compared with the significant relative risk of stroke, MI, and death. The ACC/AHA guidelines suggest that the risk of major limb amputation for a patient with intermittent claudication is approximately 1% per year, whereas the risk of cardiac death is approximately 3% to 5% per year.[15,56-58] Treatment strategies have therefore stressed cardiovascular risk factor modification and medical therapy as the best initial treatment for patients with PAD symptoms limited to intermittent claudication. Medical treatment for intermittent

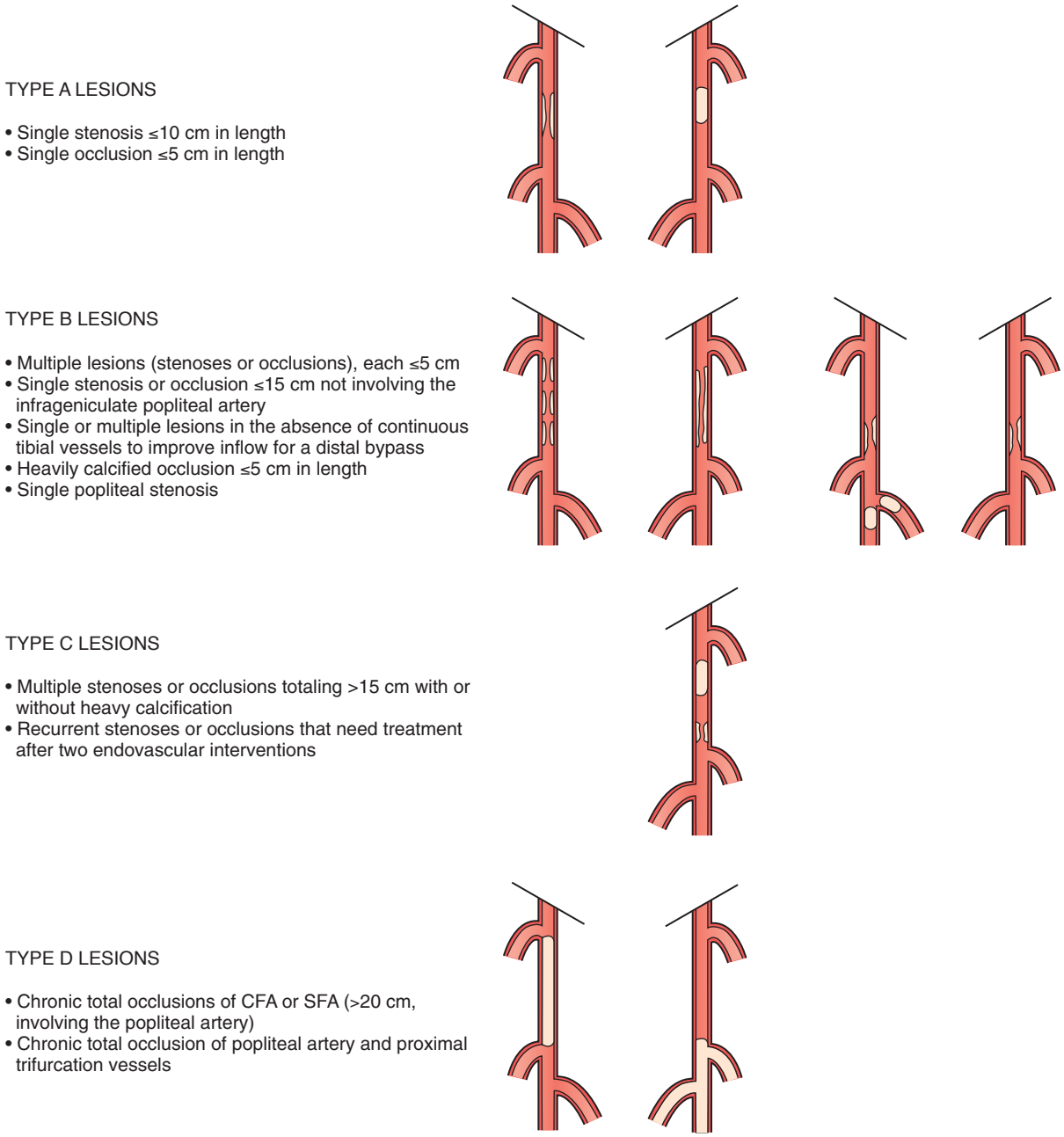

Figure 105.3 Trans-Atlantic Inter-Society Consensus classification of femoropopliteal lesions. *CFA*, Common femoral artery; *SFA*, superficial femoral artery. (Redrawn from Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg*. 2007;45(Suppl S):S5–S61.)

claudication consists of smoking cessation, exercise training, and pharmacologic therapy, as already described. Revascularization is recommended only in cases of severe claudication and only after medical therapy has failed.

Medical Therapy Versus Revascularization

The role of smoking cessation in treating the symptoms of claudication is unclear. Although studies have shown that smoking cessation can improve walking distance in some cases, these findings are not universal.[59] However, the association between tobacco cessation and the reduction of subsequent cardiovascular events is undisputed. The rationale for smoking cessation is therefore based on reducing patient mortality and slowing the overall atherosclerotic disease process.

Currently available pharmacologic agents for claudication have already been discussed (see section "Pharmacologic Treatment of Claudication"). The ACC/AHA guidelines recommend, in addition to routine antiplatelet therapy, a therapeutic trial of cilostazol (100 mg 2 times a day) as an effective method for increasing overall ambulation (class I recommendation). This agent is limited to patients with PAD and intermittent claudication and no history of congestive heart failure, because cilostazol

is a phosphodiesterase-3 inhibitor capable of exacerbating ventricular dysfunction.[15] Unfortunately, adverse effects prevent the routine use of cilostazol in up to 15% of patients.[32,33]

When comparing medical to endovascular therapy, there are abundant data supporting the efficacy of medical therapy. For instance, the Edinburgh walking study consisted of a randomized trial to determine outcome differences in patients with intermittent claudication treated with angioplasty and stent versus medical management (daily low-dose aspirin, lifestyle modification) after 2 years. These investigators found no difference in maximal walking distance, treadmill distance until onset of claudication, and QoL measures between the two groups.[60] Supervised exercise therapy has also been compared with primary stenting for disabling claudication due to aortoiliac occlusive disease in the Claudication: Exercise Versus Endoluminal Revascularization (CLEVER) trial.[61] At 6-month follow-up, they reported that change in peak walking time was greatest for supervised exercise, intermediate for stenting, and least with pharmacologic therapy (mean change versus baseline, 5.8 ± 4.6, 3.7 ± 4.9, and 1.2 ± 2.6 minutes, respectively; $P < .04$ for the comparison of supervised exercise versus stenting). QoL evaluation revealed significant improvements in both the supervised exercise and the stenting groups compared with pharmacologic therapy, but the benefit was greater in the stenting group than in the exercise group.

In summary, when weighing medical therapy versus revascularization for the treatment of intermittent claudication, the risk-to-benefit ratio favors initial medical therapy in most cases. However, medical therapy may be effective in as few as 30% of patients because of noncompliance and drug intolerance. When revascularization is chosen, modern approaches have become predominantly endovascular owing to its reduced procedural risks compared with open surgery. However, an analysis of practice patterns in New England between 2003 and 2009 demonstrated that an increasing proportion of lower extremity bypass procedures were performed for claudication in recent years (from 19% to 31%, $P < .0001$). In addition, the percent of patients with a history of previous endovascular intervention has steadily increased (from 13% to 23%, $P = .02$).[62] The authors suggest that the high rates of prior endovascular intervention seen may reflect a "treatment trap"; after the decision has been made to intervene procedurally for claudication, surgeons may feel obliged to perform an open revascularization if a prior endovascular approach has failed to resolve symptoms. Of note, the 1-year incidence of major amputation after intervention on claudicants was 1.6% in this study; although this is low, it is a devastating outcome after a procedure for claudication. Clinical decision making ultimately must incorporate not only the risks and benefits of various treatment strategies but also a discussion of realistic expectations as to the extent to which treatment will improve symptoms and improve QoL.

Endovascular Treatment Versus Open Surgery (see Chapters 106 through 110)

Ultimately, the selection of the best method of revascularization for an individual with claudication is based on a balance between the risks of the specific intervention and the degree and durability of improvement that can be expected from the intervention.[53] Because the natural history of vasculogenic claudication is relatively benign, that balance usually does not favor open surgery. In contrast, its relatively low morbidity and mortality make endovascular therapy particularly attractive,[53] and when it is anatomically feasible, endovascular therapy is often preferred to open surgery for most cases of claudication.[60] However, it is important to note that a growing body of evidence suggests that the concept that an endovascular option "does not burn any bridges" is false.[63,64]

Anatomy is one of several important considerations when selecting the best interventional modality for patients with claudication as well as those with CLTI. Prospective studies dating to the 1980s have characterized the arterial lesions and anatomy most conducive to long-term patency after angioplasty. Johnston and colleagues demonstrated in a prospective analysis that the arterial anatomy and clinical presentation most amenable to long-term patency and success using angioplasty were focal arterial lesions in large-diameter vessels with adequate outflow.[65] Outcomes were more favorable in nondiabetic patients presenting with claudication than in those with CLTI. The arterial segment best managed with percutaneous transluminal angioplasty is thus the common iliac artery, a vessel with all the favorable anatomic characteristics identified by Johnston's study. Atherosclerotic lesions in this segment are usually focal and possess good outflow. Angioplasty patency rates at 5 years generally exceed 70%.[44] Conversely, long-segment arterial disease, such as a long superficial femoral artery occlusion, is probably best treated with open bypass from the standpoint of durability of the revascularization. Diffuse multisegmental disease, more common with CLTI, can present a therapeutic dilemma.

Chronic Limb-Threatening Ischemia

CLTI is defined as chronic lower extremity PAD with either ischemic rest pain or the tissue loss (nonhealing ulcers or gangrene) (see Chapter 104). Typically, symptoms have to be present for more than 2 weeks and associated with an ankle pressure less than 50 mm Hg or a toe pressure less than 30 mm Hg.[60] Although far fewer patients present with CLTI than with intermittent claudication, CLTI patients consume the vast majority of treatment resources. A surprisingly small fraction of patients (<5%) with intermittent claudication progresses to CLTI. Patients with "chronic subclinical ischemia"—those with low perfusion and ankle pressures but who are asymptomatic for a variety of reasons—are also at risk for the development of limb ischemia.[60]

Prognosis for CLTI is considerably worse than for intermittent claudication; as many as 25% of CLTI patients progress to major limb amputation within 1 year, and 25% die of cardiovascular complications within 1 year.[66] However, CLTI populations are quite heterogeneous and it is therefore difficult to precisely define its natural history. For example, CLTI patients in the placebo arm of the Circulase trial experienced an 87% limb salvage rate at 6 months,[67] a limb salvage rate not dissimilar from the treatment arms in the BASIL trial *(Bradbury AW)* or

the PREVENT III trial.[68] Decision making for CLTI commonly poses three dilemmas: whether to treat medically or with intervention; if treating with intervention, whether to amputate or revascularize; and if revascularizing, whether to use endovascular intervention or open surgery.

Medical Therapy Versus Revascularization

The natural history of untreated CLTI is poorly understood because most functional patients receive some type of revascularization. Limb loss and cardiac death are common; 1-year mortality ranges from 20% to 30%, with cardiac deaths outnumbering noncardiac deaths four to one.[69] The best information regarding the natural history of nonrevascularized limbs in patients with CLTI comes from the placebo arms of pharmacotherapy trials of patients with unreconstructable vascular disease. Results suggest that this subgroup has a dismal prognosis, with nearly 40% of limbs progressing to amputation at 6 months.[70] Therefore, in functional patients, some type of revascularization is almost always preferable to medical therapy.

However, medical therapy for CLTI is not without some noteworthy successes. Indeed, wound care centers have become common adjuncts to many vascular surgical practices (see Chapter 115). Ischemic ulcer healing rates of 55% have been reported from dedicated centers using modern wound care methods such as negative-pressure wound therapy, intense débridement, and antibiotic therapy.[71] However, wound healing in such situations is often slow, laborious, and unpredictable. To date, pharmacotherapy for CLTI has failed to yield any major breakthroughs. The routine use of prostanoids, vasodilators, antiplatelet agents, and even hyperbaric oxygen for the treatment of ischemic ulcers remains of unproven benefit.[71]

In summary, revascularization is an essential component in the relief of CLTI. Although medical adjuncts geared at risk factor modification may be important to slow the progression of systemic atherosclerotic disease, they play a secondary role in the treatment of the severely ischemic limb. In those rare cases in which vascular disease is truly unreconstructable, a trial of intensive wound care, preferably at a dedicated wound care center, may yield satisfactory healing rates for motivated patients with superficial ulcerations, or it may avoid major limb amputation in high-risk patients who are approaching the end of life.

Limb Amputation Versus Revascularization

For the overwhelming majority of patients with CLTI, revascularization is the interventional treatment of choice. However, primary limb amputation continues to be required in 10% to 40% of CLTI patients, owing to overwhelming infection or unreconstructable vascular disease.[72] Unreconstructable vascular disease accounts for nearly 60% of patients requiring secondary amputation.[71] In many of these cases, revascularization has failed due to disease progression, recurrent ischemia, or persistent infection or necrosis despite a patent revascularization.

Although counterintuitive, limb amputation and prosthetic rehabilitation can be an excellent option, offering an expedient return to a reasonable QoL in selected cases. Maintenance of ambulation can exceed 70%, and maintenance of independence can exceed 90% in young, good-risk patients after below-knee amputation.[73] Clearly, amputation should be considered a tool capable of extending functionality and not a failure of treatment in these cases. If there is the potential for some degree of rehabilitation, the limb amputation should be performed at the lowest possible level at which healing can be expected, because the work of walking increases dramatically as the level of amputation becomes more proximal. Typically, patients with well-controlled medical comorbidities, a palpable femoral pulse, a warm calf, and no signs of infection are likely to heal after a below-knee amputation (see Chapters 111 and 112).

The use of an immediate postoperative prosthesis (IPOP) may also aid in expediting a patient's recovery following below-knee amputation. This technique, first described in the 1960s, gained favor following a publication, the Prosthetic Research Study, by Burgess and colleagues.[74] They reported that the use of a rigid cast placed intraoperatively facilitated faster healing and return to ambulation. Folsom and colleagues studied this technique in a population where the indication for amputation was not trauma, but rather severe infection or unreconstructable PAD.[75] Of 65 patients, 86% returned to independent ambulation, with an average time to ambulation of 15.2 days following below-knee ambulation. A more recent comparative analysis of IPOP compared with traditional soft dressings demonstrated no difference in complication rates, and a lower incidence of revision (soft dressings 27.6% vs. IPOP 5.4%, $P = .021$).[76]

Patients with major tissue loss who are too sick or infirm to realize the benefit of limb revascularization should undergo palliative primary above-knee amputation. However, judging patients "too sick or infirm" can be difficult. Obviously, a nonambulatory, elderly, nursing-home patient with knee contractures and neuropathic heel ulcers would qualify for a palliative above-knee amputation. For patients who are minimally ambulatory, with multiple comorbidities, the decision is less clear-cut. An individualized judgment is required to determine whether these patients will be better served by primary amputation or limb revascularization. In a single-institution study of 1000 consecutive revascularizations for CLTI, preoperative functional performance status was the most important predictor of postoperative functional outcome—even more important than limb salvage itself.[77] This finding strongly suggests that there is a definite subset of patients who are too sick or debilitated to realize the functional benefits of revascularization. Although more work is needed to better define such patients, this cohort is likely best suited for primary amputation.

Endovascular Treatment Versus Open Surgery (see Chapters 106 to 110)

For many years, the classic treatment approach for CLTI has been open surgery. CLTI is usually associated with multilevel arterial disease that is not ideally suited to percutaneous intervention. Diffuse, extensive PAD causing CLTI in both aortoiliac and femoropopliteal locations (see Figs. 105.2 and 105.3) is best treated by surgical bypass according to TASC.[78] However, the primacy of surgical bypass for CLTI management has been challenged in recent years and has become the subject of intense

debate. Those who favor open surgery for the treatment of CLTI often cite superior reconstruction patency and increased durability.[79-81] However, open surgery is usually associated with higher perioperative morbidity and longer hospitalization.[82] In addition, long-term postoperative graft surveillance is necessary to maintain a patent infrainguinal bypass, as has been shown in well-performed studies from both Europe and North America suggesting that such surveillance is economically justified by preventing vein graft occlusion and late amputation.[83,84] A re-intervention rate of 20% to 30% to treat failing grafts due to intrinsic vein graft stenoses is usually necessary to maintain the increased durability attributed to open surgery.[83,85] Last, successful surgery depends on the presence of a suitable venous conduit for bypass.[86,87] Those who favor interventional treatment cite the low morbidity and mortality associated with a procedure that is usually performed on an outpatient basis.[88] Although proponents acknowledge the limited reconstruction patency rates associated with endovascular treatment, especially for the high-risk lesions often encountered in CLTI, they argue that restenosis rarely jeopardizes subsequent surgery.[88-90] In contrast, others have found that prior ipsilateral intervention has a negative influence on subsequent bypass. An analysis of the BASIL data by treatment received found 1-year AFS was 40% for bypass that followed a failed endovascular intervention, compared with 70% for the bypass-only group.[64] The authors therefore do not endorse the concept of a "free shot" with an endovascular first approach. Nolan et al. also found a correlation of graft failure and prior endovascular intervention; in a study of CLTI patients who underwent lower extremity bypass in New England, those with a prior failed endovascular intervention had a higher incidence of major amputation (31% vs. 20%; $P = .046$) and graft occlusion (28% vs. 18%; $P = .009$) at 1 year.[91] Although a causative relationship has not been established, the concept of "burning bridges" with an aggressive endovascular-first approach clearly deserves further study.

Situational Perfusion Enhancement

Proponents of endovascular intervention frequently cite the phenomenon of situational perfusion enhancement and its role in the treatment of CLTI. They argue that there is a population of asymptomatic patients with subclinical lower extremity ischemia and very low perfusion pressures. These patients become symptomatic only when they develop incidental foot ulceration and do not have the circulatory reserve to heal. A boost in arterial perfusion, even transiently, usually allows healing of the ulcer. After the ulcer is healed, maintenance of enhanced perfusion is not critical, and recurrent ischemia is usually well tolerated as the patient resumes the subclinical ischemic state. Endovascular intervention proponents therefore argue that inferior reconstruction patency rates after such interventions are inconsequential. Although the phenomenon of situational perfusion enhancement has been observed and reported anecdotally, it should be accepted with caution. If the ulceration is a sporadic event (e.g., the result of minor incidental trauma), a situational boost to perfusion could be sufficient to accomplish healing. However, if the ulcer is the result of neuropathic changes in the foot, in which case ulcer recurrence is the rule rather than the exception, a more durable reconstruction is probably indicated. The role of situational perfusion enhancement in patients who develop ischemic rest pain is likewise unclear.

BASIL Trial

There is a striking paucity of level I data to guide decision making for endovascular treatment versus open surgery. In the United Kingdom the BASIL study represents the only randomized controlled multicenter trial comparing angioplasty to open surgery for severe limb ischemia.[92] In this study of nearly 450 patients randomized to bypass or balloon angioplasty for the initial treatment of infrainguinal disease, the findings support much of what is known about the two modalities and underscore several important caveats. Using AFS as the primary endpoint, the authors found that patients treated with bypass first had comparable outcomes to patients treated with balloon angioplasty first at 6 months (amputation or death = 21% with bypass first vs. 26% with balloon angioplasty first; P = not significant). Although the early mortality was similar in both treatment groups, surgery was associated with higher morbidity. Crossover treatment after initial therapy (surgery to angioplasty or angioplasty to surgery) was common in both treatment groups, with more than half the angioplasty arm and approximately one-third of the surgical arm requiring further intervention. At the end of 5 years, 55% of patients were alive without amputation, 8% were alive with amputation, 8% were dead after amputation, and 29% were dead without amputation. After 2 years, both AFS (hazard ratio, 0.37; $P = .008$) and overall survival (hazard ratio, 0.34; $P = .004$) were better in the surgical arm.

The BASIL trial reinforces several principles. It clearly supports the phenomenon of situational perfusion enhancement. Patients who have lower extremity ulceration that would be expected to heal with conventional wound therapy and enhanced perfusion within 6 months are good angioplasty candidates. The TASC document currently recommends angioplasty over open surgery when the desired outcomes of the two modalities are comparable.[78] However, angioplasty is probably not appropriate when recurrent ulceration and persistent ischemic symptoms are expected to exceed 6 months. The advantage of having surgery first becomes apparent at 2 years. If it appears that the patient's life expectancy or the course of the disease will exceed 2 years, surgery is probably the more appropriate first intervention. Finally, the degree of treatment crossover in the BASIL trial was arguably its most remarkable finding. It stresses that angioplasty and open surgery are not "either-or" therapies but are complementary. It underscores the importance of training surgeons who manage lower extremity ischemia so that they possess both open and endovascular skill sets.[93]

Ongoing Trials

The lack of high-quality evidence to guide therapy in patients with CLTI has prompted the initiation of two more large-scale trials that deserve mention. The BASIL-2 trial (http://www.birmingham.ac.uk/research/activity/mds/trials/bctu/trials/portfolio-v/Basil-2/index.aspx, accessed 27 March 2016) is a

multicenter, randomized clinical trial of "vein-bypass first" or "best endovascular therapy first" approach in patients with severe limb ischemia; it began recruitment across England, Scotland, and Northern Wales in June 2014.[94] The investigators seek to recruit 600 patients over a 3-year period. The primary outcome is AFS. A number of secondary outcomes will also be analyzed, including major adverse limb events, health-related QoL, crossover and re-intervention rates, and cost-effectiveness measures.

In the United States a similar effort is underway to further define the best treatment strategy for patients with CLTI, the Best Endovascular versus Best Surgical Therapy in Patients with CLI Trial (BEST-CLI) (ClinicalTrials.gov: NCT02060630; www.BESTCLI.com, accessed March 27, 2016).[95] This multicenter clinical trial seeks to randomize 2100 patients with CLTI, across the United States and Canada, to either best open or best endovascular therapy; the first patient was enrolled in September 2014. The primary endpoint is major adverse limb events. Planned secondary endpoints include freedom from clinical failure and from hemodynamic failure, health-related QoL, and cost-utility analysis.

Hopefully, these two landmark studies, if completed successfully, will better inform the complex decision-making process necessary to choose between endovascular treatment and open surgery for patients with CLTI.

Threatened Limbs, With or Without Peripheral Arterial Disease

In recognition of the fact that PAD patients are a subset of patients at risk for limb loss due to a variety of potential etiologies (diabetes mellitus, most commonly), the SVS commissioned the Lower Extremity Guidelines Working Group to create a more comprehensive classification system to serve as a more robust decision-making aid for this broader category of patients. This new classification framework, entitled the SVS Threatened Limb Classification System [Mills JL, Conte MS, Armstrong DG, et al. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection. *J Vasc Surg*. 2014;59:220–234.] incorporates three major factors that impact amputation risk and clinical management: Wound, Ischemia, and foot Infection (WIfI). The intent of this new SVS WIfI classification system is to stage patients across a broad spectrum of lower extremity arterial occlusive disease of varying severity and distribution. In the SVS WIfI system, wounds are classified from grade 0 through grade 3, based on size, depth, severity, and anticipated difficulty achieving wound healing. Ischemia is classified from grade 0 through grade 4 according to ABI, ankle systolic pressure, toe systolic pressure, or transcutaneous oximetry. Infection is classified from grade 0 through grade 3 based on simple objective clinical observations. The combination of grades is used to categorize the limb into one of four clinical stages that correlate with major amputation risk at 1 year. Multiple studies have validated the SVS WIfI system as an accurate way in which to predict amputation risk and stratify patients to permit more meaningful analyses of outcomes for various forms of therapy in this challenging heterogeneous population.[96-101]

Impact of Conduit Availability, Preoperative Functional Status, and Comorbid Disease

Decision making in the treatment of lower extremity PAD has focused on *how* to treat patients. In the future, as the financial condition of the healthcare system continues to deteriorate, decision making will focus on *who* to treat. It is naïve to believe, for instance, that all patients who present with CLTI will benefit from aggressive intervention. Indeed, in the BASIL study cited earlier, an independent data-monitoring committee overseeing patient enrollment in this trial found that half the patients with severe limb ischemia were regarded as unsuitable or unfit for any form of revascularization. The authors concluded that patients eligible for revascularization represent the tip of an iceberg, the true dimensions of which remain incompletely defined.[92] Interventional treatment cannot and should not be offered to everyone. The true task, then, is to refine definitions of success and construct tools using evidence-based data to help distinguish patients who will benefit from therapy from those who will not. This necessitates study of not just those who undergo revascularization, but also those patients for whom either palliation or primary amputation is offered in order to truly capture the denominator of this problem.

Conduit Availability

The availability of adequate conduit for open bypass plays a critical role in the decision of how best to treat a patient with lower extremity PAD, particularly CLTI. Great saphenous vein of adequate caliber, even if it must be harvested from the contralateral leg, remains the conduit of choice for open bypass.[102] It has been shown to have superior durability compared with all other conduit choices: prosthetic grafts, short saphenous vein, spliced arm vein, and vein cuffs.[103] In the absence of good-caliber great saphenous vein for bypass, an endovascular revascularization becomes a more attractive option. Having said that, multiple authors have demonstrated excellent outcomes in large surgical bypass series using alternative autogenous vein options (cephalic vein, basilic vein, short saphenous vein).[104-106] Performance of vein mapping prior to arteriography is essential because of the strong influence it can have on the decision of how aggressively to pursue an endovascular revascularization strategy.

Influence of Comorbid Conditions and Preoperative Functional Status

The patient's ability to tolerate an open revascularization must be assessed as part of the decision-making process. Several studies have sought to identify factors associated with perioperative morbidity and mortality. Using data on 9556 patients identified from the National Surgical Quality Improvement Program between 2007 and 2009, the 30-day mortality associated with lower extremity bypass was 1.8%.[107] The incidence of nonfatal cardiac complications is higher. In a cohort of 2907 patients who underwent lower extremity bypass in New England between 2003 and 2007, cardiac complications occurred in 7.2%.[62]

TABLE 105.4 Morbidity After Infrainguinal Bypass for Claudication and Chronic Limb-Threatening Ischemia

	First Year	3-5 Years
Time for healing	15-20 weeks	—
Wound complications (%)	15-25	—
Persistent lymphedema (%)	10-20	Unknown
Graft stenosis (%)	20	20-30
Graft occlusion (%)	10-20	20-40
Major amputation (%)	5-10	10-20
Graft infection (%)	1-3	—
Perioperative death (%)	1-2	—
All death (%)	10	30-50

Adapted from Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg*. 2007;45(Suppl S):S5–S61.

Several other complications, both local and systemic, have been well described (Table 105.4). These are discussed, as well as recommendations for preoperative risk assessment, in Chapter 32 and Section 7.

Beyond the risk of perioperative complications, the likelihood a patient will derive mid- to long-term benefit from an open revascularization must be included in the decision-making process. Several studies have sought to characterize risk factors for poor outcomes after open bypass. Among those with CLTI, several predictors of reduced AFS are well established (Table 105.5). Although many of these are comorbid conditions such as advanced age and chronic kidney disease, others are elements of functional status, such as preoperative ambulation or independent living. In addition, prior contralateral major amputation has been shown to predict worse outcomes after open bypass.[108] Although none of these studies identifies a single risk factor that is prohibitive for open bypass, for patients who present with a constellation of risk factors, including impaired functional status, the likelihood of long-term benefit from revascularization is reduced.

RISK PREDICTION MODELS

Decision making in lower extremity PAD requires a highly individualized approach based on a number of preoperative factors. Several risk prediction models have been developed to aid in patient-specific risk stratification. These tools use statistical modeling based on patient data to identify predictors of a specific outcome, then apply a weighting system to them, such that a score may be given that corresponds to a likelihood of that outcome. For an individual patient, the score is based on the presence or absence of these factors. The sum then corresponds to a risk category, derived from the statistical modeling. The performance of the risk score can be assessed by tests of discrimination and calibration and should ideally be validated using data from another cohort of patient data. An ideal risk score uses easily obtainable and clearly defined factors that are available preoperatively. This allows the surgeon to calculate the score and offer a bedside risk prediction. However, it is important to note that these risk scores are derived using a specific endpoint, at a specific point in time, and therefore should similarly be narrowly applied. When used properly, risk scores provide evidence-based risk stratification, individualized to each patient. Several scores have been described; they differ slightly in the outcome they predict, and the time point at which the outcome is predicted.[109-112] In addition, some have been externally validated in additional patient cohorts and have been tested using new endpoints. There is some commonality among the most widely recognized grading systems (Table 105.6), and some important differences described in more detail in later sections. However, it is important to note that prediction models complement clinical judgment rather than replace it, and more research is needed to optimize these models. In particular, some have suggested that future study should incorporate clinical inputs beyond those used in the models described later, such as the degree of ischemia, extent of tissue loss, and presence of infection.[113]

ANGIOGENESIS FOR PERIPHERAL ARTERIAL DISEASE

For patients with CLTI who lack a revascularization option, novel alternative therapies may offer benefit. Angiogenesis is a naturally occurring phenomenon in response to tissue ischemia and is promoted by proangiogenic factors, including VEGF, fibroblast growth factor, hypoxia-inducible factor-1α, and hepatocyte growth factor[114,115] Following the first case report using VEGF in a human subject by Isner and colleagues in 1996,[116] the modulation of growth factors to stimulate angiogenesis has become an area of interest in the treatment of lower extremity PAD, particularly in patients who are not candidates for surgical or interventional techniques. The concept of therapeutic angiogenesis entails efforts to increase the concentration of proangiogenic factors, thereby stimulating growth of new blood vessels from preexisting blood vessels to treat ischemic disease; this may be accomplished by administration of recombinant proteins or gene therapy that induces overexpression of these factors.[114,117] Therapeutic angiogenesis may also be induced by implantation of stem cells and endothelial progenitor cells. Both bone marrow–derived and peripheral blood–derived stem cells have been studied for their utility in stimulating vasculogenesis; both intraarterial and intramuscular techniques have been studied. The putative concept by which angiogenesis improves limb perfusion is through the enlargement of collateral blood vessels and possible direct stimulation of wound healing by growth factors. Preclinical animal models, such as the rabbit hind limb ischemia model, have clearly shown that angiogenic gene therapy can improve limb perfusion compared with placebo-treated animals. Growth factors act as mitogens that stimulate endothelial cell proliferation in response to local tissue ischemia, but the mechanism has not been completely

TABLE 105.5 Recent Studies Identifying Independent Predictors for Select Outcomes in Patients With Chronic Limb-Threatening Ischemia

Author	Year	Journal	*n*, Study Type	Inclusion Criteria	Primary Outcome Measure	Significant Predictors
Robinson et al.[117a]	2009	*JVS*	1646, single center series	Bypass surgery for CLI or claudication	Patency	High-risk conduit, CLI, smoking, age ≥65 years, African American, female
Schanzer et al.[117b]	2007	*JVS*	1404, multicenter RCT	Bypass surgery for CLI	Patency	Graft diameter, graft length, nonsingle segment GSV, popliteal artery origin
Bradbury et al.[117c]	2010	*JVS*	452, multicenter RCT	Bypass surgery and angioplasty for SLI	Death	Age, MI, stroke, tissue loss, ankle pressure, number of detectable ankle pressures, creatinine, smoking, BMI, Bollinger score, diabetes
Goodney et al.[117d]	2010	*JVS*	2306, multicenter registry	Bypass surgery for CLI or claudication	Death	CHF, diabetes, CLI, absence of single segment GSV, age >80 years, dialysis, emergent procedure
Schanzer et al.[117e]	2008	*JVS*	1404, multicenter RCT	Bypass surgery for CLI	Death	Statin therapy, age ≥75 years, CAD, CKD stage 4/5, tissue loss
Owens et al.[117f]	2007	*JVS*	456, single center series	Bypass surgery for CLI or claudication	Death	Age, CKD Stage 4/5
Schanzer et al.[117g]	2009	*JVS*	1166, multicenter registry	Bypass surgery for CLI	Amputation-free survival	Age ≥75 years, dialysis, tissue loss, anemia, advanced CAD
Schanzer et al.[117h]	2008	*JVS*	1404, multicenter RCT	Bypass surgery for CLI	Amputation-free survival	Age ≥75 years, dialysis, tissue loss, anemia, advanced CAD
Biancari et al.[117i]	2007	*World Journal of Surgery*	3925, multicenter registry	Bypass surgery for CLI	Amputation-free survival	Diabetes, CAD, foot gangrene, urgent operation
Goodney et al.[117j]	2009	*Ann Vasc Surg*	2306, multicenter registry	Bypass surgery for CLI or claudication	Amputation or loss of secondary patency	Age 40-49 years, nonambulatory preoperatively, dialysis, diabetes, CLI, composite vein grafts, tarsal bypass target, nursing home preoperatively
Rossi et al.[117k]	2003	*Ann Vasc Surg*	468, single center series	Bypass surgery for CLI or claudication or aneurysm	Amputation	Gender, nonautologous conduit, re-do bypass
Toursarkissian et al.[117l]	2002	*JVS*	124, single center series	Bypass surgery for CLI or claudication	Amputation	Angiographic score, foot score, diabetes
Alback et al.[117m]	1998	*Eur J Vasc Surg*	132, single center series	Bypass surgery for CLI or claudication	Amputation	"Ad-Hoc" grading system of outflow arteries
Simons et al.[117n]	2010	*JVS*	1457, multicenter registry	Bypass surgery for CLI	Clinical failure (persistent symptoms and/or amputation) despite bypass patency	Dialysis, preoperative ambulation with assistance, history CABG or PCI
Goodney et al.[117o]	2009	*JVS*	1400, multicenter registry	Bypass surgery for CLI or claudication	Ambulatory failure	Nonambulatory preoperatively, CLI, age ≥70 years, postoperative MI, postoperative amputation
Taylor et al.[117p]	2006	*JVS*	1000, single center series	Bypass surgery for CLI	Ambulatory deterioration/ failure	Female, diabetes, renal insufficiency, dementia, homebound preoperatively, postoperative amputation

Continued

TABLE 105.5 Recent Studies Identifying Independent Predictors for Select Outcomes in Patients With Chronic Limb-Threatening Ischemia—cont'd

Author	Year	Journal	*n*, Study Type	Inclusion Criteria	Primary Outcome Measure	Significant Predictors
Nguyen et al.[47]	2006	*JVS*	1404, multicenter RCT	Bypass surgery for CLI	Decreased improvement in quality of life	Diabetes, postoperative graft related event
Taylor et al.[117p]	2006	*JVS*	1000, single center series	Bypass surgery for CLI	Nonindependent living	Age ≥70 years, ulceration, previous stroke, dementia, nonambulatory, postoperative amputation

BMI, Body mass index; *CABG,* coronary artery bypass graft; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *CKD,* chronic kidney disease; *CLI,* critical limb ischemia; *GSV,* great saphenous vein; *JVS, Journal of Vascular Surgery; MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *RCT,* randomized controlled trial.

From Robinson WP 3rd, Owens CD, Nguyen LL, Chong TT, Conte MS, Belkin M. Inferior outcomes of autogenous infrainguinal bypass in Hispanics: an analysis of ethnicity, graft function, and limb salvage. *J Vasc Surg.* 2009;49(6):1416–1425. doi:10.1016/j.jvs.2009.02.010. PMID: 19497500.

TABLE 105.6 Comparison of the Finland National Vascular (Finnvasc), Project of Ex-Vivo Graft Engineering by Transfection III (PREVENT III), Bypass Versus Angioplasty in Severe Limb Ischemia (BASIL) Grading Systems, and the Vascular Quality Initiative (VQI)-Derived Risk Adjustment Model

	Finnvasc	PREVENT III	BASIL	VQI-Derived
Score Application				
	Critical limb ischemia	Critical limb ischemia	Severe limb ischemia	Critical limb ischemia
Factor				
Advanced age		++	+	+
Coronary artery disease	+	+	++	
Diabetes mellitus	+			+
Obesity			++	+
Chronic kidney disease/dialysis	+	++++	++	+++
Tissue loss	+	+++	+++	+
Smoking			+++	
Anatomic factors			+	+
Functional status				++
Outcome Predicted				
	Mortality and limb loss (30 days)	Amputation-free survival (1 year)	Survival (2 years)	Amputation-free survival (1 year)

delineated.[118] Several studies of therapeutic angiogenesis have now been conducted, including phase III clinical trials.[119-124]

Overall, the data have failed to demonstrate a consistently significant clinical benefit for any of these therapies. Results of several phase II and III clinical trials are summarized in Table 105.7.[117b-117c]

Future Developments

Alternative strategies for the pharmacologic treatment of vascular disease are under investigation, including those aimed at the neovascularization of ischemic tissue and the prevention of intimal hyperplasia. Similar to other fields, such as oncology, the mapping of the human genome promises to advance therapeutic approaches to the treatment of lower extremity PAD. Several target genes and small molecules that are regulated by oxygen tension have been implicated in stimulating angiogenesis via the hypoxia-inducible factor pathway; research is ongoing to define the therapeutic potential of prolyl-4-hydroxylase inhibitors, mediators of the thioredoxin systems, the peroxisome proliferator-activated receptor gamma coactivator 1-α protein, microRNAs, and oligonucleotides.[125] Therapeutic ultrasound has also been investigated in mouse models of hind limb ischemia for the potential to stimulate neovascularization via multiple angiogenic pathways.[126] Investigations of immune modulation therapy, targeting the inflammatory component of vascular disease in an effort to decrease the development and progression of atherosclerosis and possibly angioplasty-associated intimal

TABLE 105.7 Summary of Phase II and III Trials of Molecular and Cellular Proangiogenic Agents in Patients With Peripheral Artery Disease

Trial	Therapy	Population	Result
Growth Factors			
Rajagopalan et al. (RAVE) 2003[126a]	VEGF	105 patients with disabling claudication	No difference in walking distance or quality of life
Kusumanto et al. 2006[126b]	VEGF	54 patients with diabetes and critical limb ischemia	No difference in amputation rate at 100 days
Nikol et al. (TALISMAN) 2008[126c]	FGF	125 patients with critical limb ischemia	No difference in ulcer healing at 25 weeks
Powell et al. (HGF-STAT) 2008[126d]	HGF	104 patients with critical limb ischemia	No difference in adverse event rates; no difference in major amputation or death at 6 months
Shigematsu et al. (TREAT-HGF) 2010[126e]	HGF	40 patients with critical limb ischemia	Significant improvement in rest pain or ulcer size at 12 weeks (70.4% HGF versus 30.8% placebo, $P = .014$)
Belch et al. (TAMARIS) 2011[126f]	FGF	525 patients with critical limb ischemia	No difference in major amputation or death at 1 year
Stem Cells			
Walter et al. (PROVASA) 2011	BMMNC	40 patients with critical limb ischemia	No difference in ABI or major amputation at 3 months
Powell et al. (RESTORE-CLI) 2012	BMMNC (Ixmyelocel-T)	77 patients with critical limb ischemia	No difference in amputation-free survival at 12 months
Teraa et al. (JUVENTAS) 2015	BMMNC	160 patients with severe limb ischemia	No difference in major amputation at 6 months

BMMNC, Bone marrow mononuclear cells; *FGF,* fibroblast growth factor; *HGF,* hepatocyte growth factor; *PBMNC,* peripheral blood mononuclear cells; *VEGF,* vascular endothelial growth factor.

hyperplasia, are encouraging. Other areas of research aimed at advancing our understanding of vascular disease include viral-directed gene transfer, targeted antibiotic therapy, and alternative circulating cell–free oxygen delivery vectors.

Future Trends

Decision Analysis

Decision analysis is a field of study that applies statistical methods and probabilities from existing literature to model various hypothetical outcomes for a given set of competing options.[127] Decision analysis begins with identifying a problem for which there is more than one potential solution. A decision tree is then constructed that incorporates a valuation of any number of factors that would influence the decision, along with the likelihood of each branch along the decision tree occurring, such that the outcome associated with several different choices can be simulated. Rather than just imagining the outcome associated with different choices, decision analysis allows for predictions of outcomes, based on input data from the existing literature. Decision analysis is often applied to clinical scenarios where randomized controlled trials of competing therapies cannot be carried out. It often incorporates factors such as cost and QoL associated with various treatment options. One of the most important roles of model-based decision analysis is to identify which data parameters or assumptions can change policy decisions. This is done through sensitivity analysis, in which each parameter is varied through a wide range of possible values. If this variation does not lead to a change in policy conclusions, one can feel confident that the results of the analysis are likely to hold true in most clinical scenarios. Conversely, if an uncertain parameter is found to be influential, this may identify an important area for future research. Decision analysis can play an important role in clinical decision making in the treatment of PAD.

Brothers and colleagues used decision analysis to assess three different strategies for the management of CLTI: primary amputation, revascularization, or expectant management (Fig. 105.4).[128] They found that revascularization was associated with a gain of 1.1 quality-adjusted life years (QALYs) compared with primary amputation and 1.2 QALYs compared with expectant management. In terms of cost associated with the three treatment strategies, sensitivity analysis predicted revascularization to be the least costly treatment per QALY, as long as 1-month patency exceeds 11%. The authors conclude that revascularization offers the greatest benefit in terms of QALY and cost in the management of CLTI.

Nolan and colleagues applied decision analysis to treatment of claudicants with TASC B and C lesions of the superficial femoral artery.[129] Using a hypothetical cohort of claudicants with either TASC B or C lesions, they modeled treatment with either angioplasty and stenting or great saphenous vein bypass for the outcome measure of QALYs. They found that TASC B lesions were best treated with angioplasty and stenting. However,

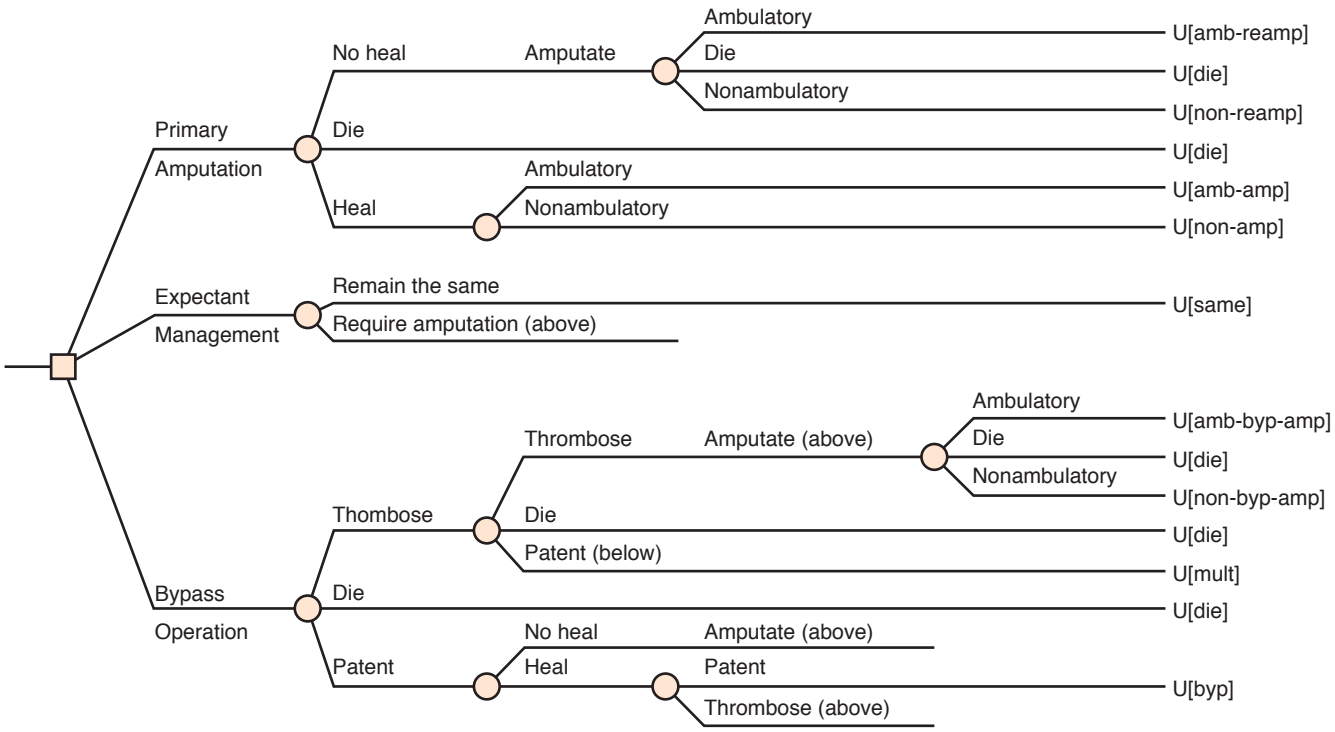

Figure 105.4 Decision tree of principal management options for patients with critical limb ischemia. Square nodes represent a decision point and round nodes represent a probability of an event occurring based on existing literature. The outcomes, which in this study are utility values (translated into quality-adjusted life years [QALYs]), are designated with the following abbreviations: *byp*, success after revascularization; *mult*, success after multiple revascularizations; *amb-amp*, ambulatory after amputation; *non-amp*, nonambulatory after amputation; *amb-reamp*, ambulatory after reamputation; *non-reamp*, nonambulatory after reamputation; *amb-by*, ambulatory after amputation following failed revascularization; *non-byp-amp*, nonambulatory after failed revascularization and amputation; *same*, condition remains the same; *die*, death occurs. (From Brothers TE, et al. Justification of intervention for limb-threatening ischemia: a surgical decision analysis. *Cardiovasc Surg*. 1999;7:62–69.)

for patients with TASC C lesions, angioplasty and stenting was preferred only in certain conditions. Using sensitivity analyses, they showed that stenting surpasses efficacy of open bypass for TASC C lesions if the primary patency of stenting is greater than 32% at 5 years, if patient age is greater than 80 years, or if operative mortality for open bypass exceeds 6%.

Cost-effectiveness analyses are another type of decision analysis with several applications in healthcare research, and clinical decision making in PAD. Barshes and colleagues recently published a review of the methods of cost-effectiveness analysis, anticipating their increased utility as a healthcare financial crisis looms in the United States (Fig. 105.5).[130] We believe that decision analysis and cost-effectiveness analyses will play a growing role in informing decision making in PAD in the coming years.

Cost Considerations

As healthcare costs continue to rise, decision making will increasingly be influenced by governmental and third-party payers. There is conflicting evidence regarding the most cost-effective methods of treating lower extremity PAD. Although there is evidence that revascularization is cost-effective compared with primary amputation,[86,131-134] the cost differential between strategies varies depending on the expense of rehabilitation after primary amputation in most series.[132] Indeed, primary amputation for patients forgoing rehabilitation (as might occur in a nursing-home patient) is cheaper than revascularization. Therefore economic decision-making depends on the patient's postoperative rehabilitation potential, which is often determined by preoperative functional status.[77] Despite the debate concerning the economic merits of one treatment over another, most would agree that the current financial system can ill afford to pay for multiple revascularizations of a single ischemic limb. The scenario becomes even more cost-prohibitive if, after multiple revascularizations, major limb amputation results anyway. Future economic decision making will therefore require the identification of the most cost-effective single treatment for patients who present with PAD and, more specifically, CLTI.

Unmet Needs

Definitive high-level evidence on which to base treatment decisions, with an emphasis on clinical and cost effectiveness, continues to be lacking. Treatment decisions in PAD are individualized, based on life expectancy, functional status, anatomy of the arterial occlusive disease, and surgical risk. For patients with aortoiliac disease, endovascular therapy has become first line therapy for all but the most severe patterns of occlusion, and aortofemoral bypass surgery is a highly effective and durable

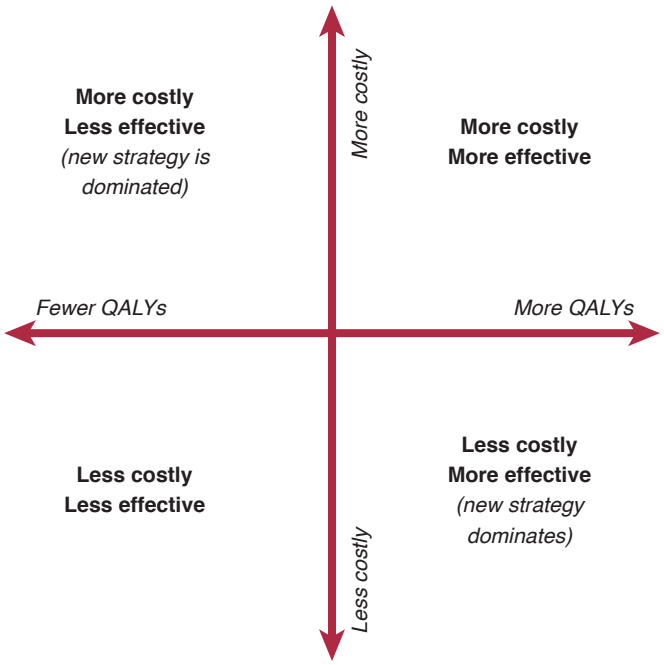

Figure 105.5 Two-dimensional plane demonstrating the relationship of incremental costs *(vertical axis)* and incremental effectiveness *(horizontal axis)* for two possible interventions. If a new intervention is both more costly and less effective than a current intervention *(upper left quadrant)*, it is not economically preferred. If a new intervention is less costly and more effective *(lower right quadrant)*, it is economically preferred. Formal cost-effectiveness analysis is useful for situations described by the upper right and lower left quadrants. Most frequently, a cost-effectiveness analysis focuses on the upper right quadrant to address the question of whether the more effective treatment is "worth" its greater cost. *QALYs*, Quality-adjusted life years. (From Barshes NR. A primer on cost-effectiveness analyses for vascular surgeons. *J Vasc Surg*. 2012;55(6);1794–800.)

treatment for the latter group. For infrainguinal disease, available data suggest that surgical bypass with vein is the preferred therapy for patients likely to survive 2 years or more, and for those with long segment occlusions or severe infrapopliteal disease who are acceptable surgical risk. Endovascular therapy may be preferred in patients with reduced life expectancy, those who lack usable vein for bypass or who are at elevated risk for operation, and those with less severe arterial occlusions. Patients with nonreconstructable disease, extensive necrosis involving weight bearing areas, nonambulatory status, or other severe comorbidities may be considered for primary amputation or palliative measures. Given the myriad of contributing factors, each with its own extensive list of possible values, the possible combinations of disease states and patient situations are perhaps too numerous to ever study individually. A "clean" study, comparing two treatments in a population that is balanced on all factors may not be achievable, even in the best of randomized controlled trials. Despite herculean efforts on the part of the BASIL-2 and BEST-CLI investigators, it stands to be determined whether either of these studies will ultimately provide conclusive enough evidence that providers feel these questions of optimal treatment have been answered once and for all.

Third-party payers in our current healthcare system will increasingly insist on the delivery of evidence-based care. Quality will be defined, increasingly monitored, and financially linked to compliance with Medicare All-Care measures. Care for lower extremity PAD will increasingly become protocol driven, placing a premium on value and durability. For all of the important reasons previously mentioned, future studies should continue to analyze the impact of comorbidities in patients with PAD. These studies need to be conducted in patients undergoing surgical bypass, endovascular repair, primary amputation, and conservative treatment because the effect of comorbidities can be very different based on the treatment type. A diverse set of standardized endpoints that attempt to capture the diverse experience relevant to patients with PAD needs to be defined. The time points at which these endpoints are studied also should be standardized. In this way, valid risk estimates can continue to inform the way we take care of patients and, in doing so, improve evidence-based patient care. Finally, the definitive treatment of lower extremity PAD has traditionally relied on procedural therapy, either open or endovascular revascularization. We are now at an exciting time point where mapping of the human genome, improved understanding of angiogenesis, and the growing ability to manipulate stem cell differentiation all hold great promise in providing meaningful medical solutions that may render many interventions unnecessary or render them more effective.

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Bradbury AW. BASIL Trial Participants. Bypass versus angioplasty in severe ischemia of the leg (BASIL): multicenter, randomized controlled trial. *Lancet*. 2005;366:1925–1934.

This rare randomized controlled multicenter trial concluded that surgery and angioplasty have similar amputation-free survival at 6 months (thus favoring angioplasty as the best first approach), but surgery has better amputation-free survival after 2 years. This study stressed the complementary nature of the two treatment approaches.

Conte MS, Bandyk DF, Clowes AW, et al. Results of PREVENT III: A multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. *J Vasc Surg*. 2006;43:742–751.

This large, multicenter trial evaluated the efficacy of edifoligide for the prevention of vein graft failure for patients who underwent lower extremity bypass for critical limb ischemia. Although it found no significant benefit associated with the drug, this cohort represents the largest and most extensively followed prospective dataset of patients with critical limb ischemia. As such, it has formed the basis for several other significant studies in this patient population.

Conte MS, Pomposelli FB, Clair DG, et al. on behalf of the Society for Vascular Surgery Lower Extremity Guidelines Writing Group. Society for Vascular Surgery practice guidelines for occlusive disease of the lower extremities: Management of asymptomatic disease and claudication. *J Vasc Surg*. 2015;61:2s–41s.

The Society for Vascular Surgery Lower Extremity Guidelines Writing Group reviewed the current evidence supporting clinical care in the management of asymptomatic peripheral artery disease and intermittent claudication. Although first acknowledging the paucity of level 1 evidence, the group recommended revascularization for claudication "in selected patients with disabling symptoms, after a careful risk-benefit analysis." They also determined that there was inadequate evidence to support screening for peripheral artery disease in asymptomatic patients.

Goodney PP, Schanzer A, Demartino RR, et al. Vascular Study Group of New England. Validation of the Society for Vascular Surgery's objective performance goals for critical limb ischemia in everyday vascular surgery practice. *J Vasc Surg*. 2011;54(1):100–108, e4.

The Society for Vascular Surgery developed objective performance goals (OPGs), as standardized metrics for expected outcomes in lower extremity revascularization for critical limb ischemia (CLI), based on aggregate data from randomized trials of lower extremity bypass. In response to this, the authors sought to confirm the validity of these targets in everyday vascular surgery practice using a large, regional database. They concluded that these OPGs are feasible, and endorsed the use of such benchmarks for quality improvement initiatives, clinical trials, and comparisons of risk-adjusted outcomes in the treatment of CLI.

Mills JL, Conte MS, Armstrong DG, et al. on behalf of the Society for Vascular Surgery Lower Extremity Guidelines Committee. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk stratification based on wound, ischemia, and foot infection. *J Vasc Surg*. 2014;59:220–234.

The Society for Vascular Surgery Lower Extremity Guidelines Committee created a classification scheme for limb threat that reflects the contribution that diabetes mellitus plays in limb threat, as well as the expanded range of current techniques for revascularization in comparison to the previously established systems. This WIfI score was intended "to permit more meaningful analysis of outcomes for various forms of therapy in this challenging, but heterogeneous population." WIfI assigns a score to grade the severity and extent of the wound, ischemia, and foot infection. The resultant score corresponds to four threatened limb clinical stages that estimate risk of amputation and potential benefit of revascularization.

Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg*. 2007;45(supplS):S5–S67.

The TASC II document updates TASC and represents the latest evidence-based data on the natural history and treatment of lower extremity PAD.

Taylor SM, Kalbaugh CA, Blackhurst DW, et al. Determinants of functional outcome after revascularization for critical limb ischemia: an analysis of 1000 consecutive vascular interventions. *J Vasc Surg*. 2006;44:747–756.

Although retrospective, this large series demonstrated that functional performance after intervention for CLI is often determined by factors other than limb salvage. Postoperative functional outcomes were most profoundly impacted by the patient's preoperative medical condition and functional status.

A complete reference list can be found online at ExpertConsult.com

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106 CHAPTER

Aortoiliac Disease: Direct Reconstruction

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Atherosclerotic disease of the abdominal aorta and iliac arteries is one of the most common therapeutic challenges encountered by vascular surgeons. The British anatomist and surgeon John Hunter first appreciated the implications of aortic bifurcation occlusive disease in the late 1700s. His dissection specimens remain on view at the Hunterian Museum in London and laid the groundwork for Leriche's later appreciation of the disease process that bears his name.[1] The modern era of surgical reconstruction for complex atherosclerotic occlusive disease began in 1947 with the successful endarterectomy of a heavily

Abstract

Aortoiliac occlusive disease may present with a variety of symptoms, ranging from claudication to critical limb ischemia. Diagnosis may be made by history and physical with noninvasive hemodynamic studies and supplemented typically by axial imaging. The most common options for inline treatment are aortoiliac endarterectomy, which is rarely performed, and aortobifemoral bypass. The latter operation has an excellent long-term patency and is well-tolerated in appropriately selected patients.

Keywords

aortoiliac occlusive disease
aortobifemoral bypass
profundaplasty
aortoiliac endarterectomy
minimally invasive bypass

diseased common femoral artery (CFA) by Portuguese surgeon dos Santos.[2] Wylie et al.[3] in San Francisco extended this new technique to the aortoiliac (AI) level 4 years later, but it would be another 10 years before synthetic grafts were regularly used for aortic bypass grafting. Early preference for aorta-to-iliac artery grafting would eventually be supplanted by the more durable aortobifemoral bypass (ABFB) procedure.

In recent years, advances in our understanding of the biology of atherosclerosis and in our ability to treat arterial occlusive disease percutaneously have had a dramatic impact on the treatment algorithms for peripheral artery disease (PAD) as a whole and for aorto-iliac occlusive disease (AIOD) in particular. The growing range of treatment options allows us to tailor therapy to the particular clinical situation, and ongoing improvements in graft material, surgical technique, and perioperative management have contributed to a steady decline in postoperative morbidity and mortality. Given the advent of less invasive therapeutic options, traditional aortobifemoral grafting is increasingly being performed for more complex patterns of disease or as a secondary or tertiary procedure in the setting of recurrent disease.[4] High levels of patient satisfaction and excellent long-term outcomes, however, remain the hallmark of aortobifemoral surgical revascularization. This chapter reviews the role of direct operative reconstruction in the current surgical management of AIOD.

PATHOLOGY AND CLINICAL PRESENTATION

Pathology

AIOD typically begins at the aortic terminus and common iliac artery origins and slowly progresses proximally and distally.[5] Progression is variable but may ultimately result in total aortic occlusion (Fig. 106.1). When collaterals are adequate, claudication symptoms are often tolerable and can be successfully managed nonoperatively for many years. Approximately one-third of patients operated on for symptomatic AIOD have significant orificial profunda femoris occlusive disease, and more than 40% have significant superficial femoral artery (SFA) disease. Disease can also extend to the level of the renal arteries (see Fig. 106.1). Although early reports indicated that up to one-third of patients with aortic occlusion went on to develop renal artery thrombosis during a period of 5 to 10 years,[6] later prospective studies failed to confirm this observation.[7] Renal or mesenteric arterial involvement sufficient to warrant concurrent repair is seen in only a minority of patients with AIOD.

Collateral Circulation

Although focal AI atherosclerotic disease commonly gives rise to claudication of varying degrees, it is rarely associated with chronic limb threatening ischemia (CLTI). This is largely the result of abundant collateralization around the point of obstruction, which reconstitutes the infrainguinal system with sufficient flow to ensure adequate resting tissue perfusion (Fig. 106.2).

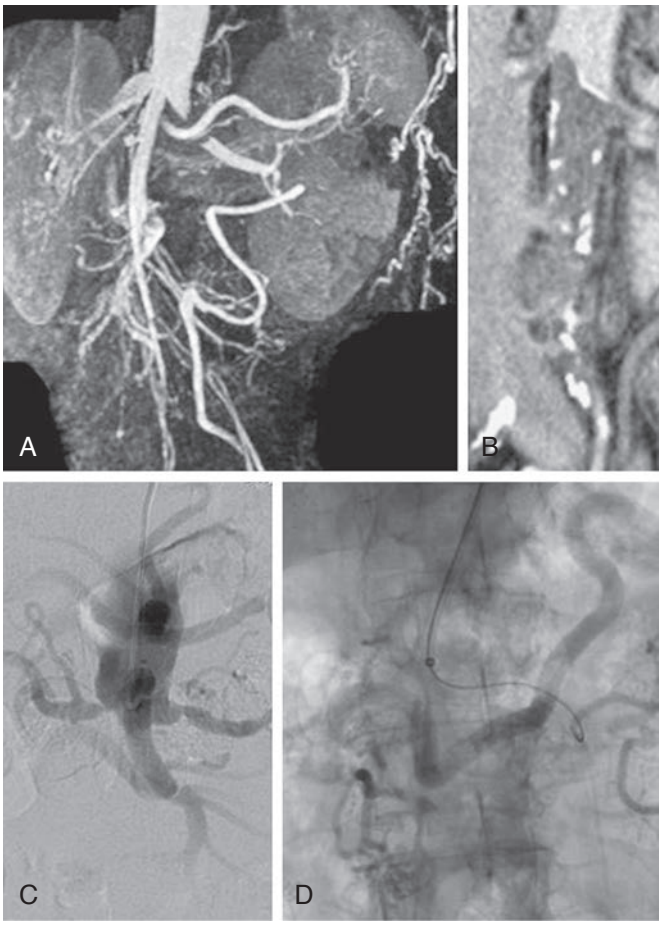

Figure 106.1 Two patients with total aortic occlusion extending to the level of the renal arteries. (A and B) Coronal computed tomography images in one patient demonstrate propagation of thrombus into the renal arteries *(arrow)*. (C and D) The second patient also has associated renal artery occlusive disease. Meandering mesenteric arteries are demonstrated in both patients.

The primary compensatory networks develop from the lumbar and hypogastric feeding vessels and connect to circumflex iliac, hypogastric, femoral, and profunda recipients. Additional collaterals that arise in more severe cases include the internal mammary artery–to–inferior epigastric connection and the superior mesenteric artery–to–inferior mesenteric artery and hemorrhoidal artery pathway. The latter connection comprises the arc of Riolan and the meandering mesenteric artery (Fig. 106.3); it is important to recognize the presence of such a large and significant collateral because it should be preserved during surgical reconstruction.

Epidemiology

The majority of patients presenting today with AIOD have diffuse disease at multiple levels of the vascular tree; in most cases, AIOD is found in combination with femoropopliteal or infrageniculate occlusive disease. Patients with isolated AIOD are generally younger, have a higher relative prevalence of smoking and hypercholesterolemia,[8] are nearly as likely to be female as male, and typically have a normal life expectancy.[9]

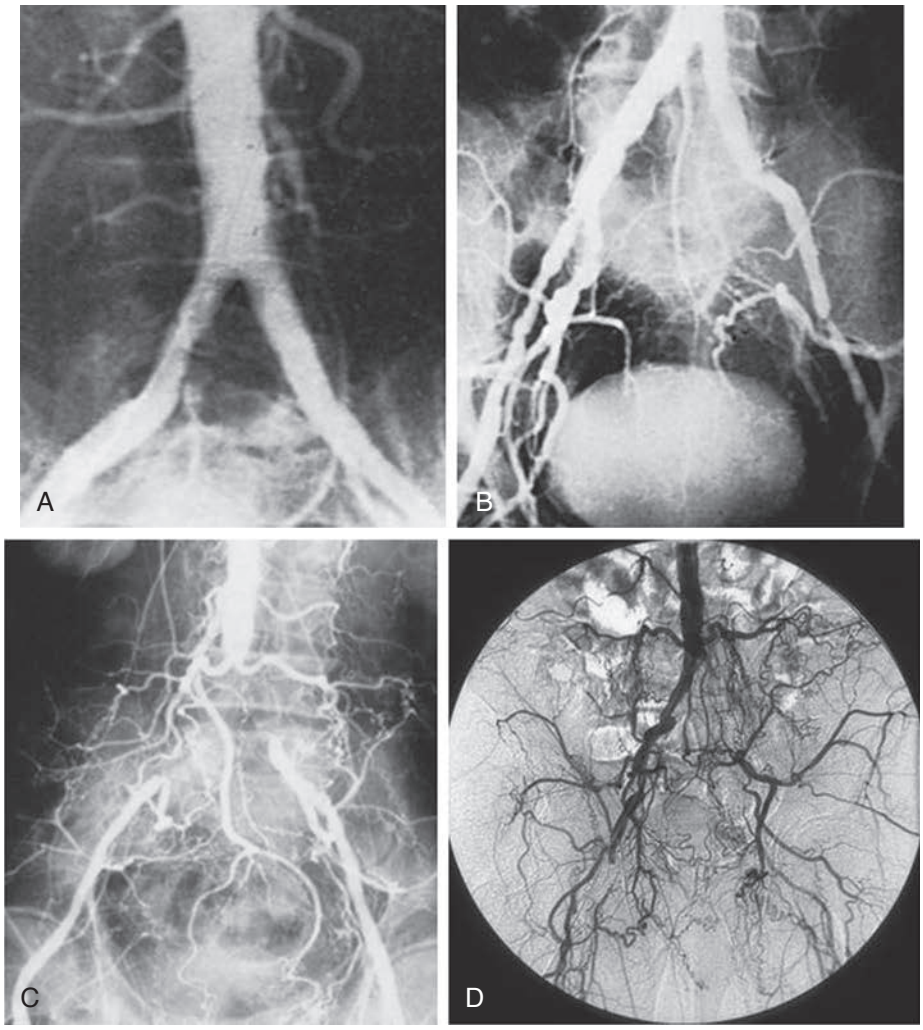

Figure 106.2 (A to D) Aortoiliac occlusive disease of increasing severity, with a progressively well-developed pattern of iliolumbar to hypogastric and femoral circumflex collateralization. Male patients with a disease distribution illustrated in B to D may be impotent secondary to compromised hypogastric perfusion.

In contrast, patients with more extensive multilevel disease are commonly older, more frequently have diabetes and hypertension, and are more likely to be male and to have concomitant cerebrovascular, coronary, and visceral atherosclerosis.[8] Not surprisingly, patients with diffuse, multisegmental disease often present with ischemic rest pain or more severe perfusion impairment, leading to tissue loss or gangrene as opposed to isolated claudication.[10] Such patients manifest a significant reduction in life expectancy compared with their age-matched counterparts.[9]

A particularly virulent form of atherosclerotic disease is often found in young women who smoke.[11,12] Radiographic imaging in this subset of patients typically reveals atretic, narrowed vasculature with diffusely calcific atherosclerotic changes. Frequently, a focal stenosis is found posteriorly at or proximal to the aortic bifurcation (Fig. 106.4). This disease distribution and characteristic patient profile have been termed *small aortic syndrome* or *hypoplastic aortic syndrome*.[13] Such patients invariably have an extensive smoking history but may lack other typical risk factors for atherosclerosis. The diminutive size of the aorta and iliac vessels has important treatment implications in such patients; the durability of endovascular intervention or local endarterectomy is generally poor, particularly in the presence of continued cigarette use.

Presenting Symptoms

Chronic obliterative atherosclerosis of the distal aorta and iliac arteries commonly is manifested as symptomatic arterial insufficiency of the lower extremities, producing a range of symptoms from mild claudication to the spectrum of CLTI. Patients with hemodynamic impairment limited to the AI system may have intermittent claudication of the calf muscles alone or involvement of the thigh, hip, or buttock; patients with CLTI usually have multilevel disease of the AI and infrainguinal arteries. Those presenting with claudication secondary to AIOD are, on average, nearly a decade younger than those with claudication stemming from infrainguinal occlusive disease.[11] Up to 30% of affected men may have difficulty achieving and maintaining an erection owing to inadequate perfusion of the internal pudendal arteries.[14] In men, the well-characterized constellation of symptoms and signs known as Leriche syndrome, associated

Figure 106.3 Large meandering mesenteric artery associated with total superior mesenteric and celiac artery occlusion. Aortobifemoral bypass with an end-to-side proximal anastomosis would best preserve both mesenteric and pelvic perfusion.

Figure 106.4 Short-segment stenoses localized to the distal aorta are particularly common in young female smokers and are amenable to endarterectomy.

with terminal aortic occlusion, includes claudication (thigh, hip, or buttock), atrophy of the leg muscles, impotence, and reduced femoral pulses.[15] The equivalent impact of impaired pelvic perfusion in women remains poorly understood but has attracted investigative attention.[16]

DIAGNOSIS

History and Physical Examination

The diagnosis of AIOD can usually be made after a careful history and physical examination. In a patient with multiple vascular risk factors, claudication, and absent femoral pulses, the diagnosis of AIOD is straightforward. In other patients, symptoms of claudication can sometimes be difficult to distinguish from those of hip arthritis or nerve root irritation due to lumbar disk disease or spinal stenosis.[17]

The variability of presenting signs and symptoms in patients with AIOD may cause diagnostic confusion. Although proximal claudication is most common, patients with AIOD in isolation or those with combined infrainguinal disease may present exclusively with calf claudication. Although the involved muscle groups may be atrophic from disuse in claudicants, the lower extremities frequently appear well perfused at rest. Femoral and even pedal pulses may be palpable at rest, reflecting the presence of robust collateral networks; pulses may diminish or become absent only after exercise. Similarly, a palpable thrill or audible bruit at the lower abdominal or groin level may only become detectable after exertion. Conversely, femoral bruits or diminished femoral pulses arising from CFA or profunda femoris stenoses can mistakenly be attributed to AI inflow disease.

Noninvasive Hemodynamic Assessment

Noninvasive arterial segmental systolic blood pressure measurements and pulse volume recordings can help confirm a clinical diagnosis of PAD and define the level and degree of obstruction (see Chapter 18).[18] A resting difference of 20 mm Hg systolic or greater between the brachial and the proximal thigh pressures reflects a significant stenosis in the aorta or iliac arteries, but it may be confounded by proximal SFA occlusion. A further reduction in pressure between the thigh and ankle level suggests concomitant femoropopliteal or tibial outflow disease. In patients with disabling symptoms with normal or near-normal resting ankle-brachial indices, repeating measurements after provocative graded exercise treadmill testing can be particularly useful if there is still clinical suspicion of AIOD. A careful history and physical examination combined with noninvasive hemodynamic studies usually provide sufficient data to establish the diagnosis. Further imaging is warranted only after risk/benefit assessment and the clinical decision to intervene has been reached.

Diagnostic imaging modalities that also facilitate revascularization planning include duplex ultrasound and axial imaging in the form of computerized tomographic angiography (CTA), magnetic resonance angiography (MRA), and arteriography; this topic will be discussed in Chapter 105.

INDICATIONS FOR SURGICAL INTERVENTION

Impact of Endovascular Treatment

A significant paradigm shift has occurred in the treatment of PAD.[17,19] Angioplasty and stenting have become first-line therapy for most patients with AI, renal, subclavian, and coronary occlusive disease.[20] Whereas percutaneous treatment of the aorta and iliac arteries was previously limited to short-segment, TransAtlantic Inter-Society Consensus (TASC) type A or B iliac lesions, it is now routinely applied to even long-segment (TASC type D) occlusions extending the length of the iliac arteries. In no other vascular territory has the shift from open surgery to interventional treatment been more apparent than in the AI segment. Using the Nationwide Inpatient Sample, one report documented an 850% increase in the use of percutaneous transluminal angioplasty and stenting for AIOD from 1996 to 2000, along with a simultaneous decrease of 16% in the rate of aortobifemoral grafting.[20] Further reflecting this transformation in management strategy, in anatomically favorable circumstances, concomitant renal or mesenteric artery stenosis might be treated percutaneously as a staged initial procedure, even when subsequent open surgical AI reconstruction is planned.[21] Decision making for surgical versus endovascular treatment is discussed in detail in Chapter 105.

In the current era, in which direct reconstruction for AIOD has been relegated to a second- or even third-line therapy, open bypass is increasingly undertaken in patients in whom endovascular treatment has failed or in those with such extensive disease that an endovascular approach is deemed inadvisable. This paradigm shift has been reflected in reports documenting the increasing complexity of aortobifemoral grafting, with a higher incidence of suprarenal clamping, adjunctive visceral revascularization, simultaneous operative inflow and outflow disease, and repeated grafting.[4,22] Patients with a combination of more proximal aneurysmal disease and common or external iliac occlusive disease continue to be good candidates for open reconstruction, although this group will continue to diminish with ongoing technologic advancements. Even patients with extensive calcification at the aortic bifurcation thought to be at risk for rupture with balloon angioplasty or those with disease extending to the CFA are no longer considered unsuitable for an endovascular approach. The incidence of rupture has proved low in the former group, and the introduction of low-profile covered stents and techniques of primary stenting is likely to further increase the safety of endovascular treatment in this setting. The latter patient subgroup can be managed with a hybrid approach, whereby the CFA plaque is treated with a traditional endarterectomy and patch repair and the iliac component is concurrently addressed with endovascular techniques.[23]

Patients with early recurrence of AIOD after angioplasty or stenting represent a growing group for whom open surgical repair may be indicated. Patients with significant renal failure in whom endovascular therapy entails a prohibitive risk of triggering dialysis dependence may also be considered better suited for operative repair. Complications of endovascular treatment, including dissection and vessel rupture, are infrequent indications for surgical reconstruction.

Claudication

The traditional indications for surgical reconstruction for symptomatic AIOD are disabling claudication, ischemic rest pain, and tissue loss. Claudication is a relative indication for intervention, given the natural history of the disease. Multiple reports, among them the Framingham Heart Study, indicate that patients with claudication have increased rates of cardiovascular mortality but an overall low risk of associated limb loss.[5,24] The majority of claudicants demonstrate a stable pattern of disease throughout their lifetimes or have an improvement in symptoms as a result of risk factor modification, whereas 20% to 30% require operation within 5 years as a result of disease progression. The annual rates of mortality and limb loss in patients with claudication have historically been reported as 5% and 1%, respectively.[25] Some have suggested that claudicants with AIOD are more likely to progress to CLTI.[26] In any case, the degree of disability that a particular level of claudication represents remains a subjective assessment by both the patient and the surgeon. As the associated risks of AI balloon angioplasty and stenting have fallen and the relative success rates have risen in recent years, the threshold for offering endovascular treatment to claudicants at all points along the clinical spectrum has significantly decreased. Indeed, patients once considered appropriate only for risk factor modification, exercise therapy, and medical treatment are now increasingly being offered percutaneous revascularization as a primary treatment option. Balloon technology is also increasingly being applied to hypogastric arterial disease, primarily for buttock or hip claudication, to a degree not previously seen and not paralleled by an increase in surgical revascularization.[27]

The indications for surgical reconstruction for claudication have not shifted appreciably during this same period. Given its relatively benign natural history, conservative treatment continues to be appropriate for many patients with claudication. In contrast to patients with CLTI, it has been argued that an overly aggressive approach might place patients without limb-threatening conditions at unnecessary risk for adverse outcomes. The majority of claudicants remain stable for years, allowing time for collateral pathways to develop; this often results in sufficient improvement, making intervention unnecessary.[28] On the other hand, in patients of low surgical risk with disabling symptoms from disease limited to the aortobifemoral segment, surgical bypass is an appropriate option. With current levels of perioperative morbidity and mortality, bypass can be undertaken safely and with the expectation of excellent long-term patency.

Chronic Limb-Threatening Ischemia

Although broad in spectrum, CLTI is associated with a more significant risk of amputation without revascularization. As such, the presence of ischemic rest pain, frank ulceration, or digital

gangrene are well-accepted indications for surgical correction of AIOD. Patients with pregangrenous skin changes or frank gangrene typically have hemodynamically significant infrainguinal as well as AIOD.[10] Thus, whereas patients treated for claudication or rest pain usually require only a single-stage inflow operation, simultaneous or staged inflow and outflow revascularization should be considered in patients with tissue loss (see under the section Multilevel Occlusive Disease).

Patients with an aortic or iliac source of distal emboli, typically from an ulcerated atheromatous plaque or so-called shaggy aorta, represent another group in which operative reconstruction is usually indicated.[29] Such patients may lack symptoms of claudication, and the culprit lesion(s) may not be hemodynamically significant. In these cases, the goal of intervention is to prevent recurrent distal embolization.

Studies have documented the generally excellent outcomes of aortobifemoral grafting in elderly patients, suggesting that in older patients who are otherwise good surgical risks, surgical therapy should not be withheld.[30] Conversely, lower long-term patency rates with aortic bypass in younger patients or those with small aortic diameters suggest caution for considering early surgical intervention in such patients.[30]

SURGICAL TREATMENT

The modern therapeutic armamentarium for treatment of PAD is barely half a century old. Its development has been marked by several landmark advances, among them the discovery of the anticoagulant heparin by Best in the early 1930s, the advent of arteriography in 1927, the first application of arterial homografts by Gross in 1948 and prosthetic grafts by Voorhees in 1952, and the introduction of balloon angioplasty by Gruntzig in 1974 and of stenting by Puel and Sigwart in 1986. Continual improvements in surgical instrumentation and suture materials to facilitate vascular reconstruction and general advances in perioperative management, including cardiopulmonary care, infection control, and blood product use, have further contributed to the dramatic progress made. Historically the surgical options for AIOD included AI endarterectomy, aortobiiliac bypass, ABFB, and extra-anatomic bypass (iliofemoral, femorofemoral, or axillofemoral; see Chapter 107). Given superior long-term patency, aortobifemoral grafting is currently considered the open revascularization procedure of choice unless the patient is a poor surgical candidate.

Preoperative Preparation

Careful assessment of the factors that influence operative risk and postoperative complications is an important component of the surgical management. Patient selection should be based on an objective evaluation of the patient's comorbidities, functional limitations, and life expectancy. Particular attention should be paid to those patients with the identified risk factors of cardiac, renal, or pulmonary disease (see Chapters 42-44). Cerebrovascular, hepatic, and hematologic status should also be reviewed, with further attention given to those with a personal or family history of hypercoagulability (see Chapter 38).

In patients with known renal insufficiency, elective AI surgery should not immediately follow diagnostic angiography; if possible, it should be delayed to allow recovery from the nephrotoxic effects of contrast. Similarly, preoperative fluid status should be optimized, avoiding extremes of hypovolemia or fluid overload to minimize the risk of postoperative renal compromise or congestive heart failure. This is particularly important if concomitant renal revascularization is being considered, which necessitates a period of renal ischemia and confers additional risk in the form of potential emboli or perioperative renal hypoperfusion. Patients with significant pulmonary dysfunction can usually be identified by history and physical examination, making routine pulmonary function testing unnecessary. If compromised pulmonary reserve is present, an aggressive regimen of preoperative pulmonary rehabilitation in the form of steroid and bronchodilator therapy may be beneficial to optimize the perioperative status.[31] Smoking cessation is critical, and preoperative weight loss in obese patients is of further value in this regard. Perioperative pulmonary risk can also be reduced by the use of postoperative epidural analgesia and by strict adherence to protocols aimed at preventing postoperative deep venous thrombosis and pulmonary embolism.

Coronary Artery Disease

Nearly half of patients proceeding to surgery for AIOD have significant coronary artery disease.[32] The reduced perioperative mortality and morbidity seen with AI surgery in recent years is largely due to advances in the management of concomitant coronary disease (see Chapter 42). Specifically, better preoperative identification of the small number of patients in need of initial coronary revascularization, awareness of the benefit of a waiting period between coronary stenting and major noncoronary vascular surgery, improved perioperative pharmacologic management of patients with impaired myocardium, and more focused efforts to tailor operative and postoperative fluid administration to the individual patient's myocardial reserve are all well-recognized advances.[33,34] Nevertheless, myocardial infarction remains the leading perioperative and long-term complication of AI surgery. Although the trend has clearly swung toward less extensive preoperative cardiac evaluation, it is not unreasonable to assume that all patients undergoing AI reconstructive surgery have some degree of coronary disease and would likely benefit from basic preventive measures. The use of perioperative beta blockade in high risk patients is one example (see Chapter 42).[35] Although the administration of aspirin was routinely discontinued in the past, the cardioprotective value of continuing aspirin through the time of AI reconstruction has now been clearly documented.[36] In contrast, although lower extremity, carotid, and even coronary revascularization is increasingly being performed without discontinuation of clopidogrel, its use is still thought to be prohibitive in major aortic surgery, given the associated bleeding risk.[37,38] The use of mechanical bowel preparations and bowel-sterilizing oral antibiotics was previously common practice, but is no longer routine. Finally, all patients should receive appropriate preoperative intravenous antibiotics to ensure adequate tissue levels at the time of the skin incision.

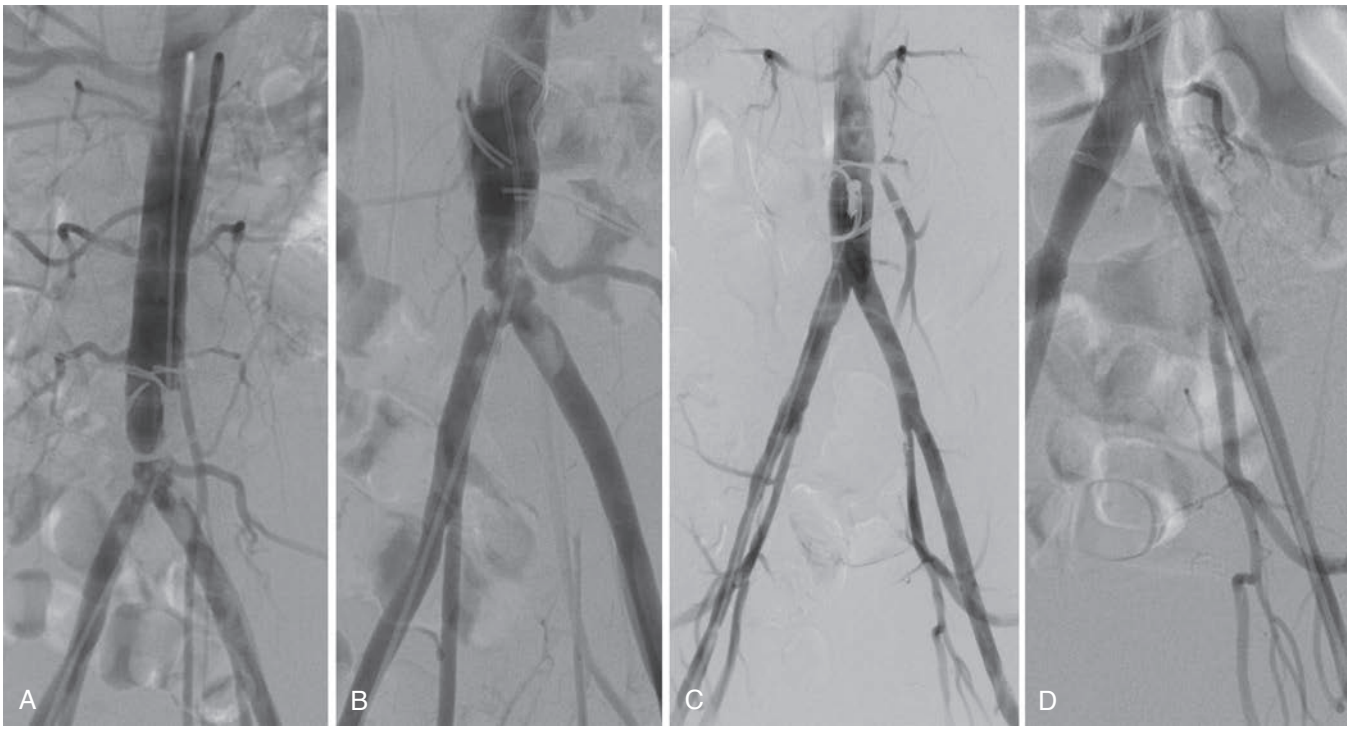

Figure 106.5 Anteroposterior (A) and left anterior oblique (B) angiographic images of bulky calcific atherosclerotic disease limited to distal aorta and proximal common iliac arteries, amenable to aortoiliac endarterectomy. Note the hypertrophic inferior mesenteric artery and iliolumbar collateral vessels. (C) Completion angiogram after distal aortic and bilateral common iliac artery endarterectomy and Dacron patch angioplasty. (D) Continued durability of result 3 years postoperatively.

Aortoiliac Endarterectomy

The first successful endarterectomy of an atherosclerotic CFA lesion by dos Santos was serendipitous, in that he had not originally intended to remove any intima or media. His success, after multiple failed attempts, was attributed to the novel use of heparin.[2] Wylie et al.[3] soon extended this technique to the AI level, and during the 1950s and 1960s, endarterectomy was the standard therapy for severe AIOD. Enthusiasm for the procedure dimmed, however, with the introduction of prosthetic graft material 10 years later, and AI endarterectomy was largely replaced by bypass grafting.

Patient Selection

Since endarterectomy eliminates the need for a prosthetic graft, it is an appealing alternative in the setting of infection and removes the possibility of myriad late graft-related complications. Advocates have likewise pointed to the advantages of endarterectomy in younger patients or those with small vessels who are less than ideal candidates for endovascular therapy or aortobifemoral grafting.[39] Patients with erectile dysfunction attributable to proximal hypogastric occlusive disease are also well suited to this approach. Such patients can be expected to have a greater degree of improved pelvic perfusion after thorough endarterectomy of their AI and hypogastric segments compared with those undergoing ABFB grafting, and high rates of restored sexual function have been reported.[39,40]

Endarterectomy is most feasible and durable when it is applied to focal stenotic lesions in large-caliber, high-flow vessels. Indeed, the technique has proved particularly efficacious in patients with localized disease limited to the distal aorta or proximal common iliac arteries (Figs. 106.4 and 106.5), and excellent long-term patency rates, on a par with aortic bypass grafting, have been reported.[39,41-43] In distinction, results in cases of long-segment disease involving the entire infrarenal aorta and extending into the external iliac arteries have been disappointing.[44] Endarterectomy is now rarely performed for AIOD, having fallen into disfavor owing to its relative technical difficulty, potential for significant blood loss, and poor durability as well as the clear advantages of bypass grafting in this location. The rise of endovascular therapy is further eroding the already small proportion of patients considered suitable for endarterectomy. As a result, the number of vascular surgeons who are comfortable and facile with this technique is limited.

Technique

Endarterectomy is a direct disobliterative, debulking technique that takes advantage of the pathologic localization of atherosclerosis to the intima and media. Typically, a cleavage plane is easily developed between the plaque and the outer layers of the vessel wall, with the exact plane dependent on the size, location, and muscle content of the involved artery. Haimovici[45] has characterized the three cleavage planes encountered in the operative setting as subintimal, transmedial, and subadventitial.

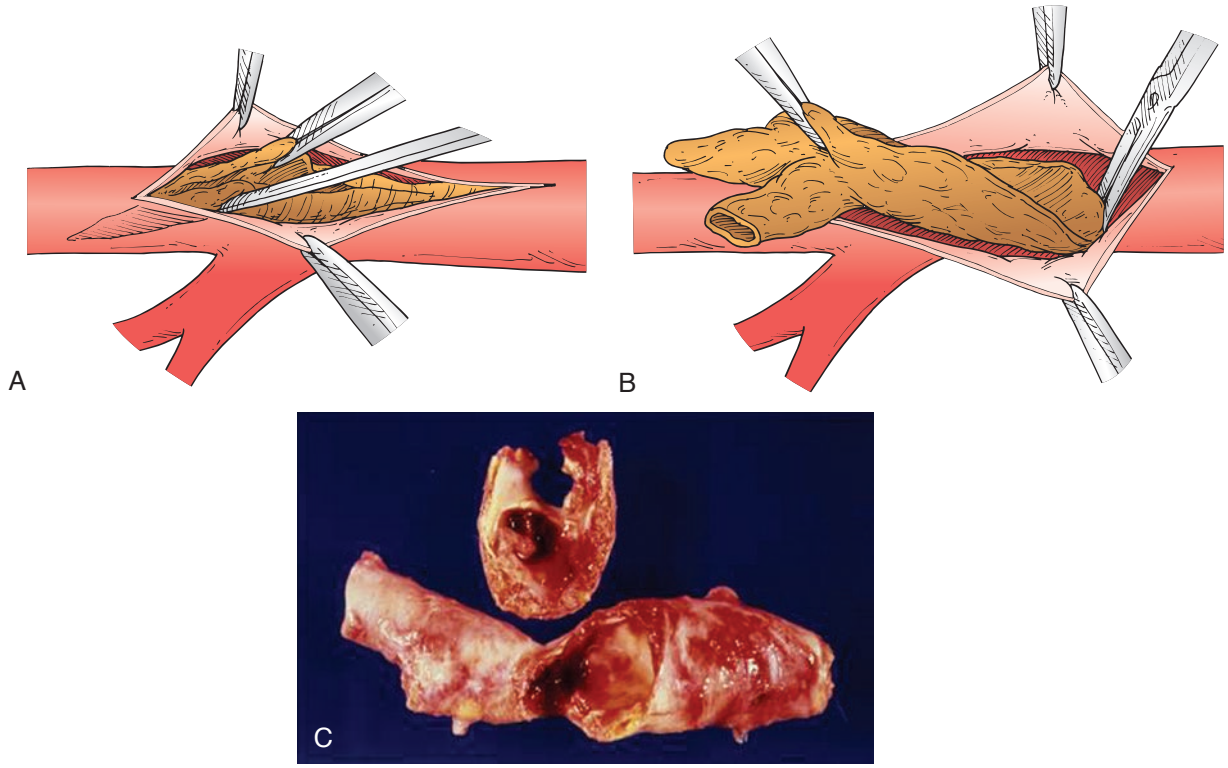

Figure 106.6 (A) The technique of endarterectomy involves the initial separation of plaque in the appropriate cleavage plane, with mobilization facilitated by a fine spatula. (B) Ideally, the endarterectomy is terminated by feathering to a tapered endpoint. (C) Photograph of an operative specimen removed by endarterectomy.

In his view, the last two planes are preferable because the subintimal plane predisposes to subsequent thrombosis. The residual outer layer is generally of sufficient mechanical strength to hold surgical sutures and to resist disruption or progressive enlargement when subjected to arterial pressure. Rarely the residual adventitia may be so attenuated that reconstruction of the wall with a patch or, in extreme cases, an interposition graft proves necessary. In practice, this most often occurs when the plaque is extensively calcified.

The various techniques all involve blunt separation of the plaque, termination by spontaneous tapering or sharp division, and careful attention to the endpoints (Figs. 106.5 and 106.6). Tacking sutures should be used when necessary, particularly to secure the distal endpoint, which must be firmly adherent to resist dissection or flap elevation leading to thrombosis. The simplest technical approach is the so-called open method, which employs a longitudinal arteriotomy that allows direct visualization of both endpoints as well as the entire endarterectomized surface; this technique is most commonly used for disease limited to the aorta and common iliac arteries. If primary closure is problematic due to small vessel caliber, patch angioplasty with vein, synthetic, or bovine pericardial material should be undertaken.

Extraction, eversion, and semiclosed methods are variations that can be helpful in specific anatomic situations. The last technique, useful to treat the external iliac arteries, involves arteriotomies at both the proximal and distal extents of the plaque and the initiation of plaque excision at the endpoints, similar to that undertaken in the open technique. A ringed stripper is then advanced between the endpoints to complete the plaque disengagement, obviating the need for full exposure of the treated segment. In the early 1970s, Inahara[46] modified the technique of eversion endarterectomy first described by Harrison et al.,[47] whereby the circumferentially dissected iliofemoral arterial segment is transected distally and passed proximally under the inguinal ligament into the pelvis before being endarterectomized and later reattached.

Aortobifemoral Bypass

Adequate intravenous access, intra-arterial pressure monitoring, Foley catheter placement, and preoperative antibiotics to minimize the risk of infection are routine aspects of aortic replacement surgery. Although the use of intraoperative blood salvage is advantageous in patients with relative anemia, its cost-effectiveness has not been firmly established in routine cases.[48] Attention should be paid to maintaining normothermia throughout the procedure to reduce the significant organ dysfunction and operative mortality associated with intraoperative hypothermia.[49] This is typically achieved with the use of forced-air body warming devices. ABFB grafting is performed under general endotracheal anesthesia. An epidural catheter is usually placed for postoperative pain control.

Exposure

The initial vascular exposure and proximal and distal vessel control are attained before the institution of systemic anticoagulation in

an effort to minimize blood loss. The femoral vessels are typically exposed first through bilateral longitudinal or oblique incisions to reduce the time during which the abdomen is open and the viscera are exposed. The extent of exposure is dictated by disease severity and the level of reconstruction planned at the CFA and its bifurcation. In general, the distal extent of the dissection involves circumferential control of the proximal SFA and profunda femoris arteries; the inferior epigastric and circumflex iliac branches at the anatomic transition from the external iliac to the CFA mark the proximal extent of the dissection. A circumflex femoral arterial branch frequently arises from the posterior aspect of the distal CFA and must be controlled to avoid troublesome backbleeding. The inferior aspects of the retroperitoneal tunnels through which the graft limbs will course to reach the femoral region are begun with blunt digital dissection posterior to the inguinal ligament, which can be partially divided posteriorly to prevent graft limb compression. The tunnels should track directly along the anterior aspect of the external iliac artery, with care taken to elevate all soft tissues to ensure that the ureters remain anterior. A crossing vein normally present beneath the inguinal ligament must be ligated or carefully avoided to prevent bleeding during the tunneling process.

Infrarenal aortic exposure is often performed through a transperitoneal approach by a longitudinal midline laparotomy, although some prefer a transverse incision. This incision typically extends from below the xiphoid process to just inferior to the umbilicus; as such, it is shorter than the incision normally employed for abdominal aortic aneurysm repair. The abdomen is explored for any intra-abdominal abnormalities, and the stomach is palpated to ensure proper positioning of the nasogastric tube. The transverse colon is retracted cephalad, and the small bowel is shifted to the patient's right side. The ligament of Treitz is then taken down, and the duodenum is mobilized to the right, allowing access to the infrarenal aorta. A fixed, self-retaining retractor is placed to aid exposure, with care taken to protect the displaced bowel from retractor blade injury. The retroperitoneal tissue overlying the aorta is dissected superiorly to the level of the left renal vein, and the larger lymphatic vessels encountered within the retroperitoneal lymphatic network are ligated. If renal artery reconstruction is not planned, the dissection can often be limited to the region between the renal arteries and the inferior mesenteric artery. Extensive dissection anterior to the aortic bifurcation and proximal left iliac artery should be avoided because the autonomic nerve plexus regulating erection and ejaculation in men sweeps over the aorta in this region. If exposure in the area of the plexus proves necessary, dissecting along the right lateral aspect of the infrarenal aorta and reflecting rather than transecting the tissue overlying the terminal aorta and proximal iliac arteries can minimize the risk of iatrogenic neurogenic sexual dysfunction.

Should thrombus or significant aortic calcification extend to the level of the renal arteries, it may be necessary to continue the proximal aortic dissection to the suprarenal level to allow safe proximal clamp placement. Alternatively, proximal control may be obtained by intraluminal balloon deployment or supraceliac clamping via the gastrohepatic ligament. In all cases, it is important to extend the reconstruction close to the level of the renal arteries to minimize the risk of failure secondary to disease progression in the remnant infrarenal aortic neck. If end-to-side repair is planned, exposure and control of all relevant lumbar or accessory renal arteries before the aortotomy is performed helps avoid backbleeding, which can be challenging to control with cross-clamps in place and the aorta compressed. The superior aspects of the graft limb tunnels are completed with further digital manipulation from above and below, again with care taken to maintain a course anterior to the iliac vessels but posterior to the ureters. The left limb tunnel passes beneath the sigmoid mesentery and slightly more laterally to avoid disruption of the autonomic nerve plexus. Moist umbilical tapes or Penrose drains are passed with a smooth aortic clamp to mark the tunnels. After vessel exposure and tunnel creation, but before vascular occlusion, a standard intravenous bolus of heparin sodium anticoagulation is given. Additional doses may be necessary, depending on the length of the operation and the requirement for additional periods of flow occlusion, and may be guided by the measurement of the activated clotting time. For peripheral vascular operations, the initial dose typically ranges between 70 and 100 units/kg, and an activated clotting time in the 250- to 350-second range is adequate.

Clamp Placement

With non–contrast-enhanced CTA guidance, when available, to delineate sites of heavy calcification, the aorta is carefully palpated to identify the optimal sites for application of the cross-clamps. In the event of asymmetrical plaque, the technique of clamping soft plaque against hard plaque minimizes the risk of emboli. It also lessens the risk of a traumatic clamp injury, which can be a formidable technical problem in a heavily calcified aorta. Anterior to posterior clamping may be necessary in the presence of a soft anterior but calcified posterior aortic wall. Appropriate atraumatic vascular clamps are selected, and after sufficient time is allowed for the heparin to circulate, the aorta is clamped first proximally or distally at the site of least disease to avoid dislodgement and potential distal embolization of plaque. The distal clamp is usually placed above or below the inferior mesenteric artery. The proximal clamp is placed just below the renal arteries if the disease pattern does not obligate suprarenal clamping, with as little dissection of the renal artery origins as possible.

If an end-to-end anastomosis is planned, the aorta is transected several inches below the proximal clamp, and the distal aorta is oversewn in two layers with running monofilament suture or stapled with a surgical stapler (Fig. 106.7A). A short segment of the distal aortic cuff is often excised to improve exposure of the aortic neck and aid precise proximal reconstruction. This maneuver also allows the graft to lie more flatly against the vertebral column rather than in an anterior orientation, and facilitates retroperitoneal coverage (Fig. 106.8). If necessary, it is important to carry out a complete thromboendarterectomy of the infrarenal neck (see Fig. 106.7B). Removal of all thrombotic debris and calcified plaque facilitates both suture placement and creation of a widely patent proximal anastomosis. Brief repositioning of the proximal clamp to the suprarenal position

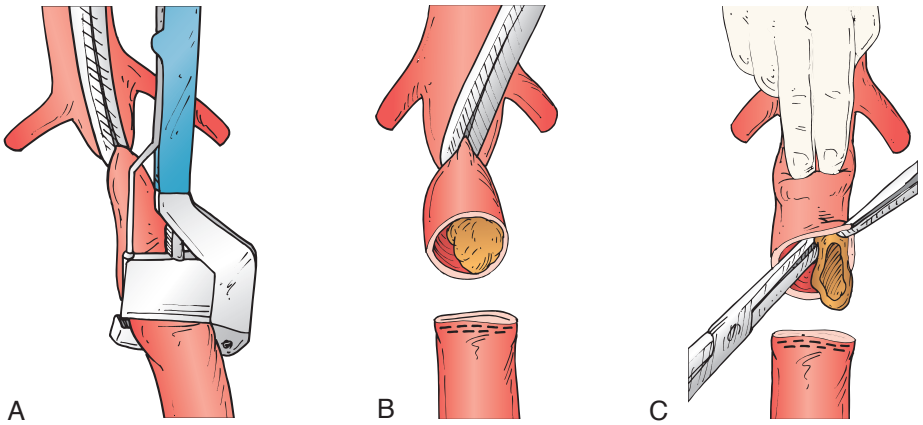

Figure 106.7 (A) The end-to-end proximal anastomosis for aortofemoral reconstruction can be initiated with the infrarenal aorta cross-clamp placed in an anteroposterior direction, as close to the origin of the renal arteries as possible. The aorta is then stapled or occluded with a second clamp just proximal to the origin of the inferior mesenteric artery. (B) After excision of a short segment of aortic cuff, a complete thromboendarterectomy of the remaining proximal cuff is carried out. (C) Brief digital or clamp control of the juxtarenal aorta may prove necessary to complete the thromboendarterectomy.

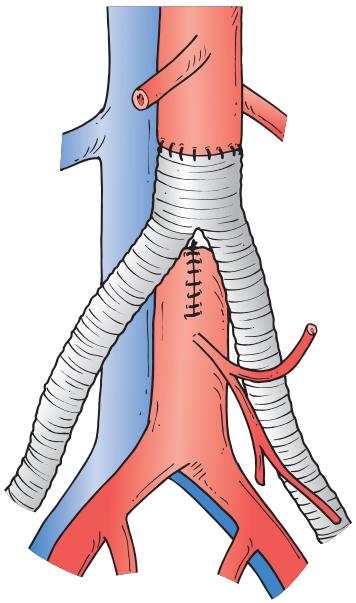

Figure 106.8 The end-to-end proximal anastomotic configuration for aortofemoral reconstruction allows the graft to lie flat against the vertebral column and results in less turbulent flow.

or the application of digital pressure sufficient to temporarily occlude the suprarenal aorta may be helpful to ensure the thorough removal of all intraluminal debris (see Fig. 106.7C). Mobilization and cephalad or caudad retraction of the left renal vein can facilitate adequate exposure of the juxtarenal aorta. Division of the left renal vein is usually unnecessary but acceptable if additional exposure is required, provided the adrenal, lumbar, and gonadal collateral branches are preserved. If suprarenal clamping is undertaken, concurrent clamping of the renal arteries is advisable to prevent the potentially adverse effects of inadvertent emboli.

A minority of patients present with an aortic occlusion extending to the level of the renal arteries. These patients are best managed by controlling the renal arteries and then thrombectomizing the infrarenal cuff, without placement of an infrarenal proximal aortic clamp, which could displace thrombotic material proximally. The aortic plug encountered at this location is often soft, propagated, secondary thrombus that can be easily removed with a Kelly clamp. After aortic pressure is used to flush out the remaining plug, suprarenal control is briefly used. Remnant debris is cleared from the infrarenal cuff, the aorta is flushed again, the renal arteries are backbled, and then an infrarenal clamp is placed.

Graft Selection

A bifurcated graft appropriately sized to match the aorta and femoral vessels is selected. Although some surgeons prefer polytetrafluoroethylene grafts, knitted polyester (Dacron) grafts are more commonly used. Current low-porosity knitted versions have excellent handling and hemostatic properties and a proven track record of durability (see Chapter 64). They also develop a more stable pseudointima than earlier woven grafts, although their tendency to dilate over time has been documented.[50] Woven polyester grafts can also be used and may tend to dilate less during long-term follow-up. Greater appreciation of the importance of sizing the graft to the runoff vessels followed an early experience with limb thrombosis believed to be secondary to sluggish flow from oversizing.[51,52] Bifurcated grafts measuring 18 by 9 mm or 16 by 8 mm are typically chosen for male patients; grafts measuring 14 by 7 mm or even 12 by 6 mm are usually suitable for female patients.

Anastomoses

One technical consideration related to ABFB grafting that has prompted considerable debate involves the type of proximal anastomosis. The published literature has established that both end-to-end and end-to-side techniques are acceptable and effective. Despite strong preferences expressed by various surgeons, neither approach has demonstrated overall superiority, but each may be preferred in certain circumstances.

End to End

Those favoring an end-to-end configuration claim that it facilitates a more comprehensive thromboendarterectomy of the proximal stump and allows a better in-line flow pattern, with less turbulence and more favorable hemodynamic characteristics (see Fig. 106.8).[53] Lower rates of proximal suture line pseudoaneurysm and better long-term patency rates reported

in some series lend support to this view.[54] Stapling or oversewing of the distal aorta with the end-to-end technique also has the benefit of reducing the risk of clamp-induced emboli to the lower extremities after release of the distal clamp compared with the end-to-side option. Further, those in favor of this approach assert that because the graft lies flatter in the retroperitoneum, this enhances the ability to close the retroperitoneum over the graft, resulting in a lower rate of late graft infection and aortoenteric fistulae; there is, however, little direct evidence to support this claim. Finally, the creation of an end-to-side anastomosis can be technically challenging in a heavily diseased aorta, particularly if it is partially occluded by a side-biting clamp (favored by some surgeons). In the setting of concomitant aneurysmal disease or complete aortic occlusion extending up to the level of the renal arteries, an end-to-end approach should be used.

End to Side

There are certain circumstances in which an end-to-side proximal anastomosis is advantageous. The most common indication is in patients with occluded or severely diseased external iliac arteries but patent common and internal iliac arteries, in whom the interruption of forward aortic flow may result in the loss of critical pelvic perfusion. Without the retrograde flow through the external iliac arteries normally present in an end-to-end configuration, pelvic ischemia, ranging from mild hip claudication to severe buttock rest pain or ulceration, may result.[55,56] Additional ischemic complications, such as erectile dysfunction in men and rarely seen paraplegia secondary to cauda equina syndrome,[57] can potentially be avoided with an end-to-side approach. Preservation of either a large inferior mesenteric artery, sometimes necessary to avert colonic or mesenteric ischemia, or an important accessory renal artery arising from the distal aorta or an iliac artery can more easily be accomplished with an end-to-side technique. Alternatively, these vessels can be reimplanted onto the side of an end-to-end graft.

Technique

For end-to-end proximal anastomoses, the main body of the graft is shortened to minimize graft redundancy and to allow the graft limbs to straddle rather than to override the transected aortic stump (see Fig. 106.8). The anastomosis is performed with running 3-0 polypropylene suture. If an end-to-side anastomosis is to be performed, a beveled anastomosis is fashioned after an approximately 3-cm longitudinal aortotomy is created as close to the renal arteries as practical (Fig. 106.9). Care is taken to remove all loose debris and mural thrombus from the excluded portion of the aorta, and a particular effort is made to ensure adequate backflushing of clot and debris before re-establishment of forward flow in the native aorta and graft. Side-biting clamps are best avoided in performing an end-to-side anastomosis because they compress the aortic sidewalls, rendering both adequate thromboendarterectomy and accurate suture placement more difficult (see Fig. 106.9).

After completion of the abdominal portion of the procedure, the graft limbs are clamped with soft-jaw insert clamps and flushed with heparinized saline. They are then passed through

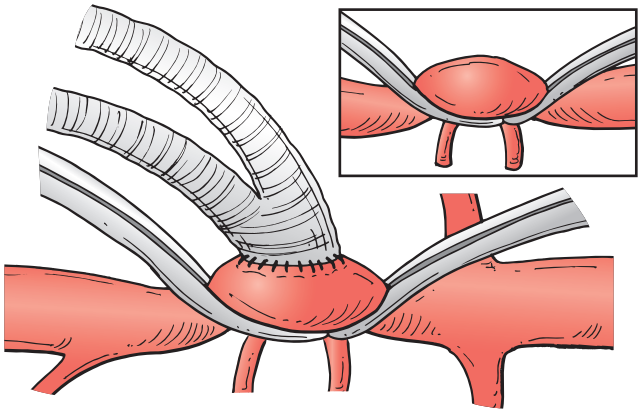

Figure 106.9 An end-to-side proximal anastomosis for aortofemoral grafting is required to preserve antegrade pelvic perfusion in situations in which retrograde flow would be compromised by heavily diseased or occluded external iliac arteries.

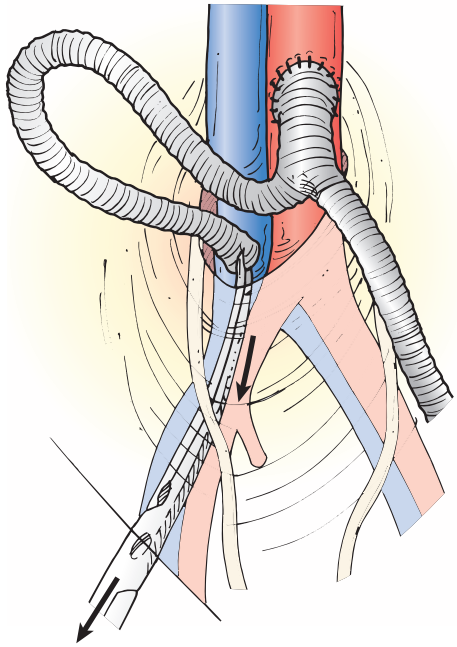

Figure 106.10 Aortobifemoral graft limbs are carefully tunneled beneath the ureters to avoid kinking.

the retroperitoneal tunnels, with care taken to prevent twisting and to eliminate excess redundancy (Fig. 106.10), and attention is turned to the distal anastomoses. Proximal femoral control is typically obtained with either a soft-jaw clamp or a Satinsky clamp placed from a lateral direction, and distal control is usually achieved with vessel loops or atraumatic bulldog or profunda clamps. For those patients with normal femoral and distal runoff, a longitudinal arteriotomy limited to the distal CFA is sufficient. More commonly, extension of the arteriotomy across the profunda femoris artery origin and profundaplasty will prove necessary (see the section Adjunctive Profundaplasty). The distal anastomoses are completed in a beveled end-to-side fashion with 5-0 polypropylene, again carrying out retrograde and antegrade flushing maneuvers before the anastomoses are completed and flow is restored. It is important to alert the

anesthetic team before clamp release, given the expected blood pressure drop with reperfusion.

Closure

Before wound closure, the surgeon must confirm adequate distal perfusion and absence of distal embolization. The quality of the pulses and Doppler signals just beyond the distal anastomosis and at the pedal level is assessed, as are the color, temperature, and general appearance of the feet. If the revascularization is deemed satisfactory and no further distal reconstruction is to be undertaken, the effects of heparin can be reversed by administering protamine sulfate (1 mg/100 units of circulating heparin) at the surgeon's discretion to help attain hemostasis. Once hemostasis is sufficient, the abdomen is irrigated and the retroperitoneum is closed over the proximal anastomosis and graft behind the duodenum to the extent possible. If adequate retroperitoneal coverage is not possible, particularly with an end-to-side proximal anastomosis, a sleeve of omentum should be fashioned to cover any exposed segment of the anastomosis and to separate the graft from the adjacent bowel. It is important to tack down this omental apron to prevent small bowel herniation. The groin wounds are copiously irrigated and the deeper tissue is closed in several layers with absorbable Vicryl sutures.

Adjunctive Profundaplasty

The important role of profundaplasty in preserving the long-term patency of anatomic or extra-anatomic grafts in patients with AIOD has been widely established.[9,44,58-61] In patients with normal proximal SFAs and profunda femoris arteries, the distal anastomosis of an aortobifemoral graft can be performed to the CFA. However, most patients with AI disease severe enough to warrant aortofemoral bypass in the endovascular era have both profunda and SFA disease that limits outflow and increases the likelihood of graft thrombosis. In patients with severe AI, SFA, and profunda disease causing CLTI, a concomitant profundaplasty may be sufficient to sustain the patency of the inflow graft and to salvage the limb, particularly if there is good profunda collateral circulation to a patent popliteal artery. Some authors have even recommended that the aortofemoral bypass graft limb should be extended to the profunda in every case of SFA occlusion, even in the absence of orificial profunda disease, arguing that a "functional" obstruction on the order of 50% stenosis is present in these patients.[62] Although this position has not been universally adopted, it is now common practice to extend the hood of the distal anastomosis over the origin of the profunda femoris artery to enhance the graft outflow, particularly if the SFA is occluded or severely diseased. In the presence of significant CFA or profunda femoris origin plaque, an endarterectomy or profundaplasty is almost always indicated (Fig. 106.11). The need for adjunctive profundaplasty should be determined at the time of preoperative angiography. Although anatomic variations are not uncommon, the profunda typically arises as a posterolateral branch off the terminal CFA. As such, proper visualization requires dedicated oblique views because subtle disease can easily be obscured by the overlying SFA in the anteroposterior projection.

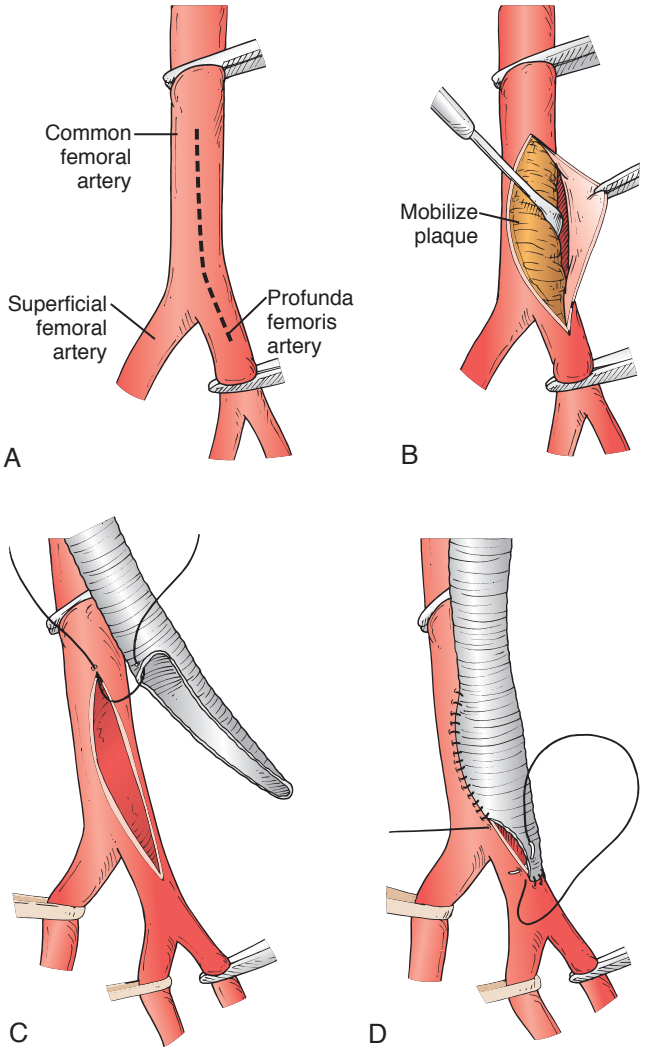

Figure 106.11 (A to D) In the setting of superficial femoral artery and orificial profunda femoris artery disease, extending the common femoral arteriotomy to the origin of the profunda and performing a profundaplasty before completion of the distal anastomosis of the aortobifemoral bypass can improve outflow and maximize graft patency.

Technique

The profunda is usually exposed by distal extension of the dissection used to access the CFA, although a lateral approach through a fresh tissue plane with medial retraction of the sartorius can be used to avoid a scarred or infected groin. Every effort should be made to spare all collateral branches arising from the CFA and profunda femoris artery because they may prove vital to preservation of lower extremity perfusion in the event of later graft thrombosis.

Once exposed, the CFA and profunda femoris should be palpated to gauge the degree of atherosclerotic plaque present, particularly given the well-known tendency of angiography to underestimate the extent of disease. Profunda arterial plaque not uncommonly ends at the first or second major branch point. The profunda orifice can be visually inspected after the CFA is incised, and its lumen can be further assessed by noting the quality of backbleeding and by gentle interrogation with a

series of sizing metal probes. The dissection is continued along the anterior aspect of the artery as necessary; the extent is guided by the location of a suitable endpoint as identified by palpation, inspection, and reference to the preoperative angiogram. The lateral femoral circumflex vein coursing deep to the SFA and crossing anteriorly over the proximal profunda must be ligated in most cases. Isolated orificial plaque can sometimes be entirely removed by an eversion technique through the CFA. If it becomes necessary to extend the arteriotomy to the profunda, care should be taken to avoid incising the crotch of the superficial and deep femoral arteries. The endarterectomy is performed as described earlier. In the event that an extensive endarterectomy proves necessary, it may be preferable to close the endarterectomy site with a vein or bovine pericardial patch, onto which the distal anastomosis can then be attached, rather than to create a long profunda patch with the graft limb.[58] If an outflow bypass is to be performed, this can be taken off either the distal patch or the graft limb.

Other Operative Considerations

External Iliac Anastomosis

Early in the operative experience for AI occlusive disease, the tendency was to place the distal anastomosis of aortic bypass grafts at the iliac level. With time came a growing appreciation of the benefits of extending the distal anastomosis to the femoral level; creation of the distal anastomosis is technically easier at the groin level, and long-term patency rates for aortobifemoral grafts are notably improved compared with AI grafts.[63] In addition, with meticulous surgical technique and improvements in graft materials, the feared increase in graft infection caused by moving the distal dissection to the femoral level has not proved to be a significant problem in the majority of patients.[64] There are certain circumstances, however, in which performing an aortobiiliac bypass remains advantageous. Patients with hostile groin creases from prior surgery or radiation therapy, for example, are likely to be better served by this option, as are obese, diabetic patients with an intertriginous rash at the inguinal crease and patent external iliac arteries. Excellent preoperative imaging and intraoperative confirmation of suitable anatomy are necessary if one chooses this reconstructive alternative.

Multilevel Occlusive Disease

The optimal management of patients with multilevel occlusive disease is often difficult to determine. The question frequently arises whether or under what circumstances concomitant versus staged outflow procedures should be performed in association with an inflow operation. The impact of synchronous SFA disease on the results of AI revascularization remains undefined in the current literature; some reports have indicated similar patency rates between patients with and without SFA occlusion,[22] whereas others have reported lower long-term patency rates in this setting.[65,66] If an atretic or prohibitively diseased profunda is present in addition to a severely diseased SFA, infrainguinal bypass grafting is likely to be necessary to ensure sufficient outflow for graft patency and perfusion of the foot. An investigation that specifically addressed the impact of diabetes concluded that diabetic patients with multilevel occlusive disease were no more likely to require subsequent infrainguinal revascularization after an inflow reconstruction than were nondiabetics.[67] Further, although up to 80% of patients with claudication and both inflow and outflow disease manifest symptomatic improvement after aortofemoral bypass grafting alone,[10,68] some studies indicate that as many as two-thirds have some degree of persistent claudication.[69]

No single criterion mandates a combined procedure; however, the severity of distal ischemia is probably the most important factor to be considered. If significant tissue loss is present, concurrent inflow and outflow procedures are probably warranted if limb salvage is to be achieved. In deciding whether a staged approach is appropriate, the patient's ability to tolerate a prolonged operative procedure must be weighed against the potential risk of wound and graft infection resulting from redissection in the groin and the risk of progressive tissue loss during the initial recuperative period. When it is performed with several teams operating simultaneously, concurrent inflow and outflow revascularization can be completed in a timely and safe manner. Indeed, several reports found no significant differences in perioperative mortality or morbidity in patients undergoing multilevel reconstruction and those having a major inflow procedure alone.[70,71]

Associated Renal or Mesenteric Artery Occlusive Disease

In recent decades, the introduction of potent new antihypertensive drugs and the growing application of percutaneous interventions have had a significant impact on treatment of renal artery occlusive disease. Balloon angioplasty and stenting are likewise playing an increasing role in mesenteric occlusive disease. Whether to address coexisting renal or mesenteric disease at the time of aortic reconstruction is a challenging decision that warrants careful consideration of multiple individual factors, the obligatory increase in operative time and complexity and the greater operative mortality and morbidity. In the setting of multidrug-refractory hypertension or ischemic nephropathy believed to have a potentially reversible functional component on the basis of a thorough diagnostic assessment, simultaneous repair of significant renal occlusive disease may be indicated. Combined repair is also appropriate when accessory renal arteries arise from the diseased aortic segment. Simultaneous revascularization is more controversial when the functional significance of the renal artery stenosis is uncertain or is thought to be clinically silent.

Advocates of an aggressive treatment approach cite the clinical deterioration seen with the progression of untreated renal artery occlusive disease and the increasing safety of combined aortic and renal reconstruction. Those who favor a more conservative position believe that the increased surgical risk does not offset the potential clinical gain. Perioperative mortality rates for patients undergoing simultaneous aortic and renal repair have consistently been in the 5% to 6% range,[72-74] in comparison to rates of 1.7% and 0.7% for those undergoing renal or aortic reconstruction alone, respectively.[72] A favorable response to hypertension has been reported in 60% to 70% of patients

undergoing combined revascularization, and improvement in renal excretory function has been reported in up to 33% of patients.[72,73] The most common reconstruction approach is aortorenal bypass from the aortic graft, with the use of either saphenous vein or prosthetic graft. In select cases, in situ thromboendarterectomy, endarterectomy with reimplantation onto the aortic graft, or extra-anatomic splenorenal or hepatorenal grafting may prove preferable (see Chapter 126). With regard to visceral artery occlusive disease, strict attention to preservation of the inferior mesenteric artery usually suffices to prevent postoperative mesenteric ischemia, and simultaneous revascularization of the celiac or superior mesenteric arteries is rarely required. Staged open or percutaneous revascularization of the renal or mesenteric arteries is another option in specific circumstances, although the role of simultaneous renal reconstruction versus angioplasty before or after surgery remains unclear.[75,76]

Coexistent Abdominal Aortic Aneurysms

While open repair of infrarenal abdominal aortic aneurysms is most typically completed with an aortic tube or aortobi-iliac graft, coexistent AIOD may necessitate aortofemoral bypass grafting. Although aortofemoral bypass grafting is more complex than aortic tube or aortobi-iliac reconstruction in patients with both aneurysmal disease and iliac outflow occlusive disease, our own institutional experience has led us to believe that concern for associated increased short- or longer-term mortality in such patients is not justified and should not be the basis for denying surgery. A review of more than 1000 consecutive open abdominal aortic aneurysm repairs performed over a recent 20-year period at the Brigham and Women's Hospital revealed a significantly higher postoperative morbidity rate in the 10% of patients undergoing aortofemoral reconstruction but similar 30-day mortality and 5-year survival (unpublished data, Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital).

Retroperitoneal Approach

Although the retroperitoneal approach to the infrarenal aorta is a well-accepted alternative to the more standard transperitoneal technique in the setting of aneurysmal disease, it is also favored by some surgeons in select patients with occlusive disease.[77,78] This option may be advantageous in patients with a history of multiple prior abdominal operations, abdominal wall stoma, concurrent renal or mesenteric arterial disease requiring suprarenal exposure, or severe cardiopulmonary disease. Stated benefits of reduced pulmonary morbidity and lower rates of postoperative ileus have not been consistently supported by the literature.[79] Clear disadvantages of the retroperitoneal approach include the attendant difficulty in accessing the right renal and iliac arteries and the right groin, particularly in obese patients.

The technique involves placing the patient on an inflatable beanbag in the partial right lateral decubitus position, with flank extension. The hips are rotated as far posteriorly as possible to maximize exposure to the right femoral arteries. An oblique incision is created from the left lateral border of the rectus abdominis to the posterior axillary line, and the lateral third of the 11th rib is excised. The retroperitoneal plane is identified, and the peritoneal contents are mobilized anteriorly to reveal the left iliac artery and infrarenal aorta (see Chapter 71).

Minimally Invasive Approaches

Reflecting widespread trends toward more minimally invasive approaches in other areas of surgery, the technique of performing aortofemoral bypass grafting through a shorter midline incision has been reported.[80] The described minilaparotomy is less than 10 cm long, and the procedure is undertaken without displacement of the small bowel. Enthusiasm for the technique is currently limited.

There has also been recent, ongoing interest in applying laparoscopic techniques to the treatment of AIOD. This approach has been supported by a small body of literature mainly composed of individual case series (Table 106.1).[81-84] Some enthusiasts have championed a more limited application with hand-assisted techniques and smaller incisions,[85] whereas others have advocated for the use of complete laparoscopic or robot-assisted revascularization.[86-88]

The presumptive benefits of reduced hospital length of stay, less perioperative pain, and fewer postoperative complications are balanced against longer operative times and the absence of long-term data to support the durability of this alternative strategy. The lack of exposure to the technique during routine general and vascular surgical training, the associated inherent technical challenges and prohibitive learning curve, and the declining indications for this approach with the advent of even less invasive endovascular alternatives have contributed to its limited popularity. Whereas morbidity and mortality rates for laparoscopic aortic bypass approach those for open aortic reconstruction (see Table 106.1), lower rates of gastrointestinal and pulmonary complications have been noted. Proponents of laparoscopic surgery also highlight the minimal incidence of incisional hernias and adhesion-related bowel obstruction. Open conversion rates in the reported series to date have generally been low but reached the 20% range in two reported series.[94,96] Although long-term patency rates for laparoscopic bypass have yet to be defined, intermediate-term results compare favorably with those reported for open ABFB.[84,97,99]

RESULTS

The short- and long-term results of both endarterectomy and ABFB have generally been excellent, particularly in more recently published series. When endarterectomy is performed for disease limited to the distal aorta and proximal iliac segments, 5-year patency rates of 95% and 10-year rates between 85% and 90% are consistently achieved.[42-44,46] In contrast to the nearly 7% perioperative mortality rates reported in the early experience of endarterectomy, more recent reports reflect improvements in patient selection and perioperative management, with rates as low as 1%.[41-44]

Several large meta-analyses evaluating the comprehensive experience with ABFB grafting from its inception in the mid-1950s through the 2000s have indicated similar overall 30-day mortality rates of between 4.0% and 4.4%.[100-102] Several more recent single-institution series that better reflect the current era

TABLE 106.1 Reports of Total Laparoscopic Aortofemoral Bypass for Aortoiliac Occlusive Disease

Series	Year	No. of Patients	Conversion to Open Repair (%)	RESULTS	
				Mortality (%)	Morbidity (%)
Said et al.[89]	1999	7	0	1 (14)	0
Alimi et al.[90]	2000	15	1 (7)	1 (7)	2 (13)
Barbera et al.[91]	2001	30	5 (17)	0	4 (13)
Dion et al.[92]	2004	49	4 (8)	1 (2)	3 (6)
Olinde et al.[93]	2005	22	2 (9)	1 (5)	4 (18)
Rouers et al.[94]	2005	30	6 (20)	0	11 (37)
Remy et al.[83]	2005	21	1 (5)	0	5 (24)
Cau et al.[95]	2006	72	2 (3)	0	3 (4)
Dooner et al.[96]	2006	13	3 (23)	0	1 (8)
Di Centa et al.[97]	2008	150	5 (3)	4 (3)	21 (4)
Fourneau et al.[98]	2010	139	19 (14)	3 (2)	23 (17)
Jongkind et al.[99,a]	2011	24	4 (14)	1 (4)	4 (14)
Novotny et al.[86,b]	2011	40	2 (5)	0	1 (2.5)
Tiek et al.[c]	**2012**	**14**	0	0	0
Ghammad et al.[d]	**2015**	**173**	**21 (12.1)**	**4 (2.3)**	**12 (6.9)**

[a]Robot assisted.
[b]Bypasses: 21 aortofemoral, 19 aortobifemoral.
[c]Tiek J, Remy P, Sabbe T, et al. Laparoscopic versus open approach for aortobifemoral bypass for severe aorto-iliac occlusive disease—a multicentre randomised controlled trial. *Eur J Vasc Endovasc Surg*. 2012;43(6):711–715.
[d]Ghammad K, Dupuis A, Amond L, et al. Total laparoscopic bypass is safe and effective for aortoiliac occlusive disease. *J Vasc Surg*. 2015;61(3):698–702.

report an operative mortality of near 1%,[22,30,67,103-105] on par with that of elective abdominal aortic aneurysm repair. Increasing age, chronic pulmonary disease, and a low-volume hospital setting predict higher perioperative mortality (Table 106.2).

The accumulated experience to date has shown that 5-year primary patency rates between 85% and 90% and 10-year rates between 75% and 85% can be expected with aortobifemoral grafting (see Table 106.2).[22,30,65,67,100-107] Age has proved to be a significant predictor of outcome[108]; in one report, primary patency rates at 5 years were greater than 95% for patients older than 60 years but only 66% for those younger than 50 years (Fig. 106.12).[30] Although it is not clear why younger patients have inferior long-term patency rates, one could speculate that they have a more aggressive form of atherosclerosis or are at a different point in disease evolution than their older counterparts.

The reported influence of gender on graft patency has been more inconsistent, with some studies indicating less favorable outcomes in women and others demonstrating equivalent long-term patency rates in men and women.[22,30,65,100] Similarly, conflicting results have been documented with regard to the impact of preexisting SFA occlusion, with some but not all reports suggesting improved late patency when a simultaneous outflow procedure is performed at the time of aortobifemoral grafting.[22,65,66] In contrast, the benefits of combining profundaplasty with the inflow procedure have been unambiguously demonstrated.[9,44,58-61] Of note, no major differences in aortobifemoral graft durability have been noted between the transperitoneal and retroperitoneal approaches, between end-to-end and end-to-side anastomotic techniques, or between the indications of claudication and CLTI.[22,30,78,79,100] The single series directly comparing percutaneous treatment of AIOD with aortobifemoral grafting demonstrated similar 3-year secondary patency and limb salvage rates.[109]

In general, patients with occlusive disease limited to the AI region can expect to have excellent relief of symptoms after aortobifemoral grafting; those with multilevel disease generally have a lesser degree of symptom reduction. In one study, more than 80% of patients reported satisfaction with their result 5 years after undergoing ABFB.[110] Similarly, although 10-year survival rates are as low as 50% in patients with diffuse disease, those with more localized AI disease have a life expectancy not appreciably different from that of their normal age- and sex-matched counterparts.[9,111,112]

It has been questioned whether the excellent outcomes of aortic bypass surgery, the result of decades of technical refinement, and accumulated experience with the procedure remain valid in the modern endovascular era.[113] In the most comprehensive report to date, a meta-analysis spanning the last 40 years, a decrease in patency rates for both ABFB and iliofemoral bypass grafts was noted over time when results were compared by decade of publication.[102] Postulated reasons for this finding have included greater operative complexity (i.e., more reoperative indications and an increased need for suprarenal clamping, adjunctive visceral

TABLE 106.2 Outcomes of Aortobifemoral Bypass: Operative Mortality and Long-Term Patency Rates

Series	Year	No. of Patients	RESULTS				
			Operative Mortality (%)	5-Year PP (%)	5-Year SP (%)	10-Year Patency (%)	15-Year Patency (%)
de Vries and Hunink[100,a]	1997	1429	4.4	88-91		82-87	75-82
de Vries and Hunink[100,b]	1997	1429	4.4	80-86		72-79	63-72
McDaniel et al.[101,c]	1997	2689	4	82-92		74-78	69
Ballard et al.[65]	1998	54	1.9	93[d]			
Onohara et al.[103]	2000	38	0	89	97	94	
Faries et al.[67]	2001	370	0	93			
Mingoli et al.[106]	2001	130	4.6	81	87		
Dimick et al.[107]	2003	3073	3.3				
Reed et al.[30]	2003	281	1	85	93		
Back et al.[4]	2003	107	3.7				
Hertzer et al.[22]	2007	224	1.2	88		81	71
Chiesa et al.[104]	2009	822[e]	0.1	97	98	90	
Burke et al.[105]	2010	118	0.8	89			
Chiu et al.[102,f]	2010	5738	4.1	86			

[a]Meta-analysis of 23 studies between 1975 and 1996, limb-based.
[b]Meta-analysis of 23 studies between 1975 and 1996, patient-based.
[c]Meta-analysis of 18 reports between 1985 and 1992.
[d]Primary patency rate at 42 months.
[e]Aortobiiliac bypass in 3.8%.
[f]Meta-analysis of 29 studies between 1970 and 2007.
PP, Primary patency; *SP,* secondary patency.

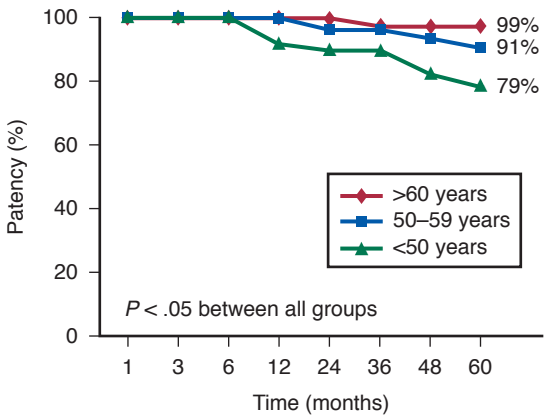

Figure 106.12 Overall 5-year cumulative secondary patency rates in a recent cohort of patients undergoing aortobifemoral bypass grafting, indicating an inverse relationship between age and graft patency.[20]

segment revascularization, or concomitant outflow procedures) and a substantial decline in the experience of more recently trained surgeons in open aortic reconstruction.[113] Supportive evidence for this view can be found in one report indicating increased mortality and lower long-term patency rates when ABFB is performed in the setting of chronic infrarenal aortic occlusion.[114] As yet, no data are available on the outcome of aortic bypass surgery after failed endovascular revascularization.

Early Complications

Reported overall morbidity rates range from 17% to 32% after aortic surgery for occlusive disease (Table 106.3).[a] Cardiac complications are the most common cause of mortality[22,68] and result from the hemodynamic stress associated with major vascular surgery and the obligatory fluid shifts during the early postoperative period. Pulmonary complications are also common and are most likely to occur in the elderly or those with chronic obstructive pulmonary disease, a significant smoking history, or poor preoperative nutritional status.[115] Adequate pain control, appropriate diuresis, and strict attention to pulmonary toilet are important measures to prevent the development of pneumonia and the progression of relatively benign alveolar collapse to more extreme degrees of pulmonary collapse.

Acute renal failure after aortic reconstruction for occlusive disease is relatively uncommon in patients with normal preoperative renal function, even when suprarenal clamping proves necessary. Adequate hydration and the avoidance of repetitive aortic cross-clamping and perioperative hypotension are valuable prophylactic maneuvers; less clear is the benefit of the adjunctive use of mannitol and furosemide (Lasix) to trigger diuresis before aortic cross-clamping. Our limited ability to alter the natural history of acute tubular necrosis or the effects of atheroemboli

[a]References 4, 36, 45, 80-82, 123, 127, 132.

TABLE 106.3 Complications of Aortobifemoral Bypass

Complication	Percentage
Early (Perioperative)	
Hemorrhage	1-2
Renal failure	<5
Acute limb ischemia	1-3
Bowel ischemia	2
Groin complications (lymphocele, lymphocutaneous fistula, wound infection, hematoma)	3-15
Sexual dysfunction	≤25
Ureteral injury	<1
Spinal cord ischemia	0.25
Pneumonia	<7
Myocardial infarction	1-5
Death	0-4
Late	
Graft thrombosis	5-30
Graft infection	0.5-3
Aortoenteric fistula	<3
Anastomotic pseudoaneurysm	1-5

results in some inevitable progression to dialysis dependence; those patients with a preoperative creatinine concentration greater than 1.8 mg/dL [159 µmol/L] are at much higher risk for this complication.[116]

Ureteral injury during dissection, graft tunneling, or retroperitoneal closure can usually be avoided with careful, diligent surgical technique. Spinal cord ischemia is a particularly devastating complication of infrarenal aortic surgery, and one that is thought to be potentially preventable. The central component of prophylaxis is careful preservation of hypogastric perfusion; however, the use of gentle technique to minimize the risk of atheroemboli and the avoidance of perioperative and postoperative hypotension have also proved to be important preventive measures.[117] Fortunately, this complication is rare, occurring in only 0.3% (4 of 1209) of reconstructions for AIOD in one series.[118]

Hemorrhage

Bleeding complications associated with AI endarterectomy, particularly for extensive disease, were partly responsible for the waning popularity of this technique. With modern suture and patch materials and the less extensive disease typically repaired in the current era, bleeding associated with endarterectomy has become less of a problem. For patients undergoing aortobifemoral grafting, postoperative hemorrhage is a relatively rare event, occurring in 1% to 2% of cases.[119] This rarity is due in part to a greater awareness of bleeding disorders, better intraoperative anticoagulation and blood product management, and improved hemostatic properties of the grafts used (see Chapter 37).

Bleeding points in the anastomotic suture line after a test release of the aortic or femoral clamps are usually effectively managed with repair sutures reinforced with felt pledgets. It is important to replace the clamp before placing any necessary repair stitches because attempted placement under tension risks extending the defect and worsening the bleeding. In cases in which the walls of the infrarenal aortic cuff are particularly thin after thromboendarterectomy, a previously positioned sleeve of graft advanced over the aortic suture line can act as a prophylactic bolster. Intraoperative venous injuries can occur during dissection between the aorta and vena cava or from a tear in a lumbar vein; such injuries can often be controlled with judicious tamponade. A number of sealants, glues, and thrombin-based hemostatic adjuncts are now available to help control troublesome diffuse oozing and persistent needle hole bleeding.

Delayed bleeding may occur if the postoperative blood pressure is appreciably higher than the pressure at the time of closure. Blood products, including platelets and fresh frozen plasma, are the preferred replacement fluid in most cases during the early postoperative period, particularly if intraoperative blood loss was significant and the patient is considered at risk for dilutional coagulopathy. Careful postoperative monitoring of the abdominal girth, hematocrit, bladder pressure, coagulation parameters, and hemodynamic status is paramount to identify ongoing bleeding significant enough to require urgent reoperation (see Chapter 34).

Intestinal Ischemia

Intestinal ischemia after aortic reconstruction has been reported in 2% of cases.[120] The involved segment is usually the rectosigmoid, and the cause is multifactorial. Although sacrifice of either the primary or the main collateral source of perfusion to the colon during reconstruction is the most common causative event, perioperative hypotension leading to insufficient perfusion and atheroemboli are other possible contributors. If compromised bowel perfusion is recognized intraoperatively after the creation of an end-to-end anastomosis, inferior mesenteric artery reimplantation is indicated. Although some surgeons advocate routine reimplantation of all patent inferior mesenteric arteries as the safest means to avoid colonic malperfusion,[121] this practice has not been universally adopted. Intraoperative detection of ischemia can be difficult, and all of the various techniques of doing so have their limitations. In addition to direct visual assessment, interrogation of Doppler flow along the antimesenteric border, measurement of the inferior mesenteric artery stump pressure, and administration of intravenous fluorescein have been used. Given the frequency of delayed presentation, maintaining a high index of suspicion and having a low threshold for performing sigmoidoscopy during the early postoperative period are critical in the effort to avoid potentially catastrophic colonic perforation.

Late Complications

Late complications after aortobifemoral grafting include graft limb thrombosis, aortoenteric fistula, graft infection, and anastomotic pseudoaneurysm (see Table 106.3).

Graft Thrombosis

Graft thrombosis is the most frequently encountered late complication (see Chapter 46). It occurs in as many as 30% of cases in some series in which the grafts were observed for 10 years or longer.[122] Occlusion of the entire graft is relatively rare and usually stems from placing the proximal anastomosis inappropriately low in relation to the renal arteries, with subsequent progression of proximal atherosclerosis. A more commonly encountered scenario is unilateral limb thrombosis, which most often reflects progressive intimal hyperplasia at the distal anastomosis or progression of outflow disease. Flow can frequently be restored with aggressive efforts using special thrombectomy catheters designed to remove the chronically adherent fibrinoid thrombus typically encountered. If inflow is successfully restored, revision of the distal anastomotic site with a profundaplasty or extension of the graft may prove necessary. If more extensive progression of outflow disease is identified, or if extraction of a distally propagating thrombus is unsuccessful, the addition of an outflow graft may be needed to ensure patency of the revascularized limb. A femorofemoral or axillofemoral graft usually suffices as a secondary source of inflow when an aortobifemoral limb is not successfully reopened.

False Aneurysm

Anastomotic false aneurysms are far less common in modern practice compared with the early experience of aortic grafting, but they continue to be seen as a late complication in 1% to 5% of cases (see Chapter 48).[119,123] They arise secondary to a weakening in the suture line as a result of structural fatigue or fabric degeneration. Undue tension, poor suturing technique, and focal weakening of the recipient arterial wall after endarterectomy have been implicated as causative factors. Infection undoubtedly plays a role in many cases, despite the frequent absence of any obvious clinical signs; *Staphylococcus* species are the predominant organisms identified in culture. Femoral anastomotic false aneurysms are most common and typically are manifested as a slowly enlarging, asymptomatic groin bulge. Proximal anastomotic false aneurysms are often discovered incidentally during radiographic evaluation for other reasons or come to attention when they rupture. Given the potential complications of thrombosis, embolization, or rupture, repair is generally recommended for femoral false aneurysms larger than 2 cm or aortic false aneurysms greater than 50% of the graft diameter. Treatment usually consists of débridement of the degenerated tissue and placement of a short interposition graft.

Graft Infection

Prosthetic graft infection is a particularly feared complication of aortic reconstruction, given its high associated morbidity and mortality (see Chapter 47).[124] The diagnosis is typically reached by a combination of clinical suspicion and computed tomography (CT) or isotope-labeled leukocyte scanning, with the groin being the most common site of presentation. On occasion, exploration is needed to confirm or to refute the diagnosis. Preventive efforts include strict adherence to sterile technique, particularly in the setting of infected, distal ulcerations, and the timely administration of preoperative antibiotics. Graft contamination at the time of implantation is difficult to prove but is believed to be common. Once infection is diagnosed, graft excision is usually indicated.

Aortoenteric Fistula

Aortoenteric fistula is another relatively rare but potentially devastating late complication associated with aortobifemoral grafting (see Chapter 49).[125] The most common pathophysiologic process is erosion of the proximal aortic suture line through the third or fourth portion of the duodenum, although fistulae between the iliac anastomoses into the small bowel or colon are also well described. The diagnosis can be challenging and typically involves some combination of CT scanning, endoscopy, and angiography. The classically described triad of gastrointestinal bleeding, sepsis, and abdominal pain is present in only a minority of patients. Far more commonly, a small, self-limited "herald bleed" presages a large gastrointestinal bleed, which can be massive in nearly a third of cases. In many respects, treatment is similar to that for graft infection; extra-anatomic bypass and graft removal are usually required, in addition to repair of the involved gastrointestinal tract. Dedicated efforts to ensure adequate tissue coverage between the graft and the overlying bowel before abdominal wall closure are important in preventing this highly lethal complication.

ISOLATED PROFUNDAPLASTY

The last 3 decades have been marked by an increased awareness of the critical role of the deep femoral artery in achieving successful lower extremity revascularization. Profunda circulation is frequently spared, even in the setting of severe obliterative disease of both the AI and femoropopliteal arterial segments. When present, profunda occlusive disease is often limited to the orifice or proximal segment (Fig. 106.13). This has important implications for the unique role of the profunda in maintaining collateral perfusion because even in the presence of proximal profunda disease, the more distal segments beyond the obstruction can continue to support key anastomotic networks. In extreme cases, these pathways can serve as the sole limb-sustaining bridge between pelvic or abdominal wall inflow vessels proximally and geniculate connections distally. In some diabetic patients, however, profunda disease is more diffuse, and distal collaterals are minimal.

The value of the profunda in supplying sufficient distal perfusion in the setting of SFA occlusion has been known since the early 1960s. Although isolated profundaplasty is less common in the current era of more aggressive percutaneous and open surgical reconstruction for lower extremity occlusive disease, it can be an effective alternative to either balloon angioplasty or surgical bypass of the SFA. It is particularly useful when infected infrainguinal grafts require removal or in the setting of failed bypass grafts when suitable autogenous conduit is absent and "redo" surgery is less appealing. It may also allow healing of a below-knee amputation in situations in which distal bypass is no longer an option.

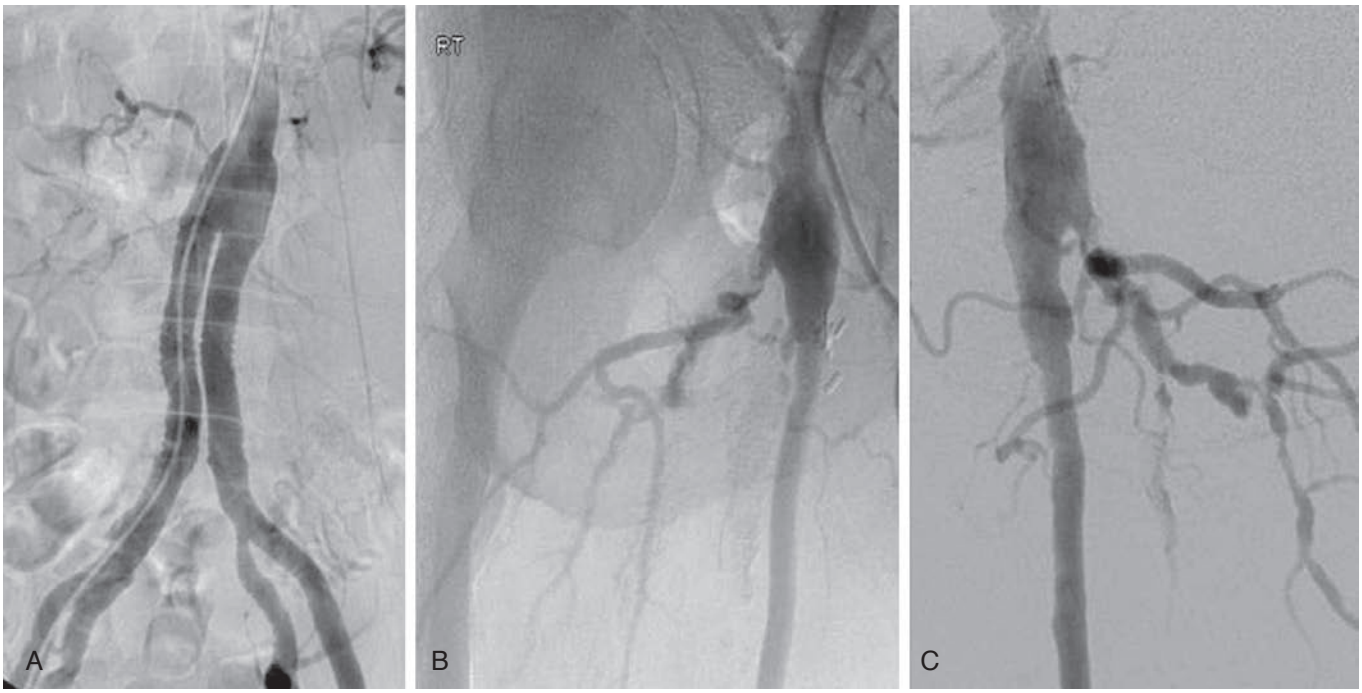

Figure 106.13 A patient with widely patent aortobifemoral and bilateral femoroperoneal bypass grafts (A) developed limiting bilateral thigh claudication secondary to profunda femoris occlusive disease (B and C). Symptoms resolved after bilateral staged isolated profundaplasties.

Although profunda femoris occlusive disease can be detected with DUS, CT, and MRA, formal angiography remains the diagnostic gold standard. The optimal conditions for an isolated profundaplasty are widely patent inflow and good distal profunda runoff beyond a diseased proximal profunda; longer diseased segments are more amenable to profunda bypass. Hemodynamic criteria assessing the resistance across the knee joint have also proved useful in predicting the clinical success of profundaplasty in particular patients. The operative technique is as described earlier for adjunctive profundaplasty. Associated mortality and morbidity are low, with morbidity most commonly related to a lymphatic leak or other groin-related issues. Three-year limb salvage rates in the range of 75% have been reported in patients with critical ischemia, and 5-year patency rates of 88% have been achieved when isolated profundaplasty was performed for claudication.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 107

Aortoiliac Disease: Open Extraanatomic Bypass

JOSEPH SCHNEIDER

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AXILLOFEMORAL BYPASS 1418
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Direct replacement or in-line bypass procedures for aortoiliac or infrainguinal arterial disease were developed in the 1950s. The procedures discussed in this chapter were generally developed shortly after that as alternatives to more direct procedures. These alternative "extra-anatomic" bypass procedures offered the potential benefit of a less formidable operation than aortofemoral bypass in patients with advanced comorbidities, a less hazardous approach in patients with "hostile abdomen" (previous surgery, visceral stomas, or active infection including infection of previously placed vascular grafts among these), and as a remote site for bypass grafts in the face of arterial infection to reduce the risk of reinfection of the newly placed grafts. Two of the procedures, axillofemoral and femorofemoral bypass, are clearly less injurious to the patient than would be direct aortofemoral bypass. However, the so-called obturator bypass is probably more injurious than a direct femoropopliteal bypass, but obturator bypass remains the standard approach to re-vascularize the lower leg in the face of groin sepsis or other problems that make a more conventional procedure in the groin undesirable. The technical demands of these extraanatomic procedures are distinct from and the hemodynamic and patency results may not be the same as those of the direct procedures that they replace. This chapter will address the indications, preoperative evaluation, conduct of the procedure, follow-up, and performance expectations for these procedures.

Although the procedures described are mature and have not changed appreciably in decades, their roles continue to evolve. Younger patients tend to have more discrete proximal arterial disease and are more likely to be treatable with the rapidly expanding set of endovascular tools. In contrast, older patients with more comorbidities tend to have more diffuse arterial disease; for them, endovascular techniques may not be optimal.[1] However, endovascular techniques continue to improve and the fraction of patients for whom endovascular solutions are applicable is likewise increasing.[2-4] On the other hand, more conventional surgical techniques such as aortofemoral bypass, once thought too invasive for older patients with multiple comorbidities, may now be extended to these patients, since anesthesia and perioperative critical care have also continued to improve, thus reducing the risks of these procedures. Nonetheless, the inexorable aging of Western populations will likely result in progressively older and frailer patients for whom these extraanatomic procedures may be appropriate. The outcome of critical limb-threatening ischemia is quite poor if the patient is not first treated with some technique to enhance limb blood flow[1,5,6]; if the patient has any level of independence and function, some procedure will ultimately be required to maintain the limb. Finally, femorofemoral bypass has become a key component of aorto-uni-iliac endovascular aortic aneurysm repair. Thus, although the procedures may be mature, the profiles of the patients for whom they are appropriate have evolved and will likely continue to do so.

As with any procedure, all efforts should be made to optimize the patient's status and to treat any coexisting problems before proceeding to surgery. In particular, any infection should be treated and controlled with drainage and antibiotics to the extent possible. Preoperative "optimization" of any medical problems including diabetes mellitus, coronary artery disease, congestive heart failure, and nutritional deficits is also desirable. Treatment of any of these problems will improve the patient's general condition and reduce the risk of infection of the graft. However, because extra-anatomic bypasses are often required

in urgent or emergent situations, such patient "optimization" may not be possible.

Preoperative planning requires enough anatomic information to assess the appropriateness of the procedure, both inflow in the "donor" artery and outflow (the common, deep, and superficial femoral arteries). This has traditionally required conventional transarterial catheter–based angiography. Computed tomography (CT) angiography has suffered from the interference of calcium in atheromas, which are nearly always present in patients with diffuse atherosclerotic disease, and artifacts from implanted metal devices as well as calcium, but the emergence of dual-energy CT has markedly improved the quality of CT angiography in these patients.[7,8] Magnetic resonance imaging (MRI) has also advanced significantly, now with the ability to produce high-quality angiograms without contrast as well,[9] although the proprietary nature (with associated lack of uniform naming) of these techniques and dependence on high-flux systems seems to have limited the deployment and publication of scientific articles describing the clinical use of these newer MR techniques. Planning with the exclusive use of ultrasound-based techniques would be unusual and would be appropriate in only a very small number of cases.

Any of these procedures may be contraindicated in patients at extreme medical risk with only brief expectations of survival. Obturator bypass in particular is a significantly invasive procedure, clearly physiologically taxing; it may constitute a larger injury than some patients can be expected to tolerate. One should seriously question performing any of these procedures in the face of active, inadequately treated infection; if there is no alternative, then one should at least consider an autologous graft, such as great saphenous vein or femoral vein or perhaps an antibiotic-soaked protein-impregnated graft.[10]

FEMOROFEMORAL BYPASS

Femorofemoral bypass was first described as a stand-alone procedure in 1952,[11] but the first substantial series of patients with follow-up information was published in 1960.[12] The procedure involves diversion of some blood from one iliac system to the contralateral leg and depends on the concept that one healthy iliac artery has the capacity to supply adequate flow to both the ipsilateral donor leg and the contralateral recipient leg.[13] Femorofemoral bypass has been a frequently applied procedure in patients with dominant unilateral iliac artery disease and more recently in patients whose suboptimal "donor" iliac artery can be improved with endovascular techniques.[14-16] Even more recently endovascular techniques have continued to improve and many patients who would have been treated with femorofemoral bypass may now be completely treated by hybrid or purely endovascular techniques. Femorofemoral bypass has also found a new application as an accompaniment to aorto-uni-iliac endovascular aortic aneurysm repair.[17] One should also consider the more direct common iliac-to-femoral bypass, which appears to have the same performance as the benchmark aortofemoral bypass procedure.[18,19]

If there is any question about the adequacy of the inflow because of disease in the iliac arterial system, one should consider a pharmacologic physiologic stress test of the inflow,[20,21] treat the diseased inflow with endovascular techniques as discussed previously, or abandon the plan for femorofemoral bypass in favor of an alternative procedure. With respect to outflow, either a minimally diseased normal-caliber deep femoral or minimally diseased superficial femoral artery provides sufficient outflow in most cases to support graft patency (as discussed further on) and adequately improve perfusion of the leg. It is rarely necessary to add a simultaneous infrainguinal bypass procedure on the recipient side to enhance distal perfusion, at least to treat resting ischemia of the recipient limb.

Femorofemoral bypass is performed with the patient in the supine position under general, regional, or—in selected patients—even local anesthesia. Prophylactic antibiotics are appropriate in elective cases and targeted antibiotics are appropriate for patients with active infection who require urgent treatment. The operation may be performed with a limited area of sterile preparation to include only the lower abdomen, groins, and upper anterior thighs, but in most cases we would perform the operation with preparation and draping to include the entire anterior abdomen to allow access to the iliac arteries or even the aorta should this become necessary and both legs circumferentially to allow intraoperative assessment of perfusion at the level of the ankles at the end of the operation. In most cases longitudinal groin incisions provide the most flexibility for the placement of anastomoses after the donor and recipient femoral arterial systems have been inspected. A graft is tunneled from one groin to the other in an inverted U configuration, usually in the subcutaneous area (anterior to the abdominal wall fascia) but on rare occasion in the retrofascial space from one groin incision to the other. This tunnel can be created with a specialized tunneler or simply with finger dissection and a large clamp. Care must be taken to avoid entering the peritoneal cavity and, in the case of previous abdominal surgery, great care must be taken in tunneling through scarred areas to prevent visceral injury. The first ever femorofemoral bypass was performed with an endarterectomized occluded superficial femoral artery autograft; a small fraction of such procedures are performed with venous or arterial autografts or allografts, primarily in the face of infection or intestinal or urinary stomas, but the vast majority are performed with prosthetic material. Although multiple prosthetic graft types have been touted as superior to their alternatives, there is no compelling evidence that polyester fabric, supported polyester, expanded polytetrafluoroethylene (ePTFE), supported ePTFE, heparin bonding, other graft lining, or any other graft type is superior in terms of hemodynamics or patency in the femorofemoral application. Thus our practice is to use a 6- or 7-mm supported ePTFE graft depending on patient size and native arterial diameter.

One key technical point is to prevent kinking of the graft in the anteroposterior direction, especially in patients with protuberant abdomens, either by shortening of the anastomosis or placing the anastomosis more distally (possibly to include the deep femoral or superficial femoral arteries or both) to allow a less acute angle at the heel of the anastomosis.[22] Another key point is to create the subcutaneous tunnel in a more uniform larger radius arc, generally by making the most superior part

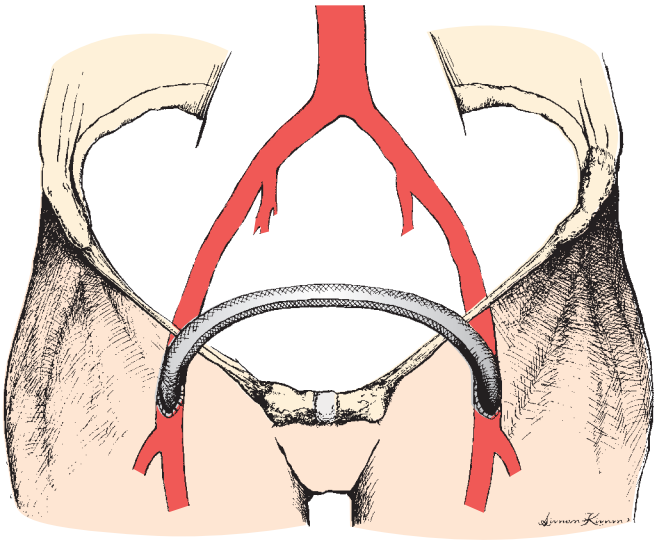

Figure 107.1 Standard "inverted C," perhaps better termed "inverted U," configuration of a femorofemoral bypass graft.

of the graft well superior to the pubis (Fig. 107.1) to reduce the risk of kinking in the coronal plane.

Intravenous heparin or, in the case of patient heparin sensitivity, another suitable short-acting anticoagulant is administered prior to clamp placement to allow arteriotomies and anastomoses. Arteriotomy and anastomotic sites are selected based on review of the preoperative arteriogram and local examination of the artery at the time of exploration of the femoral arteries; these may include the common, deep, or superficial femoral artery or some combination thereof. A conventional end graft–to-side artery anastomosis, as described in earlier chapters, is nearly always appropriate on both sides; it may be facilitated by extending the arteriotomy and the toe of the graft onto the deep or superficial femoral artery or even placing the entire anastomosis to the deep or superficial femoral artery. The right and left anastomoses may be performed simultaneously, thus saving significant time if two surgeons are available. If the anatomy dictates extension of the anastomosis onto the deep femoral artery, as may be necessary in the face of disease in the origin of that artery, this may actually reduce the tendency of the graft to kink adjacent to the anastomosis. Once the anastomoses have been completed and the clamps removed, a sterile continuous-wave Doppler should be used to confirm that flow is enhanced in the recipient side outflow artery or arteries and that there is no apparent deterioration in flow in the donor-side outflow arteries. Once again, as long as there is a normal diameter, minimally diseased or adequately improved donor iliac artery, the graft should not "steal" from the donor leg at rest.

Some authors have observed that femorofemoral graft patency is better if the superficial femoral artery is patent on the recipient side, but we and others have observed no difference.[14,23] We make sure that there is adequate outflow to at least the deep or superficial femoral artery. This is done by using adjunctive techniques such as the graft anastomotic hood to perform a "patch angioplasty" as necessary to ensure that a 3.5-mm diameter dilator will pass easily beyond the toe of the anastomosis and into at least one of the recipient superficial or deep femoral arteries. We have found that this is generally associated with adequate patency.

Patients are treated with antiplatelet agents (aspirin alone appears adequate). Hospital length of stay is determined primarily by comorbidities; some patients may be ready for discharge on postoperative day 1 or 2. Although the literature is sparse with respect to the value of surveillance noninvasive testing,[24] we have adhered to a program of surveillance with ankle-brachial indices, continuous-wave Doppler waveforms at the ankle, and graft duplex scans every 3 months for the first year, twice in the second year, and yearly thereafter if graft performance is stable, just as we do for infrainguinal bypass grafts.[25]

Operative mortality for femorofemoral bypass should be much less than 5%. A femorofemoral graft does not perform as well as a direct aortofemoral bypass based on patency or hemodynamic improvement.[14] In particular, femorofemoral bypass may not be a hemodynamically complete treatment for claudication. However, femorofemoral bypass performs acceptably and may be a better choice than direct aortofemoral bypass based on patient factors. Predicted patency at 5 years for patients whose indication is atherosclerotic occlusive disease should be about 70%, based on assessment of recent pertinent publications as detailed in this chapter in the previous edition of this text, and is probably better in patients having femorofemoral bypass as part of aorto-uni-iliac endovascular repair of aortic aneurysm.[26,27] Causes of failure include technical errors, progression of inflow or outflow disease, and perianastomotic stenosis due to intimal hyperplasia. There are few complications specific to femorofemoral bypass, but they would include visceral injury, particularly if the graft is tunneled in a retrofascial position or if there is a hernia. In difficult circumstances with a high-risk patient, a femorofemoral bypass is a relatively low-risk way to reperfuse a leg with dominant unilateral iliac artery disease and is likely to be an essential skill for the vascular surgeon for the foreseeable future.

AXILLOFEMORAL BYPASS

The first reported axillofemoral bypass procedures were performed to treat patients at unacceptable risk for conventional aortofemoral bypass and for extraanatomic bypass at the time of removal of infected grafts.[28] Examples of two of the three primary indications for axillofemoral bypass are as follows: (1) patients with symptomatic aortic and/or bi-iliac arterial occlusive disease thought to be at excessively high physiologic risk for direct aortic repair, (2) patients with infected native aortas or aortic grafts or the closely related problem of aortoenteric fistulas, and (3) patients with a hostile abdomen, generally with multiple previous surgeries, active intra-abdominal infection, or the presence of intestinal or urinary stomas. Although there was a period of popularity of axillofemoral bypass as a primary procedure for aortoiliac occlusive disease—for example, as promoted by Johnson[29] and later by the group at the Oregon Health Sciences University[30]—it is fair to say that this approach was not widely adopted. There was also a period of interest

generated by the Albany group for axillofemoral bypass combined with ligation of the infrarenal aorta as primary treatment for abdominal aortic aneurysm,[31] but this approach was generally abandoned when it was observed that a number of such patients later died of ruptured abdominal aortic aneurysm.[32] Conventional thinking in the peak period of the operation was that axillofemoral bypass should nearly always be performed in a bifemoral configuration[33]; however, some of these same advocates later reported that axillounifemoral bypass performed as well as axillobifemoral bypass.[34] Thus the choice of an axillounifemoral versus axillobifemoral configuration should be based on whether one or both legs would benefit from improved flow.

Many patients with aortic and/or bi-iliac arterial occlusive disease are now treated completely or partially with the ever-expanding endovascular armamentarium. Furthermore, it is likely that some of these patients who might have been selected for axillofemoral bypass in the past are now seen as at manageably low risk for direct aortofemoral bypass. Thus axillofemoral bypass has likely declined in volume from a peak in the 1970s and 1980s. Nevertheless, this procedure remains an essential tool for the vascular surgeon. Similar to the assumption with femorofemoral bypass, axillofemoral bypass assumes that one axillosubclavian artery has adequate blood volume flow capacity to supply the donor side arm and one or both legs, at least at rest.

One unique preoperative question is which axillary artery is to be used for the donor. The graft is generally tunneled in the midaxillary line and lateral abdomen from the donor axillary artery to the ipsilateral femoral recipient artery. Coexistent thoracic or abdominal problems may dictate the side of the procedure; the impending need for thoracotomy or abdominal surgery for other problems may dictate use of the contralateral axillary artery. The presence of intestinal or urinary stomas may dictate contralateral placement of the axillofemoral graft. Some surgeons ask the patient on which side they sleep and will place the graft contralaterally, although it is not clear that this is really necessary. If none of these alternatives seems to point to one or the other side, most surgeons would place the graft on the side of the more symptomatic leg, certainly if an axillounifemoral configuration is to be used, but there is otherwise no clear evidence to support any advantage to placement of the axillofemoral graft on the more symptomatic side. We would recommend against placement of an axillofemoral bypass based on the side of an existing arteriovenous hemoaccess fistula, since this might provoke or worsen existing steal symptoms in that arm, but we are aware of no description of such an occurrence, published or otherwise. In any case, we insist on a triphasic brachial artery Doppler waveform and a blood pressure no more than 10 mm Hg lower in the proposed donor arm than in the contralateral arm. If these criteria are not met, we will proceed to upper extremity angiography and, if necessary, inflow artery treatment prior to surgery.[35]

The procedure is performed with the patient in the supine position. Although it may be possible to perform segments of the operation with local or regional anesthesia, creating the axillofemoral tunnel would be difficult; for practical purposes, the operation is always performed with general anesthesia. We place a gel pad or a towel-wrapped 1-L bag of fluid between the operating table and the posterolateral back on the side of the axillofemoral graft to elevate the flank and lower chest to allow slightly more posterior prepping and draping for better visualization during tunneling. Some surgeons position the ipsilateral arm at the patient's side, but we have always positioned the ipsilateral arm at 90 degrees abduction both to allow visualization of the ipsilateral lateral chest and abdomen during tunneling and to elevate the clavicle slightly to enhance exposure of the donor axillary artery. The sterile preparation should be wide and should include at a minimum the anterior and ipsilateral neck base and supraclavicular fossa over to the anterior shoulder area, the axilla, anterior and ipsilateral chest and abdomen, and the groin and superior anterior thigh. In particular, we have always thought it prudent to prep widely to allow for a thoracotomy in case of an injury or other problems with the axillosubclavian donor artery, although we have never had to proceed to thoracotomy. In the case of axillobifemoral bypass, the preparation and draping must include the contralateral lower abdomen, groin, and anterior upper thigh. Prophylactic antibiotics or—in the case of active infection—targeted antibiotics are administered.

Groin exposure is identical to that outlined earlier for femorofemoral bypass. The donor axillary artery is exposed with a transverse incision a few centimeters inferior to the clavicle and by splitting of the pectoralis major muscle fibers. The axillary artery should be exposed and controlled from the clavicle medially to the pectoralis minor muscle laterally, typically over a length of 3 to 4 cm. This artery is more fragile than the more familiar common femoral artery and great care must be taken not to injure it during dissection and clamp placement and for the same reason during creation of the anastomosis, since sutures are more likely to tear through the artery.

A subcutaneous tunnel is created from the ipsilateral groin incision to the axillary artery exposure incision. In the early experience with axillofemoral bypass, a separate flank incision was required about half the distance from the axillary artery exposure incision to the ipsilateral groin incision since there were no adequate tunnelers to traverse the entire distance. However, there are now several tunnelers that will traverse the entire distance and do not require the intermediate incision in the flank. We use a 65-cm Gore tunneler, although it is no longer manufactured and the reader is advised to consult graft and instrument suppliers regarding available tunnelers. Care must be taken to remain in a subcutaneous plane, superficial to the abdominal wall deep fascia, to avoid entering the thoracic cavity during tunneling. Although some have advocated tunneling anterior to the pectoralis minor muscle or even division of the pectoralis minor, we have always tunneled posterior to the pectoralis minor.

Axillofemoral bypass is virtually always performed with a prosthetic graft and, as with femorofemoral bypass, there is no clear advantage of one graft type over another. Although both polyester and ePTFE grafts can be purchased with preconstructed connections between the axillofemoral and femorofemoral components, given the current relative infrequency of axillofemoral bypass, most surgeons probably perform the procedure with two segments of straight graft, anastomosing one graft to

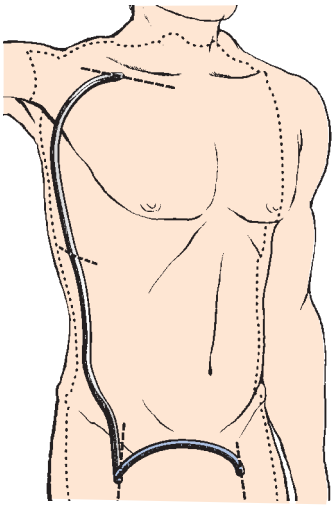

Figure 107.2 Typical area of exposure for an axillobifemoral bypass graft. The right axillary artery is the donor artery in this case. The intermediate incision in the right lower chest or upper flank is generally unnecessary if an appropriate tunneler is used.

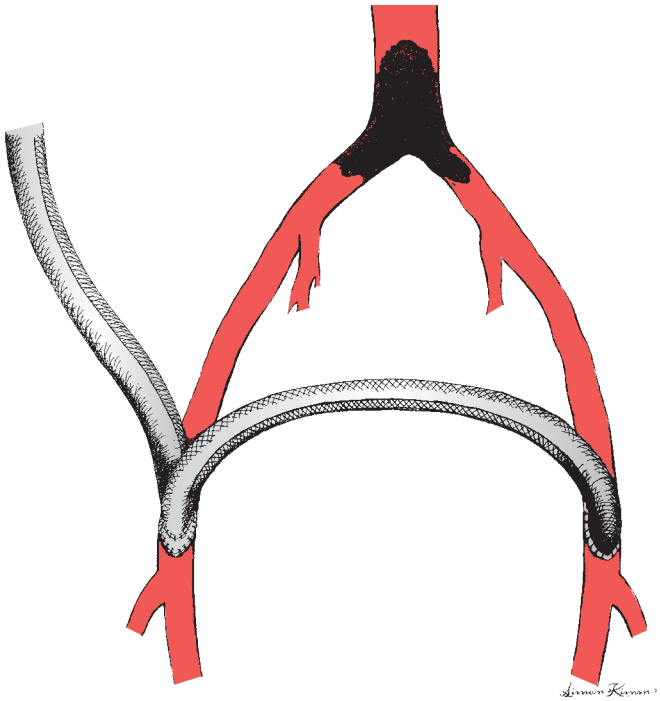

Figure 107.3 Typical configuration of an axillobifemoral bypass graft. In this case the right axillary artery is the "donor" and the axillofemoral component has been anastomosed to the native right common femoral artery, after which the right end of the femorofemoral component has been anastomosed to an ovoid graftotomy in the anterior wall of the anastomotic hood of the axillofemoral component.

the other (Fig. 107.2). We tend to use an 8-mm supported ePTFE graft for the axillofemoral component and, if the bypass is to be axillobifemoral, a 6-mm supported ePTFE graft for the femorofemoral component. On rare occasions in performing an axillounifemoral bypass in a small patient, a 6-mm-diameter graft may be used, in part to try to enhance velocity, which may improve patency.[36,37]

Heparin or another suitable short-acting anticoagulant is administered before clamps are placed on the arteries. As with femorofemoral bypass, conventional end graft-to-side artery anastomoses are usually appropriate. An axillobifemoral bypass with two separate graft segments requires four anastomoses, including one that connects the axillofemoral and femorofemoral components; pairs of these may be performed simultaneously. Thus axillofemoral bypass, particularly axillobifemoral bypass, is greatly facilitated if two surgeons are present.

It is critical to create the axillary artery to graft anastomosis such that there is no tension on this anastomosis when the arm is abducted. We employ two technical concepts to try to avoid this problem. First, the anastomosis should be placed as far medially as possible on the axillary artery, since this part of the artery will move less than the more lateral part of the artery when the arm is abducted; this tends to bring the graft into a more nearly parallel relationship to the artery, also reducing the tendency to produce traction on the anastomosis when the arm is abducted. The principle of leaving the pectoralis minor muscle intact and tunneling the graft posterior to this muscle tends to force the surgeon to keep the anastomosis medial. A second principle is to allow some redundancy of the graft and even some bowing into the axilla posterior to the pectoralis minor muscle.[38]

In the "heyday" of axillobifemoral bypass, a commonly recommended technical point was to place the connection between the femorofemoral and axillofemoral components as close to the femoral artery anastomosis as possible so as to try to maximize flow throughout the entire length of the axillofemoral graft. This concept is plausible and we adhere to it, but there is no observational evidence that it provides a real advantage. It is usually simple to either complete a conventional femorofemoral bypass and then sew the axillofemoral graft to a graftotomy in the ipsilateral anastomotic hood of the femorofemoral graft or, alternatively, to complete the anastomosis between the inferior end of the axillofemoral graft and then sew the ipsilateral side of the femorofemoral graft to a graftotomy in the femoral anastomotic hood of the axillofemoral component (as depicted in Fig. 107.3). In either case, unlike a pliable native artery, where a simple arteriotomy creates an adequate opening, a prosthetic graft tends to be rigid and not to gap adequately after a simple longitudinal graftotomy. Therefore anastomosing a graft to the side of a prosthetic graft requires excision of an oval of the graft material at the point where anastomosis is to be created. No matter whether the graft is performed in axillounifemoral or axillobifemoral configuration, the same principles described earlier for femorofemoral bypass to assure adequate outflow (e.g., using the graft hood as a patch or assuring that a 3.5-mm diameter metal dilator will pass easily into at least one outflow artery) are equally applicable to axillofemoral bypass.

A sterile handheld Doppler probe is used to confirm that flow is augmented in the outflow artery or arteries with the graft open versus with the graft clamped. The surgeon must also assure that there is normal flow in the distal arm on the donor side—for example, by confirming the presence of a palpable pulse in the radial artery or by confirming satisfactory

pulse oximetry in a digit with the graft open (with blood flowing to the lower extremity or extremities.

Just as with femorofemoral bypass, an axillofemoral graft does not perform as well as a direct aortofemoral bypass based on patency or hemodynamic improvement.[39] In fact, our previous work suggests that the predicted ankle-brachial index after axillofemoral bypass with normal (undiseased) infrainguinal outflow is less than 0.7, compared with slightly more than 1.0 after direct aortofemoral bypass.[39] However, axillofemoral bypass performs acceptably and may be a better choice than direct aortofemoral bypass based on patient factors.

The literature of axillofemoral bypass has what is likely the broadest range of reported long-term patencies for any open vascular surgical procedure, probably related to the broad range of patient characteristics in that literature.[26] However, a fair estimate for predicted patency at 5 years among patients whose indication is atherosclerotic occlusive disease should be about 60% to 70%. In a patient with bilateral iliac artery disease that cannot be improved adequately on at least one side with endovascular techniques to allow a femorofemoral bypass, a patient with an infected native aorta or aortic graft, or a "hostile" abdomen, an axillofemoral bypass provides a less invasive approach to reperfusing one or both legs.

With respect to surveillance of axillofemoral bypass, the literature is even less revealing than for femorofemoral bypass. Just as with femorofemoral bypass, since the predicted patency for axillofemoral bypass is clearly less than for aortofemoral bypass, we are much more aggressive with noninvasive surveillance and obtain ankle pressures, ankle-level Doppler waveforms, and graft duplex scans every 3 months for the first year, twice in the second year, and yearly after that.[25] Complications specific to axillofemoral bypass include disruption of the anastomosis from the axillary artery to the graft[40] and thromboembolic complications in the native arteries after thrombosis of the axillofemoral graft.[41]

OBTURATOR BYPASS

Shaw and Baue first described three cases of obturator bypass as a method to maintain perfusion of the leg after dealing with arterial infection in the groin.[42] The technique requires tunneling a graft from the iliac arterial system through the obturator fossa in the pelvis to the infrainguinal arterial system, a path proposed at least 2 years before Shaw and Baue's first description.[43]

The primary indication for this procedure is arterial infection in the femoral triangle. Our most recent experience with this operation has been predominantly in patients with infected aneurysms as complications of arterial puncture for angiography or endovascular procedures; other causes, however, are related to recreational drug use; infection early or late after direct surgical exposure of the femoral artery for embolectomy, endarterectomy, or other direct arterial surgery; or "hostile groin"—for example, after previous procedures or therapeutic radiation.

The operation is performed with the patient in the supine position with the entire ipsilateral leg circumferentially prepped and draped so that the entire leg is available and can be moved in the sterile field just as one would do for infrainguinal bypass. The groin and abdomen are also prepped and draped to allow access to the iliac arteries or the aorta if necessary. Inflow is typically from the ipsilateral common or less often the external iliac artery, although inflow could be taken from the aorta or the contralateral iliac arterial system. The approach is most often through an oblique ipsilateral low abdominal incision and retroperitoneal exposure of the iliac arteries, although a transperitoneal approach and control of the inflow artery is also possible. Outflow is usually the above knee popliteal or superficial femoral artery, exposed as would be the case for femoropopliteal bypass (see Chapter 109), although on occasion this will involve the deep femoral system or an infragenicular popliteal or other more distal artery. The graft is tunneled through the obturator foramen posterior to the adductor longus (Fig. 107.4). The obturator foramen is approached medial to the external iliac vein and posterior to the superior aspect of the pubic ramus, and the obturator internus muscle is bluntly dissected away from the obturator membrane. The obturator membrane is very strong; it cannot be perforated bluntly and requires incision with scissors, scalpel, electrocautery, or another suitable technique. It is difficult to see this well enough to perforate under direct vision, certainly if a small incision is used, and care must be taken not to damage adjacent structures

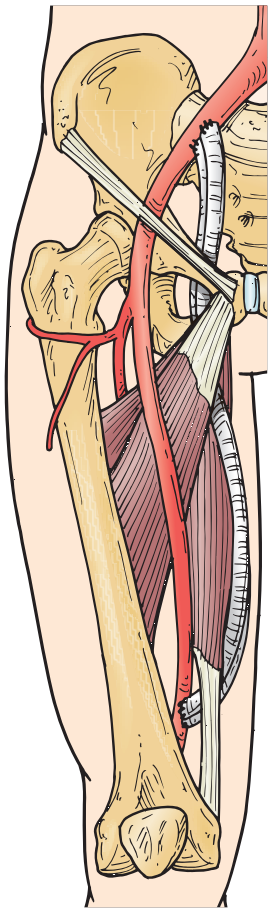

Figure 107.4 Typical course of the obturator bypass graft, in this case originating from the most proximal portion of the right external iliac artery, passing through the obturator foramen, and terminating at the popliteal artery.

such as the urinary bladder in creating the tunnel and the defect in the obturator membrane. The incision should be in the anteromedial part of the obturator membrane to avoid the obturator nerve and artery. The graft is usually placed in the potential space between the adductor magnus posteriorly and the adductor longus and brevis anteriorly, although it may be brought into the area of the superficial femoral artery by bringing the tunnel between the adductor longus and brevis muscles. Anastomoses to the inflow and target arteries are performed in conventional fashion, with heparin or other suitable anticoagulation during the time that the arteries are clamped. Conventional end graft-to-side native artery anastomoses as described elsewhere in this text are nearly always appropriate for both donor and recipient arteries.

Shaw and Baue's first three cases were all performed with polyester textile grafts. However, it is clear from the original publication that there was persistent infection in at least two of these operations, one patient ultimately dying from complications of infection, and we would recommend autologous grafts whenever possible. In our experience, we have never used other than an autologous vein graft.

As is the case of the other two procedures described in this chapter, obturator bypass probably does not perform as well as the index procedure of femoropopliteal bypass as measured by patency. Five-year estimated primary patency is probably in the range of 50% to 60%.[44-46] However, once again this procedure is far superior to the alternatives in the situations for which obturator bypass is appropriate. We use the same postoperative protocol for obturator bypass graft surveillance (ankle-brachial indices, ankle-level continuous wave Doppler waveforms, and graft duplex scan every 3 months in year 1, every 6 months in year 2, and yearly thereafter) as we do for conventional infrainguinal bypass grafts.[25] Complications specific to obturator bypass include urinary bladder injury or other visceral injury at the time of surgery.

SUMMARY

Each procedure described in this chapter will provide acceptable perfusion to the target limb and acceptable long-term patency. Limb loss is rare for all of these procedures with a patent bypass graft. Obturator bypass can be expected to perform nearly as well hemodynamically and with respect to patency as a conventional infrainguinal bypass, such as a femoropopliteal bypass. However, it is clear that femorofemoral and axillofemoral bypasses do not achieve quite the same hemodynamic and patency results as seen after direct aortofemoral bypass. Nevertheless, each of these procedures provides a way of solving difficult problems in patients who are not suitable for the more conventional approaches owing to comorbidities, infection, or other factors. The indications and patient selection criteria for femorofemoral and axillofemoral bypass have evolved and, on balance, these procedures are probably less often used than they were 20 years ago. In sum, familiarity and experience with these procedures is essential to the practicing vascular surgeon, since these may be the best way to solve some very difficult problems. Obturator bypass may actually be increasingly applicable because of the continuing rise in the frequency of transfemoral endovascular procedures and parenteral use of recreational drugs, both accompanied by a risk of femoral arterial infection. Although not often the first choice for most patients requiring infrainguinal bypass, in the face of groin infection, previous surgery or radiation in the groin, or other unusual situations that dictate avoidance of arterial reconstruction in the groin, the obturator bypass is an essential procedure to maintain perfusion of the leg.

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108 CHAPTER

Aortoiliac Disease: Endovascular Treatment

RICHARD J. POWELL and EVA M. RZUCIDLO

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Abstract

Endovascular techniques play a crucial role in the treatment of aortoiliac occlusive disease. Treatment should be tailored to the individual patient's symptoms and comorbidities, as well as the location and extent of disease. This chapter highlights the most recent developments in the endovascular management of aortoiliac occlusive disease.

Keywords

iliac
stent
endovascular
hybrid procedure
claudication

Endovascular techniques play a crucial role in the treatment of aortoiliac occlusive disease. Treatment should be tailored to the individual patient's symptoms and comorbidities, as well as the location and extent of disease. This chapter highlights the most recent developments in the endovascular management of aortoiliac occlusive disease.

BACKGROUND

Progress in endovascular surgery has resulted in a continued shift in the treatment of patients with aortoiliac occlusive disease to less invasive forms of therapy. Early pioneers such as Dotter and Gruntzig developed balloon angioplasty.[1] Subsequent work in stent development by Palmaz gradually improved the treatment of patients with aortoiliac disease.[2-4] Improvements in technology such as higher resolution imaging, lower profile systems, premounted balloon-expandable stents, self-expanding stents, and stent grafts have resulted in better outcomes with fewer complications. Vascular surgeons now widely incorporate these treatment modalities into their practices. Today the majority of patients with aortoiliac occlusive disease can be safely treated with either percutaneous endovascular procedures or, in patients with more advanced aortoiliac occlusive disease, by means of stent grafts and hybrid open-endovascular approaches.

INDICATIONS

There are both patient- and lesion-specific indications for aortoiliac intervention. Patient-specific indications for treatment include lifestyle-limiting claudication, rest pain, and tissue loss. Less frequent indications include vasculogenic impotence and atheroembolization to the lower extremities. As for all vascular reconstructions, the expected benefits of the proposed procedure must be weighed against the potential risks in view of patient comorbidities.

Limb Ischemia

Patients with hip, buttock, thigh, or calf claudication constitute the largest group of patients who undergo aortoiliac endovascular revascularization. Patients with chronic limb-threatening ischemia (CLTI) manifesting as either rest pain or tissue loss frequently have multilevel occlusive disease. In such patients, the aortoiliac disease is commonly diffuse and complex, often extending into the common femoral arteries (CFAs) and associated with infrainguinal occlusive disease. Patients without significant CFA occlusive disease can typically be treated with percutaneous approaches that improve lower extremity perfusion sufficiently to resolve rest pain or heal minor ischemic ulceration. In patients with a significant CFA disease burden, combined femoral artery endarterectomy and patch angioplasty with simultaneous aortoiliac stenting or stent grafting often provides adequate perfusion to treat CLTI and claudication.

Younger Patients

Patients younger than 50 years have worse outcomes following aortoiliac endovascular therapy. However, the same also applies to open surgical approaches such as aortobifemoral bypass.[5-8] Many younger patients cannot be absent from work for the 6 to 8 weeks of recovery required after open aortic surgery, and thus may opt for the less invasive endovascular approach acknowledging a potentially less durable outcome compared with open surgical reconstruction. In addition, many men are concerned about the relatively high incidence of erectile dysfunction following open aortobifemoral bypass and thus choose an endovascular approach.

Embolization

Less frequently encountered are patients who present with spontaneous embolization to the lower extremity, or so-called blue toe syndrome, who may benefit from endovascular therapy. This is a controversial indication for endovascular therapy and usually involves placement of a bare or covered stent to trap the underlying pathogenic atherosclerotic lesion and prevent further embolization.[9-11] Endovascular intervention is typically not indicated for patients whose atheroembolization was provoked by arterial catheterization procedures. In the absence of subsequent catheterization, the risk of recurrent embolization is low.

Improving Inflow for Concomitant Procedures

Endovascular therapy for aortoiliac disease is frequently required as an adjunct to various open infrainguinal procedures to provide adequate inflow. It may be performed simultaneously with lower extremity bypass or femoral-femoral bypass. Indications for treatment in this setting include a resting systolic pressure gradient proximal to the intended infrainguinal bypass of greater than 10 mm Hg or a vasodilator-enhanced systolic gradient of greater than 20 mm Hg.

CONTRAINDICATIONS

There are no absolute contraindications to the endovascular treatment of aortoiliac occlusive disease. Relative contraindications are largely anatomic and include juxtarenal aortic occlusion, circumferential heavy (>1 mm) calcification, hypoplastic aortic syndrome, and juxtaposition to aneurysmal disease. Renal insufficiency is also a relative contraindication owing to potential contrast-induced nephropathy (CIN), although preventive regimens and minimal contrast techniques have reduced the impact of this complication.[12-14]

RELEVANT ANATOMY: TRANS-ATLANTIC INTER-SOCIETY CONSENSUS CLASSIFICATION

Lesion-specific indications for the endovascular therapy of aortoiliac occlusive disease can be guided by the Trans-Atlantic Inter-Society Consensus (TASC) guidelines. The TASC classification (Fig. 108.1), revised in 2007, offers more current guidelines on the use of endovascular therapy based on lesion anatomy.[15] In general, endovascular therapy is the recommended first-line therapy for TASC A, B, and increasingly TASC C lesions as

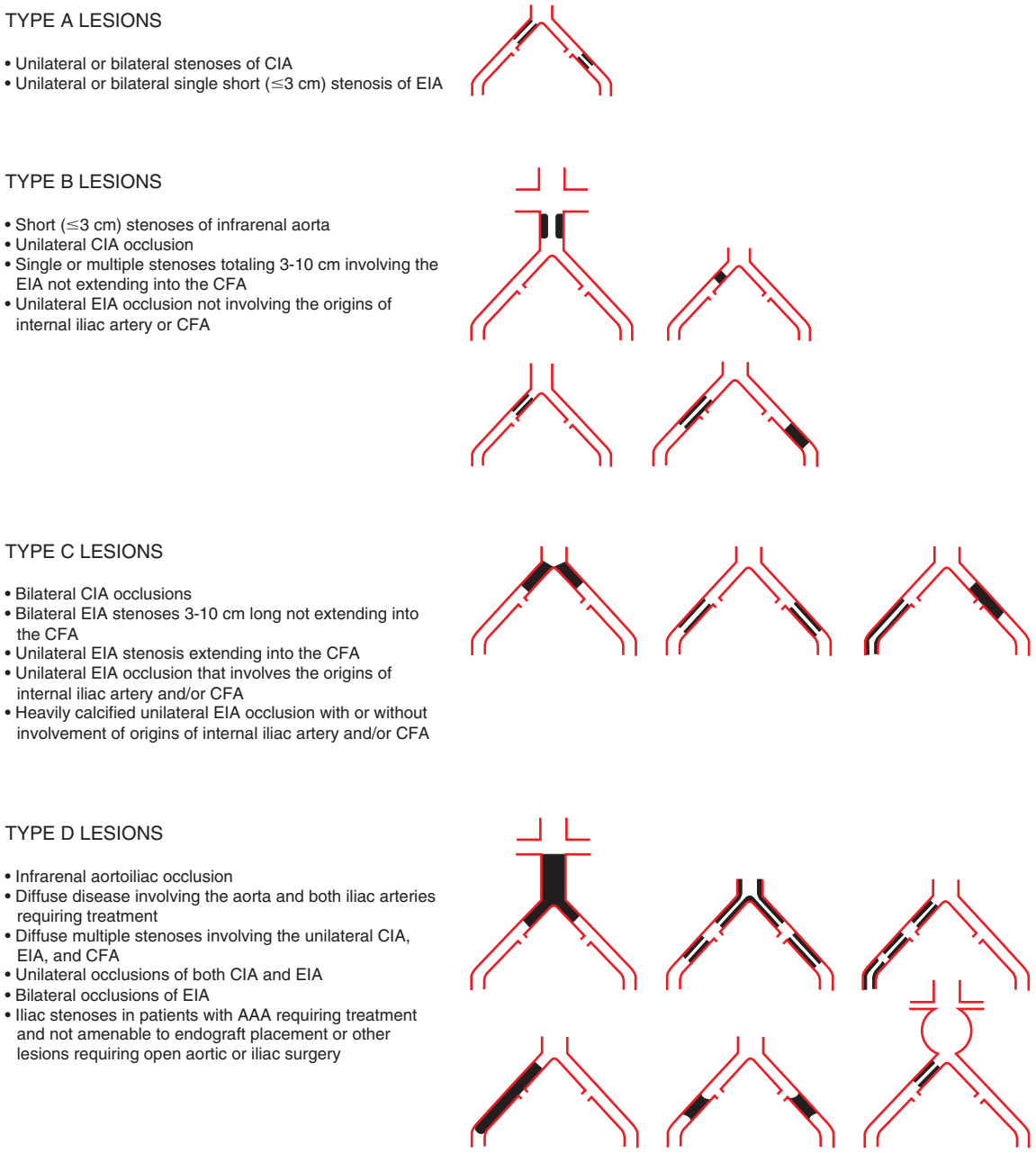

Figure 108.1 Trans-Atlantic Inter-Society Consensus (TASC) classification of aortoiliac lesions. *AAA,* Abdominal aortic aneurysm; *CFA,* common femoral artery; *CIA,* common iliac artery; *EIA,* external iliac artery. (Redrawn from Norgren L, Hiatt WR, Dormandy JA, et al. TASC II Working Group: Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg.* 2007;45(Suppl S):S5–S7.)

endovascular techniques improve. Good-risk patients with TASC type C disease can also be treated with open surgery, depending on patient preference. Surgery is usually recommended for TASC D lesions, but advanced endovascular approaches are also now being applied with good results in these lesions.[16] High-risk patients with TASC C and D disease, CLTI, and advanced comorbidities such as severe chronic obstructive pulmonary disease, unreconstructable coronary artery disease, or a low cardiac ejection fraction may be treated with endovascular therapy, acknowledging that this approach will be less durable than open surgical options.

PATIENT EVALUATION AND OPERATIVE PLANNING

Primary Evaluation

Once a decision has been made that intervention is indicated (see Chapter 105), the location and extent of the occlusive disease must be determined, beginning with a history and physical examination. The presence of hip, thigh, or buttock claudication; impotence; a lower quadrant abdominal or CFA

bruit; and diminished femoral pulses all suggest aortoiliac occlusive disease. Noninvasive physiologic arterial studies, such as ankle-brachial index (ABI) and toe pressure measurements, are usually indicated. In patients with a history consistent with vasculogenic claudication but a normal pulse exam or resting ABI, treadmill testing may help differentiate vascular from neurogenic symptoms.

Noninvasive Imaging

Just as for open aortobifemoral bypass, additional diagnostic studies are indicated before endovascular intervention to assess the disease location, extent, and degree of calcification. The use of arteriography as a purely diagnostic tool is infrequent because of the widespread availability of less invasive imaging modalities that provide anatomic detail with less risk. The choice of endovascular versus open revascularization can be made by employing imaging modalities to evaluate the aortoiliac segment such as duplex arterial mapping, magnetic resonance angiography (MRA), and computed tomographic angiography (CTA). All these modalities have benefits and drawbacks.

Duplex Arterial Mapping

Duplex arterial mapping of the aortoiliac segment and CFAs can adequately assess the location of hemodynamically significant lesions (Fig. 108.2). It is particularly helpful to assess CFA disease burden, which may potentially alter a planned percutaneous approach through the CFA to an open CFA endarterectomy and concomitant iliac stent/stent-graft placement. This modality is especially useful in patients with renal insufficiency who are at risk for contrast-induced renal dysfunction.[17] Drawbacks of duplex arterial mapping are that it provides only a semiquantitative assessment of the degree of iliac calcification, it may not adequately image the iliac system due to overlying bowel gas or body habitus, and it requires significant time and a highly trained vascular technologist.[18,19] These constraints have prevented duplex arterial mapping from becoming more widely adopted in this setting.

Magnetic Resonance Angiography

MRA can reliably assess the aortoiliac arterial segment, although its accuracy varies widely between institutions. A major drawback is that MRA fails to accurately assess the degree of calcification of aortoiliac lesions. It remains contraindicated in patients with renal insufficiency over concerns regarding increased risk of nephrogenic systemic fibrosis due to gadolinium.

Computed Tomographic Angiography

The presence of severe calcification has significant implications for planning. Circumferential calcification thicker than 1 mm is a relative contraindication to aortoiliac angioplasty and stenting because of the potential risk of fracture and arterial rupture. In patients with significant comorbidities in whom intervention is mandated by CLTI, use of a stent graft may be considered in an attempt to limit the incidence of clinically significant arterial perforation. In this setting, CTA has been used with success to assess calcification of the aortoiliac segment before intervention. The major disadvantages of CTA include exposure to ionizing radiation and the need for iodinated contrast agent, with the risk of contrast-induced renal dysfunction. In appropriate patients, CTA can accurately assess lesion location, extent, and degree of calcification, and the severity of aortoiliac and femoral disease can be classified according to TASC. This additional information allows the formulation of an appropriate procedural plan and the selection of either open or endovascular therapy.

Evaluation for Common Femoral Artery Disease

The choice of a percutaneous or an open femoral approach is based on the burden of CFA disease. Patients with greater than 50% CFA stenosis on preoperative imaging are usually treated with a hybrid approach that entails open iliofemoral endarterectomy, patch angioplasty, and simultaneous stent or stent-graft placement. Stent grafts are frequently used in

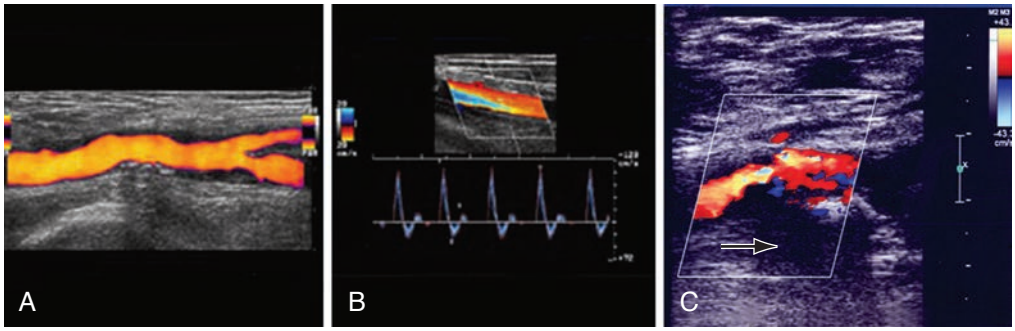

Figure 108.2 Duplex mapping of the common femoral artery. (A) Longitudinal view of the common femoral artery (power imaging) and the bifurcation of the superficial and deep femoral arteries. (B) Doppler spectral waveform from a normal right femoral artery. The Doppler signal was obtained from a longitudinal view with the Doppler sample volume placed in the middle of the lumen. The characteristic triphasic Doppler signal shows a brisk upstroke to peak systole, reversal of blood flow during early diastole, and a forward flow component during late diastole. (C) Longitudinal view of the common femoral artery with greater than 50% stenosis due to posterior plaque as depicted by the arrow.

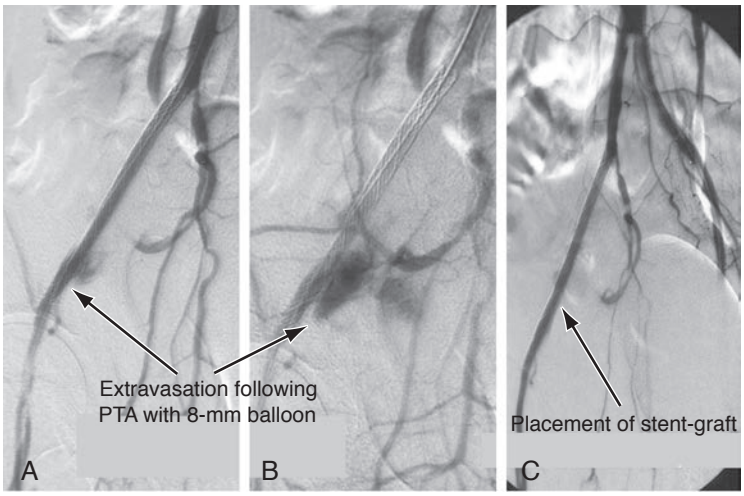

Figure 108.3 Ruptured external iliac artery treated with a stent graft. (A) and (B) After placement of bare metal stents and dilation with an 8-mm balloon. (C) Stent graft placed to achieve hemostasis.

conjunction with open endarterectomy especially in the presence of calcific external iliac artery (EIA) disease due to the risk of arterial rupture and bleeding with bare metal stents (Fig. 108.3). In patients with less severe CFA disease, a percutaneous approach can be undertaken.

Concomitant Aortic Disease

Aortic angioplasty and stenting for lesions proximal to the aortic bifurcation warrant special consideration because these lesions are frequently exophytic and calcific. Emphasis should be placed on obtaining an adequate hemodynamic response; acceptance of an imperfect completion image is critical to avoid aortic rupture. Because of the exophytic nature of these lesions, primary stent or stent-graft placement to trap potential atheroembolic debris should be considered, especially for lesions suspected of being an atheroembolic source, to minimize the potential for embolic complications.

TECHNIQUE

Pretreatment Considerations

Before intervention, the patient's history and all pertinent imaging studies are reviewed, and informed consent is obtained. Testing for coagulation and renal function are essential.

Avoiding Contrast Nephropathy

CIN is defined as an increase in serum creatinine greater than 25%, or greater than 0.5 mg/dL (44.2 µmol/L), within 3 days of intravascular contrast administration in the absence of an alternative cause. Serum creatinine usually returns to baseline within 14 days; however, some patients may progress to acute kidney failure requiring dialysis. CIN is the third most common cause of new-onset acute renal failure in hospitalized patients.[20] The incidence may be as high as 25% in patients with preexisting renal impairment or certain risk factors such as diabetes, congestive heart failure, advanced age, and concurrent administration of nephrotoxic drugs.[21] The single most important risk factor of CIN is chronic kidney disease, which increases the risk by more than 20 times. It is generally accepted that the risk of CIN in patients with estimated glomerular filtration rate (eGFR) ≥60 mL/min is extremely low. Studies have suggested that a threshold for CIN exists for patients with eGFR 40 to 45 mL/min and significant concern should be raised in patients with severe renal dysfunction with eGFR less than 30 mL/min. Patients with both renal impairment and diabetes have up to a 50% risk of developing CIN. The majority of studies regarding CIN have been in patients having intra-arterial (IA) contrast administration—in particular, cardiac interventions. It has been assumed that intravenous (IV) contrast administration has the same risk as IA injection; however, this assumption is being challenged in recent studies. Several trials in patients receiving IV contrast have shown low risk of CIN in patients with eGFR greater than 40 mL/min. Among patients that did develop CIN, none progressed to dialysis and none had fatal outcomes. Recommendations have therefore been proposed that for patients receiving IA contrast and eGFR less than 60 mL/min, full preventive measures should be done. On the other hand, for patients receiving IV contrast, preventive measures should be undertaken for eGFR less than 45 mL/min. Preprocedural volume loading and the use of low-osmolar or iso-osmolar contrast agents can decrease the risk of CIN.[22-24] However, the risk is not eliminated, even when an iso-osmolar contrast agent is used.[25,26] The risk of CIN correlates with contrast volume. Contrast volume in excess of 5 mL/kg strongly predicts CIN requiring dialysis. A second contrast dose within 48 hours also significantly increases the risk of CIN. Because free radicals are postulated to mediate CIN,[27] alkalinizing renal tubular fluid with sodium bicarbonate[28] has been shown to reduce injury. Merten and coworkers reported a single-center randomized controlled trial comparing the infusion of sodium chloride versus sodium bicarbonate as the hydration fluid to prevent renal failure in patients with stable renal insufficiency undergoing diagnostic or

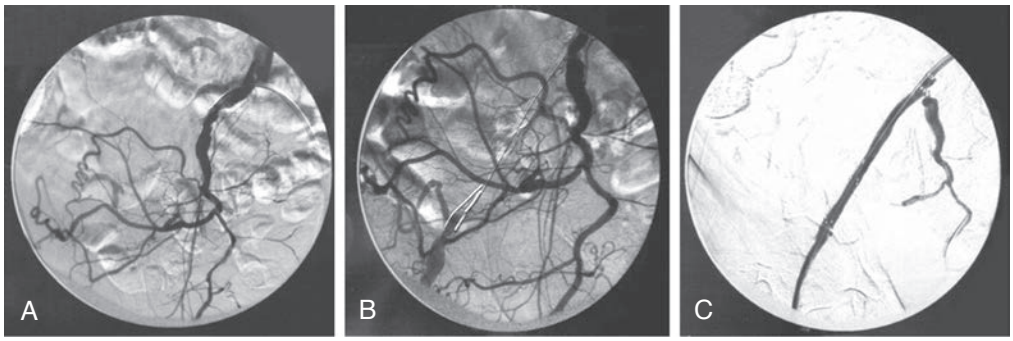

Figure 108.4 (A) External iliac artery occlusion approached through the contralateral common femoral artery. (B) Subintimal crossing of the complete occlusion with a reentry catheter. (C) Contralateral placement of a bare metal stent into the external iliac artery, allowing for placement in the proximal portion of the common femoral artery.

interventional procedures requiring radiographic contrast agent.[14] The absolute risk reduction of CIN (defined as 25% change in serum creatinine) using sodium bicarbonate compared with sodium chloride was 11.9%, resulting in a number-needed-to-treat of 8.4 patients to prevent one case of renal failure. A recent meta-analysis and systemic review of the literature confirmed that sodium bicarbonate hydration decreased the risk of CIN, without a significant risk of renal replacement therapy or in hospital mortality or congestive heart failure compared with controls. Similar results were seen for risk of CIN when sodium bicarbonate was compared with normal saline alone (OR, 0.39; 95% confidence interval [CI], 0.20-0.77). There have been conflicting results for the use of N-acetylcysteine with more than 40 trials and 13 meta-analyses, with the most meticulous meta-analysis not supporting the use of N-acetylcysteine to reduce the risk of CIN.

Patients with eGFR less than 60 mL/min receiving IA contrast should therefore receive IV hydration. If sodium bicarbonate is used, the initial IV bolus is 3 $mL \times kg^{-1} \times h^{-1}$ (154 mEq/L sodium bicarbonate in dextrose and water) for 1 hour immediately before contrast injection, followed by continuous administration of the same fluid at a rate of 1 $mL \times kg^{-1} \times h^{-1}$ during the period of contrast exposure and for 6 hours thereafter.[14] Use of the lowest volume of contrast (<5 mL/kg) to achieve satisfactory image quality is encouraged. This may require the use of dilute contrast, which can affect image quality. If possible, repeat contrast injections within 72 hours should be avoided. Diuretics should be routinely withheld on the day of contrast injection. Metformin is not a risk for CIN, and the injection of contrast is not contraindicated in patients taking this medication. However, serious complications (lactic acidosis) may rarely occur in patients taking metformin who subsequently develop acute kidney insufficiency. For this reason, it is recommended that metformin be stopped 48 hours prior to any contrast injection.

Determination of Approach

Common iliac artery (CIA) disease is generally treated through an ipsilateral, retrograde approach. If the CIA is occluded, contralateral flush catheter placement should be considered so that a complete diagnostic study can be performed before any intervention. This technique also provides access to protect the contralateral CIA from injury during ipsilateral CIA intervention. A complete diagnostic arteriographic examination includes a study of the pararenal aorta to exclude abdominal aortic aneurysm, oblique pelvic imaging of the iliac bifurcations to determine internal iliac artery patency and origin, and adequate views to evaluate CFA bifurcation disease. In general, the contralateral oblique projection shows the iliac artery bifurcations, whereas the ipsilateral oblique projection best displays the profunda origins at the femoral artery bifurcations. Finally, complete imaging of the infrainguinal runoff is requisite before inflow intervention. If such imaging is done only after completion of the intervention, differentiating preexisting distal occlusive lesions from emboli may be problematic. External iliac disease is generally better approached from the contralateral side because it permits more extensive treatment of the EIA into the proximal portion of the CFA if needed (Fig. 108.4).

The procedure begins with placement of an arterial sheath to facilitate catheter exchanges. The lesion is crossed with the use of a catheter–guide wire combination. An angle-tip catheter with a floppy-tipped guide wire is used to cross the lesion first, followed by the catheter. In difficult cases, hydrophilic wires may be used (see Fig. 108.4B). After advancing the catheter across the lesion, the wire is removed; free aspiration of blood ensures that the catheter tip is intraluminal.

Determination of Hemodynamically Significant Lesion

Pressure measurements across the lesion should be obtained by connecting the hub of the catheter and/or the side arm of the vascular sheath to the IA pressure monitor. Alternative options include the "pullback method," in which an end-hole catheter is withdrawn from proximal to distal across the lesion over a 0.014-inch wire. Most consider a peak-to-peak systolic pressure gradient of 10 mm Hg or greater at rest to be hemodynamically significant. In the absence of a resting gradient, IA nitroglycerin (100-200 μg) or papaverine (25 mg) can be administered distally to reveal the significance of a lesion. The maximal increase in pressure gradient occurs 20 to 40 seconds after vasodilator

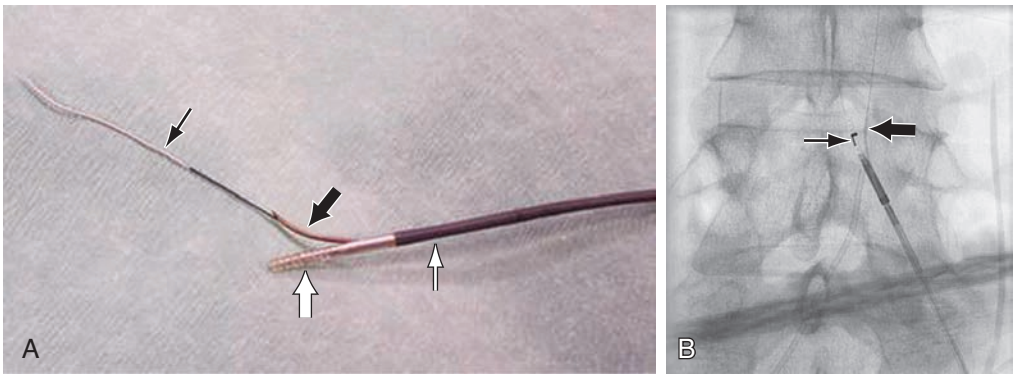

Figure 108.5 Reentry catheters. (A) Outback LTD catheter. The cannula *(large black arrow)* is deployed, and the 0.014-inch guide wire *(small black arrow)* is advanced through it. The nosecone *(large white arrow)* has the radiopaque "LT" orientation marker. The catheter shaft is indicated by the *small white arrow*. (B) Outback catheter. The cannula is deployed *(large arrow)*, with free passage of the guide wire into the true lumen of the aorta. Note the "L" configuration *(small arrow)*.

injection. If the mean pressure gradient increases to above 10 mm Hg, the lesion may be considered for treatment.

Techniques to Recanalize Chronic Totally Occluded Iliac Arteries

Contralateral Approach

When attempting to recanalize an occluded CIA in a retrograde fashion, the guide wire frequently follows a subintimal path. Once this has occurred, it may be difficult to redirect the guide wire into the lumen. An antegrade approach from the contralateral CFA is frequently successful, especially if there is a CIA stump and the CIA is not flush-occluded. A hooked catheter is used to probe the occlusion. The lesion can then be crossed with the use of hydrophilic guide wire and a supporting catheter. As soon as the guide wire has crossed the obstructive lesion and lies within the ipsilateral EIA lumen, a catheter can be advanced over the wire to confirm intraarterial placement. Depending on the proximity of the occlusion to the aortic bifurcation, a crossover sheath can be placed over a stiff guide wire or the wire can be snared from the ipsilateral CFA and a sheath can be placed in a retrograde fashion.

Brachial Approach

In the presence of a flush CIA occlusion, a contralateral femoral approach to cross the lesion is frequently unsuccessful; transbrachial or ipsilateral retrograde femoral approaches are more likely to achieve success. A brachial approach reduces the risk of creating or extending an aortic dissection and provides better "pushability." The presence of significant subclavian artery occlusive disease obviously limits this approach.

Reentry Wires and Catheters

The development of reentry wires and catheters has greatly increased the technical success of crossing arterial occlusions. Crossing wires and catheters designed to cross chronic total occlusions (CTO) typically involve a wire that based on a mechanical drive system potentiates passage of the wire through the true lumen of the CTO either through a vibration or rotating action. The majority of these devices have been tested in the femoral-popliteal vascular bed and their utility in the iliac vessels is uncertain.

Reentry catheters facilitate crossing CTO by a subintimal approach. There are no data to suggest any advantage to crossing an iliac CTO, either through the native lumen or subintimally. The Outback reentry catheter (LuMend Inc., Redwood City, California) is a single-lumen catheter designed to facilitate access and positioning of a guide wire within the peripheral vasculature from a remote vascular entry site using a retractable needle to pierce the intima and gain access to the true lumen (Fig. 108.5). The Pioneer catheter (Medtronic, Minneapolis, Minnesota) works by a similar mechanism but contains an intravascular ultrasound probe in the distal portion that assists in orienting the reentry needle toward the flow lumen. To use this catheter, a 300-cm-long, 0.014-inch guide wire is passed subintimally beyond the CTO. Usually an 0.035 wire is used to make the initial subintimal plane and then exchanged for the 0.014 wire. The reentry catheter is then advanced beyond the CTO under continuous fluoroscopy. An angiogram is performed via the contralateral access to confirm traversal of the occlusion and positioning of the lateral exit port of the catheter at the aortic bifurcation proximal to the occlusion. In the case of the Pioneer catheter, this is done with IVUS. The precise location and orientation of the lateral exit port are confirmed by aligning the fluoroscopic guide. The nitinol cannula is then advanced forward through the lateral exit port under continuous fluoroscopy. Applying firm but guarded forward pressure while deploying the cannula may contribute to a successful puncture. Free passage of the 0.014-inch wire indicates true lumen access, and is confirmed by contrast injection through a catheter placed over the wire. The catheter can be exchanged for a 3-mm-diameter angioplasty balloon that is used to dilate the subintimal tract and puncture site. This step enables a catheter to pass and allows exchange for a standard 0.035-inch guide wire to facilitate and perform stenting in a conventional manner (Fig. 108.6).

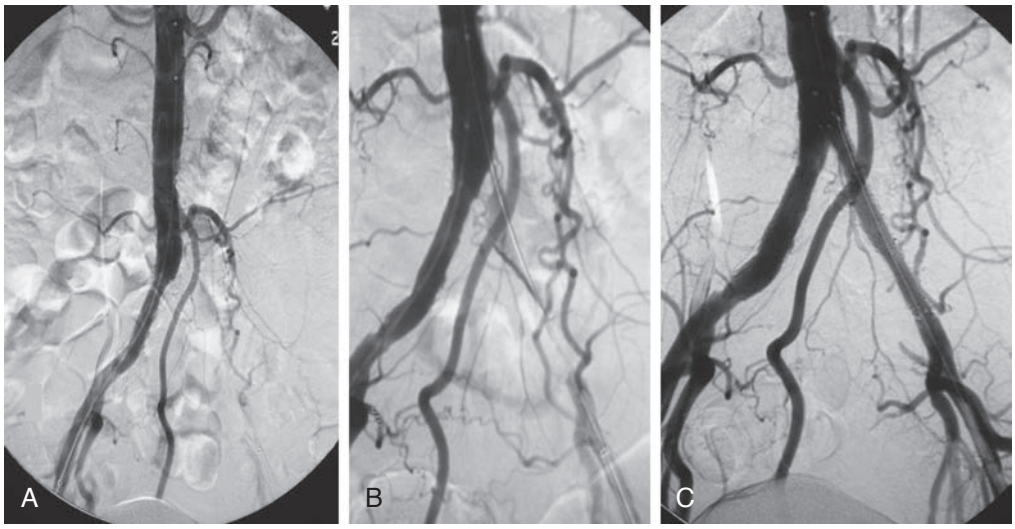

Figure 108.6 Results using a reentry catheter. (A) Pelvic arteriogram showing complete occlusion of the left common and external iliac arteries. (B) Glide catheter advancement into the aorta after reentry at the aortic bifurcation. (C) Retrograde stent-graft placement into the common iliac artery. Note the contralateral bare metal common iliac stent.

Aortic Bifurcation Lesions

Technical Approach

Lesions at the aortic bifurcation have been traditionally treated using the "kissing balloons" technique. Simultaneous balloon dilation at the origins of both CIAs is advocated, even in the presence of a unilateral lesion, to protect the contralateral CIA from dissection, plaque dislodgement, or subsequent embolization. A retrospective review of patients undergoing percutaneous treatment for unilateral CIA occlusive lesions by Smith and associates challenged this long-established practice.[29] In this report, 175 patients with unilateral ostial iliac artery lesions were treated with percutaneous transluminal angioplasty (PTA) or stenting without contralateral protection; in only two patients did the contralateral unprotected CIA develop mild stenosis (17% and 24%, respectively). The authors concluded that protection of the contralateral CIA during PTA or stenting of the ipsilateral proximal CIA is not mandatory.

Aortic Bifurcation Advancement

Because calcified lesions at the aortic bifurcation are not amenable to balloon dilation alone, the "kissing stents" or "aortic reconstruction" technique is applied (see Fig. 108.6C).[30] The aortic bifurcation reconstruction technique is technically successful; however, some have expressed fear that extension of the proximal ends of the stents into the distal aorta ("aortic advancement") may serve as a nidus for thrombus formation.[31] Recent work in a small series of 52 patients demonstrated that radial mismatch of stent to aortic lumen in which the iliac stents did not oppose the aortic wall was significantly associated with restenosis.[32]

Concomitant Femoral Endarterectomy

Preoperative duplex ultrasound, CTA, or MRA can help determine which CFA should be used for percutaneous access. If such studies identify significant CFA disease, an open femoral approach with combined endovascular iliac therapy and femoral endarterectomy should be strongly considered (Fig. 108.7A).[33] The CFA is exposed from the circumflex femoral branches down to the femoral bifurcation. The CFA is punctured under direct vision, and the iliac lesion is crossed prior to endarterectomy. This technique allows complete assurance of intraluminal wire placement distally at the endarterectomy site. For cases in which retrograde guide wire passage is not possible, a percutaneous approach from the contralateral femoral or brachial artery can be used to cross the iliac lesion or a reentry catheter can be used at the completion of the endarterectomy. The guide wire can then be brought out through the femoral artery. With wire access in place, proximal and distal control is obtained, and a longitudinal arteriotomy is created, allowing for standard endarterectomy and patch angioplasty. Before patch completion, the center of the patch is punctured with an 18-gauge needle, and the guide wire is brought out through the needle. Patch closure is then completed, and flow is restored. An appropriate sheath can then be passed over the wire to allow iliac stenting. Stents may be extended down to the proximal endpoint of the endarterectomy and patch if necessary (Fig. 108.7B).

Stent Sizing

Selection of the appropriate balloon or stent diameter is of utmost importance for a successful intervention. Slight oversizing of 5% to 10% is recommended, except in the case of heavily calcified lesions that may rupture. The optimal vessel diameter can be estimated from the adjacent normal arterial segment or by comparison to the same vessel on the contralateral side. A calibrated catheter inserted into the vessel allows measurement of the artery. The length of the balloon or stent should cover the diseased area without damaging the normal vessel. If in doubt when balloon-dilating a lesion, it is wise to undersize. A larger balloon can be used if the initial result is not satisfactory. With

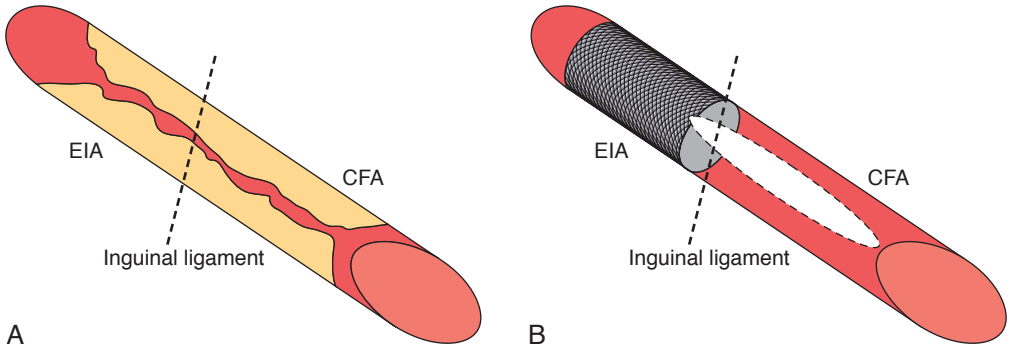

Figure 108.7 Operative technique for an open femoral approach to the diseased common femoral artery (CFA) and external iliac artery (EIA). (A) The common femoral artery is exposed from the circumflex femoral branches, distal to the femoral bifurcation. The common femoral artery is punctured under direct vision, and the iliac lesion is crossed before endarterectomy. Wire access is left in place, and a standard subintimal endarterectomy with patch angioplasty is performed. Before completion of the patch angioplasty, the patch is punctured in the center with an 18-gauge needle, and the guide wire is brought out through the center of the patch. After patch angioplasty is complete and flow is restored, a short sheath can be placed over the wire and through the center of the patch. (B) Iliac stenting can be performed such that the distal endpoint of the stent is just proximal to the endarterectomy and patch angioplasty.

balloon expandable stents, this rule does not apply, because an undersized stent usually cannot be exchanged for an optimal one. Balloon inflation should be gradual to avoid trauma to the adjacent normal vessel. A waist on the balloon indicates the lesion location; the waist disappears after successful dilation. Mild pain during dilation is acceptable and indicates stretching of the adventitia; excessive pain may indicate impending arterial rupture (see Fig. 108.3A and B). The technical success of the intervention is judged not only by the angiographic appearance, but more importantly, by measurement of any residual pressure gradient. Less than 20% residual stenosis and a less than 10 mm Hg systolic pressure gradient is considered a technical success. The determination of success should be based on the translesional pressure gradient measurement; angiographic criteria are less reliable.[31,34] Intravascular ultrasound may also be used to assess the technical result following iliac or aortic stent placement; it better demonstrates stent arterial wall apposition and gives a three-dimensional assessment of the stented iliac artery.

Stent Selection

Commercially available stents are numerous and fall into four main categories: balloon-expandable bare metal stents, self-expanding bare metal stents, balloon expandable stent grafts, and self-expanding stent grafts. Features of balloon-expandable stents and stent grafts include precision of placement, high radiopacity, and high hoop strength. However, they are less flexible than self-expanding stents and become permanently deformed if external force is directly applied to them.

Placement of a balloon-expandable stent generally requires the sheath to be advanced beyond the lesion, especially in severe stenoses, to avoid dislocation of the stent on the balloon. The stent mounted on the balloon is inserted into the sheath and positioned across the lesion using bony landmarks or road mapping. The sheath is then retracted, and the balloon is inflated to expand the stent. Since self-expanding stents and stent grafts are mounted on a carrier device and constrained by an outer sheath, the introducer sheath does not need to cross the lesion. Stent deployment is achieved by holding the carrier device with one hand and retracting the outer sheath with the other. Selection of an iliac artery stent depends on availability and the operator's familiarity with specific devices. In addition, iliac artery tortuosity, introducer sheath diameter, and intrinsic lesion characteristics influence the selection of an appropriate stent type. Short, eccentric, calcified lesions, typically occurring at the aortic bifurcation, are best treated with balloon-expandable stents owing to the ability to place them with great precision. In contrast, whenever the stent must follow a tortuous path or is to be placed from the contralateral side over the aortic bifurcation, self-expanding stents are advantageous because of their flexibility.

RESULTS

Percutaneous Angioplasty Versus Selective Stenting

PTA of focal iliac artery stenoses has demonstrated acceptable success rates (Table 108.1).[35] The reported 4-year success rates for iliac angioplasty are approximately 44% to 65%. Complications associated with angioplasty include vessel dissection, abrupt closure, spasm, and thrombus formation. Moreover, several studies evaluating the use of PTA for iliac artery occlusions showed a significant embolization incidence, which led some to question the usefulness of PTA in this patient subset.[36,37] In a study of 106 patients, kissing iliac stents showed good results in aortic bifurcation disease (a location that can be problematic for balloon angioplasty), with primary and secondary patency rates of 78% and 98%, respectively, at 3 years.[38]

Several randomized studies have compared stenting with standalone PTA. The Dutch Iliac Stent Trial Study Group

TABLE 108.1 Review of Outcomes in Interventional Treatment of Aortoiliac Occlusive Disease

Series	Year	Number of Patients	Indication	Type of Intervention	Primary Patency (%)
Parsons et al.[35]	1998	45		PTA	74 (5-year)
Klein[39]	2006	279		Primary stenting versus selective stenting	83 (5-year)
Bosch and Hunink[40] (meta-analysis)	1997	1300	Claudication vs. CLI	Selective stenting versus primary stenting	70 (5-year)
	1997	1300		Primary stenting	77 (4-year) 67 (4-year)
Murphy[41] (meta-analysis)	1998	2058		Primary stenting	73 (5-year)
Schurmann et al.[42]	2002	110	93% claudication	Primary stenting	66 (5-year)
Galaria and Davies[43]	2005	276	TASC A and B	Primary stenting	71 (10-year)
Leville et al.[16]	2006	92	TASC C and D	Primary stenting	76 (3-year)
Rzucidlo et al.[44]	2005	34	TASC B, C, and D	Stent-grafting	80 (5-year)
Chang et al.[45]	2008	171	TASC B,C, and D	Stent graft 41%, Bare metal stent 59%	60 (5-year)
Mwipatayi[47]	2011	40 24	TASC C and D	Stent graft Bare metal Stent	95 (18-month) 50 (18-month)
Psacharopulo[46]	2015	11	TASC D	Stent graft	91 (2-year)

CLI, Critical limb ischemia; *PTA*, percutaneous transluminal angioplasty; *TASC*, Trans-Atlantic Inter-Society Consensus.

performed a randomized comparison of primary balloon-expandable stent placement with primary angioplasty, followed by selective stent placement in patients with iliac artery occlusive disease. Iliac patency ranged from 97% (122 of 126 patients) at 3 months to 83% (90 of 109 patients) at the final mean follow-up of 5 years in the patients with primary stent placement; it ranged from 94% (113 of 120 patients) to 74% (67 of 90 patients) in the patients treated with PTA and selective stent placement. This difference was not significant. The study also showed that selective stent placement was more cost-effective than primary stenting of iliac artery stenosis.[34,39] However, 43% of patients randomized to balloon angioplasty underwent stent placement for a suboptimal result during the primary procedure. Twenty-five of 143 patients (17%) treated with primary stent placement needed reintervention in the iliac artery segment because of the development of symptomatic or hemodynamic (by noninvasive testing) restenosis. In the PTA and selective stent placement group, 28 of 136 patients (21%) needed reintervention. Complication rates were nearly double (4% vs. 7%) in the angioplasty group.[34]

Primary Stenting Versus Selective Stenting

Other randomized trials have shown primary stenting to be superior to selective stent placement in terms of both hemodynamic parameters and Rutherford classification (see Table 108.1). These include a meta-analysis comparing the results of PTA versus stent placement for iliac occlusive disease.[40] This meta-analysis of more than 1300 patients compared selective with primary iliac artery stenting and found significantly higher initial technical success (>90%) and improved primary patency rates (>70% at 2 and 5 years) in both claudicants and those with limb-threatening ischemia treated with primary stenting.[40] Because critical ischemia was considered an independent risk factor for failure, the authors stratified patency rates for claudication versus critical ischemia. The 4-year primary patency rate for claudication, with technical failures excluded, was 68% (range, 65%-74%) after PTA, compared with 77% (range, 72%-81%) after stenting. The 4-year primary patency rate for critical ischemia, with technical failures excluded, was 55% (range, 48%-63%) after PTA, versus 67% (range, 55%-79%) after stenting. The authors concluded that stent placement reduced the risk of long-term failure by 39% compared with PTA alone. Disease severity (claudication versus critical ischemia) was an independent predictor of long-term failure. However, whenever initial success was achievable, no statistically significant difference in long-term patency was found between stenoses and occlusions.

Long-Term Results

Murphy summarized the results of 18 published studies of primary iliac artery stent placement in a total of 2058 limbs (see Table 108.1).[41] Using weighted averages, the technical success rate was 97%, the complication rate was 6%, and the 5-year primary and secondary patency rates were 73% and 85%, respectively. Although iliac stent treatment has been in clinical use for more than 15 years, few reports of long-term patency are available. Schurmann and colleagues published a 10-year follow-up of 110 patients with iliac arterial occlusive disease who underwent implantation of self-expanding stents.[42] The mean patient age was 57 years, and 93% were claudicants. Based on angiographic or color duplex imaging follow-up in 105 patients and clinical follow-up in five patients, primary

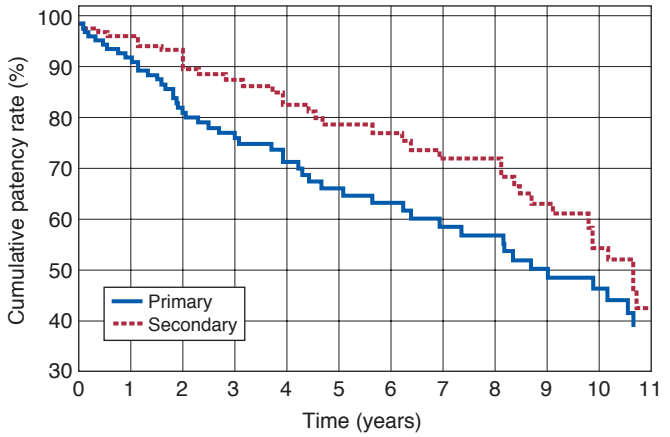

Figure 108.8 Long-term primary and secondary patency rates in 126 iliac lesions treated with stent placement. (From Schurmann K, Mahnken A, Meyer J, et al. Long-term results 10 years after iliac arterial stent placement. *Radiology*. 2002; 224:731–738.)

cumulative stent patency rates were 66% ± 5 after 5 years and 46% ± 6 after 10 years; secondary patency rates were 79% ± 4 and 55% ± 6.3, respectively. Mean follow-up time was 5.7 years. Restenosis occurred in 51 of 126 (41%) lesions after a mean of 3.9 years. Seventeen patients (16%) underwent surgical bypass of the aortoiliac segment that had been stented—14 because of stent restenosis, and three because of stenosis in other iliac arterial segments (Fig. 108.8).

Patency Based on Trans-Atlantic Inter-Society Consensus Classification

Trans-Atlantic Inter-Society Consensus Types A and B Lesions

Outcomes of iliac intervention depend on TASC lesion classification. Galaria and associates reported 10-year patencies for patients with TASC A and B lesions.[43] Indications for intervention were claudication (77%) or critical ischemia (23%). Altogether, 276 patients (all men; average age, 64 ± 11 years; range, 32-87 years) underwent 394 interventions. Sixty-two percent of the lesions were TASC type A, and the remainder were type B. Of the 394 primary interventions, 51% included the placement of stents. Technical success (defined as <30% residual stenosis) was achieved in 98% of treated vessels. The procedure-related mortality rate was 1.8% at 30 days and 4.7% at 90 days; the procedure-related complication rate was 7%. Hemodynamic success (defined as a rise in the ABI >0.15) was achieved in 82%. The average baseline Society for Vascular Surgery symptom score was 3.4 + 0.9, which improved to 1.9 ± 0.8 following intervention. Within 3 months, 84% of patients demonstrated clinical improvement. The cumulative assisted patency rate was 71% ± 7 at 10 years. The presence of two-vessel femoral runoff, two or more patent tibial vessels, or both was associated with improved patency. Limb salvage rates were 95% ± 2 and 87% ± 9 at 5 and 10 years, respectively. By Cox proportional hazards analysis, hypertension, hypercholesterolemia, and chronic renal insufficiency were associated with increased risk of primary

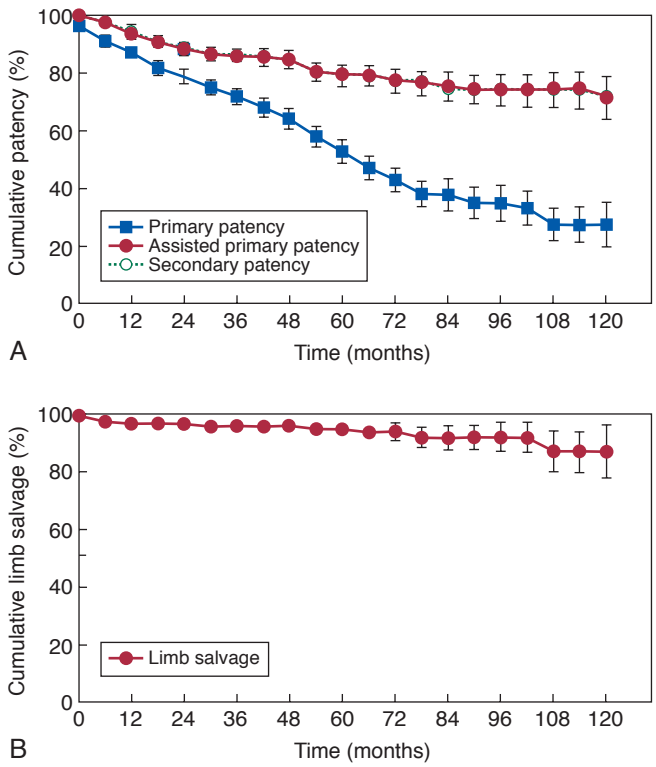

Figure 108.9 (A) Cumulative primary patency, assisted primary patency, and secondary patency (superimposed in assisted primary patency) intervals for all vessels. (B) Cumulative limb salvage for all patients. In both (A) and (B), the values are the mean ±. A standard error less than 10% for all data points by life-table analysis. (From Galaria II, Davies MG. Percutaneous transluminal revascularization for iliac occlusive disease: long-term outcomes in Trans-Atlantic Inter-Society Consensus A and B lesions. *Ann Vasc Surg*. 2005;19:352–360.)

failure, whereas the presence of immediate hemodynamic improvement was associated with increased long-term patency. Stent use did not influence outcome. These results approach those reported for surgical aortoiliac bypass grafting. For comparison, in a meta-analysis of 23 studies of aortoiliac or aortofemoral bypass grafts published between 1970 and 1996, de Vries and Hunink calculated limb-based patency rates of 91% and 86.8% at 5 and 10 years, respectively, for patients with claudication, and patency rates of 88% and 82%, respectively, for patients with critical ischemia (Fig. 108.9).[48]

Trans-Atlantic Inter-Society Consensus Types C and D Lesions

Although iliac angioplasty and stenting of TASC types A and B common iliac lesions achieve a patency similar to that of open surgical reconstruction, patients with diffuse aortoiliac occlusive disease (TASC types C and D lesions) have markedly inferior patency with bare metal stenting when compared with aortobifemoral bypass. Recently several authors have documented promising results in the treatment of more complex TASC types C and D iliac lesions. Jongkind and coworkers recently reported a meta-analysis of the late results of the endovascular treatment of complex iliac occlusive disease.[49] Five-year primary patency ranged from 60% to 86%, with secondary patency rates of 80% to 98%. In a series of 212 patients with chronic

iliac occlusions, successful recanalization was accomplished in nearly 90% of patients, with marked clinical improvement in the vast majority.[50] In another series of 109 iliac artery CTOs, primary patency at 5 years in the CTO group was 82% versus 91% in patients treated for stenosis.[51] Stent graft placement has been shown to improve outcomes in patients with TASC C and D lesions. This will be subsequently discussed later.

Patency With Concomitant Common Femoral Artery Disease

Chang and colleagues recently reported their long-term results of combined endovascular and open treatment of iliofemoral occlusive disease.[45] A total of 171 patients underwent 193 CFA endarterectomies and iliac stent or stent-graft placement. Indications were rest pain (32%), tissue loss (22%), and claudication (46%). EIA lesions were present in 39%, combined CIA and EIA lesions in 61%, and complete CIA-EIA occlusions in 41% of patients. Stent grafts were used in 41% of patients. Technical success was reported in 98%, with clinical improvement in 92% of patients. Five-year primary, primary-assisted, and secondary patency rates were 60%, 97%, and 98%, respectively. Endovascular reintervention was required in 14% of patients; inflow surgical procedures were required in 10%. By logistic regression analysis, the use of stent grafts compared with bare stents was associated with significantly higher primary patency (87% ± 5 vs. 53% ± 7; $P < .01$).

Predictors of Failure

Disease extension into the EIA increases procedural complexity and decreases the durability of the intervention. The presence of external iliac disease was a predictor of decreased primary and primary assisted patency rates.[50,52-54] In a study by Powell and coworkers, patients with severe EIA disease treated with bare metal stents had a 1-year primary patency rate of only 47%.[50,53] These patients also had poor rates of hemodynamic and clinical improvement after intervention. Many required surgical inflow procedures or subsequent endovascular reintervention to maintain aortoiliac patency. Other reported predictors of worse outcome after iliac artery angioplasty are female gender,[55] renal insufficiency, and CLTI.[54] Timaran and associates concluded that women with EIA stents had the poorest outcomes. More recent work by Danczyk and coworkers failed to find a difference in outcome between patients treated with bare metal stents for EIA versus CIA lesions.[56] Other groups have noted that small vessel diameter and female gender are factors predictive of failure.[57]

Stent Grafting

Stent grafting has in the past been used primarily to treat patients with isolated iliac aneurysms, iatrogenic perforations or ruptures, arteriovenous fistulae, and on occasion severe aortoiliac occlusive disease, especially those with small calcified EIAs, who are not candidates for open surgical intervention. These devices are stainless steel, nickel-cobalt-titanium-steel alloy (Elgiloy), or nitinol stents covered with Dacron or polytetrafluoroethylene (PTFE).[44,58,59] More recently stent grafts have become more routinely used to treat patients with aortoiliac occlusive disease, especially TASC C and D lesions.

Stent-Graft Patency

Stent-graft treatment of patients with severe aortoiliac occlusive disease (85% TASC types C and D lesions) was reported by Rzucidlo and colleagues.[44] The use of stent grafts increased the primary and primary assisted patency at 1 year to 70% and 88%, respectively, compared with patients treated with stents alone, and led to 100% early hemodynamic and clinical success. There was a trend toward improved primary iliac artery patency in patients who underwent concomitant common femoral endarterectomy. At 6 and 12 months, the primary patency rates in patients who underwent concomitant common femoral endarterectomy were 94% and 94%, respectively, compared with 79% and 53% in patients who did not undergo endarterectomy.

Long-term results of stent grafts for the treatment of complex aortoiliac occlusive disease have been reported. At 3 and 5 years after intervention, the primary patency rates of the iliac segment were 80% and 80%, respectively; corresponding primary assisted patency rates were 95% and 95% (Fig. 108.10). Primary patency using stent grafts differed significantly depending on TASC classification. Patients with TASC type B iliac lesions had a 100% 5-year patency rate. Those with TASC type C iliac lesions had the lowest 5-year primary patency—significantly lower than TASC type D iliac lesions when type B lesions were removed from the log-rank analysis (61% vs. 85%; $P = .04$; unpublished data).

Others have reported the use of stent grafts to treat diffuse iliac occlusive disease. Nevelsteen and coworkers placed 29 stent grafts in 24 patients to treat claudication ($n = 7$) or limb-threatening ischemia ($n = 17$).[60] Mean primary and secondary cumulative patency rates after 1 year were 85% and 95%, respectively. All patients in this series underwent outflow procedures—that is, profundaplasty or femoral distal grafting. Psacharopulo has demonstrated 91% 2-year primary patency in patients treated with self-expanding stent grafts for TASC D lesions.[47] These patients also underwent concomitant femoral endarterectomy.

Predictors of Failure for Stent Grafting

CFA disease was a significant predictor of failure at long-term follow-up.[44] The 5-year primary patency rate was 88% for patients who had concomitant CFA endarterectomy and iliac stent grafting, versus 66% for stent grafting alone ($P = .04$; relative risk, 8). This finding has prompted more intense evaluation of the CFA plaque burden before proceeding with iliac intervention (Fig. 108.11).

Most recently, Mwipatayi and coworkers reported the 5-year results of the COBEST trial,[47] a randomized study comparing primary patency of bare metal stents to stent grafts in patients with aortoiliac occlusive disease. The 5-year primary patency was significantly improved from 50% to 95% at 18 months in patients with TASC C and D lesions treated with a covered stent compared with bare metal stent treatment. There was no

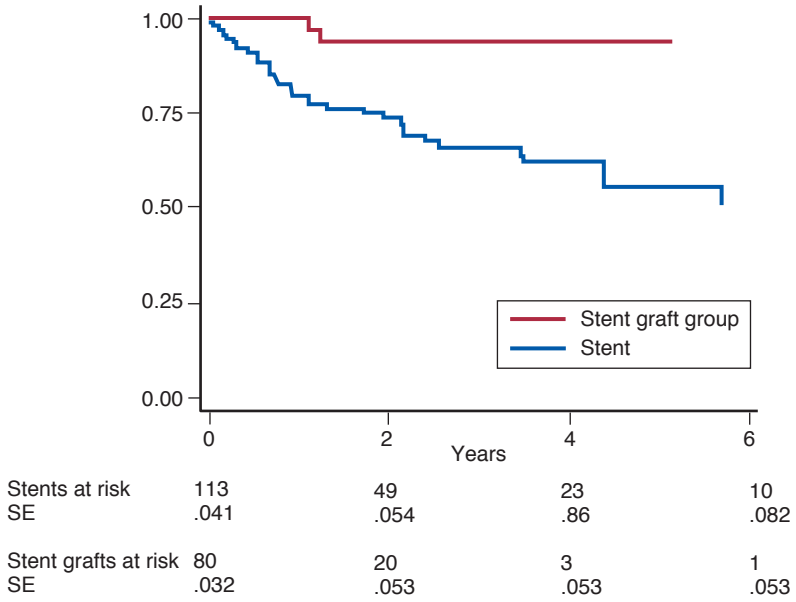

Figure 108.10 Kaplan-Meier curve estimate for primary stent-graft patency of severe occlusive iliac artery disease compared to patients treated with bare metal stents. A standard error less than 10% at 5 years.[45]

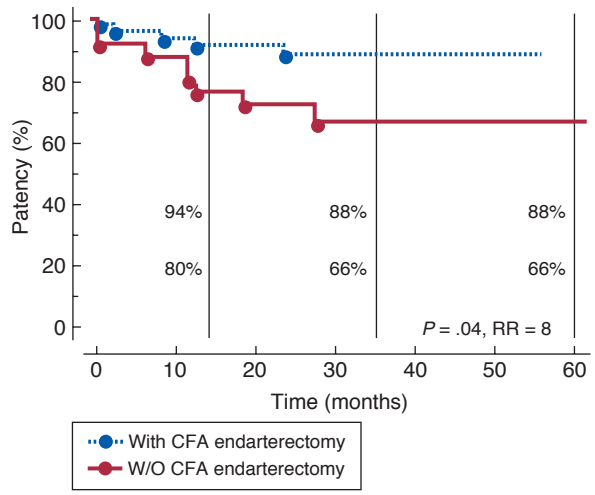

Figure 108.11 Kaplan-Meier primary patency curves for patients with common femoral artery (CFA) disease as a variable. Patients with concomitant CFA endarterectomy had significantly better patency than those without (W/O) endarterectomy (88% vs. 66% at 60 months; $P = .04$). *RR,* Relative risk.

difference in patency in patients with TASC B lesions. Use of a stent graft and Rutherford class were the only predictors of patency.

Mortality

It has been estimated that the life expectancy of patients with peripheral artery disease (PAD), especially those with intermittent claudication, is reduced by about 10 years compared with the general population.[61-63] The main cause of death in patients with PAD is cardiac disease, accounting for 40% to 60%. Overall mortality rates from all causes in patients with intermittent claudication are approximately 30% after 5 years, 50% after 10 years, and 70% after 15 years.[64] About 10% to 20% of patients die of cerebrovascular disease, and about 10% die of other vascular causes, mainly ruptured aortic aneurysms. Nonvascular causes account for about 20% to 30% of deaths, with the most frequent being cancer.[64] In a prospective follow-up study of more than 550 patients with CLTI, 21.9% of patients were deceased after 1 year, and 31.6% after 2 years.[63] The overall incidence of cardiovascular death was 34.5%, compared with 8.5% of deaths resulting from nonvascular causes. These numbers, based on large series, are well reflected in the small population studies of patients undergoing endovascular treatment for iliac occlusive disease. Long-term mortality rates reported by Schurmann and associates for patients treated with iliac stents were 17% after 5 years and 36% after 10 years.[42] Galaria and colleagues reported that patient survival by life-table analysis was 38% at 10 years for patients with TASC types A and B lesions treated with angioplasty and stenting of the iliac arteries.[43] It can be hypothesized that successful treatment of claudication might prolong survival time; however, there are no study findings proving this hypothesis.

COMPLICATIONS

Bypass surgery has superior long-term durability, with 5-year patency in excess of 80%, but it has been associated with a perioperative complication rate of up to 30%.[65-67] Recovery from aortobifemoral bypass typically requires weeks of absence from work, a financial burden that many patients cannot absorb. Thus, less invasive endovascular treatment for aortoiliac occlusive disease has largely supplanted aortobifemoral bypass, because focal iliac disease is well treated with angioplasty or stent placement. These less-invasive options are not without complications, however. These complications can be categorized as contrast related, access related, and remote.

Contrast Related

Patients with preprocedure renal insufficiency are at greatest risk for postprocedure nephropathy. As previously discussed, patients with serum creatinine greater than 1.5 mg/dL (133 µmol/L) should be treated with sodium bicarbonate infusion.[14,27,28,68] In addition, contrast volume should be limited. Patients with creatinine greater than 2.5 mg/dL (221 µmol/L) are treated with a combination of intravascular ultrasound and pre-and postprocedure pressure measurements.

Sheath Site Related

The incidence of local complications related to access and sheath insertion is 1% to 3%, but this can be reduced by accurate placement of the puncture site in the CFA, avoiding high and low punctures. Most sheath sites can be closed with suture-type closure devices to decrease the incidence of hematoma and CFA pseudoaneurysm.[69]

Iliofemoral arteriography is performed to determine the suitability for closure device use. If the femoral artery is small (less than 5–6 mm) or if significant calcification is present, the sheath is removed after the activated clotting time has decreased to less than 200 seconds and manual pressure is applied. If CFA disease is not well defined before intervention, posterior plaque disruption by means of the initial needle puncture can cause acute CFA occlusion. Femoral artery occlusion is obvious on physical examination by the loss of color and pulses; immediate operative intervention with groin exploration is necessary.

Remote

Arterial Rupture

Arterial rupture is an uncommon (<1%) but potentially serious complication. Arterial rupture most often occurs in the setting of angioplasty or stenting of small, heavily calcified EIAs. When the procedure is performed under local anesthesia, significant flank or back pain typically precedes arterial rupture. If such pain occurs, no further dilation should be performed. Patients under regional or general anesthesia do not exhibit these symptoms. Arterial rupture can usually be treated with stent graft placement to seal the injury (see Fig. 108.3A–C). A balloon occlusion catheter may be needed to stabilize hypotensive patients. This must often be placed from the contralateral femoral artery to allow upsizing of the ipsilateral femoral sheath to one sufficient to allow stent-graft placement.

Arterial Dissection

Arterial dissection has been described as a complication of PTA. Proximal or distal progression of iliac dissection can occur beyond the site of intervention. The typical cause is overdilation of a small calcified artery. Treatment consists of the extension of stenting to stop flow-limiting occlusion due to the dissection.

Embolization

Distal embolization is uncommon in the absence of aggressive predilation prior to iliac stent placement. Appropriate assessment by pre- and postprocedural arteriography, physical examination, and Doppler evaluation is important to detect this complication.

POSTOPERATIVE MANAGEMENT

There are well-accepted criteria for reporting procedural success, clinical improvement, and patency, and the proper use of these standards for outcomes is critical. Initiation of a program of ongoing care to monitor and treat modifiable risk factors is also an important aspect of postoperative management. Risk factor management is critical and is discussed in Chapter 105 and generally includes antiplatelet and statin therapy. Regular follow-up should be performed at 1 and 6 months, and then yearly to assess patient outcome. This should include a history, pulse examination, and hemodynamic evaluation such as ankle brachial index measurements.

Criteria for Reporting Significant Change in Clinical Status

Clinical assessment expressed grossly in terms of "symptomatic relief" is notoriously unreliable because it lacks objectivity. Combining standard clinical categories with objective noninvasive testing can overcome this weakness. For reporting purposes, the designation "clinically improved" requires an upward shift by at least one clinical category (see Chapter 103, Table 103.3), except for those with actual tissue loss, who must move up at least two categories and reach a level of claudication to be considered improved. In addition, to attribute the improvement to treatment, objective evidence of hemodynamic improvement must be documented; an increase of more than 0.10 in ABI is recommended. If the ABI cannot be accurately measured (e.g., those with diabetes and medial calcinosis), the systolic toe pressure (which is less commonly affected by vessel incompressibility) or any measurable pressure distal to the revascularization can be substituted.

Criteria for Patency

The determination of iliac stent patency should be based on objective findings. Although physical examination can detect the presence of a palpable femoral pulse, iliac stent patency should be demonstrated by an accepted vascular imaging technique such as arteriography, color-flow duplex ultrasound, or magnetic resonance imaging. A diameter reduction within the stented segment of greater than 50% indicates significant restenosis. A biphasic or triphasic Doppler waveform should be noted at the CFA level. Although no clear duplex criteria for the iliac segment exist, most would consider a doubling of the peak systolic velocity indicative of restenosis, especially with an ABI drop greater than 0.1.

Quality of Life Outcomes

Few trials have looked at quality of life (Qol) outcomes after the treatment of iliac occlusive disease with stents. The Dutch

Iliac Stent Trial Study Group reported that at early follow-up, all RAND 36-Item Health Survey scores increased substantially in both patients treated with angioplasty alone and patients treated with selective stenting.[70] Qol assessments (consisting of the RAND 36, time tradeoff, standard gamble, rating scale, health utilities index, and EuroQol-5D) were completed by 254 patients in telephone interviews performed before treatment and after 1, 3, 12, and 24 months. When the two treatments were compared, no significant difference was observed ($P > .05$). All measurements showed a significant Qol improvement after treatment ($P < .05$). The RAND 36-Item Health Survey, which measures physical functioning, role limitations caused by physical problems, and bodily pain, and the EuroQol-5D were most sensitive to the impact of revascularization. Compared with the external patient group (i.e., patients with intermittent claudication who participated in an exercise program), patients in the trial had lower Qol values before and higher values after revascularization. The proportion of trial patients with pre-revascularization values below the 95% CI of the reference values among the exercise group ranged from 21% (standard gamble) to 67% (RAND 36 physical functioning). After revascularization, these proportions decreased significantly. At 2-year follow-up, the proportion of trial patients with health values equal to or higher than the upper 95% confidence limit of the reference values among the exercise group ranged from 62% (EuroQol-5D) to 78% (RAND 36, bodily pain). At 5 years after treatment, all scores, except that for general health perception, were still markedly higher than the pretreatment scores in both groups.[39] Survival analyses showed no differences in RAND 36 scores between the two treatment groups over the follow-up period.

When we compared the Qol scores of the two treatment groups 5 years after treatment with data from age-matched controls in the literature, the scores of patients treated with PTA and selective stent placement were as high as those of age-matched controls in all dimensions. However, the scores of patients treated with primary stent placement were substantially lower for physical functioning, physical role functioning, vitality, bodily pain, and general health perception. Scores for emotional role functioning, social functioning, mental health, and health change were equivalent to those in age-matched controls.[39] The authors therefore concluded that cost rather than effectiveness may be the decisive factor in the choice of percutaneous treatment.

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de Vries SO, Hunink MG. Results of aortic bifurcation grafts for aortoiliac occlusive disease: a meta-analysis. *J Vasc Surg*. 1997;26:558–569.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 109

Infrainguinal Disease: Surgical Treatment

JOSEPH L. MILLS Sr.

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Abstract

Open surgical lower extremity arterial bypass remains the most durable option for infrainguinal revascularization for chronic atherosclerotic occlusive disease. Although increasingly many patients are well served by endovascular therapy, it is still important to be familiar with the available techniques of lower extremity bypass so that patients aren't denied viable options for limb salvage. Infrainguinal bypass is defined as any major arterial reconstruction using a bypass conduit, whether it be autogenous or prosthetic, originating at or below the inguinal ligament. Inflow sites may include the common, deep, and superficial femoral arteries as well as the popliteal or even the tibial arteries. The bypass insertion site may be the superficial femoral, above- or below- knee popliteal, tibial, peroneal, pedal or plantar artery. Improvements in patient evaluation and selection and in the conduct of infrainguinal bypass operations have resulted in a more aggressive and generally more successful approach to distal arterial reconstruction, especially for patients with chronic limb-threatening ischemia (CLTI), many of whom might otherwise face major limb amputation. CLTI is a broad disease spectrum and increasing evidence suggests that low to moderate risk patients with good quality autogenous conduit have better outcomes with bypass than complex endovascular therapy.

The most important keys to success when performing lower extremity bypass are the caliber and quality of the venous conduit and the application of meticulous postoperative duplex and hemodynamic-based surveillance. This chapter reviews multiple methods and techniques for obtaining a nearly "all-autogenous policy" for infrainguinal bypass and also addresses use of prosthetic conduits with adjunctive techniques to optimize bypass outcomes when vein is truly lacking. Use of alternative veins and alternate anatomic exposures of a variety of lower extremity arteries are also reviewed to broaden the readers' options when confronted with redo cases or particularly challenging anatomy, especially when faced with limited available vein conduit. Expected patency and limb salvage rates are also presented in tabular form contrasting a variety of conduit options.

Keywords

leg bypass
infrainguinal bypass
vein bypass
peripheral artery disease
duplex graft surveillance
graft stenosis
restenosis

Lower extremity arterial reconstruction is most commonly performed in patients with moderate to severe limb ischemia due to atherosclerotic peripheral artery disease (PAD). Although the techniques described that follow may also be applied to patients with traumatic, aneurysmal, and nonatherosclerotic conditions, this chapter focuses exclusively on patients with PAD. *Infrainguinal bypass* is defined as any major arterial reconstruction using a bypass conduit, either autogenous or prosthetic, that originates at or below the inguinal ligament. Inflow sites therefore include the common, deep, and superficial femoral arteries as well as the popliteal or even the tibial arteries. The bypass insertion site may be the femoral, above- or below-knee popliteal, tibial, peroneal, or pedal artery. During the past 2 decades, progress in patient evaluation and selection and in the conduct of infrainguinal bypass operations has resulted in a more aggressive and generally more successful approach to distal arterial reconstructions, especially for patients with chronic limb-threatening ischemia (CLTI), many of whom would otherwise face major limb amputation. CLTI is a spectrum. Determining whether revascularization is required for wound healing and if performed, whether open bypass or endovascular therapy is the best initial option is still contentious due to observer bias, widely variable levels of technical expertise and lack of prospective, randomized data to support any given approach. Although graft patency and limb salvage rates have demonstrated continuous improvement, there remains a critical need for detailed clinical studies examining the cost-effectiveness of infrainguinal bypass as well as patient quality of life (QoL) outcomes to ensure the appropriate use of these procedures and to permit meaningful comparison with less invasive endovascular therapies.

INDICATIONS

The two primary indications for infrainguinal bypass are claudication and CLTI.

Claudication

Patients who are significantly disabled by claudication, such that they are unable to perform their primary occupations or comfortably carry out the activities of daily living, and those whose lifestyles are significantly limited are potential candidates for infrainguinal bypass. A trial of smoking cessation, lifestyle modification, and exercise, with or without medical therapy, is usually indicated before operative intervention (see Chapter 105). There is consensus that bypass is preferable to angioplasty in patients with TransAtlantic Inter-Society Consensus (TASC) type D lesions, that is, complete common femoral artery (CFA) or superficial femoral artery (SFA) occlusions or complete popliteal and proximal trifurcation occlusions; however, bypass may also be applied to patients with types B and C lesions (see Chapter 109).[1] Operation should be offered only if the benefit-to-risk ratio is high *and* if anatomic characteristics suggest a favorable and durable result. The primary reason for intervention in claudicants is to improve lifestyle or QoL, given that the risk of severe clinical deterioration (20%) or major limb amputation (5%) during a 3- to 5-year period is low.[1,2] In most centers with extensive infrainguinal bypass experience, claudicants constitute only 15% to 30% of patients, with the majority of patients undergoing bypass for CLTI. These data reflect practice patterns in tertiary referral centers and may not reflect the realities of community-based practices.[3]

Critical Limb Ischemia and Chronic Limb-Threatening Ischemia

Patients with advanced CLTI generally require intervention. Such patients previously fell into Fontaine III and IV[4] and Rutherford 4 to 6 categories (see Chapters 104 and 105).[5-7] The most recent European consensus document defines CLI as follows: persistent, recurring ischemic rest pain requiring opiate analgesia for at least 2 weeks and ankle systolic pressure lower than 50 mm Hg or toe systolic pressure lower than 30 mm Hg; or ulceration or gangrene of the foot or toes and ankle systolic pressure lower than 50 mm Hg; or toe systolic pressure lower than 30 mm Hg (or absent pedal pulses in diabetics).[8] Wolfe and Wyatt[9] further subdivided patients meeting the longstanding definition of CLI into critical or subcritical ischemia on the basis of subsequent, observed amputation risk. Subcritical ischemia is present in patients with rest pain and ankle pressure higher than 40 mm Hg. Critical ischemia is defined as rest pain and tissue loss or ankle pressure lower than 40 mm Hg. This distinction is based on a retrospective analysis of 20 publications analyzing 6118 patients. At 1 year, 27% of patients with subcritical ischemia achieved limb survival without revascularization, in contrast to only 5% in the group of patients with critical ischemia. In practice, these data indicate that certain extremely high-risk patients with subcritical ischemia might be managed medically (nonoperatively) but that virtually all patients who are expected to live more than 1 to 2 years with true "critical ischemia" require either bypass or major limb amputation. Because of inconsistencies with terminology and the inappropriate application of the term critical limb ischemia to patients with diabetes, the Society for Vascular Surgery Lower Extremity Guidelines Committee created a more comprehensive threatened limb classification system intended to stratify amputation risk in patients across the spectrum of CLTI.[10] This system is based on objective grades Wound (W), Ischemia (I) and Foot Infection (FI) to calculate a threatened limb clinical stage from 1 to 4 has been validated in multiple studies to be highly predictive of 1-year major limb amputation risk.[11]

PREOPERATIVE ASSESSMENT

There is widespread recognition that patients requiring infrainguinal bypass frequently have medical comorbidities, including diabetes mellitus, chronic obstructive pulmonary disease, and renal insufficiency; there is a particularly high prevalence of associated coronary artery disease (CAD). The incidence of perioperative myocardial infarction ranges from 2% to 6.5% after lower extremity arterial reconstruction; approximately 70% of both perioperative and late mortality in these patients is due to concomitant CAD.[12-15] Significant CAD is a nearly universal

accompaniment of PAD. What remains controversial is determining which individuals are most likely to benefit from a detailed preoperative cardiac assessment and possible coronary intervention before undergoing infrainguinal bypass. Proposed algorithms have ranged from routine cardiac evaluation of all PAD patients to an almost nihilistic approach.[16]

Patients with CLTI pose a more complex problem because, especially for WIfI Stage 3 and 4 patients, there is a high anticipated amputation rate without lower extremity arterial reconstruction.[9] CLTI patients have an even greater prevalence of CAD than claudicants do as well as a significantly reduced 5-year mortality, primarily due to associated CAD. However, because CLTI patients also tend to be older and have more comorbidities, cardiac intervention in such individuals has higher reported morbidity and mortality rates than in the general population of patients with isolated CAD targeted for intervention.[16] My approach in CLTI patients is to assume they all have significant CAD. Perioperative blood pressure control, antianginal regimens, and treatment for congestive heart failure are optimized.[17-20] I would recommend postponement of infrainguinal bypass in CLTI patients to allow further cardiac evaluation only in the presence of frequent or unstable angina, recent myocardial infarction, poorly controlled congestive heart failure, critical aortic stenosis, or symptomatic/untreated arrhythmia. Even in these instances, the cardiac evaluation should be focused and expeditious. Invasive coronary intervention should be pursued only if patient and anatomic characteristics are favorable, the benefit-to-risk ratio is high, and the delay to perform the intervention is not prolonged. In the absence of such cardiac instability, CLTI patients are best treated with meticulous perioperative medical care and expeditious lower extremity revascularization.[21,22] Prolonged delays before limb revascularization in CLTI patients increase morbidity and amputation risk.[23] In patients requiring vascular reconstruction, the focus has turned sharply toward maximizing medical therapy rather than performing multiple, expensive, and sometimes ambiguous preoperative cardiac tests so that the patient can be "cleared for surgery." A large, well-designed prospective randomized trial failed to show a benefit of cardiac revascularization before vascular surgery in patients with stable cardiac symptoms. (see Chapter 32 for a detailed discussion of perioperative cardiac evaluation and treatment.)[24]

PREOPERATIVE IMAGING

Infrainguinal bypass requires a careful assessment of the extent of arterial disease as well as a detailed anatomic characterization of the inflow and outflow arteries (see Chapters 25 and 105). Standard arteriography is still the "gold standard" for most patients. Computed tomographic angiography has improved and is now the dominant preoperative imaging modality for aortic aneurysm disease; however, in the periphery, the small caliber of the infrainguinal arteries and the presence of calcification in multiple vessels (associated with increasing age and diabetes) limit the applicability of computed tomographic angiography, especially in CLTI patients.[25] Magnetic resonance angiography[26] is continually improving,[27-31] and particularly for patients with claudication, preoperative duplex imaging, also referred to as duplex arterial mapping (see Chapter 21),[32,33] may provide sufficient anatomic information to proceed directly to the operating room without formal arteriography. In this circumstance, immediate pre-bypass arteriography in the operating room is a reasonable approach. For most patients, however, especially for those with CLTI, I prefer to perform the initial diagnostic angiography in a separate setting, for several reasons. One reason is that for an increasing number of CLTI patients, endoluminal techniques are a reasonable option.

On the basis of a careful assessment before angiography, including the indications for intervention, anatomic considerations (based on duplex imaging), and the patient's functional status, comorbidities, and availability of vein conduit (see Chapter 105), I try to determine whether a given patient with TASC type C or D disease would be best served by endoluminal therapy or open bypass. If endoluminal therapy is the preferred option, I vigorously pursue endoluminal treatment at the time of diagnostic arteriography. If open bypass is preferable, I focus on optimal visualization of potential target arteries and obtain multiple views, as required, to ascertain that no unexpected inflow disease is present that would require treatment before proceeding with infrainguinal bypass. Detailed high-quality diagnostic arteriograms can be obtained and reviewed carefully before proceeding with bypass. In some patients, selection of outflow arteries may be difficult, and this area of decision making can be improved if films are reviewed and discussed with colleagues. Confining the initial procedure to diagnostic or therapeutic angiography obviates time constraints and scheduling difficulties that arise in the operating room when trying to perform angiography and open reconstruction in one sitting. I reserve that approach for carefully selected patients whose arterial anatomy has already been fairly well delineated by preoperative magnetic resonance angiography or duplex scanning. This confines the "one-stop approach" primarily to claudicants undergoing bypass for isolated, single-level femoropopliteal disease.

Defining Bypass Target Arteries

In nearly all patients in whom infrainguinal bypass is indicated, suitable target arteries can be identified (Fig. 109.1) if diagnostic angiography is properly performed.[34,35] Only a tiny fraction of individuals, usually those following multiple failed reconstructions, have no identifiable target artery.[36] Detailed runoff views are necessary, including magnified lateral views of the foot. Such films can be obtained in nearly all patients with adjunctive techniques such as foot warming, local administration of intraarterial vasodilators, and proper positioning of the diagnostic catheter. It is frequently helpful to advance the catheter selectively into the SFA or popliteal artery to obtain adequate views of the infrapopliteal and pedal circulations, especially in patients with diabetes mellitus. Intraarterial runoff films with bolus injections performed while the diagnostic catheter is positioned in the aorta may fail to adequately define the runoff. If percutaneous access has been achieved from a contralateral, retrograde femoral approach, selective films can be obtained by advancing a wire and an appropriate diagnostic catheter over the aortic

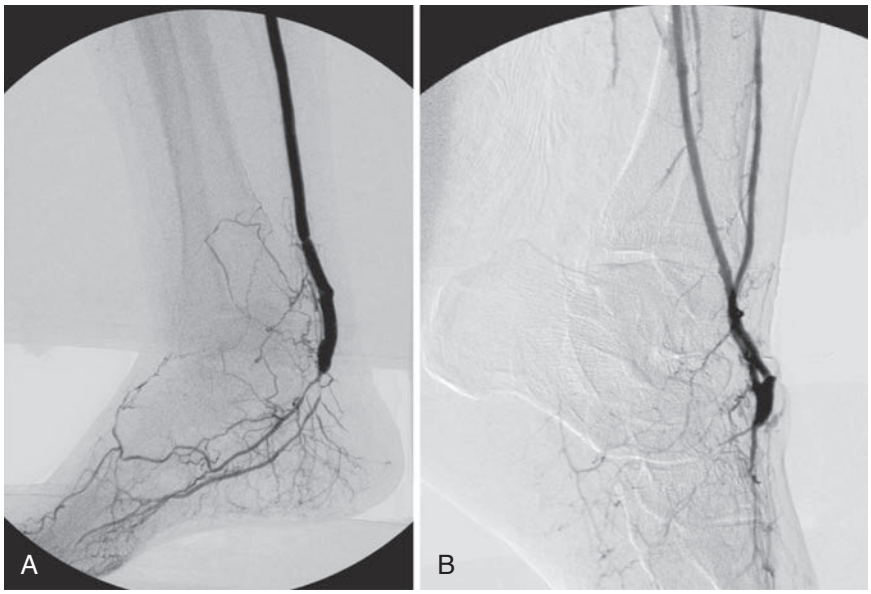

Figure 109.1 Detailed diagnostic arteriography with fixed imaging, proper timing, and appropriate catheter placement almost always identifies suitable target arteries. Each of the patients depicted had popliteal artery occlusion and extensive trifurcation and long-segment tibial disease, but diagnostic studies identified suitable target arteries in the foot. (A) Completion arteriogram after inframalleolar posterior tibial bypass in a patient with diabetes and forefoot gangrene. Despite a small-caliber outflow vessel, the bypass remains patent, and the ischemic foot ulcers healed and have not recurred at 2 years. (B) Completion arteriogram after bypass to a diseased dorsal pedal artery. Despite poor outflow and diseased arch and pedal vessels, the graft remains patent at 1 year. This patient with diabetes healed and ambulates with a transmetatarsal amputation.

bifurcation and selectively down the affected extremity. In selected patients with normal inflow based on physical examination and noninvasive studies, an ipsilateral antegrade approach may be more expeditious to identify suitable runoff vessels, with the additional advantage of requiring a reduced contrast load (Fig. 109.2). Such an approach is especially useful in diabetic patients with renal insufficiency and noninvasive studies that suggest isolated infrapopliteal disease.

Despite optimal angiographic techniques, there may be a small number of patients in whom no suitable target can be identified. Selective exploration of dorsal pedal or distal posterior tibial arteries with flow detectable by Doppler or duplex imaging may identify a graftable recipient artery. Pomposelli et al.[36] reported a surprisingly high success rate under these circumstances, although I believe that this situation is relatively uncommon if diagnostic angiography has been optimally performed. In short, there are few patients who are truly unreconstructible from an anatomic standpoint owing to the lack of a suitable outflow target vessel.

Figure 109.2 Lateral foot view obtained by distal selective superficial femoral arterial catheter injection identifies excellent collaterals from the distal peroneal artery to both the dorsal pedal and posterior tibial circulations.

Autogenous Vein Assessment

Since Kunlin's first description of the successful use of autogenous femoropopliteal vein bypass for arteriosclerosis obliterans,[37,38] there is universal agreement that autogenous vein is the best conduit for infrainguinal bypass at all levels.[39,40] Great saphenous vein (GSV) is the most readily available and durable conduit. Assessment of vein availability and quality is critical and should be carried out before embarking on the operation.[41-43] I routinely perform preoperative duplex mapping of the GSV. If the ipsilateral GSV is absent, unsuitable, or of insufficient length for the anticipated bypass, I also scan the ipsilateral small saphenous vein, the contralateral great and small saphenous veins, and the upper extremity veins, to locate a suitable vein and to identify any extenuating circumstances that might arise during the conduct of the operation. Patients are scanned with a light tourniquet in place and with the limb dependent, as described by Blebea et al.[44] I prefer to use veins that are soft, compressible, and at least 3 mm in diameter. Calcified or sclerotic veins are rejected. Soft, compressible veins between 2 and 3 mm in diameter are worthy of exploration, but if they do not distend appropriately, the operation should be modified either by harvesting a better-quality vein (based on preoperative duplex studies) or by shortening the length of the proposed bypass, if possible,

by selecting alternative inflow or outflow sites. The type and quality of the bypass conduit are the most important determinants of infrainguinal bypass success; efforts to maximize conduit quality will be rewarded.

Vein harvesting can be performed through long continuous incisions, skip incisions, or endoscopically. Endoscopic vein harvest has become common in cardiac surgery. Although there are a few enthusiasts, it has not been widely adopted by vascular surgeons for leg bypass, likely owing to equipment costs, learning curve issues, and concerns about damaging vein segments when a long conduit is needed. There are no convincing data to support any specific harvesting technique.[45-49] Regardless of the harvesting technique, poor-quality or marginal vein should be rejected. The search for high-quality vein is worth the time and effort, even if vein splicing or bypass shortening is required. Every effort should be made to perform all infrainguinal bypasses with vein conduit (all-autogenous policy). Long-term results should not be sacrificed for the sake of expediency at the initial operation. Saphenous vein performs well in the reversed,[50-54] nonreversed,[55] and in situ[56-64] configurations; the technique chosen is dictated primarily by conduit availability, anatomic considerations, and surgeon preference and experience.

OPERATIVE PLANNING

Operative planning for infrainguinal bypass involves the most complex decision making a vascular surgeon is called on to provide. More than any other operation, infrainguinal bypass taxes one's ingenuity, and requires the surgeon to anticipate and carefully consider numerous alternatives and potential complications both during preoperative evaluation and in the conduct of the reconstruction itself. Foremost, the major anatomic lesions and their hemodynamic significance must be identified.[65-67]

Concomitant Inflow Disease

Adequate inflow should be ensured before commencing with infrainguinal bypass. Selected inflow lesions can be treated either percutaneously in advance, at the time of preoperative diagnostic arteriography, or at the same operative sitting (hybrid procedure). Iliac artery lesions of hemodynamic significance should be addressed in nearly all claudicants before proceeding with infrainguinal bypass. For patients with CLTI, an iliac lesion with a resting gradient of less than 5 to 10 mm Hg may be acceptable if the pulse and Doppler waveform at the selected inflow site (e.g., femoral artery) are normal. In patients with claudication or CLTI presenting with rest pain alone in the absence of tissue loss (WIfI: W0, I3, fI 0), an isolated iliac angioplasty without concomitant infrainguinal bypass may suffice if the iliac lesion is of sufficient hemodynamic importance. In such patients with tandem lesions, the profunda-popliteal collateral index may be helpful in predicting whether an inflow procedure alone will be sufficient to alleviate the patient's symptoms.[65] An index greater than 0.25 indicates a large pressure gradient across the knee joint and suggests that inflow disease correction and profundaplasty alone are unlikely to be adequate.[68-70]

Proximal Anastomotic Site

Before operation, the surgeon must define the inflow source, which need not be the CFA. There is abundant evidence that originating shorter bypasses from the deep femoral, superficial femoral, popliteal, or, in rare cases, one of the tibial arteries results in patency rates equivalent to those achieved when the CFA serves as the bypass origin. Short bypasses are frequently useful in patients with diabetes mellitus and primary infrapopliteal arterial occlusive disease as well as in individuals with limited available vein conduit who present with failure of a previous reconstruction. On the basis of hemodynamic data and anatomic imaging, the surgeon should commence the operation with the optimal inflow site in mind. However, if unanticipated arterial disease is identified or vein quality and length are worse than anticipated once the operation is under way, the surgeon should have alternative bypass origins in mind that can be used to shorten the bypass length without compromising hemodynamics. If there is uncertainty about the appropriateness of the inflow site at exploration, its hemodynamic suitability can be assessed by direct intraarterial pressure measurements that can be compared with the transduced radial artery pressure. A resting gradient exceeding 10 mm Hg is significant, as is a drop in pressure exceeding 15% after the administration of intraarterial papaverine.[66,67,71] If a significant gradient is identified at the selected inflow site, a more proximal inflow site above the culprit lesion should be selected, or the responsible lesion should be addressed by local endarterectomy or angioplasty. This problem occasionally arises with iliac or common femoral lesions whose hemodynamic significance was not appreciated at the time of preoperative arteriography, particularly lesions consisting primarily of posterior plaque that may have been masked if appropriate oblique projections were not obtained.

Associated Femoral Endarterectomy

Whenever the CFA is used as the site of origin for bypass, significant occlusive disease involving the origin and proximal deep femoral artery should usually be addressed concomitantly. The endarterectomy often begins in the CFA. After the division of veins that cross the anterior surface of the deep femoral artery, the femoral arteriotomy is carried out beyond the posterior tongue of disease that extends a variable distance down the deep femoral artery, usually at least to its first or second portion. Tacking sutures may or may not be needed at the distal endpoint. The arteriotomy can be closed with a vein patch or a segment of endarterectomized SFA. This patch can then be opened longitudinally to serve as the origin for the infrainguinal bypass (modified Linton's patch technique; Fig. 109.3). Alternatively, if the vein caliber is excellent (>4 mm), a longer venotomy can be made in the vein conduit, which then serves simultaneously as a profundaplasty patch and the bypass origin; this technique should not be used if the arterial wall is markedly thickened or if the caliber of either the native donor artery or the vein conduit is small to avoid compromising the origin of the vein graft at the proximal anastomotic heel. Incorporation of a venous

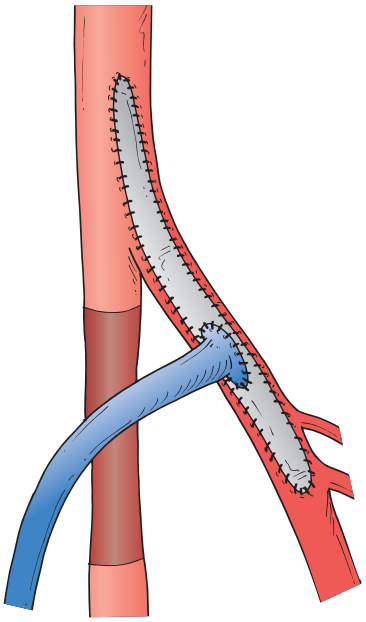

Figure 109.3 Linton's vein patch technique after endarterectomy of the distal common and proximal deep femoral arteries, with anastomosis of the reversed vein graft to the patch.

side branch as part of the anastomotic heel is another useful technique when the donor arterial wall is thick or there is a caliber mismatch between the donor artery and the vein bypass conduit (Fig. 109.4). Correction of significant deep femoral disease at the time of infrainguinal bypass is clinically important; should the bypass ever fail, adequate deep femoral artery perfusion may prevent the development of severe, recurrent limb ischemia.

Distal Anastomotic Site

Although inflow artery selection is generally straightforward, outflow site selection frequently requires greater judgment. The general principle of infrainguinal reconstruction is to bypass all hemodynamically significant disease and to insert the bypass into the most proximal limb artery that has at least one continuous runoff artery to the foot. Thus, if the popliteal artery reconstitutes distal to an SFA occlusion and at least one tibial or peroneal artery is in continuity with the foot, the popliteal artery would be selected as the outflow site. It is possible, however, and sometimes desirable to bypass to an isolated or so-called blind popliteal segment.

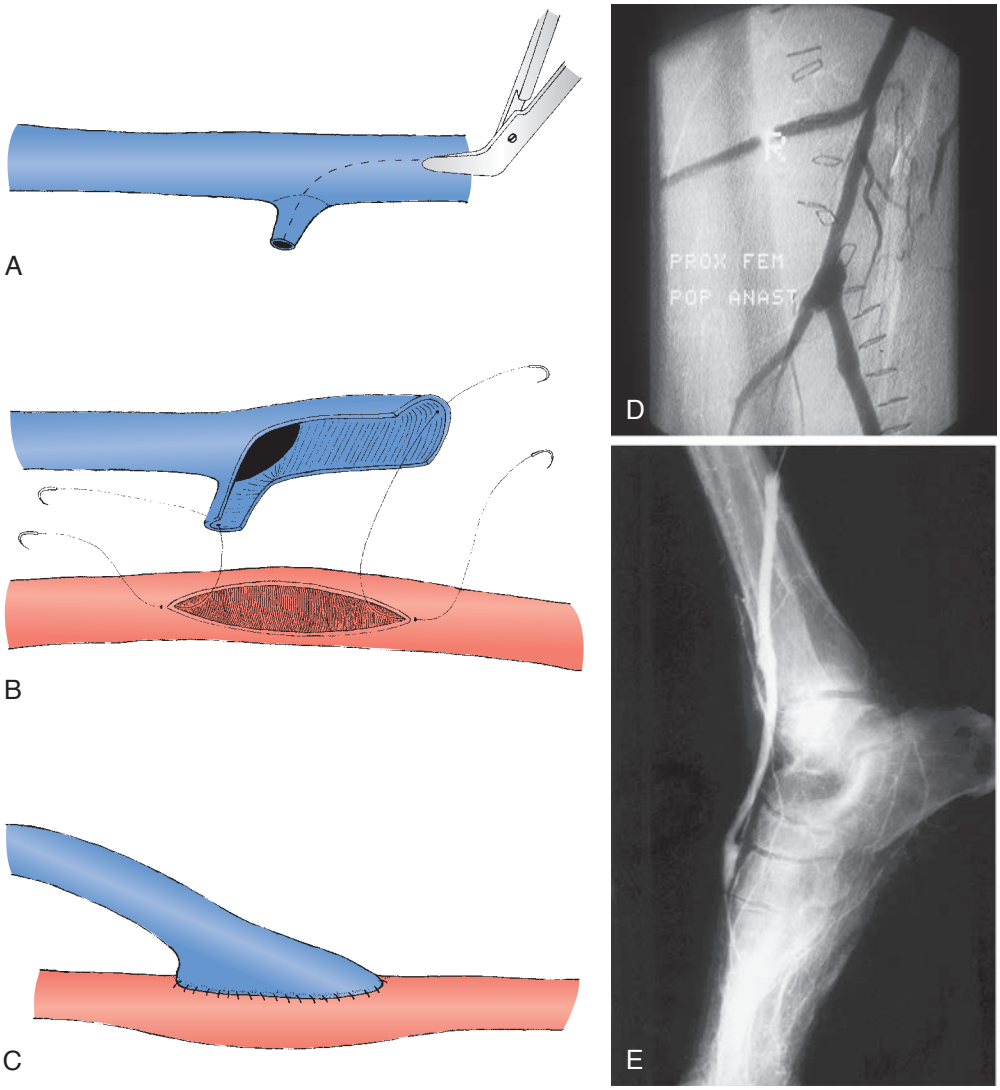

Figure 109.4 The venotomy through the reversed vein is extended through a suitable side branch (A) and anastomosed to the inflow artery (B and C) to avoid anastomotic stenosis at the graft heel.[37,72] This technique can be used at either the proximal anastomosis (D) or the distal anastomosis (E) and is useful when the vein caliber is small or the arterial wall is thickened.

Isolated Popliteal Target

An isolated popliteal artery is defined as a patent popliteal artery segment at least 5 cm long but with only geniculate collaterals and no major distal tibial or peroneal runoff artery in direct continuity with the foot. Such bypasses function surprisingly well and are especially useful in patients with limited vein availability.[73-78] They may also be more useful in patients with claudication or rest pain than in those with frank tissue necrosis, for whom anything less than providing pulsatile flow directly to the foot may be insufficient for healing. In the presence of tissue loss, I prefer bypass to an artery in direct continuity with the foot. Five-year assisted primary or secondary patency rates of 50% to 74% have been reported for such blind-segment popliteal bypasses.[76] Successful bypasses to isolated tibial artery segments have also been reported.[74]

Tibial, Peroneal, and Pedal Targets

Although most claudicants require only femoropopliteal bypass, a high proportion of patients with CLTI require tibial or pedal bypass. In general, the most proximal segment of tibial or peroneal artery that is continuous with the foot should be chosen as the outflow site. Thus, a patent anterior tibial or posterior tibial artery in direct continuity with the foot and pedal arch would be chosen over the peroneal artery as an outflow site if suitable vein length is available. There is still some controversy about whether one should choose the proximal or mid peroneal artery or a patent pedal artery for patients with tissue loss.[79] Most authors have found no adverse effects on graft patency or limb salvage for peroneal bypasses compared with tibial or pedal bypasses,[80-82] but Pomposelli and others have made a strong case for pedal bypass,[36] particularly in diabetic patients with tissue loss.[83] They emphasize the importance of restoring a pedal pulse to maximize forefoot reperfusion. The pedal arteries are also more superficial and more easily exposed than the anatomically disadvantaged, deeply located peroneal artery. If the bypass must originate in the groin and the proximal or mid peroneal artery is of good quality on arteriography and has abundant collaterals with the foot (see Fig. 109.2), I generally perform a shorter bypass to the peroneal artery, especially if vein conduit length is a limiting factor. If the peroneal artery is diseased or does not appear to collateralize well with the foot, I preferentially bypass to the foot or ankle and splice vein if required to obtain sufficient length. I prefer dorsal pedal or paramalleolar posterior tibial–plantar artery insertion sites for short bypasses originating from the popliteal artery in diabetic patients with tissue loss.[84] Shortening the bypass in such patients allows one to optimize vein conduit quality, and the choice of an inframalleolar target artery maximizes forefoot perfusion.

OPERATIVE EXPOSURES

Standard Anterior Approach to the Common Femoral and Profunda Femoris Arteries

Thorough knowledge of anatomy and facility with multiple surgical exposures are critical to the success of infrainguinal bypass.[85] The standard approach to the CFA and the profunda femoris artery (PFA) is provided by a vertical incision overlying the CFA. This anterior approach allows complete exposure and mobilization of the CFA and its bifurcation; more proximal exposure can be obtained by dividing the recurrent portion of the inguinal ligament or the entire ligament (Peter Martin incision). Distal extension allows exposure of the PFA. Division of the lateral femoral circumflex vein offers access to the proximal PFA; careful progressive division of numerous crossing veins allows extensive exposure of the PFA. In selected patients, alternative exposures have been described.

Alternative Approaches to the Profunda Femoris Artery

If previous infection or scarring from multiple previous reconstructions makes standard exposure difficult and if there are no significant occlusive lesions in the CFA or proximal PFA, the mid or distal PFA can be approached laterally, anteromedially, or posteromedially (Fig. 109.5).[74,86-89] The lateral approach is the most useful for infrainguinal bypass. The incision is placed in the upper thigh lateral to the sartorius muscle. The sartorius and SFA are retracted medially. The raphe between the adductor longus and vastus medialis is incised to expose the PFA. This approach is useful when vein conduit length is limited or femoral triangle scarring is prohibitive. The surgeon must be certain that there are no hemodynamically significant lesions proximal to the PFA if this approach is used. With these caveats in mind, use of the PFA origin for distal bypass does not compromise long-term patency.[88,89] Similarly, the SFA[90] and popliteal artery[88-91] can be used as inflow source in carefully selected patients without compromising graft patency.

Exposures of the Popliteal and Tibioperoneal Arteries

The standard exposures of the above-popliteal and below-knee arteries are through medial leg incisions, usually made by deepening the saphenectomy incision. Lateral approaches to these vessels are occasionally useful and are well described elsewhere.[91] The posterior tibial and proximal to mid peroneal arteries are usually approached medially. The distal third of the peroneal artery is most expeditiously exposed by means of a lateral leg incision directly over the distal fibula. A short segment of fibula is carefully removed to expose the distal peroneal artery immediately beneath.

Posterior exposures of the popliteal, posterior tibial, and peroneal arteries are sometimes useful (Fig. 109.6).[92,93] Diabetic patients frequently have relatively normal inflow to the popliteal trifurcation. If the inflow site is the below-knee popliteal artery and the most appropriate target artery is the distal posterior tibial or distal peroneal artery, and if the small saphenous vein is of good quality on duplex imaging, one can perform the entire operation with the patient in a prone position through a posterior approach. These approaches have been well described by Ouriel[93] and should be considered not only in selected reoperative situations (e.g., failed bypass through a medial approach), but also if conduit length is limited and ipsilateral

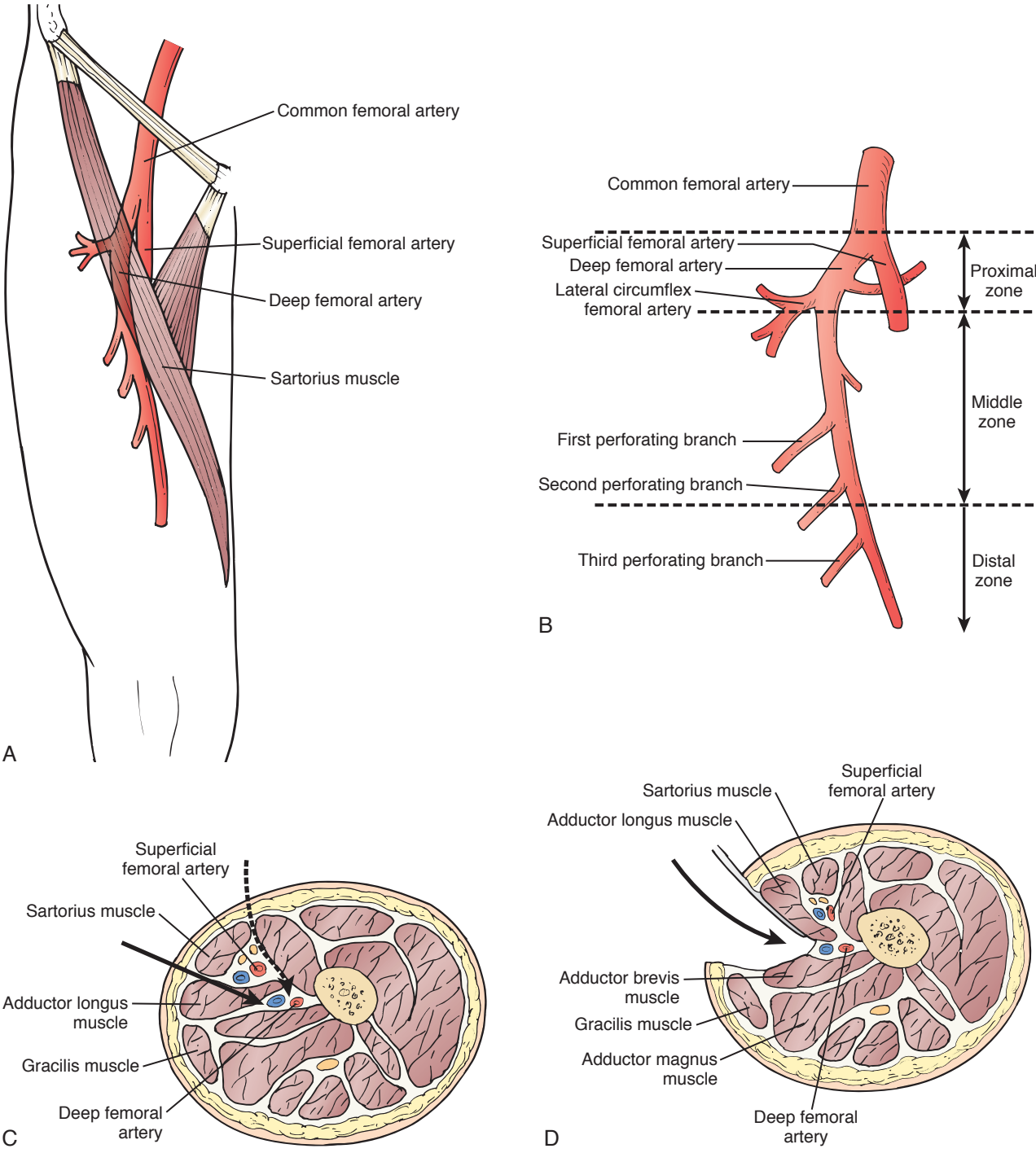

Figure 109.5 Alternative approaches to the distal deep femoral artery[88] are useful for reoperative femorodistal bypass and when it is desirable to shorten the bypass because of limited length of vein conduit.[89] (A) Location of the deep femoral artery. Note the surface landmarks used to identify its course. (B) The deep femoral artery can be divided into three zones: proximal, middle, and distal. (C) Transverse section of the thigh (viewed from above) shows the plane of dissection when the anteromedial approach *(solid arrow)* is used. Alternatively, the deep femoral artery can be approached through an even more anterior route *(dashed arrow)* by making an incision along the lateral border of the sartorius and retracting this muscle and the superficial femoral neurovascular bundle medially to reach the distal deep femoral artery. (D) Posterior approach to the distal deep femoral artery. Note the fascial plane and structures separating the deep femoral artery from superficial femoral vascular structures and isolating it from the subsartorial canal.

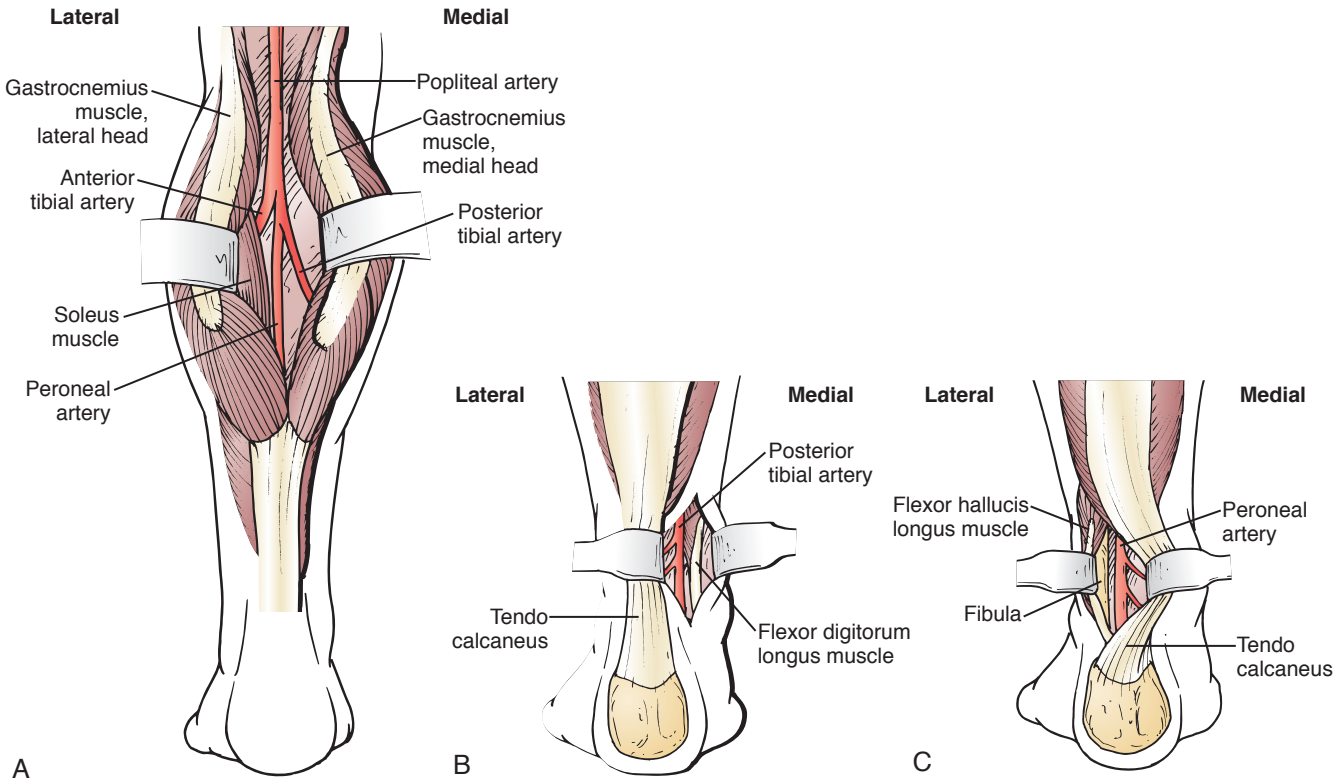

Figure 109.6 Posterior exposures.[95] (A) Exposure of the popliteal and proximal crural arteries through a posterior approach. The two heads of the gastrocnemius muscle are separated, and the soleus muscle is lysed from its tibial origin. (B) Exposure of the posterior tibial artery through a posterior approach. The tendo calcaneus is retracted laterally. The flexor digitorum longus muscle is reflected medially in the lower portion of the calf because the artery lies posterior to the lateral border of this muscle near the level of the malleoli. (C) Exposure of the peroneal artery through a posterior approach. The tendo calcaneus is retracted medially and the flexor hallucis longus muscle is reflected laterally to expose the artery in the groove next to the fibula.

SSV is unavailable. Commitment to an all-autogenous bypass approach requires ingenuity and familiarity with numerous anatomic exposures and techniques to allow shortening of the bypass or to permit operation in a virgin field that is unscarred by previous operations. When such distal origin bypass grafts are used, a pneumatic tourniquet instead of vascular Silastic loops or clamps is occasionally useful to circumvent severe distal arterial calcification.[94] A thorough working knowledge of alternative exposures and the occasional use of the pneumatic tourniquet are of great benefit in performing reoperative bypass.

CHOICE OF CONDUIT

Autogenous conduit options for infrainguinal bypass include ipsilateral and contralateral GSV,[96] small saphenous vein,[97,98] femoral vein,[99] arm (basilic and cephalic) vein,[100-105] endarterectomized segments of the SFA,[106] cryopreserved vein,[107-109] and radial artery.[110,111] Prosthetic options include Dacron, heparin-bonded Dacron, human umbilical vein, polytetrafluoroethylene (PTFE) with and without a distal cuff, and, most recently, expanded PTFE (ePTFE) covalently bonded with heparin. In my group's reported 10-year experience, we performed 93% of infrainguinal bypasses with all-autogenous conduits.[112]

Autogenous Grafts

The preferred conduit is the GSV as it outperforms all other conduit choices. If the ipsilateral GSV is absent, I do not hesitate to harvest the contralateral GSV and see no merit in saving this vein for possible use later.[96] Numerous reports suggest that the contralateral GSV is subsequently needed in no more than 20% to 25% of patients. I therefore advocate using it when necessary and performing a more difficult alternative vein reconstruction at a later time in those relatively few patients who require it. Exceptions occur whenever the contralateral limb is already ischemic, as manifested by severe claudication, rest pain, or ischemic ulceration. If the contralateral limb is asymptomatic and the ankle-brachial index exceeds 0.6, I have experienced no significant wound healing complications from harvesting the GSV from the groin to the midcalf level. This approach usually allows the bypass to be performed with one segment of GSV and obviates the need to harvest arm vein and splice veins. Other groups prefer to harvest arm vein if the ipsilateral GSV is unavailable, preserving the contralateral GSV for later use.[100,113]

Alternative veins are used when the GSV is unavailable or of insufficient length.[114] Duplex mapping is useful to identify

suitable vein sources. The small saphenous vein is suitable if the proposed bypass is relatively short. It is possible to perform a common femoral–to–above-knee popliteal bypass or a PFA–to–below-knee popliteal bypass with one complete segment of saphenous vein harvested from the ankle to the knee. If a longer bypass with spliced vein is necessary, I prefer to use arm vein because it is less awkward to harvest. LoGerfo et al.[115] and Holzenbein et al.[104] described novel techniques of harvesting the upper arm basilic, median cubital, and cephalic veins in continuity with valve lysis of the basilic segment and use of the cephalic segment in a reversed configuration to provide a relatively long, unspliced autogenous conduit. The femoropopliteal deep vein is occasionally useful for shorter bypasses but is large in caliber and more difficult to harvest; arm vein is therefore generally preferred. Treiman et al.[111] reported the use of the radial artery as a bypass conduit in selected patients requiring short infrageniculate bypasses, with good early results. Cryopreserved vein grafts are expensive and have not performed well in clinical practice[107,108]; they may serve a niche role when revascularization is required after the removal of an infected bypass graft and autogenous vein is unavailable to create a new bypass through clean tissue planes.[108]

Prosthetic Grafts

PTFE is the most commonly used prosthetic conduit for infrainguinal bypass, although reports suggest that in the above-knee position, it is not superior to Dacron.[116-118] A prospective randomized trial from the United Kingdom reported by Devine et al.[119] suggested that heparin-bonded Dacron was superior to PTFE for above-knee popliteal bypasses. The 3-year primary patency for heparin-bonded Dacron was 55% compared with 42% for PTFE ($P < .044$). Both of these patency rates are inferior to those of GSV, however, and the early apparent advantage of heparin-bonded Dacron over PTFE disappeared with longer follow-up.[120]

Vein Cuffs

For bypasses that insert below the knee, the addition of a vein cuff confers a significant patency advantage (52% patency at 2 years for PTFE with vein cuff vs. 29% for PTFE with no cuff) and also improves limb salvage (84% vs. 62%; $P < .03$).[121] My experience and that of others suggests that a distal vein cuff, patch or collar improves 2- to 3-year patency for infrageniculate bypass when PTFE is required.[122-126] Nevertheless, the results are still inferior to those of vein bypasses, even when alternative veins are used; these data emphasize the validity of the all-autogenous policy. If vein is truly limited, however, PTFE is an acceptable choice, and available data suggest that distal anastomotic modification with autogenous tissue is a worthwhile adjunct. The only prospective randomized clinical trial used a Miller cuff (Fig. 109.7).[121] A distal Taylor patch (Fig. 109.8)[122,124] and the St. Mary's boot (Fig. 109.9)[126] may yield equivalent results. Neville et al.[128,129] reported an alternative PTFE adjunct consisting of anastomosis of a PTFE graft to an infrageniculate artery using a vein patch, analogous to the technique originally described by Linton. At least in their hands, this adjunct seems to work as well as a Miller cuff or Taylor patch. However, the only randomized prospective trial of such adjuncts used the Miller cuff, and this trial has not been repeated to my knowledge.

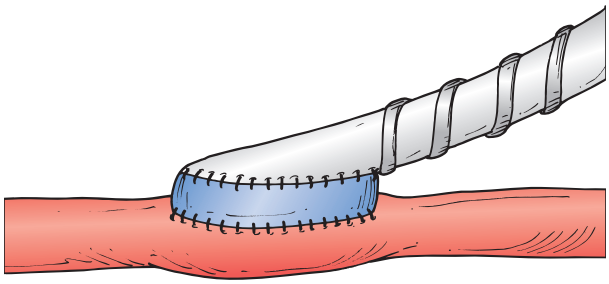

Figure 109.7 The Miller cuff technique[123,127] improved the patency of below-knee popliteal and tibial polytetrafluoroethylene bypass grafts when used as a distal anastomotic adjunct in a controlled randomized clinical trial.[121]

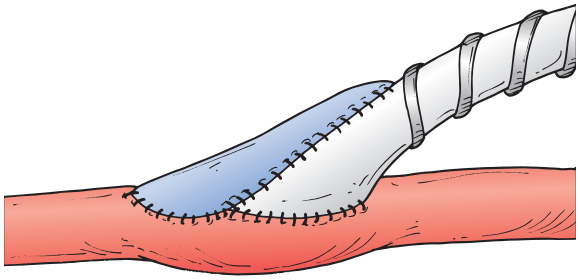

Figure 109.8 The Taylor patch technique can improve the patency of infrageniculate polytetrafluoroethylene bypass grafts.[122,124]

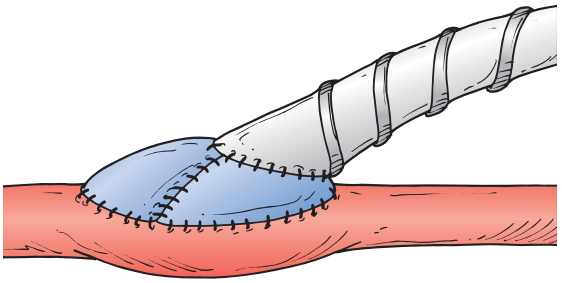

Figure 109.9 The St. Mary's boot or prosthetic venous collar technique[126] combines the attributes of the Taylor patch and the Miller cuff.

Human Umbilical Vein and Adjunctive Arteriovenous Fistula

Human umbilical vein is less commonly used than PTFE, primarily because it is thicker and more cumbersome to handle and due to concerns about subsequent aneurysmal degeneration.[130] Dardik et al.[131] reported excellent results using human umbilical vein with an adjunctive distal arteriovenous fistula to promote increased graft flow velocity; there are no prospective trials comparing this technique with alternative prosthetic conduits, such as PTFE. A single prospective trial did not demonstrate any benefit of the addition of an arteriovenous fistula to femoral-infrapopliteal bypass with vein cuff.[132]

Heparin-Bonded Polytetrafluoroethylene

The most recent addition to the inventory of prosthetic infrainguinal bypass conduits is ePTFE to which heparin has been covalently bonded. The commercially available product was originally called Carmeda BioActive Surface (CBAS).[133] Preclinical studies suggest that biologically active heparin has been successfully covalently bonded to ePTFE without causing systemic anticoagulative effects.[134] The drug is biologically active, at least in baboons and dogs, for up to 12 weeks.[135] In animal models of thromboresistance (short 3- and 4-mm grafts), CBAS appears to prevent early ePTFE graft thrombosis; this effect may persist up to 180 days, although not as strikingly. It also appears to reduce early platelet and fibrin deposition in animal models.

There is no proof, however, that these experimental findings will translate into improved prosthetic graft patency in humans. The five published reports of CBAS for peripheral infrainguinal bypass suffer from major flaws, including lack of randomization, lack of control groups, small numbers of patients, selection bias, large numbers of patients with relatively prosthetic-friendly above-knee popliteal insertion sites, lack of intermediate follow-up (beyond 2 years), and flawed or unreliable life tables.[133,136-139] In two of these five series, anastomotic adjuncts such as patches were used in addition to CBAS grafts, further confounding interpretation. In addition, aggressive combination antiplatelet therapy (oral and low-molecular-weight heparin) was used by nearly all the authors; this combination is not routinely used in North America.

If one assumes that there is no patient overlap between the two studies from the same center (an assumption that may well be false),[136,139] the published human experience with CBAS infrainguinal grafts consists of 356 grafts with the following insertion site distribution: 142 (41%) above-knee popliteal, 115 (33.5%) below-knee popliteal, 75 (21.8%) femorocrural or tibial, and 24 indeterminate (one study does not specify target arteries).[140] The estimated number of patients available with documented follow-up in all five human clinical CBAS studies combined is as follows: 95 above-knee popliteal, 45 below-knee popliteal, and 25 femorocrural at 1 year; and 48 above-knee popliteal, 16 below-knee popliteal, and 9 femorocrural at 2 years. The data and follow-up length are thus insufficient to support assertions of improved patency conferred by covalently bonded heparin grafts. Long-term studies of this intriguing bioactive graft are needed to determine whether covalent heparin bonding confers any significant patency benefit. Heparin-induced thrombocytopenia has also been rarely reported with these grafts.

Graft Comparison

Table 109.1 summarizes the available level I data comparing conduit types with outcome.[118-124,132,141-145] Vein is superior to all prosthetic materials, even in the above-knee position.[145-147] The randomized clinical trials comparing human umbilical vein with PTFE have been inconclusive.[143,144,148] The addition of rings to PTFE conferred no benefit in the single prospective randomized clinical trial conducted.[149] Thus, the most prudent recommendation is to use autogenous vein whenever possible for infrainguinal bypass. This dictum holds true not only for primary infrainguinal bypasses but also for reoperations, in which vein conduits outperform all other options.[150,151] For long bypasses, ipsilateral GSV, contralateral GSV, and spliced vein are employed in decreasing order of preference. If only 5 to 15 cm of extra length is required and a more distal origin site is not feasible, eversion endarterectomy of a proximal segment

TABLE 109.1 Patency of Above-Knee Popliteal Bypass and Below-Knee Popliteal or Infrapopliteal Bypass Grafts

Graft Type and Study	PATENCY (%)					*P* Value
	1-Year	2-Year	3-Year	4-Year	5-Year	
Above-Knee Popliteal Bypass: Dacron Versus Polytetrafluoroethylene						
Devine et al.[120] (*n* = 209)						.055
Heparin-bonded Dacron	71		54	46		
PTFE	62		44	35		
Post et al.[117] (*n* = 194)						NS
Dacron			64			
PTFE			61			
Green et al.[116] (*n* = 240)						NS
Dacron					43	
PTFE					45	
Robinson et al.[118] (*n* = 108)						NS
Dacron	70	56	47			
PTFE	72	52	52			

TABLE 109.1 Patency of Above-Knee Popliteal Bypass and Below-Knee Popliteal or Infrapopliteal Bypass Grafts—cont'd

Graft Type and Study	PATENCY (%) 1-Year	2-Year	3-Year	4-Year	5-Year	*P* Value
Above-Knee Popliteal Bypass: Huv Versus Polytetrafluoroethylene						
McCollum et al.[144] (*n* = 191)						NS (.27)
HUV	68	63	57			
PTFE	61	56	48			
Aalders et al.[143] (*n* = 96)						NS
HUV	90	67[a]			71.4[b]	
PTFE	80	63			38.7	
Eickhoff et al.[148] (*n* = 105)						.001
HUV (below knee)	74			42		
PTFE	53			22		
PTFE: ringed versus nonringed						
Gupta et al.[149] (*n* = 122; above- and below-knee popliteal bypass)						NS
Ringed			74			
Nonringed			68			
Polytetrafluoroethylene: Vein Cuff Versus No Cuff						
Stonebridge et al.[121] (*n* = 261)						
Above-knee popliteal						NS
Cuff	80	72				
No cuff	84	70				
Below-knee popliteal						.03
Cuff	80	52				
No cuff	65	29				
Above-Knee Popliteal Bypass: Vein Versus Prosthetic (Polytetrafluoroethylene or Human Umbilical Vein)						
Klinkert et al.[145] (*n* = 151)						.035
Vein					76	
PTFE					52	
Johnson et al.[147] (*n* = 752)						.01
Vein		81			73	
HUV		70			53	
PTFE		69			39	
Tilanus et al.[152] (*n* = 49)						<.001
Vein					70	
PTFE					37	
Veith et al.[153] (*n* = 845)						
Above-knee popliteal (*n* = 176)						>.25
Vein				61		
PTFE				38		
Below-knee popliteal (*n* = 153)						<.05
Vein				76		
PTFE				54		
Infrapopliteal (*n* = 204)						<.001
Vein				49		
PTFE				12		

HUV, Human umbilical vein; *NS*, not significant; *PTFE*, polytetrafluoroethylene.
[a]Patency determined at 18 months.
[b]Patency determined at 6 years.

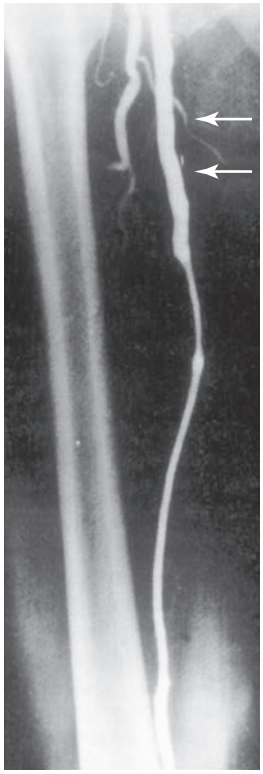

Figure 109.10 When vein length is limited, an eversion endarterectomy of a proximal superficial femoral artery segment *(arrows)* can be performed.[106] The everted arterial segment is anastomosed to the available vein graft to create an all-autogenous conduit of sufficient length for the required bypass to be performed.

of the SFA with anastomosis to the available vein conduit is a useful technique that avoids the harvesting and splicing of additional vein (Fig. 109.10).[106] For shorter bypasses, arm vein or small saphenous vein is effective, with the latter being especially useful when a posterior approach is applicable.

If vein is truly unavailable after a thorough search, PTFE, human umbilical vein, or Dacron are reasonable options for above-knee bypass. The initially favorable results with heparin-bonded Dacron were not confirmed during longer follow-up,[119,120] so there appears to be no advantage to heparin-bonded Dacron conduit for above-knee bypass. A prospective randomized trial of human umbilical vein versus heparin-bonded Dacron showed no difference in patency in the above-knee popliteal position,[154] and published trials of PTFE versus Dacron have shown no clear difference.[116-118,120] For infrageniculate insertion sites, PTFE with distal anastomotic modification (cuff, boot, or patch) is recommended if vein is unavailable. There is inadequate evidence to state a preference in terms of standard ePTFE versus heparin-bonded or carbon-coated PTFE. The single prospective randomized trial of standard PTFE versus carbon-impregnated PTFE for infrageniculate bypass showed approximately 30% primary patency, with no difference between groups at 3 years.[155]

BYPASS TECHNIQUE

Reversed, nonreversed, and in situ conduits appear to work equally well. The choice is primarily one of surgeon preference. Arm veins pose special challenges. Regardless of which type of conduit is used, meticulous technique and gentle vein handling are critical.

Reversed Vein Bypass

Harvest of the GSV begins with a groin incision two finger-breadths lateral to the pubic tubercle. Preoperative duplex vein mapping and drawing of a line with indelible ink directly over the vein conduit assist in following the course of the vein and avoiding the creation of skin flaps. The saphenofemoral junction at the fossa ovalis should be identified to ensure that the true GSV rather than an anterior or large posteromedial branch is being exposed. Once the main trunk is identified, the incision is extended distally, directly over the vein, with a No. 10 blade or Cooley scissors. I frequently leave short skin bridges, especially in the thigh and about the knee level, to avoid the creation of long skin flaps. If exposure or branch ligation is difficult or if the course of the main vein is unclear, the skin directly over the vein is divided. The periadventitial tissue, not the vein wall itself, is grasped gently to avoid damage to the conduit. Side branches are meticulously ligated with 3-0 or 4-0 silk and divided. Leaving a short stump is preferable to placing a ligature too close to the main trunk and compromising the lumen. When first exposed, the vein should be soft and blue. Sclerotic segments are whitish and rubbery. Vein spasm can turn a blue vein white and should be treated with local papaverine or lidocaine irrigation.

Sufficient length of vein should be harvested for the proposed bypass to be performed. If adequate vein of good quality is not available, alternative inflow or outflow arteries should be considered to shorten the bypass; otherwise, alternative vein must be harvested from another site and spliced on a back table. Vein quality is extremely important, and segments less than 3 mm should not be used. Once an adequate length of vein is identified, it is ligated proximally and distally and prepared on the back table by a senior surgeon while the rest of the team exposes the inflow and outflow arteries.

The vein is cannulated with a 3-mm olive or Marks tip needle and gently distended with chilled autologous blood (50-60 mL) to which 1000 units of heparin and 60 mg of papaverine have been added. With gentle irrigation, the vein should flow readily, distend smoothly, and be free of fibrotic and nondistensible segments. Missed or small avulsed branches are repaired with longitudinally oriented 6-0 or 7-0 Prolene sutures on a BV-1 or BV-175 needle. Overly forceful distention of the conduit should be avoided because it damages the endothelium. The entire length of the conduit is inspected to ensure that there are no sclerotic areas, no areas of persistent spasm, no strictures at branch ligature sites, and no bleeding branches. Once preparation is complete, the distal end of the vein is ligated with 3-0 silk, leaving the suture ends long; the prepared conduit is stored in chilled blood until the graft is ready to be tunneled. Proper intraoperative planning should result in minimal vein storage time. Many believe that autologous blood, rather than saline, better preserves graft endothelium.[156]

Proper graft tunneling of reversed grafts is important. For primary leg bypasses with GSV, I prefer to tunnel the graft in a deep anatomic plane to avoid kinking and graft exposure should wound complications ensue. For above-knee popliteal bypasses, a subsartorial plane is frequently easier than a true anatomic tunnel. A large-caliber hollow-bore metal tunneler with a removable obturator is used. For below-knee popliteal and proximal to mid posterior tibial or peroneal bypasses, I generally prefer an anatomic tunnel between the two heads of the gastrocnemius for initial bypasses. It is often wise to tunnel reoperative bypasses subcutaneously to avoid scarring and render graft surveillance and revision easier. This approach is advantageous because the alternative vein conduits often used in these circumstances are at higher risk for the development of graft stenosis. Bypasses to the anterior tibial artery can be tunneled through the interosseous membrane (anatomic) or a lateral subcutaneous plane.

Arm Vein Harvest and Vein Splicing

If leg vein length is inadequate or unavailable or if additional conduit is required, arm vein should be used. Arm veins, especially the basilic vein, are more fragile and demanding to harvest. Branches should be carefully identified and ligated a short distance away from their junctions with the main trunk to avoid troublesome bleeding from an injury at the crotch between the branch and the parent vein. Large branches are suture or doubly ligated. The initial distention of the vein is performed with heparinized saline and papaverine because defects in thinner walled arm veins are more difficult to visualize and repair if blood is used as the initial irrigant. Once major leaks have been controlled, the vein graft is prepared and stored in chilled blood as mentioned earlier. It is worth considering that arm veins frequently harbor abnormal segments containing intrinsic lesions such as webs, synechiae, and sclerotic valves. Angioscopy of such high-risk conduits may be a useful adjunct (see later under Angioscopy).

In situ Vein Bypass

In situ bypass can be used successfully in many patients with intact ipsilateral GSVs. Proponents suggest that the vein-artery size match is frequently optimized by this technique.[157] This technique requires the use of a radial cutting blade (Mills valvulotome)[58] or fixed-diameter circumferential blades such as the Hall[59] and LeMaitre valvulotomes to accomplish valve lysis.[62,158] The proximal segment of GSV is initially mobilized in the groin as it would be for reversed vein bypass. The distal GSV is then mobilized in the region of the projected distal arterial anastomosis. The vein may be exposed by an open technique along its entire length, through skip incisions, or endoscopically. After systemic heparinization, the vein is transected below a Satinsky clamp placed at the saphenofemoral junction, and the stump is closed with running 5-0 Prolene suture. The most proximal valve is excised under direct vision with Potts scissors, and the vein is spatulated and sewn end to side to the selected arterial anastomotic site, usually the CFA. Arterial flow is allowed into the vein conduit; if the conduit is of large caliber, a circumferential valvulotome can be inserted from distal to proximal to lyse the valves. Many surgeons prefer to more carefully control valve lysis by progressive serial valvulotomy through large side branches, progressing from proximal to distal. The Mills valvulotome is introduced through side branches; the leaflets are usually just distal to branches and are oriented parallel to the skin. Under arterial pressure, the valve sinuses distend, and the valve leaflets are displaced toward the center of the lumen, where they can be safely engaged by the valvulotome and cut by sharp retraction on the valvulotome under direct visualization. The final valves are lysed from the distal end of the vein. The quality of the vein and the success of lysis are then assessed; flow should be highly pulsatile from the end of the conduit before the distal anastomosis is performed.

After completion of the anastomoses, the quality of pulsation and flow is assessed by palpation and handheld Doppler interrogation. The entire graft should be evaluated from proximal to distal; it can be manually compressed or occluded distal to the Doppler probe. The presence of continuous outflow despite distal graft compression indicates an arteriovenous fistula; these branches should be ligated. With either the reversed or the in situ technique, careful handling of the vein is important. The assurance of adequate valve lysis and the detection of major arteriovenous fistulae can be challenging; the type of completion study used depends on the type, source, and quality of the conduit and surgeon preference.

INTRAOPERATIVE COMPLETION STUDIES

Infrainguinal bypass can be complicated by insufficient or inadequate arterial exposure; inappropriate inflow or target artery selection (Fig. 109.11); intrinsic conduit defects; technical defects associated with clamp injury, local endarterectomy, anastomosis creation (Fig. 109.12), and valve lysis; graft tunneling errors (Fig. 109.13); and coagulation or platelet aggregation abnormalities. The surgeon should strive to avoid these complications but must be prepared to recognize and correct them should they arise. Ignorance is not bliss, and the best opportunity to correct a problem is at the initial operation. Failing to address a significant defect and hoping for the best compromises patient outcome and increases stress on the operating surgeon. "Take-backs" to the operating room for hemorrhage or graft thrombosis are inevitable, but their frequency can be markedly reduced by meticulous technique, prudent decision making, and routine completion studies to ensure a technically optimal result.

There are four options for completion assessment that can be used alone or in combination: distal pulse palpation and Doppler flow assessment, with and without manual compression of the graft[159,160]; completion arteriography[161-163]; intraoperative duplex scanning, with and without papaverine administration[164,165]; and angioscopy.[166-178]

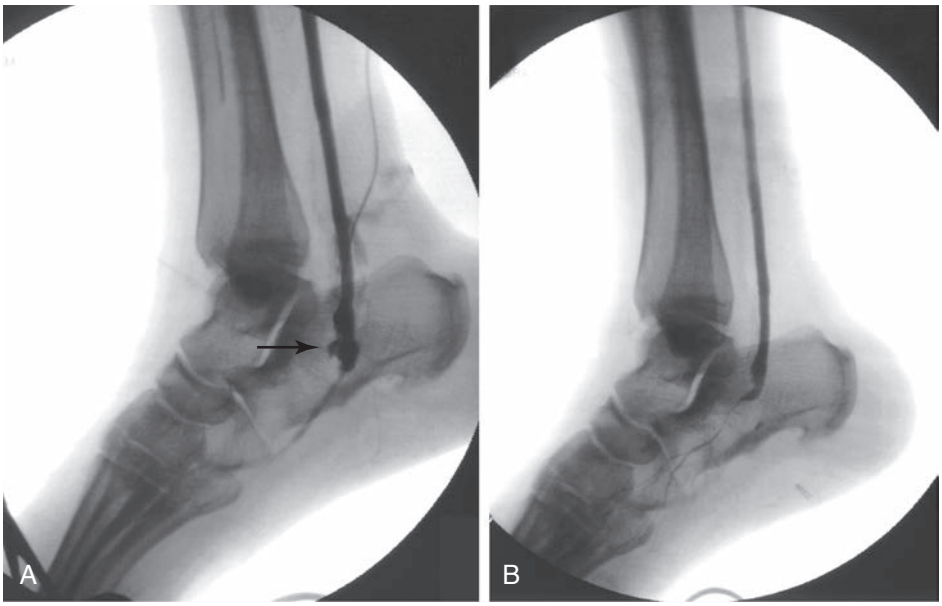

Figure 109.11 (A) Completion arteriography demonstrates poor runoff, with minimal branching of the target plantar artery *(arrow)*. The initial exposure was inadequate, leading to incorrect selection of the target artery (lateral plantar). (B) The anastomosis was relocated to the medial plantar artery, and the graft remains patent 2 years postoperatively.

Doppler Flow Assessment

Doppler flow assessment should always be performed. Restoration of a palpable distal pulse or Doppler flow that clearly diminishes with manual occlusion of the bypass graft documents graft patency. These techniques are sufficiently sensitive to detect only major conduit, technical, or outflow problems, however. Therefore other, more complex techniques should also be employed.

Arteriography

For reversed vein conduits, arteriography is the simplest and most effective completion study. With improved intraoperative imaging capabilities, it has become relatively easy to rapidly evaluate the conduit, tunnel, anastomoses, and outflow for significant graft-threatening lesions with minimal contrast material and little additional time (see Fig. 109.13). Renwick et al.[162] identified defects requiring correction in 27% of infrainguinal bypasses using intraoperative angiography, despite a normal appearance by visual inspection and external pulse palpation. The 2-week primary patency was 100%, compared with 72% in a control group without completion arteriograms. Mills et al.[161] prospectively evaluated 214 consecutive infrainguinal bypass grafts with routine completion angiography and identified significant lesions requiring revision in 8% of grafts, with a higher incidence in tibial than in popliteal reconstructions. The 30-day primary patencies were 99% for femoropopliteal bypasses and 93% for femorodistal grafts. Angiography may not be sufficiently sensitive to detect incomplete valve lysis during the performance of in situ or nonreversed grafts.[173,175]

Duplex Ultrasound

Bandyk et al.[164] Johnson et al.[165] and their colleagues have championed intraoperative duplex scanning after in situ bypasses and reported significant abnormalities requiring correction in 12% of cases. Lesions associated with focal peak systolic velocities exceeding 250 cm/s are repaired. In low-flow grafts without identifiable technical defects, if target artery relocation or graft extension is not possible, consideration is given to either the performance of an adjunctive arteriovenous fistula to augment graft flow velocity or the administration of postoperative anticoagulation. The short-term patency of infrainguinal bypasses with normal findings on intraoperative duplex scanning is superb. Intraoperative graft duplex scanning requires the availability of a machine and a technician, however, and most surgeons are less familiar with this technique and find it cumbersome to use. These issues have prevented its widespread application, although I have found it useful in difficult reoperative cases, particularly when alternative, spliced, or valve-lysed vein segments are used.[179]

Angioscopy

Angioscopy has been employed to evaluate the conduit by many clinical investigators,[166-178] who have used it to evaluate harvested arm vein[168] or as an adjunct to valve lysis to permit in situ bypass with minimal skin incisions.[180-182] Marcaccio et al.[174] analyzed the use of intraoperative angioscopy in a series of 113 arm vein bypasses and identified significant intraluminal disease in 62.8% of cases; previous thrombosis with recanalization (54%) was the most commonly encountered lesion, followed by complex weblike lesions at valve sites or possibly associated with previous venipuncture. Angioscopy was used to correct 95.8% of vein abnormalities judged to be significant and allowed an "upgrade" of the conduit quality. The 1-month patency rate was 95.5% in grafts judged to be normal initially or after repair, compared with only 70% in conduits judged to be of inferior quality even after attempted repair. Wilson et al.[167] reported a similar yield of prognostically important information with intraoperative angioscopic evaluation of conduits. Angioscopy

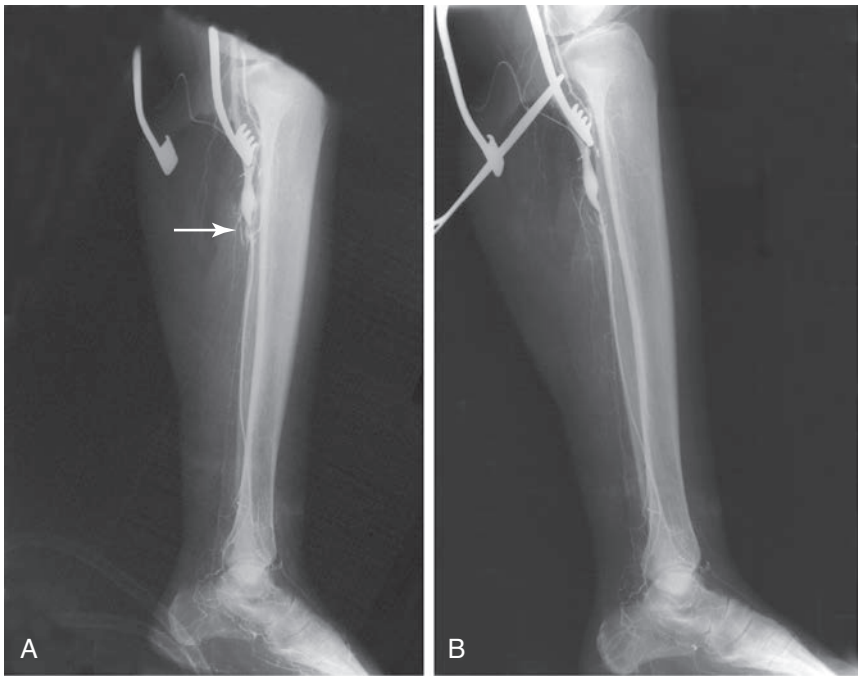

Figure 109.12 (A) Completion arteriography identifies a significant distal anastomotic defect *(arrow)*, despite a good graft pulse and distal continuous wave Doppler signal. (B) The anastomosis was re-explored, the defect was corrected, and the graft is patent at 3 years.

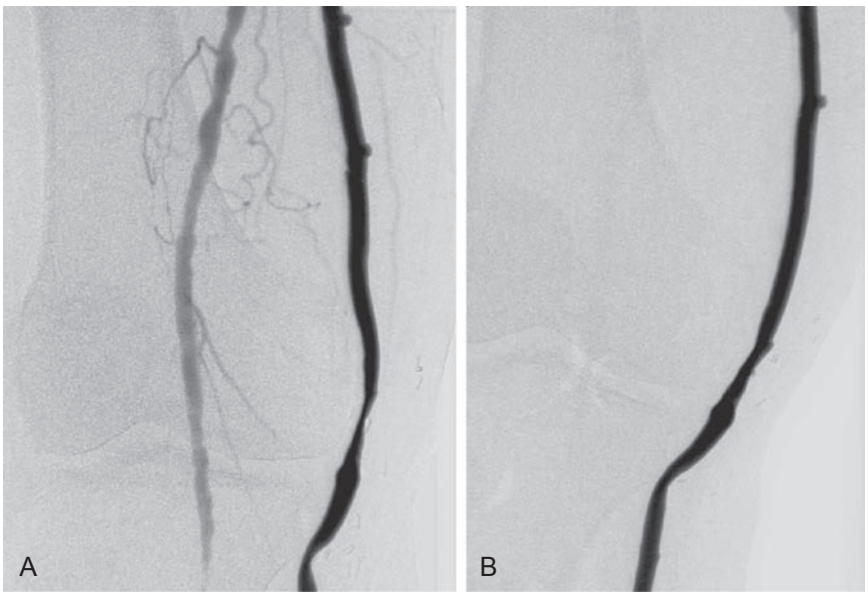

Figure 109.13 (A) Routine completion arteriography identifies an unsuspected site of graft compression in the tunnel, despite a good distal graft pulse and continuous wave Doppler signal. (B) The site was explored, the compression was released, and the graft is patent at 2 years.

thus appears to be most useful for assessing arm vein conduits or ensuring the adequacy of valve lysis for in situ conduits. Wound and vein harvest incisional complications can compromise outcome and prolong hospital stay.[183-187] Several groups have reported the adjunctive use of angioscopy both to assist in the performance of valve lysis and to allow in situ bypass to be performed with minimal skin incisions[171,180-182,187-195]; whether these techniques improve outcome is uncertain.

Some objective assessment of the bypass, its anastomoses, and the outflow is an important component of infrainguinal bypass. I still recommend completion arteriography but recognize that duplex scanning and angioscopy are important adjuncts, especially in higher risk situations and with use of nonreversed or in situ conduits in which complete valve lysis is critical. It seems even more important to perform routine completion studies in an era when the volume of open bypass procedures

has fallen at most centers owing to a paradigm shift toward endovascular therapy.

RESULTS

Outcomes must be reported according to the Society for Vascular Surgery reporting standards.[5-7,196] Graft patency, limb salvage, and mortality are objective endpoints. Somewhat subjective endpoints are durability, functional outcome, and quality of life.

Objective Endpoints

The outcomes of infrainguinal bypass procedures have traditionally been reported solely in terms of graft patency, limb salvage, and patient survival rates. Several factors affect outcome when it is considered in these terms. Conduit type is the major determinant of long-term graft patency, with vein outperforming prostheses for all varieties of infrainguinal bypass. For vein conduits, vein quality[197-199] and caliber[199-201] are the most critical determinants of success. Vein grafts less than 3 to 3.5 mm in diameter are inferior whether they are used in situ or reversed.[200,202,203] GSV is superior to alternative vein sources.[114,202] Reduced graft patency has been attributed to high outflow resistance or poor runoff,[199,204,205] although poor runoff is somewhat difficult to define, and autogenous vein grafts frequently remain patent in the presence of striking outflow disease (Fig. 109.14). Other factors, such as patient age and diabetes, do not appear to adversely affect graft patency, although diabetic patients exhibit prolonged wound healing times.[205] Most investigators agree that the presence of end-stage renal failure is associated with reduced graft patency and increased limb loss and mortality.[206-215] Anesthetic type has not been conclusively shown to influence graft patency or perioperative mortality.[216,217]

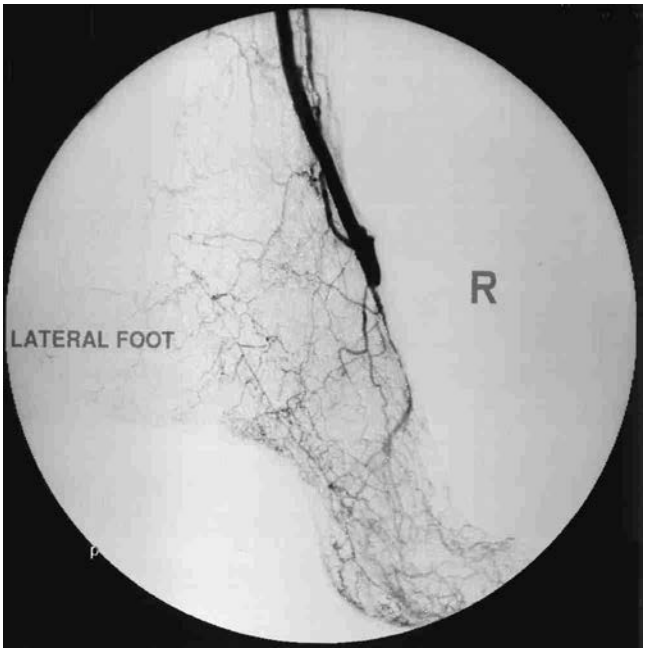

Figure 109.14 Distal view of completion arteriogram after popliteal artery–to–dorsal pedal artery reversed vein bypass in an 82-year-old diabetic man with chronic renal disease and a functioning renal transplant. Despite significant disease of the distal dorsal pedal artery, the patient's toe amputation healed and the graft has remained patent, with normal graft flow velocities, for more than 6 years.

Graft Patency

Patency Definitions

Patency may be primary, assisted primary (most applicable to vein grafts), or secondary. A graft with *primary patency* has been continuously patent without any actions being performed to maintain graft patency, except for treatment of more proximal or distal disease not involving the graft or its anastomoses. Dilations or minor revisions performed for stenoses or other structural defects before occlusion occurs do not constitute exceptions because they are intended to prevent eventual graft failure.[5-7,196] A graft with *assisted primary patency* required an intervention (either percutaneous or open surgical) to maintain patency but never occluded. A graft with *secondary patency* thrombosed but was successfully thrombectomized. Primary patency thus reflects the durability of the initial reconstruction, assisted primary patency reflects the impact of graft surveillance and timely reintervention, and secondary patency reflects the persistence of the surgeon in restoring graft patency after failure. The most meaningful endpoints are thus primary and assisted primary patency.

Comparison of Graft Types

Randomized prospective trials demonstrate equivalence between in situ and reversed vein conduits (Table 109.2).[218-225] The use of these techniques is thus dictated by operative considerations and surgeon preference and experience. Vein is superior to all prostheses, even in the above-knee popliteal position. Expected patency data, based on a review by Dalman[226] and several meta-analyses,[143,206,227-232] are summarized in Tables 109.3 to 109.6 and Figs. 109.15 and 109.16.

Subjective Endpoints

Durability

Choice of initial revascularization approach (endovascular vs. open) and conduit selection (autogenous vs. prosthetic) are likely to affect outcomes, especially in patients in whom durability of the intervention is an important consideration. Recently published data suggest that the durability of the intervention may be important for subsets of patients. In particular, the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial concluded that for patients who lived more than 2 years after randomization, a bypass-first revascularization strategy was associated with a significant increase in subsequent overall survival as well as a trend toward improved amputation-free survival. Recent studies of endovascular and open approaches to patients with CLTI suggest that for WIfI Clinical Stage 4 patients, endovascular therapy has a very high reintervention rate and high wound non-healing rate[233] and at least one publication suggests that the limb salvage rate is higher in these patients with bypass.[234] These data suggest that with proper stratification based on the underlying burden of disease, extent of ischemia,

TABLE 109.2 Patency of Reversed Vein and in situ Bypass Grafts

Series and Graft Type	PATENCY (%) RVG	In situ	*P* Value
Watelet et al.[223]: AK/BK popliteal (*n* = 100 grafts)[a]	88	71	NS
Harris et al.[220]: AK/BK popliteal (*n* = 215 grafts)[a]	77	68	NS
Veterans Administration Cooperative Study Group,[218] 1988 (*n* = 461 grafts)[b]			
BK popliteal	75	78	NS
Infrapopliteal	67	76	NS
Wengerter et al.[225] (*n* = 125 grafts)[c]			
Overall	67	69	NS
<3-mm veins	37	61	NS
Watelet et al.[224] (*n* = 91 grafts)[d]	70.2	64.8	NS

AK, Above knee; *BK*, below knee; *NS*, not significant; *RVG*, reversed vein graft.
[a]Values at 36 months.
[b]Values at 24 months.
[c]Values at 30 months.
[d]Ten-year results.

and depth of the wound as well as with an improved comorbidity index, one could select patients who would benefit more from bypass than from endovascular therapy as the initial revascularization approach.

The BASIL trial clearly demonstrated that patients who received prosthetic grafts for severe limb ischemia (constituting 25% of the surgical group) experienced reduced amputation-free survival compared with those who received vein grafts ($P = .003$).[235] In addition, the BASIL authors observed that patients who underwent bypass surgery after an initial failed angioplasty experienced significantly worse amputation-free survival than did those who underwent bypass first as the initial therapy ($P = .006$), suggesting that there is a real potential adverse impact of the endovascular-first approach for all patients with severe limb ischemia. Others, including the Vascular Surgical Group of New England, have made similar observations. Nolan et al.[236] reviewed 1153 patients who underwent lower extremity bypass from 2003 to 2008. Patients who had undergone a prior ipsilateral-failed percutaneous intervention had significantly higher rates of graft occlusion and major limb amputation at 1 year by multivariate analysis. A detailed investigation of therapy for lower extremity occlusive disease in South Carolina documented a marked increase in the number of procedures required

TABLE 109.3 Patency of Above-Knee Femoropopliteal Grafts

Graft Type	PRIMARY PATENCY (%)[a] 1-Month	6-Month	1-Year	2-Year	3-Year	4-Year
Reversed saphenous vein	99	91	84	82	73	69
Arm vein	99	—	82	65	60	60
Human umbilical vein	95	90	82	82	70	70
Polytetrafluoroethylene	—	89	79	74	66	60

[a]All series published since 1981.

TABLE 109.4 Patency of Below-Knee Femoropopliteal Grafts

Graft and Patency Type	PATENCY (%)[a] 1-Month	6-Month	1-Year	2-Year	3-Year	4-Year
Primary Patency						
Reversed saphenous vein	98	90	84	79	78	77
In situ vein bypass	95	87	80	76	73	68
Secondary Patency						
In situ vein bypass	97	96	96	89	86	81
Arm vein	97	—	83	83	73	70
Human umbilical vein	88	82	77	70	61	60
Polytetrafluoroethylene	96	80	68	61	44	40
Limb Salvage						
Reversed saphenous vein	100	92	90	88	86	75
In situ vein bypass	97	96	94	84	83	—

[a]All series published since 1981.

TABLE 109.5 Patency of Infrapopliteal Grafts

Graft and Patency Type	PATENCY (%)[a]					
	1-Month	6-Month	1-Year	2-Year	3-Year	4-Year
Primary Patency						
Reversed saphenous vein	92	81	77	70	66	62
In situ vein bypass	94	84	82	76	74	68
Secondary Patency						
Reversed saphenous vein	93	89	84	80	78	76
In situ vein bypass	95	90	89	87	84	81
Arm vein	94	—	73	62	58	—
Human umbilical vein	80	65	52	46	40	37
Polytetrafluoroethylene	89	58	46	32	—	21
Limb Salvage						
Reversed saphenous vein	95	88	85	83	82	82
In situ vein bypass	96	—	91	88	83	83
Polytetrafluoroethylene	—	76	68	60	56	48

[a]All series published since 1981.

TABLE 109.6 Patency of Ankle and Below-Ankle Grafts

Graft and Patency Type	PATENCY (%)[a]				
	1-Month	6-Month	1-Year	2-Year	3-Year
Primary Patency					
Reversed saphenous vein	95	85	81	—	—
Secondary Patency					
Reversed saphenous vein	96	90	85	81	76
In situ vein bypass	93	93	92	82	72
Foot salvage	99	94	93	87	84

[a]All series published since 1981.

to obtain similar limb salvage rates coincident with the increase in endovascular therapy during a defined period.[237] Taken together, such data strongly suggest that patients with severe limb ischemia and long-segment atherosclerotic disease who have useable vein, lack severe comorbidities, and have a life expectancy of at least 2 years are likely to be best served with an open surgical approach first with autologous vein.

Functional Outcomes

Whereas graft patency and limb salvage are objective and important endpoints, numerous investigators have recognized that functional outcomes are equally important. Nicoloff et al.[238] emphasized that an ideal outcome—defined by the expectations of a patent graft, healed wound, no need for reoperation, independent living status, and continued ambulation—was extremely difficult to achieve in patients with CLI. Only a small fraction of patients in their report (14.3%) met these basic criteria for success. Golledge et al.[239] from South Australia, using similar criteria, showed that only 22% of patients had an ideal outcome. Abou-Zamzam et al.[240] identified preoperative independence and ambulation as the best predictors of postoperative independence and continued ambulation. These data emphasize the severity of underlying comorbidities in CLI patients and the difficulties encountered in obtaining functional limb salvage.

Goshima et al.[241] from the University of Arizona analyzed a consecutive series of 318 patients undergoing infrainguinal bypass, 72% for CLI. Three nontraditional outcome measures were used to explore outcomes and to define the clinical realities of treating patients with CLI: index limb reoperation rate within 3 months of bypass, hospital readmission rate within 6 months, and wound healing time. Perioperative mortality was less than 1%, mean length of initial hospital stay was 9 days, 30-day graft patency was 97%, and 3-month limb salvage was 97%. Five-year limb salvage in a similar group of patients from the same center was 91%, and the costs of bypass combined with

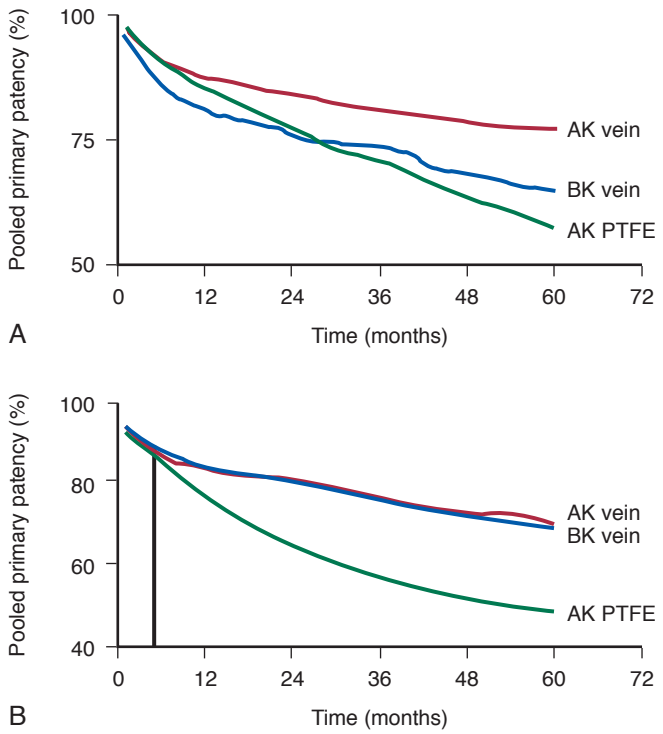

Figure 109.15 (A) Meta-analysis of primary patency in claudicants for above-knee femoropopliteal polytetrafluoroethylene (PTFE) bypass grafts *(green line)*, above-knee femoropopliteal saphenous vein bypass grafts *(red line)*, and below-knee saphenous vein bypass grafts *(blue line)*. (B) Meta-analysis of primary patency in patients with critical ischemia for above-knee femoropopliteal PTFE bypass grafts *(green line)*, above-knee femoropopliteal saphenous vein bypass grafts *(red line)*, and below-knee saphenous vein bypass grafts *(blue line)*. The *vertical line* indicates when above-knee saphenous vein grafts surpassed PTFE grafts.[141] *AK,* Above knee; *BK,* below knee.

graft surveillance and revision for 5 years were equal to or less than those for patients undergoing major limb amputation.[242] However, 49% of patients required at least one reoperation within 3 months, and 50% required readmission to the hospital within 6 months. The cumulative length of stay for all readmissions was 11 days. More than half of CLI patients required more than 3 months of postoperative care to achieve wound healing. The presence of preoperative tissue loss increased the odds of reoperation by 3.1-fold (95% confidence interval, 1.9 to 6.8), whereas ischemic tissue loss, renal failure, and diabetes were independently associated by multivariate analysis with the need for readmission. Diabetes mellitus was the sole independent risk factor for prolonged wound healing (odds ratio, 3.4; 95% confidence interval, 2.3 to 6.2).

Outcome measurements have undergone a re-examination led by the initial effort of Conte et al.[243] to develop objective performance goals. The Society for Vascular Surgery's objective performance goal criteria were externally validated in 1039 lower extremity bypass operations for CLI in patients who were not on dialysis and in whom autologous vein grafts were placed.[244] The objective performance goal criteria included patients at clinical high risk (>80 years of age and tissue loss) and anatomic high risk (infrapopliteal target and lack of single-segment saphenous vein) and showed that major adverse limb events and major adverse cardiovascular events were more common in the high-risk groups.

In sum, these data suggest that to better select patients for open bypass or endovascular therapy, reconsideration of the input (i.e., burden of disease or baseline of disease classification and a risk comorbidity index) as well as the output (i.e., objective performance goals and functional outcomes) will be necessary. Further studies using such functional or patient-related outcomes are needed to place the role of infrainguinal bypass in perspective,[232,245-252] particularly to allow comparisons with less invasive techniques such as subintimal angioplasty or even primary amputation in selected high-risk patients with CLTI. Although it is generally agreed that nearly all patients with CLTI are best treated with revascularization, it is clear that both economic and functional outcome issues mandate the consideration of alternative therapies, at least for certain subsets of patients with CLTI, such as individuals confined to chronic care facilities, those who are minimally ambulatory, and patients with extensive tissue loss and infection who are receiving chronic renal replacement therapy.[206,240,249,252-255] This issue is addressed in depth in Chapter 105.

Cost-Effectiveness and Risk Stratification

With respect to cost-effectiveness, the initial cost savings of endovascular therapy compared with open bypass for patients with severe or critical limb ischemia is lost after 1 year.[256-258] Several authors have developed predictive indices to help select patients who have better (or worse) outcomes after open bypass surgery. These include studies performed by the group in Greenville, South Carolina (LEGS score), the Prevention of Infrainguinal Vein Graft Failure (PREVENT) III trial, the Finland National Vascular (FINNVASC) registry, and metrics developed from data derived from the BASIL trial.[259-262] The Greenville group, in a series of 677 patients fairly evenly split between endovascular and open surgery, showed that impaired ambulatory status at the time of presentation, diabetes, end-stage renal disease, gangrene, and prior vascular intervention all increased the risk of failure. The presence of multiple comorbidities increased the risk of failure dramatically.

It is worth reviewing the FINNVASC, PREVENT III, and BASIL outcome prediction models. The FINNVASC score assigns one point each for diabetes mellitus, foot gangrene, CAD, and urgent operation, and the predictive model stratifies risk on a scale of 1 to 4 based on the sum of the points. The FINNVASC score has been externally validated. The PREVENT III prediction model assigns end-stage renal failure on dialysis 4 points, tissue loss 3 points, age older than 75 years 2 points, and CAD 1 point and stratifies risk into low (≤3 points), medium (4-7 points), and high (≥8 points). This prediction model has also been validated. The stratification system derived from BASIL used tissue loss, body mass index, serum creatinine concentration, Bollinger score, age, smoking, coronary disease, and ankle pressure and produced a complex model of mortality calculation that is likely too complex for standard clinical use and may not apply to all patients with CLTI because the study inclusion criteria differed from CLI as previously defined. Nonetheless, it seems that multiple comorbidities, especially those that are

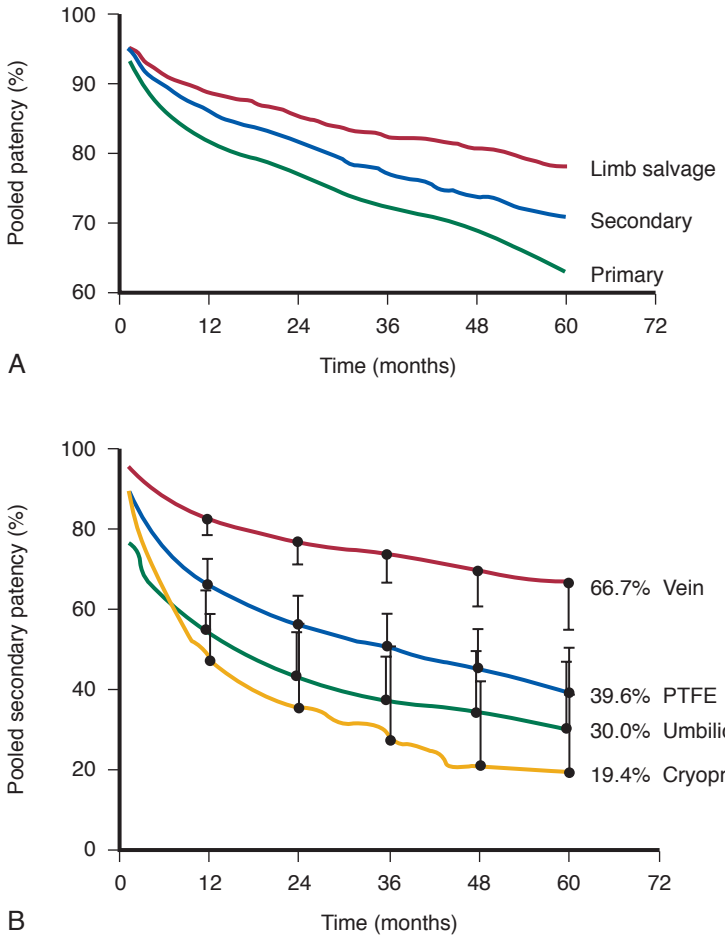

Figure 109.16 Patency of infrageniculate bypass grafts. (A) Random effects meta-analysis of popliteodistal bypass grafts for primary patency *(green line)*, secondary patency *(blue line)*, and foot preservation *(red line)*.[232] (B) Meta-analysis survival curve of secondary patency for alternative autologous vein *(red line)*, polytetrafluoroethylene *(blue line)*, umbilical cord vein *(green line)*, and cryopreserved vein *(yellow line)*. Bars are half the amplitude of 95% confidence intervals.[231] *PTFE*, Polytetrafluoroethylene.

common to the major reports, need to be considered in offering a patient a bypass and trying to gauge the outcomes (Table 109.7).

Quality of Life

A substantial amount of new data, derived primarily from two large prospective trials (PREVENT III and BASIL),[a] is beginning to put the role of successful bypass in the proper perspective. It also lends support to long-standing impressions about the effectiveness of leg bypass in relieving ischemic symptoms and improving quality of life in properly selected patients.[236-238,269-274] Patients with CLTI have a markedly reduced quality of life compared with a normal control population,[238,260] and their quality of life is markedly improved by successful bypass.[260,263,264] It is also becoming evident, especially in CLTI patients with severe ischemia and higher grade wounds, that ongoing graft patency, at least for the first 1 to 2 years, is critical to the maintenance of this quality of life improvement.[268,269,275,276] Tissue loss at presentation and graft-related events or failure of percutaneous transluminal angioplasty (PTA) during the first 1 to 2 years after the index revascularization are associated with reduced quality of life and increased resource utilization. Thus, although the early BASIL results showed no difference in outcomes between bypass and PTA for CLI,[275] the published intermediate follow-up analysis suggests that bypass is more effective than PTA in all but the most unfit patients. The bypass-first group had a better amputation-free survival (relative risk, 0.85) and a lower all-cause mortality than the angioplasty-first group (relative risk, 0.65; $P < .009$), probably because of the high failure rate of PTA and the more frequent need for reintervention to maintain patency.[257,258] For patients with severe ischemia, particularly diabetics and those with tissue loss, ongoing vascular patency is important for maintaining quality of life and preventing amputation.[241,268] These important findings may eventually lead to a gentle swing of the therapeutic pendulum away from endovascular therapy and back toward open bypass, at least for relatively fit CLI patients with TASC type C or D disease, available vein conduit, and estimated life expectancy of more than 2 years.[276,277]

POSTOPERATIVE MANAGEMENT

After bypass, patients should generally be maintained on their preoperative medical regimens for the control of angina, arrhythmia, congestive heart failure, and hypertension. Patients with a recent history of congestive heart failure are at high risk for prolonged hospital stay and readmission.[214,239,241] Care should be taken to avoid volume overloading in these patients, and

[a]References187, 202, 214, 245, 246, and 263-269.

TABLE 109.7 Comparison of the Components and Output System of the Finland National Vascular, Prevention of Infrainguinal Vein Graft Failure III, and Bypass Versus Angioplasty in Severe Ischemia of the Leg Scoring Systems

	Finnvasc	Prevent III	Basil
Variables	One point for each: Diabetes mellitus Foot gangrene Coronary artery disease Urgent operation	Dialysis = 4 points Tissue loss = 3 points Age >75 years = 2 points Coronary artery disease = 1 point	Tissue loss Body mass index Creatinine concentration Bollinger score Age Smoking Coronary artery disease Ankle pressure
Output method	Risk stratified 1-4 on sum of points	≤3 points = low risk 4-7 points = medium risk ≥8 points = high risk	6-, 12-, and 24-month mortality rates calculated by model (http://basiltrial.com/survival_predictor.htm)
Externally validated	Yes (Arvela et al.[262])	Yes (Schanzer et al.[214]; Arvela et al.[262])	No

From Moxey PW, Brownrigg J, Kumar SS, et al. The BASIL prediction model in patients with peripheral arterial disease undergoing revascularization in a university hospital setting and comparison with the FINNVASC and modified PREVENT scores. *J Vasc Surg*. 2013;57:1–7.

they may require supplemental diuresis. Perioperative beta blockade should be continued in the absence of contraindications; in moderate- and high-risk patients undergoing vascular surgery, beta blockade with targeted heart rate control reduces cardiac complications and improves mortality.[18-20]

Antiplatelet Therapy

Most patients with PAD are already receiving antiplatelet therapy, usually aspirin (81 or 325 mg daily). Aspirin has well-recognized cardiac and cerebral protective effects and may also improve early graft patency.[278-288] Clopidogrel may also be used,[289] but it is more expensive and may have an increased risk of complications compared with aspirin alone. Most vascular surgeons consider antiplatelet therapy essential for patients undergoing infrainguinal bypass.

Anticoagulation

There are insufficient data on which to base a recommendation concerning anticoagulation after lower extremity bypass. A single long-term, randomized, prospective trial of 130 patients by Kretschmer et al.[290] from Vienna demonstrated improved vein graft patency and limb salvage rates and improved patient survival in those randomized to receive phenprocoumon. An important clinical report, the Dutch Bypass Oral Anticoagulants or Aspirin (BOA) trial, summarized a study of 2690 lower extremity bypass patients randomized to anticoagulation versus antiplatelet therapy (aspirin).[291-293] Although overall differences were not significant, subgroup analysis suggested that oral anticoagulation improved vein graft patency compared with aspirin, whereas aspirin improved prosthetic graft patency compared with anticoagulation. If these data can be confirmed, it is likely to alter the typical practice in North America, where surgeons tend to treat vein graft patients with aspirin and to anticoagulate those with prosthetic grafts. The BOA trial, however, noted that anticoagulated patients had nearly double the major bleeding risk of patients receiving antiplatelet therapy, suggesting that anticoagulation should be used selectively in subgroups at greatest risk. A recent structured review suggests that anticoagulation may be beneficial in high-risk grafts, such as redo procedures or in the presence of poor arterial outflow.[294]

Such a selective approach has been recommended by the University of Florida group on the basis of a small randomized study of patients with high-risk vein grafts.[295] High-risk grafts were defined on the basis of poor arterial runoff, suboptimal vein conduit, and reoperative cases. Patency (74%) and limb salvage (81%) rates at 3 years in the high-risk group randomized to warfarin and aspirin were significantly higher than in the aspirin-only group (51% and 31%, respectively), although again, bleeding was much more common in the group receiving warfarin.

Although this seems to be a logical approach, a Veterans Affairs cooperative trial reached a different conclusion based on 665 patients with infrainguinal bypasses who were randomized to aspirin and warfarin versus aspirin alone.[296] Vein graft patency was not increased by the addition of warfarin to aspirin; in contrast, prosthetic graft patency was significantly improved by anticoagulation, but at the expense of double the risk of hemorrhagic events. These data all suggest a potential role for postoperative anticoagulation that requires larger trials with higher statistical power to permit an evidence-based recommendation. Until then, most surgeons will continue to routinely employ antiplatelet therapy (aspirin 81 to 325 mg daily) and add anticoagulation in selected groups at highest risk (e.g., prosthetic infrageniculate grafts, poor outflow, reoperative cases, poor or alternative vein conduit).

Wound Care

All patients with CLTI are at risk for pressure ulcers not only in the affected limb but also in the contralateral limb and the

sacrum. Unremitting nursing care is essential to prevent these complications. Considerable wound care is also required to achieve healing of ischemic foot lesions and forefoot amputations. FI should have been controlled before revascularization. Basic science wound studies suggest that débridement and formal toe and forefoot amputations for areas of tissue ulceration or gangrene should be delayed 4 to 10 days after bypass to maximize tissue reperfusion and to allow the clear demarcation of marginal areas (see Chapters 115 and 116).

COMPLICATIONS

The major early postoperative complications of infrainguinal bypass are wound problems, bleeding, graft occlusion, graft infection, and death (see Table 109.2). The results of the PREVENT III trial from 83 enrolling centers probably reflect realistic complication rates in clinical practice.[265] The authors of this study reported the following early complication rates in a prospective trial of more than 1400 infrainguinal vein grafts in patients with CLI: death (2.7%), myocardial infarction (4.7%), major amputation (1.8%), graft occlusion (5.2%), major wound complications (4.8%), and graft hemorrhage (0.4%). Late complications include persistent lymphedema, graft infection, graft aneurysm, and graft stenosis.

Early Graft Occlusion

With experienced judgment and intraoperative attention to detail, early graft occlusion should be uncommon. Should a graft fail in the early postoperative period, the most important principle is to identify and to correct the underlying cause.[297] If no cause can be identified, the prognosis for long-term patency is poor. The outcome is much more favorable if the cause can be ascertained and addressed. The most common correctable culprits are anastomotic, local endarterectomy, or clamp defects; valve defects; poor conduit quality; and inadequate outflow.

When the patient is returned to the operating room, one can usually begin by exploring the distal anastomosis first. If the graft hood is pulsatile, an arteriogram is obtained. If not, the hood is opened and gentle distal thrombectomy and graft thrombectomy are performed with balloon catheters of appropriate caliber. If the graft is a reversed vein, both proximal and distal anastomoses usually require exploration. An uninflated balloon catheter is passed from proximal to distal; a second catheter can be tied to the first one and drawn uninflated proximally. The tie is cut, the second catheter is inflated, and the graft is then thrombectomized from proximal to distal. Once the thrombus has been evacuated, heparinized saline is forcibly irrigated through the graft to flush any residual thrombotic debris out the distal graftotomy. Both anastomoses can then be carefully inspected; if a distal anastomotic defect is identified, the graftotomy can be extended down the outflow artery and closed with a patch. If no defects are identified, the graft incisions are closed, and thorough arteriography of the entire graft and the outflow is performed. Significant conduit or anastomotic lesions should be corrected. If unsuspected or previously unappreciated outflow disease is identified, the graft should be extended beyond the lesion or to an alternative outflow artery if one is available. If a marginal vein conduit was used at the initial procedure and no focal defect is identified at re-exploration, one should consider replacing the conduit; this decision is difficult and may require the harvesting of additional vein or, if none is available, converting to a prosthetic conduit if outflow is sufficient.

Late Graft Occlusion

Late graft occlusion should be treated only if the patient's symptoms are severe enough to warrant intervention. When vein conduit is limited, I attempt thrombolysis, mechanical thrombectomy, or both and treat the underlying lesion responsible for graft failure. The results of this approach are generally poor, however. My preference for late graft occlusions is to perform a new bypass with autogenous vein, which provides superior results and durability.[151] If vein is unavailable and thrombolysis is contraindicated or fails, a repeated bypass with PTFE and a vein patch or cuff is the best option. The optimal therapy for graft occlusion is to prevent its occurrence by identifying graft-threatening stenosis before the onset of graft occlusion through routine postoperative duplex graft surveillance.

GRAFT SURVEILLANCE

Vein graft surveillance is critical to the long-term success of infrainguinal bypass. It has been well documented for more than 3 decades that nearly one third of autogenous vein grafts develop lesions that threaten graft patency.[298] Most such lesions, especially in the first 1 to 2 years after graft implantation, are intrinsic to the graft itself and result from intimal hyperplasia.[299-301] Later, inflow and outflow lesions may develop and reduce graft flow, thus threatening ongoing graft patency. All these lesions can be readily identified, graded for severity, and monitored for progression by means of a program of ankle-brachial index determination and duplex graft surveillance.[112,222,242,302-313] I obtain the first study within 4 weeks of surgery, either before hospital discharge or at the first postoperative visit.[303] Serial studies are performed every 3 months for 1 year, every 6 months for 2 additional years, and annually thereafter. Grafts with focal lesions associated with a peak systolic velocity greater than 300 cm/s or a velocity ratio greater than 3.5 to 4.0 undergo prophylactic repair to prevent graft stenosis.[311,312] Grafts that develop low-flow velocities over time (peak systolic velocity <45 cm/s throughout the graft) or a drop in ankle-brachial index exceeding 0.15 in the absence of detectable graft lesions undergo arteriography to search for inflow, outflow, or missed graft lesions.

Abundant clinical data from multiple investigators and a single prospective randomized trial by Lundell et al.[314] suggest that vein graft surveillance improves long-term vein graft patency by approximately 15%. Although one trial questioned the benefit of vein graft surveillance,[267] that surveillance protocol was flawed, the endpoints were inappropriate, and the follow-up was too short to detect a difference.[308] Cost-benefit analyses both in Europe[313] and in the United States[242] confirm that vein

graft surveillance is cost-effective. Graft occlusion is a morbid and costly event,[242,268] and its prevention is worthwhile. Graft surveillance of prosthetic grafts has not been shown to be beneficial.[315,316]

TREATMENT OF GRAFT AND ANASTOMOTIC STENOSES

Vein graft stenoses are solitary and focal in approximately 80% of cases. Multiple focal synchronous or metachronous lesions are identified in 15% to 20% of grafts; diffuse long-segment graft narrowing, presumably due to myointimal hyperplasia, is uncommon (3% to 5% of cases).[300] If recurrent limb ischemia requires treatment in the latter circumstance, graft replacement is the treatment of choice.

There are multiple options for the treatment of focal graft lesions; selection of the optimal therapy depends primarily on the length of the lesion, the timing of its occurrence (early [<3 to 6 months] vs. late [>3 to 6 months]), and the patient's comorbidities. Focal lesions that develop after the sixth postoperative month respond fairly well to PTA,[317,318] and data suggest that use of a cutting or scoring balloon is superior to standard balloon angioplasty.[319,320] If a graft stenosis is treated by PTA, it should be closely observed by duplex ultrasound because the recurrence rate is generally higher than after open repair. Stent placement in infrainguinal vein grafts should be avoided.

If open repair is chosen, there are several options, depending primarily on the characteristics and location of the lesion. Circumferentially fibrotic midgraft lesions are best treated with excision and segmental interposition vein grafts. Less extensive lesions are amenable to vein patch angioplasty. There are no data demonstrating the superiority of patch versus interposition grafting,[307] but circumferentially fibrotic, napkin ring–like lesions are better treated with replacement. Focal, less fibrotic lesions, particularly related to valves, can be treated with valve excision and vein patch through a longitudinal graftotomy that extends proximal and distal to the site of the lesion. Intraoperative completion angiography or duplex scan should be performed to document resolution of the lesion.

Focal juxta-anastomotic lesions often develop in the vein graft itself, immediately adjacent to the arterial anastomosis.[300] These lesions can be treated by either patch angioplasty or short interposition grafts (Fig. 109.17). Another option that eliminates the need to harvest additional vein conduit is proximal anastomotic translocation.[321] This procedure involves resecting the lesion and oversewing the graft stump near its origin. If the vein graft below the stenosis is of good caliber, the graft can be transposed to an alternative inflow artery. For example, if the original anastomosis was to the CFA, and if the PFA is large and its origin is free of disease, the PFA can be exposed, and the graft can be mobilized below the proximal stenosis and swung over or transposed to reoriginate from the PFA. Distal juxta-anastomotic stenoses can usually be vein patched, but if the outflow artery has also developed progressive occlusive disease, a better option is a jump graft to a more distal target artery if one is available. These procedures have been described in detail elsewhere.[321]

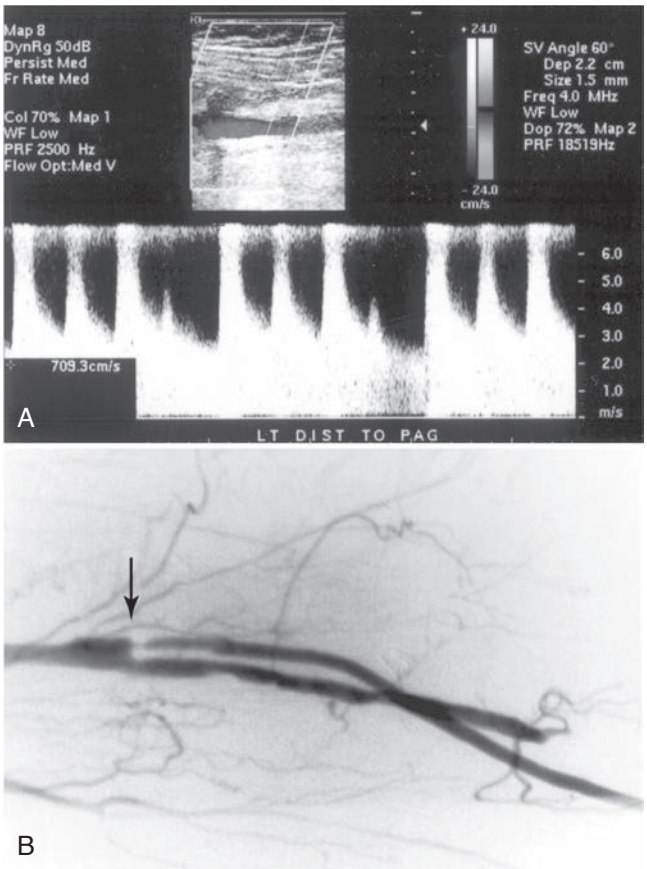

Figure 109.17 Duplex surveillance identified a critical vein graft stenosis in the proximal aspect of a femoropopliteal vein graft. (A) Marked spectral broadening and pronounced elevation of both the peak systolic and end-diastolic velocities are diagnostic of a high-grade vein graft stenosis. (B) A focal, severe proximal graft stenosis *(arrow)* was confirmed by arteriography and treated with a short interposition vein graft harvested from the upper extremity.

ACKNOWLEDGMENT

The illustrations were drawn by Joseph L. Mills, Jr.

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Although imperfect, the BASIL trial is the only published, prospective randomized trial of open bypass versus endovascular therapy for severe limb ischemia. Key points include significantly poorer outcomes for prosthetic compared with autogenous bypass conduits and trends toward improved overall survival and improved amputation-free survival in patients treated with bypass first who lived more than 2 years.

Conte MS, Bandyk DF, Clowes AW, et al. PREVENT III Investigators. Results of PREVENT III: a multicenter, randomized trial of

edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. *J Vasc Surg*. 2006;43:742–751.

Landmark study of a novel molecular therapy for the prevention of vein graft failure in patients undergoing infrainguinal revascularization for critical limb ischemia. Despite a well-conceived trial design, an impeccably executed study, and high-quality surgical results at multiple centers, the proposed molecular therapy was found to result in no significant improvement in any of the primary endpoints.

Conte MS, Geraghty PJ, Bradbury AW, et al. Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. *J Vasc Surg*. 2009;50:1462–1473.

Important paper defining objective performance goals to evaluate safety of lower extremity arterial disease treatment modalities. Major endpoints include major adverse limb events and major adverse cardiovascular events.

Faries PL, Arora S, Pomposelli FB Jr, et al. The use of arm vein in lower-extremity revascularizations: results of 520 procedures performed in eight years. *J Vasc Surg*. 2000;31:50–59.

This Boston group has long championed an all-autogenous approach. Their study shows that autogenous arm vein can be used successfully in a wide variety of lower extremity revascularization procedures and achieves excellent patency and limb salvage rates, generally much higher than those reported for prosthetic or cryopreserved grafts.

Mills JL, Fujitani RM, Taylor SM. The characteristics and anatomic distribution of lesions that cause reversed vein graft failure: a five-year prospective study. *J Vasc Surg*. 1993;17:195–206.

Postoperative duplex surveillance was prospectively performed during a 66-month period in 227 patients after infrainguinal vein graft placement to determine the causes of graft failure. The authors found that a significant portion of these failures occurred during the intermediate postoperative period (3 to 18 months), usually as a result of focal intrinsic vein graft lesions that are readily detectable by duplex surveillance. They concluded that duplex vein graft surveillance is warranted by the 21% incidence of potentially remediable graft failure.

Mills JL, Conte MS, Armstrong DG, et al; on behalf of the Society for Vascular Surgery Lower Extremity Guidelines Committee. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk Stratification based on Wound, Ischemia, and Foot Infection. *J Vasc Surg*. 2014;59:220–234.

Mills JL. The application of the Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIfI) classification to stratify amputation risk. *J Vasc Surg*. 2017;65(3):591–593.

The SVS WIfI Classification defines baseline limb risk based on grades of Wound, Ischemia and foot Infection to create Clinical Stages of amputation risk (from 1-4). Even with revascularization, limb status based on WIfI Clinical Stage stratifies amputation risk. Future application and evolution of this rubric may be helpful in selecting the best revascularization approach in a given clinical scenario.

Stonebridge PA, Prescott RJ, Ruckley CV. Randomized trial comparing infrainguinal polytetrafluoroethylene bypass grafting with and without vein interposition cuff at the distal anastomosis. The Joint Vascular Research Group. *J Vasc Surg*. 1997;26:543–550.

This study was undertaken to determine whether an interposition vein cuff improved the short- and medium-term patency and limb salvage rates of femoral above-knee and below-knee popliteal artery polytetrafluoroethylene (PTFE) bypass procedures. The authors found that there was no improvement in patency rate with the use of a distal anastomosis interposition vein cuff in above-knee PTFE grafts, but there was a statistically significant advantage when PTFE grafts were anastomosed to the popliteal artery below the knee. Vein cuffs or patches seem to be beneficial in those relatively uncommon patients requiring infrageniculate bypass in whom autogenous vein is not available.

Szilagyi DE, Elliot J, Hageman JH, Smith RF, Dall'olmo CA. Biologic fate of autogenous vein implants as arterial substitutes: clinical, angiographic, and histopathologic observations in femoro-popliteal operations for atherosclerosis. *Ann Surg*. 1973;178:232–246.

Infrainguinal vein grafts implanted in 377 patients during a 10-year period were studied by serial arteriography to determine their natural history. This study set an early standard for long-term follow-up and demonstrated its importance in patients undergoing such procedures.

Watelet J, Soury P, Menard JF, et al. Femoropopliteal bypass: in situ or reversed vein grafts? Ten-year results of a randomized prospective study. *Ann Vasc Surg*. 1997;11:510–519.

Long-term studies with good follow-up provide the best information about treating patients with chronic diseases. For example, this study reported the results of 100 femoropopliteal bypass procedures performed in 91 patients during 5 years who were randomly divided into two statistically comparable groups: 50 in situ vein grafts and 50 reversed vein grafts. One conclusion: small veins do not work as well, even when they are used in situ.

A complete reference list can be found online at www.expertconsult.com.

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110 CHAPTER

Infrainguinal Disease: Endovascular Therapy

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INTRODUCTION

Despite a lack of "level 1" evidence to date indicating durable clinical superiority over alternative treatment options, endovascular treatment (ET) is increasingly used to treat infra-inguinal peripheral arterial disease (PAD) in patients presenting with both intermittent claudication (IC) and chronic limb threatening ischemia (CLTI).[1-7] The reasons for this probably include the attractiveness to patients of reduced periprocedural morbidity and mortality; the fact that, in many countries, PAD is increasingly treated by physicians who cannot offer surgical intervention; and the marketing of endovascular devices by industry. Although practice varies considerably, in the United Kingdom (UK) and many other countries, transluminal or subintimal plain balloon angioplasty (PBA), with the use of "bail out" bare metal stents (BMS) where post-PBA angiographic appearances and/or flow are considered to be unacceptable, is still widely considered to be the current endovascular "standard of care" for the management of infra-inguinal PAD.[8] This is because newer endovascular technologies, in particular drug coated balloons (DCB) and drug eluting stents (DES), have not as yet been shown to produce superior clinical outcomes and are associated with significantly increased procedural costs. Indeed, in the UK, the National Institute for Health and Care Excellence (NICE) has currently recommended against the use of DCB and DES within the National Health Service (NHS) until such time as randomized controlled trials (RCTs) provide evidence of clinical and cost-effectiveness within the currently accepted UK "willingness to pay" (WTP) thresholds.[9,10] At the time of writing this is £20,000 per quality adjusted life year (QALY) (https://www.nice.org.uk/guidance/cg147). Although, due to their rigorous scientific methodology and unbiased provenance, UK NICE guidelines are used to inform clinical practice and healthcare spending in many other countries, even within

Abstract

Endovascular treatment of infra-inguinal disease in patients presenting with intermittent claudication and chronic limb threatening ischaemia (CLTI) still lacks a sound 'level 1' evidence base. While new endovascular technologies and techniques such as drug coated balloons, drug eluting stents, re-entry devices, debulking devices, low profile systems, and the use of novel access points may have improved anatomical outcomes, to date, there is limited evidence that this has translated into improved clinical outcomes when compared to plain balloons and stents or, indeed, lower extremely bypass. There also remains doubt as to whether such complex interventions can be cost-effective at commonly accepted willingness to pay thresholds. At the same time, the evidence base underpinning the clinical and cost-effectiveness of physical (exercise) and medical therapies for the treatment of peripheral arterial disease grows ever stronger. There is, therefore, an urgent need for a more thoughtful and evidence-based approach to endovascular therapy for infra-inguinal disease. To that end, the inter-societal (SVS, ESVS, WFVS) Global Vascular Guidelines on CLTI aim to improve outcomes and the quality of reporting; and advocate a more holistic, multi-disciplinary and evidence-based approach to the management of these challenging patients. At the same time, publicly-funded randomised controlled trials on-going in the US (BEST-CLI) and UK (BASIL-2 and BASIL-3) will help better define the role of infra-inguinal endovascular therapy in patients with CLTI characterised by different severities of clinical presentation (WIfI) and anatomic burden of disease (GLASS).

Keywords

Infrainguinal
Endovascular Treatment
Chronic limb threatening Ischemia
Intermittent Claudication
Angioplasty
Stenting

the UK, not everyone agrees with NICE's position on these matters.

Looking to the future, new ET technologies such as bioresorbable stents[11-14] and scaffolds,[15] bifurcated stents,[16] "tacking,"[17] robotic ET,[18] paclitaxel infusion,[19] angioscopic assisted ET,[20] and endovascular venous "arterialization"[21] may offer some promise but, at the present time, remain unproven and should be considered highly experimental.

The decision to proceed with infra-inguinal revascularization, and to offer ET rather than an alternative therapy, is based upon clinical presentation, physical examination, pattern of disease, co-morbidity, previous interventions, availability of autologous conduit, and the outcome of shared decision making with the patient and, where appropriate, the family.

Various recommendations regarding the indications for ET have been published over the years. Hitherto, probably the most widely referenced have been Trans-Atlantic Inter-Society Consensus (TASC) guidelines, which contain recommendations regarding the appropriateness of ET based largely upon lesion severity in the aorto-iliac (AI), femoropopliteal (FP), and most recently, infrapopliteal (IP) segments.[22] While possibly helpful in patients presenting with IC, who usually have relatively simple and discrete single level disease, treatment recommendations based upon individual lesion severity are likely to be much less useful in CLTI patients who almost always present with complex, extensive, multilevel, and increasingly, IP disease. In such patients, a more "holistic" approach to the assessment of overall burden of disease is required.[23] This is the approach taken in Global Vascular Guidelines (GVG) on CLTI, a collaborative effort between the US Society for Vascular Surgery (SVS), European Society of Vascular Surgery (ESVS), and the World Federation of Vascular Societies (WFVS), which will be discussed further below (https://vascular.org/research-quality/clinical-practice-documents/global-vascular-guidelines).

At the present time, the role of infra-inguinal ET, and which type of ET is most appropriate, in the management of IC and CLTI remains uncertain and controversial, with a very wide range of views being expressed at scientific meetings and in the literature. This controversy and lack of consensus stem primarily from the fact that the currently published literature and datasets are seriously lacking in both quantity and quality. Numerous analyses of this datasets are already readily available, as are numerous descriptions of innovative but largely unproven endovascular techniques, and the aim of this chapter is not to provide more of the same. Rather, the authors seek to respectfully challenge some of the current thinking regarding infra-inguinal ET and offer an alternative vision for the future based upon high quality, unbiased, preferably randomized, pragmatic trials that will define the clinical and cost-effectiveness of different endovascular technologies and techniques in appropriate subsets of patients presenting with IC and CLTI due to infra-inguinal atherosclerotic disease as part of overall multimodality care.

INTERMITTENT CLAUDICATION

Based upon a thorough analysis of the available published evidence, the quality of which was rigorously assessed using GRADE (http://www.gradeworkinggroup.org/), in 2012, NICE made a number of recommendations regarding the management of people with IC (Table 110.1). Although these recommendations have no direct legal force in the UK, clinicians and payers (public and private) are expected to follow them and to have good reason for not doing so. As a result of its robust and transparent processes, and strict conflict of interest policies, NICE recommendations have very considerable international reach and affect clinical practice and public and private payer

TABLE 110.1 UK National Institute for Health and Care Excellence Recommendations Regarding the Management of People With Intermittent Claudication

Supervised Exercise Program

- Offer a supervised exercise program to all people with intermittent claudication.
- Consider providing a supervised exercise program for people with intermittent claudication which involves:
  - 2 hours of supervised exercise a week for a 3-month period
  - encouraging people to exercise to the point of maximal pain

Angioplasty and Stenting

- Offer angioplasty for treating people with intermittent claudication only when:
  - advice on the benefits of modifying risk factors has been reinforced **and**
  - a supervised exercise program has not led to a satisfactory improvement in symptoms **and**
  - imaging has confirmed that angioplasty is suitable for the person.
- Do not offer primary stent placement for treating people with intermittent claudication caused by aorto-iliac disease (except complete occlusion) or femoropopliteal disease.
- Consider primary stent placement for treating people with intermittent claudication caused by complete aorto-iliac occlusion (rather than stenosis)
- Use bare metal stents when stenting is used for treating people with intermittent claudication.

Bypass Surgery and Graft Types

- Offer bypass surgery for treating people with severe lifestyle-limiting intermittent claudication only when:
  - angioplasty has been unsuccessful or is unsuitable **and**
  - imaging has confirmed that bypass surgery is appropriate for the person.
- Use an autologous vein whenever possible for people with intermittent claudication having infra-inguinal bypass surgery.

Naftidrofuryl Oxalate

- Consider naftidrofuryl oxalate for treating people with intermittent claudication, starting with the least costly preparation, only when:
  - supervised exercise has not led to satisfactory improvement **and**
  - the person prefers not to be referred for consideration of angioplasty or bypass surgery.
- Review progress after 3-6 months and discontinue naftidrofuryl oxalate if there has been no symptomatic benefit.

reimbursement in many countries. Within the UK, from a medicolegal viewpoint, a decision not to follow NICE guidance without explaining to the patient why an alternative course of action is being recommended, and without documenting that in the case records, leaves the physician vulnerable to criticism. Despite this, it is still probably the case that many patients in the UK are being offered ET, and even bypass surgery, for IC without having been offered a (supervised) exercise program, without having been given appropriate support to stop smoking, and without having been medically optimized. The reasons for this are complex but unfortunately probably reflect practice in many other countries.[24] The important question at time of writing is whether there has been any change in the evidence base since 2012 that would lead NICE, or indeed any other independent guideline body elsewhere in the world,[25] to now make materially different recommendations regarding infrainguinal ET for IC.[26]

While imperfect, the evidence that, preferably supervised, exercise therapy continues to be the most clinically and cost-effective first-line treatment for most patients with IC remains extremely convincing. A recent meta-analysis of seven RCTs concluded that an ET-only strategy for IC was not associated with any improvement in functional capacity or clinical outcomes, whereas exercise and exercise combined with ET was associated with a significant increase in total walking distance, ankle brachial index (ABI), and a reduced risk of future revascularization or amputation.[27]

Furthermore, the evidence that lifestyle modification and so-called "best medical therapy" (BMT) aimed at reducing overall cardiovascular risk significantly improves outcomes in patients with PAD, whether they undergo ET or not, grows ever stronger.[28] By contrast, unfortunately, hard evidence that advanced endovascular technologies and techniques, such as DCB and DES, durably improve important clinical outcomes in patients with IC remains lacking.[29] As discussed later in further detail, most of the literature on ET for infra-inguinal PAD comprises industry-funded trials aimed primarily at obtaining marketing approvals from various regulatory authorities. While one understands why such studies are done, one cannot help reflecting that they often represent a significant "missed opportunity" to gather clinically important data that would help physicians and their patients make truly informed, evidence-based decisions regarding ET. Arguably, the largest industry-sponsored trial with the longest follow-up is that evaluating the Zilver PTX DES.[30] Although 5-year anatomic outcomes were favorable, due to the limited and unusual method of reporting the clinical outcomes, the trial design, and the large numbers of patients in whom complete follow-up data were unavailable, it is difficult to draw any firm conclusions regarding the clinical and cost-effectiveness of this device and thus its role in current practice.[31,32] One respectfully wonders why sponsors would embark upon large and expensive RCTs of ET for (predominantly) IC without reporting treadmill walking distances (or another validated objective quantifiable measure of individual patient improvement), which, while imperfect, has been for many years and still remains the most widely accepted primary outcome in IC trials. Such reporting of symptomatic improvement would probably be mandatory in a phase III trial of a new medical or physical therapy for IC. It is also worth noting that although more than 90% of the patients in the Zilver PTX trial had IC, they also enrolled CLTI patients, and these two very different conditions and patient groups were largely conflated in the analysis. Methodologically, this is very difficult, many would argue impossible, to justify; and yet such conflation occurs repeatedly in the literature. So the thorny question is why should patients and payers be expected to accept a far inferior level of reporting in trials of ET (and open surgery for that matter) for PAD compared to that which would be expected of new medical and physical therapies? Although there have been setbacks, such as the negative results from EUCLID,[33,34] overall, the gap in terms of both quantity and quality between the evidence base for medical and interventional (ET and surgical) treatment of PAD appears to be widening in favor of the former.[35]

While the precise role, if any, of dual antiplatelet therapy for PAD patients undergoing ET remains to be defined,[34,36] data from the SVS Vascular Quality Initiative (VQI) obtained in more than 40,000 patients show that DAPT does appear to improve survival after lower extremity revascularization, especially in the higher risk patients.[37] As such, further trials of combination and novel antiplatelet agents in subgroups of PAD patients, both as part of BMT and as an adjunct to ET, would seem to be warranted. In particular, the possible adverse impact of aspirin and clopidogrel resistance on outcomes after ET requires further evaluation, and individualized antiplatelet therapy may be the future.[38]

Similarly, while the role, if any, of long-term anticoagulation with vitamin-K antagonists in PAD patients remains uncertain, the availability of a range of direct oral anticoagulants (DOACs) offers new therapeutic possibilities both as part of BMT and as an adjunct to intervention.[39] While VOYAGER (https://clinicaltrials.gov/ct2/show/NCT02504216) results still are awaited at time of writing, those of COMPASS, which randomized 27,395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily), have recently been published.[40] The primary outcome was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped for superiority (4.1% vs. 5.4%, 24% reduction) of the rivaroxaban-plus-aspirin group after a mean follow-up of only 23 months. The net clinical benefit of rivaroxaban plus aspirin over aspirin alone was estimated at 20% (4.7% vs. 5.9%) and appears to represent a very considerable additional level of risk reduction over standard antiplatelet therapy, which, in the UK, is clopidogrel (in preference to aspirin). Importantly, just more than 27% of the patients in all three arms (7470 patients combined) had a history of PAD as an entry criterion.[41] These powerful data accord with the observation that many PAD patients exhibit a prothrombotic, hypofibrinolytic diathesis. The fact that, in the COMPASS trial, rivaroxaban alone was not better than aspirin alone suggests that both coagulation and platelet function may need to be modified in order to optimize clinical outcomes.[42] This may be especially so in PAD patients who have undergone ET leading

to the exposure of prothrombotic and inflammatory surfaces, and perhaps particularly when non-bioresorbable devices have been implanted. While further careful evaluation of the COMPASS trial results is required and bleeding risks need to be carefully considered, as will the cost implications in many healthcare economies, this and other trials appear to have the potential to usher in a new "standard of care" for at least some, perhaps even the majority, of PAD patients being treated medically with and without with ET.

The evidence for lipid lowering therapy in people at increased cardiovascular risk is extensive, and although much of it concerns patients presenting with coronary artery disease, there are also a number of authoritative, strongly evidence-based management guidelines concerning the use of statins in patients with PAD. In a recent US study, the authors concluded "use of the recommended intensity of statin therapy in compliance with 2013 American College of Cardiology/American Heart Association lipid management guidelines is associated with significantly improved survival and lower major adverse limb events (MALE) rate in patients undergoing revascularization for CLTI. Adherence to current guidelines is an appealing target for quality improvement."[43]

The role of drugs for symptom relief, as opposed to cardiovascular risk reduction, in patients with IC, either as a standalone therapy or in combination with ET, remains uncertain. In the UK, NICE have recommended that it is reasonable to try naftidrofuryl for 3 to 6 months in patients who have not benefited sufficiently from supervised exercise and who do not want to consider ET or surgical revascularization. With regard to cilostazol, a recent Cochrane review concluded that the drug improves walking distance in people with IC secondary to PAD and that although there is an increase in adverse side effects, they are generally mild and treatable. However, the authors further concluded that there is currently insufficient data on whether taking cilostazol results in a reduction of all-cause mortality and cardiovascular events or an improvement in quality of life, and that further research is required.[43a] In addition to providing symptom relief as a standalone therapy, there is also some evidence that cilostazol can improve outcomes following ET. For example, in a subanalysis of the ZEPHYR study that used propensity score-matching analysis, the investigators reported that cilostazol was associated with a significantly lower incidence of restenosis 1 year after DES implantation for FP lesions.[44] This is another area arguably worthy of further study in an attempt to improve ET durability and reduce reintervention rates.

A number of groups have explored the hypothesis that lifestyle modification, BMT, (supervised) exercise therapy, and revascularization can work synergistically for the clinical benefit of patients with IC and also improve the cost-effectiveness of intervention.[27] For example, statin use is associated with a reduction in postoperative cardiovascular events[45] and may increase the long-term success of intervention. Unsurprisingly, continued smoking very significantly reduces the benefits of intervention while greatly increasing the risks.[46] Although in many countries it would be considered inappropriate to deny ET to patients with IC solely on the basis that they choose to continue to smoke,[47] hopefully, there would be wide agreement that the impact of that decision on the risks and benefits of the proposed ET would form an important part of shared decision making and be documented in the case record. The corollary is that all patients presenting with IC should be offered evidence-based smoking-cessation therapy,[48,49] and that such therapy should be given adequate time to be effective, before proceeding with ET (or surgical bypass).

In the UK, the long-term results of a RCT of supervised exercise, PBA, or combined treatment for patients with IC due to FP disease have recently been published.[50] Although follow-up was incomplete, with only 111 of 178 patients initially recruited being available for assessment a median of just over 5 years after randomization, the PBA and PBA plus supervised exercise groups had a higher ABI than the supervised exercise only group. This did not translate into a significant difference in important clinical outcomes; however, as noted previously, the patient numbers in each group were small. The authors concluded that PBA, supervised exercise, and combined treatment were equally effective long-term treatment options for patients with IC due to FP disease, and suggested that combined treatment has the potential to reduce the rate of symptomatic restenosis and reintervention. However, there was no cost-effectiveness analysis and, more generally, whether adjuvant strategies to improve the long-term clinical effectiveness of ET for IC, in terms of symptom relief, are cost-effective remains uncertain.

In the United States, the CLEVER study has also published its results. With regard to the AI segment, the authors concluded that, while supervised exercise and stent revascularization resulted in better outcomes than medical therapy alone at 18 months, they did not differ in terms in functional status or health related quality of life (HRQL).[51] With regard to cost-effectiveness, the investigators concluded that both supervised exercise and stent revascularization were economically attractive by US standards relative to medical therapy only. However, revascularization is significantly more expensive than supervised exercise and associated with uncertain incremental clinical benefits resulting in an estimated cost per QALY of around $122,000.[52]

In summary, since NICE published its recommendations in 2012, there has been no new evidence to seriously challenge the primacy of lifestyle modification,[49] BMT,[53] and (supervised) exercise therapy as first line for the majority of people who present with IC.[54-56] Not only is such therapy highly clinically effective, from a health economic (cost-utility) perspective it is likely to dominate intervention in most patients and healthcare settings. Furthermore, while "level 1" evidence for the effectiveness of, increasingly combination, medical therapy is increasing, progress in acquiring a "level 1" evidence base for ET in patients with IC appears to have stalled for the time being.

All that said, in the real world, there are many patients with IC who do not want or cannot manage to modify their lifestyle, are not concordant with BMT, have no interest in engaging with a (supervised) exercise program,[57] and who demand intervention, perhaps viewing it as a "quick fix" for their problem. At the same time, there remain many clinicians who are extremely enthusiastic about ET for IC and have a very low threshold for intervention. As noted previously, this is a highly controversial area with a

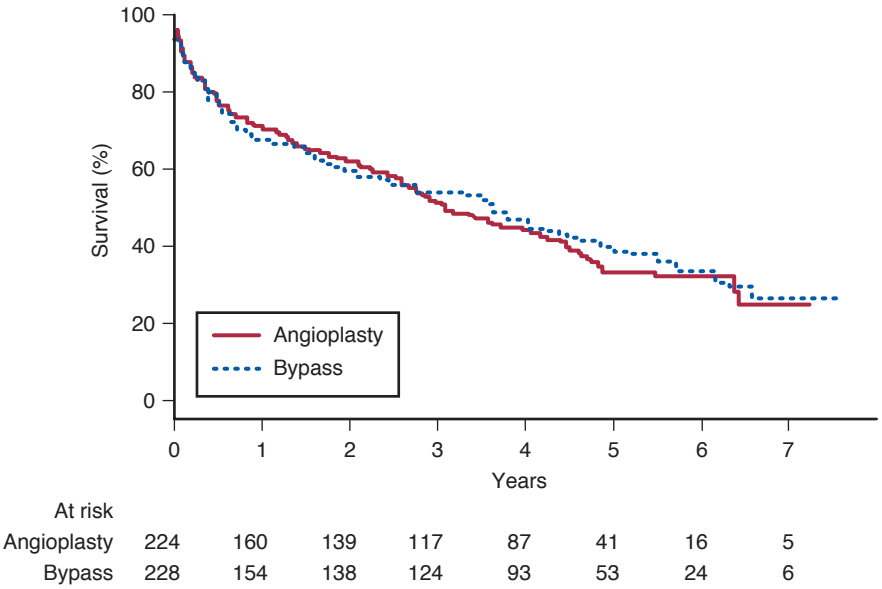

Figure 110.1 Bypass versus angioplasty in severe ischemia of the leg-1 trial (2008 analysis): survival to primary endpoint of major amputation of trial leg or death (amputation free survival). (From Bradbury AW, Adam DJ, Bell J, et al. Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. *Health Technol Assess*. 2010;14(14).)

wide range of views and practice depending on specialty and the healthcare system (re-imbursement) that pertains in each different country. However, one would hope that, given the obvious limitations of the existing evidence base, most clinicians would agree that further RCTs are required to define the appropriate role of ET in the management of IC. Indeed, calls for such trials are repeatedly made in many published papers and during conference presentations on the subject. When designing such trials, existing and emerging data strongly suggest that ET for IC should not be viewed isolation, but as part of a more "holistic" multimodality treatment package that aims not just to durably improve walking distance but also to retard disease progress, minimize further intervention, and reduce future cardiovascular and overall morbidity and mortality.[58]

CHRONIC LIMB THREATENING ISCHEMIA

Bypass Versus Angioplasty in Severe Ischemia of the Leg Trials

The UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA) funded bypass versus angioplasty in severe ischemia of the leg (BASIL) trial (now referred to as BASIL-1) remains the only completed and published RCT to have compared a "bypass-surgery-first" with a "balloon-angioplasty-first" revascularization strategy in patients with CLTI due to infra-inguinal disease.[59] The trial was conducted in 27 UK hospitals and enrolled 452 patients with CLTI who, in the opinion of the responsible vascular surgeon and interventional radiologist, required and were suitable for both bypass surgery and PBA. The primary endpoint was amputation-free survival (AFS); secondary endpoints included overall survival (OS), HRQL, and cost-effective use of hospital resources. AFS at 1 and 3 years was not significantly different for surgery and PBA. An interim analysis showed that surgery was associated with significantly lower immediate failure, higher 30-day morbidity, and lower 12-month reintervention rates than angioplasty; 30-day mortality was similar. Beyond 2 years from randomization, hazard ratios (HRs) were significantly reduced for both AFS (adjusted HR 0.37; 95% confidence interval [CI] 0.17-0.77; $P = .008$) and OS (HR 0.34; 95% CI 0.17-0.71; $P = .004$) for surgery relative to PBA. Considering the follow-up period as a whole, AFS and OS did not differ between treatments. However, for patients surviving beyond 2 years from randomization, bypass was associated with reduced HRs for AFS (HR 0.85; 95% CI 0.50-1.07; $P = .108$) and OS (HR 0.61; 95% CI 0.50-0.75; $P = .009$), equating to an increase in restricted mean OS of 7.3 months ($P = .02$) and AFS of 5.9 months ($P = .06$) during the subsequent follow-up (Figs. 110.1 and 110.2). Vein bypass and PBA performed better than prosthetic bypass. HRQL was nonsignificantly better in the surgery group. Over the first year, hospital costs for bypass were significantly higher than for PBA. However, by 3 and at 7 years the differences in cost between the two strategies were no longer significant. Patients randomized to surgery lived, on average, 29 days longer at an additional average cost of £2310. A 36-month perspective showed no significant difference mean quality-adjusted life times for PBA and surgery. However, the failure rate of PBA was high (25%), and patients who underwent bypass after failed PBA fared significantly worse than those who underwent bypass surgery as their first procedure. Only a minority of patients had been medically optimized by the time they were referred to the vascular service with CLTI, and for many patients there appear to have been missed opportunities to diagnose and manage their CLTI earlier when prospects for a successful outcome would probably have been materially greater.

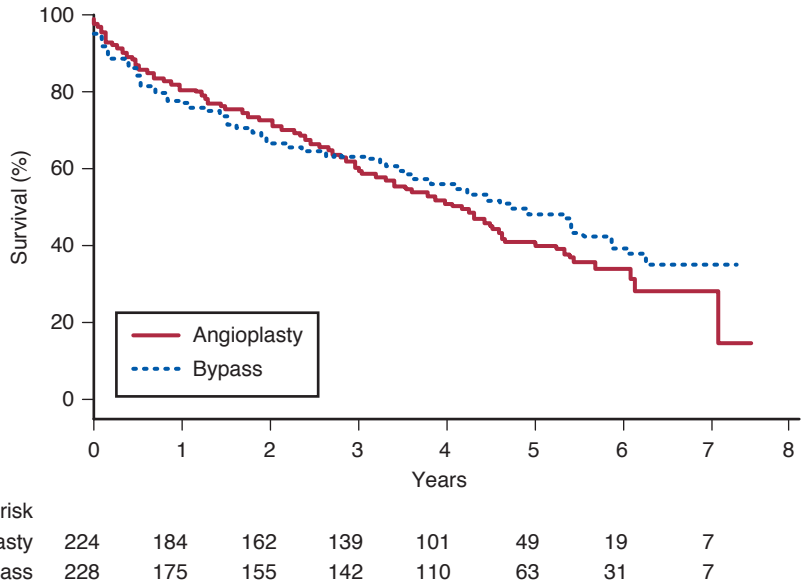

Figure 110.2 Bypass versus angioplasty in severe ischemia of the leg-1 trial (2008 analysis): survival to death from any cause. (From Bradbury AW, Adam DJ, Bell J, et al. Multicentre randomised controlled trial of the clinical and cost-effectiveness of a bypass-surgery-first versus a balloon-angioplasty-first revascularisation strategy for severe limb ischaemia due to infrainguinal disease. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. *Health Technol Assess*. 2010;14(14).)

On the basis of these data, the BASIL investigators suggested the following for patients with CLTI due to infra-inguinal disease:

- When deciding whether to perform bypass surgery or PBA first, clinicians should consider estimating anticipated life expectancy by using the BASIL survival prediction model or similar tool.
- Patients expected to live less than 2 years should be considered for ET in the first instance, as it is associated with less morbidity and cost, and such patients may be unlikely to enjoy the longer-term benefits of surgery.
- Patients expected to live beyond 2 years should be considered for vein bypass surgery first.
- Patients who cannot have a vein bypass are probably better served by an attempt at ET in the first instance than prosthetic bypass.
- A ET first approach is not necessarily a "free shot," as the success of subsequent bypass may be compromised by failed ET.
- Further research is required to:
  - confirm or refute the BASIL findings and recommendations
  - validate the BASIL survival prediction model and other such tools
  - examine the clinical and cost-effectiveness of new forms of ET

Like all RCTs, BASIL-1 has several shortcomings, and the results have to be interpreted carefully.

BASIL-1 is now quite an old study with patients having been randomized between August 1999 and June 2004. It is often argued that, given advances in endovascular expertise, techniques and technologies, were the trial to be repeated, an ET-first strategy would prove the more clinically and cost-effective option for the great majority of, perhaps all, patients. While that is possible, when comparing like for like patients and disease patterns, in reality there is limited evidence to support that contention and one cannot assume that such an outcome would be likely. So, while immediate ET technical success rates are probably higher now than they were 10 to 15 years ago, there is no evidence as yet that this translates into superior long-term clinical outcomes. Indeed, the current trend of offering complex ET to CLTI patients who, due to frailty and/or extreme disease severity, may previously have been offered primary amputation or conservative treatment seems likely to reduce the overall success of infra-inguinal ET when compared with those observed in BASIL-1. However, it is very important not to fall into the trap of comparing "apples and oranges," and using historical controls is fraught with problems. At the same time, the last 10 to 15 years have seen significant advances in anesthetic and surgical expertise and techniques, such that the results of VB in current practice may well be superior to those observed in BASIL. But again, we cannot just assume that is the case. There is no doubt that the overall performance of bypass surgery in BASIL-1 was significantly adversely impacted by the fact that 25% were completed using prosthetic grafts, which performed extremely poorly and indeed significantly worse than PBA.[60] Although that reflected practice at the time, were the prosthetic grafts to be removed from the BASIL-1 analysis, the advantages for bypass surgery over PBA, especially in the longer term, would probably become more marked. Furthermore, it is worth pointing out that the relatively good performance of PBA in BASIL-1 "intention to treat" analysis is at least partly explained by the fact that although there was a high immediate and early failure rate for PBA, many such patients went on to have successful bypass. However, enthusiasts for an ET-first revascularization strategy will justifiably point to the improved anatomic outcomes consistently reported with DCB and DES, albeit mainly in patients with IC and not CLTI. In truth, no one can confidently predict what a rerun of BASIL-1, comparing VB with current "best ET," would show, and further RCTs are required to further define the role of modern ET and bypass surgery in the management of CLTI in current practice.

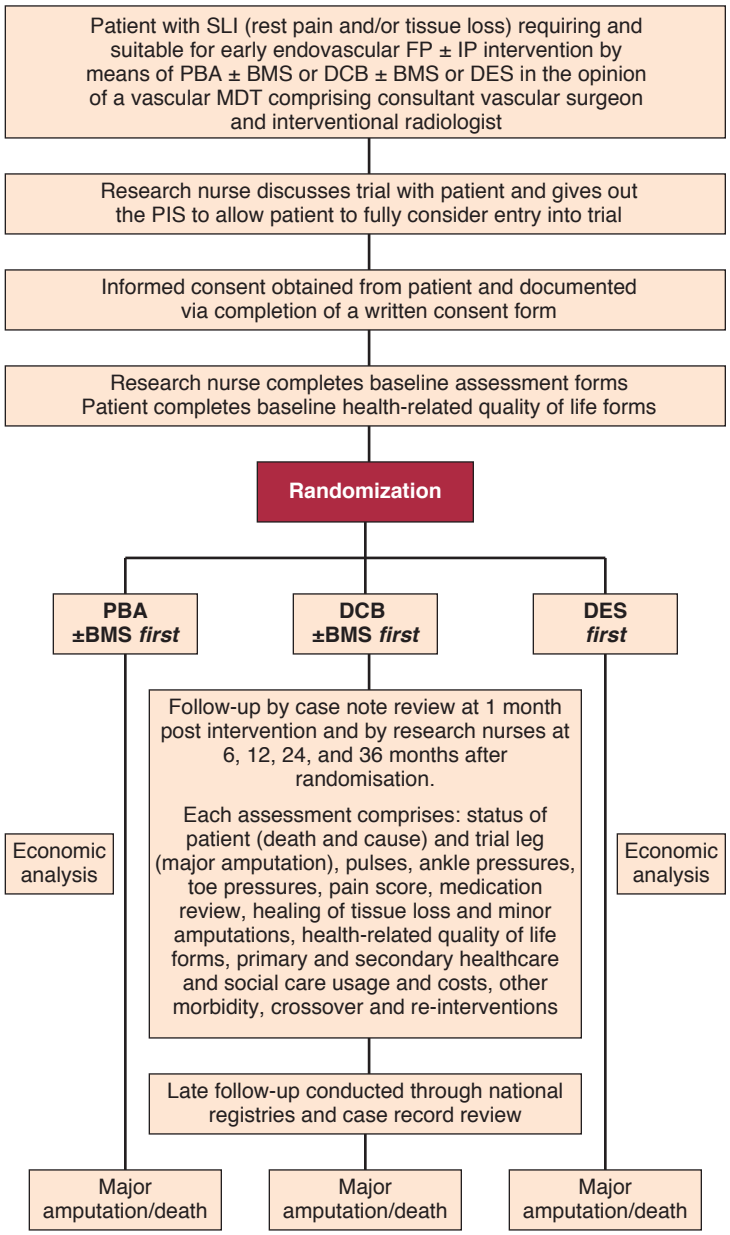

Figure 110.3 Balloon versus stenting in severe ischemia of the leg (BASIL-3) trial flow diagram of study design (CONSORT diagram). *BMS*, Bare metal stents; *DCB*, drug coated balloons; *DES*, drug eluting stents; *FP*, femoropopliteal; *IP*, infrapopliteal; *MDT*, multidisciplinary team; *PBA*, plain balloon angioplasty; *SLI*, severe limb ischemia. (From Hunt BD, Popplewell MA, Davies H, et al. BAlloon versus Stenting in severe Ischaemia of the Leg-3 (BASIL-3): study protocol for a randomised controlled trial. *Trials*. 2017;18:224.)

To that end, one of the research recommendations made in the 2012 UK NICE PAD guidelines was for a RCT to address the clinical and cost-effectiveness of DCB and DES in the management of CLTI due to FP disease. The UK NIHR HTA subsequently funded the BASIL-3 trial,[61] which is currently randomizing 861 patients to FP PBA +/– "bail out" BMS, or DCB +/– "bail out" BMS, or primary DES, and expects to publish its results in 2023 (Fig. 110.3).

A further consideration is that approximately 75% of the ET in BASIL-1 were FP. The original trial analysis of the cohort as whole does not, therefore, tell us very much about outcomes specifically in IP disease, which is increasingly prevalent in modern practice. However, a recent subgroup analysis of the 104 patients in BASIL-1 who underwent IP VB ($n = 56$) or PBA ($n = 48$) has now been published.[62] As expected, due to randomization, the two groups were very similar at baseline. Primary technical success was nonsignificantly higher for VB (86%) than for PBA (73%), as was 30-day mortality (7% vs. 2%). By contrast, in-hospital morbidity following the randomized procedure was significantly higher after VB (RR 2.86, 95% CI 1.25-6.53, $P = .01$), as was median hospital stay (18 vs. 10 days, $P < .0001$), although there was no difference in overall median hospital stay between randomization and the primary endpoint (43.5 VB vs. 42 PBA days). AFS was 32% lower in the PBA group (HR 0.68, 95% CI 0.42-1.10, $P = .1$) and OS was 40% lower (HR 0.60, 95% CI 0.36-1.02, $P = .06$). In terms of the quality of revascularization, time to healing of tissue loss was 70% quicker in favor of VB than PBA (HR 1.69, 95% CI 0.88-3.26, $P = .1$). Relief of ischemic rest pain was also more than twice as common in the VB group (HR 2.19, 95% CI 1.27-2.78, $P = .005$), with more patients pain-free at 5 years (Fig. 110.4).

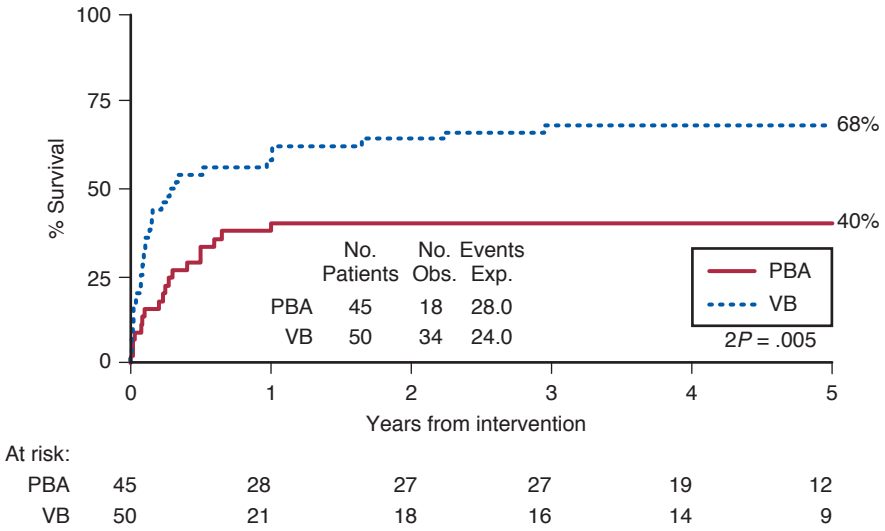

Figure 110.4 Bypass versus angioplasty in severe ischemia of the leg-1 infrapopliteal subgroup analysis, relief of ischemic rest pain (HR 2.19, 95% CI 1.27-2.78, $P = .005$). *PBA*, Plain balloon angioplasty; *VB*, vein bypass. (From Popplewell MA, Davies HOB, Narayanswami S, et al. A comparison of outcomes in patients with infrapopliteal disease randomised to vein bypass or plain balloon angioplasty in the bypass vs. angioplasty in severe ischaemia of the leg (BASIL) trial. *Eur J Vasc Endovasc Surg*. 2017;54(2):195–201.)

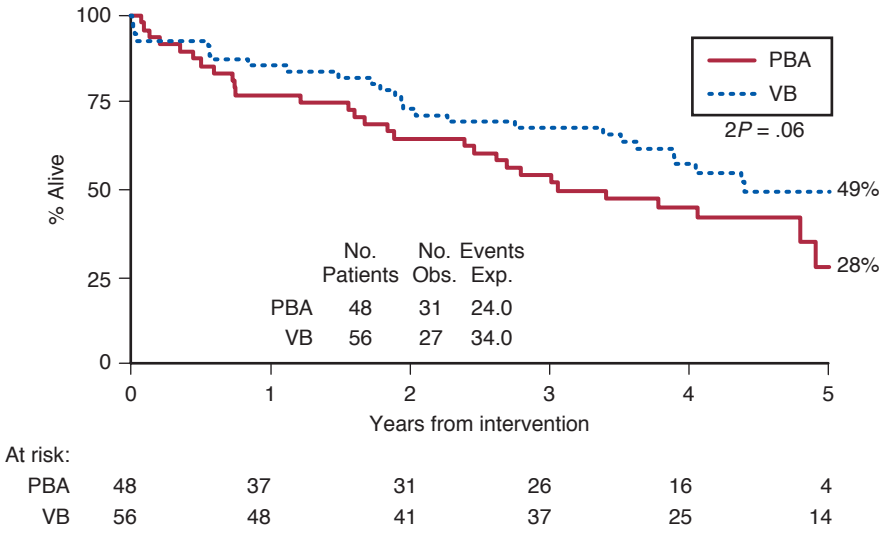

Figure 110.5 Bypass versus angioplasty in severe ischemia of the leg-1 (BASIL-1) infrapopliteal subgroup analysis, overall survival (HR 0.60, 95% CI 0.36-1.02, $P = .06$). *PBA*, Plain balloon angioplasty; *VB*, vein bypass. (From Popplewell MA, Davies HOB, Narayanswami S, et al. A comparison of outcomes in patients with infrapopliteal disease randomised to vein bypass or plain balloon angioplasty in the bypass vs. angioplasty in severe ischaemia of the leg (BASIL) trial. *Eur J Vasc Endovasc Surg*. 2017; 54(2):195–201.)

While, with the exception of relief of rest pain, the BASIL-1 IP subgroup results do not meet standard criteria for statistical significance, the direction of the effect consistently favors vein bypass and the CIs rule out the possibility of clinically important effects in favor of PBA in this cohort. The improvement in OS with bypass surgery is particularly striking and very nearly reaches statistical significance ($P = .06$), despite small numbers (Fig. 110.5).

However, ET enthusiasts will argue that PBA alone via a common femoral access point using 035 wire technology no longer represents "standard of care" and that a rerun of BASIL-1 using ultrasound guided micropunctures, low profile wires, re-entry devices, drug technologies, debulking devices, and innovative entry points[63,64] and retrograde approaches[65] would lead to dramatically different outcomes and conclusions.[66] Although this is entirely possible, as yet there is no "level 1" evidence that this is, in fact, the case, and further trials are required.

The BASIL-1 data also demonstrate that while objective binary endpoints such as AFS, OS and limb salvage (LS) are important, there is often a discrepancy between these and patient-reported outcome measures (PROMs). While the primary aim of infra-inguinal ET, and indeed bypass surgery, is to prevent major limb amputation, for a significant minority of people, retention of their leg does not necessarily result in better HRQL. Thus a significant proportion of BASIL patients undergoing ET, while they survived and retained their leg, were not relieved of their ischemic rest pain and continued to have wounds on their feet, sometimes for the rest of their lives. Of course, this was also true of some patients undergoing VB, although the proportion was smaller.

So, when designing RCTs to evaluate and compare (different types of) ET and VB for CLTI, many would argue that endpoints such as PROMs and HRQL that assess the quality of revascularization should have primacy over objective binary clinical endpoints (such as AFS); and even more so over hemodynamic

and anatomic endpoints, which have been repeatedly shown to have an unreliable relationship with clinical success. Thus, two patients with identical AFS can have very different journeys to their endpoint and so personal views as to whether their revascularization was successful for them or not. These considerations are also important when it comes to determining cost-effectiveness, which is usually assessed through cost-utility analyses resulting in estimation of cost per QALY. As discussed previously, the same arguments and considerations apply equally well to studies of patients undergoing infra-inguinal ET and bypass surgery for IC.

As such, it remains far from clear whether CLTI patients who require IP revascularization and who are suitable for VB should have bypass or ET as their primary revascularization procedure. In other words, should such patients only have ET when they cannot have VB, or vice-versa? Related to this is the question of how far the surgeon should be prepared to go in splicing together lengths of perhaps suboptimal vein and/or using prosthetic material before they conclude that ET is in their patient's best interests. Again, these are highly controversial questions, and there is a wide range of opinion and practice. A recent systematic review of IP ET revealed a pooled technical success of 91.1% but a 1-year primary patency of only 62%.[67] Mortality and amputation rates in the 6769 patients studied were 15.1% and 14.9%, respectively, at 12 months. The authors commented that considerable heterogeneity and publication bias were present in most studies and concluded that procedural and clinical outcomes in the IP segment were "suboptimal." But the results of VB can also be suboptimal, and even in centers of excellence, the associated mortality and morbidity rates remain significant.[68,69]

One of the research recommendations made in the 2012 UK NICE PAD guidelines was for a RCT to address this very important question, and the UK NIHR HTA subsequently funded the BASIL-2 trial.[70] BASIL-2 is currently randomizing up to 600 patients who require IP revascularization to a VB first versus a "best" ET first revascularization strategy and expects to publish its results in 2022 (Fig. 110.6).

Best Endovascular Versus the Best Surgical Therapy in Patients With Critical Limb Ischemia

The need for large independently funded, unbiased, multicenter pragmatic trials is also widely recognized in the United States. The US NIH–funded Best Endovascular Versus the Best Surgical Therapy in Patients With Critical Limb Ischemia (BEST-CLI) trial is a prospective, randomized, multidisciplinary, controlled, superiority trial designed to compare treatment efficacy, functional outcomes, HRQL, and cost in patients undergoing best ET or best open surgical revascularization (http://www.bestcli.com/; Fig. 110.7).[71] BEST-CLI is currently randomizing at well over 100 sites in North America and in a number of European countries. The pragmatic trial design requires consensus on patient eligibility by at least two investigators, but leaves the choice of specific procedural strategy within the assigned revascularization approach to the individual treating clinician. Patients with suitable single segment of saphenous vein available for potential bypass will be randomized within Cohort 1 (n = 1620), while patients without will be randomized within Cohort 2 (n = 480). The primary efficacy endpoint of the trial is Major Adverse Limb Event (MALE) free survival. Key secondary endpoints include reintervention and AFS, and AFS alone. As a result of close collaboration over a number of years, there are many similarities between BEST-CLI and the BASIL 2 and 3 trials. The investigators have agreed to share data so that appropriate individual patient data (IPD) meta-analyses can be conducted when all three trials have completed their collective randomization of up to 3500 CLTI patients.

At the time of writing, the authors are not aware of any other publicly funded, large pragmatic RCTs ongoing elsewhere in the world. If this is, indeed, the case, then that does seem quite extraordinary, given the global prevalence and importance of CLTI.

Global Vascular Guidelines on Chronic Limb Threatening Ischemia

GVG is collaborative effort between the US SVS, ESVS, and the WFVS, and is due to publish its full recommendations in early 2018. The main aims of GVG are to improve CLTI outcomes by:

- Promoting paradigms and tools as a framework for evidence based revascularization (EBR)
- Making specific practice recommendations based on GRADE levels of evidence
- Identifying gaps in the evidence and suggesting areas and methods for future research

GVG recommends that decisions regarding revascularization are based upon PLAn principles:

- **P**atient risk estimation
  - Candidacy for LS
  - Peri-procedural risk
  - Life expectancy
- **L**imb threat severity using the SVS Wound Ischemia Foot infection (WIfI) staging system[72]
- **AN**atomic pattern of disease using the GLobal Anatomic Staging System (GLASS; Tables 110.2 and 110.3) based upon high quality imaging that should include the foot and ankle, together with an assessment of the availability and quality of autogenous vein for bypass

The development of the GVG GLASS was considered necessary because previous anatomic schemes based on individual lesions (such as TASC) or overall burden of disease (Bollinger)[73] may not be useful in defining the infra-inguinal (FP and IP) Target Artery Path (TAP), which needs to be cleared of significant disease in order to restore and maintain in-line flow (limb based patency, LBP) to the foot, which is the primary technical goal of endovascular EBR. While the TAP usually includes the least diseased IP vessel, the choice of outflow vessel may be angiosome based, and in some patients, two outflow arteries may be treated (discussed later).

Bypass surgery requires adequate inflow and outflow and, perhaps most importantly, a suitable autogenous conduit. By

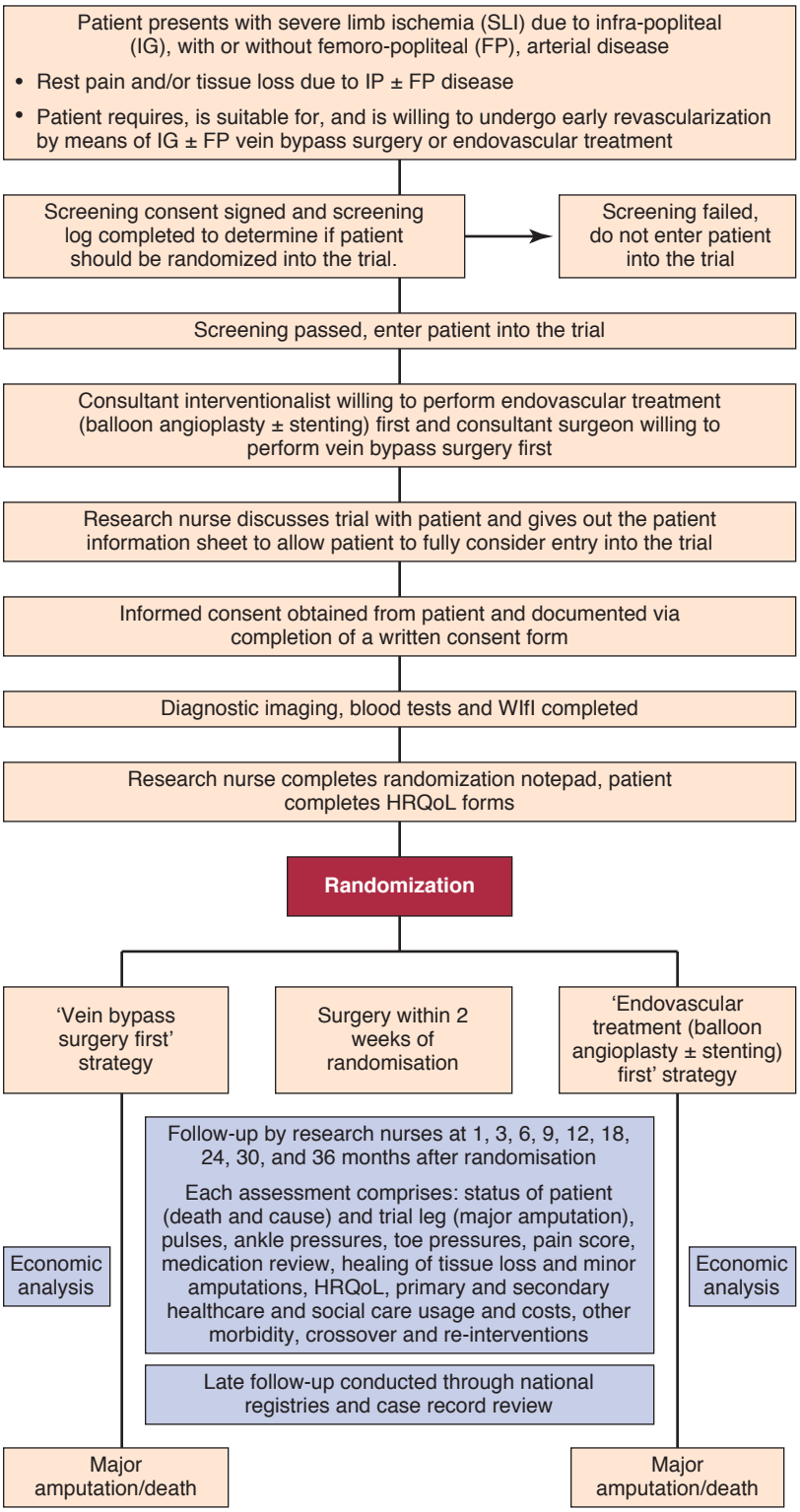

Figure 110.6 Bypass versus angioplasty in severe ischemia of the leg-2 flow diagram of study design (CONSORT diagram). *HRQoL*, Health related quality of life. (From Popplewell MA, Davies H, Jarrett H, et al. Bypass versus angioplasty in severe ischaemia of the leg-2 (BASIL-2) trial: study protocol for a randomised controlled trial. *Trials*. 2016;17:11.)

contrast, the success of ET is largely defined by the burden and complexity of atherosclerosis within the anticipated TAP.

Defining the planned ET TAP in each individual case is the basis for the GLASS framework. In defining the overall GLASS stage (I-III) for the limb, GLASS combines grade scores (0-4) from both the FP segment (origin of the SFA to the origin of the anterior tibial artery) and the IP segment (origin of the tibioperoneal trunk and the anterior tibial artery to the malleoli; see Tables 110.2 and 110.3). There are modifiers for heavy calcification and inframalleolar disease.

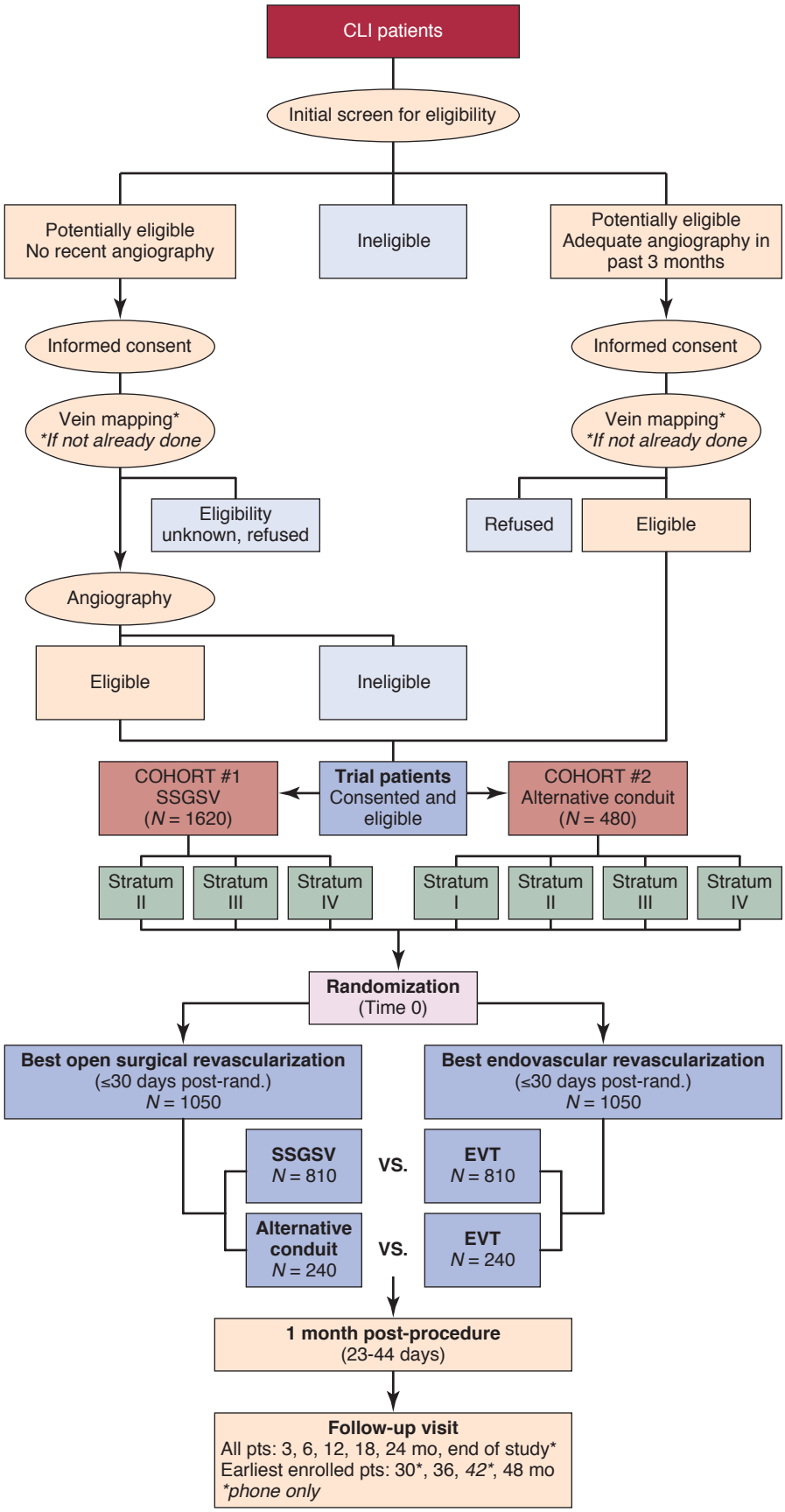

Figure 110.7 Best endovascular versus the best surgical therapy in patients with critical limb ischemia (BEST-CLI) trial patient flow chart. Stratum I: Ischemic Rest Pain (Rutherford Category 4) AND infrainguinal PAD without significant infrapopliteal occlusive disease, Stratum IL: Tissue loss with or without ischemic rest pain (Rutherford Category 5, 6) AND Infrainguinal PAD without significant infrapopliteal occlusive disease; Stratum Ill: Ischemic Rest Pain (Rutherford Category 4) AND Infrainguinal PAD with significant infrapopliteal occlusive disease; Stratum IV: Tissue loss with or without ischemic rest pain (Rutherford category 5, 6) AND Infrainguinal PAD with significant infrapopliteal occlusive disease. *CLI*, Critical limb ischemia; *EVT*, endovascular therapy; *PAD*, peripheral artery disease; *SSSGSV*, single-segment great saphenous vein. (From Menard MT, Farber A, Assmann SF, et al. Design and rationale of the best endovascular versus best surgical therapy for patients with critical limb ischemia (BEST-CLI) trial. *J Am Heart Assoc*. 2016;5(7):e003219.)

TABLE 110.2 Grading of Anatomical Severity of Disease in Global Anatomic Staging System (GLASS)

Femoropopliteal Segment	
0	Mild or no significant (<50%) disease
1	Total length SFA disease <⅓ (<10 cm); may include single focal CTO (<5 cm) as long as not flush occlusion; popliteal artery with mild or no significant disease
2	Total length SFA disease ⅓ to ⅔ (10-20 cm) may include CTO totaling <⅓ (10 cm) but not flush occlusion; focal popliteal artery stenosis <2 cm, not involving trifurcation
3	Total length SFA disease >⅔ (>20 cm) length; may include any flush occlusion <20 cm or non-flush CTO 10-20 cm long; short popliteal stenosis 2-5 cm, not involving trifurcation
4	Total length SFA occlusion >20 cm; popliteal disease >5 cm or extending into trifurcation; any popliteal CTO
Infrapopliteal Segment	
0	Mild or no significant (<50%) disease
1	Focal stenosis <3 cm not including TP trunk
2	Total length of target artery disease <⅓ (<10 cm); single focal CTO < 3 cm (not including target artery origin or TP trunk)
3	Total length of target artery disease ⅓ to ⅔ (10-20 cm); CTO 3-10 cm (may include target artery origin, but not TP trunk)
4	Total length of target artery disease >⅔ length; CTO >⅓ (>10 cm) of length (may include target artery origin); any CTO of TP trunk

IP grading is applied only to the primary selected vessel in the TAP.
Severe calcification (e.g., >50% of circumference, diffuse, bulky or "coral reef" plaques) within the TAP increases the within-segment grade by +1.
TP trunk disease is only included if the target vessel is the posterior tibial or peroneal artery.
CTO, Chronic total occlusion; *SFA*, superficial femoral artery; *TP*, tibioperoneal.

TABLE 110.3 GLobal Anatomic Staging System Stage (GLASS) of Infra-Inguinal Disease

	INFRAINGUINAL GLASS STAGE					
FP Grade	**4**	III	III	III	III	III
	3	II	II	II	III	III
	2	I	II	II	II	III
	1	I	I	II	II	III
	0	n/a	I	I	II	III
		0	**1**	**2**	**3**	**4**
	IP Grade					

FP, Femoropopliteal; *GLASS*, GLobal Anatomic Staging System; *IP*, infrapopliteal.

The intention is that GLASS stage will be used to help predict the likelihood of ET technical failure and 12-month LBP as follows:

- Stage I: Average Complexity: expected technical failure <10% AND >70% 12-month LBP
- Stage II: Intermediate Complexity: expected technical failure <20% AND 50% to 70% 12-month LBP
- Stage III: High Complexity: expected technical failure >20% AND <50% 12-month LBP

These GVG concepts and tools will require verification and validation in different cohorts of patients undergoing ET, and bypass, for CLTI. However, it is hoped that they will provide a more thoughtful and logical means of identifying those patients who should be offered an ET first revascularization strategy based upon the condition of the patient, the status of the leg and foot, and the overall burden of atherosclerotic disease. It is also anticipated that they will help improve the quality of future research, partly by better defining subgroups of patients for study with the heterogeneity of the CLTI population as a whole.

FACTORS AFFECTING OUTCOMES

A wide range of factors has been reported to impact upon the short-, medium-, and long-term success of infra-inguinal ET in patients presenting with IC and CLTI.[74]

Smoking

As discussed previously, continued smoking is arguably the most powerful of the factors determining the overall prognosis of patients presenting with IC and CLTI, and also their outcomes following ET. For example, in one recent study of 647 patients, compared with never smokers, current (HR 2.45, 95% CI 1.62-3.71) and former (HR 1.62, 95% CI 1.14-2.29) smokers with PAD had higher rates of death.[75]

Best Medical Therapy

Patients presenting with PAD, in particular CLTI, are at greatly increased risk of cardiovascular morbidity and mortality. Despite this, PAD patients often receive suboptimal medical therapy, especially when compared with patients who present with coronary artery disease.[76] In addition to nontreatment, undertreatment and patient non-concordance with BMT both remain significant issues in everyday practice that will probably adversely impact the safety and clinical benefits of infra-inguinal ET.

Diabetes Mellitus

A growing proportion of PAD patients, and now probably the majority of patients undergoing ET for CLTI, suffer from diabetes mellitus (DM).[77] Diabetes affects the presentation, diagnosis, and management of PAD in many ways. However, perhaps surprisingly, several studies, including the BASIL-1 trial, have failed to convincingly identify DM as an independent predictor of outcomes following revascularization, although as a group they may be less likely to be offered revascularization.[78] A recent US study compared outcomes following bypass and ET at and below the knee in 2566 CLTI patients with and without DM using data from the 2008 to 2014 VQI.[79] Patients with DM were more likely to be black (18% vs. 14%), had more comorbidities, and more frequently underwent revascularization for tissue loss (85% vs. 58%) (all, $P < .001$). However,

DM did not significantly affect 1-year primary patency, major amputation, or mortality following bypass or ET. The authors concluded that aggressive LS should be pursued in patients with CLTI regardless of the presence of DM. While few would argue with this sentiment, the reality is that the extensive, heavily calcified IP and pedal disease so often seen in patients with diabetes, and those with ESRD which often co-exists, is a significant challenge to conventional ET, as well as surgical bypass. Advanced ET techniques aimed at dealing with this pattern of disease, such as SAFARI, have been around for more than 10 years.[80] However, how many patients will be suitable for these innovative ET approaches, how many physicians will be able to master the skills required, and the extent to which these techniques will impact long-term LS remains to be seen.

Gender

While some studies have found women with PAD to have worse outcomes,[81] including after surgical revascularization and ET,[82,83] others appear to have found the opposite.[84] As such, the nature of the relationship and the causes of any observed differences remain unclear.[85] One possibility is that, on average, women tend to have smaller vessels, which have been shown to predict poorer ET outcomes.[86] However, it seems likely to be far more complex than that. Further research is required to determine if there is a subgroup of women at predictably high risk of poor outcomes after infra-inguinal ET, or indeed bypass.[85]

Residual and Recurrent Disease

There is a considerable body of literature looking at the outcomes of infra-inguinal ET and surgical revascularization following previous intervention. As discussed previously, in the BASIL-1 trial, secondary surgical bypass following failed ET was associated with significantly lower AFS and OS when compared with those observed after primary bypass. Whether this is because failed ET directly jeopardizes subsequent bypass, or because failed ET selects out a subgroup of patients who were likely to have poor outcomes regardless of whether they had ET or bypass as their first intervention, remains unclear. Several other groups have addressed this question, and the results are somewhat conflicting. For example, in a recent study of 142 infra-inguinal bypasses, outcomes following primary bypass were not superior to those performed after unsuccessful ipsilateral IP ET. The authors concluded that unsuccessful IP ET does not have a negative impact on the outcome of subsequent ipsilateral distal bypass in patients with CLTI.[87] By contrast, in another study that evaluated bypass outcomes after failed ET, the authors found change in the bypass target to a more distal site was identified in nearly half of patients and concluded that "poor outcomes of open interventions after EVT can be expected if ET fails."[88] A further recent study, which used data for more than 7000 patients from the National Surgical Quality Improvement Program Targeted Vascular module, found that prior revascularization in patients treated for both IC and CLTI was associated with worse perioperative outcomes when compared with primary bypass. Furthermore, prior ET was associated with increased wound infections, whereas those with prior bypass had higher re-intervention rates. The authors concluded that "the increasing prevalence of patients undergoing multiple interventions stresses the importance of the selection of patients for initial treatment and should be factored into subsequent revascularization options in an effort to decrease adverse events."[89] So, whether a CLTI patient is primarily treated with ET or bypass, there is a significant chance that they will require further intervention(s); that reality should be shared with the patient and, where appropriate, their family, and also taken into account when offering different revascularization strategies.

Restenosis and, in particular in-stent restenosis,[90,91] leading to further interventions, remains a significant obstacle to clinically durable and cost-effective ET. In the FAIR trial, where 119 patients with in-stent restenosis were randomized to DCB or PBA, the authors concluded that "DCB for superficial femoral artery in-stent restenosis is associated with less recurrent restenosis and a better clinical outcome than PBA without an apparent difference in safety." No cost-effectiveness data were presented, most of the endpoints reported were anatomic, and follow-up was only 12 months.[92] In the PACUBA trial, where 74 patients with in-stent stenosis were randomized to DCB or PBA, the authors reported that DCB provided significantly higher patency rates, although this did not appear to translate into additional meaningful clinical benefit.[93] Further research is clearly required to define how best to prevent, detect, and treat such recurrent disease.[94,95] A related question is defining the optimal ET for vein bypass grafts that are considered to be "failing" due to within-graft and anastomotic stenoses. To date, there is little evidence that DCB offer a more clinically and cost-effective option than PBA.[96] However, further studies are required.

End-Stage Renal Disease (Dialysis)

Overall and amputation-free survival remain poor in CLTI patients with end-stage renal disease (ESRD) regardless of revascularization strategy and, wisely, a prudent approach to patient selection has been advised.[97] Although comparative data are lacking, it would appear that most clinicians favor an ET over a bypass first revascularization strategy for most such patients on the grounds that it is probably the least worst option given that the morbidity and mortality associated with surgery can be very high.[98] This is an important area for research, as the number of people with ESRD presenting to vascular specialists with CLTI seems likely to continue to increase, especially in certain populations.[99,100]

Vessel Calcification

This an increasingly common finding, as the proportion of CLTI patients with DM and/or ESRD increases. Calcification can be quantified on CT angiography and related to technical failure rates.[101,102] However, how these data might alter decisions regarding ET (vs. surgical) revascularization remains unclear and such calcification remains a significant challenge.[103] Further research is required to assess the potential role of alternative technologies such as cutting balloons and debulking.[104]

Body Mass Index

There is a complex relationship between body mass index (BMI) and outcomes, including mortality, after ET (and bypass surgery) in CLTI patients. Underweight patients have the poorest prognosis both in relation to other co-morbidities but also as an independent predictor of LS. Similarly, normal weight patients appear to have a small but significant increase in mortality compared with overweight/obese patients.[105] This has been termed the "obesity paradox" and is not easily explained. In a recent study of 62,445 patients, although obesity (BMI > 30) did not impact in-hospital mortality in patients who underwent ET, obese patients did suffer more adverse events and stay in hospital longer, leading to significant cost implications.[106]

Race and Ethnicity

The relationship between race, ethnicity, and health outcomes has been widely studied and, as might be expected, varies considerably between different countries. Even within countries, the data can be conflicting.[107] Separating out the impact of genetics, environment, and socio-economic status is difficult.[108]

Re-admissions

Several studies have looked at factors that might predict early (typically 30-day) readmission to hospital after ET. In a recent study that used data on more than 60,000 hospitalizations from the 2013 to 2014 Nationwide Readmissions Databases, approximately 1 in 5 patients admitted for CLTI and undergoing revascularization were readmitted within 30 days. Presentation with ulcer or gangrene, age ≥65 years, female sex, large hospital size, teaching hospital status, known coronary artery disease, heart failure, DM, chronic kidney disease, anemia, coagulopathy, obesity, major bleeding, acute myocardial infarction, vascular complications, and sepsis were identified as independent predictors. However, the mode of revascularization was not independently associated with readmission. Infections (23.5%), persistent or recurrent manifestations of PAD (22.2%), cardiac conditions (11.4%), procedural complications (11.0%), and endocrine problems (5.7%) were the most common reasons for readmission.[109] Another study also found that unplanned readmission after ET is relatively common, especially in patients with CLTI, and was associated with substantially increased mortality. The authors concluded that awareness of risk factors for readmission may help providers identify patients at high risk who may benefit from early surveillance, and prophylactic measures focused on decreasing postoperative complications, thus reducing the rate of readmission and improving overall outcomes.[110]

INFLOW CONSIDERATIONS

Common Femoral Artery

Clinically important common femoral artery (CFA) plaque is generally bulky and eccentric and, while it may be quite focal, often co-exists with significant proximal and distal disease. Although it generally remains the case that most clinicians would favor a surgical approach for most patients, the primacy of CFA endarterectomy (CFE) over ET is being increasingly challenged.[111] In a study of 40 CFA stent procedures in 36 patients, 25 of whom had IC, mortality at 5 years was 38%; at 3 and 5 years, primary sustained clinical improvements were 77% and 73%; freedom from target lesion revascularization and target extremity revascularization were 79% and 73%; and in-stent restenosis rate was 28%. The significant predictors of in-stent restenosis were deep femoral artery (DFA) stenting and type III lesions. One stent fracture was found at 1 year and was without clinical consequence; no other stent fracture was noted. The authors concluded that "endovascular repair of the CFA and its bifurcation seems to provide sustained clinical and morphologic long-term results. Fear of stent fracture and local complications due to hip mobility are no longer relevant."[112] Other investigators have also reported encouraging results after CFA ET and the time for a large, pragmatic RCT in patients at average and high risk of CFE has probably come.[113-116]

Deep Femoral Artery

ET of the DFA, either as part of more extensive CFA stenting or more localized balloon angioplasty of often focal and heavily calcified orificial disease, remains highly controversial. Understandably, many vascular surgeons are very nervous at the thought of the origin of the DFA being covered by an endovascular device. At the present time, the number of patients in whom DFA ET would be appropriate and likely to be of clinical benefit would seem to be very small. However, with advances in endovascular devices and techniques that may change in the future.

Hybrid Procedures

The concept of the hybrid procedure has become increasingly fashionable, although few data are available.[117] As the term refers to an extremely heterogeneous collection of procedures, and identifying a suitable control population is problematic, making comparisons is difficult. Some would argue that a hybrid procedure exposes the patient to the worst to both worlds: the morbidity of open surgery and the lack of durability of ET. Others will say that it is entirely sensible to try to reduce the magnitude of open surgical revascularization whenever possible. Both positions are likely to be applicable to certain patients, and as ever, "case selection" is vital. What the concept of hybrid procedures does help to reinforce is the need for CLTI patients to be treated by physicians in centers that can offer both ET and open surgery with equal skill and facility. CFE with or without profundaplasty, combined with inflow and/or infra-inguinal ET, appears reasonable and logical and to be increasingly popular in centers where vascular specialists have both surgical and ET expertise and access to hybrid operating facilities.

OUTFLOW CONSIDERATIONS

Angiosome Targeted Endovascular Treatment

Much has been written about whether angiosome-targeted ET results in better outcomes when compared with so-called indirect revascularization. Overall, the data are somewhat conflicting, perhaps partly because different definitions of direct and indirect revascularization are used in the literature.[118] In a study of 486 patients undergoing direct revascularization (DR), indirect revascularization through collaterals (IR-tc), or indirect revascularization without collaterals (IR-wc), at 1 year the unhealed ulcer rate of the IR-wc group was significantly higher than that of the DR group and the IR-tc group; the LS rate of the IR-wc group was significantly lower than that of the DR group and the IR-tc group; and there were no differences in ulcer healing or LS between the DR and IR-tc groups. The authors concluded that directly revascularizing the feeding artery and indirectly achieving revascularization through collaterals can both be effective in patients undergoing IP ET for CLTI.[119] In another series of 139 CLTI patients undergoing IP ET, the authors concluded that "the angiosome concept had no impact on clinical success."[120] In a retrospective Brazilian study of 92 patients (109 legs) undergoing IP angioplasty, the authors "found no evidence to support revascularization based on the concept of the angiosome in preference to revascularization of the artery that is most amenable to endovascular treatment."[121] In a small series of 30 patients, the impact of isolated tibial angioplasty on the foot macro- and microcirculation was assessed. The authors reported a significant improvement in tissue perfusion immediately after the procedure but that the effect was global and not restricted to angiosome borders.[122] In another study looking at this issue, the authors concluded "in patients with CLTI and tissue loss receiving a peroneal bypass, patency of both peroneal branches and pedal arch was associated with a better healing rate and a better AFS rate irrespective of wound angiosome location."[123]

Treatment of Multiple Outflow Vessels

Related to the controversy over direct (angiosomic) versus indirect revascularization is the question of whether clinical outcomes can be improved by treating two outflow vessels. In a study from Japan, the authors treated 123 patients (137 limbs) with CLTI who had lesions of both the anterior and posterior tibial arteries. In 84 limbs, only one artery was treated, while in 53 limbs, both arteries were treated. The wound-healing rate was significantly higher (87% vs. 79%; $P = .003$), the time to wound healing was shorter (median, 83 vs. 142 days; $P = .01$), and the repeat peripheral vascular intervention rate was lower (15% vs. 35%; $P = .03$) in the two-vessel treatment group. The additional benefit of double revascularization was observed particularly in patients with a high WIfI clinical stage.[124] By contrast, a US study based on 673 limbs (528 patients) undergoing IP ET, mostly (77%) for tissue loss, multiple-vessel intervention did not improve outcomes when compared with a single-vessel intervention.[125] In a Brazilian study of 109 IP angioplasties, the authors concluded "it is unnecessary to treat the largest number of arteries possible in CLI patients. Instead, the most amenable artery for endovascular procedures should be treated to improve LS and secondary patency rates."[126] Although ET practice, especially below the knee, varies widely, that does appear to represent the majority view at the present time.

Pedal Intervention

As a result of the advances in ET technologies, techniques, and expertise, there has been increasing enthusiasm for treating pedal disease, especially via the retrograde approach, sometimes using the pedal loop technique.[127] However, as discussed previously, to date, there are few data to guide practice in this area.[128] In the RENDEZVOUS registry from Japan, 257 CLTI patients were divided into two groups according to whether pedal artery angioplasty (PAA) was performed ($n = 140$) or not ($n = 117$). The rate of wound healing was significantly higher (57.5% vs. 37.3%, $P = .003$) and time to wound healing significantly shorter (211 days vs. 365 days; $P = .008$) in the PAA group. In a multivariate analysis, non-ambulatory status, target wound depth and daily hemodialysis were as predictors of delayed healing. In the moderate-risk but not in the high-risk population, PAA significantly improved wound healing.[129]

Atherectomy

Atherectomy remains popular in some centers in some countries, but that is very much not the case in others. A recent thorough and well-referenced review of the current evidence for different forms of atherectomy concluded "atherectomy devices have continued to emerge as a major therapy in the management of peripheral vascular disease."[130] Some might take the view that, given how long these devices have been available in one form or another, it is surprising that they should still be regarded as emerging technologies. In a recent study that evaluated the combined use of directional atherectomy and DCB for CFA disease, the authors concluded that it was a "safe and effective alternative to surgery."[131] With respect to orbital atherectomy and CFA disease, in a subanalysis of the CONFIRM registry, the investigators took the view that "a randomized trial is needed to determine the ideal treatment strategy for calcified CFA disease."[132] In a review of different techniques for ET of SFA disease, the authors opined that "paclitaxel-eluting balloon (PEB) angioplasty, stenting, and directional atherectomy (DA) have provided new options for the treatment of superficial femoral artery disease; however, the comparative efficacy of these interventional strategies remains uncertain."[133] Another recent review concluded "increased use of atherectomy in all segments of the lower extremity arterial system has been observed, particularly in OBLs [office-based laboratories], without substantial evidence in the literature of increased efficacy compared with standard angioplasty with or without stenting. Generous Medicare reimbursement for in-office atherectomy procedures is likely contributing to the volume shifts observed."[134] As is

TABLE 110.4 Methodologic Issues With Existing Endovascular Literature

Almost all industry sponsored
Almost all of the patients have IC
CLTI patients almost all have rest pain only (Rutherford 4)
Outcome data for IC and CLTI conflated
Highly selected centers, patients, and lesions
Not randomized
Not controlled
Historical controls
Retrospective analysis
Exclusions and short (incomplete) follow-up
Focus on anatomic endpoints
No objective or subjective clinical endpoints
No cost-effectiveness analysis

CLTI, Chronic limb threatening ischemia; *IC*, intermittent claudication.

not infrequently the case when reviewing the ET literature, it is difficult to know what to make of the conflicting, often limited quality, data in this area. The cynic might say that one can only be reasonably confident of one thing: reimbursement drives practice.

Stent Graft

In the Japanese multicenter Viabahn trial that aimed to assess 1-year safety, efficacy, and invasiveness outcomes of endovascular stent grafting of symptomatic long lesions (≥10 cm) in the SFA as a substitute for above-knee open bypass surgery, the take-home message was "stent grafting appears to be a safe and less invasive alternative to above-knee bypass surgery, providing 88% to 92% primary patency at 12 months in long, complex lesions."[135] Of note, over 97% of the patients had IC, the follow-up was only 12 months, there was no cost-effectiveness analysis, and the only reported clinical outcome was disease-specific HRQL, which increased significantly from baseline.

CONCLUSIONS

Although ET for infra-inguinal PAD has been available for more than 20 years, and while no one doubts that it has an important role to play in the management of both IC and CLTI, at the present time, exactly what that role is, and what technologies are most clinically and cost-effective for which patients, remains unclear.[a]

While there is certainly no shortage of publications,[150] unfortunately, almost all of the reported studies have one or more serious methodologic limitations (Table 110.4) that hamper appropriate translation of the data to everyday clinical practice.[31,53,140,146,151-176] The habit of conflating data gathered in patients with IC and CLTI and focusing on often very short-term, anatomic rather longer-term clinical outcomes are particularly problematic. Given that most patients with IC, and even CLTI, will live more than 5 years, basing the choice of intervention on 6- and 12-month outcome data seems difficult to justify. Even where clinical data are presented, it is important to distinguish between clinical:

1. Efficacy: the ET results in important clinical benefit in a selected group of homogenous patients when performed by a selected group of clinicians (within an explanatory trial)
2. Effectiveness: the ET results in important clinical benefit for many different patients when delivered in most healthcare settings (within a pragmatic trial)

Although both types of trial are required to make progress, to date, virtually of the published ET data falls into the former (efficacy, explanatory) category. However, unfortunately, the results are often presented, and the ET in question marketed, as if they represent the latter, leading to ET devices and techniques being prematurely adopted by some as the new standard of care.

Although there are repeated calls in the literature and at conferences for pragmatic RCTs to demonstrate clinical and sometimes cost-effectiveness, the "inconvenient truth" is that such trials are in very short supply. The result is that to a very considerable extent we practice in absence of a credible "level 1" evidence base, especially when managing CLTI.[94,104,177-179] This leads to significant practice variations and the highly variable outcomes observed between and within countries.[180,181]

At vascular conferences around the world, discussions regarding revascularization, especially in CLTI, often take the form of adversarial debates where opposing factions set out the perceived pros and cons of surgery versus ET. While entertaining, in reality, this approach represents an oversimplification of the clinical challenge. The argument that "all" patients should receive surgery or "all" patients should have ET, or even that "all" patients should be offered revascularization, lacks credibility. The term CLTI refers to a heterogeneous group of patients with differing degrees of tissue damage, ischemia, and infection in association with a wide variety of patterns of arterial disease. As such, the remedy is likely to vary considerably between individuals. This paradigm is emphasized in the GVG on CLTI, which promotes tools such as WIfI and GLASS as a means of appropriately stratifying patients for ET and surgery as well as for future research.

The corollary of the above discussion and approach is that patients with CLTI, and indeed IC, should be managed in a center and by a multidisciplinary team that can offer all of the medical, physical (supervised exercise therapy, orthotics, rehabilitation), ET, and surgical (bypass, podiatry) treatment alternatives.[7] With regard to revascularization, although some physicians can perform ET and surgery, many do not have the skills and/or facilities to be able to offer both with equal facility. This will bias the treatment offered, probably to the detriment of patients. Given the growing complexity of ET and surgical revascularization for CLTI it is not surprising that a relationship has been observed between individual physician case volume

[a]References 3, 7, 67, 74, 94, 104, 136-149.

TABLE 110.5 IDEAL: Suggested Stages of Endovascular Innovation

Stage	1 Idea	2a Development	2b Exploration	3 Assessment	4 Long-Term Study
Patients	Single digit, highly selected and homogeneous	Few; selected and homogenous	Many; more heterogeneous	Many; expanded but well defined indications	All eligible
Vascular specialists	Very few; innovators	Few; innovators and early adopters	Many; innovators, early adopters, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement and some comparison	Comparison	Regional and international variance; quality assurance; risk stratification and adjustment
Procedure	Inception	Development	Refinement	Fully evolved	Fully evolved
Method	Structured case report	Prospective development study	Prospective cohort study; feasibility/ explanatory RCT	RCT	Registries and databases
Outcomes	Proof of concept; technical achievement; disasters; notable successes	Technical success; emphasis on safety and reproducibility	Safety; objective clinical and patient reported outcomes	Objective clinical and patient reported outcomes; cost-effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Yes, usually	Yes, always	Yes, always	Yes, always	Yes, always

RCT, Randomized controlled trial.

and outcomes.[182] While in some healthcare environments there may be barriers to referring patients on to colleagues with specific skill sets, even within the same institution, the well-established principles of comparative advantage are very likely to produce net long-term benefits to patients and clinicians alike.[183] While important, successfully overcoming the technical challenges posed by complex, multilevel, increasingly distal disease does not always guarantee optimal patient outcomes following initially successful ET, especially in the longer term. Other important ingredients of success include good relationships with community physicians and nurses, medical optimization,[184] and "prehabilitation" prior to intervention, together with well-organized, high-quality follow-up comprising, as necessary and appropriate, rehabilitation, orthotics, prosthetics, and ET/surgical surveillance protocols.

While in the wealthiest of countries, demonstrating the cost-effectiveness of adjuvant and new ET technologies may not (yet) be a requirement for reimbursement by public and private payers, in most healthcare settings around the world this is a very important issue.[185] From an economic viewpoint, each clinically and cost-ineffective intervention is associated with an opportunity cost that has both financial and nonfinancial elements in that, potentially, it prevents another patient from having an intervention that is cost-effective. From a UK perspective, the current striking difference in cost between PBA and DCB, and between BMS and DES, means that drug technologies would have to deliver highly superior clinical outcomes in order to justify their use within current commonly accepted WTP thresholds. So far, there is no evidence that this is the case for either IC or CLTI, and the outcome of BASIL-3 is keenly awaited.

In order to prevent a situation where vascular specialists are still as uncertain about the role of ET for the treatment PAD in a further 20 years as they are now, a new paradigm would seem to be required with regard to the development and evaluation of new endovascular techniques and technologies.[136] To that end, the IDEAL framework describes the advantages and disadvantages of a range of different research methodologies that can be used to provide varying levels of evidence and serve different purposes (Table 110.5; http://www.ideal-collaboration.net/). However, once the assessment stage has been reached, RCTs remain by far the most reliable means of comparing the clinical and cost-effectiveness of alternative treatment strategies and so should be the method of choice whenever practically and financially feasible.[186,187] There is no shortage of patients with IC and CLTI, and so such trials should not, in theory, be logistically difficult or take a long time to report. Funding of such trials by governmental or professional organizations greatly enhances the value of the resulting data by avoiding actual or perceived commercial sponsor bias.[188,189] Objective performance goals (OPGs) are a useful "stepping stone,"[190] but without pragmatic RCTs, OPGs cannot be refreshed, and so over time increasingly come to rely on historical controls. As such, RCTs are required to determine clinical and cost effectiveness once safety and efficacy OPGs have been met.

In summary, there is a growing realization that the quality of reporting needs to improve if advances in endovascular technology are to lead to better outcomes for patients who

TABLE 110.6 BASIL 2/3 and BEST-CLI Trial Endpoints

Endpoints	BASIL 2/3	BEST-CLI
Primary	AFS	MALE-Free Survival
Secondary	Freedom from all-cause mortality	Freedom from all-cause mortality
	In-hospital and 30-day morbidity and mortality	RAFS
	MALE	Freedom from MALE + POD
	MACE	AFS
	Relief of ischemic pain	Freedom from myocardial infarction
	Psychological morbidity	Freedom from stroke
	Re- and cross-over intervention rates	Freedom from re-interventions (major and minor) in index leg
	Healing of tissue loss (ulcers, gangrene)	Number of re-interventions (major and minor) per limb salvaged
	Extent and healing of minor amputations	
	Hemodynamic changes; absolute ankle and toe pressures, ABPI, TBPI	Freedom from hemodynamic failure
		Freedom from clinical failure
		Freedom from CLTI
	HRQL (VascuQoL and EQ-5D)	HRQL (VascuQoL and EQ-5D)
	Health economic analysis	Heath economic analysis

ABPI, Ankle-brachial pressure index; *AFS*, amputation-free survival; *BASIL*, bypass versus angioplasty in severe ischemia of the leg; *BEST-CLI*, best endovascular versus the best surgical therapy in patients with critical limb ischemia; *EQ-5D*, EuroQol five dimensions questionnaire; *HRQL*, health-related quality of life; *MALE*, major adverse limb event; *POD*, perioperative death; *RAFS*, re-intervention and amputation-free survival; *TBPI*, toe-brachial pressure index; *VascuQoL*, vascular quality of life.

present with lower limb PAD. The authors of the SVS Reporting Standards eloquently express this as follows[191,192]:

"PAD represents a spectrum from asymptomatic stenosis to limb-threatening ischemia. The last decade has seen a tremendous increase in the variety of endovascular devices and techniques to treat occlusive disease. Like many evolving technologies, the literature surrounding therapy for endovascular arterial disease consists of mixed-quality manuscripts without clear standardization. Accordingly, critical evaluation of the reported results may be problematic. As such, providers and their patients make treatment decisions without the full benefit of a comparative effectiveness framework."

In an attempt to raise the quality of the science underpinning ET, and to promote evidence-based revascularization (EBR), GVG suggests the following quality standards when designing RCTs:

1. Inclusion and exclusion criteria should be limited to those essential to trial integrity.
2. IC and CLTI patients should not be enrolled within the same trial.
3. CLTI trials should include patients with tissue loss, not just rest pain.
4. An integrated limb-based limb threat system (such as WIfI)[72,125,149,193,194] and a whole limb anatomical classification system (such as GLASS) should be used to describe the clinical and anatomic characteristics of enrolled patients.
5. Clinical efficacy and clinical effectiveness should be clearly distinguished.
6. Use a range of endpoints (Table 110.6) including:
   a. Objective clinical: for example, AFS, MALE free survival, and time to wound healing[195] and relief of rest pain
   b. Subjective clinical: for example, patient-reported outcomes measures (PROMs) and HRQL instruments[196-198]; these permit a "time-integrated measure" measure of clinical disease severity from the patient's perspective
   c. Hemodynamic: for example, ankle and toe pressures and indices[199]
   d. Anatomic; for example, patency, restenosis, TLR, TVR
7. A full heath economic (cost-utility) analysis should be included so that each healthcare system can determine whether and how the clinical data should be used in relation to individual countries' WTP thresholds based on economic, societal, and political considerations.[200]
8. Follow-up patients for at least 2 to 3 years; 6- or 12-month follow-up periods are unlikely to be adequate and may well be misleading.
9. Publish all trial protocols, together with the full statistical analysis plan, in peer-reviewed journals to allow for independent, public, and transparent scrutiny.
10. Share data between RCTs to allow subsequent IPD meta-analyses and subgroup analyses.
11. The design, conduct, and reporting of trials should be free of commercial influence.[189]

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CHAPTER 111

Lower Extremity Amputations: Epidemiology, Procedure Selection, and Rehabilitation Outcomes

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Major lower extremity amputations continue to be part of all vascular practices despite the general approach of aggressive limb salvage. Although often viewed as a failure of treatment, major amputation should be considered a reconstructive and definitive treatment option. The convergence of several important factors, including the increased life expectancy of the population and the epidemics of diabetes and peripheral artery disease (PAD), suggests that amputations will remain an important issue facing patients and surgeons for the foreseeable future.

The goal of amputation is to remove all infected, gangrenous, and ischemic tissue and provide the patient with the longest functional limb. Avoidance of repeated amputations and uncomplicated healing of operative sites is crucial for the patient's optimal recovery and best functional rehabilitation or palliation.

Abstract

Despite advances in limb salvage, major lower extremity amputations continue to be part of all vascular practices. Major amputation should be considered a reconstructive, definitive treatment option. The goal of amputation is to remove all infected, gangrenous, and ischemic tissue and provide the patient with the longest functional limb. Appropriate level selection, careful attention to comorbidities and appropriate rehabilitation goals can lead to optimal patient recovery and meaningful functional outcomes.

Keywords

amputation
indications for amputation
amputation level selection
rehabilitation
functional outcome

EPIDEMIOLOGY

In the United States, approximately 60,000 major amputations (above the ankle) are performed annually.[1-3] Diabetes and PAD remain the major risk factors for lower extremity amputation worldwide.[4] Studies show that 25% to 90% of all amputations are associated with diabetes.[2,4] Patients with diabetes have an eightfold greater risk of amputation than those without diabetes.[3] This association is due to the presence of neuropathy and infection, as well as the increased prevalence of PAD in this patient population.

Despite the increase in diabetes, current published data support an overall decrease in major amputation rates.[5-7] A review of all Medicare claims from the Centers for Medicare and Medicaid Services between 1996 and 2006 showed a 29% decline.[5] Results were not different if above-knee amputations (AKAs) were studied distinctly from below-knee amputations (BKAs), because both decreased in similar magnitude. A report from the National Hospital Discharge Survey data on nontraumatic lower extremity major amputations (NLEAs) and National Health Interview Survey data on diabetes prevalence showed the age-adjusted NLEA discharge rate per 1000 persons decreased from 11.2 in 1996 to 3.9 in 2008, while rates among persons without diabetes were unchanged.[3] These trends were validated in a Scottish national cohort study from 2004 to 2008 where major amputations rates decreased by 40.7% from 1.87 per 1000 in 2004 to 1.11 per 1000 in 2008.[7] However, some recent data suggest that these decreases may have leveled off since 2009.[8]

Variation in Amputation Rates

There is significant regional variation in the performance of amputation around the world, which suggests that factors other than strict medical issues may affect amputation rates.[4-10] A study from the United Kingdom cited significant regional variation in amputation rates and stressed the need for consensus guidelines.[9] The Global Lower Extremity Amputation Study Group reported that the highest amputation rate (for a first major amputation) was 44 per 100,000 population per year among Navajo men, and the lowest rate was 2.8 per 100,000 per year in Madrid, Spain.[4] Physician experience plays a key role in the selection of amputation as a treatment. In the treatment of critical limb ischemia, surgeon caseload and hospital volume have been shown to affect amputation rates, with low volumes being associated with higher amputation rates.[11]

A study of a Medicare claims database demonstrated that the supply of vascular specialists influences the rate of amputation. A 0.30 increase in the number of vascular surgeons per 10,000 Medicare beneficiaries was associated with a 1.6% reduction in amputations.[12] The distribution of vascular surgeons and interventional radiologists in the United States is strongly correlated not only with regional medical needs but also with local climate, education, crime, and transportation. This observation suggests that policies to increase the supply of vascular specialists in underserved areas may reduce regional disparities in amputation rates.[12] Patient and healthcare provider education has also been demonstrated to reduce amputation rates.[13] Earlier identification of patients at risk leads to timelier referral, treatment, and intervention.

Effects of Ethnicity, Economic, and Social Factors

A complex interaction exists between race or ethnicity and amputation rates. In certain groups, such as the Native American Navajo population, amputation rates appear to be related to the high incidence of diabetes.[4] However, blacks are more likely than whites to undergo amputation as opposed to revascularization, even when controlling for the presence of diabetes.[14,15] These differences have been attributed to variations in access to healthcare, treatment of comorbidities, and possible physician and patient factors. Insurance status also has an effect on amputation rates. Patients without insurance coverage have higher rates of amputation than those with access to health insurance.[16] Data from the National Inpatient Sample documented that 34% of the 691,833 patients presenting with lower extremity ischemia from 1998 to 2002 underwent amputation. The primary amputation rates were significantly higher among patients who were nonwhite, low income, and without commercial insurance.[16] Similar results showed that black patients were 1.7 times more likely to have both primary and repeat amputation than other patients.[17] These findings may be affected by the recent changes in access to healthcare put forward by the Affordable Care Act. In Massachusetts, the expanded insurance coverage initiated in 2006 appears to have decreased some disparities that previously existed between whites and nonwhites presenting with PDA.[18] Whether this can be repeated on a national scale remains to be seen.

Effect of Revascularization Rates

Trends in the interplay between revascularization and amputation rates are complicated. Over a 10-year period the Mayo Clinic reported a 50% reduction in amputation rates that corresponded to increased rates of lower extremity revascularization by both surgical and endovascular (EV) techniques.[19] A Finnish study also demonstrated that an increase in revascularization rates correlated with a decrease in major amputation rates in elderly patients.[20] A US study of two national (Nationwide Inpatient Sample and National Hospital Discharge Survey) and four state databases demonstrated that both the number of lower extremity revascularizations and the number of major amputations have declined; this has been accompanied by a substantial increase in lower extremity EV interventions. From 1998 to 2003 the volume of major amputations decreased 16% regionally[1] (New York, California, New Jersey, and Florida) and 25% nationally.[5] However, minor amputations increased 4% regionally and 3% nationally. It has been speculated that the improved limb salvage rates are partially explained by the increase in total revascularization procedures (driven by EV interventions due to the perceived less morbidity). Earlier EV interventions, in less critical lesions, and expanding EV procedures in the patient at high-risk for open bypass may contribute to the decrease rates of major

amputations. In addition, failed EV procedures may not directly translate into amputations. Other possible factors contributing to lower rates of amputation include greater awareness of PAD, clear guidelines for medical management of atherosclerosis, risk factor modification, and improved wound care methods.

High-risk patients treated with EV intervention have superior rates of limb salvage and maintenance of ambulation compared with patients undergoing primary amputation. However, these patients have no better functional benefit than those treated with primary amputation after 1 year.[21] Indeed, when autologous vein is available, the long-term results of the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial indicate that the outcomes of a bypass surgery–first approach is superior to a balloon angioplasty–first strategy in terms of amputation-free survival.[22]

The ideal balance of EV and open surgical reconstructions has yet to be determined for lower extremity ischemia. Nationwide Inpatient Sample data suggest that lower extremity revascularizations have reached a plateau of approximately 140,000; similarly, major amputation may have settled near 60,000 annually.[1,2] The total number of revascularizations has increased due to rising numbers of EV procedures, and this may be underestimated because same-day EV procedures might not be included in the Nationwide Inpatient Sample database.[2] The Trans-Atlantic Inter-Society Consensus (TASC) II Working Group documented that the incidence of major amputations varies from 12 to 50 per 100,000 population per year.[23] With the aging of the population, future trends in these areas will have a great effect on healthcare expenditures.

INDICATIONS FOR AMPUTATION

Indications for amputation have traditionally been divided into acute ischemia, chronic ischemia, foot infection, severe traumatic injury, and lower extremity skeletal or soft tissue malignancies. Trauma and malignancy are beyond the scope of this chapter and are not discussed. In the presence of acute ischemia, major amputation is undertaken for irreversible ischemia, for severe ischemia with no revascularization options, or following unsuccessful attempts at revascularization. Amputation for chronic ischemia may be performed owing to failure of revascularization, lack of suitable conduit or target arteries, severe patient comorbidities, poor functional status, or extensive gangrene or infection such that foot salvage is not possible. Pedal sepsis without ischemia constitutes another major subgroup of patients undergoing amputation; this presentation is extremely common in patients with diabetes and associated neuropathy. Because the underlying indications for amputation frequently overlap, it can be difficult to compare indications for and outcomes of amputations reported in the literature.

Impact of Diabetes

The presence of PAD and diabetes, either alone or in combination, contributes to the majority of major nontraumatic lower extremity amputations. Li et al. describe the overall incidence of diabetes in patients undergoing amputation as approximately 60%.[3] This information is based on hospital discharge diagnoses and may not be entirely accurate. However, many general classifications overemphasize the role of diabetes and understate the role of concomitant ischemia. Malone reported the indications for amputation as follows: complications of diabetes (60%-80%), infection without diabetes (15%-25%), ischemia without infection (5%-10%), chronic osteomyelitis (3%-5%), trauma (2%-5%), and miscellaneous (5%-10%).[24] These general classifications have a certain degree of overlap and mask the true interaction between ischemia and diabetes. This simplistic breakdown does not provide clear insight into the true influence of ischemia or the full potential of revascularization to reduce amputation rates. In addition, because no revascularization is universally successful, amputation may ultimately follow revascularization.

Impact of Tissue Loss and Anatomy

Attempts have been made to more clearly categorize the indications for major amputation to explain why amputations continue to be performed despite aggressive revascularization programs.[25] When identifying the indications for amputation, it must be recognized that with chronic ischemia, limb loss may ultimately occur despite revascularization. In addition, patients may present initially with acutely or chronically ischemic limbs that are beyond any hope of salvage. The influence of gangrene and pedal sepsis must also be considered because they have a significant impact on the options for limb salvage. Lastly, patient comorbidities and ambulatory status influence the decision for amputation.

The TASC II Working Group reported that the rate of primary amputation in chronic critical leg ischemia is approximately 25%. Unreconstructable vascular disease is the most common indication for secondary amputations, which account for nearly 60% of patients.[23]

To more clearly delineate the reasons for major amputation in an academic vascular practice, a series of 131 consecutive major lower extremity amputations were reviewed and the indications for amputation clearly classified (Table 111.1). In this setting, more than 50% of patients who underwent amputation had prior attempts at limb salvage via revascularization or had no anatomically feasible revascularization options. This group of patients had exhausted the armamentarium of vascular surgery. Seventeen percent of patients were not considered candidates for aggressive attempts at limb salvage owing to a preexisting nonambulatory status (8%) or the presence of excessive surgical risk (9%). In addition, 32% of patients had nonsalvageable limbs at presentation due to extensive pedal gangrene, pedal sepsis, or a nonviable foot that mandated primary amputation.

Similar findings were reported by Nehler and colleagues in a series of 172 major amputations.[26] The indication for amputation was critical ischemia in 87% and complications of diabetic neuropathy without significant ischemia in 13%. Forty-six patients (30%) had prior bypass failures or amputations despite patent reconstructions, and 10 (6%) had no revascularization options; therefore, 36% had exhausted the resources of

TABLE 111.1 Indications for Major Amputation by Vascular Surgeons

Indication for Major Amputation	Percentage of Cases ($n = 131$)
Critical limb ischemia with failed revascularization	39
Extensive pedal gangrene	15
Unreconstructable arterial anatomy	11
Overwhelming pedal sepsis	9
Excessive surgical risk	9
Nonviable, acutely ischemic foot	8
Nonambulatory status	8

From Abou-Zamzam AM, Jr, Teruya TH, Killeen JD, Ballard JL. Major lower extremity amputation in an academic vascular center. *Ann Vasc Surg*. 2003; 17:86–90.

revascularization. Eighty-five patients (55%) underwent primary amputation because of severe comorbidities, poor functional status, extensive necrosis, or a combination of these factors. Together the previous studies highlight the central role of both ischemia and tissue loss in the determination of the need for major amputation.

The recently developed SVS-WIfI classification system may help to define the factors influencing limb salvage and need for amputation.[27] This system includes the key elements of Wound, Infection, and foot Ischemia (WIfI). By stipulating and quantifying these individual contributors to the threatened limb, the WIfI score can give greater detail than other available tools. Early validation studies have demonstrated that worsening WIfI stages are associated with major amputation in patients undergoing revascularization for chronic limb-threatening ischemia (CLTI).[28]

Impact of Delay in Presentation

The significant role of delay in patient presentation cannot be overstated. The mean time to vascular surgery consultation was 73 days for pedal tissue loss and 27 days for ischemic rest pain in the report by Nehler and colleagues.[26] This delay likely accounts for the large percentage of primary amputations in their series and underscores the need for patient and physician education. Indeed, in a report by Bailey and coworkers, only 24% of patients with critical limb ischemia were perceived as needing "urgent" vascular consultation, with a mean 8-week duration of symptoms before vascular evaluation.[29] This suggests that delayed patient presentation involves not just patient factors but also access issues and physician factors.

PRIMARY AMPUTATION VERSUS REVASCULARIZATION

The most important decision in treating CLTI is the initial determination of whether to attempt limb salvage or proceed with primary major amputation. Despite widespread discussion of great triumphs in revascularization, there is a growing awareness that primary amputation may be the best approach in specific patient subsets. As stated earlier, more than 140,000 lower extremity revascularizations are performed annually in the United States. In recent years, open revascularizations have been partially replaced by EV procedures, yet nearly 60,000 major amputations are still being performed each year.[1,2] This implies that the ratio of amputation to revascularization may be close to 1:2 nationally. Many specialty centers may have a much lower ratio, owing to the filtering effect of referring physicians. Many patients perceived as not being candidates for revascularization are treated locally with amputation and are never referred to these high-volume centers specializing in revascularization.

The ratio of major primary amputation to revascularization differs among facilities and may vary because of surgeon experience and practice protocols. One prospective study demonstrated that 43% of the 224 patients presenting with limb-threatening ischemia were treated by primary amputation, and 57% were treated with revascularization.[30] Diabetes mellitus, end-stage renal disease, tissue loss, and poor functional status were all predictors of treatment with amputation as opposed to revascularization.

Groups Benefiting From Primary Amputation

A very reasoned approach to patients presenting with CLTI is necessary. A thoughtful strategy considering the patient's comorbidities, the status of the foot, and the complexity of the required revascularization has been outlined by Nehler and colleagues.[31] In a good-risk patient with minimal pedal tissue loss, an aggressive attempt at revascularization should be undertaken with appropriate EV or open bypass techniques including the consideration of alternative vein conduits. However, when the patient's overall health status is poor or the foot lesions are extensive, primary amputation must be considered. An aggressive use of revascularization, particularly EV interventions, likely has resulted in limb salvage attempts in higher-risk patients that may have helped to decrease overall major amputations.[1,2] Despite this, secondary amputations are not an uncommon occurrence. In a study that included 358 consecutive patients (412 limbs), patients with limb loss despite patent EV interventions were compared with the rest of the EV-treated group and with those who underwent amputations with patent bypasses (APBs). Amputations occurring despite a patent revascularized segment constituted 38% of limb loss in open and 80% in EV-treated patients ($P = .001$). Most amputations in the EV group were performed within 3 months and the indications were extensive tissue loss or limb dysfunction after radical débridement of infection or gangrene (37%), recurrent infection (42%), and failure to reverse ischemia (21%).[32]

The perceived improved outcomes following revascularization compared with amputation have driven the belief that revascularization is always the better option. However, an examination of the data demonstrates that functional outcomes following

amputation may not be markedly different from those following revascularization for specific patient subgroups. Taylor and associates analyzed 553 patients who underwent 627 primary major limb amputations.[33] In patients younger than 60 years, functional outcomes following BKA were similar to those of patients undergoing successful revascularization. Such information lends credence to the observation that primary amputation should be considered not a failure of therapy but a valuable, important treatment option.[26,31,33]

The advances in percutaneous revascularization have raised the question of how best to treat the patient considered "unfit" for open revascularization. Taylor and coworkers reported an analysis of 314 patients treated for critical limb ischemia who were unsuitable for open revascularization owing to medical, functional, or mental comorbidities.[21] Patients were treated with either percutaneous transluminal angioplasty (PTA) or major amputation. The 131 patients treated with PTA had higher rates of maintenance of ambulation and independent living compared with the 183 patients treated with amputation. However, the PTA group had a higher mortality rate, and the advantages in ambulation and independent living lasted only 12 months and 3 months, respectively. In the "unfit" patient, EV treatment may indeed be no better than primary amputation.

Indeed, in patients with extensive foot lesions, severe comorbidities, or very unfavorable anatomy, primary amputation is often the best treatment option.[26,31,33] Because of delayed referral, many patients ultimately undergoing amputation present to the vascular surgeon with extensive pedal necrosis, which makes limb salvage unlikely, regardless of arterial targets for revascularization. End-stage renal disease presents a particularly difficult challenge, and the presence of advanced heel gangrene in this group of patients may best be treated with primary amputation.[34,35]

PERIOPERATIVE EVALUATION

Although surgeons have traditionally focused on the preoperative evaluation and near-term (usually 30-day) results of amputations, a lengthier view of the perioperative period can be helpful. For the patient, the overall experience is important and clearly lasts longer than the 30-day postoperative period. A more global view of the patient during the first year may help to identify key issues at different points in the patient's treatment and recovery. A team approach to the patient is useful during all stages of the perioperative period because the results in any series of amputations are directly related to the skill and enthusiasm of the people involved in the program.[36] Members of the team include the patient, family, surgeon, physiatrist, therapist, rehabilitation medicine specialist, prosthetist, nurse, social worker, psychologist, peer support group, and case manager. The common goal should be maximum recovery and rehabilitation after limb loss. The team should be flexible because different team members share the leadership and service responsibilities throughout the 12- to 18-month time frame that typically defines the perioperative period following a major amputation.

Perioperative Stages

The postoperative year-long continuum does not separate easily into "stages." However, for practical purposes, five stages in the treatment of the amputation patient have been described.[37]

Stage 1: This is the preoperative stage which starts with the very difficult decision of whether to amputate. This stage includes an assessment of the vascular status and decisions on attempts to improve circulation. The preoperative evaluation of a patient undergoing major amputation should strive to reduce perioperative complications and mortality. The preoperative evaluation should be rational and expeditious. Evaluation should include the duration and severity of limb ischemia, extent of tissue loss, presence of wound infection, and anatomic considerations of revascularization. An analysis of the patient's systemic comorbidities is essential and should be performed systematically. The surgeon typically is the team leader during this stage.

Stage 2: Once the surgery is completed, the acute hospital postoperative stage begins and is the time the patient spends in the hospital after the amputation until discharge. This stage typically ranges from 3 to 10 days. During this time, transition of care to the appropriate rehabilitation experts is appropriate. The surgeon is still involved because treatment for local and systemic complications is important.

Stage 3: The *immediate post acute hospital stage* begins with hospital discharge and extends 4 to 8 weeks after surgery. This is the time of recovery from surgery, a time of wound healing, and a time of early rehabilitation. During this phase the surgeon is less involved, but uncomplicated wound healing is essential to early rehabilitation.

Stage 4: The intermediate recovery period (stage 4) is the time of transition from a postoperative strategy to the first formal prosthetic device. It is during this stage that the most rapid changes in limb volume occur, due to the beginning of ambulation and prosthetic use. This stage begins with the completed healing of the wound and usually extends 4 to 6 months from the healing date.

Stage 5: The fifth stage (transition to stable stage) is defined as a period of relative limb stabilization, although the limb will continue to change to some degree for a period of 12 to 18 months after initial healing. The newer prosthesis will still require occasional adjustments, and visits to the prosthetist will remain relatively frequent until after the first year of prosthetic use. In this phase the patient should move toward social reintegration and higher functional training. The patient should become more empowered and independent from his or her healthcare practitioner during this period.

Reducing Perioperative Risk

The quoted overall mortality for major amputations is approximately 8%. Most reports double the mortality when comparing AKAs to BKAs.[38] A study of 2911 patients enrolled in the ACS National Surgical Quality Improvement Program (NSQIP) demonstrated a 30-day mortality of 7% for BKAs. Multivariate analysis identified renal insufficiency, cardiac issues, preoperative

sepsis, COPD, steroid use, and increased patient age as predictors of mortality.[39] The same study identified preoperative sepsis, regular alcohol use, steroid use, cardiac issues, renal disease, and contaminated/infected wounds to be independent predictors of developing postoperative complications. The overall perioperative complication rate was 34.4%. Local stump complications occurred in nearly 10% of patients. Of note, the incidence of cardiopulmonary, venous thromboembolic, and cerebrovascular events ranged from 0.5% to 2.1%. The low observed incidence is probably due to the current widespread use of beta blockers, statin therapy, and antithrombotic medications in the vascular patient.[40,41] A similar study involving 8696 veterans showed that AKA patients were older (69.0 vs. 66.5) and suffered a higher mortality (16.5% vs. 9.7%) when compared with BKA patients, whereas both groups had a similar rate of postoperative complications.[10] This study found that increased age, increased patient complexity, and admission with acute thromboembolism were predictive of death.[10]

Perioperative treatment with antiplatelet agents, statin medications, and beta blockade has been extensively studied in the general vascular surgery population, but many of these important studies included few patients undergoing major amputation.[40,41] Although the data now suggest a limited role of beta blockade in naïve patients, there does continue to be support for use of antiplatelet and statin medications in the patient population presenting for amputation.[41,42] With regard to the need for preoperative "cardiac clearance," the guidelines by the American College of Cardiology and the American Heart Association state that the purpose of preoperative cardiac evaluation is not to give medical clearance but rather to evaluate the patient's current medical status and cardiac risks over the entire perioperative period.[41] These guidelines recommend that no test be performed unless it is likely to influence the patient's treatment.[4,12]

The management of associated hypertension, diabetes, and renal failure should be optimized. Antiplatelet and statin medications can be safely continued throughout the hospitalization. The timing of hemodialysis in relation to operation is important in managing fluids and electrolytes in the perioperative period. An aggressive approach to normalize glucose levels is essential to ensure proper wound healing. VTE prophylaxis with either subcutaneous unfractionated heparin or low-molecular-weight heparin appears to be safe and effective.[43] The importance of thromboprophylaxis is reflected in the fact that up to 17% of all amputation-related deaths are caused by pulmonary emboli.[39] Noteworthy is the propensity of these patients to fall, and fall precautions should be instituted during the early postoperative care.

Managing Infection

Special consideration should be given to patients presenting with extensive pedal infection necessitating amputation. Aggressive control of infection, with surgical extirpation of the source and adjunctive intravenous antibiotics, is the mainstay of treatment. The two-stage approach of guillotine amputation followed by formal amputation several days later has a lower complication rate than single-stage amputation.[44] Guillotine amputation is a rapid procedure, but an additional operation to treat the amputation stump is necessary.

Another option in patients who are moribund is a physiologic cryoamputation, which can be performed safely at the bedside.[45,46] The materials needed to perform cryoamputation are dry ice, a large plastic bag, an umbilical tape to use as a tourniquet, towels, blankets, adhesive tape, and a heating pad. After parenteral analgesics are administered, an umbilical tape is tied around the affected extremity just proximal to the diseased area. A large plastic bag is placed over the distal leg and filled with dry ice, circumferentially covering the leg. The dry ice bag is wrapped with blankets and secured with adhesive tape. A heating pad covered with a protective towel is placed around the proximal extremity adjacent to the frost line. The opposite leg should be covered with numerous blankets to avoid collateral injury. The frost line and the frozen limb should be checked periodically by the nursing staff, and dry ice added as needed. This bedside procedure alleviates any time pressures for amputation, controls infection, and allows optimal treatment of associated conditions. If necessary, a cryoamputation can be maintained for several weeks. When the patient's status improves, he or she may be taken to the operating room for a one-stage amputation.

Planning Rehabilitation

Whenever possible, preamputation evaluation of rehabilitation and prosthetic candidacy should be performed. Centers with dedicated multispecialty teams have much more successful rehabilitation outcomes.[47] Understanding the various stages of the perioperative period and adjusting the areas of focus throughout the recovery period may optimize the outcomes. Tempering the patient's expectations, the timing of prosthetic use, and reinforcing the ultimate functional goals is best undertaken by the team members throughout the perioperative period.

AMPUTATION LEVEL SELECTION

The goals of amputation are (1) to eliminate all infected, necrotic, and painful tissue; (2) to achieve uncomplicated wound healing; and (3) to have an appropriate remnant stump that can accommodate a prosthesis. The length of the preserved limb has important implications for rehabilitation. Prosthetic use following major amputation puts an increased energy demand on the patient. Unilateral below-knee amputees require a 10% to 40% increase in energy expenditure for ambulation, and above-knee amputees require 50% to 70% more energy to ambulate.[24] This differential may explain why the successful rehabilitation rate is much lower following AKA than BKA. Prosthetic use is reportedly 50% to 100% following BKA but only 10% to 30% following AKA.[26,47-49] Interestingly, the true rate of ambulation is significantly lower than that of prosthetic use and shows a steady attrition in the 5 years following amputation.[26,48,49] Partial foot or toe amputations are minor procedures that preserve the majority of the extremity and allow ambulation without the need for bulky prostheses. Most minor amputations, including

toe and ray amputations, lead to minimal increases in energy expenditure and require simple orthotic inserts.

Failure of an amputation to heal is multifactorial. Much emphasis has been placed on assessing blood flow at the level of the amputation to predict wound healing. However, failure may be caused not just by ischemia but also by infection, hematoma, or trauma related to falls. This explains why no single test can predict with 100% accuracy the ability of an amputation to heal or, conversely, its inability to heal. Most tests are better at predicting wound healing than failure to heal. Thus using any single criterion may lead to unnecessarily proximal amputation.

The importance of optimizing level selection is underlined by the need to revise BKAs to AKAs in 15% to 25% of patients.[2,25,26,50] This revision rate is frequently accompanied by a perioperative mortality rate of greater than 5%.[24] Such events also lead to increased patient anxiety and fear of repeated, more proximal amputations.

Objective Testing and Clinical Judgment

The drive to maximize limb length in amputees and to minimize the need for revisions has led to a search for the optimal modality for selecting an amputation level. Physical findings (pulses, skin quality, extent of foot ischemia or infection, skin temperature), noninvasive hemodynamic tests (segmental arterial pressures, Doppler waveforms, toe pressures), invasive anatomic tests (angiographic scoring systems), and physiologic tests (skin blood flow, skin perfusion pressure, muscle perfusion, transcutaneous oxygen measurements) have all been extensively investigated.

Physical Findings

Physical examination is the essential first step in determining the level of amputation. The extent of gangrene and infection dictates the maximal length attainable. In this evaluation the presence of dependent rubor should be considered analogous to gangrene because this tissue is ischemic. The presence of pulses should be accurately assessed. The presence of a palpable pulse immediately proximal to a proposed amputation level predicts successful healing in nearly 100% of patients undergoing either major or minor amputation.[51,52] However, the absence of a pulse does not necessarily lead to failure of wound healing; therefore, sole reliance on the presence of a pulse leads to unnecessarily proximal amputations.

Using "clinical judgment," which incorporates physical findings and consideration of the patient's overall status, yields wound healing rates of 80% in BKAs and 90% in AKAs. Wagner and colleagues found that objective data may supplement clinical judgment but not replace it; more distal amputations were achieved with clinical judgment than with sole reliance on objective examinations.[53] Experience is important in the determination of amputation level; therefore, this should not be relegated to junior surgeons or trainees.

Skin Temperature Measurements

The subjective interpretation of skin temperature as a guide for amputation is not reliable. However, several investigators have demonstrated that objective, direct skin temperature measurement may predict amputation healing with an accuracy of 80% to 90%.[53,54] In a study comparing several noninvasive techniques, direct skin temperature measurement at the level of amputation with a threshold of 90°F demonstrated the best accuracy.[53] Special attention must be paid to room temperature, and comparison with a normal contralateral extremity can be helpful.

Ankle and Toe Pressure Measurements

The use of noninvasive hemodynamic tests has been extensively evaluated. Frequently used tests are segmental arterial pressures, Doppler waveforms, and toe pressures. Absolute ankle pressures greater than 60 mm Hg can predict the healing of BKAs with an accuracy of 50% to 90%. Calf pressures and thigh pressures have shown similar reliability.[2] However, Wagner and colleagues found that Doppler-derived pressures at the thigh, popliteal, calf, and ankle levels are less reliable than clinical judgment in predicting the healing of BKAs.[53] This inaccuracy may be due in part to the high prevalence of diabetes in this population, making measured pressures less reliable because of medial calcinosis.

The ankle-brachial index (ABI) should always be obtained, regardless of the presence of a palpable pulse. Marston and colleagues reported on the role of ABI in predicting the need for amputation in a cohort of high-risk patients with critical limb ischemia treated with meticulous wound care but without revascularization. In patients with an ABI less than 0.5%, 28% and 34% of limbs required amputation at 6 and 12 months, respectively, versus 10% and 15%, respectively, of limbs in patients with an ABI greater than 0.5 ($P = .01$).[55]

The use of toe pressures has been advocated as being predictive of forefoot amputation healing. Vitti and associates demonstrated universal failure of minor amputations in patients with diabetes and toe pressures less than 38 mm Hg.[56] However, there was no similar threshold value in patients without diabetes, limiting the usefulness of this parameter.

Arteriography

Invasive testing with arteriography has been investigated as a means of determining amputation level, but the correlation between arteriographic findings and healing potential has been poor. Dwars and coworkers found that angiographic scores did not correlate with amputation healing.[52] In fact, in their report, angiographic patency tended to be greater in limbs with failed or delayed healing than in limbs with successful healing.

Radioisotope Scans, Scintigraphy, and Skin Perfusion Pressure

All physiologic tests attempt to predict wound healing based on tissue perfusion or oxygen delivery at the proposed level of amputation. One technique of measuring skin blood flow involves injecting an intradermal isotope (xenon 133 or iodine 125) and then calculating blood flow by measuring the isotope washout rate using nuclear medicine scanning devices.[24,57] Malone and associates initially reported excellent results with xenon 133 clearance, with an accuracy of 92% to 97%.[58] However, in a follow-up report, this same group found that the overlap

in values between patients with healed and failed amputations made this test too unreliable.[57]

Sarikaya and coworkers used technetium (Tc) 99m sestamibi scintigraphy to predict the healing of extremity amputation based on deep tissue perfusion.[59] Perfusion to the ischemic limb was evaluated preoperatively based on the Tc 99m sestamibi uptake pattern. Nonviable tissue in the extremity was suggested by a clear-cut edge of perfused muscle. The most distal level of amputation was determined above the nonviable tissue. In their 25 patients the proposed level of amputation based on physical examination and Doppler study was changed to a lower level after Tc 99m sestamibi scintigraphy in 65% of cases, and all amputation wounds healed.

Skin perfusion pressure is another physiologic test to determine amputation level. This test involves a scintigraphic technique in which intracutaneous iodine 123 is injected at different amputation levels. External pressure is applied, and by measuring the washout of isotope, the skin perfusion pressure is determined. A level less than 20 mm Hg was predictive of wound failure in 89% of amputations, and a reading greater than 20 mm Hg predicted healing in 99%.[52] Skin perfusion pressure can also be measured by laser Doppler velocimetry, thus avoiding the need for isotopes and markedly simplifying the test.

Skin fluorescence uses a Wood or ultraviolet light following the intravenous injection of fluorescein dye. A qualitative determination of regional blood flow is used to determine the level of amputation. Success rates in predicting healing have ranged from 86% to 100%.[24] Owing to the wide availability of these tools and no requirement for radioisotope, this technique is more accessible than scintigraphic techniques. However, the fluorescein technique may be more affected by the presence of inflammation and cellulitis than are scintigraphic techniques.

Transcutaneous Oxygen Measurements

Transcutaneous oxygen measurement is a completely noninvasive method that may be used to select an amputation level. A small sensor is placed on the skin in the area of interest. By heating the sensor and skin to 44°C, local skin hyperemia results in decreased flow resistance and arteriolarization of capillary blood. The partial pressure of oxygen measured transcutaneously ($tcPO_2$) approximates the true arterial oxygen pressure in the area of interest.[60] The sensors can be placed anywhere on the body, and readings are given in millimeters of mercury (mm Hg). Absolute readings can be recorded, or readings in areas of interest can be indexed to a reference site (often the chest). The probes are small and atraumatic, and multiple sites can be tested simultaneously, depending on the machine. Readings in the supine position are more predictive than measurements in the dependent position or during supplemental oxygen breathing.[61] The values recorded are reliable and show an acceptable day-to-day variability in repeat measurements.[62]

Transcutaneous oxygen levels have an accuracy of 87% to 100% in predicting wound healing.[51,57,63] Malone and coworkers reported no amputation failures in patients with $tcPO_2$ greater than 20 mm Hg and universal failure when $tcPO_2$ was less than 20 mm Hg.[57] Unfortunately, other investigators have not confirmed any consistent absolute $tcPO_2$ threshold.[51,53] Some authors have reported a useful $tcPO_2$ threshold of 30 mm Hg, whereas others have reported 16 mm Hg as a cutoff value. In general, $tcPO_2$ readings greater than 40 mm Hg are associated with healing and readings less than 20 mm Hg are associated with failure.[60,63] The lack of a consistent minimal level is likely due to the fact that nutrient blood flow may be present even in the setting of $tcPO_2$ readings of 0 mm Hg. The $tcPO_2$ may be artificially low in the setting of infection, inflammation, or edema, and repeat measurements are advised once such processes have resolved. Incidentally, in addition to modest utility in predicting wound healing, $tcPO_2$ has accuracy in predicting outcome following revascularization. Increases in $tcPO_2$ of greater than 30 mm Hg following revascularization are predictive of a successful clinical outcome.[63]

In direct comparisons with segmental pressures and skin blood flow, $tcPO_2$ has been the most accurate predictor of wound healing.[57] This applies not only to major amputation but also to forefoot amputation.[64] Transcutaneous oxygen measurements are also more accurate than fluorescein dye injections.[57] In addition, $tcPO_2$ has several advantages over other tests in terms of ease of measurement, reproducibility, and simple instrumentation that can be readily introduced into any vascular laboratory.

Yamada and colleagues studied 211 patients with 403 ischemic limbs using skin perfusion pressure, toe pressure, ankle pressure, and $tcPO_2$.[65] The correlations between these methods demonstrate that the combination of skin perfusion pressure and toe pressure can accurately predict wound healing. However, the combination of skin perfusion pressure and $tcPO_2$ did not result in a more accurate prediction. A meaningful approach to the accurate determination of amputation level should therefore include a combination of physical findings, clinical judgment, and objective testing.[51-53,57,60]

Technique Selection

Whether skin temperature, skin blood flow or perfusion, or transcutaneous oxygen measurements are used depends on local experience and availability. Measurement of $tcPO_2$ is easily incorporated into a noninvasive vascular laboratory, requires minimal equipment and training, and is reliable and reproducible. For these reasons, our preferred objective test is $tcPO_2$, with a threshold value of 30 mm Hg. However, strict utilization of a single objective method, rather than taking all available clinical data into account, leads to unnecessarily proximal amputations and denies patients the best opportunity for successful rehabilitation. The various methods of predicting wound healing and their accuracies are shown in Table 111.2.[65]

REHABILITATION CONSIDERATIONS

In the United States there are approximately 1.6 million people living with limb loss. Vascular disease accounts for the majority (82%) of limb loss hospital discharges. It is projected that the number of people living with the loss of a limb will more than double by the year 2050 to 3.6 million.[38,66] Rehabilitation is

TABLE 111.2 Prediction of Wound Healing by Noninvasive Vascular Studies

Study	Threshold (mm Hg)	WOUND HEALING (%)		Sensitivity (%)	Specificity (%)
		Below Threshold	Above Threshold		
SPP	40	10	69	72	88
$tcPO_2$	30	14	63	60	87
TSP	30	12	67	63	90
ABP	80	11	45	74	70

ABP, Ankle blood pressure; *SPP,* skin perfusion pressure; *TBP,* toe systolic pressure; *$tcPO_2$,* transcutaneous oxygen pressure.
From Yamada T, Ohta T, Ishibashi H, et al. Clinical reliability and utility of skin perfusion pressure measurement in ischemic limbs—comparison with other noninvasive diagnostic methods, *J Vasc Surg*. 2008;47:318.

TABLE 111.3 Energy Expenditure and Ambulation Rate at Various Amputation Levels

Amputation Level	Energy Expenditure Above Normal (%)	Ambulation Rate (%)
Below-knee amputation		80
Long stump	10	
Short stump	40	
Knee disarticulation	71.5	31 (prosthesis fitting rate)
Above-knee amputation	63	38-50
Hip disarticulation	82	0-10 (vascular patients)

From Tang PCY, Ravji K, Key JJ, et al. Let them walk! Current prosthesis options for leg and foot amputees, *J Am Coll Surg*. 2008;206:548.

crucial to maximize the functional outcome of these patients. The significant physical and psychological changes following major amputation make rehabilitation a complex process. Integrated rehabilitation requires an interdisciplinary team that incorporates members from surgery, internal and family medicine, psychiatry, physical therapy, occupational therapy, prosthetics, social services, nursing, nutrition, and recreational therapy.

As mentioned earlier in this chapter, greater energy expenditure is required for ambulation in patients with higher levels of amputation. Energy expenditure and ambulatory rates at various amputation levels are shown in Table 111.3.[67] Many studies have shown that BKA patients have a significantly greater chance to achieve ambulation than AKA patients. In general, the goal is the preservation of maximal limb length at which a healed stump wound can be achieved.

Preoperative evaluation and amputation level selection should always include postoperative rehabilitation considerations. Preoperative ambulatory ability, comorbidities, age, and mental status affect rehabilitation potential. Patients with limited preoperative ambulatory function, age older than 70 years, dementia, end-stage renal disease, and advanced coronary artery disease perform poorly following amputation.[33]

A comprehensive treatment plan should be developed at the beginning of rehabilitation and updated frequently based on the patient's condition. A dedicated team approach clearly improves the ultimate outcome for amputees.[47,64] One report documented that successful rehabilitation following major amputation increased from 69% before the institution of a coordinated team approach to 100% after the development of such a team.[47]

Medical assessment and treatment should be targeted to optimize the patient's overall condition. Addressing comorbidities increases the patient's ability to participate in the rehabilitation process. Pain management is essential to ensure that amputees can actively participate in intensive rehabilitation and prosthetic training. Assessment and modification of health risk factors can improve long-term functional outcome. All patients should be encouraged to exercise daily to improve their performance of activities of daily living.

Amputation Wound Dressings

An important aspect of rehabilitation is the uncomplicated healing of the remnant limb. The role that early wound dressings play in ultimate wound healing and rehabilitation deserves special mention. Currently, no consensus exists on the most effective postoperative management strategy for individuals who undergo major amputation. Due to the longer residual limb and functional knee, there are more dressing options for BKA than AKA. Most practitioners elect a soft dressing following a standard AKA. Typical postoperative dressings and management strategies following BKA include soft gauze dressings with an elastic wrap; thigh-level rigid plaster dressings without an immediate prosthesis; thigh-level rigid plaster dressings with an immediate postoperative prosthesis (IPOP); short, removable rigid plaster dressings; and a prefabricated pneumatic postoperative prosthesis (prefabricated pneumatic IPOP).[68-73] A soft gauze dressing with a mild compression wrap is the most widely used dressing following BKA. Patients remain non–weight-bearing on the stump until the fitting of a prosthesis 4 to 6 weeks after surgery. There are concerns that this type of dressing may delay effective physical therapy and rehabilitation.

Data from controlled trials have found that for soft dressing strategies the uncomplicated healing rates, postoperative pain, prosthetic use, and mortality were not significantly different when compared with other types of dressings.[68,74,75] However, the data from controlled studies have shown that thigh-level rigid dressings lead to significantly shorter rehabilitation times than soft dressings when measured as time to initial gait

Figure 111.1 Above-Knee Prostheses. (A) Standard mechanical knee with swing control. (B) "Intelligent" transfemoral microprocessor-controlled prosthesis (without socket). (C) Patient with "intelligent" above-knee prosthesis seated on an examination table.

training.[76-79] An alternative technique known as IPOP placement, proposed by Berlemont in the 1950s, has been documented to improve both primary healing and rehabilitation rates.[79] An IPOP, which is applied at the initial operation, combines a rigid postoperative dressing with a temporary prosthesis and has been advocated for the early rehabilitation of nonischemic amputees. Concerns from surgeons include lack of familiarity with the prosthesis, fear of placing a hard cast on a potentially compromised remnant limb, and the inability to inspect the wound frequently. To allay these fears, a report from Schon et al. found that significantly fewer patients with a prefabricated pneumatic IPOP had postoperative complications (16%) when compared with patients receiving soft gauze dressings (65%).[74] Other investigators have suggested that placement of an IPOP may actually reduce the need for surgical revision of the amputation stump.[71]

Prosthesis Selection and Training

Prosthetic training plays an important role in rehabilitation. An appropriate durable prosthesis should be prescribed based on the individual's situation. Advanced prosthetic technology provides amputees with more choices. New functional designs and ultralight materials help amputees to live independently. Various lower extremity prostheses are commercially available for patients following AKA and BKA (Figs. 111.1 and 111.2).[67]

The advantages and disadvantages of different types of prostheses and the indications for their use depend on the individual patient and should be fully explored by the experienced prosthetist.[67,80] For example, microprocessor-controlled above-knee prostheses are now typical of the high-technology products (see Fig. 111.1B). These "intelligent" prostheses can change the orifice size, based on different walking speeds, to allow the appropriate shin swing time. The shin includes numerous sensors to accumulate biomechanical data, such as vertical loading amplitude and sagittal knee movement, to determine the direction and angular acceleration of the artificial knee joint. A software analysis system can optimize prosthetic characteristics through a process of data sampling and calculations up to 60 times in a 1.2-second gait cycle.[67,80] A patient wearing one of these prostheses can easily step up and sit on an examination table (see Fig. 111.1C).

Different types of prostheses are available to meet the needs of amputees with different amputation levels, physical conditioning, and exercise demands.[67] In general, persons of smaller stature with a slow to moderate cadence are better suited to smaller, simpler, and lighter hydraulic swing-control prostheses. Taller, more active ambulators benefit from larger, more powerful hydraulic swing-control prostheses.[81] Below-knee prostheses are generally much more lightweight than above-knee prostheses. The below-knee prostheses vary and include standard passive ankle designs, energy-conserving ankles, and open-type sockets that can accommodate slowly healing stumps (see Fig. 111.2).

Reasonable goals must be set for each patient. Many patients may not walk independently, but many wear prostheses, and the large majority return to their home environments. Although

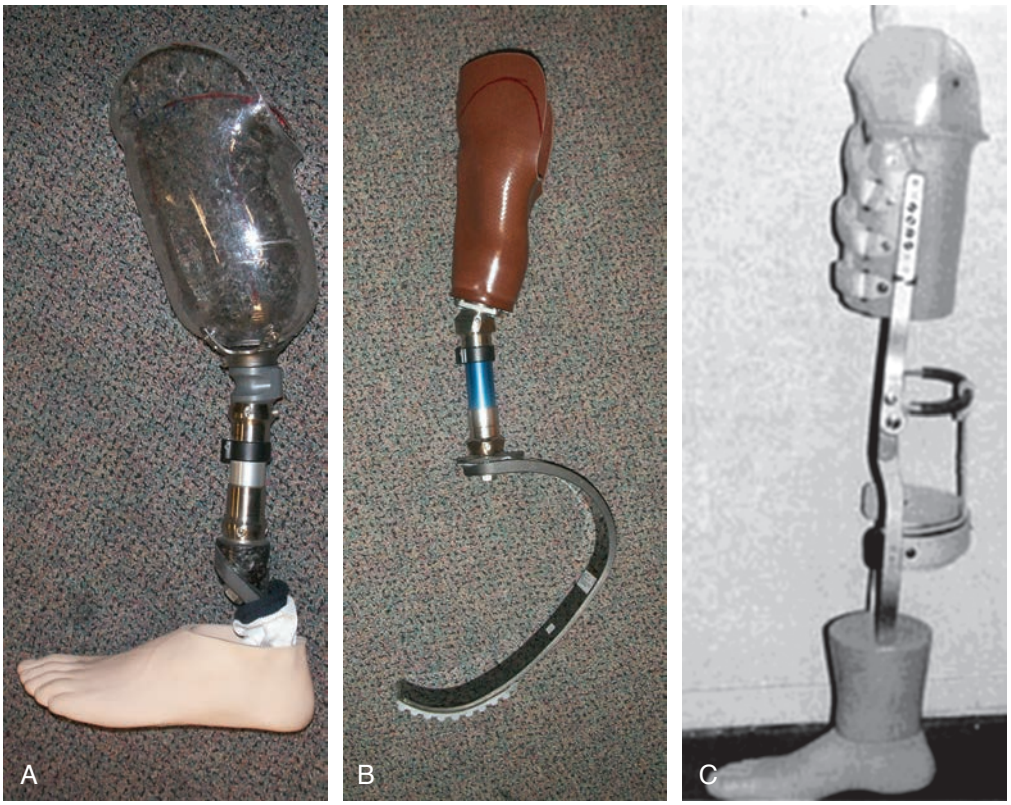

Figure 111.2 Below-Knee Prostheses. (A) Standard prosthesis with solid ankle and cushioned heel foot. (B) Dynamic, energy-conserving athletic prosthesis. (C) Below-knee prosthesis for patients with wound difficulties.

all patients may be offered the eventual fitting of a prosthesis, only a fraction will actively walk with their prostheses. In a large series of major amputations, 42% used a prosthetic limb, and 92% of patients were able to return to community living, but only 29% of patients were able to walk outside the home with a prosthesis.[26]

FUNCTIONAL OUTCOME

The assessment of functional performance following major amputation is a complex issue that influences decision-making at the outset. The most important factors that influence functional outcome are age, preoperative functional status, comorbidities, mental status, amputation level, stump healing status, unilateral versus bilateral amputation, and postoperative rehabilitation. Integrative and vocational rehabilitation combined with newly designed prostheses allow high-level amputation patients to achieve independent lifestyles. Interdisciplinary management should be used in the care of all amputees. Preoperative and postoperative optimization of a patient's medical condition, intensive rehabilitation, wound care, pain management, and proper prosthesis fitting all significantly improve the patient's ultimate functional outcome. A key concept in defining functional outcomes is that success should be defined in relation to an individual's mobility prior to the development of their limb impairment. This patient-centered measure should be the ultimate measure of a successful outcome.[82]

Impact of Amputation Level and Comorbidities

Among amputees with healed stumps, 80% of those with BKAs can achieve ambulation, compared with only 38% to 50% of patients with AKAs.[83] Taylor and coworkers documented that patients older than 70 years had a threefold greater chance of not wearing a prosthesis, a 3.1-fold greater chance of death, a 2.3-fold greater chance of being nonambulatory, and a fourfold greater chance of losing functional independence at 1 year compared with patients younger than 50 years.[33] Patients aged 70 years or older and those with limited preoperative ambulatory ability, dementia, end-stage renal disease, and advanced coronary artery disease all had a significantly higher chance of experiencing death, nonambulatory status, loss of functional independence, and never using a prosthesis. Patients receiving an AKA who were not ambulatory preoperatively had a 10-fold greater chance of not wearing a prosthesis and twice the chance of death at 1 year. Amputees with dementia were 2.4 times less likely to wear a prosthesis. Patients with advanced comorbidities, including coronary artery disease, end-stage renal disease, and severe chronic obstructive pulmonary disease also had a greater chance of not ambulating following amputation.[33]

Through-knee amputation is not commonly performed because of poor soft tissue coverage and a higher risk of wound complications. However, in the patients with adequate residual skin and subcutaneous tissue, through-knee amputation is an

option. Through-knee amputees are able to achieve higher normal and maximal walking speeds with lower relative energy expenditure than above-knee amputees. In elderly patients or those with significant comorbidities preventing them from postoperative ambulation, through-knee amputation allows earlier weight-bearing with a lower risk of wound complications compared with BKA.[67]

Minor amputations, such as digital, ray, transmetatarsal, and midfoot amputations, are considered limb salvage procedures. Patients with digital or ray amputations may walk with little additional energy expenditure. Partial foot amputations require less ambulation energy than more proximal amputations. Pinzur and associates demonstrated that energy demands after midfoot, Syme, below-knee, through-knee, and AKAs are directly related to the level of amputation.[84]

Impact of Age

Patients younger than 60 years with well-controlled comorbidities who were ambulating preoperatively can anticipate an ambulatory rate of 70%, a survival rate of 80%, and an independent living rate of 90% at 1 year following major amputation.[33] A Canadian study showed that although older patients had more comorbidities at admission, they benefited as much as younger people from an intensive rehabilitation program with a comparable length of stay.[85] However, younger amputees continued to improve after 3 months, whereas older patients tended to plateau. In selected patients who developed stump wound complications but had good perceived healing potential, a "redo" BKA yielded better functional outcomes than conversion to an AKA.[86]

Fate of the Contralateral Limb After Amputation

Following a major amputation, many patients worry about the fate of their remaining limb. Patients surviving several years after the first amputation have a significant chance of needing a contralateral amputation. Fifteen percent to 35% of amputees with diabetes lose their remaining leg within 5 years.[87] The presence of renal failure is a particularly poor prognostic indicator of second limb amputation.[25] These facts underscore the need for diligence in protecting and surveying the remaining limb. Continued efforts focused on patient education and preventive foot care are essential. Periodic evaluation and management of PAD in the contralateral limb after unilateral amputation is important for the long-term functional outcome of these patients.

Depression After Amputation

As in other areas of vascular surgery, the successful completion of the operation is only the beginning of the patient's recovery. Although the surgeon may initially focus on the surgical wounds, other considerations are unique to the recovery of an amputee. Although depression is common following major amputation, especially in younger amputees, depression may itself be associated with a higher risk of major amputation.[88,89] The loss of a limb has been compared with the loss of a spouse in terms of magnitude. Although the feeling of bereavement abates over the first year, many amputees experience a continued sense of loss extending beyond 1 year.[90] In the recovery period, positive outcomes should continually be stressed, and clinical screening with appropriate medical therapy for depression should be considered. Amputees with significant depression may become malnourished owing to loss of appetite; malnutrition may delay healing, contribute to the development of pressure ulcers, and seriously affect the patient's overall recovery.

Successful rehabilitation can decrease the severity and incidence of depression following amputation.[91] Social discomfort, the appearance of the prosthesis, and individual coping skills should be addressed to aid in the recovery process.[92-94] The psychological impact of the loss of independence may be minimized by aggressive, focused rehabilitation that openly addresses the concerns of the amputee. Dealing with these issues requires the participation of psychologists, nurses, and geriatric and rehabilitation specialists and is an integral part to the successful management of these patients.

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112 CHAPTER

Lower Extremity Amputations: Operative Techniques and Results

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Abstract

Lower extremity amputation ranging from toe amputation to hip disarticulation offers an assortment of treatment options for a multitude of diseases including limb ischemia, infection and major trauma. Above-knee amputation and below-knee amputation are frequently performed and dramatically impact a patient's life. Understanding key principles allows for better prediction of the correct level of amputation for the patient while maintaining the maximal functionality that can be offered. Many opportunities exist to more accurately predict and allow for improved wound healing and functionality.

Keywords

Amputation
toe amputation
Ray amputation
transmetatarsal amputation
midfoot amputation
hindfoot amputation
Lisfranc's amputation
Chopart's Amputation
Syme Amputation
Transtibial amputation
below-knee amputation
guillotine amputation
cryoamputation
through-knee amputation
transfemoral amputation
above-knee amputation
hip disarticulation
reamputation
myodesis
Ertl procedure
K-level
prosthesis
functional outcome

Limb amputation, practiced since the dawn of man, is one of the most effective surgical procedures.[1] With benefits ranging from pain relief in those with limb ischemia to control of sepsis and preservation of life in those with severe infection, amputation offers a clear path to cure the patient. Despite the importance of a well-executed amputation, the task is often relegated to the least experienced surgeon on the team. Meticulous surgical technique is critical to achieving an amputation that is both pain free and functional.

Historically, amputation was challenging due to the critical triad of hemorrhage, infection, and pain. In France, A. Pare introduced vessel ligatures, thus making the application of hot oil obsolete. Tourniquets were used by Morell, the French barber surgeon, in the battle of Besancon in 1674. Prior to the introduction of antisepsis by Joseph Lister in 1867, it is estimated that more than half of all amputees died from infection.[1]

GENERAL PRINCIPLES

The surgeon must ensure adequate blood supply, sufficient viable soft tissue for coverage, and intact bony architecture (Box 112.1). Other priorities include minimizing surgical trauma by avoiding crushing-type surgical instruments. Although surgical hemostasis is essential to successful amputation, there is a lack of consensus regarding the optimal methods. Beveled skin incisions should be avoided, skin should not be separated from underlying tissue, and skin flaps should not be under tension.

In general, a longer stump is preferred due to improved prosthetic fitting and biomechanics, but not at the cost of not amputating marginally perfused or infected tissue. Excessive soft tissue may interfere with prosthetic fitting and should be avoided. Overattention to minor dog ears and irregularity may satisfy immediate cosmetics at the cost of wound healing and flap viability.[2] Antagonistic muscle groups should be stabilized to prevent skeletal misalignment, a complication which is both detrimental functionally and cosmetically.[3] *Myoplasty*, the suture fixation of antagonistic muscle groups, may help in this regard, in addition to *myodesis*, the direct suturing of the musculotendinous unit to the bone. Excessive periosteal stripping may devascularize the bone, leading to the formation of ring sequestra.

Infected areas should be isolated with the use of mechanical barriers. Open "drainage" or guillotine amputation is usually warranted in the setting of gross infection.[4-8] A two-stage approach, delaying primary closure until a patient is clinically stable, may preserve limb length. Antibiotic coverage should be narrowed based on Gram stain and culture results, with discontinuation as soon as clinically warranted to prevent opportunistic infection such as *Clostridium difficile*.[9]

Protection of the amputation site with use of a rigid or soft dressing may prevent injury in the case of falls. Incisions must be well healed prior to weight bearing. Given their limited mobility, patients are at high risk for developing deep venous thrombosis (DVT) and should receive chemothromboprophylaxis.[10] Perioperative prophylactic antibiotic use is recommended to limit wound infection following amputation.[11]

BOX 112.1 General Principles of Amputation Surgery

- Assess arterial perfusion and bone architecture.
- Handle all tissue with atraumatic technique.
- Excise all nonviable and infected tissue.
- Apply tourniquet to minimize blood loss.
- Eliminate all sharp bone edges and fragments.
- Minimize number of cuts across muscle.
- Transect nerves sharply and allow retraction.
- Minimize use of electrocautery.
- Close wounds under no tension.
- Perform myodesis or myoplasty to stabilize antagonistic muscle groups.
- Use drains to reduce dead space.
- Provide prophylaxis for deep venous thrombosis.
- Administer prophylactic antibiotics.
- Avoid weight bearing until adequate wound healing has occurred.
- Use protective soft and rigid dressings.
- Avoid excessive cosmetic tailoring of wounds.
- Isolate infected or gangrenous tissue with barrier adhesive drapes.

AMPUTATION TYPES

Toe and Ray Amputation

Anatomy

The bony anatomy of the ankle consists of seven tarsal bones and five metatarsals (Fig. 112.1). The great toe has two phalanges, whereas the other toes have three. Medial and lateral sesamoid bones in the flexor tendons of the first toe provide stability. Joint capsules surround the interphalangeal and metatarsophalangeal hinge joints, and ligamentous and tendinous attachments work in concert with the plantar fascia to maintain structural integrity of the foot.

Technique: Toe Amputation

Toe amputation is appropriate for lesions of the middle and distal toe. A racket incision achieves tension-free closure. So-called for its shape like a tennis racket, the "handle" should lie longitudinally along the dorsal surface of the digit, in the midline for the second through fourth toes and away from the midline for the first and fifth toes (Fig. 112.2).

After incising the skin and soft tissues, the tendinous attachments are divided at the same level as the skin incision and the bone is trimmed back accordingly. If a disarticulation is warranted, a #15 blade is inserted into the joint capsule. Cartilage is excised with a rongeur and the bone edges are filed smooth. Excessive use of electrocautery should be avoided. Interrupted nonabsorbable monofilament sutures are used to close the wound in one layer.

Technique: Ray Amputation

A ray amputation includes resection of the digit and the metatarsal head. Ray amputations may be completed with a racket incision, with the "handle" or vertical portion extending proximal to the metatarsal head (Fig. 112.3). The skin and

soft tissues are incised, the tendinous attachments are divided and allowed to retract, and the metatarsal is transected before dividing the remaining soft tissues. Typically, the sesamoid bones are excised, associated flexor tendons are placed on tension and transected, and residual tendon is allowed to retract. Care should be taken to avoid injury to adjacent digital arteries and nerves.

Amputation of the first ray may significantly alter gait. As such, first ray amputation is prone to recurrent ulceration in up to 60% of patients.[12] Some advocate a complete transmetatarsal amputation (TMA) over first ray amputation.[13] A patient-specific approach is best.

Transmetatarsal Amputation

Anatomy

Proximal to the phalanges are five metatarsals (see Fig. 112.1). They are stabilized by the deep transverse metatarsal ligaments and plantar ligaments distally and the plantar metatarsal ligaments proximally. The proximal metatarsals articulate with three cuneiform bones and the cuboid laterally. Collectively the tarsometatarsal (Lisfranc) joint connects the midfoot and forefoot.

Technique

TMA is appropriate for wounds involving the entire forefoot or when multiple ray amputations are considered. TMA offers the ability to wear standard footwear with near-normal ambulation. TMA is contraindicated in cases of severe bony deformity of the midfoot and hindfoot which would lead to structural instability.

An incision extends transversely over the dorsum of the foot at the level of the distal metatarsals, coming to corners medially at the first metatarsal head and laterally at the fifth metatarsal head. Next, an incision extends from these corners onto the plantar surface across the base of the toes (Fig. 112.4). The extensor tendons are divided at the skin level, the periosteum is incised, and the metatarsals are divided with a bone saw, each approximately 3 mm shorter than the last, moving laterally. A gentle 30- to 45-degree plantar bevel may facilitate liftoff with

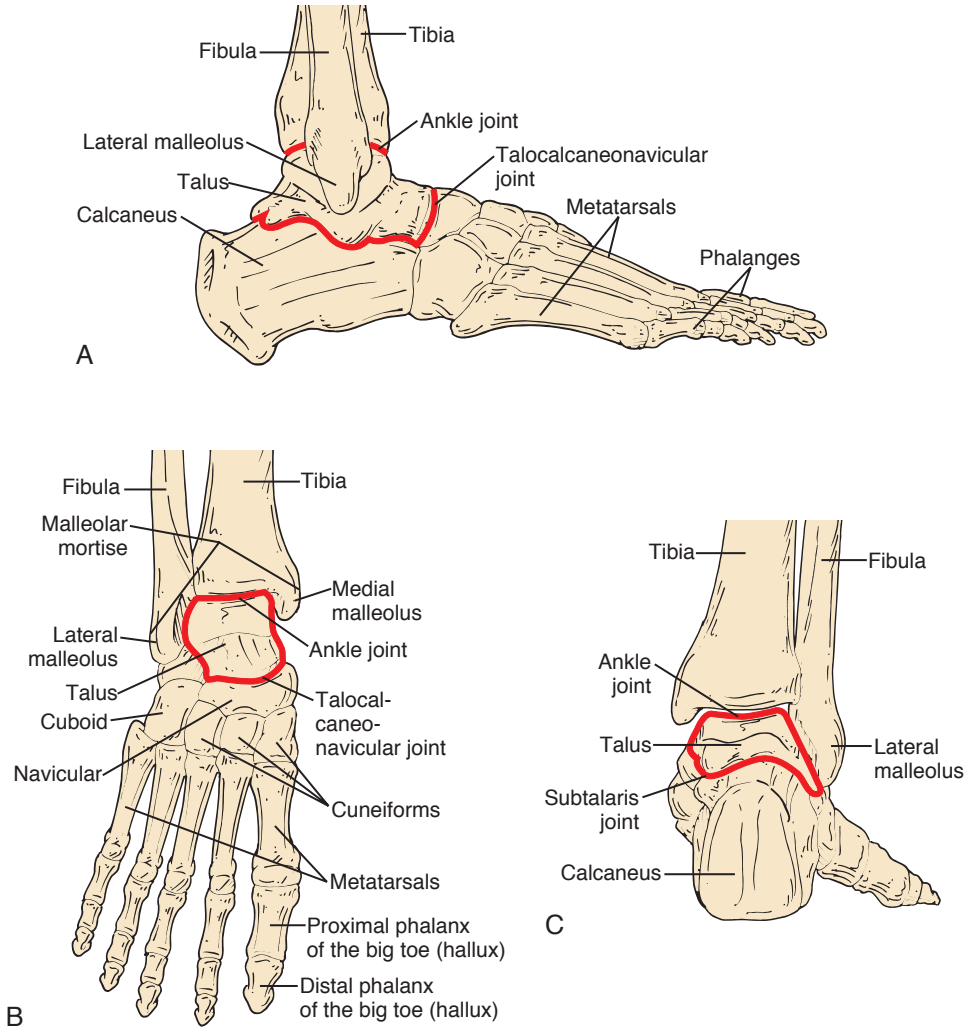


Figure 112.1 Bone Anatomy of the Foot. *Continued*

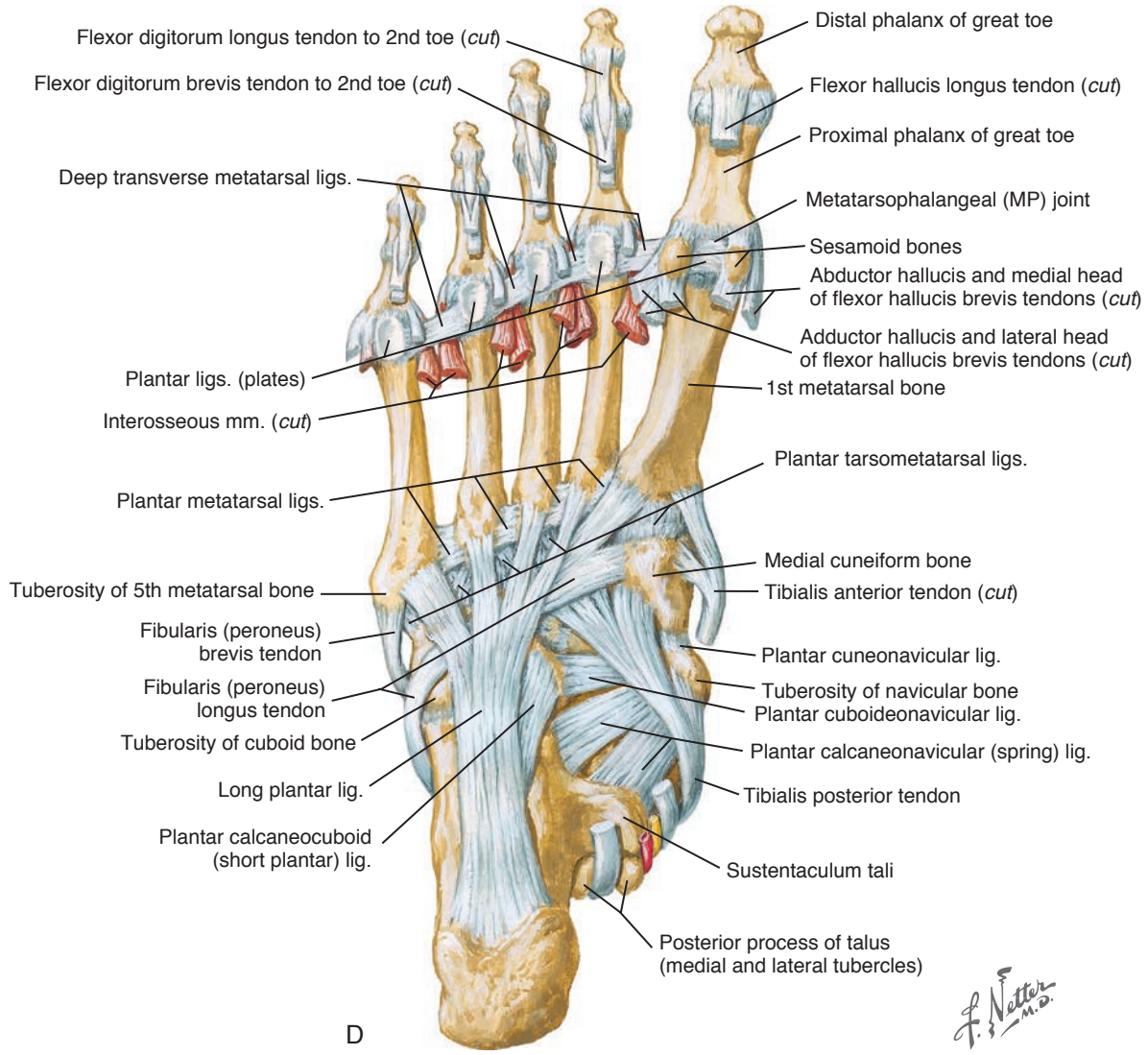


Figure 112.1, cont'd

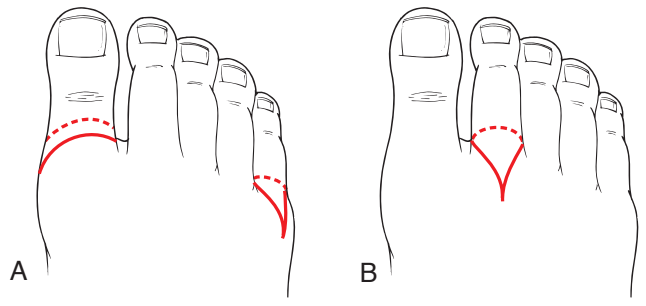


Figure 112.2 (A) Racket incision for first and fifth toe amputation. (B) Racket incision for second, third, and fourth toe amputation.

ambulation. After dividing the bone, the plantar myofascial attachments to the metatarsal heads are divided. The poorly vascularized tendons and sheaths in the plantar flap should be excised.

To reduce the risk of recurrent ulceration, some surgeons recommend Achilles tendon lengthening (ATL) or transection.[14]

MIDFOOT AND HINDFOOT AMPUTATIONS

Three proximal foot amputations are occasionally appropriate: Lisfranc tarsometatarsal disarticulation, Chopart midfoot amputation, and Syme amputation (Fig. 112.5).[15,16] Two rarely performed hindfoot amputations are the Boyd and Pirogoff amputations.[15,17-19] Hindfoot amputations are performed primarily in children to preserve length and growth centers.

Many surgeons recommend transtibial (below-knee) amputation if TMA cannot be performed or has failed. Others suggest that increased limb salvage rates can be achieved with the use of unconventional foot amputations.[18,20]

Anatomy

The tibia and the fibula articulate with the talus via the talocrural joint. The ligaments that join these bones are the deltoid, anterior and posterior talofibular, and calcaneofibular

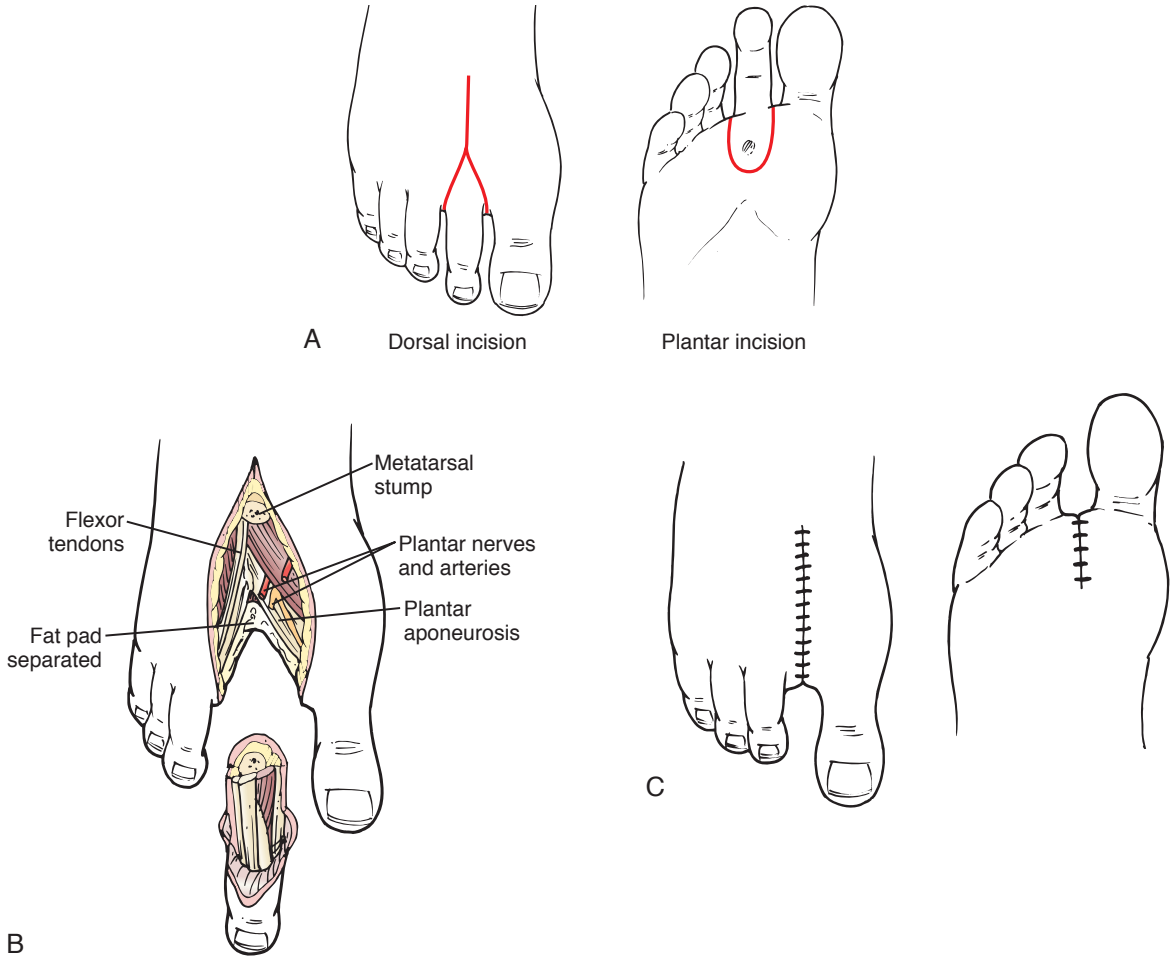


Figure 112.3 Ray Amputation Incision. (A) Note the plantar extension to include a mal perforans ulcer. (B) Transection of the metatarsal shaft. (C) Closure with nonabsorbable suture under no tension.

ligaments. The talus articulates with the calcaneus at the subtalar joint. The medial and lateral talocalcaneal ligaments and the cervical ligament support this joint. The talocalcaneonavicular joint is a multiaxial joint supported by the talonavicular and plantar calcaneonavicular ligaments. Supination (inversion) at this joint is produced by the tibialis anterior and posterior. Pronation (eversion) is produced by the peroneus longus and brevis. A heavy fibrofatty heel pad firmly adheres to the calcaneus and skin and provides protection during heel strike (see Fig. 112.1).

Because the strong ankle extensor attachments are divided in the performance of midfoot and hindfoot amputation, the Achilles tendon exerts unopposed plantar flexor forces on the residual foot. The Achilles tendon may require division or lengthening to prevent the development of an equinus deformity.

Lisfranc and Chopart Amputations

Lisfranc

Lisfranc first described this amputation in 1815. The incision results in a long plantar flap (see Fig. 112.5). Tendons and synovial sheaths are divided at the level of the skin incision. The first, third, fourth, and fifth tarsometatarsal joints are disarticulated. The second metatarsal is divided 1 to 2 cm distal to the medial cuneiform.[21] To reduce the risk of development of equinovarus deformity, Sanders recommended a modification of the Lisfranc amputation that preserves the base of the fifth metatarsal and the insertion of the peroneus brevis.[18] The Achilles tendon is released by either transection or Z-plasty.[22,23] The plantar fascia on the flap is approximated to the dorsal periosteum with absorbable sutures. The skin is approximated with interrupted monofilament sutures or staples.

Chopart

Described by Chopart in 1814, this amputation involves a long plantar flap similar to that used in the Lisfranc amputation (see Fig. 112.5) and is performed through the talocalcaneonavicular joint and the calcaneocuboid joint. An Achilles tenectomy is recommended. The extensor hallucis longus and the tibialis anterior tendons may be reattached to the talar neck. The extensor digitorum longus may be reattached to the calcaneus.[21]

Postoperative Considerations

Because the Lisfranc and Chopart amputations result in a dramatic alteration in normal foot biomechanics, their durability may be limited. A short-leg plaster cast is used over the sterile

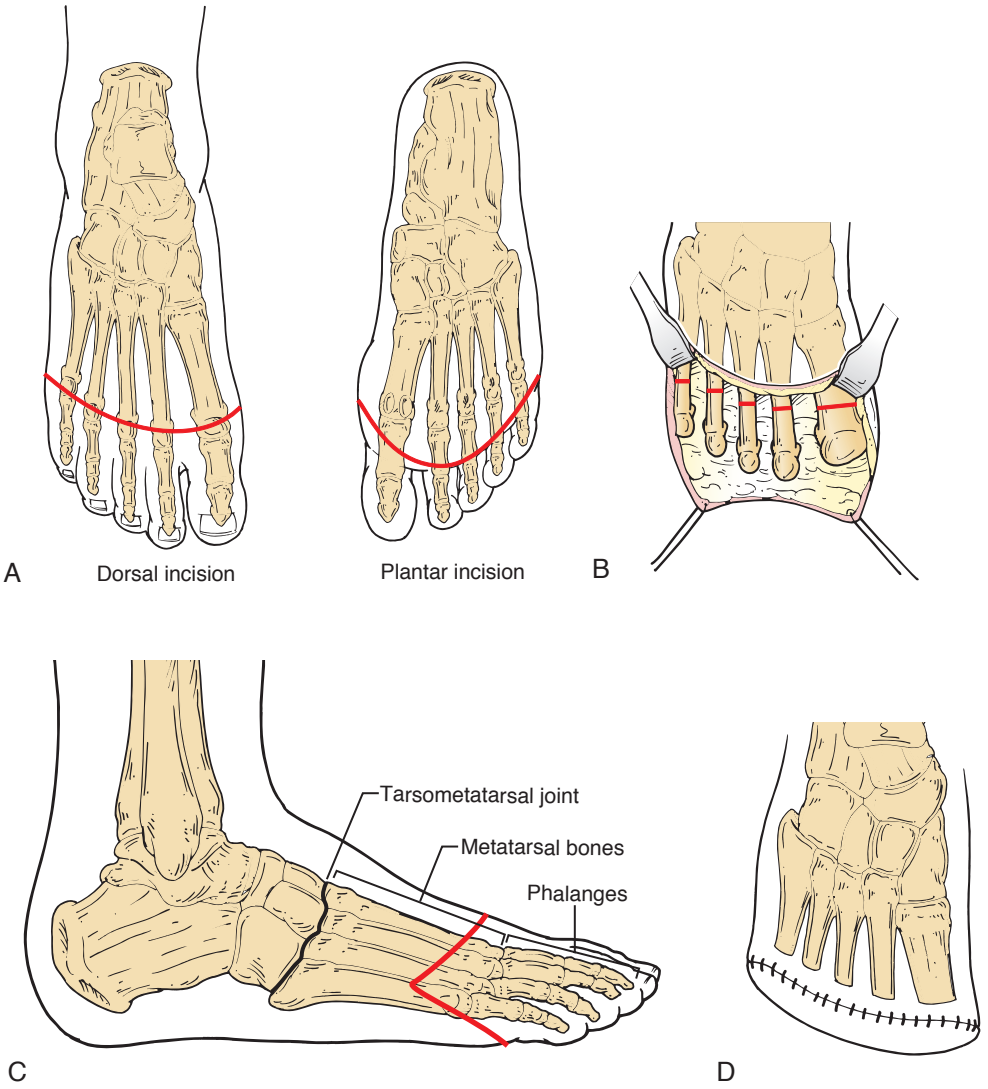


Figure 112.4 Technique of Transmetatarsal Amputation. (A) Dorsal and plantar incisions with disarticulation of the metarsophalangeal joints. (B) Level of bone transection. (C) Lateral view. (D) Closure with monofilament suture.

dressings. The cast must be molded to ensure that the talus is slightly dorsiflexed in relation to the tibia and that the calcaneal tuberosity is parallel to the long axis of the tibia. The cast is changed weekly to check wound healing. Weight bearing is allowed after 6 weeks. Patients with a Lisfranc amputation need little more than a toe filler with an ankle lace-up shoe. Patients with a Chopart amputation need a custom-fitted ankle-foot orthosis with a filler to hold the shoe adequately.

Syme Amputation

Syme first described this amputation in 1843. The anterior incision extends across the ankle just distal to the tip of each malleolus, while the posterior incision extends from the malleoli vertically down and across the sole of the foot (see Figs. 112.5 and 112.6). The extensor tendons are divided at the level of the skin incision. Next, the dorsalis pedis artery is ligated and divided. The ankle joint capsule is incised while plantar flexing the foot before dividing the medial and lateral ankle ligaments. The tendons of the posterior tibialis and flexor hallucis longus are transected, taking care to avoid injury to the posterior tibial artery. Next, the heel fat pad is carefully dissected by staying close to the calcaneus to avoid buttonholing. Finally, the ankle joint is disarticulated, and the specimen is passed off the table. In a one-stage amputation the malleoli are divided with a saw at the level of the articular surface of the tibia, and the width is reduced by vertical bone excision. Holes are drilled in the medial, anterior, and lateral parts of the distal tibia and fibula to secure the heel pad directly under the tibia. In a two-stage Syme amputation the wound is closed by suturing the heel flap to the dorsal fascia. Six weeks later the malleoli are removed through separate vertical incisions (see references by Hulnick et al.[24] and Richardson[25] for a detailed description of midfoot amputations).

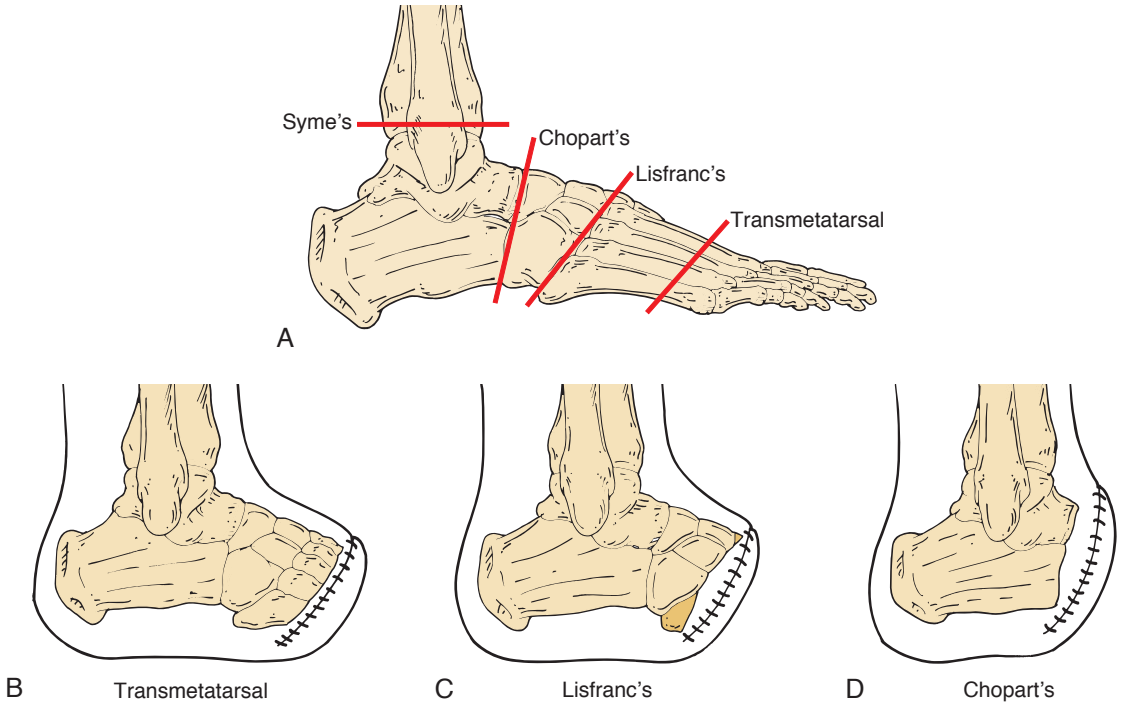


Figure 112.5 Levels of Foot Amputation.

Postoperative Considerations

The chief advantage of the Syme amputation is the preservation of limb length, which may obviate the need for a prosthesis during brief periods of weight bearing, such as during transfer from a bed to a wheelchair. The disadvantages include the slight leg-length discrepancy, which may lead to biomechanical side effects in more proximal or contralateral joints. Furthermore, the prosthesis is typically bulky at the ankle and less cosmetically appealing than a conventional below-knee prosthesis.

TRANSTIBIAL (BELOW-KNEE) AMPUTATION

Anatomy

The leg contains four muscle compartments. The anterior compartment contains the tibialis anterior, extensor hallucis longus, and extensor digitorum longus muscles, as well as the anterior tibial artery and vein and deep peroneal nerve. The lateral compartment contains two muscles: the peroneus longus and brevis, as well as the superficial peroneal nerve. The superficial posterior compartment contains the soleus, gastrocnemius, and plantaris muscles. Last, the deep posterior compartment contains the flexor digitorum longus, tibialis posterior, flexor hallucis longus, and popliteus muscles, the posterior tibial artery and veins, peroneal artery and veins, and tibial nerve. The tibial nerve courses adjacent to the posterior tibial artery and veins (Fig. 112.7). Posterior flaps, skew flaps, sagittal flaps, and medial flaps are based on corresponding musculocutaneous perforators; thus it is important to avoid separating the skin and soft tissue from its underlying muscle.[26]

Technique

Posterior Flap

The posterior-based flap described by Burgess et al.[27-29] is the most commonly used. Division of the tibia should be at minimum 12 to 15 cm (approximately four fingerbreadths) distal to the tibial tuberosity to create the most favorable biomechanics for ambulation with a prosthesis. To fashion flaps, some advocate using a two-thirds/one-third technique based on leg circumference (Fig. 112.8). The anterior incision of the amputation should be approximately two-thirds the leg's circumference. The length of the posterior flap is one-third the leg circumference and should be shaped in a gentle curve to reduce dog ears.

The skin, subcutaneous tissue, and fascia are incised starting with the transverse portion before extending along the posterior flap. The anterior and lateral compartment muscles are divided next. The periosteum of the tibia is incised and mobilized proximally and the tibia is divided using a bone saw. The fibula is divided approximately 1 to 2 cm proximal to the tibia. Removing too much fibula will result in a conical stump, both unsightly and a poor recipient of a prosthesis. A large amputation knife is used to create the posterior flap. The knife is maintained at a plane deep to the tibia and fibula, dividing the remaining posterior compartment musculature. Major vascular bundles are suture ligated. The tibial and peroneal nerves are sharply divided and allowed to retract proximally. The posterior flap musculature is trimmed of gross excess but allowed to remain sufficiently bulky to cushion impact once fit with a prosthesis.

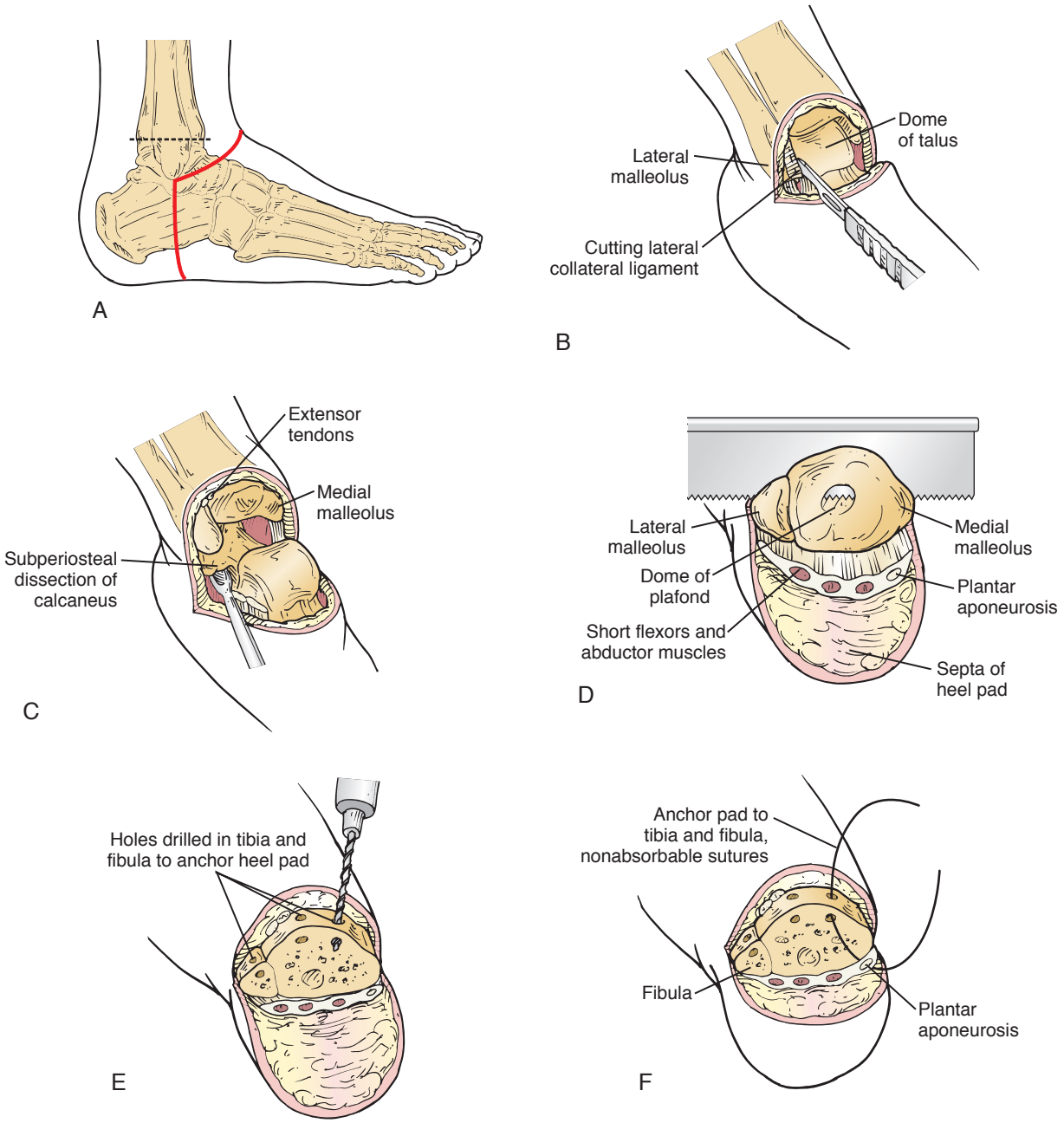


Figure 112.6 Syme Amputation. (A) Skin incision and bone transection level. (B) Exposure of the ankle and division of the ligaments. (C) Soft tissue dissection from the calcaneus. (D) Division of the tibia and fibula. (E) Holes drilled in the anterior aspect of the tibia and fibula. (F) Fascia lining the heel pad sutured to the bone.

Some surgeons prefer to advance the posterior flap 3 to 4 cm proximal to the tibial osteotomy.[30] If warranted, the soleus muscle can be excised up to the level of the tibial osteotomy, but the gastrocnemius and fascia must be preserved. The anterior tibia is beveled to avoid a sharp edge protruding through the skin. The sural nerve should be transected at least 5 cm proximal to the skin edge to prevent neuroma formation.

Some advocate a myodesis of the gastrocnemius. Two holes are drilled into the anterior surface of the tibia, and the gastrocnemius is affixed to the tibia with a nonabsorbable suture in an effort to maintain adequate coverage of the tibia. Bites are taken slightly behind the edge of the flap through the fascia as to create a lip of muscle over the anterior portion of bone. Prior to closure, the wound is irrigated with saline to remove bone dust and debris. The deep fascia is approximated with interrupted absorbable sutures. The skin is closed with staples or interrupted monofilament suture avoiding tightly compressing the flaps.

Sagittal Flap

If creation of a long posterior flap is not possible, sagittal or skew flaps may be used. In the sagittal flap technique described

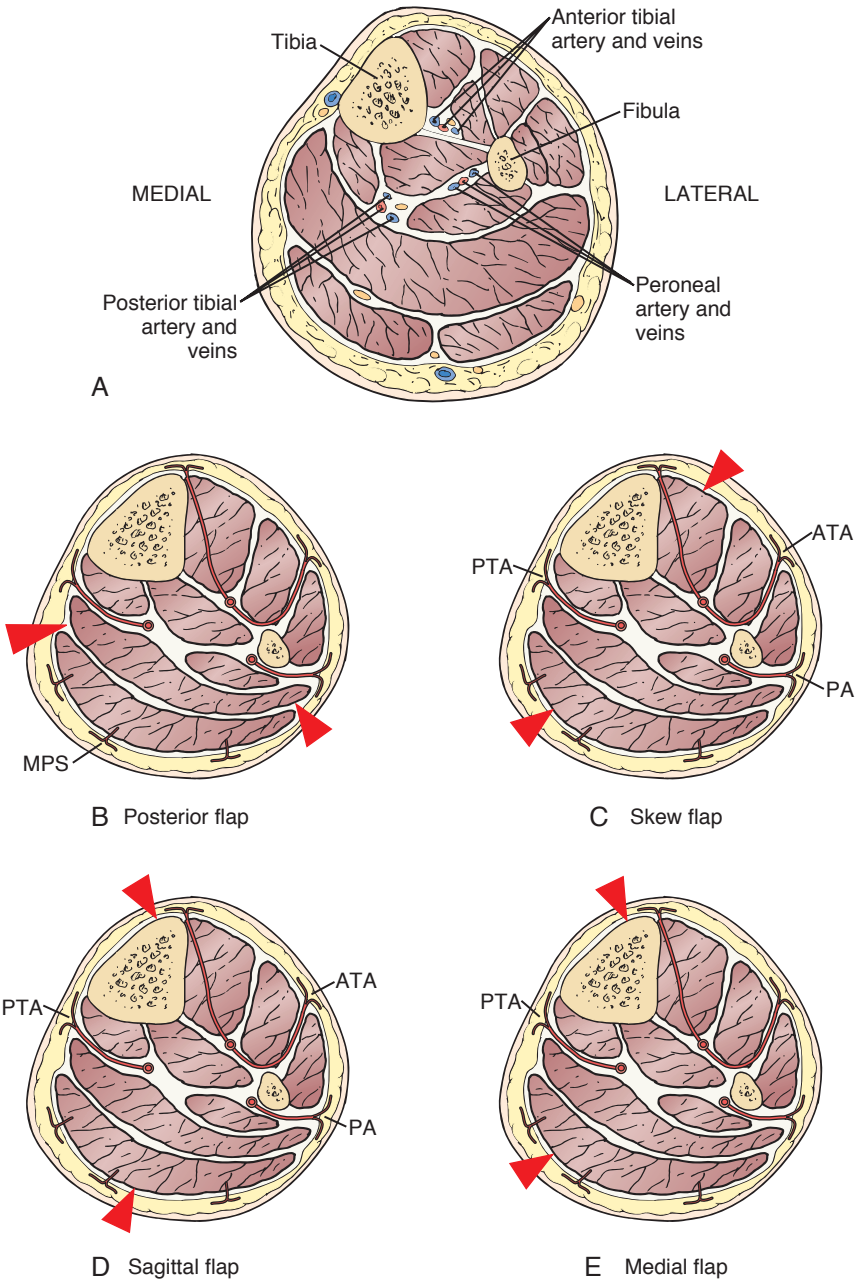


Figure 112.7 Cross-sectional Anatomy and Blood Supply to the Skin at the Level of Transtibial Amputation. Note the location of skin incisions *(red arrowheads)*. (A) Leg cross-section. (B) Posterior flap. (C) Skew flap. (D) Sagittal flap. (E) Medial flap. *ATA*, Anterior tibial artery; *MPS*, musculocutaneous perforators from the sural artery; *PA*, peroneal artery; *PTA*, posterior tibial artery.

by Persson, equal-length medial and lateral myocutaneous flaps are developed (see Fig. 112.7).[31] A myoplasty is performed to cover the tibia by suturing the anterior and lateral compartment muscles to the medial component of the gastrocnemius and soleus. A randomized comparison of sagittal versus posterior flaps showed no significant difference in outcome.[32]

Skew Flap

In the skew technique, equal anteromedial and posterolateral fasciocutaneous flaps are created (see Figs. 112.7 and 112.9). The posterior muscle flap is identical to the conventional long posterior flap based on the gastrocnemius muscle.[33] The skew technique may be of particular benefit when there is inadequate skin to create a conventional long posterior flap.

Fish-Mouth Flap

Before the development of the long posterior flap, the creation of equal anterior and posterior flaps was the most common transtibial amputation technique. The chief disadvantage was vulnerability of the anterior flap to ischemia.

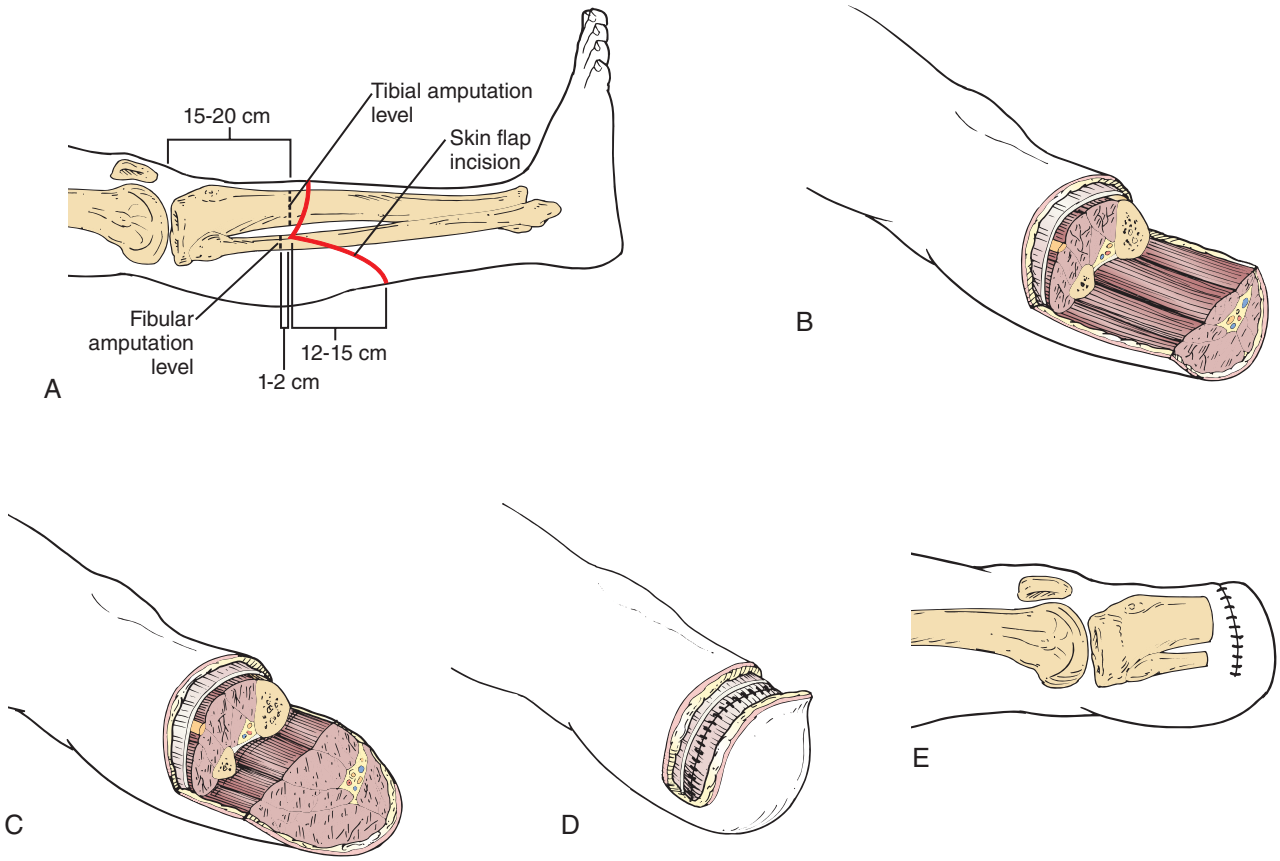


Figure 112.8 **Transtibial Amputation.** (A) Marking the skin incisions. (B) Fashioning the flaps after bone transection. (C) The soleus muscle is tailored to create a proper flap. (D) The posterior deep fascia is sutured to the anterior deep fascia and periosteum. (E) Closure of the skin flaps.

Medial Flap

A medially based flap technique, described by Jain and colleagues, may be appropriate in selected patients (see Figs. 112.7 and 112.10).[34] Based on thermographic imaging, a long medial flap and a shorter lateral flap are designed. A Cochrane review published in 2014 concluded that there was insufficient evidence to establish the superiority of one transtibial amputation technique over the others.[35]

Ertl Procedure

Tibiofibular bone bridging, known as the Ertl procedure, is thought by some to provide better transmission of energy from the distal femur to the prosthesis. The Ertl procedure uses a bone bridge between the tibia and fibula to provide a more stable weight-bearing surface. The fibula is harvested from the amputation specimen and serves as a bone graft.

Equal length skin flaps are created. The skin and soft tissues are excised, and the anterior muscle is divided. The tibia is divided with a bone saw, and the fibula is first divided approximately 2 to 4 cm distal to this point, depending on the distance from the tibia to the fibula. Next, the fibula is divided at a level of the tibial osteotomy, with care to preserve the peroneal artery and blood supply to the fibula. The posterior flap is then completed. Next, the facing portions of the tibia and fibula are trimmed parallel to accept the fibula bone bridge. The bone graft is affixed either with screws or permanent sutures. A myodesis of the soleus and gastrocnemius to the anterior tibia is completed before reapproximating the soft tissue and skin in two layers.[36-38] The superiority of this technique over traditional transtibial amputation has not been proven,[39] although one series of 32 patients receiving bone bridging of the distal tibia and fibula showed an improved quality of life with improved ambulation and decreased patient frustration.[40]

Guillotine Amputation

Patients presenting with severe infection may warrant an initial débridement amputation to obtain source control. Rapid removal of the offending limb via guillotine amputation offers the chance for patient stabilization. Revision and flap closure are completed once the patient's condition is more favorable. In two small trials, two-stage amputation was associated with lower overall infection rate.[4,5]

Cryoamputation

Cryoamputation is reserved for patients too ill for anesthesia and may be a treatment for severe gangrenous infection, severe ischemia, or myonecrosis. A tourniquet is applied proximally, and dry ice is packed around the limb. By physiologically isolating the limb, toxic byproducts and organic acids cannot circulate

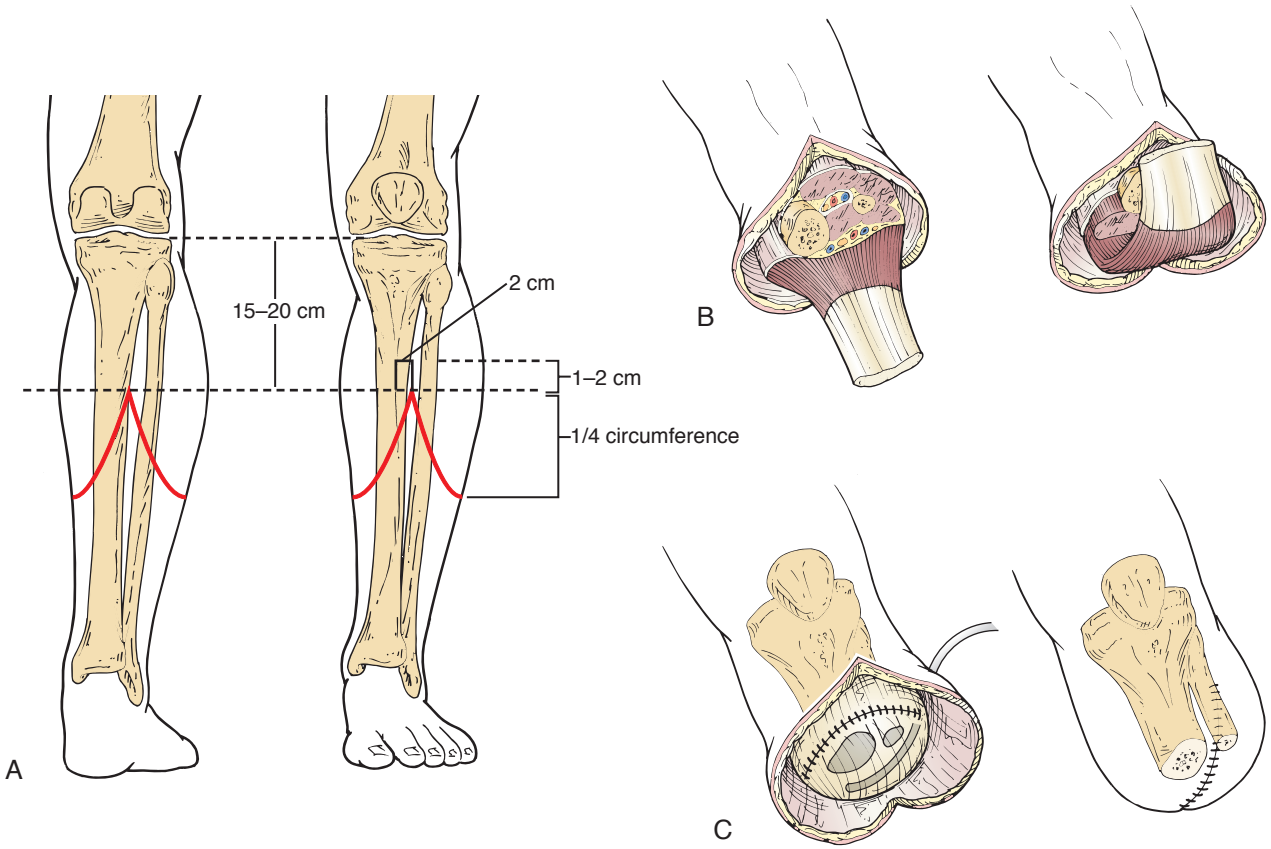


Figure 112.9 **Skew Flap.** (A) The incisions result in equal anteromedial and posterolateral skin flaps. The tibia is transected to 10 to 12 cm distal to the joint line. (B) The gastrocnemius muscle flap covers the tibia. (C) The skin is closed with nonabsorbable sutures.

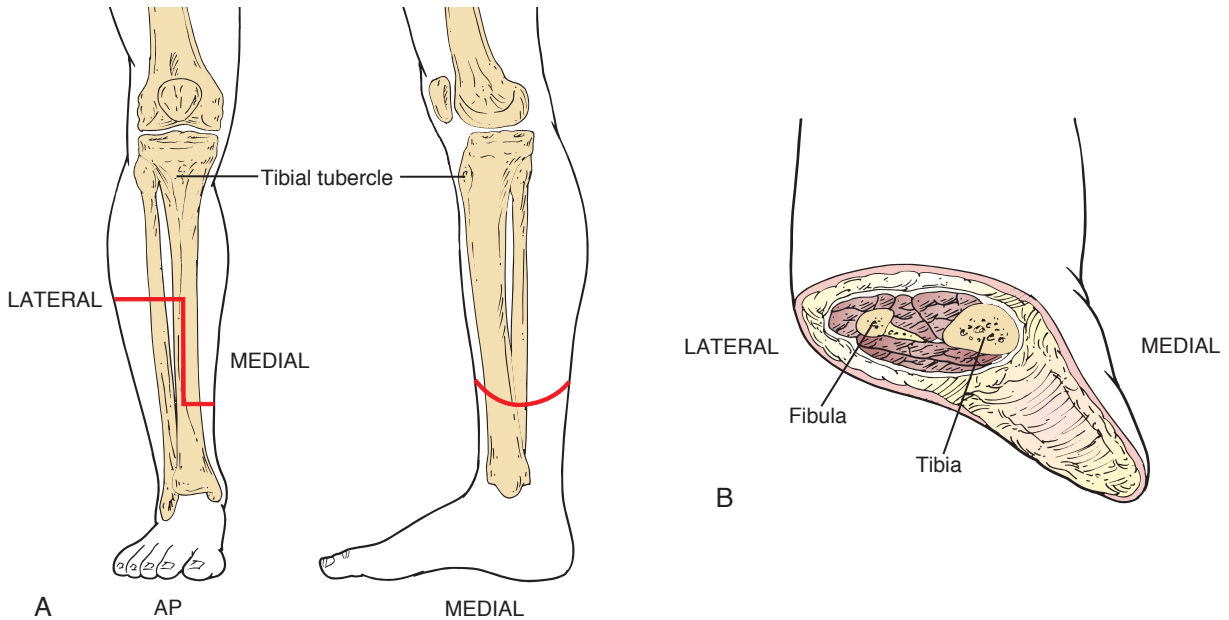


Figure 112.10 (A) Skin incision for a medially based flap. (B) View of the flap after transection. *AP*, Anterioposterior.

systemically. After the patient's status improves, a surgical amputation can be completed. Cryoamputation has been associated with improved mortality in comparison with emergency amputation in the frail and elderly.[41-43] Complications include migration of the frost line above the intended level of amputation and a substantial need for revision.[44]

Postoperative Considerations

There is a tendency for the patient to flex the knee joint, and over time a flexion contracture could occur without proper care. A knee immobilizer is kept in place with Velcro straps and be easily removed to examine the amputation wound.

Primary healing fails in 20% to 30% patients. Nehler et al. found only 55% of transtibial amputations were completely healed at 100 days, increasing to 83% at 200 days.[45] Furthermore, approximately 20% of patients undergoing transtibial amputation needed a higher-level amputation.[45,46] The decision to perform an amputation at a given level is complicated by patients who typically have significant comorbidities that limit wound healing.

THROUGH-KNEE AMPUTATION

Anatomy

Through-knee amputation requires the removal of the tibia, fibula, and articular surface of the distal femur. Of particular note is the treatment of the patellar ligament (also known as the patellar tendon), cruciate ligaments, and tendons of the hamstring muscles, because these structures are sutured to each other in a through-knee amputation. The patellar ligament is an extension of the quadriceps tendon, which stabilizes the patella and attaches distally to the tibial tuberosity. The hamstring tendons collectively are derived from the semitendinosus, semimembranosus, and biceps femoris muscles.

Technique

In patients with good rehabilitation potential who are not suitable candidates for transtibial amputation, a through-knee amputation may be an acceptable alternative. Through-knee amputation offers higher rates of successful ambulation when compared with transfemoral amputation. Some have actually advocated for primary through-knee amputation rather than transtibial amputation in selected patients.[47] However, 10% to 15% of patients undergoing through-knee amputation will require a higher level of amputation.[48]

We recommend a technique originally described by Mazet in which the distal femur is preserved and condyles are trimmed squarely (Fig. 112.11).[49,50] An alternative is the modified Gritti-Stokes amputation, which involves transection of the articular head of the femur with preservation and fixation of the patella as an end-cap to the leg. A fish-mouth incision is fashioned with its corners at the level of the mid condyles of the femur. The anterior flap is extended to the level of the tibial tuberosity and the posterior flap is extended to be the same length. Next,

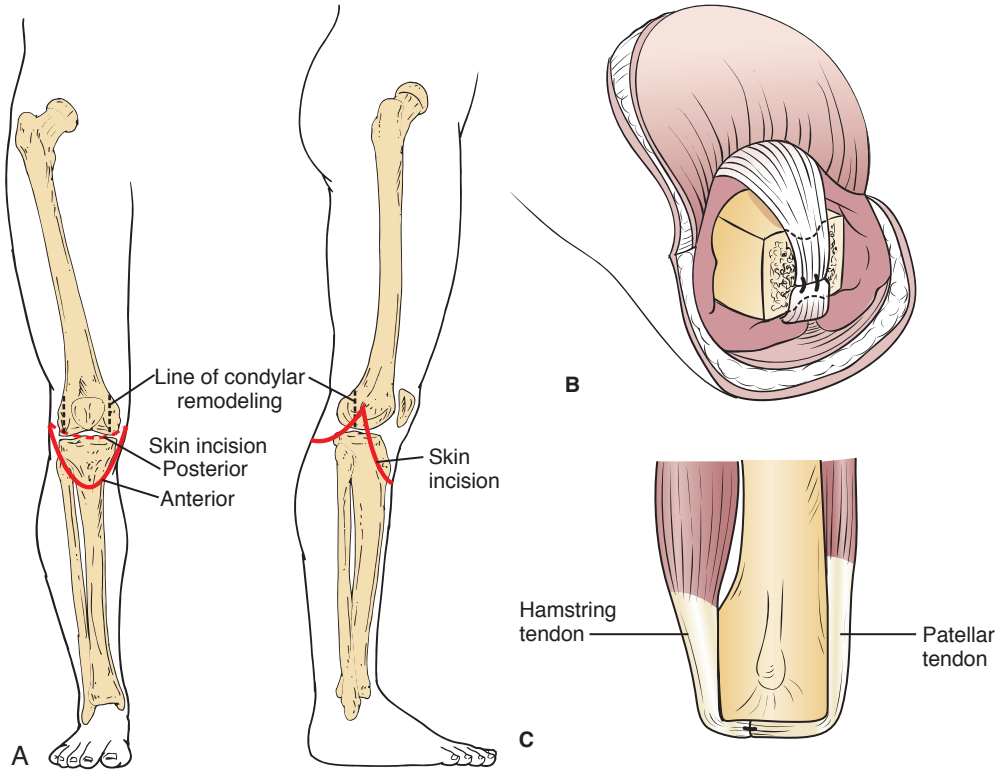


Figure 112.11 (A) Fish-mouth incision for through-knee amputation. (B and C) the patellar tendon is sutured directly to the residual cruciate ligament.

the skin is incised and the medial and lateral collateral ligaments are divided. The patellar ligament is divided from its attachment to the tibial tuberosity, preserving its length and then it is retracted proximally. The skin and deep fascial elements are dissected off the knee capsule before excising the knee capsule and dividing the cruciate ligaments. The popliteal artery and veins are suture ligated, and the common peroneal and tibial nerves are transected sharply under tension and allowed to retract. The popliteus and gastrocnemius muscles are divided along with the remaining tendons from their insertion sites; then the leg is removed. By dissecting very closely to the patella during its removal, the anterior skin flaps are preserved and buttonholing is avoided.

The menisci are removed, and the lateral one-third of the lateral condyle and medial half of the medial condyle of the femur are trimmed using a bone saw. The posterior surface is squared. The edges are smoothed with a rasp or bone saw. Next, the hamstrings are approximated to the patellar ligament while incorporating the cruciate ligaments in the bite. Finally, the fascia and skin are closed in two layers.

TRANSFEMORAL (ABOVE-KNEE) AMPUTATION

Anatomy

The thigh has three muscle groups: anterior, middle, and posterior. The anterior muscle group consists of the quadriceps femoris, sartorius, and tensor fascia latae. The medial group consists of the adductor longus, brevis and magnus, gracilis, and pectineus muscles. Posteriorly are the hamstrings: biceps femoris (long and short heads), semitendinosus, and semimembranosus. Of note, the adductors insert into the posterolateral femur along the linea aspera. The adductor magnus also inserts onto the adductor tubercle, a bony prominence on the medial epicondyle of the femur.

Technique

The femur is typically divided at the junction of the middle and distal one-third, or approximately 12 cm proximal to the femoral condyles, but if necessary division can be more proximal as long as tissue coverage exists. A fish-mouth incision is used, creating equal anterior and posterior flaps, although orientation can be varied (Fig. 112.12). After incising the skin and soft tissue, the superficial femoral artery and femoral vein are divided and controlled with suture ligature. The muscles are divided in the same plane, unless intending to perform a myodesis (see later). The femur is transected proximal to the corners of the fish-mouth incision using a mechanical saw and rough edges are filed as needed. The sciatic nerve is stretched, divided, and allowed to retract.

There is a tendency for the hip flexors to abduct and flex the thigh because the adductor muscles are no longer attached and able to oppose this motion. After creating flaps and incising the skin and soft tissue, muscles are then identified. The quadriceps is detached proximal to the patella, leaving some of its tendinous portion intact. The vastus medialis is reflected laterally off the intermuscular septum to expose the adductor magnus. The adductor magnus is sharply divided at its attachment to the adductor tubercle on the medial epicondyle and it is reflected medially to expose the femoral shaft. The vessels traversing the Hunter canal are ligated. The remaining gracilis, sartorius, semimembranosus, and semitendinosus are divided approximately 1 to 2 cm distal to the point of transection of the femur. The femur is exposed and cut with a mechanical saw, two to three holes are drilled into the lateral cortex, and one to two holes drilled into the posterior cortex of the remaining femur, approximately 1 to 2 cm from its end. The adductor magnus is wrapped over the end of the bone, with the femur held in maximal adduction then anchored using the lateral holes. Anterior and posterior sutures are used to prevent the muscle from sliding off the bone. The quadriceps muscles are wrapped over the end of the femur and sutured posteriorly, and the remaining posterior muscles are anchored posteriorly to the newly affixed adductor magnus.[51,52] Although reliable studies of myodesis have not been performed, it may benefit patients more likely to ambulate with an above-knee prosthesis.

Postoperative Considerations

The threat of wound contamination is of higher concern with transfemoral amputation. Dressings are left in place at a minimum of 4 to 5 days unless clinically compelled to remove earlier.

Patients with above-knee amputation (AKA) use 50% more energy to ambulate than those with below-knee amputation (BKA), and less than 10% of elderly vascular amputees ambulate effectively after transfemoral amputation.[53]

HIP DISARTICULATION

Anatomy

The hip joint is a ball-and-socket joint stabilized by a fibrous capsule, acetabular labrum, ligament of the head of the femur, iliofemoral, ischiofemoral, pubofemoral, and transverse acetabular ligaments. Anterior to the hip joint are the rectus femoris, iliopsoas, and pectineus muscles. Anterior to these muscles are the tensor fascia lata and sartorius. Posterior to the joint are the piriformis muscle, obturator internus and externus, superior and inferior gemelli, and quadratus femoris. These are among the other muscles of the hip and thigh not immediately adjacent to the hip joint also associated with ambulation.

Technique

The patient is positioned in a semilateral position. An anterior racket incision or a long posterior flap incision may be used (Fig. 112.13).[54] The anterior racket incision starts 2.5 cm medial to the anterior superior iliac spine, extends toward the pubic tubercle, and continues posteriorly distal to the ischial tuberosity and gluteal crease. The incision is continued anteriorly, medial

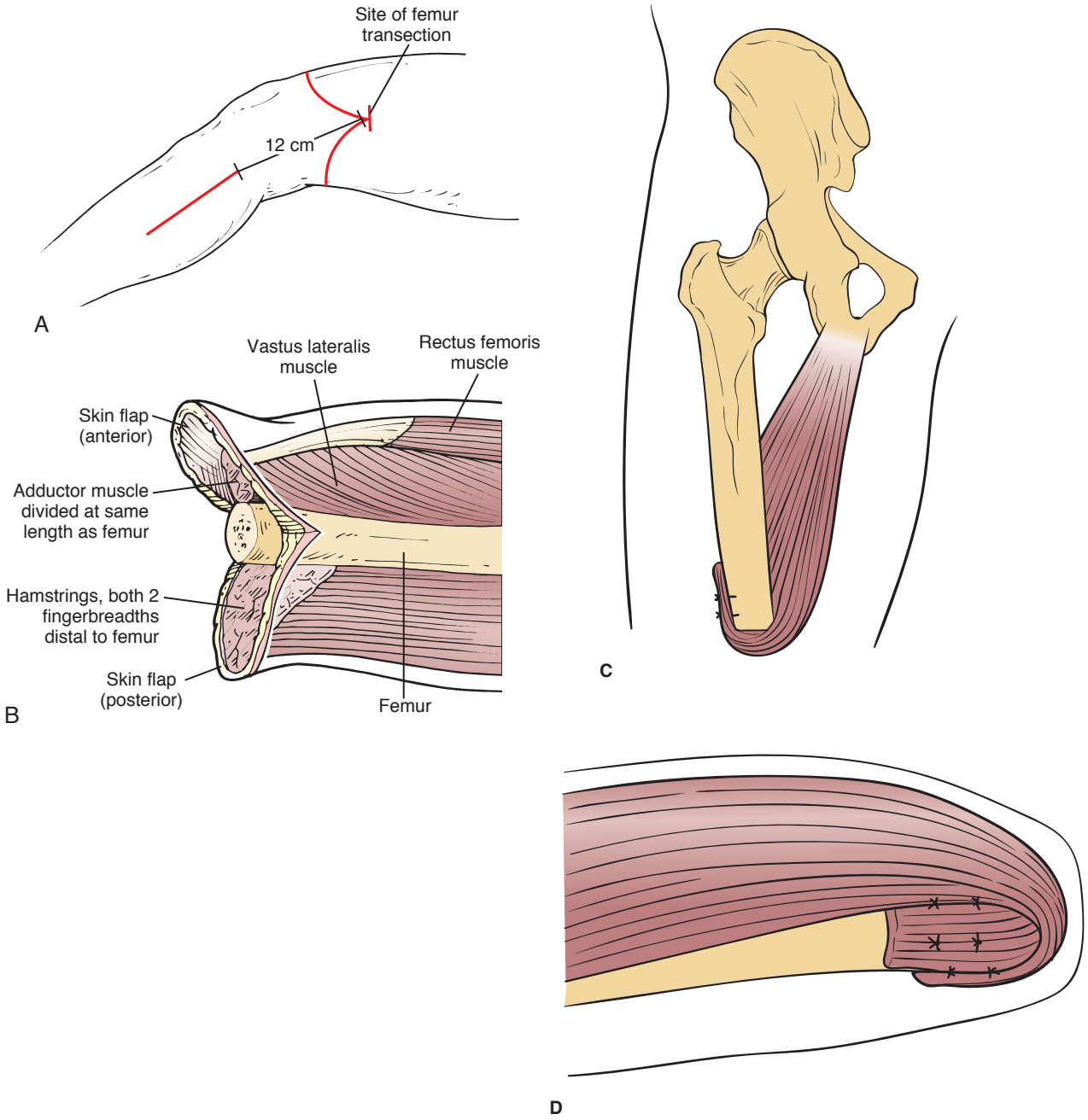


Figure 112.12 (A) Fish-mouth incision for long transfemoral amputation. (B) Cutaway view of transfemoral amputation. (C) Fixation of adductor magnus to the distal femur, performed in maximum adduction. (D) The quadriceps muscle is then anchored to the distal femur with the hip extended.

to the greater trochanter and the anterior inferior iliac spine before joining the incision at its origin. The skin and soft tissues are incised down to the external oblique aponeurosis and deep fascia of the thigh. The femoral vessels are suture ligated and the femoral nerve transected and allowed to retract. Next, the muscles of the hip joint are divided, starting with the sartorius at its origin and iliopsoas at its insertion site. The pectineus is divided at its origin on the superior pubic ramus. The gracilis muscle and three adductors are divided at their origins on the pubic rami. The obturator neurovascular bundle is divided, and the obturator externus muscle is divided from its insertion to the trochanteric fossa. The hamstrings are transected at the ischial tuberosity before dividing the tensor fasciae latae, gluteus maximus, and rectus femoris before dividing the remaining muscles attached to the greater trochanter. To complete the amputation, the ligamentous attachments and capsule of the hip joint are divided. The sciatic nerve is transected and allowed to retract and the specimen is passed off. The posterior quadratus femoris is sutured to the anterior iliopsoas and the lateral gluteus medius is sutured to the medial obturator externus. One may

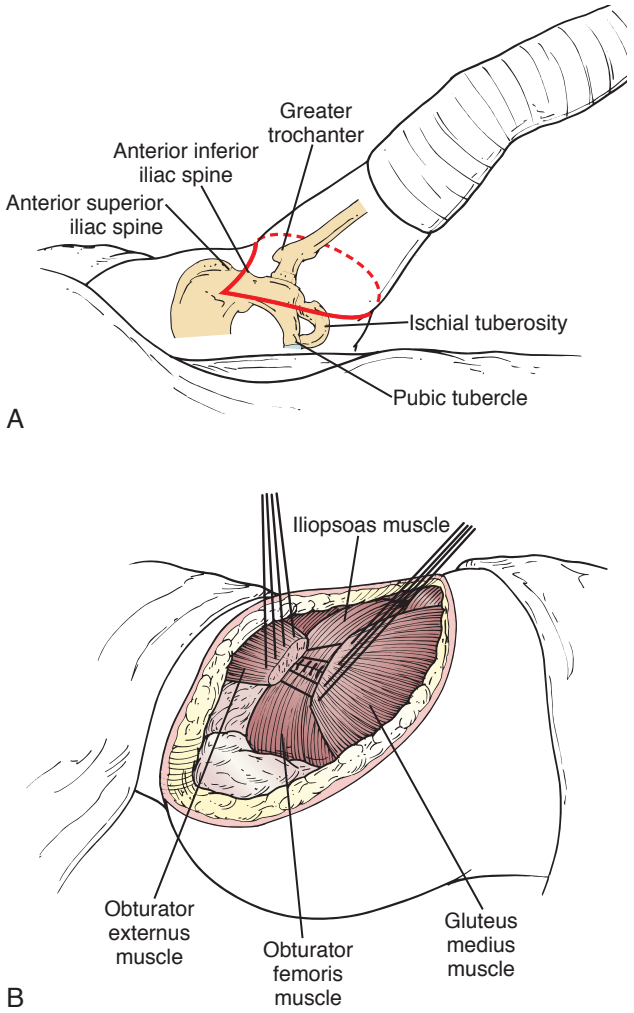


Figure 112.13 (A) Racket incision for hip disarticulation. (B) Two-layer myoplasty over the acetabulum.

elect to place closed suction drains in the subcutaneous space. Closure is in two layers: the gluteal fascia is approximated to the inguinal ligament and the skin is closed loosely with staples.[54]

Postoperative Considerations

Drains and a Foley catheter are left in place for a few days. Avoiding soilage from stool and urine may be a challenging yet important part of postoperative care. Chemothrombophrophylaxis is very important given the high risk for thromboembolic events.

PRINCIPLES OF POSTOPERATIVE CARE

In our practice, operative dressings are left in place for 5 days unless a clinical indication (e.g., fever, bleeding) warrants removal.[55,56] Some advocate for application of an immediate postoperative prosthesis (IPOP), reporting effective prosthetic ambulation at an earlier time when compared with conventional practice.[57,58] Drawbacks of IPOP include the need for a skillful multidisciplinary team, its lack of being universally available, and the inability to examine the wound when in place.[56,59,60]

Attention should be paid to control of blood sugar in the physiologic range and to maintaining adequate nutrition.

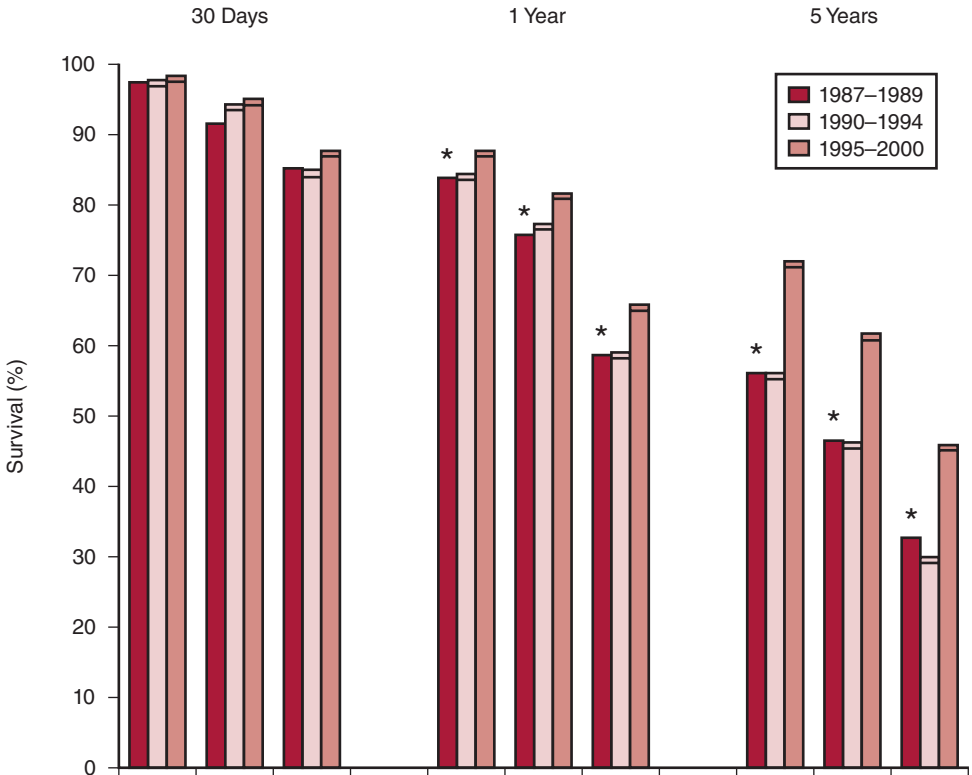
Operative Mortality

In the modern era, 30-day operative mortality ranges from 6% to 13% for major lower extremity amputations.[61-64] For minor amputations at the ankle or below, operative mortality drops to 2% to 4%.[45,46,65,66] Most lower extremity amputations are performed for ischemia and diabetes, with trauma and malignancy accounting for the remainder.[67,68] The most common causes of death following lower extremity amputation are cardiac complications (46%), sepsis (14%), and pneumonia (11%).[69] Overall 30-day mortality in a large retrospective analysis was 12.8% after AKA and 6.5% after BKA.[64] A retrospective study of 788 patients reported similar results,[69] whereas a study of more than 13,000 patients in Washington State confirmed stable 30-day survival rates dating back to 1987 (Fig. 112.14).[70]

There are many observational studies seeking to identify the predictors of operative mortality after lower extremity amputation. A study of more than 9000 patients used the ACS NSQIP database to perform a retrospective review of BKA and AKA patients. In patients undergoing AKA, 30-day mortality was more often associated with the following risk factors, in decreasing order: hemodialysis dependence, thrombocytopenia, total dependent functional status, age greater than 80 years, steroid use, congestive heart failure, preoperative sepsis, body mass index less than 18.5 kg/m^2, and dyspnea. In patients undergoing BKA, 30-day mortality was more often associated with the following risk factors, in decreasing order: age greater than 80 years, DNR status, hemodialysis dependence, totally dependent functional status, sepsis, and thrombocytopenia.[64] In another study of 30-day mortality after BKA, renal failure increased the risk of death by more than threefold to 62%.[71] Guillotine amputation for sepsis was associated with a 14.3% mortality compared with 7.8% in patients undergoing elective amputation.[60]

LONG-TERM SURVIVAL

The prevalence of major lower extremity amputation attributable to vascular disease in the United States was approximately 500,000 in 2005, with an expected increase by 50% by the year 2020.[72] One-year survival rates are lower in patients receiving a higher-level amputation (Table 112.1). The approximate 1-year survival following BKA is 65% to 80% versus 50% following AKA (Fig. 112.15).[46,63,69,70,73] In another perspective, the median survival was reported as 1 year for transfemoral amputation and 2.4 years for transtibial amputation.[74] Predictably, patients with diabetes and renal failure fare worse.[69,74] Of 390 British patients undergoing lower extremity amputation, diabetic patients' median time to death was 27.2 months versus 46.7 in nondiabetics.[69] Amputation patients on dialysis had a 1-year survival of 51.9%, amputation patients not on dialysis but with



	Toe/ trans met.	Below-knee	Above-knee		Toe/ trans met.	Below-knee	Above-knee		Toe/ trans met.	Below-knee	Above-knee
1987–1989	96.3%	90.5%	84.0%		82.6%	74.4%	57.3%		54.7%	45.0%	31.3%
1990–1994	96.4%	93.1%	83.7%		83.1%	76.0%	57.7%		54.6%	44.8%	28.4%
1995–2000	97.2%	93.9%	86.5%		86.5%	80.4%	64.6%		70.7%	60.0%	44.4%

Figure 112.14 Bar graph showing survival at 30 days, 1 year, and 5 years following foot (toe/transmetatarsal), below-knee, and above-knee amputations during three periods (1987–1989, 1990–1994, and 1995–2000). (*$P < .001$ when post-1995 is compared with pre-1995.) (From Sandnes DK, Sobel M, Flum DR. Survival after lower-extremity amputation. *J Am Coll Surg.* 2004;199:394–402.)

a serum creatinine greater than 2 mg/dL had a 1-year survival rate of 55.9%, and non–dialysis-dependent patients had a 1-year survival rate of 75.4%.[69] Overall, long-term survival has improved following major lower extremity amputation, but there are no studies completed within the past 10 years to confirm this observation.[61,70]

FUNCTIONAL OUTCOME

After toe, ray, and transmetatarsal amputations, near-normal ambulation with conventional footwear is likely. Shoe fillers and simple orthoses allow for ambulation in a majority of patients.[a]

Following transtibial amputation for vascular disease, bipedal ambulation with a prosthesis is uncommon. Two recent reports indicate only approximately 25% of major lower extremity amputees ambulate with a prosthesis outside the home.[45,75] These patients were unable to use a prosthesis for a variety of reasons, including mental illness, cardiopulmonary insufficiency, inadequate balance, and stump problems.[45,79] A prospective study of 297 patients reported that those who received care in an acute inpatient rehabilitation facility had better functional outcome at 6 months than patients who were treated at home or in a skilled nursing facility.[80] Taylor and coworkers identified significant preoperative factors independently associated with not wearing a prosthesis. In order from greatest to least risk, these patients were nonambulatory before amputation (odds ratio [OR] 9.5), AKA (OR 4.4), homebound but ambulatory, (OR 3.0), older than 60 years (OR 2.8), or diagnosed with dementia (OR 2.4), end-stage renal disease (OR 2.3), or coronary artery disease (OR 2.0).[81] Older transfemoral amputees rarely (<10%) ambulate successfully with a prosthesis.[45,75,82] Dialysis-dependent renal failure is a strong predictor of nonambulatory status.

Despite the fact that few vascular amputees ambulate with a prosthesis outside the home, most maintain their preoperative living status. Highly motivated patients—as evidenced by a commitment to a strict rehabilitation program, including smoking cessation and weight loss—are more likely to achieve

[a]References 12, 17, 65, 66, 77, and 78.

TABLE 112.1 Thirty-Day Mortality, 1-Year Survival, and Reamputation Rates

Series	Year	Number of Patients	30-DAY MORTALITY (%)		1-YEAR SURVIVAL (%)		REAMPUTATION RATE	
			Bka[a]	AKA	BKA	AKA	BKA to AKA (%)	Contralateral Major Amputation (%)
Kazmers[b]	2000	8,696	9.4	16.1				
Feinglass et al.[c]	2001	4,061	6.3	13.3	77	59		
Mayfield et al.[d]	2001	5,180	7.0	11.1				
Abou-Zamzam et al.[62]	2003	131					19.6	10.7 (at 3 year)
Nehler et al.[45]	2003	172					19	
Cruz et al.[82]	2003	296	12	17			12	17 (at 7 year)
Aulivola et al.[69]	2004	959	5.7	16.5	74.5	50.6	9.4	19.8 (at 11 year)
Sandnes et al.[70]	2004	6,919	6.1	13.5	80.4	64.6		
Subramaniam[e]	2005	954	4.2	17.5	78.2	62.1		
Ploeg et al.[63]	2005	122	5.2	17.8			14.3	
Dillingham et al.[46]	2005	3,565			64.5	49.6	9.4	9.4 (at 1 year)
Stone et al.[19]	2007	508	3.6	13.6			11.5	21 (at 5 year)
Nelson et al.[64]	2012	9,368	6.5	12.8				

[a]*AKA,* Above-knee amputation; *BKA,* below-knee amputation.
[b]Kajmers A, Perkins AJ, Jacobs LA. Major lower extremity amputation in Veterans Affairs Medical Centers. *Ann Vasc Surg*. 2000;14:216–222.
[c]Feinglass J, et al: Postoperative and late survival outcomes after major amputation: findings from the Department of Veterans Affairs National Surgical Quality Improvement Program. *Surgery*. 2001;130:21–29.
[d]Mayfield JA, et al: Survival following lower-limb amputation in a veteran population. *J Rehabil Res Dev*. 2001;38:341–345.
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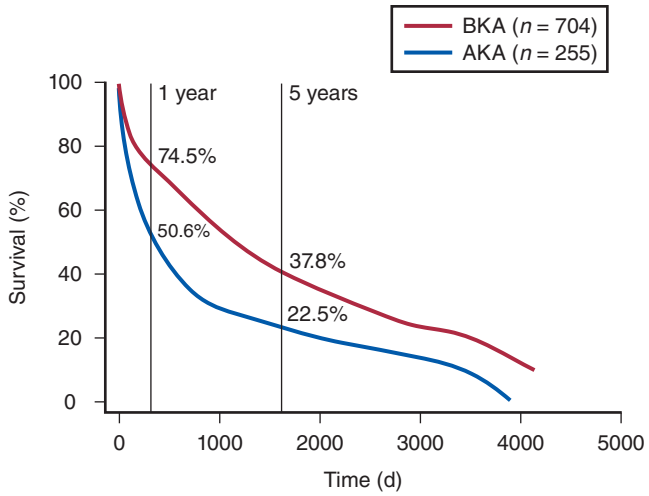

Figure 112.15 Long-term survival following below-knee amputation (BKA) and above-knee amputation (AKA). (From Aulivola B, Hile CN, Hamdan AD, et al. Major lower extremity amputation: outcome of a modern series. *Arch Surg*. 2004;139:395–399.)

long-term success.[83] In addition, patients with financial resources that allow participation in a well-organized rehabilitation program are more likely to be successful. Taylor and coworkers identified the following statistically significant preoperative factors that were independently associated with a failure to maintain an independent living status (in decreasing order of influence): age 70 years or older (hazard ratio [HR] 4.0), age 60 to 69 years (HR 2.7), level of amputation (HR 1.8), homebound ambulatory status (HR 1.6), and dementia (HR 1.6).[81] In the United States, Medicare reimbursement for a prosthesis is based on adequate patient motivation as well as the ability to achieve a defined functional state classified as a "K level" (Table 112.2).[84]

REAMPUTATION

Following an initial toe amputation, approximately 50% of patients eventually undergo additional ipsilateral or contralateral amputations. Following foot or ankle amputation, nearly 35% of patients progress to a higher-level amputation within 1 year.[46] Wound problems develop in 20% to 30% of patients following transtibial amputation.[45,69,82] Only half of these amputations are salvaged at the transtibial level. In addition, reamputation at the transfemoral level has been reported in 9.4% to 19.6% of transtibial amputees.[b] It has also been reported that 9.4% to 17% of transtibial amputees undergo contralateral major amputation within as little as 12 months.[46,62,69,82,85] Not surprisingly, the risk of ipsilateral reamputation at a higher level is inversely related to the level of the index amputation. Diabetic patients are almost twice as likely to have reamputation as are nondiabetic patients.[73,76] The 1-, 3-, and 5-year ipsilateral reamputation rate for diabetic patients are as follows: for

[b]References 45, 46, 62, 63, 69, and 82.

TABLE 112.2 K-Levels, A Classification System Created by the US Centers for Medicare and Medicaid Services Are Used to Stratify Potential Functional Ability in Amputees

Level 0:	Does not have the ability or potential to ambulate or transfer safely with or without assistance and a prosthesis does not enhance their quality of life or mobility.
Level 1:	Has the ability or potential to use a prosthesis for transfer or ambulation on level surfaces at fixed cadence. Typical of the limited and unlimited household ambulator.
Level 2:	Has the ability or potential for ambulation with the ability to traverse low level environmental barriers such as curbs, stairs or uneven surfaces. Typical of the limited community ambulator.
Level 3:	Has the ability or potential for ambulation with variable cadence. Typical of the community ambulator who has the ability to traverse most environmental barriers and may have vocational, therapeutic, or exercise activity that demands prosthetic use beyond simple locomotion.
Level 4:	Has the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels. Typical of the prosthetic demands of the child, active adult, or athlete.

toe amputees, 22.8%, 39.6%, and 52.3%, respectively; for ray amputees, 28.7%, 41.2%, and 50%, respectively; for midfoot amputees, 18.8%, 33.3%, and 42.9%, respectively; and for major amputees, 4.7%, 11.8%, and 13.3%, respectively. In a study analyzing factors that predict long-term resource use and survival after major amputation, the authors noted that complicated diabetes, renal failure, and undergoing index BKA were all associated with increased additional amputation-related procedures.[86]

COMPLICATIONS

Local

Bleeding

Reoperation for postoperative bleeding is reported in 3% to 8% of major lower extremity amputations.[45,61] Frequently, patients undergoing dysvascular amputations are on antiplatelet therapy, which may increase the likelihood of developing a hematoma. Despite this elevated risk, patients should still receive DVT prophylaxis, unless contraindicated.

Infection

The likelihood of wound infection following major lower extremity amputation ranges from 13% to 40%.[5,9,87] An increased risk of wound infection is associated with diabetes, preoperative wound infection, malnutrition, malignancy, advanced age, lack of insurance, wound hematoma, and prior prosthetic bypass grafts. Complete removal of synthetic graft material at the time of amputation can decrease the rate of stump infection.[88] A recent study reported wound infection or disruption in healing to be 10.4% after BKA and 7.2% after AKA. In this study, patients with elevated international normalized ratio (INR) and patients age 50 to 59 were more likely to develop wound complications after a BKA, whereas current smokers and obese patients were more likely to develop wound complications after AKA.[89]

Superficial infections can initially be treated by administration of broad-spectrum antibiotics and removal of skin sutures. Deeper infections necessitate more aggressive drainage and débridement. Vacuum dressings may be particularly effective in this setting.[22]

Contracture

Flexion contractures at the hip and knee joint develop in 3% to 5% of major lower extremity amputations. A fixed flexion contracture at the knee that exceeds 15 degrees prohibits effective prosthetic ambulation. After a significant contracture develops, it may be impossible to correct with physical therapy or surgery.[90] A rigid, removable dressing should be applied to prevent knee contractures. An aggressive postoperative knee exercise program should be initiated as soon as possible. Hip flexion contracture may be limited by positioning the patient in the prone position for brief periods.

Systemic

Cardiac

Myocardial infarction remains the most common cause of death following lower extremity amputation. In a study of 788 patients, 10.2% of patients experienced a cardiac complication: congestive heart failure (4.2%), myocardial infarction (3.4%), and arrhythmia (2.6%).[69] Antiplatelet agents and statins should be continued perioperatively, and one should aim to maintain adequate perfusion while avoiding overresuscitation in the perioperative and postoperative phases. Clinical suspicion of an adverse cardiac event should remain high.

Pulmonary

Following amputation, patients are at risk for respiratory complications, including pneumonia. Although there is insufficient evidence for the use of incentive spirometry, its use may limit atelectasis and at the very least engage the patient.

Venous Thromboembolism

Following lower extremity amputation, the risk of DVT is up to 50%.[10,91-93] Low-molecular-weight heparin administered prophylactically lowers this risk to 10%. It is our practice to prefer low-molecular-weight heparin for chemoprophylaxis, although unfractionated heparin is preferred in patients with severe renal impairment or weight less than 45 kg.

Renal Failure

Acute blood loss, general anesthesia, and any other cause for hypotension and end-organ malperfusion may put the patient at risk for acute kidney injury. New-onset renal failure following amputation ranges from 0.6% to 2.6%.[45,69]

Stroke

The incidence of stroke after major amputation ranges from 0.28% to 1.4%.[45,61] Stroke is a rare cause of perioperative death behind infection, cardiac event, and pulmonary embolus.[94]

Psychiatric

Posttraumatic stress disorder is common (20%-22%) after amputations for combat or accidental injuries. For vascular amputations the incidence is less than 5%. Risk factors for major depressive disorder include young age at the time of amputation, pain, neurotic personality, unhealthy lifestyle, and poor coping skills.[95,96] In addition, 16% of a sample of 239 patients undergoing vascular disease–related amputation experienced suicidal ideation.[97]

Pain

Chronic pain is reported by up to 95% of amputees.[98] Chronic ischemic stump pain may be difficult to detect by physical examination alone but is confirmed by a transcutaneous oxygen tension less than 20 mm Hg. Chronic infection, particularly related to residual prosthetic graft material, may also cause pain. Neuroma can develop at the site of transection of virtually any peripheral nerve. The pain is usually well localized and can be transiently or permanently blocked with anesthetic injection. Pressure points that develop over bone spurs or pathologic bone formation should be eliminated. Depression appears to complicate the treatment of pain in many amputees.[98]

True phantom pain is a complex, poorly understood pain syndrome. The incidence of phantom pain widely varies in the literature from 5% to 85%, depending on the diagnostic criteria.[99,100] Inadequate control of both preoperative and postoperative pain may increase the risk of chronic amputation pain.[101] Gabapentin has not been consistently effective in the treatment of phantom pain. Multimodality pain management is the cornerstone of a successful amputation rehabilitation program.[102]

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CHAPTER 113

General Considerations of Diabetic Foot Ulcers

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INTRODUCTION

Diabetic foot disease poses a growing global public health challenge and a major financial burden on healthcare systems worldwide. The prevalence of diabetes is exploding worldwide and is expected to involve more than 500 million people in the next 10 to 15 years. Diabetes is the leading cause of foot pathology, causing foot ulcerations from neuropathy, infection, and ischemia. Indeed, most nontraumatic amputations in the United States and Canada are secondary to diabetic foot ulcers.[1,2] Among people within the United States, up to 15% have active ulcers and 1 in 4 have a lifetime risk of developing a diabetic foot ulcer.[3] Infection occurs in approximately half of diabetic foot ulcers, and many of these require amputation. As such, diabetic foot ulcers are one of the most costly aspects of diabetes care, and ulcer-related complications are the leading cause of hospitalization for diabetic patients.[4] This has led to a growing risk of amputation among diabetic patients, because 85% of patients presenting with a foot ulcer are at risk for a subsequent amputation.[5]

EPIDEMIOLOGY

Beyond their devastating complications, such as amputation, diabetic foot ulcers have also been associated with poor quality of life outcomes and a significant financial burden, both to the patient and to the economy through direct costs and lost productivity. The reduced mobility, multiple and prolonged hospitalizations and clinic visits, and the deteriorating quality of life lead to cardiovascular stress and an increased risk of

Abstract

Diabetic foot disease poses a growing global public health challenge and a major financial burden on healthcare systems worldwide. The prevalence of diabetes is exploding worldwide and is expected to involve more than 500 million people in the next 10 to 15 years. Diabetes is the leading cause of foot pathology, causing foot ulcerations from neuropathy, infection, and ischemia. Indeed, most nontraumatic amputations in the United States and Canada are secondary to diabetic foot ulcers. Among people within the United States, up to 15% have active ulcers and 1 in 4 have a lifetime risk of developing a diabetic foot ulcer. Infection occurs in approximately half of diabetic foot ulcers, and many of these require amputation. As such, diabetic foot ulcers are one of the most costly aspects of diabetes care, and ulcer-related complications are the leading cause of hospitalization for diabetic patients. This has led to a growing risk of amputation among diabetic patients, because 85% of patients presenting with a foot ulcer are at risk for a subsequent amputation.

Keywords

diabetes foot
ulceration
wound
amputation

mortality compared with the general population. In fact, patients with a diabetic foot ulcer have an annual mortality rate approaching 10%, with an increase to 20% annually if an amputation is performed. Diabetic patients who undergo amputation have a median incidence of mortality at 27 months postoperatively, compared with 47 months among nondiabetic patients with amputation.[6] In all, the 5-year relative mortality rate for those with diabetes who undergo a major limb loss is 70%.[7]

On average, treating diabetic foot ulcers has been estimated at $8000 to $17,000 in medical expenditures and those patients who subsequently undergo an amputation require $40,000 to $60,000, depending on the extent of the amputation and the associated hospital stay.[8] Limb amputations are also predictors of further deterioration in the patient's health. Among patients who have undergone a major lower extremity amputation, up to 40% will undergo amputation of the contralateral limb within 3 years.[9]

PATHOPHYSIOLOGY

The etiology of diabetic foot ulceration is a well-understood, but multifactorial and complex process (Fig. 113.1). Major risk factors associated with diabetic foot ulcer formation are diabetic peripheral neuropathy and peripheral arterial disease (PAD), which act either in isolation or concurrently. Other important risk factors include soft tissue infection, biomechanical abnormalities, peripheral edema, plantar callus formation, nephropathy, poor glucose control, age, and a prolonged diabetic course.[10] Abnormal foot biomechanics often results from structural foot deformities combined with the limited joint mobility and bony abnormalities found in diabetic patients. Trauma due to poorly fitting footwear also frequently plays a major role and ulcer formation. Ulceration of the heel often combines decubitus or pressure forces with ischemia, resulting in a difficult management issue.

Diabetic Neuropathy

Diabetes results in both somatic and autonomic neuropathy. The onset of somatic neuropathy is insidious and progressive, eventually resulting in the complete loss of foot sensation and placing the patient at a higher risk of unperceived foot trauma and ulceration.[11] Examples include puncture wounds while walking barefoot, burn wounds, and iatrogenic or self-induced trauma while cutting nails or grooming the skin. Furthermore, loss of sensation places the patient at a higher risk of injury when donning improperly fitted shoes.[12] Somatic neuropathy also leads to muscle wasting and eventual flexor-extensor muscle imbalance, weakening of the anterior calf muscles, and the development of an equinus deformity. The forefoot is the most common site of neurotropic ulceration as a result of those diabetes-induced muscle imbalances.[13] Patients with isolated diabetic somatic neuropathy have been found to be at a sevenfold increased risk of foot ulceration compared with other patients.[14]

Sympathetic autonomic nerve dysfunction results in reduced sweating accompanied by dry, fragile skin that is at a higher risk of cracking and fissure formation. This neuropathy can also result in arterial-venous shunting and impaired microvascular regulation of the skin.[15] As such, the insensitive diabetic foot may appear warm and well perfused, resulting in a false sense of security by both the patient and the provider as to the risk of diabetic ulcer formation.[11]

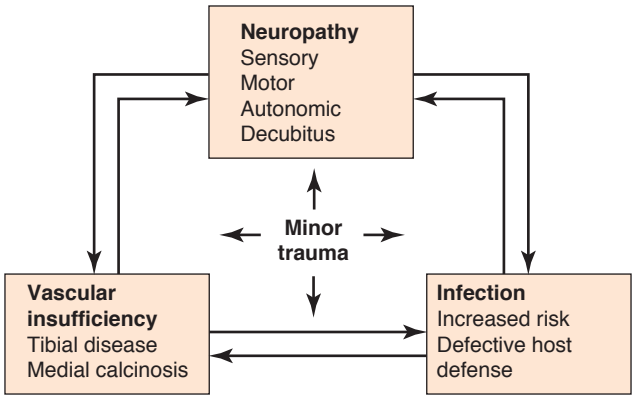

Figure 113.1 Multifactorial etiology of diabetic foot pathology.

Peripheral Arterial Disease

Arterial disease contributes to the development of 50% of diabetic foot ulcers and plays a role in 70% of the mortality among diabetic patients.[10,16] Arterial occlusive disease may be present in isolation or in combination with neuropathic disease in up to 45% of lower extremity ulcerations.[17] Although femoral artery disease occurs in an equal incidence with the nondiabetic population, infrapopliteal occlusive disease with heavy calcification is the classic picture of diabetic arterial disease. In addition, despite the basement membrane affected at the capillary level in those with diabetes, microvascular disease precluding revascularization in diabetic patients has been disproved. Diabetic patients are at a higher risk of digital artery disease with palpable pedal pulses that nonetheless can result in digital ulceration and subsequent impaired healing and gangrene. Despite the relatively common occurrence of an incomplete pedal arch in diabetic patients, tibial revascularization, especially to the angiosome in which the ulceration is located, is possible in the vast majority of diabetic patients to overcome foot ischemia.[18]

Soft Tissue Infection

Diabetic foot ulcers may present with or without infection with a classification proposed by the Infectious Diseases Society of America, including a PEDIS (perfusion, extent, depth, infection and sensation) score to guide assessment of severity and subsequent therapy (Table 113.1). A wound culture should be obtained when signs of an infection, such as purulence, cellulitis in the adjacent skin, malodor, and tissue necrosis, are present. However, ulcers that are otherwise clean and free from any local or systemic signs of infection should not be swabbed or cultured.[19] In the absence of a clinical suspicion of an active infection, a culture swab will likely report mixed skin flora that are not associated with an active infection, and unnecessary treatments might be prescribed. When a soft tissue culture is

TABLE 113.1 Summary of the Classification System of Diabetic Foot Infection by the International Working Group on Diabetic Foot Infection

Grade	Clinical Signs of Infection
1	None
2	Local process involving skin and subcutaneous tissue Erythema (if present) <2 cm No sign of systemic infection
3	Local process deeper than skin and subcutaneous tissue Erythema >2 cm Local abscess, osteomyelitis, septic arthritis, fasciitis No sign of systemic infection
4	Signs of systemic infection (>2 of the following); Temperature >38°C, or, <36°C Heart rate >90 bpm Respiratory rate >20 breaths/min $tcPO_2$ <32 mm Hg WBC >12, or, >10% bands

Signs of local infection; swelling, induration, erythema, tenderness, warmth, purulent discharge.

desired, samples obtained surgically or by curettage of the wound bed are more sensitive and specific in identifying the causative organisms and guiding therapy than swabbing the wound or drainage. In addition, diabetics have elevated serologic concentrations of adhesion molecules that bind monocytes, leukocytes, and platelets to the endothelium and impair its function, leading to diminished skin perfusion and healing, leading to a reduced ability to deliver antibiotics to sites of infection.[20,21]

Muscle and Bone Abnormalities

The changes in biomechanical forces that result from diabetic bony foot deformities create points of pressure that may eventually lead to ulceration (Fig. 113.2). These forces, combined with limited joint mobility, lead to structural deformities such as hallux valgus, claw toes, and abnormalities of the metatarsophalangeal joints. This process is exacerbated by neuropathy-induced lack of sensation in the diabetic foot. Muscular weakness can result in functional imbalances between the tendons of the foot with subsequent hammertoe development that is vulnerable to shoe trauma at bony prominences. The contracted toes also induce increased pressure at the plantar aspect of the metatarsal heads. In addition, Charcot changes and midfoot collapse due to neuro-osteoarthropathy, as well as restricted foot motion due to flatfoot deformities, equinus, and knee or back issues, may all add to the biomechanical stress experienced by the foot, worsen the degree of ulceration, and prevent adequate healing.[22]

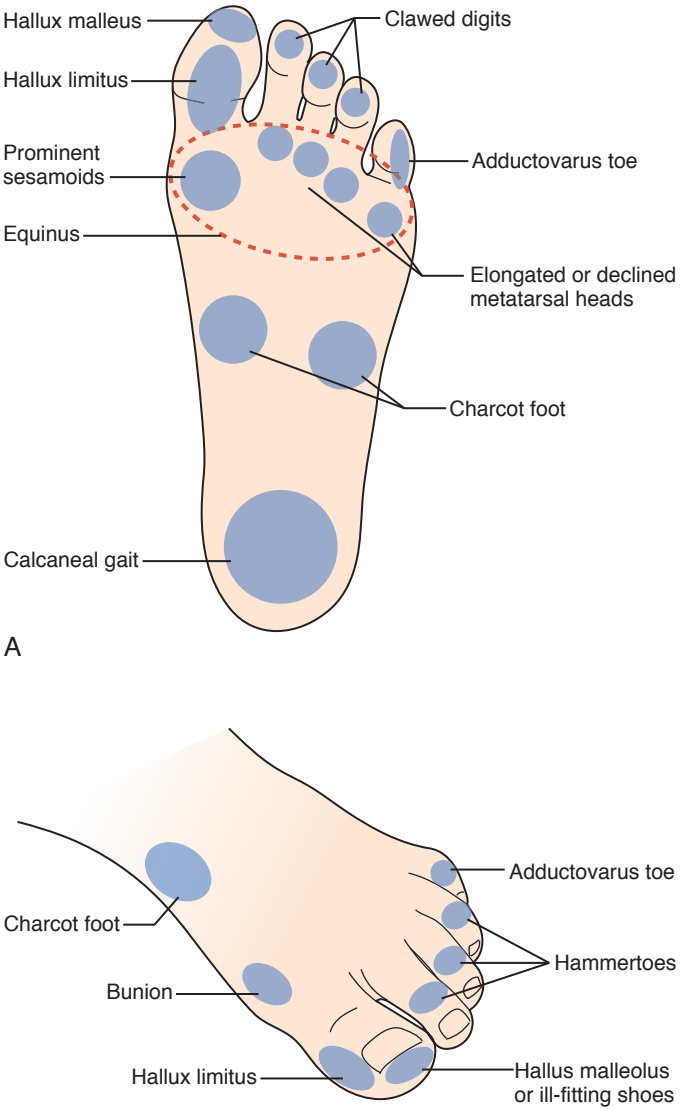

Figure 113.2 Locations of skin lesions on the diabetic foot with corresponding biomechanical etiologies related to the plantar (A) and dorsum (B) surfaces with an example of a diabetic dorsal foot wound (C).

PRESENTATION AND DIAGNOSIS

Patient History

A detailed medical and surgical history should be obtained from every diabetic patient with a foot ulcer to determine how

TABLE 113.2 The Essential Components of a Diabetic Foot Exam

Vascular	Neurologic	Dermatologic	Musculoskeletal
Palpate pedal and lower extremity pulses Look for distal hair growth on feet toes Assess capillary filling time in the toes	Test for loss of protective sensation by Semmes-Weinstein monofilament, biothesiometry, or electronic tuning fork Look for muscle atrophy of the feet	Note the ulcer depth, tissue in the wound bed, if bone is palpable Look for signs of infection around a wound (erythema, purulence) Inspect for other preulcerative lesions (blisters, calluses, corns)	Inspect for deformities Look for signs of Charcot foot (collapsed arch or hot, red swollen foot Check the dorsiflexion of the ankle and the great toe joint

Adapted from Miller JD, Carter E, Shih J, et al. How to do a 3-minute diabetic foot exam. *J Fam Pract*. 2014;63:646–656.

the patient's diabetes is managed, whether the ulcer appeared suddenly or secondary to a traumatic incident, whether the patient traveled recently or acquired new footwear, and to determine the wound's duration and any noticeable changes in its appearance and character. Any previous wounds should also be documented, as well as any wound care treatments that the patient has received. Wounds that are accompanied by systemic symptoms suggestive of infection, such as malaise or cold sweats, should be treated without delay. Risk factors for diabetic foot ulceration, such as a history of peripheral neuropathy, symptoms of arterial disease, and bony deformities, as well as any previous vascular, orthopedic, or plastic surgical interventions, should also be documented.

Physical Examination

The diabetic foot physical examination must include dermatologic, neurologic, vascular, and musculoskeletal assessments (Table 113.2).[23] The skin of patients with advanced diabetic disease is usually dry and brittle because of peripheral neuropathy. Areas of hyperkeratosis indicate pressure points that are often accompanied by preulcerative or ulcerative changes (Fig. 113.3). Preulcerative changes may be subtle and can appear as pinpoint hemorrhages or shallow hematomas within the dermis. A waxy appearance of the callus may indicate fluid beneath the lesion and should be palpated for fluctuance. A hyperkeratotic lesion suspicious for underlying ulceration should be sharply débrided to inspect the underlying skin.

Figure 113.3 Diabetic foot ulceration with dry, brittle skin in an area of pressure.

Inspection of the foot may reveal the sequelae of motor neuropathy, such as atrophy of the intermetatarsal musculature and hollowing of tissue between the metatarsals and arch of the foot. The patient should also be examined for Charcot neuropathic osteoarthropathy, also known as "Charcot foot." The classic, but late, presentation of a "rocker bottom foot" in these patients creates severe midfoot plantar pressures and subsequent ulceration.[24] A unilateral, hot, swollen foot should be considered an acute presentation of Charcot foot until proven otherwise.[25] Early offloading and immobilization can prevent further damage and prevent a rocker bottom foot (Fig. 113.4). Acute Charcot foot can often be misdiagnosed as cellulitis, osteomyelitis, deep venous thrombosis, or gout.

Sensory testing using a Semmes-Weinstein monofilament (10 g) is a predictive and easily reproducible test to assess the neuropathic risk of foot ulceration and amputation in diabetic patients.[26] Failure of the patient to perceive more than four or more of the 10 test sites has been associated with a 15-fold increase in the risk of plantar ulceration.[27] Testing perception of vibration with a 128-mHz tuning fork is also predicative of ulceration risk, although this test is less reliable than the Semmes-Weinstein test.[14]

Lower extremity arteries, including the femoral, popliteal, and tibial arteries, should be palpated to detect a pulse. However, palpation is affected by factors such as the patient's body habitus, peripheral edema, and blood pressure fluctuations, as well as the examiner's level of experience. As such, clinical decision-making should not be based solely on the presence or absence of palpable pulses without further noninvasive vascular testing. An ankle-brachial index (ABI) measurement is often obtained at the time of the initial clinical evaluation but may be falsely elevated due to the prevalence of medial arterial calcinosis in the tibial arteries of the diabetic foot.[28,29]

Figure 113.4 Charcot foot; typical "rocker bottom" appearance (A), characteristic x-ray (B), and offloading with total contact cast (C).

Diabetic Ulcer Evaluation and Classification

The diabetic ulcer should be visually inspected for the presence of viable tissue, drainage, purulence, odor, and surrounding erythema. The wound dimensions, location, and the number of ulcers should also be carefully documented. Mixed arterial/venous ulcers should also be suspected with appropriate vascular lab testing. A sterile probe should be used to interrogate the wound for any abscesses, tendons, or bone. Encountering bone using the probe places the patient at a high index of suspicion for osteomyelitis.[30]

Numerous diabetic foot ulcer classification systems have been developed and used for clinical and research purposes. The Wagner Classification is the first such system and was initially developed for pressure wounds rather than diabetic ulcers. This system has limited sensitivity and specificity and has limited clinical application.[31] The University of Texas Classification System and the PEDIS ulcer classification were subsequently developed to correlate wound characteristics with clinical outcomes (Table 113.3).[29,30] The WIfI (Wound, Ischemia, foot Infection) classification system as advocated by the Society for Vascular Surgery is the most recent foot ulcer staging system that has been clinically validated by several investigators.[32-34]

Radiologic Investigations

Numerous imaging modalities are available for the workup of diabetic foot ulcers. Foot x-rays should be obtained to rule out

TABLE 113.3 Wagner and Texas Classification Systems of Diabetic Foot Ulcers

WAGNER METHOD (29)		UNIVERSITY OF TEXAS METHOD (30)	
Grade	Details	Grade	Details
0	No open foot lesion	0	Presence of preulcer or postulcer epithelization
1	Presence of superficial ulcer, partial or full thickness	1	Superficial ulcer not penetrating tendon, bone or joint
2	Ulcer extends to ligaments, tendon, joint capsule or deep fascia without abscess or osteomyelitis	2	Ulcer penetrating through to tendon or capsule
3	Presence of deep ulcer with abscess, osteomyelitis	3	Ulcer penetrating to bone or joint
4	Gangrene localized to the forefoot or heel	A	Noninfected and nonischemic ulcer
5	Extensive	B	Infection present
		C	Ischemia present
		D	Both infection and ischemia are present

bony deformities, and, if infection is suspected, evaluate for subcutaneous gas. When ulcer healing does not progress at a satisfactory rate, other imaging studies that should be considered include computed tomography (CT), magnetic resonance imaging (MRI), labeled white blood cell scans, single-photon emission computed tomography (SPECT), and positive emission tomography (PET) scans to rule out osteomyelitis or soft tissue infections. Although PET and labeled white blood cell scans have been shown to have the highest diagnostic accuracy in confirming or excluding the diagnosis of osteomyelitis, they are time-consuming and expensive tests and many clinicians will preferentially order MRIs first for the workup of osteomyelitis.[35]

MANAGEMENT

General Principles

The decision to treat a diabetic foot ulcer in an outpatient setting or as an inpatient in the hospital often hinges on the patient's presenting clinical status. Septic patients with severely infected wounds require admission for urgent surgical management to limit the spread of the infection and tissue destruction. Conversely, patients with stable, chronic issues can be managed in the outpatient setting. Outpatient care consists primarily of wound management through local wound care and coordination of appropriate diagnostic testing and consultations. Serial wound clinic visits for dressing changes and débridement of the wounds is often required for many patients. A myriad of topical dressings exists from which to choose based on the wound etiology, availability, and cost. In addition to débridement and maintaining a moist and healthy wound bed, diabetic foot ulcers should also be treated with culture-directed antibiotics, if infected. It is sometimes possible to accomplish these goals with a dressing that serves multiple purposes: control of infection and inflammation, moisture balance, and the provision of pressure relief.

Wound Débridement

The purpose of débriding a diabetic foot ulcer is to alter the environment of the wound and to promote healing by removing abnormal tissue, such as hyperkeratotic epidermis and necrotic dermal tissue, foreign debris, and bacteria.[36] In addition to removing nonviable tissue, débridement converts a stagnant wound into an acute healing wound by releasing platelet growth factors, inhibiting proteinases, and limiting the action of bacterial biofilm.[37] Different modalities for débriding a wound include sharp, surgical, enzymatic, autolytic, mechanical, and intraoperative with ultrasonic and hydrosurgical devices. Because the majority of these patients are neuropathic, aggressive débridement can usually be carried out with minimal discomfort. If the patient is anxious or an extensive débridement is required, a local anesthetic block or sedation in an operating room setting may be helpful.

Sharp débridement at the bedside may suffice for small wounds, but larger wounds often require repetitive débridement, with the goal of a well-perfused wound bed and quantitative cultures less than 10^5/g tissue before closure. In Sinkin's series of 193 wounds in Charcot foot patients, the average number of débridements prior to attempted closure was four.[38] Exposed bone needs to be débrided to stippled punctate bleeding, and bone cultures should be obtained. The bacteria most likely to be involved in diabetic osteomyelitis are skin organisms, frequently *Staphylococcus aureus* and sometimes resistant strains.[39] Copious pulse lavage irrigation should be performed at the end of each débridement.

Between débridements, wounds may be covered with moist dressings, silver-containing dressings, or creams or treated with negative-pressure therapy. Zhang and colleagues reported that negative-pressure therapy was more likely to shrink or heal ulcers compared with standard therapy and did so in a shorter period of time.[40]

Offloading

The foot must also be offloaded to minimize pressure on the wound and to prevent ulcers from recurring. The likelihood of healing increases with the effectiveness of offloading and the compliance of the patient.[41] Offloading modalities include postoperative shoes, wedge shoes, healing sandals, braces, boots, and total contact casting. Although level one evidence for these

individual modalities is sparse, a meta-analysis showed greater wound healing efficacy with the use of total contact casting and irremovable cast walkers.[42] Multilayer customized offloading orthoses and fillers at sites of partial foot amputation are available to stabilize the position of the foot within the shoe. It is necessary to balance and offload pressure from both prior and potential ulceration sites.[43] Referral to an orthotist for prescription footwear and orthoses is recommended because the at-risk patient will need monitoring and adjustment of the devices. The patient may also benefit from additional bracing or splinting to offload pressure and will need to have these devices replaced regularly for the rest of their lives.

Patient Education

Due to the initial indolent course of diabetic foot ulcers but their potentially devastating complications, it is advisable to educate patients and their families on the nature of the disease to maximize the likelihood of compliance with medical optimization and wound care. Patients should also recognize the reasons to seek urgent medical attention, should as a spreading soft tissue infection or gangrenous changes on the foot, because many patients with diabetic foot ulcers are insensate in their lower extremities because of diabetic neuropathy. The Society for Vascular Surgery has recognized the importance of involving patients in their plans of care, and its diabetic foot guidelines recommend that patients and their families be educated about preventive foot care.[44]

Advanced Wound Treatment Modalities

There is an ever-growing list of advanced wound treatment modalities such as bioengineered cultured cell grafts, allografts, collagen xenografts, and amniotic membranes. There is evidence to support the use of these products for wounds that have demonstrated a decreased rate of healing, but the quality of the evidence is variable, and the choice of product is often based on practitioner preference.[45,46]

There is also a role for negative-pressure wound therapy (NPWT) in the management of diabetic foot ulcers, as well as in the postoperative setting after amputation or delayed primary closure as a bridge to delayed grafting. A recent study reported that NPWT improved wound granulation, reduced the time to wound closure, and reduced the incidence of subsequent minor amputations.[47]

SOFT TISSUE SURGERY FOR THE DIABETIC FOOT

Diabetic patients with foot ulceration and tracking abscesses, wet gangrenous changes, gas in the tissue on plain film radiographs, or systemic signs of sepsis require urgent surgical attention. A thorough incision and drainage of any abscesses or infectious tracks must be aggressively performed in the operating room, along with an appropriate exploration of fascial compartments and layers of the foot, because abscesses originating from a forefoot ulcer can track up to the ankle or lower leg. Amputation of digits or portions of the foot may be necessary due to gangrene or to limit the advancement of infection. If the viability of any of the patient's foot tissue is questionable, then one might consider limiting the amount of tissue that is resected, to preserve later closure options. Any resected tissue or bone should be cultured and sent for a pathology evaluation. Patients will often subsequently require multiple procedures to resect necrotic wound edges and débride the wound to promote granulation.

After treating the foot infection, the focus of care should be directed towards the need for revascularization and primary or secondary wound closure. Because of the complex altered physiology of these wounds, as well as additional systemic issues in diabetic patients, wound closure is slow and multiple interventions are frequently required. However, with meticulous attention to detail, closure rates of up to 80% have been reported.[48] Defining principles of successful wound closure include infection control, wound débridement, adequate perfusion, offloading of pressure, and moisture balance. Small superficial wounds may heal either without additional intervention or with the application of cell-based materials such as Dermagraft, Apligraft, or keratinocyte allografts.[49] Antibiotic-impregnated bone beads might also be used to enhance the treatment of any residual osteomyelitis.[50]

Local Tissue Flaps

Local flaps for wound closure should be designed according to the foot's actual blood supply. A Doppler exam to determine areas of antegrade and retrograde flow is an important guide. Flaps should contain arterial perforators detected by Doppler signal, designed in the direction of antegrade flow to the local flap. The significant advantage of using local skin flaps is the concept of "replacing like with like": replacing defects with similarly specialized skin. The downside to local flaps is the limited amount of specialized skin available to close wounds, limiting the size of wounds that can be handled in this manner. If there is a bone abnormality causing the ulcer to form, the bone must be addressed and corrected to minimize the chance of recurrence. Blume described such an approach with 67 cases of one-stage ulcer débridement and closure together with correction of underlying bone abnormalities. Results with this single-stage approach included 97% healing, 54% without complication, and 88% without recurrence at 2.5 years. Forefoot wounds healed more quickly than midfoot or rear-foot wounds, and deep wounds healed slower than superficial wounds, with a longer hospital stay. This suggests that local skin flaps in selected patients can be very successful. Double plantar rotation flaps can also be designed to either side of the defect for closure of small (<2 cm) central plantar forefoot ulcers.[52]

Free (Microvascular Transfer) Flaps

Free flaps supply a large amount of tissue and can allow for aggressive débridement because the size of the wound is less constraining than with pedicled flaps. However, the flap should

not disturb the vascular supply of the foot, so arterial end-to-side anastomoses are a better choice than end-to-end anastomoses to maintain prograde flow in the native circulation. Microvascular transfers frequently require secondary procedures such as debulking and tissue re-inset to improve aesthetics and function. Because of flap bulk, getting shoes to fit can be very difficult. All successful series report aggressive débridement of nonviable tissue, revascularization when necessary to provide normal oxygen tension, control of medical problems, gradual protected weight bearing, correction of underlying bony abnormalities before or during the flap procedure, and control of infection. Deconditioned patients with multiple, poorly controlled medical problems are better treated with local tissue closure options.

Prevention of Recurrent Soft Tissue Defects

Prevention of wound recurrence is as important as the initial closure of the wound. Unfortunately, the risk of recurrent ulceration remains high despite improvements in diabetic foot management. The continued presence of those factors leading to initial ulcer formation such as neuropathy or arterial disease contributes significantly to this recurrence rate. Ulceration of the plantar surface correlates with increased sole and midfoot pressures with ambulation. Shortening of the Achilles tendon by contraction or chronic tightness can significantly contribute to increased plantar foot pressures. Diabetic Achilles tendons examined with electron microscopy demonstrate increased collagen density and structural disorganization.[53] Elevated glucose levels may lead to abnormal cross-linking between collagen fibrils and increasing tendon stiffness. Colen looked at diabetic wound closure comparing those that were done in conjunction with Achilles tendon lengthening versus those that did not have the tendon lengthened.[54] At nearly 3 years' follow-up, 2% of the patients with Achilles tendon lengthening recurred as opposed to 25% of those without tendon lengthening. Patients who cannot dorsiflex the ankle past neutral or have forefoot pressures of more than 100 lb/in.[2] are considered at increased risk of recurrent ulceration. Achilles tendon lengthening can often be performed percutaneously to achieve neutral or within 5 degrees of dorsiflexion in an effort to prevent recurrent foot ulceration.

AMPUTATION

When wound closure is not possible, because of the size and extent of the wound, location, or irreversible ischemia, then some variant of foot amputation may be required. Proper choice and optimal performance of amputation, such as partial or complete ray, transmetatarsal, midfoot amputations, are critical components of diabetic foot management (Fig. 113.5). With current advances in revascularization and wound care treatments, a partial foot amputation may be possible where a below- or above-knee amputation would previously have been thought more likely. Although amputations often carry a social stigma and are associated with significant psychological suffering to the patient, they may also result in rapid healing, shorter hospitalizations, lower risk of reinfection or recurrence of a wound, and an acceptable functional outcome. After the patient's amputation site is healed, the focus of treatment should become the prevention of ulcer recurrence at the site of amputation through appropriate offloading and patient education, as previously discussed.

Patients often benefit from a course of physical therapy postoperatively because many patients with advanced diabetic foot ulcer wounds demonstrate impaired ambulation in a prolonged non–weight-bearing state and are physiologically deconditioned. Outpatient or acute inpatient rehabilitation and physical therapy can be useful in helping patients regain muscle strength, improving gait and balance, and returning to an active lifestyle that is essential to controlling the patients' underlying medical and vascular pathologies. Finally, the patient will need ongoing care by multidisciplinary medical and surgical teams to mitigate the risk of future diabetic ulcer complications.

PERIPHERAL ARTERIAL DISEASE AND THE DIABETIC FOOT

Lower extremity arterial disease in diabetic patients is characterized by tibial artery involvement and the sparing of the microvascular circulation.[55] In the past, clinicians often discounted the utility of revascularization for diabetic patients with lower limb ischemia. It was reasoned that, because the etiology of diabetic arterial disease was secondary to the occlusion of the microvascular circulation, bypass surgery would not improve flow within the microcirculation and would undoubtedly fail. However, this belief has been discredited, and lower extremity revascularization with open or endovascular interventions can contribute in a significant way to limb preservation in this patient population. The indications for treating arterial occlusive disease in diabetics are similar to nondiabetic patients: lifestyle limiting claudication, rest pain, and tissue loss that is associated with nonhealing ulcers and gangrenous changes.

Vascular Lab Workup

Diabetic patients with tissue loss or nonhealing ulcers without palpable pedal pulses should undergo further testing for underlying arterial disease. Although ABI measurements are a standard component of the vascular workup, these values, as previously mentioned, are often unreliable in diabetics because of medial calcinosis of the tibial vessels. However, the digital arteries are often spared the heavy calcification that occurs in the tibial arteries, and their measurements of flow more accurately reflect foot perfusion. As such, toe-brachial index (TBI) measurements may be more useful in diabetic patients with a suspected falsely elevated ABI.[56] A TBI greater than 0.6 is predictive of tissue healing.

Alternative tests that might also be useful in the workup of diabetic foot ulcers include pulse volume recordings (PVR), photoplethysmography (PPG), and transcutaneous oxygen tension ($tcPO_2$), and skin perfusion pressure (SPP) measurements. Healing is unlikely to occur if the PVR amplitude is less than 5 mm or the PPG is less than 50 mm Hg.[57] Furthermore,

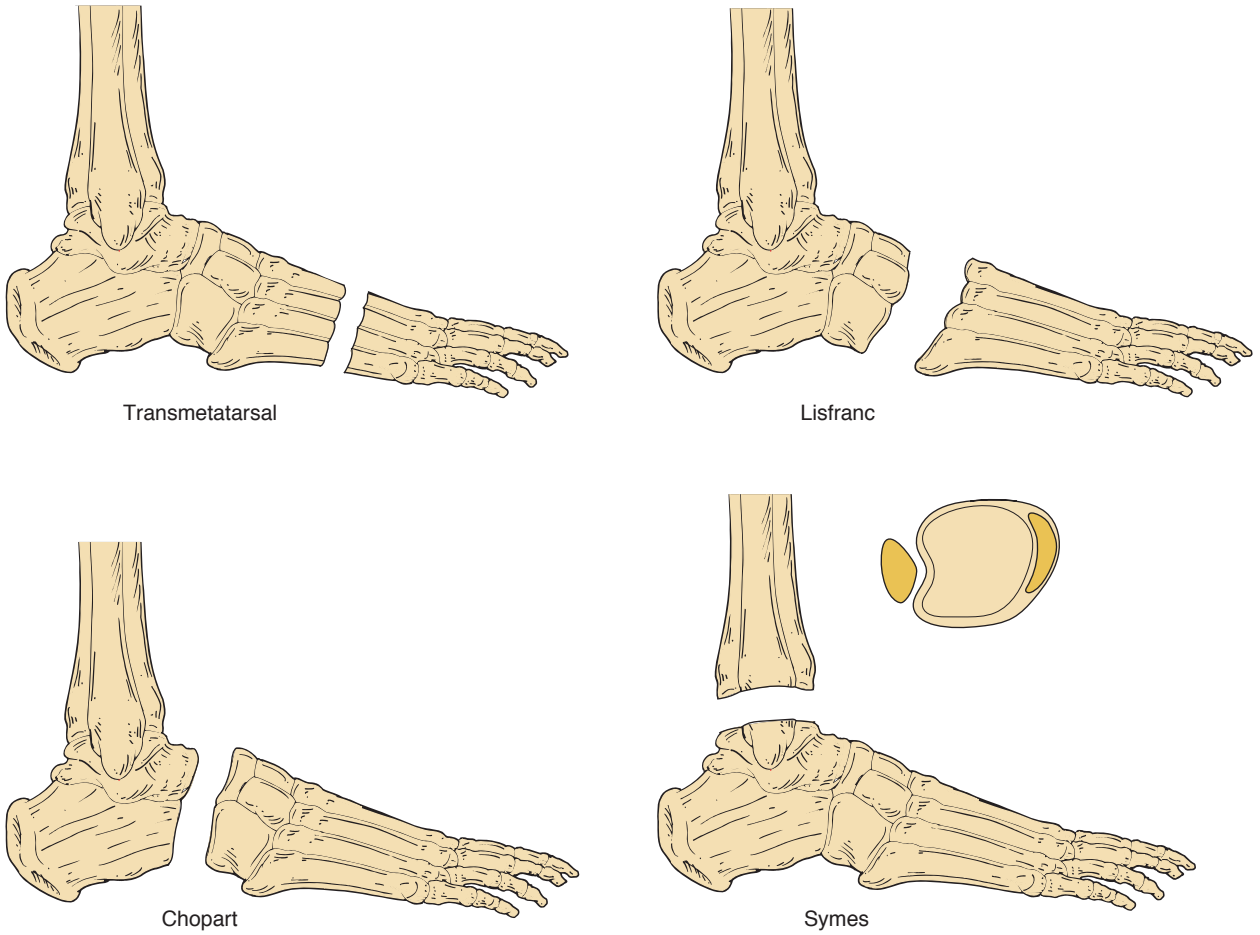

Figure 113.5 Types of midfoot amputation available for optimal maintenance of diabetic limb function: Lisfranc, Chopart, and Symes.

TABLE 113.4 Noninvasive Vascular Studies in the Diabetic Foot and Their Interpretations

Test	Normal	Mild Disease	Moderate Disease	Severe Disease
ABI	0.9-1.1	0.7-0.9	0.4-0.7	<0.4 or >1.1
TBI	>0.7	0.5-0.7	0.35-0.5	<0.35
PVR Waveforms	Triphasic	Biphasic	Biphasic	Monophasic
$tcPO_2$	>40 mm Hg	20-40 mm Hg	20-40 mm Hg	<20 mm Hg
SPP	>50 mm Hg	30-50 mm Hg	30-50 mm Hg	<30 mm Hg

ABI, Ankle-brachial Index; *PVR,* pulse volume recording; *SPP,* skin perfusion pressure; *TBI,* toe-brachial index; *$tcPO_2$,* transcutaneous oxygen.

wound healing is likely with a $tcPO_2$ greater than 40 mm Hg. A regional index can be calculated to account for variations in systemic arterial oxygen availability. To calculate this index, the foot $tcPO_2$ measurement is divided by a $tcPO_2$ reference point, usually chosen at the chest. A patient with a $tcPO_2$ index greater than 0.6 is likely to heal a wound, whereas a value less than 0.4 is unlikely to heal.[58] SPP measurements less than 30 mm Hg are predictive of nonhealing and greater than 50 mm Hg are predictive of healing. A summary of these noninvasive vascular studies and interpretive guidelines is presented in Table 113.4. Further noninvasive imaging, such as CTA and MRA, is often the next step for arterial imaging based on the vascular lab assessment. However, fine detail and definition of the tibial and pedal arteries is required to plan diabetic revascularization; therefore, arteriograms are often obtained to assist with operative planning, with CO_2 angiography considered in the setting of renal insufficiency (Fig. 113.6). Images from a CTA or MRA can allow a focused arteriographic approach that can often be combined with an endovascular therapeutic intervention if appropriate. In our experience, this occurs in approximately 60% of arteriographic studies performed for diabetic limb preservation.

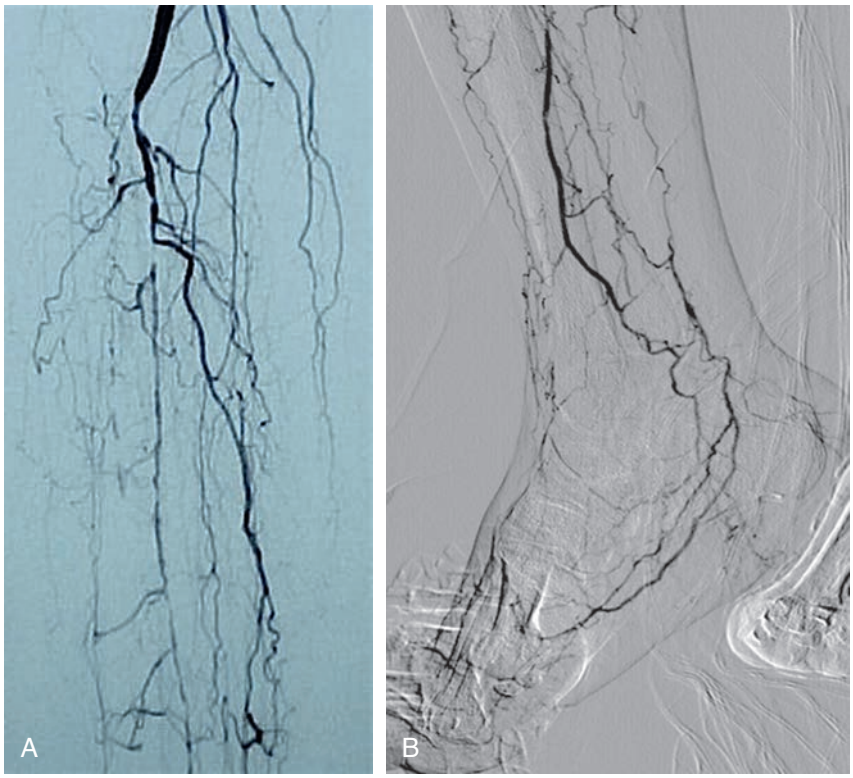

Figure 113.6 Lower extremity arteriogram with the tibial artery occlusive disease typical of a diabetic pattern (A) and the importance of adequate foot views to delineate distal targets for revascularization; in this case the distal peroneal and medial and lateral plantar branches (B).

Endovascular Interventions in the Diabetic Patient

Endovascular interventions continue to play an increasingly prominent role in the treatment of diabetic foot ulcer patients. However, tibial artery occlusive disease remains a challenge for a catheter-based approach. Several authors have demonstrated comparable outcomes after endovascular revascularization in diabetics and nondiabetics, with lower long-term primary patency rates in diabetic patients, but equivalent secondary patency and limb preservation rates.[59] Arterial runoff may be an important factor in determining the efficacy of endovascular interventions. Faglia and colleagues reported on 420 diabetic patients who underwent tibial angioplasty and found that the lack of a patent tibial artery at the end of the study resulted in a 62% amputation rate, compared with 1.7% in patients with at least one patent artery to the foot.[60]

Different modalities are available for revascularization, including standard tibial angioplasty with dedicated wires, standard balloons, and drug-eluting balloons, as well as pedal arch reconstruction with the "pedal loop" technique. The pedal loop technique involves traversing lesions in the pedal arch to establish blood flow to the foot in a prograde or retrograde manner.[61] Data of the role of stenting and drug-elution technologies in tibial artery revascularization remain limited. Although one study reported that infrapopliteal stenting can be successful, with restenosis rates of 20% at 1 year and greater than 70% primary patency, functional limb preservation was better for those patients undergoing proximal below-knee angioplasty compared with tibial stenting.[62]

SURGICAL BYPASS IN THE DIABETIC PATIENT

For diabetic ulcers to heal, it has been axiomatic to restore pulsatile blood flow to the foot. Although the femoropopliteal arterial segment is commonly affected in diabetics, tibial artery occlusive disease is the classic distribution in diabetic patients, leading to limb-threatening ischemia.[63] In our experience, functioning in a limb preservation program with a large volume of diabetic revascularization, approximately 25% of patients with limb-threatening ischemia who present with significant wounds and tissue loss are best treated by surgical bypass as the initial method of revascularization. We have found that diabetics with more extensive tissue loss (>2 cm^2) heal faster and more completely after bypass, compared with endovascular therapy. Due to the preponderance of tibial artery involvement, distal targets can include the medial and lateral plantar branches and other inframalleolar arteries (Fig. 113.7). Due to the patient's diabetic tibial distribution, a popliteal-distal bypass can often be considered because the proximal arterial tree is spared from flow-limiting occlusive disease. Use of the popliteal artery for inflow limits the length of the bypass to optimize long-term patency, as well as the length of the autogenous conduit needed for the bypass (Fig. 113.8).

Several investigators have established the superiority of lower extremity bypass with autogenous vein compared with other conduits. If vein can be used as a conduit for bypass in diabetic patients, then a patency and limb salvage rate similar to nondiabetic patients can be obtained.[64] Pomposelli and colleagues

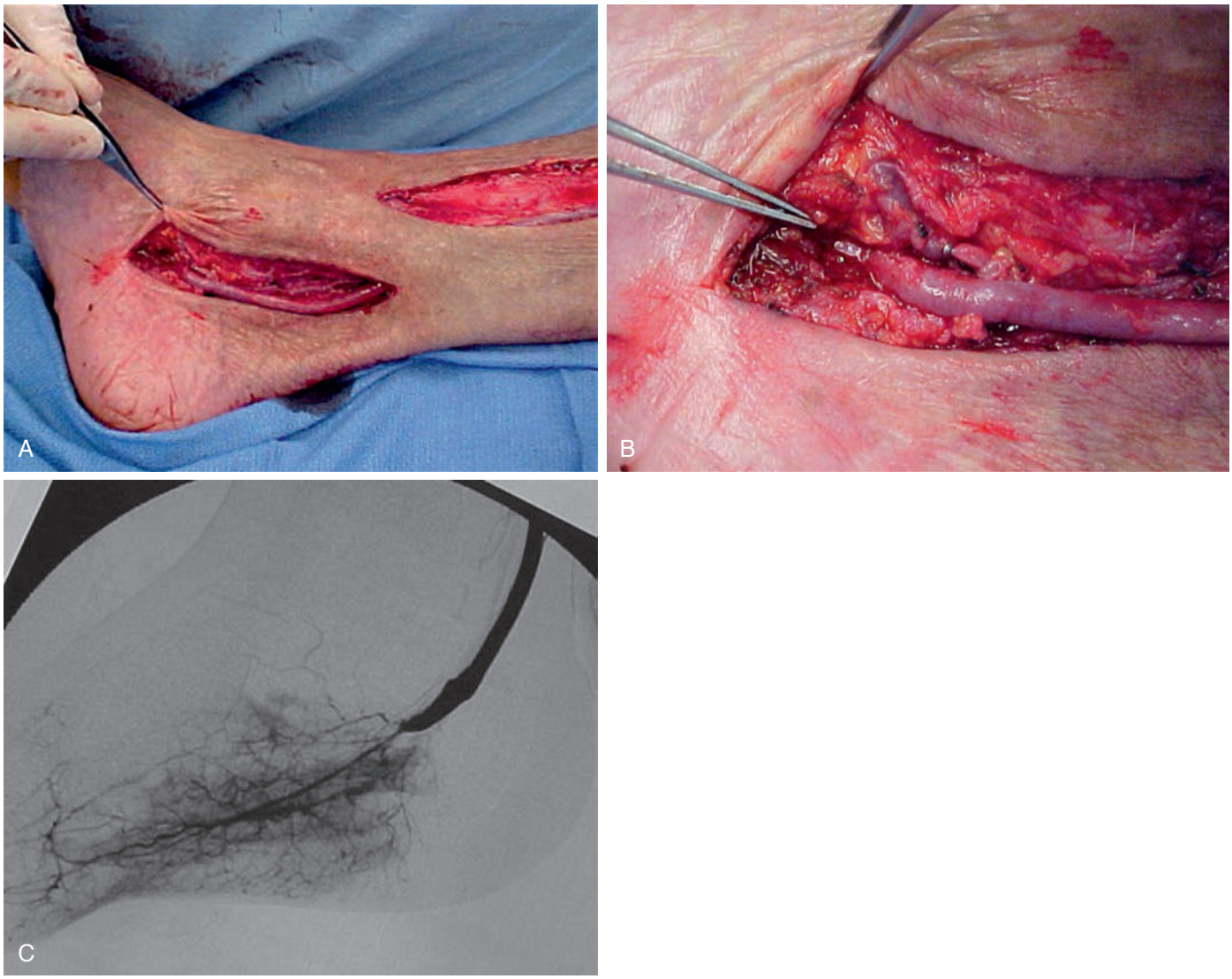

Figure 113.7 Distal bypass to the medial and lateral plantar branches of the posterior tibial artery as required in the diabetic patient (A) with the distal anastomosis (B), completion arteriogram (C).

Figure 113.8 Incisions associated with a popliteal-distal bypass in the diabetic patient with proximal extension of the skin incision to harvest optimal vein and limit the distal limb harvest incision through chronically ischemic tissue.

analyzed a cohort of 1000 bypasses, 92% of which were in diabetic patients, and reported a primary patency of 57% and 38% at 5 and 10 years, respectively.[65] A large prospective study of vein bypass grafts for critical limb ischemia (PREVENT III) evaluated bypasses in 1404 patients, 64% of who were diabetic and 75% of whom presented with tissue loss.[66] The authors reported a primary patency of 61% at 1 year and a reduced amputation-free survival at 1 year for a high-risk cohort, as determined by factors including age greater than 75 years and a history of dialysis, significant coronary artery disease, anemia, and tissue loss at presentation. However, up to 30% of diabetic patients do not have adequate saphenous vein for bypass to distal tibial targets. In reoperative patients, this figure increases to 50%.[67] In such patients, alternative conduits for bypass, such as the lesser saphenous vein, arm vein, composite veins, and a polytetrafluoroethylene (PTFE) graft with a distal vein patch with or without a distal arteriovenous fistula, should be considered. Furthermore, although these alternative conduits are

not equivalent to intact great saphenous vein for tibial bypass, they can be effective for limb preservation.[68-71]

Lower extremity bypasses in diabetic patients are not without risk. There is a certain perioperative morbidity associated with bypass surgery that approaches 20%, with a 10% incisional complication rate for vein grafts. These pulmonary, cardiac, and renal complications can delay recovery and add to hospital stay and cost. Indeed, although diabetes is not a risk factor for vein graft failure, it has been associated with increased risk of long-term mortality and limb loss in patients with critical limb ischemia when compared with nondiabetic patients.[72]

Endovascular Versus Bypass for Diabetic Revascularization

An appropriate revascularization strategy should be customized for diabetic patients according to their anatomy and comorbidities. The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial attempted to compare endovascular intervention with surgical bypass.[73] Among the 452 patients randomized to bypass or endovascular intervention, perioperative morbidity was higher with surgery, but amputation-free and overall survivals were similar in both groups at 1 year. However, at the 2-year interval, surgery was associated with a reduced risk of amputation and death. The authors concluded that angioplasty should be used first for patients with a life expectancy of 2 or fewer years and that bypass is preferred when a vein conduit is available. However, the generalizability of these results to diabetic patients is limited because only 42% of the patients in the study were diabetic. We hope that the ongoing BEST-CLI and BASIL 2 trials shed more light on the optimal revascularization strategy for diabetic patients.

Hinchliffe published a review of revascularization for the treatment of diabetic foot ulceration from 1980 to 2010.[74] Outcomes were similar, with a 1-year limb preservation rate of 85% after bypass and 78% following angioplasty. However, loss of patency was not always associated with amputation, because the initial intervention allowed for wound healing and sufficient collateralization to maintain tissue integrity, despite subsequent failure of the revascularization. Therefore although prospective, randomized data comparing surgical bypass with endovascular revascularization specifically for diabetic foot ulcer patients are lacking, similar limb preservation rates can be achieved when the physician's best judgment is used to develop an individualized revascularization plan for each patient.

MULTIDISCIPLINARY LIMB PRESERVATION PROGRAMS

A successful limb preservation program requires a coordinated effort of physicians, nurses, allied health professionals, and administrators dedicated to the preservation of functional limbs. Such a multidisciplinary approach should take advantage of protocol-driven care, involving a full complement of diagnostic and therapeutic modalities that combine revascularization with soft tissue reconstruction and medical support.[75] Unfortunately, there continues to be geographic and demographic variation in the care delivered to patients at risk of losing a limb from diabetes.[76] There are also a variety of approaches to diabetics with limb-threatening ischemia: approximately 25% undergo primary amputation, 25% receive medical therapy, and only 50% undergo any attempt at revascularization.

The Society for Vascular Surgery and the American Podiatric Medical Association have stressed the importance and prospective benefits of multidisciplinary care for diabetic foot ulcer patients.[77] Benefits to the patient include a reduction in time for vascular assessment, wound healing, and institution of treatment for infection, and the time to final correction of podiatric and orthopedic deformities. Enhanced follow-up and increased surveillance of revascularization procedures contribute to patient outcomes. Advantages for the physicians include the ability to efficiently manage complex patients with help from the appropriate medical specialties, an expected increase in patient referrals, the ability to obtain leadership roles both regionally and nationally, the development of an important clinical area to enhance the identity of the institution, and the infrastructure for clinical research and trials. Evidence is available that a multidisciplinary program can bestow these advantages, including a significant reduction in the incidence of major leg amputations (Box 113.1).[43,78]

BOX 113.1 Organizational Structure of a Multidisciplinary Team to Optimize Outcomes and Financial Viability in the Care of the Diabetic Foot

- Structure of a Limb Preservation Program
- Physician Team
  - Physician champions
- Staff
- Space
- Diagnostic Imaging
- Vascular Therapy
  - Endovascular
  - Open Surgery
- Soft Tissue Therapy
  - Wound Care
  - Reconstruction and Amputation
- Hyperbaric O_2
- Rehab/PMR program
- EMR
- Educational activities
  - Physicians
  - Patients
- Research
  - Coordinator
  - Database
  - Statistician
- Marketing
- Financial Analysis

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114 CHAPTER

Diabetic Foot Abnormalities and Their Management

PAUL J. KIM and LAWRENCE A. LAVERY

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INTRODUCTION

Diabetes detrimentally affects almost every system in the body with the foot at particularly high risk for developing complications such as recurrent ulcers and infections that require surgical procedures, interventions, and hospitalizations. The cumulative incidence of developing a foot ulcer has been reported to be 5.8% to 7.1% per year.[1-3] Further, the sequelae may result in amputations with a relative risk of greater than eight at a rate of 9.9%.[4,5] Minority populations are twice as likely to undergo amputations as compared with Caucasians, and men have twice the incidence of amputations as compared with women.[6-8] Five-year mortality rates as high as 40% in high-risk populations have been reported.[8,9] Hospitalizations are common and often require readmission, with reported rates ranging from 18% to 49%.[10,11]

The economic impact of diabetic foot ulcers (DFUs) is substantial, with an average of three times higher expenditures as compared with people with diabetes without ulcers, with 77% of the overall cost of the treatment of a DFU involving hospitalization-related costs.[12,13] The annual cumulative costs continue to rise particularly in the areas of minor amputations and endovascular procedures.[14] The costs of care of diabetic limb complications exceed that of breast cancer.[15]

The care of a DFU involves a multidisciplinary approach with a core team composed of vascular surgery, podiatric surgery/orthopedic surgery, and plastic surgery. Other services including endocrinology, infectious disease, and orthotics/prosthetics also play a pivotal role. The multidisciplinary approach at specialized wound care centers has been demonstrated to provide improved clinical outcomes including a resultant decrease in major amputations as well as a cost savings, thus it is now considered the standard of care.[16-20]

It is important to have a fundamental understanding of foot and ankle anatomy and lower extremity function to appreciate the complications associated with the diabetic foot. The foot is a complex structure with small bones with multiple articulations; intrinsic and extrinsic tendon insertions; fascia and ligaments that are both flexible and rigid; and a redundant network of lymphatics, veins, arteries, and nerves, encased in a resilient soft tissue envelope. These structures work in concert for the purpose of providing a platform for efficient and durable ambulation. The foot is designed to propel the body forward against gravity and adapt to varying surfaces it encounters. The complications associated with diabetes impart a devastating toll on foot function.

Peripheral neuropathy, patho-biomechanics (e.g., joint immobility, structural abnormalities), and peripheral artery disease (PAD) can lead to ulceration (Fig. 114.1). These conditions are magnified in the environment of an immune-compromised host. DFUs lead the patient down a pathway that frequently results in infection, ischemia, amputation, and death. PAD is an extremely important consideration, for without adequate perfusion, the diabetic foot is at extreme risk of ulceration and amputation. Ischemia and its consequences will be discussed in a limited fashion in this chapter, as they are

Abstract

The remote anatomical location of the foot and its demands during weightbearing and ambulation creates an environment that makes it susceptible to ulceration in the environment of diabetes. The diabetic foot is at particular risk of complications and is a significant problem with extensive healthcare resource demands. Peripheral neuropathy, peripheral arterial disease, and biomechanical deformity contribute to the development and chronicity of a foot ulcer. As peripheral neuropathy progresses, the foot becomes insensate and the patient does not respond to acute or repetitive tissue stress. Detrimental changes to the soft tissue envelope in the presence of underlying bony deformity places the foot at great risk. In this environment, altered biomechanics during standing and ambulation accentuates the deleterious forces that contribute to ulcer development and its chronicity. Finally, ischemia and infection are pivotal events that can lead to amputation. This chapter reviews the important pathological processes of the diabetic foot and methods of prophylactic and interventional treatment of ulcers and the underlying deformities.

Keywords

Diabetic Foot Ulcer
Foot Deformity
Biomechanics
Peripheral Neuropathy
Infection
Forces
Ambulation
Weightbearing

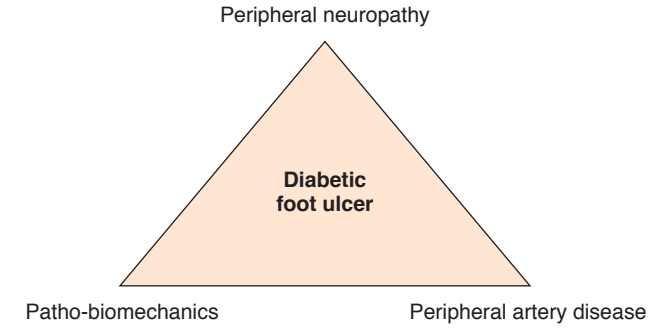

Figure 114.1 The triad of peripheral neuropathy, patho-biomechanics, and peripheral vascular disease lead to diabetic foot ulcers.

addressed in detail elsewhere in this book. The purpose of this chapter is to introduce the more important components related to the diabetic foot with a focus on the biomechanical considerations that play a critical role in the development and chronicity of a DFU.

PERIPHERAL NEUROPATHY

Peripheral neuropathy is a progressive pathologic process that develops in the environment of diabetes and prolonged poor glucose control.[21-23] Glycation-induced metabolic and vascular changes of nerve fibers result in sensory, autonomic, and motor neuropathy in the lower extremity, playing a devastating role in the cascade of events that lead to an ulceration.[24,25] Patients often present with small and large fiber neuropathy. Small fiber neuropathy is usually diagnosed based on symptoms of burning, tingling, and radiating electrical shock.[26,27] Clinical assessment of small fiber neuropathy is based primarily on history of the patient's reported inability to perceive temperature differences. Large fiber neuropathy generally presents with symptoms of numbness, tingling, and formication, and it can be easily assessed in the clinic with a 129-hz tuning fork, 10 g monofilament, or Achilles deep tendon reflexes.[28-30] Sensory neuropathy is very common and a key factor in the development of foot ulcers. Initially, diabetic peripheral sensory neuropathy with the "loss of protective sensation" (LOPS) begins distally in the toes and progresses to the ankle and legs. LOPS can lead to a 2.9 increase in the risk for an amputation and a 46-fold increase in the likelihood of hospitalization.[31,32] Large fiber sensory neuropathy is often so severe that patients lack sufficient peripheral sensation to protect their feet from injury. For example, in people with normal sensation, in response to a foreign body such as a thumbtack, the sharp object is reflexively identified and the foot spontaneously withdrawn from the noxious stimulus, thereby avoiding further injury. In an environment of sensory neuropathy with LOPS, the patient will not withdraw the foot, and the penetrated site is unrecognized by the patient. This often results in repetitive damage to the superficial and deep structures of the foot. DFUs usually develop at the site of pressure areas on the sole of the foot that are exposed to repetitive injury (walking activity) or at the site of pressure and shear forces where bony prominences (e.g., hammertoes or bunion deformities) are exposed to constant pressure from shoes. For example, tight-fitting shoes or an underlying bony deformity may cause a wound to develop over time and contribute to the ulcer's chronicity. As the nerve fibers continue to deteriorate, complete lack of sensation, lack of sympathetic vascular tone, and atrophy of the intrinsic muscles of the foot develop.

Autonomic peripheral neuropathy is related to the increase in sympathetic tone in the diabetic lower extremity.[33] A dysregulation can lead to arterial-venous shunting, small vessel ischemia, and changes in the soft tissue turgor.[34] The loss of soft tissue turgor is identified by xerosis with the loss of moisture balance and elasticity, which can lead to fissuring with subsequent ulcer formation.[35] Further, chronic edema applies tension on the compromised soft tissue envelope, increasing the susceptibility of minor tissue injury causing breaks in the skin leading to an ulceration.[36] These processes negatively impact the reparative capacity of the foot and place it at risk for ulceration. One devastating consequence of autonomic neuropathy is manifested in Charcot neuroarthropathy (CN), which will be discussed in further detail at the end of this chapter. Frequent moisturizing and edema control with compression garments are necessary to prevent ulcer formation.

Motor neuropathy in the lower extremity leads to muscle atrophy and imbalance of opposing muscle groups, and is especially apparent in the smaller intrinsic muscles of the foot. Even in people without diabetes, an imbalance of the extensors and flexors, evertors and invertors, and the abductors and adductors can cause capsular laxity and bony mal-alignment, joint subluxation, and structural foot deformity. Motor neuropathy contributes to the development of forefoot deformities such as hammertoe and hallux abductovalgus, which are reported to be major contributors of ulceration (92% related to neuropathy, and 77% related to deformities; Table 114.1; Fig. 114.2).[37] For example, the intrinsic flexors, interossei, and lumbricals in the foot normally stabilize the toes against the metatarsal heads in the stance and propulsive phases of the gait cycle. When the intrinsic muscles atrophy, the balance of the stronger long flexors and extensors causes the toes to contract and eventually to dislocate at the metatarsophalangeal joints. This imbalance and deformity can literally push the head of the metatarsals through the bottom of the foot.

Early detection and treatment of peripheral neuropathy is critical to ulcer prevention. Tighter glucose control is important for prevention and treatment for the symptoms of peripheral neuropathy. Peripheral neuropathy treatment options are largely focused on symptom management when the disease process is in its relatively earlier stages. The symptoms of peripheral neuropathy (paresthesias, burning, pins and needles, tingling, radiating pain) can be controlled through the use of oral medications including antidepressants, narcotics, antiarrhythmics, and the most frequently prescribed anticonvulsants such as gabapentin, which work through inhibiting the release of glutamate.[38] Vitamin supplementation with L-methylfolate, methylcobalamin, and pyridoxal 5′–phosphate has also been reported to be effective as well in the short term.[39] Topical medications including topical clonidine and capsaicin formulations have shown efficacy but may have limited utility.[40] Surgical decompression of the peroneal and tibial nerves may have a role if the disease is not advanced.[41,42]

TABLE 114.1 Common Biomechanical Abnormalities Encountered in the Diabetic Foot

Abnormality	Description	Problem
Digital contractures	Contracture of digit(s) at the interphalangeal or metatarsal-phalangeal joints	Causes ulcers from rubbing in shoe gear dorsally or at the distal tips of the toes
Hallux abducto valgus	Abduction frontal plane rotation of the hallux and medial deviation of the 1st metatarsal	Bony prominence causes ulcers to develop on the medial 1st metatarsal healed or medial or plantar medial hallux
Hallux rigidus	Degeneration of the metatarsal-phalangeal joint	Restriction of range of motion at 1st MTPJ causes increase in pressure un interphalangeal joint of the hallux
Tailor's bunion	Adduction of 5th digit and lateral splaying of the 5th metatarsal head	Lateral prominence of the 5th metatarsal causes rubbing in shoes as well as increased pressure on the lateral plantar aspect of the 5th toe, which results in an ulcer
Medial column collapse	Abduction of the forefoot and medial deviation of talus	Plantar and medial ulcerations develops with pressure with ambulation and shoe gear
Lateral column collapse	Subluxation of cuboid and/or base of 5th metatarsal	Plantar pressure along the lateral column of the foot
Equinus deformity	Limitation of dorsiflexion at the ankle joint	Plantar forefoot pressures increase
Calcaneal gait	Laxity to plantarflexion at the ankle joint	Plantar heel ulcerations develop due to increased and prolonged pressures
Ankle deformity	Medial or lateral deviation of the foot on the leg at the level of the ankle	Significant change in pressure distribution along medial or lateral columns as well as ulcers over the medial and lateral malleolus
Exostosis	Benign bony growth of bone which can be located anywhere on the foot or ankle	Focal areas of high pressure
Accessory sesamoids	Small cortical bone located in areas such as the plantar interphalangeal joint of the hallux	Increased focal pressure imparted on underlying tissue
Charcot neuroarthropathy	Subluxations, dislocations, fractures about joints in the foot or ankle	Most significant alteration to the biomechanics of the foot altering pressure and function throughout the foot or ankle

Figure 114.2 A photograph of a patient with type I diabetes with significant biomechanical deformities. Note the significant digital contractures as well as lateral and medial deviations of the digits which results in significant alterations in the pressure distribution across the plantar aspect of the feet. Calluses can be identified in these areas.

Appropriately fitting shoe gear with multidensity inserts (laminated layers of decreasing densities of materials), a seamless inner lining, and a wide toebox can also prevent ulcer formation. Eventually the patient will experience complete loss of sensation to the lower extremity with the sustained lack of glucose management. As this disease process progresses, the above treatment strategies become increasingly ineffective and the peripheral neuropathy is irreversible.

Preventing ulcer recurrence requires a multidisciplinary team that usually includes vascular surgery, podiatry, and a pedorthotist. The crux of prevention is understanding the role of biomechanics (joint range of motion and structural deformity), which can significantly reduce foot ulcer recurrence.[43-45] Appropriately fitting shoes and inserts as described previously can prevent ulcer reulceration. In randomized clinical studies, patients treated with "therapeutic shoes and insoles" who complied with prevention showed a two- to fourfold reduction in reulceration.[46-48]

BIOMECHANICS

Altered biomechanics of the diabetic foot are major contributors to ulcer development and chronicity. Foot biomechanics encompass the dynamics involved in ambulation. The foot must be both flexible and rigid, depending on the demands of the phase in the gait cycle. This intrinsic adaptability is maintained by the underlying bony architecture, as well the soft tissue attachments.

Structural changes occur in the diabetic foot that alter the underlying biomechanics. Stiffening of soft tissue structures, including tendons, ligaments, and joint capsules, leads to a limitation of range of motion across joints and joint subluxation, and dislocation.[49-51] The principal forces experienced by the

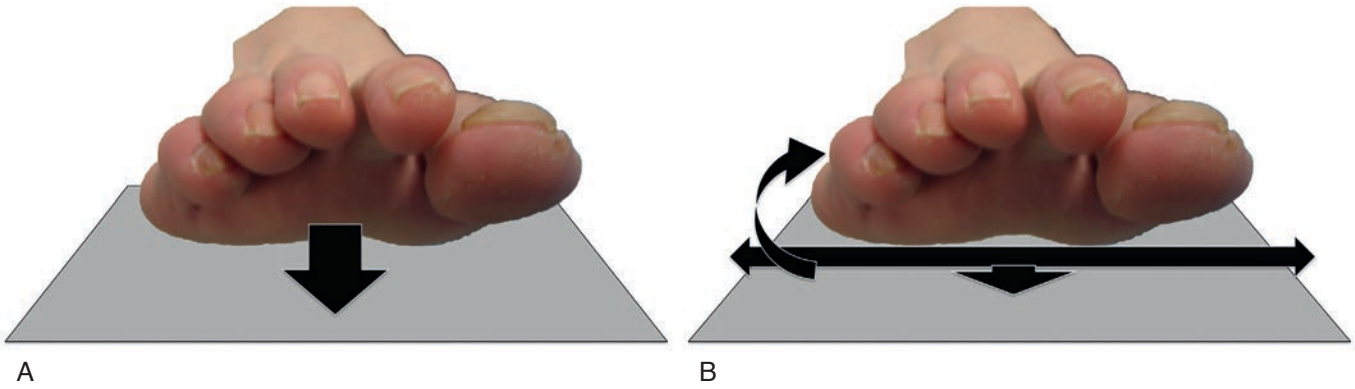

Figure 114.3 (A) A depiction of the sagittal plane forces *(arrow pointing downward)* experienced on the plantar aspect of the foot. The sagittal plane force imparts focal areas of peak plantar pressures that can lead to ulceration. (B) A depiction of the frontal *(curved arrow)* and transverse (*straight arrow* pointing from side to side of the page and arrow pointing towards the reader) plane forces experienced on the foot. These shear forces can lead to separation of the tissue thus leading to ulceration.

foot that can lead to ulceration are abnormal plantar pressures (sagittal plane) and shear (frontal, transverse plane; Fig. 114.3A, B). Shear forces experienced in the diabetic plantar soft tissue have been demonstrated to be 52% greater than in nondiabetic feet.[52] These forces are experienced between the bone-overlying soft tissue envelope, foot-ground, and foot-shoe. Both sagittal plane and shear forces are typically minimized in the sensate foot through compensation by subtle or overt changes in postural stance or positioning, but in the environment of peripheral neuropathy, compensation is compromised, leading to prolonged periods during which abnormal forces are applied until the skin and subcutaneous tissue fail.[53] Joint deviations and subluxations caused by the loss of structural integrity lead to further mal-alignment of the pull of the tendons further exacerbating biomechanical faults. Thus the stresses are magnified on the soft tissue envelope resulting in subsequent formation of calluses and blisters that lead to a separation of the epidermis from the dermis.

As an example, glycation-induced changes in the collagen of the Achilles tendon lead to shortening of the Achilles tendon with subsequent development of an equinus deformity.[54] An equinus deformity is an overpowering of the plantar flexors. Equinus results in overpowering of the Achilles tendon across the ankle joint and increased pressure and shear on the ball of the foot. This cascade of events results in plantar forefoot ulcerations under the metatarsal heads or an ulceration under the medial column of the foot caused by a collapse of the medial arch (Figs. 114.4 and 114.5).[30,55-57]

Alterations in lower extremity biomechanics are appreciated through gait analysis and biomechanical examination of the lower extremity on physical examination. Alterations in gait pattern (i.e., shuffling, antalgic, wide base, unsteady) imply an underlying abnormality.[58,59] Limited joint mobility (i.e., limitation of range of motion in the joints of the foot and ankle) and structural deformities (i.e., bony prominences or joint contractures) are signs of mal-alignment. Callus distribution is a reliable method of identifying areas of excessive sagittal plane and shear forces experienced due to the factors noted previously.[60,61]

Figure 114.4 A photograph of a sub third metatarsal head ulceration. This a typical presentation of a diabetic foot ulcer caused by plantar pressures.

Reducibility of any malaligned joint articulation is a key feature when examining the deformity. As the term implies, a reducible deformity is one that can be placed back into an anatomical position. A semireducible deformity can be somewhat reduced into an anatomical position, while a nonreducible deformity is fixed and cannot be placed into an anatomical position. This degree of reducibility is important when choosing a treatment option. Typically there is a progression from a reducible to a rigid deformity, and the options become more limited as the deformity progresses.

Figure 114.5 A photograph of a healing ulcer on the plantar aspect of the medial column of the foot. An underlying collapsed arch has increased the pressure in this area causing the wound to develop.

Biomechanics can be addressed through a combination of conservative and surgical methods (Table 114.2). Conservative methods focus on the concept of offloading focal areas of pressure and distributing pressure across a wider surface area. Offloading can be achieved through padding, multidensity orthotics, and braces, which may be helpful in ulcer prevention or recurrence.[62] Foot ulcer recurrence can be dramatically reduced when inexpensive, low-tech approaches are employed.[44,45] A multidensity accommodative insert, seamless inner, extra-depth, rocker-bottom shoe is ideal for the at-risk foot. A functional/accommodative device can also, depending on the degree of reducibility, realign the foot in a more anatomical position. Offloading is also used to treat an active ulcer. The total contact cast (TCC) is one such effective method of healing plantar forefoot ulcerations (Fig. 114.6).[63] Other methods, including a walker boot or healing shoe, are also utilized with a lesser degree of success.[64] Decubitus ulcers of the posterior heel should also be offloaded, especially when the patient is supine, utilizing a foam or airbladder filled device with complete relief of the posterior heel.

Offloading is the single most important treatment for the DFU. For instance, the proportion of DFUs that heal with silver dressings, bioengineered alternative tissues, and placental tissue products ranges from 30% to 56% in 12 weeks.[65] In comparative studies of offloading approaches for DFUs, among patients treated with TCCs, healing occurs 70% to 90% of the time.[63] A healing rate of 22% to 79% has been reported using removable cast boots compared with 21% to 58% for healing sandals or half shoes.[64,66-68] Regardless, the key to offloading treatment is patient adherence to actually wearing the device.

The goal of surgical biomechanical correction, whether it be a soft tissue or bony procedure, is to produce a rectus, balanced foot. Soft tissue corrections largely focus on tendon lengthening and rerouting and should be reserved for reducible or semi-reducible deformities. For example, Achilles tendon lengthening (TAL) has been demonstrated to reduce peak plantar pressures experienced in the forefoot by as much as 27%.[63,69,70] Randomized clinical studies and cohort studies of TAL report 93% to 100% DFU healing within 12 weeks.[63,71,72] Once the biomechanical abnormality has been addressed, not only is the ulcer healing rate high, but the incidence of reulceration is significantly less compared with patients treated with TCC alone. For the latter patients, the pressure and shear which caused the ulcer are only modified during the period of TCC therapy, remaining as pathologic forces to cause reulceration after TTC removal if no other means of offloading is utilized.

Digital flexor tendon releases have also been utilized as a simple method of relieving the pressure at the dorsal aspect of the interphalangeal joints or the distal aspects of toes.[73] Bony procedures include exostectomies (simple removal of bony prominences) and joint realignment through arthrodesis and/or osteotomies. Surgical correction can be conducted prophylactically (to prevent ulceration) or therapeutically (to heal an ulceration).[70,74,75] These surgical techniques are typically reserved for nonreducible deformities. Tendon balancing and skeletal reconstruction (e.g., TAL and midfoot arthrodesis) are often done in combination. Conservative offloading is still necessary after the surgical incisions have healed. The goal of all of these options is to optimize function while minimizing new ulcer formation or ulcer recurrence. This goal can be extended to amputations. Amputation is a viable option in maintaining or improving function. Major deformities that cannot be conservatively managed or surgically corrected, and for which the most functional option may be an amputation, will be discussed in further detail later.

ISCHEMIA

Perfusion is arguably the most critical element in DFU healing and must be addressed early. PAD is a major causative factor for amputation.[6] Referral to a vascular specialist to identify and treat vascular compromise is the first step to ulcer healing unless limb-threatening infection is present, in which case infection control is the initial priority. The assessment and treatment of PAD, or chronic limb-threatening ischemia, is beyond the scope of this chapter. However, there are a few important concepts that must be addressed.

One pertinent concept relates to angiosomes, blocks of tissue fed by a source artery, that correspond to different regions of the lower extremity. The three major vessels (posterior tibial, peroneal, anterior tibial arteries) feed specific areas of the lower extremity, and some have claimed that there is a correlation between the ulcer site and the angiosome that is compromised.[76] However, there are redundancies inherent in the

TABLE 114.2 Conservative and Surgical Strategies to Biomechanical Correction

	Method	Rationale	Limitation
Conservative	Diabetic shoe with custom inserts and rocker-bottom	Distribute areas of pressure more evenly Offload areas of pressure Reduce risk of new ulcer formation	Minor deformities
	Decubitus heel ulcer offloading device	Pressure relief of the posterior heel for prevention or treatment	Not to be used for ambulation
	Diabetic healing shoe	Multidensity insert to offload ulcers Accommodate dressings	Temporary Not meant for functional correction Not durable
	Walker boot	Multidensity insert to offload ulcers Accommodate dressings More rigid due to construct encompassing foot and ankle	Temporary Not meant for functional correction Not durable
	Custom brace (limited)	Realign single plane deformities	Moderate deformities that are reducible
	Custom brace (full)	Protect multiplane major deformities	Bulky, affects balance and contralateral limb trauma
	Total contact cast	Non-removable offloading device Healing of ulcers in forefoot and midfoot	Not a long-term solution due to need to replace weekly
Surgical	Tendon rebalancing/ lengthening	Reduce deforming force Augment the plane that is being overpowered	Reserved for reducible deformities May need to be repeated over time Immobility during healing period Rehabilitation
	Bony correction	Remove or realign bony segments through the use of hardware	Risk of associated surgical complications Immobility during healing period Rehabilitation
	Amputation	Reserved for nonsalvageble conditions	Loss of part of the foot or entire foot/ankle Can result in loss of function

Custom Brace (Limited): encompasses part of the foot and lower leg; Custom Brace (Full): encompasses the entirety of the foot/ankle, typically a clamshell design; Forefoot: toes and distal metatarsals; Midfoot: proximal metatarsals, cuneiforms, navicular, cuboid; Hindfoot: calcaneus, talus; Ankle: talus, distal tibia, fibula; Minor deformity: digital or forefoot with minor mal-alignment; Moderate deformity: midfoot, hindfoot with minor to moderate mal-alignment; Major deformity: hindfoot, ankle with significant mal-alignment; Nonsalvagable: deformity cannot be addressed through any other means.

Figure 114.6 A photograph of a total contact cast. A total contact cast provides effective immobilization and offloading for plantar forefoot ulceration and considered the gold standard in conservative diabetic foot ulcer management.

foot with arterial-to-arterial connections that may compensate for occlusive disease in one or more vessels. Successful healing of ulcers through indirect revascularization implies that in many cases, these redundancies exist and may be adequate.[77,78] Current consensus is that angiosome-targeted revascularization should be performed when possible, as it may enhance the wound-healing rate; indirect revascularization still provides benefit when it is the most practical or only choice.

Ischemic ulcers should not be debrided until revascularization has been performed. While necrotic areas or frankly gangrenous digits will ultimately require some sort of amputation, this must be performed at a level where perfusion is adequate for healing. As long as there is no significant infection, debridement and amputation for dry necrosis should also be delayed until after revascularization.

INFECTION

Infection is a significant complicating factor in the diabetic foot. Infection can be acute in nature with the classic signs of fever, erythema, edema, calor, and dolor. Infection may also be chronic or subclinical, as that seen with biofilm. Both types of infections are encountered in diabetic foot and must be addressed. Infection can lead to limb loss (42% higher risk) and will decompensate the wound and/or contribute to its chronicity.[79]

The acute infection in the diabetic foot typically enters through the ulcer or is seeded through a puncture wound. As the acute infection evolves, deep abscesses and/or osteomyelitis with possible sepsis may ensue. DFU infections are typically

bacterial and can be monomicrobial or polymicrobial, with the most common bacteria present being *Staphylococcus* and *Streptococcus*.[80,81] Fungal and yeast infections (23% of chronic wounds) can also be pathogens in the diabetic foot.[82]

Osteomyelitis has been identified in diabetics in up to 20% in an outpatient setting and 67% for hospitalized patients who require an amputation.[83,84] The majority of cases of osteomyelitis in the foot and ankle of diabetics are by contiguous spread, with the nidus being the ulcer. Thus, in many settings, there is a correlation of osteomyelitis with the clinical finding of a positive probe to bone.[85,86] The combination of clinical findings suggesting infection, bony fragmentation identified on plain radiographs, and focal areas of increased signal intensity on magnetic resonance imaging may all contribute to establishing the diagnosis of osteomyelitis.[87] The utility of laboratory biomarkers for the diagnosis of osteomyelitis is not been completely elucidated; however, they may be useful for infection monitoring.[88]

Treatment of an acute infection may include antibiotics as well as surgical decompression. Empiric antibiotic coverage is usually broad and then targeted therapy is implemented based on deep tissue and bone cultures and sensitivities. Surgical decompression may require multiple operating room visits until clean tissue cultures are obtained, at which point a plan for definitive procedure for closure or coverage can be conducted.

Biofilm are multispecies colonies of relatively senescent communities of bacteria that are encased in a glycocalyx shell that inhabit wounds, implantable medical devices, surgical material (e.g., suture), artificial joints, and orthopedic implants. Planktonic bacteria may leave the biofilm to begin other colonies or to seed acute infections. Due to the low metabolic activity of biofilm, antibiotic therapy is typically ineffective; thus disruption of the biofilm is often necessary.[89,90] Disruption can be accomplished through other methods beyond excisional debridement such as ultrasound, or antiseptics.[91-93]

THE DIABETIC FOOT ULCER

The soft tissue envelope of the diabetic foot cannot tolerate stress and has a compromised reparative process. Thus, the typical wound healing cycle is disrupted, prolonged, and the ulcer becomes chronic.[94] The reasons are multifactorial but include biomechanics, ischemia, and infection.

There are multiple DFU treatment strategies (Table 114.3).[65,95-103] Each treatment modality serves a purpose including: drainage control, edema management, infection/biofilm

TABLE 114.3 Diabetic Foot Ulcer Treatment Strategies

Method	Description and Example	Advantages	Limitations
Dressings	Materials that absorb, bolster, protect the wound and surrounding skin Example: alginates	Relatively inexpensive	Frequent dressing changes may be necessary
Compression	Edema control to decrease tension on the skin as well as emptying the venous system and the lymphatics Example: prepackaged multilayered compression dressings, sequential mechanical pumps	Provides a more predictable and reliable method of sustained compression	Weekly application with limited access to the wound Heavily exudative wounds may require additional absorptive dressings Patients may not tolerate
Topical drugs	Impart a drug directly to the surface of the wound May be antimicrobial, enzymatically debride or have other prohealing properties Example: collagenase, platelet derived growth factor	Concentrated and sustained delivery of medications directly to the wound site	Expense Frequent application Potential for adverse events
Bioengineered alternative tissues	Therapies that have viable cells or pro-healing factors imparted to the wound to stimulate healing Example: cell cultured lines of tissue, scaffold, amniotic tissue	Can directly expedite wound healing	Expense Frequent reapplication Technically more sophisticated
Sharp debridement	Regularly scheduled removal of nonviable tissue and biofilm Example: scalpel, curette, scissors	Can potentiate healing by removal of noxious factors Conversion of a chronic wound to an acute wound	Patient may not tolerate due to pain Technically more sophisticated
Advanced devices	Use of negative pressure though a foam or dressing interface Example: negative pressure wound therapy	Accelerate wound bed preparation and expedite closure	Expense Technically more complicated
Biophysical technologies	Acoustic energy or electrical current used to accelerate tissue repair Example: ultrasound, electrical stimulation	Generally well tolerated by patient Adverse events not common	Slow progression Frequent treatment Expense

This table is exclusive to outpatient treatment of the diabetic foot ulcer.

eradication, or direct wound-healing stimulation. Each modality has its own advantages and limitations with some level of evidence supporting efficacy or effectiveness. The number and diversity of treatment strategies reveal the lack of consensus for a singular algorithm. Further, the treatment rendered reflects the diversity of healthcare providers and their level of training and experience that care for DFUs (e.g., nurses, physical therapists, podiatrists, surgeons, and nonsurgical physicians). Regardless, certain fundamentals of wound care should be applied prior to implementation of any advanced therapies. These fundamentals include (1) ensuring or establishing adequate perfusion; (2) providing optimal offloading; (3) controlling/treating acute infection and biofilm formation; and (4) optimizing the patient's metabolic and nutritional status. It is also important to recognize that antibiotics and dressings serve to optimize the wound environment and do not directly heal wounds. In general, the chronic ulcer must be converted to an acute wound for healing to occur. Close monitoring is necessary including measurements taken at every clinic visit. Treatment strategies should be modified based on the changing quality of the ulcer. For example, if there is increased drainage a more absorbent dressing, compression dressings, and antibiotic/antiseptic therapy should be employed. Ulcers should be debrided regularly in clinic plans for definitive surgical closure or coverage once the ulcer is deemed "appropriately prepared" (i.e., not infected, perfusion maximized).

Minor or major amputation is a viable option for the treatment of chronic ulcerations. The decision for amputation is perhaps easier in the environment of infection and/or ischemia where there is an obvious need. However, an amputation performed to improve the *functional* ability of the patient and reduce the risk of ulceration is also acceptable.[104,105] Biomechanics must be appreciated prior to the performance of a functional amputation. For example, a transmetatarsal amputation (TMA) should be performed maintaining the anatomical parabola of the metatarsals. This allows for an even distribution of pressure at the plantar stump to prevent future breakdown. Further, an adjunctive TAL should be performed at the time of the TMA when an equinus deformity is present to compensate for the loss of the counterbalancing extension function of the long extensor tendons. The TMA results in a durable, functional foot with the addition of an accommodative shoe with a forefoot filler and a rocker-bottom shoe.[106-108] Regardless of the surgery performed, soft tissue coverage as well as the functional consequences of the procedure should always be considered.

CHARCOT NEUROARTHROPATHY

CN can be considered end stage sequela of a pathologic diabetic foot process with devastating economic and clinical consequences. CN has been reported to increase healthcare costs by 17.2% and results in an increase of hospital length of stay.[109] There is a paucity of published prevalence reports; however, an estimated less than 0.5% of patients with diabetes develop CN.[110] CN classically presents with edema, erythema, and calor with fractures and/or dislocations across joints of the foot or ankle. The prevailing theory involves demineralization of the bone, causing instability.

Figure 114.7 A lateral projection radiograph of a patient with Stage 1 Charcot neuroarthropathy. Note the significant soft tissue edema and the fracture dislocation of the talus and the joints of the midfoot.

In the environment of profound peripheral neuropathy where the patient bears weight and ambulates, fractures and dislocations occur in the joints of the foot and/or ankle (Fig. 114.7). An acute traumatic event or the cumulative effect of minor trauma can incite a CN episode. CN progresses through four stages: Stage 0—clinical stage presenting with warm, swollen, often painful foot; Stage 1—fragmentation/destruction, bony cysts, and erosion; Stage 2—joint subluxations; Stage 3—arch collapse and coalescence; and Stage 4—consolidation.[111] The key to the treatment of CN is early recognition and immobilization with non–weight-bearing. As it progresses through its stages, further destruction occurs. Once consolidation occurs, conservative management with custom molded braces/shoes can prevent ulceration and provided stability. Surgical reconstruction may be necessary to realign the foot and ankle into a rectus position. Surgical complication rates can be high with resultant major amputation rates as high as 32% (Fig. 114.8).[112] Chapter 116 discusses Charcot foot in more detail.

OTHER IMPORTANT CONSIDERATIONS

Other factors play a major role in the management of the diabetic foot. As diabetes progresses, every system in the body is detrimentally affected. Comorbidities such as end-stage renal disease and cardiac disease are particularly devastating.[113-115] Metabolic disturbances and immunologic depression impede healing that can lead to increased susceptibility to virulent and repeated infections. Other compromised host factors as well as emotional, mental, socioeconomic, and nutritional challenges make management of the diabetic patient extremely challenging.

CONCLUSIONS

Unfortunately, many complications of diabetes are manifested in the foot. The management of these complications follows a predictable course of multiple hospitalizations, operations, and progressive limb loss. Early recognition and identification of

Figure 114.8 A photograph of a custom molded, rocker bottom, clamshell, foot and ankle device that provides stability.

the at-risk diabetic foot can curtail this downward spiral by a specialized and dedicated diabetic foot team.

SELECTED KEY REFERENCES

Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, Fleischli JG. Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. *Arch Intern Med*. 1998;158:289–292.

This paper compares the specificity and sensitivity of commonly utilized instruments used to detect peripheral neuropathy and recommended the use of these instruments in combination.

Attinger CE, Brown BJ. Amputation and ambulation in diabetic patients: function is the goal. *Diabetes Metab Res Rev*. 2012;28(suppl 1):93–96.

This paper discusses the need to focus on the individual patient's functional capacity for surgical decision making.

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This paper demonstrates that a multidisciplinary team can reduce the likelihood of amputations in the vasculopathic patient with a wound.

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This study compares different methods of offloading and reports that a total contact cast as the superior method for diabetic foot ulcer healing.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 115

Wound Care

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As the populations of developed countries age and become more sedentary, the incidence of diabetes and obesity increases, along with a dramatic increase in the incidence of chronic nonhealing wounds.[1] In most medical communities, surgeons are considered the local experts in the care of wounds and are expected to manage cases that do not respond to typical treatments recommended by primary care clinicians. This chapter focuses on the diagnosis and management of chronic wounds of the extremities that are typically referred to vascular surgeons for definitive management.

Abstract

Chronic non-healing wounds of the lower extremities most often occur due to vascular abnormalities of the arterial or venous system, often in association with diabetic neuropathy. The vascular specialist is a key member of multispecialty teams that are ideally suited to manage these wounds that are frequent causes of disability and limb loss. The vascular specialist must understand the differential diagnosis, diagnostic evaluation and complete care of these patients to achieve optimal outcomes. This chapter focuses on the aspects of care other than correction of the underlying vascular etiology which is a critical component of management. However, once the vascular etiology is treated, it is equally important that the other aspects of wound management, including wound bed preparation, debridement, and infection control are applied to support healing and prevent complications. Adjuncts to standard care including drug therapies, cell and tissue based products, and negative pressure wound therapy will also be considered.

Keywords

Chronic wound
diabetic foot ulcer
venous ulcer
bioengineered tissue

The most common etiologic factors in nonhealing limb ulcers are chronic venous insufficiency, arterial occlusive disease, and diabetic neuropathy. Most reports suggest that the most common cause is venous insufficiency, but patients with arterial insufficiency and diabetic neuropathy are at the highest risk of limb loss.[2] Accurate identification and treatment of these underlying disorders is the most important determinant of ulcer healing.

In many communities, specialized wound clinics have been developed, promising major benefits in wound healing, limb salvage, and quality of life. These centers, in optimal situations, are able to effectively coordinate the efforts of diverse specialists to improve the treatment of difficult patients with chronic wounds. It is clear that a vascular specialist is critical to the team managing these patients; no other specialist can provide the comprehensive management of arterial and venous insufficiency required by a high percentage of patients treated in wound centers. Similarly, a vascular surgeon participating in a multispecialty wound center can expect assistance from other valuable specialists, including endocrinologists, plastic or orthopedic surgeons, podiatrists, orthotists, and physical therapists, to maximize positive outcomes for their patients.

NORMAL WOUND HEALING

Healing of acute wounds normally proceeds through well-defined phases of hemostasis, inflammation, proliferation, and remodeling. Although these phases are typically described separately, the process is actually a gradual progression guided and regulated by the complex interaction of platelets, neutrophils, macrophages, and other cells that respond to and produce growth factors, cytokines, proteases, and inhibitors.[3] Although the effects of many of these proteins have been described, the deficiencies that lead to the failure of timely healing are not well described. It is clear that all of the common causes of nonhealing wounds, including venous hypertension, arterial insufficiency, chronic pressure, and chronic inflammation, inhibit this orderly healing process, usually in the inflammatory stage, with little meaningful tissue proliferation demonstrated.

Inflammatory Phase

The inflammatory phase of wound healing is critical to the normal healing process. Mediated by mast cells, neutrophils, and macrophages, inflammation develops within 24 hours of acute wounding and continues for up to 2 weeks. The involved cells produce chemokines, cytokines, and growth factors that mediate the inflammatory process.[4] Cytokines such as tumor necrosis factor-α (TNF-α), interferon-δ (IFN-δ), and the interleukins (ILs) are released by activated lymphocytes and macrophages into the tissue, resulting in further recruitment and activation of fibroblasts and epithelial cells in the wound.[5] Neutrophils following chemoattractant signals migrate into the wound, releasing concentrated matrix metalloproteinases (MMPs). The MMPs are responsible for clearing damaged tissue from the wound area by breaking down collagen (MMP-1 and -8), gelatin (MMP-2 and -9), and elastin (elastase).[6] The activity of MMPs is closely controlled by tissue inhibitors of MMPs (TIMPs), which are produced principally by macrophages.

Proliferative Phase

In the proliferative phase, growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF), are secreted by multiple cell types but primarily by macrophages. They are responsible for the recruitment of fibroblasts to commence the proliferative phase and for the initiation of angiogenesis required to support tissue generation and epithelial growth.[7] Fibroblasts responding to signaling growth factors and cytokines migrate into the extracellular matrix, synthesizing collagen and proteoglycans and developing granulation tissue to fill the wound. Orderly capillary growth and networking must occur to support the developing granulation tissue; this requires a complex interplay of growth factors, including multiple isoforms of VEGF, TGF-β, and hypoxia-inducible factor-1 (HIF-1).[8,9] MMPs are also required for the normal progression of angiogenesis and must be secreted at the correct time by budding capillary loops to allow them to degrade the existing capillary basement membrane as they sprout to establish a new capillary channel.[10]

Epithelialization and Remodeling

Epithelialization occurs most rapidly on a well-granulated, confluent tissue bed, in response to signals from growth factors, such as epithelial growth factor and keratinocyte growth factor. Epithelial cells migrate into the wound from the periphery by secreting MMPs to degrade the nonviable tissue at the wound edge, allowing migration into the wound. Normally epithelial migration should continue until other epithelial cells are contacted.[11]

Remodeling is a long-term process in which type III collagen is largely replaced by mature type I collagen. This process also requires the presence of MMPs to degrade the type III collagen in a controlled fashion mediated by TIMPs, facilitating its replacement with maturing type I collagen.[12]

MECHANISMS OF ABNORMAL WOUND HEALING IN CHRONIC WOUNDS

Chronic nonhealing wounds occur when the normal healing process is disrupted. This is most frequently the result of an underlying disorder that causes a prolonged, unchecked pro-inflammatory state. These disorders include venous hypertension, chronic pressure, bacterial colonization, inadequate tissue perfusion, and cellular senescence.

Inflammation

Recurrent or prolonged inflammatory stimuli result in chronic wounds that are characterized by persistent upregulation of proinflammatory cytokines and MMPs. Although this

environment is necessary for a brief period for acute wound healing, persistence of this environment has detrimental effects. Wound fluid collected from chronic nonhealing ulcers has been reported to inhibit DNA synthesis and mitotic activity of normal skin fibroblasts and keratinocytes.[13] In contrast, fluid collected from acute wounds stimulate these measures of cellular activity. Chronic wound fluid may contain high levels of MMP-2 and MMP-9 and abnormally low levels of TIMPs.[14] In venous ulcers, MMP levels decrease after compression treatment. In a study of 56 patients with pressure ulcers, Ladwig et al.[15] found that the ratio of MMP-9 to TIMP-1 was associated with wound healing outcomes: an elevated concentration of MMP-9 in relation to TIMP-1 was predictive of poor healing. Although this upregulation of protease levels might be expected to degrade endogenous growth factors, Drinkwater et al.[16] reported that the level of VEGFs in venous ulcer tissue was not decreased and was persistently high compared with normal tissue, and was equivalent to levels in tissue from acute wounds. In a separate study, these researchers found that fluid from venous ulcers inhibited angiogenesis, postulating that this effect must be caused by the presence of inhibitors or a lack of available receptors rather than an absence of stimulatory growth factors.[17] Patients with critical limb ischemia (CLI) also demonstrate deficits of growth factor function. Palmer-Kazen et al.[18] found that distal limb tissue in patients with CLI had lower levels of VEGF compared with nonischemic proximal tissue in the same limb.

Cytokines

Upregulation of proinflammatory cytokines, including TNF-α, IL-1, and IL-6, has also been described in chronic venous wound fluid.[13] These levels were found to improve when ulcers began to heal, with a decrease in size and improvement in granulation. Diabetic foot ulcers may also display proinflammatory upregulation and low expression of angiogenic factors.[19]

Cell Senescence

Cellular senescence has been reported in fibroblasts collected from chronic nonhealing ulcers. Lal and colleagues[20] found that fibroblasts from patients with increasing levels of venous disease by clinical class, etiologic, anatomic, and pathophysiologic (CEAP) criteria displayed a progressively diminishing response to agonist-induced proliferation. Fibroblasts from CEAP class 6 patients displayed severe inhibition of the proliferative response to TGF-β1. Mendez and colleagues[21] reported a series of studies of cultured fibroblasts from venous ulcers, indicating that these typically display phenotypic characteristics of cellular senescence, including slow growth and altered morphology. Stimulation of senescent fibroblasts may be a key target of therapy for improving the healing potential of chronic leg ulcers.

Therapeutic Targets

The development of therapeutic targets based on the known mechanisms of poor healing has been difficult, given its overall complexity. Initial strategies at modulating protease expression have not yielded major improvements in healing. A dressing composed of a combination of collagen and regenerated cellulose (Promogran, Systagenix, North Yorkshire, United Kingdom) has been developed, based on its ability to bind MMPs in wound fluid in vitro.[22] However, in a prospective randomized study of 276 patients with diabetic foot ulcers, treatment with this dressing for 12 weeks failed to result in a significantly higher incidence of complete healing (37%) compared with ulcers treated with saline-moistened gauze (28%).[23]

General treatments for the reduction of inflammation such as doxycycline and nonsteroidal anti-inflammatory drugs have been studied in animal models and considered for clinical use.[24] In a pilot study of chronic venous leg ulcers, high-dose doxycycline resulted in improvement of recalcitrant wounds and reduced wound fluid MMP levels.[25] These findings have not yet been confirmed in a larger patient cohort. Some researchers believe that the simple inhibition of upregulated proteases or cytokines is unlikely to yield significant gains in healing. As evidenced by the importance of MMPs in multiple aspects of the normal healing process, gross inhibition of their function impairs capillary development, epithelial migration, and collagen maturation. Beidler et al.,[26] in an analysis of cytokine levels and venous ulcer healing, found that untreated ulcers with higher levels of proinflammatory cytokines, including IL-1, IL-12p40, and IFN-δ, healed significantly better than those with lower levels of these cytokines before compression. It is clear that strategies to address the abnormal progression of healing in chronic ulcers must consider that inflammation is necessary at various points in the process and must be suppressed at other stages. Currently no diagnostic modalities are available to rapidly test the MMP or cytokine levels in wound fluid or tissue in a nonresearch setting, but clinically relevant testing strategies are under development.

ETIOLOGY OF ULCERATION

The successful treatment of patients with nonhealing leg ulcers requires that the underlying cause of ulceration be correctly diagnosed. Common differential diagnoses of leg ulceration are provided in Table 115.1. It has been reported that multiple causes are involved in more than 20% of leg ulcers, so it is clear that each potential diagnosis must be considered in every patient.[27] Based on the history and physical examination, the proper cause or causes of chronic ulcers can be defined in the majority of patients, but if doubt remains, confirmatory noninvasive testing should be performed.

Venous Leg Ulcers

The epidemiology and pathophysiology of venous leg ulcers are described in Chapter 156. Risk factors related to the development of venous ulcers are the same as those for the development of venous disease in general. It is important to understand that venous disease in any combination of anatomic sites may result in limb ulceration, including superficial venous insufficiency alone. The anatomic sites of venous reflux defined by duplex ultrasound examination in a series of 138 patients with venous leg ulcers are listed in Table 115.2.[28]

TABLE 115.1 Differential Diagnosis of Causes of Chronic Nonhealing Leg Ulcers

Etiology of Wound	Differential Diagnosis	Method of Investigation
Infectious conditions	Mycobacterial Fungal Bacterial Treponemal/spirochetal	Wound biopsy with special stains and cultures, VDRL, PPD, CBC, ESR, C-reactive protein, chest x-ray, wound x-ray
Malignancy	Basal cell carcinoma Squamous cell carcinoma Kaposi sarcoma Lymphoma Mycosis fungoides	Wound biopsy for pathologic evaluation
Macrovascular arterial insufficiency	Arteriosclerosis Posttraumatic Embolic Acute or chronic thrombosis	Noninvasive vascular studies Bidirectional color Doppler, $tcPO_2$, Contrast arteriography Computed tomography arteriography Magnetic resonance arteriography
Vasculitis/vasculopathy (microvascular arterial insufficiency)	Diabetic microangiopathy Hypertensive microangiopathy Thromboangiitis obliterans Raynaud disorder	$tcPO_2$ Laser Doppler Possible biopsy
Venous insufficiency (deep and superficial)	Deep venous thrombosis Extrinsic compression (tumors) Deep valve insufficiency Perforator valve insufficiency Superficial venous insufficiency	Strain gauge plethysmography (maximum venous outflow) Venous photoplethysmography Bidirectional color Doppler Air plethysmography
Lymphatic obstruction/ lymphedema	Venolymphatic disease (secondary to congestive heart failure, hepatic failure, renal failure, other overload states) Primary or secondary lymphatic insufficiency Lymphangiosarcoma	Clinical diagnosis, history, physical examination, chest x-ray, liver function tests, chemistries, lymphangiography
Hematologic abnormalities	Anemia (sickle cell) Polycythemia Dysproteinemia	CBC, iron studies (Fe, TIBC, folate, B_{12}) Sickle cell prep
Collagen vascular disorders	Systemic lupus erythematosus Scleroderma Polyarteritis nodosa Wegener granulomatosis	FANA Rheumatoid arthritis prep Serum complement Rheumatologic workup
Excessive pressure	Diabetic neuropathy Alcoholic neuropathy Decubitus ulcer Postoperative deformity Bone spurs	Monofilament (10 g) Vibratory sensation (>25 mV) X-rays

CBC, Complete blood count; *ESR*, erythrocyte sedimentation rate; *FANA*, fluorescent antinuclear antibody test; *PPD*, purified protein derivative; *$tcPO_2$*, transcutaneous oxygen tension; *TIBC*, total iron-binding capacity; *VDRL*, Venereal Disease Research Laboratory.

TABLE 115.2 Anatomic Distribution of Venous Reflux in 138 Patients[28]

Venous System	Limbs (%)
Deep alone	43.5
Deep and superficial	21.0
Deep, perforator, and superficial	6.5
Superficial alone	18.1
Superficial and perforator	10.9

The pathway between chronic venous hypertension and limb ulceration has been debated for years. In some patients persistent venous hypertension with chronic limb edema leads to the gradual development of skin changes. Chronic upregulation of pro-inflammatory cytokines appear to mediate the development of tissue fibrosis and the clinical appearance of lipodermatosclerosis (Fig. 115.1). This is believed to be a preulcerative condition that should stimulate treatment to correct the underlying venous pathology or eliminate edema to reduce the risk of future ulceration. Ulceration eventually occurs either spontaneously or due to minor limb trauma in the lower calf or ankle that then does not heal.

Figure 115.1 Limb with chronic venous insufficiency illustrating wound tissue scarring and lipodermatosclerosis.

Diabetic Foot Ulcers

The epidemiology and pathophysiology of diabetic foot ulcers are reviewed in detail in Chapter 116. For management purposes, it is critical to remember that the underlying causes of ulcers, such as polyneuropathy, vascular insufficiency, and infection, must be addressed before specific wound treatments can assist in healing. Inadequate pressure offloading is the most common cause of failure to heal, and no active wound therapy can overcome persistent pressure on a plantar ulcer. The assistance of an expert orthotist and consistent patient education to achieve compliance are far more important to the healing of diabetic foot ulcers than the specific dressing or agent selected.

Limb Ulcers Associated With Arterial Insufficiency

The treatment of patients with chronic nonhealing leg ulcers associated with arterial insufficiency involves a critical assessment of the patient's suitability for invasive procedures and the potential risk of limb loss based on ulcer characteristics. Data from several clinical trials studying CLI have identified a risk of major amputation in 25% to 40% of patients at 1 year if revascularization is not performed.[29,30] However, the hemodynamic criteria for CLI are broad and further evaluation of the specific level of perfusion to the wound bed is needed to predict which patients have a good chance of healing without revascularization. It appears clear that the severity of the wound itself is important, such that a superficial partial-thickness wound (Fig. 115.2) may not require the same level of perfusion as a deep, complicated leg ulcer involving tendon or bone (Fig. 115.3) to achieve healing. The WIfI classification system (see the section on Wound Classification later) was designed to capture the severity of wound tissue damage, arterial insufficiency, and infection as an aid to prediction of healing potential.[31]

The natural history of chronic wounds with AI that do not receive revascularization was reported in a study of 169 limbs.[32] At 1-year follow-up, 52% of limb ulcers were healed, and 23% required amputation (Fig. 115.4). Risk factor analyses revealed

Figure 115.2 Wagner grade 1 diabetic foot ulcer. The wound penetrates through the full thickness of the skin, involving the subcutaneous tissue but not the deeper tissue layers.

Figure 115.3 Complex heel ulcer with exposed tendon and infected bone.

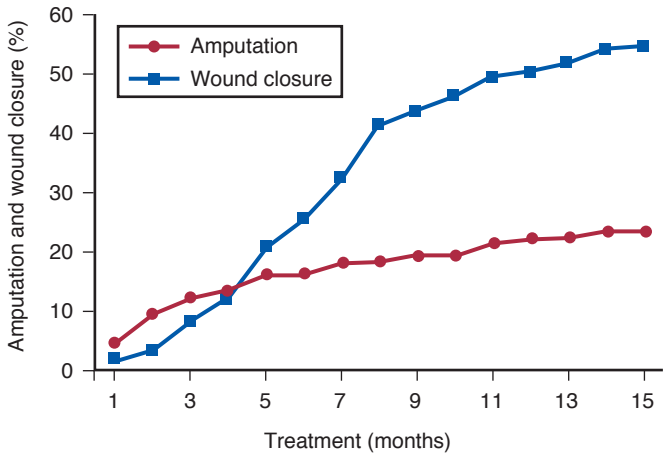

Figure 115.4 Incidence of major amputation and complete wound closure by life-table analysis in 169 limbs with tissue loss and nonrevascularized arterial insufficiency. (Marston WA, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. *J Vasc Surg.* 2006;44: 108–114.)

Figure 115.5 Chronic wound with squamous cell malignancy (Marjolin's ulcer).

that the ankle-brachial index (ABI) and wound grade were associated with amputation at 1 year. In another study of nonrevascularized patients with CLI and wounds, limbs were separated into groups based on the toe pressure in the affected limb.[33] If the toe pressure was 20 to 50 mm Hg, 85% of patients were able to achieve limb salvage with wound management using standard multispecialty wound protocols, compared with only 60% in those with a toe pressure less than 20 mm Hg. Unfortunately, survival in these patients is poor, particularly in the patients with the lowest toe pressures less than 10 mm Hg, in whom only 8% of patients achieved amputation-free survival at 3 years. This is due to severe medical comorbidities affecting these patients, including a high prevalence of renal failure and cardiac dysfunction, which also lead to higher risks for efforts at revascularization.[34] This information suggests that some patients with AI and wounds who are at high risk for a poor outcome with revascularization can be reasonably treated without revascularization, and many will experience limb salvage. Revascularization should be considered early in those who have rest pain, those with more severe wound grades, and those with pedal gangrene. Wounds treated initially with wound management without revascularization should be monitored closely for progress, and if this does not occur within 4 to 6 weeks, revascularization should be considered. Arterial insufficiency is a common complicating factor for limb ulcers associated primarily with other causes, including venous insufficiency, diabetes, and rheumatoid arthritis. It is important that the status of the arterial supply be determined in every patient at the initial evaluation.

Other Causes of Limb Ulceration

Although the preceding causes are important factors in more than 90% of nontraumatic limb ulcers, other causes, including vasculitis, sickle cell anemia, malignancy, and dermatologic disease, are routinely seen by vascular specialists. It is beyond the scope of this chapter to review these leg ulcers in detail. The key to diagnosing these atypical causes is ulcer biopsy. Many of these conditions may be confused with venous ulceration and may coexist in a patient with chronic venous insufficiency. The most important diagnosis to make is Marjolin's ulcer, which may develop when squamous transformation occurs in a preexisting benign chronic wound (Fig. 115.5). This neoplasm is often not detectable by observation, so the physician must maintain a high index of suspicion. Whenever a wound does not respond to a comprehensive treatment plan as expected or a wound that has been healing ceases to progress for no known reason, a biopsy should be performed to rule out malignancy. Further information on the diagnosis and management of atypical wounds is beyond the scope of this chapter.

CLINICAL PRESENTATION AND INITIAL EVALUATION

The primary cause of most wounds can be identified after the history and an attentive physical examination. Fig. 115.6 contrasts common types of lower extremity ulcerations.

Wound Classification Systems

The most widely recognized system for classification of diabetic foot ulcers is the Wagner grading system. Limbs with higher Wagner grades, particularly grades 3 to 5, are at increased risk for limb loss (Table 115.3).[35]

Figure 115.6 (A) Leg ulcer associated with chronic venous insufficiency. (B) Diabetic neuropathic ulcer. (C) Plantar ulcer in a patient with diabetes and chronic Charcot neuropathy. (D) Leg ulcer in a patient with both arterial and venous insufficiency. (E) Leg ulcer in a patient with systemic lupus and venous insufficiency. (F) Squamous cell carcinoma arising in a chronic foot ulcer. (G) Leg ulcer associated with rheumatoid arthritis. (H) Bacterial biofilm covering the surface of a nonhealing venous leg ulcer. (I) Same ulcer depicted in (H) after elimination of the biofilm following débridement and 2 weeks of antibiotic therapy. (J) Chronic leg ulcer in a patient with sickle cell anemia.

However, the Wagner system only incorporates the extent of anatomic wound involvement. In an attempt to improve the predictive value of a wound classification system, the Society for Vascular Surgery Lower Extremity Guidelines Committee developed a new classification of the threatened lower extremity that also includes the presence and extent of wound ischemia and infection.[31] The WIfI classification (see Table 104.3 in Chapter 104) has been validated to correlate to the risk of amputation in several subsequent publications.[31,36,37]

Wound Size Measurement

At each visit, it is important to measure the wound size to document progress and alter the treatment plan if necessary.

Subtle changes in the wound itself, including the development of inflammation or bacterial colonization, may manifest only as the suppression of healing. Routine wound measurement allows the consideration of alternative treatment methods as soon as progress in wound healing ceases.

Numerous methods are available to document and follow wound size, including digital photography with computerized planimetry, direct planimetry, and simple measurement of dimensions. Software systems are also available to allow the determination of wound size from calibrated digital photography.

TABLE 115.3 Incidence of Limb Amputation in Patients Presenting With Limb Ischemia Based on Wagner Grade[a] at Initial Presentation

Grade	Criterion	Amputation at 12 Months (%)
0	Preulcerative lesion	
1	Superficial ulcer	12
2	Ulcer extending deep to tendon, bone, or joint	19
3	Deep ulcer with abscess or osteomyelitis	31
4	Forefoot gangrene	49
5	Whole foot gangrene	100

[a]Grades 1–4 ($n = 169$).

Marston WA, et al. Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization. *J Vasc Surg*. 2006;44:108–114.

Wound Bed Assessment and Preparation

Once the history and physical examination are completed and a general idea of the underlying cause of the wound is determined, the wound itself must be assessed for local factors inhibiting healing. Numerous factors must be identified and corrected to optimize healing potential, a process termed "wound bed preparation." The components of this process include débridement of nonviable tissue, identification and correction of bacterial involvement, control of chronic inflammation, elimination of limb edema, and control of wound exudate. The first two components are addressed here.

Débridement

The majority of chronic limb ulcers are covered with nonviable tissue, including callus, eschar, fibrinous material, and slough. This tissue has no regenerative capability, harbors bacteria, and prevents the migration of healthy epithelium into the wound. Débridement is required to excise nonviable tissue and should be aggressive, particularly at the initial evaluation. Cellular senescence has been identified in wound tissue around diabetic foot ulcers and chronic venous ulcers of long duration, indicating the need for wound excision to remove all surrounding tissue in these cases (Fig. 115.7).[38] In a prospective multicenter study of becaplermin for the healing of diabetic foot ulcers, a secondary analysis suggested that centers employing more frequent wound débridement achieved better healing rates.[39]

In a retrospective review of 676 patients enrolled in clinical trials of novel therapeutic agents for venous or diabetic ulcers, the incidence of wound débridement was studied and correlated with wound closure.[40] Thirty-three centers where limbs were débrided more frequently were associated with higher rates of wound closure for both types of wounds, but an increased frequency of wound débridement per patient did not statistically

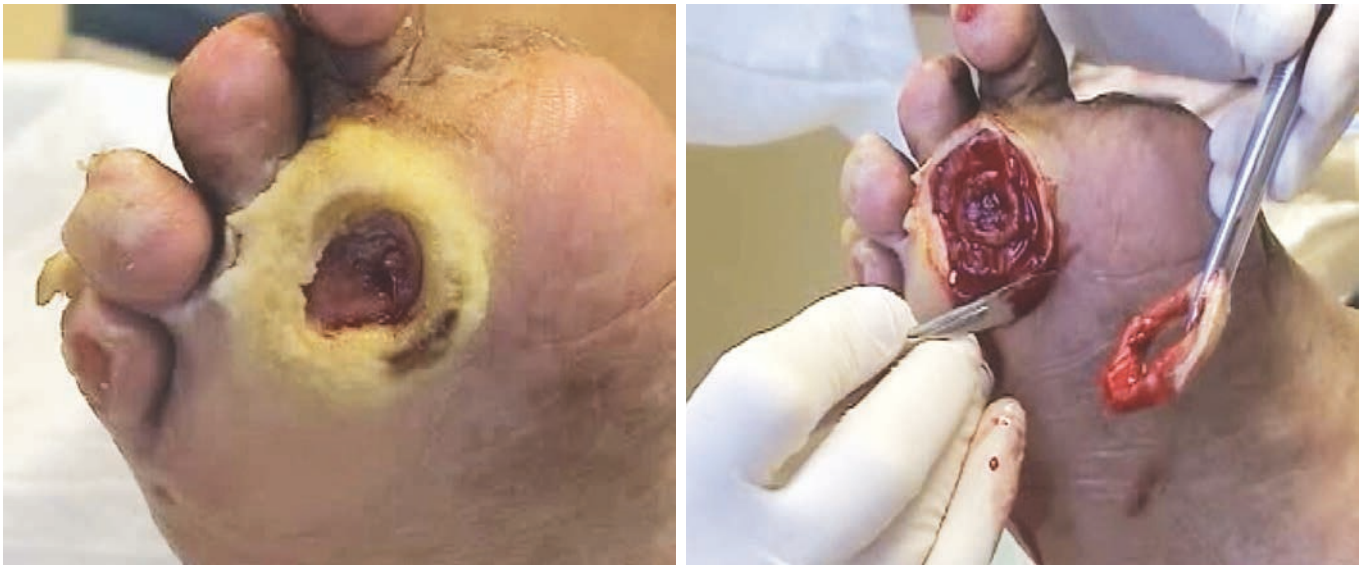

Figure 115.7 Example of aggressive débridement of senescent tissue in and around the wound bed to create an acute wound out of a chronic wound.

correlate with higher rates of wound closure. Using a large retrospective data set, Wilcox and colleagues (2013) documented faster healing with weekly débridement ($P < .001$) of a variety of chronic wounds.[41] Based on this information, it appears that débridement for chronic wounds is important to eliminate nonviable tissue, and may be required multiple times during the treatment course of the wound. However, the current body of evidence provides no definitive guidance on the question of how often chronic wounds should be débrided or the best timing.

Numerous alternatives to surgical débridement have evolved, including chemical débridement, ultrasound débridement, hydro-débridement, and larval therapy. In general, there are two situations in which alternatives to surgical débridement may be desirable: patients in long-term nursing facilities, and those who have difficulty traveling to wound or surgical clinics for surgical débridement when required. These patients may benefit from chemical débridement or some other method.

Chemical

Chemical débriding agents are typically composed of enzymatic agents, including collagenase (Santyl, Healthpoint Ltd., Fort Worth, Texas). Collagenase may be used as a maintenance débriding agent to remove moderate amounts of fibrinous slough from the wound surface, but it is usually ineffective against thick tissue or eschar.

Larval

Larval therapy using medical maggots has been studied as an alternative to conventional therapy in several nonrandomized studies. Sherman reported that 80% of maggot-treated pressure wounds achieved complete débridement, compared with 48% of conventionally treated wounds.[42] However, most of the studies evaluating maggot therapy have used autolytic or chemical débridement as comparators. A randomized study of larval therapy compared with hydrogel for the management of chronic leg ulcers was reported in 2009.[43] All other wound therapies were similar for each group. The study found that larval-treated wounds experienced significantly faster débridement than the hydrogel-treated group, but at the expense of significantly higher ulcer-related pain scores. No difference in ulcer healing or patient quality of life was demonstrated.

Ultrasound

Débridement using standard surgical techniques may be particularly painful, leading to interest in alternative methods that achieve wound débridement while increasing patient comfort. Several energy modalities, including ultrasound, have been investigated as adjuncts to débridement. Ultrasound may be used in conjunction with a surgical instrument: the instrument contacts the wound to deliver ultrasound energy to the tissue to loosen and remove nonviable tissue. Alternatively, the use of saline mist avoids the need for direct contact with the wound surface. In a study of the noncontact method of ultrasound treatment, mist ultrasound was compared with standard treatment of diabetic foot ulcers. Although there was no significant difference in the rate of ulcer healing based upon the intent-to-treat analysis, there was a significant increase in the rate of healing in patients who completed a course of properly applied mist ultrasound treatment.[44]

In summary, no other form of débridement has demonstrated superiority to standard surgical débridement, and most of these methods are less cost effective in the majority of cases. Alternative methods of débridement are generally recommended when surgical débridement is not possible or is not desirable.

Bacterial Colonization

Significant bacterial infection is a common complication in chronic wounds. In several prospective randomized clinical trials of therapies for diabetic foot ulcers, wound infection requiring systemic antibiotic therapy occurred in 20% to 25% of cases.[45,46] However, the treatment of bacteria in wounds that do not appear to be clinically infected is controversial. Moreover, it is believed that uninfected healing wounds are colonized with bacterial flora. Treatment with antibiotics is not indicated, so routine culturing of wounds in these cases is not recommended. The eradication of normal skin and nonvirulent wound bacteria is not desirable and may support the growth of more virulent and resistant bacterial strains. Of note, however, recent studies have identified an increase in the incidence of resistant organisms from cultures of chronic nonhealing ulcers that do not respond to standard treatment protocols.[47]

Biofilms harboring bacteria are well known to cover indwelling catheters, industrial surfaces, and dental structures. Bacteria in these situations secrete a polysaccharide substance that covers the colonies, which grow and interact to inhibit host-generated control mechanisms. Mechanical methods of cleansing these surfaces can minimize biofilms, but they typically repopulate rapidly after cleansing. In chronic wounds, biofilms appear to multiply to the point at which they inhibit healing by stimulating chronic inflammation, inactivating growth factors critical to the healing process, and preventing orderly angiogenesis required for healing (Fig. 115.8).[48] If untreated, it is believed that biofilms will continue to inhibit wound healing or may lead to more significant systemic infection.

Given the emergence of this clinical problem, wounds with poor progress and those demonstrating any evidence of enlargement or infection should be evaluated with quantitative cultures. If cultures demonstrate greater than 10^5 bacterial counts per cubic millimeter, the patient should receive systemic therapy guided by bacteria-specific sensitivities.[49]

In general, the management of bacterial colonization of chronic ulcers remains a controversial area with limited high quality research and contradictory results in the studies available for review. Although there is general agreement among experts that wounds with obvious signs of clinical infection should be treated with systemic antibiotics, there is no consensus on the management of wounds colonized with bacteria or bacterial biofilms without signs of systemic infection. Recent studies have described the types of bacterial biofilms that may develop in chronic wounds, with multiple species organized into colonies on the wound surface that are resistant to topical therapies. This adds complexity to treatment, and information on the clinical relevance of these biofilms and the best strategies to treat them is not yet well developed. Finally, the changing nature of

Figure 115.8 Examples of the appearance of biofilm covering chronic wounds.

bacterial behavior over time may render studies performed as recently as 5 to 10 years ago irrelevant at the present time. The importance of the bacteria affecting the wound bed remains controversial. Although some studies have reported that the information provided by wound cultures is of little prognostic significance,[50] others report improved healing with specific antibiotic treatment of cultured bacteria.[51] Diagnostic methods are becoming clinically available using polymerase chain reaction to provide more detailed descriptions of the bacteria existing in the wound bed.[52] This information may allow more specific tailored antimicrobial strategies to treat each individual wound. However, use of these methods has not yet been established to improve outcomes in the care of chronic wounds.

PROPERTIES AND CATEGORIES OF WOUND DRESSINGS

In general, the selection of a wound dressing should be based on wound characteristics, including location, inflammation, and amount of exudate. Moisture balance is important, and the dressing should maintain a moist environment conducive to tissue growth and epithelial migration. Based on the high concentration of inflammatory cytokines and proteases in chronic wound fluid, excessive fluid should be wicked away from the ulcer and the skin surface to prevent further tissue inflammation and damage from prolonged contact.

A multitude of agents with theoretical healing benefits have been added to wound dressings, including collagen, zinc, enzymes, copper, chlorophyll, honey, avocado oil, and others with little proof of benefit. Table 115.4 lists the common categories of wound dressings and their typical uses.

A common question concerning all these dressings is their worth in comparison to a simple regimen such as wet-to-dry saline gauze dressings. Although it is true that few wound products have been proved to heal significantly more wounds than saline-moistened gauze, other secondary benefits may be realized through the use of these dressings. Pain reduction, odor reduction, and longer wear time are important benefits. Also, it is assumed that wet-to-dry dressings are cost-effective because

TABLE 115.4 Dressing Categories and Primary Uses

Advantages	Disadvantages	Examples	Typical Uses
Gauze			
Mechanical débridement Permeable to gases Fills dead space Economical Readily available Absorptive	Can damage granulation tissue on removal May dehydrate wound Permeable to fluid and bacteria May require more frequent dressing changes	Kerlix Kling Nu-Gauze Sof-wick Tendersorb Mirasorb	Infected wounds Wounds requiring frequent dressing changes
Film			
Semipermeable Retains moisture Waterproof Allows wound visualization	Cannot be used on infected wounds May tear fragile skin May dislodge in high-friction areas	Bioclusive Flexfilm Tegaderm Opsite Polyskin II Cutifilm	Postsurgical wounds Partial-thickness wounds
Hydrogel			
May reduce pain Rehydrates wound Extends time between dressing changes Can fill dead space	Requires secondary dressing Sheets may be difficult to secure Can cause periwound maceration Minimal absorption	NU-GEL Curasol Safe-gel Carrasyn Hypergel Gentell Vigilon	Dry, minimally exudative wounds Diabetic foot ulcers
Hydrocolloid			
Impermeable to bacteria Facilitates autolytic débridement Water resistant Self-adhesive Reduces pain	Cannot be used in heavy exudate Cannot be used on infected wounds Softens and loses shape with heat and friction May cause skin tears	Duoderm Replicare Restore Tegasorb Cutinova	Partial-thickness wounds Low-exudative pressure ulcers
Foam			
Highly absorptive Nonadherent Conformable Protects wound from trauma Can be used under compression dressing	May require secondary dressing May macerate wound edge if dressing becomes saturated Not effective for wounds with dry eschar	Allevyn Flexan Lyofoam PolyMem	Highly exudative wounds Venous ulcers under compression
Alginate			
Forms moist gel in wound Highly absorptive Fills dead space Controls heavy exudate	Cannot be used in dry wounds with minimal exudate Can dehydrate wound bed Reports of burning sensation Requires secondary dressing	Sorbsan Kaltostat Curasorb Algisite Tegagen HG AlgiDERM	Heavily exudative, deep wounds Tunneling, draining wounds Venous ulcers under compression
Composite			
Combines two or more physically distinct products for better outcomes	Can be expensive Provider must have good understanding of dressing properties Generally requires intact skin border for anchoring dressing	Fibrocol (collagen and alginate) Versiva (foam and hydrofiber) Tielle (foam and polyurethane covering	Depends on specific composite

of the relatively low cost of the dressing materials compared with other products. However, proper utilization of wet-to-dry dressings requires dressing changes two or three times daily, resulting in increased cost of care. Particularly in situations in which skilled care such as home nursing is required, the cost efficacy of dressings with longer wear time is significantly better than that of wet-to-dry gauze dressings.[53]

Diabetic foot ulcers are typically treated with dressings that donate moisture to the wound bed, such as hydrogels, because the wound usually produces little exudative drainage. More

heavily draining wounds are better treated with alginates or hydrofibers with greater moisture removal capabilities. Venous leg ulcers are heavily exudative, with a high protease content to the fluid. This requires foam-type dressings that absorb and wick active exudate away from the wound and surrounding skin. Compression systems are placed on top of this primary dressing and should be changed as often as necessary to prevent saturation of the dressing, usually one to three times weekly.

As concern over resistant bacterial species has increased, a vast array of dressings containing antimicrobial agents has been developed. Employing these agents generally requires a balance between the positive antimicrobial effect and the inhibition of normal tissue proliferation and wound healing. The long-term use of iodine-based topical antibiotics in chronic wound healing fell out of favor after in vitro studies suggested the suppression of fibroblast function. Slow-release dressings containing cadexomer iodine were developed, designed to reduce the concentration of iodine limiting negative effects on wound healing while inhibiting bacterial growth. In a small multicenter randomized study comparing cadexomer iodine to wet-to-dry dressings in venous leg ulcers treated with compression, the cadexomer iodine treated wounds were found to heal more than twice as rapidly as the control ($P = .0025$).[54]

Silver and numerous other antimicrobial agents have been incorporated into dressing materials, many combined with other dressing characteristics that also permit moisture management in the wound bed. A Cochrane analysis of the benefit of silver-releasing dressings for the healing of chronic wounds found insufficient evidence to recommend their use for the treatment of infected or contaminated wounds.[55] In a randomized study of 129 patients with venous leg ulcers colonized with critical levels of bacteria and poor healing, a silver-containing foam dressing was compared with a non–silver-containing dressing; both groups received multilayer compression.[56] After 4 weeks, the silver-treated ulcers had closed an average of 45%, compared with 25% in the control group ($P < .05$). The wounds were not treated with the product to complete healing, so the rate of wound closure was not assessed. A prospective randomized trial performed in chronic venous leg ulcers evaluated the effect of routine use of silver-donating dressings compared with non–silver-donating dressings over a 12-week period.[57] All patients were treated with high-strength compression and primary dressings of similar absorptive capacity either with or without silver. No demonstrable effect on healing or quality of life was associated with the use of silver. Given the increased cost of these dressings, it was concluded that routine use is not indicated.

Based on this information, it may be concluded that topical antimicrobial agents should not be used routinely to treat wounds for extended periods, but targeted use in well-defined wounds with critical levels of bacterial involvement may yield a benefit, but the level of evidence supporting this practice is poor.

VENOUS LEG ULCERS

All patients with venous leg ulcers who are candidates for corrective procedures should have diagnostic studies to determine their specific anatomy and physiology. Particular attention should be paid to correctable venous abnormalities, including saphenous reflux, perforator incompetence, and iliac outflow stenosis.

The American Venous Forum and Society for Vascular Surgery published treatment guidelines for venous leg ulcers in 2014. These comprehensive practice guidelines include recommendations on therapy to prevent ulceration, therapies to heal VLUs, and methods to prevent ulcer recurrence after healing.[58]

Compression

Sustained high-strength compression of the limb remains the basis of treatment for venous leg ulcers. Discussed in detail in Chapter 157, compression must be initiated before other therapies and throughout the treatment course to attain healing. Adjuvant therapies will uniformly fail if limb compression is not maintained during treatment in an ambulatory patient.

Pharmacologic Treatment

Pentoxifylline

In a review of randomized controlled trials, Jull and Arroll[59] found five trials in which pentoxifylline and compression were compared with placebo and compression. Pooling these data resulted in the conclusion that more patients in the pentoxifylline group achieved healing. In one of the studies, Falanga et al.[60] reported a median time to healing of 100 days for placebo, compared with 71 days for pentoxifylline at 800 mg three times daily.

Flavonoids

Flavonoids are a class of plant-derived compounds that display anti-inflammatory and antioxidant properties. Two randomized controlled trials studied the benefit of flavonoids in addition to compression for venous leg ulcer healing, and both found a significant benefit for flavonoid treatment.[61,62]

Anticoagulants

In an RCT on 284 patients with VLUs treated with compression therapy and surgical intervention, daily subcutaneous injection of LMWH for 12 months was found to accelerate wound healing.[63] Patients treated in the group randomized to receive LMWH experienced complete ulcer healing in 83.8% at 12 months compared with 60.6% at 12 months in those treated without LMWH. Although the cost and complications associated with daily LMWH use for a year may not warrant therapy for most patients with VLUs, this therapy may be considered for carefully selected recalcitrant ulcers not responding to other therapies.

Indications for Intervention

Gohel et al.[64] performed a randomized study comparing the efficacy of saphenous stripping plus compression with compression alone for the healing and prevention of venous leg ulcers in patients with superficial venous reflux. Significantly fewer

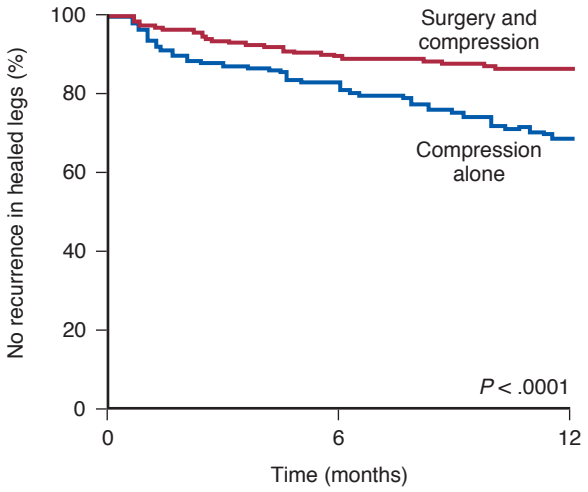

Figure 115.9 Incidence of ulcer recurrence in patients with chronic venous insufficiency due to superficial venous reflux treated with compression alone compared with compression plus surgical stripping of the saphenous vein. (Modified from Gohel MS, Barwell JR, Taylor M, Chant T, Foy C, Earnshaw JJ, Heather BP, Mitchell DC, Whyman MR, Poskitt KR. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomized controlled trial. *BMJ.* 2007;335:83.)

patients in the surgery group experienced recurrent ulceration (15%) compared with the compression-only group (34%) at 1-year follow-up (Fig. 115.9). At 4 years of follow-up, 56% of patients treated with compression alone had developed recurrent ulceration compared with 31% of those in the surgery group ($P < .01$).

Based on the results of this trial, it is reasonable to recommend venous intervention to reduce the incidence of ulcer recurrence whenever superficial venous reflux is a prominent component of the abnormal venous function. This constitutes 30% to 50% of cases seen at most venous leg ulcers centers. However, intervention cannot be recommended for most patients to accelerate wound healing. The contribution of incompetent perforators to global venous insufficiency remains controversial and is discussed in detail in Chapter 158, but it is clear that some leg ulcers are associated with large incompetent perforators that should be ligated or ablated.

There is also limited evidence supporting the removal of varicose channels extending into the ulcer bed to eliminate the final channel of venous hypertension extending into the area of ulceration.[65] This may be done surgically or with sclerotherapy. Deep venous reconstruction can be considered in some cases (see Chapter 159).

Adjunctive Therapies to Accelerate Healing

Treatment of venous leg ulcers with compression bandaging using any number of systems results in healing in approximately 60% to 70% of patients after 4 to 6 months of consistent therapy.[26,66] Numerous adjunctive methods have been studied in an attempt to accelerate this healing process, including skin grafting, growth factors, living human skin equivalents, collagen matrices, platelet releasates, topical therapies, ultrasound, electrical stimulation, and other modalities. The majority of these therapeutic strategies have limited data supporting their efficacy.

Skin Grafting

Although split-thickness skin grafts have been employed for decades in an attempt to heal recalcitrant venous leg ulcers, there is little quality information supporting the benefit of this practice. There are no adequately powered randomized studies reporting the results of skin grafts versus compression therapy alone. The Cochrane Database recently reviewed the available clinical studies and concluded that further research is needed to assess whether skin grafting increases ulcer healing.[67] Although definitive evidence is lacking, some clinicians consider skin grafting in slow responding wounds or for patients with large soft tissue deficits that are able to granulate well to provide a clean healthy bed to support graft take. In a nonrandomized study of 111 patients, Jankunas demonstrated improved healing and durability with skin grafting compared with conservative therapy for large venous wounds that were present longer than 6 months, but only 65% of cases were judged to have good take of the split-thickness skin graft.[68]

For patients with large ulcers and extensive peri-ulcer lipodermatosclerosis, radical excision and free-flap tissue transfer have been described, with durable improvement in some cases.

Human Skin Equivalents

Apligraf (Organogenesis, Canton, Massachusetts) is a cultured bilayer cellular construct (BLCC) originating from neonatal foreskin. A bovine collagen lattice is used as a base to support the organization of dermal fibroblasts and epithelial cells. A layer of allogeneic keratinocytes is cultured over the fibroblast layer to form a stratified epidermis. The bilayer has a structure similar to human skin, with the absence of hair follicles or sweat glands (Fig. 115.10). The growth factors and cytokines secreted by the cellular components of BLCC include fibroblast growth factor (FGF), VEGF, PDGF, TGF-β, and multiple ILs, paralleling those secreted by healthy human skin.[69] The product requires a well-granulated wound bed in which exudate and bacterial levels have been controlled to yield positive results. The BLCC is easily applied in a clinic or operating room setting after aggressive wound débridement and hemostasis. Standard compression bandaging is then applied to maintain control of venous hypertension.

Apligraf was studied in a prospective randomized multicenter trial of 240 patients with nonhealing venous leg ulcers present for more than 1 month.[70] Patients were randomized to a standard compression bandaging regimen or compression bandaging plus BLCC. The primary study outcome measure was complete healing at 24 weeks of treatment. In the BLCC-treated group, 57% of venous leg ulcers closed at 24 weeks, compared with 40% in the control group ($P = .02$). For ulcers that had been present for more than 1 year, 47% healed at 24 weeks, compared with 19% in the control group ($P = .002$).

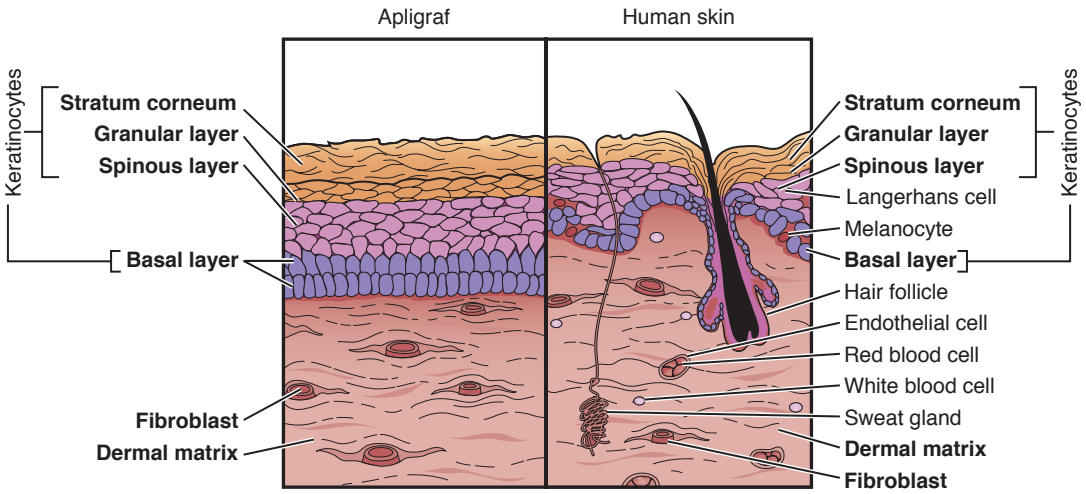

Figure 115.10 Comparison of the structure of Apligraf to human skin. (Courtesy Organogenesis Inc.)

Porcine small intestine submucosa (OASIS wound matrix, Healthpoint Ltd., Fort Worth, Texas) has been shown in a prospective RCT to accelerate healing of VLUs.[71] In a study by Mostow and colleagues, 2005 a total of 120 patients with VLUs were randomized to receive either weekly topical treatment of small intestine sub mucosa (SIS) plus compression or compression therapy alone. After 12 weeks of treatment, 55% of wounds treated with SIS healed versus 34% in the control group ($P = .0196$).

Using a large wound care-specific electronic medical record, the real-world effectiveness of BLCC and SIS for the treatment of VLUs over a 3-year period was assessed.[72] Although this method of comparison suffers from the inaccuracies of large EMR databases employed at a large number of treatment facilities, large numbers of treatment events may be captured for analysis. A comparison of 3702 VLUs treated with BLCC to 1143 treated with SIS indicated that significantly more patients treated with the BLCC achieved a healed wound. However, the overall rate of wound healing in both groups was disappointing (Fig. 115.11).

In summary, currently available adjunctive therapies for venous ulcers appear to provide only a modest benefit if used routinely to assist VLU healing. It is likely that use limited to patients with long duration wounds that are not responding well to standard treatment protocols is more cost-effective, particularly in wounds that are well prepared with good compression and little bacterial wound involvement.

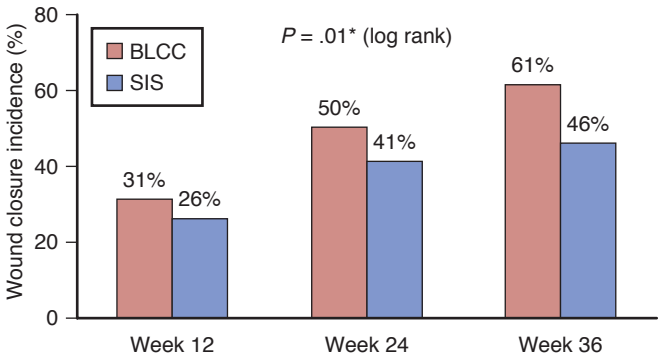

Figure 115.11 Estimated incidence of wound closure from Kaplan-Meier analysis of all available data up to 3 years. Bilayered living, cellular construct (BLCC). Apligraf, Small intestine submucosa (SIS), Oasis *P-value from a two-sided log-rank test.

DIABETIC FOOT ULCERS

See Chapter 114 for diagnostic modalities and a discussion of wound débridement, pressure offloading, and treatment of infection. The Society for Vascular Surgery also recently published comprehensive practice guidelines for the care of patients with diabetic foot ulcers in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. The reader is referred to these guidelines for additional information on optimal management of DFUs.[73]

Adjunctive Therapies to Accelerate Healing

Vitamin D

In a recent randomized clinical trial, 60 patients with Wagner grade 3 DFUs were randomized to standard wound therapy with or without supplementation of 50,000 IU of vitamin D every 2 weeks.[74] After 12 weeks of treatment, the authors reported that the vitamin D treated patients had significantly greater reduction in wound size as well as significant reductions in HbA1c, LDL, high sensitivity C-reactive protein and erythrocyte sedimentation rate. Based on this study, many clinicians believe vitamin D supplementation to be reasonable in DFU patients.

Growth Factors

Although multiple growth factors have been studied in clinical trials, to date, only PDGF has been approved by the FDA for the treatment of diabetic foot ulcers. Becaplermin (Regranex, Ortho-McNeil, Raritan, New Jersey) is a recombinant human BB isoform of PDGF suspended in a gel designed for topical application. Becaplermin is applied daily to the diabetic foot ulcer and covered with saline-moistened gauze. It has been

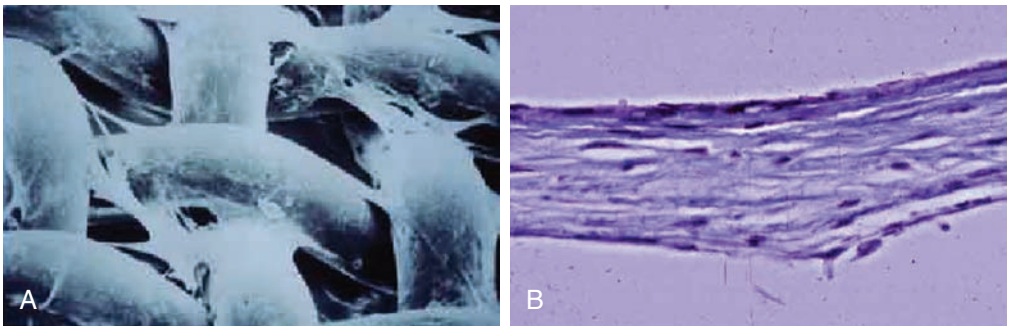

Figure 115.12 (A) Magnified view of Dermagraft showing polyglactin mesh with fibroblasts adhering to the surface. (B) Cross-section of the structure of Dermagraft with living dermal fibroblasts layered into a three-dimensional matrix. (Courtesy Advanced BioHealing, Inc.)

studied clinically in four prospective, randomized, placebo-controlled trials. In a meta-analysis of these studies, Smiell et al.[75] aggregated the 922 patients studied for analysis. Fifty percent of ulcers treated with the higher dose of becaplermin (100 mcg/g) for 20 weeks healed, compared with 36% treated with placebo gel ($P = .007$). Adverse events were rare, and the only medication-related event was local tissue sensitivity in 2%.

Kantor and Margolis[76] studied 26,599 patients from a clinical wound treatment database and reported effective wound closure at 20 weeks in 31% of those treated with standard care, compared with 43% treated with becaplermin. The incremental cost of increasing the odds of healing by 1% over standard therapy was $36.59 for becaplermin. In 2008 the FDA released a black box warning concerning the risk of fatal cancers in patients treated with becaplermin. Based on long-term follow-up studies of patients enrolled in randomized studies, there was no increased risk of malignancy in patients treated with becaplermin, but those who developed malignancies had a greater risk of dying from them.[77] This information is based on a small number of observations, so it should be interpreted with caution. It does emphasize, however, that the drug should be considered only in refractory diabetic foot ulcers failing to respond to standard therapy.

Living Tissue Substitutes

Apligraf

Described in detail earlier, Apligraf was also studied in a prospective randomized multicenter trial for the treatment of diabetic foot ulcers.[78] At 24 centers, 208 patients were treated with standard diabetic foot ulcer care (débridement, foot offloading) and saline-moistened gauze or standard diabetic foot ulcer care and Apligraf application. After 12 weeks of treatment, 56% of Apligraf-treated wounds were closed compared with 38% in the control group. The odds ratio for complete healing was 2.14 (95% confidence interval, 1.23 to 3.74). The incidence of osteomyelitis was significantly less frequent in Apligraf-treated patients (2.7%) than in controls (10.4%; $P = .04$). Ipsilateral toe or foot amputation was also significantly less frequent in the Apligraf group (6.3%) than in the control group (15.6%).

Dermagraft

Dermagraft (DG, Advanced BioHealing Inc., La Jolla, California) is an allogeneic dermal fibroblast culture derived from human neonatal foreskin samples and grown on a biodegradable scaffold.[79] The resulting three-dimensional matrix can be implanted into chronic nonhealing wounds to supply functional fibroblasts and their corresponding expressed proteins. A histologic cross-section of prepared Dermagraft is presented in Fig. 115.12. The scaffold biodegrades over a 1- to 2-week period, leaving behind only cellular components and proteins. Meticulous wound bed preparation and strict wound offloading are required for maximum benefit.

Several in vitro studies have evaluated the ability of DG to express clinically significant quantities of growth factors after cryopreservation and thawing. VEGF, PDGF-A, and insulin-like growth factor-I were all found to recover to significant levels, as measured by enzyme-linked immunosorbent assay, in wounds to which DG was applied.[80]

DG was evaluated in a single-blinded, randomized, controlled investigation in 314 patients comparing standard diabetic foot ulcer care to standard care plus a weekly application of DG for up to 8 weeks.[45] Standard care in both groups consisted of routine sharp débridement, pressure offloading, and saline-moistened gauze dressings.

Of the 314 patients enrolled, 245 evaluable patients completed the study. Results showed that treatment with DG produced a significantly greater proportion (30%) of healed ulcers compared with the control group (18%; $P = .023$). The number of ulcer-related adverse events (local wound infection, osteomyelitis, cellulitis) was significantly lower in the DG-treated patients (19%) than in the control patients (32%; $P = .007$). In a secondary analysis of risk factors related to healing, it was found that an initial ulcer size greater than 2 cm^2 was associated with a 1.5 times higher incidence of wound closure ($P = .02$).[81] Females were 2.0 times more likely to heal than males ($P = .009$). An episode of infection during the 12 weeks of treatment was associated with a 3.4 times increased risk of nonclosure ($P < .01$). Finally, patients with lower hemoglobin A_{1c} values throughout the study had significantly higher rates of wound healing with DG (Fig. 115.13).

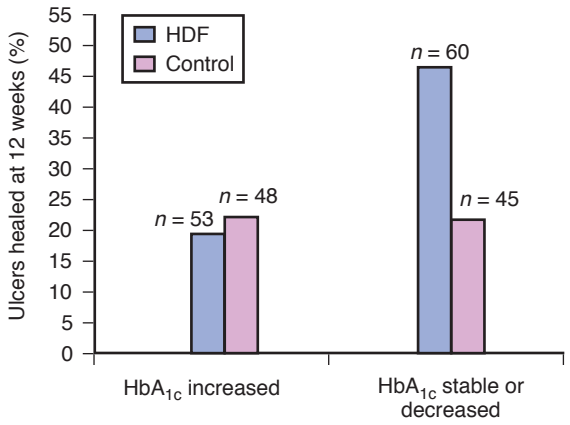

Figure 115.13 Comparison of healing rates in diabetic foot ulcers treated with standard care (control) or standard care plus Dermagraft (human-derived fibroblasts [HDF]), based on glycosylated hemoglobin A_{1c} (HbA_{1c}) levels during the 12-week study. If HbA_{1c} increased, suggesting poor glucose control, there was no difference in the healing rates in the two groups. If HbA_{1c} decreased, ulcers treated with Dermagraft healed significantly more often than did controls.

It must be stressed that DG and other active wound healing products are not substitutes for the standard principles of wound healing. If the wound is not well prepared before application of a growth factor or living tissue substitute, there is little potential for wound stimulation.

Acellular Dermal Matrix Products

Integra Dermal Regeneration Template

Integra dermal regeneration template (IDRT) is an acellular bilayer matrix designed to assist with dermal regeneration in multiple types of problem wounds. The bottom layer that is applied to the wound surface consists of a three-dimensional matrix of collagen and chondroitin-6-sulfate, a glycosaminoglycan. The top layer is a temporary layer made of silicone. This construct has been employed for years in burns, traumatic wounds, and other types of wounds with some success. The bottom layer is designed to incorporate into the wound and support tissue regeneration while the top layer provided a mechanical barrier to bacterial contamination. It is critical that the construct is applied to a clean wound that is free of bacterial that might lead to infection over time. This wound matrix has been adapted for use in diabetic foot ulcers in the outpatient clinic.

The benefit of IDRT in healing DFUs was studied in a prospective randomized study that enrolled 307 patients.[82] Complete wound closure occurred in 51% of patients treated with IDRT compared with 32% in the control group (P = .001). Assessment of quality of life indicated that patients treated with IDRT scored significantly better in physical functioning (P = .047) and bodily pain (P = .033) compared with the control group. Based on the results of this clinical trial, one of the largest prospective randomized studies of a therapy for DFUs, IDRT appears to be a useful adjunct to the care of DFUs, once excellent offloading and wound bed preparation have been achieved.

ULCERS ASSOCIATED WITH ARTERIAL INSUFFICIENCY

Patients with limb ulcers and associated arterial insufficiency should undergo diagnostic evaluation to attempt prediction of whether the ulcer can heal without revascularization. Potential studies include ABIs, toe pressures, transcutaneous oxygen/tension pressure ($tcPO_2$), and laser Doppler. These are reviewed in detail elsewhere in this text.

Local Wound Management

In general, principles of management are similar to those for diabetic foot ulcers, including pressure offloading, débridement of nonviable tissue, infection control, and moist wound healing. Close attention to the principles of wound bed preparation will maximize the wound's potential to heal, despite arterial insufficiency with success in some cases. Pressure offloading methods must be individualized, based on the specific location of the wound.

Sharp surgical débridement of nonviable or infected tissue should be performed as often as needed to maintain a clean wound bed. The primary exception is adherent eschar or dry gangrene. Most wound specialists recommend leaving this material in place (unless infected) until after revascularization is performed. The principles of moist wound healing are followed. Wounds of primarily arterial origin are typically dry, with little tissue edema or drainage. Hydrogels or similar hydrating agents should be applied to prevent desiccation of exposed layers after débridement is performed.

The need for revascularization is assessed using several variables. If the patient has severe pain at rest and is a good candidate for revascularization, this should be performed as soon as possible on an elective basis. Patients with diabetes and arterial insufficiency rarely have significant pain at rest, probably due to neuropathy. Wound size, depth, and character are all important measures. A small grade 1 ulcer on the dorsum of the foot is much more likely to heal without revascularization than is a large, complicated, deep wound on the plantar surface of the foot. The potential for healing based on noninvasive tests must be balanced with the risk of complications associated with the intervention required for revascularization. In patients in whom the risk-benefit assessment does not favor revascularization, the potential for healing should be optimized with standard wound care along with consideration of the modalities discussed next.

Pharmacologic Treatment

Pentoxifylline and Cilostazol

There is no high quality evidence suggesting that either pentoxifylline or cilostazol is able to accelerate wound healing in patients with ulcers associated with arterial insufficiency.

Prostaglandins

Prostaglandins, particularly prostaglandin E_2 and prostacyclin, in addition to their potent vasodilatory effects, can prevent

leukocyte activation and platelet aggregation. In some studies, treatment has resulted in significant improvement in patients with CLI.[83,84] However, a number of problems with prostaglandins have hindered their widespread use. Most are intravenous medications with short half-lives, requiring intravenous infusion for administration. Also, troubling side effects at clinically relevant doses, including headaches and dizziness, are frequent. Although available in other countries, no prostaglandin therapeutic agents have been approved by the FDA for the treatment of ischemic wounds.

Angiogenesis for Critical Limb Ischemia and Ischemic Wounds

Since the discovery of VEGF and techniques that allow it to be delivered to target tissue, there has been great enthusiasm for therapeutic strategies promising the development of new capillary beds to support blood supply. In numerous animal models, the transfer of VEGF to localized target tissues has resulted in angiogenesis, with the proliferation of blood vessels and increased tissue perfusion.[85] The application of this powerful technology to humans has been a long, arduous process because of concern over unintended adverse effects, such as tumor induction and the promotion of occult malignancies, resulting in accelerated growth and metastatic potential.

Local gene transfer to facilitate therapeutic angiogenesis has the theoretical advantage of producing protracted growth factor expression compared with single doses or direct applications of growth factors to wounds. Unfortunately, no angiogenic growth factor therapies have yet achieved FDA approval for use in patients with CLI and leg ulceration. Although several early phase clinical studies appeared promising, larger studies did not confirm that these therapies healed more wounds or prevented amputation. Similarly, investigations of progenitor cell therapies have also failed to demonstrate significant reduction in the incidence of amputation or improved wound healing in CLI patients. Clinical trials continue with various progenitor cell preparations in this patient population.[86,87]

Intermittent Pneumatic Compression

Numerous studies have documented the ability of various forms of intermittent pneumatic compression (IPC) to increase blood flow in ischemic limbs, suggesting that this modality may have a place in the treatment of CLI. Two general types of IPC have been described. In synchronized IPC, compression and deflation are gated to the cardiac cycle, with 55 to 80 mm Hg applied at end-diastole to maximize venous emptying. Pump decompression occurs before systole to reduce afterload and limit compression-related competition with systolic inflow to the limb.[88] Nonsynchronized IPC has been described in numerous protocols using various pressures, inflation durations, and deflation durations. Typical protocols involve an inflation pressure of 120 to 180 mm Hg, an inflation duration of 3 to 5 seconds, and a deflation time of 15 to 20 seconds. IPC of affected limbs is recommended for 2 to 4 hours daily.

There have been no direct comparisons of the beneficial effects of synchronized versus nonsynchronized IPC. Nonsynchronized IPC is generally less expensive and is more amenable to home use; this makes it attractive, given the length of therapy required in patients with CLI.

IPC reduces the edema that often occurs in patients with CLI. This, combined with improved venous emptying during IPC, may result in an increase in the arteriovenous pressure gradient in the limb. With less resistance to inflow, blood flow may increase, resulting in increased tissue perfusion, relief of rest pain, and improved ulcer healing. IPC also has been reported to increase the concentration of prostacyclin and nitric oxide in the treated limb.[89] These peripheral vasodilators in theory may stimulate improved tissue perfusion, despite the presence of large-vessel occlusive disease.

Several investigators have evaluated the hemodynamic effects of IPC on lower extremity blood flow. The velocity of blood flow in the popliteal artery increased after the initiation of IPC.[90,91] This increase was also noted in patients with significant arterial insufficiency.[92] Delis et al.[93] reported marked increases in popliteal artery blood flow during foot or calf compression, depending on the segments compressed (Fig. 115.14).

Delis et al.[94] studied 25 patients with claudication treated with nonsynchronized IPC of the foot and calf and 12 claudicants treated with an unsupervised exercise program. After 3 months of treatment, the IPC group had significant improvements in claudication distance, ABI, and mean popliteal artery blood flow. Control patients demonstrated no significant improvement. Of interest, 12 months after the cessation of IPC, the IPC group continued to demonstrate significant improvements over baseline in walking distance and ABI.

Using synchronized IPC, Vella et al.[88] reported on the treatment of 98 limbs with ulcers related to arterial insufficiency. These patients were not candidates for revascularization because of either inadequate outflow vessels or medical comorbidities. In limbs with an initial $tcPO_2$ <20 mm Hg, ulcer improvement

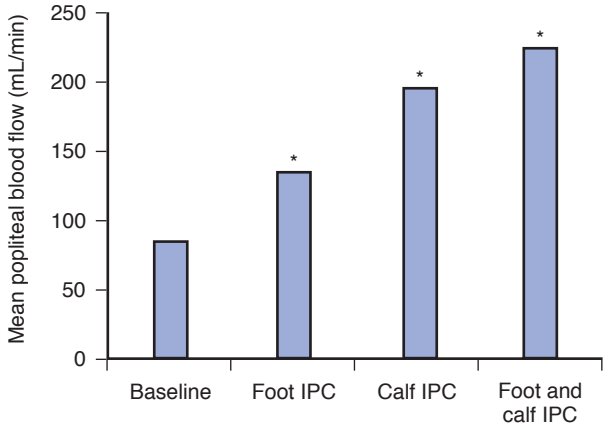

Figure 115.14 Mean popliteal artery blood flow in claudicants at baseline compared with claudicants using intermittent pneumatic compression (IPC) of various types. Each type of IPC resulted in significantly higher flows than baseline (*P < .001). (Mansbridge J, Liu K, Patch R, Symons K, Pinney E. Three-dimensional fibroblast culture implant for the treatment of diabetic foot ulcers: metabolic activity and therapeutic range. *Tissue Eng*. 1998;4:403-414.)

or healing was obtained in 19 of 29 limbs (65%); if the initial $tcPO_2$ was >20 mm Hg, 54 of 62 limbs (87%) healed or improved. From these data, the authors concluded that synchronized IPC is useful in a subset of patients with arterial insufficiency and nonhealing ulcers.

Case series of the clinical use of nonsynchronized IPC have also been published. Louridas et al.[95] reported on the use of IPC in 33 limbs with CLI, including 23 with nonhealing ulcers. Limb salvage was attained in 58%, and complete healing occurred in 26%. Chronic renal failure was a significant negative risk factor, with limb salvage attained in 86% of patients without chronic renal failure. Kavros and colleagues retrospectively compared the outcome in 24 patients with CLI and tissue loss treated with IPC compared with 24 patients treated without IPC.[96] All patients had no options for revascularization and were treated with standard wound care protocols. In the IPC treated group, 42% required amputation compared with 83% in the control group ($P < .01$).

The foregoing information is encouraging, providing a physiologic basis for IPC's positive effects in patients with arterial insufficiency and nonhealing ulcers. The question remains, however, whether the improvement in blood supply generated by this technique is sufficient to make a difference in the patient's wound-healing ability. No prospective randomized studies of IPC for ulcer healing have been performed.

Wound Management After Intervention

Management of the ischemic limb ulcer after revascularization is critical, because of the changes in the local environment that occur with a new blood supply. Limb edema after surgical bypass is common and may be severe, resulting in a breakdown of surgical incisions and worsening of ulcerated areas. Developing a strategy to combat limb edema is important in each patient, particularly at the time of hospital discharge, as the transition to the home environment may not be amenable to constant limb elevation and compression.

IPC devices are very useful for limiting limb edema in the early postoperative period. For patients with bypass grafts ending at the popliteal level, below-knee IPC for several hours a day reduces edema significantly. When the distal anastomosis extends to the lower leg or ankle, a pedal compression boot can be used, with reasonably good results.

Patients with dry gangrene of the digits or eschar over the heel or other ulcerated areas must be followed closely after revascularization. When the blood supply is successfully restored, these areas tend to heal under the eschar, and the eschar begins to separate at the interface between healing and necrotic tissue. Unfortunately, this is a favorable environment for infection, and it is common for these wounds to develop an increased bacterial load and frank infection if frequent débridement and careful wound management are not continued. Many surgeons prefer to amputate necrotic digits and perform wide débridement of eschar a few days after the arterial supply is improved to prevent further infection. After débridement, the remaining healthy tissue should be able to granulate, responding to standard wound-healing techniques.

SPECIALIZED TECHNIQUES

Negative-Pressure Wound Therapy

Negative-pressure wound therapy (NPWT) devices are designed to apply controlled suction to a wound bed at continuous or intermittent pressure settings to stimulate wound closure. Negative pressure can result in numerous alterations in the wound environment, including removal of excess exudate, stimulation of senescent cells, mobilization of macrophages, and stimulation of angiogenesis. NPWT has been used over uncovered bone, tendon, and other deep tissues, resulting in the clinical impression of a favorable response.

There are numerous reports in the literature concerning the use of NPWT for a wide variety of wound related conditions, including dehisced abdominal wounds, open infected sternotomy wounds, lymphorrhea, pilonidal cysts, and complex traumatic injuries. Little systematic study was available until 2005, when Armstrong and Lavery[97] published results of a prospective randomized study trial of NPWT for a specific indication. In this protocol, 162 patients with diabetic foot problems requiring partial foot amputation were randomized to standard moist wound care or NPWT after their surgical procedure. The primary outcome was complete healing after 16 weeks of treatment. In the NPWT group, 56% of wounds closed at 16 weeks, compared with 39% in the control group ($P = .04$). There was no difference in the incidence of adverse events between the two groups.

In another randomized multicenter trial, 342 patients with non-ischemic Wagner grade 2 or 3 diabetic foot ulcers were randomized to NPWT or moist wound therapy using hydrogels or alginates.[98] All patients were offloaded with devices specific to the wound location. At 16 weeks, 43% of wounds in NPWT patients were completely healed, compared with 29% in the moist therapy group ($P = .007$). No difference was noted in the incidence of infection or osteomyelitis in the two groups, but fewer secondary amputations (mostly digital) were required in NPWT-treated feet ($P = .035$).

NPWT has become a fixture in most hospitals and wound centers, and is a useful solution to some complex wound problems. However, the modality must be used carefully and with frequent evaluation to avoid complications. Bacterial colonization and biofilm generation may result in increased wound exudate that is not well managed by the NPWT system. Frank infection may occur if this problem is not identified early and treated appropriately, usually with wound culture, systemic antibiotics, and absorptive primary dressings changed frequently. Other complications include significant pain, particularly during dressing changes, and problems obtaining an adequate seal in irregularly shaped wounds.

The cost of adding NPWT to an outpatient wound treatment protocol can be significant, including the cost of device rental, wound dressings, and home nursing visits to perform dressings changes. Therefore utilization should be considered in patients with larger, more complex wounds who are more likely to benefit from therapy, and duration of use should be monitored carefully to maximize cost-efficacy.

In summary, NPWT has provided an alternative treatment modality for a wide variety of acute and chronic wounds. Although randomized studies are not available, it appears to be useful for complex traumatic and infected or dehisced postoperative wounds. There are prospective randomized studies that support its use in diabetic foot ulcers and postsurgical diabetic foot wounds.[97,98] It must be remembered that this modality is not a cure-all, and it must be used with a specific goal in mind rather than routinely for every wound.

Hyperbaric Oxygen

Hyperbaric oxygen (HBO) therapy involves treating the patient with 100% oxygen at elevated atmospheric pressures in a specially designed chamber (Fig. 115.15). The benefits of increasing the partial pressure of oxygen in the tissues may include improved oxygen supply, reduction of inflammation and edema, and inhibition of infection. HBO is reportedly useful in the treatment of a number of wound problems, including complex diabetic foot ulcers, osteomyelitis, necrotizing fasciitis, and the healing of tissue flaps. Typical treatment protocols for leg ulcers involve one or two treatments daily for a total of 20 to 40 treatments.[99]

HBO has long been considered a potential treatment modality for ischemic ulcers. Oxygen can stimulate angiogenesis, enhance fibroblast and leukocyte function, and normalize cutaneous microvascular reflexes.[100,101] Clinically HBO has been demonstrated to improve $tcPO_2$ in the limbs of some patients with ischemic ulcers. Significant side effects of treatment are uncommon but may be severe, including barotraumatic otitis, hyperoxic seizures, and pneumothorax.

The use of HBO in ischemic leg ulcers remains controversial. This is due to the difficulty in conducting large randomized blinded studies with HBO. The majority of the studies are small and not well controlled, leaving significant doubt concerning the validity of the findings.

Figure 115.15 Monoplace hyperbaric oxygen chamber.

Faglia and colleagues randomized 68 patients with ischemic diabetic foot ulcers to standard foot ulcer treatment with or without HBO therapy.[102] Amputation was required in 33% of the control group, compared with 8.6% of the HBO treated group ($P = .016$).

Abidia et al.[103] randomly assigned 18 patients with nonhealing ischemic diabetic limb ulcers to 100% oxygen or air at 2.4 atmospheres for 90 minutes in a hyperbaric chamber daily. In this double-blinded study, both groups received 30 sessions, after which the outcome was measured. In the oxygen group, five of eight ulcers were closed completely, compared with one of eight in the control group ($P = .027$).

In 2004, the Cochrane Collaborative reviewed HBO therapy for chronic wounds and concluded that HBO reduces the risk of amputation for patients with diabetic foot ulcers and increases the chance of healing at 1 year.[104] However, it noted that these findings were based on small, underpowered studies, and that further randomized studies are greatly needed to clarify the benefits of this costly therapy.

Since the publication of the aforementioned Cochrane review, several studies have focused on the use of $tcPO_2$ to select patients for HBO treatment. Grolman et al.[105] measured $tcPO_2$ in the ischemic limb of 36 patients breathing room air, followed by 100% oxygen. They found that a greater than 10 mm Hg increase in $tcPO_2$ in the ischemic foot was associated with a healing rate of 70%, compared with a healing rate of 11% in those with an increase of less than 10 mm Hg. Others have reported that the improvement in foot $tcPO_2$ obtained during a trial session of HBO is also predictive of wound healing.[106]

Recently, another study randomized 107 patients with Wagner grade 2–4 diabetic foot ulcers to comprehensive wound care with or without HBO therapy.[107] After 30 treatment sessions, the incidence of wound healing and freedom from criteria requiring amputation were assessed by a blinded vascular surgeon. Criteria for major amputation were met in 13 of 54 patients in the sham group and 11 of 49 in the HBOT group ($P = .846$). Twelve (22%) patients in the sham group and 10 (20%) in the HBOT group were healed ($P = .823$). All other indices of wound healing were also not statistically significantly different between groups.

Considerations of cost efficacy are important, given the effort and cost required to deliver HBO therapy. Patients often travel long distances for daily treatments at great cost to themselves and their families. Although protocols for the treatment of ischemic limb ulcers vary significantly, most involve a total cost of $15,000 to $40,000. In an assessment for the Canadian government, Chuck et al.[108] from the University of Alberta compared HBO and standard care for diabetic foot ulcers using a decision model and available outcome data. They found that the average yearly cost (in Canadian dollars) for HBO-treated ulcers was $40,695 compared with $49,786 for standard care. They concluded that adjunctive HBO was cost-effective compared with standard care alone.

Currently, HBO therapy, though controversial, is likely a useful option in a limited group of patients with complicated ischemic and diabetic limb ulcers. Unfortunately, it may be difficult to clearly identify patients who will benefit most from treatment. Until larger randomized studies are performed, HBO cannot be recommended as a primary treatment for patients with uncomplicated diabetic or ischemic ulcers. In selected cases, however, HBO may result in significant improvement, allowing healing of an ulcer in a limb that appeared to be destined for amputation.

Other Tissue/Matrix Products

Recently a proliferation of cellular- and/or tissue-based products have emerged, in part due to changes made in CMS coverage that have allowed reimbursement for a wide variety of human and animal based tissue products designed to assist with wound healing. These products are grouped together with living cellular constructs such as BLCC, DG, and IDRT into two buckets for reimbursement—one comprising a higher reimbursement value and the other a lower reimbursement value. This has resulted in broadly disparate products such as acellular porcine skin matrix, irradiated cadaver skin, and cryopreserved human fibroblasts receiving similar reimbursement despite different mechanisms of action and varying levels of supportive clinical data. One category that has emerged within this diverse group concerns wound therapies derived from placental membranes. The contents of the placenta have been described for decades as a source of regenerative materials to apply to problem wounds. Rich in progenitor cells, including mesenchymal stem cells (MSCs), placental tissue has been processed in varying ways to produce constructs that may be applied to nonhealing wounds. MSCs have been reported to have an important role in wound healing, reducing the proliferation of pro-inflammatory cytokines such as TNF-alpha and IFN-gamma that are believed to be upregulated in nonhealing wounds.[109] MSCs are also reported to have significant antibacterial activity and support upregulation of angiogenic growth factors.[110]

Numerous clinical preparations of placental contents are currently available for application to chronic wounds, but few have developed meaningful clinical data to support the theoretic benefits described previously. One strategy (Grafix, Osiris Therapeutics) is to cryopreserve living cells derived from the placental membrane, seed them into a three-dimensional cellular matrix, and apply these living cells to wounds to stimulate healing. This construct was studied in a prospective randomized clinical trial of 97 patients with recalcitrant DFUs, compared with standard DFU wound care.[111] At 12 weeks, 62% of the Grafix-treated wounds were healed, compared with 21% of controls ($P = .0001$). Wound infection occurred in significantly fewer patients in the Grafix group as well. To date, this is the largest reported prospective randomized study of a placental-derived therapy for treatment of chronic nonhealing wounds. Although this study is limited in power, the results are encouraging, and it is hoped that larger randomized studies will confirm its favorable results. If so, this will confirm the potential of this interesting adjunctive therapy for the treatment of chronic lower extremity ulcers.

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A complete reference list can be found online at www.expertconsult.com.

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116 CHAPTER

Podiatric Care

LEE C. ROGERS and DAVID G. ARMSTRONG

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A podiatrist is a doctor who practices medicine and surgery of the human foot and ankle. The scope of practice for podiatrists varies by state in the United States. When paired with vascular surgeons, podiatric surgeons are particularly well suited to augment the long-term medical, surgical, and functional care of the diabetic patient.

THE SPECIALTY OF PODIATRY

The history of podiatry is rich. The mention of foot specialists dates back to the Egyptians c. 1500 BC. Both Napoleon and Abraham Lincoln relied on the services of foot specialists. New York was the first state to license podiatrists in 1895. The *Journal of the American Podiatric Medical Association* was first published in 1907. One of the profession's early advocates, William M. Scholl, graduated from Illinois Medical College (now Loyola University) with an MD in 1904. His grandfather was a shoemaker in Germany, and Scholl was appalled by the lack of foot care in the United States. He invented several foot care products, resulting in the creation of a global company that was worth $77 million at the time of his death in 1968.

Education and Training

A candidate for podiatric medical school must first complete 4 years of undergraduate training. There are nine colleges of podiatric medicine in the United States, located in New York City, Philadelphia, Miami, Cleveland, Chicago, Des Moines, Phoenix, Oakland, and Los Angeles. Candidates must sit for the Medical College Admission Test (MCAT) to be considered for admission. Podiatric medical school consists of a 4-year program and includes course work in the basic sciences and clinical medicine. Graduates receive the Doctor of Podiatric Medicine (DPM) degree. All states require graduates to complete a residency in order to practice. Podiatric residencies are 3 years long and are accredited by the Council on Podiatric Medical Education. Some podiatrists complete additional fellowship training in diabetic limb salvage, trauma and reconstruction,

Abstract

An increase in the prevalence of diabetes and the associated peripheral complications has required more collaboration between vascular surgeons and podiatrists to prevent limb losses. Podiatric education, training, and experience is different, but no dissimilar to that of allopathic or osteopathic pathways. Limb salvage teams that include podiatrists and vascular surgeons have been successful at reducing amputations.

Keywords

Podiatry
diabetic foot
Charcot foot
limb salvage team

pediatrics, infectious disease, or research. The American Board of Podiatric Medicine now certifies podiatrists who meet certain qualifications and pass an examination in "amputation prevention."

Scope of Practice

The scope of practice for podiatric medicine is determined by state law, which accounts for geographic variations in practice. In most states a podiatrist can complete a history and physical examination, order laboratory work or imaging, and deal with a broad range of medical conditions and their treatment. Podiatrists are often allowed to perform partial foot amputations; in a few states they can perform below-the-knee amputations. In many states, podiatrists can harvest their own autologous grafts from areas proximal to the ankle if the graft is to be applied to the foot or ankle, and they can supervise the delivery of hyperbaric oxygen treatments. Privileges to perform what is within a podiatrist's scope of practice are up to each facility and its medical staff.

In practice, the podiatrist and the vascular surgeon often share patients. Podiatrists are trained to perform a clinical peripheral vascular examination and often order and interpret noninvasive vascular studies. They rely on the vascular surgeon for the treatment of impaired wound healing due to ischemic disease or when a patient as a candidate for surgery has marginal or poor perfusion—a frequent occurrence in the care of the diabetic foot.

DIABETES-RELATED AMPUTATIONS

The greatest area of overlap in which podiatrists and vascular surgeons collaborate is the foot complications of diabetes and amputation prevention. Fig. 116.1 illustrates the philosophy of cross referral. The sigmoid curve represents the probability of healing based on perfusion. When a patient is referred to a multidisciplinary team, the vascular team treats wounds that are profoundly ischemic, with the goal of improving flow and pushing the wound up the curve. Conversely, when flow is adequate, the podiatry team manages wound healing, off-loading, reconstruction, and prevention. Patients falling in the middle of the curve are frequently managed by both teams.

Epidemiology

The diabetic foot ulcer (DFU) is the most common pathway to amputation. Some 84% of amputated limbs have a foot ulcer at the time of amputation.[1] Up to 25% of patients with diabetes have a foot ulcer at some time during their lives.[2] Approximately 50% of such ulcers become infected, and in 20% amputation is required.[3] About 60% of all nontraumatic amputations occur in people with diabetes.[4] Roughly 75,000 major amputations are performed on individuals with diabetes in the United States annually.[5,6] After major limb loss, the contralateral limb will develop a serious lesion in 50% of cases.[7] The 5-year adjusted mortality rate after a major limb amputation is 70%,[8,9] which is higher than the mortality rate for many cancers (Fig. 116.2). The cost of treating DFUs and performing amputations was nearly $30 billion in the United States in 2007.[10]

Etiology and Natural History

The etiology of DFUs and their contribution to lower extremity amputation is well understood. Key factors leading to the development of DFUs are peripheral neuropathy, foot deformity, and trauma.[11] Neuropathy is the major component underlying all DFUs. A patient with a loss of protective sensation does not have the "gift of pain," as the late orthopedic surgeon and medical missionary Paul Wilson Brand wrote.[12] Pain warns of

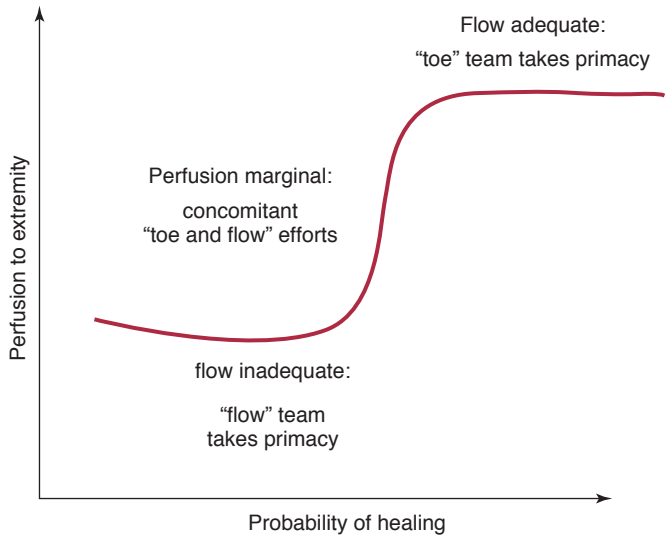

Figure 116.1 Team approach to diabetic foot care based on perfusion to the extremity.

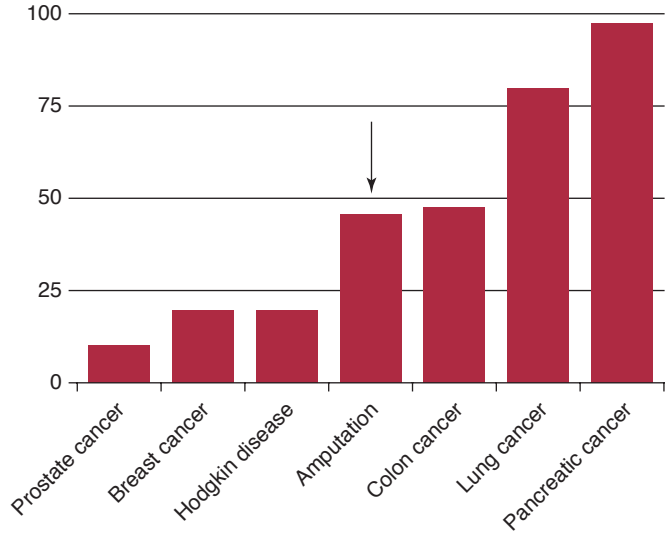

Figure 116.2 Five-year relative mortality rate for major lower extremity amputation compared with that for various cancers.[8,9]

impending tissue damage. In a sensate individual, when an area of the foot becomes tender, the gait is subconsciously altered to place less pressure on that area. Without this feedback loop, the tender area continues to receive pressure until tissue damage becomes irreversible. Trauma can be either high-pressure acute, such as that due to a puncture wound, or repetitive, due to low to moderate pressure. In an individual with peripheral sensory neuropathy, unopposed repetitive cycles of low to moderate stress first cause a callus, followed by a bulla and then a hematoma, until the skin envelope ulcerates. Foot abnormalities associated with DFUs can be visible or mechanical. Visible deformities include bunions, hammered or clawed digits, Charcot foot, or cavus foot. Mechanical deformities cannot be identified by superficial visual inspection and require an examination of joint motion.

Normal gait is divided into swing, contact, midstance, and propulsive phases. Peak pressure and the line of progression follow an orderly path from the heel, through the lateral aspect of the midfoot, coursing medially through the forefoot under the metatarsal heads, and eventually the push-off of the hallux. This allows a remarkable amount of force to be dissipated over a relatively large unit area. Diabetes, limited joint mobility, and aging alter this normal process and, in the presence of peripheral neuropathy, set the stage for the development of DFUs.

Limited joint mobility is as important as deformity in predicting ulceration.[13] If the extent of ankle dorsiflexion does not exceed 10 degrees, the abnormality is termed equinus (named after horses, which walk on their toes). In patients with diabetes, the tendons, including the Achilles tendon, become glycosylated and less elastic.[14] A less elastic Achilles tendon plantarflexes (or resists dorsiflexion) and concentrates plantar pressures under the forefoot. A neuropathic patient with ankle equinus has a risk ratio of 2.3 for developing a forefoot ulcer.[15] The most common location of a DFU is under the hallux.[16] Limited dorsiflexion at the first metatarsophalangeal joint (hallux limitus) increases plantar pressure under the distal hallux during toe-off. The hallux should normally be able to dorsiflex more than 45 degrees. Degenerative joint disease at this location is also common in people without diabetes, but the presence of pain prevents ulceration and causes them to change their gait and seek treatment. Hallux limitus in the presence of neuropathy has an associated risk ratio of 4.6 for ulceration.[15]

Foot ulceration is the main risk factor for limb loss in patients with diabetes.[1] The natural history of diabetes-related lower extremity amputation can be described as a staircase (Fig. 116.3). The first step is the diagnosis of diabetes, followed by the onset of neuropathy. If an ulcer occurs, it may be complicated by peripheral artery disease, which slows healing. The coup de grace is most often an ascending infection, leading to an urgent need for amputation. There are interventions to prevent each advancing "step" and, ultimately, to prevent major amputation. It is imperative that the ulcerated diabetic foot be free from infection and have adequate perfusion in order to heal in a timely fashion. If one can heal a DFU or at least prevent it from becoming infected, most amputations can be avoided.

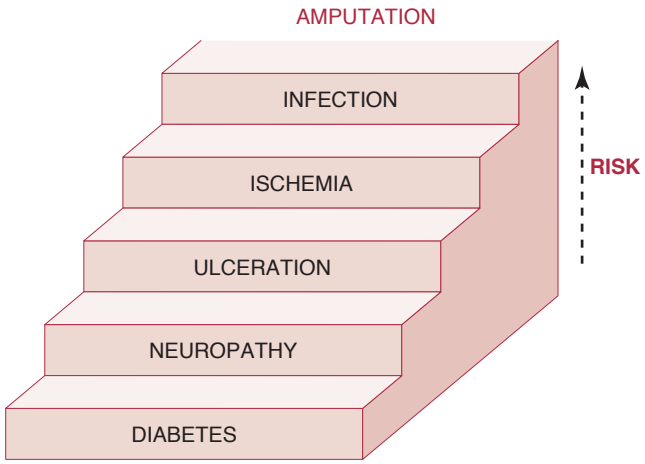

Figure 116.3 Common natural history of major lower extremity amputation. Each step in this "stairway to amputation" is a target for intervention to prevent the escalation to amputation.

Preventive Strategies

Podiatric Care

The education, training, and experience of a podiatrist can improve outcomes and reduce costs. A Duke University study of over 230,000 Medicare beneficiaries found that if a patient had visited a podiatrist in the year prior to developing a foot complication, his or her overall risk was reduced. Patients were 31% less likely to develop a foot ulcer and 77% less likely to develop cellulitis or Charcot foot when compared to visiting another health professional.[17] Another study found that patients who were under the care of a podiatrist had a 29% reduced risk of amputation and a 24% reduced risk of hospitalization, saving the insurer an average of $19,686.[18]

Team Approach

An effective means of amputation prevention is the formation of a multidisciplinary diabetic foot care team. The International Diabetes Federation has decreed that more than 85% of diabetes-related amputations are preventable and that this measure is attainable when podiatrists and vascular surgeons are partnered in cohesive teams.[19] A large population-based observational study reported a 69% reduction in the diabetes-related amputation rate over 5 years after the implementation of better organized foot care.[20] Our group was able to reduce amputations by 72% over 2 years by implementing a team concept for limb salvage that included both podiatrists and vascular surgeons.[21] Another study found that a multidisciplinary team consisting of physicians, podiatrists, and nurses led to a 51% reduction in ulceration in a high-risk population (previous ulcer history) over a 2-year period.[22]

Some 77% of the foot-related costs of a patient with diabetes are attributable to inpatient stays. Cohesive teams that follow guidelines can have an impact on the inpatient management of the patient with a complicated lower extremity. Wukich led a team of experts from the American Diabetes Association to create inpatient management guidelines[23] based on an outline developed by Fitzgerald and coworkers who identified seven

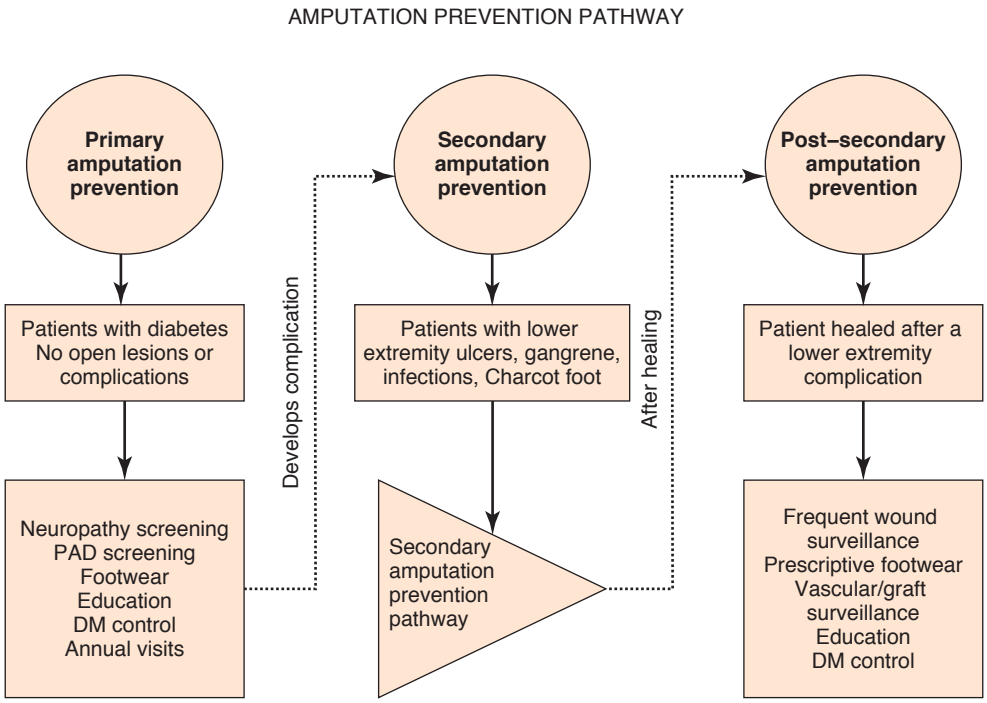

Figure 116.4 The three progressive categories of diabetic amputation prevention. *DM*, Diabetes mellitus; *PAD,* peripheral artery disease.

essential skills for limb salvage to be used by a "diabetic rapid response acute foot team."[24]

The prevention of amputations can be placed in three broad categories: primary prevention, secondary prevention, and post–secondary prevention (Fig. 116.4).

Primary Amputation Prevention

Patients in primary prevention have diabetes with or without neuropathy or mild peripheral artery disease but no open lesions or major lower extremity complications. These patients require neuropathy screening, peripheral artery disease (PAD) screening, special footwear, education, diabetes control, and annual visits for comprehensive diabetic foot exams. The primary focus in this category is to prevent lower extremity complications such as a DFU.

Neuropathy

The diagnosis of neuropathy is generally made by history and clinical exam. Neurophysiologic testing and skin biopsies to determine nerve fiber density can confirm the diagnosis. As many as 10% of patients with diabetes and neuropathy have a cause other than diabetes for their neuropathy[25]; therefore, it is prudent to seek alternate causes before making the diagnosis.[26] The Semmes-Weinstein monofilament,[27] Ipswich touch test,[28] and electronic tuning fork[29] are commonly used screening tools to determine if there is loss of protective sensation (LOPS), a more advanced neuropathy placing the patient at risk for foot ulcers.

Neuropathy can be reduced or delayed by precise glucose control. Both the Diabetes Control and Complications Trial[30] (type 1 diabetes) and the United Kingdom Prospective Diabetes Study[31] (type 2 diabetes) showed a reduction or delay in the onset of peripheral neuropathy when glucose was precisely controlled. However, there is no high-quality evidence that any treatment can *reverse* diabetic neuropathy. Some have proposed that it can be reversed by means of peripheral nerve decompression. Proponents of this approach generally cite trials that are poorly designed or use unaccepted diagnostic methods to demonstrate the restoration of sensation.[32] A position statement from the American Academy of Neurology cautioned against the use of this invasive procedure in the absence of sound evidence which are based on misconceptions regarding the pathophysiology of diabetic neuropathy.[33] Other methods have not proved effective. A double-blinded randomized controlled trial showed that monochromatic infrared light had no effect on peripheral sensory neuropathy.[34] Both alpha lipoic acid and aldose reductase inhibitors have been evaluated in well-designed trials for sensory neuropathy, with mixed results.[35,36] Additional trials are needed to determine whether the potential benefit of these treatments can translate into a restoration of sensation significant enough to reduce the incidence of DFUs. There have been single trials investigating B vitamins, magnesium, zinc, methylcobalamin, and vitamin E, but no consensus has been reached on their effectiveness.

Pressure Reduction

In individuals who already have sensory neuropathy, the focus should be on reducing areas of high plantar pressure and preventing trauma. Pressure reduction can include internal (surgical) and external (braces and shoes) approaches. Surgical reduction of pressure to heal or prevent DFUs is reviewed later in this chapter.

External pressure off-loading consists of the use of custom and noncustom devices and shoes. Abundant evidence proves that custom insoles and footwear reduce plantar pressure in diabetic patients with neuropathy.[37,38] Translating these data into clinical practice has been difficult, however. Custom-molded diabetic shoes reduced the rate of DFUs by 53% in one trial.[39] Another study showed little effect, but the control group in that study also received shoes (noncustom).[40] Shoes can prevent trauma, but proper patient education is required to ensure compliance. Such shoes should be worn at all times, including during ambulation at home.

Injection of silicone as a tissue filler to reduce pressure under bony prominences has been used with clinical success.[41] Our group has studied the injection of poly-L-lactic acid (Sculptra) to reduce pressure in areas of preulceration. The effect is determined by dynamic computerized peak plantar pressure and ultrasonic measurements of tissue thickness (unpublished data).

The home measurement of skin temperature has the most robust data of any prevention strategy. An increase in temperature is one of the cardinal signs of inflammation. Tissue inflammation increases the local temperature before dermal breakdown and can warn a patient of impending ulceration. Three randomized controlled trials have shown a reduction in the incidence of DFUs by 73% through the use of routine foot temperature monitoring.[42-45] Further study has been completed using a smart temperature-sensing mat, which was found to predict ulcers 31 days in advance (R.G. Frykberg and D.G. Armstrong, unpublished data). Thermometry as a preventive strategy is frequently not covered by payers; this is unfortunate in view of the considerable short-term financial benefit that may accrue from the prevention of DFUs.

Secondary Amputation Prevention

Once a patient develops a major complication such as a DFU, Charcot foot, gangrene, or infection, he or she is at risk for amputation; thus secondary prevention is necessary, as presented in Fig. 116.5.

Infection

First and most urgently, the diabetic foot must be inspected for signs of infection; if present, it must be managed appropriately. The diagnosis of diabetic foot infection is based primarily on the clinical presentation. Signs of infection include purulence, erythema, edema, and malodor. Because persons with diabetes may have a blunted immune response, laboratory testing should not be relied on to establish the diagnosis of infection; leukocytosis is present in only 46% of diabetic patients with moderate to severe foot infections.[46]

The Infectious Diseases Society of America (IDSA) has updated their guidelines for the diagnosis and classification of diabetic foot infection on the basis of clinical signs and symptoms (Table 116.1).[47] The IDSA divides infections into four categories: uninfected, mild, moderate, and severe. This classification system has been validated and is a good clinical predictor of the outcome of diabetic foot infection; it is also a component of the Wound, Ischemia, foot Infection (SVS WIfI) threatened limb classification.[48]

Vascular Care

Once any infection has been excluded or medical and surgical treatment started, it is important to assess the perfusion of the complicated foot. Although a clinical exam is useful and necessary, it is not sufficient in itself to rule out significant ischemia. All patients with diabetic foot ulcers require further investigation, such as ankle-brachial index (ABI), toe pressures, or skin perfusion pressure.[49] Caution should be used in interpreting the ABI result, since medial calcification, common in diabetes, can produce a falsely elevated or normal result.[50,51] Therefore toe waveforms and systolic pressures are preferred. These initial tests should be part of a foot ulcer workup, since ischemia in diabetes is often silent. The treatment of diabetic peripheral artery disease and critical limb ischemia is covered in many of the chapters of this book; it is not elaborated upon here. However, it is crucial that impaired perfusion be diagnosed promptly and staged based on the SVS WIfI classification. WIfI stage 3 and especially stage 4 patients most often benefit from revascularization; therefore, these patients should be identified early and treated aggressively. Delays result in loss of tissue and reduce the opportunity for salvage.[52,53]

Wound Care

Wound care has become exceedingly complex. However, by adhering to the important basic principles of wound inspection, ongoing reassessment, debridement, and the promotion of tissue substructure and granulation tissue as well as by applying a variety of closure techniques, healing can be achieved in most patients and accelerated in many.

Once infection and vascular insufficiency have been managed, a purely neuropathic wound should heal in a timely fashion with good wound care and off-loading. DFUs respond to debridement, promotion of granulation tissue, and closure. The modalities to achieve each of these treatment goals are displayed in Fig. 116.6.

Debridement removes devitalized tissue, bioburden, and senescent cells and promotes healing through bleeding. By debriding a wound, one transforms a chronic, slowly healing wound into one that is healthier and in a more acute state.[54] In debriding a wound, it is important to remove all necrotic and nonviable tissue. The surgeon should not be concerned about the defect caused by the initial debridement because the removal of such tissue is essential if closure is to be attained. Most wounds require serial debridements. Cardinal and coworkers found that DFUs that were debrided at each visit had a significantly greater chance of healing within 12 weeks than did ulcers debrided less often.[55] In a large retrospective analysis of almost 313,000 wounds, it was found that wound that were debrided on a more frequent basis (at intervals of 7 day or less) healed much faster than wounds debrided less frequently.[56]

There are five methods of wound debridement: mechanical, autolytic, enzymatic, surgical, and biosurgical. Mechanical debridement has fallen out of favor as a primary method; it consists of applying wet gauze dressings, allowing them to dry,

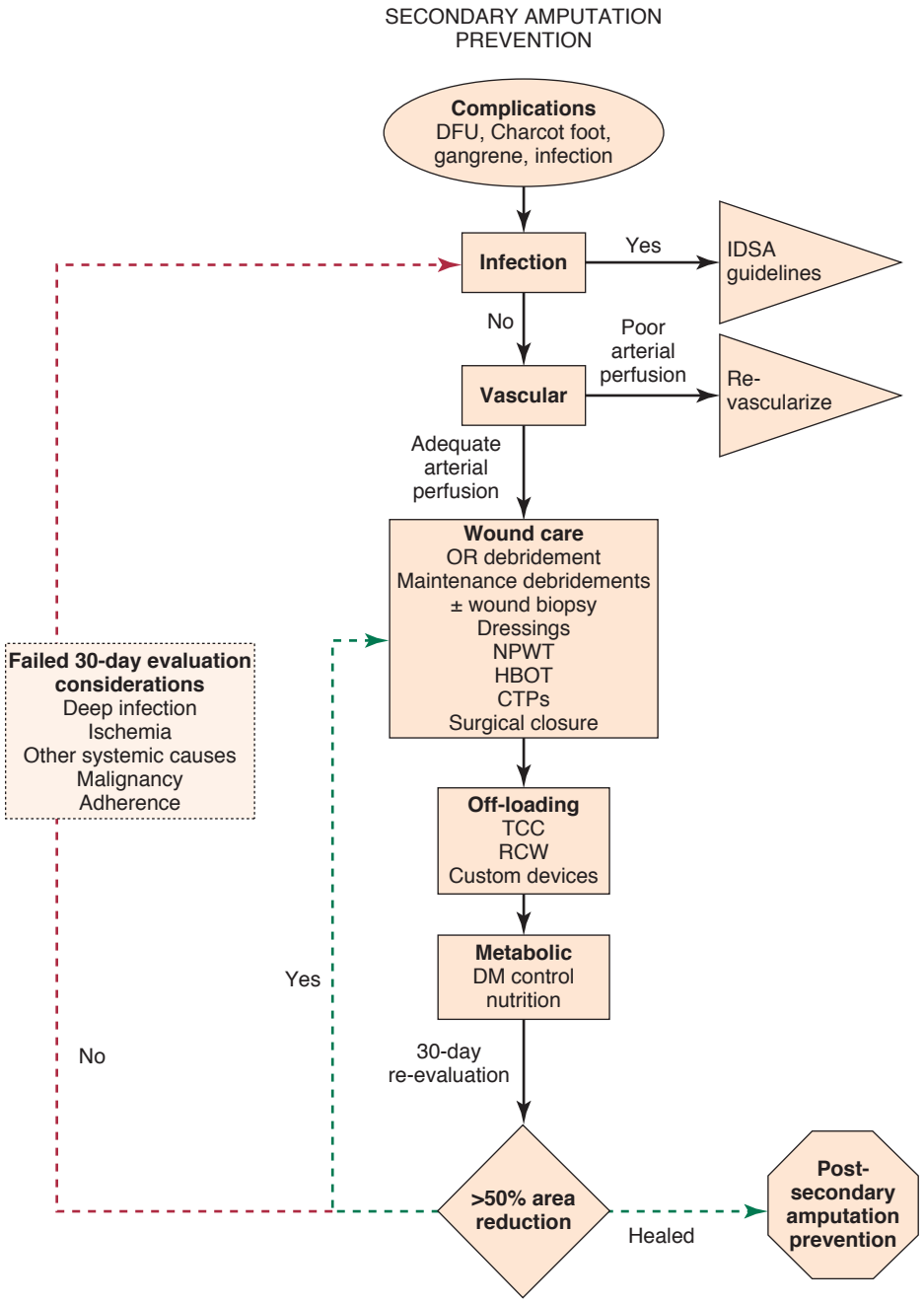

Figure 116.5 The pathway for secondary prevention of diabetes-related amputations. *CTP*, Cellular and tissue-based products; *DFU*, diabetic foot ulcer; *DM*, diabetes mellitus; *HBOT*, hyperbaric oxygen treatment; *IDSA*, Infectious Diseases Society of America; *NPWT*, negative-pressure wound therapy.

TABLE 116.1 Classification of Diabetic Foot Infections

Clinical Presentation	IDSA Infection Severity	Threatened Limb Class
Wound without purulence or inflammation	Uninfected	N/A
Presence of >2 manifestations of inflammation, cellulitis <2 cm surrounding ulcer, no systemic symptoms	Mild infection	Non–limb threatening
Infection with >2 cm of surrounding cellulitis; any infection with the presence of gangrene, abscess, deep involvement, or gas in the tissue; no systemic signs or symptoms	Moderate infection	Limb threatening
Infection as above with the presence of systemic signs or symptoms	Severe infection	Life and limb threatening

IDSA, Infectious Diseases Society of America; *N/A*, not applicable.

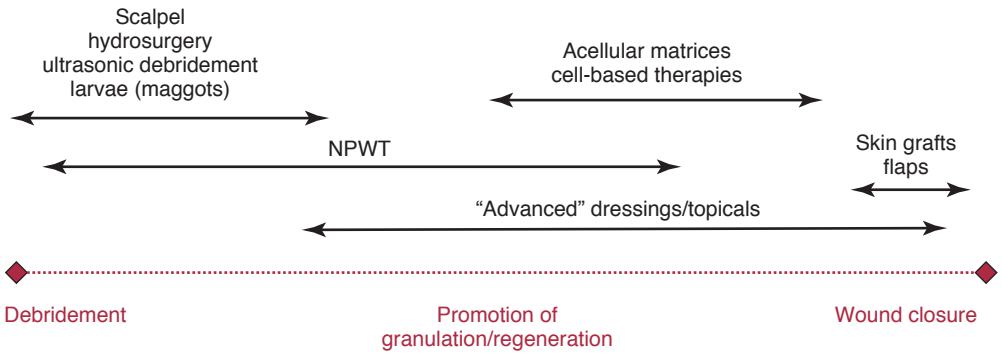

Figure 116.6 This "wound management spectrum" shows how modalities cross boundaries slightly, creating effects in multiple categories. *NPWT*, Negative-pressure wound therapy.

and then removing the dry gauze, thereby "ripping off" the surface layer (wet-to-dry dressing). Autolyic debridement is achieved by covering the wound with an occlusive dressing and allowing the wound's proteolytic enzymes to lyse the fibrotic or necrotic tissue. This is rarely recommended owing to the risk of infection and the availability of better methods. Enzymatic debridement uses a cream such as collagenase to remove devitalized tissue.

Surgical debridement is the most common and effective method.[55] It can be done simply by using a scalpel or a newer modality such as a hydroscalpel such as the Versajet (Smith & Nephew, Memphis, Tennessee), which allows for a precise depth of debridement.[57] The Versajet uses a handpiece that creates a Venturi effect and a stream of saline with a force up to 15,000 psi. It is typically performed in an operating room setting. Another recent development for wound debridement involves ultrasound. The SonicOne (Misonix, Farmingdale, New York) is a new device that combines ultrasound with an adjustable irrigation system to adequately debride a wound.

Once a wound has been thoroughly debrided, granulation tissue must form before the wound can close. This process, also called wound-bed preparation, starts by achieving an appropriate moisture balance in the wound. The principle of keeping wounds moist without maceration has been demonstrated to accelerate epithelialization.[58] Multiple dressing types and topical therapies exist (Fig. 116.7), and there is little unbiased evidence that any particular dressing is more effective than another. Most practitioners use multiple dressing types throughout the treatment cycle to adapt to the changing wound environment.

Few advances in wound healing have been as groundbreaking as negative-pressure wound therapy (NPWT). The Wound VAC (Kinetic Concepts Inc., San Antonio, Texas) is the only NPWT device with any evidence to support its use. The VAC uses a piece of foam in contact with the wound bed; it is covered with an occlusive dressing and placed under negative pressure (usually –125 mm Hg). The VAC produces high-quality granular tissue that has a characteristically rough appearance. It is essentially a wound simplification device, converting complicated (deep) wounds to simple (shallow) ones (Fig. 116.8). The VAC device can decrease the depth and area of large diabetic foot wounds, thus speeding closure.[59] In a recent randomized controlled trial evaluating its use after partial diabetic foot amputations, the VAC

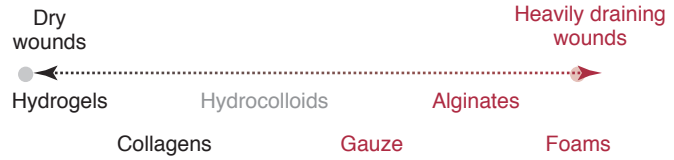

Figure 116.7 Dressings can be used to attain proper moisture balance in a wound. These dressings are categorized based on their effects on wound moisture.

was found to be more effective than the standard of care, and it limited the number of secondary amputations.[60] Because DFUs are so costly, the rapid response provided by the VAC lowers the cost of care delivered to those with chronic wounds.[61] Occasionally, in shallow DFUs, it is difficult to keep the VAC foam from shearing. To prevent this, one can reduce the thickness of the foam or bridge the track pad to the dorsal foot. Once a wound becomes shallow and covered in granulation tissue, it is time to consider discontinuing the VAC and progressing to wound closure.

Growth factor therapy has been theorized to speed the healing of chronic ulcers.[62] Recombinant human platelet-derived growth factor (PDGF) is available in the United States by prescription. Original trials reported a 32% decrease in the time to complete closure when combined with good wound care.[63] PDGF therapy is expensive and should be used only by those with experience in wound care. It has no effect on fibrotic or necrotic tissue and should be applied only to a thoroughly debrided wound. Aggressive serial debridements improve outcomes.[64]

Chronic diabetic ulcers exhibit cells that are phenotypically senescent, incapable of not only mitosis but also apoptosis. These cells may be unresponsive to growth factor application. Debridement of the superficial layer of the wound bed and margins aids in removing them. Bone marrow contributes to dermal wound healing by the mobilization and peripheral circulation of progenitor cells.[65] Direct application of autologous marrow-derived stem cells topically or by periwound injection may speed this process, resulting in robust granular tissue that will accept a skin graft or substitute.[66] Others have harvested and expanded marrow-derived stem cells in culture and reapplied them to chronic ulcers with success.[67-69]

In the diabetic foot, hyperbaric oxygen treatment (HBOT) has a role in the preservation of compromised flaps (as in the case of a partial foot amputation) and failing skin grafts. There

Figure 116.8 (A) Wound with fibrotic tissue in the base before debridement. (B) After proper debridement and promotion of granulation tissue with the Wound VAC, the wound bed is prepared for closure.

have been studies showing its use in Wagner grade 3 and 4 ulcers, leading to limb salvage.[70] A meta-analysis from the Society for Vascular Surgery concluded that there is low- to moderate-quality evidence suggesting a benefit for HBOT as an adjunct to standard treatment for DFUs.[71] HBOT is not a substitute for effective revascularization.

After preparing a vascularized wound bed, wound closure should be performed as rapidly as possible to avoid complications. Wound closure can be obtained by split-thickness skin graft, plastic surgical flaps, or bioengineered tissue.

Split-thickness skin grafting is a viable, minimally invasive, and cost-effective method for covering large granular defects.[72,73] Split-thickness grafts often perform best on non–weight-bearing surfaces of the foot, including the dorsal, medial, lateral, and arch areas; however, areas of traditional plantar weight bearing may also be considered if this process is combined with additional soft tissue or bone reconstruction.[72] Although meshed grafting can reduce the rate of seroma and hematoma formation, some have shown that unmeshed grafts perform equally well.[74] Another method to improve the adherence and survival of meshed split-thickness skin grafts is the use of NPWT as a bolster dressing,[75,76] which reduces seroma and hematoma formation and shear forces. A nonadherent interface must be interposed between the foam and the graft. The negative pressure can be used continuously for 4 to 5 days after grafting; then it is discontinued and standard dressings are applied.[75]

New technology, such as the CelluTome (Acelity/KCI, San Antonio, Texas), has made it simpler to harvest suction blister epidermal grafts (SBEGs) in the clinic without the need for anesthesia. Guidelines submitted for publication suggest that SBEGs can be used for a variety of ulcer types after the wound bed is adequately prepared. A few studies have evaluated the effectiveness of SBEGs for complex lower extremity wounds,[77,78] including our own preliminary work, which showed an 83% healing rate in 25 patients without any donor site morbidity.[79]

Large soft tissue defects and wounds with exposed deep structures such as bone require more aggressive measures to obtain closure. Multiple types of soft tissue flaps can be used to manage these defects. The flaps should be based on current vascular flow and not assumed anatomic flow because patients with diabetes may have segmental or regional arterial occlusions. With fasciocutaneous flaps, the fascia and superficial tissue are rotated into place to cover a defect. One of the more common fasciocutaneous flaps performed in the diabetic foot is a medial plantar artery flap, which can be rotated laterally to cover a subcuboid ulcer or proximally to cover a plantar calcaneal defect. The toe fillet flap can be used to cover submetatarsal head ulcers, but it requires the sacrifice of a digit.[80] For plantar central metatarsal head ulcerations, the attached toe can be filleted with a central plantar incision, the nail removed, and the skin advanced in a plantar direction to cover the ulcer site. In rare cases, the hallux may be sacrificed; however, this can have a deleterious impact on gait and plantar pressure. In these cases, the incision is made laterally between the dorsal and plantar digital neurovascular bundles; the flap is then lifted from the bone and advanced laterally (Fig. 116.9). Muscle flaps are used to cover exposed bone, such as the extensor digitorum brevis flap or the abductor hallucis (and digiti minimi) flap. The exposed muscle can be covered with a split-thickness skin graft. Free flaps involve the autotransplantation of a vascularized myocutaneous area to the recipient site and microvascular reanastomosis.[81]

In the case of shallow wounds without exposed deep structures, cellular and tissue-based products (CTPs) are viable options. Some tissues—such as Apligraf and Dermagraft (Organogenesis, Canton, Massachusetts)—are living and made from human dermal cells. Apligraf has been studied extensively and is approved by the US Food and Drug Administration (FDA) for use in DFUs and venous leg ulcers. It has a shelf life of approximately 10 days. It must be secured to the wound

Figure 116.9 Toe fillet flap of the hallux is lifted from the underlying bone. The incision is made laterally, and the soft tissue is lifted full thickness from the periosteum to ensure that the digital arteries are captured in the flap.

with sutures or another type of anchor. In a large multicenter trial, weekly applications (up to five) resulted in a 63% healing rate, compared with 38% among controls at 12 weeks.[82] Dermagraft (Advanced BioHealing, Inc., La Jolla, California) is a single layer consisting of living fibroblasts on an absorbable mesh that is FDA-approved for DFUs. It is cryopreserved and has a shelf life of 90 days. After thawing, it is applied to the ulcer and secured with a dressing. It is applied weekly for up to 8 weeks.[83] In a randomized controlled trial, Dermagraft resulted in a 30% healing rate over 12 weeks, compared with 18% in the control group. Dermagraft was also associated with a lower rate of ulcer-related adverse events.[84]

However, at the time of this writing, the living dermal-based CTPs have given way in the DFU market to amniotic membrane-based tissues. Studies have shown high healing rates with Epifix[85,86] (MiMedx, Marietta, Georgia) and Grafix[87] (Osiris, Columbia, Maryland). These tissues may not heal by engraftment, as originally thought, but rather by providing abundant growth factors to the wound, thus speeding granulation and epithelialization. In addition to good efficacy, amniotic tissues cost much less than the dermal-based tissues in a per-treatment analysis.[88] Bundled payments are creating pressure on providers to be more cost-conscious, leading to a faster adoption curve for amniotic tissues. Since amniotic tissues do not create an immune response risking host rejection, they have also found a place in the management of wounds with exposed deeper structures, such as tendon or bone.[89]

Mechanical Off-Loading

Effective pressure reduction is the cornerstone of treatment for DFUs. Repetitive trauma and pressure on the wound bed are two of the primary reasons for ulcer persistence.[90] Excessive plantar pressure and shear forces prevent the formation of adequate granulation tissue and result in undermining and hyperkeratotic tissue. The total-contact cast (TCC) has been shown to be the best practice for off-loading the ulcerated foot, and a consensus document published in the *Journal of the American Podiatric Medical Association* supports its use for all

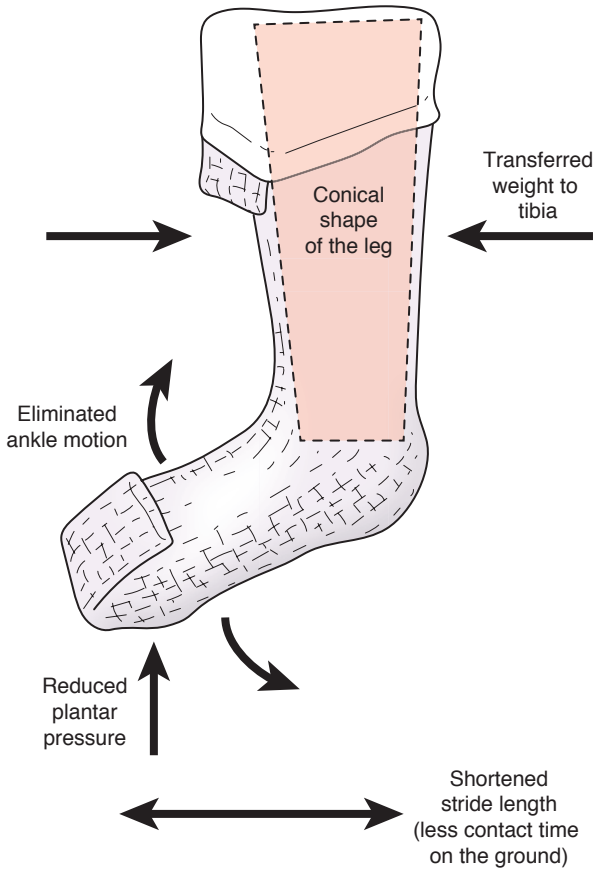

Figure 116.10 Image of a total contact cast (TCC) and the main principles by which it works.

appropriate plantar DFUs (Fig. 116.10).[91] However, the TCC is not standard practice, even in wound care centers.[92,93] The obstacles to use of TCC are multifactorial, consisting of provider-related barriers, patient-related barriers, and system-related barriers. The barriers and suggested solutions are presented in Table 116.2. Since the barriers are not often addressed, the use of noncustom off-the-shelf devices has become an alternative. In the laboratory, removable cast-walkers (RCWs) off-load the plantar foot as well as the TCC does, and they do so better than postoperative shoes and half shoes.[94] In clinical practice, however, TCCs are better at healing ulcers. This is explained by the removable nature of RCWs. Armstrong and colleagues concealed pedometers inside RCWs and also gave the same patients pedometers to wear on their hips.[95] Subjects were instructed to use the RCWs at all times while ambulating. The investigators found a significant discordance between the hip and RCW pedometers, indicating that the patients were not compliant with instructions to wear their off-loading devices at all times and suggested that improved outcomes would be achieved with a nonremovable device. The instant TCC (iTCC) is a removable walking cast-boot rendered nonremovable by applying a layer of adhesive bandage, plaster, or fiberglass. The iTCC is an effective, easy-to-use off-loading device that improves patient compliance.[96] The Society for Vascular Surgery recently published guidelines for off-loading the DFU which strongly recommend either a TCC or a fixed ankle RCW.[97]

TABLE 116.2 Barriers and Solutions to Usage of a Total Contact Cast

Barrier	Solution
Provider Barriers to TCC Usage	
Lack of proper training	Attend a training course or designate a trained staff member to apply
Timidity due to history of complications	Education about risks and benefits and improve training
Time for application	Enhance training or designate a staff member to apply
Misunderstanding of billing or global	Increase awareness of billing guidelines
Patient Barriers to TCC Usage	
Lack of desire to be in a cast	Patient education of the benefits of casting, including shorter healing time and cost
Claustrophobia	Psychologic counseling or medication
Driving with right extremity cast	Designate a family member or friend to drive, use a ride-share program
Fear of falling	Prescribe a gait aid, order physical therapy, counsel about common home environment risks
Process Barriers to TCC Usage	
Clinic/staff time for application	Improve clinic process by designating a trained staff person to apply casts, place patients in hallway or waiting area while cast dries, use a faster drying material
Misunderstanding of billing or global	Increase awareness of billing guidelines
Space to store the casts	Use cast kits to take less space and keep material in one place
Use in conjunction with HBOT	Remove cast after HBOT treatment and reapply, allowing almost 24 h prior to the next treatment

HBOT, Hyperbaric oxygen therapy; *TCC*, total contact cast.

Surgical Off-Loading

Surgical off-loading involves either an exostectomy to remove a plantar prominence or joint reconstruction to lower peak plantar pressure distal to the joint. Plantar hallux ulcers in the presence of hallux limitus respond well to a base resection of the hallux proximal phalanx (Keller arthroplasty; Fig. 116.11). This operation improves dorsiflexion and reduces plantar pressure on the distal hallux during toe-off.[98] Plantar forefoot ulcers can heal faster when a tendon of Achilles lengthening (TAL) is performed.[99] The standard TAL is accomplished through three stab incisions, posing minimal surgical risk (Fig. 116.12). Although this "lengthening" might be considered more of a "weakening" of the posterior muscle group, it results in muscle-tendon balancing and reduces forefoot pressures. This relatively short-lived pressure reduction can lead to ulcer healing and prevent recurrence (Fig. 116.13).[100] Possible complications of this procedure include Achilles tendon rupture, calcaneal gait (increased weight-bearing time on the calcaneus), and heel ulcer, which can lead to amputation in rare instances.

In a foot that demonstrates both equinus and varus—that is, the foot is inverted and pressure is placed on the plantar or lateral fifth metatarsal area—an additional tendon procedure might be of benefit. The tibialis anterior tendon transfer is performed through three anterior incisions. The tendon is transected from its normal insertion on the medial cuneiform and transposed laterally into the lateral cuneiform or cuboid; it is usually secured with a bone anchor. This eliminates the forces that pull up on the medial midfoot, transferring pressure laterally. The new function of the tibialis anterior is a more central dorsiflexory action.

With a single plantar metatarsal ulcer and no equinus, one might consider a metatarsal head resection. This procedure is commonly performed when osteomyelitis is present in the metatarsal head from a chronic ulcer tracking to bone. The incision is made dorsally over the metatarsophalangeal joint, and the head is removed by osteotomy of the neck of the metatarsal. Occasionally, when there are multiple foci of pressure or ulcerations under plantar metatarsal heads, a panmetatarsal head resection is indicated, which can significantly reduce plantar forefoot pressures (Fig. 116.14).[101] The heads of metatarsals 1 through 5 are removed through multiple dorsal longitudinal incisions or through one plantar transverse incision in the sulcus, distal to the metatarsal heads. Some surgeons prefer to perform a fusion of the first metatarsophalangeal joint instead of resecting it.

In persons with normal baseline circulation (or in those who have been revascularized), there has been increased interest in performing reconstructive diabetic foot surgery. However, this approach has led to an ill-defined mélange of indications and contraindications. To address this confusion, Armstrong and Frykberg proposed classifying nonvascular diabetic foot surgery into four categories based on indications and perceived risk: elective, prophylactic, curative, and emergency. This system, which focuses on historical variables such as neuropathy, presence of ulceration, and limb-threatening infection,[102] was validated in a study we reported in 2006.[103] Designed as a cohort model, the study involved abstracting medical records from 180 patients with diabetes requiring foot surgery and assigning them equally to the four classes. There was a strong and significant trend toward increasing postoperative infection, ulceration, reulceration, and amputation with higher surgical class (Fig. 116.15).[103]

Figure 116.11 (A) Preoperative view of limited mobility of the hallux (hallux limitus) with a distal hallux ulcer. (B) Intraoperative view illustrating an improvement in dorsiflexion after resection of the base of the proximal phalanx. (C) Hallux ulcer healed within 3 weeks of surgery.

Figure 116.12 Triple-hemisection approach to Achilles tendon lengthening. The linear markings connote the outline of the left Achilles tendon medially and laterally. Two transverse stab incisions are made medially and one is made laterally, all 1 cm apart, transecting slightly more than 50% of the tendon substance. The foot is then forcibly dorsiflexed to create a sliding effect of the tendon.

Class I: Elective

Elective diabetic foot surgery is performed on a sensate (non-neuropathic) patient to reduce pain or improve function.[102] Assuming good metabolic control, these patients are at no greater risk for the development of complications than corresponding patients without diabetes.[103]

Class II: Prophylactic

Prophylactic surgery is performed to alleviate deformity in a person with neuropathy but without an open ulcer. The goal of prophylactic surgery is to reduce plantar vertical and shear stress. Armstrong and coworkers compared postoperative complications in people with and without diabetes undergoing a single hammertoe correction (arthroplasty).[104] After a follow-up period of 3 years, there were no complications in either the neuropathic diabetic patients with no history of ulceration or the nondiabetic subjects. However, those with a history of ulceration were more likely to experience a postoperative infection (14.3%). Long-term outcomes after these procedures were uniformly good, with 96.3% of patients remaining ulcer-free

Figure 116.13 (A) Preoperative view of a plantar forefoot ulcer in the presence of Achilles contracture (equinus). (B) Three weeks after Achilles lengthening, the plantar ulcer has healed.

for a mean of 3 years. In a later work, we reported a postoperative infection rate of 6.7% following class II surgery.[103]

At least 4 in 10 people with Charcot arthropathy develop an ulcer, and their risk ratio for ulceration is up to 36-fold higher than normal.[15] Those presenting with an unstable foot secondary to this condition can often achieve bony fusion and limb salvage with surgical reconstruction; however, most people with Charcot arthropathy do not require surgical intervention.[105]

Limited joint mobility in the foot is essentially equivalent to overt deformity.[13] A common example is hallux limitus, in which limited dorsiflexion of the first metatarsophalangeal joint increases pressure at the distal hallux during ambulation, specifically during toe-off. This can lead to the formation of calluses and blistering under the great toe and the subsequent development of a wound. This is a clear indication for prophylactic surgery to increase motion and thereby reduce pressure.

Class III: Curative

Curative diabetic foot surgery is designed to heal the wound and reduce the risk of reulceration.[102] Rosenblum and colleagues reported their experience with hallux interphalangeal joint arthroplasty in 45 feet for chronic neuropathic ulcers of the great toe.[106] Overall, 41 feet (91%) healed and had no evidence of recurrence in the follow-up period. The authors reported an 11% postoperative complication rate and a 4% infection rate.

Ankle equinus (<10 degrees of dorsiflexion at the ankle joint) increases plantar forefoot pressures and may increase the risk of ulceration.[107] TAL has been shown to reduce plantar forefoot pressures by a mean 27% and is beneficial in preventing ulceration.[108] Lin and associates have reported there was more rapid healing of previously recalcitrant plantar wounds with a TAL procedure as well as a lower rate of recurrence.[109] Mueller and coworkers, in a randomized controlled trial, similarly reported a trend toward lower ulcer recurrence after performing TAL.[100]

Class IV: Emergency

Emergency surgery connotes procedures performed to reduce the risk of proximal spread of an acute infection. Patients who may require revascularization must be evaluated by a vascular surgeon in the immediate perioperative period. However, drainage or damage-control debridement of a limb- or life-threatening infection should not necessarily be delayed if the time to obtain consultation will be prolonged.[102] These procedures often include partial or whole-foot amputation.

The Charcot Foot

The Charcot foot ulcer can be particularly troublesome to off-load and deserves special mention. Charcot arthropathy or neuroarthropathy is a fracture and dislocation process of the foot and ankle that occurs in patients with sensory and autonomic neuropathy. Fracture is often associated with unrecognized injury or minor trauma that might otherwise appear innocuous.[110,111] Charcot arthropathy patients classically present with a painless, hot, swollen foot. Others may present with what initially seems to be a unilateral flatfoot deformity, with the arch of the foot "suddenly" collapsing. Patients generally have excellent arterial pulses and severe sensory neuropathy. Diabetic patients with sensory neuropathy and ischemia have been reported to

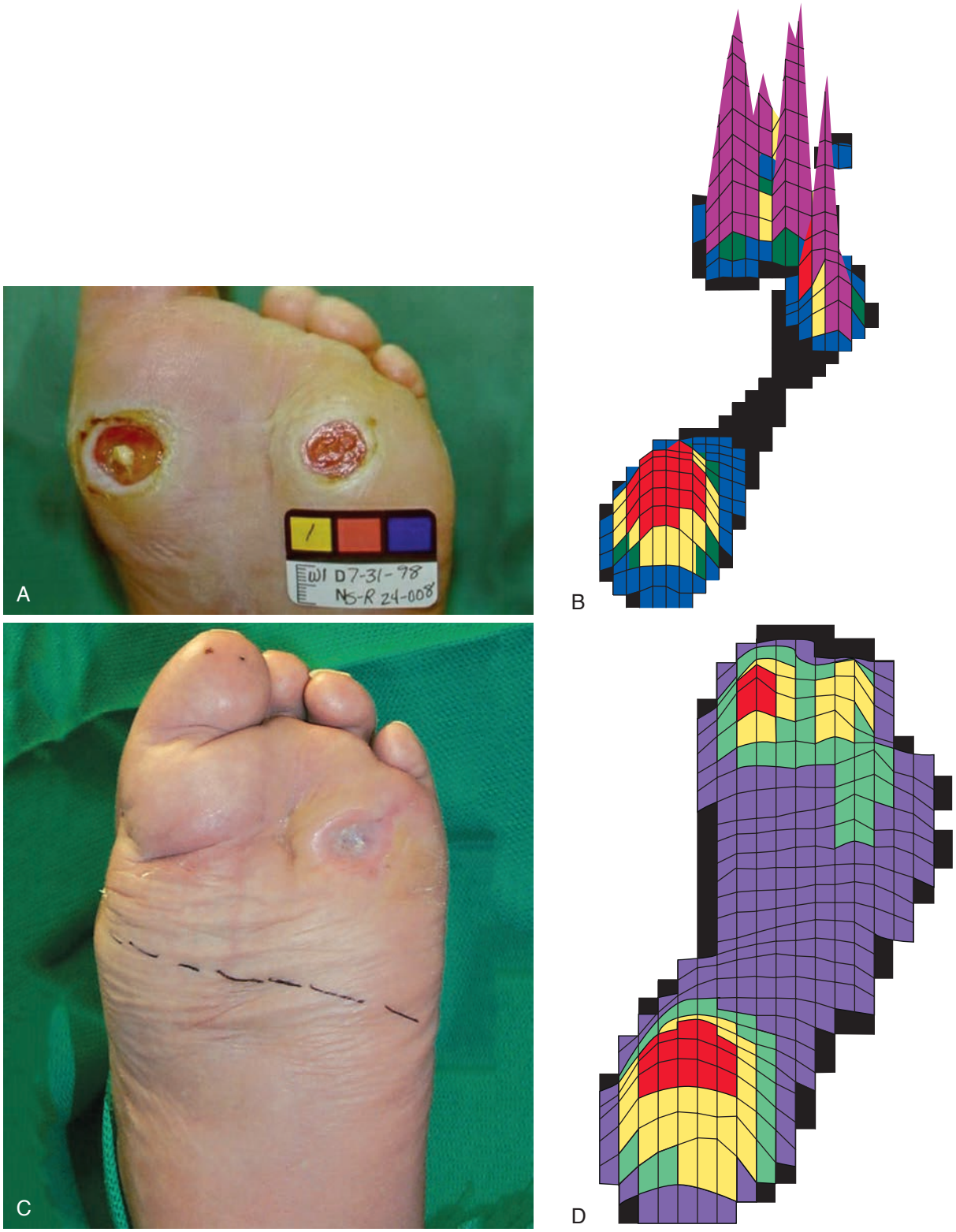

Figure 116.14 Clinical photograph (A) and peak plantar pressures (acquired using a pressure-sensitive mat) (B) of a foot with ulcers under metatarsal heads 1 and 5. After panmetatarsal head resection, the ulcers have healed (C) and the peak plantar pressures have been reduced (D). *Red color* connotes the zones of highest pressure, and the magnitude of this pressure is depicted by the height of the peaks.

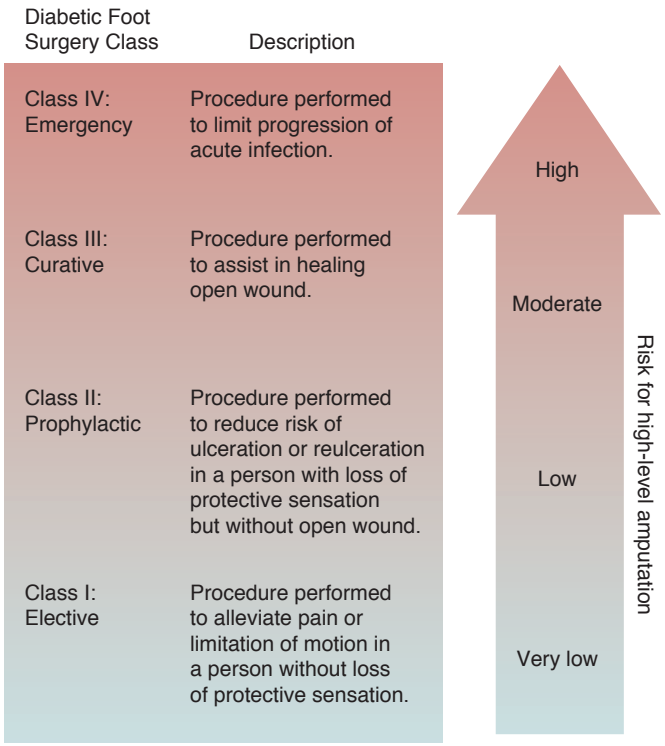

Figure 116.15 Armstrong-Frykberg classification of diabetic foot surgery. Risk of amputation increases as a function of complications and the indications for performing the given procedure.

develop Charcot arthropathy following in situ pedal bypass, after perfusion to the foot has been restored. Certain cases require surgical reconstruction and arthrodesis. In some cases, a simple exostosectomy can reduce pressure enough to heal an ulcer[112]; many others require complete foot reconstruction (Fig. 116.16).[113]

Charcot arthropathy is often misdiagnosed as an infectious process unless the treating physician has a high index of suspicion. The differential diagnosis includes infection, osteomyelitis, deep venous thrombosis, posterior tibialis tendon dysfunction, and even bone tumor. Imaging studies can be misleading, especially early in the course of the disease. Plain film radiographs often show periosteal elevation, multiple fractures, and, in some instances, osteopenia that may be misinterpreted as osteomyelitis by an inexperienced radiologist or surgeon. Many patients are treated for osteomyelitis even though they have never had a wound or injury. Bone scanning and magnetic resonance imaging are usually not reliable for differentiating bone infection, trauma, fracture, and postsurgical inflammation. The surgeon should have a clear diagnosis of bone infection before planning an amputation, especially in the absence of a wound. A bone biopsy is the "gold standard" to diagnose bone infection. A Jamshidi needle used under fluoroscopy permits the surgeon to obtain a bone specimen for a definitive diagnosis and minimizes the ambiguity associated with more expensive imaging techniques.

Figure 116.16 (A) Plantar diabetic foot ulcer under a Charcot foot deformity. (B) Healing of the ulcer 12 weeks after a midfoot reconstruction, medial plantar artery flap, and split-thickness skin grafting.

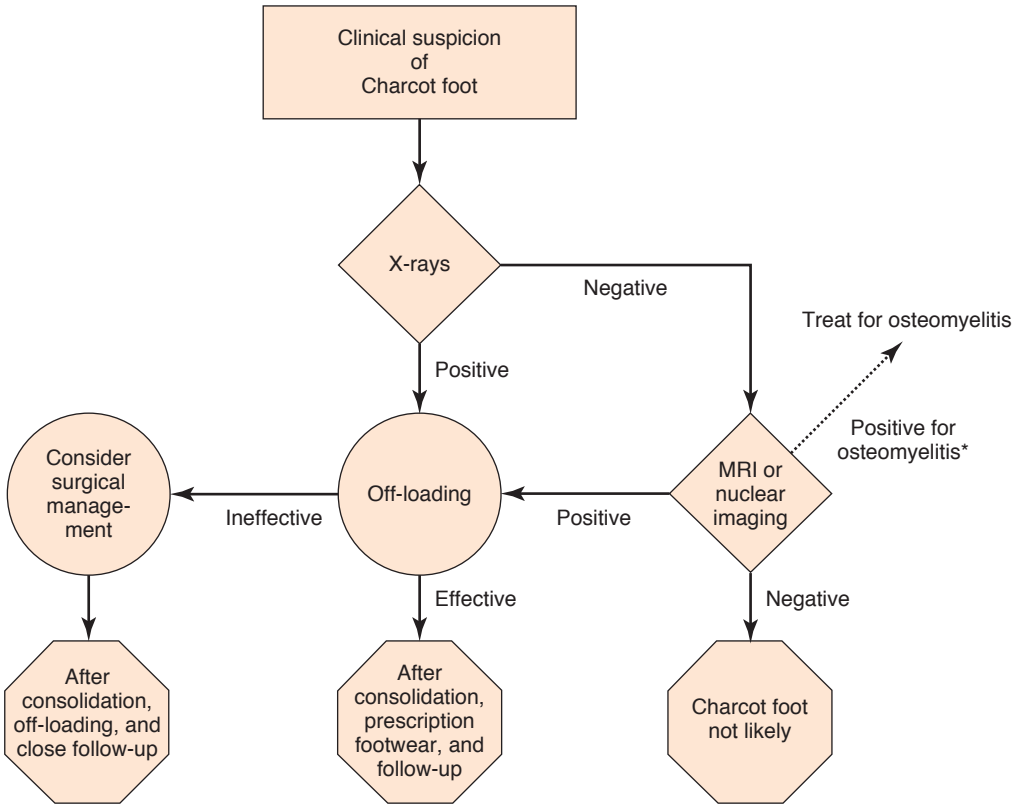

Figure 116.17 The Charcot Foot Joint Task Force basic treatment algorithm. (Reprinted with permission from Rogers LC, Frykberg RG, Armstrong DG, et al. The Charcot foot in diabetes. *J Am Podiatr Med Assoc.* 2011;101(5):437-446.)

The midfoot is the most common site of a Charcot fracture. The result is often a convex arch, with the head of the talus and navicular bones or the cuboid projecting from the bottom of the foot; in some cases, the talus bone may be destroyed, with the weight of the extremity borne by the malleolus, which easily ulcerates. Ulcers often occur because of the abnormal pressure and shear forces created by the collapse of the arch. When these wounds fail to heal, it is usually not due to ischemia but rather to a combination of neuropathy, bony abnormality, pressure, shear, and repetitive local trauma. The treatment for both ulcers and active Charcot arthropathy is cast immobilization. Charcot fractures may take 2 to 3 times longer to heal than fractures at the same site in persons without diabetes.

The American Diabetes Association and the American Podiatric Medical Association have created a joint task force on the Charcot foot which resulted in a consensus document publication in 2011[114] and the generation of a treatment algorithm (Fig. 116.17).

Metabolic Control

Chronic hyperglycemia leads to neuropathy[30,31]; but it is also associated with delayed wound healing and increases risk of postoperative complications in foot and ankle surgery.[115-118] A comprehensive management strategy for hyperglycemia should be initiated with a short-term goal of tight glycemic control and a long-term goal of a HbA_{1c} below 7.0%. Nutrition is a frequently overlooked facet of wound care. Among 478 patients with limb-threatening DFUs, 70% were at risk for malnutrition and 15% were malnourished.[119] Patients' nutritional status had a significant influence on outcomes for limb preservation.

Post–Secondary Amputation Prevention: Diabetic Foot Remission

After resolution of a lower extremity complication, patients are "in remission."[120] We find this an appropriate description and one that helps to convey the ongoing risk to patients, similar to cancer. Not only is the all-cause 5-year relative mortality rate high for those with diabetic lower extremity disease, but there is a high recidivism rate. Patients who heal from a DFU have 50% recurrence within 12 months.[121] After an amputation, there is also a 50% likelihood of a contralateral amputation within 2 years.[7]

The focus in the post–secondary prevention group is to prevent the recurrence of a diabetic foot complication or the onset of a new one. The target should be functional restoration and an increase in ulcer-free days. Strategies to achieve this include regular podiatric surveillance,[17,18] prophylactic foot surgery,[104,108] prescriptive footwear,[39] and thermometric analysis.[43]

SUMMARY

The podiatric and vascular surgeon must frequently cooperate in the care of the complicated lower extremity due to diabetes. Understanding each provider's role will streamline care. Pathway-driven teams can improve patient outcomes and reduce costs to the healthcare system. For a more complete description of such teams, we refer the reader to manuscripts outlining their components and structure.[24,122]

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117 CHAPTER

Upper Extremity Arterial Disease: Epidemiology, Etiology, and Diagnostic Evaluation

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INTRODUCTION

Upper extremity ischemia accounts for less than 5% of patients presenting for evaluation of limb ischemia, with a vast majority of cases being caused by autoimmune/connective tissue diseases. In contrast to lower extremity, atherosclerosis is not a major contributor to upper extremity ischemia. According to a Dutch study, only 2.3% of diabetic patients and no nondiabetic patients were found to have abnormal Doppler waveforms in either of the upper extremities.[1]

This chapter provides an overview of upper extremity arterial diseases. Ensuing chapters will discuss in detail the diagnosis, pathophysiology, and treatment of specific vascular conditions that affect the upper extremity.

EPIDEMIOLOGY

A wide array of pathology may contribute to upper extremity arterial disease and, as a result, little comprehensive epidemiologic data is available. One exception is Raynaud's syndrome, which is characterized by intermittent digital ischemia in response to cold, caffeine, or emotional stress (see Chapter 141). Among people living in cold climates, up to 20% to 30% will complain of cold-induced digital pain.[2] In the United States, the prevalence

Abstract

Upper extremity ischemia is less common than lower extremity ischemia and is typically classified as vasospastic or occlusive. Occlusive disease is associated with worse prognosis for developing tissue loss. Most patients with occlusive disease have their most severe symptoms at the time of presentation. Surgical bypass is a viable option in patients with occlusive disease and is associated with excellent 1- to 3-year outcomes. Vasospastic etiologies are more responsive to pharmacologic intervention.

Keywords

Upper extremity arterial disease
arterial vasospasm
upper extremity bypass
small vessel arteriopathy
large vessel arteriopathy
hand ischemia

of Raynaud's syndrome in women is approximately 9% in the Northeast and 4% in the South. The prevalence in men is approximately 6% in the Northeast and 3% in the South.[3,4]

Most patients with Raynaud's syndrome have primary (idiopathic) *Raynaud's disease*. Patients with Raynaud's syndrome who have an identifiable arterial pathology or associated disease contributing to their condition are classified as having *Raynaud's phenomenon*. This distinction has prognostic implications as secondary Raynaud's phenomenon is more likely to progress to severe occlusive disease leading to digital rest pain, and ulceration. Diseases associated with Raynaud's phenomenon include scleroderma, mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), and rheumatoid arthritis. Of these, scleroderma accounts for majority of Raynaud's phenomenon with 80% to 90% of patients presenting with Raynaud's symptoms.[5]

ETIOLOGY AND PATHOGENESIS

Upper extremity arterial disease can be categorized based on anatomic location (large vs. small vessel) and etiology (vasospastic vs. occlusive). Although the clinical appearance of occlusive and vasospastic disease may be similar, delineating between them is essential for appropriate treatment. Processes leading to upper extremity arterial disease are vast. Arterial vasospasm may occur with ergotism, vinyl chloride exposure, and idiopathic Raynaud's phenomenon.

Patients with vasospastic Raynaud's syndrome have normal digital artery pressure at baseline. In response to certain triggers (cold, stress, caffeine), they experience digital artery smooth muscle contraction leading to profound, albeit temporary, digital hypoperfusion. Upon relief of the trigger, the vasoconstriction ceases and normal flow is restored. Obstructive Raynaud's can have palmar and digital artery occlusive disease, proximal obstruction of the large arteries, or a combination of the two. They have lower resting digital blood pressure and may have symptomatic digital ischemia or tissue loss under nonstressed conditions. With cold or emotional stress, a vasoconstrictive response of the digital artery smooth muscle further causes arterial closure with resultant symptoms.

The pathophysiological mechanisms underlying Raynaud's syndrome remain poorly understood despite the fact that it has been more than a century since it was first described by Maurice Raynaud.[6,7] Multiple abnormalities including those of the sympathetic nervous system,[8,9] digital blood vessels, altered sensitivities, numbers of α-adrenoceptors,[10,11] and β-adrenoceptors,[12] and vasoactive peptides, including calcitonin gene-related peptide,[13,14] and endothelin[15] have been hypothesized. It is being increasingly recognized that the pathophysiology of Raynaud's syndrome is complex and that potentially more than a single factor might be at play.[16]

Small Vessel Arteriopathies

Numerous small vessel arteriopathies in the upper extremity, defined as those distal to the wrist, may lead to hand ischemia. The diseases leading to the most severe upper extremity arterial ischemia are autoimmune or connective tissue diseases such as scleroderma, rheumatoid arthritis, systemic lupus, and others.

Scleroderma

Scleroderma is the most common connective tissue disorder in patients with Raynaud's syndrome. It is a generalized disorder of connective tissue, the microvasculature, and the small arteries.[17] It has a female-to-male ratio of 3:1, and the incidence is approximately 10 per 1 million people in the United States. Cutaneous involvement is almost universal, and the clinical course is characterized by progressive scarring and small vessel occlusions in the skin, gastrointestinal tract, kidneys, lungs, and heart. Serology often reveals anti-centromere or anti-topoisomerase (anti-Scl-70) antibodies. It is postulated that damage seen in scleroderma is mediated through these cytotoxic antibodies to endothelium.

Systemic Lupus Erythematosus

SLE occurs most often in young females, and damage to affected organs appears to be caused primarily by immune complex deposition.[18] The diagnosis is made clinically since the available laboratory tests, while quite sensitive, are not specific.[19] Clinical criteria include fevers, arthralgias, skin rash, Raynaud's syndrome, and nephritis. Raynaud's syndrome is present in as many as 80% of patients.

Rheumatoid Arthritis

While rheumatoid arthritis is primarily a chronic inflammatory joint disease, a subgroup of patients has extraarticular involvement of the skin, eyes, lungs, spleen, and arteries. Several types of vasculitis have been described in rheumatoid arthritis, the most severe of which is termed rheumatoid vasculitis, a systemic process that involves both arteries and veins.[20] The etiology of rheumatoid arthritis is unknown, but it likely results from immune-mediated damage. Most patients have the HLA-DRW-4 allele, and it has been hypothesized to mark a genetic predisposition that in response to an unknown stimulus such as infection leads to immune complex deposition and inflammation.

Sjögren's Syndrome

Sjögren's syndrome is characterized by dry eyes and mouth and may be primary or secondary to another connective tissue disease. It may be associated with small vessel arteriopathy, which can then be subdivided into acute necrotizing, leukocytoclastic, and lymphocytic vasculitis.

Mixed Connective Tissue Disease

MCTD is a group of disease states that are autoimmune diseases but do not fall into a named disease category. Patients characteristically have high titers of antibodies to an extractable nuclear antigen, which consists of ribonucleic acid and protein. MCTD clinically presents as an overlap syndrome with features of two or more connective tissue diseases, such as SLE, rheumatoid arthritis, or scleroderma.[21]

Buerger's Disease

Buerger's disease (thromboangiitis obliterans) is characterized by segmental thrombotic occlusions of the small- and

medium-sized arteries (see Chapter 138).[22,23] The disease most commonly affects lower extremities but upper extremity is involved in as many as 50% of these patients. It classically occurs in young male smokers and is often associated with both migratory thrombophlebitis and Raynaud's syndrome. Diagnostic criteria include age less than 45 years, tobacco abuse, exclusion of other diseases with similar clinical findings, normal arteries proximal to the popliteal or brachial arteries, and documentation by objective means of digital arterial occlusion.[24]

Hand-Arm Vibration Syndrome

Hand-arm vibration syndrome (HAVS) refers to the finding of Raynaud's syndrome after long-term use of vibrating tools.[25,26] The initial group of patients were stonecutters, but the disease has been described in various occupations, including welders or grinders in shipyards, timber fellers, and windshield replacement technicians in the auto-glass industry.[27] The exact pathophysiology of this condition is not known, but it is postulated that kinetic energy imparted to the small vessels and nerves of the hand by vibrating tools with power in certain frequency bands is harmful. The damage appears to accumulate over time. Early on, patients have vasospastic Raynaud's syndrome, which over a period of time, progresses to digital artery occlusive disease.[28] (Reference occupational vascular problems chapter here.)

Fibromuscular Disease

Fibromuscular disease involving the forearm, palmar, and digital arteries is rare.[29] Patients often present with finger ischemia because of arterial embolization and occlusion. It has been postulated that the condition known has hypothenar hammer syndrome, in which patients have the acute onset of hand ischemia after using the heel of their hand as a hammer, is actually due to trauma to a preexisting fibromuscular disease lesion.[30]

Hypersensitivity Angiitis

The term hypersensitivity angiitis describes a group of patients who present with acute onset of significant digital ischemia, usually with ulceration, but have no demonstrable underlying abnormality, such as connective tissue disease or embolic source.[31] An immune-mediated arterial wall injury has been hypothesized as the underlying etiology, although strong evidence is lacking in that regard. It is a benign condition that follows a course of progressive improvement.

Malignancy

Raynaud's syndrome has been reported in association with several malignancies.[32,33] The exact mechanism is unknown, but it appears related to tumor-based immunologic processes, including both small vessel arteritis and immune complex deposition, possibly including cryoglobulins.

Frostbite

Freeze injury of the small vessels of the digits results in Raynaud's syndrome. Mild frostbite usually results in vasospastic Raynaud's syndrome, while significant freezing injury may result in occlusive disease of the digital arteries.

Large Vessel Arteriopathies

The most common large vessel arteriopathy in the upper extremity is atherosclerosis. Risk factors are the same as those for occlusive disease elsewhere in the body. These include tobacco use, hyperlipidemia, hypertension, diabetes, male gender, and age. The most common mechanism via which atherosclerosis may cause upper extremity ischemia is occlusive disease, with involvement of the origin of the left subclavian artery being the most common location. Aneurysms are rare in the upper extremity but can occur in the subclavian or axillary arteries. Chronic trauma from arterial thoracic outlet syndrome can lead to subclavian artery stenosis, which is accompanied by digital ischemia due to embolic phenomenon (see Chapter 122).

Takayasu's arteritis is a common vascular condition mainly involving the aorta and its branches. Upper extremity ischemia may occur with disease within the subclavian arteries.[34] Giant cell arteritis mainly involves the walls of medium and large arteries. The temporal artery is the most commonly involved; however, upper extremity arteries are occasionally affected.[35] Embolic occlusion from atrial fibrillation or other sources is classically seen in the brachial artery before the bifurcation of radial and ulnar arteries.

Another well-described presentation of upper extremity ischemia occurs after placement of dialysis access. Steal syndrome refers to a distal hypoperfusion ischemic syndrome after dialysis access placement. It occurs in 5% to 10% of cases when the brachial artery is used.[36]

Iatrogenic injury to the radial and brachial arteries has increased in conjunction with increased use of upper extremity for coronary and peripheral catheterization access. Initial reports of brachial artery access revealed a complication rate as high as 17%, but this has since declined to 1% to 5%.[37,38] The median nerve lies in close proximity to the brachial artery in this location within the covering fascia, and at high risk for compression from hematoma formation. Therefore, evidence of an access site hematoma should be addressed immediately to prevent long term nerve injury. Occlusion of the radial artery is seen in 3% to 10% of interventions using radial access.[39] An intact ulnar artery and palmer arch can maintain collateral flow to the hand in cases of radial artery occlusion. An Allen test should be performed before any radial access procedure to confirm adequate collateral flow.

Box 117.1 below lists the causes of hand ischemia, and Table 117.1 details the portion of the arterial system affected by these etiologies.

Clinical Findings

Acute Ischemia

Patients with acute ischemia of the upper extremity are more likely to be females and tend to be older than those with lower extremity ischemia.[40] However, symptomatology remains the same: pain, paresthesias, and paralysis. Physical examination reveals diminished or absent pulses (brachial, radial, or ulnar); pallor, dependent rubor; and reduced temperature. As mentioned earlier, classic Raynaud's phenomenon is characterized by pain,

BOX 117.1 Causes of Hand Ischemia

Arterial Vasospasm
- Ergotism
- Idiopathic vasospastic Raynaud's syndrome
- Vinyl chloride exposure

Arterial Obstruction

Large-Artery Causes
- Atherosclerosis
- Thoracic outlet compression
- Arteritis
- Takayasu's
- Giant cell
- Fibromuscular disease
- Iatrogenic injury
- Dialysis steal syndrome

Small-Artery Causes
- Connective tissue diseases
- Scleroderma
- Rheumatoid arthritis
- Sjögren's syndrome
- Systemic lupus erythematosus
- Myeloproliferative disorders
- Thrombocytosis
- Leukemia
- Polycythemia
- Buerger's disease
- Hypersensitivity angiitis
- Cold injury
- Vibration injury
- Henoch-Schönlein purpura
- Cytotoxic drugs
- Hypercoagulable states
- Arterial drug injection

Proximal Large-Artery Sources of Embolism to Distal Small Arteries
- Ulcerated or stenotic atherosclerotic plaque
- Aortic arch
- Innominate artery
- Subclavian artery
- Aneurysms
- Innominate artery
- Subclavian artery
- Axillary or brachial artery
- Ulnar artery

From Landry GL, et al. Severe hand ischemia. In: Pearce WH, Matsumura JS, Yao JST, eds. *Trends in Vascular Surgery 2003*. Chicago: Precept Press; 2004:280.

color, and temperature changes in response to cold or emotional stress. Tissue loss is rare in cases of acute occlusion due to an abundant network of collateral circulation in the upper extremity. It has been reported that acute occlusion of the axillary artery results in limb loss in less than 10% of cases and that interruption of the brachial artery distal to the deep artery branch results in digital gangrene in less than 5% of cases.

Chronic Ischemia

Patients with chronic ischemia of the upper extremity tend to have all the symptoms of acute ischemia superimposed on chronic ischemic changes in skin and musculature. This may manifest as muscle pain with use, ulcers, or gangrene in the upper extremity. Findings on physical exam may be normal at rest, but the hand and digits are cool and brachial and wrist pulses are diminished or absent. Steal syndrome may manifest by onset of symptoms in conjunction with dialysis access and remaining asymptomatic between dialysis sessions.[36] In this situation, fistula compression usually is associated with an increase in wrist pulses, Doppler signals, or both.

Diagnostic Evaluation

Clinical Evaluation

Initial evaluation of patients with upper extremity ischemia starts with a detailed history and physical examination with specific attention to signs and symptoms of an underlying connective tissue disease. Pertinent historical information includes temperature sensitivity, dry mouth, dry eyes, arthritis, history of trauma or instrumentation, as well as occupational history to evaluate for vibration arterial injury.

A complete arterial examination should be performed in a warm room and patients should be allowed to rewarm before their examination, during cold weather. Brachial and forearm blood pressures are measured. In cases of suspected claudication, they should be measured at rest and after 2 to 5 minutes of exercise. A gradient of 20 mm Hg or more is considered significant when comparing sides. All pulses are palpated, and Doppler insonation of the radial, ulnar, palmar, and digital arteries is performed to evaluate the quality of Doppler waveforms. Auscultation of the supraclavicular and infraclavicular fossa may reveal a bruit, indicating possible subclavian artery stenosis.

The hands and digits should be examined carefully, with temperature, capillary refill, and ulcers noted. Fingers should be examined for clubbing, sclerodactyly, and telangiectasia; nail beds should be checked for splinter hemorrhages. Clubbing is seen in chronic pulmonary disease. Telangiectasia and sclerodactyly are seen in scleroderma among various other connective tissue diseases. Splinter hemorrhages in nail beds are seen in embolic disease. Finally, a complete upper extremity neurologic examination may give clues to external compression of neurovascular bundle.

Vascular Laboratory Evaluation

Basic vascular laboratory evaluation consists of segmental pressure measurements of the upper extremity and finger pressure measurements and waveforms (Fig. 117.1). This allows differentiation of large artery disease (reduced wrist arterial pressure with no further reduction at the finger level) from small artery disease (normal upper extremity examination, abnormal finger pressures). Duplex ultrasonography is also particularly useful in large vessel occlusive diseases, such as subclavian artery stenosis (Fig. 117.2).

The diagnosis of Raynaud's phenomenon is made clinically. However, qualitative testing for the severity of cold sensitivity in Raynaud's syndrome can be useful. The most basic test for cold sensitivity is finger temperature recovery after ice-water immersion. If the initial battery of tests is nondiagnostic and the patients have significant obstructive disease (by vascular laboratory criteria) or digital ulceration, further testing to determine the presence of a hypercoagulable state is conducted.

TABLE 117.1 Arterial Diseases and Artery Affected

	Subclavian	Axillary	Brachial	Forearm	Hand
Atherosclerosis	•				
Giant cell arteritis	•				
Takayasu's disease	•	•			
Fibromuscular dysplasia		•			•
Embolic		•	•		•
Connective tissue disease				•	•
Diabetes mellitus				•	•
Repetitive trauma					•
Hypercoagulation					•
Cryoglobulins					•
Pressors/polyvinyl chloride					•

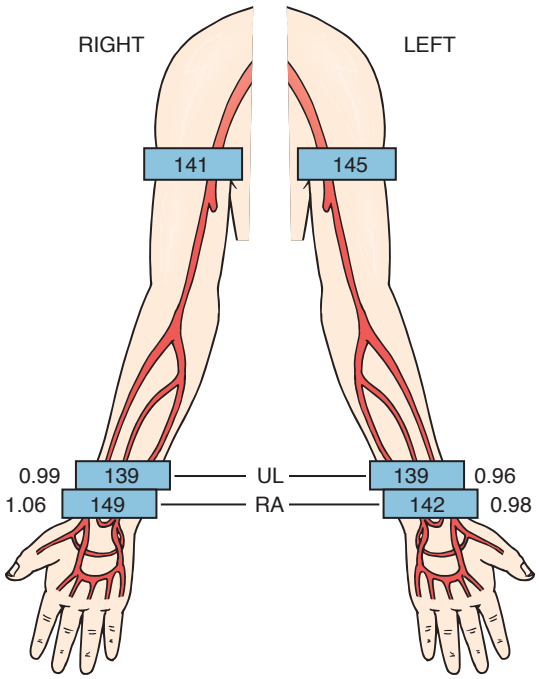

Figure 117.1 A normal wrist to brachial index study.

This screening battery consists of antithrombin III, protein C, and protein S levels, which are tests for the presence of anticardiolipin and antiphospholipid (lupus inhibitor) antibodies, Lp(a) levels in patients with hyperlipidemia, and tests for familial hypercoagulable states such as factor V Leyden (Table 117.2).

Other Imaging

Imaging can be extremely useful when the diagnosis cannot be established by clinical assessment and basic vascular laboratory studies alone. For embolic disease, both duplex ultrasound and echocardiography are recommended. If these do not reveal an embolic source, the aortic arch and intrathoracic upper extremity arteries should be imaged. Both computed tomographic arteriography (CTA) and magnetic resonance arteriography (MRA) provide excellent resolution and are less invasive than catheter-based arteriography.[41]

Finally, invasive arteriography is generally reserved for patients with unexplained digital artery occlusion in an asymmetrical distribution to rule out a surgically correctable proximal lesion where a CTA or MRA fails to reveal an etiology (Fig. 117.3). The entire upper extremity vasculature should be visualized. In addition, both upper extremities should be imaged. The presence of significant bilateral disease, even with unilateral symptoms, is an indication of a systemic disease.

Treatment

Medical

Most patients with idiopathic Raynaud's syndrome are best treated with cold and tobacco avoidance, with medication reserved for more severe cases. Several medications have been shown to be beneficial in the treatment of Raynaud's syndrome. The most effective drug to date has been the calcium channel blocker nifedipine.[42] Losartan has also been demonstrated to be effective in patients with Raynaud's syndrome in randomized trials.[43] Many of these patients are young women who do not tolerate year-round antihypertensive medications. Patients may take the medication from late fall to late spring or when they anticipate facing cold exposure. Fluoxetine, a selective serotonin uptake inhibitor, has also been shown to be effective in a double-blind, randomized, controlled trial.[44] Other drugs that have a modest clinical effect and have been used in the treatment of Raynaud's syndrome include prazosin,[45] sildenafil,[46] reserpine, cilostazol,[47] captopril.[48] Bosentan, an endothelin receptor blocker, appears to particularly benefit in patients with scleroderma.[49] These patients typically have a benign disease course and tissue loss is rare.

Unfortunately, the results in patients with obstructive Raynaud's syndrome are less satisfying. Pharmacologic

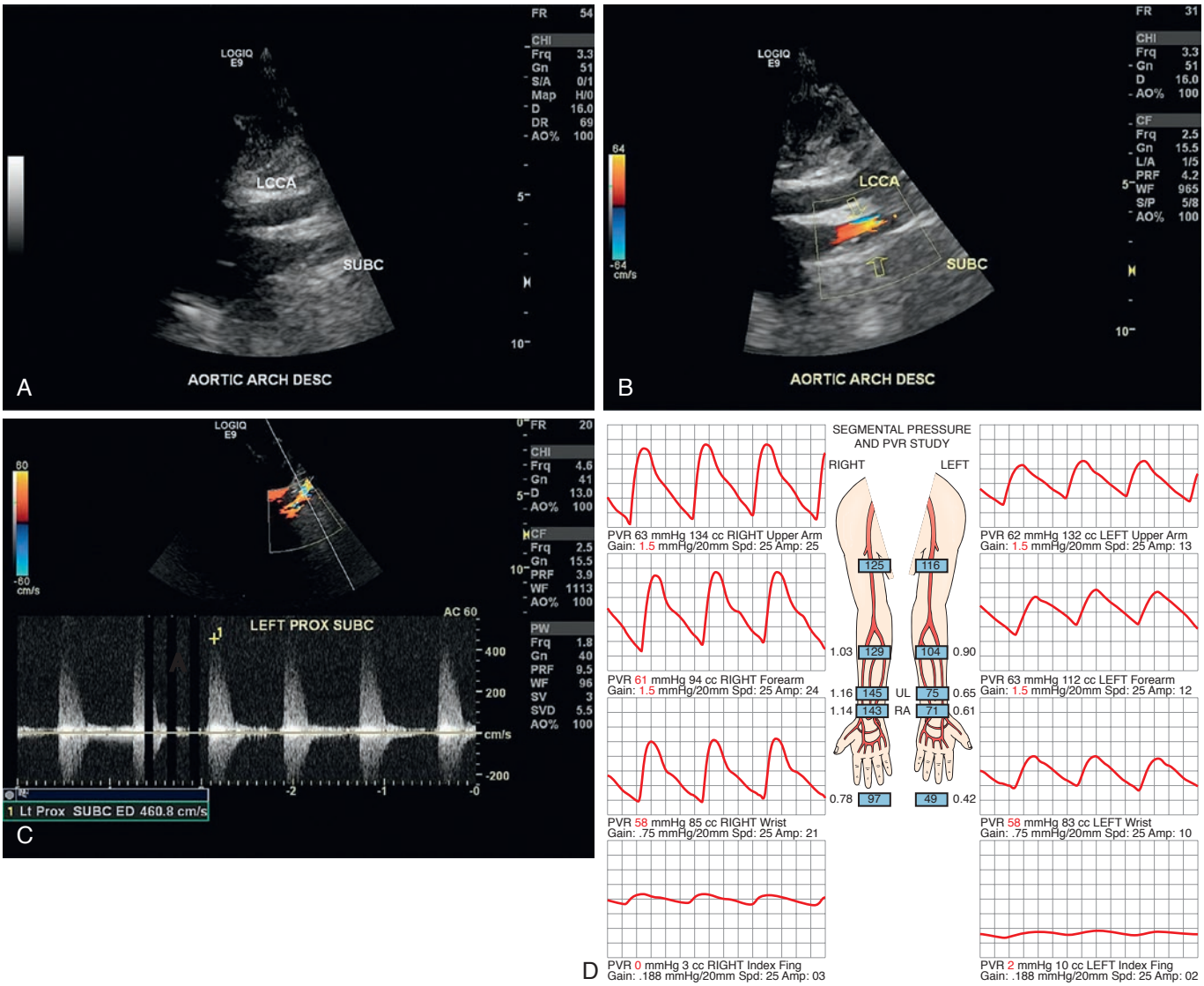

Figure 117.2 Left Subclavian Artery Stenosis Demonstrated on Ultrasound. (A) B-mode ultrasound image of the descending aortic arch with the left common carotid artery and left subclavian artery origins clearly visible. A bulky atherosclerotic plaque is narrowing the origin of the left subclavian artery. (B) Color Doppler image demonstrating arterial flow through the stenosis at the origin of the left subclavian artery *(yellow arrows)*. (C) Color duplex image with the velocity through the left subclavian artery stenosis dramatically elevated at 460.8 cm/s. (D) Segmental pressures and pulse volume recordings of the same patient identifying reduction in PVR amplitude and latency and reduced wrist and finger to brachial index.

intervention is less effective in these patients. About 20% to 30% of patients do not tolerate nifedipine because of ankle swelling, headache, or fatigue. This group has an intermediate risk for progression that is dependent on the natural history of the underlying cause of the obstruction.[5]

Patients with both arterial obstruction and an underlying disease have the worst prognosis and the highest risk for ulceration and tissue loss. These patients are likely to progress slowly over time. Of note, if ulceration is not present at the initial consultation, it is unlikely to develop in the future, and those with ulceration have only 50% chance of further ulceration developing.[5]

Surgical

Thoracic sympathectomy has been used both for treatment of digital artery vasospasm and as an adjunct for healing of digital ischemic ulceration. For vasospasm, thoracic sympathectomy is usually initially successful, but the symptoms invariably return, usually within 3 to 6 months.[50] The exact basis of this lack of durability is unknown but could be attributed to the rich network of collateral nerve pathways in the upper extremity. Alternatively, periarterial digital sympathectomy performed in the common digital arteries has been suggested as a superior strategy, and a number of small series claim long-lasting benefit from such a

procedure.[51] Thoracic sympathectomy as an adjunct measure for digital ulceration is unproven. In a study of 100 patients with digital ulceration, patient outcomes were independent of whether they underwent sympathectomy.[52] Patients with digital ulceration have obstructed digital arteries and are most likely already maximally vasodilated; thus, sympathectomy is unlikely to improve blood flow. Other treatments that have been reported include spinal cord simulation[53] and biofeedback.[54]

Thoracic outlet syndrome requires cervical or first rib resection. Large artery occlusion, arterial aneurysm, thoracic outlet syndrome with arterial damage or occlusion, fibromuscular disease, and upper extremity arterial trauma with symptoms are best treated by revascularization. Revascularization may be achieved via open bypass or by interventional techniques such as angioplasty with or without stenting.

Results for upper extremity bypass are excellent and even superior to those reported for lower extremity ischemia. Twenty upper extremity bypasses were performed for chronic upper extremity ischemia over a 13-year period at our institution with outstanding patency and limb salvage rates of 85% and 100% at 3 years.[55] Patients that underwent upper extremity bypass compared with those with lower extremity bypass were younger, less likely to be diabetic, and more likely to undergo surgery due to exercise intolerance (claudication equivalent). The inflow varied from brachial (65%), axillary (30%), and ulnar (5%). The outflow consisted of the brachial (60%), radial (25%), and ulnar (5%). The conduits used were great saphenous vein (55%), arm vein (35%), and prosthetic graft (10%). Excellent patency (90%-96%) and limb salvage rates (100%) of upper extremity bypass at 1 year have been reported by other groups as well.[56,57]

Revascularization options for the upper extremity are discussed in a separate chapter. If the revascularization is unsuccessful and the extremity is nonviable, amputation may be necessary. Fortunately, upper extremity amputation is rare.

TABLE 117.2 Most Commonly Used Vascular and Basic Clinical Laboratory Tests Used to Diagnose Upper Extremity Arterial Disease

Vascular Laboratory
Finger pressures
Finger photoplethysmographic waveforms
Cold challenge test
Basic Clinical Laboratory
Complete blood count
Erythrocyte sedimentation rate
Antinuclear antibodies
Rheumatoid factor
Additional Tests in Select Cases
Hypercoagulable screening
Protein C
Protein S
Antithrombin III
Lupus anticoagulant
Anticardiolipin and antiphospholipid antibodies
Lipoprotein A
Factor V Leyden
Thyroid panel

SUMMARY

Upper extremity ischemia is less common than lower extremity ischemia. Possible etiologies could be vasospastic or occlusive. Occlusive disease is associated with worse prognosis for developing tissue loss. Most patients appear to have their most severe symptoms at the time of presentation. Vasospastic etiologies

Figure 117.3 A sample of an abnormal hand and forearm arteriogram (A, unsubtracted; B, subtracted) where the ulnar artery *(arrow)* is occluded from an embolus *(arrow)*.

are more responsive to pharmacologic intervention, with nifedipine and losartan the best studied medications. Sympathectomy does not confer a durable response in vasospasm and is of little to no use in occlusive disease. Finally, bypass is a viable option in patients with occlusive disease with excellent 1- to 3-year outcomes.

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A complete reference list can be found online at www.expertconsult.com.

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118 CHAPTER

Upper Extremity Arterial Disease: Medical, Endovascular, and Open Surgical Management

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Upper extremity arterial occlusive disease is responsible for less than 5% of all cases of limb ischemia.[1] Even in high-volume centers, arm reconstructions account for only 3% of elective limb revascularizations. Palmar and digital artery occlusive disease is the most common cause of upper extremity arterial occlusive disease, whereas large-vessel disease, including arteries proximal to the wrist, account for less than 10%. The majority of arm emboli are cardiac in origin (75%). The most common site for emboli is the brachial artery (60%), followed by the axillary artery (26%). In situ thrombosis accounts for only 5% of episodes of arm ischemia.[2] This chapter deals with revascularization for both acute and chronic ischemia involving the intrinsic arteries of the upper extremities, including the axillary, brachial, radial, ulnar, and palmar arteries. Raynaud phenomenon (see Chapter 141), thoracic outlet syndrome (see Chapter 120), brachiocephalic artery disease (see Chapters 98 and 99), and Takayasu arteritis (see Chapter 139) are described elsewhere. Because the volume of these procedures is small, it is difficult to draw evidence-based conclusions on the optimal approach for patients with upper extremity ischemia. Upper extremity occlusive disease is far less prevalent than lower extremity peripheral vascular disease. Accordingly, research on lower extremity treatment strategies has far outpaced the upper extremity with relatively few reports added to the upper extremity revascularization literature over the last several years. Patients with diabetes mellitus and chronic renal failure make up a significant proportion of those with digital gangrene. Treatment presents a challenge that often involves difficult reconstruction, meticulous wound care, and patience.

Abstract

Upper extremity arterial occlusive disease is a relatively infrequent cause of limb ischemia. Palmar and digital artery occlusive disease is the most common cause of upper extremity arterial occlusive disease, whereas large-vessel disease, including arteries proximal to the wrist, accounts for less than 10%. The majority of arm emboli are cardiac in origin (75%), and the most common site for emboli is the brachial artery (60%) followed by the axillary artery (26%). This chapter deals with revascularization for both acute and chronic ischemia involving the intrinsic arteries of the upper extremities, including the axillary, brachial, radial, ulnar, and palmar arteries. Because the volume of these procedures is small, it is difficult to draw evidence-based conclusions on the optimal approach for patients with upper extremity ischemia. Upper extremity occlusive disease is far less prevalent than lower extremity peripheral vascular disease. Accordingly, research on lower extremity treatment strategies has far outpaced the upper extremity, with relatively few reports added to the upper extremity revascularization literature over the last several years. Patients with diabetes mellitus and chronic renal failure make up a significant proportion of those with digital gangrene. Treatment presents a challenge that often involves difficult reconstruction, meticulous wound care, and patience.

Keywords

Upper extremity ischemia
Upper extremity embolectomy
Upper extremity bypass
Axillary artery
Brachial artery
Brachial artery reconstruction

CLINICAL FINDINGS

Patients may have either acute or chronic ischemic symptoms, as discussed in detail in Chapter 117.

Acute Arm Ischemia

Arms with acute ischemia account for only one-fifth of all acutely threatened limbs. A recent systematic review found that out of 1326 acutely ischemic upper extremities, 92% were attributed to thromboembolic disease (usually of cardiac origin), with the second most common cause being iatrogenic (1.5%).[3] Women are affected more often than men, and patients are significantly older than those with acute symptoms in the lower extremity.[4] Most reports of acute arm ischemia generally involve those who required surgery; thus, the denominator is difficult to calculate. The classic symptoms involve the "six P's": pain, pallor, paresthesia, paralysis, pulselessness, and poikilothermia. The fingers and hand are often cool with obvious color changes. Numbness and tingling are common. Motor dysfunction may range from mildly diminished hand strength to paralysis. Wrist pulses are usually absent while axillary and/or brachial pulses may remain palpable. Doppler interrogation at these sites often produces an occlusive or "water hammer" signal.

Chronic Arm Ischemia

Whereas chronic leg ischemia is usually due to atherosclerosis, the causes of chronic arm ischemia are more diverse. Although atherosclerosis is still one etiology, consideration must be given to other pathologies, such as thoracic outlet syndrome, iatrogenic injury after arm catheterization, and less frequent causes, such as Takayasu or giant cell arteritis, and radiation-induced injury. Hand and finger ischemia has been reported with increasing frequency in patients with end-stage renal disease.[5,6] The etiologic backgrounds of this disease process are multiple and include thrombosis, accelerated atherosclerosis, and diffuse arterial calcification. The origin of this condition may well involve atherosclerosis, but there is a well-described association with calciphylaxis.[7]

Manifestations of chronic arm ischemia can include arm fatigue with activity, digital pain at rest, and tissue loss with ulceration or gangrene. Initial assessment is by noninvasive studies, such as pulse volume recordings or duplex ultrasound, followed by magnetic resonance angiography (MRA) or computed tomographic angiography (CTA). Confirmation of these findings can be obtained by aortic arch and arm catheter angiography. Occlusive lesions will be located in the axillary, brachial, or forearm arteries. Each requires separate treatment strategies.

Another clinical situation of hand ischemia encountered in patients with end-stage renal disease is that associated with an ipsilateral upper extremity arteriovenous fistula. The onset of hand ischemia is a devastating complication of upper extremity hemodialysis access. Arteriovenous shunts are almost always associated with some degree of reduced arterial flow to the distal circulation. Untreated, this may produce pain, ulceration, and gangrene in a previously viable extremity. Although prevention of this complication remains paramount, several techniques are available to manage this problem once diagnosed. Chapter 179 describes the diagnosis and management of steal-associated ischemia and critical upper extremity ischemia caused by infrabrachial disease in renal failure patients.

TREATMENT

Conservative Therapy

Between 9% and 30% of patients seen by vascular surgeons with upper extremity arterial occlusive disease are managed conservatively because of significant comorbid conditions or minimal symptomatology. Conservative therapy classically includes anticoagulation for acute or subacute ischemia. Adjunct therapies, such as calcium channel blockers, topical nitrates, and phosphodiesterase inhibitors, have also been used with variable success. Smoking cessation, optimizing cardiac output, avoiding vasopressors, and warming the upper extremity are also useful to obtain the best possible outcome.

Postoperative mortality rates for brachial embolectomy are as high as 12%.[8] However, after successful brachial embolectomy, 95% of patients will remain free of symptoms.[9] Patients managed conservatively are probably underreported in the literature. In the few reported series, assessment of symptoms and disability tends to be inconsistent. However, in a series of 95 patients described by Baird and Lajos in 1964 with arm ischemia managed without surgery, 32% were left with permanent disability in the arm.[10] In 1977, Savelyev and coauthors reported that 75% of patients managed conservatively had a poor functional outcome.[11] In 1985 Galbraith and associates confirmed that 50% of their conservatively managed patients had persistent exercise-induced forearm pain (a claudication equivalent).[12] Therefore, although conservative management is appropriate for some patients with acute ischemia, for those with a reasonable life expectancy, all efforts should be made to restore blood flow.

Endovascular Treatment

Endovascular therapies for the treatment of arterial occlusive disease have increased in popularity over the last decade with advancement in catheter, balloon, and stent technology. The majority of lower extremity revascularizations in contemporary vascular surgery practices are now done percutaneously. However, the upper extremity has not shared the same paradigm shift, possibly due to the relative infrequency of interventions or the underlying causes of the arterial disease. A recent Japanese multicenter study reviewed 553 patients undergoing primary endovascular therapy with angioplasty and/or stenting for subclavian artery occlusive disease, with a primary patency of 90% at 1 year and 81% at 5 years.[13] Most institutional reviews that describe treatment of occlusions in the axillary, brachial, radial, and ulnar arteries still involve surgical bypass or embolectomy.[14,15] There are scattered reports of emergency placement of covered stents in the axillary artery in trauma patients.[16] An example of such therapy is illustrated in Fig. 118.1. There are also reports of small series of patients treated by axillary artery angioplasty for radiation-induced occlusion, by brachial artery

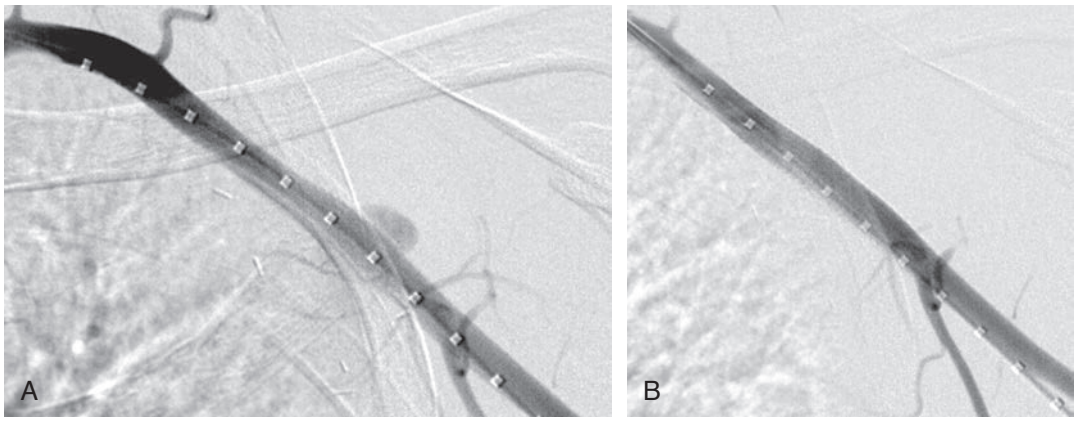

Figure 118.1 (A) Angiography of the left arm after penetrating trauma reveals a pseudo-aneurysm off the axillary artery (B). After deployment of a covered stent graft in the axillary artery, no further extravasation is seen.

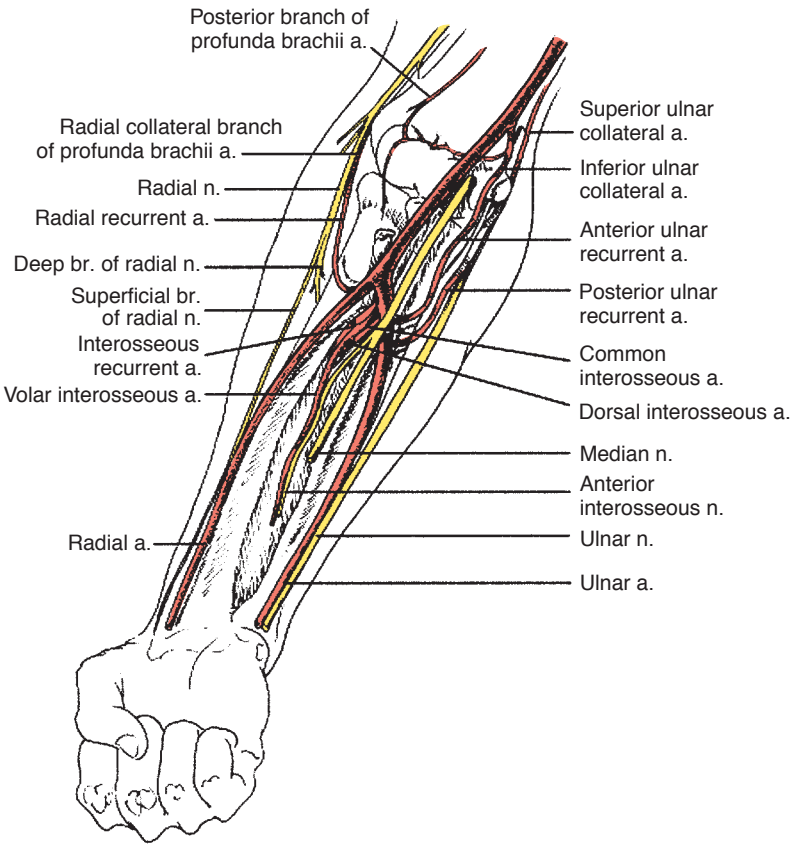

Figure 118.2 Forearm nerve and vessel anatomy. The brachial artery typically bifurcates just below the elbow. (From Valentine RJ, Wind CG. *Anatomic Exposures in Vascular Surgery*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003.)

atherectomy, and by radial artery stenting for digital gangrene, but their numbers are low and follow-up is minimal.[17-20] Therefore, dissection and exposure of the arterial anatomy for revascularization will be described at the most common levels of intervention (Fig. 118.2).

SURGICAL TREATMENT

Arterial Exposure

Axillary Artery

The patient is positioned supine and the arm is draped circumferentially. The axillary artery is exposed with a transverse incision 2 cm below the middle third of the clavicle (Fig. 118.3). The underlying pectoralis major muscle is divided, when possible, in the decussation between the sternal and clavicular portions. Despite the descriptions found in most operative texts, this point is not always readily apparent. Division of the pectoralis major exposes the clavipectoral fascia, which is divided. The axillary artery is located cephalad to the vein. It is dissected carefully to avoid injury to the surrounding cords of the brachial plexus. The second portion of the axillary artery can be exposed by dividing the pectoralis minor muscle. If needed, the distal third of the axillary artery may also be exposed. An oblique incision is made along the lateral margin of the pectoralis major muscle with the arm abducted 90 degrees relative to the thorax.

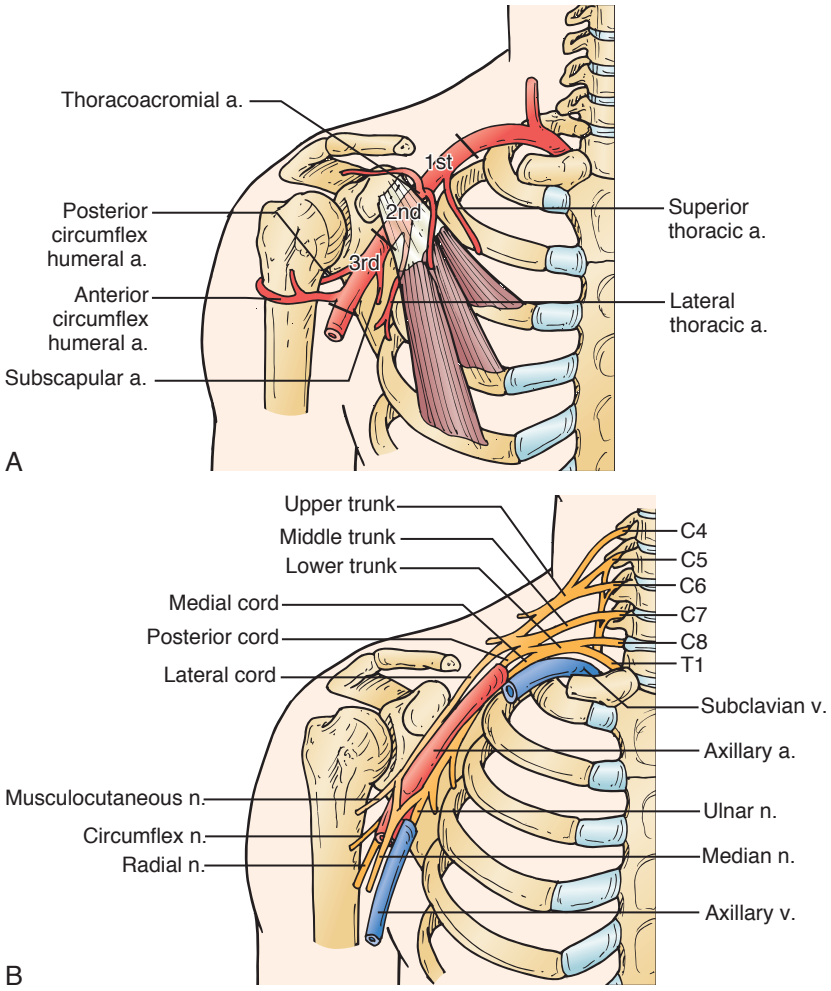

Figure 118.3 Exposure of the axillary artery. **A,** Segments of the axillary artery are defined by the relationship to the coracoid process and the pectoralis minor muscle. This muscle can be divided to provide full axillary artery exposure. **B,** The brachial plexus is intimately associated with the axillary artery at all levels and must be avoided during dissection.

Once the subcutaneous tissue is divided, the axillary sheath is located near the posterior and inferior border of the coracobrachialis. Careful dissection avoids injury to the medial and lateral cords of the brachial plexus medially and the median and ulnar nerves laterally.

Brachial Artery

The mid or distal brachial artery is exposed through a medial incision over the bicipital groove. This allows access to the proximal or middle third of the brachial artery. The basilic vein and cutaneous branches of the median nerve are located within the subcutaneous tissue and should be avoided during dissection. Traction or transection of the median antebrachial cutaneous nerve may lead to hyperesthesia or anesthesia along the medial dorsal surface of the forearm. This occasionally occurs after dialysis access (e.g., basilic vein transposition) and can be debilitating for the patient. In some cases, it can even preclude the use of a patent and mature fistula. The brachial sheath is then incised longitudinally. The median nerve is the most superficial structure encountered. The nerve is gently mobilized and retracted to allow access to the brachial artery. Crossing vein branches should be divided to minimize the risk of injury to the posteriorly located ulnar nerve.

The distal third of the brachial artery and its bifurcation, in contrast, are exposed in the antecubital fossa (Fig. 118.4). A lazy S–shaped incision is recommended to expose the origins of the ulnar and radial arteries. Sometimes a vertical incision is used. However, there is a legitimate concern about contracture of the elbow with vertical incisions. The skin and subcutaneous tissues are divided. Care is taken to preserve the superficial veins, especially the median antecubital vein, because it may be required for autogenous patch angioplasty closure. The bicipital fascia is incised and the brachial artery is seen coursing between the biceps tendon laterally and the median nerve medially. Dissection is continued distally until the ulnar and radial arteries are encountered. The radial artery is really a continuation of the brachial artery. The ulnar artery, on the other hand, comes off the brachial artery medially and, within 2 to 3 cm, dives beneath the pronator and epitrochlear muscles.

Radial Artery

The course of the radial artery in the forearm follows an oblique line from the brachial artery pulse medial to the biceps tendon to the styloid process of the radius. In the midforearm, the radial artery is medial to the brachioradialis and lateral to the flexor carpi radialis. A lateral longitudinal incision is made. The

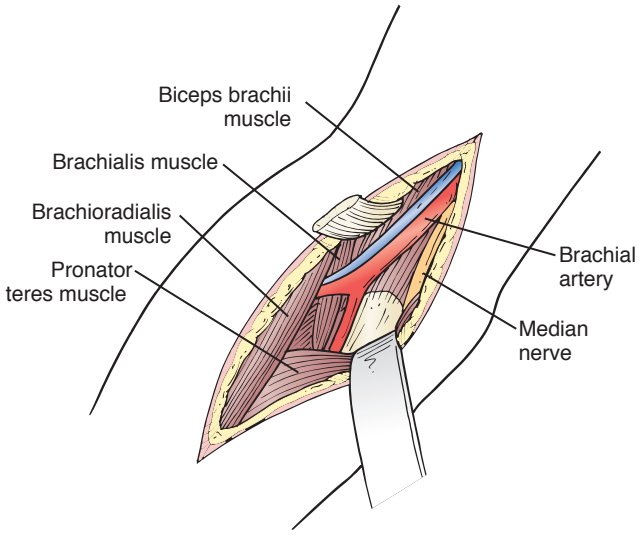

Figure 118.4 Exposure of the brachial artery at the elbow. The bifurcation of the brachial artery can be exposed by retracting the pronator teres and flexor muscle mass. The radial artery can be followed the length of the incision, but the larger ulnar artery dives between the heads of the flexor digitorum superficialis.

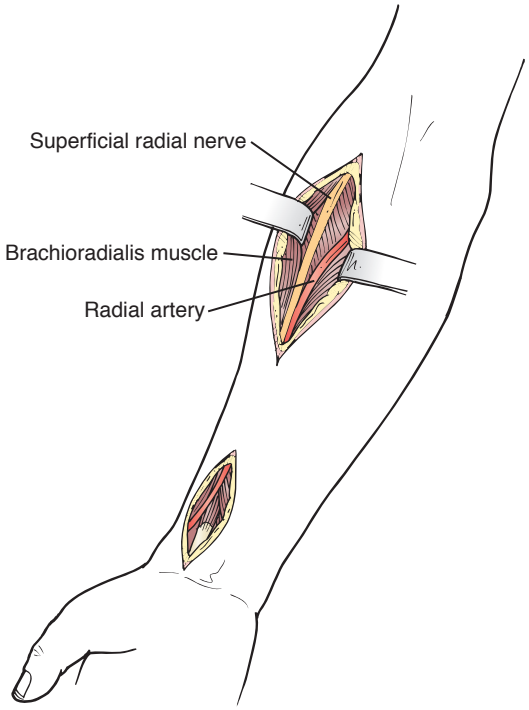

Figure 118.5 The radial artery in the midforearm can easily be exposed beneath the brachioradialis.

muscles are separated to reveal the radial artery as needed (Fig. 118.5).

At the wrist, the radial artery is exposed by a longitudinal incision between the tendons of the flexor carpi radialis and the brachioradialis muscles. This is the traditional site of the radial artery pulse in normal subjects. The artery is superficial and exposure is relatively straightforward. The superficial branch of the radial nerve is often located near the lateral aspect of the

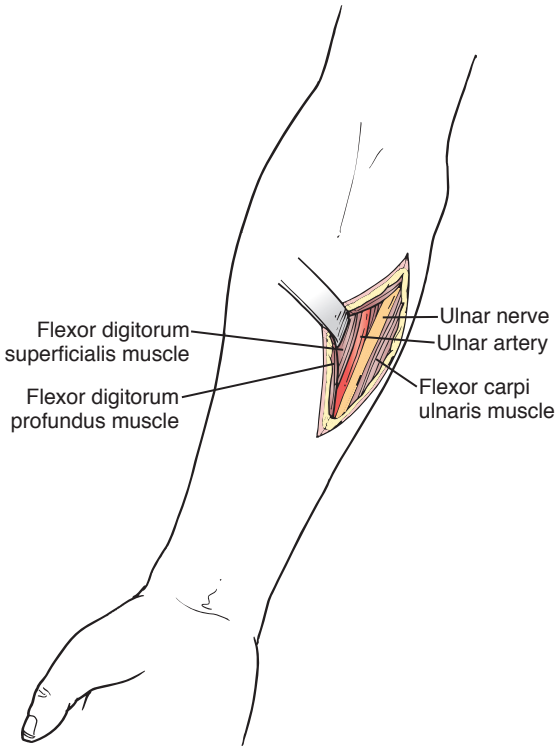

Figure 118.6 Exposure of the forearm ulnar artery. The ulnar artery in the midforearm is reached between the flexor carpi ulnaris and flexor digitorum superficialis.

artery. Injury can result in troublesome paresthesias along the lateral aspect of the thumb.

Ulnar Artery

The ulnar artery extends from the medial epicondyle of the humerus to the pisiform bone. In the midforearm, the ulnar artery lies beneath the deep fascia between the bellies of the flexor digitorum laterally and the flexor carpi ulnaris medially (Fig. 118.6). The ulnar nerve joins the artery on its lateral aspect for its distal two-thirds. It may be injured if not carefully identified and preserved.

At the wrist, the ulnar artery is lateral to the flexor carpi ulnaris (it is the most medial tendon palpable at the wrist). For exposure, this tendon is identified and a vertical skin incision is made lateral to it. The ulnar artery is relatively deeper than the radial artery at the wrist, but is just as easily exposed. The palmar cutaneous branches of the ulnar nerve are superficial to the artery here and should be preserved.

Interosseous Artery

The interosseous arteries of the forearm are naturally the smallest and most deeply situated of the forearm vessels. They are the embryologic analogue to the peroneal artery in the lower extremity, an artery of supply to the distal extremity musculature. The initial few millimeters of the common interosseous artery can be accessed by following the ulnar artery down from the brachial artery, dividing some of the fibers of the superficial flexor digitorum, and looking for the large branch going lateral and deep from the ulnar artery.

The common interosseous bifurcates into an anterior (or volar) interosseous and a posterior (or dorsal) interosseous just proximal to the forearm interosseous membrane. Exposure of the length of the anterior interosseous artery is best done through the same incision used to expose the midportion of the ulnar artery and then to separate the flexor carpi ulnaris from the superficial flexor digitorum. After an incision long enough to release the fascia is made, the superficial flexor digitorum is elevated along with the median nerve, and dissection is carried along the volar surface of the flexor digitorum profundus. Next, the flexor pollicis longus is elevated toward the radius to expose the anterior interosseous neurovascular bundle; some fibers of the flexor pollicis longus may partially cover the anterior interosseous artery and need to be divided. The posterior interosseous artery is best approached through a dorsal forearm skin incision along the medial aspect of the radius. This artery is usually smaller and less often used for revascularization.

Palmar Arteries

Exposure of the palmar arteries is not routinely performed in many vascular surgery centers. The blood supply of the hand is supplied by the superficial and deep palmar arches. The superficial palmar arch is supplied by a branch of the radial artery and the ulnar artery. The deep palmar arch is supplied by the radial artery itself and a deep branch of the ulnar artery. Exposure of the radial artery, ulnar artery, and superficial palmar arch is relatively straightforward, and these vessels match the distal tibial or pedal vessels in the leg in size. The deep palmar arch is much more difficult to expose and deeply located and thus is relatively inaccessible.

Exposure of the distal radial artery can be performed as described earlier. Alternatively, exposure can be accomplished by making a vertical incision over the anatomic snuff-box (the snuff-box lies between the extensor pollicis longus tendon posteriorly and the tendons of the extensor pollicis brevis and abductor pollicis longus anteriorly). After deepening the incision through subcutaneous tissue, the radial artery can be exposed in the floor of the snuff-box (Fig. 118.7). Because there are no significant nerves at this level, it is often chosen as a site for hemodialysis access.

Distal ulnar artery and superficial palmar arch exposure is best accomplished via a curved incision along the lateral border of the hypothenar eminence (Fig. 118.8). The aponeurotic layer is divided and the artery is then exposed in the upper part of the palm at the origin of the superficial palmar arch. No major nerves pass in the vicinity, and a reasonable length of artery can usually be exposed for an arterial anastomosis. Alternatively, the superficial palmar arch can be exposed in the palm by making an incision along one of the larger vertical or oblique skin creases.

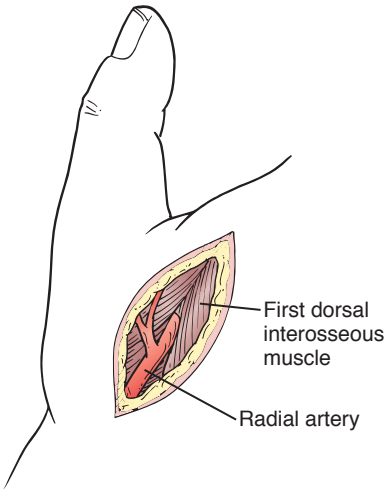

Figure 118.7 The segment of radial artery beyond the extensor pollicis longus tendon is exposed.

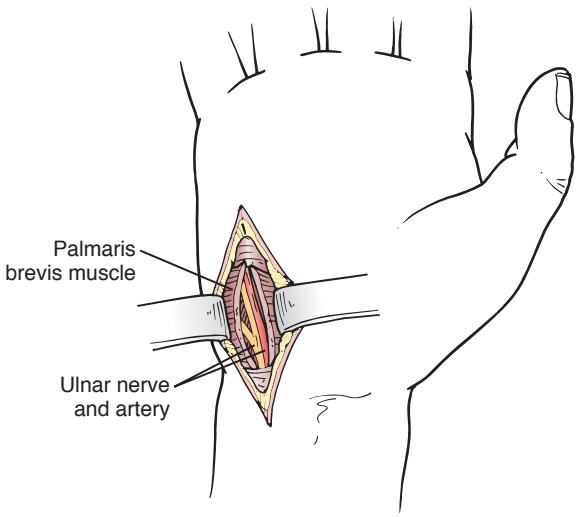

Figure 118.8 The ulnar artery and nerve beyond the tunnel of Guyon are exposed beneath the palmaris brevis muscle and the hypothenar fascia.

Bypass Conduit and Tunneling

The autogenous vein is the conduit of choice for upper extremity reconstructions. The great saphenous vein is preferable, although use of the in situ cephalic vein has been described.[21] The more joints that the bypass crosses, the lower the patency rate.[22] After systemic heparinization, the venous conduit is excised and its side branches ligated with fine polypropylene suture or silk ties. The vein is distended with a solution of dextran, heparin, and papaverine (500 mL bag of dextran 40 + 120 mg papaverine + 1000 units heparin). The excised conduit may be used in either reversed or orthograde (nonreversed) orientation, depending on the taper of the conduit. If orthograde orientation is used, the proximal anastomosis is performed, the conduit is distended, and the valves are rendered incompetent by the passage of a retrograde Mills valvulotome. Prosthetic reconstructions in this setting have lower patency rates than venous bypasses, and should be avoided.[14] The management of infection in prosthetic grafts also can be challenging.

Bypasses originating from the axillary artery are preferably tunneled anatomically along the axis of the axillary and brachial arteries because they are then less prone to movement or distortion. They may also be positioned anteriorly in the subcutaneous plane. However, superficial bypasses are more prone to distraction

Figure 118.9 Palmar artery bypass completion arteriogram.

Figure 118.10 Digital artery bypass completion arteriogram.

injuries from forcible abduction of the shoulder. Therefore, redundancy is paramount to avoid harming the conduit. As another alternative, there is at least one case report of a retrohumeral approach for tunneling.[23] This involves a more proximal reconstruction, which originates in the supraclavicular fossa and then traverses the subcutaneous plane inferior to the acromion process. The conduit continues from the posterior aspect of the upper arm around both medial and anterior aspects, where it descends through the fascia to the brachial artery.

Bypasses based on brachial artery inflow are most often tunneled in the subcutaneous plane. This facilitates physical examination for appropriate evaluation of bypass patency, ensures surveillance of the bypass with duplex if readily available, and avoids manipulation of the rich forearm nerve network. Alternatively, if good-quality basilic or cephalic veins are present, an in situ bypass may be performed.

In the case of distal radial sided reconstructions, the graft is tunneled subcutaneously over the extensor pollicis tendons toward the anatomic snuff-box onto the dorsum of the hand. The bypass ends between the thumb and index finger, where the deep palmar arch (Fig. 118.9), or even a digital vessel in the absence of a complete arch (Fig. 118.10), is exposed. In the case of ulnar-sided reconstructions, the course of the vein graft is more direct and it passes superficial to the flexor retinaculum in the subcutaneous plane at the wrist lateral to the pisiform bone to join the superficial palmar arch.

Transbrachial Embolectomy

When an embolectomy is planned, several considerations are essential. If preoperative imaging (usually duplex ultrasound) has demonstrated occlusion of the distal brachial artery, it is important to expose the origins of both forearm arteries because the embolectomy catheter must be passed down each artery. If the catheter is passed blindly down the brachial artery, it will most likely travel down the radial artery. This will probably reestablish flow to the hand in the majority of patients. However, it may fail to restore adequate flow if the ulnar is the dominant arterial blood supply or if the catheter passes down the common interosseous artery, which does not provide any direct flow to the hand. We usually make a transverse arteriotomy in the brachial artery. Clots, which are frequently encountered at the bifurcation, can be readily removed. The majority of brachial embolectomies are performed under local anesthesia with monitored anesthesia care. The brachial artery may be pulseless, indicative of an embolus lodged more proximally. However, one concern with proximal passage of an embolectomy catheter is dislodgment of debris that may embolize the vertebral artery near the origin of the subclavian artery. If there is any concern, contrast-enhanced angiography is warranted to define the anatomy. Once inflow is established, a size 2 or 3 French embolectomy catheter is passed distally down each forearm vessel. The arteriotomy can be closed primarily with running fine polypropylene suture if the artery is sufficiently large. If there is any doubt, the artery should be closed with a vein patch. Usually, a segment of vein can be harvested from the antecubital fossa.

After closure, an intraoperative continuous wave Doppler probe should be applied to each artery to ensure the presence of adequate flow. Immediate completion angiography is at the discretion of the surgeon, but should be performed if the hand still appears ischemic, especially if extensive thrombus has been extracted from forearm arteries. Occasionally, embolization may have been a chronic process and resulted in distal arterial occlusion that cannot be completely resolved with embolectomy, but arteriography can be used to detect residual fresh thromboembolic material. If there is any suspicion of an inflow lesion, intraoperative arteriography can be performed by either the femoral or brachial route to diagnose and treat such lesions. A recent Italian study by Zaraca et al. demonstrated a significant reduction in 2-year reocclusion rates in patients undergoing angiography after embolectomy (12% vs. 2% without angiography). After embolectomy, the rate of extension of the procedure was 26% in the angiography group versus 4% in the group without intraoperative angiography, suggesting that routine intraoperative angiography impacts outcomes and may be associated with a more thorough embolectomy.[24]

Postoperative Management and Follow-Up

Postoperatively, surveillance with pulse volume recordings or Doppler segmental pressure measurements can be used to document the adequacy of the bypass. Duplex ultrasonography is used to determine the patency of the reconstruction and allow early detection of stenoses during surveillance of the venous conduit. The number of series reporting long-term patency is limited. Roddy et al. identified a 90% primary patency and 100% limb salvage rate at 1 year in their cohort of 61 bypasses.[14] More recently, Spinelli and colleagues identified 23 patients with chronic ischemia that underwent upper extremity bypass.[25] At a mean of 34 months, primary patency was 83% with a limb salvage rate of 100%. Anticoagulation is essential after embolectomy. Recurrent embolization occurs in one-third of patients after successful embolectomy if systemic anticoagulation is not instituted. In an Edinburgh study, even in patients started on warfarin after embolectomy, 11% sustained a further embolus if they had ongoing atrial fibrillation.[4] In those patients without atrial fibrillation as the source of embolus and in whom no preoperative, intraoperative, or immediate postoperative angiography has been performed, formal diagnostic arteriography, CTA, or MRA should be considered to rule out alternate etiologies for thromboembolism. Intracardiac assessment with echocardiography is indicated if no arterial source is identified.

ALTERNATIVE THERAPY

Sympathectomy has been used with isolated reports of success,[26,27] but the experience in most centers has been less than optimal (see Chapter 194). Thrombolysis of acutely occluded axillary or brachial arteries has been described with reasonable outcomes.[26] However, in one large series, success was reported in just over half of the limbs treated, and 8 of 55 patients required surgical thrombectomy.[28] Thrombolysis has also been described as a treatment option for acute finger ischemia with disease distal to the wrist. In a small series, half the patients (8 of 16) experienced anatomic improvement on repeat angiography, but functional outcomes are less clear.[29]

TRAUMA

Upper extremity trauma is relatively frequent and can be iatrogenic or noniatrogenic (see Chapter 181).

Iatrogenic Trauma

Brachial Artery

Brachial artery pseudoaneurysm, or occlusion related to cardiac catheterization, is one of the most common indications for arterial surgery in the upper extremity.[30] The presence of a pseudoaneurysm may be suggested by a mass at the puncture site, evidence of distal occlusion or embolization, or neurologic complications related to median nerve compression within the sheath, usually manifesting as paresthesias. The diagnosis can generally be made with duplex ultrasonography (Fig. 118.11), and direct repair with evacuation of the hematoma compressing the median nerve can be performed under local anesthesia. Percutaneous thrombin injection is another therapeutic option described in the literature. In a report of 14 patients successfully treated with ultrasound-guided thrombin injection for iatrogenic upper extremity pseudoaneurysms, there was a low complication rate with no recurrences at 8 months.[31]

Occlusion of the brachial artery as a result of catheter insertion often requires more extensive reconstruction that usually involves a segmental bypass with either saphenous vein or cephalic vein from the ipsilateral arm. If recognized promptly, any propagated thrombus proximal or distal to the puncture site can be extracted

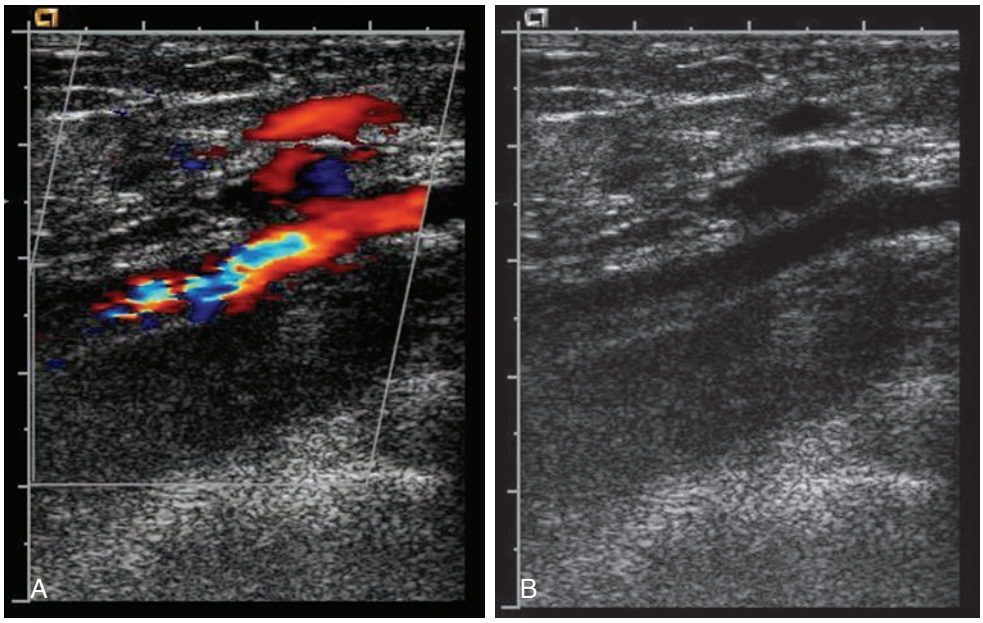

Figure 118.11 Brachial artery pseudoaneurysm after cardiac catheterization, as seen through color duplex (A) and B-mode (B) ultrasound imaging.

with a balloon embolectomy catheter. Delayed recognition of this problem will often necessitate a longer-segment interposition graft with autogenous vein.

Radial Artery

The radial artery is the second most common site of upper extremity iatrogenic arterial injury as a result of catheterization. Partial or complete occlusion of the radial artery after cannulation for monitoring purposes was apparent in 25% of 1699 patients undergoing cardiovascular surgery in a series by Slogoff and colleagues. None of these patients had hand ischemia.[32] Although the involved hand may be clinically pale, the fingers usually remain viable with intact neurologic function due to collateral filling across the palm from the ulnar artery. Unless there is some obvious evidence of severe cyanosis, demarcation, neuropathy, or sensorimotor deficit, we would generally recommend a period of observation after removal of the arterial catheter. Heparinization is desirable but not mandatory. Many of these cases will improve with conservative treatment. In the few cases in which the hand either acutely or subacutely appears to be severely ischemic, repair with a short autogenous bypass of the radial artery above and below the puncture site is usually sufficient to effect improvement. Radial and ulnar artery vascular access for cardiac catheterization using up to 6 Fr sheath systems, is increasing. Occlusion rates have been reported to be approximately 5% in either vessel,[33] and the overwhelming majority are asymptomatic and do not require reconstruction.

Noniatrogenic Trauma

Trauma related to blunt or penetrating trauma is, unfortunately, a common source of upper extremity arterial injury.[34] In civilian centers, these injuries are predominantly blunt or involve low velocity penetration. Military-associated upper extremity vascular injuries are complex because of the combined nature of the mechanism and significant multi-system injury.

Penetrating Trauma

Penetrating trauma is generally evident on evaluation in the emergency department. Repair of the injury is not usually complex, but obtaining proximal arterial control can be challenging. Injury to the subclavian arteries may require anterior thoracotomy or a trapdoor-type incision, or both (see Chapter 182). Injury to the axillary arteries is often best managed by initial proximal exposure of the subclavian artery from a supraclavicular approach. Proximal control of the brachial artery can usually be managed with a more proximal medial upper arm incision. Radial and ulnar artery injuries can often be managed with relatively local control, although exposure of the brachial artery at the elbow is always an option. Alternatively, application of a tourniquet may allow direct wound exploration. Patients with isolated radial or ulnar artery injuries and clinical evidence of satisfactory hand perfusion in all five digits can be managed by ligation of the affected artery. However, it is often not much more difficult to simply repair the involved artery with a local vein. Whether to ligate or bypass an isolated forearm arterial injury in a pink viable hand is still debated.

Delayed Recognition

Delayed recognition of arterial injury related to penetrating trauma may occasionally result in pseudoaneurysm formation, and sometimes arteriovenous fistulae are also formed by this mechanism. Consequently, there should be a relatively low threshold for obtaining arterial imaging for any penetrating trauma that may produce an arterial injury. Many forearm injuries related to broken glass may produce an occult radial or ulnar artery injury that is not identified at the initial inspection, but may result in further hemorrhage and even the development of compartment syndrome days later. Given the potential difficulty with the follow-up of these patients, imaging at the time of initial evaluation is recommended to avoid delayed recognition of these injuries. Once identified, arterial pathology, such as pseudoaneurysm, arteriovenous fistula, and compartment syndrome, should be promptly addressed. Alternatively, asymptomatic upper extremity arterial occlusions may be observed or reconstructed based on clinical condition paralleling treatment algorithms with the lower extremity.

Blunt Trauma

Management of blunt trauma producing arterial injury is somewhat more complicated because of the difficulty in diagnosing and localizing the injury. The force of an impact strong enough to injure the artery may result in associated neurologic compromise and long-bone fracture. Frequently, these patients benefit from preoperative arteriography. Ongoing hemorrhage is generally not the problem, and exposure can be directed at the injured site. However, it is also more likely that there will be associated extensive venous injury and the development of venous hypertension after reconstruction of the arterial lesion. In these cases, either direct repair of the vein or a short autogenous bypass of the injured venous segment is useful to decompress the venous hypertension in the affected arm, and thereby decrease swelling and continued hemorrhage from the wound, although this remains controversial.[35]

Pediatric Supracondylar Fractures

One area of controversy is the treatment of type III supracondylar fractures of the humerus in children who lack a palpable radial pulse after the injury. Long-term ischemia from arterial occlusion in a child may lead to Volkmann contracture, which results in permanent flexion and a claw-like deformity of the hand and fingers. The brachial artery may be pinched, avulsed, or thrombosed as it wraps around the fracture site. Orthopedic reduction is the accepted first treatment, with neurovascular reevaluation after stabilization. If the pulse returns, no further treatment is necessary besides observation. If it does not return, and the hand appears white, pale, and ischemic, operative exploration is preferred. Debate exists in the literature regarding the optimal treatment when the pulse is not palpable but the hand is pink and viable. Some describe a conservative approach with serial examination.[36] Others favor aggressive operative reconstruction whenever possible,[37] either direct arterial repair with patch angioplasty or bypass using the great saphenous vein around the area of injury. Care must be taken with arterial manipulation

in children to avoid spasm whenever possible. Fortunately, the incidence of this type of upper extremity ischemia is low. Multiple authors have found that additional imaging, such as contrast angiography or duplex ultrasonography, does not alter the course of treatment.[38,39]

Complications

Major complications that may occur after upper extremity arterial surgery include brachial plexus and median or ulnar nerve injury. Such injury is usually a result of traction and should be avoided by careful dissection during operative exposure. The use of electrocautery should be minimized to reduce the chance of direct thermal injury to the underlying nerves at all levels.

As with any arterial bypass, graft thrombosis can also occur. Some series found female smokers and patients with longer bypasses crossing multiple joints to have the lowest patency.[2,14] An inflow lesion in the subclavian artery can also cause acute arm ischemia (e.g., ulcerated plaque, thrombosed subclavian artery aneurysm, or arterial thoracic outlet syndrome). In such situations, even a technically perfect brachial embolectomy will fail to restore normal hand perfusion. Moreover, if the arteries are relatively free of atherosclerotic disease, embolectomy of the distal radial and ulnar vessels may result in arterial spasm. This problem is more commonly seen in women and children. However, it is a diagnosis of exclusion, and the first priority must be removal of retained embolic debris. If spasm is identified intraoperatively, topical or intra-arterial vasodilators, such as papaverine, warm saline irrigation and time should relieve the constriction and result in an adequately perfused hand.

Compartment Syndrome

As in the lower extremity, reperfusion of the arm may result in a significant inflammatory response and swelling. This response is more common with treatment of acute ischemia in an individual without long-standing collateralization, but overall it is a rare event. Decompressive fasciotomy is the mainstay of treatment. This involves incising the fascia on both the volar and the dorsal aspects of the arm. In severe cases, extension of the fasciotomy into the hand itself, through the carpal tunnel, may be required.

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119 CHAPTER

Upper Extremity Arterial Disease: Amputation

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Upper extremity amputation remains infrequent in today's vascular surgery practice. Loss of a portion of the arm and hand is usually a devastating and life-altering event. Although surgical therapies may be aimed either at completing initial salvage attempts or, with reconstructive principles in mind, at maximizing function after amputation, such efforts are only the beginning of a life full of challenges for these individuals. Rehabilitative, social, financial, and psychological considerations are important and may be different from those of patients who have suffered lower extremity loss.

EPIDEMIOLOGY

In 2005, there were approximately 1.6 million amputees living in the United States, with upper extremity amputees accounting for 541,000 of this number; it is anticipated that these values will more than double during the next four decades.[1] Approximately 185,000 patients undergo amputation each year in the United States, and it is estimated that anywhere from 10% to 25% of these amputations involve the arm and hand.[1,2] It seems that this relative proportion remains constant as the overall number of amputations performed increases. Most amputations in the upper extremity (93%) involve minor amputation at the wrist or within the digits.

Etiology

The majority of upper extremities requiring amputation are the result of trauma (80%-90%).[1,2] It is not surprising, then, that upper extremity amputees are generally younger (20-40 years

old on average) and predominantly male. However, other etiologies do contribute. Vascular disease and tumors are the next most common indications and represent 7% and 0.6% of upper extremity amputations, respectively.[1,2] Even less frequent causes include infections, congenital anomalies, and iatrogenic reasons, such as complications related to catheterization, vasopressor administration, and vascular access. Thus, the general indications for amputation of portions of an arm or hand include tissue destruction, vascular compromise, and tumor development. This overall distribution is in contradistinction to that of lower extremity amputation, where vascular disease is the inciting etiology in nearly 80% of cases.[1,2]

Ischemia as the cause of upper extremity amputation usually results from trauma. Atherosclerosis is distinctly less common in the arteries of the arm and is a rare form of peripheral arterial disease.[3] Even in more chronic scenarios, the most frequent reason for upper extremity revascularization is traumatic injury.[4,5] (Even emboli from more proximal atherosclerotic or cardiac origins are much more common than chronic occlusive disease).[6] Such trauma may include vibration-induced white finger, hypothenar hammer syndrome, and athletic-associated conditions, such as quadrilateral space syndrome and arterial thoracic outlet compression resulting in subclavian aneurysm. Arterial trauma or embolization related to drug use has clearly been illustrated. Apart from atherosclerosis, a variety of arterial disorders leading to extremity arterial insufficiency may affect the arm, including vasospastic disorders (e.g., Raynaud disease), small-vessel diseases (e.g., Buerger disease), and radiation-induced arteritis.

Trauma and Military Injuries

The long-standing experiences from Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF, Afghanistan) have provided continued insight into traumatic vascular injury of the upper extremity and upper extremity amputation. Such insight is mostly due to the significance of extremity injury during this conflict and during war in general. Many of the principles of amputation were developed during the American Civil War and persist today. Stansbury and colleagues characterized the amputations that occurred in 8000 United States troops after injuries to extremities during the first 5 years of OIF/OEF.[7] They found that 7.4% of major limb injuries required amputation. However, this is not unique because a purported need for amputation occurred in more than 8% of extremities during the Vietnam War. In both wars, nearly 18% of amputees required multiple limb amputations.

Interestingly, the experience in the upper extremity is somewhat different from that in the lower one. With nearly 3400 major upper extremity injuries recorded, the arm amputation rate was 3.1%. This figure is in contrast to a rate of 8.5% in almost 4000 major lower extremity injuries, even though the incidence of neurovascular injury was similar in the two groups at approximately 15%. The authors surmised that this disparity could be related to several factors. Nearly 90% of extremity injuries were due to explosive mechanisms, which are most common at ground level, so the legs may sustain more significant destruction. Furthermore, the increased infection and nonunion rates cited in the lower extremities may have played a role. Finally, the surgical push for arm salvage because of limited functional prosthetic options for the upper extremity may have created a higher threshold for amputation.

Nevertheless, experience in Iraq clearly depicts the seriousness of arterial injury in the upper extremity during OIF.[8,9] At the 332nd Expeditionary Medical Support Group (EMDG), Air Force Theater Hospital in Balad, Iraq, almost 10% of patients with upper extremity arterial injury who underwent arm salvage treatment ultimately lost the limb during the early period. Yet if those sustaining upper extremity arterial trauma are able to be successfully revascularized, the prospect of limb salvage into the later phases of treatment and rehabilitation is excellent.[10] This reaffirms a small body of literature indicating that in those with significant neurovascular, bony, and soft tissue upper extremity injury, aggressive limb salvage attempts are often successful.[11-20] Moreover, even though disability after upper limb salvage is usual, intensive therapy can lead to improvement over the longer term. Thus, unless absolutely clear from a destructive or systemic indication, early amputation should be avoided. The extreme views on this topic are seen in communications by those espousing limb reimplantation techniques.[21,22]

Yet, the visibility of upper extremity amputation from OIF/OEF troops has led to an appreciation by society and produced an increasingly supportive environment. Recently, updated OIF/OEF data describing amputation trends from January 2001 through July 2011 using the Military Amputation Database were reported.[23] Specifically, upper extremity amputation has accounted for 14% of amputations performed, 18% of amputees, with bilateral upper extremity amputation in nearly 1% of amputees. Delayed amputation beyond 90 days has accounted for 10% to 15% of amputations per year. Our ability to address, improve, and provide newer prosthetic technologies, broadened therapeutic applications, and rehabilitative principles has been advanced for those missing a segment of an arm or hand. However, even with these advances the upper extremity amputees are unlikely to be found "fit for duty." In a series of 1315 service members that sustained 1631 amputations, 173 service members were found to have an upper extremity amputation, none were found fit for duty, and only 12 were allowed continuation on active duty. In addition, upper extremity amputees were more likely to have a disability from posttraumatic stress disorder (PTSD) versus the general amputee population. These findings underscore the complexity of patients suffering an upper extremity amputation.[24]

Nontraumatic Disease

When nontraumatic vascular compromise in the upper extremity is the pathologic pathway leading to a limb-threatening process, treatment should be directed at correction of the underlying condition. This may be relatively simple and systemic, such as cessation of smoking in those with Buerger disease; operatively straightforward, as with thromboembolectomy; or more complex and infrequent, such as sympathectomy for vasospastic diseases and bypasses, with or without thrombolytic therapy, for occlusive disease. Should the process affecting the upper extremity be focal, the surgical principles of treating limb-threatening conditions apply so that the best possible function can be provided

for the patient. Unfortunately, some diseases involving the arm and hand are more diffuse; they lead to regional pain syndrome, are difficult to treat, and have less clearly described therapeutic outcomes. All of this may proceed to a final pathway that simply requires some form of amputation. If this is the case, the principle of conservatism and conservation of parts is critical because aggressive surgical procedures may both aggravate the ischemic process and impede eventual function.

GENERAL OPERATIVE CONSIDERATIONS

Initial Management

As stated earlier, the majority of amputations are secondary to trauma and are usually managed in staged fashion to preserve as much of the arm as possible. This principle dates back to the care of battlefield injuries during World War II.[25] As opposed to the lower extremity, which requires only adequate soft tissue coverage in anticipation of a functional prosthesis, an upper extremity amputation must be both functional and cosmetically acceptable. With this in mind, definitive decisions on the level and length of amputation should not be made in the acute setting. In addition, as compared to the lower extremity, the majority of patients are less willing to lose a poorly functioning hand. Sequential stepwise debridement and later definitive closure are the keys to successful technical and functional results. One of the advancements over recent years is wound care and wound bed preparation before closure. The use of negative pressure therapy to promote granulation and assist in flap and graft coverage has become a mainstay in treatment. This technology is used even in the modern battlefield scenario, with multiple debridements and placement of these devices early after injury.[26] Although the basic techniques of surgery and debridement have not changed, emotional and functional rehabilitation has dramatically improved. Advancements in prosthesis design and functionality have allowed these patients to return to meaningful positions in today's society. Factors that play major roles in individualizing the surgical strategy for upper extremity amputation include etiology, age, handedness, occupation, associated injuries and physiologic state, accessibility to state-of-the-art occupational and physical therapies, and cultural settings.

Arterial Assessment

For both traumatic and nontraumatic indications, the level of upper extremity amputation fundamentally required depends on adequate arterial perfusion. The use of physical examination in conjunction with noninvasive studies, such as duplex ultrasound, segmental pressure measurement, pulse volume recording, infrared photoplethysmography, laser Doppler techniques, transcutaneous oxygen tension ($tcPO_2$) measurement, and, occasionally, even arteriography before amputation, can ensure that no ischemic component of the injury will prevent healing. Each evaluation technique has benefits and shortcomings. As described in Chapters 117 and 118, the use of noninvasive tests can be invaluable in facilitating success. This is no less true in amputation, and though rare when compared with lower extremity evaluation, low pressure, poor arterial waveforms, and low $tcPO_2$ measurements along the extremity must be recognized and the management appropriately altered.

Guidance suggesting the appropriate blood flow for healing at specific levels has largely been described for lower extremity amputation (see Chapter 111). Within the context of tissue perfusion, however, these same principles can be applied to the upper extremity. Generally, healing will occur at the hand level when digital pressure is 40 mm Hg or higher and wrist Doppler pressure is greater than 60 mm Hg. For hand-level procedures, healing is unlikely to occur when digital pressure is less than 20 mm Hg. At the forearm and arm levels, healing will almost always take place when wrist or brachial pressure is at least 60 mm Hg or when $tcPO_2$ is 40 mm Hg or greater. Healing is less predictable when $tcPO_2$ is between 20 and 40 mm Hg and wrist or brachial Doppler pressure is less than 50 mm Hg. Pulse volume recordings may provide evidence of collateralization and suggest a higher likelihood of success, yet they remain nonspecific when blunted. Once a level for amputation is chosen, simple ligation of blood vessels during the procedure is usually sufficient as long as tissue coverage of these structures can be obtained.

Preservation of Length

Although preservation of length is a fundamental principle of amputation surgery, length does not always correlate directly with function, depending on the type of prosthetic application contemplated. However, in general, it is important to retain and salvage as much residual stump as possible to maximize the ultimate functional outcome. To this end, several reconstructive techniques have been described to salvage stump length,[27-32] including plastic and orthopedic surgery techniques, such as bone and free tissue transfer. These techniques have been applied selectively and may be helpful in certain instances, particularly elective planned procedures when the cause is tumor resection or isolated traumatic injury and the procedures may need to be performed in a staged fashion. Length-preservation techniques have a limited role when the underlying pathology involves vascular insufficiency because of concern for viability and perfusion of the grafted tissue. Moreover, selective reimplantation methods and even hand transplantation have been suggested in an attempt to maintain viable, functional tissue and length for the upper extremity.[21,22,33] In fact, in select scenarios, such as clean traumatic severing without much tissue loss or associated trauma, these methods must be given initial consideration. However, in most acute trauma settings, this decision cannot be made, and minimizing loss of length should be the goal. One concept that should be considered is that longer length may result in poorer healing, whereas shorter length results in decreased function. Thus, acute amputation should be performed at a level at which healing is likely and function is maximized. Also, if at all possible, the elbow joint should be retained to facilitate later prosthetic function.

Soft Tissue Coverage

Historically, the maintenance of length depended on local soft tissue coverage; if soft tissue coverage was not adequate, one merely shortened the extremity until closure could be achieved. As mentioned earlier, skin grafts, free flaps, and composite tissue transfer have dramatically changed this approach. Skin grafts are applicable when the underlying soft tissue bed is acceptable, but one must be sensitive to the ultimate functional needs of the amputation site; in some cases, skin grafts may not be durable enough to tolerate therapy and the use of prostheses. Local flaps (see section "Fingertip Amputation") abound, but their applicability is limited because of the anatomy at more proximal amputation sites. Pedicled flaps (regional or distal) have a long, productive history in hand surgery; however, they have been increasingly replaced by free tissue transfers. This change is based on (1) better matching of the tissue transferred (in terms of thickness and ultimate functional performance), (2) avoidance of additional surgery (whether for division or thinning of the flap), and (3) lack of the joint limitations that result from the immobility that is typically necessary with pedicled flaps. Free tissue transfer is increasingly being accomplished at sites proximal to the hand to achieve more satisfactory results.

Nerves

Prevention of neuroma is the most difficult problem in upper extremity amputation. As in all of medicine, the existence of many methods of treatment usually indicates that none of them is exceptionally good. Such is the case with prevention of neuroma. Distal ligation, proximal ligation, coagulation, chemical ablation of the end, simple division, traction and division, nerve repair to other divided nerves, and immediate burial of the transected nerve end have all been attempted with varying degrees of success. The desire to eliminate painful focal sensation must be balanced against the secondary loss of sensibility induced by many of these techniques. A divided nerve always attempts to regenerate and, in so doing, produces a neuroma of variable clinical significance. Thus, in reality, the goal is not to prevent the formation of a neuroma altogether, but to prevent the patient from experiencing the pain or dysesthesias from the neuroma that will predictably develop. In general, locating the divided, free nerve end as far from external stimuli as possible and placing it in a healthy, nonscarred bed of tissue are the best preventive measures. In addition, early postoperative therapy (desensitization or sensory re-education) is an extremely important determinant of the patient's ability to tolerate the dysesthesias that result from an amputation. Centrocentral nerve union utilizes the technique of coapting severed nerve ends to form a loop and has been reportedly successful as well.[34] Targeted reinnervation by way of nerve transfer techniques has also been described as a means of improving residual muscle function and sensory aspects of the stump and thus prosthetic utility.[35] Such procedures can be performed in either a planned elective or a staged scenario.

Bone and Cartilage

Whatever length is ultimately chosen for the amputation, the bony prominences must be optimally contoured. Lack of attention to bony prominences or irregularities in bony contour lead to aesthetic abnormalities and difficulty in obtaining optimally fitting prostheses. Inadequate debridement of traumatized tissue and displaced bony fragments, improper initial contouring of bone, or failure to identify bone-producing periosteum, which must also be contoured, are the sources of such difficulties. Visual identification of the periosteum is easiest during initial management of the injury, and achievement of a natural bone contour is greatly assisted by palpating the end of the bone through the skin before closure. This is even more important in amputations through joints, where natural anatomic flares of the bone produce aesthetically unnatural contours and interfere with prosthetic fitting.

Tendons

The hand represents a very delicate balance between extensor and flexor forces. It is extremely difficult to duplicate the balance of these forces through myodesic methods (i.e., suturing of tendons or muscles to bones) or myoplastic techniques (i.e., suturing of tendons or muscles to tendons or muscles of the opposite functional group; for example, suturing an extensor tendon directly to a flexor tendon over a bony amputation site). In general, then, such techniques are not used distally in the fingers and hand because they often add to the functional deficit. However, they do have value proximally, where the balance is not as critical, and re-education and adaptation are easier.

SPECIFIC AMPUTATIONS

Fingertip Amputation

Distal finger amputations are extremely common. The most frequent mechanism causing such injuries is a crushing blow, such as from a closing door. Although many people arrive at the emergency department with the tip of the finger available for reattachment, the injury is usually too distal for microsurgical reattachment. Many surgeons have attempted composite reattachment (i.e., reattachment without specific revascularization) with generally poor results. At present, such composite grafts are not indicated except in young children (younger than 2 years), in whom there is an increased chance of graft survival.[36] Most composite grafts fail because (1) the amount of tissue is generally more than can survive the ischemia until new circulation develops and (2) the zone of injury is greater than the area of amputation (i.e., the tip is usually damaged and thus is not capable of surviving as a composite graft).

Technique

If the proximal portion of the distal phalanx is not severely injured so the insertions of the flexor digitorum profundus and extensor tendons are intact, preservation of that portion of

bone is indicated for functional length. If these areas are damaged beyond repair, disarticulation through the distal interphalangeal joint is indicated. The flexor digitorum profundus tendon should never be sutured over the tip or to the extensor tendon because this can weaken grip in the hand (the quadriga effect).[37] The bone of the distal phalanx should be of adequate length to support the nail bed and nail growth.[38] Generally, these amputations occur through a portion of the nail bed. If enough proximal nail bed (≈50%) is present to provide a functional nail, the bed should be repaired under optical magnification with absorbable 6-0 or 7-0 suture.

The distal phalanx is usually rongeured back so the end of the bone is not exposed. The digital nerves are identified, distracted distally, and divided so they will be at least 1 cm from the fingertip stump to avoid neuroma formation in this location. If the final cutaneous defect is then less than 1 cm^2, simply allowing the wound to close by secondary intention is acceptable. Other wound closure techniques have been attempted, including every conceivable type of local or regional flap. However, given the fact that flap closures are frequently insensate and do not reduce healing time, ultimate functional recovery appears to be better after secondary healing because the resulting scar contracture diminishes the size of the sensory defect.

Skin Grafts

If the cutaneous defect is greater than 1 cm^2, the amount of time needed for closure and the ultimate functional result may not warrant healing by secondary intention. If there is no exposed bone, a skin graft is possible. The temptation is to use the amputated part as a donor source for the skin graft. This practice should be avoided because the amputated portion has been traumatized and the overall success of such skin grafts is disappointing. However, one advantage of these grafts is that they may serve as temporary biologic dressings even if they do not survive.

Nontraumatized skin graft donor sites that may be considered are:

- The ulnar border of the palm (within the operative field and a good color match)
- The forearm (the medial portion of the forearm or the elbow crease, although hypertrophic scarring can lead to some cosmetic deformity)
- The groin (a well-hidden donor area, although the color match is not good and some unwanted hair may also be transferred)

Local Flap Closure

As mentioned previously, many alternative flaps are often useful for cutaneous defects of the fingertip; some of the more common local flaps include:

- The Kutler flap,[39] a lateral V-Y flap for closure of a central tip defect
- The Atasoy flap,[40] a palmar V-Y flap
- The palmar flap,[41] based on both digital neurovascular bundles in which the entire soft tissue coverage of the digit above the tendon sheath is elevated and advanced to cover the tip of the finger
- Radius- or ulna-based local flaps, which preserve cutaneous innervation on the appropriate digital nerve,[42] with skin grafting of the donor site as necessary

In addition to these local flaps, numerous regional flaps can be used, such as dorsal skin cross-finger flaps, palmar skin cross-finger flaps, and thenar flaps. Although it is sometimes necessary to use these regional pedicled flaps, they carry significant additional morbidity by creating joint stiffness because of the obligatory period of immobility needed for attachment of the flap. Even in young people who have had good physical therapy, long-term problems can result.

Digit-Level Amputations

Midfinger Amputation

Amputations that leave more than half the proximal phalanx may be functional for the patient. These amputations represent variations of fingertip amputations. First, the bone is rongeured back a short distance to allow soft tissue coverage. Tendons that have been separated from their bony insertions by the amputation are placed on traction, divided, and allowed to retract into the palm. Digital nerves are a potentially more difficult problem. It is preferable to divide them under mild traction and allow them to retract beneath healthy vascularized tissue. Excessive traction may denervate the new tip of the digit. However, if traction is not applied, the cut nerve remains adjacent to the amputation site, which can lead to postinjury trauma and produce significant pain. The associated soft tissue defect is managed in the same manner as a fingertip amputation.

Proximal Phalanx

Amputation proximal to the midportion of the proximal phalanx is not typically a functional amputation. If enough digit remains, it may be possible for patients to wear a cosmetic prosthesis that may allow some functional restoration; however, most patients find the remaining digit a nuisance (Fig. 119.1). The effects of proximal digital amputation vary with the finger involved. For example, an index finger, which is second in importance to the thumb, when amputated proximally can become a hindrance to function of the hand. Because the patient uses the middle finger for activities such as writing, the index finger stump becomes an obstacle. With middle or ring finger amputations, each time the person reaches into his or her pocket or purse for a small object, the object falls through the opening left in the hand by the remaining short digit. The small fingers play a role in gripping objects, and if the finger becomes immobile, it may become caught on objects. Because of these issues, patients frequently choose to undergo secondary ray amputation. Regardless of the certainty of this denouement, ray amputation should not be offered to the patient at the time of initial wound closure. Elective resection of the remaining portion of the digit is a decision that each patient should reach by experience.

Ray Amputation

Ray amputation, which includes removal of the injured finger to the metacarpal base, often provides a far more cosmetically

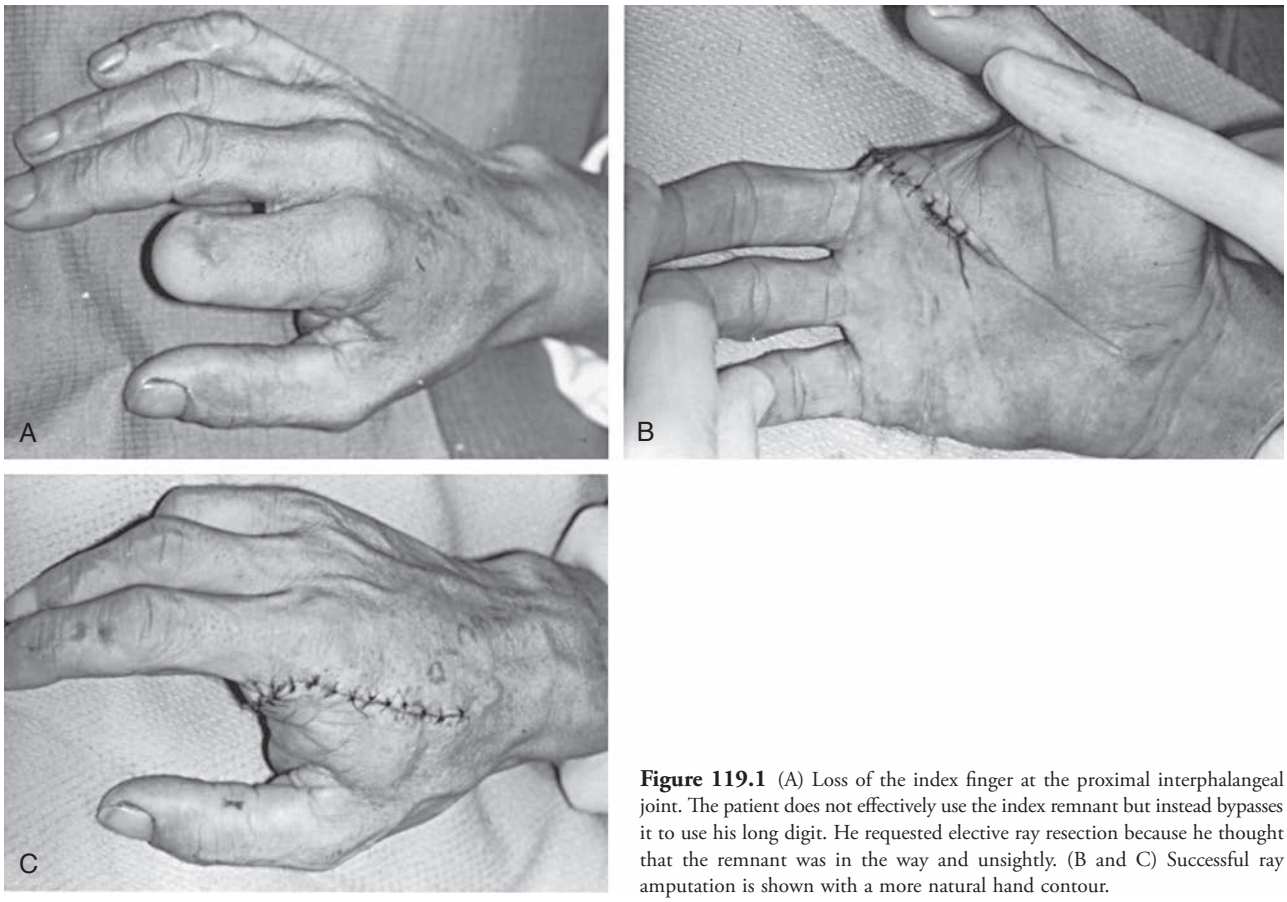

Figure 119.1 (A) Loss of the index finger at the proximal interphalangeal joint. The patient does not effectively use the index remnant but instead bypasses it to use his long digit. He requested elective ray resection because he thought that the remnant was in the way and unsightly. (B and C) Successful ray amputation is shown with a more natural hand contour.

acceptable hand, especially with an index ray amputation. This technique usually involves a dorsal longitudinal incision over the index metacarpal along with a palmar skin incision over the proximal phalangeal level. Alternatively, a circumferential racket incision may be used. Minimal digital nerve neurolysis should be done to prevent pain. Attention to myodesic and myoplastic techniques is critical because improper attachment of the remaining muscle and tendons to the lumbrical and interosseous muscle or nearby periosteum can significantly downgrade intrinsic hand function. In addition, care should be taken when performing a fifth ray amputation because the extensor carpi ulnaris inserts at the base and wrist function can be affected.

In most cases, the appearance of a three-fingered hand with normal border contours is so natural that it goes unnoticed. Nevertheless, the operation is not without its own set of risks. First, the procedure narrows the palm by 20% to 25%, which reduces the hand's ability to stabilize objects. Second, the operation is a more extensive procedure that produces more proximal postoperative pain, edema, and stiffness than that caused by the original injury to the digit. However, in the final analysis, ray amputation is very functional and cosmetically appealing, and there are few dissatisfied patients.

Thumb Amputation

Because it accounts for 40% of the function of the hand, the thumb deserves special attention in any amputation involving the hand. Clearly, the major emphasis is on reattachment of the thumb. However, the desire for reattachment has led some surgeons to attempt reimplantation in circumstances that would otherwise be considered contraindications (e.g., severe avulsion injuries). The standard of care is now to attempt reimplantation of the thumb if possible, and encouraging results have been achieved even after avulsion injuries.[43] Nonreimplantable amputations at the level of the interphalangeal joint are functional, and most patients do not request or require additional reconstruction. These stumps still provide the opposition function for the fingers. Revision of thumb amputations proximally to allow closure should not be performed as in the other fingers, and thought should be given to rotational, advancement, and free flaps.[44] More proximal thumb amputations can be reconstructed by pollicization (using a remaining finger, usually the index finger, and myodesic techniques to create a thumb), osteoplasty, bone-lengthening techniques, or toe-to-thumb transfer (great toe, second toe, or toe wraparound).

Hand-Wrist Amputations

Any tissue that can be preserved during hand amputation should be salvaged. A hand with a short palm may seem dysfunctional, but as an assist hand it may be preferable to a prosthesis. A transcarpal amputation allows supination and pronation of the forearm, as well as flexion and extension of the wrist. A prosthesis can be fitted for this type of amputation as well.

Wrist disarticulation is preferred to more proximal forearm amputation because it has the same advantages of a transcarpal amputation except that wrist flexion and extension are lost. Wrist disarticulation is performed by creating a long palmar and short dorsal flap; ligating the radial and ulnar arteries proximal to the wrist; identifying the median, radial, and ulnar nerves and distracting and dividing them; dividing all tendons; disarticulating the joint; and resecting the tips of the radial and ulnar styloid processes. The resultant smooth contour can easily be fitted for a prosthesis.

The radial, ulnar, and median nerves can present difficulties during hand-wrist amputation. The ulnar and median nerves are frequently avulsed at a more proximal level with these traumatic amputations; if they are apparent in the wound, they can be severed with mild traction and allowed to retract. Retraction of the ends usually positions the nerves away from contact with a prosthesis. The sensory branch of the radial nerve, however, is quite superficial throughout its course in the forearm (covered only by the brachioradialis muscle). Neuromas from this nerve are not uncommon, and division of the nerve in the proximal part of the forearm may be considered at the time of the initial amputation. Sensation of the forearm skin is not directly determined by these nerves but instead is controlled by the brachial cutaneous nerves, and improper management of the brachial cutaneous nerves can cause difficulties similar to those that occur with the superficial branch of the radial nerve. However, it is preferable not to divide these nerves far proximally because sensation of the forearm skin will be sacrificed.

Forearm Amputations

The optimal level for a forearm amputation is the junction of the middle and distal third of the forearm. The issue with the distal third of the forearm is the relative paucity of padding in this area because of the thin skin and subcutaneous tissue. This factor can be more evident in patients with ischemia because this area is notably prone to skin breakdown. So important is the elbow that the use of free-flap soft tissue coverage to preserve length or even distraction osteogenesis (Ilizarov technique)[29] is a viable consideration in the case of very short below-elbow amputations. However, with the exception of these very special cases, heroic efforts at preserving length are not usually indicated.

Heeding these caveats, the surgeon can trim the bony tissues adequately to permit soft tissue closure. The technique is as follows: creation of equal anterior and posterior skin flaps; ligation of the radial and ulnar arteries; distraction and division of the medial, radial, and ulnar arteries; transection of the muscle bellies; division of the radius and ulna; and closure of the deep fascia followed by the skin (Fig. 119.2). Reconstruction of the amputation is generally accomplished by means of a fitted prosthesis. However, as described by Tubiana, bilateral upper extremity amputations can be functionally improved with the Krukenberg procedure, in which a sensate pincer is created between the radius and ulna (Fig. 119.3).[45] The pincer is motorized by the pronator teres muscle, and this procedure allows preservation of proprioception and stereognosis. Although the cosmetic result is far from desirable, the functional improvement is great, and the procedure should be given serious consideration in the rare instances of bilateral injuries, in blind individuals, or when prosthetic reconstruction is not practical.[46]

Elbow Disarticulation

If the elbow joint is not salvageable, elbow disarticulation is preferred over distal humeral transection. In addition to maintaining length, humeral rotation can be transmitted to the elbow, and the broad flare of the condyles makes for a good prosthetic fit. When compared with the forearm, which has two bones with a functional noncircular cross-section and thin soft tissue coverage that allows transmission of rotational forces (pronation and supination), the upper part of the arm has a single bone with a relatively circular cross-section and less rotational stability because of its thicker soft tissue. The amputation technique is similar to that described earlier in that anterior and posterior skin flaps are created; the brachial artery is ligated; the median, ulnar, and radial nerves are distracted and divided; the joint capsule is opened and the forearm removed; and a muscle flap (brachialis or triceps) is then used to cover the humerus (Fig. 119.4). As noted, there has been an emphasis on retaining all of the humerus if possible. However, in so doing, the upper part of the arm may appear longer than the normal (unamputated) arm when fitted with an internal elbow joint prosthesis. It is possible to use an external elbow joint option, but these joints are substantially less durable. Another approach to this problem involves construction of an artificial asymmetry by means of angulation osteotomy in which bone is resected yet epicondylar stability is retained.[47] This method has gained popularity in Europe but is not routinely practiced in the United States because of the obvious cosmetic deformity in the proximal remaining stump.

Upper Arm Amputations

Surgical considerations for above-elbow amputations are essentially the same as those for forearm amputations with respect to the treatment of bone, muscles, tendons, nerves, and skin. A transcondylar amputation functions essentially the same as an elbow disarticulation. More proximal amputations must include an elbow lock mechanism to stabilize the musculature and future prosthetic joint in full extension or flexion, and a turntable mechanism that will serve as humeral rotation. Taking into account the location of the elbow lock, which extends 4 cm from the distal amputation site, the transhumeral amputation should be made 4 cm proximal to the elbow (see Fig. 119.4).[48]

Reimplantation remains a viable option, and Wood and Cooney have reported that reimplantation should be considered even with high amputations.[22] A multidisciplinary approach is required and involves early arterial and venous shunting followed by bony fixation, definitive vascular repair with attention to maximizing venous outflow, and finally nerve and soft tissue reconstruction. Functional recovery of the hand may not occur, yet it may be possible to convert an obvious above-elbow

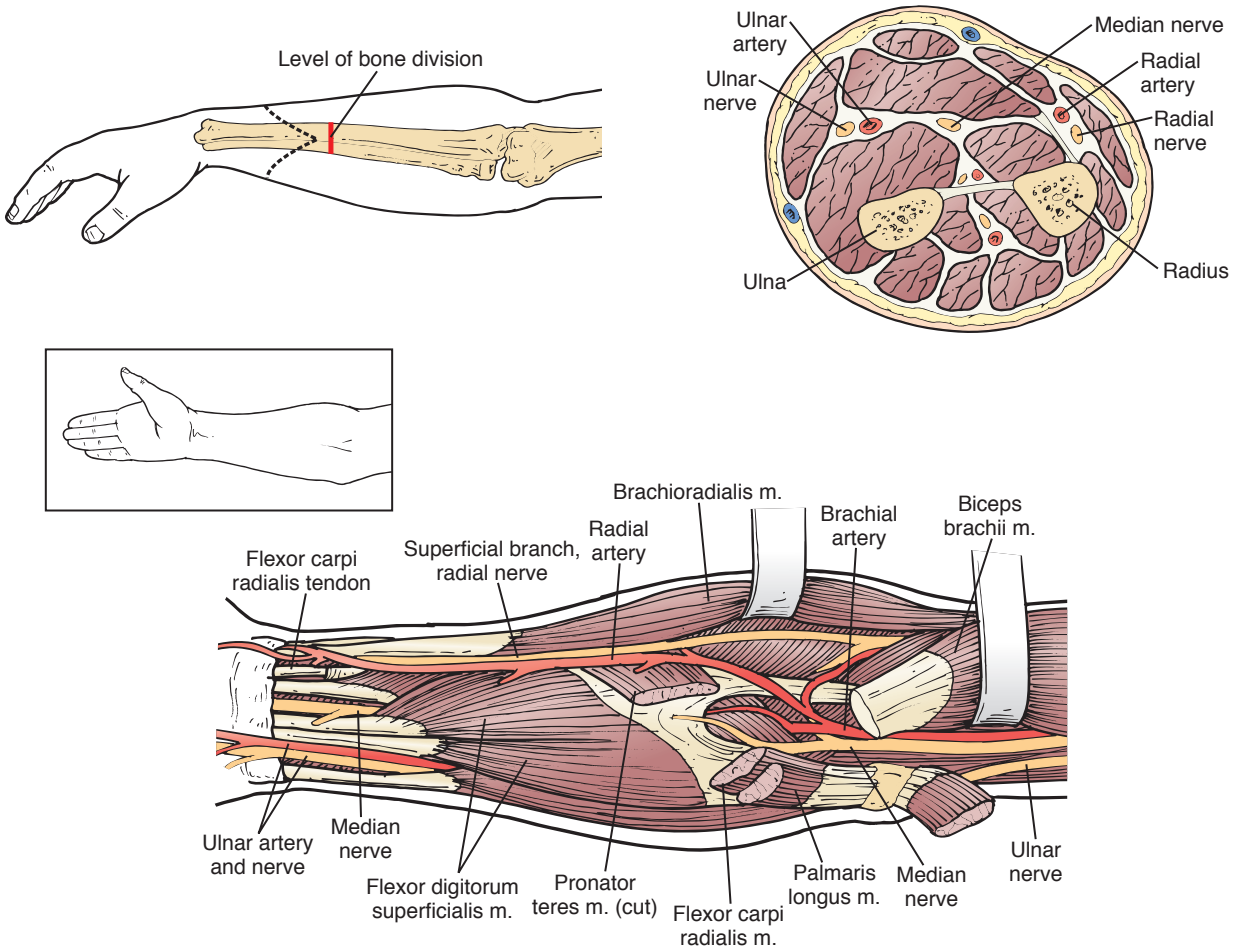

Figure 119.2 Forearm amputation is relatively straightforward: division of soft tissue at the junction of the distal third and proximal two-thirds of the forearm and several centimeters distal to the level of the bony division. Proper muscle coverage is achieved with myofascial closure. (Adapted with permission from Maxwell MC. Amputations in trauma. In: Thal ER, Weigelt JA, Carrico CJ, eds. *Operative Trauma Management: An Atlas,* 2nd ed. New York: McGraw-Hill; 2002:449.)

amputation to a below-elbow amputation, which is far more functional. The shorter the remaining stump, the more difficult the prosthetic fit and the less functional the prosthesis will be. As a result, several new techniques have been developed to facilitate this type of reconstruction. The use of free flaps can provide additional soft tissue and bone length for a short upper arm amputation. Functional restoration of the glenohumeral joint may be accomplished with a free fibular transfer. The proximal humerus can be replaced with the fibula and its proximal joint with reattachment of the muscular insertions.[27,28] Particularly in patients with malignant tumors, limbs that would otherwise have to be sacrificed can now be salvaged. Fibular flaps can also be used in conjunction with soft tissue coverage from a latissimus dorsi flap (pedicled or free) to provide acceptable upper arm length for fitting a prosthesis.

One final technique used to achieve adequate bony length is distraction osteogenesis, as mentioned previously.[29-31] Although this technique was developed in the 1960s by Ilizarov, it did not become widely recognized and used worldwide until the 1990s. The scattered reports of this method of treatment have been encouraging. As previously indicated, every effort should be made to avoid high amputations. Even when the amputation will be a functional shoulder disarticulation (amputation proximal to the insertions of the deltoid and pectoralis major muscles), maximal proximal length of the humerus should be sought for either prosthetic fitting or potential reconstruction by these complex plastic and orthopedic techniques.

Shoulder Disarticulation and Forequarter Amputations

Shoulder disarticulation and forequarter, or scapulothoracic, amputation are the most complex and difficult procedures from a prosthetic and functional standpoint. Considerations are (1) loss of potential motor units as drivers of the prosthetic device and (2) difficulty fitting the prosthesis to contours. The shoulder disarticulation (after rounding off any bony prominences that may cause wear) leaves a contour adequate to provide a snug fit for the prosthesis (Fig. 119.5). In addition, scapular function is retained and can be used (with some difficulty) as a motor

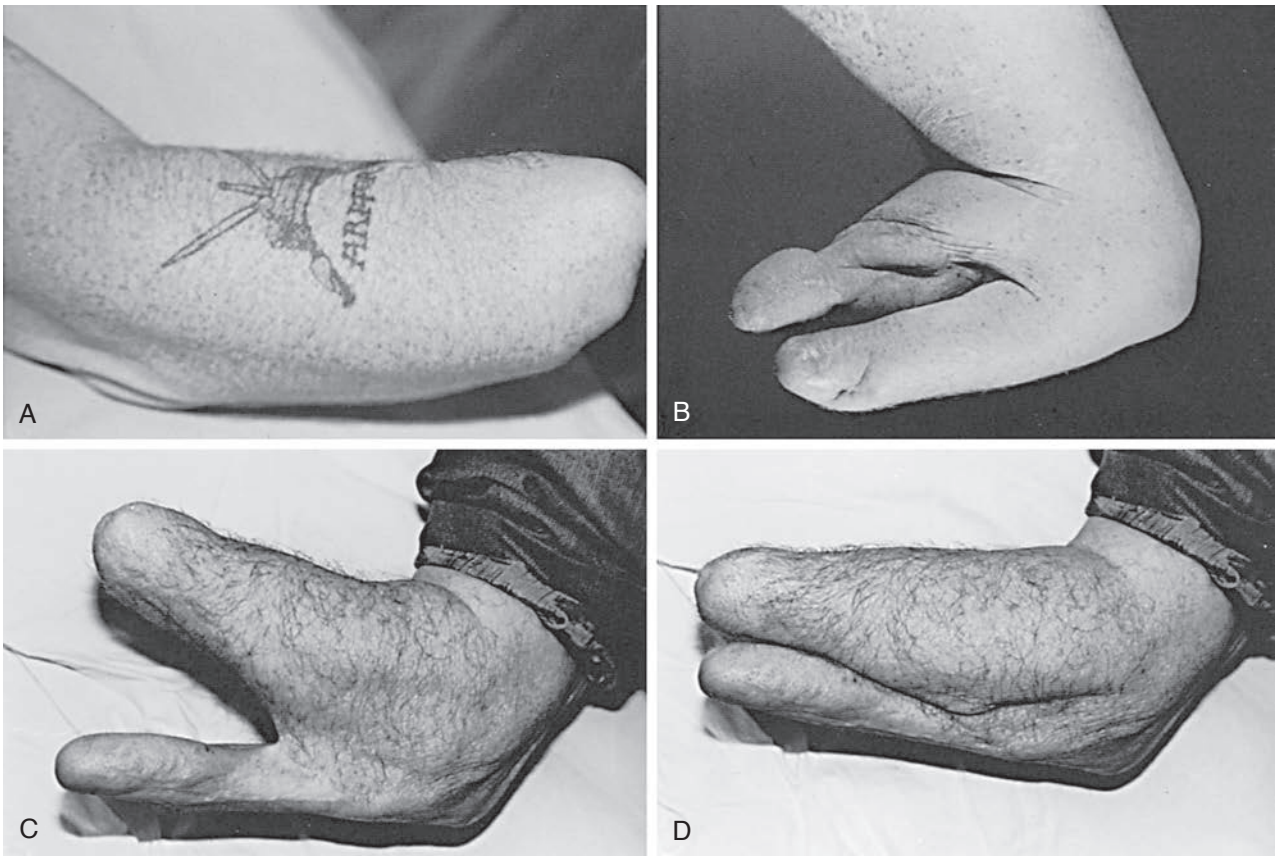

Figure 119.3 Classically, in a double-arm or blind amputee, the Krukenberg procedure has been performed. **A,** A typical below-elbow stump. **B,** The initial separation of the ulna and radius. **C,** The open and **D,** closed pincer grasp mechanism is preserved and controlled by the pronator teres muscle.

unit for the prosthetic device. However, a forequarter amputation (which is done almost exclusively for malignant processes), offers little hope for functional restoration of the limb, and prosthetic application is challenging.[49]

The surgical techniques for these amputations are well described in the literature. The shoulder disarticulation may be modified by retention of the humeral head to assist in contouring or may be a true disarticulation with complete removal of the humerus. Regardless, the deltoid and pectoral muscles, along with their overlying myofasciocutaneous tissue, provide the flap coverage. Occasionally, if the deltoid is not available, an inferior axillary fasciocutaneous flap may be necessary. The latissimus dorsi and pectoralis major are reattached to either the glenoid capsule or the humeral head remnant. The tendinous components of the rotator cuff are also attached to the glenoid capsule. In a modified technique, their insertions are undisturbed, which reduces movement and, thus, pain in the joint area. It also stabilizes the muscles for future myoelectric control points.

There are two approaches to forequarter amputation. The anterior approach, described by Berger,[50] and the posterior approach, described by Littlewood,[51] differ only in exposure of the vascular structures hidden behind the clavicle. Both approaches are well accepted. Any available remaining myofascial components are used to provide closure. The same principles that were previously described apply: removing the bony prominences, treating the nerves and muscles, and providing adequate soft tissue coverage.

POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

Wound Treatment

Aside from the standard surgical principles of postoperative wound care and post-traumatic injury care, the principles of postoperative management after upper extremity amputation are supportive. There should be a low threshold for the use of drains in areas of potential space because hematoma and seroma formation is not uncommon and might not only delay rehabilitation and prosthetic placement but also place tissue viability at risk and increase the potential for infection. Drain removal as soon as possible is encouraged to reduce infection risk. Early physical activity and rehabilitation are encouraged. Compressive dressings are used immediately. The full range-of-motion exercises of the elbow and shoulder should be started immediately when these structures are preserved. Local amputation site concerns revolve around infection, wound healing, and the viability of specialized reconstructive methods, such as free flaps if used. Infection is rare, and, even when trauma is the indication for

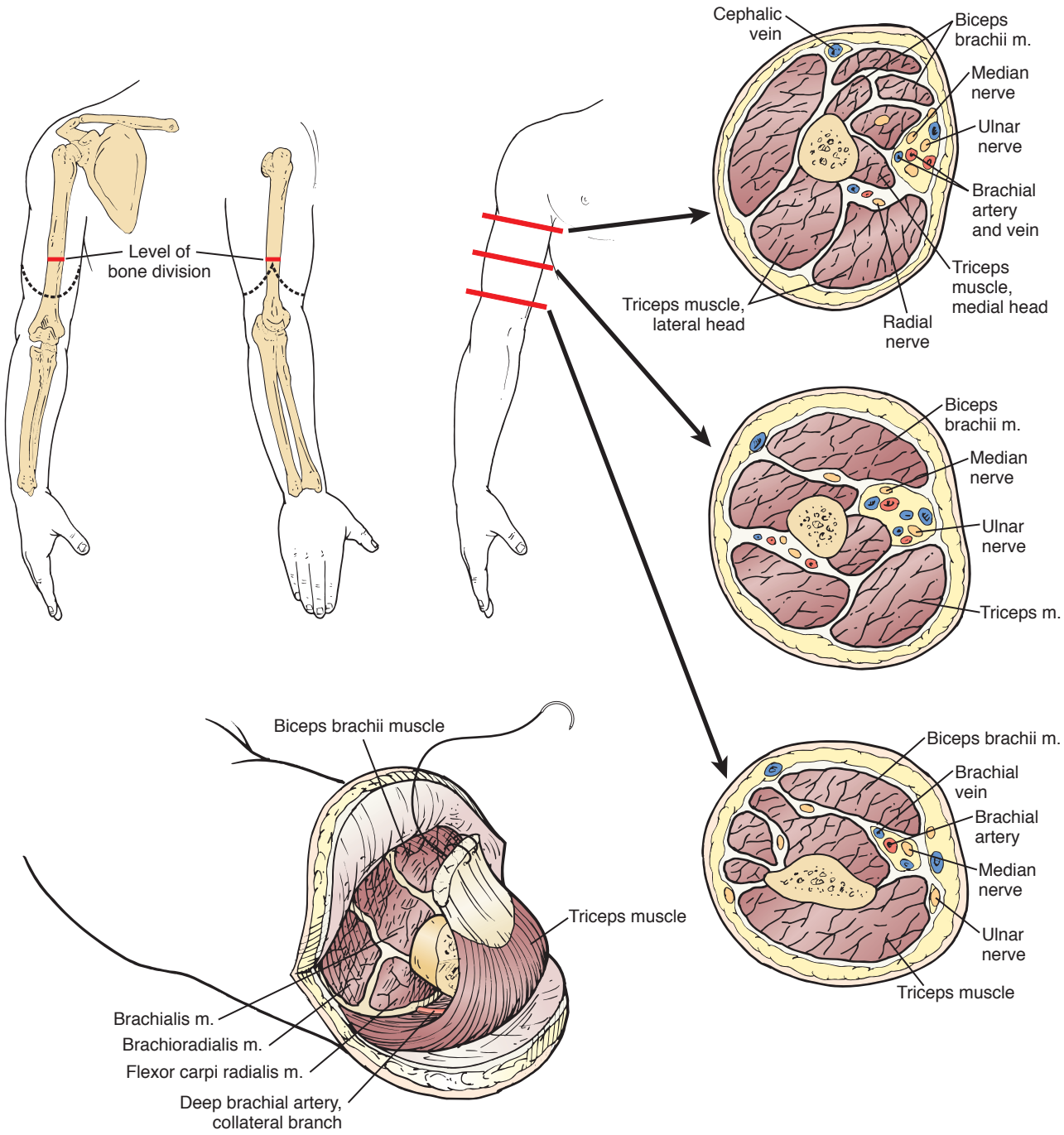

Figure 119.4 Upper arm amputation can be performed at several levels. The initial operation should be focused on maintaining as much humeral length as possible and the epicondyles, if salvageable. (Adapted with permission from Maxwell MC. Amputations in trauma. In: Thal ER, Weigelt JA, Carrico CJ, eds. *Operative Trauma Management: An Atlas,* 2nd ed. New York: McGraw-Hill; 2002:451.)

amputation, should generally occur in less than 5% of cases. Failure of complex tissue transfers, if performed, occurs in 3% to 8% of upper extremity reconstructions early and becomes even rarer in later evaluation.[52]

Poor wound healing and the concerns of flap ischemia and stump necrosis, which are well appreciated in lower extremity amputation, occur infrequently in upper extremity amputation but must be recognized if they do occur. Potential systemic complications of upper extremity amputation are related to septic events, associated traumatic injuries, or systemic consequences of either a global vascular process or an organ system comorbidity. As with treatment of any ischemic injury, should upper extremity amputation be performed subsequent to attempts at limb salvage and revascularization or after significant crush injury, one should be attuned to the potential for significant rhabdomyolysis and myoglobinuria. The threat of this problem

is usually less than in the lower extremity because of smaller muscle mass, shorter arm length, and, thus, attainment of collateral flow; yet it remains a possibility, and proper hydration and urine alkalinization should be instituted, if necessary.

Revision

Because the majority of upper extremity amputations are secondary to trauma, reoperations for residual limb revision are often required. Recently, a study describing a cohort of soldiers involved in OIF/OEF found that of 100 major upper extremity amputations, 42% required repeat surgical procedures. Interestingly, patients undergoing transradial amputation were 4.7 times more likely to have phantom pain. Revisions of these amputations resulted in an increase in prosthetic use from 19% preoperatively to 87% postrevision. Obviously, this underscores both the improved understanding and treatment of this complex patient population, as well as the complex and intensive care required to provide a reasonable endpoint for these patients.[53]

Phantom Pain

Phantom sensations occur over time in the majority of patients undergoing upper extremity amputation. Long-term phantom

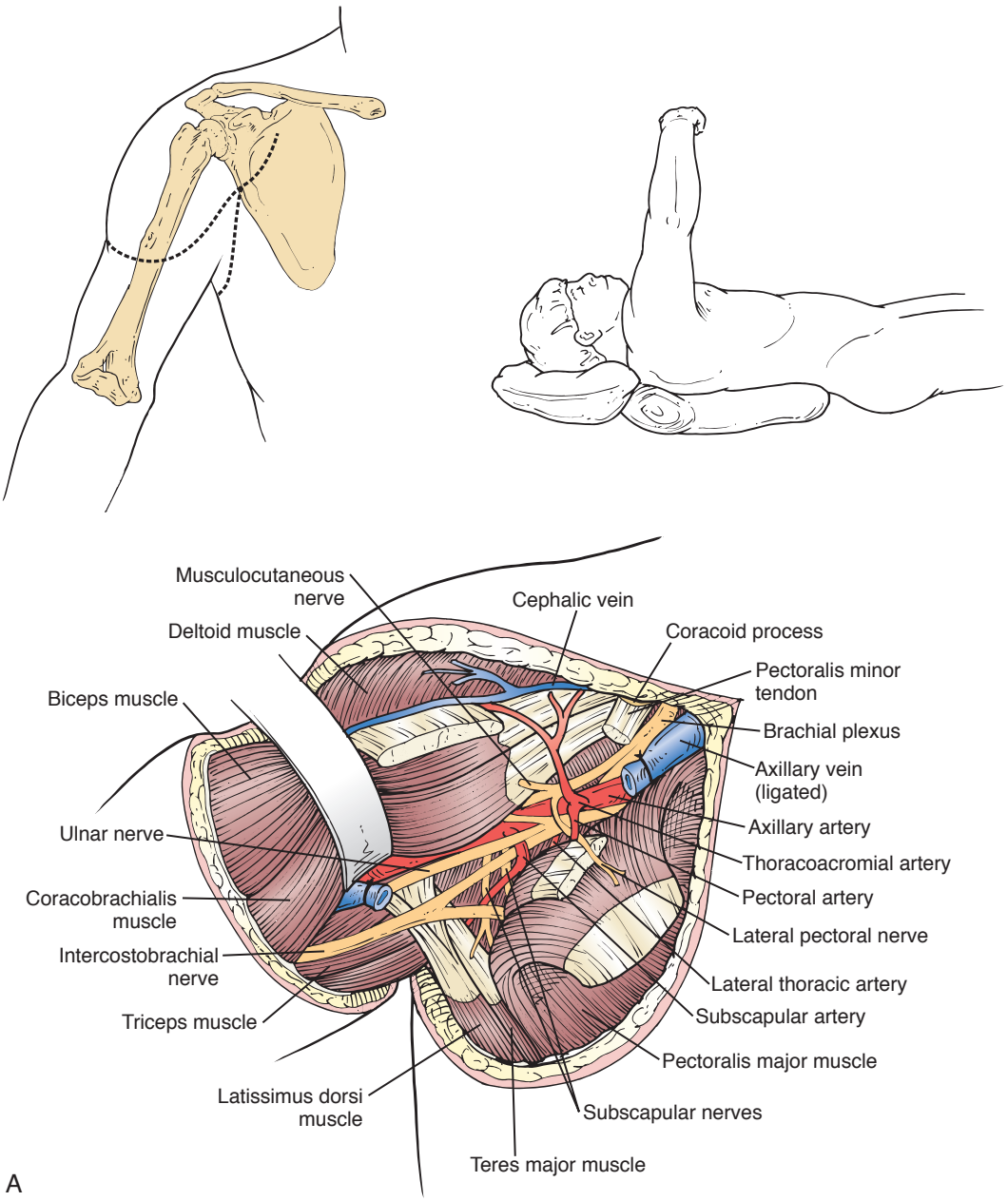

Figure 119.5 Shoulder disarticulation as classically described. (A) Skin incision and initial anterior approach with division of the anterior attachments, brachial plexus, and subclavian vessels. *Continued*

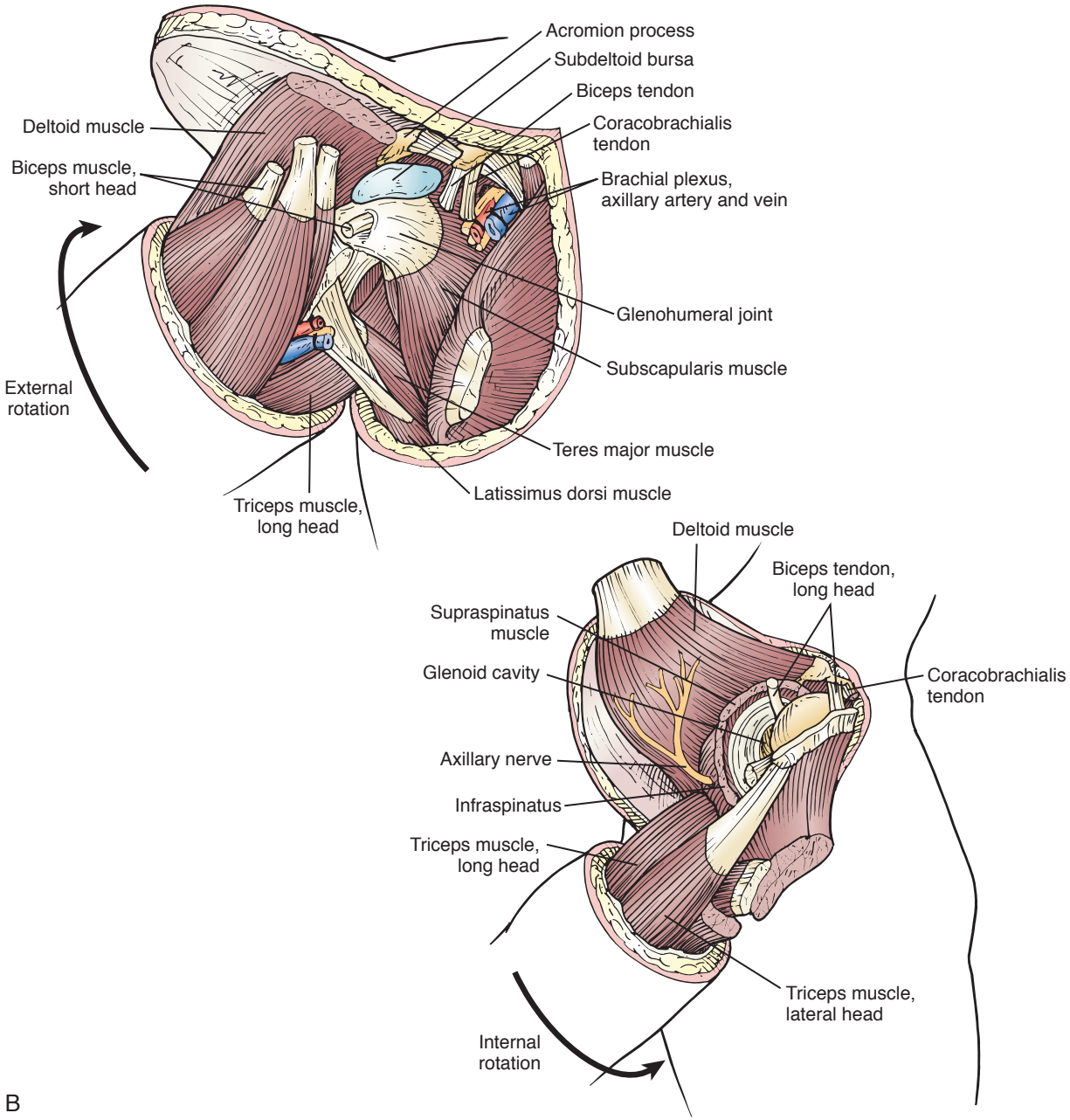

Figure 119.5, cont'd (B) Completion of all anterior and posterior attachment transections.

pain, in varying degrees, occurs in 40% to 80% of patients.[54,55] In an evaluation of upper extremity amputees from the Iran-Iraq War during an average of 17.5 years, phantom pain occurred in 32% of amputees.[56] Treatment methods for phantom pain are numerous and usually multidimensional, but can be generally categorized as pharmacologic, surgical, psychological, and neurostimulatory. Newer evaluations of motor cortical changes and alterations in hemispheric function after upper extremity amputation may, in the near future, lead to novel therapeutic methods to treat postamputation pain syndromes.[57] It has been suggested that loss of the dominant hand is an independent predictor for the development of more significant phantom limb pain.[58]

Psychosocial Rehabilitation

When compared with lower extremity amputees, those losing part of the arm or the hand suffer from a higher rate of psychological disorders, such as depression, anxiety, and PTSD. Although, overall, this area is relatively poorly studied, it appears that approximately 30% to 40% of upper extremity amputees will require psychological care afterward.[59] In a study by Desmond, it was noted that prevalence of significant depressive symptoms was 28.3%.[60] This finding is specifically related to the complex impact that the upper extremity and its components have on daily function. The effect that hand function has on both the patient's quality of life and his or her psychological

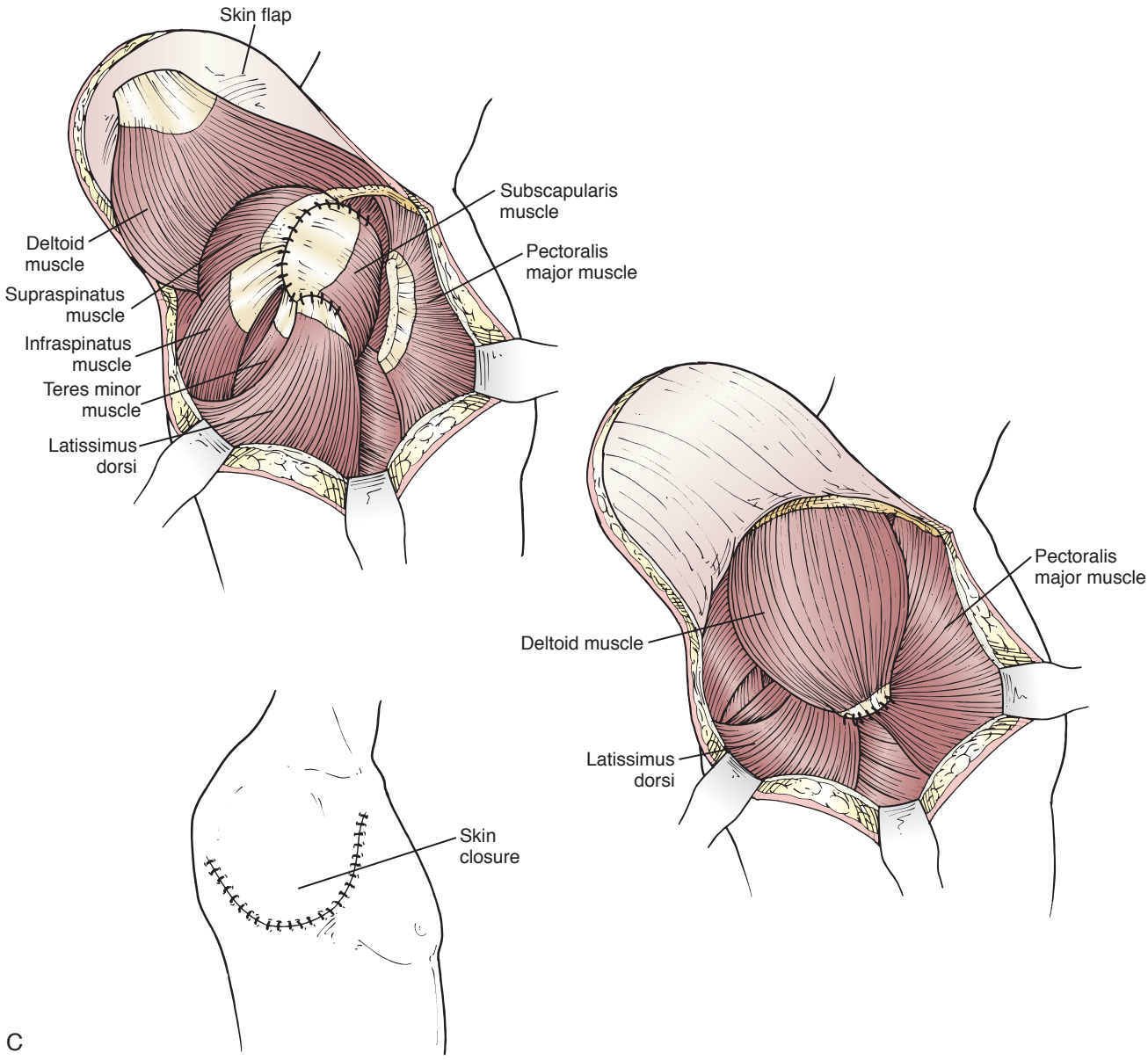

Figure 119.5, cont'd (C) Sequential closure over the glenoid of the scapularis muscle, other rotator cuff components, latissimus dorsi muscle, pectoral muscle, and deltoid muscle. (Adapted with permission from Maxwell MC. Amputations in trauma. In: Thal ER, Weigelt JA, Carrico CJ, eds. *Operative Trauma Management: An Atlas,* 2nd ed. New York: McGraw-Hill; 2002:452–457.)

well-being is recognized. It is therefore understandable that loss of hand function, not to mention the physical aspects of the hand and arm, directly leads to a grieving process and possibly longer term psychological disorders.

Physical Rehabilitation

Rehabilitation for those with upper extremity amputation is complex and onerous, and, to date, the technology and functionality of upper extremity prosthetics have lagged behind those of the lower extremity because of the intricate movements and fine sensorimotor function in the native arm and hand. Replicating these attributes has been difficult. The rehabilitative principles used for upper extremity amputees are not unique. They encompass residual limb soft tissue shrinkage and shaping, desensitization, maximization of range of motion, skin health and mobility, muscle strength, augmentation of self-reliance and daily activities, and, finally, exploration of prosthetic options.[61] These key features are focused on issues that provide a reduction in postamputation pain and maximize the potential for meaningful prosthetic use.

Prostheses

Prostheses used in the upper extremity fall into three categories: purely aesthetic, body powered, and myoelectrically powered.[62,63]

Figure 119.6 Aesthetic forearm and hand silicone prosthesis.

Aesthetic prostheses are simply that. They usually consist of silicone and are made to produce a lifelike appearance so the amputee can have a relatively normal body habitus (Fig. 119.6). They have very minimal function. Body-powered prostheses are simple mechanical devices that are controlled by residual body motion and function (Fig. 119.7). They are, in general, the most durable of prostheses and are used for most significant physical activity by amputees. Indeed, young upper extremity amputees use these types of prostheses for swimming, rock climbing, and performing most athletic activities.

Myoelectrically controlled prostheses use electrodes to convert the electrical stimulation of residual muscle groups into a current used to power the prosthesis. This has made movements, such as wrist rotation and finger movement, a reality, and many terminal devices may be attached to the prosthesis to allow various functions (Fig. 119.8). Although they permit greater degrees of freedom, these prostheses are much more complex, more expensive, and less durable for hard physical activity. Progress in myoelectric technologies continues at a rapid pace. In addition, the Defense Advanced Research Projects Agency, in affiliation with Johns Hopkins University, is now developing and testing an upper extremity prosthesis that is myoelectrically controlled with nearly all the degrees of freedom of a human arm (Fig. 119.9).[64] The residual muscles are surgically reinnervated, with or without splitting, for the maintenance of cortical functioning to enable muscle contraction and, thus, application of the myoelectric prosthesis. This technique, targeted reinnervation, has been clinically applied recently, and has improved the prosthetic function in a small number of patients. The results of this procedure have allowed this group of patients to simultaneously open and close the hand, and flex and extend the elbow.[33,65,66] Another complex, contemporary method of neural control of biomechanical upper extremity prostheses involves the placement of electrodes directly on the cerebral cortex.[67] As this technique continues to undergo study and improvement, integration of direct cortical signaling into mechanical endpoints is proving to be intricate. It is likely that in the near future a prosthetic mechanical arm controlled by the patient's own neurologic processes, and with almost normal function, may be an everyday reality.

Figure 119.7 (A) Body-powered left arm prosthesis in a young soldier after transhumeral amputation. Note the pincer terminal device, cable powered by proximal movements at the shoulder girdle harness. (B) Forearm sleeve body-powered golf prosthesis with a terminal device for the club handle.

Hand Transplantation

The first hand transplantation was performed in 1964 and it failed secondary to acute rejection. Since that time, over 70 transplantations have been performed as at 2013.[68] The improvement in surgical technique and decreasing rejection with better immunosuppressive medications has led to success in hand

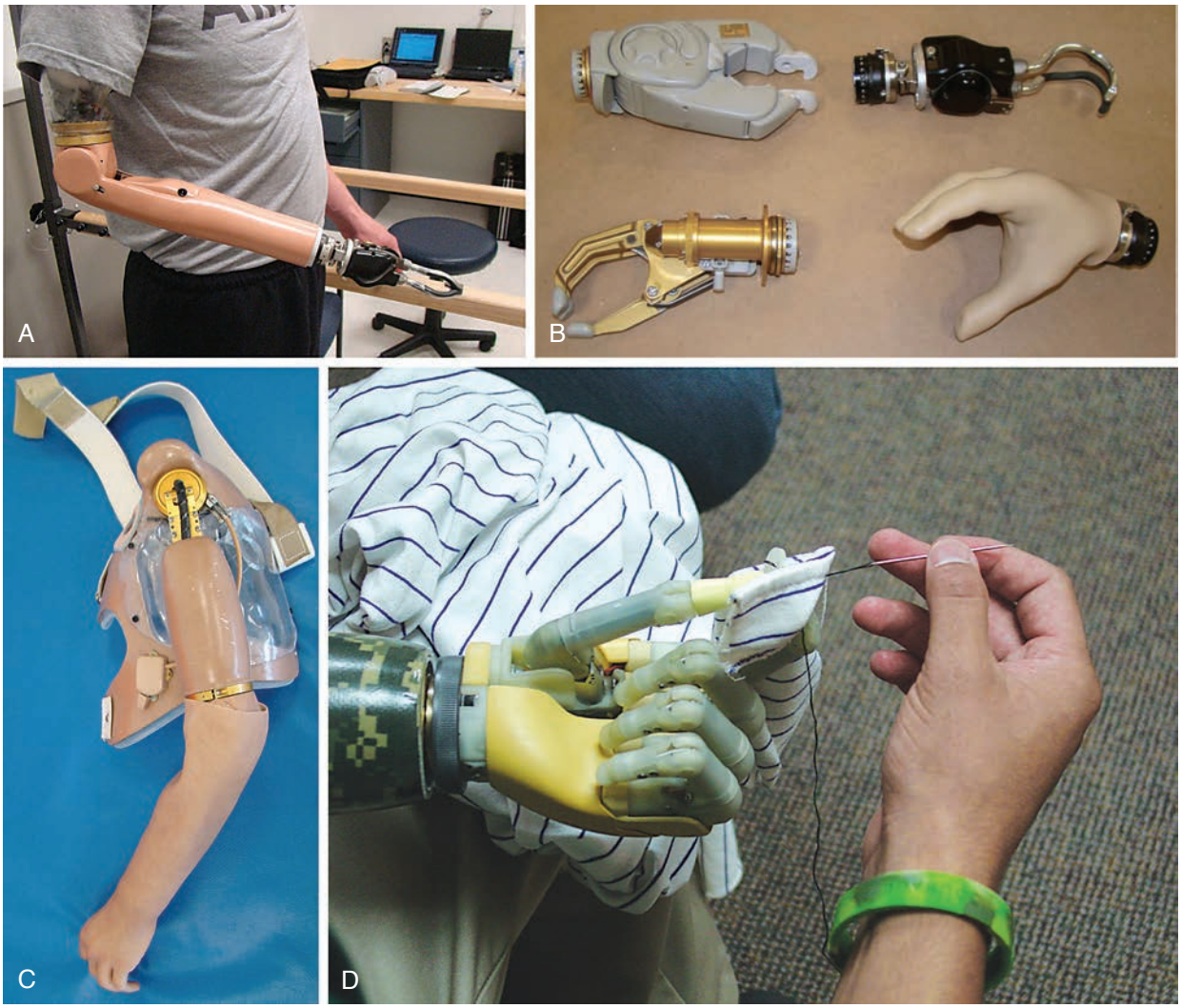

Figure 119.8 (A) Contemporary myoelectric arm prosthesis with a classic pincer terminal device. (B) Various detachable terminal devices used on myoelectric upper extremity prostheses for differing needs. (C) Shoulder girdle-mounted myoelectric arm prosthesis with a silicone aesthetic cover. (D) The i-LIMB hand (Hangar Orthopedic Group, Inc., Bethesda, MD) is a new hand prosthesis with myoelectric control that is able to simulate nearly normal hand motion.

transplantation. In a review of five bilateral hand transplant patients with a mean follow up of 7.6 years, Bernardon et al., found that the physical results achieved were considered "fair" and the functional results were considered "good," but the procedure is demanding for the patients and the rehabilitation team and carries the risk of chronic rejection.[69] Obviously, the success must be tempered by the continued need for lifelong immunosuppression. The ethical dilemma is weighing the perceived benefit of hand transplantation in regard to expected quality-adjusted life years (QALY) versus the effects of long-term immunosuppression. Alolabi studied the health utility of hand transplantation in the general public and a group of hand amputee patients and found that their results did not support a clear benefit to advocate for hand transplantation.[68] As this technique grows and more long-term studies are performed, we will identify whether it is a viable solution for patients with hand amputations.

LONG-TERM OUTCOMES

There are few reports of late outcomes after upper extremity amputation. Meaningful comparative information is difficult to obtain because of differing causes, levels of amputation, and amputee age, in addition to many other variables. The rate of late stump revision remains poorly defined for similar reasons, but late revision is not uncommon and is influenced by both disease and either prosthesis-induced or prosthetic technology–specific concerns. Such concerns may include late skin and musculoskeletal changes, and complications necessitating revision, such as ulcers, stump necrosis, dermatitis, infection, or disease recurrence in the stump, as with malignancy and vasculitis. In addition, revision of the bony and soft tissue stump components to allow the fitting and use of more modern prostheses may be chosen.

In general, attitudes toward prosthesis use in proximal upper extremity amputees are poor, and currently, as many as 40%

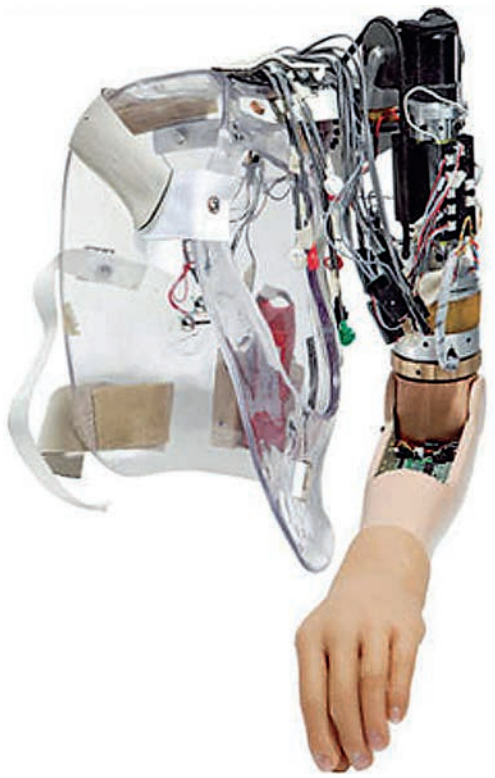

Figure 119.9 Complex myoelectric upper extremity prosthesis developed at Johns Hopkins in conjunction with the Defense Advanced Research Project Agency. Note the color-coded electrodes, which are placed on certain muscle groups for myoelectric control, or on various aspects of muscles after targeted reinnervation surgery, to allow areas of each muscle to independently transmit current.

would rather not use prostheses.[70] Even those with hand-based amputations can find the return to activities of daily living and job performance challenging.[71] Return to employment has a positive effect on prosthesis use.[72] However, the patient's education level appears to play an important role in postamputation employment. Weed and colleagues found that more than 70% of those with at least some college education were employed after amputation, whereas only 23% of those with a high school or less education were employed.[73] The potential for these long-term physical, socioeconomic, and psychological problems again reinforces the need for upper extremity amputees to have access to a multidisciplinary institution, regardless of whether they choose to seek contemporary rehabilitation and prosthetic options.

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120 CHAPTER

Thoracic Outlet Syndrome: Pathophysiology and Diagnostic Evaluation

MICHAEL J. OSGOOD and YING WEI LUM

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INTRODUCTION

Thoracic outlet syndrome (TOS) is a condition resulting from compression of the neurovascular structures traversing the thoracic outlet. The syndrome is divided into three types based on the symptoms and signs of neurovascular compression: neurogenic TOS (nTOS) results from brachial plexus compression, venous TOS (vTOS) results from subclavian vein compression, and arterial TOS (aTOS) results from subclavian artery compression. The distinct symptoms and signs of each of these syndromes are described in Table 120.1.

Most patients with TOS are 20 to 50 years of age. Fewer than 5% are teenagers, whereas 10% are older than 50 years. Seldom is any form of TOS seen in patients older than 65. Seventy percent are female. There is no explanation for the female predominance, but perhaps it is related to the observation that 70% of cervical ribs also occur in females. The exception to this is the subset of patients diagnosed with vTOS, as there is a 2:1 male predominance in this condition.

TOS is uncommon, but its true incidence is unknown because many people with upper extremity pain and paresthesias could have escaped diagnosis by healthcare providers who may have

TABLE 120.1 Comparison of the Three Subtypes of Thoracic Outlet Syndrome

	Neurogenic	Venous	Arterial
Incidence	95%+	3%	1%
Etiology	Neck trauma (i.e., auto accident with whiplash), RSI at work, falls on the floor or ice	Repetitive overhead shoulder movements and/or coagulopathy	Cervical rib or anomalous first rib; rarely, congenital band
Predisposing factors	Cervical rib, congenital band, scalene triangle muscle variations	Congenital narrowing of the costoclavicular space by the costoclavicular ligament or the subclavian tendon compressing the subclavian vein	Cervical rib or anomalous first rib eliminating space under the artery
Pathology	Scalene muscle fibrosis; occasionally anomalous first rib or cervical rib	Subclavian vein stenosis with or without thrombosis	Subclavian artery stenosis, thrombosis or aneurysm formation with mural thrombus and emboli
Symptoms	Extremity pain, paresthesia, weakness plus neck pain and occipital headache, Raynaud phenomenon, chest pain for pectoralis minor syndrome	Swelling of the whole arm, cyanosis, pain	Pain, paresthesia, pallor, coldness; digital ischemia; arm claudication; seldom are there neck or shoulder symptoms
Physical examination	Positive response to provocative maneuvers; tenderness over the scalenes, pectoralis minor	Arm swelling, cyanosis, pain	Those with arterial occlusion: decreased pulses at rest, perhaps color changes and ischemic fingertips, distal emboli
Diagnostic tests	Duplex scan, scalene muscle block, MRI to rule out other conditions, pectoralis minor block, EMG/NCV, MAC measurement[1]	Duplex scan, venogram	Neck radiograph, duplex scan, arteriogram, digital pressures and waveforms, arteriography

EMG, Electromyography; *MAC*, medial antebrachial cutaneous nerve; *MRI*, magnetic resonance imaging; *NCV*, nerve conduction velocity; *PTA*, percutaneous transluminal angioplasty; *RSI*, repetitive strain injury; *Rx*, treatment.

failed to recognize the diagnosis. Of the TOS subtypes, nTOS is by far the most common form, accounting for more than 95% of all TOS patients. vTOS occurs in 2% to 3%, whereas aTOS comprises fewer than 1% of patients.

These syndromes result from a combination of developmental and anatomic anomalies in the thoracic outlet, as well as physical activities and life events that predispose individuals to become symptomatic. A common initiating event is neck trauma, which causes symptoms in patients who may be predisposed to its development based on anatomic developmental anomalies of the thoracic outlet. In this chapter we will describe the relevant anatomy and then elaborate on the pathophysiology of each type of TOS, followed by a discussion of the diagnostic evaluation of TOS.

RELEVANT ANATOMY

There are three anatomic spaces that pertain to the thoracic outlet, including the scalene triangle, the costoclavicular space, and the pectoralis minor (PM) space (Fig. 120.1). The costoclavicular space is traversed by the subclavian vein and is the most common site of subclavian vein compression (see Figs. 120.1 and 120.2). The subclavian artery and brachial plexus traverse the thoracic outlet between the anterior and middle scalene muscles, also referred to as the scalene triangle (see Figs. 120.1 and 120.2). The scalene triangle is the most common site of brachial plexus compression. When present, cervical ribs and anomalous first ribs also compress the plexus in this location (Fig. 120.3).

Nerves

In addition to the brachial plexus, the phrenic and long thoracic nerves are seen during supraclavicular dissections. Very close to the area but rarely seen are the dorsal scapular nerve and cervical sympathetic chain.

Brachial Plexus

The brachial plexus arises from nerve roots C5 to T1. In the scalene triangle area the five nerve roots become three trunks. The anterior and posterior divisions and cords of the plexus are usually formed proximal to the PM space, so it is the branches of the plexus that lie under the PM muscle, along with the axillary artery and vein.

Phrenic Nerve

Arising primarily from C4, the phrenic nerve usually receives branches from C3 and C5. It is single in 87% and double or triple in 13% of individuals. The phrenic nerve descends 84% of the time from the lateral to the medial side of the anterior scalene muscle. In the other 16% of individuals, the phrenic nerve remains on the lateral side.[2]

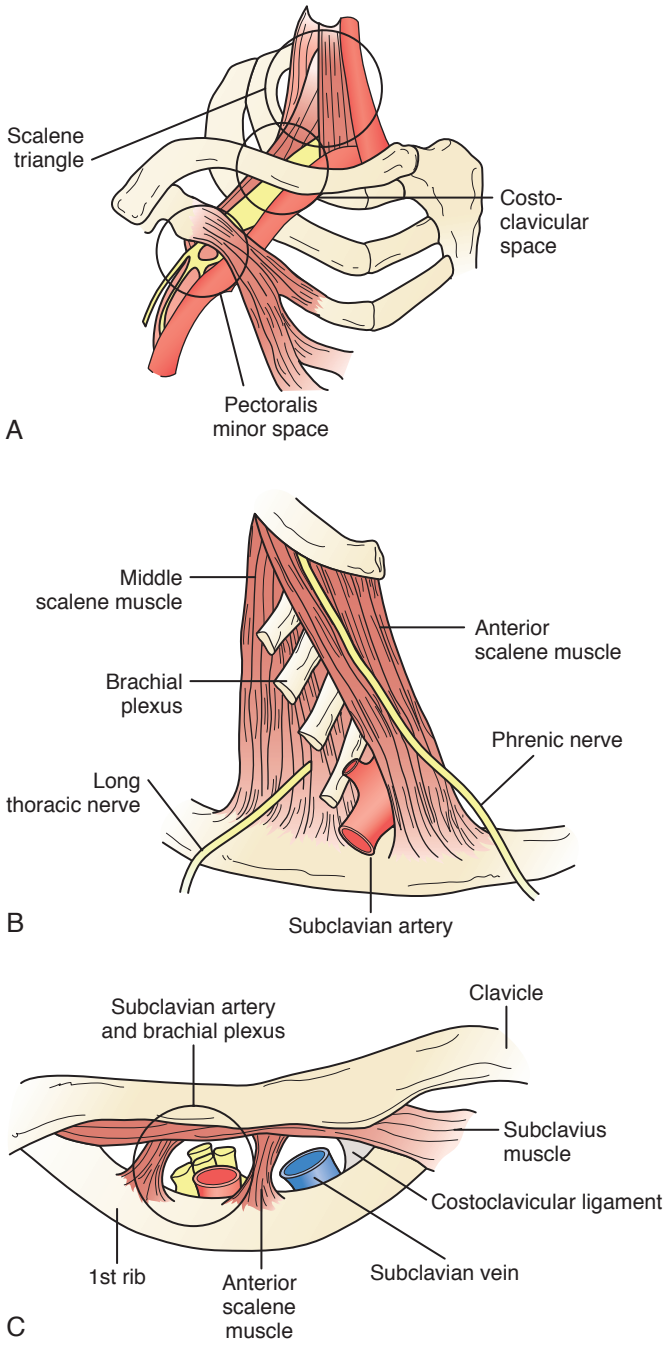

Figure 120.1 (A) Anatomy of the thoracic outlet with respect to the three major spaces. (B) Scalene triangle with the phrenic and long thoracic nerves located in the most common positions. (C) Costoclavicular space revealing the subclavian vein being separated by the anterior scalene muscle from the subclavian artery and brachial plexus.

Long Thoracic Nerve

The long thoracic nerve arises primarily from C6 and usually receives contributions from C5 and C7. The C5 and C6 branches run through the muscle belly of the middle scalene muscle, where they usually join. The C7 branch arises from the posterior aspect of the nerve root and often descends below the middle scalene before joining the other two branches.

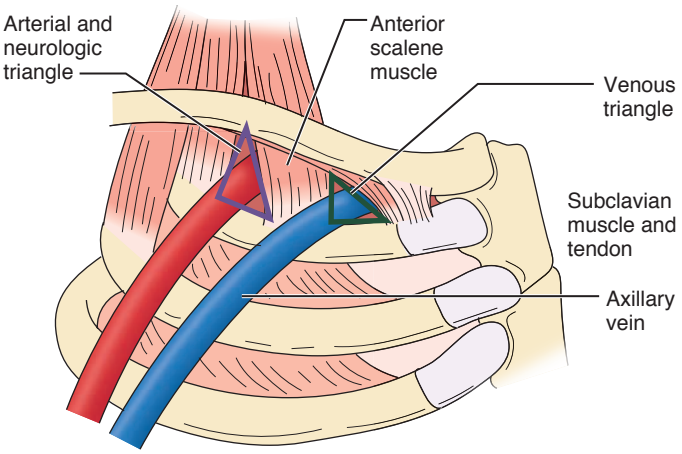

Figure 120.2 Anatomic triangles of the thoracic outlet highlighting the location of the neurovascular structures. The subclavian artery and brachial plexus traverse the thoracic outlet through the scalene triangle. The subclavian vein traverses the thoracic outlet anterior to this through the costoclavicular space. (Adapted from Moore R, Lum YW. Venous thoracic outlet syndrome. *Vasc Med*. 2015; 20:182-189.)

Dorsal Scapular Nerve

The dorsal scapular nerve, the first branch of C5, courses through the cephalic portion of the middle scalene muscle and then descends lateral to the muscle. However, it may course very close to the area of dissection in supraclavicular approaches to thoracic outlet decompression.

Cervical Sympathetic Chain

Though not usually in the operative field of supraclavicular procedures, the cervical sympathetic chain lies over the transverse processes of the cervical vertebrae and is therefore very close to the origin of the anterior and middle scalene muscles. As a result, when cautery is used to excise the scalene muscles at their transverse process origins, the current may reach and damage the cervical sympathetic chain. This is the probable explanation for the occasional case of Horner's syndrome observed after supraclavicular scalenectomy.

Variations and Anomalies of the Scalene Muscle

A significant number of anatomic variations in scalene muscles have been observed both in the normal population and in patients with nTOS. They are too common to be called anomalies. These variations might be regarded as anatomic and developmental variations predisposing to TOS, but are not regarded as causes.

Splitting of the anterior scalene around C5 and C6. Such splitting was noted in 45% of cadavers and in only 21% of nTOS patients.[3]

Scalene minimus muscle. This muscle arises from the transverse processes of the lower cervical vertebrae, runs in front of C8 and T1 and behind the subclavian artery, and inserts on the first rib or Sibson fascia. Its incidence is 25% to 55%.[4]

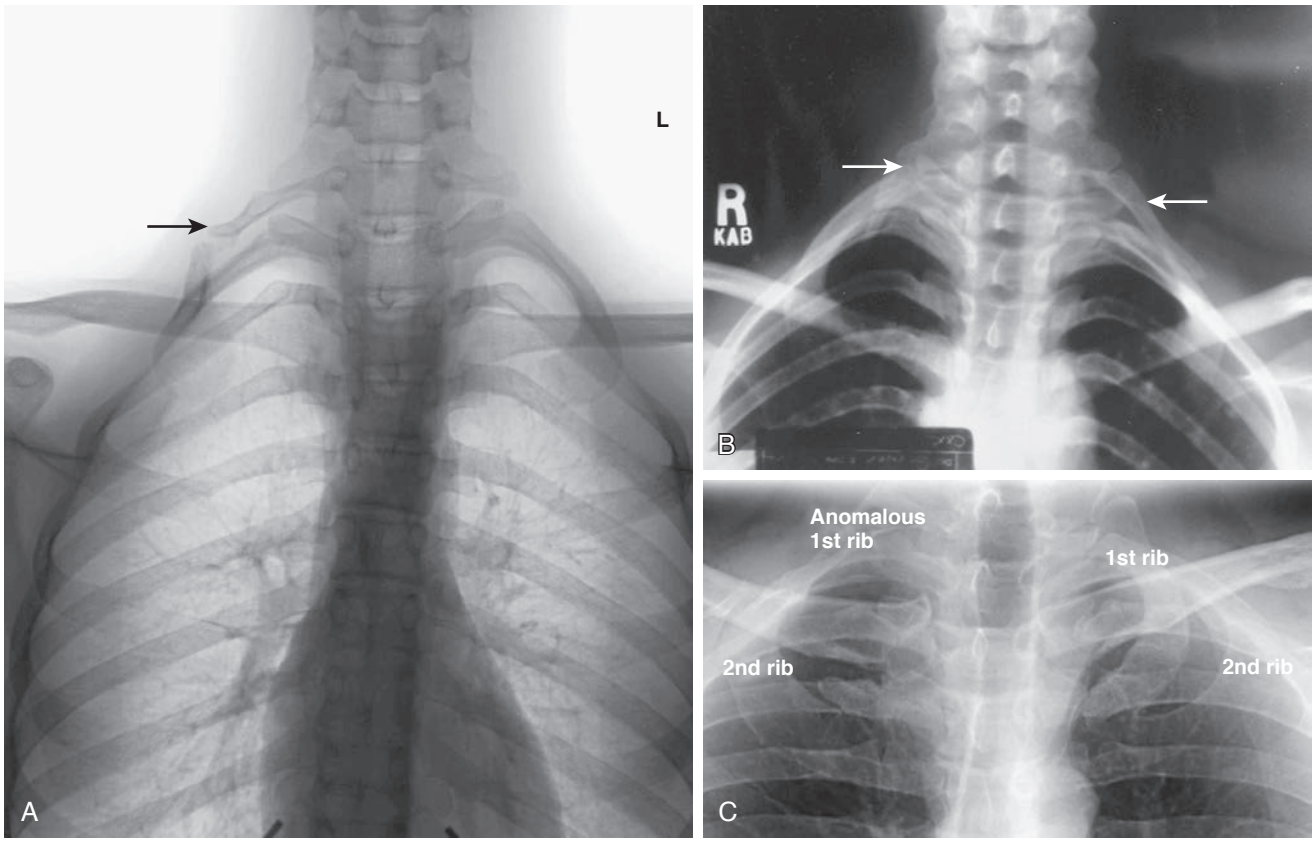

Figure 120.3 (A) Right complete cervical rib with a true joint between the cervical rib and a small process arising from the top of the first rib. (B) Bilateral cervical ribs, incomplete on the right and complete on the left. (C) Anomalous first rib.

Interdigitating muscle fibers. Such fibers commonly run between the anterior and middle scalene muscles. They were noted in 75% of nTOS patients and in only 40% of cadavers.

Scalene triangle width. The width of the scalene triangle varies from very narrow to quite wide, with the distance between the two scalene muscles at their insertion on the first rib ranging from 0.3 to 2.0 cm. The nerve roots emerge lower in a wide triangle compared with their pathway in a narrow triangle (Fig. 120.4). Observations during surgery have revealed that most nTOS patients have the narrower type of triangle.[2]

Congenital bands and ligaments. These structures are frequently observed in the normal population, with an incidence as high as 63%.[5] Although bands have been observed in almost every area of the scalene triangle and have been nicely classified,[6] their role is as a predisposing factor rather than a direct cause.

Relationship of the subclavian vein to the phrenic nerve. The phrenic nerve usually runs posterior to the subclavian vein. However, in 5% to 7% of individuals, the phrenic nerve runs anterior to the vein and in this position can be a rare cause of subclavian vein obstruction.[7]

Relationship of the subclavian vein and costoclavicular ligament. The subclavian vein passes cephalad to the first rib just before it is joined by the jugular vein. It is bounded medially by the costoclavicular ligament and superiorly by the subclavius tendon. A variation in the position of the vein is its position more medially on the first rib so that it is partially compressed by the costoclavicular ligament. Variations in the thickness of the subclavius tendon can also result in compression of the vein from above. These variations in position between the three structures predispose to the development of subclavian vein obstruction. Obstruction is then caused by excessive abduction of the upper extremity, which results in compression of the vein against the dynamic outlet created by the costoclavicular ligament, subclavius tendon, and the first rib.

Skeletal Abnormalities

As many as 29% of patients with TOS have been reported to have skeletal anomalies, including cervical ribs, clavicular anomalies, and isolated first rib abnormalities, the majority of which are congenital.[8] Anomalous or rudimentary first ribs are often overlooked on routine chest radiographs. In a study conducted in 1939, 5000 chest radiographs were reviewed, and it was found that the incidence of anomalous first ribs and cervical ribs in these subjects was 0.76% and 0.74%, respectively. Anomalous ribs occurred equally in women and men. In contrast, the female-male ratio of cervical ribs was found to be 7:3.[9] Cervical ribs and anomalous first ribs are both narrower and are positioned more cephalad than a normal first rib. The only difference between the two is that a cervical rib arises from the transverse process of C7, whereas an anomalous first rib arises from the transverse process of T1 (see Fig. 120.3).

Figure 120.4 Scalene Triangle Variations. (A) The usual relationship found in cadavers. The triangle is wider and the nerves emerge lower in the triangle than in most patients with neurogenic thoracic outlet syndrome. There is minimal contact between nerve and muscle. (B) Narrow scalene triangle in which the nerves emerge high and are touching the muscles as they emerge. Contact between nerve and muscle is more significant compared with A. (Adapted from Sanders RJ, Roos DB. The surgical anatomy of the scalene triangle. *Contemp Surg.* 1989; 35:11-16.)

About 30% of cervical ribs are complete ribs fused to the first rib by a true joint or a fibrous attachment. The other 70% are incomplete cervical ribs with no direct attachment to the first rib. However, most of these incomplete ribs have a tight fascial band extending from the tip of the cervical rib to the first rib.[6] The cervical rib and attached band lie within the middle scalene muscle, thereby narrowing the space within the scalene triangle through which the nerve roots of the brachial plexus course. Thus an incomplete cervical rib with associated band can behave like a complete rib. Cervical and anomalous first ribs can compress the subclavian artery and cause stenosis with or without poststenotic aneurysm formation. More commonly, these anomalous ribs compress the lower trunk of the brachial plexus and cause neuropathy. However, most cervical and anomalous first ribs remain asymptomatic throughout life.

When symptoms do develop, they are usually neurogenic (see Chapter 121). In a recent review of 47 nTOS operations involving abnormal ribs, 15% were performed in the setting of anomalous first ribs and 85% were performed in the setting of cervical ribs. Spontaneous onset of symptoms occurred in 50% of patients with complete cervical ribs versus only 20% with incomplete ribs. Neck trauma preceded the onset of symptoms in the other 80% with incomplete ribs and in the 50% with complete ribs.[10] All patients with cervical ribs are predisposed to the development of some form of TOS—most commonly nTOS. Cervical ribs or anomalous first ribs are almost always present in patients with aTOS. On the other hand, symptomatic cervical ribs are more likely to produce symptoms of nTOS than aTOS. Over a 28-year period during which more than 1000 nTOS operations were performed, there were 39 cervical ribs and 7 anomalous first ribs treated in this group of patients, with an incidence of 4%. Among the same group of TOS patients, there were only nine with aTOS—five with complete cervical ribs and four with anomalous first ribs, with an incidence of less than 1%.[10]

Contribution of the Pectoralis Minor

The PM can also cause compression of the structures of the thoracic outlet, leading to nTOS, vTOS, and aTOS in rare circumstances. Pectoralis minor syndrome (PMS) results when this muscle causes compressive symptoms in the subcoracoid or PM space. The PM space is actually outside the thoracic outlet area, but compression of the upper extremity neurovascular bundle can occur in this space between the PM muscle and ribs of the chest wall. Although this might better be termed "axillary compression syndrome," it is appropriate to consider the PM space as an extension of the thoracic outlet area, because compression here is common and the axillary and the thoracic outlet neurovascular bundles contain the same elements (see Fig. 120.1). The PM syndrome results from excessive trauma or exercise of the shoulder girdle caused by hyperabduction. The PM muscle becomes tight and hypertrophied and can compress the brachial plexus, axillary vein, and rarely the axillary artery. PMS is frequently responsible for recurrent nTOS after thoracic outlet decompression and can be responsible for up to 75% of cases of recurrent nTOS.[11] It is this PM space that should be evaluated more carefully, particularly in patients with recurrent or persistent symptoms after initial operation for nTOS.

Neurogenic Thoracic Outlet Syndrome

There are no established diagnostic criteria or reference standards for the diagnosis of nTOS (see Chapter 121).[12] Unlike the diagnostic algorithm for aTOS and vTOS, the diagnostic criteria for nTOS are highly disputed. Such extensive debate exists regarding nTOS being a nebulous diagnosis that there are even classifications by which nTOS is classified as "true" nTOS (with objective changes such as muscle atrophy) or "disputed" nTOS.[13] Regardless, a standardized approach in the diagnosis and workup of nTOS patients selects a group of individuals who have an excellent chance of symptomatic relief from thoracic outlet decompression.

Pathogenesis

In nTOS, predisposing factors include scalene muscle anomalies, narrow scalene triangles, congenital ligaments or bands, roots

of the plexus arising high near the apex of the scalene triangle, and cervical ribs. A common cause of nTOS is neck trauma that involves a hyperextension neck injury. Whiplash in a motor vehicle accident is the most common injury. Other frequent causes are repetitive stress injuries in the workplace and falls on slippery floors or icy walkways. The presence of a cervical rib predisposes to the development of nTOS. In such patients, neck trauma may precipitate symptoms, but in some patients with no history of trauma, activities of daily living can also cause nTOS when the anatomic relationships between the rib and arm cause nerve compression.

Pathology

The common pathologic findings in most patients with nTOS are (1) developmental anomalies of the thoracic outlet and fibrosis of the scalene muscle, and (2) conversion of muscle fibers from fast twitch to slow twitch.[14,15] The fact that transaxillary first rib resection for the treatment of nTOS has become popular since its introduction by Roos in 1966 has led some to believe that the first rib is the underlying cause of the pathology.[16] This is not universally believed to be true. Many think that the attachments to the first rib are the more likely cause of nTOS. Support for this theory is that there are reports demonstrating that the results of anterior and middle scalenectomy without first rib resection are similar to those of scalenectomy with first rib resection.[15]

Pathophysiology

Although the pathophysiology of nTOS may vary depending on the specific predisposing and causative factors, it is usually associated with a narrowed scalene triangle. These patients are asymptomatic until neck trauma stretches and tears some of the anterior and middle scalene muscle fibers. This mechanism explains the neck pain that usually appears within the first 24 hours of a neck injury. Over the next few days, swelling of the muscles from bleeding or inflammation, or both, results in compression against the nerve roots of the brachial plexus. This compression then causes upper extremity pain and paresthesias, the onset of which is usually delayed a few days or weeks after the initial trauma. As the muscle injury heals and the swelling subsides, scar tissue replaces the blood that collected within the muscle, which accounts in part for muscular fibrosis. The upper extremity neurologic symptoms persist due to compression of the nerves by scar tissue. This may manifest as persistent neck pain resulting from scalene fibrosis, and occipital headaches may occur as referred pain from scalene muscle spasm. When nerve compression involves the C8 and T1 branches of the lower trunk of the brachial plexus, the sympathetic nerve fibers supplying the extremity may also become irritated or compressed where they associate with the lower trunk of the brachial plexus at this location, traversing the scalene triangle. This may result in the development of a unilateral Raynaud phenomenon that manifests as intermittent subjective coolness and color change.[17]

Data supporting the scalene muscles as the site of pathology include (1) histologic studies of the scalene muscles that demonstrate an average of three times more scar tissue in the scalene muscles of nTOS patients compared with control patients, (2) the strong correlation between positive responses to scalene muscle blockade and positive responses to surgery, and (3) the fact that the rate of improvement after surgery for nTOS is the same as that for scalenectomy with or without first rib resection.

History

Obtaining a history of some type of neck trauma preceding the onset of symptoms is helpful for all types of TOS, but particularly when considering a diagnosis of nTOS. Although nTOS may occur spontaneously, more than 80% of patients have a history of some type of neck trauma, the most common being whiplash injuries from motor vehicle accidents, history of clavicular fracture, falls on slippery surfaces or down stairs, and repetitive stress injury from hours on keyboards, assembly lines, or in various other occupations. However, the absence of such a history should not exclude the diagnosis of nTOS.

The patient should be asked specifically about occipital headache and pain over the trapezius, neck, chest, and shoulder girdle. A patient who has symptoms confined to the forearm and hand is more likely to have carpal or cubital tunnel syndrome and not nTOS. A history of other interventions related to the musculoskeletal system associated with the cervical spine, shoulder, and upper extremity should also be documented in the medical history. Last, patients with nTOS should be asked about subjective coldness and color changes consistent with the Raynaud phenomenon, which may develop as a result of sympathetic nerve compression.[17]

Physical Examination

The standard neurologic examination often fails to detect nTOS. In addition to tenderness over the scalene muscles and reduced sensation to very light touch in the fingers, an examination for nTOS should include eliciting symptoms by a variety of provocative maneuvers. The three notable provocative maneuvers that should be executed and documented in patients with TOS, particularly nTOS, are as follows:

Adson test. The examiner palpates the radial pulse and then moves the patient's upper extremity into an extended, abducted, and externally rotated position. The patient is then asked to rotate and laterally flex the neck to the ipsilateral side while inhaling deeply. A positive test results in reduction in the amplitude or complete obliteration of the radial pulse.

Elevated arm stress test (EAST or Roos test). The patient is seated with arms abducted at 90 degrees in external rotation, with elbows flexed to 90 degrees and the head in neutral position. The patient is asked to open and close the hands for 3 minutes or until pain/paresthesia sets in and the patient is unable to continue. This test has a high negative predictive value for nTOS if the patient is able to perform the maneuver for 3 minutes.[18]

Modified upper limb tension test (Elvey test). The patient is asked to abduct both arms to 90 degrees with the elbows extended. The patient is then progressively asked to dorsiflex both wrists. The test is considered positive if symptoms are elicited on the ipsilateral side. A subsequent maneuver is carried out

by having the patient laterally flex the head on each side. The test is then considered positive if symptoms are elicited on the contralateral side.

Some authors believe that the most effective provocative test is the upper limb tension test of Elvey.[17,19] This test is analogous to the straight-leg raise test in the lower extremity for sciatica and is worth incorporating into every examination for upper extremity symptoms.[17] A positive response indicates compression of either the cervical nerve roots or brachial plexus at the level of the spine, thoracic outlet, or PM space. A negative response is usually adequate to rule out the diagnosis of nTOS.

The Adson test, however, is the most widely recognized of these maneuvers. In Adson's original description of his test, he noted "A decrease or obliteration of the radial pulse or blood pressure is a pathognomonic sign of scalenus anticus syndrome (this is one of the syndromes included in TOS)."[20,21] However, in 1947, the same year of Adson's last report, Gage and Parnell noted that 50% of normal individuals had a positive Adson test.[22] Subsequently others have demonstrated similar high rates of positive Adson tests in healthy volunteers.[1,3,18,23-25] Therefore the Adson test is unable to rule in or rule out a diagnosis of nTOS.[17] Despite the abundant evidence indicating its unreliability, the Adson test is still currently popular among many clinicians, probably because it is the only objective test available on physical examination.

These provocative maneuvers, while occasionally helpful in establishing the diagnosis of thoracic outlet compression, are neither highly sensitive nor specific for identification of thoracic outlet syndrome and are not reliable for identifying a specific anatomic region of pathology.[3,17] Indeed, positive findings on these maneuvers frequently lead to an erroneous diagnosis of vTOS or aTOS in patients whose symptoms and physical findings are typical of nTOS but who have no symptoms or physical findings of aTOS or vTOS. Many patients undergo electromyography (EMG) and nerve conduction velocity (NCV) tests in the course of workup for nTOS. These tests usually have normal or nonspecific results and do not play a helpful role in the diagnostic evaluation for nTOS, except to exclude other compressive neuropathic syndromes.[17]

Anterior Scalene Muscle Block

As elaborated previously, the diagnosis nTOS can be challenging based on history and physical examination alone. The anterior scalene muscle block (ASMB) is a useful adjunct in the diagnostic evaluation of this syndrome, and we have incorporated it into the diagnostic evaluation for nTOS.[17,26,27] ASMB involves injection of the anterior scalene muscle with 1% lidocaine.[12] The subsequent relaxation in the scalene muscle results in a change in configuration of the costoclavicular space, with a subsequent decompression of the thoracic outlet and relief of neurologic symptoms caused by neurovascular compression.[12] Symptomatic suppression subsequent to performing ASMB offers information that is helpful in localizing a pathologic process to a specific inciting anatomic site in the thoracic outlet that responds well to surgical decompression. Thus performing ASMB selects patients who have a high likelihood of responding to surgical management. In our practice, we rarely select patients for surgical thoracic outlet decompression for nTOS until they have symptomatically improved following ASMB.

VENOUS THORACIC OUTLET SYNDROME

vTOS is defined by the presence of compression and subsequent thrombosis of the axillo-subclavian vein (see Chapter 123). This condition is synonymous with Paget-Schroetter syndrome and "effort thrombosis," an older term originating before the pathogenesis of vTOS was understood. Primary effort thrombosis of the axillo-subclavian vein, also known as Paget-Schroetter syndrome, was first described by Paget in 1875[28] and subsequently by Von Schroetter in 1884.[29] There exists a further subset of patients who have symptoms characteristic of vTOS, but without the presence of venous thrombosis; it is a condition termed intermittent obstruction or McCleery syndrome.[30]

Pathogenesis

Venous TOS is most often the result of developmental anomalies of the costoclavicular space and repetitive arm activities such as throwing, swimming, or working with the arms overhead for long periods. In vTOS, the predisposition is the relationship of the subclavian vein to the subclavius tendon and costoclavicular ligament and dimensions of the costoclavicular space. In most patients with vTOS, the subclavian vein is situated closely adjacent to the costoclavicular ligament, and the subclavius tendon compresses the top of the vein within a narrowed costoclavicular space. With the vein in this compressed position, repetitive arm movements can easily traumatize the vein and produce fibrosis, stenosis, and eventually thrombosis. Therefore vTOS is a condition characterized by primary thrombosis of the axillo-subclavian vein secondary to compressive symptoms from thoracic outlet pathology and should be differentiated from secondary thrombosis. Secondary thrombosis of the vein may ensue following injury or iatrogenic causes, including central line or pacemaker lead placement.

Pathology

Many patients with vTOS have coexisting anatomic abnormalities. Some of the recognized anatomic anomalies include abnormalities of the scalenus minimus, pectoralis minor, subclavius, and anterior scalene muscles; ligamentous abnormalities of the costocoracoid ligament; and bony abnormalities of the clavicles and ribs.[31-37] In addition, as many as 43% of the patients treated for vTOS have been demonstrated to have evidence of occult first rib fractures.[38] A significant proportion also has osteophytic degeneration and costochondral calcification. The subclavian vein develops intimal injury and subsequent luminal narrowing. If thrombosis occurs, this event occludes the vein and precipitates acute symptoms of upper extremity deep venous thrombosis. Also characteristic of this condition is the formation of extensive venous collaterals when the occlusion is chronic.

Pathophysiology

Repeated compression injury of the subclavian vein is the inciting event leading to vTOS. As the vein traverses the thoracic outlet, the subclavian vein is in an anatomically tight space bounded by the subclavius muscle and costoclavicular ligament medially, the anterior scalene muscle laterally, the clavicle superiorly, and the first rib inferiorly (see Figs. 120.1 and 120.2).[30] Significant forces result from compression of the clavicle and first rib in a fulcrum-like effect during certain motions and maneuvers, particularly in young athletic males participating in activities that require repetitive overhead movement of the upper extremities. Cumulative trauma to the subclavian vein causes scarring, inflammation, and eventual thrombosis.[39] If left untreated, venous hypertension then ensues and prompts the subsequent development of venous collaterals. The symptoms of swelling and pain resulting from venous hypertension then subside once collaterals mature. Symptoms improve as a result of collateral formation and eventual recanalization of the vein in some patients, even in those untreated. However, thrombus may propagate into the venous collaterals and acute thrombosis of these vessels may occur, resulting in another relatively acute episode of arm swelling and pain characteristic of the presentation of Paget-Schroetter syndrome or vTOS.[40]

Clinical Findings

Consistent with the pathophysiologic mechanism leading to this condition, vTOS is most common in young athletic individuals who perform frequent repetitive overhead movement in the upper extremities, such as pitchers, weightlifters, and mechanics, to name a few.[30] Historical series have suggested a male preponderance, but the largest case series to date actually demonstrated an equal gender ratio.[41] Patients with vTOS are typically asymptomatic until the thrombotic event that results in pain, swelling, and cyanosis with a markedly blue appearance in the acute thrombotic episode. This acute episode is frequently preceded by intense physical exertion, exercise, or labor, and the arm may become severely swollen and edematous, enlarging up to double its normal size in a distribution from the shoulder extending distally to the hand.[42] Important elements in the history would be to rule out any secondary causes of upper extremity deep vein thrombosis such as upper extremity central venous catheters, pacemakers, or symptoms suggestive of malignancy (see Chapter 149).

A minority of patients develop pulmonary embolism, and this complication occurs in 12% or fewer of patients with axillo-subclavian venous thrombosis.[31,43-47] The surprisingly lower rate of venous thromboembolism in these patients is explained by the small clot burden present in vTOS, as well as the anatomic subclavian vein narrowing resulting from vTOS, which sequesters thrombus and prevents embolization.

Physical Examination

In a large case series of vTOS, 93% of patients presented with arm swelling, 77% presented with bluish cyanosis, 66% had worsening of aching pain with exercise, and 8% had minimal findings or symptoms.[41] In addition to pronounced swelling and edema of the involved arm, dilated subcutaneous veins may be present over the upper arm, neck, and chest, and herald chronic venous obstruction. On occasion a tender palpable cord can be appreciated on physical exam in the axilla.[30]

Diagnostic Evaluation

While the physical exam alone may be sufficient to reliably diagnose vTOS with a high degree of certainty in many cases, confirmatory testing is indicated. Duplex ultrasound is the imaging study of choice for the initial diagnosis of vTOS, as it is highly sensitive (78% to 100%) and specific (82% to 100%) for the diagnosis of venous thrombosis (Fig. 120.5).[48-54] Duplex evaluation of vTOS should encompass the entire length of the vein to avoid missing the presence of a subtle or short-segment thrombus and to evaluate the extent of vessel involved. In vTOS, duplex ultrasound typically demonstrates near-complete or complete occlusion of the subclavian vein with loss of flow. It is important to conduct the venous duplex in a variety of provocative maneuvers, with the arm in abduction with flow assessed through the axillo-subclavian vein with color Doppler in these various positions. In the absence of axillo-subclavian vein thrombosis, these maneuvers help establish the diagnosis of McCleery syndrome, which is characterized by intermittent compression of the subclavian vein resulting in upper extremity swelling without venous thrombosis.[55] This condition is diagnosed when significantly elevated velocities or flow occlusion are demonstrated at the thoracic outlet with these provocative maneuvers.

Venography is rarely necessary as an initial diagnostic maneuver, as ultrasound is both highly sensitive and specific for the diagnosis of subclavian venous thrombosis. In the rare instance that a negative duplex ultrasound result is obtained and the clinical suspicion remains high for venous thrombosis, contrast venography may play a helpful role (Figs. 120.6 and 120.7).[30] Contrast venography may also be utilized in the process of performing an initial endovascular intervention—most commonly thrombolysis.[30] Other imaging modalities described for venous imaging, including magnetic resonance venography (MRV) and computed tomographic venography (CTV), do not offer any advantages over venous duplex ultrasound, have equivalent sensitivity and specificity, are costly and time-consuming, and should generally be avoided in the diagnostic evaluation for vTOS.[56] In addition, thrombophilia may play a role in the pathogenesis of vTOS. Some series have documented that a significant proportion of patients presenting with vTOS have a contributory thrombophilia in the pathogenesis of their condition.[57] As such, when a family history or personal history of prior venous thrombosis is present, patients should also be evaluated for the presence of thrombophilia.

ARTERIAL THORACIC OUTLET SYNDROME

The least common form of TOS, aTOS, accounts for 1% of cases,[17] but represents the most firm indication for operative

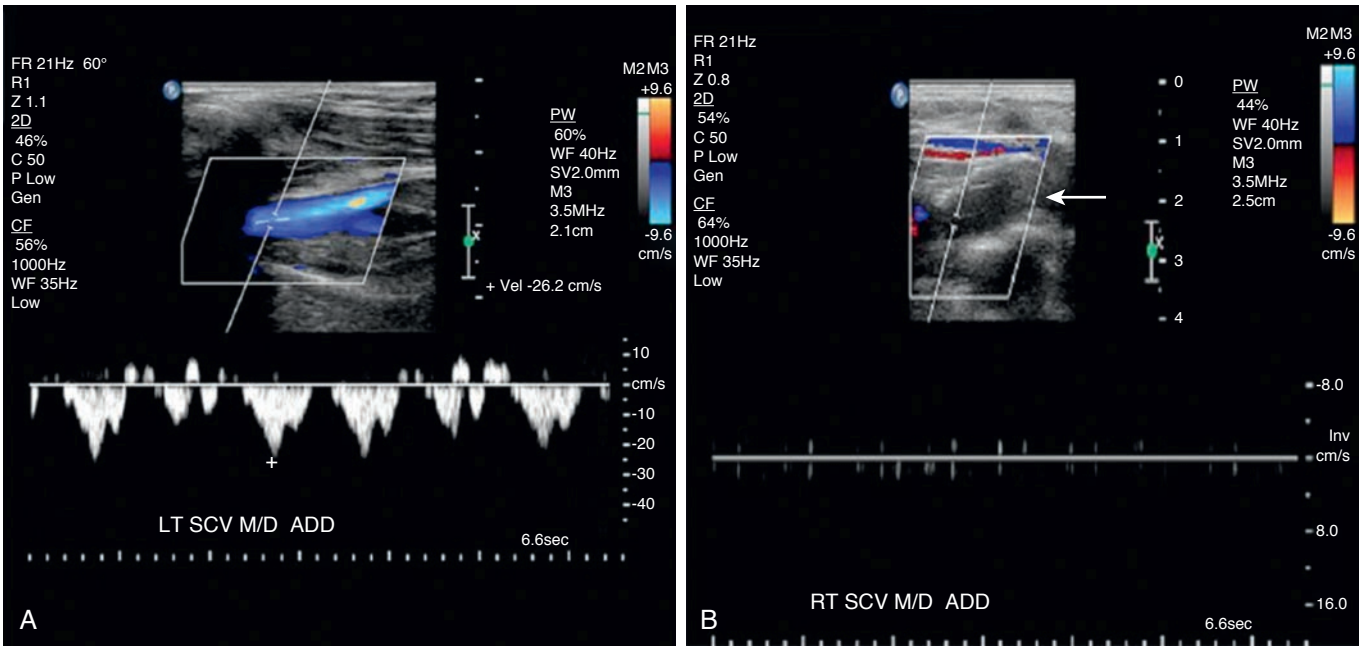

Figure 120.5 Duplex Ultrasound Images of the Axillosubclavian Vein. (A) Demonstrates a normal axillosubclavian vein. (B) Demonstrates a thrombosed axillosubclavian vein, as demonstrated by lack of both color flow and venous waveform, with the presence of an acute thrombus (see *arrow*).

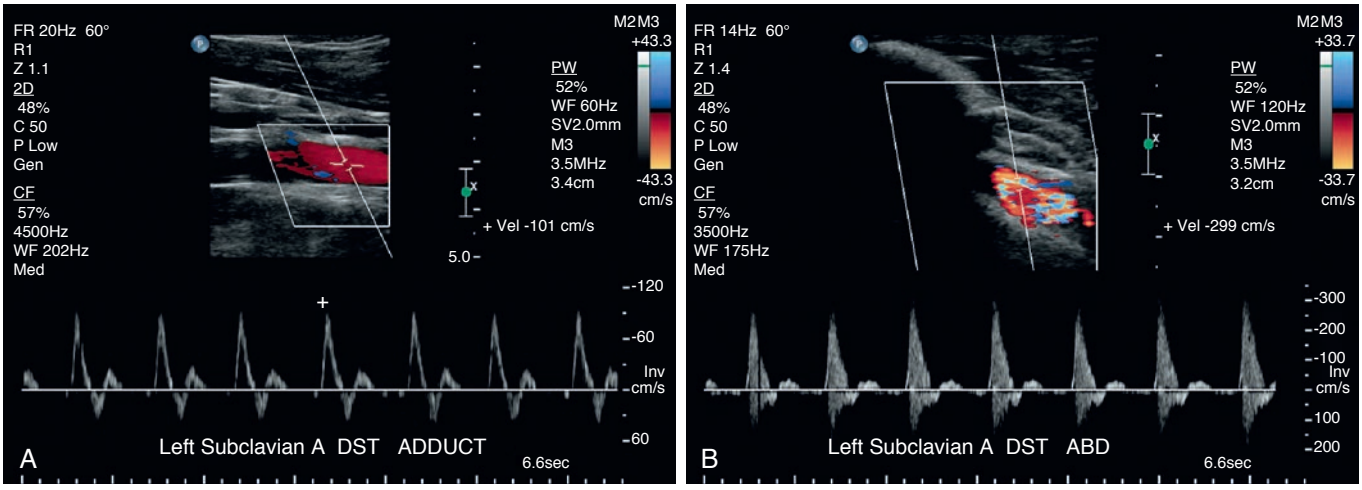

Figure 120.6 Duplex Ultrasound of the Subclavian Artery. (A) Normal arterial flow velocities at rest. (B) Abnormal (>50% increase) arterial flow velocities with provocative maneuvers.

intervention, as this condition confers the potential for embolic phenomena and ischemic complications (see Chapter 122).[58] The syndrome is characterized by a predictable course of events resulting from arterial compression, poststenotic dilation resulting in aneurysmal degeneration, and finally secondary embolism.

Pathogenesis

Arterial TOS is usually associated with a congenital or post-traumatic abnormality in the thoracic outlet. The inciting abnormality is usually a cervical or anomalous first rib, clavicular fracture, or rarely, an anomalous insertion of the anterior scalene muscle. Symptoms and signs are the result of arterial emboli arising from subclavian artery aneurysms or stenosis that resulted from the aberrant anatomy. In a compilation of case series representing 122 reported patients with aTOS, cervical ribs were present in 60%, anomalous first ribs in 18%, fibrocartilaginous bands in 15%, clavicular fracture in 6%, and an enlarged C7 transverse process in 1%.[59] The ensuing arterial compression results in subclavian artery stenosis accompanied by poststenotic dilation that causes the appearance of an aneurysm. Thrombus forms within the dilated portion of the artery just distal to the stenosis, as mural thrombus does in an aneurysm. The disease process is usually asymptomatic until emboli are dislodged.

The pathophysiology is based on the effects of arterial compression by an anomalous first rib, cervical rib, or anterior scalene muscle. Subclavian artery stenosis produces fluid hemodynamics that result in poststenotic dilatation or aneurysm

Figure 120.7 Subclavian venogram in a patient with venous thoracic outlet syndrome demonstrating subclavian vein narrowing due to compression *(arrow)* as the vein traverses the costoclavicular space.

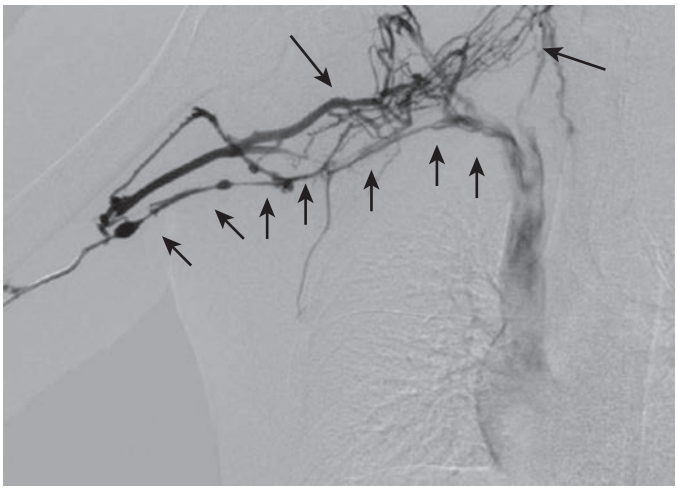

Figure 120.8 A contrast venogram demonstrating near-complete occlusion of the subclavian vein due to thrombus, prior to intervention, in a patient with venous thoracic outlet syndrome (TOS). *Large black arrows* indicate collateral venous drainage around thrombus. *Small black arrows* indicate the native axillary and subclavian vein.

formation, mural thrombus, and distal embolization. The most common presentation is microembolization to the hand, which causes ischemic symptoms.

History

Patients with arterial TOS are usually asymptomatic until arterial emboli occur. Symptoms include digital ischemia, claudication, pallor, coldness, and paresthesia and pain in the hand, but seldom in the shoulder or neck. Patients may complain of exertional pain, easy fatigability, or a "dead arm" sensation.[58] It is important to document if other systemic constitutional symptoms such as fever or malaise are present, which could suggest the possibility of vasculitis, particularly in younger patients. A history of an anomalous first rib or a cervical rib in any prior evaluation should also heighten the suspicion for arterial TOS.

Physical Examination

Evaluation for aTOS should focus on the presence of a subclavian aneurysm and on any signs of distal embolic phenomena. The supraclavicular fossa should be palpated for the presence of a cervical rib and for pulsatile mass. Auscultation should be performed to assess for the presence of a bruit. Additional abduction maneuvers may be employed to elicit a bruit or a pulsatile mass if there is not an obvious finding on exam in the seated position with arms relaxed. In addition, brachial blood pressure measurements should be recorded bilaterally.[58] Additional provocative maneuvers may be employed in the evaluation for aTOS. Obliteration of the radial pulse with the Adson test, costoclavicular maneuver, and hyperabduction maneuver may be observed in patients with aTOS. However, these tests are nonspecific, and many normal individuals have a positive result. The examiner should also pay particular attention to the fingers and hands, which should be inspected for skin changes consistent with thromboembolic or ischemic sequelae, including pallor, cyanosis, delayed capillary refill, mottling, discoloration, petechiae, and gangrene.

Diagnostic Evaluation

Duplex ultrasound should be performed in all patients presenting for evaluation of aTOS, with attention directed to the subclavian and axillary arteries and the presence of aneurysm, thrombus, turbulence, and elevated velocities consistent with luminal narrowing (Fig. 120.8). Duplex should be performed with the patient upright, and provocative maneuvers should be employed. In addition, chest radiography should be obtained on all patients presenting for evaluation of aTOS in order to identify the presence of bony abnormalities such as cervical ribs.

Spiral CT angiography may play a role in the diagnostic evaluation of patients with equivocal findings on duplex ultrasound (Figs. 120.9 and 120.10). Additional diagnostic information is obtained when the CT is performed with the arms at the sides, and again in a hyperabducted and externally rotated position in an effort to reproduce the arterial compression.[60,61] The advantage of CT in the evaluation of this condition is the ability of this modality to identify the relationship between the vasculature and the bony structures of the thoracic outlet.[58] CT is superior to conventional angiography for diagnostic purposes, as conventional contrast angiography has a high (32%) false negative rate when performed in the supine position.[62] Angiography can also play a role in the management of aTOS, and is mainly indicated when intervention such as thrombolysis is performed, or when planning for surgical revascularization.[17]

Figure 120.9 Three-dimensional–reconstructed computed tomography angiogram of patient presenting with arterial thoracic outlet syndrome and post-stenotic dilation of the subclavian artery.

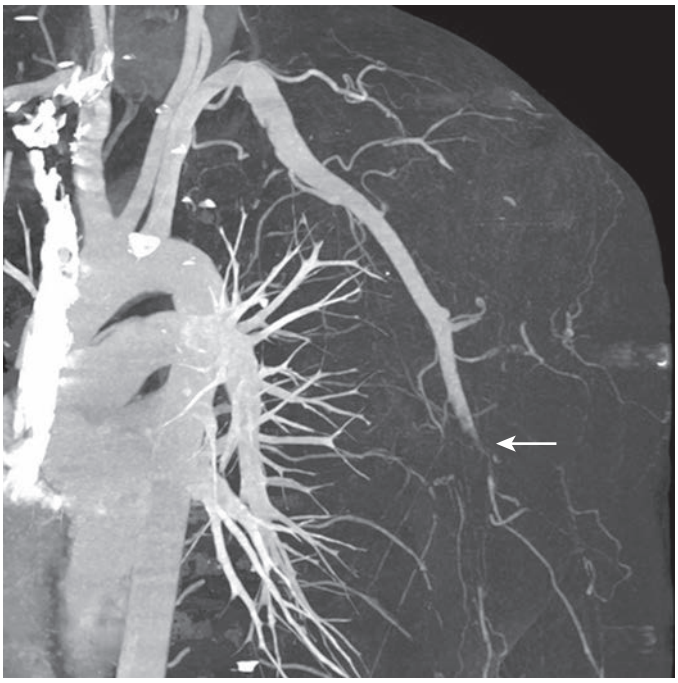

Figure 120.10 Three-dimensional–reconstructed computed tomography angiogram of patient presenting with arterial thoracic outlet syndrome, poststenotic dilation of the subclavian artery, and left arm ischemia resulting from thromboembolism to axillary artery *(arrow)*, with resulting intraluminal filling defect and distal outflow thrombosis.

Coexisting Thoracic Outlet Syndromes

Some patients being evaluated for TOS present with coexisting thoracic outlet syndromes as a result of the compression of multiple neurovascular structures traversing the thoracic outlet. For this reason, the workup of TOS should be broadly directed toward evaluating for the presence of neurologic, venous, and arterial TOS during the initial physical and diagnostic evaluation. It is our practice to obtain vascular duplex ultrasound on patients presenting with signs and symptoms of nTOS.[63] In our series from The Johns Hopkins Hospital, 5% of 423 patients presenting with nTOS were found to have coexisting aTOS.[64]

Challenges in Diagnosis

Several modalities of imaging and testing have been described for the evaluation of a patient suspected to have TOS. Occasionally, an anomalous first rib or cervical rib is overlooked during the workup. It is therefore important to obtain chest and/or neck radiographs to detect cervical and anomalous first ribs. Other tests that frequently accompany patients suspected to have TOS are noninvasive vascular lab studies such as photoplethysmography and duplex ultrasonography. It has been demonstrated that ultrasonography in combination with provocative maneuvers improves the specificity for diagnosis of TOS over either test alone.[65] Therefore patients with vTOS or aTOS should undergo duplex ultrasonography in conjunction with provocative maneuvers to evaluate for compression of the subclavian vessels in vTOS or aTOS. Patients being evaluated for nTOS have been shown to demonstrate vascular compression on duplex ultrasound in up to 50% of cases.[63] When this is demonstrated, the suspicion for nTOS being the primary cause of their symptoms should be heightened, and standard management for nTOS should ensue.

One might suspect that compression of the nervous structures in the thoracic outlet would lead to abnormalities in neurophysiologic tests such as EMG studies and nerve conduction studies (NCS). However, the results of EMG and NCS studies are often negative or inconclusive. While these results may seem superfluous in the diagnosis for nTOS, they are nevertheless still useful in excluding other nerve entrapment syndromes that can mimic nTOS.

Emerging Diagnostic Studies

Two additional studies have demonstrated promise in the diagnosis of nTOS: measuring the responses of the medial antebrachial cutaneous (MAC) nerve, and magnetic resonance (MR) neurography. The MAC nerve is the lowest branch of the inferior trunk of the brachial plexus and appears to be more sensitive to compression compared with other branches of the plexus. Abnormal measurements of MAC amplitude were recorded in patients with clinical signs of nTOS and normal electromyography/nerve conduction velocity studies.[66] In all patients, the amplitude of the symptomatic arm was lower than that of the asymptomatic arm. Another study of the MAC test was performed between 2004 and 2006 in 41 patients operated on for clinical signs of nTOS.[67] Although Seror's study measured only amplitude,[66] the later study found that latency was a little more helpful than amplitude. In applying these criteria, it is important that each electrodiagnostic laboratory establish its own diagnostic criteria in healthy volunteers, because precise technique and equipment may vary.[66,67]

There has been improvement in MR technology such that new 3 T MRI scanners can perform MR neurography by processing high resolution 2D STIR (Short Tau Inversion Recovery)

and isotropic three-dimensional (3D) T2 SPACE (Sampling Perfection With Application Optimized Contrasts Using Varying Flip Angle Evolutions, Siemens, Germany) imaging sequences. These processes result in imaging quality that can delineate subtle signal alterations, size changes, and mechanical course deviations of the brachial plexus within the thoracic outlet.[68]

As both these techniques gain further widespread usage and acceptance, they may offer further diagnostic options that could prove to be better objective tests compared with what is currently available to support the diagnosis of nTOS. Nevertheless, more studies are needed for confirmation before accepting their validity.[66-68]

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121 CHAPTER

Thoracic Outlet Syndrome: Neurogenic

ROBERT W. THOMPSON

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An increasing body of experience demonstrates that excellent outcomes can be achieved by a comprehensive, multidisciplinary approach to neurogenic thoracic outlet syndrome (NTOS), including a prominent role for surgical treatment in well-selected patients.[1-3] Nonetheless, uncertainties in diagnosis and disappointing results of treatment have led some authorities to question the need for surgical management of NTOS, and even to challenge whether the condition actually exists.[4-6] The purpose of this chapter is to review current understanding of the diagnosis, optimal management, and surgical techniques for NTOS. Because the vascular (arterial and venous) forms of TOS give rise to distinct clinical syndromes and require variations in management, these conditions are covered in other chapters.

ANATOMY

As shown in Fig. 121.1, the anatomy of the thoracic outlet region is composed of several bony and soft tissue structures, as well as the nerves and blood vessels that pass through this area (see Chapter 120).

Nerves in the Thoracic Outlet

The space formed by the scalene triangle is traversed by the five nerve roots arising from cervical spine levels C5 through T1 that make up the *brachial plexus*. The three trunks of the brachial plexus include the *upper trunk* (formed by fusion of the C5 and C6 nerve roots), the *middle trunk* (composed of the C7 nerve root), and the *lower trunk* (formed by fusion of the C8 and T1 nerve roots). Further merging and branching of these trunks outside the thoracic outlet results in formation of the divisions, cords, and terminal nerves of the brachial plexus. Additional nerves of surgical importance pass through the thoracic outlet, including the phrenic nerve, the long thoracic nerve, and the cervical sympathetic chain. The *phrenic nerve* passes lateral to medial as it descends along the anterior surface of the scalene muscle, and then behind the subclavian vein into the mediastinum, where it innervates the diaphragm. The *long thoracic nerve* passes through the middle scalene muscle, where its three components typically fuse to form a single nerve. It then descends to supply the serratus anterior muscle. The *cervicodorsal sympathetic chain* lies along the posterior inner aspect of the ribs. At the level of the first rib, a fusion of several ganglia results in formation of the large stellate ganglion.

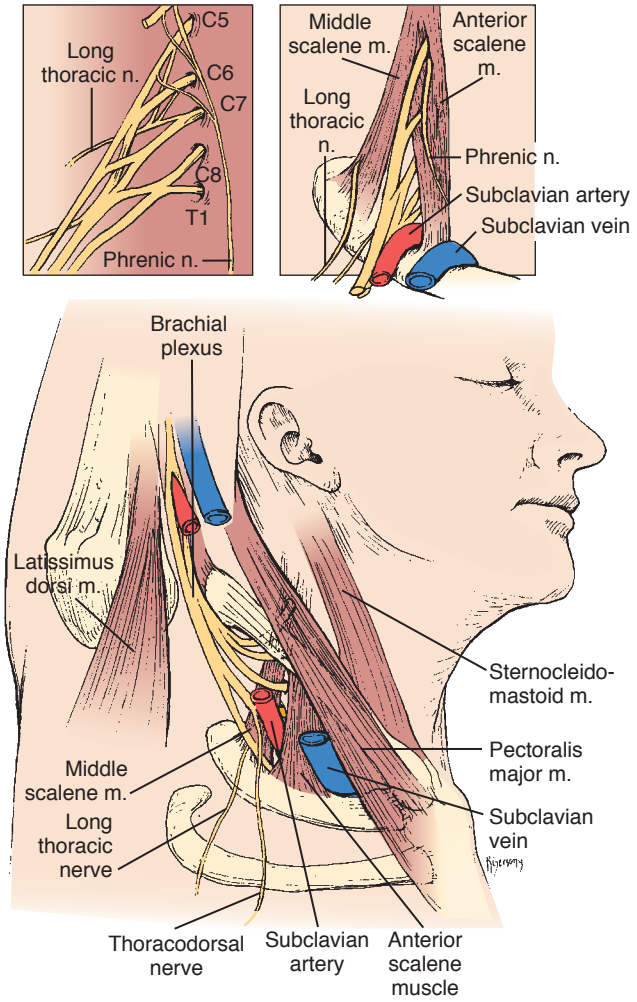

Figure 121.1 Anatomy of the Thoracic Outlet. The surgical anatomy of the thoracic outlet is centered upon spinal nerve roots C5 through T1, which interdigitate to form the brachial plexus as they cross under the clavicle and over the first rib. The long thoracic and phrenic nerves also arise within the thoracic outlet region. The brachial plexus nerve roots pass through the scalene triangle, bordered by the anterior and middle scalene muscles on each side and the first rib at the base. The subclavian artery also courses through the scalene triangle in direct relation to the brachial plexus nerve roots. The subclavian vein crosses over the first rib immediately in front of the anterior scalene muscle, before joining with the internal jugular vein to form the innominate vein. Symptoms of neurogenic thoracic outlet syndrome are often exacerbated by arm elevation, where greater strain is placed on the neurovascular structures passing through the scalene triangle. (Modified from Thompson RW, Petrinec D. Surgical treatment of thoracic outlet compression syndromes. I. Diagnostic considerations and transaxillary first rib resection. *Ann Vasc Surg*. 1997;11:315–323.)[67]

Musculofascial Variations

The conventional description of scalene triangle anatomy probably occurs in no more than one-third of individuals, with variations in the soft tissue structure of this region being very common.[7,8] The most frequent muscular variation in this region is known as the *scalene minimus muscle*, a structure that originates within the plane of the middle scalene muscle. This muscle passes between various nerve roots of the brachial plexus and inserts upon the first rib in conjunction with the anterior scalene muscle; thus it may contribute to nerve root compression when present. Additional soft tissue variations include fascial bands that pass across or between individual nerve roots, subsequently attaching to either the first rib or the extrapleural fascia. During operations for TOS, it is particularly common to encounter a dense fascial band crossing over the origin of the T1 nerve root, where it passes from underneath the first rib to contribute to the brachial plexus. A spectrum of other muscular and fascial variations in this region have been described and classified (Table 121.1).[9,10]

TABLE 121.1 Classification of Congenital Bands and Ligaments Within the Scalene Triangle

Type 1:	Extending from anterior tip of an incomplete cervical rib to the middle of the first thoracic rib; inserts just posterior to the scalene tubercle on the upper rib surface.
Type 2:	Arises from an elongated C7 transverse process in the absence of a cervical rib and attaches to the first rib just behind the scalene tubercle; associated with extension of the transverse process of C7 beyond the transverse process of T1 on AP spine radiographs.
Type 3:	Both originates and inserts on the first rib; starts posteriorly near the neck of the rib and inserts anteriorly just behind the scalene tubercle.
Type 4:	Originates from a transverse process along with the middle scalene muscle and runs on the anterior edge of the middle scalene muscle to insert on the first rib; the lower nerve roots of the brachial plexus lie against this band.
Type 5:	The scalene minimus muscle, arising with the lower fibers of the anterior scalene muscle, runs parallel to this muscle but passes deep to the muscle to cross behind the subclavian artery and in front of or between the nerve roots, and inserts on the first rib; any fibers passing anterior to or between the plexus but posterior to the artery.
Type 6:	Scalene minimus muscle inserting onto Sibson fascia over the cupula of the pleura instead of onto the first rib; labeled separately to distinguish its point of insertion.
Type 7:	Fibrous cord running on the anterior surface of the anterior scalene muscle down to the first rib, attaching to the costochondral junction or sternum; lies immediately behind the subclavian vein where it may be a cause of partial venous obstruction.
Type 8:	Arises from the middle scalene muscle and runs under the subclavian artery and vein to attach to the costochondral junction.
Type 9:	Web of muscle and fascia filling the inside posterior curve of the first rib, compressing the origin of the T1 nerve root.

Modified from Roos DB. Congenital anomalies associated with thoracic outlet syndrome. *Am J Surg*. 1976;132:771–778.

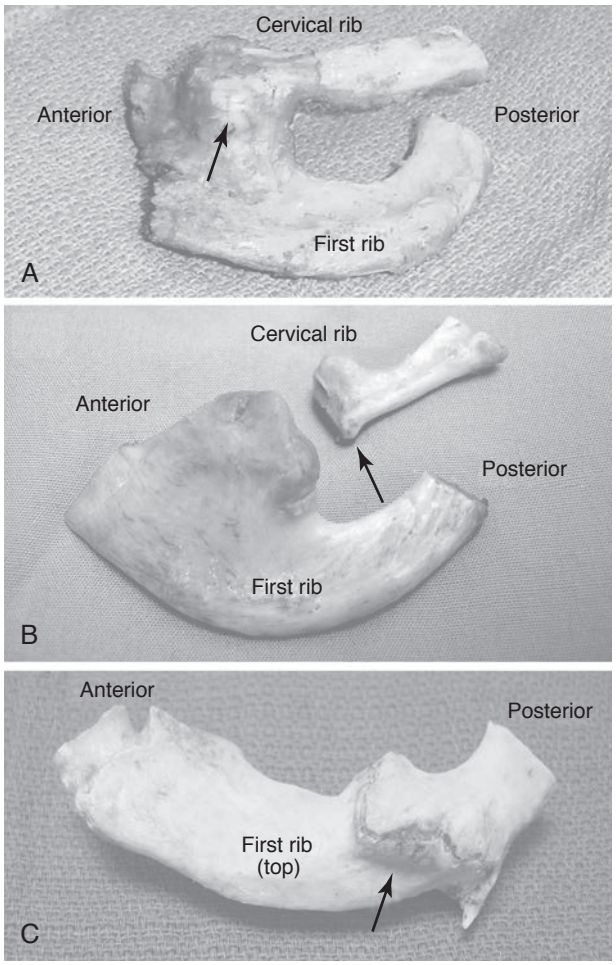

Figure 121.2 First Rib Anomalies. Operating room photographs depicting bony abnormalities associated with neurogenic thoracic outlet syndrome. (A) Resected specimen of cervical rib and attached first rib, exhibiting a completely formed joint *(arrow)*. (B) Resected specimen of cervical rib and accompanying first rib, with attachment through a fibrous connection and a large exostosis on the first rib *(arrow)*. (C) Resected specimen of a first rib that contained thickened callous associated with a healed fracture site from previous trauma *(arrow)*.

Bony Anomalies

Cervical ribs occur in approximately 0.45% to 1.5% of the population and in up to 5% of patients with TOS. They arise in the plane of the middle scalene muscle and typically attach to the midlateral portion of the first rib; the anomalous rib may join the first rib as an immobile bony fusion or as a fully developed joint (Fig. 121.2A).[11] *Incomplete cervical ribs* may also occur, arising as a bony or cartilaginous extension from the C7 cervical vertebrae without extension to join the first rib, and in some cases are attached to the first rib only by a band of cartilage or tendinous tissue (see Fig. 121.2B). *Rudimentary (hypoplastic) first ribs* are not as frequently recognized as cervical rib anomalies, and their actual incidence is unknown. These structures consist of a first rib that tends to lie higher in the neck than normal and often insert into the second rib rather than the sternum. *Previous trauma* may also result in abnormalities of the first rib, such as fractures with formation of thickened callous at the site of bony healing (see Fig. 121.2C).

Histopathology

Microscopic studies of the scalene muscles from patients with NTOS have consistently revealed two major abnormalities: (1) type I muscle fiber predominance and (2) endomesial fibrosis (Fig. 121.3).[12,13] Although the anterior scalene muscle normally exhibits an equal distribution of type I ("slow-twitch") and type II ("fast-twitch") muscle fibers, type I fibers compose up to 78% of the scalene muscle fibers in patients with neurogenic TOS associated with atrophy and pleomorphism of type II fibers. Alongside these changes there is marked thickening of the connective tissue matrix that surrounds individual muscle fibers, with a twofold increase in connective tissue content compared with normal scalene muscles, and in some cases there are mitochondrial abnormalities resembling those seen in

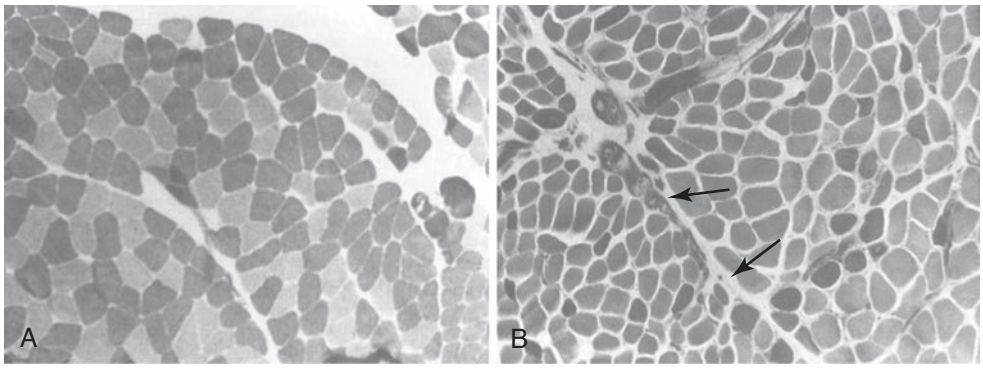

Figure 121.3 Scalene Muscle Histology in Neurogenic Thoracic Outlet Syndrome (NTOS). Muscle histopathology showing changes consistently observed in NTOS. Sections of the anterior scalene muscle were stained with myosin ATPase (pH 9.4) to visualize fiber types, with type I fibers staining lightly and type II fibers staining dark (original magnification 100×). Normal muscle has an equal distribution of type I and type II fibers *(left panel)*. The muscle from a patient with TOS *(right panel)* exhibits predominance of type I fibers, atrophy of type II fibers, and a significant increase in the connective tissue matrix between fibers *(arrows)*. (Modified from Sanders RJ. *Thoracic Outlet Syndrome: A Common Sequelae of Neck Injuries,* Philadelphia: J. B. Lippincott Company; 1991.)

muscular dystrophy. These changes do not represent a local abnormality, thought to reflect the histopathologic changes occurring after long-standing muscle injury, sustained muscle spasm, and abnormal tissue remodeling, and are therefore consistent with the frequent history of neck trauma that occurs in patients with NTOS.

ETIOLOGY

Predisposing Anatomic Factors

Current concepts indicate that NTOS is caused by a combination of predisposing anatomical factors and previous neck trauma. Indeed the normal anatomy of the thoracic outlet serves as a predisposing factor in the development of NTOS, since the neurovascular structures that traverse this region are prone to compression even during the course of regular daily activity. Activities involving sustained or repeated elevation of the arm or vigorous turning the neck may place additional tension on the scalene muscles, thereby potentiating any positional compression of the underlying nerve roots. This anatomical predisposition may be further increased by congenital structural variants, such as scalene muscle variations, abnormal tendinous bands, or cervical rib anomalies. However, because many individuals harbor such variations in the absence of neurogenic symptoms, anatomical factors are only considered a predisposing factor for NTOS rather than a distinct and separate cause, and they appear only to lower the threshold for the development of symptoms following injury.

Neck Trauma and Repetitive Strain Injury

Most patients with NTOS describe some form of previous trauma to the head, neck, or upper extremity, followed by a variable interval from days or weeks to several years before the onset of progressive upper extremity symptoms.[1] This is thought to reflect the variable time frame for scalene muscle injury to result in sustained compression and irritation of the brachial plexus nerve roots, and may obscure the relationship between a specific injury and development of NTOS. Persistent use of the upper extremity in activities that promote brachial plexus compression may further exacerbate symptom progression over time, resulting in progressive disability, and many patients do not seek medical attention until symptoms are well advanced. Not all patients with NTOS have their condition brought on by a specific traumatic event. In many cases, the injury may be the result of repetitive activities that inadvertently place strain on the scalene muscles over long periods of time, such as prolonged work at computer keyboards. TOS occurring in this circumstance is considered a form of repetitive strain injury (RSI). In these cases, it is likely that age-related changes in posture (e.g., slumping of the shoulders and stooping of the neck) may be significant factors leading to the development of extrinsic neural compression.

CLINICAL FINDINGS

The diagnosis of NTOS rests largely upon clinical pattern-recognition, with diagnostic suspicion raised by a stereotypical history and a description of symptoms typical of the disorder. The provisional diagnosis of NTOS is supplemented by physical examination and may be supported by a limited number of diagnostic studies. In most cases such studies are of value primarily in the exclusion of other (more common) conditions within the differential diagnosis. No single diagnostic test has a sufficiently high degree of specificity to completely prove or exclude the diagnosis of NTOS.[14]

Symptoms

Demographics

Neurogenic TOS most frequently occurs in individuals between 20 and 40 years of age, and approximately 70% of affected patients are women. Neurogenic TOS may arise in individuals

engaged in a variety of occupational or recreational activities, most often those involving heavy lifting or repeated use of the arm(s) in elevated positions, or following a spectrum of injuries to the head, neck, or upper extremity. Patients with no apparent predisposition, either due to anatomical variations or a history of trauma, may also develop NTOS. There are no medical conditions or known inherited patterns predisposing to NTOS.

Pain and Paresthesia

The primary symptoms of NTOS include pain, dysesthesias, numbness, and weakness. These symptoms usually occur throughout the affected hand or arm without any localization to a specific peripheral nerve distribution, and they often involve different areas of the entire upper extremity. Extension of symptoms from the hand to the shoulder, neck, and upper back is not infrequent, and in many patients the symptoms in the neck or upper back may be perceived as the most functionally disabling. Although most patients with NTOS have symptoms affecting just one upper extremity, bilateral symptoms are not uncommon; in such cases the dominant extremity is often more symptomatic at first presentation, but the opposite extremity may become involved over time, perhaps as a result of compensatory overuse. The lack of distribution of symptoms into patterns referable to a single peripheral nerve, and the frequent extension of symptoms to the shoulder, neck, and back, allows the distinction of NTOS from nerve compression disorders affecting the ulnar nerve at the elbow (cubital compression syndrome), the median nerve at the wrist (carpal tunnel syndrome), or other related conditions. Almost all patients affected by NTOS describe reproducible exacerbation of symptoms by activities that require elevation and/or the sustained use of the arms or hands. Positional complaints may also be brought on by lying supine, especially when the arms are positioned overhead, resulting in pain and difficulty sleeping at night.

Headache

Headaches are a common complaint associated with NTOS.[15] This most likely occurs as a result of referred pain to the occiput, due to secondary spasm within the trapezius and paraspinous muscles. Although NTOS and migraine headaches are often seen together, there is currently no evidence for a specific link between these conditions.

Weakness and Muscle Atrophy

Prolonged severe extrinsic compression of peripheral nerves can result in muscle weakness and atrophy, but such findings are actually rare in patients with NTOS, probably due to the intermittent nature of nerve compression in NTOS. Most commonly, hand or arm pain with use of the affected extremity may lead to the perception of weakness, causing the patient to avoid use of the arm or positions that exacerbate symptoms. This distinction should be sought during evaluation to help identify other conditions that may be responsible for symptoms of muscle weakness. The presence of authentic muscle weakness may therefore indicate particularly severe and long-standing compression of the brachial plexus nerve roots, either due to NTOS or another condition.

Disability

The majority of individuals with positional complaints related to NTOS are affected to only a mild and tolerable degree, usually due to transient irritation of the brachial plexus in certain positions of the arm or during certain activities. There is little risk of progressive injury in these situations, and no specific intervention is warranted. There remains a smaller subset of patients with clinically significant NTOS, however, who exhibit progressively disabling symptoms that effectively prevent them from working or carrying out simple daily activities. These patients often describe progressive disability and a long history of consultations with different physicians and partial or ineffective treatments. It is particularly helpful to obtain a detailed description from the patient of activities that exacerbate symptoms associated with NTOS, as well as those activities normally required in the workplace. Documentation of this assessment is often important if restrictions from work are necessary in the management of these patients and in guiding decisions about the role of surgical treatment.

Vascular Symptoms and Complex Regional Pain Syndrome

Vascular symptoms should be specifically sought in the history of patients with suspected TOS—particularly discoloration or coldness in the hands and fingers. It is important to note that ischemia is actually very unusual in such patients, whereas symptoms of vasomotor disturbance are not uncommon in those with longstanding or severe NTOS. Indeed, in some the symptoms of TOS may have progressed to resemble those of complex regional pain syndrome type I (CRPS-I; formerly known as reflex sympathetic dystrophy), with persistent vasospasm, disuse edema, and extreme hypersensitivity. The acuity of these symptoms often leads to avoidance and withdrawal from even light touch of the affected extremity. The diagnosis of CRPS-I can be supported by vascular laboratory studies revealing abnormal vasoconstrictive responses (cold-pressor tests) or imaging studies of the hand microcirculation, but in most cases the diagnosis is made on clinical grounds and the response to sympathetic blockade. The identification of this condition in patients with NTOS is quite important, because it may lead to an earlier recommendation for operative treatment and consideration of concomitant cervical sympathectomy.

When a history suggesting arterial insufficiency or thromboembolism exists, vascular laboratory studies and contrast-enhanced arteriographic imaging are necessary to exclude the presence of subclavian artery aneurysm or occlusive disease. Conversely, a history of arm swelling, cyanotic discoloration, and distended subcutaneous collaterals may indicate venous TOS due to obstruction of the subclavian vein, which requires contrast venography for full evaluation.

Physical Examination

Physical examination is initially directed toward eliciting the degree of neurogenic disability and identifying particular factors that exacerbate painful hand and arm complaints. The range

of motion of the upper extremity and lateral motion of the neck are assessed under both passive and active conditions. Pain and tenderness over the shoulder joint is evaluated as potentially related to rotator cuff pathology, and tenderness over the trapezius muscle may indicate fibromyalgia. A thorough peripheral nerve examination is performed to exclude ulnar nerve entrapment or carpal tunnel syndrome, two conditions that may mimic the symptoms of NTOS. The base of the neck is examined to identify the extent of any local muscle spasm over the scalene triangle itself, as well as over the trapezius, pectoralis, and parascapular muscles, and to localize specific "trigger points" to identify specific sites where palpation recreates the patient's typical symptoms of upper extremity pain and paresthesia. Localization of such trigger points over the scalene triangle or subcoracoid space serves to strongly reinforce the diagnosis of NTOS.

Perhaps the most useful component of physical examination is the 3-minute elevated arm stress test (EAST), in which the patient is positioned with the arms elevated in a "surrender" position and asked to repetitively open and close the fists. Most patients with NTOS report the rapid onset of their typical upper extremity symptoms with EAST, often being unable to complete the exercise beyond 30 to 60 seconds. When there is no difficulty performing the 3-minute EAST, the diagnosis of NTOS is suspect, and an alternative explanation for the symptoms should be sought more vigorously.

In some patients, compression of the neurovascular bundle as it passes underneath the pectoralis minor muscle tendon is a substantial factor contributing to NTOS. This situation is identified by localized tenderness and reproduction of upper extremity neurologic symptoms upon palpation over the pectoralis minor muscle. Given that pectoralis minor tenotomy may be an effective primary or adjunctive treatment in such individuals, it is important during the initial physical examination to identify this component of NTOS.

Vascular Examination

The Adson maneuver is commonly used to identify positional compression of the subclavian artery by detecting dampening of the radial pulse when the patient inspires deeply and turns the neck away from the affected extremity with or without elevation of the arm. Although this maneuver does not specifically reveal nerve root compression, positive findings may be associated with NTOS. However, a positive Adson sign is also quite common in the asymptomatic general population.

Patients presenting with symptoms of NTOS may on occasion have vascular findings related to either arterial or venous TOS (see Chapter 122 and Chapter 123).

Diagnostic Tests

Radiography

Plain radiographs of the neck are helpful in determining if an osseous cervical rib or abnormally wide transverse processes of the cervical vertebrae are present. Although either of these findings may solidify the diagnostic impression of TOS, neither of them is essential.

Cross-Sectional Imaging

The results of computed tomography (CT), magnetic resonance imaging (MRI), and other cross-sectional imaging examinations are usually negative in NTOS because the anatomical factors leading to intermittent or positional nerve compression are usually beyond the resolution of these studies. Even in situations where an apparent imaging abnormality exists in the region of the scalene triangle, it is usually impossible to prove the functional importance of such abnormalities with respect to the patient's upper extremity complaints. Imaging studies are nonetheless valuable to exclude other conditions that could be responsible for upper extremity symptoms, such as degenerative cervical disc or spine disease, shoulder joint pathology, or various forms of intracranial pathology.

In recent years, advances in MRI and data processing have led to higher resolution scans with three-dimensional reconstruction, along with the ability to detect localized abnormalities in nerve function (MR "neurography").[9,10,16,17] As this technique becomes utilized more frequently in patients with and without NTOS, it may provide a useful diagnostic tool to supplement clinical evaluation.

Neurophysiologic Testing

Electromyography (EMG) and nerve conduction studies (NCS) are often utilized in the evaluation of patients suspected of having NTOS, particularly when symptoms are suggestive of a specific radiculopathy, a peripheral nerve syndrome, or a general myopathy. Positive results of neurophysiologic testing are therefore quite useful, as they point to specific alternative conditions that must be evaluated further. Unfortunately, the results of conventional EMG/NCS studies are usually negative in NTOS, because nerve root compression occurs in an extremely proximal location, and is intermittent and not usually associated with permanent changes in motor nerve function.[18] Negative results from these studies nonetheless help exclude other conditions from further consideration. Positive EMG/NCS findings in patients with NTOS are a poor prognostic finding in the absence of an alternate explanation, indicating an advanced stage of neural damage that is unlikely to resolve despite adequate decompression. Recent evidence suggests that electrophysiologic testing of sensory nerve abnormalities may be more useful in the diagnosis of NTOS than conventional EMG/NCS. For example, Machanic and Sanders reported studies using the response to medial antebrachial cutaneous nerve (MAC) and C8 nerve root stimulation in patients with a clinical diagnosis of NTOS compared with asymptomatic controls, indicating that this form of electrophysiologic testing had a high degree of sensitivity and specificity.[19]

Scalene Muscle Blocks

Injection of local anesthetic into the anterior scalene muscle may be used as an adjunct to the clinical diagnosis of NTOS, particularly in predicting the potential response to surgical decompression.[20] Successful scalene muscle block is indicated by relief of symptoms in the hand or arm, along with a reduction in local tenderness over the anterior scalene muscle. Injection

of anesthetic to the level of the brachial plexus precludes accurate interpretation of this test, since there will be temporary numbness and weakness in the arm, making the assessment of pain relief unreliable. A scalene muscle block is not necessary in patients with clear-cut symptoms where the diagnosis is not questioned, but it can be useful in patients with an equivocal diagnosis of NTOS. Sanders and others have also reported a strong correlation between the relief of symptoms following scalene muscle block and the success of surgical decompression.[20-22] A variation of scalene muscle block as a treatment for NTOS is the use of locally injected botulinum toxin.[23] However, side effects of botulinum toxin may occur early after treatment (e.g., dysphagia); the duration of beneficial effects with botulinum toxin is often limited from 2 to 3 months, and repeated treatment effects are diminished by the systemic immune response to the injected protein. Thus botulinum toxin injections cannot yet be generally recommended.

Angiography and Vascular Laboratory Studies

Vascular laboratory studies and angiography are usually not necessary in making the diagnosis of NTOS, unless the patient presents with symptoms suggestive of an arterial or venous component.

Making the Diagnosis

The differential diagnosis may include a number of conditions (Table 121.2), and some of these entities can be distinguished by specific findings or diagnostic tests. The surgeon recognizing NTOS should not be dissuaded by the impression that these problems are frequently associated with psychiatric overtones, dependency on pain medications, and ongoing litigation. Careful evaluation using clinical diagnostic criteria can usually detect patients with strong clinical evidence of NTOS, as well as identify those most likely to respond to treatment (Table 121.3).[24] The evaluating surgeon must be willing to expend considerable time and energy to provide these patients with a thorough evaluation, detailed information, lengthy discussion, and ongoing support. The suspected nature of the condition is explained, the diagnostic and therapeutic uncertainties that surround NTOS are discussed, and an honest but reassuring outline of treatment expectations is presented. Surgeons making this effort are typically rewarded by grateful patients with renewed hope for long-awaited improvement.

TABLE 121.2 Differential Diagnosis of Neurogenic Thoracic Outlet Syndrome

Condition	Differentiating Features
Carpal tunnel syndrome	Hand pain and paresthesia in median nerve distribution; positive findings on nerve conduction studies.
Ulnar nerve compression	Hand pain and paresthesia in ulnar nerve distribution; positive findings on nerve conduction studies.
Rotator cuff tendinitis	Localized pain and tenderness over biceps tendon and shoulder pain on abduction; positive findings on MRI; relief from NSAIDs, local steroid injections or arthroscopic surgery.
Cervical spine strain/sprain	Posttraumatic neck pain and stiffness localized posteriorly along cervical spine; paraspinal tenderness; relief with conservative measures over weeks to months.
Fibromyositis	Posttraumatic inflammation of trapezius and parascapular muscles; tenderness, spasm and palpable nodules over affected muscles; may coexist with TOS and persist after surgery.
Cervical disc disease	Neck pain and stiffness, arm weakness, and paresthesia involving thumb and index finger (C5-6 disc); symptom improvement with arm elevation; positive findings on CT or MRI.
Cervical arthritis	Neck pain and stiffness; arm or hand paresthesia infrequent; degenerative rather than posttraumatic; positive findings on spine radiographs.
Brachial plexus injury	Caused by direct injury or stretch; arm pain and weakness, hand paresthesias; symptoms constant not intermittent or positional; positive findings on neurophysiologic studies.

CT, Computed tomography; *MRI*, magnetic resonance imaging.

CONSERVATIVE MANAGEMENT

Physical Therapy

Physical therapy serves as the initial treatment for almost all patients with NTOS.[25] It is important that the patient be referred to a therapist with experience, expertise, and interest in TOS, since the management of this condition is different from that of other disorders affecting the neck, shoulder, and upper extremity.[26] Many physical therapists do not have great experience with NTOS, and incorrect approaches to therapy can result in the worsening of symptoms and premature failure of conservative management.[27]

Evaluation

The physical therapist treating the patient with NTOS outlines a specific plan for initial treatment over a 4- to 8-week period, to be followed by reassessment of progress. Initial assessment includes evaluation of posture, alignment, and movement patterns of the patient, specifically focusing on areas of impairment that may contribute to compression of the brachial plexus. These areas include the slope of the shoulder girdle, the angle of the clavicle, the position of the scapula on the thorax, the position of the humerus in the glenoid, the posturing of the head and neck, and the alignment of the cervical and upper thoracic spine. The therapist also examines dynamic patterns, such as scapular mechanics and timing during upper extremity movements, as well as any changes in muscle length, strength, and/or recruitment that may put stress on the brachial plexus (Fig. 121.4).

TABLE 121.3 Clinical Diagnostic Criteria for Neurogenic Thoracic Outlet Syndrome

Upper extremity symptoms which extend beyond the distribution of a single cervical nerve root or peripheral nerve, have been present for at least 12 weeks, have not been satisfactorily explained by another condition, AND meet at least 1 criterion in at least 4 of the following 5 categories:

Principal Symptoms

1A: Pain in the neck, upper back, shoulder, arm and/or hand
1B: Numbness, paresthesias, and/or weakness in the arm, hand, or digits

Symptom Characteristics

2A: Pain/paresthesias/weakness exacerbated by elevated arm positions
2B: Pain/paresthesias/weakness exacerbated by prolonged or repetitive arm/hand use, including prolonged work on a keyboard or other repetitive strain tasks
2C: Pain/paresthesias radiate down the arm from the supraclavicular or infraclavicular spaces

Clinical History

3A: Symptoms began after occupational, recreational, or accidental injury of the head, neck, or upper extremity, including repetitive upper extremity strain or overuse
3B: Previous ipsilateral clavicle or first rib fracture, or known cervical rib
3C: Previous cervical spine or ipsilateral peripheral nerve surgery without sustained improvement in symptoms
3D: Previous conservative or surgical treatment for ipsilateral TOS

Physical Examination

4A: Local tenderness on palpation over the scalene triangle and/or subcoracoid space
4B: Arm/hand/digit paresthesias on palpation over the scalene triangle and/or subcoracoid space
4C: Objectively weak handgrip, intrinsic muscles, or digit 5, or thenar/hypothenar atrophy

Provocative Maneuvers

5A: Positive ULTT
5B: Positive 3-minute EAST

Exclusion of other conditions typically includes nonspecific or negative findings on physical examination (Spurling test, axial compression test, Tinel sign over the carpal tunnel or cubital tunnel, and Phalen test), imaging studies (MRI of cervical spine and shoulder), and conventional electrophysiologic tests (upper extremity electromyography and nerve conduction studies).
EAST, Elevated arm stress test; *TOS*, thoracic outlet syndrome; *ULTT*, upper limb tension test.
Modified from consensus diagnostic criteria developed by the Consortium for Research and Education on Thoracic Outlet Syndrome (CORE-TOS).

Treatment

The therapist utilizes the results of individual-based assessment to help educate the patient on specific faults that may be contributing to their condition, instruct them in an exercise program, and possibly implement the use of external devices, such as bracing or taping, to take stress off of the anatomical compression sites.[28] The principal areas addressed include the scalene triangle, the costoclavicular space, and the area between the pectoralis minor and the coracoid process. In addition, scapular mechanics may be at a disadvantage in patients with NTOS, leading to additional stresses with overhead motion.[29] The initial goals of physical therapy are therefore to maintain and improve the range of motion of the neck and affected upper extremity, using a combination of passive and assisted exercises.[30-32] In particular, exercises designed to relax and stretch the scalene muscle are used, combined with hydrotherapy, massage, and other techniques. These efforts may be accompanied by the use of nonsteroidal antiinflammatory agents, muscle relaxants, and nonnarcotic pain medications, as needed. Once initial improvement has been achieved, subsequent efforts can be focused on strengthening muscles of posture and increasing achievable levels of activity.

Results

Most patients with mild symptoms of NTOS, or those in whom therapy has been started early after the onset of symptoms, will exhibit significant improvement. Therapy is then continued with the expectation that continued benefits will preclude the need to consider surgical treatment. Although in our experience this outcome is obtained in only 20% to 30% of patients referred for management of NTOS, the proportion of patients responding to conservative treatment is much higher in a more general (nonreferral) population.[33] If progress with the initial course of conservative management has been unsatisfactory, the basis for the diagnosis of NTOS is reviewed, and any further testing thought to be appropriate is carried out. When the physician is confident of the diagnosis of NTOS, the level of symptoms is disabling, and the patient has not responded sufficiently to conservative management, surgical treatment is considered.[34]

SURGICAL TREATMENT

Historical Background

The first operations for thoracic outlet compression were focused on the treatment of subclavian artery aneurysms in patients with a cervical rib, as described by Coote in 1861.[35] By the turn of the century the "cervical rib syndrome" was widely recognized, and in 1927 Adson and Coffey described the use of anterior scalenotomy in treatment of this condition, including symptomatic patients without a cervical rib anomaly.[36] The term "thoracic outlet syndrome" was introduced by Peet in 1956,[37] and in the 1960s several new operative approaches to TOS were described, including posterior thoracotomy (Clagett) and transaxillary first rib resection (Roos).[38,39] Although transaxillary first rib resection became popular and widely used during the 1970s, disenchantment arose when results were found to be no better compared with scalenectomy and when a national survey indicated a significant incidence of permanent nerve injuries following this operation.[22,40] It also became appreciated that symptomatic recurrences following transaxillary first rib resection often involved reattachment of the unresected scalene muscles to the remaining end of the first rib or adjacent tissues,

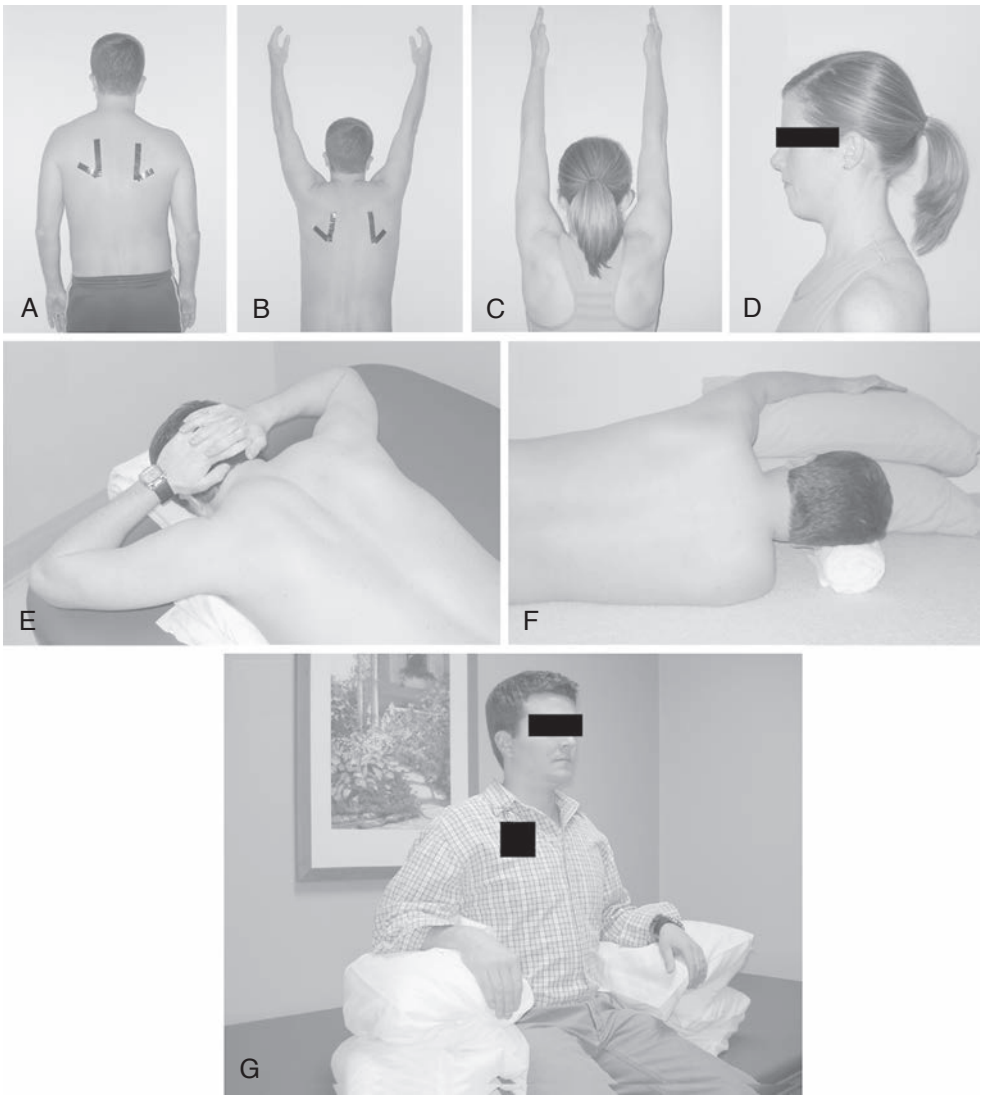

Figure 121.4 Physical Therapy for Neurogenic Thoracic Outlet Syndrome. (A) An example of postural assessment including scapular depression with an increased slope of the right shoulder girdle. (B) Implementing an exercise to improve a scapular depression fault. (C) Upper trapezius muscle recruitment in standing while facing a wall. (D) Addressing cervical spine alignment. (E) Strengthening the middle trapezius musculature. (F) Exercises addressing overhead mechanics are initiated in a gravity-lessened position. (G) Sitting with arms supported helps to take weight off the shoulder girdle.

leading to diminished enthusiasm for first rib resection and a reemphasis on complete scalene muscle resection.[41] The combined use of supraclavicular and transaxillary approaches was reported in 1984 by Qvarfordt et al.,[42] followed by further description of the supraclavicular approach by Sanders and Raymer and by Reilly and Stoney.[43,44] During the past decade the supraclavicular approach appears to have become the most commonly employed approach in current practice.

With regard to the selection of operative approach, it is now generally accepted that NTOS may arise from compression of the brachial plexus nerve roots at several different levels by different etiologic factors, not solely as a consequence of bony deformation by the first rib. Numerous soft tissue anomalies within the thoracic outlet have been described and classified, each of which can give rise to symptomatic neural compression. Significant factors playing a role in this process appear to include scalene muscle injury with spasm, scarring, and fibrotic inflammatory reactions surrounding the brachial plexus nerve roots, which may also be associated with pathologic changes in the scalene musculature. Current approaches to surgical treatment must take each of these potential contributing factors into account in selecting the optimal treatment for individual patients.

Transaxillary Approach

The primary advantages of *transaxillary first rib resection* include a relatively limited field of operative dissection, a cosmetically placed skin incision, and sufficient exposure to reliably accomplish resection of the anterolateral first rib. This approach also makes it possible to achieve at least partial resection of the anterior scalene muscle, as well as identification and removal of most anomalous ligaments and fibrous bands that may be associated with TOS. The disadvantages of the transaxillary approach include incomplete exposure of the structures comprising the scalene triangle, inability to achieve complete anterior and middle scalenectomy or brachial plexus neurolysis, and the necessity for first rib resection in all cases. This approach is also limited when vascular reconstruction is needed, and in such cases repositioning of the patient and the addition of a separate incision are required.

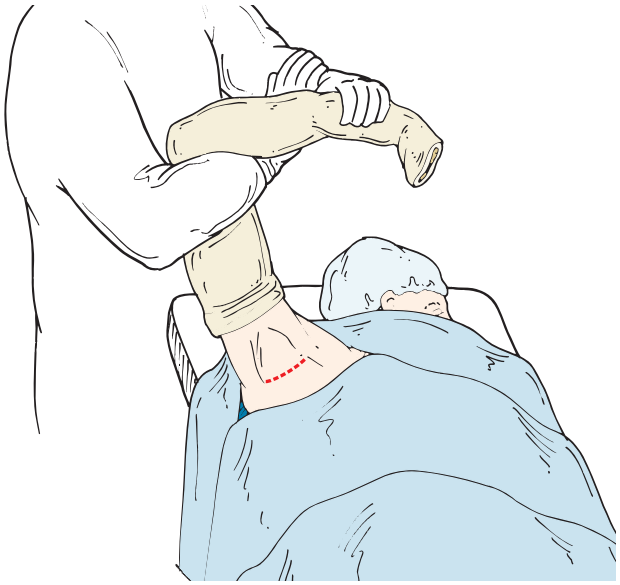

Figure 121.5 Positioning for Transaxillary First Rib Resection. With the arm carefully elevated by a reliable assistant, the initial skin incision is made at the lower edge of the axillary hair line. (Modified from Thompson RW, Petrinec D. Surgical treatment of thoracic outlet compression syndromes. I. Diagnostic considerations and transaxillary first rib resection. *Ann Vasc Surg.* 1997;11: 315–323.)[67]

Under general anesthesia, the patient is positioned supine with the back of the table raised about 30 degrees. A small towel pack is placed behind the shoulder to elevate the affected side. The arm is prepped circumferentially and wrapped in stockinette, and the sterile field includes the neck, upper chest, and posterior shoulder to the scapula. The arm is held and positioned by a reliable, flexible, and sturdy assistant (Fig. 121.5), or by a special retractor.

A transverse skin incision is made at the lower border of the axillary hairline, extending from the anterior border of the latissimus dorsi to the lateral edge of the pectoralis major (see Fig. 121.5). The long thoracic, thoracodorsal, and second intercostobrachial nerves are identified near the chest wall to avoid direct injury. Excessive elevation of the arm (unique to transaxillary exposure) is a potential mechanism of injury to the second intercostobrachial cutaneous nerve, resulting in postoperative pain and numbness along the medial aspect of the upper arm. The first rib is typically palpable at the upper reaches of the areolar tissue plane along the chest wall. Using a Deaver retractor to gently lift the subcutaneous tissues and axillary contents away from the chest wall, the first rib is more clearly exposed in the upper aspect of the wound. It is necessary to carefully lift the arm to facilitate this exposure, both at this stage and throughout the remainder of the procedure, and the operating surgeon should use a fiberoptic headlight to properly illuminate the operative field.

Exposure obtained during the transaxillary approach is generally limited to the operating surgeon. In order to avoid serious injury, the blades of the retractors must not apply excess traction to the neurovascular structures visible above the first rib. In addition to the nerve roots of the brachial plexus, proper attention must be given to avoid traction on the long thoracic nerve, which exits the plane between the middle and posterior scalene muscles before coursing over the first rib to the serratus anterior muscle. Periodic inspection of the retractors and relief for the assistants is recommended, using a staged approach to the operation as described by Machleder.[45]

Once the first rib is sufficiently exposed, the subclavian vein and subclavian artery are identified, along with the intervening anterior scalene muscle (Fig. 121.6A). These structures are carefully dissected such that the anterior scalene tendon can be encircled with a right-angle clamp just above its insertion onto the scalene tubercle of the first rib, which is typically palpable as a slight bony prominence. The anterior scalene muscle is exposed over several centimeters superior to the first rib, and while taking care to avoid the phrenic nerve, the muscle is divided using scissors at the highest level feasible. The importance of resecting a portion of the scalene muscle, rather than simply dividing it at the level of the first rib itself, has been underscored by analysis of the factors causing recurrent TOS.

The soft tissues attaching to the inferior and medial borders of the first rib are progressively divided with scissors, beginning with the attachments medial to the subclavian vein (the subclavius muscle tendon and the costosternal and costoclavicular ligaments). A periosteal elevator is used along the inferior border of the rib, extending underneath the rib from the vantage point of the exposure used. The intercostal muscle is fully divided, and the parietal pleura is pushed away from the deep aspect of the rib by blunt dissection. The middle scalene muscle is detached from the superior surface of the rib, posterior to the brachial plexus nerve roots (see Fig. 121.6B). Although the proximal aspect of the long thoracic nerve is not directly visualized during this maneuver, injury to this nerve must be prevented to avoid postoperative serratus anterior muscle weakness. This is best accomplished by keeping the periosteal elevator directly upon the rib during scalene muscle detachment, avoiding any tendency to stray laterally where the long thoracic nerve can be easily injured. The long thoracic nerve is thereby gently pushed away from the rib indirectly as the middle scalene muscle is detached, effectively protecting it despite the lack of direct visualization. Once the posterior surface of the first rib is exposed and the T1 nerve root is in full view to protect it from injury, a bone-cutting instrument is carefully applied across the neck of the rib. The lateral portion of the divided rib is pulled downward, and its anterior aspect is cut in a similar fashion, just medial to the subclavian vein at the costochondral junction. The first rib is then fully detached and removed from the operative field (see Fig. 121.6C). A bone rongeur is used to trim the remaining ends of the bone to a smooth surface well beyond the neurovascular structures. With an additional amount of extrapleural dissection, the same exposure can be used to perform adjunctive cervical sympathectomy for patients with neurogenic TOS complicated by reflex sympathetic dystrophy.

Any additional soft tissue bands found to be crossing the brachial plexus nerve roots are sought and carefully divided, particularly those that may insert upon Sibson's fascia, the thickened aspect of the apical pleural surface. After hemostasis is achieved, the wound is irrigated and the lung is inflated to detect any breaks in the pleural lining. If small air bubbles are

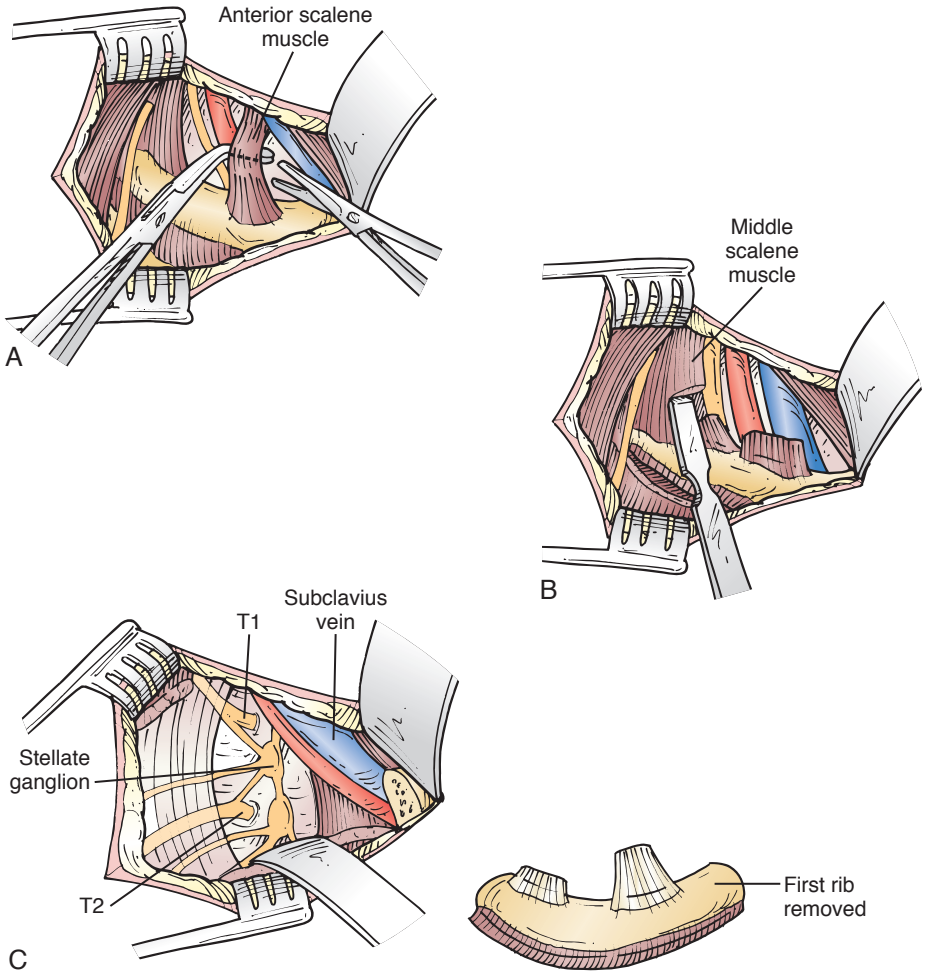

Figure 121.6 Transaxillary First Rib Resection. (A) Transaxillary division of the anterior scalene muscle. The tendinous insertion of the anterior scalene muscle onto the first rib is elevated with a right-angle clamp and divided with a scissors. (B) Detachment of the middle scalene muscle. After the intercostal attachments to the first rib are divided, a periosteal elevator is used to detach the middle and posterior scalene muscles. Injury to the proximal portion of the long thoracic nerve is prevented by staying directly on the rib. (C) Removal of the first rib. The anterior and posterior aspects of the first rib are divided, with the operative specimen including the resected portion of the anterior scalene muscle and the site of attachment of the middle scalene muscle. (Modified from Thompson RW, Petrinec D. Surgical treatment of thoracic outlet compression syndromes. I. Diagnostic considerations and transaxillary first rib resection. *Ann Vasc Surg*. 1997;11:315–323.)[67]

observed during positive-pressure ventilation or if the irrigation fluid appears to be lost into the pleural space, a small chest tube may be placed through a separate wound. The incisional wound is closed in two layers after placing a small closed suction drain in the operative field.

Supraclavicular Approach

The *supraclavicular approach* carries the major advantages of wider exposure of all anatomical structures associated with thoracic outlet compression. This allows complete resection of the anterior and middle scalene muscles to be achieved, as well as brachial plexus neurolysis with direct visualization of all five nerve roots. In many cases symptomatic relief of NTOS can be achieved by extended scalenectomy without the need for first rib resection, an option permitted by the supraclavicular approach. This approach also allows for resection of cervical ribs, anomalous first ribs, or the normal first rib. A further advantage is that all forms of vascular reconstruction can also be accomplished through supraclavicular exposure; although removal of the anteromedial portion of the first rib and distal control of the vessels may require addition of a second infraclavicular incision, this is performed without the need for repositioning the patient. The balance of advantages and disadvantages between these two operative approaches has led many groups to prefer the supraclavicular approach to TOS, with some adopting a highly selective approach in which resection of the first rib is reserved solely for patients with vascular complications.[46]

Under general anesthesia, the patient is positioned supine with the head of the bed elevated 30 degrees. The hips and knees are flexed and the neck is extended and turned to the opposite side. The neck, upper chest, and upper extremity are prepped into the field with the arm wrapped in a stockinette, then held comfortably across the abdomen. This allows for arm movement through an extended range of motion during the operation, when it may be necessary to assess any residual neurovascular compression following scalenectomy. A transverse skin incision is made two fingerbreadths above the clavicle, beginning at the lateral border of the sternocleidomastoid muscle (Fig. 121.7A). This incision is carried through the platysma muscle layer to expose the scalene fat pad, which is mobilized beginning at the lateral border of the internal jugular vein. As this tissue plane is entered, the fat pad is progressively dissected off the anterior surface of the anterior scalene muscle and reflected laterally (see Fig. 121.7B). The phrenic nerve is

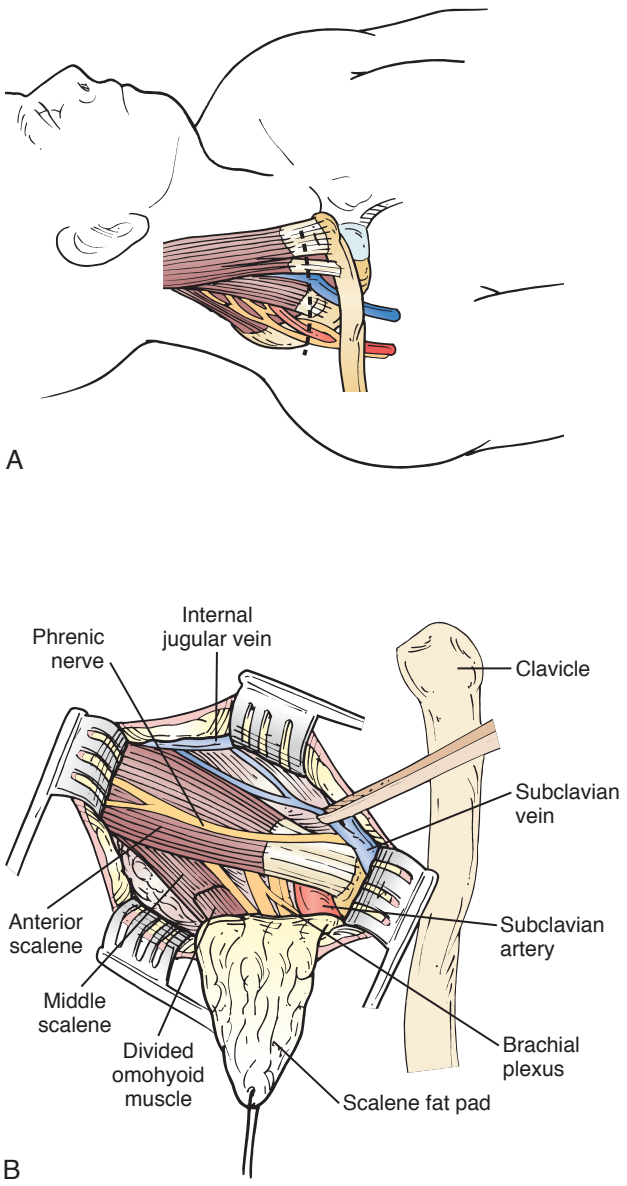

Figure 121.7 Positioning for Supraclavicular Thoracic Outlet Decompression. (A) A transverse skin incision is made two fingerbreadths above the clavicle to obtain full exposure of the structures associated with the scalene triangle. (B) The scalene fat pad is mobilized laterally to expose the underlying anterior scalene muscle, with identification and protection of the phrenic nerve. The omohyoid muscle is divided. The subclavian artery and the upper roots of the brachial plexus are identified behind the lateral edge of the anterior scalene muscle. (Modified from Thompson RW. Treatment of thoracic outlet syndromes and cervical sympathectomy. In: Lumley JSP, Hoballah JJ, eds. *Springer Surgery Atlas Series: Vascular Surgery*. London: Springer-Verlag; 2009:103–118.)[68]

identified within the investing fascia of the muscle, coursing in a lateral to medial direction ("lateral to medial" may be clearer to students and residents). Lateral retraction of the scalene fat pad then permits exposure of the underlying roots of the brachial plexus. The anterior scalene muscle is dissected, taking special effort to avoid excessive traction on the phrenic nerve (Fig. 121.8A). After circumferential mobilization of the anterior scalene muscle to its site of attachment to the first rib, a finger is passed behind the muscle and the muscle tendon is sharply divided at its insertion using a curved scissors (see Fig. 121.8B). There may be additional slips of muscle or tendon that must be divided more posteriorly, including direct attachments of the muscle to the thickened pleural lining behind the rib itself.

The anterior scalene muscle is lifted superiorly to detach it from the additional structures underneath, including the pleural apex, the subclavian artery, and the brachial plexus nerve roots (see Fig. 121.8C). This dissection is carried superiorly to the level of the scalene muscle origin on the transverse process of the sixth cervical vertebrae. Great care must be taken to avoid irretrievable neural injury while muscle fibers interdigitating with the proximal roots of the upper brachial plexus are removed. The entire anterior scalene is then removed, weighed, and sent to the neuromuscular pathology laboratory.

Following anterior scalenectomy and removal of any scalene minimus fibers, each of the nerve roots contributing to the brachial plexus is identified and meticulously dissected free of inflammatory scar tissue (see Fig. 121.8D). Moderately dense fibrotic tissue encasing the nerve roots is not uncommon in patients with neurogenic TOS, and failure to perform an adequate neurolysis may be one cause of persistent symptoms. This aspect of the operation is not complete until each nerve root from C5 to T1 is completely dissected throughout its course in the operative field.

Osseous cervical ribs or their soft tissue counterparts occur within the same plane as the middle scalene muscle. While the middle scalene muscle lies posterior to the roots of the brachial plexus, in some cases its insertion upon the first rib may occur as far anteriorly as the scalene tubercle (the site of attachment of the anterior scalene muscle). The attachment of the middle scalene muscle is divided from the first rib using a periosteal elevator or curved Mayo scissors, extending to a point posterior to the brachial plexus nerve roots (see Fig. 121.8E). If a cervical rib is present in the plane of the middle scalene muscle, it may also be detached from the first rib at this time. It is important to note the separation between the middle scalene and posterior scalene muscles, as defined by the oblique course of the long thoracic nerve. Muscle tissue anterior to this nerve is detached along the plane delineated by the long thoracic nerve while leaving the nerve intact. It is important to recognize that the long thoracic nerve may be represented by two or three branches at this level, rather than a single nerve, as often described.

Following resection of the anterior and middle scalene muscles and completion of a thorough brachial plexus neurolysis, an intraoperative decision is made regarding the potential role of the first rib in neurovascular compression. The surgeon's finger is placed alongside the brachial plexus nerve roots while the arm is elevated through a normal range of motion at the shoulder, allowing any residual compression to be detected during arm elevation. In many patients with NTOS, there is little residual compression by the first rib following adequate scalenectomy, and in these cases retention of the first rib may be considered. In contrast, the first rib should be removed if there is any question that it might contribute to residual neurovascular compression, as well as in all patients with arterial or venous TOS.

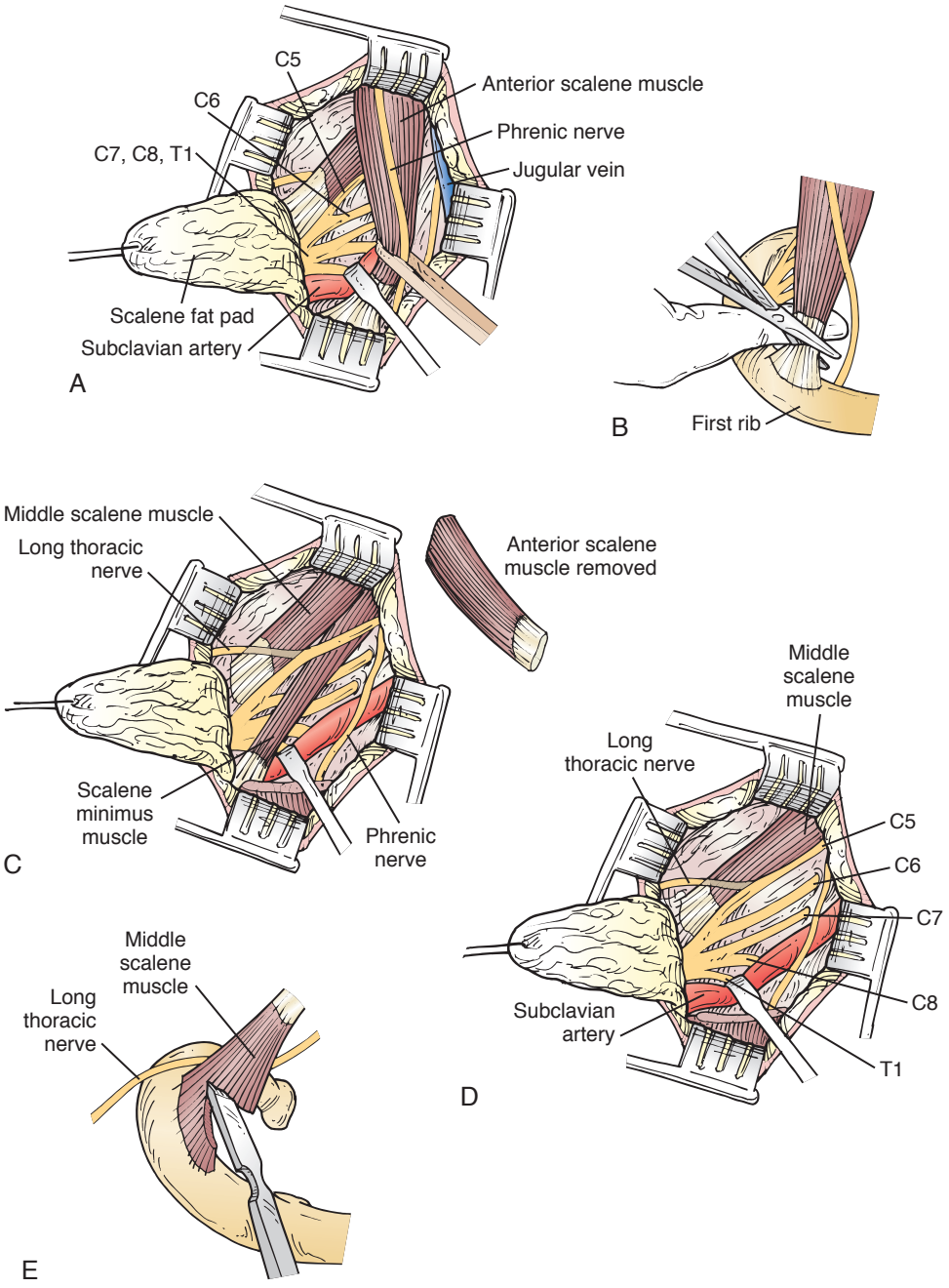

Figure 121.8 Supraclavicular Scalenectomy and Neurolysis. (A) The anterior scalene muscle is circumferentially mobilized from the underlying subclavian artery and roots of the brachial plexus. (B) The insertion of the anterior scalene muscle upon the first rib is sharply divided with scissors, with the surgeon's finger protecting the subclavian artery and the roots of the brachial plexus. (C) The anterior scalene muscle is reflected superiorly and dissected free of underlying structures to the level of its origin. Any muscle fibers passing between the upper nerve roots of the brachial plexus are also removed, including a scalene minimus muscle if present. (D) Complete dissection of the brachial plexus nerve roots from C5 to T1 is accomplished by resection of all perineural scar tissue. (E) The middle scalene muscle is detached from the first rib using a periosteal elevator, taking care to protect the long thoracic nerve. All muscle tissue lying anterior to the long thoracic nerve is resected. (Modified from Thompson RW. Treatment of thoracic outlet syndromes and cervical sympathectomy. In: Lumley JSP, Hoballah JJ, eds. *Springer Surgery Atlas Series: Vascular Surgery*. London: Springer-Verlag; 2009:103–118.)[68]

First, rib resection is readily accomplished through the supraclavicular approach, given the exposure already achieved at this stage of the operation (Fig. 121.9). Using a periosteal elevator, any remaining muscle fibers of the middle scalene muscle are detached from their insertion on the top of the posterior first rib. This dissection is always performed under direct vision, to protect the C8 and T1 nerve roots. Using a fingertip covered with gauze, the pleural membrane is bluntly dissected away from the inferior aspect of the first rib. Intercostal muscle attachments to the first rib are divided using a periosteal elevator, to relieve the posterior and lateral aspects of the first rib of all soft tissue attachments, and any remaining attachments are divided along the anterolateral aspect of the rib up to the scalene tubercle. The brachial plexus nerve roots are displaced anteriorly to expose the posterior neck of the rib. While the nerve roots are protected with a fingertip, a rib cutter is inserted over the neck of the isolated first rib and applied. A Kerrison bone rongeur is used to resect additional amounts of bone as needed to ensure that the end of the rib will not impinge upon the lower nerve roots and to create a smooth surface on the posterior stump of the first rib. The proximal portion of the rib is displaced inferiorly to open the anterior costoclavicular space, and a bone cutter is inserted at a level immediately medial to the scalene tubercle to divide the proximal rib. The first rib

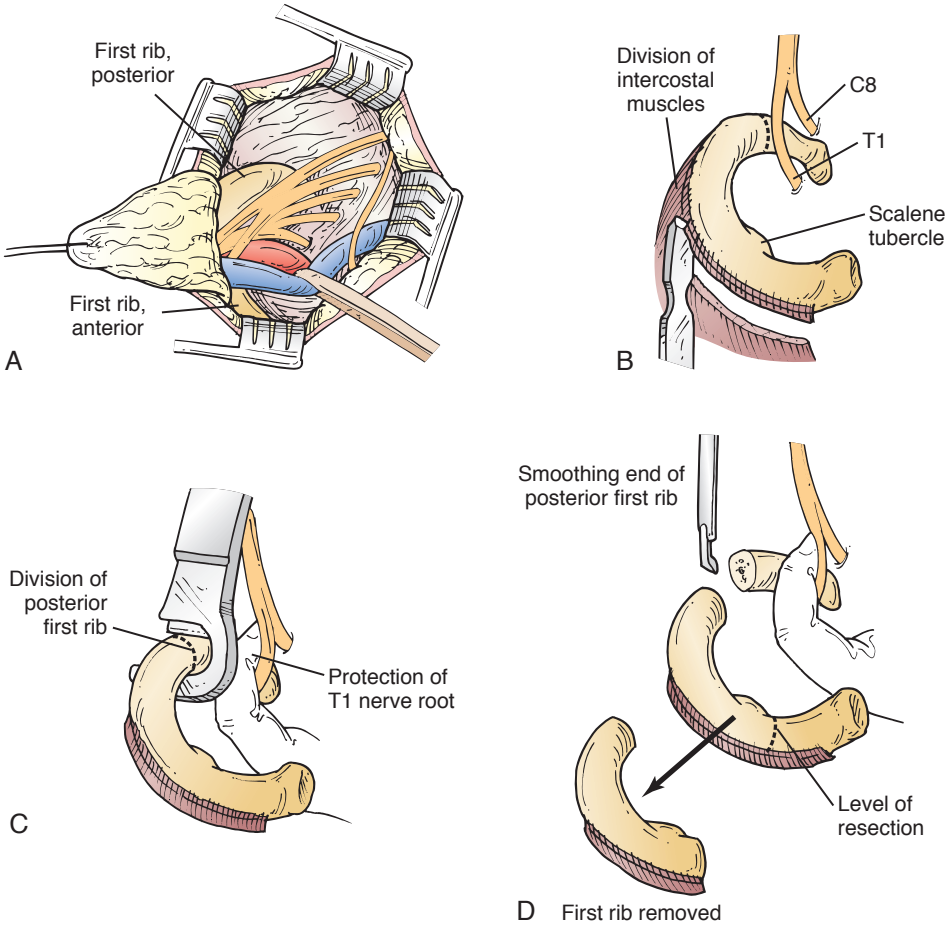

Figure 121.9 Supraclavicular First Rib Resection. (A) The first rib is shown in relation to the brachial plexus roots and the subclavian artery. (B) Intercostal attachments to the first rib are divided. (C) After division of the anterior first rib just proximal to the level of the scalene tubercle, the brachial plexus is reflected anteriorly to visualize the posterior neck of the rib. The T1 nerve root is displaced by a finger while the neck of the rib is divided. The anterior rib is cut and the specimen is removed from the field. (D) The remaining posterior edge of the rib is remodeled to a smooth surface using a Kerrison bone rongeur, ensuring that there is no residual impingement on the T1 nerve root. The anterior edge of the rib is similarly remodeled to a smooth surface (not shown). (Modified from Thompson RW. Treatment of thoracic outlet syndromes and cervical sympathectomy. In: Lumley JSP, Hoballah JJ, eds. *Springer Surgery Atlas Series: Vascular Surgery*. London: Springer-Verlag; 2009:103–118.)[68]

is then extracted from the operative field and discarded, and the proximal end of the rib is remodeled to a smooth surface with a bone rongeur.

Upon completion of the operation, the brachial plexus nerves may be wrapped with an absorbable film to act as a temporary barrier deterrent to the formation of perineural adhesions. A closed-suction drain is placed into the supraclavicular field, and the scalene fat pad is reapproximated over the brachial plexus prior to wound closure.

Pectoralis Minor Tenotomy

When there is evidence on physical examination for brachial plexus nerve root irritation at the level of the subpectoral space ("hyperabduction syndrome"), pectoralis minor tenotomy may be added to either transaxillary or supraclavicular decompression to ensure thorough relief of nerve compression. Pectoralis minor tenotomy may also be performed as an isolated procedure when this site is the dominant location of nerve compression symptoms, or when localizing findings are present in patients who have previously undergone thoracic outlet decompression by other approaches (persistent or recurrent NTOS). As illustrated in Fig. 121.10, a short vertical incision is made in the lateral infraclavicular space adjacent to the deltopectoral groove. The lateral edge of the pectoralis major muscle is gently retracted medially, and the underlying pectoralis minor muscle is encircled. The pectoralis minor tendon is then divided under direct vision, immediately inferior to its insertion on the coracoid process.

Postoperative Management

An upright chest x-ray is performed in the recovery room following all thoracic outlet decompression procedures, in part to detect residual pneumothorax or pleural fluid. Small air or fluid collections are carefully observed with the expectation of spontaneous resolution, although transthoracic aspiration may be necessary for a large or expanding pneumothorax. Postoperative pain medication is provided by intravenous opioids until adequate control can be achieved by oral medications, and we routinely prescribe oral narcotics, muscle relaxants, and nonsteroidal antiinflammatory agents for at least the first 2 to 4 weeks following surgery. The closed suction drain is removed 5 to 7 days after surgery unless there is persistent lymphatic fluid present, in which case the patient is discharged and the drain is removed in the outpatient office once the leak has subsided. In several hundred operations for TOS, we have only rarely had to perform a secondary procedure to control a persistent lymph leak.

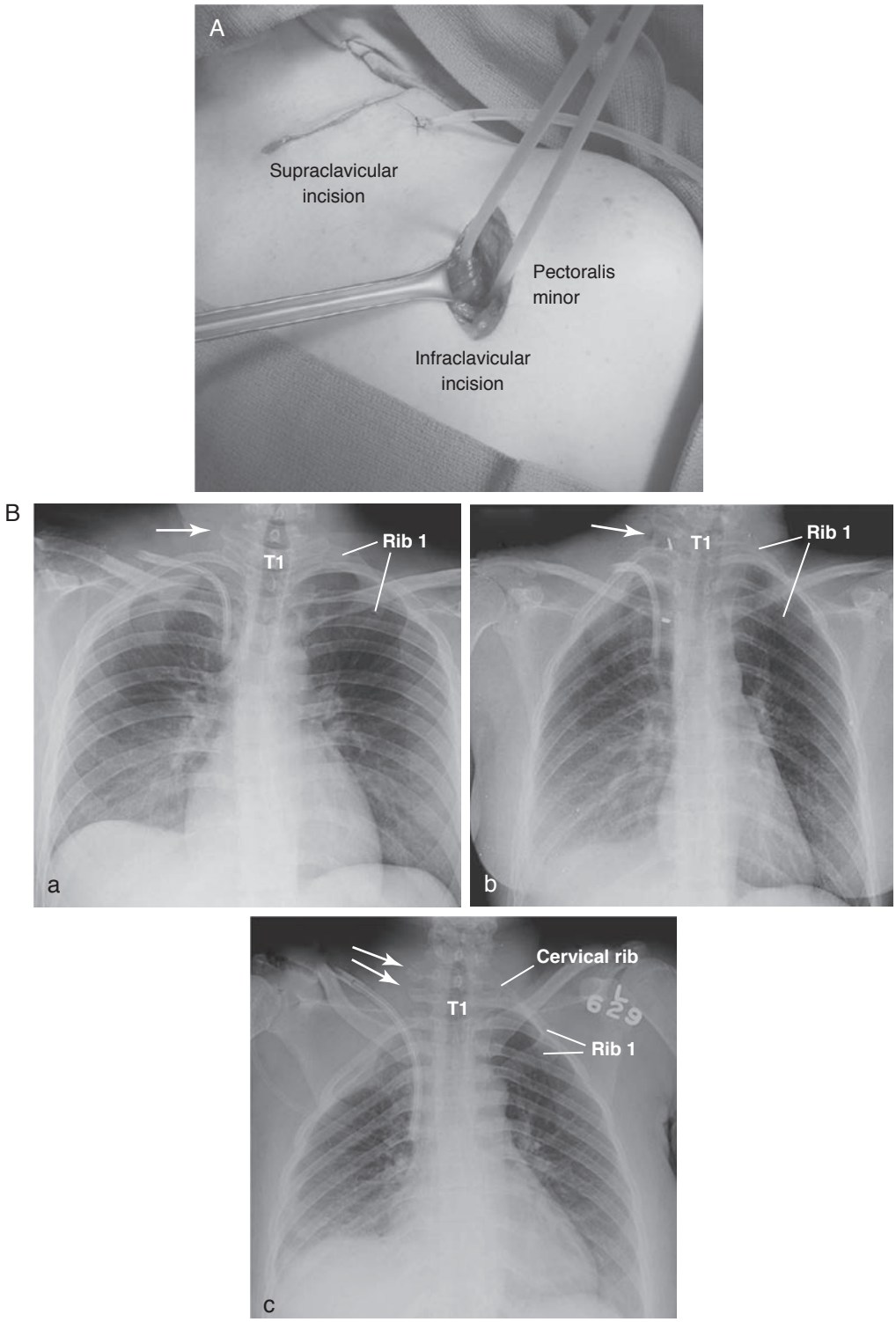

Figure 121.10 Pectoralis minor tenotomy and postoperative chest radiographs. (A) Operative view of left lateral infraclavicular incision used to isolate the pectoralis minor muscle tendon, performed in conjunction with a supraclavicular thoracic outlet decompression procedure. Operative view of left lateral infraclavicular incision used to isolate the pectoralis minor muscle tendon, performed in conjunction with a supraclavicular thoracic outlet decompression procedure. (B) Postoperative chest radiographs. *a*, Chest radiograph after right supraclavicular decompression. The closed-suction drain is seen extending from the neck into the pleural apex, and the posterior end of the resected first rib is indicated *(arrow)*. *b*, Chest radiograph after right supraclavicular decompression with an adjunctive cervical sympathectomy for reflex sympathetic dystrophy. The posterior end of the resected first rib is indicated *(arrow)*, with the extent of sympathetic chain resection demonstrated by the position of radiodense clips at the first and fourth thoracic levels. *c*, Chest radiograph after right supraclavicular decompression with resection of the cervical and first ribs. The posterior ends of the resected cervical and first ribs are indicated *(arrows)*.

There are no strict restrictions with respect to use of the upper extremity after operation, but patients are advised to avoid excessive reaching overhead or heavy lifting. Physical therapy is resumed as soon as feasible, usually upon discharge from the hospital or in the first postoperative week. Patients are cautioned against activities that can result in muscle strain, spasm, and significant pain in the trapezius and other neck muscles, and a gradual return to use of the upper extremity is encouraged. The majority of patients resume fairly regular activity within several weeks after the operation, and in most cases are permitted a cautious return to light-duty work by 4 to 6 weeks. Work restrictions are recommended to prevent heavy activity during the early stages of return to work, particularly to avoid excessive use of the upper extremity by lifting or repetitive activities that may contribute to postoperative complaints. It is important to recognize that patients with longstanding NTOS often display residual symptoms of dysesthesias, numbness, or other complaints that may not be eliminated by thoracic outlet decompression; while these symptoms may be tolerable, the surgeon must provide continuing support and reassurance during the period of recovery and rehabilitation. Physical therapy is continued for as long as necessary to allow the patient to return to an optimal level of function, and patients are seen at least yearly to assess the long-term results of operative intervention.

SURGICAL COMPLICATIONS

Nerve Injuries

The most serious complications associated with thoracic outlet decompression are injuries to the brachial plexus nerve roots. Although infrequent, the rate of nerve injuries reported to occur following transaxillary first rib resection was one of the factors leading many to diminish their enthusiasm for this procedure in the 1980s.[22,40] Although these factors are decreased in procedures done through the supraclavicular route given the improved exposure of the nerve roots, brachial plexus palsies can still occur secondary to retraction. In the absence of direct injury, however, these complications are temporary and will resolve within weeks to several months of the operation.

Temporary phrenic nerve dysfunction after supraclavicular thoracic outlet decompression occurs in approximately 10% of patients, is most often associated with retraction of the nerve necessary to accomplish anterior scalenectomy, and results in temporary diaphragmatic paralysis. Although most patients with phrenic nerve palsy are asymptomatic and only exhibit respiratory difficulty with extremes of exertion, patients with underlying lung disease prior to operation may have more significant symptoms. While these symptoms will typically resolve with recovery of phrenic nerve and diaphragmatic function within weeks to months of operation, in some cases full recovery may take up to 10 months. In patients with bilateral TOS requiring operation on the contralateral side, it is essential to ensure that any degree of phrenic nerve paresis has completely resolved prior to the second operation, since contralateral operation in this setting may result in a patient with complete diaphragmatic paralysis and severe ventilatory incapacity. We therefore routinely perform fluoroscopic visualization of diaphragmatic function to ensure complete return of innervation before planning any form of contralateral operation.

Lymph Leakage

It is not uncommon to observe minor postoperative lymphatic fluid collections in the area of the wound or emanating from the closed-suction drain, at least within the first week of operation. It is notable that this may occur despite ligation of the thoracic duct on the left side, usually due to lymph fluid leakage from small tributaries subjected to higher fluid pressures than normal. In the majority of cases, these lymph leaks will resolve spontaneously with time, usually within several weeks, and it is rare to encounter a patient in whom a secondary procedure is necessary for persistent lymph drainage.

RESULTS OF SURGERY

Outcome Measures

Since functional results depend in large part on the extent of disability existing prior to operation, reported results may vary considerably for patients with differing degrees or duration of disabling symptoms before surgical treatment. Unfortunately, there are no well-defined classification schemes in common use by which to stratify patients undergoing surgical treatment. A second difficulty in assessing the results of surgery remains the absence of well-established outcome measures or reporting standards for thoracic outlet decompression. Most authors describe results as divided into separate categories: (1) excellent, with complete relief of all symptoms; (2) good, with relief of major symptoms but some persistent symptoms; (3) fair, with partial relief but persistence of some major symptoms; and (4) poor, with no improvement. Another variable complicating the interpretation of outcomes for surgical treatment is the type of operation performed. It has been difficult to demonstrate a significant difference in outcome between the different procedures in common use. Further complicating these assessments is the fact that some reports do not distinguish between patients undergoing operations for NTOS versus arterial or venous TOS, making it impossible to separate the results for the treatment of NTOS alone.

It is recognized that the overall success of operations for NTOS can only be considered in the context of long-term outcomes. Most of these operations are performed in relatively young and active individuals, with the aim of improving function for many years. Because the degree of improvement obtained in the first few months after surgery may diminish with time, the durability of successful outcomes becomes another important measure of results. Unfortunately, many reports in the literature do not include follow-up or assessment of results beyond several months to a few years, making it difficult to assess differences that may exist between different operations over longer periods.

Finally, it is uncertain if the results reported by those regularly performing operations for NTOS can be extended to those who only perform thoracic outlet decompression on an occasional

basis, since these are technically demanding operations not often performed by the majority of vascular surgeons.

Operative Results

Anterior Scalenotomy/Scalenectomy

A summary of eight reports published between 1947 and 1987, describing results in a total of 241 patients undergoing anterior scalenotomy, indicates that the overall outcomes for this operation were good in 26% to 89% (mean 58%), fair in 0% to 39% (mean 9%), and poor in 7% to 60% (mean 33%).[47-54]

Anterior scalenectomy was popularized by Adson as a means to avoid potential injury to the brachial plexus in patients with cervical ribs. In six reports of this procedure published up to 1989, encompassing a total of 338 patients, there were good results in 26% to 89% (mean 56%), fair in 0% to 39% (mean 13%), and poor in 7% to 60% (mean 31%).[55-60] At present, neither of these operations are performed frequently for NTOS, in part because the long-term results do not appear as good as those achieved with approaches involving the resection of the first rib.

Transaxillary First Rib Resection

Since its introduction by Roos in 1966, transaxillary first rib resection has been one of the most frequently performed operations for NTOS. By 1989, more than 3000 of these operations were reported in 21 separate publications. The largest of these series included 1315 patients, with a successful outcome in 92% and a failure rate of 8%. As summarized in Table 121.4, the overall rate of good outcomes for transaxillary first rib resection has ranged from 37% to 100% (mean 80%), with fair outcomes in 0% to 14% (mean 6%) and failure of operation in 0% to 41% (mean 15%).

TABLE 121.4 Collected Results for Transaxillary First Rib Resection

First Author	Year	# Operations	Outcomes Reported (%)		
			Good	Fair	Failed
Sanders et al.[69]	1968	69	90	0	10
Roeder et al.[70]	1973	26	92	4	4
Hoofer and Burnett[71]	1973	135	100	0	0
Dale[72]	1975	49	94	0	6
Kremer and Ahlquist[73]	1975	48	86	0	14
McGough et al.[74]	1979	113	80	13	7
Youmans and Smiley[75]	1980	258	75	16	9
Roos[76]	1982	1315	92	0	8
Batt et al.[77]	1983	94	80	0	20
Sallstrom and Gjores[78]	1983	72	81	12	7
Heughan[79]	1984	44	75	0	25
Qvarfordt et al.[42]	1984	97	79	0	21
Narakas et al.[53]	1986	43	77	0	23
Tagaki et al.[54]	1987	48	79	0	21
Davies and Messerschmidt[80]	1988	115	89	0	11
Selke and Kelly[81]	1988	460	79	14	7
Stanton et al.[82]	1988	87	85	4	11
Wood et al.[83]	1988	54	89	9	2
Cikrit et al[60]	1989	30	63	0	37
Lindgren et al.[84]	1989	175	59	0	41
Lepantalo et al.[85]	1989	112	52	25	23
Jamieson and Chinnick[86]	1996	380	53	25	22
Totals		3824	80%	6%	15%

Modified from Sanders RJ. *Thoracic Outlet Syndrome: A Common Sequelae of Neck Injuries.* Philadelphia: J. B. Lippincott Company; 1991.

Supraclavicular First Rib Resection With Anterior and Middle Scalenectomy

Table 121.5 summarizes results of operation from seven different publications including a total of 1222 patients), the largest being the series reported by Hempel et al. (770 operations). Overall, the results for supraclavicular decompression were good in 59% to 91% (mean 77%), fair in 5% to 33% (mean 15%), and poor in 3% to 18% (mean 8%).

Comparison of Surgical Approaches

One of the most comprehensive analyses of results for NTOS has been presented by Sanders, in which the life-table method was used to compare outcomes for different operative procedures,[1,22,61,62] including patients undergoing transaxillary first rib resection (n = 112), anterior and middle scalenectomy (n = 286), or supraclavicular scalenectomy with first rib resection (n = 249); there was no difference in the initial success rate between these three procedures (91%, 93%, and 93%, respectively). As shown in Fig. 121.11, the percentage of patients with successful outcomes also declined over time with all three procedures. Although the long-term success with supraclavicular scalenectomy and first rib resection appeared somewhat better at 10 to 15 years (71%) than the results with either anterior scalenectomy (66%) or transaxillary first rib resection (64%), there was no statistically significant difference between these operations.

Predicting the Outcomes of Surgery

Franklin et al. examined injured workers in the state of Washington that had undergone an operation for NTOS between 1986 and 1991, finding that 60% of those with a work-related injury remained disabled 1 year after surgical treatment.[63] There appeared to be no differences in outcome based on the type of operation performed, the presence of any particular provocative test results, or the experience of the operating surgeon, but significant predictors of ongoing disability included the amount of work disability before surgery, longer time intervals between

TABLE 121.5 Collected Results for Supraclavicular Scalenectomy/First Rib Resection

First Author	Ref	Year	# Operations	Outcomes Reported (%) Good	Fair	Failed
Graham and Lincoln	87	1973	78	91	5	4
Thompson and Hernandez	88	1979	15	87	0	13
Thomas et al.	89	1983	128	83	13	4
Reilly and Stoney	44	1988	39	59	33	8
Loh et al.	59	1989	22	68	23	9
Hempel et al.	3	1996	770	86	13	1
Axelrod et al.	64	2001	170	65	17	18
Totals			1222	77%	15%	8%

Modified from Sanders RJ. *Thoracic Outlet Syndrome: A Common Sequelae of Neck Injuries.* Philadelphia: J. B. Lippincott Company; 1991.

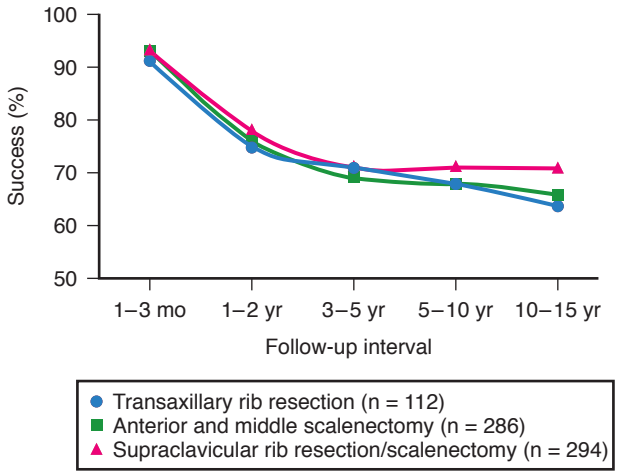

Figure 121.11 Long-Term Results of Three Operations for Neurogenic Thoracic Outlet Syndrome (NTOS). Outcome of 692 patients undergoing a primary operation for NTOS are shown in life-table format extending to follow-up intervals of 10 to 15 years. Data indicate results for patients having transaxillary first rib resection (circular symbols, n = 112), anterior and middle scalenectomy (square symbols, n = 286), or supraclavicular scalenectomy with first rib resection (triangular symbols, n = 249). There was no statistically significant difference between the three operations. (Modified from Sanders RJ. *Thoracic Outlet Syndrome: A Common Sequelae of Neck Injuries.* Philadelphia: J. B. Lippincott Company; 1991.)

injury and a diagnosis of NTOS, and older age at the time of operation. This study has been frequently cited to indicate poor outcomes for surgical treatment of NTOS in the presence of work-related injury and disability claims. However, the scope of its applicability is limited as a database study restricted to injured workers, and the results can be interpreted to suggest that better outcomes might be achieved with more accurate diagnosis of NTOS after work-related injury and earlier application of surgical treatment in this clinical setting. Axelrod et al. also examined potential associations between preexisting psychological factors and socioeconomic characteristics and the long-term outcomes of patients undergoing surgery for NTOS.[64] Supraclavicular thoracic outlet decompression in 170 patients was considered successful in 65%, with 35% remaining on medications and 18% reporting ongoing disability. Multivariate logistic regression models revealed several independent risk factors significantly associated with persistent disability, including major depression, not being married, and having less than a high school education. The authors suggest that further prospective studies are needed to address the potential impact of preoperative treatment for depression in patients undergoing operations for NTOS. In evaluating the potential role of specific anatomic factors in outcomes of surgery, Sanders et al. reviewed their long-term operative results in 54 patients with NTOS associated with a cervical rib or anomalous first rib.[11] While the overall success rate of operation was 72%, the etiology of symptoms was a significant variable in outcome, with failure in 42% of those with symptoms following a work-related injury or repetitive stress, 26% in those with symptoms following an automobile collision, and 18% in those with symptoms of nonspecific etiology. The failure rate was also substantially affected by the operation performed: 75% for those undergoing cervical rib resection without first rib resection in the work-related injury group (and 38% in the non-work-related group), compared with 25% for those undergoing cervical rib resection along with resection of the first rib in the work-related group (and 20% in the non-work-related group). The authors concluded that (1) the presence of a cervical rib or anomalous first rib in patients with NTOS does not improve the success rate from surgery compared with patients without rib abnormalities; (2) neck trauma is the most common cause for NTOS, even in patients with abnormal ribs; (3) cervical and anomalous first ribs are predisposing factors rather than the cause of NTOS; and (4) surgery for NTOS in patients with cervical ribs should include both cervical rib and first rib resection.

In a valuable study of 85 patients with NTOS treated with either surgery or botulinum toxin chemodenervation, Jordan et al. reported no differences between treatment-responsive and treatment-resistant patients with respect to work disability status or compensation claims, anomalous anatomy detected by ultrasonography, or subclavian artery flow alterations detected by duplex sonography.[24] They did observe, however, that treatment-resistant patients had a higher frequency of sensory complaints extending beyond lower trunk dermatomes (42% vs. 10%), weakness extending beyond lower trunk myotomes (19% vs. 2%), a history of previous non-TOS surgery of the neck or upper limbs (50% vs. 17%), and comorbidities of fibromyalgia or CRPS (81% vs. 12%), and depression (35% vs. 10%). Importantly, treatment-resistant patients also responded less frequently to scalene muscle test blocks compared with treatment-responsive patients (38% vs. 100%). This study thereby demonstrates the adverse effect on surgical outcomes associated with certain comorbid conditions and diffuse upper extremity symptoms, and highlights the clinical value of diagnostic scalene muscle blocks in the modern management of NTOS.

Freischlag and colleagues examined a series of 162 patients that had undergone transaxillary first rib resection using the

Short-Form 12 (SF-12), Brief Pain Inventory (BPI), and Cervical-Brachial Symptom Questionnaire (CBSQ) instruments, with a mean follow-up of 44.7 months.[65] They found no significant difference in QOL scores associated with long-term compared with short-term follow-up, but significantly poorer scores on all instruments associated with comorbid chronic pain syndromes, opioid use, and unfavorable clinical assessment. Significantly poorer scores on specific instruments were associated with smoking, age over 40 years, neck and/or shoulder pathology, and postoperative complications, but a positive preoperative scalene block was not significantly associated with long-term QOL scores. It was concluded that while clinical assessment can accurately reflect patient-reported outcomes and gauge postoperative improvement, patient factors are more predictive of long-term QOL than preoperative scalene blocks and should also be considered when selecting patients for surgical intervention.

Caputo et al. used the Disabilities of the Arm, Shoulder and Hand (DASH) survey, the CBSQ, and a 10-point visual analog scale (VAS) for pain, as well as a composite score combining these measures (the NTOS Index, scaled 0-100) to assess outcomes in a series of 189 patients at 3 and 6 month intervals after supraclavicular thoracic outlet decompression for NTOS.[66] Compared with adults (n = 154), adolescent patients (n = 35) had a significantly lower incidence of depression (11.4% vs. 41.6%), motor vehicle injury (5.7% vs. 20.1%), previous operations (11.4% vs. 29.9%), preoperative use of opiate medications (17.1% vs. 44.8%), and preoperative symptom duration greater than 2 years (24.2% vs. 50.0%). The mean preoperative NTOS Index (scale 0-100) was significantly lower in adolescents versus adults (46.5 ± 3.6 vs. 58.5 ± 1.7). Although both groups exhibited significant improvement in functional outcome measures at 3 and 6 months, the adolescent patients had a significantly lower mean NTOS Index (10.4 ± 3.1 vs. 39.3 ± 3.3) and less use of opiate medications (11.4% vs. 47.4%). This study demonstrates that adolescents undergoing supraclavicular decompression for NTOS had more favorable preoperative characteristics and enhanced functional outcomes than adults, and further illustrates the use of quantitative PROMs to help address factors that can improve surgical outcomes for NTOS.

It can be concluded from the studies cited here that certain preexisting clinical features appear to be associated with diminished success for operative treatment of NTOS, particularly work-related injury, longstanding symptoms, major depression, diffuse upper extremity symptoms, and lack of a response to anterior scalene muscle blocks.

Ongoing Symptoms

Persistent Neurogenic Thoracic Outlet Syndrome

Persistent symptoms are those that were not relieved even for a short period of time by the initial operation. In most cases, persistent symptoms are due to another condition, and the diagnosis should be completely reevaluated. If the symptoms cannot be attributed to another condition and they resist conservative management for at least several months, the possibility of persistent NTOS is then considered. If the initial operation was a transaxillary first rib resection, persistent symptoms may occur if there was inadequate relief of compression of the upper nerve roots, since scalenectomy was not performed. In these cases, a reoperative supraclavicular scalenectomy should be considered. Although it is unusual to observe persistent NTOS after supraclavicular scalenectomy, this may be considered if the procedure did not include first rib resection. In such cases it may be reasonable to consider reoperation to remove the first rib, by either the transaxillary or supraclavicular route.

Recurrent Neurogenic Thoracic Outlet Syndrome

The majority of such recurrences occur within the first 2 years of the primary operation. The symptoms are often the same as those present prior to the initial operation, and the diagnosis is made in the same manner as described earlier. If reoperation is considered, the choice of procedure again depends on the type of operation performed initially. If a transaxillary first rib resection was performed, reoperation should be through supraclavicular exposure to include scalenectomy, brachial plexus neurolysis, and resection of any remaining portion of the first rib. Experience with such operations shows that the stump of the anterior scalene muscle has often become attached to the extrapleural fascia or the brachial plexus nerve roots; it is also common to find a segment of the posterior rib still present, since this portion cannot be resected easily through the transaxillary approach. If the initial operation was a supraclavicular scalenectomy, a repeat operation should include first rib resection. Because the cause of recurrent NTOS following supraclavicular scalenectomy and first rib resection is usually the formation of perineural adhesions, reoperation through the supraclavicular route may still be of value since it permits a complete brachial plexus neurolysis to be achieved. Because reoperations are associated with a higher risk of nerve and vascular injury than primary procedures, the decision to reoperate should not be taken lightly, and the procedure should be performed by an individual with considerable experience in these operations.

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This study indicates that excellent outcomes can be obtained for isolated pectoralis minor tenotomy in selected patients with NTOS.

A complete reference list can be found online at www.expertconsult.com.

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122 CHAPTER

Thoracic Outlet Syndrome: Arterial

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Arterial complications from subclavian artery compression represent the least common type of thoracic outlet syndrome (TOS) in adults, but they also represent the strongest indication for operative intervention. Arterial manifestations usually follow a progressive course characterized by extrinsic compression, poststenotic dilation, aneurysmal degeneration, thrombus formation, and secondary embolization. Because arterial TOS is typically associated with anomalous osseous structures, this form of TOS has a more easily definable clinical picture. In fact, arterial TOS was probably the first form to be described as early as 1831.[1] The first reported resection of a bone abnormality causing a subclavian aneurysm was by Coote in 1861.[2] Compression of the subclavian artery and brachial plexus was first termed Naffziger syndrome[3] and evolved to the modern term *thoracic outlet syndrome* after a 1956 publication by Peet and coworkers.[4]

PATHOPHYSIOLOGY

Arterial complications of TOS are associated with bone abnormalities in almost all cases. Cervical ribs that cause subclavian artery damage tend to extend beyond the transverse process with partial or complete fusion to the first rib by a bony pseudarthrosis.[5] This differs from the longer, thinner, and incomplete cervical ribs usually associated with neurogenic TOS. The cervical rib pushes the subclavian artery forward, angulating and compressing it between the first rib and the anterior scalene muscle. This compression causes injury to the inferior wall of the third segment of the subclavian artery, which may lead to localized intimal damage or poststenotic dilation. Less common causes of arterial TOS include anomalous first ribs, fibrocartilaginous bands associated with the anterior scalene muscle, muscular hypertrophy in athletes, and hypertrophic callus from healed clavicle or first rib fractures.[6-8] Poststenotic dilation associated with chronic arterial compression may progress to aneurysmal change, whereas localized intimal damage may lead to embolization or thrombosis. The relative frequencies of anatomic abnormalities are shown in Table 122.1.

EPIDEMIOLOGY

The frequency of arterial TOS in the general population is undefined. The largest single-institution experience of patients

TABLE 122.1 Relative Frequency of Anatomic Abnormalities Causing Arterial Thoracic Outlet Syndrome

Abnormality	Frequency (%)[a]
Cervical rib	60
Anomalous first rib	18
Fibrocartilaginous band	15
Clavicular fracture	6
Enlarged C7 transverse process	1

[a]Percentages represent a compendium of 122 patients from five large series (references 6, 7, 13-15).

treated for all varieties of TOS was reported by Urschel and Kourlis.[9] During 6 decades, the authors performed primary neurovascular decompression on 5102 patients, including 4183 (82%) for neurogenic TOS, 625 (12%) for venous TOS, and 294 (6%) for arterial TOS. In another series of 594 consecutive first rib resections performed at Johns Hopkins Medical Institutions, Orlando et al.[10] reported that 308 (52%) were performed for neurogenic TOS, 261 (44%) for venous TOS, and 25 (4%) for arterial TOS. In contrast, arterial TOS is a relatively more common form in children and adolescents, accounting for 20% to 38% of cases.[11,12]

Most patients presenting with symptoms of arterial TOS are young, active adults. The mean age in published series ranges from 32 to 37 years, with a similar proportion of men and women reported.[7,10,13-15] No familial predisposition has been described. The condition appears to be related to bone abnormalities or trauma in nearly every circumstance. Orlando et al. reported arterial TOS is significantly more likely to be associated with a cervical rib than either venous TOS or neurogenic TOS: in their series, 60% of arterial TOS patients had a cervical rib versus 2.3% of venous TOS and 9.4% of neurogenic TOS.[10] Cormier[13] has reported that only 5 (11%) of 55 patients with arterial TOS had fibrous bands without any definable osseous abnormality.

CLINICAL PRESENTATION

Patients with arterial TOS have a characteristic history and physical examination, but diagnosis requires confirmation with objective testing.

Signs and Symptoms

The most common presentation is hand ischemia due to microembolization. However, arterial TOS can be associated with less dramatic symptoms, and many cases go unrecognized because the condition tends to occur in young patients without atherosclerotic risk factors. Early in the disease process, patients may present with mild symptoms of exertional arm pain or unilateral Raynaud syndrome. Moderate to severe exertional pain may be associated with subclavian artery thrombosis. On occasion, a subclavian artery aneurysm may be palpable in an asymptomatic patient. Although rare, cerebrovascular accidents from retrograde propagation of subclavian thrombus have been reported.[16-20]

Clinical Assessment

Clues to the diagnosis of arterial TOS include the young age of the patient and the tendency for symptoms to be unilateral, which helps differentiate the condition from systemic pathologic states. The directed physical examination should consist of measuring blood pressure in both upper extremities and auscultating for bruits in the supraclavicular fossa. A bruit may be elicited on shoulder abduction or the overhead arm position if it is not present in the relaxed position. Specific findings on physical examination include a palpable cervical rib and a pulsatile supraclavicular mass. Evidence of microembolization to the hand, including digital ischemia and splinter hemorrhages, may also be present.

DIAGNOSTIC EVALUATION

Arterial TOS is a clinical diagnosis made by combining important elements from the history and physical examination. The following adjuncts may help support the diagnosis or suggest an alternative cause of the patient's symptoms.

Compression Maneuvers

Compression maneuvers such as the Adson test, costoclavicular maneuver (exaggerated military position), and hyperabduction maneuver (shoulder abduction beyond 90 degrees) have historically been used to aid in the diagnosis of TOS, but none is accurate. Ablation or reduction of the radial pulse with these maneuvers is considered a positive test result, but the incidence of false-positives in normal, healthy volunteers ranges from 9% to 57%.[21-24] Another compression maneuver is the abduction–external rotation test, also referred to as the elevated arm stress test popularized by Roos et al.[25] Development of hand pain or paresthesias within 60 seconds is considered a positive test result. This test is used in the diagnosis of neurogenic TOS but is not helpful in arterial TOS (see Chapter 121).[26]

Noninvasive Vascular Laboratory Studies

Duplex Ultrasonography

Duplex ultrasound examination of the subclavian and axillary arteries may demonstrate aneurysmal change or elevated flow velocities correlating with a compressive stenosis. The clavicle may interfere with complete ultrasound imaging of the subclavian artery, but significant ulcerations and intimal disruption may be visible. Compression maneuvers have been recommended during sonographic evaluation, with decreased subclavian artery diameter or changes in peak systolic velocity thought to be diagnostic of arterial TOS. One study evaluating multiple compression maneuvers and imaging locations found that arm abduction to 130 degrees while imaging in the costoclavicular space was the most discriminating technique.[27] However, as

with the pulse-monitored compression maneuvers described before, there are a high number of false-positives in normal, healthy volunteers. Studies have shown that compression maneuvers are associated with complete occlusion or significant stenosis of the subclavian artery in approximately 20% of normal subjects.[28,29] Therefore an abnormality detected on ultrasound during compression maneuvers should be used only to confirm a suspected diagnosis of arterial TOS.

Pulse Volume or Segmental Pressure Recording

Pulse volume or Doppler segmental pressure recordings taken at multiple levels in the upper extremities can help localize the level of arterial obstruction if embolization has occurred from arterial TOS. Diminished digital waveforms in the affected extremity coupled with normal findings in the contralateral extremity indicate arterial insufficiency consistent with stenosis or distal embolism.

Radiographic Studies

Radiography

The American College of Radiology recommends chest radiography as the initial imaging modality in patients suspected of having TOS, given that it is easy to perform, noninvasive, and a low-cost test that can assess for several potential abnormalities.[30] Chest radiographs including cervical spine views will often demonstrate the offending bone abnormality. Cervical ribs, elongated transverse cervical processes, and large clavicle fracture calluses are easily seen (Fig. 122.1). Soft tissue abnormalities such as Pancoast tumors can also be detected, but anomalous first ribs and fibrocartilaginous bands are not likely to be detected on plain radiographs.

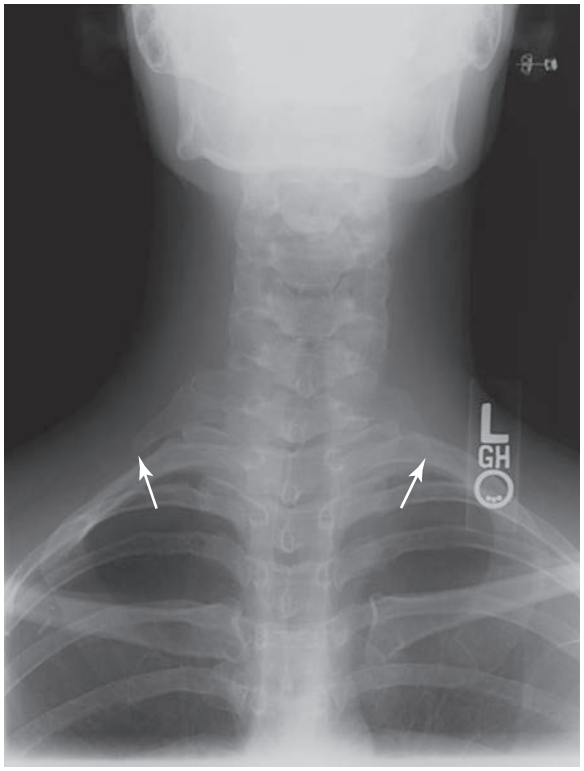

Figure 122.1 Chest radiograph demonstrating bilateral cervical ribs *(arrows)* in a patient with arterial thoracic outlet syndrome.

Computed Tomography

Computed tomographic angiography (CTA) with the intravenous administration of a contrast agent is a useful test to secure the diagnosis and to aid in surgical planning. CTA is typically performed in two views: one with the affected arm adducted, and the other with the arm abducted at 170 degrees or greater. CTA may identify the exact point of compression and the extent of arterial disease that requires treatment. According to American College of Radiology standards, an increase in arterial narrowing of 30% or more between the two views is considered significant.[30] With the ability to manipulate these images in three dimensions, there is usually no need for catheter-based arteriography (Fig. 122.2). In fact, CTA has replaced catheter-based angiography as the main radiographic test for diagnosis of arterial TOS at most centers. CTA can also be used to evaluate the distal arterial circulation, but catheter-based angiography may still be necessary to visualize the small arteries of the distal arm and hand. Because compression of the neurovascular structures in the thoracic outlet is common in normal, healthy subjects,[31] dynamic compression maneuvers should be used only to confirm the diagnosis in patients with suspected arterial TOS. In patients with arterial TOS, CTA findings show a strong correlation to both operative findings and success of operative decompression, in contrast to findings venous TOS, which are less predictive (see Chapter 123).[30]

Magnetic Resonance Angiography

Although magnetic resonance angiography (MRA) may be an acceptable substitute for CTA or catheter angiography in some centers, the sensitivity of MRA for diagnosis of arterial TOS appears to be low. Two reports of MRA in patients with arterial

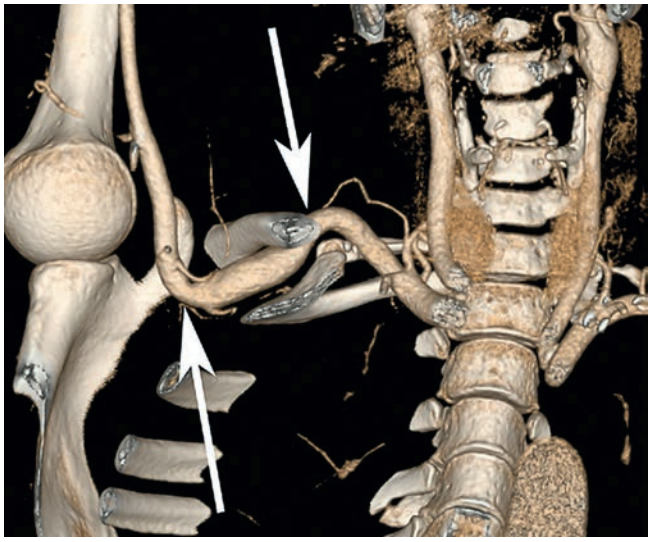

Figure 122.2 Three-dimensional reconstruction of a computed tomography angiogram showing compression of the right subclavian artery with poststenotic dilatation *(arrows)*. (From White P, Fox CJ, Feuerstein IM. Cervical rib causing arterial thoracic outlet syndrome. *J Am Coll Surg.* 2009; 209:148-149.)

symptoms had 37% and 42% incidence of false-negative findings, respectively.[27,32] Therefore a normal finding on MRA should not be used to rule out the diagnosis of a clinically suspected arterial TOS. To improve vascular imaging, a protocol of contrast-enhanced three-dimensional MRA with provocative arm positioning has been recommended.[33] However, further experience with the technique is needed before it can be recommended as more than a complementary test to diagnose arterial TOS.

Catheter-Based Angiography

Upper extremity arteriography was considered the "gold standard" for evaluation of arterial TOS. Compared to CTA, arteriography is less reliable in demonstrating impinging structures and other anatomic abnormalities. However, arteriography can localize the exact point of arterial compression, provide an assessment of the nature and extent of arterial damage, and permit evaluation of the distal circulation (Fig. 122.3). As noted before, CTA for operative planning is gradually replacing catheter-based arteriography. However, arteriography with magnified views remains the best method for demonstrating embolic occlusion of the small arteries of the hand and fingers (Fig. 122.4).

Laboratory Testing

There are no specific laboratory tests that are necessary to diagnose arterial TOS. However, specific laboratory assays are important to exclude systemic causes of upper extremity ischemia, such as vasculitis and connective tissue disorders (see Chapters 137 and 140).

DIFFERENTIAL DIAGNOSIS

Although arterial TOS has a characteristic presentation, other causes of upper extremity ischemia may be suspected from the history and physical examination (Box 122.1). A history of cardiac disease, particularly mitral valve stenosis or atrial fibrillation, supports a cardioembolic etiology. A family history of venous thromboembolic disease suggests an underlying hypercoagulable state, and further tests to exclude paradoxical embolus may be warranted. Risk factors for atherosclerosis, particularly heavy tobacco use, raise the possibility of atherosclerotic occlusive disease as the underlying etiology. Associated symptoms of polymyalgia rheumatica suggest the possibility of vasculitis, whereas symptoms of arthritis, dermatitis, and esophageal dysmotility warrant evaluation for connective tissue disease. Other possible causes include dissection, radiation injury, and trauma, all of which can be suspected from the history and evaluated with imaging studies discussed before.

Screening

There is no role for screening of asymptomatic patients to diagnose arterial TOS. As noted before, dynamic compression maneuvers are associated with a significant rate of false-positive results in asymptomatic patients; therefore, positive test results

BOX 122.1 Differential Diagnosis of Arterial Thoracic Outlet Syndrome

Embolization from other sources
Cardiac
Aortic arch
Hypothenar hammer syndrome
Acquired or congenital coagulopathies
Vasculitis
Takayasu arteritis
Giant cell arteritis
Radiation arteritis
Connective tissue disorders
Marfan syndrome
Ehlers-Danlos type IV
Pseudoxanthoma elasticum
Arterial dissection
Atherosclerotic upper extremity disease
Thromboangiitis obliterans
Traumatic
Humeral head compression of axillary artery
Circumflex humeral artery pseudoaneurysm (baseball pitchers)

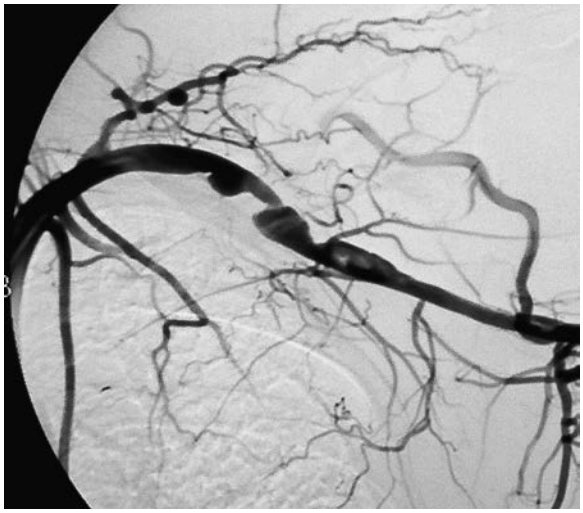

Figure 122.3 Left subclavian arteriogram demonstrating subclavian aneurysm with thrombus.

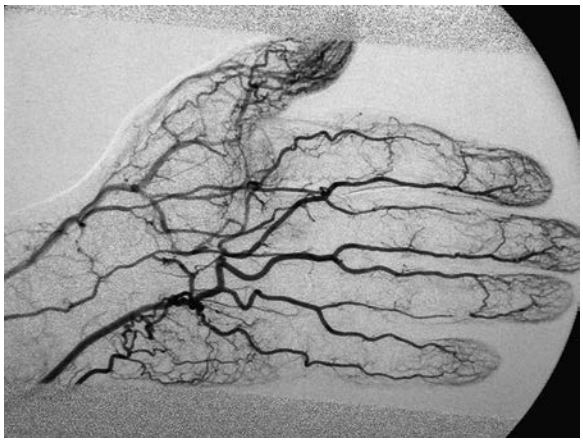

Figure 122.4 Hand arteriogram demonstrating distal embolization in the first, second, and third digits.

should be viewed with caution. On the other hand, it is reasonable to evaluate the opposite side in a patient with symptomatic arterial TOS. The incidence of bilateral arterial TOS is not known. Among patients with cervical ribs, the prevalence of bilaterality has been reported to be 40% (Viertal). The reported frequency of bilateral TOS of all types is reported to be 9% to 26%.[10,34-36] Treatment may be indicated for evidence of arterial dilatation or severe intimal degeneration, even in asymptomatic individuals.

TREATMENT

Medical Treatment

Contrary to neurogenic TOS, there is no role for conservative treatment of symptomatic patients with arterial TOS. On the other hand, conservative treatment may be appropriate for some asymptomatic patients. Although the natural history is not well known, simple compression without evidence of arterial degeneration does not appear to carry a significant risk of complications in the asymptomatic patient. Therefore watchful waiting with use of serial noninvasive tests, such as duplex ultrasonography, may be a reasonable approach. In addition, every attempt should be made to reduce compression forces in the thoracic outlet. This is especially true for high-performance athletes engaged in repetitive overhead arm motion, such as professional baseball pitchers and tennis players. Aggressive physical therapy and modification of arm motion have been recommended in these cases.[37]

The natural history of arterial abnormalities in asymptomatic patients with arterial TOS is not completely understood. However, some patients present with profound hand ischemia as the first manifestation of arterial TOS. Therefore it seems reasonable to treat patients with subclavian artery compression and documented arterial disease, such as arterial dilatation or severe intimal disruption, before symptoms ensue, especially in young, active individuals. The role of anticoagulation in these circumstances is not known.

Surgical Treatment Principles

The three main components of treatment include relieving the arterial compression, removing the source of embolus, and restoring the distal circulation. At a minimum, relieving the arterial compression involves resection of cervical ribs and any other identified anomalies causing impingement in the thoracic outlet. As discussed later, most authors also recommend routine division of the anterior scalene muscle and resection of the first rib to avoid recurrence. Removal of the source of embolus involves resection of a subclavian aneurysm or repair of an arterial stenosis with intimal damage. The success of arterial reconstruction is usually related to the status of the arterial outflow in the limb. Restoration of the distal circulation may involve any combination of thrombolysis, thromboembolectomy, or bypass.

The decision to repair an artery after thoracic outlet decompression should be individualized. Resolution of poststenotic dilation after decompression of the thoracic outlet has been described,[6,38,39] but it is not certain that all lesions will heal spontaneously. Likewise, it is not known whether associated intimal damage will resolve after decompression. At some point, poststenotic dilation progresses to the point of being considered an aneurysm. Symptomatic patients with subclavian artery aneurysms tend to have recurrent thromboembolic complications that may lead to digit or limb loss. Because of the numerous collaterals around the shoulder, the natural history of a subclavian artery thrombosis is uncertain. However, arterial repair may be indicated in asymptomatic patients with subclavian artery thrombosis due to the reported risk of retrograde propagation with resultant stroke.[16-20] Further, most patients will have significant arm fatigue with exercise.

Treatment Selection

The appropriate treatment is dictated by the degree of arterial damage and the status of the distal circulation. Some definitions are important to consider here, as they differ from other anatomic sites. Aneurysm of the subclavian artery associated with TOS is defined as an increase in diameter of more than two times the diameter of the adjacent artery.[38,40] Poststenotic dilation associated with TOS is then defined as an increase in diameter of less than twice that of the adjacent artery.

Scher Classification

The Scher classification system for arterial TOS provides a guide to appropriate treatment and is summarized in Table 122.2.[40] Stage I describes compression of the subclavian artery with minor poststenotic dilatation and no intimal disruption.

TABLE 122.2 Scher Staging Classification of Arterial Thoracic Outlet Syndrome Complications

Stage	Arterial Complication	Treatment
Stage 0	Asymptomatic subclavian artery compression	No treatment indicated
Stage I	Stenosis of subclavian artery with minor poststenotic dilatation; no intimal disruption	Decompression of the thoracic outlet
Stage II	Subclavian artery aneurysm with intimal damage and mural thrombus	Decompression of the thoracic outlet Subclavian artery reconstruction
Stage III	Distal embolization from subclavian artery disease	Thrombolysis or thromboembolectomy Decompression of the thoracic outlet Vascular reconstruction

Modified from Matsumura JS, Rilling WS, Pearce WH, et al. Helical computed tomography of the normal thoracic outlet. *J Vasc Surg.* 1997; 26:776-783.

Appropriate treatment consists of decompression of the thoracic outlet including cervical or first rib resection, division of the anterior scalene muscle, and resection of any anomalous fibrous bands. Regression of poststenotic dilation after TOS decompression has been reported.[6,38,40] Scher stage II includes subclavian arteries with intimal damage, aneurysmal change, and mural thrombus. Appropriate treatment includes decompression of the thoracic outlet and subclavian artery reconstruction. Scher stage III includes those patients presenting with distal embolization. Treatment should include a combination of thrombolysis or thromboembolectomy, thoracic outlet decompression, and vascular reconstruction.

Surgical Treatment

Surgical treatment is indicated for all symptomatic patients with ischemia and for asymptomatic patients with aneurysmal degeneration or intimal damage. Asymptomatic individuals with compression of the subclavian artery at the thoracic outlet do not require surgical intervention, but they should be monitored because their natural history is unknown. There are no specific contraindications to repair of arterial TOS; however, a few patients may be unfit for open surgery because of severe uncorrectable comorbidities.

Relevant Anatomy

The most common offending osseous abnormality in arterial TOS is a cervical rib, accounting for about three fifths of cases (see Table 122.1). Multiple other abnormalities may be encountered, including abnormal first ribs, fracture calluses, fibromuscular bands, and soft tissue defects.[5-7] Fig. 122.5 demonstrates several of these abnormalities.

Operative Planning and Strategy

The first principle of treatment is decompression of the thoracic outlet. This may involve resection of a cervical rib, resection of fibrous bands, or anterior scalenectomy, but most experts agree that the first rib should usually be resected in addition to other associated disease.[13,14,36] The first rib is a fixed structure that maintains tension in the thoracic outlet, and once it is released, the neurovascular bundle is allowed to relax and fall inferiorly. More important, it represents a common insertion for fibromuscular structures that cause vascular compression but are not recognized at the time of operation.

There are two main approaches to thoracic outlet decompression: supraclavicular and transaxillary. Each has some advantage (see Chapter 124). Proponents of the transaxillary approach describe a more complete visualization of the first rib for resection. However, this approach is generally not suitable for vascular reconstruction and is therefore more commonly used to treat neurogenic TOS.[41] The supraclavicular approach facilitates removal of cervical ribs. This exposure allows identification of the cause of compression, visualization of brachial plexus trunks and scalene muscles, resection of the first rib, and subsequent vascular reconstruction. For this reason, we favor a supraclavicular exposure whenever an arterial reconstruction is necessary. A

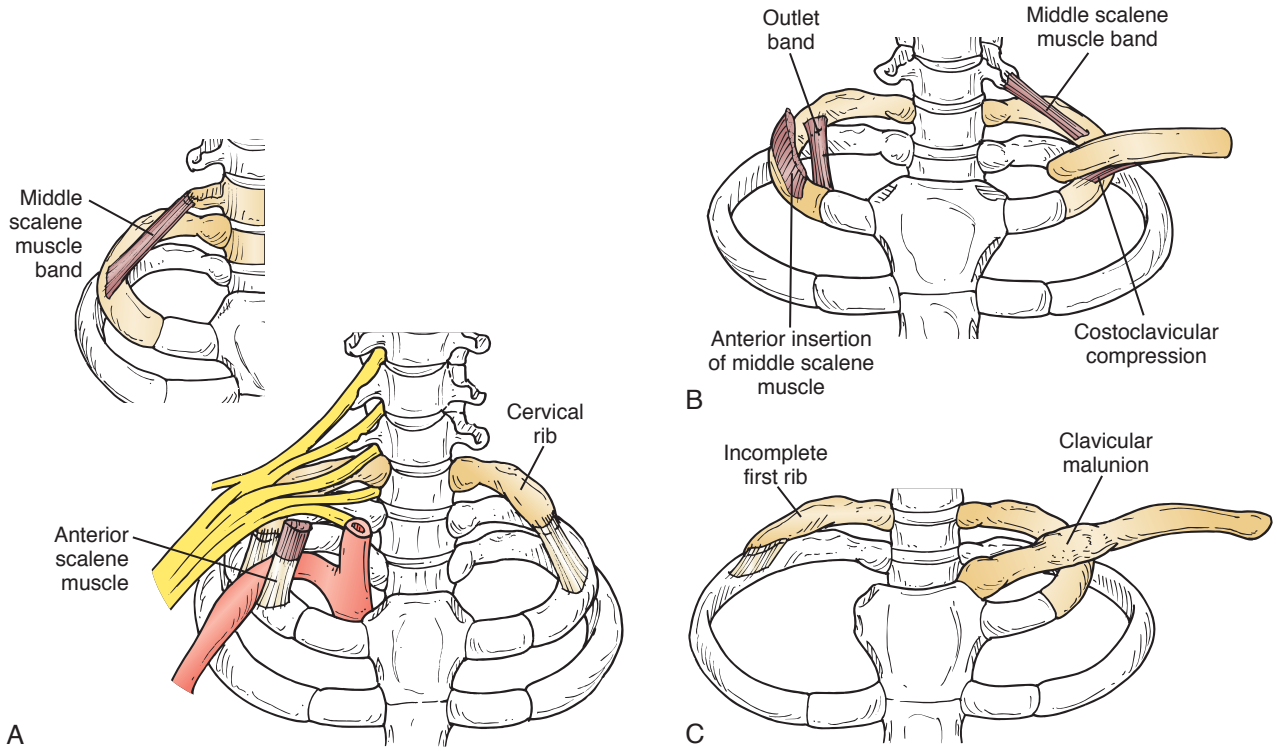

Figure 122.5 Pathologic Conditions Commonly Associated With Arterial Thoracic Outlet Syndrome. (A) Cervical ribs with associated fibrous bands and middle scalene muscle band. (B) Fascial bands and anomalous muscle insertions. (C) Incomplete first rib and clavicular fracture callus. (From Wind GG, Valentine RJ. *Anatomic Exposures in Vascular Surgery.* 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2013.)

large subclavian aneurysm or intimal damage that extends beneath the clavicle may require infraclavicular exposure in addition to the supraclavicular incision. This allows complete exposure of the subclavian and axillary arteries for vascular reconstruction. A single incision that affords both supraclavicular and infraclavicular exposure has been described.[42] Rarely, the subclavian artery has a focal abnormality that can be repaired with simple resection and primary anastomosis. More commonly, a conduit is required for replacement of the subclavian artery. Although some consider the great saphenous vein to be the conduit of choice, reconstruction can be accomplished with femoral vein, ringed polytetrafluoroethylene, or Dacron. Ringed polytetrafluoroethylene or femoral vein may offer some advantage in longer bypasses because these grafts resist kinking as they traverse under the clavicle. The femoral vein conduit also appears to offer superior patency.[43]

Description of Technique

The details of the supraclavicular exposure are presented in Chapter 124 and elsewhere.[44,45] However, a few technical points are worth additional emphasis. After the scalene fat pad is elevated, the phrenic nerve is mobilized off the surface of the anterior scalene before the muscle is divided (Fig. 122.6A). The subclavian artery is situated immediately behind the anterior

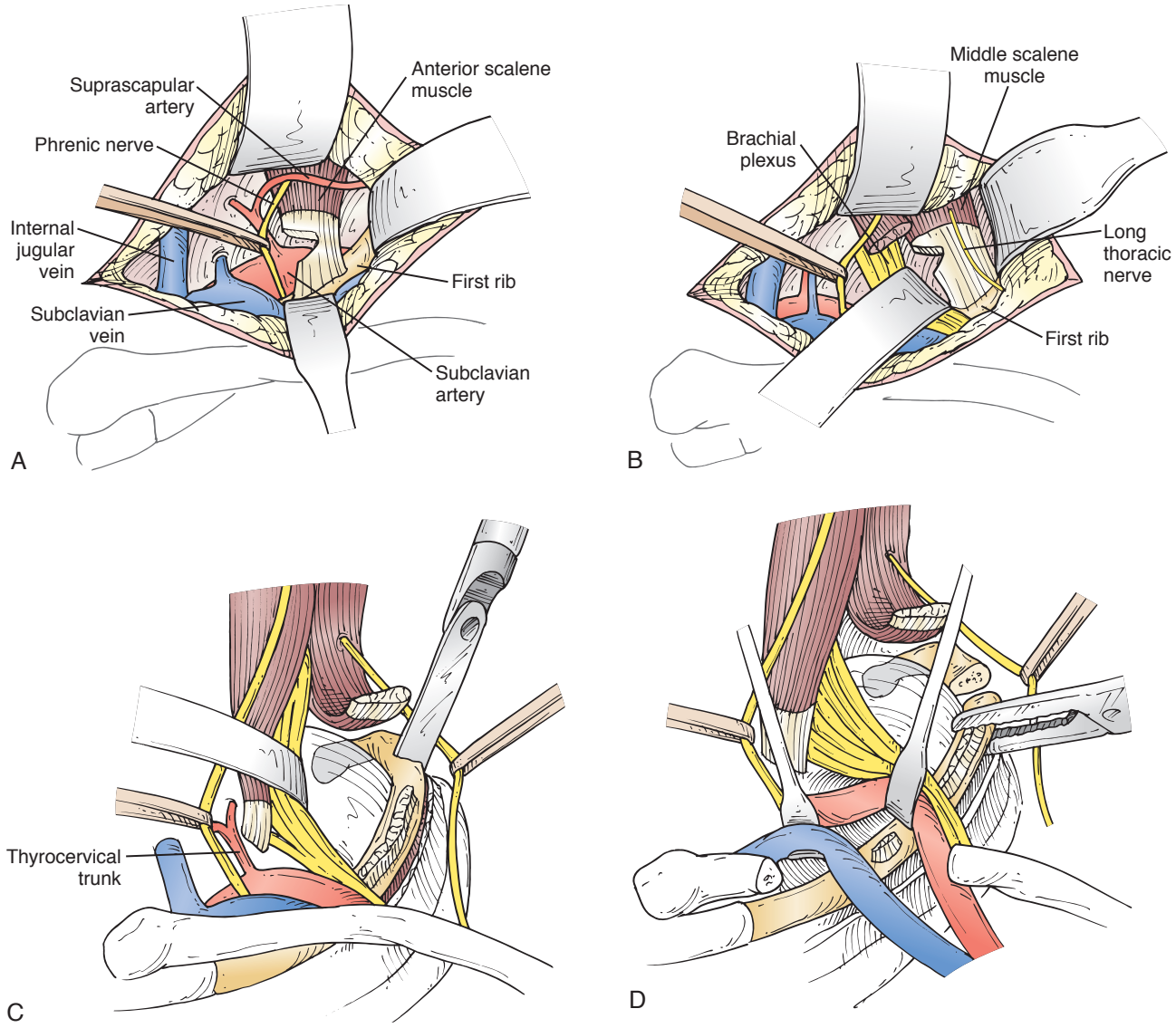

Figure 122.6 (A) Operative view of the supraclavicular approach to thoracic outlet decompression. After mobilization of the scalene fat pad, the phrenic nerve should be identified and carefully elevated before the anterior scalene muscle is divided. (B) The long thoracic nerve should be identified and protected during division of the middle scalene muscle. (C) Attachments are freed by an extraperiosteal approach to prevent recurrent symptoms from reossification of the periosteal bed. (D) Division of the first rib should be performed under direct vision to minimize the possibility of damage to the brachial plexus. After the first rib is divided just distal to the tubercle, the divided rib can be held as a lever to aid in clearing the overlying vessels. (From Wind GG, Valentine RJ. *Anatomic Exposures in Vascular Surgery.* 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2013.)

scalene muscle. The middle scalene muscle is then divided off the first rib, with care taken to avoid the long thoracic nerve that is located on the posterior aspect of the middle scalene (see Fig. 122.6B). Intercostal muscles are freed from medial and lateral edges of the first rib with a periosteal elevator, and the first rib is divided just distal to the tubercle (see Fig. 122.6C). The divided rib can then be used as a lever to assist with mobilization before it is divided anteriorly (see Fig. 122.6D).

Endovascular Options

Although the open surgical reconstruction is the standard approach to arterial complications of TOS, there have been scattered reports of endovascular repair of minor subclavian artery stenosis combined with surgical decompression of the thoracic outlet.[46,47] The importance of adjunctive decompression cannot be overemphasized because failure to decompress the thoracic outlet can lead to stent fracture or collapse, restenosis, and thrombosis.[48] However, at least one report has raised concern for stent fracture after decompression, casting doubt on the long-term outcome of endovascular therapy in these patients.[49] Longer term outcomes data are needed to determine the validity of this approach.

Distal Revascularization

Patients with Scher stage III present with upper extremity ischemia due to distal embolization. Any degree of motor deficit or a significant sensory deficit should be considered an indication for immediate operation including embolectomy. Brachial artery embolectomy does not always require a separate distal arm incision, as large emboli can be extracted through the subclavian artery in some cases. Although embolectomy is usually sufficient, distal bypasses are sometimes necessary in patients with chronic embolization. Patients who present with milder ischemia may be appropriate for thrombolysis before surgical repair.[50] This may be particularly important in patients who have complete thrombosis of the forearm and hand vessels on arteriography. Sympathectomy does not have a significant role in management of these patients.

Postoperative Management

In addition to supportive care, patients may benefit from physical therapy and range of motion exercises to shorten convalescence. Arterial repairs should be monitored with serial physical examinations and noninvasive studies such as duplex ultrasound. Examination intervals vary from institution to institution, but the Oregon group has recommended examinations at 3 months postoperatively and every 6 months thereafter.[15]

Definition of Success and Determinants of Outcome

Successful outcome after treatment of arterial TOS is determined by relief of symptoms, avoidance of recurrence, patency of arterial bypasses, and limb salvage. Published series report complete relief of symptoms in more than 90% of patients.[6,13,15] Gelabert and Machleder[51] have identified the following reasons for failed procedures: inaccurate diagnosis, failure to identify and correct the proximal embolizing lesion, and inadequate decompression. Unlike neurogenic TOS, recurrence of arterial TOS is very rare in patients who have undergone complete TOS decompression and adequate arterial reconstruction. Bypass patency is reported in the range of 90% to 100%, depending on the status of the outflow vessels.[6,13,50] Limb salvage should approach 100% in Scher stage I and stage II lesions; distal embolization may result in finger amputation in patients with Scher stage III lesions, but arm amputation is distinctly uncommon.[8,22,51]

Results

Long-term results are related to the status of the distal vasculature. For Scher stage I lesions, decompression of the thoracic outlet alone is sufficient, with excellent results and the expectation that poststenotic dilation will regress within a year.[6] Limbs with compromised outflow secondary to embolization have a poorer prognosis. One of the largest series examined 55 cases of arterial TOS.[13] The early results showed no mortalities and low rate of morbidity (7%). The long-term results (mean follow-up of 5 years, 8 months) of thoracic outlet decompression and vascular reconstruction were excellent, with 91% remaining asymptomatic and 9% experiencing exertional symptoms only. Of the four cases that were symptomatic at late follow-up, three originally presented with distal ischemia and required thromboembolectomy for brachial artery occlusions. There were no amputations in this series. In their series of 24 patients with arterial TOS, Orlando and colleagues[10] reported 100% positive results after 1 year of follow-up.

Complications

Operative mortality is negligible in these typically young patients. Morbidity is related to the closely related anatomic structures in the thoracic outlet and includes pneumothorax, hemothorax, chylous leak, brachial plexopathy, and vascular injury. Injury to the phrenic or long thoracic nerves is also possible. Rarely, injury of the cervical sympathetic chain may result in Horner syndrome. The overall morbidity rate in published series ranges from 7% to 40%,[6,15,52] with pleural entry and transient brachial plexus injury being most frequent.

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CHAPTER 123

Thoracic Outlet Syndrome: Venous

MISTY D. HUMPHRIES and JULIE A. FREISCHLAG

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Venous thoracic outlet syndrome (vTOS) is thrombosis or severe stenosis of the subclavian-axillary vein secondary to chronic extrinsic mechanical compression. The eponym Paget–von Schroetter syndrome was coined by Hughes in 1949 after a comprehensive review of the world's literature related to thrombosis of the subclavian and axillary veins.[1] Paget described the original disease process in 1875 as a syndrome of acute arm swelling and pain. He hypothesized the disease was due to vasospasm.[2] In 1884, however, von Schroetter described the symptoms of acute upper extremity pain and swelling as a result of subclavian and axillary vein thrombosis.[3] A final name for vTOS is *effort thrombosis*, which describes the association with young healthy individuals who engage in activities requiring repetitive arm and shoulder motion.[4-7]

EPIDEMIOLOGY AND ETIOLOGY

Primary Subclavian-Axillary Vein Thrombosis

Upper extremity deep venous thrombosis (DVT) represents approximately 9% of reported episodes of DVT.[8] Subclavian-axillary vein thrombosis in vTOS is a direct result of repetitive injury to the subclavian vein at the level of the costoclavicular space, the most anterior and medial aspect of the thoracic outlet (Fig. 123.1). The key anatomic structures resulting in compression of the subclavian vein are the first rib, the clavicle with its associated subclavius muscle and fibrous costocoracoid ligament, and the anterior scalene muscle/tubercle.[1,6] A cycle of alternating posttraumatic inflammation and quiescence leads to perivenous fibrosis, endothelial injury, stasis of blood flow, and thrombosis.[9]

Although vTOS has been reported to occur in the absence of any identifiable anatomic abnormality,[9,10] a diverse array of anomalies associated with the thoracic outlet has been reported at the time of surgery. These include abnormalities of the anterior scalene muscle and subclavius tendon, the presence of a scalenus minimus muscles, bone abnormalities of the clavicle and ribs, and ligamentous abnormalities of the costocoracoid ligament.[6,9-13] Frequently compression of the subclavian vein occurs at the costoclavicular space without the development of thrombosis. This point is underscored by venographic studies evaluating the contralateral subclavian vein in patients with confirmed subclavian-axillary vein thrombosis. Although narrowing of the contralateral vein with provocative measures is visualized in 56% to 80% of contralateral limbs, the incidence of bilateral thrombosis is markedly less, at 2% to 15%.[5,14-16]

McCleery Syndrome

Described in 1951 by McCleery and colleagues, this syndrome represents intermittent obstruction of the subclavian vein without thrombosis.[17] The pathology results from compression of the vein between the subclavius tendon and the anterior scalene muscle that is worsened with arm abduction (Fig. 123.2). This syndrome manifests with blue discoloration of the arm, superficial vein distention, and swelling. Despite the lack of venous thrombosis, these patients are usually limited in use of the affected extremity and should be treated with surgical decompression.

Abstract

Venous thoracic outlet syndrome is the thrombosis or severe stenosis of the subclavian-axillary vein. It may be caused primarily by chronic repetitive motion or secondary to trauma, indwelling catheters, pacemaker wires, or tumors. Treatment of vTOS is based on understanding the etiology and the functional goals of the patient. Controversies exist as to whether patients need to undergo surgical decompression, if pre-operative thrombolysis provides benefit, and how to manage venous stenosis after decompression. Here we present the most up to date data on management of patients with primary and secondary vTOS.

keywords

Thoracic Outlet Syndrome
Subclavian Thrombosis
Effort Thrombosis
Upper Extremity Thrombosis

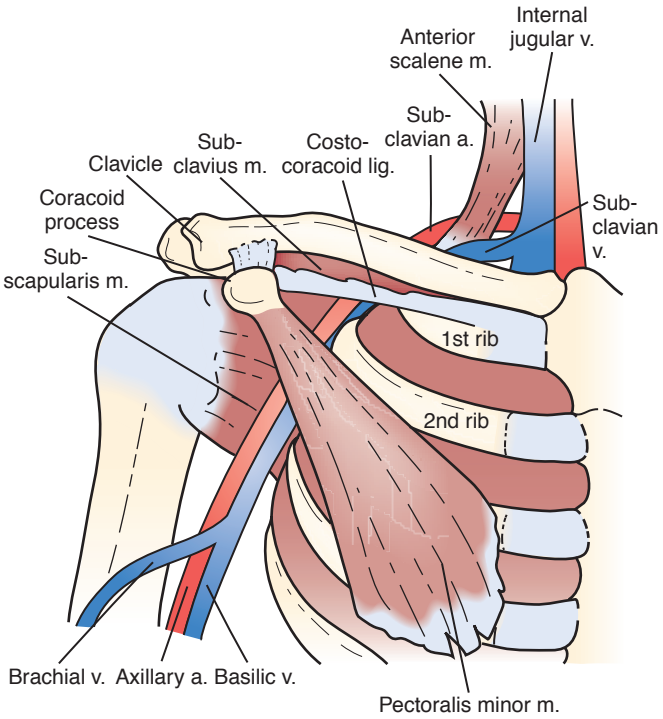

Figure 123.1 Anatomy of the Thoracic Outlet.

Secondary Subclavian-Axillary Vein Thrombosis

Although vTOS typically refers to primary subclavian-axillary vein thrombosis, the differential diagnosis should include secondary upper extremity DVT (see Chapter 149). Issues associated with secondary upper extremity DVT include nephrotic syndrome, mediastinal tumors, malignancy, local surgery or trauma, hypercoagulable states, renal failure requiring dialysis, long term use of peripherally inserted central catheters, and cardiac conditions requiring pacemaker placement. The two most common causes of mechanical secondary upper extremity DVT are the placement of central venous catheters and pacemaker wires.

Catheter-related venous thrombosis is suggested to occur in 5% or less of all inserted central venous catheters.[4,18] Risk factors associated with a higher rate of catheter-related thrombosis in adult patients are either catheter-related (malposition of the catheter, insertion of the catheter on the left, multiple catheter lumens), treatment-related (use of long-term antibiotics or total parenteral nutrition, bolus vs. dilute chemotherapy infusions), or patient-related (malignancy or hypercoagulable states).[19-22] Patients with catheter-related venous thrombosis can be

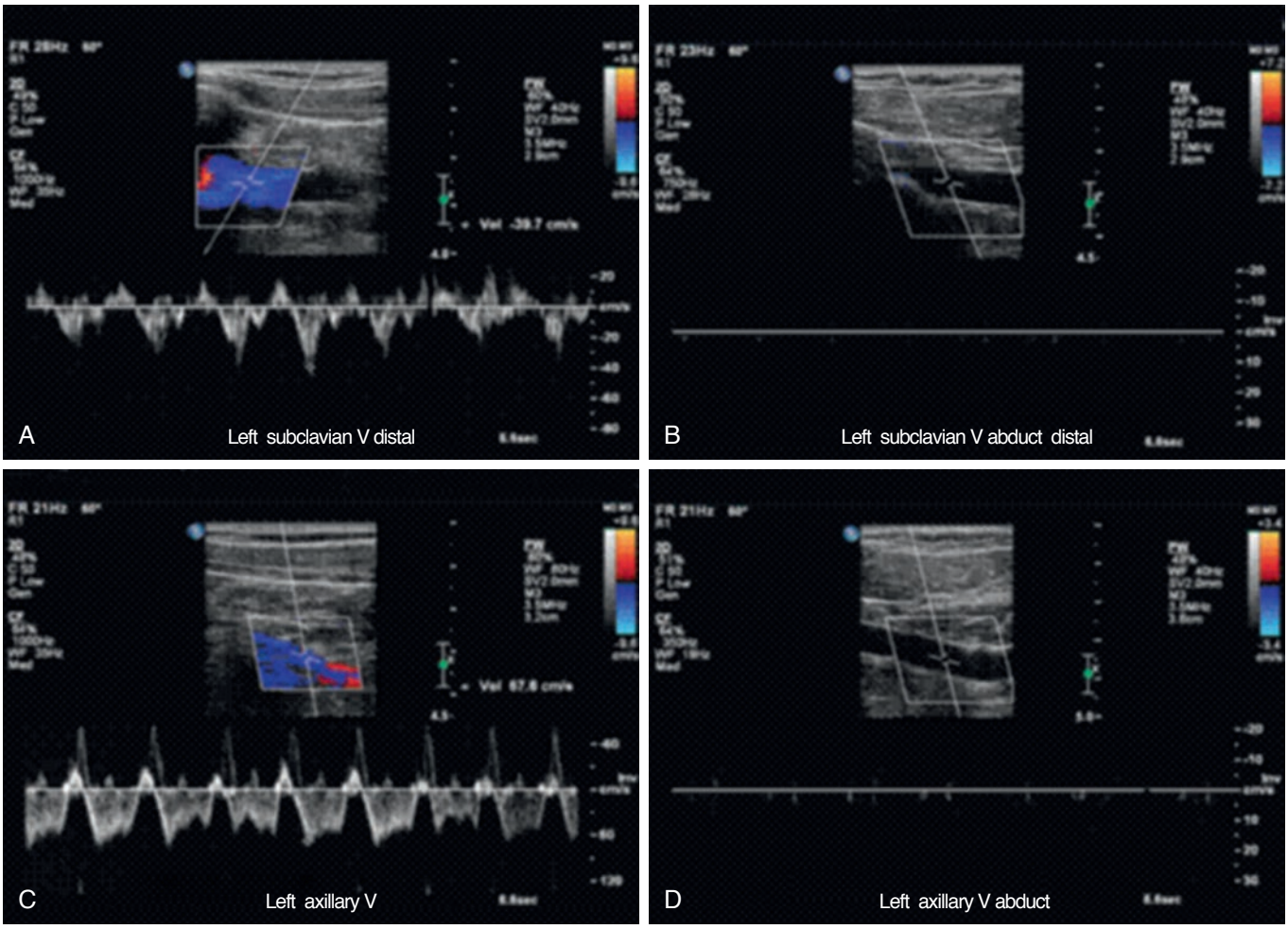

Figure 123.2 **Venous Compression of the Left Subclavian and Axillary Vein.** With the arm in the neutral position the subclavian **(A)** and axillary **(C)** veins demonstrate normal phasic flow. With elevation of the arm to 180 degrees, there is cessation of flow in the subclavian **(B)** and axillary **(D)** veins.

asymptomatic, but significant symptoms such as pulmonary embolism can be as high as 15% and 25%.[23] It is important to remember that the rate of thrombosis is not necessarily due to the duration of catheter placement.[24]

In addition to catheters, pacemaker wires are an increasing cause of secondary subclavian-axillary vein thrombosis. The number of leads, previous use of a temporary pacemaker, and left ventricular ejection fraction ≤40% are predictive of venous stenosis.[25,26] Infection of the pacemaker insertion site has also been shown to increase the risk of venous stenosis and occlusion.[27] The use of anticoagulation is protective against the development of occlusion of the subclavian vein, but has not been shown to prevent venous stenosis.[28]

Just as in the case of primary upper extremity vTOS, the pathophysiology of secondary upper extremity subclavian-axillary thrombosis is vein wall damage. In some cases, catheter removal causes the fibrin sheath to break loose and subsequently embolize into the pulmonary circulation.[29]

CLINICAL PRESENTATION

The mean age at diagnosis for vTOS is 32 years, with the majority of patients affected between the second and fourth decades.[15] Despite early reports showing a female predominance, more recent literature including the largest series published to date (312 affected extremities) have reported an equal gender ratio.[15,30] Individuals who perform strenuous or sustained upper extremity activities, whether athletic or occupational, are particularly prone to the development of subclavian-axillary vein thrombosis. The dominant arm is involved in the majority of cases.[16]

Upper extremity edema is the hallmark characteristic associated with subclavian-axillary vein thrombosis. The edema is often but not always accompanied by pain and cyanosis of the affected extremity. The edema usually involves the shoulder, arm, and hand, and is characteristically nonpitting. Dilated superficial veins over the shoulder, neck, and anterior chest wall can often be visualized as collateral veins try to accommodate the increased venous pressure (a pattern often referred to as *first rib bypass venous collaterals*).[31] A minority of patients may demonstrate symptoms resembling neurogenic TOS, such as numbness and tingling in the distribution of the inferior trunk of the brachial plexus (see Chapter 121). This association is likely due to the presence of muscular anomalies of the thoracic outlet anatomy and the performance of repetitive upper extremity arm activities.

Patients may report some degree of pain. The description can include aching, stabbing, or a feeling of tightness that worsens with exertion.[6] Extended use of the arm leads to increased arterial blood flow, for which the limited collateral venous bed is unable to compensate. The subsequent venous hypertension worsens symptoms of venous stasis and arm congestion. Urschel and Razzuk reported that out of the 312 patients with extremities with vTOS in their 30-year experience, 93% complained of arm swelling, 77% demonstrated bluish discoloration, 66% had aching pain with exercise, and 8% were asymptomatic.[15] Similarly, Van Rooden et al. reported that 52% of patients were symptomatic, 39% were completely disabled, and 9%, were asymptomatic.[28]

The two most potentially severe complications of subclavian-axillary vein thrombosis are pulmonary embolism and upper extremity phlegmasia cerulea dolens (venous gangrene). The reported incidence of pulmonary embolism due to subclavian-axillary vein thrombosis is less than 10%.[1,4,6,32,33] Compared with iliofemoral DVT, the small clot burden of upper extremity DVT may reduce the clinical impact of pulmonary embolism. Venous gangrene is exceedingly rare and has been limited to case reports in patients with malignant disease or an underlying hypercoagulable state.[34] No reports of venous gangrene occurring secondary to vTOS have been published.

DIAGNOSTIC EVALUATION

Duplex Ultrasound

Duplex ultrasonography is the most frequently used diagnostic modality for the evaluation of patients thought to have DVT of the upper limb. The study is noninvasive, does not require the use of a nephrotoxic contrast agent, and does not involve ionizing radiation. In addition, it can be performed at the bedside or in the emergency department. The use of diagnostic ultrasound in the upper extremity is different from that in the lower extremity. Overlying structures, such as the clavicle, make duplex interrogation of the vascular structures coursing through the thoracic outlet challenging. In the upper extremity, compressibility of the targeted vein is not possible beneath the clavicle, nor is it possible to compress the brachiocephalic vein or SVC. Therefore duplex examinations relying on B-mode ultrasound alone have historically demonstrated low sensitivity (54%) and high specificity (100%) for the detection of subclavian-axillary vein thrombosis.[35] The standard use of color-flow duplex imaging in conjunction with indirect criteria suggesting the presence of an occlusion (evaluation for phasicity of flow with respiration and augmentation with compressive maneuvers) have led to markedly increased sensitivity (81% to 100%) while maintaining high specificity (82% to 100%).[36,37,38]

Magnetic Resonance and Computed Tomographic Venography

Magnetic resonance venography (MRV) and computed tomographic venography (CTV) are additional noninvasive imaging modalities that have been used with increasing frequency for the diagnosis of vTOS.[39,40] The sensitivity and specificity of both modalities are comparable to those of duplex ultrasound.[23] CTV has the added advantage of being able to detect central vein thrombosis and the presence of pulmonary emboli, with appropriate arterial timed contrast. However, MRV and CTV are rarely necessary for patients with suspected vTOS. The cost and time required for completion of the examination are substantial. MRI is routinely used in patients with neurogenic TOS, as dynamic MRI has the ability to identify the location and etiology of brachial plexus compression, as well as associated vascular compression.[41]

Venography

Digital subtraction venography is considered the gold standard (Fig. 123.3). However, it is generally reserved for patients whose condition warrants an intervention. Venography is invasive and uses a nephrotoxic agent, in addition to requiring exposure of the patient to ionizing radiation. Up to 20% of patients do not qualify for venography because of a severe allergy to the contrast agent or the inability to cannulate the veins in the edematous extremity. The primary role of venography is in the patient whose duplex ultrasound findings are equivocal. In such patients, an additional objective study should be performed to confirm or to reject the diagnosis of upper extremity DVT.

When performed, venography should be done at rest and with positioning of the arm at 90 and 180 degrees (Fig. 123.4). These positional images are essential to confirm the presence of extrinsic compression of the subclavian vein at the level of the thoracic outlet. Evaluation of the collateral circulation is another important function of venography. The extent of collateralization provides information about the hemodynamic significance of the occlusion or stenosis and about the chronicity of the occlusion. Chronicity of the occlusion in turn plays a key role in dictating management. Patients may be classified into one of three categories on the basis of their history and venographic findings: (1) acute subclavian-axillary vein thrombosis, (2) chronic or recurrent subclavian-axillary vein thrombosis, or (3) high-grade symptomatic subclavian-axillary vein stenosis.

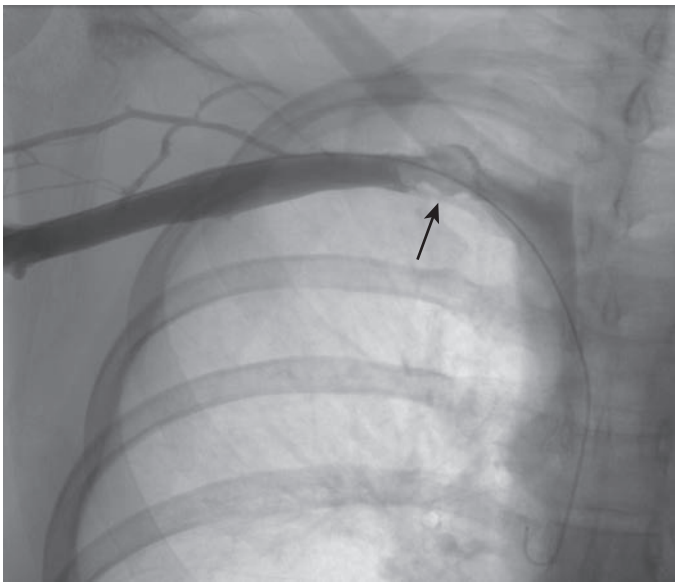

Figure 123.3 Venogram indicating an acute primary subclavian-axillary vein thrombosis *(arrow)*.

TREATMENT

Debate continues over the optimal treatment of vTOS. The disease has not been studied in a prospective fashion, and given the lack of consensus that experts in the field have over anticoagulation, thrombolysis, and surgical decompression, a prospective study is unlikely. Recently a collaborative national registry has been developed at the University of California-Davis. The registry has invited leaders in the field to add patients with both operative and nonoperative therapy in order to determine long-term outcomes for all patients with TOS.

Figure 123.4 Venogram of the subclavian-axillary vein after successful thrombolysis with the extremity in full adduction (A) and in full abduction (B).

Anticoagulation Alone

Historically, treatment of acute primary subclavian-axillary vein thrombosis consisted of rest, elevation of the affected extremity, and a variable duration of systemic anticoagulation. Retrospective reviews on this approach have demonstrated variable outcomes, but the initial report by Hughes on the conservative management of 320 patients with primary subclavian-axillary vein thrombosis found that 40% of patients had persistent symptoms or limited recovery.[1] More recent studies report the use of the objective Disability of the Arm, Shoulder, and Hand (DASH) questionnaire to assess quality of life after upper extremity venous thrombosis. In a retrospective review of patients treated with surgical decompression versus anticoagulation alone, patients that underwent surgical decompression had significantly improved quality of life and functionality DASH scores.[42] Specific factors contribute to failure and should be considered when devising a patient-centered treatment plan. Young age, active lifestyle, and participation in sports at a competitive level are all associated with the long-term failure of anticoagulation.[43-45]

The goals of treatment in secondary upper extremity DVT are to prevent pulmonary embolism and to achieve recanalization of the vein. Most patients with secondary upper limb DVT improve after removal of the venous catheter and institution of anticoagulation therapy. If a catheter causes extensive axillary vein thrombosis resulting in marked edema, thrombolytic therapy may be considered. If the catheter is nonfunctioning or no longer needed, it should be removed and the patient should be treated with 3 months of anticoagulation.[46] Patients with a functional catheter needed for ongoing treatment should be systemically anticoagulated. Anticoagulation should continue for the entire time the catheter is left in place.

Patients with secondary upper limb DVT who may have contraindications to systemic anticoagulation, such as concurrent gastrointestinal bleeding, recent neurosurgery, or the presence of pulmonary embolism despite anticoagulation, may be candidates for SVC filter placement. SVC filters are not used widely, but in small limited studies they have been shown to be effective in preventing recurrent pulmonary embolism. The long-term patency rates of the small number of SVC filters that have been placed are reportedly high.[47] Nonetheless, concerns persist about the risk of SVC filter migration or thrombosis resulting in SVC syndrome. Because fatal pulmonary embolism from upper extremity DVT has been documented to be very rare and evidence of the safety of filters is limited, clinical judgment must be used in recommending their deployment.[48]

Thrombolytic Therapy

Catheter-directed thrombolysis has emerged as an initial management strategy in the modern treatment paradigm of vTOS. The goal of catheter-directed therapy is to remove thrombus, restore the patency of the vein, and alleviate symptoms. Because subclavian-axillary thrombus is much more localized than lower extremity DVT, this approach usually lyses the subclavian-axillary vein thrombus quickly to restore luminal patency. In 1981, Zimmermann and associates documented, in a small case series, the successful use of systemic urokinase in 82% of patients with acute primary subclavian-axillary thrombosis.[49] Since this initial series, many authors have demonstrated high rates of success in reestablishing patency with catheter-directed thrombolysis (Fig. 123.5). Lee and colleagues reported their experience treating 64 patients with primary subclavian-axillary thrombosis. As the first step in their treatment algorithm, 54 patients with symptom onset within 7 days underwent attempted catheter-directed thrombolysis; 100% experienced successful restoration of luminal patency.[44] When thrombolysis is initiated within 14 days of the onset of symptoms, the results are generally

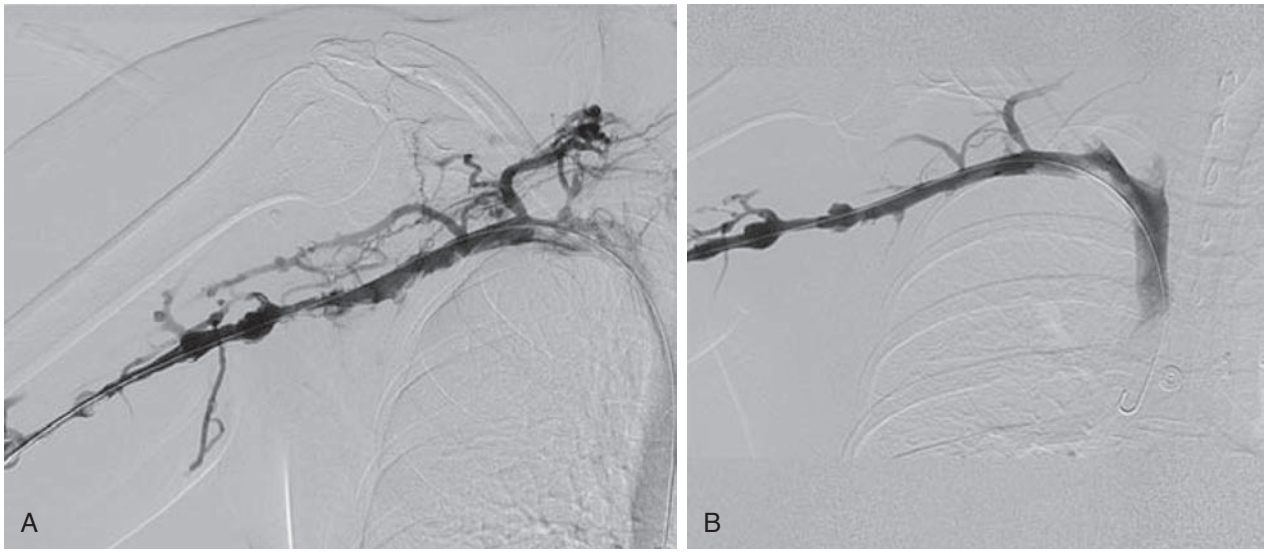

Figure 123.5 Venogram of the subclavian-axillary vein before (A) and after (B) thrombolysis.

reported to be excellent.[5] Treatment with thrombolysis in patients with more than 14 days of symptoms is possible, albeit with a decreased chance for successful reestablishment of luminal patency.[50,51] Technical aspects of thrombolysis performed prior to surgical decompression that are associated with poor long-term results include overly aggressive balloon venoplasty to achieve an optimal angiographic result and the use of venous stents.[44,52]

Despite the excellent results with thrombolysis, whether or not preoperative thrombolysis affords any benefit to long-term venous patency is questionable. In a retrospective review of a decade treating 34 patients with vTOS, primary subclavian-axillary vein patency at 5 years was 84% in patients who underwent thrombolysis followed by surgical decompression and 83% in patients who underwent surgical decompression without thrombolysis.[53] A second study by Guzzo et al. retrospectively reviewed 110 patients with vTOS. At 1 year they too found the primary patency was identical in patients treated by thrombolysis followed by decompression and those treated with anticoagulation followed by surgical decompression (91% vs. 91%, P = .99).[52] Given the risks of bleeding, procedural expense, and use of limited resources, the cost effectiveness of thrombolysis deserves future study.

Post-Thrombolysis Management

Patients with unsuccessful thrombolysis, defined as persistent total occlusion of the subclavian-axillary vein, should receive anticoagulation and measures aimed at control of local symptoms, such as rest, compression, and elevation. Unsuccessful thrombolysis of acute subclavian- axillary vein thrombosis is rare, and almost always seen in patients who have had repeated episodes of lysis with overly aggressive venoplasty or long-standing symptoms treated only with anticoagulation.

Whether or not these patients benefit from surgical decompression has only been reviewed in small series. In a group of 42 patients, Urschel and Razzuk reported a 57% rate of recanalization and resolution of symptoms with surgical decompression and extended length anticoagulation.[15] In a second series of 16 patients with chronic venous occlusion due to vTOS reported by Chang et al., first rib resection followed by anticoagulation resulted in 88% recanalization at 6 months. The mean duration of anticoagulation in this study was 3 months.[54] Given the potential for recanalization, high volume centers do offer first rib resection to select patients with chronic occlusion.

Patients in whom thrombolysis was successful, defined as those with reestablishment of subclavian-axillary vein patency, can be further classified on the basis of completion positional venography, according to the absence or presence of demonstrable extrinsic compression at the thoracic outlet. Patients without extrinsic compression will not benefit from thoracic outlet decompression and should be treated with 3 to 6 months of systemic anticoagulation.[46]

In patients found to have extrinsic compression, no effort should be made at the completion of successful thrombolysis to dilate a persistent subclavian vein stenosis. The resultant intimal injury of angioplasty without addressing the extrinsic compression results in inflammation and decreases the likelihood of reestablishing long-term patency of the vein.[55] Also, in no case should a patient that has not undergone surgical decompression have a stent placed in the subclavian vein. Multiple studies have documented the dismal results of subclavian vein stents.[56-58] Immediate thoracic outlet decompression and subsequent subclavian-axillary vein venography/angioplasty should be performed early to decrease the risk of rethrombosis (discussed later).

Surgical Decompression of the Thoracic Outlet

Technical details of surgical decompression are reviewed in Chapter 124. The decision to perform surgical decompression should be considered in all patients with persistent stenosis or signs of extrinsic compression on positional venography after thrombolysis. These patients remain at significant risk of recurrent thrombosis with anticoagulation alone.[50] When the underlying pathophysiologic process is not appropriately addressed, adjunctive therapies such as balloon angioplasty or stent placement may provide satisfactory immediate results but lack sufficient durability to be accepted as definitive therapy.[44,51,56-58] Multiple reports have confirmed that the radial force associated with either a self-expanding or balloon-expandable stent is not adequate to compensate for the compressive force between the first rib and clavicle; stent deformation, fracture, and thrombosis in this setting are the norm rather than the exception (Fig. 123.6). Therefore stents have no role in the treatment of vTOS before surgical decompression.

To alleviate extrinsic compression, first rib resection with external venolysis should be performed. Early studies advocate deferring surgical decompression for 1 to 3 months after thrombolysis to allow healing of the venous endothelium and

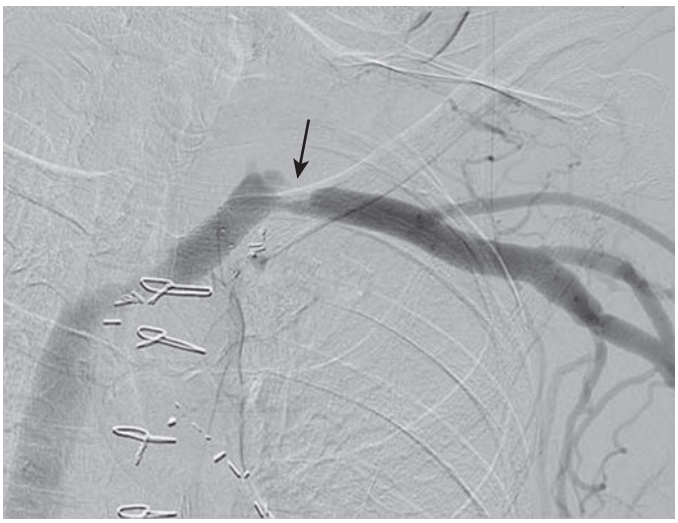

Figure 123.6 Deformed balloon-expandable stent *(arrow)* 6 weeks after treatment of primary subclavian-axillary thrombosis.

resolution of the acute inflammatory process.[59,60] However, early decompression, even during the same hospitalization as the thrombolysis, has been shown to significantly decrease the risk of reocclusion that may occur between thrombolysis and deferred surgery.[5,15,50,51,55,61,62] The shift to immediate surgery has virtually eliminated the vein rethrombosis rate of 6% to 18% that has been reported to occur during the waiting period.[5,60]

Vein Treatment After First Rib Resection

The optimal management of the subclavian-axillary vein after surgical decompression of the thoracic outlet remains open for debate. The presence of residual subclavian-axillary vein stenosis, even after relief of the extrinsic compression, is not uncommon (Fig. 123.7). Recommended strategies to deal with these intrinsic lesions have spanned a diverse spectrum, ranging from completion venography and angioplasty with or without stenting to extensive venous reconstructions including thrombectomy, patching, or bypass. No direct comparisons between these strategies have been performed to date, but it is clear that extensive venous reconstructions are accompanied by a higher complication rate. This issue is underscored by the experience of Melby and colleagues, in which 44% of their 32 patients underwent direct subclavian-axillary vein reconstruction and 100% experienced resolution of their symptoms (no patency data reported).[51] However, 22% of their patients required secondary operations for complications. Furthermore, if closure of adjunctive radiocephalic fistulae is also included as a secondary procedure, the overall rate of secondary procedures increases to 53%. In this experience, no intraoperative venography was used to assess the status of the subclavian-axillary vein after decompression of the thoracic outlet. Consequentially, no attempts at intraoperative angioplasty of residual lesions were undertaken.

Most groups favor an endovascular approach after thoracic outlet decompression. Endovascular treatment can occur during the surgical rib resection case, or within 2 weeks of the initial surgery. Advocates of the intraoperative strategy believe this approach can direct the surgeon to the most appropriate treatment of a residual stenosis before the patient leaves the operating room. In a study of the intraoperative strategy, 25 patients routinely underwent completion venography, with angioplasty as necessary, at the time of thoracic outlet decompression. Their overall results demonstrated 100% technical success, 100% resolution of symptoms, and 1-year primary and secondary patency rates of 92% and 96%, respectively.[50] Proponents of the delayed approach consider the possible complications with venoplasty and the need for immediate anticoagulation as risky. Routine postoperative venography within 2 weeks after thoracic outlet decompression was studied in 84 patients. Although technical success of 100% was not achieved in this cohort, 1 year primary and secondary patency rates were 94% and 98%, respectively.[54] Until a prospective comparison of the two strategies is undertaken, at this time the best recommendation is to evaluate and address any residual venous stenosis with intravascular imaging after surgical decompression.

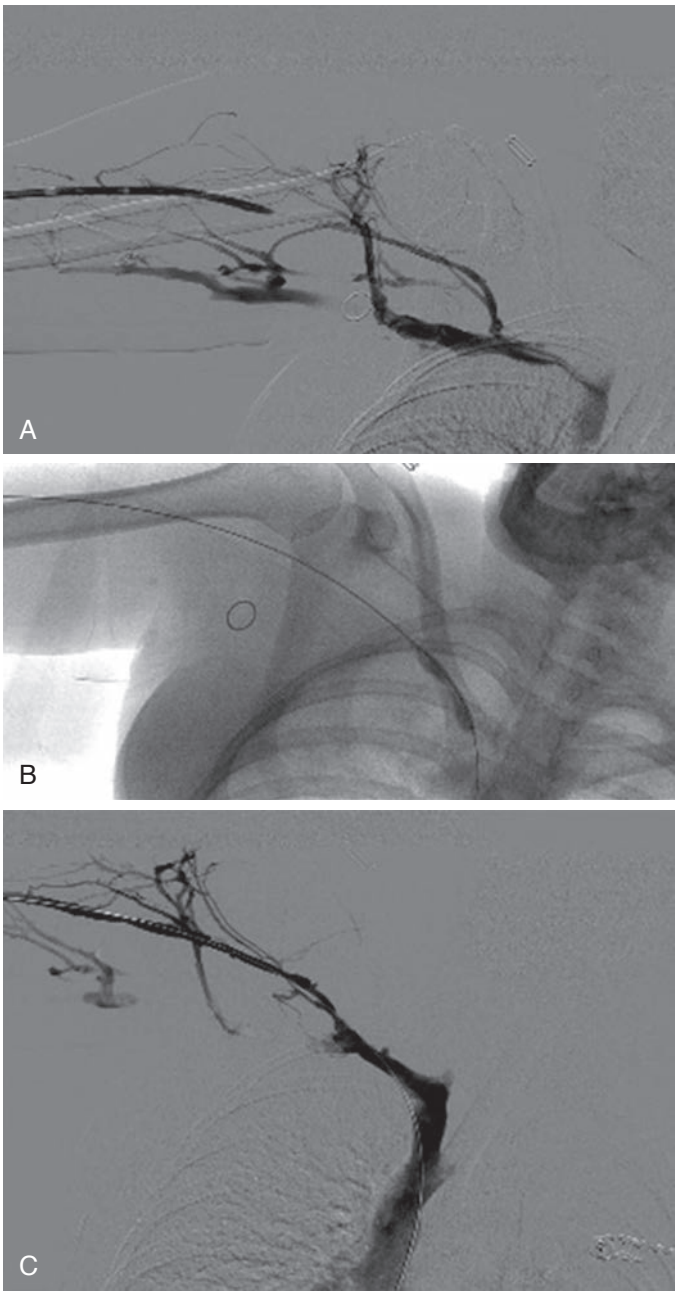

Figure 123.7 Venogram of the subclavian-axillary vein demonstrating (A) a fixed filling defect (B) treated by angioplasty after first rib resection (C) and demonstrating resolution.

Postoperative Care

Patients who undergo surgical decompression of the thoracic outlet for vTOS should start physical therapy after complete postoperative treatment of the subclavian-axillary vein. The physical therapy should be tailored for patients with TOS. This protocol should address soft tissue mobilization of the scar as well as restoration of movement of the entire shoulder girdle; improved function and flexibility to the upper cervical spine; activation and strengthening of the anterior, middle, and posterior scalene muscles (especially focused on maintaining

posture throughout the day); stretching of the trapezius, the sternocleidomastoid, the levator scapular, and the pectoralis minor muscle; and finally graduated resistance shoulder elevation exercises. The minimum duration of physical therapy should be 6 weeks. It is important to have a strong working relationship with the physical therapist and understand that patients should not be "fast tracked" through physical therapy. Severely fibrotic scarring develops in the surgical field without adequate physical therapy. This results in the tethering of the brachial plexus and can result in neurologic symptoms. Patients should not be released from physical therapy early simply because they demonstrate the ability to have full range of motion. This cannot be overly stressed in young high-level athletes. In order for them to return to full function in their sport, a slow and consistent approach to recovery is essential.

Recurrence

Recurrent thrombosis after first rib resection is most likely due to residual anterior rib left in place at the initial operation or inadequate cutting of the subclavius tendon to free up the vein. When rethrombosis is identified early, thrombolysis should be considered. The patient should be maintained on anticoagulation and undergo a workup to determine the cause. Plain radiographs can identify residual anterior rib that was left behind at the first operation. If the cause of recurrent thrombosis is scaring of the subclavian-axillary vein, an infraclavicular incision with repair of the vein can be considered. When thrombosis is thought to be due to inadequate first rib resection, either a supraclavicular or transaxillary approach may be used. Care must be taken when operating in a redo field, especially in the small space of the thoracic outlet. Injury to the vein, artery, or nerve can easily occur when the patient has large amounts of residual scar tissue.

Results

For the most part, reports on the treatment of vTOS are limited to case series, often with relatively small sample sizes. Nonetheless, in aggregate, the overwhelming evidence suggests that in properly selected patients, restoration of subclavian-axillary vein patency and decompression of the thoracic outlet result in excellent and durable outcomes. Table 123.1 summarizes the results of multiple series that have been used, albeit with varying techniques, strategies to achieve the goal of vein patency and decompression of the thoracic outlet in patients with vTOS. It should be mentioned again that although subclavian vein occlusion after abduction can be documented in a high percentage of the contralateral limbs of these patients, the risk of thrombosis has proved to be low. For this reason, prophylactic procedures should not be considered for routine patients with vTOS. In specific cases of high functioning athletes, contralateral surgical decompression should be considered in order to maintain full function and performance.

TABLE 123.1 Reported Patency Results of Surgical Thoracic Outlet Decompression for Primary Subclavian-Axillary Thrombosis Published Since 2000

Author	No. of Patients	Technical Success (%)	Secondary Patency (%)	Follow-Up (Mean)
Urschel et al.[15]	277	95	NR	NR
Schneider et al.[50]	25	100	96 (1 year)	10 months
Lee et al.[44]	29	93	97 (4 years)	52 months
Doyle et al.[53]	34	100	92 (5 years)	33 months
Molina et al.[61]	97	100	100 (5 years)	62 months
Melby et al.[51]	32	100	NR	43 months
Bamford et al.[63]	35	91	91	44 months
de León et al.[64]	67	96	96 (1 year)	10 months
Guzzo et al.[52]	110	91	91 (1 year)	16 months
Hawkins et al.[65]	30	100	100 (2 years)	24 months
Stone et al.[66]	36	100	94 (5 years)	65 months

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Molina JE, Hunter DW, Dietz CA. Paget-Schroetter syndrome treated with thrombolytics and immediate surgery. *J Vasc Surg*. 2007;45:328–334.

This study reports one of the largest series of patients to undergo treatment of venous thoracic outlet syndrome. The outcomes were excellent, and the discussion emphasizes many key issues that are central to the management of this challenging syndrome.

Sajid MS, Ahmed N, Desai M, Baker D, Hamilton G. Upper limb deep vein thrombosis: a literature review to streamline the protocol for management. *Acta Haematol*. 2007;118:10–18.

Comprehensive review of key studies describing the etiology, diagnosis, and management of upper limb venous thrombosis.

Schneider DB, Dimuzio PJ, Martin ND, et al. Combination treatment of venous thoracic outlet syndrome: open surgical decompression and intraoperative angioplasty. *J Vasc Surg*. 2004;40:599–603.

This study describes the first significant series of patients who underwent venothrombolysis, immediate surgical decompression of the thoracic outlet and intraoperative venography, and definitive treatment of residual stenosis. The outcomes indicate that it is unnecessary to delay surgical decompression in most patients, and the study emphasizes the importance of intraoperative venography to determine the optimal strategy for treating any residual stenosis.

Urschel HC Jr, Razzuk MA. Paget-Schroetter syndrome: what is the best management? *Ann Thorac Surg*. 2000;69:1663–1668, discussion 1668–1669.

This study provides a clear and detailed description of the transaxillary approach to thoracic outlet decompression.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 124

Thoracic Outlet Syndrome: Surgical Decompression of the Thoracic Outlet

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Although there is little debate over treatment of arterial thoracic outlet syndrome (aTOS), treatment for venous thoracic outlet syndrome (vTOS) and especially neurogenic thoracic outlet syndrome (nTOS) remains highly controversial. Because subjective findings are utilized in developing the diagnosis, nTOS is best treated at specialized centers where large numbers of patients are seen yearly and standard treatment protocols are in place. Not all patients with nTOS will require surgical treatment, so the surgical option should be reserved for patients who will most benefit and only after a complete trial of nonoperative treatment.

INDICATIONS

Indications for decompression of the thoracic outlet in patients with aTOS are the most clear, and the Scher criteria for treatment have been established based on the pathology of the subclavian artery (Table 124.1; see Chapter 121).[1] Because the subclavian artery cannot be adequately controlled and repaired through the transaxillary approach, Scher class 2 and 3 disease should be approached through a supraclavicular or a combination of supra- and infraclavicular incisions.

There are no absolute indications for surgical treatment of nTOS and vTOS. However, nTOS patients who have improvement with a TOS-specific physical therapy protocol but have residual symptoms or those with recurrent symptoms when physical therapy ends may obtain long-term relief with surgical decompression. In the case of vTOS, the likelihood of recurrent thrombosis must be balanced with the risks of surgical decompression. Indications for surgery can be anatomic or lifestyle-related. Patients with persistent stenosis or signs of extrinsic compression on positional venography after thrombolysis remain at significant risk of recurrent thrombosis with anticoagulation alone and should be considered for decompression.[2] In high-performance athletes, body builders, patients that perform repetitive movements during work using the affected extremity, or those with recurrent episodes of thrombosis, thoracic decompression provides the best long-term outcomes.[3]

In the past authors have advocated for deferment of surgical decompression for 1 to 3 months after thrombolysis to allow healing of the venous endothelium and resolution of the acute inflammatory process.[4,5] Now most agree that decompression should take place during the same hospitalization as the thrombolysis so as to decrease the significant risk of reocclusion that may occur between thrombolysis and deferred surgery.[2,3,6-8] Immediate operative decompression, even as early as 4 hours after thrombolysis, has been demonstrated to be safe and effective.[9] This shift to immediate surgery has decreased the venous rethrombosis rate of 18% that has been reported to occur during the waiting period.[5,6,10]

TABLE 124.1 Scher Classification of Surgical Treatment for Subclavian Artery Pathology

Stage	Arterial Pathology	Treatment
0	Asymptomatic subclavian artery compression	No surgical treatment except in high-performance athletes or patients required to perform repetitive movements with the affected arm. Should be monitored intermittently for arterial wall degeneration and injury.
1	Subclavian artery stenosis with mild dilation but no intimal injury	Decompression of the thoracic outlet and reimaging of the subclavian artery.
2	Subclavian artery aneurysm with mural thrombus	Decompression of the thoracic outlet and reconstruction of the subclavian artery.
3	Arterial thrombosis or distal embolization with occlusion	Thrombectomy vs. thrombolysis Decompression of the thoracic outlet and reconstruction of the subclavian artery.

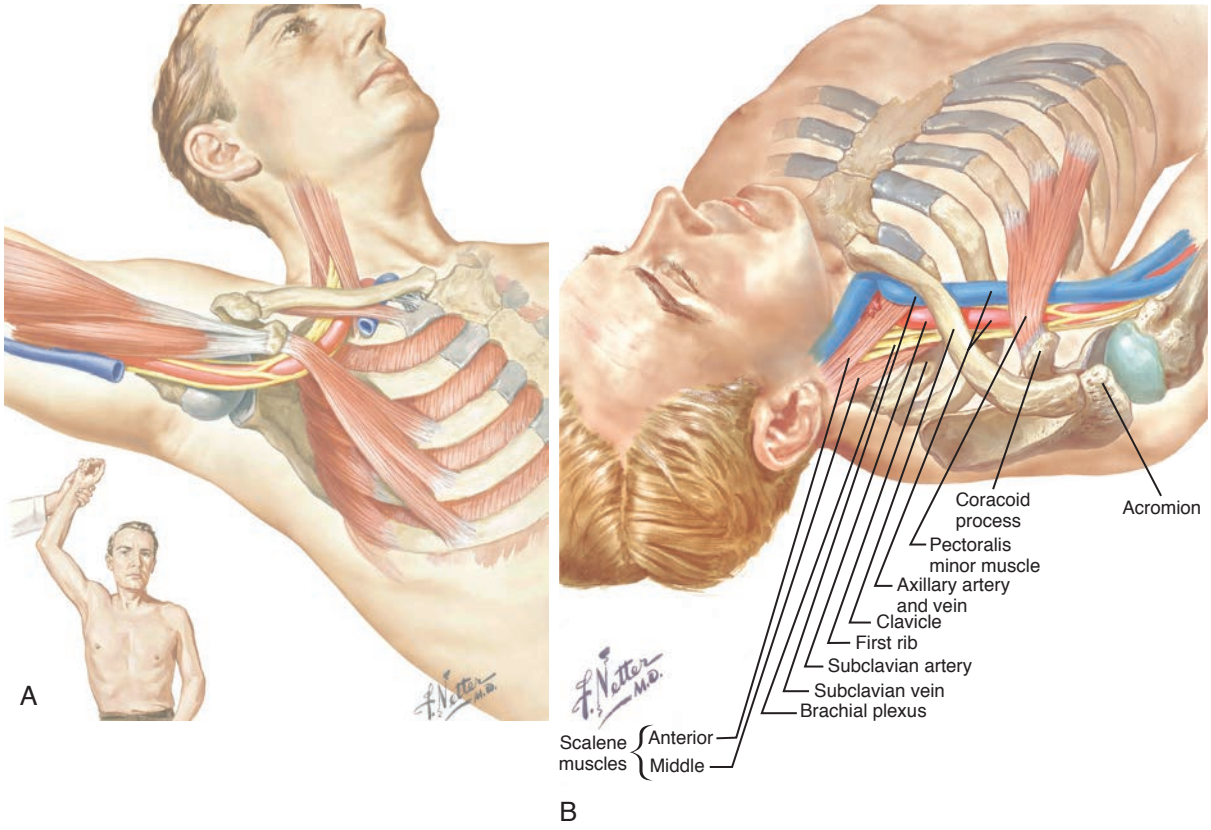

Figure 124.1 (A and B) Two views of the thoracic outlet area, demonstrating the pectoralis minor space in the foreground. The axillary artery and vein are continuations of the subclavian artery and vein. At the axillary level the brachial plexus has already formed its cords, so it is the branches that are seen under the pectoralis minor. (From Lord JW, Jr., Rosati LM. Thoracic outlet syndromes. *Ciba Symp.* 1971;23:1-13.)

PREOPERATIVE PLANNING

Appropriate preoperative planning is the core of successful surgical treatment. An understanding of the anatomy is critical to any surgical treatment (Fig. 124.1), but specific attention should be paid to prior injuries and daily activities in the patient's history. Knowledge of any prior surgical treatment in the vicinity of the surgical field is essential, as this may change the approach. Documentation of the complete preoperative vascular and neurologic examination is critical. A chest x-ray should be performed to evaluate for anomalous first ribs or a cervical rib. In patients with aTOS, imaging of the subclavian artery should be performed to evaluate for aneurysmal degeneration or intravascular thrombus. If reconstruction is planned, appropriately sized prosthetic grafts should be available or vein mapping should be performed if autologous conduit is being considered. Patients with vTOS do not necessarily need a hypercoagulable workup prior to surgery, but they will need to be bridged from oral anticoagulants with the last dose the night prior to surgery.

Selection of Arterial Conduit

Single-segment autologous great saphenous vein (GSV) is the preferred conduit for vascular bypass in the lower extremities due to its ability to resist infection and superior patency over

prosthetic grafts, but it is not the optimal conduit for subclavian artery bypass. Unlike long infrainguinal bypass grafts, subclavian reconstructions are shorter. Because the subclavian artery is subjected to forces of compression, elongation, and twisting, the selected conduit must be able to perform well under these challenging conditions. Prosthetic options include externally supported polytetrafluoroethylene (PTFE) or Dacron. Small single-institution retrospective reviews of patients who have undergone arterial bypass after TOS decompression show 96% patency at 5 years with PTFE and 94% patency with GSV at 12 years.[11,12] However, a larger series of 51 patients undergoing bypass grafting from the carotid artery to the subclavian artery beyond the clavicle indicates that PTFE had better 5 year patency (96%) compared with Dacron (84%) and saphenous vein (65%).[13] Because of the small numbers in these series, a definitive recommendation on choice of conduit cannot be made at this time.

SURGICAL TECHNIQUES

Removal of the first rib can be performed through a supraclavicular, infraclavicular, or transaxillary incision. Cervical ribs, however, may only be reached through the transaxillary or supraclavicular approach. As already mentioned, repair of the subclavian artery requires a supraclavicular approach to obtain control of the vessel. Venous repair may be performed through a supraclavicular or infraclavicular approach. Regardless of which approach is ultimately chosen, the procedure should be performed under general endotracheal tube anesthesia. The tube should be secured on the opposite side of where the surgeon will be working, and the use of neuromuscular blocking agents should be avoided because of the numerous nerves within the surgical field.

Supraclavicular Approach

The patient is placed on the operating room table in the semi-Fowler position. A small roll is placed transversely just below the shoulders. The head is extended and rotated away from the operative site. The neck, chest, and affected extremity are prepped and draped sterilely. The arm, forearm, and hand are wrapped in a stockinette or towel and secured with a towel clamp. Prepping the entire arm allows it to be moved if needed for additional exposure. During the procedure, the arm is maintained in the adducted position. The elbow may be flexed at 90 degrees and the arm secured to the abdomen or left straight at the patient's side. Both positions prevent tension on the brachial plexus.

External landmarks are identified and marked on the skin. These include the sternocleidomastoid muscle, sternal notch, and clavicle. A transverse incision is made 2 cm above the clavicle beginning at the lateral border of the sternocleidomastoid muscle and extending just beyond the external jugular vein. The platysma muscle is incised and inferior and superior subplatysmal flaps are created. Flaps should be created as widely as possible to provide adequate exposure. Portions of the clavicular head of the sternocleidomastoid muscle can be divided to provide exposure. The scalene fat pad is dissected along the medial, inferior, and superior borders, which allows it to be retracted laterally. This mobilization is initiated by taking down the medial attachments of the fat pad at the level of the internal jugular vein. The tissue should be tied with 3-0 sutures to prevent postoperative lymph leakage. Alternatively, a Ligasure (Medtronic, Minneapolis, Minnesota) or harmonic scalpel can be used. The dissection is carried down to the junction of the internal jugular and subclavian veins and extended laterally to the insertion of the external jugular vein into the subclavian vein. Finally, the fat pad is mobilized superiorly until the cutaneous nerves of the chest and shoulder region are encountered. Self-retaining retractors—Omni-Tract, Weitlaner, or cerebellar—are put into position to maintain exposure.

The medial and lateral borders of the anterior scalene muscle are mobilized, and the phrenic nerve is identified (Fig. 124.2A). The phrenic nerve is never directly grasped with an instrument. Rather, a generous length of fascia on either side of the nerve is incised and used to retract the nerve and expose the anterior surface of the anterior scalene muscle. The nerve may also be encircled with a vessel loop and the loop used to retract it, with care taken to avoid excessive retraction. Mobilization of the phrenic nerve is continued down to the thoracic inlet. The anterior and posterior borders of the anterior scalene muscle are dissected. A right-angle clamp is passed behind the muscle, which is divided sharply at least 1 cm off the first rib. Bipolar cautery may also be used to divide the muscle and maintain hemostasis. If a portion of the anterior scalene muscle or a separate scalenus minimus is present behind the subclavian artery, it should be divided as well. The anterior scalene muscle is dissected proximally as able and then excised. The plane in the deep cervical fascia is developed laterally with a moistened sponge or Kittner to expose the brachial plexus and the middle scalene muscle. After the long thoracic nerve is located, the middle scalene muscle is mobilized (see Fig. 124.2B). A periosteal elevator is used to dissect the attachments of the middle scalene muscle from the first rib. Often, some of the fibers of the middle scalene muscle extend to the second rib and may be incised with Metzenbaum scissors if needed. The intercostal fibers are taken off the first rib with the elevator (see Fig. 124.2C). The first rib is resected with a bone cutter or a Kerrison rongeur just proximal to its articulation with the vertebra (see Fig. 124.2D). Similarly, it is excised as medially as possible near its junction with the sternum. The subclavian vein is inspected and dissected from any surrounding perivenous fibrosis if present.

It is critical that the first rib be resected at its junction with the sternum. To accomplish this, it is sometimes helpful to make a small counterincision just beneath the clavicle. The pectoralis major and minor fibers are separated and the rib is identified. The remainder of the surface of the rib is then dissected with a periosteal elevator while care is taken to note the location of the subclavian vein. This requires resection of a portion of the subclavius muscle. After the rib is dissected thoroughly, it is resected up to the sternal junction. The scalene fat pad is reattached with interrupted 3-0 Vicryl suture. A Blake drain is placed routinely because of lymphatic leak, and the platysma and skin are closed.

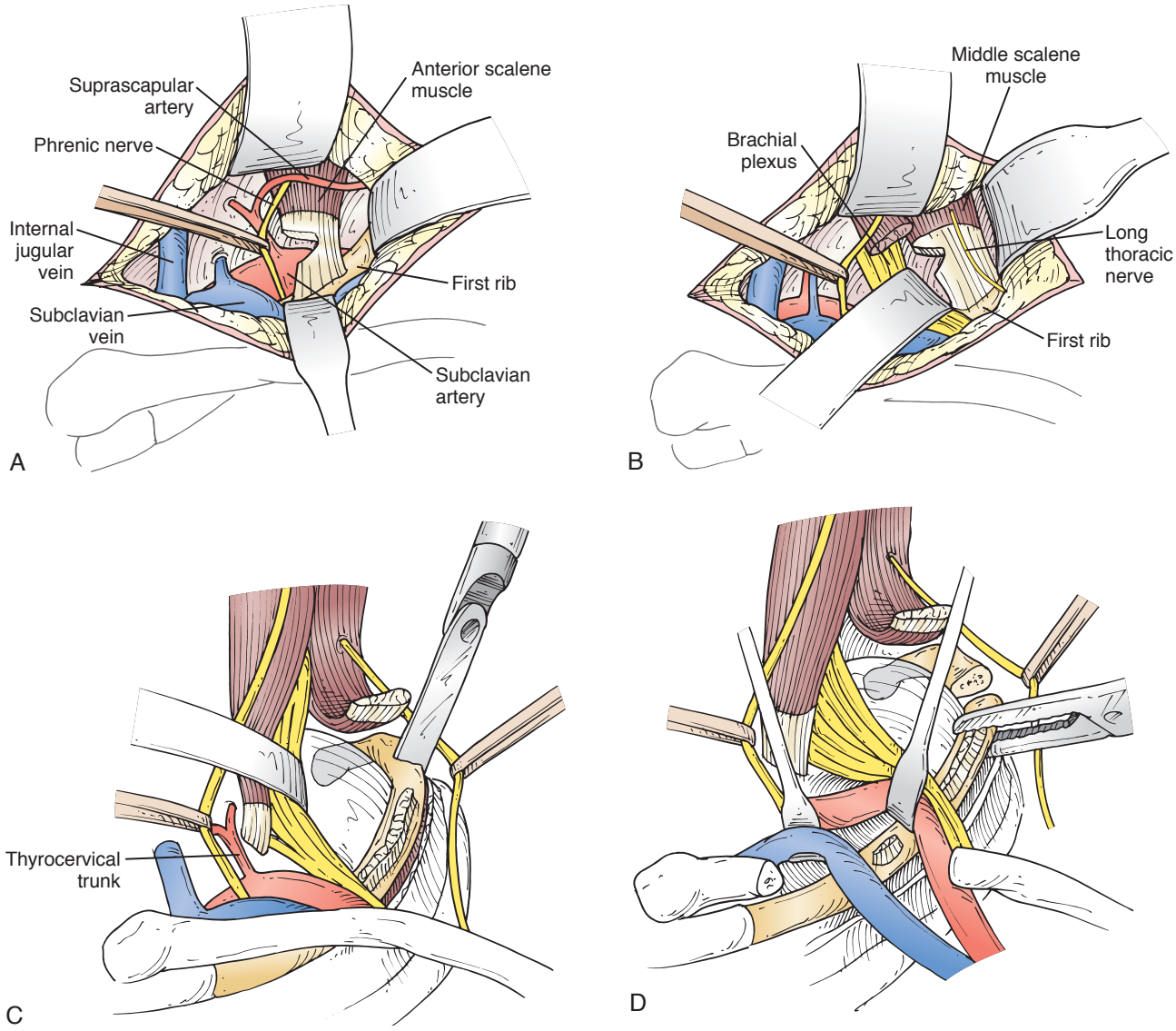

Figure 124.2 (A) Operative view of the supraclavicular approach to thoracic outlet decompression. After mobilization of the scalene fat pad, the phrenic nerve should be identified and carefully elevated before the anterior scalene muscle is divided. (B) The long thoracic nerve should be identified and protected during division of the middle scalene muscle. (C) Attachments are freed by an extraperiosteal approach to prevent recurrent symptoms from reossification of the periosteal bed. (D) Division of the first rib should be performed under direct vision to minimize the possibility of damage to the brachial plexus. After the first rib is divided just distal to the tubercle, the divided rib can be held as a lever to aid in clearing the overlying vessels. (From Valentine RJ, Wind GG. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003.)

Transaxillary Approach

Several groups prefer the transaxillary surgical approach and have reported excellent results when it was used for first rib resection, scalenectomy, and venolysis.[7,14,15] The patient is positioned in the lateral decubitus position with a beanbag used for support. The legs and body are padded accordingly. An axillary roll is created and positioned under the patient.

The axillary hair is clipped and the entire arm, axilla, and shoulder are prepped into the field. The hand is placed in a stockinette that is extended just above the level of the elbow. The arm is wrapped with two Kerlex gauze wraps to provide additional padding. White terry cloth towels are placed in the Machleder retractor to pad it (see Fig. 121.5). The arm is then secured to the retractor using a Coban wrap. If a Machleder retractor is not available, a strong assistant at the 90-degree angle can hold the arm. To open the axillary space during dissection, the assistant should be placed on two steps (see Fig. 121.5).

The external landmarks are identified and marked on the skin, including the pectoralis major and latissimus dorsi muscles. A transverse incision is made just above the inferior aspect of the hairline between the two muscles. The subcutaneous tissue is dissected down to the chest wall. Placement of a Weitlaner

or cerebellar retractor allows the field to be held open during the dissection down to the chest wall. Once the avascular space over the chest wall has been entered, the arm is elevated with the Machleder retractor or by the assistant. The connective tissue over the thoracic outlet is bluntly dissected with a Kittner. A lighted retractor and a Dever are used to open up the anterior and posterior aspects of the field.

The subclavian vein, anterior scalene muscle, subclavian artery, and inferior nerve root are dissected in that order, using a Kittner. A large periosteal elevator is used to free up the intercostal muscle fibers along the lateral aspect of the rib and lift the middle scalene muscle fibers off the first rib. A smaller periosteal elevator is used to separate the pleura from the inferior aspect of the rib. A right-angle clamp is passed posteriorly to the anterior scalene muscle and the muscle is divided sharply as high as possible (see Fig. 121.6A). The phrenic nerve is rarely encountered through the transaxillary approach because it typically separates from the anterior scalene muscle and enters the chest above where the anterior scalene muscle inserts on the first rib. The entire anterior scalene muscle does not have to be divided at once and dividing the muscle slowly allows the surgeon to make sure that no surrounding structures are injured. The subclavius tendon is divided sharply, with care taken not to injure the subclavian vein.

If a cervical rib is present, the periosteal elevator is used to remove any muscle fibers from the rib. A right-angle clamp is passed under the rib and used to separate any additional medial attachment to the first rib. The anterior aspect of the first rib is transected with a Bethune rib cutter; this allows the rib to lift up from the pleura and act as a lever for cutting the posterior aspect. The rib is then cut posteriorly (see Fig. 121.6C). It is important that the rib be cut behind the nerve root but that the nerve not be injured during the cutting of the rib. This may require the rib to be cut more than once. The cervical rib is also cut with the rib cutter. A first-rib rongeur is used to remove any residual rib anterior to the sternum and posterior to the vertebra. Sterile saline is instilled into the wound and a Valsalva maneuver is performed to test for a pleural leak. The axillary space is closed in two layers of absorbable suture. The skin is also closed with absorbable suture.

Infraclavicular Approach

The infraclavicular approach is used to treat vTOS only. Only the anterior portion of the rib is removed during this approach, which enables control of the vein for patch venoplasty. In Molina and colleagues' relatively large series of 114 patients who underwent treatment for venous TOS, all thoracic outlet decompressions were performed through an infraclavicular-only approach.[8] This approach is well described and involves partial resection of the anterior half of the first rib, removal of the subclavius tendon, and division of both the anterior scalene tendon and part of the middle scalene muscle to the level of the subclavian artery. In this series, all patients underwent vein patch angioplasty of the subclavian vein with a segment of harvested great saphenous vein (Fig. 124.3). Of note, in 12 patients found to have long (>2 cm) stenoses, transmanubrial extension of the incision was performed. This consisted of extending the incision medially across the sternum to the midline and then angling 90 degrees up toward the sternal notch. These select patients were then managed with 6 weeks of postoperative arm immobilization. Angioplasty plus stent placement was used as an alternative strategy in seven patients with residual stenoses not amenable to local patch angioplasty. In this small group of patients, all stents were reported to remain patent on duplex follow-up (mean follow-up of 14 years). To date, this remains the largest published experience of central vein stenting after thoracic outlet decompression.

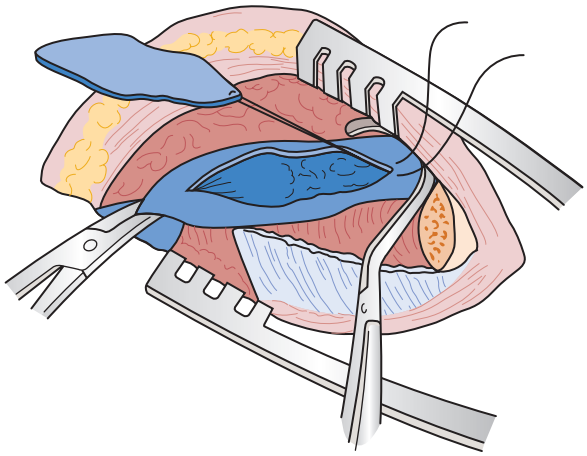

Figure 124.3 Infraclavicular Approach. The saphenous vein patch is laid over the strictured segment of the vein. The key to success is complete mobilization of the subclavian vein by detaching it anteriorly from the sternum until the vein is easily exposed in the operative field. This allows sufficient margin for placement of the medial clamp between the site of the stricture and the normal innominate vein. (From Molina JE, Hunter DW, Dietz CA. Paget-Schroetter syndrome treated with thrombolytics and immediate surgery. *J Vasc Surg.* 2007;45:328-334.)

POSTOPERATIVE CARE AND REHABILITATION

The type of TOS that is treated dictates the postoperative course regardless of which surgical approach is chosen, and appropriate physical therapy after surgery can prevent many long-term complications, such as brachial plexus entrapment in scar tissue.

Pain Management

Prior to surgical closure, the area is generously anesthetized with local anesthetic. A combination of long-acting bupivacaine and shorter-acting lidocaine is used. The addition of ketorolac can greatly improve patients' postoperative pain as well. Narcotic pain medication may be required for a short time in patients with arterial or venous TOS.

Patients with nTOS may have been treated with narcotics prior to surgery and therefore have a higher tolerance to pain. These patients may require narcotic pain relief through their physical therapy as well. The addition of gabapentin may help some patients, but overall it has not been effective at relieving symptoms in these patients long term.

Physical Therapy

Patients with aTOS and nTOS who undergo surgical decompression should start physical therapy (PT) within 7 to 10 days. Patients with vTOS should start PT after complete postoperative treatment of the subclavian vein. The same TOS-specific preoperative PT protocol used in patients with nTOS may also be used postoperatively for all types of TOS with the addition of soft tissue mobilization of the scar. The minimum duration of PT should be 6 weeks; however, this may extend to several months in nTOS patients with longstanding preoperative symptoms. It is important to have a strong working relationship with the physical therapist and an understanding that patients should not be "fast tracked" through the 6-week protocol. Without adequate PT, severely fibrotic scar develops in the surgical field. This results in tethering of the brachial plexus and the development of recurrent symptoms.[16] Patients should not be released from PT early simply because they demonstrate the ability to have full range of motion. This cannot be overly stressed in young high-level athletes. In order for them to return to full function in their sport, a slow and consistent approach to recovery is essential.

Follow-Up

Routine follow-up for all patients is 7 to 10 days after surgery. At this time the wound should be checked for adequate healing without infection. Patients with drains left in place should have them removed. Patients who have undergone venous or arterial bypass with a prosthetic conduit should have a duplex ultrasound of the graft. This serves as a baseline of comparison for identifying any subsequent stenosis in the graft. Finally, patients should be evaluated for adequate postoperative pain control in anticipation of PT.

Further follow-up is tailored to each patient's condition. VTOS patients who do not require vascular reconstruction or venoplasty are asked to return should their symptoms recur. When mild venous dilation is required, patients are left on anticoagulation for an additional 4 weeks and brought back for duplex ultrasound of the vein at that time. If the vein is patent without thrombosis or stenosis, anticoagulation may be stopped and follow-up is required only for recurrent symptoms. In patients who have extended residual subclavian vein thrombus and stenosis on postoperative venography, anticoagulation is continued for 6 to 8 weeks and patients are brought back at that time for duplex ultrasound. If the ultrasound shows persistent stenosis and thrombus, anticoagulation is continued and the patient is reevaluated at 2-month intervals with duplex ultrasound to assess patency of the vein. Again, even in patients with thrombosis, continuous anticoagulation for up to 1 year may allow for favorable recanalization and patency of the vein. If patency is not established in this time frame, the likelihood of the vein opening is less than 10%.[17]

Patients with aTOS who undergo subclavian artery bypass should be followed long term for possible graft stenosis. Although a specific regimen for upper extremity duplex ultrasound graft surveillance has not been established, acute occlusion of bypass grafts due to unrecognized stenosis can be devastating. In the first year, patients are seen at 3- to 6-month intervals to discuss symptoms of arm claudication or pain with use, and a duplex ultrasound is performed to evaluate for possible stenosis. With normal ultrasound findings, surveillance can be extended to longer intervals from 12 to 18 months.

PITFALLS AND COMPLICATIONS

Complications are best avoided with a solid patient selection algorithm, meticulous surgical technique, and appropriate postoperative treatment protocols.

General

Appropriate patient selection for surgical treatment, especially in nTOS, cannot be overemphasized and plays a central role in achieving successful outcomes. Although decompression surgery can be relatively straightforward, it should be avoided at all costs when a patient is not likely to have improvement in symptoms. Studies comparing outcomes for nTOS have found that older patients with longer preoperative symptomatology are more likely to have unresolved symptoms postoperatively. In addition, patients who smoke, have concomitant neck and shoulder injuries, and have other chronic pain syndromes are more likely to have residual symptoms after surgery.[16] Although many patients come with the mindset that surgical treatment will completely relieve their symptoms, a step-by-step approach for each patient should be carried out. This is especially true when patients have been seen by multiple specialists or have had numerous outside treatments. In all patients, reasonable activity expectations should be set. Patients with the previously mentioned comorbidities should be counseled to understand that surgery will not return them to a prior "normal" state. It is also important for patients with long-term nTOS to understand that even after surgery, activity limitations must be observed in order to prevent recurrent symptoms. This includes limitations of heavy lifting or strenuous upper extremity physical activity. When expectations and future limitations are explicitly laid out, patients will hopefully better understand the chronicity of nTOS and the dedication to long-term treatment that is needed.

Scar tissue after surgery is inevitable, but in some patients the scar becomes the nidus of postoperative pain. This is especially true for patients that do not undertake appropriate postoperative PT. It is imperative for patients to understand that there is no quick return to activity after surgery. Because vTOS patients may be healthy and athletic, therapists will occasionally "fast track" them through the 6-week protocol after surgery. This should be avoided, as patients may be noncompliant with the performance of therapy and exercises on their own. Supervised therapy for at least 6 to 8 weeks ensures the best possible outcome for all patients and improves their ability to return to activity as pain free and symptom free as possible. In patients with nTOS who have had long-term symptoms, the postoperative protocol may have to be extended to make sure that the neck and shoulder muscles previously injured for years are adequately worked and loosened.

Specific Surgical Complications

Meticulous operative technique and an understanding of anatomic aberrations help to avoid complications. Injury to the neurovascular bundle of the thoracic outlet is avoided by meticulous dissection in an anterior-to-posterior fashion and additionally by making sure that each structure is identified prior to cutting the muscles or the rib. Small arterial or venous branches can easily be injured with aggressive blunt dissection. Use of sharp dissection with Metzenbaum scissors around the artery and vein can help to avoid this. If a small vessel is avulsed or cut, closure should be accomplished with a 5-0 or 6-0 nonabsorbable monofilament suture.

Nerve injury after first rib resection is devastating. Rarely are the brachial plexus nerves cut during dissection if all structures are identified early, but stretch on the inferior nerve can occur with aggressive retraction in order to visualize the posterior aspect of the first rib. The risk is less severe with the transaxillary approach but injury still can occur. Postoperative pain from nerve stretch after surgery can last 3 to 9 months and be severely debilitating. From the supraclavicular approach, this is avoided by retracting the middle scalene muscle in order to visualize the posterior rib. The transaxillary approach is less likely to cause a stretch type of injury since the nerve is elevated off the rib but not retracted during rib cutting. Visualization of the tips of the rib cutter in the transaxillary approach by the surgeon ensures that the nerve is not inadvertently cut. If the nerve is cut during the surgical rib resection, intraoperative consultation should be obtained. Outcomes are best if the repair is performed early, although this can still be devastating. Stretch neuropathy after surgery can be managed with oral analgesia and should resolve in time.

When the rib is adherent to the pleura, a small pleural tear may result in a pneumothorax. If there is an injury to the visceral pleura, a small 12-Fr chest tube can be placed and left in place until any air leak resolves. If only the parietal pleura is injured, a flat Jackson-Pratt or round Blake drain may be inserted through the pleural tear and connected to a pleural vac. This is left in place overnight and removed the next day. If the patient is seated in the upright position (as in the supraclavicular approach), a red rubber catheter can be placed into the pleural tear with the opposite end placed under water. The air can be evacuated by Valsalva maneuvers prior to allowing the scalene fat pad to drop down and seal the pleural tear, thus avoiding the need for a chest drain.

Lymphatic leak may occur with the supraclavicular and infraclavicular approaches. Injury to the thoracic duct as it enters the posterior aspect of the subclavian vein can result in a leak of several hundred milliliters per day. Again, meticulous dissection and attention to the posterior vein can help to prevent this. Avoiding blunt dissection in this area is also essential. Repeat exploration to repair the lymph leak can be difficult. The application of a sealant product at reexploration is not usually effective when the lymphatic leak is large. Keeping the drain in place, making the patient NPO, and placing him or her on parenteral nutrition for high-output leaks allows the area to scar down over a period of 7 to 14 days.

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Scher LA, Veith FJ, Haimovici H, et al. Staging of arterial complications of cervical rib: guidelines for surgical management. *Surgery*. 1984;95(6):644–649.

This study established the arterial classification system for subclavian artery pathology due to cervical ribs. It established early treatment recommendations based on the severity of arterial injury.

Schneider DB, Dimuzio PJ, Martin ND, et al. Combination treatment of venous thoracic outlet syndrome: open surgical decompression and intraoperative angioplasty. *J Vasc Surg*. 2004;40(4):599–603.

This study was the first to report outcomes after decompression and intraoperative treatment of the diseased subclavian vein. It showed that intraoperative venoplasty could be done at the same time and that it did not lead to increased complications.

Molina JE, Hunter DW, Dietz CA. Paget-Schroetter syndrome treated with thrombolytics and immediate surgery. *J Vasc Surg*. 2007;45(2):328–334.

This study demonstrated that patients that underwent thrombolysis could have early surgery without increased complications. The authors were the first to report on a large number of patients with acute symptoms that underwent expedited resection, which lead to improved outcomes.

Rochlin DH, Likes KC, Gilson MM, Christo PJ, Freischlag JA. Management of unresolved, recurrent, and/or contralateral neurogenic symptoms in patients following first rib resection and scalenectomy. *J Vasc Surg*. 2012;56(4):1061–1067.

This study serves at the definitive paper on how to manage the challenge of patients with nTOS that have recurrent symptoms. While this is a very challenging group, the authors found specific indications for repeat surgery.

A complete reference list can be found online at ExpertConsult.com.

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125 CHAPTER

Renovascular Disease: Pathophysiology, Epidemiology, Clinical Presentation, and Medical Management

ASHLEY K. RICKEY and RANDOLPH L. GEARY

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Renovascular disease (RVD) encompasses a range of disorders that affect renal artery structure and kidney blood flow. The primary importance of RVD relates to associated hypertension (HTN) and loss of renal excretory function, which in turn contribute to cardiovascular morbidity, dialysis dependence, and death.[1-5] The most common pathology and major focus of the present chapter is atherosclerotic renal artery stenosis (RAS), which can be found in up to 7% of elderly individuals in the United States (Fig. 125.1).[1] Less common etiologies include renal artery fibromuscular dysplasia (FMD)[6] (see Chapter 142); dissection, aneurysms, and trauma (see Chapters 128 and 129)[7]; arteritis (see Chapter 139); and developmental abnormalities of the middle aorta and its branches (see Chapter 130).[8,9]

HISTORICAL PERSPECTIVE

Late in the 19th century Tigerstedt and Bergman isolated a substance from rabbit kidneys they called "renin" that when infused into control animals elevated their blood pressure (BP).[10] Decades later experiments would link reduced kidney blood

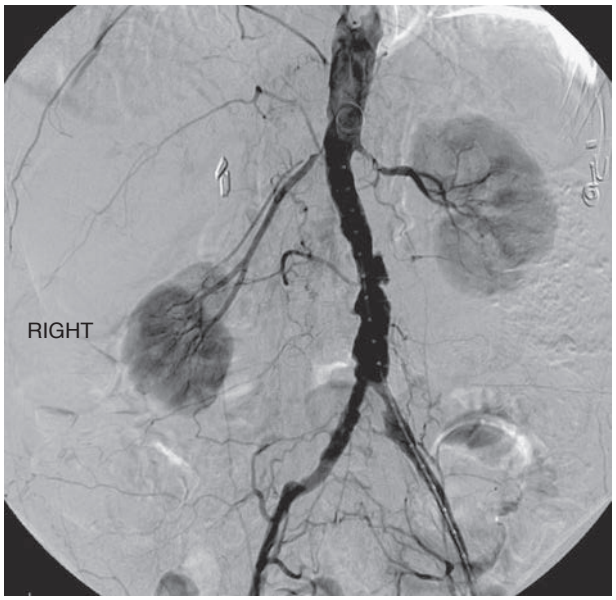

Figure 125.1 Digital subtraction angiogram illustrating bilateral atherosclerotic renal artery stenosis.

flow to elevated BP, and Goldblatt's landmark experiments in the 1930s would show that HTN from RAS could be reversed by correcting the stenosis or by removing the ipsilateral kidney.[11] These studies laid the foundation for research that would eventually define components of the renin-angiotensin-aldosterone system (RAAS) as biochemical mediators of BP regulation.

In 1938 Leadbetter reported that removing an ischemic ectopic kidney normalized BP in a child with severe HTN.[12] Nephrectomy was later popularized for the treatment of adults with uncontrolled HTN attributed to RVD, but results were inconsistent, as it was difficult to predict the impact of nephrectomy on BP control and on renal function.[13]

Successful renal artery reconstruction was first reported by Freeman in 1954, who treated a patient with bilateral ostial RAS and uncontrolled HTN, and in whom the BP normalized following endarterectomy.[14] As surgeons gained experience with open renal artery reconstruction for HTN, reports emerged that revascularization could also improve renal excretory function.[15-20] Dean and others coined the term *ischemic nephropathy* to describe renal insufficiency resulting from RAS or occlusion and explored the limits of renal salvage with provocative reports of patients removed from dialysis after revascularization.[15-20] As open renal revascularization was refined, the use of nephrectomy was largely abandoned.

Open revascularization proved effective at improving HTN, but not every patient benefited. Surgery carried significant risk, particularly in the elderly, with advanced atherosclerosis and ischemic nephropathy. In a series of 500 patients undergoing open renal reconstruction for atherosclerotic RAS at Wake Forest, the 30-day mortality was 4.6% and was 7% in the subset with ischemic nephropathy.[21,22] Mortality for 6608 renal bypass patients across a broad range of hospitals was 10% based on the U.S. National Inpatient Sample from 2000 to 2004.[23] Surgery improved BP in up to 85% of patients but in 15% BP was no better or worse.[21] Greater experience with open revascularization demonstrated that the major benefit in terms of improving survival related to the impact of surgery on renal function rather than HTN.[21,22] If estimated glomerular filtration rate (eGFR) stabilized or improved after surgery, then patients demonstrated improved dialysis-free survival, independent of the impact on HTN.[21,22]

Less invasive approaches to the management of RVD were developed in parallel with the emergence of new classes of antihypertensive agents that greatly reduced the number of patients requiring revascularization for refractory HTN.[24,25] Balloon angioplasty catheters were first used to treat RAS by Gruntzig et al. in the 1970s.[26] An increase in the number of patients treated for atherosclerotic RAS followed, but results were tempered by high rates of restenosis. Within a decade, however, balloon-expandable stents were developed that reduced renal restenosis rates substantially.[27-29] What followed was an explosion in renal stenting that rapidly reduced the number of open renal reconstructions. Statistics in the United States from 2000 showed that 21,000 renal revascularization procedures were performed under Medicare,[30] while the number of open reconstructions fell by 30% from 2000 to 2004.[23] As a result, open renal artery reconstruction has become uncommon in contemporary vascular surgery practice, except in centers with a particular interest in RVD.

Novelty often drives application of new technology, and renal stenting was employed enthusiastically prior to rigorous studies.[30] Only recently have large prospective randomized clinical trials compared stenting with medical management in atherosclerotic RAS, and have found no clear advantage for stenting.[31-34] These trials have shortcomings, and many patients included in these trials (e.g., ASTRAL and CORAL) would not have met the threshold for intervention at our center and others (see Chapter 127), but the impact of these trials has been to appropriately (in our opinion) limit application of stenting to select subsets of patients with atherosclerotic RVD. Few studies have directly compared open renal revascularization with medical management, angioplasty, or stenting, and all were too small to provide meaningful guidance.[35-37] Therefore the application of open surgery in RVD is guided largely by single center cohort studies and expert opinion (discussed later).

PATHOGENESIS OF RENOVASCULAR DISEASE

Etiology of Renal Artery Lesions

More than 90% of patients referred for renal artery stenting have atherosclerotic lesions.[38,39] In 840 patients undergoing open renal revascularization at our institution, 81% had atherosclerotic lesions, 14% FMD, and 1% dissection. The other 3% were children with hypoplastic renal arteries, midaortic syndrome, or dissection.

Atherosclerotic RVD is typically most severe at the renal artery ostia, but stenosis may occur at any level, including small

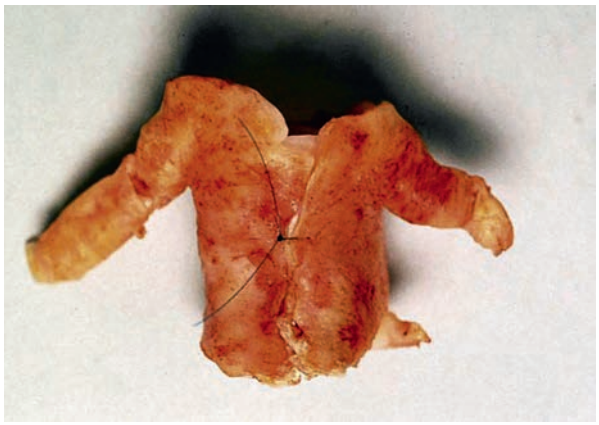

Figure 125.2 Operative specimen from transaortic sleeve endarterectomy illustrating ostial renal artery plaque extending perpendicular to a contiguous sleeve of calcified aortic plaque.

intraparenchymal branches.[40,41] Ostial lesions are typically contiguous with a sheet of aortic plaque oriented perpendicular to the renal artery (Fig. 125.2). This sheet is often heavily calcified and resistant to simple balloon dilation and more effectively overcome with balloon-mounted stents, which have become the standard endovascular approach.[28,38]

FMD in contrast typically affects the main renal artery and its branches away from the ostia (see Chapter 142).[6] In adults, FMD often creates a series of web-like stenoses, alternating with segments of normal or dilated lumen caliber, giving rise to the classic "string of beads" morphology typical of the medial fibroplasia subtype. Renal FMD in children is more often the intimal fibroplasia subtype and less likely to cause this stereotypical angiographic appearance.

Dissection of the renal arteries can be spontaneous or caused by blunt or penetrating trauma, endovascular manipulation (e.g., guide wires and catheters), severe HTN, or by renal artery wall pathology, such as FMD. Renal dissection often originates from aortic dissection that can obstruct the ostia with flaps or extend out the renal artery and branches. Dissection can result in acute occlusion or thrombosis of the renal artery with infarction of the kidney. Dissections may extend into the kidney parenchyma, limiting options for revascularization, and as they heal, dissections may create stenosis or aneurysmal degeneration (see Chapter 128).

Less common renal artery pathologies include the various arteritides and congenital syndromes covered elsewhere in this text (see Chapters 130 and 137, Chapter 139, Chapter 140, and Chapter 142).

Pathophysiology of Renovascular Hypertension

HTN in response to RVD results from a complex cascade of molecular and cellular events precipitated by hypoperfusion of one or both kidneys. A flow-limiting RAS creates a pressure drop sensed downstream by juxtaglomerular cells that then respond by releasing renin into the systemic circulation in an attempt to normalize sensed BP.[42] Renin catalyzes cleavage of angiotensinogen to form the decapeptide angiotensin I, which is then cleaved in the pulmonary circulation by angiotensin converting enzyme (ACE) to form the octapeptide angiotensin II (Ang II).[43] Circulating Ang II is then the primary effector of renin-mediated increases in systemic BP, promoting peripheral vasoconstriction and blood volume expansion.[43,44]

Ang II acts on a variety of cell-types through specific G protein–coupled receptors designated ATR1 and ATR2.[45] Ligation of ATR1 activates intracellular pathways that promote vasoconstriction and mitogenic responses within the vessel wall and myocardium.[43-46] In addition to direct vasoconstrictor activity, Ang II indirectly promotes vasoconstriction by upregulating expression of norepinephrine and endothelin-1.[45] ATR1 signaling also leads to formation of reactive oxygen species that can inactivate the vasodilator nitric oxide. Cross-talk between ATR1 and other receptors (e.g., growth factor-activated receptor tyrosine kinases) amplifies smooth muscle cell vasoconstrictor and proliferative signaling pathways.[45,46]

Fluid retention also contributes to renovascular HTN. Ang II acts directly on renal tubules to promote sodium and water reabsorption[47] but also stimulates adrenal release of aldosterone, a potent mediator of renal tubular sodium reabsorption.[48] Adaptive responses can limit volume expansion in patients with unilateral RAS as the contralateral normal kidney mounts a compensatory natriuresis.[11,49,50] Patients with bilateral RAS or RAS in a solitary kidney cannot compensate, resulting in so-called Goldblatt "volume-dependent" renovascular HTN, which can be severe.[11] The RAAS also contributes to HTN by acting on specific regions of the brain responsible for autonomic control of BP or by release of vasopressin from the pituitary to promote thirst and water reabsorption.[50,51]

While renovascular HTN is initially mediated by activation of the RAAS, chronic structural changes sustain and amplify the problem.[52,53] Longstanding HTN causes chronic tangential vessel wall strain that promotes hypertrophic remodeling in the myocardium and resistance vessels, a response likely amplified by mitogenic effects from Ang II excess. Wall thickening, stiffening, and amplified mechanical leverage in constrictor function characterize a remodeled vasculature that promotes cardiovascular embarrassment, even after RAS is corrected.[52-53] Structural changes in RVD are distinct from those observed in essential HTN in which resistance vessels exhibit eutrophic remodeling, with little change in wall mass. Hypertrophic remodeling in RVD may be reversed over time with inhibition of the RAAS (e.g., ACE inhibition).[52]

Pathophysiology of Ischemic Nephropathy

Ischemic nephropathy refers to loss of renal excretory function attributed to RVD, but its molecular and cellular basis are incompletely understood.[53,54] The kidney lacks significant collateral arterial flow, so acute renal artery occlusion generally leads to kidney infarction within minutes to hours. In contrast, the kidney adapts to a broad variation in pressure, preserving parenchymal oxygenation and glomerular filtration. Chronic hypoperfusion eventually impairs kidney function through a number of mechanisms, some of which are irreversible. Severe

hypoperfusion drops glomerular filtration pressure and leads to ischemic damage.[53,54] Chronic excess Ang II and aldosterone promote expression of profibrotic cytokines and growth factors, including transforming growth factor-β, a master regulator of extracellular matrix production, and platelet-derived growth factor, a potent mitogen for smooth muscle cells, renal fibroblasts, and glomerular mesangial cells.[53-55] Ang II also induces nuclear factor-κB, a potent master switch for proinflammatory pathways. Each of these contributes to glomerulosclerosis and tubulointerstitial injury.[53-57] Atherosclerotic lesions themselves may contribute to loss of excretory function by chronically releasing microembolic debris.[58-61] If perfusion is severely compromised, the renal parenchyma will become hypoxic, with resulting ischemic injury and inflammatory infiltration associated proinflammatory cytokine release, but the contribution of frank ischemic necrosis to renal parenchymal atrophy is less well-established.[53,54]

In the setting of unilateral RAS, the opposite kidney may suffer injury directly from compensatory systemic HTN, which persists despite medical control of HTN or renal revascularization. The etiology of chronic kidney disease is often complex and multifactorial, particularly in patients with established atherosclerosis[53,54,62] where risk factors overlap significantly with those for medical renal disease, including diabetes, hyperlipidemia, essential HTN, smoking, and others. So as with HTN, many patients with atherosclerotic RAS may have other factors contributing to renal insufficiency.

EPIDEMIOLOGY

While animal experiments and clinical experience have proven that reduced kidney blood flow can cause renin-mediated HTN, loss of excretory function, kidney atrophy, and even infarction, many individuals found to have RAS on imaging will be asymptomatic or have minimal change.[1-3] These individuals have "anatomic" disease that is "functionally" silent, because their lesions are hemodynamically inconsequential, their intrinsic adaptive responses are robust enough to maintain BP and glomerular filtration, or the ipsilateral kidney may be so damaged that it is incapable of significant renin release.[3,53]

Attributing clinical impact to a particular renal artery lesion is further confounded by the high prevalence of essential HTN and intrinsic kidney disease among individuals with atherosclerosis.[1,3] Provocative tests and chemical assays have been of limited value in helping prove a particular renal lesion is driving HTN or renal dysfunction. This creates the awkward dilemma that in order to prove a particular RAS will respond to reconstruction with improved BP and renal function, one often has to first do the reconstruction. Thus the prevalence of RVD defined by imaging alone overestimates the prevalence of a disease that will benefit from intervention.

Prevalence of Renovascular Disease

No studies have measured the prevalence and natural history of RAS in the general population, and the majority of estimates come from screening of high-risk cohorts (see below and Table 125.1). To address this, Hansen and colleagues used renal duplex ultrasonography (RDU) to screen 870 individuals for RAS without regard to BP or renal function.[1] Subjects were recruited within the Community Health Study (CHS), an NIH-sponsored prospective analysis of individuals 65 and older living independently in the community. Subjects were screened for CV disease at enrollment and then monitored for incident disease over time. The prevalence of a hemodynamically significant RAS at baseline was 7%, of which one in eight had bilateral disease, so a significant number of relatively healthy older individuals in the United States have undiagnosed RAS.[1] This study also highlights the high rate of essential HTN found in older adults, as 50% with normal RDU had elevated BP versus 72% of those with RAS. Therefore many individuals with RVD likely had HTN unrelated to their stenosis, and 28% were normotensive.[1,3] The vast majority of subjects in both groups had normal renal function, but creatinine was more likely elevated in those with RAS (16% vs. 8%).[3,62]

The prevalence of RAS has also been estimated from autopsy series. Schwartz and White examined 154 consecutive cases and reported RAS in 6% of individuals <55 years of age and 40% of those >75. Approximately half had bilateral lesions.[40] In another series of 295 autopsies, Holley reported 22% had

TABLE 125.1 Prevalence of Renal Artery Stenosis in High-Risk Populations

Series	Year	Number of Patients	Risk Factor	Patients With RAS (%)	Comments
Hansen et al.[99]	2002	834	Age >65 years	6.8	Elderly living independently
Jean et al.[65]	1994	196	CAD	22	Suspected CAD, undergoing angiography
Miralles et al.[67]	1998	168	Peripheral arterial disease	40	Aortoiliac occlusive disease
Appel et al.[73]	1995	45	Dialysis	22	New-onset dialysis
Davis et al.[72]	2009	434	Hypertension (adult)	32	—
Lawson et al.[125]	1977	74	Hypertension (children)	78	—
Wu et al[68]	2007	163	Carotid stenosis	20	—

CAD, Coronary artery disease; *RAS*, renal artery stenosis.

significant RAS.[41] The high prevalence of atherosclerotic RVD in autopsy series is certainly impacted by bias toward atherosclerosis as the leading cause of death in developed countries.

Angiographic series have screened for RVD in patients with coronary, carotid, and peripheral artery disease (PAD; see Table 125.1).[63-71] RAS was found in up to 22% of patients undergoing heart catheterization,[63,66] 27% with carotid stenosis,[67-70] and up to 40% with PAD (see Table 125.1).[67,71]

Given the impact of RAS on BP and renal function, its prevalence will be higher in cohorts prescreened for HTN[72] or renal failure. We used RDU to evaluate 629 adults with newly diagnosed HTN and found 25% had significant RAS. This doubled in patients with severe HTN who were over 60 years old. RAS has been reported in 9% to 41% of patients requiring dialysis, but prevalence varies significantly by age, gender, and ethnicity. It is highest in the elderly and surprisingly infrequent among African Americans with end-stage renal disease.[73-77]

Natural History of Renal Artery Stenosis

Anatomic Progression

Understanding the natural history of RAS is critical in order to properly balance risks and benefits of various treatment options. Older studies used serial arteriography to monitor the severity of stenosis and reported progression in 11% to 35% of lesions managed medically.[78-81] Arteries with severe baseline stenosis went on to occlude in 10% of individuals.[78,80] Zierler employed serial RDU to follow 80 patients with established renovascular HTN after classifying baseline stenosis for each artery as >60%, <60%, or normal.[82] After 3 years, 8% of normal arteries and 43% with <60% stenosis had progressed to a high-grade stenosis, and 7% with >60% stenosis at baseline went on to occlude. Factors associated with progression included age, systolic BP, smoking, female gender, and poorly controlled HTN.[82]

Functional Progression

Chronic activation of the RAAS, severe HTN, and impaired renal excretory function each contribute to cardiovascular morbidity, dialysis, and death. This relationship provides the rationale for treatment of RAS.

Loss of functioning nephrons is accompanied by a rise in serum creatinine and fall in eGFR, although an individual must lose more than half of functioning nephron mass before creatinine rises. So surrogates for loss of kidney function, such as kidney shrinkage, can be valuable in understanding the progressive impact of RVD. Kidney atrophy can be assessed with RDU and cross-sectional imaging as loss of kidney length, cortical thickness, or volume. Schreiber reported a significant loss of renal function over time in patients with RAS, regardless of whether the degree of stenosis progressed,[79] and Dean randomized 41 patients with RAS and severe HTN to medical management and found 46% had a significant rise in serum creatinine while 37% showed loss of kidney length on follow-up.[78] In a prospective study of 122 patients with renovascular HTN, Caps reported that 21% of kidneys ipsilateral to >60% RAS lost more than 1 cm in length at 2 years with an increase in creatinine, and that atrophy correlated with degree of stenosis and systolic BP.[83] Others have also documented shrinking kidneys and loss of excretory function in patients with RAS,[84,85] and progression to dialysis has been reported in 7% to 12% of patients managed medically within 3 to 4 years.[84,85]

In contrast, none of the subjects that had >60% RAS at baseline that were followed prospectively in the CHS substudy (described previously) progressed to complete occlusion at a mean follow-up of 8 years.[86] However, nine kidneys with normal renal arteries at baseline went on to develop critical RAS, including one complete occlusion. In this relatively healthy cohort, enrolled independent of HTN or renal dysfunction, the rate of progression was 4%, far below the previously mentioned series in patients preselected for severe concomitant HTN.

Taken together, these studies demonstrate that progression of RAS is less likely in low-risk patients in whom lesions are found incidentally,[1,3] but that loss of renal mass and function are common in older patients with high-grade RAS and severe HTN.

Associated Morbidity

RAS has been associated with cardiovascular morbidity and mortality, and progression to dialysis. Risk of end-organ damage is much higher in patients with atherosclerotic RAS compared with patients with essential HTN, as measured by left ventricular hypertrophy, elevated serum creatinine, and proteinuria.[87] Mailloux projected that RVD accounts for 10% to 18% of incident dialysis dependence among the elderly,[75] and others have associated RAS with cardiovascular events, including stroke and perioperative complications.[71,87,88] Conlon showed that among 1235 patients with coronary artery disease (CAD) on angiography, the 4-year survival was significantly lower in those with concomitant RAS (67% vs. 88%). Increased mortality was attributed mostly to excess cardiovascular events.[89] Edwards reported that the incidence of new coronary events among 870 CHS participants was twice as high in those with RAS after only 14 months follow-up, and the association remained significant after controlling for HTN and preexisting cardiovascular disease.[2]

CLINICAL PRESENTATION

History and Physical Examination

The high volume of cross-sectional imaging employed in contemporary medicine has resulted in a large number of patients being referred for RAS found incidentally. The most common indications for referral to our vascular laboratory for RDU screening are severe HTN (e.g., resistant to three or more medications); unexplained renal insufficiency in patients with risk factors for RVD; and regular surveillance of patients with known RVD or for patients with prior renal revascularization. In addition, all children with unexplained HTN should be screened for RVD, and practitioners should be reminded that definitions of HTN in children are far lower than in adults (e.g., a systolic BP of 110 mm Hg is 99th percentile for a 1-year-old child).[90,91]

TABLE 125.2 Demographics of Patients Undergoing Open Renal Revascularization

Parameter	Value
Age	65 ± 9 years
Gender	49% male, 51% female
Systolic BP	200 ± 35 mm Hg
Diastolic BP	104 ± 21 mm Hg
Number of antihypertensive medications	2.6 ± 1.1
Creatinine concentration (mean)	2.6 mg/dL (230 µmol/L)
Comorbid extrarenal atherosclerosis	90%
Coexisting coronary artery disease	70%
Diabetes	16%

BP, Blood pressure.

HTN associated with critical RAS is typically more severe and refractory to medical therapy than essential HTN.[3,21] For example, in 500 patients with atherosclerotic RAS treated with open renal revascularization at Wake Forest, the mean preoperative systolic and diastolic pressures were 200 mm Hg and 104 mm Hg, respectively, on an average of three antihypertensive medications (additional demographics in Table 125.2).[21]

Advanced age, atherosclerosis risk factors, or a history of coronary, carotid, or peripheral arterial disease should raise suspicion in adults with severe HTN. Patients with RAS can have impaired renal function, but the etiology is often multifactorial. Ischemic nephropathy caused by RAS in our experience is nearly always associated with severe HTN.[20,21] Renal insufficiency in patients with only mild or moderate HTN typically have medical disease unlikely to stabilize or improve with renal revascularization.[20] Patients who demonstrate acute renal insufficiency after starting an ACE inhibitor or angiotensin II receptor blockers (ARB) should be screened by RDU for bilateral RAS where both kidneys rely on efferent arteriolar tone mediated by Ang II to maintain glomerular filtration.[92,93]

Individuals with unrecognized or poorly controlled renovascular HTN may present in "hypertensive crisis" with neurologic or cardiovascular embarrassment when HTN is severe (e.g., systolic BP >200 mm Hg).[94] Long-standing HTN leads to left ventricular hypertrophy and abnormal diastolic relaxation. A stiff ventricle then predisposes patients to "flash pulmonary edema" after relatively minor changes in volume status or further increases in BP. Severe HTN also drives fluid into the extravascular space, causing edema and inflammation of various tissues, including the brain. Neurologic manifestations may include headache, visual disturbance, mental status change, acute stroke, or intracranial hemorrhage. HTN can also damage the opposite kidney in patients with unilateral RAS, resulting in proteinuria and elevated serum creatinine that corrects as BP is normalized.[54,94] It is important to allow a patient in this setting to recover before imaging or intervention with iodinated contrast.

On physical examination patients may manifest severe systolic and diastolic HTN, peripheral edema, abdominal bruits, and nonspecific stigmata of atherosclerotic heart and vascular disease. Diminished lower extremity pulses can be found in adults with associated atherosclerotic PAD, Takayasu arteritis, and aortic dissection, while in children decreased lower extremity pulses may indicate aortic coarctation or midaortic syndromes. Differential diagnostic considerations are provided in Table 125.3.

TABLE 125.3 Differential Diagnosis in Patients Evaluated for Renovascular Hypertension

Essential hypertension	Hyperthyroidism
Glomerulonephritis	Coarctation of the aorta
Nephrotic syndrome	Hyperparathyroidism
Primary aldosteronism	Sleep apnea
Cushing syndrome	Increased intracranial pressure
Pheochromocytoma	Volume overload
Carcinoid	

Modified from Lawton WJ, DiBona GF, Kopp UC, Luft FC. Normal blood pressure control and the evaluation of hypertension. In: *Comprehensive Clinical Nephrology*. 5th ed. Philadelphia: Elsevier; 2015:392–406.

Laboratory Findings

Laboratory testing in individuals being evaluated for HTN may include urinalysis, blood chemistries, fasting blood glucose or hemoglobin A1c, lipid panel, and 12-lead EKG.[95] Although nonspecific, blood urea nitrogen and creatinine concentrations may be elevated in patients with RVD. An electrocardiogram may show a strain pattern and increased voltage consistent with left ventricular wall thickening. Echocardiography can confirm ventricular hypertrophy with impaired diastolic relaxation, and in the pediatric patient can also exclude aortic coarctation. Measuring systemic renin levels in patients with RVD is rarely useful unless combined with invasive selective renal vein renin sampling (see the Renal Vein Renin Assays section that follows). In patients with diabetes, urinary albumin excretion should be measured to assess the extent of intrinsic kidney damage.

Spontaneous hypokalemia (<3.5 mmol/L) or severe hypokalemia after initiating diuretics should raise suspicion for primary hyperaldosteronism (Conn syndrome), which can be confirmed by measuring plasma aldosterone (see Table 125.3).[48,96] These patients also typically manifest a metabolic alkalosis and depressed or unmeasurable plasma renin activity. An incidental finding of adrenal adenoma on abdominal imaging in a patient with refractory HTN should prompt screening for hypersecretion of aldosterone and catecholamines. Patients with catechol-excreting adrenal tumors (pheochromocytoma) may have episodic HTN associated with headache, palpitations, sweating, panic attacks, and pallor. In these patients, paroxysms of HTN can be triggered by starting β-blockers or MAO inhibitors, or by micturition and other activities that increase intraabdominal pressure.[97] Patients with MEN2, neurofibromatosis type-1, and von Hippel-Lindau are also at risk for pheochromocytomas. Diagnostic algorithms are influenced by local expertise, and our preferred screen is a 24-hour urine assay

for fractionated metanephrines and catecholamines. Fractionated plasma metanephrine assays are also commonly employed.

Diagnostic Imaging

Renal Duplex Ultrasonography

RDU is an excellent screening test for RAS (see Chapter 21). When performed by an experienced technologist, a typical study is rapid, noninvasive, accurate, and reproducible. RDU avoids ionizing radiation and iodinated contrast material, does not require intravenous access, is safe in patients with medical implants, and is relatively inexpensive. Thus RDU has become the primary tool in most centers for screening and following patients with RAS.[98] Limitations include that it is technically demanding relative to other studies performed in the average vascular laboratory and thus somewhat operator-dependent, and RDU is also of limited use in characterizing other manifestations of RVD (e.g., aneurysm, dissection, FMD, etc.). Patient factors that can interfere with renal artery insonation include obesity, bowel gas, and excessive resistance from advanced disease within the kidney parenchyma.

In our laboratory the exam begins after an overnight fast with the patient supine. Imaging from the anterior approach, the perirenal aorta is examined for aneurysmal change, stenosis, or occlusion and a peak systolic velocity (PSV) is recorded. Each renal artery is then imaged and velocities and waveforms recorded from proximal, mid-, and distal segments. Patency and phasicity of the renal veins is evaluated using color flow and Doppler. Velocity profiles are recorded within the kidney parenchyma at the superior, mid-, and inferior pole to calculate resistive index (RI) and acceleration times. The exam concludes with the measurement of pole-to-pole kidney lengths.

The accuracy of RDU in detecting significant RAS (e.g., >60%), validated against conventional arteriography, can exceed 90% in experienced hands.[99-102] Criteria used to define a critical stenosis vary, but in our hands a PSV of >200 cm/s in the main renal artery when associated with poststenotic turbulence has proven accurate in defining a >60% stenosis.[99,103,103] Other centers rely on the ratio of renal artery to aortic PSV (RAR) to define a critical RAS (e.g., >3.5),[99,103,104] but in our hands the RAR has been unreliable.[103] Others have proposed different criteria for their laboratories, including slightly higher PSV cutoffs (e.g., 285 cm/s) and higher RAR (e.g., 3.7).[102]

Hilar and parenchymal analyses have been proposed as less complicated approaches to identify an RAS. Blunted waveforms with delayed systolic upstroke are indicative of proximal stenosis. Acceleration times estimate delay in systolic upstroke from onset of systole to its peak, with values exceeding 100 ms, suggesting flow-limiting RAS.[100,103,105] In our hands acceleration time provides a positive predictive value of 97%, but sensitivity is too low to be used alone for screening.[103] The RI has been proposed to screen for RAS but is best suited to identify patients with intrinsic kidney disease. A normal value is <0.7. Values >0.8 may indicate a critical RAS but more often are nonspecific, frequently caused by intrinsic medical parenchymal kidney disease. Radermacher measured RI in 131 patients undergoing renal revascularization and found a value >0.8 predicted a poor BP response and likely progression of renal insufficiency after surgery, consistent with irreversible medical renal disease.[100] In contrast, 94% of patients with a RI <0.8 showed improved BP and freedom from dialysis after reconstruction. The role of the RI in managing RVD is controversial, and we place little emphasis on RI in guiding treatment decisions.[104]

Computed Tomographic Angiography and Magnetic Resonance Angiography

Advances in speed, resolution, and postprocessing have contributed to the widespread application of computed tomographic angiography (CTA) for vascular imaging (see Chapter 27). Modern multichannel scanners provide precise three-dimensional visualization of vascular abnormalities not possible with digital subtraction angiography (DSA) alone.[106-109] CTA is noninvasive and widely available, and image acquisition and formatting are less technically demanding than for RDU or for contrast-enhanced magnetic resonance angiography (MRA) of the renal arteries. Disadvantages of CT include exposure to ionizing radiation and iodinated contrast. CTA delivers 87 to 260 times more radiation to the patient than a chest x-ray,[107] and a typical renal CTA uses 120 to 140 mL of contrast, often a problem given renal insufficiency in many patients being evaluated for RVD.[108,109] Studies comparing CTA with DSA report a sensitivity, specificity, and accuracy approaching 100% for defining significant lesions of the main renal artery (Table 125.4). CTA also provides detailed information about surrounding tissues and organs, such as kidney length and parenchymal thickness and quality of the adjacent aorta and visceral arteries. The latter

TABLE 125.4 Accuracy of Duplex Ultrasonography, Computed Tomographic Angiography, and Magnetic Resonance Angiography for the Evaluation of Renal Artery Stenosis

Series	Year	Modality	Number of Kidneys	Sensitivity (%)	Specificity (%)
Hansen et al.[115]	1990	Duplex	122	93	98
Hua et al.[101]	2000	Duplex	58	91	75
Fraioli et al.[106]	2006	CTA	50	100	98.6
Rountas et al.[109]	2007	Duplex, CTA, MRA, DSA	129	75 (duplex) 94 (CTA) 90 (MRA)	89.6 (duplex) 93 (CTA) 94.1 (MRA)

CTA, Computed tomographic angiography; *DSA*, digital subtraction angiography; *MRA*, magnetic resonance angiography.

are helpful when planning surgery, identifying locations suitable for cross-clamping and inflow sources for bypass.

MRA has also proven useful for imaging RVD and has the advantages that it avoids ionizing radiation and iodinated contrast.[109-112] As with CTA, data sets can be extensively postprocessed and viewed from virtually any projection. Limitations include long scan times subject to motion artifact and a lower spatial resolution than for CTA or DSA. Patients can become claustrophobic in typical closed scanners and many have metal implants incompatible with the magnetic field.[111] Contemporary ceMRA protocols typically employ gadolinium contrast, which cannot be used in patients with significant renal impairment because of the risk for nephrogenic systemic fibrosis, a scleroderma-like syndrome most commonly affecting the extremities that may also involve the lung, diaphragm, esophagus, heart, and vasculature.[113-115] The pathogenesis is ill-defined, but most patients have end-stage renal disease, and a dose-effect is likely.[115] The Food and Drug Administration has issued a black-box warning to avoid the administration of gadolinium to patients with eGFR less than 30 unless it is absolutely necessary. If exposure is unavoidable, patients should be dialyzed immediately afterward, but this may not provide complete protection. When comparing MRA with DSA, accuracy in defining critical RAS is similar to CTA but MRA can overestimate degree of stenosis, although negative predictive value of a normal study is excellent (see Table 125.4).

Digital Subtraction Angiography

DSA remains the gold standard for renal imaging, providing lumen morphology in high resolution and allowing for endovascular treatment. DSA does not provide three-dimensional information on vessel wall structure or adjacent tissues and organs, as seen on axial imaging (Fig. 125.3), and image quality can be degraded by a number of patient factors, including obesity, bowel gas, heavy calcification, retained gastrointestinal contrast material, and movement (see Chapter 25). DSA is invasive, with risk of access site bleeding and other complications that are higher than generally appreciated (e.g., 13% in the roll-in phase of CORAL),[33] and it exposes patients to nephrotoxic contrast and patients and operators to heavy doses of ionizing radiation. DSA is also labor-intensive, requiring a team of trained specialists, and is expensive.

Given these issues, and noninvasive alternatives outlined previously, DSA is generally reserved for patients undergoing planned renal artery reconstruction (see Chapters 126 and 127). In this group, it is important to define accessory renal arteries, branch vessel disease, blood supply to the contralateral kidney, and status of the adjacent aorta and visceral vessels as potential inflow sources. In patients with renal insufficiency it is important to provide preprocedural hydration and strategies to limit volume of contrast, such as using carbon dioxide to reduce risk of contrast-induced nephropathy (Fig. 125.4; see Chapter 60).

Functional Studies

A pervasive problem in caring for patients with RVD has been a lack of practical screening tests to identify patients who respond to revascularization.[55,116] Each imaging modality described previously can detect anatomic RAS, but none can link a particular lesion to HTN or impaired renal function that will correct after revascularization. To address this, a number of adjuncts to imaging have been developed, including direct pullback pressure measurements to define gradients during DSA[33] and loss of kidney length on RDU[82,83] as a surrogate for ischemic nephropathy, indicating severe kidney hypoperfusion more likely to progress without intervention. Split renal function studies using radionuclide renography can screen for loss of excretory function ipsilateral to a RAS that can be compared with an opposite normal kidney in patients with unilateral disease. While each of these methods can help support or refute functional impact to a known RAS, none has proven reliable in identifying patients who respond to revascularization.[116] New

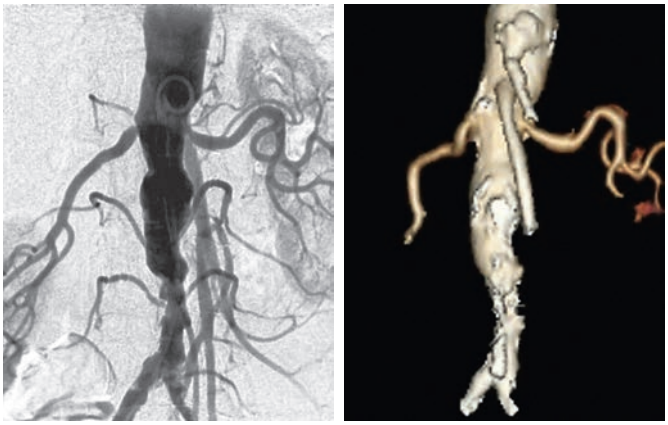

Figure 125.3 Comparison of digital subtraction angiography *(left)* and volume-rendered computed tomographic angiography *(right)* in a patient with bilateral proximal renal artery stenosis.

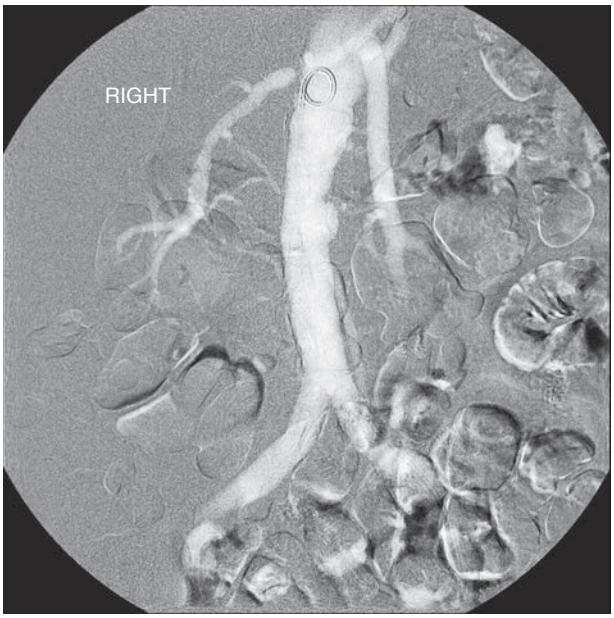

Figure 125.4 Strategies to limit exposure to nephrotoxic contrast material during renal angiography include the use of alternative contrast agents, such as carbon dioxide (shown) and gadolinium.

tools to define renal parenchymal ischemia are being tested but have yet to be validated for clinical decision-making.[53,54,116] Two older functional assays that have been studied extensively and remain in use in some centers today are captopril renography and selective renal vein renin sampling.

Radionuclide Renography

Split renal function can be measured by quantifying the uptake and excretion of radiolabeled molecules, such as technetium Tc 99m–labeled mercaptoacetyltriglycine.[117-120] Abnormal uptake and excretion by a kidney downstream of a RAS suggests a causal relationship, but renography is often normal in patients with RAS. In patients with unilateral RAS and renal insufficiency, a defect on renography is as likely to be in the contralateral kidney.[120]

ACE inhibitor renography, commonly called "captopril renography," uses pharmacologic inhibition of Ang II or its ATR1 receptor to unmask intrinsic renal compensation to RAS, creating a pressure drop that impacts glomerular filtration (see the Pathophysiology section noted previously). With unilateral critical RAS, the affected kidney will show an acute decline in excretion of the radiolabel after inhibiting Ang II with an ACE inhibitor or ARB.[117,118,120] The contralateral kidney may show enhanced excretory function after ACE inhibition, as efferent arteriolar dilatation leads to increased glomerular filtration in the setting of a normal perfusion pressure.[120]

In patients with unilateral RAS, ACE inhibitor renography may distinguish between renovascular and essential HTN, and thus identify patients more likely to benefit from revascularization.[118] A normal study effectively excludes renovascular HTN. The assay is inaccurate in patients with severe azotemia or small, poorly functioning kidneys. In these settings, an abnormal baseline renogram is less likely to change significantly with ACE inhibition, causing false-negative or indeterminate results. However, Erbsloh-Moller studied 20 azotemic patients with serum creatinine levels greater than 1.8 mg/dL (159 μmol/L) and reported that sensitivity and specificity of a positive study exceeded 90% in predicting BP response to revascularization.[120]

Renal Vein Renin Assays

Renovascular HTN is mediated by excess renin production. Thus documenting excess renin production by the affected kidney should support a functional link between RAS and HTN. Selective renal vein renin assays can be used for this purpose, but the complexity and invasive nature of the procedure limit its use as a screening tool. Renin levels can be altered by a number of variables unrelated to RAS, so careful patient preparation and standardization of the procedure are essential.

We start patients on a low-sodium diet and attempt to stop all antihypertensive medications except diuretics and calcium channel blockers 5 days before the assay. Furosemide (40 mg, PO) is given the evening before. The following morning patients are kept supine at strict bed rest 4 hours before and during the assay. Separate catheters are placed percutaneously under fluoroscopy into the inferior vena cava and each renal vein. A reference systemic sample is drawn from the cava, followed by simultaneous aspiration of right and left renal vein catheters. Sampling is repeated two or three times at 5-minute intervals and then a final systemic caval sample collected.

Reporting standards vary, but a ratio of renal vein renin to systemic renin of 1.5 times or higher is typically considered positive, linking RAS to excess renin production.[95,121] Lateralizing renins are generally informative, predicting a BP benefit from open revascularization,[95,121] but failure to lateralize has a low negative predictive value. The ratio for the opposite uninvolved kidney may be low because of compensatory suppression of renin release in response to HTN.[121]

Renin assays are of little use in patients with bilateral RAS, with solitary kidneys, or with RAS in accessory renal arteries. The value of renin ratios in predicting a positive response to revascularization in patients with ischemic nephropathy is also unclear. In these circumstances, decisions regarding intervention are left to clinical judgment factoring in degree of stenosis, severity of HTN, and trajectory of any decline in eGFR. Presently in our practice we only occasionally obtain renin assays, but they can be useful when making decisions about open revascularization in patients with unilateral RAS.

TREATMENT OF RENOVASCULAR HYPERTENSION

A diagnosis of RAS is associated with a high risk of cardiovascular morbidity and mortality[2,4]; significant risk of lesion progression and loss of kidney mass, particularly in cohorts with severe RAS and HTN (Table 125.5)[82,83]; and risk of progression to dialysis and death.[2,4,75] Despite these compelling statistics, the

TABLE 125.5 Natural History of Renal Artery Stenosis: Selected Series

Series	Year	Number of Patients	Imaging Modality	Anatomic Progression (%)	Occlusion (%)
Dean et al.[78]	1981	41	Angiography	17	12
Schreiber et al.[79]	1984	85	Angiography	44	11
Tollefson et al.[80]	1991	48	Angiography	53	9
Zierler et al.[82]	1994	80	Duplex ultrasonography	8	3
Crowley et al.[81]	1998	1178	Angiography	11	0.3
Caps et al.[83]	1998	170	Duplex ultrasonography	31	3

Modified from Corriere MA, Edwards M, Hansen K. Abdominal aortic aneurysm and renal artery stenosis. *Vasc Dis Management*. 2008;5:16–21.

benefits of renal revascularization have been challenged by better medical treatments,[97] an evolving experience with open renal revascularization,[20,21,122] and by a growing body of Level I data contesting the value of renal stenting for many patients with atherosclerotic RAS.[34] As a result, many centers are now appropriately limiting revascularization to patients with severe manifestations of atherosclerotic RAS and those with nonatherosclerotic RVD.

No large prospective randomized trials have compared open renal artery reconstruction to medical management, angioplasty, or stenting in patients with atherosclerotic RAS.[35-37] However, multiple randomized trials comparing renal artery stenting with medical management for atherosclerotic RAS and a meta-analysis summarizing these data,[34] including the recent CORAL trial,[33] have concluded that stenting provides no advantages over medical treatment alone (Fig. 125.5). The strengths and weaknesses of these studies are discussed in detail in Chapter 127. However, it is worth pointing out that patient demographics in ASTRAL[32] and CORAL[33] differ substantially from the average patient undergoing revascularization at our center.[21,22] Consider the baseline systolic BP in CORAL, which was only 150 mm Hg, and for ASTRAL mean BP was only 149/76 or 152/76 for the stent and control groups, respectively.[32,33] The number of antihypertensive medications taken by patients to achieve these values averaged 2.1 and 2.8 in CORAL and ASTRAL, respectively.[32,33] Contrast these values with baseline BP in 500 patients undergoing open repair of atherosclerotic RAS at our center that averaged 200/104 mm Hg on a mean of 2.6 antihypertensive medications. These differences suggest major variation in criteria used to select patients for revascularization, and we would argue that we could have predicted that many of the patients enrolled in these trials would not have shown a response to stenting.

Despite these criticisms, we agree that most patients with RVD can be approached conservatively. Interventions should be reserved for those with severe disease that fails to respond to aggressive medical therapy, or patients with nonatherosclerotic RVD. Clearly, the days of "drive-by" or "prophylactic" renal stenting in patients with atherosclerotic RVD are over.

Medical Management of Atherosclerotic Renovascular Disease

Mounting Level I data from randomized trials support a recommendation that most patients with atherosclerotic RAS should receive medical therapy without intervention.[34,97,116,122-124] Risk factors for atherosclerosis and renal impairment should be aggressively controlled.[33,97,122-124] Patients should be provided resources to help promote healthy lifestyles, including smoking cessation, regular exercise, and appropriate nutrition. Lipid levels should be monitored, and if high, lowered to accepted targets for secondary prevention in cardiovascular disease (e.g., LDL <100 mg/dL).[124] Patients should receive antiplatelet and statin therapy regardless of baseline lipid levels, unless there is a specific contraindication.[124] Statins may reduce progression of RAS[125] and inhibit restenosis after renal stenting,[126] and they clearly protect from cardiovascular morbidity and mortality in patients with established atherosclerosis. The protocol for medical treatment in CORAL included statin therapy adjusted to achieve these targets,[33] which along with aggressive protocol-driven BP treatment likely contributed to low rates of RVD progression, cardiovascular events, and death.

As mentioned previously, renal dysfunction in RVD patients is often multifactorial, given the overlap in risk factors for medical renal disease and atherosclerosis. Renal function should be monitored regularly, and patients with abnormal eGFR should be evaluated for common causes of chronic kidney disease and treatment tailored to limit further injury, generally in concert with a nephrologist. Individuals with a BMI >25 should be encouraged to lose weight, and those with diabetes should carefully manage glucose.

In centers experienced with RDU, patients with RAS and those with prior renal revascularization should be studied annually to assess patency and kidney length, particularly after stenting, given high rates of restenosis.[29,33] RDU should also be considered for sudden worsening of HTN or renal impairment to assess for progression.[127]

HTN should be treated aggressively, and BP goals for adults with RVD are the same as for essential HTN. Current consensus recommendations in the United States[97] and Canada[123] include a systolic BP of <140 mm Hg and diastolic BP <90 mm Hg. These targets drop to <130/80 for patients with concomitant diabetes or renal insufficiency.[97,123] Hypertensive patients should avoid excessive salt intake, limit alcohol consumption, reduce stress, and get regular exercise.

Renovascular HTN typically requires multiple classes of antihypertensive medications to achieve BP goals, and a number of individuals will never reach consistent control without revascularization.[21] There are no large randomized trials comparing efficacy of different combinations of antihypertensive medications in RAS, but given the central role of the RAAS, ACE inhibitors and ARBs should be among first-line choices.[97,123] The safety of these agents in RVD has been demonstrated in a number of studies, including CORAL,[33] but when initiating treatment in patients with bilateral RAS or solitary kidneys, the creatinine should be monitored for a sudden decline in eGFR. If this occurs, the offending medication should be promptly discontinued and renal function typically returns to baseline.[92,93] Other first-line agents for treating renovascular HTN include thiazide diuretics, calcium channel blockers (dihydropyridines; e.g., amlodipine), and beta blockers.[97,123] Diuretics are often helpful in RVD because of associated volume excess, particularly in patients with bilateral lesions, but patients should be monitored to avoid hypokalemia. Spironolactone should be used with caution with ACE inhibitors or in the setting of impaired renal function to avoid hyperkalemia. In patients intolerant or refractory to first-line agents, second-tier agents can be considered with caution (e.g., hydralazine, clonidine, etc.).[97,123]

Renal Revascularization

When an intervention is deemed appropriate, the approach should be tailored to the patient's anatomy and clinical status with consideration to local expertise, as described in Chapter 126 and Chapter 127. Fewer open surgical procedures are being

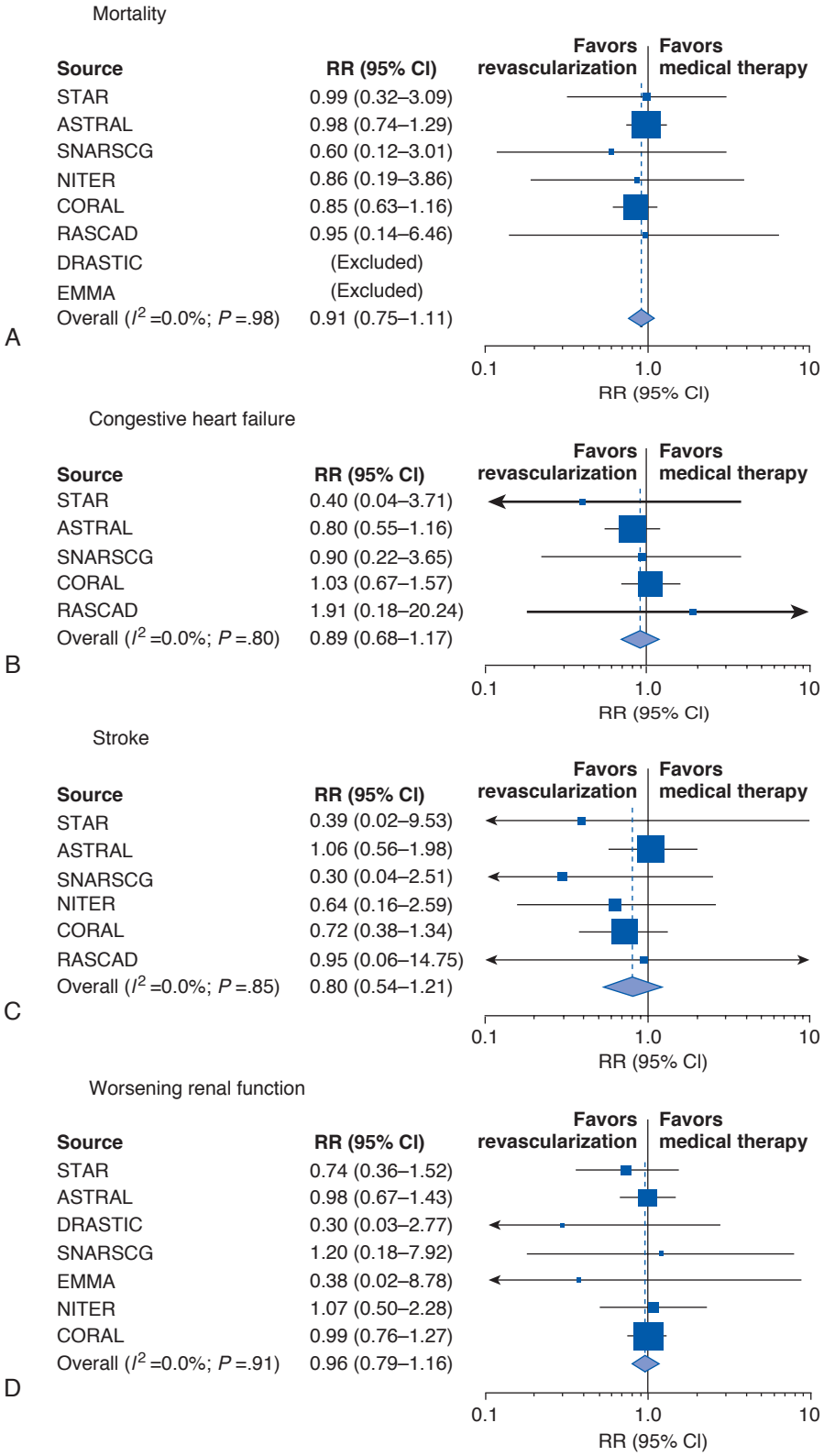

Figure 125.5 Histogram summarizing data from randomized trials of renal revascularization.

performed for symptomatic RAS because of a better understanding of the natural history of RAS without intervention, the availability of less invasive alternatives, refinements in patient selection,[21,22,116] and improved outcomes with medical management.[33,34] Results from prospective series by our group and others have helped shift the focus of surgery in RVD away from BP control to preservation of excretory renal function.[22] We consider open repair in good-risk patients with bilateral RAS or branch vessel disease who have failed to respond to medical treatment and for children with developmental RVD. Other

select populations in which the risks of open repair are justified are discussed in detail in Chapter 126. Open repair of atherosclerotic RAS is much more durable than stenting, with patency rates well over 90% on long-term follow-up, but carries a higher mortality.[21,22,128-130] Restenosis rates for stenting have declined over time, but in recent prospective trials were still >10%.[33,34] BP responses vary in the literature, but in our experience 85% of patients with successful open repair of all hemodynamically significant renal lesions improve or are cured of HTN,[21,22] which is much higher than for our results with stenting.[130,131]

At Wake Forest we reserve renal artery stenting or open renal revascularization in atherosclerotic RAS for patients that have failed aggressive medical management with severe refractory HTN; those with a recent significant decline in eGFR without another explanation with concomitant severe HTN, particularly when RAS is bilateral; and those with hypertensive crises precipitating cardiopulmonary or neurologic embarrassment (e.g., flash pulmonary edema).[97,116] Our threshold for renal revascularization is much lower for children with severe RVD[8,9,132] (see Chapter 130) and for adults with FMD complicated by severe HTN.[6,133]

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A complete reference list can be found online at www.expertconsult.com.

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126 CHAPTER

Renovascular Disease: Open Surgical Treatment

MARSHALL E. BENJAMIN and KIMBERLEY J. HANSEN

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Following Goldblatt's innovative work defining the causal relationship between renovascular disease and hypertension in 1934,[1] the surgical management of renovascular disease evolved through three eras; nephrectomy, open surgical correction, and finally renal artery angioplasty with or without stenting (Fig. 126.1). Each era was met with initial enthusiasm, which was soon tempered by the modest results of each treatment. Nephrectomy is now rarely indicated in the management of renovascular disease, and recent randomized clinical trials comparing renal artery stenting with best medical management have demonstrated no advantage of catheter-based intervention (see Chapter 127). This chapter reviews patient selection for open repair of renovascular disease and then describes specific surgical approaches and their expected outcomes in contemporary practice.

INDICATIONS FOR SURGICAL REPAIR

The rationale for the treatment of renovascular disease by any method is to improve event-free survival. Our experience with 500 consecutive patients treated for atherosclerotic renovascular disease suggests that severe hypertension can be viewed as a key preoperative characteristic favoring clinical benefit, whereas renal function after operation can be considered the key clinical response.[2] An early incremental increase in excretory renal function has been the primary determinant of dialysis-free survival for all atherosclerotic patients.[3,4]

Unfortunately, once renovascular disease is identified in combination with severe hypertension, discriminating predictors of blood pressure and renal function response are lacking. Lateralizing renin assays have predicted blood pressure benefit but not blood pressure cure.[5,6] Moreover, renal function response in patients with ischemic nephropathy is uncertain after renal artery intervention.[4] Studies have also described a significant correlation between parameters derived from segmental renal artery Doppler spectral analysis (i.e., resistive index) and response to intervention as well as progression to dialysis dependence.[7,8] However, we have not been able to reproduce these results for open operative management of renal artery disease.[9] Rather, in

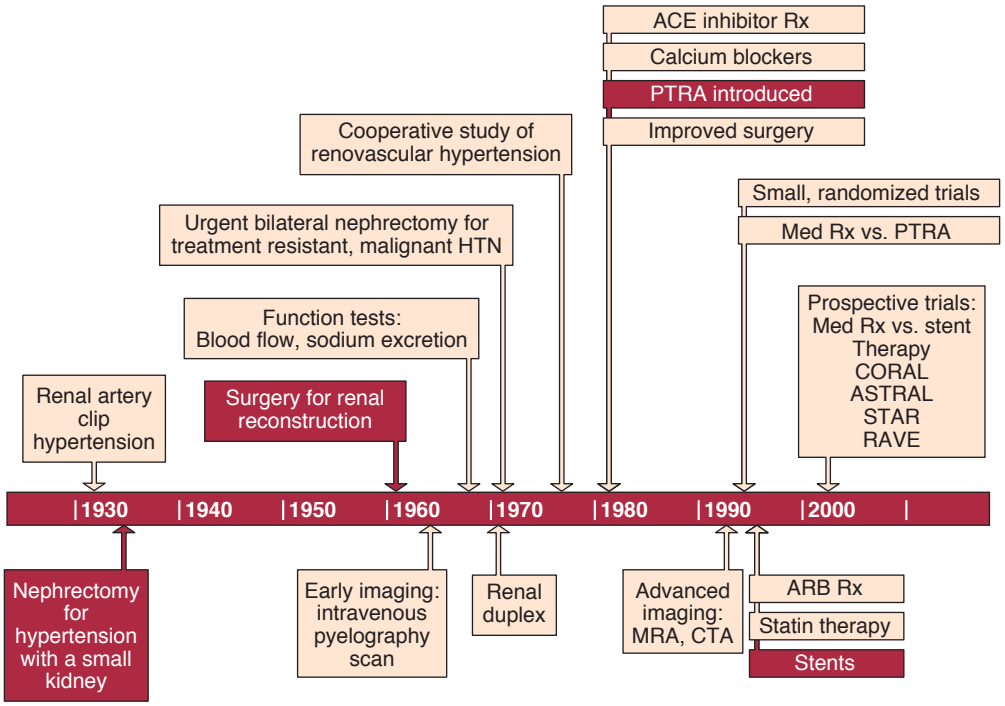

Figure 126.1 Time line showing evolution of the surgical management of renovascular disease through three eras. *ACE,* angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *CTA,* computed tomographic angiography; *HTN,* hypertension; *MRA,* magnetic resonance angiography; *PTRA,* percutaneous transluminal renal angioplasty; *Rx,* therapy.

our clinical experience with more than 1000 patients with atherosclerotic renal artery disease submitted to open operative repair, factors favoring the recovery of renal function after operation have included severe preoperative hypertension, bilateral or global atherosclerotic renovascular disease due to high-grade (>90%) stenosis or renal artery occlusion, and rapidly deteriorating renal function before surgery.[4,6,10-13] When each of these favorable features was expressed in patients considered permanently dialysis dependent, 70% of those submitted to open operative repair were permanently removed from dialysis.[4,13]

The quality of studies designed to define the natural history of the atherosclerotic renal artery has varied widely.[10,14-23] Most commonly authors have considered anatomic progression of atherosclerotic renovascular disease a certainty, one associated with an inevitable decline in kidney size and kidney function. This view has been cited to support intervention for renal artery disease whenever it is discovered, even in the absence of hypertension or renal insufficiency.

On the basis of a recent prospective, population-based study of progression of atherosclerotic renovascular disease in the elderly, we do not favor "prophylactic" intervention for asymptomatic renovascular disease.[24] This longitudinal cohort study included 119 Cardiovascular Health Study participants, with 235 kidneys for study, and no kidney progressed to a renal artery occlusion during a mean follow-up of 8.5 years. Among participants with mild to moderate hypertension in the Cardiovascular Health Study, progression to hemodynamically significant renal artery stenosis was observed in only 4%, or an annualized rate of 0.5% per year.[24]

When a patient has bilateral renal artery stenosis and severe hypertension, the decision for empiric open renal reconstruction is based on the severity of the hypertension and the renal artery lesions. When disease consists of severe stenosis of one renal artery and only mild to moderate contralateral disease, it is treated as a unilateral lesion. If both renal artery lesions are moderately severe (60%-80% diameter-reducing stenosis), revascularization is undertaken only if associated hypertension is severe. In contrast, if both renal artery lesions are severe (>80% stenosis) and the patient has severe hypertension, bilateral simultaneous renal revascularization is performed, especially when excretory renal insufficiency is present. However, because the degree of azotemia usually parallels the severity of hypertension, a patient who presents with severe excretory renal insufficiency but only mild hypertension usually has concomitant renal parenchymal disease from another cause (e.g., diabetes). Characteristically, renovascular disease contributing to severe azotemia or dialysis dependence is associated with severe hypertension and severe bilateral stenosis or renal artery occlusion.[3,4,10,13]

Open Operative Strategy

The presence of severe hypertension is considered a prerequisite for renal artery intervention, and functional studies are used to guide the management of unilateral lesions. Empiric renal artery repair is performed without functional studies when hypertension is severe, renal artery disease is bilateral, or the patient has ischemic nephropathy.[3,6,25] Prophylactic renal artery

repair in the absence of hypertension, whether as an isolated procedure or in combination with aortic reconstruction, is not recommended. During surgical reconstruction, all hemodynamically significant renal artery disease is corrected in a single operation with the exception of disease requiring bilateral ex vivo reconstructions, which are staged. Nephrectomy is reserved for a nonfunctioning kidney (i.e., ≤10% function by renography) with unreconstructable renal artery disease.[4,10,18] Direct aortorenal reconstructions are preferred to indirect methods because concomitant disease of the celiac axis is present in 40% to 50% of patients and bilateral repair is required in half.[4,6] Failed renal artery repair is also associated with a significantly increased risk of dialysis dependence.[25] To minimize these failures, intraoperative duplex ultrasonography is used to evaluate the technical results of surgical repair before closure.[26]

Our experience with percutaneous management as a substitute for open operative repair has demonstrated only modest hypertension and renal function response.[27-29] Consequently we continue to advocate open operative repair for select patients. These include children with hypoplastic lesions,[30] adults with dysplastic lesions other than medial fibroplasia, and patients with medial fibroplasia involving branch and segmental renal arteries complicated by a renal artery aneurysm.[31] We advocate open operative repair for atherosclerotic renovascular disease in good-risk patients, younger than 65 years of age, who demonstrate global renal ischemia manifested by critical renal artery stenosis or occlusion, especially when severe hypertension is associated with excretory renal insufficiency and rapidly deteriorating excretory function.[3,4,13] Selection criteria for the repair of renal artery aneurysms are discussed in Chapter 128, but we have continued to favor open operative repair as opposed to coiling, stenting, or stent-grafting of these lesions.[31]

MANAGEMENT OPTIONS

Certain measures are used in almost all open renal artery operations. Mannitol is administered intravenously in 12.5-g doses early in the operation during aortic and renal artery dissection. Repeated doses are administered before and after periods of renal ischemia, up to a total dose of 1 g/kg of patient body weight. Just before renal artery cross-clamping, 100 U/kg of heparin is given intravenously, and systemic anticoagulation is verified by activated clotting time. Unless it is required for hemostasis, protamine is not routinely administered for reversal of heparin at completion of the operation.

Mobilization and Dissection (see Chapter 58)

Midline Exposure

A midline abdominal incision is made for operative repair of atherosclerotic renal artery disease when bilateral renal artery repair or combined aortic and renal repair is planned. The patient is positioned supine with the umbilicus at the level of the table break, with the operating table flexed 10 to 15 degrees. To obtain full exposure of the upper abdominal aorta and renal branches, it is important that the last 1 or 2 cm of the proximal incision be made coursing to one side of the xiphoid (Fig. 126.2A). Some type of fixed mechanical retraction is also advantageous, particularly when combined aortic and renal procedures are required. Otherwise, extended flank and subcostal incisions are reserved for correction of unilateral branch renal artery lesions or splanchnic-renal bypass.

When the midline xiphoid-to-pubis incision is used, the posterior peritoneum overlying the aorta is incised longitudinally and the duodenum mobilized at the ligament of Treitz (see Fig. 126.2B). During this maneuver, it is important to identify and spare the meandering mesenteric vessel that may be found at this level. Finally, the duodenum is reflected to the patient's right to expose the left renal vein. By extending the posterior peritoneal incision to the left along the inferior border of the pancreas, an avascular plane posterior to the pancreas can be entered (see Fig. 126.2B) to expose the entire left renal hilum. This exposure is of special importance when there are distal renal artery lesions to be managed (Fig. 126.3A). The left renal artery lies posterior to the left renal vein. In some cases, the

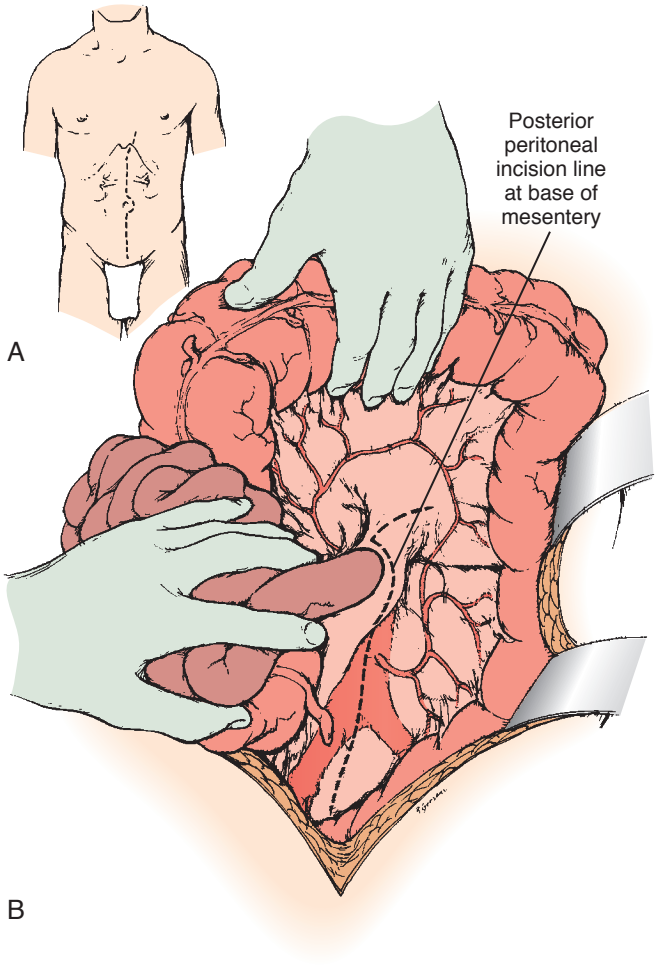

Figure 126.2 (**A** and **B**) Exposure of the aorta and left renal hilum through the base of the mesentery. Extension of the posterior peritoneal incision to the left, along the inferior border of the pancreas, provides entry to an avascular plane posterior to the pancreas. This allows excellent exposure of the entire left renal vein and hilum as well as of the proximal right renal artery. (From Benjamin ME, Dean RH. Techniques in renal artery reconstruction: part I. *Ann Vasc Surg.* 1996;10:306–314.)

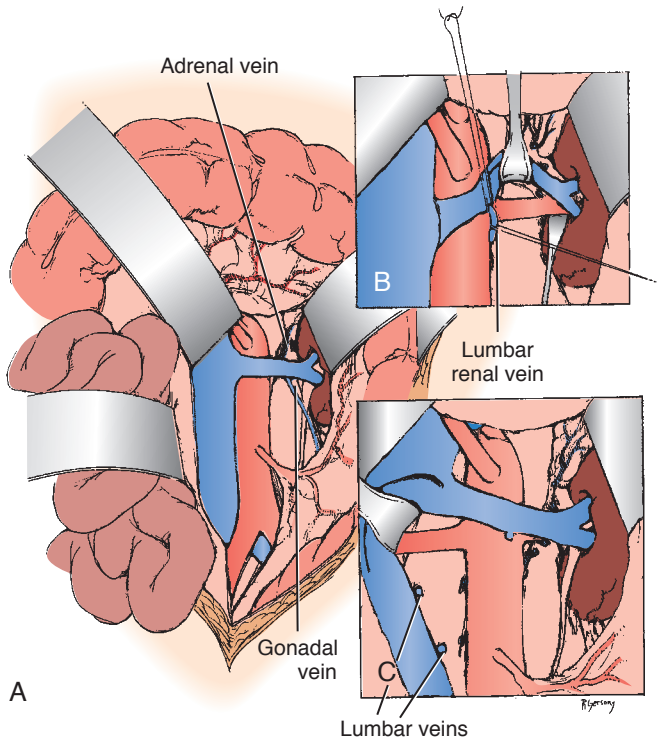

Figure 126.3 **(A)** Exposure of the proximal right renal artery through the base of the mesentery. **(B)** Mobilization of the left renal vein by ligation and division of the adrenal, gonadal, and lumbar-renal veins allows exposure of the entire left renal artery to the hilum. **(C)** On occasion, lumbar veins are ligated and divided to allow retraction of the vena cava to the right. Often, adequate exposure of disease of the proximal renal artery can be obtained without this maneuver. (From Benjamin ME, Dean RH. Techniques in renal artery reconstruction: part I. *Ann Vasc Surg*. 1996;10:306–314.)

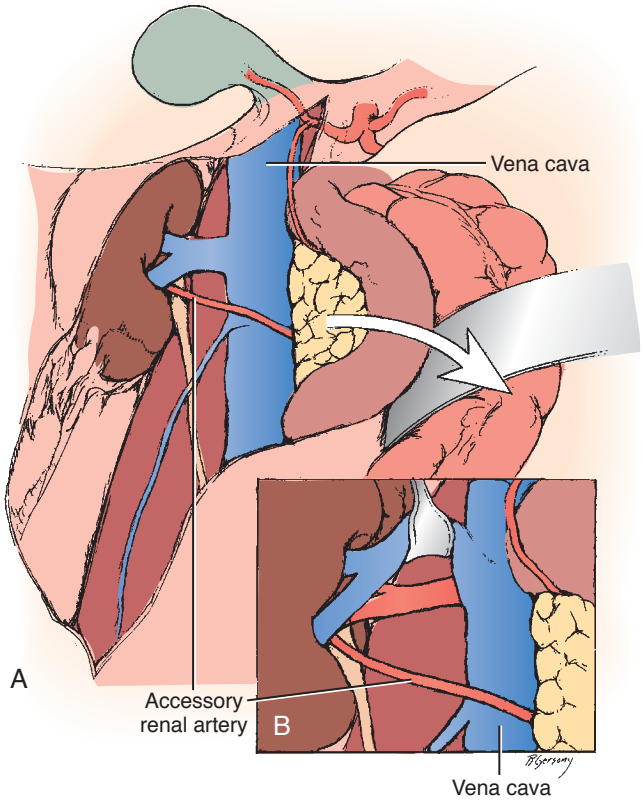

Figure 126.4 **(A)** Arteries encountered anterior to the vena cava should be considered accessory renal arteries and preserved. **(B)** The right renal vein is typically mobilized superiorly for exposure of the distal right renal artery. (From Benjamin ME, Dean RH. Techniques in renal artery reconstruction: part I. *Ann Vasc Surg*. 1996;10:306–314.)

vein can be retracted cephalad to expose the artery; in other cases, caudal retraction of the vein provides better access. Usually, the gonadal and adrenal veins, which enter the left renal vein, must be ligated and divided to facilitate exposure of the distal artery. Frequently, a lumbar vein enters the posterior wall of the left renal vein; it can easily be injured unless special care is taken (see Fig. 126.3B). For full mobilization of the left renal vein, ligation and division of the lumbar branch is also required. The proximal portion of the right renal artery can be exposed through the base of the mesentery by retracting the left renal vein cephalad and the vena cava to the patient's right (see Fig. 126.3C). However, mobilizing the duodenum and right colon medially best exposes the distal portion of the right renal artery; the right renal vein is mobilized and usually retracted cephalad to expose the artery.

Flank Exposure

When a branch renal artery repair is required, especially when ex vivo technique is used or when the supraceliac aorta is used as an inflow source for aortorenal bypass, an extended flank incision is useful. With the ipsilateral flank bumped, the incision extends from the opposite semilunar line into the flank, bisecting the abdominal wall between the costal margin and iliac crest. A left or right visceral mobilization allows access to the renal vasculature and the aortic crus. The crus can be divided, and an extrapleural dissection of the descending thoracic aorta can provide access to the T9–10 thoracic aorta for proximal control and anastomosis.[32,33]

Whether right or left branch renal artery exposure is required, the key is creation of the correct dissection plane between the mesentery anteriorly and Gerota's fascia posteriorly. The renal vein is identified first and mobilized from caval origin to renal hilum. On the right, small venous branches at the junction with the vena cava require ligation. The adrenal, gonadal, and lumbar branches on the left may be sacrificed to facilitate exposure.

Branch renal artery exposure on the right is achieved by colonic and duodenal mobilization. First, the hepatic flexure is mobilized at the peritoneal reflection (Fig. 126.4). With the right colon retracted medially and inferiorly, a Kocher maneuver mobilizes the duodenum and pancreatic head to expose the inferior vena cava and right renal vein (see Fig. 126.4A). Typically, the right renal artery is located just inferior to the accompanying vein, which can be retracted superiorly to provide the best exposure. Although accessory vessels may arise from the aorta or iliac vessels at any level, all arterial branches coursing anterior to the vena cava should be considered accessory right renal branches and carefully preserved (see Fig. 126.4B).

DIRECT SURGICAL TECHNIQUES

A variety of open operative techniques have been used to correct renal artery disease, but three basic operations have been used most frequently: aortorenal bypass, renal artery thromboendarterectomy, and renal artery reimplantation. No single approach provides optimal repair for all types of renovascular lesions in all patients. Aortorenal bypass using saphenous vein is probably the most versatile technique; however, transaortic thromboendarterectomy is especially useful for orificial atherosclerosis involving multiple renal arteries. On occasion, the renal artery will demonstrate sufficient redundancy to allow reimplantation; this is probably the simplest technique and one that is particularly appropriate to hypoplastic renal artery lesions in children.[29,30]

Aortorenal Bypass

Three types of materials are available for aortorenal bypass: autologous saphenous vein, autologous hypogastric artery, and synthetic graft. The decision as to which graft should be used depends on a number of factors. In most instances, the authors prefer the saphenous vein for older adults. However, if the vein is small (<4 mm in diameter) or sclerotic, the hypogastric artery or a synthetic graft may be preferable. In addition, vein enlargement can be anticipated in virtually all young adults. Although structural immaturity has been cited[30] for enlargement and aneurysmal degeneration when saphenous vein is used for renal artery reconstruction in children, the normal renal blood flow in the young resembles that of an arteriovenous fistula with continuous forward flow. This fact alone may account for vein enlargement in the young patient with normal renovascular resistance. In lieu of vein, a 6-mm thin-wall polytetrafluoroethylene (PTFE) graft is satisfactory when the distal renal artery is of sufficient caliber (≥4 mm). Hypogastric artery autograft is preferred for aortorenal bypass in children when reimplantation is not possible.[27,30,34,35]

End-to-side distal anastomoses are occasionally used to include polar renal arteries. In this instance, an end-to-side anastomosis between the polar renal artery and the graft is performed after the proximal aortic anastomosis. After the end-to-side anastomosis has been completed, the most distal main renal artery reconstruction is made in an end-to-end fashion (Fig. 126.5).

In creating the distal anastomosis, the length of the arteriotomy should be at least three times the diameter of the renal artery so as to guard against late suture-line stenosis. An anastomosis with 7-0 monofilament polypropylene as a continuous suture is created with loupe magnification. Just before completion of the renal artery anastomosis, the occluding clamps are temporarily removed to flush air and small debris. When renal artery bypass can be accomplished rapidly enough so that cold perfusion preservation is not required, the aortic anastomosis is performed first, removing an ellipse of the anterolateral aortic wall. This is especially important when the aorta is relatively inflexible because of atherosclerotic involvement. A 4.0-mm aortic punch applied two or three times creates a satisfactory ellipse in most instances. In combined aortorenal reconstructions, the proximal anastomosis is performed first with a thin-wall 6-mm PTFE graft for renal artery bypass attached in end-to-side fashion to the larger polyester aortic graft. The distal aortic reconstruction is completed, and the distal renal anastomosis is created as the last step.

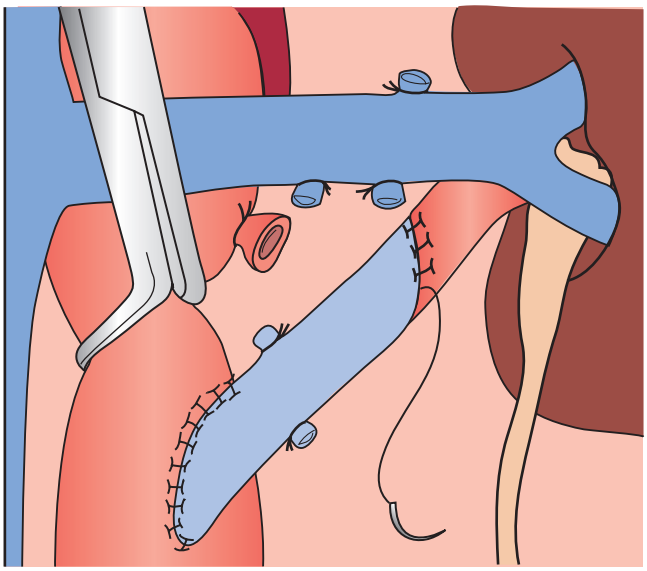

Figure 126.5 Technique for end-to-end aortorenal bypass grafting. The length of arteriotomy is at least three times the diameter of the artery so as to prevent recurrent anastomotic stenosis. For the anastomosis, 6-0 or 7-0 monofilament polypropylene sutures are used in continuous fashion with loupe magnification. If the apex sutures are placed too deeply or with excess advancement, stenosis can be created, posing a risk of late graft thrombosis. (From Benjamin ME, Dean RH. Techniques in renal artery reconstruction: part I. *Ann Vasc Surg*. 1996;10: 306–314.)

Thromboendarterectomy

In cases of ostial atherosclerosis of both renal artery origins, simultaneous bilateral endarterectomy may be the most suitable procedure. Endarterectomy may be either transaortic or transrenal.

For the majority of renal endarterectomies, the transaortic technique is used.[3] This method is particularly applicable in patients with multiple renal arteries that demonstrate ostial disease. In this instance, all visible and palpable renal artery atheromas should end within 1 cm of their aortic origin. Transaortic endarterectomy is performed through a longitudinal aortotomy with sleeve endarterectomy of the aorta and eversion endarterectomy of the renal arteries (Fig. 126.6). The aortotomy is closed with 5-0 polypropylene as a continuous suture. When combined aortic replacement is planned, the transaortic endarterectomy is performed through the transected aorta. Whether a longitudinal aortotomy is used or an endarterectomy is performed through the divided aorta, it is important to mobilize the renal arteries extensively to allow eversion of the artery into the aorta. This allows the distal endpoint to be completed under direct vision. When the aortic atheroma is divided flush with the adventitia by the use of scissors, tacking sutures are not usually required.

As is the case for thromboendarterectomy at all sites, the procedure is contraindicated by the presence of preaneurysmal degeneration of the aorta and transmural calcification. Transmural calcification can be subtle and may be missed unless careful attention is given to gentle palpation of the aorta. Aortic atheroma complicated by transmural calcification resembles fine-grade sandpaper on palpation of the outer surface of the aorta. Endarterectomy in this setting is characterized by numerous sites of punctate bleeding after blood flow is restored.

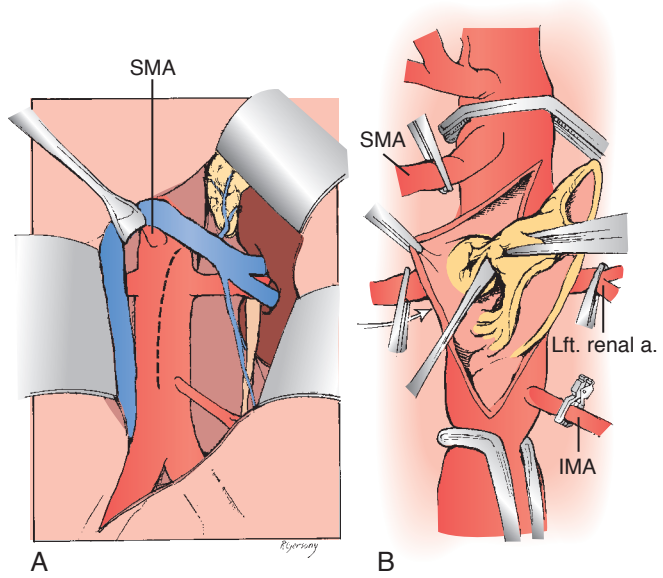

Figure 126.6 Exposure for a longitudinal transaortic endarterectomy is made by the standard transperitoneal approach. The duodenum is mobilized at the ligament of Treitz in standard fashion, or for more complete exposure, the ascending colon and small bowel are mobilized. **(A)** The dotted line shows the location of the aortotomy. **(B)** The plaque is transected sharply, and with eversion of the renal arteries, the atherosclerotic plaque is removed from each renal ostium. The aortotomy is typically closed with a running 4-0 or 5-0 polypropylene suture. *IMA,* inferior mesenteric artery; *SMA,* superior mesenteric artery. (From Benjamin ME, Dean RH. Techniques in renal artery reconstruction: part I. *Ann Vasc Surg*. 1996;10:306–314.)

Reimplantation

After the renal artery has been dissected from the surrounding retroperitoneal tissue, the vessel may be somewhat redundant. When the renal artery stenosis is orificial and there is sufficient vessel length, the renal artery can be transected and reimplanted onto the aorta at a slightly lower level. The renal artery must be spatulated and a portion of the aortic wall removed, as in renal artery bypass (Fig. 126.7). This technique has particular application to children with orificial lesions, avoiding the need for graft material[30]; however, it is suitable for selected atherosclerotic lesions as well.[36] Unlike prosthetic bypass performed during combined aortic replacement in adults, anastomosis from the renal artery to the graft is usually performed immediately after the proximal aortic anastomosis, followed by distal aortic reconstruction.

INDIRECT SURGICAL TECHNIQUES

Splanchnic-Renal Bypass

Splanchnic-renal bypass and other indirect revascularization procedures have received increased attention as alternative methods for renal revascularization.[37] The authors do not believe that these procedures demonstrate durability equivalent to that of direct aortorenal reconstructions, but they are useful in a highly select subgroup of high-risk patients.[3,38]

Hepatorenal Bypass

A right subcostal incision is used to perform hepatorenal bypass.[37] The lesser omentum is incised to expose the hepatic artery both

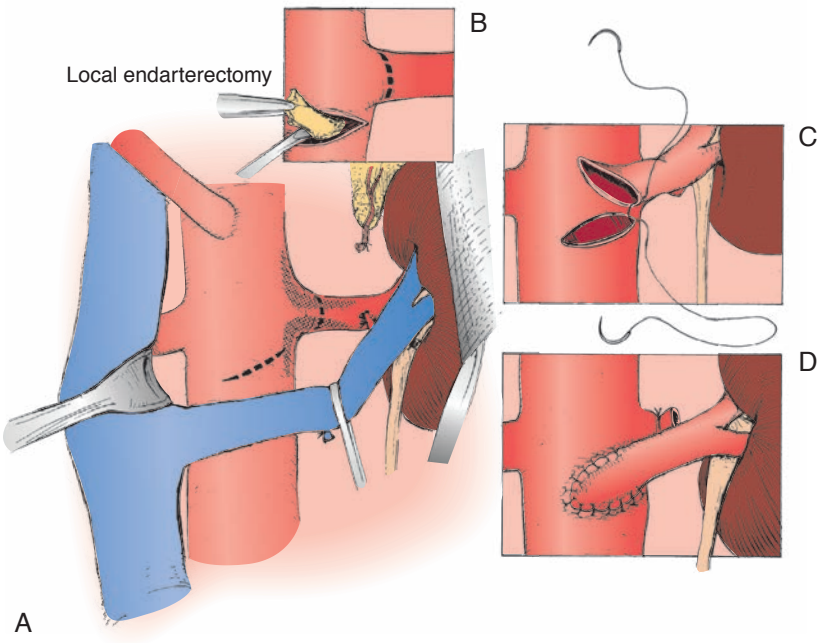

Figure 126.7 When the renal artery is redundant, the vessel can be reimplanted at a lower level **(A)**. Local endarterectomy **(B)** allows placement of the monofilament suture in the aortic wall **(C)**. The native renal artery is then ligated, proximally spatulated, and reimplanted **(D)**. (From Benjamin ME, Dean RH. Techniques in renal artery reconstruction: part II. *Ann Vasc Surg*. 1996;10:409–414.)

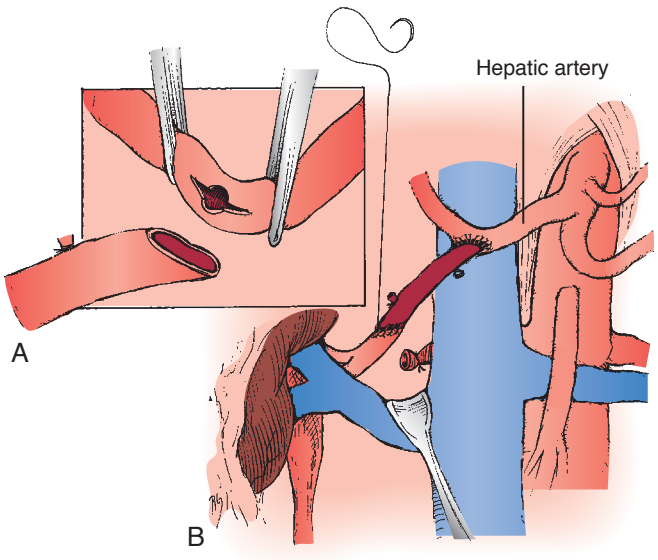

Figure 126.8 The reconstruction is completed with a saphenous vein interposition graft between the side of the hepatic artery **(A)** and the distal end of the transected right renal artery anterior to the vena cava **(B)**. (From Benjamin ME, Dean RH. Techniques in renal artery reconstruction: part II. *Ann Vasc Surg*. 1996;10:409–414.)

proximal and distal to the gastroduodenal artery (Fig. 126.8). Next, the descending duodenum is mobilized by a Kocher maneuver, the inferior vena cava is identified, the right renal vein is identified, and the right renal artery is exposed either immediately cephalad or caudad to the renal vein.

A greater saphenous vein graft is usually used to construct the bypass. The hepatic artery anastomosis of the vein graft can be placed at the site of the amputated stump of the gastroduodenal artery (see Fig. 126.8A). However, this vessel may serve as an important collateral for intestinal perfusion. Therefore the proximal anastomosis is usually made to the common hepatic artery, routing the graft through the foramen of Winslow. The renal artery is then transected and brought anterior to the vena cava for anastomosis end to end to the graft (see Fig. 126.8B).

Splenorenal Bypass

Splenorenal bypass can be performed through a midline or a left subcostal incision.[37,38] The posterior pancreas is mobilized by reflecting the inferior border cephalad. A retropancreatic plane is developed and the splenic artery mobilized from the left gastroepiploic artery to the level of its branches. The left renal artery is exposed cephalad to the left renal vein after division of the adrenal vein. After the splenic artery has been mobilized, it may be divided distally, spatulated, and anastomosed end to end to the transected renal artery (Fig. 126.9). Alternatively, a segment of saphenous vein may be used as a bypass.

Ex Vivo Reconstruction

Because of the widespread use of percutaneous techniques for main renal artery diseases, a significant proportion of open renal artery reconstructions require branch exposure and branch reconstruction. These procedures may require a complex repair,

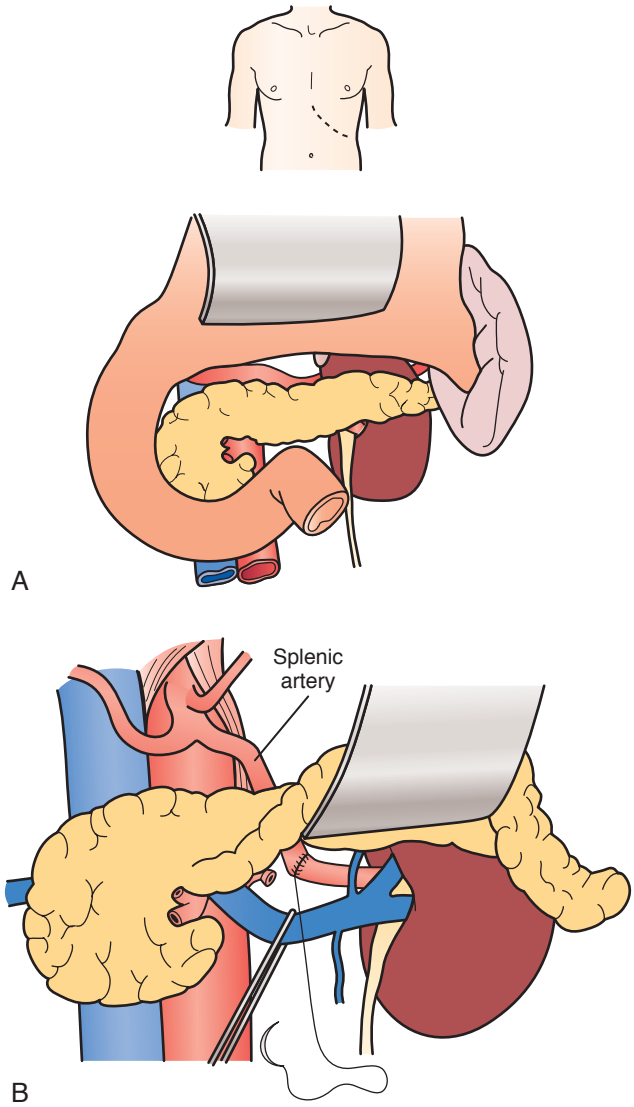

Figure 126.9 Exposure of the left renal hilum in preparation for splenorenal bypass **(A)**. The pancreas has been mobilized along its inferior margin and retracted superiorly **(B)**. The transected splenic artery may be anastomosed end to end to the transected left renal artery. A splenectomy is not routinely performed. (From Benjamin ME, Dean RH. Techniques in renal artery reconstruction: part II. *Ann Vasc Surg*. 1996;10:409–414.)

culminating in prolonged renal ischemia. Available data suggest that when more than 40 minutes of warm renal ischemia is required for renal revascularization, measures to protect renal function should be instituted.[39-42]

Several pharmacologic therapies have been promoted to provide protection during renal ischemia; however, no therapy to date has surpassed hypothermia for protection when renal ischemia exceeds 1 hour.[41,43-46] Surface cooling and hypothermic perfusion have been proposed, but the advantages of each are not well defined. Renal tolerance to ischemia is, in part, related to the duration of ischemia, the adequacy of collateral circulation, and the method of vascular control. Unprotected warm renal ischemia is best tolerated when only the renal artery is controlled.[41] In a similar manner, intermittent renal perfusion is associated with greater dysfunction than is isolated arterial control.[9]

Numerous methods for renal cooling and hypothermia during branch renal artery repair have been described. Our preference has been intermittent hypothermic perfusion and topical ice slush. Otherwise, several steps are common to each branch renal artery reconstruction. To promote renocortical perfusion, small doses of mannitol are administered intravenously throughout renal artery exposure and reperfusion.[46-48] Prior to division of the renal artery, heparin (100 U/kg) is administered intravenously and monitored, as described earlier.

Hypothermia appears to be more important than the composition of the perfusate; however, our preference is a perfusate with an intracellular composition of electrolytes. This composition theoretically limits ion exchange and intracellular volume shifts that contribute to organelle dysfunction associated with decreased activity of membrane-bound sodium-potassium adenosine triphosphatase.[41,49,50] Regardless of whether the renal vein is divided and reattached, branch renal artery repairs with use of cold perfusion preservation are made in an orthotopic fashion, with the kidney returned to the renal fossa rather than autotransplanted into the pelvis.

Several exposures for hypothermic branch renal artery reconstructions are available. When isolated branch renal repair is performed with orthotopic replacement, an extended flank incision is made from the midline to the posterior axillary line, as described earlier. This method is the authors' preferred approach for ex vivo reconstruction. The ureter is mobilized to the pelvic brim along with a large amount of periureteric soft tissue. A Silastic sling is placed around the ureter to control ureteric collaterals and to prevent subsequent renal rewarming.

Gerota's fascia is opened with a cruciate incision; the kidney is completely mobilized, and the renal vessels are divided. Hypothermia may be accomplished by topical ice slush placement, as illustrated in Fig. 126.10. To perform hypothermic perfusion, the kidney is placed in a plastic sling and the renal artery perfused with a chilled renal preservative solution. Continuous perfusion during the period of total renal ischemia is possible with perfusion pump systems, and this may be superior for prolonged renal preservation.[51] However, simple intermittent flushing with a chilled preservative solution provides equal protection during the shorter periods (2-3 hours) required for ex vivo dissection and branch renal artery reconstruction. The chilled (5-0°C) solution is hung at a height of at least 2 m. Immediately after its removal from the renal fossa, the kidney is flushed with 300 to 500 mL of solution until the venous effluent is clear and all segments of the kidney have blanched. As each anastomosis is completed, the kidney is perfused with an additional 100 to 200 mL of chilled solution. In addition to maintaining satisfactory hypothermia, periodic perfusion demonstrates suture-line leaks that are repaired before reimplantation. With this technique, renal core temperatures are maintained at 10°C or below throughout the period of reconstruction.

Even though it is an accepted method after ex vivo reconstruction, autotransplantation to the iliac fossa is unnecessary for most ex vivo reconstructions. This technique was adopted from renal transplantation. Reduction in the magnitude of the operative exposure, manual palpation of the transplanted kidney, and ease of removal when treatment of rejection fails are all practical reasons to place the transplanted kidney into the recipient's iliac fossa. However, none of these advantages applies to the patient requiring autogenous ex vivo reconstruction. Because many ex vivo procedures are performed in relatively young patients, the durability of the operation must be measured in terms of decades. For this reason, attachment of the kidney to the iliac arterial system within or below sites that are susceptible to subsequent atherosclerosis subjects the repaired vessels to disease that may threaten their long-term patency. Moreover,

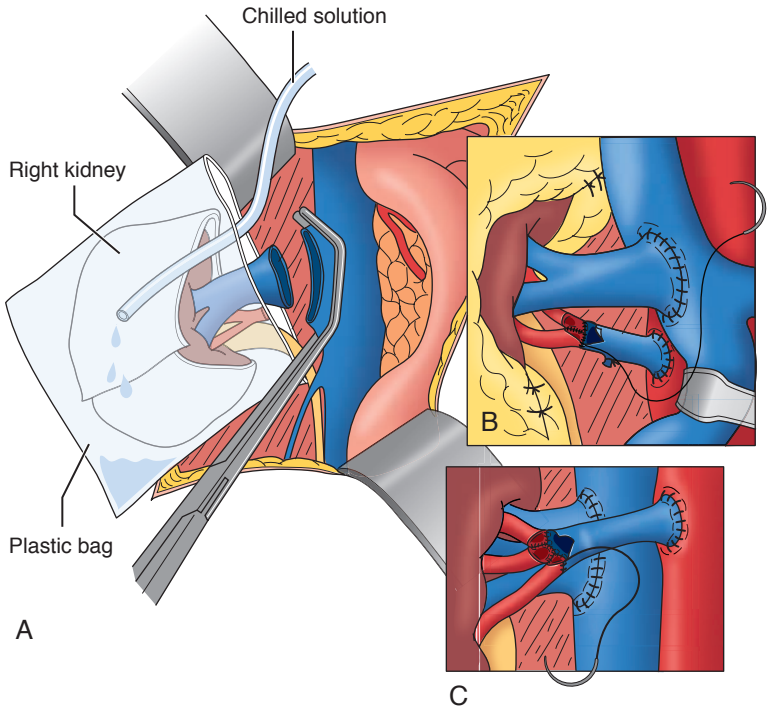

Figure 126.10 An ellipse of the vena cava containing the renal vein origin is excised by placement of a large partially occluding clamp **(A)**. After ex vivo branch repair, the renal vein can be reattached without risk of anastomotic stricture **(B)**. The kidney is returned to its native bed after ex vivo repair. Gerota's fascia is reapproximated to provide stability to the repaired kidney. Arterial reconstruction can be accomplished by end-to-end anastomoses after syndactylizing the distal branch or combined with end-to-side anastomoses **(C)**. (From Benjamin ME, Dean RH. Techniques in renal artery reconstruction: part II. *Ann Vasc Surg*. 1996;10:409–414.)

subsequent management of peripheral vascular disease may be complicated by the presence of the autotransplanted kidney. Finally, if the kidney is replaced in the renal fossa and the renal artery graft is properly attached to the aorta at a proximal infrarenal site, the result should equal those of the standard aortorenal bypass and thus carry a high probability of technical success and long-term durability.

INTRAOPERATIVE ASSESSMENT

Provided that the best method of reconstruction is chosen for renal artery repair, the short course and high blood-flow rates characteristic of direct renal reconstructions favor their patency. Consequently, flawless technical repair plays a dominant role in determining postoperative success.[52-59] The negative impact of technical errors unrecognized at operation is implied by the fact that we have observed no late thromboses of renovascular reconstructions free of disease after 1 year.[60]

Intraoperative Duplex Sonography

The risks and inherent limitations of completion angiography are not shared with intraoperative duplex sonography.[26] Because the ultrasound probe can be placed immediately adjacent to the vascular repair, high carrying frequencies may be used to provide excellent B-scan detail sensitive to 1.0-mm defects. Once defects are imaged, they can be viewed in a multitude of projections during conditions of uninterrupted pulsatile blood flow. In addition to excellent anatomic detail, important hemodynamic information is obtained from the spectral analysis of the Doppler-shifted signal proximal and distal to the imaged defect.[26] The freedom from static projections, absence of potentially nephrotoxic contrast material, and hemodynamic data provided by Doppler spectral analysis make duplex sonography a useful intraoperative method to assess both renovascular and mesenteric repairs. For these advantages of intraoperative duplex sonography to be realized, close cooperation between the vascular surgeon and the vascular technologist is required for accurate intraoperative assessment.

Currently, we use a 5/7.0-MHz compact linear array probe with Doppler color flow designed specifically for intraoperative assessment. The probe is placed within a sterile sheath with a latex tip containing sterile gel. After the operative field has been flooded with warm saline, B-scan images are first obtained in longitudinal projection. Care is taken to image the entire upper abdominal aorta and renal artery origins along the entire length of the repair. All defects seen in longitudinal projection are imaged in transverse projection to confirm their anatomic presence and estimate associated luminal narrowing. Doppler samples are then obtained just proximal and distal to the imaged lesions in longitudinal projection, determining their potential contribution to flow disturbance. The author's (K.J.H.) criteria for major B-scan defects (>60% stenosis) of a peak systolic velocity greater than 2.0 m/s associated with a distal turbulent waveform have been validated in a canine model of graded renal artery stenosis.[26] They have also proved valid in a retrospective study when preoperative radiographic studies were compared with intraoperative duplex images before surgical repair.[19] In more than 1000 open renal artery repairs, intraoperative duplex sonography has been 86% sensitive and 100% specific for technical defects associated with postoperative stenosis and occlusion of direct aortorenal reconstruction.[3,4,13]

Designation of B-scan defects according to Doppler velocity criteria provides accurate information to guide decisions about intraoperative revision. However, there are special circumstances that deserve comment. Unlike the case in surface duplex sonography, in which the Doppler sample volume is large relative to the renal artery diameter, a small Doppler sample volume can be accurately positioned within midcenter stream flow. Despite a small, centered Doppler sample, renal artery repairs demonstrate at least moderate spectral broadening. Transaortic endarterectomy gives the audible Doppler signal an oscillating characteristic, which is normal and not associated with anatomic defects. In addition, an infrequent intraoperative study will demonstrate peak systolic velocities that exceed criteria for critical stenosis when no anatomic defect exists. In these cases, the peak systolic velocities will be elevated uniformly throughout the repair, there will be no focal velocity change, and there will be no distal turbulent waveform. This scenario is most commonly encountered immediately after renal artery reconstruction for nonatherosclerotic renovascular disease. Moreover, renovascular repair to a solitary kidney will frequently demonstrate increased velocities throughout. Finally, an increase in peak systolic velocity is observed in transition from the main renal artery to the segmental renal vessels after branch renal artery repair; however, no distal turbulent waveform will be observed.

Finally, there are B-scan abnormalities observed in conjunction with renal endarterectomy that deserve comment. Infrequently, an irregular B-scan abnormality will evolve during performance of a completion scan. This B-scan finding may be associated with either increased or decreased (blunted) peak velocities but reflects formation of intra-arterial thrombus. Unlike acute venous thrombus, which is usually echolucent, acute arterial platelet aggregates are characterized by irregular echogenic material. Regardless of the associated velocity estimates, the endarterectomy site should be reopened and revised immediately. Last, a B-scan defect otherwise minor by velocity criteria may be revised according to its location and appearance. A mobile flap longer than 2 mm at the distal endpoint of an endarterectomy site is usually revised on the basis of its mere presence and potential for dissection or thrombosis.

RESULTS OF OPEN OPERATIVE MANAGEMENT

Anatomic Results

Our center's cumulative open operative experience from January 1987 through January 2012 has included more than 1700 renal artery repairs in more than 1000 patients. Our consecutive operative experience for atherosclerotic renovascular disease from January 1987 through June 1997 is described in Table 126.1.[25] During this 10.5-year period, 720 renovascular reconstructions

TABLE 126.1 Summary of Operative Management (n = 534 patients)

Total renal reconstructions				720
Aortorenal bypasses			445	
Vein		288		
PTFE		127		
Dacron		19		
Hypogastric arteries		11		
Ex vivo	33			
Reimplantations			52	
Thromboendarterectomies			223	
Total nephrectomies				57
Total kidneys operated				777

PTFE, Polytetrafluoroethylene.
From Hansen KJ, Deitch JS, Oskin TC, et al. Renal artery repair: consequence of operative failures. *Ann Surg*. 1998;227:678–690.

and 57 primary nephrectomies were performed in 534 patients. Postoperative stenosis or thrombosis occurred in 3.3% of renal artery repairs, resulting in recurrent hypertension and declining renal function in 3.7% of patients during a mean follow-up of 36 months.[3] However, because complete anatomic failure of repair (i.e., thrombosis) may result in blood pressure benefit equivalent to nephrectomy, anatomic failure is potentially more common than the rate of recurrent hypertension or reoperation.[26] To examine the authors' rate of anatomic failure, the results of 277 postoperative duplex studies in 128 consecutive patients were reviewed.[25] During a mean follow-up of 22 months, 6 of 177 (3.4%) operative renal artery repairs developed stenosis.[3]

Operative Morbidity and Mortality

Perioperative morbidity accounting for prolonged hospital stay has been observed in 15% to 20% of patients.[3,4] Less than half of 1% of patients with ischemic nephropathy have undergone operation resulting in permanent dialysis dependence within 1 month of repair.[4] Perioperative mortality within 30 days of surgery has demonstrated significant and independent association with advanced age and depressed left ventricular systolic function (i.e., ejection fraction <25%).[3] Overall, during the past 10 years, mortality after isolated renal artery repair has averaged 0.8%, compared with 1.6% for bilateral renal artery repair and 3.3% for bilateral repair combined with aortic repair for correction of atherosclerosis. This compares with 6.9% when visceral, renal, and aortic repairs are combined as one procedure.[61]

Blood Pressure Response

Considering open renal reconstruction for atherosclerotic renal artery disease and criteria for response including both blood pressure measurements and medication requirements at least 2 months after operation, 85% of surgical survivors had been cured or improved and 15% had no blood pressure response.[3]

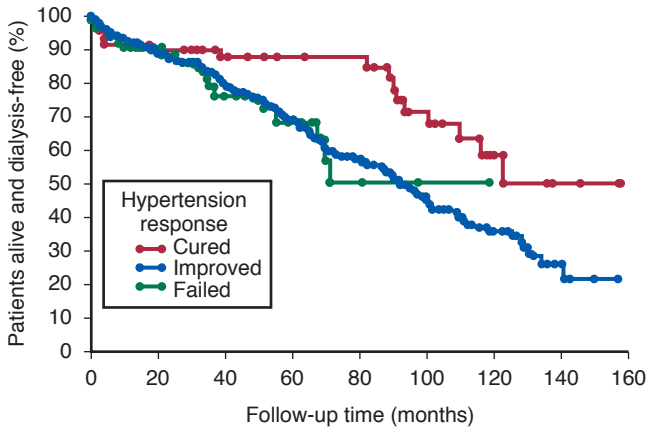

Figure 126.11 Product-limit estimates of time to death or dialysis according to blood pressure response to operation. (From Cherr GS, Hansen KJ, Craven TE, et al. Surgical management of atherosclerotic renovascular disease. *J Vasc Surg*. 2002;35:236–245.)

When patients with atherosclerosis were stratified according to blood pressure response and dialysis-free survival, only blood pressure cured was significantly associated with improved estimated survival.[3]

Renal Function Response

Considering renal function response in consecutive patients treated for atherosclerotic renovascular disease, renal function improved significantly when all patients are considered. In patients with atherosclerotic renovascular disease and ischemic nephropathy, defined by a preoperative serum creatinine concentration above 1.8 mg/dL, 58% demonstrated improved renal function at 3 weeks after repair.[3,4] When 45 patients considered permanently dependent on dialysis were examined, 70% were permanently removed from dialysis dependence after open operation.[4,13] Although other authors have considered that recovery of renal function is limited by elevated serum creatinine concentration, when patients are selected on the basis of severe hypertension and rapidly deteriorating renal function, the proportion of patients improved increases with increasing severity of preoperative renal dysfunction. This association between increased preoperative serum creatinine concentration and improved postoperative renal function is independent and highly significant ($P < .0001$).[3,4]

Hypertension and Renal Function Benefit: Clinical Outcome

Progression to death or dialysis among patients with atherosclerotic renovascular disease has demonstrated significant associations with both preoperative parameters and postoperative blood pressure and renal function response. Preoperative factors that have demonstrated a significant association with death or dialysis include the presence of diabetes mellitus, severe aortic occlusive disease, and poor renal function.[3] Postoperatively, significant associations were noted for blood pressure cured compared with blood pressure improved or worsened (Fig. 126.11).

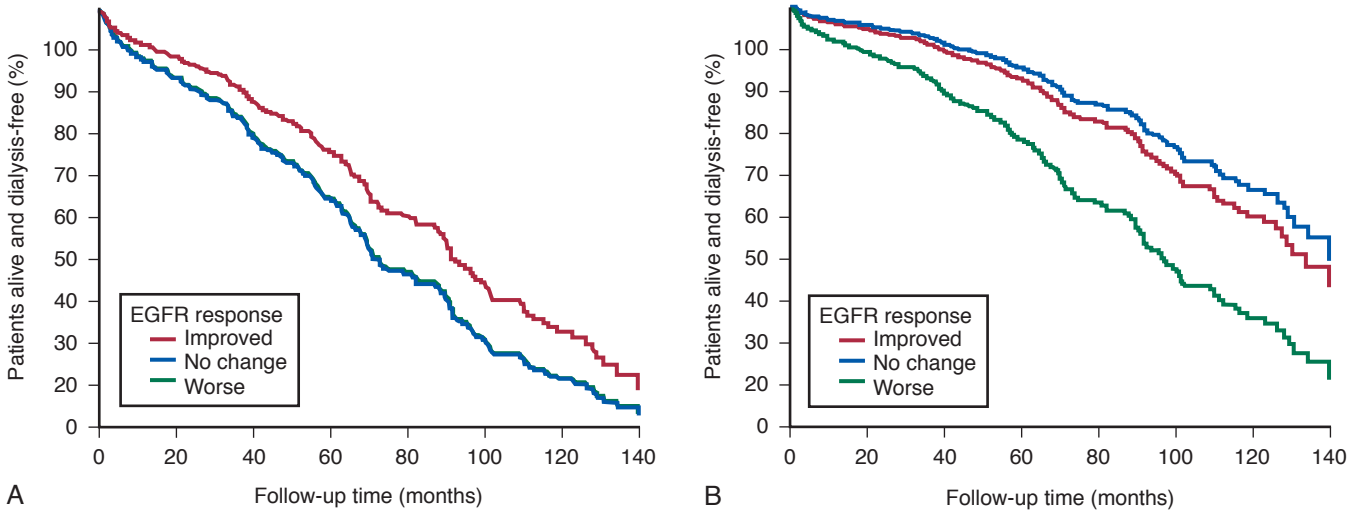

Figure 126.12 Predicted dialysis-free survival according to postoperative renal function response for patients with a preoperative estimated glomerular filtration rate *(EGFR)* of 25 mL/min per m^2 (25th percentile, **A**) or 39 mL/min per m^2 (median value, **B**). The interaction between preoperative EGFR and renal function response for dialysis-free survival was significant and independent. (From Cherr GS, Hansen KJ, Craven TE, et al. Surgical management of atherosclerotic renovascular disease. *J Vasc Surg*. 2002;35:236–245.)

Moreover, improved postoperative renal function demonstrated significant associations with increased dialysis-free survival compared with renal function unchanged. The relationship between each category of renal function response and dialysis-free survival demonstrated significant interaction with preoperative renal function. For patients with renal function unchanged, an increased risk of death or dialysis was observed for those with poor preoperative renal function.[4] For patients who worsened, an increased risk of death or dialysis was significant for those with preoperative renal function at median values of estimated glomerular filtration rate or greater. These significant interactions are shown for predicted dialysis-free survival according to preoperative renal function in Fig. 126.12.

Consequence of Failed Open Renal Artery Repair

Our secondary management of surgical repairs has included 10 repeat reconstructions and 10 nephrectomies for unreconstructable renovascular disease.[25] Regardless of the type of management (repeat reconstruction versus nephrectomy), and regardless of the blood pressure or renal function benefit after reintervention, the product-limit estimates for dialysis-free survival for patients experiencing failure of open operative renal artery repair were decreased compared with patients with primary patency. Patients requiring secondary intervention also demonstrated a significant and independent risk of eventual dialysis dependence (relative risk: 12.6; confidence interval: 4.5, 34.9; $P < .001$) and decreased dialysis-free survival (relative risk: 2.4; confidence interval: 1.1, 5.4; $P = .035$).[25] Whether failed balloon angioplasty with endoluminal stenting demonstrates significant associations with eventual dialysis dependence or death is not known.[29]

This experience with failed open renal artery repair reinforces two management strategies. First, irretrievable loss of excretory renal function observed after failed renal artery repair supports the view that renal revascularization should be performed for clear clinical indications, not as a prophylactic procedure in the absence of either severe hypertension or renal insufficiency.[3,6,61] Second, the direct aortorenal reconstruction used in the majority of these patients is durable.[25] The short length and high blood flow characterizing aortorenal repair has favored prolonged patency.

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Management of atherosclerotic renovascular disease has focused solely on hypertension. Along with the article by Hansen and colleagues (later in this list), this work establishes an incremental increase in excretory renal function as the dominant determinant of dialysis-free survival on follow-up. Among patients with severe hypertension and renal insufficiency, changing renal function at 3 weeks predicts dialysis-free survival—a relationship that is stable at 10 years of follow-up.

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The renin-angiotensin system has been demonstrated in virtually every tissue studied. This report summarizes the classic experiments of Goldblatt and provides an overview of the importance of tissue renin and angiotensin in both health and disease.

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See the annotation for Cherr and colleagues.

Rimmer JM, Gennari FJ. Atherosclerotic renovascular disease and progressive renal failure. *Ann Intern Med*. 1993;118:712–719.

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A complete reference list can be found online at www.expertconsult.com.

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127 CHAPTER

Renovascular Disease: Endovascular Treatment

MATTHEW S. EDWARDS and CHRISTOPHER J. COOPER

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The endovascular treatment of renovascular disease is controversial. Several adequately powered randomized trials have failed to support the efficacy of renal artery stenting. Nonetheless, renal revascularization remains a commonly used treatment option for selected patients who have clearly failed adequate medical therapy.[1-4] Endovascular techniques offer the benefits of decreased morbidity, mortality, patient recovery time, and hospital resource utilization compared with conventional open surgical revascularization.[5-10] This chapter provides an overview of the technical aspects involved in the performance of endovascular renal revascularization as well as current data concerning the technical results, clinical outcomes, and associated complications.

INDICATIONS AND CONTRAINDICATIONS

Indications

The indications for renal artery revascularization are controversial in light of the absence of level I data demonstrating the efficacy of such therapy in improving adverse event–free survival in patients with renovascular disease. Two clinical trials conducted in Europe, the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial[11] and the stent placement and blood pressure and lipid-lowering for the prevention of progression of renal dysfunction caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) trial,[12] and the more recent North American Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial[13] demonstrated no evidence to support the widespread application of renal stents to patients with renovascular hypertension or ischemic nephropathy. Both of the European trials have been criticized for methodologic shortcomings that limit the generalizability of their results and conclusions. Those limitations aside, the data presented in ASTRAL strongly suggest that the application of renal revascularization therapy to patients without strong clinical indications (i.e., prophylactic or "drive by" revascularization) lacks demonstrable benefit for the patient. The results from the CORAL trial, which was more scientifically rigorous and robust, also demonstrate no clinical benefit for the widespread application of revascularization to patients with renal artery stenosis and significant hypertension

with or without associated renal dysfunction. Furthermore, no interactions were observed for bilateral renal stenosis, degree of stenosis, or other clinical factors in terms of clinical benefit. Subsequent secondary analyses of the CORAL data and other reports have directly examined the prognostic value of translesion pressure gradients, baseline blood pressure, stenosis severity, and fractional flow reserve; no evidence of prognostic value for these parameters was observed.[14,15] Additional secondary analyses are planned for the CORAL data, which may be of assistance in identifying patient subgroups more likely to benefit from RA-PTAS, and CORAL-2 is being planned to try to address these remaining questions as well. In the meantime, guidance can be provided by existing consensus documents for severely affected patients or patients not representative of the CORAL study population. In general, those documents recommend renal revascularization based upon the presence of hemodynamically significant renal stenosis in the setting of severe, difficult-to-control hypertension with or without associated renal dysfunction or in instances of hypertension-associated cardiac disturbance syndrome.[16]

Hypertensive indications and manifestations of renovascular disease include a spectrum of clinical presentations, such as chronic, severe hypertension that is refractory to pharmacologic management; renovascular hypertension associated with cardiovascular disturbance; and more acute hypertensive emergencies, which refer to acute blood pressure elevations associated with target organ damage, including flash pulmonary edema, hypertensive encephalopathy, myocardial infarction, and acute renal failure. Given the recent findings of ASTRAL and CORAL,[11] which demonstrated no reduction in adverse cardiovascular or renal events despite significant blood pressure decreases after RA-PTAS, as well as other large case series demonstrating a lack of survival benefit in association with blood pressure improvement alone,[5,7,8,17,18] many authorities on renovascular disease are advocating the application of renal revascularization only to cases of truly refractory hypertension and those cases of hypertension complicated by defined end-organ effects.[14,19,20]

Renal dysfunction in patients with hemodynamically significant atherosclerotic renovascular disease is commonly referred to as ischemic nephropathy,[3,21] although definitive establishment of a causal relationship between anatomic renovascular disease and renal dysfunction can be challenging in an individual patient despite extensive diagnostic testing. The diagnostic evaluation and pathophysiology of atherosclerotic renovascular disease are discussed in detail in Chapter 125. Conditions that would support a causative relationship between anatomically defined renal artery stenosis and disease manifestations are primarily based on reported predictors of response to intervention and include a significant observed decline in renal function over a short period of time and the presence of anatomic disease affecting perfusion to the entirety of the functioning renal mass (i.e., bilateral renovascular disease or renovascular disease affecting a solitary kidney).[7,22-26] In truth, though, a causative relationship can be proved only by a physiologic response after revascularization. Available data from numerous authors indicate that documented improvement in renal function after renal revascularization is the most important predictor of clinical benefit, suggesting that renovascular disease associated with renal dysfunction may represent the most appropriate contemporary indication for RA-PTAS.[5,7,27-29]

Contraindications

Contraindications to the treatment of renovascular disease by endovascular means can be broadly classified into anatomic reasons, cases in which open revascularization is optimal, and prophylactic treatment. Anatomic contraindications involve situations in which the disease exists in renal arteries not easily treated with currently available endovascular devices or, more commonly, those arteries unable to be treated with any reasonable expectation of durable result. Renovascular disease extending into the terminal portion of a main renal artery and that involving a very short main renal artery represent two instances in which treatment with currently available technology may be a problem (Fig. 127.1). Renovascular disease existing in the branch arteries beyond the main bifurcation, lesions in multiple small renal arteries (Fig. 127.2), and lesions in children (most commonly hypoplastic lesions) are poor candidates for endovascular treatment because of durability concerns. When encountered, these situations are likely best treated with open surgical revascularization unless the patient represents a prohibitive surgical risk. Surgical revascularization should also be considered in patients with indications for renal revascularization who require open aortic surgery for other reasons.

With regard to prophylactic revascularization, the high rate of technical success and low incidence of periprocedural complications associated with endovascular renal artery revascularization have led to increasingly aggressive application of this technique, with rapid growth in utilization in recent years.

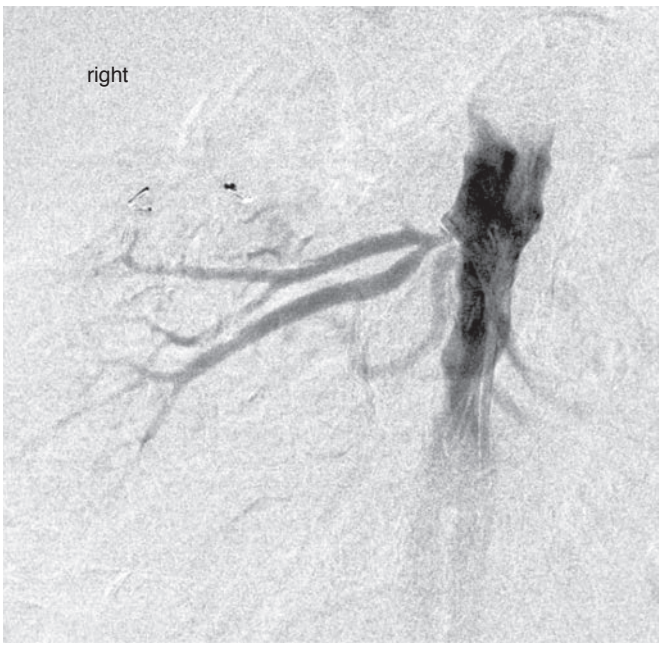

Figure 127.1 Arteriogram demonstrating early bifurcation of the *right* main renal artery.

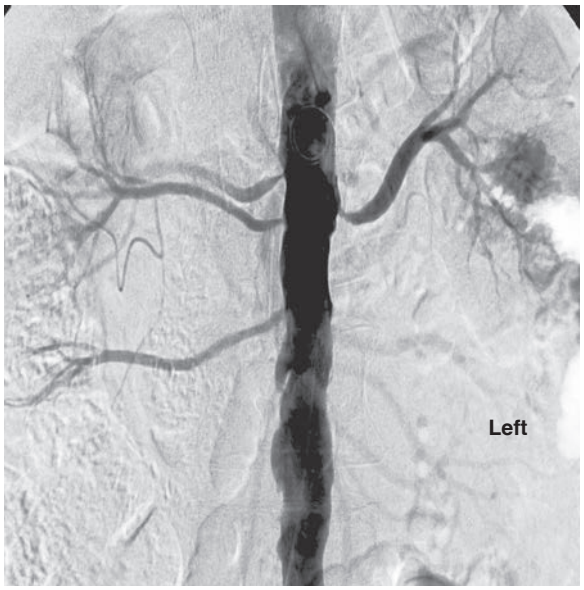

Figure 127.2 Abdominal aortogram demonstrates hemodynamically significant stenosis involving multiple renal arteries.

There is currently no evidence supporting prophylactic renal revascularization (i.e., endovascular treatment of renal artery stenosis in patients with normal renal function and hypertension that is well controlled with conventional medical therapy). Furthermore, the results of ASTRAL,[11] the conduct of which approximated prophylactic treatment in a large percentage of its participants, confirmed the lack of efficacy for such an approach in terms of blood pressure control, protection of renal function, reduction of cardiac events, or improved survival.

The natural history of atherosclerotic renal artery stenosis is associated with anatomic progression in only 10% to 30% of patients and progression to occlusion in 0% to 7%.[30-34] When anatomic disease progression does occur, it is not consistently associated with increases in blood pressure or serum creatinine concentration.[32] Considering the benign clinical course of asymptomatic renal artery stenosis in the majority of patients together with the risk of procedure-associated deterioration in renal function with intervention (see later) and the recent results from the CORAL trial, we support a nonoperative, noninterventional management strategy for asymptomatic patients with anatomic renovascular disease, normal or well-controlled blood pressure, and normal renal function.

RESULTS

Definitions of Success

Criteria for procedural technical success include reduction in stenosis as assessed by completion angiography and, when endoluminal stenting has been performed, complete coverage of the stenotic lesion by the deployed stent. Postintervention residual stenosis of less than 30% has been suggested as a threshold for technical success versus failure.[35] When contrast angiography demonstrates anatomically successful treatment of the stenotic lesion, these findings should be further confirmed with transduced pressure measurement immediately proximal and distal to the treated lesion. We consider a persistent systolic pressure gradient of 10 mm Hg or more to be suggestive of inadequate treatment and will repeat angioplasty in this setting in the absence of a significant residual stenosis on the completion angiogram.

Whereas technical success implies delivery of the intended treatment with satisfactory anatomic and hemodynamic results, determination of whether patient benefit has been derived requires consideration of the indications for intervention and the clinical responses observed. Approaches to the assessment of hypertension response have evaluated systolic, diastolic, and mean blood pressure and number of antihypertensive medications (both as continuous outcome measures and in a categorical fashion) using a combination of blood pressure and medication criteria.[35] The categorical definitions generally describe hypertension responses as cured, improved, or failed. Serum creatinine, cystatin C, estimated glomerular filtration rate (eGFR), and renal length and volume all represent continuous outcome measures indicative of renal function response to intervention. Categorization of renal response based on these measures has generally been determined as improved, unchanged, or worsened on the basis of postintervention change within a predefined range. We have generally used an increase or decrease of 20% or more in eGFR to define improvement or worsening in renal function, respectively, with all other patients categorized as unchanged. Alternative analytic approaches have evaluated the impact of renal revascularization on the rate of decline in renal function, defining worsened or unchanged rates of eGFR decline as failure and attributing procedure-related benefit to patients experiencing improvement, stabilization, or slowed rate of decline in eGFR.

Unfortunately, none of the previously discussed parameters assesses the impact of intervention on patient morbidity or survival. Survival free from dialysis, renal death, or cardiovascular morbidity represents an outcome that provides the most direct means of assessing the true benefit of intervention and likely represents the outcome of greatest importance in measuring the true value of renal revascularization to the patient.

Early Outcomes

A large body of literature exists reporting results of RA-PTAS in adult patients.[22,24,25,28,29,36-65] Technical success rates ranged from 88% to 100% and periprocedural 30-day mortality was 0% to 5%. Procedure-related complications associated with RA-PTAS occurred in 0% to 43% of patients. In general, these early results mirror those of ASTRAL and STAR.[11,12] In CORAL, technical success rates exceeded 95%, with no early patient deaths. Procedural complications were rare (less than 5% of cases) with the most common being dissection of the treated artery.

Late Outcomes

Late outcomes associated with endovascular renal artery intervention may be considered in terms of hypertension control, renal

function change, anatomic durability, and survival free of dialysis or cardiovascular morbidity.

Hypertension Response

Long-term hypertension response to RA-PTAS performed for atherosclerotic renovascular disease is most often improvement or failure, whereas cure (defined as normal blood pressure off all antihypertensive medications) is very uncommon. In the case series data,[22,24,25,28,29,36-65] hypertension improvement was seen in a majority of patients, but failure to improve blood pressure control was also a common outcome. In ASTRAL, no significant improvement in systolic blood pressure was observed when stenting was directly compared with medical therapy. A modest decrease in diastolic blood pressure was observed, and a statistically (although probably not clinically) significant decrease in the number of antihypertensive medications administered was also observed.[11] In CORAL, a small but significant decrease in systolic blood pressure was observed with no resultant decrease in medications.[13]

Reported predictors of hypertension response have included severity and duration of preoperative hypertension,[22,24,25] age of the patient,[66] percentage angiographic stenosis,[22] bilateral disease,[24] female gender,[25] and preoperative brain natriuretic peptide level,[67] although the brain natriuretic peptide finding is now in question.[68] Durable hypertension responses have been reported by several authors,[41,48,49,60] but others have observed a loss of initial hypertension response at 6-month post–RA-PTAS follow-up associated with a return to the preoperative number of blood pressure medications.[64,69] Given the data from ASTRAL[11] and CORAL[13] and the lack of association between blood pressure improvements and improved adverse event–free survival reported by multiple authors, there is increasingly limited enthusiasm for RA-PTAS for management of hypertension in the setting of normal renal function. For hypertensive indications, we would recommend limiting intervention for patients with truly uncontrollable and severe hypertension (which is increasingly uncommon given the potency of contemporary antihypertensive medications) and severe hypertension associated with target organ damage.

Renal Function Response

Although several case series have reported improvement as the most frequent categorical renal function response to RA-PTAS,[25,54,61] others have observed postoperative deterioration with a frequency equal to or greater than that of improvement,[40,45,47,48,53,60,62,63] and renal function was unchanged in the majority of patients after intervention. Reported rates of postintervention improvement versus deterioration in renal function vary widely in these series. The heterogeneous results may be partly attributable to differing patient selection criteria, particularly regarding the percentage of patients with baseline renal dysfunction (because patients with normal baseline renal function have no prospect for improvement through intervention). Weighted averages across series of unprotected RA-PTAS (see Table 146.1) demonstrate renal function improvement in approximately 25% of patients, with a roughly equal proportion experiencing postinterventional decline.

Rather than assessing renal function response as mean or categorical change in outcome measures, several studies have instead analyzed renal responses to RA-PTAS using breakpoint analysis based on the slope of either eGFR or reciprocal of serum creatinine concentration, with categorization of effect as improvement, stabilization, or failure.[35] Whereas these studies have demonstrated that RA-PTAS can reduce the rate of renal function decline,[36,55,61,69] interpretation of clinical benefit based on breakpoint analysis is controversial. Reciprocal creatinine analysis was employed in ASTRAL,[11] and RA-PTAS demonstrated no benefit in slowing the rate of renal function decline relative to the use of best medical management alone. One interesting finding from ASTRAL that deserves to be stressed was the observation of a much lower rate of renal function decline in the medical therapy arm than expected. This most likely represents the effects of ever-improving medical management on the natural history of atherosclerotic renovascular disease.

Case series data do suggest that improvement in renal function after renal revascularization is associated with improved survival. Hansen et al.[7] observed improved dialysis-free survival after open surgical revascularization in patients with early postoperative improvement in renal function, but no similar survival effect was noted in patients with unchanged renal function. Similar associations with improvement in renal function have also been demonstrated after RA-PTAS.[27,28,36,70] Although patients with increases in postoperative eGFR (or decline in serum creatinine concentration) appear to experience a survival benefit, clinical benefit resulting from stabilization of renal function or reduction in rate of decline is not clear. We therefore believe that in interpreting either categorized change in eGFR or breakpoint analysis data, patient benefit can be assumed only for patients with improvement, whereas presuming benefit in patients with unchanged or stable renal function may be conceptually flawed. Reported predictors of renal function response to RA-PTAS have included bilateral disease,[29] elevated baseline serum creatinine concentration,[25,29] higher levels of chronic kidney disease,[7,27] rapid preoperative decline in renal function,[23,36] impaired left ventricular function,[25] absence of metabolic syndrome,[71] smaller prerevascularization renal parenchymal volume,[72,73] and improved renal volume after revascularization.[73,74]

Renal Artery Restenosis After Intervention

Restenosis after RA-PTAS has been defined on the basis of angiography,[40,45,64] duplex ultrasound,[60] or both.[53,62,75] Reported rates of restenosis after RA-PTAS range from 5% to 66% and vary with duration of follow-up and criteria for repeated imaging.[37,39-41,45-48,53-55,62,64,65,75] Restenosis is more common in women and in patients exhibiting metabolic syndrome[76] and less common in patients treated perioperatively with statins.[6] Other factors that may occasionally contribute to restenosis include misplacement of the stent, most frequently inadequate proximal coverage of an ostial lesion, stent fracture, and severe calcification resulting in stent compression.

Anatomically identified recurrent stenosis must be considered in combination with clinical manifestations in formulating a management strategy. Conversely, acute worsening of hypertension or decline in renal function should prompt suspicion of

disease recurrence. Lederman et al.[40] identified recurrent disease twice as frequently when anatomic imaging was performed in the setting of clinical suspicion as opposed to routine postintervention screening (42% vs. 21%, respectively). The relatively frequent occurrence of recurrent disease should be considered when primary intervention is being contemplated, particularly in asymptomatic patients, and raises additional concerns about the long-term benefits achieved in patients with unchanged renal function after RA-PTAS.

Survival

Long-term survival data for patients undergoing RA-PTAS are presently limited to retrospective studies, ASTRAL, and CORAL.[11] Dorros et al.[49] observed a 74% 3-year survival rate after RA-PTAS; although renal failure was not a frequent cause of death, they observed decreased survival among patients with both baseline renal dysfunction and bilateral disease. Similar overall survival was reported by Kashyap et al.,[36] who also observed a 63% rate of dialysis-free survival; lack of postintervention improvement in renal function was associated with subsequent dialysis in that series. Similar relationships between baseline renal dysfunction, renal function response, and survival have been described by Kennedy et al.[28] Survival benefit associated with angiotensin-converting enzyme treatment[77] and statin use after RA-PTAS has also been described,[28,78] whereas preoperative congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease are additional factors that adversely affect postintervention survival.[28,40,78]

Similar data have come from ASTRAL and STAR.[11,12] In ASTRAL,[11] 5-year survival was 58% for the entire study sample, with no improvement demonstrated for those undergoing RA-PTAS. Improvement in diastolic blood pressure and reduced medication use observed for the stent arm participants were not demonstrated to have any effect on survival. As previously stated, no differences were observed in renal function, rate of renal function decline, or systolic blood pressure. In the results from STAR,[12] 2-year survival was slightly in excess of 80%, with no differences observed according to postrevascularization blood pressure control or renal function.

DESCRIPTION OF TECHNIQUE

Relevant Anatomy

The renal arteries originate laterally from the abdominal aorta and commonly assume an oblique orientation in their proximal course relative to the aortic axis (Fig. 127.3). Because aortography performed in a straight anteroposterior position can produce contrast overlap between the aorta and proximal renal arteries, resulting in inadequate visualization of ostial disease, oblique imaging is frequently necessary for renal arteriography and intervention. Multiple renal arteries are present in 18% of patients and may not be accurately characterized with renal artery duplex ultrasound.[32,79] Accessory arteries may therefore be an unanticipated finding in patients imaged with duplex ultrasound alone before intervention and must be assessed for occlusive disease during procedural planning. Distal renal artery diameter in patients undergoing endovascular intervention is usually 5 to 6 mm.[38,40] Poststenotic renal artery dilatation is common[40] and may result in size mismatch between the luminal diameter and stent or protection device; small-diameter arteries (<4 mm) increase the technical difficulty of ostial engagement and endovascular treatment. Endovascular treatment of atherosclerotic disease is most often performed for lesions of the ostial and proximal main renal artery. Branch vessel atherosclerosis is less frequently encountered and is seldom ideal for endovascular management.

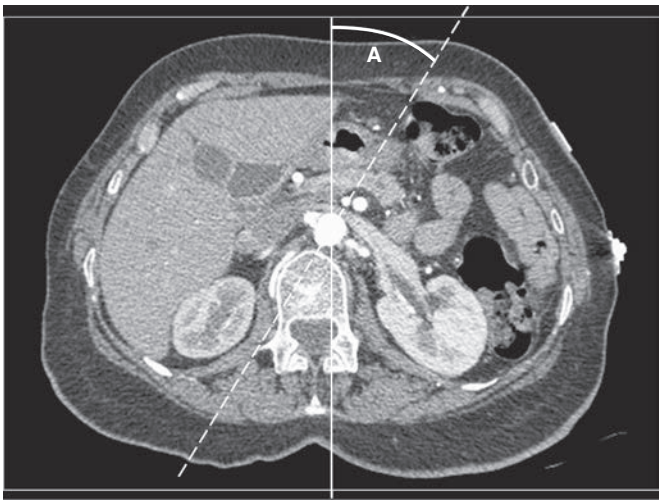

Figure 127.3 Oblique orientation of proximal renal arteries. Computed tomographic angiography demonstrates the axis perpendicular to the proximal renal arteries *(dashed line)* relative to the axis perpendicular to straight anteroposterior imaging *(solid line)*. The resulting angle *(A)* indicates the oblique correction needed to avoid artifact resulting from contrast overlap between the aorta and the proximal renal artery, which could result in underestimation of the degree of renal artery stenosis.

Operative Planning and Options

Contrast Considerations

Angiographic visualization of arterial anatomy is a fundamental element of both diagnosis and endovascular treatment of atherosclerotic renovascular disease. In addition to associated renal dysfunction and hypertension, common conditions among patients with renovascular disease that may predispose to contrast-induced renal function impairment include diabetes mellitus, congestive heart failure, and anemia.[40,80-85] Chronic volume depletion may represent an additional risk factor in patients taking diuretic medications. Procedure-related factors affecting risk of contrast-induced nephropathy include the volume, osmolality, and viscosity of the contrast agent administered.[83,86,87] Accordingly, procedural planning should incorporate assessment of the likelihood of contrast-induced nephropathy and implementation of protective measures for high-risk patients. Prophylactic strategies for the prevention of contrast-induced nephropathy have included a variety of measures directed toward maximizing renal perfusion, reducing oxidative stress, and inhibiting vasoconstriction. Hydration is a generally accepted

prophylactic measure, but evidence supporting the routine use of additional measures such as *N*-acetylcysteine, sodium bicarbonate, and ascorbic acid is inconsistent.[84,88] Currently, we prepare all patients for aortorenal arteriography with preoperative hydration using isotonic saline (reduced in the setting of significant congestive heart failure), administration of *N*-acetylcysteine, and routine use of iso-osmolar, nonionic contrast material at the lowest volume possible. For patients with renal dysfunction, we also administer sodium bicarbonate. In the setting of severe renal dysfunction (eGFR <30 mL/min per 1.73 m^2), carbon dioxide can be used as the primary contrast agent or as an adjunct during initial aortography and selective cannulation to reduce the administered volume of iodinated contrast material.[89,90]

Medical Management

In the setting of acute symptomatic presentations of renovascular disease (i.e., hypertensive emergency and acute renal failure), clinical stabilization is usually possible through medical management, making it possible to perform intervention in a lower-risk elective setting. Acute renal failure in the setting of renovascular disease can be precipitated by the initiation of angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists in patients with bilateral disease or hypovolemia.[91,92] Deferring renal intervention until functional recovery is complete in these patients avoids additional renal insult from the administration of nephrotoxic contrast material. For elective revascularization, nonsteroidal anti-inflammatory drugs, diuretics, metformin, and warfarin are withheld during the periprocedural period. Preoperative antiplatelet and statin therapy is initiated in all patients unless contraindicated. Routine antihypertensive medications are taken with a sip of water on the morning of the procedure.

Primary Angioplasty Versus Angioplasty and Stenting

Whereas primary angioplasty is currently considered appropriate endovascular management for renal artery fibromuscular dysplasia, primary endoluminal stenting for the treatment of ostial atherosclerotic renovascular disease is associated with superior technical success and a lower incidence of recurrent stenosis versus angioplasty alone.[9,37] Primary angioplasty is still commonly used for the management of recurrent disease. Nonostial atherosclerotic lesions may also respond well to angioplasty alone, but secondary stent placement should be considered if primary angioplasty is unsuccessful.

Bilateral Atherosclerotic Renovascular Disease

In patients with bilateral, hemodynamically significant atherosclerotic renovascular disease and significant renal dysfunction, one can initially proceed with unilateral treatment. If the clinical response is inadequate and there is no evidence of recurrent stenosis, contralateral RA-PTAS can be performed in a staged fashion. Compared with simultaneous bilateral RA-PTAS, a staged management approach can reduce the volume of contrast material administered during a single procedure setting and decrease the likelihood of acute renal injury. Downsides to this approach include the additional costs of two separate procedures, the incremental risk of vascular access complications, and patient inconvenience. However, this strategy may be useful in patients who are at a high risk for contrast-related complications.

Access

Common femoral artery access is safe, versatile, and our preferred access method for RA-PTAS. When selective renal artery cannulation is planned, selection of the femoral location contralateral to the targeted renal artery for access facilitates ostial cannulation through a tendency for the catheter to preferentially track along the contralateral aortic wall (Fig. 127.4). The brachial artery is an alternative access site that may be preferred in patients with aortoiliac occlusive disease, in patients with renal arteries with significant inferior angulation, or when selective cannulation through a femoral approach has been unsuccessful. Compared with the femoral artery, disadvantages of brachial access include higher incidence of access-related complications and limitations of the catheter or sheath diameter.[44,93] Recently, successful use of radial artery access for RA-PTAS has been described, although the technical challenges can be formidable.[94]

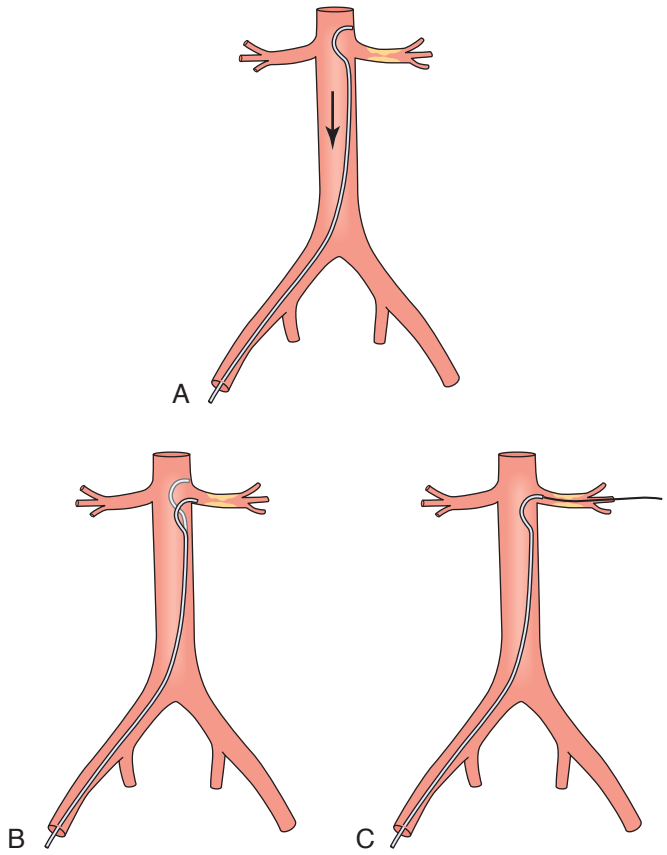

Figure 127.4 (A–C) Contralateral femoral access often facilitates selective renal cannulation. (From Schneider PA. More about how to get where you are going: selective catheterization. In: Campbell B, ed. *Endovascular Skills: Guidewires, Catheters, Arteriography, Balloon Angioplasty, Stents.* St. Louis: Quality Medical Publishing; 1998:71.)

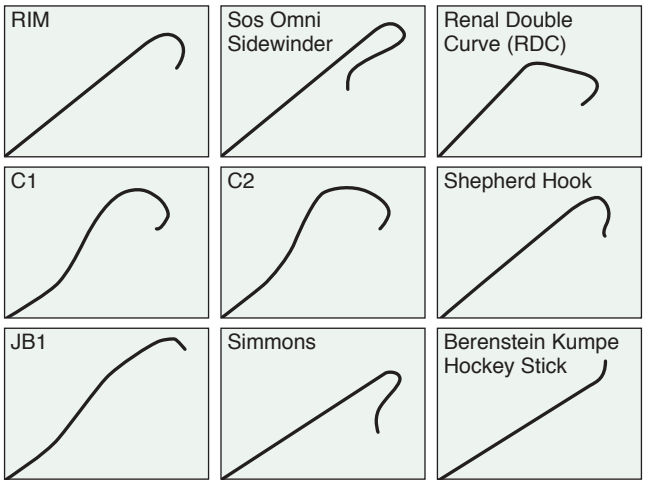

Figure 127.5 Various selective catheters commonly used to cannulate a renal artery.

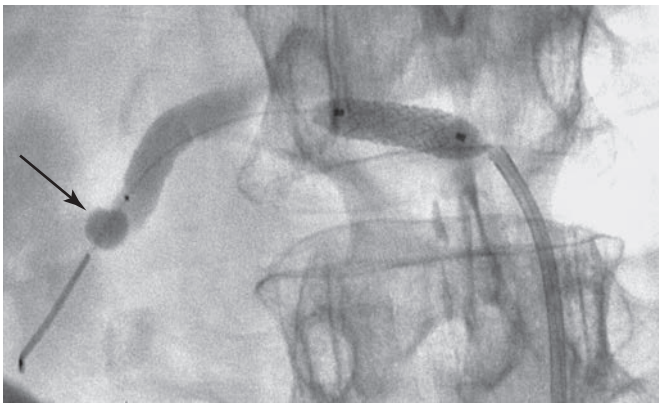

Figure 127.6 Renal angioplasty and stenting with distal renal artery balloon occlusion for embolic protection. A static column of contrast material is visible proximal to the occlusion balloon *(arrow)* during stent deployment.

Angioplasty and Stenting

After initial aortography, the patient is systemically heparinized and the target renal artery is accessed. Access can be gained by use of a selective catheter in the form of a guide catheter or a diagnostic catheter (Fig. 127.5). If a diagnostic catheter is used for engagement, the selective catheter and sheath are exchanged over a 0.014- to 0.035-inch guidewire for a guide sheath, which is advanced to the origin of the renal artery. Guide sheath and guide catheter access platforms both provide mechanical support during guidewire exchange and facilitate delivery of therapeutic devices to the targeted lesions. The choice of platform type is a matter of preference. Multiple device configurations are commercially available, and a luminal diameter of 6F will accommodate the majority of angioplasty and stenting systems. The tip of the guide sheath or catheter is positioned at or within the orifice of the targeted renal artery, and then a guidewire is passed across the stenotic lesion. We believe that smaller wire systems minimize renal artery trauma and are associated with technical advantages in crossing critical lesions. We prefer a 0.14-inch guidewire with a floppy, radiopaque tip for lesion passage. Once guidewire access across the stenotic lesion has been obtained, care must be taken to avoid advancement of the nontapered guide sheath or catheter, which could potentially result in injury to the luminal surface of the renal artery.

If renal artery distal embolic protection is being used, a wire system incorporating a distal renal artery occlusion balloon or filter is used for crossing the lesion and is subsequently deployed distally. If an occlusion balloon device is used, complete renal artery occlusion is confirmed by hand injection of contrast material (Fig. 127.6). Angioplasty with stenting is then performed, followed by aspiration of the static column of blood distal to the treated lesion, irrigation with heparinized saline, and repeated aspiration. The distal occlusion balloon is then deflated, and completion angiography is performed. Filter devices permit ongoing distal renal artery flow in their deployed configurations and use a porous membrane to trap embolic material. After angioplasty and stenting, the filter is collapsed to trap any captured embolic material before device withdrawal.

Both coaxial and monorail systems are available for RA-PTAS. For critical lesions, initial predilatation angioplasty may be necessary to permit subsequent endoluminal stenting. Angioplasty balloon diameter should be selected on the basis of quantitative angiography measurements; we select angioplasty balloons sized to the adjacent normal artery for primary RA-PTAS and select smaller balloons if predilatation is required (we commonly use a 2- to 4-mm × 20-mm low-profile balloon for predilatation). For predilatation, the angioplasty balloon should be inflated to nominal pressure for 15 to 30 seconds before deflation; noting the location of the balloon's "waist" before full inflation is helpful for subsequent endoluminal stent positioning. Patients may experience pain or discomfort during angioplasty that resolves with balloon deflation; symptoms persisting after deflation suggest renal artery injury; in the worst cases, they coincide with renal artery rupture. Guidewire access is maintained during balloon deflation and removal.

RA-PTAS is most commonly performed with balloon-expandable stents that have greater radial strength and can be deployed with precision; self-expanding stents offer greater flexibility but are used less frequently. Stents are placed with 1 to 2 mm of extension into the aorta for treatment of ostial or proximal disease; more distal stent placement frequently fails to support the true renal artery orifice; it is associated with increased risks of both technical failure and recurrent stenosis[41,42,46,95] and also increases the technical difficulty of subsequent surgical revascularization.[96] The shortest stent that will adequately cover the lesion should be used, and positioning can be guided by frequent hand injection of small volumes of contrast material into the guide catheter or sheath. A balloon-expandable stent is deployed by fully inflating the angioplasty balloon. Currently available stents are supplied premounted on low-profile delivery systems that often permit primary RA-PTAS without predilatation. If a residual waist is visible on fluoroscopy or completion angiography after stent deployment, the narrowed area can be postdilated with an appropriately sized angioplasty balloon (Fig. 127.7). However, dense calcifications sometimes preclude full stent expansion, and overly vigorous attempts to fully dilate the vessel can lead to the risk of vessel rupture. In all

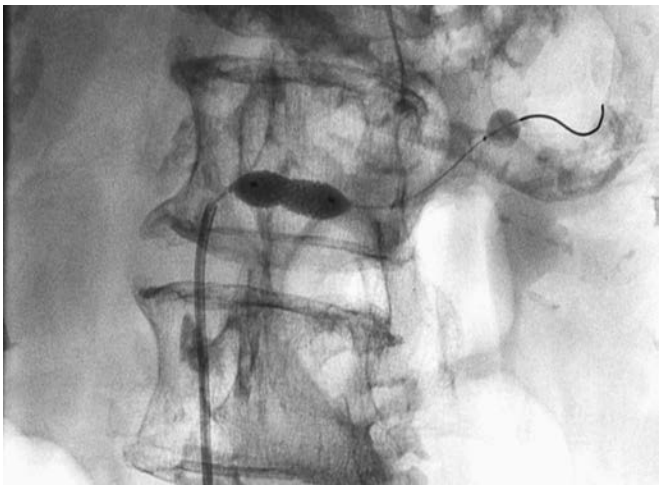

Figure 127.7 "Waisting" of an endoluminal stent being treated with postdeployment dilatation. The distal renal artery occlusion balloon is also visible.

cases, the vessel should be dilated only to the diameter of the nondilated segments, not to the diameter of areas of poststenotic dilatation.

After RA-PTAS, technical results may be assessed by completion angiography, intravascular ultrasound, or measurement of the pressure gradient. When RA-PTAS has been performed with protection of the distal renal artery by balloon occlusion, we find it useful to measure pressure gradients through the aspiration catheter, which has already been positioned distal to the treated lesion before balloon deflation. Use of the aspiration catheter to check pressure gradients during its withdrawal therefore avoids the need for passage of an additional catheter past the newly stented lesion, which could potentially lead to stent deformation or migration. Pressure gradients of the renal artery to the aorta can also be measured by pressure-sensing guidewires,[96,97] which also afford the advantage of allowing both pre- and postrevascularization pressure measurement without catheter exchanges. Once a satisfactory result has been obtained, the guidewire and sheath are removed and hemostasis is obtained. An adequate result includes a residual stenosis of less than 30% on angiography and a pressure gradient of less than 10 mm Hg between the distal renal artery and the aortic lumen. Intravascular ultrasound can also be used as an adjunct measure to assess lesion coverage, stent extension into the aorta, and patency.

Embolic Protection

Atheroembolization during RA-PTAS may occur, with the liberation of an alarming amount of debris of a size sufficient to occlude the arterioles of the kidney.[51,98] Embolic protection devices can be used during RA-PTAS, although none is currently approved by the U.S. Food and Drug Administration for such a purpose. Case series data have been published demonstrating infrequent deterioration of acute renal function and higher rates of renal function improvement after RA-PTAS when embolic protection devices were used.[50,51,56-58,99] One prospective randomized trial of the use of an embolic protection device has been published, the Randomized Comparison of Safety and Efficacy of Renal Stenting (RESIST) trial.[100] RESIST demonstrated an improvement in the rate of adverse renal events by embolic protection with the Angioguard filter device (Cordis Johnson & Johnson, Bridgewater, New Jersey), but only when the filter device use was combined with the potent glycoprotein IIb/IIIa inhibitor abciximab. The beneficial effects were most pronounced in those patients with greater degrees of renal dysfunction.[101]

Postoperative Management

After intervention, patients are monitored overnight for access site problems and hemodynamic instability. We routinely check a serum creatinine concentration the day after the procedure, before hospital discharge. Clopidogrel is continued after intervention for a minimum of 30 days; aspirin and statin therapy is continued indefinitely. Clinical follow-up with surveillance renal duplex ultrasonography is performed within the first month after intervention and subsequently at 6-month intervals for 2 years and annually thereafter. We consider a renal artery peak systolic velocity of more than 180 cm/s suggestive of disease recurrence[102] and consider all anatomically identified recurrent lesions in combination with their clinical manifestations. For patients experiencing anatomic recurrence in the setting of maintained blood pressure or renal function response to intervention, we increase the frequency of clinical follow-up and imaging surveillance but do not intervene unless clinical manifestations occur. When repeated intervention for recurrent disease is required, an endovascular approach is most often used.[76] In-stent stenosis due to intimal hyperplasia should be suspected with early disease recurrence; this pathologic process is difficult to manage with routine balloon angioplasty alone; technical results may be improved by initial dilatation with a cutting balloon[103] or by the use of a balloon-expandable covered stent.[104]

COMPLICATIONS

Reported major complications include hemorrhage, access site pseudoaneurysm, bowel or extremity ischemia, myocardial infarction, renal artery thrombosis, and acute renal failure.[105,106] Hemodynamic instability after endovascular renal intervention must be presumed to be hemorrhagic in etiology until proven otherwise, and computed tomography scanning is a useful tool for the identification and localization of bleeding. Hemorrhage is most commonly related to bleeding at the site of arterial access, but potentially fatal bleeding can also occur at the site of renal artery rupture secondary to angioplasty balloon, or guidewire perforation[107] of the parenchyma of the kidney, resulting in a perinephric hematoma. Retroperitoneal or perinephric hematoma accumulation that is undetectable on physical examination may be identified by non–contrast-enhanced computed tomography (Fig. 127.8); if no apparent bleeding is identified, other causes (such as myocardial infarction, heart failure, or reaction to the contrast agent) should be investigated. Bleeding due to renal artery perforation may be managed most commonly with endovascular techniques; surgical

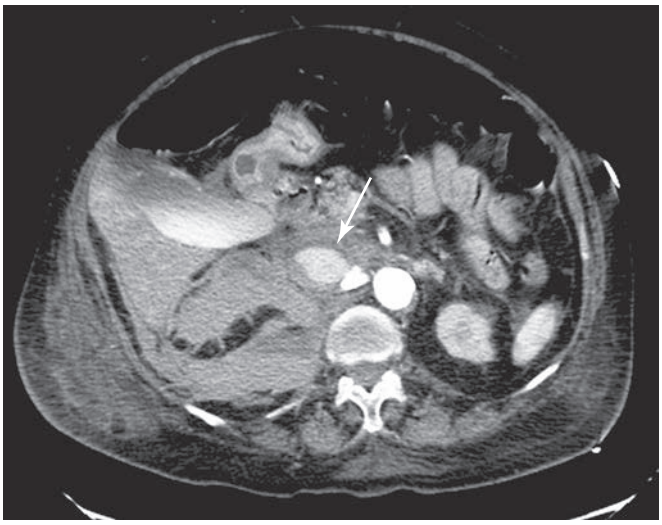

Figure 127.8 Right renal artery rupture resulting from angioplasty and stenting. A retroperitoneal pseudoaneurysm *(arrow)* is visible adjacent to the deployed right renal artery stent on a contrast-enhanced computed tomography scan. The patient required surgical exploration to achieve hemostasis.

exploration is rarely required. A perinephric hematoma due to guidewire perforation is a medical emergency and should be treated immediately and definitively with either endovascular embolization, coiling, or open surgical treatment. Successful endovascular treatment of procedure-related renal artery thrombosis by thrombolysis has also been described.[106]

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CHAPTER 128

Renovascular Disease: Aneurysms and Arteriovenous Fistulae

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RENAL ARTERY ANEURYSMS

Epidemiology

Even in referral centers, few vascular surgeons have extensive experience with the clinical management of renal artery aneurysms.[1,2] Autopsy studies have revealed an incidence of 0.01% to 0.09%, which is probably an underestimation because renal artery aneurysms may be small, intrarenal, or not specifically sought.[1,3] In two angiography studies, renal artery aneurysms were documented in 0.73% (7-965) to 0.97% (83-8525) of arteriograms; in a computed tomographic (CT) angiography study, the incidence was 0.7% (6-862).[4-6] Conversely, these reports might overestimate the prevalence of these lesions. At Pennsylvania Hospital (Philadelphia, Pennsylvania), we documented renal artery aneurysms in only 0.12% (1-845) of abdominal aortograms. Renal artery aneurysms are bilateral in about 10% of cases.[1,5] If fibrodysplastic cases are omitted, there is an equal incidence in males and females.[1,2,7]

Pathogenesis

Types of renal artery aneurysms include true (saccular and fusiform), false, dissecting, and intrarenal aneurysms.

True Aneurysms

More than 90% of true renal artery aneurysms are extraparenchymal.[2,8-10] The peak incidence is in patients between the ages of 40 and 60 years. Stanley[2] and Stanley et al.[10] have suggested that true aneurysms are probably due to either atherosclerosis or a congenital defect. Although arteriosclerotic changes have been identified in most aneurysms in patients with multiple lesions, these aneurysms are more likely due to a congenital medial degenerative process with weakness of the elastic lamina.[7,10] Lesions typically occur at the primary or secondary renal artery bifurcations and are rarely confined only to the main trunk of the renal artery.

Approximately 75% of true renal artery aneurysms are saccular. Saccular aneurysms occur almost invariably at the main renal artery bifurcation.[11] Fusiform aneurysms are usually associated with atherosclerosis or are a result of a poststenotic dilatation distal to a hemodynamically significant renal artery stenosis, the latter of which results from atherosclerosis or fibromuscular disease.[7,8,11,12] Fusiform aneurysms usually affect the main renal artery trunk.[8]

Arterial fibrodysplasia is often a direct contributor to the development of an aneurysm.[2,10] Medial fibroplasia is typically associated with multiple stenoses and poststenotic dilatation of

Abstract

Renal artery aneurysms and arteriovenous fistula are rare conditions, but indications for treatment need to be understood by vascular surgeons. Asymptomatic renal artery aneurysms in men and in women not of childbearing age can generally be followed until they are more than 3 cm in diameter because of the low risk of rupture. However, any size renal artery aneurysm needs to be repaired in women of childbearing age. Treatment includes insertion of a stent graft, embolization, or open surgical repair. Renal arteriovenous fistulae (AVFs) are usually asymptomatic, but when symptomatic or causing hypertension, can usually be treated by coil embolization.

Renal artery aneurysms and renal AVFs are rare entities but are encountered frequently enough that vascular surgeons need to be well-acquainted with the natural history, diagnosis, and management of these lesions. Endovascular interventions represent the newest advances in the treatment of these problems. Aneurysms and AVFs are discussed separately because they rarely occur concomitantly, and their clinical course and treatment differ.

Keywords

Renal artery aneurysms
renal artery arteriovenous fistula

the distal two-thirds of the renal artery. Renal artery aneurysms in association with fibromuscular dysplasia are generally only a few millimeters in diameter. The typical angiographic appearance of a renal artery involved with medial fibroplasia is a "string of beads." Larger aneurysms can also occur, however, and in one study, renal artery microaneurysms were found in 9.2% of adults with fibromuscular dysplasia.[10]

A rare cause of renal artery aneurysms is Ehlers-Danlos' syndrome. This disorder is associated with extreme arterial fragility and spontaneous rupture.[13]

False Aneurysms (Pseudoaneurysms)

False aneurysms of the renal artery arise from blunt or penetrating trauma and occasionally from iatrogenic causes such as renal artery catheterization or after nephrectomy. They represent contained ruptures of the renal artery, with only inflammatory and fibrous tissue encasing the leak.

Dissections

Spontaneous dissections confined to the renal artery that do not arise from the adjacent aorta are rare. However, primary dissections causing pseudoaneurysms affect the renal arteries more than any other peripheral artery.[2,11,14-17] Poutasse[11] and Stanley et al.[10] reported that 14 of 57 cases of renal artery aneurysms were due to spontaneous dissection. An intimal defect of the renal artery due to atherosclerosis is probably the underlying cause of spontaneous renal artery dissection causing aneurysms, along with dysplastic renovascular disease and trauma.[8] The incidence of dissection in patients with fibrodysplastic renal arteries ranges from 0.5% to 9.0%.[2,14] Dissection often extends into the branches of the renal artery and may pose particularly challenging reconstruction problems.

Traumatic renal artery dissection can occur secondary to blunt abdominal trauma or catheter-induced injury. Blunt trauma accounts for the higher prevalence of dissection in men and is more likely to result in right-sided injuries, possibly because of ptosis-related physical stresses affecting the renal pedicle.[2] Blunt trauma can cause renal artery dissection by either severe stretching of the artery, with fracture of the intima, or compression of the artery against the vertebra. Renal artery dissection caused by guide wires or catheters can occur, but is rare, having been observed in only 4 of 2200 selective renal artery arteriograms.[14]

Intrarenal Aneurysms

Less than 10% of renal artery aneurysms are intraparenchymal.[9,10] Intrarenal aneurysms are usually multiple and may be congenital, are associated with collagen vascular disease, or are posttraumatic. They may be associated with arteriovenous fistulae (AVFs), possibly as a result of spontaneous closure of a fistula. Intrarenal aneurysms can occur with polyarteritis nodosa and are usually in the renal cortex.[18,19]

Clinical Manifestations and Diagnosis

Most renal artery aneurysms are asymptomatic and are found on imaging studies, such as arteriography, ultrasonography, magnetic resonance angiography (MRA), or CT performed to investigate other intraabdominal pathology.[2,20,21] Clinical manifestations of renal artery aneurysms include rupture, hypertension, pain, and hematuria.

The most dreaded complication of renal artery aneurysm is rupture. Typical associated findings include acute abdominal pain and distention and hypotension. Intuitively, a stable renal artery aneurysm should not cause pain or symptoms, similar to a stable abdominal aortic aneurysm, so the clinician should hesitate to attribute chronic abdominal pain to a stable, noninflammatory renal artery aneurysm.

Renal artery aneurysms may be associated with severe hypertension. Macroaneurysms were found in 2.5% of arteriograms performed for the evaluation of hypertension.[10] Renal artery aneurysms may cause renovascular hypertension by distal embolization with segmental hypoperfusion, renin-mediated vasoconstriction, and fluid retention. Compression of an adjacent renal artery branch or luminal stenosis due to extensive thrombus may also lead to renin-mediated hypertension. Frequently, significant renal artery stenosis causes a poststenotic fusiform aneurysm, and the renal artery stenosis is responsible for the hypertension. Saccular and intrarenal aneurysms are much less likely to be associated with hypertension. We urge that caution be exercised in attributing the cause of hypertension to a renal artery aneurysm, especially if intervention is being considered. Just as renal artery stenosis without an aneurysm is currently less likely being treated with intervention and more likely treated with medical management, the clinician should hesitate to recommend endovascular or surgical intervention to treat hypertension potentially due to a renal artery aneurysm.

Patients with renal artery aneurysms caused by dissection may present with severe flank pain, hematuria, or acute hypertension, although most dissections are asymptomatic. CT angiography or MRA is essential to detect dissection.

Intrarenal aneurysms may rupture into calices.[3] In addition to pain, microscopic or gross hematuria may occur. Similarly, renal artery aneurysms may rarely cause obstruction of the collecting system.

Indications for Intervention

Indications to repair a renal artery aneurysm are related to the risk of rupture, hypertension, acute dissection, and other clinical symptoms. Because of the lack of controlled data, controversy persists regarding indications for repair of asymptomatic renal artery aneurysms. The optimal method of repair is also controversial.

Rupture and Prevention of Rupture

Rupture of a renal artery aneurysm is an indication for emergency intervention, as it is for virtually any arterial aneurysm. Probably less than 3% of renal artery aneurysms rupture.[2,10] This complication is associated with a mortality rate of approximately 10% in men and nonpregnant women.[2,10,22,23] In a hemodynamically stable patient, an emergent CT scan may reveal the pathology and allow the surgeon to plan the operative repair.

Prevention of rupture is the most common indication for intervention in cases of asymptomatic renal artery aneurysms.

Traditionally, repair has been recommended for renal artery aneurysms greater than 2 cm in diameter.[8,12] We strongly believe this recommendation is overly aggressive, and more conservative guidelines for intervention based on more recent studies with longer follow-up have been suggested.

Older series suggested higher rates of rupture. Harrow and Sloane[24] reported one of the highest rates of rupture of renal artery aneurysms, noting 14 ruptures in 100 cases. In another series of 126 renal artery aneurysms, six ruptured.[25] However, most other series of asymptomatic renal artery aneurysms in men and nonpregnant women report a much lower incidence of rupture. Only 1 of 62 patients with aneurysms 4 cm in diameter or smaller ruptured after follow-up from 1 to 17 years.[26] None of 19 small aneurysms in another series ruptured.[22] A group of 21 patients was observed for an average of 3 years without rupture.[21] In another series of 18 patients, no renal artery aneurysms ruptured that were less than 2.6 cm who were followed for 1 to 16 years.[1] There were no ruptures in a series of 32 patients (who eventually underwent surgery) with renal artery aneurysms that ranged from 0.7 to 9 cm.[13] Of 83 renal artery aneurysms found on arteriography and followed without surgery,[27] none ruptured or became symptomatic after a mean of 4.3 years.[5] In a pooled analysis, there were no ruptures in more than 200 renal artery aneurysms observed for up to 17 years.[7] Because of the very low risk of rupture and the relatively high rate of significant postoperative complications, especially with open surgery, we recommend that a more conservative approach be used for these cases and that a 2-cm guideline for intervention is too aggressive and unwarranted.

Besides size, other factors may play a role in the consideration of elective surgery for asymptomatic renal artery aneurysms. Calcification of the aneurysm has been thought to protect against rupture. Poutasse[12] suggested that a heavily calcified renal artery aneurysm may be less likely to rupture than a noncalcified or minimally calcified one. In a review of cases through 1959, 14 of 100 noncalcified aneurysms ruptured.[24] In a more recent series, 15 of 18 ruptured renal artery aneurysms were noncalcified.[28] However, in a series of 62 solitary aneurysms less than 4 cm in diameter, one-third were not calcified, and only one aneurysm in the entire series ruptured after 1 to 17 years of follow-up.[23] Because of these conflicting data, some authorities believe that the presence or absence of calcification is not relevant when predicting the risk of rupture.[2]

Most authorities agree that pregnancy is associated with a significantly increased risk of rupture for renal artery aneurysms.[2,10,20,29] Pregnancy may increase the risk of rupture because of a hyperdynamic state with increased blood volume and cardiac output, hormonal influences, and increased intraabdominal pressure due to the gravid uterus.[1,10] Cohen and Shamash[29] reported 18 cases of rupture during pregnancy. In another series of 18 patients who underwent surgery for renal artery aneurysms, the only two ruptures were in women at childbirth; both of these aneurysms measured only 1 cm in diameter.[1] In a review of 43 ruptured renal artery aneurysms, 81% occurred in women; 21 of the 35 women in this series were younger than 40 years old, and 18 were pregnant. Of the 18 aneurysms of known size, three ruptured when they were less than 2 cm.[30] Rupture of renal artery aneurysms in pregnancy has been associated with a maternal mortality rate of 55% and a fetal death rate of 85%.[29,31] Vascular surgeons should maintain an aggressive surgical or endovascular approach for pregnant women with renal artery aneurysms of any size, namely more than 1.5 times the diameter of the normal adjacent artery.

It seems prudent to recommend repair of renal artery aneurysms in men and women older than childbearing age when the diameter is at least greater than 3 cm in good-risk patients when there is reasonable certainty that nephrectomy will not be required.[24,27] In a recent review of 865 renal artery aneurysms from 16 institutions, the authors concluded that these aneurysms rarely rupture when asymptomatic (even if >2 cm), major complications occurred in 10% of patients postoperatively, and recommended repair for renal aneurysms greater than 3.0 cm in asymptomatic patients of non-childbearing age (Klausner et al., 2015). An even more conservative approach reserving repair for aneurysms greater than 4 cm has been suggested; in our opinion, this is not unreasonable.[32] As previously mentioned, any renal artery aneurysm in women of childbearing age should be repaired—namely, more than 1.5 times the diameter of the normal adjacent artery.

Hypertension

Although the prevalence of hypertension in patients with renal artery aneurysms is approximately 80%, there is no conclusive evidence that the aneurysms themselves are the direct cause of hypertension, unless there is an associated stenosis or compression of an adjacent artery.[1,10,20] In a series of 39 patients with renal artery aneurysms, 26 had diastolic hypertension, but only nine (23%) patients had hypertension that was of renovascular origin.[1] The indication for intervention for renovascular hypertension due to renal artery stenosis continues to be failure of medical management. The same criterion should be applied when a renal artery aneurysm is present (if large size alone is not otherwise an indication for repair). If the primary indication to repair a renal artery aneurysm is poorly controlled hypertension, a nephrology consult should be routinely obtained to be sure there are firm indications for intervention for this reason. Both the stenotic artery and the aneurysm should be repaired.

Dissection

Emergent intervention is required for dissections that cause renal artery aneurysms and threaten the viability of the kidney. Nephrectomy is frequently required because of the extensive damage to the renal branch vessels and the limited time available to salvage a previously healthy kidney that cannot tolerate prolonged periods of ischemia. If hypertension is the only manifestation of a chronic dissection and the hypertension is well controlled by blood pressure medications, or if the patient is asymptomatic and a renal artery dissection is found incidentally (without an associated aneurysm), endovascular or surgical repair is not justified.[10]

Other Clinical Manifestations

If a patient with an intact renal artery aneurysm as documented by CT or magnetic resonance imaging (MRI) is symptomatic,

repair may be indicated. Acute onset of symptoms is more worrisome than a patient referred for months of abdominal pain or fullness, unless the renal artery aneurysm is very large. Symptoms may be a harbinger of impending rupture. Embolization of mural thrombus from the aneurysm to the renal parenchyma may also account for these symptoms.[9] Nonetheless, it is difficult to attribute chronic abdominal pain to an intact 2-cm diameter renal artery aneurysm. Other causes need to be thoroughly investigated.

Treatment: Medical, Endovascular, Surgical

Repair of a Ruptured Renal Artery Aneurysm

If emergent surgery is required for a ruptured renal artery aneurysm, a sizable juxtarenal hematoma may not allow safe exposure of the proximal renal artery or even of the aortic immediately above the renal arteries for clamping to obtain proximal control. Therefore, in many cases, a midline approach and supraceliac aortic control may be temporarily required. If the bleeding is quickly controlled, the patient is hemodynamically stable, and the proximal and distal renal arteries lend themselves to a relatively quick and straightforward bypass, consideration can be given to reconstruction. In most cases, however, nephrectomy is required because of the instability of the patient or the limited warm ischemic time of the kidney (less than 30-60 minutes in healthy patients). The prolonged ischemia of the kidney and the technical and time-consuming nature of surgical repair with a bypass generally result in a nonsalvageable kidney.[2,10,11,26] If the aneurysm extends into the renal parenchyma or if a "bench" repair of the kidney is required, the patient is generally best treated by nephrectomy, as long as the contralateral kidney is intact with normal function.

A stable patient with a ruptured renal artery aneurysm may be treated with endovascular techniques. The use of a stent graft may be the preferred treatment for lesions not involving the distal renal branches, as reported by Bloemsma et al.,[33] and Routh et al.[34] reported thrombosis of a leaking saccular aneurysm using Gianturco coils, thrombin, and bucrylate.

Elective Repair of Renal Artery Aneurysm

Elective repair of a renal artery aneurysm is usually more challenging than revascularization for renal artery stenosis. Most renal artery aneurysms extend past the bifurcation of the main renal artery and frequently extend into the renal parenchyma. For in situ repairs of a renal artery aneurysm, the left kidney can be exposed through a left retroperitoneal or midline transperitoneal approach. The right kidney can be exposed through a midline transperitoneal approach with a Kocher maneuver to reflect the right colon and duodenum medially or with a right subcostal incision.

Several methods have been used to repair renal artery aneurysms. The most straightforward technique for saccular aneurysms involves aneurysmorrhaphy with primary repair or patching. In three combined series of patients who underwent surgical repair of renal artery aneurysms, approximately one-third (6/18, 3/10, and 6/23) of the aneurysms were able to be repaired in this manner.[1,9,20] A common renal arterial reconstruction is an end-to-side anastomosis of a small renal artery branch to the main renal artery or a side-to-side anastomosis of two small renal arteries to create a common inflow channel with a single, larger diameter lumen, which can then be anastomosed to the more proximal renal artery (or to the distal end of a bypass). Because the small branches of the main renal artery are often involved with the aneurysm, a branched autologous graft is preferred to reconstruct these lesions. The internal iliac artery is an excellent choice in these reconstructions because of its multiple small side branches.[27,35] Alternatively, the saphenous vein is preferred.[8,20] The proximal anastomosis of the graft is usually the infrarenal aorta. Useful alternative reconstructions include a splenorenal bypass for a left-sided renal artery aneurysm and hepatorenal bypass for a right-sided aneurysm.

If multiple branch vessels are involved and renal ischemic time is expected to exceed 30 to 60 minutes, and especially if the cause of the renal artery aneurysm is dissection resulting in a friable vessel, extracorporeal or bench surgery may be required.[36,37] Ex vivo surgery requires nephrectomy, followed by hypothermic perfusion of the kidney with a heparinized renal preservation solution. The kidney can then be autotransplanted to its original bed, as Dean et al.[38] and Crutchley et al.[39] prefer, or to the iliac fossa. For renal autotransplantation into the iliac fossa, a flank incision with a retroperitoneal approach is used for exposure of the kidney, ureter, and iliac artery. Gonadal and adrenal veins are divided to obtain an adequate length of renal vein. If the reconstruction can be safely performed by placing the kidney on the anterior abdominal wall, the ureter does not need to be divided. The procedure is occasionally best performed at a separate table after dividing the ureter and removing the kidney from the operative field. Perfusion is carried out through the main renal artery to preserve the kidney, while selected branches are individually repaired and other branches are perfused. The kidney may be perfused with a heparinized crystalloid solution, such as Collins solution or lactated Ringer's solution with heparin 1000 U/L with 12.5 g of mannitol, while the kidney is wrapped with gauze and placed in a chilled solution at 4°C.[8,34,40] The use of continuous pulsatile perfusion is controversial.[34]

When performed for proper indications by well-trained vascular surgeons, elective repair of renal artery aneurysms has been associated with very low mortality.[2,9,40,41] English et al.[42] reported a 1.7% perioperative mortality rate in 62 patients with 72 renal artery aneurysms with a 4-year patency of 96% and cured or improved hypertension in three quarters of patients. Pfeiffer et al.,[43] from Germany, reported similar excellent long-term surgical results in a series of 94 patients. A series of 26 renal artery aneurysms that required reconstruction of first- or second-order branches were repaired primarily with in situ techniques. Autogenous vein bypasses resulted in a mortality of 0%, with long-term patency of 95% at an average follow-up of 99 months (range, 1-300 months).[44] Ex vivo repairs have been shown to be safe and effective by Dean et al.,[38] Crutchley et al.,[39] and others.[36] In a review of ex vivo repairs, postoperative mortality rates ranged from 0% to 9.6%.[45] The use of bifurcated internal iliac artery autografts was also highly successful in a

series of 11 patients, most with fibrodysplastic aneurysms who were treated by in situ or bench repair.[35]

Recent technologic and surgical developments have allowed less invasive surgical repair of complex renal artery aneurysms. Both laparoscopic and robot-assisted techniques have been described.[46-48]

An alternative approach to the treatment of renal artery aneurysms includes the use of endovascular techniques.[27,49-51] Degenerative renal artery aneurysms have been treated with transcatheter embolization with detachable platinum coils that occlude the aneurysms but maintain renal flow.[50-52] In a small series of endovascular repairs, Klein et al.[50] treated 12 renal artery aneurysms using selective endovascular embolization with nondetachable microcoils or Guglielmo's detachable coils. In another series, 13 patients with renal artery aneurysms were successfully treated using a variety of endovascular techniques with combinations of coil embolization, liquid embolization, stenting, and stent grafts, with no complications after an average follow-up of 43 months (range, 13-103 months).[53] A series of 18 renal artery aneurysms were also treated with endovascular intervention.[54] Sixteen of the 18 aneurysms were embolized utilizing adjunctive techniques to protect embolizing into the main renal artery. There was a 100% technical success rate, with only one aneurysm showing residual minor flow into the sac and with no long-term complications. Alternatively, several authors have recently reported using ethylene vinyl alcohol copolymer to ablate renal artery aneurysms.[55-57]

Endovascular stent graft exclusion as a definitive treatment for renal artery aneurysms has been widely reported. Many aneurysms extend to branch vessels, making this approach risky or ill-advised, but it may be ideal for aneurysms of the main renal artery not involving branches. Advances in stent graft technology, with smaller diameter devices and lower profile delivery systems, have made definitive treatment of renal artery aneurysms feasible. A review of the English literature analyzing the use of stent grafts to treat renal artery aneurysms up to 2010 yielded 22 cases with a technical success rate of 91% (20 cases), without any deaths or significant morbidity reported.[58] Although most published series have been small, results have been excellent, and this approach will undoubtedly become more common as technology improves.[59-63]

A nationwide inpatient sample of 6234 isolated renal artery aneurysms from 1998 to 2011 revealed an increase in endovascular repairs without a decrease in open repairs (Buck et al., 2016). Although the in-hospital mortality was low for both endovascular intervention (1.8%) and open repair (0.9%), complication rates were greater than 10% for both. The authors concluded that indications for repair of renal artery aneurysms should be re-evaluated and possibly be less aggressive.

Fibromuscular Dysplasia

Poststenotic dilatation causing hypertension resulting from fibromuscular disease can be treated by balloon angioplasty of the stenotic lesion. When the lesion extends into the branches of the main renal artery, surgery can yield excellent results. Dean et al.[38] reported 24 patients with fibromuscular disease, many of whom had branch aneurysms; all but one did well.

Intrarenal Aneurysms

Intrarenal aneurysms represent particularly challenging lesions. Frequently, a partial nephrectomy is required.[45] Intrarenal aneurysms in association with polyarteritis nodosa have also been successfully treated with renal artery embolization, with preservation of the kidney.[64]

RENAL ARTERIOVENOUS MALFORMATIONS AND FISTULAE

Arteriovenous malformations (AVMs) and AVFs are uncommon lesions that can be associated with hematuria, hypertension, renal dysfunction, high-output congestive heart failure, and even rupture. More than 200 cases have been reported since the first description in 1928.[65] Fistulae may be congenital or acquired. Multiple diagnostic modalities are now available, although conventional selective arteriography remains critical in therapeutic interventions. Many asymptomatic lesions do not require treatment. In the past, symptomatic lesions were treated surgically, but endovascular treatment has now supplanted surgery in most cases.

Epidemiology and Pathogenesis

Congenital Arteriovenous Malformations

True congenital AVMs of the kidney are rare, with an incidence of only 0.04%.[66] In a large series, only 1 congenital AVM was noted in 30,000 autopsies.[67] These lesions represent approximately one-fourth of all renal AVFs.[68,69] The right kidney is involved more often than the left, and although multiple lesions can occur, a single focus is more common.[36] The angiographic appearance of the lesions is similar to that of AVMs elsewhere, with large coils of dilated vessels. An early "blush" is noted and correlates with the degree of arteriovenous shunting.

These lesions have been described as cirsoid or varix-like, and are generally focal and located in the renal medulla. AVMs are not neoplastic, but enlargement presumably can occur because of vessel dilatation and hypertrophy associated with high-flow volume from arteriovenous shunting. Symptomatic AVMs have been reported in pregnancy,[65,70] and it is thought that the hyperdynamic state of the gravida leads to increased AVM flow and symptoms. Histologically, involved vessels have irregular fibrosis or intimal hyperplasia, as well as medial hypertrophy.

Acquired Arteriovenous Fistulae

Acquired AVFs may occur spontaneously. Spontaneous AVFs have been documented in association with fibromuscular dysplasia[71] and are thought to develop when a dysplastic or aneurysmal renal artery erodes into a neighboring vein.[72] This may also occur with renal malignancy, and significant arteriovenous shunting is a hallmark of renal cell carcinoma.[73] With arteriography, it can be difficult to differentiate a renal malignancy from a congenital or acquired AVF, although CT and MRI generally reveal a mass distinct from the renal parenchyma in malignancy.

Traumatic AVFs are the most common lesions, accounting for more than 70% of all renal AVFs.[65] These lesions may occur after nephrectomy, and are related to the erosion of the arterial stump into the vein with mass ligature,[67,74,75] after renal artery angioplasty,[65] after blunt[76] or penetrating[74] trauma, after nephrostomy,[76] and most commonly, after percutaneous renal biopsy. With the routine use of needle biopsy for the diagnosis of rejection in renal allografts, the incidence of acquired AVFs has grown, although only 1% to 2% of patients who undergo needle biopsy develop symptomatic AVFs.[77,78] However, the true incidence of AVF is 15% to 18% when arteriography is routinely used.[79,80] Similarly, Ozbek et al.[81] found AVFs in 8 of 64 patients (12.5%) monitored by color duplex ultrasonography, whereas only 5% developed AVFs in the study of Rollino et al.[82] In the prospective study of Merkus et al.,[79] who used routine color duplex surveillance, 10% of patients who underwent biopsy developed AVFs.

Clinical Presentation

The majority of both congenital and acquired AVFs do not produce clinical symptoms, and many lesions are noted incidentally in studies done for other reasons. The most common symptom of congenital AVM is hematuria, which occurs in 72% of cases.[67] Hematuria occurs when subepithelial varices erode transitional epithelium into the collecting system. A dramatic presentation with massive hematuria can occur,[70,83,84] although minor or microscopic hematuria is more common. Hypertension occurs in congenital AVMs and is also the primary abnormality in most acquired AVFs that are described as symptomatic. The hypertension is renin-mediated, based on diminished glomerular filtration pressure distal to the fistula because of arterial "steal."[69,85,86]

Although AVFs are generally painless, intermittent perilumbar discomfort has been reported in some patients.[73,75] This discomfort is generally associated with hematuria and may re-present as renal colic. In addition, dyspnea and other symptoms of congestive heart failure may be the primary complaint in some patients; this is more common with acquired lesions, and only with those having a large communication between the artery and vein. This "high-output" type of heart failure manifests as tachycardia, left ventricular hypertrophy, and cardiomegaly, and a palpable thrill in the flank. A continuous abdominal bruit is a hallmark of acquired AVFs and is frequently noted with congenital AVMs as well. Retroperitoneal or intraabdominal hemorrhage rarely occurs with AVMs and AVFs.[83,87] However, patients with rupture present with severe abdominal and flank pain and shock, a clinical picture indistinguishable from ruptured abdominal aortic aneurysms.

Diagnosis

Excretory urography is performed in many patients presenting with hematuria or flank pain. A filling defect may be noted in the kidney, and dilated vessels can compress the collecting system, although these findings are not specific.

CT can usually define AVFs and AVMs within the kidney, but it is not always possible to differentiate these lesions from other hypervascular abnormalities (e.g., renal cell carcinoma). Similarly, radionuclide imaging can demonstrate early augmented perfusion, but differentiation from malignancy is not possible.[88] In contrast, CT angiography has significantly improved the noninvasive imaging of AVFs and AVMs.[89] Likewise, contrast-enhanced MRA allows three-dimensional reconstruction that can provide visualization not possible with conventional angiography.[90]

Color duplex imaging is also of growing importance in the diagnosis of AVMs and AVFs. Because it is inexpensive and noninvasive, it is the ideal study for screening purposes. Color duplex imaging has been used liberally to assess for AVFs after percutaneous renal biopsy.[79,91,92] Marked turbulence is noted on color examination, and Doppler spectral analysis reveals an elevation of peak systolic flow velocity and a larger increase in end-diastolic flow velocity compared with the normal renal artery, with a resultant low resistive index.[81,91]

In the past, contrast arteriography was the definitive diagnostic modality for renal AVMs and AVFs. Rapid opacification of the inferior vena cava is noted. Depending on the size of the fistula, the nephrogram may be diminished distal to the AVF. With congenital AVMs, multiple segmental and interlobar arteries communicate with varix-like veins, whereas a single arterial communication is generally present with acquired AVFs.[67]

Treatment: Medical, Surgical, Endovascular

The majority of both congenital and acquired AVFs do not cause symptoms and do not require treatment. However, patients may become symptomatic, and even if asymptomatic, should be closely observed for the development of hypertension, hematuria, or high-output cardiac failure. Most AVFs occurring after percutaneous renal biopsy close spontaneously.[79,81,85,92,93] Periodic duplex surveillance, along with clinical follow-up for the development of hypertension or renal insufficiency, is indicated. If a postbiopsy AVF persists at 1 year, it is not likely to close spontaneously,[77] although intervention should still be delayed until the development of symptoms.[79,86] Spontaneous regression of AVMs unrelated to trauma has also been reported.[94,95] Although hypertension related to an AVF may be readily controlled with angiotensin-converting enzyme inhibitors,[71] the long-term effect on renal function is not known. In most published reports, patients with hypertension have undergone surgical or endovascular therapy; thus the natural history of medically treated patients with hypertension secondary to AVFs remains undefined.

For patients with symptomatic AVFs, surgery remains an option, although a declining one (Chimpiri and Natarajan, 2009).[96,97] Except for very peripheral lesions, a transperitoneal approach is preferred to establish proximal arterial and venous control at the renal pedicle. Because of the frequent presence of thin-walled dilated veins and channels, surgery can be challenging. With surgery, ligation of the feeding vessel or vessels alone is often not possible, and partial or total nephrectomy is often required. The resultant loss of functional renal mass, as well as the morbidity of the operation itself, makes endovascular treatment an attractive approach.

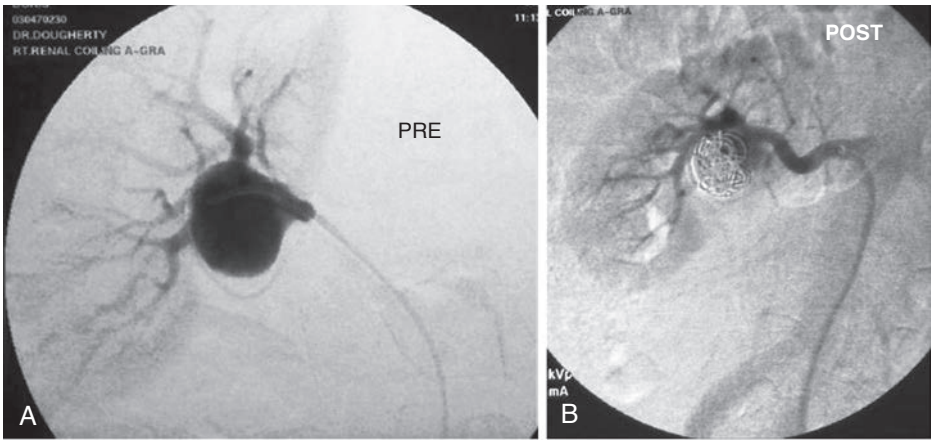

Figure 128.1 (A) Arteriogram showing a post-traumatic arteriovenous fistula. This patient experienced a stab wound to the flank and presented with hematuria. (B) After Gianturco coil embolization of multiple arterial branches, venous communication is no longer present. Hematuria resolved, and the patient recovered uneventfully.

There are now more than 3 decades of experience with percutaneous arterial embolization therapy for congenital and acquired AVFs.[98] Because renal arteries are "end arteries," they are especially amenable to therapeutic occlusion using gelatins, glues, alcohols, silicon, steel and platinum coils, and detachable balloons.[23,68,87,92,99,100] The development of co-axial catheter systems has allowed highly selective embolization, which can preserve renal function; loss of functional renal parenchyma is reportedly between 0% and 30% with modern techniques. In general, smaller AVFs are treated with glues or macroparticles, whereas coils and balloons are used for larger vessel fistulae (Fig. 128.1; Wetter et al., 2012).[101] Because Gelfoam (Pfizer, New York) and autologous clot resorb, recanalization with recurrence of symptoms can occur in up to 50% of cases.[102,103] For this reason, and because of the perception that microcoils are associated with less indiscriminate embolization than glues and alcohols, recent trends favor the use of microcoils even for smaller AVFs and AVMs[23,87,92]; however, the success rate has been reported to be higher if liquid agents are used in addition to coils (Murata et al., 2014).

For very large AVF, covered stent exclusion has been described,[104] and others have utilized bare metal stents to provide a barrier to coil extrusion.[105] Radiofrequency ablation has recently been described as well (Kwak and Shim, 2008).

Very large AVFs may present a technical challenge because of the risk of central embolization. Some authors recommend surgery in this setting.[96,97,106,107] Others have reported success in this setting using the Amplatz spider device (Cook Medical, Bloomington, Indiana) to provide a scaffolding that can then engage other embolic materials.[68,74] Staging the procedure—beginning with large coils, followed weeks later by smaller coils and other materials to close off persistent flow channels, may also be an effective strategy.[108] Because very large arteriovenous communications tend to be at the renal pedicle rather than intraparenchymal, surgical treatment is feasible and probably preferable for good-risk patients. In the case of surgical therapy, ex vivo techniques may be of value.

Complications of embolization are unusual but not insignificant. In addition to arterial access site morbidity and contrast agent toxicity, pulmonary or peripheral arterial embolization can occur. Large AVFs require large devices such as coils or detachable balloons, but even these can embolize centrally. Gelfoam, alcohol, and various glues may be more appropriate for very small communications, but the delivery is less precise, and renal parenchymal infarction seems to be greater with these materials.[85] It is common for patients to have transient fever, leukocytosis, and even hypertension after embolization.[80] With modern techniques, endovascular treatment is successful in more than 80% of patients, although repeat treatments are sometimes necessary (Eom et al., 2015)[109] and is clearly the treatment of choice for symptomatic congenital and most acquired AVFs.

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A complete reference list can be found online at www.expterconsult.com.

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CHAPTER 129

Renovascular Disease: Acute Occlusive and Ischemic Events

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Acute renovascular ischemia is defined as a sudden interruption of arterial and/or venous renal blood flow; it may involve either partial or complete ischemia of one or both kidneys. Because the renal arteries are considered "end arteries," acute ischemia can rapidly progress to irretrievable loss of renal function if it goes unrecognized or untreated. Appropriate clinical management of acute renal ischemia is therefore quite time-sensitive; the duration and severity of ischemia are therefore key considerations for decision making related to both medical and procedural intervention. In the setting of acute renal ischemia, salvage of a functioning kidney requires a high index of suspicion, rapid diagnosis, and quick implementation of a definitive treatment plan.

Causes of acute renal ischemia include renal artery thrombosis, embolism, trauma, aortic or renal artery dissection, iatrogenic injury, and renal vein thrombosis (Table 129.1). Evidence supporting specific management strategies for acute renal ischemia is limited and primarily comes from case reports and small cohort studies, perhaps because of the relative rarity of this diagnosis.

Main renal artery occlusion occurring during endovascular aortic aneurysm repair is discussed in Chapter 72. Similarly, other iatrogenic injuries of the renal artery, including complications occurring during angioplasty and stenting, are specifically covered in Chapter 127. Acute renal ischemia associated with aortic dissection is covered in Chapter 81; and detailed discussions of open surgical revascularization are found in Chapter 126. Further discussion of the management of renal artery trauma, including penetrating injury, can be found in Chapter 183.

PATHOPHYSIOLOGY

Renal ischemic injury is characterized by glomerular collapse and tubular necrosis, resulting in reduced glomerular filtration and loss of tubular function.[1] Reperfusion further induces endothelial dysfunction in acute ischemic renal failure, resulting in excess cytokine secretion and the expression of adhesion molecules that promote leukocyte influx. Reperfusion injury also leads to excessive production of nitric oxide and reactive

TABLE 129.1 Causes of Acute Renal Ischemia

Renal artery thrombosis
Atherosclerotic disease
Aneurysmal disease
Dissection (aorta or renal artery)
Fibromuscular dysplasia
Arteritis (e.g., Takayasu)
Stent thrombosis
Hypercoagulable state
Renal artery embolism
Chronic atrial fibrillation
Valvular heart disease
Aortic plaque
Paradoxical embolism in setting of patent foramen ovale
Cardiac tumor
Trauma
Iatrogenic
Direct injury or embolization
Ostial occlusion by aortic endograft
Renal vein thrombosis
Hypercoagulable state
Mechanical obstruction
Malignancy

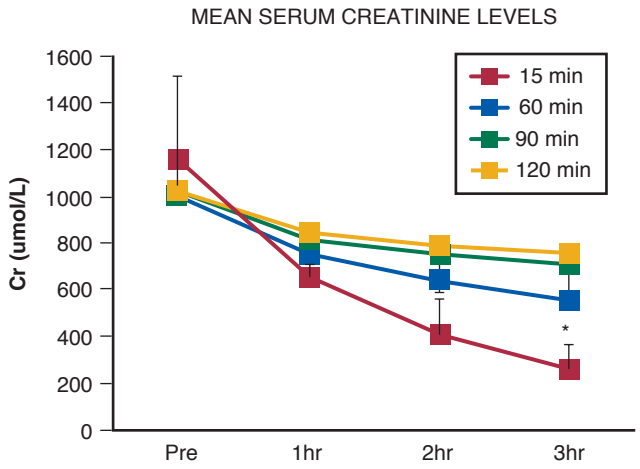


Figure 129.1 Duration of Warm Ischemia and Mean Serum Creatinine. Mean serum creatinine levels following 15, 60, 90, and 120 minutes of warm ischemia and 2 hours of static cold storage. (From Hosgood SA, Shah K, Patel M, and Nicholson ML. The effect of prolonged warm ischaemic injury on renal function in an experimental ex vivo normothermic perfusion system. *J Transl Med.* 2015;13:207).

oxygen species, which result in additional parenchymal damage and impaired autoregulation of renal blood flow.[2]

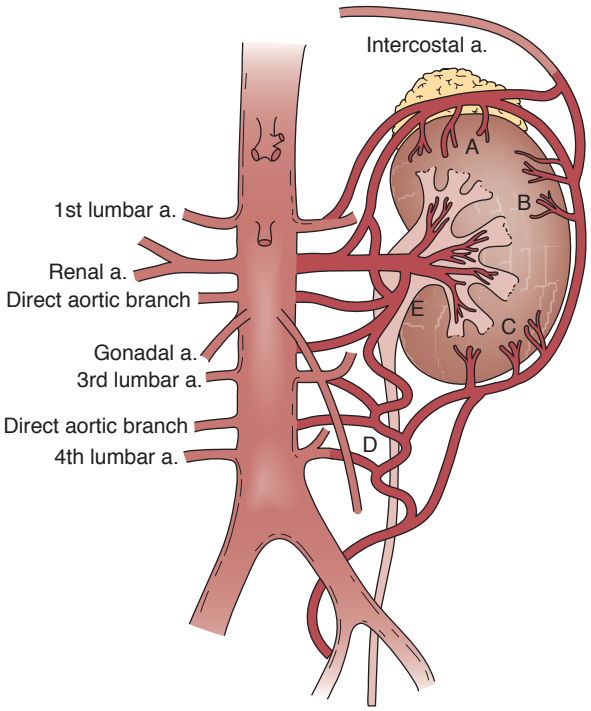
The baseline kidney function and duration of acute warm renal ischemia affect the potential for recovery of renal function and are therefore important considerations when revascularization is being considered. Age and diabetes have been identified as patient-specific risk factors associated with increased susceptibility to injury from acute renal ischemia in experimental models.[3,4]

Duration of Ischemia

In a normal kidney, 1 hour of warm renal ischemia is associated with loss of 70% to 80% of renal function, but complete recovery can occur within weeks; increasing the duration of ischemia to 2 hours diminishes long-term recovery to 30% to 50% of baseline.[5] In vivo models of acute, total renal artery occlusion have demonstrated irreversible ischemia after a period of 3 to 4 hours, but this varies substantially by species.[6,7] Figure 129.1 shows serum creatinine levels in a porcine model following periods of warm renal ischemia lasting 15, 60, 90, and 120 minutes.[8] Prolonged ischemia time (>45 minutes) has been identified as a predictor of poor early graft function following living donor kidney transplantation,[9] and more than 90 minutes of acute warm ischemia has been suggested as a cut point for the retrieval of renal function.[10] Technically successful revascularization performed after longer durations of acute ischemia therefore may not be followed by functional recovery, especially when overt renal failure or anuria is already present.[10,11]

Gradual Versus Acute Renal Occlusion

In contrast to acute renal artery occlusion, gradual main renal artery occlusion (e.g., main renal artery stenosis, which progresses in severity over months or years) may result in the development of collateral circulation, which may lessen the severity of



A. Superior capsular complex
B. Lateral capsular complex
C. Inferior capsular complex
D. Periureteric complex
E. Peripelvic complex

Figure 129.2 Collateral Circulation of the Kidney. (From Flye MW, Anderson RW, Fish JC, Silver D. Successful surgical treatment of anuria caused by renal artery occlusion. *Ann Surg.* 1982;195:346-353.)

the ischemic insult. Renal artery collaterals originate from the inferior adrenal, gonadal, ureteral, internal iliac, lumbar, intercostal, and capsular arteries (Fig. 129.2).[12-15] Less commonly, collaterals may also originate from the inferior mesenteric artery.[16] Prerenal communication may exist at the hilum, while intrarenal

communication occurs through capsular perforating arterioles. As much as 80% of renal arterial collateral communication may be independent of the main renal artery,[7] potentially allowing maintained kidney viability in the setting of main renal artery occlusion (particularly in the setting of acute thrombosis of a chronic critical stenosis).[14,17] Extrarenal arteries (alternatively referred to as accessory, aberrant, or duplicated renal arteries) may also preserve direct arterial flow from the aorta and have a reported prevalence of 24% to 42% based on imaging and cadaver studies.[18-21]

Glomerular collapse and tubular necrosis occur following acute reduction of renal perfusion pressure; in the setting of gradual reduction of renal perfusion, however, maintained tubular function (reflected by low fractional excretion of sodium and normal *N*-acetyl-glucosaminidase excretion) has been observed despite reductions in both glomerular filtration rate and filtration fraction.[1] In a canine model of gradual renal artery occlusion induced incrementally over a period of 7 weeks, collateral circulation developed, which was sufficient to maintain both renal viability and life.[22] Reports of functional recovery following periods of main renal artery occlusion exceeding 24 hours underscore the importance of collateral perfusion and demonstrate that the potential for kidney salvage is not a function of warm ischemia time alone.[23-31] Main renal artery occlusion accompanied by the visualization of good renal vein flow on duplex ultrasound suggests the presence of collateral arterial flow.[31]

Renal Vein Thrombosis

Renal vein thrombosis, which may occur primarily or in association with thrombosis of the inferior vena cava, can also produce acute renal ischemia. Renal vein thrombosis may be unilateral or bilateral; as with acute arterial ischemia, the degree of functional impairment and severity of clinical presentation are related to the acuity of venous occlusion and presence or absence of collateral flow.[32] When renal vein thrombosis occurs rapidly in the absence of developed collaterals, congestion and edema of the affected kidney can produce pain due to capsular distension as well as hemorrhagic infarction.[33,34] Experimental models have demonstrated that renal injury and blood flow reduction are both more severe with acute venous versus arterial occlusion.[35]

CLINICAL PRESENTATION

Symptoms and signs of acute renal ischemia include abdominal or back pain, dyspnea, nausea, vomiting, hematuria, anuria, and acute hypertension.[24,26,29,30,36-39] Since many of these symptoms are relatively nonspecific, the differential diagnosis for acute renal ischemia is broad and includes a variety of nonrenal pathologies. Renal colic with nephrolithiasis is a common initial presumptive diagnosis owing to the similarity of presenting symptoms, and several reports have recommended that absence of renal calculi on an unenhanced computed tomography (CT) scan performed for suspected renal colic should prompt a contrast-infused study to rule out acute ischemia.[40-43] Other diagnoses with symptoms similar to renal ischemia include pyelonephritis, renal carcinoma, mesenteric ischemia, cholecystitis or biliary colic, gastritis, splenic infarction, myocardial infarction, and pulmonary embolism.[24,30,37,40,44]

The presentation of acute renal ischemia is often delayed for hours or days after symptom onset, adversely affecting the possibility of functional salvage through revascularization. In a series of patients with embolic renal artery occlusion secondary to atrial fibrillation described by Hazanov et al., the majority of patients presented more than 24 hours following the onset of symptoms[40]; Huang et al. reported a median time of 31 hours between symptom onset and presentation to the emergency department for acute renal infarction.[36]

Renal vein occlusion may also present with unilateral renal congestion and tenderness, although the enlarged kidney is rarely palpable in adult patients.[33] In a retrospective cohort study of neonates with renal vein thrombosis, the "classic triad" of flank mass, gross hematuria, and thrombocytopenia was identified in only 13% of patients.[45]

DIAGNOSTIC EVALUATION

Laboratory Tests

Because no single laboratory test is diagnostic of acute renal ischemia, tests must be selected and interpreted in combination with the clinical presentation and findings on physical examination.

Laboratory findings associated with acute renal ischemia include leukocytosis, elevated lactate dehydrogenase (LDH), microscopic or gross hematuria, proteinuria, elevated D-dimer, and eosinophilia.[26,28,30,36,40,41,46,47] Eosinophilia may be indicative of atheroembolism.[47,48] In a series of 20 patients with acute renal ischemia, 19 patients had an elevated serum LDH, while 16 had the triad of flank/abdominal pain or tenderness, elevated serum LDH, and proteinuria.[36] Only half of patients presenting with acute renal ischemia have an elevated serum creatinine,[41] so a normal serum creatinine does not exclude this diagnosis. In the setting of a contralateral kidney with normal function, asymptomatic unilateral renal ischemia may be identified as an incidental imaging finding, the acuity of which cannot be determined.

Imaging Tests

Imaging plays a critical role in the diagnosis of acute renal ischemia because of the frequently nonspecific nature of the presentation, physical examination, and laboratory findings. The ideal diagnostic imaging test for renal ischemia would be rapid, widely available, noninvasive, inexpensive, and with no need for either radiation exposure or contrast administration. Although no imaging technique has all of these characteristics, consideration of these attributes can be helpful in choosing the most appropriate study based on the clinical presentation.

Computed Tomography Angiography

Computed tomography angiography (CTA) is a widely available imaging technique that is rapid and useful for ruling out other soft tissue abnormalities when acute renal ischemia is being considered. Although CTA results in radiation exposure and requires contrast administration for definitive diagnosis, it is

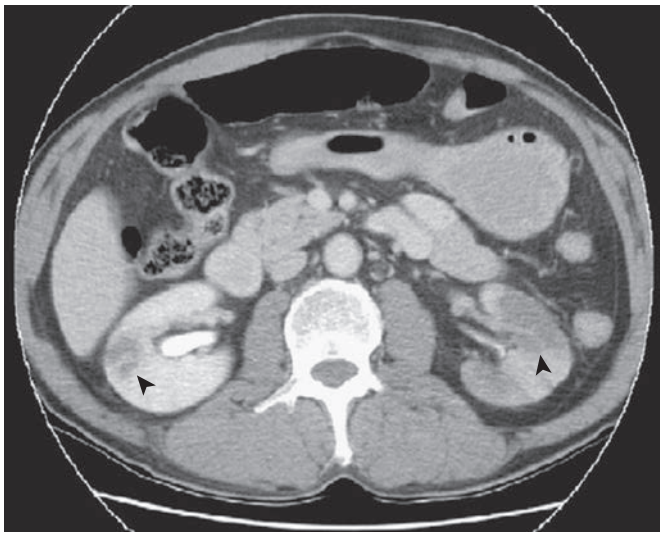


Figure 129.3 Computed Tomography Angiography Demonstrating Bilateral Renal Infarcts. Patient had sudden onset bilateral flank pain with a history of atrial fibrillation. Bilateral wedge-shaped, hypodense lesions (arrowheads) are consistent with embolic renal infarcts. (From Huang C-C, Lo H-C, Huang H-H, et al. ED presentations of acute renal infarction. *Am J Emerg Med*. 2007;25(2):164-169.)

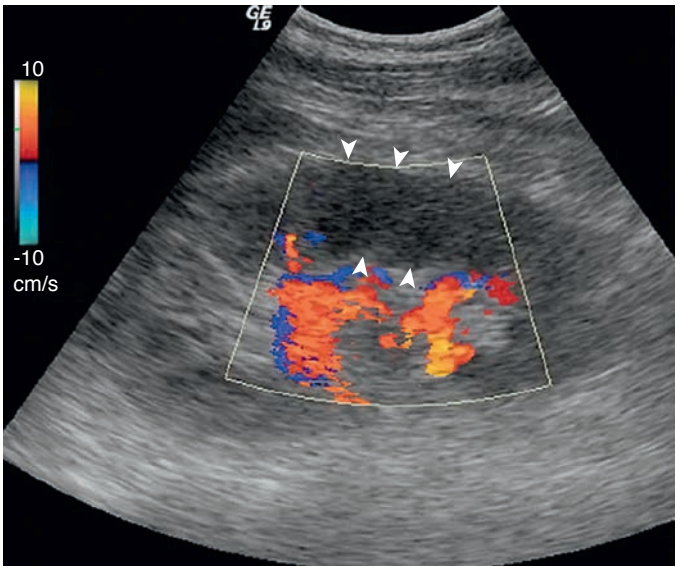


Figure 129.4 Renal Infarction Demonstrated by Duplex Ultrasound. Renal infarction caused by arterial embolism appears as a wedge-shaped hypoechoic area with absence of blood flow signal (arrows). (From Cai S, Ouyang YS, Li JC, et al. Evaluation of acute renal artery thrombosis or embolism with color Doppler sonography. *Clin Imaging*. 2008;32(5):367-371.)

more sensitive than ultrasound and less time consuming than magnetic resonance angiography (MRA), with a reported sensitivity of 80%.[40] CTA also provides a thorough evaluation of aortic and iliac anatomy and/or disease, which may be useful when revascularization is being planned. CTA, which should routinely include both noncontrast and venous phase images, has also been suggested as the diagnostic imaging study of choice for renal vein thrombosis, with a sensitivity and specificity that both approach 100%.[34] Features of a renal infarct on CTA imaging include areas of hypoattenuation with associated mass effect (Fig. 129.3) or a "cortical rim sign," described as a rim of functioning nephrons supplied by capsular collaterals surrounding an otherwise nonfunctioning kidney.[40,41,49,50]

Magnetic Resonance Angiography

Renal MRA is capable of the anatomic evaluation of renal artery disease with the additional capability of physiologic assessment through flow-dependent imaging.[51] Unenhanced MRA is capable of characterizing renal artery disease with a reliability similar to that of CTA; its distinct advantages for evaluating renal segmental arteries and parenchymal disease[52] make it a potentially valuable technique when contrast imaging is contraindicated due to renal dysfunction. Although these advantages have resulted in the increasing utilization of MRA for the evaluation of chronic renal artery occlusive disease, MRA has not been utilized extensively as a first-line imaging modality for acute renal ischemia. This may reflect the practical limitations of MRA when rapid imaging assessment is required because it is more time-consuming and may require extensive image postprocessing prior to interpretation. Compared with CTA and/or ultrasound, rapid access to MRI is often relatively limited within emergency department and hospital environments, where acute renal ischemia is commonly evaluated.

Ultrasound

By comparison, ultrasound requires neither contrast nor radiation exposure but is less sensitive than CTA for renal ischemia. Renal infarcts typically appear as wedge-shaped, hypoechoic lesions with absent blood flow on duplex ultrasound (Fig. 129.4). Ultrasound imaging is also technician-dependent and may be challenging in patients who are obese or have excessive bowel gas. In a series of 44 patients with renal embolism, only 3 of 27 (11.1%) ultrasound studies were positive. In a retrospective review of 10 patients with renal artery thrombosis or embolism, Cai et al. concluded that color Doppler ultrasonography was useful for the detection of large infarcts resulting from main renal artery occlusion but that other imaging modalities were needed to confirm smaller infarcts.[53] They also reported decreased renal artery peak systolic velocity as a finding that may be associated with intrarenal embolism. In addition to renal vein thrombus, other ultrasound findings indicative of ischemia due to venous thrombosis may include unilateral kidney edema or congestion.

Nuclear Renal Scan

Nuclear renal isotope scanning has been suggested as the most sensitive imaging technique for the diagnosis of acute renal ischemia, but this modality is seldom practical because it is time-consuming and less widely available. The reported sensitivity of nuclear imaging for acute renal ischemia is 97%,[40] and infarcts are characterized by a marked reduction of renal blood flow with preserved kidney size.[54]

Angiography

Although catheter angiography potentially allows endovascular treatment of renal ischemia during the same procedure when

anatomically suitable disease is identified, use of this method for diagnostic purposes should be limited to situations where other imaging studies are equivocal or the index of suspicion is especially high (e.g., suspected iatrogenic injury).

RENAL ARTERY EMBOLISM

Epidemiology

Risk factors for renal artery embolism include atrial fibrillation, ischemic heart disease, cardiomyopathy, previous arterial thromboembolism, mitral or aortic valve disease, cardiac tumor, atherosclerotic aortic plaque, and paradoxical embolism in the setting of a patent foramen ovale (Fig. 129.5). Renal artery embolism is uncommon, with an incidence among hospitalized patients of 0.007% (or 6.1 per million per year).[55]

Renal artery branches are more commonly occluded by emboli than the main renal artery, making it challenging, unless a proximal source can be found, to distinguish between embolism and thrombosis when branch occlusion with a partial infarct is identified.

Cholesterol crystal embolization (CCE) is a distinct type of embolism characterized by multiple small renal emboli comprising cholesterol debris. Chronic CCE has an incidence of 6.2 per million people per year; risk factors include male gender, hypertension, and atherosclerosis.[56] CCE may also occur during arterial catheterization and/or procedural intervention, especially with repeated instrumentation of a diseased thoracic or abdominal aorta. CCE is associated with a 30% incidence of progression to dialysis within 2 years and increased mortality.[57] Additional discussion of CCE can be found in Chapter 103.

Treatment

Once embolic renal artery occlusion is established or strongly suspected, heparin anticoagulation should be initiated immediately to prevent local propagation of renal artery thrombus as well as additional embolic events at other anatomic locations.

Besides anticoagulation, patients with renal embolism also require thorough evaluation for the embolic source to determine whether additional treatment (such as repair of proximal aneurysmal disease, thrombectomy, repair of patent foramen ovale, or heart valve replacement) is warranted for definitive management and reduction of the long-term risk of repeat embolism. Among patients presenting with renal artery embolism, over 20% have a history of previous thromboembolism.[40,55,58]

Although successful management with anticoagulation alone has been described,[12,40] revascularization may be considered in patients presenting with acute ischemia and potentially salvageable renal function, especially in the setting of bilateral embolism. Conversely, anticoagulation alone can be used for definitive management in patients with unilateral embolism and limited potential for renal salvage (e.g., patients with preexisting chronic kidney disease or other renal pathology). In the report of Hazanov et al., over 80% of patients presenting with renal embolism were managed using anticoagulation alone, without procedural intervention.[40] One-month mortality was 11% in this series; 61% of patients had normal renal function at long-term follow-up, and only 8% required dialysis.

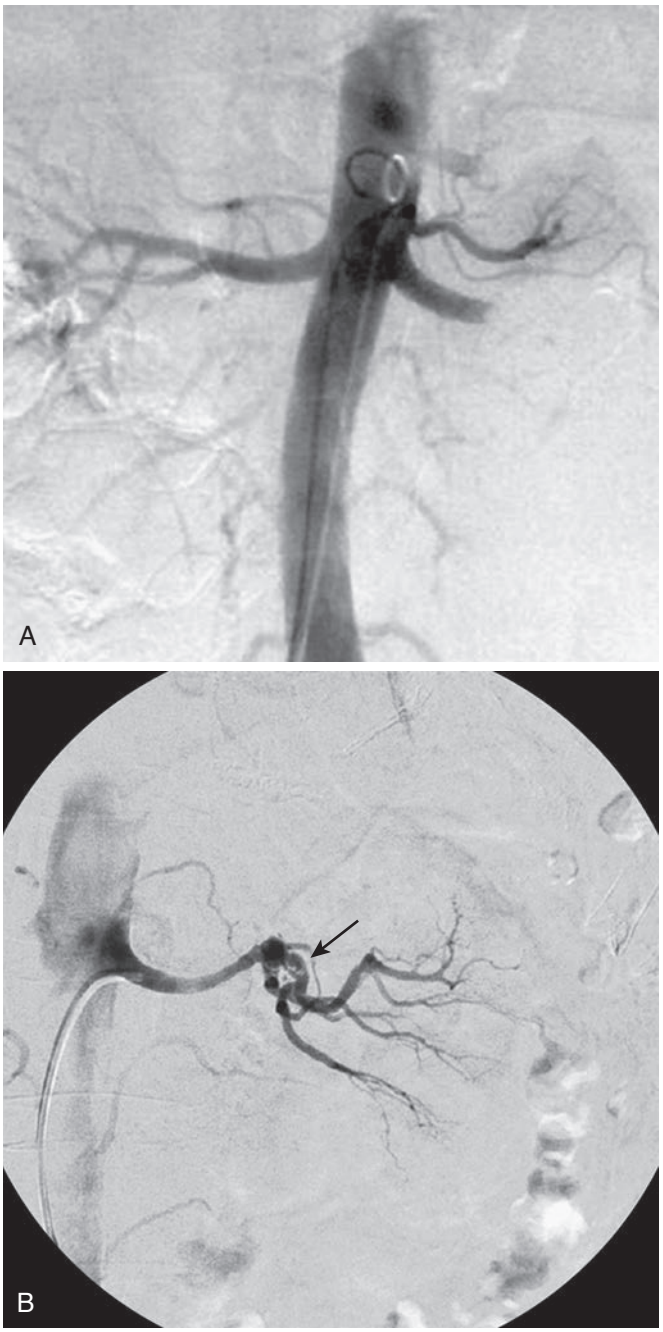


Figure 129.5 Renal Artery Embolism. (A) Contrast angiogram demonstrating left main renal artery occlusion resulting from embolism in a patient with atrial fibrillation (From Syed MI, Shaikh A, Ullah A, et al. Acute renal artery thrombosis treated with t-PA power-pulse spray rheolytic thrombectomy. *Cardiovasc Revasc Med.* 2010;11(4):264.e1-7.) (B) Contrast angiogram demonstrating branch renal artery thrombosis resulting from cardiac tumor embolus. (From Boggetto-Graham L, Chavanon O, Hacini R, et al. An uncommon cause of renovascular hypertension. *Can J Cardiol.* 2012;28(3):397.e1-3.)

Endovascular Treatment

Catheter-directed thrombolysis can be a valuable treatment strategy in the setting of acute renal ischemia resulting from

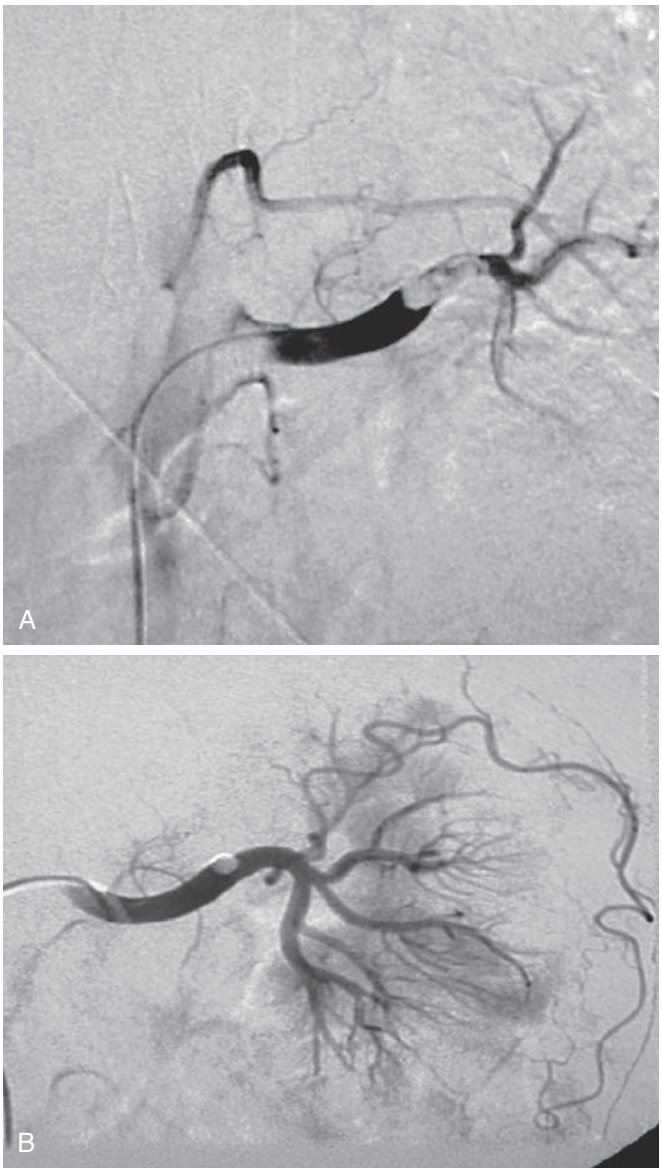


Figure 129.6 Management of Renal Artery Embolism With Catheter-Directed Thrombolysis. (A) Distal left renal artery embolus demonstrated by angiography. (B) Patent left renal artery demonstrated following catheter-directed thrombolysis. (From Robinson S, Nichols D, Macleod A, et al. Acute renal artery embolism: a case report and brief literature review. *Ann Vasc Surg.* 2008;22(1):145-147.)

arterial embolism, where the occlusion is typically located at the renal artery bifurcation or distal segmental branches (Fig. 129.6).[11,37,59,60] Rheolytic thrombectomy can be used in combination with thrombolysis and may permit definitive intraprocedural management with no need for placing a catheter for extended thrombolytic infusion.[28,38] Aspiration thrombectomy, angioplasty, and stenting may also be utilized as adjuncts to thrombolysis in the setting of embolic renal artery occlusion.[30] In a series of 14 patients with acute embolic renal artery occlusion, Blum et al. did not observe recovery of renal function in any patients presenting with complete main renal artery occlusion, whereas partial functional recovery was observed in the setting of either segmental branch or incomplete main renal artery occlusion.[10]

Open Surgery

Surgical embolectomy can be performed through a midline or flank incision[61,62]; following renal artery exposure, the artery and vein are mobilized and encircled with vessel loops. Embolectomy can then be performed through either a transverse or longitudinal incision in the renal artery, with removal of thrombus using forceps and a Fogarty catheter. Suprarenal control of the aorta should be obtained if thrombus extension into the aortic lumen is suspected. Following removal of the embolism and associated thrombus, the arteriotomy can be closed either primarily or with a patch angioplasty.

Intraoperative completion duplex ultrasound should then be considered to evaluate patency and rule out residual stenosis or other technical complications. Lacombe et al. reported a 25% mortality associated with surgical management of renal artery embolism; these authors noted a similar mortality but a lower rate of renal function recovery among patients managed medically.[63]

At present, surgical embolectomy is infrequently utilized for acute renal embolism because it is relatively invasive and time-consuming compared with endovascular treatment.

RENAL ARTERY THROMBOSIS

Epidemiology

Nonembolic renal artery thrombosis may result from a variety of both renal and extrarenal disease processes, including atherosclerotic renal artery stenosis, distal aortic occlusion from aneurysmal or atherosclerotic disease with proximal thrombus propagation, aortic or renal artery dissection, renal artery aneurysm, fibromuscular dysplasia, arteritis (e.g., Takayasu), stent thrombosis, hypercoagulable state, or trauma. Iatrogenic thrombosis may also result from renal artery coverage or injury during endovascular procedures. Other less common causes of renal artery thrombosis include antiphospholipid antibody syndrome,[64] factor V Leiden mutation,[65] heparin-induced thrombocytopenia,[66,67] and Beçhet disease.[68]

Thrombotic occlusion of preexisting atherosclerotic disease is most common among individuals over age 55 (Fig. 129.7). Although atherosclerotic renal artery stenosis has an incidence of 7% among elderly individuals,[69] progression to thrombosis is uncommon in the absence of other contributing factors, such as dehydration or hypotension.[54,70] In a study by Caps et al., the 5-year incidence of renal artery thrombosis in the setting of known stenosis was less than 5%; risk factors for thrombosis included systolic blood pressure greater than 160 mm Hg, diabetes mellitus, and the presence of high-grade (≥60%) stenosis.[71]

Spontaneous renal artery dissection leading to thrombosis is rare. In contrast to atherosclerotic renal artery stenosis, renal artery dissection commonly occurs in younger patients and has similar incidence in men and women. An intimal flap is the most characteristic imaging finding associated with renal artery dissection (Fig. 129.8), but diagnosis may be challenging in the setting of false lumen thrombosis; other findings may include

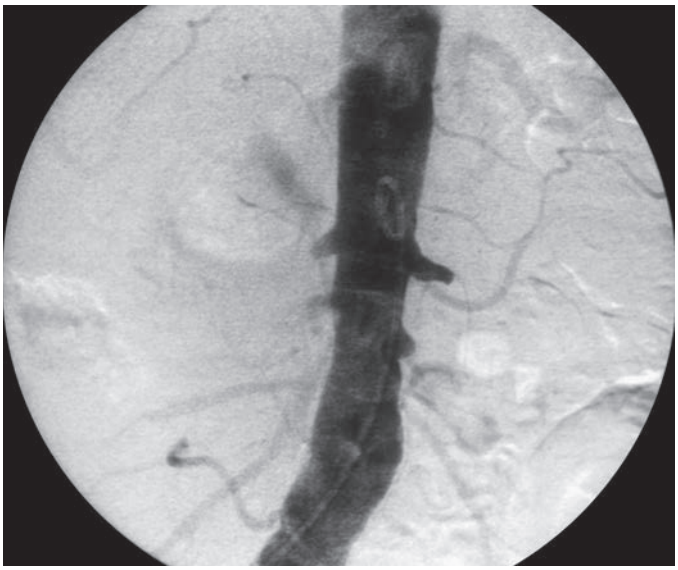


Figure 129.7 Thrombotic Bilateral Renal Artery Occlusion. The patient presented with acute renal failure and anuria. Nuclear medicine study demonstrated renal perfusion by collateral vessels and indicated viable kidneys.

an enlarged renal artery or a long, tapered stenosis. Dissection may be unilateral or bilateral at the time of diagnosis, therefore potentially affecting the entire renal mass.[72] Risk factors include fibromuscular dysplasia,[73-75] Ehlers-Danlos syndrome,[76] cocaine use,[77] and strenuous exercise.[78,79] Iatrogenic renal artery dissection has been reported following a variety of procedures including diagnostic angiography,[80] peripheral or aortic endovascular intervention,[81,82] and extracorporeal shock-wave lithotripsy.[83]

Treatment

Medical treatment—including systemic anticoagulation, control of hypertension, and assessment and management of intravascular volume status—is an important component of the management of acute renal ischemia regardless of whether revascularization is undertaken. Systemic anticoagulation should be initiated in the setting of acute presentation to prevent propagation of thrombus and preserve collateral flow.

Endovascular Treatment

Endovascular options for the management of acute renal ischemia include angioplasty and stenting, thrombolysis, mechanical catheter thrombectomy, and aspiration thrombectomy; these treatments are frequently used in combination with one another depending on the angiography findings and suspected etiology.

Angioplasty and stenting are useful for the treatment of ischemia resulting from thrombosis of a critical primary renal artery or in-stent lesion.[26,31,84] Use of catheter-directed thrombolysis in combination with angioplasty and stenting is frequently described for restoring the patency of thrombosed distal branch vessels in the setting of main renal artery occlusion.[85] Alternatively, aspiration thrombectomy combined with angioplasty and stenting plus intraoperative bolus thrombolytic administration

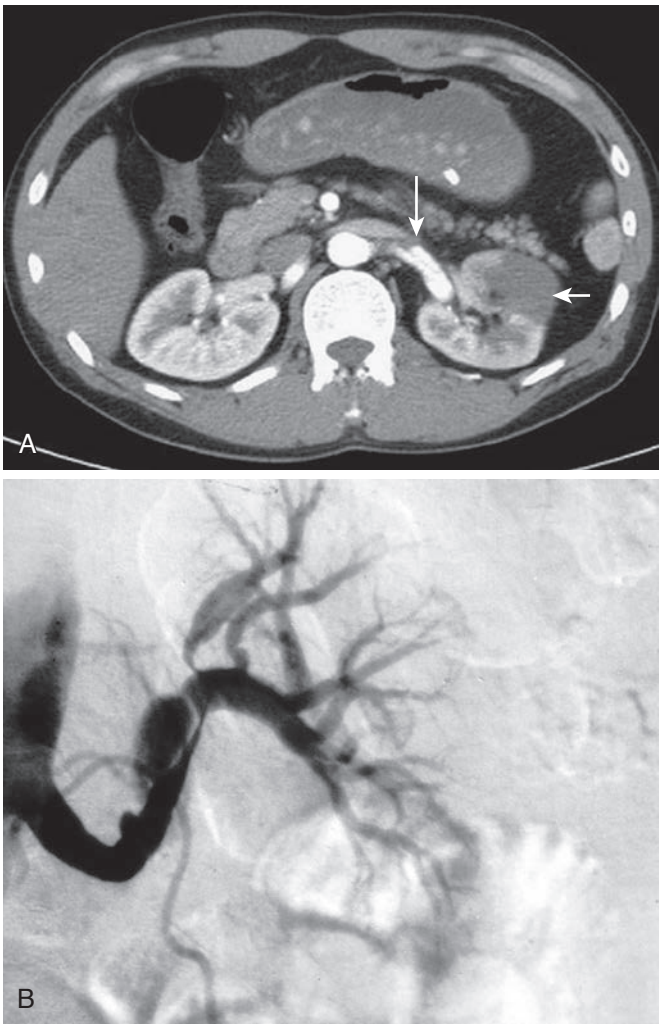


Figure 129.8 Spontaneous Renal Artery Dissection. (A) Axial computed tomography angiographic image shows left renal artery dissection (long arrow) with ipsilateral upper pole renal infarction (short arrow). (From Tsai TH, Su JT, Chao CC et al. Spontaneous renal artery dissection complicating with renal infarction. *Urology*. 2010;76:1371-1372.) (B) Contrast angiogram demonstrating spontaneous renal artery dissection extending into the hilar branches of the left kidney. (From van Rooden CJ, van Baalen JM, van Bockel JH. Spontaneous dissection of renal artery: long-term results of extracorporeal reconstruction and autotransplantation. *J Vasc Surg*. 2003;38(1):116-122.)

may also restore renal perfusion with no need for continuous infusion.[30] Use of catheter-directed thrombolysis to reestablish patency in the setting of an acutely thrombosed renal artery aneurysm has also been reported, permitting subsequent treatment of the aneurysm in a staged fashion.[59] Systemic thrombolysis prior to angioplasty and stenting has also been described as a means of reestablishing renal artery patency in the setting of acute bilateral occlusion.[86] In a series of 10 patients with renal artery thromboembolism from a variety of causes treated by Salam et al. with catheter-directed thrombolysis, adjunctive angioplasty and/or stenting was necessary in half of the procedures and the rate of anatomically successful revascularization (defined by completion angiography) was 70%.[11] In this series of patients presenting with acute renal failure, however, only one of four recovered renal function after intervention.

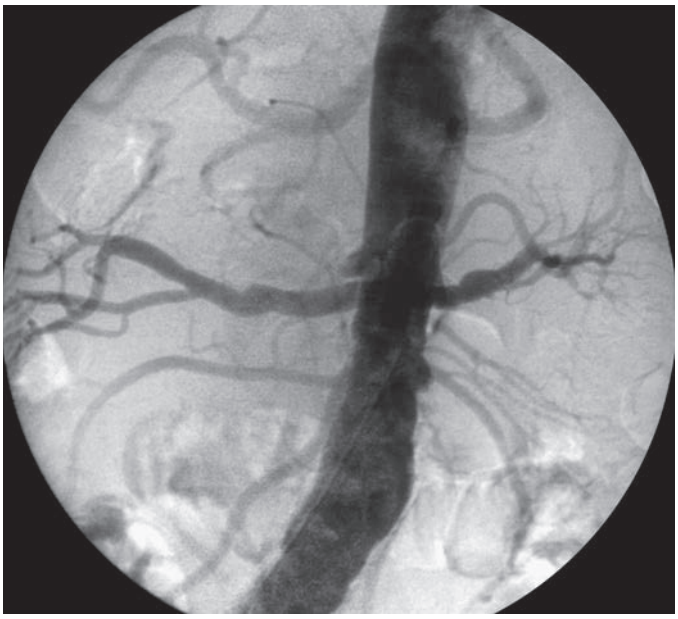


Figure 129.9 Bilateral Aortorenal Vein Graft Bypasses Performed for Thrombotic Occlusion. (Preoperative angiogram is shown in Fig. 129.7.) Renal biopsy showed partial infarction, but renal function recovered immediately following revascularization and gradually returned to normal over several months.

Open Surgery

Surgical revascularization options include renal artery thrombectomy, bypass, and/or endarterectomy (Fig. 129.9).[61,62] Because surgical revascularization is more invasive and time-consuming (therefore necessitating a longer duration of ischemia), these procedures are typically reserved for situations where the chance of renal salvage is deemed substantial (limited ischemia, normal preexisting kidney function, acute thrombosis of preexisting chronic stenosis with existing collaterals, etc.) and where endovascular treatment has failed or may be ill advised owing to technical or anatomic considerations.

Surgical exposure for renal artery revascularization is similar to that described earlier for embolectomy. Revascularization techniques—including endarterectomy, aortorenal bypass, and extra-anatomic bypass—are described in detail in Chapter 126. Renal artery bypass for ischemia resulting from delayed thrombosis after renal artery angioplasty and/or stenting has been described by several authors, with successful salvage of renal function.[87,88] As with endovascular treatment, the maintenance of collateral perfusion is critical to renal salvage in the setting of acute ischemia. In a series that included 16 patients treated with surgical revascularization, Ouriel et al. noted that renal salvage with thrombectomy and aortorenal bypass was dependent on a distally reconstituted renal artery regardless of the duration of ischemia; recovery of renal function among patients with embolism or traumatic injury in this series was less common.[89]

Perioperative mortality associated with surgical revascularization for acute renal artery thrombosis is 15% to 25%, with salvage of renal function in approximately 65% of patients.[90,91] Surgical management may also be preferred over endovascular therapy in situations where the thrombus burden is extensive or thrombolysis is contraindicated. Chevalier et al. described complete recovery following surgical thrombectomy in a patient with acute aortic and renal artery thrombosis due to heparin-induced thrombocytopenia.[66]

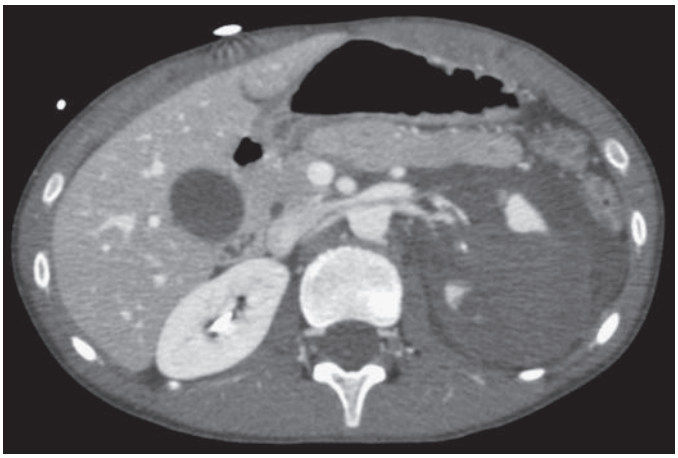


Figure 129.10 Traumatic Injury to the Left Kidney. Contrast CT demonstrates large left renal perfusion defect caused by acceleration-deceleration trauma of the renal pedicle, resulting in vascular injury and kidney rupture as well as injury of the urinary collecting system.

There is inadequate evidence to support a particular management strategy for spontaneous renal artery dissection. Reported outcomes associated with surgical revascularization are predominantly derived from series of elective procedures performed for hypertension associated with dissection-related stenosis rather than acute thrombosis.[92,93] Resolution of symptoms with preservation of renal function has been reported in patients presenting with dissection and segmental renal infarction managed nonoperatively with antihypertensive agents and/or anticoagulation.[94,95]

RENOVASCULAR TRAUMA

Epidemiology

Renovascular injury has a prevalence of less than 1% in the setting of blunt abdominal trauma.[96,97] In addition to renovascular injury, approximately 75% of patients also have an abdominal solid organ injury involving the kidney, liver, or spleen, and over 17% have multiple abdominal vascular injuries (most commonly to the renal vein or inferior vena cava).[97] Acute ischemia resulting from traumatic renal artery injury frequently involves rapid deceleration or compression between the abdominal wall and vertebral bodies, resulting in subintimal tears and/or dissection in addition to thrombosis. Renovascular injury may also be associated with injury to the urinary collection system (Fig. 129.10).[98-100]

Treatment

A selective approach to revascularization in the setting of renovascular trauma is warranted. Factors that should prompt consideration of revascularization in the setting of traumatic injury include bilateral injury or injury to a solitary functioning kidney.

As with nontraumatic etiologies, the duration of ischemia and baseline kidney function prior to injury influence the

potential for kidney salvage. In contrast to nontraumatic renal ischemia, where the time of symptom onset may be ill defined and patients often present more than 24 hours later, the duration of ischemia is often known with some degree of accuracy in the setting of traumatic injury, thus facilitating relatively informed decisions regarding revascularization. In addition to prolonged warm ischemia, other factors favoring management without attempted revascularization include hilar injury, extensive kidney injury, and a normal contralateral kidney in a patient with multiple other injuries and/or hemodynamic instability.[101,102] A thorough evaluation for other injuries is also important to determine whether intraoperative anticoagulation can be safely administered during revascularization.

Selection of a revascularization approach requires consideration of renal and other solid organ injuries, hemodynamic stability, and anatomic characteristics of the vascular injury.

Management options for blunt renovascular injury other than revascularization include nephrectomy, embolization, and observation with or without anticoagulation. Even complex blunt injuries have a potential to heal without revascularization (Fig. 129.11).

Results

In a review of 517 renal artery injuries from the National Trauma Data Bank by Sangthong et al., 73% of patients were managed nonoperatively, whereas 18% had immediate nephrectomy, 9% underwent surgical revascularization, and 1.5% were treated with stenting.[97] Surgical revascularization approaches in this series included both direct repair and well as autotransplantation. Overall mortality was 21%, the majority of which occurred within 24 hours of admission; these deaths were attributed to other associated injuries. Mortality among patients without other major abdominal injuries was 10.3%. Despite similar injury severity scores, patients who underwent revascularization or nephrectomy had longer stays in the intensive care unit or hospital, leading the authors to conclude that revascularization should be undertaken only to avoid long-term dialysis in the setting of bilateral injury or a solitary kidney. A similar conclusion was reached by Haas and Spirnak, who reported a kidney salvage rate of approximately 25% in the setting of unilateral traumatic renal artery injury.[103]

A multicenter study by Knudson et al. of severe kidney injuries (defined as American Association for the Surgery of Trauma as grade IV/V injuries) identified blunt mechanism and severity of injury as predictors of poor outcomes (defined as renal failure requiring dialysis, serum creatinine >2 mg/dL, <25% function of the injured kidney on renal scan, postinjury hypertension, or nephrectomy). Interestingly, neither physician specialty nor time to definitive surgery were associated with the composite outcome.[104] Ten percent of patients in this study developed renal failure or hypertension postoperatively, and arterial repairs had inferior outcomes when compared with repair of isolated venous injuries.

Lopera et al. reviewed eight consecutive patients presenting with renal artery occlusion or dissection following blunt abdominal trauma who underwent endovascular treatment.[105] Intervention resulted in contrast extravasation requiring embolization of the main renal artery in two patients in this study. Of the remaining six patients who underwent a technically successful renal artery recanalization and stenting, half required nephrectomy or underwent subsequent embolization during a follow-up period ranging from 2 to 24 months.

RENAL VEIN THROMBOSIS

Epidemiology

Renal vein thrombosis has an incidence of less than one case per million annually among adults and is the most common

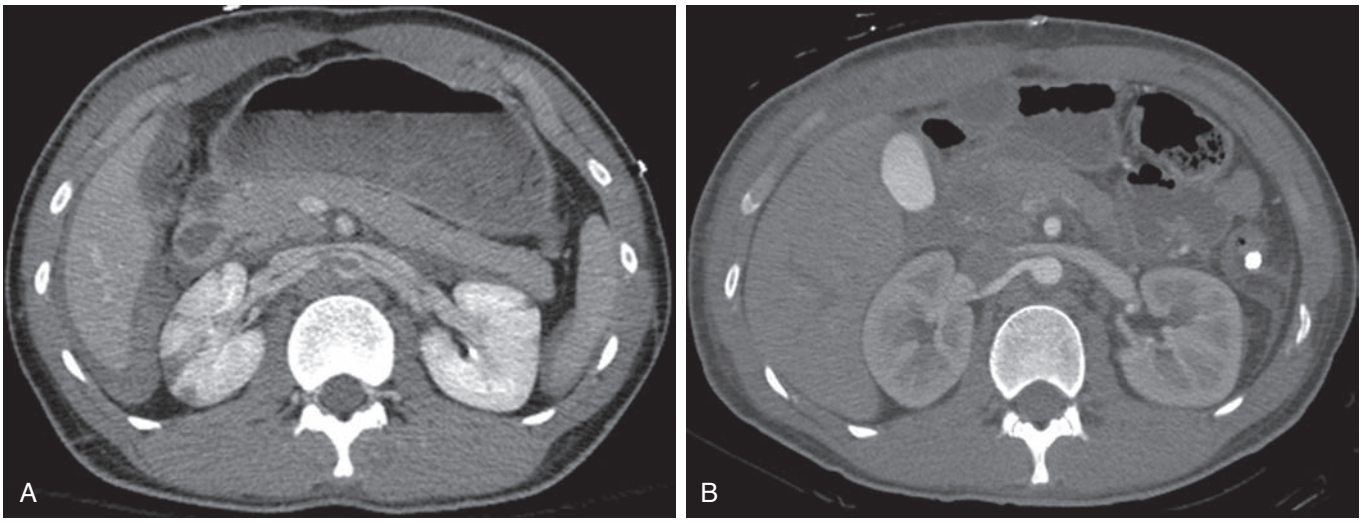


Figure 129.11 Renal Artery Dissection and Infarcts Associated With Blunt Traumatic Injury. Renal artery dissection associated with aortic dissection and multiple right renal infarcts visible on contrast computed tomography at the time of initial presentation (A). Follow-up scan 1 month later, after initial management with observation and anticoagulation, demonstrates healed dissection without residual perfusion defects (B).

non–catheter-related thrombosis in neonates.[106,107] Risk factors for renal vein thrombosis include malignancy (especially renal cell carcinoma, lymphoma, and other retroperitoneal tumors), nephrotic syndrome, inherited thrombophilia, local surgery or inflammation, oral contraceptive use, pregnancy, and infection.[32] Malignancy and nephrotic syndrome were identified as the underlying cause of renal vein thrombosis in 66% and 20% of patients, respectively, in a single-center review of 218 adult patients by Wysokinski et al.[108] Mean age at presentation in this cohort was 55 years, and 35% were women. Iatrogenic renal vein thrombosis may also occur in the presence of a vena cava filter or central venous catheter. Among children, more than 80% of renal vein thrombosis is diagnosed during the first month of life; risk factors include central vein catheters, dehydration, inherited hypercoagulable state, and prolonged hypotension.[45,107]

Treatment

Although treatment of renal vein thrombosis once centered on thrombectomy and/or nephrectomy, anticoagulation is now recognized as the treatment of choice in the majority of patients. As with treatment of renal artery embolism, goals for the treatment of renal vein thrombosis include both preservation of renal function and prevention of additional thromboembolism.[33]

Anticoagulation

Therapy should be initiated with unfractionated or low-molecular-weight heparin at the time of diagnosis; the duration of long-term anticoagulation depends on the presumed etiology and identified risk factors for venous thromboembolism. Patients with a temporary or modifiable risk factor (such as infection, hormone use, pregnancy, or immobilization due to surgery) can be treated for 3 to 6 months with a vitamin K antagonist or other oral anticoagulant, while those with idiopathic thrombosis or ongoing long-term risk factors (such as inherited thrombophilia or malignancy) should be managed, in the absence of contraindications, with lifelong anticoagulation.[32]

The overall incidence of recurrent renal vein thrombosis is 1% per patient year of follow-up, and survival following renal vein thrombosis is inferior to that of individuals with deep venous thrombophlebitis of the lower extremity.[108] Laville et al. reported a 6-month mortality rate of approximately 40% following diagnosis of acute renal vein thrombosis.[109] Active malignancy and infection affect survival negatively, whereas warfarin therapy is associated with a survival advantage.[108]

Anticoagulation is also considered the definitive treatment for renal vein thrombosis in neonates. Zigman et al. observed long-term renal functional impairment in one third of patients treated with heparin anticoagulation versus 100% of those who were not anticoagulated.[45] No patients in this study required dialysis or surgical intervention for renal salvage.

Thrombectomy

Use of thrombectomy or thrombolysis in the setting of acute renal vein thrombosis should be reserved for select situations, including failure or complication of oral anticoagulation (such as thrombus propagation or pulmonary embolism), bilateral thrombosis or thrombosis of a solitary kidney, associated caval thrombosis, acute renal failure, or persistent severe symptoms (most commonly flank pain).[34,110,111] Thrombectomy should be considered in the setting of a contraindication to anticoagulation, failure of thrombolysis, or when nephrectomy for an associated renal malignancy is anticipated. Nephrectomy has a limited role but may be the treatment of choice in the setting of postinfarction hemorrhage.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 130

Renovascular and Aortic Developmental Disorders

DAWN M. COLEMAN, JONATHAN L. ELIASON, and JAMES C. STANLEY

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Developmental abdominal aortic disease is complex and can be associated with stenotic lesions of the aortic branches to the kidneys and splanchnic organs. The etiology and clinical spectrum of this disease have been well defined in past decades.[1,2] A variety of interventions exist with the expectation that the majority of patients will benefit from appropriately planned and conducted vascular reconstructive procedures.

DEVELOPMENTAL ABDOMINAL AORTIC COARCTATION AND HYPOPLASIA

Classification

Descriptions of abdominal aortic narrowings are varied in the existing literature. Abdominal aortic coarctation or segmental aortic hypoplasia accurately describes the majority of these lesions. The pattern of aortic narrowing distinct from isthmic coarctation involving the pediatric population was first categorized in 1963 by Sen et al.,[3] who used the phrase "middle aortic syndrome" to describe 16 patients, although the majority of patients included in this original report were actually older than 20 years of age. In this work, a distinction was made between coarctations arising above the diaphragm and those that were infradiaphragmatic, which many refer to as midaortic syndrome.

A more contemporary classification of developmental aortic narrowing is based on the most cephalad extent of the involved aorta, which distinguishes suprarenal (69%) from intrarenal (23%) and infrarenal (8%) narrowings (Figs. 130.1-130.3).[1] Diffuse hypoplasia of the abdominal aorta is included in the spectrum of disease, but is often considered separately.[1,4]

Etiology and Pathogenesis

Embryology

Overfusion of the two dorsal aortas during the fourth week of gestation is thought to be the cause of most developmental abdominal aortic narrowings. Prior to this event, both dorsal aortas extend along the entire length of the embryo, with each segment of the paired aortas containing dorsal intersegmental, lateral segmental, and ventral segmental branches. As the two dorsal aortas fuse, these branches persist, involute, dilate, or

Abstract

Developmental abdominal aortic disease is complex and is often associated with stenotic lesions of the aortic branches to the kidneys and splanchnic organs of which renovascular hypertension is a common manifestation. The etiology and clinical spectrum of this disease have been previously well defined and a variety of surgical interventions exist with the expectation that the majority of patients will benefit from appropriately planned and conducted vascular reconstructive procedures.

Keywords

Abdominal aortic coarctation
mid-aortic syndrome
aortic hypoplasia
renal artery stenosis
renovascular hypertension
pediatric
embryology

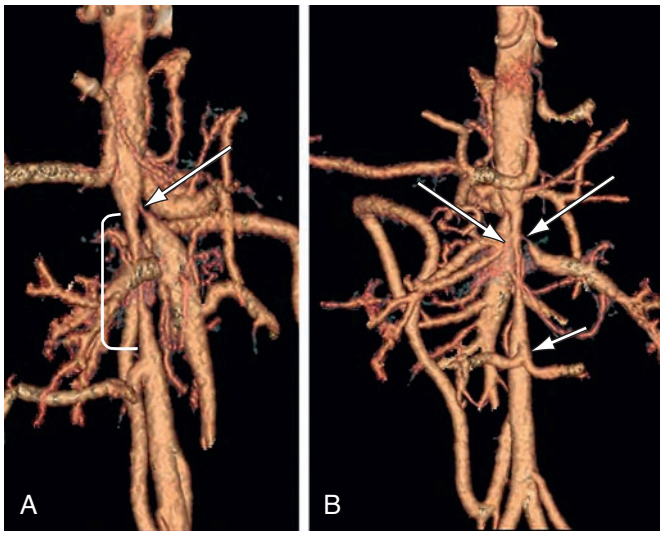

Figure 130.1 **(A)** Suprarenal abdominal aortic coarctation *(bracket)* with superior mesenteric artery stenosis *(arrow)*. **(B)** Bilateral renal artery stenoses *(arrows)*. Note common trunk of lower lumbar artery *(arrow)* on posterior projection. (From Stanley JC, Criado E, Eliason JL, et al. Abdominal aortic coarctation: surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. *J Vasc Surg*. 2008;48:1073–1082.)

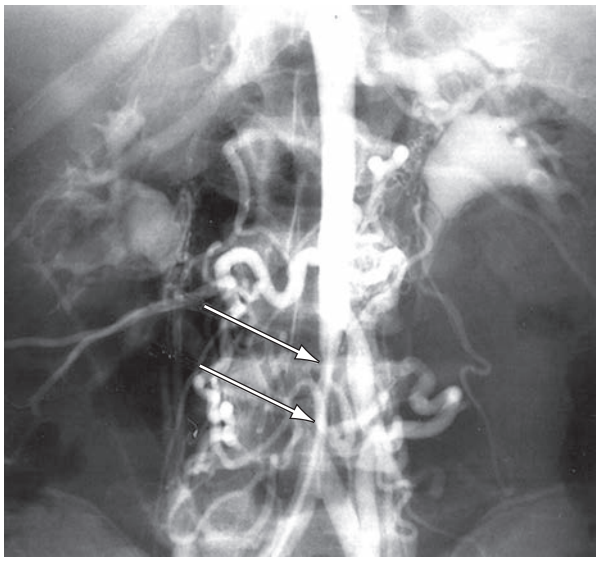

Figure 130.3 Infrarenal abdominal aortic coarctation manifest by tubular stenosis extending from a dilated inferior mesenteric artery to the aortic bifurcation. (From Stanley JC, et al. Pediatric arterial disease. In: Coran AG, Caldamone A, Adzick NS, et al, editors: *Pediatric Surgery*, 7th ed. Philadelphia: Elsevier Saunders; 2012: 1631–1645.)

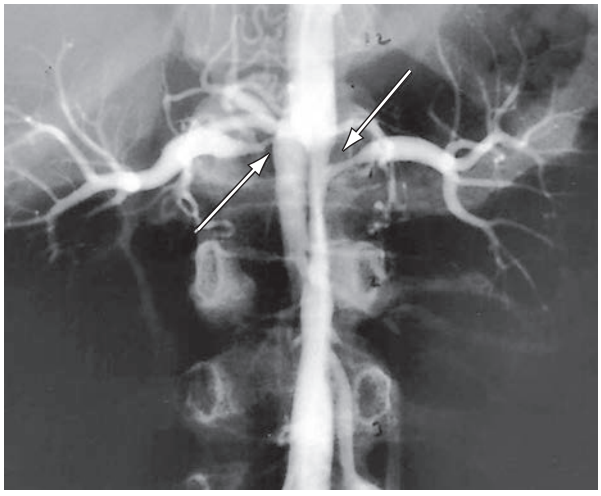

Figure 130.2 Intrarenal abdominal aortic coarctation with bilateral artery stenosis *(arrows)*. (From Stanley JC, Criado E, Eliason JL, et al. Abdominal aortic coarctation: surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. *J Vasc Surg*. 2008;48:1073–1082.)

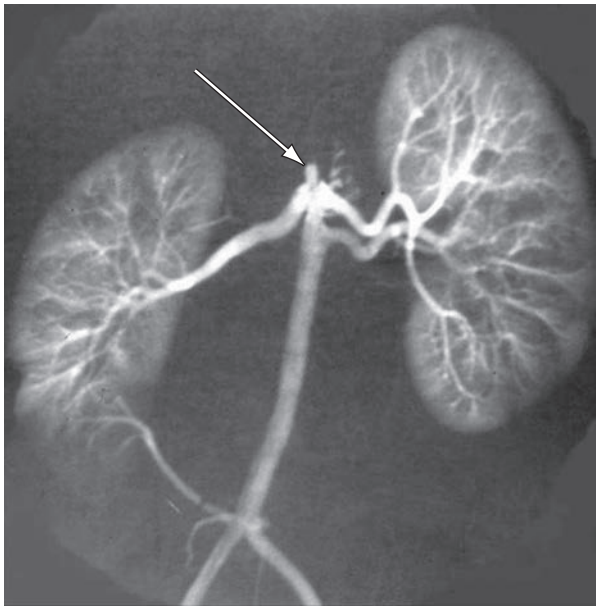

Figure 130.4 Multiple bilateral renal arteries in a patient with a near-occlusive coarctation of the suprarenal aorta *(arrow)*.

join together to form the named branches found at birth. A clinical finding supporting the overfusion theory of segmental aortic hypoplasia is the loss of paired lumbar arteries within a hypoplastic aortic segment, with only a single lumbar artery trunk exiting the dorsal aorta.[5] A developmental etiology for aortic hypoplasia is also supported by the observation that multiple renal arteries to one or both kidneys occur in these patients, with nearly twice the frequency that occurs in the general population.[1,6,7] Aortic development occurs concurrent with the involution of multiple metanephric arteries to leave a single renal artery to each kidney in the majority of fetuses. It is plausible that developmental aortic narrowings result in flow disturbances near what would usually be the principle renal artery; this diminishes its hemodynamic advantage and allows adjacent metanephric channels to persist as multiple or accessory renal arteries (Fig. 130.4).

Associated Genetic Syndromes and Infectious-Inflammatory Disorders

Certain genetic diseases or in utero events have been associated with abdominal aortic coarctations. The most frequent is

neurofibromatosis-1 (NF-1).[1,7-11] Others include William syndrome, Alagille syndrome, and tuberous sclerosis.[12-18] It is theorized that each of these diseases results in the interference of cell growth in vascular tissue or cellular death during development. The NF-1 phenotype deserves particular note. It is highly variable, and a wide spectrum of vascular involvement exists. Although aneurysms, arteriovenous malformations, cardiac valvular anomalies, and direct neural tumor invasion or compression of vascular structures have been reported, hypertension due to renal artery stenotic disease or abdominal aortic narrowing is the most common presentation of NF-1, reflecting vascular involvement.[19-22] It is difficult to find a unifying cause for this phenotype of NF-1, although the variable influence of modifying genes in addition to a primary NF-1 mutation, as well as alterations in the tissue specific elastin gene transcription, may play a role.[23,24] In our experience, more than 25% of patients with abdominal aortic coarctation or segmental aortic hypoplasia carry a confirmed diagnosis of NF-1.[1] In another large series of patients who had NF-1–related vascular involvement, only 13% exhibited abdominal aortic coarctations.[22]

Maternal rubella during the first trimester is an infectious-inflammatory disorder that has been associated with abdominal aortic hypoplasia.[25-27] Takayasu aortoarteritis is another recognized cause of abdominal aortic coarctation that must be differentiated from developmental narrowings, although this disease is more likely to involve the aortic arch and proximal descending thoracic aorta.[28] Such an active or latent arteritis may be the most common cause of abdominal aortic narrowings encountered in the subcontinents. Nondevelopmental abdominal aortic coarctation has been associated with umbilical artery catheterization during the neonatal period, although aortic thromboses and mycotic aneurysms have been reported more frequently than aortic narrowings.[29,30]

DEVELOPMENTAL RENAL AND SPLANCHNIC ARTERIAL STENOSES

Abdominal aortic coarctations are associated with stenoses of the splanchnic and renal arteries, in 87% and 62% of cases, respectively.[1] Similar to abdominal aortic coarctation, pediatric renal artery stenoses represent a spectrum of diseases. Etiology of pediatric renal artery stenosis is most commonly developmental in North American Caucasian children,[2,7] compared with more common inflammatory aortoarteritis and Takayasu-related stenoses that dominate reports from Asia, Africa, and South America.[31-34] Large clinical reports suggest that the causes of most developmental renal occlusive lesions are the same as those causing abdominal aortic coarctations,[1,2] and that many of these patients have NF-1.[2,22,35-37] The majority of renal artery narrowings are ostial in location, representing true hypoplastic stenoses. The affected arteries are very small, with derangements of all three vessel wall elements, including intimal proliferation, medial thinning, and excessive adventitial elastin (Fig. 130.5).

Similar ostial stenoses of the celiac artery (CA) and superior mesenteric artery (SMA) also occur in areas of abdominal aortic coarctations (Fig. 130.6). These stenotic narrowings usually are incidentally recognized most often during studies for suspected aortic or renal artery pathology. Developmental lesions appear related to embryonic phenomena similar to those causing aortic and renal artery narrowings. These events likely affect the reorganization of the ventral segmental vessels associated with the cephalic roots of the vitelline arteries that form the CA and SMA. This results in an ostial stenosis or occlusion. Minimal CA and SMA narrowings at a young age may not increase in diameter as the child grows. In these circumstances, the artery's origin becomes proportionately narrower as the adjacent artery

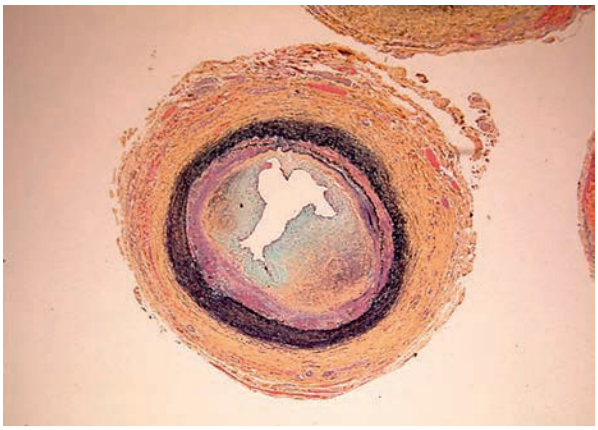

Figure 130.5 Typical developmental renal artery ostial stenosis exhibiting proliferation of intimal tissues, medial thinning, and excessive adventitial elastin (Movat stain).

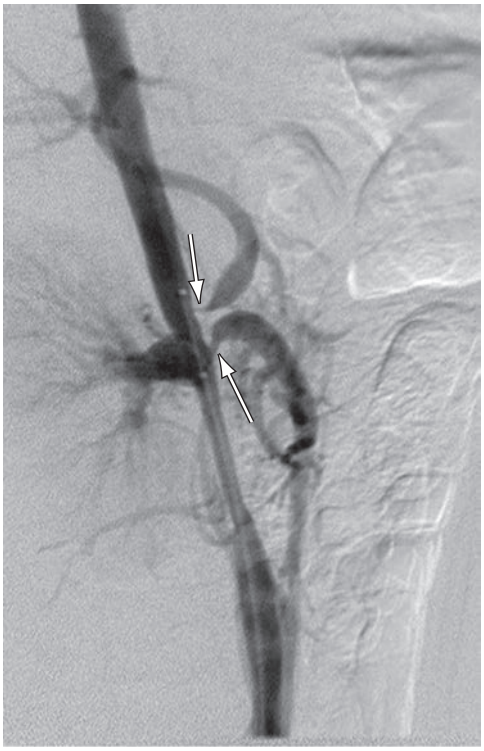

Figure 130.6 Severe celiac artery and superior mesenteric artery ostial stenoses evident on a lateral aortogram *(arrows)*. (From Stanley JC, et al. Pediatric arterial disease. In: Coran AG, Caldamone A, Adzick NS, et al, eds. *Pediatric Surgery*, 7th ed. Philadelphia: Elsevier Saunders; 2012:1631–1645.)

becomes bigger, until the narrowing becomes a critical stenosis. This entire process suggests a major growth arrest of the aortic origins of these splanchnic arteries.

CLINICAL MANIFESTATIONS

Occlusive disease affecting the renal arteries ranks as the third most prevalent cause of hypertension in children, behind parenchymal renal disease and coarctation of the thoracic aorta.[38-40] The exact incidence of renovascular hypertension as a cause of secondary hypertension in the pediatric population is unknown, but is likely to account for 8% to 10% of those exhibiting marked blood pressure elevations.[41] Although the overall incidence is low, renovascular disease accounts for a much larger proportion of hypertension in children than in the adult population.

Hypertension due to suprarenal or intrarenal aortic narrowings may be compounded by occlusive lesions of the renal artery. The resulting secondary hypertension in these cases is often refractory to simple pharmacologic control. Encounters with such patients who are receiving three or more antihypertensive agents are commonplace. Lower extremity fatigue with exercise due to abdominal aortic narrowing has been reported infrequently as the presenting complaint, and true claudication is rare.[1]

Despite the high rate of CA and SMA occlusive involvement with developmental narrowing of the abdominal aorta, symptomatic intestinal ischemia affected only 6% of these cases.[1] When these patients have functionally relevant splanchnic arterial narrowings, they present with postprandial intestinal angina manifest by periumbilical discomfort that lasts for the duration of small bowel transit of ingested food. These patients develop a food adversion and exhibit weight loss from a failure to eat.

Initial presentations of pediatric renovascular hypertension are quite varied and include asymptomatic high blood pressure, headache, seizure, epistaxis, visual disturbances, and acute renal insufficiency. The spectrum of neurologic dysfunction includes an isolated facial nerve paralysis, reported as Bell's palsy.[41,42] More chronic effects of elevated blood pressure may be evident by the arrest of kidney growth or atrophy with chronic renal insufficiency.[43] When unrecognized and untreated, renovascular hypertension in children is associated with hemorrhagic stroke, hypertensive encephalopathy with impaired cognitive development, and failure to thrive. Poorly controlled hypertension also may result in severe diastolic dysfunction and left ventricular hypertrophy (LVH). When untreated, the resulting hypertensive cardiomyopathy can progress to heart failure. If the entire renal mass is involved, flash pulmonary edema associated with renal insufficiency may occur, although this is an uncommon complication.

Definition of Hypertension in Children

The National Health and Nutrition Examination Survey (NHANES) data are the basis for definitions of hypertension in children and adolescents. Blood pressure tables for the 50th, 90th, 95th, and 99th percentiles by sex, age, and height are included in The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents published by the US Department of Health and Human Services (http://www.nhlbi.nih.gov/health/prof/heart/hbp/hbp_ped.pdf).[44]

Normal pressure is defined as systolic blood pressure (SBP) or diastolic blood pressure (DBP) that is less than the 90th percentile for sex, age, and height, whereas hypertension is defined as an average SBP or DBP that is greater than or equal to the 95th percentile for sex, age, and height on at least three separate occasions.

It is recommended that children older than 3 years of age who are seen in a medical setting have their blood pressure measured; the preferred method is by auscultation. It is critical that an appropriate sized cuff be used for the size of the child's upper arm. Children younger than 3 years of age should also have blood pressure evaluations if congenital heart disease is identified, if there are known renal diseases or urologic malformations, if they require hospitalization, or if other systemic illnesses associated with hypertension are identified (e.g., neurofibromatosis, tuberous sclerosis).

The prevalence of LVH in children and adolescents with hypertension underscores the importance of recognizing and treating this disease. Although 43% of hypertensive children in one study were being treated with antihypertensive medication at the time of evaluation, LVH was present by echocardiogram in 41% using pediatric criteria and in 16% using adult criteria.[43] Additional documented effects of pediatric hypertension include impaired cognition or failure to thrive.[45-47]

DIAGNOSTIC EVALUATION

Imaging to accurately define renal artery stenotic disease requires significant detail.[2,7,48,49] Renal Doppler sonography and axial imaging with both computed tomography angiography (CTA) and magnetic resonance angiography (MRA) are utilized increasingly as first-line imaging modalities for pediatric renovascular hypertension; their respective risks and benefits are outlined in Table 130.1.[50] Renal sonography is an appropriate first-line study to detect renin-mediated hypertension caused by aortic or main renal artery disease, offering up to 90% sensitivity and 68% specificity.[51] Axial imaging certainly produces increased anatomic yield. Moreover, contemporary low-dose CTA protocols may reduce radiation exposure in this sensitive age group, without compromising diagnostic imaging modality, and time-resolved three-dimensional (3D) cine phase-contrast MRI may permit the evaluation of renal blood flow pre- and postintervention.[52,53] If a strong suspicion of a renovascular lesion exists, then catheter-based digital subtraction angiography should be pursued, in that conventional angiography remains the most valuable diagnostic study for patients with renovascular hypertension and remains the authors' diagnostic modality of choice for preoperative planning.[1,2,49,54]

Cerebral vascular abnormalities are described in a small percentage of patients with MAS (3%-13%), including intracranial arterial occlusive disease and cerebral aneurysms.[55,56] For this reason, screening children with contrast-enhanced axial imaging (CTA or MRA) should be considered.

TABLE 130.1 Imaging Modalities for Pediatric Renovascular Hypertension

Diagnostic Modality	Risks	Benefits
Renal doppler sonography	• Operator dependent • Small vascular structures (i.e., accessory renal arteries and segmental branches) may be difficult to visualize directly	• No ionizing radiation • Relatively low cost • Widespread availability
CTA	• Ionizing radiation • Iodinated contrast	• Rapid imaging of thoracoabdominal arterial structures decreases motion-related artifact and decreases need for sedation • Excellent spatial resolution • Excellent contrast resolution • Permits high-quality multiplanar 2D re-formats and 3D reconstructions
MRA	• High cost • Limited availability • Lower spatial resolution (in comparison to CTA) that limits evaluation of small accessory arteries and intra-renal segmental branches • May exaggerate areas of arterial narrowing • Artifacts may result from implanted metal or patient motion • Younger patients may require sedation or general anesthesia during the study period	• Excellent contrast resolution allows for 2D reformats and 3D reconstructions • No ionizing radiation • May obtain images with and without intravenous contrast material
Conventional catheter-based digital subtraction angiogram	• Invasive with procedural risk • Younger patients may require general anesthesia • Ionizing radiation	• Best spatial and temporal resolution • Produces excellent images of the renal arterial lumens and branches • Advantage of concurrent therapeutic intervention

CTA, Computed tomography angiography; *MRA*, magnetic resonance angiography.
Modified from Castelli PK, Dillman JR, Smith EA, et al. Imaging of renin-mediated hypertension in children. *AJR Am J Roentgen*. 2013;200:W662–W672.

MEDICAL MANAGEMENT

Pharmacologic treatment of hypertension in a very young child may be difficult and requires frequent and careful monitoring. Failure of medical therapy to halt the progression or diminish LVH should be a reason to consider surgical or endovascular therapy.

All children with secondary hypertension should be treated. The goal of therapy is reduction of the pressure to the 95th percentile for sex, age, and height, unless LVH or other target organ damage is identified, in which case the goal should be less than the 90th percentile. Although no specific recommendations regarding pharmacologic agents have been made, there are accepted classes of medications used in the management of hypertension in children ages 1 to 17 years old.

Antihypertensive Drug Treatment

Common classes of antihypertensive drugs for the ambulatory management of hypertensive children include angiotensin converting enzyme (ACE) inhibitors (benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril); angiotensin receptor blockers (ARBs; irbesartan, losartan); combined alpha and beta blockers (labetalol); beta blockers (atenolol, metoprolol, propranolol); combined beta blockers and diuretics (bisoprolol/hydrochlorothiazide [HCTZ]); central alpha agonists (clonidine); calcium channel blockers (amlodipine, felodipine, isradipine, extended-release nifedipine); diuretics (hydrodiuril, chlorthalidone, furosemide, spironolactone, triamterene, amiloride); peripheral alpha antagonists (doxazosin, prazosin, terazosin); and vasodilators (hydralazine, minoxidil).[44] It is recommended that a single agent be initiated until target blood pressure is reached or until maximum dose or a side effect of the drug is encountered, at which time an additional agent should be added.[44]

The nuances of medical pharmacologic treatment of renovascular hypertension are numerous and complicated, but several specifics deserve note. First, the ACE and/or ARB classes of medicine are potent antihypertensives, sometimes controlling blood pressures with monotherapy, whereas multiple agents from other classes of drugs fail. Antihypertensives that block any part of the renin-angiotensin-aldosterone system are relatively contraindicated until critical main renal artery stenosis or bilateral renal artery disease is excluded. When initiated, this medial therapy requires careful monitoring of serum potassium and creatinine. A decline in renal function is most apt to occur when blood flow to the entire renal mass is compromised (i.e., bilateral renal artery disease or unilateral disease in the presence of a solitary kidney). Discontinuation of these drugs usually results in a return to baseline renal function. Second, the existence of rebound hypertension and tachycardia seen with the sudden withdrawal of clonidine is particularly troublesome in children. When clonidine patches are used in a very young child, they may be accidentally detached, resulting in dramatic fluctuations in blood pressure and heart rate. A functioning, properly applied patch should be carefully monitored by those

caring for these children. In these cases, one should confirm the adequacy of the patch placement before undergoing a complex search for the cause of an abrupt change in blood pressure control. Finally, diuretics should be used as combination therapy, as their isolated use may increase renin release and exacerbate hypertension.[57]

SURGICAL TREATMENT

Isolated abdominal aortic coarctations are preferentially treated by patch aortoplasty when technically feasible, whereas thoracoabdominal bypass may be favored in patients in whom the hypoplastic segment of the aorta is too narrow to facilitate placement of a patch, or in cases of complex disease affecting the renal and splanchnic arteries.[1,58] Expanded polytetrafluoroethylene (ePTFE) grafts are favored over woven or knitted grafts for both patch aortoplasty and thoracoabdominal bypass grafting, due to the greater stability of ePTFE regarding postimplantation dilatation.

A novel treatment for MAS has more recently been described in a single case report involving the placement of a retroaortic tissue expander to induce longitudinal growth of the normal distal aorta.[59] The tissue expander is sequentially inflated through a subcutaneous port over the course of many months to elongate the nonaffected aorta such that it can be anastomosed to the proximal normal aorta, after resection of the aortic segment that is narrowed. Long-term follow-up of such therapy is lacking.

Patch Aortoplasty

Patch aortoplasty is performed when the narrowed segment of the aorta has a large enough diameter to allow completion of the anastomosis without an overlap of sutures from the opposite side of the patch. Aortic patches in children are sized large enough to facilitate and match the growth of the remaining aorta, but these patches are not so large as to favor low-velocity flow and potential thrombus formation (Fig. 130.7). Aortoplasty in these patients is often accompanied by complex renal and splanchnic arterial reconstructive procedures (Fig. 130.8).

Thoracoabdominal Bypass

Thoracoabdominal bypass grafts should originate above the narrowed area, either from the distal thoracic aorta above the diaphragm using a thoracoabdominal approach or from the supraceliac aorta at the diaphragmatic hiatus by an abdominal approach (Fig. 130.9). The grafts are positioned behind the left kidney with a gentle curve to the distal aorta. The sizing of bypass grafts follows the sizing principles used for patch aortoplasty. The intent is to use oversized grafts compared with the aorta, recognizing anticipated growth; otherwise the result is a graft that is too small to maintain normal distal pressures and flow. Basic diameter guidelines are as follows: 8- to 12-mm grafts in young children; 12- to 16-mm grafts for early adolescents; and 14- to 20-mm grafts in late adolescents and adults. It is not essential to leave significant graft redundancy in older children and adolescents, because axial growth from the diaphragm to the pelvis is not significant after reaching 9 or 10 years of age. Thoracoabdominal bypass procedures are frequently undertaken with concurrent complex renal and splanchnic artery reconstructions (Figs. 130.10 and 130.11).

In very early childhood, the use of large conduits may not be possible.[1] Aortic reoperations may be required for anastomotic narrowings, or if a patient outgrows the primary reconstructive

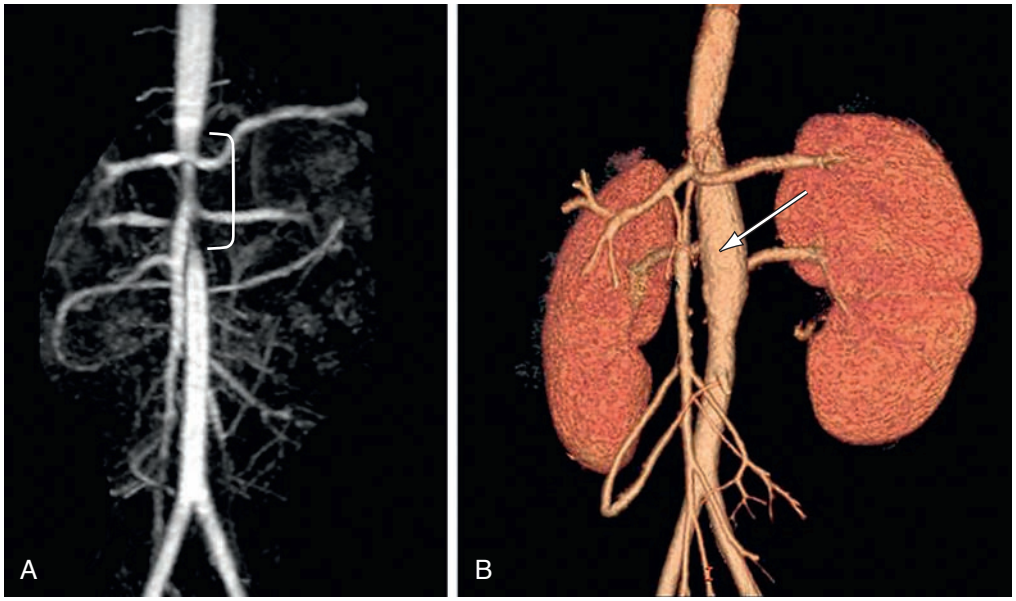

Figure 130.7 (A) Suprarenal coarctation *(bracket)* with bilateral renal artery ostial stenoses. Preoperative magnetic resonance angiography. (B) Subsequent patch aortoplasty *(broad arrow)*, with aortic diameter exceeding that of uninvolved proximal and distal aorta. Reimplantation of the renal arteries accompanied the aortic reconstruction. (From Stanley JC, Criado E, Eliason JL, et al. Abdominal aortic coarctation: surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. *J Vasc Surg.* 2008;48:1073–1082.)

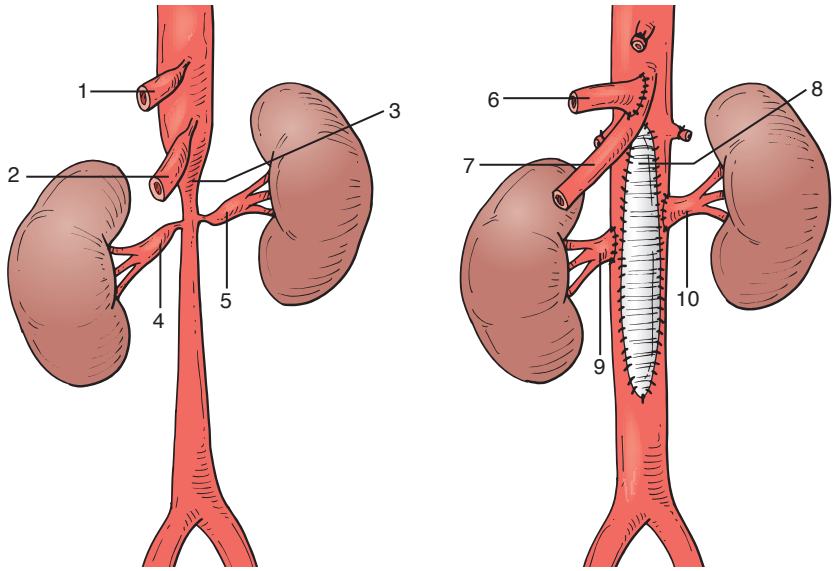

Figure 130.8 Complex aortic, splanchnic, and renal arterial reconstruction: *1*, Celiac artery (CA) stenosis; *2*, superior mesenteric artery (SMA) stenosis; *3*, interrenal midabdominal aortic coarctation; *4* and *5*, right and left renal artery stenosis; *6*, CA implanted onto stenotic SMA origin; *7*, widely patent SMA; *8*, polytetrafluoroethylene patch aortoplasty; *9* and *10*, bilateral implantation of renal arteries onto aorta. (From Upchurch GR, Jr, Henke PK, Eagleton MJ, et al. Pediatric splanchnic arterial occlusive disease: clinical relevance and operative treatment. *J Vasc Surg*. 2002;35:860–867.)

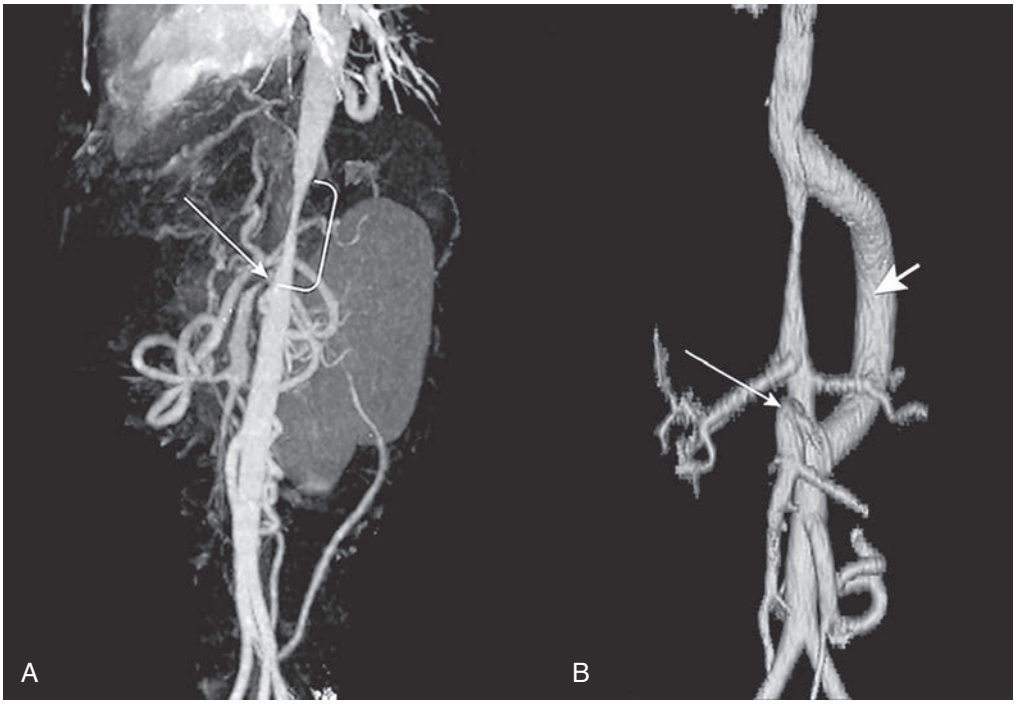

Figure 130.9 **(A)** Suprarenal coarctation *(bracket)* with superior mesenteric artery stenosis *(arrow)*. **(B)** Subsequent thoracoabdominal bypass *(broad arrow)* with aortic implantation of superior mesenteric artery *(arrow)*. (From Stanley JC, Criado E, Eliason JL, et al. Abdominal aortic coarctation: surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. *J Vasc Surg*. 2008;48:1073–1082.)

procedure. Long-term follow-up of these patients is essential for this reason.

Primary open surgical treatment of abdominal aortic coarctation for renovascular hypertension benefits more than 90% of patients when treated with a patch aortoplasty or a thoracoabdominal bypass.[1,58] Postoperative morbidity is low, with infrequent bleeding and postsurgical pancreatitis being the most noteworthy complications. Surgical mortality and unintended nephrectomy rates should approach zero. The patency of patch aortoplasty, thoracoabdominal aortic bypass, or endoluminal treatments may be followed indirectly by noninvasive blood pressure measurements of the upper and lower extremities, with and without exercise. If the ankle-brachial index measurements are noted to decline, then detailed imaging should be considered. MRA is favored to avoid excessive radiation exposure accompanying CT studies. Late, secondary operations at the authors' institution following surgical treatment of abdominal aortic coarctation or segmental hypoplasia approached 10% and were performed 5 to 12 years after the initial reconstruction.[1]

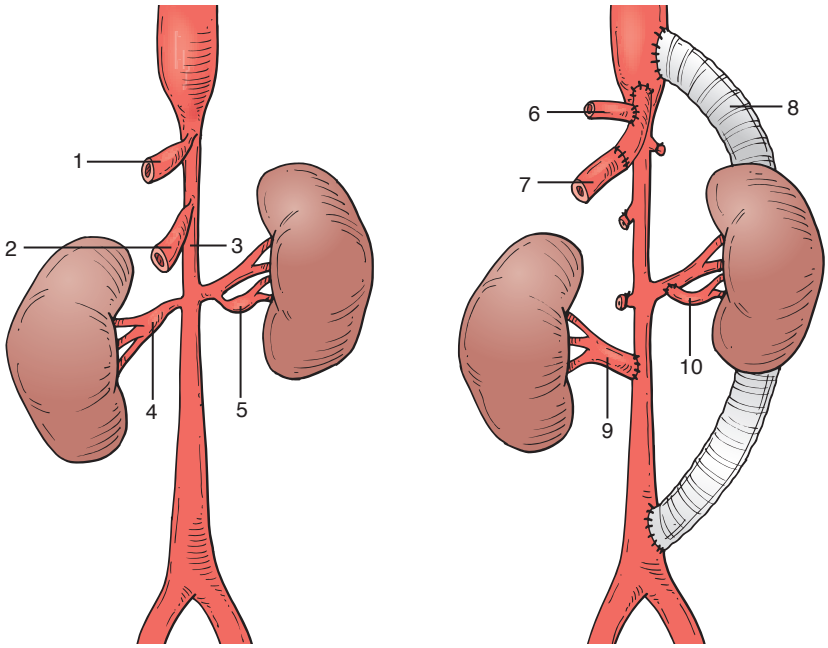

Figure 130.10 Complex aortic, splanchnic, and renal arterial reconstruction: *1*, Celiac artery (CA) stenosis; *2*, superior mesenteric artery (SMA) stenosis; *3*, suprarenal midabdominal aortic coarctation; *4*, right renal artery ostial stenosis; *5*, left segmental renal artery stenosis; *6*, CA implanted onto aorto-SMA bypass (with autogenous internal iliac artery graft); *7*, reconstructed SMA; *8*, thoracoabdominal aortic bypass; *9*, right renal artery reimplantation onto aorta; *10*, left segmental renal artery implantation onto adjacent segmental renal artery. (From Upchurch GR, Jr, Henke PK, Eagleton MJ, et al. Pediatric splanchnic arterial occlusive disease: clinical relevance and operative treatment. *J Vasc Surg*. 2002;35:860–867.)

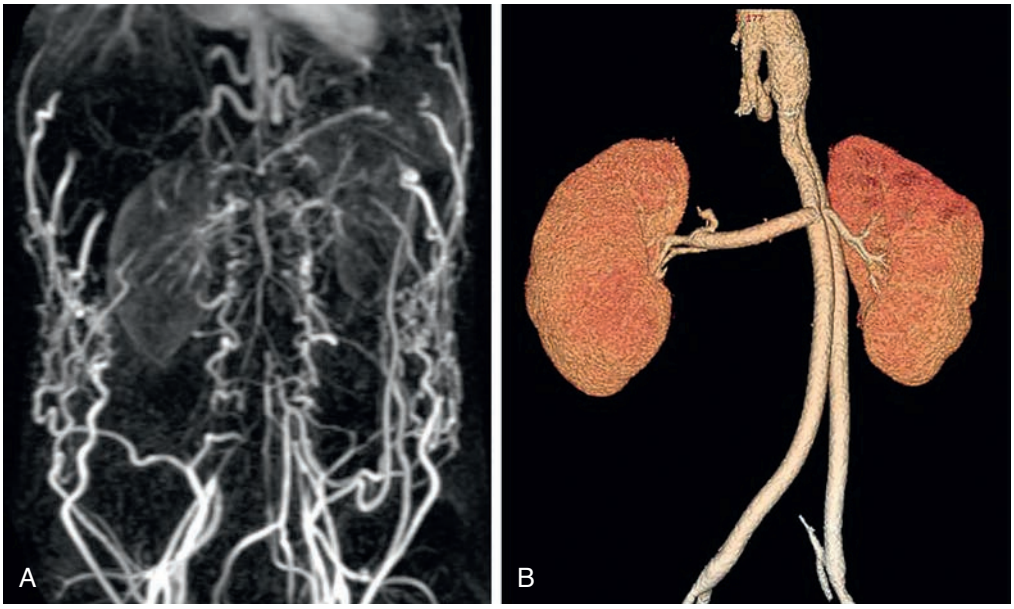

Figure 130.11 (A) Absence of the abdominal aorta and agenesis of the proximal main renal arteries, with reconstitution of the distal renal arteries and iliac arteries by way of extensive collateral vessels. **(B)** Complex thoracic aortobi-iliac bypass with bilateral renal artery reconstructions.

Renal Artery Repair

Repair of renal artery stenoses found independently of an aortic narrowing or in conjunction with an aortic coarctation is most often undertaken to prevent long-term sequelae of hypertension. The surgical options and reconstructive configurations should be considered carefully to minimize kidney ischemic times and facilitate unobstructed and durable renal artery reconstructions (Figs. 130.12 and 130.13).[2,7]

There should be a degree of caution regarding the timing of operation. Significant technical challenges exist in reconstructing the very small and highly vasoactive arteries in infants. Uncontrolled severe hypertension or renal failure in a rare instance may require the surgeon to undertake an operation in the very young. However, renal revascularizations are more likely

Figure 130.12 Bilateral renal artery-aortic implantations. Note the residual origins of the native renal arteries. (From Stanley JC, Zelenock GB, Messina LM, Wakefield TW. Pediatric renovascular hypertension: a thirty-year experience of operative treatment. *J Vasc Surg*. 1995;21:212–227.)

Figure 130.13 Aortorenal bypass with an internal iliac artery graft. (From Stanley JC, Zelenock GB, Messina LM, Wakefield TW. Pediatric renovascular hypertension: a thirty-year experience of operative treatment. *J Vasc Surg*. 1995;21:212–227.)

to be successful and more durable after the age 3 years, and deferring reconstructive procedures in infants when possible is reasonable and appropriate.

Determining the optimal surgical therapy depends on the specific character of the renal artery disease being treated. Considerations may include whether or not both renal arteries are involved, the length of the stenotic disease, and whether segmental renal branches are also narrowed. The most common method of surgical reconstruction has been renal artery implantation of the normal artery beyond the stenosis into the aorta or an undiseased adjacent artery.[2,7] Use of the internal iliac artery for aortorenal bypass grafts, when needed, has proven to be a suitable conduit and is currently recommended if reimplantation of the vessel cannot be performed.[2] An aortorenal bypass with a vein graft, as utilized in the past, is no longer recommended due to aneurysmal degeneration, seen in more than half of these grafts at follow-up.[60]

The common coexistence of splanchnic arterial narrowings in patients with renal artery stenoses and the propensity for the CA to develop stenosis as a young child grows are reasons why splenorenal reconstructions with a direct anastomosis of the involved vessels are not favored in the pediatric population. Using this type of reconstruction may perpetuate or result in a recurring hypertensive state.

Less common renal artery reconstructive procedures include resection of the stenotic segment of artery with a primary reanastomosis, a focal arterioplasty, or an open operative dilation. It may be necessary to consider nephrectomy in patients with nonreconstructable disease. Indications for nephrectomy include multiple intrarenal stenoses not amenable to open in-situ or endovascular treatment, or diminutive nonfunctioning kidneys 2 to 3 cm in size. Nephrectomy is only appropriate when the contralateral kidney is assumed to be sufficient in preventing the patient from going into renal failure, while partial nephrectomy may offer a nephron-sparing cure for segmental renovascular hypertension, as diagnosed by selective renal vein renin sampling.[61]

Large clinical experiences with pediatric-aged renovascular hypertension are uncommon.[7,62-69] The published University of Michigan series included 97 children (39 girls and 58 boys), ages 3 months to 17 years, who underwent operation from 1963 to 2006.[2] All but one patient had refractory hypertension not responsive to medical therapy. Renal artery stenoses in this series were developmental in 80% of cases. Mesenteric arterial occlusive lesions affected 24%, and abdominal coarctations affected 33%. Primary renal artery operations were performed 132 times, with procedures including resection beyond the stenosis and implantation into the aorta in 49 cases, renal artery in 7, or SMA in 3 cases; aortorenal and iliorenal bypasses with vein or iliac artery grafts in 40 cases; focal arterioplasty in 10 cases; resection with reanastomosis in 4; operative dilation in 4; splenorenal bypass in 2; and primary nephrectomy in 13, when arterial reconstructions proved impossible. The complexity of this disease is underscored by the fact that 32 children required bilateral renal artery operations, 17 patients underwent a simultaneous CA or SMA reconstruction, 19 had a patch aortoplasty, and 11 underwent a thoracoabdominal aorto-aortic bypass. Thirty secondary renal artery procedures were performed in 19 of this series' patients, including nine nephrectomies. Hypertension was cured in 68 children (70%), improved in 26 (27%), and was unchanged in 3 (3%). There was no perioperative mortality, and no patient required dialysis during a mean follow-up of 4.2 years.

Another large experience was reported from the Hospital Beaujon in France.[63] This series included 78 children (35 boys and 43 girls), ranging in age from 1.4 to 18 years. There were 91 primary revascularization procedures and 15 nephrectomies. These numbers were quite similar to the University of Michigan series. A third series from the Cleveland Clinic involved 56 children (23 boys and 33 girls), ranging in age from 8 months to 21 years.[65] They reported 46 primary operations and 10 primary nephrectomies. A fourth series, from both Vanderbilt University and the Children's Hospital of Philadelphia, included 50 children (24 boys and 26 girls), ranging in age from 5 months to 16 years.[66] The authors reported on 28 primary reconstructive procedures and an additional 12 primary nephrectomies. The latter two series, unlike the experiences at the University of Michigan or Hospital Beaujon, did not contain many patients treated for aortic or splanchnic arterial disease.

When blood pressure control outcomes were analyzed in the three major reports on pediatric renovascular hypertension from the University of Michigan, Vanderbilt University–Children's Hospital of Philadelphia, and the Cleveland Clinic, a great deal of similarity was found in the results. Respective

cure rates were 70%, 70%, and 66%; reported improvement rates were 27%, 26%, and 23%; and failure rates were 3%, 4%, and 11%. Each of these reports reflected the open surgical management of renal artery stenoses in children.

Renal autotransplantation has been suggested in case reports and more contemporary retrospective single institution series as safe and efficacious for complex and segmental renal artery disease without associated mortality, negligible morbidity, and reasonable long-term follow-up.[70-72] Hypertension cure rates in the latter setting may approach 62% and improvement rates 38% with concurrent preservation of renal function.

Splanchnic Artery Repair

Splanchnic artery repair depends on whether obstructions of the CA and SMA are symptomatic. Any mandate to reconstruct the CA or SMA applies only to symptomatic cases. A relative indication to prophylactically reconstruct these vessels exists when performance of an aortoplasty or renal revascularization would make a subsequent CA or SMA revascularization exceedingly difficult (Fig. 130.14).[73] Aortic reconstructions remote from the mesenteric vessels make prophylactic mesenteric revascularization less likely to be warranted.

The operative treatment of pediatric splanchnic arterial occlusive disease is complex. Internal iliac artery grafts are used to treat lengthy CA or SMA stenoses in young patients. Anastomoses are fashioned with interrupted sutures when reconstructing small arteries 2 to 3 mm in diameter. In older adolescents, a continuous suture may be used to complete anastomoses of larger splanchnic arteries. In other children, aortic implantation of the CA or SMA after spatulation of the transected vessel beyond its stenotic origin is favored over an aortosplanchnic bypass. Patients treated by both methods are quickly able to gain weight and are rapidly freed from abdominal discomfort. Developmental CA or SMA stenoses in adults may be reconstructed with either vein grafts or synthetic conduits. Percutaneous transluminal balloon angioplasty with or without stenting in children for these splanchnic ostial lesions is not appropriate and ill-advised.

Splanchnic arterial occlusive disease encountered in childhood has an uncertain natural history. Long-term follow-up of these children with periodic imaging studies in those operated upon seems appropriate, and regular clinical assessment of those not subjected to surgical therapy is recommended. With regard to the latter, it is important to remember that most CA and SMA stenoses are asymptomatic because of the inferior mesenteric artery serving effectively as a source of collateral circulation. Unoperated patients should be aware of their splanchnic arterial anatomy and be able to pass this information to a surgeon performing a later abdominal operation. Inadvertently interrupting the collateral circulation might cause catastrophic intestinal ischemia in these individuals.

Figure 130.14 Superior mesenteric artery implantation into infrarenal aorta *(arrow)*, as treatment of intestinal ischemia due to an ostial stenosis of this artery, in a child with near occlusion of the supraceliac abdominal aorta who underwent a concomitant thoracoabdominal bypass to the distal aorta (not visualized on this lateral aortogram).

ENDOVASCULAR TREATMENT

Endovascular treatment of abdominal aortic narrowings is increasingly reported. Endoluminal interventions may have utility in the treatment of select focal abdominal aortic coarctations distant from the renal and splanchnic branches, and this therapy has been most commonly employed for the treatment of stenotic disease due to an aortitis.[74-78] Developmental aortic narrowings are prone to significant recoil from the hypoplastic and fibrotic segments, and stenting may be required to overcome this.[79-81] Percutaneous measures may be successful in the procedural setting at decreasing a pressure gradient across a stenosis or reducing the degree of luminal stenosis, but at the cost of increased perioperative morbidity in comparison to open surgery, with complication rates that approach 30%, including aortorenal injury ("tears"), aneurysm formation at the site of angioplasty, and stent embolization.[55,56] In addition, endovascular treatments are associated with an increased incidence of restenosis and reintervention with freedom from reintervention of only 55% at 1 year and 33% at 5 years in larger series.[55] Long-term benefits of endovascular interventions remain unproven in children with developmental aortic narrowings, and subsequent operations following stent failure are considerably more difficult.

Endoluminal interventions have provided major benefits in treating renovascular disease, particularly in young adults with fibromuscular dysplasia, and are being utilized with increasing frequency in the treatment of pediatric renovascular disease with several contemporary reports suggesting success.[82-85] It warrants mention that in the largest published series, hypertension cure and improvement rates combined approximate 60%, with failure rates ranging 32% to 44% and high rates of early restenosis.[84-86] These results may be anticipated, given the

Figure 130.15 Renal arteriogram demonstrating incomplete stent expansion across an ostial, developmental renal artery stenosis with notable in-stent stenosis in a child with multidrug resistant renovascular hypertension.

underlying developmental arterial derangement associated with excessive elastic tissue and unyielding fibrosis, which may result in early postdilation arterial recoil. Importantly, the excessive degree of radial force required to dilate a fibrotic lesion and the accompanying injury to the diminutive artery risks thrombotic complications. The role of endovascular interventions in the treatment of pediatric renal artery stenoses remains controversial.[2,87-89] Remedial operations following failed endovascular therapy are more complex (e.g., distal bypass in lieu of direct aortic reimplantation) and are not as successful as primary operations.[89] Outcomes following remedial operations included hypertension cure rates of only 25% and improvement rates of 54% (in comparison to 70% and 27%, respectively, with open procedures). Patient selection for endovascular intervention should consider the small vessel size and fibrotic nature of these lesions. Stents are to be avoided, as they increase the risk of neointimal hyperplasia and recurrent stenosis and do not take into account later necessary growth of the artery, both in diameter and length (Fig. 130.15). Finally, endovascular therapies should only be performed at high volume centers by an experienced team.

The management of developmental aortic, renal, and splanchnic artery disease remains a complex process that is best managed with the collaboration of multiple specialties. Nephrology, vascular surgery, diagnostic and interventional radiology, and cardiology all may routinely contribute valuable insights into the diagnosis, follow-up, and management of these patients. A disease specific, multidisciplinary, patient- and family-centered focus will afford the most salutary outcomes.

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131 CHAPTER

Mesenteric Arterial Disease: Epidemiology, Pathophysiology, and Clinical Evaluation

RUBY C. LO and MARC L. SCHERMERHORN

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Mesenteric ischemia occurs when perfusion of the visceral organs fails to meet normal metabolic requirements. This disorder is categorized as either acute or chronic, based on the duration of symptoms. Acute mesenteric ischemia (AMI) occurs rapidly over hours to days and frequently leads to acute intestinal infarction requiring resection (see Chapter 133). The most common causes are embolization to the mesenteric arteries or acute thrombosis related to a preexisting plaque. Chronic mesenteric ischemia (CMI) is a more insidious process and progresses over weeks to several months (see Chapter 132). The most common cause is progressive occlusive disease of the visceral arteries, usually related to atherosclerosis. Because CMI is relatively uncommon, it is frequently misdiagnosed as a gastrointestinal disorder. Patients typically have undergone an extensive workup for other potential etiologies before being diagnosed with CMI.

The first case of AMI was diagnosed and treated successfully with intestinal resection and re-anastomosis by Elliott in 1895. Goodman first described chronic intestinal angina as a clinical disorder in 1918.[1] Dunphy, a surgical resident at the Peter Bent Brigham Hospital in 1936, reported a case of a patient with weight loss and pain out of proportion to abdominal findings who subsequently died and was found to have mesenteric occlusive disease on autopsy. After reviewing the medical records of 12 patients who died of intestinal angina, he found that 7 of the 12 (58%) had a history of chronic abdominal pain, thus introducing the potential for early intervention to prevent disease

Abstract

Mesenteric ischemia occurs when perfusion of the visceral organs fails to meet normal metabolic requirements. This disorder is categorized as either acute or chronic, based on the duration of symptoms. The most common causes of acute mesenteric ischemia (AMI) are embolization to the mesenteric arteries or acute thrombosis related to a preexisting plaque. Chronic mesenteric ischemia (CMI) is a more insidious process and progresses over weeks to several months. The most common cause is progressive occlusive disease of the visceral arteries, usually related to atherosclerosis. Endovascular revascularization is now considered first-line therapy for CMI and is being increasingly used to manage AMI. However, it has been associated with high rates of symptom recurrence, restenosis, and reintervention.

Keywords

acute
celiac
chronic
intestinal
ischemia
mesenteric

progression and death.[2] Warren and Eberhard were the first to describe mesenteric venous thrombosis (MVT) as a distinct cause of intestinal infarction in 1935, differentiating it from occlusion of the mesenteric arteries.[3]

In the modern era, Klass performed the first superior mesenteric artery (SMA) embolectomy in 1950, avoiding intestinal resection.[4] Although the patient died several days later of a heart-related condition, autopsy revealed the bowel to be normal. In 1958, Shaw and Maynard performed the first successful thromboendarterectomy of the SMA at the Massachusetts General Hospital.[5] Morris and colleagues performed the first successful retrograde bypass graft from the infrarenal aorta to the SMA in 1962.[6] Stoney and Wylie at the University of California, San Francisco, first described antegrade aortovisceral bypass and transaortic visceral thromboendarterectomy in 1966.[7] Ushering in the current era of percutaneous treatment of visceral arterial occlusive disease, Furrer and Novelline separately published the initial reports of endovascular dilation of the SMA in 1980, and in 1992, Finch was the first to report of treatment of a celiac artery stenosis with a Palmaz stent.[8-10]

ANATOMY OF THE VISCERAL ARTERIES

The primitive dorsal aorta gives rise to the abdominal aorta during fetal development. Ventral segmental arteries emerge from the primitive ventral aorta, which disappears around the fourth week of gestation. Multiple segmental branches from the primitive ventral aorta—the 10th, 13th, and 21st—persist and develop into the celiac artery, SMA, and inferior mesenteric artery (IMA), respectively. Disparity in the regression of the primitive ventral aorta and its segmental branches infrequently causes deviations in the visceral arterial anatomy.

The celiac artery arises from the abdominal aorta just caudal to the diaphragm at the level of L1 and is bordered by the median arcuate ligament (MAL) at the aortic hiatus superiorly and the superior border of the pancreas inferiorly. Traditionally, the three branches from this common trunk include the left gastric, splenic, and common hepatic arteries. However, multiple variations of the true "trifurcation" can exist. Most frequently, the common hepatic artery and its branches arise from the SMA or directly from the abdominal aorta.

Exposure of the celiac trunk is best achieved through a midline transabdominal incision, which also allows visual assessment of bowel viability during surgical revascularization (see Chapter 54). The celiac trunk and its branches are surrounded by the celiac plexus of nerves, which must be divided for proximal exposure. A midline laparotomy is performed, and the triangular ligament is divided.

The SMA arises a few centimeters caudal to the celiac trunk; its origin is crossed by the neck of the pancreas and the splenic vein. It arises at a less acute and downward-sloped angle than the celiac trunk and lies superior to both the uncinate process of the pancreas and the third portion of the duodenum. The superior mesenteric vein runs parallel adjacent to the artery, usually along its right border. The first important branch of the SMA is usually the inferior pancreaticoduodenal artery, which supplies collateral circulation with the celiac artery through the gastroduodenal and superior pancreaticoduodenal arteries. The second major branch of the SMA is frequently the middle colic artery, which arises at the inferior border of the pancreas. The right colic, ileocolic, and third-order mesenteric branches arise distally, supplying the small bowel within the mesentery.

The IMA is usually located 3 to 4 cm cephalad to the aortic bifurcation, just to the left of midline, and usually arises at the level of the third lumbar vertebra. The main trunk frequently divides into sigmoidal branches and the left colic artery. The ascending left colic artery forms the inferior marginal artery of Drummond, which is the major collateral arcade between the SMA and IMA. The SMA and IMA are also linked by the meandering mesenteric artery (of Moskowitz), known historically as the "arc of Riolan." This vessel runs more centrally, medial to the mesenteric border of the colon and through the middle of the mesenteric arcade near the inferior mesenteric vein. The meandering mesenteric artery is likely produced by the dilation of a normal collateral vessel in response to significant stenosis or occlusion of the SMA and/or IMA.[11] Sigmoidal branches lead to the left and right superior rectal arteries, which collateralize with branches of the hypogastric arteries in the pelvis.

PHYSIOLOGY OF SPLANCHNIC BLOOD FLOW

Normal intestinal function and nutrient absorption rely on adequate perfusion and oxygenation to the microvascular splanchnic circulation. Various autoregulatory mechanisms ensure adequate gut circulation through both vasoconstriction and relaxation of arterial smooth muscle. The degree of visceral artery dilation and constriction determines the relatively large fluctuations in splanchnic blood flow during fasting, postprandial states, and periods of extreme stress. Visceral blood flow can vary dramatically, ranging from 10% of cardiac output in the setting of shock or hypovolemia, 20% to 25% at rest or while fasting, and up to 35% after a large carbohydrate meal.[12,13] Seventy to eighty percent of mesenteric blood flow supplies the mucosal and submucosal layers. The extremely diminished blood flow observed in patients with nonocclusive mesenteric ischemia results from severe vasospasm related to this process. Duplex studies demonstrate moderate to high arterial resistance in the SMA circulation, with low diastolic flow and slight flow reversal during fasting states. In the postprandial period, low-resistance signals are noted throughout both systole and diastole, indicative of dilated splanchnic arteriolar beds; flow reversal does not occur. In contrast, low arterial resistance signals are noted in the celiac artery circulation regardless of feeding, likely due to the influence of the low-resistance hepatic vascular bed. Perko and colleagues also noted that in fasting subjects performing submaximal exercise, splanchnic vascular resistance doubled and exhibited a 50% reduction in hepatosplenic blood flow and a 25% reduction in mesenteric blood flow.[14]

Multiple mechanisms are responsible for regulating mesenteric arteriolar smooth muscle tone, and they are often interdependent. Extrinsic factors include sympathetic efferent nerves in the prevertebral celiac and mesenteric ganglia, which initiate stimuli for arterial vasoconstriction. Hormonal pathways also contribute to extrinsic regulation of splanchnic blood flow. The renin-angiotensin feedback mechanism causes mesenteric vasoconstriction through the direct action of angiotensin II during hypovolemic states. Low-volume states and hyperosmolarity stimulate the neurohypophysis, which releases vasopressin,[15] a hormone that causes splanchnic vasoconstriction, reduction in portal venous pressure, and venodilation.[15] Additionally, when subjected to shear stress, activation of the nitric oxide synthase enzymes on the surface of red blood cell membranes occurs, leading to significant dilation of mesenteric arteries under hypoxic conditions.[16]

Intrinsic regulation also occurs through metabolic and myogenic feedback mechanisms.[15] In the metabolic pathway, mucosal ischemia prompts the release of metabolic byproducts, causing vasodilation in arteriolar smooth muscle and preferentially shunting increased blood flow to the intestinal mucosa. In the myogenic pathway, which dominates the regulation of blood flow in the small intestines,[17] abrupt decreases in perfusion pressure are sensed by arteriolar baroreceptors, which respond by decreasing arteriolar wall tension to maintain blood flow.[18] Together, these mechanisms maintain mucosal perfusion and integrity during periods of relative ischemia.

EPIDEMIOLOGY

Asymptomatic occlusive disease of the visceral arteries is a common finding in elderly patients. Wilson and coworkers demonstrated that 17.5% of 553 consecutive patients older than 65 years examined with duplex ultrasonography (DUS) had a critical stenosis of at least one visceral vessel.[15] Additionally, autopsy studies have estimated the prevalence of atherosclerosis involving the mesenteric arteries to be between 6% and 10%.[19] Despite an aging population, the total number of deaths associated with CMI per year remained flat between 2000 and 2012 (0.7 per million to 0.6 per million, $P = .50$), while the total number of deaths associated with AMI have actually declined from 12.9 to 5.3 per million during this same time period.[20] Likely in part because of differences in longevity, AMI and CMI disproportionately affect women, with a female-to-male ratio of approximately 3:1.[21]

Since the majority of patients with mesenteric occlusive disease manifest no symptoms, the exact incidence of CMI is not known. Admissions for CMI account for fewer than 1 per 100,000 admissions[22]; however, they have been increasing steadily in recent years in the United States.[21] Whether these figures represent an actual increasing incidence or simply increased reintervention due to restenosis from endovascular therapy remains to be determined. Despite the high prevalence of individuals with asymptomatic mesenteric arterial occlusive disease, patients usually demonstrate involvement of two or more mesenteric vessels before symptoms arise owing to the development of extensive collateralization over time. In fact, in a study by Thomas et al., who followed 980 consecutive patients with asymptomatic significant (50%) stenosis of at least one mesenteric artery, only four patients developed mesenteric ischemia and all of them had significant three-vessel disease after follow-up of 1 to 6 years.[23] The variability of symptoms in patients with chronic abdominal pain often makes the diagnosis challenging, resulting in treatment delays and increased morbidity.

PATHOPHYSIOLOGY

Chronic Mesenteric Ischemia

Atherosclerosis is the most common cause of CMI, and these patients frequently have a history of smoking, hypertension, and hyperlipidemia. They may also have evidence of atherosclerotic disease in other vascular beds, particularly coronary, cerebrovascular, renal, aortailiac, and other peripheral arteries. Although much less common, CMI may also be seen in association with vasculitis and other inflammatory conditions, such as lupus, Buerger disease, and radiation arteritis. Median arcuate ligament syndrome (see Chapter 135) is a separate entity that may lead to symptoms of CMI and is caused by the compression of the celiac artery by the MAL.

Acute Mesenteric Ischemia

Arterial Embolism

Arterial emboli are the most common cause of AMI, comprising 40% to 50% of cases.[24] The proximal source of the embolus is frequently intracardiac mural thrombus that develops in patients with atrial tachyarrhythmias, myocardial infarction, cardiomyopathy, structural heart defects, and cardiac tumors. Endocarditis can result in septic emboli from affected valve leaflets. Mural thrombus in proximal aneurysms in the thoracic or proximal abdominal aorta can also serve as embolic sources, as can atheromatous plaque even in the absence of aneurysm. The SMA is the most common final destination for mesenteric emboli, perhaps because of its relative size and the decreased angle of takeoff from the abdominal aorta compared with the other mesenteric vessels. Additionally, such emboli tend to lodge several centimeters from the vessel's origin, usually distal to the middle colic artery (Fig. 131.1A). The angiographic hallmark of an embolic occlusion seen on CTA or MRA is an abrupt cutoff just beyond the origin of the middle colic artery.[25]

Arterial Thrombosis

Arterial thrombosis constitutes the next most common cause of AMI and occurs in 20% to 35% of cases.[26,27] Preexisting atherosclerotic plaque affecting all visceral vessels is the most common finding. Hypercoagulability syndromes can also predispose to acute visceral artery thrombosis. The affected segment of artery is usually its origin at the level of the aorta. Patients with acute arterial thrombosis frequently have preexisting symptoms of CMI. Schoots and associates reviewed 45 observational studies comprising 3692 patients with AMI

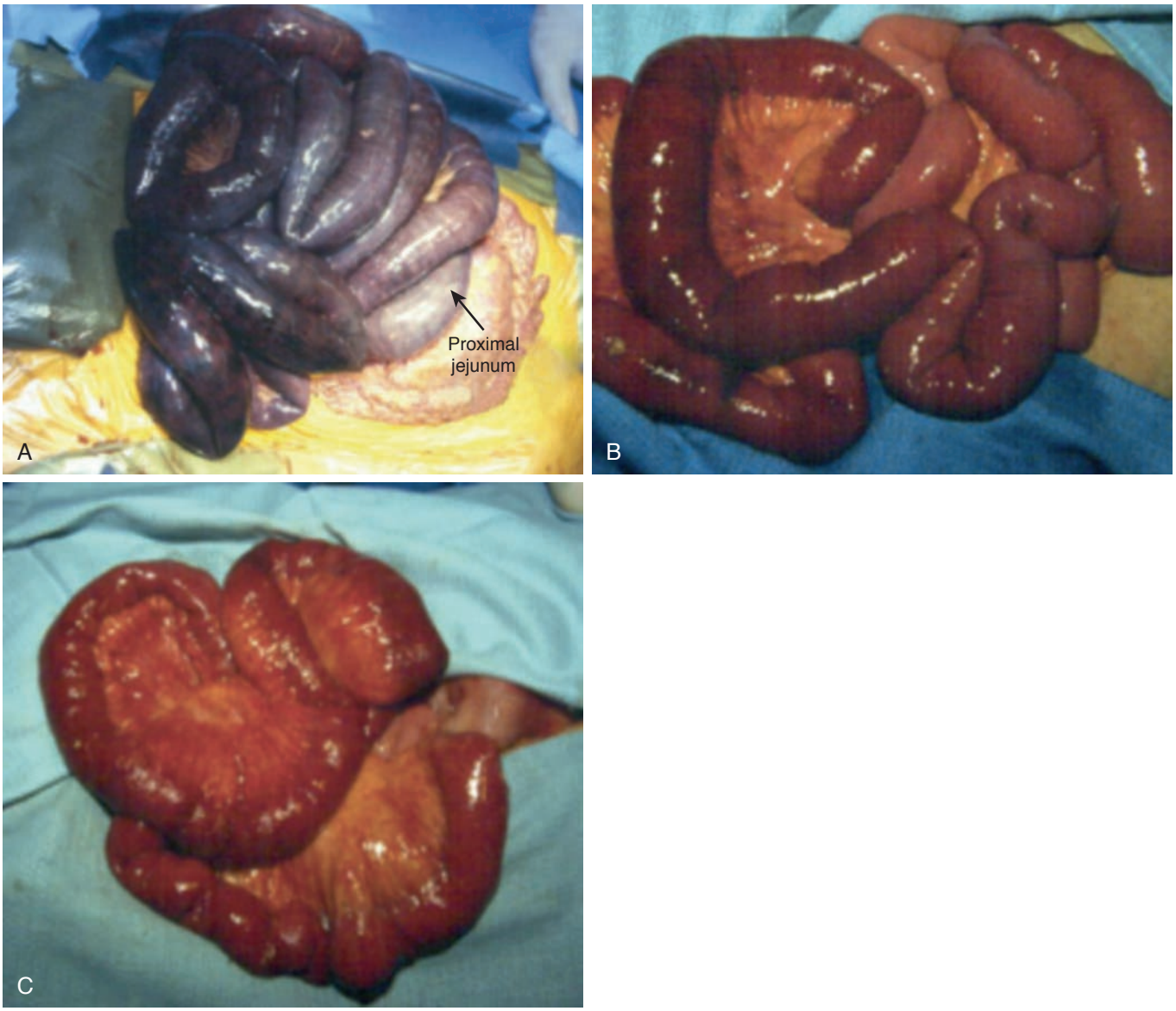

Figure 131.1 (A) Operative findings typical of acute mesenteric ischemia secondary to an embolus. Note that the first portion of the jejunum is spared because the embolus lodged distal to the middle colic artery. (B) Operative findings typical of acute mesenteric ischemia secondary to arterial thrombosis. Note that the entire bowel is affected. (C) Appearance of the small bowel at second-look surgery after revascularization. Note the hemorrhagic changes in the mesentery.

and found that mortality from acute thrombosis of a mesenteric artery was 77.4%, compared with 54.1% for patients with acute arterial embolism to visceral vascular beds.[28] This increased mortality is likely due to the involvement of larger segments of bowel, since occlusions are typically within the first 2 cm of the SMA origin (Fig. 131.1B). This theory was corroborated in a Swedish study, in which 213 patients with acute thromboembolic occlusion of the SMA and intestinal infarction were examined postmortem.[29] The cause of occlusion was embolic in 57.3% of patients and thrombotic in 41.3% (indeterminate in 1.4%). The extent of intestinal infarction was significantly greater in patients with SMA thrombosis compared with embolus. Acute extension of an aortic dissection can also serve as a mechanism for abrupt mesenteric vessel occlusion and thrombosis.

Nonocclusive Mesenteric Ischemia

Impaired intestinal perfusion in the absence of thromboembolic occlusion is termed nonocclusive mesenteric ischemia (NOMI) and makes up approximately 5% to 15% of cases.[30] Visceral ischemia can occur due to a low-flow state, which is exacerbated by the presence of any intestinal atherosclerotic disease. It is theorized that in such circumstances, in an effort to maintain cardiac and cerebral perfusion, excessive sympathetic output results in mesenteric vasospasm. NOMI most commonly occurs secondary to cardiac disease, particularly severe congestive heart

failure and in patients who have undergone cardiac surgery. Atrial fibrillation, commonly a cause of cardiac thrombi and visceral embolization, can also induce NOMI by reducing left ventricular function and causing low cardiac output. Other risk factors for NOMI include older age, hypovolemia, systemic vasoconstrictors, vasoactive drugs (e.g., digoxin, α-adrenergic agents, β-receptor blocking agents, cocaine), aortic insufficiency, cardiopulmonary bypass, abdominal and cardiovascular surgery, abdominal compartment syndrome, and liver failure.[24,31]

In recent years, NOMI has been increasingly observed in patients on hemodialysis (HD). Quiroga et al. reported incidence rates more than 40 times greater among patients on HD compared with the general population.[32] Using the Taiwan National Health Insurance Research Database, Li et al. similarly reported a 44-fold higher risk of mesenteric ischemia in patients on HD or peritoneal dialysis compared with the general population.[33] Older age and a heavier burden of cardiovascular risk factors undoubtedly contribute to these disparities. Additionally, patients with end-stage renal disease are frequently on erythropoietin, which elevates red cell mass and can lead to relative hyperviscosity. However, hypotension during dialysis has been implicated as the most important and immediate precipitating risk factor for development of NOMI.[34] Therefore special care should be taken to avoid dialysis-related hypotension in patients at particularly high risk. High-risk patients include those who are older, taking erythropoietin, have a longer history of dialysis, and diabetics.[32,34]

Mesenteric Venous Thrombosis

MVT constitutes 5% to 15% of all cases of mesenteric ischemia (see Chapter 136).[35,36] Involvement is usually limited to the superior mesenteric vein but can also involve the inferior mesenteric, splenic, and portal veins. MVT is classified as either primary (idiopathic) or secondary. Secondary MVT occurs when an underlying disease process is present; this type accounts for 90% of all patients with this disorder. Conditions associated with MVT can be grouped into three major categories: direct injury, local venous stasis/congestion, and thrombophilia. Causes of direct injury include abdominal surgery, trauma, and local inflammation, such as that seen with inflammatory bowel disease, pancreatitis, and diverticulitis.[37,38] Splanchnic venous stasis may occur in the case of increased intra-abdominal pressure, obesity, and with intraoperative manipulation of the mesenteric vessels. Inherited or acquired hypercoagulable diseases—including deficiency of proteins C and S, myeloproliferative disorders, antithrombin III deficiency, antiphospholipid antibody syndrome, and factor V Leiden mutation—are frequent causes of thrombophilia and thus also predispose to MVT.[39]

The extent of bowel ischemia depends largely on the degree of venous involvement and the presence of collateral vessels. The transition from normal to ischemic intestine is slower with MVT than with arterial occlusive disease.[24] Edema and hemorrhage of the intestinal wall are frequently seen, followed by focal sloughing of the mucosa.[24] The origin of thrombosis varies depending on the etiologic process. When an intra-abdominal process is the cause, thrombosis begins in the larger mesenteric veins and progresses to involve the smaller venous arcades and arcuate channels.[40] MVT caused by hypercoagulable conditions usually begins in the smaller mesenteric veins. Symptomatic acute MVT is associated with a 20% to 50% mortality rate.[40] A Swedish population-based autopsy study showed that MVT-related death is more likely in patients with portal vein thrombosis, systemic venous thromboembolism, and obesity.[41]

CLINICAL PRESENTATION

Acute Mesenteric Ischemia

The most common symptom of AMI associated with arterial thromboembolic disease is the sudden onset of abdominal pain. Due to a lack of collateral flow to the visceral organs, the presentation of AMI is dramatic and severe, often with rapid clinical deterioration. Nausea, vomiting, diarrhea, emptying symptoms, and abdominal pain and distention can also occur. Classically, the pain is out of proportion to the findings on physical examination. Initially, bowel sounds are hyperactive, as the failure to relax the bowel smooth muscle leads to emptying symptoms. Bowel sounds are typically diminished in the later stages. Abdominal guarding and rebound tenderness are absent in the early stages of AMI; however, as intestinal ischemia and infarction progress, these signs become more pronounced. They are typically late findings, so their absence should not delay the diagnosis and treatment of AMI. Other late findings include fever, oliguria, dehydration, confusion, tachycardia, and shock.[24] Metabolic abnormalities can include leukocytosis, metabolic acidosis, hyperamylasemia, elevated liver function values, and lactic acidemia.

Patients with NOMI or MVT typically present with a slower, more insidious clinical course. Frequently those with NOMI are critically ill, hospitalized, intubated patients who experience a sudden deterioration in their clinical condition. These patients are often administered intravenous pressors, worsening mesenteric vasoconstriction and thus decreasing splanchnic perfusion. In patients with MVT, fever, abdominal pain and distention, nausea/vomiting, and bloody stools are the most common findings. Dehydration and profound fluid shifts lead to bloody ascites and a hypovolemic state, causing further propagation of venous thrombosis.[24] Though nonspecific, normal D-dimer levels may help rule out MVT.[42]

In order to develop better diagnostic criteria to reduce delays in diagnosis, Mitsuyoshi et al. reviewed their 13-year experience treating 22 patients with NOMI.[43] Multidetector-row computed tomography (MDCT) was unavailable at the time the first 13 patients were treated, and 9 subsequently died owing to intestinal necrosis. These first 13 cases were used to devise four criteria for determining which patients warranted MDCT evaluation once this technology became available: (1) ileus or abdominal pain, (2) catecholamine requirement, (3) an episode of hypotension, and (4) a gradual rise in serum transaminase level. If three of the four criteria were present, patients received MDCT and underwent treatment with high-dose intravenous

Figure 131.2 Typical patient with chronic mesenteric ischemia with significant weight loss and cachexia. The patient is placed in a right semilateral decubitus position in preparation for retroperitoneal transaortic endarterectomy.

prostaglandin E1 (PGE1). Of the 9 patients treated using this algorithm, only 1 died.

Chronic Mesenteric Ischemia

Postprandial abdominal pain and progressive weight loss are the most common symptoms in patients with CMI. Pain is often described as dull and crampy located in the midepigastric region. Pain often occurs 15 to 45 minutes after a meal, and the severity varies according to the size and type of meal. Patients typically develop "food fear" and decrease their oral intake in anticipation of severe pain after meals. Consequently weight loss is a common finding; in fact, when present, it can help to distinguish CMI from other functional bowel disorders when the diagnosis is in question.[44] Changes in bowel habits, nausea, and vomiting are less common findings. CMI is seen more frequently in elderly women, who represent 70% of patients. The variable nature of symptoms often makes the diagnosis confusing and can result in delayed treatment. The traditional risk factors for atherosclerosis are usually present. A heavy smoking history is frequently obtained and the majority of patients also have a history of symptomatic manifestations in other vascular beds, most commonly cerebrovascular, coronary, and peripheral arteries.[45]

Physical examination findings are usually nonspecific. Patients are commonly undernourished and cachectic (Fig. 131.2). An abdominal bruit can sometimes be auscultated but is not always present. Bowel sounds are frequently hyperactive. Guarding and rebound tenderness are usually absent. Low prealbumin and albumin levels are often seen, owing to the patient's chronic malnourished state.

DIAGNOSTIC EVALUATION

Noninvasive Evaluation

DUS is a useful tool for the early, noninvasive diagnosis of visceral ischemic syndromes (see Chapter 21). Color Doppler scanning can be used to assess the flow velocities and resistance index in the splanchnic arteries and their arterial beds as well to evaluate end-organ vascularity. The intestinal wall can also be assessed with a high degree of accuracy using high-resolution transabdominal ultrasound.[46] Transmural hemorrhage, inflammation, and necrotic thickening in the bowel wall can be imaged sonographically. Asymmetric wall thickening with associated ileus can be seen in patients with AMI as well as ascites and free peritoneal air.[47] DUS combined with expiratory maneuvers is also an excellent screening exam for MAL syndrome. Limitations of transabdominal duplex scanning include the wide variation in examination quality, which is operator-dependent. Patient-related factors such as obesity, excessive intraluminal bowel gas, variation in local anatomy, and effects of respiration can affect image quality.[48] Care must be taken to clearly define the origin of each vessel to avoid inaccurate measurements. DUS is generally not recommended in the workup of AMI.

Moneta and colleagues performed blinded DUS studies in 100 patients who previously underwent arteriography of the celiac trunk and SMA.[49] They hypothesized that lack of flow or a peak systolic velocity (PSV) in the SMA of greater than 275 cm/s, or no flow, or a PSV of greater than 200 cm/s in the celiac trunk was a reliable indicator of 70% or greater angiographic stenosis.[50] Using these criteria, duplex sensitivity for detecting lesions in the SMA and celiac artery was 92% and 87%, respectively. Overall accuracy for detection of a 70% lesion in the SMA and celiac artery was 96% and 82%, respectively. The IMA is not generally assessed, since it is generally difficult to visualize and is of lower clinical importance. However, patency of the IMA can usually be determined. In a more recent study with the largest number of mesenteric duplex and angiography correlations to date (151 SMAs and 150 celiac arteries), AbuRahma et al. found that for the SMA, a PSV ≥295 cm/s had the highest accuracy for detecting ≥50% stenosis (sensitivity 87%, specificity 89%), whereas a PSV ≥400 cm/s had the highest accuracy for detecting ≥70% stenosis. The corresponding PSVs for the celiac artery were 240 cm/s and 320 cm/s, respectively.[51]

DUS is also the primary imaging modality used for surveillance following both bypass and stenting. However, duplex criteria used for diagnosing stenosis in the native mesenteric vessels have been shown to overestimate stenosis in stented vessels.[52] Baker and colleagues evaluated the accuracy and utility of DUS for detecting in-stent stenosis in 23 patients who underwent successful (<20% residual stenosis on completion angiography) mesenteric stenting for CMI (20 SMA alone, 3 both SMA and celiac artery).[53] Preprocedure DUS was performed on 13 patients, with a mean PSV of 464 cm/s. Initial surveillance DUS was performed in 21 patients at a mean of 0.9 months following revascularization. Mean PSV at this time was 335 cm/s and for 12 of these patients, the first postoperative PSV in

successfully stented vessels was higher than the 275 cm/s threshold used to diagnose high-grade native SMA stenosis. Additionally, there was no correlation between surveillance PSV and the degree of angiographic stenosis seen at the time of reintervention.

Similarly, in their review of 107 patients who underwent endovascular therapy for CMI,[54] Schoch et al. reported that although 83% of patients had recurrent stenosis on surveillance DUS, 53% of patients remained asymptomatic and required no further intervention. These findings therefore mandate obtaining an early baseline DUS against which future surveillance scans can be compared. They also stress the importance of considering the clinical context and symptom recurrence when making the decision to reintervene. Soult et al. analyzed 103 paired DUS and angiograms (66 SMA, 37 celiac arteries) to try to define duplex criteria for high-grade in-stent restenosis in previously treated mesenteric arteries. They proposed PSVs of ≥445 cm/s in stented SMAs and ≥289 cm/s in stented celiac arteries for detecting stenosis ≥70%.[55]

The predictive value of DUS for detecting disease recurrence after mesenteric bypass has also been studied. Liem and colleagues evaluated 167 duplex exams used in the surveillance of 43 bypass grafts in 38 patients.[56] Comparing antegrade and retrograde bypass configurations, differences in mean PSV were demonstrated only at the inflow artery. There were no differences in PSV at the proximal or distal anastomosis, the mid-graft, or in the outflow artery. Between the first postoperative DUS and the latest follow-up scan (on average 38 months), PSV measurements did not change significantly. Graft failure occurred in two patients, both of whom had no findings to suggest impending occlusion on the DUS exams immediately preceding failure. No predictors of graft thrombosis were identified on multivariable analysis.

Computed tomography (CT) is an accurate, noninvasive imaging modality for diagnosing mesenteric ischemia. Modern multidetector CT (MDCT) enables imaging with excellent spatial and temporal resolution. A meta-analysis of six studies published between 1996 and 2009 on the diagnostic accuracy of MDCT in AMI showed a pooled sensitivity of 93% and specificity of 96%.[57] Advantages over conventional angiography include the relative ease and speed of performance, the rapid infusion of contrast agent through peripheral intravenous lines, and the ability to simultaneously image the mesenteric arteries, veins, and visceral organs. CTA is also useful for evaluating patency of previous placed grafts and stents. Common radiographic findings in the bowel wall related to AMI include increased thickening, dilation, and attenuation, which can be easily detected using CT. Pneumatosis intestinalis, portal venous air, mesenteric edema, and ascites can also be detected. During the arterial phase of contrast infusion, the mesenteric vessels can be evaluated for thrombosis, embolus, dissection, and aneurysm. Venous engorgement and subtle intestinal findings may be identified in cases of mesenteric venous occlusion. A "target sign" may be seen in the SMV with thrombus in the center of the lumen and surrounding contrast enhanced blood flow peripherally. The portal venous phase is more accurate for diagnosing MVT and images during the venous phase may be acquired if the diagnosis is still in question or for surveillance of clot burden or extension in patients with MVT. In many centers a biphasic scan, which includes a delayed venous phase in addition to an arterial phase, has been used in the diagnosis of AMI, since it enables detection not only of arterial occlusion, but also MVT and improves the ability to detect changes in the bowel wall as well.

Disadvantages of CT include radiation, the risk of contrast nephropathy and hypersensitivity reactions to iodinated contrast agents. Inaccurate timing of contrast infusion during the arterial phase may provide indeterminate images and delay diagnosis. Because calcification at the vessel origins enhances in a similar fashion to intravenous contrast material, it is possible to underestimate the degree of stenosis. Therefore, the non–contrast-enhanced images should be reviewed. Additionally, with careful adjustment of the window and level, calcification can usually be distinguished from intravascular contrast. Last, CT serves strictly as a diagnostic modality; treatment must be performed via a separate angiographic procedure or laparotomy.

Magnetic resonance angiography (MRA) is useful for diagnosing mesenteric occlusive disease. Although MRA takes significantly longer to perform than CTA, it avoids the radiation exposure associated with CTA. Patients with hypersensitivity to iodinated contrast agents may also benefit from MRA. However, CTA has superior spatial resolution and allows better visualization of the IMA, peripheral splanchnic vessels, calcified plaque, and previously placed stents, giving it a distinct advantage.[25] For these same reasons CTA is also preferred over MRA for surveillance after revascularization. Our standard workup includes DUS to screen those suspected of having CMI. CTA is used routinely prior to intervention for AMI, CMI, and MVT.

Invasive Evaluation

Conventional angiography remains the "gold standard" in the diagnosis of mesenteric ischemia. Anteroposterior and lateral views of the visceral aorta (Fig. 131.3A–C), as well as selective catheterization of the celiac trunk, SMA, and IMA, provide the most accurate and specific localization of stenotic and occlusive lesions. Therapeutic alternatives such as balloon angioplasty, stenting, and thrombolysis and percutaneous thrombus extraction can all be used to restore luminal visceral blood flow.

Gastric tonometry, or the measurement of pCO_2 levels in the gastric, jejunal, or colonic mucosa via a nasogastric catheter, has been shown to be a useful adjunct for the diagnosis of mesenteric ischemia[58,59] but is not currently widely used in the United States.

TREATMENT OF ACUTE AND CHRONIC MESENTERIC ISCHEMIA

The goal of therapy for patients with mesenteric ischemia is the prompt restoration of blood flow to the visceral organs (see Chapters 132 and 133).

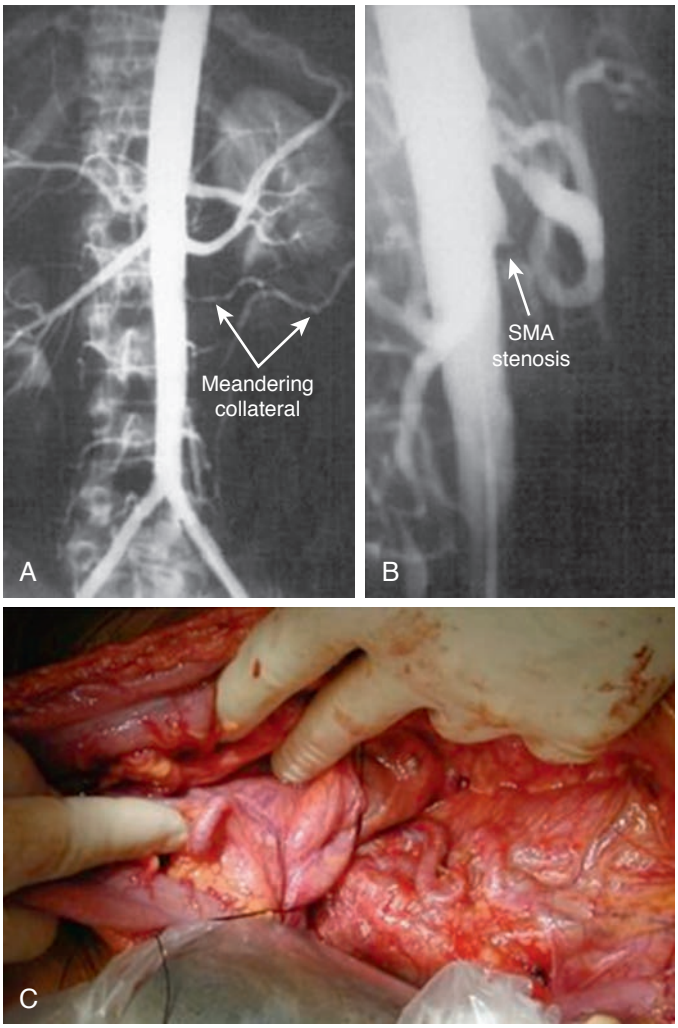

Figure 131.3 (A) Anteroposterior angiogram of a patient with chronic mesenteric ischemia. Note the meandering mesenteric collateral vessels. (B) Lateral aortogram of a patient with chronic mesenteric ischemia. Lesions are typically located at the origin of the vessel and often protrude into the aortic lumen. *SMA*, Superior mesenteric artery. (C) Meandering mesenteric collateral vessels in a patient with chronic mesenteric ischemia at the time of exploration. In patients undergoing surgery for other reasons, this finding should raise the suspicion of significant mesenteric occlusive disease.

Medical Treatment

Preventive risk factor modification helps control the progression of atherosclerosis in the mesenteric circulation. Statins have been shown to reduce the risk of cardiovascular events, cardiovascular mortality, and all-cause mortality.[60] High-intensity statins, in particular, reduce cardiovascular events in patients after stroke,[61] acute coronary syndrome,[62] and in those with stable coronary artery disease.[63] Though there are no studies specifically evaluating the role of statins in reducing ischemic events in patients with mesenteric insufficiency, it is reasonable to extrapolate to this population given the similar risk factor profile. Additionally, murine models have shown that statins may be able to mitigate reperfusion injury following gut ischemia.[64,65] Medical treatment alone is not effective in patients with symptomatic mesenteric ischemia. Patients with known risks for inheritable hypercoagulable disorders should undergo screening and should be treated with systemic anticoagulation if indicated.

Before operation, aggressive fluid resuscitation with restoration of adequate urine output is required, owing to the frequent finding of severe dehydration on presentation. Electrolyte abnormalities and metabolic acidosis should also be corrected. Patients with CMI are frequently malnourished, so albumin, prealbumin, transferrin, and C-reactive protein levels should be checked before revascularization. Preoperative total parenteral nutrition or enteral nutrition should be considered in severely malnourished patients. Finally, because the intestinal mucosa is damaged during periods of prolonged ischemia, bacterial translocation can occur, contributing to systemic sepsis. Broad-spectrum intravenous antibiotics with aggressive fluid resuscitation can lead to decreased mortality in these patients.[66] Treatment against gram-negative and anaerobic organisms is especially important.

Following mesenteric stenting, unless contraindicated, our practice is to administer an initial 300 mg clopidogrel load after the procedure followed by 1 to 3 months of treatment. Patients are also started and maintained on aspirin and high dose statins indefinitely.

Endovascular Treatment

Advances in endovascular techniques have greatly expanded the role of percutaneous interventions for patients with mesenteric ischemia in recent years. Balloon angioplasty and stenting has surpassed open surgery as the dominant method of revascularization for CMI and an endovascular approach is now generally accepted as primary therapy.[21,67-69] In contrast, the adoption of endovascular modalities for treating AMI has been slower and a decline in the number of open revascularization has not been observed.[21] This is likely because most patients with AMI have some degree of bowel ischemia and many require laparotomy for adequate evaluation and potential resection. In those with short-segment stenoses, cardiac and pulmonary co-morbidities, prior abdominal surgery, coagulopathy, or malnutrition, endovascular therapy is often favored.

Surgical Treatment

Laparotomy with visceral revascularization can be used to treat patients with both AMI and CMI. Patients presenting with signs and symptoms of AMI require urgent abdominal exploration, assessment of bowel viability, and revascularization. Several techniques for the restoration of intestinal perfusion are available to the vascular surgeon, and familiarity with a variety of options is crucial. Before revascularization, large segments of both small and large intestine may appear dusky, ischemic, or necrotic. Because SMA emboli typically lodge distal to its origin, the middle colic artery and ileocolic branches may remain patent. Thus, the pattern of bowel necrosis following embolus may be less extensive and spare the proximal jejunum and transverse colon distribution from ischemia (Fig. 131.1A). Acute thrombosis usually occurs at the orifice of the SMA, and a more extensive

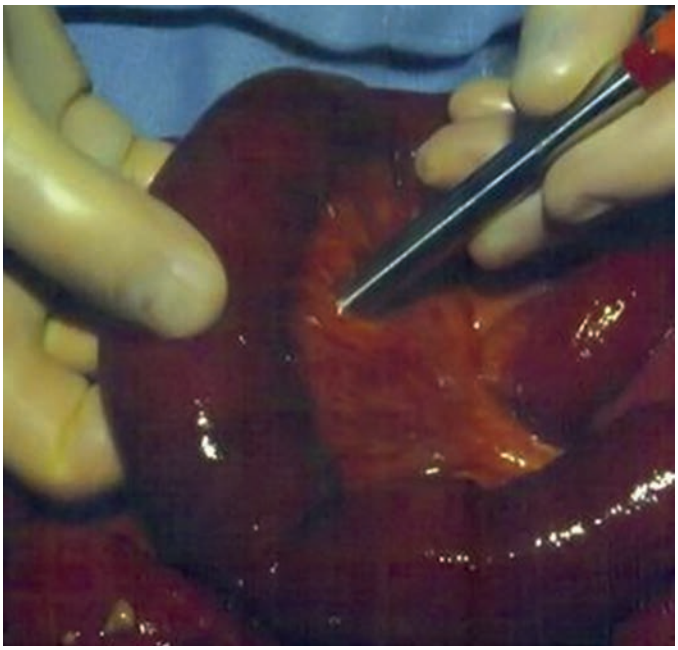

Figure 131.4 Doppler examination of the intestine should be done both at the mesentery and at the antimesenteric border. This is most useful following revascularization.

pattern of hypoperfusion and necrosis is present owing to the involvement of proximal SMA branches (Fig. 131.1B).

Following vascular reconstruction and reperfusion, the bowel should be reassessed. Segments of bowel that otherwise would have been resected may be spared owing to improvement following revascularization. A wide range of techniques to assess bowel viability have been described, including pulse oximetry, measurement of oxygen tension, spectrophotometry, Doppler ultrasound, fluorescein dye and examination with Wood's lamp, laser Doppler flowmetry and infrared imaging. At our institution, we favor a combination of clinical assessment (using criteria such as serosal color, bowel peristalsis, and vessel palpation) and Doppler ultrasound (Fig. 131.4). Intraoperative angiography following vascular reconstruction may be performed to accurately assess the restoration of mesenteric flow. Most patients should undergo "second-look" laparotomy in 24 hours to reassess bowel viability and the need for further resection (Fig. 131.1C). The decision to perform a second-look laparotomy should be made during the initial procedure and should not be changed based on subsequent clinical improvement. For those in whom bowel resection is performed at initial exploration the ends are stapled and no anastomosis is performed until second look laparotomy.

TREATMENT OF NONOCCLUSIVE MESENTERIC ISCHEMIA

NOMI represents an insidious disease process that is distinct from thromboembolic AMI but has a similarly high mortality. Cardiac surgery and low-flow states are the most common causes of this disorder, and treatment is directed toward improving circulatory support and increasing cardiac output. Selective mesenteric angiography remains the best invasive diagnostic modality, which can be followed by catheter-based interventions. These include direct infusion of intra-arterial vasodilators such as papaverine and prostaglandin E1(PGE1), as well as angioplasty and stenting if necessary.[27] Intravenous rather than intra-arterial PGE1 has also demonstrated efficacy in treatment of vasospasm associated with NOMI.[43] In a model of cardiac tamponade–induced acute NOMI, Kang and associates demonstrated that low doses of intra-arterial iloprost (prostacyclin), a potent inhibitor of platelet aggregation with fibrinolytic activity, exhibited a significant vasodilatory effect on mesenteric blood flow.[70]

TREATMENT OF MESENTERIC VENOUS THROMBOSIS

The mainstay of treatment for acute and subacute MVT is the prompt initiation of systemic anticoagulation, which improves survival and reduces the risk of recurrence.[40] (A detailed discussion of the diagnosis and treatment of MVT is contained in Chapter 136.)

Patients with suspected peritonitis, severe gastrointestinal bleeding, or intestinal stricture require abdominal exploration and resection of nonviable bowel. Bowel resection should be conservative in patients with MVT. We frequently perform a second-look laparotomy 24 hours after the initial operation, which helps avoid resection of viable bowel during the initial operation. Lifelong anticoagulation with vitamin K antagonists (VKAs) is recommended for patients with MVT, since recurrence is common (up to 36% without anticoagulation) and potentially catastrophic. Patients may be transitioned from heparin to a VKA once bowel function has normalized.

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132 CHAPTER

Chronic Mesenteric Arterial Disease: Clinical Evaluation, Open Surgical and Endovascular Treatment

GUSTAVO S. ODERICH and MAURICIO RIBEIRO

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BACKGROUND

The term *intestinal angina* has been coined to describe the classic symptom of chronic abdominal pain that occurs after meals, which is the cardinal symptom of *chronic mesenteric ischemia* (CMI). Current estimates indicate that CMI accounts for less than 1 per 100,000 hospital admissions in the United States and less than 2% of all admissions for gastrointestinal conditions.[1] Since the first successful mesenteric endarterectomy by Shaw and Maynard in 1958, techniques of revascularization have greatly evolved.[2] Balloon angioplasty was first used to treat mesenteric arterial stenoses by Uflacker, Furrer, Gruntzig, and colleagues in 1980.[3,4] In the last 15 years, primary mesenteric stenting gained widespread acceptance and became the most frequently utilized treatment for CMI, relegating open surgery to patients who fail endovascular therapy or have complex lesions not amenable to endovascular intervention.[5] This chapter provides a comprehensive review of the clinical evaluation, treatment options, and results of mesenteric revascularization for patients with CMI.

PATHOPHYSIOLOGY

Approximately 20% of the cardiac output goes through the mesenteric arteries under normal conditions.[6] Blood flow to the gastrointestinal tract increases shortly after the ingestion of

a meal, remaining elevated at levels approaching 100% to 150% of normal (2000 mL/min) over the next 3 to 6 hours.[7] This normal hyperemic postprandial response is mediated by cardiovascular changes that accompany the ingestion and digestion of food, and its latency and duration depend upon the type and quantity of a meal, with high fat and protein-containing foods producing the most profound and sustained intestinal hyperemia.[8]

Patients with mesenteric ischemia fail to provide the postprandial hyperemic response that is required to supply oxygen for the metabolic processes of secretion and absorption, and for increased peristaltic activity.[9] Just as in the patient with ischemic cardiomyopathy, where angina pectoris occurs as a result from inadequate supply of oxygen, intestinal angina results from the relative imbalance between tissue supply and demand for oxygen and other metabolites. Because the mesenteric circulation has a rich collateral network, most patients only develop symptoms when at least two of the three mesenteric arteries are severely narrowed or occluded (Fig. 132.1). However, this is not an absolute requirement and some patients present with single vessel disease.[10,11] The clinical significance of ischemia correlates not only to the extent of disease, but also to the adequacy of collateral pathways, acuteness of symptoms, and presence of arterial steal.

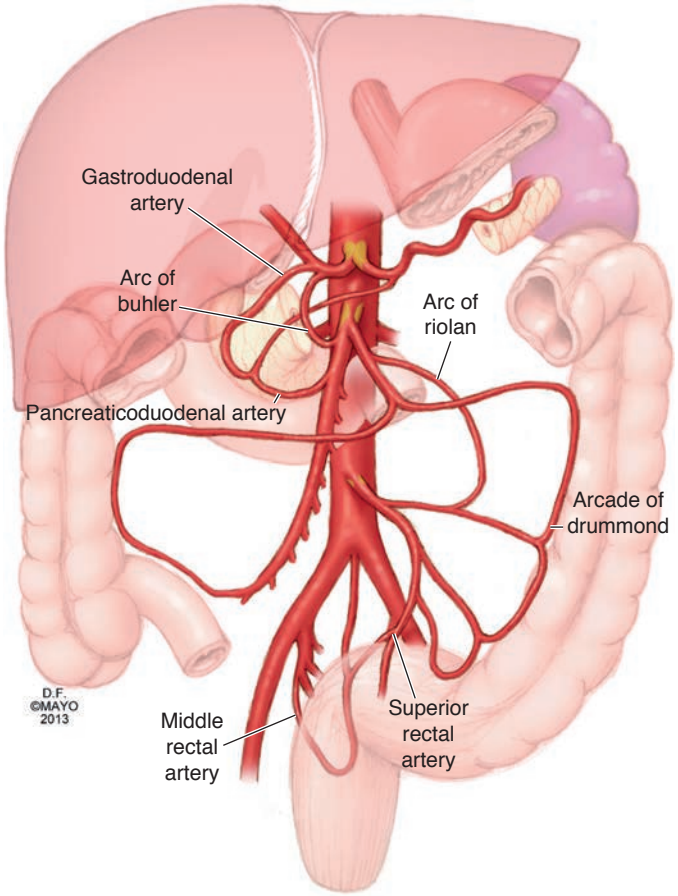

Figure 132.1 Mesenteric artery circulation and common collateral pathways in patients with severe occlusive mesenteric artery disease. Note severe disease at the celiac axis (CA), superior mesenteric artery (SMA), and inferior mesenteric artery (IMA). Common collateral pathways include the Arc of Riolan between the left colic artery (IMA) and middle colic artery (SMA). The CA and SMA have collateralization via pancreaticoduodenal arcade (Arc of Buhler) and the gastroduodenal arteries.

ETIOLOGY

The most common cause of CMI is atherosclerotic disease, accounting for more than 90% of cases in most series. Atherosclerotic lesions usually affect the origin or the proximal 2 to 3 cm of the mesenteric arteries, frequently with associated plaque in the aorta and renal arteries. Nonatherosclerotic lesions can also affect the mesenteric arteries. These patients tend to be younger. Nonatherosclerotic pathology includes vasculitis (giant cell arteritis, Takayasu disease, and polyarteritis nodosa), systemic lupus, Buerger disease, spontaneous dissections, fibromuscular dysplasia, neurofibromatosis, radiation arteritis, coarctation, mesenteric venous stenosis or occlusion, and drug-induced arteriopathy from cocaine or ergot use.

NATURAL HISTORY

Asymptomatic mesenteric stenoses carry a benign course. Nonetheless, 15% to 50% of patients who present with bowel gangrene have thrombosis of preexisting lesions with no antecedent warning signs.[12,13] Wilson and associates[14] reported a large prospective cohort study of 553 elderly patients who were screened with duplex ultrasound. The prevalence of mesenteric stenosis or occlusion was 18%, and none of the patients developed symptoms after a follow-up period of 7 years, but most had single-vessel disease. Thomas and associates reviewed 980 aortograms and found 60 patients (6%) with significant mesenteric artery disease.[15] Of these, 15 had involvement of all three visceral arteries. During follow-up of 2.6 years, four patients (27%) developed symptoms; three had successful revascularization, but one died from acute ischemia.

DIAGNOSTIC EVALUATION

The diagnosis of CMI is suggested by clinical history and confirmed by one or more diagnostic studies, such as duplex ultrasonography, magnetic resonance angiography (MRA), computed tomography angiography (CTA), or conventional aortography. Endoscopy with 24-hour or exercise tonometry, if available in centers with established protocols, can be useful in the differential diagnosis of patients with atypical symptoms, single-vessel disease, or median arcuate ligament syndrome (MALS; see Chapter 135). Tests of intestinal absorptive and excretory function have not been useful.[16]

CLINICAL PRESENTATION

The typical patient with CMI is female (3:1) with median age of 65 years, the age ranging from 40 to 90 years old.[5,17,18] The classic symptoms of CMI include abdominal pain, weight loss, and "food fear." The abdominal pain is often postprandial and begins within a few minutes to 30 minutes after meals, persisting for as long as 5 to 6 hours. It is usually midabdominal in

location, crampy, or dull. Patients may describe tolerance to certain types of food, and consequently they alter their eating habits to avoid foods that precipitate symptoms. In fact, some patients do not refer to any pain at the time of presentation because of their adaptive strategies to reduce or relieve it. Unintentional weight loss progresses to malnutrition and cachexia, which is often present at the time of intervention. In the last review of the Mayo Clinic experience with 357 consecutive patients, 96% had abdominal pain (postprandial in 74%) and 84% had weight loss. The average duration of symptoms prior to revascularization was 15 months. The pattern of symptoms often changes and progresses in intensity, frequency, and severity. Subacute mesenteric ischemia is characterized by progression of pain from intermittent to unremitting or continuous over days or a few weeks, warranting immediate revascularization. Atypical presentation such as diarrhea or bloating can occur in some patients. Physical examination is nonspecific, does not commonly reveal any pathognomonic findings, but can point to the diagnosis. Many individuals are thin at the onset of their symptoms and progress to cachexia. These patients have obvious signs of malnutrition, muscle wasting, and a flat or scaphoid abdomen. Pain may be present but not localized or aggravated by abdominal palpation; the finding of pain out of proportion to physical findings should point toward the diagnosis of acute mesenteric ischemia (see Chapter 133). An abdominal bruit may be noted in up to 50% of patients, and differs from the bruit caused by compression of the celiac axis (CA) by the median arcuate ligament, which is elicited by deep expiration and elevation of the diaphragm. A complete vascular examination may document diminished peripheral pulses and bruit. Laboratory tests are nonspecific or unremarkable in the absence of acute symptoms, but may demonstrate malnutrition.[19]

The clinical presentation can be less specific in some patients. Vague abdominal pain, nausea, vomiting, or change in bowel habits, without the classic postprandial component to the pain, can make the diagnosis difficult to ascertain. Diffuse small ulcerations in the stomach or proximal duodenum, liver function abnormalities, or patchy areas of ischemia in the colon are not uncommon. Previous history of smoking and the diagnoses of hypertension and hyperlipidemia are documented in more than 60% to 70%.[17,20,21] Consequently, patients often have other manifestations of atherosclerotic disease affecting the coronary (50%-70%), cerebrovascular (20%-45%), and peripheral arteries (20%-35%). Concomitant renal artery disease with difficult to control hypertension or ischemic nephropathy is common.[22]

DIAGNOSTIC IMAGING

It is not infrequent for patients with CMI to undergo an extensive evaluation to rule out other causes of chronic abdominal pain and weight loss. The differential diagnosis is extensive, including inflammatory, infectious, and malignant disease. The investigation often includes upper and lower gastrointestinal endoscopy and cross-sectional studies of the abdomen. Often the finding of mesenteric artery stenosis in an imaging study is the first clue to the diagnosis.

Mesenteric Duplex Ultrasound

Mesenteric duplex ultrasound is the recommended screening study (see Chapter 21). A negative duplex ultrasound study essentially excludes the diagnosis of mesenteric artery disease. In 1993, Moneta and associates reported the first prospective validation of mesenteric diagnostic criteria in 100 patients.[23] In that study, the most accurate criteria to indicate ≥70% stenosis was a peak systolic velocities greater than 275 cm/s for the superior mesenteric artery (SMA) and greater than 200 cm/s for the CA (Fig. 132.2).[23] As a criterion for ≥70% SMA stenosis, a peak systolic velocity greater than 275 cm/s had a sensitivity of 92%, specificity of 96%, positive predictive value of 80%, and a negative predictive value of 99%. A velocity of 200 cm/s in the CA as a predictor of a ≥70% stenosis had somewhat lower values. The Bowersox criteria,[24] later validated prospectively by the Dartmouth group,[25] is based on ≥50% arterial stenosis. For the SMA, an end diastolic flow velocity of 45 cm/s or higher had 90% sensitivity, 91% specificity, 90% positive predictive value, 91% negative predictive value, and 91% accuracy. For the CA, reversal of blood flow in the hepatic and splenic arteries was 100% predictive of stenosis. An end diastolic velocity greater than 55 cm/s or no flow signal had the best overall accuracy (95%), with high sensitivity (93%) and specificity (94%).

Multidetector Computed Tomography

Cross-sectional imaging of the abdomen provides an anatomic analysis to plan revascularization.[26-28] The choice of CTA or MRA is somewhat related to individual expertise at the institution. Multidetector computed tomography (MD-CT) technology is readily available in most centers, has the highest spatial resolution and finest image detail, and is considered by most the best study to evaluate anatomic characteristics (calcification, thrombus, diameters, and lengths) that are important to plan mesenteric interventions (Fig. 132.3). In patients with classic symptoms, CTA may supplement or even replace duplex ultrasound, and is often the only imaging study that is obtained prior to intervention. It is also useful to objectively assess patency of grafts and stents.

Magnetic Resonance Angiography

Gadolinium-enhanced MRA has advanced in recent years to provide improved imaging resolution with shorter acquisition times.[29,30] This imaging modality is used to a lesser extent, but provides functional information by integrating flow dynamics, and blood oxygen saturation techniques, with the anatomic detail, which can be useful in patients with questionable diagnosis of CMI.[31,32]

Contrast Arteriography

Diagnostic catheter-based arteriography is considered the "gold-standard" diagnostic study for evaluating mesenteric artery disease. However, its role as a confirmatory test and for planning revascularization has diminished, in favor of the aforementioned

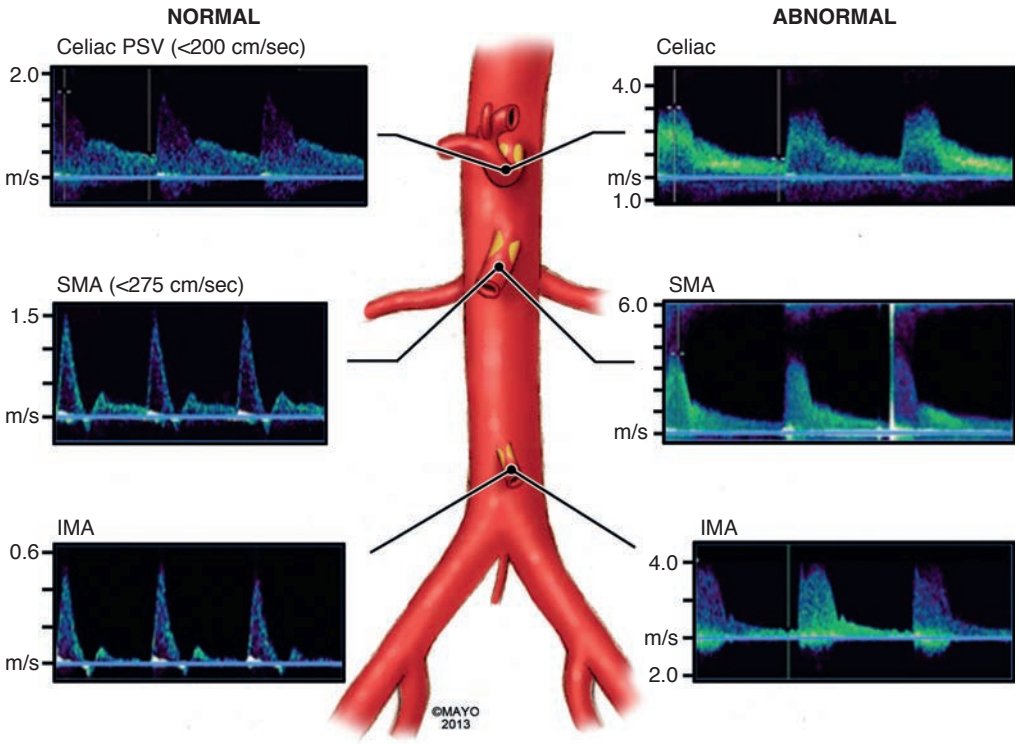

Figure 132.2 Mesenteric duplex ultrasound with normal and abnormal waveforms patterns during fasting state. *IMA*, Inferior mesenteric artery; *PSV*, peak systolic velocity; *SMA*, superior mesenteric artery.

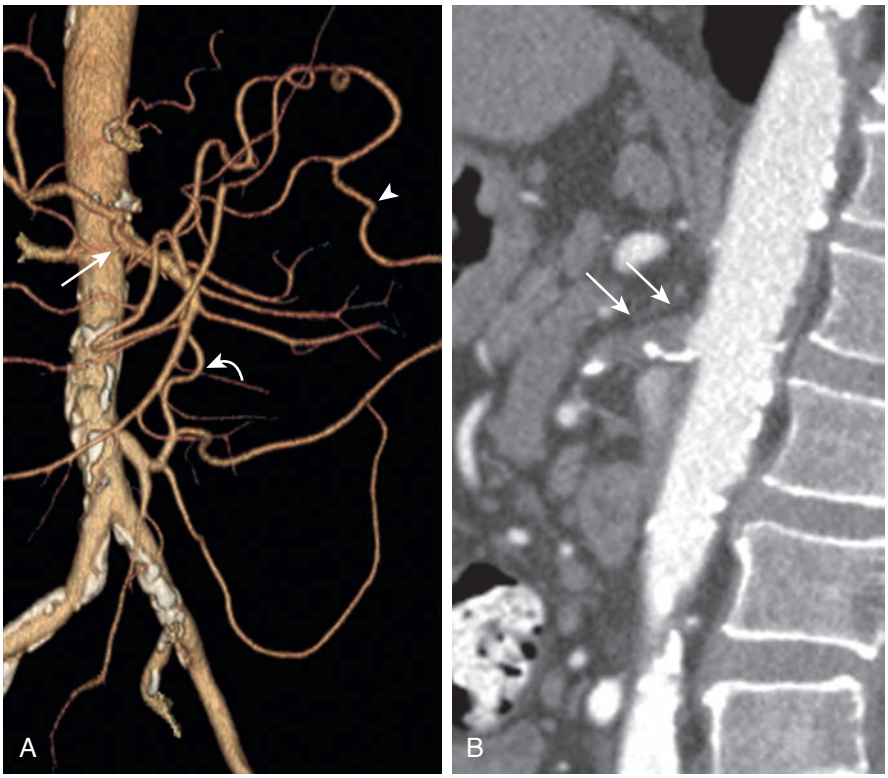

Figure 132.3 Computed tomography angiography with three-dimensional reconstruction in a patient with severe three-vessel mesenteric occlusive disease. Note occlusion of the celiac axis (CA) and superior mesenteric artery (SMA), with collateral flow via a large inferior mesenteric artery (IMA) and meandering artery. Collateralization is shown from the IMA to SMA via Arc of Riolan *(curved white arrow)* and Arcade of Drummond *(arrow head)*, and from the SMA to CA via large gastroduodenal artery *(straight white arrow)*, **(A)**. Axial views of the SMA demonstrate occlusion with a small stump *(double arrow)*, **(B)**.

noninvasive modalities. More frequently, angiography is obtained in conjunction with a planned endovascular intervention. Exceptions are patients with suboptimal imaging studies and those with extensive calcification, small vessels, or multiple prior stents causing metallic artifact.

Other Ancillary Studies

Endoscopy can demonstrate inflammatory and/or ischemic changes, most noticeable in the stomach, duodenum, or right colon. Erosive ischemic gastritis, gastroduodenitis, or ischemic

colitis noted on endoscopy have been described in association with CMI.[33] Gastric tonometry has been shown to be a valuable diagnostic test to assess intestinal perfusion.[33-39] Tonometry can be performed as part of a 24-hour monitoring study during fasting and postprandial state, or as an exercise test using a small nasogastric tonometry catheter with serial pCO_2 measurements in the stomach, duodenum, or upper jejunum.[35,36,38,40,41] Visible light spectroscopy is a new technique that enables noninvasive measurements of mucosal capillary hemoglobin oxygen saturation during endoscopy using white light from a fiber-optic probe.[42,43]

TREATMENT STRATEGIES

There is no role for a conservative approach with chronic parenteral nutrition and noninterventional therapy in patients with symptomatic mesenteric artery disease. Excessive delays in proceeding with definitive revascularization or use of parenteral nutrition alone have been associated with clinical deterioration, bowel infarction, and risk of sepsis from catheter-related complications.[44,45]

Indications for Revascularization

Revascularization is indicated in all patients with symptoms of CMI. Treatment goals are to relieve symptoms, restore normal weight, and prevent bowel infarction. The indication of prophylactic revascularization in patients with asymptomatic disease remains controversial. Based on the report by Thomas and colleagues, there may be a role for prophylactic revascularization in patients with severe three-vessel disease, particularly for those with difficult access to medical care who live in remote or underserved areas.[15] Our approach in these patients has been close surveillance and counseling regarding symptoms of mesenteric ischemia, with a low-threshold to proceed with revascularization if any gastrointestinal symptoms (e.g., bloating, diarrhea, atypical pain) arise. Revascularization has been advised in asymptomatic patients with severe three-vessel disease undergoing aortic reconstructions for other indications.

Choice of Open Versus Endovascular Revascularization

Treatment selection has evolved in most centers. The number of mesenteric revascularizations has increased 10-fold in the United States in the last decade, largely because of improved diagnosis and decreased morbidity of endovascular therapy.[5] Primary stenting is currently the first choice of treatment in greater than 80% patients with CMI who have suitable lesions, independent of their clinical risk (Fig. 132.4). A careful review of preprocedure CTA with attention to anatomic factors determines selection of an open or endovascular approach. The SMA is the primary target for revascularization, and as such the anatomy of the SMA is the most important determinant of choice of therapy. The ideal lesion for angioplasty and stenting is a short, focal stenosis or occlusion with minimal to moderate calcification or thrombus. For CA lesions, angioplasty and stenting carry higher rates of restenosis,[46] and should not be performed if there is active compression by the median arcuate ligament, unless this has been surgically released.

The technical difficulty of endovascular procedures is increased by the presence of severe eccentric calcification, flush occlusion, and in patients with longer lesions, small vessels, and tandem lesions affecting branches. Although these anatomic features do not contraindicate the use of stents, the technical result is often not optimal, and there is increased risk of arterial complications (e.g., distal embolization, dissection) and restenosis.[47,48] Our preference in lower risk groups has been to offer open revascularization if the anatomy is unfavorable for angioplasty and stenting.[49,50] Mesenteric bypass has also been indicated in patients who have failed a percutaneous intervention, in those with recurrent in-stent stenosis after multiple failed reinterventions, and for nonatherosclerotic lesions.

PREPROCEDURE EVALUATION

Preoperative evaluation should focus on a critical review of surgical risk, nutritional status, and anatomic factors that affect choice of reconstruction. Mesenteric revascularization carries definitive risk, regardless of which technique is used. These patients typically undergo a comprehensive medical evaluation to identify and optimize cardiovascular risk factors and their nutritional status. The evaluation should be tailored but typically includes noninvasive cardiac stress test, pulmonary function tests, carotid ultrasound, and noninvasive lower extremity arterial studies. Optimal medical therapy in these patients ideally should include cessation of cigarette smoking, acetylsalicylic acid, and beta-blocker and cholesterol lowering medication, preferentially a statin.

Revascularization should not be excessively delayed. Patients who present with deterioration of symptoms should be admitted, given nothing by mouth, started on intravenous heparin, and treated urgently within 24 to 48 hours. Patients with iodinated contrast allergy should be premedicated with steroid preparation. Those with chronic kidney disease with a serum creatinine level greater than 1.5 to 2.0 mg/dL (133-177 mmol/L) undergo intravenous hydration with sodium bicarbonate and oral acetylcysteine, starting the day prior to intervention, although there is conflicting data on its benefit.

ENDOVASCULAR REVASCULARIZATION

Diagnostic Angiography

Diagnostic angiography (Fig. 132.5) is most often done immediately prior to a planned intervention, either through the femoral or brachial approach. Access is established using ultrasound guidance and 0.035-inch guide-wire system. A 5 Fr sheath is positioned in the external iliac artery, and a 5 Fr diagnostic flush catheter is advanced to T12 level over a 0.035-inch guide wire. Modest intravenous heparinization (40 units/kg) is recommended prior to selective catheterization of

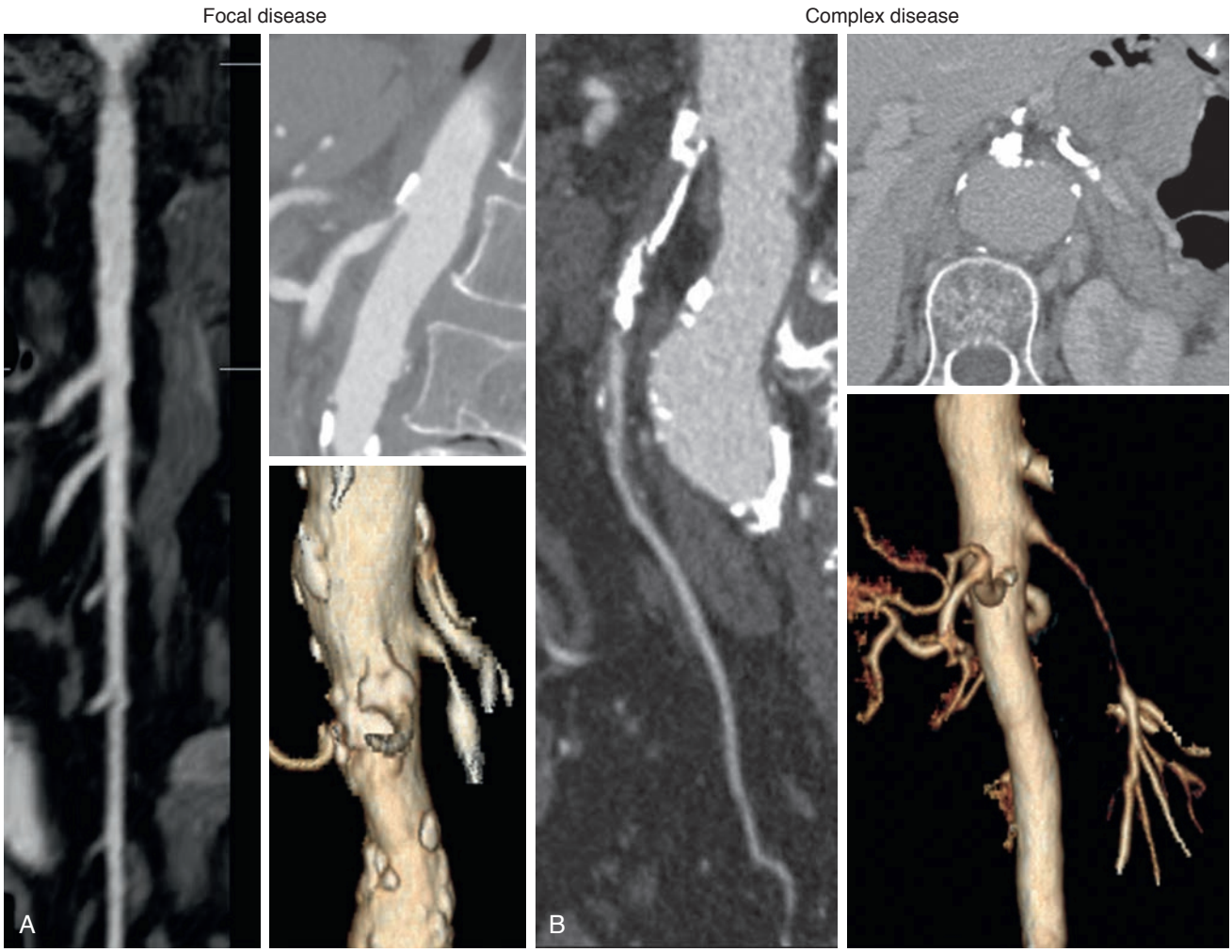

Figure 132.4 Computed tomography angiography is the most useful imaging study to plan revascularization. Anatomic characteristics of the superior mesenteric artery can be used to identify patients with focal disease where angioplasty and stenting is favored **(A)**, or patients with complex disease where endovascular therapy is technically more challenging **(B)**. Lesions with unfavorable anatomy for stenting include heavily calcified occlusions, long segment occlusions, and long segment stenosis involving multiple branches.

the mesenteric arteries. Low-osmolar contrast agent (e.g., Visipaque) minimizes abdominal discomfort during selective injections. Choice of catheter shape is dependent upon access site, angle of origin, and individual preference. The MPA catheter is ideal for selective catheterization via the brachial approach, whereas a secondary curve catheter (e.g., SOS or Simmons) or a catheter with more acute curve (e.g., Cobra 2) can be used for interventions done via a femoral approach. A complete study includes abdominal aortogram with anterior-posterior and lateral views to define the location, severity, and extent of visceral artery involvement, and to identify concomitant lesions in the aorta, renal, or iliac arteries. The optimal projection to display the proximal CA and SMA is a lateral view, and for the origin of the inferior mesenteric artery (IMA), it is a 15-degree right lateral-oblique view. Selective angiography is necessary to confirm the severity of disease and to identify tandem lesions and collateral patterns. In patients with questionable lesions, pressure gradients can be measured using pressure wire, "pull-back," or simultaneous pressure measurement technique.[51]

Angioplasty and Stenting

The primary goal of percutaneous treatment is to restore antegrade flow into at least one of the three mesenteric arteries, preferentially the SMA. Routine stenting is recommended because of elastic recoil and restenosis that occurs with angioplasty of ostial lesions. In patients with CA compression by the median arcuate ligament, there is risk of stent fracture and compression. There is no proven benefit that routine two-vessel stenting provides more durable relief, and a second intervention adds cost and potential risk of complications.[46,52]

The intervention can be done via a brachial or femoral approach. Access via the brachial artery is preferred for patients with a very acute origin of the SMA from the aorta and in those with occlusions. The authors prefer the brachial artery approach whenever possible (Fig. 132.6). This offers excellent support with smaller profile system and precise stent deployment in patients with an acute SMA angle. To minimize the risk of puncture-related complications with brachial access, a small

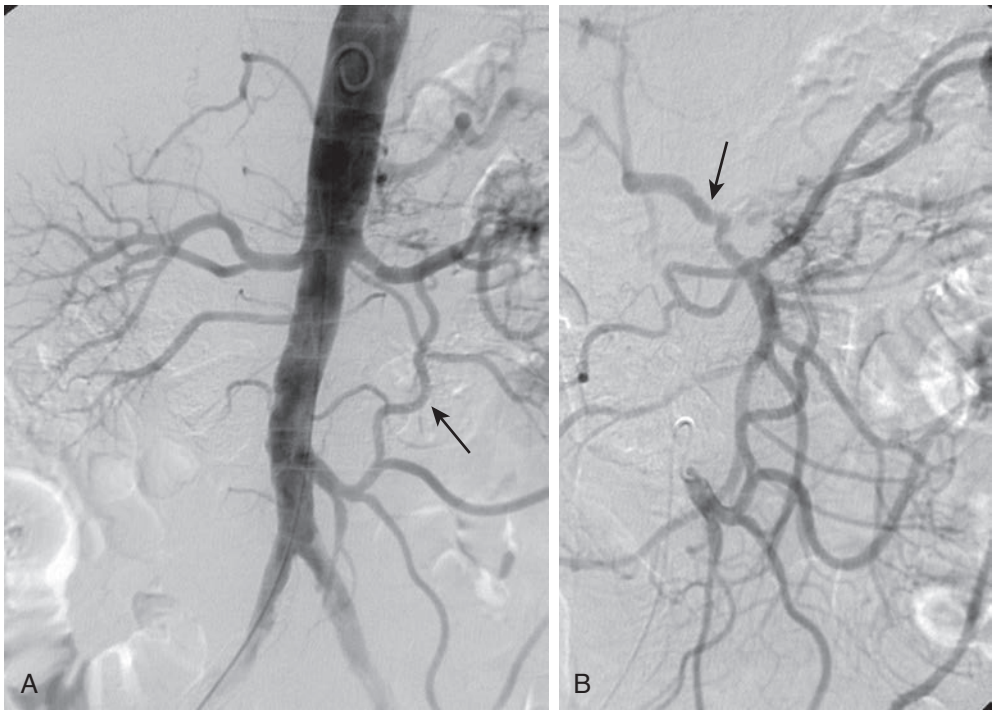

Figure 132.5 Abdominal aortogram with right anterior-oblique view demonstrates large patent inferior mesenteric artery (IMA), **(A)**. Selective IMA angiography confirms collateralization to the superior mesenteric artery via arc of Riolan *(arrow)*, and collateralization to the celiac axis via gastroduodenal artery *(arrow)* **(B)**.

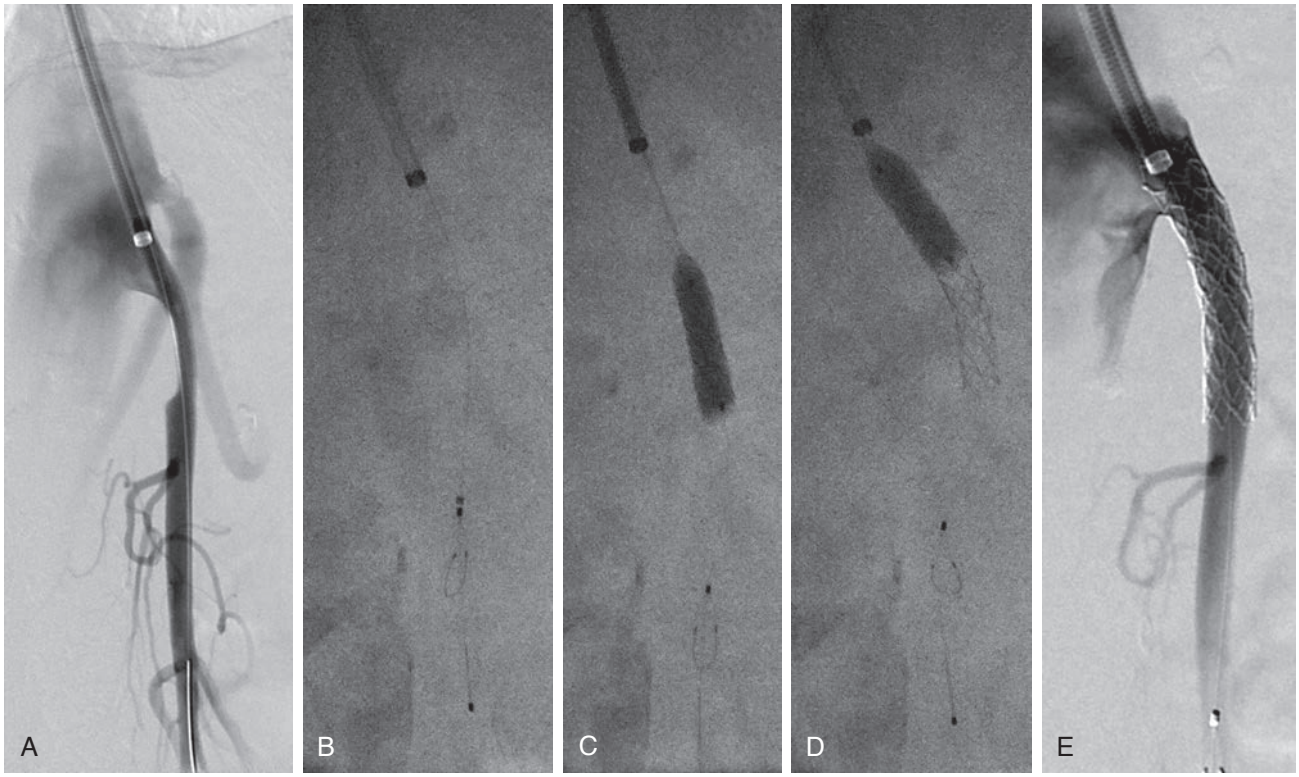

Figure 132.6 Angioplasty and stenting of a focal stenosis of the superior mesenteric artery (SMA) stenosis using brachial approach. After selective angiography (A), the lesion is crossed and a 0.014-inch Spider Rx filter wire (Covidean, Plymouth, Minnesota) is deployed in the main trunk of the SMA (B), avoiding jejunal branches. The entire lesion is treated by balloon-expandable stent (C), which is extended 1-2 mm into the aorta and flared proximally (D). Completion angiography demonstrates the patency of the stent without embolization or dissection (E).

1- to 2-cm incision just above the antecubital crease is used to expose and repair the brachial artery.[53]

Percutaneous access is established with a micropuncture set, which is exchanged to a 0.035-inch system. Full systemic heparinization (80 mg/kg) is administered prior to catheter manipulations. A 6 or 7 Fr 90-cm hydrophilic sheath is positioned in the descending thoracic aorta, and mesenteric catheterization is done with a 5 Fr MPA catheter. A SOS or VS1 catheter can be used if the procedure is performed from the femoral approach. The initial selective angiogram should demonstrate the area of stenosis and should document the distal runoff branches for comparison with postintervention views. The target lesion is initially crossed using a 0.035-inch soft angled glide wire, which is exchanged for the interventional wire of choice. The tip of the guide wire should be visualized and positioned within the main trunk of the SMA, rather than within small jejunal branches, which are prone to perforate or dissect (Fig. 132.7). Embolic protection may be useful in select patients with occlusions, long lesions (>30 mm length), severe calcification, thrombus, acute, or subacute symptoms. When utilized, the author's preference is to use a 320-cm working length 0.014-inch filter wire (Spider RX, Medtronic Covidean, Plymouth, Minnesota). If an over-the-wire 0.035-inch stent is selected, a two-wire technique can be used by combining a 0.014-inch filter wire with a 0.018-inch "buddy wire." Most recently, our practice has changed to covered stents (0.035-inch), based on a recent report that indicates superior patency rates compared with bare metal stents.[54] The stent is introduced via both wires for better support and to facilitate subsequent retrieval of the embolic protection device (Fig. 132.8). Predilatation is recommended only if there is a tight stenosis, occlusion, severe calcification, or to size stents. A balloon-expandable stent with

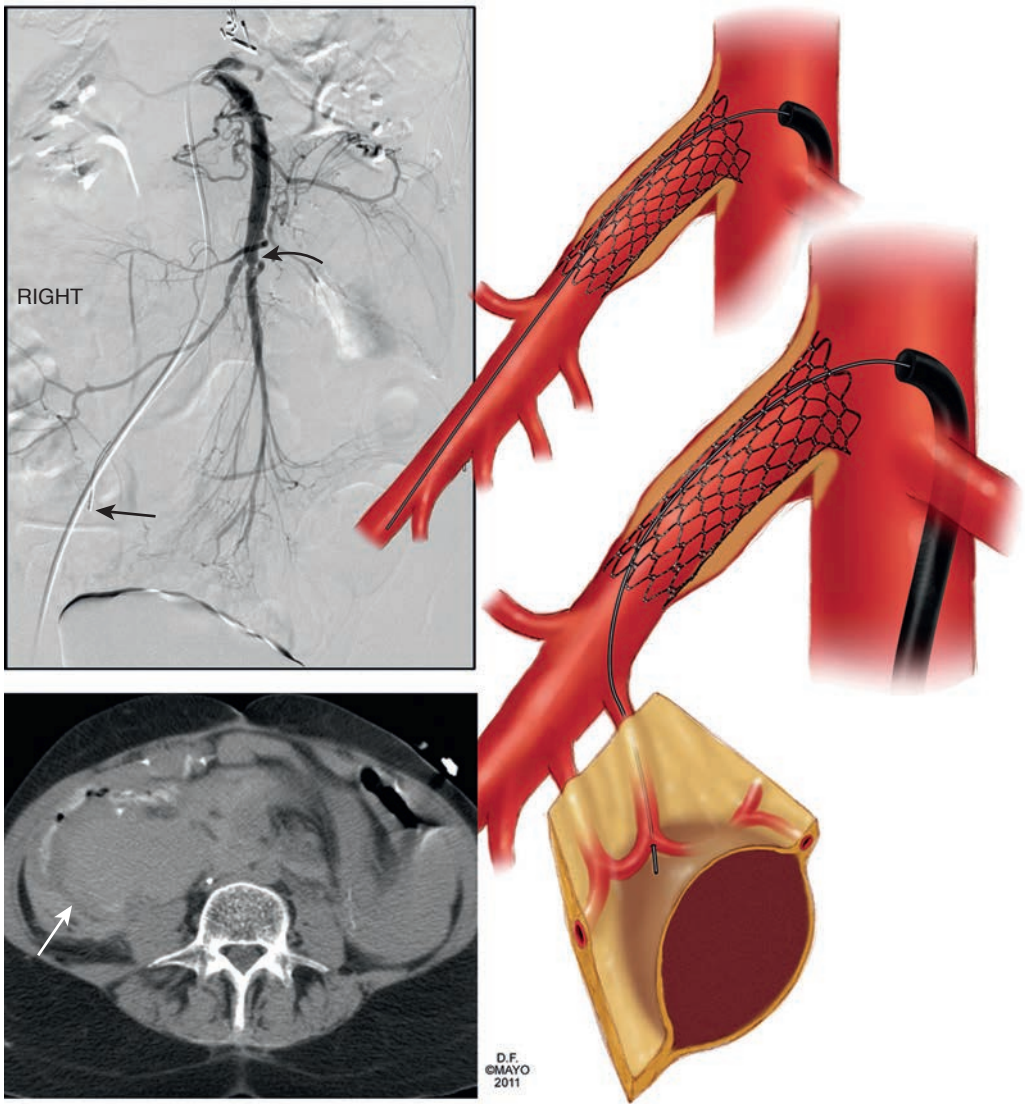

Figure 132.7 An important technical point is to visualize the tip of the guide wire during the intervention and to position the guide wire in the main trunk of the superior mesenteric artery *(curved black arrow)* as opposed to distal jejunal branches *(black straight arrow)*, which are prone to perforation resulting in a mesenteric hematoma *(white straight arrow)*.

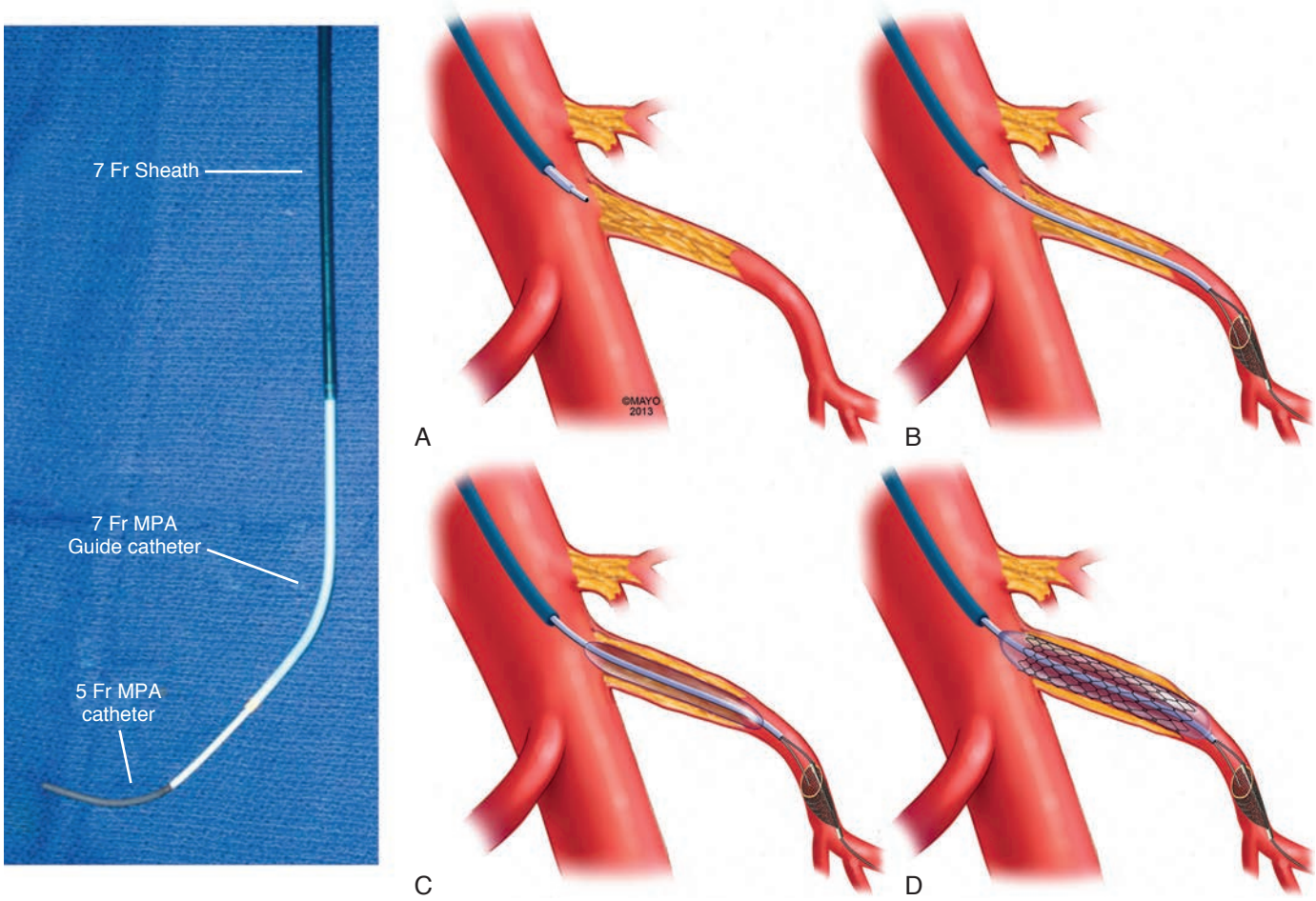

Figure 132.8 Technique of recanalization and primary stenting of a total superior mesenteric artery (SMA) occlusion. In these cases, a coaxial stiff support system is built, with combination of a 7 Fr 90-cm hydrophilic sheath, 7 Fr 100-cm MPA guide catheter, and 5 Fr 125-cm MPA catheter. The stump of the occluded SMA is engaged by the sheath-catheter combination (A); the lesion is crossed using a straight glide wire. After true lumen access is confirmed, a 0.014-inch filter wire and a 0.018-inch buddy wire are deployed into SMA via 0.035-inch catheter (B); the lesion is predilated (C) and stented using a balloon-expandable stent (D).

diameters ranging from 5 to 8 mm is used in greater than 95% of cases, allowing precise deployment and greater radial force. The stent should cover slightly more than the entire length of the lesion and should be 1 to 2 mm into the aortic lumen. Ideally the stent should be flared gently into the aorta to prevent missing the ostia and to facilitate recatheterization if needed. Occasionally a self-expandable stent is used to treat narrowing in tortuous segments.

Recanalization of Mesenteric Occlusions

Occlusions require a stiffer support system to cross the lesion and deliver the stent. A coaxial support system uses a 7 Fr sheath, 7 Fr MPA guide catheter, and 5 Fr MPA catheter (see Fig. 132.8). Attempting difficult recanalization from the femoral approach adds time, contrast, catheter manipulations, and is fraught with failure. The tip of the MPA catheter engages the stump of the occluded SMA (Fig. 132.9), whereas the support system allows the lesion to be crossed using a straight tip, hydrophilic, soft 0.035-inch glide wire. Occasionally, 0.018 or 0.014-inch guide wires are needed. It is important to avoid the subintimal plane because of risk of dissection or disruption, which is best achieved using straight tip guide wires. A Quick-cross catheter (Spectranetics, Colorado Springs, Colorado) or an alternative support catheter, or even a small coronary balloon, may be needed to cross a tight lesion. Once the lesion is crossed, access into the true lumen should be confirmed. Our preference has been to use an embolic protection device with a two-wire technique routinely in cases of total occlusion.

Following deployment and flaring of the stent, the embolic protection device is retrieved with careful attention to avoid entrapment into the stent. The basket is examined for debris. A formal completion angiography should be obtained. The angiogram should provide a focal magnified view of the stent with the sheath in the aorta. Demonstration of the vessel origin and a panoramic view of the entire SMA and its branches to rule out embolization or perforation are critical. The stiff guide

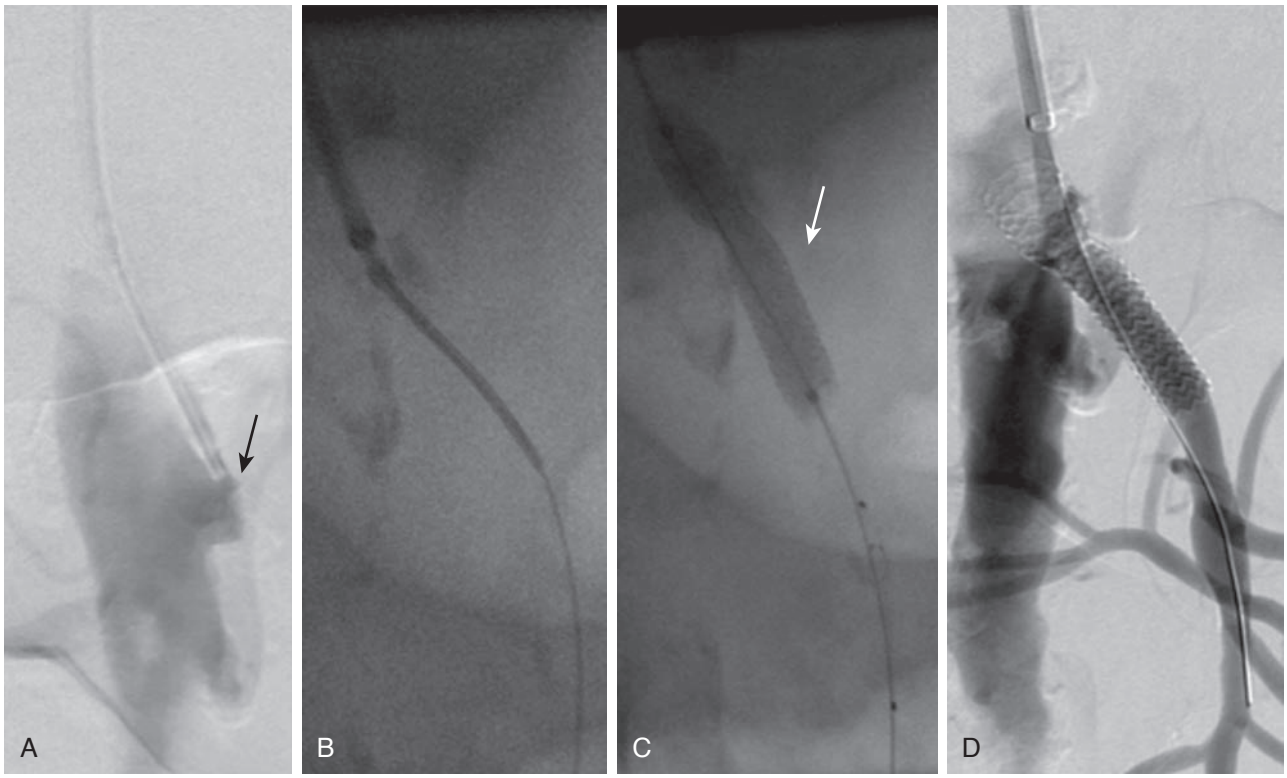

Figure 132.9 Recanalization of superior mesenteric artery (SMA) occlusion utilizing the technique described in Fig. 151.8. After the stump is engaged by the catheter, guide catheter, and sheath (A, *black arrow*), the lesion was crossed (B) and stented using embolic protection (C). Note that the balloon is used to flare the proximal part of the stent (C, *white arrow*). Completion angiography shows a flared widely patent SMA stent (D).

wire should be retracted, and nitroglycerin may be administered via the sheath to minimize spasm or kinks caused by the guidewire tip.

Adjunctive Techniques

A number of adjunctive techniques can be used to optimize results in complex lesions, but the authors acknowledge that these techniques are anecdotal. The presence of acute and subacute symptoms suggests fresh thrombus or a complicated plaque. In these cases local administration of t-PA into the diseased segment 20 to 30 minutes prior to stent placement may improve technical success. For eccentric, calcified lesions, percutaneous atherectomy has been used selectively.[55] It is critical to have an appreciation of the limitations of this technique when applied as an off-label use in the mesenteric arteries.

Complications

The most common causes of death after mesenteric stenting are cardiac events, gastrointestinal bleeding, and bowel ischemia. The latter is typically associated with intraprocedural complications such as distal embolization, thrombosis, or dissection. Distal embolization occurs in 8% of patients treated by SMA stents without embolic protection, with higher rates among patients with subacute symptoms, SMA occlusion, long lesions (>30 mm), and severe calcification.[50] The most commonly reported complications are access-related problems in 3% to 16%, renal insufficiency in 2% to 8%, acute bowel ischemia in 1% to 7%, gastrointestinal bleeding in 1% to 5%, cardiac events in 1% to 7%, and respiratory complications in 1% to 7%.[17,21,52,56-68]

Postprocedure Management

The postprocedure care after mesenteric interventions is comparable to that of other peripheral endovascular procedures. All patients are admitted for observation overnight. Worsening abdominal pain after the procedure is unusual and warrants evaluation to rule out thrombosis, embolization, or a mesenteric hematoma from jejunal branch perforation (see Fig. 132.7). Patients are allowed to resume a regular diet within 6 to 8 hours. Antiplatelet therapy is typically started prior to the intervention with acetylsalicylic acid, and continued indefinitely thereafter. Clopidogrel is started the day of the intervention with a loading dose of 300 mg followed by a dose of 75 mg daily for 6 to 8 weeks as a dual antiplatelet agent, or indefinitely if a covered stent is used. A duplex ultrasound scan prior to discharge or within the first few days after the procedure serves as a baseline for future comparison. Follow-up includes clinical examination and duplex ultrasound every 6 months during the first year and annually thereafter.

OPEN REVASCULARIZATION

Choice of Open Surgical Revascularization

A variety of open surgical techniques have been described to revascularize the mesenteric arteries. Selection involves the type of incision (transperitoneal vs. retroperitoneal), conduit (vein vs. prosthetic), graft configuration (antegrade vs. retrograde), source of inflow (aortic vs. iliac), and the number of vessels to be reconstructed (single vs. multiple).

The type of open reconstruction is selected on the basis of the anatomy and the patient's clinical risk assessment.[26] Two-vessel reconstructions (CA and SMA) using a bifurcated polyester graft from the supraceliac aorta compromises more than 80% of open mesenteric reconstructions.[17,26,69] This approach is selected in lower risk patients who are not candidates for endovascular treatment and have multivessel disease, with no evidence of significant supraceliac aortic calcification or thrombus. Elderly patients and those with cachexia or severe cardiac, pulmonary, and renal dysfunction are not good candidates for supraceliac aortic-based procedures, and are best treated with retrograde grafts based in the infrarenal aorta or the iliac arteries. A hybrid approach using retrograde open mesenteric stent via midline laparotomy may be selected for patients with extensive aortoiliac disease and no good source of inflow.[70,71] Transaortic endarterectomy is rarely indicated, but may be considered in patients who failed or are not candidates for endovascular therapy and have bacterial contamination or perforated bowel, previous abdominal irradiation, extensive abdominal wall hernias, or other hostile conditions.

Antegrade Mesenteric Bypass

The distal thoracic or supraceliac aorta is often spared from severe atherosclerotic disease. Bypass with antegrade graft configuration based in the supraceliac or lower thoracic aorta[72] offers potential hemodynamic advantage, while avoiding kinks that can occur with grafts placed in retrograde fashion. The operation is done through a transperitoneal upper midline or bilateral subcostal incision, depending on the patient's body habitus and costal cartilage flare (see Chapter 54). Abdominal exploration includes an evaluation for other intraabdominal pathology and careful inspection of the small bowel for unsuspected ischemic perforations. A third arm retractor or an Omni self-retaining retractor can be used. The lesser omentum is opened and the left lobe of the liver is retracted after division of the left triangular ligament. The esophagus is retracted toward the patient's left side with a nasogastric tube in place, and the stomach is gently retracted caudally. The diaphragmatic crura are divided longitudinally to expose the supraceliac aorta (Fig. 132.10). Approximately 5 to 10 cm is dissected free in preparation for clamping. While doing so, care should be taken not to enter the pleural cavity on either side of the aorta. Usually only the celiac trunk and the proximal hepatic and splenic arteries need isolation, but with more extensive disease, the common hepatic artery may be a better target for the anastomosis. The left gastric artery is often small and may be divided without sequela, which facilitates celiac anastomosis and makes tunneling of the SMA graft behind the pancreas easier.

The transverse mesocolon is retracted cephalad, and the root of the mesentery is incised longitudinally over the SMA just below the pancreas. Several lymphatic and small venous tributaries require meticulous ligation. The SMA and several jejunal branches are dissected free and carefully controlled with Silastic vessel loops. Excessive traction on these vessel loops can easily result in avulsion of small branches and should be avoided. In most cases, as much as 4 to 5 cm of the SMA is dissected distal to the lower border of the pancreas, but additional dissection may be required in patients with extensive disease. In these cases, one or more crossing venous branches from the superior mesenteric vein may require ligation and division to allow exposure of the SMA.

Patients are given systemic heparin (60-80 mg/kg), and diuresis is induced with mannitol prior to placement of the supraceliac clamp. Partial aortic cross clamping can be performed using a Satinsky or multipurpose clamp, or alternatively total aortic clamping with two cross-clamps affords better exposure for the proximal aortic-graft anastomosis. A straight or angled aortic clamp (Cherry supraceliac clamp) and a Wylie hypogastric clamp work well (see Fig. 132.10). Placed appropriately, occlusion of the lumbar vessels is achieved as well. A gentle slightly oblique or vertical aortotomy is made. A 14×7 mm knitted polyester graft is beveled in an oblique fashion with a short main body and anastomosed to the supraceliac aorta in an end-to-side fashion using running 4-0 Prolene suture. Aortic cross-clamp time rarely exceeds 20 minutes and most often ranges from 12 to 15 minutes. The risk of renal ischemia or embolization is low when patients are properly selected and have a relatively disease-free supraceliac aorta.

The left limb of the bifurcated graft is positioned slightly posterior and is tunneled retro-pancreatic and anterior to the left renal vein toward the SMA (Fig. 132.11). The anastomosis to the SMA is performed in an end-to-side fashion when the anastomosis is performed at the base of the mesentery below the pancreas. If the SMA is extensively diseased or the patient has had prior stents, the lumen may require modest endarterectomy or removal of stent struts. Any endarterectomy should be done carefully, so not to result in tear or an excessively thin arterial wall that cannot be reconstructed. In a few cases with very extensive plaque, the distal graft can be beveled into a long patch or anastomosed end-to-side into a bovine pericardium patch. It is important to relax retraction when cutting the graft limbs to length to avoid angulation or kinking with either an antegrade or retrograde bypass. Next, the celiac axis anastomosis is performed in end-to-end fashion, or more frequently the anastomosis may be performed end-to-side to the common hepatic artery.

Retrograde Mesenteric Bypass

Sources of inflow for retrograde grafts are the infrarenal aorta, prior infrarenal aortic grafts, or the iliac arteries (Fig. 132.12). In general, we reconstruct only one artery (SMA) if a retrograde graft is used. The infrarenal aorta may be replaced, if diseased,

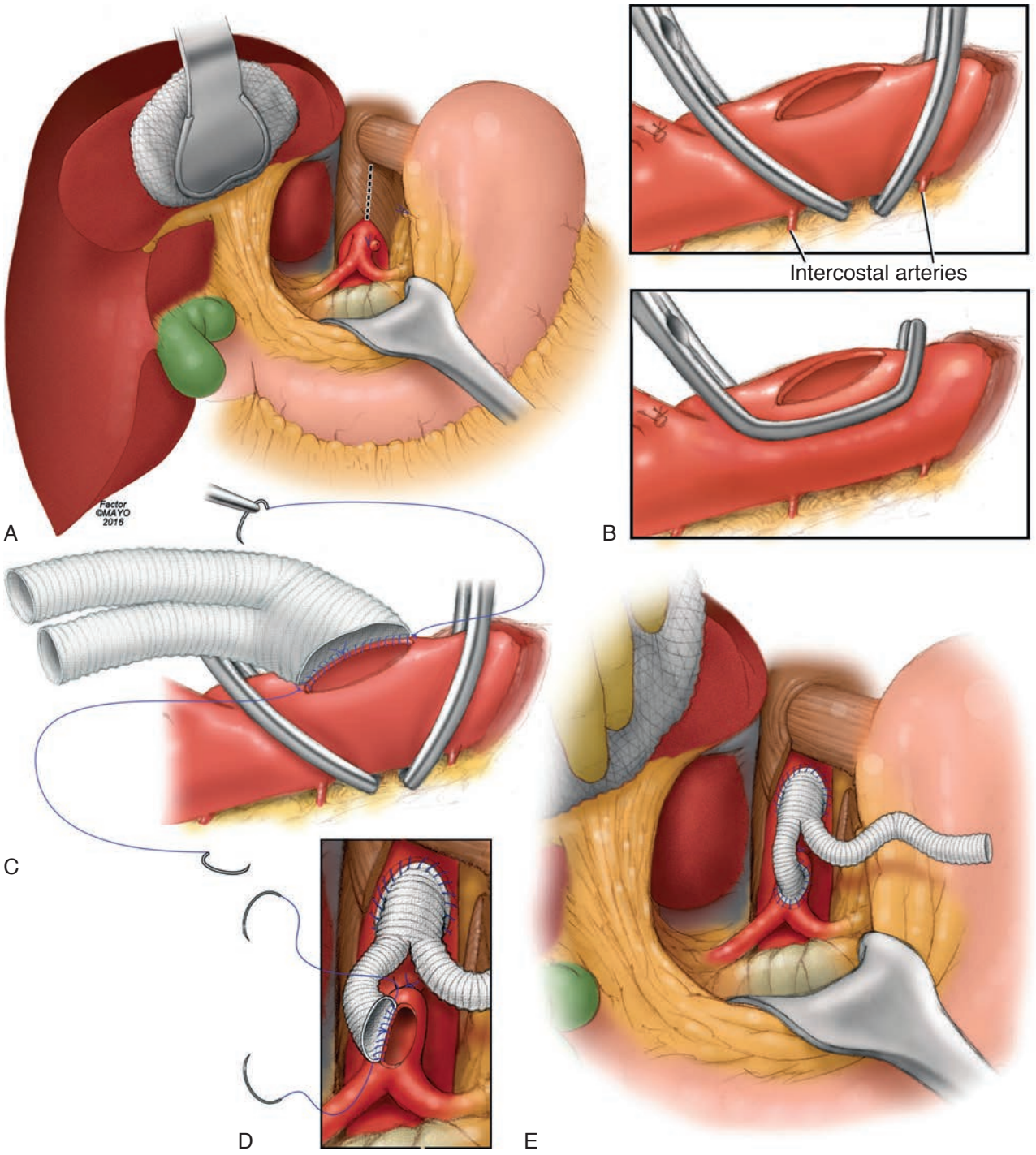

Figure 132.10 The supraceliac aorta is exposed after division of the diaphragmatic crura (A). Following systemic heparin, the supraceliac is clamped using either two aortic clamps or a Satinsky clamp (B). A slightly oblique aortotomy is made for the proximal anastomosis of the bifurcated graft (C). Note that the graft is gently beveled and that the right graft limb is anastomosed end-to-side to the celiac axis or hepatic artery (D). The left limb of the graft is tunneled behind the pancreas (E).

but concomitant aortic reconstruction increases operative mortality and should be avoided unless absolutely necessary.[17] The proximal anastomosis is performed to the anterolateral wall of the aorta and can be done with either two cross-clamps or a partial occlusion clamp, depending on the aortic size and the presence of atherosclerosis or calcification within that segment. A 6-mm coronary punch can be used to remove portion of the aortic wall. However, our preference is to select the common iliac artery as source of inflow whenever possible, thus avoiding an aortic cross-clamp.

The key to prevention of graft elongation, angulation, or kinking is to cut it to length, with the SMA in a nearly anatomic

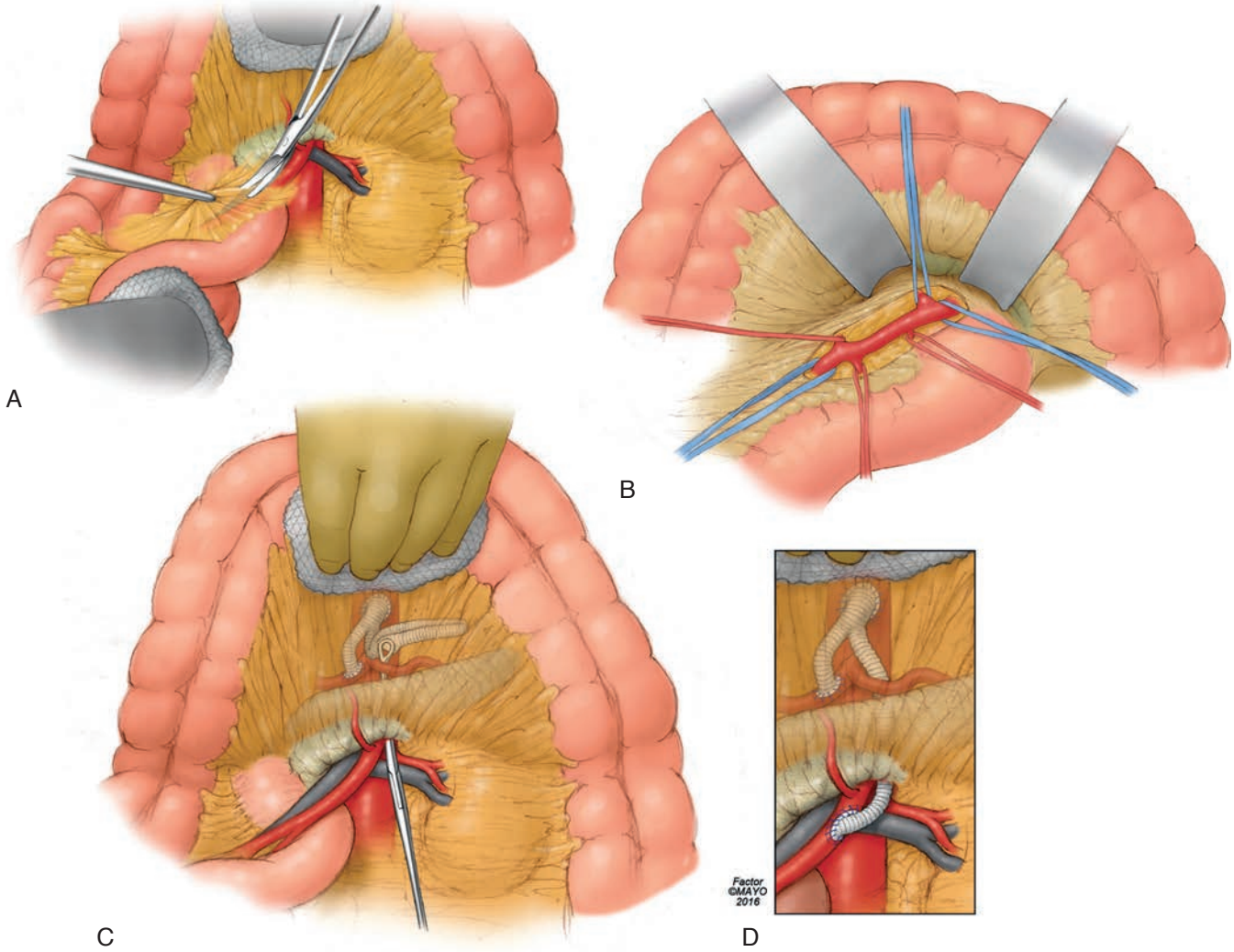

Figure 132.11 The superior mesenteric artery (SMA) is dissected free in the mesentery after the transverse colon is retracted cephalad (A). Once the SMA and branches are dissected and controlled with silastic vessel loops (B), the left limb of the graft is tunneled behind the pancreas (C) and anastomosed end-to-side to the SMA (D).

position. This is done by relaxing the retractors prior to cutting the graft and after the proximal or distal anastomosis is done. A large 8- or 10-mm graft should be used for a retrograde, straight aortomesenteric graft, and it is imperative to perform the distal anastomosis first and then push the mesentery close to the aorta and select the appropriate aortic site for the anastomosis. We prefer a C-shaped graft when the iliac artery is the source of inflow. In these cases, the proximal anastomosis may be done first to the iliac artery or distal aorta, followed by the distal anastomosis to the SMA. There are some patients who have extensive circumferential aortic calcification but soft common or external iliac arteries, which can serve as good donor vessels. Either the right or left common iliac artery can be chosen for inflow, depending on the orientation of that artery to the normal anatomic position of the SMA. In general, the right iliac artery lays better if both vessels are suitable. Two-vessel reconstructions can also be performed with retrograde grafts by doing a side-to-side anastomosis to the SMA and an end-to-side anastomosis to the common hepatic artery. These grafts may be passed on top of or beneath the pancreas and curved in a C-fashion toward the hepatic artery.

Retrograde Open Mesenteric Stenting

A hybrid approach using retrograde open mesenteric stenting (ROMS) via midline laparotomy to expose the SMA (Fig. 132.13) has been reported by Milner and colleagues from the University of Pennsylvania and Dartmouth Group.[70,73] This option is selected in patients with acute mesenteric ischemia due to in situ thrombosis when there is an indication for laparotomy. It is also well suited in patients with severe aortic and iliac calcifications when there is not a good source of inflow for bypass. The SMA is dissected below the pancreas as previously described. Several jejunal branches are controlled with Silastic vessel loops and occluded prior to manipulation to avoid distal embolization. Retrograde SMA access is established using a micropuncture set with 0.018-inch guide wire. This is exchanged for a 0.035-inch guide-wire system, and a 6 to 7 Fr sheath is advanced to the

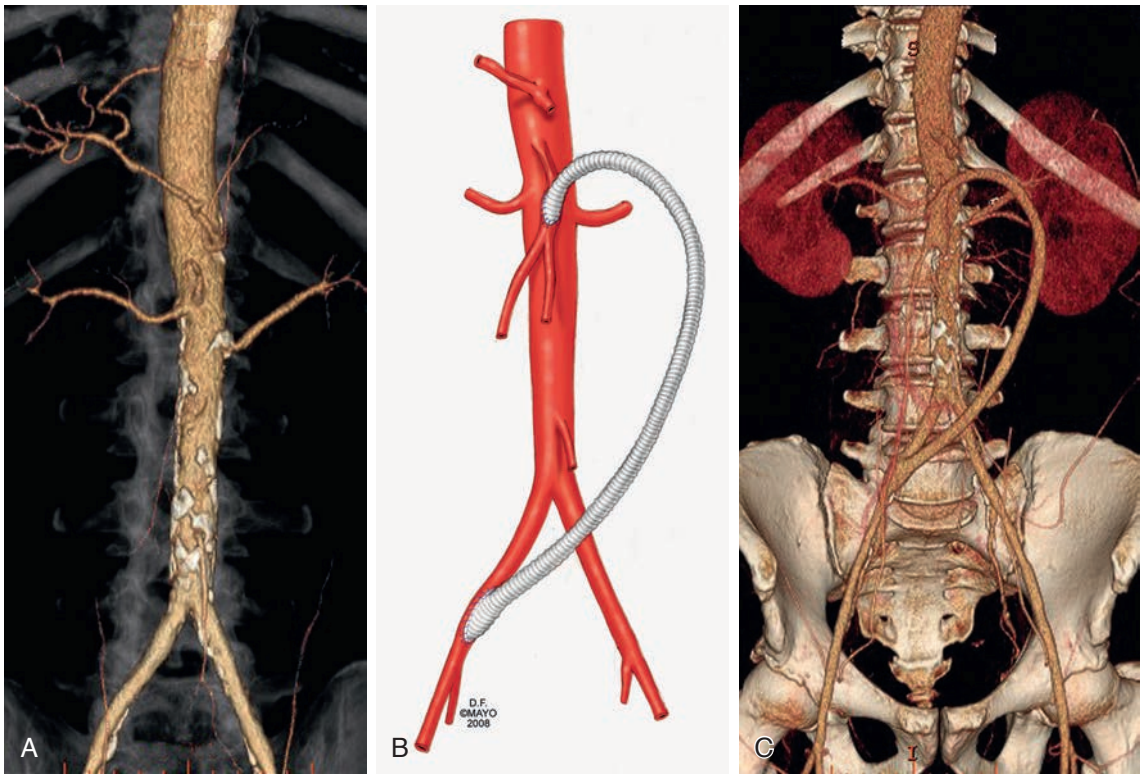

Figure 132.12 Computed tomography angiography (CTA) of a patient with vasculitis and occlusion of the superior mesenteric artery **(A)**. The patient was treated by retrograde C-shaped iliac artery to superior mesenteric artery bypass **(B)**. Follow-up CTA revealed widely patent bypass graft **(C)**.

SMA. Retrograde angiography is obtained and the SMA occlusion or stenosis is crossed, predilated, and stented with a balloon-expandable stent. Prior to restoring antegrade flow to the SMA, the sheath is flushed to prevent distal embolization. The puncture site may be closed with interrupted sutures or opened longitudinally and closed over a patch if severely diseased.

Transaortic Mesenteric Endarterectomy

Transaortic endarterectomy is performed using a full-length midline abdominal or subcostal incision or a thoracoabdominal incision for patients who have narrow costal flares or are truly obese (see Chapter 54). The aorta is exposed using medial visceral rotation with the left kidney remaining in its bed and dissection carried anterior to the renal vein. The diaphragmatic crura is transected longitudinally, allowing exposure of the left anterior-lateral wall of the aorta and origins of the SMA and celiac axis (Fig. 132.14). The SMA is dissected free over several centimeters. After systemic heparin and induced diureses, the supraceliac and infrarenal aorta are clamped. A longitudinal or trapdoor aortotomy is performed, starting at the level of the renal arteries up to just above the celiac axis origin. Endarterectomy of the paravisceral aorta, the celiac, and SMA is performed, ending at the renal artery orifices. In the rare patient in whom there is symptomatic renal artery stenosis, the endarterectomy should include the renal artery ostia as well. The aortotomy is closed longitudinally and rarely requires a patch. Endarterectomy of the celiac artery usually has an endpoint at its bifurcation, whereas SMA disease may extend beyond the limits of the ostial endarterectomy. This requires a separate transverse or longitudinal SMA arteriotomy after flow is restored through the distal aorta and celiac artery. If a longitudinal arteriotomy is done, this can be closed with a patch.

Intraoperative Duplex Ultrasound Monitoring

Technical imperfections may be a cause of early graft failure after mesenteric revascularization. We have routinely performed intraoperative duplex ultrasound (IOUS) surveillance in all patients who undergo open mesenteric or renal reconstructions. We have found technical defects in 15% of the reconstructions. Minor defects (7%) are typically left untreated and include arterial abnormalities with normal velocities such as small kinks, mild residual stenosis, and small intimal flaps. Major defects (9%) consist of hemodynamically significant arterial abnormalities such as significant stenosis, kinks, thrombus, and large intimal flaps. These require prompt immediate revision.

Complications

Complication rates after open mesenteric revascularization average 20% to 40%.[5,18,74-79] Pulmonary (15%), gastrointestinal (14%), cardiac (10%), and renal (4%) complications are the most frequent. Patients with severe malnutrition require perioperative nutritional support. Prolonged ileus occurs in 8%.[17] Meticulous wound closure is important, particularly in the

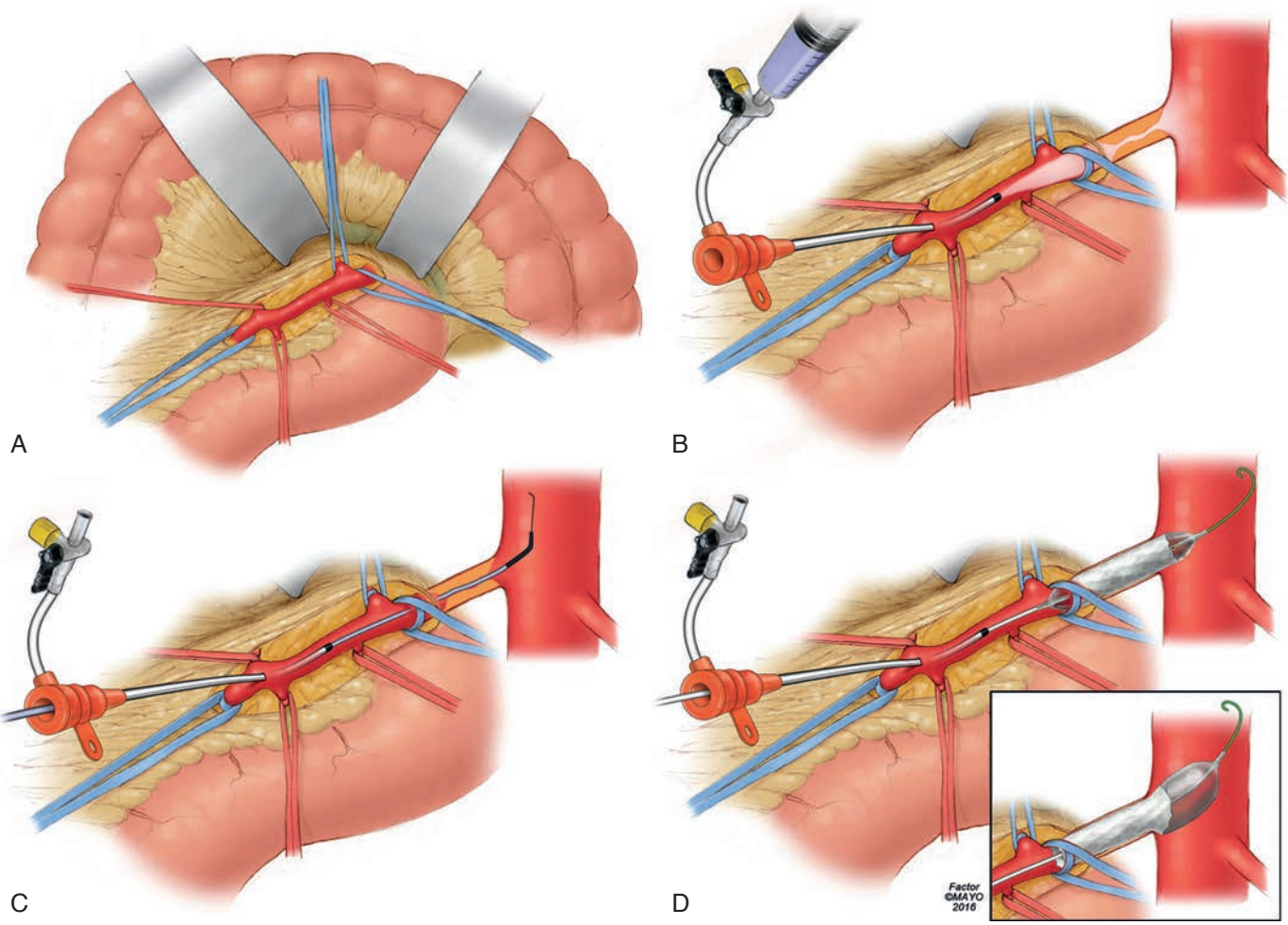

Figure 132.13 Technique of retrograde open mesenteric stenting requires open surgical exposure of the superior mesenteric artery (SMA) (A). Retrograde access is established using a 7 Fr sheath and catheter (B). After retrograde angiography, the occluded SMA is crossed using a glide wire (C). Stenting is performed using a covered stent or bare metal stent (D).

patient with malnutrition or severe ascites, due to risk of wound related complications (4%-8%).[15,72,76,77,79-81] Early graft thrombosis is uncommon (<2%) and indicates a technical problem (e.g., kink, intimal flap, dissection, thrombus), poor runoff, or hypercoagulable state.[17] If not recognized, early graft thrombosis is a lethal complication.

Postoperative Management

Patients undergoing open mesenteric reconstruction are admitted for 1 to 3 days to the intensive care unit for monitoring. The average length of hospital stay is 12 days.[17] Patients with severe ischemia typically experience major fluid shifts and have a high volume requirement over the first 48 hours because of the loss of autoregulation of the mesenteric arterioles and the systemic inflammatory response. Persistent hypotension, tachycardia, leukocytosis, reduction in urinary output with elevated bladder pressures, or increase in abdominal pain may indicate graft occlusion, ischemic bowel, or abdominal compartment syndrome. CT, abdominal reexploration, or both are needed to exclude these problems.

Return of oral intake varies, but many patients develop prolonged postoperative ileus and may need enteral or parenteral nutritional support. Total parenteral nutrition is started early after the operation once fluid requirements diminish if an ileus is anticipated in the malnourished patient. The "food fear" many patients have preoperatively does not resolve quickly after the operation, as it is often a "learned behavior." Furthermore, absorptive capacity of the gut changes, and patients often experience diarrhea over the first few postoperative weeks. Postoperative medical therapy includes ongoing recommendations for smoking cessation, antiplatelet, and cholesterol-lowering agents. Imaging surveillance is recommended using duplex ultrasound, which is obtained every 6 months during the first year and annually thereafter.

RESULTS

Despite the lack of prospective randomized comparisons between open surgery and endovascular treatment, mesenteric angioplasty and stenting have been widely adopted in most centers, resulting in a decline in the number of open surgical reconstructions. Endovascular revascularization has been associated with decreased

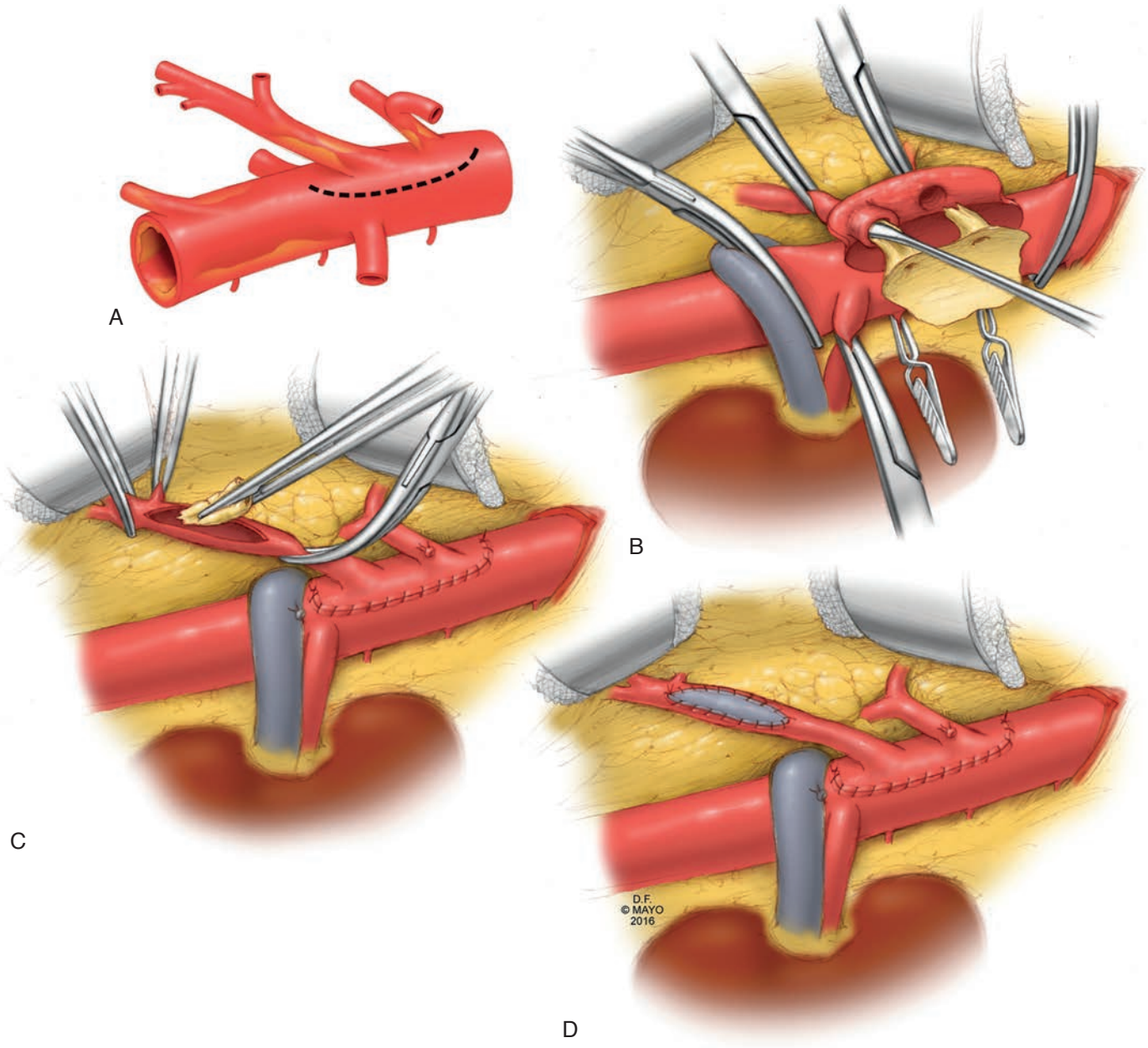

Figure 132.14 Technique of transaortic mesenteric endarterectomy using medial visceral rotation and a trapdoor aortotomy (A). The endarterectomy includes the origins of the celiac axis and superior mesenteric artery (B). The aortotomy is closed and the end point of the superior mesenteric artery is revised if needed (C). This is closed using vein patch angioplasty (D).

morbidity, length of stay, and convalescence time, but similar mortality compared with open repair.[17,82] Mesenteric bypass offers improved patency, with lower rates of reinterventions and better freedom from recurrent symptoms.[5,17,21,57,58,82-90]

Morbidity and Mortality

Based on a review of single-center reports and a systematic review, endovascular revascularization has been associated with decreased morbidity, length of stay, and convalescence time (Tables 132.1 and 132.2).[82] Morbidity and length of stay averages 11% and 3 days with endovascular, compared with 33% and 14 days with open surgery.[82] Mortality rates are similar, with average 30-day mortality of 6% (0%-15%) for open and 5% (0%-21%) for endovascular revascularization.[82] Open surgical bypass can be performed with low mortality in good risk patients operated on referral centers.[5,86] The Mayo Clinic group[17] reported a 2.7% mortality for open and 2.4% for endovascular revascularization. Mortality was 1% for low-risk and 6.7% for high-risk patients treated by open bypass, with the highest mortality rate (8.9%) in those patients who had a concomitant aortic reconstruction. Nonetheless, these operations carry high mortality in the community, reaching 20% in the state of New York and 13% in the United States.[5,86]

TABLE 132.1 Results of Contemporary Reports of Angioplasty and Stenting for Treatment of Chronic Mesenteric Ischemia

Author (Year)	*N*	Vessels	Stented Vessels (%)	Technical Success (%)	Mortality (%)	Morbidity (%)	Recurrence (%)	Reintervention (%)	Primary Patency (%)	Follow-up (Months)
Bare Metal Stents										
Kasirajan (2001)	28	32	82	100	11	18	34	—	73 at 3 years	24
Matsumoto (2002)	33	47	32	88	0	13	15	15	—	20
van Wanroij (2004)	27	33	94	93	0	11	—	19	81 at 19 months	19
Landis (2005)	29	63	27	97	7	10	45	37	70	28
Silva (2006)	59	79	100	96	2	—	17	17	71	38
Biebl (2007)	23	40	96	—	0	4	26	22	—	10
Atkins (2007)	31	42	87	100	3.2	13	23	16	58	15
Sarac (2008)	65	87	100	—	8	31	—	31	65	12
Lee (2008)	31	41	—	98	14	6	44	10	69 at 7 years	32
Dias (2010)	43	49	100	98	0	23	12	33	—	43
Oderich (2009)	83	105	72	95	2.4	18	31	31	41 at 5 years	36
Fioole (2010)	51	60	100	93	0	4	25	22	86	25
Peck (2010)	49	66	89	100	2	16	29	29	64 at 3 years	37
Schoch (2011)	107	116	78	100	0	—	42	42	67	16
Turba (2012)	166	221	74	92	3	10	17	19	67	34
AbuRahma (2013)	83	105	100	97	2	2	35	30	19	31
Grilli (2014)[a]	47	41	100	87	2	7	17	17	78 at 24 moths	19.1
Sundermeyer (2014)	27	27	74	100	0	0	22	22	50 at 24 months	16
Barret (2015)	43	—	77	95	0	19	37	37	—	63
Zacharias (2016)	116	143	—	—	5.2	—	23	23	74 at 36 months	37
Covered Stents										
Schoch (2011)	14	14	100	100	0	—	—	0	100	16
Oderich (2012)	42	42	100	98	0	12	10	10	92 at 3 years	19
Total	1197	1453	84	96	3	12	27	23		25

a. Considering only occluded SMA. In one case was used covered stent and, in other ones, bare metal stent.

Symptom Relief

Both methods of revascularization are highly effective in patients who have the correct diagnosis of CMI. In a systematic review, symptom improvement averaged 88% with endovascular and 93% with open revascularization.[82] Single-center reports indicate symptom improvement in greater than 90% of patients treated by stents. Angioplasty alone may be associated with lower rates of technical success (78%) compared with stenting (>95%).[86] Symptom improvement is noted immediately after revascularization, but it is not uncommon for patients to experience modest bloating and worsening diarrhea. The presence of persistent abdominal pain may suggest another diagnosis.

TABLE 132.2 Results of Contemporary Reports of Open Surgical Revascularization for Treatment of Chronic Mesenteric Ischemia

Author (Year)	*N*	Vessels	Mortality (%)	Morbidity (%)	Recurrence (%)	Reintervention (%)	Primary Patency (%)	Follow-up (Months)
Leke (2002)	17	25	6	41	0	0	100 at 34 months	34
Cho (2002)	25	41	4	—	32	20	57 at 5 years	64
Brown (2005)	33	51	9	30	9	7	100 at 6 months	34
Sivamurthy (2006)	46	66	15	46	32	12	83 at 6 months	9
Biebl (2007)	26	48	8	42	11	8	—	25
Kruger (2007)	39	67	2.5	12	5	3	92 at 5 years	39
Atkins (2007)	49	88	2	4	22	22	90	42
Mell (2008)	80	120	3.8	26	11	11	90	46
Oderich (2009)	146	265	2.7	36	6	5	88 at 5 years	36
Low risk	101	—	0.9	37	6	6	94 at 5 years	—
High risk	45	—	6.7	38	11	11	90 at 5 years	—
Concomitant aortic reconstruction	23	—	8.4	—	—	—	—	—
Rawat (2010)	52	75	13	32	15	13	81	41
Ryer (2011)	116	203	2.5	50	14	16	86 at 5 years	43
Lejay (2015)	86	123	3.5	13.9	—	—	—	83
Complete revascularization	46	—	—	—	—	—	84 at 10 years	—
Incomplete revascularization	40	—	—	—	—	—	88 at 10 years	—
Barret (2015)	11	—	0	64	27	27	—	59
Zacharias (2016)	45	72	11	—	—	—	91 at 3 years	37
Total	1026	1244	6	34	14	12		38

Restenosis, Symptom Recurrence, and Reintervention

Most single-center reports and a systematic review indicate that open reconstructions are more durable (see Table 132.2).[17,57,58,68,76,78,87,89,91-96] Bypass is associated with lower rates of restenosis, better patency, and higher freedom from recurrent symptoms or reinterventions compared with mesenteric angioplasty and stenting. Primary patency of open bypass averaged 89% at 5 years in a recent review of the pooled literature (57%-92%), with freedom from reinterventions of 93%.[86] Ryer and colleagues indicated that open bypass has been increasingly performed in patients with more comorbidities and worse anatomy. Despite these adverse characteristics, open surgery had excellent primary patency of 76% at 5 years.[78] In the systematic review of van Petersen and associates,[82] endovascular treatment was associated with more restenosis (37% vs. 15%), symptom recurrences (30% vs. 13%), and reinterventions (20% vs. 9%). Primary patency was lower for mesenteric stenting (51% vs. 86%), with similar secondary patency rates (83% vs. 87%).

Endovascular treatment has been plagued by high rates of restenosis, affecting as much as 20% to 66% of the patients, not matching the excellent patency rates reported for open reconstructions (see Table 132.1).[17,21,52,56-68,89,90,92,96-100] Contemporary reports of primary stenting indicate that restenosis occurs in 40% of patients and that half of these require reintervention.[47] The average 3-year primary patency rate for bare metal stents is 52% (range, 30%-81%), calculated from pooled literature.[86] The secondary patency rate is better than 90%, as evidenced by reports of mesenteric reinterventions.[47,86] Oderich and associates recently reported a nonrandomized comparison of covered versus bare metal stents in 225 patients treated for CMI.[54] In that study, covered stents had 92 ± 6% primary and 100% secondary patency rates at 3 years, rivaling the results of open bypass. Covered stents outperformed bare metal stents, with less restenosis, symptom recurrences, reinterventions, and better patency rates. These observations held true both in primary interventions for native artery lesions and in reinterventions for in-stent or native artery restenosis after endovascular procedure. Independent predictors of restenosis were use of bare metal stents, cigarette smoking, advanced age, and female gender.

Patient Survival

Poor prognostic indicators for long-term patient survival after mesenteric revascularization include advanced age and presence

of severe cardiac, pulmonary, or renal disease.[17,101] The type of revascularization has not been shown to affect survival, but comparative analysis is limited by selection bias, favoring open bypass for good risk and endovascular revascularization for higher risk patients. Tallarita and associates reported long-term survival in a cohort of 343 patients treated for CMI, with nearly identical 5-year survival rates using propensity matched scores for patients treated by open (57%) or endovascular (60%) revascularization.[101] Five-year patient survival averaged 71 ± 4% for low-risk, 49 ± 6% for intermediate-risk, and 38 ± 7% for high-risk patients. Freedom from mesenteric-related death was 91 ± 2% after open and 93 ± 4% after endovascular revascularization at 5 years. Independent predictors of any cause mortality were age greater than 80 years (OR 3.3, CI 1.03-1.06, $P = < .001$), chronic kidney disease stage IV or V (OR 5.5, CI 1.4-16.6, $P < .01$), diabetes (OR 1.7, CI 1.2-2.6, $P < .01$), and home oxygen therapy (OR 3.7, CI 1.2-9.1, $P < .001$). Chronic kidney disease stage IV or V (OR 3.4, CI 3.3-345, $P = .003$) and diabetes (OR 4.2, CI 1.7-10.5, $P = .005$) were independently associated with mesenteric related death. In that study, the most common causes of late death were cardiac events, followed by cancer, respiratory complications, and mesenteric-related complications. The combined rate of early and late mesenteric-related death was 8% for patients treated by open and 6% for those who underwent endovascular revascularization.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 133

Acute Mesenteric Arterial Disease

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Acute arterial mesenteric ischemia (AMI) is a diagnostically and technically challenging disease process with three distinct subtypes—embolic, thrombo-occlusive, and nonocclusive. The first superior mesenteric artery (SMA) embolectomy for AMI was reported by Klass in 1951, who was the first surgeon to focus on the restoration of arterial blood supply in an attempt to salvage acutely ischemic bowel.[1] Several reports were produced over the next two decades, demonstrated increasing success with SMA thromboembolectomy and thromboendarterectomy[2] for the treatment of acute embolic SMA occlusion. Unfortunately, successful outcomes after the treatment of acute thrombotic SMA occlusion remained elusive, with mortality rates as high as 70% to 90%. Early and liberal use of angiography was championed by Boley[3,4] and Clark[5,6] in the early 1970s. With an aggressive approach, including the use of vasodilators, they demonstrated a reduction in the AMI mortality rate to approximately 50%. Mortality has not been significantly improved upon despite major advances in the subsequent years. Most contemporary reviews still report mortality rates between 60% and 80%.[7,8] However, a review of the Nationwide Inpatient Sample (NIS) data from 1988 to 2006 did show an apparent reduction in in-hospital mortality for AMI after 2000, when endovascular techniques became more commonplace.[9] Overall, the treatment for acute mesenteric arterial occlusions still remains traditionally surgical, with intensive medical support, and the addition of limited interventional options for nonocclusive mesenteric ischemia (NOMI). However, there are recent reports of endovascular or hybrid endovascular-surgical treatments for all forms of AMI that can be applied to the treatment of well-selected patients.

INCIDENCE AND RISK FACTORS

AMI is uncommon, accounting for less than 1 of every 1000 hospital admissions.[10] Females are affected up to three times as frequently as males,[9] typically presenting in their 60s to 70s, and often have a number of medical comorbidities. Clinical risk factors often provide clues to the specific pathophysiology. Patients at risk for an SMA embolus include those with a history of atrial fibrillation/flutter, recent myocardial infarction, congestive heart failure, or peripheral arterial emboli. Alternatively, a history consistent with chronic mesenteric ischemia—such as postprandial abdominal pain, weight loss, and food

Abstract

This chapter focuses on the arterial forms of acute mesenteric ischemia (AMI) - embolus, acute thrombotic occlusion and non-occlusive mesenteric ischemia. Diagnosis of AMI can be challenging but must be recognized early and treated aggressively in order to improve patient survival. Dedicated mesenteric CT angiography is the most important imaging modality to confirm the diagnosis and to plan the best revascularization strategy. There are limited percutaneous endovascular approaches that may apply in highly selected patients but more traditional operative exploration with mesenteric embolectomy or bypass is more often required. Retrograde open mesenteric stenting (ROMS) to revascularize the SMA is effective, quick and avoids the need for bypass conduit in the setting of peritoneal soilage.

Keywords

Mesenteric Ischemia
SMA Embolus / SMA Embolectomy
SMA occlusion / SMA Bypass
Non-Occlusive Mesenteric Ischemia
Visceral dissection
ROMS (Retrograde open mesenteric stent)
Mesenteric CT Angiography
Second look

intolerance—should raise the suspicion of an acute on chronic thrombosis of an SMA stenosis (see Chapter 132). In a national database review, it was found that patients who underwent angioplasty/stenting for AMI had higher rates of comorbidities than those who underwent open surgical repair, including those with hypertension, peripheral vascular disease, coronary artery disease, atrial fibrillation/flutter, and chronic renal failure.[9] In contrast, patients with NOMI are likely to be critically ill, having suffered significant hemodynamic insults in the preceding hours to days. Cardiac surgery and hemodialysis patients are classically at highest risk for NOMI. Overall, the diagnostic algorithm should be tailored to the suspected cause—arterial embolization, arterial thrombosis, or nonocclusive ischemia.

PATHOPHYSIOLOGIC CLASSIFICATION

Arterial Embolism

Arterial embolism is the most common pathophysiology of AMI, accounting for 40% to 50% of cases.[11] Nearly one-third of patients with an SMA embolus have had an antecedent embolic event, most commonly arising from a cardiac source. Atrial tachyarrhythmia, low ejection fraction (congestive heart failure, cardiomyopathy), recent myocardial ischemia or infarction, and ventricular aneurysm are elements that place a patient at risk for a thromboembolic event. There is some speculation, however, that the overall incidence of thromboembolism in patients with atrial fibrillation is declining secondary to better guidelines for and compliance with anticoagulation.[12]

Although less common than a cardiac source, additional consideration should be given to atheroembolic material from a proximal arterial source, such as in instances of a cardiac valvular disease, endocarditis, proximal aneurysm, aortic mural thrombi, or recent catheter-based angiography.[13]

Because of its oblique origin from the visceral aortic segment, the SMA is the most common mesenteric vessel to undergo thromboembolism. Thromboemboli tend to lodge in the proximal SMA, just beyond the first few jejunal branches as the SMA tapers. A minority (15%) may lodge at the SMA origin, but 50% lodge distal to the middle colic artery,[14] creating a classic pattern of ischemia that spares the first portion of the small intestine and the ascending colon (Fig. 133.1). Atheroembolic emboli, in contrast, tend to be smaller and therefore lodge in the more distal mesenteric circulation; as a result, they affect bowel perfusion less often and in more localized areas.

Arterial Thrombosis

Acute arterial thrombosis superimposed on preexisting severe atherosclerotic disease is the next most common cause of AMI, accounting for 25% to 30% of cases.[11,15] Many patients with visceral atherosclerotic disease are asymptomatic prior to a thrombotic event. Autopsy studies have shown that 6% to 10% of people have a greater than 50% stenosis in at least one mesenteric artery; in those with peripheral vascular disease, the incidence may be as high as 27%.[16,17] In these instances, bowel infarction is more insidious in onset because extensive collaterals are able to maintain viability until there is final closure of a critically stenotic vessel or collateral. Consideration must also be given to how vascular collaterals, interrupted by previous abdominal surgery or bowel resection, may affect the region or extent of bowel involvement. Overall, the pattern of infarction, due to the involvement of the SMA from its origin, is more confluent without sparing of the proximal jejunum or right colon.[18,19]

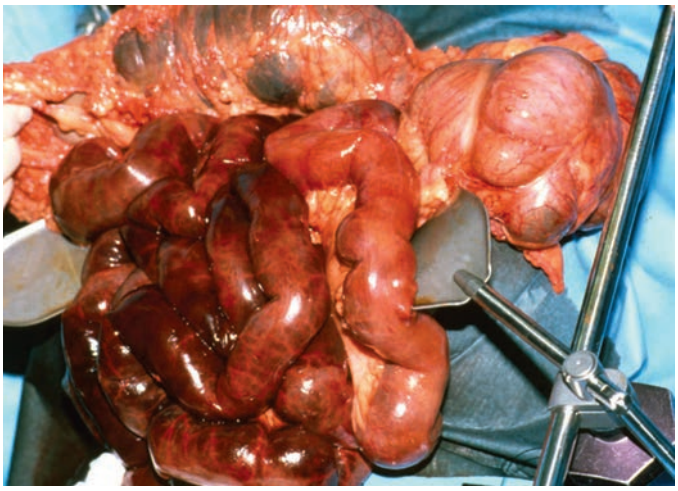

Figure 133.1 Intraoperative photograph of a patient with a superior mesenteric artery embolus. Note the relative sparing of the proximal jejunum and proximal transverse colon. (Courtesy of R. M. Zwolak.)

Acute-on-chronic presentations are not uncommon. Up to 20% of AMI patients have demonstrated a history of chronic mesenteric ischemia, with symptoms of abdominal pain, food avoidance, or weight loss.[17] Even for patients with asymptomatic mesenteric arterial lesions, the natural history of mesenteric occlusive disease is progressive and potentially morbid. In one report, 86% of patients with advanced asymptomatic three-vessel mesenteric atherosclerosis eventually developed abdominal discomfort, frank mesenteric ischemia, or died during a 2.6-year mean follow-up interval.[20] Therefore it is critical to elicit a history of symptoms of chronic mesenteric ischemia to determine if AMI has an acute-on-chronic etiology.

Complications of mesenteric revascularization can also lead to acute mesenteric ischemia. Immediate endovascular failures—including distal embolization, vessel perforation, dissection, stent migration, and thrombosis—result in higher mortality, morbidity, and longer hospital length of stay.[21] In addition, owing to high recurrence rates, both short and long-term follow-up is critical for maintaining the patency of open and especially endovascular revascularized vessels.[9,22,23]

Nonocclusive Mesenteric Ischemia

Mesenteric vasospasm, usually in the distribution of the SMA, is the sine qua non of NOMI. This form of AMI accounts for approximately 20% of presentations and carries the highest mortality rates because of its frequent association with multisystem organ failure.[24,25] Initial descriptions were in postmortem

observations of small intestinal gangrene in patients who had shown no evidence of arterial or venous occlusive disease.[26] Several reports have described this diagnosis in patients with severe cardiac failure, sometimes but not always with concomitant visceral atherosclerosis.[3,14,27-31] These observations formed the basis for the hypothesis that cardiac failure, peripheral hypoxemia, paradoxical splanchnic vasospasm, and reperfusion injury may all contribute to the development of NOMI. Perhaps resulting from excessive sympathetic activity during cardiogenic shock or hypovolemia, the vasospasm represents a homeostatic mechanism that attempts to maintain cardiac and cerebral perfusion at the expense of visceral and peripheral organs. Vasopressin and angiotensin are the likely neurohormonal mediators of this process.[32,33] In the current era, vasoactive medications such as epinephrine, norepinephrine, and vasopressin have also been associated with the development of NOMI.[31-34] Once mesenteric vasospasm is initiated, it may persist even after correction of the initiating event. Although intestinal autoregulation may initially offset reductions in blood flow, the autoregulatory capacity is exceeded after several hours.[30]

The exact mechanism of persistence of vasospasm is unknown, but it plays an important role in the development and maintenance of occlusive and nonocclusive mesenteric ischemia as well as reperfusion phenomena complicating mesenteric revascularization.[35] The degree of ischemia-reperfusion injury appears to be related to the frequency as well as the duration of ischemic episodes. Clark and Gewertz demonstrated that two 15-minute periods of low flow followed by reperfusion resulted in more severe histologic injury than a single 30-minute period of ischemia.[36] NOMI results in an analogous scenario, whereby hypoperfusion may be partial and occasionally repetitive. Episodic reperfusion is thought to prime the ischemic tissue with leukocytes that are attracted to and produce reactive oxygen species.[37] This concept is supported by studies demonstrating attenuation of ischemia-reperfusion injury by reperfusion with leukopenic blood or blockade of endothelial cell surface receptors for leukocyte adherence.[38,39] Reports of NOMI after elective mesenteric revascularization further support reperfusion injury in the pathogenesis of NOMI.[35]

FINAL COMMON PATHWAY OF BOWEL ISCHEMIA

The degree of reduction in blood flow that the bowel can tolerate without permanent cellular damage is remarkable. Only one-fifth of the mesenteric capillaries are open at any given time, and normal oxygen consumption can be maintained with only 20% of maximal blood flow.[40] Proposed mechanisms that result in the preservation of splanchnic tissue perfusion include direct arteriolar smooth muscle relaxation and a metabolic response to adenosine and other metabolites of mucosal ischemia.[41] In addition, the intestinal mucosa is able to extract increasing amounts of oxygen during hypoperfusion[42] to preserve mucosal integrity during periods of metabolic insult. Prolonged ischemia, whatever the pathophysiologic cause, leads to disruption of the intestinal mucosal barrier, primarily through the actions of reactive oxygen metabolites and polymorphonuclear neutrophils.[8] The mucosal surfaces are affected first because the mucosal metabolic demand is much higher than that of the serosa. Clinically, this may present with malabsorption and heme-positive diarrhea before the onset of other symptoms.

DIAGNOSTIC EVALUATION

The pathologic causes of abdominal pain and tenderness in the elderly population fluctuate; all too frequently, AMI is not included in the initial differential diagnosis. Delays in diagnosis and treatment remain the greatest challenge to reducing morbidity and mortality for all forms of AMI.[43] It has been shown that survival decreases from approximately 50% to 30% when the diagnosis of SMA embolism is made more than 24 hours after the onset of symptoms.[14] More recent reviews suggested that only one-third of AMI patients were correctly identified before surgical exploration or death.[44,45] Bowel necrosis is probably the best indicator that there has been a delay in diagnosis; together with advanced patient age, this has been linked to higher mortality rates.[9,43] A high index of suspicion in the setting of a compatible history and physical examination serves as a cornerstone of prompt treatment. Once AMI is suspected, the clinician should quickly move to appropriate testing to confirm the diagnosis, keeping in mind that the best first "test" may be an operation.

There has been a developing paradigm shift in the diagnostic algorithm for AMI. Older models[4,46] advocated early and aggressive use of diagnostic arteriography, although computed tomographic angiography (CTA) has supplanted this when AMI is suspected. With nearly universal 24-hour access to high-resolution CTA, the diagnosis of SMA embolus or thrombotic occlusion can be confirmed, with a simultaneous evaluation of the intestine that may help support or refute the diagnosis. Nevertheless, angiography still plays an important role in the diagnosis and treatment of AMI, especially with the growing number of endovascular treatments or adjuncts now available. Streamlined diagnosis and treatment are now increasingly performed in an operating room environment, allowing general and vascular surgeons to work together to provide definitive treatment while saving precious time.

Clinical Presentation

The signs and symptoms of AMI can easily be mistaken for other, more common intra-abdominal pathologies such as pancreatitis, cholecystitis, appendicitis, diverticulitis, or bowel obstruction. The classic symptomology of "pain of out proportion to exam" for early mesenteric ischemia may be absent in 20% to 25% of cases, depending on the cause and timing of presentation.[24] Until transmural ischemia has developed, there is relatively little peritoneal irritation, thus minimizing tenderness to palpation. For patients who present with SMA embolism, the onset is more abrupt and without a prodrome, progressing rapidly with clinical decline because of the lack of established collateral circulation. Occasionally, there may be a sudden and forceful bowel evacuation shortly after the onset of pain.[1]

In contrast, with SMA thrombosis there can be a more intermediate rate of progression as a result of developed collaterals. The subacute presentation may start weeks or days before the final acute insult that prompts the patient to seek medical attention. Patients may have abdominal pain, distention, diarrhea, acidosis, sepsis, or gastrointestinal bleeding singly or in combination.

NOMI patients can have the most insidious onset, with a protracted clinical course. Because they are already critically ill and frequently in a hospital critical care setting, they are least able to offer any history. The pain associated with NOMI can be variable in location as well as in character and often difficult to ascertain based on sedation related to their critical illness.

Laboratory Evaluation

The most useful laboratory studies for mesenteric ischemia are those that assess fluid status, electrolyte and acid-base imbalances, as well as signs of infection. Due to poor oral intake and fluid sequestration, patients are often acidotic and dehydrated on presentation, reflected by laboratory abnormalities such as hemoconcentration, leukocytosis, and a high anion gap. Lactic acidosis demonstrates severe and sometimes irreversible bowel injury; ideally identification and intervention will have occurred before this develops. High amylase, aspartate aminotransferase, and lactate dehydrogenase can also be observed, yet all are insensitive and nonspecific for the diagnosis of mesenteric ischemia.[47,48] Elevated D-dimer levels have been shown in rat models of AMI as well as in AMI patients who presented within 24 hours of the onset of symptoms, in contrast to patients with inflammatory conditions or bowel obstruction.[44,49] No patient with a D-dimer concentration of 0.3 μg/mL (1.6 nmol/L) or less had acute SMA occlusion, suggesting this as a possible exclusionary test.[44] More recent investigations of urinary and plasma intestinal fatty acid–binding protein (iFABP) levels holds promise as a diagnostic test for AMI.[50-52] First discovered in rodents, the human homologue was found to be elevated in cases of documented bowel infarction.[53,54] Elevated plasma and especially urinary levels of intestinal FABP, liver FABP, and ileal bile acid binding protein (I-BABP) were demonstrated in patients diagnosed with intestinal ischemia. In a small series of 50 consecutive patients suspected of AMI, Acosta[50] correlated intestinal FABP, liver FABP, and I-BABP levels with clinical findings. Of the 50 patients, 22 were confirmed to have AMI; in these patients, all three levels were elevated. Furthermore, urinary I-BABP was elevated specifically when the ileum was involved, allowing for localization. Overall, the test was rapid and potentially useful for early diagnosis of intestinal ischemia.[50] However, it has yet to be routinely used in clinical practice as a diagnostic tool for AMI.

Diagnostic Imaging

Abdominal Plain Radiographs

Abdominal plain radiographs are normal in up to 25% of patients with AMI.[55] However, ileus may be an early finding consistent with mesenteric ischemia, and advanced cases of intestinal ischemia may show evidence of bowel wall edema ("thumbprinting") or pneumatosis. Plain abdominal radiography is most useful in excluding other causes of abdominal pain such as bowel obstruction or perforation.

Duplex Ultrasonography

Duplex ultrasonography accurately identifies high-grade stenoses of the celiac artery and SMA but may miss an SMA embolus that is lodged beyond the proximal segment. It is the noninvasive diagnostic study of choice in the workup of chronic mesenteric ischemia. However, it has little to no role in the diagnosis of AMI and can delay treatment. Many hospitals do not have ready access to such specialized vascular laboratory testing, especially during off hours, and it is highly technologist-dependent. In addition, the presence of intestinal gas—which is the rule in any nonfasting patient and especially someone suspected of having AMI—can easily obscure visualization of the mesenteric vessels. Finally, any abdominal tenderness compromises the study and only adds to the patient's discomfort.

Computed Tomography

The use of ultrafast multidetector CTA (MDCTA) for the evaluation of both acute and chronic mesenteric ischemia is well described.[56-59] The widespread availability of the newest generation of CT scanners has advanced the diagnostic algorithm for AMI, providing a significant amount of information about the central arterial and venous circulations. Accurate timing of contrast injection and fine slices through the upper abdomen usually provide excellent visualization of the celiac artery and SMA (Figs. 133.2A-E and 133.3). Main branches of the celiac artery and SMA are also seen remarkably well using MDCTA because of thinner collimation (0.5-1.5 mm) and overlapping data acquisition. This reduces the amount of volume averaging and creates higher-quality three-dimensional (3D) volume sets for reformatting and interpretation.

CT also excludes or identifies alternate causes of abdominal pain and can assess bowel perfusion to some extent. The timing of intravenous contrast administration is tailored to the specific clinical question but most often is ordered as early arterial phase, as would be any CT angiographic protocol. The use of traditional oral "positive" contrast agents detracts from image quality; instead, a visceral CTA protocol should include the use of a "negative" oral contrast agent such as water (500-750 mL) given immediately before the scan. This prevents image artifact from pooled areas of high opacification within the intestinal tract and also enhances the ability to see bowel wall enhancement (or the lack thereof) in the late arterial phase of the arterial contrast bolus.[55] Biphasic CT, which includes an arterial phase and a delayed phase, can improve sensitivity in order to detect early findings of AMI by allowing time-based visualization of the portal venous system and bowel wall perfusion. Therefore a single scan can identify arterial occlusions as well as findings that support the diagnosis of AMI, such as changes in bowel wall thickness, pneumatosis, and mucosal or bowel wall enhancement patterns (Fig. 133.4A-C). Kirkpatrick and coworkers[60] sought to improve on a previous retrospective report that used single-detector

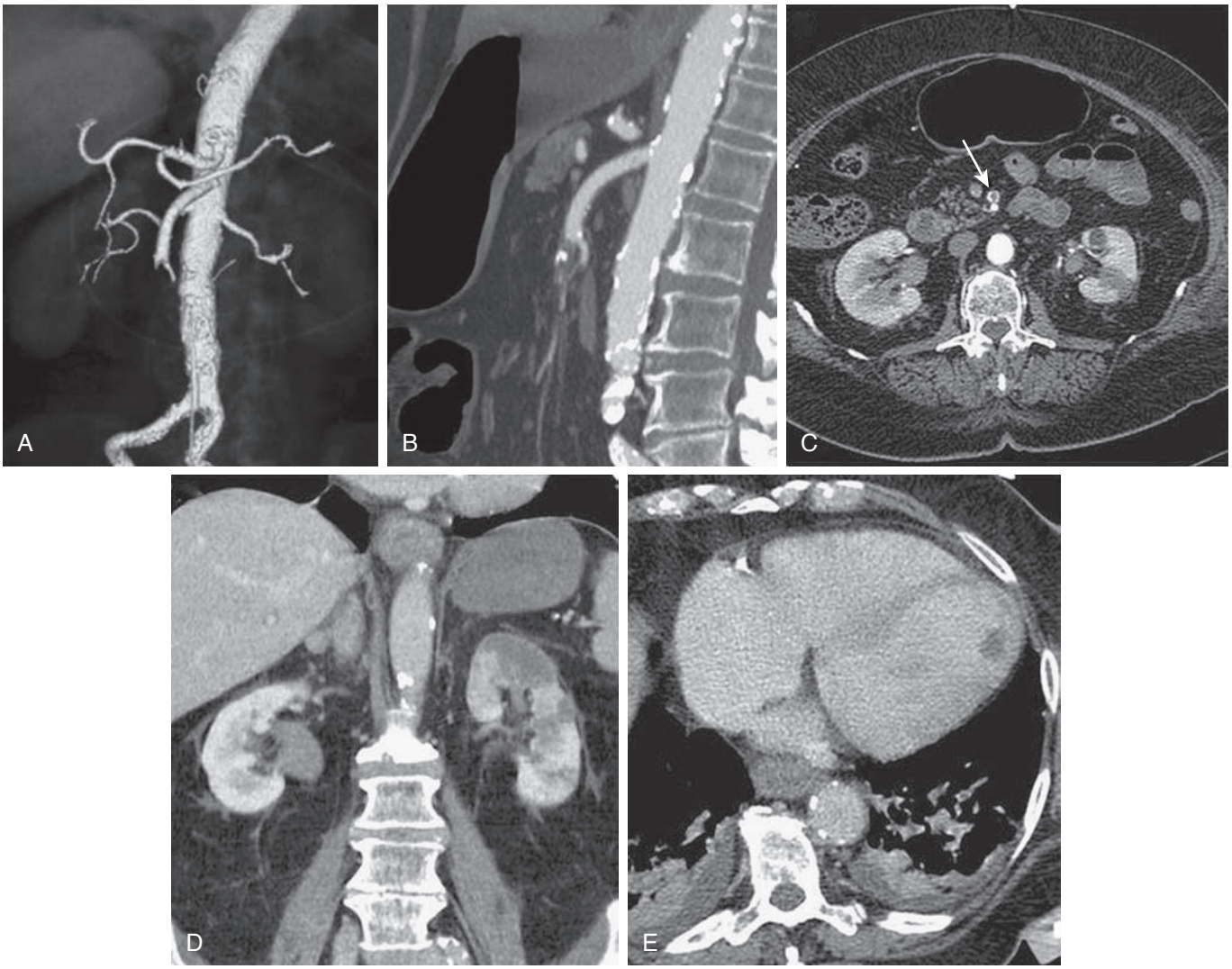

Figure 133.2 (A) Three-dimensional volume rendering of arterial-phase multidetector computed tomographic angiography (MDCTA) shows an abrupt mid-superior mesenteric artery (SMA) occlusion consistent with embolus. (B) Sagittal multiplanar reformat shows the same occlusion. (C) SMA occlusion seen on an axial CTA slice *(arrow)*. (D) Coronal multiplanar reformat reveals left kidney infarction. (E) Transverse portal venous-phase MDCTA depicts thrombus in the left ventricle as the likely embolic source. (From Aschoff AJ, Stuber G, Becker BW, et al. Evaluation of acute mesenteric ischemia: accuracy of biphasic mesenteric multi-detector CT angiography. *Abdom Imaging*. 2009;34:345–357.)

helical CT.[61] A total of 62 patients suspected of having AMI underwent biphasic MDCTA and were evaluated prospectively. As in the previous study, no single CT finding was both sensitive and specific (Table 133.1). However, 26 patients had AMI confirmed at surgical exploration or based on pathologic examination, and all of these had been correctly identified by the interpreting radiologist as having AMI. An additional four scans interpreted as demonstrating AMI turned out to be false-positives, with the ultimate diagnosis of Crohn disease (2), neutropenic enterocolitis (1), and infectious enterocolitis (1). Thus, the initial interpretation had a sensitivity of 100% and a specificity of 89% for the diagnosis of AMI. In the same study, CTA visualization was judged to be satisfactory in all cases up to second-order branches of both the celiac artery and the SMA. Angiography was available in only three patients but correlated well with the CTA findings. In a more recent retrospective chart review using similar MDCTA protocols and even higher-resolution CT, Aschoff and associates were able to duplicate Kirkpatrick's findings in terms of overall accuracy.[62] Again, no one CT finding was perfectly sensitive or specific for AMI, but using a combination of CT criteria (pneumatosis, bowel edema, other solid-organ infarction) to generate an overall impression, these authors were able to achieve positive and negative predictive values of 100% and 96%, respectively.

Arteriography

Although traditional catheter-based arteriography (Fig. 133.5) has been replaced by MDCTA as the definitive diagnostic study for occlusive forms of AMI, patients with strongly suspected NOMI may still benefit from a more traditional angiographic approach as long as there is no immediate need for exploration

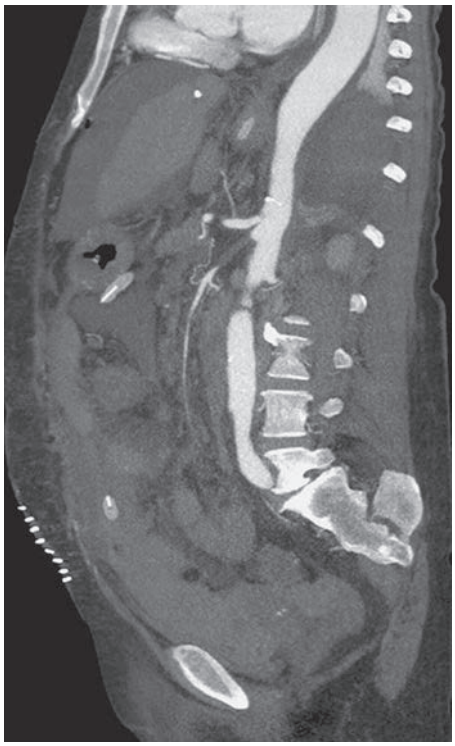

Figure 133.3 Computed tomographic angiography sagittal multiplanar reformat shows an acute thrombotic occlusion of the proximal superior mesenteric artery. Bowel resection was performed 3 days before this image was obtained. The concomitant celiac stenosis suggests an acute-on-chronic presentation of acute mesenteric ischemia. (From Aschoff AJ, Stuber G, Becker BW, et al. Evaluation of acute mesenteric ischemia: accuracy of biphasic mesenteric multi-detector CT angiography. *Abdom Imaging*. 2009;34:345–357.)

based on the overall clinical presentation. Arteriography's role in the therapy of all forms of AMI, however, has been strengthened. It offers several complementary or stand-alone treatment options depending on the specific pathology, including injection of intra-arterial vasodilators,[63] thrombolysis,[64] and angioplasty with or without stenting (see further on).[65] As vascular surgeons become accomplished interventionalists with better intraoperative imaging options, the confirmatory diagnostic arteriogram can be followed immediately by the most appropriate and definitive revascularization option (bypass, endovascular, or hybrid approach) combined with abdominal exploration if required by the patient's clinical presentation.

Magnetic Resonance Angiography

MRI can incorporate both functional and anatomic evaluations of the mesenteric vasculature, which holds promise for the diagnosis of chronic mesenteric ischemia.[66,67] Gadolinium-enhanced magnetic resonance angiography (MRA) is theoretically appealing because it is noninvasive and avoids the risk of allergic reaction and nephrotoxicity associated with iodinated contrast agents. However, MRA is too lengthy a study, requires too much postprocessing, and is not as readily available for the emergency evaluation of these critically ill patients. In addition, the secondary signs of AMI, such as indurated fat or bowel wall thickening, which are routinely delineated by CT, are more difficult to assess with MRA.

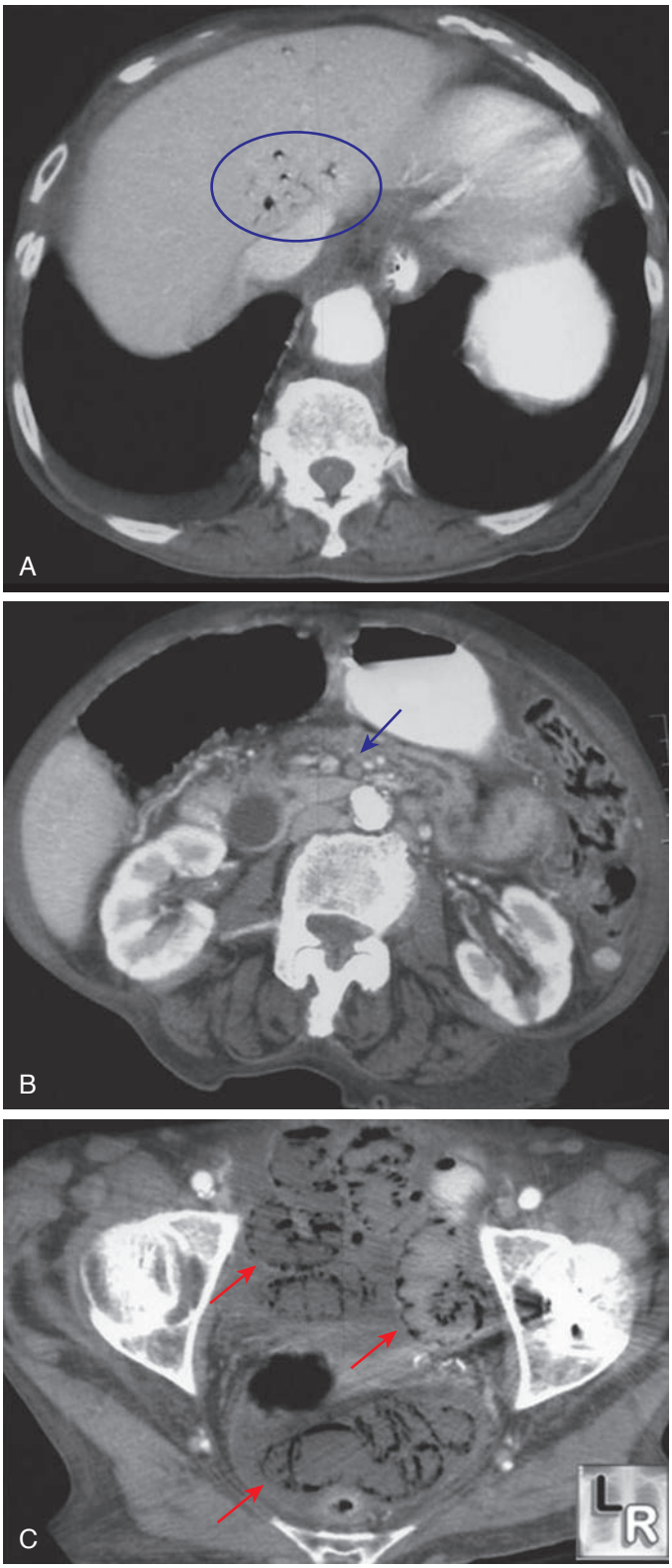

Figure 133.4 (A) Computed tomographic angiography demonstrating hepatic venous air *(circle)*. (B) The superior mesenteric artery is occluded *(arrow)*. (C) There is extensive colonic pneumatosis and ascites *(arrows)*. (From http://www.learningradiology.com/notes/ginotes/mesentericischemiapage.htm.)

TABLE 133.1 Mesenteric CT Angiography Findings of Acute Mesenteric Ischemia

Finding	Patients With AMI ($n = 26$)	Control Group ($n = 36$)	Sensitivity (%)	Specificity (%)
Pneumatosis intestinalis	11	0	42	100
SMA or combined celiac and IMA occlusion[a]	5	0	19	100
Arterial embolism	3	0	12	100
SMA or portal venous gas	3	0	12	100
Focal lack of bowel wall enhancement	11	1	42	97
Free intraperitoneal air	5	2	19	94
Superior mesenteric or portal venous thrombosis	4	2	15	94
Solid organ infarction	4	2	15	94
Bowel obstruction	3	2	12	94
Bowel dilation	17	6	65	83
Mucosal enhancement	12	7	46	81
Bowel wall thickening	22	10	85	72
Mesenteric stranding	23	14	88	61
Ascites	19	24	73	33

[a]Patients with both celiac and IMA occlusion also had evidence of distal disease in the SMA distribution.
AMI, acute mesenteric ischemia; IMA, inferior mesenteric artery; SMA, superior mesenteric artery.
From Kirkpatrick ID, Kroeker MA, Greenberg HM. Biphasic CT with mesenteric CT angiography in the evaluation of acute mesenteric ischemia: initial experience. Radiology. 2003;229:91–98.

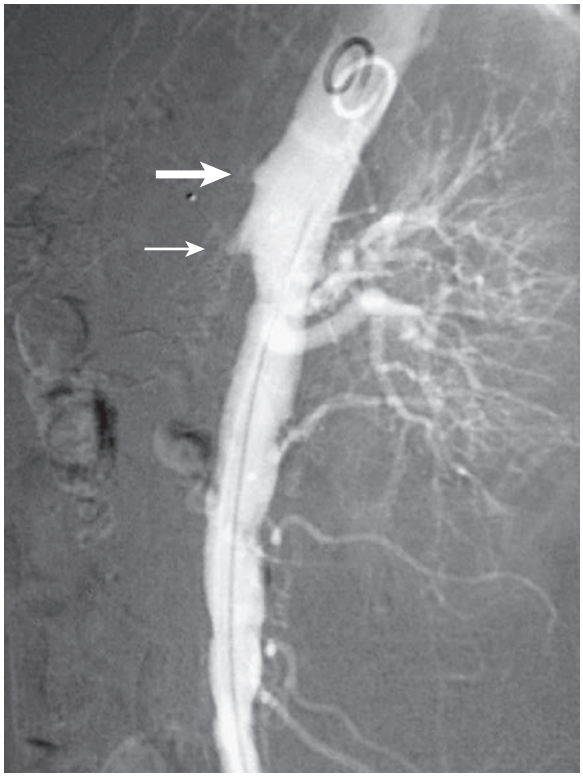

Figure 133.5 Lateral aortogram of a patient with acute mesenteric ischemia due to superior mesenteric artery thrombosis *(small arrow)*. Note the chronic occlusion of the celiac artery *(large arrow)*.

Diagnostic Laparoscopy

Laparoscopy in the setting of AMI has limited ability to assess bowel viability. Serosal color can be difficult to judge, and segmental ischemia can be missed because of the difficulty in "running" the bowel along its entire length and over all surfaces. To increase the sensitivity of diagnostic laparoscopy, some authors have successfully used fluorescein with a laparoscopic ultraviolet light.[68-70] Nevertheless, diagnostic laparoscopy for this indication has not been widely accepted[71] because it may still miss areas of nonviable bowel.

TREATMENT

Initial Resuscitation and Critical Care

Fluid resuscitation of a patient with AMI should begin immediately with isotonic crystalloid solution and then continue with blood, if necessary. Electrolyte imbalances should be monitored and corrected. Invasive monitoring (hourly urine output, continuous central pressure, and arterial pressure monitoring) is indicated to ensure that all parameters are optimized before intravenous contrast administration or operative exploration. Broad-spectrum antibiotics should be given to guard against translocated bacteria and sepsis. If there are no contraindications, intravenous heparin should also be administered to maintain a partial thromboplastin time greater than twice normal.

The presentation of sepsis and organ dysfunction in these patients is common; for the most part, these disorders are managed as they would be in other situations. Vasopressors, however, may worsen ischemia in marginally viable bowel and exacerbate visceral

vasospasm. Before the initiation of any vasopressor, volume resuscitation must be confirmed by the presence of adequate right heart filling pressures. Because of the large and ongoing fluid sequestration in these patients, massive 24-hour crystalloid requirements are not uncommon. When necessary, better vasopressor options include low- to mid-dose dopamine (3-8 μg/kg per minute) and epinephrine (0.05-0.10 μg/kg per minute). Pure alpha-adrenergic agents should be avoided if possible, even after successful revascularization.[8]

Treatment of Nonocclusive Mesenteric Ischemia

NOMI accounts for more than 10% to 20% of cases of acute mesenteric circulatory disorders and leads to extensive irreversible intestinal necrosis. The prognosis is poor despite the absence of organic obstruction in the principal arteries. The primary treatment for NOMI is medical, with extensive critical care support and prompt arteriography. Operative exploration is reserved for signs of peritonitis that suggest the presence of gangrenous bowel that requires resection.

Boley and coworkers reported favorable mortality rates of 40% to 50% with the aggressive use of intra-arterial vasodilators; they suggested that the extent of bowel resection during laparotomy (whatever the cause of ischemia) could be significantly reduced if vasodilation were performed preoperatively.[4] Interventional therapies are targeted at relieving vasospasm using intra-arterial infusions of vasodilator medications (Fig. 133.6A and B). The angiographic appearance of NOMI can be subtle, but four reliable arteriographic criteria have been described for the diagnosis of mesenteric vasospasm: (1) narrowing of the origins of multiple branches of the SMA, (2) alternate dilation and narrowing of the intestinal branches—the "string of sausages" sign (Fig. 133.7), (3) spasm of the mesenteric arcades, and (4) impaired filling of the intramural vessels (Fig. 133.8A and B).[72] Once the angiographic diagnosis of NOMI is made and other causes of acute abdomen are excluded, directed intra-arterial vasodilators are infused and often continued for several days as long as the patient's condition remains stable or until there is improvement. The most common intra-arterial agent used in the majority of reports is the phosphodiesterase inhibitor papaverine[19,73,74] initiated at a dose of 30 to 60 mg/h, but there are reports of prostaglandin analogues[75] that also lead to improvement. Because papaverine is metabolized primarily in the liver, hypotension is uncommon as long as the catheter remains in the SMA; but careful monitoring of the blood pressure, heart rate, and rhythm is appropriate. If a sudden decrease in blood pressure is noted, saline should be substituted for the papaverine infusion and a plain abdominal radiograph should be obtained to confirm the position of the catheter. Finally, heparin sodium is chemically incompatible with papaverine and should not be infused simultaneously through the same catheter. In the case of resolved abdominal symptoms, a second arteriogram is advisable before the cessation of papaverine unless the risk of contrast nephropathy precludes it (see Fig. 133.6B).

Surgical Treatment

Surgical exploration is required for all patients who have evidence of any threatened bowel regardless of the underlying cause. The

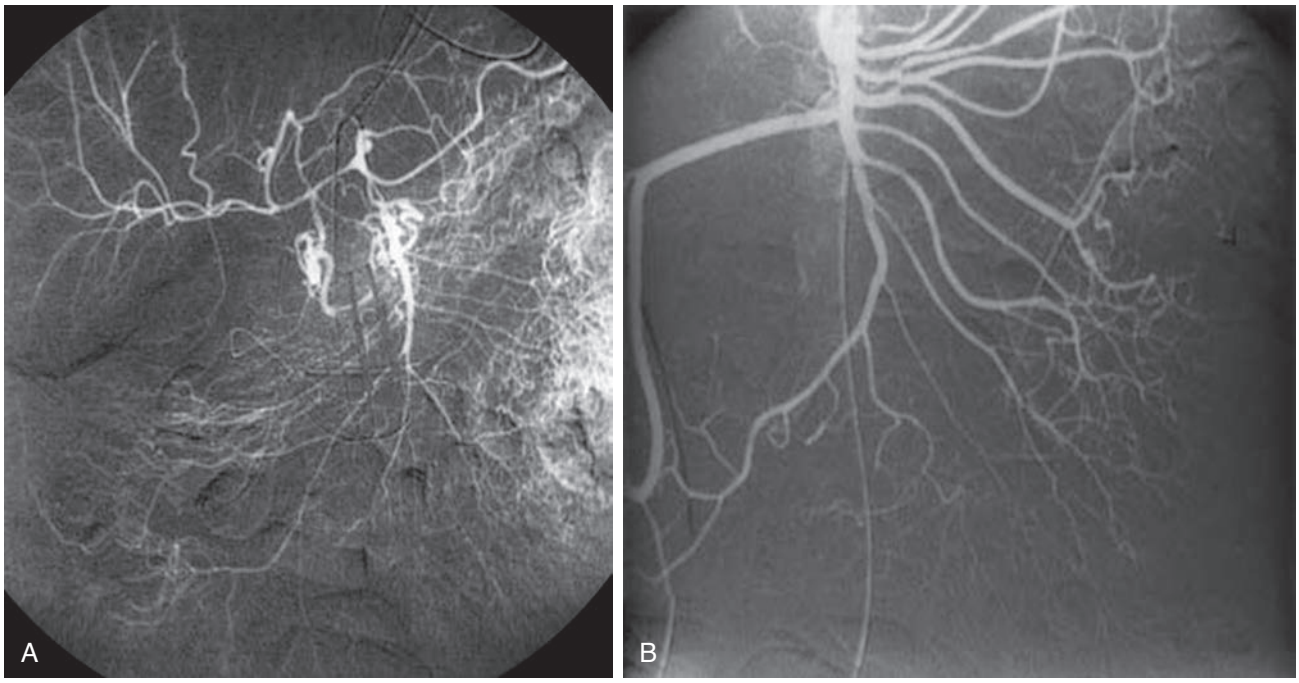

Figure 133.6 Arteriogram With Selective Superior Mesenteric Artery (SMA) Injections. (A) Severe SMA vasospasm with narrowing of all SMA branches. Intramural vessels are not seen owing to severe ischemia. (B) There is significant improvement after several hours of vasodilator administration. (From Trompeter M. Non-occlusive mesenteric ischemia: etiology, diagnosis, and interventional therapy. *Eur Radiol.* 2002;12:1179–1187.)

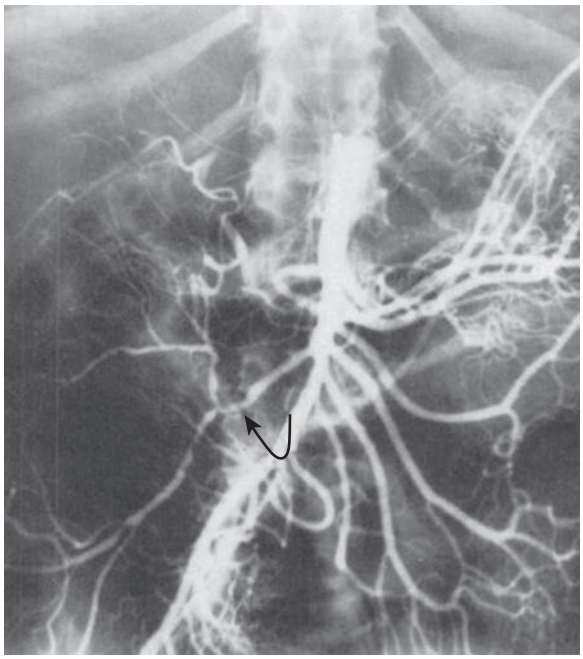

Figure 133.7 Selective superior mesenteric artery arteriogram in a patient with nonocclusive mesenteric ischemia. Note the "string of sausages" appearance of some of the ileocolic branches *(arrow)*. (From Clark RA, Colley DP, Jacobson ED, et al. Superior mesenteric angiography and blood flow measurement following intra-arterial injection of prostaglandin E1. *Radiology*. 1980;134:327–333.)

intraoperative appearance of the bowel can be deceiving. Bowel that is nearing irreversible necrosis can be deceptively normal in appearance; conversely, bowel that appears severely ischemic may be viable after revascularization. Thus the surgeon should in all cases proceed with revascularization before resecting any intestine unless faced with an area of frank necrosis or perforation and peritoneal soilage. In this case, resection of the affected bowel without reanastomosis and with containment of the spillage should be achieved rapidly before revascularization. Only in a very few patients—those who are already in extremis and present with massive bowel necrosis—can revascularization ethically be withheld. Preparation and draping of all patients undergoing laparotomy for presumed AMI should include both lower extremities at least to the knee to allow the harvest of saphenous or femoral vein for bypass.

The abdomen is best explored via a vertical midline incision (Fig. 133.9A and B). There are two variations in the technique for exposing the SMA below the pancreas. Selection between the two is based on the surgeon's level of confidence regarding the need for simple embolectomy or more complex arterial repair with or without bypass. In the case of a confirmed embolus and a more normal-appearing SMA, the artery can be approached anteriorly at the base of the transverse mesocolon without formal mobilization of the fourth portion of the duodenum or ligament of Treitz. If the SMA is diseased or thrombosis is the cause, a more lateral approach to the SMA above the fourth portion of the duodenum is preferred so as to facilitate a retrograde bypass

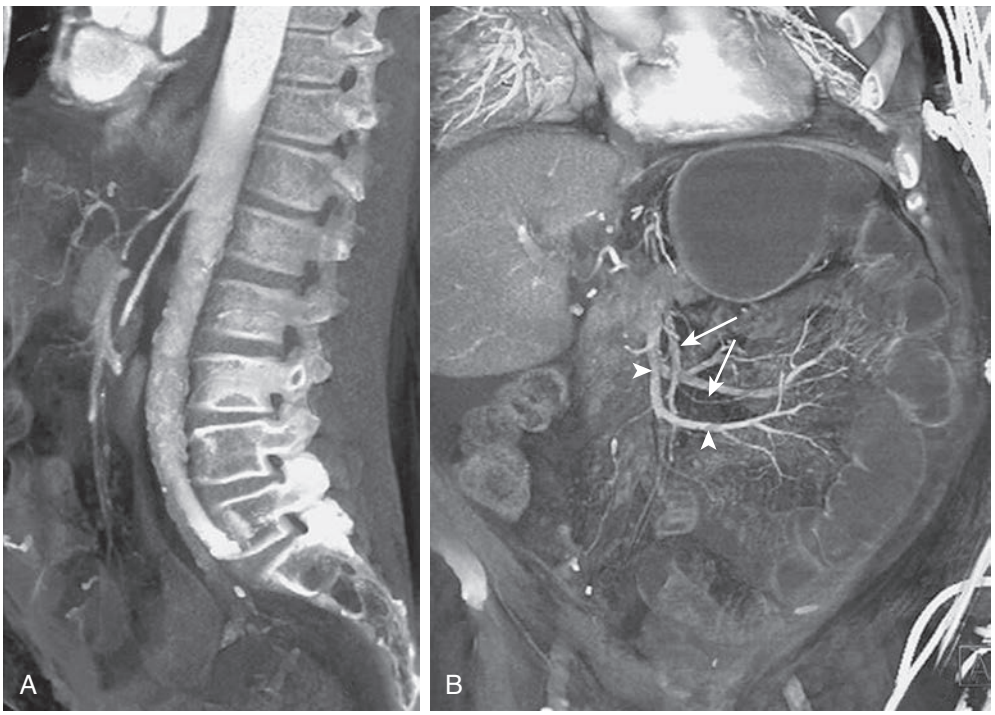

Figure 133.8 Computed Tomographic Angiography Appearance of Nonocclusive Mesenteric Ischemia. (A) Sagittal volume-rendered image shows diffuse narrowing of the main celiac and superior mesenteric arteries. (B) Coronal oblique volume-rendered image of the same patient shows pruning of the superior mesenteric artery branches *(arrows)*. Note the dilated fluid-filled small intestine and the superior mesenteric vein *(arrowheads)*. (From Horton KM, Fishman EK. Multidetector CT angiography in the diagnosis of mesenteric ischemia. *Radiol Clin North Am*. 2007;45:275–288.)

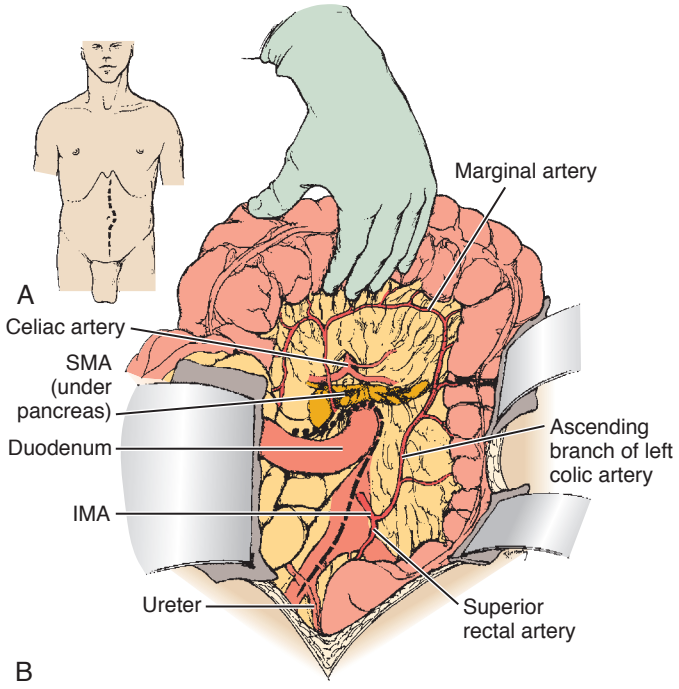

Figure 133.9 (A and B) Operative exposure of the infrapancreatic superior mesenteric artery (SMA). *IMA,* Inferior mesenteric artery. (From Kazmers A. Operative management of acute mesenteric ischemia. *Ann Vasc Surg*. 1998; 12:187–197.)

if necessary (see Figs. 133.9A and B and 133.10A-F) (see Chapter 54).

Superior Mesenteric Artery Embolectomy

Anterior exposure of the SMA for straightforward embolectomy is achieved by elevating the omentum and transverse colon; the small intestine is wrapped in moist laparotomy pads and retracted to the right. A horizontal incision is made in the peritoneum at the base of the transverse mesocolon (see Fig. 133.9B, *dotted line*). Careful dissection in the mesentery initially uncovers venous tributaries of the superior mesenteric vein, autonomic nerve fibers, and small lymphatics that are divided to gain exposure of the SMA. The SMA lies to the left of the superior mesenteric vein and can be fragile. Exposure of the more proximal segments is possible by judicious mobilization of the inferior pancreatic border (exercising caution to minimize trauma to the pancreas), the nearby splenic vein, and its tributaries from the pancreas.

A segment of the proximal SMA between the middle and right colic branches is isolated. Near circumferential dissection is frequently required to isolate and control any of the jejunal branches in this segment. After systemic heparinization, the artery is opened transversely (Fig. 133.11) in a segment of sufficient diameter to allow direct repair. For diminutive vessels, a short longitudinal arteriotomy with patch closure may be considered. The proximal SMA is vented to allow any clot to be expelled without the use of an embolectomy catheter if possible. When necessary, catheter embolectomy is typically performed with a 3- or 4-Fr balloon catheter. With extraction of the embolus, torrential, pulsatile inflow should be expected.

Distally, a smaller embolectomy catheter, typically 2 or 3 Fr, is employed. Great care must be taken to avoid damaging or rupturing the fragile ileocolic and jejunal arteries. Difficulty passing a catheter down multiple small branches adds to the complexity of the distal embolectomy. An alternative or adjunct to balloon embolectomy of the distal mesenteric vessels is for the surgeon to place a hand on either side of the mesentery and "milk" thrombotic material out of the vessels. After all macroscopic clot is cleared, consideration can also be given to the administration of a small one-time dose of a thrombolytic agent (recombinant tissue plasminogen activator or urokinase) into the distal vessels. When all thrombus has been removed, the arteriotomy is closed primarily with interrupted sutures or with a vein patch and flow is reestablished.

Superior Mesenteric Artery Bypass

As mentioned previously, when bypass is considered, the lateral portion of the SMA is exposed, rather than the more limited exposure provided by a strictly anterior approach. The peritoneum is opened lateral to the duodenum, down over the aorta, and onto the left or right common iliac artery (see Fig. 133.9B, *dashed line*). Several combinations of graft orientation and conduit are available. The decision is influenced largely by the suitability of potential inflow vessels for a proximal anastomosis and by the presence or absence of peritoneal soilage, respectively. In the emergent setting, a single bypass to the SMA is all that is required. The preference for two-vessel revascularization,[76] which most surgeons espouse in the performance of elective bypass for chronic symptoms, does not apply.

Graft orientation is influenced mainly by the degree of atherosclerosis and occlusive disease present in the inflow vessels and by the overall lie of the graft. Given the choice, most surgeons prefer a retrograde graft orientation with its origin from the right common iliac artery in a "lazy C" configuration (Fig. 133.12A-C). This avoids any aortic clamping and usually provides a good lie to prevent kinking. Second-choice inflow sources for retrograde bypasses involve similar lazy-C grafts from the left iliac artery or distal infrarenal aorta. With any of these configurations the graft lie tends to be improved by increasing the graft length slightly and performing an end-to-end graft-to-SMA anastomosis, as pictured in Fig. 133.10C to E. Alternatively, a very short retrograde bypass using a larger-diameter graft (8-10 mm) can be configured from the immediately infrarenal aorta (Fig. 133.13), but the potential for kinking with shorter grafts can be more difficult to anticipate until all the retractors are removed. When distal inflow sources are unclampable, heavily diseased, or aneurysmal, an antegrade bypass can be considered. Advantages of the antegrade bypass include the fact that the supraceliac aorta is often relatively free of disease and that the straighter graft orientation is less prone to kinking. Dissection of the supraceliac aorta is technically more demanding, however; it requires more time and adds a hemodynamically and physiologically stressful aortic cross-clamp if a partially occluding clamp is not possible.

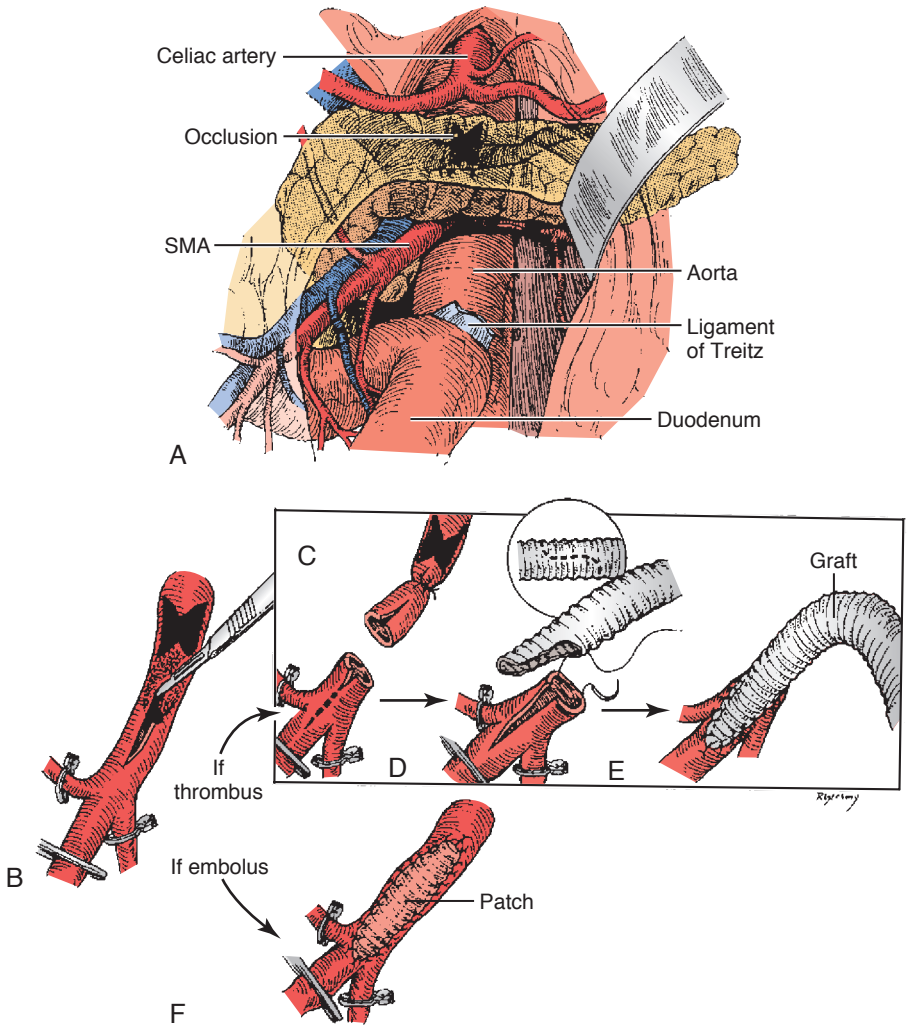

Figure 133.10 (A) Operative exposure and preparation of the superior mesenteric artery (SMA) for bypass or patch. (B) Linear arteriotomy. (C-E) Creation of a beveled, end-to-end anastomosis. (F) Patch closure of the SMA. (From Kazmers A. Operative management of acute mesenteric ischemia. *Ann Vasc Surg*. 1998;12:187–197.)

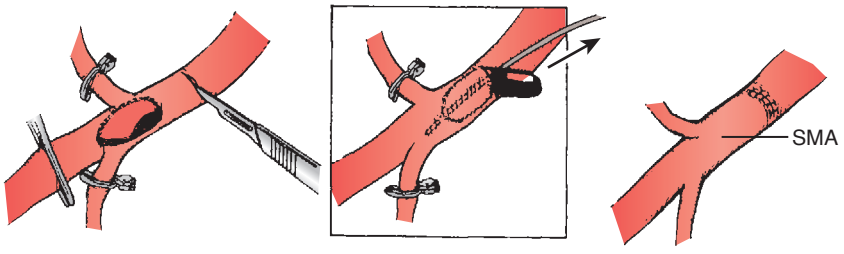

Figure 133.11 Traditional transverse arteriotomy for superior mesenteric artery (SMA) embolectomy. (From Kazmers A. Operative management of acute mesenteric ischemia. *Ann Vasc Surg*. 1998;12:187–197.)

Synthetic bypass grafts of 6- to 8-mm Dacron or externally supported polytetrafluoroethylene are preferred because of the better size match, ease of handling, availability, kink resistance, and general perception that long-term patency is better. The superior patency of prosthetic mesenteric bypasses, however, is not well documented. Therefore the choice of conduit is heavily influenced by the degree of abdominal contamination and the perceived risk of subsequent graft infection. The actual rate of mesenteric graft infection is not known with certainty, but when present, it is potentially catastrophic and likely to involve virulent organisms. Therefore rifampin-soaked Dacron could be used. However, if good-quality vein is available, it is preferred in the presence of significant peritoneal soilage. Great saphenous vein and thigh femoral vein are the primary options. Modrall and colleagues have reported that symptomatic recurrences were less common in patients bypassed with femoral vein compared with great saphenous vein conduit.[77] In practice, however, the additional time and expertise required to harvest a deep leg vein is too much to consider in such critically ill patients. Great caution must be used in fashioning vein grafts because their smaller diameter and thin-walled nature make them more prone to kinking and external compression than synthetic grafts. When

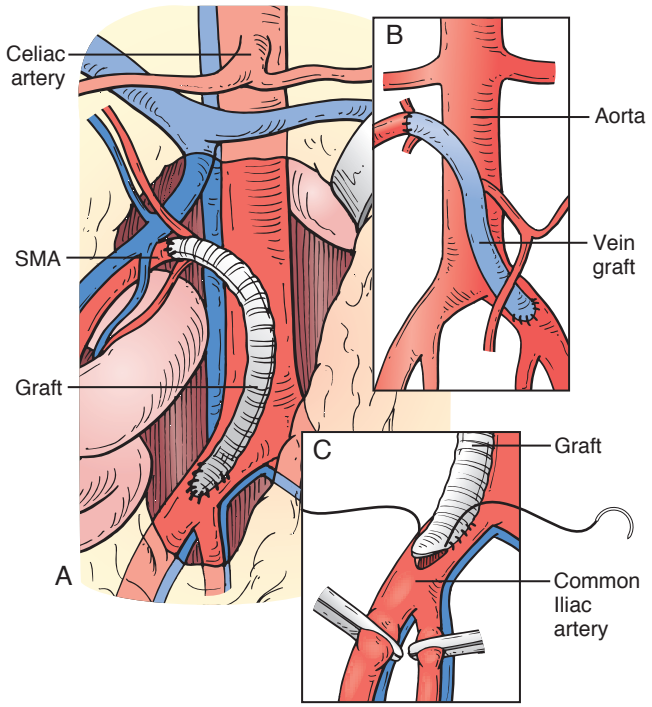

Figure 133.12 Optimal Orientation for Retrograde Superior Mesenteric Artery (SMA) Bypass. (A) Prosthetic. (B) Vein. (C) Proximal iliac graft anastomosis. (From Kazmers A. Operative management of acute mesenteric ischemia. *Ann Vasc Surg*. 1998;12:187–197.)

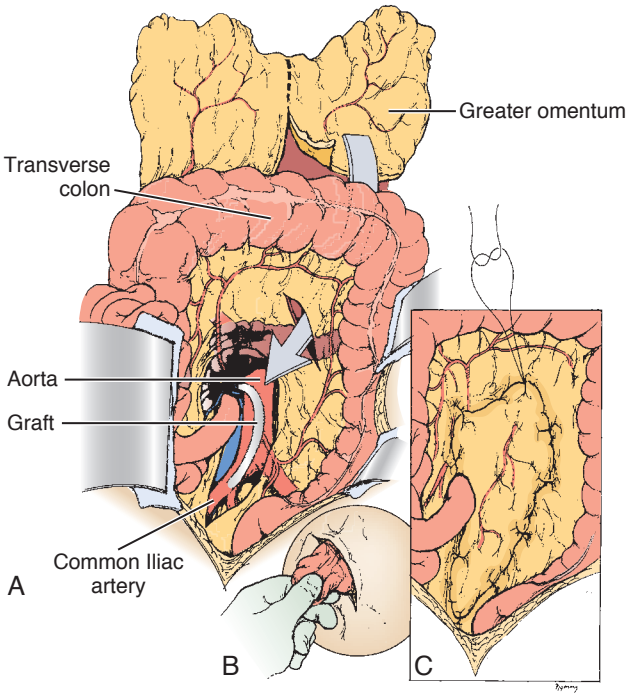

Figure 133.14 (A-C) Technique for omental flap coverage of a retrograde superior mesenteric artery bypass. (From Kazmers A. Operative management of acute mesenteric ischemia. *Ann Vasc Surg*. 1998;12:187–197.)

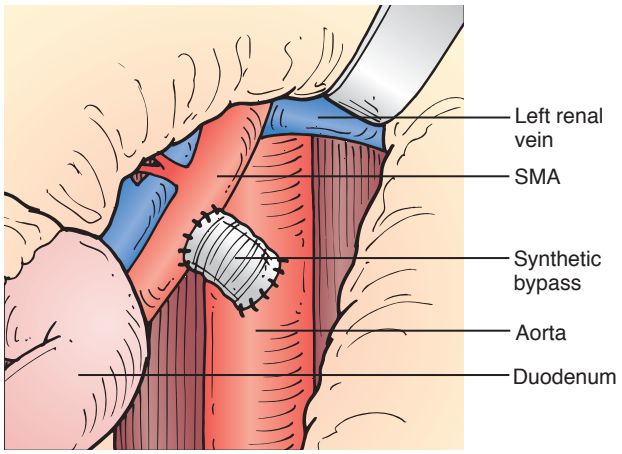

Figure 133.13 Short retrograde aorta–superior mesenteric artery (SMA) bypass. (From Valentine RJ, Wind GG. *Anatomic Exposures in Vascular Surgery.* 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2003:281.)

the use of a prosthetic graft is unavoidable, Kazmers and colleagues illustrate a useful technique to provide coverage of a retrograde bypass by bringing an omental flap through the transverse mesocolon (Fig. 133.14A-C).[78]

Assessment of Bowel Viability

After revascularization has been accomplished, the viability of the bowel must be reassessed. If possible, before making a decision about viability, 20 to 30 minutes of reperfusion time should be permitted while retractors are being repositioned.[78] The initial clinical evaluation of the bowel consists of assessment for visible and palpable pulsations in the mesenteric arcade, normal color and appearance of the bowel serosa, peristalsis, and bleeding from cut surfaces. Each of these is subjective and prone to inaccuracy; with the use of clinical criteria alone, bowel viability can be successfully determined with a sensitivity of only 82% and a specificity of 91%.[79]

Wright and Hobson reported that absence of pulsatile signals on the antimesenteric border of the intestine as detected with a continuous wave 9- to 10-MHz Doppler ultrasound probe implies a nonviable segment.[80] The clinical practicality of this technique combined with surgical judgment has been demonstrated in multiple studies.[79,81,82] As a stand-alone method of determining intestinal viability, however, Doppler assessment has limitations because it may miss weak signals in small vasoconstricted vessels in otherwise viable bowel.[83] Other adjunctive methods of assessing bowel viability have been proposed. Highly accurate quantification of perfusion is possible using fluorescein and a perfusion fluorometer[84] or a laser Doppler flowmeter,[85] but special equipment requirements and technical considerations make this less practical for routine clinical use. Whitehill and associates found that Doppler ultrasound evaluation, photoplethysmography, and fluorescein injection may be too sensitive in some cases for an accurate determination of bowel viability, yielding false-positive results by detecting levels of flow below those needed to sustain tissue viability.[86]

Ultimately, accurate determination of intestinal viability is the product of clinical judgment and timely reevaluation, with the goal of preserving as much bowel length as possible. The option of deferring extensive bowel resection and reanastomosis underscores the fundamental importance of a mandatory second-look procedure.

Endovascular Treatment

Superior Mesenteric Artery Embolization

As acute arterial occlusion caused by thromboembolization rapidly progresses to bowel necrosis and the incipient downward spiral that frequently results in death, restoration of flow must be accomplished within a few hours. Based on this, one would suspect that thrombolysis takes too long to achieve timely revascularization. Nevertheless, there are increasing numbers of reports of successful percutaneous endovascular procedures using mechanical and chemical thrombectomies.[87-97] However, these reports should be interpreted with caution, as it is difficult to determine technical failure rates from single-center case reports, which by their nature focus on positive results.

In the case of an SMA embolus, if endovascular lysis was more broadly applied, the failure rate would not compare favorably with open mesenteric thrombectomy. Wang and coworkers have offered a retrospective report of 7 patients with SMA emboli who were treated with catheter-based thrombolysis, which was successful in only 4 cases.[98] Despite a shorter time to diagnosis and initiation of treatment in the lysis group compared with a similar cohort of 9 surgically treated patients, there was no survival difference. However, even when technically successful, percutaneous catheter thrombectomy and certainly chemical thrombolysis can be very time-consuming compared with a straightforward open embolectomy.

Raupach et al. recently reported a retrospective single-center 12-year experience of 37 patients who all underwent primary endovascular therapy for acute SMA embolism with subsequent on-demand laparotomy (73%). With a 92% technical success rate, they reported that 40% required bowel resection and there was an overall 27% in-hospital mortality.[89]

A review of 20 case reports and 7 small series published over a 47-year span for a total of 48 patients[10] reported that only 33% of patients demonstrated total or near-total arteriographic occlusion of the SMA before treatment. Technical resolution of thrombus was achieved in 43 patients, but 18 still required operative exploration for bowel resection, with only one surgical embolectomy required. This review does not give any credence to the use of percutaneous thrombolysis as an efficacious or even safe mode of therapy for acute SMA embolism. It only serves to magnify the enormous publication bias inherent in the literature on this topic.

Another shortcoming of a purely endovascular approach to SMA embolism is the lack of a built-in assessment of bowel viability, which is routine with open embolectomy. Patient mortality is closely associated with bowel necrosis, and when resection is necessary, it cannot be delayed. Therefore a significant weakness of a less invasive intervention is that there is no direct intestinal evaluation. In avoiding abdominal exploration, close monitoring of the patient's overall clinical condition, laboratory markers, and occasionally laparoscopy are substituted. However, these modalities are known to be unreliable.[71]

Superior Mesenteric Artery Thrombosis

Endovascular treatment for mesenteric ischemia has been well described for subacute or chronic presentations, especially in patients at high operative risk or as a bridge to elective surgical bypass after the acute illness has resolved.[99-102] However, it not generally applied to patients with AMI who require emergent revascularization with the potential need for bowel resection. Terminal thrombosis of an atherosclerotic SMA is perhaps the most challenging AMI cohort to treat in endovascular fashion. As described previously, operative bypass to the SMA is traditionally required owing to the extent of disease. A less invasive option for SMA revascularization in these critically ill patients has appeal. But in order to be successful, a percutaneous recanalization is needed of a long-segment occlusion that, unlike with embolic presentations, typically occupies the origin and initial 3 to 6 cm of the SMA.

Therefore endovascular treatments necessitate advanced endovascular skills and, even in the most experienced hands, can take substantial time, which might actually delay revascularization. Nevertheless, a few case reports of percutaneous interventional treatment for AMI have been published.[90-93,95,103] Widespread experience is lacking, and this approach has shortcomings similar to those discussed for the endovascular treatment of SMA embolism. Indeed, our own experience with percutaneous stenting in acutely ischemic patients has been very disappointing in terms of both technical success and patient outcome.[104] This experience led directly to a more efficacious hybrid technique. In our practice, we now reserve percutaneous mesenteric stenting for patients with chronic or subacute presentations who do not require a detailed assessment of bowel viability.

Hybrid Procedure: Retrograde Open Mesenteric Stenting

Wyers et al. have reported a hybrid open-interventional approach for the treatment of acute atherosclerotic SMA thrombosis that involves an efficient, less invasive mesenteric revascularization without compromising important general surgical principles.[104] In fact, the general surgical principles of thorough abdominal exploration, sepsis control, and a low threshold for second-look operations must be honored in order to increase the chances of a favorable outcome. Similar to a technique in an earlier case report by Milner and associates,[105] the authors described retrograde open mesenteric stenting (ROMS) of the SMA in 6 patients. In this ROMS approach, the visceral peritoneum is incised horizontally or longitudinally at the base of the transverse mesocolon, the SMA is controlled, and a local thromboendarterectomy of the SMA is performed if necessary (Fig. 133.15A and B). Placement of a patch angioplasty then facilitates retrograde cannulation of the SMA with a long flexible sheath directed toward the aorta (Fig. 133.16). Because of the superior pushability with sheath access so close to the obstruction, technical success was 100%, even in the five patients who had previous unsuccessful attempts to cross the SMA from a percutaneous antegrade approach. Often, more than one balloon-expandable stent is required to fully treat these SMA lesions, which are typically 3 cm long or longer (Fig. 133.17A-C).

Although derived from a small series with no statistically significant results, the ROMS outcomes were promising. The

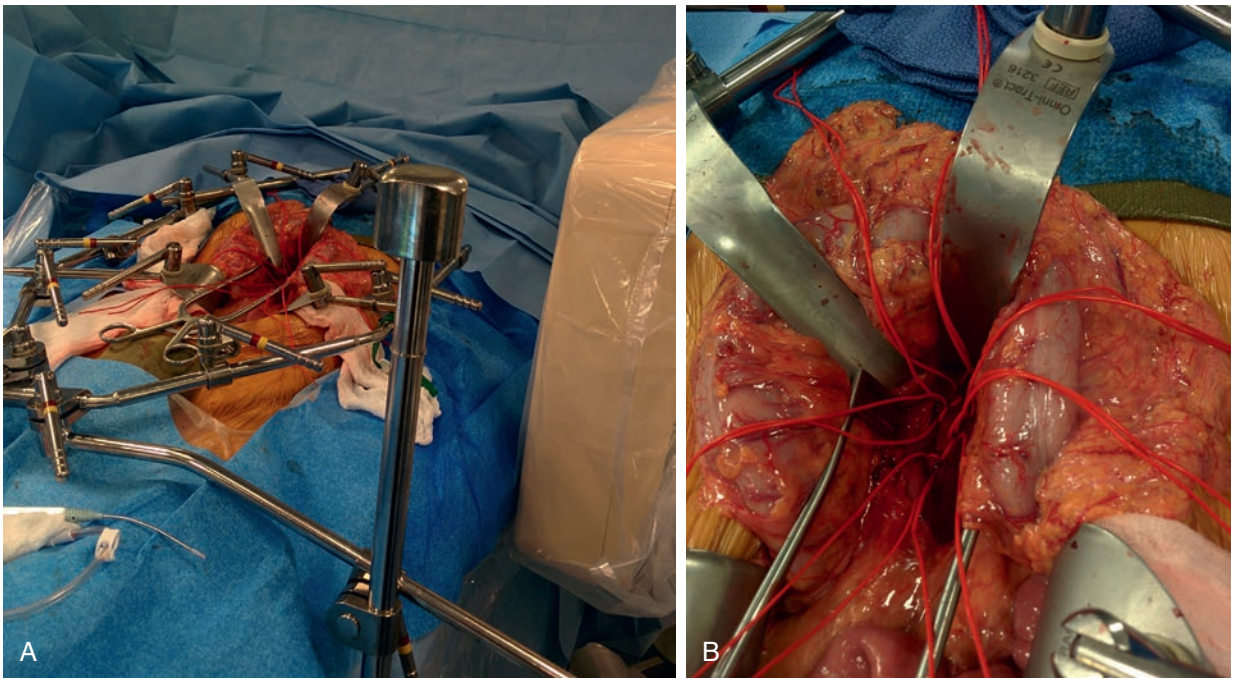

Figure 133.15 (A and B) Operative exposure of a retrograde open mesenteric artery stenting with Omni retractor and vessel loop control, lateral fluoroscopy imaging in hybrid operating room. (Courtesy Mark C. Wyers, MD).

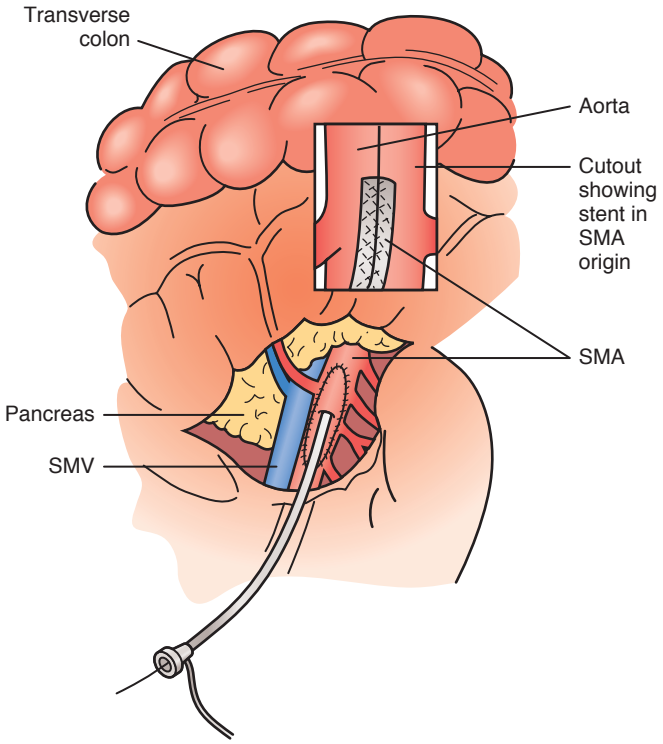

Figure 133.16 Retrograde open mesenteric stenting with a long 6-Fr sheath placed through the patched superior mesenteric artery (SMA). The *inset* illustrates a stent deployed in the proximal SMA. *SMV,* Superior mesenteric vein.

ROMS group suffered only 17% in-hospital mortality, compared with 80% among five patients treated with conventional mesenteric bypass. Recurrent stenosis after ROMS, as with all forms of mesenteric stenting,[65,100] occurs frequently and relatively early; therefore, close duplex surveillance for the first month and every 3 months thereafter is recommended. Most patients with recurrent stenosis can be retreated with a percutaneous approach as outpatients. Many of these patients remain poor operative candidates and have limited life expectancies because of comorbidities.[106] In this situation, even repeated SMA dilations are a viable, safe option. For patients who make a good recovery and are nutritionally sound, a more durable operative bypass may be considered.[99] ROMS during emergent laparotomy for AMI is a promising technique and an attractive alternative to emergent surgical bypass.[107]

OTHER CONSIDERATIONS

Spontaneous Visceral Dissection

Spontaneous visceral dissection is a rare vascular pathology. Usually patients present with acute abdominal pain, but there are reports of intestinal angina with weight loss from a chronic dissection, causing lumen compromise. However, with the increasing popularity of CT scans for the investigating abdominal pain combined with technical advances in MDCTA, spontaneous isolated celiac and SMA dissection (SIDSMA) has been reported more frequently in recent years as an incidental finding. Most commonly identified by CT, it can be diagnosed by duplex ultrasound, MRI, and angiography.[108,109] Reported risk factors include hypertension, male gender, atherosclerosis, pregnancy, connective tissue disorders, fibromuscular dysplasia, vasculitis, and trauma; however, a definitive pathologic cause is rarely identified.[110] Spontaneous dissections of the SMA are associated with a broad spectrum of clinical pictures, from asymptomatic incidental findings to acute catastrophic bowel ischemia/infarction or rupture of an aneurysmal SMA. Treatment options

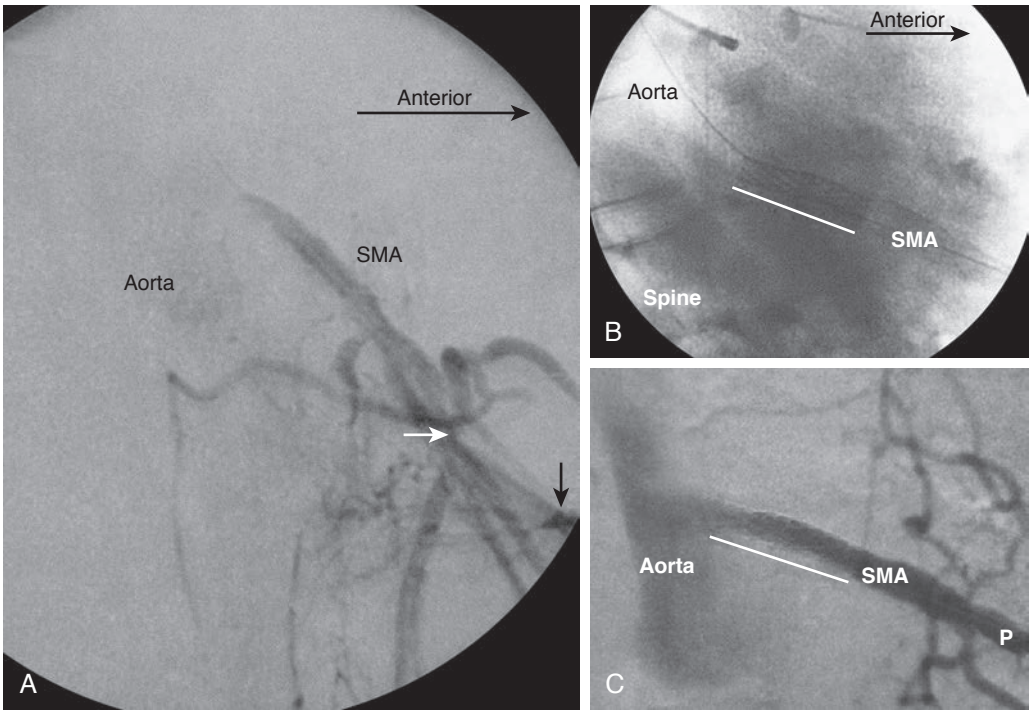

Figure 133.17 Retrograde Open Mesenteric Stenting. (A) Intraoperative arteriogram during retrograde superior mesenteric artery (SMA) injection. Note the proximity of the sheath's point of entry *(black arrow)* and the sheath's tip *(white arrow)* to the proximal SMA occlusion. There is no reflux of contrast material into the aorta. (B) Intraoperative lateral fluoroscopic image of two stents (underscored by a *white line*) deployed in the SMA origin with the 0.018-in wire still in place. Note the lumbar vertebral bodies to the left. (C) Completion retrograde arteriogram with free reflux of contrast material into the aorta and no residual angiographic stenosis. *P,* Approximate location of SMA patch angioplasty. (From Wyers MC, Powell RJ, Nolan BW, Cronenwett JL. Retrograde mesenteric stenting during laparotomy for acute occlusive mesenteric ischemia. *J Vasc Surg*. 2007;45:269–275.)

range from conservative management, anticoagulation, endovascular stenting, and open surgical repair, although no consensus guidelines exist for management.[111]

Many studies suggest operative intervention for all symptomatic patients, although there are numerous case reports describing successful nonoperative management for both symptomatic and asymptomatic patients.[111,112] Gobble et al.[113] identified 106 articles on SIDSMA and found only 55% (31 of 56) success with expectant management (bowel rest and observation), with an almost 50% mortality identified in those who failed expectant management. This extensive literature search identified the average age at presentation as 54 years, four times more prevalent in men, with approximately half of the patients presenting with aneurysmal degeneration of the SMA. Anticoagulation therapy was successful in 65% of cases (15 of 23), with 7 of the 8 failures salvaged with surgery. Rescue stenting and primary surgical treatment had a 100% success rate, and primary endovascular stenting had 80% success (4 of 5), with rescue stent success for the one case of delayed aneurysmal degeneration. The authors proposed treating symptomatic patients with primary endovascular stenting, the use of anticoagulation for failed stenting, and open surgery for unsuccessful anticoagulation (Fig. 133.18).

Similarly, Min et al.[111] demonstrated only 50% success with expectant management without anticoagulation or antiplatelet therapy, with two failures successfully rescued with endovascular stenting, and 100% successful primary endovascular stenting. The authors recommended endovascular treatment for aneurysms greater than 2.0 cm, concern for bowel ischemia, stenosis greater than 80%, and patients with recurrent or nonresolving abdominal pain.[111]

Finally, a recent retrospective review from our institution, one of the largest patient cohorts in the literature on spontaneous visceral dissection, suggests an overall relatively benign clinical course despite persistent CT findings and supports a nonoperative approach with a short course or anticoagulation followed by lifelong antiplatelet therapy (aspirin) and surveillance for both symptomatic and asymptomatic patients without evidence of mesenteric ischemia or aneurysm (>2.0 cm).[112]

Second-Look Surgery

Even after reperfusion and careful assessment, bowel viability cannot be determined with certainty at the time of initial exploration. The frequency of bowel resection is routinely higher during second-look surgery (53%) compared with the initial exploration and revascularization procedure (31%).[43] The decision to perform this second-look surgery is made at the time of initial operation. This plan is essentially inviolate regardless of the clinical status of the patient. Typically, at the conclusion of the initial procedure, the surgeon leaves transected ends of the intestine stapled shut without reanastomosis. Likewise, if bowel edema is significant,

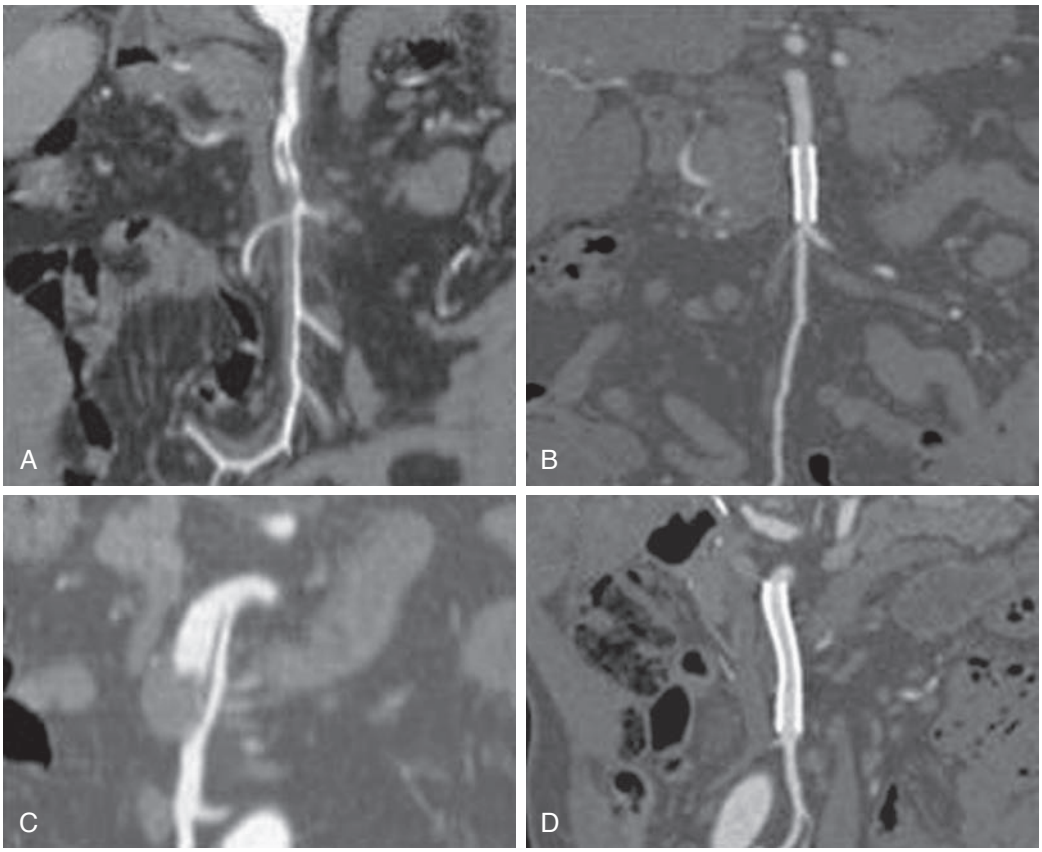

Figure 133.18 Reconstructed Computed Tomography Angiography (CTA) Findings Indicated for Primary Endovascular Stenting. (A) Severe compression of the true lumen and (B) a patent superior mesenteric artery stent and complete obliteration of the false lumen at 60-month follow-up CTA in patient no. 12. (C) Large dissecting aneurysm (20.0 mm in diameter) and (D) near complete disappearance of the aneurysm at 36-month follow-up CT in patient no. 13. (From Min SI, Yoon KC, Min SK, et al. Current strategy for the treatment of symptomatic spontaneous isolated dissection of superior mesenteric artery. *J Vasc Surg*. 2011;54(2):461–466.)

the abdominal fascia can be left open in anticipation of a return to the operating room within the next 48 hours. Certainly if the patient's clinical condition deteriorates at any point, reoperation is immediate. This strategy allows the preservation of as much bowel as possible, resecting only areas of bowel that are clearly nonviable at each procedure. The patient is returned to the operating room 12 to 48 hours later, and the abdomen is reexplored. By this time, the viability of the bowel has usually declared itself, but occasionally a third look is required. This mandatory return protects the patient from ongoing bowel necrosis before irreversible physiologic changes develop and before perforation, which would risk further sepsis, abscess, or graft infection. Mesenteric blood flow is reassessed, and the bowel anastomoses are performed if the condition of the bowel is satisfactory.

Intraoperative Vasodilators

Splanchnic vasospasm may persist for variable periods of time, causing continued bowel ischemia after a successful revascularization.[14,114] Low flow after ischemia can also result from relative hypovolemia, myocardial depression, and sepsis. To treat local vasospasm in the mesenteric arcades, papaverine can be administered selectively in the SMA. Alternatively, intravenous glucagon administration increases cardiac output and flow to all layers of the small and large intestine as well as the liver while inhibiting gastrointestinal motility and secretory function. This has been shown to improve survival in an animal model[115,116] but has not been tested extensively in humans. Glucagon administration should be coupled with additional volume resuscitation to avoid vasodilation-mediated hypotension.

Duplex Follow-Up

Visceral duplex remains technologist-dependent and may not be universally available. However, duplex ultrasound appears to be the most reasonable, cost-effective way to obtain objective data for clinical decision making after various forms of mesenteric revascularization. Large series reports of its use after mesenteric bypass have been lacking. However, Liem and coworkers characterized duplex-derived flow velocities in mesenteric artery bypass grafts for the first time.[117] Postprandial scans demonstrated higher midgraft flows in smaller-diameter (6 mm) grafts and saphenous vein grafts compared with larger-diameter (7 mm) grafts without being affected by graft orientation or inflow source. No duplex scan characteristics were found to predict graft thrombosis.

Restenosis is common and happens early after mesenteric stenting,[65,100] including ROMS patients. Therefore frequent duplex surveillance is required to judge the need for reintervention. Although the published data on Doppler ultrasound of native (unstented) mesenteric arteries is very good,[118-120] the literature that focuses on stented mesenteric vessels is limited. Mesenteric duplex following interventional visceral artery therapy is promising but still empiric, based on an anticipated high rate of restenosis. Absolute velocity thresholds that indicate the need for prompt reintervention have yet to be identified. However, the traditional velocity criteria for native vessels seem to provide reasonably accurate information to guide clinical decision making.

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Excellent demonstration of hybrid approach to AMI.

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134 CHAPTER

Mesenteric Arterial Dissection

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Spontaneous isolated arterial dissection within the splanchnic circulation without associated aortic dissection is a rare entity, but is being reported with increasing frequency. This most likely reflects improved imaging modalities (particularly abdominal computed tomography [CT]) and increasing awareness of this condition rather than an increasing prevalence. Spontaneous isolated superior mesenteric artery dissection (SISMAD) was first reported by Bauersfeld in 1947.[1] There are currently greater than 622 cases of SISMAD reported in the literature as well as more than 100 cases of spontaneous isolated celiac artery dissection (SICAD) and an assortment of other splanchnic artery dissections.[2,3] Due to the low prevalence of spontaneous isolated visceral artery dissection and the variety of clinical presentations, there is a lack of consensus regarding treatment guidelines.[4] The goal of this chapter is to review the current literature on visceral dissection and help establish the best treatment guidelines for the contemporary vascular surgeon.

INCIDENCE

Spontaneous isolated dissection of the splanchnic arteries is a rare condition. The superior mesenteric artery (SMA) is the most common visceral artery affected, followed by the celiac artery.[5,6] In 1959, Foord reported an incidence 0.06% SISMAD from a cohort of 6666 autopsies.[7] Prior to 2001, only 46 cases of SISMAD were reported. As of 2016, that number has increased to more than 622 cases.[2,8] There is a lower incidence of SICAD with approximately 100 cases reported to date.[9] There are even fewer reports of concomitant SISMAD and SICAD. Garrett et al. reviewed the literature through 2008 and reported 13 concomitant spontaneous isolated visceral artery dissections (SIVADs).[4] Spontaneous isolated dissection of the splenic, hepatic, middle colic, and inferior mesenteric arteries have also been reported.[10–13] Sixty-seven percent to 88% of isolated splanchnic artery dissection have been observed in males.[2,4,10,14–16] Typically, patients present in the fifth to sixth decade of life.[2,4,17,18] Sixty percent to 70% of patients with an aortic dissection present with hypertension; in contrast, only 30% to 40% of patients with isolated splanchnic dissections present with hypertension.[2,4,14,19,20] Although isolated splanchnic dissections have been reported on all continents, the majority of cases have been reported in Korea, China, and Japan, suggesting a genetic predisposition.[4]

ETIOLOGY

There are multiple theories on the etiology of isolated splanchnic artery dissections and the cause may vary between different visceral vessels. Proposed etiologies of SIVAD include connective tissue diseases (Marfan's syndrome, Ehlers-Danlos syndrome, Loeys-Diez syndrome), cystic medial necrosis, segmental arteriole mediolysis, Bechet disease, and fibromuscular dysplasia.[2,4,21–24]

Abstract

Spontaneous isolated arterial dissection within the splanchnic circulation unassociated with aortic dissection is a rare entity, but is being reported with increasing frequency. This most likely reflects improved imaging modalities (particularly abdominal computed tomography) and increasing awareness of this condition rather than an increasing prevalence. Due to the low prevalence of spontaneous isolated visceral artery dissection and the variety of clinical presentations, there is a lack of consensus regarding treatment guidelines. The goal of this chapter is to review the current literature on visceral dissection and help establish the best treatment guidelines for the contemporary vascular surgeon.

Keywords

Spontaneous isolated arterial dissection
Splanchnic artery dissections
Mesenteric artery dissections
Celiac artery dissection
Superior mesenteric artery dissection
Segmental arterial mediolysis

However, the majority of patients with SIVAD do not have any of these arteriopathies. Tobacco use, atherosclerosis, alcohol abuse, obesity, heavy weight lifting, and pregnancy have also been suggested as risk factors for SIVAD.[7,19,25–27]

In the majority of SISMADs, the dissection originates 1 to 3 cm from the SMA ostium.[2,4,6,28–32] At this position, the SMA transitions from a fixed retropancreatic position with an acute turn into a mobile mesenteric root. Hyperdynamic forces occurring at this transition point most likely result in this zone's becoming the origin for most SISMADs.[14] Park et al. conducted flow dynamic studies using computational fluid dynamic models that showed greater shear stress on the anterior convex portion of the SMA just distal to the ostium. These authors suggested that the etiology of SISMAD is more likely due to elevated shear stress at this location in the SMA rather than an underlying connective tissue disease or uncontrolled hypertension.[19] Solies et al. also suggested high shear stress as the etiology of SISMAD due to the 1- to 3-cm origin of SISMAD.[33,34] This theory is analogous to type II aortic dissections originating at the ligamentum arteriosum due to luminal stress at the transition from a fixed to an unfixed point. Another proposed hypothesis is development of primary hemorrhage in the media due to a rupture of the vasa vasorum, which then leads to dissection.[10] Jia et al. have linked chromosome locus 5q13-14, which is associated with familial ascending aortic aneurysms and dissections, with SISMAD.[35]

There is no clear etiology for SICAD.[9,36–38] In theory, the median arcuate ligament may represent a fixed transition point for the origin of celiac dissection. However, DiMusto et al. did not find any evidence of SICAD originating from the median arcuate ligament in their reported series of 19 SICAD.[5]

There are several case reports describing the histologic findings of SIVAD. Common features include fragmentation of elastic fibers, loss of smooth muscle cells, myxoid degeneration, and atheromatous changes. No definitive correlation to arteritis, cystic medial necrosis, or other arteriopathies was identified.[2,14,19] Since most patients with SIVAD are not currently treated with open surgery, fewer specimens are available for histologic examination. However, it appears that only a minority of SIVAD cases are associated with other arteriopathies.

The majority of current published literature on SIVADs comes from east Asian countries. Corrected for population, Korea appears to have the highest number of reports per capita, followed by Japan and then China.[2,19] This suggests, but does not prove, a higher prevalence of SIVAD in Asian populations.

CLINICAL PRESENTATION

SIVAD has a wide range of presentations including an incidental finding, an association with bowel ischemia, or aneurysmal formation with or without rupture. With modern CT and computed tomography angiography (CTA), a larger number of incidental SIVADs have been identified. In some series, as many as one-third of SIVADs are found incidentally.[31,39] Symptomatic SIVAD presents with abdominal pain in 90% of cases. Pain is described as severe and tearing in the mid-epigastric area with occasional radiation to the back. Other potential SIVAD symptoms may include nausea, emesis, melena, and diarrhea.

Abdominal pain out of proportion to physical findings suggests the diagnosis of mesenteric ischemia, which may be a clue to the diagnosis of SIVAD. Without the presence of bowel ischemia, abdominal pain is believed to originate from the visceral nerve plexus due to inflammation from the arterial dissection. It has been suggested that increased length of a SISMAD causes more periarterial inflammation and more severe pain.[14,40,41] Persistent abdominal pain that does not resolve is more likely due to mesenteric ischemia rather than inflammation of neural tissue.[20] Patients with SIVAD have a wide variety of clinical presentations and, thus, multiple treatment algorithms have been proposed. This creates diagnostic and therapeutic management challenges for the clinician.

DIAGNOSIS

There are no specific laboratory tests for SIVAD; however, elevated lactate levels correlate with end organ malperfusion. In patients with SIVAD without mesenteric ischemia, leukocytosis as well as elevated C-reactive protein and/or erythrocyte sedimentation rate may be present.[2]

Prior to 1975, all SIVAD cases were diagnosed by autopsy. The first case of SISMAD was reported in 1947. This patient had a SISMAD originating 2 cm from the SMA ostium that led to bowel infarction and death.[1] The first documented survivor after treatment of SISMAD was reported in 1992, wherein angiography demonstrated the lesion after laparotomy for ischemic bowel.[42] Digital subtraction angiography (DSA) supplanted conventional arteriography by minimizing contrast exposure and providing improved definition of distal mesenteric branch vessels compared to other imaging modalities. However, DSA is a more invasive test with limited ability to identify end organ malperfusion when compared with contrast-enhanced CT.[10]

CTA and contrasted-enhanced CT are now used to diagnose more than 95% of contemporary cases of SIVAD. Less commonly used are duplex ultrasonography (DU), DSA, and magnetic resonance imaging (MRI), repectively.[2] Although DU is a reliable, inexpensive, and noninvasive modality for diagnosis and surveillance of mesenteric vascular disease, in some cases it has low diagnostic sensitivity. Subhas et al. reported that DU only identified 56% of SISMADs.[10] An intimal flap may be difficult to visualize sonographically and acute thrombosis of the false lumen may hinder discrimination of the false channel. Bowel gas and obesity also render DU studies difficult to perform successfully even with experienced technologists. MRI may demonstrate similar evidence of disease, but is both less efficient and less commonly available in the acute setting compared to CT.

Contrasted-enhanced CT is capable of identifying dissection flaps, false lumens, re-entry tears, thrombus, intramural hematomas, aneurysm formation, and rupture of splanchnic arteries. When visualization of the dissection itself is limited, increased attenuation of the mesenteric fat may suggest the diagnosis.[10,43,44] CT not only identifies the SIVAD, but also demonstrates the characteristics of the dissection such as its origin, length, and

concomitant lesions.[32] CT is also able to identify other markers of end organ malperfusion. CTA should now be considered the gold standard for diagnosis of SIVAD.[10]

CLASSIFICATION SYSTEM

A number of classification systems have been developed for SISMAD. The goals of a classification system are to assist with risk assessment and determination of the best treatment algorithm for different types, extent, and characteristics of SISMADs. In 2007, Sakamoto et al. reported the first classification system for SISMAD. This group characterized SMA dissections based on CT appearance: Type I, patent false lumen with both entry and re-entry; Type II, a "cul-de-sac" shaped false lumen without re-entry; Type III, thrombosed false lumen with ulcer defect; and Type IV, a completely thrombosed false lumen without ulcer (Fig. 134.1). In Sakamato's series, all Type 1 SISMAD were treated successfully with conservative measures such as anticoagulation and medical management. In patients with Type II SISMAD, the true lumen may be compromised by false lumen compression. They recommended that these patients be followed very closely for signs of mesenteric ischemia. Type III SISMADs had the highest rate of intervention in contrast to Type IV SISMADs that did not require any intervention. Although this series only included 12 patients, it was the first classification system that attempted to determine best treatment using image classification.[45] A criticism of this system is the exclusion of patients with total thrombotic occlusion.[46]

Yun et al. reported a classification system with 3 types of SISMADs. Type I, patent true and false lumen revealing entry and re-entry sites; Type IIa, patent true lumen but no re-entry of the patent false lumen; Type IIb, patent true lumen but no re-entry of thrombosed false lumen; and Type III, dissection with occlusion of SMA (Fig. 134.2). This classification system was based on a clinical series of 32 patients. The authors were able to correlate pain severity with length of dissection, but could not predict outcome or recommend treatment guidelines based on the classification system due to small sample size. Four of the 32 patients underwent intervention (one endovascular and three open surgeries) for persistent pain due to bowel ischemia, but the type of SISMADs in these patients was not described.[40] Notably, due to the simplicity of Yun's classification system, it has become the most commonly used.

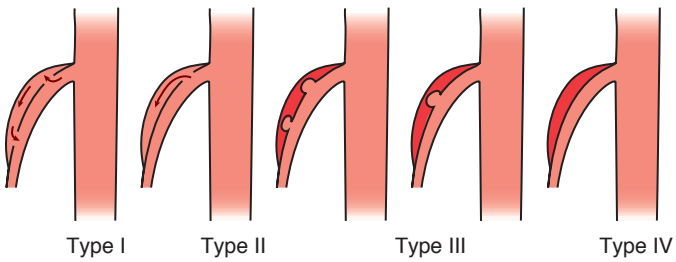

Figure 134.1 Spontaneous isolated superior mesenteric artery dissection classification system proposed by Sakamoto et al: Type I, patent false lumen with both entry and re-entry; Type II, a "cul-de-sac" shaped false lumen without re-entry; Type III, thrombosed false lumen with ulcer defect; and Type IV, a completely thrombosed false lumen without ulcer. (From Sakamoto I, Ogawa Y, Sueyoshi E, et al. Imaging appearances and management of isolated spontaneous dissection of the superior mesenteric artery. *Eur J Radiol.* 2007;64:103–110.)

Zerbib et al. described a more complex classification system by adding more categories to Sakamato's scheme. Type V is aneurysmal dissection with stenosis of the distal segment of the SMA. Type Va is total thrombosis of SMA and Type VIb shows partial SMA thrombosis. These authors compared outcomes of reported cases in the literature using their classification system. Their results showed that Types II and III lesions required more interventions in contrast to Types I and IV. Unfortunately, they were unable to predict clinical outcome based on this classification system.[47]

Luan et al. described a classification system based on the location and extent of the SMA dissection rather than luminal patency. These authors suggest four types of dissection. Type A is described as a dissection at the curve of the SMA and extending proximally to the SMA ostium. Type B is described as a dissection limited to the curve of the SMA. Type C is described as extending from the curve of the SMA distally, but not involving the ileocolic or distal ileal artery. Type D is described as extending toward the ileocolic and/or ileal artery (Fig. 134.3). In this series, patients with Type B dissection were symptomatic less often in contrast to patients with Type D dissection who presented with more severe pain. Unfortunately, management strategies are difficult to assess due to a sample size of only 20 patients. Type B patients were more likely to have successful treatment with conservative treatment compared with Type C and D patients.[32]

Other classification systems have been proposed, but unfortunately have not added to improvement of clinical management strategies.[30] Dissections of other visceral vessels have not been included in these systems. There is lack of wide acceptance of any one algorithm at this point in time.

TREATMENT

Management of SISMAD or other visceral vessel dissection depends on the clinical circumstances including morphology of the dissection, resultant symptoms, and the patient's clinical course. Little can be stated with authority at this time due to the low prevalence of reported SISMAD cases in the English medical literature worldwide and fewer cases including vessels other than the SMA. The majority of these cases have been reported within the last 2 decades, a time period with major advances in diagnostic imaging and therapeutic interventions.

Asymptomatic Patients

Technical improvements in multi-helical CT in the last decade, as well as increasing frequency of the use of CT in evaluating patients with various conditions, have led to an increase in the reported incidence of SIVAD. As a result, SIVAD has been observed in a number of asymptomatic patients. There is consensus that these patients should be managed medically.[7,20,40,48–53] However, the role of antiplatelet agents and anticoagulants is not well defined in either asymptomatic or symptomatic patients.

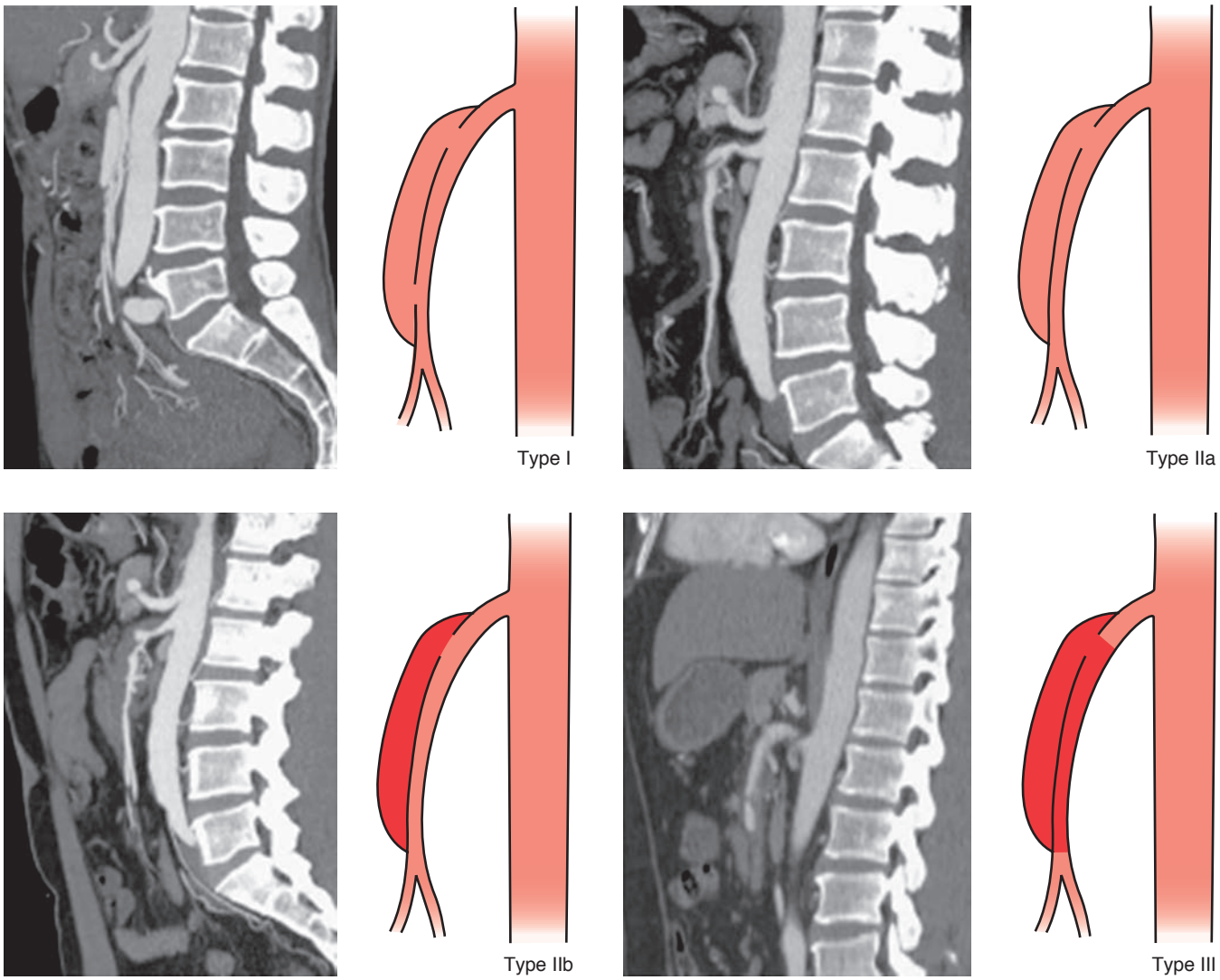

Figure 134.2 Yun et al. classification system for spontaneous isolated superior mesenteric artery dissection: Type I, patent true and false lumen revealing entry and re-entry sites; Type IIa, patent true lumen but no re-entry of the patent false lumen; Type IIb, patent true lumen but no re-entry of thrombosed false lumen; and Type III, dissection with occlusion of superior mesenteric artery. (From Yun WS, Kim YW, Park KB, et al. Clinical and angiographic follow-up of spontaneous isolated superior mesenteric artery dissection. *Eur J Vasc Endovasc Surg*. 2009; 37(5):572–577.)

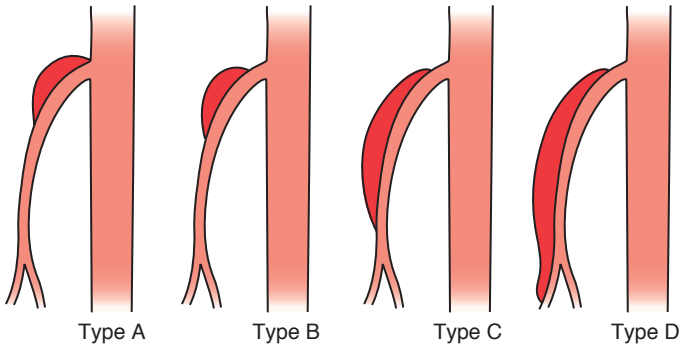

Figure 134.3 Classification system by Laun et al: Type A dissection at the curve of the superior mesenteric artery (SMA) and extending proximally to the SMA ostium; Type B dissection limited to the curve of the SMA; Type C extending from the curve of the SMA distally, but not involving the ileocolic or distal ileal artery; Type D extending toward the ileocolic and/or ileal artery. (From Luan JY, Li X. Computed tomography imaging features and classification of isolated dissection of the superior mesenteric artery. *Eur J Vasc Endovasc Surg*. 2013;46(2):232–235.)

Symptomatic Patients

As previously noted, a minority of patients that present with acute symptoms of SIVAD have vessel perforation and/or hemorrhage. Most patients report abdominal pain. The pain may be due to the dissection itself or to visceral malperfusion with end organ ischemia.

Most would agree that an incidental finding of a SIVAD without significant aneurysmal dilation or symptoms does not require intervention. However, there is controversy regarding management of patients presenting with symptoms of abdominal pain. The variability of collateral networks to maintain intestinal perfusion creates unpredictability regarding the persistence or resolution of ischemic symptoms.

Initial treatment is typically bowel rest and observation, particularly for patients with normal serum lactate level and lack of leukocytosis. Patients with persistent pain may be treated

with parenteral nutrition to reduced visceral "demand ischemia." Recruitment of collateral flow pathways or resolution of dynamic obstruction with dissection stabilization may explain resolution of ischemic pain. Pain secondary to the inflammatory process created by the dissection itself may persist for days. The role of anticoagulation is not well defined. Most authors have utilized at least short-term anticoagulation, but the benefit of this treatment has been questioned in recent reports.[5,40]

Some patients found to have SIVAD who present with abdominal pain and without bleeding may be managed medically. Ambo et al. was the first to report this treatment approach in 1994.[54] Yang et al. reported a series of 46 SIVAD patients with CTA surveillance for a mean of 23 months.[14] These authors observed remodeling and improvement of the dissection in a majority of patients (Fig. 134.4). More importantly, none of these patients developed extension of the dissection, bowel ischemia, or arterial rupture. However, in a different series by Li et al., 3 of 24 patients initially managed conservatively developed progression, including one patient with a fatal bowel infarction.[30] Overall, a majority of patients with SIVAD reported in the last two decades have undergone successful medical management.[20,30,55–57] There is a small number of patients with SICAD that have also undergone successful medical manangement.[5,36,52,58,59] In patients whose symptoms resolved with conservative management involving gradual return to enteric nutrition, radiographic follow-up is recommended.[8] There is no well-defined role for long-term anticoagulation or antiplatelet therapy.[60] A majority of patients treated expectantly in recent reports have not been treated with oral anticoagulation, and some authors do not utilize antiplatelet therapy in patients who do not undergo intervention.[40,46]

Surgical Treatment

A majority of early publications regarding treatment of SIVAD, mostly SISMAD, reported surgical treatment. The first documented successful surgery for SIVAD was reported in 1992. This patient was diagnosed with SISMAD via arteriography after laparotomy for mesenteric ischemia. The patient underwent a right gastroepiploic-to-SMA bypass.[42] In most patients

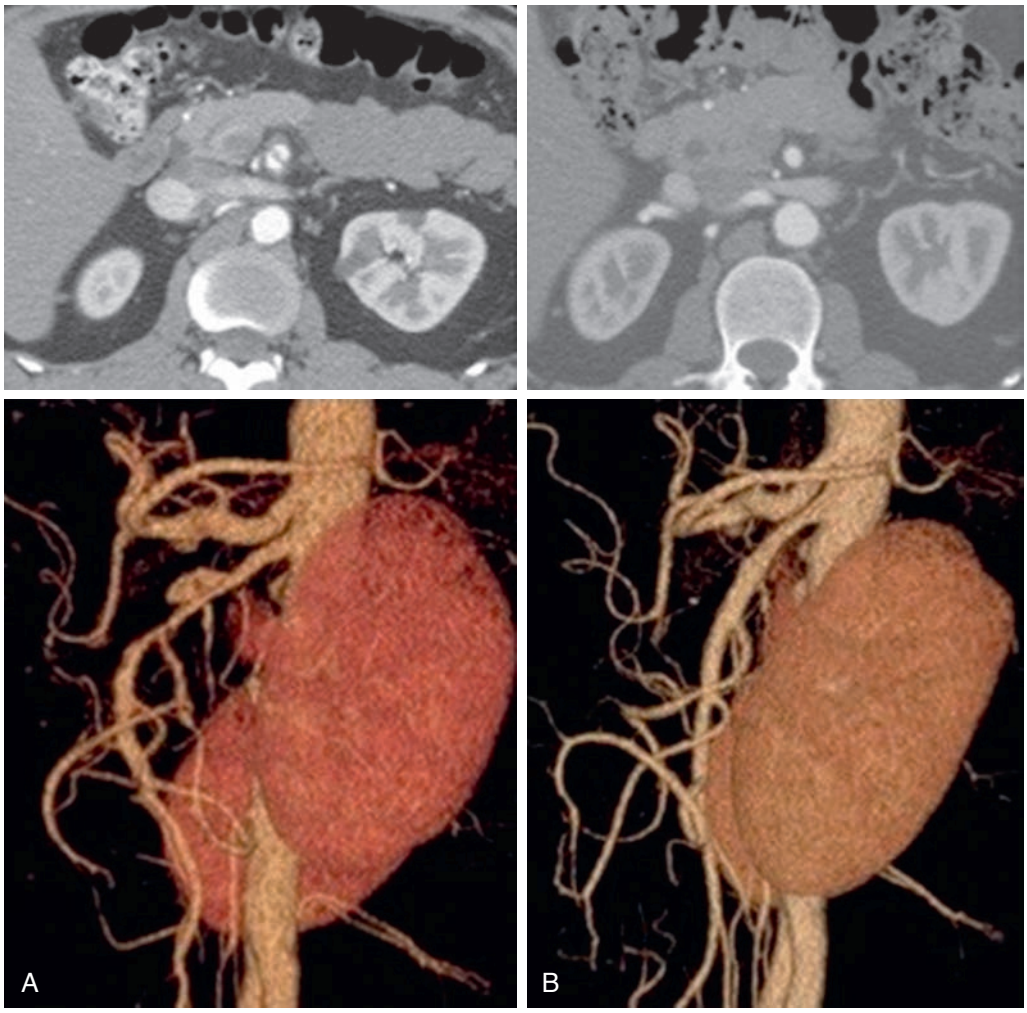

Figure 134.4 Computed tomography angiography demonstrating remodeling of spontaneous isolated superior mesenteric artery dissection before (A) and after (B) without intervention. (From Park YJ, Park KB, Kim DI, et al. Natural history of spontaneous isolated superior mesenteric artery dissection derived from follow-up after conservative treatment. *J Vasc Surg*. 2011;54:1727–1733.)

presenting with intra-abdominal hemorrhage or advanced bowel ischemia, open surgery remains the preferred option. Aside from resecting necrotic bowel when necessary, direct treatment of the arterial dissection can be accomplished by direct arterial repair. When operating for bleeding, ligation alone is appropriate if collateral flow appears sufficient.[61] When bowel is threatened, surgery may include aorto-visceral bypass, extra-anatomic bypass (with gastroepiploic or hepatic artery inflow for SMA dissection), and intimectomy/fenestration often combined with vein patch repair. Autogenous graft material, most commonly the greater saphenous vein, has been utilized in most reports.[42]

Endovascular Treatment

Thrombolysis

Thrombolytic therapy has rarely been employed in the setting of visceral vessel thromboembolism. There are few reports of its utilization in the setting of SIVAD, usually in combination with stenting. Mixed results have been observed.[62–64]

Embolization

Occasionally patients present with aneurysm formation or vessel perforation by the false channel as the primary concern. Endovascular coil embolization has been utilized in this setting (Fig. 134.5).[30,64,65]

Stenting

The first report of endovascular stenting to treat a SISMAD was published in 2000 by Leung et al.[66] Cumulative experience with stenting in the published English literature totals only a few dozen cases; thus it is difficult to make broad conclusions regarding indications, technique, and efficacy.[31,67] The majority of patients treated with stents had ongoing abdominal pain as the primary indication for treatment.[68,69] Many theorize that

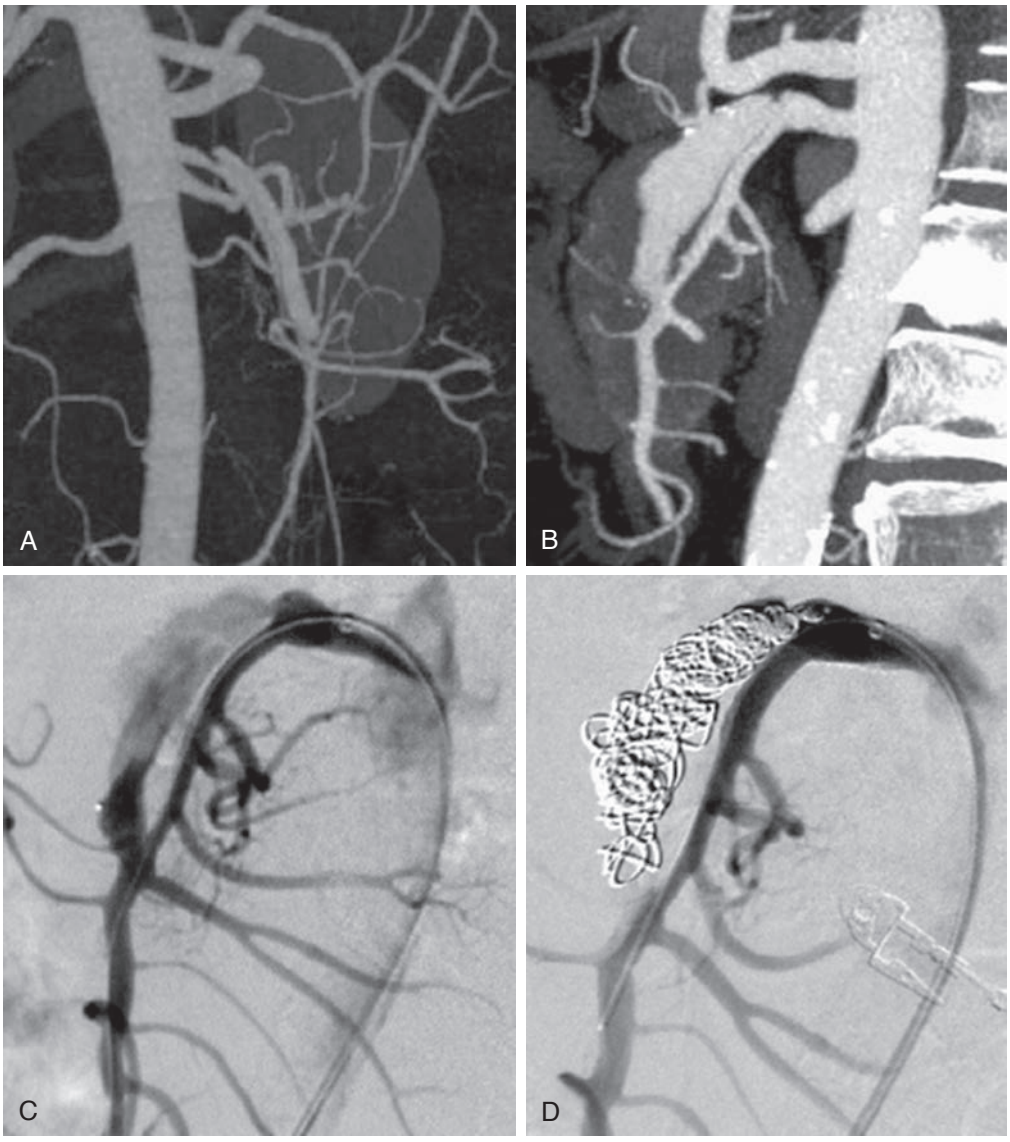

Figure 134.5 Imaging of superior mesenteric artery dissection (A), with pseudoaneurysm (B), treated with coil embolization of false lumen and pseudoaneurysm (C and D). (From Ozaki T, Kimura M, Yoshimura N, et al. Endovascular treatment of spontaneous isolated dissecting aneurysm of the superior mesenteric artery using stent-assisted coil embolization. *Cardiovasc Intervent Radiol.* 2006;29:435–437.)

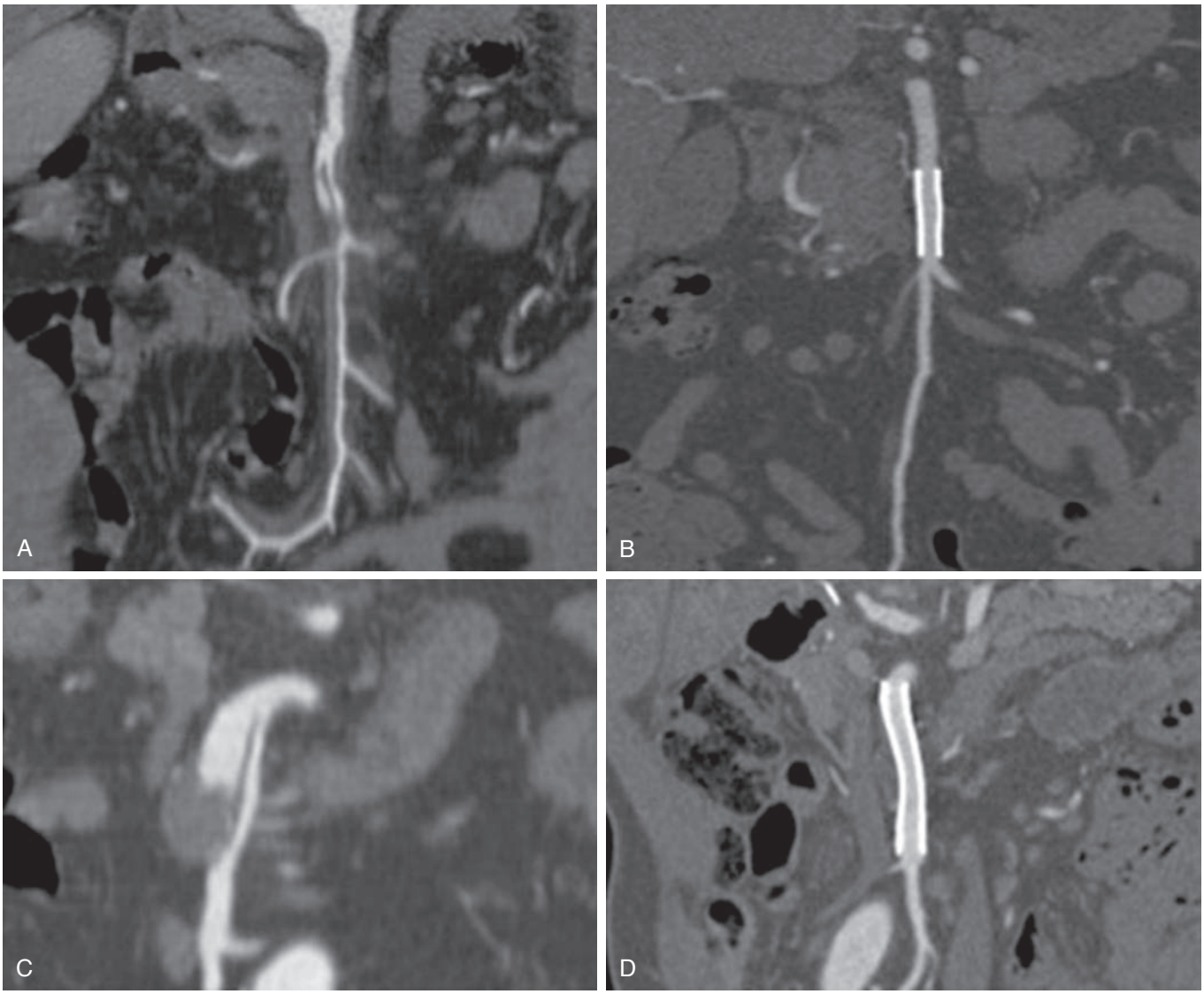

Figure 134.6 Superior mesenteric artery dissection (A and C), and successfully treated with endovascular stenting (B and D). (From Min SI, Yoon KC, Min SK, et al. Current strategy for the treatment of symptomatic spontaneous isolated dissection of superior mesenteric artery. *J Vasc Surg*. 2011;54:461–466.)

the symptom of pain is more commonly due to the dissection itself with an inflammatory response to the vessel injury rather than from mesenteric malperfusion and ischemia. A disadvantage of endovascular treatment compared to surgery is the inability to inspect the bowel for evidence of ischemia or necrosis. Accordingly, almost all patients treated with endovascular stents had variable symptoms of abdominal pain, rather than advanced ischemia or bowel necrosis.

The goal of endovascular treatment is elimination of stenosis caused by false lumen encroachment, as well as stabilization of vessel integrity to avoid late degeneration and aneurysm formation. According to the limited available natural history data, aneurysm formation appears to be a relatively rare occurrence; thus stenting should be primarily used for the former indication. Persistent pain is considered an indication for intervention in several series, analogous to the treatment of aortic dissection. Some authors have noted that patients having intervention with stenting have had an accelerated return to normal dietary intake and hospital discharge.[28,70] Others advocate a more selective application of stenting. Min et al. suggest that SMA stenosis of greater than 80% or dilation to more than 2 cm are indications for primary stenting (Fig. 134.6).[28] However, other authors have observed radiographic improvement in the degree of stenosis with conservative management in the large majority of patients.[57,63]

Visceral vessel stenting via transfemoral artery access has been reported most commonly. However, left brachial artery access provides significant advantage because it allows antegrade tracking of the acutely angulated proximal vessel, particularly the SMA. Caution must be taken to gain wire access to the true lumen, which may be challenging.[71] As the entry point for SMA dissection is rarely ostial, self-expanding stents are preferred over the balloon expandable design for most lesions. Nitinol bare metal stents have been utilized in most reports.[72]

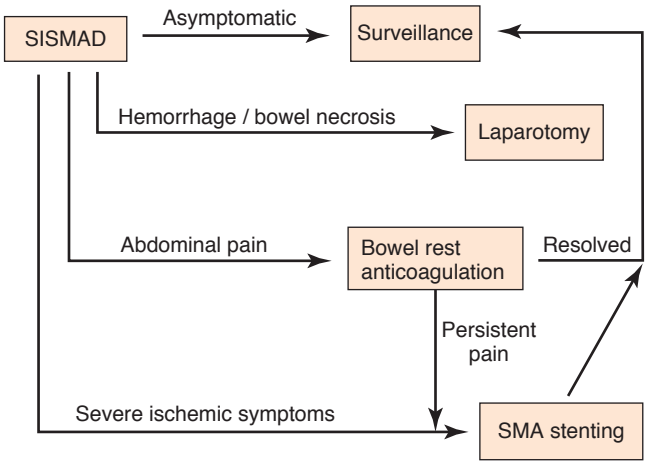

Figure 134.7 Suggested treatment algorithm for spontaneous isolated superior mesenteric artery dissection (SISMAD). *SMA*, Superior mesenteric artery.

Covered stents may have occasional utility, particularly when excluding aneurysmal vessels.[73–75] However, in most situations, preservation of flow to the remaining patent SMA branches is the priority and bare stents are preferred. Most authors have utilized stents long enough to treat the entire length of the dissection rather than only the entry tear. Multiple stents have been reported in about one third of patients.[76] Published long-term results with stenting are limited, but few failures have been reported to date.[30,77–80] Intermediate-term patency appears to be high and late recurrent dissection or arterial degeneration appears to be very low. Most authors recommend long-term antiplatelet therapy as adjunctive therapy.

In comparison with medical management, the majority of the current literature available on endovascular management of SIVAD pertains to lesions of the SMA. However, there are a few reports of successful surgical and endovascular management of SICAD. Similar to SISMAD, recognizing which branch of the celiac artery has the dissection is more challenging than the technical aspects of the treatment.[5,36,59]

Fig. 134.7 demonstrates a suggested treatment algorithm we endorse based upon the available data.

OTHER CONSIDERATIONS

Segmental Arterial Mediolysis

Segmental arterial mediolysis (SAM) has recently gained recognition as a distinct pathologic entity. Although dissections may occur with this non-inflammatory arteriopathy, aneurysms are more common and multiple lesions in various vessels are often present at the time of diagnosis (Fig. 134.8). Visceral vessels are at highest risk for SAM, often with multiple areas of aneurysmal dilation and occasionally dissections. Intra-abdominal hemorrhage is more common than thrombotic or ischemic complications. Open surgical treatment has often been utilized on an emergent basis; however, endovascular management with coil embolization has played an increasing role in more recent reports.[21,22]

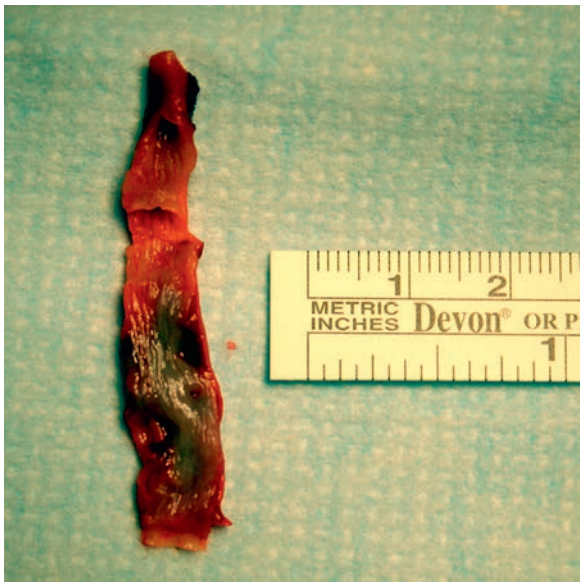

Figure 134.8 Segmental arterial mediolysis affecting the superior mesenteric artery in a patient presenting with rupture—distal superior mesenteric artery specimen opened, revealing dissection. (From Tameo MN, Dougherty MJ, Calligaro KD. Spontaneous dissection with rupture of the superior mesenteric artery from segmental arterial mediolysis. *J Vasc Surg*. 2011;53:1107–1112.)

SURVEILLANCE

There is no consensus on surveillance of patients with SIVAD; however, most clinicians suggest some type of routine follow-up.[10,14,81] CTA is the surveillance study of choice; however, DU may also be used. The rationale for surveillance is the potential for SIVAD to form a splanchnic aneurysm.[82] The true incidence of aneurysm formation is unknown, but this has been reported.[67] Imaging at 1 month post initial SIVAD, every 6 months for the first year, then annual surveillance has been proposed. This is a reasonable approach until the natural history of this disease entity is better defined.[4,14]

REMODELING

Surveillance of SIVAD has shown that more arteries remodel than form aneurysms. Park et al. showed that 41% of SISMAD treated medically had improvement on surveillance CTA and 15% of patients had complete remodeling of the SMA. Positive predictors for complete remodeling included type II lesions from the Yun classification system. These are SISMADs that had a single tear and no re-entry tear. This leads to false lumen thrombosis and more complete remodeling of the SMA. It is unclear if remodeling leads to better clinical outcomes, but there is no report to date of late morbidity in a patient whose dissection was described as improving.[14]

SUMMARY

Isolated visceral artery dissections are rare, but have been increasingly recognized with advanced imaging techniques in recent years. No single etiologic factor has been identified, but

a higher prevalence is observed in the east Asian population. Although bowel ischemia and hemorrhage can complicate these SIVADs, the majority can be managed medically. Endovascular treatment has played a growing role in management of symptomatic lesions with high procedural and intermediate-term success. Radiographic surveillance is recommended in patients regardless of initial treatment.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 135

Median Arcuate Ligament Syndrome: Pathophysiology, Diagnosis, and Management

BENJAMIN R. BITEMAN and FREDRICK BRODY

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INTRODUCTION

"Compression of the celiac artery by the median arcuate ligament is well-documented."[1] Stanley and Fry published this statement in 1971 after reviewing "provocative xylose absorption tests" in ten female and five male patients over a 3.5-year period. After transecting the median arcuate ligament in these 15 patients, they concluded that intestinal ischemia was the underlying disorder in median arcuate ligament syndrome (MALS). However, 45 years later, MALS continues to be difficult to qualify, quantify, and diagnose. MALS (also known as celiac artery compression syndrome and Dunbar syndrome) is an anatomic and clinical illness resulting from extrinsic compression on the celiac axis. Clinical manifestations include postprandial and exercise induced epigastric abdominal pain, nausea, vomiting, weight loss, and "food fear," or fear of pain triggered by eating. Lipshutz[2] offered the first anatomic description of the celiac artery in 1917, and Harjola performed the first surgical release in 1963.[3] In 1967 Dunbar et al.[4] reported a larger case series in which operative division of the MAL resulted in clinical improvement in 13 of 15 patients. Anatomically, up to 24% of the population may have MAL compression; however, less than 1% of these patients are symptomatic.[5] Over the last several years, the etiology of MALS has shifted from a vascular disease to a neurogenic illness with compression of the surrounding celiac plexus and ganglion. Presently, patient selection remains critically important in order to obtain optimal clinical outcomes following treatment.[6]

Anatomy

Embryologically, the diaphragm is derived from the septum transversum and descends from the neck toward the celiac axis between weeks 9 and 12 and ultimately forms the MAL. Typically the diaphragmatic crura arise from the anterior aspect of L1 to L4 and project cephalad to join the anterior longitudinal ligament of the spine overlying the celiac axis. The MAL is composed of the fibrous edge of the diaphragmatic crura that crosses the aorta at the level of the celiac artery. These fibers splay over the aorta and extend laterally toward the suspensory ligament of the fourth portion of the duodenum (Fig. 135.1). In the majority of the population, the ligament does not encroach on the celiac artery and causes no compression (Fig. 135.2). As noted previously, as much as 10% to 24% of the population may have MAL compression without symptoms.[5] The celiac nerve plexus branches across the abdominal aorta between vertebral levels T11 to L1.

Pathophysiology

Multiple theories exist regarding the pathophysiology of the epigastric pain associated with MALS. One theory hypothesizes

Keywords

Median Arcuate Ligament
Epigastric pain
Celiac Artery
Exercise induced pain
Laparoscopic
Ganglion

that increased blood demand through a compressed celiac artery leads to foregut ischemia and pain. However, collateral blood flow between the mesenteric vessels compensates for either subtotal or intermittent occlusion of the celiac artery. Also, studies performed using gastric exercise tonometry document that mucosal oxygen delivery does not correlate with celiac artery compression or clinical symptoms.[7] Similar findings exist with gastric perfusion studies.[8] In addition, MAL compression has never been reported as a cause of gastric necrosis or even gastric ischemia on endoscopic evaluation.[6] Another theory states that midgut ischemia induces abdominal pain through a vascular steal syndrome. In theory, blood flow from the superior mesenteric artery may be diverted through collaterals to compensate for inefficient delivery through a stenotic celiac artery, and this mechanism results in small bowel ischemia and pain. This mechanism would be difficult to document with retrograde flow studies. Others suggest that the epigastric pain is caused by overstimulation of the celiac plexus with subsequent splanchnic vasoconstriction and ischemia (Fig. 135.3).[9] Other authors favor a neurogenic hypothesis for symptoms of MALS. Histologic analysis of the celiac plexus shows that the nerves consist of pain fibers and inhibitory motor fibers to the stomach. Thus entrapment of the ganglion by the MAL may alter gastric myoelectrical activity and impair antral motility,[10] and the compression may induce pain.[11] Since the underlying pathophysiology of MALS is unknown, the diagnosis of MALS is difficult. Consequently, to enhance the benefit of surgical intervention, efforts aimed at improving the ability to reliably diagnose MALS are required.

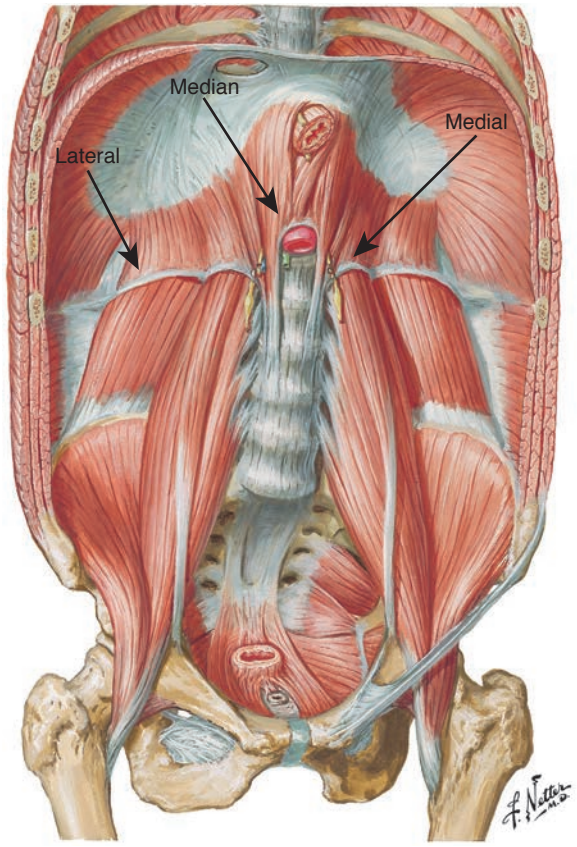

Figure 135.1 Artistic rendering of the retroperitoneal musculature and diaphragm. *Arrows* depicting the median, medial, and lateral arcuate ligaments. (February 28, 2018. Used with permission of Elsevier. All rights reserved.)

DIAGNOSIS

History and Physical Exam

The ultimate goal of surgical intervention begins with accurately identifying patients with symptomatic MALS and those patients who would benefit from surgery. Initially the workup includes consultation with a vascular and general surgeon for a detailed history and physical examination. Overall, history and physical often prove nondiagnostic or equivocal. The history may yield previous surgical interventions, including cholecystectomy and/or diagnostic laparoscopy. The most common presenting symptom is abdominal pain, and an overwhelming majority of symptoms are classified as postprandial. Other symptoms include weight loss, bloating, nausea, vomiting, and exercise-induced pain (Box 135.1; Fig. 135.4). Recently, patients with autonomic neuropathy, including postural orthostatic tachycardia

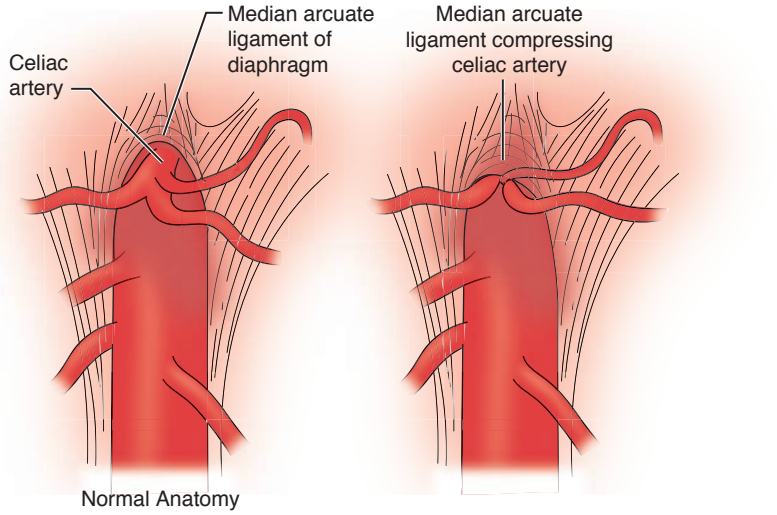

Figure 135.2 Artistic rendering of the proposed pathophysiology of celiac artery compression in those patients with median arcuate ligament syndrome.

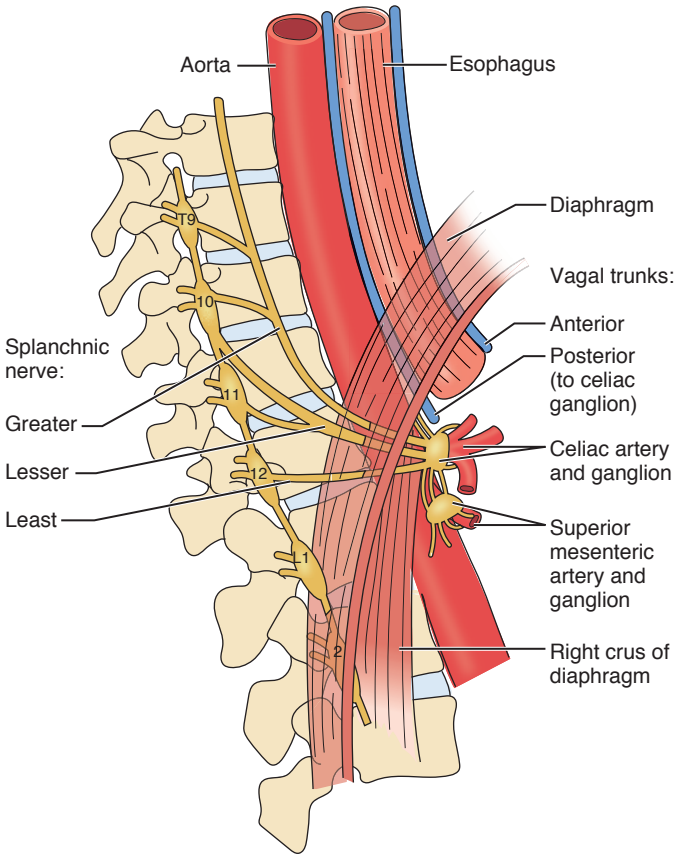

Figure 135.3 Artistic rendering of a sagittal view of the median arcuate ligament and proposed neural networks entering and exiting the celiac ganglion and plexus. Compression of the celica axis by the median arcuate ligament simultaneously can cause compression of the celiac ganglion.

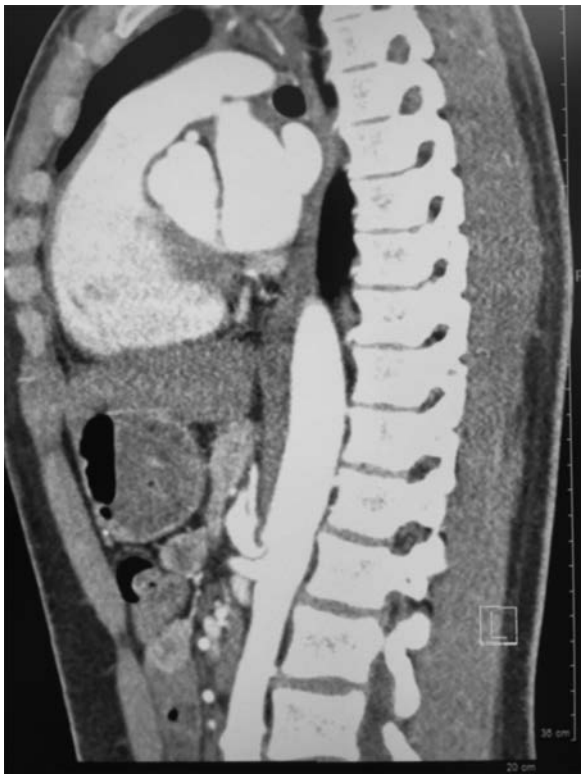

Figure 135.4 Sagittal view from a computed tomography angiography depicting celiac stenosis and poststenotic dilation due to median arcuate ligament compression.

BOX 135.1 Signs and Symptoms of Median Arcuate Ligament Syndrome

Median Arcuate Ligament Syndrome

More Common

Second to sixth decade of life
- Female:Male 3:1
- Postprandial abdominal pain
- Nausea
- Vomiting
- Unintentional weight loss
- Exercise induced pain

Less Common

Autonomic dysfunction
- Fibromyalgia
- Postural
- Orthostatic tachycardia syndrome

syndrome (POTS), have been diagnosed with MALS.[12] Physical examination typically reveals a thin, flat, nontender abdomen. Despite the suspected underlying pathology, an abdominal bruit is usually not detected with auscultation.

There is a female predilection at 2:1 to 3:1, and typical ages range in the fourth and fifth decade. Some recent literature challenges the classic age range and shifts the disease onset to the second and third decades.[13] However, there are many cases where the diagnosis is delayed, with patients complaining of several years of symptoms prior to diagnosis.

Often patients have had multiple evaluations regarding their abdominal symptoms. Many patients face an inherent bias from their physicians following an initial negative workup, and many of these patients frequently carry a "psychiatric" or noncompliant diagnosis. Anecdotally, fibromyalgia, autonomic dysfunction, and pain medication–seeking behavior may be included in these patients' charts. Most patients have already had an extensive gastrointestinal workup, including gallbladder ultrasounds, esophagogastroduodenoscopy, colonoscopy, enteric motility studies, computed tomography (CT), and magnetic resonance imaging (MRI). In one series, 54% of patients had undergone a prior abdominal procedure, including cholecystectomy, exploratory laparoscopy/laparotomy, and/or biliary and pancreatic sphincterotomy.[14]

RADIOLOGIC STUDIES

During the 1960s and 1970s, lateral aortography was the most reliable and objective means of documenting the presence and extent of celiac artery compression. Using inspiratory and expiratory images, this invasive test was considered pathognomonic for MALS. Today, CT angiography (CTA) and magnetic resonance arteriography (MRA) have emerged as the two most common diagnostic studies for MALS. CTA and MRA can

evaluate the structural elements of the celiac artery, the MAL, and the surrounding viscera, in addition to providing aortic and celiac branch anatomy. CTA and MRA may also identify concomitant abdominal disease such as a co-existing neoplasm, mesenteric thromboses, or atherosclerosis. Although CTA and MRA provide information about the relationship of the celiac artery with the diaphragm and help visualize the compressed artery from various angles, they are not dynamic and therefore do not provide information during the respiratory cycle (see Fig. 135.4).

At some institutions, MALS is now diagnosed initially with transabdominal duplex ultrasound scanning of the celiac artery. Several studies have demonstrated varying degrees of compression of the celiac artery during the respiratory cycle. Normally the distance between the celiac artery and MAL increases during inspiration and decreases with expiration.[15] During expiration, the aorta moves in a cephalad direction and may subject the celiac artery and its surrounding celiac plexus to compression by the MAL. During inspiration, the celiac artery moves away from the MAL as the aorta moves caudally.[15] These distinct anatomic findings during normal breathing induce dynamic celiac artery velocities during inspiration and expiration. However, diagnostic ultrasound is technician-dependent and requires a high degree of expertise to reliably assess the mesenteric vessels.

Ultrasound scanning is performed during inspiration and expiration by using 3.5 to 5.0 MHz probes with linear array or convex sector probes. Arterial inflow is based on B-mode and the peak systolic velocity (PSV). Ultrasound measurements focus on the proximal portion of the celiac artery just distal to the ostia. According to criteria published by Moneta et al.,[16] a PSV greater than 200 cm/s, no flow, or retrograde common hepatic arterial flow during inspiration or expiration were consistent with a significant (>70%) stenosis of the celiac artery (Fig. 135.5). Turbulent flow with elevated peak systolic velocities on expiration, which normalize or decrease with inspiration and standing erect, are suggestive of MALS (see Fig. 135.5). The ultrasound findings should document a peak expiratory velocity of greater than 200 cm/s to entertain a diagnosis of MALS and should be greater than resting and inspiratory velocities. Peak expiratory velocities of greater than 500 cm/s have been reported.[13] Other ultrasound findings associated with MALS include abnormal origins of the celiac and superior mesenteric arteries, poststenotic bulbar dilation, and reverse flow in the hepatic artery.[17] Gruber et al. were able to correlate a diagnosis of MALS with celiac artery end diastolic velocity of 350 cm/s or greater, a 210% change in pulse volume amplitude with inspiration and expiration, and a celiac artery deflection angle of 50 degrees. These findings by Gruber showed a sensitivity of 83% and specificity of 100% compared with angiographic evidence of MALS.[18] A combination of ultrasound, CTA, and MRA usually provides enough information, coupled with the patient's symptoms, to confirm or exclude a diagnosis of MALS (see Fig. 135.4).[13]

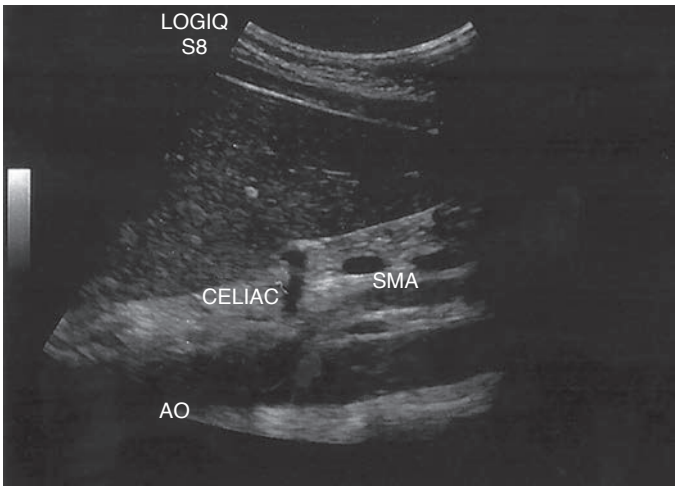

Figure 135.5 Doppler ultrasound image representation of normal findings and positioning during dynamic studies for median arcuate ligament syndrome.

Aortic angiography may reveal an asymmetric focal narrowing of the proximal celiac axis with poststenotic dilation. Narrowing is accentuated on expiration and relieved on inspiration. Increased collateral vessels in the celiac artery distribution may be evident and is indicative of significant stenosis.

Gastric exercise tonometry has been used as well to diagnose MALS. This test uses arterial blood gases and nasogastric fluid with a standardized protocol to measure arterial and gastric carbon dioxide levels before, during, and after 10 minutes of submaximal exercise. After acid suppression with a proton pump inhibitor or H2 blocker, baseline measurements of gastric PCO2 and arterial blood gases are obtained. Following a 10-minute bicycle test and a 20-minute recovery period, blood gases and gastric PCO_2 are measured during peak exercise and recovery. A positive pathologic test consists of (1) a gastric-arterial PCO_2 gradient greater than 0.8 kPa after exercise, (2) an increase in gastric PCO_2 from baseline to peak exercise, and (3) an arterial lactate level less than 8 mmol/L.[7]

MANAGEMENT

Percutaneous celiac ganglion block has been used for decades to control intractable pain from intraabdominal cancer or chronic pancreatitis.[14] In a series of 36 patients from the Mayo Clinic, preoperative celiac ganglion block was successfully performed on nine patients diagnosed with MALS, and all nine improved after surgery.[19] Theoretically, a visceral block could be used as a preoperative diagnostic and potentially therapeutic test. However, there is limited data to support this algorithm.

Endovascular treatment alone does not benefit patients with MAL compression of the celiac axis. Matsumoto et al. reported immediate failure after performing five percutaneous transluminal angioplasty (PTA) procedures for symptomatic visceral artery stenosis, secondary to extrinsic compression by the MAL or occult malignancy.[20] In 2002 Matsumoto also described patients who immediately failed PTA in the setting of mesenteric ischemia but had immediate relief of symptoms after surgical release of the MAL.[21] It is not uncommon to find patients with celiac artery stenosis who have had PTA attempted and subsequently required open or laparoscopic release of the MAL. Due to the angulation and compression of the celiac artery, PTA in patients

with MALS may be associated with fractured stents and stent migration into various visceral arteries. Although data is limited to case reports, PTA alone is not successful without removal of the extrinsic compression of the MAL. PTA or stenting are now relatively contraindicated in the setting of MALS, as the extrinsic compression of the ligament would only obstruct or crush the stent and result in early restenosis.[22] Thus purely endovascular treatment of MALS is not recommended.[14]

Currently most surgeons agree that laparoscopic division of the MAL and the associated celiac ganglion tissue are critical for a successful treatment.[13] In addition to sympathetic pain fibers, the celiac ganglion contains inhibitory sympathetic motor fibers, which modulate the intrinsic neural circuit of the stomach.[23] As noted earlier, decompressing or dividing the neural fibers would therefore decrease pain and improve gastric motility.[10,13]

Laparoscopic Technique

A laparoscopic MAL release typically uses a standard five-port laparoscopic technique with the patient in the supine position (Fig. 135.6). The midline port is placed slightly more cephalad to visualize the aorta and celiac artery over the pancreatic body during the dissection. The ultrasonic scalpel is used to enter the lesser sac after the liver is retracted cephalad. A window is created to circumferentially expose the left gastric artery and coronary vein. With gentle retraction, the artery and vein are retracted from left to right to obtain an optimal view of the left and right borders of the aorta as it approaches the origin of the celiac artery. An extensive dissection of the common hepatic, left gastric, and splenic arteries is performed.[1] Typically the dissection extends 4 cm distal to the celiac artery bifurcation in order to divide all the neurovascular bundles surrounding the three associate vessels. The crural and MAL fibers are then divided from the overlying aorta using the hook cautery (Video 135.1). The aortic dissection extends 5 cm proximal to the origin of the celiac artery to ensure a complete division of the celiac plexus (Video 135.2; Figs. 135.7-135.9). The dissection extends to the prevertebral fascia on the right of the aorta and to the suspensory ligament of the fourth portion of the duodenum on Fig left. All ganglionic fibers that are visualized are divided with the electrocautery or ultrasonic scalpel.

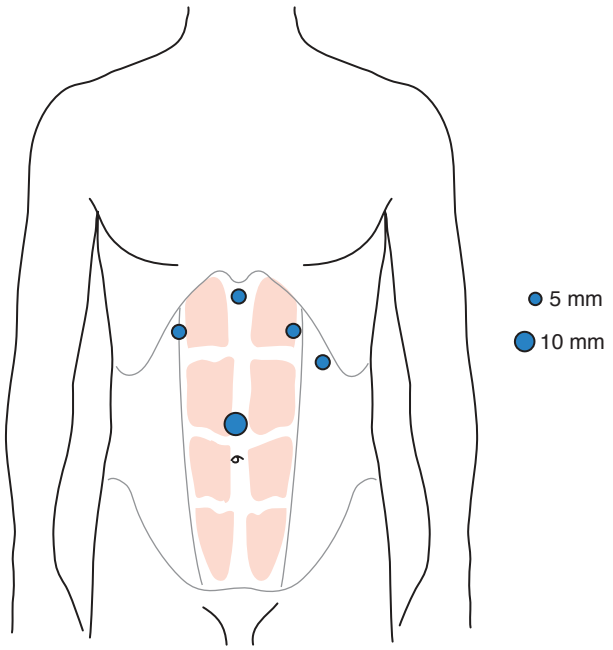

Figure 135.6 Port placement.

Results

Prior to laparoscopic release, open surgical treatment of MALS was described by a number of authors. Harjola[3] and Dunbar et al.[4] performed a midline laparotomy with decompression or division of the MAL and the associated celiac plexus. Reilly reported 51 patients with 9 years follow-up (1964–1980) who

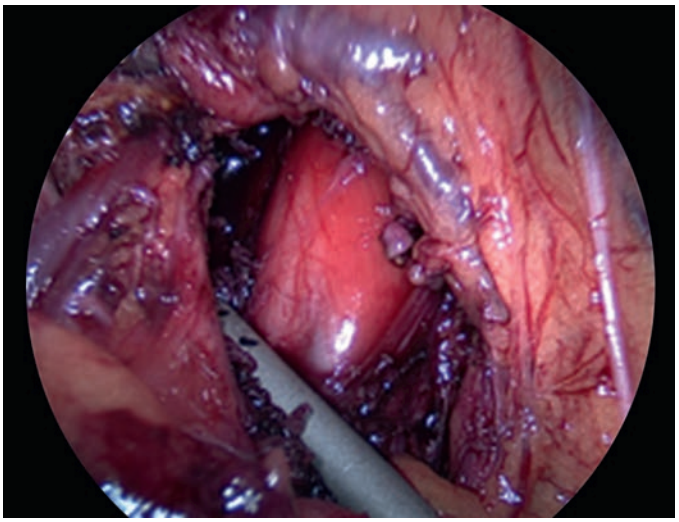

Figure 135.7 Midline view following aortic dissection during median arcuate ligament release. The released celiac origin can be appreciated as it branches from the aorta.

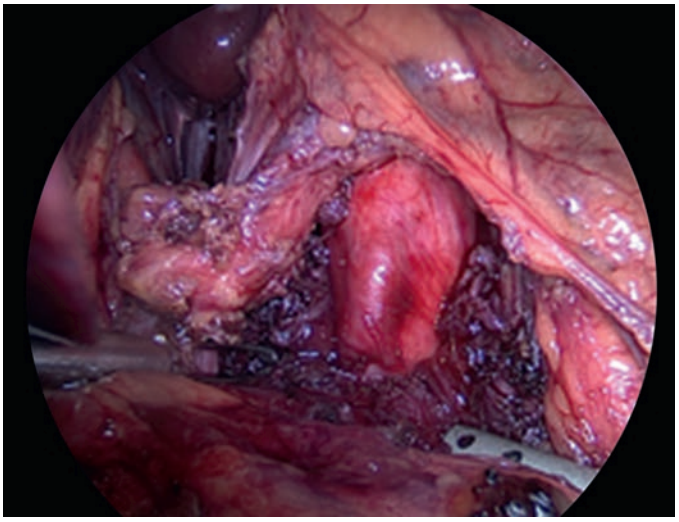

Figure 135.8 Further imaging showing release of median arcuate ligament and decompression of the celiac plexus

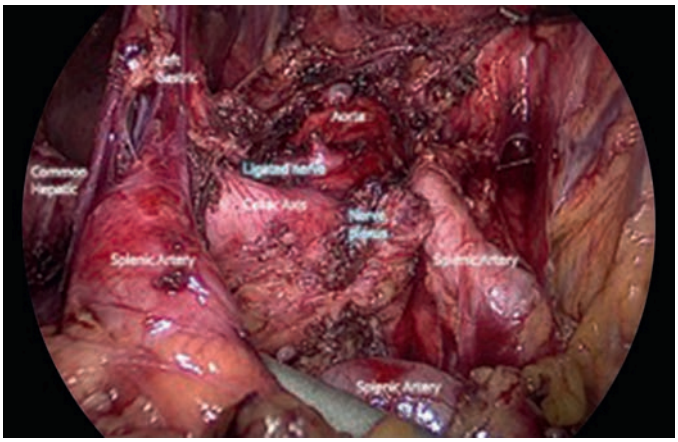

Figure 135.9 Competed dissection of the celiac axis with exposure of vasculature and neural lysis completed.

underwent a combination of decompression alone, decompression with graduated celiac artery dilation through a celiac or splenic arteriotomy, or decompression with reconstruction and bypass of the stenotic arterial segments.[24] Of those 16 patients who underwent MAL decompression alone, 9 (56%) achieved symptom relief. Of 35 patients who underwent decompression and reconstruction, 27 (77%) achieved symptom relief. Ten (40%) of 25 patients who received postoperative arteriograms remained symptomatic, and seven of those patients (70%) showed persistent celiac stenosis. In 2009, Grotemeyer et al. reported a case series of 18 patients, with three patients lost to follow-up, who underwent open decompression, and 11 of which (73%) had good resolution of their symptoms. However, five of the 11 patients (45%) required additional interventions on the celiac trunk prior to pain resolution.[25] Major postoperative complications following the open approach included a thrombosed bypass graft (2%), cerebrovascular accidents (1.4%), gastroesophageal reflux disease (1%), pancreatitis (1%), hemothorax (0.3%), and splenic infarction (0.3%).[26,27]

Several series have demonstrated successful laparoscopic treatment of MALS. In a single center report of data from 1999 to 2009 including 14 patients, 10 patients underwent a laparoscopic MAL release and two patients were converted to a laparotomy for bleeding from either the celiac or left gastric artery. An additional four open MAL divisions were included. Median follow-up was 14 months, and 38% of the laparoscopic group and 50% of the open group had persistent pain at last follow-up.[28] The authors concluded that late recurrence was frequent but seemed to be milder than the initial clinical presentation. Laparoscopy was associated with a shorter hospital stay and decreased time to feeding. The authors also concluded that optimal patient selection, as a predictor of clinical response, remains a challenge.

A retrospective review was published in 2012, which encompassed 20 studies; 13 studies reported open MAL division and seven studies reported laparoscopic MAL division. Nearly 25% of patients in the open series underwent concomitant arterial reconstruction. Of those in the laparoscopic group, 9% underwent celiac artery angioplasty and stenting after laparoscopic division of MAL. Follow-up in the open group extended as far as 229 months, and laparoscopic follow-up extended to 44 months. Laparoscopic conversion to a laparotomy was 9.1%. Intraoperative complications included visceral bleeding, pneumothorax, aortic bleeding, and phrenic artery laceration. All of these complications occurred at a rate of less than 4%. The authors documented immediate postoperative symptom relief in 85% of patients, with a recurrence rate of 6.8% in the open group and 5.7% in the laparoscopic group.[27]

In 2013, El-Hayek et al. reviewed their treatment of 15 patients from 2007 to 2012, including one procedure performed with robotic assistance. They reviewed postoperative celiac velocities in 12 of the 15 patients. Ten patients showed a statistically significant decrease in celiac artery velocity. Of note, two patients showed celiac occlusion, but all but one patient reported the resolution of preoperative pain.[29]

Recently the two largest laparoscopic series to date have been published. Weber et al. reported on 39 patients, of whom 70% reported symptom relief following laparoscopic treatment of MALS despite persistent celiac artery stenosis on postoperative duplex ultrasound. In the same study, all nonresponders with regard to symptom improvement had normal celiac artery velocities after surgery.[6] Brody reported that 33/38 patients had complete resolution of preoperative pain at follow-up, ranging from 6 months to 3 years.[13] In this study, a short form (SF) 36 question survey was used pre- and postoperatively in addition to pre- and postoperative dynamic Doppler ultrasound. The reported postoperative complications from this study included pancreatitis and dehydration.[13] Based on this experience, Brody and his group recommend a predictive formula utilizing SF-36 questionnaire values and celiac artery ultrasound values to identify patients for operative success.[13] Such a formula may enhance preoperative patient counseling with regard to symptom improvement. This series also reported several patients that required supplemental nutrition through enteric tubes or total parenteral nutrition before surgery. Following the laparoscopic MAL release, oral nutrition was restored in all patients, and two patients on TPN were transitioned to intermittent fluids on a weekly basis.[13] There appears to be a scale of improvement based on symptom resolution that does not directly correlate with ultrasound velocity or other imaging changes.

With the adoption of the robotic platform, a few cases have been reported using a robotic-assisted laparoscopic MAL release. In 2013, Do et al. reviewed 16 patients, four of which were completed with robotic assistance. The only significant difference found between laparoscopic and robotic approaches was a shorter operative time for laparoscopy (101.7 min vs. 148.8 min).[22] Thus far no clear advantage for a robotic-assisted MAL release has been demonstrated.

Van Peterson et al. reported their experience using an endoscopic retroperitoneal approach to divide the MAL in 46 patients. Complications included a 2% conversion rate to a laparotomy and a pneumothorax in 4% of patients. Overall, 78% (36/46) of patients had postoperative angiography confirming normal vessel anatomy. Six of the remaining 10 patients underwent endovascular treatment; five patients had a successful dilation with resolution of the celiac artery stenosis. Symptoms were

based on three responses: free of symptoms, improved, or persistent symptoms. In this group, 41/46 (89%) patients reported improvement of symptoms and 65% reported resolution of symptoms with surgical intervention. The authors did not mention whether persistent symptom complaints resulted in endovascular intervention. But no patient who reported persistent symptoms received endovascular intervention. This further supports the theory that MALS is a neurogenic disease, and the vascular abnormalities are only a physiologic marker for ligamentous compression on the artery and nerve plexus. Their median follow-up of 20 months gave sufficient evidence to suggest comparable results to open procedures available at that time.[30]

Based on a literature review and institutional experience, Kim et al. recently proposed an algorithm for diagnostic evaluation and intervention in patients with MAL syndrome.[31] As previously mentioned, patients begin with a workup for abdominal pain, including right upper quadrant ultrasound, abdominal CT, upper endoscopy, and/or HIDA scan. Abnormal findings on these studies result in appropriate treatment for the diagnosed pathology. Normal findings in these studies lead to a duplex ultrasound of the celiac artery. Findings suggestive of MALS or equivocal ultrasound findings may be supplemented with CTA or MRA of the abdomen, or angiography of the celiac artery with pressure gradient measurements for confirmation. Evidence of celiac artery compression is an indication for laparoscopic or robotic MAL release, including celiac ganglionectomy. Follow-up included postoperative celiac artery duplex ultrasound and assessment of symptom resolution. If symptoms persist, angiography of the celiac artery with pressure gradient measurement is used to diagnose residual stenosis. If stenosis remains, angioplasty or stenting of the celiac artery is recommended. If symptoms still persist, vascular reconstruction should be considered if ischemia is felt to contribute to the patient's pain.[31]

CONCLUSION

MALS can be a difficult disease to diagnose, but recent publications document an increasing incidence of surgical treatment for this apparently rare disease. Compression of the proximal celiac artery by the MAL results in image-apparent stenosis, with detectable changes in dynamic ultrasound velocities. However, celiac compression and change in arterial velocity are only markers for neural compression. The true pathophysiologic dysfunction lies within the neural network of the celiac ganglion, which is subjected to the same compression as the celiac artery by the MAL. The celiac plexus is composed of pain fibers and inhibitory motor fibers to the stomach. The rationale for MAL release rests on the theory that MAL syndrome results from compression of the celiac plexus. The compression creates a variety of symptoms, including nausea, vomiting, and gastric dysmotility. Furthermore, the neural compression may contribute to other neurogenic diseases, such as POTS.[12]

As more patients are accurately diagnosed, treated, and followed, the true parameters that mark a successful treatment will continue to change. To date, case series remain small, with both open and laparoscopic approaches and follow-up remains limited to less than 3 years. The complex nature of the disease process requires subjective and objective data to create an algorithm to identify patients who may benefit from surgical intervention.

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The authors provide a unique preoperative methodology to diagnose median arcuate ligament compression and then provide a relatively large cohort with significant follow-up.

A complete reference list can be found online at expertconsult.com.

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136 CHAPTER

Mesenteric Vascular Disease: Venous Thrombosis

STEFAN ACOSTA and MARTIN BJÖRCK

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The common definition of mesenteric venous thrombosis (MVT) refers to a single entity involving thrombosis within the superior mesenteric vein with or without extension to the portal or splenic vein. Recovery following resection of infarcted intestine secondary to mesenteric vessel occlusion was first reported by Elliot in 1895.[1] MVT was recognized as an entity distinct from mesenteric arterial occlusion by Warren and Eberhard in 1935.[2]

EPIDEMIOLOGY

MVT is most commonly encountered in middle-aged and older adult patients, with an equal gender distribution when age differences between genders are taken into account.[3,4] In a population-based study with an average autopsy rate of 87%, MVT was found to be present in 63 of 402 patients (16%) with acute mesenteric ischemia (Fig. 136.1).[5,6] Additionally, the overall incidence of MVT with transmural intestinal infarction was estimated to be 1.8 per 100,000 person-years in Malmö, Sweden, between 1970 and 1982, and the cause-specific mortality ratio was 0.9 per 1000 autopsies.[5] The overall incidence of MVT increased to 2.7 per 100,000 person-years in the same city between 2000 and 2006.[4] An important factor contributing to an underestimation of the latter incidence estimate was the declining autopsy rate, from 87% to 10%, between the two periods. In contrast, factors increasing the incidence estimate over time were the growing proportion of older adults in the population and the greater amount of diagnostic activity and its higher quality. Patients with MVT were diagnosed at autopsy, at operation, or with computed tomography (CT) in 12% (6 of 51), 19% (10 of 51), and 69% (35 of 51) of cases, respectively,[4] during the latter period.

PATHOGENESIS

Etiology

Primary MVT is defined as spontaneous, idiopathic thrombosis of the mesenteric veins not associated with any other disease or etiologic factor. Patients with any condition known to predispose to MVT (Box 136.1) are considered to have secondary MVT.[7] Approximately 90% of MVTs are secondary.[8]

Risk Factors

Several conditions are associated with MVT (see Box 136.1); these can be divided into three main categories: direct injury, local venous congestion or stasis, and thrombophilia (i.e., the classical three factors identified by Virchow: vessel wall, flow, and blood). Splenectomy is a risk factor for the development of thrombus propagation from the ligated splenic vein to the

Abstract

Mesenteric venous thrombosis is a very difficult disease to diagnose on clinical grounds. However, owing to the increased availability and evolution of computed tomography in developed countries, early diagnosis prior to the development of peritonitis is often possible. First-line therapy is full-dose anticoagulation, whereas endovascular therapy including thrombolysis may be considered in cases refractory to anticoagulation therapy. Exploratory laparotomy and bowel resection for this disease will always be a treatment option in patients developing peritonitis or not responding to anticoagulation in a clinically favorable way. At present, it is recommended that risk-factor evaluation for mesenteric venous thrombosis should include screening for inherited disorders such as factor V Leiden mutation, prothrombin gene mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency as well as acquired disorders such as *JAK2* V617F mutation, lupus anticoagulant, and cardiolipin antibodies.

Keywords

mesenteric venous thrombosis
acute mesenteric ischemia
risk factors
factor V Leiden mutation
thrombophilia
anticoagulation

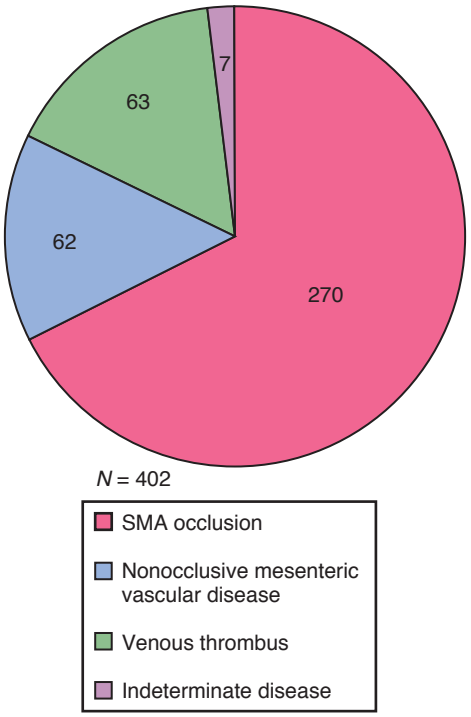

Figure 136.1 Acute mesenteric ischemia: distribution of etiologies in 402 patients in Malmö, Sweden, between 1970 and 1982.[4,5] Mesenteric venous thrombosis, acute SMA occlusion (embolus/thrombus ratio = 1.4), and nonocclusive mesenteric ischemia were found in 16%, 68%, and 16%, respectively. *SMA*, Superior mesenteric artery.

BOX 136.1 Conditions Associated With Mesenteric Venous Thrombosis

Direct Injury

- Abdominal trauma (blunt and penetrating)
- Postsurgical (particularly postsplenectomy)
- Intra-abdominal inflammatory states (pancreatitis, inflammatory bowel disease)
- Peritonitis and abdominal abscess

Local Venous Congestion or Stasis

- Portal hypertension; cirrhosis of the liver
- Congestive heart failure
- Hypersplenism
- Obesity
- Increased abdominal pressure; abdominal compartment syndrome

Thrombophilia

- Protein C and protein S deficiency
- Antithrombin III deficiency
- Activated protein C resistance (factor V Leiden gene mutation)
- Presence of 20210 A allele of prothrombin gene
- Methylenetetrahydrofolate reductase mutations
- *JAK2* V617F gene mutation
- Neoplasms (particularly pancreatic and colonic)
- Oral contraceptive use
- Polycythemia vera
- Essential thrombocytosis
- Heparin-induced thrombocytopenia
- Lupus anticoagulant–antiphospholipid syndrome
- Cytomegalovirus infection
- Extramesenteric venous thromboembolism

portomesenteric venous system.[9] In retrospect, after scrutinizing the multidetector computed tomography (MDCT) images, the prevalence of incidental, probably asymptomatic, nonanticoagulated MVT in patients with inflammatory bowel disease was reported to be as high as 27%[10] and was located at the periphery, limited to the territory of inflammatory bowel disease. The detection of MVT was associated with disease severity and factors such as bowel wall thickening, ascites, bowel stenosis, and intestinal surgery.[10] Severe acute pancreatitis may lead to MVT but more frequently to splenic vein thrombosis due to its very close proximity to the inflamed pancreas.[11,12] In a case-control study, obesity was found to be a risk factor.[5] Inherited thrombophilia[13-15] was reported in 42%[3] to 55%[4] of patients with MVT. Factor V Leiden mutation (activated protein C resistance) was present in 45% of the patients with MVT in Malmö, Sweden[4]; this was considerably higher than the known prevalence rate of 7% in the background population.[16] Although factor V Leiden mutation is a genetic defect, peripheral venous thrombotic manifestations are frequently delayed until adulthood, even in homozygotes.[16,17] Case-control studies suggest that factor V Leiden[18] and prothrombin G20210A gene mutations[18,19] are overrepresented in patients with MVT. MVT has been reported to be a common first clinical manifestation of patients with newly diagnosed myeloproliferative disorders such as polycythemia vera or essential thrombocytosis and often occurs before a rise in peripheral blood counts. The *JAK2* V617F (Janus-activated kinase gain-of-function substitute of valine to phenylalanine at position 617) mutation is diagnostic of myeloproliferative disorders[20]; in a meta-analysis of four case-control studies it was—in contrast to patients with other venous thromboembolisms—found to be strongly associated with thrombosis within the mesenteric, portal, and hepatic veins (splanchnic venous thrombosis).[21] Primary cytomegalovirus infection has also been associated with MVT.[22] Neither liver cirrhosis nor abdominal cancer was a risk factor in a population-based case-control study based on autopsies.[5] Synchronous venous thromboembolism in the systemic circulation frequently occurs in patients with MVT, especially pulmonary embolism.[5] There may be an increased risk of MVT following laparoscopic surgery because of venous stasis from increased intra-abdominal pressure, especially in obese patients undergoing Roux-en-Y bypasses, or when there is a more extensive intraoperative mobilization of the mesenteric, portal, or splenic vein. Together with the presence of any systemic thrombophilic state, development of MVT seems to be more likely.[23,24]

NATURAL HISTORY

It is difficult to pinpoint the natural history of MVT. The disease is uncommon, patients often have diffuse symptoms, and the condition is not always detected, even with contemporary diagnostic routines. Thus we have no absolute knowledge of the total number of patients with symptomatic and asymptomatic disease. However, in a population-based study with a high autopsy rate (87%), it was found that 35 of 31,015 patients (0.1%) examined postmortem had MVT.[5] The majority of

patients with MVT at autopsy (27 of 35, or 77%) had a transmural intestinal infarction, judged to be the cause of death. The patients diagnosed at exploratory laparotomy all had transmural intestinal infarction and required bowel resection for survival. The mortality rate among those undergoing exploratory laparotomy was 30% (12 of 40). Portal venous thrombosis (PVT) was studied in the same cohort, and there were some interesting differences: PVT was 10 times more common than MVT at autopsy, patients with PVT more often had asymptomatic disease, and PVT was seldom considered the cause of death.[25] Two studies[26,27] suggest that superior MVT, in contrast to isolated PVT, is associated with symptoms in the overwhelming majority (92%[26]) of cases and also often results in bowel gangrene (33%[27]-45%[26]), depending on diagnostic and therapeutic activity. On the other hand, recent MDCT imaging studies have reported that one-fourth of the patients with inflammatory bowel disease have thromboses in the peripheral mesenteric veins and that most of these thromboses are probably asymptomatic.[10]

PATHOLOGY AND MANIFESTATIONS

The degree of intestinal ischemia that develops depends on the extent of venous thrombosis within the splanchnic venous circulation and whether there is occlusion and collateral flow. Patients with isolated PVT without peripheral propagation to the superior mesenteric vein are asymptomatic in the majority of cases (61%[26]) and almost never experience intestinal infarction (0%[26]-10%[27]). In 270 patients with porto-MVT found at autopsy, 29 of 31 (94%) patients with MVT had intestinal infarction and 0 of 239 (0%) with isolated PVT had intestinal infarction.[27]

At operation, MVT is characterized by a limited segment of intestinal ischemia, with edema, swelling, and reddish discoloration of the affected small bowel and its adjacent mesentery and a palpable pulse in the superior mesenteric artery (SMA) and its branches.[28] In contrast, intestinal ischemia due to arterial occlusive or nonocclusive disease is often characterized by extensive ischemia that includes the jejunum, ileum, and colon,[29] with patchy cyanosis, reddish black discoloration, and no palpable pulsations. MVT can be confirmed during surgery if an infarcted bowel segment is removed. Division of a small part of the adjacent mesentery, without previous vessel ligation, reveals thrombosis within the veins, whereas a pulsatile hemorrhage arises from the arteries. The extent of intestinal infarction is often limited to the jejunum or the ileum (Fig. 136.2).[5]

DIAGNOSIS

Patients with symptoms of less than 4 weeks' duration are classified as having acute MVT. Those with symptoms lasting longer than 4 weeks but without bowel infarction or those with clinically insignificant MVT diagnosed incidentally on abdominal imaging are classified as having chronic MVT. The majority of patients—71% and 74% in two large clinical series[4,7]—have acute MVT.

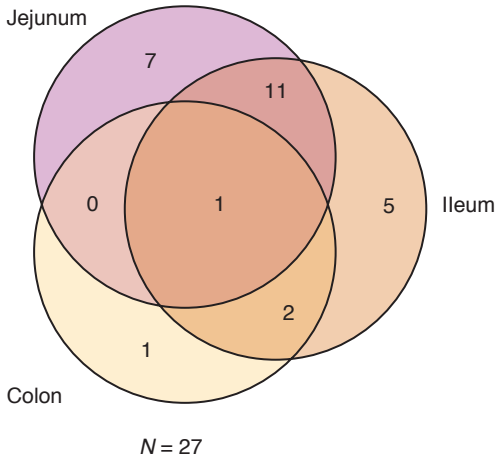

Figure 136.2 Venn diagram showing the extent of intestinal infarction in 27 patients with mesenteric venous thrombosis and transmural intestinal infarction.

Recognition by History and Physical Examination

Acute and particularly chronic MVT is a difficult diagnosis among patients presenting with acute or subacute abdominal pain. Awareness of the disease, a careful risk factor evaluation, and positive findings at physical examination may lead the clinician to the diagnosis. The onset of acute MVT is often insidious, and diffuse abdominal pain may be present for days or weeks. Abdominal pain is often[7,8] but not always present at admission. The second most common symptom is nausea/vomiting, whereas diarrhea and lower gastrointestinal bleeding are present in less than 20% of cases.[30,31] Typically a middle-aged patient with a personal or a family history of deep venous thrombosis presents with abdominal pain of a few days' duration, vomiting, and abdominal distention as well as a clearly raised C-reactive protein (CRP) level. The patient may develop localized peritonitis. With progression to transmural intestinal infarction, peristalsis ceases and signs of generalized peritonitis appear.

Laboratory Testing

There are no accurate plasma biomarkers for diagnosing intestinal ischemia. D-dimer has been reported to be a sensitive but not specific marker of acute thromboembolic occlusion of the SMA.[32] From a theoretical point of view, we have reason to believe that a normal D-dimer level may be useful to exclude MVT as well. This view is supported by experience from a small series of patients.[4]

Further, because inherited thrombophilic factors are common in MVT, it is recommended for risk factor evaluation that all patients with MVT should be screened for the following inherited disorders: factor V Leiden mutation, prothrombin gene mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency. Simultaneously, the patient should be checked for acquired disorders such as *JAK2* V617F mutation,[20,21] lupus anticoagulant, and cardiolipin antibodies. Whether the presence of these thrombophilic factors influences recurrence rates and/or duration of anticoagulation treatment or not is unclear.

Since MVT may be diagnosed before a rise in peripheral blood counts in myeloproliferative disorders,[20] it may be wise to obtain a full blood count with white blood cell differentiation at follow-up.

Noninvasive and Invasive Testing

MDCT of the abdomen, with intravenous contrast injection and imaging in the portal venous phase, is the most important, available, and accurate diagnostic tool.[33-35] The protocol for acute CT of the abdomen varies with the clinical history provided by the referring physician who requests the examination. Of note, MVT is seldom suspected by the clinician before ordering CT; in fact, the diagnosis is often first made by the radiologist.[36] In one series, MVT or intestinal ischemia was suspected before CT in only 1 patient with congenital portal vein occlusion out of 20 with verified MVT (5%).[36] Optimally, the CT protocol would include biphasic imaging in the arterial and portal phases with 1-mm thin slices and reconstructions in the coronal and sagittal planes.

The vascular and intestinal findings of MVT on MDCT (Figs. 136.3-136.5) are summarized in Table 136.1.[36] MDCT often demonstrates extensive thrombosis of the portomesenteric system, with extension of thrombosis to at least the extrahepatic portal and splenic veins. Intestinal findings are less common and more subtle. Hence the radiologist should always examine the mesenteric vessels in cases of an acute or unclear abdomen. An optimized CT protocol should be used in MVT patients in whom the discontinuation of oral vitamin K antagonist (VKA) treatment is being considered or when patients on anticoagulation treatment are suffering from abdominal pain or experiencing a general deterioration in their condition.

Exploratory laparoscopy or laparotomy will continue to be a necessary diagnostic tool for some patients, even after CT, especially those presenting with peritonitis. In experienced hands, laparoscopy (see film sequence) can be the preferred method to assess intestinal viability.[37,38] Major obstacles for

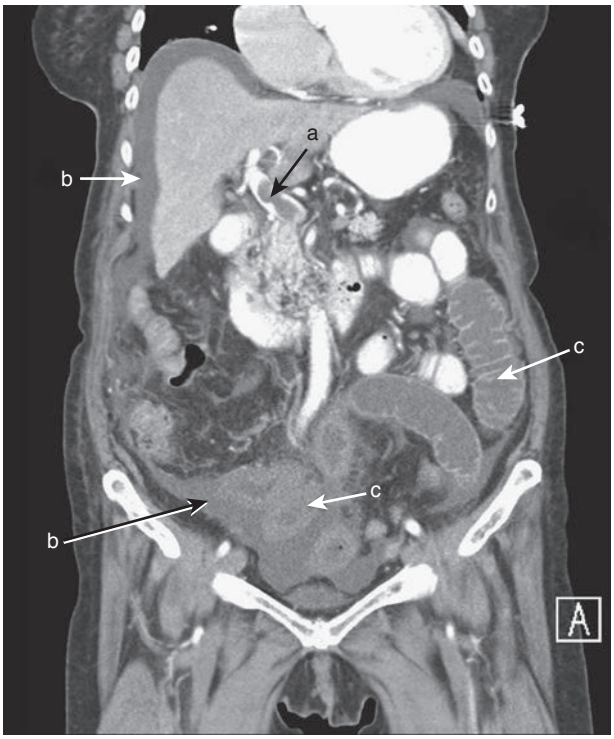

Figure 136.4 Multidetector computed tomography with multiplanar reconstruction in the coronal view shows thrombosis in the extrahepatic portion of the portal vein *(a),* ascites *(b),* and dilatated and edematous small bowel loops *(c).*

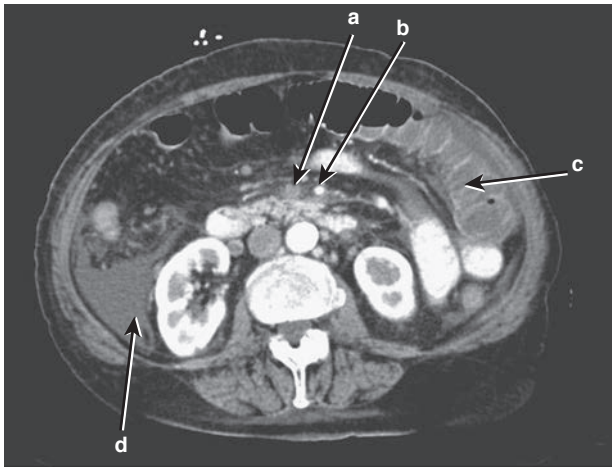

Figure 136.3 Multidetector computed tomography of the abdomen in the portal venous phase, in the axial projection, shows thrombosis of the superior mesenteric vein *(a),* an open superior mesenteric artery *(b),* dilatated and edematous small bowel loops *(c),* and ascites *(d).*

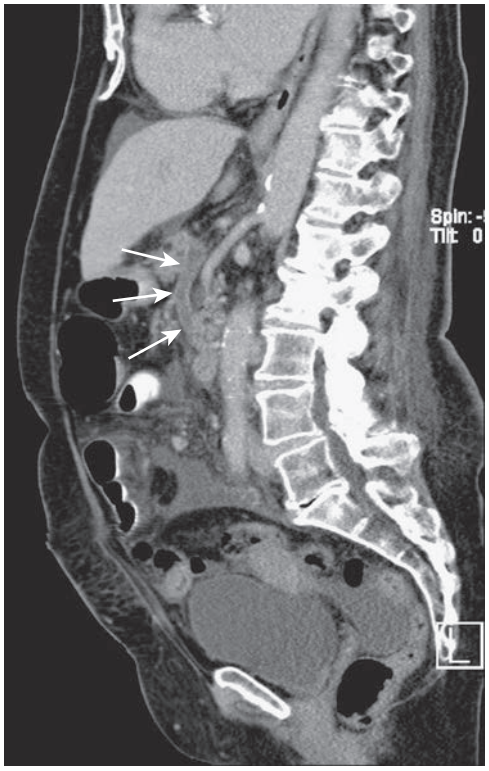

Figure 136.5 Multidetector computed tomography with multiplanar reconstruction in the sagittal view shows thrombosis in the superior mesenteric vein *(arrows).*

TABLE 136.1 Findings With Multidetector Computed Tomographic Venography of the Abdomen in 20 Patients With Mesenteric Venous Thrombosis[36]

Finding	Frequency (%)
Vascular	
Mesenteric venous thrombosis	20 (100)
Central[a] mesenteric venous thrombosis	20 (100)
Peripheral mesenteric venous thrombosis	6 (30)
Portal venous thrombosis	17 (85)
Extrahepatic portal venous thrombosis	17 (85)
Intrahepatic portal venous thrombosis	9 (45)
Splenic venous thrombosis	15 (75)
Venous collaterals	12 (80)
Intestinal	
Mesenteric edema	10 (50)
Small bowel wall edema	5 (25)
Local small bowel dilatation[b]	4 (20)
Gas in portomesenteric venous system	0 (0)
Ascites	8 (40)

[a]The first 5 cm of the proximal superior mesenteric vein is defined as central.
[b]Greater than 4 cm in diameter.

full visualization and macroscopic evaluation of the small intestines are extensive paralysis with bowel dilatation and prior adhesions.

TREATMENT AND RESULTS

The first-line treatment option is conservative with anticoagulation, fasting, nasogastric tube, fluid and electrolyte replacement, analgesics, and administration of total parenteral nutrition. The use of antibiotics directed toward intestinal flora is logical in cases of advanced MVT with risk of sepsis secondary to bacterial translocation or bowel perforation.[39] A few patients will undergo laparotomy and bowel resection at three different time points: at admission due to late presentation or diagnosis, after some weeks due to failure of anticoagulation therapy to reverse the condition, and after some months due to late bowel stricture. Systemic thrombolysis in MVT has not been evaluated systematically, but extensive MVT can be successfully treated with recombinant tissue plasminogen activator (rt-PA; total dose of approximately 100 mg for 48 hours).[40] Endovascular treatment in combination with heparin infusion, with or without bowel resection, is an additional treatment tool in those few patients who do not respond satisfactorily to heparin infusion alone. A multidisciplinary stepwise management strategy involves modern surgical and endovascular treatments that focus on early mesenteric recanalization and bowel viability salvage. This is best done in an integrated intestinal stroke center composed primarily of gastroenterologist and gastrointestinal and vascular surgeons. Such a center seems to be able to generate favorable outcomes, with overall recanalization rate of 91% and 30-day mortality rate of 12% or lower in acute superior MVT.[41]

Medical Treatment

Immediate full anticoagulation with a continuous infusion of unfractionated heparin is used in surgical as well as nonsurgical cases to obtain an activated partial thromboplastin time of 50 to 70 seconds monitored at 4-hour intervals. In the early phase, unfractionated heparin offers two advantages over LMWH: the anti-inflammatory effect is greater and it can be reversed with protamine if laparotomy becomes necessary. Every patient should initially be closely observed, with repeated abdominal evaluations and body temperature readings as well as daily CRP and leukocyte measurements. In the absence of recovery, with rising CRP values, or in the case of any clinical deterioration, repeat CT examinations with intravenous contrast can show changes such as extension of venous thrombosis and can evaluate the severity of ischemic bowel lesions, providing help in the often difficult decision-making process of when to proceed to laparotomy.[42]

When gastrointestinal function has normalized, LMWH or oral VKA or new direct oral anticoagulants (DOAC) are advocated. The anti-inflammatory effects of LMWH (compared with VKA or DOAC) may be advantageous in the early follow-up period.[43] The thrombotic status within the splanchnic venous system after VKA treatment has not been evaluated systematically with repeated CT scans, but it seems that most thrombosis shows either no change or regression after a short period (3 months) of VKA treatment.[36] Lifelong treatment with VKA is recommended[44] owing to the high recurrence rate of MVT, up to 36%, without anticoagulation.[7] Long-term treatment with LMWH is reserved for patients with liver dysfunction or other conditions in which oral VKA treatment is contraindicated, inappropriate, or a less reliable treatment option. Most patients can be treated conservatively if they are diagnosed in a timely manner.[8] One series showed that MDCT in the portal venous phase was diagnostic in all 20 investigated patients, and conservative management was possible in 19 (95%).[36] The duration of anticoagulation therapy must be carefully balanced against risk factors for bleeding, such as the presence of varices, low platelet count and previous bleeding, risk for recurrence due to persisting risk factors, previous venous thromboembolism, and consequences of recurrence or progression due to extensive bowel involvement.[45] An alternative medical option is the use of a fixed dose of DOAC. The advantages include fewer interactions with other medications and lack of need of frequent monitoring; the disadvantages include the present lack of antagonists to factor Xa inhibitors and lack of specific safety data in patients with MVT. However, the effects of another DOAC, dabigatran, a thrombin inhibitor, can instantly be reversed with idarucizumab.[46,47]

In-hospital mortality among identified and actively treated patients has decreased to 20%, probably because of earlier detection with CT and identification of a higher proportion of patients without peritonitis and not requiring laparotomy.[3,8]

Anticoagulation with or without bowel resection in patients with acute MVT has also improved survival in comparison with observation alone.[7] The overall 30-day survival in a contemporary series was 80% (41 of 51), and the estimated 5-year survival for the 51 patients was 70%.[4] Prognosis of patients with MVT after hospital discharge seems to be highly associated with the underlying disease, and cancer patients have the poorest survival.[4] Gastrointestinal bleeding,[7] late small bowel perforation, and intestinal stricture[8] have been described as specific gastrointestinal complications.

Endovascular Treatment

A number of endovascular procedures for the treatment of MVT have been developed in recent years, including percutaneous transjugular intrahepatic portosystemic shunting (TIPS) with mechanical aspiration thrombectomy[48] and direct thrombolysis,[49,50] percutaneous transhepatic mechanical thrombectomy,[51] percutaneous transhepatic thrombolysis,[52,53] thrombolysis via the SMA,[54] and thrombolysis via an operatively placed mesenteric vein catheter.[55] Rapid thrombus removal or dissolution can be achieved through these techniques, especially after TIPS and stent placement to create a low-pressure runoff.[56] Mechanical thrombectomy is performed using a variety of thrombectomy devices and is most effective in cases of acute rather than chronic thrombus. Before considering thrombolysis, checking for relative and absolute contraindications such as recent cerebral infarction (within 6 weeks), history of cerebral hemorrhage, malignant tumor, arteriovenous malformation in the brain, severe diabetic retinopathy, gastrointestinal hemorrhage, or esophageal varices should be performed. Local direct thrombolysis into the portomesenteric circulation through the transjugular or transhepatic route is useful for clearing residual clots and restoring venous flow. Indirect thrombolytic therapy via the SMA is less effective and more time-consuming, may require longer infusion times and higher doses of thrombolytic agent, and is also associated with an increased bleeding risk. There is some experience with both rt-PA and urokinase as thrombolytic agents.[54] Balloon angioplasty is an alternative technique of clot fragmentation in cases of refractory thrombus and fixed venous stenosis. Aspiration thrombectomy is performed with a stiff, large-diameter (at least 8F), angled catheter connected to a Luer-Lok syringe to create a vacuum effect.[49] A potential drawback of thrombectomy and angioplasty is intimal trauma that can promote rethrombosis.

Endovascular techniques have been successful in terms of survival, patency of the portomesenteric veins, lower rates of portal hypertension,[53] low complication rates, and avoidance of bowel resection[53] in selected patients. However, in a larger series of 16 patients with MVT treated with local thrombolysis, 1 had complete lysis, 11 had partial lysis, and 4 had no lysis of the superior mesenteric vein.[54] Local thrombolysis was associated with significant bleeding complications in 60% of patients, including intra-abdominal bleeding, bleeding from the access site, perihepatic hematoma, nosebleed, and hematuria.[54] Accumulation of blood from the portal vein in the right pleural space, causing right-sided hemothorax, has been reported during percutaneous transhepatic thrombectomy and thrombolysis,[57] as have deaths due to gastrointestinal hemorrhage and sepsis.[54,57]

Patients should be anticoagulated with unfractionated heparin following endovascular treatment, and the bowel should be rested. VKA or DOAC replaces heparin when gastrointestinal function is normalized. Patency of the portal system after TIPS can be evaluated by follow-up Doppler ultrasound at 1 and 3 months and then again at 6 months to check the portal system and shunt function.[49] Clearance of thrombus can be evaluated with CT, but a clear correlation between radiologic findings and clinical symptoms does not appear to exist.

There are no comparative studies between anticoagulation alone and endovascular treatment to help establish the indication for endovascular treatment. Most patients are treated successfully with medical treatment only, but a small proportion (5%[4]) of patients deteriorate during medical treatment. In those situations, clinical practice in some centers during the last decade has been to initiate endovascular treatment.

Surgical Treatment

The indications for surgery are peritonitis, severe gastrointestinal bleeding, small bowel perforation, and intestinal stricture; the last is often associated with chronic diarrhea. When a clear clinical deterioration or peritonitis develops in a patient with MVT, laparotomy is indicated. In very select cases, open surgical thrombectomy may be considered worthwhile.[58] When an emergency laparotomy must be performed, endovascular treatment with thrombolysis is contraindicated. If there are signs of extensive intestinal ischemia, which is rare, one possible strategy may be surgical thrombectomy combined with bowel resection of the gangrenous bowel, heparinization, and second-look laparotomy. Bowel resection should be performed in cases of frank transmural intestinal necrosis, uncertain bowel viability, or severe ischemic bowel lesions (Fig. 136.6). However, signs of peritonitis are not always associated with transmural intestinal infarction, and some patients with rebound tenderness can still be treated conservatively.[8] Primary bowel anastomosis after resection is recommended. This is a straightforward treatment in the typical patient in whom a short segment of the small bowel is affected. In the less common situation, in which a longer segment of the intestines is threatened, an alternative is to staple off the infarcted intestine, perform skin-only closure rather than fascial closure, and delay reconstruction until a second-look laparotomy, when the viability of the remaining small intestine can be evaluated. At the second look, areas of intestinal ischemia with doubtful viability may have recovered, and there is usually a clearer demarcation of the infarcted segments. The purpose of the second-look laparotomy is to reduce unnecessary bowel resections at the primary exploration, thus permitting salvage of segments of bowel with doubtful viability.

Immediately after surgery, a heparin infusion is administered. The patient should be on bowel rest and receive total parenteral nutrition for a few days until the return of

Figure 136.6 Ischemic bowel due to mesenteric venous thrombosis (see also film sequence). A 47-year-old man with a history of deep venous thrombosis and pulmonary embolism treated with a vena cava filter and a vitamin K antagonist (VKA) presented with a 3-day history of lower abdominal pain and obstipation. He had discontinued VKA treatment 4 days previously. At admission, plasma D-dimer was 9.6 mg/L (reference value, <0.2 mg/L), and plasma lactate was normal. He developed signs of generalized peritonitis with rebound tenderness in the abdomen 12 hours after admission. Laparoscopy showed signs of ischemia in the proximal ileum. At laparotomy, 1.2 m of the small bowel was ischemic. It was decided to remove the two most reddish, discolored, severely ischemic segments *(arrows)* by resecting a total length of 0.4 m, followed by one small bowel anastomosis. Note the edema of the affected small bowel loops and their adjacent mesentery. Treatment with a full dose of low-molecular-weight heparin was started at the end of surgery. Second-look laparotomy was performed after 30 hours. Reassessment of bowel viability showed that the intestines had normal turgor and color and the anastomosis was intact. Recovery thereafter was uneventful, and lifelong treatment with VKA was prescribed. Histopathology of the resected bowel did not show transmural infarction but did show infarcted mucosa and venous thrombosis.

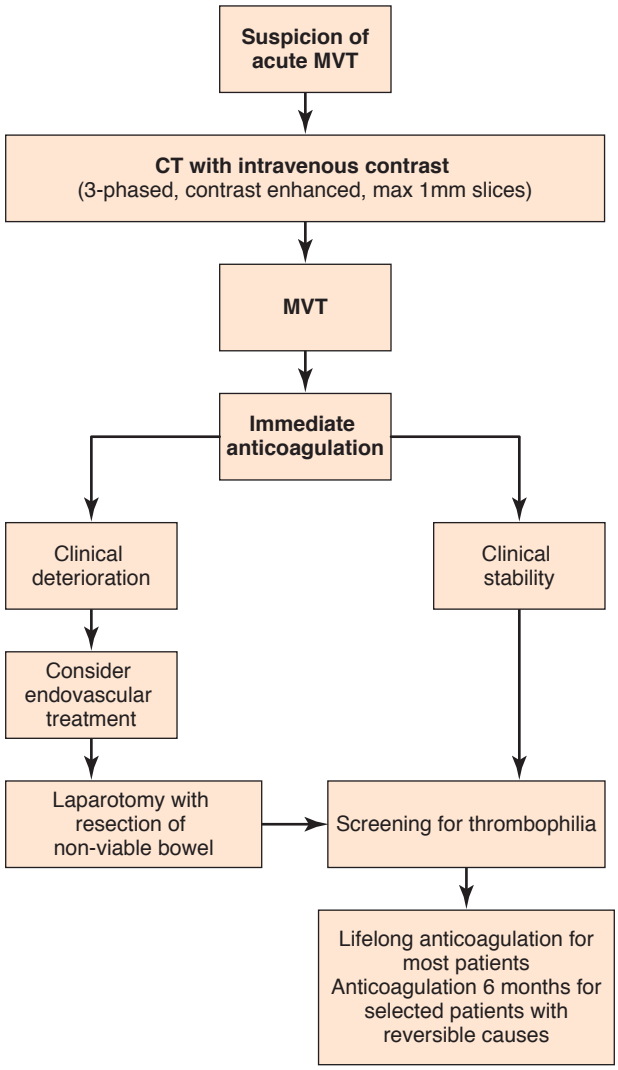

Figure 136.7 Management algorithm for patients with acute mesenteric venous thrombosis (MVT). *CT*, Computed tomography.

gastrointestinal function. All patients should then receive anticoagulation with either LMWH or VKA. Lifelong treatment should be considered for most patients owing to the high recurrence rate and the often fatal outcome in case of recurrence. The value of a postoperative CT scan to evaluate the extension of thrombosis and the frequency of thrombus recanalization is unclear. However, a repeat CT scan after 6 months of anticoagulation therapy may be helpful in determining the duration of treatment if lifelong treatment is not being considered.

Morbidity rates in cases managed with and without surgery are similar,[8] although it must be recognized that these are different groups of patients, and no randomized studies exist. The short-term[3] and 2-year[8] survival rates are comparable between groups undergoing surgery and medical treatment. The survival rate after bowel resection is around 80%.[3,7] The most common complications following surgery are pneumonia, wound infection, renal failure, sepsis, and gastrointestinal bleeding.[7,8] Fortunately the occurrence of short-bowel syndrome after bowel resection for MVT is rare.[2,7] In a recent series, none of the 12 patients who underwent bowel resection developed short-bowel syndrome.[4] The median length of the resected intestinal segment in that series was 0.6 m (range, 0.1-2.2 m). The relatively high frequency (23%) of short-bowel syndrome in patients with acute MVT in an older study might be attributable to unnecessarily extensive bowel resections or suboptimal pharmacologic therapy.[7] Among patients with MVT, bowel resections should always be conservative. A pragmatic management algorithm for patients with acute MVT is shown in Fig. 136.7.[59]

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137 CHAPTER

Vasculitis and Other Uncommon Arteriopathies

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Vasculitis refers to a group of inflammatory disorders that result in inflammation and necrosis of blood vessels with subsequent impairment of flow resulting in ischemia and infarction of distal tissues.[1,2] Often, vascular surgeons are the first physicians consulted in cases of vasculitis, and vasculitis should be considered in patients with ischemic occlusive disease or aneurysmal disease in the absence of traditional risk factors and in association with features of a systemic inflammatory process. Prompt involvement of a rheumatologist can expedite diagnostic testing and treatment. Vessels of any location may be affected by vasculitis, and the classification nomenclature has been defined by the International Chapel Hill Consensus Conference,[3] as outlined in Table 137.1

VASCULITIS PRESENTATION

There is no single presentation of vasculitis, but clinical manifestations often suggest the size of vessel affected and thus can help guide the likely diagnosis and necessary work-up. For example, patients with large-vessel vasculitis often present with limb

TABLE 137.1 International Chapel Hill Consensus Conference Nomenclature[3]

Nomenclature		Vasculitis
Large-vessel vasculitis		Giant cell arteritis (also known as temporal arteritis) Takayasu's arteritis
Medium-vessel vasculitis		Polyarteritis nodosa Kawasaki disease
Small-vessel vasculitis	Immune complex-mediated	Antiglomerular basement membrane (anti-GBM) disease Cryoglobulinemic vasculitis IgA vasculitis (Henoch-Schönlein purpura) Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)
	Antineutrophil cytoplasmic antibody-mediated (ANCA-associated pauci-immune)	Granulomatosis with polyangiitis (previously known as Wegener's granulomatosis) Microscopic polyangiitis Eosinophilic granulomatosis with polyangiitis (previously known as Churg-Strauss syndrome)
Variable-vessel vasculitis		Behçet's disease Cogan syndrome Thromboangiitis obliterans (Buerger's disease).
Single-organ vasculitis		Cutaneous leukocytoclastic vasculitis Cutaneous arteritis Primary central nervous system (CNS) vasculitis (isolated angiitis of the CNS) Isolated aortitis Others
Vasculitis associated with systemic disease		Lupus vasculitis Rheumatoid vasculitis Sarcoid vasculitis Others
Vasculitis secondary to other etiology		Hepatitis C-associated cryoglobulinemic vasculitis Hepatitis B-associated vasculitis Syphilis-associated vasculitis Drug-associated immune complex vasculitis (hypersensitivity vasculitis) Cancer-associated vasculitis Others

Thromboangiitis obliterans (Buerger's disease) was not classified at the Chapel Hill conference but fits best in to the variable-vessel vasculitis group.

claudication, vascular bruits, asymmetric blood pressures, or absence of pulses. The medium vessel vasculitides often present with cutaneous nodules and ulcers, livedo reticularis, digital gangrene, mononeuritis multiplex, and renovascular hypertension. In contrast, patients with small vessel vasculitis tend to present with palpable purpura, pulmonary-renal syndromes (glomerulonephritis and alveolar hemorrhage), urticarial skin rashes, and scleritis.

Histologic Characteristics of Vasculitis

The vasculitides typically cause characteristic histologic features, including infiltration of the vessel wall by neutrophils, mononuclear cells, and/or giant cells. Fibrinoid necrosis is seen with pan-mural destruction of the vessel wall and evidence of leukocytoclasis (disruption of leukocytes resulting in the histologic finding of "nuclear dust"). It should be noted that perivascular infiltration alone is a nonspecific histologic finding, which is not diagnostic of vasculitis.

Histologic findings in the specific diseases are dependent on the vessel size affected and the underlying disease physiology. Giant cell arteritis (GCA), Takayasu's arteritis, and primary central nervous system (CNS) vasculitis are cell mediated, whereas polyarteritis nodosa (PAN), Henoch-Schonlein purpura, cryoglobulinemic vasculitis, and cutaneous leukocytoclastic angiitis are immune complex mediated. The ANCA-associated vasculitides (AAV) involve both cellular and humoral immune responses and often involve granulomatous tissue injury without immune complex formation.

Angiography

When tissue biopsy is not feasible, angiography imaging can be helpful for assessing specific types of arteritis. For example, angiography of the celiac trunk, superior mesenteric, and renal arteries can be diagnostic of PAN; imaging of the aortic arch is essential for the diagnosis of Takayasu's arteritis and GCA with large-vessel involvement; angiography of the extremities can be helpful in the diagnosis of thromboangiitis obliterans (TO); and angiography of the cerebral circulation is essential for the diagnosis of primary CNS vasculitis. Angiographic findings that are characteristic of vasculitis include irregular asymmetrical tapering and narrowing as well as "beading" with segmental stenosis and aneurysm formation.

Noninvasive Vascular Imaging

Noninvasive vascular imaging is used to evaluate some vascular beds, although it is somewhat controversial. In GCA, Doppler ultrasound of the temporal arteries has been shown to demonstrate inflammatory changes and can be used to assist with biopsy site selection; however, utility as a diagnostic tool is highly dependent on the experience of the sonographer; thus it should not replace temporal artery biopsy as a diagnostic tool.[4] Magnetic resonance angiography of the aorta has utility in larger vascular beds and can be used to image the aorta in Takayasu's arteritis and GCA. Aortic wall enhancement with gadolinium indicates active inflammation.[5] Positron emission tomography (PET) has also been used to demonstrate enhancement in the aortic and subclavian vascular beds in Takayasu's and GCA[6] but has not gained widespread use as a diagnostic tool.

LARGE-VESSEL VASCULITIS

Takayasu's Arteritis

Takayasu's arteritis is a cause of large-vessel vasculitis affecting the aorta and its branches that presents in younger individuals. It is discussed in Chapter 139.

Giant Cell Arteritis (Temporal Arteritis)

Epidemiology

GCA primarily affects patients over 50 years of age and is more common in Caucasian patients of Northern European descent. While relatively rare in African Americans, GCA has been reported in all racial groups; thus patients of other races presenting with a consistent history should be fully evaluated.[7] The incidence of GCA increases dramatically with age and is approximately 10 times more common in patients in their 80s than in patients aged 50 to 60.[8] GCA is more common in women than men with a lifetime risk of 1% in women and 0.5% in men.[9]

Pathogenesis

The exact cause of GCA is unknown. Genetic polymorphisms of the human leukocyte antigen class II region, specifically HLA-DRB1*04 and DRB1*01, are associated with susceptibility to GCA.[10] Notably, the T-cell cytokine IFN-gamma is abundantly expressed in GCA but absent from arteries of polymyalgia rheumatica (PMR) patients without GCA.[11] It is thought that in response to immunologic injury, the artery releases growth and angiogenic factors that induce proliferation of myofibroblasts, new vessel formation, and marked thickening of the arterial intima. This leads to vessel narrowing and occlusion resulting in symptoms of ischemia including jaw claudication, visual loss, and stroke.

Clinical Characteristics

GCA should be suspected in individuals over the age of 50 presenting with new-onset headache and evidence of systemic inflammation. Approximately 20% of GCA patients present with cranial symptoms, including headache, scalp tenderness, jaw and tongue claudication, diplopia, and blindness. New onset of diplopia in an elderly patient is highly suggestive of GCA.[12] Jaw claudication is also a very specific symptom.[13] PMR is also a common presentation with 40% of cases presenting with complaints of symmetric pain and stiffness of the shoulder and thigh girdle muscles. It should be noted that some patients develop PMR without GCA and only 10% to 20% of patients presenting with PMR go on to develop GCA. In 20% of GCA cases, symptoms of both cranial GCA and PMR are present at presentation. GCA may also have a more indolent presentation

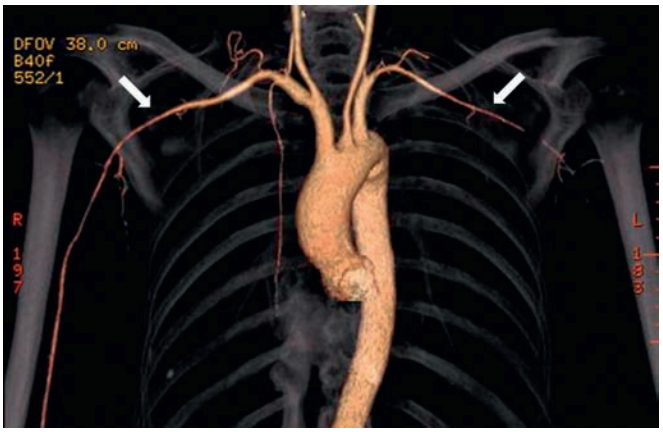

Figure 137.1 Computed tomography angiography with 3D reconstruction images reveals bilateral subclavian, axillary, and proximal brachial artery stenoses in a patient with giant cell arteritis. Moderate narrowing of both proximal common carotid arteries is also noted.

with 15% of cases exhibiting fever and systemic symptoms with no other localizing symptoms. GCA is the cause in 15% of elderly patients with an FUO. Finally, around 5% of GCA cases present with claudication symptoms, cough, tenosynovitis, and the syndrome of relapsing seronegative symmetric synovitis with pitting edema can also occur.

Physical findings in GCA include scalp tenderness and reduced pulse and tenderness of the temporal artery. Of GCA patients presenting with cranial and/or PMR symptoms, approximately 20% have clinical evidence of large-vessel vasculitis impacting subclavian arteries and other vascular territories (Fig. 137.1); thus it is important to check for discrepancies in blood pressure between the extremities, and the carotid and subclavian arteries should be auscultated for bruits. GCA patients have a 17-fold increased risk of development of thoracic aortic aneurysms and a 2.4-fold increased risk of developing abdominal aortic aneurysm compared to controls. Long-term monitoring with periodic imaging of the aorta is recommended.[14]

Abrupt onset of painless blindness may occur as a result of ischemic optic neuritis in 15% of patients and this is usually related to arteritis of the posterior ciliary branches of the ophthalmic arteries. Amaurosis fugax is the strongest predictor for future blindness with a relative risk of 6.3.[15] Thrombocytosis is also associated with visual loss. Patients may additionally complain of blurring of vision, iritis, conjunctivitis, scintillating scotoma, photophobia, glaucoma, and opthalmoplegia from ischemia of extraocular muscles. Retinal and ophthalmic artery thromboses and occipital strokes are less common. It should be noted that risk of visual loss also drops significantly once steroids have been commenced, with less than 10% of patients developing blindness after steroids have been initiated.[16]

Involvement of the intracranial vasculature in GCA is relatively rare, because these vessels lack an internal elastic lamina; however, involvement of internal carotids and vertebral arteries can occur and lead to strokes, seizures, acute hearing loss, vertigo, cerebral dysfunction, and depression.

TABLE 137.2 American College of Rheumatology Criteria for Diagnosis of Giant Cell Arteritis (1990)

Criterion	Definition
Age at disease onset > 50 years	Development of symptoms or findings beginning at age 50 or older
New headache	New onset headache
Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation without evidence of arteriosclerosis of cervical arteries
Elevated erythrocyte sedimentation rate (ESR)	ESR > 50 mm/h by Westergren method
Abnormal artery biopsy	Biopsy specimen showing vasculitis characterized by predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

To meet criteria for a diagnosis of giant cell arteritis, at least three out of the five criteria should be present.[17]

Diagnostic Criteria

The 1990 American College of Rheumatology criteria for the diagnosis of GCA[17] are listed in Table 137.2. For diagnosis of GCA, at least three out of five criteria must be present. The presence of three or more criteria yields a sensitivity of 93.5% and specificity of 91.2% for distinguishing GCA from other forms of vasculitis. While the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often markedly elevated in GCA, only a minority of patients have a normal ESR. Often, patients will have other evidence of systemic immune response, including normocytic anemia and elevated platelet count (see Table 137.2).

The gold standard diagnostic test for GCA is temporal artery biopsy. An adequate length of temporal artery (2-3 cm) should be obtained at biopsy, and bilateral biopsies (particularly if the first is negative) are recommended by some groups.[18] Up to 50% of biopsies show diffuse lymphocytic infiltrate without evidence of granulomatous inflammation or giant cells. Fragmentation and fraying of the internal elastic lamina can be seen in normal aging, so in the absence of inflammation, this finding is not diagnostic of GCA. Ideally, biopsy specimens should be obtained prior to or within 7 days of starting corticosteroids. However, corticosteroid therapy does not normalize the affected artery; it simply reduces the inflammatory infiltrate, so "healed temporal arteritis" can still be diagnosed by the presence of intimal fibrosis, medial scarring, and asymmetric destruction of the internal elastic lamina.[19]

Large-vessel involvement may be assessed using conventional angiography, magnetic resonance angiography, or computed

tomography (CT) angiography.[5,6,12] Newer imaging modalities including ultrasound and PET are being evaluated as diagnostic tools in GCA.[6]

Medical Treatment of Giant Cell Arteritis

Corticosteroid therapy is standard of care in the management of GCA, and the initial dosing should be 40 to 60 mg daily. In patients with incipient visual loss, intravenous methylprednisolone (1000 mg per day for 3 days) may be considered. The initial prednisone dose should be maintained until inflammatory markers normalize (usually at least 1 month). Various tapering methods are used, but a rule of thumb is to reduce the prednisone by 5 mg every 1 to 2 weeks until 30 mg per day is reached and then to reduce the amount by 2.5 mg every 1 to 2 weeks until 15 mg per day. The subsequent taper should be 2.5 mg every 4 weeks until 10 mg and then 1 mg every 4 weeks until the patient is off prednisone. Alternate-day steroid dosing regimens are not effective. Clinical symptoms, ESR, and CRP should be monitored for every change in dose, and it should be noted that spontaneous recurrence may occur in as many as 50% of cases. Up to 40% of cases (especially women) need long-term corticosteroid therapy for several years. All patients are recommended to also receive low-dose aspirin 81 mg per day to reduce the risk of cardiovascular events and blindness. It was recently shown that methotrexate is an effective steroid-sparing agent and may allow more rapid steroid tapering. Tumor necrosis factor (TNF)-α inhibitors were ineffective, but the anti-IL6 antibody Tocilizumab was effective for steroid-dependent, treatment-resistant GCA. Other trials of biologic and nonbiologic disease-modifying antirheumatic drugs (DMARDs) are ongoing. Fig. 137.2 shows marked improvement in diffuse arterial wall thickening caused by GCA in response to steroids.

Role for Vascular Surgical Intervention in Giant Cell Arteritis

Revascularization procedures are rarely required in GCA due to development of collaterals. Balloon angioplasty in combination with immunosuppressive treatment has been tried in small case series, but unless the inflammatory process is well controlled, the risk of restenosis is high. For patients with aortic aneurysms, surgery is indicated with surgical results similar to those seen in patients with aneurysms from other etiologies.[20]

Idiopathic Aortitis

Inflammation of the aorta discovered incidentally on histology is seen in 3% to 10% of surgical aortic aneurysm repairs. Miller et al. recorded 45 cases of incidental aortitis in a retrospective review of 514 ascending aortic specimens (frequency 8.8%). In the thoracic aorta, some of these lesions are histologically indistinguishable from GCA, but others demonstrate

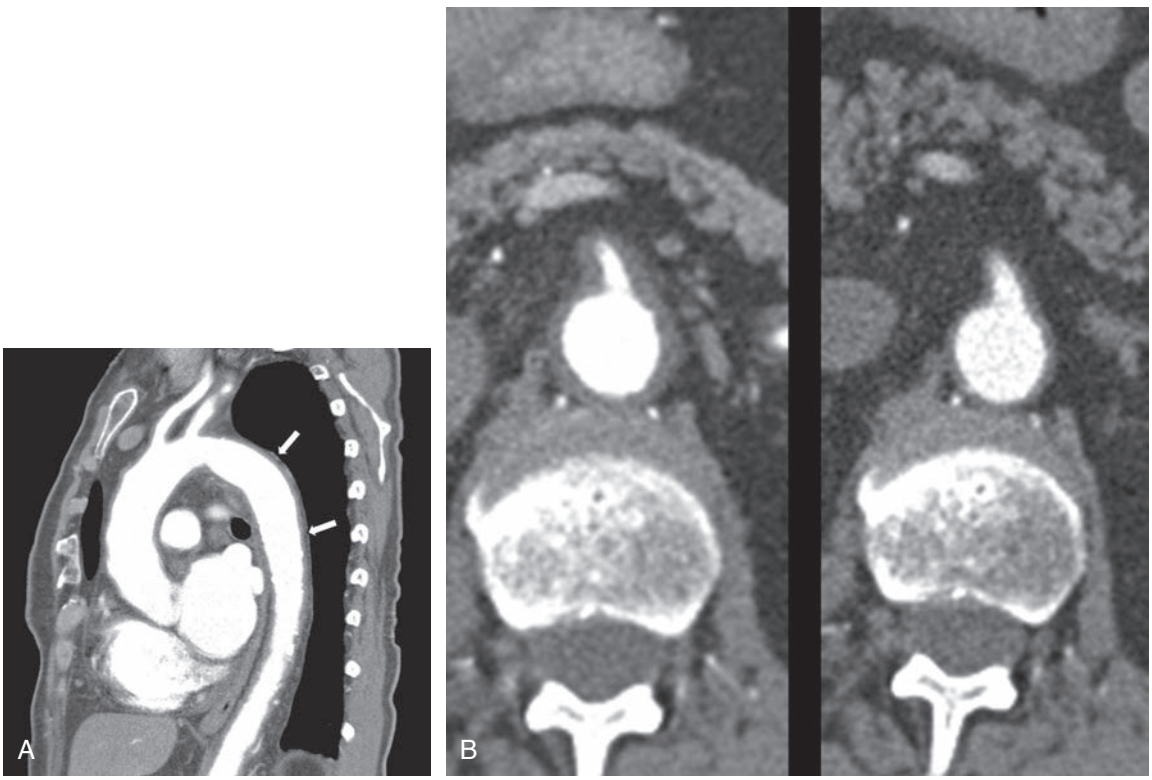

Figure 137.2 Computed tomography angiogram of a patient with giant cell arteritis and involvement of the aorta. (A) This sagittal image demonstrates thickened arterial walls, most prominent in the great vessels, and throughout the entire descending thoracic aorta. (B) Arterial wall thickening extended into the upper abdominal aorta and superior mesenteric artery (SMA), which was stenosed *(left panel)*. Reimaging after 6 months of treatment with corticosteroids revealed marked improvement in the diffuse arterial wall thickening and SMA stenosis *(right panel)*.

lymphoplasmacytic infiltrate, and 75% of these are due to IgG4-related disease. In the abdominal aortal, lesions can be grouped into idiopathic retroperitoneal fibrosis (Ormond Disease) and inflammatory aortic aneurysms that are often associated with smoking and a family history of aortic aneurysm, which some of these lesions are due to IgG4 related systemic disease. The syndrome of idiopathic abdominal peri-aortitis has also been described without associated aneurysm or retroperitoneal fibrosis. In these patients, rarer etiologies including Erdheim-Chester disease should be considered.

Idiopathic Retroperitoneal Fibrosis (Ormond Disease)

Idiopathic retroperitoneal fibrosis is rare, affects men more than women (3:1), and presents in patients in middle age (40-60 years old). Typically, patients present with pain in the lower back, abdomen, flank, and scrotum. Some patients also demonstrate systemic symptoms including fever, anorexia, and malaise. Patients have hypertension in 75% of cases and lower extremity edema and phlebitis can be seen. Serologic work-up is usually negative, but inflammatory markers are elevated in 75% of cases. Classic CT findings include presence of a homogeneous mass around the aorta following the iliac bifurcation with associated medial deviation of the mid-part of the ureter and secondary hydronephrosis. Usually, lymphadenopathy is absent. Biopsy may be performed laparoscopically or through open procedure, and histology shows sclerosis with infiltration of mononuclear cells. The pathophysiology of this process is unknown, but an exaggerated local inflammatory response to oxidized low-density lipoprotein in aortic plaque has been postulated. Treatment with high-dose prednisone is recommended (60 mg daily for 1 month followed by tapering off to 10 mg/day by 3-6 months). Maintenance therapy with prednisone is recommended for 1 to 3 years. The disease recurs in 10% to 30%, and use of mycophenolate mofetil, tamoxifen, or methotrexate should be considered for these patients. Monitoring with inflammatory markers and CT scan should be continued every 3 months while on treatment and every 6 months when off treatment.

IgG4-Related Systemic Disease

IgG4-related systemic disease affects older males with 60% to 80% of cases affecting patients older than 50 years. Often, there is a past medical history of allergic diseases and atopy (eczema and asthma). Patients develop tumor-like lesions in one or more organs and on biopsy-dense lymphoplasmacytic infiltrates with storiform fibrosis and obliterative phlebitis.[21] Lesions should be stained to demonstrate IgG4 positive cells (with >30 per high-powered field and IgG4/IgG positive ratio >50% confirming the diagnosis). Elevated serum IgG4 is seen in 60% to 80% of cases but is not always detected. Serologic work-up is usually negative. Several organs may be affected simultaneously with the most common presentations being type I autoimmune pancreatitis, sclerosing cholangitis, salivary gland involvement (Mikulicz disease), and sclerosing sialadenitis (Kuttner tumor). The disease may be associated with chronic lymphoplasmacytic aortitis and aneurysm formation. This more commonly affects the thoracic than abdominal aorta and can be mistaken for idiopathic retroperitoneal fibrosis. Treatment for IgG4-related disease includes high-dose steroids along with DMARDs; in recent years, rituximab (a monoclonal antibody targeting B cells) has been shown to be effective.[22]

Erdheim-Chester Disease

Erdheim-Chester disease is a rare histiocytic disease that is associated with periaortic fibrosis (referred to as "coated aorta"), periarterial infiltration of coronary arteries, and pericardial thickening and effusion. Retroperitoneal involvement may also manifest with mass-like infiltrative lesion or with perinephric changes known as "hairy kidney."[23] It may be confused with idiopathic retroperitoneal fibrosis and IgG4-related disease,[24] but the distinguishing feature is that most patients also have bone lesions, often in the lower extremities that present with juxtaarticular pain. Biopsy of involved tissue reveals tissue infiltration by sheets of foamy histiocytes interspersed with inflammatory and multinucleated giant cells. In recent years, it has become clear that the disease is associated with gain-of-function mutations in the proto-oncogene BRAF (the BRAFV600E mutation), and treatment with BRAF inhibitors has been found to be effective with less toxicity than prior treatment options such as interferon.[25]

MEDIUM-SIZED VESSEL VASCULITIS

Polyarteritis Nodosa

PAN is a necrotizing vasculitis of small and medium arteries and is characterized by the absence of glomerulonephritis and anti-neutrophil cytoplasmic (ANCA) antibodies.[26] Diagnosis is based on presence of 3 out of the 10 American College of Rheumatology criteria (Table 137.3).

Pathogenesis

PAN may be idiopathic or secondary to hepatitis B infection. In hepatitis B associated PAN, the mean time between hepatitis diagnosis and PAN is 7 months. PAN may also be associated with other viral infections including HIV and has been seen as a paraneoplastic manifestation of hematology malignancy (particularly, hairy-cell leukemia).

Histology

The histologic lesion in PAN is a focal, segmental necrotizing vasculitis affecting medium-sized arteries. It commonly affects arterioles with sparing of large vessels and veins. The arterial wall inflammation is characterized by fibrinoid necrosis of the media along with neutrophilic and lymphocytic infiltrate. Active necrotizing lesions are often seen alongside healed and fibrotic lesions. Localized thromboses may occur at the site of inflammatory injury, and arterial aneurysms may form as a result of weakening of the vessel wall by the inflammatory process, ultimately leading to end organ injury from ischemia, infarct, and hemorrhage.

TABLE 137.3 American College of Rheumatology Diagnostic Criteria for Polyarteritis Nodosa

Criterion	Definition
Weight loss >4 kg	Loss of at least 4 kg since illness began without dieting or other confounding factors
Livedo reticularis	Mottled reticular pattern over the skin of extremities or torso
Testicular pain or tenderness	Pain or tenderness of the testicles not due to infection, trauma, or other causes.
Myalgias, weakness or leg tenderness	Diffuse myalgias or weakness of muscles, tenderness of leg muscles.
Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy
Diastolic BP > 90	Development of hypertension with diastolic BP >90 mm Hg
Elevated BUN or creatinine	Elevation of BUN > 40 mg/dL or creatinine >1.5 mg/dL
Hepatitis B infection	Presence of Hepatitis B Surface antigen or antibody in serum
Arteriographic abnormality	Arteriogram showing aneurysms or occlusions of visceral arteries not due to arteriosclerosis, fibromuscular dysplasia, or noninflammatory causes.
Biopsy of small or medium-sized artery demonstrating polymorphonuclear neutrophils	Histologic changes showing presence of granulocytes, and or mononuclear leukocytes in vessel wall.

Epidemiology

BP, Blood pressure; *BUN*, blood urea nitrogen.

Polyarteritis nodosa (PAN) is rare, with annual incidence 2 to 9 cases per million and is declining likely related to reduction in prevalence of hepatitis B infection as vaccination has been more consistent. It may present at any age and in any racial group but is more common in men aged 40 to 60 years. To meet criteria for a diagnosis of PAN, 3 out of the 10 criteria need to be present.[26]

Laboratory Testing

There are no diagnostic serologic tests for PAN. Elevated systemic inflammatory markers are common, and patients may also exhibit normocytic anemic and thrombocytosis. Usually, complement levels are normal. Hepatitis B serology should be tested, and patients with hepatitis-B associated PAN demonstrate hepatitis B surface antigen positivity, HBeAg, and positive PCR for hepatitis B virus DNA. ANCA testing, rheumatoid factor (RF), cryoglobulins, and antinuclear antibodies (ANA) should be negative.

Clinical Features

Patients with PAN present with constitutional symptoms (fever and weight loss) in the setting of organ dysfunction. Commonly seen manifestations include skin lesions—including palpable purpura, livedo, necrotic lesions, and digital infarcts; peripheral neuropathy and mononeuritis multiplex; abdominal pain due to mesenteric vasculitis; and hypertension with microscopic hematuria or proteinuria. Biopsy of affected tissue is crucial for establishing the diagnosis. If the presenting symptoms are related to mesenteric ischemia or renal involvement, then visceral angiogram can be helpful confirming the diagnosis. Angiographic findings include presence of saccular aneurysms, microaneurysms, occlusions and cutoffs with luminal irregularity, and stenosis of small and medium vessels of abdominal viscera. Severe gastrointestinal (GI) involvement is a major cause of morbidity in PAN. Renal biopsy is usually unhelpful, since the renal injury is not glomerular in nature. Microaneurysms of renal artery branches can occasionally rupture and cause renal hematomas. Myalgias due to skeletal muscle involvement and large joint arthralgias are common. Importantly, PAN does not affect the lungs or upper respiratory tract, which is an important feature in distinguishing this disease from the ANCA-associated vasculitides.

Treatment

In patients with hepatitis B associated PAN, antiviral therapy should be initiated prior to immunosuppression. Some patients with severe manifestations of hepatitis virus-associated PAN benefit from short-term treatment with glucocorticoids and plasma exchange until the antiviral therapy becomes effective.[27] Plasma exchange has not been shown to be effective in PAN that is not associated with hepatitis B. Prolonged immunosuppression should be avoided to facilitate immunologic clearance of hepatitis B infected hepatocytes.

In patients with PAN not associated with viral disease, excellent 5-year survival rates of over 80% can be achieved with appropriate immunosuppressive therapy and use of steroids improves survival.[28] For mild and isolated cutaneous disease, initial monotherapy with daily oral prednisone (1 mg/kg ideal body weight up to a maximum of 60 mg per day) is recommended. The initial dose should be continued for 4 weeks, and the taper should be guided by clinical improvement, tapering below 20 mg per day should be done slowly, not faster than by 2.5 mg every 14 days. Most patients remain on prednisone for approximately 6 to 8 months. Many patients with mild disease respond to glucocorticoid monotherapy, but for those patients who do not achieve remission with glucocorticoids alone, addition of a DMARD agent, such as azathioprine (2 mg/kg per day) or methotrexate (20-25 mg weekly) is recommended, with monitoring through rheumatology to allow prednisone to be weaned. Methotrexate should not be used in patients with renal disease or hepatitis.

For patients with moderate to severe disease, data from long-term follow-up studies in several cohorts of patients with PAN shows improved outcomes from induction therapy with steroids and cyclophosphamide[27,29,30] followed by either azathioprine or methotrexate for remission maintenance. There has been no comparison of oral versus IV cyclophosphamide use in PAN; however, one small randomized controlled trial of 18 patients with PAN and 47 with microscopic polyangiitis (MPA) demonstrated that use of steroids with 12 monthly pulses of IV cyclophosphamide had a lower risk of relapse and higher event-free survival than patients receiving only 6 monthly pulses of IV cyclophosphamide. Mortality did not differ, and

this study did not investigate remission maintenance regimens. Some investigators also extrapolate use of the "CYCLOPS" cyclophosphamide dosing regimen that was shown to be comparable to oral cyclophosphamide for induction and remission of ANCA-associated vasculitis, but this has not been studied in PAN. It should be noted that in the management of other forms of vasculitis, the IV dosing of cyclophosphamide often allows effective disease control with lower cumulative dose and potentially reduced bone marrow, bladder, ovarian, and testicular toxicity; but many of the original studies of cyclophosphamide use for vasculitis used the daily oral dosing regimen that is preferred by some due to a higher effective dose and better long-term response rates. In addition, cyclophosphamide should not be dosed without involvement of rheumatology, because this drug carries several adverse effects including cytopenias, gonadal failure, and risk for hemorrhagic cystitis and increased risk of malignancy. Dose reduction is necessary for renal insufficiency and advanced age, and the dose should be adjusted based on the nadir white blood count to minimize bone marrow toxicity. In addition, prophylaxis for pneumocystis jirovecii (PJP) infection should be employed in patients receiving high-dose steroids in combination with DMARDs.

Prognosis

Untreated PAN is associated with poor prognosis (13% 5-year survival, but with treatment the 5-year survival improves to ~80%).[31,32] Age greater than 65, cardiac symptoms, GI involvement, and renal insufficiency (creatinine >1.7 mg/dL) are associated with higher mortality. Renal transplant has been performed in patients with PAN and end-stage renal disease. Of the 112 cases reported in the European Renal Association-European Dialysis and Transplant Association, registry transplantation was associated with significantly lower patient and allograft survival compared to those with renal disease from other causes.[33] Approximately 13% of graft failures were due to disease recurrence.

Other Diseases Showing Aneurysms on Abdominal Visceral Angiography

Several other diseases may demonstrate aneurysms on abdominal angiography. Segmental arterial mediolysis (SAM) is a rare, nonatherosclerotic, noninflammatory disease that affects muscular arteries and can mimic PAN. Classically, this involves the splanchnic arteries in middle aged and elderly patients, the basilar cerebral arteries in adults, and coronary arteries in children and young adults, but the aorta is spared. Patients present with life-threatening hemorrhage due to aneurysm rupture, and histologically, there is lysis and loss of the muscular layer of the media, resulting in arterial dilatation and aneurysm formation. It is thought that this is a variant of fibromuscular dysplasia. Other diseases that can mimic PAN include pseudoxanthoma elasticum, neurofibromatosis, and vascular type Ehlers-Danlos syndrome in which a defect in type III collagen results in vascular wall weakening and aneurysm formation. Finally, a newly described syndrome associated with genetic deficiencies in adenosine deaminase-2 can present with a phenotype similar to PAN, with fever, systemic symptoms, livedoid rash, and early-onset stroke.[34]

Thromboangiitis Obliterans (Buerger's Disease)

TO is an inflammatory obliterative nonatheromatous vascular disease that affects the small and medium-sized arteries, veins, and nerves.[35] While it is only associated with mild inflammatory changes, the presence of inflammation means that this disease is considered to be a vasculitis.

Epidemiology

TO is predominantly a disease of young men, most commonly affecting individuals between the ages of 18 and 50 years; and men are more commonly affected than women. The disease is also more common in the Middle and Far East than in North America and Western Europe.[35]

There is a strong association with tobacco exposure, although TO has been reported even in individuals who only smoke small amounts, and it has also been seen in pipe smokers, marijuana users, and tobacco chewers.[36]

Clinical Presentation

The initial manifestation of TO is lower extremity claudication, and this sometimes progresses to digital ischemia. Pedal, instep claudication is also a very specific symptom and patients often present initially to podiatrists for initial evaluation. Gangrene, ulceration, or rest pain is the presenting complaint in one-third of patients; often, this can be triggered by minimal trauma such as nail trimming or pressure from tight shoes. Superficial thrombophlebitis and Raynaud's syndrome are also described.[37]

Diagnostic Testing

TO is a diagnosis of exclusion, prothrombotic states, diabetes, and other autoimmune diseases; especially scleroderma should be excluded before attributing digital gangrene to TO. Patients should also undergo echocardiogram to rule out infectious endocarditis and arteriogram to rule out atherosclerosis. Arteriographic features of TO include bilateral focal segmental stenosis and occlusion with relatively normal intervening vessels. Collateral development around areas of occlusion lead to the appearance of "tree-root," "spiders web," or "corkscrew" collaterals. The most important finding is that proximal arteries are normal without evidence of atherosclerosis or emboli.[35]

Pathologic Findings

Most pathologic specimens come from amputated limbs and show panvasculitis with highly cellular thrombosis and microabscesses in the thrombus and vessel wall. In the subacute phase, the thrombus is less cellular and may recanalize. Unlike most other forms of vasculitis, the internal elastic lamina is preserved, and venulitis is often seen.

Treatment

Treatment of TO involves total cessation of tobacco, and nicotine replacement products. Calcium channel blockers and pentoxifylline are sometimes helpful. Intravenous iloprost can assist with

the period of critical ischemia.[38] Sympathectomy can also be tried.[35] Approximately 50% of patients who continue to smoke will require amputation.[39] Surgical recanalization and bypass grafting is challenging, but several groups are now reporting promising results in patients who remain abstinent from nicotine.[39-41]

Kawasaki Disease

Kawasaki disease is an acute vasculitis typically seen in children, in which there is involvement of small and medium-sized arteries, especially the coronary arteries.[42] Most patients are under the age of 5 years, and boys are more commonly affected than girls (1.5 : 1), and high-grade fever is one of the cardinal presenting signs in Kawasaki disease. Coronary artery dilatation and aneurysm formation can occur in up to 20% to 29% of patients,[43] and the main cause of death is myocardial infarction. Treatment with high-dose aspirin and IV immunoglobulin is effective and reduces the incidence of coronary artery aneurysms.[44]

SMALL-VESSEL VASCULITIS

Antineutrophil Cytoplasmic Antibody-Associated Vasculitides

The AAV primarily affect small arteries, and their cardinal finding is the presence of ANCA. ANCAs are antibodies directed against specific proteins in granules in the cytoplasm of neutrophils and lysosomal proteins in monocytes. Classification of the diseases associated with ANCA was recently revised to granulomatosis with polyangiitis (GPA, previously known as Wegener's syndrome), MPA, and sosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg-Strauss syndrome).

Granulomatosis With Polyangiitis (Previously Known as Wegener's Granulomatosis)

GPA is a granulomatous vasculitis of the upper and lower respiratory tract that also causes pauci-immune focal, segmental, cresentic glomerulonephritis. There is a strong association with cANCA antibodies with proteinase-3 specificity (PR-3). Patients may be classified by organ involvement into generalized GPA, where there is involvement of upper and lower respiratory tract and kidney, and limited GPA, where there is only respiratory tract involvement with sparing of the kidney.

Epidemiology

GPA is rare, affecting 8 to 10 patients per million per year. The mean age at diagnosis is 41 years, although it has been reported in children as young as 5 years old and in elderly patients. Only 16% of cases present in childhood. The disease is more common in Caucasians than in African Americans (7 : 1).

Clinical Presentation

Patients present with chronic sinusitis, epistaxis, and chronic purulent nasal drainage along with chronic inflammation of the auditory canal causing acute suppurative otitis media and chronic serous otitis media. New onset of otitis media in an adult should prompt rheumatologic evaluation for GPA. Chronic inflammation of the laryngeal and tracheal mucosa can lead to hoarseness and subglottic stenosis. The peripheral nervous system may also be involved with development of mononeuritis multiplex. CNS involvement includes chronic pachymeningitis, cranial neuropathies, pituitary involvement, brainstem, and spinal cord lesions.

Pulmonary involvement is seen at presentation in 50% of cases and ultimately affects almost 90% of patients. Some patients may be only mildly symptomatic, but pulmonary imaging should be completed. Nodules and fixed infiltrates are often seen. During the acute phase, pulmonary capillaritis develops with infiltration of neutrophils, and other inflammatory cells in the alveolar septa. As lesions become chronic, granulomas develop in the alveolar septa and within vessels and airway walls. These nodules may cavitate and sometimes become secondarily infected.

Renal involvement is present at presentation in 15% to 30% of cases and ultimately affects 50% to 80%. Renal pathology shows pauci-immune, focal, segmental, crescentic, necrotizing glomerulonephritis. Immunofluorescence demonstrates absence of immunoglobulin, immune complex, and complement deposition.

Laboratory Testing

ANCA positivity is seen in 90% of patients with generalized GPA and approximately 60% of limited cases. Of the patients with positive ANCA 80% to 90% have cANCA positivity with PR-3 specificity. The overall specificity of PR3-ANCA for generalized GPA is thus 98%. All patients with possible GPA should have screening urinalysis to check for evidence of active urinary sediment (hematuria, pyuria, proteinuria, or casts).

Often, ANCA titers correlate with GPA disease activity, and rising ANCA titer may herald a flare, a feature that is helpful in distinguishing flare from infection in patients with chronic disease.[45] Patients on maintenance therapy with PR-3 positivity have an increased risk of flare if therapy is stopped; thus current recommendations are for this group of patients to remain on maintenance immunosuppression.[46]

Treatment

Patients with severe GPA should receive induction therapy with IV steroids (methylprednisolone 1000 mg daily for 3-5 days) followed by daily oral steroids. If alveolar hemorrhage is present, plasmapheresis is also used acutely. Therapy with monthly IV cyclophosphamide or rituximab should be used for induction of remission. Rituximab is as effective as cyclophosphamide and is particularly useful for patients who have relapsed and those who do not respond to cyclophosphamide.[47-49] In addition, rituximab is removed by plasmapheresis but not hemodialysis. In limited GPA, prednisone plus methotrexate has been used if the renal function is normal.

During the remission maintenance phase, clinical trials show that azathioprine is equally as cytoxan at maintaining remission[50] but carries fewer side effects. The MAINRITSAN study recently showed that rituximab every 6 months was further

superior to azathioprine in maintaining remission and preventing relapse.[51]

The relapse rate of GPA is high. Patients who have been in complete remission for 12 to 18 months have a 50% risk of relapse when therapy is weaned. Maintenance therapy for more than 36 months is associated with lower relapse rate; however, many rheumatologists continue patients on long-term maintenance therapy due to the known high relapse rate in this disease.

All patients receiving immunosuppression with steroids and biologic or nonbiologic DMARDs should also receive prophylactic therapy for PJP[52] and therapy to reduce osteoporosis.[53] Patients receiving cyclophosphamide are at risk for gonadal failure and should be monitored for hemorrhagic cystitis and secondary malignancy.

Microscopic Polyangiitis

MPA is a systemic necrotizing vasculitis of small vessels (capillaries, venules, and arterioles) that is associated with ANCA formation but classically on histology has few or no immune deposits (pauci-immune) and in which there is no granuloma formation.[54]

Epidemiology

MPA can affect men and women and may occur at any age, although it is most common between the ages of 30 to 50 years.

Clinical Presentation

Patients present with pulmonary-renal syndrome with almost all patients developing a rapidly progressive pauci-immune glomerulonephritis and approximately 30% of patients developing pulmonary capillaritis with diffuse alveolar hemorrhage.

Laboratory Testing

pANCA with myeloperoxidase specificity (MPO) is seen in 60% of patients, although some patients have evidence of cANCA with specificity against PR-3. In the presence of PR-3, patients with MPA can distinguished from GPA by the absence of upper-respiratory tract involvement.

Renal Histopathology

Renal histopathology shows focal, segmental necrotizing glomerulonephritis with crescent formation, but on immunofluorescence and electron microscopy, no immune deposits are seen (pauci-immune). Lung biopsy shows pulmonary capillaritis with negative immunofluorescence, and biopsy of involved skin usually reveals leukocytoclastic vasculitis.[54,55]

Treatment

Treatment for MPA is similar to that for GPA and EGPA with induction therapy with IV steroids followed by oral daily prednisone and either cyclophosphamide or rituximab. During the acute phase of pulmonary hemorrhage, plasmapheresis with IVIG has been used. Maintenance therapy is similar to that for GPA.[56,57] The prognosis for MPA is guarded,[58] with 33% of patients relapsing and 20% of patients requiring dialysis. The overall 5-year survival rate is 70% to 75%.

Eosinophilic Granulomatosis With Polyangiitis (Previously Known as Churg-Strauss Syndrome)

Epidemiology

EGPA is a rare (1-4 patients per million) granulomatous vasculitis of the small and medium-sized vessels associated with eosinophilia. Patients with EGPA often have a prior history of allergic disease with 70% having a history of rhinitis often with nasal polyps and greater than 95% having a history of adult-onset asthma.[59,60] The ACR criteria for EGPA include asthma, eosinophilia greater than 10%, mono- or poly-neuropathy, nonfixed pulmonary infiltrates, paranasal sinus abnormalities, and biopsy showing eosinophilic infiltrate. The presence of more than four of these six criteria carries sensitivity of 85% and specificity 99.7% for the diagnosis.[60]

Pathophysiology

Characteristic histopathologic changes in EGPA include extravascular small necrotizing granulomas near small arteries and veins. In contrast to other granulomatous lesions that have a basophilic core, the granulomas in EGPA have a central eosinophilic core surrounded radially by macrophages and giant cells.[59] It is thought that the disease is driven by cytokine pathways that stimulate eosinophils including IL-5. There have been suggestions that leukotriene inhibitors such as montelukast (singulair) may contribute to the pathogenesis of this disease, since it often becomes clinically apparent when a patient with chronic asthma is started on a leukotriene inhibitor and systemic corticosteroids are weaned. This co-temporal relationship is well recognized, but it remains unclear whether it is causative.[59]

Clinical Presentation

The clinical presentation of EGPA is often a triphasic process, although it should be noted that these phases are not always sequential and may present simultaneously. The prodromal phase lasts on average 28 months but may persist for 2 to 7 years. Patients present with symptoms of allergic rhinitis, asthma, and nasal polyposis. In 50% of cases, there are symptoms of recurrent fevers. In addition, during the second phase, peripheral blood and tissue eosinophilia develop with shifting pulmonary infiltrates, chronic eosinophilic pneumonia, and eosinophilic gastroenteritis. Flares during this phase are associated with fever, and myocarditis may also develop during this phase. Life-threatening systemic vasculitis develops on average 3 years after the onset of the prodromal phase, and at this time, the asthma dramatically resolves.[61] Patients develop myocarditis, valvular insufficiency, vasculitic peripheral neuropathy, eosinophilic gastroenteritis, purpura, and testicular pain.

Laboratory Findings

The cardinal laboratory finding in EGPA is eosinophilia (>1500 cells/μL).[60] Serologic testing reveals pANCA pattern with anti-MPO specificity, and patients also sometimes have a positive RF. Patients who are ANCA positive have a higher risk of renal disease, alveolar hemorrhage, mononeuritis multiplex, and purpura.

Treatment

Treatment of EGPA involves induction therapy with IV glucocorticoids followed by daily oral prednisone with either monthly IV cyclophosphamide, or more recently, rituximab has been shown to be beneficial.[62] Some EGPA patients may respond to steroid monotherapy.[63]

VASCULITIS SECONDARY TO CONNECTIVE TISSUE DISEASES

Vascular Manifestations of Behçet's Disease

Behçet's disease (BD) is a systemic vasculitis of unknown etiology that classically presents with oral and genital ulcers (Fig. 137.3), uveitis, skin lesions, and vascular manifestations. Vascular issues were seen in up to 50% of patients in a large study in Turkey,[64] and vascular complications are more common in men who develop the disease at a young age. Vascular manifestations include arterial and venous thrombosis and unusual aneurysms, particularly affecting the pulmonary arteries.[65] Patients are at high risk for thrombotic complications and may develop superficial and deep vein thrombosis, as well as thrombosis of the large central veins, especially the superior and inferior vena cava. Other recognized manifestations include development of hepatic vein thrombosis causing Budd-Chiari syndrome, mesenteric vein thrombosis, renal vein thrombosis, and intracranial thrombosis involving the dural sinus. In BD, thrombus is adherent to the vessel wall and thrombosis may progress despite anticoagulation. Arterial complications are less common than venous problems, occurring in 1% to 7% of patients. Occlusive arterial disease can involve both upper and lower extremities resulting in ischemic symptoms. The aorta is the most common site of aneurysm formation, with pulmonary, femora, popliteal, brachial, and iliac arteries also reported in descending order of frequency. Patients often have multiple arterial aneurysms with a saccular configuration, and there is a high risk of rupture, thrombosis, and aneurysm recurrence. Pulmonary artery aneurysms, in particular, can lead to massive and fatal hemoptysis.[66] Intracranial aneurysms can occur in BD, and successful endovascular treatment has been reported. Care should be taken with line insertion in these patients, since arterial puncture for angiography can result in aneurysm rupture.

Figure 137.3 Large, painful, oral ulcers in a patient with Behçet's disease.

Epidemiology

BD is seen worldwide but it is more common in Turkey, the Mediterranean basin, and the Middle and Far East along the historic Silk Road trade route. Typically, the disease presents in young adults aged 20 to 40 years. The pathogenesis of BD is unknown but genetic, infectious, and immunologic factors have been implicated. There is a high prevalence of disease in patients with HLA-B51 genotype, and it is thought that polymorphisms in genes for several proinflammatory cytokines might play a role in disease susceptibility.[67]

Treatment

Treatment of BD involves systemic immunosuppression with glucocorticoids and steroid-sparing DMARD agents, and mucocutaneous lesions often respond to colchicine.[68] Thalidomide has been used for refractory oral and genital ulcers, and high-dose steroids and cytotoxic agents are used in patients with vasculitis. Relapses are frequent and patients should be closely monitored.[68]

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by autoantibodies to various nuclear antigens. Vasculitis may occur in up to one-third of SLE patients[69] and most commonly affects the small vessels of the skin (leukocytoclastic vasculitis). Patients often present with tender punctate lesions on the fingertips and palms, but ischemic lesions nodules and ulcers may also occur. Vasculitis of medium-sized vessels can result in mononeuritis multiplex and lesions in the abdominal viscera, and large-vessel vasculitis with a similar distribution to Takayasu's arteritis has also been described. Pulmonary capillaritis in SLE may present with alveolar hemorrhage and carries a high risk of mortality. Inflammatory vasculitis in SLE merits escalation of therapy with steroids and DMARD agents.

Ischemic events related to the antiphospholipid syndrome may mimic vasculitis in SLE and should be considered in the differential diagnosis in lupus patients presenting with digital and skin ulcerations.[70,71] If antiphospholipid antibodies are present, then anticoagulant therapy and therapy with the antimalarial agent hydroxychloroquine can be of benefit.

Rheumatoid Vasculitis

Rheumatoid arthritis vasculitis is a known complication of longstanding rheumatoid arthritis (RA), and RA is an inflammatory symmetric polyarthritis. Vasculitis occurs in 10% to 15% of cases, which is usually those with more aggressive disease and high-titer RF. Patients may develop cutaneous ulcers,[72] peripheral neuropathy, and scleritis, and mesenteric vasculitis and aortitis may also occur but is rare. Rheumatoid vasculitis

is associated with significant morbidity and mortality and should be treated aggressively with high-dose steroids and biologic DMARDs.[73-76]

Relapsing Polychondritis

Relapsing polychondritis is a rare autoimmune disease manifested with recurrent inflammation of cartilaginous tissues. This disease can also be complicated by large-vessel involvement with aortitis leading to thoracic and abdominal aortic aneurysms.[77]

Cogan's Syndrome

Cogan's syndrome may present with large and medium-sized vasculitis in a Takayasu's like distribution.[78] Cogan's syndrome is an immune-mediated disorder characterized by interstitial keratitis, vestibular dysfunction, and sensorineural hearing loss. Keratitis symptoms include bilateral redness, pain, and photophobia with increased lacrimation. Other forms of ocular inflammation, including uveitis, scleritis, choroiditis, and retinal artery occlusion, may also occur with or without concomitant keratitis. Vestibular dysfunction presents with tinnitus, vertigo, and sensorineural hearing loss, which may be fluctuating but leads to deafness in more than 50% of cases. Eye and ear involvement usually develop within 1 to 6 months of each other. The mean age of onset is around 30 years, although it has been reported in children and in the elderly. The syndrome is equally distributed in men and women, and there is no racial predilection. Typically at presentation, patients are systemically unwell with constitutional symptoms, fever, athralgias, serositis, mononeuritis, hepatomegaly, and splenomegaly. Laboratory work-up reveals elevated inflammatory markers but negative autoantibodies, and keratitis usually responds to topical steroids. Vestibular dysfunction merits oral prednisone, and if systemic manifestations are also present, then a steroid-sparing agent such as azathioprine, methotrexate, mycophenolate, or cyclosporine should be added.[79,80]

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum is an inherited systemic disease that can cause early and diffuse arteriopathy in the absence of traditional risk factors.[81] Small and medium-sized arteries are affected more commonly than the aorta, and patients often present with symptoms of claudication in the lower extremities. Both traditional surgical bypass and percutaneous angioplasty have been used successfully in the management of claudication due to pseudoxanthoma elasticum. In patients with pseudoxanthoma presenting with peripheral vascular symptoms, screening for coronary disease is advised since equally severe coronary disease can be identified and can manifest with heart failure due to widespread coronary ischemia or restrictive cardiomyopathy. Because pseudoxanthoma can affect the internal mammary arteries, vein conduits are recommended for coronary bypass. In addition, arterial rupture can occur in the GI and genitourinary tracts, resulting in a higher risk of bleeding with antiplatelet and anticoagulant therapy.

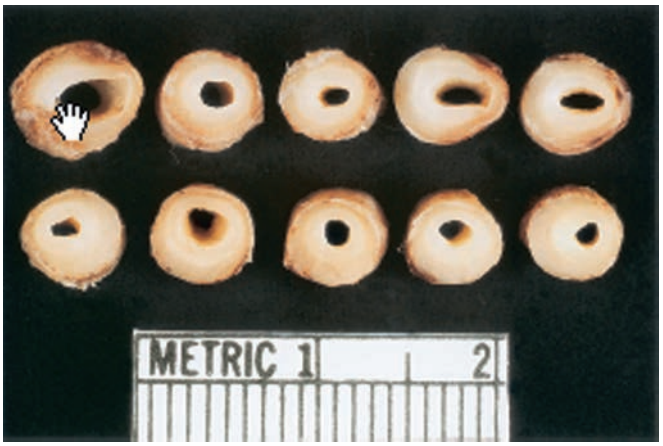

Figure 137.4 Exercise-related external iliac arteriopathy. Photograph of resected external iliac artery, cut in cross-sections, showing luminal stenosis.

Exercise-Related External Iliac Arteriopathy

Exercise-related external iliac arteriopathy is a syndrome seen in competitive bicyclists and those cycling on average 8000 to 33,000 km/year. The condition occurs in both men and women, and both external iliac arteries may be affected. Repetitive bending and compression of the external iliac artery between the psoas branch, circumflex iliac, and internal epigastric arteries lead to fibrosis and thickening of the arterial wall. Smooth muscle proliferation and intimal thickening is seen (Fig. 137.4), and some cases report complete occlusion as well as spontaneous dissection of the external iliac artery. Typically affected patients report claudication with exercise and diagnosis can be confirmed with resting and exertional ABI following an exercise that is known to induce symptoms. Treatment includes bypass with prosthetic grafts, endarterectomy with patch, angioplasty, and bare metal stenting. Patch angioplasty results in better reoperation rates and higher patient satisfaction than balloon angioplasty.

VASCULITIS MIMICS

Several disorders can mimic vasculitis and should be considered in the differential diagnosis when evaluating a patient. Typically, these syndromes do not require long-term immunosuppressant therapy.

Fibromuscular Dysplasia

Fibromuscular dysplasia is a noninflammatory vascular disease that most commonly affects the renal and carotid arteries but may also affect any vascular bed.[82] It should be considered in the differential diagnosis of a patient presenting with noninflammatory vascular lesions and is well reviewed in Chapter 142.

Radiation Arteritis

Epidemiology

External beam radiation for malignancies may cause inflammation and fibrosis in adjacent large arteries and lead to clinically

significant stenosis and aneurysm formation. The prevalence of stenosis following radiotherapy can be as high as 30% in the carotid arteries.[83] In the early phase after irradiation, pathologic changes include endothelial damage, intimal thickening, and smooth muscle loss with fibrosis; over time, calcification and more typical atherosclerosis develop, in some cases, leading to bulky stenosis. Radiation-related vasculopathy has been described in many vascular beds, including cervicocranial stenosis following radiotherapy for esophageal squamous cell carcinoma, the visceral vessels following treatment for lymphoma, and in the iliac arteries after treatment for cervical cancer. There may be a delay of decades between the initial radiation exposure and the presentation with vascular insufficiency.[84]

Pathogenesis

Radiation arteritis results in damage to all layers of the arterial wall, and endothelial cell injury with resultant inflammation predisposes to thrombus formation. Medial necrosis has been described with late fibrosis, and the vasa vasorum may be obliterated as a result of adventitial scarring. Structural injury further predisposes to atherogenesis with lipid deposition and atheroma formation in the region of the prior scar. The result is stenotic lesions similar to those seen in atherosclerosis but in the region of prior radiation exposure rather than a typical location (Fig. 137.5).

Clinical Presentation

Presentation of radiation-induced arteritis is similar to vascular insufficiency from atherosclerotic disease. Carotid lesions may present with transient ischemic attacks, amaurosis fugax, or stroke. Visceral involvement presents with mesenteric angina, and irradiation of iliac and pelvic vasculature can result in lower extremity intermittent claudication. Embolization with acute vascular ischemia has also been described. Aneurysm formation and rupture are rare but may occur spontaneously or following surgical repair or stenting.

Diagnostic Evaluation

Angiography is the mainstay of work-up with lesions appearing similar to the tapered narrowing of extracranial GCA. The development of accelerated atherosclerosis in regions of previous radiation-induced vascular damage may also lead to the angiographic appearance of friable, typical atheromatous lesions.

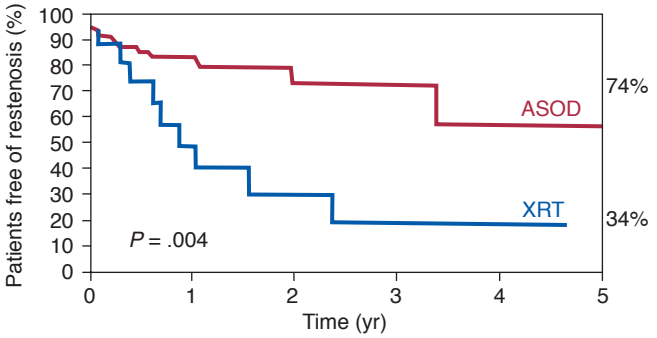

Figure 137.5 Rates of restenosis following carotid artery stenting for radiation-induced carotid artery stenosis. *ASOD,* Atherosclerotic occlusive disease; *XRT,* radiation induced occlusive disease. (From Protack CD, Bakken AM, Saad WE, Illig KA, Waldman DL, Davies MG. Radiation arteritis: a contraindication to carotid stenting? *J Vasc Surg.* 2007;45:110–117.)

Treatment

Because of the risks of postoperative wound infection and poor wound healing associated with open surgical procedures, the use of endovascular techniques to manage radiation-induced arterial stenosis is growing. The most prominent example is carotid stenting (CAS) for symptomatic, and sometimes asymptomatic, radiation-induced carotid stenoses.[85] In a recent series of 23 patients treated with primary CAS, the 30-day survival and 3-year neurologic-event–free survival rates were similar, but the risk of restenosis was greater compared with 127 patients treated with CAS for atherosclerotic carotid disease (Fig. 137.6).[86] In this series, late restenosis occurred up to about 2.5 years following the procedure. Case series also describe good results from endovascular treatment of renal artery stenosis related to radiation for Hodgkin lymphoma and iliofemoral stenosis related to radiation for genitourinary malignancies.[87]

Neurofibromatosis Type-1

Neurofibromatosis type-1 is an autosomal dominant disorder that results in a loss-of-function mutation of the tumor suppressor gene NF-1. The disease affects 1:3000 individuals. Patients develop neurofibromas along with other tumors including schwannomas and pheochromocytomas. Vascular manifestations are a known complication of NF-1 but are rare,[88] affecting only 0.4% to 6.4% of NF-1 patients. In young patients, the vascular lesions resemble fibromuscular dysplasia with development of saccular and fusiform aneurysms, stenotic lesions, arteriovenous malformations, and extrinsic compression from

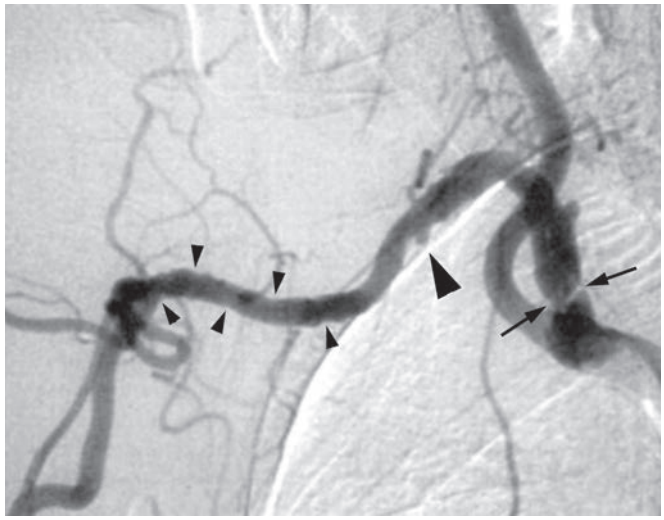

Figure 137.6 Angiogram of a 66-year-old patient presenting with acrocyanosis of the fingers and livedo of the skin occurring 21 years after local adjuvant radiation therapy for breast adenocarcinoma. This view of the aortic arch and right upper extremity demonstrates radiation-induced atherosclerosis with an ulcerated plaque at the origin of the subclavian artery *(arrows)* with diffuse atheromatous changes in the area of prior radiation *(arrowheads).* (From Rubin DI, Schomberg PJ, Shepherd RF, Panneton JM. Arteritis and brachial plexus neuropathy as delayed complications of radiation therapy. *Mayo Clin Proc.* 2001;76:849–852.)

neurofibromas. The average age for vasculopathy diagnosis is 38 years. Spontaneous aneurysm rupture can result in life-threatening hemorrhage, and rupture of vertebral artery aneurysms may lead to cervical vertebral arteriovenous malformations. Surgical intervention for vascular lesions in NF-1 is safe and has been determined to be effective and durable.[88]

Drug-Induced Vasculitis

Several drugs are known to result in hypersensitivity vasculitis[89] including chemotherapeutic agents, growth factors, interferons, antithyroid drugs,[90,91] hydrochlorthiazide,[92,93] hydralazine,[94] minocycline, penicillamine, and vaccines.

Beta-blockers can cause a milder form of vasospasm and exacerbate Raynaud's phenomenon. Ergot preparations used to treat migraine headaches can cause a diverse spectrum of vascular syndromes including acute arterial thromboembolism, dissection, and severe vasospasm that angiographically resemble Takayasu's arteritis.

Cocaine has been associated with venous and arterial thrombosis, aortic dissection, and hemispheric and lacunar stroke. Cocaine adulterated with levamisole causes a dramatic small vessel cutaneous vasculitis that results in skin necrosis and cause tissue loss in the nose, ears, breasts, and digits.[95] Lesions classically begin as palpable purpura, but as they enlarge, they develop a "cookie cutter" edge. Typically, these lesions are multicentric, do not conform to typical vascular territories, and they are extremely painful. The pain is worse with elevation and improves with dependency. Unless concomitant atherosclerosis is present, patients should have normal pulses. Lesions typically respond to withdrawal of the offending agent, and aggressive wound care and immunosuppressive therapy, occasionally, is warranted.

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138 CHAPTER

Thromboangiitis Obliterans (Buerger Disease)

AHMET RÜÇHAN AKAR and BAHADIR INAN

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INTRODUCTION

Definition

Thromboangiitis obliterans (TAO), also known as Buerger disease (BD) or von Winiwarter-Buerger syndrome, is a chronic, non-atherosclerotic, segmental, obliterative, inflammatory vasculopathy primarily involving infrapopliteal and infrabrachial medium and small-sized arteries and veins.[1-5] It is predominantly a disease of young men, with onset typically before the age of 45 to 50 years.[1,4-6] The prevalence in women, however, has been increasing likely related to increased tobacco use.[1,7,8] The disease is more common among people of Middle East, Asia, Mediterranean region, and Eastern Europe but is rare in Africa, central Europe,

Abstract

Buerger disease (BD) is a chronic, inflammatory vasculopathy primarily involving infrapopliteal or infrabrachial medium and small-sized arteries and veins typically detected in men before the age of 50 years. Features of advanced BD include ischemic ulcerations and digital gangrene as a result of critical limb ischema. Smoking cessation is the first line therapy for BD, and revascularization is often not feasible. Intravenous iloprost is an effective treatment option for patients with critical limb ischemia. Endothelin receptor antagonists, immunoadsorption, growth factors, and gene and stem cell-based therapies may have a role for the treatment of patients with BD and critical limb ischemia.

Keywords

Buerger disease
Thromboangiitis Obliterans
Vasculitis
Critical Limb Ischemia
Ischemic ulcers
Revascularization
Stem Cells
Intravenous prostanoids
Endothelin receptor antagonists

and America. TAO is typically manifested by distal extremity ischemia involving the feet, legs, or hands as a result of infrapopliteal or infrabrachial occlusive disease leading to critical limb ischemia (CLI). Advanced TAO features are rest pain, ischemic ulcerations, and digital gangrene.

TAO develops as response to environmental factors primarily with smoking resulting in major and minor amputations with high degree of morbidity and disability resulting in unemployment, psychological, behavioral, social, and financial costs. Pathologically, TAO is characterized by a highly cellular arterial thrombus, extensive intimal inflammation, and preserved all layers of the arterial wall including internal elastic lamina.[9] The disease frequently involves adjacent or superficial veins and nerves. TAO is classified under nonnecrotizing, nongranulomatous medium and small vessel vasculitis.[7] However, TAO has not been included in the revised 2012 Chapel Hill consensus conference nomenclature of vasculitides.[10,11] Absence of markers of inflammation and autoantibodies is unique for TAO in comparison to other types of vasculitis.[1,12] Patients experience periods of acute exacerbation leading to CLI associated with smoking. Remissions follow abstinence from tobacco or occur in the fifth to sixth decades of life. Rare reports of cerebral, coronary, visceral, ophthalmic, and multiorgan involvements have also been described. Reduction in extremity amputation rate can be achieved by smoking cessation. For optimal outcome, multidisciplinary approach is required for the management of TAO patients including vascular surgery, rheumatology, hematology, dermatology, smoking cessation counseling, dental care, rehabilitation medicine, analgesia, and wound care specialists.

Brief Historical Review

Reports resembling TAO have appeared in medical writings since the mid-1800s, but the cases were labeled arteriosclerosis obliterans (ASO) or frostbite because of the lack of pathologic confirmation.[13] In 1879, Felix von Winiwarter described a 57-year-old man with a prolonged history of foot pain that eventually progressed to gangrene and limb loss, which is now recognized as the first published case of a patient with CLI.[1,13,14] In 1898, Haga reported similar clinical features resulting in spontaneous gangrene.[15] In 1908, Leo Buerger described a new and unusual form of progressive vaso-occlusion in Polish and Russian immigrants with who underwent amputation for "*Spontan-gangrän*."[16] Based on his findings, Buerger called the disease "*thromboangiitis obliterans*" to distinguish it from ASO. Subsequently, Buerger emphasized the association of migrating thrombophlebitis with thromboangeitis.[17] Buerger's 32-chapter, 628-page monograph entitled "The Circulatory Disturbances of the Extremities" was published in 1924.[18] Allen and Brown reviewed 200 patients diagnosed with TAO who were evaluated at the Mayo clinic from 1922 to 1926.[19] However, between the 1930s and 1960s, numerous investigators expressed skepticism concerning the identity of TAO.[20-22] In the early 1960s, several authorities considered TAO a distinct diagnosis that should be separated from ASO.[23-27] Today, TAO is accepted as a definite medium and small vessel vasculitis with a typical clinical picture, natural history, and histopathology.[1,4,8,28-30]

TABLE 138.1 Proportion of Thromboangiitis Obliterans Patients Within Peripheral Vascular Disease Throughout the World

Region/Country	%	Reference
North America	0.75	42, 48-51
Western Europe	0.5-5.6	42, 48-51
Eastern Europe	3-39	45, 50, 52
Poland	3.3	32
Turkey	6.6	154
Mediterranean	3-39	35, 304, 370
Israel (Jews of Ashkenazi ancestry)	80	62
Japan	16	138, 371, 372
Korea	66	1
India	45-63	1

EPIDEMIOLOGY

Population Affected

TAO is found worldwide, and it affects both sexes and all races.[1,7,12,29,31] However, the incidence varies by geographic location (Table 138.1) and with uneven gender distribution.[1,32-35] Buerger's view of the disease as being largely restricted to the Jewish race is no longer valid.[18,36] TAO is more common among people of the Middle East, Asia, the Mediterranean, and Eastern Europe but is rare in Africa, central Europe, and America. TAO has a striking predominance in men, especially in series reported before 1960. The reported incidence of TAO in women was less than 1% in most published series in that era.[37] Indeed, only 2 of Buerger's 500 reported cases were women.[18] However, TAO is no longer exclusively seen in male population.[7,38-41] Over the last three decades, this apparent gender discrimination for TAO is disappearing, probably as a result of the rising use of tobacco products by young women.[3,39,42] In recent series, 9.8% to 23% of patients were women.[3,8,33,43,44] Currently, TAO affects men at a 5-fold to 10-fold higher rate than women.[3,29,33,38,44,45] A limited number of pregnancies among patients with active TAO have also been reported.[46-49]

There was an eightfold decrease in the annual incidence of TAO at the Mayo Clinic, which has steadily declined from 104 per 100,000 patient registrations in 1947 to 12.6 per 100,000 patient registrations in 1986.[8,50] The number of new patients with TAO in Japan has also been decreasing,[51] the ratio of TAO to ASO patients has declined from 1:3 in 1990s to 1:10 after 2000 in Japan.[51] Currently, TAO affects approximately 10 in 100,000 people in the European Union (estimated from the applications to the Committee for Orphan Medicinal Products). The number of patients affected by TAO is estimated about 51,000 in European Union, and 4000 in Japan.[52] Pooled characteristics of patients with TAO are listed in Table 138.2.

TABLE 138.2 Pooled Characteristics of Patients With Thromboangiitis Obliterans From Different Regions Globally

Prevalence	Uncommon
Prevalence in woman	Increasing
Incidence	Declining
Involved arterial size	Small and medium
Age at diagnosis (years)	29-42
Age at hospital admission (years)	42.5 ± 8.4
Male, %	77-98
Female, %	2-23
History of smoking, %	93-94
Intermittent claudication, %	17-62
Rest pain, %	13-89
Ischemic ulcers and gangrene, %	38-85
Upper extremity	2-28
Lower extremity	35-100
Both	16-20
Migratory superficial phlebitis, %	34-62
Deep vein thrombosis	Unusual
Raynaud's phenomenon, %	10-45
Sensory findings, %	69
Abnormal Allen's test, %	63
Joint manifestations, %	12.5

Modified from Olin JW. Thromboangiitis obliterans (Buerger's disease). *N Engl J Med*. 2000;343:864–869; Puechal X, Fiessinger JN. Thromboangiitis obliterans or Buerger's disease: challenges for the rheumatologist. *Rheumatology (Oxford)*. 2007;46:192–199; Mills JL, Sr. Buerger's disease in the 21st century: diagnosis, clinical features, and therapy. *Semin Vasc Surg*. 2003; 16:179–189; Ates A, Yekeler I, Ceviz M, et al. One of the most frequent vascular diseases in northeastern of Turkey: thromboangiitis obliterans or Buerger's disease (experience with 344 cases). *Int J Cardiol*. 2006;111:147–153; and Igari K, Inoue Y, Iwai T. The epidemiologic and clinical findings of patients with Buerger disease. *Ann Vasc Surg*. 2016;30:263–269.

Risk Factors

The only risk factor consistently reported is smoking. The strong correlation between tobacco use and the pathogenesis, initiation, and progression of the disease is well established.[3,6,28,29,31,53-55] There is also a higher incidence of TAO among individuals with cigar and pipe smoking; habitual home-made cigarette smoking such as "*bidi*" smoking in India, Bangladesh, and Ceylon;[56] "*kawung*" smoking in Indonesia;[57,58] and chewed "*miang*" (steamed tea leaves) or "*khiyo*" (the home-made raw tobacco in handrolled banana leaves) smoking in Thailand, as well as in users of smokeless tobacco and marijuana.[29,59-61] Higher rate of tobacco consumption and higher carboxyhemoglobin levels were detected in patients with TAO than ASO patients and control subjects.[62] Lower socioeconomic status, poor oral hygiene, nutritional deficits, a history of viral or fungal infection, cold injury, abuse of sympathomimetic drugs, and arsenic intoxication are reported as other possible risk factors.[9,57,62-67] An emerging body of evidence demonstrates that ischemia induced by cocaine, amphetamines, and cannabis addiction can closely mimic TAO symptoms[68-73] or may accelerate TAO onset and presentation.[73] Furthermore, a close relation between long-term arsenic exposure from artesian well water and endemic blackfoot disease has been reported in Taiwan.[74,75] In fact, arsenic adulteration of tobacco as a causative agent for TAO has been suggested in populations smoking bidis or kawung.[66,76-78]

Etiology

The etiology of BD is unknown; however, the close association between disease activity and use of tobacco in any form is beyond any debate.[1,8,34,55,79-81] Genetic predisposition, immune-mediated mechanisms, hypercoagulable states, endothelial dysfunction, and an oral infection-inflammatory pathway have been implicated as potential etiologic factors.[44,82-84]

Immune-Mediated Injury

Several observations implicate an immunologic phenomenon and hypersensitivity to tobacco antigens in the etiology of TAO.[85] It is clearly demonstrated that there is a close relationship between active smoking (high levels of urinary cotinine) and the aggravation of TAO.[86,87] Increased cellular sensitivity to collagen type I,[88-90] type III,[89] and type IV[91] has been reported in patients with TAO compared to ASO patients and healthy male controls. Circulating immune complexes have been reported in the peripheral arteries of some patients with TAO.[92-94] It has been suggested that an unidentified antigen possibly related to a constituent of tobacco smoke triggers immunologic damage to the arterial intima.[95] Recent research has shown that T-cell–mediated cellular and B-cell–mediated humoral immunity associated with the activation of macrophages or dendritic cells in the intima play a key role in TAO.[9]

Previous studies showed activation of endothelial cells associated with TNF-alpha secretion by tissue-infiltrating mononuclear inflammatory cells and expression of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin on endothelial cells in TAO patients.[96] Increased levels of TNF-alpha, IL-1beta, IL-4, IL-6, IL-12, IL-17, and IL-23 and reduced expression of IL-10 were reported in patients with TAO compared to the controls suggesting the involvement of autoimmune pathology.[97,98] An experimental study further reported the key role of high-mobility-group box protein 1 (HMGB1) which may contribute to the pathogenesis of TAO by binding its receptor RAGE in sodium laurate-induced TAO rats.[99] HMGB1 not only induces the production of inflammatory mediators by mononuclear cells, but also activates endothelial cells, leading to the upregulation of the adhesion molecules. rA box, the antagonist of HMGB1, improved the pathologic condition by inhibiting the release and injury of inflammatory mediators and improving the hypercoagulable state of blood.[99] Furthermore, a recent clinical study confirmed significant increases in HMGB-1, MMP-9 and ICAM-1 levels compared with controls in patients with TAO.[100] Thus, immunologically mediated inflammation of the vessels is thought to be the cause of arterial or venous thrombosis and vascular occlusions in TAO.

The clinical picture of antiphospholipid syndrome in young smokers may mimic TAO symptoms.[101] The prevalence of anticardiolipin antibodies was significantly higher in patients with TAO (36%) than in those with premature atherosclerosis (8%; $P = .01$) and in healthy individuals (2%; $P = .001$).[102] Patients with TAO and high anticardiolipin antibodies tended to be younger and to have a significantly higher rate of major amputations and poor prognosis than did those without the antibody.[103,104] Antineutrophil cytoplasmic antibodies (ANCAs)[105] and anti-endothelial cell antibodies[106] were also reported in small series of TAO; however, in another study from Germany, ANCA was not detected in any of the active or inactive TAO patients.[107]

Genetic Predisposition

The importance of a genetic predisposition to tobacco sensitivity is debatable.[89,95,108] One percent of TAO cases in Japan consisted of members of the same family.[109] Genes of the major histocompatibility complex, particularly HLA-A9 and HLA-B5, have been linked to TAO in a study from England.[110] In Israel, a higher frequency of HLA-DR4 and a significantly lower frequency of HLA-DRW6 antigen were reported.[95] However, in the Japanese population, haplotypes of various HLA groups were associated with TAO.[111,112] These haplotypes are rare among Caucasians. In North Indian patients, there was a strong positive association between HLA-DRB1*1501 and TAO.[113] Current concepts suggest that the arterial vasospasm of TAO may be caused by an interaction between smoking and several gene polymorphisms that reduce endogenous nitric oxide, an endothelium-derived vasodilator. Recently, higher incidence of mutations associated with arterial vasospasm; 5A/6A stromelysin-1, also called matrix metalloproteinase-3; and homozygosity were reported in TAO cases compared to controls.[114] Findings regarding genetic predisposition of TAO should be confirmed in larger studies. A recent case-control study from China reported three single-nucleotide polymorphisms, namely rs376511 (OR = 24.4, 95% CI: 8.68-68.62, $P < .0001$), rs7632505 (OR = 29.47, 95% CI: 7.16-121.3, $P < .0001$), and rs10178082 (OR = 18.09, 95% CI: 6.56-49.92, $P < .0001$), are associated with TAO in the Uyghur population.[115,116]

Hypercoagulability

The role of thrombotic risk factors including factor V Leiden and prothrombin 20210G/A mutations, antithrombin, protein C and S deficiency, hyperhomocysteinemia, and platelet aggregation responses in the etiology of TAO remains controversial.[117-126] Most authorities have failed to identify a specific hypercoagulable state in patients with TAO,[29,117] while others have shown one or more abnormalities.[117,118] In one study, the level of urokinase-plasminogen activator was twofold higher and the level of free plasminogen activator inhibitor 1 was 40% lower in patients with TAO than in healthy volunteers.[127] Some authors suggest that hyperhomocysteinemia may have a role in the pathogenesis of TAO.[120-123] Elevated platelet contractile force values were reported in two patients with TAO despite the use of anticoagulation drugs and the suppression of adenosine diphosphate–mediated platelet aggregation.[125] Whether high platelet contractile force plays a role in the pathogenesis of TAO or simply serves as a marker of enhanced platelet function, endothelial dysfunction, or both remains to be elucidated.

Oral Infection-Inflammatory Pathway

Historically, Buerger and then Allen and Brown suspected that infectious foci, including oral and throat infections, might serve as contributory factors in TAO.[19] Higher prevalence of severe periodontal disease in TAO patients is well documented,[82,128,129] suggesting oral infection-inflammatory pathway as a possible etiologic link in TAO.[82] Elevated immunoglobulin G titers against *Treponema denticola*, *Porphyromonas gingivalis*, and *Actinobacillus actinomycetemcomitans* were detected in patients with TAO.[128] Furthermore, several bacterial DNAs of periodontal pathogens were identified in the biopsies from the arterial samples and samples of phlebitis migrans in patients with TAO.[82,130,131]

Vascular Endothelium and Circulating Progenitor Cells

Endothelium-dependent vasorelaxation was impaired even in the nondiseased limbs of patients with TAO.[132] TAO during the exacerbation phase is associated with diffuse increase in vasomotor tone in the conduit arteries that aggravates ischemia.[133] In another study, similar to ASO patients, flow-mediated vasodilation was impaired compared to normal control subjects; however, the number and function of circulating progenitor cells (CPCs) were restored despite endothelial dysfunction in patients with TAO.[134] Increased levels of plasma endothelin-1 were also reported during the exacerbation periods of TAO.[135]

Pathology

The specific pathologic mechanisms in TAO are still unknown.[83] BD is characterized by segmental inflammatory cell infiltration of the vessel wall and arterial or venous thrombotic occlusions.[9,31,136] Hypercellular thrombus formation and preserved architecture of vessel walls is well established in TAO.[137] Earlier studies suggested TAO as a thrombotic disorder complicated by vasculitis, namely transmural neutrophilic infiltration.[36,138] Today, there are compelling reasons to believe that the primary event is the activation of antigen-presenting cells following endothelial cell damage induced by an unidentified antigen, possibly tobacco glycoproteins.[9,51,95,137] Cellular and humoral inflammation, which leads to thrombotic occlusion of the blood vessels, is restricted to the intima of the artery, which defines TAO as an endarteritis.[9,51] Intimal inflammation followed by T-cell infiltrations might result in early arterial occlusion, which is the pathognomonic finding in TAO.[139] Regardless of the pathologic stage, the internal elastic lamina and the architecture of the vascular walls are well preserved in TAO, which is in contrast with atherosclerosis and systemic vasculitis.[1,9,36,54,137,140] Inflammatory cell infiltration is found in the intimal layer and the thrombus.[9,141]

The evolution of TAO is often categorized into three stages.[36] In the acute phase, inflammation affecting the small-caliber and medium-caliber (1- to 5-mm diameter) arteries and veins is observed (Fig. 138.1). The primary features of TAO during

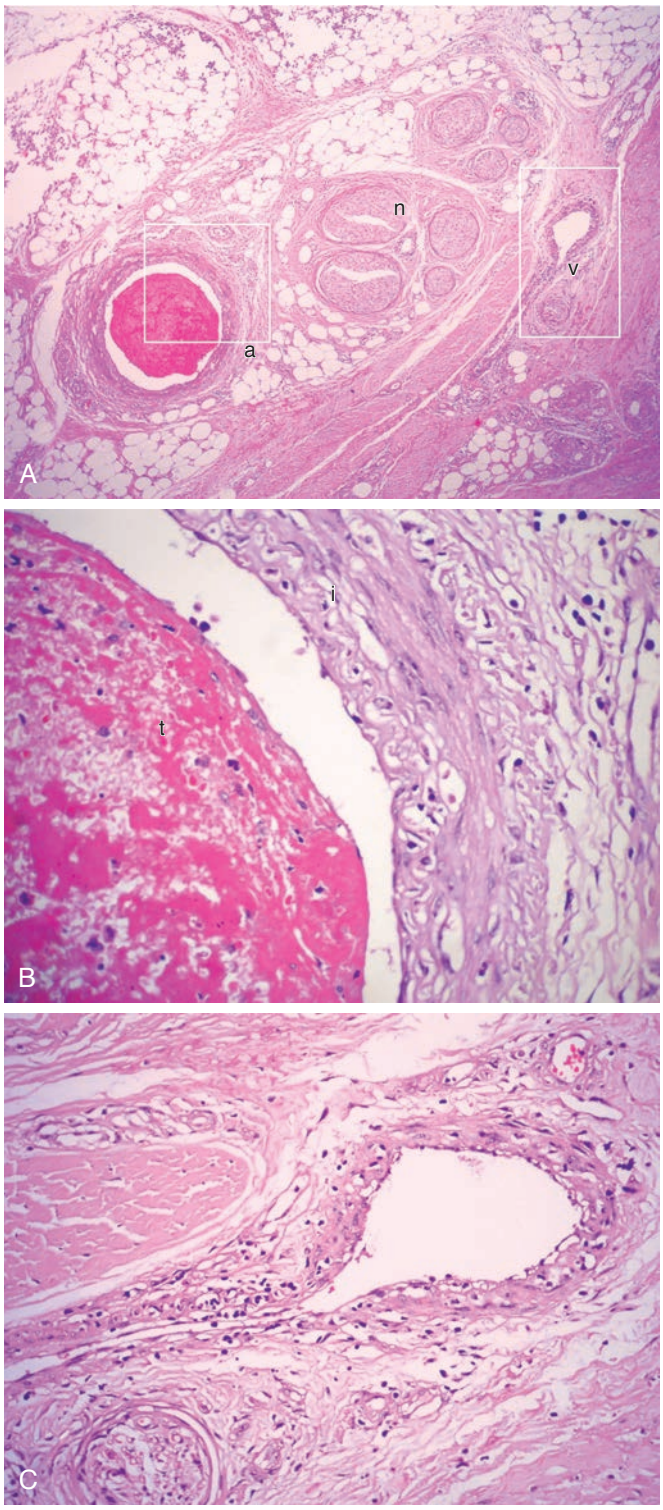

Figure 138.1 (A) Typical subacute thrombotic occlusion of the right digital artery in a 37-year-old male smoker with Buerger disease (H&E, ×64). (B) High-power view of area *a* in A demonstrating the digital artery with cellular arterial thrombus *(t)* and remarkable inflammation in the intima *(i)* (H&E, ×400). (C) High-power view of area *v* in A demonstrating the adjacent digital vein with phlebitis (H&E, ×400). *n*, Nerve.

the acute phase include an occlusive, highly cellular arterial thrombus, polymorphonuclear cell infiltrate with leukocytoclasis, giant cells, and microabscess formation; marked inflammation of the entire vessel wall; and neurovascular bundle.[24,50,54] However, most of the infiltrating cells are detected in the intima.[51] The intense inflammatory infiltration and cellular proliferation seen in acute lesions are distinctive, especially when veins are involved. Multinucleated giant cells can be seen, but fibrinoid necrosis and granuloma are not observed.[9] During the intermediate or subacute phase, there is progressive organization of the occlusive thrombus, with partial recanalization and disappearance of the microabscesses.[9] An inflammatory response, including CD3+ pan–T cells, CD4+ T helper-inducer cells, and CD20+ pan–B cells, against the internal elastic lamina of the affected vessels has been shown in detail (Fig. 138.2).[9,139,141] In addition, CD68+ macrophages or S-100+ dendritic cells are found in the intima during both the acute and subacute stages.[51] IgG, IgM, and IgA and complement factors 3d and 4c are deposited along the inner aspect of the internal elastic lamina.[9] The chronic phase or end-stage lesion is characterized by thrombus organization followed by recanalization, prominent vascularization of the media, and perivascular fibrosis.[36,54,136] Regardless of the pathologic stage, the internal elastic lamina and the architecture of the vascular walls are well preserved in TAO, in contrast with atherosclerosis and other types of systemic vasculitis (Fig. 138.3).[1,9,36,54,140]

CLINICAL PRESENTATION

TAO usually presents with distal extremity ischemia in a smoker younger than 50 years old,[4,142] and the median age at diagnosis is 34 years.[29,143] Characteristically, distal extremity ischemia involves the feet, legs, hands, or arms (Fig. 138.4A and B); and as the disease progresses, it may involve more proximal arteries.[54] Frequently identified signs and symptoms of TAO are listed in Table 138.2, and the most common symptoms are forefoot arch or lower calf claudication as a manifestation of infrapopliteal occlusive disease.[54] Foot claudication is particularly characteristic,[144] but foot or arch claudication may be misattributed to orthopedic problems. Early symptoms may include coldness or burning pain in the feet and hands, associated findings of dependent rubor,[145] cyanosis, migratory superficial thrombophlebitis (see Fig. 138.4C),[130,146] and Raynaud phenomenon.[3,57,147,148] Patients with TAO commonly report cold sensitivity, and sensory findings may be one of the earliest manifestations. In the Cleveland Clinic series reported by Olin and colleagues, 69% of cases revealed sensory findings.[3] Ischemic neuritis or superficial thrombophlebitis may also produce severe pain.[149] In addition, migrating phlebitis (phlebitis saltans) may occur as an early sign and has been reported in 40% to 65% of TAO patients during the course of the disease.[146,150,151] Ascending venography and histologic investigations suggest that 60% of the cases have venous involvement.[152] Occasionally, superficial thrombophlebitis may extend into the deep venous system; however, deep venous thrombosis in BD is unusual[151] In the acute phase of the disease, involved vessels are tender and indurated and reflect the local inflammatory reaction.

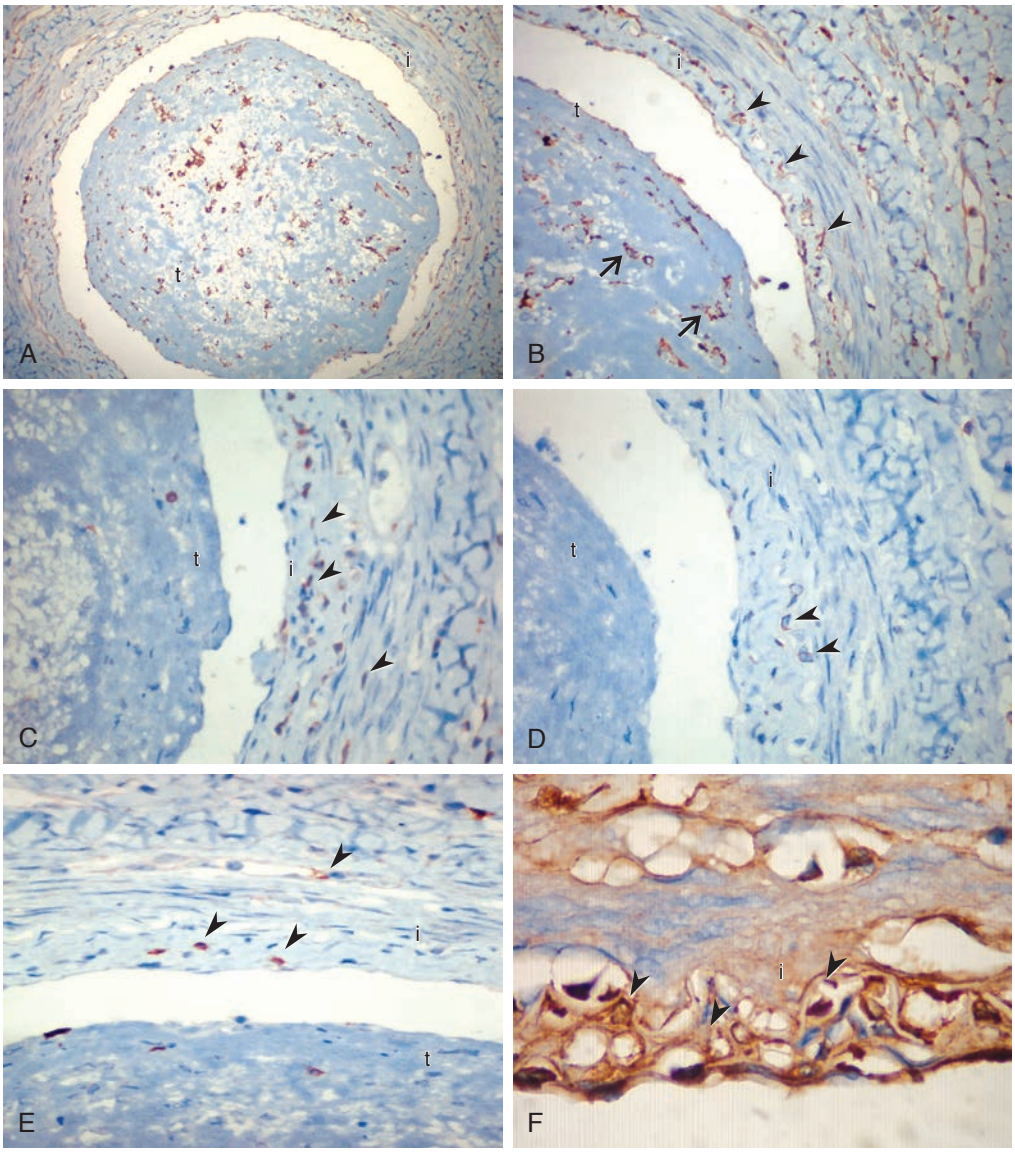

Figure 138.2 (A) Microphotograph of an acute-stage lesion with highly cellular thrombus *(t)* and inflammatory infiltration along the vessel wall with increased anti-CD68$^+$ (clone: KP1) histiocytes. (B) High-power view showing highly cellular thrombus *(arrows)* and abundant histiocytes in the intimal layer *(arrowheads)*. (C to E) Anti-CD3$^+$ (rabbit polyclonal) stained T cells (C), anti-CD4$^+$ (clone: 1F6) T-helper cells (D), and anti-CD8$^+$ (clone: C8/144B) cytotoxic T cells (E) in the intimal layer (*arrowheads;* brown membrane staining, ×400). (F) Deposition of immunoglobulin G (brown, *arrowheads*) within the interstitial intimal tissue (×600). Immunohistochemistry was performed with a Ventana iVIEW DAB detection system. *i,* Intima.

Late findings may present as trophic nail changes, ischemic ulcerations, and digital gangrene,[29,35,54,150,153-155] and almost all ulcers occur in patients between 20 and 50 years of age.[156] Superinfection commonly develops, and the ischemic ulcerations progress toward necrosis and distal gangrene. At this stage, the pain is often excruciating. Ischemic ulcerations often appear dry and irregular with a pale base and various shapes.[40,157] Joint manifestations, mainly transient, migratory episodes of large joint arthritis involving wrist and knees, may occur in approximately 12.5% of patients before the onset of digital ischemia.[12,151,158,159] Subungual splinter hemorrhages may also be detected as an early sign.[151,160,161] Coexisting psychological conditions are also common and mainly are anxiety, depression, amputation, and unemployment-related fears.[162] No difference in clinical presentation in women compared with men has been observed.[3,163]

TAO does not occur in only one limb.[151] Multiple limb involvement is a common feature of TAO.[1,54,60,164,165] In the series reported by Shionoya, two limbs were affected in 16% of patients, three limbs in 41%, and all four limbs in 43% of patients.[164] The Intractable Vasculitis Syndromes Research Group of Japan reported isolated lower extremity involvement in 75%, only upper extremity involvement in 5%, and both upper and lower extremity involvement in 20% of patients with TAO (Table 138.3).[166] Therefore, it is recommended that noninvasive imaging of all extremities be performed in patients with suspected

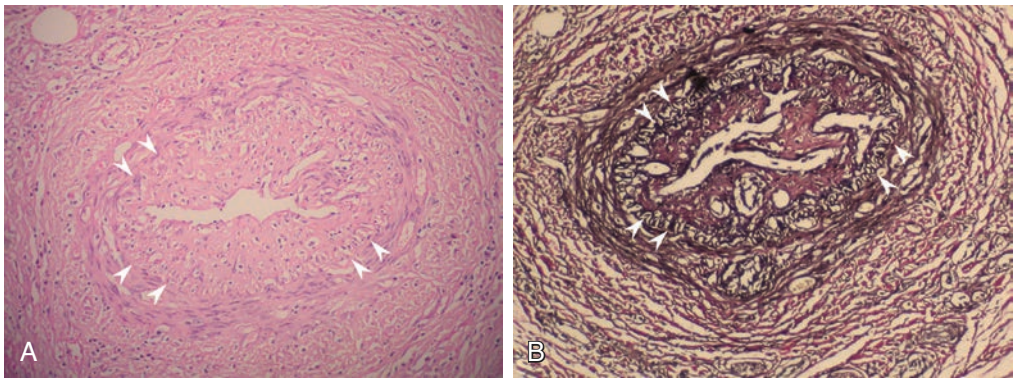

Figure 138.3 (A) Microphotograph of a chronic-stage lesion of Buerger disease, with recanalized arterial thrombus and striking intimal thickening (H&E, ×200). The internal elastic lamina *(arrowheads)* and the architecture of the vascular wall are well preserved. (B) The same vessel stained with elastic van Gieson (×200).

Figure 138.4 (A) Ischemic ulceration of the right second toe with a previously amputated great toe in a 42-year-old man who smoked three packs of cigarettes a day for 15 years. (B) Necrosis of the ends of almost all fingers led to autoamputation in the same patient after continued smoking. (C) One of the cardinal signs of thromboangiitis obliterans is superficial thrombophlebitis, seen here on the left leg of a 28-year-old smoker. Note the hairless skin distally. (D) Infected left metatarsal ulceration with osteomyelitis untreated for several weeks in a 32-year-old male patient with previous great and 5th toe amputations.

TAO.[1,167] It is common to see angiographic abnormalities consistent with TAO in limbs that are not yet clinically involved. Rarely, TAO has been associated with visceral,[168-188] cerebral,[189-193] coronary,[194-203] internal thoracic artery,[196,197] and multiorgan involvement.[204,205] Involvement of the cerebral vessels may result in progressive cognitive decline and migraine,[206] transient ischemic attack, ischemic stroke, or schizophrenia-like symptoms.[189-193] Coronary artery involvement may result in myocardial ischemia or infarction.[194-202] Visceral vessel involvement may manifest as abdominal pain, nausea, vomiting, fever, diarrhea, melena, weight loss, and anorexia and result in ileus, ischemic colitis, mesenteric infarction, intestinal perforation, or liver hypoxia.[169-174,178,180,185-187] Involved vascular beds exhibit similar pathologic characteristics as vessels in the extremities. Even rarer are instances of TAO in saphenous vein arterial grafts,[207] the temporal arteries,[208] the ophthalmic circulation,[209-211] and intrarenal arterial branches[212] of smokers. Also uncommon is the occurrence of TAO in pudendal,[213,214] testicular and spermatic arteries and veins, as was originally described by Buerger.[18] Rare cases of nephropathy as a result of mesangial immunoglobulin A deposition,[215] or renal artery thrombosis; cutaneous manifestations presenting as painful nodular erythema with livedo

TABLE 138.3 Distribution of Arterial Involvement in 825 Patients With Thromboangiitis Obliterans (1650 Upper and 1650 Lower Extremities)

Lower extremity involvement only	616 (74.7%)
Upper and lower extremity arteries	167 (20.2%)
Upper extremity involvement only	42 (5.1%)
Lower Extremity ($n = 783$)	
Anterior tibial artery	683 (41.4%)
Posterior tibial artery	667 (40.4%)
Dorsalis pedis artery	349 (21.2%)
Peroneal artery	304 (18.4%)
Popliteal artery	301 (18.2%)
Digital arteries	180 (10.9%)
Plantar arteries	149 (9.0%)
Other	296 (19.8%)
Upper Extremity ($n = 209$)	
Ulnar artery	189 (11.5%)
Digital arteries	133 (8.1%)
Radial artery	115 (7.0%)
Superficial or deep palmar arch	75 (4.5%)
Brachial artery	13 (0.8%)
Other	26 (1.6%)

Modified from Sasaki S, Sakuma M, Kunihara T, et al. Distribution of arterial involvement in thromboangiitis obliterans (Buerger's disease): results of a study conducted by the Intractable Vasculitis Syndromes Research Group in Japan. *Surg Today*. 2000;30:600–605.

reticularis,[216] and avascular necrosis of femoral heads[217] have also been reported. TAO in unusual locations should be diagnosed only when the histopathologic findings are classic for the acute-phase lesion and the clinical presentation is consistent with the diagnosis of BD.[167]

DIAGNOSIS

A century after its first description, the major clinical challenge in TAO is the absence of universally accepted diagnostic criteria.[1,28,218-220] Shionoya has identified five major criteria for the diagnosis of TAO: (1) smoking history, (2) onset before age 50, (3) infrapopliteal arterial occlusive lesions, (4) either upper limb involvement or phlebitis migrans, and (5) an absence of atherosclerotic risk factors other than smoking.[28] In 1992, Papa and Adar proposed various clinical, angiographic, histopathologic positive and negative criteria, and in a second report, they proposed a point-based scoring system to improve the diagnostic certainty.[55,221] More stringent major and minor supportive criteria were developed by Mills and Porter, based on a cohort of patients in Oregon.[222] Olin's criteria include (1) age less than 45 years; (2) current (or recent) history of tobacco use; (3) the presence of distal-extremity ischemia (indicated by claudication, pain at rest, ischemic ulcers, or gangrene) documented by noninvasive vascular testing; (4) exclusion of autoimmune diseases, hypercoagulable states, and diabetes mellitus by laboratory tests; (5) exclusion of a proximal source of emboli by echocardiography and arteriography; and (6) consistent arteriographic findings in the clinically involved and noninvolved limbs.[1,3] All investigators accepted the exclusion of atherosclerotic risk factors other than smoking. Therefore, TAO is a clinical diagnosis, and the diagnosis requires investigations aimed at excluding other possible diagnoses.

Vascular Evaluation

A complete vascular examination is critical for the diagnosis. Physical examination reveals involvement of small and medium-sized arteries with normal brachial and femoral pulses. The radial, ulnar, dorsalis pedis, or posterior tibial pulses may be absent. Digital arteries may be occluded. An abnormal Allen test, which suggests ulnar artery occlusion in a young smoker with lower extremity ulcerations, is highly suggestive of TAO, since abnormal Allen tests occurred in 63% of cases in the Cleveland Clinic series.[3] Superficial phlebitis may be another clue to the diagnosis. Neurologic examination may document peripheral nerve involvement, with sensory findings in up to 70% of patients.[1] Calculation of the ankle-brachial index, toe-brachial index, and wrist-brachial index at rest and after *exercise* is recommended as the initial screening test. Seasonal variation, with exacerbation of TAO occurring more frequently in the winter, has been reported;[223,224] this may be attributed to cold weather and the stimulation of vasospasm and Raynaud phenomenon.[223]

Noninvasive Testing

Four-limb segmental arterial pressure measurements and pulse volume recordings are usually normal above the knee and markedly reduced distally.[80] Abnormal digital plethysmographic patterns in both lower and upper extremities would objectively document distal occlusive disease in a patient meeting the clinical criteria for TAO.[29,55,65,79,225] Calcification of the involved arterial wall is almost always absent on plain radiography,[31] and arterial duplex scanning is used not only to exclude proximal atherosclerotic lesions and to demonstrate distal arterial occlusive disease, but also to visualize and functionally evaluate the corkscrew shaped collaterals. Using continuous wave Doppler ultrasound monophasic waveform pattern within the corkscrew-shaped collaterals is also known as Martorell sign ("snake" or "dot" sign) (Fig. 138.5).[226,227] In a recent study from Poland, Doppler spectral waveform analysis in 40 TAO patients and 40 healthy subjects revealed a reduction of reversed diastolic flow amplitude with no significant decrease in peak systolic amplitude in patients with TAO.[228] The authors concluded that decreased vascular resistance may develop as a result of increased collateral blood flow and low-resistance cutaneous arteries; thus, resistance index can be a useful Doppler parameter in the early diagnosis of TAO and probably in monitoring disease progression. Another study confirmed augmented flow-mediated

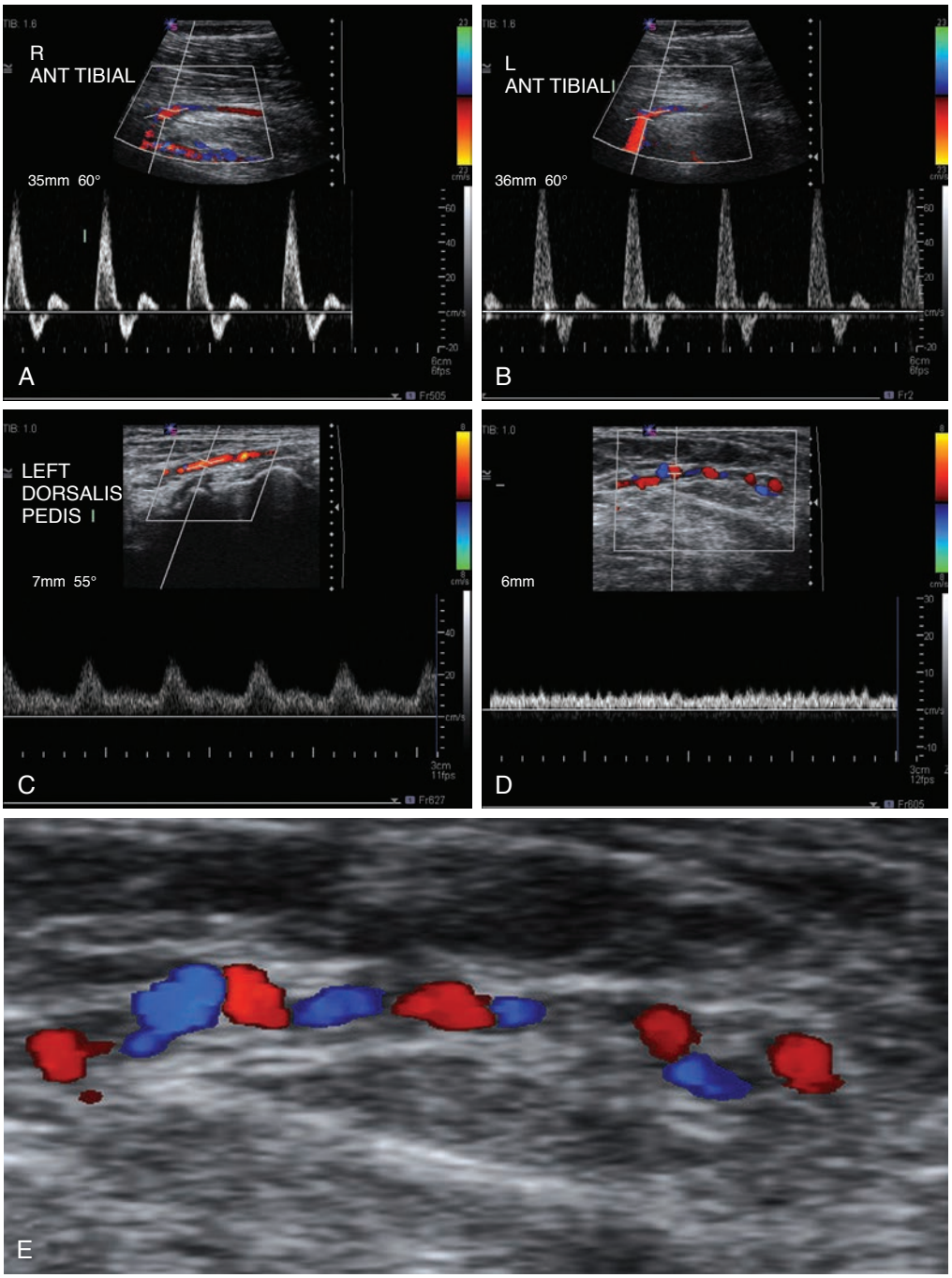

Figure 138.5 Color-flow Doppler studies demonstrating triphasic flow within the right (A) and left (B) anterior tibial arteries, monophasic flow within the left dorsalis pedis artery (C), and the "dot" sign because of continuous flow within corkscrew collaterals at the toe level (D and E).

vasodilation in a corkscrew collateral artery but impaired flow-mediated vasodilation in a native artery in patients with TAO.[229] These findings indicate selective impairment of vascular endothelium, but not smooth muscle cells in native arteries in patients with BD.[229] Laser Doppler flowmetry, transcutaneous oxygen, and carbon dioxide pressures can help evaluate the severity of ischemia and the effectiveness of treatment.[230]

Emboli as a cause of distal ischemia should be ruled out, as the signs and symptoms of embolic occlusions can mimic those of TAO. Cardiac investigations, including electrocardiography, rhythm monitoring, and echocardiography, are recommended to rule out cardiac and thoracic aortic sources of emboli to the involved extremity.[231] In addition, abdominal ultrasonography may be considered to rule out a proximal source of emboli from an abdominal aortic aneurysm or atherosclerotic aorta.

Gadolinium-enhanced magnetic resonance angiography and multidetector computed tomographic angiography (Fig. 138.6) may be useful diagnostic alternatives in patients with TAO. Furthermore, ischemic ulcerations with signs and symptoms of secondary infection should be evaluated using conventional

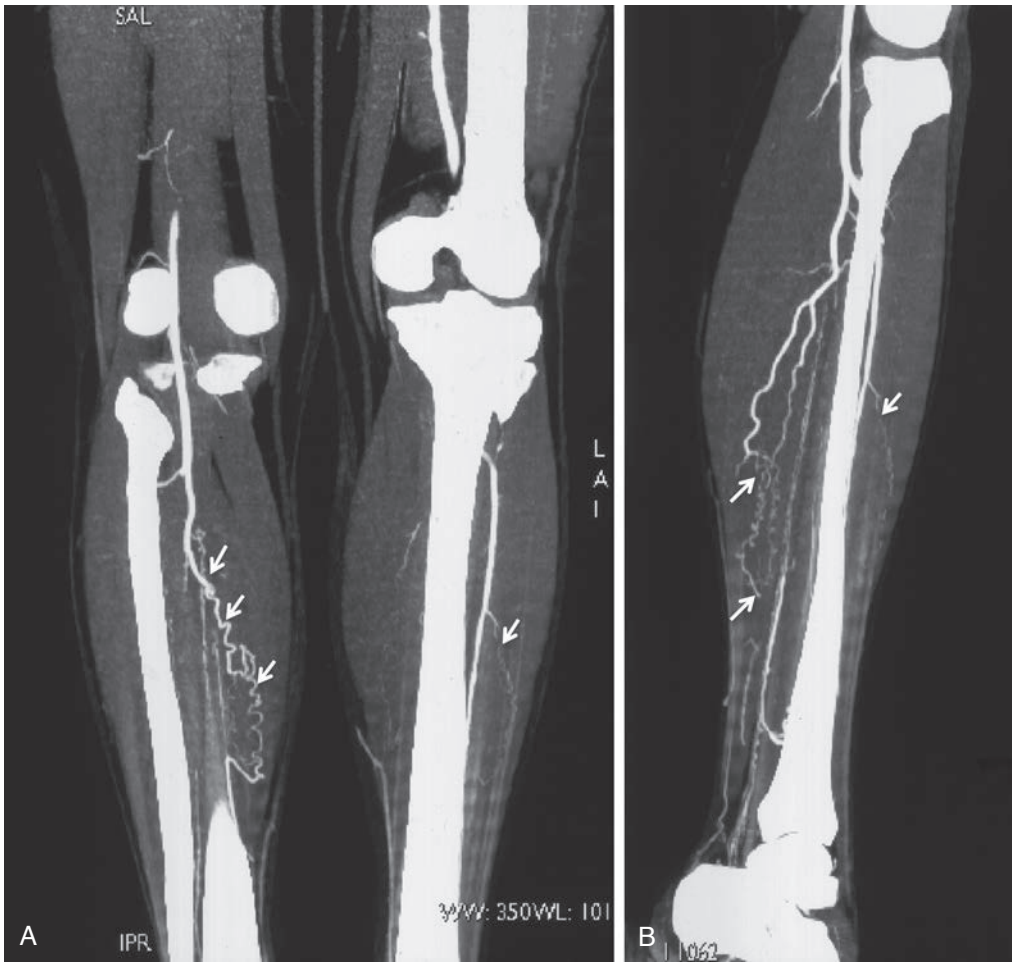

Figure 138.6 (A and B) Abrupt right tibial vessel occlusion with corkscrew collaterals *(arrows)* in a 34-year-old man detected with 64-slice multidetector computed tomographic angiography.

radiography and magnetic resonance imaging to determine the presence of osteomyelitis.[232] Recently, 18F-flourodeoxyglucose positron emission tomography has been investigated in TAO case series but have been found to be unsuitable investigative procedure for the diagnosis of TAO.[233]

Laboratory Testing

There are no specific laboratory tests for the diagnosis of TAO; however, serologic testing for autoimmune antibodies, thrombophilia, and vasculitides should be included in the screening process. Acute-phase reactants, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are typically normal or slightly elevated in the absence of extensive trophic lesions. Absence of immunologic markers including complement levels, rheumatoid factor (RF), antinuclear antibodies (ANA), anticentromere antibodies, anti–SCL-70 antibodies, ANCAs, and cryoglobulins are characteristic for TAO. However, anticardiolipin antibodies may be present in patients with TAO, and the toxicology panel should include cocaine, amphetamines, and cannabis. A suggested diagnostic algorithm for the diagnosis of TAO is summarized in Table 138.4.

Angiography

Thoracoabdominal digital subtraction angiography plays an important role in both supporting the diagnosis of TAO and ruling out other causes of ischemia. Arteriographic findings in TAO may be suggestive but not pathognomonic. Thus, this method is not a "gold standard" for diagnosis. Segmental occlusive lesions (diseased arteries interspersed with normal-appearing arteries), more severe disease distally, involvement of digital arteries,[65] normal proximal arteries without evidence of atherosclerosis, and collateralization around areas of occlusion with corkscrew shape (Martonell sign) also known as "tree root" or "spider's leg" collaterals are the common features of TAO (Fig. 138.7).[44,234] The infrapopliteal or infrabrachial arteries are the most common sites of occlusion. In addition, small corkscrew patterns (types III and IV) are associated with higher prevalence of ischemic ulcers compared to large corkscrew collaterals (types I and II).[235] Although corkscrew collaterals, which represent widened vasa vasorum, suggest TAO to many clinicians,[44] this finding is not pathognomonic. In one study, 27% of 144 limbs affected by TAO had a corkscrew appearance.[236] Corkscrew-shaped collaterals can also be seen in connective tissue diseases

TABLE 138.4 Suggested Diagnostic Algorithm for the Diagnosis of Thromboangiitis Obliterans

1. Young smoker (confirm tobacco, bidi, kawung, cannabis, or cocaine use)
2. Document distal lower or upper extremity ischemic symptoms and signs (claudication, ischemic rest pain, ulcerations, and gangrene)
3. Note the maximal pain-free walking distance, and pain scale (0-10 scale)
4. Document distal nature of disease
   - Blood pressure measurements, ankle-brachial and/or ankle-toe pressure indices
   - Transcutaneous oxygen tensions
   - Arterial duplex scanning
   - Intraarterial digital-subtraction angiography (IA-DSA)
   - Computed tomographic angiography (CTA)
   - Magnetic resonance angiography (MRA)
5. Laboratory tests to exclude connective tissue diseases and hypercoagulable states
   - Routine complete blood count and biochemistry including fasting blood glucose, renal function, and liver enzymes
   - Thyroid function tests
   - Urinalysis
   - Lipid profile
   - Serum homocysteine, vitamin B12, red blood cell folate
   - Coagulation profile: prothrombin time, activated partial thromboplastin time, protein C, protein S, antithrombin III, factor V Leiden, prothrombin gene mutation 20210, antiphospholipid antibodies, anticardiolipin antibodies
   - Autoimmune screen: erythrocyte sedimentation rate, C-reactive protein, complement measurements, antinuclear antibody, antineutrophil cytoplasm antibody, rheumatoid factor, cryoglobulins, scleroderma-specific antibodies (antibodies SCL-70)
   - Measurements of serologic markers for the CREST syndrome (calcinosis, Raynaud phenomenon, esophageal disease, sclerodactyly, telangiectasia)—Anticentromere antibodies
   - Hand radiographs (to exclude calcinosis)
   - Hepatitis B, C serology
   - Venereal Disease Research Laboratory test
6. Exclusion of proximal sources of emboli
   - Electrocardiography, rhythm monitoring
   - Echocardiography (transthoracic, transesophageal if necessary)
   - Abdominal ultrasonography
   - Arteriography (IA-DSA, CTA, MRA)
7. Nielsen digital hypothermic challenge test (Raynaud evaluation)
8. Toxicology screen for cocaine, amphetamine, and cannabis
9. Biopsy indicated only for unusual features
   Age >45 years at onset
   Documented disease in unusual locations (proximal disease, central nervous system disease)

Modified from Lazarides MK, Georgiadis GS, Papas TT, et al. Diagnostic criteria and treatment of Buerger's disease: a review. *Int J Low Extrem Wounds*. 2006; 5:89–95; Mills JL, Sr. Buerger's disease in the 21st century: diagnosis, clinical features, and therapy. *Semin Vasc Surg*. 2003;16:179–189; and Olin JW. Thromboangiitis obliterans (Buerger's disease). In: Rutherford RB, ed. *Vascular Surgery*. 6th ed. Philadelphia: Elsevier Saunders; 2005:404–419.

such as scleroderma, CREST syndrome (calcinosis, Raynaud phenomenon, esophageal disease, sclerodactyly, telangiectasia), systemic lupus erythematosus, rheumatoid vasculitis, and the antiphospholipid-antibody syndrome.[1] Furthermore, cocaine, amphetamine, or cannabis addiction can cause BD-like clinical and angiographic signs.[69-72,77,151,237] The angiographic features that support a diagnosis of TAO are listed in Table 138.5, and a study from Japan determined the distribution of arterial involvement in TAO on the basis of a nationwide survey in 1993 by the Intractable Vasculitis Syndromes Research Group (see Table 138.3).[166]

Biopsy

A biopsy is rarely needed unless the patient presents with atypical features, such as large-artery involvement or age older than 50 years.[1] Biopsy of an acute superficial thrombophlebitis often demonstrates the typical histopathologic lesions of acute TAO.[50] Kroger suggested that the possibility of arteriosclerosis should be discounted only in young patients aged 20 to 30 years.[220]

TABLE 138.5 Angiographic Findings in Thromboangiitis Obliterans

- Involvement of small and medium-sized arteries
  Digital arteries of fingers and toes
  Palmar, plantar, tibial, peroneal, radial, and ulnar arteries
- Segmental occlusive lesions: diseased arterial segments interspersed with normal-appearing segments
- More severe disease distally
- Tapering or abrupt arterial occlusions with collateralization around areas of occlusion: described as "corkscrew collaterals," "spider leg" or "tree root appearance" (not pathognomonic)
- Normal proximal arteries free of atherosclerosis, aneurysms, or other sources of emboli

Differential Diagnosis

Differential diagnosis of TAO includes a broad range of disorders, and diagnostic evaluations should exclude ASO, thromboembolism, and other vasculitides.[7,54,220] TAO differs from ASO with infrapopliteal or infrabrachial arterial involvement and

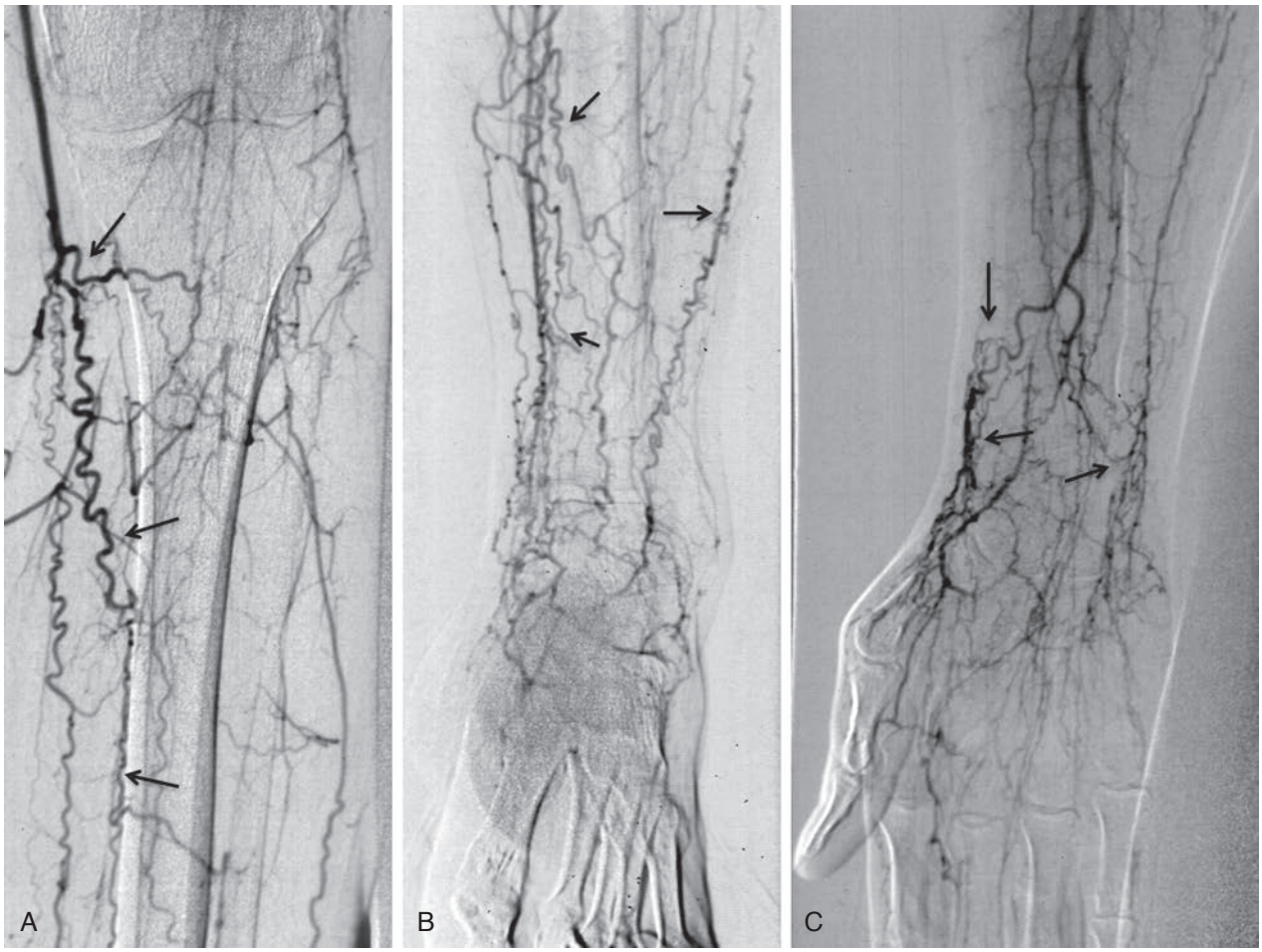

Figure 138.7 Digital subtraction angiography reveals left popliteal and tibial vessel occlusions with corkscrew collaterals *(arrows)* proximally (A) and distally (B) and right radial and ulnar artery involvement (C) in a 32-year-old man with a nonhealing left toe ulceration.

associated migratory thrombophlebitis. TAO differs from most other types of vasculitis with nonnecrotizing, nongranulomatous inflammation of medium and small size arteries; preserved internal elastic lamina; and media; and serologic markers (elevated acute phase reactants such as ESR and CRP, presence of circulating immune complexes, and presence of autoantibodies such as antinuclear antibody, RF, and complement levels) are usually normal or negative.[12,54] Causes of distal arterial ischemia, including scleroderma, CREST syndrome, systemic lupus erythematosus, Takayasu arteritis, polyarteritis nodosa, giant cell arteritis, rheumatoid vasculitis, mixed connective-tissue disorders, antiphospholipid syndrome, vascular compression syndromes (thoracic outlet syndrome, hypothenar hammer syndrome, repetitive vibratory injury, popliteal artery entrapment, carpal tunnel syndrome), malignancies, hematologic thrombophilia disorders (lupus anticoagulant, anticardiolipin antibody syndrome), drug-induced hypersensitivity, ergot abuse, cannabis arteritis, and microbial infection, should also be considered in the differential diagnosis. If TAO and ASO or other vasculitides cannot be differentiated, the diagnosis can be confirmed by biopsy of a subcutaneous nodule or involved vein, which may show the characteristic acute-phase lesion.[54,151] TAO has important features that are distinguishable from other forms of vasculitis,[167] such as a highly inflammatory thrombus with relative sparing of the blood vessel wall. Preservation of the internal elastic lamina distinguishes TAO from the true necrotizing forms of vasculitis.[238-240] Kimura disease presenting with Raynaud phenomenon and digital infarcts, and marked eosinophilia may mimic TAO symptoms.[241]

Natural History

Exacerbations and remissions are characteristic features of TAO. In one study, at a mean follow-up of 10.7 (range: 2-30) years, patients experienced an average of 5.4 (range: 1-20) acute episodes with severe symptoms.[143] Patients have a significantly diminished quality of life compared with age- and sex-matched controls.[242,243] TAO population and a matched coronary artery disease population had similar degrees of tobacco dependence and Fagerström scores.[244] In one study, the life expectancy of patients with TAO was comparable to that of the normal population.[25] In contrast, Cooper and colleagues reported that survival among the TAO cohort was significantly lower than that in the matched US population in the TAO group, and the

average age at death was 52.2 ± 8.9 years.[242] The risk of any amputation during mean follow-up of 15.6 years was 25% at 5 years, 38% at 10 years, and 46% at 20 years.[242] The risk of major amputation, defined as above-knee, below-knee, or hand amputation, was 11% at 5 years, 21% at 10 years, and 23% at 20 years.[242] In this analysis, the amputation rate was significantly reduced in those who discontinued tobacco use. The authors concluded that the risk of amputation in previous smokers is eliminated 8 years after smoking cessation.[242] Cumulative survival rates in the series reported by Ohta and colleagues were 97.0% at 5 years, 94.4% at 10 years, 92.4% at 20 years, and 83.8% at 25 years (mean follow-up, 10.6 years).[243] These investigators also demonstrated that the occurrence or recurrence of necrotic lesions was usually arrested in patients older than 60 years. There was a strong correlation between continued smoking and limb amputation leading to poor quality of life and job loss.[243] Another study from Turkey reported similar survival rates: 95.0% at 2 years, 92.4% at 5 years, and 88.4% at 10 years (mean follow-up, 11.6 years).[154] A study from Japan confirmed that failure to cease smoking was the most significant factor affecting the risk of ulcer formation (OR: 1.71) and risk for amputation (OR: 2.73; 95% CI: 1.86-4.01).[150]

TREATMENT

Lifestyle Changes

Smoking Cessation

The first step in management of TAO is complete and permanent discontinuation of smoking in any form,[29,54,81,167,245] including passive smoking.[87] The hazards of continued smoking in patients with TAO seems to be independent of factors such as the number of cigarettes smoked per day[167]; whether the tobacco product is in the form of cigarettes, bidis, cigars, chewing tobacco, or snuff;[56,60,246] cigarette characteristics; and smoking behavior, including degree of inhalation. Counseling, smoking-cessation programs, pharmacotherapy using bupropion or varenicline, and exercise training form the cornerstone of treatment.[45] Nicotine replacement therapy may result in disease progression, thus this should be avoided;[1,247] however, in terms of limb salvage in a stage of CLI in patients with TAO, smoking cessation may not be sufficient.[248]

Exercise Training

Benefits of exercise training in claudication are well established.[249] Regular exercise training (sessions lasted more than 30 minutes and 3-5 times per week) improves pain-free walking time by an average of 180% and maximal walking time by an average of 120% in patients with claudication.[250] Randomized trials confirmed that ischemic exercise training triggers the release of CPCs from the bone marrow and promotes homing of CPCs into vascular networks.[251]

Foot, Hand, and Dental Care

Daily foot and hand hygiene as well as avoidance of trauma, thermal injury, vibration, chemicals, and cold are easily applied measures to prevent ischemic ulcers.[252] Any injury to the involved extremity should be treated promptly. Adequate oral hygiene, controlling the bacterial biofilm, and periodontal treatment might be useful measures preventing the recurrence of the disease.[130,253]

Pharmacologic Treatment

Treatment must be tailored to the individual and is often based on the patient's clinical presentation. TAO has conventionally been treated with antiplatelet agents including oral anticoagulants, clopidogrel, dextran, pentoxifylline, phenylbutazone, pyridinolcarbamate, inositol niacinate, nonsteroidal antiinflammatory agents, and immunosuppressive drugs including cyclophosphamide[254] and corticosteroids.[255] However, no randomized controlled trials have been reported assessing the efficacy of previously mentioned agents in TAO.[256,257] Reported two cases of steroid-responsive TAO[255] with remarkable eosinophilia is controversial.[241] Appropriate antibiotics and nonsteroidal antiinflammatory agents should be used in patients with complicated phlebitis, cellulitis, or osteomyelitis.

Calcium Channel Blockers

Calcium channel blockers have been used for TAO patients associated with the Raynaud phenomenon. Nifedipine, nicardipine, or amlodipine may similarly be used in patients with significant vasospasm.[1]

Prostacyclin Analogs

Prostaglandin I2 (Prostacyclin), a main product of arachidonic acid metabolism by endothelial cells, is a potent vasodilator through vascular smooth cell relaxation, and it inhibits platelet aggregation, chemotaxis, and cell proliferation.[258,259] Epoprostenol is a freeze-dried preparation of prostacyclin for intravenous administration.[260] Iloprost is a stable and synthetic analogue of epoprostenol with a plasma half-life of 20 to 30 minutes. It is commonly used in the treatment of peripheral vascular disease because of its vasodilating and platelet inhibitory effects. Iloprost also downregulates the expression of intercellular adhesion molecule-1 and endothelial leukocyte adhesion molecule-1 on interleukin-1β–stimulated endothelial cells and inhibits lymphocyte adhesion to endothelial cells.[261]

Iloprost Infusion

Moderate quality of evidence exists with limited number of randomized trials in pharmacologic treatment of TAO with CLI.[257] In a European multicenter, randomized, double-blinded trial involving patients with TAO and CLI, Fiessinger and Schafer compared 6-hour infusion of iloprost (0.5-2.0 ng/kg per minute) and oral aspirin (100 mg/day) for a 28-day trial period.[262] Among 152 patients, 133 patients fulfilled the entry criteria of rest pain, ischemic ulceration, or gangrane.[262] At 28 days of treatment, iloprost was superior to aspirin at achieving ulcer healing or relief of ischemic pain; 85% of patients in the iloprost group improved versus 17% in the aspirin group. Furthermore, at 6 months, the response rate was 45 of 51 (88%) patients treated with iloprost compared with 12 of 44 (21%) patients treated with aspirin. Only 6% of patients in the iloprost group ultimately

required amputation compared with 18% in the aspirin group.[262] In a randomized, multicenter study, the Turkish Buerger's Disease Research Group compared the results of lumbar sympathectomy ($n = 78$) to 28 days of intravenous iloprost ($n = 84$) in 162 patients with CLI and TAO.[263] The primary endpoint of the study was complete healing without pain or major amputation at 4 and 24 weeks. Complete healing was achieved in 61.9% of the iloprost group and 41% of the lumbar sympathectomy group at 4 weeks ($P = .012$) and in 85.3% versus 52.3%, respectively, at 24 weeks ($P < .001$).[263] The risk of amputation is also reduced with combination of iv iloprost infusion and supervised smoking cessation in TAO patients with CLI.[264] Thus, reported evidence suggests that intravenous iloprost is effective pharmacologic treatment option in healing ulcers and relieving rest pain in patients with TAO and CLI.[257] Iloprost has been authorized in some European Union Member States for the treatment of TAO.

Oral Iloprost

The European TAO Study Group conducted a double-blinded, randomized, placebo-controlled trial comparing oral iloprost (100 or 200 mcg) with placebo for 8 weeks among 319 patients with ischemic rest pain or ulcerations recruited from 22 centers in six countries in Europe,[258] and the duration of treatment was 6 weeks. The primary endpoint was total healing of the most important lesion, and the secondary endpoint was total relief of pain at rest without the need for analgesics at six months. The combined endpoint consisted of the patient's being alive with no major amputation, no lesions, no rest pain, and no analgesic use. After 6 months of therapy, low-dose iloprost was significantly better than placebo at relieving rest pain without the use of analgesics, and for achieving the combined endpoint.[258] However, neither dose of oral iloprost showed a significant effect on the total healing of lesions compared with placebo.

Prostaglandin E1 Analogs

Limaprost alfadex, a prostaglandin E1 analogue, was developed in Japan to treat ischemic symptoms of TAO also has strong vasodilatory and antiplatelet activity similar to Prostacyclin. In a randomized, double-blinded trial in 136 Japanese patients primarily with TAO, there was no significant difference in the improvement of ischemic symptoms between patients receiving limaprost 30 μg/day and those receiving oral ticlopidine 500 μg/day.[265]

Phosphodiesterase Inhibitors

Phosphodiesterase 3 Inhibitors (Cilastazol)

Phosphodiesterase 3 (PDE3) isoenzyme is found in vascular smooth muscle and platelets. Inhibition of PDE3 isoenzyme increases intracellular cyclic adenosine monophosphate (cAMP) results in smooth muscle relaxation and decreases platelet aggregation. In one small study, cilastazol was effective at improving ischemic ulcerations in patients with refractory digital ischemia.[239] The role of cilostazol in TAO is, however, still not clear.

Phosphodiesterase 5 Inhibitors (Sildenafil, Tadalafil)

PDE5 isoenzyme is found in the corpus cavernosum of the penis and vascular smooth muscle. Inhibition of PDE5, a cyclic guanosine monophosphate (cGMP)-dependent phosphodiesterase increase intracellular cGMP, results in decreased intracellular calcium and increased nitric oxide leading to vascular smooth muscle relaxation and vasodilation. There are few reported cases of TAO with digital symptoms successfully treated with off-label use of PDE5 inhibitors, namely sildefanil (20 mg tid) or tadalafil (40 mg every other day).[266-268]

Endothelin Receptor Antagonists

Bosentan, an oral dual endothelin-1 receptor antagonist targeting two transmembrane receptors, namely ETA and ETB, has been useful in patients with TAO and ischemic lesions.[268-271] Bosentan has selective vasodilatory, antiinflammatory, and antifibrotic properties. Previous case series showed clinical and angiographic improvement in 10 out of 12 patients with ulcers and/or pain at rest.[272] De Haro et al. reported that Bosentan therapy (125 mg/12 h) maintained for four months resulted in clinical improvement and complete healing of the ulcers in a single-center prospective study with 48 months follow-up data in patients with TAO and ischemic ulcers unresponsive to conventional therapies.[273] Only 2 out of 22 extremities (9%) underwent major amputation. Well-conducted randomized clinical trials are, however, still needed, especially in patients with pain at rest and ischemic ulcers.

Thrombolytics

Selective intraarterial infusion of urokinase and streptokinase as a treatment option for TAO has been reported.[274-278] However, in the series of Hussein et al., limb salvage rate was 33%, and bleeding complications occurred in 17% of the patients treated with intraarterial streptokinase.[275] Matsushita and associates administered a continuous intraarterial infusion of urokinase (20,000 U/h) and heparin (800 U/h) in a 19-year-old woman with CLI and TAO.[39] Although her symptoms improved temporarily, thrombolytic therapy did not enable recanalization of the occluded popliteal artery. High-quality trials assessing the effectiveness of thrombolytics in patients with TAO are needed.

Folate Supplementation

Folate therapy in TAO patients with increased homocysteine levels has been investigated in one randomized trial from Iran.[279] Single dose of folic acid (5 mg) and placebo were compared in 30 patients with TAO.[279] The authors concluded that single dose folic acid has homocysteine lowering effect but did not inhibit the risk of minor or major amputation rate.[279] Further clinical evidence about folate therapy for TAO patients is required.

Statins

There is increasing experimental evidence that the pleiotropic effects of statins may improve or restore endothelial function and decrease oxidative stress and vascular inflammation.[280-282]

However, the therapeutic role of statins in inflammation-induced thrombosis is still an unresolved issue.[283]

Analgesia

Analgesia is often required in patients with rest pain and ischemic ulcers. Opioids, nonsteroidal antiinflammatory drugs, antidepressants, and neuronal block may relieve symptoms.

Regional Sympathetic Blockade

Guanethidine, an adrenergic neuron blocker that inhibits the presynaptic release and subsequent reuptake of noradrenaline from postganglionic sympathetic nerve endings, has been proposed for the treatment of TAO.[284-287] Intravenous regional sympathetic blockade with guanethidine has been described by Hannington-Kiff.[288] This "chemical sympathectomy" is based on multiple sessions of intravenous regional sympathetic blockage with lidocaine and guanethidine using Bier's arterial arrest.[289,290] However, despite promising case reports in patients with ischemic rest pain and nonhealing ulcerations, limitations regarding the use of this therapy still exist.[284]

Spinal Cord Stimulation

There are increasing reports in the literature regarding the use of implantable spinal cord stimulators in patients with TAO.[291-296] Electrical spinal cord stimulation relieves pain through several mechanisms, including preventing transmission of painful stimuli through the corresponding dermatomes, stimulation of the production of inhibitory neurotransmitters in the spinal cord, and inhibition of sympathetic vasoconstriction with consequent improvement in peripheral microcirculation.[291,294,296] Spinal cord stimulation successfully addresses the neurogenic, but not the somatic, aspects of pain in patients with TAO.[287] Spinal cord stimulation can be attempted when other forms of therapy are ineffective.[167]

Surgery

Lumbar or Thoracic Sympathectomy

In a randomized, multicenter study, the Turkish Buerger's Disease Research Group compared the results of lumbar sympathectomy ($n = 78$) to 28 days of intravenous iloprost ($n = 84$) in 162 patients with CLI and TAO.[263] The primary endpoint of the study was complete healing without major amputations or pain at 4 and 24 weeks. Complete healing was achieved in 61.9% of the iloprost group and 41% of the lumbar sympathectomy group at 4 weeks ($P = .012$) and in 85.3% versus 52.3%, respectively, at 24 weeks ($P < .001$).[263] Kothari et al. recently reported that thoracoscopic dorsal sympathectomy reduces pain in patients with upper limb involvement in a recent case series of 25 TAO patients from India.[297]

Distal Surgical Revascularization

The role of surgical revascularization in TAO is not clear. Revascularization is often not feasible because of the distribution of diffuse, segmental arterial involvement, and the distal nature of the disease.[54] Distal arterial spasm during dissection and poor-quality veins owing to phlebitis are other disease-specific handicaps. The arterial circulation of the lower extremity generally cannot serve as the distal anastomotic site for bypass surgery, resulting in suboptimal patency rates. However, if the patient has CLI and a distal target vessel is present, bypass surgery using autologous vein should be considered.[298,299] Arterial bypass of the larger vessels may be used in selected cases. In 1974, Inada and associates demonstrated that of their 236 patients with TAO, only 11 (4.6%) had lesions that were amenable to surgical revascularization,[300] whereas a vasculitis database from Japan revealed that 15.5% of TAO patients underwent surgical revascularization.[150] Dilege and associates reported that 36 of their 94 patients with TAO (38.3%) were deemed eligible for revascularization, but only 27 patients (28.7%) actually underwent revascularization procedures.[301] In this study, any crural vessel with at least 10 cm of patency, preferably in continuation with the pedal arch or draining with a good collateral network, was considered appropriate for revascularization. The patency rates at 12, 24, and 36 months were 59.2%, 48%, and 33.3%, respectively. The limb salvage rate was, however, 92.5%. Bypass surgery was most frequently required below the trifurcation segment of the knee joint, with a cumulative patency rate of 54.6% at 5 years.[302] In a retrospective review of 216 patients with TAO over a 10-year period, Sayin and colleagues reported that lumbar sympathectomy was performed in 85% and thoracic sympathectomy in 9.3% of TAO patients.[303] Twenty-one patients (9.7%) underwent direct arterial reconstruction of varying types. The investigators noted that four of the five endarterectomized segments had occluded by the 7-year follow-up.[303] Sasajima and associates showed that a strategy of aggressive distal bypass surgery using autologous disease-free vein grafts for TAO may provide acceptable primary and secondary patency rates.[298] The patency rates in the postoperative nonsmoking group were significantly higher than in the smoking group (66.8% vs. 34.7%; $P < .05$).[298] Predictors of early graft failure were poor quality vein, inadequate technique for anastomosis, inadequate tunneling, anastomosis to a diseased artery, arterial spasm, and vein graft intimal hyperplasia.[298] Late failures were due to disease progression, especially in smokers, vein graft intimal hyperplasia or aneurysm, atherosclerosis, and competition with collateral flow.[298] Bozkurt and colleagues reported cumulative secondary patency rates of 57.9% for bypass grafts at a mean follow-up of 5.4 years in 19 patients with BD.[304] Cumulative patency was 70% (7 of 10) for saphenous vein grafts, 50% (3 of 6) for polytetrafluoroethylene grafts, and 33.3% (1 of 3) for composite grafts. Different distal bypass techniques and routes have been described to obtain better anatomic orientation and patency rates in patients with TAO.[305-307] Collateral artery bypass is an option when the main arteries are affected by TAO,[308] and successful local flap transfers after distal bypass surgeries have been reported in selected cases.[309-312] The prevalence of amputation and the primary and secondary patency rates after revascularization in patients with TAO are summarized in Table 138.6.

Pedicled Omental Graft

For foot salvage, paramalleolar arterial bypass grafts may be combined with microvascular free tissue transfer.[309] Successful

TABLE 138.6 Prevalence of Amputations, Primary and Secondary Patency Rates After Arterial Revascularization in Patients With Thromboangiitis Obliterans

Authors	Year	Study Type	Number of Patients	Number of Bypasses	Primary Patency	Secondary Patency	Limb Salvage	Amputations
Sayın[19]	1993	R	21	21	62.5% at 5 years[b]		[a]	4 Major
Sasajima[20]	1997	R	61	71	49% at 5 years 43% at 10 years	63% at 5 years 56% at 10 years	59%	3 Major 8 minor
Nakajima[21]	1998	R	26		65% at 2 years[b]		[a]	[a]
Bozkurt[22]	1998	P	14	14	57% at 8 years[b]		89%	[a]
Shindo[23]	2002	R	8	10	[a]	[a]	[a]	[a]
Dilege[24]	2002	P	27	24	59% at 1 year 48% at 2 years	33% at 3 years	93% at 3 years	2 Major
Bozkurt[4]	2004	P	19	20	[a]	57.9% at 5.4 years	90%	2 Major
Ohta[25]	2004	R	31	46	41% at 1 year 32% at 5 years 30% at 10 years	54% at 1 year 48% at 5 years 39% at 10 years	91% at 1 year 89% at 5 years 85% at 10 years	5 Major (14%)
Ateş[26]	2006	R	27	27	44.8% at 1 year[b] 37% at 5 years		[a]	12 (total)

[a]Not mentioned.
[b]Not stated primary or secondary.
P, Prospective; *R*, retrospective.
Modified from references 5 and 238.
Lazarides MK, Georgiadis GS, Papas TT et al. Diagnostic criteria and treatment of Buerger's disease: a review. *Int J Low Extrem Wounds*. 2006;5:89–95; Dargon PT, Landry GJ. Buerger's disease. *Ann Vasc Surg*. 2012;26:871–880.

local flap transfers after distal bypass surgery has been reported in selected cases,[309-312] and omental transfer to areas not amenable to arterial reconstruction has been proposed as a therapeutic option in TAO.[313-319] In two retrospective series from India, complete healing was achieved in more than 80% of the patients, and limb salvage was 100% with pedicled omental graft.[314,317] This surgical technique, however, has not been used in Europe or the United States.

Distal Venous Arterialization

Distal venous arterialization may be offered as a last surgical resort for limb salvage in the absence of graftable distal arteries.[320-324] Distal venous arterialization can successfully salvage the critically ischemic lower limb with few serious complications. A recent meta-analysis showed that overall 1-year foot preservation was 71% (95% CI: 64%-77%), and 1-year secondary patency was 46% (95% CI: 39%-53%) after distal venous arterialization.[321]

Local Wound Care

In clinical practice, wound toilette, including limited surgical or ultrasound debridement and appropriate antibiotics, is often useful in the treatment of infected ischemic ulcerations.[29] Caution is advised for excessive local debridement, which may widen ulcers.[325] Topical agents for elimination of necrotic tissue and infection, maintaining a moist environment, and management of wound margin are the hallmarks for the treatment of ischemic ulcers associated any vasculitis.[325] Given the absence of a proven benefit and its high cost, hyperbaric oxygen therapy should be considered only in selected patients with ischemic ulcers, osteomyelitis, or necrotizing fasciitis who have not responded to other forms of treatment.[40,72,326-331] Negative-pressure wound therapy may be helpful, as continuous or intermittent vacuum-assisted settings may have a role in the treatment of debilitating complex chronic ulcers in patients with TAO.[332-334]

Endovascular Treatment

Percutaneous subintimal angioplasty for limb salvage in patients with nonhealing ulcers has been proposed,[335-338] but it would be premature to claim that this method might provide new opportunities for patients with TAO. However, extended endovascular management for tibial or foot artery obstruction was recently achieved in 17 patients with TAO and CLI with a technical success rate of 95%.[339] Successful use of Silver-Hawk directional atherectomy in two TAO patients with popliteal occlusions was recently reported; however, this endovascular procedure requires further validation by larger studies.[340]

Other Interventional Procedures

Immunoadsorption

Recent pilot studies demonstrated near complete pain relief, increased maximum walking distance, and tissue perfusion after selective removal of circulating immunoglobulins and antibodies from patient's plasma using immunoadsorption techniques.[341,342] In one study, agonistic autoantibodies directed against G-protein coupled receptors were identified in 9 out of 11 patients. The

Figure 138.8 Limb salvage after autologous bone marrow–derived mononuclear cell therapy. Preoperatively *(left)*, this patient had a nonhealing ischemic wound of the great toe and required high doses of narcotic analgesics. After surgical débridement *(right)*, complete healing was achieved at 3 weeks and maintained at 24 months.

authors concluded that elimination of agonistic autoantibodies by immunoabsorption may relieve immune-mediated vasospasm and improve microcirculation.[343]

Growth Factors

Basic fibroblast growth factor and vascular endothelial growth factor (VEGF) may play a role in patients with CLI due to BD. Isner and colleagues treated seven limbs in six patients with TAO (three men, three women; mean age, 33 years) in an open-label, dose-escalating, phase 1 clinical trial to document the efficacy and safety of gene transfer of naked plasmid DNA encoding VEGF (phVEGF165) via intramuscular injection in the treatment of CLI.[344] Ulcers, which had not healed for more than 1 month before therapy, healed completely in 3 of 5 limbs after intramuscular phVEGF165 gene therapy. Nocturnal pain at rest was relieved in the remaining two patients, although both continued to have claudication. Two patients with advanced distal forefoot gangrene ultimately required below-knee amputation despite evidence of improved perfusion. This report suggests that angiogenesis induced by phVEGF165 gene transfer may provide an effective therapy for patients with advanced TAO that is unresponsive to standard interventions.[344] Another study demonstrated higher VEGF plasma levels in patients with TAO compared with controls ($P = .008$), showing the existence of a natural defense mechanism for ischemia and new collateral formation.[345] A recent Phase I/IIa open-label four dose-escalation clinical study assessing the safety, tolerability, and efficacy of a single intramuscular administration of DVC1-0101 in patients with PAD also involved two patients with TAO.[346] DVC1-0101 is a new gene transfer vector based on a nontransmissible recombinant Sendai virus (rSeV) expressing the human fibroblast growth factor-2 (FGF-2) gene (rSeV/dF-hFGF2). The investigators concluded that DVC1-0101 was safe, effective, and resulted in significant improvements of limb function.[346]

Stem Cell-Based Therapeutic Angiogenesis

Angioblasts isolated from peripheral blood or bone marrow–derived CPCs can be incorporated into sites of active angiogenesis, providing a key factor in re-endothelialization.[347] Culture-expanded CPC transplantation in an animal model of limb ischemia improved neovascularization and blood flow recovery and reduced limb necrosis and autoamputation by 50% compared with controls.[348] Preclinical,[349] and clinical studies in patients with peripheral artery disease and CLI,[350] including TAO, suggest that the implantation of autologous bone marrow mononuclear cells,[351-354] autologous peripheral blood stem cells,[355,356] mesenchymal stem cells derived from human umbilical cord blood,[357] autologous adipose tissue-derived stem cells,[358] and autologous whole bone marrow stem cells[359] into ischemic limbs can restore limb function by increasing new collateral vessel formation.[360] We and our colleagues have also demonstrated that the implantation of autologous bone marrow mononuclear cells in the ischemic limbs of patients with TAO is associated with improved rest pain scores ($P < .0001$), peak walking time ($P < .0001$), quality of life ($P < .0083$), and augmentation of collateral formation at 24 weeks in 78% of patients.[352,361,362] Healing of ischemic ulcers was achieved in 83% of the study group (Fig. 138.8). Subsequent studies and meta-analysis supported intramuscular bone marrow cell administration as a relatively safe, feasible, and potentially effective therapy in patients with CLI and TAO.[360,363] Bone marrow-derived mononuclear cell therapy induced long-term improvement leading to an amputation-free rate of 91% (95% CI: 82%-100%) at 3 years in the Therapeutic Angiogenesis by Cell Transplantation (TACT) Trial.[364] A combined approach of intraarterial and intramuscular injections may maximize the chances of local deposition of stem cells in the ischemic limb.[365]

Another method of stimulating angiogenesis by inserting intramedullary K-wires has been suggested by Inan and associates.[366] Fenestration of the tibia at six sites with EPC mobilization from bone marrow using recombinant human granulocyte colony-stimulating factor was also reported recently by Kim and associates in 27 patients (34 lower limbs) with BD.[367] Over a mean follow-up period of 19 months, 13 of 17 limbs with nonhealing ulcers healed. This technique resulted in a similar degree of new vascular collateral network development[367] compared with autologous bone marrow mononuclear cells aspirated from the iliac crest and implanted into the intermetatarsal region, the gastrocnemius muscle, and the dorsum of the foot or forearm.[352] Recently, functional impairment of endothelial progenitor cells was confirmed in TAO patients compared to healthy nonsmokers and smokers.[368] Ongoing work is focused on understanding the mechanisms of therapeutic angiogenesis, including vascular stem cell niches, mobilization, homing, and vascular repair.[369]

ACKNOWLEDGMENTS

We sincerely thank Drs. Shigehiko Shionoya and Jeffrey W.Olin, the authors of this chapter in previous editions, for their

outstanding work, which has provided invaluable insights into Buerger disease, and Drs. Isinsu Kuzu and Suat Aytac of the Ankara University School of Medicine for their scientific assistance and the provision of pathology and radiology illustrations.

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This is an important update assessing the effectiveness of any pharmacologic agent (intravenous or oral) compared with placebo or any other pharmacologic agent in patients with Buerger disease. In this review, five randomized controlled trials were identified (n = 602) comparing prostacyclin analogue with placebo, aspirin, or a prostaglandin analogue, and folic acid with placebo.

Cooper LT, Tse TS, Mikhail MA, McBane RD, Stanson AW, Ballman KV. Long-term survival and amputation risk in thromboangiitis obliterans (Buerger's disease). *J Am Coll Cardiol*. 2004;44:2410–2411.

This study describes the time-dependent event rates for major or any amputation and death in a cohort of patients with TAO. In contrast with previous studies, the investigators report an excessive late mortality in patients with TAO compared with the US population. However, the risk of amputation in previous smokers is eliminated by 8 years after smoking cessation.

Durdu S, Akar AR, Arat M, Sancak T, Eren NT, Ozyurda U. Autologous bone-marrow mononuclear cell implantation for patients with Rutharderford grade II-III thromboangiitis obliterans. *J Vasc Surg*. 2006;44:732–739.

This is the first study investigating the use of autologous bone marrow mononuclear cell implantation for patients with Rutherford grade II-III thromboangiitis obliterans resulting in new vascular collateral networks across the affected arteries in 78.5% of the patients. Total healing of the most important lesion was achieved in 83% of patients with ischemic ulcers. Relief of rest pain without the need of narcotic analgesics improved in all patients.

Isner JM, Baumgartner I, Rauh G, et al. Treatment of thromboangiitis obliterans (Buerger's disease) by intramuscular gene transfer of vascular endothelial growth factor: preliminary clinical results. *J Vasc Surg*. 1998;28:964–973.

The first report that documents the results of six patients with Buerger disease who were treated with gene therapy as part of a larger phase-I clinical trial to document the safety and efficacy of intramuscular gene transfer of naked plasmid DNA-encoding vascular endothelial growth factor (phVEGF165) in the treatment of critical limb ischemia.

Kim DI, Kim MJ, Joh JH, et al. Angiogenesis facilitated by autologous whole bone marrow stem cell transplantation for Buerger's disease. *Stem Cells*. 2006;24:1194–1200.

This intriguing study documents the angiogenesis facilitated by fenestration of the tibia bone and autologous whole bone marrow stem cell transplantation for Buerger disease.

Kobayashi M, Ito M, Nakagawa A, Nishikimi N, Nimura Y. Immunohistochemical analysis of arterial wall cellular infiltration in Buerger's disease (endarteritis obliterans). *J Vasc Surg*. 1999;29:451–458.

This original study describes important histologic observations from 33 specimens of nine patients with Buerger disease. The investigators concluded that Buerger disease was a vasculitis (endarteritis) induced by an antigen in the intimal layer and subsequent activation of T-cell mediated cellular immunity and B-cell-mediated humoral immunity associated with activation of macrophages or dendritic cells in the intima.

Kobayashi M, Sugimoto M, Komori K. Endarteritis obliterans in the pathogenesis of Buerger's disease from the pathological and immunohistochemical points of view. *Circ J*. 2014;78:2819–2826.

This review demonstrates important pathologic characteristics of arteries affected with Buerger disease. The authors' observations support activation of antigen-presenting cells by an unidentified antigen in the blood, resulting in an immunoreaction closely linked to Notch signaling pathway. The authors conclude that restriction of cellular and humoral immune reaction to the arterial intima defines Buerger disease as an endarteritis.

Mills JL Sr. Buerger's disease in the 21st century: diagnosis, clinical features, and therapy. *Semin Vasc Surg*. 2003;16:179–189.

This is another important update on the clinical features and fundamental management principles of Buerger disease. The concept "No tobacco, no Buerger disease" is reintroduced.

Ohta T, Ishioashi H, Hosaka M, Sugimoto I. Clinical and social consequences of Buerger disease. *J Vasc Surg*. 2004;39:176–180.

This original investigation documents the natural course of TAO in Japan. The investigators report that occurrence or recurrence of necrotic lesions usually subsides after the age of 60, and arterial reconstruction is associated with poor long-term results although it shortens the healing process of ischemic ulcers.

Olin JW. Thromboangiitis obliterans (Buerger's disease). *N Engl J Med*. 2000;343:864–869.

This landmark review summarizes the clinical features, pathogenesis, diagnostic criteria, and recommendations for the treatment of thromboangiitis obliterans and currently is still relevant.

Shionoya S. Diagnostic criteria of Buerger's disease. *Int J Cardiol*. 1998;66(suppl 1):S243–S245.

The article outlines the current need for well-defined clinical diagnostic criteria for Buerger disease and important hallmarks of the clinical picture.

The European TAO Study Group. Oral iloprost in the treatment of thromboangiitis obliterans (Buerger's disease): a double-blind, randomized, placebo-controlled trial. *Eur J Vasc Endovasc Surg*. 1998;15:300–307.

The first randomized trial comparing oral iloprost with placebo conducted in 22 centers in six European countries.

A complete reference list can be found online at www.expertconsult.com

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139 CHAPTER

Takayasu Disease

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INTRODUCTION

Takayasu disease is an immune arteritis causing inflammation of the aorta, its major branches, and pulmonary arteries. It is predominantly a disease of young women, with onset typically in the second or third decade of life.[1] The disease is more common among Asians, although all ethnicities can be affected. The annual incidence in North America is approximately 2.6 per million people.[2]

The first description of a patient with Takayasu arteritis (TA) may have occurred as early as the 18th century. Morgagni found large-vessel aneurysms and stenoses at autopsy in a 40-year-old woman in 1761.[3] In 1830 Yamamoto described a 45-year-old man who originally presented with complaints of fever and developed pulselessness in the radial arteries 1 year later.[4] TA is named after Japanese ophthalmologist Mikito Takayasu, who presented his findings of arteriovenous anastomoses of the ocular papilla in a 21-year-old woman with sudden vision loss in 1908.[4] Two other ophthalmologists at the same meeting presented similar findings in patients with absent radial pulses.[5] The term *Takayasu arteritis* was first coined in 1939 by Yasuzo Shinmi when reporting on a patient with comparable symptoms and physical findings.[6] In 1975 the research committee of the Japanese Department of Health and Welfare officially proposed adopting the term *Takayasu arteritis* for the disease.

Although TA is a chronic disease, it is characterized by a waxing and waning course. Symptoms range from fever, myalgias, and loss of appetite to cerebral, visceral, and extremity ischemia.[7] This variation in presentation frequently leads to a delay in diagnosis.

EPIDEMIOLOGY

TA most commonly affects patients from East Asia, and the incidence varies by geographic location. The estimated incidence in Japan is approximately 150 new cases per year,[7] and postmortem studies reveal a prevalence of 1 in 3000 patients.[8] The incidence in India is 200 to 300 per million,[9] whereas the incidence in Sweden is 0.8 per million, with a prevalence of 0.64 per 100,000.[10] In Birmingham, England, the incidence is 0.2 per million.[9] Finally, a population-based study in Olmstead County, Minnesota, found an incidence of 2.6 per million.[2]

TA affects women 6 to 8 times more frequently than men, although this distribution may depend on the region being studied. Authors from India have found female to male ratios of 4:1,[11] whereas others from China have reported ratios of 3:1.[12] The median age at diagnosis in a cohort of 60 patients from the National Institutes of Health (NIH) was 25 years.[13] Although the detection of TA in some patients after age 40

Abstract

Takayasu disease is an immune arteritis predominantly affecting the aorta, its major branches and the pulmonary arteries of young women. The disease is most prevalent in Asians, with an annual incidence in North America of approximately 2.6 per million people. It is characterized by a waxing and waning clinical course with symptoms from fever, myalgias, and loss of appetite to cerebral, visceral and extremity ischemia. Both genetic predispositions and immune-mediated mechanisms have been implicated as etiologies for the disease.

Patients often present at varying courses of the disease process, including constitutional symptoms of fever, headache, myalgia, or weight loss; or, symptoms of vessel inflammation such as carotidynia. Patients may also be diagnosed with advanced stages of disease where the vessel fibrosis or aneurysmal degeneration has occurred. There is no global consensus for diagnostic criteria, and other vasculitides must be ruled out prior to a final diagnosis. Furthermore, no single serologic test has been identified for the diagnosis of Takayasu's. Advancements in radiological imaging, such as computed tomography angiography, magnetic resonance angiography and duplex ultrasound have allowed for better evaluation of vessel wall changes consistent with Takayasu disease. Positron emission tomography has also been integral to evaluate responses to medical therapy.

Treatment is aimed at immunosuppressive therapy with glucocorticoids in the active phase or additional immune-modulators for patients who relapse. Revascularization may need to be performed in select patients with refractory disease suffering from cerebral, visceral or extremity ischemia or aneurysmal degeneration. Such procedures should be performed when disease activity is minimal. Open revascularization has been the gold standard therapy, and while some have seen success with endovascular therapies, there is not enough data available to suggest this is superior to open bypass grafting.

Keywords

Takayasu disease
vasculitis
immune disease
immunosuppression
aortic fibrosis

years may be related to delays in diagnosis, it is now understood that a significant number of patients do not develop symptoms until later in life. When the results from most major studies are examined, the majority of patients develop symptoms between the ages of 20 and 40 years, with no trend by region.[13–19]

PATHOGENESIS

Etiology

A genetic predisposition to the disease has been suggested because of the predilection for patients of Asian descent, especially those with a Japanese background,[20] and the occasional familial clustering of the disease.[21] HLA-Bw52 occurs in approximately 44% of Japanese patients with TA, compared with 13% in the general Japanese population.[22] Furthermore, the haplotype of Bw52-Dw12 confers a greater likelihood of an active inflammatory state and rapid disease progression.[23] Other studies have found increased susceptibility in patients with gene mutations in the HLA-A, -D, and -DR regions.[24,25] In a group of North American patients with TA, there was no significant association between any HLA antigen and disease severity or complications.[26] In fact, there was a negative association between TA and the HLA-DR1 antigen, suggesting a possible protection against disease development. Further studies examining the genetic factors associated with TA must be performed because consistent associations are lacking.[27]

Immune-mediated mechanisms, including both antibody- and cell-mediated mechanisms, have also been suggested as a cause of TA. TA has been associated with rheumatoid arthritis,[28] systemic lupus erythematosus,[29] inflammatory bowel disease,[30] and glomerulonephritis.[31] All these conditions have autoimmune mechanisms associated with their pathology, which suggests a common mechanism with TA.

Cell-mediated mechanisms of endothelial damage have been implicated in TA. Gamma/delta T cells in patients with TA are reactive to Hsp60 and exhibit cytotoxicity to aortic endothelial cells, suggesting a role in the pathogenesis of TA.[32] This mechanism occurs via increased production of interferon gamma and is distinct from other similar rheumatologic disorders.[33]

Antibody-mediated mechanisms of TA have been advocated based on elevated levels of antiaortic endothelial cell antibodies. These lead to the induction of endothelial adhesion molecules, cytokines, and apoptosis.[34] Levels of antiaortic endothelial cell antibodies are 20 times greater in patients with TA compared with healthy controls[35] and with patients with other autoimmune disorders.[36]

The fact that TA is commonly found in women of childbearing age suggests that sex hormones may play a role in its development. Studies of patients with TA compared with healthy controls have shown elevated urinary estrogens.[37] Furthermore, the association of Klinefelter syndrome in patients with TA may implicate elevated estrogens in the disease.[38]

Many causative factors have been implicated in TA, but none is found consistently. The cause of TA is likely multifactorial, and further studies are necessary to elucidate the associations among the various suggested mechanisms.

Pathology

Histologic examination of inflammatory lesions of TA reveals a panarteritis of all three layers of the vessel wall, with skip areas along the length of the vessel (Fig. 139.1).[39] These lesions can range from acute exudative inflammation to chronic, nonspecific productive inflammation to various types of granulomatous inflammation.[40] Active inflammatory lesions begin in the vasa vasorum, extend through the media and adventitia, and terminate in a diffuse or nodular fibrosis. Smooth muscle cells and fibroblasts invade the intima and produce excessive ground substance. Occasionally, intimal thickening of the peripheral branches of inflamed arteries may lead to end-organ ischemia.

Immunohistochemical examination of postoperative aortic specimens with active inflammation has shown replacement of the muscular and elastic layers of the media and adventitia by dense fibrous tissue.[41] In certain patients, inflammatory nodules of numerous T cells and B cells colocalized with dendritic cells have been observed in the deep portion of the intima and adventitia. This colocalization suggests that interactions between dendritic cells and lymphocytes may be important in the pathogenesis of TA.

In the chronic phase of TA, inflammation leads to thickening of the entire vessel wall. The vessel lumen narrows owing to proliferation of the intima, destruction of the elastic fibers of the media, and fibrosis of the adventitia.[42]

Aneurysmal disease may also be associated with TA, although it is less frequent than stenotic disease. It has been hypothesized that aneurysmal disease occurs when destruction of the elastic component of the media occurs before fibrosis of the adventitia, leading to a weakened vessel wall.[43]

CLINICAL PRESENTATION

TA was first thought to progress in three phases. The first phase was characterized by an inflammatory period with constitutional symptoms such as fever, headache, weight loss, myalgia, and arthralgia. The second phase was characterized by vessel inflammation with symptoms of vessel pain and tenderness, or carotodynia. The third and final phase, called the "burned-out" phase, was characterized by vessel fibrosis or aneurysmal degeneration. In this phase, patients presented with the classic signs of ischemia or aneurysm. It is now understood that although most patients with TA experience these three phases, many do not; and patients with TA can endure very diverse courses. In a group of North American patients, 10% were asymptomatic at presentation, 57% never had any constitutional symptoms, and only 33% developed systemic symptoms.[13] Some TA patients present with inflammatory and fibrotic changes simultaneously, further emphasizing the diverse nature of this disease.[7]

It is likely that the nonspecific nature of constitutional complaints leads to the delay in diagnosis that is common in patients with TA. We reported a median delay of 1 year before diagnosis in a group of North American patients, similar to the 10 to 15.5 months reported in other studies.[13,20] Approximately 90% of patients see more than one medical doctor, with

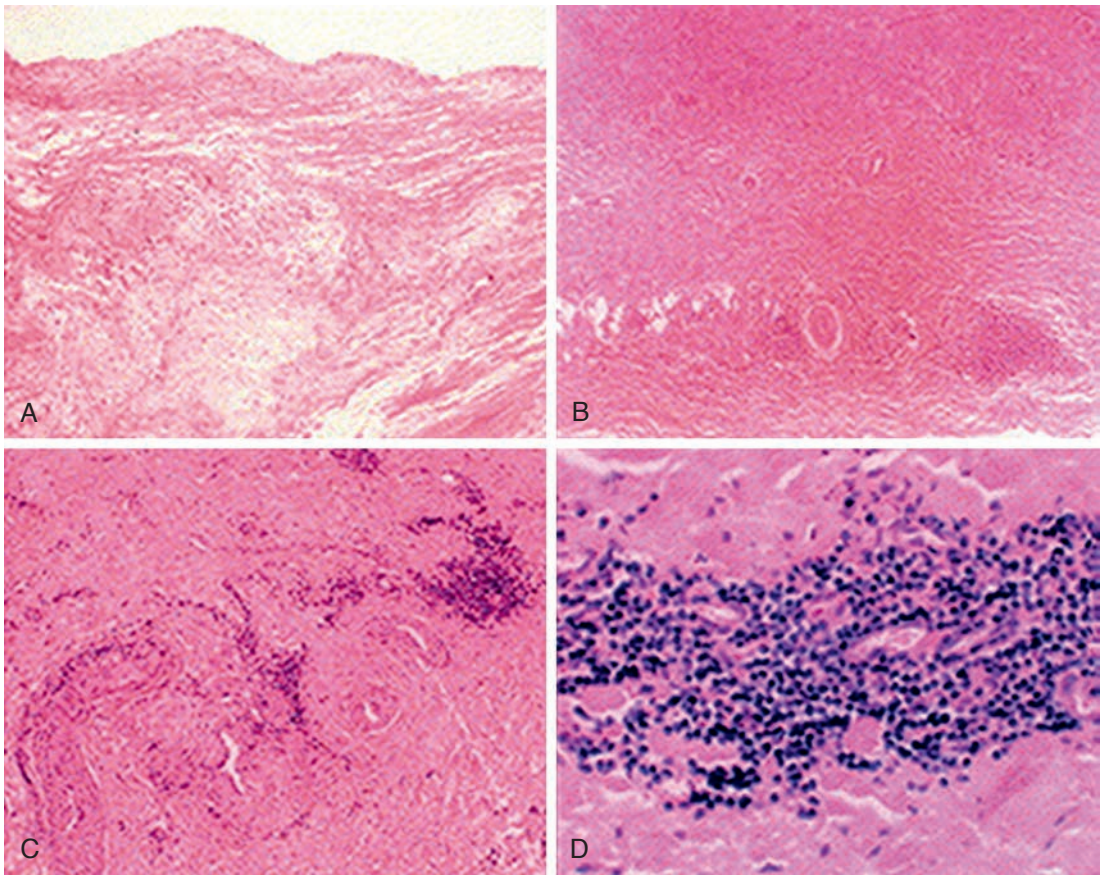

Figure 139.1 Histologic Findings in Takayasu Arteritis. (A) Aortic cusp with intimal fibrosis and myxoid degenerative changes in media without inflammatory cells. (B) Aortic wall with fibrosis of media and infiltration of inflammatory cells around vasa vasorum. (C and D) Inflammatory cell infiltrate consists of predominantly mononuclear lymphocytes. (From Song JK, et al. Echocardiographic and clinical characteristics of aortic regurgitation because of systemic vasculitis. *J Am Soc Echocardiogr*. 2003;16:850–857.)

a mean of five doctors, before obtaining the correct diagnosis of TA.[42]

Physical examination may help in diagnosis but is not particularly sensitive. However, normal physical exam findings should not be thought to exclude the presence of arterial disease.

The clinical presentation of patients with TA varies by geographic region (Table 78.1).[7] The most frequent finding in patients from North America and Italy were carotid bruits,[13,20] versus absent pulses in Mexico[44] and hypertension in India.[45]

Overall, arterial involvement is often symmetric in paired arteries and contiguous in the aorta.[46] Cerebrovascular signs and symptoms are common because of the frequency of aortic arch and branch involvement. Approximately 32% of patients present with carotodynia.[13] Many patients report syncope or presyncope at some point during the disease course. Ischemic symptoms of stroke, transient ischemic attack, or amaurosis fugax occur in 5% to 20% of patients.[47] Visual disturbances occur in up to 30% of patients and are statistically associated with vertebral and common carotid artery involvement (Fig. 139.2).[13] The retinal disease pattern described by Takayasu also leads to visual disturbances due to central retinal hypoperfusion.[48]

Upper extremity involvement is common in patients with TA. Diminished or absent pulses occurs in 53% to 98% of patients.[13,49] Claudication is more frequent in the upper extremities than the lower extremities and occurs in approximately 62% of patients.[13] This may be because the left subclavian artery is more commonly affected by TA than other arteries (Fig. 139.3).[13,20] It has been hypothesized that subclavian steal syndrome is rare in patients with TA because the subclavian artery is involved both proximal and distal to the origin of the vertebral artery. More recent studies have shown that this may not always be true, with angiography demonstrating isolated disease in the proximal subclavian artery 80% of the time.[46]

Cardiac manifestations of TA are common. Coronary artery involvement occurs in 6% to 16% of patients with TA and may lead to ischemic symptoms or congestive heart failure.[49] Aortic valve regurgitation occurs in 12% to 24% of patients and is generally caused by dilation of the aortic root.[20] Aortic valve regurgitation seems to be more common in TA patients from India.[22] Mitral valve regurgitation occurs in 3% to 11% of patients.[7,50] The cause of mitral valve regurgitation is unclear but is thought to be independent of aortic regurgitation.[51] Pulmonary artery involvement with TA may be underdiagnosed. In studies in which pulmonary angiography was performed, up to 70% of patients had evidence of disease.[52,53] These patients most often present with symptoms of pulmonary hypertension. Finally, diffuse vascular involvement of the myocardium has been reported in the absence of coronary stenosis or aortic valve

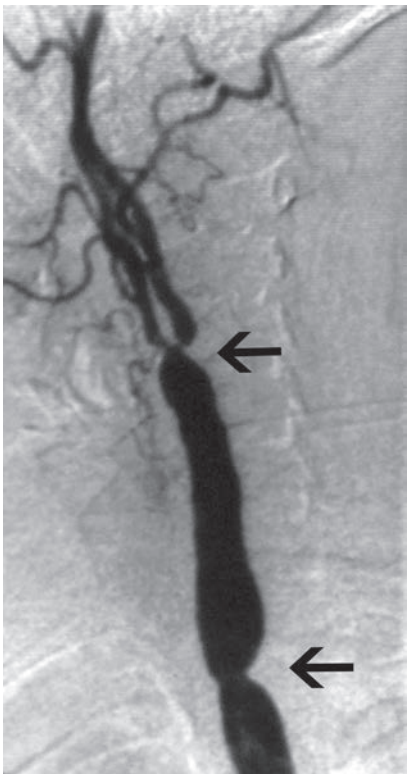

Figure 139.2 Selective carotid angiogram of a 34-year-old woman with symptoms of cerebral ischemia. Note the stenoses of both the common carotid artery and the carotid bifurcation *(arrows)*.

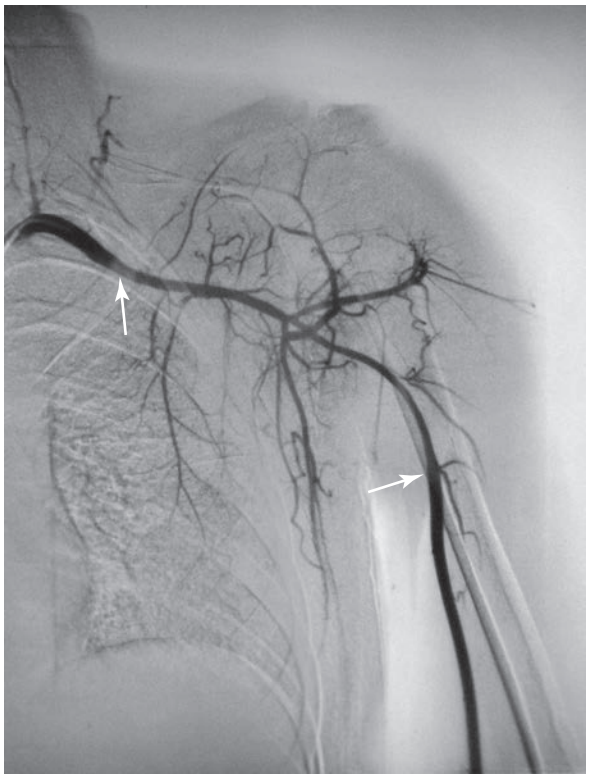

Figure 139.3 Selective left subclavian angiogram of a 26-year-old woman with claudication of the left upper extremity. Note the long, tapered stenosis of the left subclavian and axillary arteries.

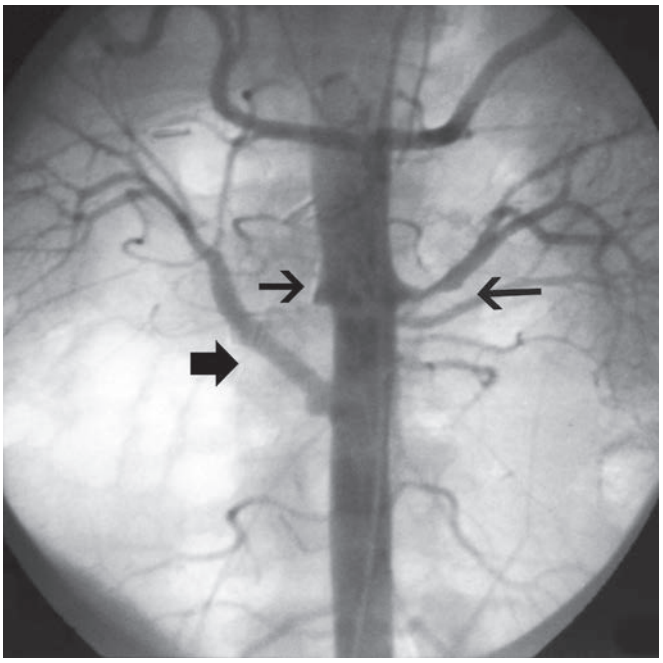

Figure 139.4 Abdominal aortogram of a 48-year-old hypertensive woman with known Takayasu arteritis. Note the short-segment left renal artery stenosis *(long arrow)*, right renal artery occlusion *(small arrow)*, and right aortorenal artery bypass *(broad arrow)*.

regurgitation. Patients present with symptoms of congestive heart failure, and biopsies of the myocardium show diffuse myocarditis.[54]

Hypertension is one of the most common presenting signs in patients with TA and occurs in 33% to 60% of patients.[12,13] Bilateral stenosis of the subclavian arteries occurs in up to 92% of patients with TA and can mask hypertension.[13] Therefore blood pressure measurements of both upper and lower extremities should be performed in any patient suspected of having TA. Renal artery stenosis is a significant cause of hypertension in patients with TA. Involvement of the renal arteries occurs in approximately 20% to 50% of patients.[50,55] The stenoses are frequently bilateral and involve the ostia of the vessels (Fig. 139.4).[50] Hypertension in the absence of renal artery stenosis occurs in 5% to 30% of patients.[13,20] Causes of hypertension in this group of patients include middle aortic syndrome, reduced compliance of the aorta, and dysfunction of the carotid baroceptors (Fig. 139.5).[56,57] Sen and colleagues first reported on 16 patients with middle aortic syndrome in 1963.[58] All patients presented with hypertension, and more than half of them had decreased or absent lower extremity pulses. In a 1991 report from the Japanese Ministry of Health and Welfare, middle aortic syndrome occurred in 16% of surgically treated patients with TA.[59] Long-segment narrowing of the descending thoracic or abdominal aorta is characteristic, and interscapular or abdominal bruits are frequently heard on auscultation. According to one report, the majority of patients with middle aortic syndrome die by age 35 if left untreated.[60] Middle aortic syndrome is not unique to TA and may be due to congenital hypoplasia, von Recklinghausen disease, fibromuscular dysplasia, and tuberculosis.[61–63]

Figure 139.5 Abdominal aortogram of a 37-year-old hypertensive woman. Note the long, tapered stenosis of the infrarenal aorta *(arrow)* and sparing of the distal aorta and iliac arteries.

Figure 139.6 Aortic arch angiogram depicting extensive aneurysmal disease of the arch vessels of a 54-year-old man.

Visceral arterial involvement occurs in 3% to 31% of patients with TA.[20,50] Despite these findings, symptoms of mesenteric ischemia are rare. Aortic endarterectomy for visceral ischemia has been performed, with mixed results. It is controversial in patients with TA because the inflammatory lesions typically involve all three layers of the arterial wall, making the procedure difficult.[64,65]

Lower extremity ischemic symptoms occur in 24% to 32% of patients and, as stated previously, are less common than upper extremity symptoms.[13,49] Iliac artery disease is seen in approximately 20% of patients undergoing angiography.[13,20] Angiographic data suggest that claudication of the lower extremities may be related to abdominal aortic involvement because stenotic disease of the femoral, popliteal, and tibial arteries is rare.[20]

Aneurysmal disease in patients with TA varies by geographic location. In South Africa, up to 71% of patients underwent surgery for aneurysmal disease.[66] In a study of Thai patients, 60% of patients had aneurysms, with the abdominal aorta being the most common location, followed by the subclavian artery and the thoracic aorta.[60] In North America, 27% of patients had aneurysms, with the aortic arch being the most common site, followed by the abdominal aorta (Fig. 139.6).[13] Elsewhere, 13.7% of patients in India and 7% of patients in Italy had aneurysms on angiography.[20,50] A study from Japan reported 32% of patients with aneurysmal disease and noted that the aneurysms were frequently multiple and associated with stenotic lesions (Fig. 139.7).[67] In most series the incidence of aneurysm

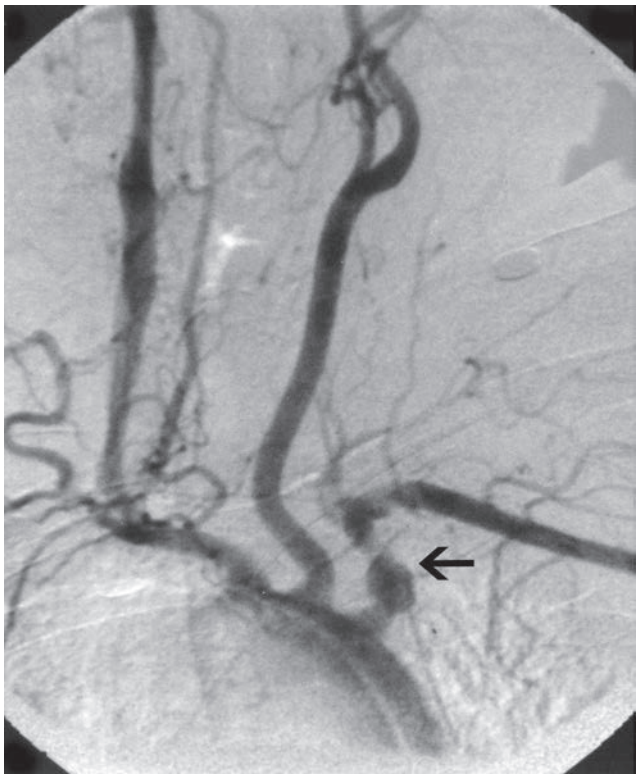

Figure 139.7 Aortic arch angiogram of a 33-year-old woman with left upper extremity claudication. Note the left subclavian aneurysm and concomitant distal stenosis *(arrow)*.

rupture is low compared with that of noninflammatory aneurysms.[68]

Patients with TA may present with nonischemic symptoms. Raynaud phenomenon has been reported in approximately 8% to 14% of patients.[20] Skin changes have been reported in 8% to 25% of patients.[13,49] These cutaneous manifestations of TA range from erythema nodosum to pyoderma gangrenosum to a lupuslike malar flush.[69,70]

DIAGNOSTIC EVALUATION

Diagnostic Criteria

Because TA affects patients in myriad ways, there have been many proposed diagnostic criteria. The first diagnostic criteria were set forth by Ishikawa, based on a cohort of 96 Japanese patients with TA and 12 patients with other diseases of the aorta.[16] These criteria included an obligatory age less than 40 years. The Ishikawa criteria identified 96% of young patients and 80% of older patients with active disease but, unfortunately, only 67% of young patients and 64% of older patients with inactive disease.

In 1990 the American College of Rheumatology created new diagnostic criteria based on a North American group of patients with TA (Table 78.2).[71] It removed Ishikawa age criterion because 13% of patients developed the disease after age 40.[13] The presence of at least three of the six criteria from the traditional classification demonstrated a sensitivity of 90.5% and a specificity of 97.8%. The same group also created a classification tree with five of these six criteria, omitting claudication of an extremity. The classification tree demonstrated a sensitivity of 92.1% and a specificity of 97.0%.

In 1996 Sharma and associates devised a third set of diagnostic criteria. The Ishikawa criteria were modified in an effort to improve early diagnosis and to take into account geographic and racial variations (Table 78.3).[72,73] The presence of two major criteria, one major criterion and two minor criteria, or four minor criteria was found to have a sensitivity of 92.5% and a specificity of 95% in a group of Indian patients and 96% sensitivity and 96% specificity in a group of Japanese patients.

Although there is no global consensus on the best diagnostic criteria, it is generally agreed that the diagnosis of TA should not be made without ruling out all other vasculitides, vascular infections, fibromuscular dysplasia, and idiopathic inflammatory syndromes.[74]

Laboratory Markers

TA is not associated with any specific laboratory abnormality but is characterized by generalized inflammatory markers. Patients are frequently anemic, with hematocrits in the 20s or 30s.[42] The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most common markers used. At presentation, approximately 72% of patients with TA have an elevated ESR.[7] However, the ESR is very nonspecific; 56% of patients have an elevated ESR with disease remission, and 28% have a normal ESR with clinically active disease.

Investigators have begun to examine the role of other laboratory markers in TA, including serum interleukin-6 (IL-6) and regulated upon activation, normal T-cell expressed, and presumably secreted (RANTES). IL-6 enhances T-cell cytotoxicity and natural killer cell activity,[75,76] whereas RANTES is a selective chemoattractant for most mononuclear cell types implicated in TA.[77] A recent study showed increased levels of IL-6 and RANTES in patients with TA.[78] Furthermore, both IL-6 and RANTES paralleled disease activity.

Other investigators have examined matrix metalloproteinases (MMPs) in patients with TA.[79] MMP-2 levels were elevated in patients with TA compared with controls, although no correlation was found between serum MMP-2 and disease activity. MMP-3 and MMP-9 levels in patients with active disease were elevated compared with those in controls and patients in disease remission, and a positive correlation was found between MMP-3 or MMP-9 level and disease activity.

At present there is no single serologic test for TA, and the role of specific serum markers is still being delineated.

Radiologic Evaluation

Although histopathologic examination of arterial specimens provides the most accurate determination of disease, radiologic evaluation can provide a more extensive assessment of pathology. In the past, digital subtraction angiography of all possibly affected arteries was considered the only reliable radiologic method of evaluating patients with TA.[80]

More recently, noninvasive methods such as ultrasound, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA) have been used to assess the mural changes of the arterial wall seen in TA before the development of stenotic or aneurysmal disease.[81] Duplex ultrasound has been useful for evaluating the carotid arteries in patients with TA. Active disease is characterized by prominent wall thickening with a maintained outer diameter, whereas inactive disease is characterized by mild wall thickening with a decreased outer diameter (Fig. 139.8).[82] A comparison of duplex ultrasound and arteriography of the carotid arteries reveals that the two closely correlate in terms of disease assessment and that ultrasonographic mural thickness is a more sensitive indicator of early, latent inflammation.[83]

Findings on CTA may include high density and calcifications of the aortic wall on precontrast images, a thickened wall with enhancements in the arterial and venous phases, and a low-attenuation ring in the venous phase (Fig. 139.9).[84] CTA is also useful to assess the extent of disease involvement. In one study the extent assessed by mural change was wider than that assessed by luminal change in 61% of patients.[85] Skip lesions were seen in 16% of patients, although contiguous arterial involvement was more common (81%). Finally, CTA revealed the coexistence of active and inactive lesions in 11% of patients. A comparison of CTA with conventional angiography showed that the two correlated in 71% of patients, but CTA

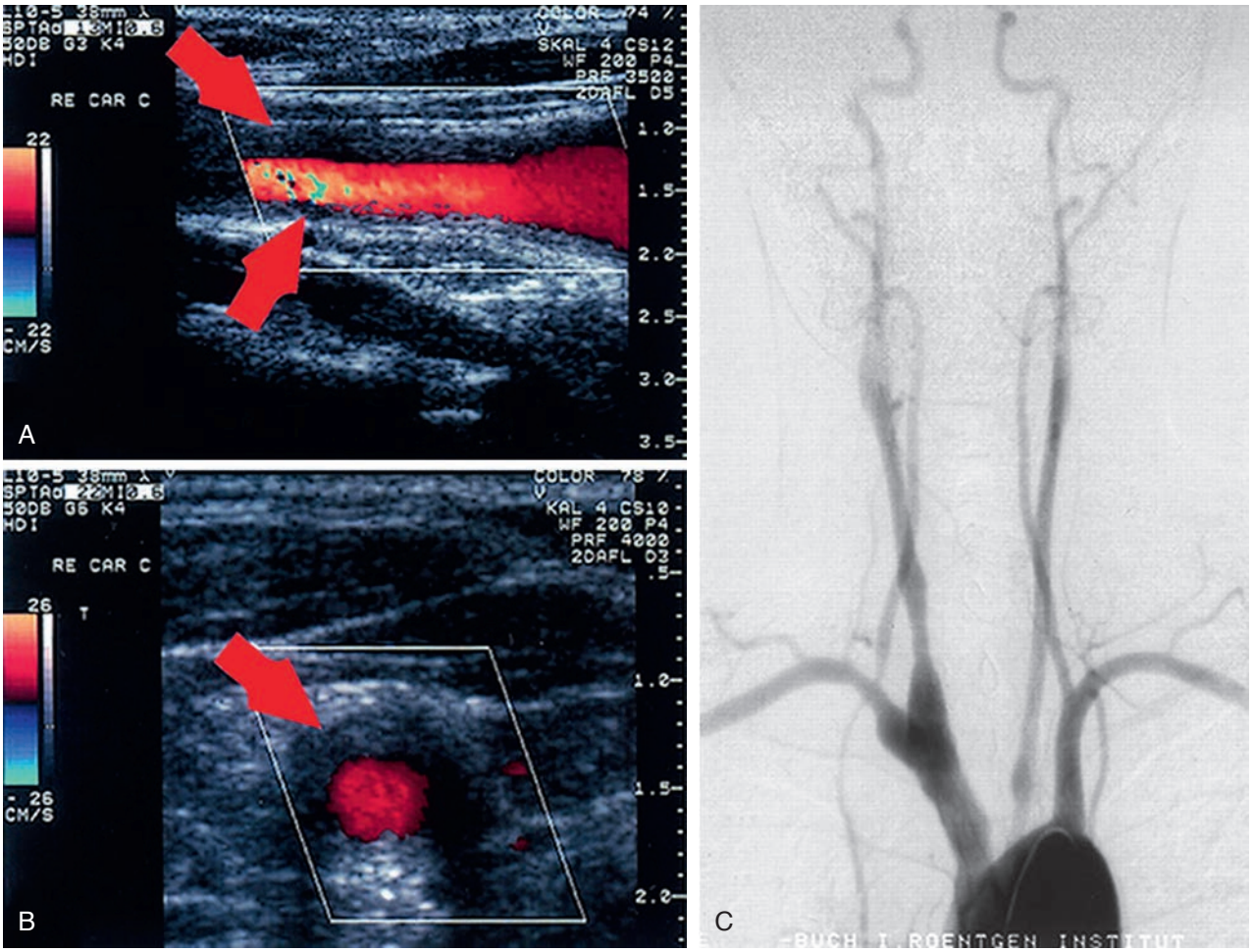

Figure 139.8 Patient With Early Takayasu Arteritis. (A and B) Ultrasound images: longitudinal plane (A) and transverse plane (B) of the right common carotid artery with the typical morphologic appearance of Takayasu arteritis indicated by *arrows*. (C) Angiography of the branches of the aortic arch, confirming the ultrasound diagnosis and revealing narrowing of up to 40% as well as post-stenotic dilations at the right common carotid artery, the left proximal common carotid artery, the proximal right subclavian artery, and the proximal right vertebral artery. (From Schmidt WA, et al. Diagnosis of early Takayasu arteritis with sonography. *Rheumatology (Oxford)*. 2002;41:496-502.)

depicted more extensive disease, owing to its ability to assess mural inflammation.[86]

MRA is also useful for the noninvasive assessment of patients with TA. Spin-echo MRA depicts early arterial wall thickening similar to CTA.[87] Significant enhancement of the aorta and carotid arteries may be seen before the development of stenoses, and greater contrast enhancement in the aortic wall as compared with myocardium correlates positively with disease activity (Fig. 139.10). T2-weighted images may show bright signal correlating with vessel wall inflammation and edema.[88] MR does have limitations: although MRA accurately depicts approximately 98% of arterial involvement in TA, 2% of stenotic arteries are overestimated as occluded.[89] Furthermore, vessel wall edema can be found in up to 56% of patients who are in clinical remission.[90] The new intravascular contrast agent gadofosveset trisodium (MS-325) shows promise in the use of MR for the detection of TA, and more specifically for differentiation between active and inactive disease.[91]

The inflammation associated with TA has led investigators to evaluate the role of positron emission tomography (PET). Quantification of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake can be used to evaluate active vascular inflammation before the development of hemodynamically significant stenoses.[92] It may be useful not only in identifying disease activity but also in accurately monitoring treatment efficacy (Fig. 139.11). In one study, ^{18}F-FDG PET had a 92% sensitivity, 100% specificity, and negative and positive predictive values of 85% and 100%, respectively, in disease activity assessment.[93]

Overall, ^{18}F-FDG PET strongly correlates with the response to medical therapy and may prove useful for managing patients whose serum inflammatory markers remain elevated despite inactive disease.

Despite the development of these noninvasive imaging modalities, digital subtraction angiography remains the "gold standard" for evaluation of vascular lesions associated with TA (see Figs. 139.2–139.7). Panangiography depicts the extent of

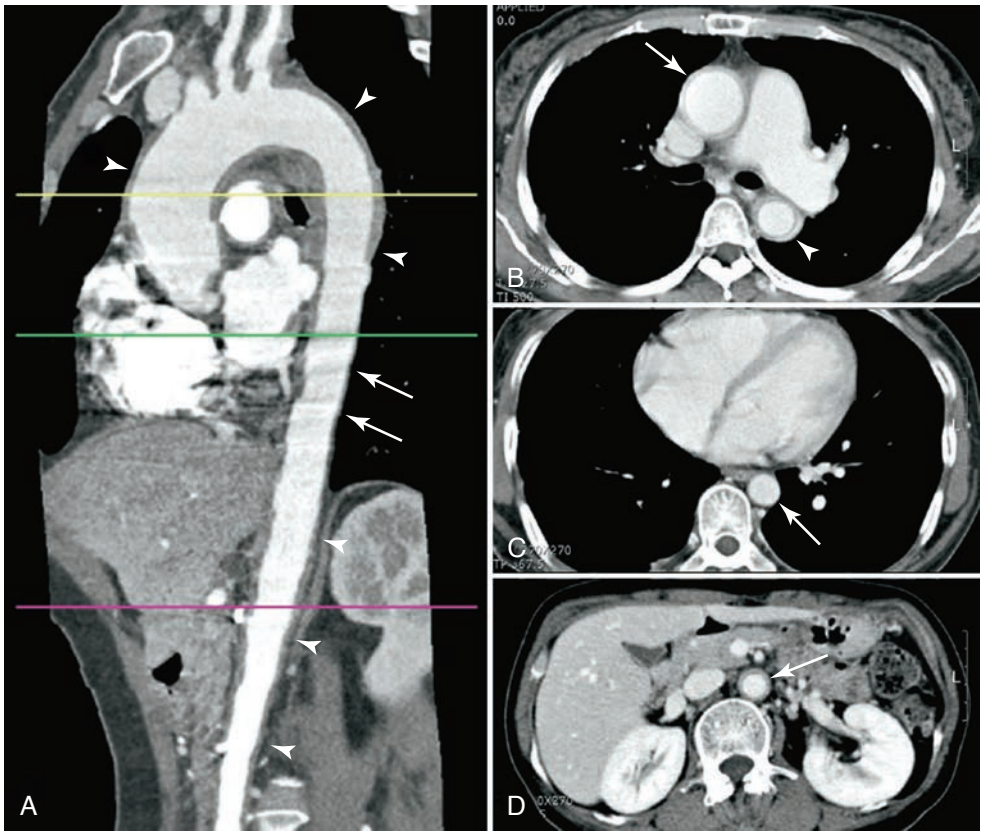

Figure 139.9 Takayasu Arteritis Involving the Aorta With a Skipped Segment in a 50-Year-Old Woman. (A) Multiplanar reformation image shows wall thickening *(arrowheads)* of ascending thoracic aorta, aortic arch, proximal descending thoracic aorta, and abdominal aorta. No wall thickening of distal descending thoracic aorta is noted. Motion artifact (pulsation artifact) was not observed in the thickened segment, such as the aortic arch and abdominal aorta, because of stiffness of the involved aorta but was observed in the distal descending thoracic aorta *(arrows)* owing to pulsation of the noninvolved segment. (B) Computed tomography (CT) scan at the proximal descending thoracic aorta shows diffuse wall thickening and inner low-attenuation ring of ascending *(arrow)* and descending thoracic aorta *(arrowhead)*. (C) CT scan at the distal descending thoracic aorta *(arrow)* shows no wall thickening of aorta. (D) CT scan at the abdominal aorta shows diffuse wall thickening and inner low-attenuation ring of abdominal aorta *(arrow)*. (From Chung JW, et al. Patterns of aortic involvement in Takayasu arteritis and its clinical implications: evaluation with spiral computed tomography angiography. *J Vasc Surg*. 2007;45:906-914.)

disease, which ultimately correlates with disease severity, and is useful in preoperative planning. Lesions characteristic of TA include stenoses, either short and segmental or long and diffuse; aneurysmal dilation, either fusiform or saccular; or a combination of the two.[94] Serial angiographic examinations may be useful in tracking disease activity and response to therapy.[95] Comparison of direct aortic blood pressure measurement at the time of angiography to measurements in the upper and lower extremities is important considering the nature of stenotic lesions and their interference with extremity cuff pressures. Finally, the classification of TA is based on arteriographic findings and correlates with clinical manifestations and prognosis.[42]

CLASSIFICATION

The classification of TA was originally proposed by Ueno in 1967.[96] He divided TA into three types based on aortic involvement (Table 78.4). Type I disease was confined to the aortic arch and its branches, type II involved the descending and abdominal aortas and their branches, and type III was a combination of types I and II. Lupi-Herrera added a type IV to this classification for pulmonary artery involvement.[23] Nasu and others described a variation on Ueno's classification based on the distribution of aortic disease.[8,15,97] In 1994 a new classification was proposed at the Tokyo International Conference on Takayasu Arteritis that divided TA into six patterns of disease.[98] Type I disease was limited to the aortic arch branches. Type IIa disease involved the aortic arch and its branches, and type IIb disease the aortic arch, its branches, and the descending thoracic aorta. Type III disease involved the descending thoracic and abdominal aorta and its branches. Type IV disease involved the abdominal aorta and its branches. Type V disease involved the entire aorta and its branches. A "C" or "P" was added if a patient had coronary or pulmonary artery involvement, respectively.

Classification of disease activity is important in determining response to treatment but has not been uniform throughout the literature. Because steroids play a major role in the treatment of TA, certain authors have relied on steroid use as the sole determinant of active disease. This definition is ultimately too

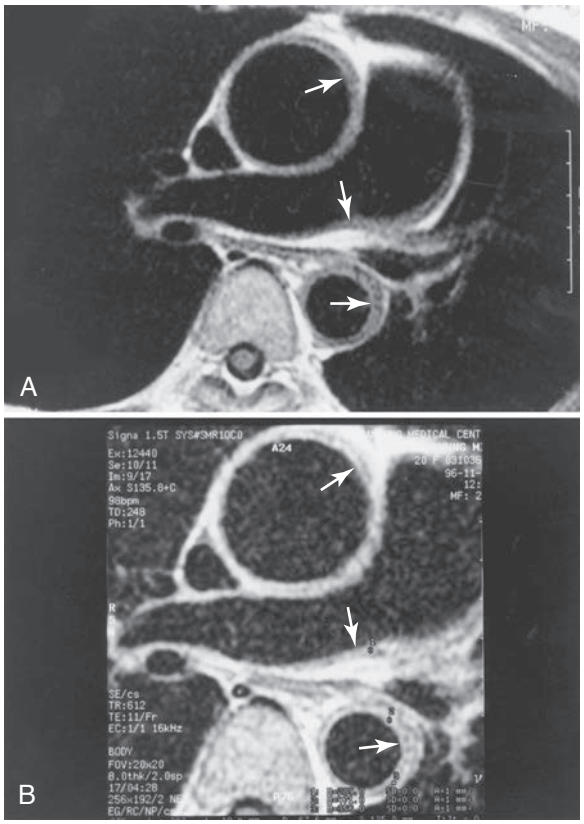

Figure 139.10 **Clinically Active Takayasu Arteritis in a 25-Year-Old Woman.** (A) A T1-weighted axial magnetic resonance image before contrast media injection shows diffuse and concentric mural thickening of the thoracic aorta *(arrows)* and mild mural thickening of the right pulmonary artery *(arrow)*. (B) Immediately after contrast media injection, a T1-weighted axial image shows enhancement in the thickened aortic and pulmonary arterial walls *(arrows)*, which suggests increased vascularization in the inflamed vessel walls. (From Choe YH, et al. Magnetic resonance imaging diagnosis of Takayasu arteritis. *Int J Cardiol.* 1998;66(Suppl 1): S175-S179.)

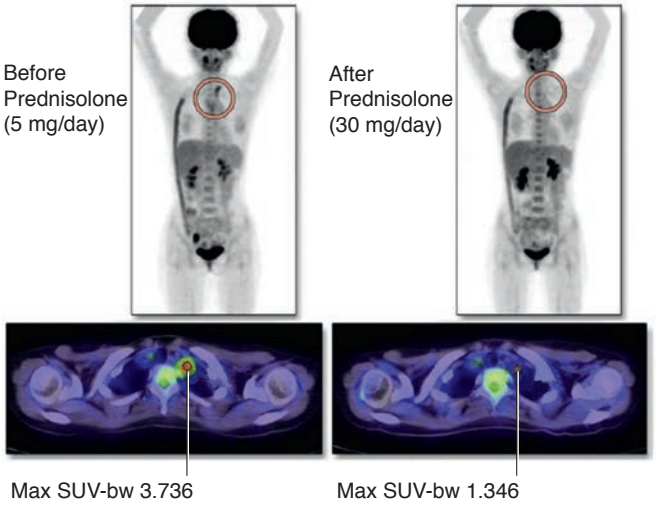

Figure 139.11 A 23-year-old woman with Takayasu arteritis was taking corticosteroids at a dose of 5 mg/day. The erythrocyte sedimentation rate was 18 mm/h, but she had left arm pain with slight elevation of the C-reactive protein level up to 1.1 mg/dL. The ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography imaging showed uptake in the left subclavian artery, and the maximum standardized uptake value (max SUV) was elevated *(left)*. After the dose of prednisolone was increased to 30 mg/day, the uptake disappeared, and max SUV decreased *(right)*. Strong ^{18}F-fluorodeoxyglucose uptake on her right side is uptake due to an artificial graft from the right axial artery to the right external iliac artery. (From Tezuka D, et al. Role of FDG PET-CT in Takayasu arteritis: sensitive detection of recurrences. *JACC Cardiovasc Imaging.* 2012;5:422-429.)

narrow and may equate patients in remission and off steroids with patients acutely presenting with active disease and not yet on steroids.[99] The NIH followed 60 patients between 1970 and 1990, with an average age at disease onset of 25 years.[13] Active disease was defined as new onset or worsening of two or more features of TA (Box 78.1). These included systemic manifestations, elevated ESR, signs of vascular disease, and typical angiographic findings. Researchers at the Mayo Clinic have used a similar definition of two or more features of TA but have substituted elevated CRP and active inflammation at the time of operation and in the pathologic specimen.[100] These criteria may be more stringent, but they make the diagnosis of active disease difficult without open surgical operation.

MEDICAL TREATMENT

Approximately 12% to 20% of patients diagnosed with TA have a self-limited, monophasic illness and may not need immunosuppressive therapy.[20,79] All other patients typically require some regimen of immunosuppression to control disease activity. Glucocorticoids are the first line agents for patients with TA and are begun at a dose of 1 mg/kg per day for 1 to 3 months. If there is improvement in disease activity, the prednisone dose may be tapered and ultimately discontinued. The clinical response to oral glucocorticoids is varied and ranges from 20% to 100%.[23,101] Determining clinical response is complicated by the difficulty of assessing disease activity based on laboratory markers and symptoms alone. In the NIH cohort, oral glucocorticoids induced remission in 60% of patients at least once.[13] In the 40% who did not achieve disease remission with oral glucocorticoids, the addition of other cytotoxic agents induced remission in another 40%.

Relapse is common even in patients who achieve remission on oral glucocorticoids and is seen in 45% to 96% of patients.[13,51] Alternative immunosuppressive agents are typically added in 40% to 73% of patients who relapse or who never achieve remission.[19,51] These regimens may include oral glucocorticoids with the addition of methotrexate, cyclophosphamide, azathioprine, or mycophenolate mofetil.

Although the results of immunosuppressive regimens are promising, limitations of therapy still exist in larger series of patients. In the Cleveland Clinic cohort, only 28% of patients had sustained remission,[51] and 23% of patients in the NIH cohort had continuous disease regardless of therapy.[13] These results, along with the hypothesis that autoimmunity contributes to the disease, have led investigators to examine the role of immunomodulating medications for the treatment of TA.

REFRACTORY THERAPY

Immunomodulating medications have been used with some success in patients unable to achieve remission on standard

drug therapies. Long-term data from the Cleveland Clinic on patients treated with anti-TNF therapy found that remission was achieved and prednisone was discontinued in 60% of patients and tapered to less than 10 mg/day in an additional 28%.[102]

Anti-IL-6 therapy (tocilizumab) has also been used successfully to induce remission and decrease the need for steroid therapy.[103,104] When comparing anti-TNF agents to tocilizumab, there were no significant differences in efficacy between therapies. More recently, B-cell depletion strategies using rituximab have also been used successfully in patients refractory to other immunosuppressive therapies.[105]

INDICATIONS FOR AND RESULTS OF REVASCULARIZATION PROCEDURES

The need for surgical procedures in patients with TA varies by geographic region. Approximately 50% of patients from the United States and Italy need surgery,[7,20,51] whereas only 10% to 12% of patients in Japan and India undergo surgical intervention.[21,50] If possible, surgery should be performed when disease activity is minimal.[53] In fact, one study showed a decrease in the 5-year patency rate from 88% to 53% when bypass was performed in patients with active disease.[106] Another study found that patients with active disease were more likely to require revision or develop progressive symptomatic disease at another site.[100] In a group of 42 patients with TA, the rate of bypass revision or disease progression at 5 years was 0% in patients with quiescent disease not on steroids, 10% in patients with quiescent disease on steroids, 57% in patients with active disease on steroids, and 67% in patients with active disease not on steroids. Again, disease activity assessment is not perfect, and surgical specimens show active disease in up to 44% of patients who were thought to be in remission.[7]

General indications for surgical revascularization include hypertension in the setting of renal artery stenosis, lifestyle-limiting extremity ischemia, cerebral ischemia or greater than 70% symptomatic stenosis of cerebral vessels, moderate (grade II New York Heart Association) aortic regurgitation, cardiac ischemia in the setting of proven coronary artery stenosis, severe aortic coarctation, or progressive aneurysmal enlargement and dissecting aneurysm.[18]

Endovascular Treatment

Initial reports of percutaneous vascular interventions in patients with TA were promising. Sharma reported 1-year success rates for percutaneous transluminal angioplasty (PTA) of the renal arteries and the abdominal aorta of 80% and 100%, respectively.[107] Others reported initial success rates in 74% of patients.[108] In a report of subclavian artery PTA, initial success rates were 88% for stenotic lesions and 67% for total occlusions. On mean 4-year follow-up, restenosis occurred in 20% of patients.[109]

Despite these results, long-term evaluation of percutaneous interventions is less encouraging. In a study of 20 patients treated with PTA, the initial success rates of PTA for renal artery stenosis and middle aortic syndrome were 83% and 100%, respectively, but the 5-year patency rate was 33.3% for each.[110] In a study of Korean patients, patency rates decreased from 90% at 1 year to 50% at 10 years.[111] Stable disease activity and treatment with glucocorticoids and immunosuppressive agents were found to aid in the maintenance of arterial patency.

In the NIH cohort, 11 patients underwent a total of 20 endovascular interventions: 8 subclavian, 7 renal, 4 iliofemoral, and 1 thoracic aorta angioplasty.[13] The initial success rate was 56%; it was only 33% on the second attempt. Restenosis was frequent and occurred within 3 to 13 months. In the Cleveland Clinic cohort, 20 patients underwent PTA: 8 renal, 4 subclavian, 2 iliofemoral, 2 carotid, 2 axillary, 1 abdominal aorta, and 1 coronary angioplasty.[51] Restenosis was common and occurred in 78% of patients. Thirteen of those patients required reintervention, and 6 required subsequent bypass.

PTA's poor long-term results in patients with TA may be explained by the fibrotic and noncompliant nature of diseased vessels. Many authors have reported the need for higher balloon pressures to achieve success.[112] Other impediments to successful angioplasty include the fact that stenoses in TA are often long, and PTA results have been poor for eccentric stenoses and diffuse aortic disease.[100]

With developments in the technology of endovascular devices, the long-term results of percutaneous interventions in TA are beginning to show some improvement. Although the number of patients reported is small, stent-grafts have been found to have better patency rates in the treatment of TA than PTA or bare metal stents.[113] In this retrospective study, none of the stent-grafts occluded or became severely stenosed during follow-up ranging from 2 to 6 years, as compared with bare metal stents that had a higher rate of in-stent restenosis.

The poor results of endovascular treatment of TA have led some to use drug-eluting technology for the treatment of restenoses. Spacek et al. reported restenosis within a bare metal carotid stent 1 year from the index procedure.[114] This was treated using an off-label coronary drug-eluting stent. Six months after drug-eluting stent placement, the patient developed restenosis within the bare metal stent, but outside the drug-eluting stent. This second restenosis was treated with a drug-eluting balloon. At 30-month follow-up, the patient did not develop restenosis.

Open Surgical Treatment

Open vascular surgical intervention has been a mainstay in the treatment of complications associated with TA. The majority of vascular lesions associated with TA cause ischemic symptoms and are best managed with bypass grafts.

Common carotid bypass is typically performed for stroke prevention and is one of the most common procedures performed for ischemic disease.[13] Unlike atherosclerotic carotid disease, the lesions of TA are longer, poorly amenable to endarterectomy, and cause symptoms through thrombosis rather than embolism. Endarterectomy in patients with TA is more difficult because of the transmural nature of the inflammation and the difficulty in determining the correct plane of dissection.[115,116] In the

Cleveland Clinic cohort, two-thirds of endarterectomy and patch angioplasty procedures failed.[52] Carotid bypass in patients with TA should originate from the aortic arch rather than an aortic branch artery because the arch is typically less involved with disease compared with its branches.[1]

Upper extremity bypass for subclavian and axillary lesions is one of the most common surgical procedures performed in patients with TA. In the NIH and Cleveland Clinic cohorts, upper extremity bypass was performed in 17% and 11%, respectively.[13,51] Again, the aortic arch may be preferred for inflow, owing to its less common involvement.

Coronary artery revascularization is frequently necessary because of ostial narrowing and subsequent ischemia. Excellent results have been obtained with bypass surgery. Aortic regurgitation may present along with coronary artery disease in up to 45% of patients, necessitating concomitant aortic valve replacement.[117]

Renal artery revascularization is commonly performed after failed endovascular therapy and may be more beneficial as a first-line therapy in patients who have disease beyond the ostia.[118] Inflow is typically taken from the aorta but may be limited to the visceral vessels if the abdominal aorta is significantly diseased. An autologous conduit is preferred, owing to the lower complication rate.[13] In one of the largest series of renal revascularization for TA-induced renal artery stenosis, 27 patients underwent 40 interventions: 32 aortorenal bypasses, 2 repeat implantations, 4 nephrectomies, and 2 transluminal angioplasties.[119] These interventions significantly decreased both the mean arterial blood pressure and the number of antihypertensive medications, and they increased the mean glomerular filtration rate. The 5-year primary and secondary patency rates were 79% and 89%, respectively.

Open surgical treatment remains the gold standard for the treatment of middle aortic syndrome. Endovascular repair of middle aortic syndrome has been attempted, with successful initial results, but 5-year patency rates were approximately 33%.[120] This has led other investigators to examine aortic stenting. Again, initial success rates were excellent, but long-term results are lacking.[121,122] Patch aortoplasty has been performed in the past, but it has the same complications related to endarterectomy for carotid revascularization. Definitive repair typically consists of aorto-aortic bypass, owing to the long length and calcification of the affected segment.[123] Inflow should be taken from the suprarenal aorta because the infrarenal aorta is frequently involved with disease (Fig. 139.12). The iliac arteries are commonly used as a distal target because the distal aorta is usually spared. Open surgical revascularization can lead to a greater than 75% improvement in hypertension, with 50% of patients no longer requiring antihypertensive medications.[124] Postoperative event-free survival is greatest in those who experience resolution of hypertension.

Revascularization of the visceral arteries may occasionally be necessary in patients with chronic mesenteric ischemia. Although some reports have recommended bypass or endarterectomy even in asymptomatic patients,[125] reports from North America suggest that only the rare patient with TA and symptoms of chronic mesenteric ischemia should undergo mesenteric bypass.[13,51]

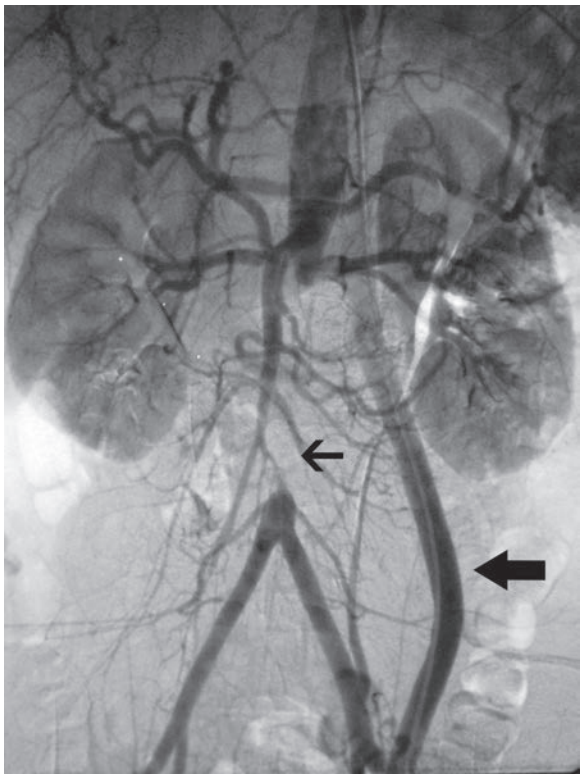

Figure 139.12 Angiogram of a 46-year-old woman who originally presented with hypertension and lower extremity claudication. Note the occlusion of the infrarenal aorta consistent with middle aortic syndrome *(small arrow)* and the bypass from the thoracic aorta to the left external iliac artery *(large arrow)*.

As stated previously, symptoms of lower extremity ischemia are much less common than upper extremity ischemia. Lower extremity ischemia is frequently caused by middle aortic syndrome (see earlier for details of its treatment), but it may also be due to involvement of iliac and femoral vessels. In these cases, standard bypass may be performed, with reasonable success.[1]

Few reports of endovascular aneurysm repair exist in the literature, and the majority of patients have undergone open aneurysm repair. The fact that the incidence of rupture is lower for TA-related aneurysms must be weighed against the fact that these patients develop aneurysms at such a young age.[1] Therefore aneurysm repair is typically performed for the same indications as in patients with non-TA aneurysms.

Certain authors have hypothesized that patients with TA are at increased risk for anastomotic aneurysms due to vessel wall inflammation. In a large study of 103 patients with TA treated surgically, over 40 years with 259 anastomoses, the anastomotic aneurysm rate was 12%.[126] The investigators found that the incidence of anastomotic aneurysms was increased only after operations for aneurysmal lesions and not in patients with systemic inflammation or on steroids.

Overall results suggest that open surgical treatment of TA can be performed with minimal morbidity and mortality.[100] In the NIH cohort, 30% of the bypasses resulted in complications, including 24% restenosis and 4% thrombosis,[13] whereas 36%

of the bypasses in the Cleveland Clinic cohort had restenosis or occlusion.[51] Reports from Japan have shown similar results. In a series of 106 patients followed up to 40 years, the 10-year cumulative patency rates of carotid, subclavian, aorto-aortic, renal, and mesenteric revascularizations were 88%, 64%, 100%, 68%, and 67%, respectively.[127] Overall 20-year survival was 74%. Early death occurred in 12% of patients (0% after 1980). Late death occurred in 31% of patients and was most frequently due to congestive heart failure.

Direct Comparison of Endovascular and Open Surgical Treatment

Due to the low incidence of TA, few studies have compared endovascular therapy and open surgery. However, one large retrospective multicenter study examined the outcomes of 79 patients with TA, of whom 63% were treated with an open surgical procedure and 34% with endovascular intervention, including angioplasty and/or stenting.[128] Follow-up ranged from 2 to 11 years. Surgical intervention was associated with a 38% vascular complication rate compared with 50% for endovascular intervention. Biologic inflammation, as manifested by elevated ESR, CRP, and serum fibrinogen levels at the time of intervention, was independently associated with complications after intervention.

Analysis of outcomes in patients with symptomatic supraaortic arterial occlusive disease has also shown the superiority of open surgical treatment in long-term outcomes. Kim et al. compared endovascular intervention with angioplasty and bare metal stent placement to open surgical treatment with bypass for short (<5 cm) occlusive lesions.[129] Restenosis was observed in 53% of patients in the endovascular group and 13% of patients in the bypass group. However, serious early postoperative complications, such as intracerebral hemorrhage or cardiac tamponade, were more common in the surgical bypass group.

Patients who undergo revascularization for symptomatic TA lesions should be carefully followed because they are likely to develop symptoms requiring intervention in another vascular bed or revision of the original procedure. A study from UCLA of 40 patients with TA who underwent revascularization from 1980 to 2009 (60 bypass procedures and 4 endovascular interventions) showed that during a mean follow-up of 6.4 years, 40% of patients exhibited progression of TA requiring intervention.[105]

SPECIAL CONSIDERATIONS

Pregnant Patients

Because TA is most commonly a disease of women of childbearing age, many authors have examined the effects of TA on pregnancy. In the NIH cohort, five women became pregnant, and all delivered healthy children without complications related to the delivery.[13] One patient in this group had an exacerbation of TA-related symptoms. Similarly, the Cleveland Clinic cohort reported one spontaneous abortion in four pregnancies. All three children brought to term were healthy.

Overall, prognostic indicators of poor maternal and fetal outcome include hypertension, aneurysmal disease, cardiac failure, and extent of disease.[7] Interestingly, the state of pregnancy may alter TA physiology, as evidenced by improvement in inflammatory markers and hemodynamic parameters.[130] Pregnancy itself has not been found to have an adverse effect on the state of TA.[131]

Pediatric Patients

The youngest patient ever diagnosed with TA was 7 months old.[116] This patient presented with an aneurysm of the right common iliac artery and an iliocaval fistula. Overall, patients presenting with TA before age 20 years represent approximately 13% to 77% of reported cases.[13,23,52] The propensity for nonspecific systemic symptoms makes diagnosis difficult, although it is unclear whether the development of TA before age 20 actually leads to a delay in diagnosis. The thoracic and abdominal aorta are most commonly involved, and ischemic symptoms are less frequent.[7]

One of the largest series of children diagnosed with TA comes from China and reviews the presenting signs and symptoms, and outcomes of treatment of pediatric patients with TA.[132] Fourteen children, with a mean age of 10, were diagnosed with TA in the 12-year-long review. Median time to diagnosis after onset of symptoms was 2 months. The most common presenting symptom was hypertension (in 93%), and most patients had an abnormal pulse exam. Medical treatment was successful in 50% of patients. Imaging may show arterial stenosis, dissection, or aneurysm.[133]

Quality of Life

Recent studies suggest that the impact of systemic vasculitis may be far more significant than previously thought. An estimate of expenditures for vasculitis-related hospitalizations for polyarteritis nodosa, hypersensitivity vasculitis, Wegener granulomatosis, giant cell arteritis, and TA amounted to $150 million per year.[112] Beyond monetary concerns, quality of life (QoL) issues are central to patient well-being.[120]

We examined QoL in a group of 158 patients with TA using the Short Form (36) Health Survey, a validated health-related QoL questionnaire, and found that the effect of TA on physical and mental health was more extensive than expected.[48] More than half the patients reported a worsening in their mood, happiness, and energy level; almost half reported a change in work duties or hours, and a quarter resigned their jobs as a direct result of TA. Younger age and freedom from immunomodulating medications were associated with superior physical QoL, and disease remission was associated with superior physical and mental QoL. Similar studies from Italy and Turkey have reported impaired QoL in patients with TA.[134,135] As diagnostic capabilities and therapeutic options develop, the prognosis of patients with TA continues to improve.[136] Future advances in imaging and biochemical methods of diagnosis, as well as immunomodulatory approaches to treatment will continue to improve the QoL of patients with TA.

PROGNOSIS

The overall prognosis of patients with TA is guarded. The effects of TA extend into all aspects of patients' lives, especially given the fact that the disease develops at such an early age and progresses despite both medical and surgical therapy. Relapse is common and occurs in 29% to 90% of patients.[19,51]

A study from Japan found that the presence of a major complication (retinopathy, hypertension, aortic regurgitation, aneurysmal disease), progressive disease course, and elevated ESR were poor prognostic indicators for survival in patients with TA.[21] The overall survival rate in 120 patients 15 years after the diagnosis of TA was 83%. For patients with both a major complication and a progressive disease course, survival decreased to 43% at 15 years. Congestive heart failure is the most common cause of death in patients with TA across geographic regions.[21–23]

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CHAPTER 140

Aneurysms Caused by Connective Tissue Abnormalities

JAMES H. BLACK III

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The primary structural proteins of connective tissue are composed of collagen and elastin, which vary in type and amount within each of the body's tissues; those constitutive of blood vessels are listed in Table 140.1. A *connective tissue disease* is a genetic disease in which the primary target is either collagen or elastin protein assembly, disruption of which leads to an inherent predisposition to degeneration, loss of structural integrity, and consequent aneurysm formation or spontaneous vascular dissection and rupture. Although inflammation may affect these proteins and induce structural damage in some patients, such conditions often imply some element of autoimmune disorder and are termed *collagen vascular diseases* or *mixed connective tissue diseases*. Such conditions and arteritides related to the vascular tree, which are considered in Chapter 137, may have genetic profiles that predispose to their development. Although clustering of aneurysms in multiply affected family members within these arteritides may indicate some element of an inheritance pattern, there are often greatly varying levels of expression and penetrance, and no defined genetic test is available to assist treatment. Herein we seek to define the common

Abstract

A connective tissue disorder is a genetic disease in which the primary target is either collagen or elastin protein assembly, disruption of which leads to an inherent predisposition to degeneration, loss of structural integrity, and consequent aneurysm formation or spontaneous vascular dissection and rupture. These "heritable disorders of connective tissue" can have severe vascular manifestations and most commonly include Marfan syndrome, the vascular type of Ehlers-Danlos syndrome (EDS IV or VEDS), Loeys-Dietz syndrome (LDS), and familial thoracic aortic aneurysm and dissection (TAAD).

Keywords

Marfan syndrome
Loeys-Dietz syndrome
vascular Ehlers-Danlos syndrome
familial thoracic aortic aneurysm
genetic aortic disease
connective tissue disorder

TABLE 140.1 Structural Elements of Blood Vessels

Structural Proteins	Approximate Amount (% Dry Wt)	Function
Type I collagen	20-40	Fibrillar network
Type III collagen	20-40	Thin fibrils
Elastin, fibrillin	20-40	Elasticity
Type IV collagen, laminin	<5	Basal lamina
Types V and VI collagen	<2	Function unclear
Proteoglycans (>30 types)	<3	Resiliency

connective tissue diseases affecting the arterial tree, which have a studied natural history, a defined basis for genetic inheritance, and sufficiently understood pathophysiologic mechanisms to guide treatment paradigms. These "heritable disorders of connective tissue"[1] have severe vascular manifestations, and most commonly include Marfan syndrome (MFS), the vascular type of Ehlers-Danlos syndrome (EDS IV), Loeys-Dietz syndrome (LDS), and familial thoracic aortic aneurysm and dissection (TAAD).

MARFAN SYNDROME

Antonin-Bernard Marfan, a professor of pediatrics in Paris, in 1896 encountered a 5-year-old girl with congenital deformation of all four limbs.[2] By the time she was 11 years old, thoracolumbar kyphoscoliosis, pectus carinatum, and signs of tuberculosis had developed.[3] She died at age 16 from infection, and no autopsy was performed to document any vascular involvement. The first description of aortic pathology in MFS was published in 1943, a year after Marfan's death.[4] Although he correctly identified the many mendelian features of the condition that would eventually bear his name, the pleiotropic disorder has benefited from decades of further description of clinical manifestations, molecular pathogenesis, and emerging therapeutic options.

Epidemiology and Natural History

The incidence of MFS is about 2 to 3 per 10,000 individuals, but this estimate relies on proper recognition of all affected and genetically predisposed individuals.[5] A population-based study in Scotland found an incidence of 1 in 9,802 live births,[6] although this number would underestimate the true incidence inasmuch as the features of MFS, particularly the skeletal ones, become more apparent with growth. Furthermore, even though the disorder is passed as a dominant Mendelian trait, about 25% of cases are due to sporadic de novo mutations.[7] The disease has no gender predisposition. Its incidence is increased in athletes, particularly in basketball and volleyball players, because the characteristic tall stature with long-bone overgrowth (dolichostenomelia) confers a competitive advantage. In a screening study of 415 high-school basketball and volleyball athletes performed with standard echocardiography, 4 (1%) of these subjects exhibited aortic root enlargement greater than 4.6 cm, and MFS was diagnosed in 2.[8]

The life span of individuals with MFS was significantly shortened before the widespread use and successful refinement of aortic root surgery. Before the adoption of thresholds for aortic root replacement, the cause of death was cardiovascular (aortic rupture, aortic dissection, or valvular disease) in 90% of cases at a mean of 38 years old.[9] A report in the 1970s on the life expectancy of patients with MFS described longevity as only two-thirds that of unaffected individuals, with life-table mortality curves deviating in infancy.[9] However, a later assessment of longevity in patients with MFS describes a nearly normal life expectancy as a result of improvement and refinement in diagnosis and treatment, particularly of the cardiovascular manifestations of the disorder.[10]

Pathogenesis

As early as 1955 it was suggested that the basic structural defect in MFS was localized to the elastic fiber,[11] with skin and aorta from affected patients showing decreased elastin content and fragmentation of elastic fibers.[12,13] Yet the elastin gene and molecule were poor targets to explain the clinical manifestations of MFS in tissues that are devoid of elastin, such as bone and the ciliary zonules in the eye. Further histochemical analysis demonstrated that the amorphous fragmented elastin tissues were surrounded by a rod-like material with a distinct staining pattern and distinguishable susceptibility to enzymatic digestion.[14,15] These so-called microfibrils are 10 to 14 nm in diameter and are constituents of all connective tissue.[15] Sakai et al.[16] first identified fibrillin-1 (FBN1) as the principal component of the extracellular matrix microfibril, present in all tissues with the phenotypic manifestations of MFS. Additional linkage analysis mapped the MFS locus to 15q21.1.[17] The mutation is passed in an autosomal dominant manner with complete penetrance, so 50% of the offspring of an affected individual can inherit a genetic predisposition to the disorder.[5]

Role of Fibrillin

The *FBN1* gene contains 65 exons spanning 235 kilobases of genomic DNA.[18,19] The gene encodes a 350-kD glycoprotein that is highly conserved among different species, thus suggesting its critical homeostatic importance.[19] These models demonstrated that normal FBN1 molecules are not needed to assemble an elastic fiber; rather, microfibrils are required to maintain normal elastic fibers during postnatal life. If proper connections among elastic fibers and vascular smooth muscle cells are not suitably maintained, cells adopt matrix-degrading enzymes such as matrix metalloproteinase types 2 and 9. Thereafter, aortic wall homeostasis is perturbed, and inflammation as well as calcification and structural weakening of elastic fibers may ensue. This pathology has been observed in large muscular arteries from patients with MFS,[20] leading to appreciation of the classic lesion of cystic medial necrosis in large arteries of individuals with MFS. Verhoeff–van Gieson staining of elastic fibers in the aorta

demonstrates classic lamellar disorganization in MFS secondary to errant elastic fiber maintenance (Fig. 140.1).

Interaction With Transforming Growth Factor

The discovery of the role of microfibrils in regulating cytokines has further advanced our understanding of the pathogenesis of MFS and raised the possibility of a new treatment paradigm. FBN1 shares a high degree of homology with the latent transforming growth factor-β (TGF-β)–binding proteins. The TGF-β cytokines are secreted as large latent complexes consisting of TGF-β, a latency-associated peptide, and one of three latent TGF-β-binding proteins (Fig. 140.2).[21] In normal trafficking, the large latent complex is sequestered and bound to microfibrils, and TGF-β cytokine signaling is prevented. As depicted in Figure 140.2, without proper microfibrils, the TGF-β complex cannot form, thereby leaving TGF-β in the milieu to incite excess signaling. This pathogenetic mechanism of dysregulated TGF-β activity seems more plausible in explaining the clinical features of MFS that are poorly reconciled with structural failure, such as long-bone overgrowth, craniofacial abnormalities, and muscle hypoplasia.[22,23]

Clinical Manifestations and Diagnostic Evaluation

MFS is a multisystem disorder with manifestations principally within the cardiovascular, ocular, and skeletal systems. The disorder occurs worldwide, with no gender or race predilection.

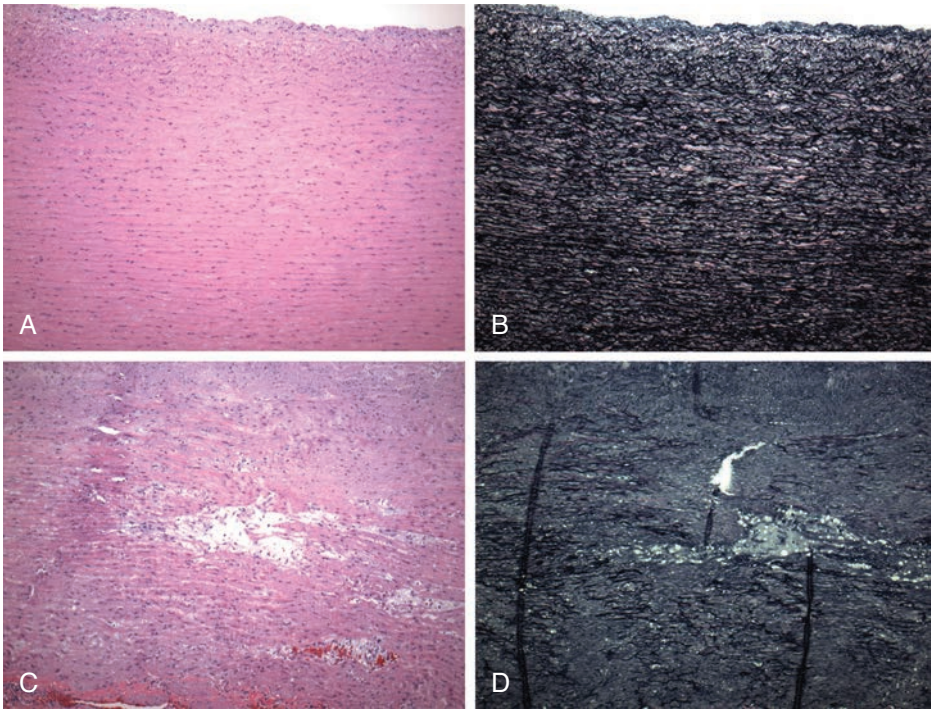


Figure 140.1 (A and B) Photomicrographs illustrating the regular and parallel nature of the elastic lamellae found within the media of the normal ascending aorta. The lamellae are composed of elastic fibers running in parallel with intervening smooth muscle, ground substance, and collagen. The Verhoeff–van Gieson (VVG) stain highlights these major elastic fibers *(black)* (A, hematoxylin-eosin [H&E], ×100; B, VVG, ×100). (C and D) Photomicrographs showing profound fragmentation of the elastic fibers, with spaces left within the media of the ascending aorta. Though often referred to as cystic medial degeneration, the spaces created by this fragmentation lack a lining and hence are not truly "cysts." These spaces often contain increased amounts of glycoproteins. The VVG stain further highlights the severe elastic fiber *(black)* fragmentation. The *vertical black lines* are fixation artifacts from folding of the elastic sheet (C, H&E; D, VVG). (Plates courtesy Joseph Maleszewski, MD, Johns Hopkins Hospital Department of Pathology.)

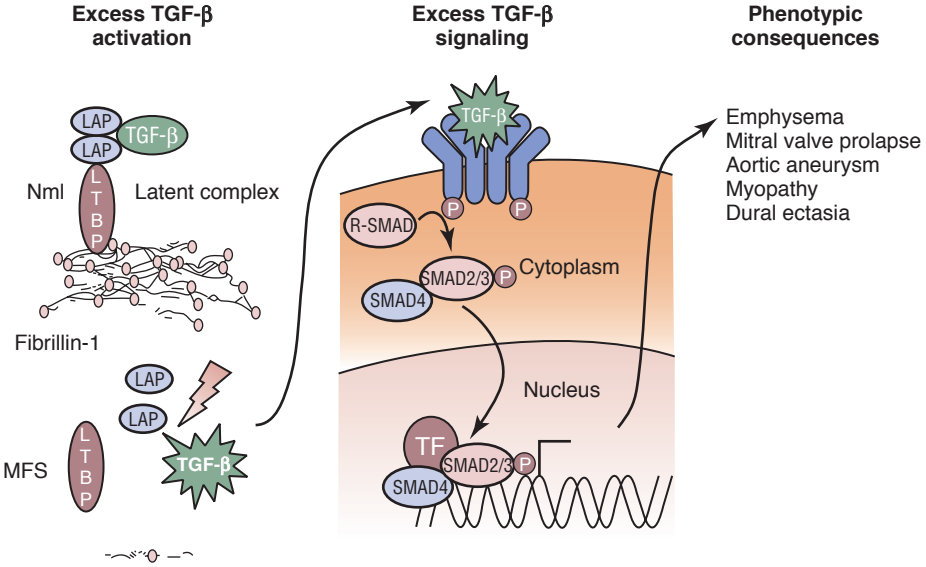


Figure 140.2 Excess activation of transforming growth factor-β (TGF-β) causes many of the features of Marfan syndrome. Normal TGF-β metabolism requires binding of the cytokine to several proteins, including microfibrils, to prevent excess signaling. In Marfan syndrome, lack of normal microfibrillar assembly allows TGF-β to remain unsequestered in the extracellular space. As a consequence, excess TGF-β signaling can occur on the cell surfaces of TGF-β receptors. Once the TGF-β binds to its receptor, downstream receptor–associated SMAD proteins translocate to the nucleus to modulate transcriptional activity, alter protein expression, and yield phenotypic change. *LAP,* Latency-associated peptide; *LTBP,* latent TGF-β binding protein; *MFS,* Marfan syndrome; *Nml,* normal; *TF,* tissue factor.

However, the cardinal manifestation of aortic root aneurysm and its risk of life-threatening aortic dissection or rupture can lead to a shortened life expectancy. Consequently the leading cause of mortality has been cardiovascular in more than 90% of cases (aortic dissection, valve disease, or congestive heart failure), which decreased life expectancy to approximately two-thirds that of unaffected individuals.[5] Improvements in the recognition of MFS and surgical advances have returned life expectancy to the nearly normal range by addressing the most threatening manifestations of MFS—aortic catastrophe in the form of dissection or rupture of the ascending aorta.

Diagnostic Criteria

Ghent Criteria

Clinical diagnostic criteria for MFS were outlined at the International Nosology of Heritable Connective Tissue Disorders in 1986 during the Connective Tissue Meeting in Berlin.[24] Thereafter, the recognition that many individuals diagnosed by means of these original criteria did not have the *FBN1* mutation (genetic testing became possible after 1986) led to a focused revision in 1996 and another in 2010.[25,26] Termed the *Ghent criteria,* the current nosology places emphasis on the cardinal manifestations of the syndrome, namely aortic root aneurysm, ectopia lentis, and *genetic testing*, versus the less predictive skeletal findings (Box 140.1). Once MFS is diagnosed in an individual, all first-degree relatives should be evaluated for the presence of the condition. In children, repeated evaluations may be required to avoid missing the disorder in its evolution.

BOX 140.1 2010 Revised Ghent Criteria for the Diagnosis of Marfan Syndrome and Related Disorders

In the absence of family history:

1. Ao (Z >2) AND EL = MFS
2. AO (Z >2) and FBN1 = MFS
3. AO (Z >2) and systemic score (>7 pts) = MFS
4. EL and FBN1 with known Ao = MFS
   EL with or without systemic *and* with an FBN1 not known with Ao or no FBN1 = ELS
   Ao (Z <2) *and* systemic (>5 with at least one skeletal feature) without EL + MASS
   MVP *and* Ao (Z > 2) *and* systemic (<5) without EL = MVPS

In the presence of family history:

1. EL and FH of MFS (as defined above) = MFS
2. Systemic (>7) and FH of MFS (as defined above) = MFS
3. Ao (Z >2) above 20 years old, >3 below 20 years old + FH of MFS (as defined above) = MFS Caveat: without discriminating features of SGS, LDS, VEDS (as defined in Table 140.1) *and* TGFBR1/2, collagen biochemistry, COL 3A1 testing as indicated. Other conditions/genes will emerge over time.

Ao, Aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection; *EL,* ectopia lentis; *ELS,* ectopia lentis syndrome; *FBN1,* fibrillin-1 mutation (as defined in Box 140.2); *FBN1 not known with Ao,* FBN1 mutation that has not previously been associated with aortic root aneurysm dissection; *FBN1 with known Ao,* FBN1 mutation that has been identified in an individual with aortic aneurysm; *MASS,* myopia, mitral valve prolapsed, borderline Z-score (<2) aortic root dilatation, striae, skeletal findings; *MFS,* Marfan syndrome; *MVPS,* mitral valve prolapsed syndrome; *Systemic,* systemic score (see Box 140.2); and *Z,* Z-score.

Differential Diagnosis

Other conditions also associated with *FBN1* mutations may be considered in the differential diagnosis of MFS. The MASS phenotype is based on the association of *m*itral valve prolapse, myopia, mild *a*ortic root dilatation, *s*triae, and mild *s*keletal changes.[27] The skeletal features of MASS often include the mild manifestations of tall stature, mild dolichostenomelia (long-bone growth), and scoliosis. Occasionally, a major Ghent criterion from the skeletal system may be met but no other major criteria are noted. For patients with MASS, mutations in the *FBN1* gene have generally created premature termination codons, and the mutant transcript can be easily and rapidly degraded.[28]

Shprintzen-Goldberg syndrome is characterized by craniosynostosis, facial hypoplasia, anterior chest deformity, arachnodactyly (long, spider-like fingers), and aortic root dilatation. Developmental delay is also common. Point mutations in *FBN1* have been found in some affected individuals, but phenotypic heterogeneity—specifically regarding development, retardation, and aortic root involvement—probably indicates substantial genotypic variation.[29] The aortic root enlargement in Shprintzen-Goldberg syndrome is similar to that in MFS.

Homocystinuria is caused by a deficiency of cystathionine β-synthase. Patients with homocystinuria often have tall stature, long-bone overgrowth, and ectopia lentis but no aortic enlargement. The inheritance is autosomal recessive, and affected individuals often have mental retardation, a history of thromboembolism, and coronary artery disease. Plasma homocysteine values are typically markedly elevated, easily distinguishing this disease from MFS.[5]

Congenital contractural arachnodactyly (CCA) shares many skeletal features with MFS but without the ocular and cardiovascular manifestations. The mutation in the few patients reported in the literature is located in the *FBN2* gene,[30] and physical therapy is key to maintaining joint range of motion. It has been suggested that President Abraham Lincoln had MFS, but pictures of him in his later years suggest large joint contractures, which are more typical of CCA.

The overlap of LDS and MFS is considered later in this chapter.

BOX 140.2 Criteria for Causal *FBN1* Mutation

- Mutation previously shown to segregate in Marfan family
- De novo (with proven paternity and absence of disease in parents) mutation (one of the five following categories):
- Nonsense mutation
- In-frame and out-of-frame deletion/insertion
- Splice-site mutations affecting canonical splice sequence or shown to alter splicing on messenger RNA/complementary DNA level
- Missense mutation affecting/creating cysteine residues
- Missense mutation affecting conserved residues of epidermal growth factor consensus sequence
- Other missense mutations: segregation in family if possible + absence in 400 ethnically matched control chromosomes; if no family history, absence in 400 ethnically matched control chromosomes
- Linkage of haplotype for n > 6 meioses to the *FBN1* locus.

Surveillance

MFS is a pleiotropic disorder, and surveillance of the many systems at risk for abnormality is prudent. The cardinal manifestations are ocular, skeletal, and cardiovascular. Regular examinations by an ophthalmologist for slit-lamp testing, a cardiologist for imaging of the aortic root, and an orthopedist for the development of scoliosis should be performed on an annual basis. In this section, focus is placed on aortic and vascular pathology. For recommendations with regard to the other body systems, the reader may find useful information at the National Marfan Foundation website (www.marfan.org). The clinical manifestations within the cardiovascular system that require preventive attention involve the atrioventricular valves, the annuloaortic valve mechanism, and the aortic root and ascending aorta.

Aortic Disease

Aortic aneurysm and dissection are the most life-threatening manifestations of MFS. The threat depends on age, with rupture and dissection rates increasing as the aortic root dilates.[31,32] Because root dilatation at the sinuses of Valsalva can begin in utero, lifelong transthoracic echocardiographic monitoring is needed. For patients in whom the aortic root and ascending aorta are poorly visualized as a result of anterior chest deformity, computed tomographic angiography or magnetic resonance angiography (to avoid radiation exposure) is a viable substitute. Absolute thresholds for replacement of the aortic root in children have not been established, given the observation that dissection is very rare in the young.[5] However, if the aortic root is noted to grow more than 1 cm over consecutive annual assessments or if significant aortic regurgitation is present, early surgery may be necessary.[26] In children and teenagers, a nomogram reflects the number of standard deviations of the patient's aortic root from the mean aortic root diameter in the population and is termed a *Z-score*. If the child's Z-score deviates rapidly from that of the population (>2 to 3 SD) under surveillance, aortic root repair may be justified to prevent rupture. In adults, surgical repair of the aortic root and ascending aorta to prevent aortic rupture and dissection is recommended when its greatest diameter exceeds 50 mm.[26,32] Earlier intervention may be warranted with a family history of aortic dissection at lesser diameters.

Prevention

Lifestyle modifications are routinely recommended once the diagnosis of MFS is established. On the basis of data from the United States, genetic cardiovascular diseases account for 40% of deaths in young athletes.[33,34] A consensus document states that "burst" exertions such as sprinting, weightlifting, basketball, and soccer should generally be avoided. Favored are recreational sports in which energy expenditure is stable and consistent over long periods, such as informal jogging, biking, and lap swimming.[35] Importantly, litigation results suggest that physician reliance on consensus statements to determine medically reasonable levels of activity in patients with cardiovascular abnormalities is appropriate.[36]

Medical Treatment

Medical treatment with β-adrenergic receptor blockade to delay aortic root growth or prevent aortic dissection in patients with MFS is currently considered a standard of care.[5,26] General recommendations are a resting heart rate lower than 70 beats per minute and a heart rate less than 100 beats per minute with submaximal exercise. The rationale for this treatment paradigm is focused on decreasing proximal aortic shear stress and dP/dt. The only randomized trial assessing the effect of beta blockade studied 70 patients, 32 of whom received propranolol.[37] Treated patients received titrated dosages via an open-label approach to keep the heart rate at 100 beats per minute during exercise or a 30% rise in the systolic time interval. Serial echocardiograms were performed and correlated with age, height, and weight over a mean follow-up of 7 years. Fewer patients in the propranolol-treated group reached the primary endpoint of aortic regurgitation, aortic dissection, surgery, heart failure, or death (5 in the treatment group and 9 in the control group). Aortic growth after normalization was lower in the propranolol-treated group (0.023 cm/year) than in the control group (0.084 cm/year, $P < .001$).[37] For patients with increased body weight or an end-diastolic aortic diameter greater than 40 mm, the response to beta blockade was worse, thus suggesting that beta-blockers must be given at an adequate doses and early in the course of the disorder to optimize benefit.[26,37]

The 2006 publication of the ability of losartan, a US Food and Drug Administration–approved antihypertensive medication and selective angiotensin II receptor antagonist, to inhibit aortic aneurysm in murine models of MFS[38] has opened a potential new medical treatment paradigm. The exact mechanisms by which losartan inhibits TGF-β in the aortic wall are not completely understood, but a variety of feedback mechanisms are likely.[39] A multicenter trial comparing beta blockade and losartan therapy for the control of aortic root growth in children and young adults with MFS has been initiated through the National Institutes of Health and was reported in 2014.[40] In comparison of Marfan patients taking atenolol or losartan, both were equally effective at controlling aortic root dilatation.[40] Currently, losartan dosing is titrated to maximum 2 mg/kg, or 100 mg for adults. In a study of 600 Marfan patients followed for a median of 6 years, angiotensin II receptor blocker therapy was associated with reduced risk for type b dissection.[41]

Surgical Treatment

The traditional threshold for prophylactic surgical repair of the aortic root is 5 cm in patients with MFS. Operations on the arterial tree outside the ascending aorta have been reported (Fig. 140.3) and can have acceptable outcomes.[42] Indeed, as the life expectancy of individuals affected by MFS has increased with prophylactic root replacement, it is plausible that the remaining aorta or other large arteries may progress to require repair in the absence of antecedent dissection. For aortic arch and descending thoracic or thoracoabdominal aneurysms, standard criteria for repair generally follow that of atherosclerotic aneurysms—a threshold of 5.5 to 6.0 cm.[26]

Descending Thoracic and Thoracoabdominal Aorta

The first successful replacement of the thoracoabdominal aorta in a patient with MFS was performed by Crawford[43] in the 1980s. Elective surgical repair of descending thoracic aortic aneurysm and thoracoabdominal aortic aneurysms (TAAAs) in MFS has benefited from the general refinements and the introduction of adjuncts to reduce spinal cord injury and other major complications in a manner similar to standard atherosclerotic aneurysms (see Chapter 77). Prophylactic aortic replacement is indicated when the aortic diameter reaches 5.5 to 6.0 cm or if symptoms related to the aneurysm occur. Because of the frequent involvement of the descending and thoracoabdominal aorta with aneurysms of chronic dissection etiology, the extent of repairs in MFS tend to be greater, with 42% to 78% of all TAAAs being DeBakey type II.[44] Paraparesis and paraplegia rates after TAAA repair in MFS compare favorably with those for nonconnective tissue disease when matched for the extent of repair required.[44] Because of the very young mean age of patients with MFS undergoing TAAA repair versus the older mean age of patients with degenerative TAAA, overall long-term survival was better for those with MFS.[44]

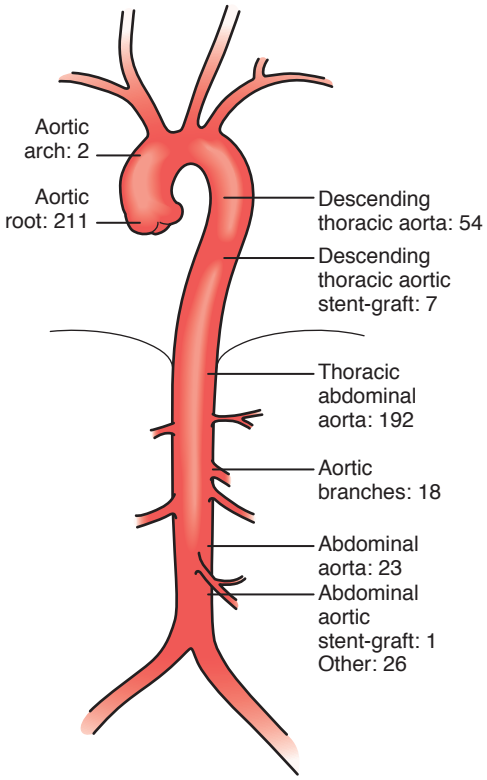


Figure 140.3 Distribution of vascular repairs in 300 patients with Marfan syndrome. (From Lemaire SA, Carter SA, Volguina IV, et al. Spectrum of aortic operations in 300 patients with confirmed or suspected Marfan syndrome. *Ann Thorac Surg.* 2006;81:2063–2078.)

Given the preponderance of type II TAAA repairs in the available series, the rate of freedom from further aortic repair is high because little aorta remains to degenerate. However, secondary aortic procedures after TAAA repair in patients with MFS are often performed for pseudoaneurysm or for aneurysmal degeneration of the inclusion or Carrel patch (Fig. 140.4). Indeed, in the series reported by Lemaire et al.,[42] 95% of reoperations (19 of 20) after previous TAAA repair ($n = 178$) in patients with MFS were performed for visceral patch aneurysm.[42] In our series of 107 patients who underwent TAAA repair, including creation of visceral patches, 17 were known to have a connective tissue disease.[45] With a mean time to diagnosis of 6.5 years, 3 of these 17 patients (17.6%) were found to have aneurysmal degeneration of the visceral patch. By comparison, visceral patch aneurysms were noted after only 5.6% of atherosclerotic TAAA repairs.[45] All of these patients with MFS had inclusion patches that encompassed the celiac axis, superior mesenteric artery, and both renal arteries, thus suggesting that the visceral patch should have been much smaller in all patients with connective tissue diseases to prevent late degeneration.[46] I, along with many surgeons, avoid patch inclusion entirely and use a prefabricated four-branch graft to perform individual bypasses to the renal and visceral aortic branches.[47] Intercostal inclusion patches can be limited also,

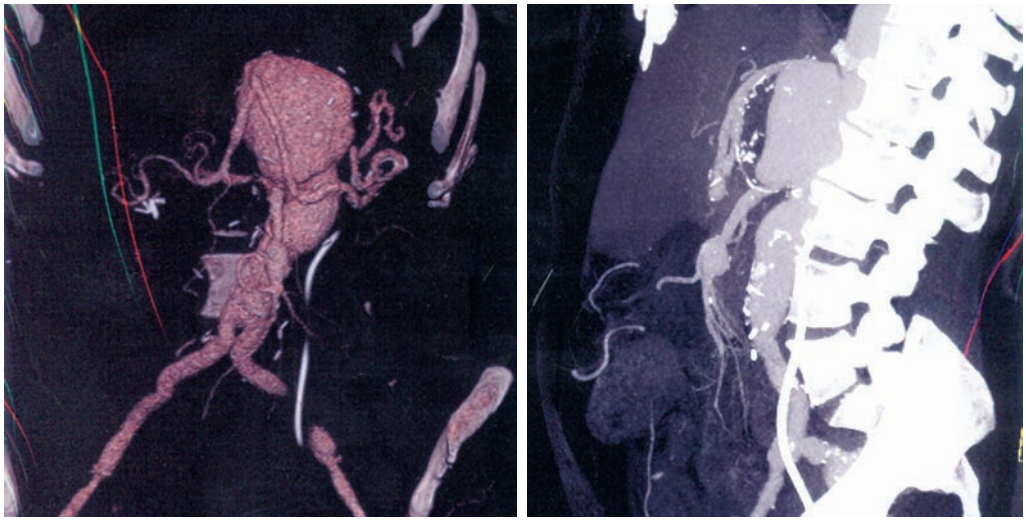


Figure 140.4 Ten-centimeter visceral patch aneurysm 7.5 years after a type II thoracoabdominal aortic aneurysm repair in a 48-year-old woman with Marfan syndrome. A hybrid open/endovascular stent-graft approach was used to repair the region. VRT reconstruction *(left)*; lateral view demonstrating effacement of distance between superior mesenteric artery and celiac axis *(right)*.

but those that degenerate to aneurysm may be treated with stent-graft therapy, although paraplegia concerns are paramount. Given the morbidity associated with repair of the patch aneurysm (2 intraoperative deaths in 5 of our patients taken to the operating room), Dardik et al.[45] recommend maintaining an indication for repair of 6.0 cm or larger.

Endovascular Treatment

In general, aortic stent-grafts should not be used in the thoracic or abdominal aorta or in patients with other connective tissue diseases. The currently approved devices have never been studied in the fragile milieu of the MFS aorta (connective tissue disorder was an exclusion criteria during pivotal trials), and the question of physical damage to the aorta from the persistent radial force of the stent-graft (Fig. 140.5) remains unanswered. A summary publication recommends endovascular repair only in instances of late localized pseudoaneurysm and stenting across native tissue aneurysm from "graft to graft" (see Fig. 140.5).[48,49,50]

Series of patients with MFS who were treated with endovascular therapy with reasonable follow-up periods to determine clinical effectiveness are now emerging. Botta et al.[51] examined 12 patients treated for dissection of the descending thoracic aorta after previous open aortic root/arch surgery. Five procedures were performed urgently and seven electively. In the immediate postoperative period, no paraplegia was encountered. However, after a mean follow-up period of 31 months, 25% of the patients had new dissection, either retrograde into arch or distal into the abdominal aorta. Waterman et al.[52] have published the largest series of patients with MFS undergoing endovascular therapy, and the results are sobering. Forty-four percent of patients experienced primary failure of the stent-grafts, many of which were converted to conventional surgical repairs. Among the primary treatment failures (7 of 16 patients), the mortality was 42%.

Indeed the issue of stent-graft–induced new entry (SINE) tears seems a persistent theme in patients with MFS.[53] The investigator concludes that the stress-induced injury of the stent-graft against the fragile aortic wall should be accounted for during design and placement of the endograft (Fig. 140.6). Although excessive oversizing should also be avoided, it is important to note that the extent of oversizing in this series was within the instructions for use for the available devices to date. Reported experiences with stent-graft therapy in MFS, stating that after stent grafting, retrograde type A dissection was the most common complication among patients with MFS after TEVAR.[54]

VASCULAR-TYPE EHLERS-DANLOS SYNDROME

EDS is a heterogeneous group of heritable disorders of connective tissue characterized by joint hypermobility, skin hyperextensibility, and tissue fragility affecting the skin, ligaments, joints, blood vessels, and internal organs. There are many subtypes of the disorder (Table 140.2 or www.ednf.org), with classic EDS (types I and II) being the most common.[55] The importance of identifying the correct type cannot be overstated, because the natural history and modes of inheritance differ among the subtypes. Historically, the older literature did not clearly differentiate among the types, and the severe complications of the vascular type of EDS were cited as being representative of the whole syndrome, thereby creating unnecessary anxiety. The current nomenclature (i.e., naming the vascular phenotype as vascular

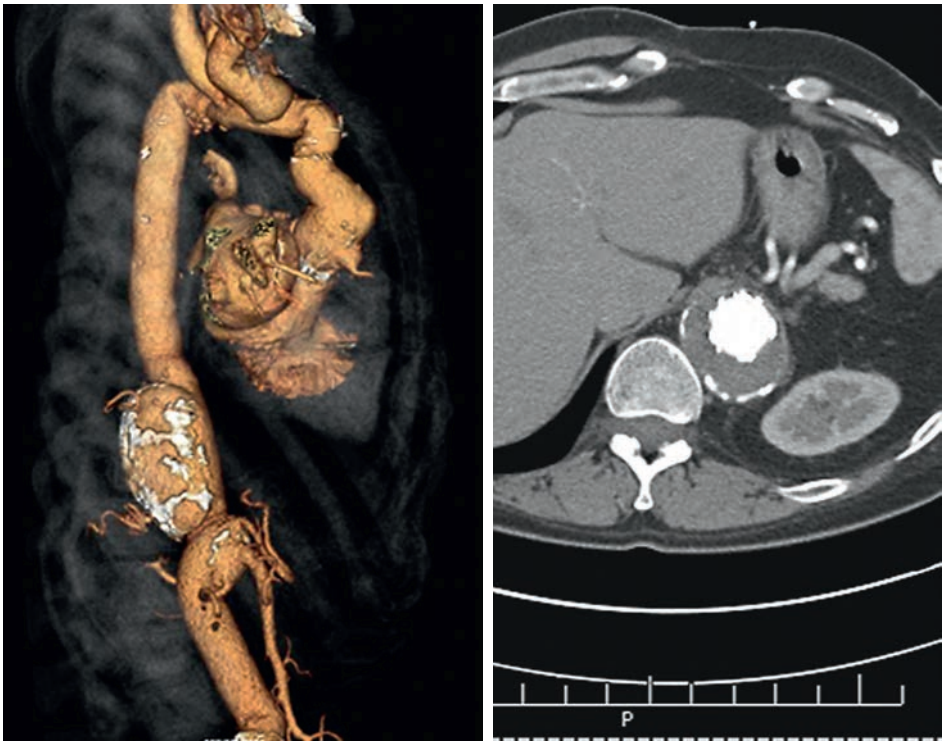


Figure 140.5 Intercostal patch aneurysm after thoracoabdominal aortic aneurysms repair. In this clinical scenario, the stent-graft has "graft-graft" fixation proximally and distally *(left)* in surgical graft material. Notably, intercostal patch aneurysms that are opposite the visceral patch may contraindicate stent-graft placement. Stent graft in position with thrombosis of intercostal patch aneurysm *(right)*.

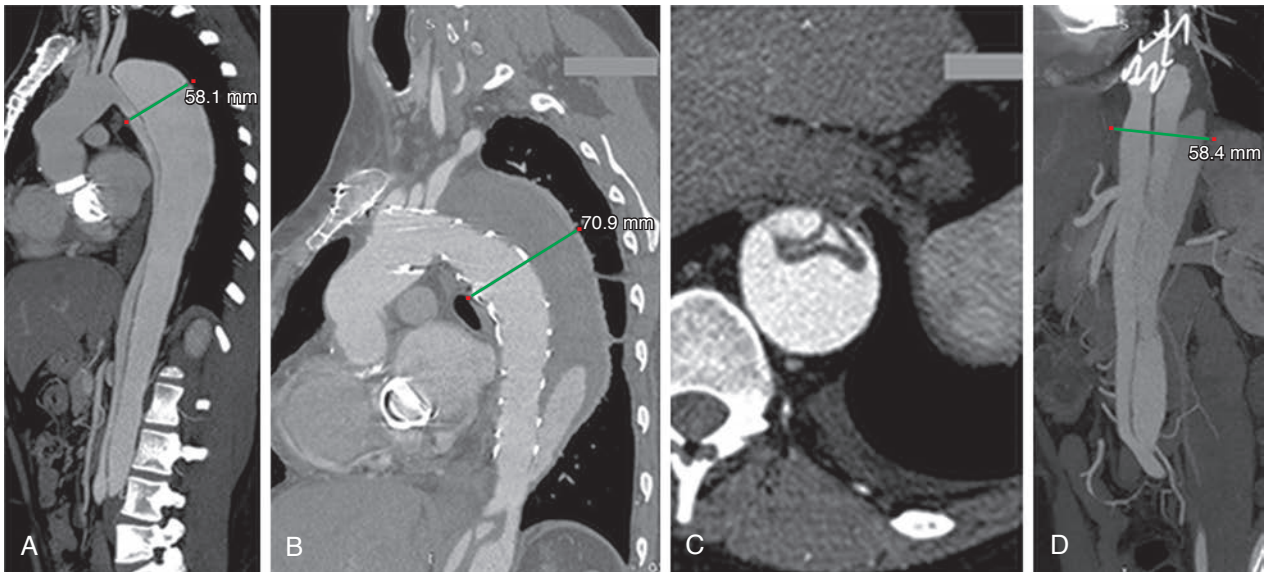


Figure 140.6 Progression of aneurysm in a patient with Marfan syndrome after thoracic endovascular aortic repair. (A) Initial stent-graft placement. (B) New distal entry tear caused by stent-graft edge seen on 1-month CT scan. (C) New presentation at 4 months with acute back pain and near-circumferential dehiscence of the intimomedia. The patient was treated medically until 6-month CT scan revealed (D) new progression to thoracoabdominal aortic aneurysms, which led to referral to the author for repair.

TABLE 140.2 Subtypes of Ehlers-Danlos Syndrome

Nomenclature (New Terms)	Type	Skin (0 to 4+) (Elastic-Fragile)	Joint Laxity (0 to 3+)	Features	Inheritance
Classic	I, II	+++/+++	+++	Vascular complications rarely	AD
Hypermobile	III	+/+	+++	Arthritis	AR
Vascular	IV	−/++++	+	Rupture of arteries, uterus, intestine; thin skin	AD
Kyphoscoliotic	VIA, VIB	+++/++	+++	Hypotonia, osteoporosis, Kyphoscoliosis; rupture of arteries, globe of eye	AR
Arthrochalasic	VIIA, VIIB	++/+	+++	Hip subluxation, osteoporosis	AD
Dermatosparactic	VIIC	−/++++	+	Skin doughy and lax	AR
Other	V	++/++		Skin lax	X-linked
	VIII	+/++	++	Periodontal disease	AD
	IX	+/−	+	Lax skin, osteoporosis, bladder diverticula, retardation	X-linked
	X	+/+	++	Petechiae	?

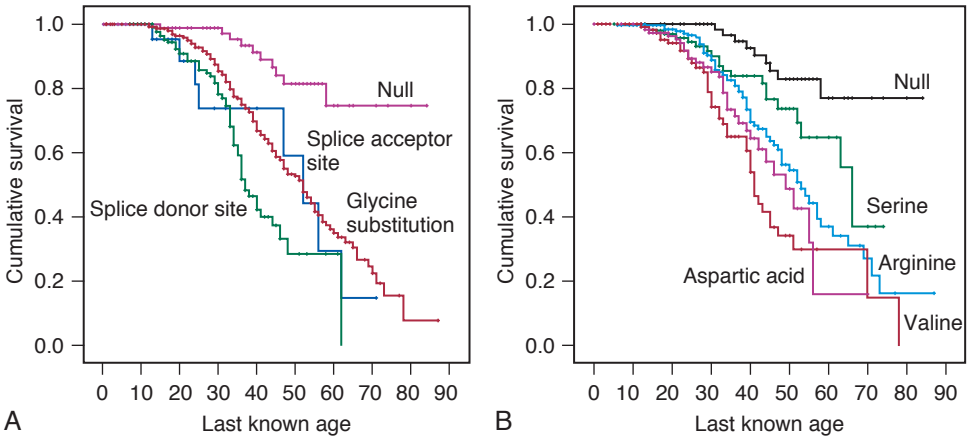
AD, Autosomal dominant; *AR,* autosomal recessive.

EDS) attempts to reinforce this important separation from other subtypes. This section focuses on the vascular type (EDS IV), its pathogenesis (defective type III procollagen encoded by the *COL3A1* gene leading to extreme vascular fragility), and its management.

Epidemiology and Natural History

The prevalence of EDS IV is currently estimated to be 1 in 50,000 to 90,000, and it is inherited in an autosomal dominant manner.[55,56] Approximately 50% of cases represent new mutations that occur sporadically and without an antecedent family history. As a rule, each patient or family carries a unique mutation in the *COL3A1* gene, which codes for type III procollagen.[57,58]

The overall life expectancy of patients with EDS IV is dramatically shortened, largely as a result of vascular rupture, with a median life span of 48 years (range, 6-73 years).[59] In a study of 220 patients with EDS IV confirmed by abnormal type III procollagen molecules and 199 relatives with a clinical diagnosis of EDS IV, major complications in childhood were rare, but 25% of the subjects suffered medical or surgical complications by the age of 20. By 40 years of age, major complications in



Substitution	Median survival in years	Estimated hazard ratio	95% CI
Null		(ref)	(ref)
Alanine	43	5.54	(2.2,14.1)
Cysteine		9.88	(2.9,34.0)
Aspartic acid	49	5.30	(2.7,10.6)
Glutamic acid	34	5.66	(2.7,11.8)
Arginine	52	4.01	(2.1,7.8)
Serine	66	2.62	(1.2,5.5)
Valine	41	7.17	(3.7,13.8)

C

Figure 140.7 Kaplan–Meier survival curve of vascular Ehlers-Danlos syndrome study population comparing mutation type (A) to null mutations (B), and overall survival (C). (From Pepin MG, Schwarze U, Rice KM, Liu M, Leistritz D, Byers PH. Survival is affected by mutation type and molecular mechanism in vascular Ehlers-Danlos syndrome (EDS type IV). *Genet Med.* 2014;16(12):881–888.)

the vascular or gastrointestinal systems (men and women) or reproductive system (women, e.g., uterine rupture in pregnancy) had developed in 89%.[59] Death had occurred in 131 subjects, with rupture of thoracic or abdominal vessels in 78 (60%), central nervous system hemorrhage in 9 (7%), and an unspecified bleeding source in 16 (12%). Organ rupture (heart, uterus, spleen, liver) caused death in 13 (10%) of the patients, and intestinal rupture led to death in 10 (8%).[59]

Pathogenesis

EDS IV is due to mutations in the *COL3A1* gene, which encodes a protein for type III collagen assembly. Because most arteries and arterioles have significant amounts of type III collagen, defects in *COL3A1* lead to inherent weakness of these vessels.[59] The gene encodes a procollagen molecule, proa1(III), and basic collagen synthesis requires three polypeptide procollagen chains, referred to as α chains, to be folded tightly into a triple helix.[55] The abnormal collagen III molecule cannot fold stably into a triple helix, is slowly degraded in the rough endoplasmic reticulum of the fibroblast, and is never secreted extracellularly.[55]

The central concept of heterozygous mutations leading to structural defects of collagen α chains and instability or nonsecretion of the mutant protein has proved correct in several collagen disorders and has been termed "protein suicide."[60] A study by Pepin et al. recently demonstrated that different types of mutations may be associated with different overall survival. This genotype/phenotype correlation may have a basis in the high prevalence of glycine substitutions or deletions, as the very small molecular size of glycine is critical for proper folding of the collagen triple helix (Fig. 140.7).[61]

Clinical Evaluation

Common Manifestations

EDS IV has the worst prognosis among the types of EDS; for this reason, proper diagnosis is essential, because the physical findings may mimic those of other EDS subtypes or other connective tissue diseases (Box 140.3).[62] The presence of any two or more of the major criteria (easy bruising, translucent skin, facial features, and history of arterial, uterine, or intestinal rupture) is highly indicative of the diagnosis, and collagen testing

BOX 140.3 Diagnostic Criteria for Ehlers-Danlos Syndrome, Vascular Type

Major Diagnostic Criteria

- Thin, translucent skin
- Arterial/intestinal/uterine fragility or rupture
- Extensive bruising
- Characteristic facial appearance (thin delicate nose, thin lips, hollow cheeks)

Minor Diagnostic Criteria

- Acrogeria (taut, thin skin)
- Hypermobility of small joints
- Tendon and muscle rupture
- Talipes equinovarus (clubfoot)
- Early-onset varicose veins
- Arteriovenous carotid–cavernous sinus fistula
- Pneumothorax/pneumohemothorax
- Gingival recession
- Positive family history, sudden death in one or more close relatives

Data from Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet*. 1997;77:31–37.

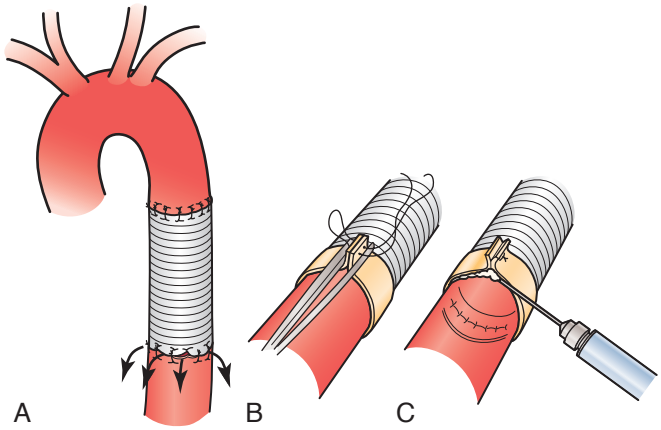


Figure 140.8 (A) Lack of adventitial and medial thickness in type IV Ehlers-Danlos syndrome promotes suture-line bleeding. Buttressing with felt (B) and the application of BioGlue (C) may reduce suture-line tension and promote hemostasis.

is strongly recommended. Such testing is both labor- and time-intensive but should strongly be considered before any treatment course is chosen for the suspected affected individual. The diagnosis of EDS IV is most commonly confirmed by demonstration of structurally abnormal collagen III.[63] Direct molecular genetic analysis of the *COL3A1* gene is also possible from a blood or serum sample.

Differential Diagnosis

The differential diagnosis of EDS IV includes disorders of bruisability and wound healing such as von Willebrand disease, platelet disorders, and scurvy. Bruisability is often elicited in children and may mimic nonaccidental injury ("battered child").[64] Indeed, excessive bruising with hematoma formation is a common first manifestation. In EDS IV, rupture or dissection of arteries occurs most often in medium-sized vessels, as opposed to the predominant occurrence of rupture and dissection in the aortas of patients with MFS. The vessel's tortuosity and elongation may be similar to findings in the arterial tortuosity syndrome or LDS, but vascular surgery is often much better tolerated in the latter. Multiple aneurysms through the visceral vessels may also be noted in polycystic kidney disease and hereditary forms of cerebral cavernous malformations.[65] Varicose veins and venous aneurysms are commonly seen in EDS IV but have little clinical or diagnostic significance versus nonsyndromic venous disease unless stripped, at which point bruising and skin injury can be extensive.

Selection of Treatment

Although no specific medical therapies exist for EDS IV, knowledge of the diagnosis can influence management strategies, assist in reproductive counseling, and direct the treatment of major complications. All patients with a confirmed diagnosis of EDS IV should carry medical attention bracelets as well as papers noting information on the condition and their blood groups. General recommendations for anesthesia also exist, including cross-matching of adequate blood, avoidance of intramuscular injection, adequate peripheral access, avoidance of arterial lines and central venous catheters, and gentle intubation maneuvers.[66] If central access is required, the use of ultrasound guidance for access is mandatory.

True Aneurysms

True aneurysms in EDS IV are rare and occurred in only 14% of patients in one series.[67] Given the difficulty of handling the fragile tissues and vessels, management of spontaneous bleeding should be conservative as long as possible, especially in the interstitial (muscular, retroperitoneal) spaces.[67,68] Bleeding within the peritoneal cavity usually requires immediate transfusion; if surgery is required, vessel ligation with umbilical tape appears to be the safest course, as opposed to direct repair.[67] Direct reconstructions must be tensionless, often pledgetted to reduce suture trauma, and reinforced circumferentially (Fig. 140.8). Angiography should be avoided because of severe morbidity and the risk of vessel dissection or perforation (or both) during selective catheterization or from the puncture site itself. In one study, the major complication rate from arteriography was 67% with 12% mortality,[69] although the benefit of more contemporary, lower-profile catheter and endovascular devices may have a favorable impact on this historically high percentage.

Vascular Complications

When there was bleeding from vascular rupture, the recommendation of avoiding any operation until faced with imminent risk of death remained axiomatic for many decades. This axiom further complicated the condition of patients with known aneurysms, whose vessels were allowed to dilate progressively under regular surveillance, which caused much angst for the surgeon and patient. For the individual patient, elective aneurysm

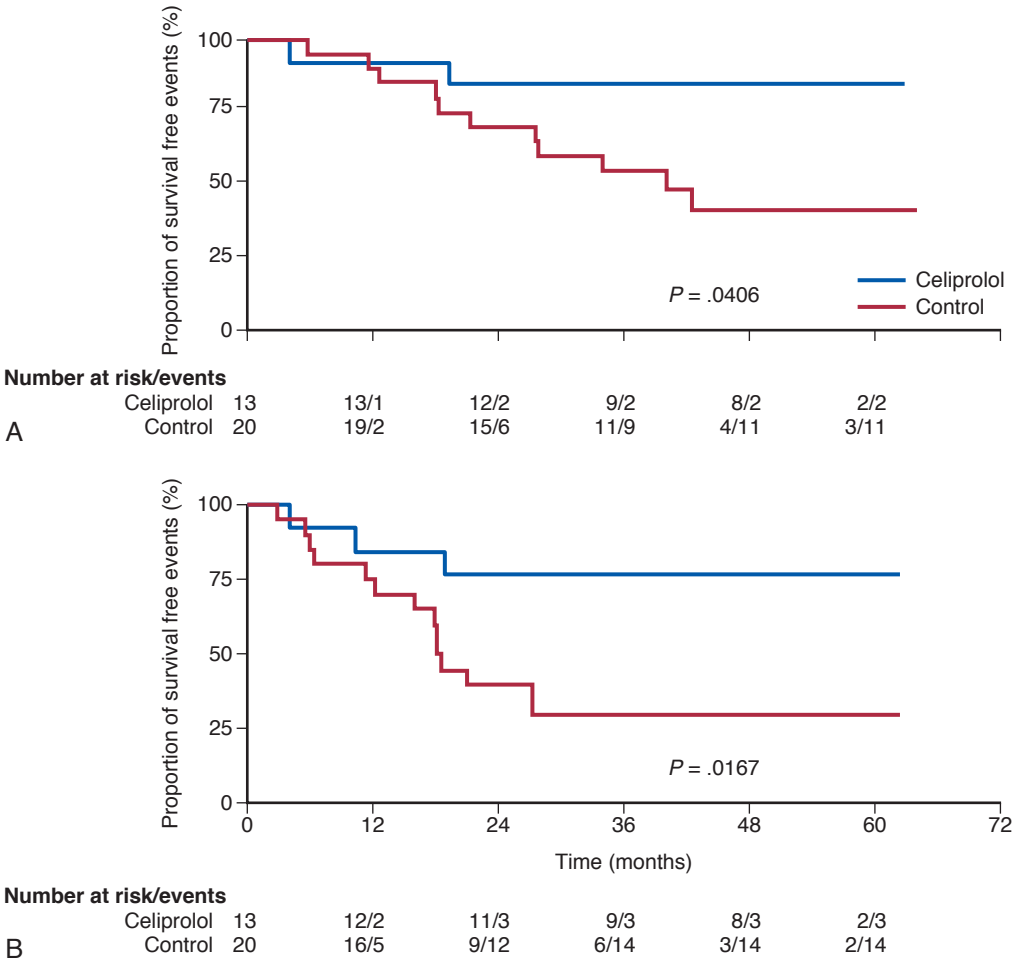


Figure 140.9 Kaplan-Meier survival curves in celiprolol study. Vascular event–free survival was improved in patients taking celiprolol who had a *COL3A1* mutation. (From Ong KT, Perdu J, De Backer J, et al. Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective, randomized, open, blinded endpoints trial. *Lancet*. 2010;376(9751):1476–1484.)

repair must be considered, especially if previous operative therapies did not report excessive fragility. Patients with EDS IV at highest risk of inoperable tissue fragility can be identified if seen at a very early age (<20 years) or multiple asymptomatic dissections or aneurysms apart from the index vascular lesion are noted.[70]

Nonvascular Complications

Gastrointestinal perforations account for 25% of all EDS IV complications.[59] The sigmoid colon is the location of most perforations, and prompt diagnosis and immediate colostomy are favored.[59] For small bowel intestinal rupture, ostomy is also preferred, and most patients undergo restoration of bowel continuity in a staged fashion without complication.[59] Recurrent bowel perforation is always a risk, occurring between 2 weeks and 26 years after the first event in 17% of patients in one study.[59]

Uterine and pregnancy-related complications are discussed under "Pregnancy in Patients with Type IV Ehlers-Danlos Syndrome."

Medical Treatment

Celiprolol has been advanced as a treatment of choice to reduce the incidence of vascular ruptures in patients with EDS IV.[71] In a 5-year randomized study of 53 patients with suspected or proven EDS IV, celiprolol therapy reduced the incidence of vascular rupture to 20%, compared with 50% in control subjects (Fig. 140.9). The trial has been criticized for the lack of uniform genetic testing to prove that all subjects had the disorder (only 33 of 53 had a *COL3A1* mutation) and the fact that mean heart rate and blood pressure were actually higher than in the control patients. This last finding would suggest a mechanism for the drug other than simple dP/dT effects. Therefore prophylactic measures to control blood pressure and reduce atherosclerotic risk factors are recommended. Lifestyle modifications for EDS IV follow the general recommendations for other genetic diseases, as reviewed in the earlier discussion of MFS.[35]

Spontaneous abdominal bleeding without identifiable source (by CTA or angiography) is associated with an advanced stage of the disorder. Factor VII transfusion may be an acceptable

option, as surgical exploration should be deferred unless compartment syndrome develops.

Surgical Treatment

Surgical management of EDS IV is a formidable challenge. The traditional risk assessment paradigm cites invasive procedures so fraught with complications that intervention should be performed only for imminent risk of death.[67,68] The findings in patients with EDS IV can include arterial manifestations throughout the entire vascular tree (Fig. 140.10).

A report of patients treated at Johns Hopkins Hospital from 1994 to 2009 reveals some very important distinctions regarding the triage of patients with EDS IV.[70] Unlike in the Mayo Clinic series, in which the preponderance of patients were treated emergently, most of the patients in the Hopkins series were treated electively. Overall perioperative bleeding rate and mortality were greatly reduced by comparison (Table 140.3). Given the success of elective procedures, it may be worthwhile to consider elective intervention in patients with EDS IV, before rupture and the ensuing stress compound operative repair. Furthermore, it is also likely that some improvement in the Hopkins series rests in its more contemporary time period. Undoubtedly operative techniques have improved, and the researchers offer several methods to explain their admirable results:

1. Liberal use of adjunctive techniques to reduce operative trauma in both the endovascular and operative setting
2. Padded surgical clamps
3. Permissive hypotension (systolic blood pressure between 70 and 80 mm Hg) during vascular clamping and suture line testing

Patients with EDS IV have been found to have unique iliac aneurysms. The configuration usually spares the aortic bifurcation, and the common iliac arteries "balloon" in a bell-bottom fashion (Fig. 140.11). In such instances, repair should be entertained in young patients electively, with emphasis on adjunctive measures to secure anastomoses as described earlier.

Ultimately, patient risk-to-benefit assessment compels any decision to proceed with a major surgical intervention. It is worthwhile to note that genetic analysis of specific mutations and collagen III biochemical assay may not predict clinical

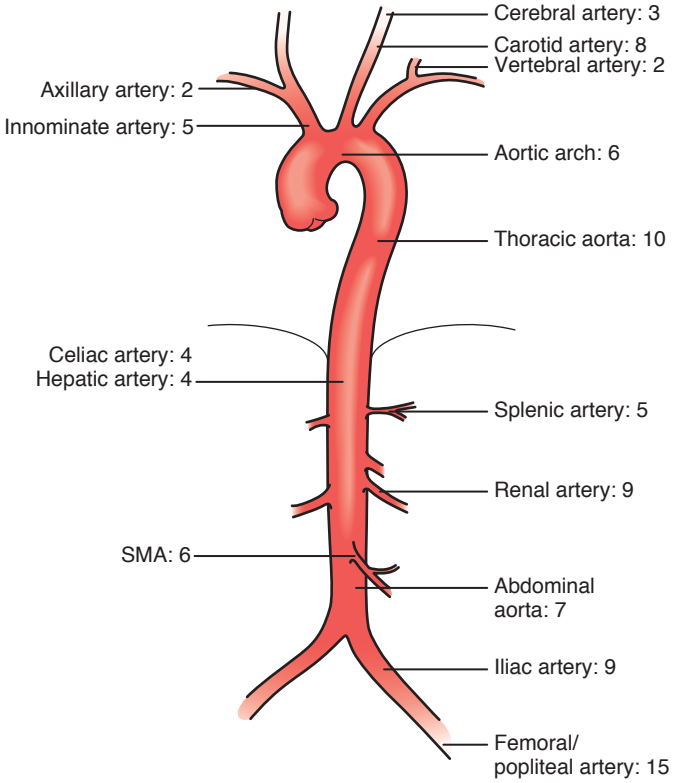


Figure 140.10 Arterial distribution of vascular complications in 24 patients with a clinical diagnosis of type IV Ehlers-Danlos syndrome. *SMA,* Superior mesenteric artery. (From Oderich GS, Panneton JM, Bower TC, et al. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30 year experience. *J Vasc Surg.* 2005;42:98–106.)

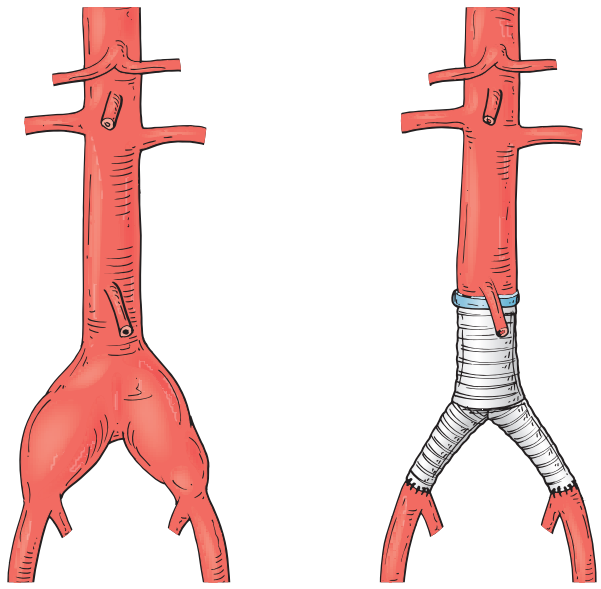


Figure 140.11 "Bell-bottom" configuration iliac aneurysms in vascular Ehlers-Danlos syndrome. In my experience, this is a typical aneurysmal configuration. The aortic bifurcation is preserved, and adjunctive felt reinforcement secures hemostasis.

TABLE 140.3 Outcomes of Endovascular and Open Procedures in Ehlers-Danlos Syndrome Type IV

Procedure	Operative Death, No (%)	In-Hospital Death, No (%)	Length of Stay (Days), Median (*Interquartile Range*)	Any Complication, No (%)
Endovascular (n = 11)	0 (0)	0 (0)	3 (1-6)	0 (0)
Open (n = 9)	1 (11)	1 (13)	7 (6-8)	3 (38)

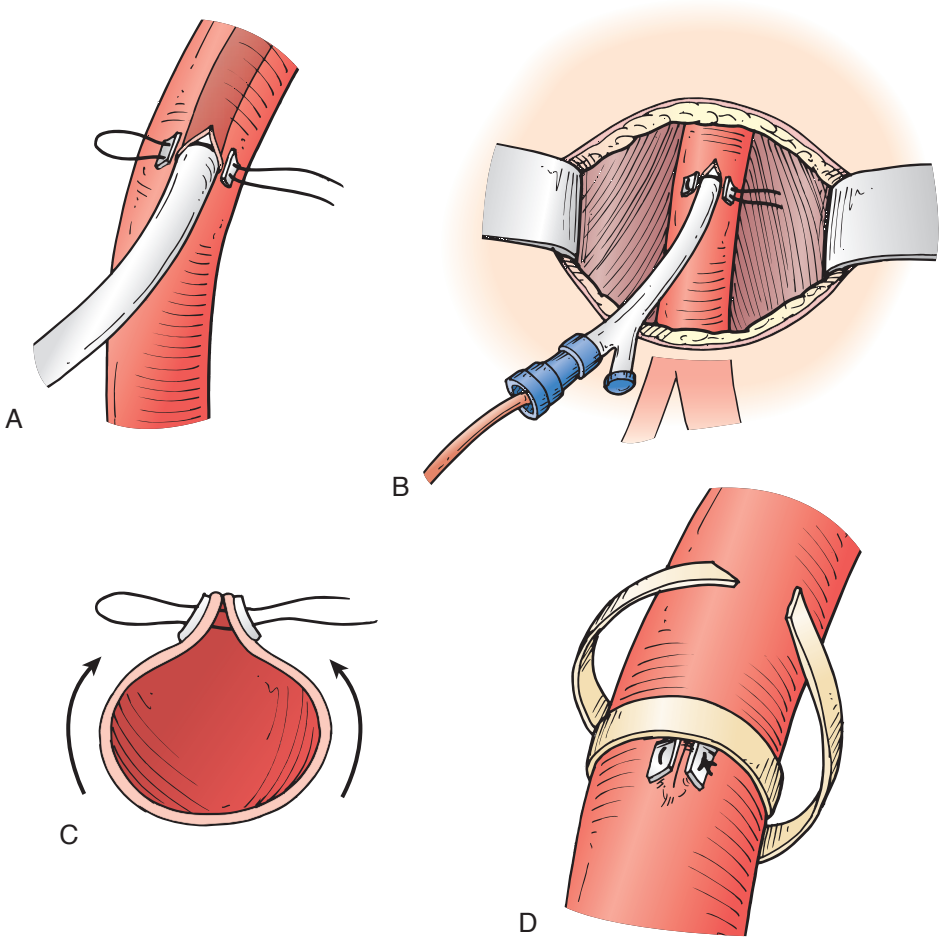


Figure 140.12 Techniques for access in severe fragility of VEDS without femoral clamp. The initial small bore sheath access through pledgetted "U" stitch **(A)** can be upsized to a large bore sheath **(B)**. The initial stitch can be tied down **(C)** for hemostasis and the vessel circumferentially reinforced **(D)** to prevent a late pseudoaneurysm.

course. However, those patients with "null" mutations have been appreciated to have a higher incidence of aortic and iliac pathology and are associated with better surgical handling.[72] But as with most connective tissue disorders, clinical history can be informative. For patients with severe phenotypic features (such as very affected skin or facial morphology), those with early-age onset, and those with prior complicated courses, complications can be expected. Furthermore, as median survival is 48 to 54 years, older patients may develop intolerance to procedural manipulations versus prior uncomplicated medical or surgical events, assuming a higher risk profile as vessel fragility worsens over a lifetime of EDS IV.

Endovascular Treatment

Endovascular approaches for coil embolization of aortic branch vessels and other medium-sized arteries have been successful in patients with hemorrhage.[67,70] Such approaches should be strongly considered for spontaneous splenic and hepatic arterial tears, many of which occur without previous trauma and may be imparted by relatively routine activities of daily living. Indeed, a report of endovascular interventions in a spectrum of patients with EDS revealed a very favorable safety profile.[73] Arterial access can precipitate femoral rupture and pseudoaneurysm formation, especially when large devices are necessary. Consideration should be given to open repair of any access puncture (Fig. 140.12), particularly when a larger French size is introduced, given the rate of complications reported.[73] Accordingly, stent-graft therapy for aortic aneurysms has not been reported in a significant sample, and long-term durability and threat to the fixation zones in the setting of chronic outward radial force may increase the frequency of secondary interventions. Consequently it is generally agreed that stent-graft therapy for EDS IV (and other connective tissue diseases) should be avoided.[50] Carotid–cavernous sinus fistula is a classic complication of EDS IV that is amenable to coil embolization in selected patients. It may manifest as subtle, progressive proptosis or headache, and high-quality imaging is key to determining whether the fistula can be addressed without risk of internal carotid sacrifice and resultant major stroke (Fig. 140.13).

Pregnancy in Patients With Type IV Ehlers-Danlos Syndrome

Pregnancy in women in EDS IV should be closely monitored. Whether elective cesarean section is warranted before labor or spontaneous vaginal delivery should be allowed is not known.[74] In the largest study of 220 patients with EDS IV, 81 women had 183 deliveries; 12 women (15%) died during the peripartum period or within 2 weeks after delivery.[59] The cause of death

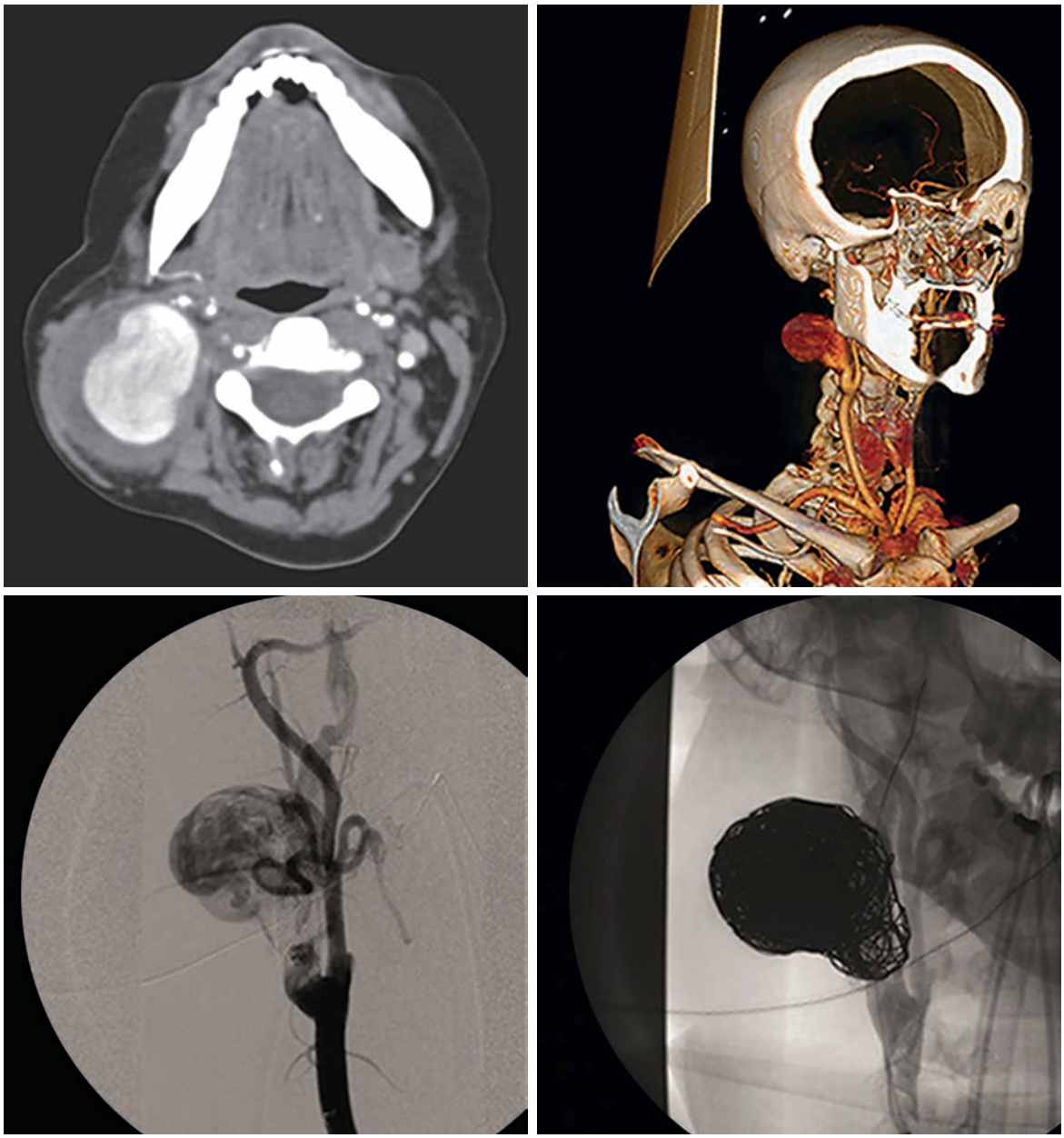


Figure 140.13 Acute development of internal carotid artery aneurysm in a woman with vascular Ehlers-Danlos syndrome 10 days postpartum, which caused significant dysphonia, dysphagia, and pain. Stent-assisted endovascular embolization was performed, and the aneurysm decreased by 50% at 3 months after the procedure.

in these women was uterine rupture in 5, vessel rupture during labor in 2, and death in the postpartum period from vessel rupture in 5. Women with EDS who become pregnant should be considered high-risk patients and managed at high-risk centers. Genetic counseling is also mandatory, because the disorder is inherited as an autosomal dominant trait and 50% of offspring of an affected individual would be expected to manifest the disorder in their lifetimes.

LOEYS-DIETZ SYNDROME

LDS is a newly described aortic syndrome typified by aortic aneurysm and vascular tortuosity, the characteristic craniofacial abnormality of a bifid uvula or cleft palate, and, finally, hypertelorism (Box 140.4).[75] The disease is caused by heterozygous mutations in the genes encoding TGF-β receptors 1 and 2 (*TGFBR1* and *TGFBR2*), SMAD3 genes, and TGF-B 2 receptors.[76,77] Since the original report, four subtypes of LDS have been proposed. LDS type I has both severe craniofacial features and aortic aneurysms.[77] LDS type II is characterized by less severe craniofacial abnormality, usually only a bifid uvula or high palate, and aortic aneurysms. LDS type III is characterized by aneurysms and early-onset osteoarthritis. LDS type IV includes aneurysm of the aorta and cerebral with arterial tortuosity. The cardinal manifestation involves the aortic root, but the aggressive nature of the root aneurysm to dissect or rupture (or

BOX 140.4 Scoring of Systemic Features

- Wrist *and* thumb sign: 3 (wrist *or* thumb sign: 1)
- Pectus carinatum deformity: 2 (pectus excavatum or chest asymmetry: 1)
- Hindfoot deformity: 2 (plain pes planus: 1)
- Pneumothorax: 2
- Dural ectasia: 2
- Protrusio acetabuli: 2
- Reduced upper segment/lower segment ratio *and* increased arm/height *and* no severe scoliosis: 1
- Scoliosis or thoracolumbar kyphosis: 1
- Reduce elbow extension: 1
- Facial features (3/5): 1 (dolichocephaly, enophthalmos, downsliding palpebral features, malar hypoplasia, retrognathia)
- Skin striae: 1
- Myopia >3 diopters: 1
- Mitral valve prolapse (all types): 1
- Maximum total: 20 points; score ≥7 indicates systemic involvement.

both) at small diameter and in childhood separates this condition from MFS and EDS IV. Identification of affected patients and testing of all first-degree relatives are of paramount importance to motivate individuals for prophylactic surgery.

Epidemiology

Comparison of survival in the two subtypes of LDS was also reported.[76] In LDS type I, the mean age at death was lower (22.6 years) than in LDS type II (31.8 years, $P = .06$). The mean age at the first surgery was 10 years younger in patients with LDS type I than in those with type II (16.9 years versus 26.9 years, $P = .03$). Craniofacial abnormalities, when scored according to a craniofacial severity index, correlated inversely with the time of first surgery (more severe craniofacial abnormality indicated more aggressive aortic pathology).[76] LDS type III and LDS type IV may have a later onset of disease.

Clinical Evaluation

LDS is a multisystem disorder with a classic triad consisting of craniofacial abnormality (90%), hypertelorism (wide-set eyes, 90%), and arterial tortuosity/aneurysm (98%). In 40 patients with LDS who underwent anthropometric evaluation, there were findings additional to the classic triad throughout the craniofacial, skeletal, and cutaneous systems.[77] Developmental delay was infrequent (15%) and was occasionally associated with craniosynostosis, hydrocephalus, or Arnold–Chiari malformation, thus suggesting that learning disability is a rare primary manifestation of LDS.[77] A recent series had demonstrated peripheral vascular involvement is not predicted by prior aortic root repair. Thus, some LDS patients may present with nonaortic root aneurysm as their index aneurysm, in which case full body imaging is required.

Common Manifestations

The craniofacial manifestations encountered are most commonly hypertelorism and cleft palate or bifid uvula (Fig. 140.14).

Figure 140.14 Hypertelorism is noted in 90% of patients with Loeys-Dietz syndrome. In addition, this patient demonstrates malar hypoplasia (underdeveloped and flattened midface/zygomatic arches) and retrognathia (the mandible recedes under the maxilla). (From Williams JA, Loeys BL, Nwakanma LU, et al. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. *Ann Thorac Surg.* 2007;83:S757–S763.)

Craniosynostosis was present in 48%, malar hypoplasia (flat midface) in 60%, and blue sclerae in 40% in the first study describing the syndrome. In distinction to MFS, lens dislocation (ectopia lentis) was not recorded in any patient with LDS.[76,77]

Cardiovascular involvement is a hallmark of LDS, but aneurysms are not limited to the aortic root and can occur throughout the vascular tree. Arterial tortuosity, particular of the supra-aortic vessels, should prompt consideration of the disease, especially for LDS type III and IV.[77] Vessel elongation within tortuous segments can be difficult to diagnose without three-dimensional imaging (Fig. 140.15) and centerline measurement.

Differential Diagnosis

Because of the early age of appearance of dramatic pathology, vascular-type EDS is often considered along with LDS. It could not be more critical to differentiate the two, either by clinical examination to determine the LDS triad or by biochemical testing to confirm EDS IV, because surgical management and tissue fragility are dramatically more challenging in patients with EDS IV than in those with LDS.

Selection of Treatment

Risk assessment for prophylactic repair in patients with LDS must account for the aggressive nature of the aneurysms in this disorder. In adults, aneurysms of the thoracoabdominal and infrarenal aorta are repaired when they are 4.0 cm or greater. A new diagnosis of LDS should prompt a head-to-toe computed tomography or magnetic resonance imaging study to determine the presence of arterial pathology outside the aortic root (Fig. 140.16).[77] Because involvement of the supra-aortic trunks and vertebral vessels is not uncommon, surgical exposure may be difficult, and embolization approaches should be considered.

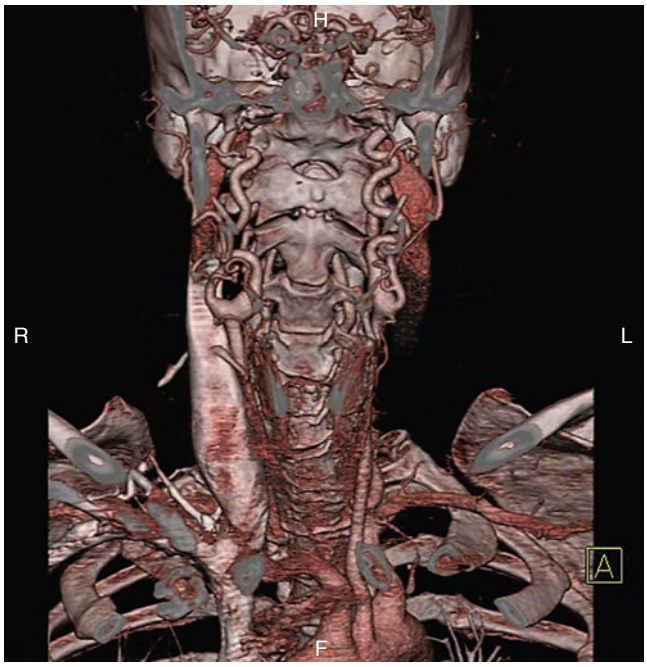


Figure 140.15 Bilateral carotid and vertebral arterial tortuosity is a common peripheral vascular finding in patients with Loeys-Dietz syndrome.

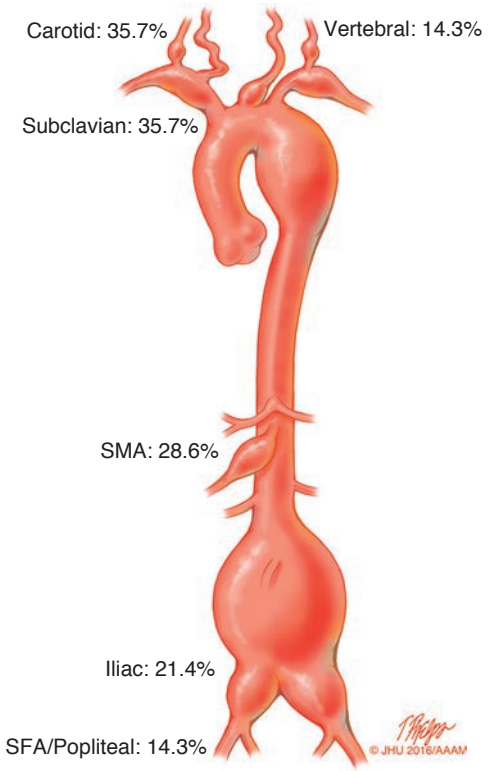


Figure 140.16 Vascular involvement of the supra-aortic branches and entire aorta is common in patients with Loeys-Dietz syndrome. *SMA,* Superior mesenteric artery. (From Beaulieu R, Lue J, Ehlert BA, Grimm JC, Hicks CW, Black JH. Surgical management of peripheral vascular manifestations of Loeys-Dietz syndrome. *Ann Vasc Surg.* 2016;38:10–16.)

Given the widespread involvement of the arterial pathology in this disorder, multiple operations or interventions in a single patient are not uncommon.[78,79]

Medical Treatment

Current recommendations for medical management and surveillance in LDS are predicated on the beta-blockade regimen recommended for patients with MFS, with the threshold for repair being more aggressive in LDS. Nonetheless, the pathophysiologic mechanism of increased TGF-β activity in the vessel wall compels some clinicians to initiate losartan therapy for the disease on the basis of the mechanisms demonstrated in the pathophysiology of MFS. However, randomized trials for this therapy are lacking, and preliminary data for losartan therapy are not conclusive to date. Lifestyle modifications should also restrict "burst" activity, as in MFS restrictions.[35]

Surgical Treatment

Early results after surgical treatment of aneurysm in LDS are now emerging because of the characterization of clinical and genetic features specific to the disease. Tissue handling and aortic anastomoses are favorable, and a small series of aortic root replacement in adults and children demonstrated no operative mortality, although 3 of 21 patients died in follow-up of thoracic aortic (n = 2) and abdominal aortic (n = 1) rupture.[78,79] In the accumulated experience at Johns Hopkins, patients returned to surgery for descending thoracic aortic replacement after previous ascending aortic aneurysm repair or valve-sparing aortic root aneurysm repair. Three of these patients returned thereafter with patch aneurysms after previous thoracoabdominal repairs and were confirmed as having LDS on subsequent *TGFBR* testing. As in MFS, this limited experience suggests that inclusion patch size should be limited or preferably avoided by direct anastomosis to the renal and visceral origins with prefabricated, branched Dacron grafts (Fig. 140.17) to the renal and visceral vessels.[78] On the basis of experience in the aortic root with premature rupture at small diameters, a general recommendation for repair of any aortic segment in adults would be 4 to 5 cm or growth of the aneurysm more than 0.5 cm in 1 year.[79] Recommendations for repair of peripheral aneurysms in LDS may be dependent on the patient's age, body size, and history, with rate of growth factoring into the decision, thus making regular surveillance with high-quality imaging critical.[79] Vessel tortuosity may also be progressive, even though arterial dissection or degeneration in the vascular "hairpins" has not been seen.

FAMILIAL THORACIC AORTIC ANEURYSM AND DISSECTION

Although it has been recognized that TAAD occurs in individuals with known genetic syndromes, a genetic basis for patients with TAAD who do not have a defined connective tissue disease has been investigated. These patients typically exhibit minimal or no outward anthropometric evidence of MFS, EDS IV, or LDS

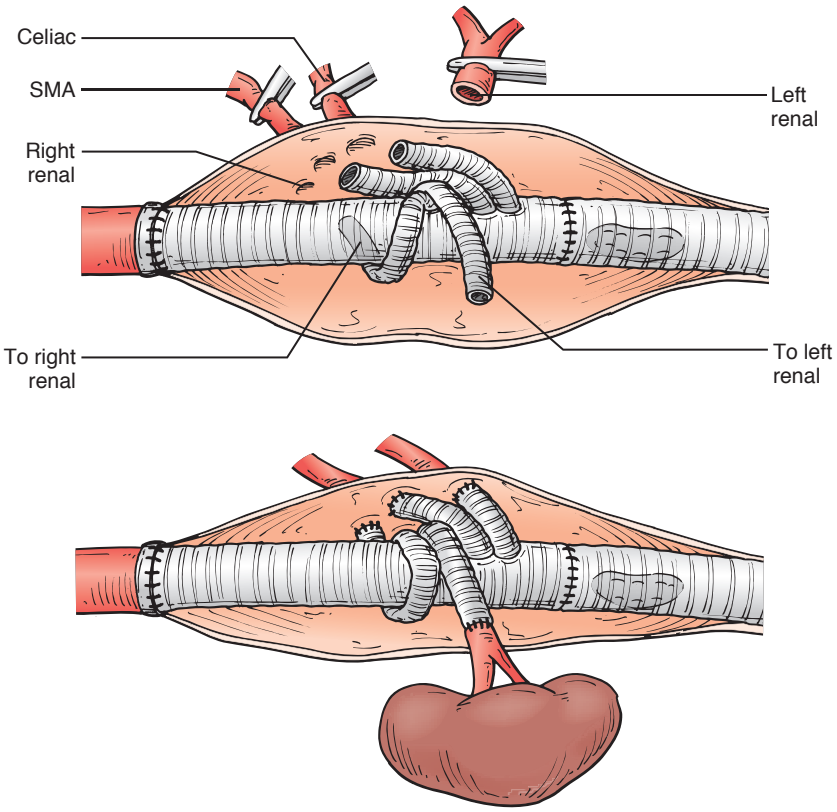


Figure 140.17 Technique for thoracoabdominal aortic reconstruction in patients with connective tissue disorder. Individual branch grafts are anastomosed in the visceral and renal origins, thus avoiding any late inclusion patch aneurysms. The 360-degree wrap helps reduce kinking of short direct branches as the retroperitoneum is closed. *SMA,* Superior mesenteric artery.

yet often relate an impressive history of aortic catastrophe in antecedents. Familial studies suggest that 11% to 19% of all nonsyndromic patients with TAAD have a first-degree relative with the disorder.[80,81] Pedigree analysis suggests that familial TAAD is inherited as a predominantly autosomal dominant disorder with decreased penetrance and variable expression that yields considerable clinical heterogeneity.[82] Genetic mapping of loci in familial TAAD has provided new insight into the pathogenesis of aneurysms throughout the aorta.

Pathogenesis

Five loci have been mapped for familial TAAD to date, including three identified genes. Despite locus heterogeneity, the final common pathologic change in the aortic wall is medial degeneration.[83,84] Disarray of smooth muscle cells and the accumulation of proteoglycan are also typically present. The first locus mapped for familial TAAD was the *TAAD1* locus at 5q13-14.[84] The initial genetic screen identified the location of the defective gene by using two families with similar phenotype for mapping. Subsequent to this mapping, 15 other families with familial TAAD patterning were found to carry the same genetic defect, which was segregated as an autosomal dominant disease. In families with this gene, women seemed to be less affected, thus suggesting reduced penetrance of expresssion.[85] Involvement of the ascending aorta is the primary finding.[84]

Alpha-actin mutations have been discovered to cause 14% of cases of familial TAAD.[86] The actin proteins are highly conserved and are critical cytoskeletal elements. Aortic tissue demonstrates cystic medial degeneration with focal areas of marked vascular smooth muscle proliferation. Interestingly, familial TAAD patients with *ACTA2* mutations are also noted to have significant livedo reticularis, a physical finding not encountered in the other connective tissue diseases. The overall penetrance to express aneurysm or dissection in individuals with familial TAAD and *ACTA2* mutations was low (0.48) and did not change with age. This fact distinguishes *ACTA2* mutations from other genes in familial TAAD, in which penetrance is clearly age-related.[86]

Fundamentally, the recognition of these local proteins and the critical role of maintenance of the extracellular matrix highlights the fact that aortic disease is a very local, not global issue. Research into defective mechanosensing by these contractile elements may provide valuable insight into why the aortic wall becomes vulnerable to aneurysm and dissection.[87,88]

Clinical Manifestations

Patients with familial TAAD are seen at a younger age than those with sporadic thoracic aortic aneurysms (mean age, 58.2 vs. 65.7 years), thus suggesting a more aggressive clinical entity.[80] In familial TAAD, thoracic aneurysms are the most common

(66%), followed by AAAs (25%) and cerebral aneurysms (8% to 10%).[80] Although the ascending aorta is more commonly affected by aneurysm (82%) than by dissection (18%), an equal distribution of aortic dissections and aneurysms is observed in the descending thoracic aorta (50% each) in affected individuals.

Selection of Treatment

Selection of treatment for patients with familial TAAD is complicated by the variable penetrance and expressivity of the disorder and the lack of an established genotype-phenotype correlation. In some families, the clinical history may suggest aortic catastrophe at very minimal aortic diameter dilatation, and treatment thresholds should be considered in the context of the pedigree history. For patients with a minimal contributory family history, treatment recommendations should follow typical sporadic thresholds—of 6.0 cm for thoracic aortic aneurysms and 5.5 cm for AAAs. Thoracic aortic growth rates in familial TAAD are comparatively higher than those of sporadic aneurysms, on average 0.21 versus 0.16 cm per year, respectively.[80] Endovascular stent-grafting approaches have not been reported in familial TAAD, but as in other connective tissue diseases, concerns about the inherent weakness and fragility of the aortic wall are paramount. Consensus on stent-graft therapy for patients with familial TAAD is not available, but one should follow the previous documents advising against such approaches for connective tissue diseases.[50]

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 141

Raynaud Phenomenon

GREGORY J. LANDRY

EPIDEMIOLOGY 1859
NORMAL ARTERIAL FLOW TO THE HAND 1859
REGULATION OF BLOOD FLOW IN THE DIGITS 1859
PATHOGENESIS 1860
Vascular 1860
Impaired Vasodilatation 1860
Increased Vasoconstriction 1860
Neural Factors 1860
Humoral Factors 1861
Risk Factors 1861
Associated Diseases 1861
CLINICAL FINDINGS 1862
DIAGNOSIS 1862
Physical Examination 1863
Vascular Laboratory Evaluation 1863
Segmental Pressure Measurements and Duplex Ultrasonography 1864
Finger Systolic Blood Pressure 1864
Cold Challenge Testing 1864
Nail Fold Capillary Microscopy 1865
Serologic Evaluation 1865
TREATMENT 1865
Preventive Measures 1865
Behavioral Therapies and Maneuvers 1865
Pharmacologic Therapy 1865
Calcium-Channel Blockers 1866
Alpha Adrenergic Blockers 1866
Prostaglandins and Analogues 1866
Phosphodiesterase Inhibitors 1866
Endothelin Inhibitors 1866
Other Medications 1866
Surgical Therapy 1866
Sympathectomy 1868
Nerve Stimulation 1868
Alternative Therapies 1868

Raynaud's phenomenon (RP) was first described by Maurice Raynaud (1834–1881) in 1862 when he reported 25 patients with intermittent digital ischemia and recognized the relationship of local cold and emotional stress in the causation of the episodes.[1] Raynaud's is an exaggeration of the normal physiologic response, which is defined as episodic pallor or cyanosis of the fingers caused by vasoconstriction of small digital arteries or arterioles occurring in response to cold or emotional stress. Although this term typically applies to the fingers, the toes can also be affected. The hallmark of RP is the change in skin temperature and color brought on by exposure to cold. A typical vasospastic attack is characterized by the sudden onset of pallor of part or all of one or more digits. Cyanosis follows as static blood in the capillaries becomes desaturated. The attack subsides with the return of arterial inflow, and postischemic vasodilatation results in hyperemia and rubor of the skin (Figs. 141.1 and 141.2).

Raynaud's through the years has been described as both a disease and phenomenon. Early literature referred to Raynaud's as "Raynaud's disease" almost exclusively until the 1940s. The nomenclature "Raynaud's phenomenon" started appearing in the literature soon thereafter. People have differentiated Raynaud disease, which is primary Raynaud's, versus Raynaud phenomenon, which is secondary or associated with other diseases. This nomenclature can be confusing, as many patients who start out with primary Raynaud's will develop associated connective tissue disorders over time. We have preferred to refer to all people with this condition as having Raynaud's syndrome.

RP consists of two sub-types: primary and secondary RP. Primary Raynaud's phenomenon (PRP) is the most common and is the idiopathic form. Secondary Raynaud's phenomenon (SRP) is associated with an underlying disease process, such as systemic sclerosis, rheumatoid arthritis, or other connective tissue disease (CTDs). Primary Raynaud's is considered to be a benign process and is not associated with structural vascular change. In contrast, patients with secondary Raynaud's have some degree of fixed vascular obstruction to blood flow, which decreases the threshold for cold-induced vasospasm. This can progress to digital ulceration, scarring, or gangrene.

Figure 141.1 Palmer view of the hands of a patient with a typical example of Raynaud's phenomenon. Note that attacks of digital vasospasm cause well-demarcated pallor affecting one or more fingers brought on by exposure to cold or emotional stress.

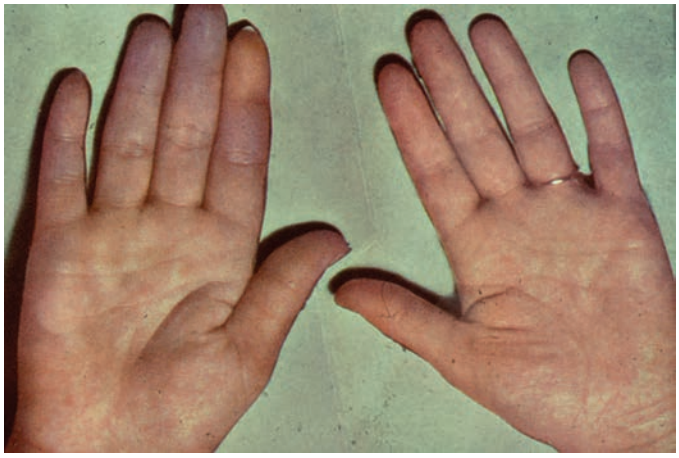

Figure 141.2 Palmer view of the hands of a patient with Raynaud's phenomenon demonstrating both pallor and cyanosis in multiple fingers.

EPIDEMIOLOGY

Prevalence of RP in the general population varies greatly with climate and ethnic origin. Several epidemiologic studies investigating disease prevalence have been performed, primarily in populations in colder climates. Overall estimates of disease prevalence in the general population range from 3.3% to 22%. Women are also more commonly affected than men, with a prevalence of 0.5% to 8.3% in men and 2.5% to 21% in women.[2-6] Two longitudinal population based studies have been performed to determine the incidence of PRP. In a 14-year study in a community in southern France, the annual incidence of new case of PRP was 0.25%.[2] In addition, similar findings were noted in the epidemiologic analysis of the Framingham off-spring study cohort. Over a 7-year period, the incidence of RP was 2.2% in women and 1.5% in men.[6]

Figure 141.3 Normal hand arterial anatomy. *1*, radial artery; *2*, Ulnar artery; *3*, deep palmer arch; *4*, common digital (metacarpal) artery; *5*, proper digital artery.

NORMAL ARTERIAL FLOW TO THE HAND

Circulation in the hand is complex with frequent anatomic variants. The deep and superficial arches supply the metacarpal arteries and in turn the proper digital arteries (Fig. 141.3). In most patients, branches of both the deep and superficial arches provide blood flow to all five fingers, and the two palmar arches provide important collateral flow between the radial and ulnar systems.[7] The superficial arch is incomplete in 21.5% of people.[8,9] Severe digital ischemia can occur with occlusion of the radial or ulnar artery and an incomplete superficial arch.

The metacarpal arteries in the palm originate from the superficial arch and provide blood flow to the digits. At the web space, the common digital (metacarpal) arteries branch to supply the proper digital arteries that run the length of each finger. In at least 86% of extremities, all five digits are supplied by arteries from both the deep and superficial arches.[7] Each finger has two digital arteries, which is important in preventing critical ischemia if one digital artery becomes occluded. The end of the finger is highly vascular with a dense network of blood vessels in the pulp of the fingers.

REGULATION OF BLOOD FLOW IN THE DIGITS

Blood flow in the digits is highly variable and can range from less than 1 mL/min per 100 L of tissue to 180 mL/min.[10] Blood flow to the skin of the digits has two functions, nutritional and thermoregulatory. Approximately 80% to 90% of blood flow through the digits is controlled by thermoregulatory mechanisms and serves an important role in controlling body temperature.[11] Blood vessels that are superficially located in the skin dilate to radiate excess heat to the environment, and this reduces body core temperature. In response to cold, these arteries constrict to decrease blood flow and conserve body heat.

Maximum vasoconstriction in response to cold occurs at 10°C to 20°C. At lower temperatures, cold-induced vasodilatation results in slight reopening of arteries to allow a trickle of blood

into the digits.[12] With cold exposure, there is a regular rhythmic fluctuation in finger flow caused by periods of vasoconstriction and vasodilatation in the fingers every 30 seconds to 2 minutes.[13] Other investigators have found similar rhythmic fluctuations in finger flow with a frequency of 5 to 10 per minute.[14] These alternating periods of vasoconstriction and dilatation have been called the hunting response.[15] This cold induced vasodilatation, which protects the fingers from freezing in a cold environment, is impaired in those with SRP because of the presence of occlusive arterial disease.

PATHOGENESIS

The exact pathogenesis of RP is unknown. Originally, Raynaud proposed that hyperactivity of the sympathetic nervous system was the cause. Lewis in 1929, disproved this theory by demonstrating that blockade of digital nerve conduction did not prevent vasospasm. Lewis in turn, theorized that "local vascular fault" in the digital arteries causing increased sensitivity of the blood vessel to cold led RP.[16] It is most likely a multifactorial problem involving a combination of vascular, neural, and humoral factors (Fig. 141.4).[17]

Vascular

Impaired Vasodilatation

Vascular endothelial cells synthesize several vasodilating and vasoconstricting substances.[18-21] Endothelial-derived relaxing factors include nitric oxide (NO), prostacyclin, adenosine triphosphate (ATP), and bradykinin. NO is a potent vasodilator synthesized from amino acid L-arginine by the activity of the enzyme NO synthase. NO diffuses from the endothelium into smooth muscle, where it activates guanylate cyclase to increase intracellular guanosine monophosphate (cGMP), which leads to vascular relaxation. Decreased NO formation can be found in patients with both systemic sclerosis and RP.[22-25] S-nitrosothiols are bioactive forms of NO that are involved in cell signaling and have been shown to be decreased in patients with systemic sclerosis and RP.[26] Additionally, decreased levels of asymmetric dimethyl-arginine, an inhibitor of endothelial NO synthase, has also been demonstrated in patients with SRP. A deficiency of one or more of these factors could potentially increase responsiveness of digital arteries to vasoconstrictive influences and increase the likelihood of vasospasm.

Endothelial dysfunction has been shown to be an important cause of RP in numerous studies. In one study, patients underwent a series of sequential infusions with acetylcholine, prostacyclin, glyceryl trinitrate, and L-arginine. Patients with a history of RP had a greater digital artery vasodilator response to intra-arterial glyceryl trinitrate (an endothelium-independent vasodilator), whereas in control patients, the difference in response was less pronounced.[27]

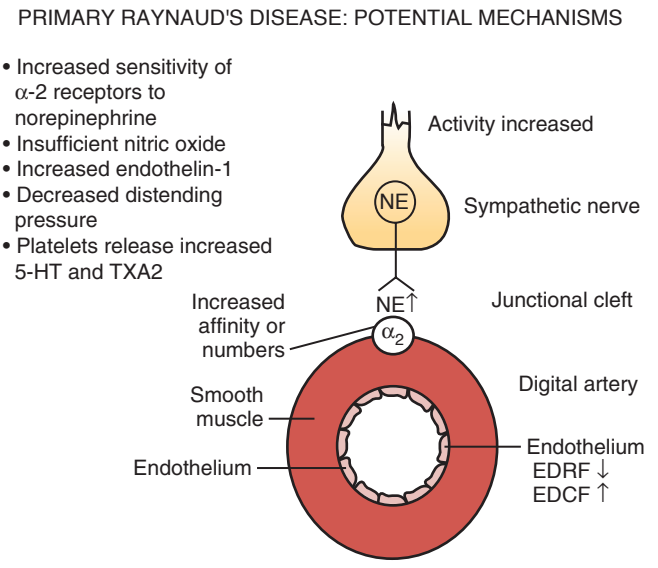

Figure 141.4 There are many potential causes of vasospastic attacks in primary Raynaud's phenomenon. Norepinephrine *(NE)* released from the sympathetic nerve ending acts on the post junctional α-2 receptor located on vascular smooth muscle. Local cooling enhances the response of the α-2 receptor, thereby causing increased arterial contraction. Endothelial dysfunction may lead to insufficient nitric oxide or increased endothelin-1, which changes the balance toward arterial constriction. Activated platelets release thromboxane A2 *(TXA2)* and serotonin (5-hydroxytryptamine *[5-HT]*), which may aggravate arterial vasospasm. A decrease in intraluminal distending pressure may decrease the "critical dosing pressure" threshold and result in a vasospastic attack. *EDCF*, Endothelium-derived contracting factor; *EDRF*, endothelium-derived relaxing factor.

Increased Vasoconstriction

The endothelial cell also produces factors that cause vessel contraction, such as endothelin-1 (ET-1), which is a potent vasoconstrictor, as well as a promoter of fibroblast and smooth muscle proliferation. Plasma ET-1 levels become elevated in response to cold, which may suggest an association between the rise in ET-1 levels and cold induced vasoconstriction.[28] A threefold rise in ET-1 concentration has been reported in subjects with PRP. However, more recent literature has challenged the relationship of ET-1 and RP. Smyth and colleagues found that increases in ET-1 levels in patient with both primary RP and scleroderma were similar to control subjects with cooling induced vasospasm.[29]

Angiotensin is another endogenous peptide with vasoconstrictive effects that has been implicated in the mechanism of vasospasm. The exact mechanism of involvement of angiotensin in RP remains unclear. Increased levels of angiotensin II have been shown in patients with scleroderma.[30] However, activation of the renin-angiotensin system has not been demonstrated in PRP.[31]

Neural Factors

More recently, the focus of RP pathophysiology has been on alterations in peripheral adrenoceptor activity. Early laboratory studies showed a marked reduction in cold-induced digital arterial vasospasm after the intra-arterial administration of reserpine.[32] This suggested that patients with RP may possess abnormal adrenergic receptors that become increasingly sensitive to stimulation after exposure to cold.

Characterization of α1- and α2-adrenoceptors has led to an improved understanding of the mechanisms of RP. Sympathetic nerves can respond to cold and emotional stress by releasing

neurotransmitters such as norepinephrine, which act on the postsynaptic α2-receptor and cause vascular smooth muscle contraction. Cold also causes increased affinity of the α2 receptor for norepinephrine, which results in enhanced smooth muscle contraction in the cold.[33-37] The initiation of the α2 adrenoceptor to cold is due to the activation of Rho-protein kinase signaling.[36,38,39]

Freedman and colleagues studied the effects of brachial artery infusions of an alpha-1, an alpha-2 antagonist, or both while vasospastic attacks were induced by cooling in 23 patients with idiopathic Raynaud's.[40] They found that in patients who were infused with yohimbine (α2 antagonist), there were significantly fewer attacks compared to the non-infused hand and compared to the group receiving prazosin (α1 antagonist) alone, demonstrating the importance of a2 adrenoceptors. However, in another randomized, controlled trial to evaluate the efficacy of a high potency α2c-adrenoceptor antagonist (ORM-12741) in patients with systemic sclerosis, subjects randomized to ORM-12741 had a longer time to temperature recovery time. These mixed results show continued investigations regarding the effect of α-adrenoceptors in the pathophysiology of Raynaud's and the therapeutic potential of adrenoceptor antagonist are needed.

Humoral Factors

Many circulating humoral factors have been implicated in the pathogenesis of RS. These include hormonal, genetic, platelet activation, and fibrinolysis. RP is more frequent in women than men and tends to be more frequent and severe between menarche and menopause. Investigators have demonstrated elevated sympathetic tone and decreased basal cutaneous circulation in women in comparison to men.[41] The role of estrogen is less clear. In human cell culture and in mouse models, estrogen has been demonstrated to increase expression of α-2 adrenoceptors.[42] Approximately one-quarter of patients with PRP have a family history of Raynaud's in a first-degree relative.[43] However, it has been difficult to differentiate genetic factors from shared environmental causes. Although a number of chromosomal regions have been evaluated in genomic studies, no significant differences in allelic frequency have been directed between patients with RP and normal controls.

Activation of platelets and increased levels of serotonin in the plasma have been detected in patients with RP.[44] Elevated circulating levels of activated platelet products, such as thromboxane and B-thromboglobulin, have been induced by cooling of subjects with RP. The relationship between serotonin elevations in the pathogenesis of RP is less clear and remains to be defined.

Abnormalities of fibrinolysis have been primarily implicated in patients with SRP, and elevated levels of tissue plasminogen activator inhibitor have been shown in patients with scleroderma.[45] Impairment in thrombolysis is also thought to predispose to fibrin deposition and vascular obstruction.[22]

Risk Factors

Many factors have been found to be associated with RP. These include genetic factors, such as gender; occupational; and drug exposure. RP predominantly affects young women, and has a male-female ratio close to 1:1.6.[46] The usual age of onset ranges from 11 to 45, while older patients with RP are more likely to have a contributing underlying arterial disease. The relationship between smoking and RP is less clear. In a study of the Framingham heart study offspring cohort, no association was found between smoking and RS in women; however, there was a significant association in men, particularly in those with other cardiovascular risk factors, with an odds ratio of 2.6.[47] Similar to smoking, the relationship between alcohol and RP remains to be clarified. A recent systematic review and meta-analysis of observational studies reported smoking as a major risk factor with an odds ratio of 1.27, while alcohol had an odds ratio of 0.33.[4]

Vibration-induced RP was first recognized in 1918 by Hamilton,[48] and it has been estimated that as many as 1.2 million American workers involved in a variety of occupations using vibrating tools are now at risk.[49] Chronic vibration appears to cause structural damage to the arterial wall with hypertrophy of the intima and media. Vibration is believed to cause sympathetic overactivity, endothelial damage, and smooth muscle hypertrophy, leading to vibration-induced vasospasm.[50-52] The prognosis may be poor because of the development of digital artery obstruction after prolonged exposure to vibration.

Several drugs have been implicated in the development of RP. For example, the incidence of RP in hypertensive patients taking beta blockers was 40% in a Scandinavian study in which patients responded to a questionnaire.[53] Vasospasm occurs with both selective and nonselective beta-blockers. Despite this, many patients with RP tolerate beta blockers, and many studies show no adverse effects on digital blood flow. Therefore, beta blockers are not contraindicated in patients with RP. Other drugs associated with RP include chemotherapeutic agents such as vinblastine and bleomycin,[54] bromocriptine, amphetamine, cocaine, and ergot preparations used for migraine headaches, which are a well-known cause of severe extremity vasospasm and ischemia.[55]

Associated Diseases

Secondary causes of RP are typically associated with some degree of fixed digital arterial obstruction. When the artery is narrowed because of preexisting large- or small-vessel disease, there is a lower "critical closing pressure," and a relatively normal vasoconstrictor response to cold or other stimuli will result in temporary closure of the vessel. RP is common in CTDs such as scleroderma, where intimal hyperplasia, thrombosis, and fibrosis result in luminal narrowing of the digital arteries, but this process may also involve the more proximal arteries of the hand and forearm.

The list of secondary causes of RP is extensive (Box 141.1). In a large series of 1,039 patients with RP referred to the Oregon Health and Science University from 1970 to 1995, more than half had primary vasospasm with no identifiable disease.[56] In those with associated abnormalities, the most common underlying disorder was CTD, which accounted for 27% of cases of RP. Scleroderma was the most likely CTD, followed

BOX 141.1 Conditions Associated With Secondary Raynaud's Phenomenon

Connective Tissue Diseases

- Progressive systemic sclerosis (scleroderma)
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Sjögren's syndrome
- Mixed connective tissue disease
- Overlap connective tissue disease
- Dermatomyositis and polymyositis
- Vasculitis (small, medium-sized vessels)

Occlusive Arterial Disease

- Atherosclerosis
- Thromboangiitis obliterans (Buerger's disease)
- Giant cell arteritis
- Arterial emboli (cardiac and peripheral)
- Thoracic outlet syndrome

Occupational Arterial Disease

- Hypothenar hammer syndrome
- Vibration induced

Drug-Induced Vasospasm

- β-Adrenergic blocking drugs
- Vasopressors
- Ergot
- Cocaine
- Amphetamines
- Vinblastine/bleomycin

Myeloproliferative and Hematologic Disease

- Polycythemia rubra vera
- Thrombocytosis
- Cold agglutinins
- Cryoglobulinemia
- Paraproteinemia

Malignancy

- Multiple myeloma
- Leukemia
- Adenocarcinoma
- Astrocytoma

Infection

- Hepatitis B and C antigenemia
- Parvovirus
- Purpura fulminans

by undifferentiated and mixed CTD. Atherosclerosis was less common, followed by "hypersensitivity angitis," Buerger's disease, cancer, and vibration-induced white finger. A wide range of cancers have been associated with SRP. The most common associated malignancies are adenocarcinomas and hematologic malignancies, and possible mechanisms of arterial disease caused by malignancy include coagulopathy, cryoglobulinemia, or small-vessel vasculitis (Fig. 141.5).

CLINICAL FINDINGS

The diagnosis of RP is made mainly by clinical findings. The typical patient describes attacks of pallor involving part or all

Figure 141.5 Paraneoplastic vasculitis with gangrene of several digits in a patient in whom small cell lung cancer was recently diagnosed. The digital ischemia improved with chemotherapy.

of one or many fingers brought on by cold exposure with full and rapid recovery on rewarming of the digits. The episodes are self-limited and may last from less than a minute to generally not more than 10 to 20 minutes. Pallor may involve part of the digit or the entire finger. Vasospastic attacks most commonly involve the fingers but can affect both the fingers and toes in up to a third of patients. For reasons that have never been clarified, the thumbs are frequently spared. Thumb involvement generally portends secondary RP.

Attacks may occur several times a day to several times a week. In addition, episodes of vasospasm are more common in the cooler winter months, and some patients have few or no attacks during the summer. Pain is not usually a feature during the pallor or cyanotic phase of PRP. The absence of pain and lack of tissue damage during arterial vasospasm may be due to concomitant cold-induced intermittent vasodilatation allowing just enough blood flow to protect the fingers from severe ischemia or freezing. Other vascular beds prone to vasospasm include coronary and cerebral vessels. Patients with Prinzmetal's angina and migraine are more likely to have RP, suggesting a common factor causing generalized vasospasm.[57]

In contrast, patients with underlying occlusive disease have little or no reserve and cannot increase digital blood flow, with the result that ischemic damage can occur during exposure to cold. Patients with SRP are more likely to complain of digital pain on rewarming of cold fingers, because the blood flow cannot increase to match the increased metabolic activity of the finger.

DIAGNOSIS

Although many tests have been used for the diagnosis of RP, no consensus exists on the optimal battery of clinical and diagnostic tests. A suggested list of criteria for the diagnosis of primary RP and differentiation of primary from SRP is as follows: (1) vasospastic attacks precipitated by cold or emotional stress, (2) attacks involving both hands, asynchronous and/or asymmetric, (3) absence of tissue necrosis or gangrene, (4) no history

or physical findings suggestive of a secondary cause, (5) normal nail fold capillaries, and (6) negative serologic findings, particularly a negative test or low titer antinuclear antibodies (ANA).[58-61]

Physical Examination

The diagnosis of RP is primarily made by history and physical examination. The physical examination in patients with suspected RP is often normal. Nonetheless, determination of primary or secondary disease is aided by a focused physical examination. The vascular examination should determine the presence of large-, medium-, or small-vessel occlusive disease and should detect signs of a CTD.

The hand and fingers should be examined for evidence of skin thinning, tightening, sclerodactyly, or telangiectasia's, all of which may suggest associated autoimmune disease (Fig. 141.6). The skin of the hand and fingers should be inspected for ulceration or hyperkeratotic areas on the fingertips suggestive of healed ulceration (Fig. 141.7). Splinter hemorrhages under the nails may be an indicator of distal atheroemboli, although this finding may be a normal finding in manual workers (Fig. 141.8).

Pulse examination should include palpation of the subclavian, brachial, radial, and ulnar arteries. However, a palpable radial or ulnar pulse at the wrist does not mean that arteries are patent into the hand. The most common site of blockage of the ulnar artery is at the hypothenar eminence where it crosses the hook of hamate. The Allen test should be performed in every patient with suspected RP to detect the presence of radial or ulnar artery occlusion and to test for completeness of the ulnar arch.

Vascular Laboratory Evaluation

The noninvasive vascular laboratory is an important adjunct to the office-based clinical assessment of patients with RP.[62] Vascular laboratory testing can assist in differentiating between fixed arterial obstruction and pure vasospasm and can provide assessment of the location and severity of the circulatory impairment. However, the diagnosis of RP should not be made based on any laboratory test,[63] and the vascular laboratory should not take the place of a good history and physical examination.[7]

The most useful noninvasive laboratory tests for RS include room-temperature evaluation of arm, hand, and digital arterial perfusion, supplemented by measurement of digital temperature, systolic blood pressure, and laser Doppler flow of the fingers before and after local digital cooling.

Figure 141.6 Raynaud's phenomenon secondary to limited systemic sclerosis in a young male patient. Cyanotic discoloration is apparent on the left second and third fingers, and the diagnosis of scleroderma can be made by physical examination. There is resorption with healed ulcerations of several fingertips.

Figure 141.7 Advanced scleroderma with flexion contracture of the fingers and ulceration of multiple fingertips. Even with the best wound care, these ulcers can be difficult to heal.

Figure 141.8 Splinter hemorrhages under the nails may be a normal finding with local trauma but can also be an important indicator of distal atheroembolism, as seen in the patient. Note the splinter hemorrhages under the nail and subtle skin mottling consistent with microembolization.

Segmental Pressure Measurements and Duplex Ultrasonography

To evaluate for large-vessel occlusive arterial disease, segmental blood pressure measurements in the upper extremity can be obtained. Pneumatic cuffs are placed on the brachial, upper elbow, and wrist levels, and systolic blood pressure is measured. A pressure differential exceeding 10 mm Hg between levels may be significant and indicative of proximal occlusive disease.

Duplex scanning is useful for evaluation of proximal upper extremity arterial obstruction and aneurysmal disease. Traditionally, its role in the diagnosis of RP has been limited; however, power Doppler has emerged as a means of evaluating the digital arteries for the diagnosis of RP. Lee and colleagues compared power Doppler with a 10-MHz scan head focused at 5 mm with nail fold capillaroscopy for the diagnosis of primary and secondary RP.[64] The investigators could correctly diagnose RP in all cases and were able to correctly classify patients as having primary or secondary RP in 89% of cases.

Finger Systolic Blood Pressure

Finger systolic pressure is measured by applying small digital cuffs to the proximal part of the finger. The cuff is inflated above systolic blood pressure to occlude the digital artery. As the cuff is slowly deflated, the pulse returns to the distal part of the finger, and systolic blood pressure can be assessed by pulse-volume recording, strain-gauge plethysmography, or photo-plethysmography.[65,66] Decreased systolic pressure usually indicates fixed arterial occlusive disease in that finger; however, the range of normal digital pressure is variable and is influenced by temperature. A difference of more than 15 mm Hg between fingers or an absolute finger systolic blood pressure of less than 70 mm Hg may indicate occlusive disease.[67]

Evaluation of digital plethysmographic waveforms is also useful, particularly identifying obstructive RP. For example, patients with obstructive RP have blunted waveforms, whereas patients with vasospastic RP have either normal waveforms or a "peaked pulse." The peaked pulse pattern, first described by Sumner and Strandness, appears to reflect increased vasospastic arterial resistance (Fig. 141.9A and B).[68]

Cold Challenge Testing

The first vascular laboratory test used widely for the objective diagnosis of RP was the measurement of recovery in fingertip temperature after digital exposure to ice water.[69] There are many variations of the cold immersion test with various immersion times and temperatures. Baseline digital temperatures are recorded with a temperature probe at the end of the finger pulp. The hands are then immersed in cold water at 4°C for 20 seconds. The hands are dried, and digital skin temperature is recorded for each finger as the hands and fingers gradually warm to ambient room temperature. The length of time that it takes for the hands to rewarm to baseline is noted by recording finger temperatures or laser Doppler flux at 5-minute intervals until recovery of pre-immersion temperatures. A delay in rewarming suggests a tendency for vasospasm. Patients with RP typically take more than 10 minutes and sometimes 30 minutes or longer. However, although the ice water immersion test is 100% specific, it is only 50% sensitive and therefore is neither sufficiently accurate nor reproducible for routine clinical use.[70,71]

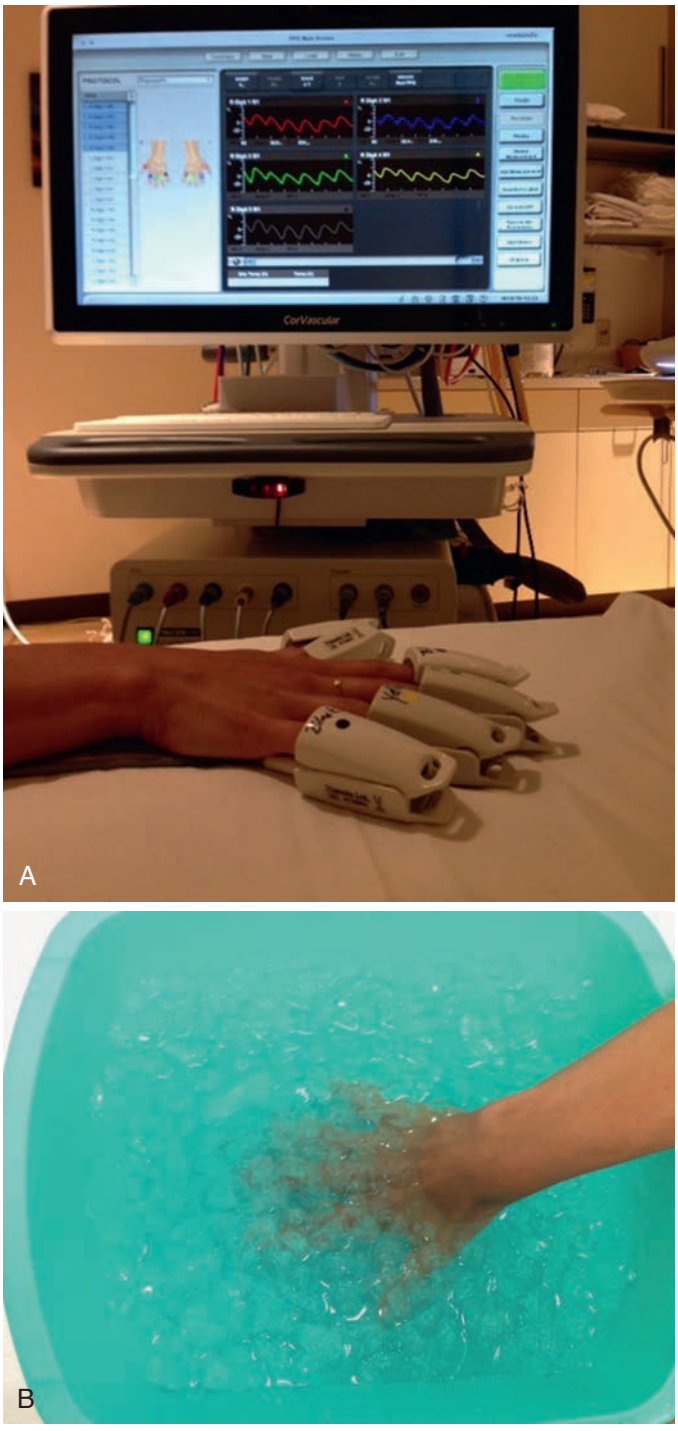

Figure 141.9 (A and B) Photoplethysmogram (PPG) may be completed as part of the work up for Raynaud's phenomenon. PPG's may be combined with a cold challenge. When completed together, a room temperature PPG is done, followed by submersion of the hands in ice cold water for 1 minute or as long as tolerated, then PPG's are done and recorded every minute thereafter until recovery is complete.

Nail Fold Capillary Microscopy

The superficial capillaries in the nail fold can be visualized with a low powered microscope or an ophthalmoscope at 40 diopters by applying a drop of immersion oil over the cuticle of the finger to make it translucent. Normal capillaries are seen as regularly spaced hairpin loops with a venous limb and an arterial limb. The arterial limb has a narrower diameter with more rapid flow, and the venous limb has a larger diameter with slower capillary flow.[7]

Abnormal capillaries are seen in scleroderma and mixed CTDs as enlarged, tortuous, and deformed or as loop dropout causing avascular areas.[72,73] The presence of abnormal nail folds in patients without CTD is a strong predictor of the subsequent development of CTD. With a mean follow-up of 6.5 years, Meli and colleagues demonstrated that 80% of patients with abnormal nail fold findings at the time of initial diagnosis of RS eventually developed CTD, primarily scleroderma, CREST, and mixed CTD. Thus, there may be significant prognostic utility in the use of nail fold capillaroscopy in the early phases of RS.[74]

Figure 141.10 A vascular mitten protects and maintains warmth of the hands. Patients with critical hand and finger ischemia can have further compromise in distal perfusion because of cool ambient room temperature causing vasoconstriction. A vascular mitten keeps the hands at body temperature and maximizes distal finger blood flow by avoiding cold-induced vasoconstriction.

Serologic Evaluation

Serologic studies may help confirm the diagnosis of CTD and are useful in screening for occult underlying CTD. Several screening tests can be done, and the most useful include ANA and rheumatoid factor (RF). ANA is present in 95% of patients with systemic sclerosis,[75] but they are not specific for scleroderma and can be present in several other CTDs. A positive ANA raises the suspicion for CTD but does not make the diagnosis. RF is a commonly used diagnostic marker for rheumatoid arthritis.[76]

TREATMENT

Treatment for RP varies greatly, and the natural history differs greatly between primary vasospastic and secondary obstructive causes. The approach to therapy must be individualized according to the patient's symptoms, the frequency of vasospastic attacks, the underlying disease, and the risk for development of ischemic ulceration, gangrene, or digital loss. For most patients with primary RP, there is no cure; however, several simple measures can be effective in reducing the frequency and duration of attacks.

Preventive measures consisting of education, reassurance, and avoidance of exposure to cold constitute the basis for most patients. Management principles can generally be considered in three groups: nonpharmacologic behavioral therapy, pharmacologic treatment, and interventional-surgical procedures. Connective tissue disorders associated with SRP are frequently managed with immunosuppression or immunomodulation.

Preventive Measures

Most patients with primary RP have only mild symptoms that do not require the use of vasodilatory medications. Primary RP is a benign disease, with few patients progressing to digital ulcers or tissue loss. In a longitudinal study from Oregon, digital ulcers occurred in 5% of patients in whom vasospastic RP was initially diagnosed when observed for more than 10 years.[56] These patients are best managed with a conservative program involving preventive measures, and education and reassurance is the mainstay of therapy.

Simple measures to maintain warmth and avoid cold are effective (Fig. 141.10). Ceramic-impregnated gloves that absorb ambient infrared light to generate heat resulted in significantly improved hand function and visual analog pain scores when compared with a placebo group wearing cotton gloves.[77] Situations likely to cause vasospasm should be avoided or minimized. Finally, avoiding agents that cause vasoconstriction, such as nicotine and vasoconstricting medications, is also an important aspect of therapy.[78,79]

Behavioral Therapies and Maneuvers

Temperature biofeedback is a type of mind/body therapy whereby patients are taught methods of self-regulation of skin temperature.[80] The primary goal is to teach methods of avoiding RP attacks; however, with training, individuals can learn to reverse the existing vasospasm. Temperature biofeedback has been studied in randomized trials with variable results. A recent meta-analysis suggests that biofeedback is not superior to placebo.[81] However, they also concluded that the literature is inconclusive, and more robust trials are needed to further evaluate complementary and alternative therapies.

Pharmacologic Therapy

Pharmacologic therapy is indicated in patients who have failed conservative therapy. Some patients will require medications only during the colder winter months. The goal of pharmacologic therapy is to decrease the frequency and severity of attacks

rather than cure the underlying disease, and medications may be useful for both primary and secondary RP. However, patients with secondary RP often have fixed obstructive arterial disease, and vasodilators are less effective or at times have no benefit at all.

A number of medications have been used for RP (Table 141.1). Choosing the best medication is difficult given the lack of large prospective, randomized, double-blind studies comparing the efficacy of different medications. There is also a significant placebo effect in published clinical trials ranging from 20% to 40%,[82] which needs to be considered when interpreting the results of uncontrolled trials. Additionally, most clinical trials rely on the patient's self-assessment of the frequency and severity of RP.

Calcium-Channel Blockers

Calcium-channel blockers are the most extensively researched medications and remain first-line therapy for RP. Nifedipine is considered by many to be the drug of first choice for RP. One multicenter, randomized controlled trial of 313 patients with primary RP treated with sustained-release nifedipine compared with placebo showed a 66% reduction in frequency in attacks.[83] In addition, a meta-analysis of 12 randomized, controlled trials demonstrated an overall reduction in severity of attacks graded on visual analog scale of 33%, with an average of 2.8 to 5.0 fever attacks per week in patients treated with nifedipine.[84] However, a recent Cochrane review found only moderate quality evidence showing that oral calcium channel blockers are minimally effective in the treatment of PRP as measured by frequency of attacks. Participants experienced 1.72 fewer attacks per week on calcium channel blockers compared to placebo,[85] but other calcium channel blockers may be used. Drugs in the dihydropyridine class are more potent vasodilators than the nondihydropyridine class, but they are more frequently associated with side effects.

Alpha Adrenergic Blockers

Sympathetic nerve simulation results in norepinephrine release, which acts on the α1 receptor located on vascular smooth muscle, causing vasoconstriction. This action is completely inhibited by α1-selective blockers. Prazosin is a selective α1 adrenergic antagonist that significantly reduces the number of attacks in both primary and secondary RP.[86] In a double-blind, placebo-controlled, crossover study of 24 patients, prazosin was reported superior to placebo in the treatment of RP. In contrast, the results for α-2 antagonist have been mixed. OPC-28326, a selective α2-antagonist, improved skin temperature recovery in patients with scleroderma compared to placebo.[87] However, more recently, ORM-12741, a α2c-adrenoceptor antagonist, was found to increase skin temperature recovery time.[88]

Prostaglandins and Analogues

Prostacyclins are vasodilators that have been used to treat critical digital ischemia secondary to fixed occlusive disease. Iloprost is a prostacyclin analogue reported to reduce the severity, frequency, and duration of RP attacks and promote healing of ischemic ulcers. Intravenous iloprost was directly compared with oral nifedipine in two randomized controlled trials. Forty-six patients with systemic sclerosis were randomized in one and 12 patients with systemic sclerosis in the other. Although medication regimen differed, both showed reduced mean number, duration, severity of RP attacks, and improved ulcer healing.[89,90] Hand temperature and blood flow increased with iloprost but not nifedipine.[89]

Phosphodiesterase Inhibitors

The phosphodiesterase type 5 (PDE5) inhibitors are selective inhibitors of cGMP-specific PDE5, which increase cGMP, resulting in enhanced cGMP-dependent micro- and macrovascular dilatation. In a placebo-controlled, double blind crossover trial comparing 4 weeks of therapy with sildenafil, 50 mg twice daily, versus placebo in 16 patients, the frequency of RP attacks was reduced by 33%, and the duration of attacks were reduced by 44% in the sildenafil group. Tadalafil and vardenafil have longer half-lives than sildenafil but have been less well studied in RP. Tadalafil has been shown to be efficacious in case series and small open-label pilot studies, randomized trials using tadalafil as monotherapy have not shown significant benefits in patients with SRP.[91] However, as combination therapy with other vasodilators, tadalafil use resulted in improved frequency and duration of attacks and ulcer healing.[92]

Endothelin Inhibitors

Endothelin is a potent endogenous vasoconstrictor. Bosentan is an endothelin receptor antagonist currently used to treat pulmonary hypertension. In the RAPIDS-2 trial, bosentan was shown to significantly decrease the incidence of new digital ulcers in patients with scleroderma, although there was no change in rates of ulcer healing, in pain, or in disability.[93]

Other Medications

Numerous other medications have been used in the treatment of RP with various results. Nitrates have been used in the treatment of RP as oral, topical, or intravenous preparations, but, in general, they are not first-line therapy. All forms are limited by side effects, particularly headaches and hypotension.

ACE inhibitors, angiotensin II receptor blockers, and serotonin reuptake inhibitors have all been used to treat RP. Captopril has been the most extensively used ACE inhibitor. A randomized controlled crossover trial of 15 subjects with primary RP, captopril caused a significant increase in cutaneous blood flow, but there was no change in frequency or severity of RP attacks.[94] Losartan, a angiotensin II receptor blocker, was found to be more effective than nifedipine in reducing the frequency and severity of vasospastic episodes in a randomized controlled trial in patients with PRP and those with SRP due to systemic sclerosis following 12 weeks of therapy.[95] Fluoxetine, a serotonin reuptake inhibitor, was shown to reduce the frequency and severity of attacks in both primary and secondary RP in a randomized cross-over trial with nifedipine (Fig. 141.11).[96]

Surgical Therapy

Surgical intervention tends to be reserved for patients who have failed conservative and pharmacologic therapy. Surgical therapies

TABLE 141.1 Medical Therapy for Raynaud's Phenomenon

Drug Class	Drug Names	Dosage	Results	Most Frequent Side Effects
Calcium channel blockers (dihydropyridine)	Nifedipine	10-30 mg PO qd-tid	33%-66% reduction in frequency and severity of attacks; most extensively studied medication	Hypotension, flushing, edema, palpitations, dizziness (similar for entire class of drugs)
	Nicardipine	20-50 mg PO bid	Mixed results compared with placebo	
	Amlodipine	10 mg PO qd	27% reduction in frequency of attacks	
	Felodipine	5-20 mg PO qd	Similar to nifedipine	
	Nisoldipine	5-10 mg PO qd	Mixed results improving severity and frequency of attacks	
Calcium channel blockers (non-dihydropyridine)	Diltiazem	30-120 mg PO tid	Some improvement but less efficacious than dihydropyridine class	Fewer side effects than dihydropyridine class
	Verapamil		No proven benefit	
Alpha 1 receptor antagonists	Prazosin	1 mg PO tid	1-2 fewer attacks per day, decreased duration; modest benefit in secondary RP	
	Terazosin	1 mg PO qhs	Not systematically studied	Orthostatic hypotension; palpitations
	Doxazosin	1 mg PO qhs		
Renin-angiotensin system mediators (ACE inhibitors)	Captopril	12.5-25 mg PO bid-tid	Improved finger blood flow; symptom relief mixed	Dry cough, headaches, fatigue, dizziness (similar for entire drug class)
	Enalopril	20 mg PO qd	Mixed results in clinical trials	
	Quinapril	80 mg PO qd	No clinical benefit	
Renin-angiotensin system mediators (angiotensin II receptor blockers)	Losartan	12.5-50 mg PO qd	Up to 50% reduction in severity and frequency of attacks	Dizziness
Serotonin reuptake inhibitors	Fluoxetine	20-40 mg PO qd	Significant decrease in severity and frequency of attacks vs. nifedipine	Headaches, nausea, palpitations, lethargy
Phosphodiesterase V inhibitors	Sildenafil	50 mg PO qd-bid Extended release 100-200 mg qd	Decreased duration and frequency of attacks; improvement of capillary blood flow; benefit primarily in secondary RP	Headache, flushing, nausea, muscle pain, dyspepsia, dizziness (similar for all drugs in this class)
	Tadalafil	20 mg every other day	Decreased frequency and duration of attacks and improved ulcer healing as add on therapy; less beneficial as monotherapy	
	Vardenafil	10 mg PO bid	Improved digital blood flow and symptoms in secondary RP	
Nitrates	Topical nitroglycerin (MQX-503)	0.5 gm of gel up to four times a day	Improved Raynaud Condition Score, no change in duration or frequency of attacks	Headache, upper respiratory tract infection; dizziness
Prostaglandins	Epoprostenol	1-2 ng/kg/min IV	Decreased severity of symptoms in patients with scleroderma and pulmonary hypertension	Flushing, headache, nausea, vomiting, hypotension
	Iloprost	0.5-2 ng/kg/min IV or 50 µm PO bid	IV form effective in ulcer healing and reducing symptoms; PO form not more effective than placebo	Headache, nausea, vomiting
Endothelin receptor antagonist	Bosentan	62.5 mg PO bid	Decreased new ulcer formation in patients with scleroderma. No effect on healing of existing ulcers	Elevated hepatic transaminases, peripheral edema

ACE, Angiotensin-converting enzyme; *bid*, twice a day; *IV*, intravenous; *PO*, orally; *qd*, once a day; *qhs*, every evening; *tid*, three times a day.
From Landry G. Current medical and surgical management of Raynaud's syndrome. *J Vasc Surg*. 2013;57:1710–1716.

Figure 141.11 This patient was evaluated for acute ischemia of the fingertip. She was found to have positive antinuclear antibody and anticentromere antibody. An angiogram showed severe digital artery occlusive disease consistent with a connective tissue disease. Topical nitroglycerin ointment often fails to improve blood flow in the setting of critical ischemia because of severe underlying fixed small-vessel disease. The patient was treated with multiple agents, including oral, topical, and intravenous vasodilators; antiplatelet therapy; doxazosin; and nifedipine.

TABLE 141.2 Surgical and Other Invasive Therapy for Raynaud's Phenomenon

Invasive Therapy	Results
Botulinum Toxin	Improved pain and ulcer healing in small case series
Sympathetic block	Improved ulcer healing in small case series
Thoracoscopic symphathectomy	High recurrence rate in primary RP; improved ulcer healing and pain control in selected patients with secondary RP
Digital sympathectomy	Anecdotal reports of improved pain and ulcer healing
Spinal cord stimulators	Reduced pain and improved ulcer healing in small case series

RP, Raynaud's phenomenon.
From Landry G. Current medical and surgical management of Raynaud's syndrome. *J Vasc Surg*. 2013;57:1710–1716.

include botulinum toxin injection, sympathetic block, thoracoscopic sympathectomy, digital sympathectomy, and spinal cord stimulator (Table 141.2). Local debridement of dead tissue or removal of the fingernail is sometimes necessary. Partial or complete phalangectomy may be necessary in 10% to 20% of patients with digital ulcers or gangrene.

Sympathectomy

Sympathectomy is rarely if ever indicated in patients with primary RP, in which recurrence rates are high, but it may be effective in some patients who have critical ischemia of the digits. The evidence regarding thoracic sympathectomy was summarized by Coveliers and associates,[97] who found thoracic sympathectomy, may maximize tissue preservation or prevent amputation. Currently, thoracoscopic sympathectomy has supplanted open cervicothoracic sympathectomy as a technique of choice. Coveliers, more recently, showed moderate long-term efficacy of thoracoscopic sympathectomy in thirty-five patients with both PRP and secondary systemic disorders.[98]

More favorable results have been seen in lumbar sympathectomy, with long-term symptomatic relief noted in more than 90% of patients undergoing this procedure.[99] Lumbar sympathectomy remains a viable option in the rare patient with severely symptomatic lower extremity vasospasm.

Adventitial stripping of hand and digital arteries has been successful in healing ulcers and improving ischemic pain.[100,101] Results are anecdotal with no controlled trials comparing digital arterial sympathectomy with other less invasive treatment modalities, and in general, arterial sympathectomy should be reserved for refractory cases with risk for tissue loss.

Botulinum toxin is a commonly used medication that primarily inhibits muscle contraction. Botulinum toxin-A (BoNT-A) is injected into the interstitial space around the digital neurovascular bundles causing a chemical sympathectomy. Recently, increased use of botulinum toxin in the treatment of RP has been reported. A recent review of current literature found that BoNT-A injection is a valid therapeutic modality for both primary and secondary RP. It has been shown to reduce pain, promote ulcer healing, and increase blood flow.[102,103] More robust evidence is needed, but thus far, the limited evidence available is encouraging.

Nerve Stimulation

Transcutaneous nerve stimulation has been used in some patients to induce vasodilatation with varying results.[104] In addition, spinal cord stimulators are occasionally indicated for the treatment of various intractable pain syndromes of the upper extremities. A spinal cord stimulator may reduce pain and promote ulcer healing in severe cases of secondary RP with trophic lesions.

Alternative Therapies

Acupuncture may be of benefit in some patients. In a small, randomized trial, acupuncture was found to be effective in reducing the frequency and severity of attacks in patients with PRP. The mechanism of action is believed to be stimulation of sensory nerves, causing release of vasodilators such as substance P and calcitonin gene-related peptide.[105]

Seredine, a high-potency extract of Ginkgo biloba, has had mixed results in the treatment of PRP. A randomized placebo-controlled trial in patients with PRP showed a 56% drop in event rates in the group treated with ginkgo compared to placebo.[106] However, more recently, a placebo-controlled, double-blind, pilot study of 41 patients randomized to either ginkgo biloba special extract EGb 761 versus placebo for 10 weeks found no statistically significant reduction in clinically relevant symptoms.[107]

Fish oil and arginine have also been investigated. Fish oil failed to demonstrate any benefit in patients with SRP in a

small controlled trial.[108] Arginine, which is a substrate for NO synthesis and has a theoretical benefit of improving endothelial dysfunction, has failed to show benefit in patients with both primary and secondary RP.[109,110]

Laser therapy has been investigated as a potential treatment for a variety of vascular and rheumatologic disorders including RP. A randomized controlled trial evaluated low-level laser therapy with 685-nm wavelength diode laser versus sham in forty-eight patients with PRP.[111] They found the frequency and intensity of RP attacks were significantly reduced in the laser treated group. More recently, a group in Poland studied the effects of multiwave locked system (MLS) laser therapy on clinical features, microvascular changes in nailfold videocapillaroscopy (NVC), and circulating modulators, such as vascular endothelial growth factor (VEGF), and angiopoietin 2 (Ang-2) in patients with primary and secondary RP.[112] All patients with RP received MLS laser irradiation for 3 weeks. After 3 weeks, patients with RP reported a decrease in the number, mean duration, and pain intensity of attacks. In addition, 65% of patient with primary and 35% of patient with secondary RP were noted to have an increase in the loop number and/or a reduction in avascular areas in NVC. Patients with RP had higher levels of both VEGF, and Ang-2 compared to matched controls prior to laser therapy; however, post therapy Ang-2 levels were found to be reduced in patients with RP. The authors concluded that Ang-2 may be a useful marker of microvascular abnormalities in RP patients treated with laser therapy.

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CHAPTER 142

Fibromuscular Dysplasia

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INTRODUCTION

Fibromuscular dysplasia (FMD) is a nonatheromatous, noninflammatory, proliferative process first described in 1938 as a rare cause of renovascular hypertension with a "string-of-beads" appearance. The pathogenesis is still unknown, but up to 10% of cases are familial. Its principal pathologic form involves primarily the media; it affects long, unbranched segments of medium-sized conduit arteries such as the renal artery and the internal carotid artery but has been observed in almost every artery in the body (Table 142.1).[1,2]

FMD occurs most frequently (>90%) in women between 20 and 60 years of age but may also be seen in men, older persons, or pediatric individuals. Although many clinicians believe that FMD is a rare disease, its prevalence in the general population is not known. There is evidence to suggest that FMD may be more common than previously thought.[3]

Abstract

Fibromuscular dysplasia (FMD) is a nonatheromatous, noninflammatory proliferative process affecting long unbranched segments of medium-sized conduit arteries such as the renal artery and the internal carotid artery; however, it has been observed in almost every artery in the body. It typically affects women. The clinical manifestations involve the spectrum of arterial obstruction and/or aneurysmal degeneration and depend on the arterial bed involved. Based on angiographic criteria, it can be be multifocal, characterized by the "string-of-beads" appearance, or focal, with a single area of stenosis. FMD is the second most frequent cause of renal artery stenosis after atherosclerosis and the most common cause of renal hypertension in young individuals. Carotid FMD is less frequent and may most often be related to cerebrovascular symptoms, although it remains asymptomatic and has a benign natural history. Treatment options can be medical/conservative, endovascular, and/or surgical depending on the patient's comorbidities and the severity and anatomy of the lesions.

Keywords

carotid stenosis
fibromuscular dysplasia
renal artery stenosis
string of beads

TABLE 142.1 Arterial Involvement in Fibromuscular Dysplasia Based on the US Registry for Fibromuscular Dysplasia

Arteries Involved	Number of Investigated Arteries in the US Registry[a]	Frequency of Involvement (%)[b]
Total number in US Registry	447	
Renal arteries	369	80 (75–89)
Bilateral renal arteries		(23–65)
Unilateral Renal Artery—Localization		
Right renal artery		(66–81)
Left renal artery		(19–34)
Other Arteries		
Carotid artery	338	74 (3–74)
Vertebral artery	224	37
Aorta	145	0
Lower extremity arteries	70	60
Mesenteric arteries	198	26
Coronary arteries	447	7
Upper extremity arteries	63	16
Intracranial carotid arteries	206	17
Multiple vascular involvement		35 (8–35)

[a]Data from Olin JW, et al. The United States Registry for Fibromuscular Dysplasia: results in the first 447 patients. *Circulation.* 2012;125:3182-3190.
[b]Data shown in parentheses are based on results in various published studies.

Although FMD is a systemic process, it is usually described in terms of the artery in which it occurs; its principal clinical manifestations involve the spectrum of arterial obstruction and/or aneurysmal degeneration and depend on the arterial bed involved: the renal arteries are often associated with hypertension and the extracranial carotid or vertebral arteries with headache (migraine-type), pulsatile tinnitus, transient ischemic attack (TIA), or stroke.[3-6]

PATHOGENESIS OF FIBROMUSCULAR DYSPLASIA

Etiology

Several theories have been proposed as to the etiology of FMD, including environmental and genetic factors, each with partial supporting evidence.

The fact that FMD is more common among women suggests that hormonal factors may be important. Of the 57 women in one study, 9, or 16%, had a previous diagnosis of hypertension during pregnancy, compared with 4% to 5% of pregnancies affected by hypertension in the general population.[7] The number of pregnancies and the frequency of oral contraceptive use or hormonal therapy did not differ between patients with FMD and the general population, however.[8]

Vessel wall ischemia may also be important for the development of FMD. The vasa vasorum of muscular arteries, which supply oxygen and nutrients to the arterial wall, originate from branch points of the parent arteries. Occlusion of the vasa vasorum induces the formation of dysplastic lesions in animal studies.[8] The vessels most commonly affected by FMD—such as the renal, internal carotid, and vertebral arteries—have long segments that lack branches and thus have fewer vasa vasorum. These arteries are subjected to repeated stretching during motion and respiration, which may injure the sparse vasa vasorum, causing arterial wall ischemia and subsequent development of FMD. This hypothesis is supported by the observation that FMD is more common in the right renal artery,[9] which is longer than the left. Its greater length makes the right kidney more susceptible to renal ptosis, which is also common among patients with renal FMD.[10] Vasospasm in the vessel wall might also induce ischemia in the vasa vasorum, and cases of FMD combined with Raynaud disease have been reported.[11] In vitro studies have also demonstrated increased production of collagen, hyaluronan, and chondroitin sulfate in arteries exposed to cyclic stretching.[12] Mural ischemia due to functional defects in the vasa vasorum, possibly in association with developmental renal malposition, has also been postulated as a cause of FMD.[13] However, these theories do not explain the gender difference.

FMD is associated with cigarette smoking. The prevalence of smoking is higher among patients with FMD than in matched controls, and patients with FMD who smoke have more severe arterial disease than nonsmokers.[14] In the US Registry for Fibromuscular Dysplasia, 37% of patients were current or former smokers compared with 18% reported for US women.[15] The mechanisms by which smoking contributes to FMD have not been elucidated.

The occurrence of renal FMD in siblings and identical twins suggests possible inheritance of the disease.[16] Rushton suggested that FMD is transmitted in an autosomal dominant manner, with incomplete penetrance and variable clinical symptoms.[17] A French study of renal FMD showed that 11% of patients had at least one sibling with renal FMD.[18] The US Registry study reported a 7% incidence in relatives; however, it also reported that stroke (54%), aneurysm (24%), and sudden death (20%) were common in first- or second-degree relatives.[15] The presence of FMD can be easily overlooked in relatives because it may be associated with only mild hypertension or may be asymptomatic. Subclinical dysplasia of the carotid artery also occurs in patients with renal FMD, in accordance with a possible autosomal dominant transmission.[19]

Associations with polymorphisms in the angiotensin-converting enzyme (ACE) insertion allele ACE-I have been reported, and an autoimmune origin of FMD has been suggested by genetic associations with HLA-Drw6.[20] Currently several groups are trying to delineate further gene patterns predisposing individuals for the development of FMD.[21]

FMD might coexist with other diseases of the vessel wall and endocrine system. Ehlers-Danlos syndrome type IV has been associated with medial fibroplasias and should be suspected in patients with multiple aneurysms and FMD.[22] FMD has also been reported in association with pheochromocytoma, Marfan syndrome, Alport syndrome, and Takayasu arteritis.[23-25]

Differential Diagnosis

Important differential diagnoses for FMD are type 1 neurofibromatosis, vascular Ehlers-Danlos syndrome, Williams syndrome, and vasculitis.[23,26] The diagnoses of these conditions rely on associated phenotypic traits: characteristic skin lesions in type 1 neurofibromatosis[27]; acrogeric dysmorphism, skin elasticity, and distal joint laxity in vascular Ehlers-Danlos syndrome[28]; and facial dysmorphism, supra-aortic stenosis, and particular behavior in Williams syndrome.[29] Genetic tests can also be used to rule out these conditions as alternative diagnoses.

Because FMD is a noninflammatory process, it is not associated with anemia, thrombocytopenia, or the increased acute-phase reactants that often occur in patients with vasculitis. Large-vessel vasculitis sometimes occurs in the absence of changes in acute-phase reactants, however. It might therefore be difficult to distinguish FMD from inflammatory vessel disease in the absence of tissue samples and without laboratory markers confirming inflammation.

Classification

Traditionally a histopathologic scheme was used to classify FMD, but in the current era fewer patients are undergoing surgical procedures to obtain specimens. The classification now uses an angiographic systems, the most common of which is the American Heart Association system adopted in 2014 that distinguishes between multifocal, characterized by the string-of-beads appearance, and focal FMD, with a single area of stenosis.[6] Unifocal FMD has less female predominance, is diagnosed in younger individuals, and is treated with better short- and long-term results than multifocal FMD.[30] This classification has not been applied to FMD in children.

The histopathologic scheme classified FMD into three categories related to the pathologic layer of the arterial wall affected— fibroplasia of the intima, media, or adventitia (periarterial fibroplasia) (Table 142.2; Figs. 142.1–142.4). FMD

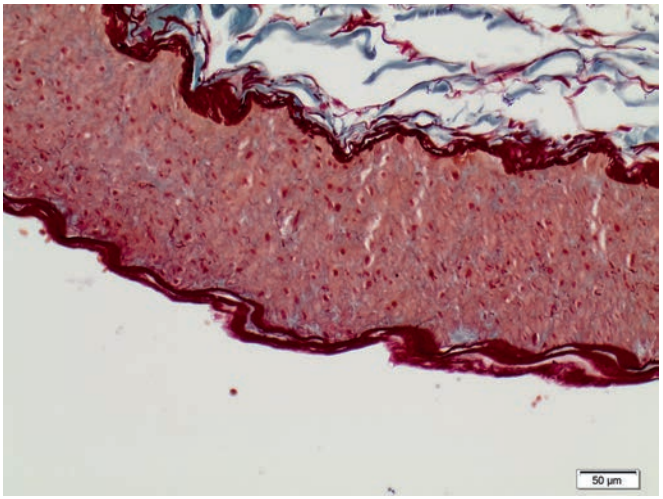

Figure 142.1 Normal renal artery with distinct wall layers. (Courtesy J Malina Department of Pathology, Malmö, Sweden.)

TABLE 142.2 Classification of Dysplasias

Classification	Gender/Age	Cases (%)	Pathologic Features	Angiographic Appearance
Intimal fibroplasia	Often young; no gender difference	5–10	Collagen deposition within the intima internal elastic lamina may be disrupted	Unifocal—Ring-like focal stenosis or a long, irregular tubular stenosis
Medial Dysplasias				
Medial fibroplasia	Adolescents and females 20–70 years of age; female-to-male ratio 5–9:1	80	Areas of thinned media alternating with thickened fibromuscular ridges containing collagen Advanced medial dysplasia, especially in children, also shows secondary intimal hyperplasia (see Figs. 142.1 and 142.2)	Multifocal—"String of beads" appearance, with the "bead" larger than the proximal vessel Normally involves distal two-thirds of main renal artery but can also extend into branches (25%) (see Fig. 142.3)
Perimedial fibroplasia	Young girls and women up to 50 years of age	1–5	Patchy collagen deposition between media and adventitia External elastic lamina intact	Multifocal or unifocal—Can also result in "string of beads" appearance, but diameter of "beads" does not exceed diameter of proximal artery (see Fig. 142.4)
Adventitial fibroplasia	No gender difference	<1	Dense collagen replaces normally loose connective tissue of adventitia and may extend into surrounding tissue	Unifocal—Long stenosis

affecting the media is by far the most common type and is further subdivided into medial fibroplasia, perimedial fibroplasia, and medial hyperplasia. Although this classification was initially proposed for the renal arteries, it is also applicable to other arterial beds and has been angiographically correlated with FMD elsewhere. Complications of arterial dysplasia—such as aneurysm formation (in 17% of patients with FMD, one-third in the renal artery) and dissection (in 20% of patients with FMD, more common in carotid and vertebral arteries, one-fifth in the renal artery)[15]—should be classified as secondary events and differentiated from primary dysplastic lesions.

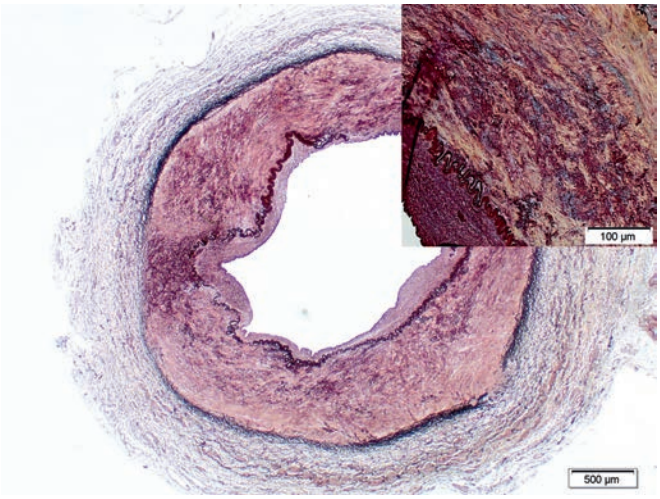

Figure 142.2 Medial fibrodysplasia with dense fibrous connective tissue in the outer media and disordered inner medial smooth muscle. (Courtesy J Malina, Department of Pathology, Malmö, Sweden.)

RENAL ARTERY FIBROMUSCULAR DYSPLASIA

FMD is the second most frequent cause of renal artery stenosis (RAS), after atherosclerosis, and the most common cause of renal hypertension in young individuals, predominantly Caucasian women in their 20s to 40s with normal kidney function.

Epidemiology

Symptomatic fibrodysplastic RAS occurs in 0.4% of the population,[3] but the prevalence of asymptomatic FMD in potential renal donors is around 4%.[19,31-33] The true prevalence is difficult to ascertain because there are no easily applicable screening tests. FMD is most often diagnosed in patients 15 to 70 years of age but it has been reported from infancy to age 89.[1,15,34,35] The medial type of FMD is most common and is more than four times more prevalent in females than in males.[15,19,31] In contrast, the less common intimal type is more prevalent in men.[18,19] Lesions may be bilateral, but in unilateral disease the right renal artery is affected more often than the left.

FMD is more likely to manifest in patients with treatment-resistant or malignant hypertension than in the general hypertensive population and accounts for up to 10% of all cases of renovascular hypertension[36-39]; the remaining cases of renovascular hypertension are caused mainly by atherosclerosis. Compared with patients with atherosclerotic RAS, patients with FMD are younger and have both fewer risk factors for atherosclerosis and a lower occurrence of atherosclerosis in other vessels.

FMD is diagnosed most often in whites and is reported less frequently in Hispanic and Asian populations. Few reports have

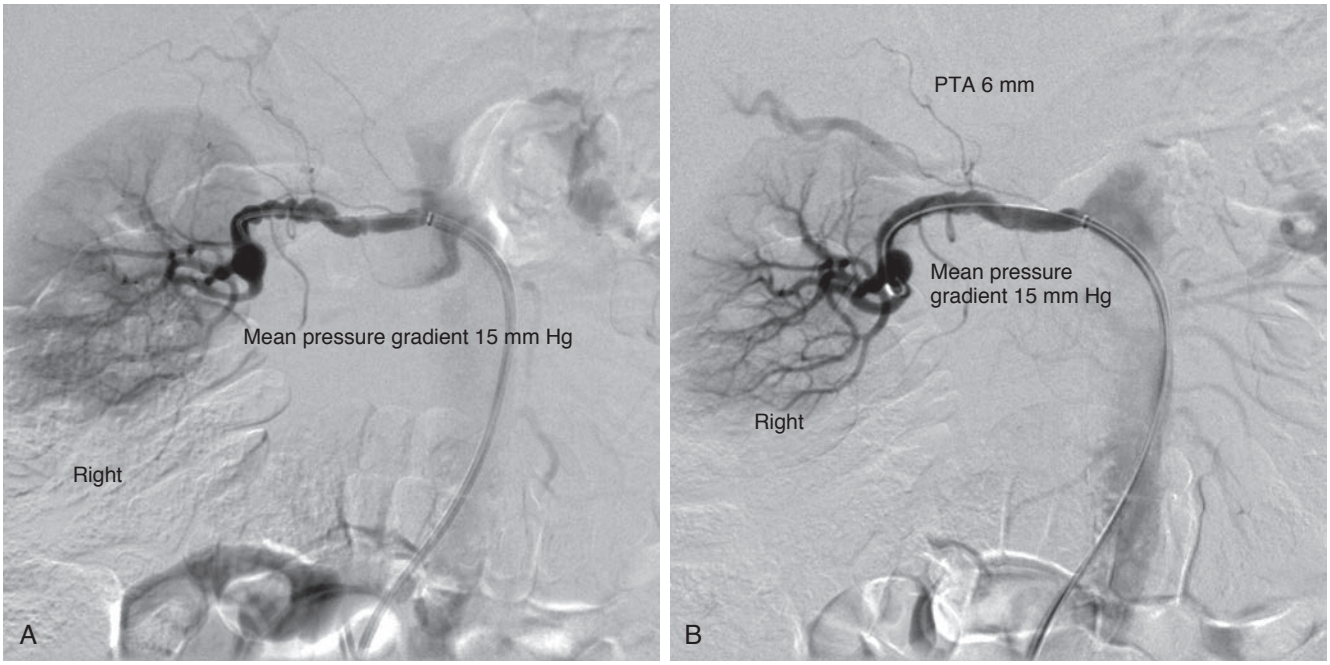

Figure 142.3 Typical selective angiographic multifocal appearance of medial fibrodysplasia with the "string of beads" in the distal main artery before (A) and after (B) percutaneous transluminal angioplasty dilation (PTA).

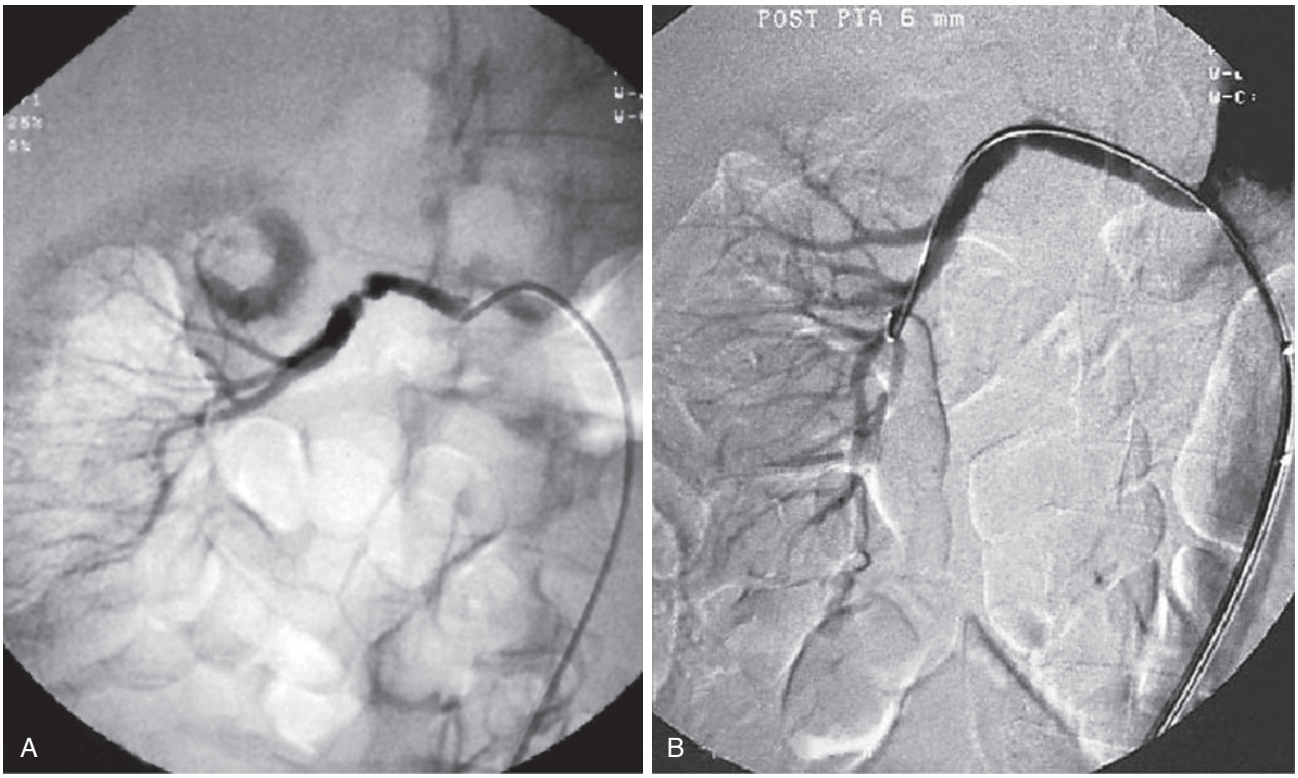

Figure 142.4 Short unifocal stenosis of the distal main artery, perhaps of the perimedial dysplastic type, before (A) and after (B) balloon dilation.

been published from Africa and South America. In the U.S. Registry, which contains data for 447 patients, 95% are white, 2% are African American, and 1% are Hispanic and Asian.[15] Diagnostic criteria vary and prevalence data are often derived from selected cohorts or autopsy studies, so the prevalence of FMD might be overestimated because of the difficulty of estimating the clinical significance of a morphologic stenosis.

Multiple arterial involvements have been reported in 8 of 34 and 9 of 102 renovascular patients with FMD in earlier series; in the U.S. Registry report, two vascular beds were affected in 35% and three in 22%.[9,15,40] This new information reinforces the need for a good clinical examination and at least a carotid artery investigation if FMD is found in other vascular beds.

In childhood, renovascular hypertension is a more important cause of hypertension. It is found in 8% to 10% of all hypertensive children and in up to 25% of those with secondary hypertension. The causes of pediatric RAS differ in different populations.[34,41] FMD is the most common cause of pediatric renovascular hypertension in North America and western Europe, whereas Takayasu arteritis dominates in Asia and Africa.[42]

Pathophysiology

Multiple septa in the renal arteries may together induce a significant reduction in renal perfusion in patients with FMD, resulting in renovascular hypertension, but the degree of RAS is often difficult to evaluate from imaging.

Subsequent reduction of arterial perfusion pressure leads to activation of the renin-angiotensin-aldosterone (RAA) system, resulting in volume expansion and hypertension. Several mechanisms—including increased endothelin-1 (ET-1) production, local RAA activation, arterial wall remodeling, and oxidative stress—help to sustain the hypertension, which now depends not only on the RAA system but also on local vasoconstrictive proliferative effects in the arterial wall, gradually leading to resistance to therapy.[43] Inflammatory mediators such as high-sensitivity C-reactive protein, tumor necrosis factor-α, interleukin-6, and neopterin and vasoconstrictive mediators such as ET-1 are increased in patients with renovascular hypertension. A separate analysis of patients with FMD, however, showed that neopterin and ET-1 were lower in patients with renovascular hypertension due to FMD than in those with RAS of atherosclerotic origin.[7,44] This finding suggests that inflammatory activation might be less important for the pathophysiology of renovascular hypertension caused by FMD than for that caused by atherosclerosis.

Luminal narrowing leads to renal parenchymal damage and ischemic nephropathy in patients with FMD.[45] However, this seems to be less important in patients with FMD than in those with atherosclerotic RAS; the latter show more pronounced reductions of total kidney and cortical perfusion. In addition, renal perfusion correlates inversely with the degree of stenosis in FMD but not in atherosclerotic RAS, further emphasizing that FMD hypertension is more truly renin-dependent than hypertension due to atherosclerosis.[46]

The contralateral kidney may be damaged by exposure to hypertension in FMD.[45] Deterioration of renal function in a patient with FMD affecting one renal artery suggests the development of bilateral stenosis, parenchymal disease, or both.

NATURAL HISTORY

Data with regard to stenosis progression and risk of deteriorating renal function in patients with FMD do exist, but they are not as robust as in patients with atherosclerotic RAS. Progression is less severe in FMD than in atherosclerotic stenosis.[19] About one-fourth of subjects with asymptomatic FMD demonstrate hypertension within 4 years of diagnosis,[31,32] and serial angiograms confirm FMD progression in up to 40% of cases.[47] Because angiography is not routinely performed in patients with FMD who have favorable clinical outcomes, these progression rates may be overestimated. FMD might also result in decreasing renal size and deterioration of renal function, although less often than in patients with atherosclerotic RAS. Aneurysms and dissection are fairly frequent, but complete vessel occlusion, renal infarction, and severe renal insufficiency as well as regression of stenosis have been reported only infrequently in patients with FMD.[5,15,48-50]

CLINICAL PRESENTATION

History and Physical Examination

Arterial hypertension of acute onset or that is increasingly difficult to treat suggests the presence of secondary hypertension—that is, a specific cause of blood pressure elevation, which can be identified in about 5% of adult hypertensive patients.[36] Renovascular hypertension caused by one or more stenoses of the extrarenal arteries is the second most common cause of secondary hypertension (after renal parenchymal disease) and occurs in approximately 2% of adult patients with blood pressure elevation assessed in specialized centers.[51] A physical sign suggesting RAS is abdominal bruit with lateralization. In patients with either high-grade stenosis of a single kidney or bilateral disease, often with one renal artery occluded and the other stenosed, acute pulmonary edema may occur, with or without renal failure. Typically, these patients present with severe and rapid-onset "flash" pulmonary edema, which can also occur in FMD and may be confused with coronary syndromes.[15] Among patients with RAS, the absence of general atherosclerosis suggests that the stenosis is caused by FMD, whereas signs of atherosclerotic disease in other vessels indicate a greater possibility of an atherosclerotic cause.

Screening for Secondary Hypertension

The patient's history can reveal acute-onset hypertension, concomitant flushing, or other paroxysmal symptoms. Physical examination may reveal abdominal bruits, and routine laboratory investigations may show signs of renal disease, hypokalemia, or hyperthyroidism. Secondary hypertension is also suggested by a severe blood pressure elevation, a sudden onset or worsening of hypertension, and blood pressure that responds poorly to appropriate doses of at least three drugs, including a diuretic. In these cases, specific diagnostic procedures for the evaluation of potential secondary hypertension should be considered, as outlined in Box 142.1.

BOX 142.1 Indications for the Evaluation of Secondary Hypertension

Secondary hypertension should be considered in hypertensive patients with the following characteristics:

- Requirement of more than three antihypertensive drugs to control hypertension
- Sudden acceleration of serum creatinine and hypertension
- Young age (<50 years)
- Worsening of previously well-controlled hypertension
- Spontaneous hypokalemia
- Bruit
- Unexplained (flash) pulmonary edema

DIAGNOSTIC EVALUATION

In patients with suspected renovascular hypertension due to FMD, the same diagnostic tools as for arteriosclerotic RAS are used. A limitation of renal artery duplex ultrasonography (DUS), magnetic resonance angiography (MRA), and computed tomographic angiography (CTA) is their unreliability to exclude FMD, because 20% to 25% of patients with FMD have branch lesions. Because MRA and CTA can identify vessels as small as 2 mm but have limited resolution for distal and intrarenal arteries, these techniques can be used to screen for possible FMD but not to exclude FMD. In terms of specificity and sensitivity, gadolinium-enhanced MRA and CTA are better than ultrasound for the detection of RAS, but intra-arterial digital subtraction angiography is most accurate for confirmation or exclusion of an FMD diagnosis.[30,52] This is still the "gold standard" for the detection of renal artery FMD (Fig. 142.5), and is especially useful in the evaluation of branch vessel disease. Intra-arterial measurement of the pressure gradient across the stenosis may be performed before treatment of RAS. Different methods have been used for such assessments, and there is no consensus regarding what level of mean or systolic pressure gradient indicates a hemodynamically significant RAS.[1,30,52] A renal-to-aortic pressure ratio less than 0.90 has been correlated with increased renin levels in the renal vein, suggesting a physiologically relevant stenosis.[53] A mean pressure gradient across the stenosis of more than 10 mm Hg predicts a favorable response to dilation.

TREATMENT SELECTION

The treatment options in renal artery FMD are medical, endovascular, and surgical. Treatment of patients with all forms of renovascular hypertension is controversial owing to the limited number of randomized long-term-outcome trials comparing

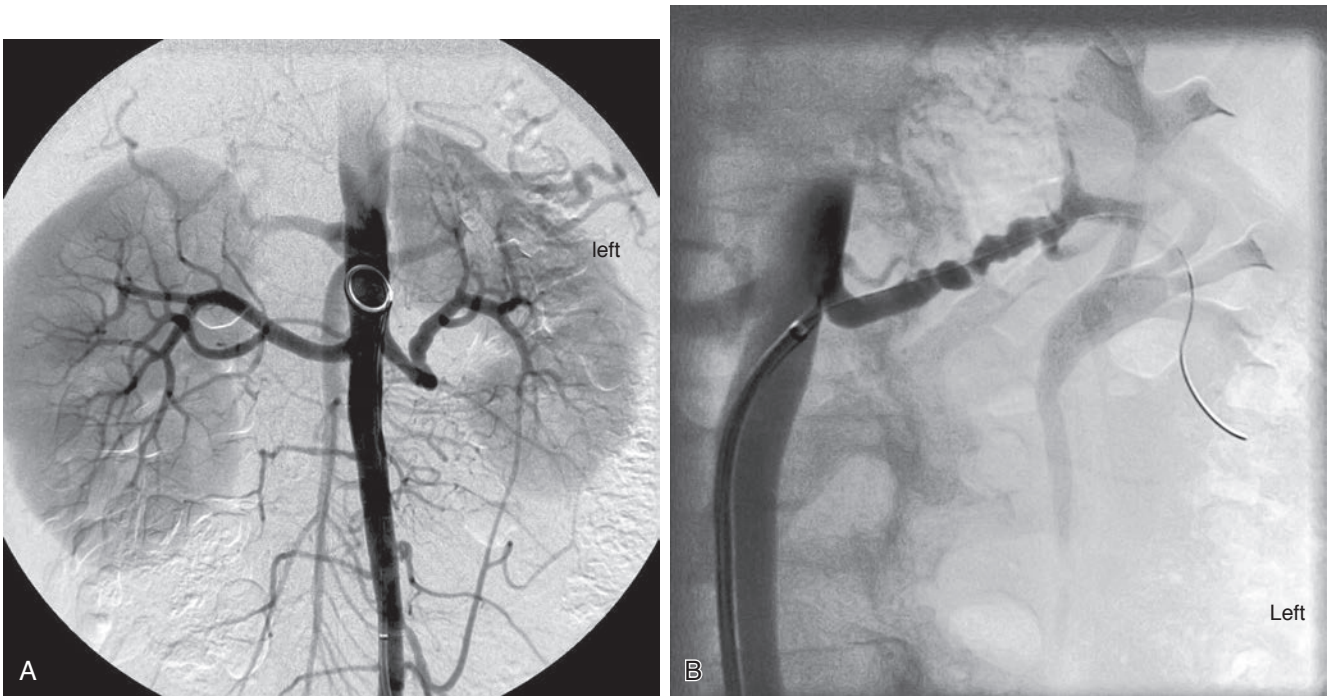

Figure 142.5 (A) Aortogram in a hypertensive young man reveals only minor findings in the left renal artery. (B) Selective angiogram from another angle shows the multifocal fibromuscular dysplastic lesion, across which a pressure gradient of 60 mm Hg was noted. The patient's hypertension was cured by percutaneous transluminal renal angioplasty.

different therapeutic approaches as well as to the difficulty of predicting the blood pressure response to renal revascularization procedures in individual patients.[3] In patients with FMD, endovascular or surgical treatment should be considered in those whose hypertension cannot be controlled with antihypertensive drugs, who are intolerant of or noncompliant with medication, and those with impaired renal function or ischemic nephropathy.[1] To identify progressive disease in patients undergoing medical therapy only, blood pressure and renal function should be monitored regularly. Some authors have also recommended that renal size be monitored by regular ultrasound examinations and that revascularization be recommended if that size decreases by 1 cm or more.[19]

MEDICAL TREATMENT

Many controlled trials have convincingly shown that lowering blood pressure reduces cardiovascular morbidity and mortality. All patients with renovascular hypertension caused by FMD are therefore candidates for antihypertensive treatment in accordance with current guidelines.[36,54,55] Blood pressure should be reduced to 130 to 139 mm Hg systolic and 90 mm Hg diastolic (130 to 139/80) in hypertensive patients and further to less than 130/80 mm Hg in patients with diabetes. These guidelines specify five different groups of first-line antihypertensive treatment: ACE inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers, and diuretics. Single or combined, all of these drugs can be used in the treatment of renovascular hypertension due to FMD.

ENDOVASCULAR TREATMENT IN ADULTS

Percutaneous transluminal renal angioplasty (PTRA) has become the treatment of choice for renovascular hypertension due to FMD. Unlike the case in patients with atherosclerotic renovascular hypertension, progressive loss of renal function is uncommon in patients with FMD. Thus the main reason for treating FMD is unsatisfactorily controlled hypertension, and treatment often leads to cure or improvement.

Technical Considerations

The technique for PTRA in FMD is similar to that used to treat atherosclerotic renal artery lesions (see Chapter 127). Most operators are using guidewire systems based on 0.014- or 0.018-in guidewires to reduce vasospasm. All the components in such systems have low profiles. In patients with FMD, the right renal artery often takes off from the aorta proximally. Even in the right renal artery, which is often longer than normal in patients with FMD, the diversity of available guiding catheters usually allows catheterization from a femoral puncture. A brachial approach is seldom needed to get a better angle and/or "pushability" for renal catheterization.

Heparinization is the same as for other endovascular procedures. However, patients with FMD are often younger and have more pronounced vasoreactivity than those with atherosclerotic RAS. Many patients with FMD are already receiving antihypertensive treatment with calcium channel blockers; if

not, premedication with a short-acting dihydropyridine such as nifedipine can be used to reduce the risk of vasospasm. Even so, vasospasm in the kidney vasculature is so frequent in patients with FMD that some operators infuse 0.15 mg nitroglycerin into the renal artery just after catheterization in hemodynamically stable patients. If required, this dose can be repeated during the procedure.

A diagnostic aortogram and selective renal angiograms at different angles are obtained (see Fig. 142.5). In addition, many centers routinely measure pressure gradients. Because there is no optimal tip-pressure catheter, pressure measurements are usually made through a 4-Fr catheter.

In patients with FMD, the stenotic lesion is most often located in the middle part of the main renal artery. The diameter of the selected balloon is normally the same as the diameter of the unaffected proximal part of the renal artery. If the distal parts of the renal artery or its branches are affected, the use of multiple guidewires may be necessary. A kissing balloon technique can be used in branches. However, multiple guidewires or kissing balloons are normally not required; inserting a balloon into the main artery first, followed by the branches, often achieves good results.

The use of cutting balloons is not a first choice in patients with FMD, because ruptures have been reported with their use.[56,57] Before a cutting balloon is used in a procedure, CTA, MRA, or intravascular ultrasound (IVUS) may yield information about whether the lesion is dysplastic or hypoplastic. A hypoplastic lesion is a narrowing of the entire vessel with thin walls, which implies a higher risk of rupture. IVUS may add information on wall thickness. If cutting balloons are required, it is wise to start with an undersized balloon. Good results have been reported with the use of cutting balloons in complex lesions.[56]

Stenting

In FMD the stenotic lesion is normally highly amenable to PTRA. Balloon angioplasty enlarges the arterial lumen in FMD by breaking the septa and stretching the arterial wall, leading to separation of the intima from the media, fracture of the media, and stretch of the adventitia beyond its elastic recoil. Subsequent changes include smooth muscle cell necrosis, fibrosis, and some degree of neointimal formation. In the vast majority of cases, PTRA provides good results; pressure gradients are completely abolished, and there is no indication for stent placement. Also, given the relative youth of patients with FMD, stenting should be avoided; it is also reported to give a high rate of restenosis.[58] Surgical intervention may be more appropriate in cases of complex stenosis and should not be made more difficult with stent placement.

Indications for stenting of FMD lesions include severe procedural complications and perhaps suboptimal results with persistent pressure gradients after repeated angioplasty attempts or small aneurysms in the renal artery.

Procedure-Related Complications

Puncture-site hematoma is the most common complication of PTRA in FMD, reported in 3% to 26% of cases.[59,60] The trend toward using micropuncture to optimize puncture-site location and the fact that smaller introducers can be used further reduce this risk.

Renal artery dissection occurs rarely (1.4%-6.7%) if the balloons are not too oversized.[7,59-61] The majority of these dissections are small, and few require treatment. Repeated and prolonged balloon treatment is recommended, and dissections that are not hemodynamically significant can be left alone without jeopardizing the kidney. However, an extensive dissection that is limiting flow should be treated with stent deployment.

Rupture of the renal artery is uncommon in medial or perimedial dysplasia. Rupture is reported to occur in 2% to 6% of cases and is more common in patients with FMD who have complex stenoses.[7] Some small ruptures stop leaking after prolonged balloon treatment; others require stents, covered stents, or emergency open surgery after the balloon provides initial hemostasis. Both endovascular rescue equipment and resources for emergency operative repair must be available if complex stenoses are being treated.

Branch occlusion can be caused by guidewire misadventures or by dissection during balloon treatment close to a branch takeoff. Branch occlusion is seen in 1% to 5% of patients with FMD after PTRA procedures.[7,59] Still, most of these patients seem to have a favorable outcome.

Thrombosis of the renal artery after endovascular reconstruction in adults is very rare. Main artery occlusions have not been reported.

Early and Late Outcomes

The favorable results of endovascular treatment of main artery FMD lesions are obvious in most reports, even though follow-up information varies from less than 1 year up to 9 years in the different series.[57-59,62-64] PTRA can today be performed with good results even when branch arteries are affected. However, patients with branch artery involvement show less pronounced blood pressure responses and less optimal long-term effects after PTRA.[7]

Comparisons of published series are difficult because of the large variation in selection criteria and length of follow-up. Further, "cure," "improvement," and "benefit" are not always defined according to current guidelines. In a systematic review by Trinquart et al., the cure rate was around 65% for 30-year-old patients while 55-year-old patients had only about a 20% cure rate.[62] This striking decline in cure rate with age is also reported by others.[64] The review also reports a decline in cure rate from about 60% in series from 1980 to 1985, to about 30% in more recent series.[62] Another limitation in comparing series is that it may be unclear whether diuretics and nitrates were considered to be blood pressure–lowering drugs. When evaluating treatment, attention to 24-hour blood pressure measurements is essential because effects on nocturnal blood pressure are important.

Alhadad and coworkers found that 34% of their patients required a second PTRA procedure; however, the majority of these were either planned contralateral PTRAs or redo operations within 6 months of an initial suboptimal PTRA.[7] In the majority of cases, the restenosis lacks clinical significance. Savard and coworkers analyzed 1-year cure rates depending on the

angiographic type of FMD and found that 15 of 28 (54%) patients with unifocal FMD versus only 13 of 50 (26%) with multifocal FMD were cured.[30] Today most centers perform control angiography only if the initial PTRA procedure was suboptimal or if branches were treated.[7,59] In summary, in patients with a main-artery string-of-beads appearance and a good initial effect after PTRA, the long-term durability is good; for more complex lesions and branch vessel lesions, results are acceptable but reinterventions are needed more frequently.

SURGICAL MANAGEMENT

Patient Selection

Surgical revascularization in patients with FMD is currently reserved for patients with severe PTRA complications such as thrombosis, perforation, or dissection that cannot be handled with endovascular techniques. Another option in most of these cases is the use of a stent or a stent graft; the choice of treatment depends on the extension of the lesion and the current renal flow situation. It is therefore important that PTRA procedures be performed only in institutions where such complications can be handled. Open surgery should also be considered after repeated failure or restenosis of PTRA. In a series of 19 patients with FMD and failed PTRA, Wong and associates reported one emergent surgical revascularization due to thrombosis.[65] Among the remaining patients, two underwent nephrectomy and one was revascularized with aortorenal bypass. Among groups experienced with operative treatment after PTRA failure, the results are favorable.[34,65-68] Patients with FMD and large aneurysms should also be considered for open surgery; in cases of pediatric RAS (see the section titled Pediatric RAS and Arterial Dysplasia, further on, and Chapters 126 and 128), a careful choice between open and endovascular treatment should be made.

Techniques

Aortorenal Bypass

Ostial lesions are normally seen in atherosclerotic disease; the technique for the operative repair of these lesions is covered elsewhere (see Chapter 126). In patients with FMD requiring open surgery, lesions are most commonly located in the distal portion of the main artery, often combined with branch artery stenosis, and are normally repaired with in situ techniques. Many institutions use transverse, subcostal incisions and expose the kidney retroperitoneally or transperitoneally, depending on how much exposure of the aorta is required (Fig. 142.6). In most patients with FMD the aorta or iliac arteries can be used for proximal anastomosis without atherosclerosis limiting its placement.

Graft material for the reconstruction may be either saphenous vein or arterial homograft. In the treatment of FMD, autologous vein grafts are usually preferred for reconstructions in adults, and autologous hypogastric artery grafts are favored for bypass in children.[34,69] The hypogastric artery may also be used in adults, especially if several branches must be reconstructed.[67] Dacron or expanded polytetrafluoroethylene grafts can be used in renal artery lesions but are not the first choice. After resection even of a short part of a renal artery, direct anastomosis is often not possible in adult patients with FMD.

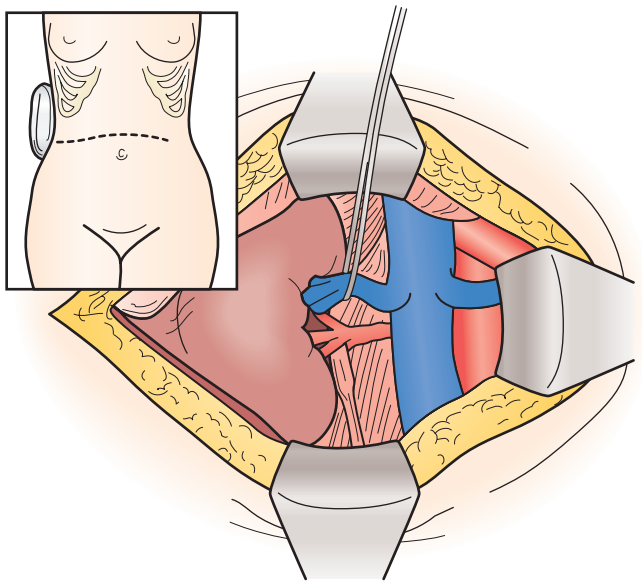

Figure 142.6 Operative approach through a transverse supraumbilical abdominal incision, with an extraperitoneal dissection and reflection of the colon and foregut structures providing exposure of the renal and great vessels.

Before renal circulation is clamped proximally, adequate diuresis must be established. Mannitol 12.5 to 20 g is administered intravenously before renal ischemia to optimize diuresis. Mannitol also acts as a specific hydroxyl free radical scavenger. A generous anastomotic circumference of the saphenous vein can be achieved by using a branch to widen the anastomotic area (Fig. 142.7). The choice of retrocaval or antecaval positioning of the right renal bypass should be made on a case-by-case basis. Some authors prefer not to pressurize the proximal anastomosis until reconstruction is complete. In patients undergoing in situ reconstructions, some surgeons use cool perfusion during renal ischemia. However, it is challenging to maintain cooling intra-abdominally, and such an effort does not convincingly optimize the outcome for the kidney. If cooling is used, clamping of the renal vein and a small venous incision prevent the cool perfusate from having systemic effects. Thereafter the renal anastomosis is made. Intraoperative assessment of the reconstruction is imperative; DUS is reported to be valuable.[67] Most centers do not routinely perform an early postreconstruction angiography.

In hypertensive patients with FMD in whom an aneurysm constitutes part of the indication for surgery, suturing of the aneurysm (aneurysmorrhaphy) is normally not adequate. A saphenous vein graft interposition is usually required.

Autotransplantation

Autotransplantation and renal repair in patients with FMD should be considered in the following situations: reoperation for failed renal artery repair, failed complex endovascular reconstruction after several attempts, multisegmental arterial dysplasia, and a single kidney and stenosis in several renal arteries.

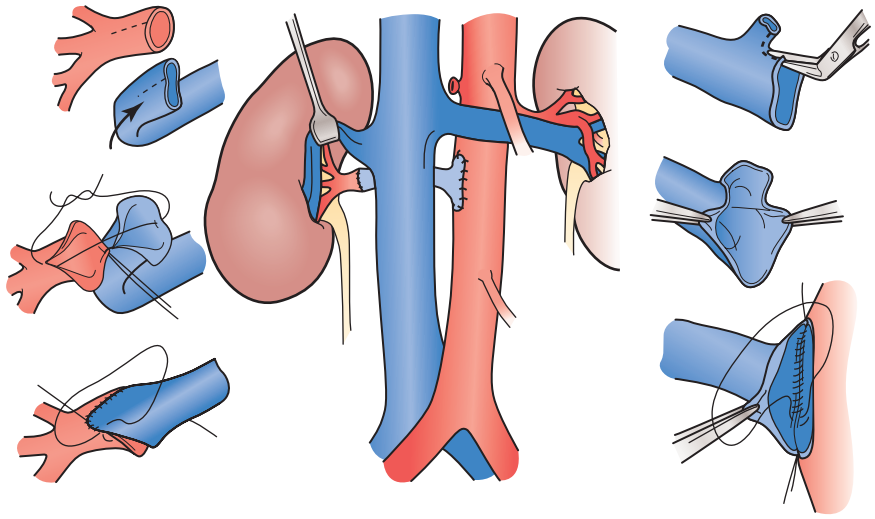

Figure 142.7 Techniques of an end-to-end spatulated renal artery anastomosis and retrocaval placement of the vein graft, with use of a branch of the vein graft to create a wide posteriorly oriented aortic anastomosis.

Current indications for autotransplantation and ex vivo repair have changed somewhat owing to refinements in endovascular techniques. PTRA has shown acceptable results in branch artery stenoses. Autotransplantation of the kidney was originally devised as a method for managing patients with high ureteric injury, and it was first used in renovascular hypertension in 1964. Today when renal FMD is treated surgically, it is usually for very complex disease, with a multisegmental distribution in not only first-order but also second-order branches. Ex vivo repair and autotransplantation, placing the kidney in the iliac fossa, are often required in the same manner as in renal homotransplantation.[66,70,71]

Many institutions preferentially use transverse left or right subcostal retroperitoneal exposure for mobilization of the kidneys. Adequate access may also be obtained with a median or paramedian incision. The renal vasculature is exposed, and the ureter with its surrounding small vessels is freed to at least the level of the iliac vessels. The ureter can be divided and reimplanted in the bladder. This allows optimal separate benchwork after the renal vessels are divided and the kidney is cooled with perfusate. The right kidney has a shorter vein, and a small patch of surrounding vena cava facilitates later vein anastomosis without causing any significant stenosis of the vena cava. The right renal artery is exposed on the back side of the vena cava as long as required. The artery is ligated first; thereafter, the vein is controlled.

The kidney is perfused with saline, Ringer solution, or Wisconsin solution, normally at a temperature of 4°C, until the venous effluent is clear. This normally requires 300 to 500 mL of perfusate. All renal arteries should be perfused. The kidney is kept in Ringer solution at 4°C and some ice slush; thereafter, further meticulous dissection can be undertaken.

Dissection into the renal hilum should be avoided if possible, because the numerous small veins may constitute a challenge. Depending on the type of repair that is planned, further autologous material for vessel repair must be harvested: parts of the proximal "healthy" renal artery, saphenous vein with or without branches, or internal iliac artery with several branches. The risk of unidentified renal arteries is reduced today with better imaging, but during cool perfusion of the kidney especially, the renal poles should be controlled so that blanching of the entire kidney is achieved.

After reconstruction of the renal vessels, reimplantation of the kidney in the left or right iliac fossa is performed. If the ureter has not been divided, it is important to avoid rotating the kidney while positioning it in the iliac fossa. Normally the vein anastomosis is performed first; the reconstructed renal artery is then anastomosed either end to side to the external or common iliac artery or end to end to the internal iliac artery (Fig. 142.8).

Results of Open Surgery

The published series on open surgery include various reports on aortorenal bypass, branch artery reconstructions, and autotransplantation. With each of these different techniques, the early outcome is excellent.

The proportion of cured patients has been somewhat lower during the last 10 years, however, owing to older patients, longer duration of hypertension before surgery, and more complex lesions, because PTRA is now used for main artery lesions. A recent review reported a reduction in cure rate with the increasing age of patients with FMD and also with open surgery.[62] Likewise, cure rate has decreased in recent publications probably due to more refined definitions of cure. The different failure rates among series can be explained by the varying complexity of the cases reported, but it may also reflect an overly optimistic expectation that reconstruction should be successful in patients with small kidneys with branch artery or multisegmental lesions. The number of nephrectomies required is low, however.[68,72]

Complications of Open Surgery

Only a few fatal outcomes have been reported after FMD surgery in adults. Overall morbidity from surgery is between 19% and 28%, mainly caused by minor complications such as urinary tract infection and postoperative pneumonia.[40,68]

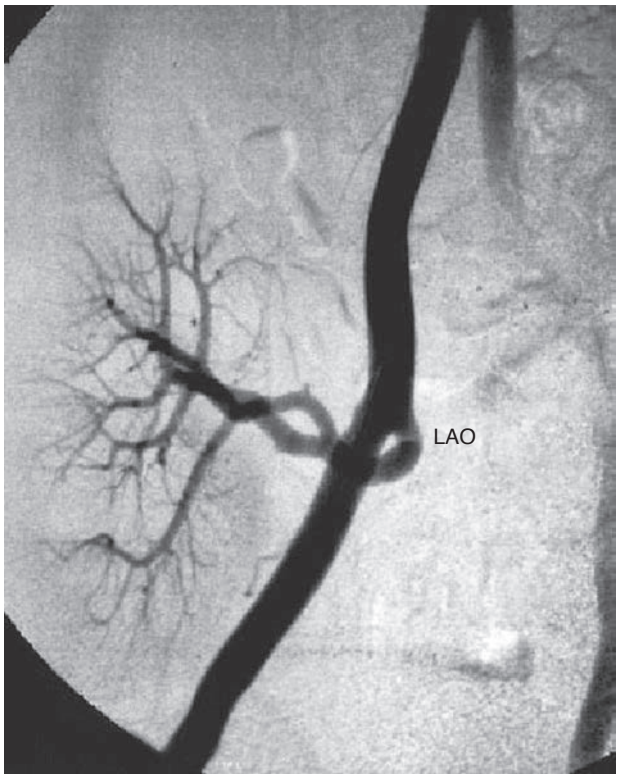

Figure 142.8 Control angiogram after autotransplantation with an arterial allograft (internal iliac artery) and three-branch reconstruction. Slight, insignificant hemodynamic stenosis is seen at the proximal reanastomosis of the internal iliac artery.

Figure 142.9 Ectatic vein bypass after an aortorenal bypass 6 years earlier. No further dilation has occurred during the 10-year follow-up.

Early postoperative occlusion after FMD reconstructions is seen in 3.8% to 13% of cases, and it occurs more often with venous grafts than with arterial autografts.[40,68,69,72] It is more frequent after the repair of renal arteries with small dimensions or branches with low flow. Optimal intraoperative assessment of the reconstruction is of the utmost importance to ensure that no technical defects will induce graft thrombosis.[67]

If pain over the kidney increases postoperatively, diuresis is reduced (which is often hard to evaluate because mannitol has been given and ischemia time differs), or episodic hypertension occurs during the postoperative course, graft occlusion should be ruled out. This can be achieved with ultrasound, conventional angiography, contrast CTA or MRA. Symptoms may be minor, however, which is reflected by the fact that Reiher and coworkers found 9 unsuspected thromboses in 90 reconstructed patients on routine postoperative angiography.[68] If occlusion is found, reestablishment of the renal circulation should be attempted, depending on both the time elapsed between the supposed occlusion and its diagnosis and the collateral circulation, which often helps in delaying irreversible ischemia. Rescue surgery can be considered several days after an occlusion if the renal parenchyma is enhanced by contrast examinations.

Late restenosis has become less common because most anastomoses are now made in an ovoid shape. Restenosis has been reported in 0% to 16% of patients[40,68,69] and in less than 8% of vein graft bypasses.[73] It is even rarer in arterial allografts; branch artery reconstructions also show low rates of restenosis.

The need for redo procedures in patients with FMD differs depending on the technique used and the complexity of the initial lesion.[40,68,69] Secondary treatment using endovascular technology has shown good results, perhaps because a restenosis treated by a redo is more fibrotic.[7,67,68]

Late vein graft dilations were documented in 20% to 44% of patients in early series of aortorenal bypasses in adults.[73,74] Normally a nonprogressive increase in vein diameter is seen (Fig. 142.9). Vein graft dilation has not been reported in series from the last decade, perhaps reflecting the fact that patients with FMD are now older and have a longer duration of hypertension before diagnosis and treatment than in early series.

Renal failure is very uncommon after surgery in patients with FMD.

FIBROMUSCULAR DYSPLASIA AND ANEURYSM

A large proportion of patients with FMD exhibit the string-of-beads appearance, with small aneurysmal areas interspaced by webs in the renal artery. "Macroaneurysms" with obvious aneurysmal development are not infrequent, however; in the U.S. Registry, 25 of 294 patients with renal artery FMD had aneurysmal changes.[15] The University of Düsseldorf group reported on 11 cases of renal artery aneurysm among 101 patients with FMD with renovascular hypertension and treated 48

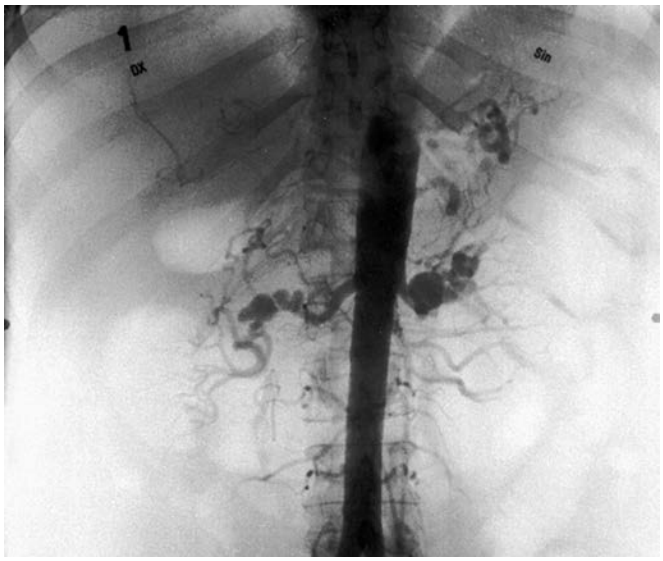

Figure 142.10 Bilateral fibromuscular multifocal dysplasia and aneurysm formation in both renal arteries. Hypertension was fairly well controlled on two drugs. No progression of the aneurysms or hypertension has been seen during 18 years of conservative treatment.

Figure 142.11 Female patient with a fibromuscular dysplastic multifocal lesion treated with endovascular dilation. The medium-sized aneurysm at the branch site decreased in size during follow-up, and the hypertension has clearly improved.

patients with FMD for renal artery aneurysm. Vuong and associates found that of 131 histologically examined renal arteries in patients with FMD, 35 specimens showed aneurysms measuring 0.5 to 2 cm.[9] Most renal artery aneurysms have a low risk of rupture and only a few ruptured FMD lesions have been reported. How FMD-related aneurysms measuring 1 to 2 cm should be handled is uncertain. Conservative treatment may be successful (Fig. 142.10). If additional risk factors are present, treatment may be justified. Aneurysms larger than 2 cm should probably be excluded.[67,68] Among pediatric patients with FMD undergoing open surgery, renal artery aneurysms are reported in 5% to 12%.[34,75]

Endovascular experience is limited. In some patients with renovascular hypertension, small aneurysms may shrink after successful PTRA of stenotic areas (Fig. 142.11). Favorable outcomes have been reported with both embolization and the use of stent grafts.[76]

PEDIATRIC RENAL ARTERY STENOSIS AND ARTERIAL DYSPLASIA

Renovascular disease is among the most common causes of hypertension in children, after thoracic aortic coarctation and renal parenchymal disease (Fig. 142.12).[34] Approximately 8% to 10% of all pediatric cases of secondary hypertension are due to renovascular disease, and pediatric RAS may occur in many different conditions, including FMD, developmental RAS, vascular neurofibromatosis type 1, Moyamoya, vasculitis such as Takayasu disease, Alagille syndrome, and Williams syndrome.[34,77] Up to 40% of children with renovascular hypertension have developmental renal artery lesions with midaortic syndrome and coexisting lesions in both the mesenteric and carotid arteries (see Chapter 130).[77]

Endovascular Treatment in Children

Technical success rates are high in published series, with cure or improvement reported in about 90% of cases. Because children have a greater tendency than adults for vasospasm during endovascular procedures, many centers give small doses of nitroglycerin at every exchange of catheters or wires to minimize this problem.

The string-of-beads type of lesion is not frequent in children. After ballooning of a stenosis, the frequency of recoil is high. If this persists after more prolonged dilation, oversized or cutting balloons should not be used until it has been determined whether the artery is dysplastic or hypoplastic. Patients with a suspected hypoplastic renal artery or a complex stenosis should be considered for open surgical repair. Long-term data on PTRA in children demonstrate variations in outcome. Restenosis is reported in up to one-third of patients. Follow-up examinations are recommended, especially if the initial treatment was for a complex or branch stenosis. A high rate of failure is also reported after treatment of multisegmental stenosis. Overall, the results may be encouraging, but they must be weighed against the results of open surgical repair in children. Because series are small, centralization of treatment is recommended. Treatment of very young children to achieve a moderate improvement may allow open surgery to be delayed until they are older, when the procedure can be performed with better long-term results.

Open Surgery for Pediatric Renovascular Hypertension

A high proportion of pediatric patients with FMD have ostial lesions. In the University of Michigan Pediatric Renovascular Group's report, 12 of 97 children undergoing open operation had multisegmental disease, 6 had aneurysms, 70 had ostial lesions, 15 had main artery changes, and 18 had branch involvement.[34] Unilateral stenosis was seen in 65 children and bilateral

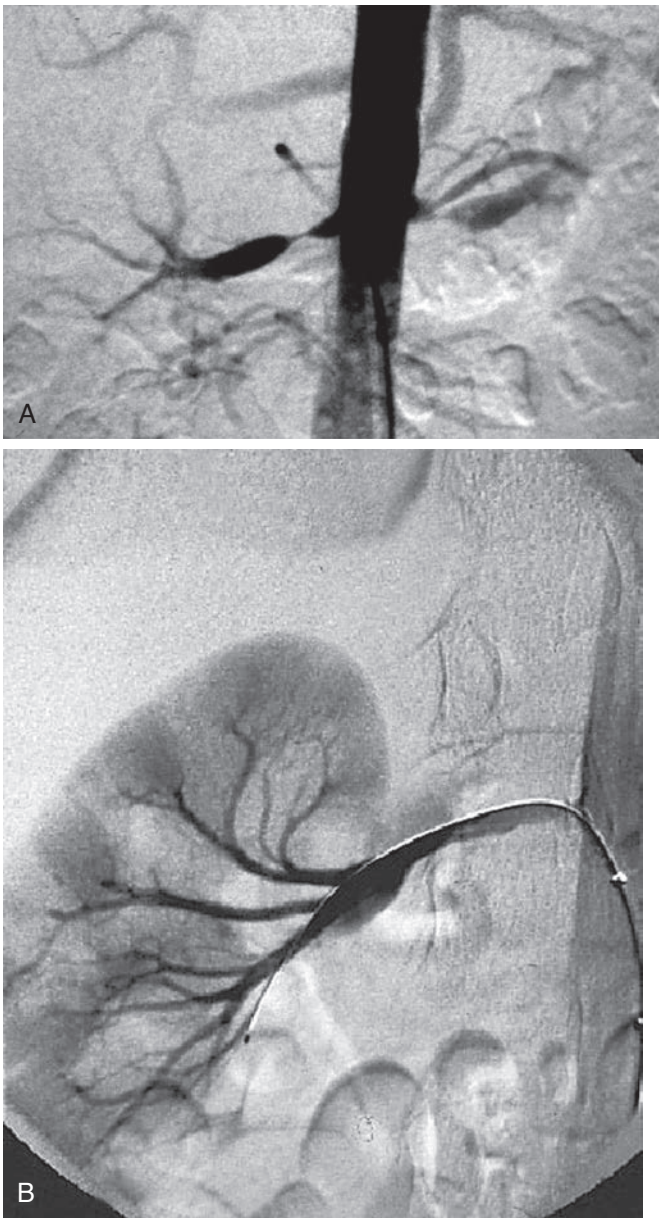

Figure 142.12 (A) Bilateral renal artery unifocal stenosis in a 6-year-old boy with tapered narrowings close to the takeoff from the aorta. Hypoplasia was ruled out. (B) He was treated first on the right side, after which the left stenosis was treated. He required a redo of the right lesion 4 years after the initial treatment.

stenosis in 47. Few girls younger than 10 years of age were treated; at that age, boys were three times more likely than girls to be affected. For children between the ages of 10 and 17, no gender difference was noted. Eleven children with irreparable renal disease required planned and one child unplanned nephrectomy due to technical failure of the reconstruction. The Michigan group has avoided aortorenal bypass with saphenous vein grafts owing to aneurysm formation in 6 of 25 pediatric vein bypasses.[74,77] Huang and colleagues reported on one case of aneurysm development among 12 pediatric venous bypasses requiring redo procedures.[78] Centers of excellence advocate direct aortorenal anastomosis if feasible, and the University of Michigan experience showed that direct anastomosis was possible in 41 of 58 recent reconstructions.[34] Arterial allograft is recommended, and the internal iliac artery is usually preferred over a saphenous vein bypass.

The procedural mortality after renal surgery in children is low, and few children develop renal impairment requiring dialysis. Long-term follow-up shows excellent results, with minimal restenosis and reintervention rates following reconstruction in spite of the children's growth. Centralization of the operative treatment of children is required.

EXTRACRANIAL CEREBROVASCULAR FIBROMUSCULAR DYSPLASIA

FMD is most commonly believed to affect the renal arteries and less frequently the carotid and vertebral arteries; however, data on the first 447 patients in the U.S. Registry show the extracranial carotid and vertebral arteries to be nearly as often involved as the renal arteries, primarily in middle-aged women.[15] Carotid FMD is associated with cerebral aneurysms and FMD involving the renal arteries.

Epidemiology

Although the prevalence in the general population is not well known, the incidence of carotid FMD was 0.42% in 3600 patients undergoing cerebral arteriographic examination in one study.[79] Many of these examinations were performed for suspected cerebrovascular disease, and thus the true frequency of carotid FMD in the general population is probably lower. In one series of 2000 carotid operations, FMD was the identified pathology in 3.4% of cases.[80] Carotid FMD is bilateral in 35% to 85% of reported cases.[1,2,80] Women 40 to 60 years of age predominate in most series, constituting 60% to 90% of patients.[1,2,80,81] This lesion is rare in African Americans. As described in the earlier section titled Renal Artery Fibromuscular Dysplasia, a patient may have evidence of FMD in a single artery or in multiple vascular beds; therefore, appropriate diagnostic evaluation is recommended.

Pathophysiology

This topic is discussed earlier in this chapter, under "Pathogenesis of Fibromuscular Dysplasia." Complications occurring with carotid FMD include encroachment on the arterial lumen, causing reduced perfusion, formation and brain embolization of thrombus, and dissection leading to aneurysmal dilation and possible rupture. These complications occur in less than 10% of cases.

Among the four types of FMD, the internal carotid artery is most often affected by medial fibroplasia, which results in an arteriographic appearance resembling a string of beads (Fig. 142.13), seen in 80% to 95% of the lesions.[1,2,80,81] The arterial segments involved tend to be more distal than in the case of arteriosclerosis; they are located in the middle and distal segments of the extracranial internal carotid artery without any appearance of disease at the carotid bifurcation. The serial stenoses are

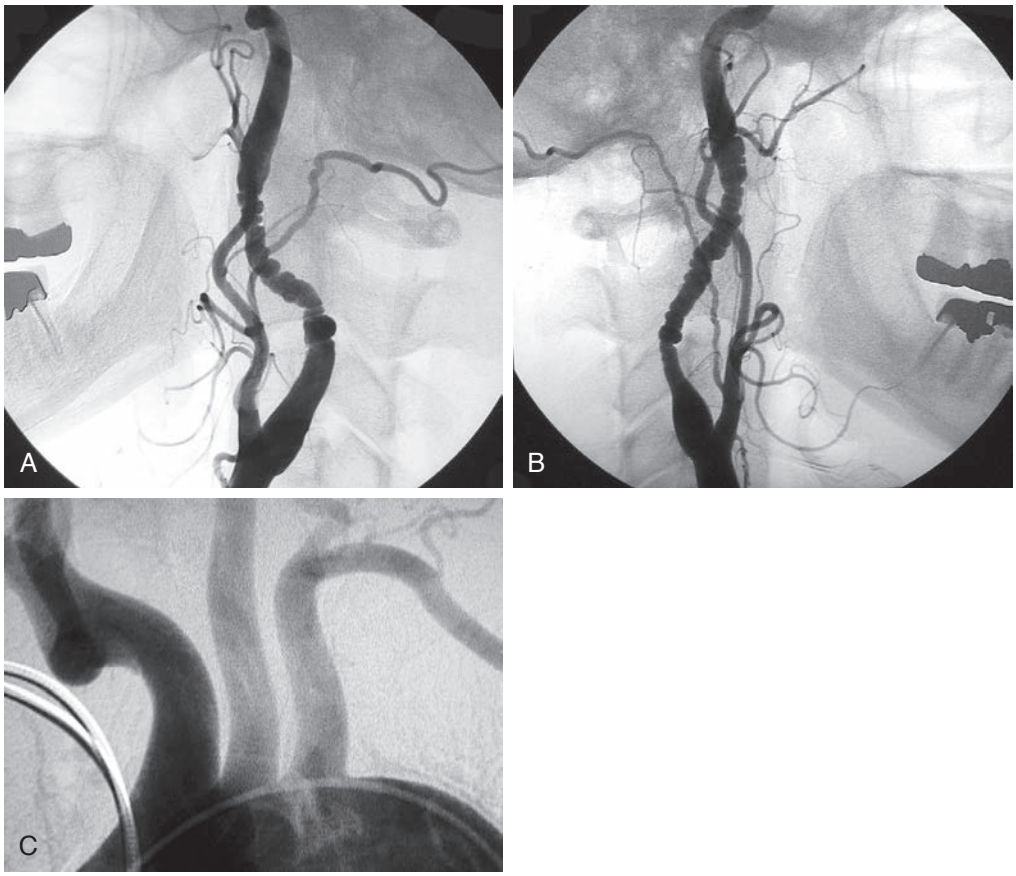

Figure 142.13 (A and B) Carotid arteriograms demonstrating the classic appearance of fibromuscular dysplasia in the usual location opposite the C1-C3 vertebral bodies and intervening disks. Note the low bifurcation and long internal carotid artery. The lesions are present bilaterally in this 43-year-old woman. (C) The aortic arch shows no evidence of disease.

frequently evident on examination of the external surface of the artery (Fig. 142.14). The artery is often elongated and tortuous, and kinking occurs in approximately 5% of cases (Fig. 142.15). Similar disease of the external carotid artery or the intracerebral arteries is rare.

Concurrent Pathology

Concurrent lesions that frequently complicate the management of carotid FMD include the following:

1. Atherosclerotic occlusive disease at the carotid bifurcation, which is seen in as many as 20% of individuals with carotid FMD.[80,82]
2. Extracranial carotid artery aneurysms. In the U.S. Registry, carotid aneurysms (including the extracranial and intracranial internal carotid artery and the ophthalmic artery) were reported in 16 (21.1%) of 76 patients with carotid FMD.[15]
3. Carotid artery dissection. In the U.S. Registry, carotid dissection was identified in 14.8% of 447 patients enrolled. Carotid artery dissection was prevalent in patients with carotid FMD and was seen in 68 of 88 (75.0%) patients.[15] The frequency of FMD in carotid dissection registries varies widely; however, in the most recent large multicenter series of 983 patients, its prevalence was 5.6%.[83]
4. Vertebral artery FMD. This is identified in 7% to 38% of patients with carotid lesions and is occasionally an isolated finding.[80,84] Vertebral artery disease is usually located at the level of the C2 vertebral body and does not extend intracranially.[81]
5. Intracranial aneurysms and occlusive disease. This is found in at least 10% of patients with FMD in general and as many as 51% of patients with internal carotid FMD in particular.[1,2,81,84] Solitary intracranial aneurysms are present in 80% of these patients, but multiple aneurysms occur in the remaining 20%. In the U.S. Registry, intracranial FMD, manifesting primarily as intracranial aneurysms, was reported in 8.3% of patients.[15] These aneurysms tend to be on the same side as the extracranial carotid FMD. They pose an independent threat of rupture and hemorrhage, and their natural history has the potential to be worsened by relief of a proximal stenosis.
6. Renal artery FMD coexists with carotid FMD in 8% to 40% of patients.[1,2,80]

Natural History

Our understanding of the natural history of FMD of the carotid circulation is not complete. Many series have documented the potential for carotid FMD to cause symptoms, as discussed

Figure 142.14 Medial fibrodysplasia of the extracranial internal carotid artery. Operative exposure of the artery reveals an external beaded appearance due to serial narrowing.

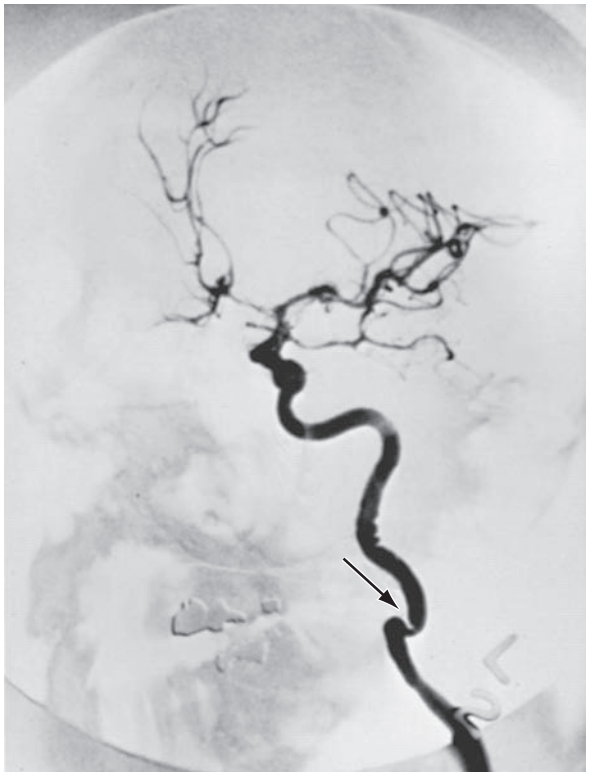

Figure 142.15 Medial fibrodysplasia of the extracranial internal carotid artery, with angulation and stenosis *(arrow)* affecting a tortuous elongated segment. (From Stanley JC, et al. Extracranial internal carotid and vertebral artery fibrodysplasia. *Arch Surg.* 1974;109:215-222.)

earlier, but the natural history of asymptomatic lesions is less well documented. In one series of 79 patients, most of whom were found to have carotid FMD incidentally on cerebral angiography (0.6% of the total), only 3 (4%) subsequently suffered a cerebral ischemic event during an average follow-up of 5 years.[85] When small groups of asymptomatic patients were studied prospectively, less than 10% went on to experience new neurologic symptoms. Roughly one-third of carotid FMD lesions demonstrate significant angiographic progression with time.[2,84,85] Most cases of asymptomatic carotid FMD are known to remain clinically silent, and there is no optimal method of noninvasive follow-up of these lesions to reliably grade progression. None of the existing studies has included a significant number of patients with high-grade asymptomatic stenoses, a group in which the risk for stroke would be expected to be higher.

Clinical Presentation

Extracranial cerebral artery FMD may be either an incidental finding without symptoms or the cause of neurologic events. Symptomatic manifestations in large, contemporary series of treated patients include TIA, stroke, and disability. Stroke is the initial finding in 12% to 27% of patients. Hemispheric TIA occurs in 31% to 42%, and amaurosis fugax in 22% to 28%.[80,84-86]

Physical examination findings at the time of enrollment were available for 414 patients (92.6%) in the U.S. Registry. Findings consistent with Horner syndrome (pupil abnormality or ptosis) were reported in 12.4% of patients. Cranial nerve abnormalities were reported in 9.4%, and other focal neurologic deficits in 13.6%. Bruits were reported over the carotid arteries (30.5%; 18.1% bilateral), epigastrium (17.5%), and flanks (6.1%). Among 306 patients with reported imaging of the extracranial circulation (carotid and vertebral) and a documented physical examination for carotid bruits, 227 (74.2%) had FMD. The sensitivity of a carotid bruit for extracranial FMD was 103 of 227 (45.4%), and the specificity was 74 of 79 (93.7%).[15]

Patients can also present with nonspecific symptoms or signs that frequently occur with carotid or vertebral artery FMD, such as dizziness, headache, altered mentation, pulsatile tinnitus, neck pain, headache, wooziness, and a swishing (swooshing, whooshing) sound in the ears. Such symptoms should trigger diagnostic evaluation for carotid FMD, especially in younger patients with no classic risk factors for atherosclerotic disease. Patients can report significant disability because of the constant noise in their ear and they seek support and help with others who are similarly afflicted.[3,87]

More focal and specific neurologic signs and symptoms may be related to one or more of the following mechanisms: (1) severe stenosis producing hypoperfusion, (2) embolization, (3) thrombosis, (4) dissection, and (5) aneurysm rupture.[88,89]

Other than this process occurring in a relatively young, mostly female population, the history and physical findings may be notable for the absence of additional identifying factors. There may be no particular history or inciting factors. The presence of atherosclerotic risk factors is variable. Physical examination may detect bruits in other locations.

Diagnostic Evaluation

Most asymptomatic patients with carotid bruit and those with hemispheric or nonfocal neurologic symptoms undergo carotid duplex ultrasound (DUS; see Chapter 88). DUS may reveal elevated velocity as a result of FMD, but the lesion may be missed because it is located more distally than the usual atherosclerotic plaque.[81,90] If the lesion is detected, the DUS study may not be able to evaluate the artery distal to the lesion because FMD may involve the artery all the way to base of the skull. Standard arteriography is excellent at delineating the anatomic features of FMD of the extracranial cerebral arteries. Many cases of carotid FMD are discovered during arteriography.[81] Severe tortuosity in the distal carotid arteries, an interesting finding, is seen in patients with FMD. This may occur in the absence of other findings such as beading. However, it is unclear whether this represents another manifestation of FMD.[3,87]

CTA may replace standard catheter-based arteriography in the evaluation of carotid FMD when enough experience has been gained for clinical and anatomic correlation, just as CTA has done in relation to other vascular beds and disease processes. When carotid FMD is identified, the intracranial vascular anatomy should be evaluated to check for the presence of intracranial aneurysms as well as contralateral carotid stenosis and vertebral artery disease. MRA has not been particularly useful in the diagnostic evaluation of carotid FMD because of the tendency for signal dropout with tight lesions and the propensity to produce a "beaded" appearance in normal conduit arteries, which may be confused with FMD. MRA may be beneficial in the follow-up of known FMD. Computed tomography or magnetic resonance imaging of the brain should be performed in patients with carotid FMD to look for evidence of infarction as well as for cerebral aneurysms.

Treatment Selection

Given the generally benign behavior of asymptomatic disease, patients with asymptomatic carotid FMD should be monitored and treated medically, with antiplatelet therapy for primary stroke prevention. There is no evidence to suggest a role for lipid-lowering therapy in patients with isolated FMD, although it should be considered as part of a primary prevention strategy in those with abnormal low-density lipoprotein cholesterol (LDL) levels and evidence of atherosclerotic occlusive disease.

Most reported cases of symptomatic carotid FMD have been treated with dilation of the responsible artery. There is no study in which a large number of patients with carotid FMD and focal cerebral ischemic events were treated medically. In a small series, 13 patients with either TIA (10 patients) or stroke (3 patients) did not undergo surgical intervention; only 1 patient remained symptomatic.[91]

Another rare potential indication for invasive therapy in patients with carotid FMD includes disabling intractable headaches. Percutaneous interventions have been offered to such patients, although the pathogenesis of headache in such patients is not known. The key lies in careful patient selection, reserving invasive therapy for patients with severe disabling symptoms after other common etiologies have been evaluated and ruled out and conservative therapies have been exhausted.[3,87]

At present we are left with a rare cause of focal cerebral ischemic events—extracranial carotid stenosis—which can be repaired with a fairly simple open operation or with percutaneous balloon dilatation.

Therapeutic Challenges

Because of the lack of sophisticated data on carotid FMD, the following challenges frequently arise in its management and must be considered during the treatment planning stage:

1. One of the key driving factors in the treatment of atherosclerosis of the carotid bifurcation, the degree of stenosis, cannot be determined with any reliability in carotid FMD. This problem makes the severity of the disease in a given patient extremely difficult to assess. The indication for mechanical treatment is driven primarily by the development of cerebral ischemia. The problem also compromises the follow-up of asymptomatic patients.
2. It is not always possible to determine which of two concurrent lesions is causing the cerebral symptoms, as is the case with coexistent carotid FMD and significant atherosclerotic disease of the carotid bifurcation. These lesions are usually treated simultaneously. Carotid FMD may also be associated with a coexistent cerebral aneurysm, presenting the same dilemma of competing suspected lesions.
3. When symptomatic carotid FMD is treated, it can be a challenge to decide how to manage a contralateral severe but asymptomatic lesion. Although asymptomatic lesions seem to have a generally benign course, such may not be the case in a patient who suffered a stroke on the contralateral side from the same pathology.
4. Patients with carotid FMD often have nonfocal symptoms, some of which may be due to global ischemia. The indications for intervention in this situation are ambiguous.
5. The presence of an intracranial aneurysm may alter the treatment sequence or the surgical approach.
6. The presence of hypertension secondary to renal artery FMD may complicate any procedure performed for carotid FMD.

Clinical Considerations

Because of the relative safety and effectiveness of mechanical intervention (see the section titled "Mechanical Repair," further on), dilation of the artery is appropriate for lesions causing focal ischemic events (hemispheric or ocular) or episodes of cerebral hypoperfusion. A lesion causing a focal cerebral ischemic event should be considered for treatment because it remains a significant threat. Hypoperfusion is rare but can occur in the setting of critical bilateral carotid FMD or even unilateral disease when there is a significant defect in the circle of Willis. Percutaneous transluminal angioplasty (PTA) has been successful in the treatment of renal artery FMD, and carotid angioplasty with stenting has a growing role in the management of carotid disease; however, the results and durability of balloon angioplasty for carotid FMD with or without stent placement are not known.

Symptomatic patients at high surgical risk should be considered for percutaneous balloon angioplasty, especially if the anatomy allows the use of cerebral protection devices.

Anatomic Considerations

Cerebral Protection

The lesion requiring treatment in carotid FMD is usually a series of webs with intervening pockets, in between which platelet thrombi and cellular debris have accumulated. Disruption of the webs, whether by balloon dilatation or rigid dilatation, produces potentially embolic debris. Some type of cerebral protection is warranted. Carotid FMD tends to involve the carotid artery for several centimeters distal to the bifurcation and may affect the length of the artery to the base of the skull, thus precluding a "landing zone" for an embolic filter to be placed during the procedure. Most distal filters require a few centimeters of straight, healthy artery proximal to the petrous portion of the carotid artery to be functional and safely placed. Cerebral protection using flow reversal devices and proximal occlusion of the common and external carotid arteries may be the best method of protection during percutaneous intervention because the safety and efficacy of these devices has been demonstrated in patients undergoing carotid angioplasty and stenting for atherosclerotic occlusive disease.

Stents

It is not clear whether carotid balloon angioplasty should be accompanied by stent placement in FMD. Stent placement is not usually required after PTA in renal artery FMD because the results are excellent without stents and the patients are usually otherwise young and healthy with good life expectancies. However, stents are routinely placed when atherosclerotic stenosis of the carotid bifurcation is treated percutaneously, and there is some likelihood that stent placement after PTA helps stabilize flaps and disrupted dysplastic tissue. Experience with PTA for carotid FMD is limited, and there are even fewer cases of carotid stent placement for FMD. In light of this paucity of cases, more time will be required to determine the role of PTA with or without stenting in the treatment of patients with carotid FMD.

Medical Management

Patients with asymptomatic carotid stenosis secondary to FMD should be started on a regimen of antiplatelet agents. Diagnostic evaluation should be undertaken to rule out other arterial pathology. If associated conditions are identified, either in the carotid circulation (e.g., carotid aneurysm) or in other vascular beds (e.g., RAS), they should be treated as needed.

Carotid FMD should be monitored at intervals of 6 months with a noninvasive study such as DUS, CTA, or MRA. If DUS follow-up is used, the internal carotid artery must be interrogated as distally as possible. If symptoms develop or there is a significant change in the pathologic lesion (e.g., dissection), mechanical repair of the artery should be considered. There is no established role for anticoagulation or for anti-inflammatory medications such as steroids in carotid FMD. Chiropractic manipulation of the neck should be avoided, as should sports that are likely to produce whiplash-type neck injuries.

Mechanical Repair

Methods of mechanical intervention for the treatment of carotid FMD include open surgical graduated rigid dilatation, open access for transluminal balloon dilation with proximal clamping and back-bleeding to avoid embolization, and PTA (with or without stent placement or cerebral protection devices). Although open surgical treatment has been successfully used in the past, percutaneous balloon therapy with flow reversal represents the optimal current approach, as discussed later. Surgical therapy or endovascular therapy with stents or coils may also be needed for patients with concomitant aneurysms or with aneurysmal complications.

Open Surgical Dilation

The usual fibrodysplastic lesion encountered in the internal carotid artery responds to mechanical dilation. Over the past several decades such treatment has been performed with relative success and safety by means of rigid dilators of progressively enlarging size passed antegrade into the internal carotid artery with arterial control.[1,7,26,30,31] This approach permits gentle disruption of the obstructive webs while allowing associated debris to be flushed out of the artery and has been shown over the years to have reasonable results.

The main disadvantage of this approach is that it is performed without imaging of the luminal surface. The length of the arterial segment to undergo treatment must be estimated. Kinks and coils must be managed by "feel" without direct guidance. There is no simple method of assessing the results of treatment in real time, the way interval arteriography can guide a procedure during percutaneous treatment. The other disadvantage is the need for a neck incision and arterial exposure.

Exposure for the open approach is similar to that for carotid endarterectomy except that higher internal carotid artery exposure is usually required to ensure that dilation is carried out under direct vision and that the extracranial carotid artery can be safely straightened during passage of the dilator (see Chapter 90). The posterior belly of the digastric muscle may be divided, but subluxation of the mandible is rarely required. If the distal internal carotid artery is not accessible, balloon angioplasty should be considered (see the section titled Open-Access Balloon Dilation, further on). The normal arterial segment above the highest point of involvement is apparent with direct inspection, and the internal carotid artery is encircled at this point.

The surgeon should take care to not manipulate the intervening segment of the internal carotid artery as it is gently exposed throughout its length. Determination of stump pressure or electroencephalographic monitoring is not ordinarily needed for this brief procedure but may be indicated if a more extensive procedure is planned (e.g., bifurcation endarterectomy, correction of redundancy, interposition grafting). Except in such unusual circumstances, a shunt is unnecessary.

Heparin is administered (75-100 U/kg) before flow is interrupted. Dextran 40, 25 mL/h beginning at the time of surgery and continued during the immediate postoperative period, may

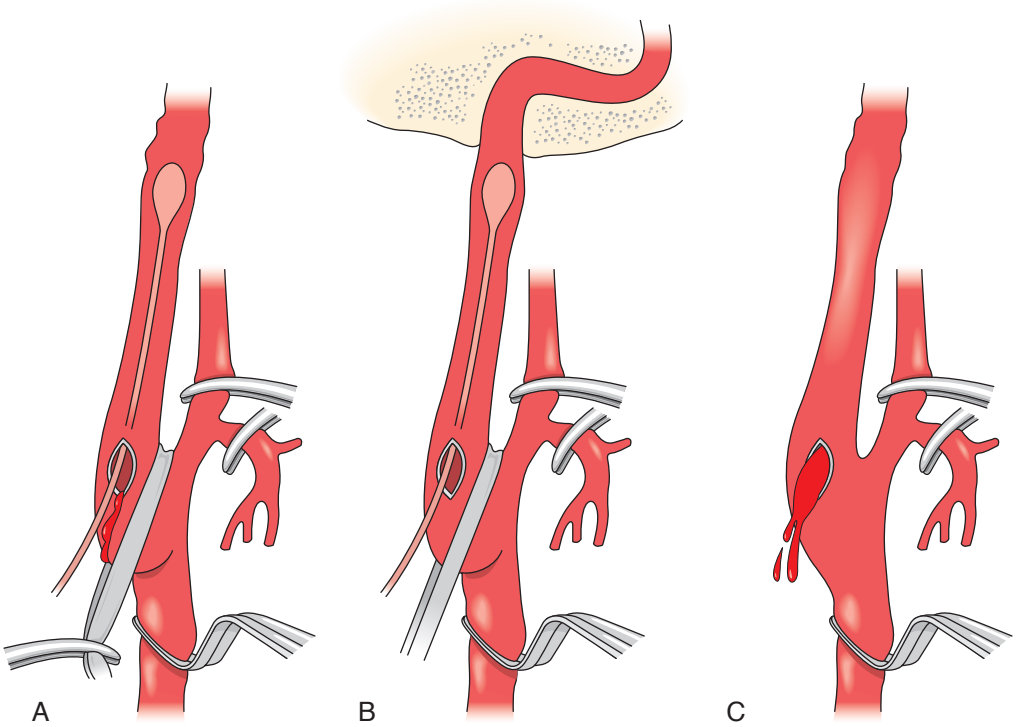

Figure 142.16 Drawings showing the main features of the open surgical technique. (A) Straightening of the carotid artery with downward traction on a polymeric silicone (Silastic) sling. (B) Gentle, graduated dilation of the internal carotid artery from 2 to 4 mm. Passage of the dilator to the bony canal at the base of the skull is shown. (C) Back-bleeding of the artery to remove dislodged debris. (From Wylie EJ, et al. Nonatherosclerotic diseases of the extracranial carotid arteries. In: Egdahl R, ed. *Manual of Vascular Surgery,* New York: Springer-Verlag; 1986: 184-185.)

help prevent early deposition of thrombotic material on the inner surfaces of the arteriotomy and the fractured septa. The common carotid artery is cross-clamped. Traction on a polymeric silicone (Silastic) sling placed around the internal carotid artery just above the bifurcation is performed to straighten the artery. A short arteriotomy is made in the internal carotid artery at the base of the bulb. Graduated metal dilators are then gently passed up the straightened internal carotid artery, beginning with a probe 1.5 mm in diameter probe and progressing up to a 3.5-mm diameter probe or, occasionally, one 4.0 mm in diameter (Fig. 142.16). A series of "giving" sensations is usually felt as each septal stenosis is gently fractured for the first time, but such sensations are not felt thereafter.

The procedure is terminated after the segment has been gently stretched to full diameter throughout its course. This step can usually be observed under direct vision. It is important not to exceed this gentle stretching and therefore not to proceed beyond a 4-mm diameter. Back-bleeding after passage of the dilators should be thorough because large debris is sometimes retrieved. The short arteriotomy is closed rapidly with a simple running suture of 6-0 polypropylene. Careful interrogation of the entire segment with a Doppler ultrasound probe or DUS scanner after restoration of flow ensures patency without turbulence and residual defect.

There are three large series of surgically managed patients.[18,92,93] These reports consist primarily of patients undergoing rigid carotid dilation but also include some instances of carotid replacement and vertebral revascularization. The incidence of perioperative stroke during surgical treatment in these series ranged from 1.4% to 2.6%. TIA occurred in 1.4% to 7.7%, and perforation occurred twice in 318 operations (0.6%). Cranial nerve injuries, most of which were transient, resulted from extensive distal operative exposure of the internal carotid artery and were reported to occur in 5.1% to 16.7% of cases.

Excellent long-term follow-up data are available. Late stroke developed in 1.2% to 3.8% of patients, and nearly all late deaths (up to 22 years) were due to nonneurologic causes. In one series, 94% of patients underwent DUS scanning (mean follow-up, 7 years).[92] Actuarial rates of primary patency, survival, and stroke-free survival were 94%, 96%, and 94%, respectively, at 5 years and 94%, 82%, and 88%, respectively, at 10 years. When follow-up angiography is performed, it usually demonstrates a normal-sized lumen (Fig. 142.17).

Despite the acceptable outcomes reported with surgery, most writers believe that similar outcomes can be achieved with percutaneous techniques and cerebral protection (see later).[3]

Open-Access Balloon Dilation

When the length of the diseased internal carotid artery extends too far distally to be dissected and adequate control of manual dilation is ensured, some writers have advised balloon angioplasty combined with open arterial control, as described under Open

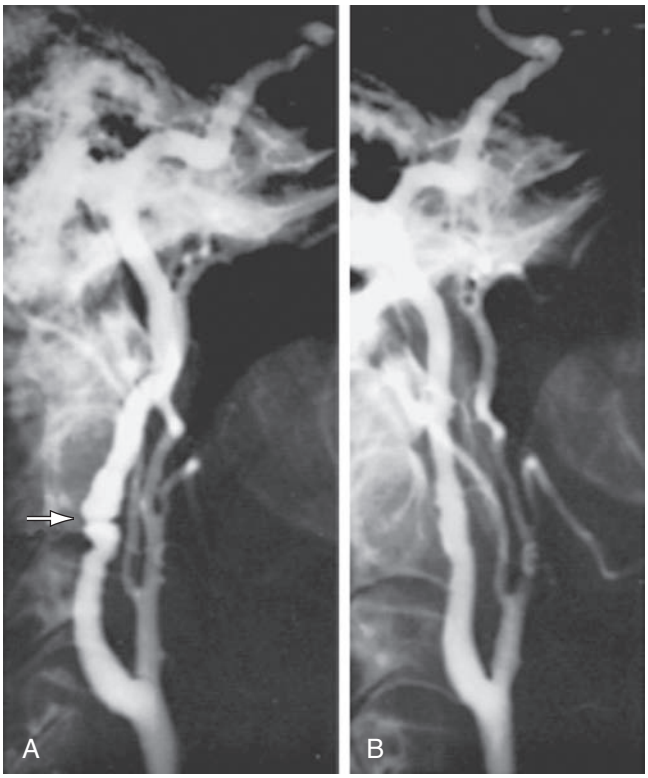

Figure 142.17 (A) Preoperative right carotid arteriogram showing a localized zone of fibromuscular dysplasia characterized by an intraluminal diaphragm *(arrow)*. (B) Postoperative right carotid arteriogram after graduated intraluminal dilatation. The carotid lumen is now widely patent.

Surgical Dilation.[94,95] The benefit of this approach is the opportunity for controlled dilation with interval arteriography while maintaining the ability to back-bleed the artery and avoid embolization of debris from the dilated lesion. Among a small number of patients in several reports, it appears that early results with this approach may be comparable to those of rigid dilation.

Percutaneous Transluminal Angioplasty

PTA has become the preferred approach for more proximal internal carotid artery FMD. The rationale for this approach is based on the success of PTA in the treatment of renal artery FMD and dramatic improvement in the technology, which supports balloon angioplasty and stenting of the atherosclerotic carotid bifurcation.

Diagnostic evaluation for carotid FMD is likely to include an arch aortogram and carotid and cerebral arteriograms, as noted earlier. These are valuable tools for planning carotid PTA. Arteriography provides important information with respect to the optimal strategy that should be pursued on the basis of the demonstrated anatomy. Lesions that have signs of aneurysm formation should not be considered for endovascular management; they may be better treated with open arterial replacement. On the other hand, lesions that show some evidence of dissection should be considered for stent placement, and care should be taken to avoid overdilation and possibly rupture.

If significant kinking of the distal artery at the diseased segment is noted, there are additional considerations for technique. Kinks are not favorable for stent placement because the stent can make them worse. During open, rigid dilation, the artery is dissected and straightened before treatment, and surgical shortening of the artery may be required. Such shortening obviously cannot be done during balloon angioplasty.

It is not always possible to tell where the lumen is located when angiography is used to help with passage of the guidewire, and patience and persistence may be required to safely cross the lesion. Having the sheath tip close by to use as a stable platform is helpful. In addition, an angled catheter may be used to support and direct the guidewire as it traverses the web-like internal carotid artery lesions, which sometimes have only pinhole openings. As the guidewire passes through each lesion, the responsiveness and directionality of the guidewire decrease.

Heparin is administered to provide an activated clotting time in excess of 250 seconds. Most patients with carotid FMD are young, and they are much more likely than other patients with vascular problems to have an arch favorable for percutaneous carotid artery access, one with less tortuosity and less ectopic vascular disease. The carotid arteries frequently arise from the superior aspect of the arch rather than on the upslope of the proximal arch (see Fig. 142.13). The carotid artery sheath may be placed in the distal common carotid artery because the bifurcation is not usually diseased (Fig. 142.18). The external carotid artery is generally normal in appearance and can be used as a place to anchor the stiff exchange guidewire for sheath placement.

After the stiff exchange guidewire is placed, the carotid sheath is advanced. Once the sheath is in place, its position is confirmed with an arteriogram and an arteriographic "road map" of the bifurcation is obtained. Because internal carotid artery lesions may extend to the base of the skull, the image intensifier must be placed so that the operator can observe the distance from the tip of the sheath inferiorly to the area distal to the lesion superiorly. Use of some type of cerebral protection is highly desirable but not always possible, as discussed previously. If there is no safe landing zone for a distal protection device, it is better to perform the procedure without it or, preferably, to use flow reversal techniques and devices. The distal filter or occlusion balloon may move slightly during the procedure, even when it is performed with meticulous technique. Therefore the distal protection device must be placed at least 1.5 to 2 cm distal to the lesion. If stent placement is anticipated, the nose cone on the stent delivery catheter typically requires at least 2 cm of clearance. Care must also be taken to avoid interactions of the guidewire with any associated intracranial pathology that may be present.

If a distal occlusion balloon or filter is used, placement is likely to be in the petrous carotid or above, so that the balloon is distal to the disease. This segment of the internal carotid artery is more prone to spasm and dissection than the extracranial segment, so caution should be exercised. The distal protection device with the shortest landing zone is the distal occlusion balloon. A proximal occlusion device, with or without flow

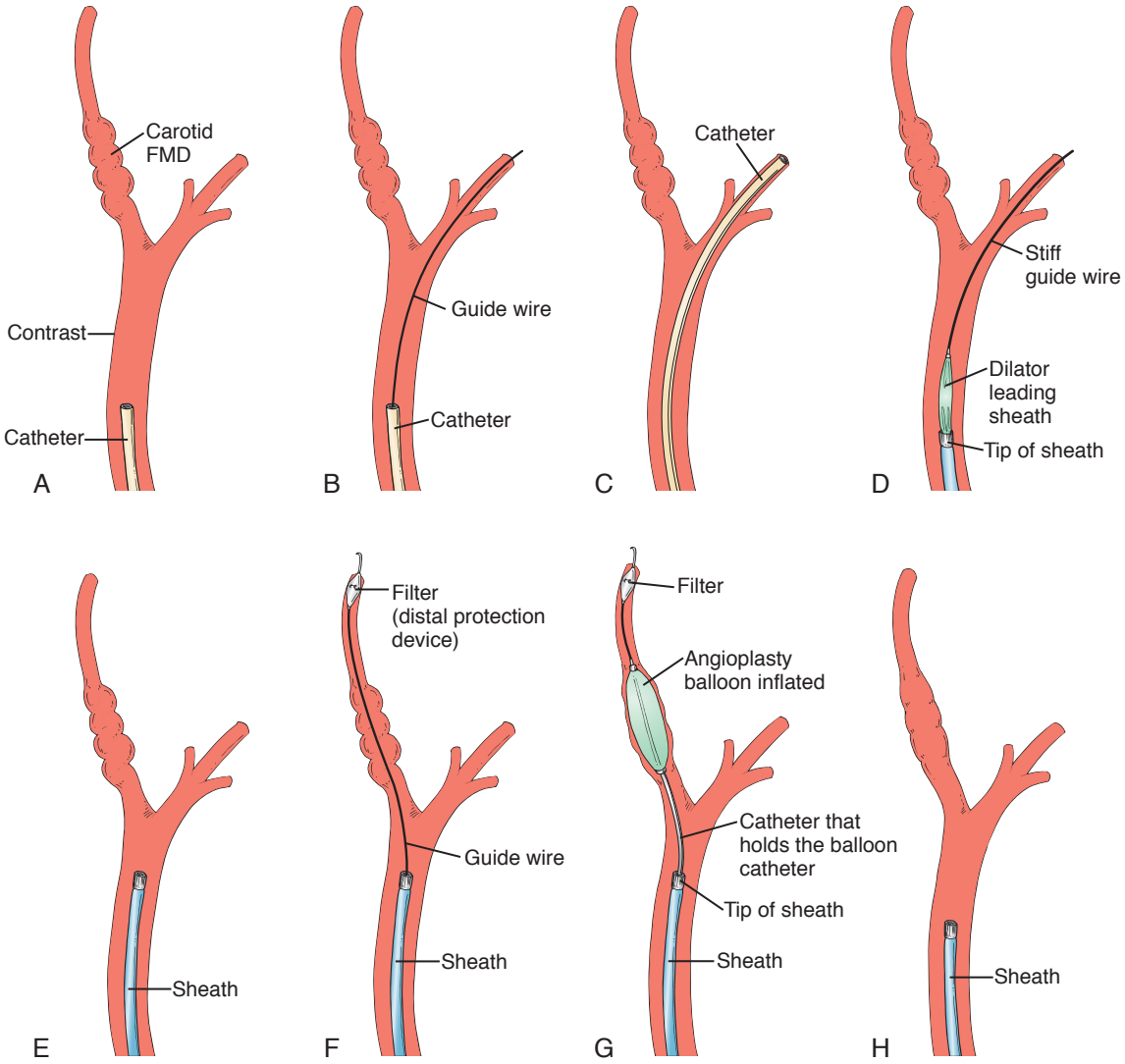

Figure 142.18 Endovascular Technique. (A) Internal carotid artery narrowed by fibromuscular dysplasia (FMD). An arteriogram was performed through a carotid catheter. (B) Guidewire placed in the external carotid artery through use of a road-map arteriogram of the carotid bifurcation. (C) Cerebral catheter advanced into the external carotid artery. (D) Stiff guidewire advanced into the external carotid artery. The carotid access sheath is advanced over this exchange guide wire. (E) Carotid sheath in place with the tip of the sheath in the distal common carotid artery. (F) Cerebral protection device in place in the distal internal carotid artery. (G) Balloon angioplasty of the fibromuscular lesion in the internal carotid artery. (H) After balloon angioplasty, the lumen improved significantly.

reversal, is a reasonable alternative for cerebral protection in the patient with distal internal carotid artery lesions and no safe filter landing zone; in fact, this may be a safer first-line choice for cerebral protection not only owing to the possibly compromised internal carotid landing zone but also because of the amount of debris that can be generated.

FMD generally covers a longer distance of the internal carotid artery than carotid atherosclerosis and may therefore require a longer balloon (4 cm). It is best to dilate the entire lesion with a single balloon inflation. The balloon should be slightly undersized with regard to the intended diameter of the artery to help avoid dissection or rupture.

Fortunately the most frequently encountered extracranial carotid FMD pathologic lesion is medial fibroplasia, which is amenable to dilation and less likely to include aneurysmal dilation. For FMD lesions that contain aneurysmal segments, PTA is probably not advisable.

Carotid stent placement may be challenging in patients with carotid FMD because many of them have redundancy, kinks, and coils of the cervical internal carotid artery. The segments involved by FMD tend to be longer than those involved by atherosclerosis, in which almost all lesions are shorter than 2 cm, and experience with stent placement near the base of the skull is limited. In addition, no one knows the implications of stent placement in patients with a life expectancy of many decades, as is the case with many FMD patients.

Given a track record of success with PTA of FMD lesions in other locations, primary stent placement is probably not

warranted, at least without more data. In addition, FMD tends to occur in a younger group of patients with a reasonably long life expectancy, and the performance of carotid stents over decades is not known. However, if dissection, residual stenosis, or flaps are evident on completion arteriography, a stent should be considered. Smaller stents are used than is normally the case with bifurcation disease because self-expanding stents are sized for the distal internal carotid artery (5 or 6 mm) rather than the common carotid artery (8 or 10 mm). The minimum length of artery required to cover the disease should be stented because stents confer stiffness and create compensatory bends or even kinks in the more relaxed, nonstented segment of artery. Preexisting kinks, coils, and redundancies are common in FMD. These configurations present unique challenges for stenting. Stent placement in a kink should be performed cautiously because the extra curvature is usually transferred to another segment of the artery and may exacerbate a kink in that area. Stent placement in a coil should be avoided altogether.

Unfortunately it is not possible at present to provide a comprehensive assessment of the results of PTA because few data are available regarding perioperative complications or longer-term success.[3] Since the 1980s, only a few dozen patients have been reported in the literature as having undergone PTA for carotid FMD, usually as part of larger series of those undergoing angioplasty. Periprocedural complications are very rare and may include dissection or stroke. No follow-up is available beyond the perioperative period.

FIBROMUSCULAR DYSPLASIA IN OTHER ARTERIAL BEDS

Fibrodysplasia is considered a systemic arteriopathy; although it may be clinically overt when it affects the renal and extracranial carotid, it can frequently be identified in lower limb vessels (mainly iliac arteries) and less frequently in the visceral and coronary arteries.[3,6,15,92]

Although fibrodysplasia is usually asymptomatic, presenting symptoms of lower extremity involvement include claudication or other atypical lower extremity symptoms.[96] In the viscera, FMD usually involves more than one vessel. Although typically asymptomatic, mesenteric ischemia can occur, but owing to extensive collateralization rarely results in infarction.[97] Epicardial coronary artery involvement has rarely been reported. Coronary FMD typically appears as a well-demarcated long smooth lesion in the distal portion of the artery. There is an abrupt transition from an angiographically normal coronary artery to the abnormal area. Rarely, the string-of-beads appearance will be noted in the coronary arteries.[3,98]

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143 CHAPTER

Nonatheromatous Popliteal Artery Disease

THOMAS L. FORBES and AHMED KAYSSI

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INTRODUCTION

Most lower extremity ischemic symptoms occur in patients with atherosclerotic occlusive disease. Nonatheromatous causes must be considered, however, in the absence of significant atherosclerotic risk factors, especially in younger and more active individuals. The two most common nonatheromatous causes of popliteal artery disease are popliteal artery entrapment syndrome (PAES) and adventitial cystic disease (ACD). Clinical symptoms associated with these pathologies range from claudication to critical limb ischemia (CLI). Given their rarity and the younger age of presentation, these conditions are often not diagnosed in a timely fashion, resulting in prolonged disability and occasional progression to CLI.

POPLITEAL ARTERY ENTRAPMENT SYNDROME

Epidemiology

PAES was first described in 1879 by University of Edinburgh medical student Anderson Stuart.[1] It was not until 1965, however, that Love and Whelan at the Walter Reed Army Medical Center in Washington, DC, coined the term "popliteal artery entrapment syndrome" to describe this clinical entity.[2,3] The anatomic abnormalities associated with PAES have been observed in 3.5% of individuals in a postmortem study,[4] and up to 60% of young individuals with claudication symptoms suffer from the syndrome.[5] Those affected tend to be active and otherwise healthy, which has led some clinicians to describe PAES as the "jogging disease."

The majority (up to 80%) of reported cases are in men, with a median age of 32 years (range, 20.7 to 41 years).[6] Cases of PAES have also been described in children and women, but are unusual.[7] While the anatomic variant in affected individuals is first developed in utero, several decades are sometimes necessary before the syndrome is detected. Bilateral lower-extremity symptoms in PAES have been described in approximately 30% of cases, and two thirds of patients with unilateral symptoms were found to have bilateral anatomic abnormalities.[8] Rare instances of bilateral popliteal artery occlusion secondary to popliteal artery entrapment have also been reported,[9] and concurrent entrapment of the popliteal and anterior tibial arteries has been described.[8,10]

Pathogenesis

Etiology

The anatomic variations observed in PAES are best understood by considering the embryologic development of the structures within the popliteal fossa.

The lower extremity arterial system arises from two arteries, the axial and external iliac arteries, which originate from the umbilical artery. The femoral artery originates from the external iliac artery and progresses distally in the anterior compartment, whereas the axial artery elongates distally in the posterior compartment. At around 42 days of intrauterine life, the axial artery is divided into three segments, depending on its relationship to the popliteus muscle: proximal, deep, and distal. A bridging artery, the ramus communicans superius, joins the femoral artery and the proximal segment of the axial artery through the adductor hiatus. During the following week of development, the proximal component of the axial artery gives rise to a branch that runs superficial to the popliteus muscle and joins with the distal segment of the axial artery. The deep segment of the axial artery involutes, and the fully developed popliteal artery results from the fusion of these arterial elements (Fig. 143.1).[2]

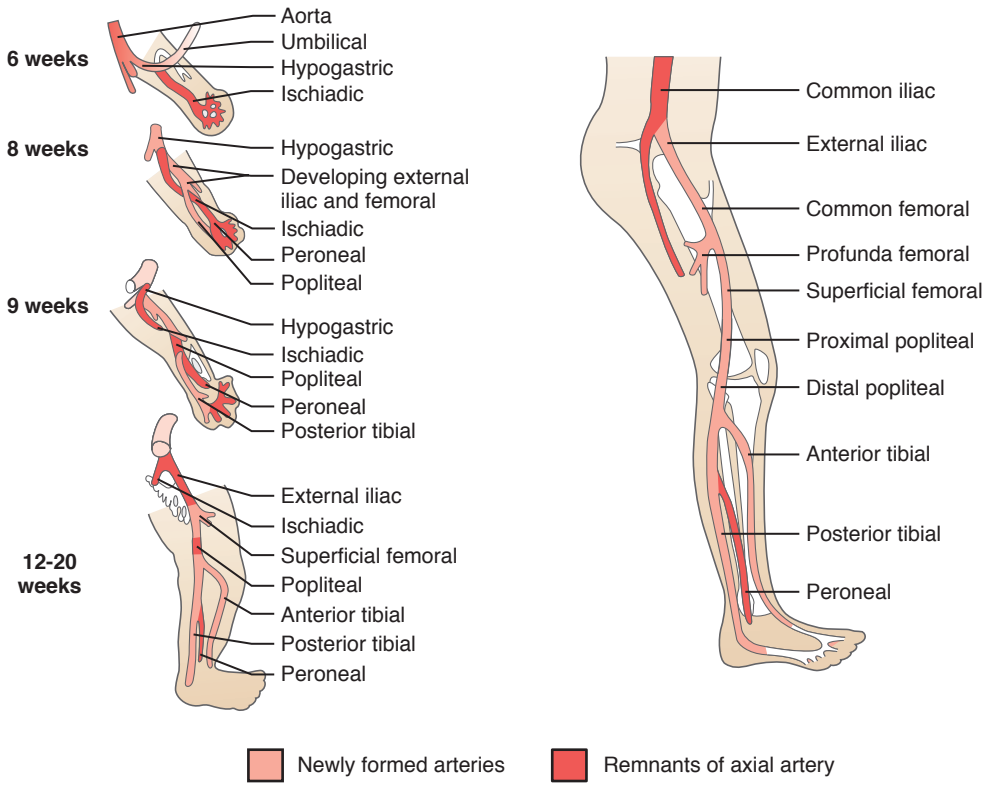

Figure 143.1 Embryologic derivation of the popliteal and other lower limb arteries. Remnants of the axial artery and arteries that develop with later differentiation are indicated. (From Levien LJ, Benn CA. Adventitial cystic disease: a unifying hypothesis. *J Vasc Surg.* 1998;28:193-205.)

Initially, both heads of the gastrocnemius muscle originate from the proximal tibia. With development, these migrate cranially along the femur to different extents. The final position of the medial head of the gastrocnemius muscle is more proximal to that of the lateral head and immediately caudal to the adductor hiatus, with the popliteal artery lying immediately lateral.[2] These dynamic processes of muscle and arterial development create the potential for various anatomic variations that may lead to popliteal artery entrapment (Fig. 143.2).

Classification

The current PAES classification system consists of six variants, types I to VI, and is based on the Heidelberg classification. It accounts for variations in the anatomy of the popliteal fossa (Fig. 143.3).[11]

Type I

The popliteal artery completes its development before migration of the medial head of the gastrocnemius muscle, which then pushes the artery medially during migration. This results in the popliteal artery's medial deviation to a normally situated gastrocnemius muscle.[8]

Type II

The artery is displaced medially, but the medial head of the gastrocnemius muscle has an abnormal attachment on the lateral aspect of the medial femoral condyle or intercondylar area. In this case, the artery forms prematurely and partially arrests the migration of the gastrocnemius muscle, resulting in the artery positioned medially to an abnormally attached muscle. In contrast to the normal position of gastrocnemius muscle insertion in type I entrapment, type II is defined by an abnormal femoral insertion site.

Type III

This type is caused by an abnormal muscle slip or fibrous band that arises from either the medial or lateral femoral condyle.[8] Type III entrapment occurs when embryologic remnants of the gastrocnemius muscle remain posterior to the popliteal artery or when the artery develops within this muscle mass. Occasionally a double origin of the gastrocnemius muscle can surround and compress the popliteal artery.

Types I to III represent the same anatomic variant, the degree of which depends on the temporal relationship between popliteal artery development and migration of the medial head of the gastrocnemius muscle.

Type IV

The mechanism resulting in type IV entrapment is fundamentally different from that causing types I to III. Type IV entrapment occurs with persistence of the axial artery as the mature distal popliteal artery. This artery remains in its embryologic position, deep to the popliteus muscle or fibrous bands.[8]

Type V

Both the popliteal artery and vein are involved or entrapped by any of the previously described mechanisms. This subtype has been estimated to occur in approximately 10% to 15% of cases.[12,13]

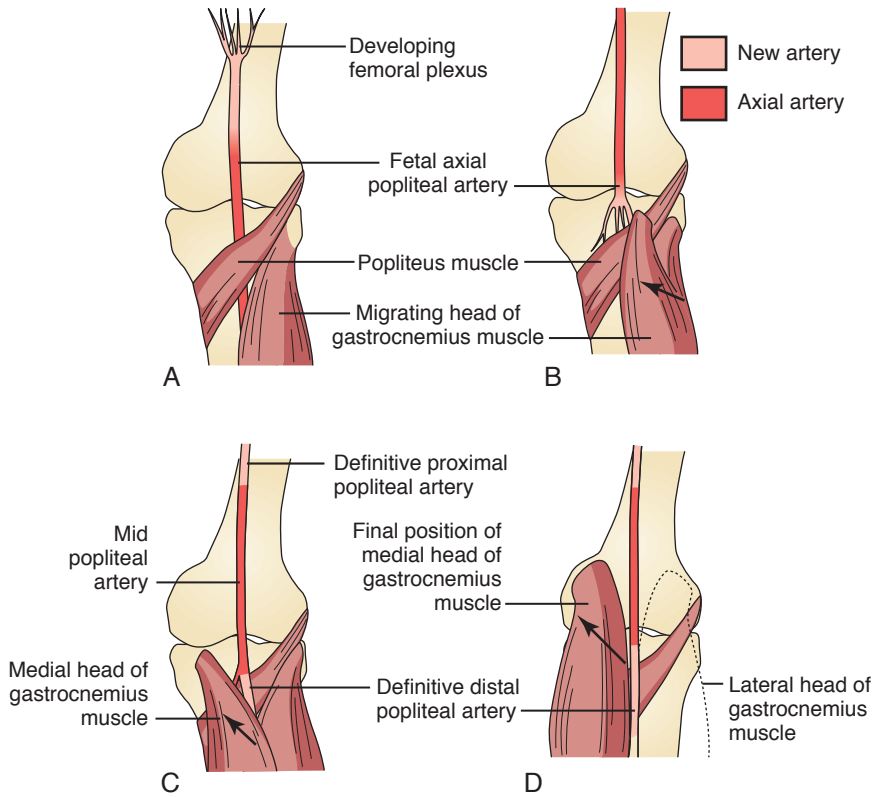

Figure 143.2 Migration of the medial head of the gastrocnemius muscle through the popliteal fossa during formation of the popliteal artery. **(A)** The medial head of the gastrocnemius muscle begins to migrate from the region of the fibula. At this stage, the axial distal popliteal artery lies deep to the popliteus muscle. **(B)** The distal portion of the popliteal artery involutes as the medial head of the gastrocnemius muscle passes from lateral to medial. The proximal popliteal artery is derived from fusion with the developing femoral plexus, whereas the midportion of the popliteal artery is formed from the persistent axial artery remnant. **(C)** A new or nonaxial distal popliteal artery now forms superficial to the popliteus muscle, after the medial head has migrated through the popliteal fossa. **(D)** Normal definitive popliteal anatomy. (From Levien LJ, Veller MG. Popliteal artery entrapment syndrome: more common than previously recognized. *J Vasc Surg*. 1999;30:587-598.)

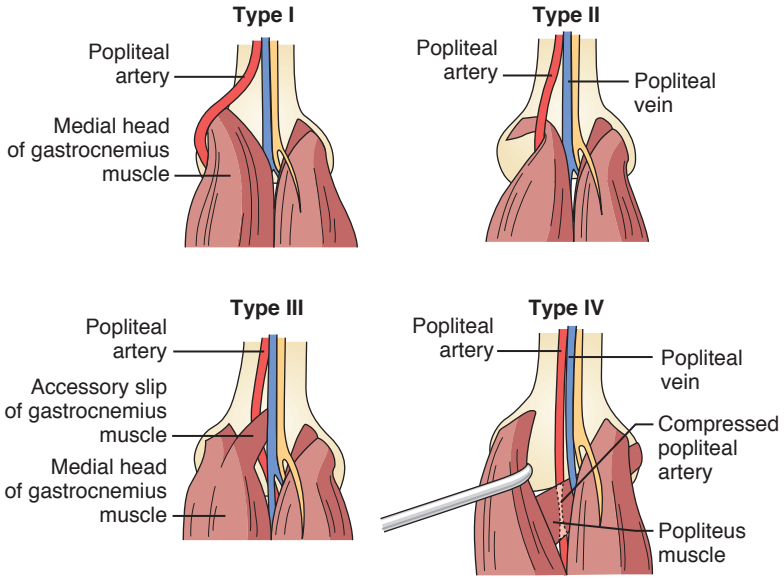

Figure 143.3 Types of popliteal artery entrapment syndromes. (From Levien LJ, et al: Popliteal artery entrapment syndrome: more common than previously recognized. *J Vasc Surg*. 30:587-598, 1999.)

Type VI

An additional type of entrapment—previously known as functional entrapment, or type F—is now commonly referred to as type VI entrapment. Patients present with the typical features of PAES in the absence of an explanatory anatomic abnormality.[8] It has been proposed that the anatomic abnormality in type VI entrapment is an especially lateral attachment of the medial head of the gastrocnemius muscle to the posterior aspect of the medial femoral condyle. Alternatively, hypertrophy of gastrocnemius following regular exercise is thought to result in compression of the posteromedial aspect of the popliteal artery. When subjected to MRI examination, individuals with type VI PAES and popliteal artery occlusion with stressor maneuvers tend to have a more extensive midline position of the medial head of the gastrocnemius muscle. When compared with normal controls, patients with type VI PAES have more of this muscle attached toward the supracondylar femoral midline, around the lateral border of the medial femoral condyle, and within the intercondylar fossa.[14]

Recent advancements in imaging technologies have led to the discovery of other etiologies for popliteal artery entrapment, such as anomalous slips of the lateral head of the gastrocnemius or plantaris muscles.[15–17] Such cases are extremely rare, however, and have not warranted a modification of the current classification system.

Pathology

The pathologic classification of PAES describes the continuum of histologic changes that result with chronic popliteal compression, from fibrosis of the various arterial layers to complete occlusion and thrombosis.[8] In stage 1, the fibrosis is confined to the adventitia. In stage 2, it extends into the media, which may result in poststenotic dilation or aneurysm formation. In stage 3, the artery may become thrombogenic as the fibrosis extends into the intimal layer.[13] However, the degree of arterial damage does not appear to be directly related to the duration of compression or popliteal entrapment.

Clinical Presentation

PAES patients are typically young, physically active men who present with lower-extremity claudication. However, a range in the severity of associated symptoms, along with a grading scale for their description, has been described (Table 143.1).[2]

Claudication symptoms may be atypical and paradoxical, worsening with standing or walking and improving with more vigorous exercise, or they may occur immediately, rather than after walking for a long distance. Patients occasionally describe symptoms of coldness, blanching, and numbness. All types of entrapment (except type VI) can involve the tibial nerves and result in paresthesia. A minority of patients (10%) present with signs and symptoms of chronic CLI, and even fewer present with acute limb ischemia. Venous entrapment (type V) is suggested by calf cramping or symptoms more typical of a compartment syndrome, including swelling and a feeling of fullness.[13]

Pedal pulses are typically palpable and normal at rest, but disappear with passive dorsiflexion or active plantar flexion of the foot. These maneuvers tense the gastrocnemius muscle against the entrapped artery, temporarily occluding the patent lumen. They should also be performed on the contralateral asymptomatic limb. If left untreated, chronic entrapment causes progressive fibrosis of the popliteal artery, resulting in a thrombogenic intimal surface and eventual arterial thrombosis and occlusion.[8] Occlusion of the popliteal artery can be heralded by the sudden onset of more severe calf claudication and absent pedal pulses. This can occur after an episode of strenuous exercise, and should result in a high degree of suspicion for PAES when it occurs in a young adult with no risk factors for atherosclerosis.

Poststenotic dilation or aneurysmal degeneration of the popliteal artery, when it occurs, can be a source of distal emboli.[8]

Diagnostic Evaluation

The differential diagnosis for nonatherosclerotic lower-extremity peripheral arterial disease is outlined in Table 143.2.[18]

Noninvasive Testing

Exercise treadmill testing is commonly performed as an initial investigation. The patient is instructed to walk or jog until symptoms develop. Ankle-brachial pressure measurements are obtained before and following the treadmill test, and should drop significantly. Subsequently, duplex segmental pressures are taken with the Doppler probe placed on the posterior tibial artery. Active plantar flexion and passive dorsiflexion of the ankle with the knee in full extension results in gastrocnemius muscle contraction.[12] Readings are repeated several times, and care should be taken to avoid moving the probe during muscle contractions. Similarly, duplex studies are performed with visualization of the popliteal artery during calf muscle contraction and relaxation. The duplex interrogation must be repeated several times, because the popliteal artery can be pushed deeper into the popliteal fossa during muscle contraction, negatively affecting visualization and volume recordings. A positive duplex test with provocative maneuvers should prompt further investigative studies. While some investigators have had excellent results with duplex ultrasound,[19] others have reported high (72%) false-positive studies, resulting in an overestimation of popliteal artery compression.[13]

TABLE 143.1 Classification of Popliteal Artery Entrapment Syndrome Symptoms

Class	Description
0	Asymptomatic
1	Pain, paresthesia, and cold feet after physical training (e.g., jogging, heavy work)
2	Claudication while walking (>100 m)
3	Claudication while walking (<100 m)
4	Rest pain
5	Necrosis

From di Marzo 2005.

Angiography

Angiography remains the mainstay of investigation at many centers, with a reported median sensitivity of 97% (range, 85% to 100%).[6] In general, the diagnosis of PAES should be considered when at least two of the following angiographic features are present:[2]

- Medial deviation of the proximal popliteal artery
- Focal occlusion of the mid-popliteal artery
- Poststenotic dilation of the distal popliteal artery

Angiography has the additional advantage of delineating tibial artery anatomy following embolization from a poststenotic dilation of an entrapped popliteal artery or a thrombogenic entrapped artery. Angiographic views should be obtained in the neutral position and during provocative maneuvers (Fig. 143.4). Angiography is useful to distinguish PAES from ACD of the popliteal artery. In contrast to PAES, the arterial stenosis

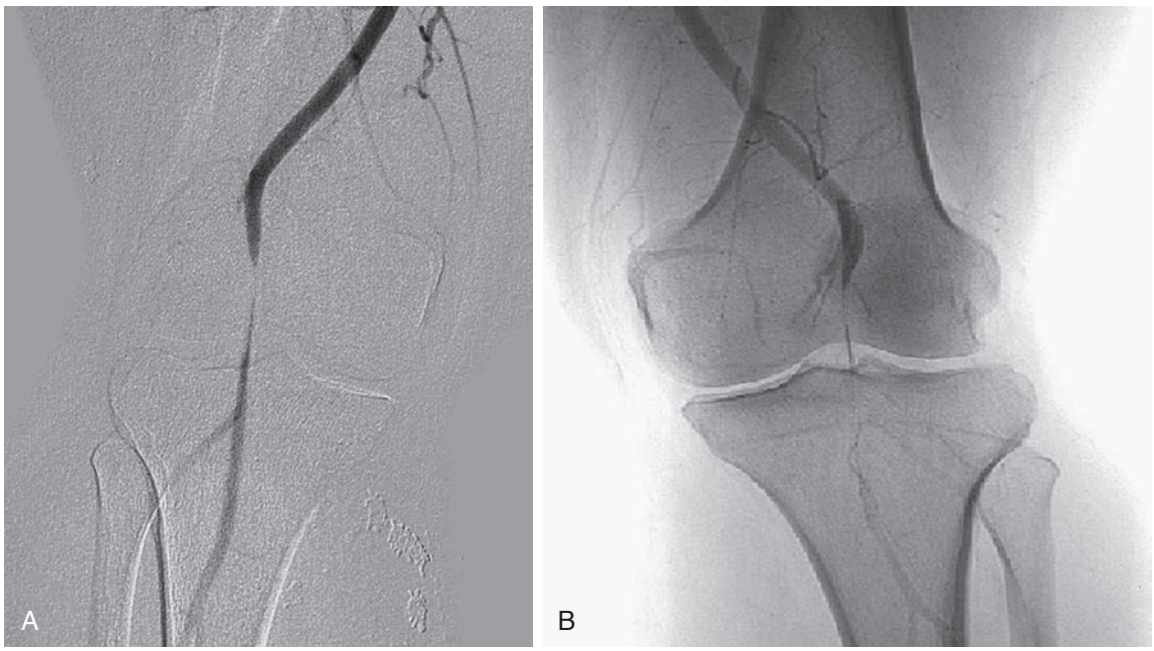

Figure 143.4 Angiogram reveals popliteal artery occlusion with plantar flexion of the foot. (From Causey MW, Singh N, Miller S, et al. Intraoperative duplex and functional popliteal entrapment syndrome: strategy for effective treatment. *Ann Vasc Surg*. 2010;24:556-561.)

TABLE 143.2 Differential Diagnosis of Nonatherosclerotic Peripheral Artery Disease

		Age	Sex	Key Features	Diagnosis
Popliteal artery entrapment syndrome		Young adults	M > F	Exertional claudication pain, paresthesias, and poikilothermia after exertion external compression of popliteal artery from muscles and ligaments in popliteal fossa	Loss of Doppler signaling with provocative maneuvers demonstration of compression on active pedal plantar flexion against resistance CT/MRI to demonstrate entrapment of vascular structures
Adventitial cystic disease		4th and 5th decades	M > F	Exertional claudication with extended recovery time compared to aPAD symptoms caused by compression of arterial lumen by mucinous containing cystic lesion within the adventia	Loss of pedal pulses with sharp knee flexion (Ishikawa sign) CT/MRI
Iliac artery endofibrosis		2nd and 3rd decades	M = F	Competitive athletes, common in cyclists intimal thickening by collagen fibers, fibrous tissue, and smooth muscle proliferation femoral bruit with hip flexion	Arterial duplex ultrasound and digital subtraction angiography with hip flexion and extension intravascular ultrasound with intraarterial translesional pressure gradients
Fibromuscular dysplasia		2nd to 5th decades	F > M	"String of bead" appearance symptoms based on vascular bed involved	Digital subtraction angiography with intravascular ultrasound
TAO (Buerger disease)		<50 years		Tobacco smokers intermittent claudication, Raynaud phenomena, superficial thrombophlebitis skipped lesions and corkscrew collaterals	CT/MRI digital subtraction angiography
Medium and large vessel vasculitis	TA	15–30 years	F > M	Asian and Latin decent pulseless upper extremity	Elevated inflammatory markers Duplex ultrasound CTA MRA temporal artery biopsy (GCA)
	GCA	>50 years	M = F	Headache, jaw claudication, visual disturbances	
	Behcet's	<30 years	M = F	Recurrent mucosal ulcers, uveitis, pathergy	
Chronic exertional compartment syndrome		>40	M = F	Athletes typically bilateral complete symptom resolution 10-20 min after rest	Imaging to rule out other causes elevated intra-compartment pressures before and after exercise

CTA, Computed tomographic angiography; *MRA,* magnetic resonance angiography; *TA,* Takayasu arteritis; *GCA,* giant cell arteritis; *aPAD,* atherosclerotic peripheral artery disease; *TAO,* thromboangiitis obliterans.
From Mintz 2015.

or compression from adventitial cysts is readily visible in the neutral position.

Computed Tomography and Magnetic Resonance Imaging

Less invasive imaging alternatives such as computed tomography (CT) or magnetic resonance imaging (MRI) can be particularly useful in cases of popliteal artery entrapment syndrome when the artery is occluded, because they illustrate the anatomic relationships between the vessels and muscles in the popliteal fossa and identify anomalous muscular insertions (Fig. 143.5). Some investigators believe that MRI is superior to CT in this regard, and should be the diagnostic test of choice in young patients presenting with intermittent claudication.[13]

Treatment

In most cases of symptomatic PAES, surgical intervention is indicated and should be offered. This is especially true for types I to V entrapment, and depends on the severity of symptoms in type VI entrapment. The approach to treatment is dictated by the patient's anatomy, clinical presentation, and the status of the popliteal artery (Table 143.3).

In general, early intervention allows for a more limited operation with myotomy alone, rather than arterial reconstruction. Because the natural history of PAES progresses from arterial fibrosis to thrombosis and eventual occlusion, most authors advocate surgical correction of types I to V PAES to prevent arterial degeneration. The principles of surgical treatment include release of arterial entrapment, restoration of normal anatomy, and restoration of arterial flow.[13]

Endovascular therapies are limited because they do not address the underlying muscular entrapment. There have been reports of small numbers of patients with occluded popliteal arteries undergoing endoluminal interventions and thrombolysis followed by myotomy several weeks later. These patients were anticoagulated for various periods.[20] However, anticoagulation and the preservation of a potentially thrombogenic popliteal artery are

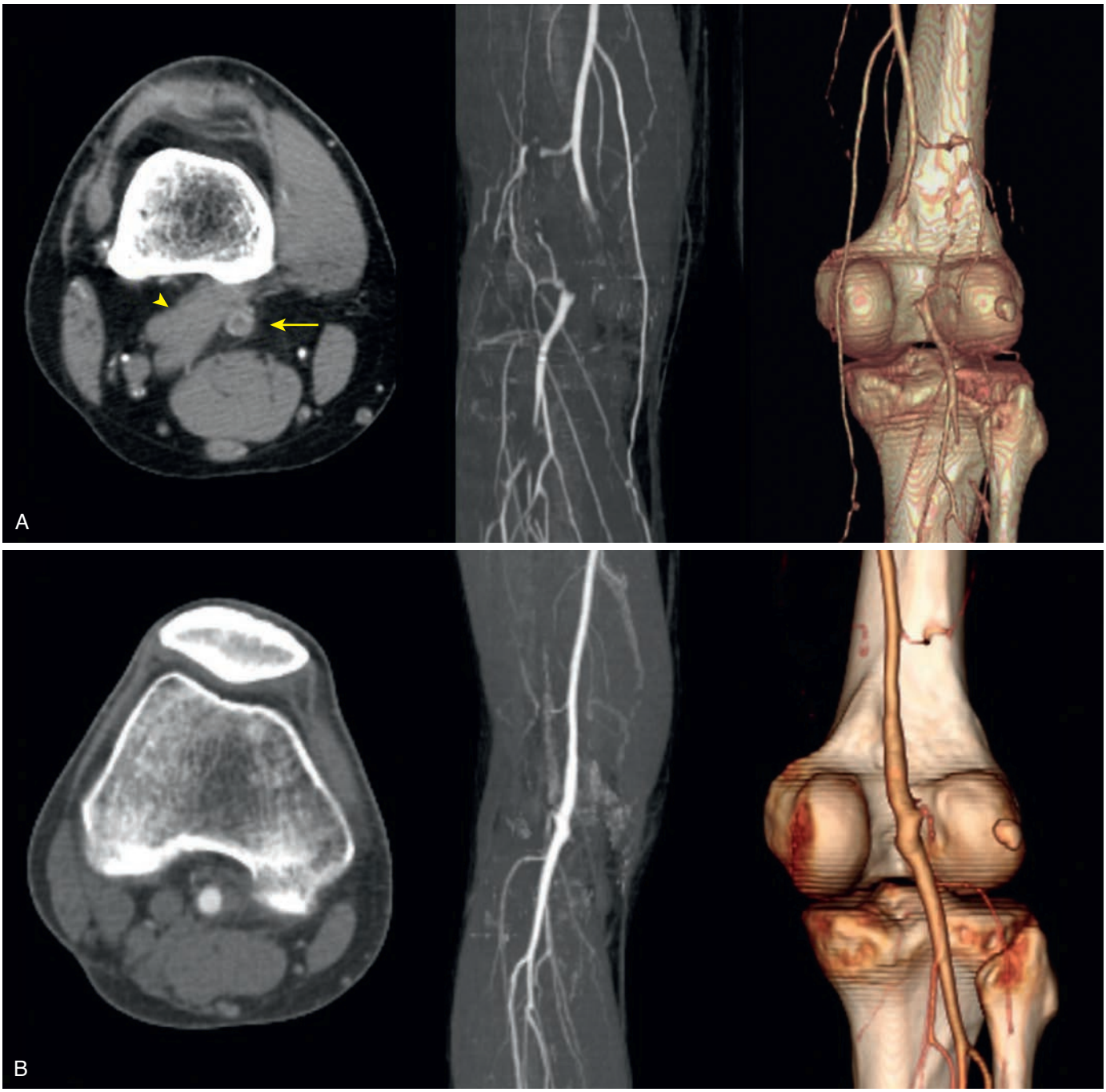

Figure 143.5 Popliteal entrapment syndrome type I **(A)** medial head of gastrocnemius muscle *(arrowhead)* occludes popliteal artery *(arrow)*. **(B)** Patent artery following musculotendinous resection and popliteal artery interposition venous graft. (From Kim SY, Min SK, Ahn S, et al. Long-term outcomes after revascularization for advanced popliteal artery entrapment syndrome with segmental arterial occlusion. *J Vasc Surg*. 2012;55:90-97.)

suboptimal treatment options in this young and active patient population.

Type I to V, Normal Popliteal Artery

In the absence of arterial fibrosis in an otherwise normal-appearing popliteal artery, musculotendinous release alone is sufficient to restore normal anatomy.[13] Musculotendinous release can be performed through either a posterior or a medial approach. Proponents of the posterior approach highlight the operative flexibility that it offers the surgeon, the wider degree of inspection possible, the greater ease of identifying and addressing the specific anatomic abnormality, and an adequate exposure to complete an arterial reconstruction if necessary.[13,21] Following an S- or Z-shaped incision, flaps are raised to expose the deep fascia, which is incised longitudinally, avoiding injury to the median cutaneous sural nerve. Sacrifice of the lesser saphenous vein

TABLE 143.3 Management Options for Popliteal Artery Entrapment Syndromes

Status of Artery	Entrapment Type	Operation	Surgical Approach
Normal	I and II	Myotomy	Medial
	III and IV	Myotomy	Posterior
	V	Myotomy	Medial or posterior
	VI	Myotomy if symptomatic	Medial or posterior
Abnormal (occluded, stenosed, or poststenotic dilatation or aneurysm)	I to VI	Decompression and arterial resection and replacement or exclusion and bypass	Medial or posterior

can facilitate exposure. As the vessels are approached, the tibial nerve is encountered and mobilized. The popliteal vein is identified, passing between the heads of the gastrocnemius muscle deep in the popliteal fossa. The popliteal artery, which is not in its normal position, is identified higher in the popliteal space and followed distally. The artery's abnormal course can be medial to the medial head of the gastrocnemius muscle or entrapped by anomalous muscular structures or tendinous tissue.[21]

Through this posterior exposure, the medial head of the gastrocnemius muscle or the entrapping musculotendinous bands are completely divided, with no adverse functional sequelae, even in these young, active patients.[22] In entrapment types III and IV, mobilization of the muscular portion of the medial head of the gastrocnemius off of the posterior aspect of the femoral condyles usually suffices to relieve compression of the artery.

The medial operative approach is most suited for PAES types I and II and is less appropriate for types III and IV, where it may be more difficult to delineate the arterial and muscular anatomy. Entrapment types III and IV may best be explored via the posterior approach. Type V entrapment can be explored through either route, depending on the underlying muscular abnormality. The medial approach seems to result in a quicker return to normal athletic activities in these active patients and less incision-related morbidity.[8] Similar to the posterior approach, the medial head of the gastrocnemius muscle is divided when approached from its medial aspect, permitting complete arterial decompression.

Types I to V, Abnormal Popliteal Artery

Arterial bypass or replacement is indicated in cases of complete thrombosis, arterial wall degeneration from the chronic entrapment, thrombus formation on the intimal surface, fibrotic narrowing of the artery, and poststenotic dilation or aneurysm formation. When the popliteal artery demonstrates evidence of chronic damage, even if the extent is only minimal fibrosis, it should be replaced or bypassed in its entirety. Early reports of this syndrome described numerous instances of thromboendarterectomy with or without vein patch angioplasty. This approach produced inferior results, with a higher incidence of arterial thrombosis and reocclusion compared with arterial replacement with an autogenous conduit.[13]

Intraoperative duplex ultrasound can be useful for determining the need for arterial bypass. White and colleagues recently proposed the following intraoperative duplex ultrasound criteria for performing an interposition graft bypass in PAES patients: peak systolic velocity of 250 to 275 cm/s or greater, velocity ratio of 2 or greater, arterial occlusion, or aneurysmal (poststenotic) degeneration.[23]

The entrapment is first relieved by dividing the muscle or tendinous segment causing the arterial compression. Resection of the thrombosed artery and a short interposition venous graft are then performed. Alternatively, a short venous bypass graft can be performed, with exclusion of the occluded artery to prevent distal thromboemboli. If poststenotic dilation or aneurysm formation has occurred, arterial resection and venous replacement are performed.

Arterial reconstruction can be performed through a posterior or a medial approach. The posterior approach permits use of the lesser small vein as the venous conduit, but it is less useful in cases requiring a more distal reconstruction. Conversely, the medial approach allows for the harvesting of the more proximal great saphenous vein if a conduit of larger caliber is required. In addition, it is much easier to expose the more distal popliteal artery, or tibial arteries, through a medial exposure if a more distal revascularization is required. This may be the case with extensive poststenotic dilatation or with tibial artery occlusion secondary to thromboemboli from the entrapped popliteal artery.

Type VI, Symptomatic

Most authors support surgical intervention for symptomatic type VI PAES. Hislop and colleagues in Australia have advocated for the injection of *Botulinum* toxin (Botox BTX-A) as an initial intervention in those patients.[24] Botox's proposed mechanism of action is through paralyzing the slip of muscle responsible for the dynamic arterial occlusion, inducing muscle atrophy that increases the space available for the popliteal artery, and relaxing the arterial smooth muscle, which results in popliteal vasodilation. However, this treatment remains untested in prospective studies.

Other authors have advocated for the use of surgical decompression for these patients, either through a medial or a posterior approach. Transection and resection of the muscular portion of the medial head of the gastrocnemius muscle, with preservation of the tendon, is usually sufficient to relieve symptoms.[13] To ensure adequate decompression, one must take care to completely transect the muscular fibers from the posterior aspect of the lateral femoral condyle and the intercondylar area. Adequacy of the extent of the myectomy can be determined with intraoperative duplex. Before resection, arterial systolic velocities are measured and compared with post myectomy velocities in

neutral, plantar, and dorsiflexion positions. Myectomy is continued until no further changes in velocity are observed.[25]

Type VI, Asymptomatic

Up to half the normal asymptomatic population may exhibit signs of popliteal artery compression, with provocative measures such as active plantar flexion and passive dorsiflexion of the foot. When these individuals are truly asymptomatic, little evidence supports prophylactic operative intervention, and these asymptomatic patients are best followed.[13]

Similarly, although bilateral popliteal artery entrapment is common, often only one extremity is symptomatic (43% of cases).[26] These asymptomatic contralateral extremities should be investigated, but surgical exploration is seldom indicated in the absence of symptoms.[4]

Treatment Outcomes

Myotomy alone for the management of PAES with a normal popliteal artery is associated with excellent results. In one large series, patients were able to return to their prior sports activities, did not require any further interventions, and maintained arterial patency at 10 years of follow-up.[8]

Bypass surgery with vein graft for PAES with an abnormal popliteal artery is associated with 65% to 100% graft patency at 10 years of follow-up.[27–29] Interposition grafts have better patency rates compared with long bypass grafts.[30] Reports of outcomes after hybrid procedures that combine angioplasty with musculotendinous resection and popliteal artery release are limited, but Ozkan and colleagues from Turkey reported primary and secondary patency rates of 60% at a median follow-up of 5 years.[31]

ADVENTITIAL CYSTIC DISEASE

Epidemiology

ACD was first reported in 1947 by Atkins and Key in London. The patient was a 40-year-old policeman with claudication and ACD of the external iliac artery.[32] It was not until 1954, however, that Ejrup and Hiertonn from Sweden described the first case involving the popliteal artery.[33] Since then, more than 700 cases have been reported, with the popliteal artery most commonly affected (80.5% of cases).[34]

ACD accounts for 0.1% of lower-extremity claudication.[35] In the majority of cases, popliteal artery involvement is unilateral, and only five cases of bilateral lesions have been reported.[34] The next most commonly involved arteries are the external iliac and femoral arteries,[36,37] but the disease has been reported in most of the arteries lying adjacent to joint spaces (Fig. 143.6).[38] Although it is most commonly a disorder of the arterial system, ACD of the iliofemoral and saphenous veins has also been described.[39]

ACD affects males predominantly, with a male to female ratio of 5 to 1, and patients are typically in their mid-40s.[34] Some investigators have reported a slightly older age at diagnosis in women.[40] Cases of pediatric patients (5 to 15 years old) have also been described.[34] It must be emphasized, however, that the diagnosis is often delayed because of the relatively young age of these patients and the absence of atherosclerotic risk factors. The prevalence of ACD has been variously reported as 1 in 1200 patients with claudication, regardless of age, and 1 in 1000 diagnostic angiograms.[41] These reports include predominantly symptomatic patients, so the incidence of ACD in the general asymptomatic population is unknown.

Pathogenesis

Etiology

The precise cause of ACD remains unclear and somewhat controversial. Five theories of etiology and pathogenesis have been proposed: the repetitive trauma, ganglion, systemic disorder, developmental, and articular theories.[40,41] Although convincing data to support the validity of the first three theories are scarce, they are briefly described as follows.

Repetitive Trauma Theory

Proponents of this theory suggest that repeated flexion and extension of the knee joint result in chronic injury of the popliteal artery that is characterized by cystic degeneration.[38,40,42] This repetitive distraction movement of the popliteal artery causes intramural hemorrhage between the adventitia and media. Subjecting the knee joint to repetitive movement and stress leads to joint degeneration and changes in the surrounding connective tissue, which in turn secrete hydroxyproline that acts on the intramural hemorrhage to result in adventitial cyst formation.[42]

Although this theory is simple and relatively intuitive, scientific data to support it are scarce. Repetitive trauma as a causative factor does not explain cases occurring in arteries that are not subjected to such stress or in younger patients who have not been subjected to the same duration of this stimulus. Furthermore, one would expect more cases of adventitial cystic disease in athletes, and there would be a positive correlation between age and incidence of the disease. Such trends, however, have not been observed.

Ganglion Theory

Proponents of this theory have been prompted by the similar content of simple ganglions and popliteal artery cysts.[38,40,43] Both types of cystic structures contain high levels of hyaluronic acid. In addition, there have been case reports of synovial cystic structures and Baker's cysts directly involving adjacent vascular structures.[44] Presumably, in the case of the popliteal artery, these synovial cysts enlarge and track along arterial branches, where they implant in the adventitia of the popliteal artery itself.[45] However, there is no evidence of histologic similarities between the lining and chemical content of the cystic fluid in the synovium and popliteal artery cysts. In fact, fluid from adventitial cysts has a much higher hyaluronic acid content than synovial cysts.[46]

Systemic Disorder Theory

This theory postulates that a systemic mucinous or myxomatous degenerative condition leads to development of ACD. Despite

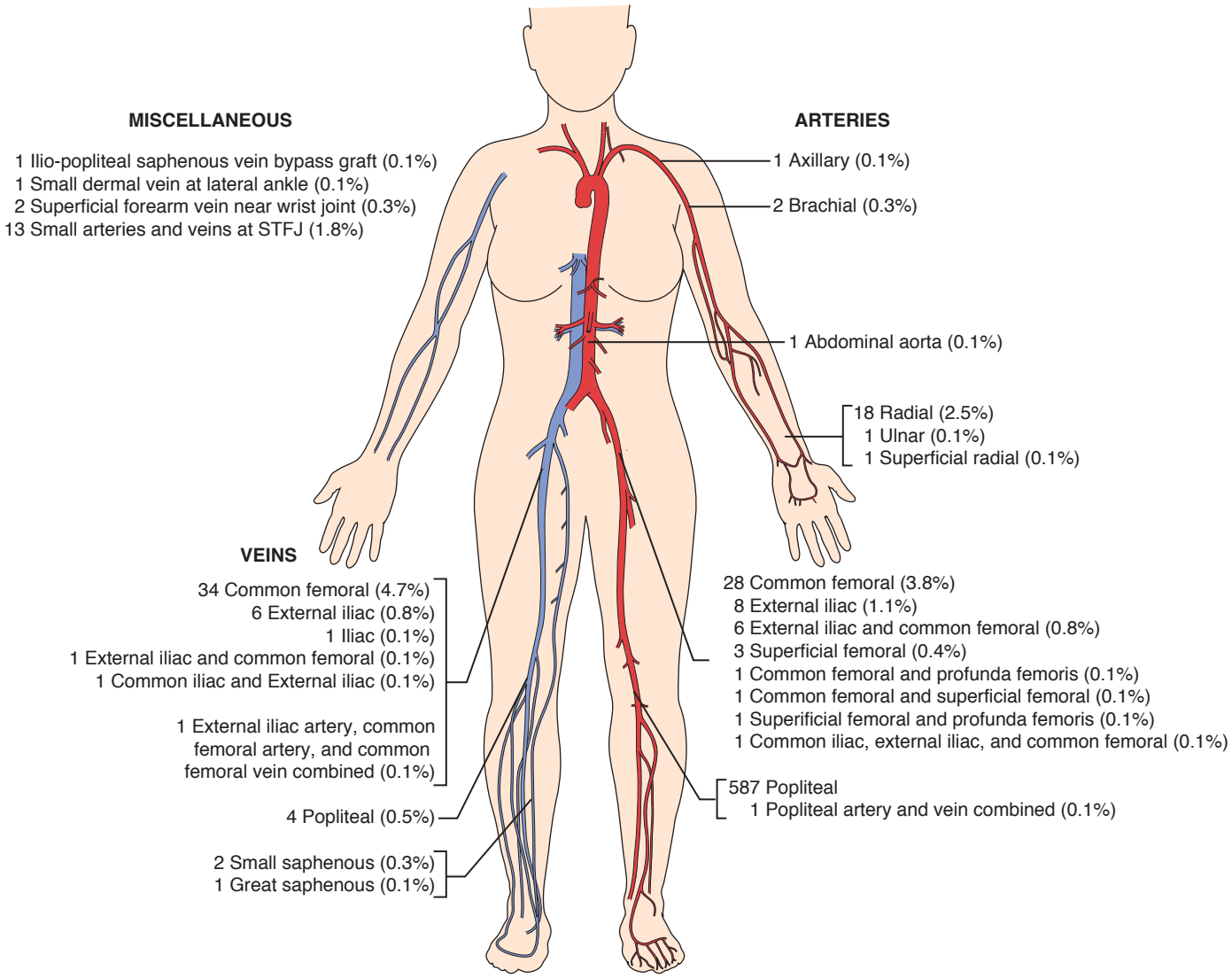

Figure 143.6 Artistic drawing demonstrating the various sites of adventitial cystic disease. *STFJ,* Superior tibiofibular joint. (From Desy 2014.)

being proposed in 1967,[47] no systemic disorder has ever been identified to support this theory. In addition, reports of bilateral disease are very rare,[48] as are cases of synchronous or metachronous cysts in different vascular locations that one would expect with a systemic disorder.

Developmental Theory

Also known as the cellular inclusion theory, this theory proposes that ACD occurs when mesenchymal mucin-secreting cells are implanted in the adventitia of the vessel during development. Levien and Benn noted that nonaxial arteries form from vascular plexuses between 15 and 22 weeks of embryologic development adjacent to developing joints.[38] During this time, mesenchymal cells that form these joints can be incorporated into closely adjacent vessels and may be responsible for subsequent cyst formation when these mesenchymal cells start to secrete mucoid material.

Articular (Synovial) Theory

Connections between the knee joint capsule and an adjacent popliteal artery adventitial cyst have been identified both intraoperatively and by preoperative imaging.[32,40,45,47,49–52] The articular (synovial) theory postulates that synovial fluid from a neighboring joint egresses and dissects along the adventitia of an articular (capsular) branch to the parent vessel.[52–54] Proponents of this theory argue that ligation of the joint connection along with simple cyst incision and drainage provides definitive treatment for this disease while decreasing the need for vein harvest.[34]

On the one hand, the presence of such a connection lends support to the ganglion theory of development, with the connection representing a direct communication between the joint capsule and the arterial adventitial layer through which synovial cysts can migrate.[45,49,51] Alternatively, proponents of the developmental theory claim that these communications represent a

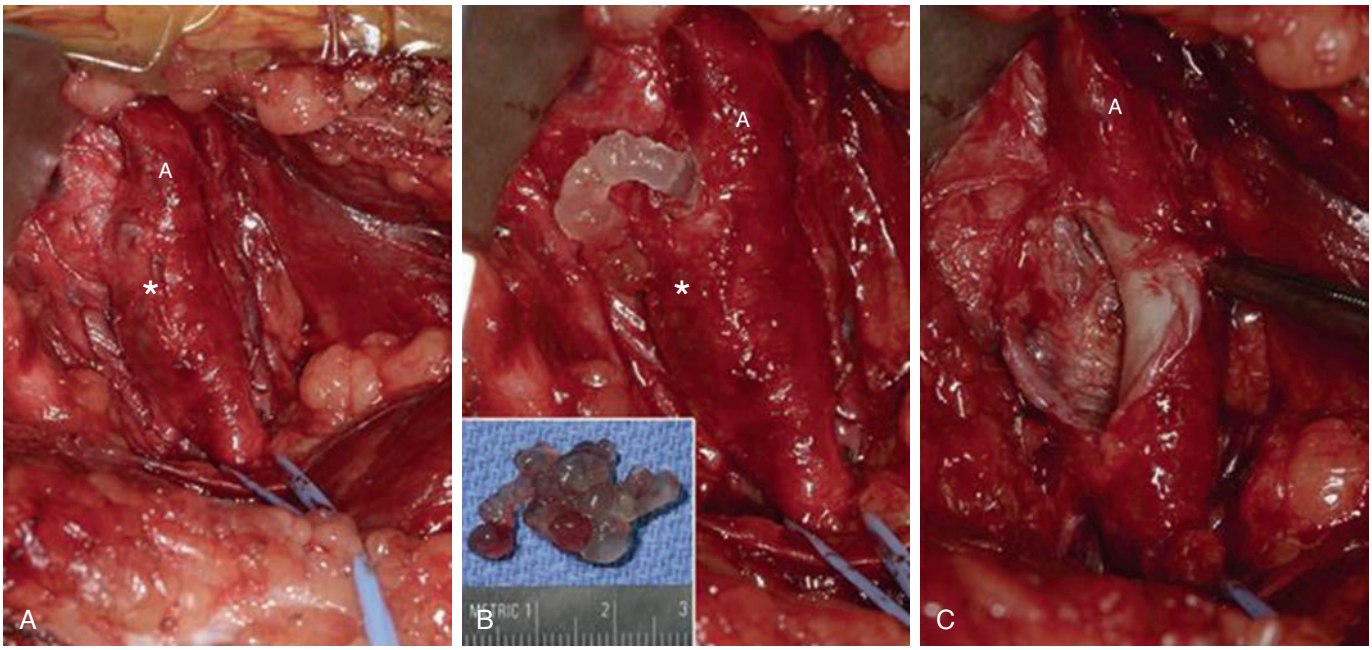

Figure 143.7 Adventitial cystic disease of the popliteal artery opened and evacuated. **A,** Cystic adventitial disease of the popliteal artery. **B,** Incision of adventitia with drainage of mucoid material (inset). **C,** The popliteal artery after evacuation of mucoid cyst. (From Spinner 2013.)

residuum of the embryologic process, when mesenchymal cells of the adjacent joint are included in the adventitia of the nearby developing artery.[38,45]

Pathology

Popliteal artery adventitial cysts are filled with a gelatinous mucoid material. Microscopic examination reveals a simple cuboid cell lining in the adventitial layer, with a notable absence of any coexisting microscopic features of atherosclerotic disease. Grossly, the popliteal artery may appear enlarged and sausage-like, connected by adhesions to adjacent structures (Fig. 143.7). The cyst is usually unilocular but can be multilocular. Cyst contents are usually clear or yellow, but can be dark red following hemorrhage. At the time of operation, these cysts are apparent following incision of the adventitial layer.

Clinical Presentation

Arterial

The typical patient with ACD of the popliteal artery is a young male who complains of sudden onset of short-distance calf claudication.[41] The disease can present in all ages, however, and has been described in young children.[55] The duration of symptoms is generally relatively short (weeks to a few months) and unilateral. Claudication symptoms may completely resolve for a period of time and then recur, or they may progress rapidly. Recovery time is often prolonged, up to 20 minutes, compared with that of typical claudicants.[56]

Given the focality of these cysts, the young age of patients, and the otherwise normal status of inflow and outflow vessels, progression to CLI is unusual with ACD, although the severity of claudication can progress and become disabling. It appears that the cysts need to be present and slowly enlarging for extended periods before patients enter the symptomatic phase. These enlarging cysts lead to progressive compression of the arterial lumen and can result in a "functional" occlusion of the artery without causing complete thrombosis. In cases of apparent arterial occlusion without thrombosis, evacuation of cyst contents can restore arterial patency. Nonetheless, prolonged compression of a compromised lumen can lead to popliteal artery thrombosis and a fixed occlusion.

Approximately two thirds of patients present with popliteal artery stenosis rather than occlusion. On physical examination, this may be demonstrated by normal or diminished pedal pulses and by an audible bruit in the popliteal fossa. Pedal pulses that are present at rest may disappear with flexion of the hip and knee (Ishikawa sign),[57] representing a functional stenosis that progresses to vessel occlusion with this physical manipulation. This is in contradistinction to popliteal artery entrapment, in which pedal pulses disappear with gastrocnemius muscle contraction caused by active plantar flexion or passive dorsiflexion of the foot.[41]

There have been case reports of spontaneous cyst resolution,[58–61] possibly because of cyst rupture into the popliteal fossa. However, this is extremely unusual and should not be considered a feature of this disorder. Furthermore, Zhang and colleagues from Manitoba described a recurrence of the disease after an apparent spontaneous cyst resolution in a female patient who eventually required surgery.[62]

Venous

Venous ACD of the lower extremities is very rare.[39,63] As with arterial ACD, it occurs predominantly in young males and has

been described in children.[64] However, it most commonly involves the iliofemoral rather than the popliteal segments. Typically the diagnosis is made when a young, previously healthy male presents with painless swelling of the lower extremity and is investigated for deep venous thrombosis. Venous ACD should be considered when there is evidence of extrinsic compression on venous duplex imaging or a filling defect on venography. The optimal method of management is not well defined, but most authors advocate operative exploration with venotomy and evacuation of the cyst contents, followed by cyst wall excision to minimize the risk of recurrence. A recurrence rate of 11.5% has been reported.[63]

Diagnostic Evaluation

Ankle-brachial indices in patients with ACD are unaffected at rest and drop following exercise. This pattern should raise the suspicion of an arterial cause of the patient's symptoms and prompt further investigation.

As with all other arterial pathologies, there has been a steady progression of diagnostic modalities from standard angiography and Doppler ultrasound technologies to cross-sectional imaging with CT and MRI. Although each method has advantages and disadvantages, current recommendations advocate the use of duplex ultrasound scanning followed by CT or MRI as the best diagnostic approach.[41]

Noninvasive Testing

Duplex ultrasound should be the initial diagnostic tool for this disorder.[65,66] The number of cysts and their dimensions can be easily evaluated. Elevated Doppler velocities and cystic extraluminal compression of the affected popliteal artery segment is considered diagnostic. The boundary between the cyst and the arterial lumen is depicted by a fine bright line that pulsates. Ultrasound can also differentiate these cysts from popliteal artery aneurysms by an absence of flow within the cysts. Following intervention, duplex scanning is a useful postoperative surveillance tool to exclude cyst recurrence and residual or recurrent stenosis.

Angiography

Traditionally, angiography was the gold standard for diagnosing ACD, but this has now been largely replaced by noninvasive methods. Complete popliteal artery occlusion is demonstrated with angiography in up to one third of cases, and the remaining studies demonstrate an eccentric compression of the popliteal artery lumen known as the "scimitar" sign, or an "hourglass" sign secondary to concentric compression (Figs. 143.8 and 143.9).[65] These imaging features can be detected with CT and MRI as well.

Angiography lacks sensitivity compared with other imaging modalities, because stenosis can be missed on anteroposterior views and may be evident only with lateral projections. Angiograms that demonstrate eccentric stenosis in the absence of thrombosis and poststenotic dilation are specific for ACD. However, the diagnostic capability of conventional angiography is limited in patients with arterial occlusion and provides little information about arterial wall pathology and the surrounding soft tissues.[41]

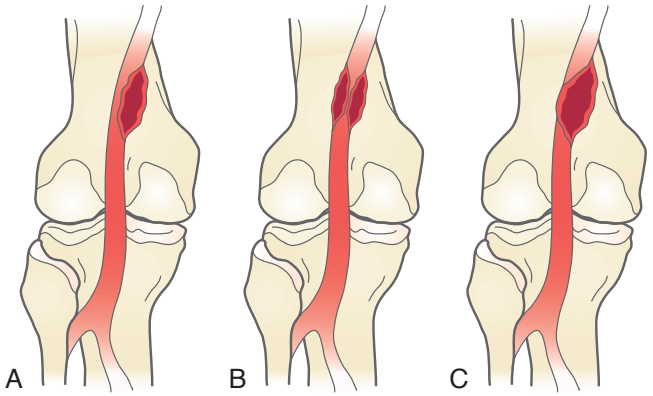

Figure 143.8 Adventitial cysts can occur in variable locations on the popliteal artery. The expanding cyst may indent the artery, resulting in the "scimitar" sign **(A)**; encircle the artery, resulting in the "hourglass" sign **(B)**; or completely occlude the vessel **(C)**.

Computed Tomography and Magnetic Resonance Imaging

CT is being used more extensively in cases of popliteal artery disease. It allows for the differentiation of ACD from PAES and aneurysmal disease, especially in cases of popliteal artery occlusion or thrombosis. CT also has the ability to demonstrate the size of the cysts and their relationship to surrounding structures (Fig. 143.10).[67]

At some institutions, MRI is frequently used for the workup of ACD (Fig. 143.11).[68] Advantages of MRI include the avoidance of ionizing radiation and intravascular contrast agents. MRI clearly depicts the extent of cystic involvement, and many authors consider it essential during the planning of surgical intervention.[34] Some authors recommend protocolling the MRI to include T2-weighted and gradient-echo sequences for suspected cases of ACD.[41] Others have described the use of T3 high spatial resolution MRI imaging, but there are concerns that significant increases in spatial resolution may adversely affect the image signal-to-noise ratio and limit the study's usefulness.[69,70]

Despite the lack of convincing evidence to support the use of MRI over CT, few investigators would argue against the use of cross-sectional imaging for the diagnosis of ACD and subsequent treatment planning. Duplex ultrasound remains useful as an initial diagnostic test and for postoperative surveillance. Emerging diagnostic technologies such as intravascular ultrasound and optical coherence tomography (Fig. 143.12) might also play an important role in the vascular surgeon's diagnostic toolbox as they become more widely available.[71]

Treatment

Given the rarity of ACD, treatment recommendations are mostly based on an evaluation of cumulative single-center experiences as opposed to randomized-controlled studies or prospectively maintained databases.

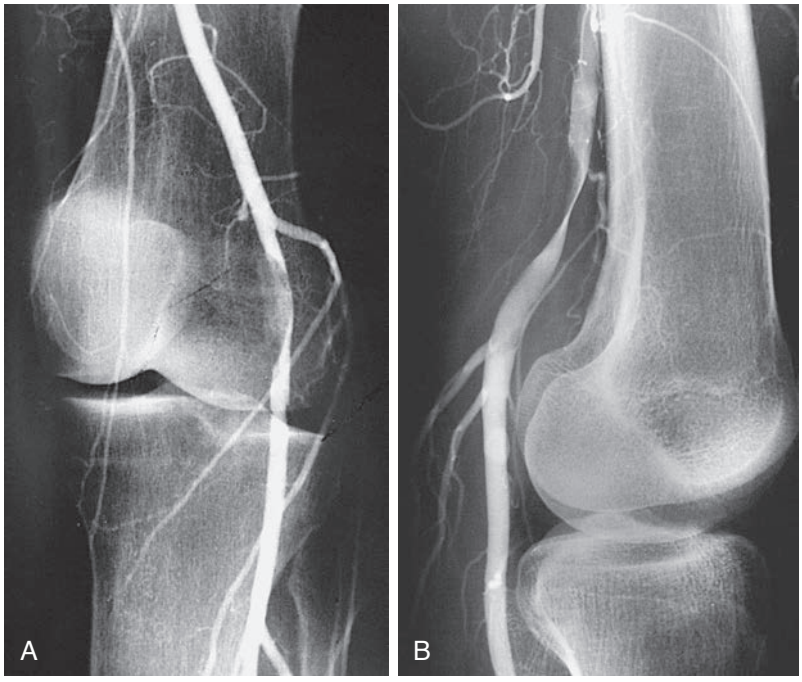

Figure 143.9 **(A)** Femoral angiogram shows compression of the right popliteal artery by an adventitial cyst. **(B)** Lateral view of another patient shows anterior compression of the popliteal artery above the knee.

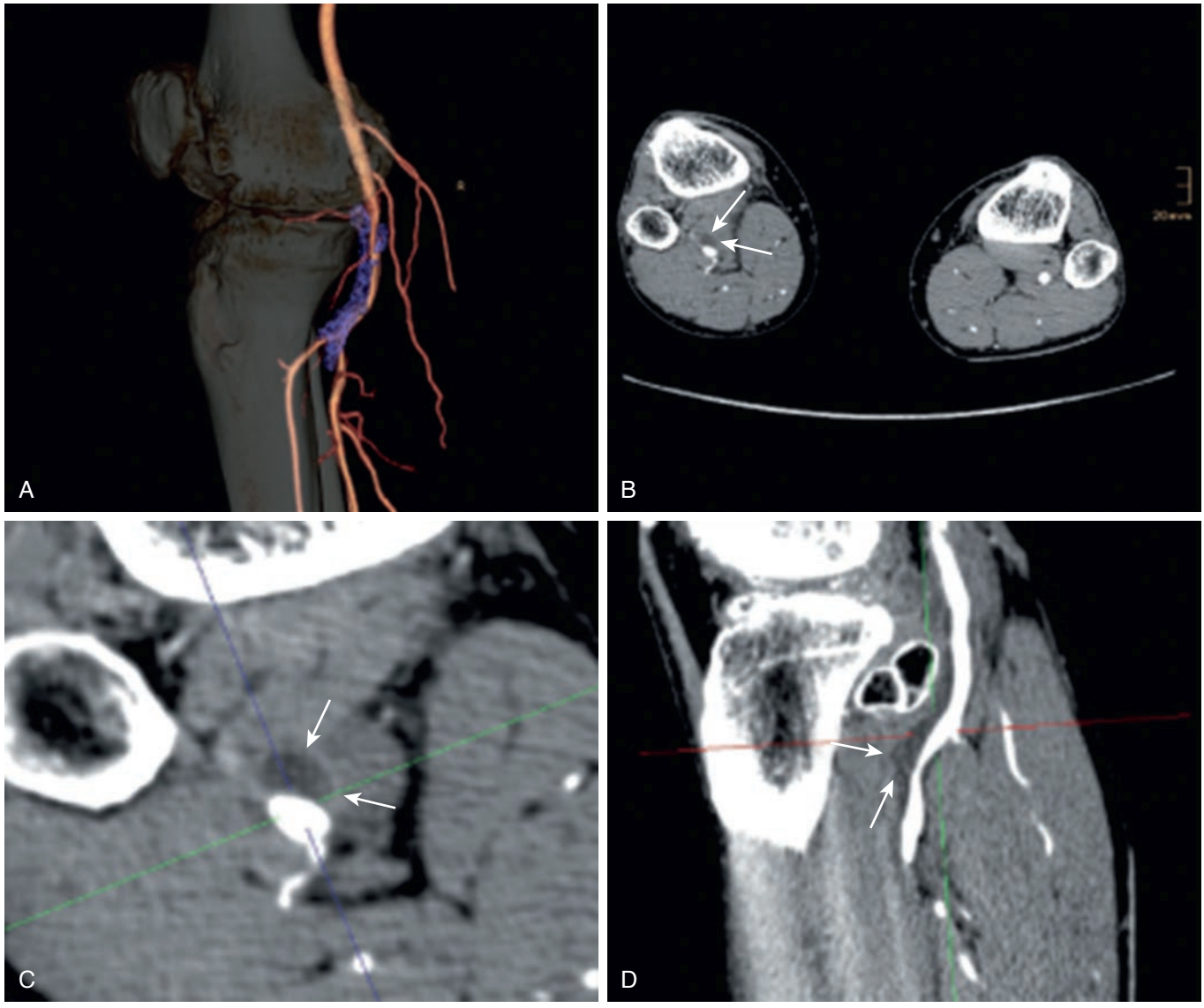

Figure 143.10 Contrast medium–enhanced CT angiography with three-dimensional reconstructions **(A)** shows a cystic extraluminal mass along and around the popliteal artery (**B** and **C,** *arrows*) extending to the tibiofibular trunk (**D,** *arrows*). (From Wick 2012.)

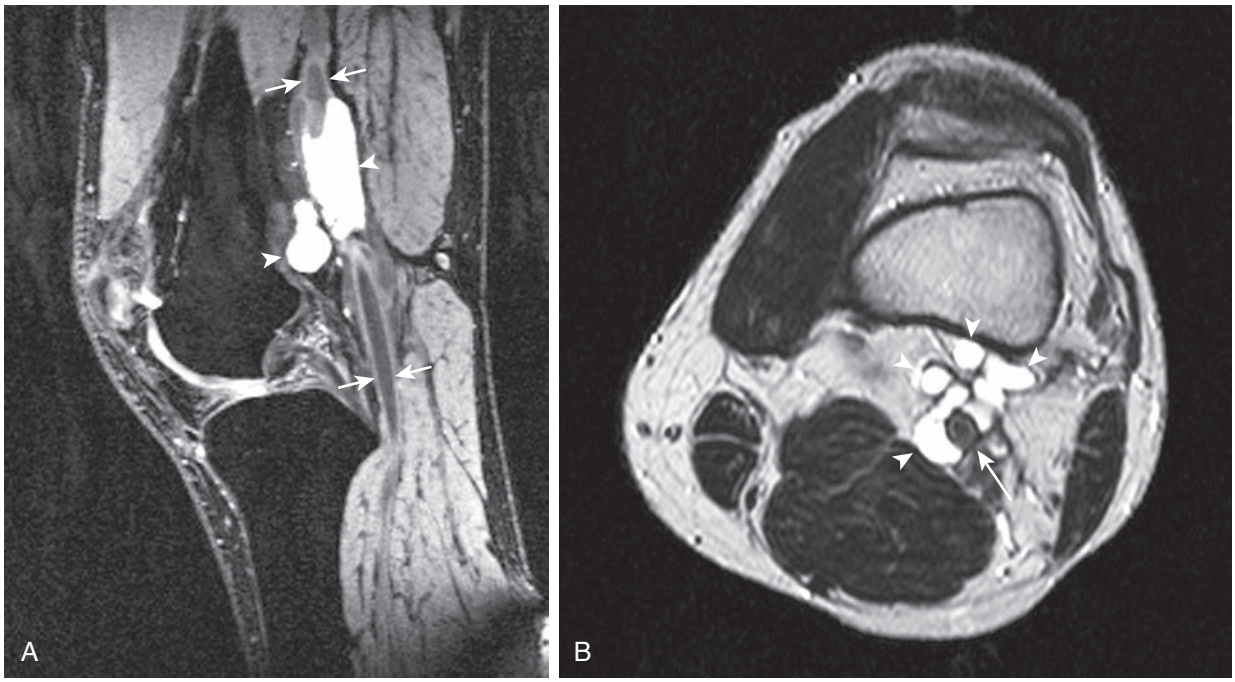

Figure 143.11 **(A)** Cystic structures *(arrowheads)* in close contact with the popliteal artery *(arrows)*. **(B)** Cystic structures *(arrowheads)* in close proximity to popliteal artery *(arrow)*. (From van Rutte PWJ, et al. In treatment of popliteal artery cystic adventitial disease, primary bypass.)

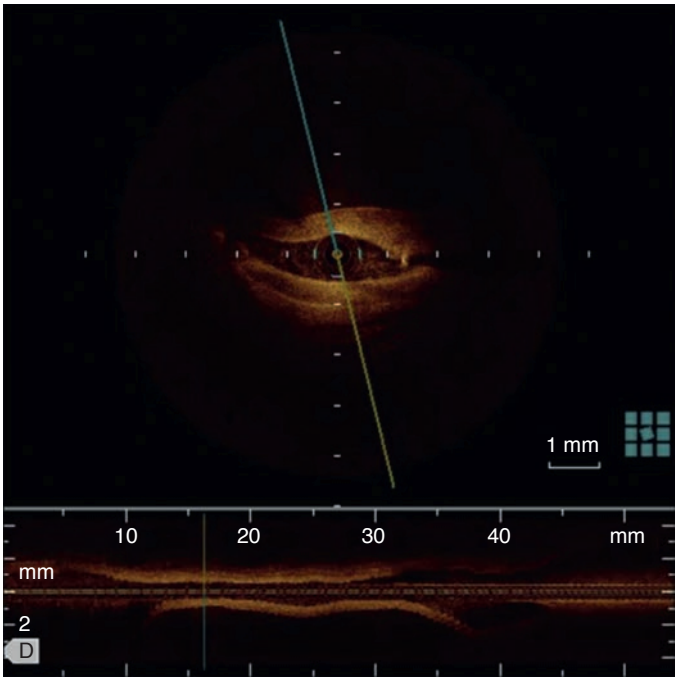

Figure 143.12 Optical coherence tomography cross-sectional images showing ACD of the popliteal artery extending from the 11 to 8 o'clock position. Multiloculated anechoic lesions around the stenosis area are more evident than by intravascular ultrasound. (From Takasawa 2016.)

Management options for ACD can be divided into nonresectional and resectional interventions.[34,41] In the majority of instances where nonocclusive stenoses are encountered, nonresectional methods are recommended. Resection, with subsequent arterial reconstruction, is more commonly used in cases of complete popliteal artery occlusion secondary to thrombosis or in the presence of extensive degeneration of the arterial wall.

Nonresectional Methods

Nonresectional methods of treatment include percutaneous transluminal angioplasty (with or without stenting), CT- or ultrasound-guided percutaneous cyst aspiration, and cyst evacuation (with or without cyst excision). These treatment methods are described as follows, in order of increasing chance of initial success and decreasing recurrence rate.

Transluminal Angioplasty

Angioplasty, with or without stenting, has been largely discarded as a treatment option. It is ineffective because the normal intimal layer of these arteries and the compliant arterial segment can recoil and restenose as early as 24 hours following balloon dilation.[72]

Cyst Aspiration

Promising short-term outcomes have been achieved with CT- or ultrasound-guided cyst aspiration. The technique is well-described, including the imperative for precise positioning of the needle tip in order to avoid the popliteal vein and the tibial and peroneal nerves.[41,73–75] Despite the simplicity of this treatment modality, failures are not unusual in cases of multiple loculations and highly viscous cyst fluid. Spontaneous cyst resolution has been described after an unsuccessful attempt at aspiration, highlighting a possible role for disrupting the cyst wall in cyst resolution.[76] Given the risk of incomplete evacuation and recurrence, cyst aspiration should be limited to patients

who refuse operative intervention and agree to close imaging surveillance and probable reintervention.

Cyst Excision and Evacuation

Operative exposure of the involved popliteal artery is best achieved via a posterior approach with the patient prone. In the case of a stenotic popliteal artery, incision into the cyst and evacuation of its contents is usually sufficient to restore arterial patency.

Resectional Methods

In instances of popliteal artery thrombosis or extensive arterial degeneration, a resectional treatment approach is preferred. The affected popliteal artery is explored through a posterior approach, and the extent of resection is determined by the length of arterial involvement on preoperative cross-sectional imaging and intraoperative findings. Arterial reconstruction is performed with an autogenous venous conduit or prosthetic graft of the surgeon's choice.

Choice of therapy is determined by the luminal status of the popliteal artery. In nonoccluded arteries, nonresectional methods, including imaging-guided cyst aspiration or operative cyst evacuation and excision, offer good short-term outcomes. In instances of popliteal artery thrombosis, resection is advocated, with excision of the involved artery and reconstruction with an autogenous conduit.

Treatment Outcomes

Recurrence of popliteal ACD has been described following all methods of therapy, although it is less likely with resection of the cyst or the involved artery.[77] Symptoms recur in 10% to 30% of patients undergoing cyst aspiration at a mean follow-up period of 15 months.[56,78] Treatment failure or recurrence has also been reported in 15% of patients undergoing cyst evacuation and 6% to 10% of those undergoing resection.[41,79] Arterial segment revascularization with autogenous venous conduit is associated with the highest success rate,[35] although disease recurrence has been reported in the vein graft after popliteal bypass surgery.[80,81] Conversely, short-term failure of treatment after endovascular therapy has been reported in 37.5% of patients undergoing percutaneous transluminal angioplasty and 50% of patients undergoing angioplasty and stenting.[82] Given the recurrence risk with all of these therapies, indefinite and periodic postoperative duplex surveillance is necessary.

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CHAPTER 144

Infected Arterial Aneurysms

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Management of an infected arterial aneurysm remains a daunting surgical challenge. These infections occur in any named vessel and often affect elderly patients with multiple medical comorbidities. Medical treatment alone with culture directed antibiotics rarely eradicates the infection, and excision of the involved vessel with anatomic or extra-anatomic arterial reconstruction is usually required. Reports of using endovascular stent-grafts as the primary treatment or a bridging therapy to arterial reconstruction have been published; however, the specific role of endovascular devices in the treatment of this difficult problem remains to be defined.

HISTORY AND EPIDEMIOLOGY

Osler in 1885 was the first to publish a comprehensive discussion of infected aneurysm.[1] His series described infected peripheral arterial aneurysms in patients with endocarditis. In addition, his proposed pathogenesis included embolism of bacteria-laden material from infected heart valves to peripheral arteries resulting in destruction of the arterial wall. He termed the resulting aneurysm "mycotic," since the eccentric saccular configuration resembled a mushroom. Unfortunately, this term led to confusion, with some assuming that it applied only to infections caused by fungi, and others applied the term to all infected aneurysms rather than just those associated with bacterial endocarditis. For this reason, the term is best avoided.

In 1923, Stengel and Wolfert demonstrated that infected aneurysms could result from a variety of blood borne septic conditions, not just endocarditis.[2] Sommerville in 1959 reported a third type of arterial infection, one that occurred in preexisting atherosclerotic aneurysms.[3] Later, infected pseudoaneurysms due to illicit drug use or iatrogenic arterial trauma were described. The overall incidence of infected arterial aneurysms has risen in recent decades with the increasing prevalence of immunosuppressed patients, invasive hemodynamic monitoring, catheter-based procedures, and illicit drug abuse.[4-17]

PATHOGENESIS AND ETIOLOGY

Infected arterial aneurysms are classified into four types based on etiology: (1) microbial arteritis with aneurysm formation due to noncardiac origin bacteremia or contiguous spread of a localized infection; (2) post-traumatic infected pseudoaneurysms, most commonly related to illicit drug abuse; (3) infection of

TABLE 144.1 Clinical Characteristics of Infected Aneurysms

	Microbial Arteritis	Posttraumatic Infected Pseudoaneurysms	Infection of Preexisting Aneurysms	Infected Aneurysms From Cardiac Source
Etiology	Bacteremia, contiguous spread	Narcotic addiction, trauma	Bacteremia, contiguous spread	Endocarditis
Age	>50 years	<30 years	>50 years	30-50 years
Incidence	Common	Common	Unusual	Rare
Common location	Aorta Iliac artery Intimal defects	Femoral Carotid	Infrarenal Aorta	Aorta Visceral Intracranial Peripheral
Common bacteriology	*Salmonella* Others	*Staphylococcus aureus* Polymicrobial	*Staphylococcus* Others	Gram-positive cocci

Adapted from Wilson SE, Van Wagenen P, Passaro E Jr. Arterial infection. *Curr Probl Surg*. 1978;15:1–89.

a preexisting atherosclerotic aneurysm from bacteremia or contiguous spread; and (4) infected aneurysms from septic emboli, as classically described by Osler (Table 144.1).[1]

Microbial Arteritis

Bacterial seeding can occur in nonaneurysmal arteries with preexisting wall irregularities caused by atherosclerosis or congenital abnormalities (e.g., aortic coarctation, patent ductus arteriosus).[18,19] Additionally, normal arteries can be infected by a local invasive infection. Once established, suppuration, localized perforation, and pseudoaneurysm can result. Alternatively, more diffuse infection can result in rapid development of a true aneurysm, although often the aneurysm is saccular rather than a typical fusiform degenerative aneurysm. All named arteries are at risk, but the aorta is most commonly involved, likely due to its large intraluminal surface area and propensity for atherosclerotic involvement.[15,20-23]

Conditions associated with microbial arteritis include diabetes, cirrhosis, chronic hemodialysis, posttransplant immunosuppression, human immunodeficiency virus infection, alcoholism, chronic glucocorticoid therapy, chemotherapy, and malignancy.[11,16-19,24-29] In a study of 43 patients with infected aneurysms, Oderich et al.[7] found that 70% of patients had at least one of the aforementioned immunocompromised conditions.

Post-Traumatic Infected Pseudoaneurysms

Arterial trauma leading to direct bacterial inoculation of the arterial wall can result in an infected arterial aneurysm. Bacteria can be introduced at the time of endovascular access or during drug abuse with inadvertent or intentional intra-arterial injection (Fig. 144.1A and B). Notably, the use of percutaneous closure devices for endovascular procedures has been reported to be associated with infected pseudoaneurysms.[30,31] Not surprisingly, the common femoral artery is the most common location, but posttraumatic infected pseudoaneurysms involving the carotid, brachial, external iliac, and subclavian arteries have also been reported.[10,24,25]

Infection of Preexisting Aneurysms

Preexisting aneurysms can be secondarily infected by hematogenous or contiguous spread. Aneurysms are susceptible to infection, because the diseased intima or intraluminal thrombus permits bacterial seeding (Figs. 144.2A and B).[3] Of interest is that bacteria can be cultured from thrombus associated with asymptomatic degenerative aneurysms in up to 4% of patients,[3] and both Bennett[20] and Jarrett[19] demonstrated this finding and suggested that aneurysms associated with bacterial growth in the thrombus were more apt to rupture.[19,20] Furthermore, Ernst[32] showed that a greater number of positive cultures were found in those patients with ruptured aneurysms compared with asymptomatic and symptomatic aneurysms (38% vs. 9% and 13%, respectively). Recent research has suggested the possibility that multi-bacterial infection in the aortic wall may contribute to the development of degenerative aortic aneurysms.[33]

Infected Aneurysms Due to Endocarditis

Currently, less than 10% of infected arterial aneurysms originate as classically described by Osler.[15,34,35] Septic cardiac emboli may lodge in the lumen or occlude the vasa vasorum of the arterial wall, leading to ischemia and arterial wall infection. Once the artery is infected, rapid, focal, and progressive deterioration occurs and results in the characteristic saccular or multilobulated "mushroom-like" aneurysms. This process often leads to a locally contained rupture and formation of a false aneurysm.[14,21] Infected aneurysms associated with cardiac emboli are frequently multifocal, involving the aorta, intracranial circulation, and splanchnic and femoral arteries, typically at arterial bifurcations.[1,2,36]

MICROORGANISMS

The predominant microorganisms found in infected aneurysms depend on the type and etiology of the aneurysm, the patient's geographic location, and immune system. The bacteriologic spectrum is extensive and may be broader than was once

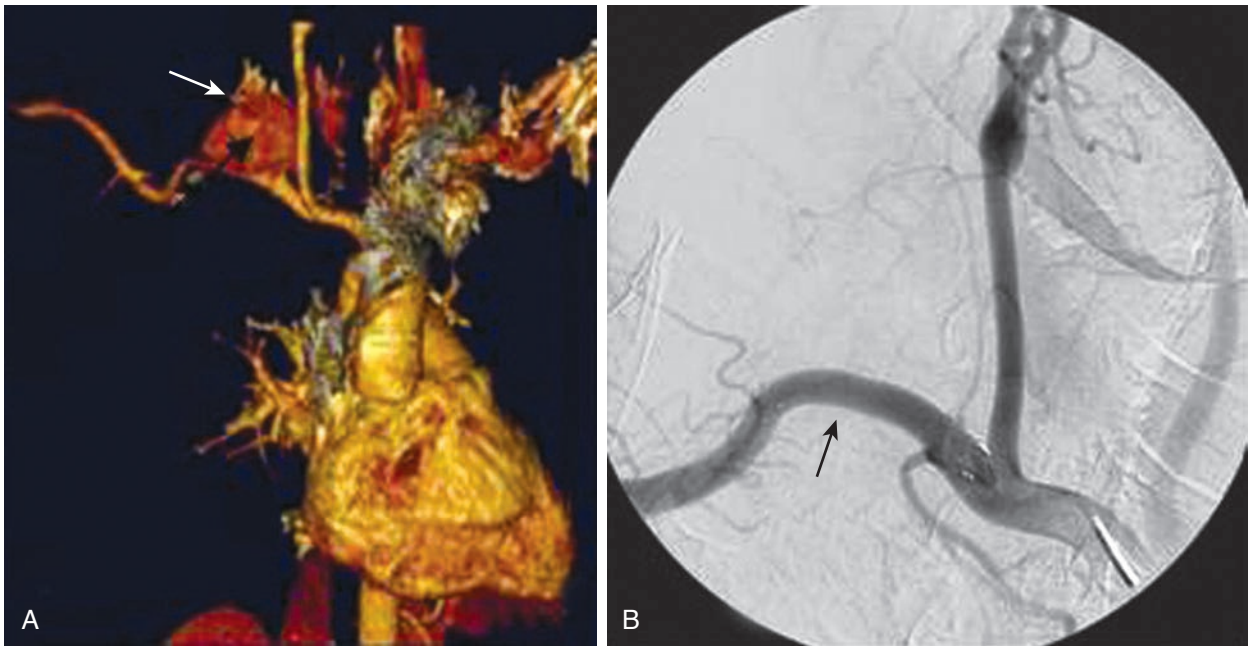

Figure 144.1 (A) Three-dimensional reconstruction computed tomographic angiography image in a patient with a polymicrobial posttraumatic false aneurysm of the right subclavian artery caused by repeated percutaneous cervical injection of illegal narcotics *(arrow)*. (B) Treatment with a covered stent-graft for control of hemorrhage *(arrow)*. Adjuvant therapy included open debridement and irrigation along with intravenous antimicrobial therapy.

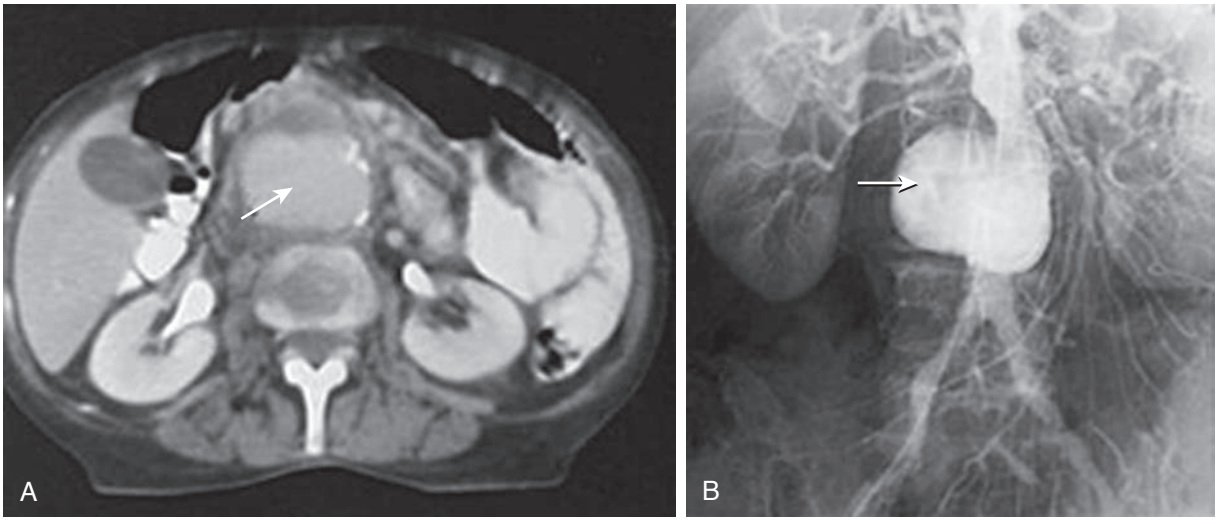

Figure 144.2 Diagnostic radiology studies of a patient with salmonella infection of a preexisting small atherosclerotic aneurysm. (A) Contrast-enhanced computed tomography scan showing a saccular aneurysm with calcification *(arrow)*. (B) Transfemoral aortogram showing a saccular atherosclerotic infrarenal aneurysm *(arrow)*.

believed.[37] *Staphylococcus* species, of which many are methicillin resistant, are the most common organisms and account for 28% to 71% of cases. *Salmonella* species are the second most common and have been reported in 15% to 24% of patients. *Streptococcus* species account for less than 10% of the cases in the postantibiotic era.[8,13,38] Overall, blood cultures are positive in 50% to 85% of infected aneurysm patients, and organisms have been isolated from aneurysmal tissue in up to 76% of patients with a suspected infected aneurysm.[7,15,39-43] As endoluminal device implantation has increased, infection in an existing aneurysm and microbial arteritis has also increased.[44,45]

Specific Organisms

Although less common, gram-negative infections are more virulent than gram-positive infections as demonstrated by rates of aneurysm rupture (84% vs. 10%) and patient mortality (84% vs. 50%).[19] The increased virulence is postulated to occur due to the ability of gram-negative organisms such as *Pseudomonas aeruginosa* to release alkaline proteinase along with a variety of elastases that cause vascular wall necrosis.[46] Furthermore, gram-negative organisms are commonly implicated in graft disruption and arterial stump hemorrhage after

reconstruction. Consequently, the presence of gram-negative organisms is an important consideration when contemplating repair strategies.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become an important public health problem. New strains of *S. aureus* with multiple resistant traits have been associated with high morbidity and mortality, and several recent series report MRSA as the predominant organism in infected aneurysms.[47-49] In particular, infected arterial aneurysms with MRSA have been reported as the primary organism found in patients due to illicit drug abuse.[50,51]

The diseased aorta appears to be particularly vulnerable to seeding by *Salmonella* species, and this pathogen is frequently found in infected preexisting aneurysms and in the infected atherosclerotic nonaneurysmal aorta. Specifically, *Salmonella choleraesuis* and *Salmonella enteritidis* account for more than half of reported cases of *Salmonella* aortitis.[34,52]

Clostridia infections of the aorta have been reported as well. One species, *Clostridium septicum*, has a propensity to cause fulminant infected aortic aneurysms. *C. septicum* aortitis is usually related to a gastrointestinal or hematological malignancy.[53] The proposed pathogenesis involves micro perforation of the gastrointestinal malignancy leading to hematogenous seeding in areas of the aorta with existing abnormalities, such as ulcerated plaques.[54,55] If not aggressively managed by wide debridement of involved aorta and reconstruction, the overall prognosis is poor with rapid deterioration of the aortic wall leading to rupture and death in 64% to 100% of patients (Fig. 144.3).[54-56]

Fungal infections, although rare, have been reported in patients with diabetes mellitus, immune suppression, and those with a history of systemic fungal disease.[4,57,58] Reported fungal pathogens include *Candida*, *Cryptococcus*, *Aspergillus*, and *Pseudallescheria boydii*.[59-62]

Treponema pallidum and *mycobacterium* species have also been found in infected aneurysms.[32,63-65] *T. pallidum* (syphilis) once caused up to 50% of infected aneurysms, but is much less common since the advent of penicillin. Finally, tuberculosis (TB) is a rare cause and is generally secondary to erosion of TB infected periaortic lymph nodes into the aortic wall.[66] More recently, it has been reported that the use of Bacillus Calmette-Guerin (attenuated bovine TB bacillus) as an intravesical treatment for superficial bladder cancer has led to remote arterial infections involving the infrarenal aorta and popliteal artery.[67,68]

DIAGNOSIS

Clinical Findings

The patient presentation of an infected aneurysm will depend on the anatomic location, the virulence of the organisms, and the duration of the infection. General symptoms can include malaise, fever, and/or chills. Although some patients can manifest more dramatic signs of overt sepsis, most have a nonspecific clinical picture that can be associated with back or abdominal pain, distal embolization, a pulsatile tender abdominal mass, or pulsatile peripheral mass with overlying cellulitis.[16,19,69-71] Hemodynamic instability due to rupture can be the initial clinical event.

Laboratory Studies

Leukocytosis and an elevated erythrocyte sedimentation rates are common, but nonspecific findings in patients with an infected aneurysm.[72] Positive blood cultures without an obvious source in patients with a known arterial aneurysm should raise diagnostic suspicion. Negative blood cultures are not sufficient to rule out the diagnosis of an infected aneurysm.[12] The diagnostic utility of blood cultures is limited if patients have been treated with antibiotics prior to the lab draw.[58]

Imaging

Radiologic studies are essential to establishing the diagnosis and determining surgical management. Ultrasonography and arterial duplex are helpful for initially assessing potentially infected peripheral aneurysms, but they are of limited value for infections of the aorta.[16] Computed tomographic angiography (CTA) is the imaging modality of choice when an infected aneurysm is suspected. Typical CTA findings include saccular, multi-lobulated, or eccentric true and false aneurysms; adjacent soft tissue inflammation and fluid; air within the aneurysm and in the aneurysm wall; or evidence of aneurysm rupture. Serial scans obtained days to weeks apart can be particularly valuable when the initial clinical and CTA findings are suspicious but not diagnostic. The findings of a rapidly enlarging aneurysm or the interval development of aneurysms in previously uninvolved aorta are highly suggestive of infection (see Fig. 144.3).[73-76]

Positron emission tomography (PET) alone or in combination with CTA has also been used effectively, given the often avid uptake of the radionuclide tracer by infected tissues.[77-79] Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are highly sensitive for inflammation and can also be helpful in patients with contraindications to iodinated contrast and when the CTA is equivocal.[80,81] Finally, indium 111–labeled white blood cell scanning has been used to identify prosthetic graft infections, but its use has not always been accurate in infected aneurysms.[82,83] Although not sensitive or specific, these studies can be of assistance when other imaging studies are equivocal.

MANAGEMENT

Antibiotics

Antibiotic therapy has a critical role in the treatment of all infected aneurysms and should be initiated immediately and continued for at least 6 weeks to indefinitely after surgical treatment. Pre- and postoperative antibiotic therapy should be broad spectrum, until organism-specific therapy can be instituted. Because of the importance of organism-specific therapy, obtaining a set of blood cultures before initiating antibiotics and obtaining tissue and fluid cultures at the time of operation is paramount. The actual duration of antibiotic therapy varies from weeks to lifelong and is guided by organism virulence and antibiotic sensitivity profile as well as the arterial segment involved and type of reconstruction.[84,85] At a minimum, 6 weeks of intravenous antibiotic therapy should be employed.[21,86] Especially in locations

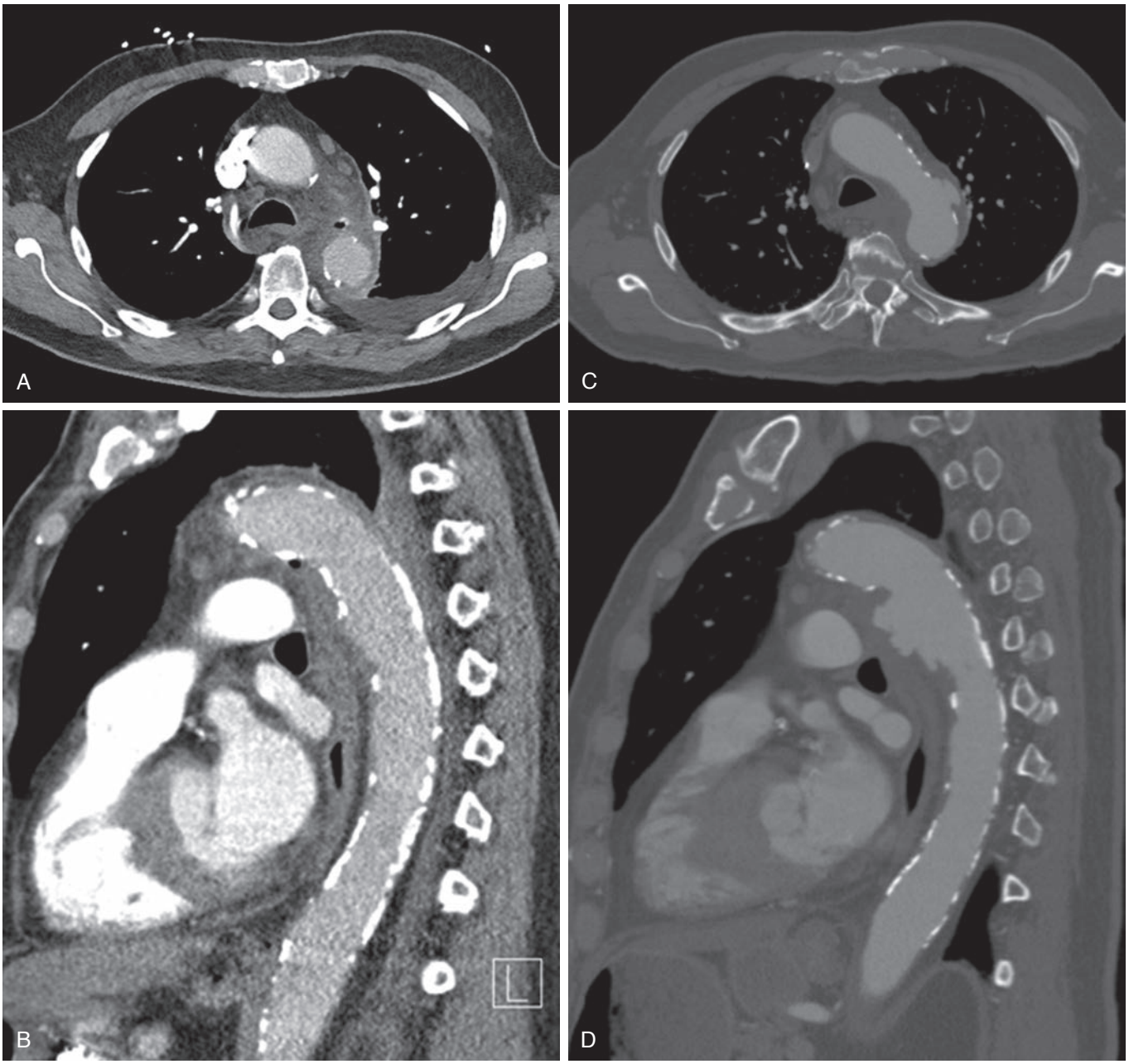

Figure 144.3 *Clostridium septicum* aortitis of the proximal descending thoracic aorta: (A and B) Proximal descending thoracic aorta with periaortic gas formation, and thickened wall. (C and D) Interval computed tomographic angiography in 10 days showing rapid enlargement of the aortic pseudoaneurysm. Patient underwent open aortic debridement via posterolateral thoracotomy, and in-situ reconstruction.

where recurrent infection is often lethal, such as aortic infections, most surgeons lean toward longer, even lifelong, suppressive antibiotic treatment.

Operative Treatment

While the nuances of the operative treatment depend on anatomic location, the following general principles apply to the treatment of all infected aneurysms.

1. To minimize excessive bleeding proximal and distal arterial control should be obtained early in the course of the operation.
2. Intraoperative cultures should be obtained in all patients. Intraoperative gram stain can be useful in certain patients to assist intraoperative decision making regarding arterial conduit and method of revascularization. Importantly, a negative intraoperative gram stain does not rule out infection.[87]
3. Infection control requires resection of the involved arterial segment and wide debridement of adjacent tissues, including all surrounding necrotic or infected tissues.
4. Either in-situ or extra-anatomic reconstruction can be used. Graft conduits for in-situ reconstruction include autogenous vein (saphenous, femoral), cryopreserved arterial allograft, or prosthetic graft that is either silver impregnated or soaked

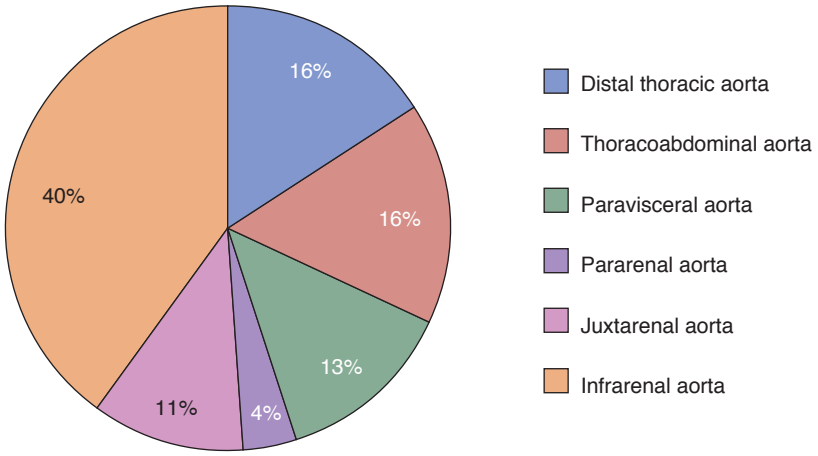

Figure 144.4 Distribution of infected aortic aneurysms in a report of 43 consecutive patients from the Mayo Clinic. (From Oderich GS, Panneton JM, Bower TC, et al. Infected aortic aneurysms: aggressive presentation, complicated early outcome, but durable results. *J Vasc Surg.* 2001;34:900–908.)

in antibiotics such as rifampin. The type of reconstruction used is guided by multiple factors, including the surgeon's experience, the patient's surgical risk, the anatomic location of the aneurysm, and the availability of autogenous conduit.

5. Following in-line reconstruction, the graft should be covered by well vascularized tissue such as omentum or muscle flaps. The use of antibiotic beads placed into the infected bed and/or surrounding the arterial reconstruction has also been reported to be of benefit.

AORTA

Infected aneurysms have been described in all segments of the aorta from the aortic root to the aortic bifurcation. Oderich reported the following distribution: infra-renal 40%, distal thoracic 16%, thoracoabdominal 16%, para-visceral 13%, and juxta-renal aorta and para-renal aorta 4% (Fig. 144.4).[7] The presence of a leukocytosis and positive blood culture have been reported in approximately 75% of patients.[7] CTA evidence of a peri-aortic mass or stranding is common and has been reported in 48% of patients.[88,89] Infected aortic aneurysms often involve parts of the aorta that are not commonly involved with atherosclerosis.[89] Despite the significant morbidity and mortality, outcomes have improved in the last 15 years, with the rupture status and expeditiousness of intervention impacting the outcome.[90]

Thoracic Aorta

Infected thoracic aortic aneurysms are highly lethal with a reported mortality of 30% to 50%. Gram-positive bacteria such as *Staphylococcal* species, *Enterococcal* species, and *Streptococcus pneumoniae* are the most common organisms.[91] *Salmonella* species infection does occur and is associated with a poor clinical outcome. Aneurysm formation can cause localized compressive symptoms such as dysphagia, dyspnea, hoarseness, cough, and superior vena cava compression.[91] However, the most common presentation is rupture.

Surgical excision of the infected segment, wide debridement, and long-term intravenous antibiotics remain the definitive treatment. Specific measures such as a spinal drain may be indicated to enhance spinal cord perfusion.[92] Depending on the aortic involvement, exposure may require a median sternotomy, left thoracotomy, or left thoracoabdominal incision. In-situ reconstruction is the most common approach, usually with a cryopreserved arterial allograft or rifampin soaked Dacron graft.

Another option for descending thoracic aorta infections is the ascending to infra-renal aortic reconstruction or "exclusion-bypass" first described by Kiefer.[93] A bypass from the ascending to infrarenal aorta is created through a median sternotomy and laparotomy. The ascending aorta is partially clamped, and an end-to-side proximal anastomosis is performed to a prosthetic graft, which is then tunneled through the right pleural cavity, across the diaphragm behind the left lobe the liver, through the lesser sac, and behind the pancreas to reach the infra-renal aorta. The distal anastomosis is performed to the infra-renal aorta with the cross-clamp applied below the renal arteries. The operation is generally well tolerated, since aortic clamping does not result in visceral or renal ischemia. Upon completion of the bypass, the distal aortic arch and supra-celiac aorta are stapled close, excluding the descending thoracic aorta. Complete debridement of the infected descending aorta is performed usually as a staged procedure through a posterior-lateral thoracotomy.

More recently, treatment using endovascular stent grafts combined with antibiotic therapy has been used as an alternative to conventional thoracotomy in managing infected aneurysms of the thoracic aorta. When combined with prolonged antibiotic therapy, this may be an especially attractive option in patients who are at high risk for open surgical repair.[94] Although published experience is limited, these grafts can serve as a bridge to definitive repair or as definitive palliation.[95,96]

Surgical complications are similar to those related to non-infected thoracic aneurysm repair. Infected Crawford type II thoracoabdominal aneurysms, age greater than 65, and contained rupture are associated with a 20% 30-day mortality.[97] Mortality of 85% has been reported in patients who were managed with antibiotic therapy only, with in-hospital rupture occurring in two-thirds of patients.[98]

Abdominal Aorta

Surgical intervention is dependent on the location and extent of the infection and associated patient comorbidities. Infection of the aorta without a preexisting aneurysm tends to affect the posterior wall of the supra-renal or supra-celiac segments. Infections of a preexisting aneurysm occur most commonly in the infra-renal location due to the frequency of aneurysms in this location.[99] Para-renal or para-visceral aortic infections are a greater surgical challenge, and the need to preserve the renal/visceral perfusion dictates that an in-situ reconstruction is preferred rather than over sewing of the aortic stump coupled with aortic based bypasses to maintain visceral and renal perfusion.[100-103] Overall, surgical mortality due to infected abdominal aortic aneurysms varies between 15% to 38%.[104]

Currently, an in-line reconstruction is preferred for most infected abdominal aortic aneurysms. Conduit options include cryopreserved arterial allografts, antibiotic treated Dacron grafts or creation of a "neo-aorta-iliac system" (NAIS) with the autogenous femoral-popliteal vein.[26,27,105-111] When an in-situ reconstruction is considered not possible or prudent, extra-anatomic reconstructions in a clean tissue plane with excision and debridement of the infected aneurysm and surrounding tissues may be employed. For all surgical reconstructions, liberal use of omental or rectus muscle flaps is important. Recently, endovascular approaches have been utilized as either a bridge or definitive therapy in selected patients.

Cryopreserved Arterial Allografts

Arterial allografts for in-situ aortic reconstruction have been shown to be quite resistant to re-infection by gram-negative organisms as well as other bacteria and microorganisms.[112] Allografts are procured from organ donors, processed using antimicrobial blends, and then cryopreserved using liquid nitrogen. When requested, the allografts can be thawed in under 45 minutes. They are surgically easy to handle and can be used in most infected fields without concern for re-infection. The main limitation to the use of arterial allografts is expense and availability. Grafts need to be ordered usually 24 hours in advance and supply may be limited. Depending on the number and segments of allograft needed, the cost can be more than $20,000. Nevertheless, cryopreserved arterial allografts are an excellent option and are our preferred option for in-situ revascularization, especially for those infections involving the para-renal and para-visceral aorta (Fig. 144.5A to D). A recent multicenter review demonstrates 75% 1-year survival and 51% at 5 years with freedom from graft explant of 99% at 1 year and 88% at 5 years.[113]

Complications associated with allograft reconstruction include peri-anastomotic hemorrhage, graft limb occlusion, and pseudo aneurysm. A higher rate of graft failure and hemorrhage has been associated with aorta-enteric fistulas, and this should be taken into consideration when planning repair.[114] In a recent series, allograft-related morbidity was 11.8% compared with 57.1% in patients who underwent extra-anatomic bypass or in-situ reconstruction with a prosthetic graft.[115]

Antibiotic Soaked Dacron Grafts

In-situ reconstruction with prosthetic grafts has reported re-infection rates as high as 20%.[116] For this reason, antibiotic, usually rifampin, soaked Dacron grafts are used for infected aneurysms with para-visceral and thoracoabdominal extension

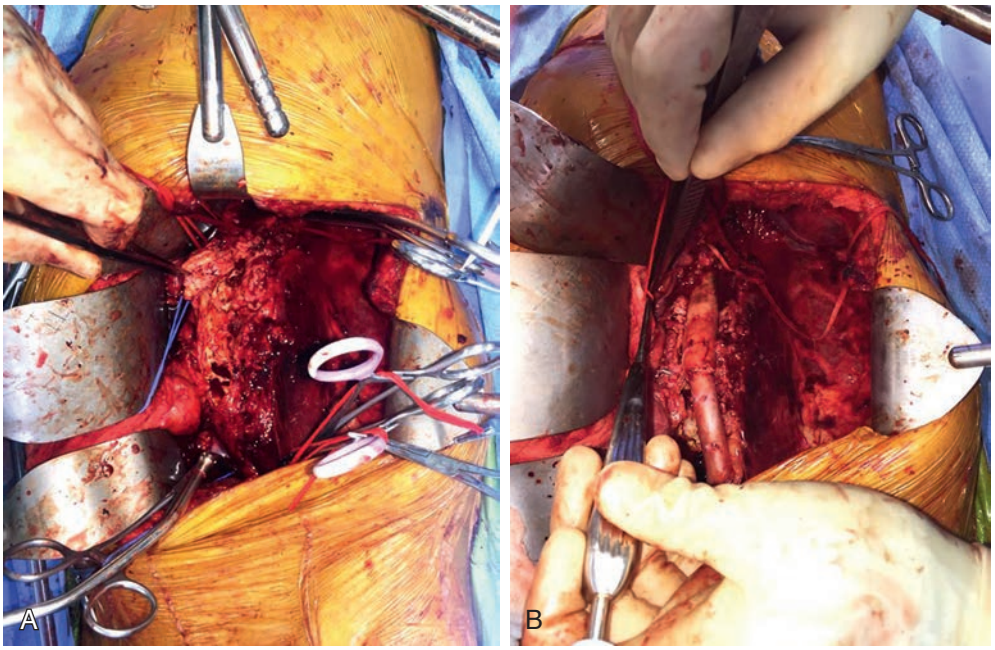

Figure 144.5 Paravisceral abdominal aortic pseudoaneurysm, caused by *methicillin resistant staphylococcus aureus* aortitis. (A) Debridement of the infected aorta revealed rupture of the posterior aortic wall as well as thickened inflammatory phlegmon surrounding the paravisceral aorta. (B) In-situ reconstruction using cryopreserved homograft. Celiac, superior mesenteric, and right renal arteries were incorporated with the beveled proximal anastomosis. The left renal artery was reimplanted.

and in patients who present in extremis and require rapid surgical management for control of hemorrhage and sepsis. Antibiotic soaked grafts maintain their bactericidal activity by being coated with collagen or gelatin to provide a bond between the graft and antibiotic.[117] Rifampin has been the agent of choice given that it has broad-spectrum activity against gram-positive and gram-negative organisms.[117]

A cumulative review of antibiotic soaked grafts found perioperative morbidity to occur in 20% to 60% of patients with a reported graft reinfection rate of 4% to 22%.[118] A series from the Mayo Clinic in patients who were treated with an in-situ rifampin soaked Dacron graft had an operative mortality of 20%, but no patients had a late graft reinfection.[119] Another series from the same group focused on 54 patients in whom in-situ rifampin soaked Dacron graft reconstruction was performed for aortic graft enteric erosion or fistula. The protocol was excision of the infected graft, intestinal repair, placement of in-situ rifampin-soaked Dacron graft with omental wrap and long term antibiotics.[120] Patient survival at 1 year, 5 years, and 10 years were 85%, 59%, and 40%, respectively, with no patients dying from graft-related complications.[120] Late graft-related complications occurred in 16% with 4% developing graft reinfection.[120] Another recent single center series reported a 30-day mortality of 18% and a 2-year survival of 73% with silver coated Dacron grafts bathed in 5000 IU neomycin/250 IU bacitracin solution.[121]

Small case series have reported high rates of graft reinfection in rifampin soaked Dacron grafts when used in patients with active MRSA infection at the time of implantation.[122] In vivo canine experiments comparing resistance to MRSA growth with rifampin soaked and silver impregnated Dacron grafts have found in both graft configurations diminishing levels of bacterial growth suppression after 7 days.[123] Consequently, some authors advocate limiting antibiotic soaked grafts to patients with low virulence organism infection.[124]

Neo-Aorta-Iliac System

Described by Clagett, the NAIS procedure utilizes deep femoropopliteal vein to create a neo-aorta-iliac conduit.[125] The procedure has a prolonged operative time, averaging 10 hours, and because of that, it may be of limited use in the patient with overt sepsis or the elderly with a multitude of comorbidities.[126]

The femoral-popliteal vein can be used in a number of different configurations to achieve in-line revascularization, depending on the extent of infection, the necessary reconstruction, and the availability of conduit. The most common configuration is demonstrated in Fig. 144.6, and an intraoperative picture is demonstrated in Fig. 144.7. Further details are provided in Chapter 47.

The femoral-popliteal veins provide a reasonably good size match for the aorta in most cases and are resistant to recurrent infection. Re-infection is rare, occurring in less than 2% of patients.[127] Primary patency rates are 87% and 82% at 2 and 5 years, respectively, along with primary assisted patency rates of 96% and 94% at 2 and 5 years, respectively.[128-130]

Despite the magnitude of the operation, the reported 30-day mortality rate is less than 10%, and the 5-year survival is 60%

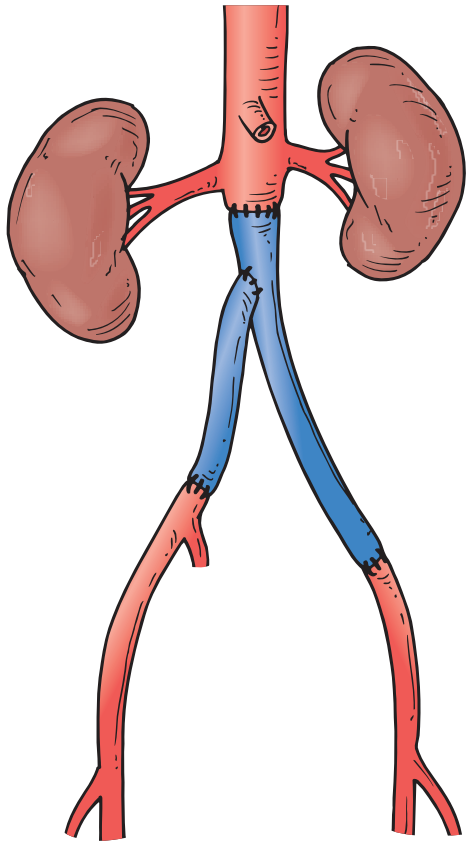

Figure 144.6 A common configuration of neo-aorto-iliac system reconstruction using an autogenous femoral vein. Various configurations can be used to accommodate more or less extensive infection or occlusive disease. (Courtesy G. Patrick Clagett, MD.)

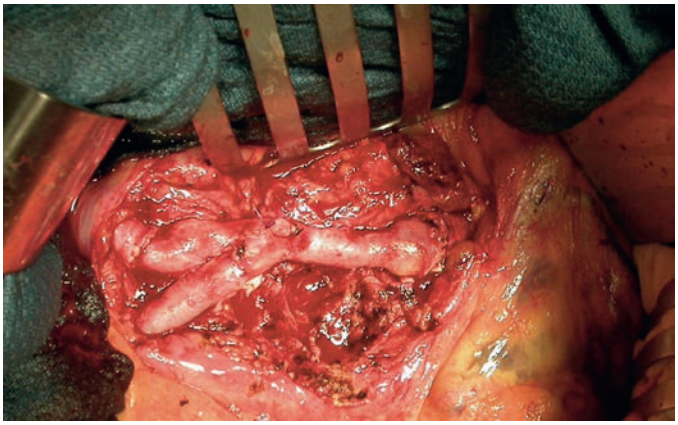

Figure 144.7 Neo-aorto-iliac system reconstruction with femoropopliteal vein in a patient with salmonella infected infrarenal aortic aneurysm. (Courtesy of G. Patrick Clagett, MD.)

when used for an infra-renal aortic graft infection.[130] As evidenced by the excellent patency, graft stenosis after NAIS reconstruction is uncommon. The risk factors for stenosis include small graft size (<7 mm), history of coronary artery disease, and smoking.[128] Patients should be monitored by duplex ultrasonography to promptly detect and treat graft stenosis.

Specific morbidity associated with femoral-popliteal vein harvest includes the need for fasciotomy in 12% of patients,

with a higher rate in patients with previous ipsilateral saphenous vein harvest. Compartment syndrome can also occur and is related to the compromised venous outflow following the vein harvest coupled with the large volume crystalloid resuscitation often required in these critically ill patients.[127] Late clinically significant chronic venous insufficiency develops in less than 15% of patients and is generally mild when it occurs.[131]

Extra-Anatomic Abdominal Aortic Reconstruction

The primary extra-anatomic approach is an axillary-femoral bypass in a clean operative field followed by aneurysm resection, debridement of surrounding tissues, and aortic stump closure. In stable patients, the procedure can be staged with the extra-anatomic bypass being performed first, followed in a day or so by the definitive resection of the aneurysm. The axillary artery with the highest brachial pressure should be selected for inflow. Generally, an 8-mm-ringed polytetrafluoroethylene graft is sufficient. Aortic stump closure can be difficult due to the limited and friable aorta available for closure. A two-layer closure is recommended buttressed with anterior spinal ligament and an omental pedicle when possible.

Although this method of reconstruction may seem like an attractive option in older, more debilitated patients, it is associated with significant perioperative morbidity and mortality. Because the infected aneurysm tissue must still be resected and the aorta closed, the added benefit of using an extra-anatomic bypass is less than would be expected. Furthermore, aortic stump disruption, which may occur late in the patient's course, has been reported in up to 12% of patients.[132] Five-year patency of the axillary-femoral graft is reasonably good at 70%.[133] However, infection of the extra-anatomic reconstruction can occur in 6% to 20% of cases, often necessitating a very difficult in-situ reconstruction.[19,71,134-137] In a contemporary series, Lee reported long term survival to be equal to in-situ reconstruction but with a higher rate of late complications, 33% versus 0%. This suggests that this approach should be limited to patients who are considered unsuitable for in-situ revascularization.[138]

Endovascular Aortic Repair

Endovascular aortic repair (EVAR) for infected abdominal aortic aneurysms has increased in recent years. A recent meta-analysis of 48 patients treated with EVAR found that a ruptured aneurysm and fever at time of operation were the two most significant predictors of persistent infection. Persistent infection after EVAR, in turn, had a poor outcome with 12-month survival of 39%. Persistent sepsis and re-bleeding were reported in 23% of the cases, but overall 30-day and 2-year survival were reasonable at 89.6 ± 4.4% and 82 ± 5.8%, respectively.[139] Another recent study found no significant difference between EVAR and open repair in the 24-month actuarial aneurysm-related event-free rate (78.3 ± 9.7% vs. 80.1 ± 8.9%).[140]

Salmonella, however, has been associated with persistent and extended infection, and the virulence of the organism involved is an important consideration when contemplating EVAR.[141] In addition, EVAR outcomes appear to be adversely impacted by the presence of aorta-aero-digestive fistulas with a reported 30-day mortality rate of 33% and overall mortality of 67%.[142,143] Finally, other authors have demonstrated that re-operation for these infected aneurysms, after initially treated by EVAR, is more likely to be unsuccessful or more complicated, leading to higher operative mortality (Fig. 144.8A and B).[139,141,144,145] Consequently, if EVAR is chosen as the initial approach, it should be considered only a bridge to more definitive therapy in the patient who can tolerate an open reconstruction.[143]

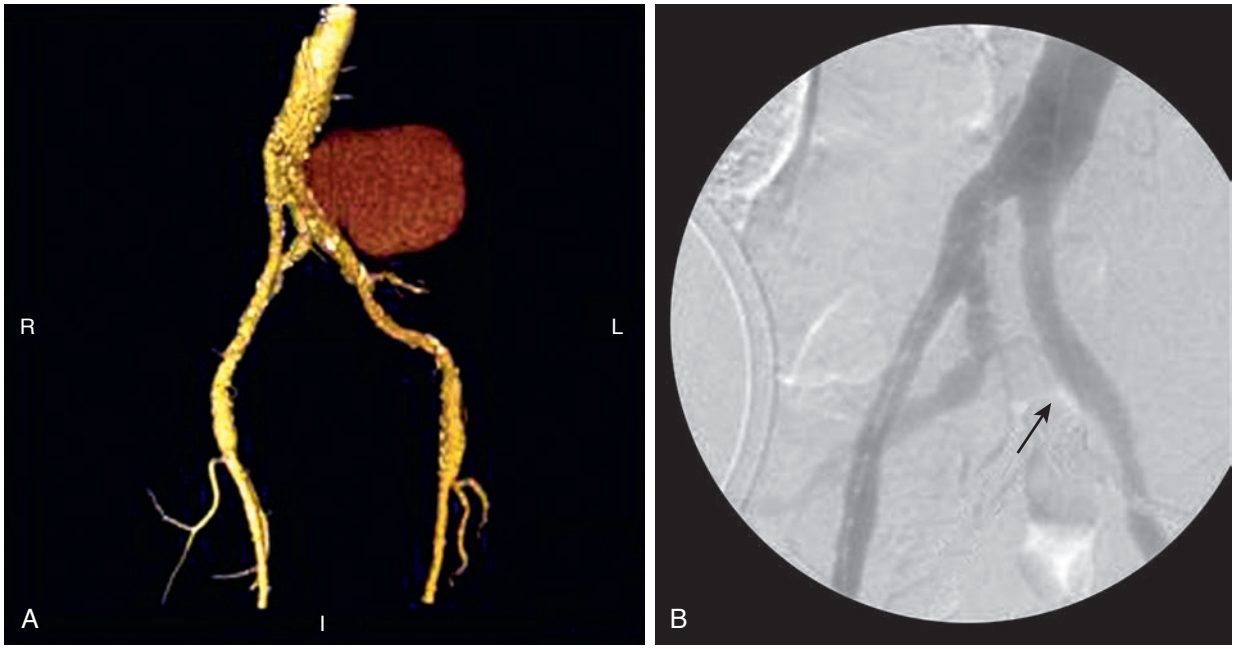

Figure 144.8 (A) Computed tomographic angiography findings in an 80-year-old debilitated woman demonstrating a large infected false aneurysm of the left common iliac artery. (B) Digital subtraction angiogram revealing exclusion of the pseudoaneurysm after emergency stent-graft *(arrow)* deployment for control of hemorrhage.

FEMORAL ARTERY

Infected femoral artery aneurysms are most commonly due to endovascular arterial access or illicit drug injection, and involve organisms that are highly resistant to conventional antibiotics. Clinically, these infections present with fevers, groin pain, cellulitis, and a pulsatile mass. Risk factors include obesity, diabetes mellitus, and groin hematomas after endovascular intervention. *S. aureus* and gram-negative organisms are commonly cultured.

The reported rate of infectious complications related to femoral percutaneous procedures is less than 1%, but the innumerable procedures performed through femoral artery access on a daily basis means that it is not an infrequent clinical problem. Notably, some authors have described an association between the use of percutaneous closure devices with braided nonabsorbable suture and infected femoral artery aneurysms.[31,146-150]

The development of an infected femoral aneurysm in the setting of illicit drug abuse is a particularly challenging problem due to the presence of highly resistant organisms. These patients have a high rate of limb loss, and aggressive definitive treatment should be quickly undertaken. Because of organism virulence, the method of revascularization should be carefully considered, and wide debridement of the infected tissue with tissue culture should always be performed to guide antibiotic therapy.

Options for revascularization are described in Fig. 144.9A and B and include an in-situ interposition graft with autogenous vein or cryopreserved arterial allograft covered with a sartorius or other rotational muscle flap. Extra-anatomic reconstructions include obturator bypass, lateral femoral bypass, and axillary-femoral bypass with distal target either the superficial femoral or profunda femoris artery. With the exception of the infected aneurysms due to illicit drug injection, an interposition graft using cryopreserved arterial allograft is in our practice the preferred option.[151,152] Due to the virulence of organisms associated with aneurysms due to illicit drug injection, ligation and an extra-anatomic method of revascularization or ligation alone is advisable.[153]

Ligation of the common femoral artery alone without reconstruction allows for limb preservation in cases in which the profunda-superficial femoral artery junction is maintained.[154] Collateral flow between the internal iliac artery and the distal extremity circulation, including the inferior gluteal artery, the obturator artery, and the inferior epigastric artery can provide sufficient perfusion for limb viability. However, the absence of a pedal artery Doppler signal during test occlusion of the distal iliac artery indicates inadequate collateral flow, thus precluding femoral artery ligation.[154,155] When ligation in the acute phase is performed, symptoms of ischemia can develop in up to 88% of patients, with disabling claudication the most common complaint (Fig. 144.10).[156-158] Finally, if ligation of the common femoral, superficial femoral, and profunda femoris arteries are required for control of the infectious process, the amputation rate has been reported to be as high as 33% in the absence of an extra-anatomic reconstruction (Table 144.2).[5,14,16,159]

POPLITEAL ARTERY

Infected popliteal artery aneurysms are rare, and the available data comes mostly from case reports. This condition usually presents as a tender pulsatile mass with associated cellulitis, deep vein thrombosis from compression, lower extremity edema, and fever. Acute lower extremity ischemia may be present due to thrombosis or rupture.[160,161] The most common etiology is septic embolization from endocarditis due to *Streptococcus* and *Staphylococcus* species.[162] *Salmonella* infections are associated with

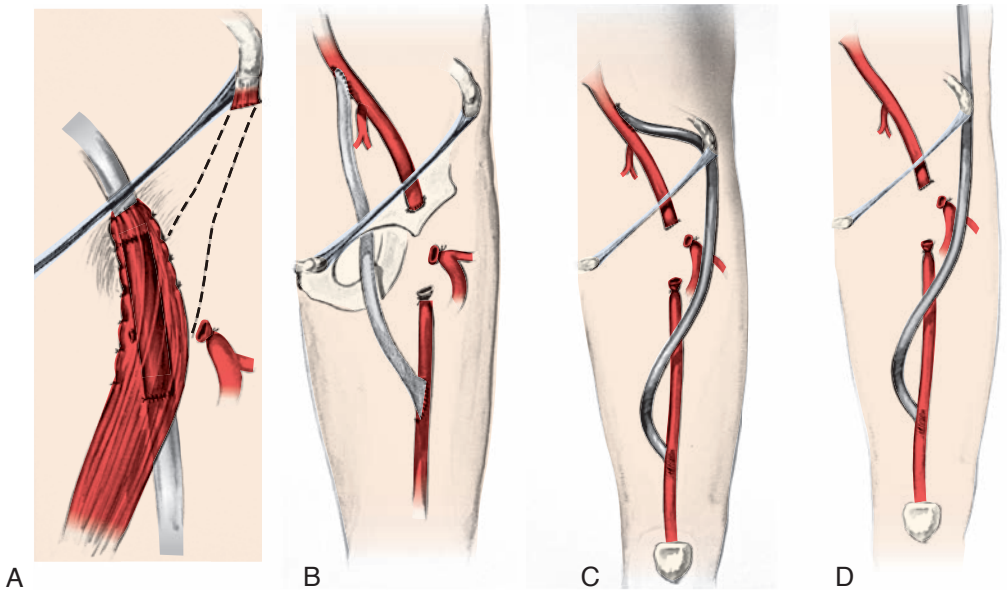

Figure 144.9 Methods of femoral artery reconstruction. (A) Interposition vein autograft covered by rotated sartorius muscle. (B) Obturator bypass. (C) Lateral femoral bypass. (D) Axillary-to-distal femoral bypass. (A, B, and D, From Reddy DJ, Smith RF, Elliott JP Jr, Haddad GK, Wanek EA. Infected femoral artery false aneurysms in drug addicts: evolution of selective vascular reconstruction. *J Vasc Surg.* 1986;3:718–724.)

microbial arteritis and spontaneous rupture of a nonaneurysmal popliteal artery. Antibiotics against suspected organisms should be instituted early, and the duration of therapy should be guided by the treatment of the causative endocarditis. Arterial duplex and CTA are used to confirm the diagnosis, define the extension of the infection, and plan revascularization.[163]

Figure 144.10 Arteriogram after ligation of the femoral artery bifurcation showing prompt reconstitution of the deep femoral artery by numerous collaterals *(large arrow)* with faint visualization of the slightly more distal superficial femoral artery *(small arrow)*.

Surgical treatment includes wide debridement and excision of all infected segments. In many patients, the popliteal vein is also involved, and this should be excised as well. Reconstruction with an autogenous saphenous vein bypass is the preferred option performed through a medial approach. Other reports have described the use of in-situ interposition cryopreserved arterial allografts with good results.[115,162]

CAROTID ARTERY

Historically, most primary carotid infected aneurysms were the result of pharyngeal infections. With the inception of antibiotics, carotid artery infections have become rare. Currently, as is the case with infected popliteal aneurysms, embolization due to endocarditis is the most common cause, and *S. aureus* and *Streptococcus pyogenes* are the most common organisms.[164-166]

Common clinical findings include fever, chills, and a pulsatile tender neck mass. The carotid mass is often medially deviated, leading to misdiagnosis as a pharyngeal mass. Patients can also present with dysphonia and dysphagia due to structural compression or with a neurologic deficit.[166] If left untreated, these aneurysms can shower septic emboli to the brain or rupture.[167] As in other arterial segments, diagnosis is confirmed by arterial duplex and CTA.

Because of the potential consequences of disruption and hemorrhage after in-situ reconstruction, some authors recommend ligation and excision alone.[168,169] Ehrenfeld demonstrated that ligation of the internal carotid artery is safe if the systolic carotid stump pressure exceeds 70 mm Hg and long-term anticoagulation is used.[170] However, some authors have reported late neurologic events after ligation in up to 20% to 60% of patients.[171,172] Extracranial-intracranial bypass has been utilized following ligation as has in-situ reconstruction of the carotid artery with an autogenous femoral or a saphenous vein.[25,165,173] Covered stents have been used to allow temporary exclusion of the aneurysm and control bleeding prior to definitive surgical

TABLE 144.2 Treatment Method and Results of Infected Femoral Artery False Aneurysms Secondary to Drug Addiction

Type of Aneurysm and Treatment	No. of Aneurysms	No. of Viable Limbs	Cases of Graft Sepsis (%)	No. of Amputations (%)
Common femoral artery: ligation-excision	14	14	–	0
Deep femoral artery: ligation-excision	11	11	–	0
Superficial femoral artery: ligation-excision	4	4	–	0
Common Femoral Bifurcation				
Ligation-excision	21	14	–	7 (33)
Reconstruction with autogenous vein	6	6	1	0
Reconstruction with synthetic prosthesis	3	3	3 (100)	0
Reconstruction by primary anastomosis	1	1	0	0
Total	60	53	4	7 (12)

From Reddy DJ, Smith RF, Elliott JP Jr, Haddad GK, Wanek EA. Infected femoral artery false aneurysms in drug addicts: evolution of selective vascular reconstruction. *J Vasc Surg*. 1986;3:718–724.

management.[174] The rarity and complexity of these patients with an infected carotid artery aneurysm emphasizes the need for individualized and creative patient management.[175-177]

UPPER EXTREMITY ARTERIES

Most infected aneurysms of the upper extremities are secondary to trauma and are occasionally the result of emboli from endocarditis. The use of percutaneous catheterizations and indwelling catheters for diagnostic procedures and arterial monitoring can lead to the development of infected brachial and radial artery aneurysms.[178] A tender mass with or without cellulitis is usually present, along with fever, chills, and leukocytosis. Infected radial artery aneurysms from indwelling catheters often have digital embolization as the first manifestation.[179] As with most pseudoaneurysms from direct arterial trauma, gram-positive bacteria are the most frequently isolated organisms. Intravenous drug users are a frequently affected population, and as with femoral artery infections, the arterial involvement is often extensive, making management difficult. Additionally, autogenous vein conduit may be limited in this patient population, and distal arterial runoff may also be compromised from long-term use of illicit drugs.[180]

Ligation and excision of the infected arterial segment with debridement of surrounding tissue followed by revascularization is required if the infectious process involves the brachial artery. If the radial or ulnar artery alone is involved, ligation and debridement is generally well tolerated. When revascularization is needed, the use of the greater saphenous vein is the preferred choice; however, in the case of patients who use illicit drugs, an autogenous conduit may not be available. In these patients, prosthetic graft tunneled in a clean tissue plane may be required. Six weeks of culture-directed intravenous antibiotic therapy is recommended.

VISCERAL ARTERIES

Visceral artery infected aneurysms are rare, with the superior mesenteric artery (SMA) being the most common site, followed by the celiac artery and its branches. These infected aneurysms usually result from an embolic event due to infectious endocarditis.[181] As reported in a recent series, intravenous drug abuse can also have an etiologic role.[181,182] When symptomatic, patients can have severe abdominal or back pain with a nonfixed tender pulsatile mass. Fever, nausea, gastrointestinal bleeding, and jaundice may also be present.[182,183] It is important to recognize that a significant percentage (19%) of patients have synchronous infected aneurysms at remote locations.[182] Diagnosis is confirmed by CTA, but in some patients, angiography may also be helpful. Location is usually within 5 cm of the SMA origin, and a single segment is affected. Rupture has been reported to occur in 38% to 50% of cases, and mortality after rupture approaches 30%.[182,184]

Surgical treatment includes ligation and excision of the affected segment; further revascularization is required in approximately 15% of patients, and is dependent on visceral collateral flow and the location of the aneurysm. An autogenous conduit, usually the greater saphenous vein, is the preferred conduit.[177,185,186] After open repair and prior to closure, careful examination of bowel perfusion and viability is of utmost importance.[182]

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Kan CD, Lee HL, Luo CY, Yang YJ. The efficacy of aortic stent grafts in the management of mycotic abdominal aortic aneurysms institute case management with systemic literature comparison. *Ann Vasc Surg*. 2010;24(4):433–440.

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Kieffer E, Petitjean C, Richard T, Godet G, Dhobb M, Ruotolo C. Exclusion-bypass for aneurysms of the descending thoracic and thoracoabdominal aorta. *Ann Vasc Surg*. 1986;1(2):182–195.

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Lew WK, Rowe VL, Cunningham MJ, Weaver FA. Endovascular management of mycotic aortic aneurysms and associated aortoaerodigestive fistulas. *Ann Vasc Surg*. 2009;23(1):81–89.

Single institution case series that reports experience with endovascular management of mycotic aortic aneurysms and associated aorta-aerodigestive fistulas. Results suggest that EVAR can be used to treat acute complications from infected aneurysms and serve as a bridge to open repair.

Oderich GS, Bower TC, Hofer J, et al. In situ rifampin-soaked grafts with omental coverage and antibiotic suppression are durable with low reinfection rates in patients with aortic graft enteric erosion or fistula. *J Vasc Surg*. 2011;53:99–106, 107.e1-e7; discussion 106-107.

Large series consisting of 54 patients with aortic graft enteric erosion of fistula who were treated with in-situ rifampin-soaked grafts. No late graft related deaths were noted, and in this cohort, 4% experienced graft re-infection.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 145

Acute Deep Venous Thrombosis: Epidemiology and Natural History

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Acute venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), are the most common preventable cause of hospital death[1] and a source of substantial long-term morbidity.[2-4] The impact on health is so great that the Surgeon General of the United States issued a "Call to Action" to combat VTE.[5] An understanding of the risk factors and natural history of VTE is essential in guiding prophylaxis, diagnosis, and treatment. In addition, recognizing underlying risk factors and the multifactorial nature of VTE may aid in the identification of situations likely to provoke thrombosis in both high-risk individuals and those with unexplained thromboembolism. Furthermore, understanding the natural history of VTE is important in defining the relative risks and benefits of anticoagulation, as well as the duration of treatment in individual patients.

EPIDEMIOLOGY

Incidence

The incidence of recurrent, fatal, and nonfatal VTEs is estimated to exceed 900,000 cases annually in the United States alone.[6] A 35-year population-based study using the Rochester Epidemiology Project database of Olmsted County Minnesota demonstrated an overall average age- and sex-adjusted annual VTE incidence of 122 per 100,000 person-years (DVT, 56 per 100,000; PE, 66 per 100,000).[7] This study also demonstrated higher age-adjusted rates among men than women (134 vs. 115 per 100,000, respectively). First-time VTEs are approximated to occur in 250,000 US white individuals annually.[8] When compared with other racial populations, whites have a lower incidence of VTE than do African Americans (104 vs. 141 per

Abstract

The incidence of recurrent, fatal and nonfatal venous thromboembolism (VTE) is estimated to exceed 900,000 cases annually. VTE is associated with a number of risk factors. These include age, immobilization, travel, history of VTE, malignancy, surgery, trauma, pregnancy, oral contraceptives and hormonal therapy, blood group, geography and ethnicity, inflammatory bowel disease, systemic lupus erythematosus, varicose veins, iliac vein compression, popliteal vein entrapment, among others. The main complications of VTE include recurrent thrombosis and mortality, especially related to pulmonary embolism, along with post-thrombotic morbidity related to deep venous thrombosis.

Keywords

venous thromboembolism
recurrent thrombosis
DVT
PE
risk factors

100,000) and a higher incidence of VTE than do Hispanics and Asian/Pacific Islanders combined (104 vs. 21 per 100,000).[9] However, the problem of VTE is not just isolated to the United States; it is a global issue. The estimates of VTE across the European Union were 684,019 cases of DVT, 434,723 cases of PE, with 543,454 VTE-related fatalities.[10]

Populations Affected

The incidence of VTE varies with the population studied, use of thromboprophylaxis, the intensity of screening, and the accuracy of the diagnostic test employed. For example, individuals with acute spinal cord injury who were screened systematically with venography demonstrated DVT at a rate of 81%.[11] However, medical-surgical intensive care unit (ICU) patients who received thromboprophylaxis had a DVT rate reported at 10% to 18%,[12] compared with those who were not given DVT prophylaxis having a rate of 25% to 32%.[12,13] Interestingly, the risk of VTE in the critically ill is not limited to the time actually spent in the ICU. A single-center study showed that of the VTEs diagnosed in the critically ill, 64% were diagnosed with a VTE after discharge from the ICU. It is suggested that prolonged immobility after discharge from the ICU may have contributed to the high rate of DVT.[14] Similarly, prolonged immobility contributes to increased rates of VTE in nursing home residents.[15] In summary, it appears that medical-surgical ICU patients are at lower risk for DVT compared with acute spinal cord injury, trauma, or neurosurgery patients, but at a comparable risk to patients who have had major orthopedic surgery, and at higher risk than medical-surgical ward patients.[13,16] Furthermore, a more recent study noted a high (15.2%) rate of DVT in critically ill trauma patients within the first week that did not vary regardless of whether or not prophylaxis was used.[17]

TABLE 145.1 Risk Factors for Acute Deep Venous Thrombosis and Pulmonary Embolism

Risk Factor for DVT or PE	Odds Ratio	95% Confidence Interval
Hospitalization		
With recent surgery	21.72	9.44-49.93
Without recent surgery	7.98	4.49-14.18
Trauma	12.69	4.06-39.66
Malignant Neoplasm		
With chemotherapy	6.53	2.11-20.23
Without chemotherapy	4.05	1.93-8.52
Prior central venous catheter or pacemaker	5.55	1.57-19.58
Prior superficial vein thrombosis	4.32	1.76-10.61
Neurologic disease with extremity paresis	3.04	1.25-7.38
Varicose Veins		
Age 45 years	4.19	1.56-11.30
Age 60 years	1.93	1.03-3.61
Age 75 years	0.88	0.55-1.43
Congestive Heart Failure		
Thromboembolism not categorized as a cause of death at postmortem	9.64	2.44-38.10
Thromboembolism categorized as a cause of death at postmortem	1.36	0.69-2.68

DVT, Deep venous thrombosis; *PE,* pulmonary embolism.
Modified from Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med.* 2000;160:809.

Risk Factors

DVT occurring in the setting of a recognized risk factor is often defined as a secondary event, whereas those that occur in the absence of risk factors is termed primary or idiopathic.[18] Known risk factors for DVT are listed in Table 145.1.

The high incidence of acute DVT in hospitalized patients, the availability of objective diagnostic tests, and the existence of clinical trials evaluating prophylactic measures have helped to more readily identify high-risk groups in this population compared with the outpatient population. Malignancy, surgery, and trauma within the previous 3 months remain significant risk factors for outpatient thrombosis, whereas the prevalence of surgery and malignancy is higher among inpatients with DVT.[19,20] Approximately 47% of outpatients with a documented DVT have one or more recognized risk factors.[19] The incidence of VTE proportionally increases with the number of risk factors.[21] The 2005 Caprini score is currently the most used system in the country (Fig. 145.1).[12,22]

Age

VTE occurs in all ages, although a higher incidence has consistently been associated with advanced age. In a community-based study of phlebographically documented DVT, the yearly incidence of DVT was noted to increase progressively from almost 0 in childhood to 7.65 cases per 1000 in men and 8.22 cases per 1000 in women older than 80 years.[23] The incidence of DVT increased 30-fold from those age 30 years to those older than 80 years. Rosendaal[24] similarly noted an incidence of 0.006 per 1000 children younger than 14 years, which rose to 0.7 per 1000 among adults 40 to 54 years old. Furthermore, Hansson and colleagues[25] found the prevalence of objectively documented thromboembolic events among men increased from 0.5% at age 50 years to 3.8% at age 80 years.

The influence of age on the incidence of VTE is likely multifactorial. The number of thrombotic risk factors increases with age, with three or more risk factors being present in only 3% of hospitalized patients younger than 40 years but in 30% of those 40 years and older.[21] Interestingly, it also appears that the number of risk factors required to precipitate thrombosis decreases with age.[24] This may be related to an acquired prothrombotic state associated with aging because higher levels of thrombin activation markers are found among older people.[26] Advanced age also has been associated with anatomic changes in the soleal veins

Patient's name:_____ Age: ___ Sex: ___ Wgt: ___ lbs

Choose all that apply

Each risk factor represents 1 point
- Age 41–60 years
- Minor surgery planned
- History of prior major surgery
- Varicose veins
- History of inflammatory bowel disease
- Swollen legs (current)
- Obesity (BMI >30)
- Acute myocardial infarction (<1 month)
- Congestive heart failure (<1 month)
- Sepsis (<1 month)
- Serious lung disease incl. pneumonia (<1 month)
- Abnormal pulmonary function (COPD)
- Medical patient currently at bed rest
- Leg plaster cast or brace
- Other risk factors_____

Each risk factor represents 3 points
- Age over 75 years
- Major surgery lasting 2–3 hours
- BMI >50 (venous stasis syndrome)
- History of SVT, DVT/PE
- Family history of DVT/PE
- Present cancer or chemotherapy
- Positive factor V leiden
- Positive prothrombin 20210A
- Elevated serum homocysteine
- Positive lupus anticoagulant
- Elevated anticardiolipin antibodies
- Heparin-induced thrombocytopenia (HIT)
- Other thrombophilia
  Type_____

Each risk factor represents 2 points
- Age 60–74 years
- Major surgery (>60 minutes)
- Arthroscopic surgery (>60 minutes)
- Laparoscopic surgery (>60 minutes)
- Previous malignancy
- Central venous access
- Morbid obesity (BMI >40)

Each risk factor represents 5 points
- Elective major lower extremity arthroplasty
- Hip, pelvis or leg fracture (<1 month)
- Stroke (<1 month)
- Multiple trauma (<1 month)
- Acute spinal cord injury (paralysis) (<1 month)
- Major surgery lasting over 3 hours

For women only (each represents 1 point)
- Oral contraceptives or hormone replacement therapy
- Pregnancy or postpartum (<1 month)
- History of unexplained stillborn infant, recurrent spontaneous abortion (≥3), premature birth with toxemia or growth-restricted infant

Total risk factor score ☐

Please see following page for prophylaxis safety considerations
revised May 16, 2006

Prophylaxis regimen

Total risk factor score	Incidence of DVT	Risk level	Prophylaxis regimen
0–1	<10%	Low risk	No specific measures; early ambulation
2	10–20%	Moderate risk	ES or IPC or LDUH, or LWMH
3–4	20–40%	High risk	IPC or LDUH, or LMWH alone *or* in combination with ES or IPC
5 or more	40–80% 1–5% mortality	Highest risk	Pharmacological: LDUH, LMWH*, Warfarin*, or Fac Xa* alone *or* in combination with ES or IPC

Legend
ES — Elastic stockings
IPC — Intermittent pneumatic compression
LDUH — Low dose unfractionated heparin
LMWH — Low molecular weight heparin
Fac Xa — Factor X inhibitor

Prophylaxis safety considerations: Check box if answer is 'YES'

Anticoagulants: Factors associated with increased bleeding
☐ Is patient experiencing any active bleeding?
☐ Does patient have (or has had history of) heparin-induced thrombocytopenia?
☐ Is patient's platelet count <100,000/mm^3?
☐ Is patient taking oral anticoagulants, platelet inhibitors (e.g., NSAIDS, clopidigrel, salicylates)?
☐ Is patient's creatinine clearance abnormal? If yes, please indicate value ————————
If any of the above boxes are checked, the patient may not be a candidate for anticoagulant therapy and you should consider alternative prophylactic measures.

Intermittent pneumatic compression (IPC)
☐ Does patient have severe peripheral arterial disease?
☐ Does patient have congestive heart failure?
☐ Does patient have an acute superficial/deep vein thrombosis?
If any of the above boxes are checked, then patient may not be a candidate for intermittent compression therapy and you should consider alternative prophylactic measures.

Figure 145.1 The Caprini risk factor tool to predict the risk of venous thromboembolism. *DVT,* Deep venous thrombosis; *PE,* pulmonary embolism. (From Wakefield T, Henke P. *Complications in Surgery*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2011:353.)

and more pronounced stasis in the venous valve pockets.[27,28] We have also noted biologic changes with aging in our research laboratory, such as elevations in P-selectin, tissue factor (TF), antiphospholipid antibodies, and procoagulant microparticles, supporting the effect of age on venous thrombogenesis.

Venous diseases, including VTE, are usually regarded as rare in young children,[3] with an incidence of 0.006 per 1000 children younger than 14 years,[24] whereas the incidence in hospitalized children younger than 18 years has been estimated to be 0.05%.[29] Early mobilization and discharge may partially explain the lower incidence in children.[29] However, the diagnosis is often not considered in pediatric patients, and few studies have systematically evaluated children for DVT. Over time the number of recognized cases in hospitalized children has increased from 0.3 to 28.8 per 10,000 from 1992 to 2005.[30]

VTE in children is almost always associated with recognized thrombotic risk factors,[24,31-33] and multiple risk factors are often required to precipitate thrombosis.[24] DVT may occur in as many as 3.7% of pediatric patients immobilized in halo-femoral traction for preoperative treatment of scoliosis,[34] 4% of children hospitalized in the ICU,[35] and 10% of children with spinal cord injuries.[36,37] Symptomatic postoperative DVT is regarded as unusual in children, although there are few data from studies using routine surveillance,[38] and autopsy-identified PE is approximately four times more frequent in pediatric patients who have undergone surgery than in the general pediatric medical population.[31] Other thrombotic risk factors in hospitalized children are local infection and trauma, immobilization,[33] inherited hypercoagulable states,[24] oral contraceptive use,[39] lower limb paresis,[34] and the use of femoral venous catheters.[40] Outpatient DVT is often associated with a prior DVT and thrombophilia.[30]

Immobilization

Immobilization is a risk factor for VTE. Stasis in the soleal veins and behind the valve cusps is worsened by inactivity of the calf muscle pump,[28] which is associated with an increased risk of DVT. The prevalence of lower extremity DVT in autopsy studies also parallels the duration of bed rest, with an increase during the first 3 days of confinement and a rapid rise to very high levels after 2 weeks. DVT was found in 15% of patients dying after 0 to 7 days of bed rest, in comparison with 79% to 94% of those dying after 2 to 12 weeks.[27] Preoperative immobilization is also associated with a twofold increase in risk of postoperative DVT,[41] and DVT among stroke patients is significantly more common in paralyzed or paretic extremities (53% of limbs) than in nonparalyzed limbs (7%).[42] Patients with neurologic disease and extremity paresis or plegia have a threefold higher risk for DVT and PE, which appears to be independent of hospital confinement.[43]

Travel

Immobilization as a thrombotic risk factor extends to include prolonged travel, particularly the "economy class syndrome," which occurs in people who have sat in a cramped position during extended aircraft flights.[44] Several case series have reported the occurrence of PE in relation to extended travel,[44-49] although none has rigorously examined the prevalence relative to that of the general population, and few have thoroughly reported the presence of other risk factors. A high prevalence of preexisting venous disease and other thrombotic risk factors in this group of patients has sometimes been noted.[26,49] The question of prolonged travel as a risk factor is moderated by observations that extreme duration of venous stasis alone may fail to produce thrombosis[50] and that no consistent rheologic or prothrombotic changes have been demonstrated during prolonged travel.[26,51] However, PE is the second leading cause of travel-related death, accounting for 18% of 61 deaths, suggesting that a relationship cannot be excluded.[48]

More evidence that a connection between travel and DVT and PE has accumulated. In a case-control study, Ferrari and associates found[52] that long distance travel increased the risk of DVT, with an odds ratio (OR) of 4.0, and Samama[53] made similar observations (OR, 2.3). Scurr and colleagues[54] found a 10% risk of calf DVT in patients who traveled without compression stockings. Lapostolle and coworkers[55] observed that over an 86-month period, 56 of 135.3 million airline passengers had severe PE. The frequency among those who traveled more than 5000 km was 150 times as high as those who traveled less than 5000 km. In another case-control study, Paganin and associates[56] observed a high incidence of VTE in patients with risk factors for DVT who traveled long distances: in particular, history of previous VTE (OR, 63.3), recent trauma (OR, 13.6), presence of varicose veins (OR, 10), obesity (OR, 9.6), immobility during flight (OR, 9.3), and cardiac disease (OR, 8.9) increased the risk of DVT. These investigators concluded that low mobility during flight was a modifiable risk factor for development of PE and that travelers with risk factors should increase their mobility.[57]

After a consensus meeting, the World Health Organization published the following conclusions: an association probably exists between air travel and DVT; such an association is likely to be small and mainly affects passengers with additional risk factors for VTE; similar links may exist for other forms of travel.[58] The available evidence does not permit an estimation of actual risk.

History of Venous Thromboembolism

Approximately 23% to 26% of patients presenting with acute DVT have a previous history of thrombosis,[23,59] and histologic studies confirm that acute thrombi are often associated with fibrous remnants of previous thrombi in the same or nearby veins.[60] Depending on sex and age, population-based studies have demonstrated that recurrent VTE occurs in 2% to 9% of people.[3]

The risk of recurrent VTE is higher among patients with idiopathic DVT.[61] In addition, primary hypercoagulability appears to have a significant role in many recurrences. Simioni and associates[61] reported the cumulative incidence of recurrent thrombosis among patients who are heterozygous for the factor V Leiden mutation to be 40% at 8 years of follow-up, 2.4-fold higher than in patients without the mutation, although the importance of heterozygous factor V Leiden to recurrent thrombosis has been questioned.[62] den Heijer and colleagues[63] estimated that 17% of recurrent thromboembolic events may

be due to hyperhomocysteinemia. A similar relationship between impaired fibrinolysis and recurrent DVT has been suggested by several investigators, although the methodologic validity of these findings has been questioned.[64]

Malignancy

Approximately 20% of all first-time VTE events are associated with malignancy.[65] An estimated 1 in 200 individuals with malignancy will develop either DVT or PE, a fourfold higher risk than those without malignancy.[43] Considering all-cause mortality of in-hospital death for cancer patients, one in seven will die of PE.[66] Strikingly, the discovery of an occult malignancy associated with an otherwise first-time idiopathic VTE is as high as 12% to 17% in some series.[67,68] In another 5% to 11% of patients, malignancy appears within 1 to 2 years of presentation for DVT.[67-69] Several series have documented a significantly higher risk of malignancy in patients with presumed idiopathic DVT.[67,70] Among such patients, 7.6% have been noted to have a malignancy during follow-up, with an OR of 2.3 in comparison with those with secondary thrombosis.[68] The incidence of occult malignancy diagnosed within 6 to 12 months of an idiopathic DVT is 2.2 to 5.3 times higher than that expected from general population estimates.[71,72] The highest rates of VTE are associated with pancreatic malignancies, followed by kidney, ovary, lung, and stomach.[73]

The underlying mechanisms contributing to the hypercoagulable state in malignancy have been well studied and are multifactorial. Venous compression secondary to tumor growth, cancer-associated thrombocytosis, immobility, indwelling central lines, and chemotherapy or radiation therapy are all risk factors that increase the possibility of VTE.[74] However, the systemic prothrombotic response seen in malignancy is mediated by cytokines, inhibitors of fibrinolysis, and procoagulants.[75]

Tumor cells can directly initiate hemostasis through constitutive expression of TF. TF is not normally expressed on resting vascular endothelium but rather induced by chemical mediators during times of inflammation or vessel damage to bind factors VII and VIIa. This complex of TF and factor VII activates factors X and XI through proteolysis, leading to the generation of thrombin.[76] Another mediator in malignancy-associated VTE is cancer procoagulant (CP). The role of CP in coagulation is limited to its association with malignancy because it has not been identified in normal healthy tissue. CP serves as a direct activator of factor X, independent of the presence of factor VIIa. The platelet adhesion molecules glycoprotein Ib and glycoprotein IIb/IIIa (GPIIb/IIIa) have also been identified on tumor cells, allowing for platelet activation and aggregation.[77]

The prothrombotic contribution of cytokines such as vascular endothelial growth factor (VEGF), tumor necrosis factor-α (TNF-α), and interleukin-1 (IL-1) mediate their actions through induction of TF on vascular endothelium, monocytes, and leukocytes.[76,78] In addition, IL-1 and TNF-α downregulate the expression of thrombomodulin, the receptor for thrombin, on the endothelial surface. This results in a decrease in thrombin-thrombomodulin complexes, the activating complex of protein C, a natural anticoagulant.[76,78] Furthermore, IL-1 and TNF-α stimulate the production of plasminogen activator inhibitor 1 (PAI-1), the main physiologic inhibitor of fibrinolysis.[79]

As many as 90% of patients with cancer have abnormal coagulation parameters, including increased levels of coagulation factors, elevated fibrinogen or fibrin degradation products, and thrombocytosis.[80] Elevated fibrinogen and thrombocytosis are the most common abnormalities, perhaps reflecting an overcompensated form of intravascular coagulation.[80] Levels of the coagulation inhibitors antithrombin, protein C, and protein S also may be reduced in malignancy.[81]

Markers of activated coagulation are elevated in the majority of patients with solid tumors and leukemia.[80] Fibrinopeptide A levels reflect tumor activity, decreasing or increasing in response to treatment or progression of disease, suggesting that tumor growth and thrombin generation are intimately related.[80] Furthermore, these levels may fail to normalize after administration of heparin to patients with cancer and DVT, perhaps explaining why these DVTs may be refractory to anticoagulants.[80]

VTE is also associated with the treatment of some cancers. DVT complicates 29% of general surgical procedures for malignancy.[81] Preoperative activation of the coagulation system, as reflected by elevated thrombin-antithrombin complex values, is associated with a 7.5-fold increased risk of postoperative DVT.[80] Some chemotherapeutic regimens also predispose to DVT, and thrombotic complications may be as common as the more widely recognized infectious complications.[82] VTE has been reported in up to 6% of patients undergoing treatment for non-Hodgkin's lymphoma, and in 17.5% of those receiving therapy for breast cancer.[83] Among patients with stage II breast cancer, thrombosis was significantly more common in those randomly assigned to 36 weeks of chemotherapy (8.8%) than in those receiving only 12 weeks of treatment (4.9%).[82] Potential thrombogenic mechanisms associated with chemotherapy include direct endothelial toxicity, induction of a hypercoagulable state, reduced fibrinolytic activity, tumor cell lysis, and use of central venous catheters.[83,84] Some intravenous chemotherapeutic agents are associated with activation of coagulation and increased markers of thrombin generation, a response that is blocked by pretreatment with heparin.[85] An additional risk factor in some cancer patients is an elevated soluble P-selectin.[86]

Surgery

The high incidence of postoperative DVT, as well as the availability of easily repeatable, noninvasive diagnostic tests, has allowed a greater understanding of the risk factors associated with surgery than in other conditions. Surgery constitutes a spectrum of risk that is influenced by patient age, coexistent thrombotic risk factors, type of procedure, extent of surgical trauma, length of procedure, and duration of postoperative immobilization.[87] The type of surgical procedure is particularly important.[41] Historically, the overall incidence of DVT is approximately 19% in patients undergoing general surgical operations, 24% in those having elective neurosurgical procedures; and 48%, 51%, and 61% among those undergoing surgery for hip fracture, hip arthroplasty, and knee arthroplasty, respectively.[87] On the basis of these data, patients can be classified as being at low, moderate, or high risk for thromboembolic

complications. Approximately half of postoperative lower extremity thrombi develop in the operating room, with the remainder occurring over the next 3 to 5 days.[88] However, the risk for development of DVT does not end uniformly at hospital discharge. In one study, 51% of the thromboembolic events occurred after discharge from gynecologic surgical procedures.[89] Similarly, up to 25% of patients undergoing abdominal surgery have DVT within 6 weeks of discharge.[90] Heit and associates found a nearly 22-fold higher risk of DVT and PE among patients who were hospitalized following previous surgery.[89]

All components of the Virchow triad may be present in the surgical patient—perioperative immobilization, transient changes in coagulation and fibrinolysis, and the potential for gross venous injury. Immobilization is associated with a reduction in venous outflow and capacitance during the early postoperative period.[91] Surgery is also accompanied by a transient, low-level hypercoagulable state, presumably mediated by the release of TF, which is marked by a rise in thrombin activation markers shortly after the procedure begins.[91] The thrombogenic potential of different surgical procedures appears to differ, with greater rises in thrombin activation markers during hip arthroplasty than after laparotomy.[92] Increased levels of PAI–1 are also associated with a decrease in fibrinolytic activity on the first postoperative day, the "postoperative fibrinolytic shutdown."[93] This relationship between impaired fibrinolysis and postoperative DVT may be particularly important,[64] with preoperative and early postoperative elevations in PAI-1 correlating with the development of thrombosis in orthopedic patients.[93] Complications are also an important trigger: in a large VA study involving more than 76,000 patients, the strongest predictors of postoperative VTE included myocardial infarction, blood transfusion (>4 units), and urinary tract infection.[94]

Trauma

The prevalence of DVT among autopsied trauma casualties has been reported to be as high as 65%, comparable to the 58% incidence among injured patients in modern venographic series.[11] Substantially lower DVT rates, ranging from 4% to 20%,[95] have been noted in series using duplex ultrasonography, although many patients studied were receiving prophylaxis and the limitations of ultrasound in screening asymptomatic patients are well recognized. Recent trauma was associated with nearly a 13-fold increase in risk.[89]

Although the risk of DVT may be less than 20% in some injured patients,[11] certain subgroups are at particularly high risk. Age (OR, 1.05 for each 1-year increment), blood transfusion (OR, 1.74), surgery (OR, 2.30), fracture of the femur or tibia (OR, 4.82), and spinal cord injury (OR, 8.59) have been significantly associated with the development of DVT in this population.[11] Other reported risk factors are a hospital stay longer than 7 days,[96] increased Injury Severity Score (ISS),[96-98] pelvic fractures,[99] major venous injury,[100] presence of femoral venous lines,[101] the duration of immobilization,[102] and prolongation of the partial thromboplastin time.[103]

As with postoperative DVT, several pathophysiologic elements may be responsible for the high incidence of DVT in trauma patients. Immobilization by skeletal fixation, paralysis, and critical illness are associated with venous stasis, whereas mechanical injury is important after direct venous trauma and central venous cannulation. Less well appreciated is the hypercoagulable state after depletion of coagulation inhibitors and components of the fibrinolytic system. Fibrinopeptide A levels rise after injury,[104] consistent with activation of coagulation, whereas fibrinolytic activity has been found to increase initially and then decrease.[105,106]

Pregnancy

The incidence of VTE in the pregnant population is 6 to 10 times greater than matched controls[107] and causes approximately 10% of all maternal deaths.[108] Using clinical evaluation, VTE has been reported at a rate of 1.3% to 7% during pregnancy and 6.1% to 23% in the postpartum period.[109] However, studies that used venography, Doppler ultrasonography, or ventilation-perfusion scans for evaluation of clinically suspected thromboembolism have suggested an incidence of 0.029% to 0.055% in this population.[110] The risk of thrombosis appears to be two to three times greater during the puerperium, with the highest incidence found after cesarean section.[111] Interestingly, when VTE has been objectively documented, the occurrence of thrombosis is equally distributed throughout all three trimesters.[112]

DVT in pregnancy has been attributed to impaired venous outflow due to uterine compression because 97% of reported thromboses have been isolated to the left leg.[112] Furthermore, pregnancy is associated with a transient hypercoagulable state due to increases in the levels of fibrinogen, von Willebrand factor, and factors II, VII, VIII, and X. Compounding this acquired functional resistance to activated protein C is also seen during pregnancy.[113] Similarly, protein S levels are decreased by 50% to 60% early during pregnancy, with free protein S levels comparable with hereditary heterozygous protein S deficiency.[114,115] The fibrinolytic system is also altered in pregnancy: levels of tissue plasminogen activator (tPA) are decreased and PAI-1 and PAI-2 increased.[116]

Both retrospective and prospective studies have demonstrated that between 30% and 50% of women with a pregnancy-associated VTE also have an inherited thrombophilia. This high incidence has led to the recommendation of screening for thrombophilia in those pregnant patients with a personal or family history of VTE.[117,118] The risk of puerperal DVT also increases with maternal age, suppression of lactation, hypertension, and assisted delivery but not with the number of pregnancies.[119]

Oral Contraceptives and Hormonal Therapy

As suggested by case reports in the early 1960s, further studies have now established the use of oral contraceptives as an independent risk factor for the development of DVT. These studies noted ORs of 3.8 to 11.0 for thrombosis,[120] and an unweighted summary relative risk among 18 controlled studies was 2.9.[121] Approximately one-quarter of apparently idiopathic thromboembolic events among women of childbearing age have

been attributed to oral contraceptives. Early studies also suggested that thromboembolism is responsible for approximately 2% of deaths in young women, with contraceptive-associated mortality rates of 1.3 and 3.4 per 100,000 among women aged 20 to 34 and 35 to 44 years, respectively.[122] The increased risk of thromboembolism appears to diminish soon after oral contraceptives are discontinued and is independent of the duration of use.[123]

Risk is correspondingly higher when oral contraceptive use is combined with other factors, such as surgery[124] and inherited inhibitor deficiencies.[125] The factor V Leiden mutation may be particularly important in this regard; resistance to activated protein C has been reported in up to 30% of patients with contraceptive-associated thromboembolism.[126] The use of third-generation oral contraceptives may act synergistically with the factor V Leiden mutation, raising thromboembolic risk 30- to 50-fold.[127-129]

Estrogenic compounds also increase the risk of VTE when used for lactation suppression[119] in treatment of carcinoma of the prostate and as postmenopausal replacement therapy.[130] Although estrogen doses used for postmenopausal replacement therapy are approximately one-sixth those in oral contraceptives, some data support an increased thromboembolic risk at these doses as well. Several studies show a twofold to fourfold higher risk of VTE among women taking hormone replacement therapy.[130-134] This increased risk is greatest during the first year of treatment.[131,134] However, given the relative infrequency of thromboembolism, this risk represents only one or two additional cases of thromboembolism per year in every 10,000 women in this age group.

Estrogen in pharmacologic doses is associated with alterations in the coagulation system that may contribute to this thrombotic tendency. Such alterations include decreases in PAI-1[135] and increases in blood viscosity, fibrinogen, plasma levels of factors VII and X, and platelet adhesion and aggregation.[136,137] An associated prothrombotic state is implied by rises in markers of activated coagulation occurring in conjunction with elevations of circulating factor VIIa and decreases in antithrombin and protein S inhibitor activity.[136,138] The extent to which antithrombin and protein S are depressed is significantly less with lower-estrogen preparations.[139]

Blood Group

There also appears to be a relationship between VTE risk and the ABO blood groups, with a higher prevalence of blood type A and correspondingly lower prevalence of blood type O groups.[140,141] In reviewing the literature, Mourant and colleagues[142] found the relative incidence of type A to be 1.41 times higher among patients with thromboembolism than among controls. The effect of blood type was greater in young women who were taking oral contraceptives or were pregnant; the relative incidence of type A among patients with thromboembolism was 3.12 in those taking oral contraceptives and 1.85 in those who were pregnant. A relationship between soluble endothelial cell markers and ABO blood group is known to exist, with significantly lower levels of von Willebrand factor among those with type O blood.[143]

Geography and Ethnicity

There are also geographic differences in the frequency of VTE, as the incidence of postoperative DVT in Europe has been noted to be nearly twice that of North America.[81,87] Higher rates of thromboembolism have also been noted in the central United States compared with either coast.[144] Autopsy series suggest that although the prevalence of thromboembolism is identical among American black and white patients, it is significantly higher than in a matched Ugandan black population.[145] A similar autopsy series noted the prevalence of thromboembolism to be 40.6% in Boston and 13.9% in Kyushu, Japan.[146]

Unfortunately, regional variations in underlying medical and surgical conditions, as well as in prophylactic measures and diagnostic methods, may confound any apparent differences in the incidence of thromboembolism among different ethnic and geographic groups. Nevertheless, it is certainly conceivable that differences between ethnic groups might arise from either genetic and/or environmental factors. Such differences seem likely based on recognized geographic differences in the spectrum of mutations leading to congenital anticoagulant deficiencies.[147] Such theoretical concerns are also supported by geographic variability in the incidence of the factor V Leiden mutation. The factor V Leiden allele has a prevalence of 4.4% in Europeans, corresponding to a carrier rate of 8.8%, but the allele has not been identified in Southeast Asian or African populations.[148]

Inflammatory Bowel Disease

Clinical series have reported VTE to complicate inflammatory bowel disease (IBD) in 1.2% to 7.1% of cases.[149,150] Crohn disease has incidence rates of 31.4/10,000 person-years and 10.3/10,000 person-years for DVT and PE, respectively. Ulcerative colitis also has a high incident rate of 30.0/10,000 and 19.8/10,000 person-years for DVT and PE, respectively. Such thromboses frequently occur among young patients, are more common with active disease, and may affect unusual sites, such as the cerebral veins.[149,150] Greater extent of colonic disease in ulcerative colitis portends a higher risk of VTE. Most cases are not associated with inherited hypercoagulable states. However, fibrinopeptide A elevations in IBD suggest that active inflammation is associated with activation of coagulation, possibly mediated by endotoxin-induced monocyte activation.[149-151]

Systemic Lupus Erythematosus

A syndrome of arterial and venous thrombosis, recurrent abortion, thrombocytopenia, and neurologic disease may complicate systemic lupus erythematosus (SLE) when accompanied by the presence of antiphospholipid antibodies.[152] Lupus anticoagulant and anticardiolipin antibodies may be seen in association with SLE; with other autoimmune disorders; with nonautoimmune disorders, such as syphilis and acute infection, with drugs, including chlorpromazine, procainamide, and hydralazine; and with older age.[153]

Lupus anticoagulant is present in 34% of patients with SLE and anticardiolipin antibodies in 44%, in comparison with 2% and 0% to 7.5%, respectively, of the general population.[153]

Among patients with SLE, those with lupus anticoagulant are at a sixfold higher risk for VTE, whereas those with anticardiolipin antibodies are at a twofold greater risk.[154] The incidence of arterial or venous thrombosis is 25% in patients with lupus anticoagulant and 28% in patients with anticardiolipin antibodies.[153]

Varicose Veins

Varicose veins are also included as a risk factor for acute DVT, although frequently only as a marker of either previous venous disease.[155] Most studies evaluating thrombotic risk have been performed in inpatients with other major risk factors for DVT. Such studies have inconsistently supported varicose veins as a risk factor in postoperative, post-stroke, or postmyocardial infarction cases.[155-157] The importance of varicose veins in otherwise healthy outpatients with DVT has been questioned by some researchers[158] because varicose veins were not identified as independent risk factor in young women,[159] although some studies of postmenopausal women have reported varicose veins or superficial thrombophlebitis to be associated with ORs of 3.6 to 6.9 for the development of thromboembolism.[131,134]

However, Heit and associates[160] found that varicose veins were independent predictors of DVT. They also reported that age is an important factor in these patients, reporting a higher correlation between DVT and varicosity in young patients. For example, 45-year-old patients with varicose veins had a fourfold higher risk of VTE, 60-year-old patients had a twofold greater risk, and 75-year-old patients had no increase in risk. This group also found that patients with previous superficial vein thrombosis were more than four times more likely to have DVT or PE.[160] See Chapter 150.

Iliac Vein Compression

The association of VTE and anatomic anomalies or syndromes represents a congenital risk factor responsible for DVT in both the upper and lower extremities. Left iliac vein compression by the right iliac artery and fifth lumbar artery was first described by May and Thurner in cadavers who hypothesized that chronic pulsation of the right iliac artery and mechanical obstruction led to intimal hypertrophy of the vein wall and subsequent venous obstruction.[161] In actuality, it was Virchow who had initially observed iliofemoral vein thrombosis was five times more likely to occur in the left leg than in the right leg over a century earlier.[162] Although left lower extremity venous hypertension associated with or without left iliofemoral DVT has come to be known as May-Thurner syndrome, it is important to recognize, if only for historical nomenclature, that a similar syndrome was described by Cockett in 1965 (Cockett syndrome) and took popularity over the term May-Thurner syndrome in Europe. However, it was Cockett who associated the acute phase of iliofemoral DVT secondary to compression of the iliac vein with the long-term consequence of chronic venous insufficiency (CVI). In addition, it was Cockett who noted surgical intervention for the purpose of alleviating the skin ulcers and varicosities associated with iliac vein compression was ineffective unless the underlying disease process was identified.[163]

May-Thurner syndrome is more common in young to middle-aged women, especially after multiple pregnancies. The presenting symptom is often acute onset of left leg pain and swelling secondary to thrombosis. Atypically, patients may present with symptoms of CVI that are unresponsive to compression stockings, leg elevation, and a calf exercise program.[164] Early 20th century postmortem dissections revealed a 22% to 32% incidence of left iliac vein compression.[165] Modern computed tomography imaging has revealed that in an asymptomatic population, the average amount of compression on the left iliac vein was 35%, and 24% of this population demonstrated greater than 50% compression.[165] Although individuals in such series were asymptomatic, the incidence of symptomatic left common iliac vein compression presenting with either edema or DVT is estimated to be between 37% and 61%.[166,167] Interestingly, the presence of an abdominal aortic aneurysm was associated with a significantly less amount of compression on the left common iliac vein by the right common iliac artery secondary to a higher prevalence of tortuosity in that artery.[168]

Popliteal Vein Entrapment

Although arterial entrapment syndrome is well described in the literature, popliteal vein entrapment has been reported to occur either alone or with the artery in 10% of cases.[169] Anatomic anomalies of the medial head of the gastrocnemius have been associated with popliteal vascular entrapment. However, when venous entrapment occurs in a setting without arterial entrapment, both the medial or the lateral head of the gastrocnemius have been shown to contribute.[170] Bony tumors and hypertrophied fibrous fascia have also been associated with isolated venous involvement.[171,172] Traditionally, popliteal artery entrapment has been more associated with the male gender; venous entrapment has been reported to occur 70% of the time in females.[173] The presentation is often that of a young adult with signs of CVI, including leg swelling varicosities, skin changes, and DVT.

Other Risk Factors

Risk factors for VTE covered in other sections in this book include inherited thrombophilias (Chapter 38), thoracic outlet syndrome (Chapter 123), central venous catheters (Chapter 149), and inferior vena cava anomalies (Chapter 163). Traditional risk factors for VTE have included obesity and cardiac disease; however, the evidence supporting these risk factors remains equivocal. Among postmenopausal women, a body mass index of greater than 25 to 30 kg/m^2 has been associated with a significantly increased risk of VTE.[132,134] Some investigators have reported obesity to be associated with a twofold greater risk for postoperative DVT, although multivariate analyses by others has not shown obesity to constitute an independent risk.[155] Obesity (and past tobacco smoking) was not an independent risk factor of DVT in the Olmsted County study[160] and has not been proven to be a risk factor for the development of DVT after stroke.[157] However, obesity is a risk factor for recurrent DVT.[174]

Systemic hypercoagulability, congestive heart failure, and enforced bed rest may predispose patients who are hospitalized with acute myocardial infarction to DVT. The incidence of DVT in this population has been reported to be 20% to 40%.[87,156,175] Some investigators have noted the incidence of DVT to be higher among patients in whom myocardial infarction was confirmed (34%) than in those in whom the diagnosis was excluded (7%). The prevalence of PE among autopsied patients has also not differed substantially from that in other inpatients.[144,145]

Although MI as a risk factor may be in question, those older than 60 years with congestive heart failure have a DVT rate of 54%.[176] However, the evidence supporting congestive heart failure as an independent risk factor for DVT is also conflicting. A variety of thromboembolic complications account for nearly half the deaths among patients who did not undergo anticoagulation after hospitalization for congestive heart failure, but congestive heart failure has not been identified as an independent risk factor for postoperative DVT. The balance of evidence suggests that severely ill medical patients are at significant risk for VTE,[177] although it is difficult to define the additional risk associated with cardiac disease.

NATURAL HISTORY

The relative balance between organization, thrombolysis, propagation, and rethrombosis determines outcomes after human thrombosis. From a clinical perspective, the most important events after thrombosis are recanalization and recurrent thrombosis.

Recanalization

Impedance plethysmography was the first widely available noninvasive test permitting serial evaluations of outflow obstruction due to an acute DVT. Although this test could not distinguish between recanalization and the development of collateral venous outflow, results of such studies were found to normalize in 67% of patients by 3 months and in 92% of patients by 9 months.[178] Venous duplex ultrasonography allows individual venous segments to be observed over time and has further documented that recanalization does occur in most patients after acute DVT. In 21 patients monitored prospectively with duplex scanning, recanalization occurred in 44% of patients at 7 days and in 100% of patients by 90 days after the acute event.[179] Several additional studies[180,181] confirm the histologic findings that recanalization begins early after an acute DVT, with the greatest reduction in thrombus load occurring within 3 months of the event. Complete thrombus resolution has been reported in 56% of patients monitored for 9 months.[179,182] However, recanalization may continue for months to years after the acute event.[181]

Recurrent Venous Thrombosis

Nearly 30% of patients will develop a recurrence within a 10-year time span.[183] Recurrences are more likely with the same event type as the incident event; for example, those who initially developed a PE are more likely to develop another PE instead of a DVT.[184] Independent predictors for recurrent DVT include increasing age, obesity, malignant neoplasm, and extremity paresis. In a series of landmark trials, among patients with proximal DVT, recurrent thromboembolic events were found in 5.2% of patients treated with standard anticoagulation for 3 months, compared with 47% of patients treated with a 3-month course of low-dose subcutaneous heparin.[185,186]

Despite the significance of these observations, reports of serial noninvasive follow-up examinations suggest that these studies may underestimate the incidence of new thrombotic events. In a series of 177 patients, most of whom were treated with standard anticoagulation measures, recurrent thrombotic events were observed in 52% of patients.[187] New thrombi were observed in 6% of uninvolved contralateral extremities, whereas propagation of thrombi to new segments occurred in 30% of involved limbs and rethrombosis of a partially occluded or recanalized segment in 31% of extremities. Propagation in the ipsilateral limb tended to occur as an early event at a median of less than 40 days after presentation, whereas rethrombosis and extension to the contralateral limb tended to occur sporadically as late events.

Mortality

The severity of PE is shown in 30-year autopsy studies, which demonstrated a 26% incidence of PE in hospitalized patients, of which 9% was fatal. This translates to a 1% incidence of PE and a 0.36% incidence of death from PE in all hospitalized patients per year.[188] See Chapter 151.

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A complete reference list can be found online at www.expertconsult.com.

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146 CHAPTER

Venous Thromboembolic Disease: Mechanical and Pharmacologic Prophylaxis

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The incidence of venous thromboembolism (VTE) is variable depending on the setting. For patients with a recent or current hospitalization, the rate is 330 per 100,000, compared with 8 per 100,000 for those in the community.[1] These hospitalizations are 2.5 times more costly to the healthcare system than for those without VTE. The greatest cost related to treating VTE patients occurs in the first 3 months, almost $17,000 per patient. The risk of death among those who suffer a pulmonary embolism (PE) is 18 times higher compared with patients who have deep venous thrombosis (DVT) only. For approximately 1 in 4 patients with PE, the presentation is sudden death. The crude percentage of postoperative DVT is reported to be as high as 22% in groups with no prophylaxis.[2] Given these figures and the higher probability of VTE in the postoperative scenario, it is of utmost importance to have defined strategies for targeted prevention.

In this chapter we provide an overview of the process of personalizing VTE prevention based on risk estimates and available evidence of efficacy.

RATIONALE FOR RISK STRATIFICATION AND PROPHYLAXIS

Both patient specific and procedural factors confer various degrees of thrombotic risk, thus, individualized risk assessment is recommended.[3] Risk factors associated with the development of VTE have been known for a long time (Fig. 146.1).[3a] Pioneering work by Maxwell Borow in 1983 identified risk factors including length of surgery, age, obesity, infection, length of surgery over 1 hour, and cancer. In addition, there was a linear

Abstract

This chapter begins by emphasizing the importance of individual risk assessment for surgical patients; it describes the use of the Caprini score to stratify patients according to risk and suggest appropriate prophylactic regimes. The current data regarding physical and pharmacologic methods are presented, along with specific recommendations for individual surgical populations. The chapter concludes by presenting the concept of selecting prophylaxis based on combining evidence-based guidelines and clinical practice experience.

Keywords

Caprini risk assessment
direct oral anticoagulants
mechanical methods
pharmacologic prophylaxis
thrombosis prophylaxis
venous thromboembolic disease
venous thromboembolism

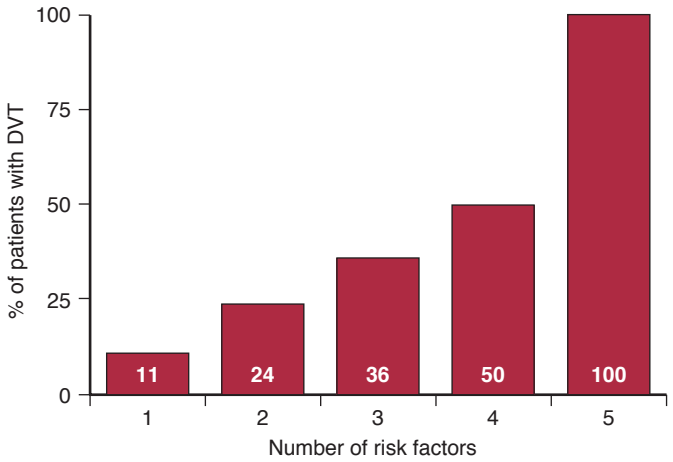

Figure 146.1 Proportion of patients with confirmed deep venous thrombosis (DVT) relative to number of risk factors. Study of 1464 patients who underwent impedance plethysmography for DVT diagnosis. (Data adapted from Wheeler HB, Anderson FA Jr, Cardullo PA, Patwardhan NA, Jian-Ming L, Cutler BS. Suspected deep vein thrombosis. Management by impedance plethysmography. *Arch Surg*. 1982;117(9):1206-1209.)

relationship between the length of surgery and the incidence of thrombosis.[4] Historically, operations to replace a joint of the lower extremity without prophylaxis are associated with a 20% to 50% incidence of VTE.

Patients with a prior history of VTE are at greatly increased risk for recurrent events, particularly when they have surgery, develop a serious illness, or are immobilized for long periods of time. Borow found in a series of 500 surgical patients that 66% of those with a history of VTE developed postoperative VTE.[4] Samama reported in a case-control study that patients with a VTE history of VTE were eight times more likely to develop a new VTE during a high-risk period compared with those without a prior history.[5] Similarly, an important yet often overlooked risk factor for VTE is a family history of thrombosis, usually among first-degree relatives.

The incidence of VTE varies with congestive heart failure, depending on the ejection fraction. This observation illustrates the fact that a risk factor can be associated with a variable incidence of thrombosis.[6] Preoperative pneumonia is associated with postoperative VTE.[7] A number of studies support an association between increasing age and a higher incidence of VTE, the risk approximately doubling with each decade. In a prospective observational cohort study of cancer patients' history of VTE, superficial phlebitis or the presence of varicose veins was associated with an elevated incidence of VTE.[8] Inflammatory bowel disease, including regional ileitis and ulcerative colitis, is a powerful risk factor for the development of VTE, and the risk remains even when the disease is not active.

Early ambulation is important after surgical procedures. Ambulatory status was defined in the MEDENOX study as the ability to attain, unassisted, a walking distance of greater than 10 m (~33 ft). Nonambulatory patients without prophylaxis had a statistically significant increase of VTE (19.7% vs. 10.6%; $P = .03$). The incidence of DVT is also higher among patients with leg plaster casts.[9]

Hypercoagulable states are important risk factors for VTE and may be inherited or acquired. Factor V Leiden is the most common congenital thrombophilic defect, affecting 5% of the Caucasian population. For these patients the lifetime probability of developing VTE is approximately 10%; an adjusted hazard ratio (HR) of 2.2 (95% CI, 2.0 to 2.5) for people with heterozygous mutations and 7.0 (95% CI, 4.8 to 10) for homozygous mutations has been reported. The prothrombin gene (*G20210A*) mutation is the next most common thrombophilic defect, and prevalence in the United States is approximately 1% to 2%. The adjusted risk for VTE in patients with a homozygous prothrombin gene defect is higher (HR 11 [95% CI, 2.8 to 44]) than for those with a heterozygous mutation (HR 1.5 [95% CI, 1.2 to 1.9]).[10]

Defects of the natural anticoagulant proteins include antithrombin and proteins C and S. The latter two defects are vitamin K–dependent anticoagulants synthesized in the liver. These inherited thrombophilic defects are relatively uncommon but represent significant thrombotic risks and must be accounted for.

Hormonal contraceptives represent a risk factor for VTE. The rates of VTE in users of oral contraceptives are estimated to be 9 to 10 per 10,000 women per year compared with 4 to 5 per 10,000 in nonusing women of childbearing age. It has also been estimated that VTE rates in pregnancy average 29 per 10,000 overall and approach 300 to 400 per 10,000 individuals in the immediate postpartum period. Oral contraceptives with less than 35 μg of ethinyl estradiol are associated with a slightly lower incidence of VTE in the community compared with those containing more than 50 μg.[11]

Last, VTE is a common cause of death among surgical patients with cancer. In a large study of patients (2373) undergoing a wide variety of abdominal surgical procedures, the incidence of VTE was 2.1%.[12] Forty percent of the events occurred more than 21 days post surgery. The death rate was 1.72%, and 46.3% of these events were due to VTE.

Patients suffering multiple trauma are subject to a very high risk of developing VTE. In a study by Geerts, thrombosis was seen in 47% of trauma patients, including a 12% incidence of proximal venous thrombosis within the first 2 weeks. This study included 56% of patients with lower extremity orthopedic or pelvic injuries. Spinal cord injury is associated with thrombosis in approximately 35% to 40% of patients during the first 3 months of a paralytic event. Once a flaccid paralysis occurs, the incidence of VTE is dramatically reduced.[13]

Risk-Assessment Models

Prophylaxis suggested for each individual should be based on the relative balance between the incidence of thrombosis and the risk of bleeding as well as available resources within the institution. A number of risk-assessment models have been proposed over the years, but most of them have not been formally validated. For nonorthopedic surgical patients, the Rogers score was derived from 183,069 patients in the Patient Safety and Surgery Study involving general, vascular, or thoracic procedures in the Veterans Administration system between 2002 and 2004. This score used

factors found to be independent predictors of VTE risk. The level of the score correlated with the incidence of symptomatic thrombotic events. Well-known risk factors not captured in the model include obesity, inflammatory bowel disease, obstetric accidents, personal or family history of thrombosis, congestive heart failure, myocardial infarction, stroke, and central lines.

The Caprini score, which was first described in 1991 (Fig. 146.2), discriminates between patients at low, moderate, and high risk for VTE and has been widely validated in a variety of patient populations.[13a] Up to now a total of 32 publications in peer-reviewed journals involving more than 128,000 combined medical and surgical patients have evaluated the Caprini score. Recently Pannucci presented the results of a meta-analysis (unpublished data) indicating that the Caprini score predicts both the baseline VTE risk and effectiveness of chemoprophylaxis. The analysis included 13,412 patients and identified a 22-fold variation in VTE risk among 5216 surgical patients who received no prophylaxis.[14] Patients at each ascending risk level were significantly more likely to have a VTE event than patients at lower risk levels. Patients with a score greater than 8 were significantly less likely to have a VTE event when chemoprophylaxis was provided. The Caprini score did not correlate with bleeding outcomes.

One recent case study consisted of a program of early mobilization, intermittent pneumatic compression (IPC), and mandatory risk stratification linked to specific anticoagulant prophylaxis protocols using the Caprini score.[15] Before implementation of this program the incidence of DVT was 1.9% in 1569 patients. Following implementation the thrombosis rate decreased to 0.3% (1323 patients), an 84% decrease. PE was seen in 1.1% of these 1569 patients and dropped to 0.5% in the 1323 patients after the program was initiated (Table 146.1).

1 point	2 points
○ Age 41-60	○ Age 60-74
○ Minor surgery	○ Arthroscopic surgery
○ Prior major surgery (<1 mo)	○ Malignancy
○ Varicose veins	○ Major surgery >45 min
○ Inflammatory bowel disease	○ Laparoscopic surgery >45 min
○ Swollen legs	○ Confined to bed (>72 h)
○ Obesity	○ Immobilizing cast (<1 mo)
○ Congestive heart failure	○ Central venous access
○ Sepsis (<1 mo)	**3 points**
○ Lung disease, i.e., pneumonia (<1 mo)	○ Age > 75
○ Abnormal pulmonary function (COPD)	○ History of VTE
○ Medical patient in bed	○ Family history of VTE
○ Other _____	○ Factor V Leiden
○ On estrogen supplementation	○ Prothrombin gene mutation
○ Pregnant or puerperium	○ Elevated homocysteine
○ History of unexplained stillborn, recurrent abortions, premature birth with toxemia or growth-restricted infant	○ Lupus anticoagulant
5 points	○ Positive anticardiolipins
○ Elective lower extremity arthroplasty	○ Heparin induced thrombocytopenia
○ Hip, pelvis, or leg fracture (<1 mo)	○ Other thrombophilia
○ Stroke (<1 mo)	**Total score =**
○ Multiple trauma (<1 mo)	
○ Spinal cord injury (<1 mo)	

Figure 146.2 Validated 2005 Caprini Risk Score. *VTE*, Venous thromboembolism. (Adapted from Caprini JA. Thrombosis risk assessment as a guide to quality patient care. *Dis Mon*. 2005;51(2-3):70-78.)

METHODS OF PROPHYLAXIS

Venous stasis plays a major role in the pathogenesis of thrombosis because it prevents the local clearance of activated coagulation factors and reduces their binding and inactivation by physiologic inhibitors. In addition, when associated with venous dilation, stasis may alter the normal linear blood flow, allowing platelets and leukocytes to contact the endothelium. In this regard, dilated veins may result in endothelial cracking and exposure of subendothelial collagen and other molecules, such as vitronectin and fibronectin, resulting in local thrombosis. Endothelial damage may also occur in patients undergoing manipulation of or trauma to deep veins, as is the case during pelvic operations for tumors, hip or knee arthroplasty, and hip fracture surgery. For these reasons, available methods for the prophylaxis of VTE include either mechanical measures, based on compression of the lower limbs and aiming to reduce stasis by improving venous flow, or pharmacologic interventions, using anticoagulants to prevent or counteract hypercoagulability. These methods may be used separately or combined, depending on the potential thrombotic and hemorrhagic risk faced by the patient.

General Measures

Adequate hydration, analgesia, and ambulation are important measures to improve postoperative recovery and reduce the risk of VTE. For those patients who are immobile in bed, active flexion and extension of the ankle joints and leg elevation will reduce stasis by enhancing venous flow. From this perspective, we should encourage early and progressive ambulation rather than early *angulation*, or having patients seated in a chair, which will promote venous stasis in the legs.

Mechanical Methods of Prophylaxis

Depending on their mechanism of action, mechanical methods may be divided into two main categories: passive and active. Among passive methods, elastic compression stockings are the preferred modality, particularly in surgical patients. Regarding active methods, intermittent pneumatic compression (IPC) of the legs is widely used alone, as in patients who cannot receive pharmacologic prophylaxis with anticoagulants or in combination with anticoagulants in patients at very high thrombotic risk.

TABLE 146.1 Boston University Algorithm for Prescribing Thrombosis Prophylaxis

Caprini Score	Risk	Recommendation	Duration
0	Lowest	Early ambulation only, OR Compression boots, OR Low dose Heparin; OR Low molecular weight heparin	Hospitalization
1-2	Low	Compression boots, OR Low dose Heparin, OR Low molecular weight heparin	Hospitalization
3-4	Moderate	Compression boots, AND Low dose Heparin, OR Low molecular weight heparin	Hospitalization
5-8	High	Compression boots, AND Low dose Heparin, OR Low molecular weight heparin	1-10 days
9 or more	Highest	Compression boots, AND Low dose Heparin, OR Low molecular weight heparin	30 days

Compliance was 100% in the low- and moderate-risk groups, 89% in the high-risk group, and 77% in the highest-risk group.
(Adapted from Cassidy MR, Rosenkranz P, McAneny D. Reducing postoperative venous thromboembolism complications: in reply to Lau and colleagues. *J Am Coll Surg*. 2014;219(5):1103-1104.)

Elastic Compression Stockings

Graduated elastic compression stockings (GCSs) reduce the cross-sectional area of the veins and increase the velocity of venous blood flow. The optimal pressure profile is around 18 to 23 mm Hg at the ankle, decreasing to 8 mm Hg in the popliteal fossa or upper thigh. Noticeably, this profile is different from that of therapeutic compression stockings, used for the management of established chronic venous insufficiency or to attempt to prevent postthrombotic syndrome after a DVT (30 to 40 mm Hg at the ankle).

In surgical patients, a systematic review from the Cochrane Collaboration analyzed seven randomized controlled trials.[16] The incidence of postoperative DVT was significantly reduced from 29% in the control group to 15% in the GCS group (P <.001). Similarly, a meta-analysis of 11 studies evaluated the efficacy of GCSs in moderate-risk patients undergoing mainly abdominal surgery, showing a significant 68% reduction in the incidence of DVT.[17]

Most studies with GCS have important limitations, including small samples, incomplete blinding, uncertain concealment of treatment allocation, and use of asymptomatic DVT as an outcome. However, evidence suggests that GCSs used alone are effective in moderate-risk general surgical patients; there is lack of data in high-risk patients, such as those undergoing cancer or major orthopedic surgery. In addition, there is no evidence indicating that GCSs reduce the incidence of PE in surgical patients. A more recent systematic review and network meta-analysis shows that GCSs with pharmacologic prophylaxis is more effective than knee-length GCSs without anticoagulants for the prevention of VTE in surgical patients.[18] Overall, patients prefer knee-length stockings.

In medical patients, two trials evaluated GCSs in immobilized patients after acute stroke. The first trial compared thigh-length GCSs with no stockings in about 2500 patients and found that GCSs were ineffective at preventing the combined outcome of asymptomatic, ultrasound-detected, and symptomatic proximal DVT (odds ratio [OR] 0.98).[19] This trial did not demonstrate that stockings were effective at preventing VTE in stroke patients (OR 0.98). However, the use of GCSs was associated with a fourfold increase in the risk of skin complications (5.1% vs. 1.3%), including breaks, ulcers, blisters, and necrosis. The second trial compared thigh-length with below-knee stockings in more than 3000 patients with acute stroke and found fewer cases of VTE with thigh-length stockings (OR 0.69).[20] In this study, skin complications were observed in 3.9% of patients in the thigh-length-stocking group.

Advantages of GCSs are that they are less expensive and easier to use than IPC devices. Moreover, GCSs may be combined with pharmacologic agents in patients at very high risk of VTE. On the contrary, limitations of GCSs include lack of standardization of pressure profiles and difficulty in their application in patients with unusual leg shapes or sizes. Stockings should not be used in patients with peripheral artery disease with lack of palpable foot pulses or an ankle-brachial index less than 0.8, in patients with severe leg edema secondary to congestive heart failure, or in patients with dermatitis.

Regarding compliance, one study identified that 65% of patients in acute-care units were actually wearing GCSs as prescribed.[21] However, complaints about discomfort were higher among patients using thigh-length stockings compared with those using knee-length stockings. The most common and concerning issue was that stockings were folded or rolled down, creating a garter-like or rubber-band effect. Williams and coworkers reported similar results in orthopedic patients, with 56% of thigh-length stockings producing constriction bands, compared with 13% of knee-length stockings.[22]

Intermittent Pneumatic Compression of the Legs

IPC of the lower limbs is the most extensively studied of the mechanical methods of thromboprophylaxis and is considered the most effective. Most IPC devices consist of inflatable boots or sleeves, wrapped around the legs and secured by Velcro, that are connected to an electrical compressor that intermittently insufflates air to a preselected pressure. The sleeves can be applied to the calf alone, calf and thigh, foot and calf, or whole limb.

Some types of IPC devices inflate the sleeves sequentially, first distally, then proximally to increase venous flow. Some hemodynamic studies have shown that uniform IPC devices might trap blood in the distal veins of the leg, whereas sequential compression enhances venous return. The frequency of

compression cycles can be fixed, or it can vary in more sophisticated systems, depending on the rate of venous refill and based on a plethysmograph incorporated in the garment.[23] Portable battery-operated IPC devices offer the potential advantage of continued use during ambulation and the early postoperative period. In contrast, conventional nonportable devices must be removed or disconnected when patients ambulate or are transferred to another unit.

Apart from improving venous hemodynamics, IPC stimulates local fibrinolytic activity and could reduce hypercoagulability by different mechanisms, including the release of endothelial tissue-type plasminogen activator (t-PA), prostacyclin, and tissue factor pathway inhibitor (TFPI).[24-26]

Regarding the prevention of VTE in surgical patients, most studies show that IPC is effective in preventing postoperative DVT in general and major orthopedic surgery, neurosurgery, gynecologic, and urologic procedures. In major orthopedic surgery, the ninth American College of Chest Physicians (ACCP) guideline considers that the available evidence is of low quality, based on the lack of blinding.[27] However, a relative risk reduction of 50% is observed for both DVT and PE, and the estimated absolute risk difference is 16 fewer symptomatic VTE events per 1000 patients receiving IPC compared with controls without compression after major orthopedic surgery. In nonorthopedic surgery, the ACCP estimates a reduction in symptomatic VTE from 60 to 30 per 1000 as a result of using IPC in high-risk patients.[3]

A systematic review of the literature that analyzed 19 trials including 2225 patients concluded that IPC as monotherapy reduced DVT from 23% in patients without IPC to 10% in those receiving IPC ($P < .0001$).[28] Similarly, a meta-analysis of 15 studies with 2270 patients who underwent different types of surgery showed that, in comparison with no prophylaxis, IPC reduced the risk of DVT by 60% ($P < .001$).[29] A very recent review has shown that in high-risk surgical patients undergoing hip or knee arthroplasty, there were no significant differences between IPC and pharmacologic prophylaxis in the incidence of postoperative DVT.[30] The same review suggests that the combination of IPC plus anticoagulants might provide better protection than pharmacotherapy alone.

As the risk of bleeding complications is not increased by mechanical methods, IPC is an attractive alternative to anticoagulants in patients at high risk of bleeding (trauma and pelvic surgery) or in whom minor bleeding may be serious, as in neurosurgery. A recent meta-analysis evaluated IPC in major orthopedic and neurosurgical patients, showing a significant reduction in the incidence of DVT from 5.3% in the control group to 2.26% in patients with IPC ($P = .004$) and low major bleeding events. However, there were no significant differences in the incidence of PE.[31]

IPC is particularly useful in patients with contraindications for the use of anticoagulants. In this regard, the ENDORSE study revealed that 9% of surgical patients considered at high VTE risk had some contraindication to receive pharmacologic prophylaxis and therefore would be good candidates for mechanical prophylaxis.[32] For these reasons, the ninth edition of the ACCP guidelines recommends using IPC in surgical patients at high risk for VTE and contraindications to receive anticoagulants and in combination with pharmacologic agents in those at very high thrombotic risk without such contraindications.[3]

In medical patients immobilized with acute stroke, the CLOTS 3 trial evaluated the efficacy of IPC for the prevention of VTE. A compression duplex ultrasound of both legs (femoral and proximal veins) was performed 7 to 10 days and 25 to 30 days after randomization.[33] The mean duration of IPC use was 12.5 days and mean adherence was 59%. The rate of proximal DVT detected by compression ultrasound was 8.7% and 5.8% in the control and IPC groups, respectively ($P = .003$). Likewise, there was a significant reduction in the incidence of symptomatic DVT (proximal or calf), from 6.3% to 4.6% ($P = .045$). Although the rate of skin breaks was higher in the IPC group (3.1%) than in the control group (1.4%) ($P = .002$), only 0.7% of patients had skin breaks attributed to IPC.

Apart from the aforementioned skin problems, IPC has occasionally caused peroneal nerve palsy. IPC should be avoided in patients with skin infections and severe edema of the legs secondary to congestive heart failure. The presence of an acute DVT contraindicates the use of IPC because theoretically the thrombus could be detached from the venous wall and embolize to the lungs, although direct evidence for this is lacking.

A significant limitation of IPC is related to lack compliance, inadequate fitting, and discomfort reported by patients. In a study conducted in several acute nursing units, only 29% of patients with prescribed sequential compression devices (SCD) had the devices applied to their legs. The most common reasons for noncompliance with IPC were that devices were not reapplied after bathing or ambulating or were removed because patients complained of discomfort.[21] Overall, patients preferred and were more compliant with knee-length sleeves. Similar results have been reported in urologic patients[34] and after cesarean delivery.[35] A small trial found better adherence with a portable calf IPC device (77%) than with a conventional SCD calf device (59%).[36]

Foot Compression Devices

Also known as foot pumps, these devices consist of inelastic slippers or boots with an air bladder in the area of the sole of the foot. This chamber is rapidly inflated to a pressure up to 200 mm Hg over 3 seconds every 20 seconds. This plantar compression increases venous outflow and reduces stasis in the legs. Several studies showed a reduction in venographically detected DVT in patients with the foot pump compared to controls without prophylaxis after major orthopedic surgery.[28] Nonetheless, several trials have documented better results with low-molecular-weight heparin (LMWH) than with foot compression devices after total knee replacement.[37,38] A trial assessed foot compression under a plaster cast in patients with Achilles' tendon repair.[39] At 2 and 6 weeks postoperatively, the incidence of DVT was assessed by color duplex scans. The study was prematurely interrupted after 24 patients were included because of the high rate of DVT in both the foot pump group (75%) and control group (50%).

In summary, there are limited and conflicting data demonstrating a beneficial effect of foot compression in surgical patients.

However, foot pumps could represent an alternative in trauma patients in whom anticoagulants are contraindicated and leg IPC cannot be used because of the presence of casts or external fixators.

Pharmacologic Methods of Prophylaxis

Aspirin

There is renewed interest in aspirin as a simplified strategy for postoperative VTE prevention. Even at small doses of less than 100 mg, aspirin irreversibly acetylates cyclooxygenase 1 which inhibits platelet generation of thromboxane A2, mediating the antithrombotic effect. In a multicenter randomized controlled trial powered for noninferiority, 778 patients were randomized after elective unilateral total hip arthroplasty. All patients received 10 days of LMWH prophylaxis and then either aspirin (81 mg) or LMWH (dalteparin 5000 U) for a total of 28 days. Aspirin was noninferior to the LMWH strategy; however, it should be noted that the study was stopped prematurely and the allowed clinically relevant difference was a rather large 2%, indicating that the results should be interpreted with caution. There was no significant benefit on major bleeding or clinically significant nonmajor bleeding rates between both strategies.[40] In a meta-analysis evaluating aspirin versus an anticoagulant in the orthopedic population with pooled information on 1408 participants, the rates of DVT did not differ statistically between aspirin and anticoagulants (relative risk [RR]: 1.15 [95% CI, 0.7 to 2.0]). The risk of bleeding, however, was lower in the aspirin group.[41] There is less agreement regarding validation of aspirin as a single preventive agent for the population at highest risk.

Warfarin

The onset of action of warfarin is slow, requiring at least 3 to 5 days; it is not typically practical for acute perioperative prophylaxis. In a study of 149 consecutive patients who underwent total joint arthroplasty, the VTE incidence using warfarin was 16% compared with a VTE incidence of 24% in the pneumatic compression group.[42] Patients with a subtherapeutic international normalized ratio (INR) have the highest postoperative rate of DVT.[43] In a study of 125 patients all receiving compression as well as heparin and warfarin, the rate of proximal DVT at 1 month after total hip replacement was 8.2%. The INR was less likely to be therapeutic among those who suffered an event (61% vs. 11%, $P < .001$) compared with those with a therapeutic INR.

Heparins

Unfractionated heparin (UFH) is a sulfated polysaccharide with a molecular weight of 15,000 Da; anticoagulant effects include inactivation of thrombin and factor Xa and reducing thrombin-induced platelet activation. In a prospective trial involving 84 patients undergoing total hip arthroplasty, the frequency of DVT in those receiving 5000 U/8 hours of UFH was 32%, compared with 69% in the control group using I-125 fibrinogen scanning confirmed with venography.[44] The small size of these trials has limited the certainty with which we can estimate the benefit of UFH on the prevention of fatal PE. The largest trial evaluating the use of UFH prophylaxis was a multicenter randomized trial involving 4121 postoperative patients. Sixteen patients in the control group and 2 in the heparin group had autopsy-confirmed fatal PE ($P < .01$).[45] A large meta-analysis involving 8874 patients evaluating thrombosis prophylaxis using UFH was associated with an odds reduction of 68% (95% CI, 65 to 71%) regarding the risk of DVT.[2] The odds reduction for PE was 47% ± 20 (20 of 2230 UFH versus 38 of 2250 controls). Fatal PE in this study using UFH included 243 deaths among 7307 patients versus 287 deaths among 6777 controls; $P < .02$). The absolute bleeding risk was 2% higher in the UFH group.

LMWH is derived from UFH using enzymatic or chemical depolymerization to create fragments of ~5000 Da. The mechanism of action includes inhibition of factor Xa and to a lesser extent thrombin. The reduced protein binding capacity results in more predictable pharmacodynamic behavior obviating the need for routine testing. LMWH is excreted by the kidneys and requires adjustment for those with renal insufficiency. It is not recommended for patients with renal failure. Among postoperative patients with high VTE risk, LMWH is at least as effective as UFH and has become a preferred prevention strategy.[46] In a meta-analysis assessing 24 orthopedic and 34 general surgery studies comparing LMWH to UFH prophylaxis, the relative risk of DVT was lower for LMWH (RR 0.7; 95% CI, 0.6 to 0.9). The effect was similar between general (RR 0.8; 95% CI, 0.6 to 0.9) and orthopedic surgery (RR 0.7; 95% CI, 0.5 to 0.9).[47] For PE, LMWH was superior for prevention (RR 0.4; 95% CI, 0.3 to 0.7). There was no statistically significant increase in major bleeding.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide administered via subcutaneous injection and has a half-life between 17 and 21 hours, is renally excreted, and is a valid alternative to LMWH. The mechanism of action is inhibition of factor Xa. Several studies support its efficacy.

In a double-blind study that included 1711 high-risk orthopedic surgery patients, there was a significant risk reduction by day 11 (RR = 56; 95% CI, 39% to 70%) among patients who received fondaparinux at 2.5 mg compared with enoxaparin 40 mg once daily. There were no differences in bleeding outcomes.[48] Among patients with hip fracture in the PENTHIFRA study, 656 patients undergoing hip fracture were randomized to placebo after 8 days of receiving therapy. The patients on fondaparinux had a reduced incidence of venographically proven VTE, with 1.4% versus 35% on placebo (RR 96% 95% CI, 87% to 99.7%). Moreover, the incidence of symptomatic events was also reduced from 2.7% to 0.3%. There was no significant increase in the rate of major bleeding, validating the use of extended prevention strategies in this high-risk population.

In a meta-analysis of four randomized trials among 7344 patients undergoing orthopedic procedures, the efficacy of a subcutaneous 2.5 mg, once-daily regimen of fondaparinux starting 6 hours after surgery and continued for 11 days was superior to LMWH (RR = 55.2; 95% CI, 45.8 to 63.1%;

$P < .001$). The incidence of major bleeding at 11 days was higher in the fondaparinux arm (2.7% vs. 1.7%; $P < .01$).[49]

Direct Oral Anticoagulants

The currently approved direct oral anticoagulants (DOACs) include dabigatran, a direct thrombin inhibitor, and the factor X inhibitors including edoxaban, apixaban, and rivaroxaban. The data do not allow direct comparisons among these agents, but there is robust information individually when these agents are compared with LMWH. Dabigatran used at 220 mg daily for total knee or hip replacement was similar to LMWH (RR 0.95; 95% CI, 0.8 to 1.1) in a pooled analysis of the prevention trials without significant differences in bleeding. Rivaroxaban ($n = 4657$), when used at a dose of 10 mg orally, compared with LMWH ($n = 4692$) in a pooled analysis comparison of 9581 patients was more effective for the composite outcome of symptomatic VTE and all-cause mortality (OR 0.4; 95% CI, 0.2 to 0.8), with a similar bleeding risk of 0.2% per arm.[50] Similar meta-analytic data exist for apixaban. For the outcome of postoperative VTE among orthopedic surgery patients, apixaban ($n = 6145$) compared with enoxaparin ($n = 5976$) was not superior (RR 0.8; 95% CI, 0.4 to 1.6). There was, however, a small benefit in the rate of clinically relevant bleeding (RR 0.8; 95% CI, 0.69 to 0.98).[51] Edoxaban 30 mg once daily ($n = 307$) in a phase 3 randomized trial was superior to enoxaparin 20 mg twice daily ($n = 303$), with a 2.4% versus 6.9% VTE rate and a statistically similar major bleeding rate of 0.7% for edoxaban versus 2% for enoxaparin.[52] For total knee arthroplasty, edoxaban 30 mg once daily started 6 to 24 hours after surgery, compared with enoxaparin 20 mg twice daily was also superior for efficacy (22/299 patients on edoxaban versus 41/295 on enoxaparin) with a relative risk reduction of 46.8%. The cumulative incidence of major bleeding or clinically relevant nonmajor bleeding was numerically higher for edoxaban 6.2% versus 3.7% but not statistically different ($P = .13$).[53]

There are good-quality data for VTE prophylaxis with DOACs in orthopedic patients. Using pooled data accumulating 15,977 participants, extended-duration DOAC compared with heparin was not significantly better (OR 0.7; 95% CI, 0.3 to 1.7). The rate of major bleeding (OR 1.1; 95% CI, 0.8 to 1.5) and clinically relevant nonmajor bleeding (OR 1.1; 95% CI, 0.9 to 0.3) was also similar.[54]

In summary, there are several distinct agents that may be used for VTE prevention postoperatively. A direct comparison among all of them is not feasible with the current literature outside a network meta-analysis. However, such data do exist, at least for artificial joint replacement. In a pooled population of over 30,000 patients, warfarin was more effective than LMWH and DOACs.[55]

Combination of Mechanical and Pharmacologic Methods

The combination of mechanical and pharmacologic methods for VTE prevention will theoretically improve the efficacy of these methods used separately, because this approach will address two of the components of the Virchow triad: stasis and hypercoagulability. After all, they should be considered as complementary rather than being competitive. In a systematic review of the literature from the Cochrane Collaboration, the combination of heparin and GCSs was better than heparin alone in the prevention of VTE in patients who underwent colorectal surgery.[56] In a study of 2551 cardiac surgery patients randomized to receive either heparin alone or in combination with IPC, the incidence of PE was 62% lower in patients who received combination therapy (4% vs. 1.5%).[57]

Further support for the benefit of combined mechanical and pharmacologic prophylaxis for the prevention of postoperative VTE came from the APOLLO study. In this double-blind, placebo-controlled trial, patients who underwent major abdominal surgery received IPC with or without fondaparinux. The incidence of VTE was reduced from 5.3% (IPC alone) to 1.7% (IPC plus fondaparinux).[58]

A recent meta-analysis has compared combined compression and anticoagulants with either modality alone in surgical patients.[59] This study shows that most compression studies were of low quality because of methodologic weakness and publication bias. On the contrary, studies using anticoagulants were considered of moderate quality because of more frequent blinding of physicians and outcome assessors. The addition of compression to anticoagulants decreased the risk of DVT by 49% ($P < .001$) (47% reduction with GCS and 57% with IPC) compared with anticoagulants alone. However, these differences were not significant regarding proximal DVT or symptomatic DVT. The addition of anticoagulants to compression reduced the risk of all DVT by 44% ($P < .001$) and of proximal DVT by 57% ($P < .001$) without resulting in significant reduction of symptomatic DVT or PE. The risk of any bleeding increased by 74% with the addition of anticoagulation to compression ($P < .001$). Similarly, there was a nonsignificant 73% increase in major bleeding with the addition of anticoagulants ($P = .08$).

In conclusion, adding anticoagulation to compression significantly reduces the risk of DVT after major surgery, a benefit counterbalanced by an increased risk of bleeding. Although adding compression to anticoagulation was also shown to reduce DVT risk, this finding is undermined by strong evidence of publication bias.

SPECIFIC SURGICAL GROUPS

Cancer

Among nearly 7000 patients having major oncologic operations, the safety and efficacy of adding preoperative chemoprophylaxis was evaluated among patients with colorectal, gastric, mixed tumor, gynecologic, thoracic, or urologic surgical procedures. The rates of DVT were (1.3% vs. 0.2%; $P < .001$), and PE (1.0% vs. 0.4%; $P < .02$) were significantly lower in the postintervention group, with no significant bleeding increase. The duration of the prophylactic strategy in this high-risk group has also been studied. Among 225 patients with colorectal cancer who underwent laparoscopic surgery, a complete compression ultrasound was done at day 28. Compared with 1 week of prevention, the extended 4 weeks of prevention group had

a lower rate of VTE at 3 months (9.7% vs. 0.9% RR 91% 95% CI 30% to 99%).[60]

Vascular Surgery

Thirty-day postoperative outcomes were recorded in over 4000 patients having percutaneous endovascular aneurysm repair (PEVAR) versus open endovascular aneurysm repair (OEVAR). The incidence of VTE was twice as high (1%) in OEVAR compared to PEVAR (0.5%) procedures. Unfortunately the National Surgical Quality Improvement Program (NSQIP) database does not record details regarding thrombosis prophylaxis.[61] As a general observation, endovascular interventions will have lower rates of VTE compared with open surgery equivalents.

Cardiac Surgery

The results regarding the incidence of VTE in cardiac surgery patients are mixed. In one study, 3% of patients after cardiac surgical procedures developed silent VTE events. In a large cohort of 92,699 patients undergoing coronary artery bypass grafting, the overall incidence of VTE with mechanical versus pharmacologic prophylaxis or combined therapy was not statistically different. It was also noted that there were no differences in major bleeding whether or not mechanical or pharmacologic prophylaxis was used. It is recommended that individual risk assessment be done for these patients and, based on the level of risk, prophylaxis be provided similar to what was done in other groups.[62] This population has a high incidence of seroconversion to heparin antibodies, making HIT a consideration. Another factor that increases the incidence of VTE is congestive heart failure.[63] Surgeons should pursue aggressive thromboprophylaxis in these patients.

Bariatric Surgery

The bariatric surgical population is at very high risk for developing VTE due to the presence of obesity. It has been estimated that these patients are 2 to 3 times more likely to have a VTE and twice as likely to suffer from delayed thrombotic events. The postthrombotic syndrome is another problem frequently seen in these patients. High intra-abdominal and venous pressure occurs secondary to extensive truncal obesity. Pharmacokinetic studies have demonstrated that standard fixed doses of prophylaxis are suboptimal in these patients, so investigators either adopt a fixed high-dose LMWH strategy (enoxaparin 40 mg twice daily), or adjusted dose LMWH (0.5 mg/kg per day). In one recent study using this strategy, the incidence of VTE was cut in half, from 1.48% to 0.77%, without an increased risk of bleeding.[64]

A large database of 97,218 bariatric surgical procedures was queried for concurrent prophylactic placement of an inferior vena cava filter at the time of surgery. The authors concluded that this practice was associated with increased health resource utilization and a higher mortality in patients undergoing bariatric surgical operations.[65] They were unable to establish an outcomes benefit for the placement of these filters. In addition, in considering oral anticoagulants, one must be aware that gastric bypass operations may interfere with the gastrointestinal absorption of the oral drugs.

Neurosurgery

Patients undergoing neurosurgical procedures are at high risk for developing VTE, since they tend to have additional risk factors including benign and malignant tumors, immobility, prolonged hospitalizations, and prolonged courses of corticosteroids. A NSQIP database containing 94,620 patients identified 0.60% of patients with DVT and a 1.12% incidence of PE. The authors concluded that the relative risk of hemorrhage versus thrombosis must be evaluated in each individual. Most studies suggested that prophylaxis with anticoagulation is safe within 48 to 72 hours following most intracranial surgical procedures.[66] In the Computerized Registry of Patients with Venous Thromboembolism (RIETE) database, containing 40,663 patients with VTE, 0.96% had VTE in less than 60 days after neurosurgery.[67] Subtherapeutic doses of anticoagulation were given in one-third of these patients and 2.6% of them died from a fatal PE. No bleeding deaths were seen in these patients and the authors conclude that neurosurgical patients developing VTE were more likely to die from PE than from bleeding in the first week despite anticoagulation.

Trauma

Critically ill trauma patients with severe injuries are at high risk for VTE and bleeding simultaneously. Mechanical prophylaxis when possible and starting anticoagulation as soon as the bleeding risk decreases are important strategies. Studies have shown that mortality due to PE in trauma patients with severe injuries is low relative to other causes of mortality. Despite these data, the placement of a temporary vena cava filter is often advocated. One important study evaluated the cost-effectiveness and outcomes of three VTE prophylaxis strategies from a cohort of trauma patients with severe injuries (ISC >12) admitted to the intensive care unit (ICU) of a regional trauma center.[68] The incidence of DVT at 12 weeks was 14.9% in patients treated with IPC, 15.0% for those followed with serial ultrasound screening, and 25.7% in those receiving vena cava filters. Expected mortality and quality-adjusted life years were nearly identical for all three management strategies. Costs were slightly lower using the ultrasound screening protocol compared with the other strategies. It would appear from these data that a combination of IPC plus serial screening would be the best approach for those patients who cannot receive appropriate anticoagulant prophylaxis.

EVIDENCE-BASED GUIDELINES VERSUS REAL CLINICAL PRACTICE

Many patients are encountered who do not fit the guidelines, since every clinical scenario cannot be tested in clinical trials. Clinically based registry data that identify what was actually

done in real-world practice are valuable for making individual decisions regarding thrombosis prophylaxis not covered by the guidelines. The RIETE registry contains 63,698 patients from 10 countries, including one site in the United States. A RIETE manuscript published in 2008 evaluated the issue of when patients developed VTE relative to their hospitalization. The study included 1602 postoperative patients, and most of the thrombotic events (77%) developed following discharge, including 55% that appeared after prophylaxis was stopped.[69] The average time elapsed from surgery to VTE was 22 ± 16 days. The incidence of fatal PE was 1.3% at 3 months. Although guidelines lack advice for many patients regarding postdischarge prophylaxis, these registry data can be used to guide decisions for patients at very high risk.

The Million Woman Study is another data source that can help to guide decisions regarding prophylaxis in situations where guideline data are unavailable. Participants included 947,454 middle-aged women followed for 6 years. Operative procedures were necessary in 239,614 patients, including 5419 hospital admissions that resulted in 270 VTE deaths.[70] The authors concluded that the risk of VTE after surgery is substantially increased in the first 12 postoperative weeks and varies by type of surgery. Postoperatively, women were 70 times more likely to be admitted with VTE in the subsequent 6 weeks (RR 69.1; 95% CI, 63.1 to 75.6).

SUMMARY OF RECOMMENDATIONS FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS IN SURGICAL PATIENTS

The basis for deciding about thrombosis prophylaxis in surgical patients is best done using an individual risk assessment to determine the likelihood of clinically relevant VTE. Important new data have emerged since 2012 identifying a very high-risk group of individuals. Patients with a Caprini score of greater than 8 were found to have clinically relevant risk of developing VTE ranging from 6% to 18%. These findings provide data suggesting that patients in this risk category should have their anticoagulant prophylaxis continued following discharge. There are insufficient data to indicate how long this prophylaxis should be continued, but the experience of the Boston University group would suggest at least 30 days of prophylaxis to be appropriate (Fig. 146.2).

When possible, we advocate that in patients with a Caprini risk of 1 to 2, early ambulation is an adequate preventive measure. Among those with a score of 3 to 4, pneumatic compression before, during, and after surgery should be added. In addition, a physician declining to use anticoagulant prophylaxis in these low-risk patients should document the rationale for such a decision. Patients with a score of 5 or more are at high risk for developing VTE; for them we recommend anticoagulant prophylaxis and IPC in addition to ambulation. The anticoagulant prophylaxis should be continued for the period of time shown in clinical trials to be efficacious, usually 7 to 10 days. Finally, among patients with a risk score greater than 8, we recommend that prophylaxis be extended for 30 days after discharge.

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CHAPTER 147

Acute Lower Extremity Deep Venous Thrombosis: Presentation, Diagnosis, and Medical Treatment

FEDOR LURIE, DAVID PAOLINI, and JOHN FISH

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Acute thrombosis of the lower extremity deep veins remains one of the most significant public health problems. It affects more than 350,000 people in the United States annually and is responsible for between 100,000 and 300,000 deaths.[1,2] Its economic impact is substantial; in the United States alone, the annual cost of deep venous thrombosis (DVT) was estimated to be 7.5 to 39 billion US dollars in 2010.[3]

New therapeutics extend the ability to safely treat acute thrombotic episodes, prevent recurrent thrombosis, and prevent DVT in high-risk patients. The result is a continuous shift toward early treatment of the majority of the patients based on the clinical information, reserving more expensive diagnostic tests for patients who require invasive treatment.[4]

CLINICAL ASSESSMENT

The clinical manifestations of acute DVT vary from an absence of symptoms and signs to the dramatic presentation of phlegmasia cerulea dolens and venous gangrene. Such broad variation is a result of multiple pathologic processes, with different timing and severity occurring during an acute thrombotic episode. Anatomic distribution of thrombosed venous segments, degree of occlusion in each affected vein, time of thrombus development, severity of inflammation, functional status of the lymphatic system, preexisting venous and lymphatic insufficiency, and many other factors determine the presentation at the time of clinical evaluation. Symptoms tend to be more severe in proximal

DVT and when more venous segments are involved, and symptoms tend to be less severe in calf vein thrombosis and in older and postoperative patients. The most common symptoms and signs of DVT are dull ache or pain in the leg, tenderness, swelling, erythema, cyanosis, and fever. Edema, cyanosis, and pain are features of phlegmasia cerulea dolens. Venous gangrene is a rare condition that occurs usually in patients with cancer, can occur with heparin-induced thrombocytopenia with thrombosis, and is generally associated with warfarin-mediated protein C depletion.[5,6]

The diagnostic value of signs and symptoms of DVT and their combinations have been extensively studied.[7-11] The most common symptom, calf pain, has been reported to have sensitivity between 75% and 91% and specificity between 3% and 87%. The reported sensitivity of calf swelling for DVT diagnosis ranges from 35% to 97%, and its reported specificity ranges from 8% to 88%. In part, such variability is due to the high prevalence of the same signs and symptoms in patients without DVT.[11] In patients at high risk for DVT, the diagnostic value of clinical signs and symptoms is substantially higher. For example, in cancer patients, the negative predictive value of absence of swelling is as high as 97% for outpatients and 92% for inpatients.[12] A valid alternative diagnosis, such as cellulitis or a musculoskeletal disorder that explains the presence of signs and symptoms, may also improve the negative predictive value of the clinical examination.[13]

High variability and lack of specificity limit the role of clinical examination in patients with suspected DVT. A meta-analysis of studies evaluating individual clinical features of DVT showed that only a past history of DVT and malignant disease are useful for diagnosis, and no individual clinical feature is useful for ruling out DVT.[14] The delay of clinical manifestations makes the clinical diagnosis of DVT even more challenging. On average, patients are seen by a medical professional 4.4 days after onset of symptoms, and in more than 22% of patients, the onset of symptoms occurred more than 10 days before presentation.[15,16] For these reasons, withholding treatment on the basis of clinical evaluation in primary care settings leads to inadequate management of more than 10% of patients with DVT.[17]

DIAGNOSTIC TESTS

D-Dimer

The concentration of D-dimer (DD) in plasma has become a widely used marker for the diagnosis of DVT. DD is a product of fibrin proteolysis by plasmin; therefore, its elevated levels signify that fibrinolysis of complexed fibrin is occurring. This commonly occurs as part of the response to injury in patients undergoing surgical procedures or trauma, part of the normal physiologic changes during pregnancy, and part of the pathophysiologic process in patients with cancer or thrombotic disorders. The degree of DD elevation in patients with DVT varies with the size and extent of the thrombus, the time from its onset, and the use of anticoagulation. Currently used assays differ in the specificity of antibody to various binding sites on the DD molecule, in units of measurements, and in reference values. In addition, their sensitivity for DVT diagnosis ranges from 60% to 96%.[18,19] Assays also vary with respect to speed of testing, cost, and labor involved. The most sensitive of the assays, conventional enzyme-linked immunosorbent assay, is also the most laborious and slow.[18,20-22] Rapid point-of-care assays are probably the most practical, as the results are obtained within minutes and their sensitivity is comparable to that of the enzyme-linked immunosorbent assay.[23,24]

Low specificity limits the use of DD in patients with suspected DVT. However, concentration of DD below the cutoff value indicates a very low probability of DVT, and it does not exclude it with sufficient accuracy, especially in cases of distal thrombi, use of anticoagulation, or long duration between the onset of thrombosis and testing.[19,22,25] Similar to clinical evaluation, the use of DD as a single diagnostic tool may result in inadequate management of more than 15% of patients with suspected DVT.[19] DD is best integrated with a clinical risk assessment of the patient, as discussed later in this chapter.

Duplex Ultrasonography

Duplex ultrasonography remains the dominant diagnostic test of choice for the detection of DVT. It has almost completely replaced venography because of its accuracy, lack of radiation, portability, noninvasiveness, and relative cost-effectiveness. In addition, ultrasound can distinguish among nonvascular pathologic processes such as inguinal adenopathy, Baker's cyst, abscess, and hematoma.

The technique of venous duplex scanning is discussed in Chapter 23. Duplex ultrasound diagnostic criteria for DVT include increased intraluminal echogenicity, increased venous diameter, inability of the vein to collapse under moderate pressure from the transducer, absence of spontaneous blood flow, and absence of flow augmentation with distal compression (Figs. 147.1–147.5). Among these factors, inability to compress the vein is the most widely used objective criterion for the diagnosis of DVT.[26] Even as a stand-alone criterion, noncompressibility has excellent sensitivity and specificity for the detection of proximal DVT, with sensitivity and specificity of 97% and 94%, respectively, for proximal DVT.[27]

A significant limitation of compression ultrasound is its lack of accuracy in the evaluation of calf veins, fresh thrombi, and small segmental thrombi. Compression ultrasound has limited use in obese patients[28] and when significant edema, especially in the deep tissues, is present.[29] Addition of evaluation of venous flow with color Doppler and spectral Doppler can improve the accuracy of compression ultrasonography.

Because the risk of proximal extension of the thrombus exists in patients with DVT even when they receive appropriate anticoagulation,[30] repeated ultrasonography has been advocated.[31] Additional ultrasound 7 to 14 days after an initial examination can reduce the rate of thromboembolic complications to 1% during a 3-month follow-up period[32] compared to 2.5% with no additional testing.[33,34] The diagnostic gain from repeated ultrasound is estimated to be 1.34% of positive studies, with a positive predictive value of 89%,[14] which makes this option cost-ineffective.[35] Limiting indications for repeated ultrasonography to

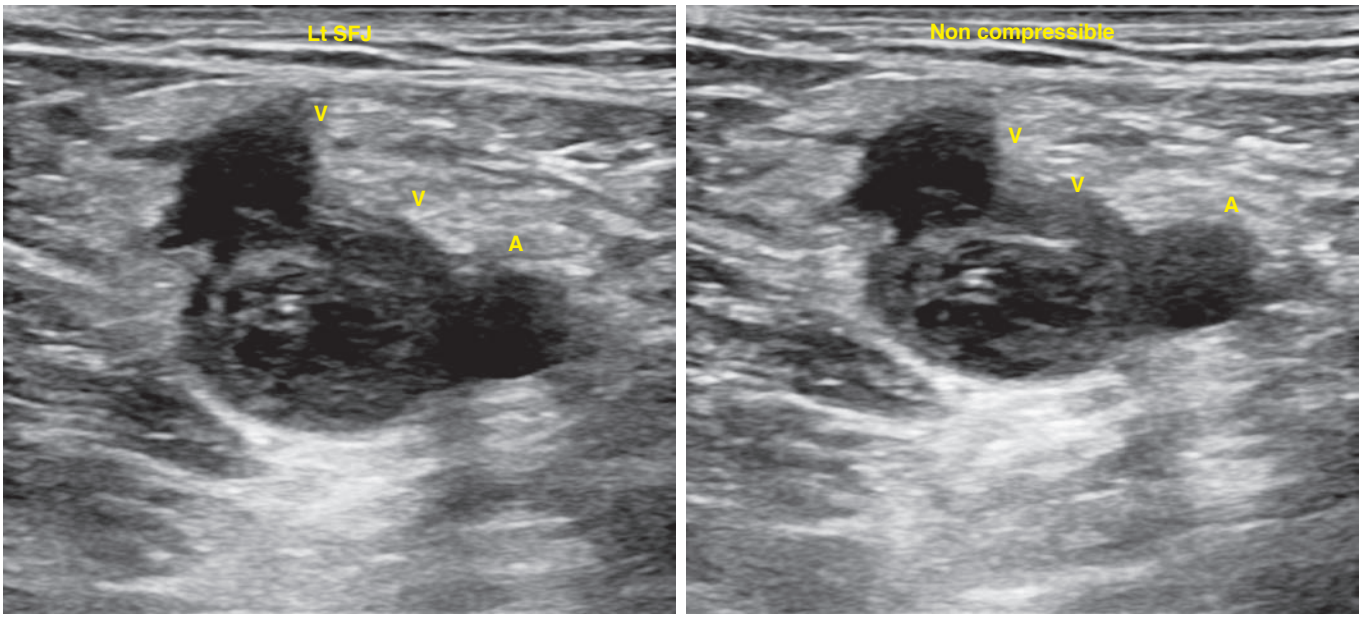

Figure 147.1 Totally occluding, acute common femoral vein (CFV) thrombosis. Size of the CFV is increased, intraluminal echogenicity is increased, and the vein does not collapse under pressure from the transducer. *A*, Artery; *V*, vein; *SFJ*, sapheno-femoral junction.

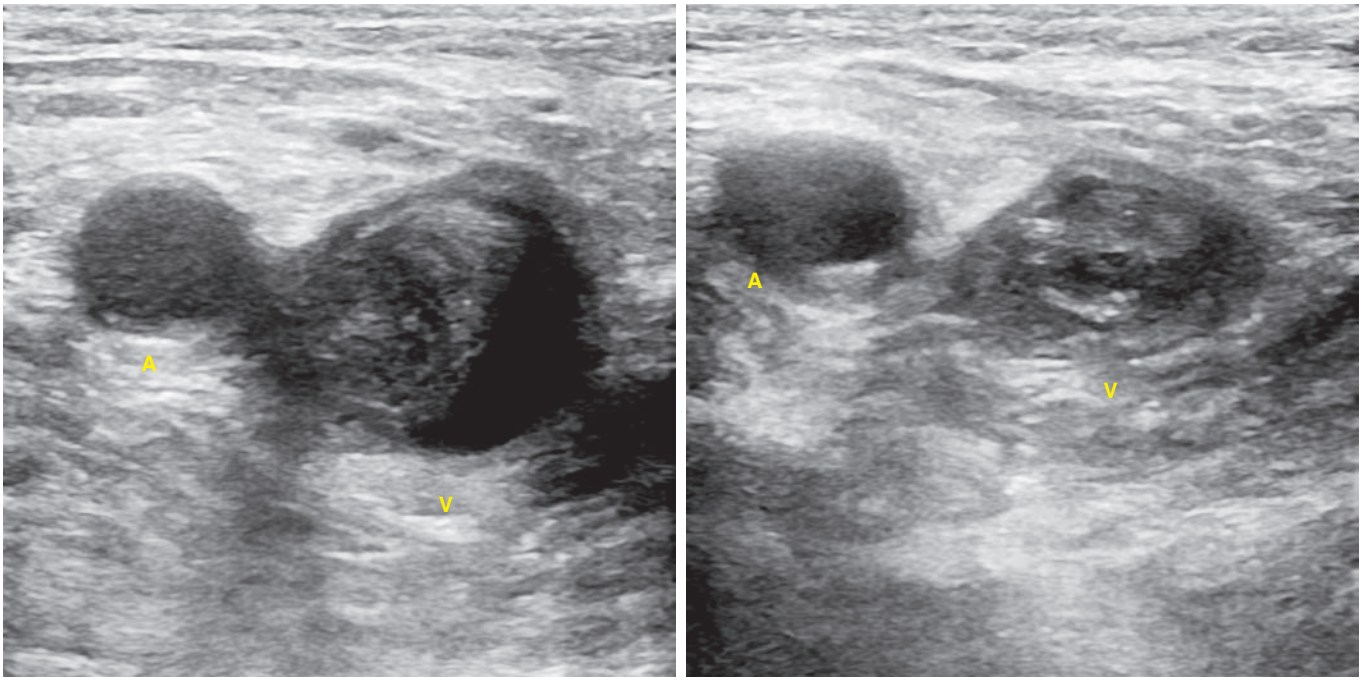

Figure 147.2 Age-undetermined thrombus in the femoral vein. The size of the vein is normal, intraluminal echogenicity is increased and uneven suggesting chronicity. The lumen is partially occluded suggesting either recanalization, or nonocclusive thrombosis. The vein partially collapses under pressure from transducer. *A,* Artery; *V,* vein.

patients with positive DD assays and normal initial ultrasound findings increases its clinical utility.[13,32,36]

Pitfalls in venous duplex imaging include misidentification of veins; missing of duplicate venous systems; systemic illness or hypovolemia resulting in decreased venous distention; suboptimal imaging in obese or edematous patients; and areas not amenable to compression such as the iliac veins, the femoral vein at the adductor canal, and the subclavian veins. As with most ultrasound-based imaging studies, the quality of the examination depends on the skill of the technologist performing the study.

Recent systematic reviews and meta-analyses challenge the common perception that duplex ultrasound is sufficiently accurate in all patients. In contrast to 94.2% sensitivity of

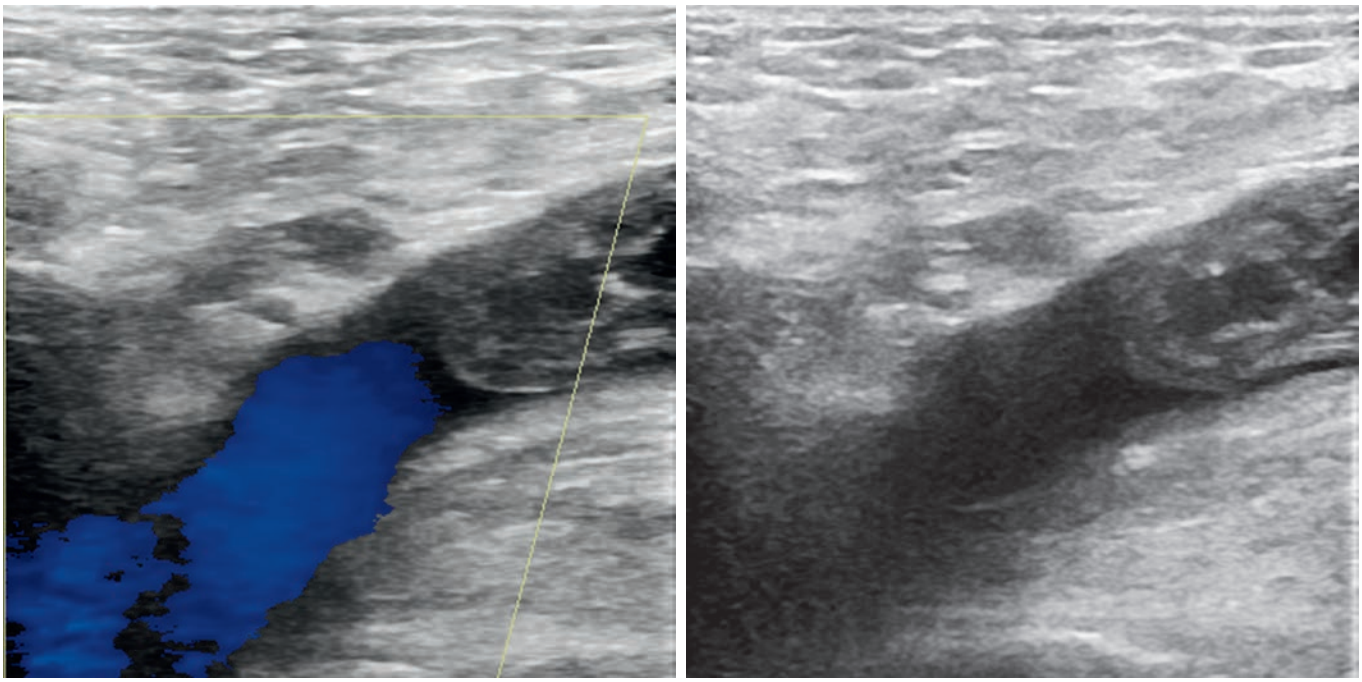

Figure 147.3 Thrombus in the Common Femoral Vein Extending Into the External Iliac Vein. The most proximal part of the thrombus appears free-floating. The flow from tributaries is present proximal to the thrombus.

compression ultrasound for detection of proximal DVT, the sensitivity is only 63.5% for distal DVT. This result of overall sensitivity was 89.7% and specificity 93.8%.[14] The diagnostic properties of duplex ultrasound are substantially different in the subpopulations of symptomatic outpatients. In patients with a high Wells score, sensitivity is 91% and specificity approaches 100%, whereas sensitivity and specificity are 61% and 99%, respectively, in patients with an intermediate Wells score (see later), and 67% and 98% in patients with a low Wells score.[37] In asymptomatic patients, sensitivities of duplex ultrasound for detection of proximal and distal DVT are 66.7% and 39.0%, respectively, with an overall specificity of 96.5%.[14] These data indicate that the use of duplex ultrasound in low-risk patients may result in a significant number of false positives. In symptomatic patients, duplex ultrasound can reliably rule out proximal but not distal DVT; and in asymptomatic patients, ruling out DVT based on sonographic findings is highly questionable.

Although clinical relevance of calf vein DVT is still debated, significant limitations of existing data have become apparent recently. Studies consistently showed that about half of all calf vein DVTs are calf muscle vein thromboses (CMVT). The overall pulmonary embolism (PE) incidence in patients with calf DVT is in the range of 10% to 15%.[38] However, in patients with CMVT, the incidence of PE is as high as 50%.[39]

CMVTs are also more symptomatic and more likely to propagate proximally compared to tibial and peroneal DVTs.[40] However, reliability of ultrasound detection of CMVT is low, which can be largely explained by a lack of training and irregularity of reporting.[29] The lack of studies that separate CMVT from tibial and peroneal DVT is a substantial obstacle in our understanding of clinical importance of distal thrombosis, which led to the absence of appropriate management guidelines. The existing limited literature suggests that the duplex ultrasound reports should be more specific in identification of which calf veins are affected by thrombosis, and patients with CMVT should be treated and followed more aggressively.

Venography

Contrast venography for the sole purpose of diagnosing DVT is largely of historical interest; however, it is invaluable when it is used as part of the treatment plan (see Chapter 26). Reasons for its dramatic decline are obvious in light of the utility, accuracy, and safety of duplex ultrasonography. It is expensive and inconvenient compared with other diagnostic modalities and potentially causes patient discomfort.[41,42] Potential complications of the examination include nephrotoxicity, allergy, phlebitis, and the need for intravenous access. Venography may be helpful in cases when duplex ultrasound suggests the presence of proximal obstruction by demonstrating a loss of the flow phasicity but fails to visualize the thrombus in iliac veins.

There are two basic techniques for the performance of contrast venography. The Rabinov-Paulin technique uses spot film, and the long-leg technique uses cine film. Although both techniques are useful, Lensing et al.[43] demonstrated that 20% of examinations were inadequately interpreted by the Rabinov-Paulin technique versus only 2% by the long-leg technique. In addition, they went on to show a 21% interobserver disagreement with the Rabinov-Paulin technique, whereas the long-leg technique had only a 4% disagreement.

Despite the disadvantages of contrast venography, it continues to be perceived as the "gold standard" for the diagnosis of acute DVT. Comparisons of contrast venography with duplex ultrasound using DD for the confirmation of thrombus with both

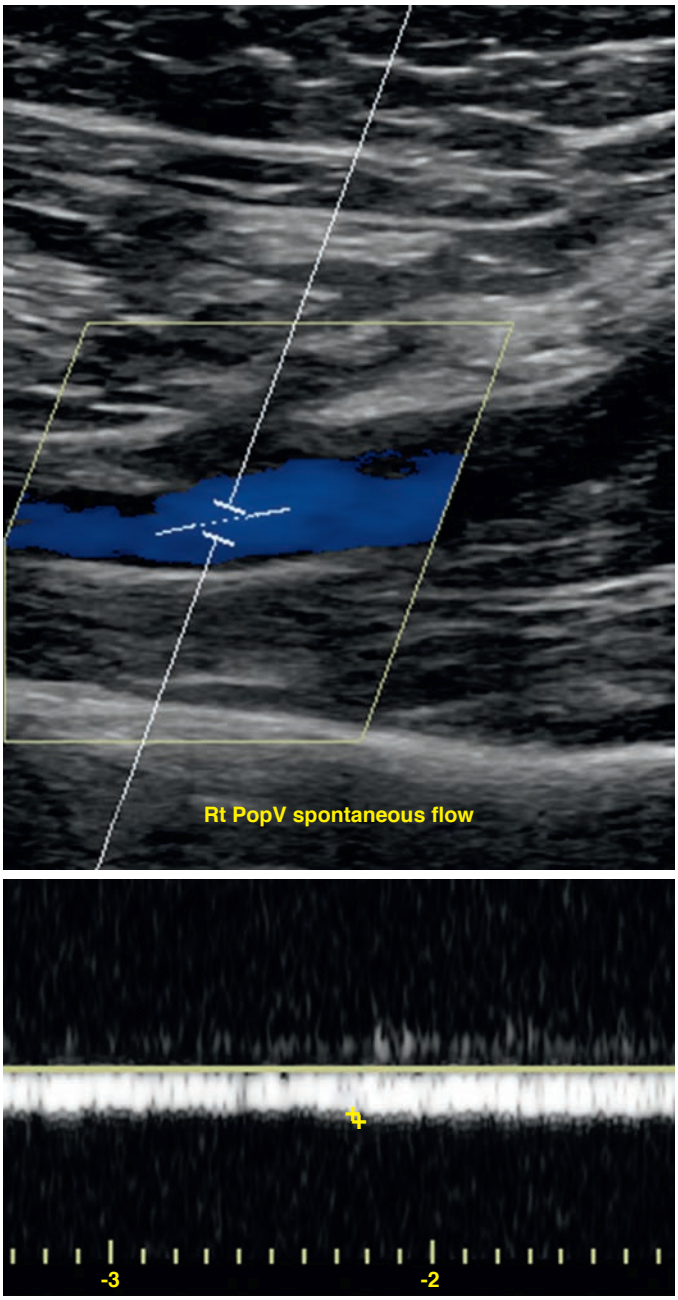

Figure 147.4 Triplex ultrasound image of popliteal vein in extremity with acute femoral-popliteal venous thrombosis during spontaneous flow. Color Doppler indicates the presence of the flow in the popliteal vein. The spectral Doppler demonstrates low-velocity continuous flow with lost phasicity (respiratory and cardiac) indicating more proximal obstruction.

diagnostic modalities confirmed a sensitivity and specificity of 96% and 91%, respectively, for contrast venography and 78% and 97%, respectively, for duplex ultrasonography.[44] Moreover, in the same study, calf vein acute DVT was diagnosed in only 74% of patients already positively diagnosed with contrast venography. Similarly, Ozbudak et al.[45] showed that contrast venography diagnosed 19% of acute DVT that duplex ultrasound failed to identify. de Valois et al.[46] demonstrated that duplex ultrasonography obtained 92% sensitivity and 90% specificity compared with contrast venography, concluding that contrast

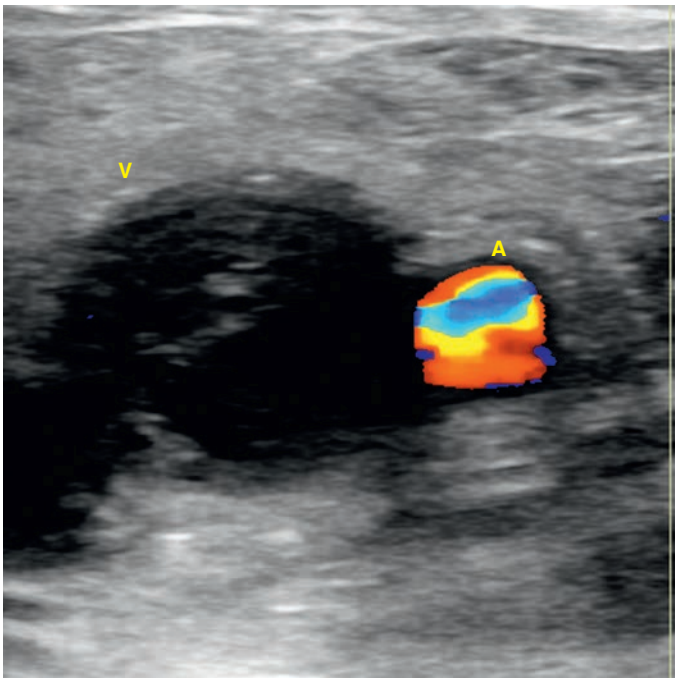

Figure 147.5 Duplex ultrasound image of acute thrombosis of the common femoral vein (CFV). Size of the CFV is increased, intraluminal echogenicity is increased, and the color Doppler demonstrates the absence of venous flow. *A*, Artery; *V*, vein.

venography should be used as the "golden backup" when the diagnosis of acute DVT remains in question after a venous duplex examination.

Computed Tomographic Venography

Computed tomographic arteriography is an excellent technique for the diagnosis of PE. However, its venous counterpart, computed tomographic venography (CTV) has yet to gain traction for the diagnosis of acute DVT in the lower or upper extremities. The diagnostic capabilities of CTV are remarkable in the thigh and pelvis compared with duplex ultrasound; it has a sensitivity of 98% and specificity of 100% in the thigh and sensitivity and specificity of 94% and 100%, respectively, in the pelvis. Overall positive predictive and negative predictive values are 92% and 100%, respectively.[47-50] Thomas et al.[51] conducted a meta-analysis of 13 studies evaluating CTV for the diagnosis of DVT in patients with suspected DVT and PE. The sensitivity ranged from 71% to 100% and the specificity ranged from 93% to 100%. The pooled estimate of sensitivity was 95.5%, whereas the pooled estimate of specificity was 95.2%. They concluded that CTV has a sensitivity and specificity similar to those of ultrasonography for the diagnosis of acute DVT but must be viewed with caution, as duplex ultrasound does not have perfect sensitivity or specificity, which may lead to overestimation of the accuracy of CTV. In addition, when CTV is used in conjunction for evaluation of PE, it adds only 3 to 5 minutes to the examination, making it an attractive option as the sole diagnostic modality for acute lower extremity DVT.[52]

Not all authors have shown as promising results for diagnosis of acute DVT with CTV. Peterson et al.[53] demonstrated that although the sensitivity is high at 93%, producing a 97% negative predictive value, the ability of CTV to accurately diagnose DVT has a specificity of 71%, giving a positive predictive value of only 53%. Others have shown a 50% false-positive rate for CTV for pelvic DVT; at the same time, magnetic resonance venography (MRV) had a 100% rate of false positivity.[54]

Magnetic Resonance Venography

MRV has become an attractive option for vascular imaging. The technology is based on the detection of moving versus stationary tissues. MRV is less expensive than contrast venography but more expensive and less operator dependent than duplex ultrasound. In addition, MRV overcomes many of the anatomic limitations encountered with duplex ultrasound when the inferior vena cava (IVC) and iliac vessels are imaged.

MRV can be used with or without contrast enhancement. Non–contrast-enhanced techniques include time-of-flight imaging and the phase-contrast technique relying on flow-related enhancement.[55] Contrast-enhanced MRV can provide the user with three-dimensional imaging, provided contrast material is injected in a timed sequence. Postprocessing can then remove the arterial anatomy, leaving only the venous segments in the display image.[56] Although it is not used to diagnose DVT, Figure 147.6 is a good example of time-resolved magnetic resonance imaging (MRI) of the central veins.

When MRV is used to diagnose acute DVT, results are impressive for larger venous segments, but sensitivity diminishes when smaller diameter veins are evaluated. Carpenter et al.[56] reported nearly identical findings compared with contrast venography in 97% of patients with acute DVT and 100% agreement in the extent of thrombus burden and whether thrombus was occlusive. Laissy et al.[57] found 100% sensitivity and specificity compared with contrast venography, with 95% sensitivity in detection of the extent of thrombus. The femoropopliteal venous segment had a 97% sensitivity for the same readers, whereas the iliofemoral segment had a 100% sensitivity.[58] Moreover, vessel wall enhancement can be visualized with acute thrombus, allowing the examiner a crude detection of thrombus age.[59]

Comparisons between the two modalities of MRV have also been examined. Time-of-flight MRV and duplex examinations had sensitivities and specificities of 100% and 96%, respectively, compared with contrast venography. Positive and negative predictive values were 90% and 94%, respectively.[56] When more proximal iliocaval DVT is examined, time-of-flight MRV had 100% sensitivity and specificity compared with contrast venography versus 87% and 85%, respectively, for duplex ultrasonography.[57] Perhaps the most impressive and useful aspect of time-of-flight MRV was its 95% sensitivity and 99% specificity in detection of the proximal extent of thrombus in the iliocaval segment compared with 46% and 100%, respectively, for duplex ultrasonography.[56] Contrast-enhanced MRV provides the examiner with 100% sensitivity and specificity for iliac thrombus and 100% sensitivity with a 97% specificity for the detection of femoral thrombus,[60] while being more reliable in distinguishing the proximal extent of these thrombus burdens.[59] With the addition of axial true fast imaging with steady-state precession, MRV has a sensitivity and specificity of 100% for iliocaval thrombus, 100% and 98% for femoral thrombus, and 68% and 94% for below-knee thrombus, producing an overall lower extremity sensitivity and specificity of 87% and 98%, respectively.[60]

Figure 147.6 Time-resolved magnetic resonance imaging after intravenous administration of a long-acting contrast agent in a female patient with symptoms consistent with pelvic congestion syndrome. The image shows early reflux through the left ovarian vein into pelvic varices. The patient also has compression of the left renal vein between the superior mesenteric artery and aorta, consistent with the "nutcracker syndrome."

Although MRV technology demonstrates excellent accuracy for the detection of acute DVT, several disadvantages can make the examination prohibitive. The examination demands a nonmoving patient and long imaging times that, when paired, can be a significant hurdle. The below-knee segments of venous anatomy are often paired, accounting for significant artifact during postprocessing of the images.[55,61] In addition, gadolinium can be toxic in patients with renal dysfunction, and the need for frequent examinations can produce problematic utilization issues in larger institutions. However, MRV certainly has a role in the diagnosis of DVT, especially in the detection of thrombus in centrally located venous structures not always accessible to duplex ultrasonography. Not only is MRV useful for detection

of hypogastric venous thrombosis,[56] a remarkable 27% of patients who sustained a PE with no detectable source of thrombus by duplex ultrasound had thrombus identified with MRV.[62]

A meta-analysis of the accuracy of MRI for the diagnosis of acute DVT[63] showed a range of sensitivity from 0% to 100% with a specificity of 43% to 100%. The pooled estimate of sensitivity was 91.5%, and pooled estimate of specificity was 94.8%.[63] The sensitivity and specificity were higher for proximal DVT than for below-knee thrombus.

^{18}F-Labeled Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

During the past several years, technology used for detection of primary and metastatic cancer has shown value in the diagnosis of acute DVT. Largely by serendipity, ^{18}F-labeled fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been shown to detect acute DVT, to determine thrombus age, and to differentiate acute thrombus from tumor thrombus.[64] ^{18}F-FDG is a glucose analogue that is actively and avidly absorbed by tissues and cells with rapid metabolism. Among these are tumor cells, endothelial cells, macrophages, and lymphocytes. Several studies have reported the ability to detect acute DVT with ^{18}F-FDG PET/CT,[65-68] but until recently, only one study has examined its utility for the direct diagnosis of acute DVT. Rondina et al.[69] studied 12 patients with duplex ultrasound–proven proximal acute DVT with ^{18}F-FDG PET/CT for a mean of 32.5 days. They demonstrated a sensitivity of 87.5% and specificity of 100% using a maximum standardized uptake value of 1.645 or higher. Decreasing the maximum standardized uptake value to 1.49 or higher increased the sensitivity to 100% but decreased the specificity to 84.2%. Sharma et al.[64] showed that depending on the maximum standard uptake value, one could reliably differentiate tumor thrombus from acute DVT, with the higher value corresponding to tumor thrombus and the lower corresponding to acute DVT.

DIAGNOSTIC STRATEGIES

Risk Assessment

In the absence of a single reliable, accurate, and inexpensive diagnostic test, stratification of patients based on their risk of DVT substantially enhances clinical decision making. In addition to increased accuracy of diagnostic tests in high-risk patients, the very low incidence of DVT in low-risk patients allows the clinician to differentially order expensive options without sacrificing clinical outcomes. Availability of effective, convenient, and safe therapeutics for initial and extended treatment of DVT makes additional diagnostic testing unnecessary in low and moderate-risk patients.[4] In high-risk patients, however, treatment should be initiated immediately, and duplex ultrasound or other diagnostic tests can be safely delayed in most patients to the next business day. Such a contemporary approach to management of patients with suspected DVT requires identification of risk factors for development of DVT and stratification of patients based on predicted probability of a thrombotic event.

The relatively low prevalence of inherited causes of DVT combined with the high cost and questionable clinical value of their detection makes testing for thrombophilias impractical for assessment of DVT risk in an individual patient. However, the known presence of such coagulation abnormalities is valuable clinical information (see Chapter 38). The risk of DVT in patients with heterozygous antithrombin (AT) deficiency is increased by 5 to 50 times.[70-72] In patients with protein C deficiency, it is increased 3-fold;[71] and in patients with protein S deficiency, it is increased up to 10-fold.[72] The lifetime probability of symptomatic DVT in patients with heterozygous factor V Leiden mutation is about 10%, but concurrent thrombophilic conditions increase this risk significantly.[73] Other thrombophilias, such as elevated factors VII and IX, hyperhomocysteinemia, dysfibrinogenemia, and hypofibrinolysis, increase the risk of DVT twofold or less.

Acquired risk factors include age, malignant disease, immobility, exposure to surgery or trauma, use of oral contraceptives or hormone replacement therapy, obesity, pregnancy, and history of venous thromboembolism (VTE). The relative role of each individual risk factor in estimation of DVT probability varies. In the absence of prophylaxis, the risk of DVT is 36% after hip arthroplasty, 33% after urologic surgery, 25% after general surgery, 23% after neurosurgery, 19% after abdominal surgery, and 15% after peripheral vascular surgery. Half of the patients with hip fractures and one-third of burn patients develop DVT.[74] This risk continues after discharge from the hospital.[75]

The risk of DVT increases when several risk factors are present, which is the basis for the development of clinical scores that risk-stratify patients by combining several risk factors with clinical symptoms and signs. The most widely used score for symptomatic patients with suspected DVT is the Wells score. This instrument assigns one point to each of the nine clinical characteristics and subtracts two points if an alternative diagnosis is at least as likely as DVT. The nine clinical characteristics are as follows: (1) active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment); (2) paralysis, paresis, or recent plaster immobilization of the lower extremities; (3) recently bedridden for 3 or more days or major surgery within the previous 12 weeks requiring general or regional anesthesia; (4) localized tenderness along the distribution of the deep venous system; (5) entire leg swollen; (6) calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below the tibial tuberosity); (7) pitting edema confined to the symptomatic leg; (8) collateral superficial veins (nonvaricose); and (9) previously documented DVT.[76] The Caprini score is used as a risk assessment tool for selection of DVT prophylactic measures in asymptomatic hospitalized surgical patients.[77] The Wells score has been shown to be a consistent, reproducible instrument to stratify patients into high, intermediate, and low risk of DVT. It has been validated in a variety of patient populations, confirming its clinical utility. A meta-analysis of 24 studies that used the Wells score showed that in a population with 15% prevalence of DVT, the Wells score alone will classify 18% of the patients as high risk

with a DVT prevalence of 47%, 40% as intermediate risk with a DVT prevalence of 12%, and 42% as low risk with a DVT prevalence of 4%.[14]

Diagnostic Strategies for Symptomatic Deep Venous Thrombosis

Currently, there is no single modality that has perfect characteristics for diagnosis of DVT. To achieve a combination of reasonable accuracy, reliability, convenience for patients, practicality, and reduced costs, the clinical strategy should be selected based on the risk-benefit ratio of treating patients with and without DVT and the clinical and cost benefits of performing a sequence of diagnostic tests. It is increasingly recognized that the optimal approach to DVT diagnosis includes risk stratification based on simple low-cost methods, such as the Wells score and DD assay, followed by diagnostic testing in high-risk patients and in patients who require advanced treatment modalities.

In low-risk patients, the combination of a Wells score and negative DD result reaches a negative predictive value approaching 100%.[78,79] Because most of the studies of low-risk patients were done in outpatient settings and excluded patients with a history of DVT, a clinical suspicion of PE, and the use of anticoagulants,[37,80] these factors should be considered in addition to the Wells score.

Similar results were shown in intermediate-risk patients when a combination of Wells score and DD assay was used for DVT diagnosis.[20,81,82] Without treatment, the incidence of DVT during 3 months in patients who are classified as intermediate risk by a Wells score and have a negative DD result is 0.6%,[83] indicating that no additional testing is necessary in these groups, as it is unlikely to improve clinical outcome.

Evaluation of patients with a high probability of DVT is more problematic. Negative DD results in these patients are associated with PE rates of up to 15%.[84] This unexpectedly high rate of VTE indicates that treatment should be started before additional testing is completed. When anticoagulation is initiated, delay in definitive diagnostic studies has been shown to be safe.[4,85] The majority of inpatients fall into the high-risk category, which complicates use of the Wells score for this patient population. In hospitalized patients who could be classified as low risk based on a Wells score, the incidence of DVT has been reported as high as 10%.[86] In addition, both sensitivity and specificity of DD testing are substantially lower in inpatients than in outpatients. Unlike outpatients, most hospitalized patients with a clinical suspicion of DVT need confirmatory diagnostic testing.

The diagnosis of DVT during pregnancy adds an additional level of complexity. The risk of bleeding complications limits the use of anticoagulation to cases with confirmed DVT. DD levels have been known to increase during the course of a normal pregnancy and are of unproven utility during pregnancy.[87] For these reasons, ultrasound remains the preferred diagnostic test for detection of DVT in pregnancy. In pregnant patients thought to have DVT, repeated ultrasound is recommended if the initial examination findings are normal.

Several diagnostic algorithms for evaluation of suspected DVT in symptomatic patients have been published. However, as the new generations of anticoagulants become available, the utility of such algorithms may change. In outpatients, a combination of a low Wells score and a negative DD result is sufficient to rule out DVT. A positive DD result in intermediate and high-risk patients is an indication for immediate anticoagulation to be started and venous duplex examination to be scheduled for the next business day.

Diagnosis of Deep Venous Thrombosis in Emergency Departments

The diagnostic approach to patients with suspected DVT in the emergency department setting may be influenced by the available access to additional testing and the volume of cases that need to be triaged. The high number of emergent priorities and the substantial waiting time to obtain duplex ultrasound testing make fast and safe strategies more desirable. Patients with a low Wells score and no additional risk factors may be safely discharged from the emergency department to continue follow-up care by their primary care physician. A negative DD test result in these patients and in patients with intermediate probability effectively excludes the diagnosis of DVT. For patients with high probability of DVT, immediate anticoagulation without any additional testing is a valid choice while duplex ultrasound is obtained. If patients present at times when venous duplex ultrasound is not available, this approach is efficient and effective (Figs. 147.7 and 147.8). This approach is recommended by the American College of Chest Physicians based on a rigorous analysis of available evidence,[4] age of the thrombus, and diagnosis of recurrent thrombosis.

Thrombus Age and Diagnosis

Venous thrombosis initiates a sequence of biologic processes within the thrombus itself and in the venous wall. Organization of the thrombus and vein wall remodeling occur at a variable pace; within 7 to 10 days thrombus becomes adherent to the vein wall, making treatment modalities such as systemic thrombolysis and thrombectomy less effective and impossible in 30% of patients.[88-91] It is desirable, therefore, to be able to diagnose an acute DVT and to determine the age of the thrombus.

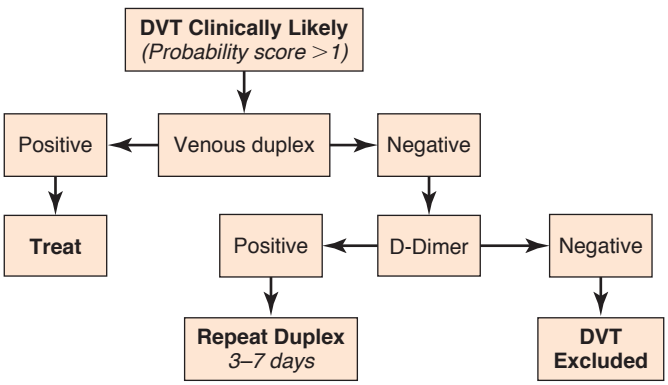

Figure 147.7 An example of a diagnostic algorithm for evaluation of symptomatic patients with high probability of deep venous thrombosis *(DVT)*.

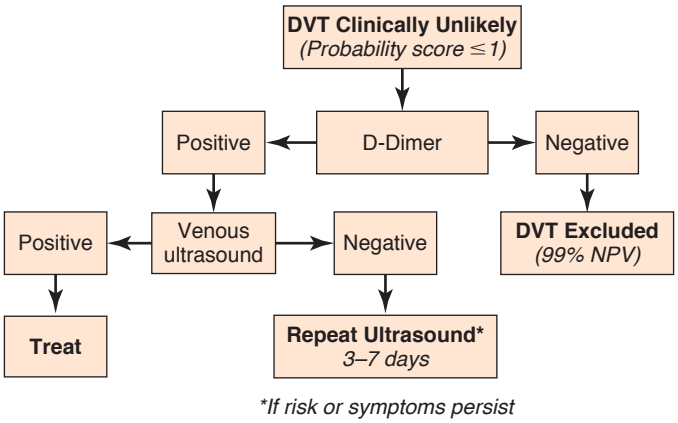

Figure 147.8 An example of a diagnostic algorithm for evaluation of symptomatic patients with low probability of deep venous thrombosis *(DVT)*. *NPV,* Negative predictive value.

The onset of the clinical manifestations of DVT is an unreliable indicator of the start of thrombosis, and conventional imaging techniques are rarely helpful in determining the age of the thrombus.[7] Initial results with ultrasound elastography to gauge thrombus age were promising[92,93] but were later shown to be inconsistent.[94] Most of the studies of ultrasound elastography were done in animal models or ex vivo,[95] and clinical validation of this technique has yet to be performed.

Use of radiolabeled markers, such as recombinant tissue plasmin activator, showed the ability to determine if the thrombus is more than 30 days of age,[96] and MRI may show that the time from onset of thrombosis exceeds 6 months.[97] These tests, however, are more suitable in the diagnosis of rethrombosis than in determining the age of the initial thrombus.

If thrombus neither lyses spontaneously nor is removed by treatment, pathologic processes continue, leading to postthrombotic disease in some patients and predisposing patients to recurrent thrombosis.[98] Recent data from placebo groups of randomized controlled trials showed that recurrent DVT occurs in 11% to 18% of patients during the first year after DVT.[99-101]

Diagnosis of recurrent ipsilateral DVT is a challenging task. Conventional risk assessment tools, such as the Wells score, are not helpful as they classify all patients with a known history of DVT as high risk. Clinical presentation of rethrombosis is frequently identical to manifestations of postthrombotic disease. Imaging diagnostic modalities are unable to reliably detect acute thrombus when postthrombotic changes are present in the venous wall and vessel lumen. Postthrombotic changes lead to partial or complete incompressibility of deep veins. In one study, 70% of patients at 3 months and 40% of patients at 12 months had abnormal compression test results after their first episode of proximal DVT.[102] This would increase the frequency of false-positive results when this criterion is used for recurrent DVT. The false-negative results of compression ultrasound have been reported in 5% of patients with suspected recurrent DVT.[102,103] Availability of ultrasound images obtained before an episode of suspected recurrence may be helpful; however, the interpretation of such images has been shown to have poor to moderate intraobserver agreement.[104]

MRI may be able to differentiate thrombi from fibrotic changes in the vein at 6 months after acute DVT,[97] but neither MRI nor CTV has been tested in patients with suspected recurrence. Despite its high negative predictive value, the DD test does not perform well in patients with recurrent DVT. In 46% of patients who have their warfarin discontinued, DD remains elevated for at least 3 months.[105] Other causes of DD elevation contribute to even more prevalent positive results, which limits the ability of DD to exclude recurrence in only 15% to 18% of patients, even when it is used in combination with risk assessment tools.[106,107]

Because no evidence is currently available to suggest that any test may be useful to determine the age of thrombus, and no evidence exists to show that the diagnostic approach to recurrences should be different from what is used for initial DVT, the practice remains dependent on conventional testing and good clinical judgment.

MEDICAL TREATMENT OF ACUTE LOWER EXTREMITY DEEP VENOUS THROMBOSIS

Treatment of DVT depends on the ability to stabilize a developing thrombus within the deep veins of the lower extremities, to prevent thrombus extension and embolization, and to permit the body's natural fibrinolytic system to dissolve fibrin using anticoagulant therapy. Since the landmark paper in 1961 by Barritt and Jordan,[108] anticoagulation therapy in both enteral and parenteral forms has remained the mainstay of VTE treatment.

The introduction of a new class of oral anticoagulants has led to the increasing safety of outpatient treatment for lower extremity DVT (see Chapter 39). Many patients can begin treatment in the outpatient clinic or emergency department and be sent home, even if imaging diagnostics are delayed. Contraindications for outpatient treatment of lower extremity DVT should be considered, such as the following: active or high risk bleeding, severe symptomatic venous obstruction, thrombocytopenia, poor hepatic function, unstable renal function, noncompliance, and a poor support environment at home.

Beyond anticoagulation, nonpharmacologic measures such as compression therapy and leg elevation have been long accepted within the doctrine of DVT treatment in both the acute and chronic settings. Early ambulation has been added to these recommendations from data over the past two decades, which have replaced the prior dogma of strict bed rest.

The objectives for DVT treatment therefore can be divided into two major categories: (1) immediate reduction of morbidity and mortality in the short term and (2) reduction of late postthrombotic morbidity (see Chapter 156). The latter category concentrates on thrombus burden and recurrence.

Medical Treatment of Calf Deep Vein Thrombosis

Guidelines for the treatment of this group have been conflicting. In electronic polls performed in 2009 at the American Venous

Forum and the American College of Phlebology annual meetings, there was true clinical equipoise regarding anticoagulation for calf deep vein thrombosis (C-DVT). The antithrombotic guidelines of the 2016 American College of Chest Physicians (ACCP) gives a grade 2C recommendation for 3 months of anticoagulation for C-DVT but states that it is "anticipated" that not all patients with distal DVT will be prescribed anticoagulants.[109] A different contemporary guideline published by Streiff et al. places a higher value on anticoagulation for 3 months over duplex surveillance,[110] although the latter approach is preferred over IVC filter placement for individuals who are thought to be too high risk for bleeding. Risk factors for thrombus extension should be considered if surveillance is to be considered rather than anticoagulation; these factors include elevated DD, which veins are involved, thrombotic burden, history of VTE, or significant thrombophilic state such as active cancer.

Medical Treatment of Femoropopliteal Deep Vein Thrombosis

Involvement of the femoral and/or popliteal veins is most frequently encountered in proximal lower extremity DVT, and it is the most straightforward to diagnose with compression ultrasound. With isolated femoral vein thrombosis, even if limited to the upper thigh, patients often do well with anticoagulation alone. This is mostly due to the excellent collateral drainage from the popliteal vein via the profunda femoris vein. Early, and even late, recanalization of thrombus is not particularly important if the common femoral and popliteal veins remain unobstructed.

Distal popliteal vein thrombosis involving the so-called "trifurcation" can result in severe acute symptoms due to obstruction of venous outflow from the calf, which can lead to significant postthrombotic complications.[111] When axial drainage of the calf is compromised, early thrombus removal is likely to prevent postthrombotic morbidity.[111]

Medical Treatment of Iliofemoral Deep Vein Thrombosis

The most severe DVT symptoms and long-term morbidity is associated with iliofemoral DVT. This is due to obstruction of the main outflow tract of the lower extremity. Anticoagulation alone commonly results in incomplete resorption of thrombus leaving a persistently obstructed lumen containing a fibrous "scar" consisting mostly of type 1 and type 3 collagen.[112] In a cohort of patients with iliofemoral DVT treated with anticoagulation alone, Akesson and colleagues observed that 5 years after the initial DVT 95% had valvular dysfunction, with 30% of patients having either venous claudication or ulceration.[113] Recurrence is higher than infrainguinal DVT due to the greater thrombus burden and residual venous obstruction.[114] External compression such as the classic May-Thurner syndrome is implicated, especially in left-sided iliofemoral DVT. Recanalization with correction of the common iliac vein stenosis is now accepted as a standard of care supported by the SVS.[115] Beyond anticoagulation, surgical and interventional therapies should be strongly considered in such patients; a discussion of these methods supported by evidence is reviewed in Chapters 160 and 161.

Anticoagulation (see Chapter 39)

Anticoagulation should be initiated as soon as there is a high level of suspicion for DVT and should not be delayed for confirmation with objective imaging. This can be facilitated with a high Well's score of greater than 2 in the presence of a positive DD utilizing a sensitive enzyme-linked immunosorbent assay. The traditional treatment to achieve timely therapeutic anticoagulation was unfractionated heparin (UFH) followed by vitamin K antagonist (VKA) therapy with warfarin, but (despite refinements in management and delivery over time) there continues to be pharmacologic and logistical limitations with this approach. In addition to intravenous or subcutaneous UFH followed by warfarin, there are fortunately now several other options for the initial anticoagulant treatment of VTE: subcutaneous low-molecular-weight heparin (LMWH), subcutaneous pentasaccharide (fondaparinux), intravenous direct thrombin inhibitors (DTIs), and direct-acting oral anticoagulants (DOACs). A review of the anticoagulants used in treating DVT is presented in Table 147.1.

Unfractionated Heparin

Intravenous UFH is an effective method for treatment of DVT that is still commonly used for the initial 5 to 10 days to bridge oral anticoagulation with warfarin. Its anticoagulant activity is dependent on binding to the serine protease inhibitor AT to potentiate its activity, which for various reasons may be deficient in some individuals.

Monitoring is necessary because of the nonspecific binding of heparin to other sites such as plasma proteins, endothelial cells, platelet factor 4, and macrophages, which leads to its sometimes unpredictable pharmacodynamics and its narrow therapeutic window.[116] The therapeutic range is 1.5 to 2.5 times the control. Alternatively, establishing a therapeutic range using an anti-factor Xa assay to establish a plasma heparin level with a concentration in the range of 0.3 to 0.7 IU/mL can be used as a more accurate method of monitoring. A high incidence of recurrent VTE has been reported in individuals who failed to promptly reach a therapeutic aPTT.[117]

Major drawbacks with the use of UFH include the need for hospitalization, frequent blood draws, variable response, difficulties in promptly achieving the target therapeutic range, and the potential for life-threatening allergenic response causing heparin-induced thrombocytopenia (HIT).

Low-Molecular-Weight Heparin

Since their discovery in 1976, LMWH fractions have been developed, each having slightly different pharmacokinetic profiles. These include the current fractions that are marketed in the United States: enoxaparin, tinzaparin, and dalteparin. The LMWHs have improved bioavailability, more consistent response, and more predictable pharmacokinetics and pharmacodynamics

TABLE 147.1 Comparison of Anticoagulant Drugs for the Treatment of Deep Venous Thrombosis

	Mechanism	Venous Indications	Efficacy vs. LMWH/VKA	Bleeding Risks (vs. LMWH/VKA)	Other Risks	Reference
UFH	Factor II and X inhibition via AT	VTE treatment VTE prophylaxis	Equivalent	**Major:** 2.0%	HIT 0.5%-2%	Mismetti et al.[151]
LMWH Enoxaparin, Dalteparin, Tinzaparin	More selective factor X inhibition via AT	VTE treatment VTE prophylaxis	n/a	**Major:** 2.0%	HIT <1%	Mismetti et al.[151]
Fondaparinux	Selective factor X inhibition via AT	VTE treatment VTE prophylaxis	Equivalent	**Major:** 1.2% vs. 1.2%	Thrombocytopenia 0.5%	Büller et al.[152]
Parenteral DTI Argatroban	Direct factor II inhibition	VTE treatment HIT treatment (initial)	n/a	**Major:** 1.3%[a]	Hypotension tachycardia	Koster et al.[153]
Bivalirudin	Direct factor II inhibition	VTE treatment	n/a	**Major:** 3.5%; (vs. UFH): OR 0.49 (0.36-0.67)[a]	Hypotension bradycardia	Farag et al.[154]
VKA/warfarin	Vitamin K-dependent factor inhibition (II, VII, IX, X)	VTE treatment VTE prophylaxis HIT treatment (longitudinal)	n/a	**Major:** 1.2%-1.9% (see below)	Multiple drug-drug, drug-food interactions	See below
DOACs Apixaban	Oral direct inhibitor of factor Xa	VTE treatment VTE prophylaxis (for hip and knee replacement in apixaban and rivaroxaban only)	Noninferior	**Major**: 0.6% vs. 1.8%; HR 0.31 (0.17-0.55) **Major+CRNM:** 4.3% vs. 9.7%; HR 0.44 (0.36-0.55)	CrCl <30: 44% increased exposure	Amplify[b]
Rivaroxaban			Noninferior	**Major**: 0.8% vs. 1.2%; HR 0.65 (0.33-1.30) **Major+CRNM:** 8.1% vs. 8.1%; HR 0.97 (0.76-1.22)	CrCl <30: 64% increased exposure Child-Pugh B: 2.3-fold increased exposure	Einstein-DVT
Edoxaban			Noninferior	**Major:** 1.4% vs. 1.6%; HR 0.84 (0.59-1.21) **Major+CRNM:** 8.5% vs. 10.3%; HR 0.81 (0.71-0.94)	CrCl <30: 72% increased exposure Abnormal LFT (7.8%)	Hokusai-VTE[b]
Dabigatran	Oral direct factor IIa inhibitor	VTE treatment	Noninferior	**Major:** 1.6% vs. 1.9%; HR 0.82 (0.45-1.48) **Major+CRNM:** 5.6% vs. 8.8%; HR 0.63 (0.47-0.84)	CrCl < 30: 6.3-fold increased exposure	Re-cover[b]

[a]Bleeding data is based on patients with acute coronary syndrome.
[b]Pulmonary embolism patients were analyzed in these trials alongside deep venous thrombosis patients; bleeding data therefore includes a pooled analysis.
CRNM, clinically relevant nonmajor; DOACs, direct-acting oral anticoagulants; *DTI*, direct thrombin inhibitor; *DVT*, deep venous thrombosis; *HIT*, heparin-induced thrombocytopenia; *LMWH*, low-molecular-weight heparin; *n/a*, not available, not applicable; *VKA*, vitamin K antagonist; *VTE*, venous thromboembolism; *UFH*, unfractionated heparin.
Major bleeding generally defined as including fatal bleed, intracranial bleed, bleeding into a critical site.

compared to UFH. They are also more uniformly absorbed from subcutaneous depots with a longer half-life in the range of 3 to 5 hours. LMWHs do not require routine monitoring, but patients with renal insufficiency or significant obesity may require dose adjustments or monitoring of LMWH-anti factor Xa activity (0.5-1.0 IU/mL) to determine proper dosing.

LMWHs have undergone rigorous testing in clinical trials showing less major bleeding and reduced mortality versus UFH with a nonsignificant trend toward reduction in minor bleeding.[119]

Malignancy poses a particularly high risk for VTE. Patients with cancer and VTE have poorer survival than those with cancer alone.[120] The failure rate of VKA therapy in malignancy has been shown to be higher than with LMWH,[121] which generated studies that eventually led to guidelines recommending LMWH over VKA for the treatment of acute VTE.[122,123] The

10th edition of the ACCP guidelines (2016) continues to recommend LMWH over VKA or DOACs for the initial 3 months of treatment of acute VTE associated with cancer (Grade 2C).

Parenteral Direct Thrombin Inhibitors

Direct inhibition of the thrombin molecule blocks its interaction with other substrates and reduces thrombus formation and activation. HIT is increasingly recognized and parenteral DTIs are the treatment of choice for this condition. With a suspicion of HIT, heparin or LMWH (in rare cases fondaparinux) should be discontinued and an appropriate alternative anticoagulant, such as a DTI, should be started while awaiting serologic test results. As of 2016, parenteral DTIs are the only class of anticoagulants that carry a specific Food and Drug Administration (FDA) package label to treat HIT. Although three intravenous DTIs have been licensed in North America, lepirudin, argatroban, and bivalirudin, only the latter two have been commercially available in the United States since 2012.

Vitamin K Antagonists

Oral anticoagulation with VKAs such as warfarin produces their anticoagulant effects by inhibiting the production of vitamin K-dependent coagulation factors. There is also significant inhibition of the natural anticoagulants protein C and protein S, which have a much shorter half-life than the procoagulant factors. This explains why VKAs produce a procoagulant state in the first 3 days of their administration before they reach their anticoagulant effect, irrespective of the INR in this early phase. Warfarin compounds must therefore be administered alongside parenteral anticoagulation for the initial 4 to 5 days or longer to achieve therapeutic anticoagulation. Unopposed VKA therapy in the setting of acute thrombosis can lead to thrombus propagation, early recurrence, and devastating thrombotic complications, not the least of which is the scourge of warfarin skin necrosis because of the rapid depletion of protein C and S. The effective reduction in the concentration of factors II and X (below 30% activity) usually requires at least a 5-day overlap with heparin.

Ongoing monitoring with the protime (typically an INR range of 2.0-3.0 for standard VTE treatment and secondary prophylaxis) is necessary with VKAs for a variety of reasons. This includes the presence of a narrow therapeutic window, variability in dose-response among individuals, interaction with dietary vitamin K and other dietary substances, and many drug-to-drug interactions. One common interaction is the prolongation effect on the INR caused by certain antibiotics when an individual is taking warfarin. This is the result of the destruction of the natural gut flora that otherwise produces vitamin K and acts as a major source of this nutrient.

Direct-Acting Oral Anticoagulants

The DOACs have generated justifiable enthusiasm ever since rivaroxaban was the first in this group to be approved by the FDA for the treatment of VTE in 2012. These drugs selectively target either the factor Xa molecule (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran) and obviate the need for routine monitoring and frequent dose adjustments. They have predictable pharmacokinetics and high bioavailablity with relatively few drug-to-drug and no significant food interactions compared to VKA therapy. Efficacy of these drugs has been shown to be equivalent to warfarin in the large industry-sponsored trials that is reviewed in greater detail later. Safety in these trials was also shown to be equivalent although intracranial bleeding and fatal bleeding were significantly lower in all three of the Xa inhibitors. No head-to-head comparisons of these drugs have been published as of the writing of this chapter.

The EINSTEIN trials of rivaroxaban[124,125] reported recurrent VTE in 2.1% of patients receiving rivaroxaban versus 3% in the standard group ($P < .001$ for noninferiority, $P = .08$ for superiority). Major and clinically relevant nonmajor bleeding was 8.1% in each group. An extended treatment study showed superiority for rivaroxaban versus placebo with an 82% relative risk reduction for recurrent VTE.[126]

Apixaban was investigated in a double-blinded noninferiority study.[100] Recurrent VTE occurred in 2.3% of the apixaban group and 2.7% receiving conventional therapy ($P = .001$ for noninferiority). Major bleeding occurred significantly less in the apixaban group versus conventional therapy (0.6% vs. 1.8%; $P < .001$ for superiority). Apixaban has less renal clearance (27%) than the other factor Xa inhibitors and, for its VTE indication, does not require dose adjustment for renal dysfunction.

Edoxaban[127] trial demonstrated similar efficacy to warfarin but proved to be superior to standard therapy with respect to bleeding.

Dabigatran is the only oral DTI approved for the treatment of VTE.[128,129] Two trials showed noninferiority of dabigatran to warfarin. The safety analysis showed significantly less major or clinically relevant nonmajor bleeding (HR 0.62; 95% CI: 0.45-0.84) and less any bleeding (HR 0.67; 95% CI: 0.56-0.81). In 2016, the humanized monoclonal antibody fragment, idarucizumab, was approved as a specific reversal agent for dabigatran for emergency surgery or for life-threatening bleeding in dabigatran.[130] Idarucizumab is generally administered as a single 5 g IV dose with immediate reversal of anticoagulation effect, which persists for more than 24 hours.

Adjunctive Measures for Acute Deep Venous Thrombosis Management

Elevation of the legs above the heart reduces the acute edema and reduces pain. However, bed rest is no longer recommended for patients with VTE. The benefit of compression with ambulation was observed in two randomized trials that applied gradient elastic compression and began early ambulation for the acute treatment of lower extremity DVT compared to bed rest with elevation.[131,132] Reductions in the progression of thrombus length and volume along with reduced pain and edema were observed in those with compression and ambulation. There was no increase in the incidence of PE with early ambulation, which has been further supported by large registry data.[133] A more recent study, using surveillance lung scanning, showed that bed rest did not reduce PE.[134] Some studies indicate that immobility increases the risk for development of PE.[135] Furthermore, structured leg exercise may decrease the incidence of postthrombotic syndrome

(PTS).[136] Most guidelines recommend initiating anticoagulation prior to allowing patients to ambulate.[110]

Apart from ambulation, the value of using graduated compression for DVT treatment has been debated. In a widely referenced randomized trial in 1997, Brandjes et al. demonstrated that 30 to 40 mm Hg thigh-length gradient compression stockings (GCS) were shown to be effective at reducing pain and the incidence of PTS by 50% when used consistently for 2 years.[137] Further evidence supporting the use of GCS was provided by Prandoni et al. who also showed a 50% decline in PTS sequelae using knee-high 30 to 40 mm Hg GCS.[138] The assumption was that the calf compression aided in priming the calf muscle pump. More recently, however, these data have been scrutinized by the ACCP due to inadequate blinding in light of the more contemporary SOX trial.[109] This larger, placebo-controlled trial with over 800 participants found that the routine use of GCS neither reduced the incidence for PTS, nor did it show benefit in the reduction in pain during the first three months following DVT diagnosis.[139] This publication led to a reversal in the former recommendation of GCS in the 9th Edition of the ACCP guidelines to a grade 2B suggestion against their routine use for PTS prevention in the 10th Edition of the Guidelines for Antithrombotic Therapy. The ACCP authors are careful to note, however, this recommendation focuses on the chronic complication of PTS and does not constitute a statement on the use of GCS to treat symptoms; they further state that for both acute and chronic symptoms, a trial of GCS is often justified.

Longitudinal Treatment of Deep Venous Thrombosis

The proper duration of anticoagulation treatment is the pivotal question determining freedom from VTE recurrence. Risk factor analysis is often complex and confusing. Duration of anticoagulation needs to be balanced with the risk of bleeding for individuals being considered for extended treatment.

Thrombus burden has been shown to be a predictor of recurrence.[140] This supports approaches using duplex ultrasound to assess residual deep vein obstructions to guide duration of therapy. Prandoni et al. demonstrated that the risk of recurrence was significantly higher in patients with residual venous obstruction (HR 2.9; $P = .001$).[141] In a follow-up study, recurrence rate of 17.2% in those randomized to the fixed-duration arm versus 11.9% in those allocated to flexible-duration therapy was found.[142] Patients in this cohort with a history of unprovoked DVT realized the greatest benefit with an adjusted hazard ratio of 0.61 compared to 0.81 for those with a provoked event.

Increased thrombus activity as measured by the DD tests is associated with an increased risk of recurrence. The presence of elevated levels of DD along with residual postthrombotic luminal obstruction assessed by compression ultrasound has been associated with an increased risk of recurrent VTE. Extending anticoagulation when either or both these markers exist has been shown to significantly reduce recurrence.

Trials have been performed to evaluate the role of DD for the duration of anticoagulation. In the PROLONG trial, those with an abnormal DD were randomized to either resume anticoagulation or remain off anticoagulation. Those with a normal DD remained off therapy.[143] This trial showed a significant increase in recurrence at 1.4 years for patients with elevated DD who went untreated compared to untreated patients with a normal DD ($P = .003$). Several studies independently confirmed these relationship.[144,145]

Platelet inhibition can also play a role in the long-term treatment for patients with VTE.[146-148] The WARFASA and ASPIRE trials showed a 32% reduction in VTE recurrence and a 34% reduction in major vascular events without a significant increase in bleeding. These studies along with an ongoing INSPIRE collaborative have reopened the discussion of aspirin as an adjunct for long-term secondary VTE protection.

Another approach to extended treatment is the role of subtherapeutic doses of anticoagulants. The concept is to offer protection against recurrence while reducing risk of hemorrhagic complications.[149]

Extended anticoagulation was investigated in the AMPLIFY-EXT trial using apixaban at a therapeutic dose (5 mg bid) or a reduced dose (2.5 mg bid) compared to placebo after 6 to 12 months of therapeutic anticoagulation.[150] The primary outcome of symptomatic recurrent VTE or death occurred in 8.8% receiving placebo versus 1.7% who were receiving both 2.5 mg and 5 mg of apixaban ($P < .001$ for both groups compared to placebo). Clinically relevant nonmajor bleeding was 2.3% in the placebo group, 3.0% in the apixaban 2.5 mg group (RR 1.29 vs. placebo; 95% CI 0.72-2.33), and 4.2% in the apixaban 5 mg group (RR 1.82 vs. placebo; 95% CI 1.05-3.18). The NNT of 14 to prevent one VTE recurrence in 1 year appears sufficiently low to justify incorporating this into patient management protocols. The number needed to cause one episode of major or clinically relevant nonmajor bleeding was sufficiently high at 200. There were only 15% of patients over the age of 75 and few patients with CKD ≥3 or low body weight such that these results may not be generalizable to all patients.

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Ascher E, Depippo PS, Hingorani A, Yorkovich W, Salles-Cunha S. Does repeat duplex ultrasound for lower extremity deep vein thrombosis influence patient management? *Vasc Endovascular Surg*. 2004;38:525–531.

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DVT can be ruled out in a patient who is judged clinically unlikely to have DVT and who has a negative D-dimer test result; moreover, ultrasound testing can be safely omitted in such patients.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 148

Acute Lower Extremity Deep Venous Thrombosis: Surgical and Interventional Treatment

ANTHONY J. COMEROTA and FAISAL AZIZ

POSTTHROMBOTIC SYNDROME 1950
Morbidity 1950
Etiology 1951
RATIONALE FOR THROMBUS REMOVAL 1952
Recurrence 1952
Valve Function 1952
RANDOMIZED TRIALS OF CATHETER-DIRECTED THROMBOLYSIS 1953
STRATEGIES FOR THROMBUS REMOVAL 1954
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CHOOSING THE APPROPRIATE TREATMENT OPTION 1961
Risk Assessment 1961
Patient Selection 1961
Pretreatment Evaluation 1962
Importance of Imaging 1962
PUBLISHED GUIDELINES 1965

Acute deep venous thrombosis (DVT) represents a disease spectrum ranging from asymptomatic calf vein thrombosis to the painful, blue, swollen limb of phlegmasia cerulea dolens resulting from extensive multisegment thrombosis involving the iliofemoral venous segment. Until 2008, national and international guidelines for the treatment of patients with acute DVT recommended only anticoagulation. However, the eighth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic and Thrombolytic Therapy[1] and the American Heart Association Scientific Statement on the management of iliofemoral DVT (IFDVT)[2] as well as the Society of Vascular Surgery (SVS) guidelines[3] suggest interventional strategies for thrombus removal that include surgical and catheter-based techniques to reduce the incidence of post-thrombotic syndrome (PTS), especially in patients with extensive venous thrombosis. This chapter reviews the evidence for the severe morbidity associated with PTS following IFDVT, the avoidance of the severe postthrombotic sequelae when the thrombus is eliminated and unobstructed venous drainage to the vena cava is restored, and a review of the contemporary techniques used to successfully eliminate thrombus.

POSTTHROMBOTIC SYNDROME

The most important consideration leading to guideline recommendations for thrombus removal in patients with extensive DVT is the severe morbidity associated with the PTS and the evidence that early elimination of thrombus prevents or reduces postthrombotic morbidity.

Morbidity

PTS is defined as the signs and symptoms resulting from acute DVT. This is usually the consequence of venous hypertension resulting from valve reflux and/or luminal obstruction. Studies have shown that patients with PTS have a significant reduction in quality of life (QoL).[4,5] The severity of the patient's acute DVT is predictive of postthrombotic morbidity, especially when

Abstract

The underlying premise of this chapter, Acute Lower extremity Deep Venous Thrombosis: Surgical and Interventional Treatment, is that patients with a large burden of thrombus occluding the single common outflow channel from their leg are at high risk of developing disabling postthrombotic syndrome (PTS), and that adopting a management strategy of thrombus removal reduces their risk of severe PTS.

Technology has continuously evolved and improved with catheter based techniques which integrate mechanical methods of thrombus removal with the judicious use of plasminogen activators replacing surgical thrombectomy in the majority of patients. The majority of these techniques are reviewed with their associated outcomes presented.

However, just as catheter based techniques have advanced, so have operative procedures, which now integrate contemporary imaging, venous balloon dilation and stenting and adjunctive, low dose plasminogen activators in addition to regionally delivered anticoagulation. These advances improve outcomes and reduce procedure related complications.

Unfortunately, randomized trial results often lag behind technology. None-the-less, randomized trial data provide big picture analysis of treatments, with subset observation suggesting important details which can be used as the hypothesis for developing future care.

Keywords

Acute DVT
Surgical Venous Thrombectomy
Thrombolysis
Catheter Directed Thrombolysis
Pharmacomechanical Thrombolysis
Post-Thrombotic Syndrome

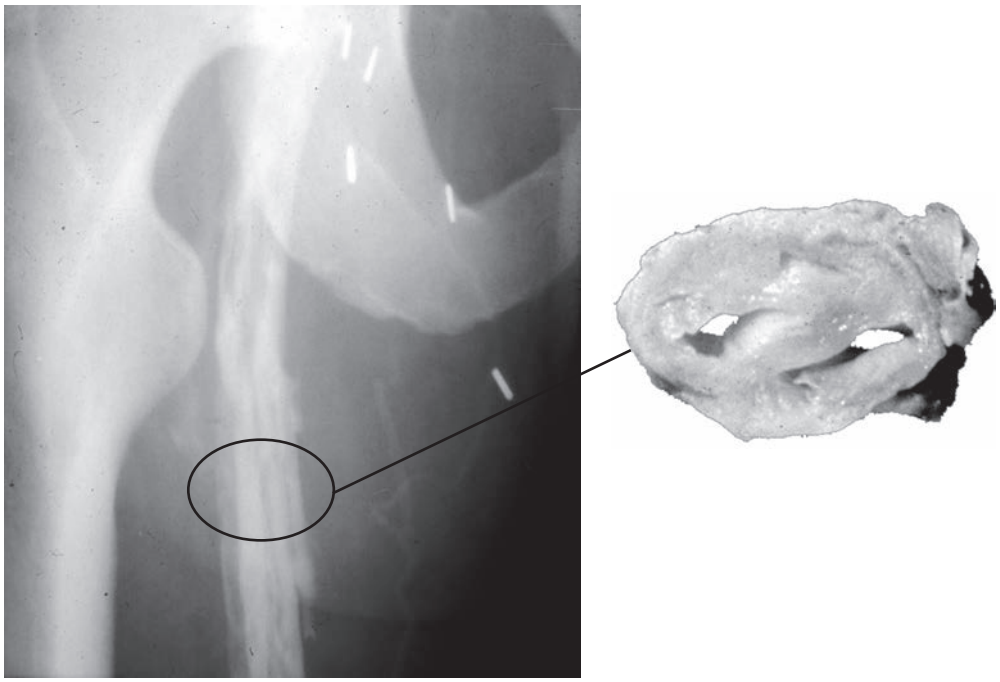

Figure 148.1 Postthrombotic venous disease illustrating the inability to identify obstruction as part of the pathophysiology of chronic venous disease. This patient had had iliofemoral deep venous thrombosis 10 years earlier and was treated with anticoagulation alone. Severe postthrombotic syndrome developed, and the patient underwent multiple hospitalizations for venous ulceration. An ascending phlebogram showed recanalization of the iliofemoral venous system; however, the radiologist's interpretation was that there was "no obstruction" of the deep venous system, and a 3-second maximal venous outflow test was "normal." A classic Linton procedure was performed and showed *(insert)* the cross section of the femoral vein at the corresponding location on the phlebogram, just below the profunda femoris vein.

it involves the iliofemoral segment. Patients with IFDVT appear to be a clinically relevant subset with acute venous thrombosis. They have occlusion of their single venous outflow channel from the leg, resulting in severe postthrombotic morbidity when treated with anticoagulation alone.[6-9] In a prospective observational study of anticoagulation for acute DVT, IFDVT was found to be the most powerful predictor of severe PTS (HR 2.23).[9] Labropoulos et al.[10] monitored venous pressures in patients with PTS after treatment for their acute DVT. They found that patients who were treated for IFDVT had the highest venous pressures. This confirmed prior observations that IFDVT patients treated by anticoagulation alone had ambulatory venous hypertension, with 40% demonstrating venous claudication and up to 15% developing venous ulceration within 5 years.[6-8] Essentially all these patients will have a reduced QoL. The morbidity of PTS escalates substantially with ipsilateral recurrence.[11] A meta-analysis of outcomes after treatment for acute DVT demonstrated that recurrence occurs more commonly in patients with a large burden of thrombus.[12]

Etiology

The pathophysiology of postthrombotic venous disease is ambulatory venous hypertension, which is defined as elevated venous pressure during exercise.[13,14] Ambulatory venous pressure is linearly linked to the pathophysiologic changes observed with chronic venous disease, such as swelling, pigmentation, and lipodermatosclerosis.[15] Microcirculatory changes leading to dermal breakdown follow.

The anatomic components contributing to ambulatory venous hypertension are venous valvular incompetence and luminal obstruction. The most severe postthrombotic morbidity is associated with the highest venous pressures, which occur in patients with both valvular incompetence and luminal venous obstruction.[13,16] Although valvular function can be reliably assessed with ultrasound by quantifying valve closure times, techniques are not yet available to assess the relative contribution of venous obstruction to the pathologic venous hemodynamics leading to clinical postthrombotic morbidity. Fig. 148.1 succinctly illustrates the difficulty of identifying even extensive venous obstruction, either hemodynamically or radiologically. Neither ascending phlebography performed and interpreted by a skilled radiologist nor the maximal venous outflow test performed in an accredited vascular laboratory identified venous obstruction in the patient presented. A cross-section of the proximal femoral vein removed during a classic Linton procedure clearly showed recanalization channels through what was once occlusive thrombus, which resulted in chronic obstruction of a large proportion of the luminal surface area. Unfortunately noninvasive physiologic techniques cannot detect venous hemodynamic impairment of even this advanced degree of obstruction when they are performed on resting patients. This example is not unique but rather is common to postthrombotic morbidity. It is evident that venous hemodynamics are adversely

affected long before imaging techniques can detect obstruction. Our inability to noninvasively quantitate obstruction has led physicians to underappreciate its contribution to postthrombotic pathophysiology. Luminal venous obstruction causes the most severe forms of PTS, especially when it involves the common femoral and iliac veins. Obstruction of the distal popliteal vein is also associated with significant PTS. Therefore treatment strategies for thrombus removal should be developed during the initial encounter with the patient and, if successful, can eliminate obstruction as part of the long-term pathophysiology and should significantly reduce the incidence of PTS. We and others have observed that successful elimination of thrombus can also preserve venous valve function.[17]

Experimental observations in canine models of acute DVT have shown that successful thrombolysis preserves endothelial function and valve competence.[16,18] These experimental observations appear to translate into improved clinical outcomes when put into the perspective of natural history studies of acute DVT treated with anticoagulation alone. Investigators have found that distal valve incompetence can develop in patients with persistent venous obstruction treated with anticoagulation alone, even when the distal veins are not initially involved with thrombus.[19] When spontaneous lysis occurred, defined as clot resolution within 90 days, valve function was frequently preserved.[20] These investigators confirmed that the combination of valvular incompetence and venous obstruction was associated with the most severe postthrombotic morbidity.[21,22] It is intuitive that successful elimination of acute venous thrombus eliminates luminal obstruction and increases the likelihood that normal valve function will be preserved. It follows, then, that in patients whose thrombus is mechanically or pharmacologically eliminated, postthrombotic morbidity should be avoided or at least significantly reduced.

RATIONALE FOR THROMBUS REMOVAL

There is a large body of evidence supporting the rationale for a strategy of thrombus removal, especially in patients with IFDVT. When a strategy of thrombus removal is successful, venous patency is restored, valve function is maintained, QoL is improved, and the risk of recurrence is reduced. Qvarfordt and Eklof[23] measured compartment pressures in patients presenting with acute IFDVT before and after operative venous thrombectomy. Compartment pressures (a surrogate for venous pressures) were pathologically elevated upon presentation, consistent with acute compartment syndrome pressures, and normalized after operative thrombectomy. These important observations documented significant physiologic benefit by restoring the main venous outflow to the lower extremity and formed the basis for a randomized trial of operative venous thrombectomy and anticoagulation alone.

Scandinavian investigators randomized patients with IFDVT to operative venous thrombectomy plus arteriovenous fistula (AVF) and anticoagulation or to anticoagulation alone. This multicenter randomized trial demonstrated that patients undergoing venous thrombectomy enjoyed improved iliac vein patency ($P < .05$), lower venous pressure ($P < .05$), less edema ($P < .05$), and fewer postthrombotic symptoms ($P < .05$) than did patients receiving anticoagulation alone.[24-26] They also observed that patients undergoing venous thrombectomy were more likely to retain venous valve function in the femoropopliteal segment than were those treated by anticoagulation alone. This observation is consistent with that reported by Killewich and coauthors, who demonstrated that persistent proximal obstruction leads to distal valve incompetence in veins not initially involved with thrombus and that elimination of iliofemoral thrombosis maintains distal valve function.[19]

A rapidly growing body of evidence suggests that catheter-directed thrombolysis (CDT) is of benefit, especially in patients with IFDVT.[27-30] A case-controlled study demonstrated significantly improved QoL in patients treated by CDT versus anticoagulation alone for IFDVT.[31] In a subsequent analysis, the QoL benefit associated with CDT directly correlated with the volume of thrombus removed.[27] The more residual thrombus at the end of CDT, the worse the QoL. This also correlated with objective measures of PTS: the greater the degree of lysis, the fewer symptoms of PTS observed.[30]

Baekgaard et al.[32] followed 103 patients for 6 years after they were treated with CDT for IFDVT. They reported that 86% of veins were patent without reflux and only 6% of patients developed recurrence during the follow-up period.

Pharmacomechanical techniques have been shown to improve outcomes compared with CDT using the drip technique alone. Pharmacomechanical techniques have shortened treatment time, reduced dose of lytic agent, and reduced length of ICU and hospital stay.[33-35]

Recurrence

An underappreciated but important benefit of successful thrombus removal is the reduction in the rate of recurrent DVT. As mentioned earlier, patients with IFDVT have an exceptionally high recurrence rate compared with those with less extensive thrombosis.[12,36] Hull et al.[12] performed a systematic review and showed that treated patients with a large thrombus burden had a greater risk of recurrence than those with a smaller thrombus burden. As mentioned previously, Baekgarrd observed an unexpectedly low 3-year recurrence after CDT for IFDVT. Aziz et al.[29] observed that patients with IFDVT treated with catheter-directed techniques appeared to have a low recurrence rate. Upon further analysis, the benefit accrued to those patients who had successful thrombus removal, whereas those with the bulk of the thrombus remaining (unsuccessful lysis) had a significantly higher recurrence rate.

Valve Function

Vogel et al.[17] addressed the issue of whether pharmacomechanical techniques compromised valve function, presumably due to valve injury. In a sequential analysis of CDT versus pharmacomechanical thrombolysis, there did not appear to be any adverse effect on valve function using pharmacomechanical

techniques. The important observations were that valves functioned best in patients who had successful results. An interesting observation was that 35% of the veins in the noninvolved limbs had incompetent valves.

There is no argument that data from large randomized trials are the best evidence. The results of recent randomized trials of CDT versus anticoagulation for acute DVT combined with the substantial body of observational, clinical, and case-control evidence support a strategy of thrombus removal, especially in patients with extensive venous thrombosis.

RANDOMIZED TRIALS OF CATHETER-DIRECTED THROMBOLYSIS

Elsharawy et al.[37] reported a small randomized trial comparing anticoagulation versus CDT. Based upon point estimates used to calculate sample size, they appear to have achieved their goal. They demonstrated that patients treated with CDT had significantly improved venous patency and a reduction in valvular incompetence compared with those treated with anticoagulation alone. These observations are often overlooked in the absence of measures of QoL and objective analysis of postthrombotic morbidity using such measurements as the Villalta scale or the Venous Clinical Severity Score. However, very few if any patients with patent deep veins with normal valve function develop PTS.

The recently published CaVenT trial reported the long-term outcome after additional CDT to anticoagulation versus anticoagulation alone for acute IFDVT.[28] These investigators randomized 209 patients. Their primary endpoint was iliofemoral patency at 6 months and PTS at 2 years. CDT was performed with the UniFuse catheter (AngioDynamics, Latham, New York). Alteplase was infused at a dose of 0.01 mg/kg per hour for a maximum of 96 hours. The alteplase was prepared by mixing 20 mg in 500 mL of 0.9% NaCI. This would result in a 70-kg man being infused with 0.7 mg of recombinant tissue plasminogen activator (rt-PA) in 17.5 mL of infusate. This appears to be an unusually small volume of infusate, which might potentially disadvantage patients.

The mean duration of thrombolysis was 24 hours; 43% had complete thrombolysis, 37% had partial thrombolysis, and 10% were deemed unsuccessful. Patients receiving CDT had a mean clot resolution of 82%. Patients treated with additional CDT had significantly improved iliofemoral venous patency at 6 months ($P = .012$) and less PTS at 2 years ($P = .047$). The authors reported that lower thrombus scores at completion of CDT were associated with increased patency ($P < .04$) and that patency of the iliofemoral venous system correlated with a reduction in PTS ($P < .001$). There was an absolute risk reduction in PTS of 14.4% in patients receiving CDT. Major bleeding complications occurred in 3.3% of patients undergoing CDT. Only one inferior vena cava filter was used in this group and there was no symptomatic pulmonary embolism (PE) observed.

These results demonstrate a significant benefit in those patients receiving additional CDT. The actual benefit would likely have been substantially greater if patients entered into this trial truly had IFDVT. In reality, only 45% of the patients randomized to thrombolysis and 36% of those in the anticoagulation group had IFDVT. Therefore although approximately 60% of patients randomized in this trial had less than IFDVT, significant benefit was observed. The authors reported that the number needed to treat (NNT) to prevent one PTS was seven, but this author believes that the relative reduction of postthrombotic morbidity would have been substantially greater (and the NNT smaller) if indeed all patients in CaVenT had truly had IFDVT.

The largest study to date, the ATTRACT trial, sponsored by the National Institutes of Health, prospectively randomized 692 patients with symptomatic proximal DVT.[38] Patients with iliofemoral and femoropopliteal DVT were stratified at entry into the study to catheter-based techniques of thrombolysis versus anticoagulation alone. The primary endpoint was PTS at 24 months. The ATTRACT trial will also evaluate the relative benefits of pharmacomechanical techniques versus the CDT drip technique and will include a careful cost analysis. Recruitment concluded in December of 2014. The basic design of ATTRACT is illustrated in Fig. 148.2.

The ATTRACT Trial (NCT00790335) is the largest randomized trial to date designed to evaluate whether a strategy of acute thrombus removal using pharmacomechanical catheter-directed thrombolysis (PCDT) plus anticoagulation reduces post-thrombotic syndrome (PTS) compared to patients assigned to anticoagulation alone (ref). This NHLBI funded clinical trial randomized 692 patients with proximal DVT to PCDT plus anticoagulation (N = 336) to anticoagulation alone (N = 355). Upon entry into the study, patients were stratified by extent of their thrombosis (Iliofemoral vs. Femoral-Popliteal DVT) prior to their randomization (see figure ATTRACT Trial). The primary efficacy outcome was any PTS (Villalta Score >4) at two years post-treatment. The primary safety outcome was major bleeding. Clinically important secondary outcomes were resolution of acute pain and swelling, moderate to severe PTS and quality of life at two years (Veines QOL Sym).

Results demonstrated that there was no difference in PTS at two years between those randomized to PCDT and those randomized to anticoagulation alone, 47% and 48% respectively. Major bleeding was low in both groups, but significantly higher with PCDT, 1.7% than in the anticoagulation group, 0.3%, p = 0.049. Fewer patients in the PCDT group developed moderate to severe PTS (Villalta Score >9) at two years compared to the anticoagulation group, p = 0.035. Although there was a trend in improved QOL in the PCDT group at two years, the difference did not reach significance, p = 0.08.

Data have not yet been released whether PCDT benefitted patients with the larger thrombus burden, ie: Iliofemoral DVT, compared to femoral-popliteal DVT patients. Such observations will be important for the future selection of patients for catheter based strategies of thrombus removal.

Future analyses from the robust data set from the ATTRACT Trial are anxiously awaited, as are the results from the Dutch CAVA Trial (NCT00970619).[38a]

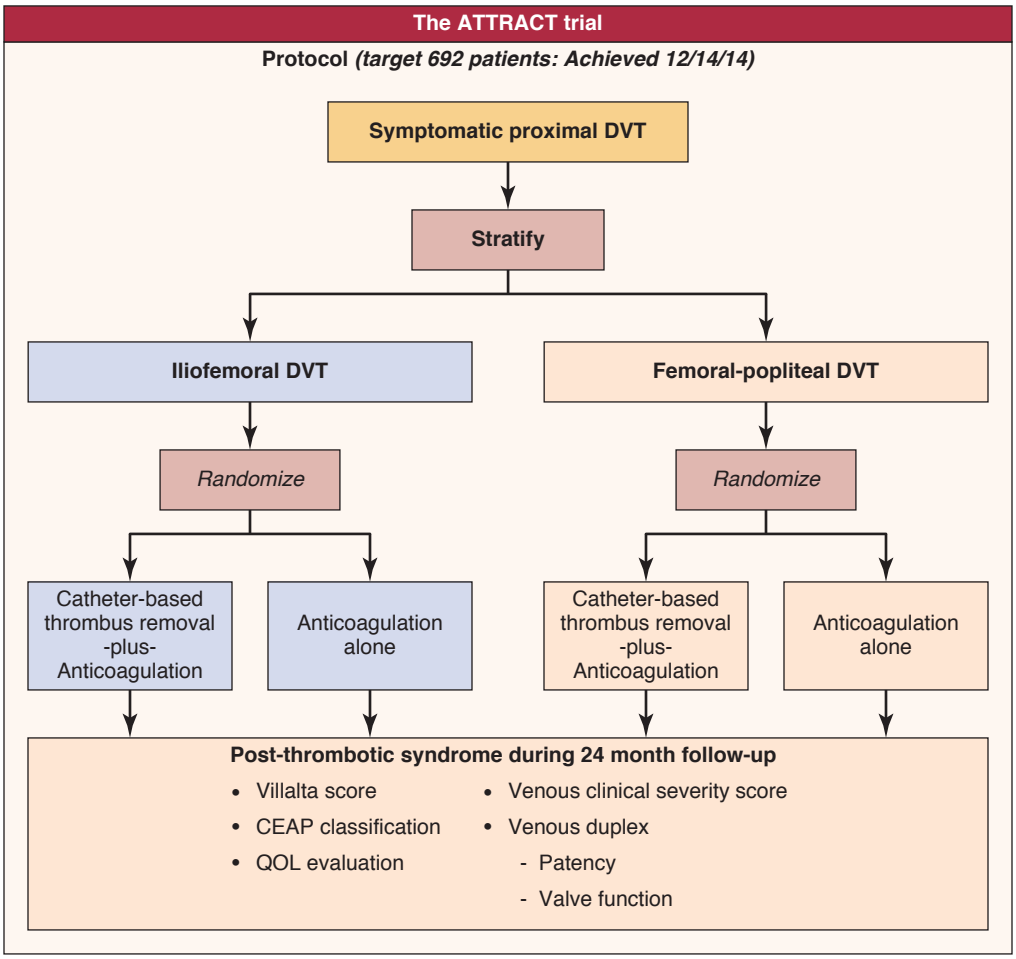

Figure 148.2 Basic design of ATTRACT.

STRATEGIES FOR THROMBUS REMOVAL

Randomized trials demonstrating positive outcomes for patients undergoing a strategy of thrombus removal are now available,[24-26,28] and the largest is in its follow-up phase.[38] CDT is the preferred treatment option for most patients who have no contraindication to thrombolytic therapy. Pharmacomechanical techniques are becoming increasingly popular and tend to shorten treatment time and reduce the lytic dose.

Contemporary venous thrombectomy is generally available to all patients from vascular surgeons who are comfortable operating on the venous system. There are few contraindications to operative thrombectomy short of old remote thrombus that is adherent to the vein wall and cannot be removed. All thrombus or chronic fibrous obstruction within the operative field can be removed. The goal of venous thrombectomy is to remove the iliofemoral and infrainguinal thrombus and restore unobstructed venous return to the vena cava. Knowing the full extent of thrombosis preoperatively and having good imaging intraoperatively are crucial for a well-planned and successful procedure.

Thrombolytic Therapy

Initial attempts at pharmacologic resolution of acute DVT used systemic thrombolysis. Early studies involving systemic delivery of plasminogen activators resulted in high rates of bleeding complications and less than optimal lytic results. Many patients were treated for infrainguinal DVT; therefore, even when lytic therapy was successful, the benefits were not as apparent as in patients with IFVDT. A summary of studies comparing anticoagulation with systemic thrombolysis has been reported.[39] Results were disappointing, considering the increased bleeding risk. However, an important observation demonstrated the improved long-term outcome in patients with phlebographically successful systemic thrombolysis. Catheter-based procedures have rapidly replaced systemic thrombolysis as the preferred method of treating patients with extensive DVT.

Intrathrombus Catheter-Directed Thrombolysis

During the process of thrombosis, Glu-plasminogen binds to fibrin, which is converted to Lys-plasminogen. This modification produces more binding sites for plasminogen activators and therefore more efficient production of plasmin. The basic mechanism of thrombolysis is the activation of fibrin-bound

plasminogen and resultant production of plasmin. It is intuitive that delivery of the plasminogen activator within the thrombus is more effective and potentially safer than systemic infusion of plasminogen activators. Additionally, intrathrombus delivery protects plasminogen activators from circulating plasminogen activator inhibitor and, more importantly, protects the active enzyme plasmin from neutralization by circulating antiplasmin. This neutralization of circulating plasminogen is so effective that the half-life of plasmin in the systemic circulation is only a fraction of a second.

Numerous reports have demonstrated good outcomes of CDT for acute DVT and most have been tabulated.[39] In general, when patients with acute DVT are treated, success rates in the range of 75% to 90% can be anticipated. The rate of bleeding complications generally ranges from 5% to 11%. Fortunately, serious distant bleeding is uncommon and intracranial bleeding a rarity. Most bleeding complications are localized to the venous access site. Symptomatic PE during infusion is uncommon and fatal PE a rarity.

An interesting report by Chang and coworkers documents the benefit of sequential intrathrombus bolus dosing of rt-PA without a continuous infusion in a small group of patients (12 lower extremities with acute DVT).[40] His careful observations lend credence to high-pressure bolus dosing (pulse-spray) of plasminogen activator into the acute thrombus. These observations underscore the importance of saturating the thrombus with a plasminogen activator and the effective activation of Lys-plasminogen.

Outcomes From the National Venous Registry

The report of National Venous Registry is the largest one to date of patients treated with lytic therapy for acute DVT, with 71% having IFDVT.[39] Although significant advances in treatment have been made since the publication of this report, a number of the early observations remain important for clinicians to recognize.

There was a significant correlation ($P < .001$) of thrombosis-free survival with the results of initial therapy. At 1 year, 78% of the patients with initially complete clot resolution had patent veins versus only 37% of patients who had less than 50% lysis. In the group of patients with first-time IFDVT who initially had successful thrombolysis, 96% of the veins remained patent at 1 year. Initial lytic success also correlated with valve function at 6 months. Of patients with less than 50% thrombolysis, 62% had venous valvular incompetence, whereas 72% with complete lysis had normal valve function ($P < .02$).

A cohort-controlled QoL study was performed to determine whether lytic therapy altered QoL in patients with IFDVT in the National Venous Registry.[41] The results demonstrate that CDT is associated with better QoL than anticoagulation alone. QoL was directly related to initial success of thrombolysis. Patients who had a successful lytic outcome reported a better Health Utilities Index, improved physical functioning, less stigma of chronic venous disease, less health distress, and fewer overall postthrombotic symptoms. Not surprisingly, patients in whom CDT failed had outcomes similar to those treated with anticoagulation alone. As mentioned earlier, successful thrombus elimination appears to reduce the risk of recurrence.

Available data to date present a compelling argument for CDT. Institutions participating in randomized trials should make every effort to enroll patients who are eligible. Those not participating in trials should adopt a strategy of thrombus removal that is based on evidence to date.

Pharmacomechanical Thrombolysis

Although good results can be achieved with CDT, treatment times are often unacceptably long; therefore, bleeding risk and cost associated with therapy are unacceptably high. This was succinctly characterized by Sillesen and colleagues when they reported that 93% of their patients were successfully treated and discharged with patent veins and that more than 90% of the patients discharged with patent veins had normal venous valve function at 1 year. The treated patients had a mean duration of symptoms of just 7 days, and patients with symptoms exceeding 14 days were excluded. Therefore lysis would be expected quickly in these patients because they truly represented acute DVT. However, treatment time for CDT averaged 71 hours. This duration of acute care is logistically difficult if not impossible for many practitioners and many medical centers to manage. The associated cost is high because all patients receiving lytic therapy are generally monitored in intensive care units (ICUs).

Endovascular Mechanical Thrombectomy

Mechanical techniques alone or in combination with thrombolysis have been developed to more rapidly clear the venous system. Vedantham and associates evaluated the effectiveness of mechanical thrombectomy alone or in combination with pharmacologic thrombolysis in 28 limbs of patients with acute DVT.[42] They evaluated multiple devices, including the Amplatz (ev3, Inc., Plymouth, Minnesota), AngioJet (Possis Medical, Minneapolis, Minnesota), Trerotola (Arrow International, Reading, Pennsylvania), and Oasis (Boston Scientific/Medi-tech, Natick, Massachusetts) catheters. Venographic scoring was performed at each step of the procedure. Some 26% of the thrombus was removed by mechanical thrombectomy alone, whereas adding a plasminogen activator solution to the mechanical technique (pharmacomechanical) removed 82% of the thrombus. This tabulation includes patients with chronic occlusion who did not respond. Mechanical thrombectomy alone was successful in removing intraprocedural thrombus, which is generally gelatinous and not cross-linked with fibrin. The average infusion time was approximately 17 hours per limb, and 14% of patients had major bleeding complications.

Lin and coauthors reported their 8-year experience with pharmacomechanical thrombolysis (via a rheolytic thrombectomy catheter).[32] Of their 98 patients, 46 received CDT alone and 52 underwent pharmacomechanical thrombolysis. Pharmacomechanical thrombolysis with the AngioJet catheter was associated with significantly fewer phlebograms, shorter ICU stays, shorter hospital stays, and fewer blood transfusions. Bleeding complications were not different between the two groups. A smaller patient group treated by rheolytic thrombectomy was reported by Kasirajan and associates, who demonstrated that mechanical thrombectomy alone was less effective than combined pharmacomechanical thrombolysis.[42]

Ultrasound-Accelerated Thrombolysis

Parikh and coauthors reported their initial clinical experience with ultrasound-accelerated thrombolysis in 53 patients treated for acute DVT with the EKOS EndoWave (Bothell, Washington) system.[34] Unfortunately both upper- and lower-extremity DVT patients were included in this report, and a variety of lytic agents were used. Complete lysis (≥90%) was observed in 70% of patients and overall lysis (complete and partial) in 91%. The median infusion time was 22 hours, and 4% of the patients had major complications, which were essentially puncture site hematomas. The authors' impression was that as compared with historical controls (a weakness of this report), treatment time and the doses of lytic agents were reduced with ultrasound-accelerated thrombolysis.

A randomized trial evaluating the benefit of adding ultrasound accelerated thrombolysis (USAT) to CDT for IFDVT was reported by Engelberger et al.[43] They randomized patients with IFDVT to CDT alone (ultrasound infusion catheter without ultrasound activation) versus USAT. Patients' thrombus was quantified at baseline. Patients received 20 mg of rtPA over 1.5 hours and a repeat phlebogram performed with residual thrombus quantified by a physician blinded to treatment allocation. Patients receiving CDT alone had 54% lysis and those with USAT had 55% lyisis ($P = .91$).

Isolated Segmental Pharmacomechanical Thrombolysis

An interesting technique is isolated segmental pharmacomechanical thrombolysis (ISPMT), which is achieved by using the Trellis catheter (Covidien, Mansfield, Massachusetts). This double-balloon catheter is inserted into the thrombosed venous segment with the proximal balloon positioned at the upper edge (cephalic end) of the thrombus. When the balloons are inflated, plasminogen activator is infused into the thrombosed segment isolated by the balloons. The intervening catheter assumes a spiral configuration and spins at 3500 rpm for 15 to 20 minutes. The liquefied and fragmented thrombus can be aspirated and treatment success evaluated by repeat segmental phlebography. If successful, the catheter is repositioned and additional thrombosed segments are treated; if residual thrombus persists, repeat treatment or other appropriate intervention (rheolytic thrombectomy, balloon angioplasty, and stenting) is performed. Martinez and coworkers reviewed 52 consecutive limbs treated for IFDVT, the first 27 with CDT and the following 25 with ISPMT plus CDT when necessary.[30] Thrombus burden and treatment outcomes were quantified. Ninety-three percent of the patients were treated with rt-PA, venoplasty and stenting were used to correct underlying stenoses in all patients, and all received long-term therapeutic anticoagulation. Sixteen of the 27 legs treated by CDT required other adjunctive mechanical techniques to clear the thrombus, such as the AngioJet, ultrasound-accelerated lysis, or pulse-spray techniques, whereas only 7 of the 25 limbs treated with ISPMT required additional adjunctive techniques. A larger percentage of the thrombus was removed with ISPMT than with CDT. Complete lysis (≥90%) was achieved in 11% of the limbs of CDT patients as opposed to 28% of the limbs treated by ISPMT ($P = .077$). Treatment time was shorter (23.4 vs. 55.4 hours, $P < .001$), and the rtPA dose was lower (33.4 vs. 59.3 mg, $P = .009$) with ISPMT. Hospital and ICU length of stay was no different, which is the result of underlying patient comorbid conditions. If the ISPMT catheter was used alone, only 18% of the limbs underwent complete lysis. This is consistent with the observations of O'Sullivan and associates.[44] Bleeding complications occurred in 5% of patients undergoing CDT alone, as well as 5% of the patients treated by ISPMT.

Endovascular Aspiration Thrombectomy

Although CDT is effective in reducing the thrombus burden, it can be associated with increased risk of bleeding, prolonged time required for effective lysis, need for close monitoring during lysis, and increased cost of treatment. Similarly, mechanical thrombectomy devices can be associated with hemolysis and hemoglobinuria. Aspiration thrombectomy can be an effective alternative to these techniques. This includes use of large-sized catheters or sheaths for aspiration of thrombus. Jia et al.[45] performed a retrospective analysis on 68 patients with IFDVT treated with aspiration thrombectomy. A retrievable IVC filter was placed in all patients. Large-sized catheters (either a 9 Fr guiding catheter [Vista Brite Tip Guiding Catheter, Johnson & Johnson, Miami, Florida] or a 10 Fr OptEase retrieval catheter [Cordis, Miami, Florida) was advanced over a 0.035-in guidewire with the catheter tip placed in either the iliac or femoral vein. The guidewire was then removed and the catheter slowly pulled back while aspirating the catheter with a large syringe. This process was repeated until thrombus was completely removed. The authors reported a 100% technical success rate. Aspiration alone was successful in 47 patients; the remaining 21 required additional thrombolysis, and 32 required venous stenting. At a mean follow-up of 21.9 months, 11% recurrent thrombosis was found.

Operative Venous Thrombectomy

Contemporary venous thrombectomy for iliofemoral venous thrombosis offers effective short- and long-term outcomes with relatively few complications. In a report of 230 patients, no fatal PE and only one operative death occurred.[46] The long-term benefits of venous thrombectomy relate to its ability to achieve proximal patency and maintain distal valve competence. Both are influenced by the initial technical success and avoidance of recurrent thrombosis. Therefore attention to operative detail, removal of all thrombus, and correction of underlying lesions as well as maintenance of therapeutic anticoagulation postoperatively are crucial.

Pooled data from a number of contemporary reports on iliofemoral venous thrombectomy (Table 148.1)[25,47-58] indicate that the early and long-term patency rates of the iliofemoral venous segment is 75% to 80% versus 30% in patients treated by anticoagulation alone.[7] Femoropopliteal venous valve function is preserved in the majority of patients. The Scandinavian investigators reported their randomized trial of operative venous thrombectomy versus anticoagulation alone in patients with

TABLE 148.1 Venous Thrombectomy With Arteriovenous Fistula: Long-Term Iliac Vein Patency

Author/Year	No.	Follow-Up (Months)	Patent Iliac Vein (%)
Plate et al., 1984	31	6	76
Piquet et al., 1985	57	39	80
Einarsson et al., 1986	53	10	61
Vollmar, 1986	93	53	82
Juhan et al., 1987	150	102	84
Torngren and Swedenborg, 1998	54	19	54
Rasmussen et al., 1990	24	20	88
Eklof and Kistner, 1996	77	48	75
Neglen et al., 1991	34	24	88
Meissner et al., 1996	27	12	89
Pillny et al., 2003	97	70	90
Hartung et al., 2008	29	63	86
Holper et al., 2010	25	68	84
Rodriguez et al., 2017	40	36	76
Total	796	54 (mean)	80 (mean)

Modified from Comerota AJ, Gale SS. Surgical venous thrombectomy for iliofemoral deep vein thrombosis. In: Greenhalgh RM, ed. *Towards Vascular and Endovascular Consensus*. London: BIBA Publishing; 2005. Used with permission.

BOX 148.1 Overview of the Technique of Contemporary Venous Thrombectomy

1. Identify the cause of the extensive venous thromboembolic process
   a. Complete thrombophilia evaluation
   b. Rapid CT scan of the chest, abdomen, and pelvis
2. Define the full extent of the thrombus
   a. Venous duplex examination
   b. Contralateral iliocavagram, MRV, or spiral CT
3. Prevent pulmonary embolism (numerous techniques)
   a. Anticoagulation
   b. Vena caval filter (if nonocclusive caval clot)
   c. Balloon occlusion of the vena cava during thrombectomy
   d. Positive end-expiratory pressure during thrombectomy
4. Perform complete thrombectomy
   a. Iliofemoral (vena cava) thrombectomy
   b. Infrainguinal venous thrombectomy (if required)
5. Ensure unobstructed venous inflow to and outflow from the thrombectomized iliofemoral venous system
   a. Infrainguinal venous thrombectomy (if required)
   b. Correct iliac vein stenosis (if present)
6. Prevent recurrent thrombosis
   a. Arteriovenous fistula
   b. Continuous therapeutic anticoagulation
   c. Catheter-directed postoperative anticoagulation (if infrainguinal venous thrombectomy is required)
   d. Extended oral anticoagulation

CT, Computed tomography; *MRV*, magnetic resonance venography.

iliofemoral venous thrombosis.[21-23] Patients underwent systematic follow-up with venous imaging and physiologic measurements. As a result, 6-month, 5-year, and 10-year follow-up showed that patients randomized to venous thrombectomy demonstrated improved patency ($P < .05$), lower venous pressure ($P < .05$), less leg edema ($P < .05$), and fewer postthrombotic symptoms ($P < .05$) than did patients treated with anticoagulation alone.

Rodriguez et al.[59] recently reported their experience treating 71 patients with IFDVT. They compared the results of 40 patients treated with a hybrid operative thrombectomy with 31 treated with catheter-directed thrombolysis. The hybrid operative thrombectomy included balloon catheter, thrombectomy completion venogram, and balloon venoplasty and stenting if needed. An AVF was not performed.

The investigators reported eight major bleeds in patients with CDT compared with those in the operative thrombectomy group ($P = .04$). CDT patients had a longer length of hospital stay (13.3 vs. 10 days; $P = .028$) compared with thrombectomy patients. At 2-year follow-up there was no difference in femoropopliteal reflux. Although operative thrombectomy patients had a lower clinical class of their CEAP score, there was no difference in their Villalta scores (2.1 vs. 1.9, $P = .8$).

Technique of Contemporary Venous Thrombectomy

A brief summary of the important points of contemporary venous thrombectomy is provided in Box 148.1. The principles of venous thrombectomy are those of basic vascular surgical technique: remove the thrombus, provide unobstructed outflow from the iliofemoral venous segment into the vena cava and unobstructed inflow from the infrainguinal venous segment, correct any underlying lesions, and prevent rethrombosis. The sequential salient technical points follow.

Preoperative Care

Preoperative anticoagulation is generally initiated with unfractionated heparin (UFH) because it has a short half-life and can be controlled more easily than low-molecular-weight heparin or direct factor Xa inhibitors. The full extent of thrombus (distal and proximal) is identified (see Box 148.1 and Fig. 148.3).

Vena caval filtration is not routinely used except in patients who have nonocclusive thrombus extending into the vena cava (see Fig. 148.3). Permanent or optional vena caval filters and proximal balloon occlusion of the cava during thrombectomy are reasonable options.

The thrombectomy is performed under fluoroscopic guidance with the balloon of the venous thrombectomy catheter filled with contrast material. The entire abdominal vena cava and pelvic venous system must be in the fluoroscopic field. An autotransfusion device should be available.

Operative Care

General anesthesia is usually recommended for patients undergoing operative venous thrombectomy.

A longitudinal inguinal incision exposes the common femoral vein, femoral vein, saphenofemoral junction, and profunda

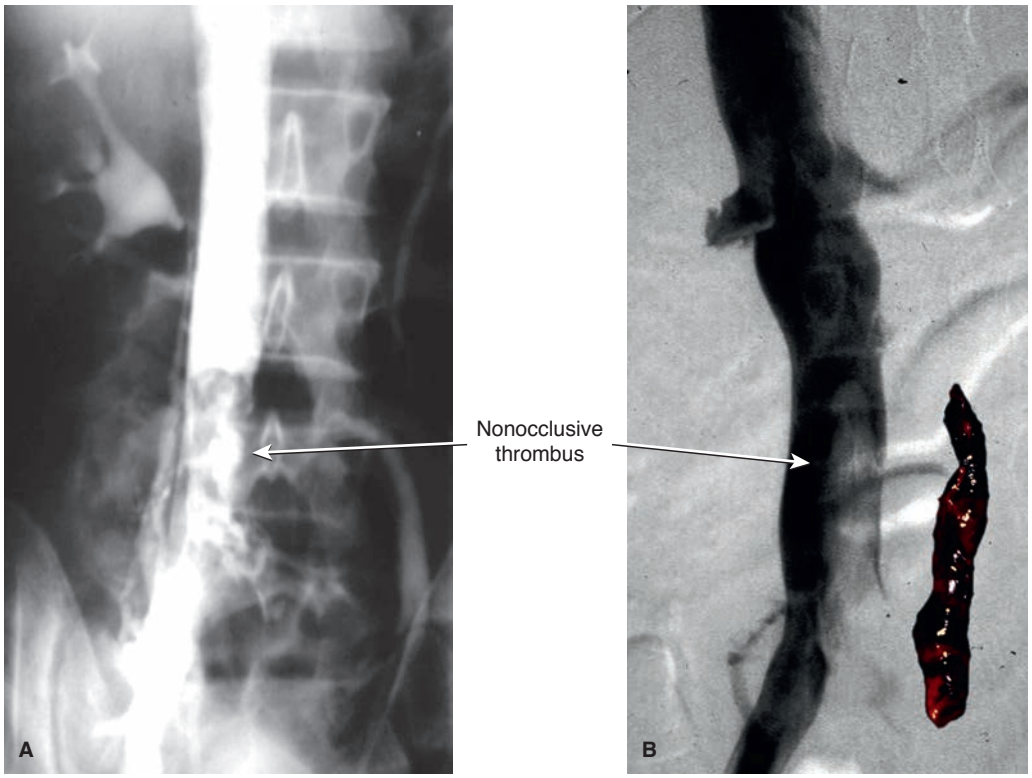

Figure 148.3 A, Contrast iliocavagrams show nonocclusive thrombus in the vena cava and illustrate the importance of imaging to detect the proximal extent of thrombus. In B, the outlined area shows where the adjacent thrombus was extracted from the vena cava by balloon catheter thrombectomy. The proximal vena cava was protected with the balloon catheter (see Fig. 148.6).

femoris vein or veins (Fig. 148.4A). A longitudinal venotomy is made in the common femoral vein to ensure access to the origin of the saphenous and profunda femoris branches.

If infrainguinal thrombus is present, the leg is elevated and compressed with a tightly wrapped rubber bandage. The foot is dorsiflexed and the calf and thigh are squeezed. If all infrainguinal thrombus is removed, balloon thrombectomy of the iliofemoral venous system then proceeds.

If the infrainguinal thrombus persists, a cut-down is performed to expose the distal posterior tibial vein. A No. 3 Fogarty catheter is advanced from the distal posterior tibial vein to and through the common femoral venotomy. The Silastic stem of an intravenous catheter (12- to 14-gauge) is amputated from its hub and slid halfway onto the balloon catheter exiting the common femoral venotomy. Another balloon catheter (No. 4 Fogarty) is placed in the opposite end of the Silastic sheath (see Fig. 148.4A). Pressure is applied to the two balloons by a single operating surgeon to ensure that the catheters remain secure inside the sheath. The No. 4 balloon catheter is guided distally through the thrombosed venous valves and clotted veins (see Fig. 148.4B) to the level of the posterior tibial venotomy (see Fig. 148.4C). The infrainguinal venous thrombectomy is then performed, with passage repeated as necessary (see Fig. 148.4D and E).

After infrainguinal balloon catheter thrombectomy, the infrainguinal venous system is flushed by placing a large red rubber catheter into the proximal posterior tibial vein and vigorously flushing with a heparin-saline solution via a bulb syringe to hydraulically force residual thrombus from the deep venous system (Fig. 148.5). Frequently an impressive amount of thrombus will be expelled with this maneuver. Once the infrainguinal venous system is adequately cleared, a vascular clamp is applied below the femoral venotomy and the infrainguinal venous system is filled with dilute plasminogen activator solution consisting of approximately 4 to 6 mg of rt-PA in 200 mL of saline. The plasminogen activator solution remains in the infrainguinal veins for the remainder of the procedure. This amount of local rt-PA will bind to fibrin-bound plasminogen in residual thrombus and promote further clot dissolution; however, it will not cause a systemic lytic response. If the infrainguinal venous thrombectomy is not successful because of chronic thrombotic disease of the femoral vein, the femoral vein is ligated and divided below the profunda femoris vein. Patency of the profunda is ensured by direct thrombectomy if necessary.

Floppy guidewire passage from the common femoral venotomy distally can be attempted. If successful passage is achieved, a distal thrombectomy with an over-the-wire balloon thrombectomy catheter is performed. All other principles remain the same except for the heparin-saline flush from below. In these cases, a small catheter would be placed into the posterior tibial vein under ultrasound guidance for postoperative anticoagulation. An arbitrary dose of 800 IU UFH is infused into the LE catheter. It is believed that the target vein will receive a high concentration of heparin, but an overall lower dose will be systemically delivered, thereby reducing the risk of bleeding at the operative site.

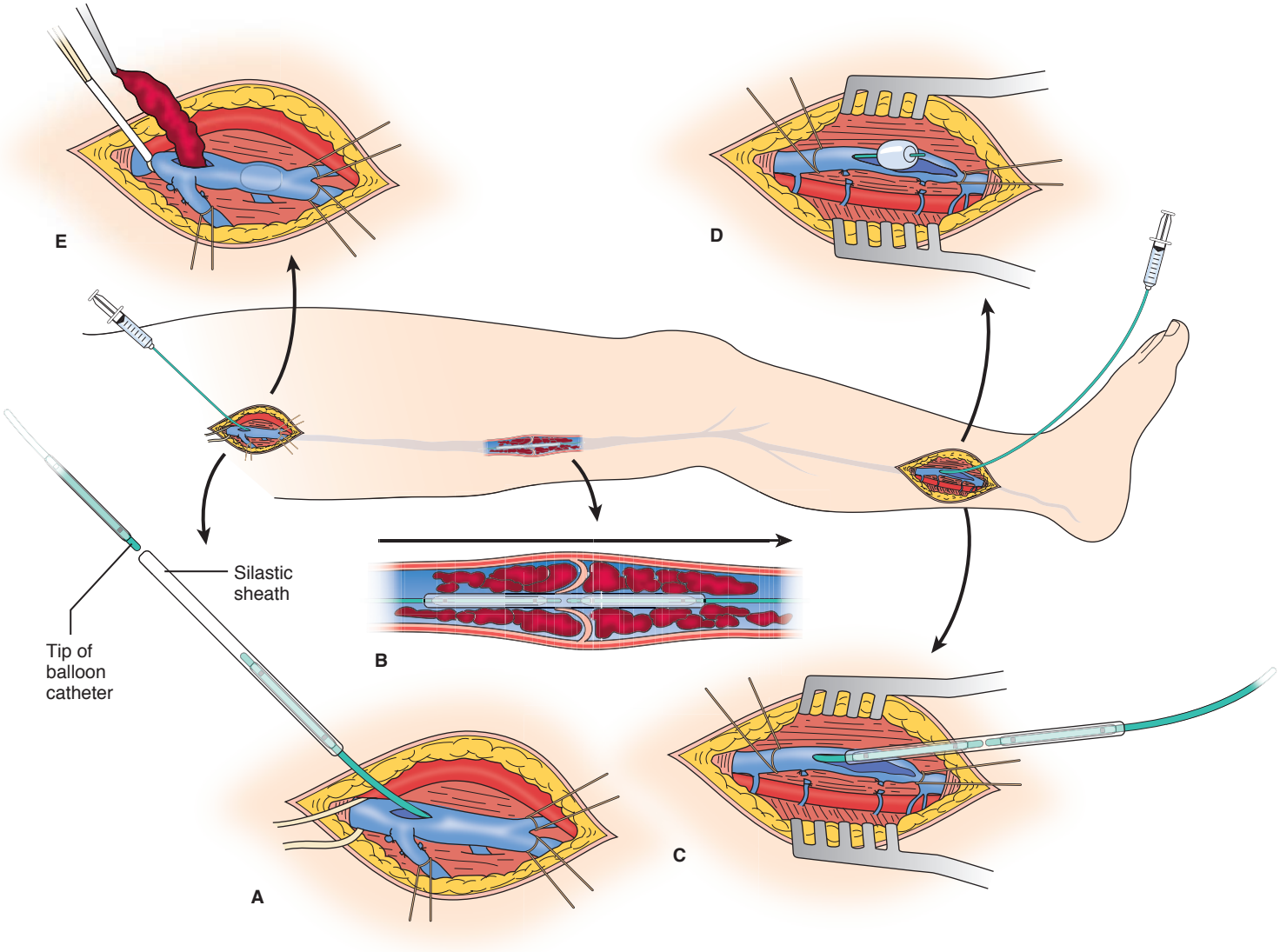

Figure 148.4 Operative thrombectomy for acute venous thrombosis. (A) Longitudinal inguinal incision to expose the common femoral vein, femoral vein, saphenofemoral junction, and profunda femoris vein. (B and C) The balloon catheter is guided distally through the thrombosed venous valves and clotted veins to the level of the posterior tibial venotomy. (D and E) Performance of infrainguinal venous thrombectomy, with passage of the balloon catheter repeated as necessary.

Iliofemoral venous thrombectomy is then performed by passing a No. 8 or 10 venous thrombectomy balloon catheter partially into the iliac vein for several passes to remove the bulk of the thrombus before advancing the catheter into the vena cava. The proximal thrombectomy is always performed under fluoroscopic guidance with contrast material in the balloon, especially if a vena caval filter is present, there is clot in the vena cava, or resistance to catheter passage is encountered. During this part of the procedure, the anesthesiologist applies positive end-expiratory pressure to further reduce the risk of pulmonary embolization. If a clot is present in the vena cava, caval thrombectomy can be performed with a protective balloon catheter inflated above the thrombus as an alternative to vena caval filtration (Fig. 148.6).

After completion of the iliofemoral venous thrombectomy, intraoperative phlebography/fluoroscopy is performed to evaluate for underlying iliac vein stenosis and assess the nature of the venous drainage into the vena cava. Intravascular ultrasound is often better than single-view phlebography for detecting iliac vein stenosis. Any underlying iliac vein stenosis is corrected by balloon angioplasty and stenting if venous recoil occurs. If an iliac vein stent is used, a 12-mm or larger-diameter stent is recommended.

Once the venotomy is closed, an end-to-side AVF is constructed by anastomosing the amputated end of the proximal saphenous vein or a large proximal branch of the saphenous vein to the side of the superficial femoral artery. The anastomosis should be limited to 3.5 to 4.0 mm in diameter. The purpose

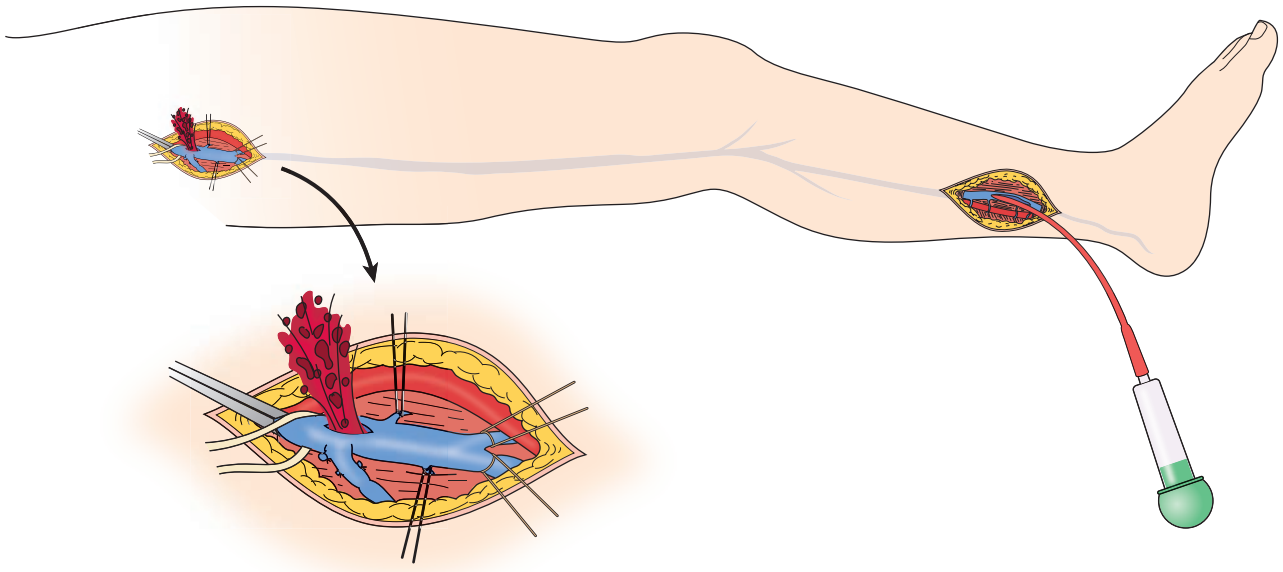

Figure 148.5 After infrainguinal balloon catheter thrombectomy, flushing of the infrainguinal venous system with a heparin-saline solution is performed by placing a large red rubber catheter into the proximal posterior tibial vein and flushing vigorously with a bulb syringe.

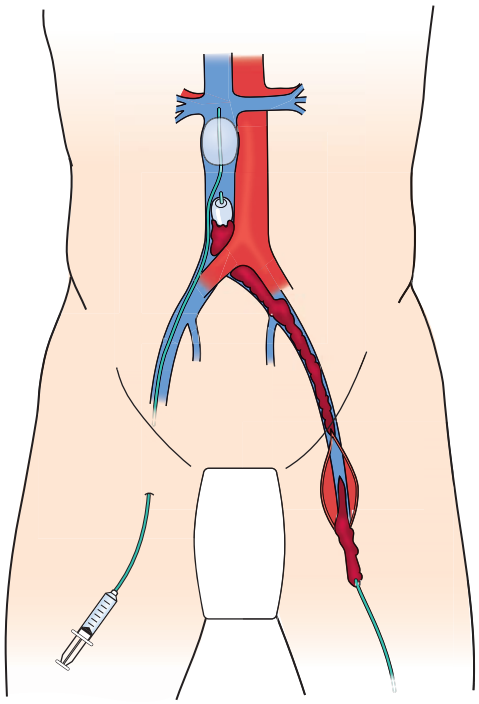

Figure 148.6 If a clot is present in the vena cava, caval thrombectomy can be performed with a protective balloon catheter inflated above the thrombus as an alternative to vena caval filtration.

of the AVF is to increase venous velocity but not venous pressure. Common femoral vein pressure is recorded before and after the AVF is opened. No increase in pressure should be observed when the AVF is opened. If the pressure increases, the proximal iliac vein should be reevaluated for residual stenosis or obstruction and the proximal lesion corrected. If the pressure remains elevated, the AVF is constricted to decrease flow and normalize pressure.

A piece of polytetrafluoroethylene or Silastic is placed around the saphenous AVF and a large permanent monofilament suture (No. 0) looped and clipped, with approximately 2 cm left in the subcutaneous tissue (Fig. 148.7A). This will serve as a guide for future dissection in the event that operative closure of the AVF becomes necessary; however, most do not.

If serous wound accumulation is observed, a diligent search for transected lymphatics is performed with careful ligation and coagulation. A closed suction drain is generally placed in the wound to evacuate any serosanguineous fluid that may accumulate postoperatively. The drain exits through a separate puncture site adjacent to the incision. The wound is closed with multilayered running absorbable sutures to achieve hemostatic and lymphostatic wound closure and ensure elimination of all dead space.

The distal posterior tibial vein is ligated. A small infusion catheter (pediatric feeding tube) is brought into the wound via a separate stab incision in the skin and inserted and fixed in the proximal posterior tibial vein (see Fig. 148.7B). This catheter is used for postoperative anticoagulation with UFH and predischarge phlebography. Anticoagulation via this catheter ensures maximum heparin concentration in the thrombectomized veins, as previously stated. A 2-0 monofilament suture is looped around the proximal posterior tibial vein (and catheter), and both ends exit the skin. The ends of the suture are passed through the holes of a sterile button, which is secured snugly to the skin when the catheter is removed. This obliterates the proximal posterior tibial vein at the time of catheter removal and eliminates the risk of bleeding. As mentioned, before removal of the catheter, an ascending phlebogram is performed through the catheter to assess patency.

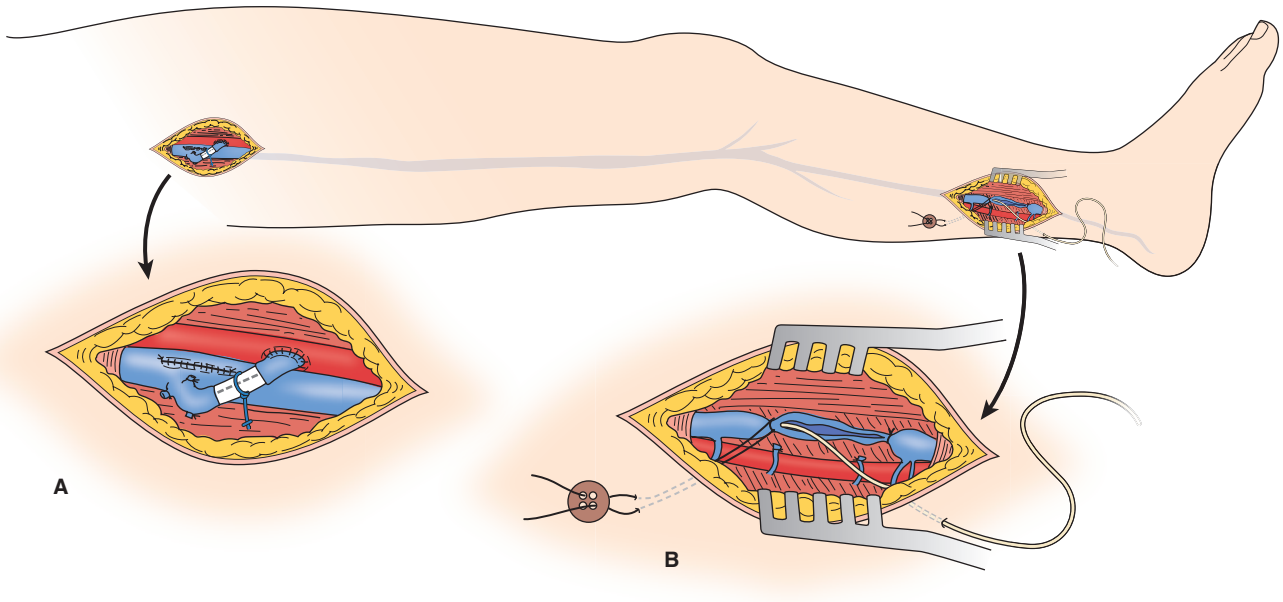

Figure 148.7 (A) Placement of a piece of polytetrafluoroethylene or Silastic around the saphenous arteriovenous fistula. A large permanent monofilament suture is looped and clipped, with approximately 2 cm left in the subcutaneous tissue. (B) Placement of a small infusion catheter (pediatric feeding tube) into the wound via a separate stab incision in the skin. It is inserted and fixed in the proximal posterior tibial vein.

Antibiotic ointment is applied to all wounds beneath sterile dressings. The patient's leg is wrapped snugly with sterile gauze and multilayered elastic bandages from the base of the toes to the groin. The posterior tibial vein catheter exits between the layers of the bandage.

Postoperative Care

Anticoagulation is continued with UFH at 800 IU/hr through the posterior tibial vein catheter attached to a pump on an intravenous pole with wheels so that the patient can ambulate. Before removal of the posterior tibial vein catheter, an ascending phlebogram is performed. Oral anticoagulation is begun when the patient awakens and resumes oral intake. Heparin infusion is continued for an overlap of 4 to 5 days if warfarin is used until the international normalized ratio reaches 2 to 3. Oral anticoagulation is continued for an extended period, generally for 1 year or more.

Intermittent pneumatic compression garments are used on both legs postoperatively when the patient is not ambulating. Before discharge, the patient is fitted for 30- to 40-mm Hg ankle-gradient below-knee compression stockings and instructed to wear the stockings from waking in the morning until bedtime. Randomized trials have demonstrated at least a 50% reduction in postthrombotic morbidity with the use of such stockings.[60,61]

If an IVC filter was used, it is removed early after completion of the procedure. When the patient is fully recovered and back to baseline activity, repeat venous duplex and venous function studies are performed to evaluate patency and vein valve function, which serve as a baseline for future studies.

CHOOSING THE APPROPRIATE TREATMENT OPTION

Risk Assessment

One concern of many physicians is the risk for procedure-related PE. Patients at highest risk for procedure-related PE are those with nonobstructive (free-floating) thrombus in the vena cava (see Fig. 148.3). Therefore it is important to know the proximal and distal extent of thrombosis and particularly the amount and level of vena caval involvement. This helps guide the decision whether vena caval filtration or other forms of embolic protection (i.e., balloon occlusion) are indicated.

Traditional contraindications to the use of thrombolytic agents that focus on bleeding risk are softened by direct intrathrombus infusion and the adoption of pharmacomechanical techniques. Reducing the dose and duration of lytic infusion lessens or eliminates a systemic response to the infused plasminogen activator. Circulating plasminogen activator inhibitors and antiplasmins serve to neutralize the systemic effects of lytic therapy if the dose is limited, thereby reducing bleeding risk, especially bleeding distant from the procedural entry site.

Patient Selection

Patients with IFDVT should be considered for a strategy of thrombus removal. Our current approach to patients with IFDVT is summarized in Fig. 148.8 and by the patient described

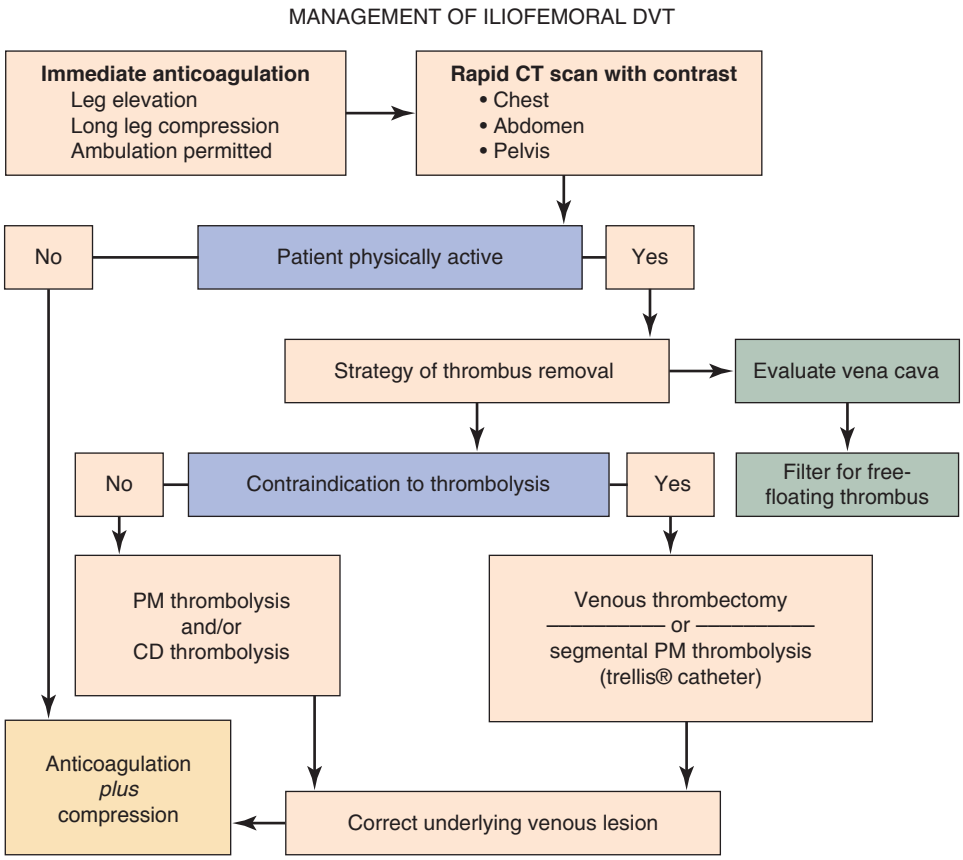

Figure 148.8 Algorithm illustrating our current treatment protocol for patients with iliofemoral deep venous thrombosis (DVT). *CD*, Catheter-directed; *CT*, computed tomography; *PM*, pharmacomechanical.

in Fig. 148.9. Assuming that the patient is ambulatory, contraindications to either surgical or catheter-based techniques should be objectively reviewed. In general, our approach is to offer all patients with IFDVT a strategy of thrombus removal unless a reason exists otherwise (see Fig. 148.8). Individuals with occlusive thrombus of the common femoral vein have effectively obliterated venous drainage from the lower extremity and are subject to severe postthrombotic morbidity. This is the ultrasound diagnostic equivalent of IFDVT. Although most patients in whom acute DVT is diagnosed are treated as outpatients, those with occlusion of the femoral vein should be admitted and considered for a strategy of thrombus removal.

Another subset of patients likely to have severe postthrombotic morbidity are those with thrombotic obliteration of the popliteal vein and the adjoining proximal tibial veins. Adequate collaterals around this area often do not develop, leaving patients with severe distal venous hypertension. This subgroup of patients should also be considered for a strategy of thrombus removal.

Pretreatment Evaluation

Patients with spontaneous, extensive venous thrombosis frequently have a clinically obvious etiology (trauma) or perhaps an occult cancer. Although we routinely performed a full thrombophilia evaluation earlier in our experience, we now know that it is unnecessary, as the patient's extensive DVT imparts such substantial risk for future recurrence that the risk conferred by the acute thrombotic event exceeds the risk of any identified thrombophilia.[62,63] A potentially serious issue is the underestimation of future thrombotic risk resulting from a negative thrombophilia evaluation. However, it is important to test first-degree female relatives of childbearing potential for factor V Leiden, prothrombin 20210 mutation, and antithrombin III, as the results may impact their care during subsequent pregnancy.

Importance of Imaging

The proximal and distal extent of thrombus should be well characterized in all patients. Imaging of the vena cava is important to assess the degree of vena caval involvement. If catheter-based techniques are being offered, a vena caval filter is recommended for patients with free-floating nonocclusive vena caval thrombus. During surgery, either proximal balloon occlusion of the cava or caval filtration is appropriate.

In patients with normal renal function, a computed tomography (CT) scan of the head, chest, abdomen, and pelvis with contrast enhancement is an important part of the pretreatment evaluation. In at least 50% of these patients an asymptomatic pulmonary embolus will be found. Although such emboli require no specific change in the treatment plan, the value of this diagnosis is often not appreciated until 3 to 5 days later, when

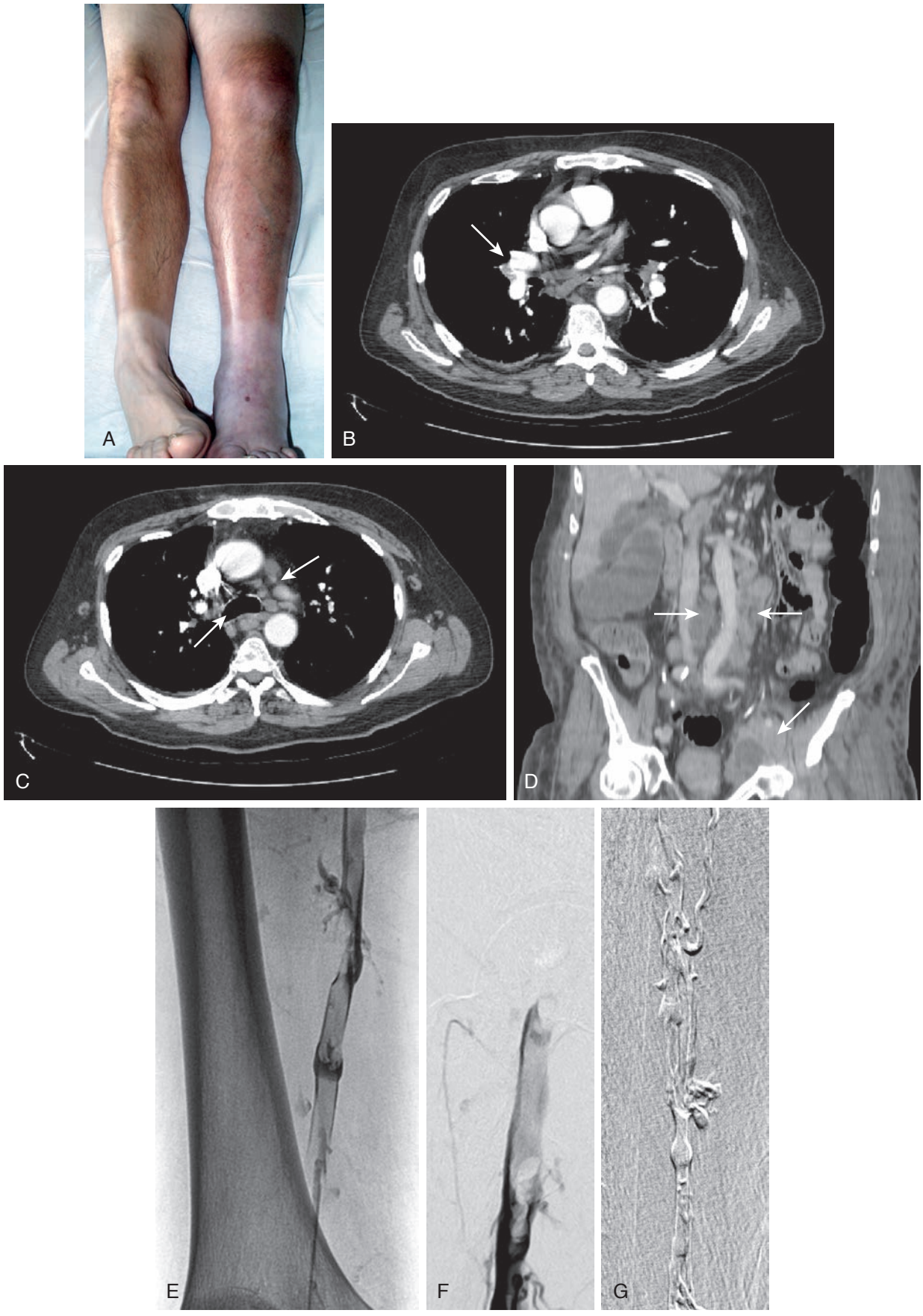

Figure 148.9 A 65-year-old man was referred with phlegmasia cerulea dolens of his left leg (A) 36 hours after major abdominal laparotomy. Venous duplex demonstrated clot in the posterior tibial veins extending to the external iliac vein. A contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis was performed and demonstrated asymptomatic pulmonary emboli (B) and mediastinal (C), retroperitoneal (C, *arrows*), and pelvic lymphadenopathy (D, *arrows*). The extensive thrombus is demonstrated by a catheter phlebogram of the femoral vein (E and F) and the silhouette of the calf thrombus (G) by the catheter in the posterior tibial vein at the ankle.

Continued

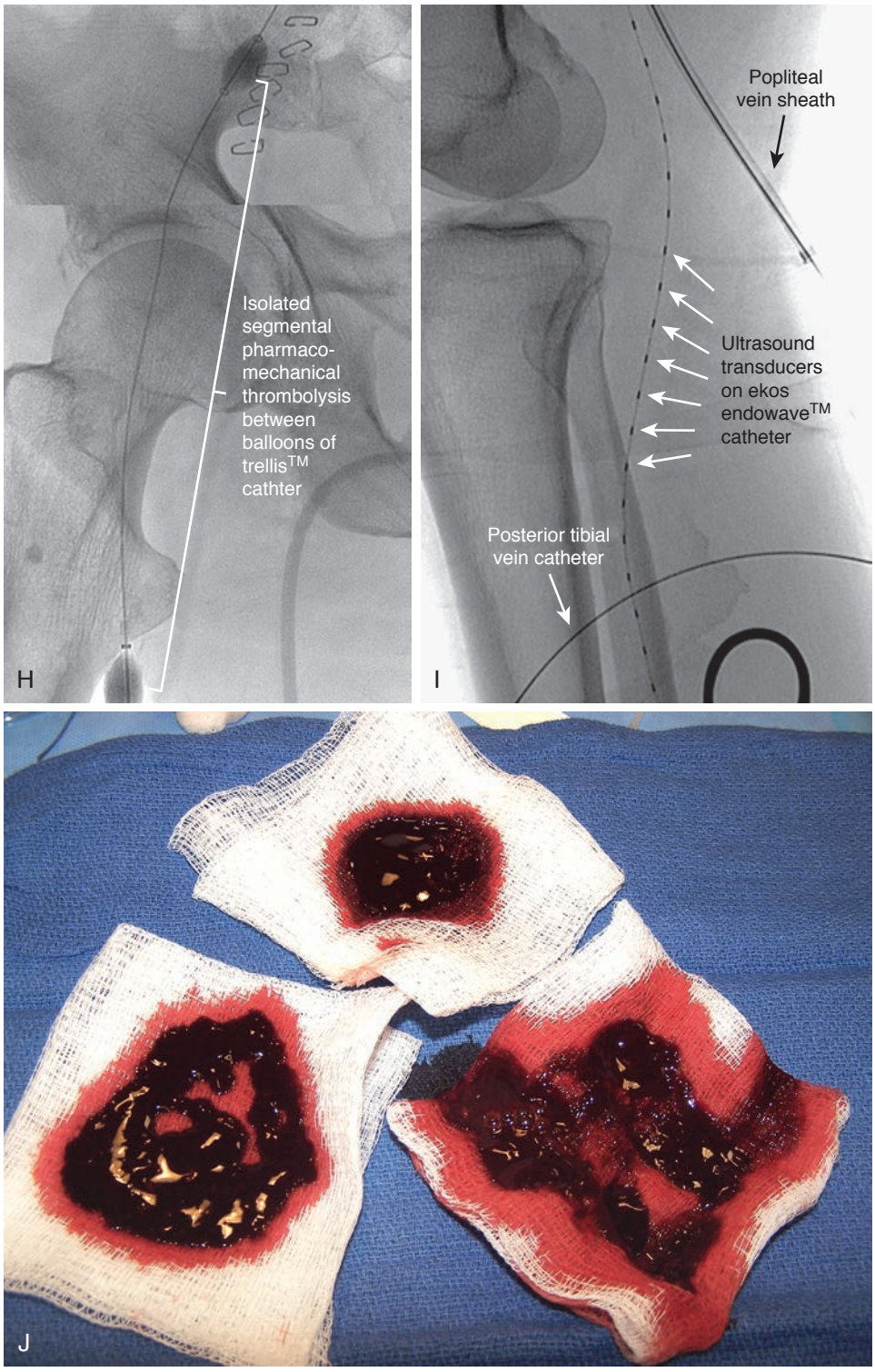

Figure 148.9, cont'd The bulk of the thrombus from the proximal popliteal vein to the common iliac vein was treated with the Trellis catheter via an ultrasound-guided popliteal vein approach (H). The clot in the posterior tibial and popliteal veins was treated with the EKOS EndoWave system (I). Liquefied and fragmented thrombus resulting from ISPMT was aspirated via the Trellis catheter (J).

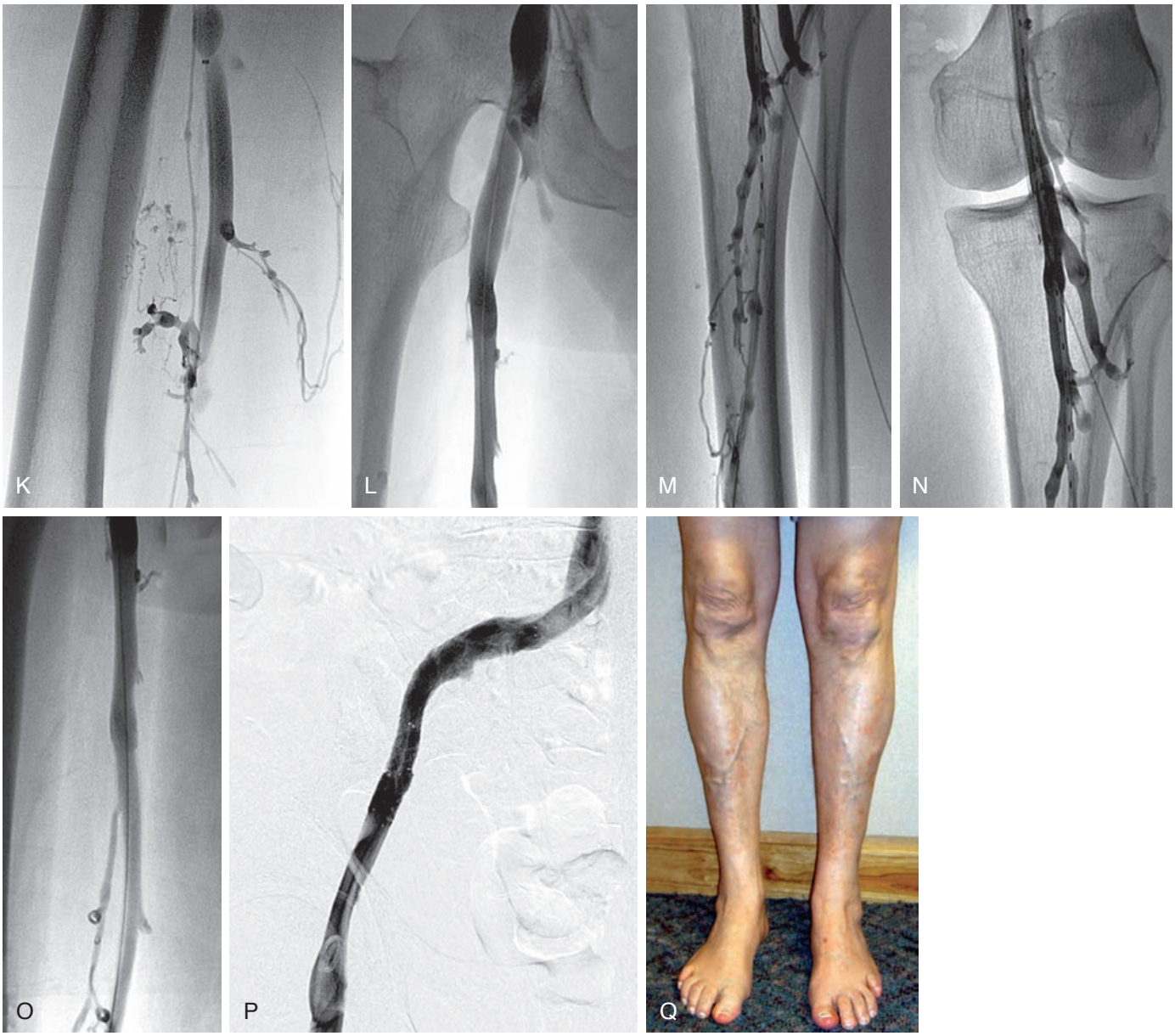

Figure 148.9, cont'd Segmental phlebography is performed to check the results of treatment before moving to an adjacent thrombosed segment (K and L). Residual thrombus is removed by rheolytic thrombectomy with the AngioJet, and the iliac vein compression is treated with a stent. A completion phlebogram shows patency of the calf, popliteal, femoral, and iliac veins as well as supple valve cusps, thus suggesting that valve function persists (M–P). The patient was treated with systemic chemotherapy for his underlying lymphoma. At 16 months (Q) the patient was asymptomatic, had no postthrombotic symptoms, maintained lower extremity venous patency with normal valve function, and fortunately had no evidence of lymphoma recurrence.

pleuritic chest pain develops in up to 25% of patients.[56] Without a previous diagnosis of PE, physicians may assume that this is a "treatment failure" or an embolic complication of either lytic therapy or venous thrombectomy. Realizing that this is merely a delayed manifestation of the previous PE assists in putting these symptoms in proper perspective. The CT scan often identifies additional thoracic, abdominal, or pelvic pathology (see Fig. 148.9B–D). Martinez and colleagues reviewed the results of CT scan evaluation of 47 patients with IFDVT and found PE in 48% and other unexpected thoracic, abdominal, or pelvic pathology in 23%.[64]

PUBLISHED GUIDELINES

It was gratifying that the 8th ACCP Consensus Committee on Antithrombotic Therapy for Venous Thromboembolic Disease made definitive recommendations regarding treatment strategies for thrombus removal in patients with acute IFDVT.[1] These recommendations were continued in the American Heart Association (AHA) guidelines[2] and those published by the SVS.[3] However, suggestions for thrombus removal as primary therapy for selected patients were dropped from the ACCP 2012 and 2016 guidelines, predominantly due to their focus on the

methodologic quality of the available studies. A strategy of thrombus removal for patients with IFDVT was validated by the CaVenT trial results, which were published 6 months after the ACCP 2012 guidelines. However, contemporary venous thrombectomy is an effective treatment option in patients who are not otherwise candidates for CDT or in medical communities where catheter-based techniques are not available.

The AHA Scientific Statement on the management of IFDVT states that CDT or pharmacomechanical CDT is reasonable as the first-line treatment of patients with acute IFDVT to prevent PTS in selected patients at low risk of bleeding complications (class IIA; level of evidence: B). Patients with IFDVT at centers that lack endovascular thrombolysis should be considered for transfer to a center with this expertise if indications for endovascular thrombolysis are present (class I; level of evidence: C). Surgical venous thrombectomy by experienced surgeons may be considered in patients with IFDVT (class IIB; level of evidence: B). Systemic fibrinolysis should not be given routinely to patients with IFDVT (class III; level of evidence: A). Stent placement in the iliac vein to treat obstructive lesions after CDT, pharmacomechanical CDT, or surgical venous thrombectomy is reasonable (class IIA; level of evidence: C). Following either operative venous thrombectomy or percutaneous catheter techniques, patients should receive the same intensity and duration of anticoagulation as patients not receiving a strategy of thrombus removal (class IIA; level of evidence: C).

Salient features of the SVS guidelines include the following: A recommendation against routine use of the term "proximal venous thrombosis" in favor of a more precise characterization of thrombi involving the iliofemoral or femoral popliteal venous segments grade (IA); early thrombus removal strategies in ambulatory patients with good functional capacity and a first episode of IFDVT of <14 days duration (grade 2C). A strategy of thrombus removal recommended in patients with limb-threatening ischemia due to iliofemoral venous outflow obstruction (grade IA); and suggests pharmacomechanical strategies over CDT alone if resources are available. Surgical thrombectomy should be considered if thrombolytic therapy is contraindicated (grade 2C).

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Comerota AJ. The ATTRACT trial: rationale for early intervention for IFDVT. *Perspect Vasc Surg Endovasc Ther*. 2009;21(4):221–224.

The ATTRACT trial has been fully enrolled (N = 692). Patients with acute femoropopliteal DVT and IFDVT were stratified and randomized to catheter-based strategies of thrombus removal versus anticoagulation. The primary endpoint is PTS at 2 years. There were no safety concerns during the treatment phase.

Comerota AJ, Grewal N, Martinez JT, et al. Postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis. *J Vasc Surg*. 2012;55(3):768–773.

This retrospective analysis of patients treated with CDT for IFDVT demonstrated a direct correlation of the amount of residual thrombus at the end of CDT with postthrombotic morbidity. Patients who had ≥90% lysis had no PTS.

Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*. 2012;379(9810):31–38.

This randomized trial of CDT added to anticoagulation versus anticoagulation alone for patients with IFDVT demonstrated significant benefit (reduced PTS) of CDT. The reduced postthrombotic morbidity was directly correlated with patency of the iliofemoral venous segment.

Kahn SR, Kearon C, Julian JA, et al. Predictors of the post-thrombotic syndrome during long-term treatment of proximal deep vein thrombosis. *J Thromb Haemost*. 2005;3(4):718–723.

This prospective evaluation of patients with acute DVT was the strongest predictor of severe postthrombotic syndrome (PTS). The odds ratio for patients with IFDVT to develop PTS was 2.23.

Plate G, Akesson H, Einarsson E, Ohlin P, Eklof B. Long-term results of venous thrombectomy combined with a temporary arterio-venous fistula. *Eur J Vasc Surg*. 1990;4(5):483–489.

The Scandinavian investigators report the long-term follow-up of patients with IFDVT randomized to operative thrombectomy and AVF with anticoagulation versus anticoagulation alone. Patients randomized to operative thrombectomy had better patency, lower venous pressures, and less postthrombotic morbidity.

A complete reference list can be found online at www.expertconsult.com.

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149 CHAPTER

Acute Upper Extremity and Catheter-Related Venous Thrombosis

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INTRODUCTION

Acute upper extremity deep venous thrombosis (DVT) characterizes a disease process that ranges from an acutely swollen and painful extremity to one that is asymptomatic. This condition can be classified as either primary or secondary. Primary upper extremity DVT is related to either effort thrombosis (i.e., Paget-Schroetter syndrome) or is idiopathic. Secondary upper extremity DVT develops in patients with either a cancer or an indwelling central venous catheter. As the prevalence of central venous catheter placement increases, secondary thromboses are increasingly outnumbering those related to primary causes.

The Computerized Registry of Patients with Venous Thromboembolism (RIETE) study is the largest known prospectively collected registry of all patients with DVT. Approximately 4.4% of patients in the registry have an upper extremity DVT, almost half of which are catheter-related.[1] Furthermore, in comparison with lower extremity DVT, patients who suffer from upper extremity DVT have a higher mortality rate (up to 48% vs. 13% at 6-months). The high mortality rate in this population is reflective of the associated severe comorbidities, rather than the central catheter or the thrombosis itself.[2]

In the United States, greater than five million catheters are inserted yearly to administer fluids, antibiotics, nutrition, and provide hemodialysis needs.[3] With an increasing number of central venous catheters inserted, the overall incidence of catheter-related venous complications, including thrombosis, sepsis, pulmonary embolism (PE), and death, is simultaneously becoming a considerable issue. There is certainly an elevated incidence of thrombosis in cannulated veins versus noncannulated veins. This was demonstrated in an autopsy study as the risk of venous thrombosis among cannulated versus noncannulated vessels was 36% versus 1.6%, respectively.[4,5] Therefore our discussion will focus on acute upper extremity catheter-related deep venous thrombosis.

CLINICAL FINDINGS

Patients with catheter-related upper extremity DVT can be asymptomatic. For example, in a study documenting catheter-related thrombosis in cancer patients, the authors demonstrated that asymptomatic thrombi were present in 29% of patients (range 5%-62%) versus symptomatic thrombi in 12% of patients (range 5%-54%).[6]

Abstract

Indwelling central venous catheter placement is associated with a significant incidence of upper extremity deep vein thrombosis (UEDVT). Prior data has demonstrated that an upper extremity deep venous thrombosis (DVT) can lead to pulmonary embolism, postthrombotic syndrome, and death. In patients with acute upper extremity deep vein thrombosis, full systemic anticoagulation is recommended with or without catheter removal for a period of 3 to 6 months.

Keywords

Upper extremity
DVT
anticoagulation
PICC
arm pain
arm swelling
RIETE
heparin bonded
central line

Erythema, pain, or swelling located at neck, chest, or arm are few of the common symptoms, if present.[7-13] In patients with significant disease, there is often tremendous engorgement of the veins along the chest wall or the extremity. In rare instances, phlegmasia cerulean dolens has been reported.[14,15]

Pulmonary embolism is known to occur in 5% to 20% of patients with upper extremity DVT. A prospective study of patients with upper extremity DVT routinely performed ventilation-perfusion scans to determine the prevalence of PE among all patients with upper extremity deep vein thrombosis (UEDVT). The scans demonstrated that 13 out of 86 (15.1%) patients developed a PE. The most common underlying comorbidity for these patients was cancer (31.4%). In addition, Monreal et al. found that the higher incidence of PE (20%) occurred in the patients that had DVT associated with an underlying indwelling catheter.[16,17] In many cases these are not hemodynamically significant.

Postthrombotic syndrome (PTS), consistent with a painful and swollen extremity after the acute episode, is also known to occur after upper extremity DVT. In a retrospective study by Hingorani et al., a 13-month follow-up of 170 patients yielded a 4% prevalence of symptoms consistent with PTS. However, others have reported the incidence of postthrombotic syndrome to be as high as 35%.[18]

DIAGNOSTIC STRATEGIES

Duplex ultrasonography is the mainstay for diagnosis of most upper extremity DVT. It is noninvasive and more cost-effective than other diagnostic modalities. The diagnosis is confirmed with augmentation maneuvers without clinical response in flow, compressibility of the venous segment, or the signal echogenicity in B-mode along a venous segment.[19]

A 2009 review article demonstrated duplex ultrasonography to be 86% to 100% specific and 78% to 100% sensitive in the diagnosis of upper extremity DVT. Diminished sensitivity of duplex ultrasonography may be seen with studies that incompletely assessed the veins, or when the thrombus was located at the proximal subclavian or brachiocephalic veins. Furthermore, a prospective study in 66 patients with leukemia evaluated the role of ultrasonography and venography to evaluate patients with asymptomatic upper extremity DVT. These patients underwent bilateral venography and duplex ultrasound evaluation. The authors found an overall prevalence of 29% upper extremity DVT in this cohort. They then concluded that the sensitivity of their ultrasound (37%) was far inferior to venography (79%). It was also determined by these authors that the most common missed thrombotic sites were internal jugular vein during venography and subclavian vein during duplex ultrasonography.[20] It was also their recommendation that in those patients with suspected thrombosis, but without a confirmed diagnosis based on one test, additional testing with or without the use of adjunctive maneuvers should be performed.

We recommend that if the duplex ultrasound fails to reveal a thrombus and clinical suspicion is elevated for acute upper extremity DVT, then obtain venography by either a computed tomography (CT) or magnetic resonance (MR). Use of D-dimer may be useful in this circumstance; if negative, the likelihood of DVT is almost nil. Although catheter-directed venography is seldom used, it remains the gold standard to determine central thrombosis.

RISK FACTORS AND PREVENTION

Biomarkers

Biomarkers, along with clinical exam and blood tests, are often utilized to identify patients at high risk for thrombosis. In a 2014 study by Kleinjan et al., the authors aimed to generate a management strategy for patients based on a risk assessment score.[21] They used the clinical decision score to predict UEDVT based on a single point assigned to the presence of catheter in a venous system, localized pain, or unilateral edema. If another diagnosis was at least as likely to be present as thrombosis, a negative point was assessed to the patient and resulted in risk of 12%, 20%, or 70% for 1, 2, or 3 points, respectively.

A prospective study by Boersma et al. evaluated 212 patients with a 9% incidence of catheter-related thrombosis. The authors determined that patients with symptomatic thrombosis presented with elevated levels of factors VIII ($P = .023$), elevated white blood cell count ($P = .042$), and plasminogen activator inhibitor-1 ($P = .008$).[22] The authors advocated for the use of thromboprophylaxis in this selected population.

Role of Thromboprophylaxis

While limited prior series had shown promise with the use of chemical thromboprophylaxis using anticoagulation for all patients with central catheters, published guidelines and most recent data have failed to support the idea. One of such studies was by Timset et al. in 1998. The authors of the study demonstrated that for age ≥65 years ($P = .001$), internal jugular vein use ($P = .005$) and absence of therapeutic anticoagulation at time of catheter placement ($P = .04$) were all associated with increased risk of thrombosis.[23] Further support of anticoagulation prophylaxis comes from a small series of cancer patients that were evaluated by D'Ambrosio et.al. Their analysis determined a lower risk of symptomatic catheter related thrombosis than control among patients that received anticoagulation for prophylaxis (RR = 0.61, 95% CI, 0.42-0.88).[24] In addition, Monreal demonstrated in a 1994 series that dalteparin infusion 2 hours prior to central catheter insertion in cancer patients reduced the risk of thrombosis.[25] Yet the results have been largely irreproducible, and the role of chemical thromboprophylaxis use prior to or during catheter insertion is not clearly supported.[26] Therefore we do not recommend routine anticoagulation for patients with central venous catheters.

Measures to address catheter thrombogenicity have also been addressed to diminish thromboses. Murray et al. demonstrated increased catheter thrombogenicity of polyethylene catheters compared with polyurethane catheters and rigid catheters compared with compliant catheters.[27] A number of authors have also lamented that less trauma to the vessel wall during

insertion and during the life of the implant, as well as the persistence of the catheter to remain in an optimal location, was paramount in safeguarding against catheter-related thrombosis.

Moreover, the role of heparin-bonded catheters remains inconclusive at best. Their prophylactic effects against upper extremity DVT in adults have not been consistent. In 2014 a Cochrane review compared heparin-bonded catheters with nonheparin bonded catheters in the pediatric population. The review failed to demonstrate a difference in thrombotic outcomes (RR = 0.34, 95% CI, 0.01-7.68).[28]

Catheter/Patient-Related Causes

It is prudent to understand that thrombosis can be due to multiple causes: patient-related, catheter-insertion related, or a combination of both. One of the earliest series to warn against the dangers of indwelling catheters associated with upper extremity DVT was completed in 1970. Tilney and Griffeths documented their 25-year experience and demonstrated that 31 of 48 (65%) of upper extremity DVT were associated with catheters.[29] In 1998 Horattas et al. documented their cohort of patients with upper extremity DVT and found that 39% were catheter-related and 12% of those patients with upper extremity DVT presented with a PE. Horattas et al. further found that the risk of upper extremity DVT increased with larger catheter diameter, multiple punctures needed during insertion, and overall duration of catheter placement.[30]

A patient's history of a previous thrombotic event, inherited thrombotic disorders, malignancy, and an acute infection have also been associated with an increased risk of thrombosis. A retrospective study evaluated 105 consecutive cancer patients undergoing chemotherapy with clinical suspicion of upper extremity DVT. The authors concluded that patients with acute catheter-related infection were more likely to have DVT than those without acute infection (RR 17.6, 95% CI, 4.1-74.1).[31]

Peripherally inserted central venous catheter (PICC) associated UEDVT has an incidence of 1.6% to 3.5%. Large PICC diameter (≥ 5Fr) (OR = 3.9, 95% CI, 1.1-13.9) and concurrent malignancy (OR = 4.1, 95 %CI, 1.9-8.9), as demonstrated in a study among all patients that underwent PICC placement over a 1-year period, were found to be associated with a higher risk of development of upper extremity DVT.[32] In a study of a fluid analysis model utilizing different PICC diameters, the authors noted a decrease in up to 80% of segmental venous flow rate with the use of a 6 Fr. PICC.[33] This finding was consistent with a prospective study with an established increased risk of symptomatic DVT in patients with 4 Fr. PICC (up to 2.9%) compared with patients with a 6 Fr. PICC (up to 9.8%). Another study to demonstrate the flow limit concept was performed in patients with cardiac lead devices. The study retrospectively evaluated patients with implanted cardiac leads and demonstrated a higher risk of upper extremity DVT in patients with multiple pacemaker leads (27%) versus a single pacemaker lead (7%; RR = 3.8, 95% CI, 1.0-15.0).[34]

In addition, catheter site selection and distal tip position have also been demonstrated to be of great significance. The French National Federation of Cancer Centers workgroup on Standards, Options, and Recommendations established their guidelines on prevention of catheter related thrombosis by reviewing 36 publications over an almost three decade period (1990–2007).[35] Their analysis found that catheter position is one of the most important factors and recommended the distal tip of all central venous catheters be located at the junction of right atrium and the superior vena cava.

A systematic review of an internal jugular vein versus subclavian vein insertion site for central venous catheters found that internal jugular vein route had a lower rate of malposition (5.3% vs. 9.3%; RR = 0.66, 95% CI, 0.44-0.99).[36] Yet the analysis failed to demonstrate a difference in thrombotic outcomes based on site of insertion. Furthermore, a study evaluating left versus right side central catheter insertion in cancer patients found that the incidence of thrombosis was much more common after left-sided catheter insertion (25.6%) than right-sided catheter insertion (6.8%). This result was reproducible in two additional studies that documented a relative risk in cancer patients of 2.6 and 4.4 for upper extremity DVT occurring after left-sided insertion and right-sided catheter insertion, respectively.[37]

The correlation between the routes of catheter insertion to incidence of DVT was addressed in a 2012 Cochrane review. The authors evaluated three randomized controlled trials and compared internal jugular vein versus subclavian vein insertion sites of central venous catheters and assessed risk for associated thrombosis.[38] The review failed to find a difference in thrombotic complications (RR = 1.97, 95% CI, 0.87-4.48) between internal jugular or subclavian vein route. The analysis did find a significantly increased risk of thrombosis for femoral vein insertion compared with subclavian vein catheter insertions (RR = 11.53, 95% CI, 2.80-47.52). The authors concluded that the subclavian route was preferred to femoral vein insertion for central venous catheters, but no clear thrombotic difference was noted between the internal jugular and the subclavian vein routes.

TREATMENT

The standard treatment for upper extremity DVT is anticoagulation. We present a proposed treatment algorithm (Fig. 149.1). These data, in large part, have been extrapolated from lower extremity data. In addition, the recent addition of direct oral anticoagulants as an effective and efficacious treatment modality for lower extremity DVT should yield them to be considered as enhanced alternatives to vitamin K antagonists.

The American College of Chest Physicians' (ACCP) guidelines recommend UEDVT to be treated with 3 to 6 months of anticoagulation and removal of the central catheter if the patient does not require it.[39-41] The role of thrombolytic agents or thrombectomy is not clearly established, but the use of this therapy may be beneficial in patients with phlegmasia.[42] Specifically, according to the 2016 *Chest* guidelines, the following cohort of patients may benefit from catheter-directed thrombolysis: those with severe symptoms, thrombus involving most of the subclavian and axillary veins, symptoms present for less than 14 days, good functional status, life expectancy greater than 1 year, and low risk for bleeding.[43]

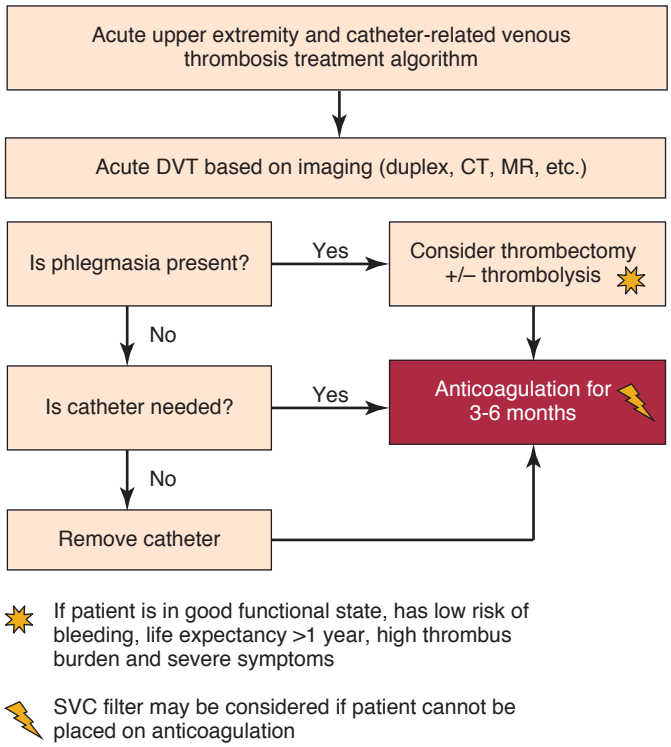

Figure 149.1 Proposed treatment algorithm for upper extremity catheter-related venous thrombosis treatment. *CT*, Computer tomography; *DVT*, deep venous thrombosis; *MR*, magnetic resonance.

Superior vena cava filter placement to prevent PE may be considered in a subset of patients that are unable to receive anticoagulation or catheter removal.[44-46] It is crucial to note the study by Usoh et al. demonstrated that a high degree of caution should be noted in younger male patients who undergo superior vena cava filter placement. They documented that among 154 patients with a mean follow-up of 256 days after filter placement, there were three cases of caval perforations. All three cases occurred in males less than 60 years old. No other cases of perforation occurred in older males or females of any age. Whether an SVC filter decreases mortality is unknown.

CONCLUSION

Acute upper extremity venous thrombosis occurs frequently after the insertion of indwelling catheters. Although patients with this condition may remain asymptomatic, some will develop a classic clinical picture including pain, erythema swelling, and even signs of PE. If possible, the indwelling catheter should be removed when a catheter-related upper extremity DVT is noted. However, if the patient does not have a safe alternative, the catheter can be left in place. The current treatment guidelines recommend full anticoagulation for a period of 3 to 6 months.

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A complete reference list can be found online at www.expertconsult.com.

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150 CHAPTER

Superficial Thrombophlebitis and Its Management

SUMAN WASAN

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Superficial venous thrombophlebitis (SVT) has been the focus of increased attention because of growing recognition of its potential morbidity and mortality associated with it. Although a global disorder, SVT develops in approximately 125,000 people per year in the United States; nonetheless, it is underestimated because many cases go unreported.[1]

It has been historically assumed that SVT is a self-limited process of little consequence and of small risk. However, new evidence on the natural history of SVT has led to improvements in evaluation and treatment. A meta-analysis reported a 6% to 44% incidence of deep venous thrombosis (DVT), a 20% to 33% incidence of asymptomatic pulmonary embolism (PE), and a 2% to 13% incidence of symptomatic PE in patients in whom SVT is diagnosed.[2] Improved diagnostic evaluation of SVT with duplex scanning, lung scanning, and blood tests has helped to identify predisposing risk factors and potential complications.

This chapter examines current data regarding SVT and its management, with the goal of improving recognition and treatment of the underlying disorders to prevent recurrence and its life-threatening complications.

EPIDEMIOLOGY AND PATHOGENESIS

Although SVT is a frequently observed condition, its incidence and prevalence have never been adequately assessed. The classic Tecumseh Community Health Study from 1973 reported that the incidence of SVT increases with age from 0.05 per 1000 per year in males in their third decade to 1.8 per 1000 per year in their eighth decade. In females the incidence similarly rises from 0.31 per 1000 per year to 2.2 per 1000 per year from their third decade to their eighth decade.[3] Moreover, other studies have also demonstrated an increased prevalence of SVT in females.[4,5]

Overall, the incidence of lower extremity SVT has been reported to be 3% to 11% in the general population. A useful classification is the recognition that SVT may occur in two forms, those with, and those without varicose veins, or alternatively, SVT may be primary involving the vein wall only or secondary involving a more systemic inflammatory process. Primary SVT is most common in the saphenous veins and their tributaries, followed by the upper extremity cephalic and basilic veins. The greater saphenous vein (GSV) is affected in 60% to 80% cases, followed by the small saphenous vein (SSV) in 10% to 20%, and bilateral lower extremity SVT in 5% to 10%.[6] Patients with varicose veins are affected far more frequently than in the general population, with a prevalence of SVT ranging from 4% to 62%.[3,5,6]

Risk factors can be classified in accordance with Virchow's triad: endothelial injury from trauma or insertion of venous catheters; venous stasis as seen in varicosities; and hypercoagulable states such as factor V Leiden, prothrombin G mutation, protein C and protein S deficiency, antithrombin III abnormalities, and malignancies including both solid tumors and hematologic

conditions of Hodgkin lymphoma, leukemia, thrombocytosis, polycythemia vera, cryoglobulinemia, and nocturnal paroxysmal hemoglobinura.[6,7] Patients in whom SVT develops without an inciting physical event or varicosities may need to be fully evaluated for the presence of such disorders.

Other secondary causes for the development of SVT include the use of oral contraceptives, hormonal replacement therapy, pregnancy, obesity, prolonged immobilization, recent surgery, trauma, sclerotherapy, history of venous thromboembolism, and some drugs (e.g., diazepam, amiodarone, vancomycin, heroin, some chemotherapy). Intravenous catheter use with or without bacterial infection places patients more at risk for the development of SVT.[3,5-8] In addition, patients with autoimmune disorders, including systemic lupus erythematosus and vasculitis, such as Behçet and Buerger disease, have also been identified as being susceptible to the development of SVT. A 2006 review of 2319 patients with Behçet's disease found that 14.3% of these patients have vascular involvement. Of these 332 patients, 53.3% had SVT and 29.8% had DVT.[9] Patients with Buerger disease appear to have an increased incidence of SVT because the inflammatory process involves small arteries and veins of the extremities. It can be diagnosed from biopsy findings of acute superficial thrombophlebitis showing the characteristic acute phase lesion—inflammation of all three layers of the vessel wall with occlusive cellular thrombosis.[10]

The main concern related to SVT is the likelihood that the thrombus will extend into the deep veins, causing DVT and potential PE. Several older studies have evaluated this risk especially in relation to the proximity of GSV SVT to the deep veins. Chengelis et al. followed 263 patients with isolated SVT and performed follow-up ultrasound at 2 to 10 days (mean 6.3 days).[11] Thirty (11%) patients experienced progression to DVT while not receiving anticoagulation. The most common site was propagation of the SVT in the GSV into the common femoral vein. In a small retrospective review, 185 patients with SVT and 370 age- and sex-matched controls were evaluated.[12] A minority (13%) received nonsteroidal antiinflammatory drugs (NSAIDs) or rarely LMWH therapy. At 6 months, overall 2.7% had developed DVT and 0.5% PE. SVT conferred a 10-time increased risk of developing DVT compared with controls without SVT. This study represents an estimate of the natural history of SVT because few patients received pharmacologic management. Another focused study evaluated the incidence of PE in 21 patients with isolated SVT in the thigh.[13] Nuclear perfusion lung scans were performed within 3 hours of SVT diagnosis and demonstrated seven patients with PE (33%), including one symptomatic patient. Of note, there were no significant differences in the distance of the SVT from the common femoral vein, or the presence of common risk factors for thrombosis compared with those with SVT that did not experience a PE. Although a small study, these findings highlight the potential serious consequences of SVT and suggest the need for anticoagulant therapy to prevent these complications.

Two recent large studies have evaluated the epidemiology and natural history of SVT in patients, most of whom received medical therapy. In the POST trial, Decousas et al. prospectively followed a cohort of 844 consecutive patients with symptomatic SVT of the lower limbs confirmed by ultrasound testing.[14] Patients with recent surgery within 10 days or SVT due to sclerotherapy in the previous 30 days were excluded. Patients were initially assessed for concomitant DVT, and then those with isolated SVT (634 patients) were followed with ultrasound again at 10 days and then at 3 months. A secondary outcome was overall mortality at 3 months. DVT or PE was confirmed in 24.9% of patient with SVT (82 patients with proximal DVT, 33 patients with PE). In 41.9% of patients with DVT, both proximal and distal, the DVT was not contiguous with the SVT. Of 634 patients with SVT, 90.5% received one or more anticoagulant medications, mostly therapeutic LMWH. Sixty patients (10.2%) had venous surgery. Fourteen patients were lost to follow-up. Of the remaining 586 patients, 58 had thromboembolic complications (10.2%), including seven with symptomatic proximal DVT, three with PE, and five with extension of SVT to DVT. Multivariate analysis showed that male sex, history of DVT or PE, previous cancer, and no varicose veins were independent risk factors for symptomatic VTE at 3 months including recurrence or extension of SVT.

A recent pooled analysis of the POST study and the OPTIMEV trials involving 1074 cases revealed that in symptomatic patients with SVT, only male sex significantly and independently increased the risk of VTE recurrence after multivariate analysis. Cancer and saphenofemoral/popliteal junction proximity were associated with VTE recurrence on univariate analysis.

The OPTIMEV study evaluated 788 patients with SVT of 8256 patients that were referred for VTE.[15] The median age of these patients was 65 years, 36% were men and 16% were inpatients. Similar to the POST study, 29% were found to have concomitant DVT. Patients with both SVT and DVT had risk factors of presence of nonvaricose veins involved, age greater than 75 years, inpatient status, and active cancer, compared with isolated SVT, which was independently associated with anticoagulant treatment at inclusion and pregnancy or post-partum state. Compared with SVT of varicose veins, SVT in nonvaricose veins was a strong risk factor for concurrent DVT but did not convey a higher risk of 3-month adverse outcomes of death, VTE recurrence, or bleeding. In this study, 76% of those with isolated SVT were treated with anticoagulants, including 92.5% with full-dose LMWH.

More recently, there has been greater awareness of the presence of hypercoagulable states in patients with SVT. These patients have a higher probability of developing DVT and recurrent SVT and may require long-term anticoagulation to prevent complications. Milio et al. evaluated 107 patients with unprovoked SVT for common thrombophilic conditions.[16] The patients underwent duplex evaluation at baseline and every 48 hours for 8 days, with notation whether the SVT occurred in varicose or nonvaricose veins. In the overall cohort, factor V Leiden was detected in 22.4%, MTHRF in 17.7%, and factor II G20210 mutation in 8.4%. Patients with thrombophilia and SVT in nonvaricose veins had a higher rate of extension of thrombus to deep veins. However, because all patients were treated with either LMWH or NSAIDs and the results were not analyzed by treatment group, it is difficult to draw definitive conclusions regarding the role of thrombophilia and DVT extension. Similar

studies have supported the presence of acquired and inherited thrombophilic disorders as being a risk factor for the development of SVT, such as factor V Leiden and prothrombin (G20210A) gene mutations; deficiencies of antithrombin, heparin cofactor 2, protein C, and protein S; lupus anticoagulant; anticardiolipin antibodies; and abnormal fibrinolytic activity.[3,5,9,10,17-19]

An analysis published in 2014 including 1294 patients with SVT concluded that in patients with SVT not associated with varicose veins, malignancy, or autoimmune disease, thrombophilia screening may be considered due to a higher incidence of thrombus progression.[20]

Although a number of studies have described the pathophysiology and various changes that take place in leukocyte–vessel wall interactions, cytokines/chemokines, and various other factors involved in the development and resolution of DVT, data on changes in patients with SVT have not been identified. Although some authors have alluded to the observation that the underlying pathologies of SVT and DVT may be analogous, this viewpoint remains mostly unsupported to date.

CLINICAL PRESENTATION

Evaluation for SVT by physical examination is based on the presence of erythema and tenderness in the distribution of the superficial veins and with the thrombosis being suspected by a palpable cord. Pain, erythema, and swelling are the most common symptoms.[21] There are a number of conditions discussed later that present unique risk factors or clinical presentations of SVT.

Superficial Thrombophlebitis With Varicose Veins

The most common predisposing risk factor for the development of SVT is varicose veins. Because it has been reported that DVT will develop in only 3% to 20% of SVT patients with varicose veins as compared with 44% to 60% of SVT patients without varicose veins,[22,23] therefore it appears that patients with varicose veins may have a different pathophysiology from those without varicose veins.

SVT involving varicose veins may remain localized to the cluster of tributary varicosities or may extend into the GSV.[5,6,10,24,25] SVT of varicose veins themselves may occur without antecedent trauma. SVT is frequently found in varicose veins in conjunction with venous stasis ulcers. This diagnosis should be confirmed by duplex ultrasound because the degree of SVT may be much greater than that based solely on clinical examination. SVT in varicosities may manifest as tender nodules with localized induration and erythema.

Traumatic Thrombophlebitis

Traumatic SVT is often seen in individuals using illicit drugs or undergoing drug therapy in a hospital or outpatient setting. It is associated with direct endothelial injury from the intravenous catheter used for the infusion of medications and irritating solutions, particularly when the indwelling catheter has been in place for long periods. Its onset is usually heralded by the development of pain, tenderness, and erythema at the site of catheter insertion or infusion. Treatment usually consists of cessation of the infusion, removal of the offending access device, and sometimes anticoagulation depending on the severity of symptoms and underlying hypercoagulable condition. The induration may take weeks to months to resolve.

Septic and Suppurative Thrombophlebitis

Suppurative SVT (SSVT) is also associated with the use of an intravenous cannula; however, SSVT may cause additional morbidity because of its association with septicemia. Signs and symptoms of SSVT include pus at an intravenous site, fever, leukocytosis, and local intense pain.[26] Aerobic, anaerobic, and mixed infections have been reported in SSVT. Organisms associated with SSVT include *Staphylococcus aureus*, *Pseudomonas* species (spp.), *Klebsiella* spp, *Enterococcus* spp, *Fusobacterium* spp, and recently, fungi such as *Candida* spp.[26] Treatment begins with removal of the foreign body and intravenous administration of antibiotics. Excision of the vein is rarely needed to clear the infection, although occasionally speeds the healing process.

Migratory Thrombophlebitis

Migratory thrombophlebitis was first described by Jadioux in 1845 as an entity characterized by repeated thrombosis developing in superficial veins at varying sites but most commonly in the lower extremity.[25] This entity may be associated with carcinoma (Trousseau syndrome) and may precede diagnosis of the carcinoma by several years. Consequently, evaluation for occult malignancy is warranted when the diagnosis of migratory thrombophlebitis is made. Migratory thrombophlebitis also occurs in the presence of some forms of vasculitis such as Behçet disease, Buerger disease, and polyarteritis nodosa.[7]

Mondor Disease

Mondor disease is defined as thrombophlebitis of the thoracoepigastric vein of the breast and chest wall (Fig. 150.1). It is thought to be associated with breast carcinoma or hypercoagulable states, although cases have been reported with no identifiable cause.[18] Tender, cordlike structures can be seen extending from the lower portion of the breast toward the costal margin or in the anterolateral aspect of the breast.[27] The condition is considered benign and self-limited, and treatment is conservative, rarely involving systemic anticoagulation.[28]

The term *Mondor disease* has also been applied to SVT of the dorsal vein of the penis. This phenomenon occurs in patients with DVT, after hernia operations, and in association with excessive sexual intercourse. Treatment consists of NSAIDs and dorsal penile vein resection if the symptoms are refractory.[29]

Small Saphenous Vein Superficial Thrombophlebitis

Although the bulk of attention has been focused on SVT of the GSV, SVT of the SSV is also clinically significant. SSV SVT may

Figure 150.1 Mondor disease: superficial thrombophlebitis of the thoracoepigastric vein of the breast.

progress to popliteal DVT. In a group of 56 patients with SSV SVT, 16% had PE or DVT.[24] In one study, it was found that 65.6% of 32 patients with SSV SVT also had DVT over a 1-year period.[30] Therefore it is crucial that patients with SSV SVT be treated similarly to those in whom GSV SVT is diagnosed—the same careful duplex examination, follow-up, and anticoagulation or ligation if the SVT approaches the popliteal vein.

Upper Extremity Superficial Thrombophlebitis

Although very little appears in the literature, upper extremity SVT often results from intravenous cannulation and infusion of caustic substances that damage the endothelium. Typically, the basilic or cephalic veins are involved particularly if the catheter is inserted at or near the antecubital fossa. Interestingly, progression of upper extremity SVT to upper extremity DVT or PE is less common when compared with lower extremity SVT.[31] Initial treatment of upper extremity SVT is catheter removal followed by conservative measures with anticoagulation occasionally required.

Superficial Thrombophlebitis After Endovascular Venous Obliteration

Minimally invasive endovascular techniques have emerged and gained popularity as alternatives to GSV ligation and stripping for GSV insufficiency and treatment of varicose veins. Endovenous laser ablation and radiofrequency ablation (RFA) have become widespread because of superior pain scores and feasibility as office-based procedures. In a prospective study of 67 patients undergoing EVLT and 66 patients undergoing RFA of the GSV or SSV, the rate of SVT was 1.5% in the EVLT group compared with 0% in the RFA group.[32] In another prospective study of 155 patients who underwent RFA of the GSV or SSV, only one patient (1.4% treated veins) developed SVT that occurred at a puncture site.[33] The incidence of SVT was higher in 150 patients who underwent SSV RFA (4%).[34] Zuniga et al. also reported a higher incidence of SVT of 10% to 15% in 667 RFA procedures of the GSV.[35] A meta-analysis of 104 studies evaluating the use of endovenous foam sclerotherapy for the treatment of venous disorders found an incidence of SVT of 11%.[36] This is somewhat higher compared with what has been reported for other endovenous procedures. Similarly, in a large randomized prospective study of 500 consecutive patients comparing EVLT, RFA, foam sclerotherapy, and stripping for GSV varicose veins, SVT occurred in 4 patients (3.2%) undergoing EVLT, 12 (9.6%) patients undergoing RFA, 17 patients (13.7%) with foam sclerotherapy, and 5 patients (4%) with surgical stripping.[37]

DIAGNOSIS

A positive diagnosis of SVT is primarily established by identifying the clinical and physical signs described earlier. Typically, pain, erythema tenderness, and induration corresponding to one or more superficial veins or dilated varicose veins are evidence with possible edema over the inflamed vein. Painful "cords" are palpable, and fever or leukocytosis may be present if associated with a systemic infection. Typically, the inflammatory reaction may last 2 to 3 weeks, and either vein fibrosis or vein recanalization occurs over the ensuing 6 to 8 weeks. Postinflammatory hyperpigmentation may occur and last several months.[7] However, the potential presence of occult or symptomatic DVT or PE concomitantly with SVT warrants further imaging studies. A study of 141 patients with SVT of the GSV found a significantly greater thrombus extension when examined by ultrasound compared to physical exam, affirming the value of imaging for SVT evaluation.[38] A small study found that recurrent SVT correlated with thrombus in tributary veins, but other risk factors of varicose veins, previous DVT, cancer, or hypercoagulable state were not predictive.[39]

Duplex ultrasound scanning has become the initial test of choice for the diagnosis of DVT and evaluation of SVT since first introduced by Talbot in 1982. The availability of reliable duplex ultrasonography of the deep and superficial venous systems has made routine determination of the location and incidence of DVT in association with SVT precise and practical (Fig. 150.2; see Chapter 23). Furthermore, the extent of involvement of the deep and superficial systems can be more accurately assessed with this protocol. Duplex ultrasound imaging also offers the advantage of being inexpensive and noninvasive and can be repeated for follow-up examination. Because venography may contribute to the onset of phlebitis and duplex imaging affords an accurate diagnosis, venography is not a first choice for investigation. Although initial studies generated enthusiasm for the use of scintigraphy and computed tomographic venography, their poor specificity and lack of anatomic detail have led to duplex ultrasonography remaining the primary diagnostic modality for SVT.

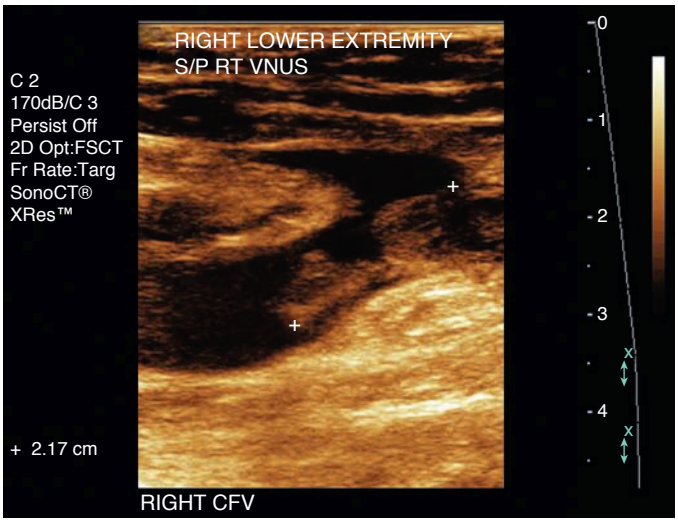

Figure 150.2 Ultrasound image of thrombophlebitis with free-floating thrombus extending from the great saphenous vein into the femoral vein.

Patients with SVT may or may not have elevated levels of D-dimer, thus offering little assistance with respect to the negative or positive predictive value of the disease. Blood tests in patients with SVT should be directed toward testing for acquired and congenital hypercoagulable states or malignancies if clinically indicated, particularly in patients with nonvaricose vein SVT.

TREATMENT

Treatment depends on the cause and location of the SVT. The goals of therapy are decreasing the acute symptoms of SVT including pain and erythema and preventing potential serious complications such as DVT and PE, as well as extension or recurrence of SVT. Historically, treatment was dictated by the proximity of the thrombus to the deep veins. Treatment for SVT has evolved from primarily surgical options to emphasis on medical treatment with the introduction of LMWH. Although warm compresses and compression hose have been recommended, there are little data supporting their use. A trial of 73 patients with SVT comparing use of compression stockings for 1 week compared with no compression revealed no difference in quality of life, pain, or use of analgesics, although thrombus regression measured on ultrasound was faster in the compression group.[40]

LMWH

One of the first trials evaluating modern medical management of SVT was the STENOX trial, a randomized double-blind trial of 427 patients with acute SVT of at least 5 cm length of the legs.[41] Patients were randomized to receive enoxaparin 40 mg daily, enoxaparin 1.5 mg/kg daily, oral tenoxicam 20 mg daily, or placebo for 8 to 12 days. Follow-up ultrasound was performed between day 8 to 12. The study excluded patients who were at high risk, such as those with thrombophilia; a history of DVT, PE, or SVT; two or more episodes of SVT; a history of venous sclerotherapy; or pregnancy. The overall rate of DVT by day 12 was 3.6% placebo group. 0.9% enoxaparin 40 mg group, 1% enoxaparin 1.5 mg/kg group, and 2.1% tenoxicam group. The study found that 30% of patients in the placebo group eventually had the combined outcome of extension of the SVT toward the saphenofemoral junction, recurrent SVT, and progression to DVT or PE by day 12. Fifteen percent of the NSAID group, 8% of those receiving 40 mg enoxaparin, and 7% of those receiving 1.5 mg/kg enoxaparin had the combined outcome for thrombotic events showing that all active treatment groups significantly reduced DVT and SVT progression. At 3-month follow-up after cessation of therapy, there was still a significant decrease in the combined outcome of DVT and SVT in the active treatment groups, but not in DVT alone. There were no episodes of major bleeding or death during the study. Overall, this study showed a significant risk for DVT and SVT extension in the absence of medical treatment and suggested that LMWH, used either as a prophylactic or treatment dose, was the most effective therapy for prevention of thrombotic complications. Furthermore, the results suggest that the duration of therapy required further evaluation because most the recurrent VTE events in the treatment groups occurred after active treatment halted.

Since publication of the STENOX trial in 2003, there have been four additional randomized trials evaluating the use of medical therapy for the treatment of STP. The Vesalio investigators randomized 164 consecutive patients with acute SVT of the GSV not within 3 cm of the SFJ to nadroparin fixed prophylactic dose (2850 units) subcutaneously versus body weight–adjusted therapeutic doses of nadroparin for 1 month in a double-blind double-dummy fashion.[42] The main outcome of VTE complications at 3 months occurred in 7 prophylactic dose patients compared with six treatment dose patients (NS). No patients in either group developed major bleeding.

The CALISTO study group randomized 3002 patients with acute SVT not within 3 cm of the SFJ to fondaparinux 2.5 mg subcutaneously daily or placebo for 45 days. At 47 days follow-up,[43] the primary combined outcome of symptomatic VTE, death, extension to the SFJ, or symptomatic SVT recurrence occurred in 13 or 1502 patients (0.9%) of the fondaparinux group and 88 of 1500 patients (5.9%) receiving placebo. Major bleeding occurred in one patient in each group. Except for the outcome of death, all components of the primary outcomes were significantly reduced in the fondaparinux group.

A post hoc analysis revealed that SVT extension occurred in 3.6% of patients and DVT/PE occurred in 9.3% and 8.9%, respectively, in the placebo group compared with less than 1.0% SVT extension and no DVT/PE in the fondaparinux group. This analysis supported the conclusion that symptomatic SVT extension confers significant morbidity whether near the deep saphenous junction or not. Fondaparinux treatment was associated with less consumption of medical resources related to thromboembolic complications.[44]

Rathbun et al. randomized 72 patients with acute SVT of the upper or lower limb regardless of proximity to the deep veins to dalteparin 200 units/kg body weight (maximum dose, 18,000 units) day 1 then 10,000 units daily for up to 13 additional days versus ibuprofen 800 mg three times daily for up to 14 days with the primary outcome of SVT extension or

VTE at 14 days and 3 months.[45] Four patients receiving ibuprofen compared with no patients receiving dalteparin had thrombus extension at 14 days ($P = .05$); however, there was no difference in thrombus extension at 3 months. Both treatments significantly reduced pain. There were no episodes of major or minor bleeding during the trial. Of note, extension of thrombus during the time after ibuprofen and dalteparin were discontinued suggested that the treatment duration of 14 days may have been too brief or that there is a rebound phenomenon after the medication is halted. Finally, most recently, Cosmi et al. randomized 664 patients with SVT of the GSV or SSV or tributaries of at least 4 cm in length to parnaparin either 8500 IU daily for 10 days followed by placebo for 20 days (group A), or 8500 IU daily for 10 days followed by 6400 IU daily for 20 days (group B) or 4250 IU daily for 30 days (group C) in a double-blind fashion. The primary outcome of the composite of symptomatic and asymptomatic DVT, symptomatic PE, and relapse and/or symptomatic or asymptomatic SVT recurrence in the first 33 days with 60 days follow-up occurred in 15.6% group A, 1.8% group B, and 7.3% group C. No major hemorrhages occurred. The authors concluded that an intermediate dose of parnaparin for 30 days was superior to either 30-day prophylactic dose or 10-day intermediate dose treatment of SVT.[46]

A post hoc analysis for evaluation of risk factors showed that previous VTE, SVT, and/or family history of VTE were associated with the measured composite outcome. After LMWH treatment was stopped, the absence of varicose veins, previous VTE/SVT, or family history of VTE were associated with the outcomes. The authors suggested that these patients may deserve a higher intensity or longer duration of anticoagulant treatment.[47]

Nonsteroidal Antiinflammatory Medications

In addition to the trials discussed previously, the effectiveness of NSAIDs for SVT treatment has been the focus as part of a Cochrane systematic review.[2] Five trials overall (including STENOX) were evaluated. This analysis found that NSAIDs significantly reduced the risk of SVT extension or recurrence by 67% (OR 0.33; 95% CI 0.16-0.068), compared with placebo. However, there was no difference in the rate of VTE or resolution of symptoms. No episodes of major bleeding were recorded in these trials.

A JAMA clinical evidence synopsis of treatment for lower extremity SVT concluded that LMWH and NSAIDs are associated with lower rates of SVT extension or recurrence, but the effect on the reduction of symptomatic VTE was inconclusive. The authors stated that the data regarding topical or surgical therapy were inconclusive.[48]

Surgery

For SVT within 1 cm of the saphenofemoral junction, management by high saphenous ligation with or without saphenous vein stripping has been suggested to be the treatment of choice because of the recognized potential for extension into the deep system and embolization.[11,49-52] There have been only two randomized trials over the past 15 years that have evaluated surgery for the treatment of SVT. The first was a prospective study consisting of 444 evaluable patients randomized to six different treatment plans for the management of superficial thrombophlebitis: compression only; early surgery, with and without stripping; low-dose subcutaneous heparin; LMWH; and oral anticoagulant treatment.[53] Patients with SVT and large varicose veins but without any suspected/documented systemic disorder were included in this study. Criteria for inclusion were venous incompetence (by duplex investigation), a tender indurated cord along a superficial vein, and redness and heat in the affected area. Exclusion criteria were obesity, cardiovascular or neoplastic diseases, nonambulatory status, bone/joint disease, problems requiring immobilization, age older than 70 years, and the presence of superficial thrombophlebitis without varicose veins. Color duplex ultrasound scans were used to detect concomitant DVT and to determine extension or reduction of SVT at 3 and 6 months.

The incidence of SVT extension at 3 and 6 months was higher in the elastic compression alone group and in the saphenous ligation alone group ($P < .05$) compared with the groups with medical therapy or surgical therapy with ligation and stripping. There was no significant difference in the incidence of DVT at 3 months in any of the treatment groups. The results of this study are difficult to evaluate because the details of the treatment protocols were lacking. Furthermore, the exclusion criteria would eliminate many of the patients in whom SVT is routinely diagnosed in clinical practice limiting the generalizability of the findings.

Lozano et al. randomized 60 patients with above knee GSV SVT to saphenofemoral disconnection under local anesthesia with short-term compression bandage or enoxaparin 1 mg/kg twice daily for 1 week and then once daily for 3 weeks.[54] All patients in the trial were instructed to use compression stockings. Although the rate of VTE was less in the enoxaparin group (RR 0.2; 95% CI: 0.01-4), it did not reach statistical significance. The rate of wound infections was 6.7% (2/30 patients) in the surgical group. A systematic review of six studies included 246 patients altogether that received GSV ligation with or without stripping compared to 88 patients that received intravenous heparin followed by vitamin K antagonist for 6 weeks to 6 months showed no difference in SVT progression, DVT, or PE. The overall surgical complication rate including hematoma, seroma, or infection was 7.7%.[55]

Topical Therapy

As part of the previously mentioned Cochrane systematic review, seven trials that included topical treatment for SVT were evaluated.[2] One of these small trials compared the use of a novel liposomal heparin spray versus LMWH (Clexane 40 mg daily subcutaneously) in 46 outpatients. The main outcomes measures of erythema size and duplex assessment of thrombus regression were comparable in the two groups; however, there were three cases of DVT in the heparin spraygel group compared with one in the LMWH group.[56] To date, no further follow-up

studies have been published and the spray is not available for commercial use. Other topical treatments that have been evaluated include methythioadenosine, diclfenac gel, and etofenak gel. Although these treatments did demonstrate reduction in local signs and symptoms, none of these studies evaluated the effect on VTE or SVT extension.

Other therapies that have been evaluated in small trials include oral vasotonin, venoruton, oral heparansulfate, oral sulodexide, oxyphenbutazone, oral vitamin K antagonists, enzyme therapy, and desmin.[2] Most provided local symptomatic relief. The most recent Cochrane systematic review that included analysis of 30 randomized controlled trials for treatment of SVT concluded that both LMWH and NSAIDs reduced the incidence of extension or recurrent SVT without any significant effect on VTE. Topical treatments improved local symptoms.[55] More information will be forthcoming from two RCT: A clinical trial based on Europe is underway evaluating the use of the oral anticoagulant rivaroxaban 10 mg daily compared with fondaparinux for the treatment of SVT (NCT 01499953 clinicaltrials.gov). A second clinical trial for treatment of SVT in Canada compares rivaroxaban 10 mg to placebo (NCT 02123524).

To summarize, LMWH seems to provide the best outcomes for treatment of SVT with the least complications. However, questions remain regarding the duration of therapy, with 1 week likely being too short. The most recent American College of Chest Physicians guidelines have not changed and give the following recommendations for treatment of patients with SVT of the lower limb[57]:

1. *In those with SVT at least 5 cm in length, the use of a prophylactic dose of fondaparinux or LMWH for 45 days is suggested over no anticoagulation (Grade 2B).*

2. *In those with SVT who are treated with anticoagulation, fondaprinux 2.5 mg daily over a prophylactic dose of LMWH is suggested (Grade 2C).*

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Decousus H, Prandoni P, Mismetti P, et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med*. 2010;363:1222–1232.

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The most recent ACCP guidelines 2012 state low-level recommendations for the treatment of symptomatic SVT: 8.1.1. In patients with superficial vein thrombosis (SVT) of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (grade 2B). 8.1.2. In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (grade 2C). The updated 2016 ACCP guidelines do not change these recommendations.

The Superficial Thrombophlebitis Treated by Enoxaprin Study Group (Decousus H et al). A pilot randomized double-blind comparison of a low-molecular-weight heparin, a nonsteroidal anti-inflammatory agent, and placebo in the treatment of superficial vein thrombosis. *Arch Intern Med*. 2003;163:1657–1663.

This double-blind study of 427 patients with symptomatic SVT compared the efficacy of enoxaparin prophylactic and therapeutic dose with NSAID and placebo for prevention of SVT progression and VTE and found all active treatments superior to placebo. Interestingly, there was no difference in outcomes for prophylactic and therapeutic enoxaparin.

The Vesalio Investigators Group (Prandoni P et al.). High vs. low doses of low-molecular-weight heparin for the treatment of superficial vein thrombosis of the legs: a double-blind randomized trial. *J Thromb Haemost*. 2005;3:1152–1157.

This multicenter, prospective, controlled, double-blind, double-dummy trial,164 patients with great saphenous vein SVT were randomized to receive fixed versus weight-adjusted nadroparin for 1 month. Therapeutic weight-adjusted nadroparin was found to be no more effective in preventing SVT progression and VTE at 3-month follow-up.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 151

Pulmonary Embolism: Presentation, Natural History, and Treatment

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INTRODUCTION

Acute pulmonary embolism (PE) is a partial or complete occlusion of the pulmonary arteries, with hemodynamic consequences determined by the size and location of the embolus, preexisting cardiopulmonary disease, and the severity of ventilation and oxygenation compromise.

Acute PE is the third leading cause of cardiovascular mortality, with well over 100,000 deaths per year in the United States.[1] Recent registries and cohort studies suggest that approximately 10% of all patients with diagnosed acute PE will die within 3 months after diagnosis.[2,3] Despite being the most preventable cause of hospital mortality and despite advances in diagnosis and management, it accounts for 5% to 10% of in-hospital deaths.[4] The annual incidence rate of PE is estimated between 75 and 269 cases per 100,000 individuals as shown by studies in Western Europe, North America, Australia, and southern Latin America, with individuals 70 years of age or older having an incidence of up to 700/100,000.[5] The incidence continues to rise both because the population is aging and because contemporary diagnostic modalities are more sensitive.[6]

The physical obstruction of the pulmonary arteries is accompanied by hypoxemic vasoconstriction and release of potent pulmonary arterial vasoconstrictors, which further increase pulmonary vascular resistance and right ventricular (RV) afterload. The increasing RV afterload can cause RV hypokinesis and dilation, tricuspid regurgitation, and ultimately RV failure with subsequent life-threatening reduction in coronary perfusion and cardiac output. Although in the majority of the survivors pulmonary thromboemboli will gradually resolve, in

Abstract

Acute pulmonary embolism (PE) is a leading cause of cardiovascular mortality. Clinical presentation varies from asymptomatic to fatal; symptoms depend on the embolic burden and the severity of any underlying cardiopulmonary disease. While in the majority pulmonary thrombo-emboli will gradually resolve, in some patients, it may organize into fibrotic deposits permanently occluding the pulmonary arteries leading to chronic thromboembolic pulmonary hypertension (CTPH). Computed tomographic pulmonary arteriography (CTPA) is the method of choice for imaging the pulmonary vasculature in patients with suspected PE and transthoracic echocardiography (TTE) is the most common first-line examination to diagnose the signs of right ventricular dysfunction. The main goal of therapy is to prevent mortality; a secondary goal, recently suggested, is the prevention of late-onset CTPH to improve quality of life. Systemic anticoagulation is the standard of care and treatment can be escalated in the setting of high or intermediate risk PE. Treatment options include systemic thrombolysis, catheter directed interventions and surgical thromboembolectomy. Patient selection criteria, hemodynamic and clinical outcomes continue to be defined to determine the indications and benefits of invasive interventions.

Keywords

venous thromboembolic disease
pulmonary embolism
anticoagulation
thrombolysis
catheter-directed thrombolysis
pulmonary hypertension

some patients, it may organize into fibrotic deposits permanently occluding the pulmonary arteries, leading to chronic pulmonary hypertension and RV dysfunction. In the majority of patients with PE the cause is lower extremity or pelvic venous thrombosis.

CLINICAL PRESENTATION

Clinical presentation varies from asymptomatic (incidentally diagnosed) to fatal. Development of symptoms depends on the embolic burden and the severity of any underlying cardiopulmonary disease. The diagnosis of PE is never made in approximately 70% of those who survive the initial event. Thus it is critical that a high level of suspicion is maintained.

In most patients, PE is suspected on the basis of dyspnea, chest pain, presyncope or syncope, and/or hemoptysis. The onset of dyspnea may be acute and severe usually representing a PE in the main or lobar vessels; in small peripheral PE, it is often mild and may be transient. Chest pain is a frequent symptom and is usually caused by pleural irritation due to distal emboli causing pulmonary infarction. In central PE, chest pain may have a typical angina character, possibly reflecting RV ischemia and requiring differential diagnosis with acute coronary syndrome or aortic dissection. Hemoptysis can occur in case pulmonary infarction.

Common clinical signs include tachypnea, tachycardia, rales or decreased breath sounds, jugular venous distension, and rarely fever mimicking pneumonia. Half of the patients will also present with symptoms of leg deep venous thrombosis (DVT) or rarely with symptoms of upper extremity DVT. Arterial hypotension and shock are rare (<10%) but critical clinical presentations because they indicate central PE and/or a severely reduced hemodynamic reserve. Syncope is infrequent but may occur regardless of the presence of hemodynamic instability.[7]

DIAGNOSIS

A high index of suspicion is required for the diagnosis of PE because symptomatology is nonspecific and overlaps with other pathologies, such as acute coronary syndromes, aortic dissection, pericardial tamponade, new onset arrhythmia, pneumonia, and pneumothorax.[8,9] Clinical impression alone has a sensitivity and specificity of 85% and 51%, respectively.[10] For this reason, clinical prediction algorithms have been developed (see later). Various laboratory and imaging tests are complimentary of the clinical suspicion.

Laboratory Tests

Routine blood tests in patients with PE are nonspecific and may include leukocytosis, elevated LDH and AST, CRP, and ESR. Plasma D-dimer levels, preferably using a high-sensitivity assay, are useful in patients who are unlikely to have PE or the clinical probability is low or intermediate targeting to reduce unnecessary computed tomography pulmonary arteriography (CTPA) or lung scans. In these cases a normal D-dimer level (<500 ng/mL) practically excludes PE. On the contrary, a positive D-dimer test is associated with a notoriously low specificity and should prompt further testing. Fibrin is otherwise produced in a wide variety of conditions such as cancer, inflammation, bleeding, trauma, surgery, and necrosis. For patients in whom PE is likely, a normal D-dimer is not sufficient to rule in or out PE. Overall, D-dimer is a sensitive but not specific diagnostic tool for patients with suspected PE. The specificity decreases even more with age. However, if D-dimer cutoff values are adjusted to age (age × 10 mg/L older than 50 years) the rate of patients in whom PE can be excluded increases from 6.4% (using 500 mg/L as cutoff level) to 30%, without any additional false-negative findings.[11,12]

Biomarkers of RV dysfunction include troponin and brain natriuretic peptide (BNP). Their diagnostic value is limited because they are neither sensitive nor specific. However, in patients with confirmed PE, cardiac troponin (TnT or TnI) and BNP (or its precursor NT-proBNP) tests are recommended for further stratification of patients at intermediate risk (see later).[13,14] The standard cutoff values for TnT, TnI, and BNP are 0.1 ng/mL, 0.4 ng/mL, and 90 pg/mL, respectively, although they may vary depending on the assay and the lab. Similar to D-dimers, age-adjusted and not standard values are better predictors of adverse outcomes for troponin (e.g., high sensitivity TnT is prognostic at 45 pg/mL instead of 14 pg/mL for patients older than 75 years).[15] NT-proBNP has its optimal prognostic value when it exceeds 600 pg/mL instead of the previously proposed 300, 500, or 1000 pg/mL.[16] An alternative novel marker of myocardial injury is the heart-type fatty acid–binding protein emerging as a significant predictor of mortality in patients with intermediate risk PE.[17-19]

Arterial blood gases are also nonspecific and do not assist in the diagnosis of PE. However, hypoxemia may have a prognostic value for confirmed PE as an indicator of anticipated complications, respiratory failure, or death.[20] However, pulse oximetry is a more reasonable noninvasive alternative, at least for the low- or intermediate-risk patients.

Electrocardiogram

Electrocardiographic changes associated with acute PE are neither sensitive nor specific. They are similar to all other causes of pulmonary hypertension (e.g., acute bronchospasm, pneumothorax). The S1Q3T3 (prominent S wave in lead I, Q wave and inverted T wave in lead III) pattern is a sign of acute RV overload (acute cor pulmonale) and reflects strain; it is seen in less than 20% of diagnosed PEs. The greatest utility of the ECG in a suspected PE is to rule out acute myocardial infarction.

Chest X-ray

Chest radiographs are not sensitive or specific for PE but can rule out alternative diagnoses (e.g., pneumothorax). Frequently patients with PE have a normal chest x-ray. Atelectasis or parenchymal density and pleural effusion are probably the most frequent findings. Radiographic signs such as the Fleischner sign (enlarged pulmonary artery), Hampton hump (peripheral

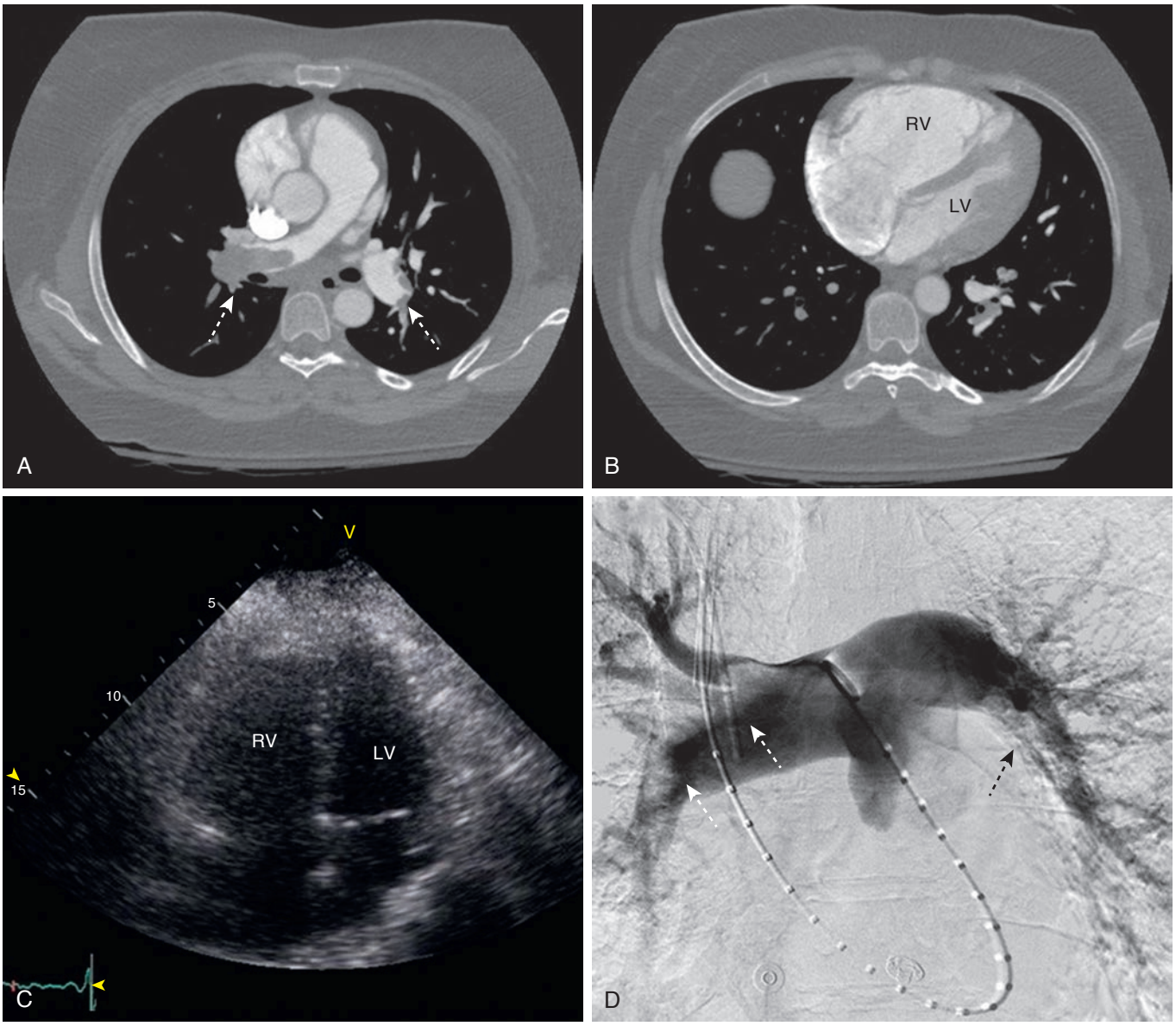

Figure 151.1 Pulmonary embolism (PE) and right ventricular imaging. (A) PE is primarily diagnosed with CT pulmonary arteriogram; notice bilateral main pulmonary and segmental arteries with thrombus. (B) RV dilatation as seen in the CT pulmonary arteriogram. (C) Transthoracic echocardiogram four-chamber view showing RV dilatation. (D) Pulmonary arteriogram; notice bilateral main pulmonary and segmental arteries with thrombus. *LV,* Left ventricular; *RV,* right ventricular.

wedge of airspace opacity—lung infarction), Westermarck sign (regional oligemia), and knuckle sign (abrupt tapering or cutoff of a pulmonary artery) are rare but should raise the suspicion of PE.[21]

Computed Tomographic Pulmonary Arteriography

Computed tomographic pulmonary arteriography (CTPA) is the method of choice for imaging the pulmonary vasculature in patients with suspected PE (Fig. 151.1A). It allows adequate visualization of the pulmonary arteries down to at least the segmental level and has a high predictive value, particularly when combined with clinical probability. Based on the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II trial, CTPA has a sensitivity of 83% and a specificity of 96% and several studies have demonstrated its efficiency as a stand-alone imaging test for confirming or excluding PE.[22-26]

CTPA, particularly if it is electrocardiogram gated, can further serve as a prognostic tool for the severity and outcomes of PE.[22-30] Heart chamber dimension measurements may detect RV enlargement as an indicator of RV dysfunction, typically defined as a right-to-left ventricular end-diastolic dimensional ratio ≥0.9 (see Fig. 151.1B).

Echocardiogram

Transthoracic echocardiography (TTE) is the most common first-line examination to diagnose the signs of RV dysfunction but cannot definitely diagnose PE because an elevated RV pressure may be the result of other conditions such as pulmonary hypertension and RV infarction. Echocardiography is most useful in patients with diagnosed PE, for prognostic purposes. Confirmation of RV dysfunction is a key determinant of PE prognosis because it seems to increase the risk of death by at least twofold.[31]

A variety of different methods for the assessment of RV dysfunction on TTE have been proposed, and the literature shows variable results for the prognostic power of TTE signs of RV dysfunction to predict adverse outcomes.[32]

RV/LV end-diastolic diameter ratio has been commonly used as an indicator of RV dysfunction, defined as RV/LV end-diastolic ratio greater than 1, but its reproducibility is fair because the ventricular walls cannot always be well defined (see Fig. 151.1C).[33,34] Tricuspid annular plane systolic excursion (TAPSE) is a quantitative echocardiographic parameter that is the least user dependent and most reproducible. Another sign of RV dysfunction is the depressed contractility of the RV free wall compared with the RV apex (McConnell sign), reported to retain a high positive predictive value for PE, even in the presence of preexisting cardiorespiratory disease.[33-35] Finally a relatively rare finding suggestive of PE is thrombus in the RV, also known as thrombus in transit. Thrombus in the pulmonary arteries can be seen with transesophageal echocardiography.

Overall, echocardiography is not recommended as part of the routine diagnostic workup in patients with suspected PE, unless they are hemodynamically unstable. On the other hand, confirmation of RV dysfunction may justify emergency reperfusion treatment for PE if immediate CTPA is not feasible.[8]

Other Imaging Modalities

Ventilation/perfusion (V/Q) scans are rarely used currently unless the patient with a suspected PE is pregnant or has renal insufficiency that prohibits CTPA. V/Q scanning is a highly sensitive but poorly specific study for the diagnosis of PE. When the V/Q scan is inconclusive (and CTPA contraindicated) magnetic resonance pulmonary angiography can be a reasonable alternative, acknowledging the complexity of the protocol, suboptimal resolution, and low sensitivity. Finally, invasive pulmonary angiography is a historical "gold standard," that currently would be justified only for diagnostic purposes provided that some kind of catheter-directed intervention (CDI) is planned (e.g., catheter thrombolysis or aspiration thrombectomy) upon confirmation of PE (see Fig. 151.1D).

Lower extremity venous duplex will show a DVT in 30% to 50% of patients with PE, and finding a proximal DVT in patients suspected of having PE is considered sufficient to warrant anticoagulant treatment without further testing. Out of those who have symptoms or clinical signs of DVT, only half will have it confirmed by ultrasound. Patients with acute symptomatic PE and confirmed DVT have an almost twofold higher risk of short-term death when compared with those without a DVT.[8,36]

Probability Algorithms and Diagnostic Strategies

Despite the limited sensitivity and specificity of symptoms, signs, and common tests, the combination of findings evaluated by clinical judgment or by the use of probability algorithms allows the classification of patients with suspected PE into distinct categories of clinical or pretest probability that correspond to an increasing actual prevalence of confirmed PE. Clinical judgment is crucial and of outmost importance; however, it lacks standardization; therefore, several explicit clinical prediction rules have been developed. These rules apply to ***nonpregnant hemodynamically stable*** patients. Hemodynamically unstable patients with suspected PE are expected to receive an expeditious life-saving reperfusion therapy (e.g., systemic thrombolysis), skipping a potentially time-consuming probability assessment. For these hemodynamically stable patients in whom PE is suspected, following clinical and laboratory assessment, the pretest probability is most frequently assessed using the Wells or modified Geneva scores, both of which were recently simplified and validated (Table 151.1).[37-42]

Among patients who are likely to have PE based on these scores or unlikely but with a D-dimer level ≥500 ng/mL, CTPA is the imaging modality of choice. If negative, no further testing is required; if positive, treatment (anticoagulation) should be initiated. While awaiting the CTPA, initiation of empiric anticoagulation can be individualized based on the clinical scenario. Patients who are unlikely to have PE do not require a CTPA but a sensitive D-dimer test. If the levels are less than 500 ng/mL, no further testing is required (Fig. 151.2).

RISK STRATIFICATION

PE severity should be based on an individual estimate of PE-related early mortality risk rather than the extent of pulmonary vascular obstruction. Although it is attractive to stratify types of acute PE on the basis of the anticipated mortality, this approach is hampered by the presence of comorbidities; for example, a non–high risk PE might be associated with a high mortality risk in a patient with obstructive airway disease or congestive heart failure.[43] Despite this relative weakness, PE risk stratification guides major treatment decisions in all major guideline documents.[8,44,45]

PE is classified as low, intermediate (or submassive), and high (or massive) risk based on the anticipated 30-day mortality rate. The terms "submassive" and "massive" were initially suggested on the basis of angiographic burden of emboli by use of the Miller Index, but these are now of limited use as the embolic burden is a poor indicator of mortality.[46,47]

With small variations in their definitions as given by societal guidelines, low-, intermediate-, and high-risk PE are defined as follows:

- Low risk: normotensive patients without imaging evidence of RV dysfunction or elevated cardiac biomarkers. Approximately 40% of all PE patients fall into this category. They have excellent short-term prognosis with a mortality rate approximately 1% to 2% or less.[44,48]

TABLE 151.1 Probability Scores for Pulmonary Embolism

Wells Score[41]	PROBABILITY SCORE Original	Simplified
Previous PE or DVT	1.5	1
Heart rate ≥ 100 b.p.m	1.5	1
Surgery of immobilization within the past 4 weeks	1.5	1
Hemoptysis	1	1
Active cancer	1	1
Clinical signs of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Clinical Probability		
Three-level Score		
Low	0–1	n/a
Intermediate	2–6	n/a
High	≥7	
Two-level Score		
PE unlikely	0–4	0–1
PE likely	≥5	≥2
Revised Geneva Score[40]	**Original**	**Simplified**
Previous PE or DVT	3	1
Heart rate 75–95 b.p.m ≥95 b.p.m	3 5	1 2
Surgery or fracture within the past month	2	1
Hemoptysis	2	1
Active cancer	2	1
Unilateral lower limb pain	3	1
Pain on lower limb deep venous palpation and unilateral edema	4	1
Age >65 years	1	1
Clinical Probability		
Three-level Score		
Low	0–3	0–1
Intermediate	4–10	2–4
High	≥11	≥5
Two-level Score		
PE unlikely	0–5	0–2
PE likely	≥6	≥3

DVT, Deep venous thrombosis; *PE*, pulmonary embolism.

- Intermediate risk: normotensive patients with either imaging evidence of RV dysfunction or elevated cardiac biomarkers or both. This group constitutes approximately 55% of all PEs, and the mortality rate ranges between 3% and 15%.[44,49-51]
- High risk: hemodynamically unstable patients with sustained shock or hypotension (<90 mm Hg) or cardiac arrest. These patients are rare, approximately 5%, but in-hospital mortality ranges between 15% and 30% or may exceed 60% for those requiring cardiopulmonary resuscitation.[3,50-53]

Several scoring systems have been devised for risk stratification, the most widely used being the Pulmonary Embolism Severity Index (PESI) and its simplified version, both validated to identify clinical factors associated to poorer outcomes (Table 151.2).[43,54] Approximately one-third of PE patients are at low mortality risk of an early adverse outcome as indicated by a PESI class I or II (mortality up to 3.5%) or a simplified PESI of 0 (mortality up to 2.1%). Patients in PESI class III to V have a 30-day mortality rate of up to 24.5%, and those with a simplified PESI ≥1 up to 11%. Normotensive patients in PESI class ≥III or a simplified PESI of ≥1 are considered to constitute an intermediate-risk group. The prediction is enhanced when these scores are combined with imaging or laboratory findings, because there is no single test with sufficient positive predictive value that could justify an aggressive treatment. Within the intermediate-risk category, further risk assessment can be elaborated focusing on the status of the RV and/or on cardiac biomarkers (Table 151.3). Multiple observational studies and meta-analyses have suggested that the combination of clinical variables (e.g., tachycardia, mild hypotension), myocardial injury (e.g., high troponin), and RV dysfunction (e.g., RV dilatation, high BNP) particularly in those with concomitant DVT, identifies the more severe intermediate-risk patients with acute PE.[55] Recently, the European Society of Cardiology introduced the terms intermediate low and intermediate high risk, with intermediate high risk encompassing patients having both imaging findings of RV dysfunction and positive biomarkers (troponin or BNP/proBNP).[8]

TREATMENT

The main goal of therapy is to prevent mortality; a secondary goal, recently suggested, is the prevention of late-onset chronic thromboembolic pulmonary hypertension (CTEPH) to improve quality of life.[4,8,44-46,56-59]

Initial Supportive Therapies

Although patients classified as low-risk PE do not require any specific support, it is vital that those with intermediate- or high-risk PE receive supportive treatment. The initial approach to patients suspected with PE should assess hemodynamic stability; if a patient is unstable (or borderline stable), general support should be provided while diagnostic evaluation is ongoing and includes:

- Airway, breath, and oxygenation assessment using pulse oximetry
- Oxygen supplementation targeting O_2 saturation ≥90. Severe hypoxemia or respiratory failure should prompt consideration for intubation. When mechanical ventilation is required, positive end-expiratory pressure should be applied with caution because it may reduce venous return and worsen RV failure in patients with massive PE.
- Pulse rate and blood pressure assessment

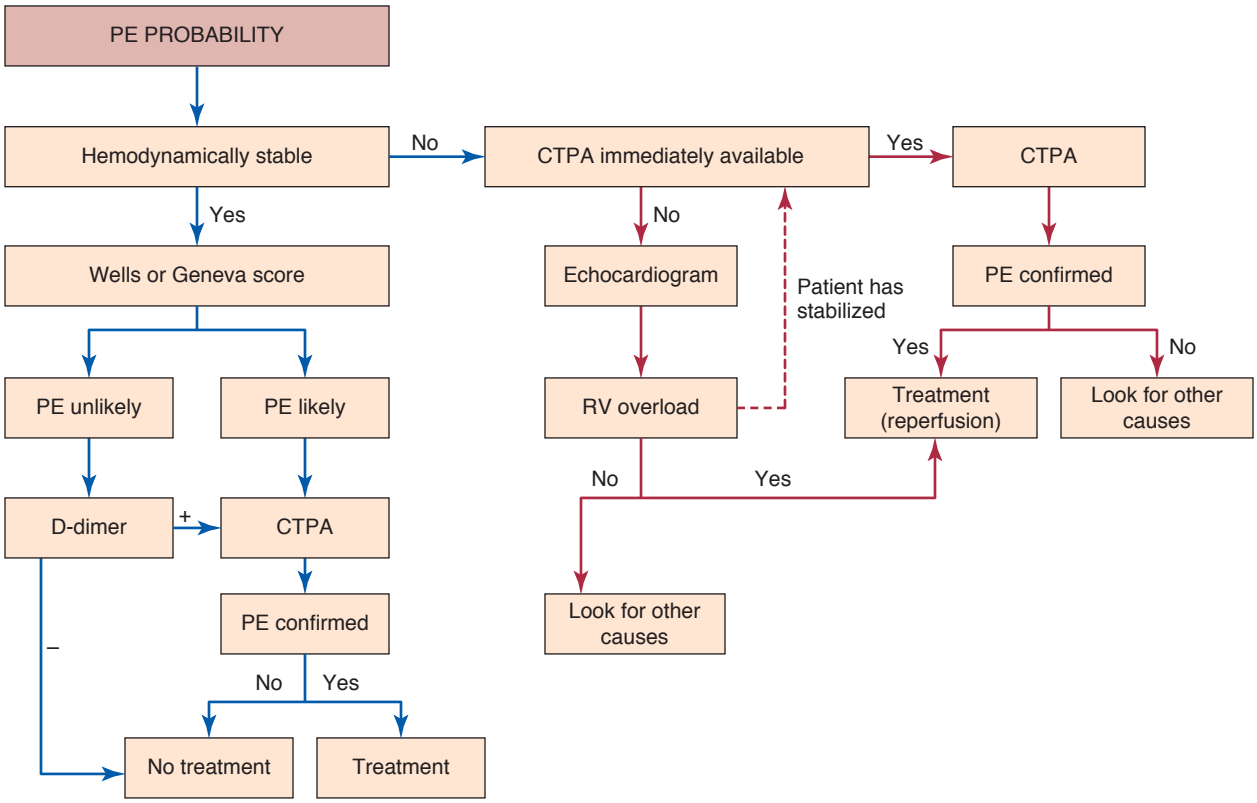

Figure 151.2 Diagnostic algorithm for patients with suspected pulmonary embolism. *CTPA,* Computed tomography pulmonary arteriography; *PE,* pulmonary embolism; *RV,* right ventricular.

TABLE 151.2 Pulmonary Embolism Risk Stratification Based on the Pulmonary Embolism Severity Index (PESI)

Predictor	PESI SCORING	
	Original	Simplified
Age	Age in years	1 (if >80 years)
Men	10	—
Cancer	30	1
Heart failure	10	1
Chronic lung disease	10	
Pulse ≥110 b.p.m	20	1
Systolic pressure <100 mm Hg	30	1
Respiratory rate ≥30	20	—
Temperature <36°C	20	—
Altered mental status	60	—
Saturation <90%	20	1
Risk		
Very low risk (class I)	≤65	0
Low risk (class II)	66–85	
Intermediate risk (class III)	86–105	≥1
High risk (class IV)	106–125	
Very high risk (class V)	≥126	

- Peripheral intravenous access with or without fluid administration. In hypotension, intravenous fluid should be administered in small volumes (500-1000 mL of normal saline) to avoid overloading an otherwise stretched RV. Should the fluid challenge fails, vasopressor therapy should follow. Norepinephrine is the most suitable agent because it is less likely to cause tachycardia and exacerbate hypotension. Norepinephrine improves RV function via a direct positive inotropic effect, while also improving RV coronary perfusion by peripheral vascular alpha-receptor stimulation.
- Empiric initiation of anticoagulation balancing the clinical suspicion of PE, the hemodynamic profile, the risk of bleeding, and the expected timing of the diagnostic tests should be considered. For the hemodynamically unstable patients who are anticipated to receive thrombolysis or embolectomy, unfractionated heparin is preferred. Empiric anticoagulation can be also initiated in hemodynamically stable patients with a high or moderate clinical suspicion of acute PE, when the diagnostic evaluation is expected to take longer than 4 hours.[45,60]

Anticoagulation

Unless contraindicated, all patients with acute PE should receive systemic anticoagulation with the objective of preventing both early death and recurrent symptomatic or fatal event. Anticoagulation should be initiated during the diagnostic workup in

TABLE 151.3 Imaging and Laboratory and Clinical Tests for Risk Stratification of Pulmonary Embolism (PE)

	Markers of Non–Low Risk PE	Remarks
Echocardiogram[31-35]	RV/LV EDD >1 TAPSE ≤ 1.6 cm TRJV >2.6 m/s^{-1} Estimated RVSP ≤52 mm Hg McConnell Sign + IVC collapsibility >50% + RV hypokinesia + Leftward shifting of IVS +	RV dysfunction parameters have been identified as independent predictors of death. With the exception of TAPSE, the complex geometry of the RV and the subjective nature of the measurements are limiting factors.
CT Angiogram[22-30]	RV/LV EDD ≥0.9	RV dilatation has been identified as independent predictor of death. No clear association has been shown for clot burden.
Lower Leg Duplex[36]	DVT +	Proximal DVT in patients with symptomatic PE is an independent predictor of death (OR 1.9; 95% CI 1.5-2.4).
Troponin[13,15,16]	TnT >0.1 ng/mL TnI >0. 4 ng/mL	High troponin levels are independent predictors of death. Limited detection time-window (peak at 8 hours). Optimal cutoff values are yet to be defined. High sensitivity assays and age adjusted values may be more accurate.
BNP[13,14,16]	>90 pg/mL	High levels predict death (OR 6.5; 95% CI 2.0–2.1)
Pro-BNP[14,16]	>600 pg/mL	High levels predict death (OR 6.3; 95% CI 2.2-18.3)
HFAB[17–19]	>6 µg/lt	Novel biomarker with significant prognostic value for mortality (OR 40.8; 95% CI 11.8-140.1).
PESI[43,54]	Original: ≥86 (class III-V) Simplified: ≥1	Validated widely used clinical score.

BNP, Brain natriuretic peptide; *CI*, confidence interval; *CT*, computed tomography; *DVT*, deep venous thrombosis; *EDD*, end-diastolic diameter; *HFAB*, Heart-type fatty acid–binding protein; *IVC*, inferior vena cava; *IVS*, interventricular septum; *LV*, left ventricle; *OR*, odds ratio; *PESI*, Pulmonary Embolism Severity Index; *RV*, right ventricle; *RVSP*, right ventricle systolic pressure; *TAPSE*, tricuspid annular plane systolic excursion; *TRJV*, tricuspid regurgitant jet velocity.

patients with intermediate or high clinical probability of PE. The standard duration of anticoagulation should cover at least 3 months (see Chapter 39).[8,44,45]

In the acute PE phase, parenteral anticoagulation (unfractionated heparin, low-molecular-weight heparin [LMWH], or fondaparinux) should be initiated first, followed by the parallel administration of a vitamin K antagonist (warfarin) for at least 5 days and until INR reaches the desired therapeutic level (2.0-3.0). Novel oral anticoagulants, factor Xa inhibitors (rivaroxaban, apixaban, edoxaban), and direct thrombin inhibitors (dabigatran) do not require monitoring and dose adjustments or prolonged bridging therapy. These agents are noninferior to warfarin.

Inferior Vena Cava Filter

As a general guideline, inferior vena cava (IVC) filters are indicated in patients with acute PE who have absolute contraindications to anticoagulant drugs and in patients with objectively confirmed recurrent PE despite adequate anticoagulation.[8,44,45] This is irrespective of the presence of lower extremity thrombus because it may remain undetected in the pelvis. Current guidelines are against the routine use of IVC filters in patients who can be anticoagulated. However, because it is uncertain if there is benefit to placing an IVC filter in anticoagulated patients with severe PE (e.g., hypotension), this recommendation against insertion may not apply to this select subgroup (see Chapter 152).[61]

Thrombolysis

Thrombolysis is reserved for high-risk and selected cases of intermediate-risk PE.[8,44,45,62] The greatest benefit is observed when treatment is initiated within 48 hours of symptom onset, but thrombolysis can still be useful in patients who have had symptoms for up to 14 days. The standard route for administration of lytics is intravenous through a peripheral line; however, catheter-directed lytic administration directly into the pulmonary arterial tree is increasingly entering clinical practice. Contraindications to thrombolysis in PE patients have not been exclusively studied in this patient population but have been extrapolated from patients with myocardial infarction.[44,63] It is unclear to what extend these apply for catheter-directed thrombolysis, and preliminary data are controversial regarding bleeding events in the setting of a "contraindication."[64-68]

Systemic Thrombolysis

Systemic intravenous thrombolysis is universally recommended for high-risk PE but remains controversial for intermediate-risk PE. The most widely suggested regimen is 100 mg alteplase (recombinant tissue plasminogen activator [rtPA]) over 2 hours.

Other rtPAs such as reteplase and desmoteplase have been tested against alteplase in acute PE, with similar results in terms of hemodynamic parameters; tenecteplase has been tested against placebo (heparin alone) in patients with intermediate-risk PE.[8,58,69,70] Heparin infusion is typically held during thrombolysis.

An analysis of the US nationwide inpatient sample (1999-2008, $n = 72.230$) demonstrated an all-cause (47% vs. 15%) and PE-related (42% vs. 8.4%) mortality benefit for thrombolysis in massive PEs.[71] A large meta-analysis of thrombolysis for PE reported pooled data from 16 trials comprising 2115 patients (1775 intermediate risk).[72] Thrombolysis was associated with lower mortality risk compared with standard anticoagulation (2.17 vs. 3.89%, $P = .01$). The mortality benefit persisted when the analysis was limited to patients with intermediate-risk PE (1.39% vs. 2.92%, $P = .03$). However, thrombolysis was associated with higher rates of major bleeding (9.24 vs. 3.42%, $P < .001$) and intracranial hemorrhage (1.46 vs. 0.19%, $P = .002$). The increased major bleeding was primarily driven by patients older than 65 years.

A meta-analysis (1990-2013, 440 patients) suggested that a low-dose protocol (e.g., 50 mg) has similar efficacy and may be safer than the standard 100 mg dose.[73]

Interestingly, despite the marked reduction of case fatality rate with systemic thrombolysis in unstable patients, only 30% receive it, partly because of various contraindications to lytics and concerns for complications.[53,71] Still, data suggest that withholding thrombolytic therapy in the elderly or those with comorbid conditions might not be the safest approach in terms of mortality. Unstable patients with PE who received thrombolytic therapy have a lower in-hospital case fatality rate irrespective of age and comorbid conditions.[74] For intermediate-risk PE, given that mortality is infrequent, it is difficult to demonstrate a survival benefit. Quality of life measures such as late-onset CTEPH and functional disability may be more relevant outcomes, so the verdict is still out.

Catheter-Directed Interventions

The limitations and complications of systemic thrombolysis are driving contemporary practice toward CDIs as a first-line treatment in the appropriate clinical setting as a way to provide the benefits and minimize adverse events of systemic thrombolytic therapy. Despite the publication of the first comparative studies (CDIs vs. anticoagulation or vs. high- or low-dose systemic lysis), there is lack of sufficient robust evidence to confirm the assumption of combined efficacy and safety, particularly in the high-risk population.[46,65,75,76]

The Ultrasound Accelerated Thrombolysis of Pulmonary Embolism (ULTIMA) trial was the first randomized controlled trial to include CDIs for intermediate-risk PE comparing standardized fixed-dose ultrasound-assisted thrombolysis (USAT) (10 mg of tPA per lung for 15 hours) and anticoagulation with anticoagulation alone.[75] In the USAT group but not in the anticoagulation group, the mean RV/LV ratio was significantly reduced at 24 hours but became comparable between the two groups at 90 days. The RV systolic function was significantly improved in the USAT group versus the heparin group at both 24 hours and 90 days. In both study groups, minor bleeding complications were rare, and there were no major bleeding complications. However, in real-world practice, CDIs are not risk-free procedures.[64,65,72] The pooled major bleeding rate, from 10 studies with 469 patients is 3.5% (Fig. 151.3).[64] This pooled major bleeding rate is similar to that obtained from the U.S.

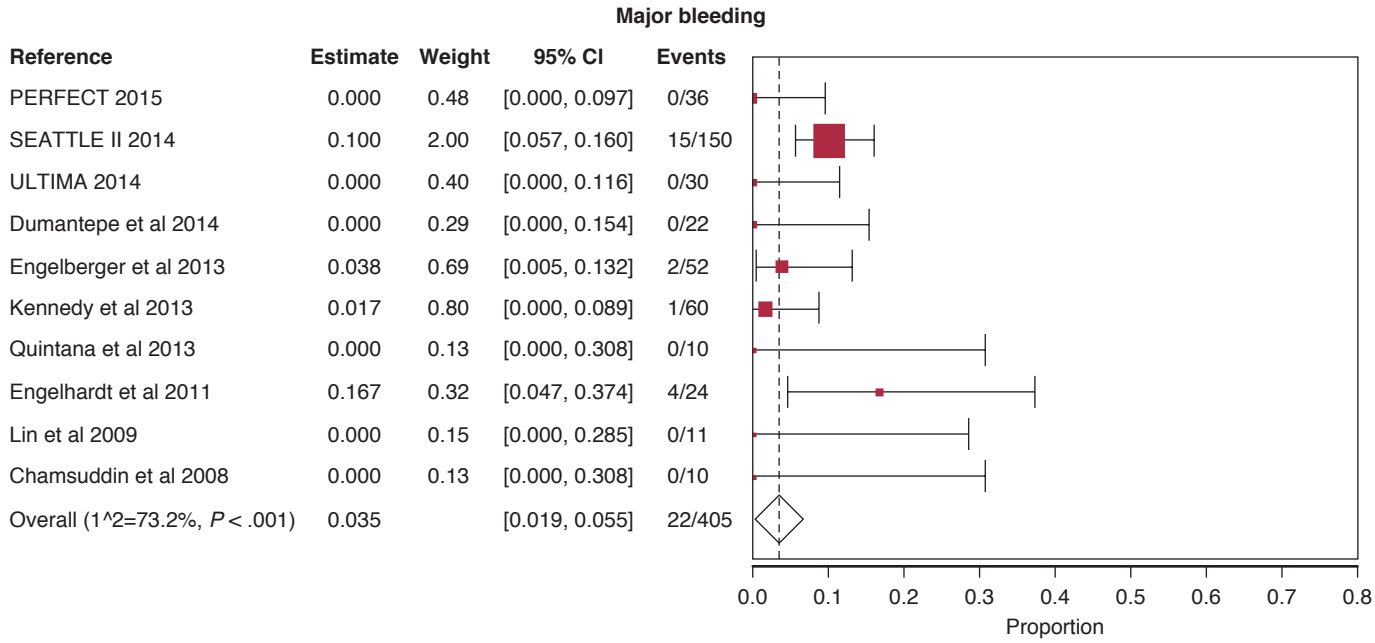

Figure 151.3 Fixed-effect meta-analysis for major bleeding in ultrasound-assisted catheter-directed interventions for pulmonary embolism. The figure presents major bleeding rates from individual studies, 95% confidence interval (CI) for each trial and overall estimate of pooled proportion with 95% CI. (Figure obtained with permission from Abou Ali AN, Liang NL, Chaer RA, Avgerinos ED. Catheter interventions for pulmonary embolism: are they really that safe? *Am J Cardiol.* 2016;118:307–308.)

Figure 151.4 Catheter-directed thrombolysis. (A) Five-French standard multi-sidehole catheter. (B) Ultrasound-assisted thrombolysis catheter, EkoSonic (Endovascular System, EKOS Corporation; Bothell, Washington). The catheter is composed of a 5.2-F multi-sidehole infusion catheter and a microsonic core wire containing the ultrasound elements.

nationwide inpatient sample analysis (4.9%) and our recently published experience (6.2%).[65,74] Catheter interventions can be related to unique adverse events like heart and lung injuries, contrast-induced nephropathy and other device-related complications.[67] A combination of these major adverse events with major bleeding rates exhibits better the safety profile of these interventions, which still seems to be better than that of systemic lysis. The stroke rate in the majority of studies is essentially 0%. CDIs should be provided in selected patients where appropriate expertise is available. These interventions appear to be safer than systemic thrombolytics for the treatment of acute PE, but they are definitely not as safe as initially thought.

As a general rule, whenever thrombolysis is considered as a treatment option, either in the setting of high- or intermediate-risk PE, CDIs may be the only alternative for patients at a high bleeding risk (e.g., recent surgery) and can be considered a reasonable alternative in patients at low risk for bleeding.

Technical Considerations for Catheter-Directed Interventions

Contemporary CDIs are variable and can be performed with or without thrombolysis. The latter include thrombus fragmentation and/or aspiration techniques, with no lytic agents, for patients with absolute contraindications to thrombolysis; however, their efficacy and safety remain controversial.[46,67,77,78]

The standard technique involves administration of local thrombolytics through a multi-sidehole catheter placed unilaterally or bilaterally into the pulmonary artery thrombus (transjugular or transfemoral). The use of ultrasound to enhance thrombolytic permeation of large emboli holds currently the highest level of evidence in both efficacy and safety.[75,77] The EkoSonic Endovascular System (EKOS Corporation; Bothell, Washington) combines a multi-sidehole drug infusion catheter with a multielement ultrasound core wire and was approved by the U.S. Food and Drug Administration (FDA) for use in patients with PE (Fig. 151.4). However, the clinical superiority of USAT over conventional catheter-directed thrombolysis has not been proven.[66,79] With or without ultrasound acceleration the optimal tPA dose has not been set yet, but in published studies it ranges between 15 and 25 mg, reflecting an uncertainty as to when to terminate lysis. A clinically relevant improvement, rather than thrombus reduction, should guide therapy. Apart from clinical parameters (pulse rate, blood pressure, oxygen requirements), invasive pressure tracings (right atrium, right ventricle, main pulmonary artery) or cardiac echocardiographic parameters can be used as adjuncts to monitor the progress of therapy. In high-risk PE, reversal of hemodynamic instability should primarily guide the termination of treatment. In patients with intermediate-risk PE, termination should be guided by improved pulmonary artery pressures and/or reversal of right heart strain

and/or overall clinical improvement (e.g., reduced oxygen requirements, improved pulse rate). It remains unclear at what rate heparin infusion should be maintained during lytic infusion. Some recommend DVT therapeutic heparin protocols; others recommend minimal heparin (500 units/hour) just to prevent sheath thrombosis. Our group has established a therapeutic low-dose heparin protocol (atrial fibrillation protocol: target aPTT 60-80 seconds).

Several adjuncts and technical alternatives have been described in various combinations, targeting rapid clot debulking for the unstable patients, particularly when lytics are contraindicated. The majority of these technical adjuncts and devices lack background evidence and are not approved by the FDA for treatment of PE. As such, no standardized technical algorithm yet exists, and as new technology evolves many of the adjuncts that were used a few years ago are currently obsolete.[46,78]

Rotating pigtail or balloon embolectomy catheters have been broadly reported for thrombus fragmentation.[78,80-82] Because fragmentation may lead to distal clot embolization, adjunctive aspiration thrombectomy and subsequent lysis may be needed. The rational of fragmentation is that it allows exposure of a greater embolic surface area to the lytic drug's effect; otherwise local thrombolytic infusion will be no more efficacious than systemic delivery because it tends to rapidly wash into nonoccluded arteries.[78,81] The Angio-Jet Rheolytic Thrombectomy System (Boston Scientific, Marlborough, Massachusetts) provides pharmacomechanical thrombolysis and has been used in the past for PE, with several adverse events and deaths reported. As a result, the FDA has issued a black box warning on the device label. Despite a recent study advocating its use in the setting of massive PE, it should probably by avoided.[46,78]

Thrombus aspiration can be performed as an adjunct to any CDI or as a stand-alone technique using dedicated large bore suction devices. The simplest aspiration technique is by using any 5- to 9-F end-hole catheter, or dedicated steerable aspiration catheters 10- to 14-F in size (Fig. 151.5). A novel, but with limited evidence in the PE setting, device is the Vortex AngioVac aspiration system (AngioDynamics, Latham, New York) that is composed of an extracorporeal bypass circuit that facilitates drainage, filtration, and reinfusion of blood cleared from clot.[83] A funnel-shaped distal tip facilitates en bloc removal of the embolus. The technique is FDA approved, and successful outcomes in the setting of PE have been reported in small case series. The device requires a 26-F delivery sheath and can be used from the femoral or jugular approach and allows embolectomy without the use of lytic agents (Fig. 151.6). Smaller profile devices are being evaluated, such as the Aspire Mechanical Thrombectomy System (Control Medical Technology, Park City, Utah), the Indigo System CAT 8 Aspiration Catheter (Penumbra Inc., Alameda, California), and the Flowtriever (Inari Medical, Irvine, California).

Surgical Thrombectomy

Traditionally, surgical pulmonary thromboembolectomy is reserved for patients with documented central PE and refractory cardiogenic shock despite maximal supportive therapy and who have absolute contraindications to or have failed thrombolytic therapy. Surgical thrombectomy aims to rapidly reduce RV afterload by physically removing proximal pulmonary artery thrombi.[84-87]

Outcomes have improved in the past 2 decades, with mortality declining from 30% to well below 10% in centers with appropriate expertise.[87-90] Mortality should be anticipated to be significantly higher when surgical thrombectomy follows a failed thrombolysis and even worse after a cardiac arrest; best results are achieved with primary early surgery.[88,91,92]

Surgical embolectomy is performed through a median sternotomy using a normothermic cardiopulmonary bypass. Aortic cross-clamping and cardioplegic cardiac arrest are usually not needed. The main pulmonary artery is opened and the thrombotic material is extracted. The right atrium and ventricle are also explored for possible thrombi and a patent foramen ovale is closed, if present.

Extracorporeal Membrane Oxygenation

Transportable extracorporeal membrane oxygenation (ECMO) assistance systems with percutaneous femoral cannulation can be helpful in critical situations, ensuring circulation and oxygenation until definitive diagnosis. ECMO unloads the acutely failing right heart, providing effective hemodynamic and respiratory support for patients who develop massive PE until recuperation of the initial pulmonary insult. It has been increasingly used in some centers for unstable PE patients who are not responding to other treatment modalities or as a bridge for catheter-based or surgical embolectomy.[93-96]

There are no clear prognostic indicators to appropriately select unstable PE patients who are likely to benefit from ECMO support. Although it seems reasonable to offer ECMO as a last resort to PE patients who are otherwise expected to die, this decision has to be reached on an individual basis to avoid providing futile care and wasting resources. Several factors should be considered in this decision, including patient's comorbidities and the local expertise.

Early Discharge and Home Treatment

Outpatient treatment of PE, giving the first dose of anticoagulation in the hospital, can be safe and effective in select patients who fulfill certain criteria. Clinical probability scores, mainly the PESI score, are predominately used to preselect these patients. The value of NT-proBNP as a laboratory biomarker for selecting candidates for home treatment has been evaluated, and, among those with clinically defined very-low-risk PE and NT-proBNP levels less than 500 pg/mL, none died or suffered recurrence of VTE or major bleeding complications during a 3-month follow-up.[97] Still, the value of cardiac biomarkers or echocardiography to exclude RV dysfunction before early discharge have not been thoroughly investigated, and they are not routinely recommended.[45]

Randomized studies and meta-analyses have set the following features as mandatory for consideration of early discharge[98-101]:

- Low-risk PE as defined by the original or simplified PESI score

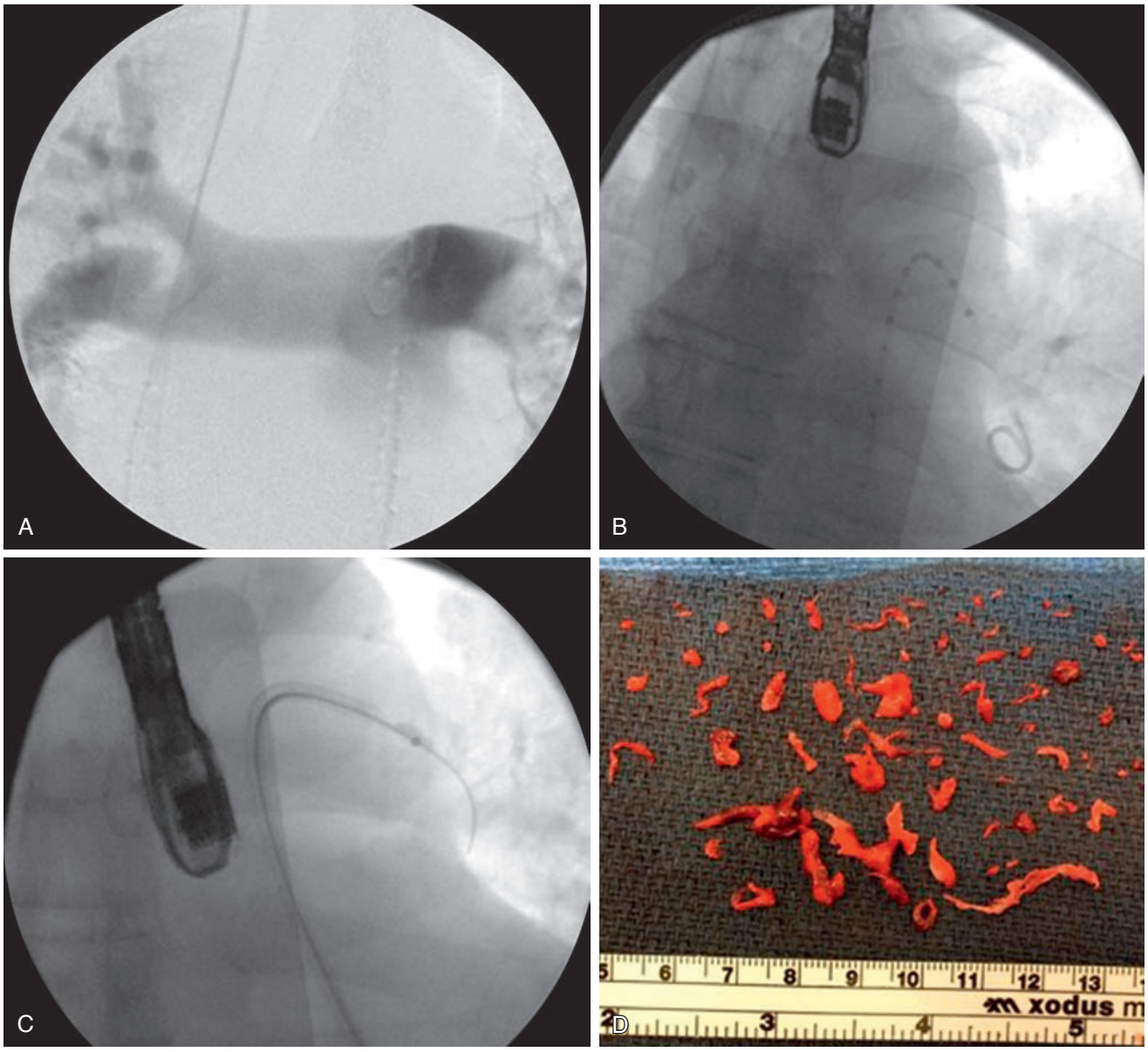

Figure 151.5 Massive pulmonary embolism (right ventricular strain and hemodynamic decompensation) on a patient with recent surgery and with intrapulmonary bleed due to the pulmonary infarct. (A) Intraoperative pulmonary angiogram indicating bilateral thrombus *(arrows)* (L>R). (B) Pigtail rotation within the major clot burden. (C) Aspiration thrombectomy using a10-F Pronto catheter (Vascular Solutions, Minneapolis, Minnesota). **D,** Extracted thromboembolic material. (Figure obtained with permission from Avgerinos ED, Chaer RA. Catheter-directed interventions for pulmonary embolism. *J Vasc Surg*. 2015;61:559–565.)

- Normal pulse and blood pressure
- No oxygen requirements
- No risk factors for bleeding including thrombocytopenia (<70.000/mm^3)
- No serious comorbid conditions (e.g., coronary artery disease, heart failure, chronic pulmonary disease, renal or liver failure)
- Mental capacity to understand the risk and the benefits
- Patient not living alone and having access to telephone and ability to return to hospital promptly if there is clinical deterioration
- Absence of major symptomatic DVT

Treatment Algorithm

Hemodynamic status remains the most important short-term prognostic factor for patients with acute PE, so patients need to be practically divided to stable and unstable, the unstable ones requiring emergent revascularization and systemic thrombolysis being their first alternative. The stable ones should be further divided to those who are at low and those who are at intermediate risk for a PE complication. Among the intermediate-risk patients, the clinician needs to further identify those who are most likely to decompensate and may benefit from a more

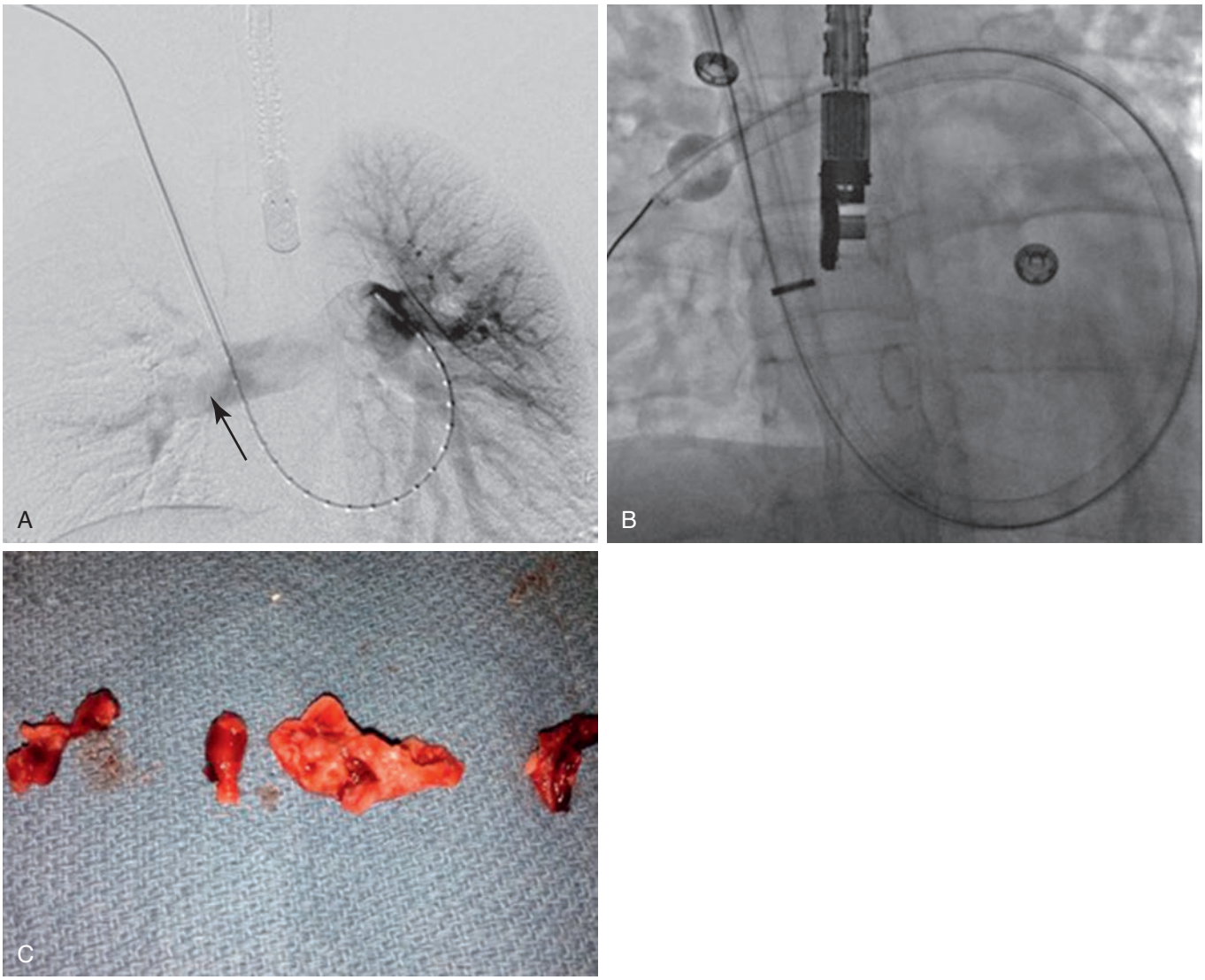

Figure 151.6 Submassive pulmonary embolism (right ventricular strain without hemodynamic decompensation) with increasing oxygen requirement, in a young patient, following brain abscess evacuation. (A) Pulmonary angiogram showing bilateral thrombus (R>L) (*arrow* points to the occluded right main pulmonary artery). (B) Angiovac (AngioDynamics, Latham, New York) aspiration from a jugular approach. (C) Extracted thromboembolic material. Cardiopulmonary parameters subsequently normalized. (Figure obtained with permission from Avgerinos ED, Chaer RA. Catheter-directed interventions for pulmonary embolism. *J Vasc Surg*. 2015;61:559–565.)

aggressive treatment. Current guidelines are summarized in Table 151.4.[8,44,45]

Due to lack of appropriate high-quality evidence, these guidelines lack strong recommendations for all but the lowest-risk PE patients. Many times, treating physicians will face dilemmas to what approach will best balance the benefits of intervention against potential risks of cardiopulmonary failure or death. The proliferation of novel interventional devices and technology underscores the need to have an integrative multidisciplinary approach flexible enough to evaluate and use multiple options, even in the absence of controlled clinical trial data or guideline recommendations. This need has been recently addressed by the creation of Pulmonary Embolism Response Teams (PERTs). A PERT brings together multiple specialists to rapidly evaluate intermediate- and high-risk patients with PE, formulate a treatment plan, and mobilize the necessary resources to provide the highest level of care. The PERT is staffed by select experts from cardiovascular medicine, vascular and cardiac surgery, interventional cardiology, radiology, echocardiography, emergency medicine, hematology, pulmonary, and critical care medicine, all of whom have a particular interest and competency in treating PE.[102,103]

An algorithm combining the recommended therapeutic strategies and our institutional experience on acute PE is suggested in Fig. 151.7.

Special Populations

Incidental Subsegmental Pulmonary Embolism

The clinical relevance of incidentally diagnosing subsegmental (asymptomatic) PE in a chest CT is uncertain, and the optimal therapy is controversial.[45,104] As a general rule,

TABLE 151.4 Societal Guidelines, Levels of Evidence, and Strength of Recommendation on the Early Management of Acute Pulmonary Embolism

	American Heart Association (2011)[44]	European Cardiology Society (2014)[42]	American College of Chest Physicians (2016)[45]
	I = Benefit ≫> Risk IIa= Benefit > Risk IIb= Benefit ≥ Risk III = Benefit ≤ Risk	I = Benefit ≫> Risk IIa= Benefit > Risk IIb= Benefit ≥ Risk III = Benefit ≤ Risk	1 = Strong recommendation 2 = Weak recommendation
	A = Multiple RCTs or MA B = One RCT or nonRCTs C = Expert consensus	A = Multiple RCTs or MA B = One RCT or nonRCTs C = Expert consensus	A = High-quality evidence B = Moderate-quality evidence C = Low-quality evidence
LMWH, iv or sc UFH, or sc fondaparinux (if no contraindication to anticoagulation)	IA	—	—
IVC filters are not recommended if patients are treated with anticoagulation	IIIC	IIIA	1B
IVC filters may be considered for patients with very poor cardiopulmonary reserve	IIbC	—	—
Hypotension (<90 mm Hg)			
IV anticoagulation with UFH	—	IC	—
Systemic thrombolysis if low bleeding risk	IIaB	IB	2B
Surgical pulmonary embolectomy if high bleeding risk or if systemic thrombolysis failed	IIaC	IC	—
Catheter directed treatment if high bleeding risk or if systemic thrombolysis failed	IIaC	IIaC	2C
Normotension			
LMWH or fondaparinux (IA) are recommended for most patients	—	IA	—
In parallel to parenteral anticoagulation, VKA should be initiated (IB)	—	IB	—
As alternative to parenteral anticoagulation with a VKA, rivaroxaban, apixaban, edoxaban or dabigatran, except for renal impairment	—	IB, IIIA[a]	—
For most patients, systemic thrombolysis is not recommended	—	—	1B
Systemic thrombolysis should be considered for intermediate high–risk PE[b] with low bleeding risk	—	IIaB	2C
Surgical pulmonary embolectomy may be considered for intermediate high–risk PE[b] if bleeding risk for systemic thrombolysis is high	IIbC	IIbC	—
Catheter-directed treatment may be considered for intermediate high–risk PE[b] if bleeding risk for systemic thrombolysis is high	IIbC	IIbB	2C
Early discharge and home treatment may be considered for low-risk PE if proper outpatient care and anticoagulation can be provided	—	IIaB	2B

[a]IIIA is the level of recommendation for renal impairment.
[b]Intermediate high risk is defined differently by each society but generally entails combination of imaging signs of RV dysfunctions with positive biomarkers or worsening clinical signs.

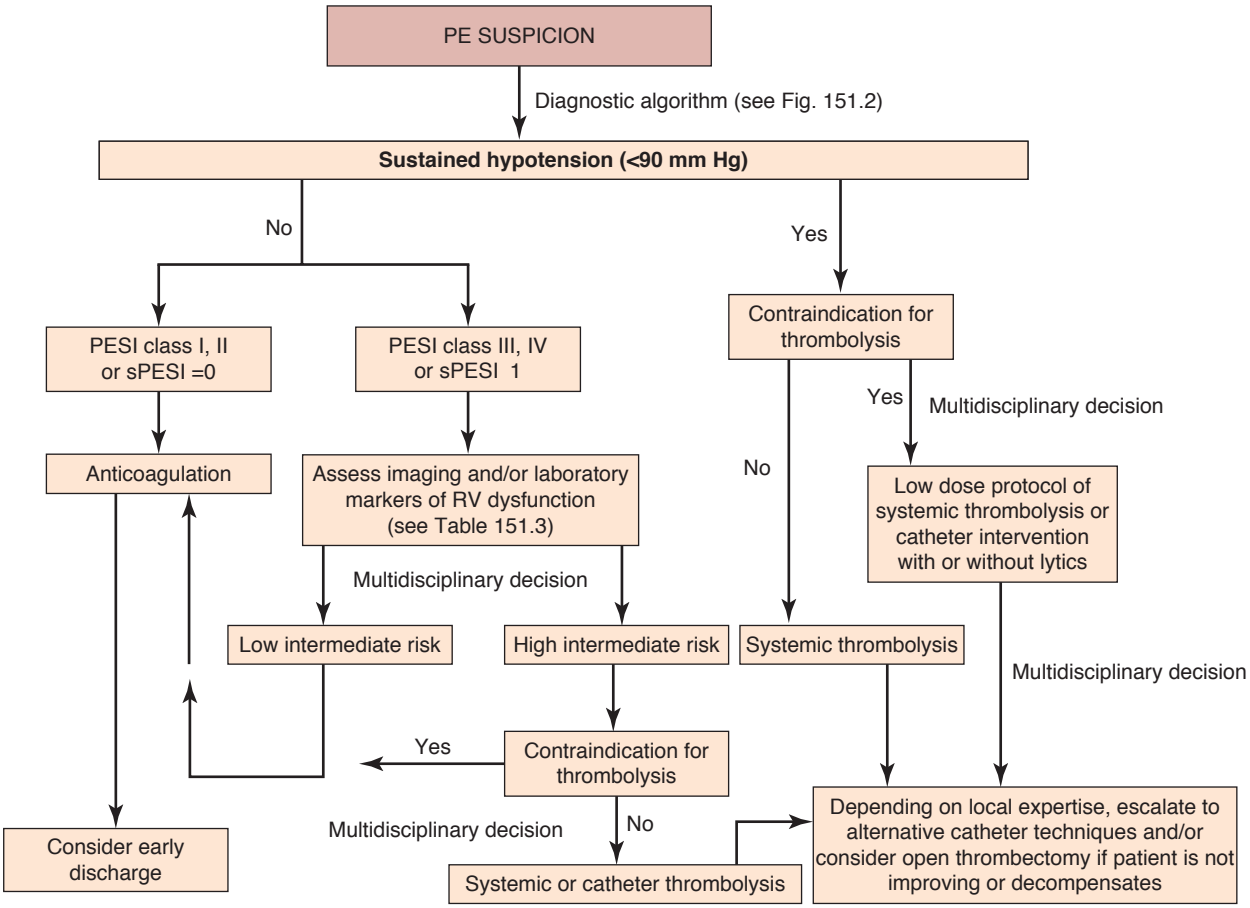

Figure 151.7 Suggested algorithm for the management of acute pulmonary embolism. *PE*, Pulmonary embolism; *PESI*, Pulmonary Embolism Severity Index; *RV*, right ventricular.

patients with risk factors for recurrent or progressive venous thromboembolism, who are hospitalized or have reduced mobility for another reason, have active cancer or a low cardiopulmonary reserve or marked symptoms, favor anticoagulant therapy; a high risk of bleeding favors no anticoagulant therapy.

Thrombus in Transit

Floating right heart thrombus, also known as "thrombus in transit," is a rare but potentially fatal condition of varying etiology, most commonly clots transiting toward the pulmonary vasculature from peripheral venous circulation. It is encountered in approximately 4% of all PEs according to ICOPER[105]; it usually coincides with massive PE, and the mortality rate can be as high as 40%.[106] There are no distinct guidelines established for the management of free-floating thrombus, and the results of anticoagulation only, thrombolysis, or surgical thrombectomy are variable.[107]

Pregnancy

PE is the leading cause of pregnancy-related maternal death in developed countries. The risk of PE is higher in the postpartum period, particularly after a caesarean section. Because pregnant women frequently complain of shortness of breath, this symptom should be interpreted with caution.[8] Data on the validity of clinical prediction rules for PE in pregnancy are lacking, but a retrospective series of pregnant women who were referred for CT angiography showed that no patient with an original Wells score of less than 6 points had a PE.[108] The usefulness of D-dimer is controversial, and although D-dimers physiologically increase throughout pregnancy, the usual cutoff values are used to rule out PE.[8] With a positive D-dimer, lower extremity duplex ultrasound can rule in DVT and anticoagulation initiated to avoid a CT scan. However, if duplex ultrasound is negative, a CT angiogram will be necessary. The radiation delivered is well below the threshold for fetal injury.[109] Nevertheless, lung scintigraphy, when available, may be preferred over CT, mainly to avoid radiation to the female breast and its potential effect on breast cancer.[110]

Adjusted dose of LMWH is the anticoagulant of choice in pregnancy. For high-risk PEs that will require thrombolytics, published data on 28 pregnant women treated with 100 mg of rtPA suggest that the risk of complications for the mother may be similar to that in the nonpregnant population.[111] Catheter interventions have a promising role, but evidence is still scarce.[112,113] Thrombolytic treatment should not be used peripartum, except for critical cases; surgical or catheter mechanical thrombectomy may have better results.

Cancer

Venous thromboembolism is four and six times more prevalent in cancer patients and in those undergoing chemotherapy, respectively.[1,114] Cancer is a risk factor for adverse outcomes in acute PE; patients are at a higher risk for bleeding, shock and death, or recurrent PE.[115,116] For most cancer patients with DVT, first-line therapy should be weight-based LMWH monotherapy for at least 3 to 6 months or as long as the cancer or its treatment is ongoing.[8,44,45]

Long-term anticoagulation with LMWH instead of warfarin appears to be more effective at preventing recurrent venous thrombosis without a statistically significant increase in bleeding risk. It is recommended to wait 6 months after cure or complete remission before stopping therapy, but consideration should be given to stopping therapy earlier in patients with a high bleeding risk, if the PE occurred post surgery or in those with lower risk of recurrence.[116]

Nonthrombotic Pulmonary Embolism

Nonthrombotic PE refers to the pulmonary arterial embolization of cell clusters (e.g., adipocytes, amniotic or tumor cells), bacteria or fungi, gas, or foreign materials.[8] Although clinical symptoms are similar to those of thrombotic PE, diagnosis can be a challenge and relies on a high index of suspicion and typical imaging findings.

Fat embolism is a rare entity, usually occurring after long bone fracture or orthopedic surgery and is classically described as triad of pulmonary (respiratory distress), central nervous system (altered mental status) and skin manifestations (petechial rash).[117] Treatment mainly includes supportive measures, although the use of steroids has been controversial.[8]

Amniotic fluid embolism is a rare but catastrophic condition. It involves a complex sequence of events triggered by entrance into the maternal circulation of material from the fetal compartment, resulting in an abnormal activation of proinflammatory mediators and a subsequent systemic inflammatory response. The typical presentation of amniotic fluid embolism includes a triad of sudden hypoxia and hypotension, followed in many cases by coagulopathy, all occurring in relation to labor and delivery. It should be considered in the differential diagnosis in any pregnant or immediately postpartum woman who suffers sudden cardiovascular collapse or cardiac arrest, seizures, severe respiratory difficulty, or hypoxia, particularly if such events are followed by a coagulopathy that cannot be otherwise explained.[118] Analysis of the national U.S. registry reveals that 70% of cases of amniotic fluid embolism occur during labor, 11% after a vaginal delivery, and 19% during a cesarean delivery.[118] Management is mainly supportive.

Tumor cell embolization is rarely diagnosed before death. Carcinoma of the prostate gland, digestive system, liver, and breast are the most commonly implicated. Tumor cell macroembolism is indistinguishable from the thrombotic PE. Treatment should target the underlying malignant disease.[8]

Septic embolism to the pulmonary circulation is a rare event commonly associated with right-sided endocarditis and manifests as sepsis with respiratory distress. Risk factors include intravenous drug abuse, infected indwelling catheters or pacemaker wires, and septic thrombophlebitis from the tonsils and the jugular, dental, and pelvic regions.[8,119] Eradication of the responsible bacterial or fungal microorganism and its source is the cornerstone of treatment.

Air embolism is an iatrogenic complication, with the lethal volume estimated between 100 and 500 mL. Supportive measures include high oxygen concentrations, volume expansion, aspiration with a central catheter, and patient placement in the left lateral decubitus position to prevent RV outflow obstruction by airlock.[8]

Pulmonary embolization of foreign materials has increased proportionally to the increase of venous endovascular interventions. Filter, stent, wire, or catheter particles have all been reported to have embolized in the pulmonary circulation. Retrieval when possible to prevent thrombosis and sepsis is recommended.[8]

PROGNOSIS

The prognosis of acute PE strongly varies, depending on the severity of pulmonary arterial obstruction and its impact on the RV function. RV failure is the most common cause of death in acute PE. As discussed earlier, RV strain is associated with an adverse in-hospital outcome, not only in hypotensive but in hemodynamically stable patients too. PE without RV dysfunction has a less than 2% death rate. RV dysfunction shifts mortality rates to 3% to 15% for normotensive and greater than 15%.[50,51,120] Anticoagulation, contemporary supportive treatment, and thrombolytic therapies continuously decrease these rates.[121,122] Among survivors, later mortality is unlikely to be related to PE, and it is most frequently attributed to other cardiovascular risk factors or underlying malignancies.[123,124] However, PE recurrence or CTEPH should be anticipated.

PE recurrence is not infrequent; for this reason, certain patient cohorts (e.g., cancer or unprovoked PE) are candidates for indefinite anticoagulant treatment after an initial episode. Recurrence while on anticoagulation is commonly the result of subtherapeutic anticoagulation. As a general rule, anticoagulants are discontinued when the perceived risk of anticoagulation-related bleeding and the inconvenience of remaining on treatment outweigh the risk of recurrent PE. Late recurrence has been reported to be 13% at 1 year, 23% at 5 years, and 30% at 10 years.[125,126] Interestingly, a recent large prospective study showed similar recurrence rates in patients with symptomatic subsegmental versus more proximal PE; however, the topic remains controversial.[127,128]

CTEPH is usually the result of at least one or multiple recurrent PEs, even if many times they may go unnoticed. Residual accumulating thrombus in the pulmonary arterial tree is remodeled into connective and elastic tissue, leading to vessel narrowing and remodeling. This will subsequently progress to small-vessel arteriolar vasculopathy.[44,129] Pulmonary hypertension results when the capacitance of the remaining healthy vascular beds cannot absorb the cardiac output. It is defined as mean pulmonary-artery pressure greater than 25 mm Hg that persists 6 months after the PE event, and, although it may be subclinical

for a long period, it may eventually manifest as dyspnea, fatigue, and exercise intolerance. It is estimated to occur in 2% to 4% of patients after acute PE, usually within 2 years.[130,131] There is some evidence that thrombolysis may potentially decrease the clinical occurrence of CTEPH because it seems to alter exercise tolerance and quality of life.[56,58,59,132] It is recommended that patients 6 weeks after an acute PE should be screened with an echocardiogram for persistent pulmonary hypertension that may predict the development of CTEPH.[44]

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 152

Vena Cava Interruption

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Venous thromboembolism (VTE) is a significant cause of morbidity and mortality that affects approximately 1 per 1000 of the population, with an annual estimate of 600,000 cases of clinically significant pulmonary embolism (PE) and approximately 200,000 deaths in the United States.[1,2]

Understanding that lower extremity deep venous thrombosis (DVT) can fragment and travel through the inferior vena cava (IVC) to the lung, the concept of vena cava interruption has been around since the 1700s. In 1784 John Hunter performed the first femoral vein ligation for thrombophlebitis, and in 1893 Bottini reported successful ligation of the IVC to prevent PE. Since then, numerous techniques of vena cava interruption have been described for the prevention of PE, including femoral vein and IVC ligation and partial interruption of the IVC by means of plastic clips, plication, or mechanical staplers.[3-6] These later measures were developed to compartmentalize the vena cava to allow blood flow but trap large emboli, and they were the mainstay of treatment through the 1950s and 1960s. Despite these measures, there were high rates of IVC occlusion and significant lower extremity venous-related problems with little improvement in outcome of patients with PE. With the development of techniques to allow transvenous delivery of intravascular vena cava devices, in 1967 the Mobin-Uddin umbrella filter was introduced. Structured as a silicone membrane with a hole to allow blood flow, it was associated with a high rate of vena cava thrombosis and was subsequently discontinued. In 1973 the original stainless steel Greenfield filter was introduced, followed by titanium Greenfield filter in 1989 and lower profile stainless steel Greenfield filter in 1995, and, as the most extensively studied filter, is the filter design with which all modern filters are compared. Over the past few decades, several additional filter designs have been developed that have favorable properties, including ease of deployment, clot-trapping effectiveness, preservation of IVC flow, and in more recent years, optional filter designs that allow retrieval of the filter.

FILTER DESIGN

Design Considerations

The functional goal of filters is to prevent PE by trapping venous thromboemboli in the vena cava, not to prevent or treat venous clots. Based on this design goal, there are several features that are preferred for optimal function and minimal compromise,

Abstract

Use of Vena Cava Filters continues to evolve. This chapter reviews filter design features, current available filter types, clinical indications and evidence based guidelines for use, anatomic considerations, and techniques for placement and retrieval.

Keywords

IVena Cava Filter
Deep Venous Thrombosis
Pulmonary Embolism
Inferior Vena Cava
Superior Vena Cava

including the use of nonthrombogenic, biocompatible, nonferromagnetic, durable implantable material. Filtering efficiency should be high without impedance of flow, and there should be a single trapping level and conical design, which provides the highest filtering-to–flow volume ratio (Fig. 152.1). Ideally, the filter should have a self-centering mechanism with secure fixation to the vena cava wall, a filter hook length and angle sufficient to prevent migration when the filter is in place, and the ability to be retrieved when no longer needed without limitation of the time frame for incorporation. The optimal filter should be highly visible on imaging with ease of percutaneous delivery through a low-profile system and a simple release mechanism. Repositioning and retrievability should also be possible, and the potential for complications should be negligible. The financial cost of filter delivery should be low.

Vena cava filter design categories include the following:

1. *Permanent filter*. Placed with the intention of providing permanent, lifelong filtration, permanent filters have design characteristics that maximize secure fixation.
2. *Temporary filter*. Not currently available in the United States, these filters are not designed for permanent placement and do not have any means of fixation to the vena cava wall. Rather, temporary filters are attached to a wire or catheter that traverses the venous system and either protrudes from the skin or is buried in adjacent subcutaneous tissue. Removal is required before the filter or tether becomes incorporated.
3. *Convertible filter*. Functioning initially as a permanent filter with elements allowing attachment to the vena cava wall, convertible filters can be altered structurally after implantation to a nonfiltration state with removal of the filtration portion through a separate percutaneous procedure.
4. *Optional/retrievable filter*. Similar to a conventional permanent filter, optional or retrievable filters have the added feature of removal capability. Retrievable filters adhere to the wall of the vena cava with hooks, barbs, or radial force (or any combination of the three) but can be retrieved by image-guided catheter techniques within a device-specific time interval.[7]

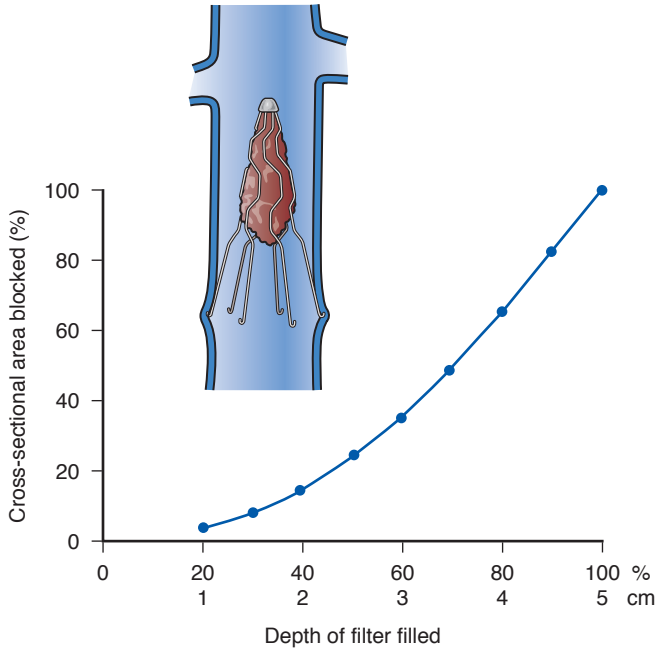

Figure 152.1 Relationship between the percentage and depth of thrombus trapped within the filter and the percentage of cross-section occluded.

Filter Types

Understanding individual filter designs, advantages, and limitations is important before placement to ensure proper filter selection. For the purpose of this chapter, only US Food and Drug Administration (FDA)-approved permanent and optional/retrievable filter designs are discussed (Table 152.1 and Fig. 152.2).

Conical filter design is most optimal and permits progressive central filling while allowing circumferential blood flow peripherally, which helps to maintain vena cava patency. For example, the conical geometry of the Greenfield filter makes it possible for thrombi to fill and occlude 70% of the filter cone, a volume of thrombus of approximately 4 cm^3 (34.3% of the total volume), while reducing the cross-sectional area by less than 50%. If the cone is filled to 80% of total volume, the reduction in cross-sectional area is 64%, at which point venous flow begins to decrease and venous pressure proximal to the filter begins to increase.[8] The ability of this conical filter design to trap clinically significant emboli without impeding flow has been demonstrated.

Although other filter designs have double trapping levels or double basket designs and have higher capacity to capture smaller emboli, flow dynamics are reduced compared with single trapping conical designs and may be associated with higher vena cava occlusion rates. In addition, although rapid and stable incorporation may be desirable for permanent filter design to maintain position and prevent migration, retrievable filter designs need to have sufficient incorporation to prevent migration but not so much that retrieval cannot be accomplished. Altering the filter hook contact point to allow retrievability may have the disadvantage of an increased tendency for filter leg penetration or filter migration. This has also resulted in different filter hook length and angle configurations. Although some filters (such as Greenfield filter) incorporate recurved configuration to create a contact angle of 80 degrees, allow better hook incorporation without full penetration into the vena cava, other filters (such as Celect, Denali, OptionElite, ALN Optional filters) use different hook configuration to prevent excessive incorporation and facilitate retrievability. Filter designs such as Vena Tech LP, OptEase, and Crux filters do not depend on filter legs for fixation, thereby minimizing potential for penetration. Similarly, although some filters do not have self-centering features, others have included independent self-centering mechanisms. To improve self-centering of the filter, some designs have increased contact points with the vena cava wall, which prevents tilt but may lead to increased incorporation and a possible tendency for vena cava occlusion. These additional filter features do not offer any additional filtering capacity, may change flow dynamics, and can potentially lead to filter centering strut penetration of the vena cava wall.

TABLE 152.1 Comparison of Design Features for Current US Food and Drug Administration–Approved and Commercially Available Vena Cava Filter Devices (2013)

Filter Device	Manufacturer	Material	Design	Approach	Delivery Catheter Size: Inner Diameter (Fr)	Maximum Caval Diameter (mm)	Maximum Deployed Length (mm)	FDA-Approved Use
Stainless steel Greenfield filter	Boston Scientific, Natick, Massachusetts	Stainless steel	Conical Single trapping	Femoral/ jugular	12	28	49	Permanent
Titanium Greenfield filter	Boston Scientific, Natick, Massachusetts	Titanium	Conical Single trapping	Femoral/ jugular	12	28	47	Permanent
Simon nitinol filter	Bard Peripheral Vascular, Tempe, Arizona	Nitinol	Conical Bilevel	Femoral/ jugular/ antecubital	7	28	38	Permanent
Denali	Bard Peripheral Vascular, Tempe, Arizona	Nitinol	Conical Bilevel	Femoral/ jugular	8.4	28	50	Permanent or optional
Vena Tech LP filter	B. Braun/Vena Tech, Bethlehem, Pennsylvania	Phynox	Conical Single trapping	Femoral/ jugular	7	28	43	Permanent
Vena Tech Convertible	B. Braun/Vena Tech, Bethlehem, Pennsylvania	Phynox	Conical Single trapping	Femoral/ Jugular	12.9	28	—	Permanent or convertible
TrapEase filter	Cordis Endovascular, Miami, Florida	Nitinol	Double basket	Femoral/ jugular/ antecubital	6	30	50	Permanent
OptEase filter	Cordis Endovascular, Miami, Florida	Nitinol	Double basket	Femora l/ jugular/ antecubital	6	30	54	Permanent or optional
Bird's nest filter	Cook Inc., Bloomington, Indiana	Stainless steel	Variable	Femoral/ jugular	12	40	80	Permanent
Günter Tulip filter	Cook Inc., Bloomington, Indiana	Conichrome	Conical Single trapping	Femoral/ jugular	Femoral 8.5 Jugular 7	30	50	Permanent or optional
Celect Platinum	Cook Inc., Bloomington, Indiana	Conichrome	Conical Single trapping	Femoral/ jugular	7	30	51	Permanent or optional
ALN Optional Filter	ALN, Bormes Les Mimosas, France	Stainless steal	Conical	Femoral/ jugular/ brachial	7	28	55	Permanent or optional
Option, Option Elite	Argon Medical Devices, Inc., Plano, Texas	Nitinol	Conical	Femoral/ jugular/ antecubital/ popliteal	6.5	30	56.5	Permanent or optional
Crux Vena Cava Filter System	Phillips Volcano, San Diego, California	Nitinol	Helical	Femoral/ jugular	9	17-28	Depends on vena cava diameter	Permanent or optional

FDA, US Food and Drug Administration.

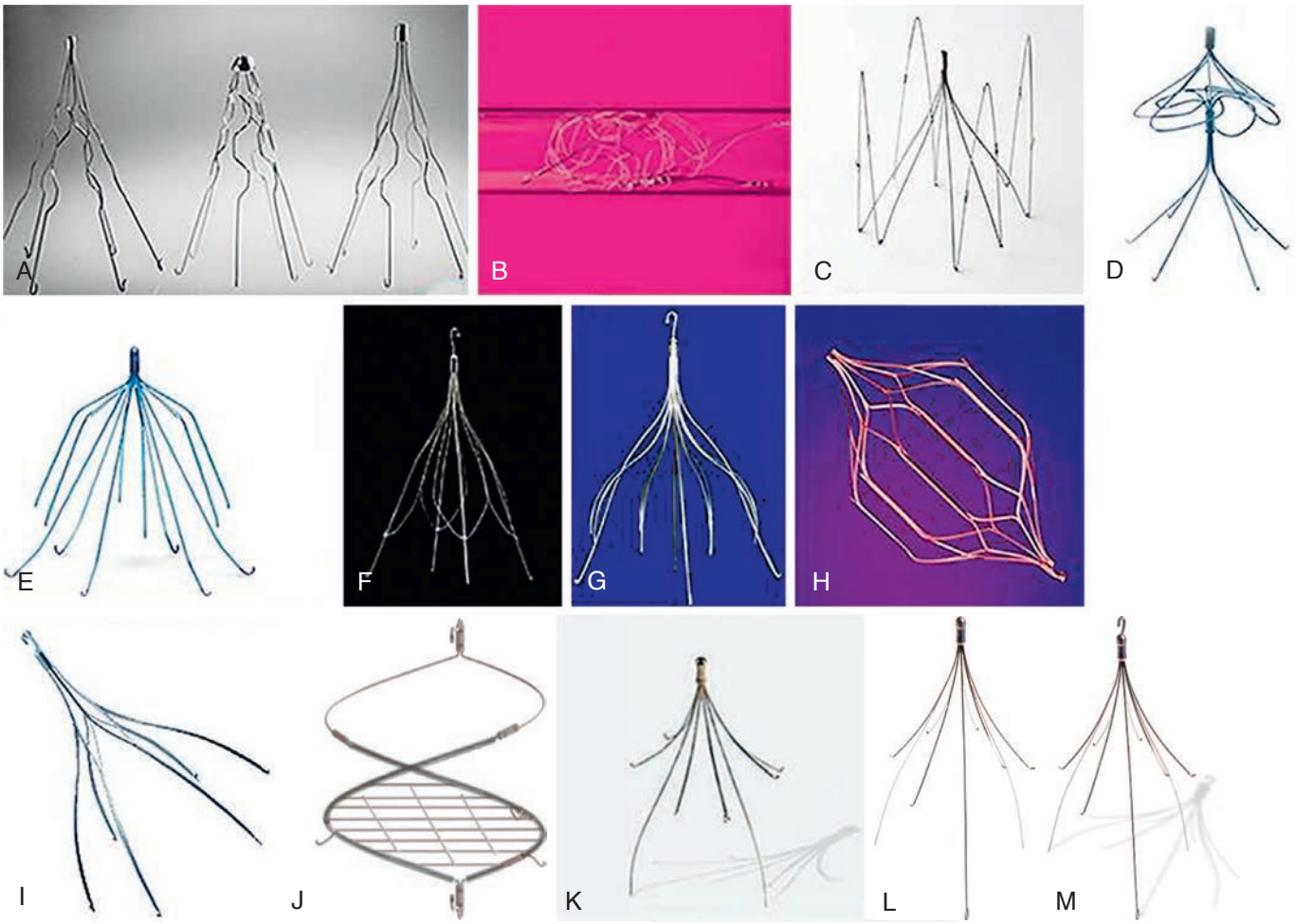

Figure 152.2 Current US Food and Drug Administration–approved filter designs. **(A)** Boston Scientific Titanium Greenfield filter, original Stainless Steel Greenfield filter, and low profile Stainless steel Greenfield filter (from left to right); **(B)** Cook Gianturco-Roehm bird's nest filter; **(C)** Bard Simon nitinol filter; **(D)** Bard Denali filter; **(E)** B Braun Vena tech LP filter; **(F)** B Braun Vena tech convertible filter; **(G)** Argon Option Elite filter; **(H)** Cook Gunter Tulip filter; **(I)** Cook Celect Platinum filter; **(J)** Cordis OptEase filter; **(K)** Phillips Volcano Crux Vena Cava filter; **(L)** ALN Optional filter; and **(M)** ALN Optional filter with hook.

Newer filter technology has led to availability of convertible filter designs (such as Vena Tech Convertible) which functions as a filter upon deployment but allows for removal of the filter portion and conversion to an open configuration when clinically indicated. When choosing the best filter option, these design characteristics should be considered, weighing the risks and benefits of the filter design to the clinical scenario for filter placement.

CLINICAL INDICATIONS

Recommended indications for the use of vena cava filters are shown in Box 152.1. Without anticoagulation, the risk of PE developing in patients with VTE is high, and it may be fatal in as many as 25% of patients (see Chapter 151). Because of this significant risk, vena cava interruption with an implantable filtering device should be considered in patients with documented VTE and contraindications to anticoagulation. Resumption of anticoagulation as soon as possible is recommended because, although vena cava filters are effective in preventing PE, they are not effective for prevention of DVT.

Evidence-based guidelines from the 2012 American College of Chest Physicians (ACCP)[9] recommend vena cava filter placement in patients with documented VTE and a contraindication to anticoagulation, complication of anticoagulation, or recurrent VTE despite therapeutic anticoagulation. Contraindications to or complications of anticoagulation can include need for major surgery, intracranial hemorrhage, pelvic or retroperitoneal hematoma, ocular injury, solid intra-abdominal organ injury, uncorrected major coagulopathy, coagulation disorder, peptic ulcer disease, and other associated medical problems. In the updated 2016 ACCP guidelines on Antithrombotic Therapy for VTE Disease, there is further recommendation against the routine use of vena cava filters in addition to anticoagulation for acute DVT or PE if the patient can be therapeutically anticoagulated, thereby supporting the prior recommendations.[10]

Beyond these strong evidence-based guidelines, expanded relative indications based on inconclusive evidence have included

BOX 152.1 Evidence-Based Guidelines, Relative Expanded Indications, and Contraindications to Vena Cava Filter Placement

Evidence-Based Guidelines

- Documented VTE with contraindication to anticoagulation
- Documented VTE with complications of anticoagulation
- Recurrent PE despite therapeutic anticoagulation
- Documented VTE with inability to achieve therapeutic anticoagulation

Relative Expanded Indications

- Poor compliance with anticoagulation
- Free-floating iliocaval thrombus
- Renal cell carcinoma with renal vein extension
- Venous thrombolysis/thromboembolectomy
- Documented VTE and limited cardiopulmonary reserve
- Documented VTE with high risk for anticoagulation complications
- Recurrent PE complicated by pulmonary hypertension
- Documented VTE—cancer patient
- Documented VTE—burn patient
- Documented VTE—pregnancy
- VTE prophylaxis—high-risk surgical patients
- VTE prophylaxis—trauma patients
- VTE prophylaxis—high-risk medical condition

Contraindications

- Chronically occluded vena cava
- Vena cava anomalies
- Inability to access the vena cava
- Vena cava compression
- No location in the vena cava available for placement

PE, Pulmonary embolism; *VTE*, venous thromboembolism.

BOX 152.2 Relative Recommendations for Vena Cava Filter Use as Venous Thromboembolism Prophylaxis, Including High-Risk Patient Factors and/or High-Risk Situation Combined With an Increased Bleeding Risk

Prophylaxis in High-Risk Patients

- Critically ill
- Previous DVT
- Family history of DVT
- Morbid obesity
- Malignancy
- Known hypercoagulable state
- Prolonged immobility

Prophylaxis in Trauma

- Multiple traumatic injuries
- Spinal cord injury
- Closed head injury
- Complex pelvic fractures
- Multiple long-bone fractures

Increased Bleeding Risk

- Major operation
- Intracranial hemorrhage
- Solid intraabdominal organ injury
- Pelvic or retroperitoneal hematoma
- Ocular injury
- Medical problems (cirrhosis, end-stage renal disease, peptic ulcer disease, medication, coagulation disorder)

DVT, Deep venous thrombosis.

poor compliance with anticoagulation; free-floating iliocaval thrombus; renal cell carcinoma with renal vein extension; placement in conjunction with venous thrombolysis or thromboembolectomy; presence of DVT and limited cardiopulmonary reserve or chronic obstructive pulmonary disease; recurrent PE complicated by pulmonary hypertension; proven DVT in an oncology, burn, or pregnant patient; and venous prophylaxis in high-risk surgical, medical, or trauma patients. A clinical decision algorithm for vena cava filter use for prophylaxis of VTE is shown in Box 152.2. Recommendations should be based on a combination of high-risk patient factors or situations with a high risk of bleeding prohibiting use of anticoagulation for prophylaxis.

Permanent Versus Optional Retrievable Filter

Filter use has expanded significantly in the United States over the past few decades, especially for prophylaxis of VTE.[11] Unfortunately, evidence-based recommendations for vena cava filter use are derived predominantly from nonrandomized data, with substantial differences existing among studies in terms of study populations, immediate and long-term end points, and duration of follow-up. Because of difficulties comparing data on different filters, several guidelines outlining reporting standards for filter devices have been published.[12-14] Overall reported complications for vena cava filters include PE (2%–5%), fatal PE (0.7%), death linked to filter insertion (0.12%), venous access site thrombosis (2%–28%), filter migration (3%–69%), vena cava penetration (9%–24%), vena cava obstruction (6%–30%), venous insufficiency (5%–59%), filter fracture (1%), and guide wire entrapment (1%).[15,16]

Although it is unclear whether filters actually improve survival, they do provide protection against PE. Because the risk for PE in patients with proven VTE and contraindications to anticoagulation is high, potential complications of filters must be balanced against the risk of no filter. Despite the large number of filters placed, randomized evidence on permanent filters is limited. In the PREPIC (Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption) trial, 400 patients with proximal DVT with or without PE were randomized in a 2 by 2 factorial study design to filter placement versus no filter and unfractionated heparin versus enoxaparin. There was a significantly lower incidence of PE with filter protection during the first 12 days (1.1% vs. 4.8%), but the filter group had a significantly increased incidence of recurrent DVT at 2 years (20.8% vs. 11.6%).[17] Eight-year follow-up data from the PREPIC trial confirmed the previous findings of cumulative recurrent PE (6.2% vs. 15.1%, filter versus no filter, respectively) but increased recurrent DVT (35.7% vs. 27.5%) and no difference in postthrombotic venous insufficiency or survival.[18] The authors concluded that although permanent filter use may be beneficial in patients at high risk for PE, systematic use in the general

population with VTE is not recommended. Unfortunately, no firm conclusions regarding filter efficacy in the prevention of PE can be drawn from the PREPIC trial given that the study design varies significantly from the wider application in current clinical practice (i.e., patients with documented VTE in whom anticoagulation has failed or cannot be administered).

Although the potential for significant adverse outcomes with permanent filters is low, there are long-term complications that could be avoided with optional filters. However, given the paucity of randomized data, determining the best permanent versus optional filter design is difficult. Some studies have used meta-analysis of data to compare the different filter designs and document the efficacy of filters in the prevention of PE and complication rates.[19-21] In the randomized open label, blinded end point PREPIC-2 trial for hospitalized patients with acute PE, the use of retrievable vena cava filters plus anticoagulation compared with anticoagulation alone did not reduce the risk of symptomatic recurrent PE at 3 months. Although PREPIC-2 did not support the use of retrievable filter in patients with acute PE who can be anticoagulated, the role of retrievable filters in patients who cannot be anticoagulated, those with DVT but no PE, or for other selected relative indications remains unclear based on current evidence.[22]

Table 152.2 summarizes data on different filter types. Overall, most of the available filters are approximately equivalent in prevention of PE, but there is some variation in complication rates.[23,24] Penetration of the IVC wall by filters is also being noted with increasing frequency. In a systematic review of the literature from 1970 to 2014, overall frequency was 19%, with 8% exhibiting symptoms usually due to organ/structure involvement. Although asymptomatic filter penetration is often noted incidentally on imaging, endovascular retrieval or surgery is usually required for symptomatic patients.[25]

Data on the efficacy and safety of retrievable filters are derived from small series with insufficient long-term data in comparison to other permanent filter designs to warrant permanent implantation. With the lack of extended outcome data for optional filters, the decision to use a retrievable filter instead of a permanent filter should be based on the intent to discontinue filtration. Factored into this decision should be the anticipated required duration of protection from VTE versus the risk associated with anticoagulation. In patients with proven VTE, anticoagulation should be resumed as soon as possible when the risk has diminished. For patients in whom filters are placed for prophylaxis of VTE, anticoagulation should be restarted in accordance with published VTE prophylaxis guidelines. When the risk of resuming anticoagulation is extended, permanent filtration would be preferable.

Further complicating the decision to use retrievable filters is poorly defined timing of possible retrieval. Based on FDA indications for use (IFU), retrieval of Günther Tulip filters is recommended within 20 days, OptEase filters within 14 days, and the Celect filter within 52 weeks. More recently approved filters like Denali, OptionElite, ALN Optional, and Crux do

TABLE 152.2 Comparison of Vena Cava Filter Types for the Prevention of Pulmonary Embolism and Complication Rates Based on Systematic Reviews of Vena Cava Filter Studies

		COMPLICATION RATES			
Filter Device	PE: Overall (%)	PE: Fatal (%)	Insertion Site Thrombosis (%)	Vena Cava Thrombosis (%)	Filter Migration (%)
Stainless steel Greenfield	3.5	1.3	8.6	3.5	[a]
Titanium Greenfield	3.4	1.8	13.1	4.4	[a]
Percutaneous stainless steel Greenfield	2.7	0.3	4.3	3	[a]
Simon nitinol	3.3	1.8	11.5	5.2	[a]
Bird's nest	3.4	1.5	7.4	2.8	[a]
Vena Tech LP or LGM	3.6	0.9	15.3	9.5	[a]
TrapEase	0.9	[a]	0.4	2	[a]
OptEase	1.6	[a]	0.8	3.7	0.3
G2	3.4	[a]	—	3.7	4.5
Recovery G2	1.0	[a]	10.4	1.o	0.8
Günter Tulip	0.9	0.4	[a]	2.3	0.7
Celect	1.1	[a]	1.2	0.6	0.6
ALN Optional	0.7	[a]	14.0	1.8	0.5
Rex Option	4.0	[a]	18.0	1.0	[a]
G-2 Express, Eclipse, Meridian, Denali, Crux[a]	[a]	[a]	[a]	[a]	[a]

[a]Insufficient systematically reviewed published data to report.

PE, Pulmonary embolism.

Data from Hann CL, Streiff MB. The role of vena cava filters in the management of venous thromboembolism. *Blood Rev.* 2005;19:179–202; and Angel LF, Tapson V, Galgon RE, et al. Systematic review of the use of retrievable inferior vena cava filters. *JVIR.* 2011;22(11):1522-1530.

not have clearly specified time windows based on FDA IFU. Further confusing optimal timing are case reports suggesting that potential retrieval at extended periods is possible for all filters but can be more problematic with a higher failure rate.[26-29] Regardless, the longer a filter is in place, the less successful retrieval will be, as shown in a recent systematic review showing technically successful retrieval rates of 99% at 1 month and 94% at 3 months, falling to 37% at 12 months.[30] Until further data are available, the optimal period for retrieval of currently available optional filters probably falls within a few months of placement, after which the technical success of retrieval will diminish.

With the expanding use of retrievable vena cava filters, there has been a growing body of literature and reports to the FDA Manufacturer and User Facility Device Experience (MAUDE) database that led FDA to issue a communication of risk of adverse events with long-term use[31] on August 9, 2010: "Since 2005, the FDA has received 921 device adverse event reports involving IVC filters, of which 328 involved device migration, 146 involved embolizations (detachment of device components), 70 involved perforation of the IVC, and 56 involved filter fracture." The FDA raised concern that some of these events may be related to retrievable filters being left in place for extended time, beyond the time when risk of PE has subsided. As a result, the FDA recommended that "implanting physicians and clinicians responsible for the ongoing care of patients with retrievable IVC filters consider removing the filter as soon as possible when protection from PE is no longer needed." In an external follow-up study of the MAUDE database of 1606 reported adverse events involving 1057 filters, 86.8% involved retrievable filters versus 13.2% for permanent filters, although this data source is limited by self-reporting mechanisms and may underestimate true filter complication rates.[32] To determine optimal timing for filter retrieval based on a mathematical model, the FDA published a quantitative decision analysis weighing risk of PE versus risk of IVC filters over time showing a risk-benefit profile cross point favoring removal of IVC filter between 29 and 54 days.[33] The FDA has since updated the original 2010 safety communication on May 6, 2014, reiterating the importance of filter removal as soon as protection from PE is no longer needed and when the risk/benefit profile favors removal based on the patients overall health status.[34] In addition, the FDA is now requiring collection of clinical data for currently marketed IVC filters in the United States to address further safety questions for both permanent and retrievable filter designs either by manufacturers conducting postmarket studies (522 studies) or through manufacturer's participation in the ongoing PRESERVE (PREdicting the Safety and Effectiveness of InferioR VEna Cava Filters) study, which began enrolling in 2015.[35]

Also limiting retrieval has been patients being lost to follow-up. Once a retrievable filter has been placed, evidence has suggested that active protocols that follow patients after filter placement and determine optimal timing of retrieval are more successful than passive protocols in terms of limiting lost to follow-up and improved filter retrieval rates.[36-39]

In conclusion, retrievable filters should be considered in the following clinical scenarios: (1) indications for permanent filters are not present, (2) the risk of clinically significant PE is acceptably low, (3) return to high risk for VTE is not anticipated, (4) life expectancy is long enough that the benefit of filter removal will be realized, and (5) the filter can be removed safely or converted.[7] Optional/retrievable filters should not be used as a replacement for a permanent filter if permanent PE prevention is needed.

Specific Patient Groups

Trauma Patients

The risk of VTE in trauma patients is high, with a reported incidence of DVT without prophylaxis as high as 50% and incidence of PE as high as 30%.[40,41] The 2012 ACCP recommendation for trauma patients with at least one risk factor is to receive some form of thromboprophylaxis, preferably with an anticoagulant if there is no contraindication based on bleeding, or mechanical prophylaxis.[42] For patients who cannot receive anticoagulation, mechanical thromboprophylaxis is recommended but not the use of vena cava filters. Although VTE prophylaxis with anticoagulation protocols is recommended by the 2012 ACCP and also by the 2002 Eastern Association for the Surgery of Trauma guidelines,[43] there is a lack of level I data supporting any recommendation for or against filters.

Because of the risk of bleeding in severely injured trauma patients, standard pharmacologic thromboprophylaxis may not be possible. Routine prophylactic filter placement has been recommended by some for use in trauma patients who were considered at very high risk for VTE, with most series reporting a decreased incidence of all PE and fatal PE with the use of vena cava filters in appropriately selected high-risk patients.[44-47] Level II and III data would indicate that the risk to benefit ratio of prophylactic filter placement is favorable in high-risk trauma patients. In a retrospective review of 9721 patients, high-risk categories included head injury plus spinal cord injury, head injury plus long-bone fracture, severe pelvic fracture plus long-bone fracture, and multiple long-bone fractures.[48] A meta-analysis demonstrated a 0.2% incidence of PE with filters as opposed to 1.5% in controls without a filter and 5.8% in historic controls.[41] In a comparison of 40 critically injured patients who received a filter and 80 matched historic controls, PE occurred in 3% versus 18%, respectively.[49] At a 5-year follow-up of 132 trauma patients receiving prophylactic filters, Rogers and coauthors reported a 2.3% incidence of PE after filter placement and a mortality of 4.4% with one fatal PE episode.[50]

With the availability of optional filters, there has been an increased trend in many trauma centers for the use of prophylaxis. Most studies evaluating retrievable filters in high-risk trauma patients have reported a high technical success rate and low incidence of PE, but the actual rate of retrieval has been variable.[51] In a large multicenter study, 446 patients received a retrievable vena cava filter, with the majority (76%) being placed for prophylaxis, but only 22% were retrieved.[52] Meier and coworkers analyzed 35 trauma patients in whom prophylactic retrievable vena cava filters were placed; retrieval was possible in 86%, and 36% had trapped clot or thrombus within the

device.[53] In a study of 127 multitrauma patients with retrievable filters, Rosenthal and coauthors reported that 52% underwent uneventful retrieval after pharmacologic prophylaxis was initiated. Of the remaining filters not removed, most were left because of contraindications to anticoagulation and only a few because of thrombus trapped within the filter.[54]

Analysis of the results of filter placement in trauma patients is limited mainly by the lack of adequate control groups, with most series using unmatched cohorts or historical data for comparison. Several reports and a meta-analysis of prospective studies found no difference in rates of PE in patients with and without prophylactic filters.[55] In a review of a trauma quality collaborative registry, use of IVC filter placement had no effect on reduction of trauma patient mortality and were associated with an increase in DVT events.[56] To date, there have been no randomized clinical trials in which the prophylactic use of vena cava filters was shown to be more beneficial than other effective prophylactic measures. Until these issues are resolved by level I evidence-based data, use of IVC filters is indicated in patients with proven DVT and a contraindication to therapeutic anticoagulation. Based on level II and III data in patients without documented DVT, use of vena cava filters as prophylaxis for thromboembolism may be considered only for those who have very high-risk criteria and cannot receive anticoagulation.

Bariatric Patients

Obesity is a strong independent risk factor for the development of VTE. PE is considered the most important cause of perioperative mortality in bariatric surgical patients, with an incidence of 1% to 3%, but the incidence has been reported to be as high as 17%, especially in superobese patients (body mass index = 55 kg/m^2).[57-59] Combined with the added risk associated with surgery, the potential risk for VTE is increased.

Difficulty in proper dosing of anticoagulation thromboprophylaxis in obese patients increases susceptibility to venous thromboembolic–related morbidity and mortality. In a 2000 survey of American Society of Bariatric Surgery members, more than 95% of participants reported using prophylaxis routinely, and 38% used two prophylactic measures simultaneously.[60] Despite the routine use of thromboprophylaxis, the incidence of PE in bariatric surgery patients has remained relatively stable, even with the addition of standardized heparin protocols and the application of minimally invasive approaches to bariatric surgery. Several authors have compared various thromboprophylactic regimens, but no conclusive results on the safest and most effective form of anticoagulation were reached.[61-64] Furthermore, several studies suggest that the risk for PE after bariatric surgery extends to the period after hospital discharge, a finding compounded by the decreased hospital stays after minimally invasive bariatric surgery.[65,66]

Because of these limitations of anticoagulation, placement of vena cava filters for thromboprophylaxis in bariatric surgical patients has become increasingly common. In a study of 5554 bariatric operations by Hamad and Bergqvist, risk factors for postoperative VTE, including body mass index greater than 60, truncal obesity, and hypoventilation syndrome, were identified and recommended as indications for prophylactic filters.[67] In a comparison of the incidence of VTE in 248 high-risk bariatric patients receiving vena cava filters and 2852 low-risk patients who did not receive filters, Obeid and colleagues showed that the incidence of PE was not significantly different.[68] The use of prophylactic IVC filters reduced the risk for PE in high-risk obese patients, a group known to have a much greater incidence of morbidity and mortality, to a rate comparable to the baseline risk of a low-risk group.

With the recent availability of optional/retrievable filters, there is the potential for using vena cava filters as a bridge during the highest risk period with subsequent removal. Piano and colleagues analyzed outcomes from a standardized approach in which retrievable filters were inserted in 59 patients undergoing bariatric surgery who met high-risk criteria.[69] All filters were placed immediately before surgery, and removal was attempted 4 weeks postoperatively. There was one postoperative PE (1.7%) and no fatal PE or deaths.

However, evidence from these studies favoring prophylactic vena cava filters in high-risk bariatric patients is significantly limited by small study sample size, lack of prospective data, no adequate control populations, and variable approaches to VTE prophylaxis. In a recent systematic review of IVC filter use for prevention of VTE in obese patient undergoing bariatric surgery, published data reporting safety and efficacy was noted to be heterogeneous and there was no clear evidence to suggest the potential benefit of IVC filters outweighing risk in this population.[70] Given the relative infrequency of fatal PE after bariatric surgery, much larger trials are required before the indications for and efficacy of vena cava filter placement in the bariatric surgery population can be better defined.

Orthopedic Patients

Patients undergoing major orthopedic surgery, including total hip arthroplasty, total knee arthroplasty, and traumatic lower extremity fracture repair, have a significantly increased risk for VTE.

The role of the IVC filter in elective major orthopedic procedures is not well delineated. Several studies support the efficacy of filter placement for the prevention of VTE in selected orthopedic patients. In a cohort of 95 joint arthroplasty patients either with confirmed PE or at high risk for the development of PE in whom an IVC filter was implanted, Austin and colleagues showed that vena cava filter placement was effective in preventing fatal PE in all patients.[71] Golueke and coauthors reported no filter-related complication or PE in 88 joint arthroplasty patients who received a vena cava filter in the perioperative period.[72] Vaughn and associates observed fatal PE in 1 of 24 total joint arthroplasty patients who underwent filter insertion and concluded that placement of an IVC filter is a safe, easy, and effective method of preventing fatal PE in selected joint arthroplasty patients.[73]

Optional filters may be more appropriate in these high-risk orthopedic patients because they provide temporary protection at the time of increased risk and are intended to be retrieved when the risk for VTE has diminished. Strauss and coworkers reported on 58 high-risk orthopedic patients in whom retrievable IVC filters were placed as an adjunct to standard venous

thromboprophylaxis.[74] There was minimal morbidity associated with filter placement and two deaths unrelated to the filter or PE. Sixty-four percent of the filters were removed at a mean of 37.8 days, whereas others were left in place for up to 238 days, which allowed them to serve as temporary prophylaxis and avoid the development of long-term complications. The authors concluded that for high-risk orthopedic patients, placement of a retrievable IVC filter as an adjunct to standard pharmacologic or mechanical prophylaxis is an effective means of preventing PE.

Although the use of retrievable filters has the advantage of bridging high-risk orthopedic patients during the period of most increased risk, in the absence of randomized studies their use should be limited at this time. Based on current evidence-based guidelines, use of either permanent or optional vena cava filters in high-risk orthopedic patients should be reserved for those with documented VTE and a contraindication to or complication of anticoagulation.

Cancer Patients

Malignancy is an independent risk factor for the development of VTE, with a reported incidence of 7% to 50% and a risk for PE twofold to fourfold higher in patients with malignancy than without.[75] Although some authors have suggested that primary filter placement in patients with malignant disease may be beneficial, others have favored anticoagulation.[76-78] Lin and associates suggested that vena cava filters may be a reasonable alternative to long-term anticoagulation in a subgroup of patients at high risk for recurrence, provided that their quality of life is reasonable and a decrease in the risk for fatal PE is justified.[79] In a review of 308 patients, Wallace and colleagues showed that filters can be placed in patients with VTE and cancer without higher rates of procedure- or filter-related complications than in historical controls, although patients with a history of DVT and bleeding or metastatic/disseminated disease have the lowest survival.[80]

The fiscal impact of filter placement in cancer patients may be less than anticoagulation therapy because of the added costs of treating bleeding complications of anticoagulation therapy.[81] Marcy and associates reviewed 30 patients with malignancy who had filters placed; 76% were alive at 1 month, 56% at 3 months, and 40% at 6 months.[82] In comparing the complication rates and cost, vena cava filter placement was favored if reasonable survival was expected. Chau and coworkers used a Markov model to compare the cost-effectiveness of filters versus anticoagulation.[83] Vena cava filters were not cost-effective in patients with brain tumors, but when the model was applied to the anticipated 5-year survival for a breast cancer population, vena cava filter placement appeared to be more cost-effective than did anticoagulation alone. From the available data, it appears that filter placement is most cost-effective in cancer patients with documented VTE, good functional status, and anticipated survival.

A problem with filters as primary therapy for cancer patients is the finding of increased VTE events—PE, recurrent DVT, or vena cava thrombosis. The rate of recurrent VTE events after filter placement in cancer patients varies from 4% to 62%.[84-86] Inhat and colleagues, in a review of 166 cancer patients with VTE, showed that although technical complications of filter placement are low, serious life-threatening or limb-threatening thromboembolic complications developed in 17% of patients, and survival was poor in all patients regardless of treatment,[87] thus leading to support for a conservative approach of routine anticoagulation therapy with selective filter placement. Thus filters should be reserved for cancer patients with documented VTE, contraindications to or complications of anticoagulation, and longer anticipated survival and should be discouraged in patients with advanced malignant disease and a poor prognosis.

High-Risk General Surgical Patients

The incidence of DVT in general surgical patients not receiving prophylaxis varies between 15% and 30%, with rates of fatal PE between 0.2% and 0.9%.[88-92] The type and duration of surgery clearly influence the risk for VTE, with most outpatient surgeries having a low frequency, and more extensive inpatient operative procedures increasing risk. Although mechanical methods of prophylaxis are attractive options in general surgery patients who are at high risk for bleeding, they have not been studied as extensively as pharmacologic thromboprophylaxis but appear to reduce rates of DVT. The ACCP 2012 consensus statement recommends that mechanical prophylaxis be considered for patients who have a particularly high risk of bleeding.

Overall use of prophylactic vena cava filters for high-risk general surgery patients is not well defined. There are some perceived advantages of IVC filters in high-risk surgical patients in avoiding the bleeding risk associated with thromboprophylaxis and extending VTE prophylaxis past discharge. In a registry of 1375 consecutive patients with DVT who had undergone recent major surgery, VTE prophylaxis was used in only 44%, and IVC filters were more common in these surgical patients than in medical patients.[93] Vena cava filter use in general surgery patients should be limited to the standard indications for documented VTE in patients with contraindications to or complications of anticoagulation.

Pregnant Patients

Indications for IVC filters during pregnancy fall in line with the standard indications for documented VTE and complications of or contraindications to anticoagulation. What differs for vena cava filter placement in pregnancy is the recommendation for suprarenal positioning because of compression of the infrarenal portion of the vena cava by an enlarging pregnant uterus, especially in the third trimester. Use of jugular access may also be preferred to avoid catheterization of the vena cava adjacent to the gravid uterus. Matchett and associates have shown in a series of 22 patients that suprarenal permanent filter insertion is safe without kidney dysfunction,[94] and AbuRahma and Mullins showed that placement of a permanent IVC filter in 18 pregnant patients with DVT significantly decreased maternal morbidity and mortality with low complications.[95] Suprarenal insertion of optional filters can be problematic during pregnancy because of higher potential for possible migration than with permanent filters.[96] Use of optional filters seems to

be an attractive alternative for providing VTE prophylaxis to high-risk patients with proven DVT, particularly those with a short-term contraindication to anticoagulation. In eight pregnant women with DVT, Kocher and colleagues showed that suprarenal placement and removal can occur in the perinatal period without major complications.[97]

INFERIOR VENA CAVA FILTERS

Anatomic Considerations

The normal IVC is located on the right side and is composed of four main segments in the craniocaudal direction: the hepatic, suprarenal, renal, and infrarenal segments (Fig. 152.3). The IVC is formed by the confluence of the left and right iliac veins and drains the venous return from the lower extremities, pelvis, and abdomen back to the heart. At its origin around the L4 to L5 vertebral level, the IVC is posterior to the right common iliac artery, where it ascends to the right of the aorta and receives additional branch drainage from lumbar veins. The renal veins drain into the IVC at the L1 to L2 vertebral level, with the right renal vein shorter and more caudal and the left renal vein longer, more cephalic, and crossing over the aorta. The left gonadal vein typically drains into the left renal vein, whereas the right gonadal vein is more variable and sometimes drains into the right renal vein, directly into the IVC, or at the confluence of the IVC and the right renal vein. At this level the IVC runs posterior to the head of the pancreas and ascends posterior to the liver as the infrahepatic portion. The left, middle, and right hepatic veins and often a separate branch from the caudate lobe join the infrahepatic vena cava before it passes behind the right crus of the diaphragm to enter the right atrium.

There are some anatomic variations of the IVC that reflect incomplete involution or persistence of the cardinal veins during embryologic development (see Chapter 2).[98-100] These variations are important to identify before filter placement because their presence and location may affect filter placement.

1. *Renal vein anomalies*. Multiple bilateral renal veins and retroaortic or circumaortic left renal vein anomalies are the most common and may be present in 5% to 7% of the population. Although a retroaortic renal vein will not affect filter placement, circumaortic renal veins may have a large confluence with the IVC or may have separate drainage. Although the tip of the filter should be positioned inferior to the lowest portion of any circumaortic vein, it is critical to identify any additional renal veins to avoid inadvertent tilting caused by entrapment of one of the filter legs.
2. *IVC transposition*. Transposition of the vena cava occurs in 0.2% to 0.5%. The left-sided IVC usually drains into the left renal vein, which crosses to the right and continues cephalad in the normal position. Filters can still be positioned in a transposed vena cava, but anatomic landmarks, especially the location of the right renal veins, need to be accurately defined, and suprarenal vena cava placement may be preferred.
3. *IVC duplication*. Vena cava duplication is present in 0.2% to 0.3%. The right-sided IVC typically drains the right iliac vein and right renal vein, whereas the left-sided IVC, which is usually smaller in diameter, drains the left iliac veins and joins the left renal vein, where it crosses over into the right-sided vena cava. Demonstration of this anomaly is important because placement of a filter in the right IVC only may not provide adequate prevention of PE in a patient with a left-sided DVT. For duplicated vena cava anomalies, placement of a filter in each vena cava or in the suprarenal vena cava after the left renal vein crosses over is required.[101]
4. *IVC agenesis*. Absence of the infrarenal segment of the IVC is an extremely rare anomaly, but hepatic segmental anomalies occur when the right subcardinal vein fails to anastomose with the hepatic sinusoids and is referred to as an abnormal IVC with azygos drainage or infrahepatic interruption of the IVC with azygos continuation. In this anomaly the infrarenal IVC is normal, whereas the renal segment drains into the azygos system and right atrium through the superior vena cava. Cardiovascular defects, such as dextrocardia, atrial septal defect, and pulmonary artery stenosis, and visceral anomalies, such as polysplenia/asplenia and renal defects, are associated with this anomaly.[102,103] Filter placement in an enlarged azygos vein pathway in patients with this congenital anatomic variation of the IVC has also been described.[104]

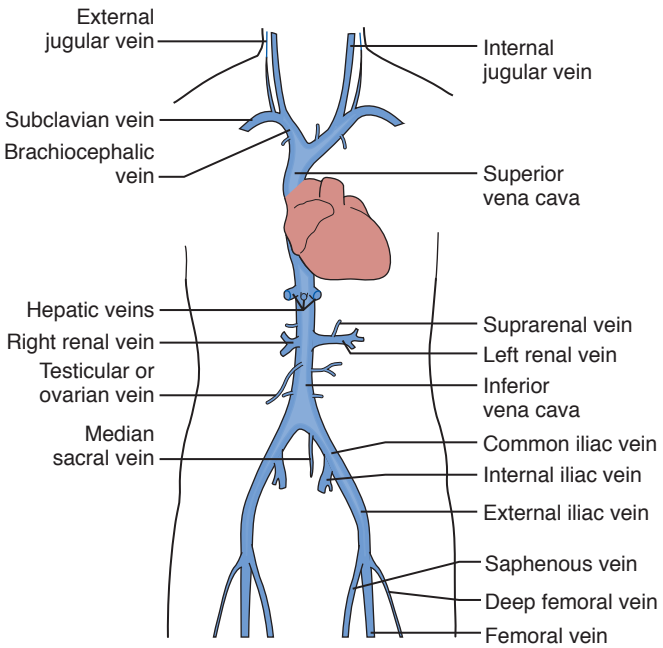

Figure 152.3 Normal inferior vena cava anatomy.

Technical Considerations

The reported technical success rate is usually 98% to 100% with low complication potential. Overall, acute procedure-related complications of venographic-guided filter placement include malpositioning (1.3%), hematoma (0.6%), air embolism (0.2%), arterial puncture (0.04%), arteriovenous fistula (0.02%), and pneumothorax (0.02%).[105] Fatal complications are rare and occur in 0.13% of insertions. Although a higher procedural mortality rate has been noted to be associated with the bird's

nest filter (0.34%) than with the titanium Greenfield filter (0.15%), stainless steel Greenfield filter (0.11%), and Vena Tech filter (0.07%), with scant reports for the other filters, most of these fatal events are more likely due to patient comorbid factors and not necessarily filter-related problems.[106,107]

Suprarenal filter placement may be required if thrombus is present in the IVC; for malpositioning of an infrarenal filter, a duplicate IVC, and ovarian vein thrombosis; or when a filter is needed during pregnancy. In a series of 22 suprarenal filters, Matchett and coauthors reported renal insufficiency in 6%, recurrent PE in 6%, filter migration in 28%, filter fracture in 6%, and filter penetration in 6%.[108] In a series of 148 suprarenal filters, Greenfield and Proctor reported that recurrent PE occurred in 8%, caval occlusion in 8%, filter penetration in 7%, and migration in 15%.[109] Although data are limited, suprarenal filter placement can be performed but should be reserved for selected patients in whom the risk for PE outweighs the potential development of these filter complications.

Bedside placement of IVC filters under either transabdominal duplex ultrasound or intravascular ultrasound guidance has been shown to be safe, effective, and reliable.[101-104,110-113] Transport of critically ill and immobilized patients to the interventional suite for filter placement is not without complications; requires extra support staff, cost, and time; and poses additional risk from exposure to radiation and contrast agents.[114,115] In a collective reported experience, 498 patients were initially imaged by transabdominal duplex ultrasound, and technical feasibility was determined in 435 patients (87.3%).[116-118] The procedural technical success rate for filter placement with transabdominal duplex ultrasound guidance when IVC visualization was adequate was 97.7% (n = 425 patients). If visualization with transabdominal duplex ultrasound was determined to be inadequate, bedside imaging with intravascular ultrasound was then performed. Of 53 patients imaged with intravascular ultrasound, technical feasibility was determined to 96.2% (n = 51 patients), and the procedural technical success rate for placement under intravascular ultrasound guidance was 96.1% (n = 49 patients). The potential for malpositioned IVC filters as a result of suboptimal imaging remains a risk with bedside insertion, but this risk is low, approximately 2% to 3%. In an experience of 396 bedside filter placements using IVUS in critically ill patients over a 5-year period, IVUS guidance continued to be a safe and effective option in a high-risk population, with noted time-dependent improvement in outcome measures.[119] Although malpositioned filters have traditionally been managed by either observation or insertion of a second filter, percutaneous retrieval and repositioning techniques have been described, even for "nonretrievable" filters, thus allowing an effective rescue technique without significant additional morbidity or mortality.[120]

Venographically Guided Filter Placement

Use of fluoroscopy either in an operating room setting with a mobile C-arm fluoroscope or in an endovascular or radiology suite with fixed-arm imaging is the standard approach for most filter placements. Depending on the clinical situation and the filter type used, femoral, jugular, or antecubital percutaneous access is obtained. Although some techniques described included placement of filters based on bony landmarks alone, this approach should be discouraged because there is some variability in renal vein positioning and potential venous anomalies that need to be better defined before filter delivery. Guide wire and catheter access into the vena cava is obtained for initial nonselective venography. Venographic images of the IVC are obtained for confirmation of venous landmarks, correlation with bony vertebral levels, and exclusion of the presence of thrombus at the intended deployment level.[121,122] Correlation of bony landmarks with venography showed that the lowest most renal vein corresponded to the L1 vertebral body in 17.3%, the L1 to L2 disk space in 36.5%, the L2 vertebral body in 34.6%, the L2 to L3 disk space in 7.7%, and the L3 vertebral body in 3.8%. Similarly, the common iliac vein confluence corresponded to the L5 to S1 disk space in 3.8%, the L5 vertebral body in 80.8%, the L4 to L5 disk space in 11.5%, and the L4 vertebral body in 3.8%.[123] Although guidance by nonselective venography is usually adequate for defining the iliac confluence and renal vein levels before filter deployment, additional selective venography may be an important consideration if these important venous landmarks cannot be defined. With selective catheterization of the renal veins and across the iliac confluence, important venous anomalies, especially a duplicate IVC, can be identified. With the addition of selective venography, detection of aberrant anatomy or some abnormal finding that leads to a change in the intended location for filter deployment occurred in 11% to 30% of patients in some series.[124-126] Additional large venous branches in the infrarenal portion of the IVC are also identified to avoid deployment of a filter leg into the branch and prevent tilting of the filter. Based on venographic guidance, the filter is then ideally positioned with the tip at the lowest most renal vein and the base above the iliac confluence.

If suprarenal filter placement is required, venographic imaging of the suprarenal vena cava is required to confirm the level of the renal veins for the distal landmark and the position of the hepatic vein confluence. Usually this will align with the T11 to L1 vertebral body levels. The suprarenal vena cava is generally larger than the IVC, and accurate diameter measurements should be made to confirm a diameter smaller than 28 mm. For suprarenal filter positioning, it is important to align the filter leg attachment point just above the most cephalic renal vein to avoid deployment of the filter hook into a renal vein, which may cause the filter to tilt. Although the level of the tip of the filter is less important, if possible it is best for it to be below the hepatic vein confluence to avoid potential hepatic vein thrombosis (Fig. 152.4).

Transabdominal Duplex Ultrasound–Guided Filter Placement

Transabdominal duplex ultrasound is performed to determine whether visualization of the IVC at the renal vein level is adequate in both the transverse and longitudinal axis views.[127] Identification of the right renal vein is important because it is usually the lowest most renal vein. In the longitudinal axis, the level of the right renal artery serves as an indirect landmark for the right renal vein. Percutaneous venous access is obtained and a guide wire is passed into the IVC under duplex ultrasound

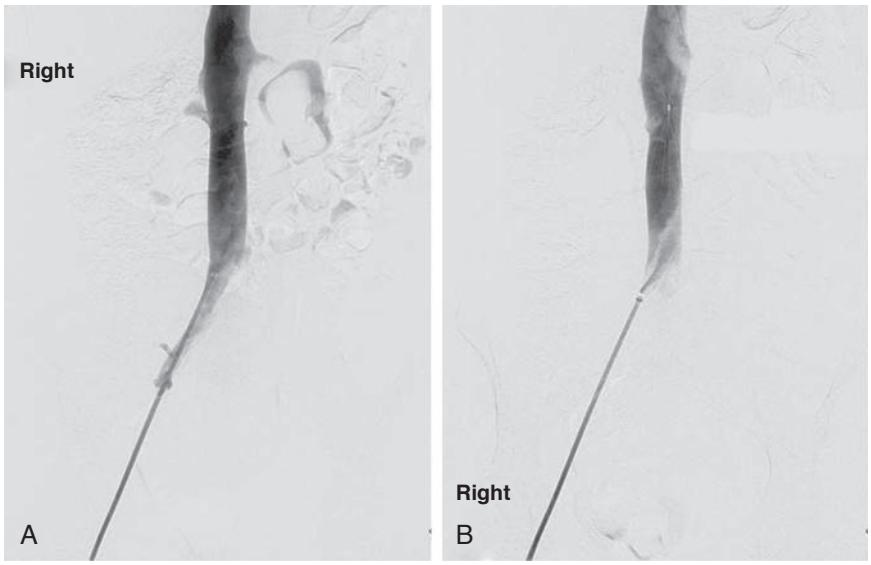

Figure 152.4 Suprarenal vena cava filter placement in a patient with a tortuous and enlarged infrarenal segment **(A)**. Note the base of the filter just above the renal vein origins, the tip below the hepatic vein confluence, and the filter in straight axial alignment in the suprarenal segment of the vena cava **(B)**.

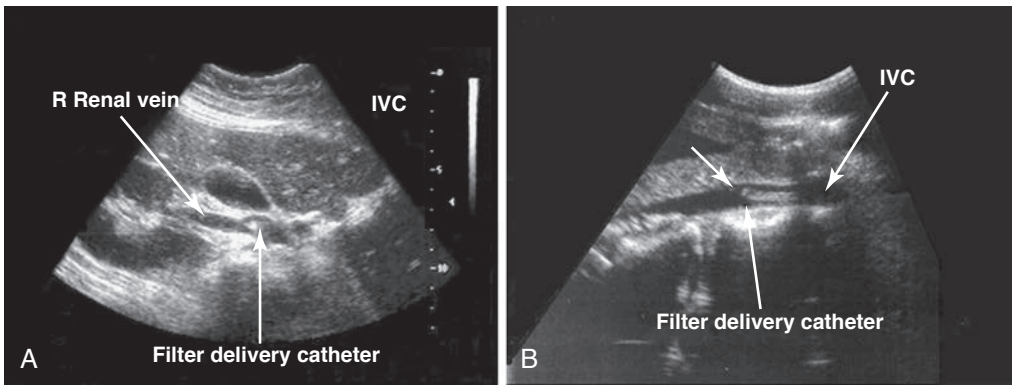

Figure 152.5 Visualization of the tip of the filter delivery catheter at the right renal vein–inferior vena cava (IVC) junction in the transverse **(A)** and longitudinal planes **(B)** during bedside placement of the filter under transabdominal duplex ultrasound guidance. (Reprinted with permission from Passman MA, Dattilo JB, Guzman RJ, Naslund TC. Bedside placement of inferior vena cava filters by using transabdominal duplex ultrasonography and intravascular ultrasound imaging. *J Vasc Surg.* 2005;42:1027–1032.)

visualization. The introducer sheath is inserted to a level just past the renal vein confluence under duplex ultrasound guidance. For over-the-wire filter systems, the guide wire needs to be removed to be able to differentiate the end of the filter delivery catheter. The right renal vein–IVC junction is visualized transversely, and the filter delivery catheter is advanced inside the sheath to the renal vein level (Fig. 152.5). With the filter delivery catheter in the correct position, the sheath is slowly pulled back to expose the filter delivery catheter tip at the renal vein level. The filter delivery catheter can be moved back and forth to confirm its position, and when the tip of the filter delivery catheter disappears and reappears in this view, the intended deployment position has been reached. In the longitudinal view the tip of the filter delivery catheter should be easily visualized and in proper alignment. Under direct visualization with duplex ultrasound in the longitudinal view, the filter is deployed. Postdeployment duplex ultrasound imaging confirms full expansion and proper position of the filter in the IVC (Fig. 152.6).

Intravascular Ultrasound–Guided Filter Placement

After adequate local anesthesia, percutaneous femoral venous access is obtained. Depending on the intravascular ultrasound system used, usually an 8-Fr sheath is needed. Although smaller profile intravascular ultrasound probes can be used, the image size produced with the increased-megahertz probe is generally too large for adequate visualization of adjacent anatomic landmarks. The intravascular ultrasound probe is inserted into the sheath over the guide wire and directed into the IVC to the level of the right atrium of the heart. Using a pull-back technique, the venous anatomic landmarks are sequentially identified, including the right atrium, hepatic veins, renal veins, and confluence of the iliac veins (Fig. 152.7). If the location of the iliac vein confluence is unclear, additional contralateral femoral venous access is obtained for passage of a second guide wire to allow precise identification of this confluence at the level where this second contralateral wire is visualized in the IVC. The intravascular ultrasound probe is directed just below the level of the lowest most renal vein, and IVC diameter

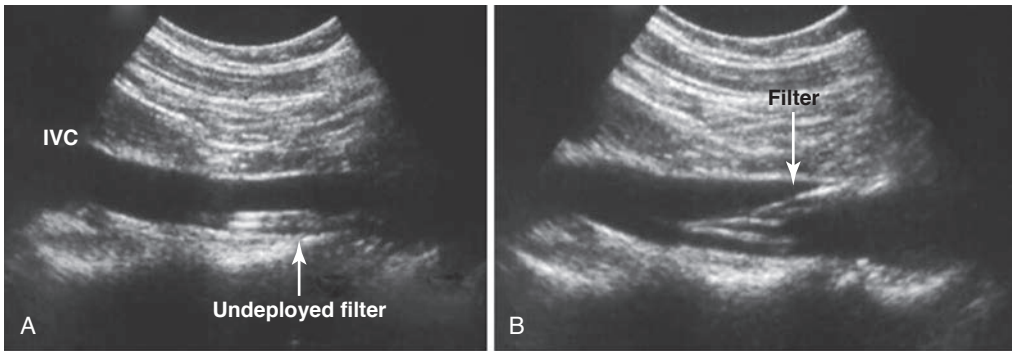

Figure 152.6 Confirmation of proper filter deployment in the inferior vena cava (IVC) after bedside placement under transabdominal duplex ultrasound guidance, both undeployed **(A)** and after deployment **(B)**. (Reprinted with permission from Passman MA, Dattilo JB, Guzman RJ, Naslund TC. Bedside placement of inferior vena cava filters by using transabdominal duplex ultrasonography and intravascular ultrasound imaging. *J Vasc Surg.* 2005; 42:1027–1032.)

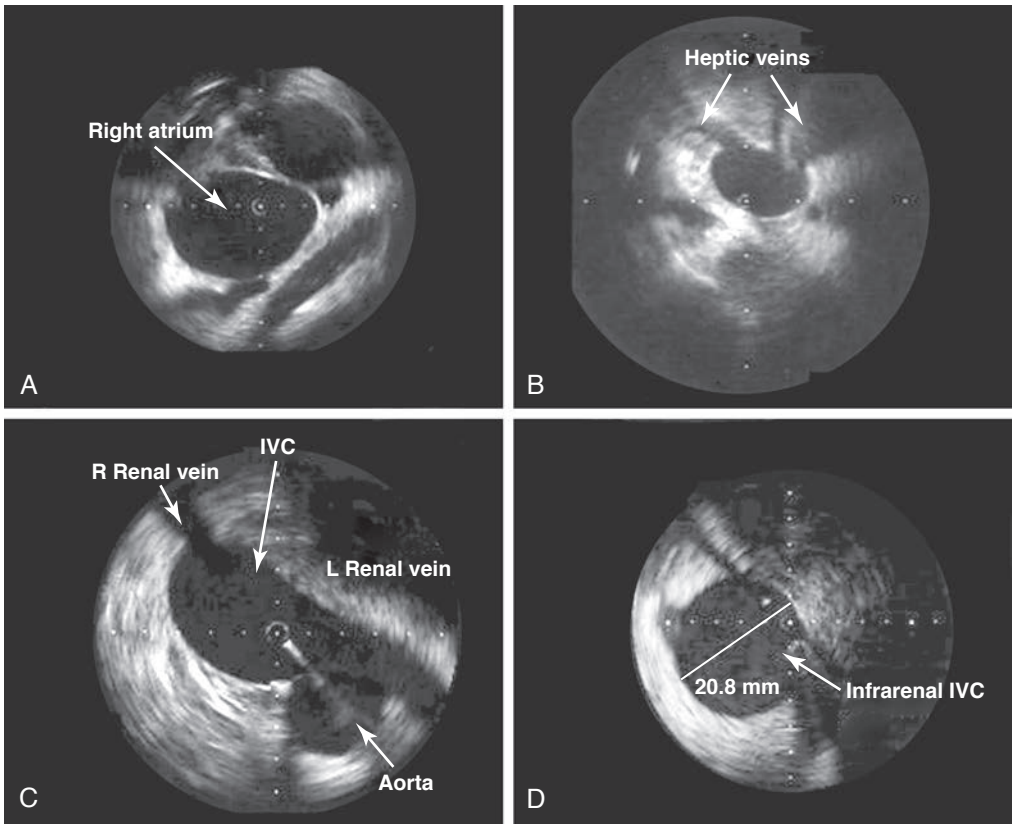

Figure 152.7 Preprocedure imaging of the inferior vena cava (IVC) with intravascular ultrasound to identify venous anatomic landmarks at the right atrium **(A)**, hepatic veins **(B)**, renal veins **(C)**, and infrarenal IVC above the iliac vein confluence **(D)**. (Reprinted with permission from Passman MA, Dattilo JB, Guzman RJ, Naslund TC. Bedside placement of inferior vena cava filters by using transabdominal duplex ultrasonography and intravascular ultrasound imaging. *J Vasc Surg.* 2005;42:1027–1032.)

measurements are made before proceeding with deployment of the IVC filter.

A single–venous access technique can be used if the filter delivery kit sheath exceeds 8 Fr. Sheath exchange is performed over the guide wire, and the sheath is advanced to the predetermined level of the renal veins. The intravascular ultrasound probe is used to precisely direct the end of the sheath to the level of the lowest most renal vein. For filter systems with predetermined marks (such as the Günther Tulip and Celect filters), the filter delivery catheter is advanced to the mark by aligning the tip of the filter with the end of the sheath, and then the sheath is withdrawn in a "pin-pull" fashion to allow deployment of the filter at the infrarenal level.[128] For filter systems without predetermined marks (such as the Greenfield filter), the sheath is first pulled back over the intravascular probe a distance equivalent to the length that the filter delivery catheter extends beyond the sheath (for the Greenfield filter, this distance is approximately 7 cm) so that when the filter delivery catheter

is loaded into the sheath, the tip of the filter will precisely align with the lowest most renal vein on deployment.

If filter placement is not feasible with the single-puncture technique or for lower profile filter systems, a dual–venous access technique is required.[129,130] The intravascular ultrasound probe is left at a position just below the renal veins. Separate percutaneous access is obtained, preferably in the contralateral femoral vein, which allows confirmation of the iliac confluence and avoids double large sheaths in the same femoral vein. If contralateral venous thrombosis is present, the ipsilateral femoral vein adjacent to the intravascular ultrasound probe can be used, but the potential for access site thrombosis is increased. With real-time intravascular ultrasound imaging, the filter delivery catheter is directed to the level of the renal veins through the additional femoral access (Fig. 152.8). Once position of the filter delivery catheter tip is confirmed, the intravascular ultrasound probe is pulled back and the filter is deployed. The intravascular ultrasound probe can be carefully advanced to confirm apposition of the filter legs to the IVC wall, but care should be taken when advancing the filter tip to avoid dislodgement. Postprocedure plain abdominal radiographs are obtained to verify filter position and alignment.

Filter Retrieval

When an optional/retrievable filter is placed, a retrieval timeline should be determined. Retrieval should be timed for a period when the risk for PE is low, when anticoagulation can be restarted if continued VTE treatment or prevention is required, and when retrieval can be performed safely with low complication potential. At the time of retrieval, the integrity of the filter should be radiographically confirmed to make sure that there are no filter-related problems that would make retrieval not possible. Venography should be performed first to determine whether thrombus is present within the filter, in which case the filter should be left in place. Depending on the type of optional filter used, different approaches and techniques are required. For the Cordis OptEase filter, percutaneous femoral access is obtained and a snare is used on the caudal hook to recapture the filter into a 10-Fr sheath. For the Cook Günther Tulip and Celect filters, percutaneous jugular access is obtained and a snare is used on the cephalic hook to recapture it into an 11-Fr sheath. For the Bard Denalifilter, ALN Optional filter, and OptionElite filter which incorporates a hook at the apex of the filter, retrieval options using snare techniques via jugular access are also performed. The Crux filter has bidirectional retrieval options from either jugular or femoral access using snare techniques. The VenaTech Convertible filter has a release mechanism at the filter apex which when retrieved using a snare catheter allows open conversion and deactivation of the filter portion leaving the attachment struts in place.

Independent of filter type, during the retrieval process difficulty releasing the filter from the IVC attachment may occur, and retrieval should be aborted if the filter does not release with modest tension. For malpositioned or difficult-to-retrieve filters, additional advanced techniques using various wire/catheter combination techniques to free up filter hook, balloon angioplasty of attachment points, and bronchoscopic forceps to directly grab filter hook have also been described but should be reserved for special situations.[131-133]

SUPERIOR VENA CAVA FILTERS

Upper extremity DVT is becoming increasingly common, especially with the expanding use of central venous access, pacemakers, and implantable defibrillators. Other contributing factors, including thoracic outlet–related venous occlusion, malignancy, congestive heart failure, sepsis, and thrombophilia, have also been implicated. The risk for PE with upper extremity DVT is approximately 5% to 10% in most series, but risk as high as 28% and several cases of fatal PE have been reported.[134-138]

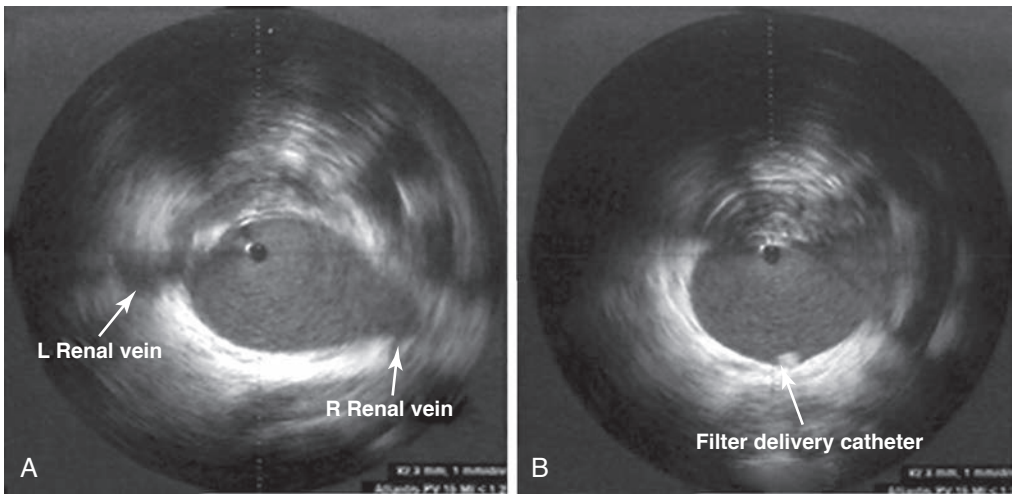

Figure 152.8 Visualization of the tip of the filter delivery catheter just below the right renal vein **(A)** at the level of the infrarenal inferior vena cava **(B)** during bedside placement of the filter under intravascular ultrasound guidance using a dual–venous access technique. (Reprinted with permission from Passman MA, Dattilo JB, Guzman RJ, Naslund TC. Bedside placement of inferior vena cava filters by using transabdominal duplex ultrasonography and intravascular ultrasound imaging. *J Vasc Surg.* 2005;42:1027–1032.)

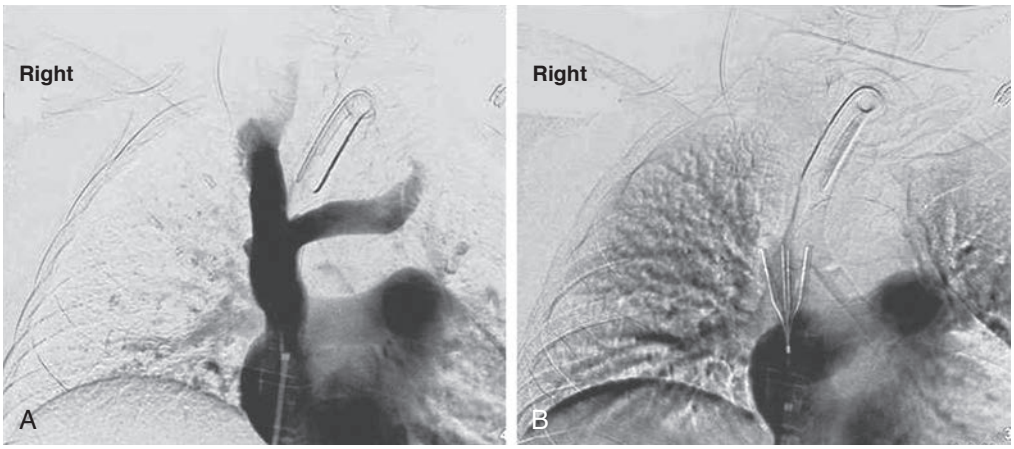

Figure 152.9 Venogram of the superior vena cava **(A)** followed by superior vena cava filter placement with the filter base just distal to the confluence of the brachiocephalic veins and the tip at the junction of the right atrium **(B)**.

Although standard treatment of upper extremity DVT is anticoagulation, when anticoagulation is contraindicated or complications of anticoagulation develop,[9] superior vena cava placement may be an option in selected cases, with experimental data on the use of filters in the superior vena cava based on animal models, case reports, and case series growing.[139-147]

For patients with both upper and lower extremity DVT, simultaneous placement of both inferior and superior vena cava filters has been described. Although use of permanent Greenfield filters for superior vena cava placement has mostly been described, there have been some reports of optional filter use and retrieval.[144,148,149] Because of superior vena cava anatomic constraints, conical filters with filter leg hook attachment points are preferred over more rigid filter designs.[150] Until a specifically designed filter for superior vena cava use is available, current IVC filters will continue to be adapted to this use.

Superior vena cava filter placement can be performed via jugular or femoral percutaneous venous access. For proper filter orientation, a jugular set is used for femoral insertion and a femoral set for jugular insertion. If inferior and superior vena cava filters are being placed simultaneously, the sequence of filter placement is dependent on the site of venous access, with the most distal filter requiring placement first. Any previously placed central venous catheters need to be removed or retracted before placement to avoid entrapment. Detailed venography is performed to define the anatomic landmarks of the superior vena cava. Any superior vena cava anatomic anomalies must be appreciated and a decision made whether safe and effective placement of the filter is possible. A duplicated superior vena cava occurs in approximately 0.1% to 0.3% of the population and can be a potential bypass for emboli if not identified.[151] Thrombus or occlusion of the superior vena cava and azygos or hemiazygos enlarged collaterals needs to be assessed if present. The intended filter position for filter leg attachment is just at the confluence of the innominate veins and is defined by venography (Fig. 152.9). The filter length deployed must be taken into consideration to avoid extended protrusion into the right atrium. Superior vena cava measurements are based on preprocedure computed tomography, venography, or intravascular ultrasound, and filter placement in a superior vena cava with a diameter greater than 28 mm is not recommended. With correct positioning and sizing, the filter delivery catheter is passed through the sheath and the filter deployed.

No randomized controlled study of superior vena cava use has been published to date. In the largest experience of superior vena cava filter placement for upper extremity DVT reported by Ascher and colleagues, 72 patients were included with a mean follow-up of 22 months.[147] Complication occurred in 1.3% and included filter malpositioning without migration, but no PE. Although mortality in this series was 47%, causes of death were unrelated to filter placement and were more reflective of the serious illness in this patient population. Others have documented complications, including superior vena cava perforation, cardiac tamponade, dislodgement by central line placement, guide wire entrapment, superior vena cava thrombosis, pneumothorax, and erosion into the thoracic aorta.[152] Based on the limited available evidence, superior vena cava filter placement is a safe and effective alternative for prevention of PE in selected patients with upper extremity DVT when anticoagulation is not possible.

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CHAPTER 153

Compartment Syndrome and Venous Gangrene

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INTRODUCTION

Phlegmasia cerulea dolens (PCD) and venous gangrene are the most severe manifestations of acute deep venous thrombosis (DVT), yet their pathophysiology is different and often misunderstood. This chapter addresses the proper definition of terms and differentiates the complex pathophysiology underlying these conditions. It also addresses the associated conditions of symmetric peripheral gangrene, purpura fulminans, cancer-associated disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), and the common warfarin-associated coagulopathy, all of which are frequently associated with venous limb gangrene.

Digit or limb necrosis in the face of palpable distal pulses or documented patent arteries is a particularly difficult clinical scenario; venous limb gangrene is such a condition. It occurs in patients with large vein thrombosis who generally have multiple comorbidities. These comorbidities are often associated with fulminant prothrombotic states that produce unchecked and excessive thrombin generation at the microvascular level, which can be paradoxically accelerated by anticoagulants, particularly vitamin K antagonists. The magnitude of the venous thrombosis and tissue necrosis depends on the patient's underlying prothrombotic condition. Our present understanding of venous limb gangrene is clouded by statements equating PCD with venous limb gangrene and describing phlegmasia alba dolens as iliofemoral DVT (IFDVT) causing early compromise of arterial flow,[1] neither of which is correct.

Initial descriptions of venous limb gangrene described acral necrosis in a limb with extensive DVT. These early descriptions focused on the extensive nature of the large vein thrombosis compromising proximal venous return. The underlying pathophysiology of the tissue necrosis was attributed to the obstruction of large veins and their collaterals, leading to venous hypertension, severe tissue edema, and subsequent occlusion of arterioles and capillaries as a consequence of the venous hypertension.[2] This view of the pathophysiology of venous limb gangrene has led to misconceptions that continue today. Unquestionably, venous hypertension due to large central vein occlusion increases venous pressures, increases compartment pressures, produces edema, and reduces arterial perfusion; however, the underlying common denominator leading to tissue necrosis is small vein and microvascular thrombosis, which occur in very few patients with extensive DVT and very few patients with PCD. These patients with microvascular thrombosis are

among the most difficult to manage, due to their multiple and serious comorbidities, with high limb morbidity and high patient mortality.

Fasciotomy has been proposed as part of a management strategy for patients with extensive acute and chronic venous disease. The underlying pathophysiology is venous hypertension, producing increased compartment pressures. Since venous hypertension is the result of large vein obstruction, it is intuitive that the elimination of the venous obstruction and restoring venous return reduces venous pressures, often to normal.[3] Reducing venous (and compartment) pressures is a more preferable approach than enlarging the leg compartments with a fasciotomy, in order to accommodate the persistently high venous pressure. Often overlooked by advocates of fasciotomy are the adverse outcomes and persistently deranged venous hemodynamics in those who have lower extremity fasciotomy for acute IFDVT.[4]

PHLEGMASIA CERULEA DOLENS

The term *phlegmasia* is derived from the Greek root *phlegma*, indicating inflammation. The remaining two terms, *cerulea* and *dolens*, have Latin roots. *Cerulea* derives from the Latin word *caeruleus*, which means "dark blue." The Latin term of *dolens* refers to "hurting or suffering." Put together, phlegmasia cerulea dolens is the swollen, blue, painful limb that is most often observed in patients with iliofemoral DVT.

Phlegmasia alba dolens is the swollen, "white," painful limb. It is observed in patients with IFDVT who have enough venous drainage to remove subdermal and dermal venous blood before cyanosis occurs.

Phlegmasia alba dolens and PCD (Fig. 153.1) are found in patients with limb manifestations of large central venous obstruction. The clinical picture reflects the severity of their thrombosis.

Phlegmasia cerulea dolens is not synonymous with venous limb gangrene. Venous limb gangrene is associated with other comorbidities producing complex prothrombotic conditions. The paradoxical presentation of tissue ischemia and necrosis without arterial compromise, often in patients receiving anticoagulants, underscores the importance of recognizing the confounding clinical scenarios contributing to venous limb gangrene. While this form of tissue necrosis can rarely be observed in patients with PCD, the underlying pathology leading to tissue necrosis is thrombosis involving the microcirculation.[5] In these patients, distal pulses are often palpable or at least detectable with a Doppler.

Most patients with IFDVT present with swelling that involves the entire limb, causing varying degrees of discomfort. Phlegmasia alba dolens (see Fig. 153.1A) generally results from a more limited occlusion of the iliac veins, which causes leg discomfort and edema. However, the venous return is efficient enough to clear the dermal and subdermal venous blood before cyanosis occurs. The difference between phlegmasia alba dolens and PCD (see Fig. 153.1B and C) is the amount of deoxyhemoglobin in the venous plexus of the skin and subcutaneous tissue and the degree of discomfort produced by the associated venous hypertension and elevated compartment pressures.[6]

Cyanosis is caused by an increase in deoxyhemoglobin in the subdermal tissues at levels of 1.5 to 5 mg%.[6] With central deep venous occlusion leading to venous hypertension and sluggish venous return, there is stagnation of venous blood in the dermal and subdermal venous plexus, resulting in bluish discoloration of the leg.

PCD is characterized by extensive thrombosis, usually involving the iliofemoral venous system, most often involving the common femoral vein and perhaps the infrainguinal venous segments as well. The clinical presentation of PCD is often preceded by phlegmasia alba dolens.[7] Progressive lower extremity edema from the thigh distally is a constant feature that can

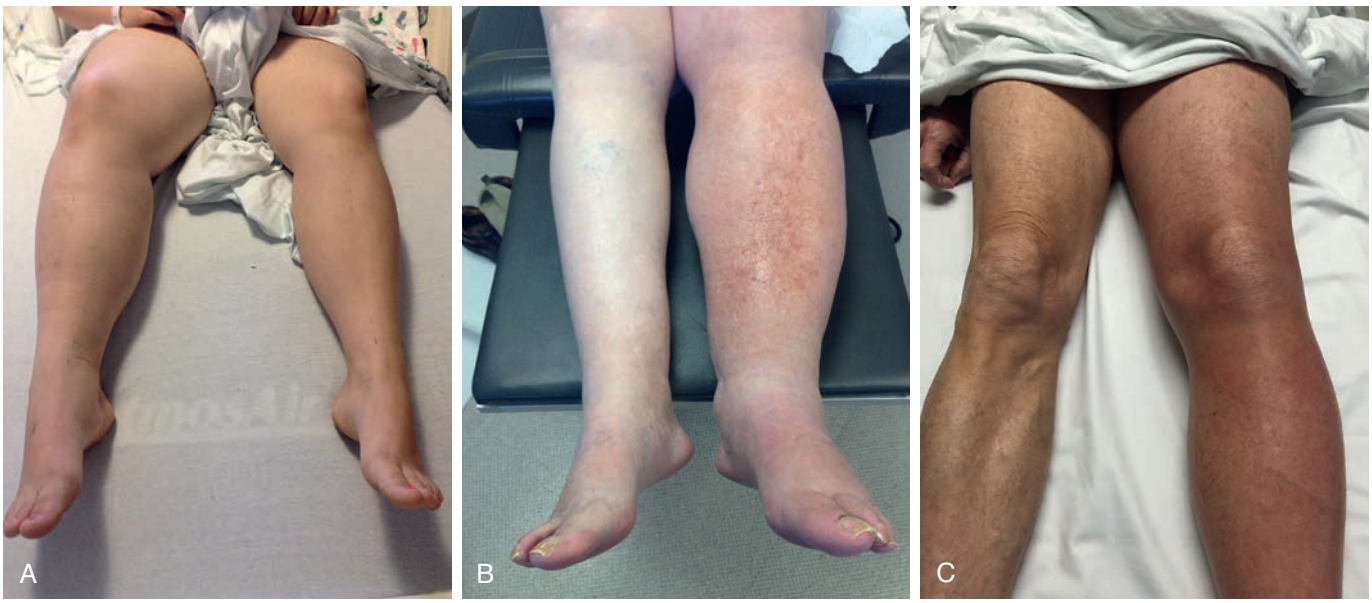

Figure 153.1 Clinical examples of phlegmasia alba dolens (A) and phlegmasia cerulea dolens (B and C).

occur rapidly after occlusion of the venous drainage from the limb. When the edema is massive, the skin is often tight and has a shiny appearance. The edema can range from pitting to firm and tense and be described as indurated on palpation. Cyanosis is a constant feature and may range from a slight bluish hue to a deep violaceous discoloration. Patients can have petechiae or purpuric areas scattered about their extremity, which quickly resolve after venous drainage is restored. Pain is a constant feature of PCD, ranging from an aching discomfort to a severe bursting pain causing extreme disability.

In some patients with advanced PCD, cutaneous blisters or bullae develop, which are usually filled with serous tissue. If hemorrhagic bullae develop, this portends a poorer prognosis indicating underlying tissue necrosis, associated with venous limb gangrene.

Early in the course of PCD, distal pulses are palpable. As the venous hypertension increases and as the edema becomes more tense, palpation of distal pulses becomes difficult; however, arterial Doppler signals usually remain audible. In patients who progress to venous gangrene, the extreme hypoperfusion leading to tissue death is the result of small vessel and microvessel thrombosis rather than primary arterial hypoperfusion of occlusion.

Clinically patients with lower extremity PCD have extreme discomfort, difficulty walking, and a tense swollen cyanotic limb. The degree of pain and disability is related to the extent of venous occlusion and the efficiency of collateral venous drainage, which determines the severity of their venous hypertension and compartment pressures. Although arterial perfusion is reduced when venous pressures are elevated, PCD alone rarely results in tissue necrosis. PCD is fully reversible if thrombus is successfully eliminated from the deep venous system, and unobstructed drainage to the vena cava re-established.

Animal studies have improved our understanding of the acute hemodynamic changes that occur with extensive proximal venous occlusion.[7,8] The hemodynamics of acute massive venous occlusion were studied in anesthetized dogs by Snyder et al.,[9] after they ligated all the iliac and femoral veins and all of their branches. One hour after venous occlusion, the limbs were circumferentially swollen and cool with violaceous mottling. Although arterial pulses were palpable, arterial blood flow was diminished by 25%. Total body blood volume fell by 13% due to serous fluid sequestration into the soft tissue of the swollen limbs, with limb volume increasing by 117% and hematocrit increasing to 115% of normal. Tissue pressure increased from 1 to 7 mm Hg and limb venous pressure increased 12-fold. Six hours after occlusion the animal showed hypovolemia with tachycardia and hypotension. Limb swelling was pronounced, as was limb cyanosis. In most animals, arterial pulses were no longer palpable due to the massive edema, blood volume was reduced by 40%, and hematocrit was increased by 35%. Interestingly, arteriography demonstrated a patent arterial system.

Patients presenting with phlegmasia alba dolens or PCD are best treated with a strategy of thrombus removal, as reviewed in Chapter 148. Upon diagnosis, patients are therapeutically anticoagulated, their limbs elevated and wrapped snuggly from their toes to their inguinal crease. This reduces their pain and edema. Within 24 hours, these patients will either undergo a contemporary operative venous thrombectomy or more commonly a catheter-based technique, to remove their thrombus.

As soon as a lumen is restored, permitting at least some degree of venous drainage, cyanosis rapidly resolves, venous and compartment pressures fall, the leg softens, and pain disappears. The best outcomes occur in patients who have complete or near complete thrombus resolution.[10]

VENOUS GANGRENE

Venous limb gangrene indicates soft tissue necrosis in a limb with DVT. Tagariello reported the clinical presentation of venous limb gangrene more than 50 years ago.[7] He described that venous gangrene was always the result of an extensive venous obstructive process, which passes through successive clinical phases. The first phase is phlegmasia alba dolens, indicating central large-vein obstruction with preservation of compensatory collateral venous drainage. The next phase, PCD, is characterized by progressive edema with pain in the calf and/or thigh and diffuse cyanosis of the limb. He attributed the eventual loss of arterial pulsations to "arterial spasm," which we now know is not part of the pathophysiology. He indicated that the changes characterizing the phase of PCD were still reversible and did not necessarily lead to gangrene.

He reported that venous gangrene is always preceded by PCD, which must be considered an obligatory phase. In the final analysis, the anatomic specimens at autopsy showed that all small veins were obstructed by thrombus. He stated, "*It seems logical to attribute all the pathogenic importance of venous gangrene to the thrombotic obstruction involving the extreme venous ramifications [small veins and microvasculature]*." In other words, venous gangrene was ultimately the result of small vein and microvascular thrombosis, not central large-vein thrombosis.

In early reports, malignancy was observed in many of the patients who developed venous gangrene. In the authors' clinical experience, all patients treated for venous limb gangrene have had malignancy and other serious conditions complicating their proximal DVT. These additional conditions include heparin-induced thrombocytopenia with warfarin exposure, disseminated intravascular coagulation, the procoagulant state of warfarin, sepsis, purpura fulminans, hypotension requiring pressors, and/or acute hepatic dysfunction. In most patients with venous limb gangrene managed by the authors, multiple prothrombotic conditions co-existed with malignancy, resulting in their limb loss and excessively high mortality.

Venous limb gangrene indicates soft tissue necrosis in a limb with large burden proximal DVT. The previously accepted pathophysiology of high venous and interstitial pressures causing compression of small nutrient vessels[11,12] was only recently supplanted by our understanding of the underlying coagulopathy leading to their microvascular thrombosis. Their acquired prothrombotic state(s) invariably include cancer-associated consumptive coagulopathy,[13] heparin-induced thrombocytopenia,[14] antiphospholipid antibody syndrome,[15] and warfarin administration.[16]

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) is a serious, potentially fatal, immunologically mediated drug reaction, usually to unfractionated heparin (UFH) or, less commonly, low molecular weight heparin (LMWH; see Chapter 38). HIT develops twice as often in women than men.[17,18] Thrombotic complications lead to the high morbidity and can be associated with a 20% to 30% mortality rate.[19]

Two distinct types of HIT have been identified.[20] Type I is the innocuous benign thrombocytopenia occurring within 2 days of heparin initiation, which has been reported in 10% to 30% of patients receiving UFH. Platelet counts generally normalize with continued heparin administration, and these patients are not at increased risk for thrombotic events. Type II HIT refers to the antibody mediated disorder that requires cessation of heparin, avoidance of vitamin K antagonists, and immediate treatment with an alternative anticoagulant (direct thrombin inhibitor) to avoid further thrombosis. When physicians discuss HIT, they typically refer to the immunologically mediated thrombocytopenia.

HIT is a prothrombotic immune-mediated reaction most commonly produced by an immunizing exposure to UFH. IgG antibodies bind heparin to platelet factor-4, producing a prothrombotic state. Patients with malignancy and those undergoing orthopedic surgery have been recognized as being particularly at risk for HIT. Women and patients with malignancy have a twofold increased risk for HIT. Furthermore, the combination of HIT with cancer is strongly associated with thrombosis compared with HIT alone.[21] Patients undergoing orthopedic surgery and those with malignancy are known to have high levels of inflammatory cytokines and other procoagulant proteins.[22]

HIT typically develops 5 to 10 days after the start of UFH infusion. Those with a recent exposure to heparin (1 to 12 weeks) can develop a "rapid onset" HIT, such as an intraoperative thrombosis after a single bolus dose of UFH, due to existing platelet-heparin antibodies (Fig. 153.2). Depending upon the magnitude of the HIT response, HIT sera can activate platelets in the absence of heparin. This has been termed heparin independent activation of platelets, which is the scenario when HIT begins or worsens after heparin is discontinued, often after the patient is discharged from the hospital. This phenomenon is termed "delayed onset" HIT.

Dr. Ted Warkentin characterized HIT as "the greatest paradox in medicine."[23] That is, patients develop clotting in the presence of therapeutic anticoagulation, tissue necrosis occurs in the presence of patent arteries, and patients have additional clotting with the administration of more anticoagulants with a particularly aggressive prothrombotic state developing when warfarin is administered. Clotting causing tissue necrosis occurs at the venular and microcirculatory level. Two examples of warfarin-induced tissue necrosis are shown in Fig. 153.3. Warfarin-induced skin necrosis can occur in central skin and subcutaneous tissue typically overlying areas of adipose tissue, illustrated by the breast and thigh necrosis in these examples. Venous limb gangrene is a result of DVT progression, usually in the setting of a supra-therapeutic international normalized ratio (INR).[5]

HIT is a prothrombotic condition that can precipitate large artery and large vein thrombosis. Left untreated, 50% to 89% of patients will develop a thrombotic complication.[19] If warfarin is administered or if the patient has cancer or concurrent DIC, a powerful prothrombotic state is produced, resulting in excessive production of thrombin in the absence of naturally occurring anticoagulants (proteins C and S), leading to microvascular thrombosis and tissue necrosis.

Since the platelet fibrin thrombus causing the large vessel occlusion appeared white when removed from thrombosed arteries (Fig. 153.4), vascular surgeons initially characterized this as "white clot syndrome."[24]

Venous thromboembolic complications are the most common thrombotic consequence of HIT. However, arterial thrombotic events are frequently observed in patients who have been treated for complications of atherosclerotic arterial disease. Patients with HIT are at risk for macro- and microvascular thrombosis, especially when warfarin is administered, or when HIT is complicated by disseminated intravascular coagulation.

The use of vitamin K antagonists in patients with HIT increases the risk of venous limb gangrene or other thrombosis. A characteristic feature of HIT patients who receive warfarin

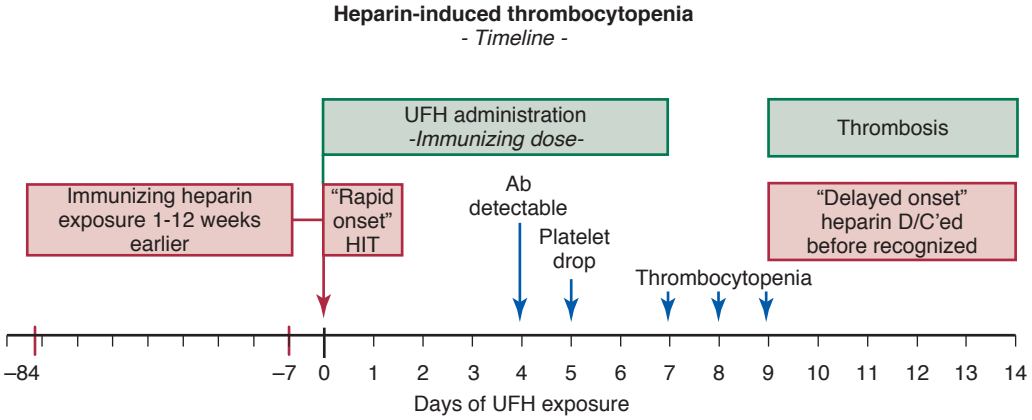

Figure 153.2 Schematic of timeline for heparin-induced thrombocytopenia (HIT). *UFH,* Unfractionated heparin.

Figure 153.3 Two examples of warfarin-induced skin necrosis in patients with heparin-induced thrombocytopenia (HIT). A 74-year-old male who was being treated for postoperative deep venous thrombosis (DVT), following total hip replacement. Three days after the initiation of warfarin, he developed skin necrosis of the calf and thigh of the involved limb (A). A 69-year-old woman developed HIT after being treated with heparin for acute postoperative lower extremity DVT after a hysterectomy for endometrial cancer. The patient also developed catheter induced axillo-subclavian DVT. Two days after warfarin was initiated, the patient began to develop skin necrosis of the right breast (B).

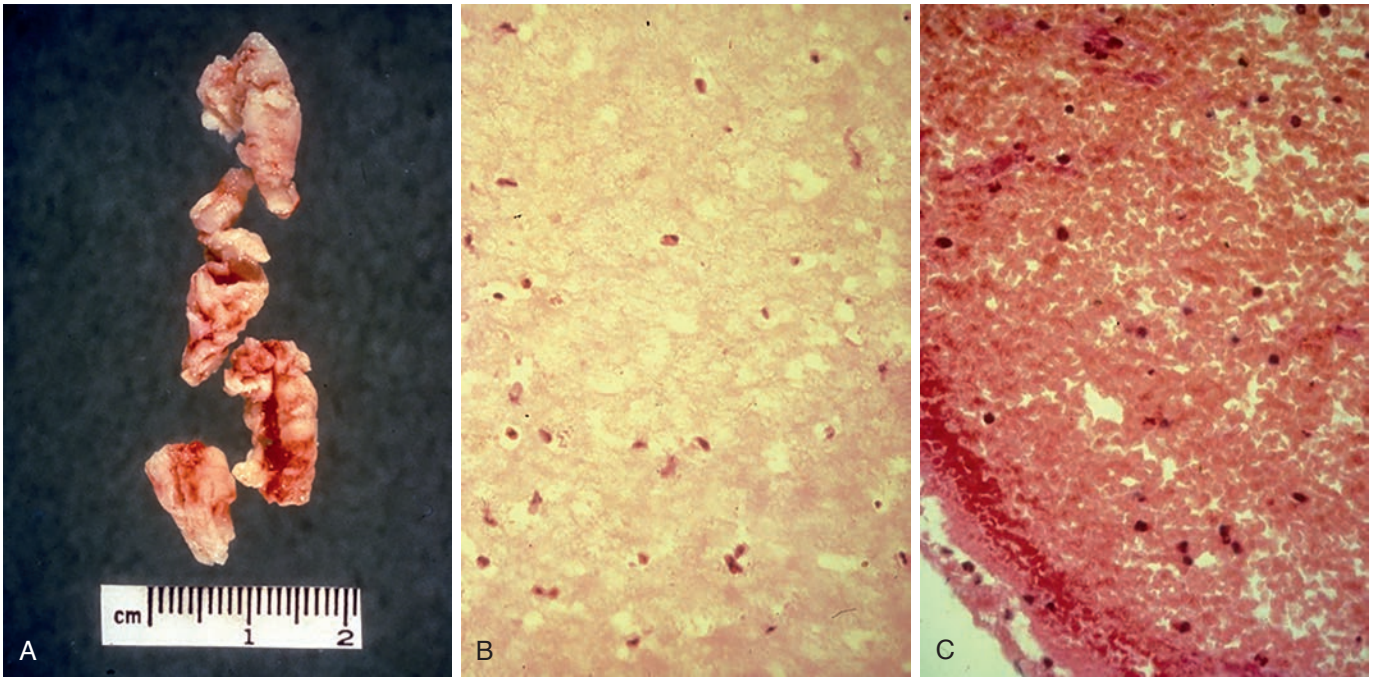

Figure 153.4 Thrombectomy specimen removed from the femoral arteries in a patient who developed heparin-induced thrombocytopenia, causing acute lower extremity ischemia. Specimen (A) is a platelet-fibrin thrombus, demonstrating why the term "white clot" was coined. The microscopic exam of the "white clot" shows a platelet-fibrin histologic appearance (B), compared with a standard acute thrombus with large amounts of RBCs (C).

is a markedly elevated INR in the face of clinically progressive thrombosis.[5] The elevated INR is due to the rapid depletion of factor VII, which has a short half-life, and the progressive thrombosis occurring because of the near complete depletion of protein C, which is also vitamin K dependent and has an equally short half-life.

When warfarin is given to patients with HIT, an accelerated prothrombotic state develops with unchecked thrombin generation. Protein C, a naturally occurring anticoagulant, is vitamin K dependent and has a half-life of 9 hours. Factor VII, also vitamin K dependent, has a half-life of 5 hours. After a patient is given warfarin, protein C production is significantly diminished (<10%), as is factor VII. Low factor VII levels result in a markedly elevated INR, which is also an indirect indicator of reduced protein C (plasma concentrations of 65 nm). This value is substantially lower than the major procoagulant factor prothrombin, which has a half-life of 60 hours and a plasma concentration of 1500 nm.[5] These facts explain why despite

the high INR, thrombin generation is accelerated and microthrombosis occurs. In these patients, the administration of vitamin K (at least 10 mg by slow intravenous infusion, with 5 to 10 mg repeated 12 hours later if the INR remains prolonged) will blunt the warfarin effect and allow the liver to produce protein C. Therapeutic anticoagulation is required with either a direct thrombin inhibitor or a direct Xa inhibitor.[14]

CANCER-ASSOCIATED DISSEMINATED INTRAVASCULAR COAGULATION WITH VENOUS LIMB GANGRENE

When venous limb gangrene occurs in patients with cancer, an underlying procoagulant state is often related to the pathogenesis of their limb ischemia. In many such patients, their extensive DVT and venous limb gangrene often precedes the diagnosis of cancer.

Cancer is a strong risk factor for DVT. High levels of tissue factor, tumor necrosis factor, inflammatory cytokines, and disordered coagulation often leads to extensive DVT.[22] Cancer alone, without its associated DIC, has rarely been implicated as causing venous limb gangrene.

Anticoagulation is effective treatment for these patients. Until recently, heparin followed by warfarin was the most commonly prescribed method of anticoagulation. Warkentin et al.[13] described the problem of warfarin-induced venous limb gangrene complicating cancer as a distinct syndrome, separate from heparin-induced thrombocytopenia associated with thrombosis. They outlined a clinical picture of which a consumptive coagulopathy is the characteristic basis for this prothrombotic condition. In patients with cancer-associated DVT who were initially treated with heparin, there was an initial rise in the platelet count. After warfarin was given, there was frequently a supratherapeutic INR. When heparin was discontinued, the platelet count dropped and thrombosis progressed. Limb ischemia, consistent with venous limb gangrene, developed due to the underlying consumptive coagulopathy. These patients have a severely disturbed procoagulant-anticoagulant balance. When warfarin is given, thrombin generation is accelerated, confirmed by a marked increase of thrombin-antithrombin complexes and reduced protein C levels. Warfarin does not inhibit cancer-associated hypercoagulability, but paradoxically predisposes the patient to microvascular thrombosis.

Warkentin et al. performed a detailed analysis of the clotting factors and platelet specific antibodies in patients with cancer-associated venous limb gangrene.[13] It is interesting that all had cancer-associated DIC, were receiving warfarin, had a supratherapeutic INR, and were subsequently diagnosed with metastatic disease. In this detailed analysis, vitamin K dependent clotting factors, proteins C and S, and thrombin-antithrombin complexes (TAT; a marker of in vivo thrombin generation) were analyzed in addition to other indicators of DIC (fibrinogen and fibrin-D-dimer).

In all patients, venous limb gangrene occurred only in the limb with proximal venous thrombosis. In the three patients with bilateral DVT, venous limb gangrene occurred in the limb with the largest burden of thrombus, which had the most recent DVT. The most meaningful blood test results indicating the degree of prothrombotic activity were the TAT/PC (thrombin antithrombin/protein C activity) ratio. This ratio was high, indicating a marked imbalance of thrombin production uninhibited by protein C.

The supra-therapeutic INR explains the parallel reduction of factor VII and protein C, both of which are vitamin K dependent and have short half-lives; therefore, both rapidly fall after warfarin is given. An elevated INR can be considered a surrogate for the depletion of protein C (a strong inverse relationship). Since the other clotting factors with longer half-lives remain functional and in high concentration, the administration of warfarin induces a significant paradoxical prothrombotic state. When heparin was resumed, platelet counts increased, consistent with heparin, reducing the existing consumptive coagulopathy. Others have shown that cancer-associated DIC can be controlled with therapeutic dose heparin.[25]

When a patient presents with unexplained extensive DVT and a rise in platelet count is observed after the initiation of heparin, a cancer-associated DIC should be suspected. In this clinical scenario, vitamin K antagonists should be avoided, as they will generate an aggressive prothrombotic state.

DISSEMINATED INTRAVASCULAR COAGULATION

DIC occurs when there is disordered activation of hemostatic mechanisms. Platelet aggregation and pathologic thrombin generation occur, resulting in intravascular deposition of fibrin uncontrolled by endogenous fibrinolysis and the naturally occurring anticoagulant proteins C and S.[26] If allowed to progress, the microvascular thrombosis leads to organ dysfunction, digital and limb gangrene, and is associated with significant limb loss and mortality.

The clinical diagnosis of DIC is made by (1) an underlying disease state known to be associated with DIC; (2) prolongation of the thrombin time and partial thromboplastin time; (3) a platelet count of less than 100,000 or a rapid fall in platelet count; (4) presence of fibrin (fibrinogen) degradation products; and (5) low levels of antithrombin III.[26]

Often DIC occurs and contributes to patient deterioration before it is recognized. The predisposing factors that ignite the disordered coagulation are mediators which include proinflammatory cytokines such as tissue factor and tumor necrosis factor (cancer patients), alpha-1 interleukin-1 beta, interleukin-6 (or -7), monocytes, leukocyte stimulated endothelial damage, and sepsis induced downregulation of endothelial thrombomodulin. Disordered endogenous fibrinolysis also occurs, allowing microvascular thrombosis to continue unchecked. The fibrinolytic system is suppressed by an increase in plasminogen inhibitor-1. Clinical studies have demonstrated that the residual fibrinolytic capacity is too low to control the systemic deposition of fibrin.[27]

Bacterial endotoxins (producing inflammatory cytokines), tissue injury, shock, metabolic acidosis, and tumor-derived procoagulant microparticles trigger the initiation of DIC. Venous limb gangrene, whether associated with a malignancy or a severe nonmalignant comorbidity, is usually a soft tissue manifestation of DIC, often accelerated by the procoagulant effect of warfarin and the hypoperfusion of shock magnified by pressors. In patients with symmetric peripheral gangrene, DIC is often a common denominator.

SYMMETRIC PERIPHERAL GANGRENE (PURPURA FULMINANS)

Symmetric peripheral gangrene is often associated with or can be called purpura fulminans and can be mistaken for venous gangrene. Large vein thrombosis is not part of this clinical picture. This is a complication of infection and often septic shock (requiring pressors) and disseminated intravascular coagulation, resulting in skin and soft tissue necrosis. Septicemia, heart failure, metabolic acidosis, and hypotension requiring vasopressor support are the common predisposing factors leading to the coagulopathy resulting in microvascular thrombosis.

Warner et al. reported 70 cases of purpura fulminans. More than half were infants or children, most commonly infected with Neisseria meningitides (69%) or streptococcus (13%). Older adult patients were predominately infected with streptococcus.[28]

With sepsis, endothelial dysfunction occurs. Endothelial cells become edematous, capillaries dilate, and RBC extravasation occurs, producing petechial hemorrhages, which can coalesce producing areas of ischemic necrosis. Excessive thrombin generation is triggered by the proinflammatory cytokines produced by the underlying infection, tissue factors from tissue damage, and procoagulant microparticles, among others. This sets the stage for the intravascular coagulopathy that is the foundation for microvascular thrombosis, leading to tissue necrosis. This process is often magnified by the administration of warfarin, the presence of HIT, or both.

Patients develop acral necrosis involving their toes, forefoot, and fingers of their hands (Fig. 153.5A and B). Other nonlimb areas can be affected, such as genitalia, ears, nose, and scalp. In patients with purpura fulminans, nonacral tissue necrosis is common. However, in those who are hypotensive requiring pressors, finger and toe and foot ischemia are usually present.

Patients initially develop pale, cool feet and toes, which progress to nonblanching cyanosis. Blisters containing serous fluid may occur. When hemorrhagic bullae develop, underlying tissue necrosis is usually present. As the necrosis progresses, it often becomes sharply demarcated. Tissue biopsies generally show dermal microthrombi involving capillaries and venules (see Fig. 153.5C and D).[29]

Patients deteriorate as other organs become involved with the systemic nature of microthrombosis.[30,31] Mortality often exceeds 50% in these critically ill patients. Table 153.1 highlights the important differences.

FASCIOTOMY FOR VENOUS DISEASE

The most effective use of extremity fasciotomy is to relieve acutely elevated compartment pressures endangering neurologic function and tissue perfusion in patients suffering crush injury or reperfusion injury. The increase in venous pressure associated with extensive obstructive venous disease is not associated with the same pathophysiology as reperfusion injury following severe acute arterial ischemia or crush injury. An example is a recent report of two patients with extensive proximal venous thrombosis successfully treated with catheter-directed thrombolysis.[32] Despite successful lysis of large central vein occlusions in two patients, their limbs deteriorated, they became progressively acidotic, developed multiple organ system failure, and died. The focus of the authors' discussion was the "reperfusion injury" occurring as a result of successful thrombolysis. In both of these cases, however, metastatic cancer was present. The patients developed the picture of progressive disseminated intravascular coagulation associated with multiorgan system failure as a result of their consumptive coagulopathy. Microvascular venous occlusion occurred as part of the cancer-associated venous limb gangrene and DIC, leading to the patients' ultimate demise. Reperfusion could not have been achieved because of the microvascular thrombosis. A fasciotomy was performed in one of these patients without benefit.

Another misconception leading to unsuccessful fasciotomies in patients with acute large vein thrombosis is that mechanical forces are solely responsible for the ongoing deterioration of the limb and the patient. The simple theory that tissue pressure is elevated to a level that exceeds transmural pressure on the arteriole, leading to collapse of the vessel, is not entirely accurate. It is often stated that there is a decrease in hydrostatic pressure in patients with PCD due to shock and the marked increase in tissue pressure due to edema. This simple understanding fails to recognize that patients with PCD leading to venous limb gangrene uniformly have cancer, DIC, or both, which result in microvascular thrombosis, tissue necrosis, and often a fatal outcome. Once the large vein thrombosis is eliminated and venous drainage is restored, venous hypertension is rapidly relieved. In patients without microvascular thrombosis, once venous hypertension is relieved and the ongoing capillary leak eliminated, normal lymphatics resorb the excess tissue fluid.

FASCIOTOMY FOR ACUTE VENOUS THROMBOSIS (PHLEGMASIA CERULEA DOLENS)

Fasciotomy is rarely performed in patients with extensive DVT in light of the underlying pathophysiology of acute extensive venous occlusion, the lack of benefit observed in those undergoing fasciotomy, and the enormous benefit achieved with successful thrombus removal. Qvarfordt et al.[33] measured intramuscular pressures in the anterior compartment and superficial posterior compartment of the lower leg in 17 men and 17 women (normal volunteers) while at rest, during standardized exercise, and with venous and arterial occlusion. They found that men had higher

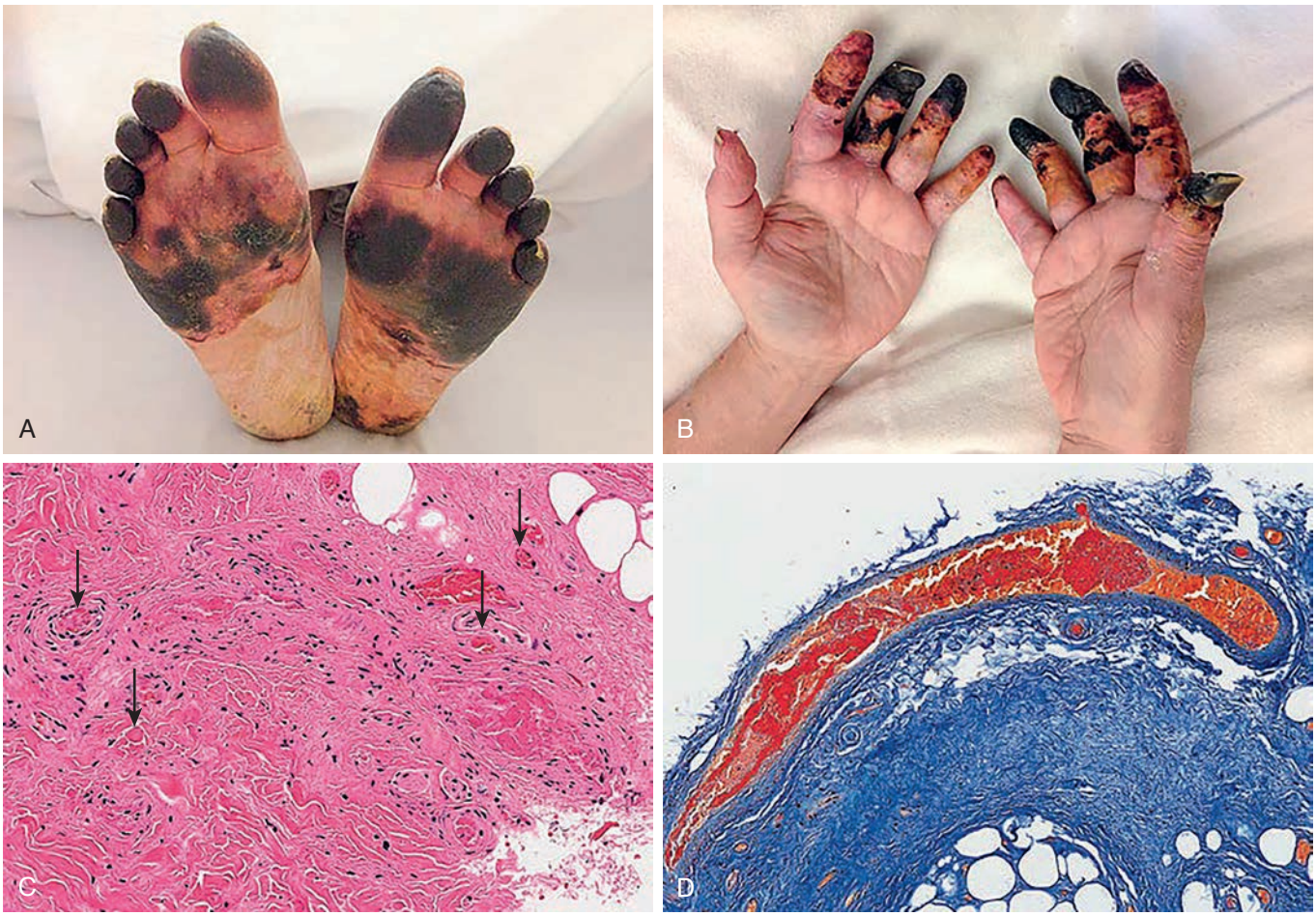

Figure 153.5 In a 62-year-old man with uncontrolled ulcerative colitis that was resistant to immunotherapy, an acute onset of swollen, discolored, and painful feet and fingers with progression to ischemic necrosis of both forefeet (A) and hands (B). No evidence of bacterial endocarditis or microvascular arterial disease was found. Laboratory evidence of inflammation included elevated C-reactive protein levels, along with hyperfibrinogenemia, hyperferritinemia, thrombocytosis, and anemia of inflammation. Autoimmune markers and antiphospholipid antibodies were negative. Studies did not support a diagnosis of decompensated disseminated intravascular coagulation: platelet count, 472,000 per cubic millimeter; international normalized ratio 1 : 1; activated partial thromboplastin time, 39 seconds; fibrinogen, 650 mg per deciliter (reference range, 160 to 420); and fibrin D-dimer, 1390 µg per milliliter of fibrinogen equivalent units (reference value <500). Skin biopsy of the left hallux showed multiple fibrin thrombi within small vessels *(arrows)*, as seen on hematoxylin and eosin staining (C) and Martius scarlet blue staining, in which fibrin is colored red (D). The patients' proinflammatory process improved after treatment with high-dose glucocorticoids and unfractionated heparin. (Reproduced with permission from The Massachusetts Medical Society. Warkentin TE. Ischemic limb gangrene with pulses. *N Engl J Med.* 2015;373:2385-2388.)

TABLE 153.1 Venous Leg Ulcer Healing in Patients With Postthrombotic Syndrome and Superficial Venous Insufficiency Grouped by Fasciotomy and Split Thickness Skin Graft[38]

	POSTTHROMBOTIC SYNDROME		SUPERFICIAL VENOUS INSUFFICIENCY	
Outcome	No Fasciotomy (*N* = 11)	Fasciotomy (*N* = 12)	No Fasciotomy (*N* = 13)	Fasciotomy (*N* = 14)
VLU healed with STG	50% (2/4)	100% (8/8)	100% (4/4)	50% (2/4)
VLU healed, No STG	29% (2/7)	75% (3/4)	100% (10/10)	56% (5/9)
Total healed ulcers	36% (4/11)	92% (11/19)	100% (14/14)	53% (7/13)
	P = .049		P = .042	

STG, Split thickness skin graft; *VLU,* venous leg ulcer.

anterior compartment intramuscular pressures than women and younger subjects had higher intramuscular pressures than older subjects, most likely due to muscle tone and muscle volume. Resting and exercise pressures were always higher in the anterior compartment. Resting pressures in the anterior compartment were 8.4 mm Hg (mean), which increased to 26.5 mm Hg with exercise. Venous occlusion increased the intramuscular pressures in the deep compartment. Arterial occlusion had minimal effect on intramuscular pressures.

The same investigators then measured the intramuscular pressures in the anterior and deep posterior compartment in patients with three different levels of acute venous thrombosis: calf DVT, IFDVT, and PCD.[3] Resting pressures were higher in those with the most extensive thrombosis. Pressures were measured after the Homan maneuver (passive dorsi flexion/plantar flexion of calf muscles).

A small but significant increase in intramuscular pressures was observed in patients with calf DVT. A larger increase in pressure was observed with iliofemoral thrombosis. Markedly elevated pressures were recorded in patients with PCD. During the Homans maneuver pressures significantly increased, especially in patients with IFDVT and PCD. The Homan maneuver was observed to cause pain when there was a significant but short-lasting increase in intramuscular pressure, indicating that the pain was related to the higher intramuscular pressure activating pain receptors. The one patient with venous gangrene (microvascular thrombosis) had persistently elevated pressures. Perhaps the most instructive of the authors' observations was the rapid fall in pressure in patients with PCD who underwent venous thrombectomy. They stated that venous thrombectomy appears to be the most specific form of treatment since venous outflow was reestablished. The literature supports strategies of thrombus removal as being the most effective form of therapy in patients with IFDVT.

In an earlier clinical experience, Fogarty and Cranley et al.[8] reported eleven patients treated for PCD. They also reviewed the United States literature of which there were 49 cases with sufficient information. They reported the marked benefit of eliminating the thrombus burden with venous thrombectomy, reported the initial results of using a balloon catheter for venous thrombectomy, and also commented on the potential benefit of ligating the femoral vein, common iliac vein, or vena cava to prevent subsequent pulmonary embolism. They also remarked that fasciotomy was not necessary in the majority of the patients if venous thrombus was removed.

Brockman and Vasco[34] performed a collective review of 279 cases of PCD. All but 9% of these cases had some other associated disease, such as malignancy, sepsis, trauma, congestive heart failure, or other serious comorbidity. Thrombectomy was recommended as the most effective form of management. The authors stated that thrombectomy was the only procedure followed by rapid cure of PCD. When fasciotomy was performed, it was associated with higher complication and failure rates. The theoretical benefits of fasciotomy were addressed; however, because of the mediocre results in a few patients, prolonged wound healing, infection, and poor results in most patients, the authors stated that fasciotomy was unwarranted.

The benefit of successful thrombectomy with restoration of unobstructed venous drainage is illustrated in Fig. 153.6. A young man sustained a high velocity gunshot wound to the right side of his abdomen, transecting his iliac artery and vein, in addition to small bowel and colon injury. His small bowel and colon injury were managed with appropriate resection and ileostomy. His iliac artery was reconstructed; however, his common, external, and internal iliac veins were ligated. Total leg fasciotomies were performed. Anticoagulation was withheld due to the risk of bleeding. The patient developed extensive

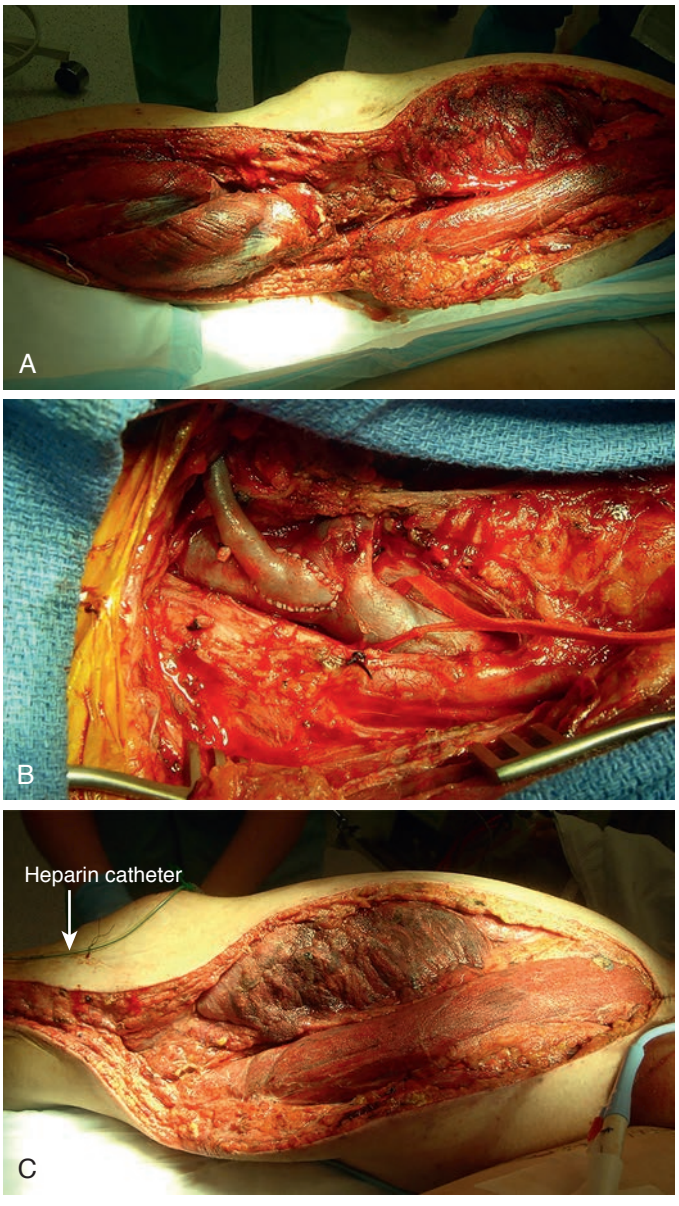

Figure 153.6 Example of massive edema resulting from iliac artery reconstruction and iliac vein ligation following a high velocity gunshot wound (A). A full-leg fasciotomy was performed. The patient developed extensive venous thrombosis. A full-leg venous thrombectomy was performed and a cross-pubic venous bypass was performed using the contralateral saphenous vein (B). The edema rapidly resolved permitting fascial closure of the calf within 48 hours (C). Note the heparin infusion catheter, which was secured into the posterior tibial vein at completion of the thrombectomy. This permits high heparin concentrations in the target leg while a low overall dose of heparin is infused, reducing the risk of bleeding.

DVT from his calf veins to the ligated external iliac vein. He presented with profound edema of his entire leg (see Fig. 153.6A). A venous thrombectomy was performed from the posterior tibial vein to the common femoral vein, and a pediatric feeding catheter was secured in the posterior tibial vein for postoperative regional heparin infusion at a dose lower than that used systemically. A cross-pubic venous bypass was constructed using his contralateral saphenous vein (see Fig. 153.6B). Within 48 hours the patient's edema resolved to the point that the fascial layer of his calf could be closed (see Fig. 153.6C). While this patient had reperfusion injury due to his iliac artery injury and repair, the remarkable resolution of his edema underscores the benefit of elimination of central venous thrombus and the restoration of unobstructed venous drainage.

Fasciotomy has been shown to alter venous physiology over the long term. Garfin et al.[35] reported the importance of an intact fascia on muscle force and calf muscle pump function. Rosfors et al.[36] performed a complete venous physiologic evaluation of 21 patients who had prior fasciotomy and concluded that an intact muscle fascia was important for normal venous return and calf muscle pump function.

Bermudez et al.[4] tested the hypothesis that fasciotomy impaired calf muscle pump function and led to chronic venous insufficiency. Seventeen patients who underwent fasciotomy were studied. Eight had fasciotomy for arterial reperfusion, six due to bone injury, and three for soft tissue infection. Follow-up physiologic evaluation demonstrated significant reduction in calf muscle pump function and elevation of ambulatory venous pressures compared with the subject's opposite unaffected limb. This suggested that fasciotomy could lead to chronic venous insufficiency.

Fasciotomy for Chronic Venous Disease

In patients with chronic anterior compartment syndrome, subcutaneous fasciotomy relieves pain, normalizes intramuscular pressure, and increases muscle blood flow and skeletal muscle metabolism.[37] It was with these observations in mind that paratibial fasciotomy was proposed as adjunctive therapy for patients with venous ulceration associated with the postthrombotic syndrome (PTS) and superficial venous insufficiency (SVI).

The most careful and objective analysis of fasciotomy for chronic venous disease was reported by Christensen.[38] He reported 25 limbs with venous ulcers, 11 due to PTS, and 14 due to SVI, treated with adjunctive subcutaneous paratibial fasciotomy, compared with 24 limbs with venous ulcers, 11 due to PTS, and 13 due to SVI, which were treated similarly but without subcutaneous fasciotomy.[38] All SVI patients were treated to eliminate their superficial reflux, and all patients were treated with 30 mm Hg compression stockings. All patients had intramuscular and subcutaneous pressures recorded, as well as $TcPO_2$ prior to, immediately after, and 3 months after surgical intervention. Ulcer healing was recorded.

The IM pressure was higher in patients with PTS compared with SVI. However, subcutaneous pressures and $TcPO_2$ did not differ between groups. When fasciotomy was performed, muscular and subcutaneous tissue pressure decreased and $TcPO_2$ increased significantly. In the SVI group IM, tissue pressure was significantly decreased at 3 months in the group without fasciotomy. Fasciotomy improved ulcer healing in both the PTS and SVI patients. In this interesting cohort of patients with difficult-to-heal venous ulcers, paratibial subcutaneous fasciotomy was associated with significant benefit to ulcer healing at 3 months. It remains unknown for how long fasciotomy remains effective in these patients with chronic venous disease, especially those with PTS. The patients in this series with PTS all had patent deep veins, which is probably not the case in those with the most severe PTS. It is not known how patients with greater degrees of postthrombotic obstruction will respond. It has been shown that subcutaneous fasciotomy is beneficial for up to 2 years for chronic anterior compartment syndrome.[39]

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Dr. Christenson has studied and reported the value of subcutaneous fasciotomy in patients with severe venous insufficiency. This provides valuable information to physicians caring for these patients.

Rosfors S, Bygdeman S, Wallensten R. Venous circulation after fasciotomy of the lower leg in man. *Clin Physiol*. 1988;8:171–180.

Many physicians believe that lower extremity fasciotomy is a benign, harmless procedure. This manuscript details the disordered venous physiology following lower extremity fasciotomy.

Salter BS, Weiner MM, Trinh MA, et al. Heparin-induced thrombocytopenia: a comprehensive clinical review. *J Am Coll Cardiol*. 2016;67:2519–2532.

HIT is a more common clinical problem than many physicians realize. This is an excellent overview for all who care for critically ill patients, most of whom have been exposed to or are receiving heparin.

Warkentin TE. Ischemic limb gangrene with pulses. *N Engl J Med*. 2015;373:2385–2388. doi:10.1056/NEJMc1511750

Dr. Warkentin is the foremost authority on HIT. This manuscript approaches an exceptionally difficult clinical problem and categorizes peripheral limb gangrene into understandable and treatable categories.

Warkentin TE, Cook RJ, Sarode R, Sloane DA, Crowther MA. Warfarin-induced venous limb ischemia/gangrene complicating cancer: a novel and clinically distinct syndrome. *Blood*. 2015;126:486–493. doi:blood-2015-01-622787 [pii];10.1182/blood-2015-01-622787 [doi]

It is now established that HIT and malignancy are linked. This is a seminal contribution revealing this association and assisting us in understanding the underlying pathophysiology.

A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 154

Varicose Veins: Surgical Treatment

MARK D. IAFRATI and THOMAS F. O'DONNELL Jr.

DECISION MAKING 2021
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Treatment Options 2021
Patient Risk Assessment 2021
Anatomic Considerations 2021
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Small Saphenous Vein 2023
Gastrocnemius Veins 2023
Intersaphenous Vein 2023
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MULTIMODALITY AND INDIVIDUALIZED CARE 2033
PATIENT MANAGEMENT AND REIMBURSEMENT CONSIDERATIONS 2034
Indications for Ligation and Stripping of the Great Saphenous Vein in the Current Climate Favoring Endovenous Ablation 2034

In the past, venous disease received relatively little attention in the public arena and in vascular training programs despite the fact that it is more prevalent in the United States than coronary artery disease, peripheral arterial disease, congestive heart failure, and stroke combined.[1] The latter half of the 20th century saw dramatic advances in diagnostic testing; however, surgical treatment of varicose veins benefited from only modest refinements after this flurry of innovation. The 21st century has begun with a resurgence of interest and innovation in venous disease. Increased awareness of thrombotic and venous reflux disease has been coupled with advances in the diagnosis and treatment of acute deep venous thrombosis (DVT) (see Chapters 147, 148, 151, and 152), and endovenous ablation (EVA) techniques for the treatment of chronic venous disease have proved appealing to patients and physicians alike (see Chapter 155). Although sclerotherapy and EVA occupy preeminent roles in the contemporary management of superficial venous disease, surgical approaches remain relevant when applied appropriately

Abstract

Surgical treatments for varicose veins have been a core component of general and vascular surgery for 100 years. The modern vascular specialist now has a broad array of options to employ in the treatment of lower extremity varicose veins. Recent years have seen an explosion in catheter-based venous ablations procedures as well as advancements in sclerotherapy techniques and compounds. The dramatic increase in endovascular ablation over the last decade has been accompanied by a gradual decline in the frequency of varicose vein surgery these techniques remain a valuable tool for the management of a wide array of venous diseases. This chapter will review current guidelines regarding varicose vein surgery and will discuss the implications of anatomical variations relating to the great saphenous, small saphenous, and popliteal area veins. This chapter will review specific techniques and anatomical considerations which impact the safe and effective performance of superficial venous surgical techniques. We will also review data comparing the outcomes of open surgical and catheter-based venous procedures. Lastly, patient management and reimbursement considerations reflecting the current economic realities will be discussed.

Keywords

varicose veins
ligation and stripping
high ligation
guidelines
popliteal fossa
ambulatory phlebectomy
CHIVDA
ASVAL
saphenous sparing

and executed expertly. In addition to treatment of the great saphenous vein (GSV) and tributary varicosities, this chapter emphasizes management of the small saphenous vein (SSV) and other veins of the popliteal fossa; these veins are increasingly being recognized as important contributors to chronic venous insufficiency (CVI), and they are particularly well suited for treatment with open surgical techniques. In a guidelines publication, Gloviczki et al.[8] recommended specific diagnostic and treatment steps for varicose veins, with the strength of recommendation and quality of supporting evidence. Recommendations specific to the open treatment of axial reflux and tributaries are reported in the table in this chapter, titled Varicose Vein Guidelines (VVGL).

DECISION MAKING

Pathophysiology and Natural History

Varicose veins are defined as "subcutaneous veins in the lower extremities which are dilated to ≥3 mm in diameter in the upright position".[9] They can occur in the axial superficial veins (GSV and SSV) and/or in any of their tributaries. Current thinking is that they represent primary venous disease and occur as a result of structural weakening of the vein wall, which can be focal in nature or diffuse. This weakening is most likely the result of underlying morphologic or biochemical abnormalities, although the exact nature of these abnormalities is not understood. Valvular incompetence in the superficial veins is usually present, but it is not clear if this represents an inciting factor or a secondary result of vein wall dilation. Varicose veins can also occur as a result of secondary venous disease—for example, as a sequela of DVT.[8,10]

Varicose veins constitute a progressive disease; remission does not occur except after pregnancy and delivery. During its course the disease produces symptoms and complications that usually prompt the patient to seek medical care. Symptoms and signs include lower extremity pain and swelling, particularly after prolonged standing, and a feeling of heaviness in the lower extremities. The most frequent complications are superficial thrombophlebitis, acute bleeding originating in one of the thin-walled varices, eczema, and skin ulceration. Depending on his or her age, general health condition, and symptomatology, a patient with varicose veins may be offered one or more of the following: no treatment, conservative management with compression, sclerotherapy, or surgical treatment (open or endovascular). CVI is extremely common in western societies and affects approximately one-third of the adult population. Fortunately only a small proportion of these patients develop the most severe form of venous insufficiency—namely venous ulcers. Though affecting only a small fraction of the population with venous insufficiency, venous ulcers are reported to occur in up to 4% of people older than 65 years.[11,12] Even though nonoperative management of venous disease—including compression, elevation, and skin care—is clearly beneficial,[13] such therapy does not correct the underlying pathology, allows recurrence of symptoms if patients are unable to comply with the elevation and compression regimen, and is associated with a high incidence of recurrent ulceration and progression of disease.

Treatment Options

Invasive treatment of superficial venous incompetence can be accomplished by techniques that result in removal, ablation, or ligation of the refluxing venous segment. Current options for eliminating this target reflux include high ligation, ligation and stripping (L&S), EVA, sclerotherapy, and ambulatory phlebectomy. Each of these techniques has a role in the treatment of patients with symptomatic varicose veins. The modern vascular surgeon should be comfortable in applying these procedures in a thoughtful manner based on the patient's individual needs. As requested by insurers, a trial of compression treatment is generally employed with compression hose (20-30 mm Hg) for patients in CEAP classification C2 to C4 to determine whether the patient's symptoms are relieved. For patients with an ulcer (CEAP C6), compression therapy with garments that exert a pressure of 30 to 40 mm Hg is recommended, because the Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) study showed that compression was comparable to compression plus L&S of the GSV in promoting healing (Table 154.1, VVGL 9.1, 9.2, and 9.3).[14]

Patient Risk Assessment

When considering any intervention, the patient's general medical status and venous anatomy should be considered. Because venous insufficiency results in chronic discomfort and stasis changes that may be ameliorated by the judicious use of compression garments, skin care, and lifestyle changes, venous surgery must always be considered somewhat elective; accordingly, prudent consideration of general medical factors is indicated. Patients who are the most fit, with longer life expectancies, have not only a reduced risk for complications from the procedure but also a longer period during which the benefits of the procedure may accrue. The advent of less invasive treatment by EVA has expanded the range of ages being treated; indeed, patients over 70 years of age are now routinely undergoing therapy, usually for more severe and recalcitrant symptoms. Patients in generally poor health with limited life expectancy or other severe comorbid conditions are typically best managed with conservative measures alone. In recognition of the shorter recovery time and reduced pain and morbidity, the VVGL recommends endovenous thermal ablation over open treatment of saphenous incompetence (see Table 154.1, VVGL 11.2).

Anatomic Considerations

The lower extremity venous system is unique in its constant need to overcome the force of gravity while returning blood toward the heart. An elegant calf muscle pump and the vein valve system normally accomplish this task efficiently. The thin bicuspid semilunar vein valves float open in the venous stream during prograde flow. During calf muscle relaxation, retrograde flow and higher supravalvular pressure cause the margins of the

TABLE 154.1 Varicose Vein Guidelines

Number	Guideline	Strength of Recommendation	Quality of Evidence
9.1	We suggest compression therapy using moderate pressure (20-30 mm Hg) for patients with symptomatic varicose veins.	2	C
9.2	We recommend against compression therapy as the primary treatment of symptomatic varicose veins in patients who are candidates for saphenous vein ablation.	1	B
9.3	We recommend compression as the primary therapeutic modality for healing venous ulcers.	1	B
11.2	Because of reduced convalescence and less pain and morbidity, we recommend endovenous thermal ablation of the incompetent saphenous vein over open surgery.	1	B
10.1	For treatment of the incompetent great saphenous vein, we suggest high ligation and inversion stripping of the saphenous vein to the level of the knee.	2	B
10.3	For treatment of small saphenous incompetence, we recommend high ligation of the vein at the knee crease, about 3 to 5 cm distal to the saphenopopliteal junction, with selective invagination of the incompetent portion of the vein.	1	B
10.7	We recommend ambulatory phlebectomy for treatment of varicose veins performed with saphenous vein ablation, either during the same procedure or at a later stage. If general anesthesia is required for phlebectomy, we suggest concomitant saphenous ablation.	1	B
10.5	We suggest that preservation of the saphenous vein using the ambulatory conservative hemodynamic treatment of varicose veins (CHIVA) technique be used only selectively in patients with varicose veins and only when performed by trained venous interventionists.	2	B
10.6	We suggest that preservation of the saphenous vein using the ASVAL under local anesthesia procedure be used only selectively in patients with varicose veins.	2	C

ASVAL, Ambulatory selective varices ablation; *CHIVA*, Cure Conservatrice et Hémodynamique de l'Insuffisance veineuse en Ambulatoire.
Modified from Gloviczki, Comerota AJ, Dalsing MC, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. *J Vasc Surg*. 2011;53(Suppl):2S–48S.

valve cusps to move to the midline and oppose, so that caudad reflux is prevented. These valves can be disrupted by a thrombotic event (secondary), can be congenitally absent or atretic, or can become dysfunctional over time as the vein wall or valve loses integrity (primary). CVI has traditionally been classified on the basis of anatomy, function, and clinical severity. The anatomic classification of CVI is important because it links the location of CVI with its subsequent clinical management.

Great Saphenous Vein

The GSV arises anterior to the medial malleolus and courses obliquely and posteriorly as it crosses the anteromedial surface of the calf. At or below the knee joint, the posterior arch vein joins it. A solitary vein is found in the calf in about two-thirds of cases, whereas a duplicated system is present in the remainder. In the vast majority of cases, the GSV at the calf level is anterior-dominant. As the main saphenous trunk continues in a slightly more superficial plane around the knee joint, an anterior accessory vein often merges. The GSV then courses cephalad on top of the deep fascia and deep to the superficial fascia (Fig. 154.1). The GSV may run within this envelope for the entire length of the thigh or may enter at some distance above the knee. If the GSV is "duplicated," both veins will run in this fascial envelope; there may be anterior and posterior accessory veins that enter the fascial envelope to join the GSV, but they exist primarily in the extrafascial plane. Three anatomic variants have been characterized and are demonstrated in Fig. 154.2.

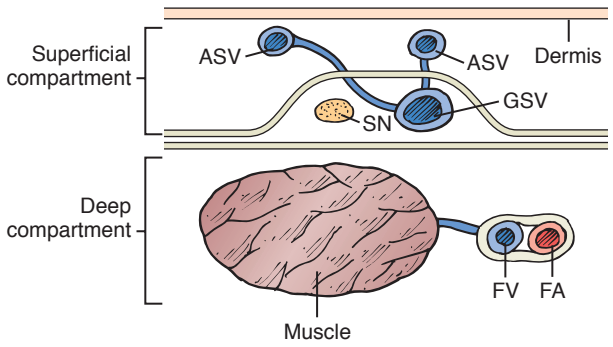

Figure 154.1 The saphenous compartment is bounded by deep and superficial layers of fascia. Tributaries to the saphenous vein pierce the superficial fascia, and it is they that become varicose. *ASV*, Accessory saphenous vein; *FA*, femoral artery; *FV*, femoral vein; *GSV*, great saphenous vein; *SN*, saphenous nerve.

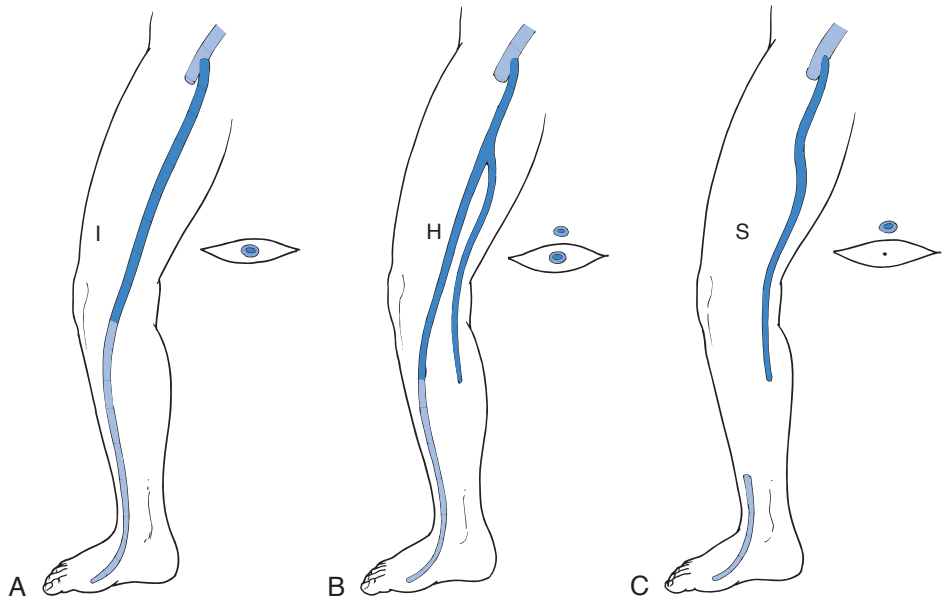

Figure 154.2 Anatomic types of the great saphenous vein (GSV) with respect to the fascial envelope. (A) I type. The GSV is present within the fascial envelope along its entire length. (B) H type. There is a subcutaneous collateral running parallel and superficial to the main saphenous trunk (left). (C) S type. The caudal portion of the GSV in the thigh is atretic, and the extrafascial tributary is dominant.

Kupinski and coauthors reported their experience with duplex ultrasound (DUS) evaluation of the GSV in nearly 1500 limbs.[15] At the thigh level in 60% of the limbs the GSV had a single medial-dominant system, whereas a branching double system was observed in nearly 20%, a complete double system in 10%, and a closed-loop system in another 10%. Of interest was a lateral-dominant system, present in 8%.

Small Saphenous Vein

The confluence of the SSV with the popliteal vein has long been recognized as variable (Fig. 154.3). Approximately 33% of SSVs terminate at a (high) above-knee popliteal vein site; a low termination site is unusual (<10%).[16-18] We have observed that DUS examination of the SSV allows exact perioperative and intraoperative localization of the saphenopopliteal junction for appropriate placement of the skin incision.

Gastrocnemius Veins

The gastrocnemius veins arise from both the medial and lateral heads of the gastrocnemius muscle and may join the popliteal vein directly or merge with the SSV to form a common trunk and then enter the popliteal vein.[19] Conversely, the SSV may join with the gastrocnemius vein to enter the popliteal vein. Hobbs and Vandendriessche reported a 20% incidence of incompetence of the gastrocnemius veins,[19] a proportion similar to that described by Gillet and colleagues in 180 operations for SSV reflux.[20] If the SSV is ligated distal to its junction with a common trunk and an incompetent gastrocnemius vein, persistent reflux will occur.

Intersaphenous Vein

The second important non-SSV vein of the popliteal fossa, the intersaphenous (formerly named Giacomini) vein, has been classically described as coursing up the posterior medial aspect of the thigh.[21] The intersaphenous vein usually arises off the SSV either as a branch or as a truncal continuation of the SSV, and it courses along a subfascial plane to join the GSV more frequently (64%) than the deep venous system (45%).[21] Reflux is less frequent in the intersaphenous vein than in either saphenous vein. The proportion of limbs with intersaphenous vein incompetence, however, is greatly increased when incompetence of the SSV is found alone (odds ratio of 11.94) or combined with GSV incompetence (odds ratio of 11.7),[21] and this vein may facilitate reflux between the GSV and SSV.[22] In our series a dominant and incompetent intersaphenous vein that formed a common trunk with the SSV was observed in 8.5% of limbs undergoing surgery for SSV reflux. Delis and colleagues' DUS study of 818 limbs also showed a low 3% incidence of popliteal area veins,[23] the third non-SSV vein of the popliteal fossa. By contrast, Dodd's classic study of 444 operations in the popliteal fossa showed popliteal area veins in 177 cases (40%), and in 60% they were branches of the SSV (50%) or gastrocnemius veins.[24] They directly entered the popliteal vein in 37% of cases.

Neurovascular Relationships in the Popliteal Fossa

Surgical exploration of the popliteal fossa can be associated with postoperative neurologic disability and, rarely, disastrous vascular complications. Two motor nerves, the tibial (medial popliteal nerve) and occasionally a low-lying sciatic nerve, can be juxtaposed near the SSV and its termination with the popliteal vein. The tendon-like appearance of both motor nerves may falsely encourage the surgeon to perform a less delicate dissection or to retract more vigorously in a deeper plane than would be carried out when a nerve is clearly identified. The sensory

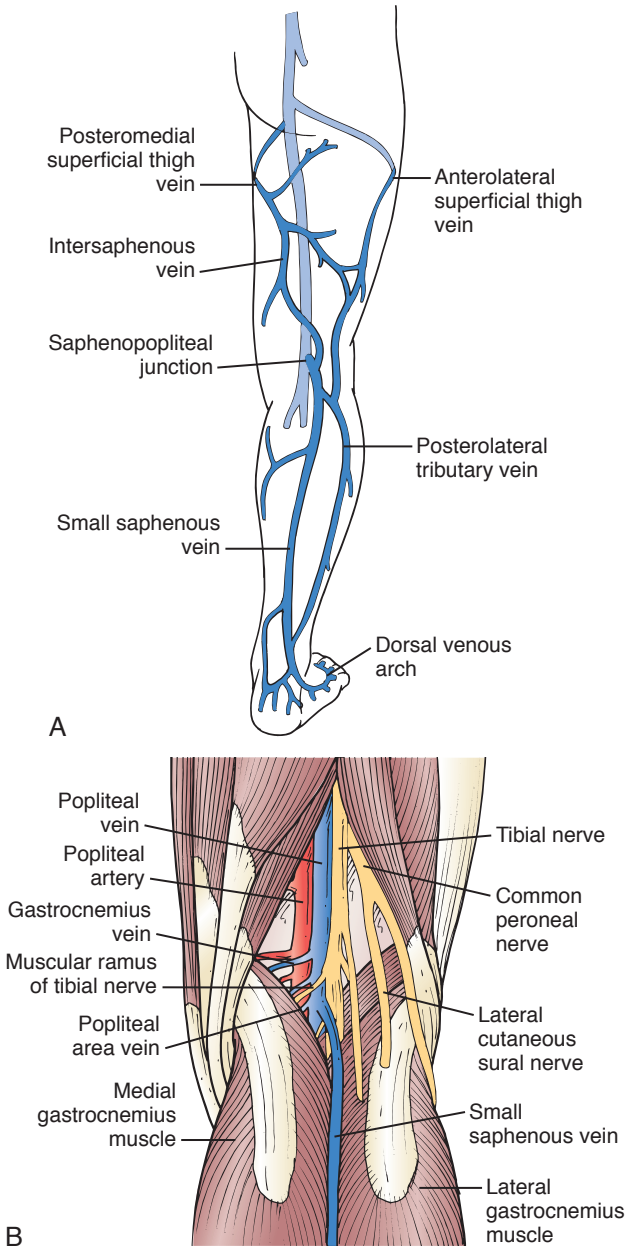

Figure 154.3 (A) The small saphenous vein dominates the posterolateral superficial venous drainage and originates in the dorsal venous arch. At the posterolateral aspect of the ankle, it is intimately associated with the sural nerve. Note the important posterolateral tributary vein and the posterior thigh vein, which ascend and connect the small saphenous venous system with the GSV. The anterolateral superficial thigh vein and the posterolateral tributary vein can be very important in congenital venous anomalies, such as Klippel-Trenaunay syndrome. (B) The most common neurovascular configuration of the popliteal fossa, although the site of anastomosis is highly variable.

sural nerve courses superficial to the SSV or may intertwine with it, and this nerve can also be damaged by retraction or dissection.

Perforating Veins

Perforating veins connect the superficial venous system to the deep venous system and are discussed in detail in Chapter 158.

SURGICAL TECHNIQUES

Surgery for superficial varicose veins should be individualized according to the patient's preoperative evaluation. A combination of ligation, axial stripping, and stab phlebectomy may be applied as needed to the GSV, SSV, tributary veins, and perforating veins. Technical considerations for each of these techniques are summarized in the following sections.

After preoperative evaluation and elucidation of the necessary scope of surgery, a decision will be made regarding the appropriate method of anesthesia and site of service. Any of the surgical procedures can be performed under general or regional anesthesia in an operating theater, and this level of care may be appropriate for patients undergoing multiple incisions requiring extended procedure times or those with medical issues requiring close monitoring by an anesthesiologist. However, extensive experience in the use of tumescent local anesthetic techniques, with or without sedation, allows essentially any of these vein operations to be performed in an office procedure room if it is appropriately equipped and staffed. Ultimately the decision is influenced primarily by local resources, physician experience, and patient expectations. Preoperative marking of the patient in the standing position with an indelible marker is important in any case where stab phlebectomy or direct perforator ligation is contemplated. Such marking is essential because visualization of varicose tributaries may be impossible once the patient is prepared and the leg elevated.

High Ligation of the Great Saphenous Vein

The GSV is most easily approached through an oblique incision 1 cm above and parallel to the groin crease. This location provides the best cosmetic results and the most reliable access to the saphenofemoral junction. The incision should start over the palpable femoral artery and extend medially to balance the better cosmesis of limited incisions with the necessity to ensure appropriate visualization of the saphenofemoral junction and its tributaries. Preoperative DUS-guided marking of the saphenofemoral junction further improves the precision of incision placement and allows minimal incision size and subcutaneous dissection. As the subcutaneous tissue is split, the main trunk of the GSV is identified. A self-retaining retractor is helpful, and the plane over the saphenous vein is extended toward the saphenofemoral junction. This anterior plane is generally free of encumbrances and allows exposure to the junction. Care should be taken to ligate a small branch of the femoral artery, which frequently crosses anterior to the saphenofemoral junction and can cause troublesome bleeding. Each of the tributaries is divided and ligated because the saphenofemoral junction must be clearly identified. Failure to clearly define the saphenofemoral junction has resulted in disastrous injuries to the femoral vein or artery.[25,26]

There are six main tributaries joining the GSV near its termination (Fig. 154.4). However, the number and position of these tributaries vary greatly; therefore, it is necessary to dissect the femoral vein 2 cm above and below the confluence to be sure that no additional tributaries join the femoral vein

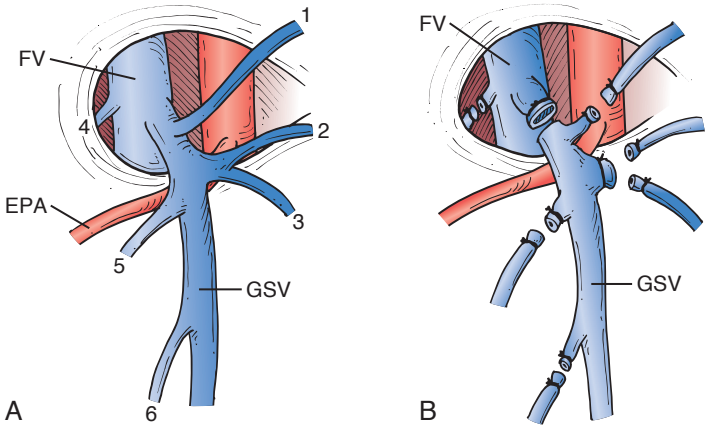

Figure 154.4 (A) The most common arrangement of tributary veins at the saphenofemoral junction. The external pudendal artery (EPA) usually runs between the great saphenous vein (GSV) and the femoral vein (FV), but it may pass above the GSV and is then more susceptible to injury during dissection. 1, Inferior epigastric vein; 2, superficial circumflex iliac vein; 3, lateral accessory saphenous vein; 4, deep external pudendal vein; 5, superficial external pudendal vein; 6, medial accessory saphenous vein. (B) All vessels must be individually divided and ligated to prevent recurrence. If no stripping of the GSV is to be performed, the proximal 5 to 10 cm of the GSV should be resected.

directly. Lateral and medial accessory saphenous veins may enter the main trunk between 2 and 20 cm below the confluence. When stripping is planned, these distal tributaries are avulsed, but if ligation alone is planned, the dissection should be extended caudal for approximately 10 cm to ensure division of these hidden tributaries. High ligation of the GSV is performed close to the femoral vein. Double ligation is generally performed on a proximal stump with the second ligation being a suture ligature. Care should be taken to avoid narrowing the femoral vein in the process. Equally important is to avoid leaving a long stump with a risk for thrombus formation and potential embolism. Alternatively, the GSV may be divided close to its termination and the femoral side closed with a two-layered monofilament suture. If high ligation alone is to be performed, one should resect the segment of GSV exposed in the surgical field, generally 5 to 10 cm in length. The incision is closed in layers by approximating the subcutaneous tissue with absorbable suture and the skin with absorbable subcuticular sutures. The requirement for sufficient exposure of the saphenous vein and its tributaries should be tempered by data suggesting that extensive dissection results in local humeral changes and upregulation of vascular growth factors that lead to neovascularization, which in turn is believed to be an important cause of recurrent varicose veins.[27]

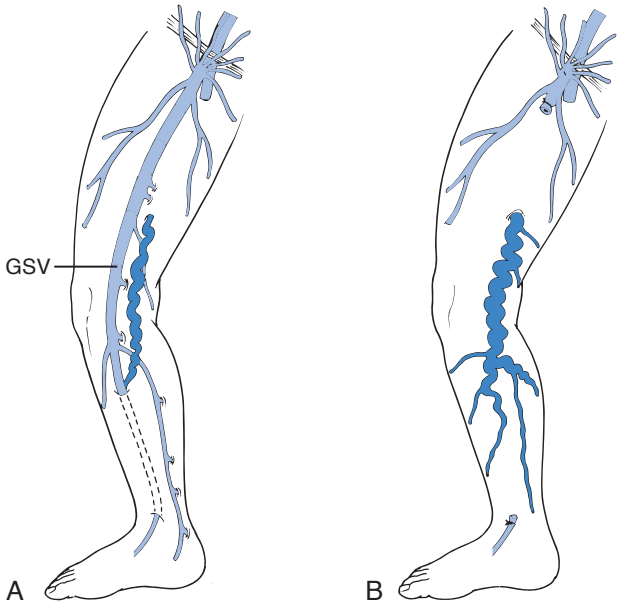

Figure 154.5 Stripping of a competent great saphenous vein (GSV) serving as runoff for a varicose collateral vein (A) results in postoperative worsening of the collateral varicosity because of resistance to outflow (B).

Great Saphenous Vein Stripping

GSV stripping is the central component of the classic operation for varicose veins. Recurrence rates are markedly reduced when the GSV is stripped as opposed to when high ligation is performed alone[28,29]; therefore, stripping is usually performed in conjunction with ligation. During preoperative marking for L&S of the GSV, the surgeon should review the extent and distribution of reflux disease in the saphenous system. The GSV in the thigh is incompetent in only about two thirds of patients undergoing surgery for symptomatic varicose veins or CVI.[30,31] In addition, unless the caudal below-knee saphenous vein is obviously incompetent and varicose, there is no need to remove it. Similarly, when H- or S-type anatomy is defined (see Fig. 154.2), it is not necessary to treat normal or atretic segments of the GSV; in fact, such treatment may worsen the clinical situation by removing competent drainage paths (Fig. 154.5). This targeted approach to stripping leaves normal distal veins, avoids injury to the saphenous nerve, and results in less postoperative pain and bruising without compromising the goals

of surgery.[32-34] Incompetent accessory saphenous veins should be addressed during the initial surgery. It is likely that the high recurrence rates noted for vein stripping in the past have resulted in part from unrecognized accessory veins. The availability of DUS and awareness of the issue may result in improved efficacy in the future; thus preoperative duplex definition of anatomy and marking is essential in any modern-day operation on the great or small saphenous vein.

After flush ligation is performed, a transverse venotomy is created and a stripper is passed distally. Wire strippers or disposable plastic strippers are commonly used. In most cases the presence of reflux allows easy passage of the stripper to the level of the knee. A second small incision is made over the palpable stripper near the knee, which can be defined by preoperative or intraoperative duplex. The caudal incision is made transversely, and the subcutaneous tissues are dissected to allow recovery of the saphenous vein. This top-down passage of the stripper not only facilitates identification of the saphenous vein at the knee and allows a small lower incision to be made but also avoids the potential for the stripper passed from below to enter the femoral vein through a thigh perforator and cause the femoral vein to be mistaken for the saphenous vein. The GSV should be stripped in a downward direction, which results in improved avulsion of tributaries and diminished injuries to the saphenous nerve.[32] To avulse the vein with the endoluminal stripper, one must affix the catheter to the most cephalad portion of the vein. This may be accomplished by attaching the classic stripper head (Fig. 154.6) to the top of the disposable stripper after first placing a silk ligature around the vein and the stripper just below the head. Using the smallest head size minimizes tissue injury and bruising, whereas a larger head size will improve the chance of recovering the entire vein and the tributary segments. A long trailing silk suture is initially attached at the stripper head and drawn through the tunnel with the vein. After all the tributaries have been avulsed and the caudal GSV has been divided and ligated, the vein and stripper are drawn back up to the groin incision, thereby minimizing the size of the distal incision.

Although many variations of this technique have been described, the most common alternative approach involves invagination of the GSV into itself. This technique may be performed with a disposable plastic Codman vein stripper without attaching a stripper head but instead intussuscepting the vein, as shown in Fig. 154.7.[35] Alternatively, a reusable metal cannula may be used in a similar fashion.[36,37] This technique minimizes the diameter of the tunnel created by vein removal in an effort to diminish local trauma to soft tissues and nerves. However, the saphenous vein is susceptible to tearing at the sites of tributary confluence; thus the technique could result in incomplete stripping of the target vein. Consequently, when the vein is removed, it should be unfurled and compared with the planned treatment length. When the vein is torn during stripping, the caudal end typically remains in place at the lower incision. In this case, if a trailing heavy silk suture has been affixed to the stripper (see Fig. 154.7), a second inversion technique can be performed in the opposite direction (Fig. 154.8) (see Table 154.1, VVGL 10.1).

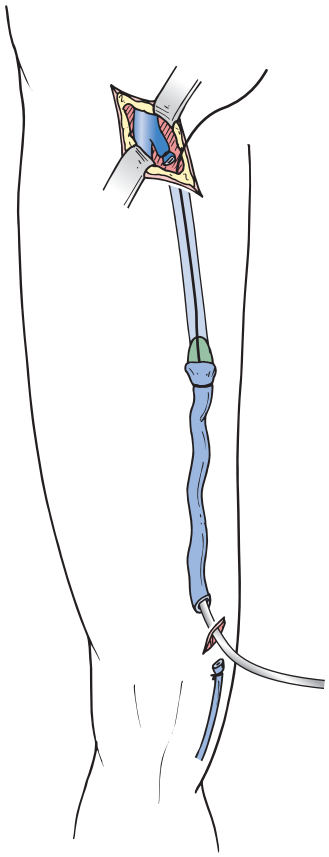

Figure 154.6 The intraluminal stripper is passed distally, the vein fixed by ligature proximally, and the stripping head secured. Stripping distally minimizes lymphatic and tributary damage and avoids avulsion of the saphenous nerve branch. When the stripper head reaches the distal incision, the distal vein fixed to the stripping device by ligature can be recovered through the proximal incision, thereby minimizing surgical trauma at the lower incision.

Adjunctive Considerations for Stripping Procedures

Saphenous vein stripping is commonly perceived as a painful and morbid procedure by patients and referring physicians alike. The memory of large incisions, extensive bruising, significant pain, and prolonged disability from antiquated techniques is a major concern of patients and referring physicians. However, these undesirable effects can be significantly ameliorated by using relatively simple adjunctive techniques.

Ultrasound Guidance

DUS should be used preoperatively to mark the saphenofemoral or saphenopopliteal junction, as well as the course and distal location of the saphenous vein at the knee. This allows precise placement of the skin incision and permits very small incisions with limited subcutaneous dissection. Incompetent accessory veins should also be marked.

Tumescent Anesthesia

The GSV in the thigh lies within a fascial envelope for most of its length, which allows modest infusion of tumescent anesthesia (200-500 mL) to fully surround the saphenous vein.

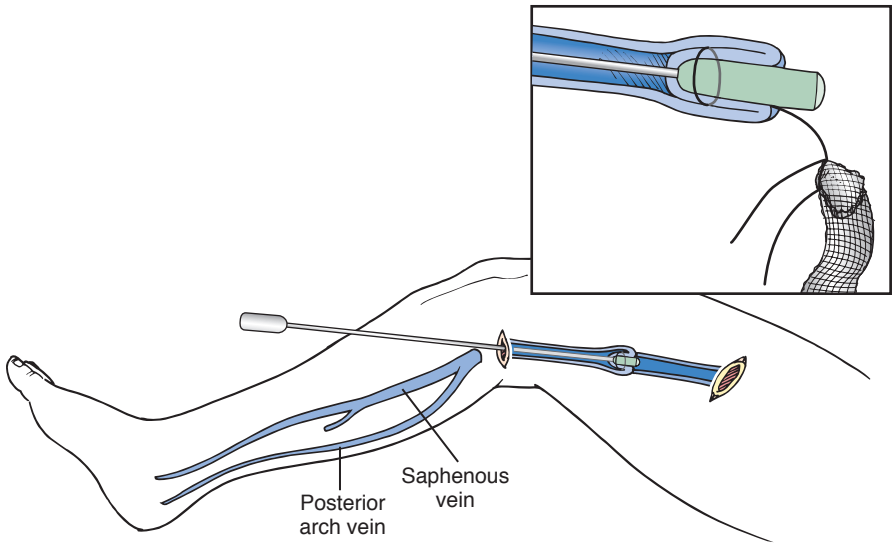

Figure 154.7 The endoluminal device, commonly a disposable plastic stripper, can be introduced from above downward and the vein ligated around the stripper proximally. As distal traction is applied, the vein is then inverted into itself and removed distally in the region of the knee. Roll gauze moistened with epinephrine may be attached to the stripper and drawn temporarily into the tunnel to enhance hemostasis.

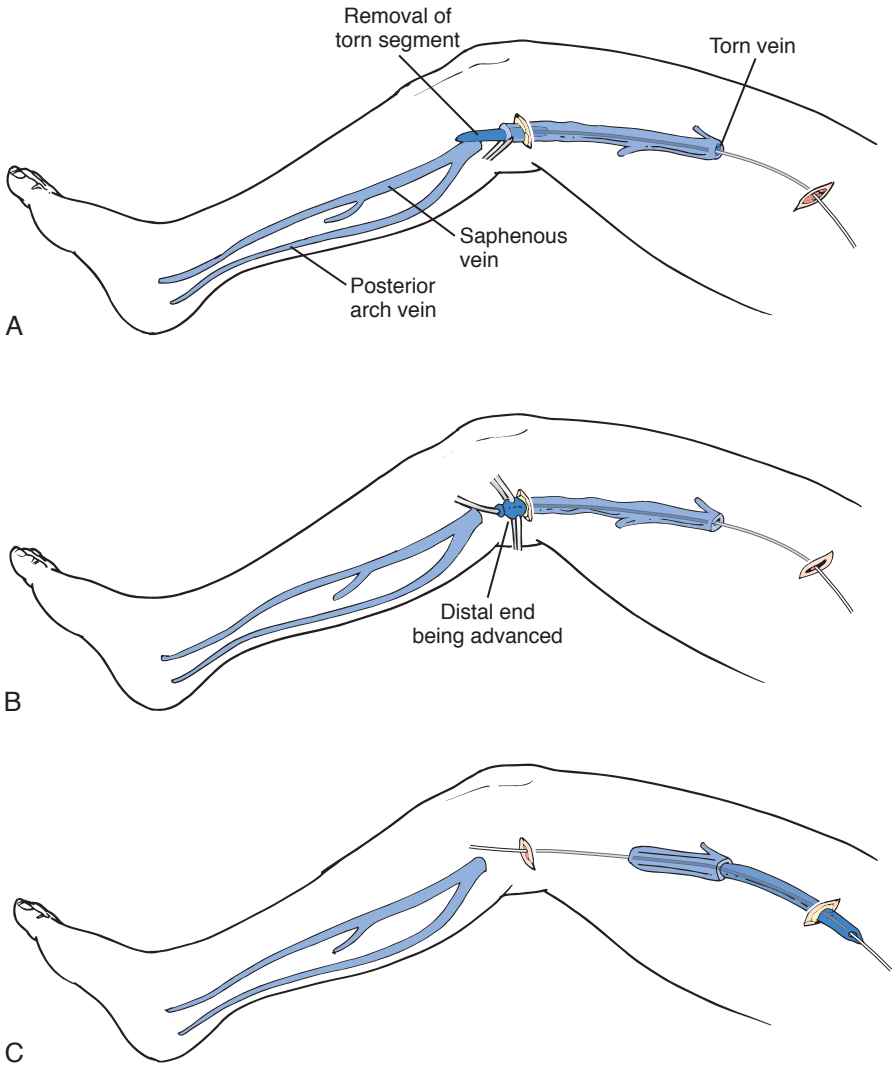

Figure 154.8 Steps in removal of a residual venous segment after proximal vein tearing. (A) Removal of the torn segment. (B) Attachment of the distal segment of vein to the intraluminal stripper and initiation of reverse invagination as the vein is removed from below upward. (C) Removal of the remaining venous segment.

We use a combination of 40 mL of 1% lidocaine with epinephrine, 10 mL of sodium bicarbonate, and 450 mL of normal saline in the tumescent mixture, which is administered under duplex scanning using an infusion pump. This technique provides excellent anesthesia and allows vein stripping to be performed under straight local anesthesia in the office. In addition, the vasoconstriction from the epinephrine and the direct compressive effects of the instilled volume result in rapid hemostasis from the avulsed tributaries and a marked decrease in postoperative ecchymosis and pain.

Minimization of Accumulation of Blood in the Stripping Tunnel

If blood is left in place in the stripping tunnel, a firm palpable cord, sometimes called pseudothrombophlebitis, results. This will eventually reabsorb but contributes to the significant early discomfort traditionally associated with vein-stripping procedures. In addition to the use of tumescent anesthesia, we recommend that stripping be performed as the last step of the procedure if concurrent tributary varices and/or perforator disease are to be addressed at the same setting. In this way the leg can be immediately wrapped in a compressive dressing and elevated after the vein stripping is performed. If the vein is to be removed from the knee incision, the groin incision can be closed with the stripper head in place and only the distal incision at the knee left to close after stripping. Alternatively, one may tie a length of roller gauze soaked in lidocaine with epinephrine to the end of the stripper (see Fig. 154.7). This provides direct compression, absorption of blood in the tunnel, and application of epinephrine to the avulsed tributary sites.[35,38] The gauze is then removed before closure.

Leg Elevation Before and During Stripping

Elevation of the leg reduces the venous bleeding and ecchymosis associated with stripping. The leg should be elevated before the actual stripping procedure is performed. Postoperatively, the patient should ambulate as soon as possible. Most varicose vein surgery is currently performed either on an outpatient basis or as an office-based procedure.

Proximal Tourniquet

This technique is usually reserved for patients with massive varices in the calf or thigh, as is common in Klippel-Trenaunay syndrome, to prevent major hematomas. Esmarch bandage drainage of the limb is followed by placement of a proximal sterile pneumatic tourniquet, which is inflated to 200 mm Hg. The tourniquet is deflated once the GSV is stripped and its branches removed.

Surgery on the Small Saphenous Vein and Veins of the Popliteal Fossa

SSV disease is often neglected or incompletely treated by surgeons. This problem may be explained in part by the following factors: (1) the paucity of studies emphasizing a significant contributory role of SSV incompetence to CVI; (2) the lower proportion of limbs with SSV reflux compared with GSV incompetence; (3) technical considerations, such as the need to reposition the patient if both GSV surgery and SSV surgery are being performed in the same treatment session; and (4) the intimate and variable neurovascular relationships of the SSV, which can present significant potential for morbidity. However, the few papers that have addressed the role of the SSV in CVI have described a strong association of SSV reflux with (1) posterior calf varicosities,[39] particularly in individuals with recurrent varicosities after superficial venous surgery; (2) isolated lateral malleolar ulcers[40]; and (3) ulcer recurrence after subfascial endoscopic perforating surgery.[41]

A survey conducted among members of the Vascular Surgical Society of Great Britain and Ireland, which was motivated by the poor outcomes and high litigation rates associated with SSV surgery, characterized surgeons' attitudes toward SSV surgery.[42] Although nearly 90% of surgeons carried out preoperative duplex imaging, only 50% added preoperative skin marking of the saphenopopliteal junction. In an effort to avoid damage to neurovascular structures and DVT, few surgeons (10%) exposed the popliteal vein during this procedure, which would make identification and treatment of gastrocnemius or popliteal area veins less difficult.

An understanding of the relationship of the SSV to other veins of the popliteal fossa—the gastrocnemius veins, the intersaphenous vein, and popliteal area veins—is important to achieve optimal results with SSV surgery. If these veins are ignored, they can be a factor in the persistence of reflux.[19,22] These veins are particularly well suited to open surgery as opposed to EVA or sclerotherapy, particularly when they enter the popliteal vein directly.

Operative Technique for Small Saphenous Vein Procedures

After the induction of general, regional, or local anesthesia, patients are positioned prone with care taken to pad bony areas and breasts. To provide laxity of the neurovascular structures in the popliteal fossa, the limb is slightly flexed at the knee. Preoperative marking guided by DUS allows a small transverse skin incision to be made just distal to the saphenopopliteal junction. The length of the incision is dictated by the thickness of the subcutaneous tissue (shorter incision for thinner legs). The fascia is opened along the line of the skin incision and the SSV is identified. The SSV is traced distally to its position between the fascia and calf muscles. Because of the effects of sustained venous hypertension, the SSV can resemble an artery (popliteal), so continuous-wave Doppler may be used to provide the surgeon with assurance that the structure is indeed venous in nature. The SSV is then divided between two right-angle clamps. Care is taken to dissect in the perivenous plane, and any nerve structure—usually sural—is carefully dissected from the SSV. Gentle retraction is used to avoid injury to the tibial nerve and to visualize the saphenopopliteal junction. However, if DUS identifies reflux in the gastrocnemius or popliteal area veins, the exposure is extended and the target veins are ligated. The stump of the SSV is ligated with a 3-0 monofilament transfixion suture. If present, the common trunk of the SSV

with either the gastrocnemius or intersaphenous veins is ligated proximally just above the popliteal vein.

If preoperative DUS identifies incompetence of individual gastrocnemius, intersaphenous, or popliteal area veins, they are ligated as well. The distal SSV is dissected to a point beneath the fascia, and a segment is excised. We do not usually strip the SSV because of the risk of injury to the sural nerve, which is generally adherent to the SSV in its distal third. The SSV is ligated distally with 3-0 monofilament suture. The popliteal wound is then irrigated and closed in layers with particular attention to approximating the fascia to avoid unsightly hernias. The short skin incision is approximated with running 5-0 subcuticular suture. The preoperatively marked posterior calf varicosities are removed by stab phlebectomy. Particular attention is paid to ligating any incompetent gastrocnemius perforating veins that connect with the SSV branches (see Table 154.1, VVGL 10.3).

Excision of Local Varicosities (Ambulatory Phlebectomy)

Ligation and/or stripping of the GSV or SSV directly reduces axial reflux and therefore results in the preponderance of hemodynamic benefit in most vein operations. However, if left uninterrupted, the remaining superficial varicosities will drain via alternative pathways and may remain both symptomatic and cosmetically displeasing. In the past, these tributary varices were dealt with by making several large incisions, and dramatic transverse scars were left in many cases. Refinements in technique have resulted in improved cosmetic results with effective elimination of tributary varices through small (1-3 mm) stab incisions.[43,44] Effective use of these minimally invasive techniques requires planning, experience, and patience. It is common for procedures to require in excess of 20 phlebectomies, which can be time consuming. Preoperative marking is very important in ambulatory phlebectomy. These target veins are often difficult to see when the patient is reclining.

Although local, regional, and general anesthesia are all options, ambulatory phlebectomy, especially performed in isolation, is well suited to local infiltration anesthesia. This can be accomplished by superficial subdermal infiltration around the vessel of interest or by large-volume tumescent techniques. At the end of the infiltration the skin appears pale because of the epinephrine-induced vasoconstriction. However, direct visualization of varicosities during phlebectomy is generally not a problem. Inclusion of epinephrine in the anesthetic may be contraindicated in patients with diabetes, glaucoma, coronary heart disease, cardiac dysrhythmias, hypertension, hyperthyroidism, and peripheral arterial disease. In such cases, epinephrine may be omitted from the anesthetic mix, which results in somewhat more bleeding, which can generally be controlled by a few minutes of digital compression. The patient is positioned to optimize surgical exposure. Phlebectomy is best performed on a horizontal plane, and because many patients are treated under a local anesthetic, it is often possible to have them rotate the extremity during the procedure to maximize exposure.

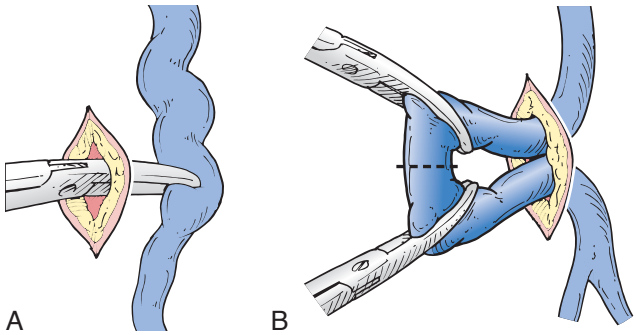

Figure 154.9 Ambulatory phlebectomy. (A) A 2- to 3-mm stab incision oriented transversely at the groin, knee, or ankle or longitudinally along Langer's lines elsewhere in the leg provides access for phlebectomy. (B) The target varicosity is drawn through the incision, divided, dissected, and avulsed.

Mueller is credited with popularizing and refining the technique of stab avulsion.[44] He considered a 2-mm incision to be large. Although the process of removing the vein often stretches the small skin incision, the combination of postoperative compression and the intrinsic elasticity of the skin allows retraction to the original small incision size. The skin incision is most commonly made with a no. 11 blade but, alternatively, 18-gauge needles and blood lancets have been used effectively. The incisions are typically oriented longitudinally except in the groin, knee, and ankle, where a transverse orientation aligns with the lines of Langer.

Three types of instruments are recommended for vein retrieval: hooks, iris forceps, and fine-pointed clamps. The small dermal varicosities are hooked and avulsed. Larger veins are grasped and brought up through the incision (Fig. 154.9). The vein loop is cleared of fat, doubly clamped, and divided. By applying in-line traction, varicosities can be teased out and several centimeters removed from each end, much like the proverbial robin pulling a worm through a small hole in the ground. Rolling of the vein onto the clamp prevents the vein from avulsing prematurely. The varicose segments should be removed in their entirety, and if the vein breaks during the process, it may be reobtained through a new incision. These varicosities are typically tributaries of the axial veins and do not require ligation unless an incompetent axial vein is to be left in place (which is generally to be avoided). On the other hand, perforating veins associated with clusters of varices should be ligated. The skin incisions are small enough that Steri-Strip closure is usually sufficient. Should an individual incision be larger than usual, a single interrupted absorbable subcuticular or nylon skin closure will suffice (see Table 154.1, VVGL 10.7).

Transilluminated Powered Phlebectomy

Transilluminated powered phelbectomy, or TriVex, uses tumescent dissection, transillumination, and powered phlebectomy to accomplish extensive ambulatory phlebectomy. Because of the tumescent anesthesia component, this technique can be carried out without general or regional anesthesia. The device used to transilluminate the veins and perform the phlebectomy is similar to devices used to remove subcutaneous fat. It is inserted into

the subcutaneous tissue through a small incision and moved forward and backward over as much area as possible to disrupt and remove the varicosities.

The technique has the proposed advantages of decreasing the number of incisions and reducing operative time. Aremu and colleagues' randomized controlled trial (RCT) of 141 patients and 188 limbs compared TriVex with conventional stab phlebectomy.[45] The TriVex group had fivefold fewer incisions (5 vs. 29), whereas postoperative pain and other patient-reported measures were comparable. There was a nonsignificant trend toward a shorter operative time with the TriVex group. A subsequent RCT of similar design carried out in Australia showed that fewer incisions were required but reduced operative time was not seen.[46] In contrast to the Aremu study, early postoperative bruising, pain, and quality of life were worse in the TriVex group. Finally, a meta-analysis conducted by Luebke and associates of five RCTs noted that the reduced operating time for TriVex applied only for large and extensive varicosities—and at the expense of more hematoma formation and a higher mean pain score than with standard hook phlebectomy.[47] This technique in rarely employed in current practice.

Saphenous-Sparing Operations

Routine use of duplex ultrasound to map flow dynamics within the great and small saphenous veins, as well as in associated varicosities, has led to the development of hemodynamic-based "saphenous-sparing operations." These procedures challenge the hypothesis, initially promulgated by Trendelenburg, that an incompetent saphenous vein is the cause of varicosities. This thesis holds that reflux from the deep to the superficial system at the saphenofemoral or saphenopopliteal "connections" produces incompetence in the saphenous trunk, which descends proximally to distally, then outward to form superficial varicosities. The detailed duplex studies of Labropoulos and others challenged this theory and supported an "ascending" cause of varicose veins, which is initiated in the "distal superficial venous network." Proponents of this theory remove only refluxing segments, concentrating on the varicosities of the peripheral venous network rather than the saphenous vein, thus sparing it. Two groups of procedures accomplish this approach: the Cure Conservatrice et Hémodynamique de l'Insuffisance veineuse en Ambulatoire (CHIVA)[48-50] and ambulatory selective varices ablation (ASVAL)[51] techniques.

Conservatrice et Hémodynamique de l'Insuffisance veineuse en Ambulatoire

A detailed preoperative duplex ultrasound study determines where the reflux starts, the entry point, and where it reenters, with the goal of promoting normal superficial-to-deep flow through reentry perforating veins during muscular diastole. Determination of the competence of the terminal and preterminal valves of the saphenous guides the decision of whether it should be ligated. The tributaries are assessed for competence (flow into saphenous) or incompetence (flow into tributaries and associated varicosities). Incompetent tributaries are ligated and the varicosities removed. Franchesci classified several types of communications between the superficial and deep system, which dictate the required surgical steps: type I, with reentry by a venovenous shunt at the saphenous trunk; type II, with no reflux from the deep system but with reflux from the superficial venous network, not surrounded by the superficial fascia or through a communicating superficial vein; type III, with reentry on an extrasaphenous superficial perforator; and type IV, with reflux from the pelvic circulation. Carandina and associates[52] compared CHIVA with standard high-ligation and stripping (HLS) in an RCT of 150 patients. Outcome measures at 10 years were as follows: recurrence of varicose veins (VVs) by objective clinical and duplex criteria; clinical outcome (Hobbs score), as judged by an independent observer; and patient-reported subjective symptoms. Although there was no difference in the Hobbs score between the two groups, recurrence of VVs at 10 years was lower in the CHIVA group (18%) than in the HLS group (35%) (P <.04).

The definitive large RCT on CHIVA conducted by Parés and colleagues[53] compared CHIVA with two control groups: HLS as marked clinically and HLS as marked by duplex. The primary outcome was recurrence of VVs as observed by independent physicians. In this RCT, "cure" of VVs was twice as frequent in the CHIVA group as in the two HLS groups, whereas the OR favoring the CHIVA group was 2.64 (95% CI, 1.76-3.97; P <.001) over the HLS clinical and 2.01 over the HLS duplex group. Several criticisms, however, have been leveled at the study: (1) the study had a high incidence of patients with mild disease, C2; (2) a significant number of patients underwent treatment for cosmetic purposes in the absence of symptoms; and (3) no patient-reported outcome measure was used—an important consideration in mild disease and particularly when cosmesis is the indication. Finally, in a small RCT, Zamboni and associates showed superiority of CHIVA over compression treatment in CEAP C6 patients.[52] This RCT, however, had narrow inclusion/exclusion criteria, no postthrombotic limbs, and no deep venous reflux/obstruction. Time to ulcer healing was shortened, and the 38% recurrence rate in the compression group was reduced to 9% in the CHIVA group. CHIVA has shown excellent results in lowering the recurrence of varicose veins; however, despite increasing facility with intraoperative DUS and minimally invasive techniques, this approach has not found widespread adoption its pure form (see Table 154.1, VVGL 10.5).

Ambulatory Selective Varices Ablation

This procedure is performed under local and tumescent anesthesia with removal of the venous varicose reservoir (multiple varicosities) through multiple stab incisions (average, 30), generally using Muller phlebectomy hooks.[51] In Pittaluga and associates' large contemporaneous and comparative trial, which was conducted in 831 limbs, ASVAL was performed in 303 limbs of 221 patients and HSL in the remainder.[51] The extent of varices to be treated was divided into 32 zones on the limb. Follow-up was at 1 and 6 months and then yearly for 4 years, reporting the following: duplex presence of reflux as well as CEAP clinical class, recurrent VVs, venous disability score, and patient reported outcomes for symptoms and esthetics. At 4 years following ASVAL, saphenous

reflux was reduced in 66.3% of limbs, symptoms disappeared or "improved" in 78%, and freedom from recurrent varicosities was 88.5%. It should be noted than one-third of the limbs were asymptomatic before treatment, whereas 16% had competent saphenofemoral junctions and only 8.6% had total SV reflux. A curious aspect of this study is that a comparison between ASVAL and HLS was limited to preoperative baseline characteristics and not postoperative outcomes. ASVAL would appear appropriate for mild disease (C2) and minimal symptoms with low-volume saphenous reflux in a mildly dilated saphenous vein. (see Table 154.1, VVGL 10.6).

Endovenous Ablation

The evolution of minimally invasive techniques for the treatment of GSV reflux has culminated in the development of EVA. These techniques are discussed in Chapter 155.

RESULTS

For a century L&S was the "gold standard" for the treatment of GSV incompetence and tributary avulsion for residual varicose veins. The preponderance of data advocating a surgical approach to CVI is derived from clinical reports of L&S. The role of L&S has diminished greatly in the United States with the advent of EVA by either thermal or nonthermal methods, and sclerotherapy has replaced tributary avulsion in many cases. L&S has decreased from 155,000 procedures in 1999 to less than 30,000 in 2016. By contrast, EVA has grown from none in 1999, to 355,000 procedures in 2016. What accounts for this change? Is there valid evidence to show that EVA is superior to L&S? This section reviews the evidence from RCTs when available.

As Ruckley and colleagues stated, "Evidence-based medicine has not so far been a strong feature of phlebologic practice."[54] Although most reports contain some meaningful information, some data are more compelling than others. Levels of evidence are often described as a pyramid, with 1A level at the top—RCTs composed of studies such as Cochrane systematic reviews, Agency for Healthcare Research and Quality evidence reports, and other systematic reviews. Well-designed single or multicenter RCTs are at the 1B level. Case-control and cohort studies are lower, at 3B, and case series fall at either level 4 or 5. Unfortunately the majority of studies that examine L&S and EVA are case series.

Results of Surgery on the Great Saphenous Vein Versus Conservative/Nonoperative Treatment

The ESCHAR trial was the first large prospective randomized trial to address this fundamental question. Patients with severe sequelae of CVI (C5-C6) and superficial or mixed deep and superficial venous insufficiency were randomized to medical therapy (elevation, compression, and exercise) either with or without surgical treatment of superficial venous reflux. Although no difference was found in rates of healing, a dramatic reduction was seen in ulcer recurrence (12% vs. 28% at 12 months; $P = .001$) in the group that received surgery as well as medical therapy. It is notable that 20% of the patients in the surgical arm refused surgery but remained in the surgical arm according to an intention-to-treat analysis plan. This probably resulted in understating the treatment effect of surgery.[14] Michaels and colleagues carried out an RCT that examined the impact of superficial venous surgery on quality of life in 246 patients with uncomplicated varicose veins who were randomized to compression and lifestyle changes versus surgery with L&S of refluxing segments and multiple phlebectomies.[55] The study was well designed and incorporated clinically relevant changes in health status as determined by the Short Form 36 (SF-36) and the EuroQol 5D (EQ5D). The surgical group showed significant improvement in quality-adjusted life years over the compression group. Quality-adjusted life years as assessed by SF-36 were improved by 0.083 over the medically treated group and by 0.13 as assessed by the EQ-5D. In addition, the surgical group demonstrated significant anatomic and symptomatic relief. These large RCTs provide a grade A recommendation for surgery in addition to conservative treatment in patients with varicose veins caused by GSV reflux.

Comparison of Results of Endovenous Ablation Versus Ligation and Stripping of the Great Saphenous Vein

Ten groups reported RCTs in which EVA was compared with L&S. Several groups provided follow-up on reports that supplemented the initial data in meaningful ways. Eight of these reports compared laser treatment with L&S,[56-61] whereas five reported on radiofrequency ablation with L&S.[60,62,63] The studies were of modest size, with 28 to 580 limbs being treated. Many of the RCTs were lacking some elements of proper study design: a priori calculation of sample size, comparability of baseline characteristics between groups, and intention-to-treat analysis. Desirable outcome measures such as quality of life were used in all but one series, whereas eight of the ten groups provided a disease-specific evaluative score so that preoperative values could be compared with postoperative values. Table 154.2 shows the objective endpoints for the comparisons between L&S and EVA. Overall, EVA showed an early postoperative advantage in quality of life; but by 1 month, the disease-specific scores were comparable. "Soft" outcome measures, such as return to normal activities or work and less postoperative pain, also favored EVA. Rasmussen,[56] Perälä,[66] and Darwood[57] and their colleagues found no differences between L&S and EVA in disease-specific scores by 1 month postoperatively. Six RCTs (Rasmussen and colleagues,[56,60] Kalteis and colleagues,[58] Carradice and colleagues,[66] Christenson and colleagues,[65] Gauw and colleagues,[59] Rass and colleagues[61]) showed no difference in quality-of-life measures, whereas two demonstrated an advantage for EVA (Rautio and colleagues[62] and Lurie and colleagues[63]). Morbidity is putatively less with EVA because the vein is ablated in place. L&S, however, involves stripping the vein with avulsion of branches and some tract bleeding, which can be mitigated but will never be completely eliminated. Certainly if thrombophlebitis develops in the ablated GSV,

TABLE 154.2 Comparison of EVA versus L & S of GSV (PRTs)

Series	Year	EVA Treatment	Earliest F/U	Latest F/U	Number of Limbs Treated	FAILURE		ADVANTAGE OF EVA		Comments
						L&S	EVA	QoL	Pain/Bruising	
Gauw et al.[59]	2016	Laser	NA	5 years	130	10/60	20/61	Φ	NA	Inc SFJ reflux at 5 years in EVA
Rasmussen et al.[56]	2007	Laser	12 days	6 months	137	2/68	3/69	Φ	⊕	Costs of laser; no change in pain medication
Rasmussen et al.[60]	2013	Laser	NA	3 years	580	22/66	24/73	Φ	NR	3-year F/U data *P* = NS
Rass et al.[61]	2012	Laser	NA	2 years	346	37161 (clin) 2/161 (SFJ reflux)	30/185 (clin) 33/185 (SFJ reflux)	Φ	NR	*P* = .15 *P* <.001
Darwood et al.[57]	2008	Laser	12 days	3 months	103	4/32	4/71	Φ	NR	No Δ in return to physical activity or work
Kalteis et al.[58]	2008	Laser	1 week	4 months	100	0/50	0/50	Φ 4 weeks	NR	HL in both groups ↓ Hematoma with EVA ↓Time to return to work with EVA
Christenson et al.[64]	2010	Laser	12 days	2 years	204	0/100	7/104	Φ		EVA failed in 4 initially. At 1 year, 2 GSVs fully and 3 partially reopened
Carradice et al.[65]	2011	Laser	1 week	12 months	208	10/132	1/137	Φ	NR	Recurrence at 1 year was lower after EVA
Rasmussen et al.[60]	2013	RFA	NA	3 years	580	22/64	17/74	Φ	NR	3-year F/U data *P* = NS
Rautio et al.[62]	2002	RFA	1 day	8 weeks	28	0/13	0/15	NR	⊕	
Perälä et al.[66]	2005	RFA (F/U)	1 day	3 years		3/13 Recurrent varices	5/15 Recurrent varices	NR	NR	
Lurie et al.[63]	2003	RFA	3 days	4 months	86	0/36	2/44	⊕	NR	↓ Time to return to normal activity and work with EVA
Lurie et al.[67]	2005	RFA (F/U)	1 year	2 years	65	1/36 Recanalized GSV 14% Recurrent VVs	2/44 Recanalized GSV 21% Recurrent VVs	⊕ 1 + 2 years	NR	

EVA, endovenous ablation; *FlU*, follow-up; *GSVs*, great saphenous veins; *HL*, high ligation; *L&S*, ligation and stripping; *NR*, not reported; *QoL*, quality of life; *RFA*, radiofrequency ablation; *VVs*, varicose veins.
Φ, No difference; ⊕, better with EVA.

the pain can be as severe as that with stripping. The use of postoperative analgesics is usual with L&S, in contrast to EVA. We have observed that local tumescent anesthesia results in reduced pain and bruising with vein stripping and phlebectomy as well as with EVA. Rasmussen and colleagues compared L&S and EVA in a randomized trial in which tumescent anesthesia was used in all patients.[56] In this report, 121 patients (137 limbs) were randomized to high L&S with local anesthesia or endovenous laser treatment. Both groups had varicosities removed through miniphlebectomies and received perivenous tumescent solution and intravenous fentanyl. L&S was performed by the perforate-invaginate (PIN) stripping technique. The two treatments were found to be equally effective in eliminating GSV reflux, with no differences in times to resume normal activities or return to work. There was more pain and bruising in the L&S group but no change in pain medication use between the groups. No difference was observed in the venous clinical severity score or in the Aberdeen score between the two groups at any time point. The bodily pain score component of the SF-36 was higher after L&S than after EVA 12 days postoperatively.

Taken as a group, these data demonstrate an early postoperative advantage in pain for the EVA procedures. We analyzed this group of RCTs in a systematic review and meta-analysis to investigate the timing and mode of failure (recurrence of varicose veins after surgery: REVAS).[68] We found no difference in the overall incidence of the recurrence of varicose veins after surgery (REVAS) between EVA and L&S, nor was there a difference in the rates of reoperation. In addition, REVAS was progressive over time, with more than a doubling of clinical recurrence in Rasmussen's trial between years 1 and 5.[60] There is a different pattern of causes, however, with the two techniques. Neurovascularization was more common after L&S, whereas recanalization occurred more frequently after EVA. Although there was individual variation as to the site of REVAS within each study, meta-analysis showed that the thigh and calf are comparable as sites of recurrence for EVA.

Results of Surgical Treatment of Veins of the Popliteal Fossa

Reported rates of recurrent varicosities and reflux after SSV surgery are often high. In a DUS survey, Tong and colleagues reported a 61% incidence of recurrent SSV reflux,[69] and Mitchell and colleagues in their series observed a 50% incidence of recurrent SSV-popliteal reflux despite using preoperative DUS.[70] The latter series would appear to underline the critical role of surgical technique in addition to preoperative DUS in achieving optimal results. In Creton's review of 125 reoperations for recurrence of SSV reflux, the majority (>60%) were due to inadequate ligation of the proximal SSV: 13.6%, intact SSV trunk; 42.4%, residual long stump of the SSV off the popliteal vein; and 3%, small residual and incompetent small saphenous trunk.[71] A less frequent cause of recurrent reflux in the popliteal fossa was an incompetent popliteal area perforating vein. A smaller series by De Maeseneer and colleagues showed results similar to those of Creton: 1 of 12 patients had a long untreated SSV stump, which they ascribed to a high SSV-popliteal junction.[72]

Although Tong and colleagues[69] found that SSV reflux was the cause of recurrent varicosities in 43 of 70 limbs (61%), an appreciable incidence of non-SSV incompetence was noted. In fact, Rettori identified incompetence of a gastrocnemius vein as the cause of recurrent popliteal fossa varices in 34% of his cases.[73] The retrospective series of Tong and colleagues,[69] Creton,[71] and De Maeseneer and associates[72] were based on patients with presumed recurrence of SSV reflux. Mitchell and colleagues, however, carried out a prospective study of SSV surgery and found SSV reflux in 33% of patients and gastrocnemius reflux in 17%. These findings underline the importance of defining by perioperative DUS exactly which veins are incompetent in the popliteal fossa as well as their relationship to the SSV. Armed with preoperative DUS findings, the surgeon can plan the operative approach accordingly but must be committed to correcting it.

A single RCT investigating surgery versus EVA of the SSV[74] reported on 106 patients. Abolition of SSV reflux was significantly higher after EVA (96.2%) than after surgery (71.7%) ($P < .001$). Postoperative pain was significantly lower after EVA ($P < .05$), allowing an earlier return to work and normal function ($P < .001$). Minor sensory disturbance was significantly lower in the EVA group (7.5%) compared with the surgical group (26.4%) ($P = .009$). Both groups demonstrated similar improvements in venous clinical severity score and quality of life. These data suggest that the application of EVLA to the SSV may have an increasing role in clinical care; however, concern about potential thermal injury to the many nerves in the popliteal fossa has limited its application at this point. By combining a thorough preoperative evaluation with an aggressive surgical approach aimed at eliminating all refluxing segments in the popliteal fossa, we found no sensory or motor nerve injuries, no hematomas or wound infections, no DVT, and no reflux of the SSV, popliteal junction, or other veins of the popliteal fossa in a recent study of 47 consecutive limbs.[75] Additionally, at 6-month follow-up, the mean venous clinical severity score had decreased significantly to 2.5 from a preoperative value of 7.0, with no cases of recurrent reflux in the popliteal fossa. These data support a continued central role for well-planned and well-executed venous surgery in the treatment of popliteal fossa venous disease.

MULTIMODALITY AND INDIVIDUALIZED CARE

The many approaches advocated by passionate and compassionate experts from around the globe serve to emphasize that no single treatment for venous disease is appropriate for all patients or, for that matter, for all venous issues in a single patient. Modern venous specialists have many tools at their disposal, and it is common to employ a combination of EVA, HLS, phlebectomy, sclerotherapy, and stenting—potentially in a single patient. For example, Kalodiki et al. randomized patients with GSV reflux and tributary varicose veins to high ligation plus either

phlebectomy or foam sclerotherapy to treat the tributaries. At 3 and 5 years of follow-up, the tributary treatments were equally effective, as demonstrated by VCSS, VSDS, and the SF-36 physical component score.[76] These authors also found that follow-up sclerotherapy was commonly used in both groups, and they suggested a "dental plan" approach, in which patients receive routine interval treatments.

PATIENT MANAGEMENT AND REIMBURSEMENT CONSIDERATIONS

Most insurers have well-defined criteria for the approval of the treatment of varicose veins, termed medical review criteria, which are used to preauthorize interventional treatments. The underlying attitude of some insurers is captured by the following statement in the overview on one insurance policy: "Most varicose veins do not require surgical or other procedures; wearing specially fitted elastic stockings is all that is needed in many cases." Policies vary between carriers and regions, but typically insurers require that three conditions be satisfied to authorize treatment for axial reflux: (1) symptomatic varicose veins; (2) duplex evidence of reflux greater than 1 second (some also require a minimum GSV diameter [e.g., >4 mm]); and (3) a trial of compression stockings for 6 weeks to 3 months without relief of symptoms. Other indications for intervention may include the following: a venous ulcer; lipodermatosclerosis; more than one episode of minor hemorrhage from a superficial varicosity; a single significant hemorrhage from a ruptured superficial varicosity, especially if transfusion was required; two or more episodes of superficial thrombophlebitis; and persistent superficial thrombophlebitis unresponsive to 4 weeks of conservative therapy.

Insurers usually do not distinguish between authorization for EVA or L&S, nor do they dictate the setting. Reimbursement to the physician, however, can vary greatly depending on the site of service. If the procedure is performed in a hospital facility or surgical center, the insurer pays a professional fee to the physician as well as a facility fee to the hospital. By contrast, in office-based procedures, the surgeon receives a global reimbursement. This system typically results in higher costs to the payer and lower margins for the physician for hospital-based venous procedures. These financial realities, the decreased invasiveness of modern venous interventions, the proliferation of vein centers, and the ease of use of the office setting have resulted in a dramatic shift of venous surgery to offices and away from hospitals. Comparing the costs of conventional surgery versus EVA, Lees reported a prospective randomized trial in which 91 patients were randomized to RFA versus L&S in the United Kingdom.[77] Ablation was more expensive (mean hospital cost per patient £1275.90 vs. £559.13 for L&S) in their setting; however, they concluded that in employed patients the quicker return to work (mean 12.2 vs. 19.8 days, $P = .006$) justified the additional procedural cost. However, in certain settings or populations, the reduced procedural costs of conventional surgical techniques may well influence surgical decision making.

Indications for Ligation and Stripping of the Great Saphenous Vein in the Current Climate Favoring Endovenous Ablation

Listed here are the indications the authors use to identify patients who will receive the most benefit from L&S of the GSV as opposed to EVA.

1. Superficial saphenous tributary. The most common indication for L&S of GSV is to treat a superficial saphenous vein or tributary that is closely adherent to the skin. This vein can be an "extrafascial" continuation of the main GSV as a superficial branch or, alternatively, a separate anterior accessory saphenous vein or a truly duplicated GSV. The inability to create at least a 1-cm buffer zone between the skin and the vein with tumescent anesthesia during thermal ablation increases the risk for skin burns and is a clear contraindication to thermal EVA. Nonthermal techniques have eliminated the burn issue, but inflammation and pigmentation remain issues when the treated vein is very superficial. These patients more frequently undergo a stab phlebectomy of this venous segment rather than the classic L&S.
2. GSV dilation or aneurysmal venous segments. Dilation of the proximal GSV to greater than 2.5 to 3 cm or large aneurysmal venous segments along the course of the GSV are also indications for L&S. Despite external compression, copious tumescent solution, and the use of newer endovenous techniques, the proximal GSV may be difficult to ablate effectively and may be more prone to thrombotic complications in these circumstances.
3. Chronic thrombophlebitis. The formation of synechiae within the GSV as a sequela of superficial thrombophlebitis may prevent advancement of the radiofrequency ablation catheter or laser sheath. This may occur even if a guidewire crosses the diseased segment. In this situation it is often possible to perform high L&S with the flexible Codman stripper or the relatively stiff wire PIN strippers. If this also fails, simple ligation plus segmental excision is performed. In addition, if the vein wall is noted to be markedly thickened on DUS, it will not constrict appropriately in response to thermal ablation and would be more effectively treated with L&S.
4. Excessive tortuosity (same considerations as in No. 3).
5. Acute superficial thrombosis. Acute superficial vein thrombosis with extension to the saphenofemoral junction remains an indication for anticoagulation, GSV ligation, or both to prevent extension to the common femoral vein. EVA is clearly contraindicated in any vein with acute thrombus.
6. Economic consideration. Capital costs for establishing an endovascular vein ablation program may easily exceed $50,000. In addition, there are high per-case consumable costs. Even though venous interventions are considered to provide a solid return on financial investment, the up-front capital costs may prove a significant barrier to entry. In addition, if patients are responsible for the costs of their treatment, they may favor the typically less costly open procedures.

In summary, L&S has decreased in popularity as a technique for treating GSV reflux because of the less invasive nature of EVA. However, for the previously stated reasons, L&S of the GSV remains a relevant procedure with a definite though diminished place in a modern venous practice.

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CHAPTER 155

Varicose Veins: Endovenous Ablation and Sclerotherapy

MIKEL SADEK and LOWELL S. KABNICK

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BACKGROUND

Endovenous treatments for varicose veins emerged in response to the disadvantages of open surgery and are now the standard of care due to improved efficacy and safety.[1,2] The most widespread technologies used for the treatment of truncal vein reflux are radiofrequency ablation (RFA) and endovenous laser ablation (EVLA). Sclerotherapy remains the treatment of choice for telangiectasias and reticular veins, but it has a smaller role for larger varicosities and truncal reflux.

RELEVANT ANATOMY

Superficial veins in the lower extremities are predominantly suprafascial and function as the principal collecting system for the lower extremity. They are highly expansible and dilate significantly to accommodate large volumes of blood, acting

Abstract

The elimination of refluxing superficial veins represents a fundamental management principle in the treatment of chronic venous insufficiency. Surgical ligation and stripping of refluxing truncal veins was once the standard treatment; however, endovenous ablation technologies have supplanted surgery as the preferred intervention. Furthermore, the application of tumescent anesthesia to the treatment of chronic venous insufficiency has enabled a transition of care from the inpatient to the outpatient setting.

Endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) are the endothermal modalities, and they use thermal energy to effect fibrosis and sclerosis of the vein wall. This chapter reviews the data demonstrating improved efficacy and reduced complication rates with EVLA and RFA as compared to surgical stripping. Non-thermal, non-tumescent technologies have recently come to the market and are gaining traction. These include mechanicochemical ablation (MOCA) and adhesive closure. Safety and efficacy have been demonstrated for the non-thermal technologies, but long-term durability has remained a question.

Sclerotherapy represents a well-established treatment for the management of venous reflux. The sclerosing agent must make contact with the vein wall in order to cause endothelial damage, and this occurs with some variability. Although efficacious for the treatment of telangiectasias and reticular veins, treatment of truncal veins with sclerotherapy is met with variable efficacy as compared to the endothermal technologies. The treatment landscape remains ever-evolving. Fortunately, there has been a trend towards improved clinical outcomes, and more significantly towards improved patient-reported outcomes.

Keywords

Adhesive closure
Endothermal heat induced thrombosis (EHIT)
Endovenous laser ablation (EVLA)
Great saphenous vein (GSV)
Mechanicochemical abalation (MOCA)
Perforator
Radiofrequency ablation (RFA)
Small saphenous vein (SSV)
Sclerotherapy
Tumescent

as temporary storage.[3] This enables the collection of blood from the superficial tissues and skin, which is then routed to the deep system for return.

Great Saphenous, Small Saphenous, and Perforating Veins

Of particular interest for endovenous procedures are the two major veins of the superficial system: the great saphenous vein (GSV) and the small saphenous vein (SSV). The GSV originates medially from the dorsal vein of the foot and continues proximally along the medial aspect of the calf and thigh before joining the common femoral vein at the saphenofemoral junction (SFJ).[4] It contains 7 to 10 valves, the most important of which are located at the level of the SFJ and 1 to 2 cm peripherally.[5] True "duplication" of the GSV is rare, and apparent duplications are typically accessory saphenous veins that run parallel to the GSV.[4,6,7]

An anterior accessory GSV is the most common, found in up to 14% of patients.[8,9] The GSV is located in its own subfascial compartment; in transverse ultrasound view it has the appearance of an eye (known as the "saphenous eye"). It has a number of fairly consistent tributaries, including the posterior accessory GSV, the anterior accessory GSV, the posterior thigh circumflex, and the anterior thigh circumflex.[10,11] Tributaries near the SFJ, such as the superficial inguinal veins, are sometimes used as markers to guide positioning of catheters in RFA and EVLA procedures.

The SSV originates inferior and posterior to the lateral malleolus and ascends the posterior aspect of the calf between the gastrocnemius heads to the popliteal fossa.[11] In two-thirds of patients, the SSV connects to the popliteal vein at the saphenopopliteal junction (SPJ), which is most often located within 5 cm of the popliteal skin crease. However, in some patients this junction may be situated as high as 7 cm above the crease. In the remaining one-third of patients, the SSV joins with another vein, such as the GSV, or may have several termination points through its thigh extension.[4,12] Similar to the GSV, the SSV lies within its own fascial compartment and contains between 7 and 10 valves.[4,13] It has one major tributary, the intersaphenous vein, which ascends across the medial aspect of the leg and connects the SSV to the GSV.[4,10]

A discussion of perforating veins can be found in Chapter 158.

Reticular Veins

Reticular veins are thin-walled blue venules lying within the superficial compartment; they have diameters ranging from 1 to 3 mm.[14,15] They may connect to the saphenous veins and form a network of vessels termed the *lateral subdermic venous system* (LSVS).[16] The LSVS is located along the lateral aspect of the leg and extends above and below the popliteal area.[17] Ultrasound studies have revealed that the reticular veins of the LSVS may connect to telangiectasias in up to 88% of patients.[18]

Telangiectasias

Telangiectasias differ from reticular veins in both size and appearance. Telangiectasias are defined as dilated venules, capillaries, or arterioles 0.1 to 1.0 mm in diameter.[12,19] The color of a telangiectasia depends on the origin of the vessel. Telangiectasias that arise from the arterial side of the capillary loop are flat and red, whereas those from the venous side are raised and blue.[12] These veins often appear in the thigh near the LSVS. Reticular veins are frequently "feeder" veins to telangiectasias.

DIAGNOSTIC EVALUATION

Clinical Scoring Systems

Most clinicians have adopted the Clinical, Anatomic, Etiologic, Pathophysiologic (CEAP) system to classify the physical findings associated with chronic venous insufficiency (Fig. 155.1; see also Chapter 156).[10] Any patient in whom an endovenous procedure is contemplated should be evaluated in terms of this classification. Photographs of the target veins should also be taken to document the clinical score and compare the pre- and postoperative results.

Patient-oriented outcomes are becoming central to evaluating venous pathology and its meaningful effects on the patient. The Venous Clinical Severity Score (VCSS) and the Villalta scale are scoring systems that assess severity of disease and quality-of-life issues.[6] As with the CEAP classification, all patients undergoing endovenous procedures should be evaluated using one or both of these systems.

Imaging

Duplex ultrasonography (DUS) of the lower extremities is the standard study for evaluating and diagnosing superficial venous insufficiency. Complete evaluation includes assessment of both reflux and obstruction in the deep, superficial, perforating, and tributary veins.[4] A more complete description of the technique can be found in Chapters 19 and 23. The goals of ultrasound are to identify and map the superficial veins to be treated and determine their locations and degrees of reflux. The deep system should also be interrogated, because obstruction in this system is a relative contraindication to the closure of superficial veins.[5]

TREATMENT SELECTION

The primary goal in treating superficial venous insufficiency is closure of refluxing superficial veins, which alleviates symptoms and prevents complications. The most proximal point of reflux should be treated first. An additional goal of the treatment of telangiectasias and reticular veins is the attainment of satisfactory cosmetic results.[7]

The most proximal point of reflux in the majority of patients is the SFJ or SPJ. Wong et al. evaluated 239 limbs with primary reflux and 225 limbs with recurrent reflux; they found SFJ incompetence in 53% and 69%, respectively, of these limbs.[8]

Figure 155.1 Clinical, Anatomic, Etiologic, Pathophysiologic (CEAP) Classification of Venous Insufficiency. (A) C0: normal asymptomatic leg. (B) C1: telangiectasias or reticular veins. (C) C2: varicose veins greater than 3 mm in diameter. (D) C3: edema. (E) C4a: pigmentation or eczema. (F) C4b: lipodermatosclerosis. (G) C5: healed venous ulcer. (H) C6: active venous ulcer.

In the same patient cohort, 21% of the primary reflux limbs and 25% of the recurrent reflux limbs demonstrated incompetence at the SPJ.[8] Similarly, Guex et al. found that 85% of limbs showed reflux in the GSV (68% at the junction) and 20% in the SSV.[13] Patients with reflux in either of these truncal veins are candidates for an endothermal or nonthermal ablation.

Patients with saphenous reflux may also exhibit varicosities, enlarged reticular veins, or telangiectasias. Currently there is debate as to whether adjunctive procedures to treat these varicosities and telangiectasias should be performed at the same time that truncal reflux is eliminated or in a staged fashion. One study in which patients were simultaneously treated with EVLA and ambulatory phlebectomy found that 94% did not have to return for additional ambulatory phlebectomy procedures.[9] Conversely, in a study of 181 patients who underwent RFA of the GSV, only 25% were able to avoid additional treatment with ambulatory phlebectomy.[20] This issue remains controversial, but it seems apparent that certain subsets of patients may benefit from concomitant ablation and microphlebectomy as compared with a staged procedure.

The Society for Vascular Surgery (SVS) and the American Venous Forum (AVF) have compiled evidence-based recommendations for the care of patients with chronic venous disease.[21] Both EVLA and RFA are considered safe and efficacious and are recommended equally for the treatment of saphenous reflux. Both are recommended in preference to open surgery because of reduced convalescence time and a decreased incidence of postprocedural pain and morbidity. They are also recommended in preference to foam sclerotherapy because of their greater efficacy. Liquid or foam sclerotherapy is recommended for the treatment of telangiectasias, reticular veins, and varicose veins. A guideline for choosing the appropriate endovenous intervention is listed in Table 155.1 and discussed in detail in the following sections.

TABLE 155.1 Endovenous Options for Treatment of Reflux

Type of Treatment	Vessels Treated
Radiofrequency ablation	Saphenous vein trunks Saphenous vein tributaries Perforators
Endovenous laser ablation	Saphenous vein trunks Saphenous vein tributaries Perforators
Ultrasound-guided sclerotherapy	Saphenous vein trunks Saphenous vein tributaries Perforators Varicose veins not connected to saphenous vein trunks
Visual or surface sclerotherapy	Varicose veins Reticular veins Telangiectasias

Thermal Ablation Techniques

Radiofrequency Ablation

RFA is a minimally invasive technology that provides efficacious treatment of superficial venous reflux with minimal postprocedural sequelae and can be performed in an outpatient setting. The current RFA technology uses the "segmental ablation" method employed by the Venefit procedure using the ClosureFAST catheter.[22] It is designed for treating both the GSV and SSV (Fig. 155.2A). The ClosureFAST catheter is constructed such that it must make direct contact with the vein wall to deliver radiofrequency energy. This results in destruction of the endothelium, contraction of vein wall collagen, and thrombus formation. Eventually, fibrosis occurs within the vein, which further constricts its lumen, resulting in a durable ablation.[17]

Contraindications to the use of RFA include superficial venous thrombosis (SVT), deep venous thrombosis (DVT), venous aneurysm, and an ankle-brachial index of less than 0.9. Although the presence of a pacemaker is not a strict contraindication, preprocedural evaluation by the patient's cardiologist should be considered.

Preoperative Planning

On the day of the RFA procedure, the patient should be well hydrated to achieve maximal distention of the leg veins. Venodilation can be further enhanced by warming of the ultrasound gel and keeping the patient warm in the procedure room. Duplex ultrasonography is performed prior to the procedure to mark the skin overlying the target treatment vein.[23]

Radiofrequency Ablation Procedure

For ablation of the GSV, access is initiated no more than a hand's breadth (~10 cm) below the popliteal area. Treatment should be performed only where the vein is deep to the saphenous fascia and at least 1 cm below the skin to avoid skin burns. With the patient in the reverse Trendelenburg position, lidocaine is administered at the selected site, and a 21-gauge needle is used to gain access under ultrasound guidance. A 0.018-in guidewire is inserted into the GSV, and the needle is removed. A 7-Fr by 7- to 11-cm sheath is advanced over the wire, the 0.018-in wire is removed, and the ClosureFAST catheter is inserted. The catheter is advanced to the point where treatment will begin. If it does not advance easily, a 0.025-inch guidewire may be backloaded into the device to assist passage. Optimal positioning of the catheter tip is 2 to 2.5 cm distal to the SFJ, which is thought to reduce the risk of an endothermal heat-induced thrombosis ("EHIT," or extension of thrombus into the common femoral vein).[24,25]

Once tip placement is confirmed by ultrasound, perivenous tumescent anesthesia is administered under ultrasound guidance along the entire treatment length to create a fluid layer around the GSV. Tumescent anesthesia serves not only as an anesthetic but also compresses the vein around the catheter and protects the surrounding tissue and skin from heat damage.[24,26] Enough should be instilled to create a 10-mm diameter around the vein (Fig. 155.3). A typical mixture includes 50 mL of 1% lidocaine

Figure 155.2 (A) Venefit. Covidien ClosureFAST Endovenous Radiofrequency Ablation Catheters brochure (Coviden, Hampshire, UK). (B) Dornier Medilas D laser (Dornier MedTech, Munich, Germany). (C) Sciton Pro-V laser (Sciton, Inc., Palo Alto, California). (D) CoolTouch CTEV laser (CoolTouch, Inc., Roseville, California). (E) Biolitec ELVeS PL laser (biolitec AG, Jena, Germany).

with epinephrine in 450 mL of normal saline neutralized with 5 to 10 mL of 8.4% sodium bicarbonate.[23] The safe limits for tumescent lidocaine administration have been described as 35 mg per kg body weight.[27]

Most physicians use a pump system with a 22-gauge spinal needle to deliver the tumescent anesthesia because it decreases the time needed for administration as well as the number of needle punctures. Ideal needle positioning is within the saphenous compartment. After administration, the patient should be placed in the Trendelenburg position to assist in vein collapse, apposition, and exsanguination.[26] Following treatment of the whole vein, the sheath and catheter are withdrawn.[26]

During the procedure, compression over the treated vein and catheter with the ultrasound transducer in a longitudinal position improves vein wall apposition and technical success.[28] With the segmental ablation technique of the ClosureFAST system, each 7-cm segment of vein is treated independently for a 20-second interval. The initial treatment segment 2 to 2.5 cm distal to the SFJ requires two 20-second cycles to ensure successful ablation. Aneurysmal or large-diameter segments may also be treated twice at the user's discretion.[24] For each 20-second cycle, the temperature must reach 120°C within 5 seconds after the initiation of delivery of the energy; if this temperature is not achieved within the stated time frame, the segment must undergo another 20-second treatment cycle.[26] The RFG Plus generator monitors all parameters during the treatment cycle and alerts the user if the parameters are not successfully met. A segment should not undergo more than three treatment cycles.[26]

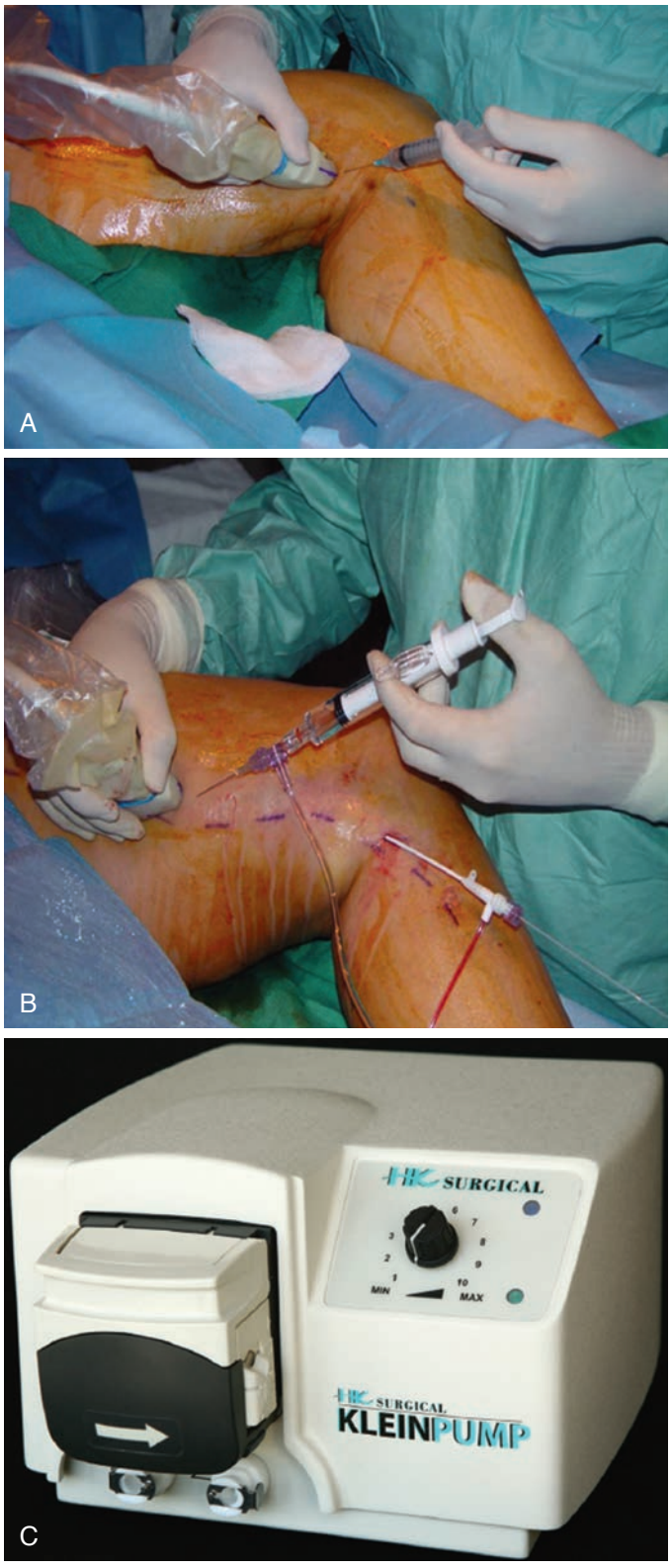

Figure 155.3 (A) Delivery of tumescent anesthesia with the hand injection method. (B) Delivery of tumescent anesthesia with a refillable syringe. (C) HK Klein tumescent pump (HK Surgical Inc., San Clemente, California).

After treatment, duplex ultrasonography is used to assess the treated vein for closure, absence of reflux, and EHIT.

Discharge and Follow-Up

Postoperative compression with a 30- to 40-mm Hg graduated stocking or a multilayer compression dressing is recommended for at least 1 week.[26,29,30] Although well accepted as postprocedural care, the mandatory use of compression is coming into question. In one randomized study of 70 patients undergoing ablation, there was no difference in patient-reported outcome between patients who wore compression and those who did not.[31,32] Patients are instructed to ambulate after the procedure to assist in occlusion of the vessel.[30] A duplex ultrasound follow-up examination is advised at 72 hours to assess for EHIT and closure of the treated veins.[30] Further follow-up evaluations are performed according to physician preference.

Clinical Results: Complications

Complications of RFA include vessel perforation, thrombosis, pulmonary embolism (PE), phlebitis, EHIT, infection, nerve injury, and skin burns or discoloration.[26] Proebstle et al. initially reported comprehensive findings from 6-month data showing a low rate of side effects: ecchymosis, 6.4%; paresthesia, 3.2%; hyperpigmentation, 2.0%; hematoma, 1.6%; erythema, 1.6%; and phlebitis, 0.8%.[24] Thermal skin injury and DVT were not observed; however, during the first year of use of the ClosureFAST in 2007, numerous adverse events related to DVT were reported.[33] The rate of these events has decreased significantly as the current procedures/catheters were developed and clinicians gained experience with the procedure.

The European Closure Fast Clinical Study Group reported on the 3-year European follow-up on the ClosureFAST device, now referred to as the Venefit procedure.[34] The incidence of complications was low; the majority manifested and subsided within the first week after treatment. They included ecchymosis, 5.8%; erythema, 2.0%; hematoma, 1.4%; and phlebitis, 1.0%. Complications persisting beyond the first week included paresthesias (initial rate of 3.4%, which declined to 0.4% at 36 months) and pigmentation (initial rate of 2.4%, which also declined to 0.4% at 36 months). There were no reported cases of DVT or PE.

Clinical Results: Outcomes

The European Closure Fast Clinical Study Group also reported the 3-year efficacy of the ClosureFAST device, demonstrating a rate of 92.6% continued occlusion of treated truncal veins.[34] The Venous Clinical Severity Score (VCSS) improved from an average of 3.9 before treatment to 0.9 at 3 months after treatment ($P < .0001$), which persisted for the duration of the study. Seventy-four percent of patients demonstrated an improvement in CEAP at 36 months.[34]

Endovenous Laser Ablation

EVLA exhibits many procedural similarities to RFA, with the primary differences related to the type of catheter and its

mechanism of action. EVLA uses a bare-tipped or jacket-tipped fiber to deliver laser energy to a target area, resulting ultimately in fibrosis and occlusion of the target vein.[35-37]

Laser Wavelength and Fiber Type

Different laser wavelengths have been used to generate endothelial destruction of varicose veins, including lengths of 810, 940, 980, 1064, 1319, 1320, and 1470 nm (see Fig. 155.2B to G).[38] Research on the optical properties of blood has shown that different wavelengths have varying absorption characteristics; these may loosely be categorized into the hemoglobin-specific laser wavelengths (HSLWs) and the water-specific laser wavelengths (WSLWs).[39]

A limited number of studies have evaluated these wavelengths for both efficacy and adverse events. The first, by Proebstle et al. in 2005, compared the 940- and 1320-nm wavelengths.[40] The study concluded that the wavelengths were equally efficacious but that ecchymosis and pain occurred significantly less often in limbs treated with the 1320-nm laser.[40] In a similar study, an analysis of the 810-nm wavelength versus the 980-nm wavelength also favored the higher wavelength.[41] Additional studies have confirmed these findings.[42] Current research suggests that the various laser wavelengths are equally efficacious but that there is a trend toward less pain and bruising with the higher-wavelength lasers. More significantly, fiber type appears to contribute to postprocedural symptoms to a greater extent than laser wavelength. Specifically, jacket-tipped fibers appear to cause less pain and bruising than bare-tipped fibers.[43]

Preoperative Planning

Preoperative planning for EVLA is the same as that for RFA.

Endovenous Laser Ablation Procedure

GSV access is obtained just distal to the popliteal area with a microaccess set (21-gauge needle, 0.018-in wire, and microsheath), and the distance from the access site to the SFJ is measured. The inner dilator is removed, and a 0.035-in guidewire is advanced through the microsheath to the SFJ under ultrasound guidance. A long sheath is then selected, exchanged for the microsheath, and advanced to a point 2 to 2.5 cm distal to the SFJ.[41] Once in place, the inner dilator and guidewire are removed and a 600-µm bare-tipped or jacket-tipped fiber is advanced into the sheath. The fiber is connected to the generator, and the aiming beam is turned on to help visualize the fiber tip under the skin. Although the fiber is held in place, the sheath is withdrawn to the locking mechanism of the fiber, with the tip of the fiber exposed approximately 2 cm past the end of the sheath. Positioning 2 to 2.5 cm peripheral to the SFJ is reconfirmed with ultrasound, and tumescent anesthesia is injected perivenously, as in RFA.[41,44,45]

Procedural Variations

Variations have developed with regard to procedural technique. Most are related to pullback time and the amount of energy delivered. In 2004, Timperman et al. introduced a modification whereby the amount of energy (joules) delivered per centimeter of vein treated (known as the linear endovenous energy density [LEED]) was assessed.[40,46] These authors found a direct correlation between the LEED and treatment efficacy. The mean energy delivered for successfully treated veins was 63.4 ± 26.6 J/cm, whereas in failed treatments an average of 46.6 ± 13.8 J/cm was emitted.[46] No failures occurred in limbs receiving energy doses of 80 J/cm or greater.[46] In a subsequent study, veins treated with an average of 95 J ± 16 J/cm had a treatment success rate of 91% 9 months after the procedure.[47] In an attempt to assess the efficacy of treatment using higher LEEDs tempered by the increased risk of complications associated with higher energy use, an evaluation of the 1470-nm laser was performed comparing an average LEED higher than 100 J/cm to a LEED lower than 100 J/cm. Although the treatment was technically successful 100% of the time in patients treated using a LEED greater than 100 J/cm, there was an increased incidence of paresthesias in the group receiving the higher LEED. In addition, postprocedural analgesia intake was significantly less in the lower LEED group.[48] Currently, 50 to 80 J/cm is the average treatment energy most often used for EVLA procedures.[41,49,50] Continuous pullback is used while the operator watches the real-time energy readout on the generator and gauges speed with the 1-cm marks on the sheath. This method has proved to be more consistent than using time to gauge pullback because the same amount of energy is delivered in each case, regardless of wattage.

Once tip positioning is confirmed, the laser is switched from standby to ready mode and the foot pedal is depressed to deliver energy. The laser fiber and sheath are drawn through the vessel simultaneously in a continuous fashion. To prevent skin burns or trauma to the entry site, the user stops treatment when the tip of the laser fiber is approximately 1 to 3 cm proximal to the entry site.[44,47] Closure of the vein is visualized by duplex ultrasound.

Discharge and Follow-Up

Discharge and follow-up for EVLA are the same as those for RFA.

Clinical Results: Complications

The incidence of procedure-related complications with EVLA has been relatively low and includes vessel perforation, thrombosis, PE, phlebitis, hematoma, infection, skin pigmentation, neovascularization, paresthesias, complications from tumescent anesthesia, irradiation of nontarget tissue, hemorrhage, necrosis, skin burns, and pain.[50] Rates vary widely in the literature: DVTs, 0% to 5.7%; skin burns, less than 1%; nerve injury, 0% to 22%; and superficial thrombophlebitis, 0% to 25%.[51,52] A rare complication reported in both RFA- and EVLA-treated patients is the development of an arteriovenous fistula, commonly occurring where the external pudendal artery crosses posterior to the GSV.[53] The natural history of these fistulas is still being elucidated, but the majority of patients remain asymptomatic.

As discussed earlier, some evidence suggests that higher-wavelength lasers produce less pain and bruising; however, a prospective large-scale study evaluating all the wavelengths is needed to further substantiate these findings. The mechanism of the EVLA procedure that causes pain and bruising remains unclear, although some experts speculate that it is due to

perforation of the vein wall by laser energy.[40,54] Aside from laser wavelengths, a novel adaptation to laser fibers that has shown a beneficial effect on perforation of the vein wall is the jacket-tipped fiber. This technology features either a stainless steel or ceramic jacket that completely covers the tip of the fiber, with the end of the tip being recessed within the jacket.[55,56] This design prevents the flat emitting face of the fiber tip from coming in contact with the vein wall.[55,56] Kabnick et al. carried out a pilot study to evaluate the efficacy and complications of jacket-tipped fibers versus bare-tipped fibers.[54] At 72 hours after the procedure, both treatment groups demonstrated 100% success; however, in the group treated with the jacket-tipped fiber, pain and bruising scores were lower.[54] Because vessel perforation has been directly linked to bruising, the study concluded that the lower bruising scores achieved in the jacket-tipped fiber group could be attributed to fewer perforations.[54] In order to assess the use of a jacket-tipped fiber in a higher-wavelength laser, Maurins et al. evaluated a 1470-nm laser and compared treatments using a bare-tipped fiber, a jacket-tipped fiber, and a fiber with a radial-emitting tip.[57] All demonstrated similar efficacy in ablation. The fiber with the radial-emitting tip had the lowest LEED requirement, resulting in less post-procedural pain than in the other two groups. In a multicomparison study involving varying laser wavelengths and fiber types, it was reported that fiber type may contribute to a greater extent to postprocedural symptomatology.[43]

Clinical Results: Outcomes

In addition to the low rate of complications demonstrated by EVLA, treatment outcomes of EVLA are at least equivalent to those of all other modalities. The seminal trial for establishing EVLA as an efficacious treatment was published by Min et al. in 2003.[44] Initial treatment results with an 810-nm laser showed a 98.2% initial success rate and an ensuing closure rate of 93.4% at 2 years.[44] Numerous trials have since been conducted for all of the wavelengths currently used. Proebstle et al. performed a study evaluating 1320- and 940-nm (15- and 30-W) lasers and reported favorable efficacy rates at 3 months of 90.3% (940 nm, 15 W), 100% (940 nm, 30 W), and 97% (1320 nm).[40] A large-scale prospective trial involving the use of a 980-nm laser on 500 limbs was published in 2007.[49] A 98% closure rate was reported at the 1-week follow-up and remained constant; the closure rate was 97.1% at the 4-year follow-up.[49]

More recently, the International Endovenous Laser Working Group evaluated long-term outcomes using EVLA for the treatment of patients with truncal reflux. The international registry evaluated 1020 limbs treated using a 980-nm bare-tipped laser. Treatment success rates were 92.3% at 1 year and 86.9% at 2 years, with no additional treatment failures at 3 years.[58]

Sclerotherapy

Sclerotherapy can be used to treat a myriad of vein types and sizes, although it is most commonly used to treat smaller vessels such as the reticular veins and telangiectasias. It is best defined as the introduction of a chemical into the lumen of a vein to induce endothelial damage that results in thrombosis and eventually fibrosis.[59]

Relative contraindications to sclerotherapy include asthma, late complications of diabetes, hypercoagulable state, leg edema, advanced peripheral arterial occlusive disease, and chronic renal insufficiency. Absolute contraindications are a known allergy to the sclerosant, acute cellulitis, acute respiratory or skin disease, severe systemic disease, phlebitis migrans, acute superficial thrombophlebitis, pregnancy, hyperthyroidism, and a bedridden status.

The method used to deliver the sclerosing agent depends on the diameter of the target vein. For smaller veins such as telangiectasias, venulectases, and small reticular veins, liquid sclerotherapy is used.[60] Larger reticular veins and varicosities may also be treated by liquid sclerotherapy with a higher concentration of sclerosing agent or by foam sclerotherapy. Foam sclerotherapy involves the addition of air to a detergent sclerosing agent by means of agitation to produce a foam-like consistency, which allows for enhanced contact with the vein wall.

Because the sclerosing agent must make contact with the vein wall to cause endothelial damage, the primary limitation of sclerotherapy is vein diameter. Until recently, sclerotherapy was not approved in the United States for the treatment of refluxing truncal veins. Polidocanol, a commonly used sclerotherapy detergent agent in both the United States and Europe, has recently gained approval from the US Food and Drug Administration (FDA) for this indication.[61]

Sclerosing Agents

Sclerosing agents are most commonly grouped into categories based on their mechanism of action.[12] Categories of currently available solutions include osmotics, alcohols, and detergents (Table 155.2).[17] Ideal sclerosing agents should effectively damage the endothelium, exhibit a low incidence of adverse events, and be painless to inject.[12]

Osmotic Agents

Osmotic agents are thought to cause dehydration of endothelial cells through osmosis, which leads to endothelial destruction.[17] The primary osmotic agent used in the United States is hypertonic saline (23.4% sodium chloride). Although not FDA-approved for use in sclerotherapy, it has been used by physicians for many years. The second agent consists of 10% sodium chloride mixed with 25% dextrose.[62] The most widely known commercial version of this agent is Sclerodex, manufactured by Omega Laboratories, LTD (Montreal, Canada).[62]

Alcohol Agents

Alcohol agents are relatively weak sclerosants that cause irreversible destruction of endothelial cells on contact.[63] The main alcohol agent used for sclerotherapy is 72% chromated glycerin (Chromex, Omega Laboratories, Ltd. Montreal, Quebec, Canada), which is popular in Europe but is not FDA-approved in the United States. Because of its weak nature, glycerin is used only for telangiectasias.[64] Nonchromated glycerin is also used but is available only through compounding pharmacies.

TABLE 155.2 Sclerosing Agents

Agent	Manufacturer	Category	FDA Approved?	Strength	Advantages	Disadvantages
Hypertonic saline	Multiple	Osmotic	Off-label use	++	Low risk of allergic reaction, wide availability, rapid response	Off-label use, painful to inject, hyperpigmentation, necrosis, rapid dilution; not recommended for facial veins
Sclerodex (hypertonic saline and dextrose)	Omega Laboratories, LTD, Montreal, Canada	Osmotic	No	++	Low risk of allergic reaction, low risk of necrosis, high viscosity	Not FDA-approved, stings when injected, hyperpigmentation
Chromex (72% chromated glycerin)	Omega Laboratories, LTD	Alcohol	No	+	Low incidence of hyperpigmentation, necrosis, and allergic reaction	Not FDA-approved, weak sclerosing agent, highly viscous and painful to inject, may cause hematuria at high doses
Nonchromated glycerin	Compounded at pharmacy	Alcohol	Off-label use	+	Low incidence of hyperpigmentation, necrosis, and allergic reaction	Weak sclerosing agent, typically used only for telangiectasias
Scleromate (sodium morrhuate)	Glenwood, LLC, Englewood, New Jersey	Detergent	Yes	+++	FDA-approved	High incidence of skin necrosis and anaphylaxis
Sotradecol (sodium tetradecyl sulfate)	BionichPharma, Inc,. Morgantown, WV (distributed by AngioDynamics, Latham, New York)	Detergent	Yes	+++++	FDA-approved, low risk of allergic reaction, potent sclerosant	Potential necrosis with extravasation, matting of telangiectasias
Varithena (polidocanol 1%)	BTG International Inc., West Conshohocken, Pennsylvania	Detergent	Yes	+++	FDA-approved, very low risk of allergic reaction, painless to inject	Matting of telangiectasias

FDA, U.S. Food and Drug Administration.

A typical mixture for this solution consists of two parts 72% nonchromated glycerin to one part 1% lidocaine with epinephrine.

Detergent Agents

Detergent agents are potent sclerosants that destroy the target vein by aggregating on the endothelial wall, disrupting the cell surface membrane, and causing thrombosis.[63] Three agents are currently FDA-approved in the United States: sodium morrhuate (Scleromate, Glenwood, LLC, Englewood, New Jersey), ethanolamine oleate, and sodium tetradecyl sulfate (STS) (Sotradecol, BionichePharma USA, Inc., Belleville, Ontario, Canada; distributed exclusively in the United States by AngioDynamics, Latham, New York).

Although sodium morrhuate is FDA-approved, it is not a preferred agent because of the associated high incidence of skin necrosis and anaphylaxis.[65] Similarly, ethanolamine oleate is a viscous solution that is difficult to inject and not commonly used.[63] STS (also FDA-approved) has a long history of safety and efficacy in treating telangiectasias, reticular veins, and varicose veins and is the most frequently used detergent sclerosant.

A fourth detergent agent popular in both Europe and the United States is polidocanol (Aethoxysklerol, Kreussler Pharma, Wiesbaden, Germany).[66] It currently has FDA approval in the United States and is distributed under the trade name Asclera (Merz Aesthetics Inc., San Mateo, California) and AngioDynamics (Latham, New York). In previous studies comparing polidocanol with STS, fewer complications were reported with polidocanol.[67,68]

The proprietary polidocanol microfoam (Varisolve Polidocanol Endovenous Microfoam; Biocompatibles, Inc., West Conshohoden, Pennsylvania) distributed as Varithena, has been approved by the FDA and is commercially available in the United States.[69,61]

Preoperative Planning

Digital photographs of the target veins should be obtained to document their appearance before sclerotherapy is performed. Larger target veins such as varicose veins should be traced with a surgical marker with the patient standing because they may be difficult or impossible to identify with the patient recumbent. Preoperative marking is typically not required for smaller veins

such as telangiectasias and reticular veins. When sclerotherapy is combined with endothermal ablation of the saphenous veins, sclerotherapy below the knee should be performed second. If a staged approach is used, the GSV or SSV should be treated first, with sclerotherapy following several weeks later. Closure of truncal veins may decompress the varicosities and smaller veins, reducing the need for sclerotherapy.[70]

Depending on the amount and severity of veins, multiple sclerotherapy treatments may be necessary. It is important to establish the expectation that several sessions may be required to achieve the desired result.

In planning sclerotherapy, another decision point is whether to use the liquid method, the foam method, or a combination of the two.[71] In the selection of an agent, the strength of the agent should match the size of the vessel to be treated so that the smallest volume and concentration can be used.[72] Sclerosants are diluted by blood immediately on injection, making treatment of larger-diameter veins with liquid sclerotherapy challenging. Liquid sclerotherapy is best reserved for small reticular veins, venulectasias, and telangiectasias.[60] Foamed agents have increased surface area related to the bubbles and stay in contact with the endothelium longer. They are therefore more effective in the treatment of larger reticular veins and varicose veins.[73]

Sclerotherapy Procedure

After preoperative preparation, the sclerosing agent is diluted with 0.9% saline according to the size of the vein (Table 155.3). In general dilutions for STS range from 0.1% to 3%, and for polidocanol from 0.25% to 1%.

Liquid Sclerotherapy

After dilution of the agent, multiple syringes are filled and assembled with 30-gauge needles. Veins should be treated from the largest diameter to the smallest diameter and in a central-to-peripheral direction.[74] For instance, the reticular veins of the LSVS feed telangiectasias. When an agent is injected into a reticular vein, the agent may flow into the telangiectasias, thereby reducing the number of treatments necessary. Transillumination can be beneficial for identifying reticular and feeding veins associated with telangiectasias. Although rare, anaphylaxis can occur, and it is essential to have resuscitation equipment available.[75]

The amount of sclerosant injected per site depends on the size of the vein; for larger varicose veins, 1 mL or less per site is advisable.[59] Reticular veins typically require 0.25 to 0.5 mL per site, with smaller telangiectasias necessitating 0.1 to 0.2 mL per injection.[71,74] While avoiding forceful pressure, injections should be made slowly and not more than a few centimeters from the puncture site (Fig. 155.4). Strong pain during injection may be an indicator of a paravascular injection; in such cases the injection should be stopped immediately.[6] Injections are delivered in 2- to 3-cm intervals until the entire length of the target vessel has been treated.[76] To help minimize bleeding, a 2- by 2-in gauze sponge is placed over each injection site and secured with tape. Graduated compression hose are applied to the treated leg or legs, and patients are instructed to wear them for 1 to 3 days to reduce thrombus formation and improve outcome. A typical initial sclerotherapy session consists of 10 to 20 injections.

Ultrasound-Guided Foam Sclerotherapy

The method widely used today involves the use of a three-way stopcock connected to two syringes; it was developed by Tessari in 1999.[77] One of the main criteria for foam to be viable is that bubble size must be 100 μm or less.[78,79] The pure form of the sclerosing agent is contained on the bubble surface; therefore, concentration is related to bubble size and the air-to-liquid ratio. For the Tessari method, a ratio of one part liquid to four or five parts air is highly effective.[80] The amount of foam to be injected can be calculated using the formula $V = \pi \times (D/2)^2 \times L$ (where V is volume, D is diameter, and L is length).[82] Other factors which contribute to success with foam sclerotherapy are stability and longevity.[79] Using the Tessari method, significant coalescence does not begin until after the first 1 to 2 minutes.[78,79,81-84]

TABLE 155.3 Recommended Concentrations for Sodium Tetradecyl Sulfate

Indications	Recommended STS Concentration (%)
Varicose veins 4-8 mm in diameter	0.5-3.0
Reticular veins 2-4 mm in diameter	0.25-0.5
Telangiectasias 0.1-2.0 mm in diameter	0.125-0.25
Recurrent varicosities	0.5-3.0
Failed segments of endothermal ablation	0.5-3.0
Unsightly veins of the hands and feet	0.25-0.5
Congenital malformations	0.125-0.25
Vascular malformations	0.125-0.25
Facial telangiectasias	0.125-0.25

STS, Sodium tetradecyl sulfate.

Figure 155.4 Liquid Sclerotherapy Injection.

Although many clinicians make their own foam, a polidocanol foam sclerosant (Varithena) is now approved and available in the United States.[61]

Depending on the size and depth of the target veins, duplex ultrasound can be helpful in guiding the injection of foamed sclerosants.[71] Foam is highly visible with ultrasound, allowing for a more accurate injection. It also enables immediate postinjection observation of vein compressibility as a predictor of treatment efficacy.[85]

Ultrasound-guided sclerotherapy using a Tessari-like method is performed in a similar fashion to foam sclerotherapy without ultrasound.[85] Target vein segments should be marked before the procedure. After the treatment area is mapped, access to the first vein to be treated is achieved with a needle or butterfly under ultrasound guidance. Access is confirmed by return of blood, and the needle/butterfly is taped to the patient's leg. The foam solution is created by a rapid mixing of the air and chemical back and forth between two syringes connected via a three-way stopcock for a total of 20 cycles.[78] After most of the solution has been moved to one syringe, the filled syringe is connected to the needle, and intravascular positioning is reconfirmed with ultrasound. A small amount of foam should be injected initially, under ultrasound, to confirm needle placement within the vein. The amount of foam delivered is determined during injection with the use of ultrasound to visualize when the targeted vein is filled with foam (Fig. 155.5). Upon completion, full-length graduated compression stockings (30 to 40 mm Hg) are applied.

Catheter-Directed Sclerotherapy

Sclerosants can also be injected using catheters. An end-hole catheter can be placed distal to the SFJ using ultrasound guidance.[81] The catheter is then withdrawn while the user delivers a foamed sclerosing agent under ultrasound guidance.[84] The technique is similar to that used in ablation procedures. Kolbel et al. achieved clinical success by injecting foamed polidocanol through a long introducer sheath as it was retracted through the GSV.[86] In 2000, Min and Navarro reported using a 5-Fr infusion catheter to deliver STS into the GSV with the patient in the Trendelenburg position.[87] Initial closure rates with this method were excellent; however, long-term efficacy diminished significantly.

Figure 155.5 Ultrasound-Guided Foam Sclerotherapy Injection.

Discharge and Follow-Up

From experience, the senior author recommends that the patient wear a 30- to 40-mm Hg compression stocking for 24 hours after treatment of reticular veins and telangiectasias and for 7-10 days after treatment of varicose veins and perforators.[88] Compression may improve the efficacy of treatment by reducing the diameter of treated veins and by lessening reflux during walking.[71] After ambulating, patients can be discharged from the facility. They may return to activities of daily living but should avoid heavy aerobic exercise involving the lower extremities for 2 weeks. Tylenol may be taken if needed; however, patients should avoid aspirin, ibuprofen, and other antiinflammatory medications for at least 48 hours. In addition, whirlpools, saunas, and hot baths should be avoided for at least 48 hours after the procedure.

Complications

The majority of complications from sclerotherapy are minor and transient.[89] They include hyperpigmentation, telangiectatic matting, pain, and urticaria.[75,89] Hyperpigmentation occurs in 10% to 30% of patients and is believed to depend on the concentration of sclerosant and to a lesser degree the vessel size and agent used (Fig. 155.6).[85,89,90] Spontaneous resolution is observed in 70% and 99% of cases at 6 months and 1 year, respectively.[90] Telangiectatic matting occurs in 15% to 20% of patients, but usually resolves in 3 to 12 months.[90,91] Pain on injection is largely related to the sclerosing agent used. Detergent agents cause little or no pain, whereas hypertonic saline is the most painful to inject. Urticaria is very common but fades within the first 24 hours.[89]

Rarely observed more serious complications include cutaneous necrosis, superficial thrombophlebitis, nerve damage (saphenous, sural), allergic reaction (anaphylaxis), DVT, PE, and inadvertent arterial injection.[75,89] Necrosis is rare and most often caused by extravasation with hypertonic saline. Superficial phlebitis is usually a result of direct injury to the vein and typically occurs 1 to 2 weeks after the procedure.[89] It is characterized by pain, tenderness to touch, heat, and erythema and can be treated by removal of the coagula via puncture extraction.[89] The incidence of DVT is low after sclerotherapy, with less than 2% of patients affected.[92] Bradbury et al.[93] evaluated one of the largest contemporary series for foam sclerotherapy used in the treatment of truncal reflux. A total of 1252 limbs were treated, 3 patients experienced DVT, and there was 1 PE. Five patients experienced neurologic sequelae in the form of transient visual disturbances, presumably from embolization of foam.[94] Treatment for neurologic sequelae consists of administration of 100% oxygen with the selective use of hyperbaric oxygen.

Clinical Results

Sclerotherapy is safe and efficacious. Kern et al., in a study using the liquid sclerotherapy method with chromated glycerin to treat telangiectasias and reticular veins, found that 76% of

Figure 155.6 (A) Reticular veins and telangiectasias before treatment. (B) Hyperpigmentation after the procedure.

patients who wore compression stockings after the procedure had a successful outcome.[95] Goldman reported the results of a prospective trial in 2002 comparing Sotradecol and polidocanol and found both agents to have a 70% rate of efficacy.[67] Belcaro et al. collected data from numerous trials evaluating STS liquid sclerotherapy versus STS foam sclerotherapy and reported efficacy rates of 90.2% and 92.2%, respectively.[86] A related study by Yamaki et al. compared polidocanol duplex ultrasound–guided liquid sclerotherapy and polidocanol duplex ultrasound–guided foam sclerotherapy of the GSV and reported complete closure rates of 17.5% and 67.6%, respectively.[87]

Studies evaluating foam sclerotherapy alone have also shown positive treatment results. Frullini and Cavezzi performed foam sclerotherapy with STS via the Tessari method and reported a success rate of 93.3%.[72] Using ultrasound-guided foam sclerotherapy with polidocanol, Bergan et al. treated 328 lower extremity veins and recorded complete absence of reflux in 79.8% of treated veins.[96] Other studies have reported similar results.[88,97-99]

Preliminary data from two phase III trials evaluating polidocanol endovenous microfoam (Varithena) have recently been published.[100] In the Polidocanol Endovenous Microfoam versus Vehicle for the Treatment of Saphenofemoral Junction Incompetence (VANISH-2) trial, elimination of reflux as demonstrated by DUS occurred in 85% of patients treated with foam compared with 2% in the placebo group. Patient-reported outcomes were improved in 80% of the treatment group compared with 20% of the placebo group. There were no cerebrovascular events or PE, but 13 patients developed DVT, of which 6 were proximal. Half were treated with anticoagulation at the discretion of the investigator, and all resolved within a median time frame of 29 days. The results were durable at 1 year, with no recurrent DVTs.[101]

A recent study published by the Varithena Study Group demonstrated that there were greater improvements in patient- and physician-reported outcomes using polidocanol endovenous microfoam compared with placebo. The HASTI score (heaviness, achiness, swelling, throbbing, itching) improved by 30.7 versus 16.7 ($P < .001$) in the Varithena group. The m-VEINES-QOL/Sym (modified Venous Insufficiency Epidemiological and Economic Study-Quality-of-Life/Symptoms) and VCSS scores also improved in the Varithena group. Adverse events were mild and transient, including contusion, hematoma, limb discomfort.[102]

Comparison of Outcomes of Radiofrequency Ablation, Endovenous Laser Ablation, Sclerotherapy, and Surgery

In a meta-analysis including 12,320 patients from 64 studies who had undergone treatment of truncal veins with RFA, EVLA, foam sclerotherapy, or surgery, the results over 32 months demonstrated better outcomes for RFA and EVLA compared with surgery and foam sclerotherapy. "Success" rates were 84% for RFA, 94% for EVLA, 78% for surgery, and 77% for foam sclerotherapy.[103] Because of long-term treatment failures, Gohel

et al. performed a cost-effectiveness analysis and concluded that foam sclerotherapy may be less cost-effective than RFA or EVLA.[102] The proposed explanation was that despite the lower initial cost for foam sclerotherapy, there was a higher incidence of reintervention than for RFA or EVLA. In a second study, Rasmussen et al. performed a randomized controlled trial comparing RFA, EVLA, ultrasound-guided foam sclerotherapy, and surgical stripping for the treatment of GSV reflux in 500 patients.[104] Concomitant microphlebectomy was performed during every procedure. Foam sclerotherapy demonstrated the highest technical failure rate at 1 year (RFA, 4.8%; EVLA, 5.8%; foam sclerotherapy, 16.3%; surgery, 4.3%; $P < .001$). One patient in the sclerotherapy group had a PE, and one person in the surgical group experienced a DVT. The highest postintervention pain scores occurred in the surgical and laser groups (RFA, 1.21; EVLA, 2.58; foam, 1.60; surgery, 2.25; $P < .001$). All subcategories of patients had similarly improved Venous Clinical Severity Scores and quality-of-life scores at 1-year follow-up.

Mechanicochemical Ablation

One of the benefits of foam sclerotherapy for the treatment of truncal reflux is that tumescent anesthesia is unnecessary. New treatments that do not require the use of tumescent anesthesia are currently being evaluated. One such methodology utilizes a combination of both mechanical and chemical treatments, foregoing the use of heat energy entirely. This mechanicochemical ablation (MOCA) is performed using the ClariVein device (Vascular Insights LLC, Madison, Connecticut). The device consists of a single-use catheter with a rotating wire that protrudes from its tip, which causes mechanical damage to the endothelium and vein wall spasm by rotating at 3500 rpm at 2- to 3-second intervals.[105] The treatment is initiated 2 cm peripheral to the SFJ and, as the catheter is withdrawn, a sclerosant, typically Sotradecol, is dispersed onto the vessel wall. In a recent study, technical success for truncal veins was 99%, and 88% of veins remained closed at 1 year. No major complications occurred. VCSS decreased from 4.0 prior to the procedures to 1.0 at 1 year ($P < .001$).[106]

These data have been corroborated for the SSV by Boersma et al. Their prospective series of 50 consecutive patients undergoing MOCA for treatment of SSV reflux demonstrated 100% technical success, with a 1-year closure rate of 100%. Clinical improvements in the VCSS were also observed.[107]

Adhesive Closure

The VenaSeal Closure System (Medtronic, Minneapolis, Minnesota), which delivers n-butyl cyanoacrylate (nBCA) glue through a catheter, also avoids the use of tumescent anesthesia. The glue polymerizes when it contacts ionic compounds such as the components of blood. The VenaSeal system is composed of an introducer sheath, an infusion catheter, a dispenser gun, and a proprietary cyanoacrylate adhesive. Access is gained into the refluxing truncal vein, and the catheter with the attached loaded dispenser gun is advanced to within 5 cm of the SFJ. Under ultrasound guidance, the glue is injected twice most centrally; then single injections are performed at 3-cm intervals while the catheter is withdrawn. Almeida evaluated the treatment of eight limbs with GSV reflux and reported a technical success rate of 100%.[108] The safety, efficacy, and durability of this procedure were evaluated in a postmarket trial, the European Sapheon Closure System Observational Prospective (eSCOPE) trial.[109] Thirty-eight patients were treated, 36 of whom were available for follow-up at 24 months. The vein occlusion rate was 92% at 24 months, and the VCSS score also improved in all patients in this period (6.1 ± 2.7 vs. 2.7 ± 2.5, $P < .0001$).[110]

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A complete reference list can be found online at ExpertConsult.com.

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156 CHAPTER

Chronic Venous Disorders: Postthrombotic Syndrome, Natural History, Pathophysiology, and Etiology

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INTRODUCTION

Chronic venous disorders (CVD) are a spectrum of venous diseases that affect the lower limb. The manifestations include varicose veins, pain, edema, skin changes, and venous ulcerations. The pathophysiology involves reflux within the deep, superficial, and perforating vein valves and/or venous obstruction, usually postthrombotic in etiology. Both reflux and residual obstruction can produce venous hypertension and the manifestations of CVD. Compared with nonthrombotic etiologies, lower extremity deep venous thrombosis (DVT) often leads to higher rates of the advanced forms of CVD, with skin changes and ulcerations.[1] DVT often begin in the legs (calf) near valve cusps and may propagate proximally.[2] About 50% of leg thrombi resolve spontaneously; however, nearly 20% will extend more proximally into the popliteal, femoral, and iliac veins.[3] The consequences can range from minor leg swelling at the end of the day to severe complications such as chronic debilitating lower-limb pain, intractable edema, and venous leg ulceration.[4] Other symptoms associated with postthrombotic syndrome (PTS) include leg cramping, pruritus, fatigue, heaviness, venous claudication, paresthesias, and bursting thigh pain with exercise, termed *venous claudication*. It is estimated that PTS occurs in 20% to 50% of patients from a few months to 1 to 2 years, following a lower extremity DVT.[5] The importance of PTS is the significant morbidity and reduction of quality of life, and the economic costs associated with treatment of this disease. Early recognition and intervention may reduce the sequela of PTS.

POSTPHLEBITIC (THROMBOTIC) SYNDROME: ETIOLOGY AND EPIDEMIOLOGY

DVT affects up to three individuals per 1000 annually in the general population. DVT is the major cause of secondary CVD, and is strongly associated with PTS.[1] Although primary CVD (CVD in which no etiologic factor can be identified; see Chapters 154, 155, and 157) is much more common than secondary

Abstract

Chronic venous disorders (CVD) are a spectrum of venous diseases that affect the lower limb. The pathophysiology involves reflux within the deep, superficial, and perforator valves and postthrombotic etiology, leading to venous obstruction and resulting venous hypertension. The postphlebitic syndrome (PPS), also termed the postthrombotic syndrome (PTS), arises because of deep venous valvular injury and persistent obstruction resulting from lower extremity venous thrombosis. Signs and symptoms of this disorder include lower extremity edema, pain, lipodermatosclerosis, and venous ulceration. The PTS will develop in 20% to 50% of patients within 1 to 2 years following a lower extremity deep venous thrombosis (DVT). The importance of the PTS is the significant morbidity, reduction in quality of life, and economic costs associated with treatment of this disease. Early recognition and intervention may reduce the sequela of PTS.

Keywords

Deep venous thrombosis
postthrombotic syndrome
chronic venous disease
recanalization
obstruction
reflux
inflammation
pathophysiology

TABLE 156.1 Clinical Progression in Relation to Duplex Ultrasound Findings

DU Findings	Progression (N = 23)	Unchanged (N = 50)	RR (95% CI)	*P*
Recurrent DVT	10	6	4.4 (1.4-13.3)	.0049
Progression reflux	7	11	0.74 (0.4-1.5)	.56
No change	6	33	0.76 (0.35-1.69)	.6

CI, Confidence interval; *DU*, duplex ultrasound; *DVT*, deep vein thrombosis; *RR*, relative risk.
From table III of Labropoulos N, Gasparis AP, Tassiopoulos AK. Prospective evaluation of the clinical deterioration in post-thrombotic limbs. *J Vasc Surg*. 2009;50:826–830.

CVD, DVT is responsible for CVD in 18% to 28% of limbs. In a study of 64 patients with 73 limbs affected by DVT, 4% of limbs had skin changes at 1 year, increasing to 25% at 5 years.[1]

Recurrent ipsilateral DVT is the most important risk factor for developing PTS, with a sixfold increased risk in one study.[5] Numerous other studies have found significant associations between ipsilateral recurrent DVT and the risk of developing PTS, with increases of up to 630% (Table 156.1).[1] Recurrent ipsilateral DVT is also the most important clinical factor for *progression* of CVD (relative risk [RR] 4.4; 95% CI, 1.4 to 13.3, $P = .0049$).[1] 630%.[4,6]

The incidence of recurrent DVT is 17% at 2 years, 24% at 5 years, and 30% at 8 years.[1,7] It is estimated that 5% to 10% of patients with recurrent DVT develop severe PTS (lipodermatosclerosis, ulceration) after a proximal DVT. Ulceration as a consequence of PTS has a cumulative incidence of approximately 5% over 10 years.[4] However, some studies have reported that the cumulative incidence of PTS continues to increase, even up to 20 years after DVT diagnosis.[8]

In one study, 355 patients (55% male) with a first time symptomatic DVT were followed at 6-month intervals for 8 years. A total of 245 patients (69%) completed 5 years of follow-up, and 148 patients (42%) completed 8 years of follow-up. The mean age was 63 years old (range 29 to 83). The cumulative incidence of recurrent venous thromboembolism was 4.9% after 3 months, 8.6% after 6 months, 17.5% after 2 years, 24.6% after 5 years, and 30.3% after 8 years.[7] Eighty-four patients developed PTS, with a cumulative incidence of 22.8% after 2 years and 28.0% after 5 years. The incidence did not change substantially thereafter. Of the 84 patients with PTS, 30.2% had severe PTS. Of note, the development of ipsilateral recurrent DVT was associated with an increased risk for PTS (hazard ratio 6.4; 95% CI, 3.1 to 13.3) and more predictive of skin damage (odds ratio 5.3; 95% CI, 1.2 to 24.2) compared with nonrecurrence ($P = .001$).[7]

Other features of venous thrombosis, including location and extent of DVT and insufficient anticoagulation, also increase the risk of developing clinically significant CVD.

In one study, patients with DVT were followed for a mean of 3.4 years with duplex ultrasound, to determine the effects of location and extent of DVT on the development of CVD. Patients were divided into a group which presented with multisegment DVT and a group which presented with single-segment DVT. More patients with multisegment disease were found to be symptomatic, and the prevalence of skin damage and ulceration was higher in this group compared with that in the group with single segment DVT (61 of 79 vs. 26 of 41, $P < .001$; 29 of 79 vs. 6 of 41, $P = .019$, respectively).[9]

The most severe forms of PTS, such as venous leg ulcers, produce adverse social and economic outcomes, and significant decreases in quality of life.[10] The economic burden of PTS is significant; costs increase by roughly 50% compared with those associated with DVT without PTS. In the United States it is estimated that the average annual cost per patient with PTS is $7000, which increases with the more severe forms (skin changes and ulceration). The high cost of treating venous leg ulcers is due largely to the need for surgery, lost workdays, and loss of employment. It is estimated that 2 million workdays are lost annually in the United States as a result of venous leg ulcers.[4]

Further examination of all causes (primary CVD and secondary PTS) of venous leg ulcers shows that the annual US expenditure for treating venous leg ulcers is approximately $14.9 billion (quantification of the incremental resource use and costs of treating these patients [$6391 per Medicare patient, and $7086 per privately insured patient]).[11] In addition, PTS has a significant impact on quality of life, which worsens with advanced forms of PTS compared with patients with DVT but no PTS. One study demonstrated that patients with venous ulceration missed more work days than those without ulceration, which resulted in increased work-related costs of 29% in the ulceration group ($P < .0001$). It has been shown that patients with PTS have a generic physical quality of life that is worse than for patients with osteoarthritis, angina, and chronic lung disease.[4]

POSTPHLEBITIC (THROMBOTIC) SYNDROME: CELLULAR AND MOLECULAR MECHANISMS

The critical factor in PTS is DVT formation, with vein wall injury, poor recanalization of thrombus, persistent obstruction of venous outflow, and valvular insufficiency.[12] This leads to ambulatory venous hypertension. Thrombosis of the valve and vein wall involves an acute proinflammatory and prothrombotic state, with damaged endothelium and expression of tissue factor and plasminogen activator inhibitor-1, release of von Willebrand factor, P-selectin and E-selectin, and amplification of the coagulation cascade. A complex process of recruiting leukocytes,

activation of adhesion molecules leading to interactions of endothelium and neutrophils via increased P- and E-selectins, activation of monocytes and macrophages, activation of toll like receptors, microparticles released from platelets, endothelial cells, and procoagulant monocytes and macrophages are then concentrated into the area of thrombosis leading to thrombus amplification, galectin-3-binding protein expression and galectin-3, chemokines, cytokines, matrix metalloproteinases, and growth factors. All are important factors involved in determining the progression or mitigation of coagulation, recanalization with resolution of thrombosis, and/or persistent inflammation and thrombosis with vein wall damage and eventual fibrosis.[13-15] Additional data addressing molecular and cellular mechanisms of PTS formation can be found in Chapters 9 and 145.

POSTPHLEBITIC (THROMBOTIC) SYNDROME: NATURAL HISTORY AND PATHOPHYSIOLOGY

Initial studies suggested that venous valvular insufficiency constituted the primary pathophysiology in patients with PTS. In an older study, strain gauge plethysmography was used measure venous outflow (a measure of chronic obstruction after DVT) and venous refilling times (a measure of valvular incompetence) in normal patients and those with PTS. The authors demonstrated that significantly reduced venous refilling times were associated with severe PTS, including skin changes and ulceration. There were no significant differences in venous outflow between patients with PTS and those without.[16]

More recently, however, studies have found that both the persistence of obstruction and valvular incompetence following DVT impart a greater risk of developing PTS as well as progression of disease.[1,17,18] In a study of 217 limbs in 183 patients, all with previous DVT, the combination of reflux in both the superficial and deep venous systems, especially when reflux involved the entire limb or below the knee, led to the most significant symptoms and signs of skin changes and ulcerations.[19] In another study of 34 patients with PTS, 65% were found to have both reflux and obstruction in the deep veins of limbs with PTS. Obstruction alone was present in 15%, reflux alone in 18%, and only normal findings in 3% (Fig. 156.1). Hyperpigmentation was present in 11 limbs; both reflux and obstruction were found in 9 of the 11 cases.[18]

Understanding the natural history of DVT and PTS is important in determining the factors that are associated with thrombus resolution and avoidance of debilitating, costly PTS. Prior investigations sought to clarify the relationships between lysis of venous thrombi and the development of incompetent valves, and to determine the relationships between development of symptoms of PTS and residual venous occlusion and valvular incompetence. An early study described outcomes in 21 patients (21 limbs) with acute DVT (mean age of 46 years) followed at intervals of 7, 30, 90, 180, and 270 days. The study endpoints were the percentage of patients with lysis of thrombosed segments, development of reflux, and development of early and late onset of venous edema (as a measure of PTS). Eight segments in the deep venous system (common iliac vein to the posterior tibial veins) were investigated using duplex ultrasound. Three patient groups were identified, including those with early recanalization, early thrombus extension, and late thrombus extension. In the early recanalization group, 53% of limbs experienced complete recanalization by 90 days, with 28% of early complete recanalized limbs occurring within 30 days.[20] Within the group with early DVT extension, 14% of patients had extension of DVT within 7 days. Within the group with late DVT extension, 19% of patients had extension of the DVT within 30 to 180 days. All patients were treated with anticoagulation. Valvular insufficiency occurred in 62% of patients; it developed much later than recanalization and in segments not previously occluded, indicating that the mechanism by which valvular insufficiency occurs must involve more than a physical effect of the thrombus on the valve. In 38% of patients valvular insufficiency was not present, and four of the five patients had complete recanalization by 30 days, suggesting that early DVT recanalization may be a protective factor for venous valve function. Assessing edema at the early times (7 to 30 days) may serve as a marker of subsequent PTS. Patients with edema were more likely to have residual occlusion than valvular insufficiency. The late development of edema at 90, 180, and 270 days was more closely correlated with valvular insufficiency.[20]

A key factor leading to valvular insufficiency following DVT appears to be the rate of lysis; preservation of valve function is greatest with early lysis. In an interesting study evaluating the natural history of DVT, 127 patients with acute DVT (55%

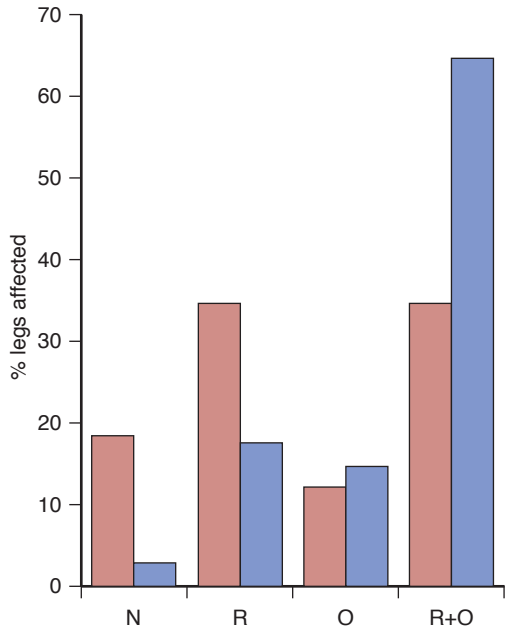

Figure 156.1 Proportion of limbs demonstrating no abnormality *(N),* reflux alone *(R),* obstruction alone *(O),* and reflux with obstruction *(R + O)* after DVT with respect to symptoms. *Blue bars* indicate asymptomatic legs; *red bars* indicate legs with clinical features of PTS. (From Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. Relationship between changes in the deep venous system and the development of the postthrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one- to six-year follow-up. *J Vasc Surg.* 1995;21:307–312.)

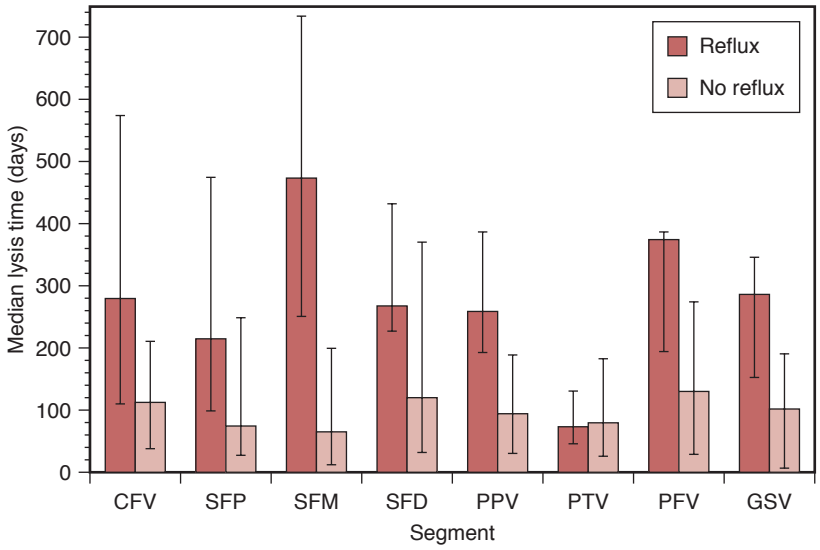

Figure 156.2 Median time from thrombosis to recanalization for all segments (lysis time), grouped according to reflux status at last visit. *Error bars* show interquartile range (25th to 75th percentile). *CFV,* Common femoral vein; *GSV,* great saphenous vein; *PFV,* profunda femoris vein; *PPV,* popliteal vein; *PTV,* posterior tibial vein; *SFD,* superficial femoral vein distal; *SFM,* superficial femoral vein middle; *SFP,* superficial femoral vein proximal. (From Meissner MH, Manzo RA, Bergelin RO, et al. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *J Vasc Surg.* 1993;18:596–605.)

male, average age of 52 years) were assessed at days 1 and 7, at 1-month and at 3-month intervals for the first year, and yearly thereafter. Duplex ultrasound was used to evaluate eight venous segments from the common femoral vein to the posterior tibial veins. Lysis of a vein segment was defined as complete recanalization. Median follow-up was 23 to 25 months for all veins except the posterior tibial vein, which was 12 months. Nearly 90% of patients had anticoagulation treatment. The important findings of the study were that the median lysis times for venous segments developing reflux (214 to 474 days) were 2.3 to 7.3 times longer than for corresponding venous segments not developing reflux (65 to 130 days), for all except the posterior tibial vein (Fig. 156.2). The differences between the two groups (increased lysis time and development of reflux versus shorter lysis time and no reflux) reached statistical significance in the mid femoral vein, popliteal vein, and profunda femoris vein segments (P = .002, .006, and .04, respectively), and a clear trend toward significance was present in all other segments except the posterior tibial vein.[21] When the cumulative percent lysis during the first 9 months was analyzed, a significantly greater proportion of proximal femoral vein segments not developing reflux had lysed by 3 months (56% vs. 13%; P = .012). A similar pattern was present in the distal femoral veins at 6 months (54% vs. 0%; P = .04) and in the great saphenous vein at 9 months (100% vs. 33%; P = .02). The median time at which reflux appeared was less than the median lysis time for all segments (development of reflux coincided with or preceded complete lysis in the venous segments); however, it was only significant for the mid femoral (P = .008) and distal femoral vein (P = .04) segments. This indicated that the onset of reflux appeared prior to complete lysis, and that valves are subject to early reflux even if small amount of recanalizing thrombus is present. If resolved, however, valve function was sometimes restored. Finally, there was a small group of patients in whom vein segments with early lysis developed reflux, and patients in whom vein segments with late lysis (>9 months) did not develop reflux. The authors concluded that early recanalization is important in preserving valve integrity, but other factors (rethrombosis and recanalization, thrombus burden, biochemical factors, incompetence of axial venous channels, residual proximal stenosis, the presence of incompetent perforators and collaterals, differences in fibrinolytic activity in the endothelium) also contribute to valvular insufficiency.[21] Additional information addressing outcomes following lysis of DVT can be found in Chapters 145 and 148.

Other studies have investigated changes in the deep venous system following DVT and development of PTS. In a study of 447 limbs in 429 patients with venous outflow obstruction, the presence of both reflux and obstruction produced more severe signs and symptoms of CVD compared with obstruction alone (CEAP class 4 to 6, 53% vs. 24%, respectively; P < .001). Importantly, venous leg ulcers in limbs with both obstruction and reflux were seen in 24%, compared with 3% in those with obstruction alone (P < .001).[22] These studies indicate that reflux in the presence of obstruction leads to significantly higher rates of severe PTS with skin changes and venous ulcer risk.

In a study of first-time DVT in 120 limbs of 105 patients (59 men, 46 women; mean age of 54 years), patients were stratified into two groups, those with DVT isolated to one venous segment and those with DVT in multiple levels. The majority of patients were treated with anticoagulation. Duplex ultrasound and clinical examination was performed at the initial visit, within the first 6 months, at 1 year, and yearly thereafter. Groups with single level and multilevel involvement were comparable in age and sex. Venous claudication was exclusively found in the multilevel group (8.8%) and was present only when iliac veins were involved. More advanced PTS (skin damage and ulceration) was found in the multilevel group compared with the single level group (26 of 41; P < .001). Skin damage developed in 35 limbs (29%) at a mean follow-up of 3.4 years. The prevalence of skin damage (usually occurring >3 years after DVT) was more common in the multilevel group. Venous pathology (reflux, obstruction, or a combination of the two) was more common in the multilevel group compared with the single level group (P < .0001). Limbs with both reflux and obstruction were more likely to develop skin damage in both

groups. The authors concluded that multisegment venous disease with iliac involvement can lead to venous claudication, and that patients with reflux and obstruction developed increased risk of skin damage than those with reflux or obstruction alone.[9]

In addition to the importance of multilevel and iliac vein involvement, other specific locations had poorer outcomes. It has been shown that poor popliteal vein function correlated with worse clinical manifestations. Patients with popliteal vein abnormalities were found to be greater than 3.5 times more likely to develop PTS when compared with those without popliteal vein involvement. A high peak reflux velocity in the popliteal vein was a strong predictor for CVD, and multisegmental occlusion involving the popliteal vein increased the risk for developing PTS. Thrombosis in multiple calf veins produced more frequent and significant PTS than thrombosis in a single calf vein, and calf vein involvement in the presence of proximal DVT increased the likelihood of PTS.[9]

The rate of progression of CVD is greater with secondary venous disease (DVT) than with primary venous disease (varicose veins and venous insufficiency). An elegant study evaluated 46 limbs in 41 patients with a first episode of DVT. Patients were assessed clinically and by duplex ultrasound at the initial visit, at 3, 6, and 12 months and yearly thereafter for up to 5 years. Outcomes in this group were compared with those in 41 patients with primary disease (50 limbs), age- and sex-matched with disease duration of 5 to 10 years. There was also a control group (15 subjects, 30 limbs), with no evidence of CVD, also matched for sex and age. In the DVT group, at 5 years follow-up, complete obstruction occurred in 9.3%; partial recanalization occurred in 50.9%, and complete recanalization occurred in 39.8%. At the 5-year follow-up, the prevalence of skin damage was 4 times higher in the DVT group compared with patients with primary CVD (23.9% vs. 6%, $P = .019$) and versus control (0%, $P < .01$). In patients with DVT the incidence of skin damage at 1 year was 4%, and significantly increased at 5 years to 24% ($P = .014$). Importantly, in patients with DVT, the combination of proximal and distal obstruction and the combination of reflux with obstruction were more common in limbs with skin damage (CEAP clinical classes 4 to 6; $P = .012$ and $P = .013$, respectively), indicating that proximal obstruction and the combination of reflux and obstruction are significant risk factor for the development of PTS.[23]

Other investigators have demonstrated that skin damage is significantly increased in patients following a first episode of DVT. In a study of 355 consecutive patients, skin damage occurred with a cumulative incidence of 22.8% after 2 years and 28% after 5 years.[7] In another longitudinal study (68 patients with a first diagnosis of lower extremity DVT, 50% male, 73 limbs), a 20.5% prevalence of skin damage was observed at a mean follow-up of 55 months. No active ulcers were present, but 2.7% of the study group had a healed ulcer.[24]

In this study, male patients were significantly more likely to have advanced signs of hyperpigmentation or ulceration compared to female patients (32.4% vs. 8.3%, respectively; $P = .01$). However, enrollment was not large enough for a multiple variable analysis, and further studies are necessary to determine if gender is a risk factor for advanced disease. There is some evidence that women may have differences in the fibrinolytic system, with higher plasminogen levels, lower plasminogen activator inhibitor levels, and increased fibrinolytic activity compared with men both at baseline and after venous occlusion.[24]

Recanalization following acute DVT was also significantly inversely related to baseline levels of activated coagulation prothrombin fragments (conversion of prothrombin to thrombin) and to fibrinolytic inhibition as measured by tPA antigen (primarily reflects PAI-1 levels). At presentation there is marked elevation of prothrombin fragments and D-dimer, which is determined by total thrombus load, and these decrease rapidly with initiation of anticoagulation therapy. However, D-dimer remains elevated long after the initial DVT.[25,26]

The pathophysiology of PTS is complex, but evidence suggests that venous hypertension is central to developing this debilitating disease. In PTS, ambulatory venous hypertension can result from outflow obstruction and/or valvular insufficiency. In this situation, ambulation does not reduce the venous pressure, and a state of ambulatory venous hypertension persists. Sustained venous hypertension can cause structural and biochemical abnormalities of the vein wall, with persistent chronic inflammation, resulting in pathologic effects in the skin and subcutaneous tissues.[4,5]

The relationship between the extent of thrombus on initial presentation and the ultimate clinical outcomes has been addressed, although some controversy remains.[4,24] In one study, PTS developed more frequently in patients who had persistent venous obstruction within the first 6 months after an episode of acute proximal DVT (relative risk 1.6; 95% CI 0 to 2.4).[27] This would suggest that proximal DVT may be more important in terms of developing PTS. In a multicenter study of 387 patients with an acute DVT, patients were evaluated for the frequency, time course, and predictors of PTS (197 men and 190 women, mean age 56 years). Patient follow-up was at 1, 4, 8, 12, and 24 months. Assessment of PTS using the Villalta scale, evaluation of anticoagulation regimens, and use of elastic compression stockings were all performed. At all study intervals, approximately 30% of patients had mild, 10% had moderate, and 3% had severe PTS. More severe postthrombotic category at the 1-month visit strongly predicted higher mean postthrombotic scores throughout 24 months of follow-up. These findings suggest that the pathophysiologic progenitor of PTS occurs in the first few weeks after DVT. Important predictors of PTS included venous thrombosis of the common femoral or iliac vein (2.23 increase in Villalta score vs. calf; $P < .001$), a higher body mass index (0.14 increase in score per 1-kg/m^2; $P < .001$), previous ipsilateral DVT (1.78 increase in score; $P = .001$), older age (0.30 increase in score per 10-year age increase; $P = .011$), and female sex (0.79 increase in score; $P = .020$). The authors concluded that patients with extensive DVT, specifically if the iliac and common femoral veins were involved, and those with more severe postthrombotic manifestations at 1 month after DVT, had much poorer long-term outcomes.[28] Patients with more extensive thrombosis involving the iliac and common femoral veins, may experience worse outcomes due to a greater likelihood of residual thrombosis. Thus early thrombus lysis may help prevent PTS (see Chapter 148). Interestingly, older age and higher BMI are associated with

higher postthrombotic scores, which may relate to age- or weight-related impaired fibrinolysis or vein wall changes.[10] In a large review, at least eight studies demonstrated the relationship between the extent of proximal DVT and the risk of developing PTS, confirming that iliofemoral DVT carries significant weight in the determination of progression to PTS.[4] Importantly, the iliofemoral location of DVT also appears to be a strong predictor of venous claudication, and other studies have found that the risk of PTS associated with proximal venous thrombosis ranges from 40% to 600%.[6]

POSTPHLEBITIC (THROMBOTIC) SYNDROME: CLINICAL SUMMARY POINTS OF NATURAL HISTORY, EPIDEMIOLOGY, AND PATHOPHYSIOLOGY

1. DVT affects up 3 individuals per 1000 annually in the general population.
2. Nearly 20% of calf vein DVT extend into the femoral-popliteal and iliac veins.
3. The greatest changes following a DVT occur during the first 3 months, with an approximate 50% reduction in thrombus burden during this time.
4. Approximately 50% of patients will show complete recanalization within 6 to 9 months of the initial DVT.
5. Median lysis times for venous segments developing reflux are 2.3 to 7.3 times longer than for corresponding venous segments not developing reflux.
6. The incidence of recurrent venous thromboembolism is approximately 17%, 24%, and 30% at 2 years, 5 years, and 8 years, respectively.
7. PTS will develop in 20% to 50% of patients within 1 to 2 years of a symptomatic DVT.
8. About 25% of limbs following DVT will have advanced skin changes at 5 years, with more aggressive progression of skin changes occurring in postthrombotic limbs compared with those with primary venous disease.
9. Ipsilateral recurrent DVT is a strong predictor of progression of CVD (RR, 4.4; 95% CI, 1.4 to 13.3, $P = .0049$).
10. The most important risk factor for developing PTS is a recurrent ipsilateral DVT, which increases the risk of PTS by as much as sixfold.
11. Limbs with the PTS have more than three times the odds of having combined reflux and obstruction compared with limbs without PTS (odds ratio [OR] 3.5, 0.95 CI, 1.4 to 8.6), and limbs with both obstruction and reflux have a higher rates and severity of PTS.
12. Ulceration may develop as a consequence of PTS, with a cumulative incidence of approximately 4% at 20 years.
13. Limbs with multisegment venous disease with iliac involvement are more likely to develop PTS, venous claudication, skin changes, venous ulceration, and venous pathology (combined obstruction and reflux) compared with limbs with only single venous segment involvement.
14. Patients with popliteal vein obstruction and/or reflux were found to be greater than 3.5 times more likely to develop PTS, and patients with multisegmental occlusion involving the popliteal vein are also at increased risk for developing PTS.
15. The pathophysiology of PTS is a complex set of events involving inflammation, thrombosis, resolution of thrombus, and vein wall damage, which result in outflow obstruction, valvular insufficiency, and calf muscle pump dysfunction, which leads to venous hypertension and subsequent signs and symptoms of PTS.
16. Greater postthrombotic symptom severity 1-month following an acute DVT strongly predicts higher mean postthrombotic scores throughout 24 months of follow-up. In other words, higher Villalta scores at 1 month predict worse PTS at later time points.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 157

Chronic Venous Disorders: Nonoperative Management

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Chronic venous disease of the lower extremity is one of the most common diseases in western Europe and the United States. The manifestations of chronic venous disease can be different and may encompass telangiectasias, enlarged reticular veins, varicose veins, lipodermatosclerosis, lower extremity pain and swelling, and venous ulcers. Its prevalence reported in studies from different countries ranges from 2% to 56% in men and 1% to 60% in women. In the Edinburgh Vein Study, varicose veins were present in 40% of men and 16% of women, ankle edema was found in 7% of men and 16% of women, and ulcers were seen in 1% of men and women.[1] In the same study, the incidence of superficial vein reflux was noted to be 9.4% in men and 6.6% in women, and to increase with age.[1] In the United States, it has been estimated that 20% of patients with chronic venous disease develop venous ulcers, and 50% of these require treatment periods of more than 1 year.[2-4] The incidence of all clinical manifestations of venous disease also increases with age.[1]

The high prevalence and significant morbidity of chronic venous disease have an important socioeconomic impact, making the appropriate choice of therapy critical to cost-effective care. The disease is progressive and has a high incidence of recurrence, especially in its most advanced stages. In France, the expenditure for patients with chronic venous disease was reported to be €2.24 billion per year in 1991, 34% of which was incurred by inpatient treatment.[4] In this study, chronic venous disease was the eighth most common cause of hospital admission, accounting for 2.6% of the healthcare budget.[4] The impact of more advanced stages of chronic venous disease is even greater. A cost analysis from the Cleveland Clinic Foundation in 1999 examined the inpatient and outpatient costs of a cohort of 78 patients with active venous ulcers from the initiation of treatment until complete healing. A total of 71 patents (91%) healed during the study. Fourteen patients underwent 18 hospitalizations for venous ulcer care.[5] The average total medical cost per patient was $9685 (median, $3036), inflated to $16,524 in 2011 U.S. dollars using the Consumer Price Index for Medical Care, with an average monthly cost of $4095.[6] In another review using the Consumer Price Index for Medical Care, it was observed that the cost to achieve complete healing at 12 weeks was

Abstract

Chronic venous disease of the lower extremities is one of the most common diseases in western Europe and the United States. The nonoperative approach to patients with chronic venous disease includes lifestyle modification, compression, and pharmacologic therapies.

Compression therapy has been shown to be an essential component of the care of patients with chronic venous disease (C2-C6). A number of compression garments are available: gradient elastic stockings, the CircAid garment, paste gauze boots, layered elastic and non elastic compression bandages, and intermittent pneumatic compression devices. High grade compression therapy is the mainstay of treatment of patients with advanced chronic venous disease (C4-C6). Gradient compression stockings (30-40 mmHg) have been shown to be effective not only in ulcer healing but mostly in reducing the risk of ulcer recurrence. The ESCHAR trial (Comparison of surgery and compression with compression alone in chronic venous ulceration) showed that surgical ablation of refluxing veins may be beneficial in addition to compression therapy to prevent ulcer recurrence.

Pharmacologic therapy in venous disease is directed toward symptom control in patients with mild to moderate chronic venous disease and the treatment of venous ulcers. Micronized purified flavonoid fraction (MPFF) is a useful adjunct in the treatment of large and long standing ulcers.

Keywords

Leg elevation
Compression therapy
Compression stockings
Unna Boot
CircAid
Intermittent compression therapy
Micronized purified flavonoid fraction (MPFF)

approximately $1357 and significantly increased to $30,765 for more than 12 weeks of treatment.[6,7] Overall it was estimated that in the United States, the annual cost for venous ulcer treatments ranges from $1.5 to $3.0 billion, with the greatest burden on the Medicare system. These costs do not include decreases in mobility and work capacity, patients' out-of-pocket expenses, and adverse psychologic effects related to venous ulcers.[7]

TREATMENT OF CHRONIC VENOUS DISORDERS

Whereas the invasive treatment of chronic venous disease includes surgical (high ligation of the saphenofemoral junction, saphenous vein stripping, stab phlebectomies) or endovascular procedures (saphenous vein thermal and chemical ablation, ultrasound guided sclerofoam/sclerotherapy), the initial treatment of chronic venous disease has traditionally been nonoperative, with the main goals of symptom control and quality-of-life improvement. In addition, conservative measures are currently mandated by most third-party payers in the United States before approval of therapeutic surgical interventions. In this setting, the success of conservative management has long been considered to be a contraindication to more definitive surgical treatments. However, a quality-of-life analysis from Lurie and Kistner[8] questions the validity of this approach. In this study, the authors compare the outcomes of surgical therapy in patients with favorable and unfavorable responses to initial conservative management using the Specific Quality of Life and Outcomes Response–Venous questionnaire. Patients who improved with conservative therapy and who elected to proceed with surgical correction were 15 times more likely to improve with surgery at 1 month and 21 times at 12 months of follow-up, compared with those who did not improve with conservative therapy.[8,9] The authors concluded that conservative therapy should be used as a benchmark to predict success after surgical therapy, rather than as a contraindication to definitive intervention.[9]

Nonoperative Treatment of Chronic Venous Disease

The nonoperative approach to patients with chronic venous disease includes lifestyle modification, compression, and pharmacologic therapies.

Lifestyle Modification

The most common initial recommendations for lifestyle modification in patients with chronic venous disease are moderate exercise and leg elevation.[10]

Exercise

In a review of the most current literature, Brown[10] concluded that although vigorous exercise may increase the likelihood of venous ulcerations, increased mobility and moderate physical activity may be beneficial for ulcer healing and may be an adjunct to compression therapies. Overall, patients with chronic venous disease should be encouraged to engage in regular moderate physical activity.[10] In a study by Roaldsen et al.,[11] it was observed that walking speed, endurance, and self-perceived exertion were significantly lower in 34 women aged 60 to 85 years with current or previous ulcers compared with age-matched controls. It was also noted that ankle plantar flexion and dorsiflexion were significantly reduced in patients with active ulcers, mostly because of pain. In another study from the same authors, patients with low levels of physical activity displayed stronger fear avoidance beliefs and more pain than those with higher levels of physical activity.[10,11] These findings and observations from other studies emphasize the need for physical therapists to be highly involved in the care of patients with advanced C4-C6 disease, highlighting the importance of adequate pain control and a supervised exercise program tailored to improve ankle mobility and overall functional ability.[10]

Leg Elevation

Leg elevation has been shown to aid venous drainage, to increase the venous return to the heart, and to reduce ankle edema.[10] Patients with significant chronic venous disease are advised to elevate their legs 30 cm above the heart several times during the day.[10] In addition, Coleridge-Smith has shown enhancement of cutaneous microcirculation after leg elevation using Doppler fluxmetry in patients with lipodermatosclerosis, with a median 45% Doppler flux increase.[12]

Transcutaneous tissue oxygen saturation levels have been used as an indicator of skin perfusion. These have been found to be reduced in patients with venous ulcers. Several authors have reported higher transcutaneous tissue oxygen saturation levels with compression strategies, standing position, and ambulation compared with leg elevation with or without compression.[13] However, it is unclear how the transcutaneous tissue oxygen saturation levels correlate with ulcer healing. A retrospective Australian study of 122 patients with previous venous ulcers observed for 12 to 40 months found that significantly lower rates of recurrence were associated with compression therapy and longer leg elevation times (33 min/day).[14] Recurrence was observed with a 14-min/day period of leg elevation. The authors of the study recognized limitations due to the retrospective design of their analysis and possible response bias, as all the measures of physical activity, psychosocial scales, and self-care activities were obtained from self-report questionnaires.[14]

Leg elevation seems to be beneficial in symptom control in all patients with chronic venous disease. There is a trend supporting some advantage in ulcer healing, despite the evidence of levels of evidence 1 and 2 studies.[10] In addition, the utility of leg elevation is limited by the practical difficulty of prolonged leg elevation for many patients.

Compression Therapy

Compression therapy is an essential component of the care of patients with chronic venous disease (C2-C6). The rationale for graded external compression is to oppose the main pathogenetic factor underlying chronic venous disease, venous hypertension, but compression therapy has been found to have a number of additional benefits.[15] Given a normal standing

resting venous pressure of 60 to 80 mm Hg, major hemodynamic effects can be expected, with an interface compression of 35 to 40 mm Hg. External compression of more than 60 mm Hg has been found to occlude lower extremity veins in standing individuals. Therefore 60 mm Hg has been considered the safe upper limit for externally applied sustained compression, as shown by dermal blood flow investigations, even in patients with an ankle-brachial index above 0.5 and absolute ankle pressure higher than 60 mm Hg.[15-17]

Compression therapy has also been shown to improve venous pump function. Enhanced venous flow velocities have been noted with low-grade interface pressure of 15 to 25 mm Hg with prevention of thromboembolic events in supine patients.[15] The biomolecular mechanisms by which compression therapy functions are unclear. Animal and clinical studies have documented that compression therapy improves cutaneous microcirculation.[18] Video capillary microscopy showed an increase in capillary density with decreased capillary diameter and pericapillary halo in 20 patients with varicose veins and lipodermatosclerosis treated with compression therapy.[18] Several authors have also noted enhancement of lymphatic drainage and cutaneous oxygenation, as demonstrated by increased transcutaneous tissue oxygen saturation levels.[13,18,19] Decreased serum levels of tumor necrosis factor-α and vascular endothelial growth factor have been observed in patients with healing ulcers treated with four-layer graduated compression.[20] The improved cutaneous microcirculatory environment has been thought to promote venous ulcer healing as has been suggested by several studies.[21-23]

A number of compression garments are available. These include gradient elastic stockings and the CircAid garment, paste gauze boots (Unna boot), layered elastic and nonelastic compression bandages, and intermittent pneumatic compression (IPC).

Gradient Elastic Stockings

Gradient elastic stockings were first developed in the 1950s; they are currently manufactured by numerous companies and are available in various strengths and lengths. The compression applied by the stocking is calculated on the basis of the mechanical properties of the fabric used by each manufacturer. The pressure applied to the ankle by the stocking is expressed as a range and is a function of in vitro measurements based on leg circumferences.

Gradient compression stockings are currently available in four strengths: 10 to 15 mm Hg (class 1; over-the-counter); 20 to 30 mm Hg (class 2; prescription); 30 to 40 mm Hg (class 3; prescription); and 40 to 50 mm Hg (class 3—high compression; prescription). They are also available in different lengths, including knee-high, thigh-high, and panty hose. They are fitted on the basis of measurements of circumference, usually at thigh, midcalf, and ankle levels, and may be individually customized in patients with atypical leg morphology, such as may be seen in the obese or patients with advanced chronic venous disease. Compression garments should be replaced every 6 to 9 months, as the elasticity is lost after this time.[21]

Gradient Compression Stockings in C1-C2 Disease. A number of studies have reported the efficacy of gradient elastic stockings in early and advanced stages of chronic venous disease. In a prospective randomized multicenter trial conducted in France of 125 women with CEAP classification of C1-3SEpAs1-5, it was noted that regular wearing of compression stockings (10-15 mm Hg) during a 15-day period was associated with significant symptom control when a high level of compliance in wearing the hose was achieved.[24] In a review of 11 prospective randomized trials, 12 nonrandomized studies, and two guidelines, no agreement was found regarding the appropriate class of compression for the management of early chronic venous disease stages. Compression improved symptoms in patients with uncomplicated symptomatic varicose veins when high compliance was reached.[25] However, the use of compression stockings was not shown to prevent disease progression or recurrence of varicose veins after treatment. The same review highlighted that the majority of the published literature was often contradictory and had methodologic flaws, and that the results of several studies were confounded by a high number of noncompliant patients.[25]

It can be concluded that wearing of light compression stockings with a pressure below 20 mm Hg may be beneficial in the following indications[16]: symptom control in C1s (grade 1B level of evidence); varicose veins in pregnancy (grade 1B level of evidence); prevention of leg edema related to prolonged sitting and standing (grade 1B level of evidence); and prevention of venous thromboembolism in nonambulatory patients or after surgery (grade 1A level of evidence). The recommendation for use of class 2 compression stockings in uncomplicated symptomatic varicose veins is also weak (grade 2B level of evidence) and only for symptom relief.[17] Class 2 stockings have also been found to be poorly associated with the prevention of varicose veins after surgery and the treatment of venous ulcers (grade 2B level of evidence).[16]

Surgery Versus Compression in C2-C3 Disease. In the "Randomised clinical trial, observational study, and assessment of cost-effectiveness of treatment of varicose veins" (REACTIV trial),[26] 357 patients were randomized to three groups: group 1 (n = 34), minor varicose veins, conservative management versus sclerotherapy; group 2 (n = 77), moderate varicose veins with reflux, conservative management versus surgery; and group 3 (n = 246), severe varicose veins with reflux, conservative treatment versus surgery. Conservative treatment included lifestyle modification, leg elevation, and compression stockings; the surgery arm included high ligation of the saphenofemoral junction, saphenous vein stripping, and phlebectomies. The study demonstrated a significant benefit in quality of life, symptom relief, and patient satisfaction in the surgical treatment at 2-year follow-up in groups 2 and 3. In group 1, sclerotherapy produced an incremental benefit over conservative therapy. Surgery was found to be more cost-effective than conservative management in patients with C2 disease. Injection sclerotherapy also appeared to be cost-effective for patients with superficial venous reflux but was found to produce less benefit compared with surgery.[26]

The most recent guidelines from the Society for Vascular Surgery and the American Venous Forum recommend against conservative therapy alone for patients with C2 and C3 disease

when there is a compelling indication for saphenous stripping or ablation.[16] These guidelines also highlight the lack of scientific evidence to support the initial period of conservative therapy mandated by many health insurers in patients who are suitable candidates for surgical therapy.[16]

Gradient Compression Stockings in C4-C6 Disease. Class 3 gradient elastic stockings are the standard of care in advanced disease (C4-C6). The authors of a cohort study from Oregon Health Sciences University reported a 15-year experience in 113 patients with C4-C6 disease who were treated with initial bed rest, ulcer débridement, dressing changes, and class 3 compression stockings.[27] Ulcer healing required an average of 5.3 months, occurring in 97% of compliant patients, with a 16% recurrence rate. The 2012 update of a Cochrane review from Nelson et al.[28] specifically assessed the effects of compression therapy in preventing ulcer recurrence. Four trials (979 patients) were identified. In one trial (n = 153), recurrence rates were significantly reduced in the compression group at a 6-month follow-up. No difference was noted between high compression (Class 3 and Class 4) and moderate compression (Class 2) in ulcer recurrence in the other three trials. Moderate compression stockings were associated with higher compliance to therapy[28].

Patient compliance with compression therapy is both critical to the successful treatment of chronic venous insufficiency (C3-C6), particularly in patients with C4-C6 disease, and at the same time one of the biggest challenges for patients, particularly those with advanced age, obesity, and arthritis. Patients must be educated about the importance of compression therapy with ongoing reinforcement of this concept. Aids have been developed to allow application of stockings in patients who are challenged; sleeves and metal frames (Fig. 157.1) have been designed and are currently available on the market, although many insurers do not cover these adjuncts.

Gradient Compression Stockings and Prevention of Post-thrombotic Syndrome in Acute Deep Vein Thrombosis. Recent data from the Centers for Disease Control and Prevention estimates that as many as 900,000 people (1-2 per 1,000) are affected by deep vein thrombosis (DVT) and pulmonary embolism (PE), with estimates of 60,000 to 100,000 patients dying from these diseases in the United States.[29] Approximately 33% of the population with DVT/PE will develop a recurrence within 10 years, and 20% to 50% of those patients will experience long term complications such as post-thrombotic syndrome (PTS).[29]

The pathogenesis of PTS is complex and includes a post-thrombotic inflammatory reaction involving the venous wall and valves with subsequent remodeling, development of venous hypertension, varicose veins, skin changes, and ultimately venous ulcers.[30] Gradient compression stockings can potentially reduce the risk of PTS by counteracting this basic pathogenetic mechanism.

In two prospective randomized trials,[31,32] a statistically significant 50% PTS absolute risk reduction was found in patients with a first episode of proximal deep vein thrombosis (iliac, femoral, and popliteal vein) who wore a class 3 compression stocking for 2 years. In a recent multicenter randomized placebo-controlled trial (SOX: Compression Stockings to Prevent the Post-Thrombotic Syndrome after Symptomatic Proximal Deep

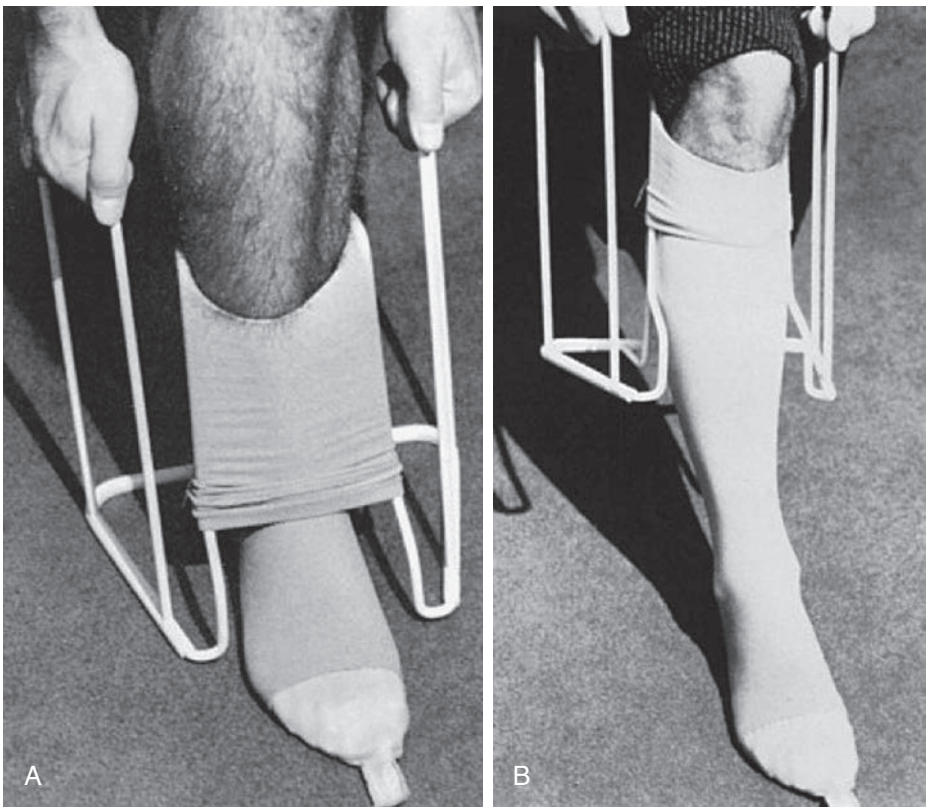


Figure 157.1 Metallic frames and plastic sleeves have been designed to facilitate the application of graduated compression stockings. (From Moneta GL, Partsch H. Chronic venous disorders: nonoperative treatment. In: Cronenwett JL, Johnston KW, eds. *Rutherford's Vascular Surgery.* 7th ed. Philadelphia: Saunders Elsevier; 2010.)

Vein Thrombosis),[33] 410 patients with proximal DVT were randomized to gradient compression stockings (class 3) versus placebo (noncompression hosieries). No statistically significant difference in the incidence of PTS (Ginsberg and Villalta PTS scores) between the two groups was found at a 2 year follow-up.[33] Lack of compliance to compression therapy (55.6% of patients compared to 90% in the previous trials) and patient characteristics, such as the initiation and duration of anticoagulation and the advent of the newer oral thrombin and factor Xa inhibitors, may have affected the results of the SOX trial compared to previous studies.[34] In another prospective randomized study, compression therapy and ambulation in the first 10 days from the acute thrombotic event were associated with benefit in mean Villalta scores, even after a secondary treatment with compression therapy for 2 years.[34]

In conclusion, the evidence that gradient compression therapy prevents PTS after a first DVT episode is currently mixed. Compression stockings may be beneficial in symptom control in patients with severe deep vein thrombosis.

CircAid Garment

The CircAid (Fig. 157.2) is a nonelastic compression appliance with multiple, stiff, pliable, adjustable Velcro bands. The system is as effective as compression stockings in reducing edema and promoting venous pump function, and may be recommended in patients who are unable or unwilling to wear class 3 stockings.[35] In a small prospective randomized trial, including 22 extremities with advanced chronic venous disease (C6) from Villavicencio et al., the CircAid system was found to have a significantly faster ulcer healing rate compared with a four-layer elastic bandage.[36] The CircAid system allows adjustment for limb size changes, ease and speed of application with improvement of comfort, and tolerance compared with compression stockings and bandaging.

Unna Boot

The Unna boot was first developed by the German dermatologist Paul Gerson Unna at the end on the 19th century. It consists of a multilayered compression dressing made of an inner layer of gauze bandage impregnated with calamine, zinc oxide, glycerin, sorbitol, gelatin, and magnesium aluminum oxide, and an outer layer of an elastic wrap exerting graded compression.

The bandage stiffens with drying, with improvement of venous return during ambulation and reduction of edema. The pressure exerted varies from 50 to 60 mm Hg. The dressing is changed weekly or sooner, depending on the amount of drainage.[37]

In a 15-year retrospective survey of 998 patients with venous ulcers, the Unna boot achieved a 91% healing rate for first-time ulcers and overall 73.3% healing rate in compliant patients. All patients were treated 12 times in 32 weeks. The overall wound healing rate was superior with the Unna boot compared with polyurethane dressings in a multiinstitutional randomized study.[38]

Layered Elastic and Nonelastic Compression Bandages

Compression bandages are single-layer or multilayer dressings commonly used in patients with advanced chronic venous disease (Fig. 157.3). Pressure, layers, components, elastic properties, and stiffness are all factors to be considered when such a dressing

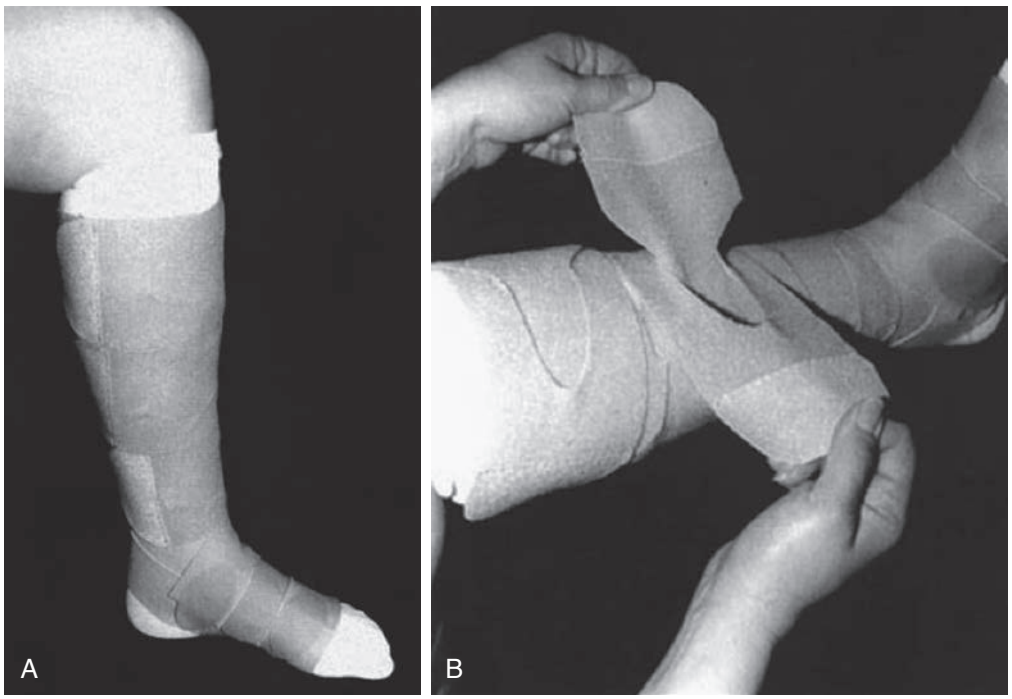


Figure 157.2 The CircAid is a nonelastic adjustable compression appliance with multiple, stiff, pliable, adjustable Velcro bands. (From Moneta GL, Partsch H. Chronic venous disorders: nonoperative treatment. In: Cronenwett JL, Johnston KW, eds. *Rutherford's Vascular Surgery,* 7th ed. Philadelphia: Saunders Elsevier; 2010.)

Figure 157.3 Compression bandages can be single layer **(A)**, nonelastic **(B)**, or multilayer (**C** and **D**). (From Enoch S, Grey JE, Harding KG. ABC of wound healing. Non-surgical and drug treatments. *BMJ*. 2006;332:900–903.)

is applied. The pressure is a function of the outer bandage, and a sustained pressure of 60 to 70 mm Hg is the upper limit, especially over bony prominences.[16,22,23] The choice of dressings varies from wet to dry, hydrocolloids or impermeable (occlusive; Table 157.1) dressings.[39] Indications for each dressing type vary by the characteristics of the ulcer, the degree of skin inflammation, and the presence of infection (see Table 157.1).[39]

Bandages can be elastic, such as the Ace, SurePress, and Perfecta, or nonelastic, such as the Putter, Comprilan, and Coban bandages. The main disadvantage of nonelastic bandages is the loss of pressure over time after application as the limb loses volume in response to compression. Training in application of the bandage is also important, because incorrect overlapping may cause additional ulcers. Elastic bandages are easier to apply. They may exert a higher resting pressure that is maintained over time. Disadvantages are possible discomfort due to higher resting pressure and the possibility of skin ulcer, especially over bony prominences if adequate skin padding is not applied.

In a systematic review from O'Meara et al., 59 prospective randomized trials with 4321 venous ulcer patients were identified. Several bandages systems were compared, with ulcer healing rate as the primary outcome. The results were consistent with an overall increased effectiveness of multicomponent systems containing an elastic bandage versus those with inelastic constituents.[40]

O'Meara et al. compared the effectiveness of four-layer and short stretch single-layer bandages in a meta-analysis published in 2009.[41] Four eligible trials with a total of 887 patients were identified. It was noted that four-layer bandages were associated with shorter healing time and larger ulcers; chronic ulceration and previous ulcerations were found to be independent predictors for delayed ulcer healing.[41]

A systematic review of compression treatment for venous ulcers identified 24 randomized controlled trials. The results confirmed that compression therapy is the treatment of choice in patients with advanced chronic venous disease, and that high compression is associated with an overall significant increase in the odds of healing at 3 months. No difference was found between high compression single-layer versus multilayer systems and the Unna boot. In the same meta-analysis, two small trials showed superiority of compression stockings (84% healed at 3 months) versus short stretch bandages (52% healed at 3 months).[42]

Two systematic reviews from Partsch et al.[43] and Coleridge Smith[44] found that the use of class 3 compression stockings promotes ulcer healing and reduces ulcer recurrence (grade 1A evidence).

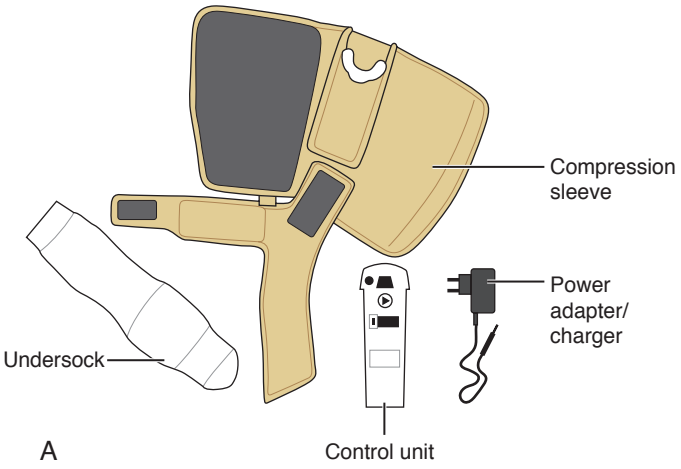
In an open, prospective, randomized, single-center trial from Milic et al.,[45] 131 patients with C6 disease (ulcer surface >3 cm^2; duration >3 months) were randomized into three groups of different types of compression systems: a tubular stocking with a colored line signifying where compression is estimated within 30 to 40 mm Hg (Tubulcus; group A); a multicomponent bandaging system composed of the Tubulcus and one elastic bandage (group B); and a multicomponent system made of the Tubulcus and two elastic bandages (group C). Pressure measurements were taken in the supine, sitting, and standing positions. The median sub-bandage pressure values in the supine position and in the standing position were 36.2 mm Hg and 43.9 mm Hg, respectively, in group A; 53.9 mm Hg and 43.9 mm Hg in group B; and 74.0 mm Hg and 87.4 mm Hg in group C. The healing rate was calculated with an intent-to-treat analysis, and it was 25% in group A, 67% in group B, and 74% in group C. Median healing time was 12 weeks in group A, 11 weeks in group B, and 14 weeks in group C. The rate of noncompliance was highest in group C (21%) and lowest in groups A and B (2%). A Cox regression analysis demonstrated that different sub-bandage pressure values, calf circumference,

TABLE 157.1 Different Types of Dressings and Their Uses

Type of Dressing	Trade Names	Features	Indications
Hydrocolloids	Comfeel Plus, DuoDERM E, Algoplaque HP, Askina Biofilm, Suprasorb H, Hydrocoll standard	Thick adhesive 1 application/2-7 days without secondary dressing	Mildly exuding ulcer
	Comfeel Plus transparent, Comfeel Plus Brûlures, Comfeel Ovale, DuoDERM extra thin, DuoDERM extra thin oval, Algoplaque film, Hydrocoll thin	Thin adhesive 1 application/2-7 days without secondary dressing	
Foam dressings Granulation and epidermization stages, exudative ulcers	Allevyn adhesive, Biatain adhesive, Cellosorb adhesive, CombiDERM, Mepilex Border, PermaFoam comfort, Suprasorb P adhesive, Tielle	Thick adhesive 1 application/2-7 days without secondary dressing	Heavily exuding ulcer, granulating ulcer, altered peripheral wound skin (nonadhesive form)
	Allevyn Lite, Cellosorb Lite, Mepilex Border em	Thin adhesive 1 application/2-7 days without secondary dressing	
	Allevyn nonadhesive, Biatain nonadhesive, Cellosorb, CombiDERM N, Mepilex Transfer, Suprasorb P nonadhesive, Tielle S	Nonadhesive 1 application/2-7 days with a secondary dressing	
	Allevyn Gentle, Biatain Contact, Mepilex, Mepilex em	Microadherent 1 application/2-7 days with a secondary dressing	
	Biatain Ibu, Biatain Ibu contact		Painful ulcer
Alginates	Algosteril, Melgisorb, SeaSorb Soft, Sorbalgon Plus, Urgosorb	1 application/1 to 2-days with a secondary dressing	Infected ulcer, hemorrhagic ulcer, heavily exuding ulcer (débridement stage)
Hydrogels	DuoDERM hydrogel, Hydrosorb gel or plaque, Hypergel, IntraSite gel conformable, Normigel, Purilon Gel, Urgo Hydrogel	1 application/2 days with a secondary dressing	Necrotic ulcer, dry ulcer
Hydrofibers	Aquacel	1 application/1-2 days with a secondary dressing	Infected ulcer, heavily exuding ulcer (débridement stage)
Impregnated or coated meshes (interface dressings or low-adherence dressings)	Adaptic (paraffin), Urgotul (lipidocolloid), Physiotulle (petroleum and hydrocolloid), Mepitel (silicone)	1 application/1-7 days with a secondary dressing	Mildly exuding ulcer, altered peripheral wound skin
Hyaluronic acid–based dressing	Hyalgan (alginate hydrogel film), Hyalofill, Hyalogran (alginate hydrogel and alginate), Jaloskin (alginate hydrogel film), Ialuset cream or impregnated gauze, Effidia	1 application/1-7 days with a secondary dressing	Mildly exuding ulcer
Charcoal dressings	Carbonet Actisorb Plus (containing silver) CarboFLEX (containing hydrofiber)	1 application/1-7 days with a secondary dressing	Foul-smelling ulcer
Silver dressings	Acticoat, Actisorb Silver, Urgotul S/Ag	1 application/1-3 days with a secondary dressing	Infected ulcer, foul-smelling ulcer
	Biatain Ag nonadhesive, adhesive (foam plus silver)	1 application/1-7 days	Infected ulcer, foul-smelling ulcer
	Cellosorb Ag nonadhesive (foam plus silver) Aquacel Ag (hydrofiber plus silver) Ialuset Plus (hyaluronic acid plus silver)	1 application/day with a secondary dressing	Exuding ulcers
Protease-modulating dressings	Promogran (collagen-based dressing) Cellostart (foam dressing)	1 application/2-7 days with a secondary dressing	Hard-to-heal ulcer
Paraffin or petroleum gauzes	Grassolind neutral, Jelonet, Vaselitulle, Tulle gras Solvay	1 application/2 days with a secondary dressing	

Modified from Senet P. Local treatment of venous leg ulcers. *Phlebolymphology*. 2010;17:7.

Figure 157.4 Intermittent compression device. (From Enoch S, Grey JE, Harding KG. ABC of wound healing. Non-surgical and drug treatments. *BMJ*. 2006; 332:900–903.)



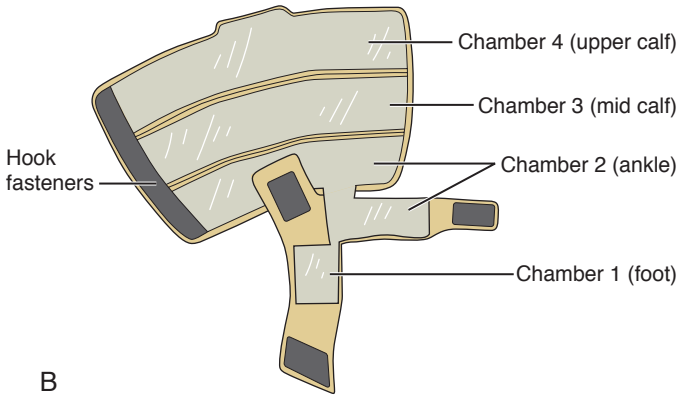


Figure 157.5 ACT Device: **(A)** outer side views and **(B)** underside views. (From Harding KG, Vanscheidt W, Partsch H, et al. Adaptive compression therapy for venous leg ulcers: a clinically effective, patient-centered approach. *Int Wound*. 2016; 13(3):317–325.)

and ulcer size were independent predictors of ulcer healing. Decreased odds of healing were observed in patients with larger calf circumference and ulcer size. The authors concluded that ulcer healing can be better achieved with multicomponent bandaging systems with sub-bandage healing pressures between 35 and 45 mm Hg. Good healing results were obtained in patients with small (<5 cm^2) ulcers and smaller (<33 cm) calf circumferences.[45]

Intermittent Pneumatic Compression

Intermittent pneumatic compression (IPC) is a mechanical compression method in which external pressure is applied by the intermittent inflation of pneumatic boots (Fig. 157.4). Some devices include a single inflation chamber at a single pressure, while others include 2 to 3 chambers with different pressures at the ankle, calf, and thigh. These devices can be used to treat venous leg ulcers and lymphedema.[46] A Cochrane review authored by Nelson et al.[47] identified seven randomized trials, including 367 patients treated with IPC. In one trial (80 patients), IPC was found to be more beneficial than compression stockings in ulcer healing (62% vs. 28%; $P = .002$). In four trials, IPC plus compression stocking therapy was compared with compression stocking therapy alone. Of these four trials, only one (45 patients) showed increased ulcer healing (relative risk [RR] for healing, 11.4%; 95% confidence interval [CI], 1.6-82) in the IPC plus compression stocking group. The remaining three trials noted no evidence of benefit of IPC over compression stockings in ulcer healing. In one trial (104 patients), a higher rate of healed ulcers was associated with devices in which the inflation was rapid compared with those with slow inflation (86% vs. 61%; log rank $P = .003$). Based on these studies, IPC may be effective in controlling edema, particularly in patients with a lymphedema component, but there is no strong evidence to support its use in the treatment of venous ulcers.[47]

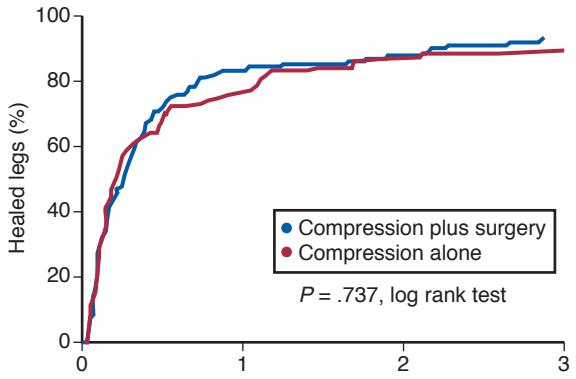
Adaptive Pressure Multichamber System. Recently, multicomponent pneumatic compression devices have become available to treat patients with C6 disease and poor compliance to compression stockings and/or bandages.[48]

The ACTitouch device (ACT; Fig. 157.5) provides adaptive, intermittent, and sustained pneumatic compression. The device consists of a foot, and ankle and calf cuffs, linked together to form one complete functional unit. The inflation of the cuffs is controlled by a small, lightweight, low voltage microprocessor that monitors and continuously adjusts the degree of inflation of each cuff to the targeted pressure.[48] The device can function in IPC and/or sustained pressure mode. When operated in sustained mode, a graded compression of 40 mm Hg is applied at the ankle, 30 mm Hg at midcalf, and 20 mm Hg at the knee. The IPC mode provided intermittent compression of 50 mm Hg at the foot and ankle, 45 mm Hg at the midcalf, and 40 mm Hg at the knee.

In a prospective randomized study, 90 patients with C6 disease were divided in two groups: ACT ($n = 38$) and a four-layer bandage system ($n = 52$). Patients were instructed to wear the device for most of the day with 2 hours of IPC mode.[48]

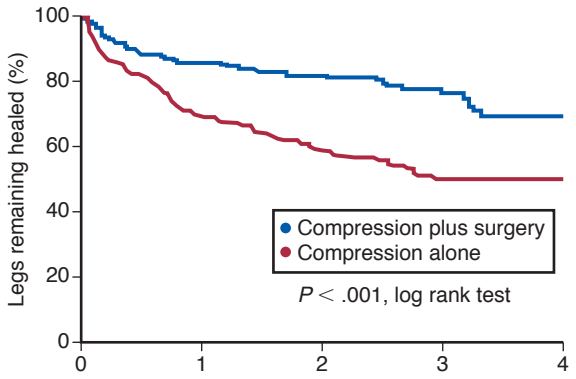
At 12 weeks, ulcer healing rate and time to ulcer healing were similar between the treatments.

In the ACT group, treatment performance was significantly higher in terms of exudate management, skin protection, removal ease, bathing, and sleep comfort. Quality of life (QoL) was



Numbers at risk				
Compression plus surgery	185	33	13	6
Compression alone	156	24	15	5

Figure 157.6 Ulcer healing rates were not statistically significantly different between the groups at 3 years (compression, 89%; surgery-compression, 93%; $P = .73$). (From Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration [ESCHAR study]: randomized controlled trial. *Lancet*. 2004;363:1854–1859.)



Numbers at risk					
Compression plus surgery	216	166	124	68	27
Compression alone	226	139	98	45	10

Figure 157.7 The rates of ulcer recurrence at 4 years were 56% for the compression-alone group and 27% for the compression-surgery group. (From Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration [ESCHAR study\: randomized controlled trial. *Lancet*. 2004;363:1854–1859.)

measured using the EQ-5D-3L health questionnaire[49] completed at baseline and at the end of the study. The quality-of-life score was found to be 0.1025 higher in patients wearing the ACT device ($P < 0.0375$). The ACT system may be considered in patients with C6 disease who failed graduated compression stockings and other means of compression therapy (Unna Boot, bandages, CircAid).[48]

Surgery Versus Compression in C6 Disease. In the Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) study, 500 patients with leg ulcers were randomized to compression alone and compression plus surgery (high ligation and stripping of the saphenous vein).[50] Compression consisted of multilayered bandaging every week until healing, then class 2 knee-high stockings. Whereas 24-week healing rates were similar in the two groups (65% vs. 65%; hazard, 0.84 [95% CI, 0.77-1.24]; $P = .85$), at 24 months the recurrence rate was significantly lower in the compression-surgery group (12% vs. 28%; hazard, 2.76 [95% CI, 1.78-4.27]; $P < .0001$). In a second report published in 2007, long-term results of the ESCHAR trial were analyzed.[44] Overall ulcer healing rates were not statistically significantly different between the groups at 3 years (Fig. 157.6). The rates of ulcer recurrence at 4 years were 56% for the compression-alone group and 27% for the compression-surgery group (Fig. 157.7).[44] The benefit of the combined compression-surgery approach was noted mostly in the subgroup of patients with superficial or segmental deep vein reflux (Fig. 157.8).[50,51]

The ESCHAR trial and other studies[52] provide strong evidence that compression therapy, in conjunction with appropriate surgical intervention (high ligation and stripping, endovenous ablation of saphenous veins by thermal and chemical methods), is a vital part of the ongoing care and treatment of patients with venous ulcers. The clinical practice guidelines of the Society for Vascular Surgery (SVS) and the American Venous Forum (AVF)[53] also support this approach.

Pharmacologic Therapies

Pharmacologic therapy in venous disease is directed toward symptom control in patients with mild to moderate chronic venous disease and the treatment of venous ulcers. Pharmacologic targets have been identified on the basis of advances in the understanding of the pathogenesis of the molecular mechanisms of chronic venous disease, and a substantial number of agents have been developed and studied.[16,54] A cost analysis of severe chronic venous disease in 19,750 German patients showed that 11% had consumed medications designed to treat venous disease in the preceding 12 months; 80% of the purchasers were women, and the majority were older than 50 years.[55] Indications for the medications were varicose veins (58%), leg pain (30%), and various degrees of lower extremity venous disease (30%). A Cochrane database review[56] published in 2005 included 44 prospective randomized trials involving 4413 patients, in which the efficacy of several medications was assessed. Outcomes included edema, venous ulcers, lipodermatosclerosis, subjective symptoms, global assessment measures, and adverse reactions. Among the different medications, phlebotropic drugs, of which the micronized purified flavonoid fraction (MPFF) is the most prominent, showed some degree of benefit (RR, 0.72; 95% CI, 0.65-0.81). The authors concluded, "There is not enough evidence to globally support the efficacy of phlebotonics for chronic venous insufficiency. There is a suggestion of some efficacy of phlebotonics on edema but this is of uncertain clinical relevance. Due to the limitations of current evidence, there is a need for further randomized, controlled clinical trials with greater attention paid to methodologic quality."[56]

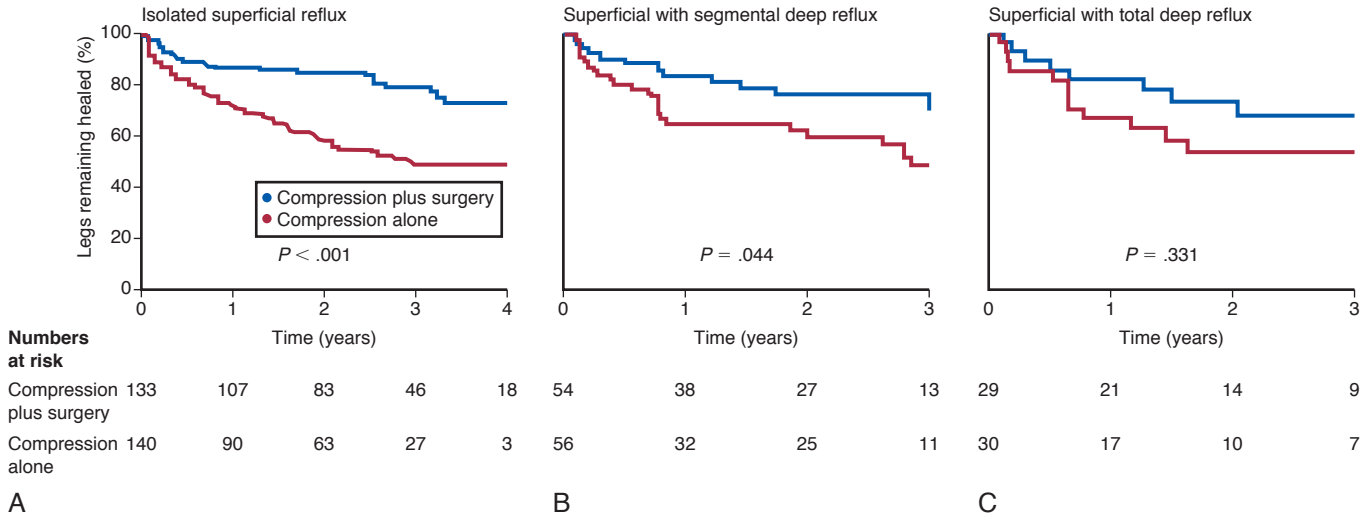


Figure 157.8 Ulcer recurrence rates were significantly reduced in the subgroup of patients with superficial **(A and C)** or segmental deep vein reflux **(B)**. (From Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomized controlled trial. *Lancet*. 2004;363:1854–1859.)

Diuretics

The role of diuretics in chronic venous disease is still debated. They may have some benefit in reducing edema in patients with chronic congestive heart failure.

Zinc

Zinc is a trace element and a cofactor of more than 100 enzymatic processes involved in DNA replication, protein synthesis, and cell division. Zinc also plays a key role in the humoral and cell-mediated immunity responses and wound-healing.[57] Despite reports of low zinc levels in patients with venous ulcers and a few reports of a beneficial effect of oral zinc supplementation in the healing of venous ulcers, a Cochrane review from Wilkinson[58] including four trials found no evidence of benefit in oral zinc supplementation on the number of ulcers healed.

Fibrinolytic Agents

In 1982, Burnand et al.[59] observed the presence of fibrin cuffs surrounding the dermal capillaries of 26 lower extremities with lipodermatosclerosis. This finding was confirmed by Falanga et al.[60] in 1987, along with reduced transcutaneous tissue oxygen saturation levels in the skin around the ulcer. Despite these observations, trials involving medications with fibrinolytic activity, such as stanozolol and sulodexide glycosaminoglycan, failed to prove beneficial in ulcer healing.[54]

Pentoxifylline

Pentoxifylline is a competitive nonselective adenylate cyclase inhibitor with several activities, including increase of intracellular cyclic adenosine monophosphate, activation of protein kinase A, inhibition of tumor necrosis factor, and promotion of leukotriene synthesis. The pharmacologic effects of pentoxifylline are related to red blood cell deformability and inhibition of platelet aggregation and thrombus formation.[61] Pentoxifylline also has an antiinflammatory effect that is probably related to the selective depression of tumor necrosis factor expression and the depression of granulocyte phagocytic activity and neutrophil-endothelium adhesion.[61] A prospective randomized trial published in 2007 compared the effectiveness of pentoxifylline, knitted viscose or hydrocolloid dressings, and single-layer or four-layer bandaging for venous ulceration.[62] The study enrolled 245 patients with venous ulcers. The main outcome was time to complete ulcer healing. The dose of pentoxifylline administered was 1200 mg by mouth daily. Initial results showed that pentoxifylline was associated with a statistically nonsignificant improvement in ulcer healing (62% vs. 53%; $P = 0.21$). Further analysis with a Cox regression model resulted in a clinically significant improvement in ulcer healing with pentoxifylline (RR for healing, 1.4; 95% CI, 1.0-2.0).[62]

A Cochrane review, also from 2007, included 12 trials and 864 patients.[63] In 11 trials that compared pentoxifylline (400 mg PO daily) with placebo, a significant benefit in ulcer healing was noted (RR, 1.70; 95% CI, 1.30-2.24). Pentoxifylline plus compression was found to be more effective than compression alone (RR, 1.56; 95% CI, 1.14-2.13). Pentoxifylline alone was more effective than placebo or no treatment (RR, 2.25; 95% CI, 1.49-3.39). Seventy-two percent of patients complained mostly of gastrointestinal adverse reactions. The authors concluded that there is evidence that pentoxifylline may be an effective adjunct to compression therapy in advanced chronic venous disease. The authors also noted the heterogeneity of the trials, which could have resulted in an overall sample bias.[63]

Phlebotropic Agents

Phlebotropic agents are medications with multiple pharmacologic microcirculatory activities that show a unique tropism for veins. The most important phlebotropics are found in the family of the γ-benzopyrone family (flavonoids).[64]

Micronized purified flavonoid fraction (MPFF) consists of 90% micronized diosmin and 10% flavonoids.[65] Although its

mechanism of action has not been fully defined, a number of pharmacologic properties have been identified. In vitro and in vivo animal studies have demonstrated inhibition of granulocytes and macrophage infiltration in the venous parenchyma. This correlates with an overall antiinflammatory pharmacologic activity.[64] Another property of MPFF is phlebotropism, with vein tissue being the most important target. In an animal model of venous hypertension, MPFF was shown to attenuate, in a dose-dependent manner, leukocyte adhesion and migration into the valvular tissue, expression of intercellular adhesion molecule-1 and P-selectin, and apoptosis of endothelial cells.[66] In the same model, venous valve degeneration was attenuated in the treatment group.[67]

A number of prospective randomized trials have been conducted to assess the effectiveness of MPFF. The most recent meta-analysis included 10 prospective randomized trials published between 1975 and 2009, with a total of 1010 patients.[68] The primary outcome was effective treatment of venous edema by ankle diameter reduction. The result was a significant reduction in ankle diameter with MPFF (0.80 ± 0.53), compared with ruscus extract (0.58 ± 0.47), hydroxyethylrutoside (058 ± 0.31), diosmin (0.20 ± 0.42), and placebo (0.11± 0.42). This confirmed 1A level of evidence assigned to MPFF in the management of symptoms and edema.[68]

Another meta-analysis published by Coleridge Smith in 2005[69] included five prospective randomized trials and 723 patients with venous ulcers. MPFF and conventional treatment (local wound care and compression) were compared with conventional treatment plus placebo in two studies ($n = 309$) and conventional treatment alone in three studies ($n = 414$). Primary outcome was ulcer healing at 6 months. At 6 months, ulcer healing was 32% higher in the MPFF group (RR, 32%; 95% CI, 3%-70%). MPFF at a dose of 500 mg twice per day was found to be more beneficial in the group of patients, with ulcers between 5 and 10 cm^2 and in ulcers with a 6 to 12-month duration.[69]

MPFF is effective in control of symptoms and ankle edema in patients with symptomatic uncomplicated chronic venous disease. In association with compression therapy, it is a useful adjunct in large and long-standing ulcers.

Prostaglandins

Prostaglandin E_1 is known to attenuate white blood cell activation and platelet aggregation.[70] In a prospective randomized trial involving 87 patients with venous ulcers, prostaglandin E_1 was administered by intravenous infusion for 20 days in addition to topical therapy. The primary endpoint was ulcer healing at 120 days. The results showed that healing time in the prostaglandin E_1 group was less than 100 days, with more than 75% of patients healing at 75 days. This was statistically significant compared with the placebo (84.2% patients healing at 120 days).[70]

Horse chestnut is an herbal medication with moderate antiinflammatory activity through the release of prostaglandin F.[71] A Cochrane review of seven placebo-controlled randomized trials showed a statistical improvement in leg pain in six trials, which was equivalent to compression therapy in patients with uncomplicated symptomatic varicose veins.[72] In a small prospective triple-blind randomized placebo-controlled trial of 54 patients with venous leg ulcers, oral therapy with horse chestnut did not show evidence of improvement in venous ulcer healing.[73]

Other Medications

Aspirin and ifetrobane (oral thromboxane A_2 receptor antagonist) have failed to demonstrate benefit in either uncomplicated or complicated chronic venous disease.[54]

Calcium dobesilate is a drug that has been shown to reduce capillary permeability. Whereas some benefit has been shown in reducing ankle edema, no advantage has been proved in the care of patients with venous ulcers.[54]

CONCLUSION

High-grade compression therapy is the mainstay of treatment for patients with advanced chronic venous disease (C4-C6). The ESCHAR trial showed that there is a subgroup of patients who may benefit from ablation of refluxing veins, in addition to compression therapy to prevent ulcer recurrence. In patients with uncomplicated C1-C2 chronic venous disease, compression therapy may be beneficial in symptom control, but it is not associated with disease regression.

MPFF is currently the most effective medication in C1-C2 chronic venous disease, and there is level 1A evidence that its use is advantageous, mainly in symptom control. MPFF may be a useful adjunct in the care of patients with C6 disease.

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In this meta-analysis of 10 prospective randomized trials, the micronized purified flavonoid fraction was found to be effective in the management of symptoms and edema, compared with other venoactive drugs (ruscus extract, hydroxyethylrutoside, diosmin).

Barwell JR, Davies CE, Deacon J, et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomized controlled trial. *Lancet*. 2004;363:1854–1859.

In this prospective randomized trial, compression alone was compared with compression plus surgery (high ligation and stripping of the saphenous vein) in patients with C6 disease. At 24 months, the recurrence rate was significantly lower in the compression-surgery group.

Gohel MS, Barwell JR, Taylor M, et al. Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomized controlled trial. *BMJ*. 2007;335:83.

The long-term results of the ESCHAR trial are analyzed in this report. Lower ulcer recurrence rate was noted in the compression-surgery group compared with compression therapy only at a 4-year follow-up. The benefit of the combined compression-surgery approach was noted mostly in the subgroup of patients with superficial or segmental deep vein reflux.

Michaels JA, Campbell WB, Brazier JE, et al. Randomized clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial). *Health Technol Assess*. 2006;10:1–196, iii-iv.

In this prospective randomized trial, surgery (high ligation of the saphenofemoral junction, great saphenous vein stripping, and phlebectomies) was found to be more cost-effective than conservative therapy (lifestyle modification, leg elevation, and compression stockings) in patients with C2 disease. Injection sclerotherapy also appeared to be cost-effective for patients with superficial venous reflux but was found to produce less benefit compared with surgery.

Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. *Cochrane Database Syst Rev*. 2012;(8):CD002303.

This 2012 update of a Cochrane review emphasizes the importance of compression therapy in preventing ulcer recurrence. No difference was noted between high compression and moderate compression in ulcer recurrence in three trials. Moderate compression stockings were associated with higher compliance to therapy.

Nelson EA, Prescott RJ, Harper DR, et al. A factorial, randomized trial of pentoxifylline or placebo, four-layer or single-layer compression, and knitted viscose or hydrocolloid dressings for venous ulcers. *J Vasc Surg*. 2007;45:134–141.

In this prospective randomized trial, pentoxifylline was associated with a statistically nonsignificant improvement in ulcer healing. However, Cox regression analysis modeling resulted in a clinically significant improvement in ulcer healing with pentoxifylline.

O'Donnell TF Jr, Passman MA, Marston WA, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery (R) and the American Venous Forum. *J Vasc Surg*. 2014;60(2 suppl):3S–59S.

Evidence-based clinical practice guidelines for the care of patients with venous ulcers are discussed in this report.

O'Meara S, Tierney J, Cullum N, et al. Four layer bandage compared with short stretch bandage for venous leg ulcers: systematic review and meta-analysis of randomized controlled trials with data from individual patients. *BMJ*. 2009;338:b1344.

In this meta-analysis comparing the effectiveness of four-layer and short stretch single-layer compression bandages, it was noted that four-layer bandages were associated with shorter healing time in larger ulcers. Chronic ulceration and previous ulcerations were found to be independent predictors for delayed ulcer healing.

Pittler MH, Ernst E. Horse chestnut seed extract for chronic venous insufficiency. *Cochrane Database Syst Rev*. 2012;(11):CD003230.

This is the 2012 update of a Cochrane database review first published in 2002. Efficacy and Safety of Horse Chestnut Seed (HCSE) versus placebo are reviewed. Leg pain was assessed in seven placebo-controlled trials. In six trials, a significant reduction of leg pain was observed with HCSE. Leg volume was also noted to be significantly decreased (95% CI 13.49 to 50.72) in the HCSE cohort in six trials. The authors conclude that HCSE is an efficacious and safe short-term treatment for CVI.

Smith PC. Daflon 500 mg and venous leg ulcer: new results from a meta-analysis. *Angiology*. 2005;56(suppl 1):S33–S39.

The micronized purified flavonoid fraction at a dose of 500 mg twice per day was noted to increase ulcer healing, particularly in patients with long-standing large (5 and 10 cm^2) venous ulcers.

A complete reference list can be found online at www.expertconsult.com.

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158 CHAPTER

Chronic Venous Insufficiency: Treatment of Perforator Vein Incompetence

FEDOR LURIE and ALESSANDRA PUGGIONI

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Perforating veins (PVs) were not described until drawings by Justus Christian Von Loder were published in 1794.[1] From that time, for more than a century, their role in venous disease remained unappreciated despite the illuminating work of M. Verneuil and subsequent analysis by John Gay.[2] In 1917, John Homans suggested that incompetent perforating veins (IPVs) played a key role in the genesis of venous ulcers.[3] Subsequently, Beecher and Warren formulated the concept of transmission of ambulatory pressure through IPVs into the superficial system, which was supported by the investigations of Cockett and Dodd and provided a physiologic basis for the surgical interruption of IPVs.[4-6] In 1938, Linton described a surgical approach to IPVs in the distal portion of the calf that became the standard in treating venous ulcers for several decades.[7] Multiple modifications of Linton's original technique were proposed to decrease wound complications and to avoid incisions too close to the ulcer. This led to a minimally invasive approach pioneered by DePalma and Edwards and culminated in the use of endoscopy, first described by Hauer.[8] Adding a tourniquet and gas insufflation, Gloviczki and Conrad transformed subfascial endoscopic perforating vein surgery (SEPS) into a reliable procedure that was disseminated around the world and replaced the open surgical approach.[9,10]

The development of endovascular treatment options for reflux in superficial veins has established a new standard for patients with chronic venous insufficiency (CVI), in whom the invasiveness and risk for wound complications associated with SEPS exceed those of the treatment of saphenous veins. As a result, new modalities, such as ultrasound-guided percutaneous ablation of perforating veins (PAPS) with sclerosing solutions or thermal energy, have become the preferable option.[11]

Renewed interest in outcomes following treatment of IPVs and their role in venous pathophysiology uncovered a lack of reliable information related to their impact on the natural history and severity of CVI. Despite a growing body of evidence substantiating decision making in the management of patients with CVI, the indications for eliminating PV reflux remain imprecise.

Abstract

This chapter describes the role of incompetent perforating veins (IPVs) in the pathogenesis and natural history of chronic venous disease (CVD) and its progression to chronic venous insufficiency (CVI), diagnostic techniques for identification of PVs, criteria for assessing their incompetence, and indications and techniques for the interruption of IPVs.

Many aspects of the topic have not been subjected to proper scientific investigation; therefore evidence-based medicine is not always available. In these cases, we have presented material as consensus-based, or even as the author's individual and group experience.

Keywords

perforating veins
venous disease
venous insufficiency
venous ulcer
SEPS
Linton procedure
sclerotherapy

In this chapter we describe the role of IPVs in the pathogenesis and natural history of chronic venous disease (CVD) and its progression to CVI, diagnostic techniques for identification of PVs, and criteria for assessing their incompetence. We discuss indications and techniques for the interruption of IPVs as well as the outcomes of these treatment modalities. We have made every attempt to stay within the framework of evidence-based medicine. However, because some or perhaps many aspects of the topic have not been subjected to proper scientific investigation, we refer to our individual and group experience when appropriate. We identify such statements because they introduce substantial bias.

PATHOPHYSIOLOGY

The role of PVs in normal physiology and in the pathogenesis of CVD are discussed in Chapter 156. In this chapter, we review only the relevant aspects of PVs to better understand the rationale for the treatment of IPVs.

Normal Perforating Veins

The venous system of the lower extremity is rich in interconnections between the individual vessels. Because of the numerous collateral circulatory routes established, disruption of venous flow as well as compression of the veins by contracting muscles during locomotion or external pressure is prevented during changes in position of the body and of the extremity itself. By crossing the proper fascia of the extremity, PVs provide a connection between the superficial and deep venous systems in the calf and thigh. There are approximately 60 PVs in a lower extremity,[12] and most if not all of them have valves directing flow from the superficial to the deep veins.

Our understanding of PV anatomy and normal physiology is based mainly on studies conducted during the 1960s and 1970s and on inferences from clinical observations of pathologic conditions. Although some anatomic studies demonstrated that all PVs have valves,[13] others showed that some PVs are avalvular.[12,14] The latter, however, are found in only a minority of extremities and not more frequently than two veins per extremity.[12] These anatomic data are consistent with findings from duplex scans of asymptomatic legs, only 3.6% of which have bidirectional flow in PVs.[15] Whether PVs provide collateral ways for blood flow to bypass areas of obstruction of the superficial veins, such as compression from outside during sitting, or their presence facilitates outflow from superficial veins when pressure in the deep veins drops during walking, or both, it is clear that flow in healthy PVs is directed from the superficial into the deep system. Although the hemodynamic role of PVs in normal circulation has not been addressed by experimental or direct observational studies, it is unlikely that the current theory could be meaningfully challenged.

The role and significance of IPVs are much less obvious. In the absence of functioning valves, blood flow in a PV is governed mainly by the pressure gradient in adjoined segments of the superficial and deep systems. Active contraction of the venous wall and compression by surrounding muscles cannot compensate for the absence of the valve, especially in enlarged PVs with significantly degenerated walls. Therefore knowledge of the hemodynamic function of the deep and superficial systems is critical for understanding the role of IPVs, and this role may differ according to the status of each of the two systems.

Hemodynamic Impact of Perforating Vein Incompetence

IPVs can be found in 40% to 60% of extremities with primary CVD and even more frequently in legs with postthrombotic disease.[16-18] Isolated incompetence of a PV is extremely rare,[19,20] and in most cases IPVs coexist with insufficiency of the superficial veins, deep veins, or both. Although the prevalence of IPVs is slightly higher in legs with both deep and superficial reflux than in limbs with only superficial reflux,[17] the presence of axial superficial reflux appears to be the major factor associated with a higher prevalence of IPVs.[18] More than 60% of extremities with axial reflux in the great saphenous vein (GSV) have incompetent PVs, as opposed to 38% of extremities with only segmental superficial reflux.[16] An association between axial superficial reflux and PV incompetence has been shown during the progression to CVI. About a third of patients with symptomatic varicose veins develop new refluxing segments in 1 year.[21,22] In half of these cases, the new IPVs also develop during the same time.[21,23]

The observation that correction of superficial reflux leads to resolution of perforator incompetence in most limbs supports the concept that superficial reflux causes an "overload" of PVs, resulting in dilation and incompetence.[24] However, treatment of saphenous reflux by either stripping or ablation results in obstruction of the superficial veins to which PVs are connected, or in a significant increase in resistance to outward flow in PVs. Therefore elimination of PV reflux after such treatment does not necessarily mean that the competence of the PV valves will be regained. Rather, it simply means that the blood cannot flow through PVs into (obstructed) superficial veins, even if the PVs themselves remain open. The presence of these incompetent perforators without demonstrated reflux may be a reason that "isolated" IPVs are found in previously treated extremities and cause new symptoms and worsening hemodynamics.[19,25] In addition, surgical treatment of superficial veins often fails to reverse PV incompetence and new IPVs develop in limbs previously treated surgically.[23,26]

The presence of deep reflux further complicates the situation. An IPV may cause reversal of flow in an adjoining segment of deep vein, which is sometimes mistakenly interpreted as deep venous insufficiency but really reflects flow from the segment of deep vein between competent valves through an incompetent perforator into a connected superficial vein. In these cases, correction of superficial insufficiency with or without IPV interruption leads to disappearance of reversed flow in the deep vein segment.[27] When deep reflux is caused by true valvular incompetence, reflux may persist after the treatment of superficial veins.[28] Thus, interpretation of IPV function based on data from clinical studies is not always possible.

Direct measurement of blood flow in IPVs and venous pressure in superficial veins has demonstrated that even when incompetent, a PV can function in a way similar to competent PVs. During standing, there is no blood flow through the IPV, and during walking, the net flow through the IPV is from superficial veins to deep veins despite the bidirectional nature of flow during muscle contractions.[29]

Occlusion of an IPV does not influence venous pressure in superficial veins, whereas occlusion of an incompetent GSV normalizes ambulatory hypertension.[29] In light of these findings, the concept of transmission of the higher blood pressure from deep into superficial veins via IPVs during ambulation becomes questionable. Indirectly, this was confirmed by the demonstration of independent pressure changes in superficial and deep veins during ambulation.[30]

Clinical Correlations of Perforating Vein Incompetence

The presence of IPVs is just one of many factors that determine the progression to advanced stages or affect the functional status and quality of life of CVD patients. The specific role of IPVs in the natural history and pathogenesis of CVD is less clear. The concept that IPVs can cause symptoms such as swelling and skin changes led to the development of more aggressive approaches to treatment and remains the latter's justification.[5] IPVs alone can cause symptoms, affect hemodynamics, and increase the severity of disease.[19,25] Even more convincing is the fact that successful treatment of an "isolated" IPV is associated with the relief of symptoms and improvement of severity scores.[19]

In addition to their role in symptom development and disease progression, IPVs can be a source of recurrent varices after treatment. This concept is supported by consistent findings of a high prevalence of IPVs in extremities with recurrent varices.[31-34] Whether this association is important only in the presence of deep reflux or also plays a role in extremities with a competent deep system remains to be investigated.[33,35]

The relationship between IPVs and skin ulcers in the leg was historically the first to be demonstrated and was consistently confirmed in multiple small case series in which it was shown that surgical interruption of IPVs promotes healing and prevents the recurrence of venous ulcers.[36] This effect is especially prominent in primary CVD and less so in limbs with post-thrombotic disease.[37] Even treating IPVs alone can promote healing of ulcers in the majority of limbs with primary CVD.[19] Large randomized controlled trials, however, have failed to confirm this effect of IPV treatment. The Dutch Ulcer Trial, for example, showed ulcer healing rates of 83% in the surgical group and 73% in the group treated by compression. Ulcer recurrence was almost the same in the two groups: 22% in the surgical group and 23% in the compression group.[38] The results of this and other trials[23,39,40] should be interpreted cautiously because their designs are far from ideal to answer the question of the role of IPVs in ulceration.

In a systematic review of the literature, O'Donnell showed that there is no level 1 evidence that treatment of IPVs alone affects ulcer healing or recurrence; level 1 evidence is available only for ligation of the GSV alone for decreasing recurrence of venous ulcers.[41] He concluded that there is a need for randomized controlled trials to prove the role of IPV treatment for classes C5 and C6 disease in the Clinical, Etiologic, Anatomic, Pathophysiologic (CEAP) classification system.

Given the uncertainty of the physiologic role of IPVs and the lack of high-level evidence of efficacy of IPV interruptions, decision making in the treatment of IPVs can be a challenging task. The relatively low risk of IPV interruption procedures may be the reason that they have been used in the past for the following indications: (1) normalization of venous hemodynamics, (2) prevention of the progression of CVD to more advanced stages, (3) resolution of symptoms and thereby a decrease in disease severity, (4) prevention of recurrent varicose veins, (5) promotion of ulcer healing, and (6) prevention of recurrent venous ulcers. Clear identification of one or more of these six points as a treatment goal in a patient or as an outcome to be measured in a study may facilitate our progress toward better understanding of the role that IPVs play in limbs with CVD.

ANATOMY

As their name suggests, PVs perforate the deep fascia of the leg, which separates the superficial and deep compartments; they can be classified as direct or indirect. Direct perforators connect the superficial to the deep venous systems, whereas indirect perforators join the venous sinuses of the calf muscles. Furthermore, PVs connect to each other via communicating veins above and underneath the deep muscle fascia. The majority of PVs are accompanied by perforating arteries (Fig. 158.1) and nerves that provide blood supply and innervation to the skin.[12,42] Within the fascial orifice the artery is usually located proximal to the vein, but the topography of the subfascial and suprafascial segments of perforator arteries varies significantly. These arteries can be clearly identified by duplex ultrasound, and their position should be taken into account, especially if sclerotherapy is being considered as a treatment option.[43]

The International Interdisciplinary Consensus Committee on Venous Anatomical Terminology recommends classifying PVs into six groups according to the segment of the lower extremity in which they are found[44]:

Perforators of the foot *(venae perforantes pedis)*
Perforators of the ankle *(venae perforantes tarsalis)*
Perforators of the leg *(venae perforantes cruris)*
Perforators of the knee *(venae perforantes genus)*
Perforators of the thigh *(venae perforantes femoris)*
Perforators of the gluteal muscles *(venae perforantes glutealis)*

Each group includes several subgroups (Fig. 158.2). One of the aims of this classification is to allow topographic description of PVs to avoid the use of personal names, which are often historically inaccurate.

Many PVs are small vessels and have little clinical significance. The most important perforators from a clinical standpoint are the direct medial calf perforators, which cross the superficial posterior compartment. The posterior tibial PVs originate from the posterior accessory saphenous vein of the calf (posterior arch vein in the old terminology). The most distal posterior

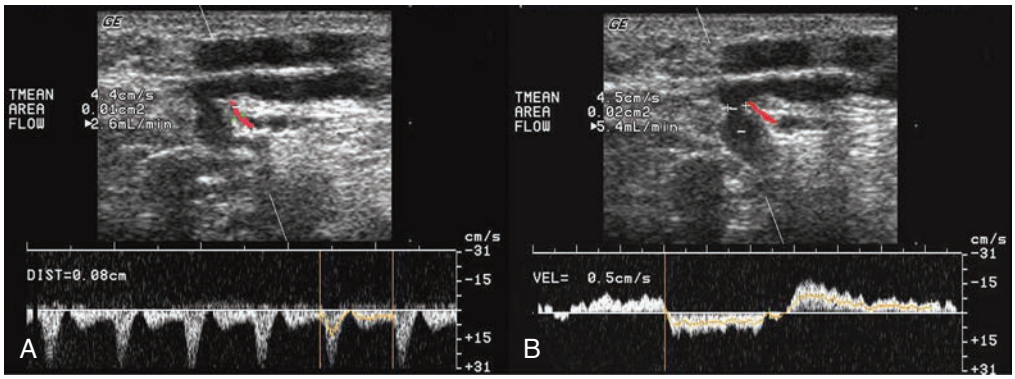

Figure 158.1 (A) A small perforating artery is located next to the perforating vein at the fascial level. Pulsed-wave Doppler confirms arterial flow. (B) Doppler signal from the incompetent perforating vein indicates bidirectional flow.

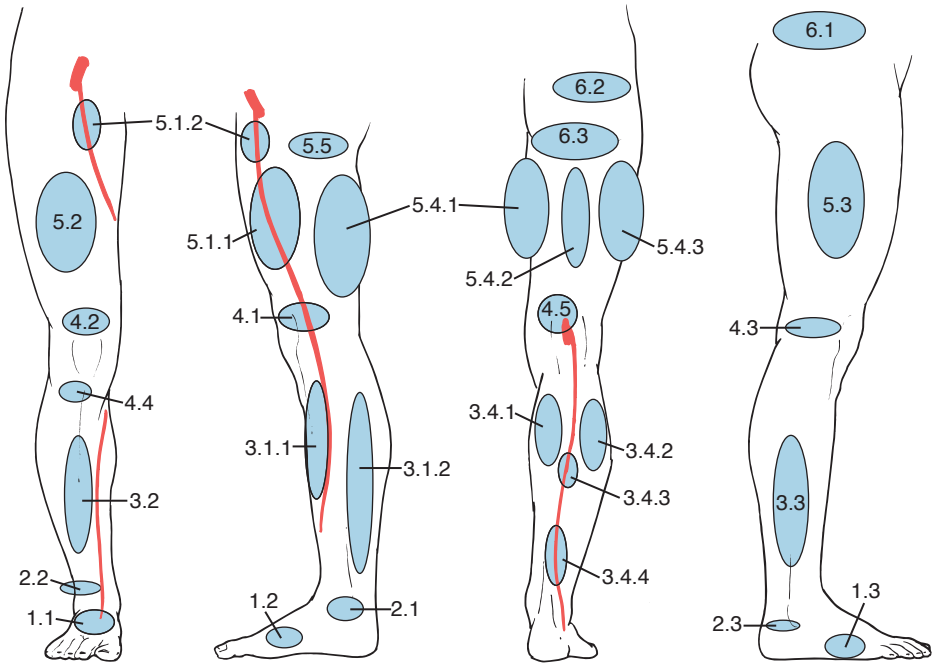

Figure 158.2 Schematic representation of the topography of the main groups of perforating veins (PVs). Foot PVs: 1.1, dorsal foot PV; 1.2, medial foot PV; 1.3, lateral foot PV. Ankle PVs: 2.1, medial ankle PV; 2.2, anterior ankle PV; 2.3, lateral ankle PV. Leg PVs: 3.1.1, paratibial PV; 3.1.2, posterior tibial PV; 3.2, anterior leg PV; 3.3, lateral leg PV; 3.4.1, medial gastrocnemius PV; 3.4.2, lateral gastrocnemius PV; 3.4.3, intergemellar PV; 3.4.4, para-achillean PV. Knee PVs: 4.1, medial knee PV; 4.2, suprapatellar PV; 4.3, lateral knee PV; 4.4, infrapatellar PV; 4.5, popliteal fossa PV. Thigh PVs: 5.1.1, PV of the femoral canal; 5.1.2, inguinal PV; 5.2, anterior thigh PV; 5.3, lateral thigh PV; 5.4.1, posteromedial thigh PV; 5.4.2, sciatic PV; 5.4.3, posterolateral thigh PV; 5.5, pudendal PV. Gluteal PVs: 6.1, superior gluteal PV; 6.2, midgluteal PV; 6.3, lower gluteal PV. (Redrawn from Caggiati A, Bergan JJ, Gloviczki P, et al. Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement. *J Vasc Surg*. 2002;36: 416–422.)

tibial perforators are located behind the medial malleolus, whereas the middle and upper posterior tibial perforators are located more proximally in the calf (at 7–9 cm and 10–12 cm from the medial malleolus, respectively) and about 1 inch medial to the tibia; these PVs connect the posterior arch vein to the posterior tibial veins (Cockett perforators). More proximal direct PVs are the paratibial direct perforators or "24-cm perforators," which are located closer to the tibia and 18 to 22 cm from the medial malleolus, as evident in anatomic cadaveric studies (Fig. 158.3). Another group of medial calf perforators, found just below the knee, is known as Boyd's perforators. They connect the GSV and its tributaries to the tibial or popliteal veins. Also of probable clinical importance are the posterolateral or peroneal perforators, which connect tributaries of the short saphenous vein to the peroneal veins. Among these, the most important are Bassi's perforator, located at 5 to 7 cm from the lateral aspect of the ankle, and the "12-cm perforator," located at 12 to 14 cm. Thigh perforators are less developed than calf PVs. The main instances are the Dodd perforators and the Hunterian perforators, which are located in the medial aspect of the thigh and connect the GSV to the popliteal or femoral veins. Other PVs connect the superficial system to the profunda femoris vein.

DIAGNOSTIC EVALUATION

Clinical Investigation (CEAP Level 1)

Large IPVs can be identified by palpation of the fascial defect, especially when varicose veins are located in the same area. By applying gentle pressure against this defect, an investigator can feel retrograde flow when a patient performs the Valsalva maneuver or coughs. Handheld continuous-wave Doppler ultrasonography can be the next diagnostic step, but its sensitivity is insufficient and its specificity is not different from that of physical examination, which is close to zero.[45]

The best test to identify IPVs is duplex ultrasound. This test should be performed in all patients with CVD. The invasive

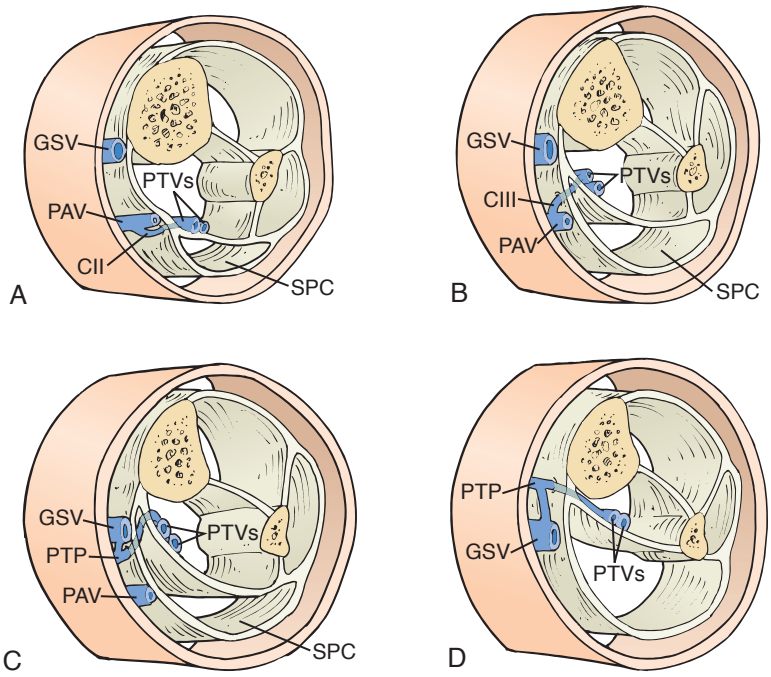

Figure 158.3 Compartments and medial veins of the leg. Cross sections are shown at the level of Cockett II (posterior tibial perforator) (A) Cockett III, (B) "24 cm," and (C) more proximal paratibial (D) Perforating veins. *CII,* Cockett II; *CIII,* Cockett III; *GSV,* great saphenous vein; *PAV,* posterior arch vein; *PTP,* paratibial perforator; *PTVs,* posterior tibial veins; *SPC,* superficial posterior compartment. (From Gloviczki P, Bergan J, eds. *Atlas of Endoscopic Perforator Vein Surgery,* London: Springer-Verlag; 1998.)

nature of venography, its questionable diagnostic properties for identification of IPVs,[45] and its inability to map the exact location of IPVs make its use in CVD limited to selected cases requiring venous reconstruction.

Noninvasive Vascular Investigation (CEAP Level 2)

The size of PVs and their hemodynamic properties are to a great extent affected by the position of the body. It is recommended that duplex scanning be performed while the patient is standing or sitting; however, the 30-degree head-up supine position gives similar results.[46] All surfaces of the extremity should be carefully scanned. The location of IPVs varies, and indirect IPVs can be found at a distance from major axial veins.

Because most PVs are rather short veins, induction of reversed flow in them is a great challenge. To initiate a reversed flow of appropriate duration, the connected superficial vein should be almost empty and the adjoined deep vein should contain a sufficient volume of blood. In many cases this is difficult to achieve, especially when the test is performed on a standing patient. To solve this problem, two sets of criteria for PV incompetence were suggested: a shorter-time cut point of 0.35 second to define the reflux[21] and the use of PV diameter instead of reflux time.[47] Diameter should be measured on a B-mode transverse section at the site where the vein penetrates the fascia (Fig. 158.4). Reflux time should be measured on a longitudinal section using a pulsed-wave mode combined with simultaneous B-mode (duplex) or with the addition of a color Doppler mode (triplex). The site for measurement of reflux time should be the same as that for measurement of diameter—at the level of the fascial orifice (Fig. 158.5).

In our experience, using both approaches simultaneously has proved beneficial. Small PVs less than 2 mm in diameter

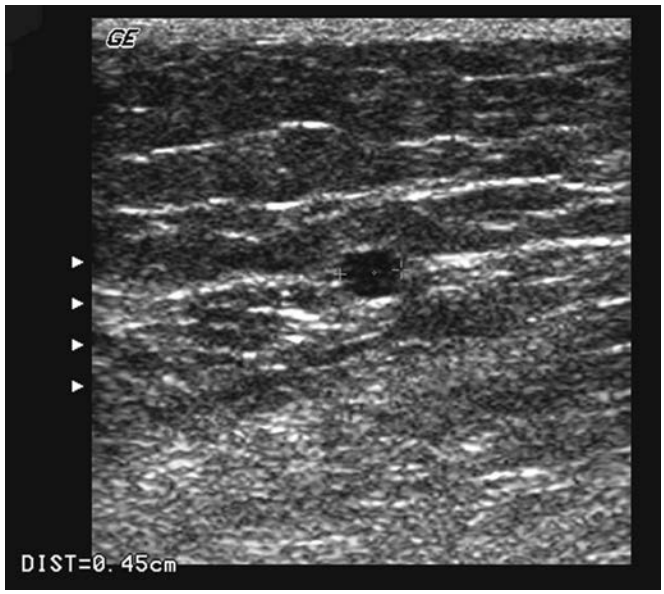

Figure 158.4 Measurement of perforating vein diameter is performed in a B-mode transverse section of the PV at the level of the fascial orifice.

have questionable clinical significance, even when reversed flow through them exceeds the cut point for reflux. They also present a technical challenge for treatment and often undergo spontaneous thrombosis and resolution after ablation of the connected segment of superficial vein. PVs larger than 4 mm in diameter are almost certainly pathologic and may be identified as incompetent even when the reversed flow through them is shorter than the cut point for reflux. Finally, PVs 2 to 4 mm in diameter should be considered incompetent only when they meet the appropriate hemodynamic criteria.

When treatment of an IPV is being considered, duplex scanning should be repeated in the exact position as the patient

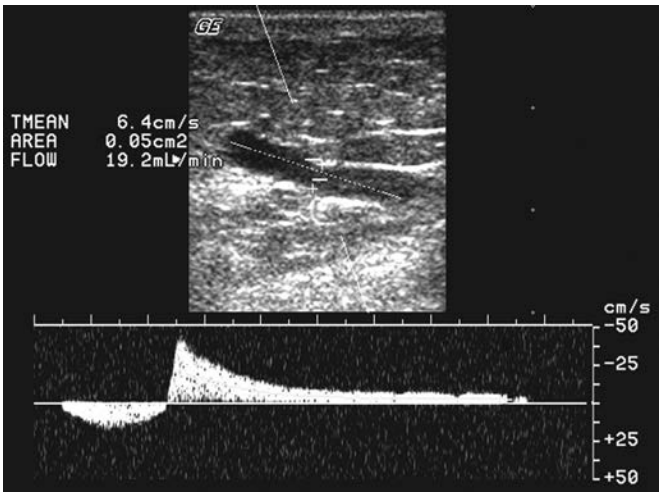

Figure 158.5 Measurement of flow velocity in a perforating vein (PV) is performed in duplex mode in a longitudinal section of the PV at the level of the fascial orifice.

will be in during the treatment. This can be supine, prone, or on the side, depending on the selected access point. Shifting of anatomic structures can markedly affect the topographic relationship between subfascial and suprafascial segments of the IPV and superficial veins, which, in turn, will change the position of a desirable access point.

INDICATIONS FOR INTERRUPTION

Precise definition of the indications for interruption of IPVs is necessary in clinical practice because it provides a basis for assessment of treatment outcomes. It is even more important when research studies are planned and executed. Although definitive studies to identify when IPV interruption should be considered are yet to be conducted, one or more of the following reasons can serve as the indication for treatment of IPVs:

1. Promotion of ulcer healing in extremities with CEAP clinical class C6
2. Prevention of ulcer recurrence in extremities with clinical classes C5 and C6
3. Diminution of the severity of CVD and resolution of symptoms in C2S to C5S extremities
4. Prevention of progression to more advanced stages in C4b extremities

The presence of an IPV alone does not justify interruption. The decision to intervene should be based on clinical judgment and assessment of the role of a specific IPV in the overall hemodynamic picture of the extremity. The benefits of interruption and the risks of leaving this PV untreated should also be considered.

Key suggestions and recommendations from the AVF/SVS guidelines[48] for the treatment of CVD include the following:

- We suggest treatment of pathologic PVs that includes those with outward flow of 500 ms duration and a diameter of 3.5 mm located adjacent to healed or open venous ulcers (class C5–C6, grade 2B).
- We suggest treatment of pathologic perforators in patients with advanced C4 disease, especially in those with pending ulceration (class C4, grade 2C).
- We recommend against selective treatment of incompetent PVs in patients with simple varicose veins (class C2, grade 1B).
- We suggest preferential use of ultrasonographically guided percutaneous techniques (thermal ablation or sclerotherapy) for perforator ablation over subfascial endoscopic perforator surgery (SEPS) or open surgical phlebectomy or perforator ligation (grade 2C).

The most recent AVF/SVS guidelines provide more specific indications for treating limbs with C4b–C6 disease.

These guidelines include the following statements:

- In a patient with a venous leg ulcer (C6) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic PVs (outward flow of less than 500 ms duration, with a diameter of >3.5 mm) located beneath or associated with the ulcer bed, we suggest ablation of both the incompetent superficial veins and perforator veins in addition to standard compressive therapy to aid in ulcer healing and prevent recurrence (grade 2; level of evidence, C).
- In a patient with skin changes suggestive of an impending venous ulcer (C4b) or healed venous ulcer (C5) and incompetent superficial veins that have reflux to the ulcer bed in addition to pathologic PVs (outward flow of >500 ms duration and a diameter of >3.5 mm) located beneath or associated with the healed ulcer bed, we suggest ablation of the incompetent superficial veins to prevent the development or recurrence of a venous leg ulcer (grade 2; level of evidence, C). Treatment of the incompetent PVs can be performed simultaneously with correction of axial reflux or can be staged with reevaluation of perforator veins for persistent incompetence after correction of axial reflux (grade 2; level of evidence, C). In a patient with isolated pathologic perforator veins (outward flow >500 ms duration and a diameter of >3.5 mm) located beneath or associated with the healed (C5) or active ulcer (C6) bed regardless of the status of the deep veins, we suggest ablation of the pathologic PVs in addition to standard compression therapy to aid in venous ulcer healing and to prevent recurrence (grade 2; level of evidence, C).

OPERATIVE PLANNING OPTIONS

The timing and technique of IPV interruption are important. Although procedures can be staged, performing simultaneous saphenous vein ablation and perforator ablation has two major advantages. First, all invasive procedures are performed in one session, which is highly desirable for the patient and reduces the cost of treatment. Second, it has been suggested that any remaining incompetent tributaries and IPVs connected to the saphenous veins can increase the chance of recanalization after thermal and chemical ablation.

Thus, treating IPVs at the time of saphenous vein ablation possibly improves the result of the saphenous vein ablation.[77] On the other hand, elimination of saphenous reflux has a

profound effect on the global venous hemodynamics of the leg. Segments not specifically targeted during surgery, such as PVs and deep veins, may partially reverse their incompetence when the total venous "overload" of the leg is reduced. In as many as 58% of IPVs, incompetence will reverse during the 2 years after stripping.[50] Even when IPVs persist after stripping of the GSV, their impact on the clinical status of the extremity is questionable. The ESCHAR (Effect of Surgery and Compression on Healing and Recurrence) study showed that presence of IPVs after stripping does not affect the healing time and rate of ulcers.[51] It has also been observed that adding SEPS to the GSV stripping does not significantly improve patients' quality of life or prevent recurrent symptoms.[52]

When simultaneous treatment of IPVs and incompetent saphenous veins is planned, selection of the IPV interruption technique is very much dependent on the method of treating the saphenous vein. The less invasive options for saphenous ablation limit the use of open surgical interruption because it may increase immediate postoperative morbidity and negate the advantages of minimally invasive procedures. When IPV interruption is performed alone, selecting a minimally invasive option still has the advantage of minimizing immediate postoperative morbidity, thereby allowing early ambulation and reducing impact on quality of life.

OPEN SURGERY

The original open perforator interruption described by Linton in 1938 was subsequently abandoned and should not be considered a choice for IPV interruption unless other options are not available. Interruption of PVs through small stab wounds plus avulsion by a vein hook is now preferred among the open surgical methods because this procedure is significantly less invasive and does not require hospitalization. With this technique, duplex scanning is used for preoperative mapping and the IPVs are marked on the skin, which allows performance of a more precise procedure. Ligation of incompetent perforators can also be done by making a short incision directly over the marked sites and ligating them at the fascia with absorbable sutures. Alternatively, the position of the vein hook can be controlled with the use of intraoperative transcutaneous ultrasound to ensure that a targeted IPV is actually interrupted. Selection of an open perforator interruption technique does not guarantee 100% success; 5% of perforators are usually missed and 32% recur within 3 years, half of them being incompetent.[53]

Subfascial Endoscopic Perforator Surgery

SEPS uses endoscopic instrumentation to achieve interruption of incompetent perforators through small incisions placed remotely from areas of lipodermatosclerosis or ulceration. First described by Hauer in the 1980s,[8] SEPS became the most accepted surgical treatment of CVI because of its minimally invasive nature and safety profile compared with the classic, more extensive Linton procedure. SEPS can be performed through one or two endoscopic ports after exsanguination of the limb with leg elevation and the Esmark bandage, followed by application of a thigh tourniquet inflated to 300 mm Hg (Fig. 158.6). Carbon dioxide is insufflated to enlarge and optimally visualize the subfascial space, with pressure maintained at around 30 mm Hg. On completion of the procedure, the ports and instrumentation are removed, the tourniquet is deflated, and the carbon dioxide is manually expressed from the subfascial space.[54]

Results and Complications

Retrospective data from the North American SEPS registry on 146 patients demonstrated an 88% ulcer healing rate at 1 year, with a median ulcer healing time of 54 days and a complication rate of 6% (Fig. 158.7).[37] Complications encountered were deep venous thrombosis (DVT) (<1%), superficial thrombophlebitis (3%), and saphenous neuralgia (7%).[37] Other complications of SEPS include wound infection, paresthesias, and subfascial space hematoma.[55] The ulcer recurrence rate was 28% at 2 years (Fig. 158.8), significantly better than most published series on nonoperative management. It was evident from the study that a significant number of ulcers did not heal or recurred; however, the recurrent disease after surgery appeared to be less severe in most patients than before surgery. Although this trial was not randomized, it must be noted that ulcers failed to heal in 101 patients until surgery was performed despite an estimated 75% good to excellent compliance with nonoperative care. Subgroup analysis demonstrated a higher recurrence rate in postthrombotic limbs than in those with primary valvular incompetence (46% vs. 20% at 2 years, $P < .05$). Similar results have been reported by several authors, so it is unclear whether SEPS is indicated in postthrombotic limbs. Several other studies have demonstrated a benefit of SEPS in early ulcer healing and decreased recurrence rates (Table 158.1). Nonetheless, other studies did not prove the clinical efficacy of PV reflux ablation, even in patients with ulcerated limbs.[56] For instance, in a report by Scriven and colleagues, combined perforator and superficial vein reflux ablation in ulcerated limbs with associated deep reflux did not result in clinical improvement compared with limbs treated by superficial reflux ablation alone.[57] In a meta-analysis, Tenbrook and coworkers analyzed pooled data of surgical treatment in 1140 limbs with advanced CVD from 20 published series.[58] Ulcers healed in 88% of the limbs treated by SEPS, with or without superficial venous ablation. The recurrence rate was 13% at a mean follow-up period of 21 months. Risk factors for nonhealing and recurrent ulcers included new or recurrent IPVs, postthrombotic syndrome, and ulcers larger than 2 cm in diameter. Surgical complications included wound infection (6%), hematoma (9%), neuralgia (7%), and DVT (1%). All these data from PV surgery trials came from nonrandomized cohorts that almost invariably lacked a comparison group. The Dutch SEPS trial, a randomized, prospective, multicenter study designed to compare SEPS with conservative treatment of venous ulcers, has been performed and published (Table 158.2). Of 200 legs with ulcers included in the study, 94 were treated surgically and 102 were treated conservatively. Healing rates were 83% in the surgical group and 73% in the conservative

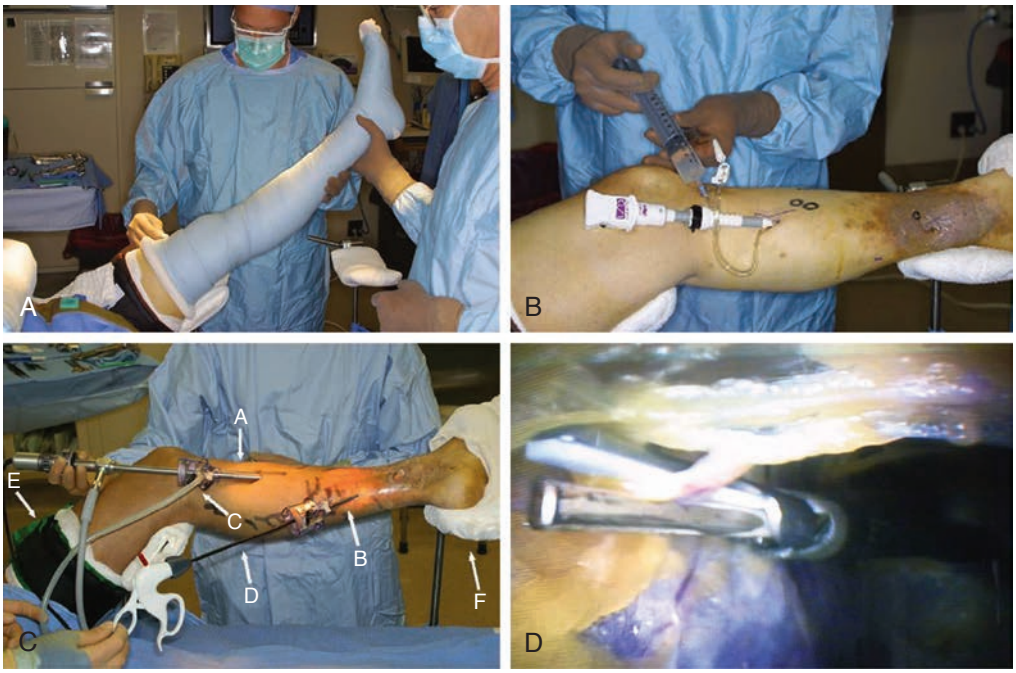

Figure 158.6 (A) Endoscopic division of a perforator is performed in a bloodless field. A pneumatic tourniquet is placed on the thigh, and the extremity is exsanguinated with an Esmark bandage. A tourniquet inflated to 300 mm Hg is used to create a bloodless field. (B) Balloon dissection is used to widen the subfascial space. (C) Subfascial endoscopic perforator vein surgery is performed via two ports: a 10-mm camera port *(A)* and a 5- or 10-mm distal port *(B)* inserted under video control. Carbon dioxide is insufflated through the camera port into the subfascial space to a pressure of 30 mm Hg to improve visualization and access to the perforators *(C)*. A harmonic scalpel *(D)* is inserted through the distal port. The leg is positioned on a holder *(F)*, and the tourniquet is kept inflated *(E)*. (D) The subfascial space is widely explored from the medial border of the tibia to the posterior midline and down to the level of the ankle. Division of the perforator is performed with endoscopic scissors after placement of vascular clips or with a harmonic scalpel placed through the second port. ([A–D] Reproduced with permission of the Mayo Foundation.)

group (difference not significant; median time to healing, 27 months). Recurrence rates were the same in both treatment groups (22% with surgical treatment vs. 23% with conservative treatment). During follow-up at a mean of 29 months in the surgical group and 26 months in the conservative group, the ulcer-free rate was 72% in the surgical group and 53% in the conservative group ($P = .11$). Patients with recurrent ulceration or medially located ulcers in the surgical group had a longer ulcer-free period than those treated in the conservative group ($P = .02$). The trial did not recognize an overall benefit of surgical treatment over compression alone except in selected cases of medial or recurrent ulceration (or both) and in patients who underwent the SEPS procedure in expert venous centers.[38]

Venous ulcers mainly occur at the area of the medial malleolus; however, about 10% develop at the lateral aspect of the ankle. Interruption of lateral calf perforators with SEPS to treat lateral ulcers has been attempted, but clinical outcomes have been unsatisfactory, and perforators were noted to persist postoperatively on duplex scan.[59] It is possible that factors other than PV reflux are behind the pathogenesis of these lesions or that SEPS is inadequate in localizing and interrupting relevant perforators in this particular location. Aside from clinical benefits, one should be able to objectively detect functional improvement after PV interruption to help establish its hemodynamic benefits and correlate it with clinical outcome. Padberg and associates used air plethysmography to assess hemodynamic improvement after perforator and superficial vein surgery and demonstrated a quantifiable improvement up to 2 years after the procedure.[60] Another study from the Mayo Clinic using strain-gauge plethysmography as a diagnostic tool demonstrated improvement in both calf muscle pump function and degree of incompetence in 26 patients 6 months after SEPS and ablation of superficial reflux. These changes correlated with clinical improvement and were significant only in limbs with primary valvular incompetence, as opposed to postthrombotic limbs.[55] Similarly, Ting and colleagues observed significant improvement in both clinical scores and the venous filling index after SEPS; this improvement was maintained at 1-year follow-up.[61] The degree of patient satisfaction was also remarkable, with 74% ± 17% and 90% ± 12% rates of satisfaction at 1-month and 1-year follow-up, respectively.

Until recently, SEPS was considered a minimally invasive alternative to open surgery for the treatment of PV incompetence. Compared with the classic open procedures, the incidence of complications such as wound infection, absence of healing, and nerve injury was significantly lower with SEPS. However, the occurrence of other complications, such as DVT, superficial thrombophlebitis, and neuralgia, as well as the complex learning curve and significant cost, stimulated interest in less invasive methods. Furthermore, the procedure is limited by an inability

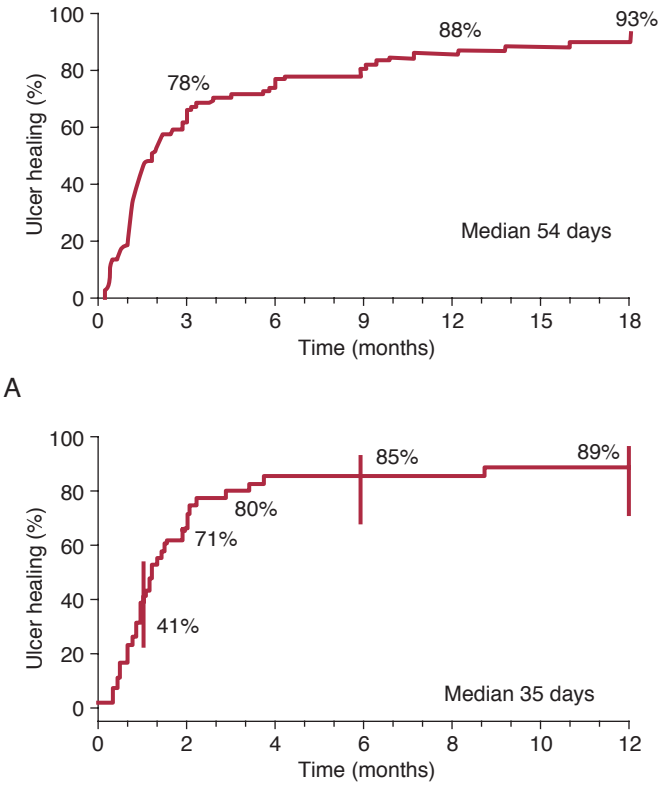

Figure 158.7 (A) Cumulative ulcer healing in 101 patients after subfascial endoscopic perforator vein surgery. The 90-day, 1-year, and 1.5-year healing rates are indicated. The standard error is less than 10% at all time points. (B) Cumulative ulcer healing in 42 patients after subfascial endoscopic perforator vein surgery. The 90-day and 1-year healing rates are indicated. The standard error is less than 10% at all time points. ([A] From Gloviczki P, Bergan JJ, Rhodes JM, Canton LG, Harmsen S, Ilstrup DM. North American Study Group: mid-term results of endoscopic perforator vein interruption for chronic venous insufficiency: lessons learned from the North American Subfascial Endoscopic Perforator Surgery [NASEPS] registry. *J Vasc Surg*. 1999;29:489–499. [B] From Kalra M, Gloviczki P, Noel AA, et al. Subfascial endoscopic perforator vein surgery in patients with post-thrombotic venous insufficiency—is it justified? *Vasc Endovasc Surg*. 2002;36:41–50.)

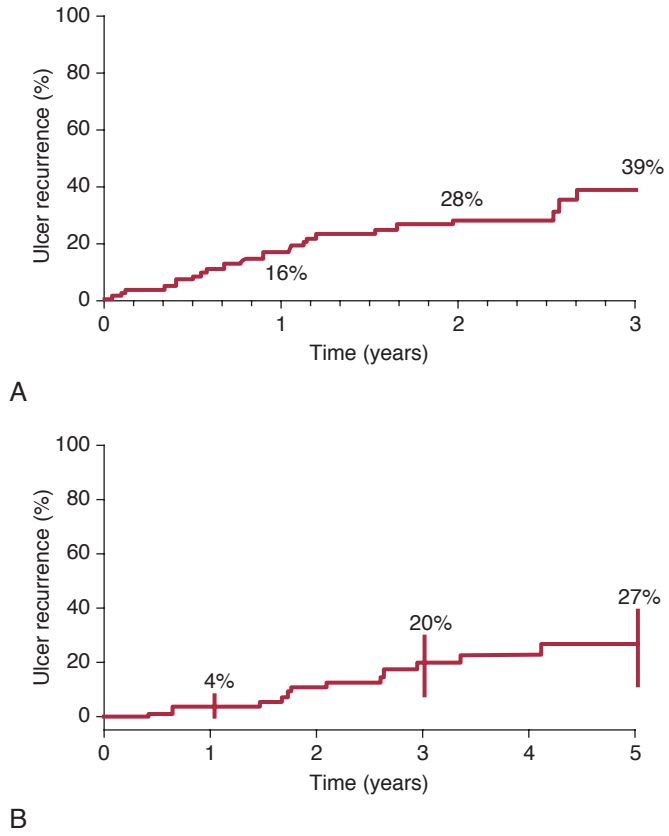

Figure 158.8 (A) Cumulative ulcer recurrence in 106 patients after subfascial endoscopic perforator vein surgery (SEPS). The 1-year, 2-year, and 3-year recurrence rates are indicated. All class 5 limbs at the time of SEPS and class 6 limbs that subsequently healed are included. The start point (day 0) for time to recurrence in class 6 patients was the date of initial ulcer healing. The standard error is less than 10% at all time points. (B) Cumulative ulcer recurrence in 72 patients after SEPS. The 1-year, 3-year, and 5-year recurrence rates are indicated. All class 5 limbs at the time of SEPS and class 6 limbs that subsequently healed are included. The start point (day 0) for time to recurrence in class 6 patients was the date of initial ulcer healing. The standard error is less than 10% at all time points. ([A] From Gloviczki P, Bergan JJ, Rhodes JM, Canton LG, Harmsen S, Ilstrup DM. North American Study Group: mid-term results of endoscopic perforator vein interruption for chronic venous insufficiency: lessons learned from the North American Subfascial Endoscopic Perforator Surgery [NASEPS] registry. *J Vasc Surg*. 1999;29:489–499. [B] From Kalra M, Gloviczki P, Noel AA, et al. Subfascial endoscopic perforator vein surgery in patients with post-thrombotic venous insufficiency—is it justified? *Vasc Endovasc Surg*. 2002;36:41–50.)

to reliably access all incompetent perforator sources and to discriminate between competent and incompetent perforators at the time of treatment.

PERCUTANEOUS ABLATION OF PERFORATING VEINS

The introduction of percutaneous endovenous therapies for superficial venous reflux (thermal and chemical ablation) has established a new standard of office-based procedures that obviate the need for general anesthesia and hospital stay. Thermal and chemical ablation of saphenous veins gained popularity rapidly, thanks to a significant reduction in patient discomfort, fewer complications, and earlier return to work.[62] PAPS combines the precision of a surgical approach with the minimal invasiveness of an injection. PAPS requires a higher level of technical skill than GSV ablation does but offers patients a truly minimally invasive procedure. After PAPS, either as the sole treatment or in conjunction with saphenous ablation, patients can ambulate immediately and experience minimal postoperative pain. PAPS has almost no negative impact on quality of life.[78]

The AVF/SVS clinical practice guidelines recommend PAPS over open surgical techniques. "For those patients who would benefit from pathologic perforator vein ablation, we recommend treatment by percutaneous techniques that include ultrasound guided sclerotherapy or endovenous thermal ablation (radiofrequency or laser) over open venous perforator surgery to eliminate the need for incisions in areas of compromised skin (grade 1; level of evidence, C)."[49]

The two most important technical aspects of PAPS are ultrasound-guided intraluminal access and verification of the

TABLE 158.1 Results of Subfascial Endoscopic Perforating Vein Surgery in Main Published Series

Series	Number of Limbs	Number of Limbs With History of Ulcer	Number of Limbs With Active Ulcer	Saphenous Vein Ablation (%)	Ulcer Healing (%)	Number of Limbs With Ulcer Recurrence	Mean Follow-Up (Months)
Jugenheimer, 1992[a]	103	NR	17	NR	94	0	27
Pierik, 1995[b]	40	40	16	10	100	1	46
Bergan, 1996[c]	31	25	15	100	93	0	NR
Gloviczki, 1999[d]	146	122	101	60	84	26	24
Lee, 2001[e]	36	19	NR	92	89	2	14
Baron, 2001[f]	45	45	37	40	89	0	10
Iafrati, 2002[g]	51	51	29	55	74	7	38
Ciostek, 2002[h]	146	74	36	90	86	11	56
Kalra, 2002[i]	103	76	42	72	90	21	39
Bianchi, 2003[j]	74	74	58	77	91	4	44
Roka, 2006[k]	92	41	21	97	95	2	44
Ting, 2006[l]	53	15	34	100	100	3	31

NR, not reported.

[a]Jugenheimer M, Junginger T. Endoscopic subfascial sectioning of incompetent perforating veins in treatment of primary varicosis. *World J Surg*. 1992;16:971–975.

[b]Pierik EG, Wittens CH, van Urk H. Subfascial endoscopic ligation in the treatment of incompetent perforating veins. *Eur J Vasc Endovasc Surg*. 1995;9:38–41.

[c]Bergan JJ, Murray J, Greason. Subfascial endoscopic perforator vein surgery: a preliminary report. *Ann Vasc Surg*. 1996;10:211–219.

[d]Gloviczki P, Bergan JJ, Rhodes JM, Canton LG, Harmsen S, Ilstrup DM. Mid-term results of endoscopic perforator vein interruption for chronic venous insufficiency: lessons learned from the North American Subfascial Endoscopic Perforator Surgery Registry. The North American Study Group. *J Vasc Surg*. 1999; 29:489–502.

[e]Lee DW, Chan AC, Lam YH, et al. Early clinical outcomes after subfascial endoscopic perforator surgery (SEPS) and saphenous vein surgery in chronic venous insufficiency. *Surg Endosc*. 2001;15:737–740.

[f]Baron HC, Saber AA, Wayne M. Endoscopic subfascial surgery for incompetent perforator veins in patients with active venous ulceration. *Surg Endosc*. 2001; 15:38–40.

[g]Iafrati MD, Pare GJ, O'Donnell TF, Estes J. Is the nihilistic approach to surgical reduction of superficial and perforator vein incompetence for venous ulcer justified? *J Vasc Surg*. 2002;36:1167–1174.

[h]Ciostek P, Myrcha P, Noszczyk W. Ten years experience with subfascial endoscopic perforator vein surgery. *Ann Vasc Surg*. 2002;16:480–487.

[i]Kalra M, Gloviczki P, Noel AA, et al. Subfascial endoscopic perforator vein surgery in patients with post-thrombotic venous insufficiency—is it justified? *Vasc Endovasc Surg*. 2002;36:41–50.

[j]Bianchi C, Ballard JL, Abou-Zamzam AM, Teruya TH. Subfascial endoscopic perforator vein surgery combined with saphenous vein ablation: results and critical analysis. *J Vasc Surg*. 2003;38:67–71.

[k]Roka F, Binder M, Bohler-Sommeregger K. Mid-term recurrence rate of incompetent perforating veins after combined superficial vein surgery and subfascial endoscopic perforating vein surgery. *J Vasc Surg*. 2006;44:359–363.

[l]Ting AC, Cheng SW, Ho P, Wu LL, Cheung GC. Clinical outcomes and changes in venous hemodynamics after subfascial endoscopic perforating vein surgery. *Surg Endosc*. 2003;17:1314–1318.

TABLE 158.2 Results of Surgical Treatment of Perforator Vein Incompetence Versus Conservative Treatment Alone in a Randomized, Prospective, Multicenter Study (the Dutch SEPS Trial)

Number of Limbs Treated	Number of Limbs With Active Ulcer (%)	Number Treated Conservatively (%)		Number Treated Surgically (%)		Mean Follow-Up (Months)
200	196 (100)	102 (52)		94 (48)		29
		Number of Ulcers Healed (%)	Number of Ulcers That Recurred (%)	Number of Ulcers Healed (%)	Number of Ulcers That Recurred (%)	
		74 (73)	23 (23)	78 (83)	21 (22)	

SEPS, Subfascial endoscopic perforating vein surgery.

Figure 158.9 Closure RFS (radiofrequency stylet).

initial anatomic success of the treatment. Selection of the access point depends on the technique and instrumentation that will be used. For example, if treatment is planned with the rigid Closure RFS (radiofrequency stylet, Fig. 158.9), an access point should be lined up with the continuation of the subfascial portion of the perforator. More flexible laser fibers allow selection of the entry point to access either the epifascial segment of the IPV or the adjoining superficial vein. A larger and straighter segment of the superficial vein can be selected to provide easier access and a more stable needle position. A guidewire can then be advanced into the perforator and a microintroducer positioned over the wire to secure the precise position for placement of the laser fiber. Alternatively, the fiber can be placed directly through a 21-gauge needle for the 400-μm fiber or through a 16-gauge needle for the 600-μm fiber. If sclerotherapy is planned as the treatment technique, the access selected should be at a safe distance from the perforating artery. If it is not clearly identifiable by duplex scan, the superficial vein connected to the perforator and located a distance of 1 to 2 cm from the fascial orifice should be selected for the access.

For all techniques, successful access and the position of the catheter or needle should be confirmed sonographically. Aspiration of blood is not sufficient because the needle may be in a neighboring vein not connected to the IPV. In the case of thermal ablation, the subfascial position of the catheter should also be verified. The advantage of using the radiofrequency stylet is the ability to measure impedance, which can confirm the intravascular position of the catheter. Sonographic verification, however, is still necessary.

Assessment of initial anatomic success is also based on duplex ultrasound. In addition to verification of the absence of blood flow in the PV, assessment of changes in diameter and echogenicity of the vein wall and lumen is necessary. An increase in echogenicity and thickening of the venous wall, increased echogenicity of the lumen, and absence of spontaneous or induced flow immediately after treatment are signs of successful ablation. An increase in diameter and a decrease in echogenicity with an absence of flow indicate thrombosis in the IPV, which is less desirable because of the risk of propagation in deep veins and the high rate of recanalization. Assessment of success after foam sclerotherapy is most challenging and should be postponed for 24 hours or more because the PV cannot be clearly visualized; flow can be induced by compression of the extremity distal to the PV immediately after successful treatment. As an indirect sign of successful PAPS, we found it helpful to use the dilation and increased flow velocity in the perforating artery accompanying the treated IPV immediately after treatment.[43]

Techniques

Laser Ablation

Several different fibers and kits have been used for endovenous laser ablation of IPVs. The use of lasers with wavelengths of 810-, 940-, and 1320-nm and 980-nm diode lasers has been reported.[63,64]

The patient is placed in the reverse Trendelenburg position and the skin is prepared with sterile technique. Incompetent perforators are visualized and marked on the skin; it is important to document the exact location by measuring its distance from the medial malleolus and tibia for localization during follow-up studies. The target perforator is visualized in transverse view by ultrasound and punctured under vision with a needle; thereafter a stiff introducer and a sheath are advanced over a 0.018-inch guidewire. The laser fiber (600 or 400 μm) is then inserted into the sheath with the tip 0.5 cm or more from the deep system. Tumescent anesthetic (saline solution containing lidocaine, sodium bicarbonate, and epinephrine) is infiltrated into the perivenous tissues to provide anesthesia, reduce dissipation of heat to the surrounding structures, and obtain apposition of the vein walls. Two or three segments of each perforator should be treated, with one of them located subfascially and another epifascially. Each segment should receive between 60 and 100 J or 100 J/cm over the treatable length of the perforator.

Radiofrequency Ablation

The Closure RFS made by Medtronic/Covidien (Mansfield, Mass.) is a rigid device that has two electrodes on the shaft and a removable needle trocar. The vein is punctured either directly with the stylet or with a needle, followed by access over a 0.035-inch guidewire (see Fig. 158.9). Ideally, extrinsic compression should be maintained during treatment (approximately 80 to 90 mm Hg of pressure). After intravascular access has been confirmed by return of blood into the device, tumescent anesthetic is infiltrated around the vein. The vein should be treated in a subfascial segment to ensure the best results, but this should be at least 0.5 cm away from the deep veins. Impedance is maintained between 150 and 350 Ω at a mean temperature of 85°C and a power level of less than 3.5 W. The Closure RFS should be angulated against all four quadrants of the vein wall for 1 minute each, thus requiring 4 minutes of treatment per segment. More segments within the same perforator, ideally two or more, may require treatment to obtain satisfactory closure.

Sclerotherapy

Sclerotherapy can be performed to treat IPVs with a diameter of 4 to 7 mm at the level of the fascia. Smaller veins are seldom incompetent, and larger veins require larger volumes of sclerosant, which can potentially increase the rate of complications. Most

commonly used are sodium tetradecyl sulfate (Sotradecol), sodium morrhuate, and polidocanol (Aethoxysklerol). Larger veins require higher concentrations. In general the patient is placed in the supine position, the skin is prepared by sterile technique, and the vein is punctured under duplex guidance. Venous blood is withdrawn first, just enough to confirm correct needle positioning, and 1 to 2 mL of sclerosing agent is injected. The needle is withdrawn and compression is applied for a few minutes. The vein is reimaged to ascertain the absence of residual flow in the treated perforator. Identification of the accompanying perforating arteries should be attempted to avoid possible skin necrosis, but when this is not possible, it is preferable to inject the perforator in a location well above the fascial opening, where the artery and vein are not so close to each other. Patients with known allergic reactions to sclerotherapy agents, those who are pregnant or lactating, and those with a known or suspected prothrombotic state should not be treated by this technique. The presence of severe arterial occlusive disease or active vasculitis is also a contraindication, because inadvertent intraarterial injection can potentially aggravate preexisting chronic ischemia.

New Treatment Modalities

Similar to thermal ablation techniques that were initially designed for saphenous veins but were adapted to treat IPVs, new technologies are either already being used or likely to be used for this purpose outside their primary indications. Mechanico-chemical ablation (MOCA) has ablation rates similar to those of thermal ablation but does not require tumescent anesthesia.[65-67]

Although the use of other new nontumescent nonthermal ablation modalities for the treatment of IPVs has not yet been reported, it is only a matter of time before technologies such as cyanoacrylate embolization[68,69] will be applied for treatment of IPVs.

Results and Complications

Early success rates with greater than 90% absence of flow within the treated perforator at 6 months have been reported with radiofrequency ablation.[70,71] Unlike GSV closure, skin burns are very rare with the Closure RFS, even when the probe is at a depth of less than 1 cm from the skin.

The early occlusion rate of IPVs treated by laser is reported to be between 85% and 100%.[72,73] Side effects included ecchymosis, induration, and pain (40% to 50%), paresthesias (16%), hyperpigmentation (8%), and phlebitis (4%).[64-68] A 6-month duplex follow-up from a series of 27 perforators treated by laser demonstrated an ablation success rate of greater than 90%.[74] Although detailed documentation of perforator location before treatment is necessary for follow-up comparison, no reliable method exists to determine whether a suspected perforator recurrence is a newly formed perforator or indeed a recanalized perforator.

The early results of duplex-guided sclerotherapy for perforators reported by Guex showed a 90% occlusion rate after three or fewer sessions.[18] In our experience, immediate PV obliteration was achieved in 98% of cases. Skin complications consisting of superficial skin necrosis occurred in 1.5%. Recurrence, defined as the presence of flow in a previously sclerosed PV at duplex follow-up, was present in 23% of cases at a mean follow-up of 17 months. Venous clinical severity scores decreased on average from 11.95 before treatment to 6.5 after treatment ($P < .05$). Likewise, venous disability scores dropped from 1.86 before treatment to 0.81 after treatment ($P < .05$). Perforator recurrence was more common in limbs with ulcerations. Except for the rare occurrence of skin necrosis, cosmetic results were excellent, often with partial reversal of preexisting skin changes and relief of symptoms. Although complications of sclerotherapy are rare, some clinical scenarios should be mentioned. Multiple needle punctures can lead to vasospasm or a hematoma (or both), which may make the procedure technically challenging or technically unsuccessful.

Pain during sclerotherapy injection may be due to intraarterial puncture, in which case the injection should be stopped immediately. Should such pain occur, injection of procaine around the injected artery, local cooling, systemic heparinization, and infusion with low-molecular-weight dextran is recommended. Extravasation in subcutaneous tissues is usually painless unless the sclerosant solution had been mixed with normal saline, which may result in skin necrosis. Another possible serious complication, although rare, is anaphylactic shock. When any sclerotherapy injection is performed, all the necessary equipment to manage this event must be readily available (oxygen, epinephrine, and steroids) because it could be a life-threatening situation.[75,76]

No comparative studies of different PAPS modalities are currently available, but published data suggest that predictors of success differ. A large size of the perforator is more likely to be a risk for failure of sclerotherapy, and a pulsatile flow pattern may cause failure of laser ablation.[64]

Postoperative Management

Immediately after treatment, deep veins should be imaged to rule out DVT, and a compression dressing should be worn continuously for 24 to 48 hours during the day only for the next 5 days. The first follow-up visit should be scheduled within 1 week after the procedure. Duplex scans should be repeated at this time to ensure the absence of DVT and to assess the early anatomic outcome of treatment. The follow-up schedule should be based on other treatment modalities used at the time of treatment of the IPV, but long-term clinical and duplex follow-up is desirable.

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CHAPTER 159

Chronic Venous Insufficiency: Deep Vein Valve Reconstruction

MICHAEL C. DALSING and OSCAR MALETI

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Chronic venous insufficiency (CVI) can be well tolerated or advance to a state of chronic venous ulceration. Skin changes such as hyperpigmentation due to CVI of the lower extremity have been reported in 6 to 7 million US citizens, with progression to venous ulceration occurring in up to 2%.[1-3] It is estimated that the cost of venous ulcer care alone in the United States is more than $2.5 billion annually.[4] The excellent early success of ulcer healing with compression is marred by the risk of recurrence in up to 40% of compliant patients and approaches 100% in noncompliant patients.[5,6] Treating all superficial and perforator vein insufficiency can reduce the recurrence risk, but it still occurs in up to 33% of patients with primary deep CVI and 70% of those with the postthrombotic syndrome. These facts demonstrate the importance of deep venous disease in the pathophysiologic process of CVI.[7] Deep venous obstructive lesions in combination with venous reflux have been noted in 55% of patients with chronic venous disease (CVD) in one series, and especially in those with the most severe symptoms.[8] Correcting iliac obstruction without addressing deep venous insufficiency can result in long-term ulcer healing of nearly 60%.[9] The 40% of patients remaining are the select group with chronic deep venous insufficiency who may benefit from valve reconstruction or other open surgical procedures.

PATHOGENESIS

Etiology

Congenital absence of lower extremity venous valves, venous aplasia, or dysplasia is rare.[10] More commonly patients with

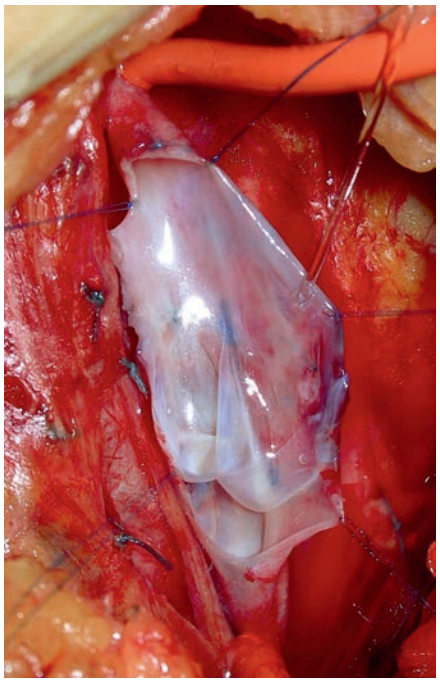

Figure 159.1 Floppy and asymmetrical venous valve leaflets seen after vein opened to reveal the valve cusps.

primary venous insufficiency have floppy, redundant, elongated valve cusps (Fig. 159.1); asymmetrical insertion or development of cusps; or an enlarged venous diameter. All these anomalies prevent normal valve apposition.[11-14] Such cases have no apparent inciting event for the anatomic changes observed, except in cases of clear congenital anomalies. As a consequence of these pathologic changes, reflux occurs in the affected valves either upon standing or with additional stresses. Disregarding aplasia or dysplasia or those with asymmetrical cusp development, in situ tightening of the structurally intact valve can render it competent and functional.

Secondary venous insufficiency is defined as having an apparent inciting event that caused valve damage. The inciting event is often acute deep venous thrombosis (DVT), and in 40% to 70% of all affected patients may be the cause of the deep venous valvular incompetence observed.[11,15-17] The resulting inflammation and scarring with recanalization can cause foreshortening and fibrosis of the valve leaflets, small perforations, or valve adhesion and luminal narrowing (Fig. 159.2).[11] The valves are so damaged that direct repair is not possible. The options remaining to prevent complete system reflux are transplantation of a competent valve from a distant location, transposition of the incompetent venous axis to a position distal to a local competent valve, or the use of less traditional valve techniques such as a neovalve or other valve substitute.

The distinction between "primary" and "secondary" (post-thrombotic) venous disease is not always clear. Diagnostic studies and direct observation at the time of valve surgery have noted both pathologic processes within the same patient.[18,11] Theories proposed to explain a thickened yet functional valve (Fig. 159.3) include potential pathologic changes, resulting simply from sustained hypertension, or from the rapid resolution of deep

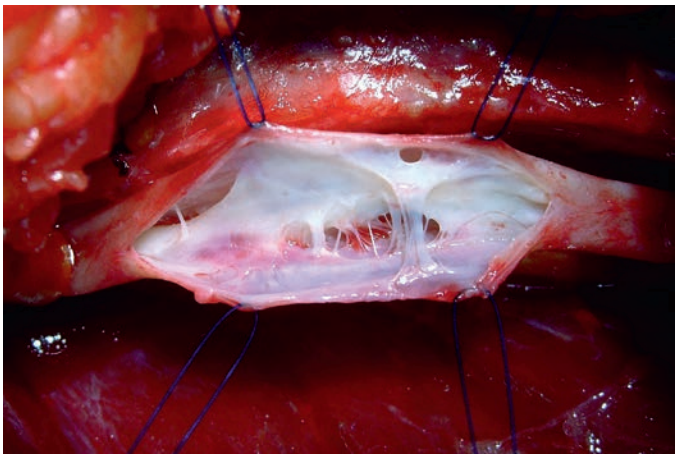

Figure 159.2 Valve destruction resulting from deep vein thrombosis with scarring within the vein, bridges of scar wall to wall, but overall patent vein due to recanalization.

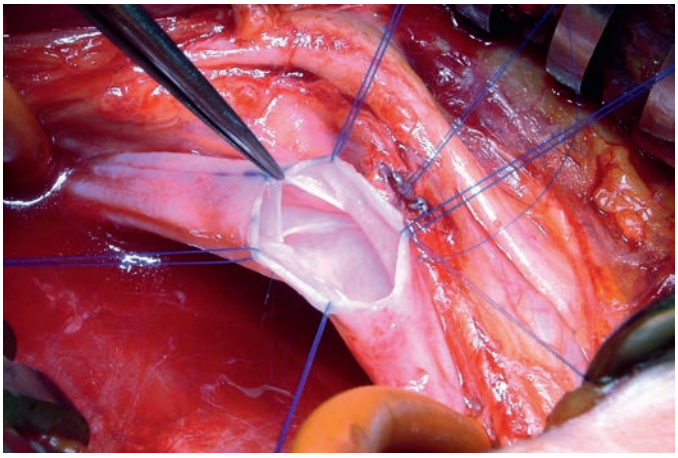

Figure 159.3 Thickened valve in relation to very thin and almost transparent valve noted in Fig. 159.1.

vein thrombus, resulting in minimal damage.[19] Alternatively, the valve itself may not be directly involved in the thrombotic process but affected by thrombotic damage in other locations (proximal or distal).[19-21] Potentially the thickened, noncompliant vein wall resulting from DVT may cause local cusps to become floppy by virtue of a decrease in wall diameter.[11] The valve remains architecturally intact, thin, compliant, and amenable to direct repair.

Hemodynamics

To realize the goal of controlling lower limb venous ambulatory hypertension, correction of deep axial reflux proximal to the calf is required (see Chapters 9 and 156). However, an isolated femoral vein valve reconstruction could be correlated with clinical failure when profunda femoris vein reflux is also present.[22] Conversely, when the profunda system is competent, repair of femoral vein incompetence does improve lower limb venous hemodynamics, since both major collateral pathways are then competent.[22,23] In some cases of femoral vein occlusion, there

is tremendous dilation of the profunda femoris vein such that only correction of reflux in it will be correlated with an improvement in venous hemodynamics (Fig. 159.4).[24] An alternative method of correcting significant axial reflux when both femoral systems are incompetent is to position a competent valve in the popliteal vein (a gatekeeper position).[25-27] At least one investigator has performed multiple tibial vein valve repairs to accomplish the same goal.[28]

DIAGNOSTIC EVALUATION

History and Physical Examination

Patients with CVD due to deep venous incompetence can present with clinical class C0 to C6 (based upon the CEAP classification) with or without associated symptoms.[29] Physical examination and evaluation of venous reflux using a simple handheld Doppler unit are considered the first step in a complete venous patient evaluation (level of investigation I).[29] In those patients with an ulcer, an arterial pulse examination and measurement of ankle-brachial index are critical to rule out the presence of arterial occlusive disease (grade 1, level of evidence B).[30]A careful history should take note of previous episodes of DVT, known hypercoagulable conditions, and any limitations in physical and occupational activity resulting from venous insufficiency. Importantly, the physical examination can eliminate other causes of the patient's symptoms, such as ischemic ulcers, diabetic ulcers, dermatologic disorders, and even skin or soft tissue cancer. A detailed list of potential causes of leg ulcers can be found in a recent review.[30] Each patient should ultimately be stratified according to the CEAP classification to clearly define the venous disease present, which will allow the formation of a focused and appropriate management strategy.[31] Candidates for deep venous valvular reconstruction typically have class C4b to C6 disease, or disabling signs and symptoms such as severe edema (C3). An in-depth extension of the clinical classification (Venous Clinical Severity Score) provides a quantification of disease severity and is a useful evaluation tool to determine a patient's response to treatment.[32] Quality-of-life surveys provide an estimation of the impact of venous disease on the patient's life and the effect that therapy has on the patient's overall well-being.[33] Performance of these evaluations is considered best practice as expressed in the Society for Vascular Surgery guidelines, a grade 1 recommendation for all classes of venous disease and critical to determining treatment success.[30,34]

Figure 159.4 Axial transformation of the profunda femoris vein. Note the remnant of the thrombosed femoral vein in the distal part of the thigh. (From Raju S, Fountain T, Neglén P, Devidas M. Axial transformation of the profunda femoris vein. *J Vasc Surg.* 1998;27:651-659.)

Noninvasive Evaluation

A complete venous duplex evaluation (see Chapter 23) comprises the major component of level of investigation II, which is defined in the CEAP classification as the next step following the basic physical examination and handheld Doppler (level of investigation I). Duplex evaluation is required prior to any interventional procedure (grade 1/level of evidence A/B).[29,30,34] It is essential to clarify the extent and anatomic location of all venous disease, to provide some indication of the etiology (congenital, primary, or secondary), and to aid in determining the pathophysiologic mechanism (reflux, obstruction, or both) of the disease present. The imaging is often so clear in primary deep venous incompetence that venous valve cusps can be seen moving in the venous stream (Fig. 159.5). Insufficiency within any segment of the deep venous system is defined as a prolonged reflux time through the valve after a provocative test. The recommended cutoff value for abnormal reversed flow (reflux) is 1 second in the femoropopliteal veins and 500 milliseconds for the deep femoral and tibial veins.[35,34] Venous obstruction is seen as

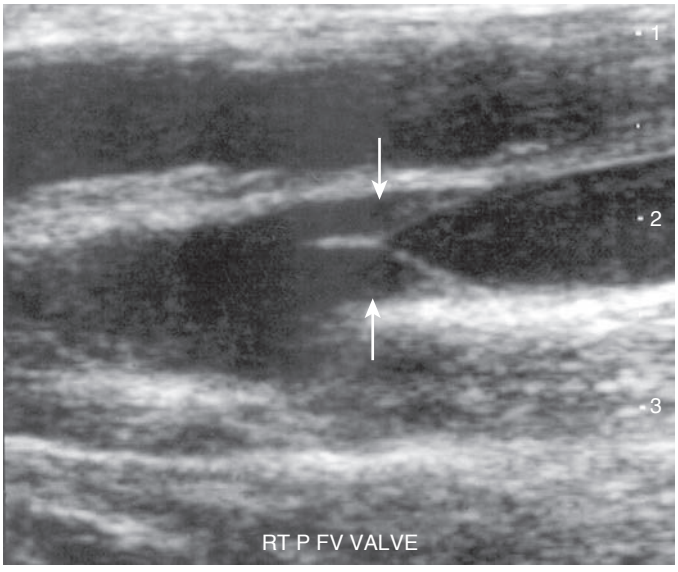

Figure 159.5 Duplex image of a complete and competent valve with both cusps easily identified.

thickened, scarred, and constricted veins or valves with poor flow and diminished augmentation after distal or proximal compression. Respiratory variation can be lost as a consequence of local disease or proximal obstruction or stenosis.

Plethysmography (see Chapter 22) can be utilized to provide an overall quantification of the impact of deep venous insufficiency before deep venous valvular reconstruction and to provide some insight into the effectiveness of treatment. Air plethysmography can quantify the efficiency of the calf muscle pump. The latter represents a crucial factor in deep venous reconstructive surgical outcomes.[36] Plethysmography is used for specific indications in patients with advanced disease or as a research tool (grade 2, level of evidence B) and can be part of a level of investigation II evaluation.[37,34,30] Air plethysmography provides a quantitative estimate of venous insufficiency in the form of venous filling index (abnormal >2 mL/s), and the residual volume fraction (abnormal >35%) has a linear correlation with ambulatory venous pressure measurements. The ejection fraction correlates with the efficiency of the calf muscle pump; a value of less than 60% is considered abnormal.

Invasive Evaluation

For patients being readied for deep venous valvular repair, venography aids in precise operative planning if no other less invasive modality can provide the same detail. Ascending venography (see Chapter 26) defines deep venous system anatomy, eliminates obvious obstruction as a factor, and provides a means of selecting the most disease-free portion of the appropriate venous system when valve transplantation is an option.[11,38] Ambulatory venous pressure with or without thigh tourniquet and venous reflux time can be measured if desired.[11,38,39,40] The importance of significant iliac vein occlusive disease is determined best by the use of intravenous ultrasonography,[40] especially when venography is not diagnostic despite multiplanar imaging. Descending venography (see Chapter 26) is used to determine valve leaflet integrity, anatomic location, and the extent/degree of reflux within the femoral, profunda femoris, popliteal, and tibial veins (Fig. 159.6).[27,41,42,43] It is not uniformly accurate in determining the presence of valvular incompetence, and direct operative inspection remains the "gold standard."[11] However, the combination of venous duplex examination and descending venography provides the best available preoperative determination of valve architecture.

Because they do not assess valve function accurately, magnetic resonance imaging and computer tomography are generally used to evaluate occlusive venous disease rather than candidates for venous valve repair. Each may be useful in detecting extrinsic compression, especially at the iliocaval level. These types of studies constitute those included in level of investigation III and are generally reserved for those with more advanced and complicated venous disorders.[29]

Evaluation of the patient with suspected venous disease follows a standard process in clinical practice. The patient's examination (including handheld Doppler investigation of the lower leg venous system) and history confirms the presence of disease, the clinical classification (C of CEAP), and the potential etiology (E of CEAP). The addition of venous duplex imaging (with or without plethysmography) provides level II diagnostics and confirms the clinical impression. It identifies the location of disease and the types of veins involved (superficial, perforator and/or deep, the A of CEAP), and whether the underlying pathophysiology is due to reflux, obstruction, or both (P of CEAP). The investigation often stops at this point if superficial/perforator disease is a prominent component of the disease process, and the superficial and/or perforator disease is treated. If the patient has recurrent problems, a more in-depth investigation for proximal (iliofemoral) venous occlusive disease is often undertaken, with invasive imaging (venography with intravascular ultrasonography). Investigation has advanced to diagnostic level of investigation III when these studies are chosen. If present and the symptoms are sufficiently severe, angioplasty and stenting of the affected vein is undertaken. If the superficial/perforator and the proximal deep venous occlusive disease has been managed successfully, and deep reflux remains the pathophysiology of the disease process as demonstrated by a combination of dedicated duplex imaging and descending venography, the appropriate valve repair is accomplished as noted in the following text.

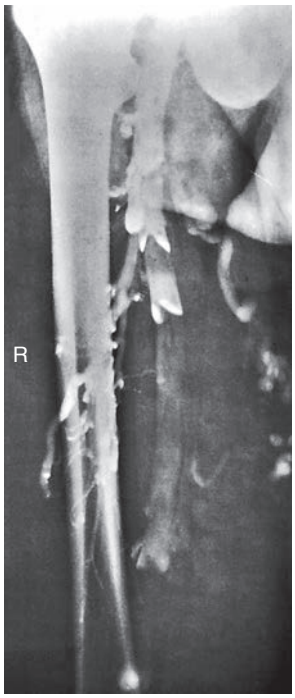

Figure 159.6 Descending venogram demonstrating the presence of valves with architecturally preserved cusps available for in situ repair.

TREATMENT SELECTION

Natural History and Patient Risk Assessment

Patients being considered for deep venous valvular repair have generally undergone previous evaluations and treatment of superficial venous disease that have failed to resolve their signs and symptoms. Thirty-three percent of patients with primary deep venous incompetence and 70% of those with

postthrombotic syndrome will experience ulcer recurrence, suggesting that their deep venous disease should be treated.[7] An algorithm for the surgical care of patients with venous ulcers, which can be extrapolated to all those who might benefit from deep venous valve repair, is found in a recent societal guidelines manuscript (Fig. 159.7).[30] Valvular reconstruction is relegated to later in the algorithm due to an increased risk to benefit ratio.

Patient risk assessment must follow the tenets of any open operative intervention. Hemodynamic instability from the operation is minimal, but because the operative intervention is time-consuming and technically challenging, general anesthesia is typically required. An acceptable cardiac and pulmonary status is required. Systemic infection should be treated before intervention. The presence of systemic disease that may impact healing, such as collagen vascular disease, diabetes, chronic renal insufficiency, or lower extremity arterial occlusive disease, is a relative contraindication to venous intervention unless it is corrected or medically optimized first.

Treatment Options

The treatment options available to correct deep venous valvular reflux are determined by the availability of structurally intact but incompetent venous valves. Selection of the operative technique when the valve cusps are preserved is determined by the degree of cusp prolapse, the surgeon's preference, and the reported long-term success. In the case of valve prolapse secondary to vein wall dilation only, decreasing the vein diameter may reestablish a competent valve. In such cases, external banding

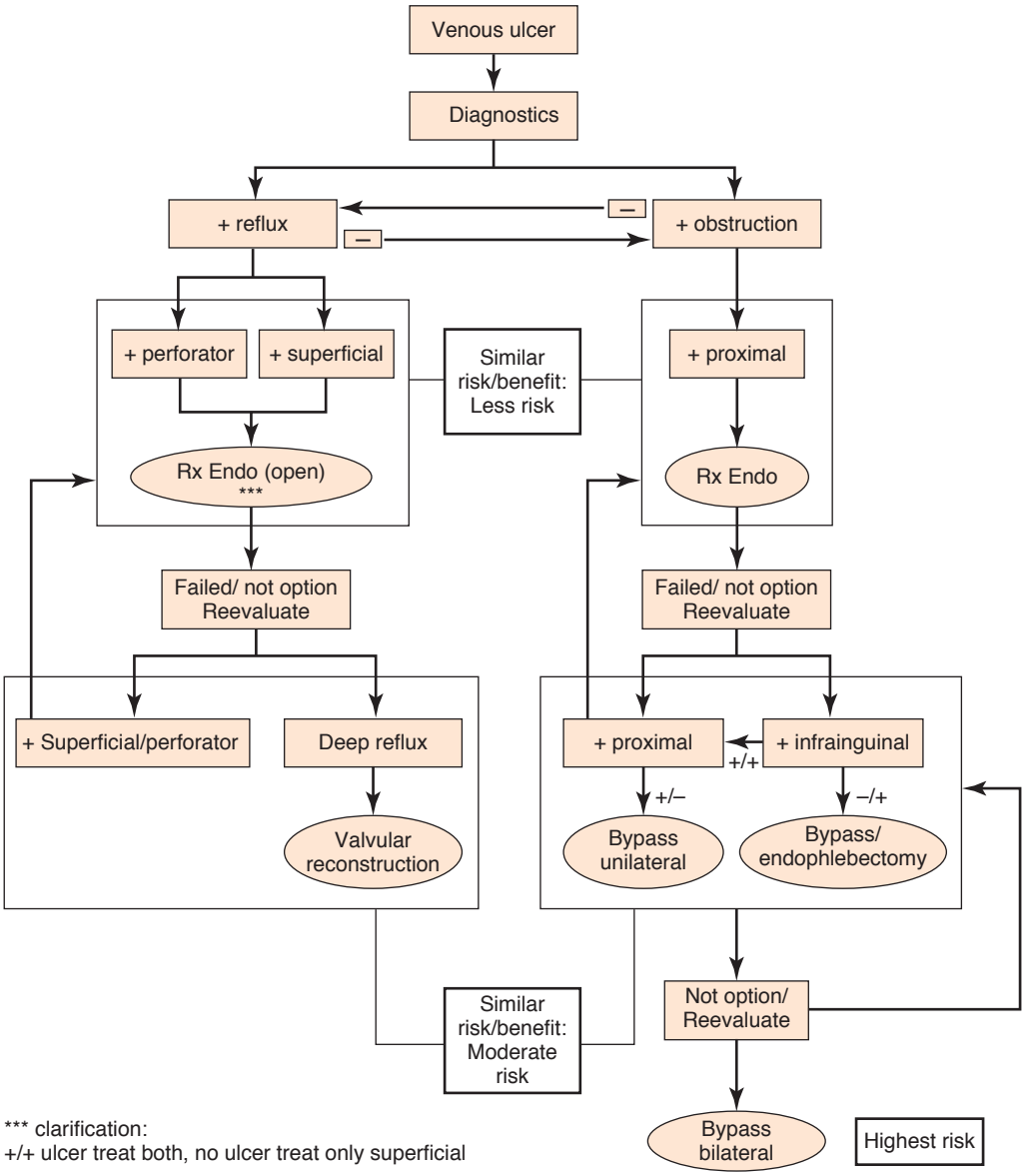

Figure 159.7 Proposed algorithm for operative and endovascular treatment of patients with venous leg ulcer based on involved anatomic venous system and presence of venous reflux or obstruction. The risk-to-benefit ratio is weighed for those procedures with more risk (lower, moderate, higher) considered later in the treatment when the benefit is similar.

of the vein may provide a workable solution to prevent reflux, although there is some question as to long-term success.[44] When wall dilation with more pronounced cusp prolapse is present, external valvuloplasty will provide a way to decrease wall diameter, and techniques are available that can simultaneously enable reefing of the valve cusps. With pronounced valve leaflet prolapse, internal valvuloplasty allows direct cusp leaflet shortening in addition to wall diameter reduction. When there is no identifiable valve structure within an incompetent system, two potential options are available. If a parallel axial system has a competent valve or one that can be made so, a transposition procedure is an option. When this is not feasible, valve transplantation of a competent valve from a distant location remains an option. Valve substitutes using autogenous tissue are a final option. Quests for a percutaneous option or valves made of nonautogenous tissues have not been successful to date. In some instances, intervention in two or more separate axial venous systems (e.g., the femoral and profunda femoris veins) or into the popliteal location will be required to prevent axial reflux into the end-organ, which in this case is the calf and ankle soft tissues/skin. Multiple valve repairs in the same incompetent axial system (e.g., two or more in the femoral vein) are being investigated in the hope of decreasing recurrent reflux and thus symptoms[28,45-47]; however, other surgeons have reported success when only one valve per incompetent system is repaired.

Recent societal guidelines suggest that in select patients with clinical class C4b, C5, and C6 disease, valve repair (internal valvuloplasty, external valvuloplasty, external banding), valve transposition or transplantation, and/or autogenous valve substitutes can aid in venous leg ulcer healing and prevent recurrence in addition to standard compression therapy (grade 2, level of evidence C).[30]

SURGICAL TREATMENT

Relevant Anatomy

The common femoral, profunda femoris, and femoral veins are covered by skin, soft tissue, and fascia in the groin and by the sartorius muscle more distally. Just proximal to the knee, the femoral vein occupies the adductor (Hunter) canal, which places it deep to the sartorius and flanked by the vastus medialis and adductor longus muscles. Distal to the adductor canal, the femoral vein becomes the popliteal vein and lies between the heads of the gastrocnemius muscle distally but is covered only by skin, soft tissue, and fascia directly behind the knee. The anterior tibial veins lie in the anterior calf compartment deep to the anterior tibialis muscle. The posterior tibial and peroneal veins lie in the deep posterior compartment and are covered by the soleus and gastrocnemius muscles, which form the superficial posterior compartment.[48]

Valves are universally present in the paired tibial and peroneal veins, with 3 to 12 valves evenly distributed in each vein.[49] The majority of popliteal veins (>90%) have one to three valves, with a slight trend to be located more caudal in the leg.[49] The femoral veins have one to five valves.[49,50] In about 90% of patients, the most constant valve location is in the proximal femoral vein 1 to 2 cm distal to its confluence with the profunda femoris vein.[49-51] In 88% of patients, the profunda femoris vein has one to four valves.[49] The common femoral vein often has no valve present, but in 30% to 50% of patients it may have one or even two valves within a few centimeters of the inguinal ligament.[49-51]

Operative Planning

In the event that an intact but incompetent valve has been confirmed by preoperative imaging, most experienced surgeons choose the proximal femoral vein for valvuloplasty or to repair both the femoral and profunda femoris valves if both systems are incompetent. This decision is based on the ease of exposure, proximity of the valves, familiarity with the approach, and size of the veins available for repair. When both the proximal femoral and profunda femoris valves are incompetent, some have chosen repair of the popliteal vein valve, which is considered the "gatekeeper" to the lower leg venous system.[25,52] However, mid or distal femoral vein valves can be repaired if they are surgically accessible and amenable to valve repair. As one proceeds more distally in the venous system, vein diameters and valve leaflets become smaller and thus more difficult to repair. Nevertheless, even tibial vein valves have been successfully repaired.[53] If a transposition operation is planned, appropriate imaging must have identified the presence of a competent valve. Valve transplantation requires having identified an architecturally preserved competent valve in the axillary or brachial vein. The vein with the intact valve is removed with proximal and distal ligation of the donor vein, which is well tolerated in the upper extremity venous system. The optimal place for implantation into the lower extremity is into the least damaged vein segment available, which will prevent axial reflux into the calf area. If transposition or transplantation is not an option, an autogenous alternative such as a neovalve may be advisable. The neovalve technique uses autogenous tissue to make a valve structure. The optimal site for this type of surgery is the proximal part of the femoral vein, but the choice depends on the vein's features, such as intraluminal fibrosis, which determines a double channel and can help in creating the neovalve.[54-57]

Prophylactic antibiotics are given during the procedure (e.g., first-generation cephalosporin) and are continued postoperatively for 2 or 3 days by most surgeons.[58,45,59] Intraoperative heparin is commonly given when venous occlusion is required; a typical dose is 2000 to 10,000 units, which is not generally reversed.[41,58,45,59,53,60]

Techniques

Overall Exposure

If reconstruction of the proximal femoral veins (femoral or profunda femoris) is the goal, a groin incision is made in the direction of the vessels to expose the first and second femoral valves.[49] Further dissection through the fascia that lies beneath the sartorius muscle will expose the profunda femoris vein if necessary. After exposure of the targeted valve and sufficient vein proximal and distally to see the valve well, the strip test

should be performed to evaluate for valve competence. This test entails milking blood antegrade past the valve while inflow is occluded, with subsequent application of retrograde pressure against the valve. Reflux is demonstrated by refilling of the vein distally. This incision may also provide exposure for valve transposition, transplantation, or neovalve, if required.

After identification of the valve station to be repaired, careful adventitial dissection to identify the valve attachment lines is useful (Fig. 159.8).[53] This dissection facilitates proper placement of the venotomy, when required, so as not to damage the valve leaflets, and verifies that the valve is present and available for repair. A lack of valve attachment lines requires alternative valvuloplasty techniques, but can also signify destruction of the valve suggesting the need for techniques other than in situ repair.[53]

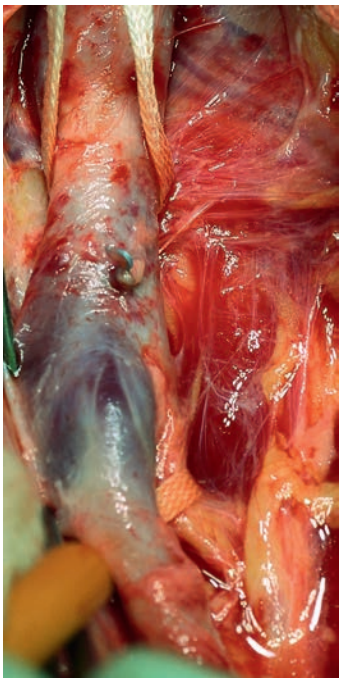

Figure 159.8 The white line clearly visible in this operative photo shows the cusp insertion site prior to opening the vein.

In other situations, a more distal femoral, popliteal, or even tibial vein may be the desired location for valve repair or transplantation. In these situations, the medial exposure is much like that used for exposure of the like-named artery.[48] The popliteal vein can also be exposed through an S-shaped incision in the popliteal fossa, with the transverse portion made in the knee crease to decrease the chance of scar contraction.[48]

Internal Valvuloplasty

The open method of direct valve cusp tightening (reefing) has been the mainstay for correction of primary deep venous valvular reflux. This technique involves venotomy and suturing of the elongated valve leaflets under direct visualization. The redundant valve cusps are plicated to the vein wall with interrupted 6 or 7-0 polypropylene suture to allow proper alignment of the cusps. In 1968, Kistner was the first to report success using a longitudinal venotomy extending through the valve commissure (Figs. 159.9A and 159.10).[61] Raju later described a supracommissural approach in which a transverse venotomy was performed at least 2.5 cm above the valve, staying away from the delicate valve itself (see Figs. 159.9B and 159.11).[62] Sottiurai described a combination approach in which a supravalvular transverse venotomy with distal extension into the valve sinus (a T-shaped venotomy) was used (see Fig. 159.9C).[63] The "trap door" approach of Tripathi and Ktenidis involved two transverse incisions on the vein connected by a single vertical incision (see Fig. 159.9D).[64] Regardless of the approach, suturing of the valve leaflets remains essentially the same (Fig. 159.12). It is estimated that plication of approximately 20% of the length of the valve leaflet can restore valve competency in the majority of cases (Fig. 159.13).[65]

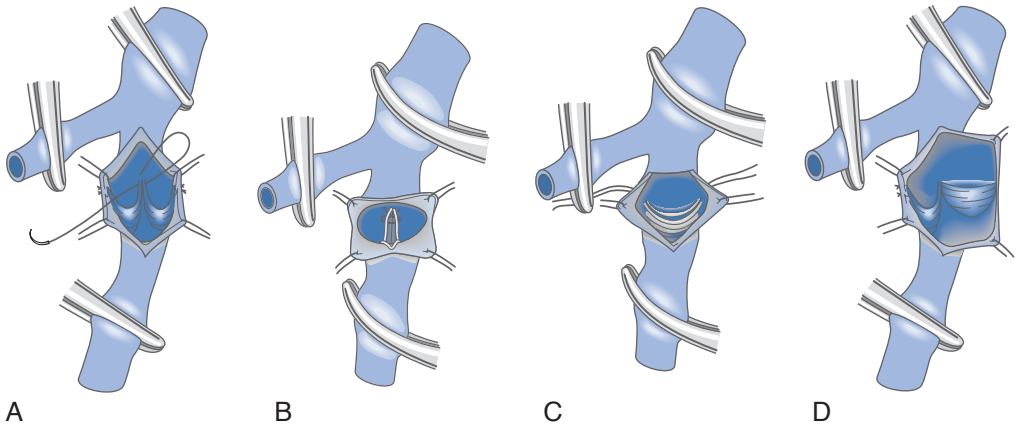

Figure 159.9 Internal valvuloplasty can be accomplished by a variety of techniques used to visualize the incompetent valve leaflets. (A) Artist's representation of the method first proposed by Kistner, in which he opens the vein through the anterior commissure. (B) Representation of the method of Raju, who uses a supravalvular transverse venotomy to view the valve from above without incising through the valve commissural angle. (C) Representation of the method of Sottiurai, who performs a supracommissural incision with extension toward a cusp sinus to improve visualization. (D) Representation of the technique used by Tripathi, who uses a "trap door" incision to provide optimal visualization of the valve cusps for repair. The method of reefing the valve to reestablish a competent valve is essentially the same in each instance.

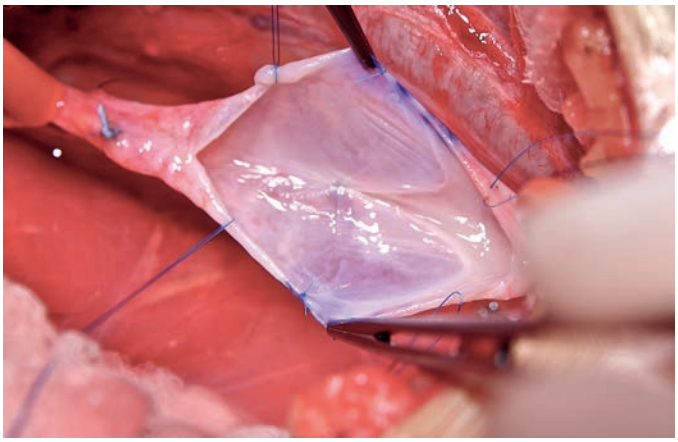

Figure 159.10 This operative photograph shows the vein opened by the technique of Kistner to visualize the valve cusps to be repaired.

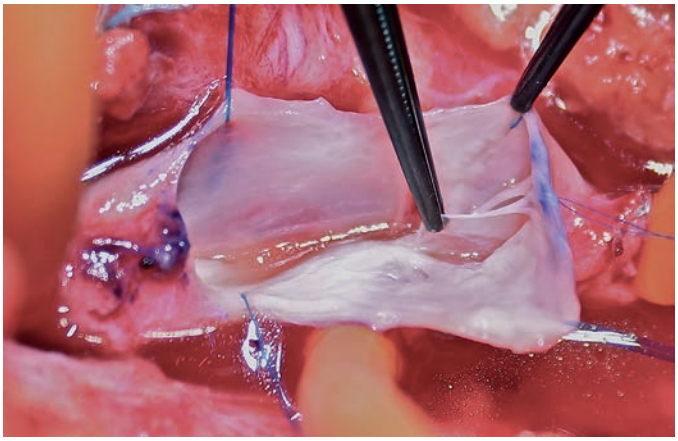

Figure 159.11 This operative photograph demonstrates the vein opened via the technique of Raju, with valves seen below the vein incision.

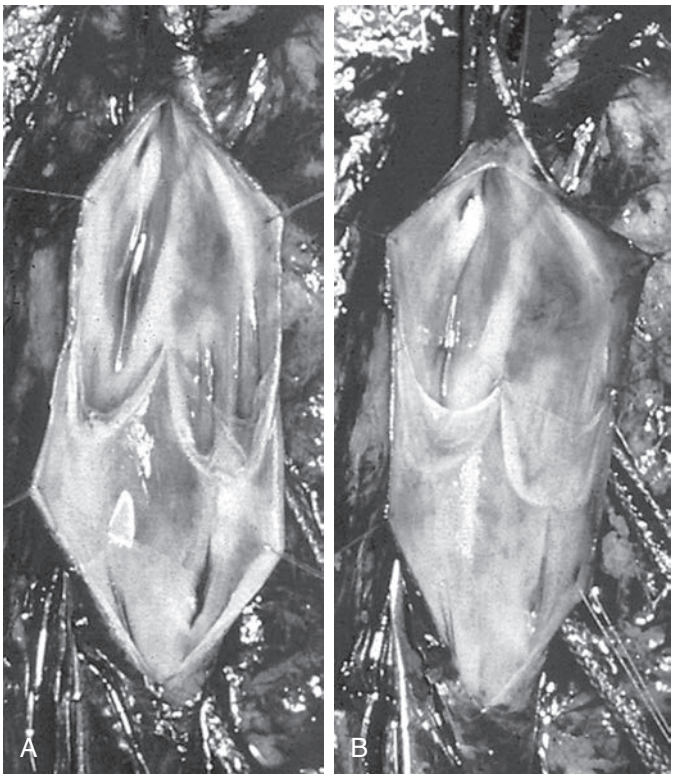

Figure 159.12 The method of Kistner is shown in these operative pictures before valvuloplasty (A) and after valvuloplasty (B). Note the laxity of the incompetent valve before intervention, whereas after reefing of the valve cusps, the normal architecture and tension are reestablished. (Courtesy Dr. Robert Kistner.)

External Valvuloplasty

The technique of external valvuloplasty was pioneered by Kistner and reported in 1990 (Fig. 159.14).[66] This approach offers the advantage of valve repair without a venotomy. It is performed by placing interrupted sutures transmurally through the valve attachment lines, which on tying leaves a decreased commissural angle, competent valve, and reduced vein diameter. Others have used a running suture to accomplish the same effect.[53] Both anterior and posterior plication can be performed. Combining this technique with angioscopy to determine the effect of limited anterior valve plication using interrupted transmural externally placed sutures has demonstrated improvement in clinical symptoms, hemodynamics, and valve competence in a limited number of patients.[60,67] A modification of external valvuloplasty involves the transluminal placement of sutures to reef the valve leaflets and to narrow the vein wall, much like internal valvuloplasty but without opening the vein. Gloviczki and colleagues reported using an angioscope to directly view the valve cusps during repair (Fig. 159.15).[68] A side branch of the great saphenous vein allows introduction of the angioscope, which is then advanced from above for optimal visualization. Interrupted external sutures are seen entering the venous lumen and

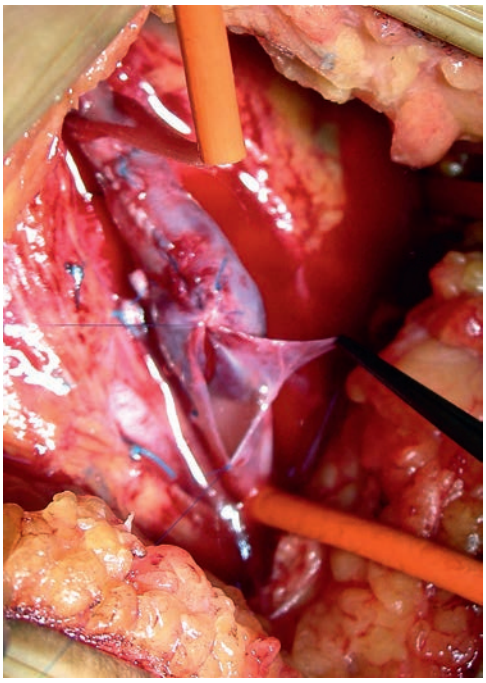

Figure 159.13 This intraoperative photograph confirms valvuloplasty competence; after the proximal extent of the incision has been closed, release of the proximal clamp shows that the valve prevents retrograde flow with no blood visible in the distal open vein.

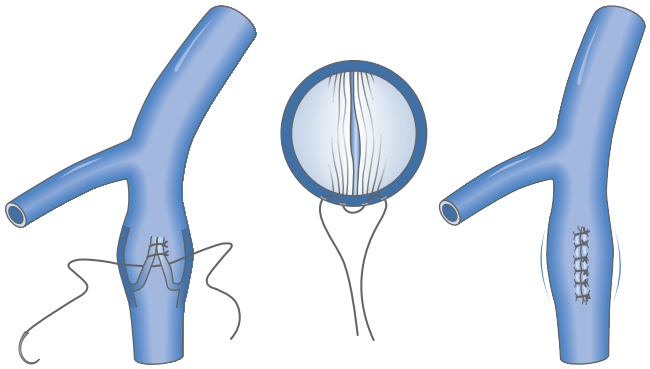

Figure 159.14 Artist's rendition of the method of external valvuloplasty. The enlarged venous diameter results in valve incompetence. Note how the placement of sutures decreases the diameter of the venous wall but protects the valve cusps. The sutures lie outside the vein lumen in this approach.

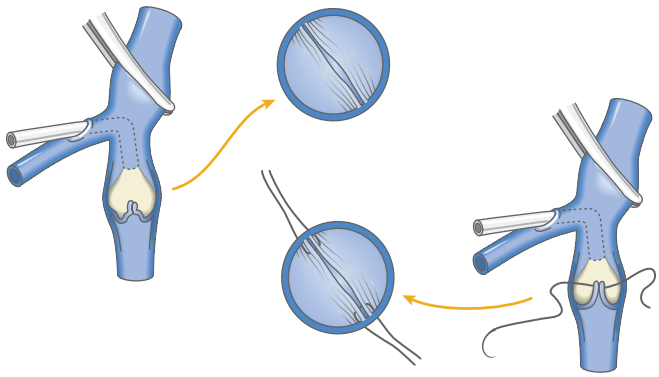

Figure 159.15 As an improvement to "blind" placement of sutures in the method of external valvuloplasty, the use of an angioscope, as suggested by Gloviczki and coworkers, allows precise suture placement within the vein lumen for tightening (reefing) of the valve cusps.

precisely placed to attach the cusps to the vein wall at the attachment line. After a learning curve, the use of the angioscope might not be required to achieve the same effect.[53] However, Raju and colleagues believe that identifying the valve cusp attachment lines externally with the use of adventitial dissection is critical to technical success. Fig. 159.16 demonstrates this technique (transcommissural valvuloplasty).[45] A continuous suture can also be used to accomplish the repair.[58,47] Limited anterior plication, a modification of this method, involves anterior vein dissection and placement of a running mattress suture at the anterior commissure, which runs from a point 3 to 4 mm proximal to the angle of the valve cusp insertion lines up to the angle of the valve cusp insertion.[69] About 3 mm of the vein wall is incorporated into the stitch to adequately approximate the cusps.[69] Limited anterior plication was developed with the aim of decreasing vein dissection and potentially reducing the progressive dilatation of the postrepair vein that occurs after some cases of valvuloplasty.[69] It has been used most commonly in conjunction with saphenous vein stripping and limited to the femoral vein valve.

External Banding

This method has most commonly been used in cases in which dissection vasospasm renders an incompetent valve spontaneously

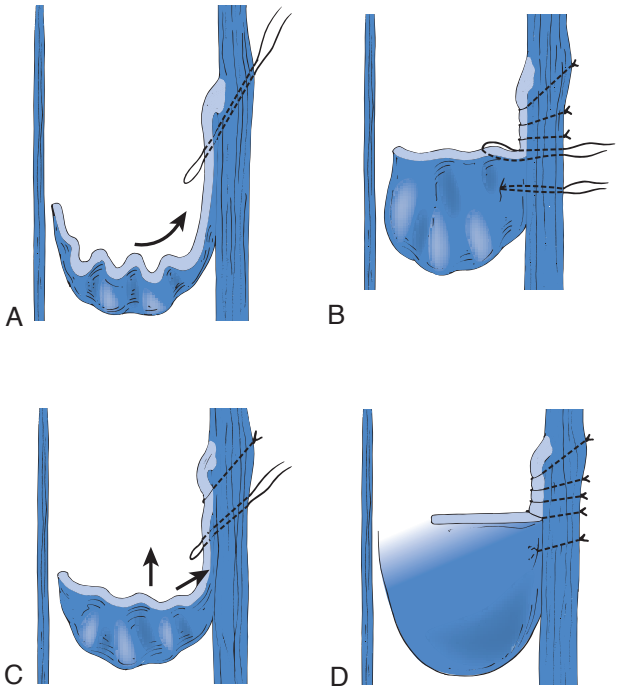

Figure 159.16 The initial through-and-through oblique transluminal suture placed at the commissural apex catches sagging leaflets and resuspends them. (A-D) Transluminal sutures, with each successive suture biting deeper and less oblique than the suture above to pull up the valve, tighten the cusp edges, deepen the sinus, and appose the valve attachment lines. Each suture is tied before the next is placed. One or two of the most caudally placed sutures may pass through the body of the leaflet rather than through the edge, with no subsequent ill effects. (Redrawn from Raju S, Berry MA, Neglén P. Transcommissural valvuloplasty: technique and results. *J Vasc Surg*. 2000;32:969-976.)

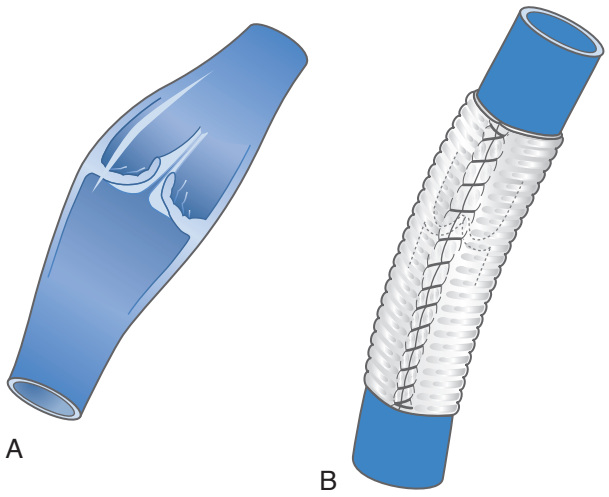

Figure 159.17 Artist's depiction of external banding to prevent venous valvular incompetence in veins that become competent during the vasoconstriction that occurs at the time of operative dissection. Some surgeons use this technique to prevent dilation after valve transplantation or other types of repair. (A) Incompetent valve before banding. (B) After banding, the valve is competent.

competent. An external sleeve made of synthetics is wrapped around the circumference of the vein at the site of the valve. It is tightened to reduce the size of the vein lumen until valve competence is achieved (Fig. 159.17). The sleeve is then anchored in place to the adventitia by sutures to avoid migration. One

investigator uses a specifically designed cuff.[59] One report described the use of a spiral device screwed around the outside of the vein to decrease the diameter until endoscopic confirmation of valve competence.[70]

Several investigators have added an external band at the conclusion of valvuloplasty (any type) to prevent delayed dilation.[58,45,71] Others have abandoned this approach because of concern for scarring with resulting valve failure.[46,72] Alternatively, it may be that modifying the valve sinus shape negatively impacts valvuloplasty outcomes, and this theory may merit future evaluation for all types of venous valve interventions.

Valve Transplantation

Venous valve transplantation provides a technique that can be used when the valve cusps have been destroyed. This procedure was first described clinically by Taheri and colleagues.[73] A 2- to 3-cm segment of upper extremity vein containing a competent valve (or one that can be made competent) is first removed. Other investigators have utilized great or small saphenous veins as the valve donor.[74] The incompetent femoral vein system is approached just distal to its junction with the profunda femoris vein, and the axillary vein segment is sutured in place after removal of an appropriate length of femoral vein. The proximal anastomosis is often accomplished first to confirm valve competency and to allow distention and lengthening of the vein to facilitate the distal anastomosis (Fig. 159.18). In trabeculated postthrombotic veins, Raju and coworkers have described excision of intraluminal synechiae to create a single lumen suitable for implantation.[75] Interrupted sutures are preferred to avoid suture line stenosis.[65] Valve competence is determined by the intraoperative strip test. An external sleeve can then be placed around the segment to prevent later dilation of the segment.[53,65,71] Because approximately 40% of axillary vein valves are incompetent at the time of explantation, bench repair may be required.[53,65] However, more proximal or distal valves in the upper extremity that are de novo competent should be sought before resorting to this added surgical intervention. Should bench repair be necessary, external or internal valvuloplasties have achieved success.[53,76]

Valve Transposition

If a single groin axial venous valve is spared from reflux, a transposition procedure can be performed by placing the incompetent venous system distal to the competent valve. Most commonly, the femoral system is incompetent and the profunda femoris valve remains competent. The incompetent femoral vein can be transected and reimplanted distal to the competent profunda valve (Fig. 159.19). Alternatively, the incompetent femoral system can be placed below a competent valve in the great saphenous vein (Fig. 159.20). When the profunda femoris valves are incompetent, the profunda femoris vein can be placed distal to a competent valve in either the femoral vein or the great saphenous vein. A technique has also been described for transposition of an ipsilateral valve (competent great saphenous vein to the femoral vein and subsequent ligation of the femoral vein proximally [distal to its junction with the profunda femoris vein]) to escape problems with diameter mismatch.[77]

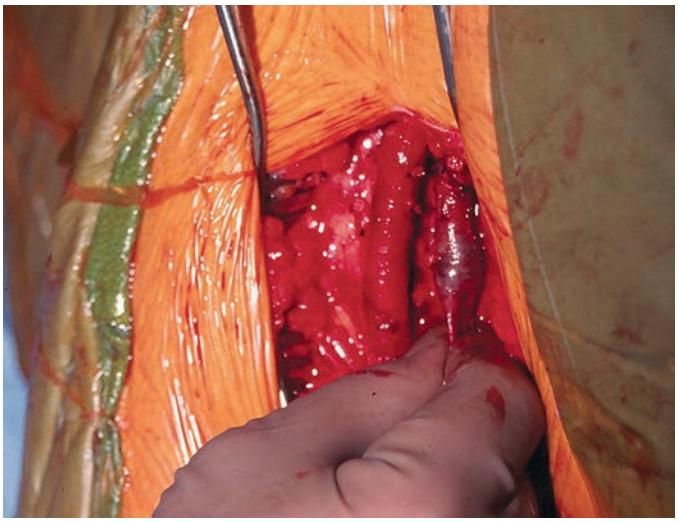

Figure 159.18 This intraoperative picture shows a valve transplant with the proximal anastomosis complete. Any fluid or blood was pushed forward from the distal vein past the valve, and the valve is competent, allowing vein elongation and therefore proper positioning of the distal anastomosis. A similar maneuver is performed when a "strip test" is used to confirm valve competence. During a "strip test" the vein distal to the valve is occluded (in this case by the surgeon's fingers but may be by a vascular clamp or forceps) and the blood is pushed or milked from the vein distal to the valve-containing vein segment. As blood is allowed to refill the vein, if the valve is competent, blood will not reflux and therefore not be present in the vein distal to the valve.

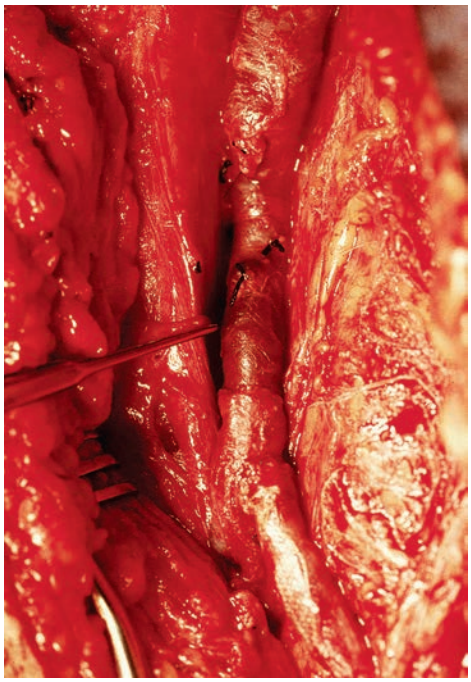

Figure 159.19 Note the competent valve (forceps point to the area) beyond which the incompetent venous system has been placed in this operative picture of valve transposition.

VENOUS VALVE SUBSTITUTES (NEOVALVE)

Valve substitutes could address difficulties in treating patients with deep venous valvular insufficiency that have no autogenous valves available for repair or transplantation. Various attempts using synthetics, xenografts, and allografts have been studied experimentally and, in some cases, reached clinical trials but without success.[78,79,80,81,82,83,84,85,86,87,88,89,90] A more in-depth discussion of these past experiences and some aspects of the endovascular experience can be found in Chapter 60 of the 8th edition of Rutherford's and in a review article.[91]

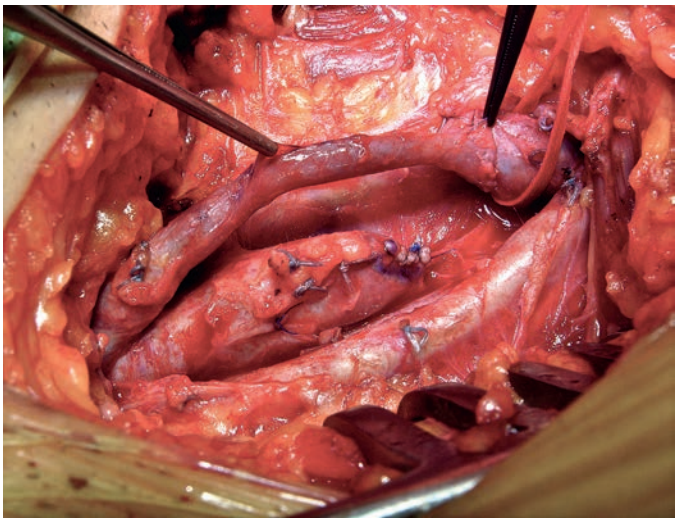

Figure 159.20 This is an operative photograph of a transposition operation using a saphenous vein with a competent valve. The saphenous vein is transposed into the subfascial area, and it is sewn in the distal femoral vein in an end-to-end fashion thereby creating a new competent axis. The suture line to the right in the photo is the oversewn proximal femoral vein. The proximal saphenous vein joins the common femoral vein to the right in this photo.

Valves constructed by invaginating an autogenous vein into itself by the method of Eiseman and Mallette have shown experimental promise but have not been studied clinically.[92,93] However, the use of autogenous tissue to reconstruct valves has been relatively successful in small series.[53] These procedures involve the use of a piece of autogenous vein as a donor. Semilunar cusps were fashioned out of a donor vein after trimming the adventitia and part of the media, and the tissue was sutured into the recipient vein with the nonendothelial surface directed toward the lumen.[53] The study has not been repeated, but good clinical results were noted in this small series. Another attempt to use autogenous vein as a valve substitute has been reported by Plagnol and associates.[94] In this approach, a stump of the great saphenous vein is invaginated into the femoral vein to fashion a bicuspid valve.

Maleti and colleagues reported a technique for constructing a bicuspid or monocuspid venous valve by dissecting the intimal-medial wall of the thickened postphlebitic vein to form the cusp or cusps (Fig. 159.21A and B). An ophthalmic knife was used to divide the vein wall into one or two sheets to fashion the valve cusps. The initial seven cases did well.[54] By 2006, 18 venous valves were constructed in 16 patients with recurrent or nonhealing venous ulcers to treat chronic deep venous insufficiency secondary to the postthrombotic process.[55] The patients received anticoagulation for 6 months. Maleti's most recent improvement has been to place two sutures on the cusp or cusps to hold the valve in the semi-open position and thereby prevent valve collapse (Fig. 159.22) and improve competence (Fig. 159.23).[56] Some excellent intraoperative images and illustrations can be found in a review article by Maleti and Perrin.[57] This interesting work has been verified by at least one investigator to date.[95]

A hybrid approach championed by Opie involves invaginating a cuboidal piece of the vein wall, still attached at its caudal edge, into the vein lumen, with two sutures attached to the cephalad edge to prevent complete reflux of the flap into the distal vein, thereby forming a monocuspid valve. The opening

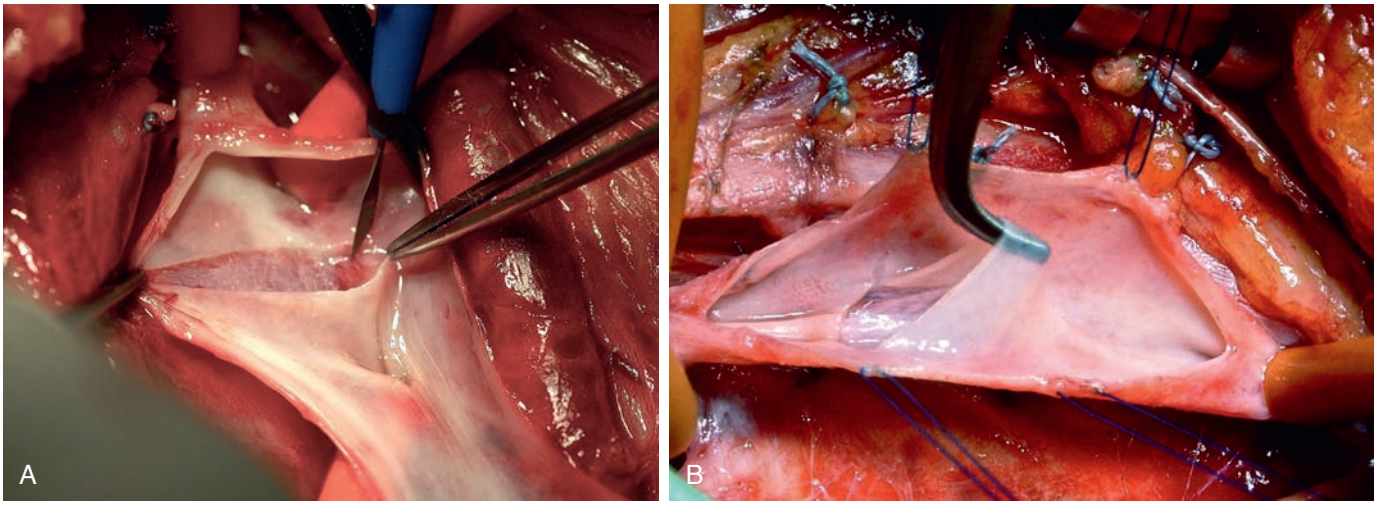

Figure 159.21 This is a neovalve construction being performed by Dr. Maleti with the first photo (A) demonstrating the use of an ophthalmic knife to construct the valve and (B) a bicuspid valve in another patient with the second leaflet yet to be constructed.

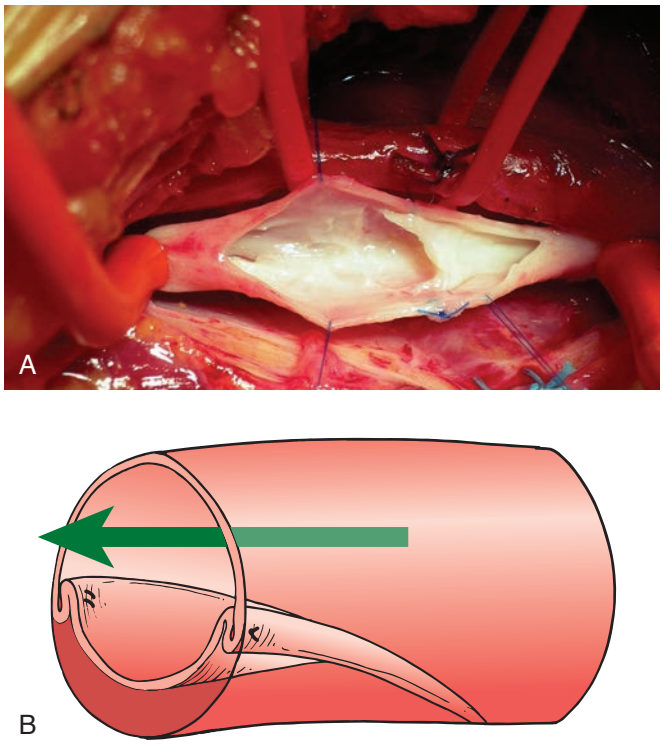

Figure 159.22 (A) This intraoperative photograph shows a monocuspid valve made from the inner wall of a postthrombotic vein with a fine ophthalmic knife. Two sutures *(blue color)* are placed near the outer edges to keep the valve from collapsing while at rest. (B) Artist's depiction of how the monocuspid valve does not completely collapse against the nonluminal wall during antegrade venous flow. The arrow demonstrates the direction of normal venous blood flow toward the heart during exercise.

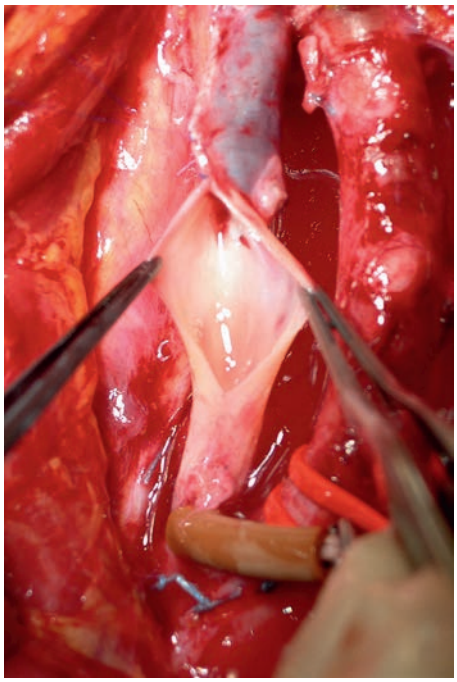

Figure 159.23 Intraoperative photograph demonstrating neovalve competence; the proximal vein is closed past the constructed neovalve; with release of the proximal clamp, the distal vein is free of refluxing blood.

in the vein wall is repaired with a specially designed and flexible expanded polytetrafluoroethylene patch.[96] It is difficult to explain how the valve can prevent all reflux since it is open on both sides, but sufficient reflux must be prevented to produce a clinical effect. Investigators from Russia have reported an 80% clinical improvement and no recurrent reflux at 8 months of follow-up using this technique.[97]

Endovascular Valve Replacements

There is an interest in repair or replacement of venous valves through a minimally invasive percutaneous "endovascular" approach. Attempts to date have been investigated in terms of hemodynamic outcomes in animal models. Some have been tested in clinical use but are currently without published success.[98,99,78,79,100,80,101,102,103,104,105,106,107,108,109,110]

Postoperative Management

Pneumatic compression devices are applied postoperatively to decrease swelling and the risk of DVT.[41,45,60,71,111] This may also increase flow through the valve repair when the patient is sedentary. Because therapeutic or low-dose intravenous heparin or low-molecular-weight heparin is generally administered postoperatively, closed drainage of wounds may avoid hematoma formation. Anticoagulation regimens include (1) warfarin on postoperative day 1 with an initial target international normalized ratio of 2.0 to 2.5 for the first 6 weeks, and then subsequently decreased to 1.7 to 2.0 until 4 months, at which point it is stopped[45]; (2) "minidose" warfarin, 1 to 2.5 mg/day, for long-term anticoagulation[53,112]; (3) warfarin at therapeutic levels for 3 months[41,46,71,111,113] or 6 months[58]; (4) no anticoagulation in procedures other than open valvuloplasty[60,69]; or (5) therapeutic low-molecular-weight heparin for 3 months.[47] Although many surgeons encourage the use of compressive support after venous valve reconstruction, compliance continues to be problematic.[11,18]

Results

Complications and Initial Results

Valve repair procedures have low morbidity and low (<1%) mortality.[114,58,45,46,53,69,71,115] Hematoma and seroma formation are seen in up to 15% of cases, with some expected variation according to the level of anticoagulation necessary.[18,41,45,46,65,71,72,111] DVT occurs in less than 10% of cases in most series.[18,41,45,59,53,65,71,72] However, this clinical experience may underestimate the actual incidence, because in a series using venographic surveillance at 2 days postoperatively, a 20% rate of DVT was noted. The thrombus was often not occlusive or extensive, nor was there a reported clinical impact.[111] An extensive review including most types of valve repair noted a DVT incidence overall of 12.4%, with 6.7% in those with primary disease but 25.4% in patients treated for postthrombotic insufficiency.[46] An aggressive approach using catheter-directed thrombolysis did result in complete resolution of thrombosis in 60% of cases (three of five) and salvage of the involved valve repair in 50% of cases (one of two).[45]

Pulmonary embolism can occur but is rare. In one series utilizing in-depth surveillance, it occurred in 1 of 129 patients.[45] Wound infections have been seen in 1% to 7% of cases.[18,45,46,53,65,71] Patency and valve competency of all types of repairs within the perioperative period (30 days) are reported as excellent by most investigators. A few series report a less than 1% incidence of early failure.[45,53] Valve leaflet trauma can occur, especially early in one's clinical experience during vertical venotomy, with seven cases reported by one investigator.[46] These injuries were successfully repaired with an 8-0 suture, and 57.1% of cases (four of seven) were competent at 2 years.

Late Results

Internal Valvuloplasty

Kistner and colleagues have monitored their patients who required internal valvuloplasty for decades and have reported life-table results of clinical success (Fig. 159.24). Table 159.1 is a compilation of series reporting success with internal valvuloplasty. It confirms excellent clinical results in patients who would otherwise have experienced unrelenting symptoms as a result of chronic deep venous insufficiency. Valves are competent in 60% to 70% of patients at 5 years in most series.[18,22,27,41,46,62,64,111,113,115,116,117,118] In general, a patent and competent valve translates into clinical improvement, whereas recurrent reflux is associated with clinical failure. A similar comment can be made regarding all types of venous valvular reconstruction.

External Valvuloplasty

External valvuloplasty may be a less durable repair than open valvuloplasty.[27] Much of the current work involving isolated deep venous reflux surgery by various techniques of external valvuloplasty has involved the repair of multiple valves within the same axial system, which can confuse interpretation of the results. Raju's group used the transcommissural technique to repair 179 valves in 141 limbs, with a valve competence rate of 63%, clinical improvement in about 70%, and statistically significant improvement in venous hemodynamics at 3 years.[45] Tripathi and colleagues reported an experience in which standard external valvuloplasty was used in the majority of cases. In 12 limbs, 19 repairs were performed, with a competency rate of 31.6% (6 of 19) and an ulcer-free rate of 50% (6 of 12) at 2 years.[46] One would surmise that six valves in six limbs were still functioning. Rosales and colleagues reported on 17 patients with 3- and 5-year competency rates of 64% and 52%, respectively, but many patients had multistation or multilevel repairs, which makes interpretation of individual results difficult.[47]

The addition of femoral vein external valvuloplasty to superficial saphenous surgery has been an interest of several investigators, probably because of the proximity of the proximal femoral valve during open surgery. Limited anterior plication in combination with superficial venous intervention has demonstrated improved venous refilling time and decreased ambulatory venous pressure at 10 years.[69] Standard femoral external valvuloplasty in addition to superficial saphenous stripping have demonstrated statistically significant improved clinical and hemodynamic results over that achieved with superficial surgery alone.[114] At 3 years of follow-up, 90.9% of valves were competent, with improved venous hemodynamics and venous severity scores. In combination with great saphenous vein ablation, the addition of an external band to the repaired femoral vein was more beneficial in preventing recurrent reflux/symptoms than external valvuloplasty alone.[58] More than 50% of patients had clinical class C5 or C6 disease, and at 5 years the competence rate was reported to be 48.5% and 69% ($P = .04$), with an ulcer-free rate of approximately 68% and 96% ($P = .008$). This occurred in addition to improved venous hemodynamics for those with and without external banding.

External Banding

The prosthetic sleeve method of valve repair has achieved acceptable results in selected patients with less advanced disease.[27]

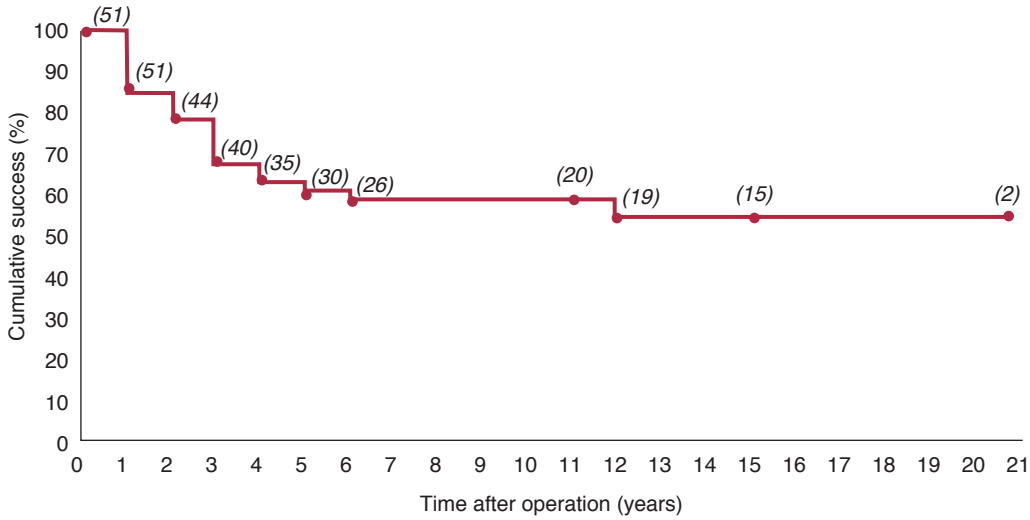

Figure 159.24 Cumulative clinical success rates for all limbs of patients with class 0 or 1 (as defined in the original article but comparable to higher CEAP clinical classifications) disease who underwent a venous valve reconstruction. Numbers in parentheses represent total limbs at risk for each time interval. (Redrawn from Masuda EM, Kistner RL. Long-term results of venous valve reconstruction: a four- to twenty-one-year follow-up. *J Vasc Surg.* 1994;19:394.)

TABLE 159.1 Results of Internal Valvuloplasty

Series	Year	Main Site	Number of Limbs	Months of Follow-Up (Average)	Number Competent[a]	Number Symptom Recurrence/ Unchanged[b]	Hemodynamic Improvement[c]
Kistner[115]	1975	FV	15	36-84 (60)	5/14	2/15	
Ferris and Kistner[116]	1982	FV	32	12-156 (72)	16/22	6/32	7/8
Raju[62]	1983	FV	15	3-40	15/15[d] 4/5[e]	0/15	10/15
Ericksson and Almgren[22]	1986	FV	19	84 (44)	13/19	5/19	12/19
Cheatle and Perrin[41]	1994	FV	52	3-54	46/52[f] 23/27[g]	7/51	40/42[f] 24/25[g]
Masuda and Kistner[18]	1994	FV	32	48-256 (127)	24/31	9/32	
Raju et al.[27]	1996	FV	81	12-144	30/71	16/68	
Lurie et al.[117]	1997	FV	49	36-108 (74)		18/49	
Perrin[118]	1997		75	24-96 (58)		6/33	54/74
Perrin et al.[113]	1999	FV	33	24-96 (51)	22/33	6/33	16/27
Perrin[111]	2000	FV	85	12-96 (58)	51/83	10/35	43/68
Tripathi and Ktenidis[64,h]	2001	FV	25	1-12 (6)	35/41	4/25	
Tripathi et al.[46,h]	2004		90	24	115/144	61/90	

[a]Determined by phlebography, duplex ultrasonography, or both.
[b]Includes C3-6 (majority C5/6).
[c]Determined by plethysmography or intravenous pressure (preoperative vs. postoperative findings).
[d]Determined by ultrasonography.
[e]Determined by phlebography.
[f]Immediately after surgery.
[g]Twelve months after surgery.
[h]More than one valve repair per limb.
FV, Femoral vein.

A more aggressive approach involving the use of banding in patients with advanced disease in which venous constriction did not necessarily result in a competent valve demonstrated the ability to achieve valve competence in a majority of cases.[59] In 42 limbs, 125 valves were repaired, and the repairs were generally in the femoral vein (60) or popliteal vein (53). The investigators reported competence in 90% of patients at 86 months and significantly improved photoplethysmographic estimates of recovery time, but the surgeons did not report competency per valve site. Long-term ulcer healing rates were directly associated with the number of valves repaired: one, 51%; two, 65%; and three, 86%. Another group confined banding to the proximal femoral vein valve in patients with grade 3 or grade 4 reflux, and only in those in whom the profunda femoris vein was competent. They reported a 78% competency rate and symptom relief at 50 months.[119]

Valve Transplantation

Table 159.2 provides a synopsis of the results that one can anticipate when valve transplantation is required to treat chronic deep venous valvular incompetence.[25,26,62,118,120,121,52,122,123] Clinical improvement is seen in about 50% of patients, even at 8 years of follow-up, and it remains an option in cases in which other options are not possible.[15,65,124] The use of great or small saphenous vein valve transplants provide similar results at 3 and 7 years.[74]

Valve Transposition

Table 159.3 tabulates the results of transposition operations.[18,23,77,116,118,125] Good results with the technique of valve transposition have been observed in 40% to 50% of patients after 5 years of follow-up.[18,23,77,116,118,124,125] The method of placing the femoral system below a competent great saphenous valve with ligation to offset the size discrepancy has resulted in 55% of the patients being free of ulcers at 10 years.[77]

Multilevel Valve Reconstruction

There is increasing evidence that multilevel valve reconstruction (more than one valve repair in the same axial system) improves maintenance of valve competence in at least one of the repaired valves and, as a consequence, improves clinical outcome. Raju and his group have been advocates of this approach for many years.[28,45] At 2 years, Tripathi and colleagues found that patients with primary reflux disease undergoing single-level valvuloplasty could expect a 59.4% valve competence rate and 54.7% ulcer healing rate, which was significantly lower ($P < .05$) than results achieved with multilevel repair, which demonstrated rates of 79.7% and 72.9%, respectively.[46] A similar

TABLE 159.2 Results of Valve Transplantation

Series	Year	Main Site	Number of Limbs	Months of Follow-Up (Average)	Number Competent[a]	Number Symptom Recurrence/ Unchanged[b]	Hemodynamic Improvement[c]
Taheri et al.[120]	1982	FV	6	12	4/4	4/4	5/5
Raju[62]	1983	FV	21	3-40	2/14	10/21	10/13
Taheri et al.[121]	1986	POP	46	8-36	22/24	5/46	12/14
O'Donnell et al.[25]	1987	POP	10	>24	0/10	0/10	1/10
Nash[52]	1988	POP	25	12-18	20/25	2/25	21/25
Rai and Lerner[122]	1991	POP	12	6-24 (16)	6/6	0/12	11/12
Bry et al.[26]	1995	POP	15	15-132 (64)		3/14	
Perrin[118]	1997	FV	30	12-120 (58)	6/20	8/20	
Sottiurai[123]	1997		31	8-156 (74)	14/31	17/31	
Tripathi et al.[46]	2004[d]		38	24	29/61	17/38	

[a]Determined by phlebography, duplex ultrasonography, or both.
[b]Includes C3-6 (majority C5/6).
[c]Determined by plethysmography or intravenous pressure (preoperative vs. postoperative findings).
[d]More than one valve repair per limb.
FV, Femoral vein; *POP*, popliteal vein.

TABLE 159.3 Results of Valve Transposition

Series	Year	Main Valve Site	Number of Limbs	Months of Follow-Up (Average)	Number Competent[a]	Number Symptom Recurrence/ Unchanged[b]	Hemodynamic Improvement[c]
Queral et al.[23]	1980	GSV	12	>3	9/12	1/12	11/12
Johnson et al.[125]	1981	GSV	12	12-18	2/2	9/12	3/12
Ferris and Kistner[116]	1982	PFV/GSV	14	12-156	4/7	3/14	10/11
Masuda and Kistner[18]	1994	PFV/GSV	14	48-256 (127)	4/14	7/14	
Perrin[118]	1997	GSV	13	12-114 (49)	5/12	2/6	
Cardon et al.[77]	1999	GSV	16	29-56 (42)	15/16	5/16	

[a]Determined by phlebography, duplex ultrasonography, or both.
[b]Includes C3-6 (majority C5/6).
[c]Determined by plethysmography or intravenous pressure (preoperative vs. postoperative findings).
GSV, Great saphenous vein; *PFV*, profunda femoris vein.

trend was noted in those requiring valve transplantation; valve competence and ulcer healing rates were 38.9% and 46.1%, respectively, for single-level repairs, versus 55.8% and 57% for multilevel repairs. Rosales and colleagues have accumulated data on external valvuloplasty that suggest improved clinical results, especially in CEAP class 4 patients, with the use of a multilevel (different locations in the same axial system) and multistation (more than one valve in the same location) technique, but statistical significance was not obtained, and clear determination of valve competence was not provided.[47] Lane and associates found that as the number of external banding repairs per axial system increased, so did long-term ulcer healing.[59]

Venous Valve Substitutes

Table 159.4 demonstrates the current state of the art regarding autogenous valve substitutes. The Plagnol type of valve has both experimental and clinical results reported, with 19 of 20 reconstructions being patent and competent at a mean of 10 months.[94] One valve demonstrated reflux because of insufficient valve length at the time of reconstruction. Invagination of an adventitial surface into the venous lumen is of some concern but was not substantiated in this study. The Maleti neovalve initial configuration resulted in early thrombosis below the valve in two patients, and there was one late occlusion shortly after starting oral contraceptives.[55] Therefore 95% of treated

TABLE 159.4 Autogenous Valve Substitutes (Neovalve) Results

Author, Year	Technique	Number of Limbs	Etiology 10 PTS/ Total	Follow-Up Month (m)	Ulcer Recurrence or Nonhealed Ulcer (%)	Hemodynamic Results	
						Competent Valves (%)	AVP–VRT
Plagnol, 1999	Bicuspid neovalve	44	44/44	6-47 (17)	3/32 (17)	38/44 (86)	
Maleti-Lugli, 2009	Monocuspid or bicuspid neovalve	19+21= 40	36/40	2-78 (28.5)	7/40 (17)	13/19 (68) 21/21 (100)	75 VRT improved
Opie, 2008	Monocuspid neovalve	14	/	(48)	0/6	13/14 (92)	

AVP, Ambulatory venous pressure; *m,* mean; *PTS,* postthrombotic syndrome; *VRT,* venous refill time.

segments remained primarily patent and competent, with significantly improved duplex and air plethysmography results at a mean of 22 months of follow-up. Ulcer healing occurred in 16 cases (88.9%), at a median of 12 weeks with no recurrences. There was no associated mortality.[55] However, at a median follow-up of 54 months, valve competence was demonstrated in 13 of 19, or 68%.[56] The one case added to the 2006 report included an episode of DVT, and the long-term ulcer healing rate was now 84%, with two recurrences. The modification noted in the techniques section was instituted to improve these results. The second group studied (modification included) consisted of 21 operations, with a median of 5 months of surveillance. All valves were competent, and there was a 95% ulcer healing rate and two recurrences (9.5%).[56] Opie reported no incompetent valves in 14 operations at 4 years and excellent clinical improvement.[96]

Overview

In general, patients with postthrombotic reflux tend to experience reduced healing rates and more recurrent venous ulcers than those with a primary cause of reflux, as noted from the results of internal valvuloplasty (generally a primary cause) versus transplantation or a transposition approach. However, Raju and associates found little difference in the results of repair of postthrombotic versus primary disease in their series.[16,27] It is possible that this difference simply reflects a delay in the appearance of ulceration after valve failure. These same investigators reported a difference in valve competence based on the method of repair (Fig. 159.25). It would appear that there is decreasing durability as one progresses from internal valvuloplasty, to external valvuloplasty, and finally to the need for transplantation and other interventions.

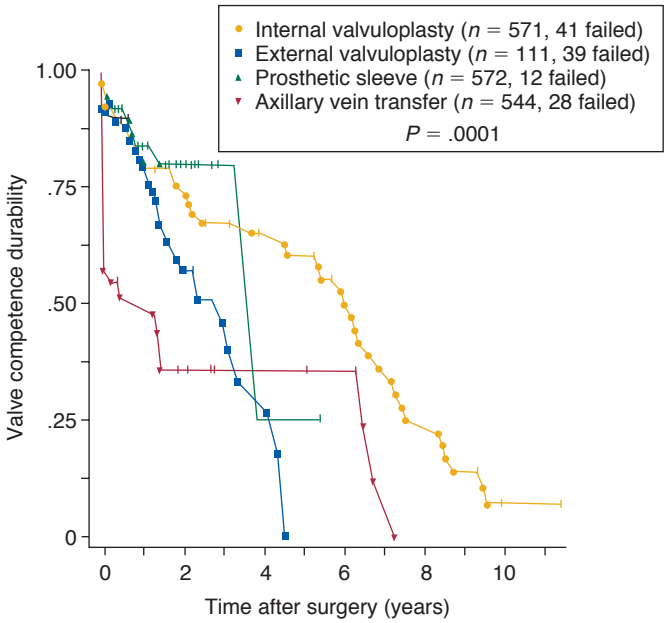

Figure 159.25 Actuarial durability of various valve reconstruction techniques assessed by serial duplex examination for competence. (Redrawn from Raju S, Fredericks RK, Neglen PN, Bass JD. Durability of venous valve reconstruction techniques for "primary" and post-thrombotic reflux. *J Vasc Surg.* 1996;23:363.)

Follow-Up

Monitoring and Management

A typical method of clinical follow-up includes physical examination at 6 weeks, 3 to 9 months, and then annually, but with considerable variability in the exact timing of visits.[41,58,45,46,59,69,111,113,115] During each visit, venous duplex ultrasonography is performed to determine valve site patency and valve competence. Noninvasive testing has generally replaced descending venography, which was often used in earlier series.[18,60] Most surgeons include some type of hemodynamic assessment. Some use a visual analogue pain score or assessment for swelling.[45,69] Reclassification by the CEAP criteria, venous severity scoring, and use of quality-of-life assessment tools are encouraged to provide quantifiable parameters of clinical success.[41,58,45,46,59,71,111,113,119]

Reoperative surgery can be difficult but is sometimes required.[53] The best approach appears to be to use a new incision remote from the original operative site. One choice of site is the femoral vein at the adductor canal, as it is easily accessible. Raju and Hardy[53] have found it difficult to perform popliteal valvuloplasty because of an often thick adventitial coat, which makes adventitial dissection and therefore visualization of the valve commissures difficult.

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Those who have the courage to be the first should be recognized for the effort, and this is one of those articles.

Kistner RL, Ferris EB, Randhawa G, Kamida C. A method of performing descending venography. *J Vasc Surg*. 1986;4:464–468.

One of the initial articles to look critically at deep venous reflux and to quantify it on the basis of venographic imaging. It is a commonly quoted article when venous reflux and valve repair are discussed.

Lugli M, Guerzoni S, Garofalo M, Smedile G, Maleti O. Neovalve construction in deep venous incompetence. *J Vasc Surg*. 2009;49:156–163.

The most recent innovative approach to treatment of the postthrombotic insufficient venous system. It was selected because it is innovative and cutting edge in the care of these patients.

Masuda EM, Kistner RL. Long-term results of venous valve reconstruction: a four to twenty-one year follow-up. *J Vasc Surg*. 1994;19:391–403.

This group was the first to report on the repair of venous valves to prevent deep venous reflux, and this study still stands as the longest follow-up of such patients.

Raju S, Fredericks RK, Neglèn PN, Bass JD. Durability of venous valve reconstruction techniques for "primary" and postthrombotic reflux. *J Vasc Surg*. 1996;23:357–367.

This report compares various methods of valve repair in terms of valve competence and clinical result. It is from one of the few centers that have sufficient numbers to make such a comparison with statistical validity.

Raju S, Hardy JD. Technical options in venous valve reconstruction. *Am J Surg*. 1997;173:301–307.

This article provides excellent technical points on the various types of venous valve repair from a group with possibly the largest experience in the world. They have the experience to teach us all something.

Sottiurai VS. Results of deep-vein reconstruction. *Vasc Surg*. 1997;31:276–278.

A large experience from a surgeon who invented one approach to open valvuloplasty.

Taheri SA, Elias SM, Yacobucci GN, Heffner R, Lazar L. Indications and results of vein valve transplant. *J Cardiovasc Surg*. 1986;27:163–168.

A landmark article on a new approach to treatment of the postthrombotic insufficient lower leg venous system.

Tripathi R, Sieunarine K, Abbas M, Durrani N. Deep venous valve reconstruction for non-healing leg ulcers: techniques and results. *Aust N Z J Surg*. 2004;74:34–39.

A large study of various methods of valve repair highlighting the use of multiple valve repairs in the same axial system to decrease clinical recurrence.

A complete reference list can be found online at www.expertconsult.com.

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160 CHAPTER

Iliocaval Venous Obstruction: Surgical Treatment

YVES ALIMI and OLIVIER HARTUNG

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SURGICAL TREATMENT OF ILIOCAVAL VENOUS OBSTRUCTION

The first successful venous reconstruction in a patient was reported more than 50 years ago by Warren and Thayer[1]; in the past 2 decades improvements in diagnosis, patient selection, surgical technique, and the availability of better graft materials have resulted in more frequent successful implantation of venous bypasses in patients.[2] More recently, endovascular treatment for iliocaval obstruction has progressed rapidly, and currently venous stenting is the primary choice for treatment of benign iliac or iliocaval venous occlusions. However, surgical treatment remains an excellent option in cases in which endovascular techniques have failed or are not possible. The endovascular treatment for iliocaval obstruction is addressed in Chapter 161.

ETIOLOGY

Deep venous thrombosis (DVT) is the most common cause of venous obstruction. Venous occlusion may also be due to trauma, radiation, external compression by retroperitoneal fibrosis or

Abstract

This chapter covers two conditions that affect the lower extremities and pelvis venous drainage: chronic iliocaval venous occlusion (CICVO) and pelvic congestion syndrome (PCS). Etiologies of CICVO are numerous but dominated by the May Thurner syndrome (compression of the left common iliac vein by the right common iliac artery and the lumbar vertebrae) and the post-phlebitic syndrome. Severe symptomatic patients due to CICVO with contraindication or failure of endovascular techniques should be recognized and treated by open surgical therapy. Main cause of pelvic pains in women, the PCS can be authentified by noninvasive explorations and, if necessary, treated by open, laparoscopic or mainly endovascular techniques.

Keywords

iliocaval venous obstruction
pelvic congestion syndrom
May Thurner syndrome
post phlebitic syndrome
surgical treatment
embolisation

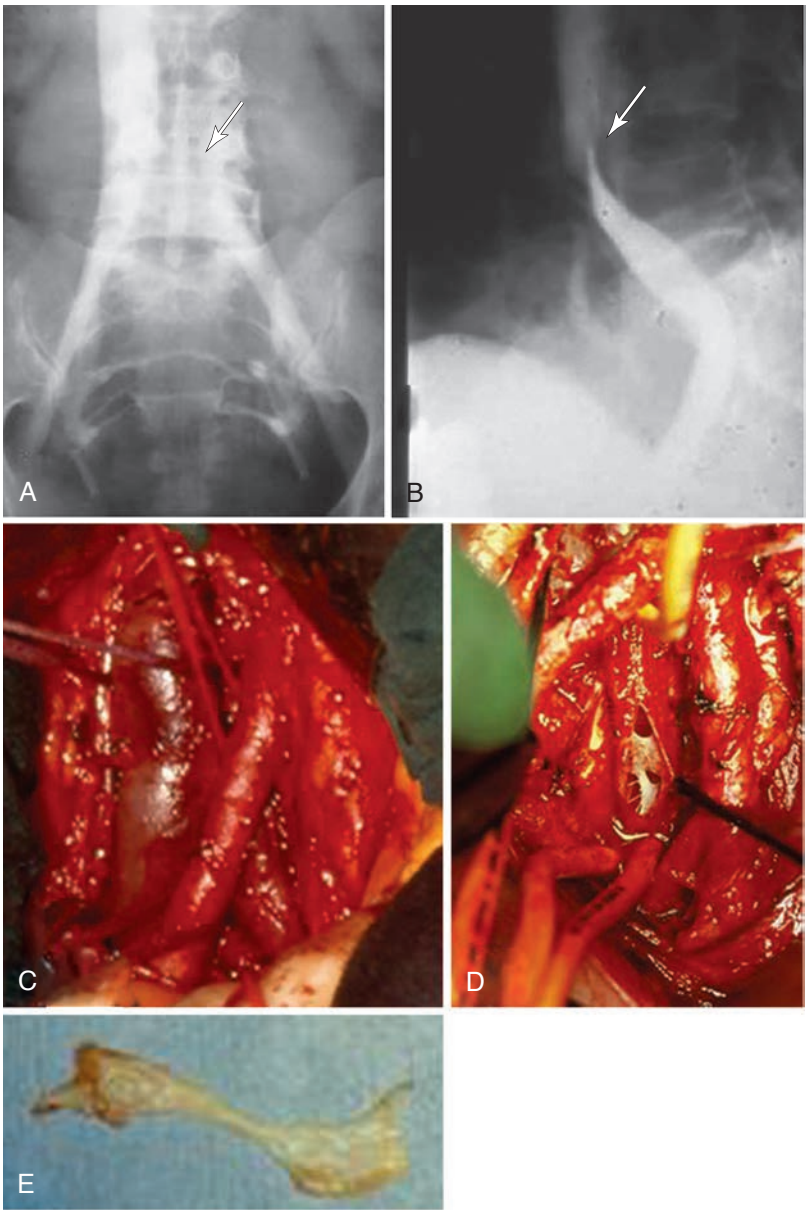

Figure 160.1 Compression of the Left Common Iliac Vein by the Right Common Iliac Artery (May-Thurner Syndrome). Anterior (A) and lateral (B) phlebograms. The *arrow* indicates compression of the vein by overriding artery. C, Intraoperative view. (D) Intraoperative visualization of the webs inside the left common vein. (E) Intraluminal web after removal.

overlying arteries (May-Thurner syndrome),[3,4-7] benign, malignant, primary, or metastatic tumors[8-10]; cysts; aneurysms; abnormally inserted muscle bands (popliteal vein entrapment)[11]; and fibrous bands or ligaments (soleal arch syndrome, femoral vein compression by the inguinal ligament[12]).

Compression of the left common iliac vein by the overriding right common iliac artery (May-Thurner syndrome) (Fig. 160.1) is considered an important cause of left iliofemoral venous thrombosis.[4-7] May and Thurner observed secondary changes, such as intraluminal webs or "spurs," in the proximal left common iliac vein in 20% of 430 autopsies.[3,4-7] Other causes of iliofemoral and caval thrombosis include congenital anomalies, such as membranous occlusion of the suprahepatic inferior vena cava (IVC) with or without associated thrombosis of hepatic veins (Budd-Chiari syndrome),[13] aplasia, and hypoplasia of the iliofemoral veins as in Klippel-Trénaunay syndrome.[14,15]

PREOPERATIVE EVALUATION

Preoperative evaluation in patients with iliofemoral and/or iliocaval venous obstruction should reveal the cause and functional significance of the obstruction and the extent and severity of associated venous incompetence. In at least two-thirds of patients with venous outflow obstruction, distal reflux due to valvular incompetence contributes greatly to development of chronic venous insufficiency (CVI).[16]

History and Physical Examination

The history and physical examination, complemented by examination with a handheld Doppler instrument, should reveal signs and symptoms typical of venous congestion. Patients have lower extremity swelling and experience exercise-induced pain

in the thigh muscles, referred to as venous claudication. This pain is described as a "bursting" pain in the thigh and sometimes the calf which is relieved by rest and leg elevation.[17]

Signs of CVI, such as edema, varicose veins, skin changes, lipodermatosclerosis, eczema, and ulceration, should be noted. Distended varicose veins are present even in the supine patient with CVI, and suprapubic and abdominal wall collaterals develop in patients with pelvic occlusion. Bleeding from high-pressure varicosities is not infrequent. The swollen leg has a cyanotic hue, and bilateral swelling indicates bilateral iliofemoral or vena caval occlusion or systemic disease. In some patients, venous congestion results in hyperhidrosis and significant fluid loss through the skin. Associated chronic high-output or low-output lymphedema may also develop.[18]

Preoperative evaluation should identify risk factors for DVT (see Chapters 145 and 147). Associated chronic arterial occlusive disease and congenital venous malformations (Klippel-Trénaunay syndrome, Parkes Weber syndrome) should be excluded. Patients with membranous occlusion of the vena cava frequently also have evidence of hepatic failure, Budd-Chiari syndrome, and portal hypertension.[13]

Imaging

Duplex ultrasound scanning (DUS) is the first test of choice to identify DVT. However, depending upon factors such as the presence of overlying bowel gas and increased body fat, the IVC and proximal iliac veins may be difficult to image in enough detail to guide further treatment. In these cases, computed tomographic venography (CTV) or magnetic resonance imaging (MRI) can be performed. These tests are also important in identifying causes of iliocaval venous thrombosis, including tumor, cyst, retroperitoneal fibrosis, and iliac venous compression.[19]

Abnormal DUS findings associated with iliocaval occlusion, such as absent flow in the iliac veins and loss of phasicity of flow in the distal veins, are discussed more fully in Chapters 23 and 156.

Ambulatory venous pressure measurements may suggest venous hypertension; measurements of arm-foot pressure differences, as described by Raju et al., can also be used to quantitate venous hypertension. In their study a resting arm-foot pressure differential greater than 4 mm Hg was considered evidence for significant obstruction justifying venous reconstructions.[20] In potential candidates for proximal venous reconstruction, femoral and central venous pressure measurements are required in our practice to document the severity of iliac or iliocaval obstruction. Either a pressure difference of at least 5 mm Hg between the femoral and the central pressures in the supine patient or a twofold increase in femoral vein pressure after exercise indicates hemodynamically significant proximal stenosis or occlusion.

In patients being considered for venous reconstruction, we perform both ascending and descending catheter-based phlebography to evaluate obstruction and associated valvular incompetence.[21,22] Femoral access is useful not only for descending phlebography and iliocavography but also for measuring femoral venous pressures. Iliocavography and abdominal venacavography through a brachial approach may also be necessary in some patients to visualize the vena cava proximal to the occlusion.

INDICATIONS FOR SURGICAL TREATMENT

Prior to the development of endovascular techniques for the treatment of venous disease, surgery was the only option following failures of conservative management. However, with the development and success of advanced endovascular treatments (see also Chapter 161),[23-26] surgery is now generally reserved for cases in which endovascular treatment fails or is deemed inappropriate. The severity of venous stenosis, the location and length of venous occlusion, the age of the thrombus, the nature of any external compression, the presence of underlying malignant disease, and the risks of surgical intervention also play a role in determining whether to attempt endovascular or direct surgical reconstruction. Currently we first attempt endovascular treatment, alone or in combination with thrombolysis, surgical thrombectomy, or excision of old thrombus from the femoral veins, before a surgical bypass is recommended.

Proper patient selection is important; the ideal patient has unilateral iliac occlusion with minimal distal thrombus and valvular incompetence. Patients with severe infrainguinal postthrombotic disease and valvular incompetence may have a decreased chance of success because the distal disease is not treated. In a series published by the Mayo Clinic, there was a trend toward a higher rate of graft occlusion in patients with infrainguinal reflux.[27]

GRAFTS IN THE VENOUS SYSTEM

Grafts placed in the venous system undergo thrombosis more frequently than those implanted for arterial reconstruction, in part because flow in venous grafts is lower. Pressure in the venous system is low, and grafts can collapse under increased abdominal pressure or in tightly confined spaces, such as the area under the inguinal ligament and the retrohepatic space, or when tunneled through the diaphragm. Many patients with previous DVT have hypercoagulable states. The thrombogenic surface of the prosthetic graft also increases the risk of graft failure.[27]

As a result of extensive efforts made in the past decades, patency of grafts implanted in the venous circulation has improved considerably.[28-41] The availability of large-diameter autologous and prosthetic grafts, use of adjuncts such as a distal arteriovenous fistula, rigid external support of the grafts, perioperative and postoperative anticoagulation, the use of perioperative intermittent-compression pumps, and postoperative surveillance with duplex scanning all contribute to improved patency and clinical outcomes.

Venous Graft Materials

Autogenous grafts for the femorofemoral, iliofemoral, and iliocaval locations have the best chance of long-term success. The great saphenous vein, because of its low thrombogenicity

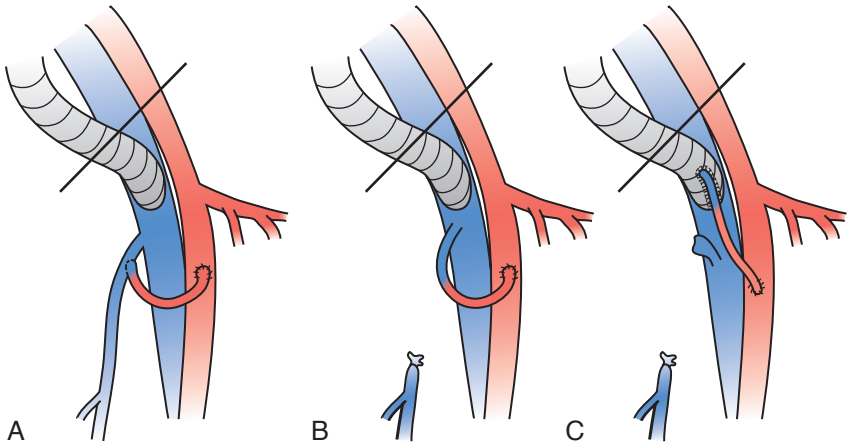

Figure 160.2 Different Types of Arteriovenous Fistulae Placed Distally to a Ringed Expanded Polytetrafluoroethylene (ePTFE) Femoral Venous Graft. The saphenofemoral vein junction is preserved with the use of either a branch of the great saphenous vein (A), or the main trunk of the great saphenous vein (B). (C) The saphenofemoral junction is divided and the main trunk of the great saphenous vein is directly anastomosed to the ePTFE graft.

and suitability in terms of length, is the best choice when available. As a spiral or panel graft, it can be used for the reconstruction of large veins, although in our experience these grafts do not perform as well for iliocaval reconstructions as they do for superior vena caval replacement.[21,22] The contralateral superficial femoral vein, arm veins, and the jugular veins are other potential sources of autogenous grafts. Although harvesting of deep veins was initially believed to result in a high level of CVI in the lower extremity, more recent data suggest it is relatively benign in the majority of patients. The only factors found to be associated with venous morbidity following lower extremity deep vein harvest in a recent study were an ankle-brachial index less than 0.4 and a concurrent great saphenous vein harvest.[42]

The efficacy of cryopreserved vein or arterial grafts in the venous circulation has not been well studied. A few reports exist regarding their use in reconstruction of the superior vena cava and innominate veins.[43] Data at this point are insufficient to support the recommendation of these grafts for routine clinical use.

Of the available prosthetic materials, the expanded polytetrafluoroethylene (ePTFE) graft has been used most frequently for large vein replacement.[a] Because of a large diameter, sufficient length, immediate availability, and external ring or spiral support associated with relatively low thrombogenicity, ePTFE grafts continue to be the best choice for prosthetic replacement of large veins.

Use of Arteriovenous Fistulae

Multiple studies have confirmed that a distal arteriovenous fistula, first suggested by Kunlin and Kunlinin in 1953,[33] improves the patency of grafts placed in the venous system.[b] An arteriovenous fistula increases flow and decreases platelet and fibrin deposition in prosthetic grafts (Fig. 160.2).[36] Prosthetic grafts have significantly higher thrombotic threshold velocities than do autologous grafts and require higher flow to maintain patency.

Disadvantages of an arteriovenous fistula include the longer operating time needed to create the fistula and the inconvenience of additional procedures to close the fistula at a later date. A potential side effect is elevated cardiac output caused by high fistula flow. In addition, high fistula flow can defeat the purpose of the operation by increasing venous pressure at the groin and causing more distal venous outflow obstruction. Experimental work revealed that to avoid deleterious effects on venous outflow from the leg, the optimal ratio between the diameters of the fistula and the graft should not exceed 0.3. Elevated intraoperative pressure in the femoral vein after placement of a fistula should be taken as a warning sign, and fistula diameter should be decreased by banding or other modifications.

The configuration and location of the fistula have also been the subject of much controversy. A large side branch of the great saphenous vein or the saphenous vein itself can be used to perform one anastomosis only. Most recently, we have placed the venous end of the arteriovenous fistula directly onto the hood of the venous graft at the distal anastomosis, using either a 4-mm vein as a free graft (saphenous vein or a large tributary) or a 4-mm ePTFE graft. The advantage of these is that flow can be calibrated with an electromagnetic flowmeter, and large flows (>300 mL/min) can then be avoided. The arterial anastomosis is usually made to the superficial femoral artery. We place a small polymeric silicone (Silastic) sheet around the fistula to prevent healing and to facilitate dissection of the fistula during a second procedure to occlude it. A 2-0 polypropylene suture is also tied loosely around the fistula, and its end is positioned in the subcutaneous tissue close to the incision for later identification. Intraoperative duplex scanning can be used later to identify the fistula. Percutaneous closure of the fistula with transcatheter embolization or a covered stent placed across the arterial side are also options.

At present, for all prosthetic grafts anastomosed to the femoral vein and all longer (>10 cm) iliocaval grafts, a femoral arteriovenous fistula is added to maintain patency (see Fig. 160.2). The fistula is left in place for at least 6 weeks after the operation, and patients without any side effects benefit from long-term fistula flow to prolong patency. For the Palma procedure (described later), we use a fistula selectively and take it down within 2 months after surgery.

[a]References 3, 8, 9, 10, 21, 22, and 44-53.
[b]References 27, 28, 31, 36, 37, and 54.

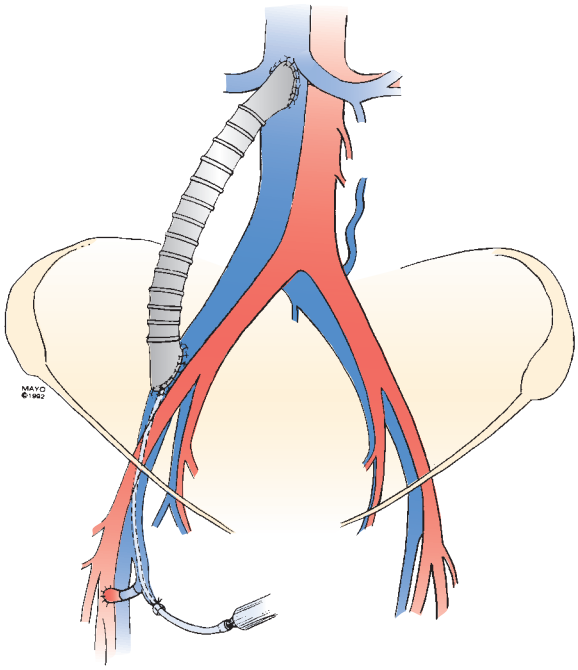

Figure 160.3 Illustration of a right iliac vein/inferior vena caval externally supported polytetrafluoroethylene graft. Note the arteriovenous fistula at the right groin and a 20-gauge catheter, which is introduced through a tributary of the saphenous vein for perioperative heparin infusion. (From Gloviczki P, Pairolero PC, Toomey BJ, et al. Reconstruction of large veins for nonmalignant venous occlusive disease. *J Vasc Surg*. 1992;16:750, with permission of Mayo Foundation.)

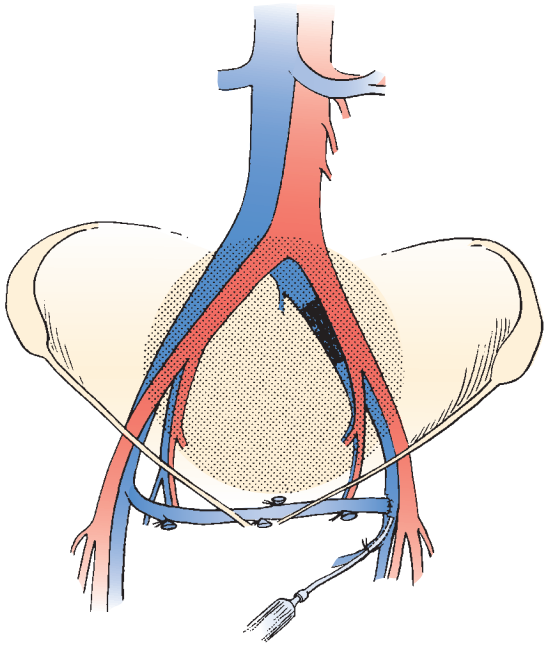

Figure 160.4 Left-to-right femorofemoral venous bypass (Palma procedure) for left common iliac vein obstruction. A small polyethylene catheter can be placed through a side branch of the greater saphenous vein for immediate perioperative heparinization to improve chances of patency. (From Rhee RY, Gloviczki P, Luthra HS, et al. Iliocaval complications of retroperitoneal fibrosis. *Am J Surg*. 1994;168:179.)

Anticoagulation

Intravenous heparin, at a dose of 50 IU/kg, is given in surgery prior to cross-clamping, and anticoagulation is maintained during and after the procedure in most patients. We frequently administer low-dose heparin (500-800 IU/h) locally through a small polyethylene catheter placed just distal to the anastomosis in the perioperative period (Fig. 160.3). This is continued until complete systemic heparinization is achieved by 48 hours after surgery. The catheter is then removed, heparinization is continued intravenously or by using low-molecular-weight heparin, and the patient begins oral anticoagulation therapy with warfarin.

An intermittent pneumatic compression pump, leg elevation, elastic bandages, and early ambulation are also used in the perioperative period to improve the success of venous reconstruction.[55] The patient is fitted with 30- to 40-mm Hg graduated-compression elastic stockings before discharge. Warfarin is continued in patients with autogenous grafts for at least 3 months. In most patients with prosthetic grafts or an underlying coagulation abnormality, oral anticoagulation is maintained indefinitely.

Graft Surveillance

Intraoperative duplex scanning is performed in most patients to ensure patency, good flow, and lack of thrombus deposition. Direct pressure measurements are made before wound closure in every patient to document the hemodynamic benefit. In venous or ePTFE conduits, fistula flow can be measured and calibrated with an electromagnetic flowmeter. If flow is higher than 300 mL/min, banding of the fistula is performed.

On the first postoperative day, we perform contrast phlebography through the catheter positioned at the distal anastomosis of the graft (see Fig. 160.3). Any stenosis or thrombosis detected at this time is revised during a reoperation. Postoperatively, grafts are observed with duplex scanning at 3 and 6 months and then twice yearly afterward. Outflow plethysmography is also performed to document the level of hemodynamic impairment/improvement in the lower extremity. In symptomatic patients, contrast phlebography is usually performed to exclude graft stenosis.

SURGICAL PROCEDURES

Cross-Pubic Venous Bypass (Palma Procedure)

Initially described 40 years ago by Palma and Esperon[56,57] in Uruguay and popularized by Dale[58] in the United States, the Palma procedure has remained a useful technique for venous reconstruction in patients with unilateral iliofemoral outflow obstruction (Figs. 160.4 and 160.5). The operation requires a normal contralateral iliofemoral venous system to ensure venous drainage. Results have been better in patients with intact inflow, when the affected limb has no infrainguinal obstruction or deep venous incompetence.[27,59]

We favor this operation especially in young women who present with residual chronic iliac vein occlusion after acute left iliofemoral venous thrombosis which develops as a result

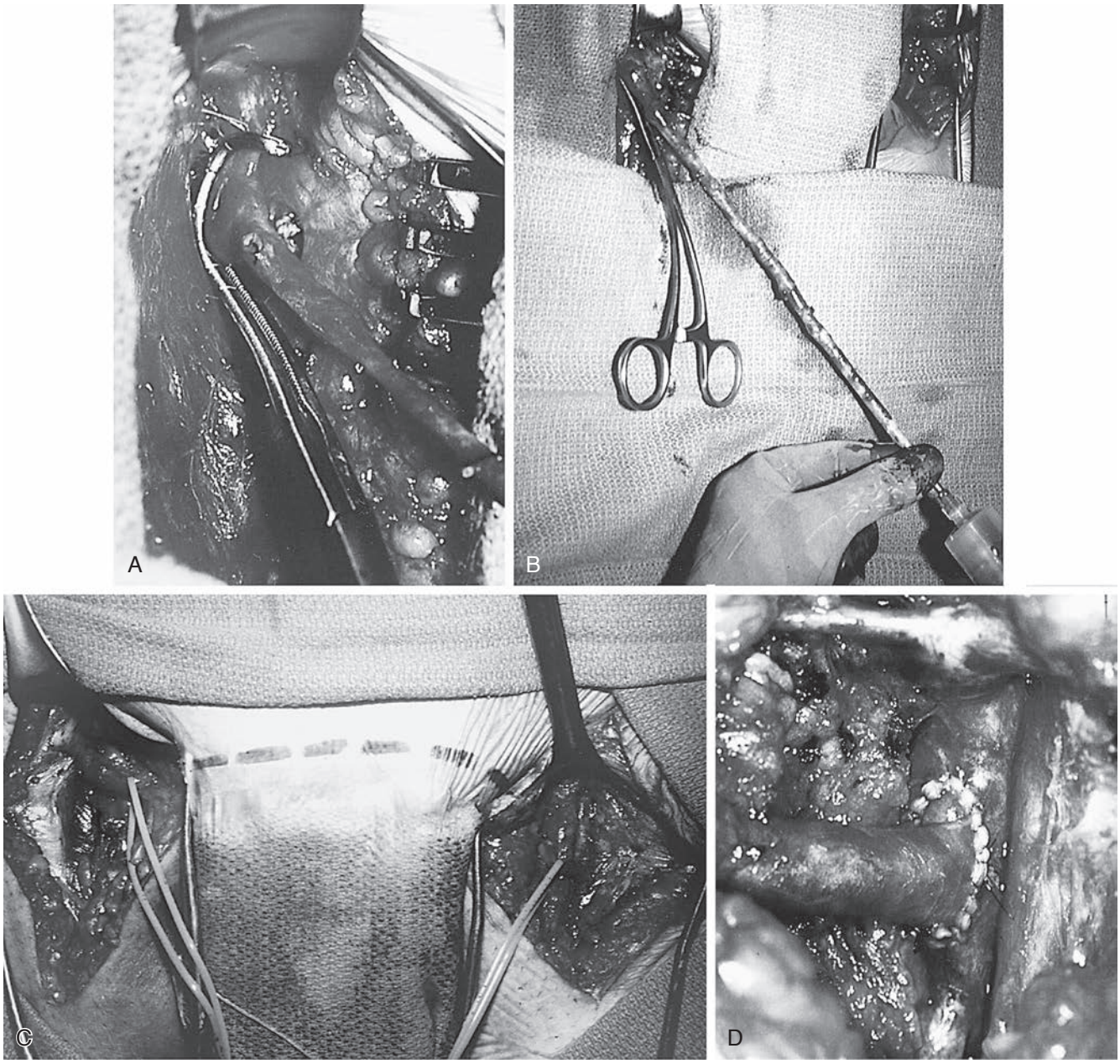

Figure 160.5 (A) Technique of Palma procedure: the contralateral saphenous vein is dissected, and its distal end divided in the thigh; then a vascular clamp is placed on the common femoral vein. (B) The vein is distended with papaverine solution. (C and D) The saphenous vein is tunneled to the left groin and anastomosed end to side to the common femoral vein. A femoral arteriovenous fistula is constructed and encircled with a Silastic sheath for easy identification for takedown 3 months later.

of May-Thurner syndrome. The operation is indicated in patients who are not candidates for iliac vein stenting or in whom previous endovascular procedures have failed.

Technique

The contralateral great saphenous vein is used in the classic Palma procedure (see Fig. 160.5). Preoperative imaging of the potential conduit with duplex scanning is recommended because varicose saphenous veins or veins smaller than 4 mm in diameter have poor chances of long-term success.

Endoscopic harvesting of a 25- to 30-cm segment of the contralateral saphenous vein ensures an excellent cosmetic result; otherwise, the vein can be dissected through two or three small skin incisions. It is divided in the distal thigh or calf and remains attached at the saphenofemoral junction. Tributaries are also ligated and divided.

The graft is gently distended (see Fig. 160.5) and tunneled to the contralateral groin in a suprapubic, subcutaneous position. Dissection of the femoral vein on the affected side should be minimal; usually, only the anterior and lateral vein wall is freed

for proximal and distal clamps or for a side-biting clamp to occlude the vein for the anastomosis. Excision of intraluminal fibrous bands after venotomy may be required. The anastomosis between the saphenous and femoral veins is performed in an end-to-side technique. If the vein is small, interrupted 5-0 or 6-0 sutures are preferred to permit later dilation of the vein and to avoid "purse-stringing" of the venous anastomosis. A small catheter can be placed through a tributary of the ipsilateral saphenous vein for immediate low-dose heparinization and postoperative phlebography (see Fig. 160.5). A temporary arteriovenous fistula can also be placed to improve flow and aid in achieving early patency.

If the traditional transposition results in significant kinking of the saphenous vein at the contralateral groin, free vein grafting should be considered, excising the saphenous vein along with a small rim of the common femoral vein and reimplanting it after a 180-degree turn. For autogenous graft material, the contralateral or even the ipsilateral saphenous vein (with lysis of any competent valves) or an arm vein can be used. When suitable autogenous conduit is not available, an 8- or 10-mm externally supported ePTFE graft is the best alternative (Fig. 160.6).[48,60]

Results

Analysis of results of 433 operations published in 10 series revealed clinical improvement in 63% to 89% of patients (Table 160.1).[c] Reported patency rates ranged from 70% to 85%, but follow-up periods were variable and objective graft assessment with imaging was rarely performed in all patients. The largest series, 85 crossover venous bypasses, was reported by Husni.[61]

[c]References 27, 44, 48, 57, 58, and 61-65.

At the last follow-up visits (6 months to 15 years postoperatively), 47 of 67 grafts were patent. Results in this study were improved when a temporary distal arteriovenous fistula was used. The patency rate of grafts implanted for extrinsic compression of the iliac vein without distal disease was 100%, as opposed to 67% in patients with post-thrombotic syndrome.[61] In a review of 50 consecutive operations performed in 47 patients, Halliday and associates reported a cumulative patency rate of 75% at 5

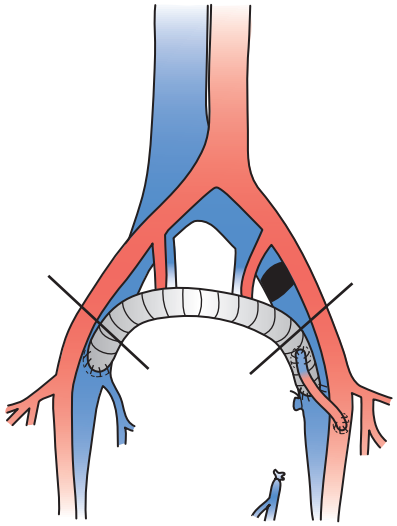

Figure 160.6 Diagram of a right-to-left expanded polytetrafluoroethylene femorofemoral crossover vein graft (Palma procedure). Note the fistula in the right groin, extending from the proximal superficial femoral artery to the hood of the graft. (From Jost CJ, Gloviczki P, Cherry KJ Jr, et al. Surgical reconstruction of iliofemoral veins and the inferior vena cava for nonmalignant occlusive disease. *J Vasc Surg*. 2001;33:320-328.)

TABLE 160.1 Published Results of Femorofemoral Crossover Bypass

First Author	Year	No. of Limbs	Follow-Up (Year)	Postoperative Imaging (%)	Patency Rate (%)	Clinical Improvement (%)	Graft Material
Palma[57]	1960	8	Up to 3	13	N/A	88	Vein
Dale[58]	1979	48	Up to 12	N/A	N/A	77	Vein
May[44]	1981	66	N/A	N/A	73	N/A	Vein
Dale[65]	1969	56	N/A	N/A	N/A	80	Veins
Husni[61]	1983	85	0.5-15	N/A	70	74	Vein ($n = 83$)
							PTFE ($n = 2$)
Halliday[64]	1985	47	Up to 18	72	75 (5-year cumulative)	89	Vein
Danza[63]	1991	27	N/A	N/A	N/A	81	Vein
AbuRahma[62]	1991	24	5.5	100	75 (7-year cumulative)	63	Vein
Gruss[48]	1997	19	N/A	N/A	71	82 overall	Vein
		32	N/A	N/A	85		PTFE
Jost[27]	2001	18	2		Primary 77; secondary 83		Vein
		3			0		PTFE

PTFE, Polytetrafluoroethylene.

years confirmed by phlebography. Clinical improvement was seen in 89% of patients.[64] Danza and colleagues reported somewhat better results with use of the saphenous vein as a free graft rather than as a transposition. Of 19 patients who underwent free saphenous vein grafting, 84% experienced either symptomatic relief or improvement versus 75% of 8 patients who underwent transposition.[63] Gruss and Gruss and Hiemer reported "long-term patency" (no time interval reported) in 22 of 26 grafts. On the basis of these results, Gruss recommended using externally supported ePTFE grafts with arteriovenous fistulae for all cross-femoral venous bypasses.[48,66]

Plethysmographic evidence of outflow obstruction was an independent predictor of clinical outcome in a report by AbuRahma and coworkers. Of their patients, 88% undergoing the Palma procedure who had abnormal preoperative maximum venous outflow showed significant clinical improvement, whereas 86% of those with normal preoperative maximum venous outflow had no improvement after surgery.[62]

Prosthetic Femorocaval, Iliocaval, and Inferior Vena Caval Bypasses

Anatomic in-line iliac or iliocaval prosthetic reconstruction can be performed for (1) unilateral disease when autogenous conduit for suprapubic grafting is not available or (2) bilateral iliac, iliocaval, or inferior vena caval occlusion. Extensive iliocaval venous thrombosis secondary to inferior vena caval filters or tumors, as well as retroperitoneal fibrosis not responding to nonoperative therapy, are potential indications. Failure of previous endovascular attempts and occlusion after placement of multiple stents are also indications for bypass.

Technique

The femoral vessels (for the arteriovenous fistula or for the site of the distal anastomosis) are exposed at the groin. The iliac vein or the distal segment of the IVC is exposed with a right oblique flank incision through a retroperitoneal approach. The vena cava at the level of the renal veins is best exposed through a midline or a right subcostal incision. The ascending colon is mobilized medially, and the vena cava is exposed. The infrarenal IVC is reconstructed with a 16- to 20-mm graft, the iliocaval segment usually with a 14-mm graft, and the femorocaval segment with a 10- to 12-mm graft. The arteriovenous fistula is constructed first in patients who undergo an iliocaval bypass (see Figs. 160.3, 160.7 and 160.8).

A short iliocaval bypass with a significant pressure gradient can be performed without an arteriovenous fistula. Reconstruction of the vena cava with a straight ePTFE graft, if inflow is good, is also usually performed without an arteriovenous fistula. In patients who undergo femorocaval bypass, we perform the

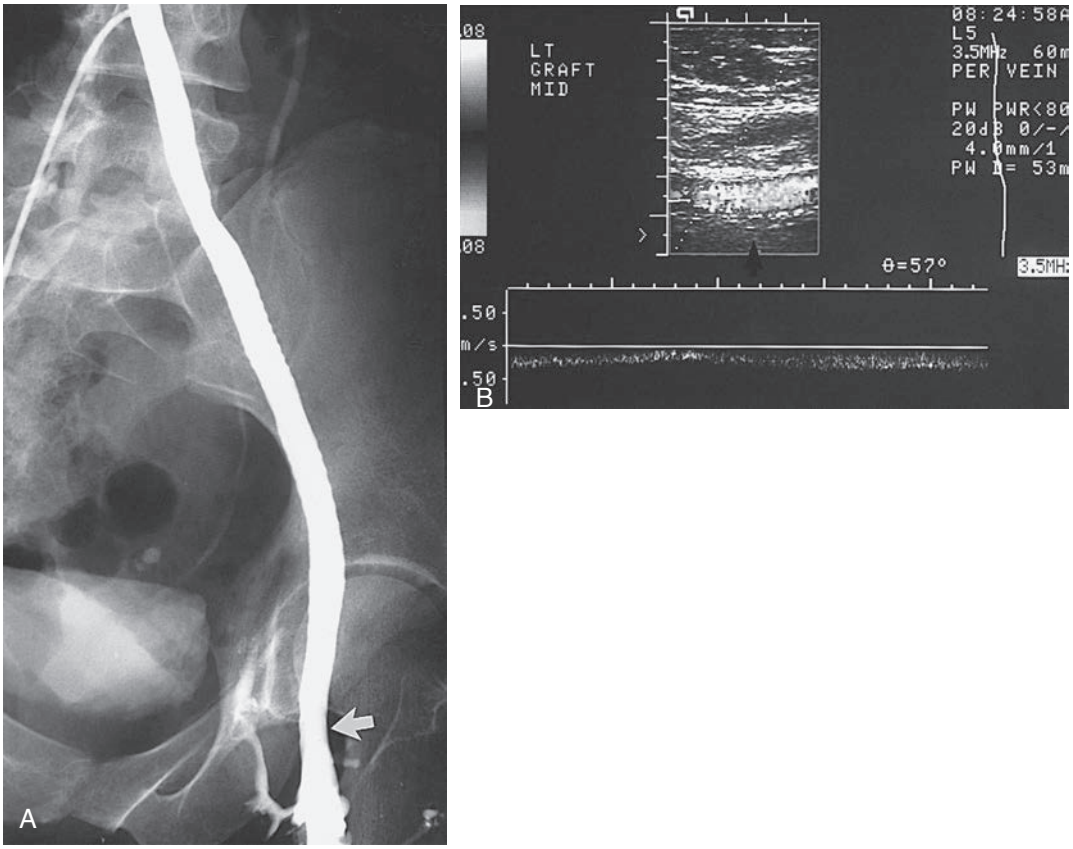

Figure 160.7 (A) Venogram 1.6 years after implantation in a 36-year-old female patient confirms widely patent 10-mm polytetrafluoroethylene graft. *Arrow* indicates site of the end-to-end femoral anastomosis. (B) This patient is free of symptoms 10 years after the operation with duplex evidence of graft patency.

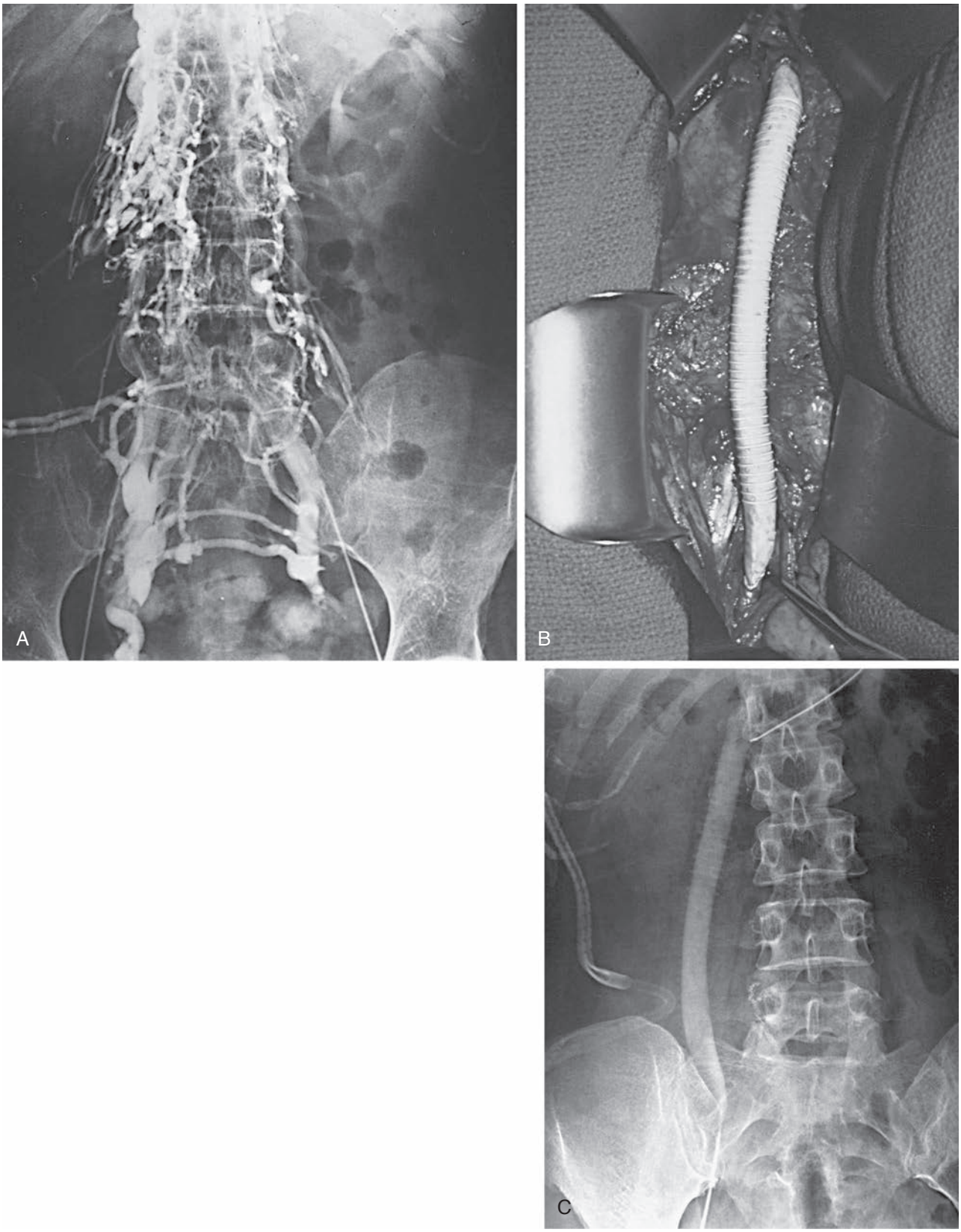

Figure 160.8 (A and B) Extensive iliocaval obstruction in a 47-year-old patient treated with right iliocaval bypass with a right saphenous vein/common femoral artery arteriovenous fistula. (C) Postoperative venogram shows patent graft.

TABLE 160.2 Published Results of Femorocaval/Iliocaval Bypass

First Author	Year	No. of Limbs	Follow-Up (Months)	Imaging (%)	Patency Rate (%)	Clinical Improvement (%)	Graft Material
Gloviczki[22]	1992	12	1-60	100	58	67	11 PTFE 1 Dacron
Husfeldt[68]	1981	4	4-30	100	100	100	PTFE
Dale[47]	1984	3	1-30	100	100	100	PTFE
Alimi[46]	1997	8	19.5 (mean)	100	88	88	PTFE
Jost[27]	2001	13	24		54		PTFE

PTFE, Polytetrafluoroethylene.

proximal and distal anastomoses of the bypass first and then create the arteriovenous fistula before opening the graft. As discussed previously, we generally use a tributary of the great saphenous vein for the fistula. The operation is performed with the patient fully anticoagulated, and prior to closure, a small polyethylene catheter is placed to the level of the distal anastomosis to infuse low-dose heparin (500 IU/h).

Results

Experience with femorocaval or iliocaval bypass is limited; only a few series have been published (Table 160.2).[22,27,46,47,67] In a Mayo Clinic series of 17 such bypasses, primary and secondary patency rates at 5 years were 63% and 86%, respectively.[27]

Alimi and colleagues reported the results of eight iliac vein reconstructions with femorocaval or iliocaval bypasses for both acute and chronic obstructions. In four patients with chronic obstruction, three grafts were patent at last follow-up.[46] Eklof and associates observed only one occlusion in five grafts followed for 14 to 22 months after surgery, in which bypass was combined with venous thrombectomy for acute DVT.[69] In 2003 the Mayo Clinic group published long-term results of femoroilial, femorocaval, and iliocaval prosthetic bypasses. They observed 5-year secondary patency rates of 86% for femoroiliac and iliocaval bypasses and 57% for femorocaval bypasses. The only factor affecting long-term patency was the presence of May-Thurner Syndrome.[59] We believe that all femorocaval or longer iliocaval grafts require the benefit of a distal arteriovenous fistula to maintain patency. Our policy now is to keep the fistula patent as long as possible.[27,54]

Combined Endovascular and Open Reconstructions

The combination of long iliac vein occlusions with chronic thrombosis of the common femoral vein precludes effective venous stenting. In these patients, open surgical thrombectomy of the common femoral vein with excision of old thrombus and recanalized intimal strands can be combined with intraoperative iliac or iliofemoral vein stenting. We perform these procedures in a hybrid operating room. A saphenous vein or bovine pericardial patch can be used to close the defect after thrombectomy in the femoral vein (Figs. 160.9 and 160.10). Two-year patency rates of these hybrid reconstructions were published in a Mayo Clinic series, including four patients with stent placement extending into the common femoral vein patch and five patients with the stent terminated proximal to the common femoral patch. All of the latter experienced early thrombosis; two underwent further stenting into the common femoral vein at the time of revision. Two-year secondary patency in patients with common femoral vein extension ($n = 6$) was 67% compared with 0% without common femoral vein stent ($n = 3$).[59]

Iliac Vein Decompression

Compression of the left iliac vein between the right common iliac artery (see Fig. 160.1) and the fifth lumbar vertebra was described first by McMurrich[67] in 1908 and later in much more detail in a large autopsy study by May and Thurner, who also recognized the clinical implications of the iliac "spurs" leading to acute DVT.[4,70] Cockett and Thomas coined the term *iliac vein compression syndrome* in 1965 and called attention to the obstructive symptoms in affected patients, who are often seen without clinical signs of previous DVT.[5] May-Thurner syndrome is observed more frequently in women between the second and fourth decades of life. Left lower extremity swelling, venous claudication, pain, and skin changes secondary to chronic stasis, including rare ulceration, may develop.[3,5-7]

An acute complication is left iliofemoral DVT. Some surgeons suggest repair of any lesion discovered,[71-78] but we advocate reconstruction only for symptomatic patients with previous iliofemoral DVT. Endovascular techniques with stenting are the first choice of treatment in most patients (see Chapter 161). However, open surgery can be performed in patients in whom endovascular treatment has been unsuccessful or is considered inappropriate.

Technique

The usual procedure is a Palma procedure. In patients with stenosis or short iliac occlusion, direct exploration of the vena caval bifurcation with the use of a variety of techniques to release the iliac venous obstruction has been recommended. The iliac vein is fully mobilized, and any external compressing bands are transected. Excision of intraluminal webs followed by vein or ePTFE patch angioplasty may be performed; other surgeons recommend transposition of the iliac artery behind the

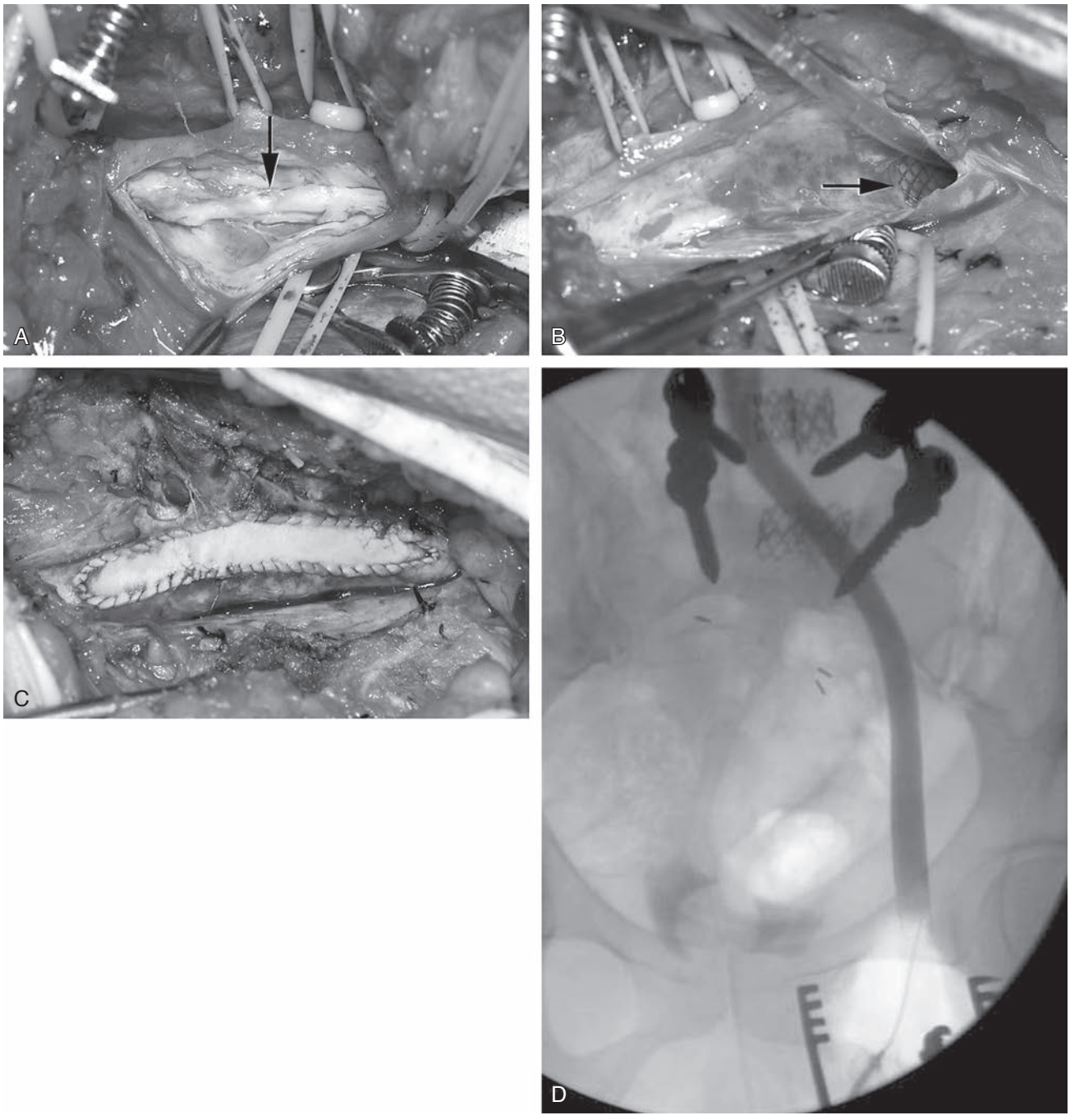

Figure 160.9 Combined Endovascular and Open Reconstruction for Chronic Iliofemoral Venous Occlusion. (A) Note old recanalized thrombus *(arrow)* in the common femoral vein. (B) The old thrombus was excised and the iliofemoral vein was stented with Wallstents *(arrow)*. (C) The femoral vein was closed with bovine pericardial patch. (D) Postoperative venogram confirms widely patent iliofemoral vein.

iliac vein.[53,71] Cormier and coworkers suggested transposition of the right common iliac artery into the left internal iliac artery to decompress the left common iliac vein.[72] Placement of a silicone elastic bridge over the iliac vein to prevent compression by the iliac artery, as suggested earlier, is not recommended.[73]

Results

Akers and colleagues found that of 80 reported patients undergoing iliac vein decompression, 65 (81%) had significant improvement postoperatively.[74]

Suprarenal Inferior Vena Cava Reconstruction

The most common reason to reconstruct the suprarenal IVC for benign disease is membranous occlusion of the IVC, which is frequently associated with occlusion of the hepatic veins (Budd-Chiari syndrome), subsequent portal hypertension, and liver failure (see Chapter 164). Occlusion of the suprahepatic IVC usually does not always cause significant congestion of lower extremity veins, although leg edema and venous claudication may develop. If percutaneous transluminal balloon angioplasty,

Figure 160.10 (A) Preoperative photograph of an 81–year-old patient with severe right lower extremity swelling and massive transudation of fluid due to right common iliac vein obstruction. Patient underwent a combined endovascular (iliac vein stenting) and open (thromboendovenectomy of the common femoral vein). (B) Photograph 9 months after the operation confirmed excellent clinical results.

stenting, or transatrial dilation of the membranous occlusion has not been successful, and portosystemic shunting is not required, venacavoatrial bypass is an effective technique to decompress the IVC. Most surgeons agree that an externally supported ePTFE graft is the best option.[13,45,52,65]

Technique

The retrohepatic segment of the vena cava and the right atrium are exposed through a right anterolateral thoracotomy, with extension of the incision across the costal arch so that the peritoneal cavity is entered through the diaphragm. The liver is retracted anteriorly, and the paravertebral gutter is exposed together with the suprarenal segment of the IVC. The pericardium is opened anterior to the right phrenic nerve, and the right atrium is isolated. The IVC is cross-clamped with a partial-occlusion clamp above the renal vein, and a 16- to 18-mm externally supported ePTFE graft is sutured end to side to the IVC. The graft is then passed parallel to the IVC to the right atrium or the suprahepatic IVC. The central anastomosis is performed after placement of a partial-occlusion clamp on the vena cava or the right atrium. Before completion of the anastomosis, air is carefully flushed from the graft to avoid air embolization.

An anterior approach was suggested by Kieffer and associates, who performed segmental replacement of the suprahepatic IVC using a short externally supported PTFE graft. Tunneling of a long cavoatrial graft anterior to the bile duct and under the left lobe of the liver was also reported (Fig. 160.11).[52]

Results

Wang and colleagues reported on 100 patients with Budd-Chiari syndrome, 12 of whom underwent cavoatrial bypasses. Clinical improvement with patent grafts was noted in 10 patients at a median follow-up period of 1.5 years after surgery.[13] In another series, Victor and colleagues reported patent grafts at 21 months to 6 years after the operation in five patients.[65]

Three cavoatrial grafts placed for nonmalignant disease were reported by the Mayo Clinic group: one patient with an ePTFE graft was asymptomatic at 10 years, a long Dacron graft became occluded at 3 years, and a spiral vein graft occluded within 1 year.[27,59]

SUMMARY

Progress in endovascular techniques has decreased the number of patients who are candidates for open surgical reconstruction for chronic occlusion of the iliofemoral veins or the IVC. Proper patient selection, attention to technical details during surgery, selection of the appropriate graft, perioperative thrombosis prophylaxis, and close follow-up are important to achieve long-term success. The Palma procedure using the great saphenous vein provides predictable long-term success for patients with unilateral iliac vein occlusion. ePTFE grafting for iliac vein or IVC occlusion is also an effective tool in the treatment of carefully selected patients with advanced, symptomatic venous disease. Combined endovascular and open procedures will likely increase the success of reconstruction of the large veins in the future.

PELVIC CONGESTION SYNDROME

The development of valvular incompetence and/or obstruction in the pelvic and gonadal veins may cause disabling symptoms, mainly in women of childbearing age; the disease is known as

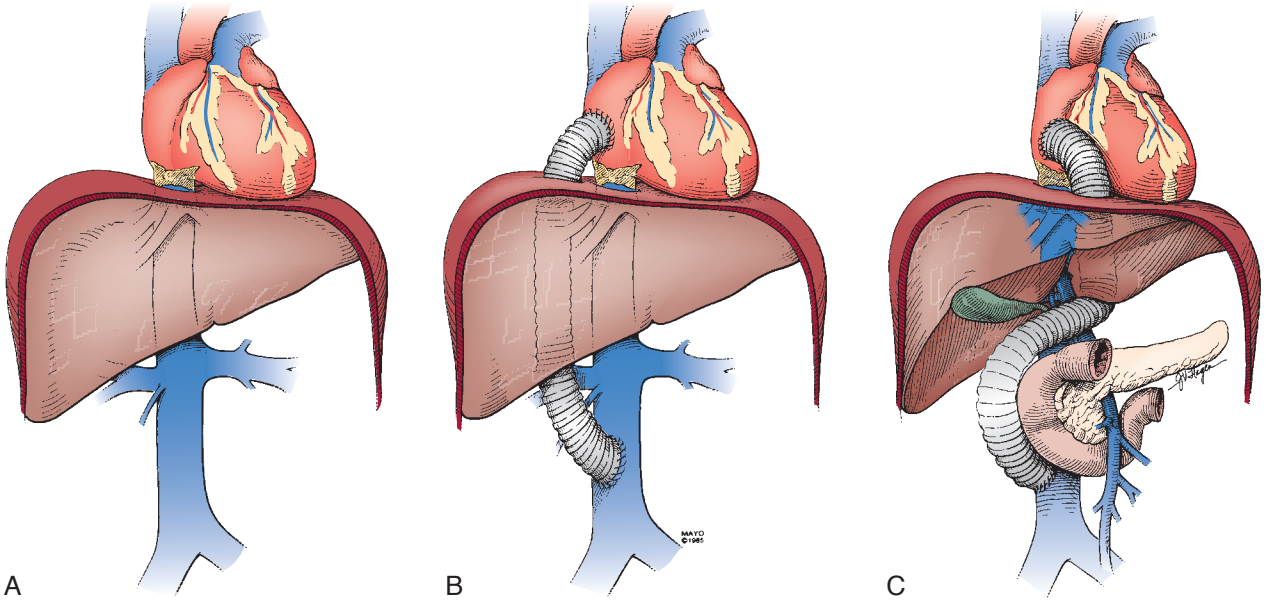

Figure 160.11 Different configurations of cavoatrial bypass performed for membranous occlusion of the inferior vena cava. Reinforced polytetrafluoroethylene graft can originate from the infrarenal (B) inferior vena cava and be routed behind the right lobe of the liver. Another potential position of the graft is behind the left lobe of the liver (C). (With permission of Mayo Foundation.)

pelvic congestion syndrome (PCS). Although first described in 1857 by Richet[79] and given its name in 1949 by Taylor,[80] this pathology was recognized only recently as a frequent cause of chronic pelvic pain.

INCIDENCE

Pelvic venous incompetence and varicose veins are found in 10% of women, and 15% of women between the ages of 18 and 50 years suffer from pelvic pain.[81] In a cohort of 148 patients with chronic pelvic pain, Soysal and coworkers noted that the incidence of PCS was 30%.[82] Belenky and colleagues found ovarian vein incompetence and varicosities in 9.9% of the general female population, with 59% of this group experiencing symptoms of PCS.[83] However, because many of these symptoms can be caused by other pelvic diseases (endometriosis, uterine fibroma, pelvic cancer, etc.), initial gynecologic examinations are mandatory before reaching the diagnosis of PCS, even in the presence of pelvic varicose veins. PCS can also cause lower limb varicose veins in atypical locations or recurrence after surgical treatment.[84]

ANATOMY OF THE PELVIC VENOUS SYSTEM

Pelvic structures are drained by both the internal iliac (hypogastric) and genital veins (Fig. 160.12).[85] The internal iliac vein rises near the upper part of the sciatic foramen, passes cranially posterior and medial to the internal iliac artery, and at the brim of the pelvis joins the external iliac to form the common iliac vein. Its tributaries correspond to branches of the internal iliac artery and are divided into parietal and visceral veins. Parietal tributaries are the superior and inferior gluteal, sciatic, sacral, ascending lumbar, and obturator veins. Visceral tributaries are the internal pudendal, middle hemorrhoidal, and vesicoprostatic plexuses in men and the uterine, gonadal, and vesicovaginal plexuses in women. Lepage and associates showed that in 27% of cases the internal iliac vein drains by means of two separated trunks.[86] In exceptional cases it can drain directly into the IVC. Valves are found infrequently in the internal iliac veins: 10% of cases in the main trunk and 9% in its tributaries.[86]

The ovarian veins form a plexus in the broad ligament near the ovary and uterine tube and communicate with the uterine plexus. They drain to the IVC on the right at an acute angle and on the left side to the LRV at a right angle. Anatomic variations can be present (see Fig. 160.12B). Multiple trunks can be present.[87] Observations based on vaginal ultrasound have revealed that the normal average diameter of ovarian veins is less than 5 mm.[88] According to Stancati and coauthors, valves are present in these veins, mainly in the distal third.[89] However, Ahlberg and collaborators found no ovarian vein valves on the left side in 15% and on the right side in 6%.[90] The ovarian veins are connected with the utero-ovarian and salpingo-ovarian veins through the broad ligament and with the rectal, vaginal, and vesical veins.

PATHOPHYSIOLOGY

According to Greiner,[91] pelvic varicose veins can be due to three different mechanisms:

- Type 1: reflux secondary to pelvic and genital (ovarian) vein incompetence. It is the most frequent etiology and of

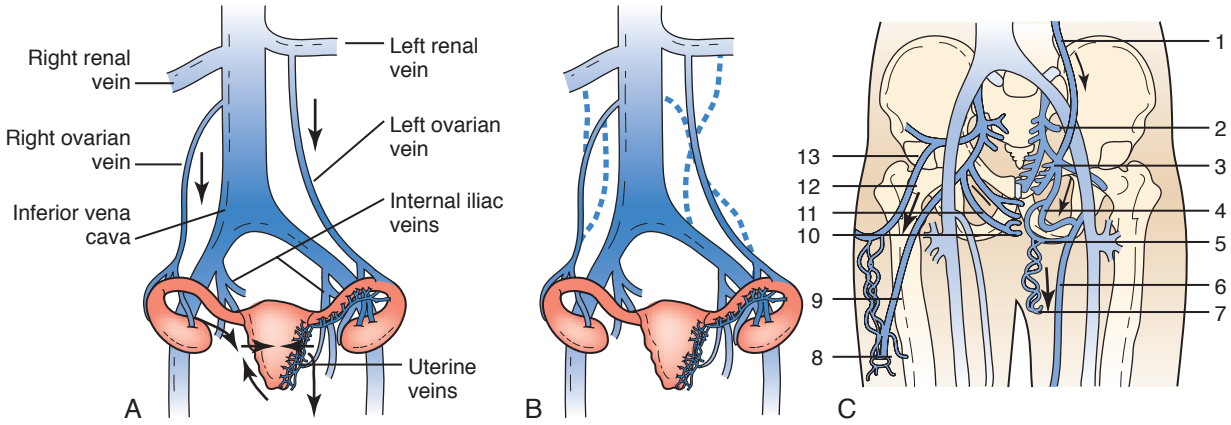

Figure 160.12 Anatomy and Reflux of the Pelvic Veins. (A) Anatomy. *Black arrows* indicate pathologic reflux in the bilateral ovarian veins and around the uterus, with varicosities developing on the left side of the uterus. (B) Anatomic variations of the ovarian veins, shown by *dashed lines*. (C) Internal iliac veins and their communications with the utero-ovarian plexus and thigh superficial veins: *1*, ovarian vein; *2*, internal iliac vein; *3*, uterine vein; *4*, obturator vein; *5*, external pudendal vein; *6*, great saphenous vein; *7*, varicosity of the anteromedial aspect of the thigh; *8*, varicosity of the posterolateral aspect of the thigh; *9*, sciatic vein; *10*, vulvar varicosity; *11*, internal pudendal vein; *12*, cystic and vaginal veins; *13*, buttock veins. Multiple collaterals are present.

uncertain cause. However, it has been shown that hormonal factors contribute to varicose veins, and that these veins are exposed to high levels of hormones. Estradiol inhibits the reflex vasoconstriction of vessels and induces uterine enlargement with selective dilation of the ovarian and uterine veins mainly during pregnancy.[92] In one study, intravenous injection of dihydroergotamine in women with pelvic congestion and pain produced a 35% reduction in vein diameters veins associated with a decrease in pelvic blood flow that resulted in pain relief.[93] Moreover, cystic ovaries are frequently associated with pelvic varicose veins.[93,94]

- Type 2: secondary to obstruction of outflow. May-Thurner syndrome,[95-97] nutcracker syndrome,[97,98] left renal vein thrombosis, post-thrombotic disease involving the common iliac veins or the IVC (or both), and Budd-Chiari syndrome can all lead to the development of pelvic varicose veins via collateral pathways.
- Type 3: secondary to a local compression phenomenon. The main cause is endometriosis, but it can also be due to tumors, posttraumatic lesions, and sequelae of infections.

CLINICAL FINDINGS

PCS often develops in young women (late 20s to early 30s) who are multiparous,[99] but treatment occurs at a mean age of 41 years.[100] The condition often disappears after menopause.[99] These lesions are rare in men except in cases of varicocele and are often due to venous obstructive disease. PCS can be described as a highly variable combination of chronic (up to 6 months) pelvic pain (heaviness that increases during the day, mostly if the patient stays sitting or standing and when lifting, and can be relieved by the supine position), dyspareunia, dysmenorrhea, and urinary (dysuria, pollakiuria, bladder urgency), and rectal (constipation) symptoms. Symptoms occur predominantly on one side but can be bilateral. Hemorrhoids are frequently found in these patients.[100]

Clinical examination can reveal cervical motion; retrocervical, paracervical, uterine, and ovarian tenderness; uterine enlargement; and uterine retroversion. According to Beard and colleagues, the combination of tenderness on abdominal palpation over the ovarian point and a history of pain after sexual activity was 94% sensitive and 77% specific for discriminating pelvic congestion from other causes of pelvic pain.[99] Perineal (mainly vulvar) varicose veins can be associated with PCS. Lower extremity findings include superficial venous insufficiency, atypical varicose veins (buttock, posterior and lateral aspect of the thigh, etc.), and recurrence after procedures for varicose veins.[100]

DIAGNOSIS

Noninvasive Investigations

Duplex Scanning

A pelvic color DUS is performed with transparietal 5-MHz and transvaginal probes after 3 days of a no-residue diet and an empty stomach.[95] Both the internal iliac and genital veins should be imaged to identify dilation and reflux, including imaging with the Valsalva maneuver. Pelvic varicose veins are defined as multiple dilated tubular structures around the uterus and ovary with venous Doppler signals and diameters larger than 5 mm.[95] The positive predictive value of a 6-mm-diameter ovarian vein for the diagnosis of PCS has been reported as 83.3%.[101] The obturator, sciatic, and internal pudendal veins should also be imaged. Collateral pathways, such as enlarged veins crossing the uterine myometrium, are often present. The common iliac veins, IVC, and renal veins should be imaged to search for venous obstruction. A lower extremity DUS can be

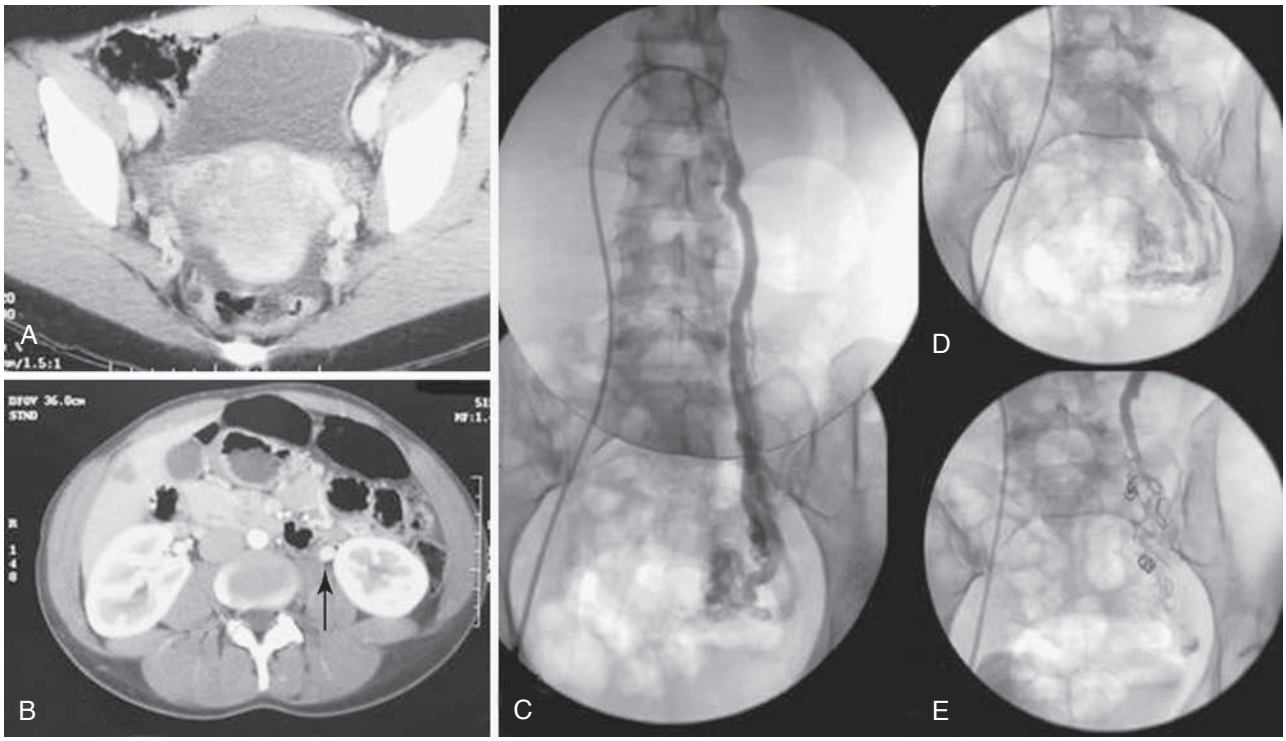

Figure 160.13 Woman With Pelvic Congestion Syndrome Secondary to Left Ovarian Vein Incompetence. (A) Pelvic varicose veins on computed tomography (CT) angiography. (B) CT angiogram showing left ovarian vein reflux. The vein is dilated and opacified early *(arrow)*. (C) Selective phlebography of an incompetent left ovarian vein with periovarian varices. (D) Delayed phlebographic imaging showing the left internal and common iliac veins. (E) Results after embolization with foam and coils.

obtained to search for valvular incompetence, which can be secondary to pelvic incompetence.

Computed Tomographic and Magnetic Resonance Venography

CTV or MR venography can be performed to confirm the presence of pelvic and genital varicose veins.[102] CTV should be timed for evaluation of the portal, genital, and renal veins, and separate imaging should be performed at later times for evaluation of the pelvic and iliocaval veins. Pelvic varices are imaged as dilated, tortuous, enhanced tubular structures around the uterus and ovary, with possible extension into the broad ligament and pelvic sidewall (Fig. 160.13A). They can also involve the paravaginal venous plexus. Rozenblit and associates define ovarian vein incompetence as opacification during the arterial phase of CT angiography and 7 mm or greater in maximum diameter (see Fig. 160.13B).[103]

On T1-weighted MRI, pelvic varicose veins have no signal intensity because of the flow void artifact; on gradient-echo MRI, varicose veins have high signal intensity. On T2-weighted MRI, they usually appear as an area of low signal intensity, although hyperintensity or mixed signal intensity may also be noted, possibly because of the relatively slow flow through the vessels. Two and three-dimensional, T1-weighted gradient-echo sequences performed after the intravenous administration of gadolinium are the most effective sequences for demonstrating pelvic varicose veins.[102,104,105]

CT and MR venography examinations can also identify other sources of pelvic pain, mainly endometriosis. Images should be evaluated for venous obstructive disease. However, because these tests are performed in the supine position, they can underestimate venous pathology.

Contrast Phlebography

This imaging technique is considered the "gold standard" for diagnosis and can be combined with interventions for treatment.[106] It is performed under local anesthesia via the common femoral or brachial vein approach.[106,107] It should image the four veins responsible for venous return from the pelvis: both internal iliac veins and both gonadal veins. The study should be performed with and without a Valsalva maneuver. A 4F or 5F Cobra 2 catheter is commonly used to catheterize and perform selective venography (see Figs. 160.13C, 160.14A and 160.15A). In some cases a Simmons catheter is required for imaging of the right gonadal vein (Fig. 160.16A). In cases of a brachial approach, a multipurpose or a vertebral catheter can be helpful. Either approach can be used, but catheterization of the right ovarian vein is more often successful from the brachial approach (18% failure for brachial approach[106] vs. 58% failure through femoral approach[107]). Kim and associates advocate the use of balloon occlusion venography to image the internal iliac veins (7F Berman wedge catheter [Arrow International, Reading, Pennsylvania] inflated in the trunk of the internal iliac vein).[108]

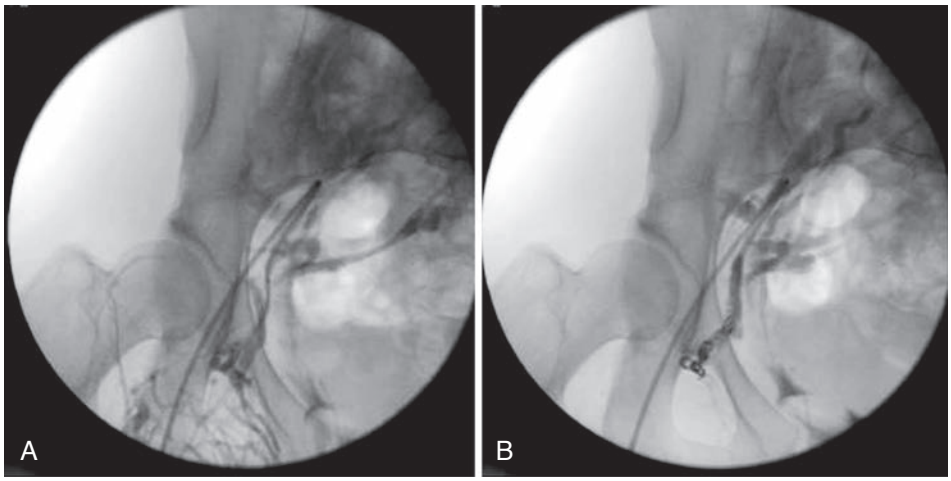

Figure 160.14 Patient With Varicose Vein Recurrence After Right Great Saphenous Vein Stripping. (A) Selective phlebography of the right obturator vein. (B) Results after treatment with foam and coils.

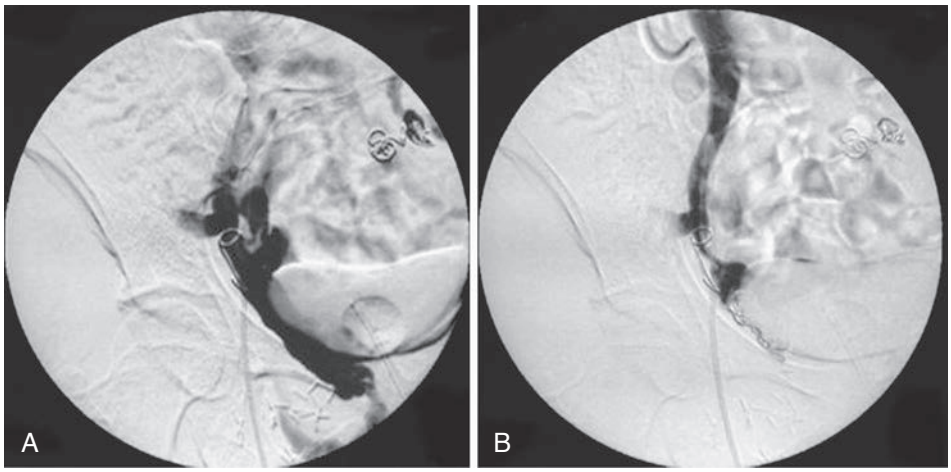

Figure 160.15 Woman With Pelvic Congestion Syndrome. (A) Phlebography showing right vesicovaginal varicose veins. (B) Completion phlebography after treatment with foam and coils.

According to Chung and Huh, criteria used for the phlebographic diagnosis of PCS caused by ovarian vein valvular incompetence are the following: ovarian vein larger than 5 mm in diameter (see Figs. 160.13C and 160.16A), retention of contrast medium in the ovarian vein for longer than 20 seconds, existence of congestion in the pelvic venous plexus, opacification of the internal iliac vein (see Fig. 160.13D), and/or filling of vulvovaginal and thigh varicosities. Each variable is assigned a value between 1 and 3, depending on the degree of abnormality, and a venogram score of 5 or higher indicates the presence of PCS.[109]

Differential Diagnosis

As suggested earlier, it is important to rule out nonvascular causes of pelvic pain, such as endometriosis, uterine fibroma, pelvic cancer, or pudendal nerve compression. The diagnosis relies on analysis of the symptoms and on investigations. Pelvic ultrasound, CT, and MRI can be of considerable help, but sometimes a more extensive evaluation is required. Laparoscopy reveals pelvic varicose veins if performed in a feet-down position while limiting the pressure of peritoneal insufflation, and it may help to eliminate other pathologies.

TREATMENT

Medical Treatment

Medroxyprogesterone acetate (Provera, Upjohn Ltd, Kalamazoo, Michigan), 30 mg/day for 6 months, was shown to be effective in relieving the symptoms of PCS by Faquhar and coworkers, with 73% of women reporting at least 50% improvement, versus 33% of those treated with placebo.[110] However, this positive effect was not maintained 9 months after discontinuation of treatment. In a prospective randomized trial, Soysal and colleagues compared the efficacy of goserelin acetate (3.6 mg/month for 6 months) and medroxyprogesterone (30 mg/day for 6 months).[82] One year after treatment, goserelin had achieved a statistically significantly better result. Micronized purified flavonoid fraction (Daflon, Servier), 500 mg twice a day for 6 months, resulted in statistical improvement at the end of

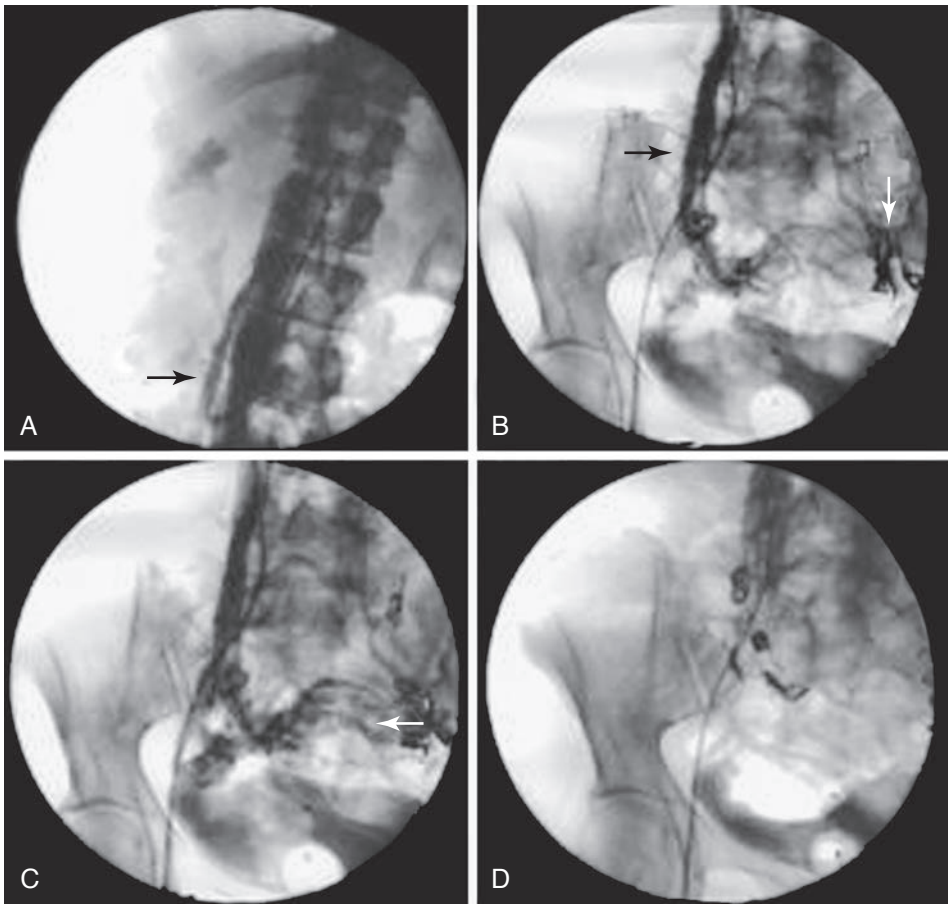

Figure 160.16 Woman With Pelvic Congestion Syndrome Caused by Bilateral Ovarian Vein Reflux. (A) Selective phlebography of a large refluxing right ovarian vein with a Simmons catheter. (B) Result after sclerotherapy and embolization with foam and coils. (C) Late pelvic view showing periovarian varices *(arrow)*. (D) Result after sclerotherapy and embolization with foam and coils.

treatment in a prospective randomized study.[111] Although these medications provide symptom relief, none have permanent effects once discontinued.

Conventional and Laparoscopic Surgery

Different surgical techniques have been reported for the treatment of PCS, including ovarian and/or internal iliac vein ligation, ovarian and uterine artery and vein ligation, oophorectomy, and even total hysterectomy with bilateral salpingo-oophorectomy. Some of these techniques can be performed laparoscopically, but they remain invasive.[112] Despite the observation that bilateral oophorectomy combined with hysterectomy and hormone replacement therapy have been shown to be effective in patients who fail medical therapy,[94] this is an invasive option, which is not acceptable for women who want to become pregnant.

Endovascular Treatment

Techniques

Endovascular therapy with embolization is now considered the first line treatment for PCS in most patients. The procedure is performed under local anesthesia either together with diagnostic phlebography or as a separate procedure. After selective catheterization and contrast-enhanced study of the refluxing vein or veins, embolization is performed. "Rules" of the embolization technique include the following: (1) the entire internal iliac vein should not be embolized, and (2) regarding the gonadal veins, embolization must be performed proximal to the last collateral to prevent recurrences. Embolization is mainly performed using coils (0.035 inch for 4F or 5F catheter and 0.018 inch for microcatheters, pushable or detachable, fibred or not). Vascular plugs (Amplatzer) can be used in cases of very large veins.[113] The number of devices used and the rate of recurrence can be reduced by the addition of foam sclerotherapy to embolization. Foam is prepared from sodium tetradecyl sulfate (Trombovar or Sotradecol) or Aetoxisclerol (polidocanol) and can be injected either before coiling or by using the sandwich technique (see Figs. 160.13E, 160.14B, 160.15B, and 160.16B). Foam is created using air or a 50/50 mixture of CO_2 and O_2 according to the Tessari method (see Chapter 155).[113a] With 3% polidocanol, we use up to 30 mL of foam. Other agents which have been used include n-butyl cyanoacrylate, ethylene vinyl alcohol copolymer, and sodium morrhuate combined with Gelfoam.[108]

When treating the internal iliac vein, Kim and coauthors recommended using balloon occlusion and avoiding embolization of the main trunk.[108] In addition, care must be taken to avoid embolization of the external iliac and common femoral veins.

In a prospective randomized study of 164 women with PCS, Chung and Huh compared ovarian vein embolization, hysterectomy with bilateral oophorectomy and hormone replacement

TABLE 160.3 Results of Embolization for Pelvic Congestion Syndrome

Series	N	Veins	Technique	Follow-Up (Months)	RESULTS (%)	
					Improved	Worsened
Capasso et al.[117]	19	OV	Enbucrilate and/or coils	15.4	74	
Tarazov et al.[118]	6	OV	Coils	24	100	
Machan et al.[119]	23	OV	Coils	15	78	
Cordts et al.[120]	9	OV	Coils +gelatin	13.4	100	
Cotroneo et al.[121]	22	OV	Coils	3	60	
Richardson et al.[122]	28	OV	Coils + foam	22.2	SS	
Maleux et al.[123]	41	OV	Enbucrilate + coils	19.9	68.2	
Scultetus et al.[124]	7	OV	Coils	27	43	
	6	IIVT	Coils		83	
	12	IIVT + OVR	Coils + OVR		83.4	
Bachar et al.[125]	6	OV	Coils	7.7	83	
Pieri et al.[126]	33	OV	3% STS	9	61	
Chung et al.[109]	52	OV	Coils	26.6	SS	
Kim et al.[108]	127	OV	Gelfoam + sodium morrhuate + coils	45	83	4
Lasry et al.[127]	30	OV ± IIVT	Coils	6	90	
Kwon et al.[128]	67	OV	Coils	40	82	
Creton et al.[107]	24	OV ± IIVT	Coils	36	76	
Gandini et al.[129]	38	OV	3% STS foam	12	100	0
Asciutto et al.[114]	35	OV and/or IIVT	Coils	45	Embolisation >>>	
Laborda et al.[130]	202	OV ± IIVT	Coils	89% at 60	93	
Nasser et al.[131]	113	OV ± IIVT	Coils	12	100	0
Hocquelet et al.[132]	33	OV ± IIVT	Coils + foam	23	93	0
Monedero[107]	215	OV and/or IIVT	Coils + foam	6	90	
Ratnam[133]	218	OV and/or IIVT	Coils + foam	0.9M	95	
Hartung[97]	78	OV +/− IIVT	Coils + foam	4	91	0

>>>, Embolization superior to other techniques. *IIVT*, Internal iliac vein tributaries; *OV*, ovarian vein; *OVR*, ovarian vein resection; *SS*, statistically improved; *STS*, sodium tetradecyl sulfate.

therapy, and hysterectomy with unilateral oophorectomy.[109] They showed that embolization was significantly more effective than the other two techniques. Asciutto showed that using embolization, untreated patients had no improvement, whereas treated patients improved.[114] Regarding the technique, Monedero and coauthors reported 1186 cases of embolization for recurrent lower limb varicose veins caused by pelvic disease; they had better results with coils and the sandwich technique (coils plus 2% polidocanol or hydroxypolyethoxydodecane foam) than with the use of coils alone (95.6% rate of improvement vs. 76% at 6 months).[106] Literature review shows better results in series reporting embolization of all incompetent veins.

Complications of embolization with or without sclerotherapy are rare and include hematoma at the access site, extravasation of contrast corresponding to vein perforation, coil or glue embolization, DVT and pulmonary embolism, and transient cardiac arrhythmia.

PCS linked to iliocaval obstructive disease (mainly May-Thurner Syndrome) should be treated by stenting of the obstructive lesions (the left common iliac vein).[97,115]

Clinical guidelines including recommendations for the treatment of PCS were recently published by the Society for Vascular Surgery and the American Venous Forum. These recommend that PCS and pelvic varices due to pelvic vein incompetence should be treated using coil embolization, plugs, or transcatheter sclerotherapy, used alone or together (grade 2B) (Table 160.3).[116]

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CHAPTER 161

Iliocaval Venous Obstruction: Endovascular Treatment

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INTRODUCTION

A web-like lesion at the iliocaval junction was described by McMurrich, a Canadian physician, in 1908.[1] Recognition of the lesion now commonly known as May-Thurner syndrome (MTS), or iliac compression syndrome, evoked a series of controversies from the start. Initial debate involved the origin of the lesion: was it ontogenic or acquired? Based upon the rarity of the lesion in embryos and infants, an acquired etiology is now generally accepted, although a few lesions occur at known fusion planes and could be classified as ontogenic.[2,3] Since neovascularization is absent, postthrombotic etiology is not likely. May and Thurner proposed that the lesions, which can range from increased wall thickness to intraluminal membranes, webs, and fibrous strands, result from the trauma of the repeated pulsations of the closely related artery. The name "iliac compression syndrome" is incomplete as compression is but one element of a complex lesion.

Later controversies arose concerning the high prevalence of MTS in the general population in silent form. Cockett reported that the lesion can be highly symptomatic in a select group, often young women of child-bearing age with preferential involvement of the left lower extremity.[4] In some patients, the lesion appeared to precipitate deep venous thrombosis of the extremity. Lea Thomas, a radiologist, developed specialized techniques to visualize the lesions with contrast, while recognizing that venographic sensitivity was only about 50%.[5] Modern imaging techniques have confirmed that iliac vein compression posterior to the crossing right common iliac artery is present in as much as two-thirds of the general population.[6] Recent use of intravascular ultrasound (IVUS) has shown the lesion to be present at more diverse locations in the pelvic venous anatomy (Fig. 161.1), and that it affects a much broader demographic than the narrow band recognized by Cockett and colleagues.[7] IVUS has a sensitivity of ≈80% for the lesion. Most lesions are silent, but symptoms, ranging from swelling to venous ulcerations, may be present. The lesion is best viewed as a permissive pathology, precipitating symptoms when a secondary insult to the limb, such as trauma, infection, or deep venous thrombosis (DVT), is superimposed. Postthrombotic iliac vein

Abstract

The last two decades have witnessed a paradigm shift in the management of femoroiliocaval venous lesions. Endovenous interventions have supplanted open surgery as the treatment of choice, with the latter reserved for patients who are not candidates for endovenous interventions or who have failed such interventions. This chapter reviews the diagnosis and endovenous treatment of femoroiliocaval lesions.

Keywords

Iliac stent
May-Thurner syndrome
Iliac vein compression syndrome
Post thrombotic syndrome
iliocaval chronic total occlusions
occluded inferior vena caval filter

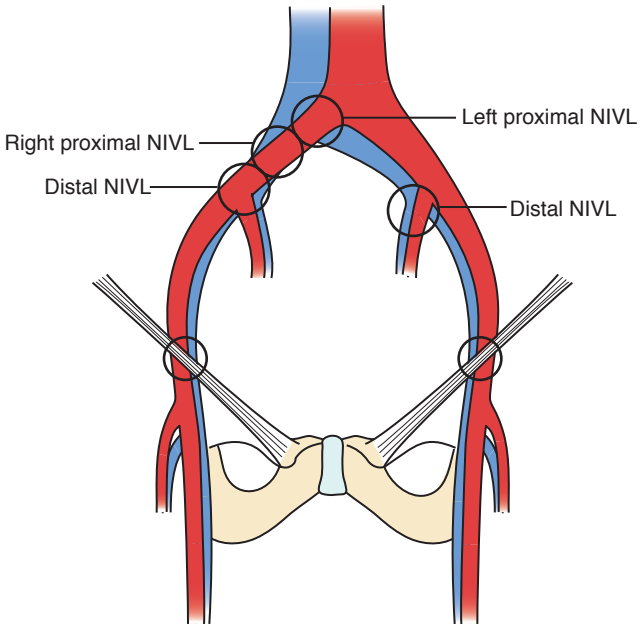

Figure 161.1 Common Sites of Iliac Vein Stenosis Seen on Intravascular Ultrasound Examination. The "classic'" proximal nonthrombotic iliac vein lesions (NIVL) lesion occurs in the left common iliac vein posterior to where it is crossed by the right common iliac artery. The distal lesion on the left side occurs posterior to the left hypogastric artery crossing. On the right side, both proximal and distal lesions underlie the right common iliac artery. Compression by the inguinal ligament is also a source of stenosis.

stenoses resulting from DVT, either precipitated by a May-Thurner type of lesion or occurring de novo, are increasingly recognized. Specific relief of symptoms after percutaneous stent placement has largely silenced earlier critics who argued that the obstructive lesion, even when associated with collaterals, is a "natural anatomic variant" not requiring specific correction. Percutaneous iliac vein stenting has rendered earlier veno-venous bypass techniques obsolete, and these techniques are now reserved only for stent failures. Stent technology has also exposed venous obstruction at the iliac level as a major cause of chronic venous disease (CVD). The safety and efficacy of venous stenting have dramatically broadened the spectrum of CVD patients who can undergo treatment for this disease with clear clinical improvement. This represents a major treatment paradigm change. An unexpected finding in recent stent experience is the observation that patients with combined obstruction and reflux appear to benefit clinically even if the associated reflux remains untreated.[8]

PATHOLOGY

Two major types of iliocaval venous obstruction are recognized, nonthrombotic iliac vein lesions (NIVL), synonymous with MTS, and postthrombotic iliac vein stenosis (PTS) resulting from a prior episode of DVT.[9] The relative incidence in major centers is roughly 50/50 but trending higher in favor of the postthrombotic variety because of improved diagnosis of iliac vein DVT with modern imaging modalities. About 10% of cases are of the mixed type, as NIVL can precipitate thrombosis, and thrombus tends to add fibrosis to compression points in the vein during organization. NIVL lesions are typically subsegmental and focal, occurring in areas where compression by the overlying artery or ligament occurs (see Fig. 161.1). PTS lesions are longer, involving one or more vein segments, with focal elements. A special form of long diffuse stenosis caused by a postthrombotic fibrous envelope surrounding the vein was first recognized by Rokitansky in autopsy studies. Milder forms of this type may not be recognizable in venograms without luminal measurements (Fig. 161.2). A focal lesion occurring in association with a Rokitansky stenosis will be underestimated as the adjacent reference segment for calculation of the stenosis is not normal but stenotic.

The majority of limbs with iliac vein obstruction will also have reflux below the inguinal ligament,[10] resulting in peripheral venous hypertension. Both the obstructive and reflux pathologies cause microvascular injury, which is sustained by the peripheral venous hypertension.[11]

Venous collateralization is poorly understood. In many venous territories, alternative pathways already exist. They normally remain dormant as flow preferentially takes the course of the lower resistance main pathway. When the main channel is stenosed or occluded and the venous pressure rises, flow is diverted through these alternative routes. When the axial stenosis is stented, flow once again takes the lower resistance pathway and the collaterals "disappear." Venographic collaterals can be demonstrated in about 30% of iliac vein stenoses.[7,9] Because of the geometric factor (r^4/L) in the Poiseuille equation, an exponential number of collaterals are needed to equal the conductance of the normal iliac vein. For example, 256 collaterals, each 4 mm in size, are required to equal the conductance of a 16-mm common iliac vein. For this reason it is rare for iliac vein lesions to be fully compensated by adequate collateralization. The exponential power of the geometric factor plays a role in venous resistance. The magnitude of its effects can be surprising. For example, a luminal stenosis of a mere 12% in the common iliac vein (16 ≥14 mm) will nearly double the resistance, and hence, the pressure with the same flow.

Using isotope lymphangiography, lymphatic dysfunction can be demonstrated in ≈30% of limbs with CVD.[12,13] The injury occurs at the pre-collector level, presumably in association with the microcirculatory injury of CVD. Normalization of these scintigraphic abnormalities occurs in about 25% of limbs following iliac stenting (Fig. 161.3).

INDICATIONS AND PATIENT SELECTION FOR ILIOCAVAL VENOUS STENTING

CVD in general is a nonlethal disease and loss of limb is a rarity. There is no role for prophylactic treatment of silent lesions. If symptoms resulting from iliocaval stenosis or occlusion are present, conservative treatment with compression is the initial treatment modality. This modality will fail in 50% or more patients because of inefficacy or, more often, noncompliance with compression regimens.[14] The nature and cause of noncompliance

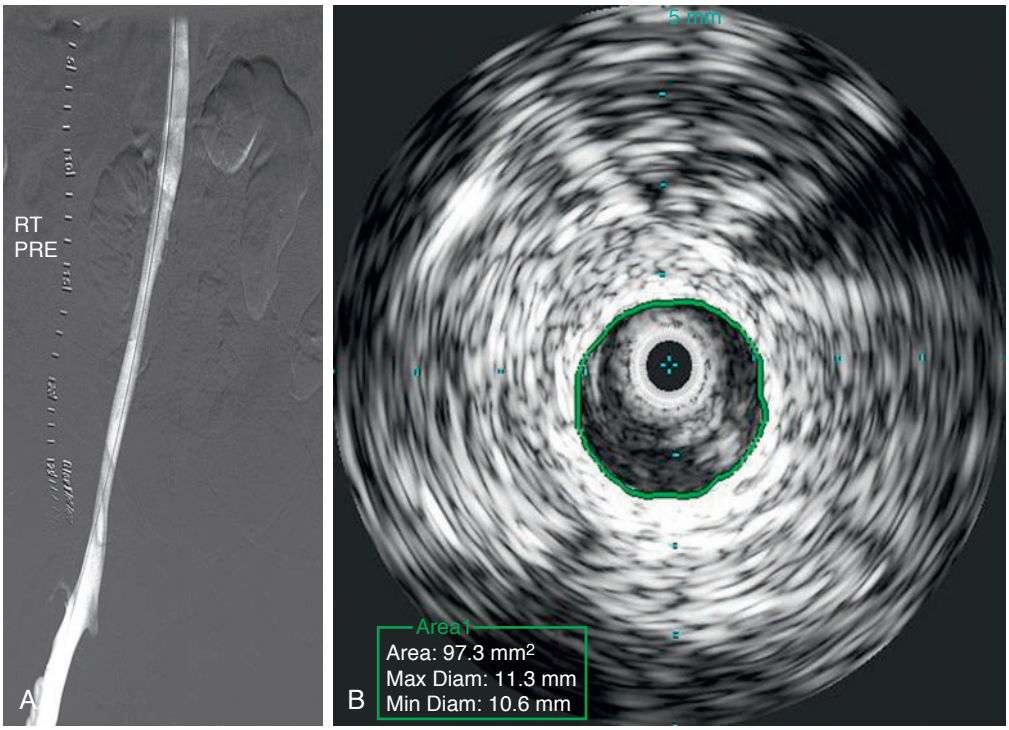

Figure 161.2 Rokitansky Stenosis. The long diffuse stenosis is not readily apparent on venography, which lacks an internal scale (A). On intravascular ultrasound examination (B) the maximum common iliac vein diameter is 11 mm with an area of 97 mm^2, constituting a 50% area stenosis.

is poorly understood. Intensive monitoring, education, and supervision have had no effect on the problem.[15,16] Iliac vein stenting may be carefully considered after failure of conservative treatment. Patients should be advised that this is not a "circulation problem" of the type that affects arteries, but a disease that usually manifests with only quality-of-life issues. Patients are often relieved by this information alone and are then able to make an informed decision regarding intervention.

In general, only patients with CEAP classes 3 to 6 are candidates for correction of iliocaval stenosis. Lesser clinical classes can occasionally be considered if they are thought to have venous claudication or the "venous hypertension syndrome." Patients with venous hypertension syndrome have diffuse limb pain (not to be confused with local pain over varices) relieved by elevation of the limb and compression stockings. Some patients have learned that ambulation can provide pain relief due to lowering of the venous pressure by calf pump action. Atypical pain syndromes include venous claudication (particularly when climbing up stairs), nocturnal leg cramps, restless legs, and dull, diffuse, achy limb pain at night even with the leg elevated. Life-style limitations and sleep deprivation from these atypical pain syndromes are appropriate indications for corrective intervention. Pain severity should be assessed by the visual analog scale (VAS). Venous clinical severity score (VCSS) is the current standard for complete clinical assessment (see Chapter 19).

Special patient subsets who may benefit from stent correction of iliocaval venous stenosis include geriatric patients who cannot self-apply compression due to arthritis or frailty, obese patients with severe venous manifestations who are not candidates for weight reduction surgery, patients with recurrent cellulitis of the limb secondary to the obstructive lesions, and cases of acute iliac vein thrombosis caused by an underlying stenosis. Lysis of the acute thrombus will initially be required in combined acute/chronic lesions. The stenosis can be stented as soon as the thrombus has cleared.

In another special category are limbs with swelling diagnosed as lymphedema. Too often, this diagnosis is based only on clinical impression without the benefit of isotope lymphangiography. "Classic" clinical features of lymphedema, such as dorsal foot hump, squaring of toes, and Stemmer sign, can be present in venous swelling as well, with or without associated lymphatic damage/dysfunction. Considering the huge prevalence of CVD in western populations and the high incidence of associated lymphatic abnormalities, it is likely that lymphedema associated with CVD ("venous lymphedema") is the most common type of secondary lymphedema in the Unites States, with a prevalence far exceeding either primary lymphedema or other secondary causes.

A diagnosis of lymphedema may consign the patient to lifelong, often ineffective conservative therapy. It is recommended that a correctible iliac vein stenosis be ruled out in individuals before a diagnosis of lymphedema is established. After stent correction of a stenosis discovered by this approach, improvement in swelling can be expected, although to a lesser degree than in obstructed limbs without lymphatic abnormalities (see Fig. 161.3).

Associated reflux is often present in patients diagnosed with iliac vein obstruction. If the reflux is in the superficial system, saphenous ablation can be performed before iliac vein stenting, or it can be accomplished concurrently.[17] Patients with deep reflux should undergo iliac vein stenting first, as good results can be anticipated despite the residual reflux.[18] Deep reflux

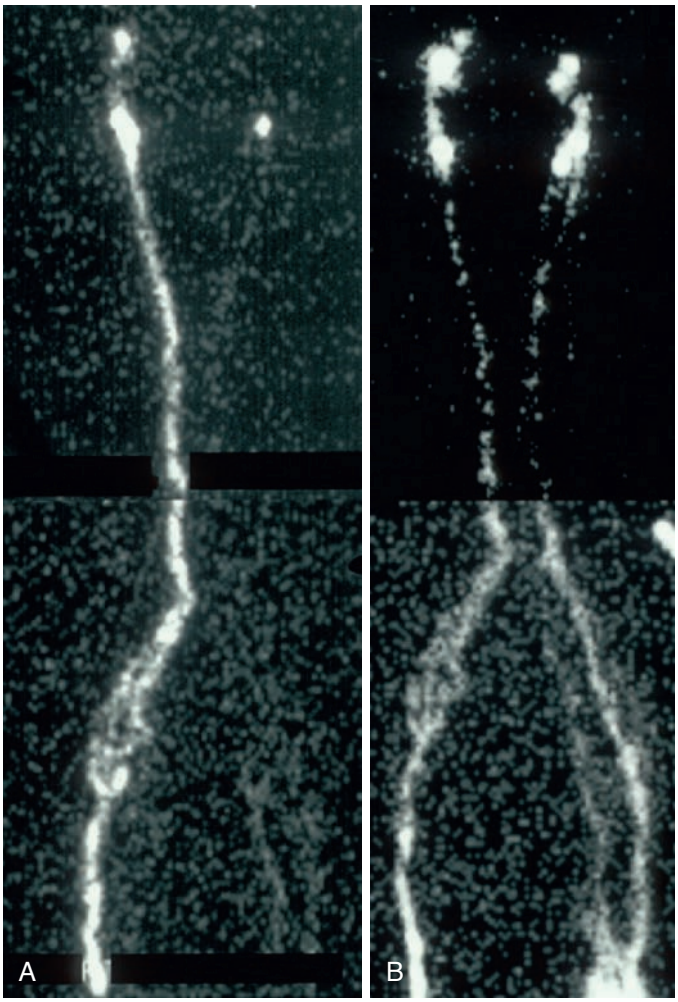

Figure 161.3 Venous Lymphedema. Note the absence of lymphatic activity in the left lower limb on lymphoscintigraphy (A). Activity recovers (B) after the underlying iliac venous stenosis is corrected with a stent.

corrective procedures which currently require complex open techniques are reserved for the salvage of nonresponders to initial stenting.

DIAGNOSIS

Venography has been the main imaging modality to diagnose iliac vein lesions. Transfemoral injection of contrast is required as adequate opacification of pelvic venous anatomy is often not obtained by pedal injection. Because iliac vein lesions are manifested as compression in the coronal (proximal lesion) or the sagittal plane (distal lesion), single plane views can be misleading (Fig. 161.4). However, subtle signs are often present to alert the astute observer (Fig. 161.5).

In a blinded comparison of IVUS and transfemoral venography in 162 limbs at our institution, the presence of a stenosis in the iliofemoral segments was altogether missed by venography in 25%.[19] Among those lesions visible with contrast, the degree of stenosis was significantly underestimated compared to IVUS ($P < .001$). In addition, the level of the iliac confluence as determined by venography varied by as much as one vertebral body length compared to that identified using IVUS. The ideal upper and lower landing zones determined by venography agreed with IVUS guidance in only 29% of limbs. Therefore IVUS guidance during stent placement is preferred. These procedural elements are crucial for technical success and outcome.

Imaging techniques (computed tomography venography, magnetic resonance venography, or duplex ultrasound) can be more definitive than venography for diagnosis, as lumen size at stenotic points can be measured by the intrinsic scale, which is not possible with venography. The diagnostic accuracy of these imaging techniques in detecting iliac vein stenosis has not been determined. At present, we consider IVUS the gold standard in the morphologic diagnosis of iliac vein lesions.

TREATMENT

Technique[20]

A mid-thigh ipsilateral femoral vein access under ultrasound guidance is preferred. Access at superficial locations over bony points, as in arterial practice, is not necessary. Low venous pressure facilitates even deep access with few hematomas or other complications. A large sheath, typically 11 Fr, is preferred for easy manipulation of inserted devices. The mid-thigh access allows enough room for the sheath to deploy stents below the inguinal ligament if needed. This approach has the advantages of the supine position, short distance to the lesion, and antegrade manipulation. Popliteal and internal jugular access are somewhat inferior, but can be used as backup sites. An optional on-table venogram may be performed for diagnostic and road-mapping purposes. The procedure can be performed solely with fluoroscopy and IVUS control without using contrast in the event of contrast allergy or renal dysfunction. IVUS examinations of the inferior vena cava (IVC), common iliac vein (CIV), external iliac vein (EIV), and common femoral vein (CFV) are carried out to identify lesions and appropriate landing sites. IVUS planimetry is used to measure areas. The degree of stenosis is best calculated using the expected normal area for the location (Table 161.1). Using the adjacent or contralateral lumen as a reference may result in underestimation of the stenosis; long diffuse narrowing of the lumen is present in an estimated 20% to 50% of cases. Most symptomatic limbs will have >50% area stenosis or greater, although some lesser lesions can be symptomatic in individual patients with PTS due to severe compliance changes. Predilation using large-caliber (16 to 18 mm) high-pressure balloons (14 to 16 atm) is routine. Because of the fibrous nature of iliac vein lesions, angioplasty alone is seldom effective as recoil is the rule. Large-caliber stents approximating the normal size of the iliofemoral segments should be used. The use of undersized stents is among the most common causes of iatrogenic stenosis with persistent symptoms (Fig. 161.6).

Treating the entire diseased segment or lesion in continuity with landing sites clear of disease is essential for successful outcomes. Skipping short segments of apparently normal vein is a source of potential recurrence. It appears that metal load is a lesser cause of stent thrombosis than uncovered lesions. From this perspective, a philosophy of liberal stent coverage

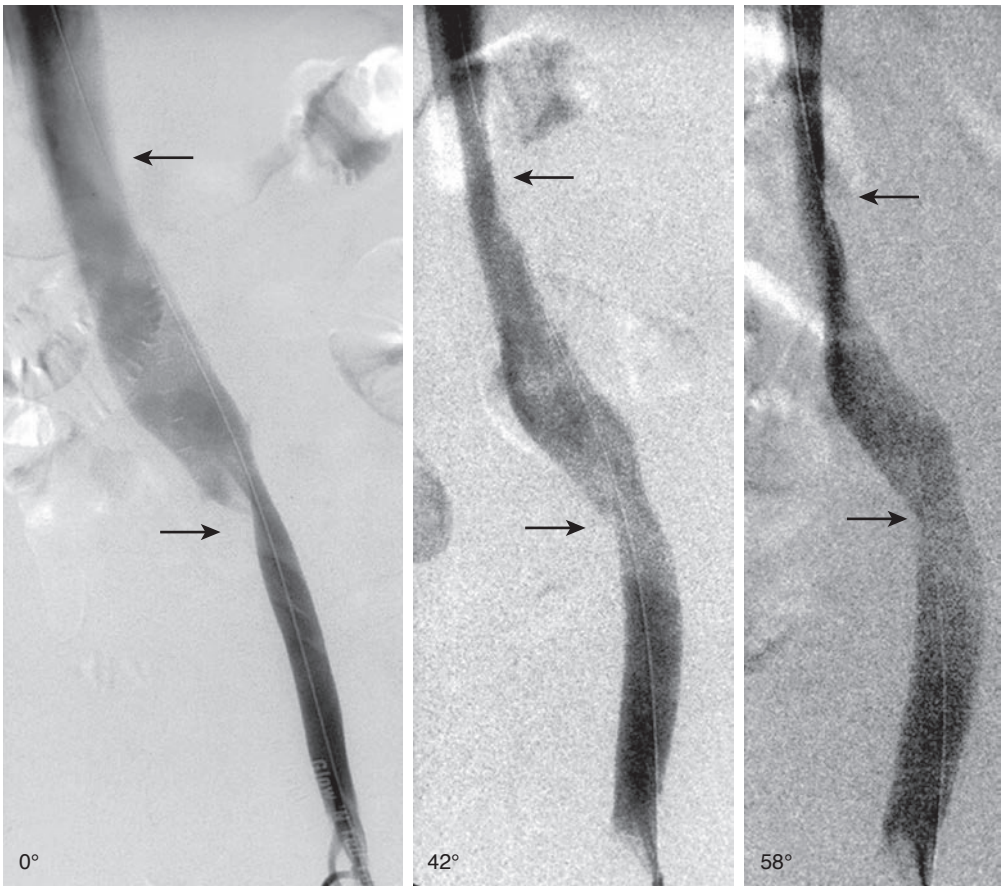

Figure 161.4 Nonthrombotic iliac vein lesions are often two-dimensional rather than circumferential. In the example shown, the proximal lesion is not apparent on frontal projection (0°) but is revealed on lateral projections (←). The distal lesion apparent in the frontal view becomes hidden in oblique and lateral projections (→). The level of iliac confluence is not readily apparent in the frontal view.

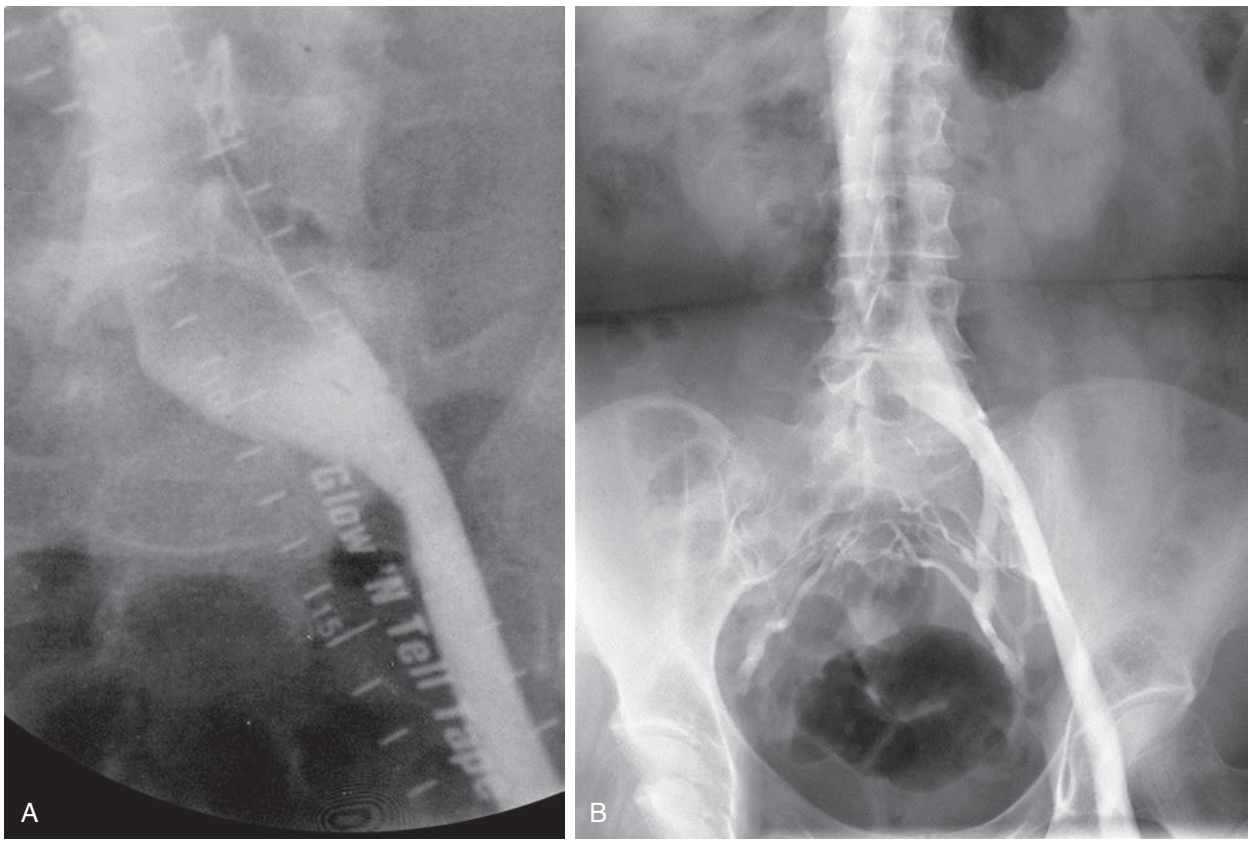

Figure 161.5 Venographic appearance of nonthrombotic iliac vein lesion: "island"-like appearance of the terminal common iliac vein (A). "Pancaking" (B) with collaterals.

TABLE 161.1 Optimal Iliofemoral Venous Segment Diameters/Areas

Vein	Diameter (mm)	Luminal Area (mm^2)
CFV	12	125
EIV	14	150
CIV	16	200

CFV, Common femoral vein; *CIV*, common iliac vein; *EIV*, external iliac vein.

Figure 161.6 An undersized 8-mm diameter stent (optimum 16 to 18 mm) was placed in the iliac vein *(proximal arrow)*. Note the caliber of the stent is smaller than the common femoral vein *(distal arrow)*. Placing an undersized stent results in an iatrogenic stenosis, which is difficult to correct.

rather than one of limited use should govern. Most limbs with postthrombotic disease will require extension of the stent below the inguinal ligament into the common femoral vein. The stent end should remain above the orifice of the deep femoral vein, which provides adequate inflow in most instances to sustain the stent. Occasionally, the stent can be delivered into the deep femoral vein (via jugular, popliteal, or direct deep femoral access) if its ostium is involved in the postthrombotic process. Stent fractures and erosions have been rare with stents crossing the joint crease, unlike arterial applications.

Since the proximal lesion at the iliocaval confluence is spiral, incomplete stent coverage in this area is a common cause of residual symptoms. This tends to occur in procedures that are totally reliant on venographic control without the use of IVUS. The best upper and lower landing sites are chosen on IVUS views using the vertebral bodies and the femoral head as fluoroscopic markers. Extension of the iliac stent for a few centimeters into the IVC is generally required to traverse the proximal lesion in its entirety. Wallstents have been used most often. An 18 or 20 mm stent dilated with 16 and 18 mm balloons, respectively, will accommodate most adults and provide a 2-mm reserve for extra dilation later if required. A Z-stent may be used proximally (within the Wallstent) for added radial strength under the artery, and to minimize jailing of the contralateral iliac outflow (Fig. 161.7). The IVC Z-stent extension greatly simplifies bilateral simultaneous or sequential stenting by eliminating the need for difficult fenestration techniques to reconstruct the iliac confluence.[21] A significant reduction in contralateral DVT has been observed with the Z-stent extension compared to the Wallstent extension.[22] Stenting the iliocaval confluence, particularly when there is bilateral disease, is an unsolved problem.[23] An ideal stent for the confluence is yet to be developed.

Postdilation is carried out after stent deployment. IVUS planimetry is used to confirm that the stenosis has been corrected to achieve the recommended caliber shown in Table 161.1.[24] If not, a larger balloon up to the maximum-rated diameter of the stent is used to achieve the desired caliber. A completion venogram is performed to confirm patency and flow.

The sheath is withdrawn slowly under ultrasound view until the tip exits the vein. A slight to-and-fro movement of the sheath confirms that it is outside the vein. A plug of Surgicel Fibrillar (Ethicon, Somerville, New Jersey) is loaded into the cylindrical plastic guard of the Seldinger needle. Using the obturator with the tip cut off, the hemostatic plug can be pushed into the sheath and delivered over the venotomy site before complete withdrawal of the sheath.

Recanalization of Chronic Total Occlusions[25,19]

Once the province of complex open surgical procedures, chronic total occlusion (CTO) lesions have been found to be surprisingly amenable to percutaneous recanalization in an outpatient setting. Procedure success rates are in the range of about 85% for both iliac and IVC lesions.[19,25] Percutaneous recanalization of extensive occlusions involving both iliac veins and the IVC up to the right atrium have been reported in large case series (Fig. 161.8).[19] Most of these will have chronically occluded renal and hepatic drainage with alternate outflow already established. Few hepatic or renal complications after successful recanalization have been reported.

The recanalization process involves blind threading of a glidewire through the trabeculated vein. Passage with the tip of the glidewire rather than a loop is more often successful. Unlike in arterial CTO, no subendothelial or deeper dissection is performed. Venography, at least in the initial stages, is necessary to define the anatomy and provide a road map. Some CTO lesions that appear daunting on venography can be traversed with surprising ease. This is because contrast may not reach loosely trabeculated segments (often appearing as a "blush")

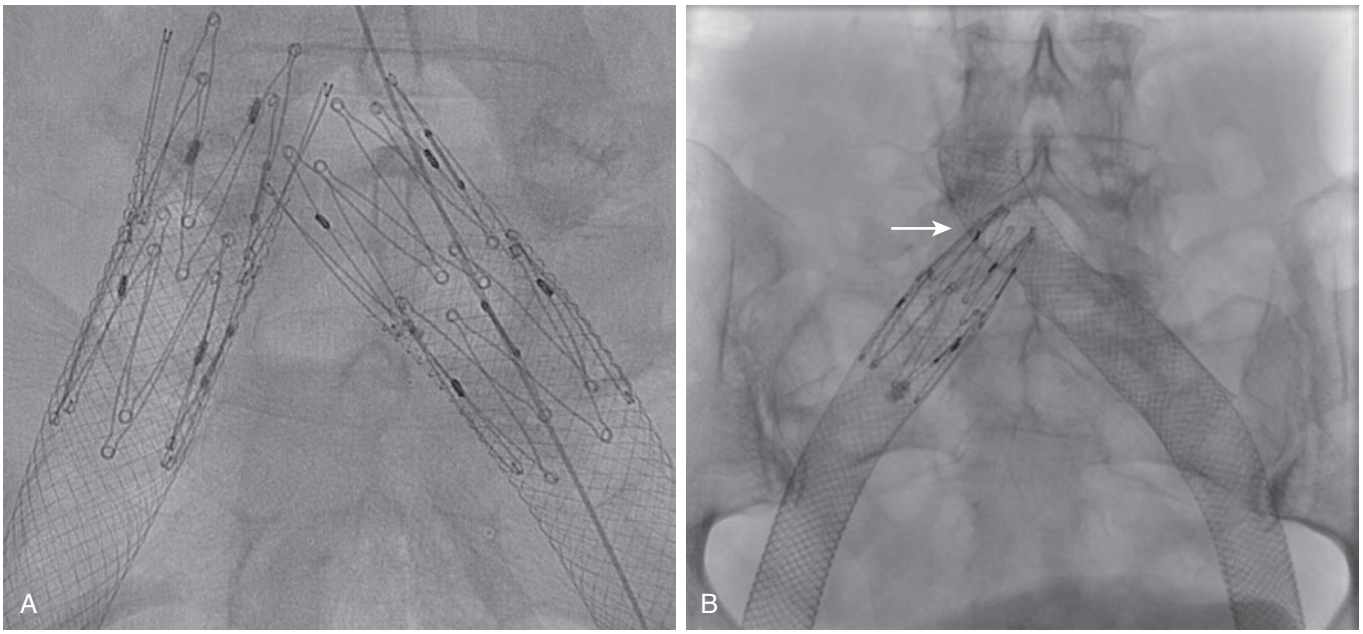

Figure 161.7 Z Stent Inferior Vena Cava Extension of the Wallstent Stack. The widely spaced struts of the Z stent minimize jailing of the contralateral iliac vein and allow easy bilateral sequential or staged iliac stenting (A). Fenestration techniques (B) are technically more demanding. In the example shown, a Z stent has been used to scaffold the fenestrum created in the contralateral Wallstent *(arrow)*. (From Raju S, Ward M, Jr., Kirk O. A modification of iliac vein stent technique. *Ann Vasc Surg*. 2014;28:1485-1492.)

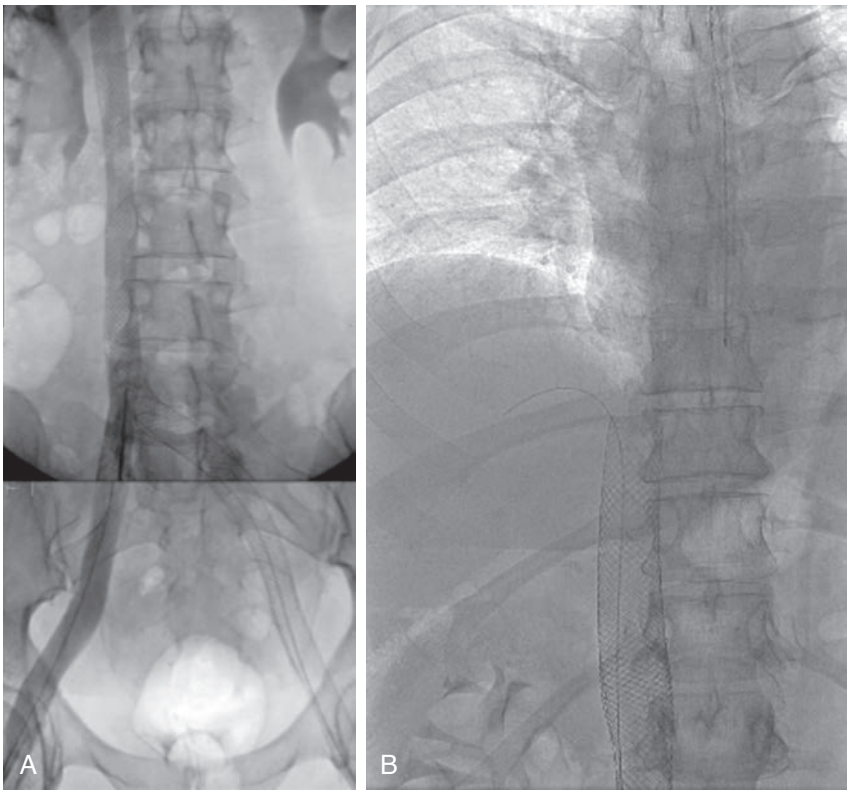

Figure 161.8 Extensive recanalization of chronic total occlusions involving the inferior vena cava and both iliacs. The stent stack extends to the common femoral vein below the inguinal ligament bilaterally (A). Stent erosions and fractures involving the Wallstent crossing joint creases are rare in venous applications. In the (B) panel, the Wallstent stack extends to the atrium.

above short segments of more densely trabeculated vein. The use of angled-tip guiding catheters is standard. Specialized catheters for CTO crossing are helpful. The recanalization course should conform to the normal anatomic course of the occluded vessel. Off-course passage into collaterals or perforations is easily recognized. Because of the low venous pressure and dense fibrous cover over CTO veins, free hemorrhage is rare. In case of perforation, the wire can simply be withdrawn and redirected without aborting the procedure. The passage of the wire into the vertebral canal through collaterals is a hazard if not recognized before balloon dilation. Since the abdominal IVC lies to the right of the vertebral column, passage of the wire in the midline is a clue to vertebral canal entry. This can be checked by oblique or lateral fluoroscopic views. Once the entire CTO lesion is traversed, proper reentry into the open upper IVC or right atrium should be confirmed by venography or IVUS. Occasionally the wire passage may require predilation to allow passage of the 6 Fr IVUS catheter. Normally, the wire tract can be dilated to the desired caliber in a single pass. Stepwise dilation is not necessary as rupture/hemorrhage is very rare.[26] We recommend dilation to 24, 18, 16, and 14 mm for IVC, CIV, EIV, and CFV segments, respectively. To conserve supplies we use 18 mm balloons for all iliofemoral segments and have not encountered problems. Wallstents of corresponding size are then deployed. Small leaks and contrast extravasations are self-limiting once the low-resistance main pathway has been established by stent placement. Completion venography and IVUS planimetry are essential to ensure that a recanalized passage of adequate caliber without conduit defects has been established.

Inadequate inflow into stents is both a short-term and long-term threat to stent viability. There is presently no reliable way to assess inflow. Some stents with rapid washout of contrast have occluded, and others with sluggish flow have surprisingly remained patent. Intraoperative flow may be affected by extraneous factors, including the presence of the sheath obstructing inflow. Preoperative venographic assessments have not been reliable as more inflow channels become visible once a low-resistance channel has been established by the stent. In extreme cases in which all the major named inflow pathways have become occluded and only multiple "twiggy" collaterals provide inflow, a temporary A-V fistula may be considered.

Inferior Vena Cava Filters[19]

Because of the recent liberal use of "retrievable" IVC filters, together with low retrieval rates, an increasing number of complications are currently seen with filter use. One of the more common complications is stenosis or thrombosis of the IVC near the filter. CTO of the IVC and one or both iliac veins produces swelling and pain of the extremities, which can be quite severe. Removal of the filter before recanalization is desirable, but retrieval of a filter encased in fibrous tissue is often impossible. In such instances, the IVC filter can be crushed by balloon angioplasty and stented across using the recanalization technique described earlier (Fig. 161.9). Filters of many types (with the exception of the Mobin Uddin filter) have been successfully treated in this fashion without malsequelae.[19]

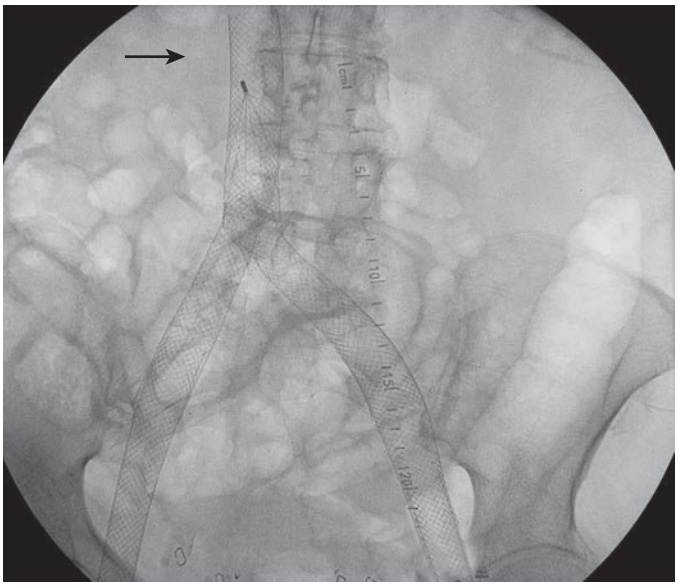

Figure 161.9 Recanalization and stenting of the inferior vena cava (IVC) and both iliac veins following thrombosis associated with an IVC filter *(arrow)* which has been compacted and stented across. Cumulative patency is excellent despite the extensive metal load.

Permanent anticoagulation is desirable after stent exclusion of the filter as thromboembolic protection is lost. Migration of the compacted filter and viscous perforations remain a potential threat in these patients, and patients should be adequately warned during informed consent discussion.

Anticoagulation

Perioperative anticoagulation is used for routine prophylaxis and because of intraoperative endothelial injury. Endothelial healing is complete by 6 weeks after injury.[27] It is believed that deployed stents are covered by pseudo endothelium or are incorporated into the vein wall within this time frame. This means thrombogenicity of the stented segments will be governed by inherent risk factors and not the presence of a stent, per se. Thrombophilia does not appear to influence long-term stent patency with proper anticoagulation.[26]

Stent anticoagulation protocols vary widely among centers. In our practice, patients receive low-molecular-weight heparin (LMWH) in prophylactic dosage before the procedure and intravenous heparin (5000 to 10,000 units) or bivalrudin (75 mg single dose) intraoperatively. Some centers use more rigorous anticoagulation using activated clotting time per cardiac protocols. Post procedure, LMWH is continued at a prophylactic dosage for 48 hours. Patients with NIVLs are discharged on aspirin 325 mg daily if there is no prior history of DVT. Stent thrombosis is extremely rare in this subset. PTS patients are discharged on aspirin as well, if the original DVT was provoked by an event that is no longer present. Long-term anticoagulation with warfarin or one of the new generation oral agents is instituted if there is thrombophilia, recurrent thrombosis, previous unprovoked thrombosis, or extensive stenting.

Reinterventions

Acute thrombosis of stents (<30 days) is rare (≈1%) and occurs almost exclusively in PTS limbs, particularly following CTO recanalizations.[20,25] Thrombolysis usually restores durable patency. In other cases, a lesion at the stent inflow is responsible, as identified by IVUS. Stent extension to cover the inflow obstruction is required in addition to thrombolysis. In our experience, late occlusions (>30 days) occur in 3.5% of stented limbs, overwhelmingly (87%) in postthrombotic limbs.[28] Both early and late occlusions in nonthrombotic disease are quite rare.[20]

Chronic Stent Malfunction[29]

Chronic stent malfunction presents with residual or recurrent symptoms. Like any bypass conduit, stent malfunction is due to problems with inflow, outflow, the conduit itself, or a combination. There are some features unique to the venous stent.[29] Inflow/outflow problems are due to either missed or new lesions obstructing stent flow. Inadequate or partial coverage of the "classic" lesion at the iliocaval confluence during the original procedure is a common problem. This can be exacerbated by downward stent migration or foreshortening of the stent by the squeezing action of the partially covered lesion. A short (<2 cm) extension into the IVC beyond the lesion can lead to coning of the upper end of the stent from compression by the nearby lesion. A small-caliber postthrombotic IVC that was missed during the original procedure is an infrequent cause of stent malfunction, usually when IVUS planimetry was not used. Small-caliber IVC is not as well appreciated on venography as it lacks an internal scale. A normal adult infrarenal IVC has a transverse diameter of 17 to 24 mm on IVUS (smaller range in women). Area planimetry is not useful as the IVC is partially collapsed in most individuals.[30]

Inflow problems can occur when the distal lesion of the MTS (see Fig. 161.1) is missed during the initial procedure. This lesion is often not visible on venography or even IVUS and requires "balloon-sizing" for detection.[18] New or missed postthrombotic lesions can occur at the common femoral vein. When a short stent is used in the common iliac vein, extending only partially or not at all into the external iliac vein, a late stenosis (denovo stenosis) of unknown cause may develop in the external iliac vein after some years.

By far the most frequent causes of chronic stent malfunction are problems associated with the stent conduit itself. There are two major types: stent compression and in-stent restenosis (ISR) (Fig. 161.10).[31] Stent compression is unique to the venous system, wherein the stent is compressed from the outside, squeezing the lumen smaller than the original deployed caliber. The outside force is focal or diffuse fibrosis/restenosis of the stented segment. Stent compression is more resistant to balloon dilation than is ISR.

In-stent restenosis occurring after iliac vein stenting is likely a different process from that affecting arterial stents. ISR that occurs early (<30 days) is probably mostly thrombus (thrombus lining/soft ISR) without cellular elements (Fig. 161.11). The thrombus lining is likely a result of sluggish flow in the now enlarged segment as the flow channel tends to modulate its caliber to correspond to the velocity of inflow. Anecdotal observation suggests that the thrombus lining may be cleared or reduced by instituting anticoagulation. It is also easily cleared at this stage by balloon maceration. After several months, this lining appears to be invested with fibrous elements (hard ISR)

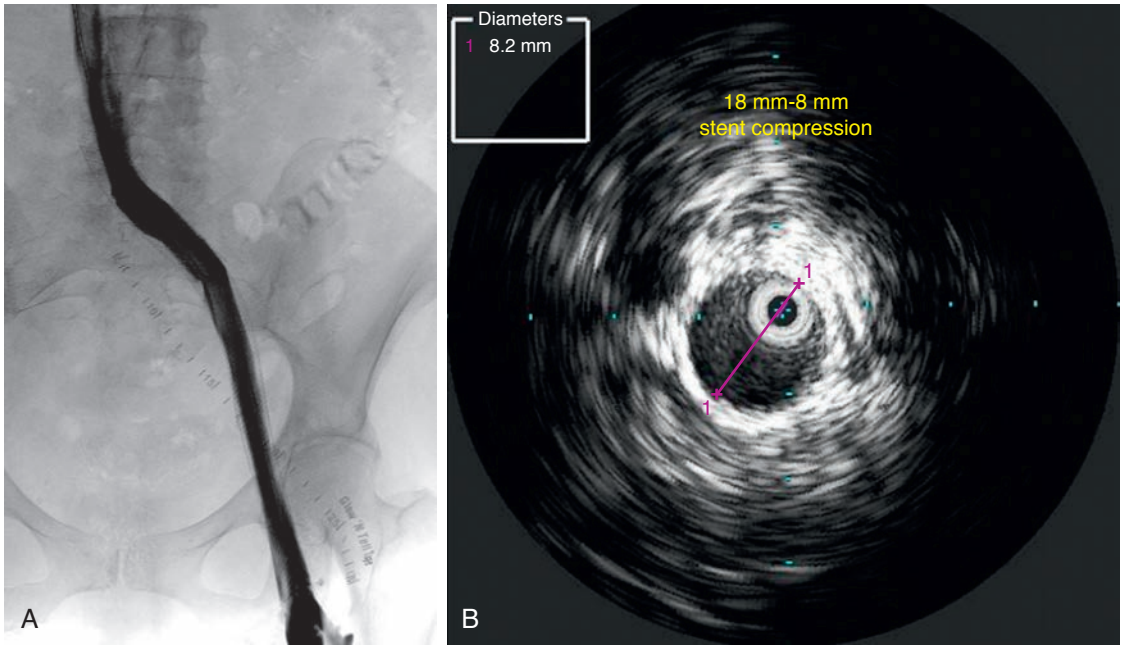

Figure 161.10 Stent compression is unique to venous stents. Compression is difficult to appreciate on venography (A). Using intravascular ultrasound, a 16-mm stent can be seen to have been compressed to 8 mm (B).

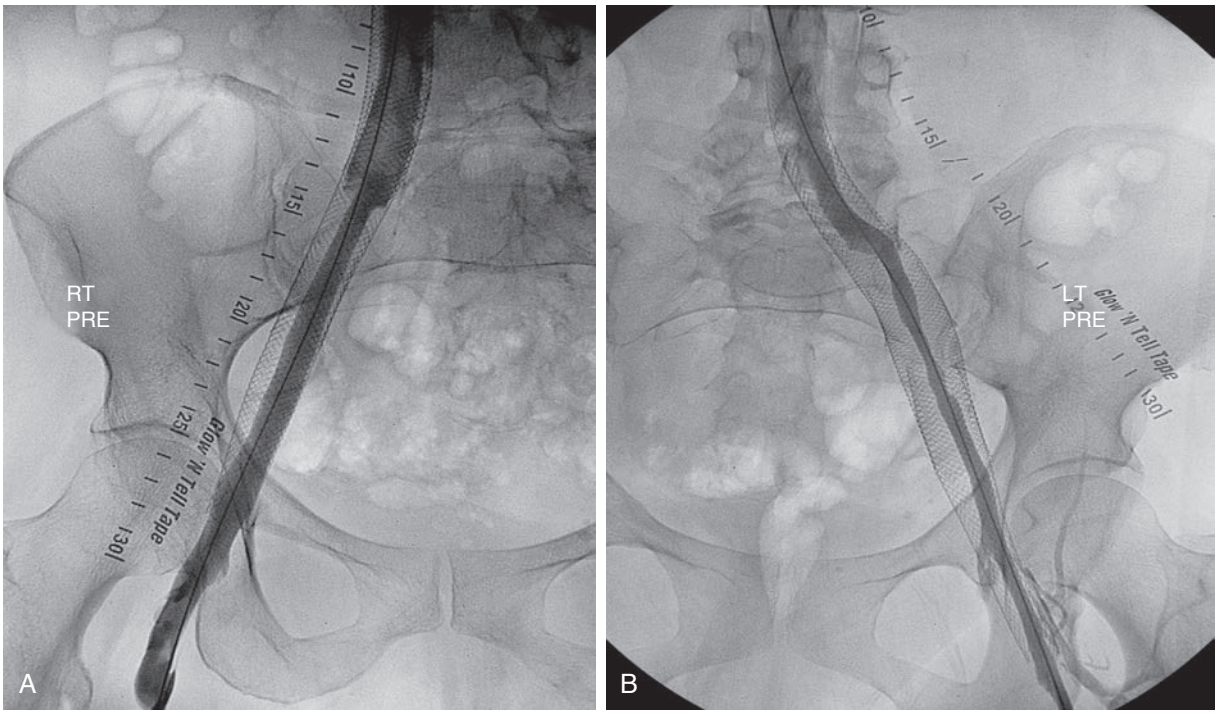

Figure 161.11 Venogram of an early in-stent restenosis (ISR) in an iliac stent (A). This likely occurs from thrombus build-up in the newly placed stent. The external iliac segment is commonly affected. Panel B shows a venogram demonstrating late ISR in a severely postthrombotic limb. The incidence and severity of ISR is higher in postthrombotic limbs and is usually of the hard variety.

and is more difficult to clear by balloon dilation. Nonetheless, the majority can be cleared using aggressive high-pressure (14 to 16 atm) balloons.

Both stent compression and hard ISR are more common in PTS limbs, particularly after CTO recanalizations.[32] Progression of hard ISR from partial to total stent occlusion appears to develop slowly over a period of years rather than in weeks or months. Most stent occlusions appear to be acute DVT events involving the stent, and differ from gradual progression of hard ISR to occlusion.[28]

Stent Surveillance

The above description of stent malfunction makes it clear that routine stent surveillance protocols will improve outcomes. Our practice is duplex screening of the stent the day after placement, followed by another ultrasound 4 to 6 weeks later to assess for acute stent occlusions and early thrombus lining (soft ISR). Later duplex surveillance intervals vary depending upon the original pathology. Lesions resulting from MTS are considered at low risk for occlusion and can be surveilled at 3- to 6-month intervals during the first year and less frequently thereafter. PTS lesions are more susceptible to stent malfunction and require quarterly surveillance during the first year and at least every 6 months thereafter. CTO recanalizations require even more intensive surveillance during the first year.

If symptoms fail to resolve or new symptoms develop, surveillance frequency should be modulated accordingly. Stent surveillance tends to promote follow-up continuity and probably reduces the number of patients "lost to follow-up." The timing of reintervention in these cases of stent malfunction is based primarily on residual/recurrent symptoms except in rare instances in which stent occlusion appears to be imminent. We place patients with hard ISR on cilostazol and optionally on prophylactic or therapeutic anticoagulation. The efficacy of these agents in venous stenting is undetermined.

OUTCOMES

Morbidity and Mortality

Endovenous correction of iliac and caval venous pathology can be done with minimal morbidity and mortality. In one large series of 982 stented limbs, access complications occurred in 0.4% despite the use of deep access sites. No procedure-related mortality occurred (30 days). DVT incidence was 3% over the 22 months of mean follow-up.[20] A recent review of worldwide experience found femoroiliocaval stenting to be a safe and effective procedure with low morbidity across multiple procedures, including recanalization for chronic total venous occlusions (Tables 161.2 and 161.3).[26]

Patency

Stent patency varies depending on underlying pathology. NIVL have excellent stent patency with very few failures compared to stenting carried out for postthrombotic (PTS) lesions. Stent placement for the correction of stenosis has better secondary

TABLE 161.2 Patencies and Procedural Complications Following Iliocaval Stenting

First Author, Year	Case Mix: n (%)	CUMULATIVE PATENCY			Procedure Complications—n (%)
		Primary	Primary Assisted	Secondary	
Hartung, 2009	NIVL: 52/89 (58) PTS: 35/89 (39) Congenital: 2/89 (3)	83% (Patency at 10 years)	89%	93%	Stent migration—2 Access site hematoma—2 Femoral artery tear—1 Contrast extravasation in CTO—2 Total—7 (8)
Knipp, 2007	PTS: 52/58 (90) NIVL: 6/58 (10)	38% (Patency at 5 years)	63%	74%	Retained balloon—1 Stent migration—1 Groin hematoma—2 Retroperitoneal hematoma—1 Total—5 (9)
Meng, 2011	NIVL: 272/272 (100)	94% (Mean follow up of 4 years)	NA	NA	
Neglen, 2007	NIVL: 518/982 (53) PTS: 464/982 (47)	79% 57% (Patency at 6 years)	100% 80%	100% 86%	Femoral artery injury—4 Guidewire trapped in stent—1 Total—5 (0.5)
Ye, 2012	NIVL: 224 (100)	99% (Patency at 4 years)	99%	99%	Local stent migration—3
Chronic Total Occlusion					
Kolbel, 2009	59	70% (Patency at 5 years)	73%	80%	Access-site bleed—1 Perforation requiring transfusion—2 Total—3 (5)
Raju, 2009	139	32% (Patency at 4 years)	58%	66%	Contrast related transient rise in creatinine—1
Rosales, 2010	34	67% (Patency at 2 years)	76%	90%	No major procedure related complication
Murphy, 2017	71 IVC filter occlusion: 38 Caval ligation/clipping: 4	52% (Patency at 5 years)	85%	93%	Access site hematoma—1 Arterial pseudoaneurysm—1 Contrast related transient rise in creatinine—1 Total—3 (4)

CTO, Chronic total occlusions; *IVC*, inferior vena cava; *NIVL*, nonthrombotic iliac vein lesions; *PTS*, post-thrombotic iliac vein stenosis.

patency than do those performed for CTO. Neglen et al. noted primary and secondary cumulative stent patency of 79% and 100% for NIVL limbs, and 57% and 86%, respectively, for PTS limbs at the 6-year follow-up (Fig. 161.12). For CTO recanalization of iliocaval segments, cumulative primary and secondary patencies were 54% and 74%, respectively, at 48 months.[20] Murphy and colleagues from the same institution recently reported results of recanalization of CTO lesions involving the IVC and one or both iliac veins in 71 patients; primary and secondary patencies were 52% and 93%, respectively, at 60 months.[19] Worldwide results generally parallel these surprisingly good secondary stent patency rates for treatment of stenosis as well as CTO recanalization, as shown in Table 161.2. The lower primary patency reflects the need for re-interventional correction in postthrombotic limbs to maintain performance.

Clinical Results

Clinical results generally mirror the excellent patency of iliac vein stents (see Table 161.3). Results reported by Neglen et al. are broadly representative. Cumulative rates of complete relief of pain and swelling were 65% and 32% with significant improvement (VAS ≥3; swelling ≥1 Gr.) seen in 74% and 62%, respectively, at 5 years. Surprisingly, clinical results after iliac vein stenting appear to be good even if co-existing reflux is left uncorrected.[8] Recently, Raju and colleagues evaluated ulcer healing with iliac vein stenting in 192 limbs with and without reflux. The overall cumulative ulcer healing rate was 75% at 5 years (Fig. 161.13). Healing was better in limbs with NIVL (87%) compared to thrombotic limbs (66%). Ulcers <1 inch diameter had better healing rates than those with >1 inch diameter. Interestingly, the presence of axial deep reflux did not necessarily affect healing. However, limbs with reflux segment scores ≥3 had lower cumulative ulcer healing compared to limbs with reflux segment scores <3.[18]

Geriatric Group

Iliac vein stenting is a safe and effective option in the elderly (>80 years).[33] Many elderly patients are unable to apply compression because of frailty or arthritis. Ulceration or recurrent cellulitis requires frequent hospitalizations, often ending in institutionalization. On the other hand, percutaneous stent

TABLE 161.3 Clinical Outcomes and Complications Following Iliocaval Stenting

First Author, Year	Case Mix: n (%)	Clinical Outcomes	Clinical Complications—n (%)
Hartung, 2009	NIVL: 52/89 (58) PTS: 35/89 (39) Congenital: 2/89 (3)	43/45 (96%) Had improvement in pain; 31 (69%) had complete relief 5/6 (83%) ulcers healed 23/26 (89%) pelvic congestion improved; 15 (58%) cured	Unrelated death—1 DVT—5 Total—6 (7)
Knipp, 2007	PTS: 52/58 (90) NIVL: 6/58 (10)	80% had significant clinical improvement; 20% had no change	
Meng, 2011	NIVL: 272/272 (100)	84% had resolution of swelling 87% with skin pigmentation showed improvement 85% ulcers healed	
Neglen, 2007	NIVL: 518/982 (53) PTS: 464/982 (47)	Severe leg pain (VAS>5) decreased from 54% to 11% 62% had cumulative total relief of pain Severe swelling (grade 3) decreased from 44% to 18% 32% had cumulative total relief of swelling Cumulative ulcer healing 58% Significant improvement in all categories	No death No pulmonary embolism DVT/stent thrombosis <30 days—14 DVT/stent thrombosis <30 days—23 Total—27 (4.5)
Ye, 2012	NIVL: 224 (100)	Edema relief: 89% Ulcer healing: 82% Pain decreased from 4.3 to 0.4 (VAS) QOL significantly improved	No death No pulmonary embolism No DVT
Chronic Total Occlusion			
Kolbel, 2009	66	Post intervention 23% asymptomatic; 52% improved; 20% same; 6% worse	No pulmonary embolism Stent thrombosis—14 (21)
Raju, 2009	139	79% had cumulative improvement in pain; 67% had complete relief 66% had cumulative improvement in swelling Cumulative healing of ulcers: 56%; complete relief in 32% QOL significantly improved	No death DVT/stent thrombosis <30 days—10[a] DVT/stent thrombosis >30 days—29[a] Contralateral thrombosis—3 Total—42 (30)
Rosales, 2010	32	Swelling and pain resolved in 32/34 (94%) 4/7 (57%) ulcers healed	Stent thrombosis—11 (34)
Murphy, 2017	60	66% had cumulative improvement in pain 41% had cumulative improvement in swelling Complete healing of ulcers in 78%	No death No pulmonary embolism Stent thrombosis 8/60 (13)

[a]Every stent thrombosis was considered a DVT.

DVT, Deep vein thrombosis; *NIVL*, nonthrombotic iliac vein lesions; *PTS*, postthrombotic iliac vein stenosis; *QOL*, quality of life; *VAS*, visual analogue scale.

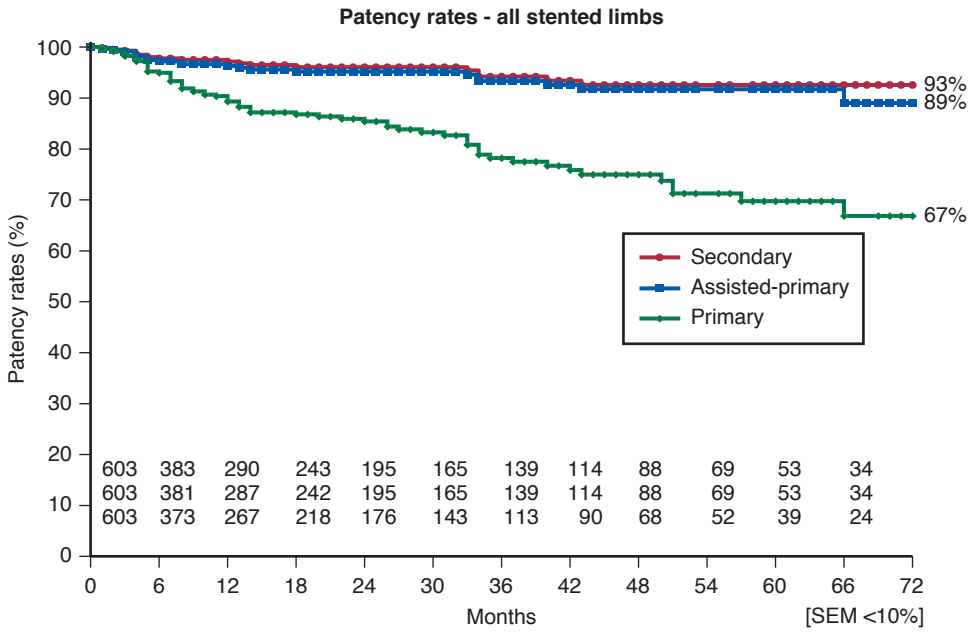

Figure 161.12 Cumulative patency rates of iliac vein stents (thrombotic and nonthrombotic limbs). All of the stent occlusions occurred in postthrombotic limbs and none in nonthrombotic limbs (NIVL) in this series. The secondary patency of NIVL in this series was a remarkable 100% (curve not shown). (From Neglen P, Hollis KC, Olivier J, Raju S. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. *J Vasc Surg*. 2007;46:979-990.)

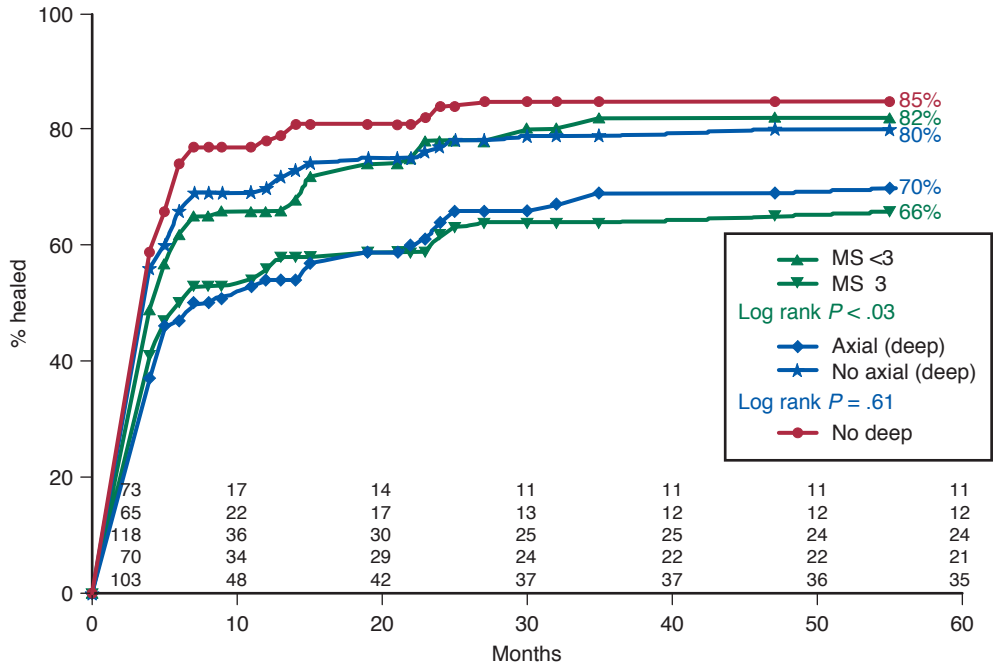

Figure 161.13 Cumulative Ulcer Healing in Limbs With and Without Deep Reflux. Note stable curve (few recurrences) after initial healing. There is no difference between limbs with and without axial reflux *(blue)*. Cumulative healing *(green)* was lower ($P < .03$) in limbs with three or more refluxing deep segments compared to those with less than 3 refluxing deep segments. The *red curve* represents limbs with isolated saphenous reflux treated by ablation. (From Raju S, Kirk OK, Jones TL. Endovenous management of venous leg ulcers. *J Vasc Surg Venous Lymphat Disord.* 2013;1:165-173.)

placement is relatively well tolerated. In a report of iliac vein stenting in 107 limbs in patients over the age of 80, there was no mortality; there was significant improvement of pain and swelling in 73% and 63%, respectively, at 6 years (cumulative data). Complete relief of pain and swelling was observed in 43% and 25%, respectively. This study also noted relief from recurrent cellulitis in 70% of limbs, and 61% (cumulative) of ulcers healed at 6 years. Stockings were able to be discarded in 31% of patients.[33]

Obese Patients

Iliocaval stenting has demonstrated benefit in CVD patients with a body mass index (BMI) >30. The incidence of bilateral CVD has been noted to be double in this subset in comparison to patients with BMI <30 (28% vs. 14%; $P < .01$).[34] Most have NIVL or PTS pathology, but venous compression can be caused by increased intra-abdominal pressure from obesity.[35] Stenting in this group has been performed with good patency (86% secondary patency at 66 months). The clinical relief of pain, plus swelling and ulcer healing, is similar to nonobese patients.[34] The main treatment choice in these patients remains bariatric surgery; venous stenting can be considered if it is declined for medical or other reasons.

Lymphedema

Secondary "venous lymphedema" can be seen in 16% to 30% of patients with CVD.[12,13] Careful attention must be paid to the diagnosis of obstructive venous lesions in this group as they may benefit from stent correction. Patients with secondary venous lymphedema have been noted to experience pain relief poststenting in a manner similar to their counterparts without lymphedema (83% vs. 87% at 40 months follow-up; P = .03). Relief of swelling is somewhat less and occurs in 45% of limbs with lymphedema compared to 66% of limbs without ($P < .01$).[13]

Iliac Vein Stenosis With Tandem Femoral Vein Occlusions

Femoral vein occlusions are easily detected in CVD patients complaining of leg symptoms. The lesion often becomes the focus in contemplating treatment. Less obvious are associated iliac vein lesions that are not as easily detected. The occult iliac stenosis is often more severe, as recanalization/collateralization in femoral occlusions is often satisfactory.[36] IVUS examination and iliac vein stenting may be considered in symptomatic limbs with tandem lesions. Good clinical relief has been reported with this approach.[37]

Thrombosed Inferior Vena Cava Filter

Murphy and colleagues reported on their experience with stent recanalization of IVC CTO with occluded IVC filters with a mean follow-up of 4 years. There was no mortality or filter-related complications. Cumulative patency of the IVC stent ($n = 34$) was 86% at 5 years, with good clinical relief (Fig. 161.14).[19]

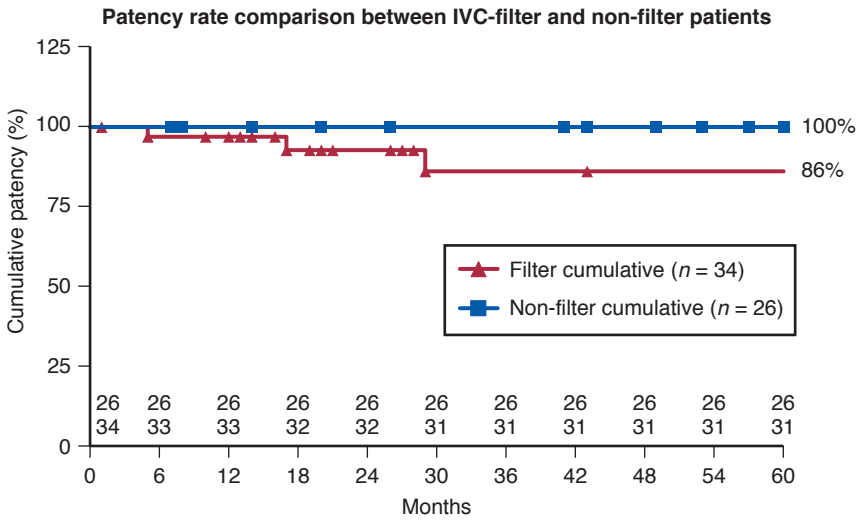

Figure 161.14 Cumulative patency of stent recanalization of inferior vena cava chronic total occlusions (IVC CTO) with (n = 36) and without (n = 24) thrombosed filter. There is no difference in patency between the two subsets. Three limbs in which iliac vein stents occluded on one side with IVC patency maintained by the remaining iliac vein stent are counted as patent. (From Murphy EH, Johns B, Varney E, Raju S. Endovascular management of chronic total occlusions of the inferior vena cava and iliac veins. *J Vasc Surg Venous Lymphat Disord*. 2017;5:47-59.)

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CHAPTER 162

Superior Vena Cava Occlusion and Management

MANJU KALRA, HARALDUR BJARNASON, and PETER GLOVICZKI

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In the United States each year about 15,000 patients develop symptoms of venous congestion of the head and neck due to occlusion of the superior vena cava (SVC) or innominate veins.[1] SVC syndrome is caused by malignant tumors of the lung and mediastinum in 60% of the cases.[2] The most frequent nonmalignant causes include placement of intravenous catheters, pacemaker wires, or mediastinal fibrosis.

Treatment for SVC syndrome involves creating outflow for the congested veins in the head and neck. Both endovascular and open surgical techniques are possible. Endovascular treatment for both acute and chronic SVC occlusion has become the first line of treatment for most patients because it is less invasive, and patients recover more quickly than following open surgery. Treatment in patients with advanced malignancy is frequently palliative, but for those with benign disease it is usually curative. Few areas of venous disease provide a more satisfying experience for both the patient and the vascular specialist. Relief from severe, frequently incapacitating symptoms of venous congestion of the head and neck is almost instantaneous, and benefit is generally long lasting. In this chapter, we review the etiology, clinical presentation, and diagnostic evaluation of SVC syndrome, and present techniques and results for its treatment with endovascular and open surgical methods.

ETIOLOGY

The first case of SVC obstruction described by William Hunter in 1757 was due to an aortic aneurysm. Aortic aneurysms

Abstract

Few areas of venous disease provide a more satisfying experience for both the patient and the vascular specialist than intervention for superior vena cava (SVC) syndrome. Relief from severe, frequently incapacitating symptoms of venous congestion of the head and neck is almost instantaneous, and benefit after reconstruction is generally long lasting. In this chapter, we review the etiology, clinical presentation, diagnosis, technique of endovascular/ open surgical treatment and outcomes of management of patients with SVC syndrome.

Keywords

Superior vena cava syndrome
Benign SVC thrombosis
Small-cell lung cancer

remained the second most common cause of SVC syndrome after primary malignant thoracic tumors until the mid-1900s. Infectious causes such as tuberculous and syphilitic mediastinitis also decreased markedly early in the 20th century. Lung cancer with mediastinal lymphadenopathy and primary mediastinal malignancy have become the most frequent causes of malignant SVC syndrome in the past three decades, constituting approximately 60% of cases.[2–4] Of these cases, nonsmall cell lung cancer is the cause in 50%, followed by small cell lung cancer (22%), lymphoma (12%), metastatic cancer (9%), germ cell cancer (3%), and thymoma (2%).[1] Other mediastinal malignant tumors leading to SVC syndrome include medullary or follicular carcinoma of the thyroid, teratoma, angiosarcoma, and synovial cell carcinoma.[1–5]

Benign disease is the cause of SVC syndrome in 40% of cases. Mediastinal fibrosis and granulomatous fungal disease, such as histoplasmosis, were formerly the most frequent benign causes. However, indwelling central venous catheters and cardiac pacemakers are now the most common benign cause.[6–14] Over 5 million central venous catheters and 170,000 pacemakers are now implanted annually in the United States and are associated with upper extremity or central deep venous thrombosis (DVT) in 7% to 33% of patients. SVC syndrome reportedly occurs in 1% to 3% of patients with central venous catheters and 0.2% to 3.3% of patients with implanted pacemakers.[2] Previous radiotherapy to the mediastinum, retrosternal goiter, and aortic dissection can also cause SVC syndrome. The risk of venous thrombosis is increased in patients with thrombophilia such as factor V Leiden mutation and deficiencies in circulating natural anticoagulants, such as antithrombin III, protein S, and protein C.

CLINICAL PRESENTATION

Signs and symptoms of venous congestion of the head, neck, and upper extremities are determined by the duration and extent of venous occlusive disease and the amount of collateral venous circulation that develops. Patients with SVC syndrome present with a feeling of fullness in the head and neck that is exacerbated when the patient bends over or lies flat in bed. The severity of disease can be graded by the number of pillows needed by the patient to sleep comfortably. Other symptoms include dyspnea on exertion, orthopnea, headache, dizziness, syncope, visual changes, confusion, and cough (Table 162.1).[1,15,16] Dilated neck veins and swelling of the face, neck, and eyelids are the physical signs most commonly seen (Fig. 162.1). Prominent chest wall collateral veins and ecchymosis and cyanosis of the face can occur. Although symptoms are usually localized to the head and neck, mild to moderate upper extremity swelling may also develop. In cases of malignant SVC syndrome, hemoptysis, hoarseness, dysphagia, weight loss, lethargy, and palpable cervical tumor or lymph nodes may be present. Patients with lymphoma may also present with fever and night sweats. In patients with end-stage renal disease (ESRD), asymptomatic SVC occlusion may be unmasked upon creation of an arteriovenous fistula (AVF), with rapid development of arm swelling and neck engorgement.

TABLE 162.1 Signs and Symptoms of Superior Vena Cava Syndrome of Benign Etiology in 70 Patients

	Number of Patients	%
Symptoms		
Feeling of fullness in head or neck	61	87
Dyspnea on exertion or orthopnea	39	56
Headache	27	39
Dizziness or syncope	25	36
Visual problems	11	25
Cough	10	22
Nocturnal oxygen requirement	3	16
Protein losing enteropathy	1	2
Head and neck swelling	65	93
Large chest wall venous collaterals	40	57
Facial cyanosis	24	34
Arm swelling	23	33
Pleural effusion	2	3

From Rizvi AZ, Kalra M, Bjarnason H, Bower TC, Schleck C, Gloviczki P. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg*. 2008;47:372–380, with permission.

DIAGNOSTIC EVALUATION

The diagnosis of SVC obstruction is usually suggested by a detailed history and physical examination. The diagnosis may be confirmed by a variety of tools, including plain radiographs, ultrasonography, computed tomography (CT), venography, and magnetic resonance imaging (MRI). The appropriate diagnostic study for an individual patient includes not only the demonstration of the underlying cause, but also the site and extent of obstruction as well as the routes of collateral venous circulation.

Radiography

Plain film radiographs of the chest are readily available and often abnormal in patients with SVC obstruction. Most common findings include mediastinal widening, right hilar mass, pleural effusion, bilateral diffuse infiltrates, and upper lobe collapse. However, a normal radiograph of the chest does not preclude the diagnosis of SVC obstruction.[1,3,17] Occasionally, dilated collateral veins may be visible, especially enlargement of the azygos vein or superior intercostal vein (aortic nipple) draining the hemiazygos system. In more than 90% of patients a diagnosis of SVC syndrome can be made on the basis of clinical presentation and plain chest radiograph.[16]

Ultrasonography

Duplex ultrasound (DUS) evaluation is an effective, noninvasive screening technique in the patient with suspected SVC obstruction. Although direct visualization of the SVC is not possible

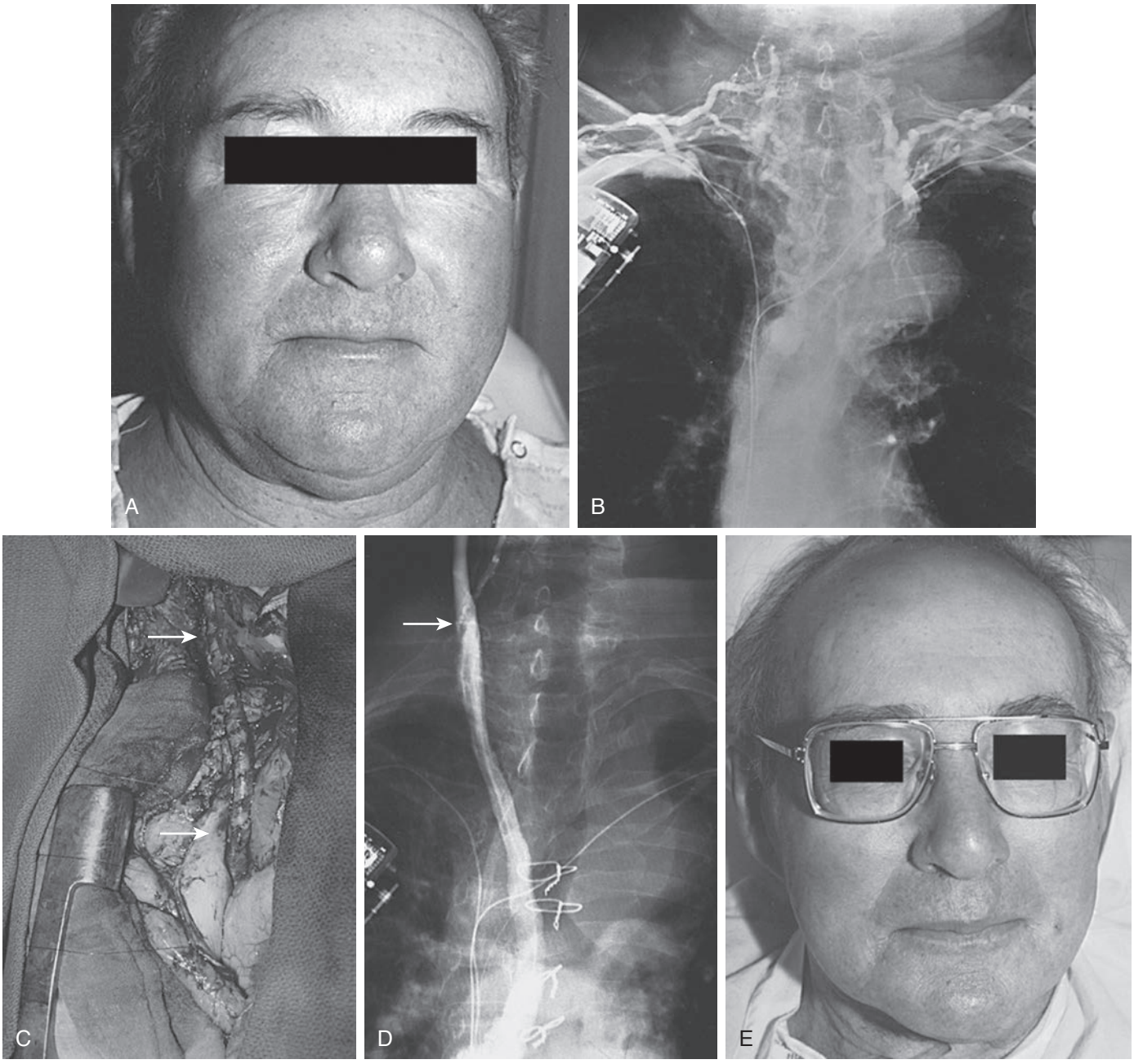


Figure 162.1 (A) Severe symptomatic superior vena cava (SVC) syndrome in a 69-year-old man. (B) Bilateral upper extremity venogram confirms thrombosis of the SVC and both innominate veins following placements of pacemaker lines bilaterally. (C) Right internal jugular vein–right atrial appendage spiral saphenous vein graft. *Arrows* indicate anastomoses. (D) Postoperative venogram confirms graft patency. (E) Photograph of the patient 5 days after spiral vein graft placement. The clinical result is excellent 8 years after the operation. (From Gloviczki P, Bower TC, McKusick M, Pairolero PC. Superior vena cava syndrome: endovascular and direct surgical treatment. In: Gloviczki P, Yao YST, eds. *Handbook of Venous Disorders*, London: Chapman & Hall; 1996:580–599.)

with transthoracic DUS, valuable information can be obtained. The subclavian and internal jugular veins are accessible to sonographic evaluation and can provide indirect evidence of SVC patency or obstruction. In the presence of SVC obstruction the normal respiratory flow variation caused by changes in intrathoracic pressure seen in patent subclavian veins is lost. This can be demonstrated by reduced or unchanged diameter and blood flow through the subclavian veins in response to respiratory maneuvers such as a sudden sniff or a Valsalva maneuver. Collateral vessels can be detected within the chest wall or in the mediastinum.

Radionuclide Imaging

Radionuclide venography has been used in the diagnosis of SVC syndrome. A technetium 99m pertechnetate scan (^{99m}Tc),

performed with bilateral simultaneous injection of the radionuclide tracer into the arm veins, can not only demonstrate the presence of SVC obstruction and associated collateral pathways but also provide functional aspects of the SVC obstruction using time–density curves. An advantage is the potential usefulness as a follow-up examination in determining therapeutic response.[18] The disadvantage of radionuclide venography is the lower-resolution anatomic detail and the inability to determine the cause of the SVC obstruction.

Computed Tomographic Angiography

Computed tomographic angiography (CTA) accurately depicts the location and extent of obstruction and can usually distinguish benign from malignant mediastinal disease.[19–22] Any mass or tumor is easily identified, and the central lines or pacemaker wires are well seen. CTA will also identify the collateral pathways, including the (1) azygos-hemiazygos pathway, (2) internal mammary pathway, (3) lateral thoracic-thoracoepigastric pathway, and (4) vertebral pathway and small mediastinal veins. Less commonly, unusual shunts, including hepatic parenchyma (an intense focal enhancement in the medial segment of the left lobe of the liver) and pulmonary pathways are identified on CTA.[23,24]

Contrast Venography

Venography has been considered the "gold standard" for accurate depiction of central venous obstruction and is used as an anatomic roadmap before reconstructive surgery. Venography also depicts the presence and direction of venous collateral flow. It is performed by simultaneous injection of contrast material in bilateral superficial arm veins. Stanford and Doty[25] described four venographic patterns of SVC syndrome, each having a different venous collateral network depending on the site and extent of SVC obstruction (Fig. 162.2). Type I is partial; type II is complete or near-complete SVC obstruction with antegrade flow in the azygos vein; type III is 90% to 100% SVC obstruction with reversed azygos blood flow; and type IV is extensive mediastinal central venous occlusion with venous return occurring through the inferior vena cava (see Fig. 162.2).

It is important to remember that during upper extremity venography only veins and collateral pathways between the injection site and right atrium are visualized; the internal jugular veins frequently used as inflow for a surgical bypass are not visualized.

Magnetic Resonance Venography

The advantages of magnetic resonance venography (MRV) include the ability to demonstrate anatomic structures in multiple planes and to delineate the central venous chest veins and collateral vessels. MRV is a relatively noninvasive modality and does not require the administration of iodinated contrast material. The disadvantage is its contraindication in patients with pacemakers and aneurysm clips. Recent problems using gadolinium in patients with renal insufficiency have also significantly decreased the utility of MRV.

INITIAL TREATMENTS

Conservative measures are used first in every patient to relieve symptoms of venous congestion and to decrease progression of venous thrombosis. These measures include elevation of the head during the night on pillows, modifications of daily activities by avoiding bending over, and avoidance of wearing constricting garments or a tight collar. Patients frequently need diuretic agents, at least temporarily, to decrease excessive edema of the neck and head.

Patients with acute SVC syndrome caused by malignant disease are generally treated with intravenous unfractionated or low-molecular-weight heparin, followed by long-term anticoagulation, to prevent recurrence and protect the collateral venous circulation. Thrombolytic treatment is considered in most patients with benign acute SVC syndrome, whereas those with chronic or malignant disease are candidates for treatment by endovascular stents, with or without thrombolytic treatment.

Symptoms of SVC syndrome caused by mediastinal malignancy frequently improve after irradiation, chemotherapy, or combination chemoradiation based on tumor histology.[1] Chen et al. treated 42 patients with malignant SVC syndrome using external beam radiotherapy and/or chemotherapy.[4] Symptoms of SVC syndrome resolved in 80% of the patients who underwent radiotherapy, with a mean interval of 4 weeks.[26] Similar benefits of radiation or chemotherapy have been noted by others as well.[27,28] Since external compression by the tumor is the usual mechanism of caval occlusion in these patients, endovascular treatment using stents, as discussed later, is the best technique to alleviate symptoms. A systematic Cochrane review by Rowell et al. evaluated 2 randomized and 44 nonrandomized studies addressing the treatment of SVC syndrome in patients with bronchial malignancy. Chemotherapy and/or radiotherapy relieved symptoms of SVC occlusion in 77% and 60% patients with small cell and nonsmall cell lung cancer, respectively. Endovascular treatment with stenting, however, relieved symptoms in 95% patients and much more rapidly.[28]

INDICATIONS FOR INTERVENTIONAL TREATMENT

The severe, incapacitating symptoms of SVC syndrome are frequently not alleviated by conservative measures. Up to one-fourth of malignant cases are resistant to radiochemotherapy, and even in cases where improvement occurs, symptomatic relief can require up to 3 weeks.[28] Further treatment options include endovenous or surgical intervention, depending upon the etiology and anatomy of the SVC lesion.

Endovenous treatment is considered the first choice for patients with malignant SVC obstruction because of the limited life expectancy. Surgical reconstruction should be contemplated only when the tumor is resectable, and life expectancy is greater than 1 year. Candidates for surgical reconstruction include those with lymphoma, thymoma, or metastatic medullary carcinoma of the thyroid gland.[29–34] In cases where endovascular treatment is not possible and major surgery is not indicated, extra-anatomic

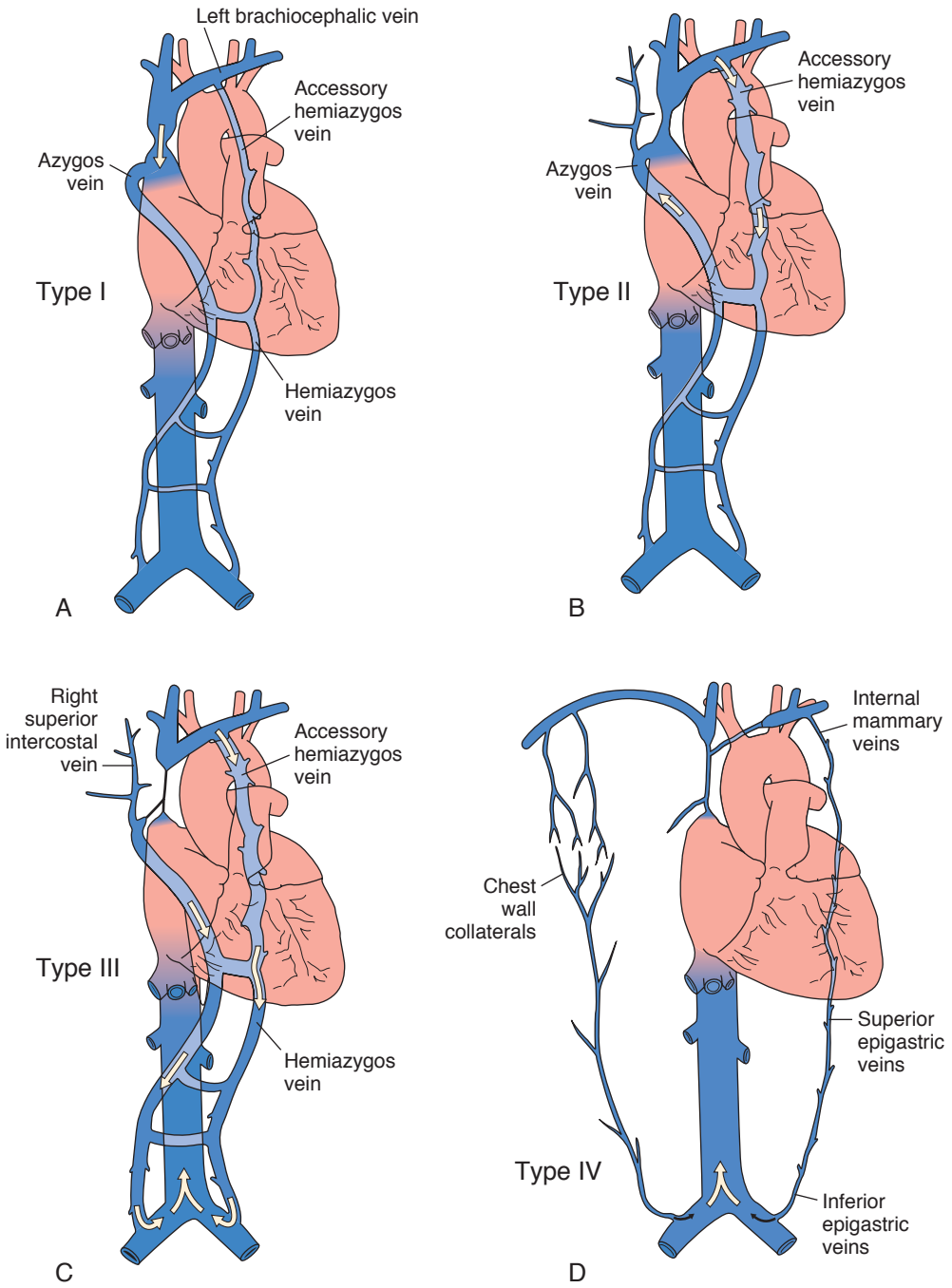


Figure 162.2 Venographic classification of superior vena cava (SVC) syndrome according to Stanford and Doty. (A) *Type I,* High-grade SVC stenosis with normal direction of blood flow, but still normal direction of blood flow through the SVC and azygos veins. Increased collateral circulation through hemiazygos and accessory hemiazygos veins. (B) *Type II,* Greater than 90% stenosis or occlusion of the SVC, but patent azygos vein with normal direction of blood flow. (C) *Type III,* Occlusion of the SVC with retrograde flow in both the azygos and hemiazygos veins. (D) *Type IV,* Extensive occlusion of the SVC and innominate and azygos veins with chest wall and epigastric venous collaterals. (From Alimi YS, Gloviczki P, Vrtiska TJ, et al. 1998; Reconstruction of the superior vena cava: the benefits of postoperative surveillance and secondary endovascular interventions. *J Vasc Surg.* 27:298–99.)

subcutaneous bypass between the jugular vein and the femoral vein using a composite saphenous vein graft is an alternative.[35,36]

In the past, patients with benign disease were treated with surgical replacement/bypass of the occluded SVC because of their longer life expectancy and the need for a durable reconstruction. However, as expertise and techniques have improved, most patients with benign SVC syndrome are considered for endovenous treatment first.[15,37–44] Surgical reconstruction is reserved for patients with extensive chronic venous thrombosis not anatomically suitable for endovascular treatment, and those with less extensive disease who have not benefited from endovascular attempts. Our group has performed reconstruction of

the SVC for obstruction caused by granulomatous and idiopathic mediastinal fibrosis, central venous catheters, pacemaker electrodes, or ventriculoatrial shunt and in patients with antithrombin deficiency or idiopathic venous thrombosis.[7,8,45,46] The indications for reconstruction in patients with benign disease were similar in the reports by Doty et al.[6] and Moore and Hollier.[47]

ENDOVENOUS TREATMENT

The first percutaneous angioplasty for an SVC lesion in an adult was performed in 1986 by Sherry. The lesion was caused by a pacemaker wire.[37] Since then there has been tremendous progress in the endovenous treatment of SVC syndrome, with increasing technical and clinical success. Endovenous treatment provides patients with rapid symptomatic relief; however, long-term results of stents placed in young patients for benign lesions are still not well known, and rethrombosis or intimal hyperplasia can be significant. In spite of this, many clinicians now consider endovenous procedures first line treatment in benign as well as malignant cases.[15,28]

Endovenous treatment includes percutaneous transluminal balloon angioplasty (PTA), stenting, and thrombolysis performed alone or in combination. Following early interventions with angioplasty alone, it became evident that this often resulted in early restenosis due to the elastic/fibrotic nature of many SVC lesions, with or without external compression from mediastinal masses. The earliest stents deployed were Gianturco Z stents, self-expanding stents with hooks for fixation to prevent migration. They are easy to place, rigid, and do not shorten with deployment. The large stent interstices, however, are worrisome for allowing tumor ingrowth. Palmaz (Cordis Corporation, Miami, Florida) balloon expandable stents are ideally suited for short, focal fibrotic/compressive lesions because of their precise deployment and good radial force. Disadvantages include poor flexibility and availability only in short lengths (Fig. 162.3). In recent years, other self-expanding stents such as Wallstents (Boston Scientific Corp., Natick, Massachusetts), Smart stents (Cordis Endovascular, Warren, New Jersey), Protégé stents (ev3, Plymouth, Minnesota), E*Luminexx (Bard GmbH/Angiomed, Karlsruhe, Germany), Sinus-XL (OptiMed Medizinische Instrumente GmbH, Ettlingen, Germany), and Zilver Vena (Cook Medical Inc., Bloomington, Indianapolis) have been used more frequently for longer SVC stenoses because of flexibility and availability in multiple sizes. Occasional reports of covered stents are also available. Covered stents are effective to prevent ongoing hemorrhage if a patent vein is perforated during the procedure, and potentially to control tumor ingrowth. Some evidence suggests they require fewer reinterventions compared to bare metal stents,[48,49] and we have used them in selected cases for this reason (unpublished data). Thrombolysis may be performed alone for acute SVC thrombosis related to indwelling catheters or prior to angioplasty/stenting to lyse the thrombus and reveal underlying stenotic lesions for definitive treatment.

The technique of endovenous repair involves ultrasound-guided percutaneous venous access of the common femoral vein and placement of 6 to 10 Fr sheaths, followed by crossing

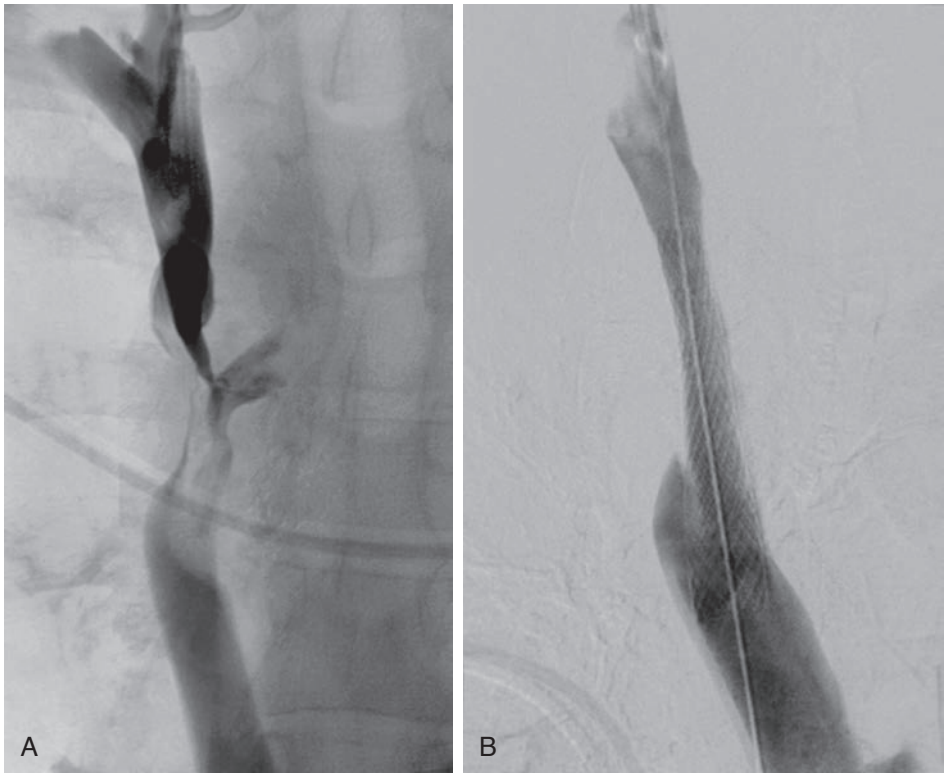


Figure 162.3 (A) Venogram showing type II superior vena cava obstruction due to mediastinal fibrosis in a 31-year-old man. Successful placement of a Palmaz stent resulted in immediate resolution of symptoms. (B) The patient has since undergone balloon dilation for in-stent stenosis 11 months later and remains asymptomatic.

the stenotic/occlusive lesion with hydrophilic guidewires and catheters. The right internal jugular or an arm vein can be an alternate or additional venous access site in patients with short focal lesions or if the lesion cannot be crossed from the femoral approach. Access of a hemodialysis AVF, if present, is also an option. Long sheaths extending to the site of occlusion can be helpful in providing the necessary support to cross the lesion. The PowerWire Radiofrequency Guidewire (Baylis Medical Company Inc., Montreal, Canada) has been reported to be useful in crossing thrombosed vessels.[50] Once wire access across the lesion is obtained, the hydrophilic wire can be exchanged for a stiff Amplatz wire (Boston Scientific) or a Lunderquist wire (Cook Medical Inc.), which is then used for PTA and/or stenting.

Primary PTA using 10 to 16 mm angioplasty balloons is performed followed by stenting. Venous stenoses can be very resistant, often requiring angioplasty with high-pressure balloons. The choice of stent is tailored to the etiology, degree, length, and tortuosity of the SVC stenosis, and more than one stent may be needed. Poststenting balloon dilation is performed when a self-expanding stent or a stent-graft is deployed (Fig. 162.4). When the confluence of the right and left brachiocephalic veins is involved in the primary lesion, or becomes so after caudal extension of stents within the SVC due to repeated stenoses, double barrel or parallel stents can be placed (see Fig. 162.4). Perforation can occur during the stenting process and if minor, manifesting as a small perivenous blush without hemodynamic changes, can be managed successfully with prolonged balloon inflation. Placement of a covered stent is required to control larger, more significant perforations, especially if associated with hemodynamic instability.[51] Rarely, SVC rupture can result in pericardial tamponade. Rapid diagnosis and immediate ultrasound guided pericardial drainage is necessary.[51]

Systemic anticoagulation with intravenous heparin (5000 U/kg) is given prior to any catheter-based intervention. Thrombolysis may be performed alone for acute nonmalignant SVC thrombosis related to indwelling catheters or prior to angioplasty/stenting to remove the thrombus and unmask the underlying stenotic lesion for definitive treatment. The original agents used for thrombolysis (streptokinase and urokinase[52,53]) have been replaced with recombinant tissue plasminogen activator (t-PA), which is utilized by us almost exclusively.[54]

If thrombolysis is determined to be appropriate prior to PTA or stenting, a suitable length catheter with side holes is placed across the lesion for catheter-directed lytic therapy. Successful catheter-directed thrombolysis with or without pharmacomechanical thrombectomy has been reported in catheter related thromboses and in malignant SVC occlusions. However, chronic occlusion with established collaterals in malignant SVC obstruction does not usually respond to lysis.[55]

Oral anticoagulation and/or antiplatelet therapy are routinely prescribed after SVC stenting for a minimum of 6 months. The need for postprocedure anticoagulation is individualized based on the cause of SVC syndrome. The majority of patients, especially those with malignancy and catheter related thrombosis, receive oral anticoagulation for at least several months until the stent is lined with pseudointima and the risk of rethrombosis decreases. Patients with mediastinal fibrosis are often treated with antiplatelet therapy alone. Both rethrombosis following cessation of anticoagulation as well as excellent results without anticoagulation have been reported.[56,57]

Figure 162.4 (A) Bilateral self-expanding kissing stents placement. (B) Poststenting balloon dilation.

SURGICAL TREATMENT

Graft Materials

Grafting of large veins has traditionally been difficult, because large-diameter autologous vein is not available to use as conduit.

Great Saphenous Vein Graft

The great saphenous vein is usually not suitable for direct reconstruction because of poor size match. However, extra-anatomic reconstruction performed by connecting the external or internal jugular vein to the ipsilateral common femoral vein, using both great saphenous veins sutured together in an end-to-end fashion and tunneled subcutaneously, has been reported by several authors with good results.[35] To prevent external compression, Panneton et al. placed the composite saphenous vein graft from the right internal jugular to the femoral vein inside an externally supported expanded polytetrafluoroethylene (ePTFE) graft.[58]

Femoral Vein Graft

The femoral vein, or the femoropopliteal vein, is a good conduit to reconstruct the SVC. It has been used with success because of its excellent suitability in terms of size and length (Fig. 162.5).[8,15] However, if the patient has underlying thrombotic abnormalities, removal of a deep leg vein may result in lower

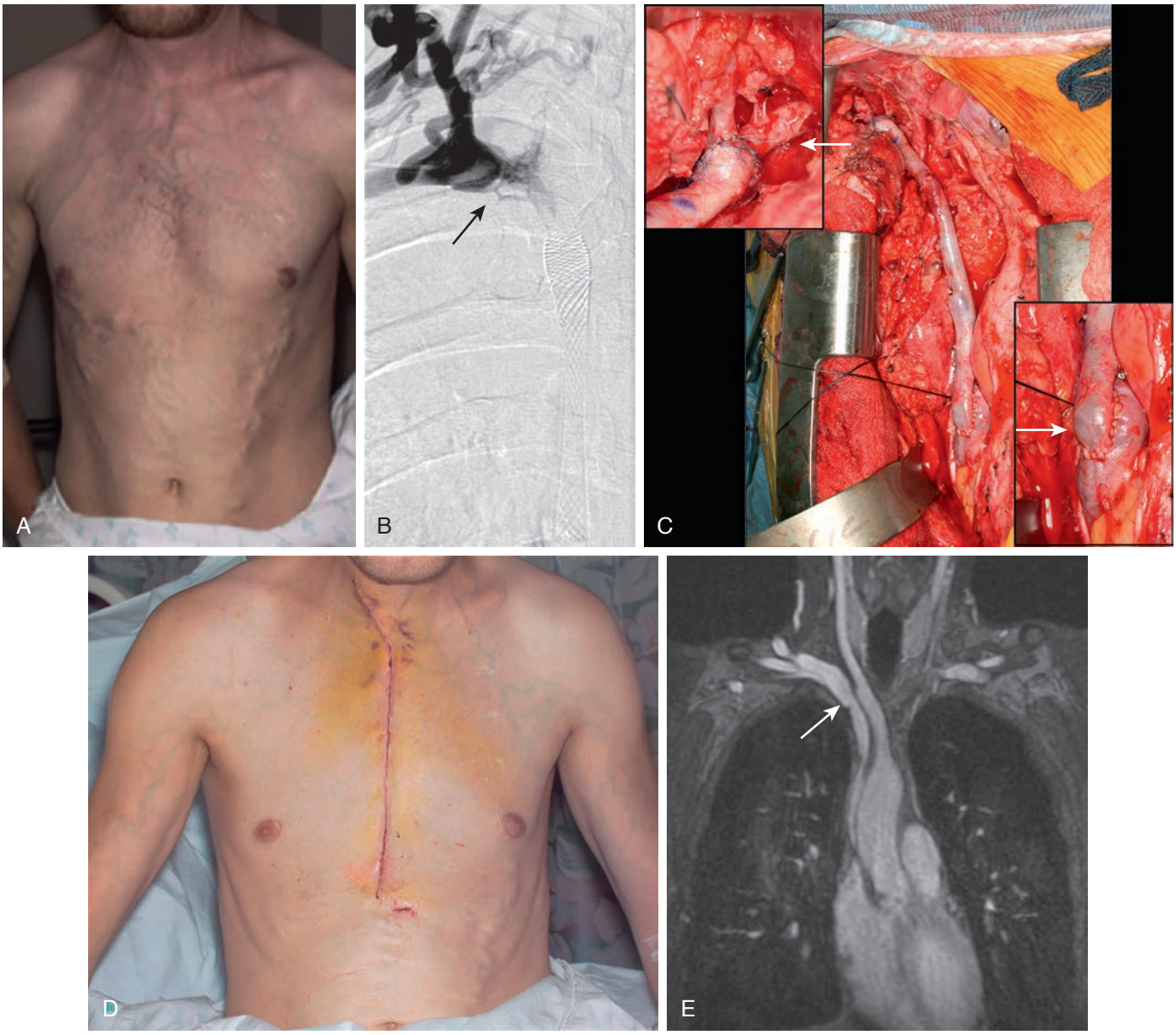


Figure 162.5 (A) Symptomatic recurrent superior vena cava (SVC) obstruction following occlusion of Wallstent prominent abdominal and chest wall collaterals. (B) Venogram demonstrating occlusion till the peripheral vein, right IJV, and subclavian veins patent with large draining collaterals. (C) Bypass from right IJV-SCV confluence *(top inset)*–right atrial appendage *(bottom inset)* using femoral vein. (D) Postoperative symptom relief demonstrated by collapse of right chest wall and upper limb collaterals. (E) Magnetic resonance Venogram 15 months after surgery confirms the graft *(white arrow)* to be widely patent.

extremity edema and pain. Compartment syndrome and chronic venous insufficiency following harvesting of longer segments of the femoropopliteal veins have been reported.[59,60] For this reason, in young patients who undergo SVC reconstruction for benign disease, the authors prefer using the spiral saphenous vein graft (SSVG).

Spiral Saphenous Vein Graft

The SSVG is autologous tissue with low thrombogenicity. Although its length is limited by the available saphenous vein segment, its diameter can be easily matched to that of the internal jugular or innominate vein (Fig. 162.6). This graft was first described in animal experiments by Chiu and colleagues,[61] and later in patients by Doty.[6,62] The technique used by the authors preparing the SSVG is illustrated in Fig. 162.5.[61]

The saphenous vein is harvested, distended with papaverine-saline solution, and opened longitudinally. The valves are excised and the saphenous vein is wrapped around a 32 or 36 French polyethylene chest tube. The edges of the vein are sutured together with running 6-0 or 7-0 monofilament nonabsorbable sutures to form the SSVG conduit, interrupting the suture line at every three-quarter turn (Fig. 162.7). Alternately, metal clips may be used with the advantage of decreased time and less chance of "purse-stringing" the suture line (see Fig. 162.7). The length of saphenous vein to be harvested to create a graft of sufficient length is determined according to the equation proposed by Chiu and coworkers ($l = RL/r$; r and l = radius and length of saphenous vein, R and L = radius and length of SSVG).[61] Harvesting vein from the groin to the knee usually results in an SSVG approximately 10 cm long.

Expanded Polytetrafluoroethylene Graft

Of the available prosthetic grafts, externally supported ePTFE is used for large vein reconstruction almost exclusively (Fig. 162.8).[7,61,63] Short, large-diameter (10 to 14 mm) grafts have excellent long-term patency, because flow through the innominate vein usually exceeds 1000 mL/min. If the peripheral anastomosis is performed with the subclavian vein, venous inflow is significantly less, and the addition of an AVF in the arm is usually required to ensure graft patency. For an internal jugular-atrial appendage bypass, a large-diameter (12 mm) ePTFE graft is a suitable alternative if the spiral saphenous vein is not possible. An externally supported prosthetic graft is a good choice in patients with a tight mediastinum and for all patients with malignancy, because its stiffness prevents recurrent tumor from compressing the graft.

Other Grafts

Fresh iliocaval allograft homografts, cryopreserved femoral vein, aortic arch grafts, and grafts prepared from autogenous or bovine pericardium have also been used.[64,65]

Surgical Technique

The operation is performed through a median sternotomy. If the internal jugular vein is used for inflow, the midline incision is extended obliquely into the neck along the anterior border

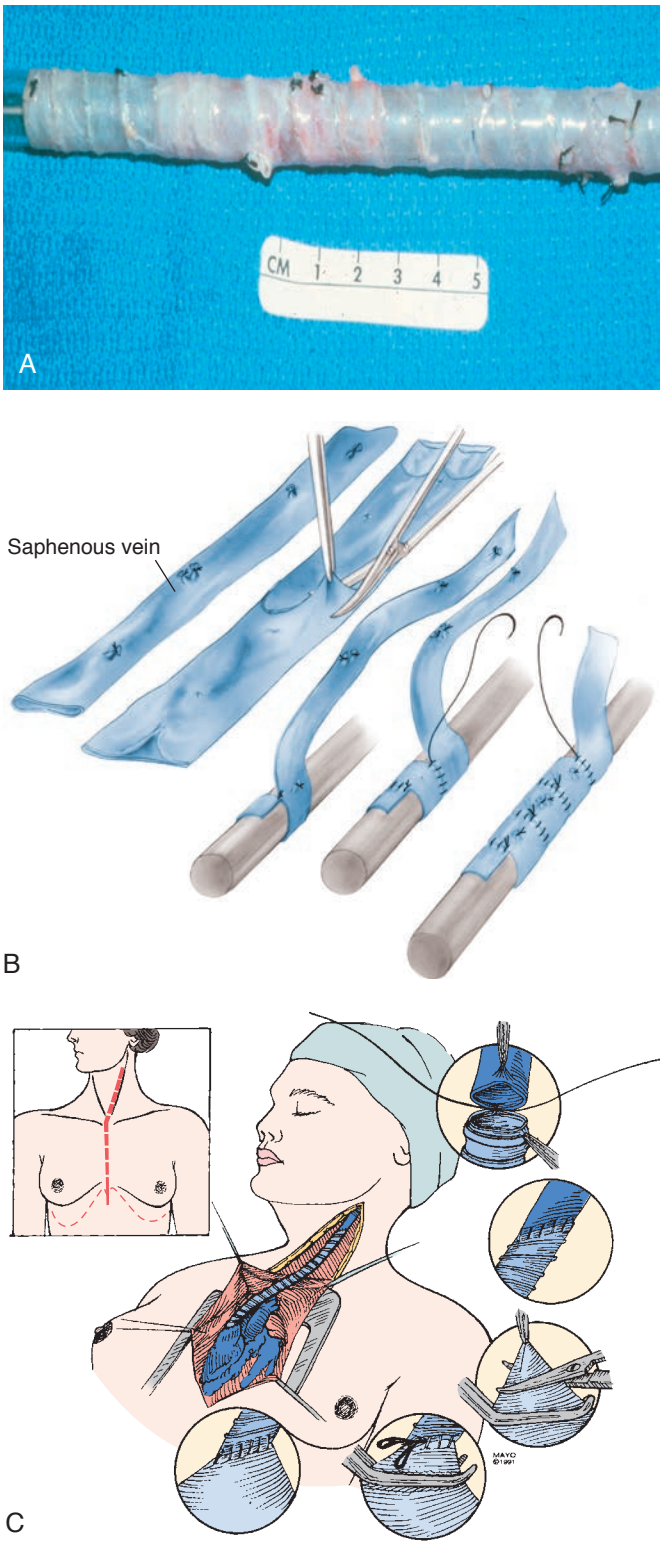


Figure 162.6 (A) Technique for a spiral saphenous vein graft. The saphenous vein is opened longitudinally, valves are excised, the vein is wrapped around an argyle chest tube, and the vein edges are approximated with sutures. (B) A 15-cm-long spiral saphenous vein graft ready for implantation. (C) Technique of left internal jugular–right atrial spiral vein graft implantation. (From Gloviczki PG, Pairolero PC. Venous reconstruction for obstruction and valvular incompetence. In: Goldstone J, ed. *Perspectives in Vascular Surgery*, St. Louis: Quality Medical Publishing; 1988:75–93.)

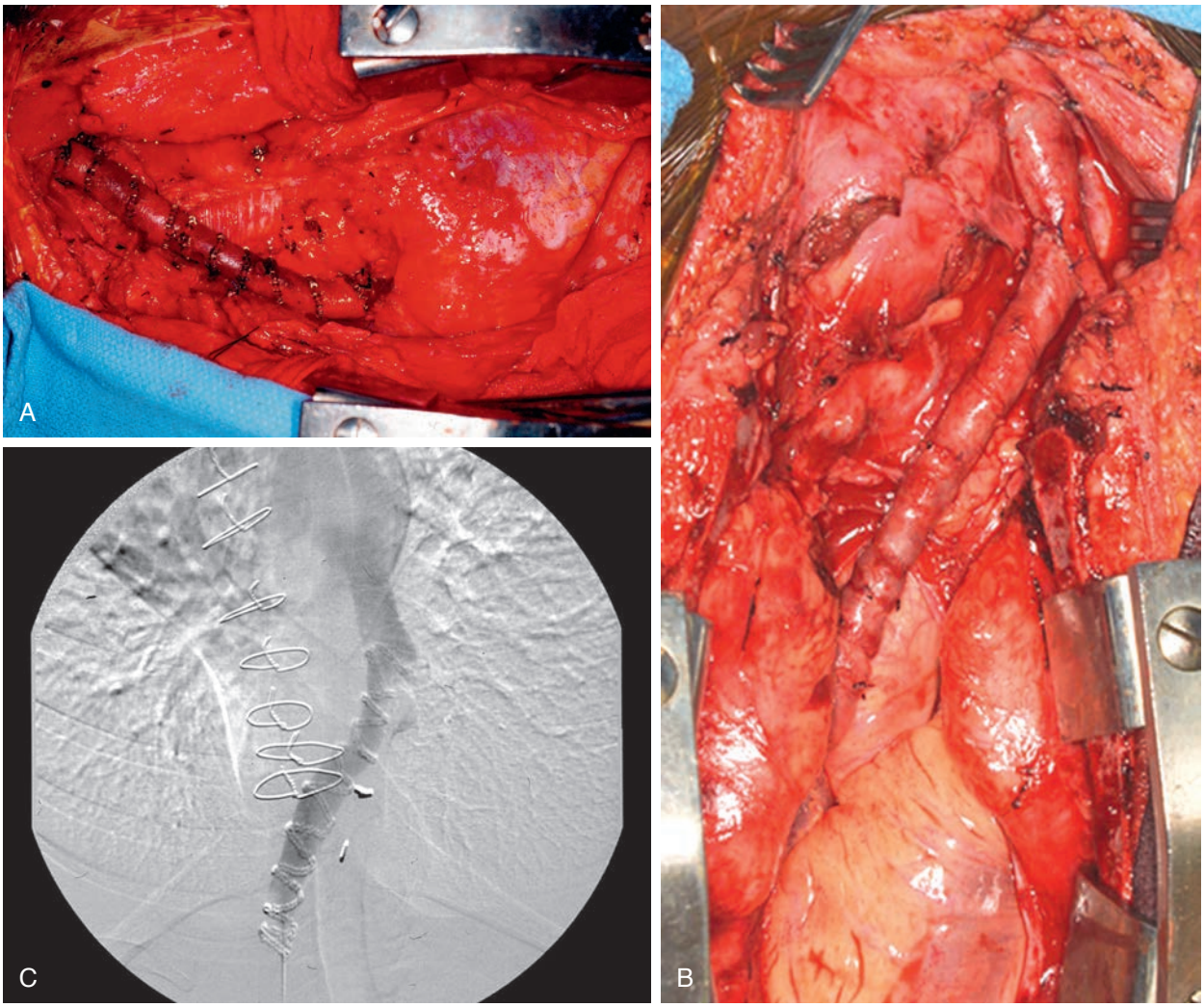


Figure 162.7 (A) Nonpenetrating vascular clips used for preparation of a spiral vein graft. (B) Intraoperative image of spiral vein graft and (C) postoperative venogram demonstrating the patent left internal jugular–right atrial appendage bypass graft. The graft is patent and the patient is asymptomatic 3 years later.

of the sternocleidomastoid muscle on the appropriate side. The mediastinum is exposed, and biopsy of the mediastinal mass or resection of the tumor is performed before caval reconstruction. Once this is completed, the pericardial sac is opened to expose the right atrial appendage, which is used most frequently for the central anastomosis. A side-biting Satinsky clamp is placed on the right atrial appendage, which is opened longitudinally. Some trabecular muscle is excised to improve inflow, and an end-to-side anastomosis with the graft is performed using running 5-0 monofilament suture (see Fig. 162.4C). If not involved in the fibrosing process, a patent SVC central to the occlusion can also be used for this purpose. The peripheral anastomosis of the graft is performed with the internal jugular or innominate vein in an end-to-side or, preferably, an end-to-end fashion.

Although we have performed bifurcated SSVGs (Fig. 162.9) or prosthetic grafts to both internal jugular veins in a few patients, a single straight graft from the internal jugular or innominate vein is our current operative choice for SVC reconstruction. Because collateral circulation in the head and neck is almost always adequate, unilateral reconstruction is sufficient to relieve symptoms in most patients. When only part of the circumference of the SVC is invaded by the tumor, resection and caval patch angioplasty using prosthetic patch, bovine pericardium, or autogenous material, such as saphenous vein or pericardium, is also an option.

Postoperative anticoagulation is started 24 hours later with heparin, and the patient is discharged on an oral anticoagulation regimen. Patients with SSVGs or femoral vein grafts who have no underlying coagulation abnormality are maintained on anticoagulation for 3 months only. Those with underlying coagulation disorders and most patients with ePTFE grafts continue lifelong anticoagulation therapy.

RESULTS

Results of Endovenous Treatment in Patients With Malignancy

Initial attempts at treating SVC syndrome by endovascular means employed PTA alone. The earliest reports of SVC stenting

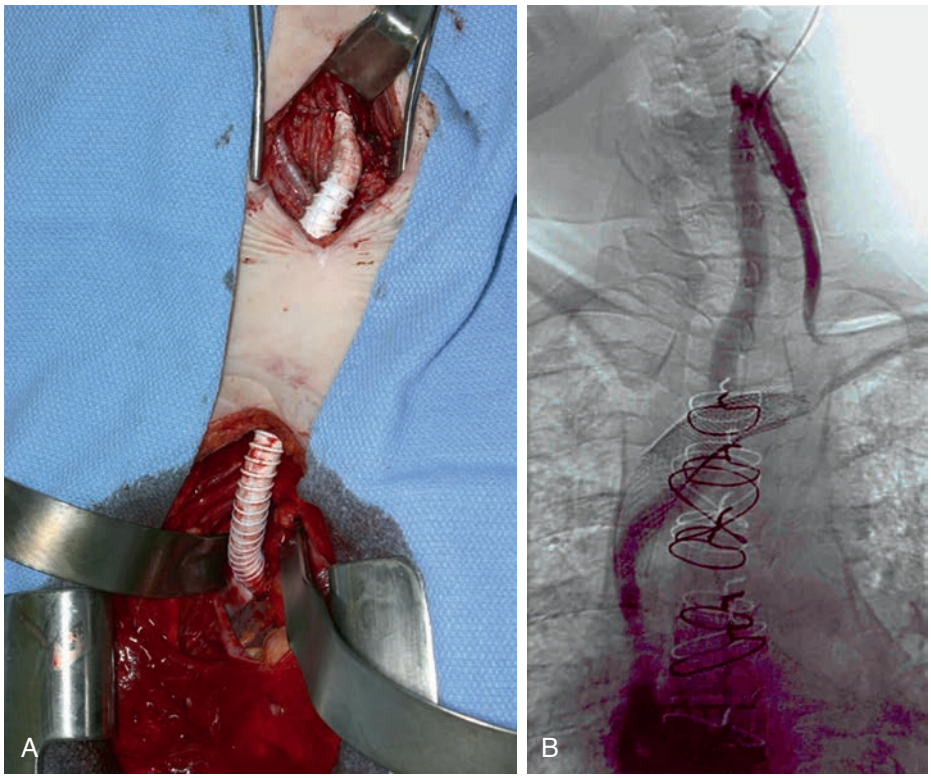


Figure 162.8 (A) Left internal jugular vein–atrial appendage externally supported expanded polytetrafluoroethylene graft. (B) Widely patent graft at 13 months after the operation.

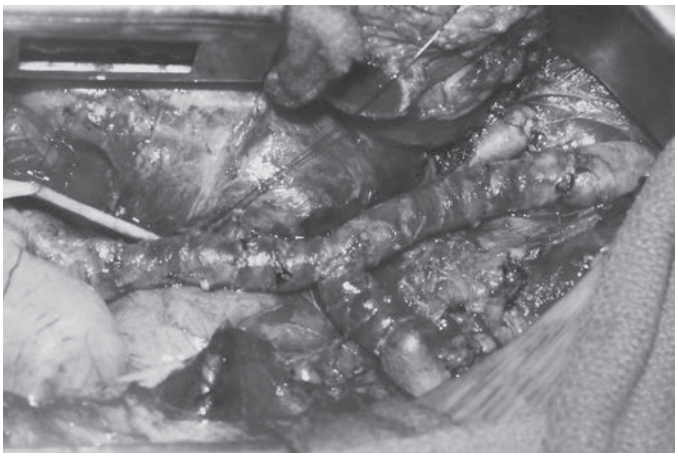


Figure 162.9 Bifurcated spiral saphenous vein graft in a 43-year-old woman. (From Alimi YS, Gloviczki P, Vrtiska TJ, et al. Reconstruction of the superior vena cava: the benefits of postoperative surveillance and secondary endovascular interventions. *J Vasc Surg.* 1998;27:298–299.)

in 1986/7 were in patients with malignant SVC occlusion; prompt relief of symptoms occurred and was maintained until death at 3 weeks to 6 months.[39,66] Relief of symptoms included "immediate" relief of headache and resolution of arm and face edema within 24 to 72 hours. These procedures were performed with Gianturco Z stents, which were subsequently modified by Rosch et al.[66] to create a multibody design that minimized stent migration. In the early 1990s occasional cases of stent deployment for pacemaker wire-induced thrombosis were reported, but repeated interventions were required to maintain patency in the short term.[39,57,66]

Nicholson et al.[67] reported the largest study of endovenous interventions to that time in 75 patients with malignant SVC syndrome. Symptomatic relief was achieved in all patients within 48 hours, and 90% remained symptom free until death. The authors compared SVC stenting with palliative radiation, and concluded that stenting had significantly greater efficacy. In a later study by Garcia Monaco et al.,[68] dramatic symptomatic improvement was seen in 91% of 40 patients with malignant SVC syndrome following stenting, and was maintained in 83% during the course of the disease. Greillier et al.[69] reported complete resolution of symptoms more frequently in stented than in unstented patients with lung cancer (75% vs. 25% respectively), as well as a lower relapse rate and longer time to relapse. Maleux et al. reported stenting in 78 patients with malignant SVC syndrome (Large bore Nitinol SE Zilver, Cook Medical), demonstrating 100% technical success rate and 89% primary patency at 12 months.[70] The recent development of large-caliber stents developed specifically for the SVC has also appeared to improve results.[71,72] Based on these data, endovenous treatment has become the first-line treatment for malignant SVC syndrome.[73–76]

Results of Endovenous Treatment in Patients With Benign Superior Vena Cava Syndrome

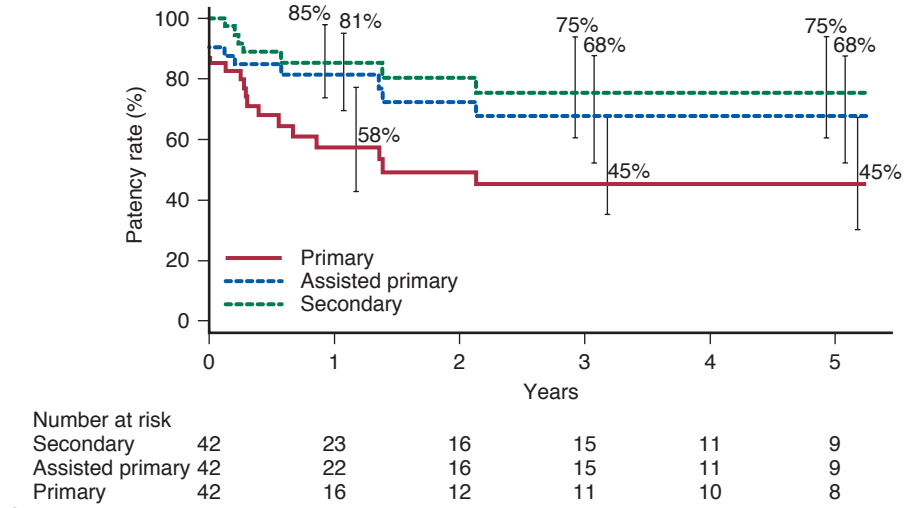
Studies reporting on the treatment of benign SVC syndrome are scarce. We have reported our results of successful endovenous

treatment of SVC syndrome of benign etiology in 28 of 32 patients, 19 with catheter related thrombosis and 9 with mediastinal fibrosis.[15] Six patients underwent PTA and 22 underwent stenting; 5 procedures (2 PTA, 3 stents) were preceded by thrombolysis. Primary patency at 1 and 3 years was 70% and 44%, assisted primary and secondary patency rates at 3 years were 96% and 96%, respectively (see Fig. 162.9). These were not significantly different from the patency of surgical reconstructions at our institution. However, more reinterventions over longer periods of time occurred in the patients treated with endovascular procedures compared to those who underwent open surgery (Fig. 162.10).[15] Other studies reported excellent technical success with secondary interventions required in approximately 10% of cases over 1 to 2 years.[38,77]

Additional studies provided evidence of the efficacy of thrombolysis followed by PTA and stenting in patients with benign SVC syndrome. Kee et al. reported on 27 patients treated with this technique. In the majority, successful lysis revealed underlying significant stenoses which were treated by stenting.[78] Although thrombolysis was generally safe, a Cochrane review concluded that when added to stenting, it resulted in increased morbidity compared to stenting alone.[28]

Complications, Restenosis, and Outcomes

Most studies have emphasized the need for customizing treatment with a combination of thrombolysis, angioplasty, and stenting to achieve an initial technical success rate of 90% to 100% and secondary patency rates up to 85% at 1 year in small numbers of patients.[43,55,78,79] Barshes et al. reported 100% technical success and 96% symptomatic relief following stenting in patients with both benign and malignant SVC



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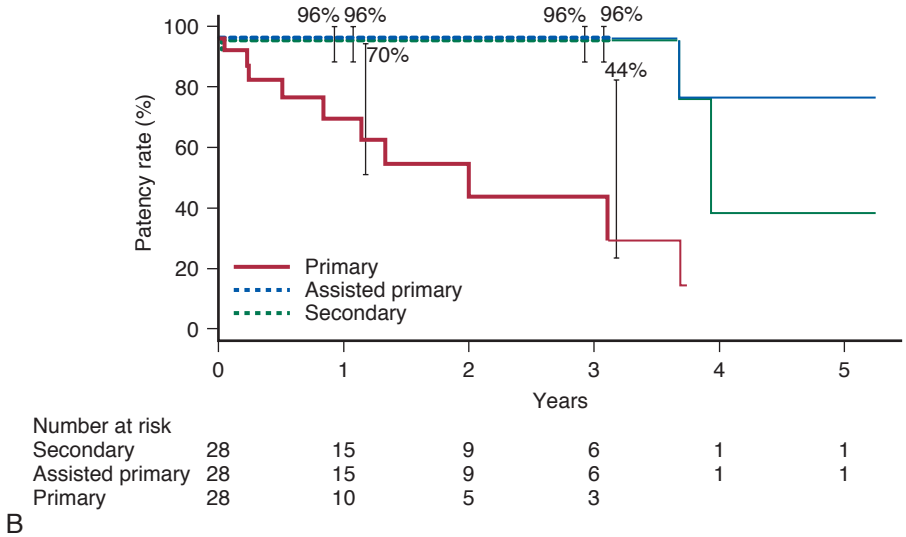

B

Figure 162.10 (A) Cumulative primary, assisted primary, and secondary patency rates at 1, 3, and 5 years of open surgical reconstruction ($n = 42$). *Solid bars* represent SEM < 10%. (B) Cumulative primary, assisted primary, and secondary patency rates at 1 and 3 years of endovascular repair ($n = 28$). *Solid bars* represent SEM < 10%. (From Rizvi AZ, et al. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg.* 2008;47(2):372–380.)

syndrome, with primary patency rates of 76% and 64% at 1 year, respectively.[80] However, to this date, prospective, randomized data comparing stent types or treatment algorithms does not exist. Oudkerk et al. compared outcomes between Giantarco and Wallstents, and reported the latter to be more prone to occlusion, possibly because of a closer weave and greater surface area of metal.[81]

Occlusion of stents because of protrusion of tumor between stent struts in patients with malignancy, as well as intimal hyperplasia, fibrosis, and extrinsic compression from mediastinitis, are real concerns following endovenous treatment. Restenosis usually results in recurrence of symptoms and necessitates repeat interventions, especially in patients with benign SVC syndrome (Fig. 162.11). Endovenous treatment

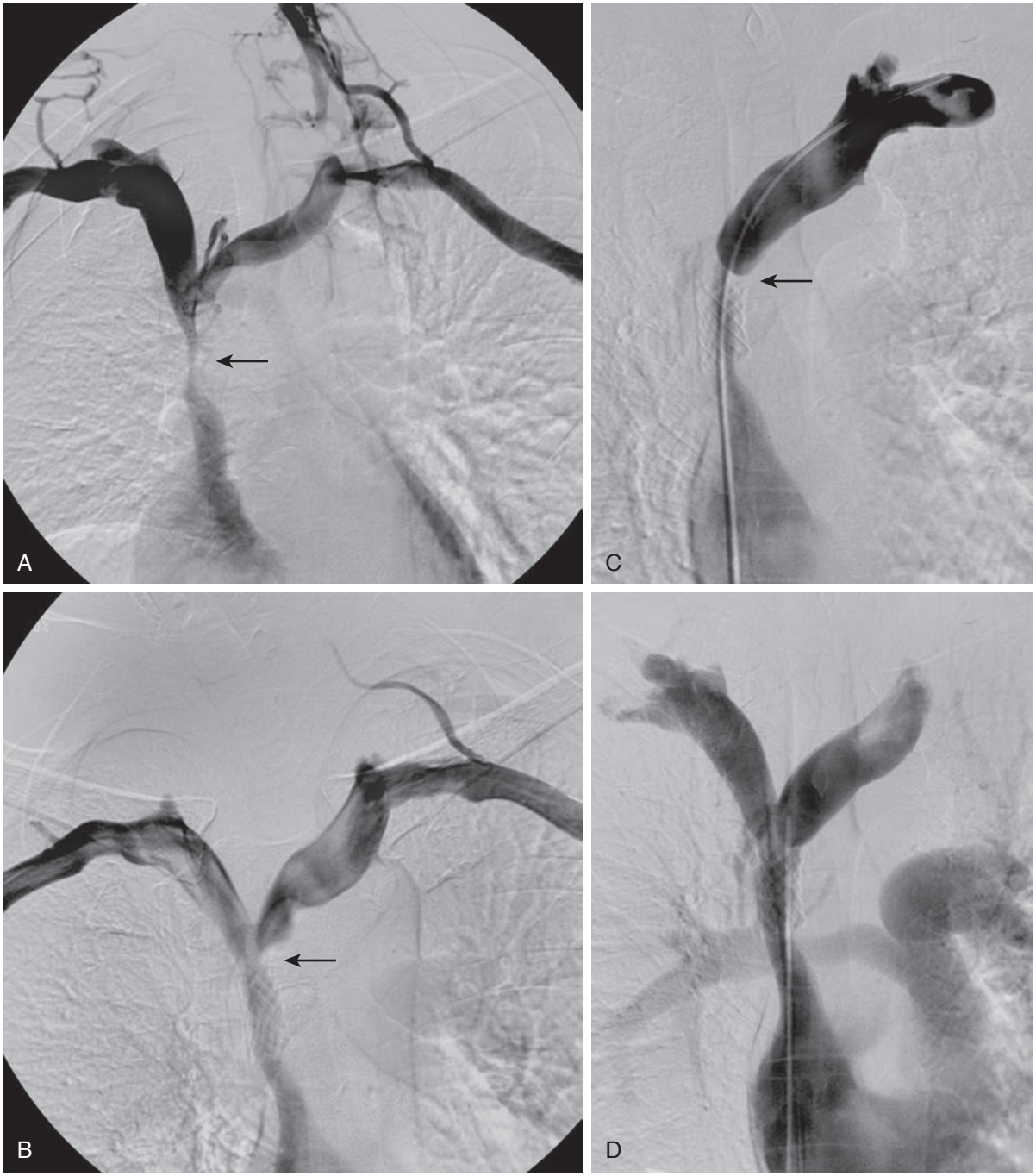

Figure 162.11 (A) Venogram showing Type II superior vena cava obstruction *(arrow)* due to mediastinal fibrosis in a 38-year-old man. Successful placement of a Palmaz stent resulted in immediate resolution of symptoms. (B) Venogram 14 months after stent placement shows high-grade stenosis of the left innominate vein proximal to the stent *(arrow)*. This was successfully treated with balloon angioplasty. (C) Venogram 8 months later shows recurrence of stenosis *(arrow)*. (D) Venogram following balloon angioplasty of stenosis left innominate vein and stent shows widely patent stent. Patient has undergone two further balloon angioplasties over the next 10 months to maintain patency.

is also associated with access site complications, bleeding related to thrombolysis/anticoagulation, stent migration, and cardiac tamponade from intrapericardial hemorrhage. The latter occurs infrequently, but has been reported after both PTA and stenting and necessitates urgent ultrasound-guided pericardiocentesis. We encountered this complication during repeat PTA in two patients.

Concerns regarding restenosis and symptomatic recurrence have led to the use of covered stents, based upon data suggesting that their use is associated with lower recurrence rates. In one study, Gwon et al. reported better cumulative patency with covered than uncovered stents (94% vs. 48%; $P = .038$).[48] Over the last decade we have used covered stents selectively in the SVC, and placed them in 13/44 patients with benign SVC syndrome (unpublished data). Although not statistically significant, we observed a decreased rate of reintervention at 1 year in the group with covered stents (15%) versus those with uncovered stents (39%). These data are preliminary, but our experience mirrors the findings reported by Gwon et al.[48,82,83]

Despite the attraction of the minimally invasive nature of SVC stenting, the need for frequent, repeated reintervention remains a limiting factor in long-term success. Given the longevity of patients with benign SVC syndrome it is not surprising that a fair number eventually opt for surgical treatment.

Results of Surgical Treatment

Open surgical treatment for SVC syndrome has excellent long-term results, but is now considered only after failure or inability to perform endovascular treatment. Outcomes depend on etiology, conduit, and the length of venous reconstruction. Of the autologous graft materials, experience with SSVG and femoral vein grafts has been the largest. Doty and colleagues reported on long-term results with 16 SSVGs used for benign SVC syndrome, demonstrating 88% patency and excellent clinical results at a mean follow-up of 10.9 years. The author's experience includes 22 SVC reconstructions with SSVG, with 86% secondary patency at 5 years and good to excellent clinical results.[6,62,84–86]

Increasing success with femoral vein as an arterial conduit has resurrected this autologous graft for large vein reconstructions as well.[87] All six femoral vein grafts performed by our group have remained patent.[15] However, two of the six patients developed mild but persistent swelling and venous claudication in the lower extremity from which the graft was harvested.

In several series, ePTFE grafts implanted into the mediastinum have resulted in excellent patency. Dartevelle and associates observed continued patency in 20 of 22 ePTFE grafts at a mean follow-up of 23 months.[32] Moore and Hollier observed no graft occlusion at a mean follow-up of 30 months in 10 patients who underwent large central vein reconstruction.[47] In 8 of these 10 patients, an additional AVF in the arm was used to increase flow. Similar results have been reported in other studies.[33,88,89]

In our experience, some thrombus formation occurs even in patent ePTFE grafts, with occlusion occurring much more frequently in patients with longer ePTFE grafts in whom the distal anastomosis is performed with the internal jugular or the subclavian veins. Long-term patency is better in patients with innominate or SVC interposition grafts, and we now use ePTFE as a conduit only when the extent of the graft is limited to within the anterior mediastinum (Fig. 162.12).

Graft Surveillance

Postoperative graft surveillance is important for maintenance of patency. DUS provides only indirect evidence of patency of an intrathoracic graft. Therefore CT or MRV is recommended before discharge and at 3 to 6 months and 1 year after surgery. In our experience, most graft stenoses presented within 1 to 2 years after implantation, and half of these had mild stenoses on the first postoperative surveillance venogram (Fig. 162.13).

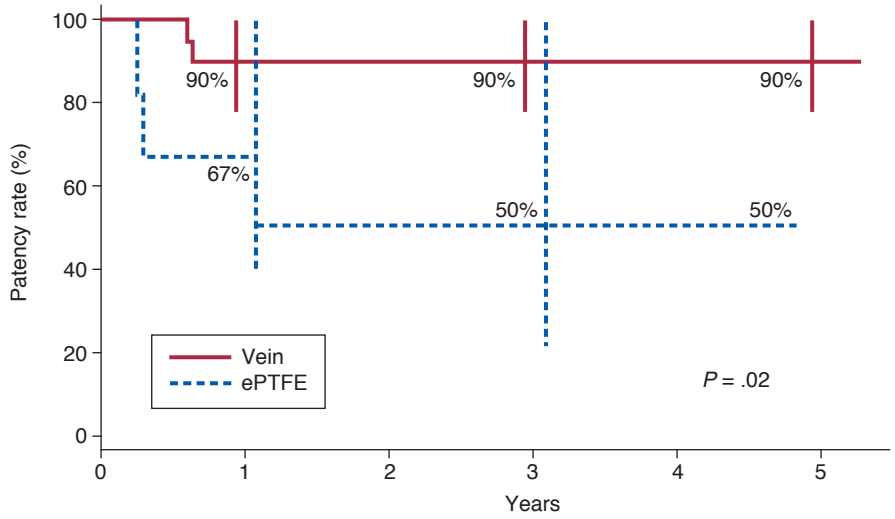

Figure 162.12 Cumulative secondary patency rates of 23 vein grafts and 6 expanded polytetrafluoroethylene bypass grafts used for reconstruction of the superior vena cava. (From Kalra M, et al. Open surgical and endovascular treatment of superior vena cava syndrome caused by nonmalignant disease. *J Vasc Surg*. 2003;38:215–223.)

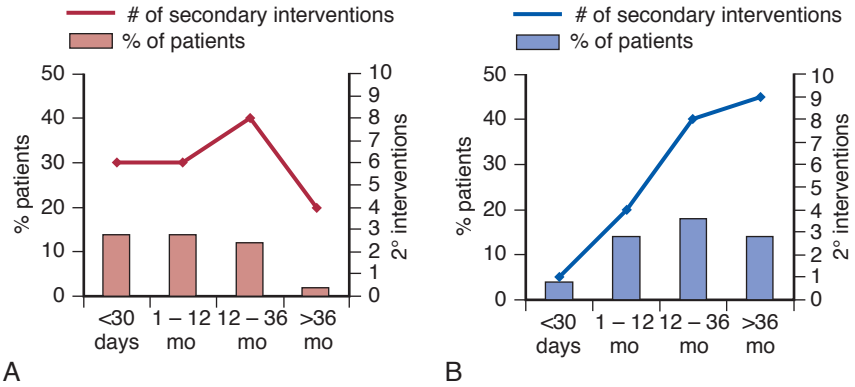

Figure 162.13 (A) Treatment of benign superior vena cava syndrome. Secondary interventions required to maintain patency in (A), the open surgical group ($n = 42$), and (B). The endovascular group ($n = 28$). The *bars* represent the percentage of patients in each group and the *line graphs* represent total number of interventions. (From Rizvi AZ, et al. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg*. 2008; 47(2):372–380.)

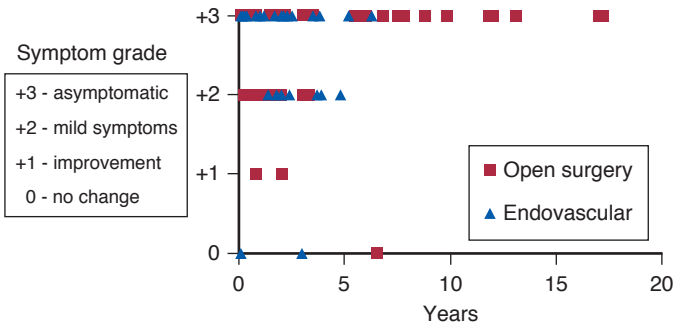

Figure 162.14 Grading of symptom relief at last clinical follow-up in patients undergoing open surgical reconstruction ($n = 42$) or endovascular repair ($n = 28$). (From Rizvi AZ, et al. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg*. 2008;47(2):372–380.)

Regardless of the treatment modality, the discovery of all stenoses was accompanied by recurrence of symptoms except in one instance. Similar outcomes have been reported by Doty and associates.[85] Based on these data, graft patency can be inferred based upon freedom from symptoms, and imaging after the first year need only be performed in symptomatic patients or in asymptomatic patients with known stenoses. Both endovascular therapy and open surgery have been used to treat graft stenoses, although endovascular treatment is more common (Fig. 162.14).[46]

CONCLUSIONS

The incidence of SVC syndrome is increasing with the growing use of indwelling catheters and pacemakers. The techniques of endovascular treatment have been refined, and experience with their use has increased. Endovascular treatment is now an appropriate primary intervention in patients with SVC syndrome of both malignant and benign etiology. It is less invasive with lower morbidity than open surgical reconstruction, with equal midterm efficacy, albeit at the cost of multiple secondary interventions. Covered stents may prove to have improved patency compared to bare metal stents, although definitive data do not exist at this time. Endovascular therapy does not adversely affect the feasibility or patency of subsequent open surgical procedures. However, surgical treatment of SVC syndrome with spiral vein grafts or prosthetic grafts is effective, provides long-term relief, and remains an excellent option in patients who are not suitable for or fail endovascular treatment.

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163 CHAPTER

Congenital Occlusion/Absence of Inferior Vena Cava

GLENN JACOBOWITZ and MIKEL SADEK

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Congenital absence of the inferior vena cava (AIVC) is a rare entity and is often first detected in the setting of an idiopathic deep venous thrombosis (DVT) of the lower extremity. The overall incidence of AIVC in the general population has been estimated to be 0.3% to 0.5%, but it may be present in up to 5% of cases of patients under the age of 30 with idiopathic DVT. This incidence was first noted by Ruggeri et al. in 2001.[1] These authors noted that in their own review of published reports from 1966 to 1999, there were fewer than 10 cases of DVT in patients with AIVC. They also noted that this could have represented an underestimation, because the most common diagnostic imaging technique, the duplex scan, does not routinely include the abdominal veins. Indeed, more dedicated abdominal duplex scanning or computed tomography (CT) is required to make the diagnosis.

It is likely that most cases of congenital absence of the IVC remain undiagnosed and are of little clinical consequence. However, it is the smaller subset of those presenting with a DVT that represents more complex management issues regarding both treatment of the acute DVT and subsequent identification and treatment of associated thrombophilia.

ASSOCIATION WITH DEEP VENOUS THROMBOSIS

Several authors have noted an association of AIVC with deep venous thrombosis.[1-4,5] It has recently been reported in adolescent males; the authors note that this entity is an important risk factor for the development of spontaneous DVT in young males.[2,6] The possible explanation for this is that the congenital absence of the IVC creates a low-flow state, making the lower extremity more susceptible to DVT. This may be further exacerbated in the presence of thrombophilia, such as factor V Leiden mutation or homocysteinemia.[4] Halparin et al. evaluated a pediatric and adolescent population and noted that congenital AIVC does not seem to present with symptoms of DVT until at least the second decade of life. The authors suggest that for the anomaly to manifest as DVT, a second "hit" is required.[6] Venous collaterals appear to be able to compensate for the lack of a normal IVC but fail when the demands for venous drainage exceed the capacity of the collateral veins, with DVT then occurring via a mechanism of stasis. Factors specific to the

Abstract

Congenital absence of the inferior vena cava (AIVC) represents a rare but underappreciated central venous condition. The impediment to central venous flow caused by AIVC results in venous stasis. Consequently, there is a strong association with deep vein thrombosis (DVT), particularly in younger individuals.

The vast majority of patients with AIVC will be identified incidentally, and therefore a high index of suspicion needs to be maintained. Given that AIVC is a congenital condition, there is also an association with other congenital anomalies such as cardiopulmonary defects that may arise during the 6th week of gestation. Moreover, hypercoagulability workups are performed frequently in this patient population due to the atypical presentation of DVT.

Venous duplex and axial imaging, including computed tomography venography and magnetic resonance venography remain the mainstay of diagnosis. The axial imaging studies allow for the accurate delineation of the anomalous anatomy. Ultimately, conventional venography may be required, especially if invasive treatment is being considered.

In general, asymptomatic patients may be managed conservatively and with regular surveillance. Symptomatic patients and patients who present with DVT may warrant medical management and / or intervention. Intervention may consist of endovascular procedures, open surgery or a combination thereof. The decision and modality for treatment are highly individualized; however, the principles are extrapolated from the treatment for other central venous and post-thrombotic processes. Often symptoms resolve with restoration of axial flow or restoration of baseline collateralized circulation. Ultimately, long-term management and follow-up are necessary to successfully manage this challenging group of patients.

Keywords

Absence inferior vein cava (AIVC)
Anticoagulation
Computed Tomography Venogram (CTV)
Congenital
Deep vein thrombosis (DVT)
Embryogenesis
Magnetic Resonance Venogram (MRV)
Pharmacomechanical thrombectomy (PMT)
Post-thrombotic syndrome (PTS)
Venous Duplex

adolescent and young adult population may include an increased demand for venous drainage, as from strenuous physical activity, a growth spurt, or the presence of inherited or acquired thrombotic risk factors. Acquired factors include immobilization, trauma, surgery, malignancy, vascular catheterization, smoking, or the use of oral contraceptives.[6]

EMBRYOGENESIS

AIVC may be associated with other congenital abnormalities, including atrial septal defects, polysplenia, or dysgenesis of the lungs.[7,8] The complex embryogenesis of the IVC begins at week 6, as it develops from three pairs of primitive veins, the supracardinal, subcardinal, and postcardinal veins. These veins form collaterals and connections during development but then regress, leading to a single continuous channel, the IVC.[9]

The IVC can be divided into four segments, the hepatic, prerenal, postrenal, and renal collar. These segments arise from the primitive veins. The supracardinal vein gives rise to the postrenal IVC as well as the hemiazygos and azygos veins. The subcardinal vein gives rise to the prerenal portion, and the renal collar is formed from the subcardinal and supracardinal segments. Hepatic sinusoids form the hepatic segment.[9] It has been proposed that AIVC may be caused by dysgenesis of this complex process or by an interruption of the process by an intrauterine insult.[10,11] The most common types of IVC anomalies are isolated left IVC, double IVC, atresia or agenesis of a segment or the total IVC, and azygos or hemiazygos continuation of the IVC (Figs. 163.1, 163.2, and 163.3).[2] Regression of the right supracardinal vein with persistence of the left supracardinal vein results in a left IVC. If both the left and right supracardinal veins persist, there will be a double IVC. Atresia of a segment of the IVC or total IVC atresia is caused by failure of anastomosis of one (segmental AIVC) or multiple (total AIVC) segments of the IVC.[2,12]

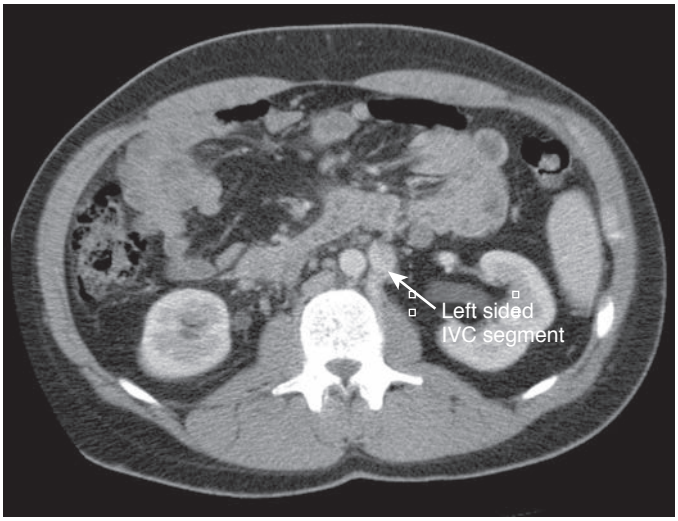

Figure 163.1 Computed tomography scan demonstrating left-sided infrarenal inferior vena cava (IVC) with an absent suprarenal IVC.

PRESENTATION

AIVC may be noted incidentally, or it may present with complications such as DVT with mild or severe symptoms of leg swelling and venous congestion. When AIVC is found, a thrombophilia workup is recommended.

Clinical Diagnosis

Diagnosis of the congenital absence or occlusion of the IVC relies on a high index of suspicion. For example, young patients (<40 years) are considered to be at lower risk for DVT compared

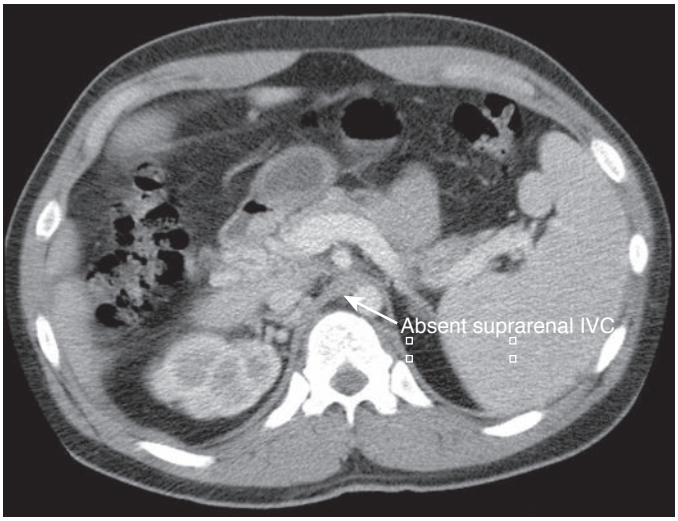

Figure 163.2 Computed tomography scan demonstrating an absent suprarenal inferior vena cava (IVC).

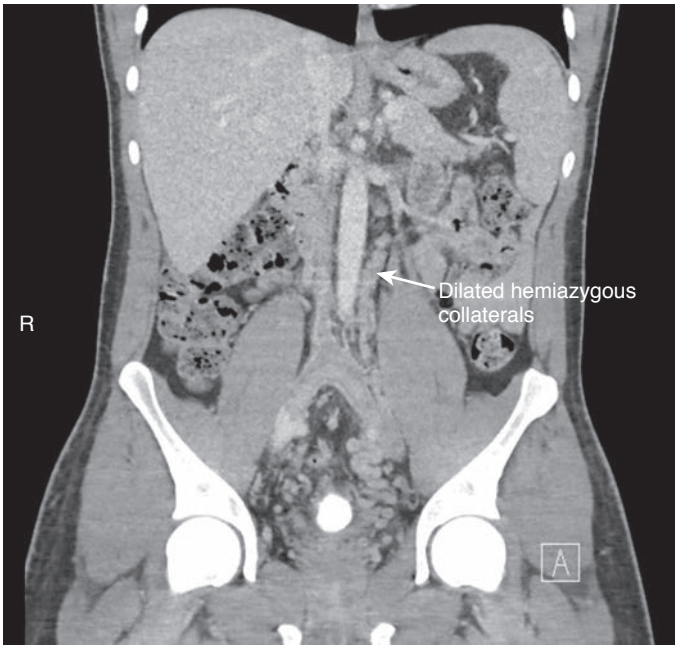

Figure 163.3 Coronal image of computed tomography scan showing hemiazygos continuation of an absent inferior vena cava.

with older ones. Therefore in a young person with an idiopathic DVT, evaluation for hypercoagulability might be accompanied by imaging looking for congenital abnormalities of the deep venous system, including absence of the IVC. This may hold true in even more particular circumstances, such as young patients presenting with severe bilateral lower extremity chronic venous insufficiency or extensive bilateral iliofemoral thrombosis. As noted previously, up to 5% of individuals between 20 and 40 years of age who develop a DVT may have an underlying congenital abnormality of the IVC.[1] Moreover, the clinical presentation may also sway the decision-making process. For example, in patients with significant evidence of collateralization (i.e., abdominal wall varicosities) in the setting of the aforementioned presentation, congenital absence of the IVC is more likely, and these findings would influence the choice of subsequent diagnostic modalities.

Imaging Modalities

Duplex Scan of the Lower Extremities and Pelvis

In the majority of cases the initial study of choice is lower extremity venous duplex. With regard to the deep venous system, duplex may identify direct or indirect signs related to central venous obstruction. In the setting of chronic venous hypertension, where the more peripheral deep veins exhibit damaged valves, significant reflux may be present to a variable extent in the iliac, femoral, popliteal, or tibial veins.[13] Even in the setting of competent deep veins, there may be signs suggestive of a central obstruction, such as diminished or absent respiratory phasicity.[13] There may also be evidence of chronic DVT in the iliofemoral and popliteal veins, suggestive of a prior history of DVT. In this setting, findings would include a contracted, thick-walled, hyperechoic lumen, possibly with associated recanalization.[14] In addition, due to the significant burden placed on the lower extremity's venous system in the setting of AIVC, reflux may be present in the truncal superficial veins or perforator veins. Significant superficial collateral networks emanating from the abdominal wall or the pelvis may also be identified by duplex ultrasound, suggesting congenital absence of the IVC. Last, direct insonation of the iliocaval venous segments may be performed and may show absence of flow in these segments or complete absence of the segments themselves. The disadvantage of duplex is that it is highly operator-dependent as well as being dependent on patient-specific factors such as size, bowel gas, and patient cooperation.[14] Once clinical suspicion for severe iliocaval disease is present and duplex ultrasound corroborates the clinical findings, confirmatory imaging is typically required. This would be performed most commonly with noninvasive axial imaging, such as CT venography (CTV) or magnetic resonance venography (MRV). Invasive methodologies, such as ascending venography or intravascular ultrasound, may also be performed as adjunctive studies.

Axial Imaging (Computed Tomography Venography and Magnetic Resonance Venography)

CTV or MRV may be utilized to diagnose and determine the exact anatomic variant characterizing congenital absence of the IVC. Both modalities have advantages and disadvantages. Each will identify acute DVT in the central veins. A possible advantage of MRI may be the ability, with certain sequences, to estimate, the chronicity of the DVT.[15]

For CTV, the significant potential complication is contrast-induced nephropathy. Therefore this modality should be used judiciously in patients presenting with chronic kidney disease. This may be especially true in patients with renal aplasia, which has a known association with congenital absence of the IVC.[5] Moreover, CT scans pose the added long-term risk of radiation, which may be of greater consideration in evaluating younger patients.[16] Patients with significant reactions or allergies to iodinated contrast may be precluded from utilizing this modality. With regard to image quality, the timing and acquisition of CTV are variable, and this variability may be exaggerated in patients with congenital absence of the IVC, given the alteration in flow dynamics leading to poor imaging of the pathology.

However, there are advantages to using CTV as opposed to MRV. It allows for the rapid acquisition of images and is readily available in most centers. In addition, if a patient has known metal implants, there is substantially less artifact with the use of CTV as compared with MRV, and the intraluminal contents of stented vasculature can be evaluated more readily. Moreover, luminal diameter may be measured more accurately, since the full extent of the vessel wall is more readily appreciated on CTV than on MRV (Figs. 163.4 and 163.5).[17]

MRV has the advantage of lack of radiation. With regard to evaluation of the vasculature, the gadolinium may dwell longer than the iodinated contrast utilized for the CTV; therefore, the vasculature may be evaluated more completely over prolonged

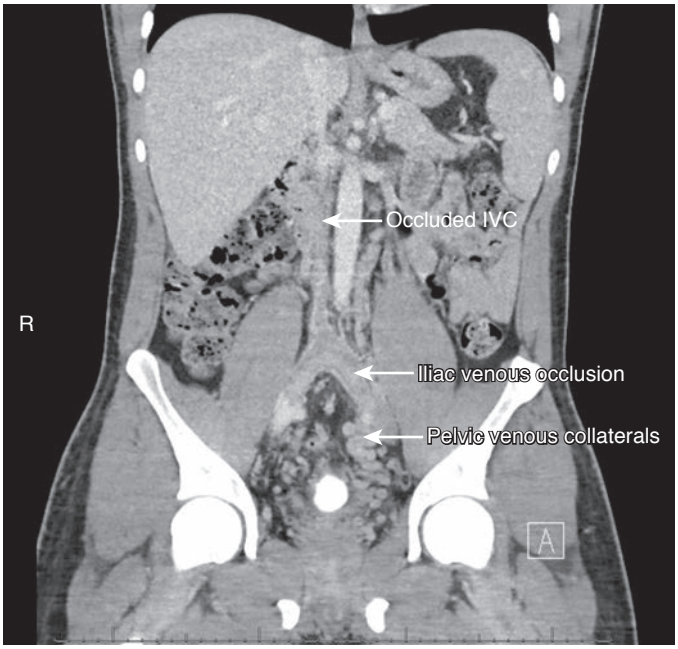

Figure 163.4 Coronal computed tomography image of thrombosed distal inferior vena cava (IVC) and iliac veins with pelvic collaterals in the setting of an absent IVC.

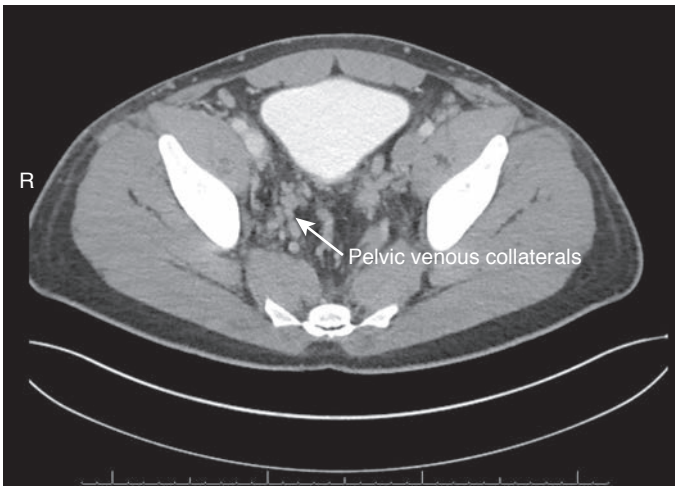

Figure 163.5 Axial computed tomography image of pelvic collaterals with an absent inferior vena cava and thrombosed iliac veins.

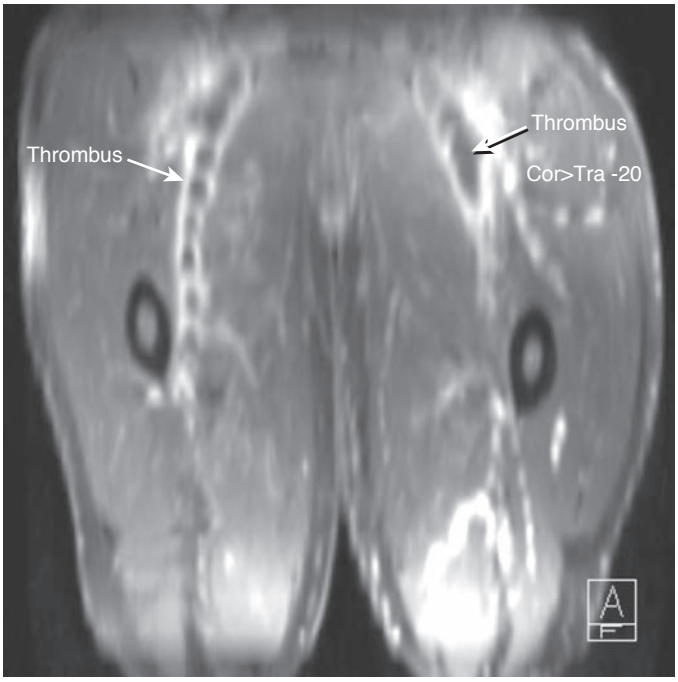

Figure 163.6 Magnetic resonance venogram demonstrating acute thrombosis of the bilateral femoral veins in the setting of an absent inferior vena cava.

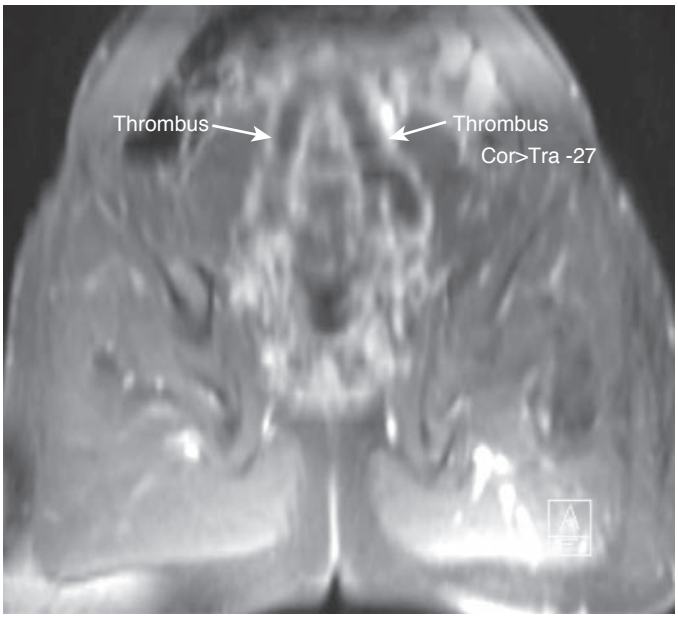

Figure 163.7 Magnetic resonance venogram demonstrating acute thrombosis of the bilateral iliac veins in the setting of an absent inferior vena cava.

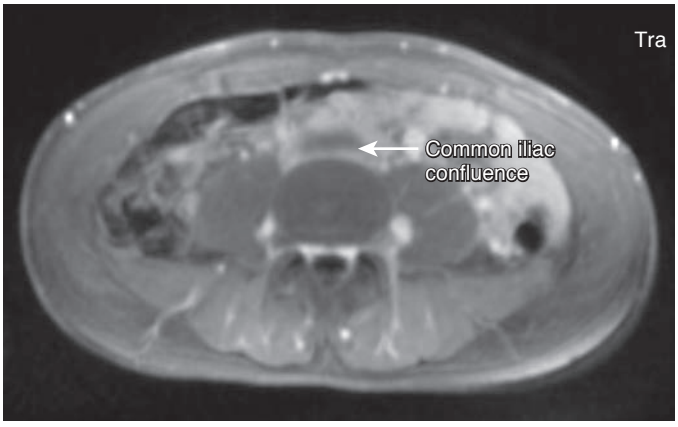

Figure 163.8 Magnetic resonance venogram demonstrating acute thrombosis of the confluence of the iliac veins in the setting of an absent inferior vena cava.

time intervals (Figs. 163.6, 163.7, and 163.8).[18] This allows for a more complete assessment of the vasculature and the ability to obtain time-resolution images. These may provide critical information with regard to collateral circulation and patterns of flow. In the elective setting, MRV may be the preferred modality by a small margin, given the improved filling of the vasculature and the possibility for improved time resolution.[19] Disadvantages to obtaining an MRV include strict contraindications in patients with certain metal implants, such as pacemakers. Moreover, patients with advanced (stages IV-V) chronic kidney disease are at risk for nephrogenic systemic fibrosis (NSF) following the administration of gadolinium.[20] There are time-of-flight sequences that do not utilize intravenous contrast agents; however, the resolution of these images is often suboptimal for full delineation of the vasculature. Last, the degree of stenosis may be overestimated by MRV owing to the way in which the image is acquired, with the associated flow voids.[21]

Venography

Venography is typically considered the gold standard for direct visualization of the venous vasculature. It serves most commonly as an adjunctive study to the aforementioned noninvasive imaging modalities. The procedure itself allows for direct visualization of flow through central and peripheral veins, and it can provide

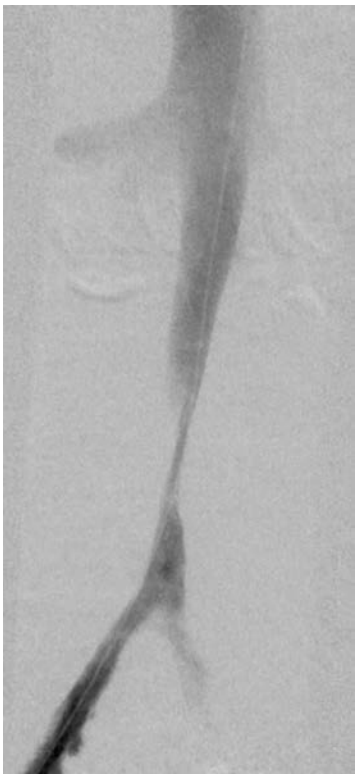

Figure 163.9 Venogram of segmental atresia of the infrarenal inferior vena cava.

for real-time visualization of the flow through axial as well as collateral pathways. As is true with other invasive imaging studies, multiple projections may be required, and selective catheterization may help to further delineate anatomy and flow. Acute and chronic processes may be visualized as well. Last, should an intervention be considered, venography will by its nature be a component of the procedure, and this is the role that it plays most commonly (Fig. 163.9).

MANAGEMENT

Owing to the absence of the IVC and the commensurate lack of axial flow, there is limited possibility for the development of pulmonary emboli in the setting of a peripheral DVT.[19] Therefore the indications for treatment are based on the presenting signs and symptoms as opposed to the prevention of a pulmonary embolus. As stated previously, the patient may be asymptomatic at presentation, or there may be signs and symptoms of an acute process, such as an acute DVT, or a chronic process, such as the stigmata of chronic venous insufficiency. In all settings the severity may vary significantly, and this also affects decision making as it relates to treatment. Truly emergent presentations are rare because patients have already developed a significant collateral network that compensates following the development of an acute process. Consequently the mainstay of treatment is anticoagulation with the concomitant use of graduated compression stockings to mitigate the sequelae of postthrombotic syndrome.[22]

Acute Deep Venous Thrombosis With Mild Symptoms

Conventional treatment for an acute DVT with mild symptoms consists of anticoagulation with the use of graduated compression stockings.[22] In the case of AIVC, the goal of anticoagulation is to prevent further propagation of thrombus, particularly into patent collateral networks that are contributing to venous return. The type of anticoagulation may be left to the discretion of the practitioner. Because of the presence of a significant fixed anatomic defect, the general recommendation is to treat with lifelong anticoagulation.[3] Warfarin and low-molecular-weight heparin may be utilized. The novel oral anticoagulants (NOACs) such as apixaban, rivaroxaban, and dabigatran are attractive alternatives due to their convenience, particularly in young patients who require long-term therapy. Treatment with systemic (as opposed to catheter-directed) thrombolytics may be considered but has demonstrated limited success in this setting, and there is a significant risk for complications that is not commensurate with the efficacy of the treatment in the setting of mild symptoms.[23] With regard to graduated compression, emerging evidence suggests that it may not prevent the development of a postthrombotic syndrome; however, it is still considered an appropriate treatment in patients in whom the postthrombotic syndrome has already been diagnosed.[24]

Even in the setting of mild symptomatology, there should be a discussion with the patient regarding invasive management for the treatment of iliofemoral acute DVT to prevent postthrombotic syndrome.[25] The relevant invasive treatments include catheter-directed thrombolysis and pharmacomechanical thrombectomy with or without adjunctive catheter-directed thrombolysis (see Chapters 148 and 161). Open venous thrombectomy would not be a consideration in the setting of mild symptoms and congenital absence of the IVC.

When they are considered, interventional treatments should typically be offered in the acute presentation period (less than 2-4 weeks). The efficacy of thrombolytic-based treatments diminishes over time. They should be utilized to treat the iliofemoral veins; there are few data demonstrating benefit in the treatment of patients with isolated femoropopliteal or more peripheral DVTs.[25] Important tools in ensuring restoration of luminal patency of the treated veins include performing venography in multiple oblique projections as well as intravascular ultrasound to assess for the full resolution of thrombus. Restoration of adequate inflow is predicated on restoration of flow from a patent femoral or profunda femoris vein into a patent iliac venous system.

The restoration of outflow is the clear obstacle in the setting of the congenital absence of an IVC. Often, the more proximal outflow collateral network that has developed over time, perhaps communicating with the azygos system, is robust enough to maintain patency with the assistance of long-term anticoagulation.[3]

The use of pharmacomechanical thrombectomy may expedite treatment and limit the dosage of the chosen lytic agent (see Chapters 148 and 161). Level 1 evidence supporting the invasive management of acute iliofemoral DVT is sparse. However, the

preponderance of case series and prospective registries suggest long-term anatomic and clinical benefits to the invasive treatment of iliofemoral DVT.[25] The primary outcomes that are commonly evaluated include anatomic patency of the iliofemoral veins as well as freedom from the development of postthrombotic syndrome. The only randomized trial at present that has evaluated the long-term outcomes for the treatment of iliofemoral venous thrombosis is the Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis (CaVenT) study.[26] This study compared the treatments of anticoagulation alone to the use of catheter-directed lytic therapy. At the 5-year time point there was an improvement in iliocaval patency from 47% to 66% ($P = .012$) in patients treated with lytic therapy and an improvement in the freedom from development of postthrombotic syndrome from 41% to 55% ($P = .047$). The remaining data are heterogeneous, but a Cochrane database review showed that catheter-directed thrombolysis improves iliofemoral venous patency and reduces the incidence of postthrombotic syndrome by approximately one-third.[25]

The most significant risk of interventional therapies using thrombolytic agents is the risk of bleeding, which ranges from 5% to 10%. However, most reported cases reference only minor bleeding at the access site.[22] Considering the lack of evidence to guide the invasive management of iliofemoral venous DVT, particularly in the setting of mild symptoms such as are often present in AIVC, a full assessment of the risks, benefits, and alternatives must be undertaken and the treatment should be individualized to the patient. Moreover, all treatments are predicated on periprocedural conservative management with anticoagulation and compression.

Acute Deep Venous Thrombosis With Severe Symptoms (Leg Swelling, Venous Congestion)

In patients who present with more severe symptoms, the risk-benefit ratio for invasive management is altered, and progressively more so as the pathology approaches limb-threatening stages. Fortunately this situation is rare in the setting of congenital absence of the IVC, given that the compensatory collateral pathways have matured over time. Nonetheless, debilitating acute limb swelling and the presentations of phlegmasia cerulea dolens, phlegmasia alba dolens, or even venous gangrene are possible. In these settings, the focus of treatment is rapid restoration of deep venous circulation for limb-salvage purposes.

The aforementioned techniques and principles remain unchanged except that pharmacomechanical thrombectomy would be favored compared with isolated catheter-directed therapy given that it restores luminal patency more rapidly (see Chapters 148 and 161). Open venous thrombectomy may also be considered (see Chapters 148 and 160).[27]

Severe Symptoms Refractory to Thrombolysis and Compression or Severe Chronic Sequelae (Venous Ulceration)

In the setting of refractory symptoms of chronic venous insufficiency, the initial consideration should be to ensure that the iliofemoral veins are patent using techniques described previously (venography and intravascular ultrasound). If there is evidence of chronic disease peripheral to the congenitally absent IVC, there may be a role for venography with or without angioplasty. Although stenting is employed widely in the treatment of thrombotic and nonthrombotic iliofemoral venous lesions, the success of stenting is predicated on a widely patent conduit with adequate inflow and outflow. In the setting of an absent IVC, the risk of thrombosis may be prohibitive with regard to iliofemoral venous stenting.

As a last resort in a patient with debilitating chronic venous insufficiency and after confirming that the peripheral veins are patent, an open venous reconstruction may be warranted.[28] The majority of the literature as it relates to open reconstruction of the IVC is in the setting of oncologic resections (see Chapter 167).[29] The principles of adequate inflow, outflow, and conduit still require strict adherence. Preoperative axial imaging is especially helpful for operative planning; it can identify the extent of the defect and the presence of abdominal wall collaterals, which, if injured or ligated during surgery, can lead to excessive bleeding.

Autologous tissue is preferred for conduit because lifelong anticoagulation may not be needed, as it would be for synthetic grafts. Aortic and IVC homografts have both been utilized.[30] In depopulated homografts there does not appear to be a concern for rejection; however, some authors report placing patients on immunosuppression for up to 1 year postprocedure.[31] Another theoretical complication is aneurysmal degeneration; however, this has not been observed in patients undergoing reconstruction of the IVC. The configuration of the proximal and distal anastomoses (end to end or end to side) is determined by the anatomy. An arteriovenous fistula may be created to ensure adequate inflow. However, in one series of three patients undergoing arteriovenous fistula construction concomitant with IVC reconstruction, high-output cardiac failure occurred in two of the three patients. The fistulas were all ligated accordingly.[32] Although the data for open IVC reconstructions are limited, anecdotal reports suggest the potential for long-term patency.[29,30] Overall, the clinical success of any open reconstruction is predicated on continued and diligent conservative management with anticoagulation and compression.

SUMMARY

It is likely that most cases of congenital absence or occlusion of the IVC remain undiagnosed and if asymptomatic are considered of little clinical importance. However, this diagnosis should be considered in patients under the age of 30 with idiopathic DVT. In association with extensive iliofemoral DVT and/or thrombophilia, management of this condition can be challenging. Based on the severity of presenting symptoms, thrombolysis should be considered in these patients, with an endpoint of restoring baseline venous flow to previously established venous collaterals. Long-term anticoagulation is often indicated, particularly if thrombophilia is identified. Table 163.1 summarizes the presentation and treatments of all recent publications.

TABLE 163.1 Clinical Data Characterizing Inferior Vena Cava Agenesis Associated With Deep Venous Thrombosis in 62 Reported Cases and 10 Patients

Reference	Number of Patients	M/F Sex Ratio	Mean Age (Years)	DVT Localization (Side)	Risk Factors	Precipitating Factor	Treatment
[17]	1	0/1	12	1 Unilateral (right)	None	None	Prolonged VKA, elastic stockings
[33]	9	8/1	29 (19-57)	6 Bilateral	None	None	7 Prolonged VKA, elastic stockings (>6-72 months) 2 VKA (6 months)
[1]	4	3/1	19	2 Bilateral, 2 unilateral (right)	None	None	Prolonged VKA, elastic stockings
[4]	1	0/1	39	Bilateral	None	None	Prolonged VKA, folic acid supplementation, elastic stockings
[34]	5	3/2	25	1 Bilateral, 4 unilateral (left)	1 Oral contraception, 2 travel >4 h	2 Major physical activity	3 Prolonged VKA, 2 thrombolysis, VKA; 5 elastic stockings
[35]	1	1/0	14	1 Unilateral (left)	None	None	Prolonged VKA, elastic stockings
[36]	2	1/1	17	2 Unilateral (right)	None	1 Major physical activity	Thrombolysis, prolonged VKA, elastic stockings
[37]	4	2/2	27	3 Bilateral, 1 unilateral (NR)	1 Oral contraception	None	Prolonged VKA, elastic stockings
[38]	1	0/1	40	1 Unilateral (right)	None	Major physical activity	Prolonged VKA, elastic stockings
[39]	1	1/0	22	Unilateral (right)	None	NR	Prolonged VKA, elastic stockings
[40]	1	1/0	26	Unilateral (left)	None	Major physical activity	Prolonged VKA, elastic stockings
[41]	1	1/0	21	Unilateral (left)	None	None	No information available
[42]	1	1/0	39	Unilateral (left)	None	None	VKA for 1 year and elastic stockings
[43]	1	0/1	67	Bilateral	None	None	Prolonged VKA, elastic stockings
[44]	1	1/0	62	Unilateral (right)	None	None	Prolonged VKA, elastic stockings
[11]	1	1/0	44	Unilateral (left)	None	None	Prolonged VAK, elastic stockings
[45]	1	1/0	49	Bilateral	NR	NR	Prolonged VKA, elastic stockings
[46]	1	1/0	30	Bilateral	None	None	Prolonged VKA, elastic stockings
[47]	1	1/0	41	Unilateral (right)	None	None	Venous bypass, prolonged VKA
[48]	1	0/1	48	NR	None	None	Prolonged VKA, elastic stockings
[49]	1	1/0	17	Unilateral (left)	None	None	Thrombolysis, 6 months LMWH
[25]	1	1/0	32	Unilateral (right)	None	None	Prolonged VKA, elastic stockings
[50]	1	1/0	37	Unilateral	None	None	Prolonged VKA
[51]	1	1/0	21	Bilateral	None	None	Thrombolysis, prolonged VKA, elastic stockings
[52]	1	1/0	27	Bilateral	None	None	Prolonged VKA, elastic stockings

Continued

TABLE 163.1 Clinical Data Characterizing Inferior Vena Cava Agenesis Associated With Deep Venous Thrombosis in 62 Reported Cases and 10 Patients—cont'd

Reference	Number of Patients	M/F Sex Ratio	Mean Age (Years)	DVT Localization (Side)	Risk Factors	Precipitating Factor	Treatment
[53]	1	1/0	18	Unilateral (right)	Behecet disease	None	Prolonged VKA
[54]	1	1/0	26	Infrarenal portion of IVC	None	None	Prolonged VKA
[55]	1	0/1	23	Unilateral (right)		Pregnancy, preeclampsia	Prolonged VKA, elastic stockings
[56]	1	1/0	19	Bilateral	None	None	Prolonged VKA
[57]	1	1/0	50	Unilateral (left)	1 Travel ≥4 h	None	Prolonged VKA
[58]	1	1/0	54	Unilateral (right)	None	None	Prolonged VKA
[59]	1	1/0	22	Right pelvic collateral vein	None	None	Prolonged VKA
[60]	1	0/1	17	Bilateral	None	None	Prolonged VKA (>1 year)
[61]	1	1/0	14	Unilateral (right)	None	None	Prolonged VKA
[62]	1	1/1	33.34	2 Unilateral (right)	Knee trauma	None	NR
[63]	1	1/0	8.5	Unilateral (right)	None	None	VKA 8 months
[64]	1	0/1	18	Pelvic DVT Bilateral	1 Oral contraception	None	Prolonged VKA
[65]	1	0/1	26	Bilateral	None	None	Prolonged VKA
[66]	1	1/0	20	Pelvic DVT	None	None	Prolonged VKA
[67]	2	1/1	24.28	1 Unilateral 1 Bilateral	None	None	1 prolonged VKA 1 VKA (12 months)
[68]	1	1/0	18	1 Unilateral	None	None	Prolonged VKA
This paper	10	8/2	25	6 Bilateral: 4 Unilateral	1 Travel ≥4 h	8 Major physical activity	9 prolonged VKA, elastic stockings; 1 VKA (25 months)
TOTAL	72	53/19	29.6 ± 13.2	28 Bilateral 4 Unilateral 28 Bilateral 40 Unilateral 1 NR 2 Right pelvic collateral vein 1 Infrarenal portion of IVC	3 Oral contraception, 3 travel ≥h 1, knee trauma, 1 bedridden for 2 days	13 Major physical activity	56 Prolonged VKA 7 VKA (<3 years) 1 LMWH (6 months) 5 thrombolysis, 1 bypass

DVT, Deep venous thrombosis; *F*, female; *LMWH*, low-molecular-weight heparin; *M*, male; *NR*, not reported; *VKA*, vitamin K antagonist.
Reprinted with permission from Lambert M, Marboeuf P, Midulla M, et al. Inferior vena cava agenesis and deep vein thrombosis: 10 patients and review of the literature. *Vasc Med.* 2010;15:451–459.

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Halparin J, Monagle P, Newall F. Congenital abnormalities of the inferior vena cava presenting clinically in adolescent males. *Thromb Res.* 2015;135(4):648–651.

Series demonstrating the association between congenital absence of the inferior vena cava and unprovoked deep venous thrombosis in adolescent males.

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CHAPTER 164

Portal Hypertension

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INTRODUCTION

Portal hypertension (PHT) occurs when there is an abnormal increase in pressure in the veins that carry blood from the visceral organs to the liver. This can be explained by Ohm's law, where the change in pressure is equal to the flow times the resistance ($P = Q \times R$). Therefore the pressure can be increased by increasing the flow or increasing the resistance. Normal portal pressure is between 5 and 10 mm Hg. Clinically significant portal hypertension (PHT) occurs at pressures of 10 mm Hg above systemic venous pressure. Both intrahepatic and portocollateral resistance can increase vascular resistance when compared to the low resistance of a normal liver.[1]

PATHOPHYSIOLOGY

PHT occurs as the result of an increase in portal flow, an obstruction to portal circulation resulting in increased intrahepatic resistance, or both. An increase in intrahepatic resistance is seen due to narrowing of the vascular lumena from distortion of sinusoidal structures and regenerative nodule formation in the cirrhotic liver. Hepatic stellate cells have also been shown to play a role in the development of increased intrahepatic resistance due to their enhanced contractility and the development of intrahepatic vasoconstriction. In normal conditions, they regulate sinusoidal blood flow by the balance between vasoconstrictors and vasodilators. In the cirrhotic liver there is a decrease in vasodilators and an increase in vasoconstrictors, as well as an increase in fibrosis, which promotes overall intrahepatic vasoconstriction and an increase in portal pressure.[2,3]

Portal blood flow is increased by vasodilation in the splanchnic vasculature. While the liver experiences vasoconstriction of the intrahepatic vessels, the splanchnic vessels are affected by endogenous vasodilators and a decrease in reactivity to vasoconstrictors. This is the main cause of the increase in portal blood flow seen in cirrhosis. Splanchnic vasodilation is

Abstract

Portal hypertension occurs when there is an abnormal increase in the pressure in the veins that carry blood from the visceral organs to the liver. It is responsible for causing many findings seen with liver disease, such as ascites, abdominal wall varicosities, spider angiomas, palmer erythema, gynecomastia, and muscle wasting. Encephalopathy, asterixis, and fatigue may also be present. Collaterals form to connect the high-pressure portal veins with the low-pressure systemic veins and thus develop into the diseased gastroesophageal varices that are susceptible to bleeding. This chapter serves to explain the pathogenesis behind the evolution of portal hypertension, as well describe common causes and up to date management.

Keywords

Portal hypertension
portal vein thrombosis
hepatic encephalopathy
esophageal varices
gastric varices
transjugular intrahepatic portosystemic shunt
TIPS
balloon-occluded retrograde transvenous obliteration
BRTO

compensated by an increase in heart rate and cardiac output early on, but eventually results in arterial hypotension. The arterial hypotension in turn activates high-pressure baroreceptors and the sympathetic nervous system. This causes the release of vasoconstrictors which affect the peripheral but not the splanchnic vessels, leading to a hyperdynamic circulation. Collaterals form to connect the high-pressure portal veins with the low pressure systemic veins and develop into gastroesophageal varices. Shunting of blood into the systemic system occurs, resulting in hepatic encephalopathy.[2]

CLASSIFICATION

PHT is classified according to anatomic location, as extrahepatic, intrahepatic, and posthepatic. Posthepatic causes include veno-occlusive disease and cardiac conditions. These categories are further subdivided according to their relationship to sinusoids within the liver (Table 164.1).

TABLE 164.1 Causes of Portal Hypertension

Presinusoidal
Portal Vein Thrombosis
Omphalitis
Pancreatitis
Trauma
Malignancy
Hypercoagulable states
Other
Polycythemia vera
Biliary atresia
Schistosomiasis
Sarcoidosis
Wilson disease
Congenital hepatic fibrosis
Sinusoidal
Cirrhosis
Toxic hepatitis
Postsinusoidal
Cirrhosis
Hemachromatosis
Veno-Occlusive Disease
Budd-Chiari syndrome
Hepatic vein webs
Malignant obstruction
Hypercoagulable states
Cardiac
Congestive heart failure
Constrictive pericarditis

Extrahepatic Presinusoidal Obstruction

Presinusoidal extrahepatic obstruction is most commonly caused by thrombosis of the portal vein. Portal vein thrombosis occurs in both children and adults. In children, the most common cause is infectious, such as appendicitis or omphalitis. In adults, there are multiple causes, including hypercoagulable states, inflammatory diseases, complications of medical interventions, malignancy, and most commonly cirrhosis. Portal vein thrombosis occurs with an incidence of 0.6% to 22% in adult patient with these conditions.[4]

Intrahepatic Presinusoidal Obstruction

Intrahepatic presinusoidal obstruction occurs from fibrosis and compression of portal venules, which subsequently restrict portal flow. This can be seen with hepatic fibrosis, sarcoidosis, chronic arsenic exposure, Wilson disease, hepatoportal sclerosis, primary biliary cirrhosis, schistosomiasis, and myeloproliferative disorders. Wilson disease is a hereditary disorder of copper metabolism, in which copper accumulates in hepatocytes due to an inability to excrete copper into the biliary system.

Schistosomiasis is the most common cause of PHT in third world countries. It occurs from ova deposition in portal vein walls, resulting in a granulomatous inflammatory reaction that causes fibrosis and restriction of portal blood flow. The mechanism of action in myeloproliferative disorders involves deposition of cellular material into the portal zones. In sarcoidosis the deposition of sarcoid granulomas within the portal vein leads to its obstruction and increase in portal blood flow.[5,6]

Intrahepatic Sinusoidal and Postsinusoidal Portal Hypertension

Sinusoidal hypertension results from alcoholic, viral, and toxic hepatitis. Postsinusoidal obstruction is caused by alcoholic liver disease, postnecrotic cirrhosis, and hemochromatosis. Together, sinusoidal and postsinusoidal hypertension resulting in cirrhosis are the most common causes of PHT in the Western world. The mechanism of action is mechanical obstruction of portal blood flow by regenerating hepatic nodules and cirrhotic bands in the liver. In addition to the effects on the hepatic sinusoids, these phenomena can also damage presinusoidal and postsinusoidal structures. The normal architecture becomes distorted.

Cirrhosis also results in increases in hepatic blood flow. The liver generates multiple arteriovenous shunts and collaterals, which lead to nearly 33% of blood flow bypassing functional hepatocytes. This causes an increase in cardiac output and diminished systemic resistance, therefore elevating hepatic wedge pressure and portal liver pressure. Moreover, since a third of portal blood is shunted away from functioning hepatocytes, the cirrhotic patient develops impaired hepatic function.[1-3]

Extrahepatic Postsinusoidal Obstruction

Extrahepatic postsinusoidal obstruction results from hepatic vein thrombosis and cardiac disease. Precipitating factors for

hepatic vein thrombosis include malignancies, trauma, pregnancy, and oral contraceptives. Hepatic vein occlusion also occurs in Budd-Chiari syndrome, which in turn is associated with myeloproliferative disorders and hypercoagulable states.[1-3]

Arteriovenous Fistulae

Arteriovenous fistulae cause PHT by increasing flow in the portal circulation. As the disease progresses to fibrosis and obstruction of the presinusoidal spaces, PHT is exacerbated. Arteriovenous fistulae can be caused by percutaneous transhepatic manipulation or penetrating trauma. They can also be associated with splenic fistulae from splenic artery aneurysms, sarcoidosis, Gauche disease, and myeloid metaplasia.[1-3]

CLINICAL PRESENTATION

Physical examination findings consistent with liver disease include ascites, spider angiomas, palmer erythema, gynecomastia, enlarged abdominal wall collateral veins (caput medusae), and muscle wasting. Encephalopathy, asterixis, and fatigue may also be present. In many cases, variceal bleeding constitutes the initial presentation.[7-9]

COMPLICATIONS OF PORTAL HYPERTENSION

Variceal Formation and Hemorrhage

The formation of portal-systemic collaterals is seen when portal pressures reach 10 to 12 mm Hg above systemic venous pressures. Due to elevated portal pressures and increased splanchnic blood flow diverted from the portal to the systemic system, the vascular resistance of the collateral beds increases. Although it is lower than the obstructed portal system, it is still higher than normal portal pressure. This phenomenon explains why the formation of portal-systemic collaterals does not normalize the elevated portal pressures.[10]

Varices are mainly the result of dilation and dysfunction of the preexisting embryonic connections between the portal and venous systems, but formation of new blood vessels via neoangiogenesis also occurs. These new vessels are abnormal, with marked hyperplasia and hypertrophy of their walls. The left gastric vein arising from the portal vein and the short gastric veins arising from the splenic vein are the vessels most often affected.[10]

Esophageal varices form when the left gastric vein becomes dilated, and both esophageal and gastric varices form as a result of dysfunction and dilation of the short gastric veins. These vessels divert portal blood flow into the azygos venous system via the venous plexus of the lamina propria and submucosa of the esophagus and stomach. Esophageal varices form from the distal to proximal esophagus and can be divided into four zones: the gastric, palisade, transitional, and truncal zones. The transitional zone is defined as the 2 cm above the gastroesophageal junction and extends superiorly for another 2 cm; it is the zone most susceptible to bleeding. Gastric varices can be divided into type I and type II, where type I are gastric varices that extend above the cardia as esophageal varices and type II are isolated to the stomach, most commonly on the fundus.[10]

Varices can also be seen on the abdominal wall from collateralization between the left portal vein and the systemic system via periumbilical veins in the falciform ligament. The physical exam finding associated with this is known as caput medusae.

Esophageal and gastric varices are present in roughly 50% of cirrhotic patients at the time of diagnosis, and the incidence increases to 90% of patients with long-term follow-up. Rupture with bleeding occurs from small varices (<5 mm) in 7% of patients over a 2-year period, and in 30% of patients with large varices over the same period.[9] The mortality rate after the first bleed reaches 35%, and 60% of patients re-bleed within the first year. Each additional bleed carries a mortality rate of 20%.[1,11]

The most widely accepted explanation as to why varices bleed is the explosion hypothesis. It suggests that when the hydrostatic pressure inside varices increases to above 10 mm Hg, variceal dilation, and a decrease in wall thickness occurs. Ruptures occur when the tension in the expanding wall can no longer be countered by wall tension (Law of LaPlace). The critical hepatic venous pressure gradient is 12 mm Hg. In the presence of varices, pressures above 12 mm Hg are associated with a significant risk of variceal bleeding; however, the magnitude above this value does not necessarily correlate with risk of hemorrhage. Medical therapy and interventions are aimed at keeping the hepatic venous pressure gradient below 12 mm Hg; pressures below this level are associated with minimal risk of bleeding.[10]

Ascites

Ascites occurs in up to 80% of patients with PHT. With the increase in portal pressure, Starling forces drive fluid out of vessels and into the interstitial space, causing ascites. Low oncotic pressure resulting from the hypoalbuminemia manifested by cirrhotic patients also occurs, exacerbating the problem. In addition, the lymphatic system typically becomes overwhelmed.[5]

The accumulation of ascites places patients at risk for spontaneous bacterial peritonitis (SBP). In the past, approximately 75% of these infections were attributed to gram-negative aerobic bacteria, suggesting the gastrointestinal tract as the source. However, more recent data show that up to one-third of cases are associated with gram-positive bacteria.[12,13] Approximately 30% of patients with ascites require hospital admission at some point for antimicrobial treatment of SBP. Its presence is associated with increased mortality in cirrhotics.[14]

Encephalopathy

Hepatic encephalopathy refers to any neuropsychiatric dysfunction caused by liver disease. The symptoms are broad, ranging from subclinical to coma or death. Due to malfunctioning hepatocytes and portosystemic shunting, increased levels of

ammonia and glutamine derived from ammonia occur in the arterial system. These cause dysfunction of astrocytes in the brain as well as mitochondrial dysfunction, ultimately resulting in alterations of cerebral function, cerebral edema, and potentially cerebral herniation. These changes are graded by the Wes Haven Criteria. Grades I and II include mild symptoms such as changes in cognition, altered sleep patterns, mood changes (anxiety or euphoria), mild disorientation, asterixis, and increasing apathy and drowsiness. Grades III and IV consist of somnolence or coma.[7,15]

Encephalopathy occurs in 30% to 40% of patients with decompensated liver failure and is associated with an increase in mortality.[7] It is thought that obstruction of blood flow in the liver together with the development of collaterals result in the shunting of neuroactive peptides into the systemic circulation. It is considered a reversible disorder; early recognition can prevent progression.[16]

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) occurs when renal function is decreased in the presence of cirrhosis and ascites. It is considered a "diagnosis of exclusion"; therefore, other causes of renal dysfunction must be ruled out to confirm its presence. Clinically it presents as oliguria, hyponatremia, and low urinary sodium output. It can occur rapidly (deterioration of renal function within 2 weeks) or as a more chronic disorder. Rapid deterioration is associated with a poor prognosis; only 10% of patients survive hospitalization.[17]

Hepatopulmonary/Portopulmonary Syndromes

These syndromes are defined as combinations of PHT, pulmonary hypertension, pulmonary vasodilation/shunting, and impaired oxygenation. They present with clubbing, dyspnea, and deoxygenation induced by the upright position. In general, mortality is the result of liver failure rather than pulmonary complications.[18]

DIAGNOSIS

Laboratory Evaluation

The initial evaluation of liver disease should include an arterial blood gas, lactate, complete blood count, International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, factor V level, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), amylase, lipase, magnesium, phosphorous, creatine kinase, and comprehensive metabolic panel. Ammonia levels are commonly obtained, although they have not been shown to correlate well with neurologic abnormalities.[9] The results of these studies in conjunction with the history of onset and physical examination findings can help determine whether liver dysfunction is acute or chronic, and determine its severity.[19]

Specific testing for etiology should also be included in the diagnostic evaluation, including viral hepatitis immunology, human immunodeficiency virus (HIV), ceruloplasmin, serum copper, antinuclear antibody, and a toxicology screen.[19]

A decrease in serum testosterone has been seen in up 90% of men with cirrhosis, and low testosterone levels are associated with an increase in mortality. The conversion rates of testosterone to estradiol are significantly increased in men with cirrhosis, while the overall plasma production rates of estradiol and clearance rates of estradiol remain similar to men without cirrhosis. These findings may be responsible for the physical examination findings described previously and are associated with liver failure. However, data supporting the specific mechanisms of action are lacking.[20,21]

Upper Gastrointestinal Endoscopy

Endoscopy is critical in the evaluation of patients with PHT to diagnose and evaluate varices, and should be performed in all patients with varices, regardless of whether they have bled. After an episode of bleeding, it is recommended that repeat endoscopy be performed every 3 to 6 months. Endoscopy can also diagnose gastropathy, gastritis, ulceration, and mucosal lacerations.[8,11,22]

Liver Biopsy

Liver biopsy can determine the etiology of liver disease as well as its acuity. Although the necessity of biopsy is controversial, determining the cause of PHT through biopsy is useful in guiding treatment. Pathologic features of cirrhosis include rounding of edges seen on low power with remodeling of hepatic architecture causing nodularity, loss of terminal hepatic venules in parenchyma between portal tracts, spacing between portal tracts, portal veins and hepatic veins, increase in vascular channels within areas of scar and fibrous tissue, and evidence of hepatocyte regeneration. Plasma cells at the portal/septal interface can be seen in chronic hepatitis B infections. Mallory-Denk bodies are seen with alcoholic liver disease, but are also present in Wilson disease, drug-induced liver disease, and primary biliary cirrhosis.[23] Mallory-Denk bodies (MDB) are eosinophilic cytoplasmic inclusion bodies that hover near the hepatocyte nucleus. The clinical and prognostic significance of MDBs is not entirely clear, but their accumulation is reversible with removal of the causal agent, such as abstaining from alcohol. Therefore if seen on biopsy, consideration may be given to postponing elective procedures to allow the liver time to heal.[24,25] Chronic schistosomiasis results in a characteristic "pipestem" fibrosis and may demonstrate calcified eggs and periportal granulomas; the acute infection will demonstrate live eggs surrounded by eosinophils.[23]

Duplex Scanning

Duplex scanning is a simple and effective way to determine portal vein patency. It can also determine direction of flow through the portal vein. This information is imperative in

preoperative planning for TIPS, shunt procedures, and liver transplant. It is also a key surveillance tool after these procedures to confirm portal vein patency.[26,27]

Computed Tomography Angiography

Computed tomography angiography (CTA) can be performed in the setting of normal renal function to determine portal vein patency and provide clues to the chronicity of thrombus, if present. CTA can also identify other pathologic features of liver disease such as nodularity of liver parenchyma and the presence of malignancy.[27]

Percutaneous Angiography

Transhepatic percutaneous portal venography is necessary for evaluation of anatomy of the portal vein prior to surgical shunting procedures. It can be achieved by evaluating the venous phase following selective catheterization of the celiac and superior mesenteric arteries. The procedure is used to define the portal tributaries as well the portal hepatic wedge pressure, which quantifies the presence and severity of PHT. It can also be useful in determining the extent of cirrhosis. In advanced cirrhosis, the network of dense collaterals and dilation of the hepatic artery will become apparent on angiogram, as will reversal of flow in the portal vein.[28-30]

NONSURGICAL TREATMENT OF PORTAL HYPERTENSION AND ITS COMPLICATIONS

The goal of treatment of PHT is to prevent and/or control complications, in particular variceal bleeding, ascites, and encephalopathy.

Prevention and Treatment of Variceal Bleeding

Prevention and treatment of variceal bleeding is divided into primary prophylaxis (treatment to prevent bleeding before it occurs), treatment of acute variceal hemorrhage, and secondary prophylaxis (treatment after a bleeding episode to prevent a second one).

Primary Prophylaxis

Preferred options for primary prophylaxis include nonselective beta blockade, endoscopic variceal band ligation (EBVL), and endoscopic sclerotherapy.

Nonselective Beta Blockade

Propranolol has been used in the prevention of both primary and recurrent variceal bleeding. It is a nonselective beta-blocker; it is thought that by reducing cardiac output and thereby systemic pressure, it reduces portal venous pressure. Nonselective beta blockers are recommended in patients with small varices and high risk of bleeding and in all patients with large varices. The decision as to which nonselective beta-blocker is better is unclear, but there is some evidence that carvedilol may offer added benefits over propranolol. Beta blockade in the treatment of acute bleeding episodes has not been studied.[11,31]

Endoscopic Variceal Band Ligation

EBVL is indicated as primary prophylaxis in patients with medium and large esophageal varices and a high risk of bleeding. In those without high bleeding risk, the efficacy is similar to that of prophylaxis with nonselective beta blockade alone. EBVL has risks of esophageal perforation, pain, and bleeding; therefore, most physicians recommend beta blockade in patients at low risk for bleeding unless contraindicated.[11] Repeat endoscopy is recommended every 3 to 6 months.[32]

Endoscopic Sclerotherapy

Endoscopic sclerotherapy is recommended in patients with gastric varices as primary prophylaxis. In these patients, the efficacy is greater than prophylaxis with beta blockers. Adverse events are rare but include pulmonary and cerebral embolization.[11]

Cyanoacrylate sclerotherapy has been used for treatment of bleeding gastric ulcers in patients with decompensated cirrhosis who are not candidates for transjugular intrahepatic portosystemic shunt (TIPS) procedures. Cyanoacrylate causes polymerization and hardening upon contact with blood. In published studies, it has been shown to stop bleeding in 93% of these patients; early re-bleeding occurred in only 7%. No postprocedural complications were seen.[33]

Endoscopic sclerotherapy is as effective as endoscopic variceal ligation in the treatment of high risk patients with esophageal varices as prophylaxis and in the acute setting of variceal hemorrhage.[32,34] In one study, both techniques were effective as prophylaxis in 80% of high risk patients.[34] Another studied demonstrated that the use of either technique achieved complete control of active bleeding in 100%.[32]

Acute Variceal Hemorrhage

Acute variceal hemorrhage will stop spontaneously in 40% to 50% of patients. This is thought to be secondary to hypovolemia and subsequent splanchnic vasoconstriction.[35] Because of this, transfusions should be given sparingly to avoid rebleeding.

Treatments used to control active hemorrhage include vasoactive agents such as vasopressin, somatostatin, and octreotide, balloon tamponade, EVBL, and/or endoscopic sclerotherapy (described previously), balloon-occluded retrograde transvenous obliteration (BRTO), and TIPS.

Vasopressin

Vasopressin was formerly considered first line therapy for active bleeding from varices, and has been shown to control bleeding in 60% to 80% of cases. Moreover, it is the only medication shown to decrease mortality.[35] Its use leads to decreased portal flow and, in turn, decreased hepatic flow. However, its vasoconstrictive effects can lower cardiac output; it is therefore used in conjunction with other pharmacologic agents that increase cardiac output without reducing the positive effects of decreased portal flow.[36]

Somatostatin/Octreotide

Somatostatin and octreotide have the same effects as vasopressin in lowering splanchnic blood flow, but have fewer side effects. Somatostatin is a tetradecapeptide derived from the hypothalamus, and octreotide is a synthetic analog of somatostatin. Octreotide has a longer half-life than somatostatin (100 vs. 2 minutes). Both have been shown to control bleeding and decrease portal venous pressure. Somatostatin appears to produce less cardiac compromise when compared to vasopressin.[5]

Balloon Tamponade

Balloon tamponade is effective in controlling acute variceal hemorrhage. A tube with one or two inflatable balloons is inserted into the stomach; the balloon or balloons are then inflated to compress gastric and esophageal varices. The technique originated in the 1950s, and the balloons are named after their developers, Linton-Nachlas and Sengstaken-Blakemore. The Sengstaken-Blakemore tube is composed of two balloons, one to control esophageal varices and the second to control gastric varices, as well as a port to suction gastric contents. It has been shown to control initial hemorrhage in up to 95% of patients and results in permanent cessation of bleeding in 40% to 50%.[37,38] The Minnesota tube is a variation of the Sengstaken-Blakemore tube that includes an additional lumen to suction esophageal secretions.

The use of balloon tamponade is generally reserved for patients unresponsive to medical therapy and is thought to be a bridge to more permanent control such as endoscopic banding, sclerotherapy, or surgery.[38] Complications associated with its use include aspiration pneumonia, airway obstruction, tube migration, and esophageal ulceration and rupture.[39] To some extent these can be avoided by using indirect laryngoscopy with a glidescope to position the tube properly.[40]

Balloon-Occluded Antegrade and Retrograde Transvenous Obliteration

Endoscopic treatments can be used in conjunction with BRTO in the management of large, high flow gastric varices when bleeding cannot be controlled by these treatments alone or by TIPS. The goal of the therapy is to occlude portosystemic collaterals that exist between the stomach and the renal vein ("gastro-renal shunts") using a systemic transvenous access such as the common femoral vein. Esophageal varices should be treated prior to utilizing BRTO. Portal vein patency should be evaluated prior to BRTO, as the presence of an occluded portal vein may mean that the gastrorenal shunts constitute the primary outflow for mesenteric and splenic veins. In this situation, occlusion of the shunts may cause mesenteric venous hypertension.

The procedure is performed using an occlusion balloon inserted percutaneously from the common femoral vein into the outflow of the gastrorenal shunt, resulting in occlusion of the tract (Fig. 164.1). Venography can be performed to define the extent of the outflow tract and varices. A sclerosing agent such as sodium tetradecyl sulfate or polidocanol is then injected into the varices and outflow track via a microcatheter advanced next to the occlusion balloon. The presence of the balloon allows the sclerosant to dwell longer and prevents reflux into the systemic or portal system. Balloon occlusion is maintained 4 to 24 hours, and re-imaging is then performed prior to balloon deflation to confirm obliteration. The efficacy is 91% to 100% in patients with gastrorenal shunts. However, it can result in increased PHT and esophageal varices if they are not treated first.[11,41]

Balloon-occluded antegrade transvenous obliteration (BATO) can also be used alone to treat bleeding gastric varices or with BRTO if it fails. The goal of BATO is to occlude portosystemic

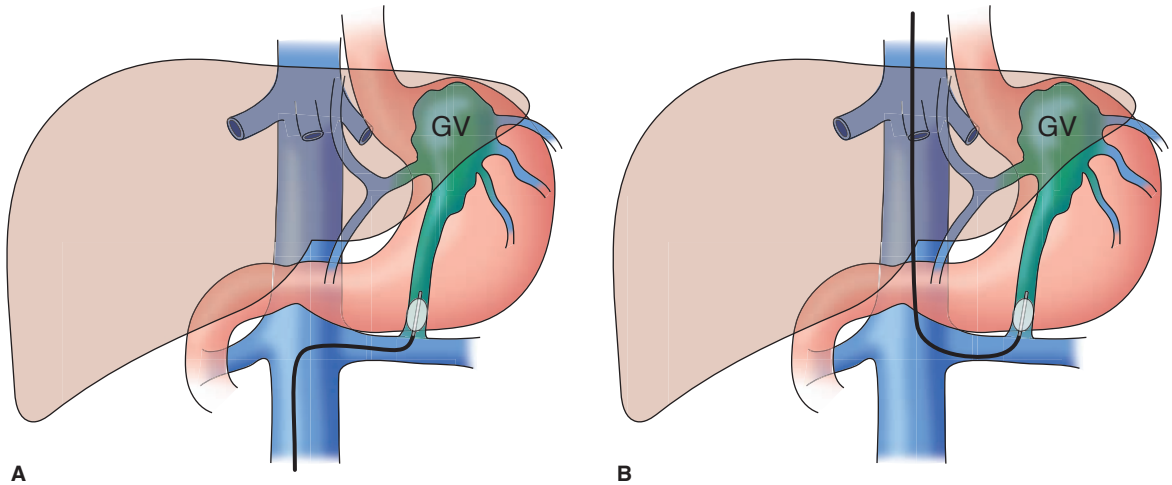

Figure 164.1 Balloon-occluded retrograde transvenous obliteration (BRTO): Illustration demonstrating the basic transfemoral (A) and transjugular (B) approaches for conventional BRTO of gastric varices *(GV)*. BRTO is approaching the GV from the systemic venous side. Balloon-occluded antegrade transvenous obliteration is approaching the gastric varices from the portal venous side. (From Saad WE, Kitanosono T, Koizumi J. Balloon-occluded antegrade transvenous obliteration with or without balloon-occluded retrograde transvenous obliteration for the management of gastric varices: concept and technical applications. *Tech Vasc Interv Radiol.* 2012;15[3]:203-225.)

collaterals from the portal system via the gastric veins or to occlude them in an antegrade fashion. BATO utilizes a portal venous approach in one of three ways, percutaneous transhepatic obliteration, an existing TIPS, or trans-ileocolic vein obliteration. The percutaneous transhepatic obliteration approach is technically similar to that of performing a percutaneous transhepatic cholangiogram, except that the target is the portal vein rather than the bile ducts. TIPS is only utilized if already present, or if the planned treatment for the patient includes TIPS. Trans-ileocolic vein obliteration is used mainly to treat mesenteric varices and is rarely done.

The technique for BATO (Fig. 164.2) is similar to BRTO. When a TIPS is present, BATO can be used routinely with BRTO as the portal vein access is already established.[42] BATO has been shown to increase the technical success of BRTO alone from 84% to 98% to 98% to 100%.[43]

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunts, commonly referred to as TIPS, are performed for refractory variceal bleeding and refractory ascites.[44,45] The TIPS procedure (Figs. 164.3 and 164.4) has been well described, and in high volume institutions, the technical success reaches 97%. The rate of major complications is low (<3%). The procedure is initiated via either internal jugular vein using ultrasound guidance. The right hepatic vein is then selected with a 5 French curved catheter,

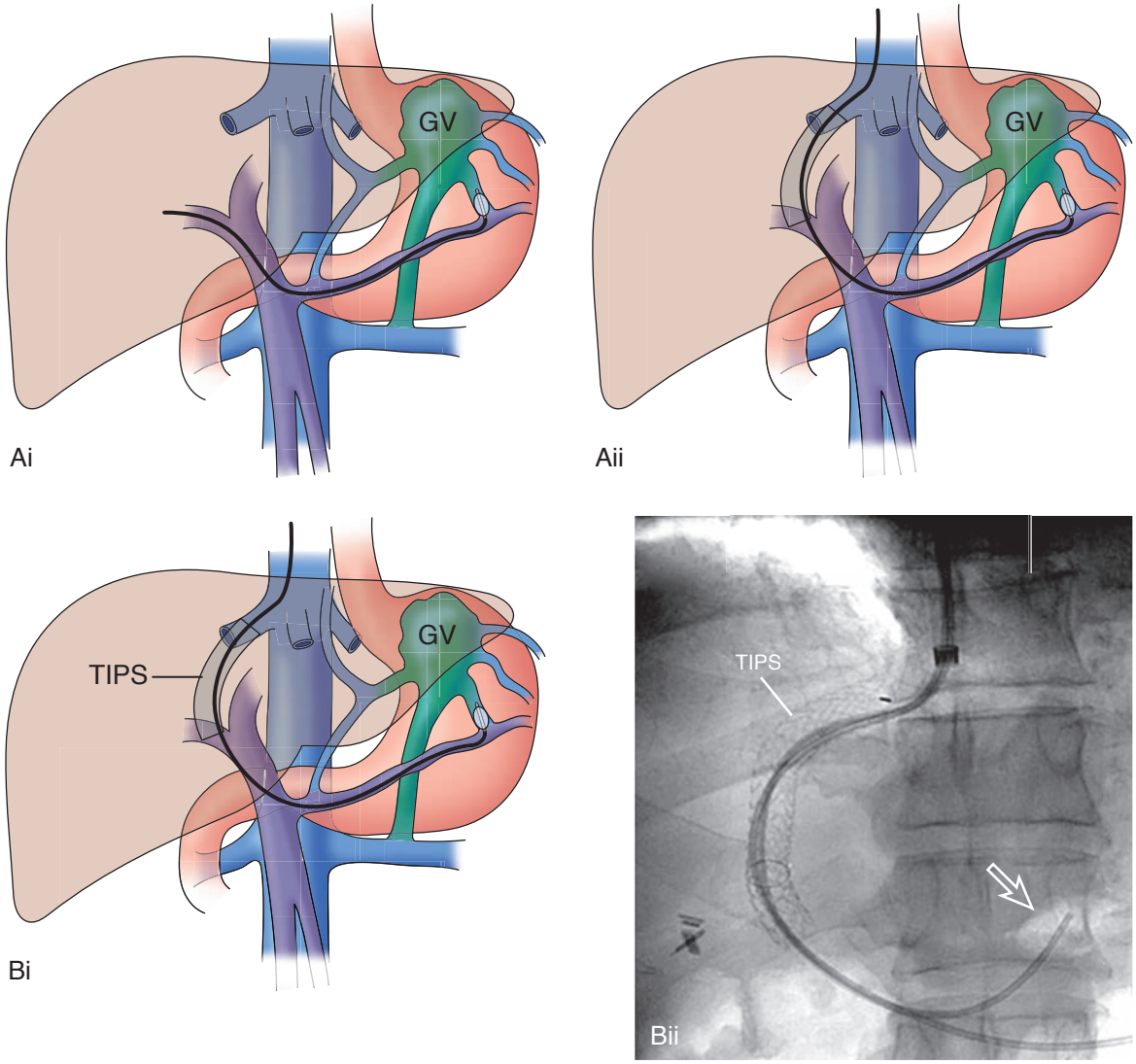

Figure 164.2 (A) Balloon-occluded antegrade transvenous obliteration (BATO): Illustration demonstrating BATO and its subclassification into percutaneous transhepatic obliteration (PTO, panel Ai) and trans-TIPS (transjugular intrahepatic portosystemic shunt, panel Aii) obliteration. (B) Illustration demonstrating trans-TIPS BATO (panel Bi) and a fluoroscopic image of a trans-TIPS BATO (panel Bii). The illustration depicts the BATO balloon in the posterior gastric vein and the fluoroscopic image demonstrates an air-filled BATO balloon *(hollow arrow)* occluding the left gastric vein (coronary vein). *GV*, Gastric varices. (From Saad WE, Kitanosono T, Koizumi J. Balloon-occluded antegrade transvenous obliteration with or without balloon-occluded retrograde transvenous obliteration for the management of gastric varices: concept and technical applications. *Tech Vasc Interv Radiol*. 2012;15[3]:203-225.)

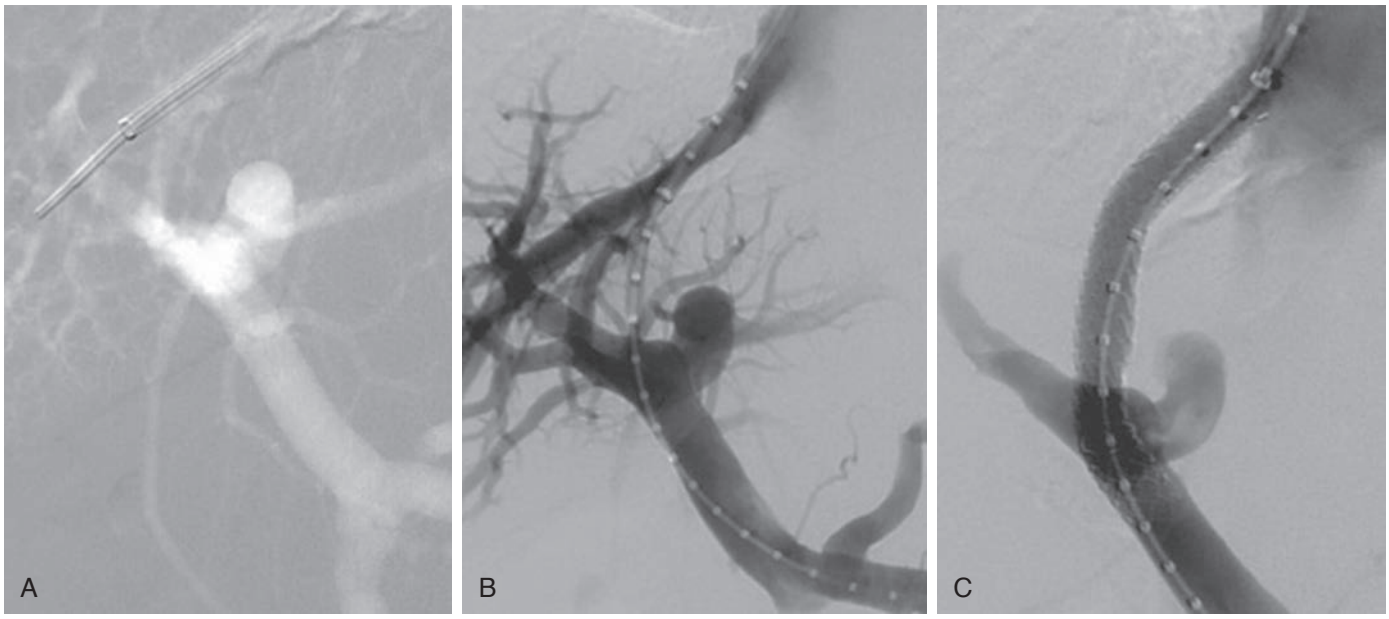

Figure 164.3 Determining the Shunt Length. (A) Wedged CO_2 contrast portogram. (B) Portography with additional contrast injection through 10 Fr sheath located at the right hepatic vein inferior vena cava junction to measure required length of endograft. (C) Portography after 7 cm covered length Viatorr endograft deployed. (Schematic of transjugular intrahepatic portosystemic shunt [TIPS.jpg]—figure 2 from Keller FS, Farsad K, Rosch J. The transjugular intrahepatic portosystemic shunt: technique and instruments. *Tech Vasc Interv Radiol.* 2016;19:2-9.)

as it has the best trajectory for portal vein access. The left or middle hepatic veins can also be used, but are technically more difficult. A balloon catheter is used to perform a wedged hepatic venogram to opacify the portal vein target. The catheter is then aimed toward the portal vein. A 10 French guide catheter is directed against the hepatic vein wall, and a locked trocar stylet and 5 French catheter are passed through the liver parenchyma and into the portal vein target. The stylet is removed, and the 5 French catheter is aspirated to confirm placement into the portal vein with adjustment as necessary. Once there is blood return, contrast is used to confirm placement. A guidewire is then advanced into the portal vein, and the access set and 10 French guide catheter are advanced into the portal system. Once in place, the inner components of the set are removed and a marker catheter is used to define the anatomy of the splenic and mesenteric vessels. The larger sheath is then also withdrawn leaving the marker catheter for pressure measurements. The large sheath is passed over a wire into the portal vein once again and is used to aid in deployment of a covered stent graft across the newly created channel. After deployment, the stent is angioplastied. Repeat pressure measurements are taken to confirm a decrease in the portosystemic gradient to less than 12 mm Hg.[46]

The hepatic venous pressure gradient can be used as a predictor of rebleeding after an episode of acute bleeding. A hepatic venous pressure gradient ≥20 mm Hg is associated with failure of treatment, greater transfusion requirements, more admissions to the intensive care unit (ICU), and decreased survival. Early TIPS placement in high risk patients reduces treatment failure, in hospital mortality, and 1 year mortality.[47] These patients have better outcomes with prophylactic TIPS performed after an initial acute variceal bleed to prevent further complications from rebleeding.[44]

In the event of gastric and ectopic variceal bleeding, TIPS has been shown to stabilize and prevent rebleeding after acute gastric bleeding and has a lower recurrence rate than BRTO. However, in cases of refractory gastric bleeding, BRTO can be used subsequently to embolize larger gastric veins, which facilitates flow toward the TIPS. BRTO can be used primarily in the treatment of gastric varices if patients are not candidates for TIPS due to hepatic encephalopathy or marginal liver function. In general, the literature lacks direct comparisons of TIPS to BRTO in the treatment of gastric varices. Severity of PHT, hepatic reserve, and complications of liver cirrhosis should be considered when deciding which procedure to proceed with in the management of gastric varices.[48]

Recently, there has been a report of using Paclitaxel-coated balloons to treat in-stent stenosis after TIPS. This technology is promising in terms of improving secondary patency.[49]

Secondary Prophylaxis

Mortality associated with rebleeding of varices approaches 40%, and most commonly occurs within the first 5 days after the initial episode. Without adequate prophylaxis, the risk of rebleeding approaches 80% at 1 year.[50]

The mainstays of therapy for secondary prophylaxis to prevent rebleeding are nonspecific beta blockade and EBVL. The combination of both treatments is more efficacious than either treatment alone, resulting in a rebleeding rate of less than 50%.[9] TIPS has been shown to reduce rebleeding by approximately

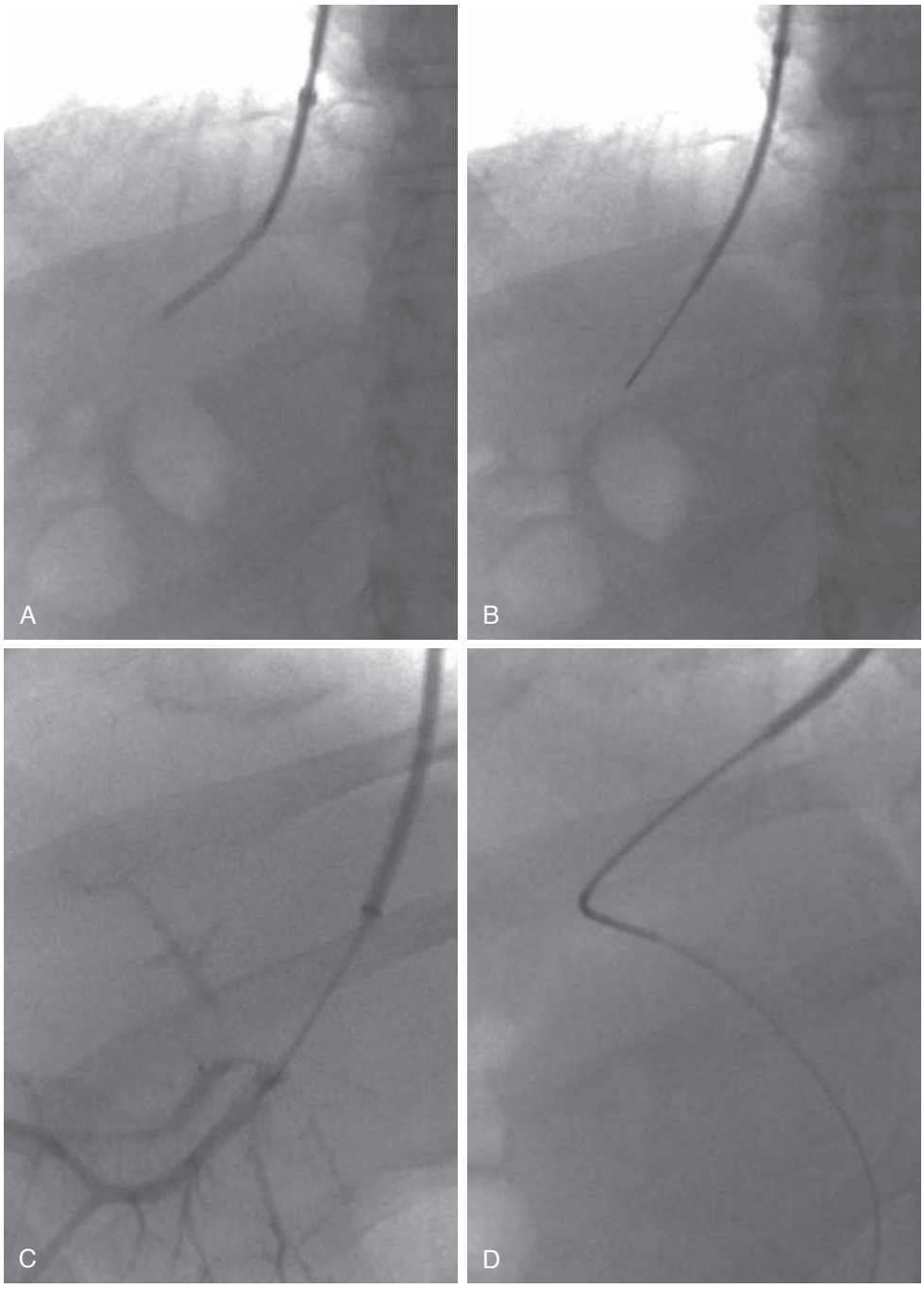

Figure 164.4 Portal Vein Access Under Fluoroscopy. (A) Transjugular intrahepatic portosystemic shunt (TIPS) set in resting position in right hepatic vein. (B) TIPS set rotated anteriorly with stylet and 5 Fr catheter extended. (C) Test injection of contrast material to confirm position of 5 Fr catheter in portal circulation. (D) Guidewire in superior mesenteric vein with tip of 5 Fr catheter in main portal vein. ([C] Adapted from Saad, ed. "*The TIPS Procedure: Technique" in Portal Hypertension*, 3rd ed., 2016, with permission from Thieme. [D] Figure 5 from Keller FS, Farsad K, Rosch J. The transjugular intrahepatic portosystemic shunt: technique and instruments. *Tech Vasc Interv Radiol*. 2016;19:2-9.)

30% compared with endoscopic treatment alone, but is associated with increased encephalopathy.[51]

Treatment of Ascites

Spironolactone and furosemide remain the most commonly used treatments for ascites, given their efficacy and lack of adverse consequences. Initial doses are 100 mg of spironolactone and 40 mg of furosemide daily; these can be increased to a maximum of 400 mg and 160 mg, respectively. Spironolactone alone is effective in promoting weight loss, but the addition of furosemide is protective against hyperkalemia. Patients in whom these medications are ineffective or not tolerated are candidates for paracentesis or TIPS.[9]

Treatment of Encephalopathy

Encephalopathy is treated by correcting inciting conditions, including variceal bleeding, infection, and electrolyte imbalances, and by restricting the production and absorption of ammonia. Lactulose is effective in preventing ammonia absorption and increasing fecal nitrogen excretion.[52]

Neomycin is also effective in the treatment of encephalopathy, but side effects (nephrotoxicity and ototoxicity) limit its use.[53]

Hepatic and Portal Vein Recanalization

In patients with PHT complicated by portal or hepatic vein thrombosis, recanalization of these veins has the potential to reduce symptoms and complications. A recent retrospective study performed in the United Kingdom reported the results of endovascular recanalization of the hepatic vein in patients with Budd Chiari syndrome.[54] The study evaluated outcomes in 63 patients treated with venoplasty of the hepatic vein ± stent placement over a 27-year period. The efficacy of the treatment was compared with a previous report using TIPS published by the same investigators.[55] Access was established via the femoral or internal jugular vein. In the event the hepatic vein could not be accessed via the inferior vena cava, a percutaneous transhepatic approach was used. Once the wire was in place, it was snared using the jugular approach, and the rest of the procedure performed from the jugular route. A large balloon catheter was used to dilate the obstructed hepatic vein. If balloon dilation was ineffective, a bare metal stent was deployed. Technical success was reported as 100%, with symptom resolution in 73%. Patency rates were similar between the patients undergoing recanalization and the historical TIPS group, ranging from 70% to 90% at 1 year and 60% to 80% at 10 years. Survival rates were also similar, but procedural complications (9.5% vs. 27.1%) and hepatic encephalopathy (0% vs. 18%) were significantly lower in patients treated with vein recanalization. The authors concluded that TIPS should be reserved for failure of recanalization.[54]

Portal vein recanalization has also been used in conjunction with TIPS to improve candidacy for liver transplant in patients with portal vein thrombosis. The procedure is performed via access from the internal jugular and splenic veins. After the TIPS stent is deployed, the confluence of the stent and the portal vein is venoplastied. This technique generally opens the portal vein without further intervention. Embolization of existing varices and/or splenorenal shunts is sometimes performed to improve patency of the portal vein.

In one study, the initial success rate approached 100%, and the patency rate was 92% at 17 months. Twenty-three of 61 patients enrolled in the study underwent successful liver transplantation.[56]

SURGICAL TREATMENT OF PORTAL HYPERTENSION

Portosystemic bypasses were first used to treat variceal bleeding with promising results; the recurrence rate was less than 3%.[57] These bypasses were then studied as prophylaxis to prevent variceal bleeding. However, prophylactic shunting did not demonstrate a benefit over medical therapy in survival rates, and demonstrated an increase in the incidence of severe hepatic encephalopathy when compared with medical therapy alone. Because of this, surgical shunting is not recommended as prophylaxis.

Portosystemic shunting has also been studied with respect to quality of life and survival. Studies demonstrated that while the rebleeding rate was greatly reduced, there was no long-term survival benefit.[58] In emergency situations with acutely bleeding varices, portosystemic shunting has been shown to stop bleeding and prevent rebleeding. However, mortality is high, and it is generally not recommended given the efficacy of nonsurgical options.[59,60]

There are two types of shunts: selective and nonselective shunts. A selective shunt preserves blood flow to the portal vein while decompressing esophageal varices. Nonselective shunts drain all portal blood flow to the caval system. The most commonly performed selective shunt is a distal spleno-renal shunt. Nonselective shunts include the portocaval shunt and mesocaval shunt. Selective shunting procedures were initially proposed in an attempt to lower the incidence of hepatic encephalopathy and liver failure associated with nonselective shunts, and early results demonstrated promise.[61]

Portocaval shunts can be performed in end-to-side and side-to-side fashion. The benefit of one technique over the other has not been demonstrated.[62] Anatomic limitations include the diameter of the portal vein as well as a history of portal vein thrombosis and recanalization. The portal vein should be at least 1.0 cm in diameter, and previous thrombosis/recanalization is a relative contraindication, as rethrombosis rates are high in these patients. The approach can be via a midline incision or a right upper quadrant subcostal incision. The duodenum is mobilized, and the IVC is exposed to the level of the hepatic veins. The portal vein is mobilized from the surrounding bile duct and hepatic artery and controlled. If performing an end-to-side anastomosis, the portal vein is divided, and the hepatic end ligated. The IVC is then clamped with a side biting clamp, and the portal vein is anastomosed to the IVC. Portal pressures should be measured and decrease by at least 50%. In the

side-to-side anastomosis, a greater length of both the IVC and portal vein is exposed to bring the two vessels in proximity for the anastomosis. Portal pressures should decrease by 50% after it is completed. An effective side-to-side portocaval shunt can also be created with a large diameter expanded polytetrafluoroethylene (ePTFE) graft.[63]

Mesocaval shunts have been used in cases of refractory variceal bleeding to control hemorrhage, as well as in patients with massive ascites, an obliterated portal vein, extreme obesity, and Budd-Chiari syndrome.[64-66] Mesocaval shunts are technically easier to perform than portocaval shunts. The procedure is performed via a midline laparotomy. The transverse colon is elevated and retracted superiorly, and the small bowel is retracted inferiorly to expose the root of the small bowel mesentery. The root of the transverse mesocolon is opened to expose the superior mesenteric vessels. The superior mesenteric vein (SMV) lies anterior to the artery. The surface of the IVC is then found in the retroperitoneum after mobilizing the duodenum. The IVC is isolated to allow for placement of a side-biting clamp. A bypass is then created between the SMV and the IVC using a large-caliber (18 to 20 mm) prosthetic graft. The IVC anastomosis is created first. When the shunt is opened, portal pressure should decrease by 50%, and there should be a palpable thrill within the graft.[65]

Selective shunting refers to creation of the distal splenorenal shunt. The goal of this shunt is to decompress esophageal varices without diverting portal-splanchnic flow. The procedure is performed via a bilateral subcostal incision. The splenic vein is identified by opening the lesser sac. The right gastroepiploic vein is divided, and the short gastric veins are preserved. The pancreas is rotated anteriorly to expose the splenic vein in its entirety; connections to the pancreas are ligated. The renal vein is isolated by dividing the ligament of Treitz and rotating the fourth portion of the duodenum inferiorly. The splenic vein is then divided, and the portion attached to the SMV ligated. A side-biting clamp is placed on the renal vein, and an end-to-side anastomosis is created between the splenic vein and the renal vein. Pressure measurements are then taken from the SMV, renal and splenic veins. The splenic vein pressure should decrease by 60% to 70%, allowing for preferential drainage of the esophageal varices. All collaterals between the portal-azygous and portal-mesenteric system must be also be divided, and care must be taken to divide the left gastric vein, umbilical vein and falciform ligament as well.[59]

Several randomized controlled studies evaluated the efficacy of the selective distal splenorenal shunt compared with the nonselective portocaval shunt for the management of patients with PHT and bleeding from esophageal varices. In one study, 88% of patients maintained portal hepatic flow in the selective shunt group compared with 5% in the nonselective group. Hepatic function was preserved and encephalopathy improved in the selective shunt group. There was no difference in rebleeding or survival between the two groups.[67] The findings of a second study showed that patients undergoing distal splenorenal shunts had a statistically significant lower incidence of hepatic encephalopathy and liver failure when compared with the nonselective group (18.7% and 62.5%, respectively). Both perioperative and late mortality were reduced in the selective shunt group.[61] In a third study, encephalopathy was decreased in the selective shunt group, but there was no difference in late mortality between the selectively shunted and nonselectively shunted groups.[68] Findings of other studies have mostly confirmed a lower rate of encephalopathy in selectively shunted patients, but whether a significant difference in mortality exists between the two groups remains unclear.[69-71]

There have been many studies comparing portosystemic shunting to endoscopic therapy for treatment of variceal bleeding in patients with cirrhosis and PTH. Twenty-two trials were included in a review from the Cochrane database. Shunt procedures significantly reduced the risk of rebleeding when compared with endoscopic therapy, but significantly increased acute hepatic encephalopathy and chronic encephalopathy. There were no differences in mortality and duration of hospital stay.[72]

TIPS was compared with selective distal splenorenal shunting in a randomized trial for control of variceal bleeding. There were no significant differences in rebleeding, first encephalopathic event, or survival at 2 and 5 years between the groups, but thrombosis, stenosis, and reintervention rates were significantly higher in the TIPS group (82% vs. 11%). The authors concluded that treatment choice should depend on available resources and expertise.[73]

Endoscopic sclerotherapy was compared with portacaval shunting in a randomized trial in cirrhotic patients presenting with acutely bleeding esophageal varices. Both techniques controlled active bleeding in most patients, but surgery was significantly more effective in terms of permanent control of bleeding (100% vs. 20% respectively), episodes of encephalopathy, and overall survival.[74]

A recent retrospective study compared outcomes of surgical shunts versus TIPS for the treatment of complicated PTH over a 20-year period. Shunt failure occurred more frequently after TIPS (16 of 31 vs. 6 of 31), and "shunt failure free" and overall survival rates were higher in the surgically treated patients.[75]

Taken together, the results of these studies suggest the continued benefit and role of operative shunting in the acute and long-term management of bleeding varices and PHT.

Liver Transplantation

Liver transplantation is indicated for end-stage liver disease and not necessarily for management of PTH or variceal bleeding. However, transplantation may be the endpoint of treatment for these patients. In general, the available data suggest that patients who undergo surgical shunt for variceal bleeding have higher survival rates after transplantation than patients treated with endoscopic procedures. In some patients, surgical shunting appeared to eliminate the need for transplantation.[76-78]

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CHAPTER 165

Nutcracker Syndrome

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INTRODUCTION

The left renal vein as it lies between the aorta and the superior mesenteric artery resembles a nut between the jaws of a nutcracker.

—JCB Grant, 1937

The anatomic configuration resulting in outflow obstruction and subsequent dilation of the left renal vein (LRV) has more colloquially been referred to as the "nutcracker syndrome" (NCS) if presenting with a constellation of symptoms, or "nutcracker phenomenon" (NCP) if LRV compression is found incidentally in otherwise asymptomatic patients.[1,2] A host of other names have been applied to this anatomic scenario, including "LRV entrapment syndrome," or "mesoaortic compression" of the LRV. However, the unique phrasing of this anatomic phenomenon was originally coined after the anatomist Grant likened compression of the LRV between the aorta and superior mesenteric artery (SMA) to that of a nut in a nutcracker in pathologic specimens from the 1930s.[3] Clinical reports of the syndrome were initially reported by the Egyptian urologists Mina and El-Sadr in 1950[4] and followed by venographic characterization by Chait et al. in the early 1970s.[5] It was eventually de Schepper's association of LRV compression, pelvic/perirenal varicosities, and hematuria in the early 1970s that completed the characterization of the syndrome and yielded further interest in the disease process.[6] Initial reports proposing surgical repair through transposition of the LRV were described shortly thereafter by Pastershank in 1974.[7] These initial accounts have given rise to numerous small case series and intermittent case reports in the timeframe since.[8-38]

Unfortunately, there remains a paucity of larger studies and thus no consensus over the optimal management of NCS, including patient selection and procedure of choice. As a result, there remains much controversy regarding the optimal diagnostic and therapeutic approach to NCS. Largely, this can be attributed to several factors, including the rarity of NCS, the nonuniformity in patient symptomatology with diagnostic uncertainty and concomitant delays in diagnosis, varying opinions of the optimal surgical approach and lack of consensus data on the durability and longevity of these different approaches, and the involvement of a host of specialists and subspecialists in the care of these patients. This chapter will focus on the anatomic, diagnostic, and therapeutic strategies with which to approach this rare, albeit challenging, disease process.

BACKGROUND

Demographics and Risk Factors

The true prevalence of NCS is unknown, and, although not limited to a specific age range, it is thought to affect females and the young more frequently, with a secondary peak in the second or third decades of life and an additional peak in middle age.[8,39] However, one study demonstrated a 10.4% prevalence of NCP on evaluation of abdominal computed tomographic

Abstract

Nutcracker Syndrome (NCS) occurs when the left renal vein (LRV) undergoes external compression, most commonly from anterior compression by the superior mesenteric artery, and less commonly when a retroaortic LRV is compressed between the aorta and the spine (posterior compression). The most common presenting symptoms are hematuria and left flank pain. In advanced cases, pelvic compression develops with concomitant lower extremity, posterior thigh, and gluteal varicosities, varicocele in men (typically left sided), as well as vulvar/labial varices in females. The diagnosis is usually made from typical symptoms together with duplex ultrasound, computed tomography, or magnetic resonance imaging. In some cases, LRV compression is diagnosed incidentally when no symptoms are present; this is referred to as "nutcracker phenomenon." Treatment is recommended in symptomatic cases only, and has traditionally consisted of surgical procedures such as LRV transposition or vein bypass, with good outcomes. Endovascular treatment with LRV stenting has been used successfully more recently, although no long-term outcomes data are available.

Keywords

nutcracker syndrome
left renal vein compression
hematuria
vulvar varices
varicocele

(CT) scans detected for other purposes, with no difference in the prevalence of NCP by gender alone.[40] Owing to causes elaborated upon later, a lower BMI has been shown to have a correlation with NCS.[41] A large proportion of the nutcracker literature stems from Asia, although it should be noted that no true population-based studies have been performed to determine if there are any ethnic or racial risk factors for NCS. Finally, as reported in the literature, there does not appear to be a hereditary link in the inheritance of this phenomenon, although there is a single case report in which it was demonstrated in two young siblings.[42]

Anatomy

A host of anatomic configurations extrinsic to the anatomy and angulation of the SMA may result in symptomatic compression of the LRV, although whether they can be truly considered as causes of the nutcracker "syndrome" is up for debate. These include compression by pancreatic neoplasms, paraaortic lymphadenopathy, retroperitoneal tumors, an overarching testicular artery, fibrolymphatic tissue or "webs" between the SMA and aorta, as well as compression of larger veins by a gravid uterus.[17,27,43,44] However, in most scenarios, NCS is thought to stem primarily from one of two anatomic variants—anterior or posterior compression of the LRV—resulting in what has been classified as "anterior" or "posterior" NCS, respectively. The normal size of the area between the SMA and aorta has been noted to average 4 to 5 mm in distance at the level of the LRV. LRV diameters average approximately 1.2 ± 0.2 cm (1.1 cm proximal segment; 1.2 cm distal segment) in cadaveric studies, with ultrasound studies showing slightly smaller diameters of LRV size in normal patients (4-5 mm).[45-47]

Anterior NCS results from compression of the LRV between the aorta and SMA (Fig. 165.1A) and can result in dilation and engorgement of the gonadal vein, as well as a preponderance of pelvic collaterals easily visualized with cross-sectional or angiographic imaging. Anatomically, there are a variety of explanations as to the mechanism of anterior compression of the LRV, including a more acute angle between the aorta and SMA (<16 degrees; normal range: 35-40 degrees), which is often attributed to a paucity of retroperitoneal or mesenteric fat, wasting of the paraspinal muscles, as well as profound weight loss.[44,48] The paucity of retroperitoneal fat correlates well with the observation that NCS is oftentimes seen in those with a particularly thin body habitus.[44] Posterior ptosis of the left kidney resulting in abnormal angulation and subsequent stretching and compression of the LRV has also been implicated as a possible cause of extrinsic LRV compression. Additional anatomic variants resulting in anterior NCS include aberrant branching of the SMA and an abnormal, particularly cephalad course of the LRV.[45,49,50]

Posterior NCS occurs most commonly in the setting of a retroaortic LRV, with resultant compression of the LRV between the aorta and vertebral column (see Fig. 165.1B). Although prior studies have demonstrated that posterior NCP may be similar in prevalence to anterior NCP,[40] there are far fewer reports in the literature of the management of posterior NCS patients, although their symptomatology is noted to be no different from that of their anterior NCS counterparts.[20] In truth, a retroaortic LRV remains an uncommonly observed anatomic phenomenon, with a recent study showing a prevalence of 0.77% to 3.18%, with only a minority of those symptomatic (6.5%).[51,52]

Although quite rare in the literature, it should be noted that there exists what could be considered a third anatomic category for NCS, that of "atypical" variants. This atypical anatomic variant class includes the scenario of the circumaortic renal vein and truncular vascular malformations—that is, the left-sided inferior vena cava (IVC).[40,53] In addition, right-sided NCS, although possible, is even more infrequently reported in the

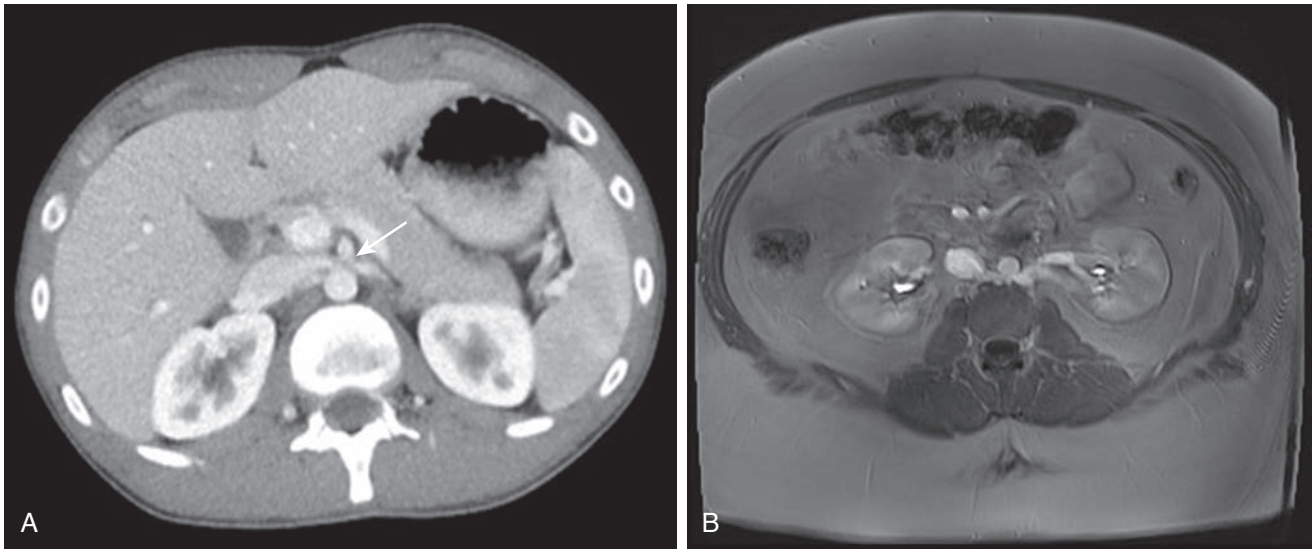

Figure 165.1 Cross-sectional imaging demonstrating (A) anterior nutcracker syndrome with compression of the left renal vein *(arrow)* between the aorta and superior mesenteric artery as observed by computed tomography, and (B) posterior nutcracker syndrome with a retroaortic renal vein as observed by magnetic resonance imaging.

literature and oftentimes results from the condition of left-sided IVC and the unique combination of left-sided IVC, hemiazygos continuation, and persistent left SVC.[54]

DIAGNOSIS

The question of why NCS exists has been posited by many, stemming from the fact that NCP exists, by definition, without symptomatology. Further skepticism around the syndrome and pathophysiology is generated by the fact that the LRV is stretched in instances of a "prominent aorta" and in abdominal aortic aneurysms (AAAs), as well as the fact that the LRV is often ligated without apparent detrimental effect during AAA repair. Although uncertain, hypotheses as to why NCS does not occur in these scenarios include a genetic propensity to the development of venous wall weakness, along with the timeframe with which collaterals are allowed to develop in NCS versus acutely as in AAA.[9] In addition, other similar venous compression syndromes, most notably May-Thurner syndrome, may be found incidentally without clinical sequelae.

Clinical Presentation

The constellation of signs and symptoms that has traditionally defined NCS (Box 165.1) is quite variable, and it is this variety along with ambiguity of symptomatology that has led to diagnostic uncertainty and delays in diagnosis. The most commonly reported symptoms have traditionally been left flank pain coupled with either gross or microscopic hematuria.[55] As compression of the LRV progresses over time and pelvic collaterals form, a host of symptoms related to pelvic congestion syndrome (PCS) may develop, such as dyspareunia, dysuria, and/or dysmenorrhea. Physical exam findings may include lower extremity, posterior thigh, and gluteal varicosities, varicocele in men (typically left sided), as well as vulvar/labial varices in females. It should be noted that there are no true physical exam findings that are pathognomonic for NCS.[56] However, a constellation of any of the previous findings in concert with hematuria and flank pain are strongly suggestive for the diagnosis of NCS.

BOX 165.1 Clinical Features of Nutcracker Syndrome

Highly Suspicious

Hematuria
Gross
Microscopic
Left flank pain

Possibly Related

Dyspareunia
Dysmenorrhea
Dysuria
Varices
- Vulvar
- Scrotal (Varicocele)
- Lower extremity
- Gluteal

Proteinuria
Abdominal pain

Hematuria is the most commonly described clinical feature of NCS[56] and can be either gross or microscopic in presentation, oftentimes resulting in further workup for urologic causes of bleeding. Microscopic hematuria is several times more common in presentation than gross hematuria.[19] Authors have described hematuria that may be isolated to the left ureteral orifice on cystoscopy, although hematuria in concert with flank pain can be due to a variety of causes that must be excluded prior to the diagnosis of NCS. The pathophysiology resulting in hematuria is not completely understood but thought to revolve around the obstruction of LRV outflow, with subsequent left renal venous hypertension leading to the diffusion of red blood cells and proteins into the glomerular filtrate.[57,58] In addition, LRV hypertension has been postulated to result in the development of thin-walled varices and valveless collaterals which are prone to rupture into the neighboring collecting system itself, resulting in microhematuria or in more severe cases macrohematuria, or in the communication of dilated venous sinuses with adjacent renal calices.[59,60] Orthostatic proteinuria has likewise been described as a common finding in patients with confirmed NCS, and NCS was once thought to result in chronic fatigue syndromes in children.[16]

Symptoms of pain are ascribed to the passage of blood or clots through the collecting system[43] and as such are typically isolated to the left flank given the propensity of NCS to affect the left side. However, more generalized abdominal pain has been demonstrated in NCS, and left flank pain has likewise been ascribed to the gonadal vein syndrome, in which abdominal or flank pain radiates to the posteromedial thigh and buttock.[30,43] In addition, although the two clinical entities are often confused, nutcracker anatomy (i.e., LRV compression) may be a cause of PCS, in which the accumulation of blood in the pelvis from reflux or obstruction of gonadal, gluteal, or periuterine veins results in a chronic pain syndrome associated with perineal or vulvar varices.[61] This pain is manifested as dyspareunia, dysmenorrhea, and/or dysuria, none of which are typical presentations of NCS. We should also note that symptoms such as scrotal/vulvar varices and pain are exacerbated with standing, physical activity, or orthostasis, because this position results in increased venous filling and distension of collateral drainage pathways.[9,30]

Imaging

If there is clinical suspicion of LRV compression and no prior imaging is available, further imaging should be performed to exclude nonvascular etiologies of LRV compression, as well as to further define the anatomy of the LRV compression. This is due to the fact that potentially treatable etiologies of LRV compression such as neoplasm require referral to a specialist other than a vascular surgeon. The utility of imaging adjuncts in the diagnosis is proven, although a dedicated clinical history is of utmost importance in workup of this syndrome and should be mandatory as the initial and primary diagnostic "test."

Historically, authors favored initial use of left renal venography with measurement of the gradient between the LRV and IVC, but this has been supplanted by noninvasive cross-sectional imaging modalities. Although there is some controversy in terms of which imaging modality is preferentially used in the initial diagnosis, both are needed as they provide different diagnostic information, as outlined later.[47]

Oftentimes, duplex ultrasonography (DUS) serves as the initial imaging modality if NCS is suspected, because it is noninvasive, lacks radiation exposure, and is readily available across most institutions. Ultrasound has the advantage of being able to delineate vascular anatomy and determine basic flow and velocity characteristics of the LRV. However, this modality is limited by patient anatomy and habitus, overlying bowel gas, and interoperator variability. In "good hands," DUS has demonstrated a sensitivity and specificity of 78% and 100%, respectively, in diagnostic accuracy for NCS and has been noted to be particularly useful when coupled with the observation of gonadal and retroperitoneal collateral veins, which demonstrate characteristic aberrant flow in a direction away from the LRV.[62] However, this observation is limited by the fact that the presence of collaterals occurs only after long-standing NCS and hence may not be detected early in the course of the syndrome. Absolute size criteria of the LRV as observed during DUS has been noted by several authors to be of particular diagnostic futility, because larger LRV diameters can be variants of normal and limited by the sonographer, patient positioning, and hydration status.[47,63,64] However, particular utility of DUS has been observed when the diagnostic criteria uses the ratios between anteroposterior diameters and flow velocities at the narrowed proximal and distended distal portions of the LRV, comparing the two to obtain a ratio (>5.0 diagnostic of NCS).[19,47,62] However, errors are rife in DUS due to upright versus supine positioning with subsequent changes in mesoaortic angles, variation of vessel diameter during systole and diastole, as well as intrinsic errors in measurement of velocities and flows.[65,66] Others have used the ratio of the anteroposterior diameter of the LRV between the most dilated and the most narrow portions as diagnostic criteria in adults (>3.7) and children (>4.3).[47,62,67] However, it should be noted that children may form a special class of NCS patients because they are in many cases observed effectively without intervention, owing to the eventual development of mesenteric and retroperitoneal fat. This allows for the widening of the mesoaortic angle and subsequent relief of LRV compression, resolution of hematuria, and improvement in LRV to velocity/flow ratios.[68] In addition, early DUS results were obtained in concert with venography to confirm diagnoses because there was uncertainty and lack of data behind the validity and applicability of DUS in diagnosis at the time of studies. Currently, DUS remains an adjunct for diagnosis in concert with other, cross-sectional imaging modalities, as described next.

In the current era, axial imaging with magnetic resonance imaging (MRI) or contrast CT has gained increasing importance in the initial imaging workup of NCS.[69] The utility of these tests is comparable and can demonstrate a characteristic "beak sign" (as defined by narrowing of the LRV in a triangular shape between the SMA and aorta), as well as the unique circumstance of the retroaortic/circumaortic LRV, retroperitoneal masses, pelvic or periaortic collaterals, and dilation of the gonadal vessels.[70] Critically important in axial imaging is the visualization of pelvic collaterals. If none are present, then the diagnosis of NCS is essentially eliminated as the cause of the patient's symptoms. According to one study, beak sign as delineated by CT imaging demonstrated the highest diagnostic accuracy as compared with LRV hilar/aortomesenteric diameter ratio and mesoaortic angle (<41 degrees), with a sensitivity of 91.7% and specificity of 88.9%.[71] Other diagnostic cutoff values have been established using CT with three-dimensional reconstruction, including an LRV hilar-aortomesenteric cutoff ratio of 4.9 and a <41 degree angle between the SMA and aorta as measured by imaging.[72] The diagnostic accuracy of MRI in relation to NCS has not been examined in the literature but, as others have noted, yields similar anatomic assessment as CT without the expense of contrast media or radiation exposure and can also give unique insight as to stagnation of flow in the LRV, which is seen with compression of the vessel observed in NCS.[73]

Axial imaging alone does not provide the necessary hemodynamic data for the diagnosis of NCS—namely, whether reflux into the gonadal and pelvic circulation is present and severe. Venography allows for the measurement of the renocaval pressure gradient (i.e., "pullback"), while also allowing for the visualization of mesoaortic-induced LRV narrowing, dilation of the LRV, reflux and opacification into the collateral pelvic network (including the gonadal, lumbar, adrenal, and other veins), and the sluggish passage of contrast through the LRV (Fig. 165.2).[70] Many of the criteria for venographic diagnosis/confirmation of NCS arise from an initial study performed by Zerhouni et al., which demonstrated a renocaval gradient of 0 to 3 mm Hg in a normal population.[74] This work was subsequently challenged by Beinart,[59] who demonstrated that 98% of normal subjects had a renocaval pressure gradient less than 1 mm Hg,[74] with later studies demonstrating a range of renocaval pressure gradients, yielding subsequent debate as to the utility of absolute cutoff values for pressure gradients versus symptomatology. A standard of sorts was established when Nishimura and colleagues demonstrated a cutoff value of ≥3 mm Hg as diagnostic of LRV hypertension, which was observed in concert with hematuria and opacification of collaterals in their cohort,[75] and subsequently propagated by Takebayashi et al.[62] In the study by Takebayashi, left renocaval pressure gradients were defined as: normal (<1 mm Hg), borderline hypertensive (1-3 mm Hg), and hypertensive (≥3 mm Hg). However, as noted in other studies, the renocaval gradient may range from 3 to 10 mm Hg in normal patients, and in those with NCS these values range from 2 to 14 mm Hg, representing an overlap and area of diagnostic uncertainty if one were to attempt to diagnose NCS by the renocaval pressure gradient alone.[45,72] It should also be noted that in those with long-standing NCS, the high renocaval gradient typically observed may not be present, due to compensation by collateral circulation and decompression of the proximal LRV obstruction, which can result in low gradient values. In addition, these values may be erroneous in the face of positioning and hydration status.[28,45]

Figure 165.2 Selective Left Renal Venography Demonstrating Characteristic Findings in Anterior Nutcracker Syndrome. Note the vast network of perirenal and pelvic collateral vessels, a dilated and incompetent gonadal vein *(long arrow)*, and stagnant flow in the left renal vein *(short arrow)*.

Historically, other imaging modalities have been reported, such as intravenous urography, retrograde pyelography, and IVC phlebography, although they are not of current diagnostic utility and hence will not be described here. Cystoscopy, which many patients receive as part of the diagnostic workup for hematuria of unknown cause, is efficacious in localizing hematuria to the left ureteral orifice and hence the left side. However, no features on cystoscopy are pathognomonic for NCS, and as such, this invasive technique remains only indirectly diagnostic.

MANAGEMENT

Although the prompt recognition of the symptomatology and the subsequent diagnosis of NCS are important, patient selection and the operative strategy used are both critical to patient outcomes. Unfortunately, there remains a marked lack of concordance regarding when/which patients should be treated and the optimal operative technique. The mere presence of radiographic compression (i.e., "bird beak") is not a sufficient indication to operate, with requirements including hematuria, the presence of collaterals, and pelvic and/or flank pain (Fig. 165.3). Ideally, interventions are directed toward reducing the hypertensive state of the LRV induced by its compression, but as authors have noted, many procedures are performed as a result of symptoms of unrelenting and disabling pain or gross hematuria resulting in anemia.[12] We have elected not to describe the "conservative" management of NCS because this treatment strategy is more suited to children presenting with hematuria and found to have NCS, as further development and weight gain can, as mentioned, result in widening of the acute aortomesenteric angle and hence relief of LRV compression.

Open Surgery for Anterior Nutcracker Syndrome

There have been a host of methods described to treat anterior NCS in an open fashion. These have included LRV transposition ± patch venoplasty, patch venoplasty alone, LRV transposition with a saphenous vein cuff, gonadal vein transposition, saphenous vein bypass, gonadocaval bypass, resection of fibrous tissue with placement of a "wedge" at the aortomesenteric angle, SMA transposition, left renal autotransplantation, nephrectomy, external stenting of the LRV, and nephropexy.[27,34,37,50,76] In this section, we will briefly describe some of the more commonly performed open surgical techniques.

The most commonly reported technique to surgically manage anterior NCS is LRV transposition (Fig. 165.4A). This technique is performed transabdominally via a midline mini-laparotomy, with cephalad and rightward retraction of the small bowel, entrance into the retroperitoneum, and subsequent mobilization of the LRV. This technique requires ligation of the gonadal vein, and frequently ligation of the adrenal and lumbar veins as additional mobilization of the LRV becomes necessary. The LRV is reimplanted into the IVC in a more caudad location, effectively avoiding the area of compression and hence relieving it. In some instances a saphenous vein patch may be required in concert with transposition of the LRV (see Fig. 165.4B). This is especially important in the case of long-standing NCS, when permanent fibrotic distortion of the LRV may occur secondary to the sequelae of LRV hypertension on the endogenous structure of the vessel wall. A great saphenous vein patch, despite requiring an additional groin incision, is preferred as it is typically readily available in this younger cohort (i.e., not expended from prior cardiovascular surgery) and carries a lower risk for infection versus synthetic graft material.

Patch venoplasty without LRV transposition is not frequently reported in the literature but is an option in those in which transposition is not feasible owing to a short LRV, an "overstretched" LRV, or in instances where the extrinsic compression of the LRV would not be alleviated by merely transposing the vein.[72] Overstretching of the LRV is a unique scenario likely resulting from a prominent aorta (as seen in AAA) or an extremely ptotic kidney. Likewise, if the anatomic limitations of the LRV transposition result in an anastomosis in which tension is unavoidable, a tension-free anastomosis can be created by employing a saphenous vein cuff directly to the IVC (see Fig. 165.4C).

An additional surgical alternative is that of gonadal vein transposition (see Fig. 165.4D). This technique is feasible as in many cases of NCS, the gonadal vein has markedly dilated, and through division of this vessel low in the pelvis, symptoms of pelvic congestion can be relieved. Additional advantages of this approach include the fact that it can be used to treat patients with posterior NCS, avoids renal vein clamping or transection, requires only a single anastomosis, and avoids saphenous vein

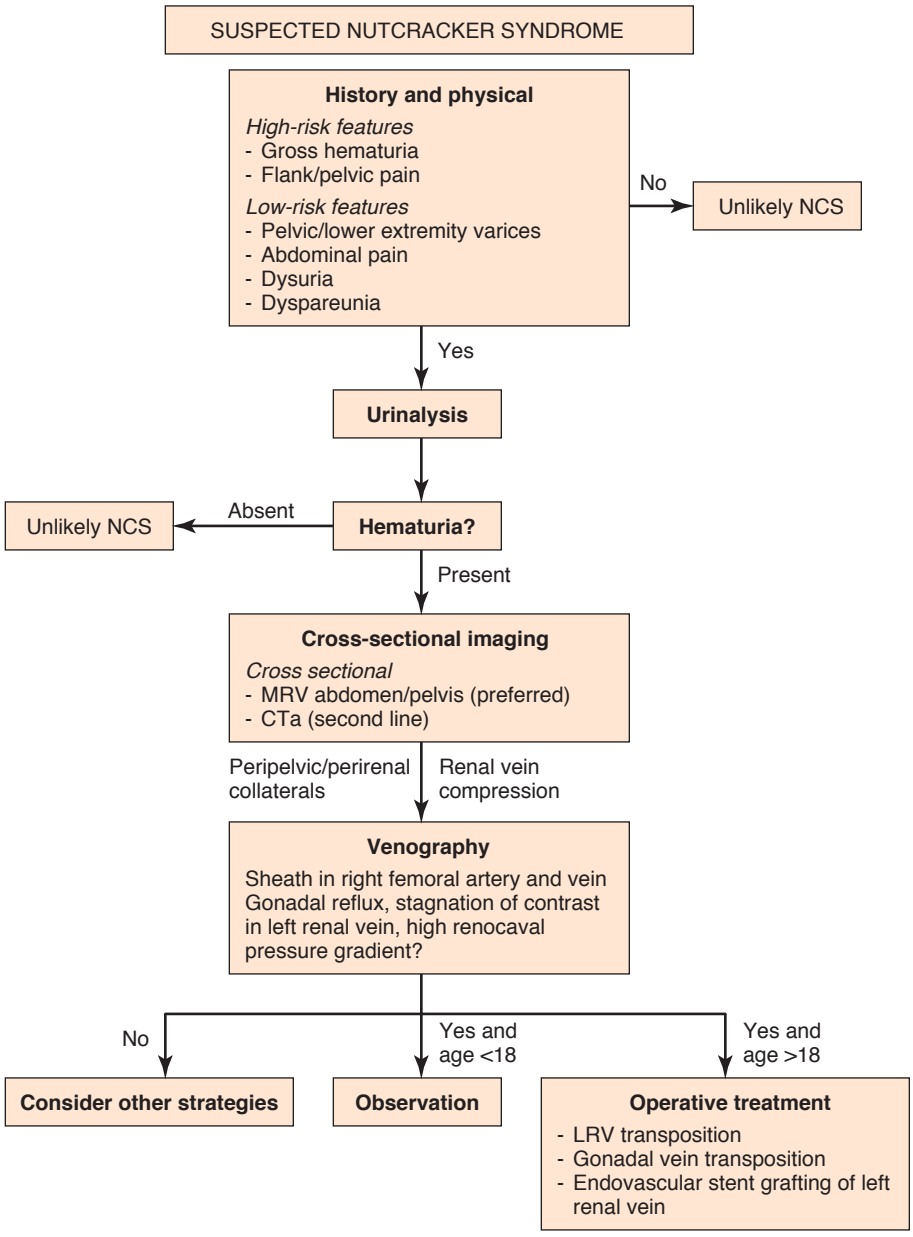

Figure 165.3 Proposed algorithm for diagnosis and management of NCS. *CTA*, Computer tomography with angiography; *LRV*, left renal vein; *MRV*, magnetic resonance venography; *NCS*, nutcracker syndrome.

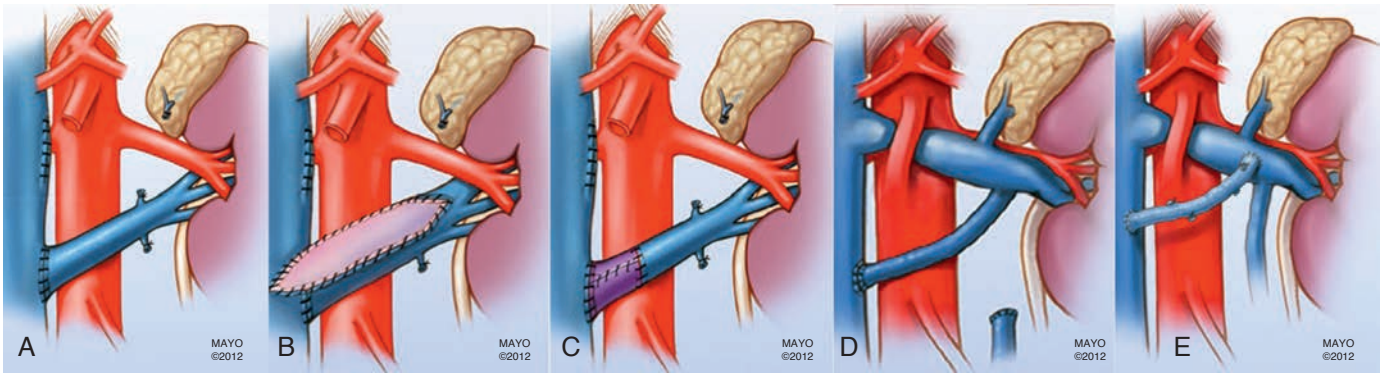

Figure 165.4 Operative Strategies for the Management of Nutcracker Syndrome. (A) Left renal vein transposition, (B) left renal vein transposition with patch angioplasty, (C) left renal vein transposition with saphenous vein cuff, (D) gonadal vein transposition, (E) saphenous vein bypass. (From Erben Y, Gloviczki P, Kalra M, et al. Treatment of nutcracker syndrome with open and endovascular interventions. *J Vasc Surg Venous Lymphat Disord*. 2015; 3:389–396.)

harvest. For this technique to be used, the gonadal vessel must be large enough in diameter to effectively decompress the LRV and must be long enough to reach the IVC without tension. These features of the gonadal vessel are easily determined by preoperative imaging. Gonadal vein transposition is performed through a mini-laparotomy, with Kocherization and cephalad retraction of the viscera, with exposure of the retroperitoneum allowing for intraoperative confirmation of the feasibility of this approach (assessment of the gonadal and renal veins). If the gonadal vein size is acceptable, mobilization of the gonadal vein with ligation of small side branches easily yields enough length to transpose the vessel. Heparin is administered, and a partially occlusive ("side-biting") clamp is used on the IVC with proximal control obtained on the gonadal vein. A simple running anastomosis is preferred to construct the new gonadocaval anastomosis.

Owing to these features and the applicability of gonadal vein transposition to both anterior and posterior NCS, this has become our preferred strategy for the surgical management of NCS. Our experience has demonstrated symptom resolution in 100% of patients treated using this strategy (n = 4). The relatively limited operation (in comparison to LRV transposition) and potential for decreased morbidity and hospital stay, coupled with excellent outcomes, have led our institutional practice pattern to prefer a "gonadal vein transposition first" type strategy, although this is limited in the face of the anatomic features, as mentioned previously.

A final surgical strategy for the treatment of either anterior or posterior NCS is that of saphenous vein bypass (see Fig. 165.4E), which like gonadal vein transposition avoids clamping or transecting the LRV. Great saphenous vein bypass is used in those infrequent situations where transposition of either the LRV or gonadal vein is not feasible. However, in addition to requiring saphenous vein harvest, this procedure requires two anastomoses and clamping of the LRV.

Outcomes with open surgery for anterior NCS are well documented and are overall satisfactory. In one of the larger and more recent contemporary cohorts as reported by Erben et al. from the Mayo Clinic, the authors report contemporary outcomes using an "LRV transposition-first" strategy of sorts over a 20-year period.[12,15] The authors show a low perioperative complication and reintervention rate, along with high patency of the LRV at discharge in 37 consecutive patients in their series.[15] However, over a median follow-up of approximately 37 months, it was determined that approximately one-third of patients required reintervention of some form—stenting of the transposed LRV in most instances—although symptom resolution was noted to be 87% over follow-up. The authors report a 24-month primary patency and freedom from reintervention of 74% and 68%, respectively. Symptoms of NCS may recur if the bypass or transposed segment becomes occluded, which mandates reintervention. Endovascular rescue has been described in this setting.[77]

Other postoperative complications of open surgical procedures for NCS are relatively uncommon and include deep venous thrombosis, retroperitoneal hematoma, paralytic ileus, and the development of chylous ascites.[12,14] The perioperative mortality rate is exceedingly low, likely due to a young and otherwise morbidity-free patient population. We recommend that, in the postoperative phase, 30 days of anticoagulation with novel agents or warfarin should be instituted, with further benefit potentially derived from additional antiplatelet agents (aspirin, clopidogrel), although this has not been examined in the literature to date.

Open Surgery for Posterior Nutcracker Syndrome

Posterior NCS is challenging from an open surgical perspective because the retroaortic position of the LRV means that the LRV must be anteriorly transposed if using LRV transposition. Dissection in the narrow window between the vertebral column and aorta poses particular hazard from difficult to visualize lumbar, perirenal, and other collateral vessels. Additional difficulties may result from neglected or unseen damage to the numerous lymphatic channels along the aorta in the retroperitoneum, mandating careful ligation to prevent lymph leak and its subsequent morbidity. Much like renal vein transposition as described previously for anterior NCS, anterior LRV transposition may also require a vein patch in the face of long-standing, fibroproliferative disease. In addition, careful attention must be paid because the retroaortic LRV is particularly friable and prone to damage during its dissection and mobilization.[72] Successful laparoscopic techniques for LRV transposition in anterior and posterior NCS have been described[23] but are not recommended for routine application, owing to the expertise required to perform a delicate anastomosis in a minimally invasive fashion.

Other strategies used for the open surgical management of posterior NCS include saphenous vein bypass, aortic transposition,[78] as well as gonadal vein transposition. Again, much as in the scenario for anterior NCS, gonadal vein transposition (if applicable) has the potential to obviate most of the hazards of dissection in the area of the renal vein. This is magnified in the instance of a retroaortic LRV. The approach to performing gonadal vein transposition is the same as in anterior NCS.

Complications for the open treatment of posterior NCS are the same as those for anterior NCS. Although a retroaortic renal vein may be a more frequent anatomic variant than originally thought,[51] treatment of symptomatic posterior NCS is rarely reported in the literature and is limited to case reports and intermittent case series.[20,23,26,78-87] As such, there remains a marked lack of long-term follow-up and description of patient outcomes, with no consensus as to optimal treatment strategies.

Endovascular Treatment of Nutcracker Syndrome

As with virtually all vascular pathologies, endovascular solutions to NCS have been proposed and attempted. However, as with other compressive entities (i.e., thoracic outlet syndrome), endovascular options have been met with limited success. Initially described by Neste et al. in 1996,[13] the utility of endovascular therapy is typically described as stenting of the LRV. The bulk of the available data describing endovascular treatment of NCS is in the form of case reports.[14,33,88-90] More recently several

larger case series have been described.[10,11,91] The largest case series to date is that reported by Chen et al., with 61 patients undergoing LRV stenting with a median follow up of 66 months.[91] The authors reported an overwhelmingly positive response in terms of outcome and symptom resolution, as well as a low perioperative complication rate. Complications included maldeployment of a stent requiring open reintervention and stent migration to the right atrium, which was particularly troublesome as it mandated open cardiac surgery. The authors report that the ideal stent should have the properties of high radial strength, conformability, and minimal shrinkage in length, all of which allow for ideal stent positioning. In fact, the propensity for these devices to migrate in this location has led some authors to recommend both the oversizing and positioning of stents from the first division of the LRV.[72] Unfortunately, recent larger series using an "endovascular first" strategy to the treatment of NCS, with longer follow-up times, have demonstrated a 6.7% migration rate of stents, which is higher than initially hypothesized using midterm follow-up data.[88] When considering these stents can migrate to the right-sided circulation or lungs, this migration rate, as reported, is quite worrisome. The types of endovascular devices used in the larger case series are overwhelmingly self-expanding and include the Wallstent, Palmaz, SmartControl, and self-expanding SMART stents. Other complications from endovascular therapy for NCS include in-stent thrombosis and fracture. Stent protrusion into the IVC, which was initially thought to be concerning, has been demonstrated to be safe.[14]

Antiplatelet medications are a necessity in the postoperative period to prevent thrombotic complications in relation to the stent. Despite the report of adequate long-term outcomes using an "endovascular-first" strategy to treat NCS,[88] a major limitation of this strategy remains the absence of direct comparisons between open and endovascular therapy for NCS performed in the same era at a single institution, raising additional concerns about the durability of these procedures. Moreover, as the cohort of patients treated for NCS are oftentimes in their second or third decades of life, the duration of imaging follow-up required has yet to be established and remains lifelong at this time. Although there are many limitations to this technology as described previously, newer venous-specific endovascular devices are likely to emerge in the near future and improve outcomes in the endovascular treatment of NCS, which could therefore serve as a treatment alternative to open surgery in poor open surgical candidates.

SUMMARY

NCS has much potential to inflict lifestyle-limiting morbidity in the form of debilitating pain, hematuria, and disfiguring varices in the lower extremities and scrotal/vulvar region. This syndrome is the result of anatomic compression of the LRV, with much speculation as to the reasons it may occur in some but not others with anatomic LRV compression. NCS is often misdiagnosed or at best is diagnosed in its later stages, after the development of renal venous hypertension, which in concert with pain and hematuria mandates operative repair. Diagnosis is most efficiently achieved through dedicated clinical examination and characteristic findings on cross-sectional imaging and venography. Although there are a variety of operative strategies applicable to this condition, much of this is dictated by the subclass of NCS (anterior or posterior), as well as intraoperative anatomy. Relief of pain and hematuria is easily achieved with decompression of the LRV. Endovascular strategies have been used and reported more frequently in the recent era, although long-term data are still necessary to prove their efficacy as a treatment modality.

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CHAPTER 166

Venous Aneurysms and Their Management

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INTRODUCTION

Aneurysms are abnormal dilations of blood vessels and occur most commonly in arteries. Venous aneurysms are rare but have been reported throughout the veins in the body, including the extremities, head and neck, and abdomen.

When defining venous aneurysms, Gillespie et al. state: "The definition of a venous aneurysm has been controversial. A venous aneurysm is best described as a solitary area of venous dilation that communicates with a main venous structure by a single channel, and it must have no association with an arteriovenous communication or a pseudoaneurysm. Most importantly, it should not be contained within a segment of a varicose vein."[1] In general, venous aneurysms can be defined as an area of dilation 2 to 3 times the surrounding normal vein.[1,2] They are rare and generally asymptomatic; thus the true incidence is unknown.

Venous aneurysms can be classified as primary (congenital) or secondary (acquired). Primary, or congenital, aneurysms are caused by a weakness in the venous wall secondary to inherited conditions such as Klippel-Trénaunay syndrome, neurofibromatosis 1(NF-1), and Parkes Weber syndrome (discussed more fully in Chapter 171).[3] Secondary, or acquired, venous aneurysms arise from etiologies such as trauma, inflammation, degenerative processes, mechanical stress, and venous hypertension. Some case reports describe a correlation between pregnancy and venous aneurysm formation, but no causative factors have been elucidated.[4] Scientific publications identify the presence of estrogen receptors in venous vascular tissue, and although it is tempting to hypothesize causality, this has not been established.[5-7]

Histologically, the intima of venous aneurysms may be thickened and fibrosed. In addition, the media may be attenuated or absent and display a paucity or total lack of smooth muscle cells. Matrix metalloproteinases (MMPs) have been noted to be expressed at higher levels in venous aneurysms compared with normal venous tissue. The established relationship between MMPs and arterial aneurysms is long standing, but more research is needed to document this relationship in venous aneurysms.[8]

Clinically, patients with venous aneurysms are usually asymptomatic; however, complications can occur and include thrombosis, embolization, rupture, local mass effects with or without edema, and localized pain or tenderness. Diagnosis may be made with physical examination in the case of superficial venous aneurysms; however, they are often misdiagnosed as soft tissue masses or even hernias.[1] Diagnostic confirmation can be performed using duplex ultrasound (DUS), computed tomography, or magnetic resonance imaging. Venography is not indicated for primary diagnosis. A thorough history should be elicited from the patient, specifically inquiring about family history of aneurysmal or connective tissue disease and any recent or remote trauma to the region. In addition, physical examination should identify any sequela of arteriovenous fistula, with imaging studies performed if needed.

Abstract

Venous aneurysms are rare and poorly characterized. Popliteal venous aneurysms warrant intervention if symptomatic or greater than 20 mm. Other venous aneurysms are usually observed if asymptomatic. Interventions include tangential aneurysmectomy, aneurysm resection with primary anastomosis, aneurysm resection with interposition grafting, or ligation of the affected venous segment. Endovascular modalities have been successfully attempted, but no evidence based guidelines exist to guide patient selection.

Keywords

Venous
Aneurysm
Tangential aneurysmectomy
Popliteal
Pulmonary embolus

Treatment of venous aneurysms is performed on a case-by-case basis because there are few evidence-based studies to guide treatment. In general, conservative management is indicated for small and/or asymptomatic aneurysms. Surgical treatment for large aneurysms or those associated with complications consists of tangential aneurysmectomy, aneurysm resection with primary anastomosis, aneurysm resection with interposition grafting, or ligation of the affected venous segment. There is no standard endovascular treatment, but endovascular modalities have been successfully implemented in select patients.[9-11]

LOWER EXTREMITY VENOUS ANEURYSMS

Lower Extremity Superficial Venous Aneurysms

Superficial venous aneurysms are usually visible and present as painless masses, often misdiagnosed as soft tissue masses. Depending on the location, these aneurysms can be confused with hygromas, or even inguinal or femoral hernias.[1] Thorough physical examination may identify a superficial venous aneurysm because the mass is more resistant to compression in the dependent position compared with when the extremity is elevated. DUS can definitively make the diagnosis. Saphenous vein aneurysms have been diagnosed during operative procedures for what were thought to be varicose veins preoperatively. Venous aneurysms on the dorsum of the foot have been described and are usually asymptomatic. Interestingly, all case reports of pedal venous aneurysms involve young women.[12]

Treatment of superficial venous aneurysms involves ligation and excision after ensuring that the deep venous system is intact. If the aneurysm is near the saphenofemoral junction, then a high ligation should also be performed.

Aneurysms of perforating veins in the lower extremity have been described only rarely. This may be secondary to the lack of specific symptoms. Ultrasound is diagnostic when the size of the perforating venous aneurysms exceeds 9 mm. Although these aneurysms are located below the deep fascia, they are included in the superficial venous aneurysm section because they are often treated the same way superficial refluxing veins are treated—subfascial ligation with or without aneurysm excision. Aneurysms are excised if they are symptomatic. Labropolous et al. also noted that these aneurysms are usually fusiform and recommended treatment if perforating vein treatment was undertaken. His group found no relation between the sizes of perforating vein aneurysms and the severity of chronic venous disease.[13]

Lower Extremity Deep Venous Aneurysms

Popliteal venous aneurysms (Fig. 166.1) are the most commonly reported and best studied of all venous aneurysms. Evidence from previous studies suggests that popliteal venous aneurysms are more commonly associated with complications than aneurysms in the superficial systems. These complications include thrombosis, pulmonary embolism, localized pain and swelling, more diffuse lower extremity swelling, and symptoms of chronic venous disease. In a report published in 1993, 24 cases of popliteal venous aneurysm were identified; all patients presented

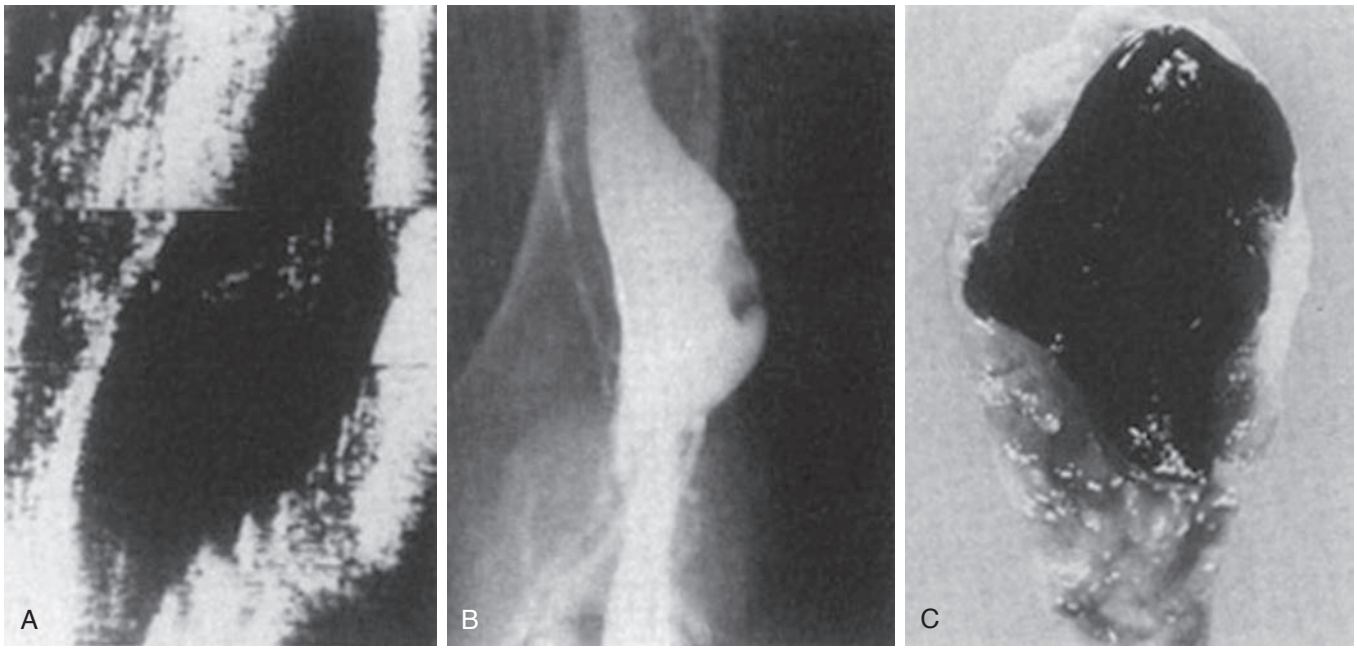

Figure 166.1 (A) Duplex image of popliteal venous aneurysm with intraluminal thrombus. (B) Ascending phlebogram confirming popliteal venous aneurysm with intraluminal thrombus. (C) Resected venous aneurysm sac with intraluminal thrombus. Note appearance of acute, jellylike thrombus despite therapeutic anticoagulation. (From Aldridge SC, Cometota AJ, Katz ML, et al. Popliteal venous aneurysm: report of two cases and review of the world literature. *J Vasc Surg*. 1993;18:708–715.)

with thromboembolic disease. Seventy-one percent presented with pulmonary embolism.[14] Other studies have shown that most popliteal venous aneurysms (45%-80%) are discovered incidentally during work-up after patients have suffered a pulmonary embolism.[15,16]

Asymptomatic patients with aneurysms less than 20 mm can be serially monitored with ultrasound to evaluate for progression. Symptomatic patients (especially those who have suffered a pulmonary embolus) should be treated regardless of aneurysm size. In general, anticoagulation alone is not considered sufficient treatment for popliteal venous aneurysms. Thrombus burden localized to the popliteal venous aneurysm has been shown to predispose to pulmonary embolus even when patients are therapeutically anticoagulated.[17,18] Surgical reconstruction is preferred in these cases and can consist of tangential aneurysmectomy with lateral venorrhaphy, aneurysm resection with primary anastomosis, or interposition grafting with saphenous vein. If no other option is available, a synthetic bypass can be used, but postoperative thrombosis is more common. Tangential aneurysmectomy with lateral venorrhaphy (Fig. 166.2) is the preferred method of reconstruction.[19] Inferior vena cava (IVC) filter placement and catheter-directed lysis should be considered on a case-by-case basis, taking into account patient-specific variables such as ability to tolerate anticoagulation and concomitant extent of ipsilateral deep venous thrombosis. Patients are routinely placed on anticoagulation for 3 to 6 months after all procedures.

Due to their rarity, few studies exist to guide the treatment of femoral and common femoral venous aneurysms. We believe that, extrapolating from the popliteal venous aneurysm literature, symptomatic aneurysms should be treated surgically and asymptomatic venous aneurysms can be monitored for increase in size and/or development of intraluminal thrombus if they are small on discovery.

Iliac vein aneurysms are rare, with only 13 cases reported in the literature. Rupture was reported in one case of a large external iliac vein aneurysm.[14] More commonly these aneurysms are asymptomatic and discovered incidentally or during evaluation for other pathology such as pulmonary embolism. Treatment is best accomplished with tangential aneurysmectomy and lateral venorrhaphy. Ligation of the iliac vein leads to a high rate of chronic lower extremity edema and post-thrombotic syndrome and should be avoided.

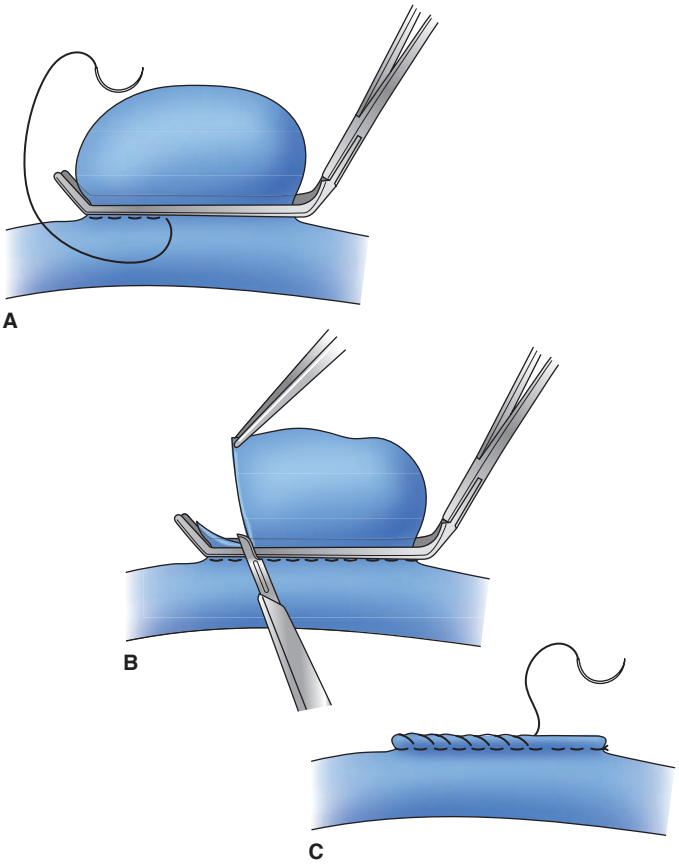

Figure 166.2 (A) Illustration of technique of tangential aneurysmectomy with lateral venorrhaphy. Clamp is placed at base of aneurysm without compromising lumen of popliteal vein. Vein walls are approximated by undersewing clamp with running horizontal mattress stitch. (B) Aneurysm is resected flush with vascular clamp. (C) Second, reinforcing running stitch is placed, approximating vein wall edges external to mattress suture. (From Aldridge SC, Cometota AJ, Katz ML, et al. Popliteal venous aneurysm: report of two cases and review of the world literature. *J Vasc Surg*. 1993;18:708–715.)

ABDOMINAL VENOUS ANEURYSMS

Inferior Vena Cava

The normal caliber of the IVC is 1.5 to 3.7 cm, and the IVC is considered aneurysmal when it exceeds 5 cm. Fewer than 60 case reports addressing IVC aneurysms have been published, which make these rare entities.[20] Clinically, IVC aneurysms are rarely symptomatic and often discovered incidentally on cross-sectional imaging performed for other reasons. In a previous report the most common presentation was iliocaval thrombosis, which occurred in 19%.[21] Gradman and Steinberg created a classification system (Fig. 166.3) defining types of IVC aneurysms, which is shown as follows.[22]

Type 1: suprahepatic aneurysms without obstruction.
Type 2: aneurysms located above or below the hepatic veins with obstruction.
Type 3: infrarenal aneurysms without obstruction.
Type 4: miscellaneous aneurysms.

Although this classification system is not intuitive, it helps to guide management.[22]

Type 1 aneurysms can usually be observed with no adverse outcomes. Types 2, 3, and 4 aneurysms are prone to thrombosis or embolization and, for this reason, are usually treated. Surgical repair is the most common treatment, either tangential excision with venorrhaphy or resection with interposition bypass grafting.[21]

Visceral Venous Aneurysms

Venous aneurysms in the visceral veins, including the portal, mesenteric, and renal systems, are extremely rare. In the only recent systematic analysis, 98 case reports were identified,

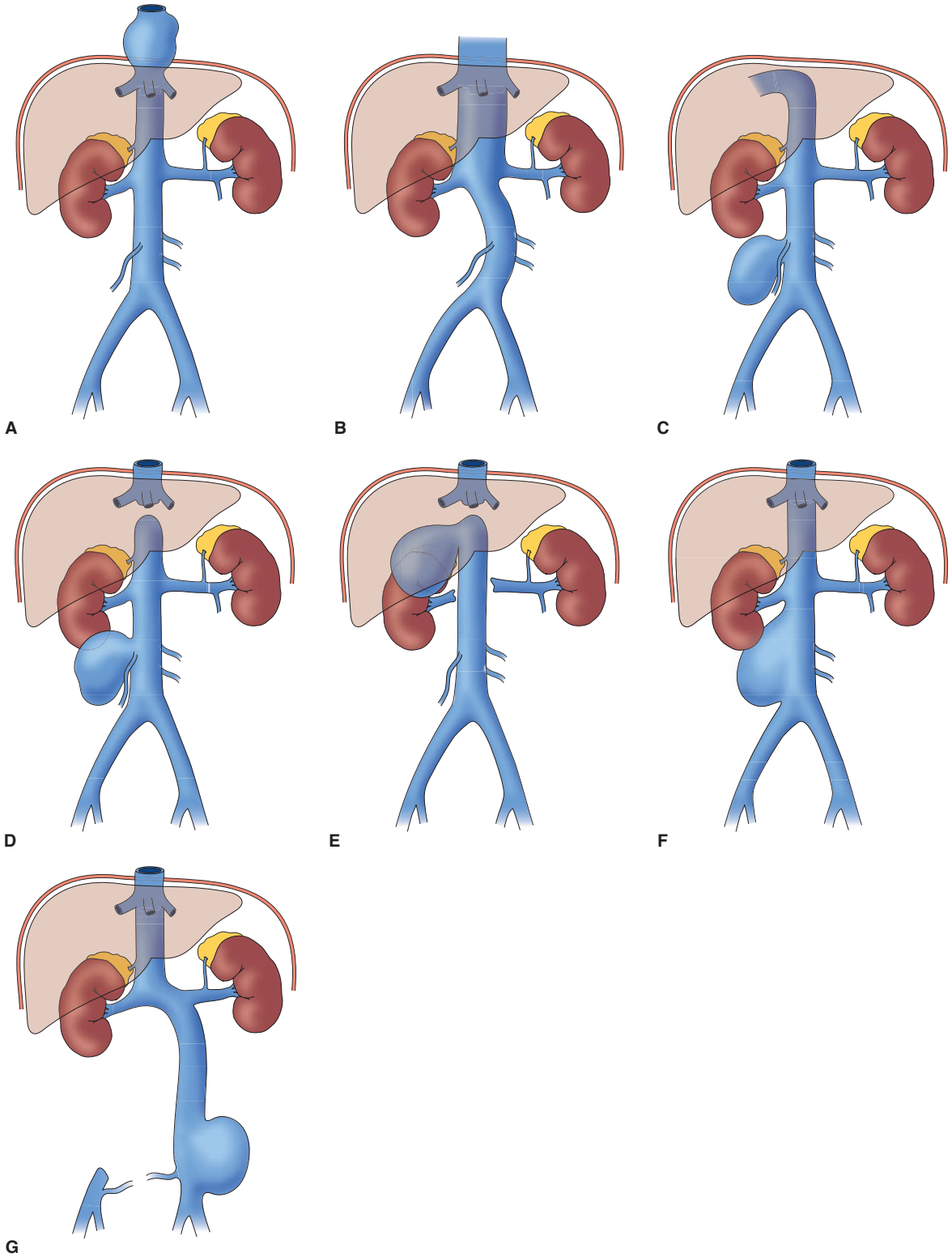

Figure 166.3 (A) Type I aneurysm showing suprahepatic location without obstruction in inferior vena cava (IVC). (B). Type I aneurysm in perihepatic location with left-sided IVC. (C). Type II aneurysm showing supraphepatic interruption of IVC with infrarenal IVC aneurysm. (D). Type II aneurysm with infrahepatic interruption of IVC and infrarenal IVC aneurysm. (E). Type II aneurysm with intrahepatic interruption of IVC, infrahepatic IVC aneurysm, and entry of renal veins into azygous and hemizygous system. (F). Type III infrarenal IVC aneurysm without venous obstruction. (G). Type IV aneurysm of iliac vein with left-sided IVC. (From Gradman WS, Steinberg F. Aneurysm of the inferior vena cava: case report and review of the literature. *Ann Vasc Surg.* 1993;7:347–353.)

including 198 aneurysms in 176 patients. The majority of aneurysms were in the portal vein (191 of 198 aneurysms).

Portal venous aneurysms are defined as a portal vein with a diameter greater than 15 mm, or greater than 19 mm in cirrhotic patients.[23] In the studies reported, one-half of patients presented with nonspecific abdominal pain, 30% were asymptomatic with incidental aneurysm discovery, and 20% of patients presented with thrombosis.[24,25] Rupture was rare.

The congenitally aneurysmal portal vein is thought to arise from incomplete regression of the right primitive distal villetine vein. Acquired portal vein aneurysms form secondary to portal hypertension, trauma, pancreatitis, or local malignancy with venous wall invasion.[26]

Treatment is indicated in portal venous aneurysms greater than 3 cm or smaller aneurysms with complications (rupture, thrombosis, pain, rapid enlargement) in appropriate surgical candidates. Patients without portal hypertension do well with tangential aneurysmectomy and aneurysmorrhaphy, although extensive perioperative bleeding can occur. In patients with concomitant portal hypertension, the treatment should address this underlying condition either through portovenous shunting or liver transplantation. Regression is rare but has been reported.[21]

Mesenteric vein aneurysms are extremely rare and have presented as asymptomatic masses discovered incidentally, or following the development of abdominal pain or thrombosis. In a review published in 2004, 10 cases were identified. The most common presenting symptom was abdominal pain.[27] The majority were treated conservatively, although there is a report of a catastrophic outcome following rupture.[28] It is recommended that surgical treatment be performed in symptomatic patients, or asymptomatic patients with aneurysms greater than 3 cm.

Splenic vein aneurysms are much less common than splenic artery aneurysms, and they have been shown to occur secondary to arterial aneurysm rupture into the splenic vein.[29,25] Treatment is aimed at symptomatic patients, women of childbearing age, or aneurysm size greater than 3 cm.

Renal vein aneurysms are also rare. In a systematic review, five cases were identified. In three cases, abdominal pain was the presenting symptom; the other two patients were asymptomatic. Surgical repair using aneurysmectomy or nephrectomy was performed in the symptomatic patients.[24]

Renal vein aneurysms can be confused with distended renal veins, particularly on the left side. The diagnosis of an aneurysm must not be confused with the nutcracker syndrome. In addition, investigation of a spontaneous splenorenal shunt should be entertained in patients with portal hypertension because this may also contribute to a dilated left renal vein.

UPPER EXTREMITY AND INTERNAL JUGULAR VENOUS ANEURYSMS

Upper extremity and internal jugular venous aneurysms also occur in both the deep and superficial venous systems. They are thought to be less common than venous aneurysms in the lower extremities; in one series, they constituted 23% of 39 aneurysms diagnosed in 30 patients.[1]

Upper Extremity Superficial Venous Aneurysms

Superficial venous aneurysms in the upper extremities often present with pain and/or swelling, but a significant proportion are asymptomatic. In these cases, they are often misdiagnosed and treated as soft tissue masses, with the diagnosis only being made when surgery is performed. This can be avoided with a thorough physical examination which includes compression of the mass with the extremity in both the dependent and elevated positions, and changes can be noted during a Valsalva maneuver. There should be differential filling (fast vs. slow) of the mass depending on the position of the extremity (dependent vs. elevated). DUS scanning is diagnostic and should be routinely used.

Surgical treatment should be directed at aneurysms that are symptomatic or if the patient desires excision for cosmetic reasons. DUS performed immediately before incision is beneficial in identifying all feeding vessels which can then be targeted early in the procedure before the aneurysm sac is excised. The procedure can usually be carried out under local anesthesia.

Pseudoaneurysms frequently develop in arteriovenous fistulae created for hemodialysis access. These are discussed in Chapter 179.

Upper Extremity Deep Venous Aneurysms

Brachial, axillary, and subclavian venous aneurysms are seldom symptomatic and usually present as a painless slowly enlarging mass. If a mass is visible through the skin, physical examination during Valsalva will show enlargement of the mass. In most cases, DUS is diagnostic. Cross-sectional imaging may be considered if adjacent structures are thought to be compromised or for operative planning.

Upper extremity deep venous aneurysms are rarely reported in the literature, and no evidence-based treatment algorithm exists. Although they have been reported to be less likely to be associated with complications, a few case reports have demonstrated pulmonary embolization from these aneurysms.[30,31] Others have reported cases of deep upper extremity venous aneurysms causing localized discomfort.[32] With this in mind, the authors recommend that symptomatic aneurysms be treated with aneurysmectomy and venous reconstruction as needed. Asymptomatic aneurysms can be surgically treated in appropriate risk patients, or serially observed for any change in size or occurrence of symptoms.

Jugular Venous Aneurysms

Venous aneurysms of the jugular veins (Fig. 166.4) are usually asymptomatic and frequently misdiagnosed. The differential diagnosis includes any soft tissue mass of the head and neck, such as lipoma, lymphangioma, malignancy, hematoma, or cystic structures. Congenital venous aneurysms of the external and internal jugular veins presenting in childhood have been described. These aneurysms may also present in adults, although this is rare. There are case reports of patients with NF-1 being predisposed to developing jugular venous aneurysms. Treatment

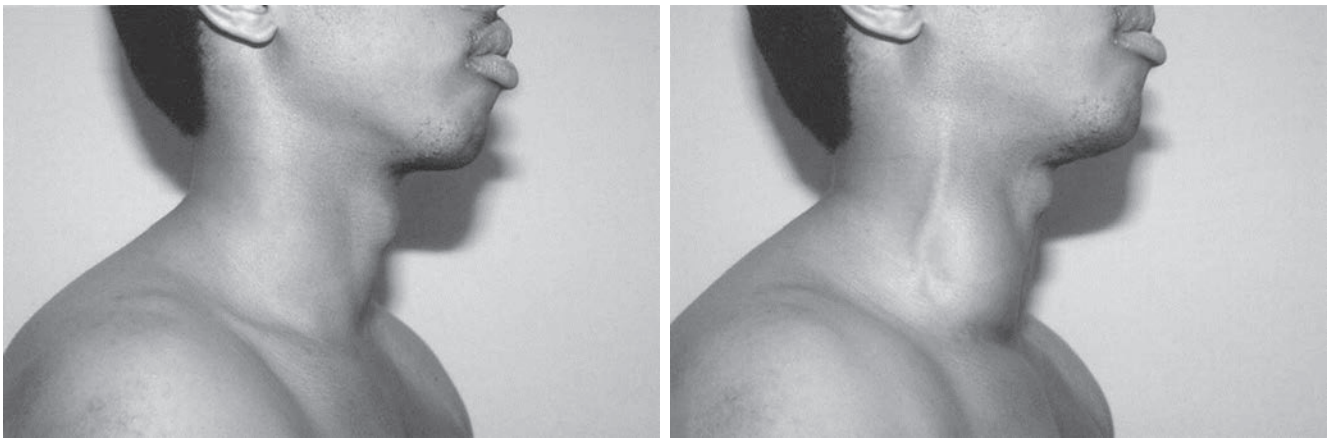

Figure 166.4 Under Valsalva maneuver, aneurysms of the internal jugular vein may become alarmingly large *(right panel).* However, their course is usually benign, and surgical excision is rarely indicated. (From Gillespie DL, Villavicencio JL, Gallagher C, et al. Presentation and management of venous aneurysms. *J Vasc Surg*. 1997;26.5:845–852.)

of these aneurysms involves surgical resection and is performed most commonly for cosmetic purposes because they rarely lead to pulmonary embolization.[33] Ligation of the feeding vessels with aneurysmectomy is frequently performed as long as there is good contralateral venous drainage.

CONCLUSION

Venous aneurysms are rare. They are usually discovered incidentally on cross-sectional imaging or in the work-up for pulmonary embolus. Although no randomized controlled trials are available, best treatment involves surgical consideration for large or symptomatic venous aneurysm, and observation of small and asymptomatic aneurysms. Tangential aneurysmectomy with lateral venorrhaphy is generally the preferred surgical procedure. More studies of these rare entities are needed to develop better treatment algorithms.

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CHAPTER 167

Venous Reconstruction in Nonvascular Surgical Oncologic Procedures

MICHAEL J. OSGOOD and JAMES H. BLACK III

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INTRODUCTION AND DEFINITIONS

The portal vein and superior mesenteric vein are intrinsically associated anatomically with the pancreas. These blood vessels can become involved with pancreatic tumors and their resection, and reconstruction is becoming a well-established adjunct to pancreatic resection in order to achieve complete tumor resection in patients with localized cancer. Likewise, the inferior vena cava can become involved with tumors or tumor thrombus from a variety of retroperitoneal, abdominal, renal, adrenal, and hepatic tumors. Extensive institutional experience has been amassed establishing the safety and feasibility of portal vein, superior mesenteric vein, and inferior vena cava resection and reconstruction as adjuncts to the resection of certain tumors. In this chapter we discuss tumors involving these blood vessels, the clinical presentation and evaluation of these patients, the surgical approach to tumor resection and vascular resection and reconstruction, methods of vascular resection and reconstruction, the use of adjunctive extracorporeal bypass techniques where available, as well as perioperative and long-term results.

PORTAL AND SUPERIOR MESENTERIC VEIN RECONSTRUCTION

Given the close anatomic relationship between the portal vein (PV), superior mesenteric vein (SMV), and the pancreas, tumors originating from the pancreatic parenchyma may abut or invade these venous structures. Although pancreatic cancer involving these blood vessels was once considered a contraindication to pancreatic resection, the resection and reconstruction of these vessels has been established as a safe and effective method of achieving complete tumor resection in appropriate candidates. Considerable experience has been amassed with PV/SMV resection, and this technique has consequently become regarded as a standard adjunct to pancreatic resection in patients in

Abstract

The performance of venous resection and reconstruction to facilitate oncologic cure is becoming more routine in advanced malignancies of the peri-portal and retroperitoneal territories. Vascular surgeons should aware of the techniques and variations of venous reconstructions, and the options to achieve resection of the nearby malignancies. Additionally, awareness of options for support of venous return during reconstruction of major veins is requisite, and coordination of intraoperative resuscitation and/or extracorporeal bypasses may be considered. As the safety and efficacy of venous reconstruction has been demonstrated in multiple reports, it is likely vascular surgeons will encounter such practice demands in future consultations.

Keywords

inferior vena cava
portal vein
superior mesenteric vein
malignancy
retroperitoneal tumors

whom a complete tumor resection can be achieved. Whereas there are no prospective data in this area, multiple retrospective reports have examined the outcomes with regard to PV/SMV resection and reconstruction.[1-5] These data are summarized herein.

Tumor Types

Patients undergoing resection of pancreatic malignancies may present with tumor involving the PV and/or the SMV. Although the majority of these patients have pancreatic ductal adenocarcinoma, a minority present with a variety of tumors or diseases of the pancreas that may necessitate PV/SMV resection and reconstruction in order to achieve pancreatectomy. The largest published series of PV/SMV reconstructions performed concomitant with pancreatectomy is the series of 173 patients undergoing portal vein reconstruction out of 6522 patients who underwent pancreatectomy over a 45-year period at the Johns Hopkins Hospital. In this series, 86% of patients had pancreatic cancer and the remaining 14% had other diagnoses.[1] These included solitary fibrous tumor, pancreatic intraepithelial neoplasia (PanIN), gallbladder carcinoma, sarcoidosis, negative final pathology, and complete response to radiation without residual carcinoma present.[1] Since the majority of patients requiring PV/SMV resection have pancreatic adenocarcinoma, we focus here on the indications, approaches, and techniques specifically involving this malignancy.

Clinical Presentation, Evaluation, and Patient Selection

Only 15% to 20% of patients diagnosed with pancreatic cancer have resectable disease at the time of diagnosis.[6] Surgical resection is the only chance for cure. The resectability of pancreatic cancer is assessed based on the presence or absence of distant metastasis as well as the degree of local involvement and invasion of neighboring organs or blood vessels. Although clinical trials focus on the tumor-node-metastasis (TNM) system of classification, a more practical and clinically relevant system by which to categorize pancreatic cancer is as follows: resectable, locally irresectable, borderline resectable, and metastatic.[7] Resectable pancreatic cancer is defined as the presence of a tumor without distant metastasis or involvement of the superior mesenteric artery (SMA) or celiac artery (CA). Locally unresectable cancer is defined by infiltration of the SMA or CA; these lesions are not generally considered amenable to pancreatectomy. Borderline resectable cancer includes tumors with abutment to visceral arteries as well as those infiltrating the SMV or PV.[7] Those in this last category—patients with borderline resectable disease—are potential candidates for SMV/PV resection and reconstruction. Patients with metastatic disease are not candidates for surgical resection.

In the process of diagnosis and workup for pancreatic resection, patients typically undergo multiple imaging and invasive studies. Vascular involvement by pancreatic cancer is best assessed by helical computed tomography (CT) with intravenous contrast imaged in multiple phases to optimize contrast passage through the arterial phase, pancreatic phase, and portal venous phases.[8,9] Assessment of SMV/PV infiltration by a pancreatic tumor is best assessed on the portal venous phase.[9] Imaging findings highly sensitive for detection of PV/SMV invasion include radiologic absence of a fat plane between the tumor and the vessel, length of tumor involvement of greater than 5 mm, venous occlusion with formation of collateral vessels, presence of a "teardrop sign" in the SMV ("tethering" of the SMV by the tumor), and irregularity of the wall of the blood vessel (Fig. 167.1).[8] Imaging findings highly sensitive for unresectability include circumferential involvement of a vessel by more than 180 degrees (see Fig. 167.1).[8] Once a determination has been made regarding vascular involvement and potential for resectability, the technical feasibility of SMV/PV resection and reconstruction is assessed in conjunction with the oncologic surgeon who is managing the patient. A subset of patients requiring SMV/PV reconstruction will have venous involvement discovered intraoperatively despite preoperative imaging studies that do not suggest vascular involvement. Therefore intraoperative consultations for PV/SMV reconstruction are not infrequent.

There remains wide variation in the interpretation of resectability of pancreatic cancer with regard to PV/SMV involvement. A recent systematic review of outcomes from synchronous PV/SMV resection during pancreatectomy for cancer highlights the variability of results achieved with PV/SMV resection but does underscore the finding that PV/SMV resection in conjunction with pancreatectomy can be potentially curative.[10] Multiple recent reports have demonstrated that perioperative morbidity and mortality rates of pancreatectomy with PV/SMV resection and reconstruction are identical to those resulting from pancreatectomy without PV/SMV resection.[11-16] These reports further suggest that complete oncologic resection including PV/SMV resection is associated with improved survival versus those with residual disease after resection.[7] Therefore there has been a trend toward more aggressive PV/SMV resection to facilitate complete tumor removal.

Surgical Approach to Pancreatectomy and Portal Vein and Superior Mesenteric Vein Resection

Resectional techniques for pancreatectomy are well described elsewhere and are not given a full review here. Ductal adenocarcinoma is the most common tumor of the pancreas and is most commonly localized to the head of the pancreas in 78% of cases. Moreover, pancreatic cancers of the body and tail are typically unresectable at presentation. Therefore pancreaticoduodenectomy is the most commonly performed method of pancreatic resection. Indeed, in a systematic review of 1334 pooled patients who underwent SMV/PV resection and reconstruction during pancreatectomy, the extent of pancreatic resection was pancreaticoduodenectomy in 71%, total pancreatectomy in 24%, subtotal pancreatectomy in 3%, and distal pancreatectomy in 2%.[10] Because pancreaticoduodenectomy is the most commonly performed method of pancreatic resection in which SMV/PV reconstruction is required, here we focus

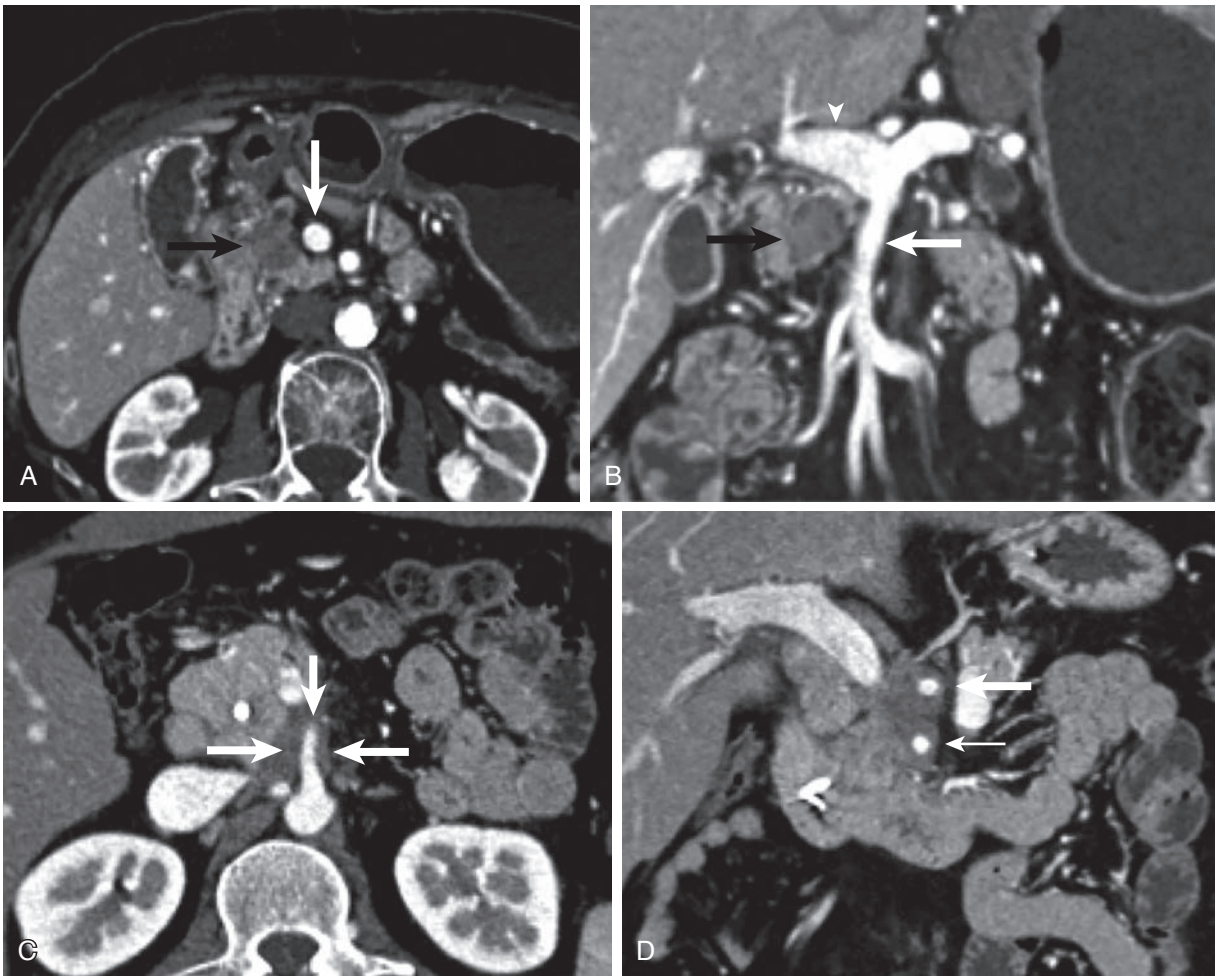

Figure 167.1 Portal Vein Invasion Is Evaluated on Preoperative Computed Tomography (CT) Imaging. (A) Axial slice of CT scan demonstrating a resectable lesion in the head of the pancreas *(black arrow)* with preservation of the fat plane circumferentially around the portal vein *(white arrow)*. (B) Coronal slice of CT scan demonstrating resectable lesion in the head of the pancreas with preservation of the fat plane around the vessel. (C) Axial slice of CT scan demonstrating an unresectable pancreatic mass with greater than 180-degree loss of the fat plane around the portal vein and circumferential encasement of the superior mesenteric artery (SMA). (D) Coronal slice of CT scan demonstrating an unresectable pancreatic tumor with complete encasement of portal vein *(large arrow)* and SMA *(small arrow)*.

briefly on the key steps of this procedure as they relate to SMV/PV resection and reconstruction.

In brief, pancreaticoduodenectomy can be accomplished via midline laparotomy or by bilateral subcostal ("rooftop") or chevron incisions. A critical early portion of the procedure is performing a wide Kocher maneuver, which allows assessment of the tumor and its relationship with the SMA for potential arterial infiltration. Many surgeons perform this portion of the procedure early in order to diagnose SMA or CA involvement, which would preclude pancreatic resection. The lesser sac is then entered by division of the gastrocolic ligament, and the hepatic flexure is mobilized. The gastroepiploic vein is ligated at its base near where it meets the gastrocolic trunk. It is at this point that the SMV is identified and traced to the inferior border of the pancreas. Supraduodenal dissection is then carried out, including cholecystectomy as well as lymphadenectomy of the hepatoduodenal ligament, common hepatic artery, and celiac trunk. The common bile duct is dissected to an extent that facilitates ligation and division. Multiple arteries in the vicinity of the pancreas require ligation, including the right gastric artery, the gastroduodenal artery, and the right gastroepiploic artery. At this point it is necessary to divide the distal stomach or proximal duodenum, depending on the oncologic surgeon's preference regarding preservation of the pylorus. Now the portal vein will be accessible which allows caudal dissection toward the superior border of the pancreas. The ligament of Treitz is mobilized and divided and the proximal jejunum is divided, which allows reflection of the distal duodenum on the specimen side into the lesser sac through a retrocolic window created in the transverse mesocolon to the right of the middle colic vessels. Dissection is then performed to mobilize the specimen off the SMV and SMA. The pancreatic parenchyma is then divided and the specimen is examined for final stages of vascular resection.

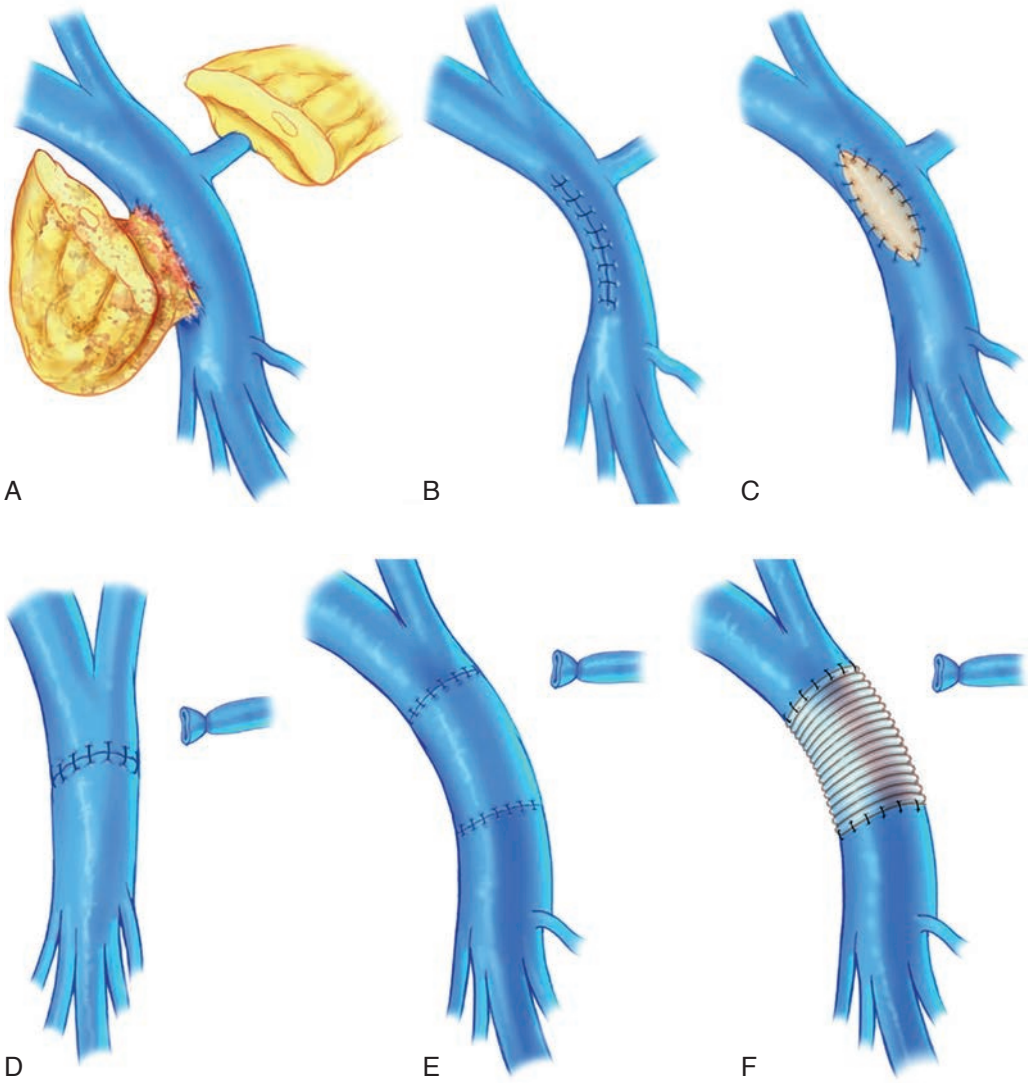

Figure 167.2 Methods of Portal Vein and Superior Mesenteric Vein Resection and Reconstruction. (A) Appearance of the pancreatic parenchyma in relation to the portal vein (PV)/superior mesenteric vein (SMV) illustrating involvement of the blood vessel in the usual anterolateral location. (B) Primary PV/SMV repair using venorrhaphy. (C) Vein patch angioplasty. (D) Primary end-to-end anastomosis. (E) Interposition graft placement using autologous vein. (F) Interposition graft placement using prosthetic.

When PV/SMV resection is required, it is typically performed during the last portion of the pancreatectomy. It is ideal for the rest of the pancreaticoduodenectomy dissection to be complete at this stage so that the specimen may be handed off and venous reconstruction can be performed expeditiously to minimize venous engorgement of the intestines during interruption of flow from the PV. The PV and SMV are circumferentially dissected and encircled with vessel loops to allow vascular control during resection. Depending on the extent and location of SMV/PV involvement, it may additionally be necessary to obtain vascular control of the splenic vein and left gastric vein. After the pancreaticoduodenectomy specimen is mobilized to the greatest extent possible, the SMV, PV, and, if necessary, the splenic and left gastric veins are occluded with vascular clamps and the involved SMV/PV wall is resected. Care is taken to preserve as much normal wall of the SMV/PV as possible in order to minimize the extent of reconstruction required while still achieving negative resection margins with the goal of achieving a complete resection. The most common area of PV/SMV involvement is the right anterolateral wall. If this is the case, the venous resection is best accomplished with the specimen retracted to the patient's right in order to optimize visualization and exposure of the PV/SMV (Fig. 167.2A).

Methods of Portal Vein and Superior Mesenteric Vein Reconstruction

The method and extent of reconstruction are dictated primarily by the anatomic location, circumference, and length of PV/SMV involvement. Reconstruction options include primary end-to-end reconstruction, lateral venorrhaphy, patch angioplasty, and interposition grafting (see Fig. 167.2). An additional factor

influencing the method of reconstruction is the physiologic state of the patient at the point in the procedure when venous reconstruction is performed. The extent of blood loss and degree of physiologic compensation will influence the extent of additional dissection for autologous vein graft procurement and length of additional operative time the patient can tolerate. Intraoperative systemic anticoagulation with heparin is not generally necessary.[1]

Primary venorrhaphy (see Fig. 167.2B) is generally possible when luminal narrowing of 30% or less is expected to result from the reconstruction. This method of SMV/PV reconstruction is both the most expeditious as well as easiest to perform. Primary venorrhaphy was performed in 37% of the SMV/PV reconstructions in our series from the Johns Hopkins Hospital.[1] Patch angioplasty (see Fig. 167.2C) is indicated when 30% to 50% of the PV/SMV circumference is involved and when primary end-to-end reconstruction is not technically feasible. The typical circumstance necessitating this method of reconstruction is a long segment of PV/SMV involvement (>2 cm) with a narrow circumferential involvement by tumor. As such, an ellipse-shaped venectomy is easily reconstructed using this method. Various patch materials have been described, including autologous vein, bovine pericardium, and expanded polytetrafluoroethylene (ePTFE).[1,17,18] We have had similar success with all of these patch materials.[1]

Primary end-to-end reconstruction (see Fig. 167.2D) of the PV/SMV is typically required when the degree of luminal narrowing exceeds 30%. In order to successfully achieve a tension-free primary end-to-end reconstruction, the length of involved vein should measure approximately 2 cm or less. In our reported experience with SMV/PV resection and reconstruction, this method of reconstruction was utilized in 24% of patients. Additional mobilization maneuvers may reduce tethering of the SMV and PV and thereby facilitate this method of reconstruction. These maneuvers can include extensive mobilization of the root of the mesentery, mobilization of the right colon, and mobilization of the liver by dividing its suspensory ligaments.[1]

Interposition grafting of the PV/SMV (see Fig. 167.2E and F) is generally required when the circumference of tumor involvement exceeds 30% and when the length of involved PV/SMV exceeds 2 cm.[1,17] A wide variety of conduits have been described for interposition grafting, including autologous vein grafts (greater saphenous vein, femoral vein, internal jugular vein, left renal vein, splenic vein (see Figs. 167.2E and 167.3), cryopreserved homografts, and synthetic grafts (see Fig. 167.2F), including Dacron and ePTFE (ringed and nonringed).[1,17-19] Conduit choice is influenced by the availability of autologous vein, degree of stability of the patient at the point in the procedure when reconstruction is required, and by size match. Although saphenous vein is an excellent material for patch angioplasty, it is not an ideal conduit for PV/SMV reconstruction owing to size mismatch.[18]

Concomitant splenic vein ligation may be necessary depending on the method and extent of reconstruction required. When lateral venorrhaphy was performed, splenic vein ligation was required in 33% of patients in our series.[1] However, when primary end-to-end reconstruction was performed, splenic vein ligation was required in 78% in our series.[1] When interposition grafting was performed at or above the level of the splenic vein, splenic vein reimplantation was not performed and the splenic vein was ligated.[1]

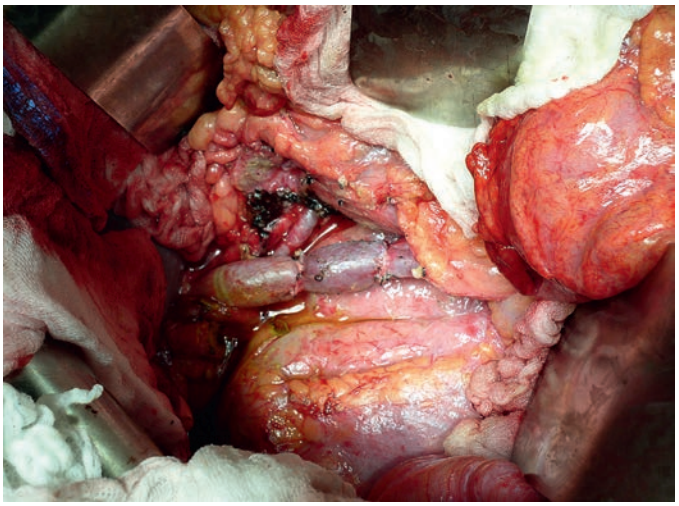

Figure 167.3 Intraoperative photograph demonstrating a portal vein reconstruction utilizing an internal jugular vein interposition graft.

Perioperative Outcomes

Variable rates of thrombosis of the PV/SMV reconstruction of 0% to 17% have been reported in several small retrospective studies examining this procedure.[15,20-25] PV/SMV thrombosis occurs with increasing incidence over time postoperatively in patients undergoing PV reconstruction. In the Johns Hopkins series, routine anticoagulation was not used following PV/SMV resection/reconstruction. Thrombosis developed in 13.3% of patients undergoing PV/SMV reconstruction with follow-up exceeding 1 year. Risk factors for portal vein thrombosis included preoperative chemotherapy, preoperative radiation therapy, long operative time, and use of a prosthetic interposition graft for reconstruction.[1] Similarly, use of prosthetic graft for reconstruction correlated with worse survival at 1 year postoperatively in this series.[1] Whereas other series support the use of ePTFE interposition grafts for PV/SMV reconstruction, the reported graft patency rate of 76% at 14 months is inferior with this modality.[19] PV/SMV thrombosis is associated with the development of ascites.[1,19]

Infectious complications arising from placement of synthetic grafts in the contaminated surgical field associated with pancreatectomy are surprisingly rare. No infectious complications were reported in a series of 33 patients in whom PV/SMV reconstruction was achieved using ePTFE interposition grafts.[19] Anecdotally described techniques employed to prevent ePTFE graft infection include perioperative administration of parenteral antibiotics, graft treatment with antibiotic solution, minimizing enteric and biliary spillage, omental wrapping, and irrigation with antibiotic-impregnated solutions.[19]

As already described, ligation of the splenic vein may be required during PV/SMV reconstruction, particularly when end-to-end reconstruction and interposition grafting are performed. Splenic vein ligation may rarely result in sinistral hypertension with concomitant esophagitis and/or gastritis and gastrointestinal bleeding. This rare complication occurred in only 3.8% of patients undergoing splenic vein ligation in our series.[1]

Long-Term Outcomes

Long-term outcomes in patients undergoing PV/SMV reconstruction are limited primarily by the natural history of pancreatic cancer rather than complications resulting specifically from the method of reconstruction. Although PV/SMV reconstruction has been demonstrated to improve overall survival in selected patients in whom no residual tumor is present and with adjunctive venous resection, the overall survival in this patient population remains poor. In the Johns Hopkins series, patients undergoing PV/SMV reconstruction had a medial survival of 15.5 months.[1] Development of PV/SMV thrombosis did not affect overall survival. Moreover, the method of reconstruction (primary repair, interposition vein graft, interposition prosthetic graft, and patch angioplasty) was not associated with a difference in overall survival, and similar findings have been reported elsewhere.[2,3]

When there is apparent tumor involvement of the PV/SMV upon gross assessment in the operating room, between 25% and 50% of these patients are found to have only a desmoplastic reaction at the interface with the PV/SMV without tumor cell infiltration.[4,21] Patients with tumor infiltration of the PV/SMV have worse survival compared with those with only a desmoplastic reaction at the venous interface.[5] Unfortunately there is no reliable method for differentiating these patients intraoperatively. Therefore PV/SMV resection is currently the accepted treatment of choice for patients with pancreatic cancer with PV/SMV involvement in whom an R0 (complete resection) can be otherwise achieved.

Ascites may develop postoperatively following pancreatic resection as well as PV/SMV reconstruction. The pathogenesis of ascites in these patients is commonly from disease progression in the form of tumor recurrence at the porta hepatis, from PV/SMV thrombosis, or from a combination of these. In our series from the Johns Hopkins Hospital, PV/SMV thrombosis was a risk factor for the development of ascites, although a significant proportion of these patients had recurrence of tumor on follow-up imaging.[1]

INFERIOR VENA CAVA RECONSTRUCTION

The inferior vena cava (IVC) rarely develops primary malignancies. More commonly the IVC may become involved secondarily with malignant tumors originating from the retroperitoneum, kidneys, adrenal glands, liver, and gastrointestinal organs. Whereas surgical resection of many tumors presenting in advanced stages may not be possible, IVC resection and reconstruction can be performed safely in selected candidates and may provide the only opportunity for cure of many of these malignancies. A significant proportion of these patients present with unresectable disease or have a poor performance status, precluding safe IVC resection and reconstruction. Surgical management of these patients is coordinated in collaboration with the medical and surgical oncologists managing their care. There are limited data evaluating outcomes following IVC resection and reconstruction; the existing literature is limited to retrospective series.[26-29] However, this technique is gaining increasing support due to its established safety, success, and ease of execution, particularly with the refinement of venovenous bypass and other extracorporeal techniques of circulatory support.

Tumor Types

Malignancies affecting the IVC may be categorized as primary or secondary. Primary IVC malignancies are extremely rare and will typically be encountered only in tertiary referral centers. Secondary malignancies involving the IVC are more common. These include a variety of renal, adrenal, retroperitoneal, abdominal, and hepatic tumors that may involve the IVC directly or with tumor thrombus. IVC resection and reconstruction may be required for complete tumor clearance in many of these conditions. Although a detailed discussion of indications for surgical resection of these various tumors is beyond the scope of this chapter, several of the more commonly encountered tumors affecting the IVC and requiring concomitant resection and reconstruction are discussed briefly in the following paragraphs.

Primary leiomyosarcoma of the IVC is an exceedingly rare condition. Fewer than 400 cases of resection of this tumor have been reported worldwide. The IVC is the most common blood vessel to be affected by vascular leiomyosarcoma and is the source of more than 50% of cases.[30,31] The mainstay of treatment is complete surgical resection, as this is the only opportunity for cure of the disease and incomplete resection is associated with poor prognosis, as this tumor responds poorly to other forms of therapy.[32] The goal of surgical resection is therefore to achieve negative margins, which has been demonstrated to improve survival.[33] Resection may require en bloc removal of the IVC with neighboring organs, commonly the kidney, adrenal gland, or gallbladder.[26,34] Long-term survival is possible but only with tumor resection.

A host of other retroperitoneal, renal, adrenal, hepatic, and abdominal tumors can secondarily involve the IVC and require concomitant IVC resection and reconstruction. In general, when the IVC is involved, these tumors require complete resection of both the tumor and the involved IVC. Renal cell carcinoma (RCC) is one such tumor that requires surgical resection for cure. In 2% to 16% of cases of RCC, tumor may spread from the lumen of the renal vein into the IVC, a condition termed tumor thrombus.[26-29] Other genitourinary tumors include transitional cell carcinoma and metastatic seminoma.[35] Adrenal tumors include adrenal lymphoma, malignant pheochromocytoma, and adrenal paragangliomas.[18] Liver tumors include hepatocellular carcinoma,[26] cholangiocarcinoma,[26] and metastatic

tumors to the liver, particularly metastatic colon cancer.[26] Other retroperitoneal tumors include liposarcoma, germ cell tumor, malignant fibrous histiocytoma, benign retroperitoneal neurofibroma, recurrent benign intravascular leiomyomatosis, Wilms tumor, teratoma, lymphadenopathy from metastatic melanoma, and duodenal carcinoma.[35,36] Successful IVC resection and reconstruction has been described for all of these tumors.

Clinical Presentation and Evaluation

The workup of patients presenting with malignancies involving the IVC requires a multidisciplinary approach between medical oncologists, surgical oncologists, and vascular surgeons managing their care.[26] Preoperative imaging using CT scanning with intravenous contrast must be performed to establish the presence or absence of distant metastases, the local resectability of the tumor, the degree of IVC involvement, and the presence of absence of IVC obstruction.[26] Particular attention should be paid to the vascular anatomy of the IVC, especially its tributaries and branches, including bilateral renal veins, hepatic veins and their confluence, as well as lumbar and gonadal veins. To this end, CT scans should be performed using arterial and venous phases for purposes of planning surgical reconstruction. Patients may present with chronic IVC obstruction; if so, they typically have well-developed venous collaterals. Imaging modalities employed to this end include a combination of chest roentgenography, CT, magnetic resonance imaging (MRI), and possibly vena cavography when other modalities are indeterminate. In patients with tumor thrombus from RCC, MRI has a high sensitivity for detection of IVC wall invasion and may assist in preoperative planning in these patients.[37]

Intracaval extension of tumor thrombus is present upon diagnosis in up to 16% of patients with renal cell carcinoma, and 1% have tumor thrombus extending to the right atrium.[38,39] The Neves and Zincke classification has been widely utilized to establish the extent of tumor thrombus present (Figs. 167.4 to 167.6).[27] In this scheme, the extent of tumor thrombus is classified according to its most cephalad location. Level I tumor thrombus extends into the IVC less than 2 cm from the ostium of the left renal vein (see Fig. 167.4). Level II tumor thrombus extends into the infrahepatic IVC more than 2 cm above the renal vein (see Fig. 167.5). Level III tumor thrombus extends into the retrohepatic IVC (Fig. 167.7). Level IV tumor thrombus extends into the supradiaphragmatic IVC to involve the right atrium. Patients presenting with tumor thrombus benefit from intraoperative transesophageal echocardiography in order to obtain an accurate assessment of the extent of tumor thrombus present at the time of operation, as tumor thrombus may have progressed since the time of preoperative imaging.[40]

Surgical Approach

The surgical approach for IVC resection is dictated by the location of the tumor and the degree of dissection required for complete vascular control of the IVC. Many cases can be approached through a midline laparotomy; this is the preferred approach if concurrent sternotomy is required for cardiopulmonary bypass (CPB). Alternatively, a chevron incision may be used. If CPB or circulatory arrest is required or if there is tumor thrombus extending to the right atrium, sternotomy or thoracotomy is performed concomitantly. If extensive dissection of the vena cava is required—for example, in the case of a tumor involving the retrohepatic IVC—a right thoracoabdominal approach through the seventh, eighth, or ninth interspace may be preferable as it is allows better access to the retrohepatic and suprahepatic IVC.[26,41]

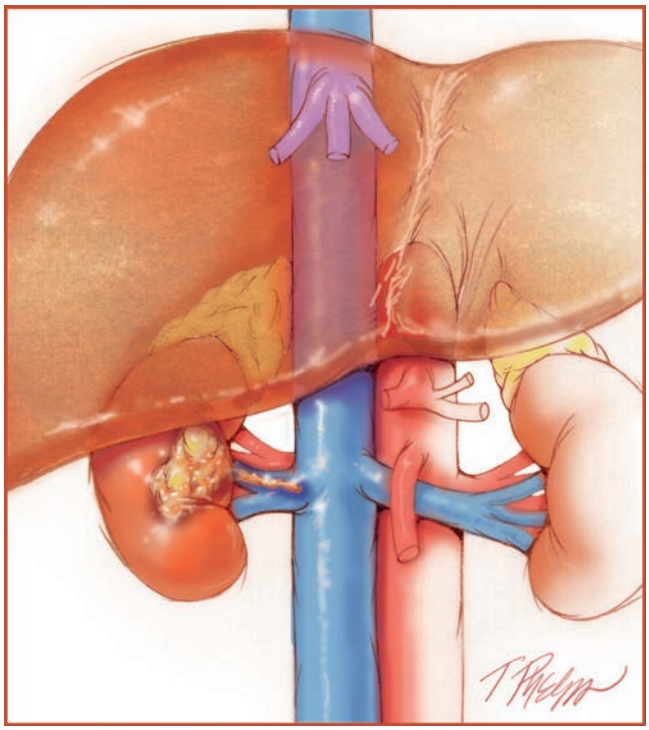

Figure 167.4 Level I Tumor Thrombus. By the Neves and Zincke classification indicating cephalad extent of inferior vena cava tumor thrombus, a level I tumor thrombus is confined to less than 2 cm above the left renal vein.

Upon entry into the peritoneal space, a thorough intra-abdominal exploration is conducted to assess for the presence of regional lymph node or peritoneal metastatic disease. Intraoperative ultrasonography may be employed to assess the relationship of tumor to major vascular structures.[26] The tumor is dissected as extensively as possible prior to IVC resection. In the case of concomitant nephrectomy, it is preferable to complete all portions of the nephrectomy except for renal vein ligation, as this structure is left in place until IVC resection. Vascular control of the IVC is achieved proximally and distally to the tumor, including all venous tributaries in the involved region. Vessel loops or umbilical tapes are placed around the IVC proximally and distally to the involved region. In the case of infrahepatic IVC involvement, control of the infrarenal IVC, renal veins, and suprarenal IVC is adequate. In the case of retrohepatic IVC involvement, total hepatic vascular isolation is necessary, which involves additional control of the suprahepatic IVC and porta hepatis to facilitate a Pringle maneuver. Total hepatic vascular isolation requires mobilization of the suspensory ligaments of the liver. Lumbar veins, if large, must also be controlled as these vessels can cause significant hemorrhage

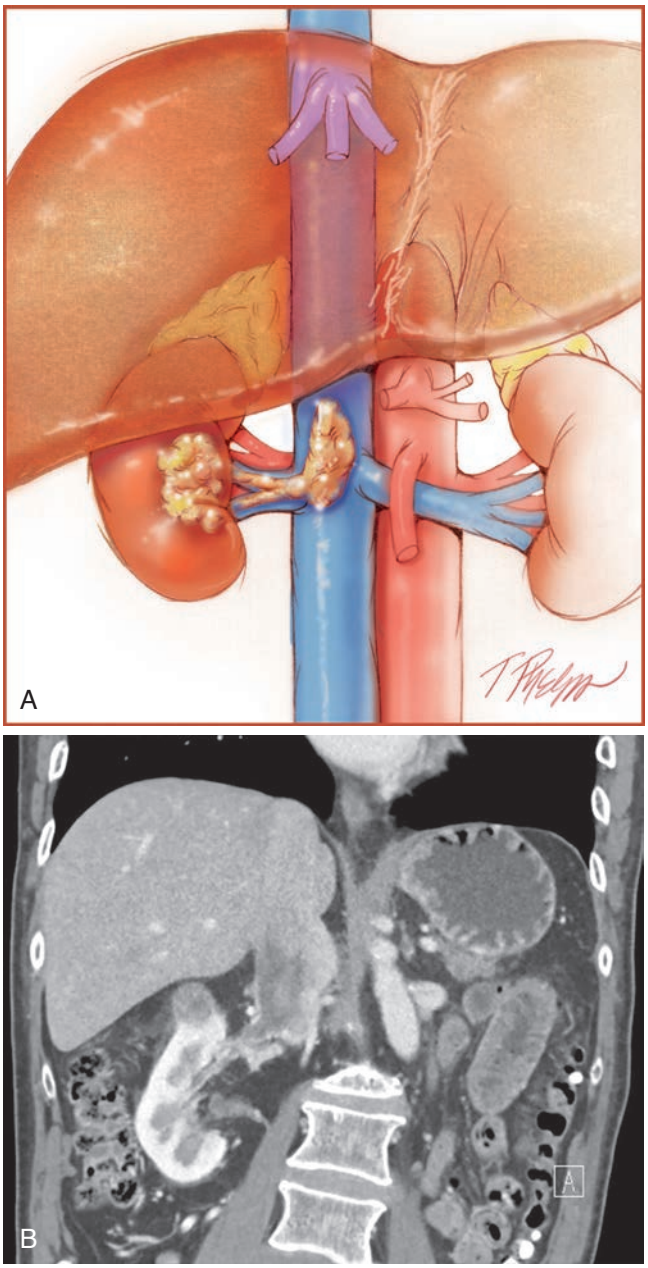

Figure 167.5 (A) Level II tumor thrombus. By the Neves and Zincke classification indicating cephalad extent of inferior vena cava tumor thrombus, level II thrombus extends more than 2 cm above the renal vein, but is still infrahepatic. (B) Representative CT scan of a patient with level II tumor thrombus.

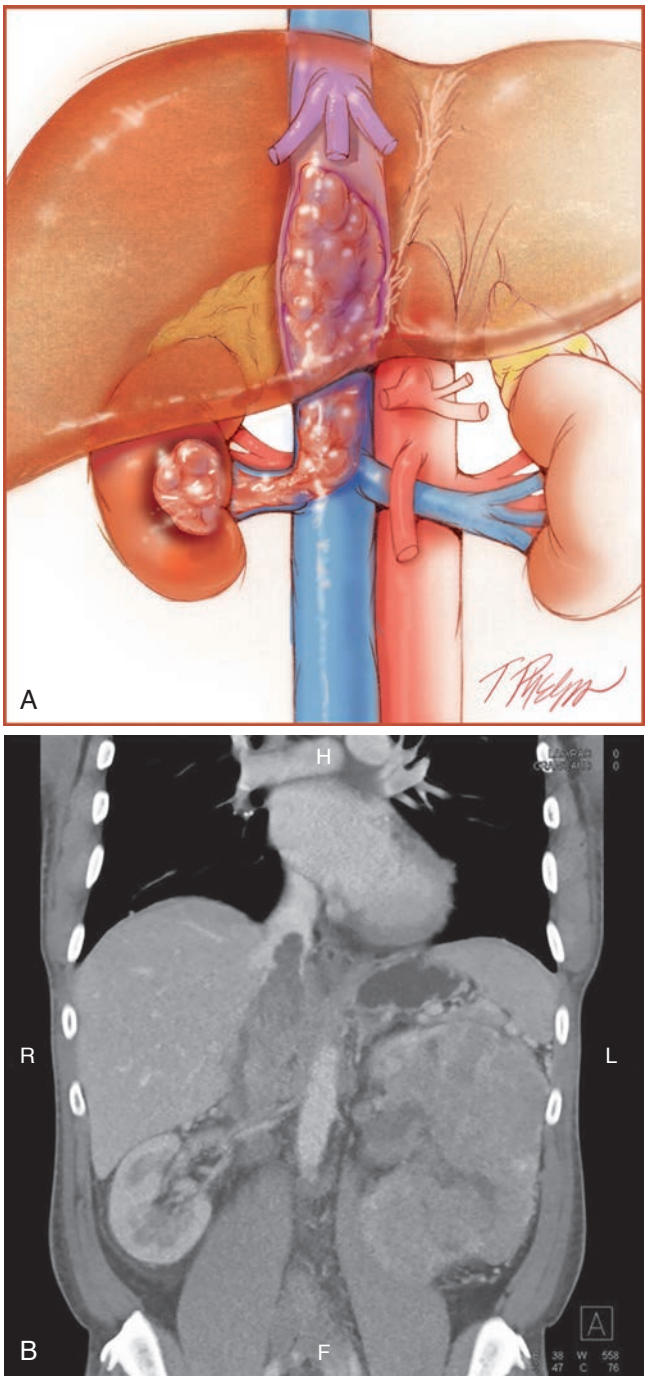

Figure 167.6 (A) Level III tumor thrombus. By the Neves and Zincke classification indicating cephalad extent of inferior vena cava tumor thrombus, level III tumor thrombus is retrohepatic but still remains below the diaphragm without extension into the right atrium. (B) Representative CT scan of a patient with level III tumor thrombus.

from venous backbleeding after IVC venotomy is performed. We routinely administer systemic anticoagulation intraoperatively using intravenous heparin (100 U/kg) administered prior to vascular cross-clamping and dosed to maintain an activated clotting time greater than 250 seconds until restoration of venous flow is achieved.[42,43]

Proper anesthetic management is vital for successful IVC resection and reconstruction. Prior to IVC interruption for resection and reconstruction, temporary IVC occlusion or "test clamping" should be undertaken as a means of assessing whether the profound decrease in venous return resulting from IVC clamping will be tolerated. Patients unable to tolerate test clamping may require more aggressive anesthetic support, including rapid administration of intravenous fluids, initiation of vasopressor support, and Trendelenburg positioning.[40,42] If IVC interruption is still not tolerated, the patient will likely benefit from extracorporeal support with venovenous bypass or CBP. Alternatively, temporary aortic cross-clamping can be performed. However, this maneuver should be minimized to

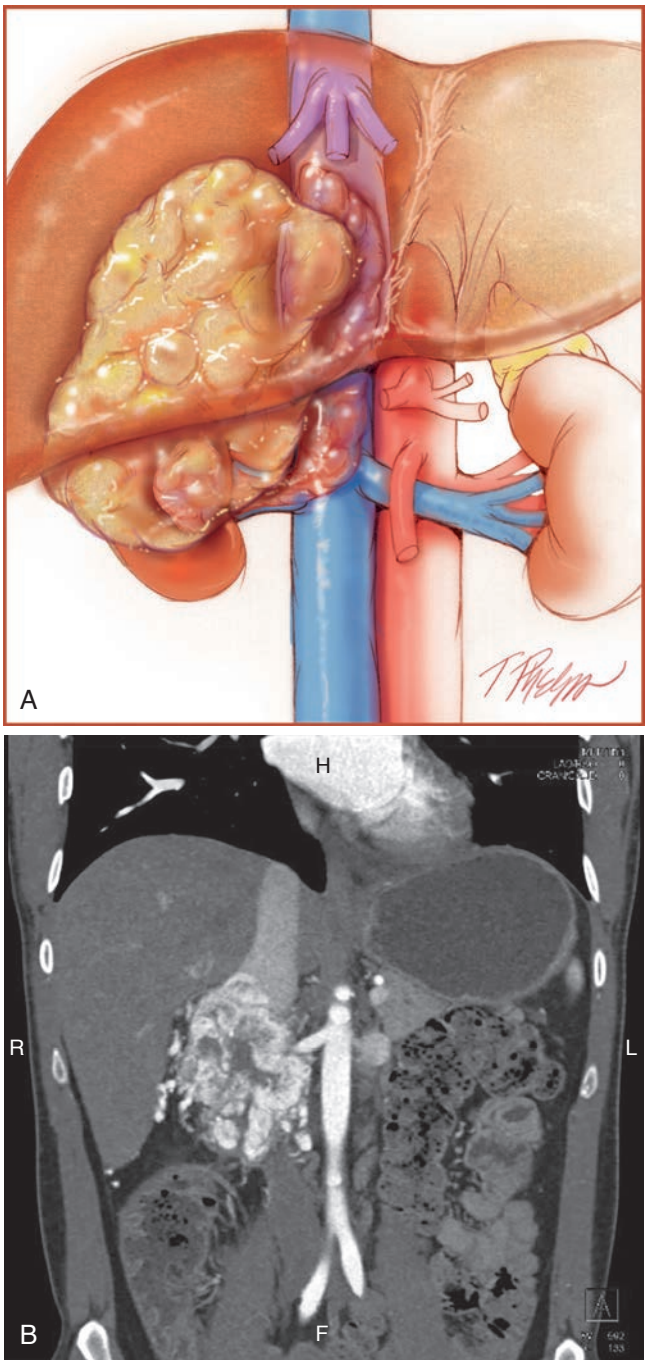

Figure 167.7 (A) Level III tumor thrombus in association with an extensive renal tumor invading the retrohepatic inferior vena cava (IVC), requiring graft replacement of the IVC. (B) Representative CT scan of a patient with adrenal tumor with invasion of the retrohepatic IVC.

30 minutes or less to prevent undue renal and end-organ ischemia; therefore, it may not be feasible during an extensive reconstruction.[44]

Methods of Inferior Vena Cava Reconstruction

The degree of IVC resection is dictated by the degree of tumor involvement of the IVC. In most circumstances, oncologic clearance of tumor requires en bloc resection with the involved portion of IVC. There are several options for reconstruction of the IVC involved by tumor. These include primary repair, patch angioplasty, interposition grafting, and ligation (Fig. 167.8). Primary IVC repair is possible when the IVC wall is partially resected, and primary repair would result in less than 50% narrowing of the vessel (see Fig. 167.8A).[40,42,43] IVC patch angioplasty is indicated when the IVC wall is partially resected, and primary repair would result in greater than 50% narrowing of the vessel (see Fig. 167.8B).[40,42,43] Various materials have been described for patch closure and most commonly include bovine pericardium, but ePTFE and Dacron patch closure may be successfully utilized.[42] Interposition grafting is indicated when the IVC requires circumferential segmental resection (see Figs. 167.8C and 167.9A). Grafts described for use in interposition reconstruction include femoral vein,[26,45] aortic homograft,[46] cryopreserved vena cava,[47] and prosthetic grafts (Dacron and ePTFE). Prosthetic grafts are the most commonly employed type of graft for IVC reconstruction. Most authors preferentially utilize externally reinforced ringed ePTFE, as this widely available graft is theoretically protective against collapse by overlying abdominal viscera in the low-pressure venous system.[18,42,43,48-55] The graft is matched to the size of the recipient IVC, and grafts 14 to 20 mm in diameter are usually appropriate.[26,42,43] In cases of contamination of the operative field by bowel contents, it may be necessary to reconstruct the IVC utilizing autologous vein (saphenous, jugular, or femoral) assembled in a spiral fashion in order to achieve a conduit of adequate caliber to match the native IVC (see Figs. 167.8D and 167.9B).

Patients undergoing interposition grafting during IVC reconstruction may require reimplantation of the renal and/or hepatic veins. In the largest existing series of IVC interposition grafting, renal vein reimplantation was required in 24% of patients, and hepatic vein reimplantation was required in 2%.[56] Renal vein reimplantation, while perhaps unnecessary to achieve adequate renal function postoperatively, certainly enhances flow through the conduit, a factor beneficial in the prevention of graft thrombosis (see Fig. 167.9A). Additionally, intraoperative oliguria or anuria during renal vein clamping may be a harbinger of impending renal failure in the absence of renal vein implantation; if either of these events develops, it would argue for performing renal vein implantation.[49]

Some authors have advocated creation of an adjunctive arteriovenous (AV) fistula in order to augment patency of the IVC reconstruction. Although data in this area are particularly lacking, AV fistula creation may augment patency in select circumstances. This includes patients undergoing reconstruction of the infrarenal IVC due to the relatively lower flow compared with suprarenal reconstructions.[26,41,49,57] An AV fistula may also enhance the patency of long grafts (e.g., in multilevel IVC replacement) or in small-diameter grafts equal to or less than 16 mm in diameter.[26,58,59] An adjunctive AV fistula may be created between the remaining ipsilateral renal vessels, between the renal artery and gonadal vein, or between the superficial femoral artery and greater saphenous vein.[26,41]

Ligation of the IVC is another option for the management of patients presenting with tumors involving the IVC. This method of management should be avoided, if possible, as it is

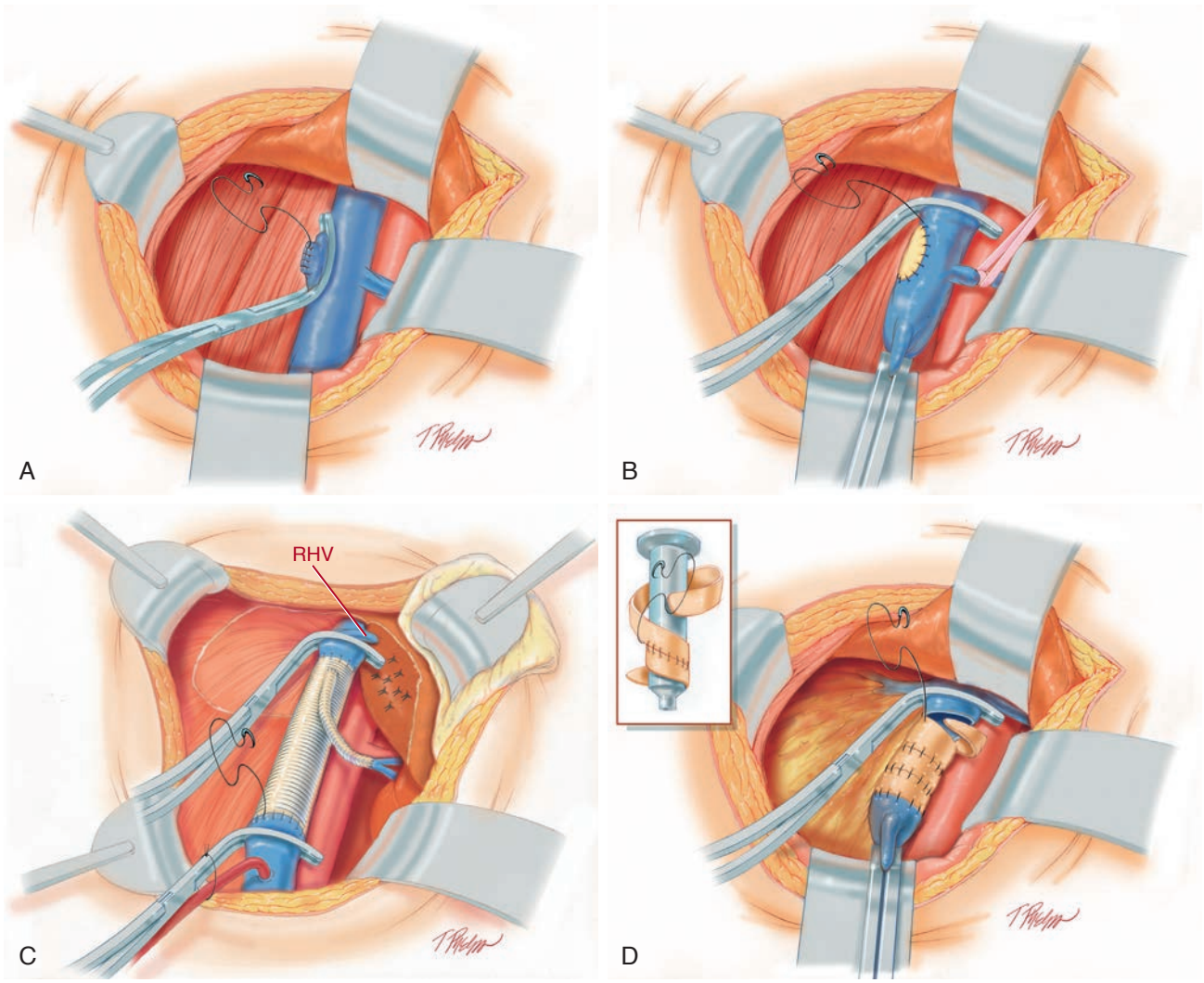

Figure 167.8 Methods of Inferior Vena Cava Reconstruction. (A) Primary repair. (B) Patch repair. (C) Graft reconstruction. (D) Spiral vein graft reconstruction. *RHV,* Right hepatic vein.

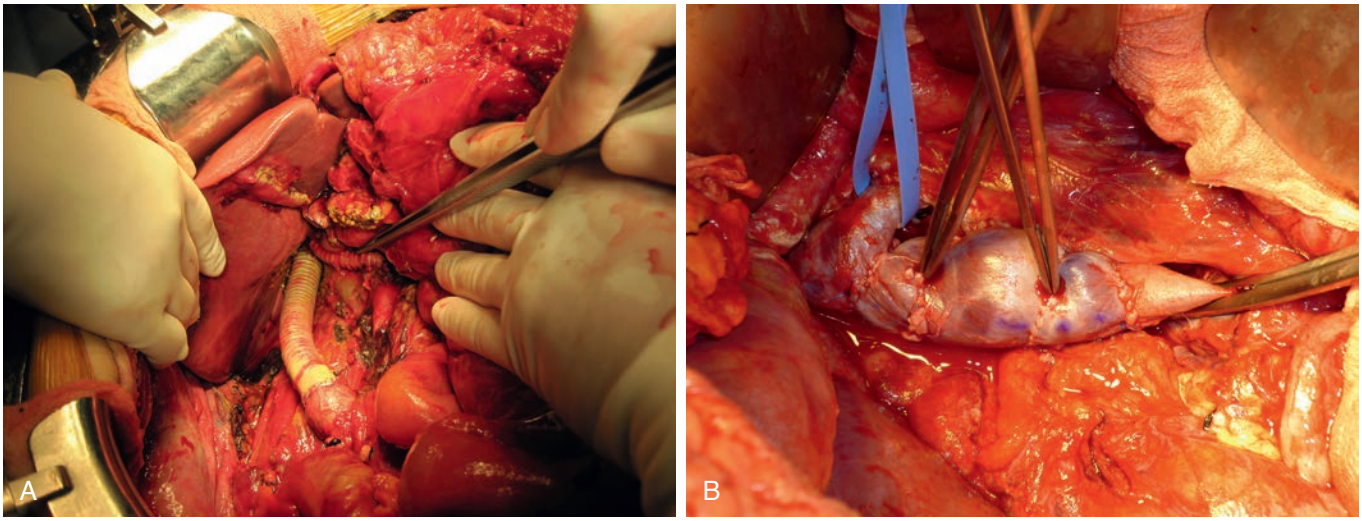

Figure 167.9 Intraoperative photographs of inferior vena cava reconstructions performed including (A) prosthetic interposition graft with reimplantation of left renal vein and (B) spiral vein reconstruction using an autologous vein graft.

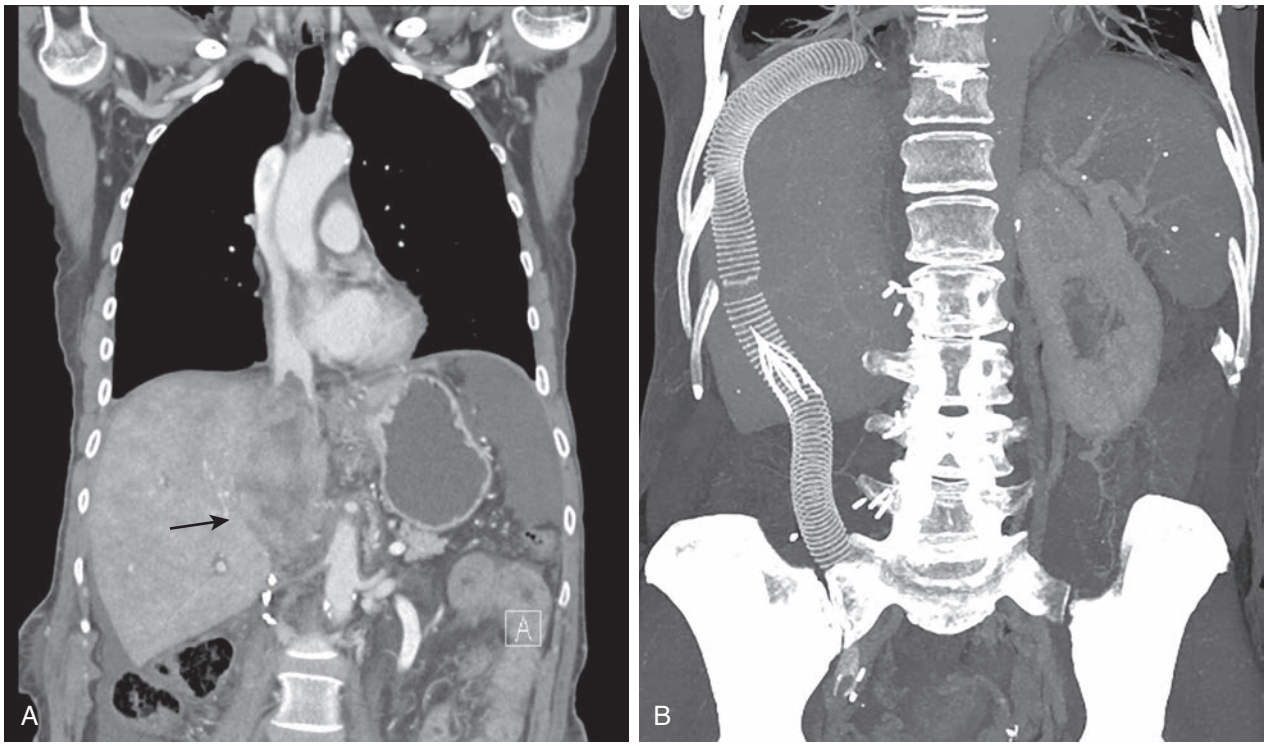

Figure 167.10 Palliative inferior vena cava (IVC) bypass may be utilized selectively in patients with unresectable tumors and/or tumor thrombus causing IVC obstruction. (A) CT scan of a patient with unresectable recurrent renal cell carcinoma involving the IVC, with tumor thrombus causing IVC obstruction *(arrow)* and resulting severe lower extremity edema. (B) This patient underwent a palliative bypass from the right common iliac vein to the suprahepatic IVC using a ringed polytetrafluoroethylene graft with an IVC filter placed within the bypass conduit for thromboembolic protection.

associated with significant morbidity.[41] Acute renal failure and severe postoperative lower extremity edema develop in up to 50% of patients undergoing IVC ligation,[33,41,60] and lower extremity DVT have been reported to occur in close to one-third of patients.[61] Although it is efficient and technically simple, IVC ligation is best reserved for patients with chronic IVC obstruction with the presence of well-developed collaterals who cannot tolerate reconstruction concomitant with tumor extirpation and IVC resection.[18,62] Even in patients with well-developed collaterals whose venous return is compensated preoperatively without venous hypertension, the extensive retroperitoneal dissection associated with removal of these neoplasms significantly disrupts existing venous collaterals and predisposes to postoperative venous hypertension.[36,49] Therefore when IVC ligation is performed, care must be taken to preserve these collaterals.[45] While some series report IVC ligation as a routine method of managing IVC tumor involvement,[60] it is our experience and that of others that IVC ligation is rarely if ever necessary and that safe IVC reconstruction is routinely possible, and indeed preferable, in most circumstances.[18,26,35,36,42,43,63,64]

Improvement in chemotherapeutic and biologic antitumor agents has extended the life expectancy of many patients with unresectable tumors and indolent progression of disease. Palliative IVC bypass is an additional option for the management of select patients with disabling lower extremity edema due to IVC occlusion in whom the primary tumor and/or tumor thrombus are unresectable. Palliative IVC bypass may be safely performed with excellent long-term results (Fig. 167.10). This procedure is best performed via right thoracoabdominal exposure through the seventh, eighth, or ninth intercostal space. The optimal choice of bypass conduit is ringed ePTFE measuring 12 to 18 mm. The proximal anastomosis may be constructed at the most cephalad extent of patent iliac vein or IVC. The distal anastomosis is best constructed at the suprahepatic IVC; it may also be constructed at the right atrium. In the latter circumstance, cardiopulmonary bypass must be instituted. Placement of an IVC filter in the bypass conduit is recommended in order to prevent pulmonary embolism.[42]

Adjunctive Extracorporeal Bypass Techniques

Venovenous bypass (VVB) is a necessary adjunct during IVC resection and reconstruction in several circumstances. These include patients unable to tolerate IVC clamping due to tenuous cardiopulmonary status or old age, level III extension of tumor thrombus, complex multilevel IVC involvement, need for full graft replacement, and those in whom an adequate oncologic resection cannot be achieved without the institution of bypass support.[42,48] The technique of VVB includes placement of a 24-Fr arterial perfusion cannula for VVB outflow. The infrarenal IVC may be cannulated directly or the femoral vein may be isolated via a groin cutdown to allow for cannula placement

outside the operative field. The cannula is then connected to the bypass circuit, which consists of a perfusion pump. Inflow to the circuit is via a "Y" connector to two cordis cannula placed into the right internal jugular (IJ) vein. VVB is then initiated and performed in a normothermic fashion with flow rates maintained at 750 to 1500 mL/min to support a mean systemic perfusion pressure of 60 to 80 mm Hg. At cessation of bypass, the inflow cannula is removed with venous repair as appropriate and the outflow tubing is disconnected from the IJ cordis cannula.

The presence of level IV tumor thrombus requires CPB. To perform this, the superior vena cava (SVC), IVC, and ascending aorta are isolated. The ascending aorta and SVC are cannulated using intraoperative transesophageal echocardiographic guidance using a 19-Fr percutaneous venous cannula. CPB is commonly performed under mild hypothermia to 32°C. When deep hypothermic circulatory arrest (DHCA) is utilized, cooling to 25°C is typical. Arterial inflow is adjusted to maintain a perfusion pressure of 60 to 80 mm Hg.[42]

Perioperative Outcomes

The performance of IVC reconstruction and resection is inherently high risk for the development of venous thromboembolic (VTE) events, as the IVC is a low-pressure system with potential for stasis. Moreover, the presence of malignancy inherently increases the risk of hypercoagulability. Perioperative VTE developed in 22% of patients in our series from the Johns Hopkins Hospital; 9% of patients developed isolated DVT and 12% developed pulmonary embolism (PE).[43] The median time to diagnosis of VTE was 6 days postoperatively in our series. Risk factors for VTE in our series were large tumor size, reimplantation of one or more renal veins, and blood product transfusion. Prosthetic graft reconstruction, preoperative IVC thrombus, and history of VTE were not associated with the occurrence of postoperative VTE. Of note, the VTE events in our series did not result in fatality, and only half were symptomatic. Intraoperative pulmonary embolism during IVC reconstruction has also been described and may require emergent pulmonary embolectomy.[65]

In our experience with IVC resection and reconstruction for malignancy, patients were given postoperative prophylaxis for deep venous thrombosis (DVT) with heparin administered subcutaneously (5000 U) every 8 hours. Antiplatelet drugs were administered if patients were taking them preoperatively. It is not our practice to administer postoperative systemic anticoagulation unless patients are diagnosed with VTE. Some authors advocate the use of selective postoperative anticoagulation in patients with a history of VTE or atrial fibrillation.[35] Others advocate routine postoperative anticoagulation with warfarin, given a high reported incidence of postoperative thrombosis of the IVC reconstruction. The Mayo Clinic group uses routine anticoagulation in patients undergoing IVC reconstruction with prosthetic graft interposition; they report a somewhat lower rate of VTE events, including a 7% rate of graft thrombosis and 3% rate of DVT.[26] Although VTE rates are lower with the routine use of systemic postoperative anticoagulation, the rate of postoperative bleeding is higher.[26,63] Even when postoperative anticoagulation is routinely administered, up to 25% of patients have been reported to develop thrombosis of the graft or of associated iliac vein graft limbs in some series.[41] Therefore it is our practice not to administer postoperative anticoagulation unless VTE is diagnosed.[42,43]

Use of adjunctive bypass support, including VVB, CPD, and DHCA, involves greater surgical complexity and therefore is associated with an increased rate of perioperative morbidity but not perioperative mortality. Utilization of bypass support is associated with increased bleeding and subsequent requirement for perioperative transfusion, coagulopathy, prolonged operative time, longer postoperative ICU length of stay (LOS), and overall hospital LOS.[29,38,42,66,67] Whereas utilization of bypass support is associated with an overall increased risk of perioperative complications, its use does not have an effect on long-term outcomes or survival.[42]

Long-Term Outcomes

Circumferential IVC resection with placement of a prosthetic interposition graft is associated with good long-term patency in several series. Patency rates of 80% to 100% at 9 months to 5 years have been reported in multiple small series, and these results were achieved utilizing postoperative anticoagulation.[26,35,48,68] In a large multi-institutional series involving the placement of prosthetic interposition grafts for IVC reconstruction, outcomes in 102 patients over a mean follow-up of 56 months were reported. These authors report excellent IVC graft patency rates of 95% at 1 year, 92% at 3 years, and 92% at 5 years.[56] Graft infection and tumor recurrence have been demonstrated to correlate with graft thrombosis.[26] Graft infection with subsequent thrombosis has been reported in several series but is still relatively rare; this event occurred in 1 of 14 patients in the Johns Hopkins series,[42] 1 of 27 patients in the UCLA series[35] and 1 of 16 patients in a series from Heidelberg.[68] Reported risk factors for IVC graft infection include duodenal leak, bile leak, and perforated diverticulitis.[26,68]

SUMMARY AND CONCLUSIONS

The PV, SMV, and IVC may be safely and expeditiously resected as an adjunct to tumor resection in appropriate surgical candidates. The safety and feasibility of these techniques have been well established on the basis of institutional experiences from multiple centers. PV/SMV resection is now a routine intraoperative technique to facilitate R0 resection for pancreatic tumors. Indeed, multiple lines of evidence are establishing that this technique facilitates a higher rate of complete resection without increasing the morbidity and mortality of pancreatectomy. Likewise, IVC resection provides the only chance for cure of a variety of retroperitoneal, renal, adrenal, hepatic, and abdominal malignancies. The best data suggest that this technique does not negatively influence survival or mortality in the long term. On the contrary, IVC resection may also provide the only chance for cure of a whole host of malignancies, and without employing this technique these tumors would otherwise

be unresectable. A variety of adjunctive bypass techniques increase the technical feasibility of IVC resection without negatively affecting long-term results. In both of these areas, future prospective or multi-institutional retrospective studies will elucidate the most successful methods of reconstruction and postoperative management, including the ideal method of anticoagulation for optimum graft patency.

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Bower TC, Mendes BC, Toomey BJ, et al. Outcomes of 102 patients treated with segmental inferior vena cava resection and graft replacement for malignant disease. *J Vasc Surg*. 2014;6(suppl):36S.

The Mayo Clinic series is a valuable review of their results with predominantly clamp-and-sew techniques and can be compared to more aggressive techniques.

Chu CK, Farnell MB, Nguyen JH, et al. Prosthetic graft reconstruction after portal vein resection in pancreaticoduodenectomy: a multicenter analysis. *J Am Coll Surg*. 2010;211(3):316–324.

Prosthetic graft reconstruction of during pancreatic surgery is expeditious, but is thought to be inferior to autologous reconstructions. This paper examines the question across institutions to provide valuable insight.

Etkin Y, Foley PJ, Wang GJ, et al. Successful venous repair and reconstruction for oncologic resections. *J Vasc Surg Venous Lymphat Disord*. 2016;4(1):57–63.

The authors describe a series of venous reconstructions across multiple venous territories.

Glebova NO, Hicks CW, Piazza KM, Lum YW, Abularrage CJ, Black JH 3rd. Outcomes of bypass support use during inferior vena cava resection and reconstruction. *Ann Vasc Surg*. 2016;30:12–21.

Use of bypass adjuncts for resection of caval tumors is controversial. This study identifies risks associated with operative strategies that surgeons can mitigate.

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This article describes the largest single institution series of pancreatic resections with portal venous reconstruction.

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This report describes technical pearls gleaned from the single institution experience at Oregon Health Sciences.

Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg*. 2004;8(8):935–949, discussion 49–50.

As vascular invasion may signal a risk for reduced life expectancy, this study examines the pathologic status of the margins on the vessels to elucidate the need for vascular reconstruction.

A complete reference list can be found online at www.expertconsult.com.

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168 CHAPTER

Lymphedema: Evaluation and Decision Making

STANLEY G. ROCKSON

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Lymphedema is the term used to characterize the various pathologic conditions in which there is progressive accumulation of protein-enriched interstitial fluid. Collectively, these forms of edema arise as a consequence of relative impairment of lymphatic vascular function. Lymphatic vascular insufficiency can result from either primary or acquired (secondary) lymphatic defects. Cryptogenic forms of lymphedema are often presumed to represent primary lymphatic dysfunction. Although impaired lymphatic function can manifest as visceral pathology, particularly in the respiratory or gastrointestinal organs, it is upper or lower extremity edema, with or without visceral involvement, that is the most common presentation of lymphatic impairment.

PATHOPHYSIOLOGY

Impairment of lymphatic outflow leads to the pathologic consequences of lymphedema. In high-input failure, such as that which occurs in venous edema, increased pressure at the venous end of the capillary leads to the accentuated production of interstitial fluid through increased capillary filtration; if the production of lymph exceeds the maximal transport capacity of the lymphatic conduits, lymphedema will ensue, even if these structures are anatomically and functionally normal. By contrast, low-output failure ensues when some pathologic condition compromises lymphatic flow. Lymph stasis can accompany lymphatic hypoplasia or aplasia, functional

insufficiency or anatomic absence of lymphatic valves, or, conceivably, blunted lymphatic contractility.[1]

Because the lymphatic circulation is responsible for the return of interstitial fluid and protein to the central circulation, lymph stasis creates an accumulation of protein and cellular metabolites in the extracellular space; with the ensuing increase in tissue colloid osmotic pressure, there is water accumulation and elevation of the interstitial hydraulic pressure (see Chapter 10).

Impaired lymphatic transport leads to the accumulation of hyaluronan and other glycoproteins within the extracellular space. This is followed by a secondary increase in the fibroblast, keratinocyte, and adipocyte content of the affected tissues along with the accumulation of mononuclear cells, including macrophages. Ultimately, an increase in collagen deposition occurs, typically accompanied by an overgrowth of connective tissue and adipose elements in the skin and subcutaneous tissue.[2] Although the contributory mechanisms are still not well understood, there is a tendency for these processes to lead to progressive subcutaneous fibrosis.

CLASSIFICATION AND STAGING

Standard clinical classifications distinguish lymphedema on the basis of cause (primary vs. secondary). Primary lymphedema is further classified on the basis of genetics (familial vs. sporadic) and time of onset (congenital, praecox, tarda).[3-5] Although these systems are useful for categorizing lymphedema, they do not address the clinical severity of the disease and are usually not relevant to therapy. More recent classifications focus on the clinical stage of lymphedema, or emphasize the causal anatomic or functional lymphatic abnormality, in an attempt to predict natural history and to identify the best therapeutic approach.[1,6,7]

Primary Lymphedema

The prevalence of the heritable causes of primary lymphedema is difficult to ascertain, and estimates vary substantially. Primary lymphedema is thought to occur in approximately 1 of every 6000 to 10,000 live births. On the basis of data collected by the Rochester group study, it affects 1.15 per 100,000 persons younger than 20 years.[8] Females are affected 2- to 10-fold more commonly than males, and the incidence peaks between the ages of 12 and 16 years.[6,9]

Of 125 patients with primary lymphedema treated at the Mayo Clinic, 97 (78%) were female and 28 (22%) were male, yielding a female-to-male ratio of 3.5:1.[10] The ratio of unilateral to bilateral lymphedema was 3:1. Congenital lymphedema occurred more frequently in males than in females. In these patients, the edema was usually bilateral and involved the entire lower extremity. In contrast, the typical patient with lymphedema praecox was female and had unilateral involvement, with swelling usually extending only to the knee.

Primary lymphedema represents a heterogeneous group of disorders; therefore, its classification schemes are numerous. Affected individuals can be classified by age at onset, morphology, or clinical setting.

Classification by Age at Onset and Inheritance

The term *congenital* is applied when lymphedema is present at birth or is recognized within the first year of life. *Lymphedema praecox* most commonly appears at the onset of puberty, but it may be delayed until the third decade of life. *Lymphedema tarda* typically begins after the age of 35 years.

Congenital. Congenital lymphedema can occur in a sporadic fashion; however, when clusters of cases occur in families, an autosomal dominant pattern of transmission is frequently observed.[11] In addition to isolated causal mutations, there is a strong association between intrauterine and congenital lymphatic dysfunction and the presence of chromosomal abnormalities, including Turner's syndrome, Klinefelter's syndrome, and trisomy 21, among others. In congenital lymphedema, the swelling can involve only a single lower extremity, but edema of multiple limbs, the genitalia, and even the face can be seen. Bilateral leg swelling and involvement of the entire lower extremity are more likely in congenital cases than in other forms of primary lymphedema.[10]

Lymphedema Praecox. Lymphedema praecox is the most common form of primary lymphedema, accounting for up to 94% of cases in large series. The name *Meige's disease* has historically been reserved for a specific familial form of lymphedema and typical onset at puberty. Lymphedema praecox displays a marked gender imbalance, with an estimated 10:1 female-to-male prevalence.[2] The edema is usually unilateral, and is limited to the foot and calf in the majority of patients.[10] Estrogenic hormones may play a role in the pathogenesis of this form of primary lymphedema.[10]

Lymphedema Tarda. Lymphedema tarda is relatively less common. Appearing after the age of 35 years, it typically accounts for an estimated 10% of cases of primary lymphedema.

Classification by Morphology

It has been suggested that a morphologic classification of primary lymphedema might provide more useful prognostic information than classification by age at onset (Fig. 168.1).[2] This alternative classification scheme relies on an anatomic description of the lymphatic vasculature.[3,11]

Aplasia. In aplasia, no collecting vessels can be identified.

Hypoplasia. In hypoplasia, a diminished number of vessels are seen.

Numerical Hyperplasia. In numerical hyperplasia (as defined by Kinmonth[3]), an increased number of vessels are seen.

Hyperplasia. In addition to an increase in number, the vessels have valvular incompetence and display tortuosity and dilation (megalymphatics, lymphangiectasia). Megalymphatics and lymphatic hyperplasia are less common than hypoplasia or aplasia. This pattern demonstrates a male predominance. These patients most often have unilateral edema involving the entire lower extremity. Cutaneous angiomas and chylous reflux also can be seen (Fig. 168.2). Megalymphatics are associated with a greater extent of involvement and a worse prognosis.

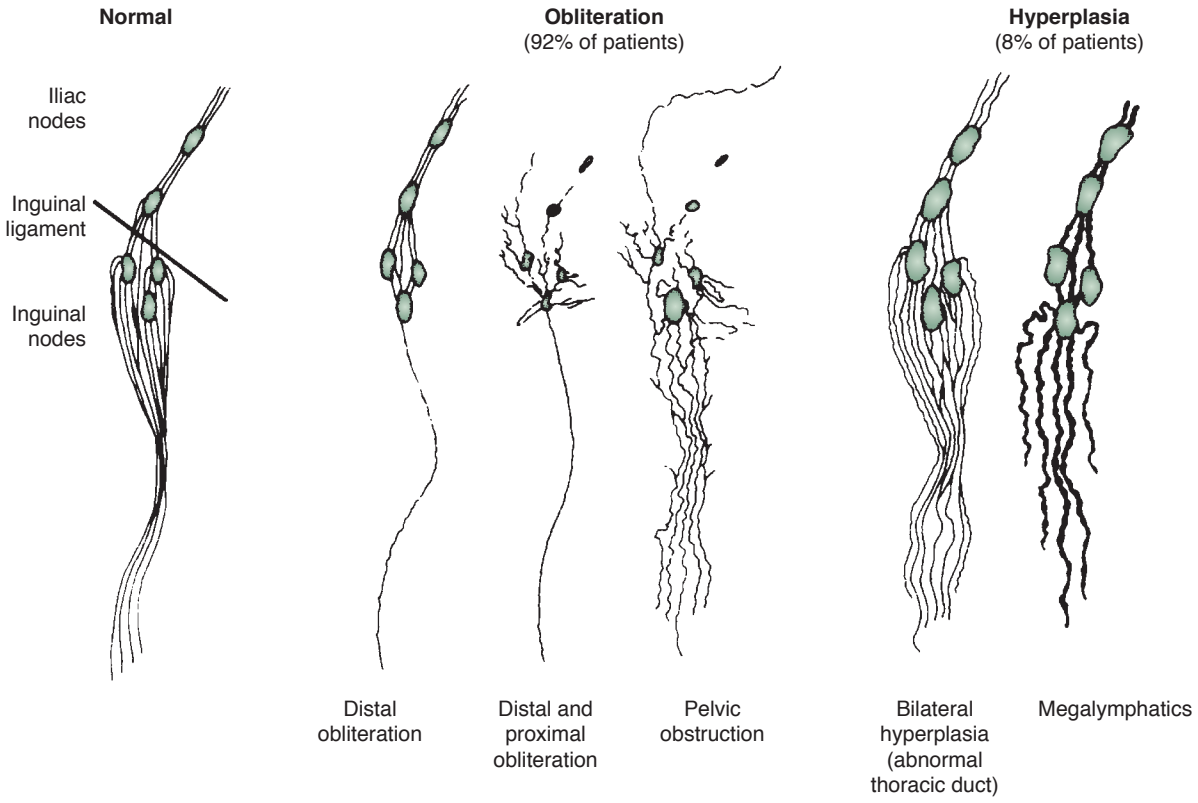

Figure 168.1 Lymphangiographic patterns of lymphatic morphology in a normal lower limb and in patients with different types of primary lymphedema. Obliteration of the lymphatic pathways may be due to aplasia, hypoplasia, or obstruction of the lymphatic channels and nodes.

Figure 168.2 Primary lymphedema of the right leg caused by hyperplasia of the lymphatics and valvular incompetence. Mid-calf skin vesicles contain a milky fluid because of lymphangiectasia and reflux of chyle.

Classification by Anatomy

Aplasia and hypoplasia have a different natural history, depending on whether they involve the distal or proximal portion of the leg.

Distal Obstruction. Approximately one-third of all cases result from agenesis, hypoplasia, or obstruction of the distal lymphatic vessels, with relatively normal proximal vessels (see Fig. 168.1).[11] In these cases, the swelling is usually bilateral and mild, and females are affected much more frequently than males. The prognosis is good. In general, after the first year of symptoms, there is little extension in the same limb or to uninvolved extremities. Although the maximal extent of involvement is established early in the disease in about 40% of patients, the girth of the limb continues to increase. Distal hypoplasia or aplasia of the lymphatics most often correlates with the presence of bilateral peripheral edema of the lower extremities. Familial occurrence, female predominance, and indolent progression characterize this pattern of lymphatic disturbance.

Proximal Obstruction. In more than half the cases, the defect primarily involves obstruction of the proximal lymphatics or nodes, with an absence of distal lymphatic involvement. Pathologic studies reveal intranodal fibrosis.[12] In these cases, the swelling tends to be unilateral and severe; there may be a slight female predominance.[11] In patients with proximal involvement, the extent and degree of the abnormality are likely to

progress, potentially requiring surgical intervention. Initially, uninvolved distal lymphatic vessels may become obliterated over time. A minority of patients have a pattern of bilateral hyperplasia of the lymphatic channels. In these less common forms of primary lymphedema, there is a slight male predominance. When isolated proximal obstructive hypoplasia is observed, clinical involvement of the entire limb is more likely, with relentless worsening of edema.

Classification by Clinical Setting

Alternatively, primary lymphedema can be classified by abnormal phenotype or associated clinical anomalies.[13]

Inheritance. Although sporadic cases of primary lymphedema are more common,[11] there is a significant tendency for congenital lymphedema to cluster in families (Fig. 168.3). A familial predisposition for congenital lymphedema, ultimately determined to have an autosomal dominant form of inheritance with variable penetrance, was first described by Milroy in 1892.[14] He reported "hereditary edema" affecting 22 individuals in one family over six generations. Although Milroy studied not only congenital lymphedema but also the praecox and tarda variants of the syndrome that bears his name, lymphedema praecox is better known as Meige's disease.[15]

In general, congenital lymphedema with recessive forms of inheritance is less common than that with dominant forms of inheritance.[11,16,17] Nevertheless, the list of heritable lymphedema-associated syndromes is long and growing.[18,19] Primary lymphedema has been described in association with various forms of chromosomal aneuploidy, such as Turner's and Klinefelter's syndromes; with various dysmorphogenic genetic anomalies, such as Noonan's syndrome and neurofibromatosis; and with a variety of, as yet, unrelated disorders, such as yellow nail syndrome, intestinal lymphangiectasia, generalized lymphatic anomaly (formerly known as lymphangiomatosis), and arteriovenous malformation.[20-25] The association of lymphedema with vascular anomalies underscores the common developmental origin of the lymphatic and blood vasculature.

Associated Disorders. Numerous disorders are associated with heritable forms of lymphedema. Increasingly, these disorders have yielded to chromosomal mapping techniques. Lymphedema-cholestasis, or Aagenaes' syndrome, has been mapped to chromosome 15q.[26] In several family cohorts of Milroy's disease, it has been determined that the disorder reflects missense inactivating mutations in the tyrosine kinase domain of vascular endothelial growth factor receptor 3 (VEGFR-3),[27,28] thus suggesting the likelihood that this condition reflects an inherited defect in lymphatic vasculogenesis. Several additional lymphedema syndromes have recently lent themselves to successful genetic mapping.[7] Lymphedema-distichiasis, an autosomal dominant dysmorphic syndrome in which lymphedema presents in association with a supplementary row of eyelashes arising from the meibomian glands, has been linked to truncating mutations in the forkhead-related transcription factor FOXC2[29]; mutations in *FOXC2* have subsequently been associated with a wide variety of primary lymphedema presentations.[30] Similarly, a more unusual form of congenital lymphedema, hypotrichosis-lymphedema-telangiectasia, has been ascribed to both recessive and dominant inheritance of mutations in the transcription factor gene *SOX18*.[30] It is plausible that further elucidation of the molecular pathogenesis of these diseases linked to *FOXC2* and *SOX18* mutations will lead to enhanced insights into the mechanisms of normal and abnormal lymphatic development.

Secondary Lymphedema

Acquired (secondary) lymphedema is the most commonly encountered form of lymphatic dysfunction (Fig. 168.4). In the United States, iatrogenic causes predominate among the acquired forms of lymphedema owing to the common occurrence of lymphatic trauma after surgery or radiotherapy for cancer.[9,31]

Figure 168.3 (A) Adult patient with congenital lymphedema. In addition to the bilateral arm lymphedema depicted, she has edema of both legs and the face. (B) Upper extremities of this patient's 18-year-old son, who has a similar distribution of lymphedema. This is an example of Milroy's disease.

Figure 168.4 Chronic acquired lymphedema of the lower extremities. Note severe skin changes (A) and swelling of the foot (B) associated with squaring of the toes (Stemmer's sign) and the typical peau d'orange. (C) Severe lymphedema with subcutaneous lymph cysts and chronic verrucous superinfection.

Cancer

Of the various clinical settings that predispose patients to lymphedema, treatment of breast cancer is most commonly associated with acquired lymphatic insufficiency (of the upper extremity). Lymph node dissection and adjuvant radiation therapy independently and synergistically predispose to lymphatic vascular insufficiency.[20]

According to the most recent estimates, 6% to 30% of breast cancer survivors experience clinically significant arm lymphedema after axillary intervention. Despite the benefits of recent surgical and radiotherapeutic enhancements, the problem of lymphedema has not been eradicated.[18]

Similar lymphatic sequelae are encountered in the lower extremities and pelvis after interventions for gynecologic or urologic malignant neoplasms. Malignant melanoma can cause either upper or lower extremity lymphedema when radical dissection is required in the axilla or groin, respectively.

Filariasis

Filariasis, caused by infestation with parasites such as *Wuchereria bancrofti, Brugia malayi,* and *Brugia timori,* is by far the most frequent cause of secondary lymphedema in third-world countries. Of the estimated 90.2 million people in the world who are infected, more than 90% have bancroftian filariasis.[32] The disease is most frequent in subtropical and tropical countries such as China, India, and Indonesia. It is transmitted by various types of mosquitoes, and transmission is closely related to poor urban sanitation.[33]

Perilymphatic inflammation and fibrosis, and sclerosis of the lymph nodes, are caused by the indwelling adult worms. Lymph node fibrosis, reactive hyperplasia, and dilation of the lymphatic collecting channels are caused by the worm products, by physical injury to the valves and vessel walls caused by the live worms, and by the immune response of the host.[34] Eosinophilia is found in the peripheral blood smear, and microfilariae can be demonstrated in peripheral nocturnal blood, centrifuged urine sediment, or lymphatic fluid.[35]

Filarial lymphedema rapidly develops into grossly incapacitating elephantiasis that is extremely difficult to treat.

Other Causes

Lymphedema can also be acquired from other types of lymphatic vascular trauma, including burns and large or circumferential wounds to the extremity. Additional causes of acquired lymphedema include pregnancy, bacterial and fungal infections, infections after snake or insect bites, contact dermatitis, and rheumatoid arthritis.[9] Autoimmune destruction of the lymphatics has been hypothesized but not directly demonstrated.

Clinical Staging

Because none of the classification schemes addresses the clinical stage of the disease, in 1985 the Working Group of the 10th International Congress of Lymphology suggested staging chronic lymphedema, regardless of cause. A latent, subclinical stage and three clinical grades were established,[36] and each grade was subclassified as mild, moderate, or severe:

Latent Phase: Excess fluid accumulates and fibrosis occurs around the lymphatics, but no edema is apparent clinically.

Grade I: Edema pits on pressure and is reduced largely or completely by elevation; there is no clinical evidence of fibrosis.

Grade II: Edema does not pit on pressure and is not reduced by elevation; moderate to severe fibrosis is evident on clinical examination.

Grade III: Edema is irreversible and develops from repeated inflammatory attacks, fibrosis, and sclerosis of the skin and subcutaneous tissue. This is the stage of lymphostatic elephantiasis.

The advantage of this classification is that it permits the evaluation of treatment effectiveness and the comparison of different treatment modalities. One drawback is that appropriate staging may be difficult in some cases without a biopsy of the subcutaneous tissue.

CLINICAL PRESENTATION HISTORY

A careful history frequently reveals the cause of the swelling and suggests the diagnosis of lymphedema. A family history that is positive for leg swelling may indicate familial lymphedema. The development of painless leg swelling in a teenage girl without any identifiable cause strongly suggests primary (idiopathic) lymphedema. A history of diarrhea and weight loss is a clue to mesenteric lymphangiectasia, whereas intermittent drainage of milky fluid from skin vesicles indicates reflux of chyle. In patients with secondary lymphedema, the cause of limb swelling should be evident from the history, such as previous lymph node dissection, irradiation, tumor, trauma, or infection. In patients who have traveled in tropical countries, filariasis is suspected. Although the causes of primary and secondary lymphedema are different, the clinical presentation and characteristic physical findings are frequently similar.

Signs and Symptoms

The clinical signs and symptoms of lymphedema largely depend on the duration and severity of the disease.

Edema

Initially, the interstitial space is expanded by an excess accumulation of relatively protein-rich fluid. The swelling produced by the fluid collection is typically soft, is easily displaced with pressure (pitting edema), and may substantially decrease with elevation of the limb. In the lower extremities, the edema typically extends to the distal aspects of the feet, resulting in the characteristic "square toes" seen in this condition. Stemmer's sign is positive when the skin at the base of the second toe becomes inelastic to the point that the examiner's fingers cannot cause the skin to tent. The dorsum of the forefoot can be involved, resulting in the typical appearance of a "buffalo hump." During a period of years, the limb may take on a woody texture as the surrounding tissue becomes indurated and fibrotic.

Skin Changes

In the early stage of lymphedema, the skin usually has a pinkish red color and a mildly elevated temperature owing to the increased capillary blood flow in the skin. In long-standing lymphedema, the skin becomes thick and shows areas of hyperkeratosis, lichenification, and development of peau d'orange. The term *pigskin* reflects the reactive changes of the dermis and epidermis in response to the chronic inflammation caused by lymphatic stasis.[37] Recurrent chronic eczematous dermatitis or excoriation of the skin may occur, but frank ulcerations are rare. Unlike the situation in venous stasis, the skin maintains a higher degree of hydration and elasticity in lymphedema, and ischemic changes due to high skin tension and disruption of the circulation to the skin and subcutaneous tissue are rare.[38]

Additional skin changes in chronic lymph stasis, primarily in patients with hyperplasia of the lymphatics and valvular incompetence, include verrucae or small vesicles, which frequently drain clear lymph (lymphorrhea). In patients with lymphangiectasia and reflux of chyle, drainage from the vesicles is milky (chylorrhea; see Fig. 168.2).

Primary lymphedema may be associated with yellow discoloration of the nails.[37-39] In the yellow nail syndrome, pleural effusion is also present. The pale yellow color of the nails is most likely caused by impaired lymphatic drainage. Severe clubbing, transverse ridging, friability, and decreased rate of nail growth are also observed.[40,41]

Pain

Although some aching or heaviness of the limb is a frequent complaint, intense pain is rare. If a patient with lymphedema complains of marked pain, infection or neuritic pain in the area of scar tissue or radiation treatment should be suspected. Other possible causes of leg swelling, such as venous edema or reflex sympathetic dystrophy, should also be considered (see the later discussion of differential diagnosis).

Complications

Infection

The propensity for recurrent soft tissue infection[42] is one of the most troublesome aspects of long-standing lymphedema. Accumulated fluid and proteins provide a good substrate for bacterial growth. Lymphatic dysfunction impairs local immune responses, which plays a permissive role in the propagation of bacterial and fungal invasion. Furthermore, once it is established, soft tissue infection exacerbates the existing lymphatic dysfunction, sometimes irreversibly. With recurrent infection, there is progressive damage of lymphatic capillaries. In primary lymphedema, the reported infection rate is as high as 31%.[10]

The clinical presentation of soft tissue infection in lymphedema varies substantially, from the acute manifestation of rapidly progressive infection to only modest exacerbations of edema accompanied by subtle cutaneous erythema in the absence of fever. Recurrent attacks of cellulitis can damage the existing cutaneous lymphatics, exacerbate the skin disease, and further aggravate existing edema.

Malnutrition and Immunodeficiency

Lymphangiectasia with protein-losing enteropathy or chylous ascites or chylothorax may result in severe loss of proteins, long-chain triglycerides, cholesterol, and calcium.[43,44] Loss of lymphocytes, immunoglobulins, polypeptides, and cytokines, coupled with impaired immune trafficking through the lymphatic vasculature, results in a state of immunodeficiency that decreases the patient's ability to resist infections or, potentially, malignant disease.[45]

Malignant Tumors

In rare cases, chronic lymphedema of any cause may be complicated by the development of malignant tumors in the involved limb. Lymphangiosarcoma after long-standing secondary lymphedema, originally described by Stewart and Treves,[46] is a rare malignant disease that frequently results in limb loss or even death. Lymphangiosarcoma is manifested as multicentric lesions with bluish nodules, sclerotic plaques, or bullous changes. Other malignant tumors that appear with increased frequency in lymphedematous limbs include Kaposi's sarcoma, squamous cell carcinoma, malignant lymphoma, and melanoma.

DIAGNOSIS

In most cases of advanced, sustained lymphedema, the characteristic clinical presentation, history, and physical findings establish the diagnosis with near certainty.[47] In more subtle presentations, it may be difficult to distinguish primary lymphedema from other edematous conditions. Additional objective data may be required to confirm the presence of impaired lymphatic flow or the typical pattern of abnormal fluid distribution within tissues. The diagnosis is more difficult to establish in the early stages of disease, particularly when edema is mild or intermittent.

Physical Examination

The physical examination of a patient with lymphedema should include inspection for cutaneous and subcutaneous fibrosis and peau d'orange and attempts to elicit the pathognomonic Stemmer sign in which the examiner is unable to tent the skin of the interdigital webs, based on the characteristic loss of cutaneous elasticity in lymphedema (see Fig. 168.4). In some cases, particularly early in the disease, the pitting edema of this condition may be indistinguishable from other local or systemic causes of edema.

Testing

Objective documentation of lymphatic dysfunction is sometimes useful. Available tests include isotopic lymphoscintigraphy, near infrared fluorescent lymphatic imaging, indirect and direct lymphography, lymphatic capillaroscopy, magnetic resonance imaging (MRI), axial tomography, and ultrasonography. Direct lymphography is rarely used today and should be restricted to those patients who are potential candidates for lymphatic surgery. Lymphatic capillaroscopy is available only in specialized centers.

Lymphoscintigraphy

Isotopic lymphoscintigraphy is a reliable and reproducible[46] method to confirm the diagnosis of lymphedema. A radiolabeled macromolecular tracer is injected intradermally or subdermally within one of the interdigital spaces of the affected limb. The lymphatic transport of the radiolabeled macromolecule is tracked with a gamma camera. The biokinetic behavior of interstitially applied colloid particles depends on their surface charge and particle size. Particles with small diameters are absorbed into capillaries, whereas those in the 10-nm range, such as antimony trisulfide (Sb2S3), are absorbed into the lymphatic system. The time needed for activity to appear in the regional lymph nodes varies according to the physical characteristics of the imaging agent. For example, small particles such as technetium Tc 99m-labeled human serum albumin may appear in the pelvic nodes within 10 minutes,[48] whereas relatively large agents, including rhenium and Sb2S3 colloid, should arrive within 30 minutes[46] to 1 hour,[49] respectively. In most centers, 99mTc-Sb2S3 or 99mTc-labeled human serum albumin is used for lymphoscintigraphy.[50,51-53]

Interpretation. Lymphoscintigraphy provides a semiquantifiable assessment of lymphatic function as well as visualization of major lymphatic trunks and lymph nodes. The data can be recorded in a standardized report format, which is helpful for creating reproducible reports when many physicians review these tracings. A sample report form, shown in Fig. 168.5, is an adaptation of one proposed by Kleinhans and colleagues for the estimation of a transport index.[54]

In normal limbs, lymphoscintigraphy shows several lymph vessels as the tracer is visualized along the anteromedial aspect of the leg. The injection site, because of the relatively large tracer dose given, does not show details, and no information about lymph distribution in the feet is obtainable. Several lymph channels may be identified in the calf. However, in the thigh, the lymph vessels run close to each other, and separate activity in each larger channel is seldom seen on lymphoscintigrams (Fig. 168.6).

Tracer activity is clear in the inguinal lymph nodes by 60 minutes (range: 15 to 60 minutes). A faint hepatic uptake, activity in the bladder, and faint traces in the para-abdominal nodes are visible at 1 hour. Three-hour images show intense uptake in the liver; symmetrical and good uptake in the lymph nodes of the groin, pelvis, and abdomen; and, occasionally, a tracer focus in the left supraclavicular area at the site of the distal thoracic duct.

The qualitative interpretation of images has resulted in moderate sensitivity and excellent specificity for the diagnosis of lymphedema.[52] Quantitative lymphoscintigraphy, with measurement of lymphatic clearance, may improve the detection of early disease,[50] but the results obtained in some studies have been equivocal.[51,52] Neither the image pattern nor the quantitative parameters can reliably distinguish primary from secondary lymphedema.[51,53]

Patient's Initials _____

Clinic Number _____ Date _____

LYMPHOSCINTIGRAPHY DATA EVALUATION

☐ Arms ☐ Legs

IMAGE	1 Hr		3 Hr		6 Hr		24 Hr	
	R	L	R	L	R	L	R	L
Lymph transport kinetics: 0 = no delay, 1 = rapid, 3 = low-grade delay, 5 = extreme delay, 9 = no transport								
Distribution pattern: 0 = normal, 2 = focal abnormal tracer, 3 = partial dermal, 5 = diffuse dermal, 9 = no transport								
Lymph node appearance time: Minutes								
Assessment of lymph nodes: 0 = clearly seen, 3 = faint, 5 = hardly seen, 9 = no visualization								
Assessment of lymph vessels: 0 = clearly seen, 3 = faint, 5 = hardly seen, 9 = no visualization								
Abnormal sites of tracer accumulation (describe)								

Figure 168.5 Evaluation form for calculation of the lymphatic transport index. (Modified from Kleinhans E, Baumeister RG, Hahn D, Siuda S, Büll U, Moser E. Evaluation of transport kinetics in lymphoscintigraphy: follow-up study in patients with transplanted lymphatic vessels. *Eur J Nucl Med.* 1985;10:349. Courtesy Springer-Verlag.)

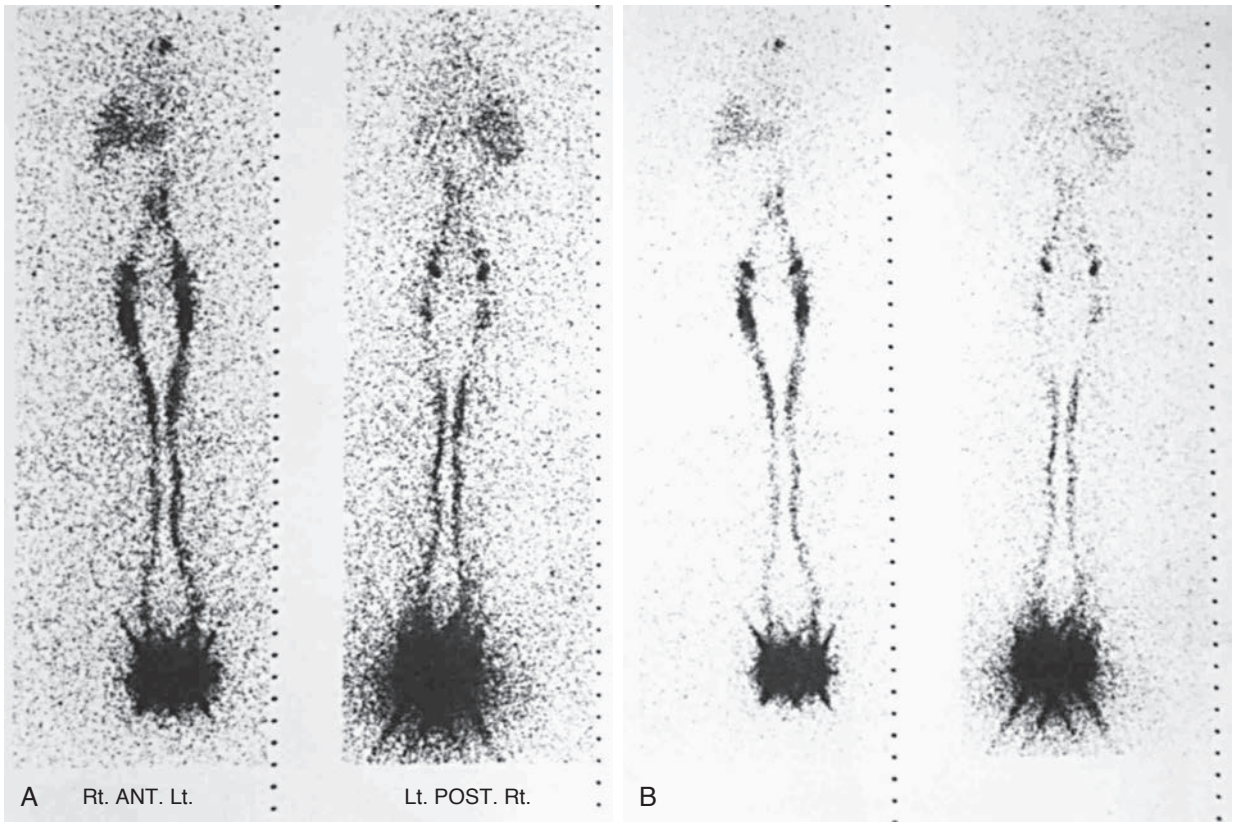

Figure 168.6 Anterior and posterior images in two intensity settings from a total-body scan with a dual-headed gamma camera. (A) Normal lymphoscintigram. (B) Higher intensity settings in the same patient. A large area of high activity and scatter is seen at the feet, where the injection was made. The single well-outlined band in each leg represents the main lymphatic channels. The lymph nodes in the groin and liver, the pelvic and para-aortic nodes, and an area at the site of the upper thoracic duct, are visualized.

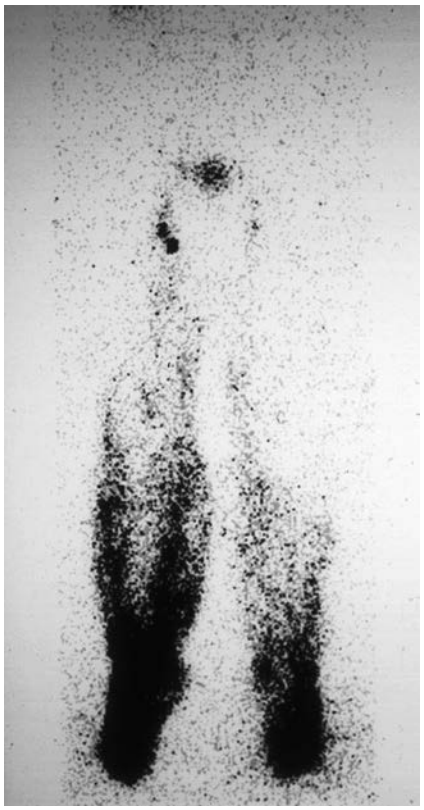

Figure 168.7 Radionuclide lymphoscintigraphy in chronic bilateral lower limb lymphedema. The study demonstrates a dramatic degree of dermal backflow, suggesting the presence of lymphatic hypertension and valvular incompetence.

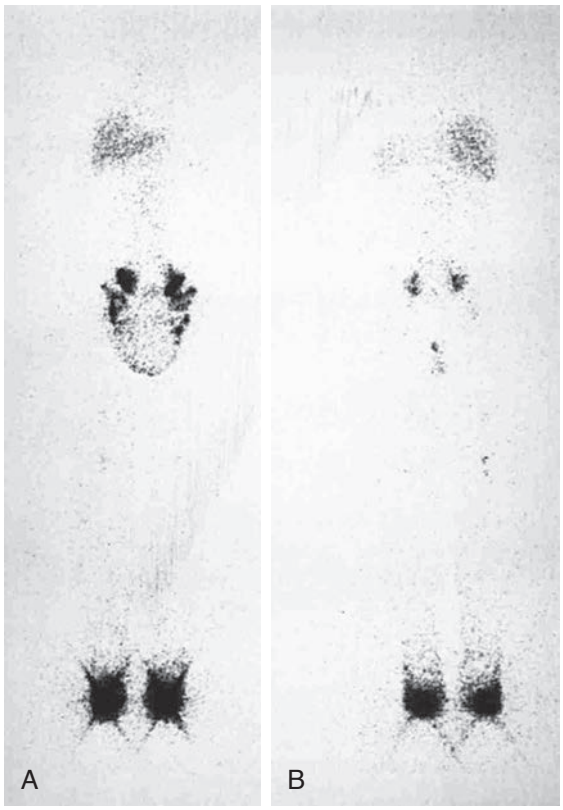

Figure 168.8 Bilateral leg scintigraphy with anterior (A) and posterior (B) views in a 24-year-old man outlines the swollen scrotum in the 6-hour image. Colloid reflux resulted from dilation and valvular incompetence of the lymphatics.

Lymphedema. Typical abnormalities observed in lymphedema include dermal backflow (Fig. 168.7), absent or delayed transport of tracer, crossover filling with retrograde backflow, and either absent or delayed visualization of lymph nodes. In primary lymphedema, channels are obliterated or absent; in a smaller percentage of cases, they become ectatic and incompetent. The asymmetry or delayed appearance of radiocontrast material in the proximal nodal tissue can be used as a semiquantitative measure of the severity of lymphatic vascular insufficiency. The density of subcutaneous accumulation of radiotracer (dermal backflow) can also be quantitated, as can the ratio of radioactivity in ipsilateral versus contralateral nodal tissues in the setting of unilateral limb edema. Quantitation has the greatest utility in predicting the likelihood of a beneficial response to therapeutic intervention.

Lymphangiectasia. Scintigraphic findings in lymphangiectasia consist of dilated lymph channels with only mild or no delay in lymph transport (Fig. 168.8). Colloid injected into the unaffected lower extremity may reflux into the affected lymphedematous leg because of lymphatic valvular incompetence. Similar reflux of the colloid may be seen in the dilated mesenteric lymphatics (Fig. 168.9) or in the retroperitoneum, perineum, or scrotum. Ruptured lymphatics cause extravasation of the colloid into the abdominal cavity or the chest in patients with chylous ascites or chylothorax. The images are generally not helpful in determining the exact site of the lymphatic leak.

Computed Tomography and Magnetic Resonance Imaging

Lymphedema is typically confined to the epifascial space of the skin and subcutaneous tissue, sparing the muscle. This characteristic absence of muscle involvement produces distinctive changes that can be observed with computed tomography (CT) or MRI. These typical imaging features facilitate the differentiation of lymphedema from other edematous entities. In lymphedema, the images reveal a characteristic honeycomb distribution of edema within the epifascial structures along with thickening of the skin. In venous edema, both the epifascial and subfascial compartments are affected, whereas, in lipedema, there is fat accumulation without fluid. MRI is also helpful in the identification of lymph nodes and enlarged lymphatic trunks and in the differentiation of various potential causes of lymphatic obstruction in secondary lymphedema. The anatomic information derived from MRI can complement the functional assessment provided by lymphoscintigraphy.[55] The greatest value of CT and MRI in the evaluation of a patient with a swollen leg is to exclude any obstructing mass in the pelvis that may result in decreased transport capacity of the lymphatic system.

Direct Contrast Lymphangiography

Contrast lymphography is used primarily before reconstructive lymphatic surgery. Imaging is accomplished through the direct

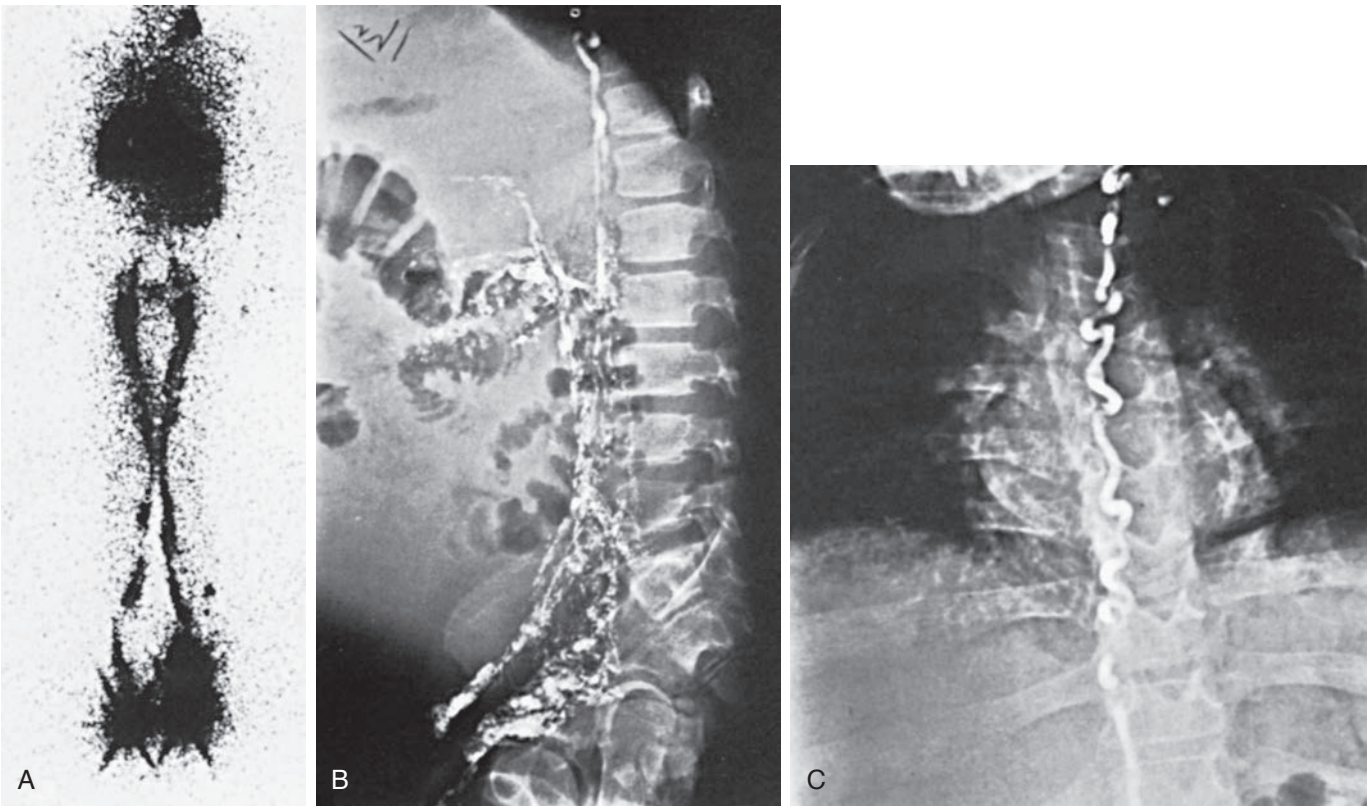

Figure 168.9 (A-C) Lymphoscintigram of an 18-year-old man with lymphangiectasia, protein-losing enteropathy, and chylous ascites. Note the large leg lymphatics (A) and reflux of colloid into the mesenteric lymph vessels (B), filling almost the entire abdominal cavity. Note the large thoracic duct (C).

injection of iodine-based, lipid-soluble agents into the subcutaneous lymphatics, which are first identified by the subcutaneous injection of dye (methylene blue) and then cannulated. Contrast lymphography poses distinct technical difficulties and may, in fact, exacerbate lymphatic malfunction through the accumulation and pooling of the oil-based contrast medium. For these reasons, its use should be limited to preoperative evaluation in specialized centers.

Differential Diagnosis

The differential diagnosis frequently includes lipedema; a lipodystrophy that typically causes symmetrical enlargement of the lower extremities, particularly in obese females; and venous insufficiency, a hydrostatic cause of lower extremity edema. In lipedema, there may be a component of pitting edema; however, in contradistinction to lymphedema, there is sparing of the feet despite pronounced enlargement of the calves and thighs. Venous stasis has relatively distinctive cutaneous attributes, including chronic deposits of hemosiderin in the skin. The patient's history and the clinical setting often determine the degree to which chronic venous insufficiency plays a role in the differential diagnosis. However, even when the clinical setting and physical examination suggest the presence of venous stasis, the accompanying venous hypertension may chronically elevate the lymphatic load and thus predispose to the secondary development of lymphatic edema. Therefore, in practice, such patients often have a mixed lymphatic-venous form of chronic edema.

Systemic Causes

During the evaluation of patients with chronic limb swelling, a systemic cause should be excluded first. Underlying cardiac diseases, such as congestive heart failure, chronic constrictive pericarditis, and severe tricuspid regurgitation, are the most frequent systemic causes leading to pitting or bilateral leg swelling. Hepatic or renal failure, hypoproteinemia, malnutrition, and endocrine disorders (myxedema) are other possible causes of leg swelling. Allergic reactions, hereditary angioedema, and idiopathic cyclic edema are rare systemic causes that should be considered. Chronic use of diuretics may lead to generalized swelling that most frequently affects the extremities and the face. Other drugs that may cause swelling include corticosteroids, some antihypertensive drugs, and antiinflammatory agents.

Venous Insufficiency

Among the local or regional causes of limb swelling, chronic venous insufficiency is much more common than lymphedema. In some patients with chronic iliac or iliocaval obstruction, massive swelling of the entire extremity can develop (Fig. 168.10). The usual causes of proximal venous occlusion are deep venous thrombosis or external compression of the vein by tumor or

Figure 168.10 Right leg swelling due to venous insufficiency, caused by chronic iliofemoral venous thrombosis.

Figure 168.11 Left leg edema associated with a congenital vascular malformation (Klippel-Trénaunay syndrome).

retroperitoneal fibrosis. Whereas lymphedema is usually painless, venous hypertension results in marked pain and cramps after prolonged standing or at the end of the day. Patients with proximal venous obstruction may complain of typical claudication, which is manifested as throbbing pain in the thigh or calf after walking. The pain resolves with rest, although elevation of the extremity provides the fastest relief. The presence of varicosity, pigmentation, induration, or venous ulcers makes the diagnosis of venous insufficiency easier. Chronic inflammation in the subcutaneous tissue due to venous stasis may result in destruction of the collecting lymph channels; a mixed venous-lymphatic edema develops in these patients.

Vascular Malformation

Patients with congenital vascular malformations frequently have a larger than normal extremity that may be difficult to distinguish from lymphedema (Fig. 168.11). An increase in the length of the affected extremity, the presence of atypical lateral varicosity, and a port-wine stain with underlying developmental abnormality of the deep venous system are characteristic of Klippel-Trénaunay syndrome.[56] Although hypertrophy of the soft tissues and bones is caused by an abnormality in mesenchymal development, congenital lymphedema may also be present in these patients. In patients with high-shunt, high-flow arteriovenous malformations, the extremity is larger than normal, and is frequently longer.[57] A bruit and thrill are present; the superficial veins are dilated and frequently pulsatile; and the distal arterial pulses may be diminished.

Lipedema

Lipedema is characterized by the deposition of a large amount of fatty tissue in the subcutaneous layers. Most of these patients have morbid obesity; some, mostly females, have fat deposition localized to the lower half of the body. Evaluation of the lymphatic system with lymphoscintigraphy or lymphangiography shows essentially normal findings.

Other Causes

Trauma and subsequent reflex sympathetic dystrophy may result in painful swelling of the extremity. Because of disuse, a varying degree of osteoporosis can be observed, and increased sympathetic activity occurs in the limbs of these patients. The swelling is usually the result of high-output lymphatic failure, and increased lymphatic transport may be demonstrated on lymphoscintigraphy (Fig. 168.12). Baker's cyst, soft tissue tumor, hematoma, and inflammation, such as tenosynovitis or arthritis, are additional local causes of limb swelling, which should be considered in the differential diagnosis of lymphedema.

DECISION MAKING

Clinical examination of the patient frequently reveals the correct cause of limb swelling. Initial laboratory examinations should include routine blood tests to look for signs of renal or hepatic failure, eosinophilia, or hypoproteinemia. Urinalysis may indicate proteinuria. Once a systemic cause

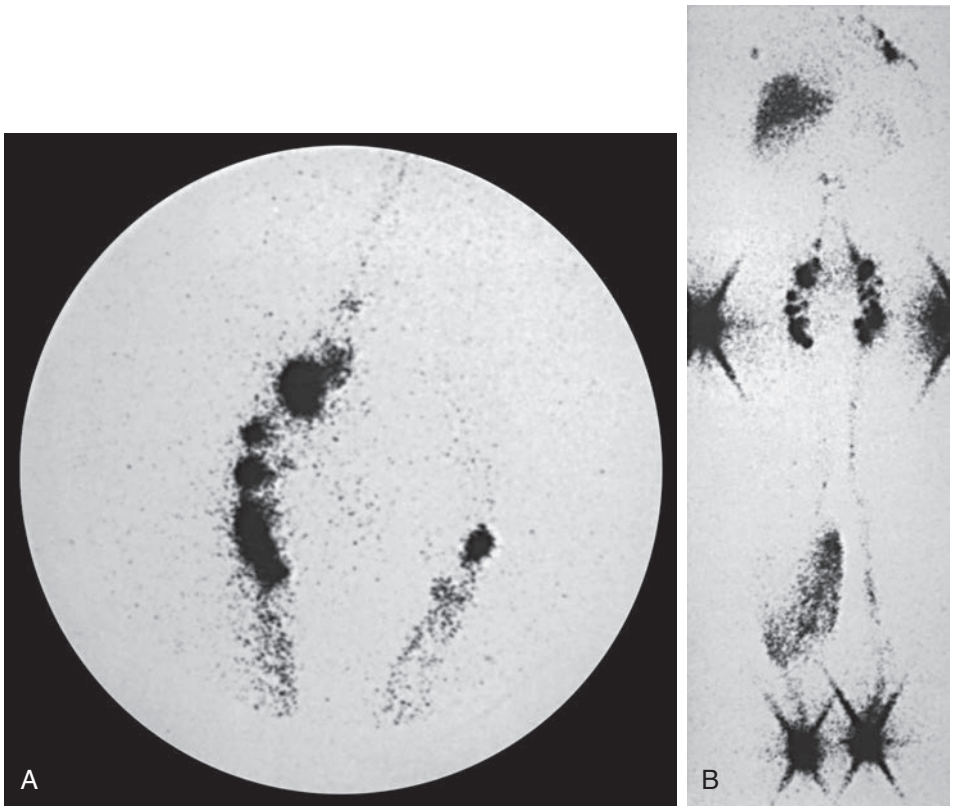

Figure 168.12 Lymphoscintigraphy in high-output lymphatic failure due to reflex sympathetic dystrophy of the right leg. (A) Fast lymphatic transport in the affected right leg compared with the normal left leg is evident in the image of the inguinal nodes 20 minutes after injection. (B) Total-body image at 3 hours shows a dermal pattern on the right, but no evidence of proximal lymphatic obstruction.

of edema is excluded, the local or regional cause should be confirmed.

Patients at risk for the development of secondary lymphedema (e.g., cancer survivors) pose a distinct challenge for decision making, because there is an imperative to recognize the evolving condition at its earliest stages. Within the last decade a new technology, bioimpedance spectroscopy, has been introduced, which provides the requisite sensitivity and specificity to detect stage 0 disease.[52] Increasingly, this technique, which is rapidly and efficiently performed at the bedside, will have applicability to the serial monitoring of the patient's treatment response as well.[58] There may also be an evolving role for the prospective analysis of body fluids to determine lymphedema risk in evolution.[59]

Venous duplex scanning confirms or excludes venous occlusion or valvular incompetence in the leg. CT has become routine for most adult patients with leg swelling to exclude underlying malignant disease. MRI provides the most accurate information in patients with clinical signs of congenital vascular malformation, soft tissue tumor, or retroperitoneal fibrosis.

Lymphoscintigraphy is the test of choice for the confirmation of lymphedema, and a normal finding on lymphoscintigraphic examination essentially excludes the diagnosis of lymphedema. Patients with chronic venous insufficiency may have abnormal results on lymphoscintigraphic examination, with delayed transport because of mixed lymphatic and venous edema. As mentioned earlier, direct contrast lymphangiography should be performed selectively and should not be part of the routine evaluation of patients with chronic limb swelling. Increasingly, near-infrared fluorescent lymphography is incorporated into the pre-surgical evaluation of lymphedema, when reconstructive approaches are contemplated.[60]

For all patients with chronic lymphedema, conservative management through physical means is the mainstay of therapy.

PROSPECTS FOR MOLECULAR THERAPY

Although current therapeutic strategies for lymphedema effectively reduce excess volume, minimize complications, and optimize function, the disease currently lacks a cure. For these reasons, there has been an emphasis on the possible application of effective molecular therapies. Among these, one of the most exciting prospects is therapeutic lymphangiogenesis, a molecular approach based on growing insights into the mechanisms of lymphatic vascular development.

Among the biological factors that initiate and regulate the growth of vascular structures, the vascular endothelial growth factor (VEGF) family plays a central role.[61,62] VEGF-C and VEGF-D direct the development and growth of the lymphatic

vasculature in embryonic and postnatal life by binding to VEGFR-3, which is nearly exclusively expressed on lymphatic endothelia.[63,64] In transgenic mice that overexpress VEGF-C, the lymphatic vessels demonstrate a hyperplastic, proliferative response, with secondary cutaneous changes.[65] Exogenous administration of VEGF-C upregulates VEGFR-3, leading to a lymphangiogenic response.[66,67]

These molecular observations have helped elucidate the mechanisms that contribute to disease expression in the most common heritable form of lymphedema, the autosomal dominant condition known as Milroy's disease. In many affected family cohorts, this disease has been linked to the flt4 locus, encoding VEGFR-3.26. Disease-associated alleles contain missense mutations that inactivate the tyrosine kinase signaling mechanism, thereby preventing downstream cellular activation. It is believed that the mutant form of the receptor is not only functionally inactive, but also excessively stable, serving as a potential "sink" for activating ligands. Thus, the normal signaling mechanism is blunted, leading to hypoplastic development of lymphatic vessels.[68,69]

The prospects for therapeutic lymphangiogenesis in human lymphedema have been underscored by the recent description of a mouse model of inherited limb edema that features a mutation in the VEGFR-3 signaling mechanism, and a pathologic process that resembles human disease.[63] In this model, the therapeutic overexpression of VEGF-C with the use of a viral vector induces the generation of new functional lymphatics and the amelioration of lymphedema. Similarly, in a rodent model of acquired postsurgical lymphatic insufficiency (resembling postmastectomy lymphedema), the exogenous administration of human recombinant VEGF-C restores lymphatic flow (as assessed by lymphoscintigraphy),[70,71] increases lymphatic vascularity, and reverses the hypercellularity that characterizes the untreated lymphedematous condition.

Intensive future investigation will be required to verify the therapeutic potential of such approaches, and to establish dose-response relationships and the durability of the therapeutic response. As with other forms of angiogenic therapy, the relative virtues of growth factor therapy versus gene therapy must be established.[72]

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CHAPTER 169

Lymphedema: Nonoperative Treatment

ALBEIR Y. MOUSA, RAMEZ MORCOS, and MIKE BROCE

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INTRODUCTION

What comes to mind when we mention that the circulatory system is the blood vessels and somehow we forgot the unique system of lymphatics? Most of our research has been focused on veins, arteries, and their related pathophysiology—mainly thrombosis and atherosclerosis. In this chapter, we will examine the lymphatic system and its malfunction with significant attention to current nonoperative approaches to treat lymphedema. Details of diagnosis and surgical approaches have been outlined in other chapters. We will examine the pathology that contributes to the malfunctioning lymphatic system. The pathology of the lymphatic system is linked mainly to lipid and protein malabsorption, defected immunologic response, accumulation of protein-rich interstitial fluid, and the inability to return lymph back to the systemic circulation leading to the development of lymphedema. Although a nonoperative approach is the main therapy in treating early stages of lymphedema, our interest is to also focus on nonoperative management of advanced incurable lymphedema. It starts with preventive medicine to high-risk patients. If lymphedema diagnosis is established, then attention is directed to the reduction of limb swelling and prevention of secondary infections, which should be the main goal of lymphedema management. Mechanical therapy is the gold standard for established lymphedema, and includes self-hygiene, compression techniques and physiotherapy. Other treatment modalities will be discussed briefly, including, but not limited to pharmacotherapy, laser therapy, and gene therapy. Unmanaged chronic lymphedema eventually results in devastating limb swelling with increasing morbidity, decreased quality of life and productivity,[1] increased risk of infection, and late onset malignancy. Lastly, we will briefly discuss the psychological status of the patients, insurance concerns, and what would be considered the ideal lymphedema clinic. Unfortunately, treatment options for lymphedema remain very limited and largely ineffective.[2]

Abstract

The lymphatic system is an essential component of the human circulatory system. The lymphatic system works in conjunction with the arterial and venous system. It has three main roles, 1) it is part of the immune system, 2) it helps to maintain fluid balance, and 3) it plays an essential part in the absorption of fats and fat-soluble nutrients. Lymphedema is a pathological condition usually associated with a significant swelling of a target body organ. Although, there are many different etiologies that could produce similar pathology, the diagnosis of lymphedema is based on clinical presentation. There are several diagnostic tools such as, magnetic resonance imaging (MRI), computed tomography (CT) and types of ultrasound (US) that can be used to detect the presence of extra fluid in tissues. With all ongoing advances in medical therapy, still lymphedema is deemed to be incurable disease in most part and the main component of therapy is non-surgical interventions. After diagnosis is established, the main components of non-surgical therapy include: Manual lymphatic drainage, compression bandages, compression garments and compression devices. Other non-surgical therapeutic measures include pharmacotherapy, laser therapy, hyperbaric oxygen and intermittent negative pressure. In addition; clinicians should also be aware of possible complications such as skin infection, malignancy and psychological impact of body disfigurement. This chapter is to highlight the most updated medical (non-surgical) interventions for lymphedema and to set an algorithm to guide clinicians in making accurate diagnosis and to establish an effective medical therapy.

Keywords

Lymphedema
compression garments
intermittent pneumatic compression
manual lymphatic drainage
complete decongestive therapy

Epidemiology

The prevalence of primary lymphedema within North America is estimated to be 1.15 per 100,000 children, and mainly affects the female gender around the menarche time. On the other hand, secondary lymphedema (i.e., arm swelling following breast cancer treatment) reportedly affects 15% to 20% of women receiving axillary dissection and/or radiotherapy as part of their breast cancer therapy.[3] Yet, the prevalence of lymphedema remains under-recognized and under-treated. It has been reported that a significant proportion of wound clinic patients had lymphedema. In addition, the management of lymphedema is difficult due to a lack of resources, a lack of awareness among primary care providers, and a lack of patient adherence to treatment.[4]

Etiology

In general terms, lymphedema is the imbalance between the uptake and the transport capacity of the lymphatic system,[5–7] which leads to an accumulation of protein-rich fluid in the interstitial spaces. This excess fluid occurs as the result of an anatomic or a functional obstruction in the lymphatics or lymph nodes.[8] Nevertheless, the imbalance could happen without even a trigging factor, and it is called primary (congenital) lymphedema. Primary lymphedema is generally related to aplasia, hypoplasia, agenesis, or fibrosis of the lymphatic system.[9] When primary lymphedema appears before the age of 35 it is called lymphedema praecox; if it appears after the age of 35, then it is referred to as lymphedema tarda.[10] As opposed to primary, when there is an identifying cause of the lymphedema it is termed secondary lymphedema, and is generally related to the dissection of lymph nodes, radiation treatment, following a traumatic injury, postinflammatory occurrence, or malignancy (Fig. 169.1). Interestingly, chronic venous disease (CVD) is a common cause of secondary lymphedema; it is sometimes misdiagnosed as primary lymphedema, and patients would not receive optimal treatment.[11]

Diagnosis, Classification, and Clinical Features

Although, not the main focus of this chapter, listed below are the current classification methods for lymphedema. The International Society of Lymphology (ISL)[5] focuses on the fibrotic soft tissue changes with lymphedema. Stage I is reversible, characterized by soft pitting edema, with neither secondary tissue changes nor reduction in swelling after elevation. Stage II is irreversible, characterized by fibrosclerotic changes, inflammation, hardening or thickening, along with nonpitting edema. Stage III lymphostatic elephantiasis is characterized by extreme increase in the size and texture of the skin often with typical papillomas and/or deep skin folds. Stemmer's sign describes the inability to pick up a fold of skin at the base of the second toe, and this is usually a positive sign of lymphedema of the legs (Fig. 169.2). Another classification method considers the malignant versus benign features of the lymphedema (Fig. 169.3).

Lastly, the approach most often used to classify lymphedema is the Common Terminology Criteria for Adverse Events v3.0,

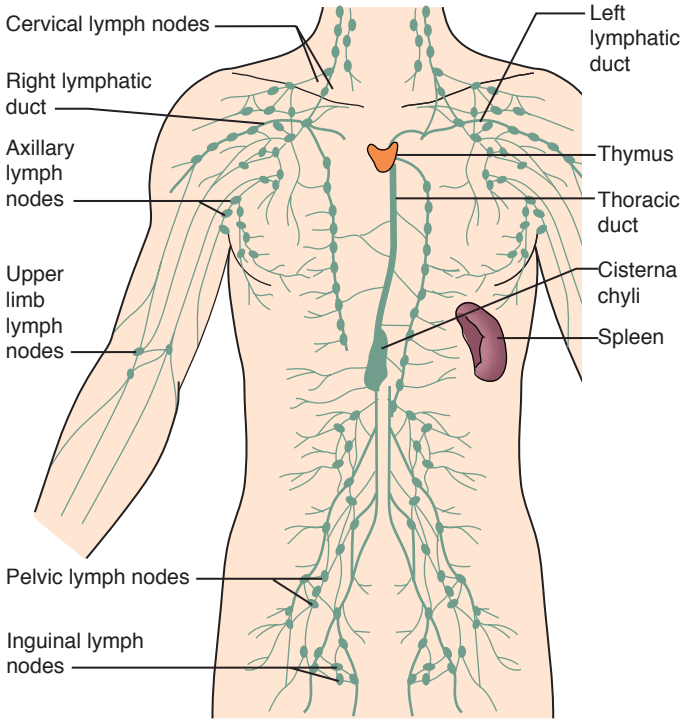

Figure 169.1 Lymphatic System.

which was developed for grading adverse events in the context of clinical trials.[12] This grading system provides not only objective measures (inter-limb discrepancy in volume or circumference), but also subjective and clinical assessments for lymphedema diagnosis (Table 169.1).

PREVENTIVE MEDICINE

Patients at Risk

Identifying patients who are at risk is the essential step for preventive medicine. In undeveloped countries, Wuchereria bancrofti is the most common cause of lymphedema and filariasis. The effort to decrease the transmission in endemic areas may decrease the incidence of lymphedema; the mass administration of diethylcarbamazine plus ivermectin significantly decreased lymphatic filariasis.[13,14] It was reported that higher doses of albendazole did not improve the result, but on the other hand was associated with more severe side effects. It was suggested that alternative regimens could be useful in the later stages of existing programs or to achieve elimination more rapidly in areas where programs have yet to start.[15]

In developed countries, there are two groups of patients who are at high risk of developing lymphedema. The first group contains patients who undergo radiation of a lymph node and/or surgical lymphadenectomy as part of their cancer treatment. Efforts to spare lymph nodes during cancer treatment have proven to be effective. For instance, for patients with breast cancer, the standard of care in staging has evolved from dissection of 2nd ± 3rd level axillary lymph nodes to performing sentinel lymph node biopsy, followed by complete dissection only if nodal metastases are detected; this approach had reduced

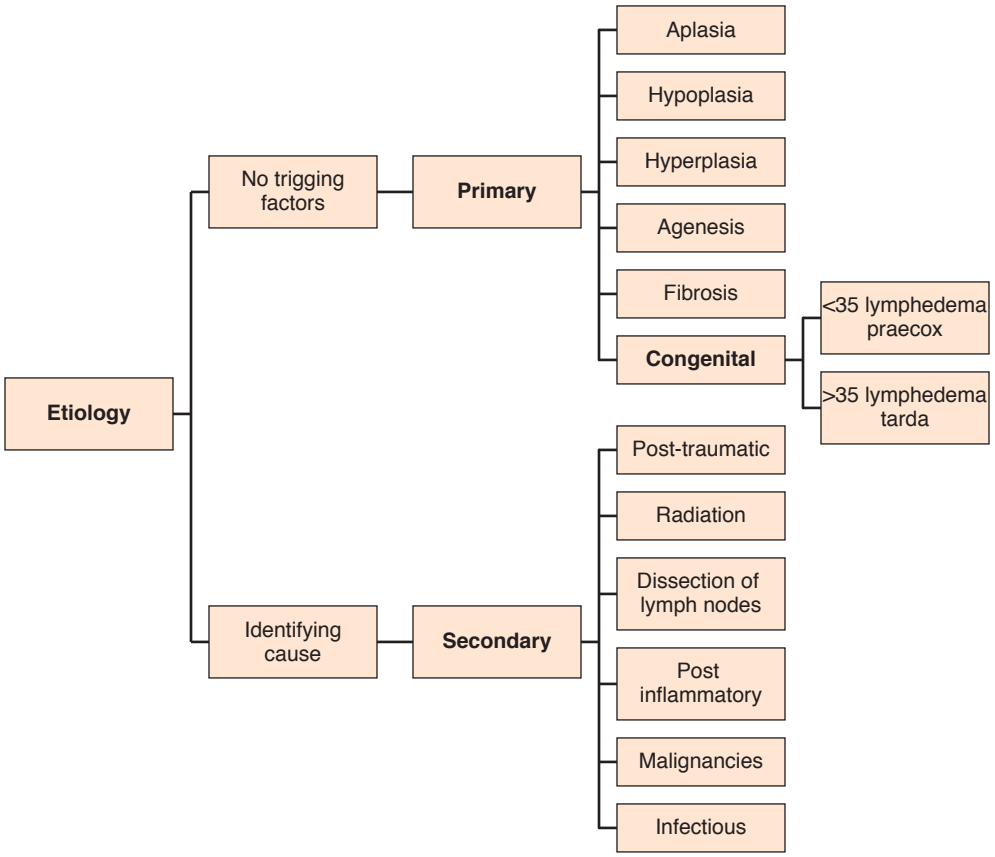

Figure 169.2 Lymphedema Etiology.

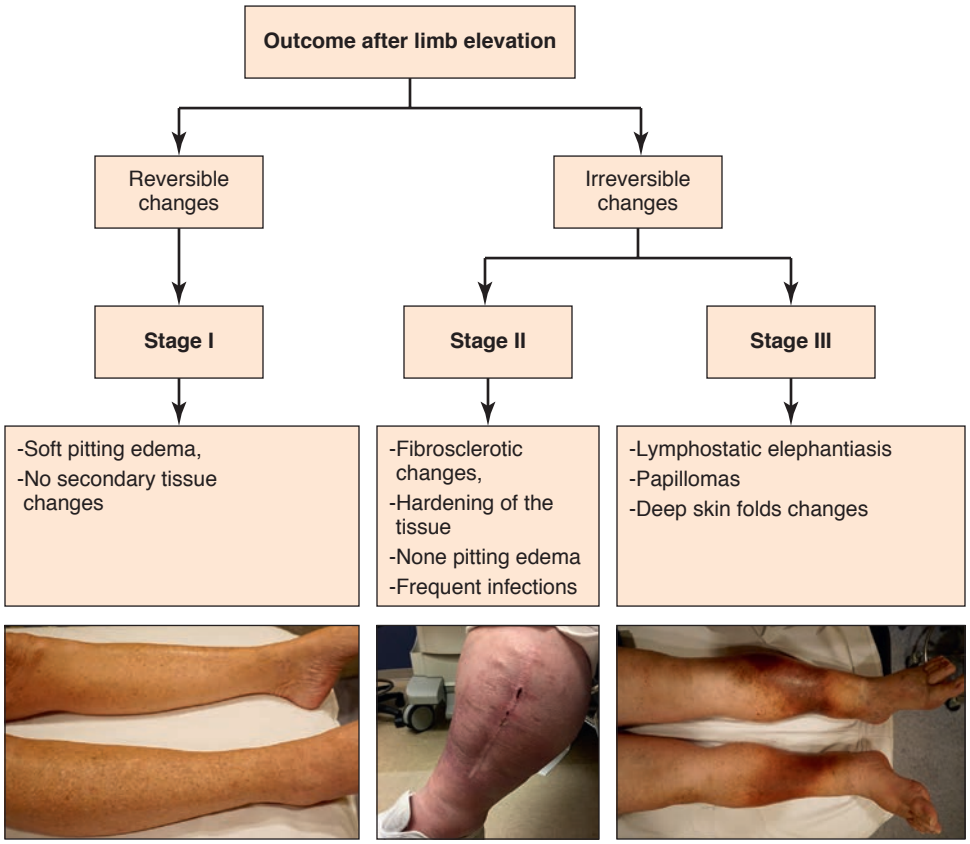

Figure 169.3 Diagnosis, Classification, and Clinical Features.

TABLE 169.1 Common Terminology Criteria for Adverse Events (CTCAE)

Grade	Inter-Limb Discrepancy	Visible Difference
I	5%-10%	Swelling or obscuration of anatomic architecture on close inspection; pitting edema
II	10%-30%	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour
III	More than 30%	Gross deviation from normal anatomic contour; interfering with activities of daily living
IV	Progression to malignancy (e.g., lymphangiosarcoma); amputation indicated; disabling lymphedema	

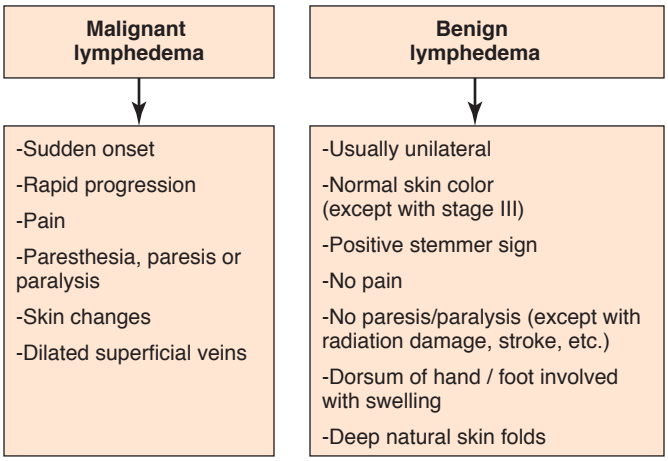

Figure 169.4 Malignant versus Benign Features.

lymphedema incidence by approximately 80%.[16–19] Similarly, the use of sentinel lymph node biopsy to identify lymph nodes involved by metastatic melanoma has significantly reduced the need for extensive inguinal and pelvic lymphadenectomy and has reduced potential lower extremity lymphedema. Interestingly, it also has been reported that being obese or overweight may place women at risk for developing lymphedema following breast cancer treatment,[20] and is considered a major risk factor for lymphedema.[21,22]

The second high-risk group is patients with recurrent cellulitis; a damaged lymphatic system undermines the system's functional capacity, and eventually, causes lymphedema. Recurrent cellulitic infections may cause permanent irreversible lymphatic compromise. Other forms of chronic infection can cause sufficient inflammation to damage the lymphatics.[23] However, because lymphedema is the strongest risk factor for cellulitis,[24,25] at times it is difficult to distinguish between cellulitis as the initial presentation of previously subclinical lymphedema or independently caused lymphedema. The low-grade chronic inflammation produced by rosacea could be caused by the lymphedema of facial structures, particularly the eyelids. The goal of starting prophylactic antibiotics for this group is necessary to prevent recurrent infection. The aim of current therapy should be directed at resolving acute infections and the prevention of recurrent episodes of cellulitis (Fig. 169.4).[26]

Patients with a history of fungal infection, including candidiasis and tinea, should use topical antifungal medications. Routine use of topical clotrimazole cream (1%) or miconazole nitrate lotion or cream (2%) is sufficient for most patients. Oral fluconazole or itraconazole may be needed for recalcitrant or extensive infection. No studies have definitively addressed the efficacy of these treatments in terms of documenting a decreased incidence of lymphedema in those patients.

Edema Preventive Measures

It has been reported that lifestyle modifications, such as changes in diet and increased exercise, have helped to decrease the progression of lymphedema.[27,28] In terms of preventive care, there are several self-care measures that can be practiced to decrease lymphedema, including maintaining daily skin hygiene (e.g., the limbs should be washed regularly with soap and water) and it is important to avoid trauma; either of these can be the nidus of infections.

Other lifestyle or daily habits include elevating the affected limb, modifying dietary intake to include less salt and more protein, wearing properly fitted compression stockings, and walking and performing aerobic exercises to promote lymphatic flow. It is important to monitor and measure limb volume as an objective parameter during the follow-up with patients with lymphedema.[29]

Exercise helps to decrease lymphedema swelling; during the contraction phase of the muscle, the lymph gets pushed to an alternative lymph node through the lymph vessels.[30,31] Historically, patients at risk for developing lymphedema have been advised against "overusing" their at-risk body parts for fear of triggering lymphedema. This recommendation is based on anecdotal associations of the initial onset of lymphedema with episodes of vigorous exercise or sustained, repetitive use of the at-risk extremity. Recently, recommendations against exercise have recently been tempered and re-phrased, based on the results of several randomized controlled trials.[32,33] These trials revealed that a gentle, incremental program of full-body resistive training, started at a low level and increased gradually, did not increase the incidence of lymphedema among at-risk breast cancer survivors, and might have been protective. Similar trials have yet to shed light on the risk-benefit profile of exercise in lower extremity lymphedema.

Exercise routines should include combinations of lymphedema remedial exercises (e.g., active, repetitive, nonresistive motion of the involved body part) along with three main types of exercise (i.e., aerobic, strength, and flexibility). Other possible types of exercise could be considered, but have not been adequately studied in people with lymphedema (e.g., Pilates, yoga, Tai Chi, Qigong, aquatic exercise, trampoline rebounding, breathing exercises, and relaxation). Finally, patients should avoid exposure

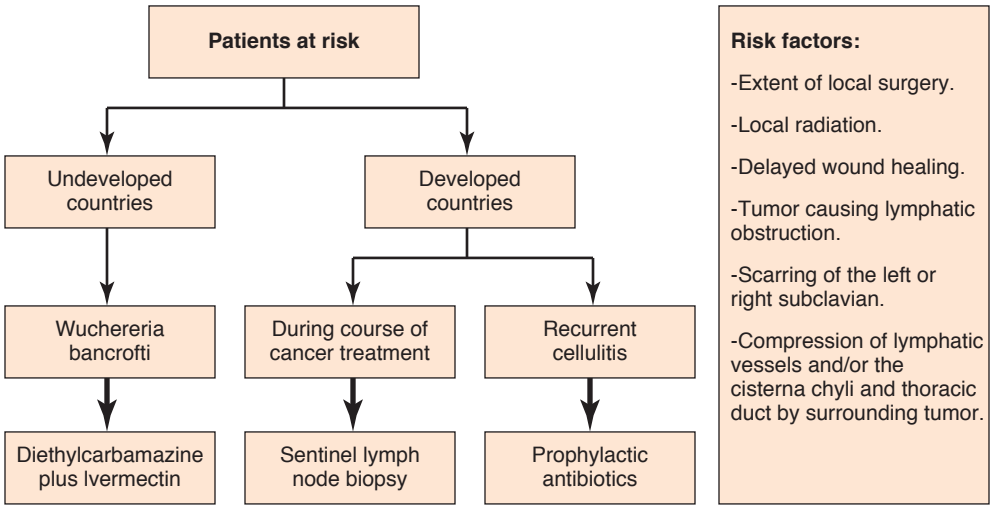

Figure 169.5 Preventive Medicine.

to extreme heat or cold, at least to the extent that tissue injury may occur, such as a burn or frostbite (Fig. 169.5).[34]

MECHANICAL REDUCTION OF LIMB SWELLING

Currently, there is no cure for lymphedema, and management is based on a series of lifelong physical therapies.[1] Practitioners at lymphedema centers or clinics should set specific goals tailored to each patient, while at the same time base treatment on the stage and grade of the lymphedema. The aim of the treatment and goals should be to minimize limb diameter, decrease edema, maintain skin integrity, prevent infection, and encourage patients to use self-care to monitor their skin care and weight reduction.

Complex Decongestive Therapy

The standard of care for lymphedema is commonly referred as complex decongestive therapy (CDT). CDT was popularized in Europe by Földi et al.,[35] Kasseroller,[36] and Leduc et al.,[37] as well as Casley-Smith[38] in Australia, and was introduced to the United States in the early 1990s; CDT continues to be first-line therapy for stage II and III lymphedema. CDT's success has been documented worldwide.[39–43] It is the combination of four components and two phases. The components are: (1) manual lymphatic drainage; (2) compression bandaging; (3) compression garments; and (4) compression devices. Volume reductions were reported after the use of compression garments, pumps, and manual lymphatic drainage. However, the greatest improvements were reported when these treatments were combined in a treatment program.[44]

The two phases are:

1. Initial or reductive phase (phase I); the aim to reduce the size of the affected area and to emphasize proper skin care.
2. Maintenance phase (phase II), which begins immediately after phase I; the main aim is to maintain the gains made during phase I, and requires life-long self-maintenance.

Although very successful, CDT requires a large investment of time from the therapist and patient. Therapists must be specially trained to perform standardized techniques of manual lymph drainage (MLD) and complex multilayered wrapping. Currently, the treatment is offered in specialized practices, but other programs are becoming more widely available. In the United States, there is a voluntary certification process that involves documentation of training, logging treatment hours, and a certification examination to ensure competence. This effort was initiated and coordinated by the Lymphology Association of North America (LANA). Certified therapists are listed on LANA's website,[45] which can be searched by name, state, or zip code. Although phase I CDT can achieve abrupt and dramatic reductions in limb volume, long-term success requires ongoing phase II home-based program maintenance. Without consistent adherence to the program, a patient's lymphedema volume will re-accumulate. The multi-week intensive treatment program also may be limited by insurance coverage in the United States; modified programs, often with inferior outcomes, may be a patient's only option. An alternative program that utilizes home compression bandaging and exercise may achieve comparable results to conventional CDT in some patients with milder (e.g., stage II) lymphedema. Patient compliance and adherence to the therapy is normally 60% to 70%, which in turn, requires trained therapists to have an average volume reduction of 50%.[41,46]

Manual Lymphatic Drainage

First developed by Emil Vodder in 1936,[47] the theory behind MLD is to apply gentle pressure to the skin to stretch the superficial lymphatics, to enhance the contraction and sequestration of lymphatic vessels, and to help the unidirectional flow of lymph to relieve congestion and to minimize subsequent subcutaneous fibrosis. MLD is performed in a series of steps. Before MLD is started, it is beneficial to divide the trunk into six areas (see Fig. 169.1), which correlate to the drainage territories of the cervical, axillary, and inguinal lymph node beds. Treatment is first initiated by massaging an intact section adjacent

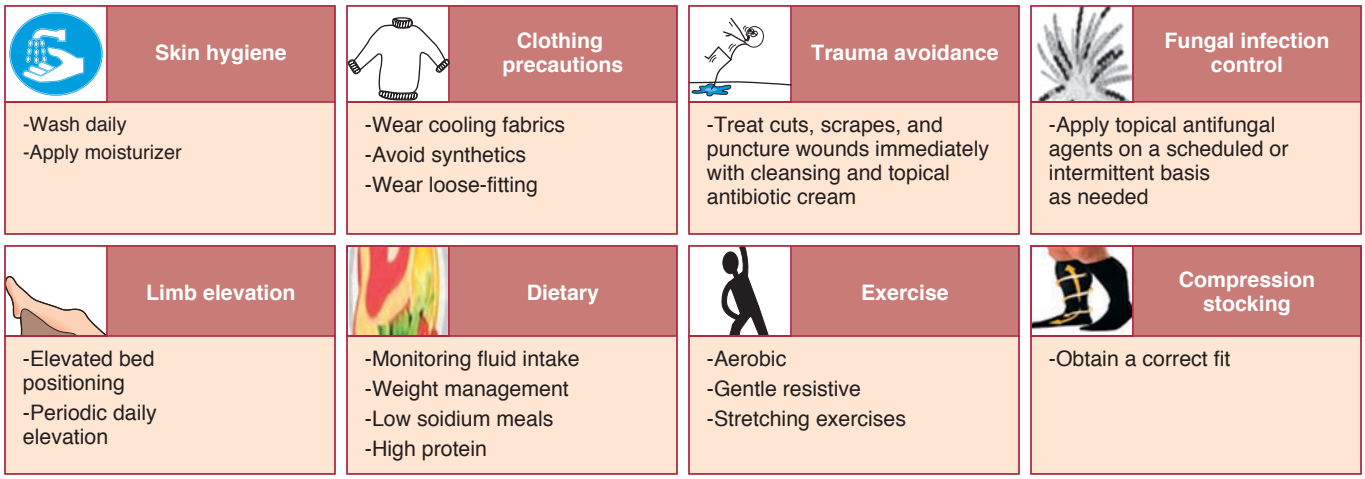

Figure 169.6 Edema Preventive Measures.

to the section that includes the affected limb or body part to prepare the area to receive congested lymph. This maneuver has been shown to redirect lymph fluid toward functioning lymphatic territories.[48] Practiced in this fashion, MLD has been shown to redirect lymph toward functioning lymphatic territories.[48] MLD techniques are particularly of great interest when treating body parts that are not conducive to sustained compression (e.g., face, breast, genitalia, and trunk) (Fig. 169.6). The evidence from a recent systematic review and other studies have shown improvement when combining MLD with compression bandages in treating lymphedema; however, the evidence did not support using MLD by itself—independent from CDT for the purpose of limb volume reduction.[49–51] Yet, Moseley et al., reported that MLD alone did contribute to improvement in self-reported symptoms when used in the palliative care setting.[5,52] In addition, there is some evidence that there are several benefits to practicing standard manual massage with a new device, Linforll.[53]

Compression Bandaging

Elastic wrapping is the principal compression technique used in phase I CDT. Short-stretch bandages have been reported to be very effective in the initial management of arm lymphedema.[54,55] The wrapping requires (1) tubular bandage lining; (2) foam, polyester, or cotton under the cast padding; (3) digit bandages; and (4) multiple layers of short bandages with limited stretch ability when pulled. A recent study described the use of upper extremity compression sleeves among breast cancer survivors whose arm volumes increased by 3% from baseline. Normalization of arm volumes was achieved for the majority of patients after 4 weeks of sleeve use and was maintained for an average follow-up of 4 months. At 1 year following diagnosis, lymphedema incidence was reduced relative to previously reported rates.[56] The goal is to create an internal pump-like action. Two different types of pressures are produced by the bandaging: (1) the low resting pressure (20 to 30 mm Hg),[57] which is the result of short-stretch bandages on the patient during resting; and (2) the high working pressure, which is the result of short stretch bandages on the patient during muscle contraction. The resulting cycling between high-working pressures and low-resting pressure under the bandages in the interstitial fluid areas mimics the action of a pump, which assists the unidirectional flow of lymph to be transported away from the congested area. Inelastic multi-component compression (ICM) bandages normally applied by specialized medical staff are considered the standard of care treatment for compression therapy related to lymphedema of the extremities. However, there are new adjustable compression wraps (ACWs), which can be self-applied by patients. To date, the ACWs have been mainly recommended during the maintenance phase; however, this could be a step toward self-management during the initial treatment phase as well.[58] The technique of applying the elastic wrap is important to achieve an effective compression gradient; short-stretch bandages must be applied with low-to-moderate tension using more layers at the ends of the extremities.[3,59–62] During phase I CDT, low-stretch wraps are worn 24 hours a day (except when the patient is receiving a massage or bathing). In the maintenance phase, a compression garment is worn during the day, and the wraps continue to be worn at night. Compression bandaging is always a part of phase I CDT. Some individuals with more severe forms of lymphedema may need to use home compression bandaging long term as part of phase II. Although somewhat debatable, especially in the past, heating combined with compression bandaging was deemed effective treatment for chronic lymphedema with dermatolymphangioadenitis.[63]

Compression Garments

Compression garments are normally used during all phases of lymphedema treatment, including prophylaxis in at-risk patients. Strict adherence to the daily use of properly fitting and appropriately graduated elastic compression garments are the key components to maintaining limb size for most patients. Fitted elastic knit two-way low-stretch compression garments generate greater pressures more distally than proximally to maintain unidirectional lymphatic flow.[10,64] Normally, compression garments deliver about 20 to 50 mm Hg of pressure (Table 169.2).[5,10] Generally speaking, the highest compression that can be tolerated by the patient is likely to be the most beneficial.[5]

TABLE 169.2 Compression Garments and Their Associated Pressure

Type	Garment Pressure
Over the counter	7-15 mm Hg. Not graduated
Anti-embolism	15-20 mm Hg. Graduated
Chronic venous insufficiency or lymphedema	20-30, 30-40, 40-50, and 50-60 mm Hg
Patients with comorbidities	20-30 mm Hg or less
Upper extremity	20-30 mm Hg
Lower limbs with recalcitrant chronic lymphedema	30–40 mm Hg

Wearing compression bandages or garments that are too tight, restrictive, or not fitting properly may worsen limb condition. When fitted correctly and when properly worn, compression garments may reduce swelling (Fig. 169.7).[52] Support garments come in a variety of sizes, compression strengths, and materials; the different features may be selected to meet the unique needs and dimensions of individual patients (Figs. 169.8 and 169.9). Although off-the-shelf prefabricated garments may fit many limbs, custom stockings may be necessary for significant swelling or an unusual shape. Compression garments should be replaced every 3 to 6 months. Contraindications for the use of compression garments include arterial insufficiency, acute cardiac failure, extreme limb shape distortion,

Figure 169.7 Manual Lymphatic Drainage.

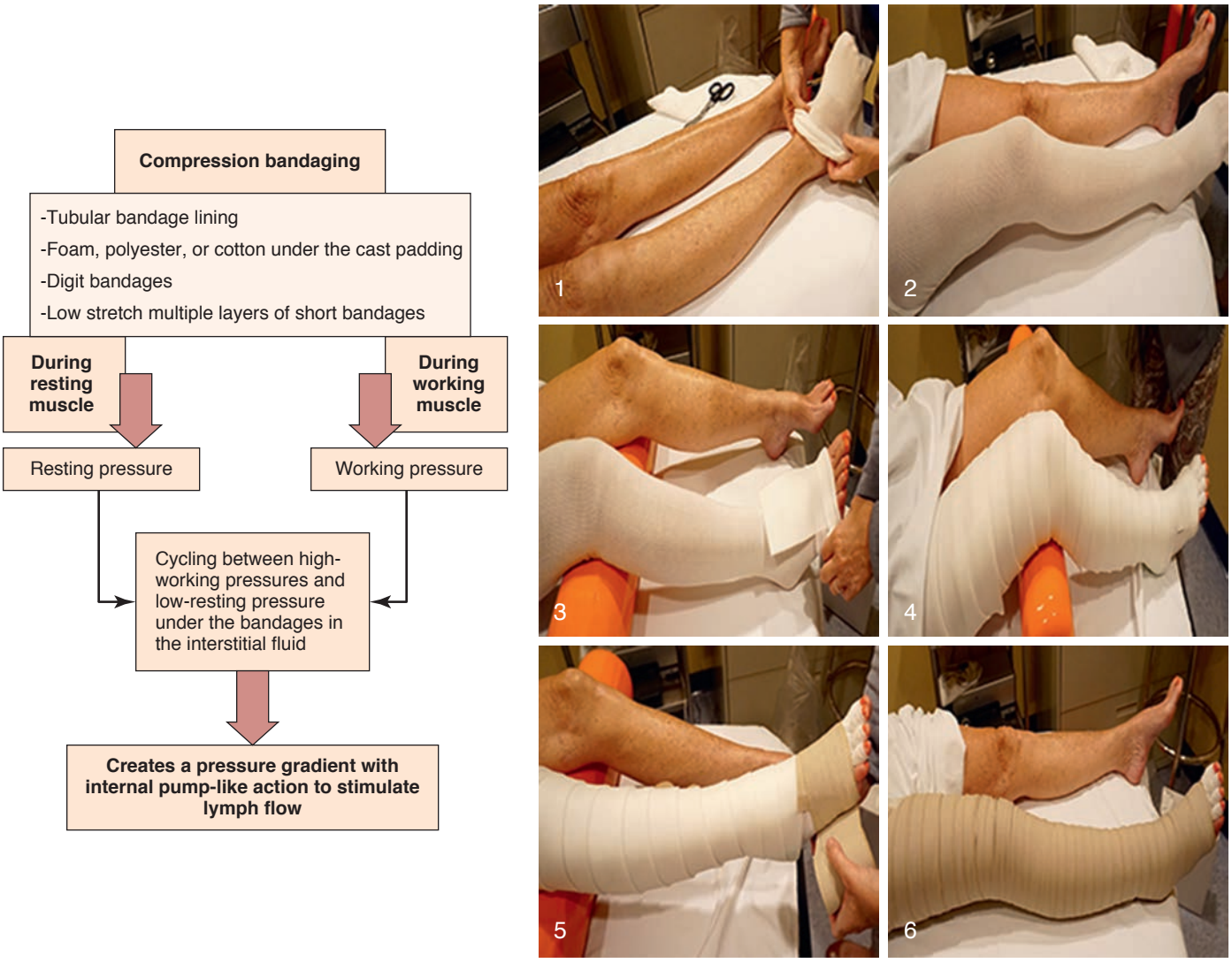

Figure 169.8 Compression Bandaging.

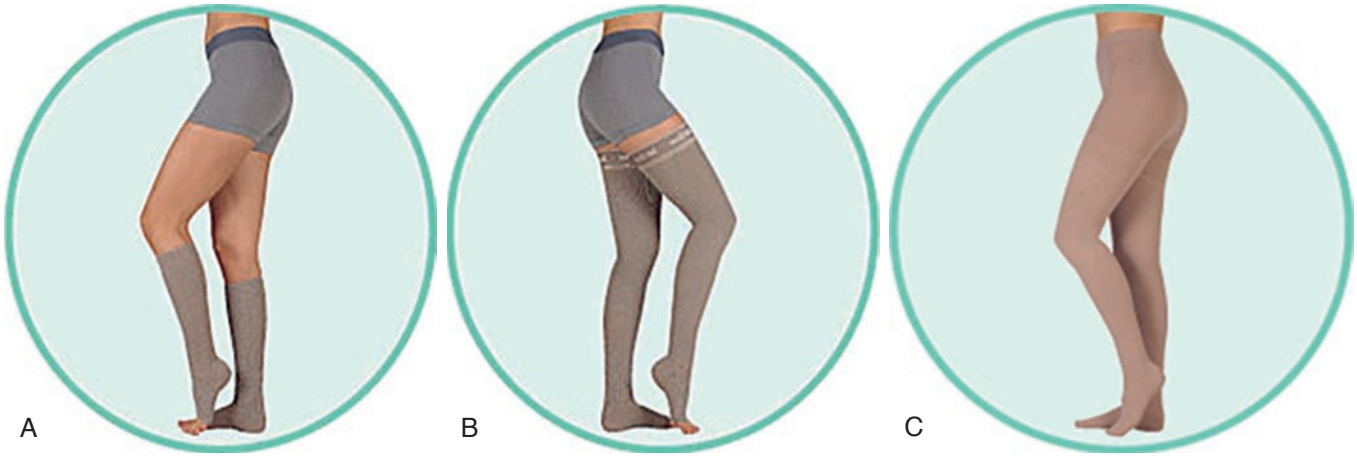

Figure 169.9 Compression Garments Length. **A**, Knee-high; **B**, thigh-high; and **C**, full-length.

very deep skin folds, extensive skin ulceration, severe peripheral neuropathy, and lymphorrhea.[65] There is a lack of evidence suggesting a positive or negative effect from a compression garment use during exercise. The results from current and previous research suggest the recommendation that garments must be worn during exercise is questionable, and its application requires an individualized approach.[66]

Stocking length is frequently an issue. As a general rule, stockings should be long enough to cover the edematous portion of the limb, but patient preference and physical limitations have to be considered. In general, knee-high or thigh-high compression garments with removable proximal pressure support (e.g., biking shorts, sport leotards) are better tolerated than full-length garments. Patient input in selecting among the wide range of options is key to promoting acceptance and adherence. Good garment fit is critical. Garments should never be rolled at the top, creating the possibility of an obstructing tourniquet. Creases at the ankle or in the popliteal or cubital areas can create enough pressure to cause skin breakdown. Skin should be carefully inspected for chafing or irritation after any new garment is worn.

Nonelastic Compression

Commercial nonelastic support devices are well received by patients as an alternative to nighttime wrapping. The Circ Aid (Shaw Therapeutics, Rumson, New Jersey) uses Velcro fastenings to adjust a series of nonelastic support bands around the leg and ankle. Another form of nonelastic support, the Reid sleeve (Peninsula Medical Inc., Scott Valley, California), is a tube of egg-crate foam, surrounded by canvas, with multiple wide Velcro bands to apply compression. Nonelastic compression options are most helpful for patients who are unable to manage a program of complex wrapping by themselves (Fig. 169.10). The efficacy of nonelastic devices has not been prospectively tested.

Sequential Pneumatic Compression

Sequential pneumatic compression (also called intermittent pneumatic compression [IPC]), is another method of compression therapy,[55] which is an ideal alternative to replace MLD for those patients who find difficulty performing the self-care MLD.[67,68] With lymphedema there is no force available to mobilize, isolate, and propel stagnant fluid to the regions where lymphatics absorb and contract; this task needs to be replaced by external massage, of which the most effective seems to be the sequential IPC.[69] The intermittent nature of pulsatile external compression produces beneficial physiologic changes, which include hematologic, hemodynamic, and endothelial effects.[70] The device enhances lymph transport by generating intermittent inflation and deflation over the affected limb, which mimics the action of muscle pump. Basically there are two phases: (1) the preparation phase, where pressure is applied in a distal-to-proximal gradient; and (2) the drainage phase, where pressure is applied in the same manner.[67] IPC also reduces lymphedema by decreasing capillary filtration, and therefore decreasing lymph formation.[71] Also the pump will lead to evacuating the edematous fluid to the area with normal lymph flow through the squeezing effect of the pump.[68] However, the efficacy of IPC may depend on the clinical situation as well as on several variables associated with the devices.[72] Bergan et al.[73] randomized 35 patients with lymphedema to a 2-hour-long treatment session with one of three types of compression pumps: (1) a uni-compartmental pump using 50 mm Hg pressure; (2) a three-compartment pump with segmental pressures of 50 mm Hg in each cell; or (3) a multi-compartmental gradient pressure pump with 10 cells ranging in pressure from 80 mm Hg distally to 30 mm Hg proximally. The mean percentage volume change was +0.4% in the first group, +7.3% in the second, and −31.6% in the third. The authors concluded that multi-compartment sequential compression achieved the best reduction of limb volume after a single treatment for chronic lymphedema.

The IPC devices may be single or multiple chambered,[74] and some pumps permit adjustment of the amount of pressure in a particular chamber; however, for the management of patients with lymphedema, the ideal pressure for the pump is unknown. Some investigators have suggested that a pressure greater than 60 mm Hg may injure lymphatic vessels. The IPC treatment is usually applied daily or 5 times per week; the optimal duration of IPC is also unknown. Among various studies, sessions have

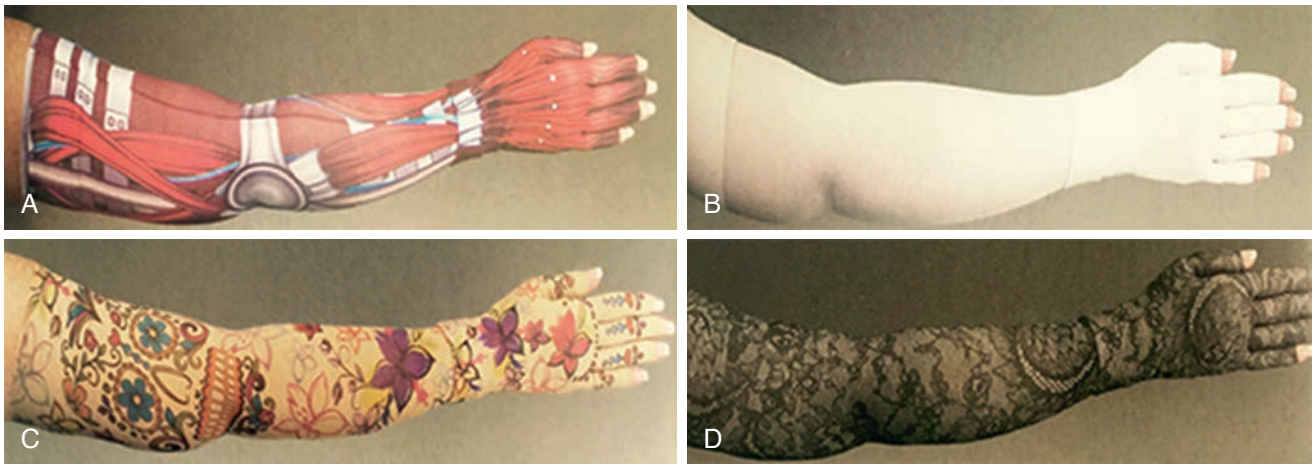

Figure 169.10 Compression Garments Materials. A, Latex; **B,** cotton; **C,** spandex; and **D,** nylon.

varied in length (90 minutes to as long as 6 hours) and duration (2 days to 4 weeks).[75–79]

After external compression therapy, a form-fitting, low-stretch elastic knit sleeve is usually applied to maintain edema reduction.[5] Outcomes of using the pump have been studied, and it was concluded that the pressure generated from the pump at the limb lymphedema tissue will cause formation of tissue channels that will work as pathways to help in clearing the accumulated fluid. The limb circumference is decreased or at least does not further increase, and the elasticity of the target limb is increased and maintained. No local complications in limb texture were observed.[5] The long-term, high-pressure IPC, long-inflation timed therapy can be safely be recommended to patients with lower limb lymphedema.[68] Contraindications to the use of IPC include local or proximal malignancy, infection in the limb, deep vein thrombosis, and patients on anticoagulation medication.[67] Current trials have failed to show the effectiveness of the addition of an IPC to the routine management of breast-cancer-related lymphedema.[80] It has been reported that IPC improved symptom relief, and reduced episodes of cellulitis and ulceration in lower-extremity lymphedema. It was well tolerated and should be recommended as supplemental to standard lymphedema therapy.[81]

Pressure Level

Provided there is no underlying peripheral arterial disease, sustained pressure of 60 to 70 mm Hg has been suggested as a maximum upper limit to treat lymphedema. Therapeutic lower extremity elastic stockings designed for chronic venous insufficiency or lymphedema are available in a variety of lengths and compression strengths (20 to 30, 30 to 40, 40 to 50, and 50 to 60 mm Hg). Lower limbs with recalcitrant chronic lymphedema generally require 30 to 40 mm Hg of compression at the ankle; however, for patients with comorbidities (e.g., diabetes mellitus, arterial occlusive disease, arthritis, or other conditions that limit the use of high-compression garments), stocking pressures of 20 to 30 mm Hg or less may be more appropriate. Upper extremity garments are typically fitted with 20 to 30 mm Hg pressure; however, 15 to 20 or 30 to 40 mm Hg are available, but their use would depend on lymphedema stage and tissue turgor. Previous studies have shown that high-pressure (90 to 100 mm Hg) sequential external pneumatic compression (SEP) reduced both limb girth and volume in a lymphedematous extremity.[82] Good evidence supporting the use of IPC for thrombosis prevention after surgery, in the treatment of post-thrombotic syndrome, and in lymphedema, has been reported.[83]

It also has been reported that IPC use with a pressure of 120 mm Hg inside the chambers effectively reduced a phlebolymphedema. Furthermore, it appeared that treatments with a pressure of 60 mm Hg were ineffective in lymphedema therapy, and perhaps are only useful in antiedematous therapy.[84] Currently, the optimal frequency and duration of IPC therapy is unclear.[74] Little known adverse events have been reported using IPC. In one study, there were no significant adverse events reported; however, there were reports of discomfort in two patients with chronic venous edema treated with IPC at 60 mm Hg, but not at 40 or 50 mm Hg. Another patient reported skin irritation, while three reported discomfort at least once during therapy.[85] Current literature indicates that IPC devices have little detrimental effect on patient safety (Fig. 169.11)[74]

Figure 169.11 Nonelastic Compression.

After reviewing current literature regarding garment characteristics, the authors of this chapter recommend applying nonelastic graduated compression stocking with 60 to 70 mm Hg when appropriate in addition to CDT.

Exercise

Exercise may be beneficial to individuals with lymphedema.[86] It provides an improved life quality[87] and a therapeutic intervention instead of worsening the lymphedema symptoms[88] by enhancing protein resorption[89] and maintaining lymphatic flow.[88,90,91] During the inspiration phase of exercise, there is a decrease in the intrathoracic pressure, which leads to an improvement of infradiaphragmatic lymph flow.[92] It can be concluded that with more exercise there is more pulmonary work, which enhances lymph flow and decreases the lymphedema.[64] Exercise will help weight reduction, which, in turn, will augment the clearance of lymph and decrease the swelling.[64] It is worth mentioning that patients with lymphedema associated with breast cancer may benefit from resistance exercise, and it is safe when it is done under the supervision of an experienced trainer to decrease symptoms exacerbation.[93,94]

Skin Care and Nail Care

Skin and nail hygiene is recommended to decrease the amount of cutaneous fungal and bacterial on the skin. Low pH moisturizers should be applied to keep skin from drying and cracking.[95] Cracks and dry areas of the skin are entry points for bacterial and fungal infections.[96,97] Regular use of a moisturizer can be used to avoid skin cracking. For arm lymphedema, good hand

TABLE 169.3 Therapeutic Approach Based on Clinical Stages

Stages	Duration	Phase I (Decongestion)	Phase II (Maintenance)
Stage I	2-3 weeks	• MLD 1-2× per day • Short-stretch bandages • Skin care • Remedial exercises	• MLD • Compression garments • Skin care • Remedial exercises
Stage II	3-4 weeks	• MLD twice a day • Short-stretch bandages • Skin care • Remedial exercises	• MLD as needed 1-2× per week • Compression garments • Skin care • Remedial exercises • Repeating phase I (1-2×)
Stage III	4-6 weeks	• MLD 2-3× day • Short-stretch bandages • Skin care • Remedial exercises	• MLD as needed 1-2× per week • Compression garments with bandages • Bandages at night • Skin care • Remedial exercises • Repeating phase I (3-4×) • Plastic surgery may be indicated

MLD, Manual lymphatic drainage.

hygiene and softening the cuticles with proper cuticle moisturizer are recommended.[98]

Therapeutic Approach Based on Clinical Stages

Multimodal therapy consists of general measures of self-care applicable for all stages of lymphedema. Treatment should be based on the stage of the disease. The intensity of compression and physiotherapy will also vary by stage. There are two general phases of therapy. The goal of phase I (intensive phase) is to mobilize accumulated protein rich fluid and initiate the reduction of fibrosclerotic tissue (if present), while the goal of phase II is to reserve and improve the success achieved during phase I (Table 169.3).

TABLE 169.4 Level of Evidence for Lymphedema Current Treatments

Therapy	Outcome	Evidence
Manual lymph drainage	Effectiveness not established	(112), (113), (114), (115)
Compression bandaging compression garments	Recommended for practice	(61), (116), (117), (118)
Pneumatic compression	Effectiveness not established	(106), (119), (120)
Exercise	Likely to be effective	(121), (122), (123)
Skin care	Expert opinion	None

Level of Evidence

CDT, including all the components, is recommended for practice.[99–106] Based on recent research, each individual component of CDT has different expected outcomes (Table 169.4).

OTHER TREATMENT

Besides the established therapies mentioned in Table 169.4, the benefits and effectiveness of several other therapies have been investigated. Pharmacotherapy has not shown to be beneficial; neither diuretics nor coumarin alleviate lymphedema. Low-level laser therapy, hyperbaric oxygen, and intermittent negative pressure have limited data to support effectiveness (Fig. 169.12). For example, the results from one low-level laser therapy study indicated edema reduction after treatment, which was sustained for several months.[107] In addition, hyperbaric oxygen therapy studies for breast-cancer-related lymphedema has had mixed results (see Fig. 169.13 for summary).[108,109]

As mentioned below, additional treatments have been investigated. It is likely, in the future, that gene therapy will be used to develop new lymphangioles in the affected limbs, which could be a potential clinical remedy. The potential efficacy of this approach was illustrated in a mouse model with lymphedema acquired by inactivating VEGFR-3 mutation, similar to that in congenital hereditary lymphedema (Milroy disease). Virus-mediated therapy with the gene for VEGF-C, which activates VEGFR-3, led to the generation of functional lymphatic vessels.[110]

Intralymphatic steroid injections also have been used in an attempt to decrease fibrotic occlusion in lymph nodes and to improve lymphatic transport. In a pilot study of 20 patients with primary lymphedema, 8 showed improvement for as long as 9 months after treatment.[111] Yet, to-date, the effectiveness of steroid treatment has not been established; however, investigators in Japan attempted to treat secondary lymphedema by injecting autologous lymphocytes into the main artery of the affected limb. Five of seven patients showed a short-term improvement.[112] In addition, the results of a larger series, which used a combined approach of lymphocyte injection and compression therapy, reported that 34 of 46 patients experienced edema reduction.[113] However, these studies have not been replicated.

Figure 169.12 **Sequential Pneumatic Compression. A,** Basic pump; **B,** Entre system with up to 18 inflatable chambers; and **C,** Flexitouch system with up to 32 inflatable chambers.

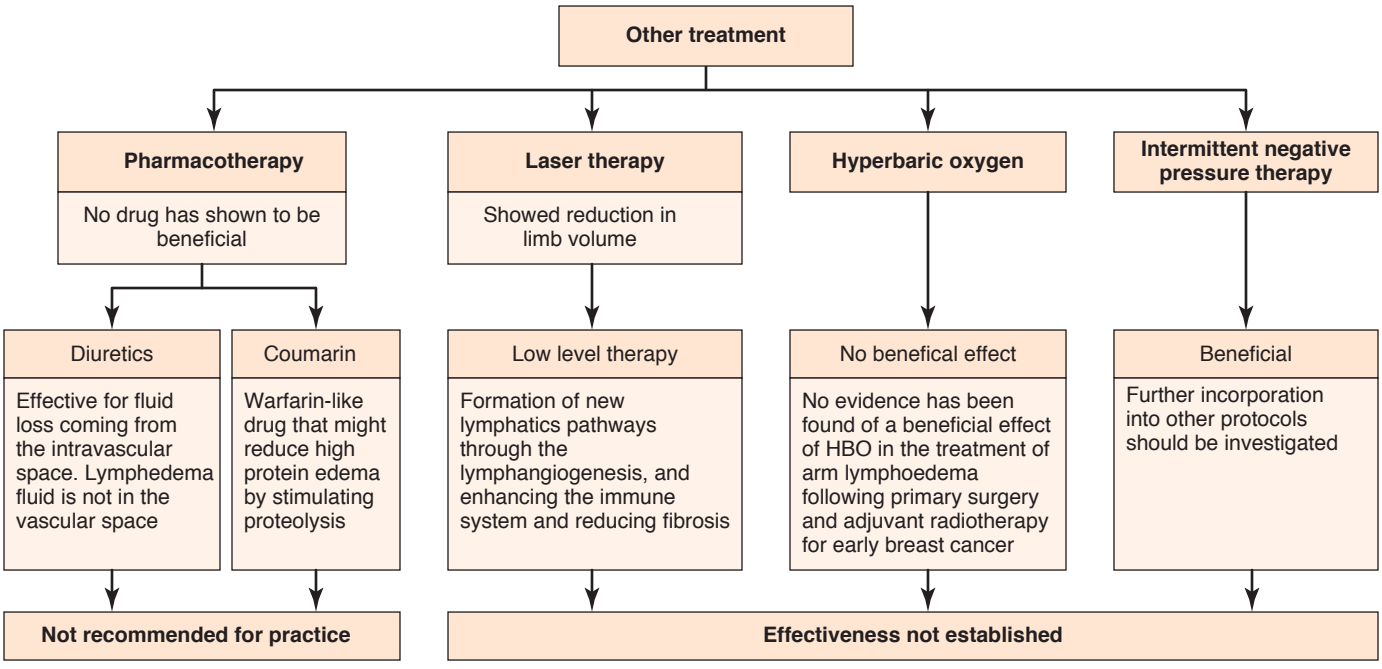

Figure 169.13 Other Treatment.

Researchers found a significant decrease in the thickness of lymphedematous ears in a rabbit animal model following extracorporeal shock wave therapy. The results indicated that there was a significant increase in the density of lymphatic vessels. The authors suggested that extracorporeal shock wave therapy may be a novel, feasible, effective, and noninvasive treatment for lymphedema.[2]

SUPPORTING EVIDENCE

Besides the standard lymphedema management and treatment techniques, there is limited information on the efficacy for other non-traditional therapies (see Figure 169.13). For example, there is little to no evidence that diuretics are effective. There are some reports supporting the use of coumarin[114,115] and laser

therapy.[2,107,116–120] On the other hand, published reports have failed to show any benefit for the use of hyperbaric oxygen[121,122] or intermittent negative pressure therapy.[123]

COMPLICATIONS

Skin Infections

Skin infection itself is a triggering factor for lymphedema, and it can be a complication of untreated lymphedema. Lymphedema is a protein-rich fluid, which is also an excellent medium for bacterial and fungal growth that may contribute to an increasing risk of infection. Lymphedematous tissue serves as an entry site for bacteria and developing erysipelas,[124] recurrent infections, and lymphangitis.[95,124–127] Approximately 20% to 30% of lymphedema patients will develop lymphangitis, erysipelas,[95] and cellulitis, especially those patients undergoing lymph node dissection.[56,128]

Malignancy

A rare, secondary, malignant tumor, called lymphangiosarcoma, can be the result of chronic lymphedema of any origin and be associated with its development.[129] It is usually seen in patients with massive and protracted edema,[130] and has been classically described as occurring in the post-mastectomy patient (Stewart-Treves syndrome),[131–133] or with primary lymphedema and chronic filarial lymphedema.[134–136] The tumor originates in vascular endothelial cells of the affected arm with lymphedema, not the lymphatic vessels.[132] It may initially appear as blue-red or purple skin lesions with a macular or papular shape. Multiple lesions are common and subcutaneous nodules may appear. Such skin lesions should be carefully evaluated in patients with chronic lymphedema.

Late-onset malignancies are a potentially devastating, but rare, complication of long-standing lymphedema. In most cases, they develop in no more than 1% of patients with lymphedema. Most common malignancies are angiosarcomas[137] and lymphangiosarcomas,[138] which are thought to represent the neoplastic transformation of blood vessels and lymphatics, respectively.

Histologically and clinically, it is difficult to distinguish these two sarcomas from each other. The occurrence of angiosarcoma (or lymphangiosarcoma) in the setting of lymphedema is commonly called Stewart-Treves syndrome.[137] Sarcomas can develop in patients with long-standing lymphedema of any cause: primary lymphedema or lymphedema secondary to filariasis,[136] hysterectomy,[139] trauma,[140] or mastectomy.[140] Other malignancies, including Hodgkin and non-Hodgkin lymphoma,[141] Kaposi sarcoma,[142] squamous cell carcinoma,[143,144] and malignant melanoma,[145] have been associated with chronic lymphedema, but a causal link has not been established.

Psychological Impairment

Chronic lymphedema continues to be an incurable and disabling condition.[146] The intensity of symptoms may differ from one patient to another; however, overall, most patients will have psychological impairment[147] and/or decreased quality of life, including social, functional, and emotional components.[148,149] Psychological and functional impairments associated with lymphedema are significant.[28] The psychological impact of long-term disfigurement, especially in adolescents, needs to be considered. The disturbance of body image is the underlying cause for younger women to have psychological distress, and often for older women to have depression.[150] Kim et al. found that lymphedema secondary to pelvic lymph node dissection among gynecologic cancer survivors decreased their quality of life due to the related symptoms and financial difficulty.[151] Winch et al. found the potential to accentuate sexual issues caused by lymphedema secondary to breast cancer, and women were reluctant to discuss these issues with anyone other than their partner.[152] Park et al.[28] found that 12% of patients reported that they were limited to jobs working at a desk or that allowed frequent sitting. Effective management of lymphedema may improve patient quality of life and reduce interference in daily activity.[153]

INSURANCE ROLE

From our local lymphedema clinic, it was reported that most insurance coverage plans cover CDT, but managed healthcare systems often limit the number of visits or units (e.g., 15 minute increments of care). In some cases, more visits may be requested with the submission of documentation. Typically, successful CDT treatment requires five visits/week for the first 2 weeks and then three visits/week for an additional 2 weeks. Hopefully, following CDT treatment, the size and volume of interstitial fluid has reduced to the point where a good assessment can be made. After which, compression garments can be fit and patients are provided with instruction for donning, along with self-care instructions and home protocols are provided to achieve the best compliance and long-lasting results. As there is no cure for lymphedema, in most cases there are few problems with coverage based on severity, as lymphedema is always progressive, if not appropriately managed. Unmanaged lymphedema places patients at great risk of infections.[95] However, it has also been reported that some third-party payers have suggested that edema is a cosmetic problem; consequently, they deny reimbursement for both treatment and garments. Such policies or beliefs often require repeated communications between payers and physicians to gain approval for treatment.[154] As part of a reconsideration of coverage policy, the Centers for Medicare and Medicaid Services requested a systematic review of the evidence on the use of pneumatic compression devices in the home environment for treatment of chronic venous insufficiency (CVI) and venous ulcers.[155] "The Lymphedema Treatment Act is a federal bill that aims to improve insurance coverage for the medically necessary, doctor-prescribed compression supplies, which are the cornerstone of lymphedema treatment."[156]

Currently Medicare does not cover compression garments, yet the lymphedema population is the one that could benefit the most. There is a rather lengthy application and a corresponding $25 fee paid by the patient. If approved, then they are

eligible for one set of garments and may apply again each year. However, the time and effort is well rewarded as thigh- and knee-high garments per leg are approximately $480 and $280, (USD, 2016), respectively.

In one study, researchers found an association between significant reductions in episodes of cellulitis and outpatient care and costs following the use of advanced pneumatic compression devices in patients with both cancer-related and noncancer-related lymphedema. Since the publication of this study in the *Journal of the American Medical Association* (JAMA),[157] healthcare payers have been more willing to reimburse for such treatments. Hopefully, these results will encourage healthcare providers to purchase comparable equipment, such as the Flexitouch System by Tactile Medical, because trial and treatment adjunct is very expensive.

IDEAL OUTPATIENT LYMPHEDEMA CLINIC

First and foremost, assessments, consultations, and treatment for lymphedema should take a multidisciplinary and team approach. The multidisciplinary team could include—but would not be limited to—specialists in nursing, podiatry, dermatology, plastics, oncology, physiotherapy, vascular, and psychology. The clinic should be a participating member of the National Lymphedema Network (NLN) because it is a good resource for healthcare professionals as well as patients. The Marilyn Westbrook Garment Fund is administered by NLN and provides garments to member patients who are in financial need and are treated by NLN-affiliated therapists. The lymphedema clinic should have a minimum of three certified lymphedema therapists who are certified by the Lymphedema Association of North America (LANA). Preferably there should be two physical therapists: one occupational and one physical, and at least one therapist experienced and certified in wound care. There should be a certified fitter for custom garments available at least 1 day a week. In addition, the clinic should have a working relationship with garment and supply vendors who provide dependable and timely service.

The necessary supplies for providing CDT should be maintained on site. In addition, under-stockinets of various sizes, compression foam of varied density, and short-stretch bandages various sizes should be kept in stock. For example, one leg

TABLE 169.5 Helpful Resources

Source	URL
Alberta Lymphedema Association	http://www.albertalymphedema.com/
British Lymphology Society	http://www.lymphoedema.org/
International Society of Lymphology (ISL)	http://www.u.arizona.edu/~witte/ISL.htm
Lymph Notes	http://www.lymphnotes.com/
Lymphatic Education & Research Network	http://lymphaticnetwork.org/
Lymphedema in the News	http://paper.li/bluebonnetfield/1313342568
Lymphedema People	http://www.lymphedemapeople.com/
Lymphedema Treatment Act	http://lymphedematreatmentact.org/
Graceful Lymphedema	http://www.gracefullymphedema.com/
Life with Lymphedema	https://lifewithlymphedema.com/
Lymphedema Diary	https://lymphedemadiary.com/
Lymphedema Runner	http://www.lymphedemarunner.com/home/
National Association for Rare Disorders	http://rarediseases.org/
Use of Hand Compression and Compression Sleeves in Lymphedema Management and Prevention	https://www.lymphedivas.com/sites/default/files/HandCompression.pdf
National Lymphedema Network Support Community (Inspire)	http://www.inspire.com/groups/national-lymphedema-network/
Ready-Made vs. Custom Sleeve	https://www.lymphedivas.com/sites/default/files/readymadevscustom.pdf
Prognostic and Therapeutic Uncertainty in Lymphedema	https://www.lymphedivas.com/sites/default/files/PrognosticUncertainty.pdf
What You Didn't Know About Compression Garments	https://www.lymphedivas.com/sites/default/files/WhatWeDontKnow.pdf
Exercise for Lymphedema	https://www.lymphedivas.com/sites/default/files/ExerciseforLymphedema.pdf
Lymphedema Risk During Air Travel	https://www.lymphedivas.com/sites/default/files/LymphedemaAirTravel.pdf
Modern Day Compression Garments	https://www.lymphedivas.com/sites/default/files/ModernDayCompressionGarments.pdf

could require three boxes of foam, two 8 cm short-stretch and four 10 cm short-stretch bandages. The clinic should work with patients to remove any financial barriers that may restrict treatment. It is beneficial for patients to receive arm and leg kits prior to starting therapy; starter kits can be expensive especially if treatment is necessary for both legs and arms. In addition, two sets are needed, one to wash and one to wear. Finally, the treatment room must have a sink, no carpeting, and be large enough to accommodate large patients. The treatment table needs to be safe for supporting up to 600 pounds and have the capability to be elevated.

HELPFUL RESOURCES

See Table 169.5.

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A complete reference list can be found online at www.expertconsult.com.

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170 CHAPTER

Lymphedema: Surgical Treatment

RUEDIGER G.H. BAUMEISTER

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The lymphatic system is the least understood part of the vascular system. Lymphatic malformations such as chylous disorders, cystic hygromas, and lymphocysts are rare; acquired disorders such as lymphoceles and chylous effusions are also uncommon. However, local interruption and obstruction of the lymphatic vessels occur frequently from either congenital or acquired causes (see Chapter 168). In developed countries, most acquired lymphatic obstructions are iatrogenic, caused by medical procedures. In developing countries, the most frequent cause of lymphatic obstruction resulting in chronic lymphedema is filariasis.

BASIS OF SURGICAL TREATMENT

The development of lymphedema can be described as an imbalance between the lymphatic load (the amount of lymph that has to be cleared from a body part within a given time) and the lymphatic transport capacity (the amount of lymph that can be transported out of a body part within a given time), which is dependent on the number and function of lymphatic vessels and nodes (see Chapter 10).[1] Reduced lymphatic flow due to obstruction leads to secondary tissue changes, a process that is not yet fully understood. Lymphatic outflow disorders

are manifested mainly with advanced secondary changes and chronic lymphedema, a condition that can be difficult to treat unless the underlying problem of reduced lymphatic outflow is resolved. Historically, secondary tissue changes leading to excess fibrous and adipose tissue were treated solely by excisional procedures, without correcting the underlying cause. However, modern surgical concepts have been developed to attempt to correct the underlying pathophysiologic mechanism to the extent possible.

Because conservative therapy consisting of limb elevation, compression garments, complex decongestive therapy, and compression pump therapy should be the first step (see Chapter 169), the question arises whether and at what time surgery is indicated. If the only purpose of surgery is resection, it is wise to reserve it as a last option. If, however, surgical reconstruction is possible, this procedure should be considered and offered to the patient early in the course of lymphedema.

HISTORICAL PERSPECTIVE

Excisional Operations

Surgical Excision

The most radical excisional approach is the classic operation first described by Charles in 1912.[2] It involves complete and circumferential resection of the skin, subcutaneous tissue, and deep fascia, followed by split-skin grafting. However, this procedure is associated with significant complications, and follow-up studies revealed hyperkeratosis, papillomatosis, and ulcerations in the grafted areas.[3,4] Modifications of this technique, using the resected skin for grafting and performing the surgery in two stages,[5-11] reduced the surgical trauma and the rate of complications.

Liposuction

A less invasive way to reduce the amount of subcutaneous tissue is liposuction. It was first described by Illouz as a method for treating lymphedema.[12] More recently, Brorson and Svensson demonstrated lasting volume reduction if elastic compression garments are worn after the surgical procedure; this can result in an extremity that is even slimmer than the healthy limb.[13]

Functional Procedures

Early Techniques

The first attempts to divert lymph from the subcutaneous to the muscular compartment through partial or complete resection of the fascia were described by Lanz and Kondoleon.[14-16] Redirection of lymph from the superficial to the deep compartment is also a component of the Thompson method. Thompson resected the fascia along with parts of the subcutaneous tissue, created a flap in two stages, and de-epithelialized the rim of the flap to allow the outflow of lymph. Subsequently, he buried the flap near the deep vessels to facilitate the creation of spontaneous lymphatic anastomoses.[17-24]

The use of veins for the reconstruction of an interrupted lymphatic system was investigated by Holle and Mandl experimentally and performed in two patients clinically.[25,26] Campisi and colleagues reported on a larger series using this technique.[27]

Modern Techniques

Currently, the most common way to drain lymph from edematous tissue is the construction of connections between the lymphatic (Fig. 170.1) and venous systems in the periphery. The first reports on lymphonodular and lymphovenous anastomoses were provided by Laine and Howard,[28] Nielubowicz and Olszewski,[29] Rivero and coworkers,[30] and Allen and Taylor.[31] Degni designed a special needle to facilitate the insertion of lymphatic vessels into veins.[32,33] Further improvements were described by O'Brien and colleagues using microsurgical techniques.[34,35] In some patients, excisional methods were combined with lymphovenous shunting. A large cohort of patients successfully treated with microsurgical lymphovenous anastomosis was reported by Campisi and associates.[36]

However, experimental studies revealed problems with thrombotic occlusion at the site of anastomosis, with a patency of 20% after 5 months of follow-up.[37-39] Specific preparations that ensured an undisturbed connection to the venous valve led to an improved patency rate of 44% after 6 months.[40,41] Gloviczki and colleagues reported on results of experimental microsurgical end-to-end anastomoses between normal femoral lymph vessels and a tributary of the femoral vein in dogs and noted a 50% patency rate up to 8 months after the operation.[42]

Direct reconstruction of the lymphatic system became a possibility only after the development of microsurgery. Before that time, it was commonly thought to be impossible to anastomose lymphatic vessels because of their extremely small diameters. Hence, Danese approximated lymphatic vessels as close to each other as possible and waited for spontaneous regeneration. He was able to demonstrate transport of contrast medium (through the lymphatics) with this technique.[43] In a patient with lymphedema of the arm, he mobilized two lymphatic channels proximally and distally, approximated them in the axilla, and achieved a reduction in edema.[44] Subsequent approaches included interpositioning veins between lymphatic vessels,[25-27] implanting microsurgical lymph node grafts,[45,46] and implanting free flaps with lymphatic vessels.[47,48]

The question of optimal reconstruction material has been the subject of two experimental studies. In a series of 14 rats, 100% of the autologous lymphatic grafts were patent (observations made between days 7 and 119 postoperatively), whereas allogeneic lymphatic grafts were patent only until day 21 after transplantation. When lymphatics were replaced by small veins ($n = 10$), a patency of 70% was observed. Expanded polytetrafluoroethylene implants ($n = 10$) used as lymphovascular conduits were already thrombosed by day 7.[49] In a comparison of lymphatic and venous interpositional autografts in 71 dogs, all 26 lymphatic autografts remained patent up to the end of the observation period at 24 weeks. Of 30 venous interpositional autografts, only 4 were patent after 1 week. None of the lympholymphatic anastomoses with silicone tubing showed patency at any time.[50]

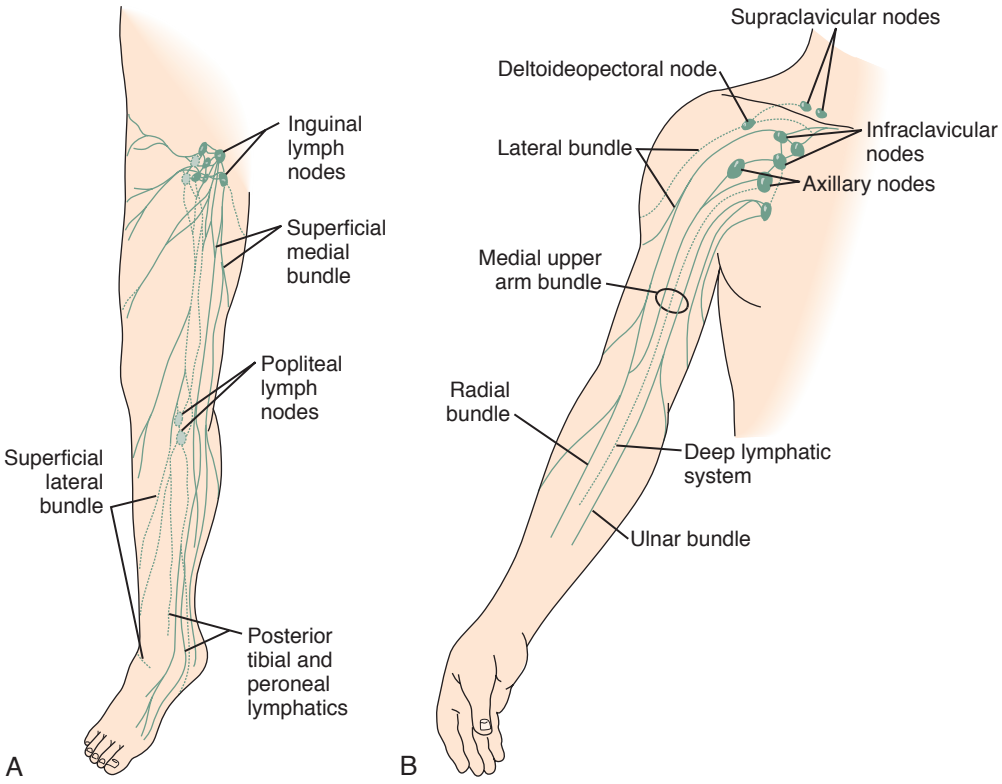

Figure 170.1 (A) Superficial lymphatic system of the lower extremity. (B) Lymphatic system of the upper extremity. (Courtesy Mayo Foundation.)

Acland and Smith were the first to attempt to anastomose lymphatic vessels.[51-53] The first successful therapeutic lympholymphatic graft was performed in 1980 by Baumeister in a patient with unilateral lymphedema of the lower extremity.[54-57] This followed extensive animal experiments on thoracic duct transplants in rats[58] and the treatment of experimental lymphedema in dogs using lymphatic autografts.[53]

PREOPERATIVE PLANNING

Visualizing Lymphatic Vessels

Lymphography

Direct contrast lymphography, using oily contrast medium and invasive administration through dissected lymphatic vessels, was introduced by Kinmonth and greatly advanced our knowledge of the lymphatic system.[59] However, owing to the invasiveness of the procedure (and injury to the lymphatic vessels and lymph nodes), it was found to worsen lymphedema and is rarely used today. Indirect contrast lymphography, using a water-soluble contrast medium injected subepidermally, cannot visualize lymphatic vessels as successfully as direct lymphography and gained only limited use.[60]

Magnetic Resonance Imaging

Attempts to visualize lymphatic vessels with magnetic resonance imaging (MRI) and subdermally administered contrast medium have been promising. This technique may be useful in the future for preprocedure planning and postoperative assessment of the patency of lymphatic reconstructions.[61] For the detection of vascular lymphatic malformations, MRI is extremely valuable both with and without contrast medium.

MR lymphangiography and lymphoscintigraphy show a clear concordance. Inguinal lymph nodes were better visualized using lymphoscintigraphy, whereas lymph vessels and their abnormalities were better depicted by MR lymphangiography.[62]

Lymphoscintigraphy

The most important test to evaluate chronic lymphedema and to plan surgical treatment is lymphoscintigraphy. It can be repeated and used for treatment planning and follow-up. It not only evaluates function but also visualizes routes of lymphatic transport. The *lymphatic transport index* summarizes the findings derived from lymphoscintigraphic studies and allows a semiquantitative evaluation of lymphatic flow without the need for standardized physical movements by the patient. The transport index ranges from 0 for an optimal lymphatic outflow to 45 for no visible transport; normal values are less than 10. It also provides a good basis for follow-up studies and can show lymphatic transport along the route of lymphatic grafts.[63,64] In measuring lymph transport at regions of interest, it is critical to standardize the dose of radiopharmaceutical and the physical activity of the patient during the procedure.[65]

Dye Injection

Another diagnostic tool that can be used to identify lymphatic channels is the subepidermal injection of a vital dye (patent blue dye in Europe; isosulfan blue [Lymphazurin] dye in the

United States). Normally, lymphatic transport is visualized in the superficial lymphatic collecting system. In pathologic situations, dermal backflow leads to the pooling of contrast medium within the skin, resulting in a cloudlike appearance. Because allergic reactions have been reported, staining of lymphatic vessels with patent blue or isosulfan blue dye is generally performed during surgery under general anesthesia.

Lymphatic Donor Site Assessment

For lymphatic grafting, it is critical to choose and carefully evaluate the proper harvest site for lymphatic vessels to avoid the development of edema secondary to the procedure. Thus, the donor lower extremity must be evaluated by lymphoscintigraphy before harvesting. During the harvest, the narrowing lymphatic system at the medial aspect of the knee and the groin must be left untouched, and all stained lymphatic vessels other than those used as grafts should be left in place. A study including 80 patients with arm edema showed that when this method was used, the harvest site and the untouched leg were not different in size.[57]

No pathologic values were detected after the harvest in a study of 19 consecutive patients, where the donor limb was examined pre- and postoperatively by lymphoscintigraphy. The scintigraphic follow-up was performed 48.6 months following harvest and transplantation. In all patients, the postoperative transport index was close to the preoperative baseline value and within the normal range.[66]

Patient Risk Assessment

Because this type of surgery is performed in the subcutaneous tissue, the surgical risk is generally low, and the procedure is well tolerated. Peripheral lymphovenous shunting is often performed under local anesthesia and is unproblematic as long as the patient tolerates local anesthetics. Because the application of patent blue or isosulfan blue dye can lead to allergic reactions, it should be used only under general anesthesia. Excisional methods typically involve more surgical trauma and the possibility of greater blood loss. Therefore, it is sometimes advisable to perform large excisional operations in two stages. For surgical intervention within the abdomen and thorax, the usual preoperative risk assessment must be done (see Chapter 32).

SURGERY

Autologous Lymphatic Grafting

Indications

Lymphatic vessel grafts can be attempted for the treatment of secondary lymphedema caused by localized obstruction or interruption of lymph vessels and lymph nodes, such as the lymphedema of the arm that develops after breast cancer surgery because of the excision of axillary lymph nodes and possible radiation treatment (see Fig. 170.1B). Patients with unilateral lower limb lymphedema due to the excision of inguinal or pelvic lymph nodes or pelvic irradiation for malignant disease are also potential candidates for such procedures. Transplantation of lymphatic vessels can be attempted in patients with primary lymphedema if it is caused by localized lymphatic obstruction or atresia, such as unilateral atresia of the pelvic or inguinal lymphatic system.

Surgical intervention should be considered only after a trial of conservative therapy. Conservative treatment should be continued for at least 6 months because spontaneous regression has been reported. However, if conservative therapy is unsuccessful during this time frame, reconstruction should be attempted soon to avoid secondary tissue changes. Unfortunately, treatment is often delayed. In my experience, the mean time between the onset of edema and the patient's presentation for surgery is more than 7 years.

Surgical Technique

The lymphatic grafts are harvested from the patient's thigh (Fig. 170.2). The ventromedial lymphatic bundle contains up to 16 lymphatic vessels.[67] About one to four lymphatic collectors are dissected in the medial area of the thigh, and great care is taken to spare the lymphatic system where it narrows at the level of the knee and groin. Additional peripheral branches often exist, and these can be dissected as well to create a greater number of peripheral anastomoses.

For free transfer of the graft, a ligature is placed on the lymphatic vessel selected as a graft beneath the inguinal lymph nodes with 6-0 polyglactin 910. One thread is left long to facilitate handling of the graft thereafter. Proximal to the ligature, the lymphatic vessel is transected. At the distal end of the proposed graft, the lymphatic vessel is transected proximal to

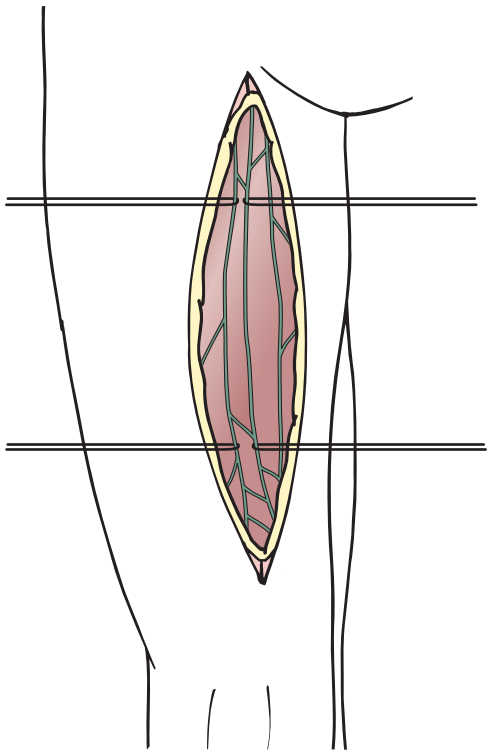

Figure 170.2 Harvesting of lymphatic grafts from the patient's thigh.

the level of the knee. The lymphatic vessel beneath the transection site is occluded by placing a suture or by using coagulation to avoid lymph leakage.

If a transposition procedure is performed, the grafts are transected distally after double ligation and tunneled subcutaneously superior to the pubic symphysis to the contralateral side, where end-to-end lympholymphatic anastomoses are performed. In free transfers and in transposition procedures, the graft has to be pulled from one incision to the other (e.g., from the upper arm to the neck or between inguinal regions). To avoid any friction during tunneling, tubes (suction catheters) are placed between the two incisions according to the proposed route of the grafts. Thereafter, the grafts themselves can be pulled through the tubes without tension. After removal of the tubes, the grafts remain undisturbed in place within the subcutaneous tissue.

Arm and Neck

For arm edema as a result of interventions in the axilla, the grafts are interposed between ascending lymphatic vessels in the upper arm and lymphatic vessels or lymph nodes in the neck (Fig. 170.3). In the upper arm, lymphatic vessels are usually epifascial (if not, they may be located subfascially in proximity to the vessels) and are best sought from an oblique incision made medially and superior to the route of the brachial vessels. The search is performed under the microscope with a medium (3× to 10×) magnification. In the early stages of lymphedema, the lymphatic vessels have a gray, shiny appearance, and the lumen can be seen clearly after transection. As the lymphatic vessels undergo fibrosis in later stages of lymphedema, it becomes more difficult to discriminate between small nerves and fibrous cords. In this case, the final decision about the potential use of grafting can be made only after transection of the structure.

The walls of lymphatic vessels are thinner in the neck than in the arms and legs. Injection of a vital dye in the hair-bearing parietal area above the ear facilitates the search for appropriate vessels. If the lymphatic vessels stain appropriately, recognition is easy. However, suturing in this area is often difficult because of the collapsing, thin-walled vessels. If this is the case, it is also possible to suture the grafts to lymph nodes. A superficial incision is made in the capsule of the node, and the graft is connected with approximately three single interrupted sutures.

To position the grafts between the sites of anastomosis, tubing from a drain is placed in the subcutaneous tissue between the incisions in the upper arm and neck. Subsequently, the grafts are pulled through the wet drain gently and without friction. After removal of the tube, the grafts remain in the subcutaneous tissue free of tension.

Leg

For unilateral edema of the lower extremity, the grafts remain attached to the inguinal lymph nodes, and the distal ends of the grafts are transposed to the opposite thigh with the help of tubing from a drain, which is temporarily interposed between the two incisions at the thigh (Figs. 170.4 to 170.6).

The tension-free technique is used to anastomose the lymphatic vessels under the operating microscope with maximal magnification (Fig. 170.7). The suture opposite the surgeon should be performed first. Because of the fragility of the vessels, the vessels are not turned over. Only the back wall is lifted as far as necessary to place a dorsal stitch. One or two additional single stitches complete the anastomosis. In my experimental studies of suture material, absorbable polyglactin was superior to nonabsorbable material. Currently, 10-0 absorbable suture (polyglactin 910) is the thinnest material available, used on a BV-75-4 needle.

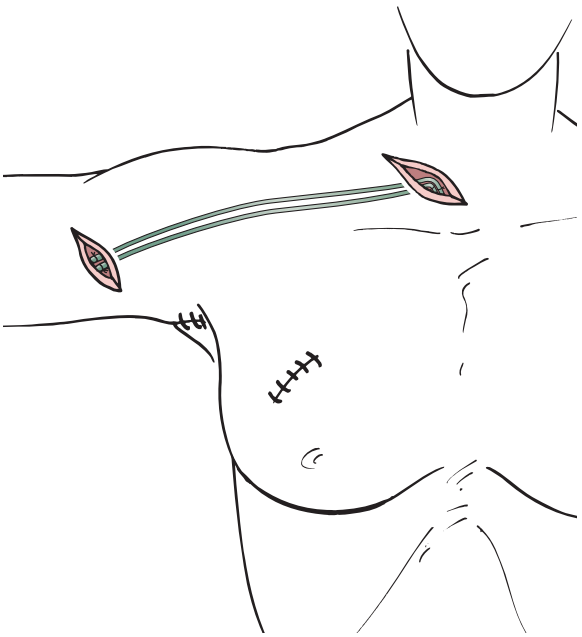

Figure 170.3 Lymphatic grafting in arm edema.

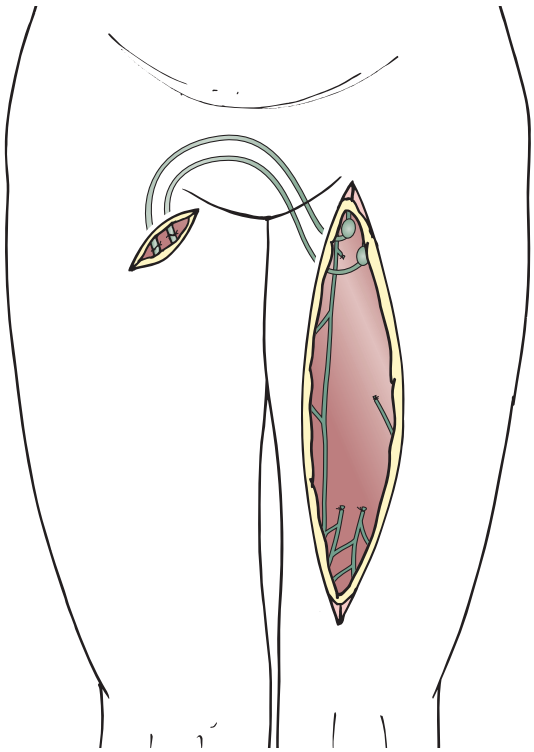

Figure 170.4 Lymphatic grafting in unilateral edema of the lower extremity.

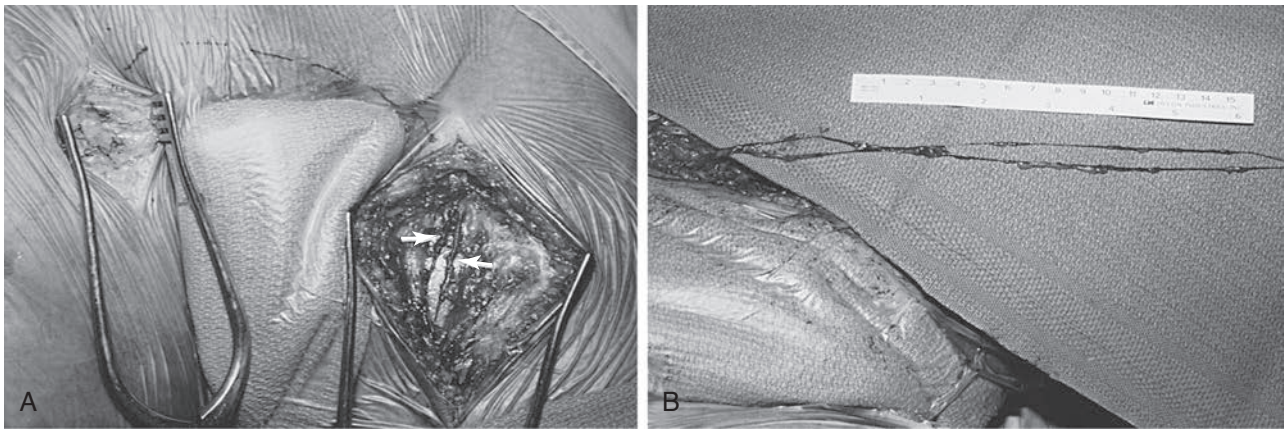

Figure 170.5 (A) Exposure of lymph vessels for suprapubic transposition. Note that two major lymph vessels of the left thigh will be used for grafting *(arrows)*. (B) Two lymphatic grafts divided at the distal thigh are prepared for grafting. (Courtesy Mayo Foundation.)

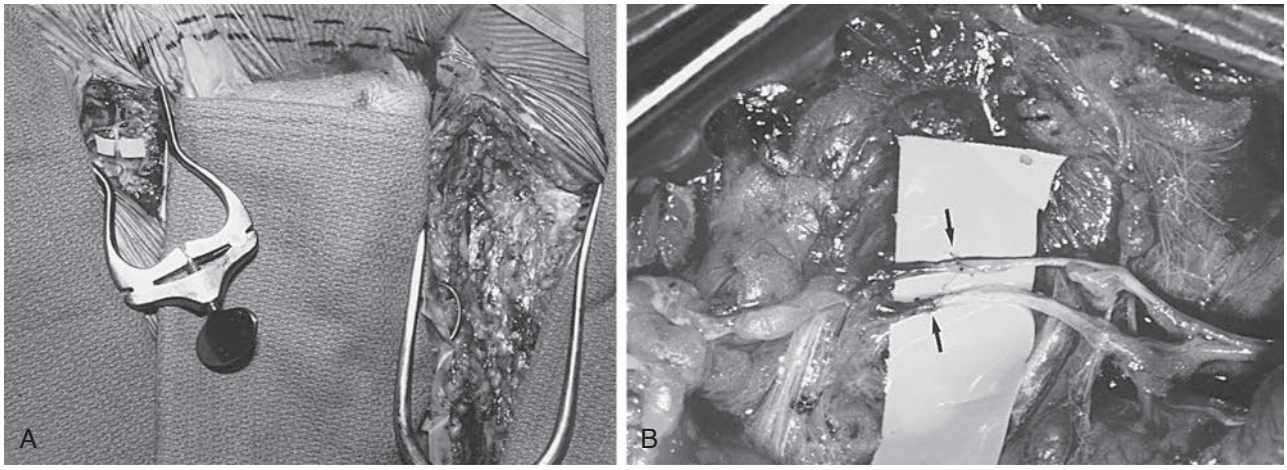

Figure 170.6 (A) Completed suprapubic lymph graft with two lympholymphatic anastomoses in the right groin. Dashed line indicates the position of the suprapubic lymphatic grafts. (B) Magnified photograph of two end-to-end lympholymphatic anastomoses *(arrows)* performed with 11-0 interrupted monofilament sutures. (Courtesy Mayo Foundation.)

Postoperative Treatment

After surgery, elastic bandages are applied, and an elastic compression garment is prescribed for 6 months, at which time discontinuation of the garment is considered. Antibiotics are given for about one week because of the reduced immunologic resistance in patients with lymphedema.

Results

Results were evaluated by volume estimation based on circumferential measurements along the limb in increments of 4 cm. Further, lymphatic outflow was measured semiquantitatively by the lymphatic transport index based on lymphoscintigraphic studies.[63] Direct visualization of the grafts is difficult because, with lymphangiography using water-soluble contrast medium, the lymphatic vessels can generally be visualized only over short distances. However, in several patients, patent grafts could be demonstrated more than 10 years after grafting with this technique.[68]

In a series of 127 patients with arm edema, a significant volume reduction was achieved, from a mean of 3368 cm^3 preoperatively to a mean of 2567 cm^3 after 8 to 10 days ($P < .001$). At a mean follow-up of 2.6 years, the mean volume was 2625 cm^3 ($P < .001$). In a group of 8 patients with long-term follow-up of more than 10 years, the mean volume was reduced to 2273 cm^3 from a mean preoperative volume of 3004 cm^3 ($P < .001$).

In 81 adult patients with unilateral edema of the lower extremities, the mean preoperative volume of 13,098 cm^3 was reduced to a mean of 10,578 cm^3 at the time of hospital discharge ($P < .001$). After a mean follow-up period of 1.7 years, the volume reduction was sustained, with a mean volume of 11,074 cm^3 ($P < .001$). In a group of 12 patients observed for more than 4 years, the volume was reduced to 10,692 cm^3 ($P < .001$).[57] The following complications were observed: two cases of erysipelas in the initial group of patients, one lymphocyst at the harvesting site, and swelling of the lower leg after thrombosis in one patient.

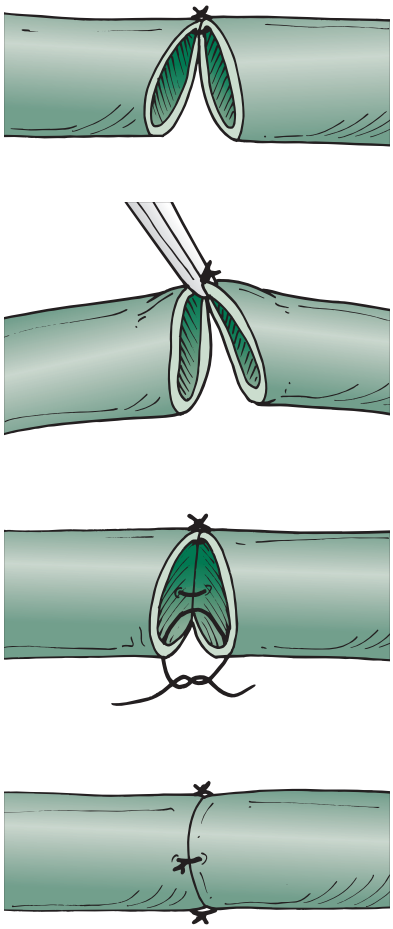

Figure 170.7 Tension-free technique for lympholymphatic anastomoses.

Lymphoscintigraphic studies were performed during a follow-up period of 8 years in 20 patients (12 upper extremities, 8 lower extremities). Of the 20 patients, 17 showed improved lymphatic outflow. In five patients, patent grafts could be demonstrated directly by visualizing the routes of activity.[69] Figs. 170.8 and 170.9 show lymphoscintigraphic studies along with the transport index for two patients with a follow-up period of 6 years. A quality-of-life study in 212 patients who underwent lymphatic grafting showed a significant improvement in the physiologic and the psychologic conditions as well.[70]

The functional outcome by dynamic imaging of lymph kinetics after autologous lymph vessel transplantation was studied recently in 177 patients suffering from upper limb lymphedemas. All patients underwent a preoperative scintigraphic baseline study and at least 1 scintigraphic follow-up. The patients were examined at four different time points after surgery: within 2 weeks (T1); between 6 and 12 months (T2); between 32 and 38 months (T3); and in 19 cases, at least 8 years (T4) after lymphatic grafting. Volume measurements were performed simultaneously.

At T1 the mean reduction in volume difference (RV) between the affected and normal extremity was 73%, and the mean improvement of the lymphatic transport index (ITI) was 28%.

At T2 the RV was 64% and the ITI was 23%, at T3 the RV was 63% and the ITI was 25%, and at T4 the RV was 68% and the ITI 25%. The mean overall correction was by a factor of 2.64.

The data confirmed the significantly improved lymph drainage after reconstruction by lymphatic autografts and showed a strong correlation between volumetric and scintigraphic findings.[71]

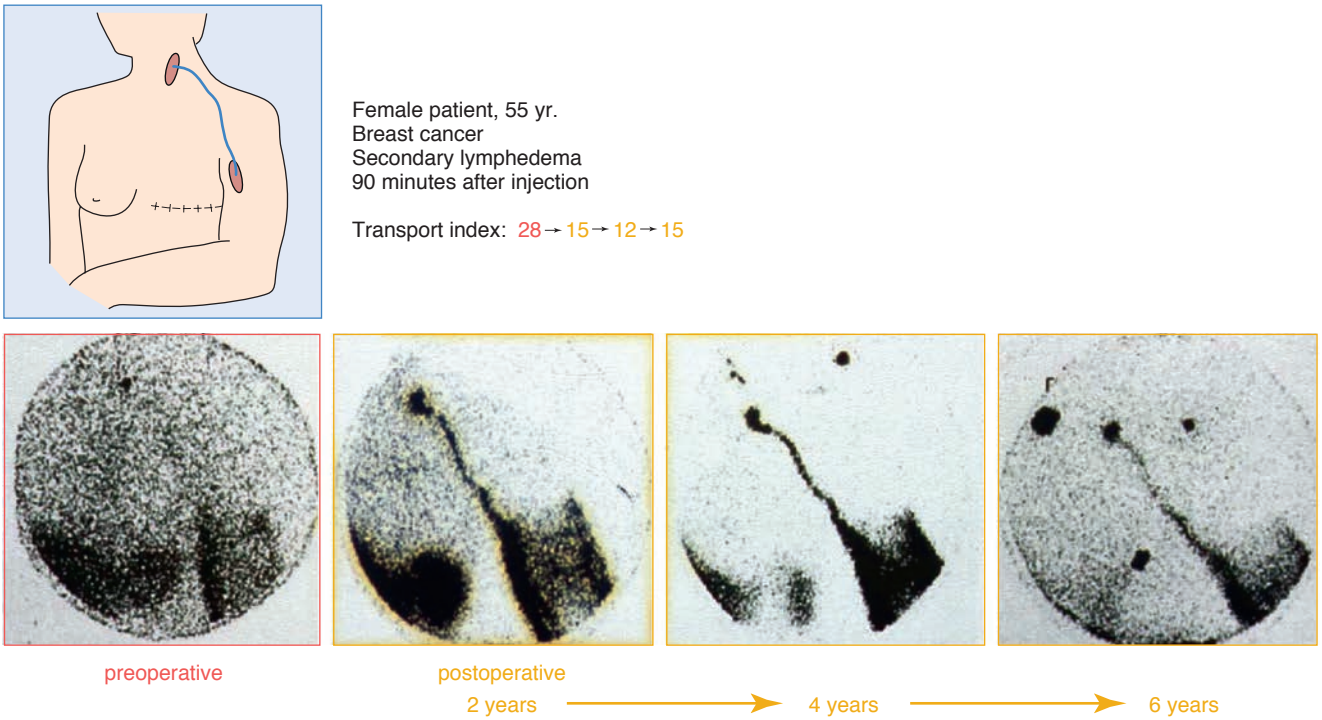

Figure 170.8 Lymphoscintigraphic long-term follow-up after lymphatic grafting in arm edema.

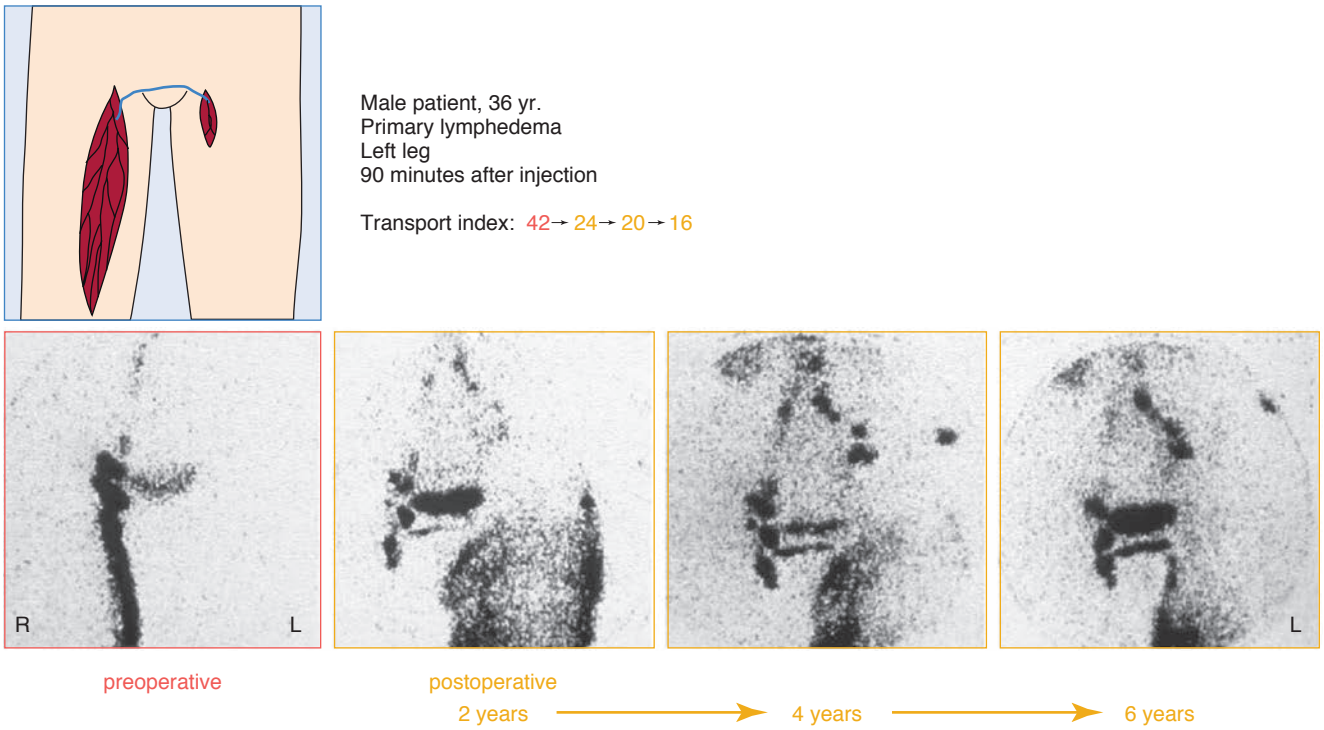

Figure 170.9 Lymphoscintigraphic long-term follow-up after lymphatic grafting in unilateral edema of the lower extremity.

Other Direct Reconstructive Methods

Trevidic and Cormier described a method of directly bridging a lymphatic defect with a free flap.[45] Li and colleagues isolated lymphatic vessels within the flap and created lympholymphatic anastomoses on both sides.[48] Ho and coworkers used the greater saphenous vein to invaginate the lymphatic vessels and also performed lympholymphatic anastomoses at the peripheral and central ends of the interposition tissue.[72] Another attempt to reconstruct a gap in the lymphatic system, described by Becker and associates, consists of free lymph node grafting with the goal of spreading lymphatic connections peripherally and centrally.[46]

Different areas of implantation of the transplanted lymph nodes were reported besides the area of the original defect, such as the wrist and the elbow at the upper limb and distal areas of the lower limb.[73]

However, reports of edema formation after the harvest have been published.[74,75]

Different aspects of the effect of vascularized lymph node transfer are postulated and under discussion: a pumping force of lymph nodes via intranodal connections between the lymphatic and venous systems, which transports along the microsurgical venous anastomoses and the enhanced presence of VEGF-C, stimulating the lymphatic network within the flaps around the lymph nodes.[76,77]

Another method of reconstructing an interrupted lymphatic system using veins was proposed by Mandl[78] and described in a series by Campisi and colleagues[27] (Fig. 170.10). The study

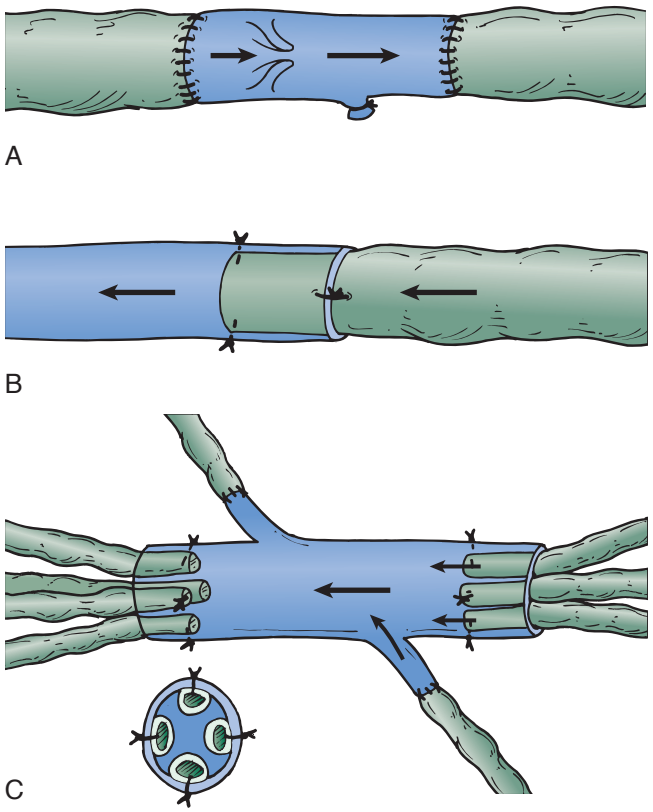

Figure 170.10 Techniques of lymphatic reconstruction with interposition vein graft (A) or lymphovenous anastomosis (B). Technique of invagination of multiple lymphatics into an interposition vein graft: lymphatic-venous-lymphatic anastomosis (C). (Courtesy Mayo Foundation.)

included 64 patients, 59 with leg lymphedema and 5 with postmastectomy edema. Marked reduction was reported in 40 patients, moderate reduction in 18 patients, and mild reduction in 6 patients.

Lymphovenous Anastomosis

Indications

Patients with secondary lymphedema of recent onset without previous episodes of cellulitis or lymphangitis are potential candidates for surgical treatment unless they can be managed easily with conservative measures. In the late stage of lymphedema, fibrosis and valvular incompetence of the main lymph vessels develop, the intrinsic contractility of the vessel wall is lost, and interstitial pressure decreases because of secondary changes in the subcutaneous tissue (see Chapter 10). The chance of successful lymphovenous anastomosis in such limbs is clearly diminished. Because venous hypertension impedes forward flow through the anastomosis, patients with chronic venous insufficiency are not candidates for this operation.

Preoperative Evaluation

Isotope lymphoscintigraphy is usually sufficient for preoperative imaging of the lymphatic system. In ideal candidates, it confirms the presence of dilated infrainguinal lymph vessels with proximal pelvic lymphatic obstruction. Although it does not differentiate between primary and secondary lymphedema, and even though it is primarily a functional study rather than an anatomic one, semiquantitative lymphoscintigraphy with technetium Tc 99m–antimony trisulfide colloid can reliably identify the pattern of lymphatic transport.[79] In selected patients, direct contrast lymphangiography can be performed to show the fine details of the lymphatic circulation.

Progress in visualizing superficial lymphatic vessels has been made with the use of indocyanine green fluorescence lymphography. Indocyanine green is injected intradermally. With the help of a near-infrared camera, the lymphatic vessels are detected as blurred linear images, whereas dermal backflow is seen as a spotty image. This facilitates the search for superficial lymphatic vessels appropriate for lymphovenous anastomoses.[80]

Other preoperative tests include noninvasive venous studies and duplex scanning of the deep veins. Computed tomography (CT) is used in most patients to exclude an underlying mass or malignant tumor. Once the decision to perform surgery is made, the patient is hospitalized for 24 to 48 hours to elevate the extremity in a lymphedema sling and to allow the use of intermittent compression with a pump to decrease the volume of the extremity.

Surgical Technique

Leg

For lower extremity lymphedema, a transverse incision at the midthigh or a longitudinal incision close to the saphenofemoral junction is performed to allow dissection of the lymphatic of the superficial medial bundle. The greater saphenous vein and any tributaries are also dissected. An attempt is made to visualize the lymph vessels by injecting 5 mL of isosulfan blue dye subcutaneously; half this amount is directed toward the first interdigital space and half toward the area 10 to 15 cm distal to the incision site. Because of lymphatic obstruction, even lymph flow in patent lymphatics may be minimal, and the dye usually is not visible during dissection. With experience, the whitish fluid-filled lymphatics, frequently with vascularized adventitia, can be distinguished from small subcutaneous nerves or fibrotic bands.

If contrast lymphangiography is performed within 24 hours of the operation, the contrast-filled lymphatics are easily identifiable and can be located during the operation with an image intensifier and a C-arm. In some patients, contrast lymphangiography helps avoid many hours of unsuccessful searching for patent lymphatics in the groin. Once the lymphatic vessels and the veins are isolated, a standard microsurgical technique is used to perform an end-to-end anastomosis with six to eight interrupted 11-0 monofilament sutures. The operation is performed with a Zeiss operating microscope with 4× to 40× magnification.

Arm

For arm lymphedema, the lymphatics are dissected through a transverse incision at the wrist or in the midcubital fossa or through a longitudinal incision at the medial aspect of the arm, a few centimeters proximal to the elbow. Lymphatics of the superficial medial lymphatic bundle are usually used for anastomoses, which are performed with the midcubital, basilic, or brachial veins or their tributaries in an end-to-side or end-to-end fashion.

Postoperative Treatment

Postoperatively, the limb is wrapped with an elastic bandage and elevated 30 degrees. For the arm, this can be accomplished with two pillows; for the lower extremity, the foot of the bed can be elevated.

Results

Objective evaluation of the long-term effectiveness of lymphovenous anastomosis has been difficult. Decrease in the circumference or volume of the extremity, patient satisfaction, decrease in episodes of cellulitis, and improvement in lymphatic clearance as measured by lymphoscintigraphy have been used as the criteria of success. In a review of 14 patients who underwent lymphovenous anastomosis at the Mayo Clinic, only 5 limbs remained improved at a mean follow-up of 46 months after surgery.[81] Improvement was observed in four of seven patients with secondary lymphedema but in only one of seven with primary lymphedema. Improvement in lymphatic clearance from the injection site was the only indirect sign of shunt patency. Therefore, the investigators were unable to provide objective evidence of late patency of the lymphovenous anastomoses in these patients.

A large experience with lymphovenous shunts was reported in Australia. O'Brien and colleagues published a well-documented report with long-term follow-up of 90 patients who underwent lymphovenous anastomoses for chronic lymphedema.[82] Although

a significant number of patients underwent additional excisional operations, improvement was documented even in those with only lymphovenous anastomoses. Of the latter, 73% had subjective improvement, and 42% had objective long-term improvement. Seventy-four percent of all patients discontinued the use of elastic stockings. However, objective imaging evidence that improvements were caused by patent and functioning lymphovenous anastomoses is still lacking.

The largest experience to date comes from Campisi and colleagues in Italy.[83,84] This group treated 665 patients with obstructive lymphedema using microsurgical lymphovenous anastomoses and achieved subjective improvement in 87% of their patients. In the 446 patients available for long-term follow-up, the authors observed volume reduction in 69% and discontinuation of conservative measures in 85%. This is a remarkable result that has not yet been duplicated elsewhere. The authors concluded that microsurgical reconstruction early in the course of lymphedema is more effective because the intrinsic contractility of the lymphatic vessel is maintained and the chance of normalizing the lymph circulation is better before significant chronic inflammatory changes develop in the subcutaneous tissue.

Koshima and coworkers from Japan reported significant improvement of lymphedema at a mean of 3.3 years after lymphovenous anastomoses in 8 of 13 patients.[85] However, Vignes and associates failed to confirm the therapeutic benefit of lymphovenous anastomoses in a group of 13 patients (10 with primary and 3 with secondary lymphedema).[86] Global assessment of clinical outcome was very good or good in five patients and intermediate in another five, but the operation failed to improve the volume of lower limbs or to reduce the frequency of erysipelas. A follow-up study of 237 lymphaticovenous side-to-end anastomoses, performed in 57 patients with lymphedema, showed at least one patent anastomosis in 34 patients by use of indocyanine green fluorescence lymphography after a mean follow-up period of 14 months. In 23 patients, no patent anastomosis was seen. There was no significant difference in limb volume reduction between the two groups.[87]

In one surgical technique, the so-called lymphaticovenous implantation, the lymph vessel is inserted into the lumen of a bigger vein together with the surrounding fat, including the lymphatic capillaries.[88] The same procedure is also used to improve lymphatic drainage of the dermal lymphatics.[80]

A large series of patients treated for secondary and primary lymphedema by supermicrosurgical lymphovenous anastomosis and lymphaticovenous implantation was published by Demirtas and colleagues.[89,90] In 40 patients with unilateral primary lymphedema, a mean reduction of 56% of the surplus volume was seen after a follow-up period of 13.3 months. Although only 17% of the patients had complex physical therapy before surgery, all stage 4 patients and most stage 3 patients (according to Campisi's classification) used custom-made pressure garments after surgery. In 20 patients with unilateral secondary lymphedema, a mean reduction of 60% was seen after a mean follow-up period of 12.8 months; 50% of the patients did not receive complex physical treatment before surgery, and continuous custom-made pressure garments were used in two of five stage 3 lymphedema patients and in all stage 4 lymphedema patients. There was no significant relationship between the number of microsurgical anastomoses or implantations and the mean reduction in volume.

Resection

Resection involves the removal of the lymphedematous, fibrotic, and frequently sclerotic subcutaneous tissue of the limb. Liposuction is a more recent technique used to accomplish resection. Other open excisions are usually performed during staged procedures. If the skin is diseased and requires resection, coverage with skin grafts may be necessary.

Liposuction

Surgical Technique

Brorson and Svensson advocate use of liposuction in patients with postmastectomy lymphedema to reduce the volume of the extremity.[13] The rationale behind this treatment is that chronic lymphedema causes hypertrophy of the subcutaneous fat. Removal of the hypertrophied and edematous adipose tissue is performed through 3-mm-long incisions (20 to 30 incisions) with vacuum aspiration. During the postoperative course, controlled compression therapy (CCT) is administered to decrease bleeding complications and to help reduce the volume of the limb.

Results

In a report by Brorson and Svensson, preoperative and postoperative arm edema volumes were measured by the water-displacement technique, and lymph transport was assessed by lymphoscintigraphy.[91] Twenty-eight patients were prospectively matched and divided into two groups. One group received liposuction combined with CCT, and one group received CCT alone. Liposuction combined with CCT was more effective than CCT alone; the edema reduction figures after 1 year were 104% for liposuction with CCT and 47% for CCT alone ($P < .0001$). Continued use of compression garments is important to maintain the primary surgical outcome. Liposuction can be useful in patients with no functioning lymphatics, but in others, the destruction of functioning lymphatics and worsening of the edema are possible.

Staged Subcutaneous Excision Beneath Flaps

Surgical Technique

The technique described by Miller and colleagues is most popular in the United States.[92-95] The excision is performed in two or sometimes three stages, starting medially during the first operation. A bloodless field is obtained with a pneumatic tourniquet. An incision is made along the ankle beginning 1 cm posterior to the medial malleolus and extending proximally into the midthigh. Flaps approximately 1.5-cm thick are elevated anteriorly and posteriorly to the midsagittal plane in the calf,

with less extensive dissection in the thigh and ankle. All subcutaneous tissue beneath the flaps is then removed, but the sural nerve is preserved. The deep fascia of the calf is incised over the tibia and resected, sparing the fascia at the knee and ankle to preserve joint integrity. Redundant skin, about 4 to 10 cm wide, is then resected; suction catheters are placed, and the wound is closed in a single layer with 4-0 nylon. In suturing around the ankle and knee, portions of the deep fascia are included in the suture to fix the skin flaps deeply and to ensure contour. The extremity is immobilized with a posterior splint and elevated. The patient is kept on bed rest for 9 days and mobilized afterward wearing tightly wrapped elastic bandages to prevent seroma formation and to promote optimal healing and contour. This regimen is continued for 3 weeks postoperatively.

The second stage, consisting of lateral excision, is performed 3 months later in a similar fashion. During lateral excision, the sensory branches of the peroneal nerve are identified and carefully preserved.

Results

Staged excision underneath skin flaps offers the most reliable improvement of all debulking operations while minimizing the likelihood of postoperative complications. Miller and colleagues reported the long-term results in 38 patients with chronic lymphedema after staged subcutaneous excisions performed beneath skin flaps.[95] Thirty patients had marked and durable reduction in extremity size with improved function. Episodes of cellulitis were reduced or eliminated. No difference in long-term results was seen in patients with primary versus secondary lymphedema. This series had a remarkably low rate of skin complications (four patients) and a low rate of late disease progression (six patients).

The clinical benefit of excisional operations is directly related to the amount of subcutaneous tissue removed. Patients are susceptible to recurrences and should continue to wear elastic compression stockings. Although good volume reduction is achievable with most of these procedures, prolonged hospitalization, poor wound healing, long surgical scars, sensory nerve loss, and residual edema of the foot and ankle can be significant problems. Because of these potential complications, these procedures are generally offered only to patients with significant, disabling lymphedema that is not responding to medical measures.

PRIMARY CHYLOUS DISORDERS

Chylous disorders are characterized by an accumulation of chyle in abnormal areas of the body. Chylous ascites, chylothorax, and chylocutaneous fistula may be caused by a malignant tumor (most frequently lymphoma) or by trauma to the mesenteric lymphatics or the thoracic duct, which may also occur during vascular surgical procedures. Primary chylous disorders are usually caused by congenital lymphangiectasia or megalymphatics, which in some patients are associated with obstruction of the thoracic duct. In patients with lymphangiectasia and lymphatic valvular incompetence, chyle may reflux into the lower extremities, perineum, or genitalia.[91-98] Depending on the site of the dilated lymphatics and the site of the chylous leak, these patients may also have protein-losing enteropathy, chylous ascites, chylothorax, chylopericardium, or reflux of chyle into the lungs and tracheobronchial tree.[91-108] In a series of primary chylous disorders at the Mayo Clinic, patients presented with lower limb edema (54%), dyspnea (49%), scrotal or labial edema (43%), and abdominal distention (37%).[100] The cause was primary lymphangiectasia in 66%, yellow nail syndrome in 11%, lymphangioleiomyomatosis in 9%, and other disorders in 18%.[100]

Medical treatment is aimed at decreasing the production of chyle by means of a medium-chain triglyceride diet or occasionally by parenteral nutrition. Repletion of proteins and calcium lost with chyle is as important as strengthening of the body's defense mechanism because lymphocytes and important immunoglobulins are also wasted in these patients. Only surgical treatment can provide long-term improvement and occasionally cure by ligation of the incompetent retroperitoneal lymph vessels and oversewing of the site of the lymph leak. Attempts to reconstruct the obstructed thoracic duct by the creation of thoracic duct–azygos vein or internal jugular vein anastomoses have been reported.[98,109-111]

Lower Extremity and Genitalia

Many patients with lymphangiectasia and reflux of chyle have unilateral lower extremity lymphedema. The main discomfort for these patients, however, is the intermittent or continuous discharge of chyle from cutaneous vesicles in the lower extremity or the genitalia. The first five patients known to have suffered from this rare condition were described in 1949 by Servelle and Deysson.[102]

The preoperative evaluation of patients with chylous reflux into the lower extremity or genitalia should include lymphoscintigraphy (Fig. 170.11A). However, contrast lymphangiography is the definitive test to confirm the diagnosis and to localize the dilated retroperitoneal lymphatics and, frequently, the site of lymph leak. MRI with contrast enhancement may provide more precise information in the future.

Surgical Treatment

The only effective technique to control the reflux of chyle and its drainage through skin vesicles in the perineum, labia, scrotum, or lower extremity is radical excision and ligation of the incompetent retroperitoneal lymph vessels. Gloviczki and coworkers used the technique of Servelle and performed the entire reflux operation in two stages through flank incisions by the retroperitoneal approach.[100] Four hours before the procedure, the patient ingested 60 g of butter and 8 oz of whipped cream. The fatty meal allowed ready visualization of the retroperitoneal lymphatics during exploration (see Fig. 170.11B to D). Ligation of the lymph vessels should be done with the utmost care to avoid tearing or avulsion of the lymphatics, resulting in residual leaks or rupture. In recent years, sclerotherapy of the dilated lymphatics has been added to ligation to increase the efficacy of the operation.

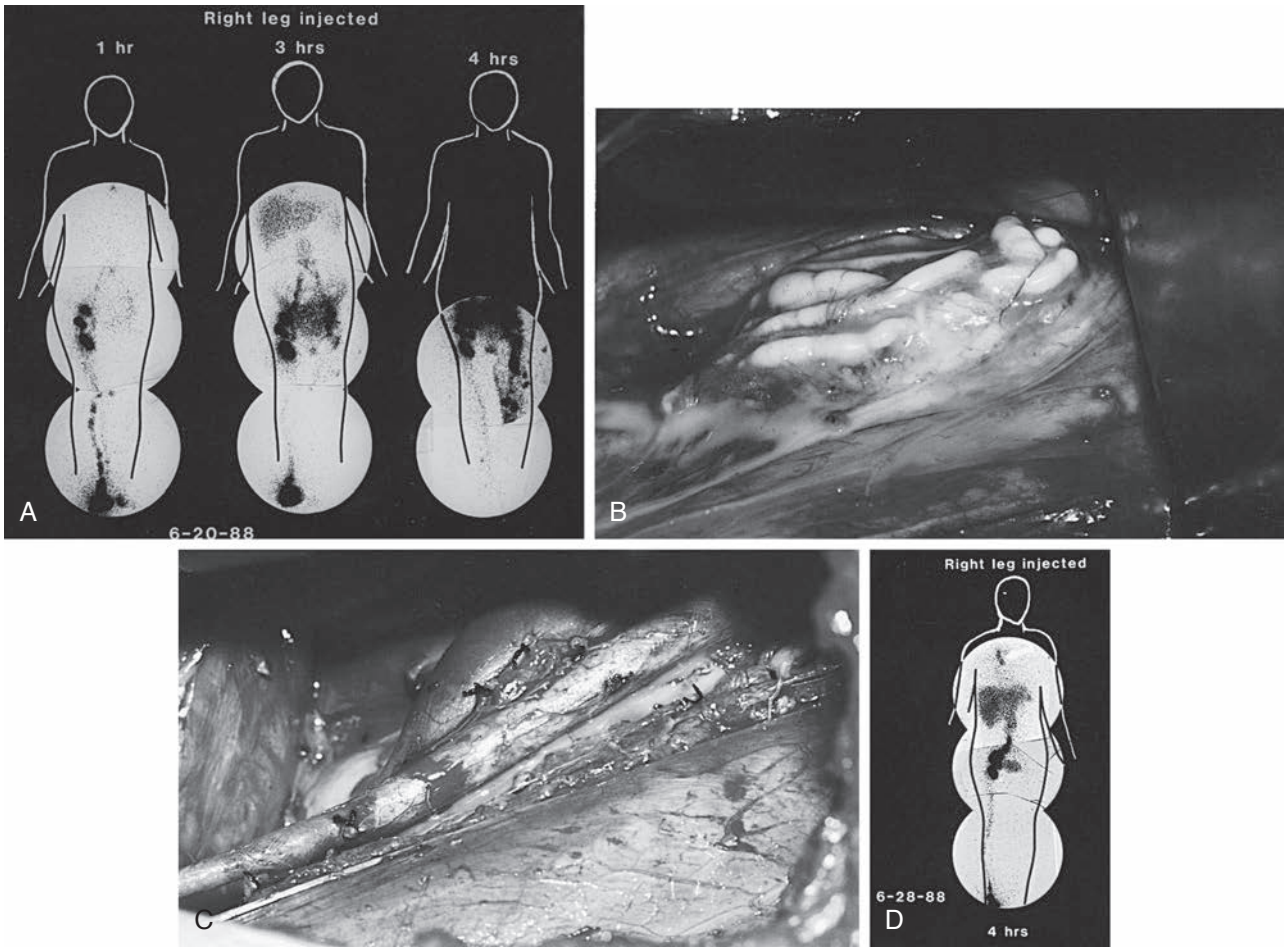

Figure 170.11 (A) Right lower extremity lymphoscintigram in a 16-year-old girl with lymphangiectasia and severe reflux of chyle into the genitalia and left lower extremity. Injection of the isotope into the right foot reveals reflux into the pelvis at 3 hours and into the left lower extremity at 4 hours. (B) Intraoperative photograph reveals dilated, incompetent retroperitoneal lymphatics in the left iliac fossa containing chyle. (C) Radical excision and ligation of the lymph vessels were performed. In addition, two lymphovenous anastomoses were created between two dilated lymphatics and two lumbar veins. (D) Postoperative lymphoscintigram reveals no evidence of reflux at 4 hours. The patient has no significant reflux 4 years after surgery. (From Gloviczki P, Calcagno D, Schirger A, et al. Noninvasive evaluation of the swollen extremity: experiences with 190 lymphoscintigraphic examinations. *J Vasc Surg*. 1989; 9:683.)

Tetracycline solution, 500 to 1000 mg diluted in 20 mL of normal saline, is injected directly into the dilated retroperitoneal lymph vessels to provoke obstructive lymphangitis.

As reported by Molitch and associates, percutaneous CT- or MRI-guided cannulation of these dilated lymphatics may be possible, and sclerotherapy to decrease reflux can be performed repeatedly if necessary.[104] Lymphovenous anastomoses with the dilated lymphatics can also be performed. Reflux of blood into the dilated and incompetent lymphatics can occur, however. A competent valve on the venous side completely avoids reflux and increases the chance of successful lymphatic drainage.[105,109]

Results

The largest group of patients studied was reported by Servelle, who operated on 55 patients with chylous reflux into the lower extremity or genitalia and reported a durable benefit in most patients.[97] In Kinmonth and Cox's series of 19 patients who underwent ligation of the retroperitoneal lymphatics for chylous reflux to the limbs and genitalia, permanent cure was achieved in 5 patients, and alleviation of symptoms—frequently after several operations—occurred in 12 patients.[98] No improvement or failure was noted in only two cases. Noel and coworkers reviewed the results of 35 patients with primary chylous disorders treated during a 24-year period.[105] Twenty-one patients (60%) underwent 27 surgical procedures. Nineteen procedures were performed for chylous ascites or reflux; 10 of these patients (53%) underwent resection of retroperitoneal lymphatics with or without sclerotherapy, 4 (21%) had lymphovenous anastomoses or saphenous vein interposition grafts, 4 (21%) had peritoneovenous shunts, and 1 (5%) had a hysterectomy for periuterine lymphangiectasia. All patients improved initially, but 29% had a recurrence of symptoms at a mean of 25 months (range, 1 to 43 months). Three patients with leg swelling had postoperative lymphoscintigraphy confirming improved lymphatic transport and diminished reflux.

Chylous Ascites

Chylous ascites usually results from intraperitoneal rupture of the mesenteric or retroperitoneal lymphatics or from exudation of chyle into the peritoneal cavity.[105] The evaluation of such patients should include CT or MRI to exclude abdominal malignant disease. The diagnosis of lymphangiectasia is confirmed by bipedal contrast lymphangiography. Paracentesis is both diagnostic and therapeutic.

Surgical Treatment

If conservative measures fail and ascites returns, abdominal exploration should be performed after a fatty meal, as described previously. If chylous ascites is due to primary lymphangiectasia, abdominal exploration may reveal ruptured lymphatics, which can be oversewn. Some patients develop large chylous cysts, which should be excised (see Fig. 170.11). If the condition is associated with protein-losing enteropathy and the disease is localized to a segment of the small bowel, the bowel segment should be resected. The outcome of the operation is usually good if a well-defined abdominal fistula is found. However, if the mesenteric lymphatic trunks are fibrosed, aplastic, or hypoplastic, and exudation of chyle is the main source of the ascites, the prognosis is poor and recurrence is frequent.

Results

Browse and coworkers treated 45 patients with chylous ascites.[99] The age at presentation ranged from 1 to 80 years (median, 12 years). Thirty-five patients had an abnormality of the lymphatics (primary chylous ascites); in the remaining 10, ascites was secondary to other conditions, principally non-Hodgkin lymphoma (6 patients). Surgery (fistula closure, bowel resection, or insertion of a peritoneovenous shunt) was performed in 30 patients. Closure of a retroperitoneal or mesenteric fistula, when present, was the most successful operation, curing 7 of 12 patients. In those patients who develop chylous ascites from iatrogenic trauma, frequently after aortic reconstructions, a short period of conservative management is justified. If chylous ascites reaccumulates, reoperation with ligation of the fistula is the most effective treatment. Campisi et al. reported on 12 patients with a mean follow-up of 5 years; there was 1 death after 1 year, 3 mild recurrences, and 1 major recurrence that was treated.[112]

Results with peritoneovenous shunts have been mixed; patency is usually judged by the recurrence of ascites. In Browse and coworkers' experience with nine peritoneovenous shunt placements, all occluded within 3 to 6 months after insertion.[99] Noel and colleagues used the LeVeen shunt with good results, although one of four patients developed symptomatic superior vena cava syndrome because of thrombosis around the shunt.[105]

Chylothorax

As with chylous ascites, the most frequent cause of chylothorax is trauma or malignant disease.[110] Primary lymphatic disorders that cause chylothorax include lymphangiectasia with or without thoracic duct obstruction. However, chylothorax may also result from chylous ascites passing through the diaphragm. In these patients, the chylothorax is cured when the chylous ascites is controlled. Preoperative lymphangiography should be performed in these patients because it may localize the site of the chylous fistula or document occlusion of the thoracic duct (Fig. 170.12).

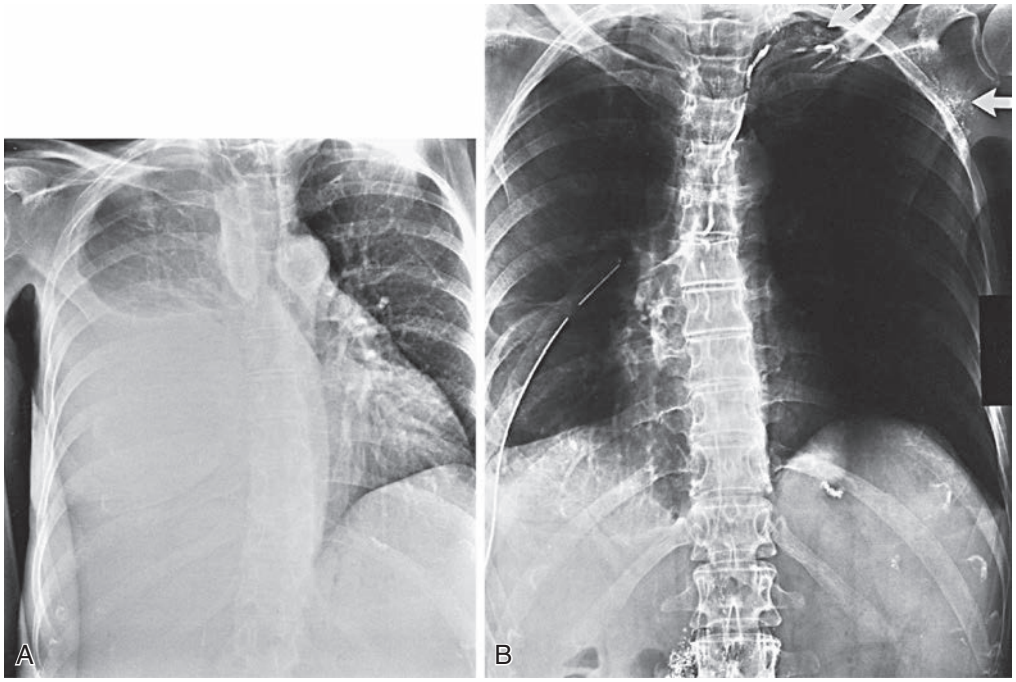

Figure 170.12 (A) Right chylothorax in a 63-year-old woman. (B) Bipedal lymphangiography confirms thoracic duct obstruction at the base of the neck. Note contrast medium in the supraclavicular and left axillary lymphatics *(arrows)*.

Thoracentesis usually is not effective in curing the disease, and chyle that leaks from the thoracic duct or one of the large intercostal, mediastinal, or diaphragmatic collaterals reaccumulates. Injection of tetracycline is frequently ineffective because it is diluted by the leaking chyle.

Surgical Treatment

The best treatment of chylothorax is surgical pleurodesis with excision of the parietal pleura and prolonged pleural suction.[106,110] After the patient has eaten a fatty meal, thoracotomy or video-assisted thoracoscopy is performed, and the leaking lymphatics are oversewn or clipped. This is followed by pleurodesis. In the Mayo Clinic series, eight procedures for chylothorax consisted of thoracotomy with decortication and pleurodesis (four patients), ligation of the thoracic duct (three patients), and resection of a thoracic duct cyst (one patient), with excellent early results in all patients.[105]

Thoracic Duct Reconstruction

If occlusion of the cervical or upper thoracic duct (Fig. 170.13) is the cause of lymphangiectasia and reflux of chyle into the pleural or peritoneal cavity, thoracic duct–azygos vein anastomosis can be attempted to reconstruct the duct and improve lymphatic transport. Preoperative imaging of the duct with contrast pedal lymphangiography is important because occlusion of the entire duct precludes anastomoses.

The operation is performed through a right posterolateral thoracotomy, and the anastomosis between the lower thoracic duct and the azygos vein is performed in an end-to-end fashion with 8-0 or 10-0 nonabsorbable interrupted sutures and magnification with loupes or an operating microscope. Only a few patients undergoing this operation have been described.[98,110] Both patients operated on by Gloviczki's group[113] had good immediate patency, and excellent flow of chyle was observed through the anastomosis intraoperatively (Fig. 170.14). Although neither had postoperative contrast lymphangiography, recurrent chylothorax (the main indication for the procedure) ultimately resolved in both. Browse et al. reported two successes in three patients who underwent thoracic duct reconstruction.[110] Kinmonth et al. performed this procedure in two patients and concluded that the anastomosis alone is not effective for decompressing the thoracic duct; ligation of the abnormal mediastinal lymphatics and oversewing of the sites of lymphatic leak are also necessary.[98]

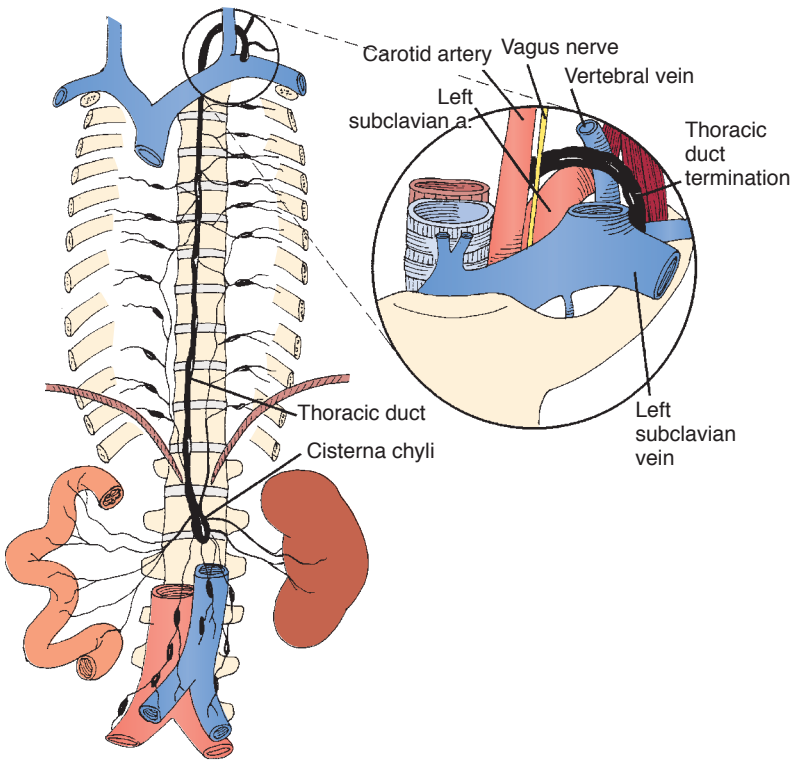

Figure 170.13 Cervical and thoracoabdominal anatomy of the thoracic duct.

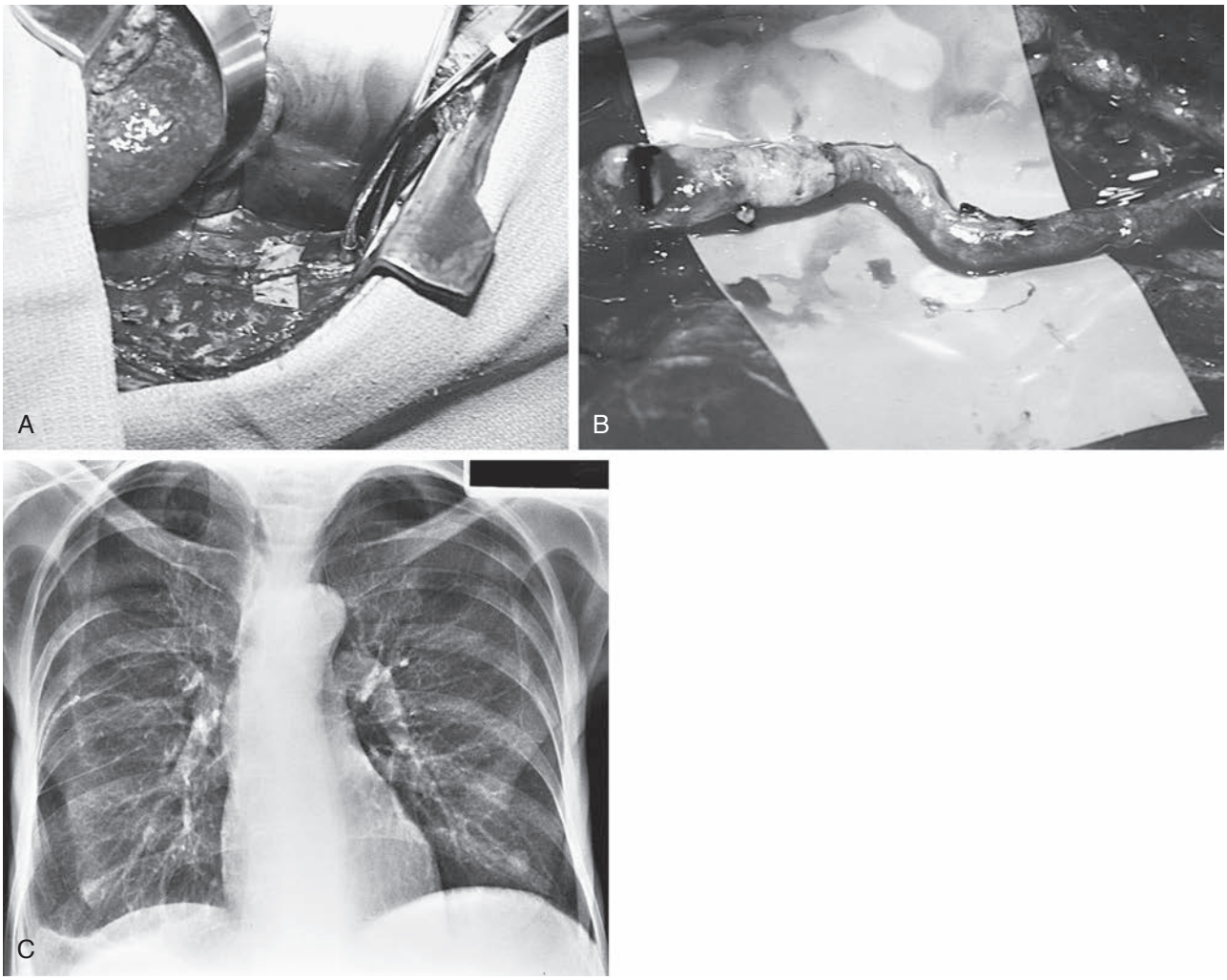

Figure 170.14 (A and B) Thoracic duct–azygos vein anastomosis performed through a right posterolateral thoracotomy in an end-to-end fashion with interrupted 8-0 polypropylene (Prolene) sutures. (C) Chest radiograph 2 years later confirms the absence of chylothorax.

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CHAPTER 171

Congenital Vascular Malformations: General Considerations

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Much progress has been made over the past 50 years in our understanding of why some children are born with imperfections, while the majority are born with normal anatomy.[1] The spectrum of congenital vascular malformations (CVMs) is very wide, and these often-disfiguring anomalies are commonly seen by both general practitioners and specialists. Successful treatment usually requires a wide range of specialists and multidisciplinary centers dedicated to their study.

DEFINITIONS

The term CVM is used to describe malformed vessels resulting from arrested development during various stages of embryogenesis.[2,3] It is present at birth, although not always immediately identifiable. CVMs may involve one or all three circulatory systems—arterial, venous, and lymphatic—either as a predominant form (e.g., venous malformation) or as a mixed condition

Abstract

This chapter aims to provide a general overview of congenital vascular malformations (CVMs); it clarifies the definition based on contemporary nomenclature and classification, more specifically the Hamburg Classification and the International Society for the Study of Vascular Anomalies (ISSVA) Classification. This should provide readers with a means to better understand its etiology, pathophysiology, diagnosis, and management.

Keywords

Congenital vascular malformation
Hamburg classification
ISSVA classification
truncular lesion
extratruncular lesion
venous malformation
lymphatic malformation
arteriovenous malformation

(e.g., hemolymphatic malformation). They continue to grow regardless of type.

CVMs may be confused with a more common vascular anomaly, the infantile or neonatal hemangioma.[4,5] Although both CVMs and hemangiomas are vascular anomalies, they are fundamentally different not only in their anatomic, histologic, and pathophysiologic findings but also in their clinical course (Fig. 171.1).[6] A true hemangioma is a vascular tumor that originates from endothelial cells, appears in the early neonatal period, grows rapidly, and then involutes, usually by age 12 years. In contrast, CVMs are generally distinctive at birth as inborn errors, and they grow steadily in parallel with the child's systemic growth. CVMs never disappear or regress.

NOMENCLATURE AND CLASSIFICATION

The nomenclature and classification of CVMs originally contained numerous terms such as *angiodysplasia, cavernous hemangioma, cystic hygroma,* and *lymphangioma,* as well as numerous eponyms (Klippel-Trenaunay [KTS], Parkes-Weber [PWS] syndromes). A new classification was needed to accommodate the contemporary understanding of CVMs, and these old terms have largely been replaced by the Hamburg classification.[2,7-9] Eponyms are still used for the combined syndromes of vascular malformations, such as KTS and PWS. However, the vascular components of KTS are termed hemolymphatic malformations (HLMs—combination of venous, lymphatic, and capillary malformations), and the components of PWS consist of venous, lymphatic, capillary, and arteriovenous malformations (Fig. 171.2).[10-13]

The term *congenital vascular malformation* now replaces the term *angiodysplasia.* The term *capillary* or *cavernous hemangioma*[14] has erroneously been used to describe a venous malformation.[15,16] To prevent confusion, *hemangioma* should be used only to identify a genuine hemangioma (i.e., a vascular tumor), not a vascular malformation.[17]

Hamburg Classification

The Hamburg classification (Box 171.1) appropriately classifies CVMs according to the underlying anatomic, histologic, pathophysiologic, and hemodynamic status derived from different embryonic stages.[2,7,9] It is based on a consensus of CVM experts who met at the Seventh International Workshop on Vascular Malformations in Hamburg, Germany, in 1988. It has clinical applicability and has been well accepted.[18] It originally divided CVMs into five types based on the predominant vascular component: arterial malformation (AM),[19,20] venous malformation (VM),[21,22] arteriovenous malformation (AVM),[23,24] lymphatic malformation (LM),[25,26] and combined vascular malformation (hemolymphatic malformation-HLM).[27,28] The initial consensus did not include the capillary malformation (CM) because it was believed to lack the clinical significance of other CVMs. However, the addition of CMs was proposed and upheld at consensus meetings in Denver (1992)[29] and Seoul (1996).[30,31]

BOX 171.1 Hamburg Classification[a]

Congenital Vascular Malformations—Types

- Arterial defects
- Venous defects
- Arteriovenous shunting defects
- Lymphatic defects
- Combined vascular defects—hemolymphatic defects
- Capillary defects

Congenital Vascular Malformations—Embryologic Subtypes[b]

Extratruncular Forms

- Infiltrating, diffuse
- Limited, localized

Truncular Forms

- Stenosis or obstruction
  - Hypoplasia, aplasia, hyperplasia
  - Membrane; congenital spur
- Dilation
  - Localized (aneurysm)
  - Diffuse (ectasia)

[a]Modified from the original classification based on the consensus reached at the international workshop in Hamburg, Germany, 1988.
[b]Represents arrested development at different stages of embryonic life, with extratruncular being an earlier stage and truncular a later stage. Both forms may coexist.

Although the Hamburg classification has been accepted worldwide, it is far from perfect, and further improvements are necessary before it completely replaces the old terminology and classifications.

Each vascular malformation is classified into extratruncular and truncular forms, based on its embryologic stage of development (see Box 171.1).[32,33] The clinical behavior of every vascular malformation is dependent on its embryologic characteristics, particularly the stage of embryogenesis when arrested development occurred. The varied embryologic characteristics result in a wide range of clinical presentations, unpredictable clinical courses, and erratic responses to treatment, along with potentially high rates of recurrence. The embryologic subclassification of CVMs into truncular and extratruncular allows clinicians to predict the clinical course, response to treatment, and likelihood of recurrence.[34,34] Further information on their distinctive characteristics is included in subsequent sections.

ISSVA/Mulliken Classification

Another classification system, introduced by Mulliken et al., is based on the hemodynamic status of the CVM and provides an excellent guideline for clinical management.[4,5] In the International Society for the Study of Vascular Anomalies (ISSVA)/Mulliken classification, all CVMs are divided into two groups, depending on blood flow: fast-flow lesions and slow-flow lesions. This helps in understanding the hemodynamic status of a CVM. Currently, many specialists have adopted parts of this system and combined it with the Hamburg classification to monitor the treatments and outcomes.

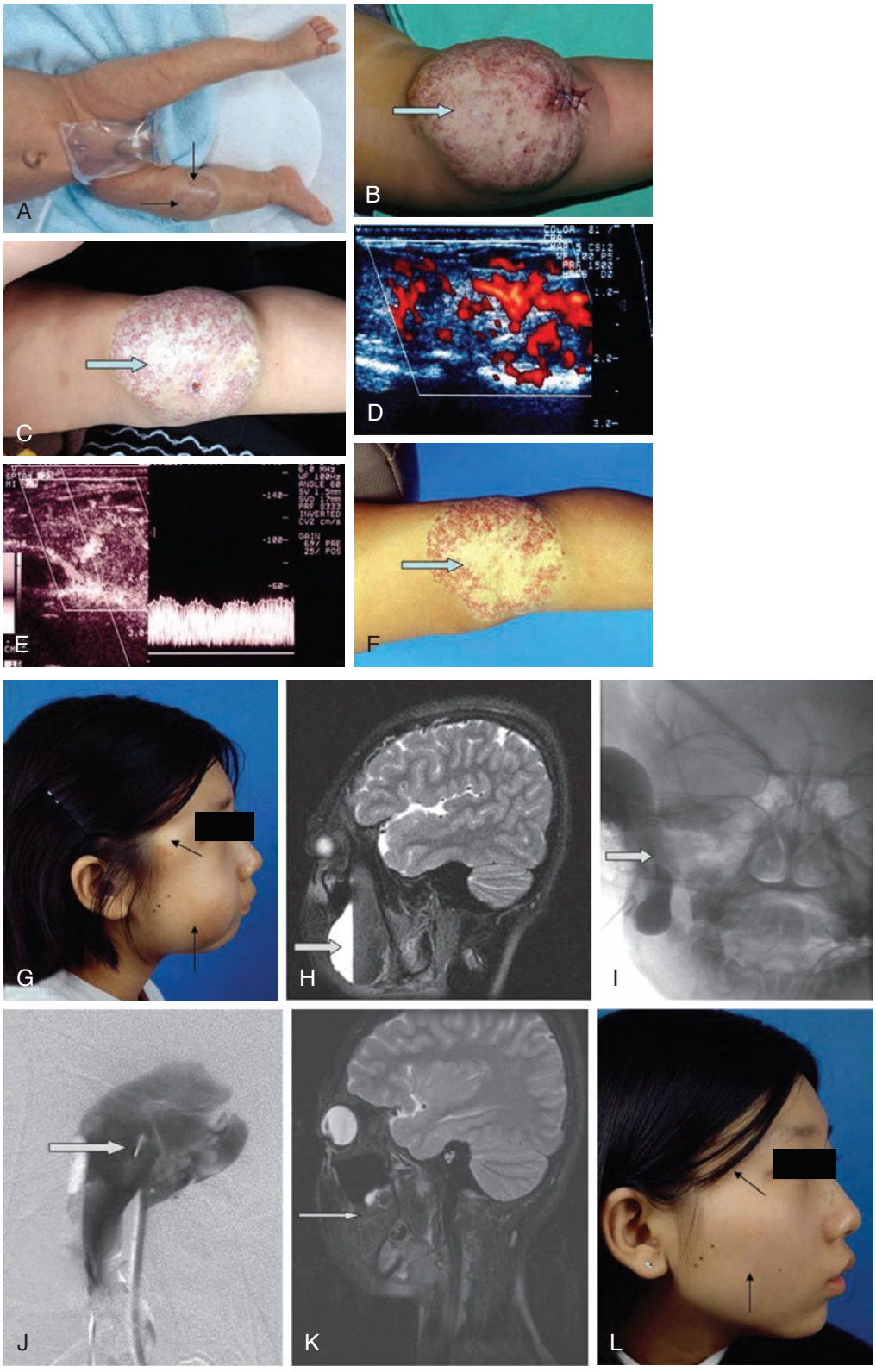

Figure 171.1 Hemangioma and Vascular Malformation. (A to F) Hemangioma. In this infant, a hemangioma appeared 1 month after birth in a normal-looking area of the right lower thigh (*arrows* in A). The swelling grew quickly, reaching its peak size within a year (*arrow* in B). This was followed by a significant reduction in size during the second year (*arrow* in C). Duplex ultrasonography during the proliferative stage shows typical vascular hyperactivity along the tumor, with distinctly large feeding arteries (D and E). The lesion regressed almost completely, leaving only an area of skin discoloration, before the child reached 4 years of age (*arrow* in F). (G to L) VM. This young girl was born with a swollen right cheek (*arrows* in G)—the site of a VM. The swelling was noticed at birth, but there was minimal change until menarche. Sagittal T2-weighted magnetic resonance imaging (MRI) depicts a large VM affecting the entire right cheek (*arrow* in H). Percutaneous direct-puncture angiography demonstrates a large cystic lesion (*arrow* in I). Percutaneous ethanol sclerotherapy resulted in complete control of the lesion (*arrow* in J), as shown by MRI (K) and a clinical photograph (L) taken at the 3-year follow-up visit.

Figure 171.2 Hemolymphatic Malformations. (A–I) Klippel-Trénaunay syndrome (KTS). In a patient with typical KTS of the left lower extremity, a port-wine stain covers most of the leg (*arrows* in A); there is limb swelling as well as leg-length discrepancy. Radionuclide lymphoscintigraphy demonstrates severe dermal backflow (*arrows* in B) due to primary lymphedema secondary to a truncular lymphatic malformation (LM). Percutaneous direct-puncture lymphangiography reveals a typical lace-pattern appearance (*arrows* in C) of an infiltrating extratruncular LM. Whole-body blood pool scintigraphy (WBBPS) shows abnormal blood pooling in the entire left lower extremity (*arrows* in D), suggesting an extratruncular venous malformation (VM) as the third component of the vascular malformation. Further evaluation with duplex ultrasonography (E) reveals a marginal vein as a truncular VM; this lateral embryonic vein is the fourth and last vascular malformation component of KTS. Transarterial lung perfusion scintigraphy (TLPS) results (F) rule out a hidden arteriovenous malformation (AVM). Coronal (G) and sagittal (H) T2-weighted MRI scans demonstrate soft tissue swelling typical of lymphedema (*arrows*). Ascending phlebography, performed to provide a roadmap for treatment, shows a marginal vein running along the lateral aspect of the left lower leg (*arrows* in I).

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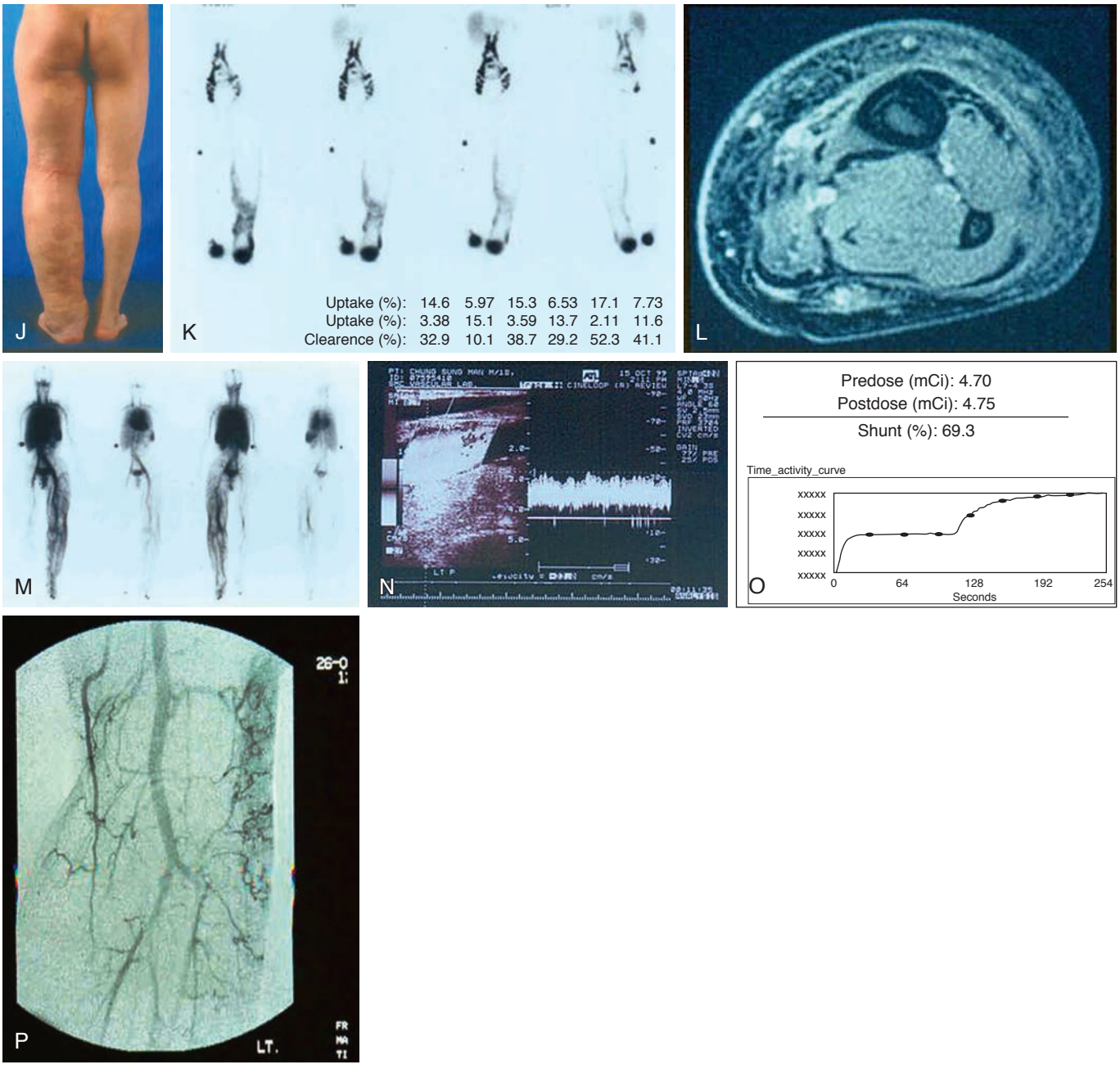

Figure 171.2, cont'd (J–P) Parkes Weber syndrome (PWS). The clinical features of PWS are localized to the left lower extremity (J), similar to the findings in KTS (see A). Radionuclide lymphoscintigraphy (K) and MRI (L) reveal primary lymphedema caused by a truncular LM. WBBPS (M) shows diffuse, abnormal blood pooling throughout the limb due to an extratruncular VM. Duplex ultrasonography (N) depicts a hyperdynamic arterial condition secondary to an AVM. TLPS (O) reveals the precise shunting percentage (69.3%) through the hidden AVM shunts. Arteriography (P) demonstrates multiple superficially located microshunting AVMs scattered throughout the lower extremity. The clinical diagnosis of PWS was confirmed (with LM, VM, AVM, and capillary malformation components).

INCIDENCE

Because of confusing nomenclature and definitions of CVMs in the past, epidemiologic data regarding CVMs are difficult to obtain.[36-38] In a comprehensive study of the incidence and geographic distribution of CVMs, Kennedy surveyed the world literature and published data based on 238 studies reporting more than 20 million births.[39] The overall incidence was 1.08%, ranging from 0.83% in data obtained from hospital records, birth certificates, and retrospective questionnaires to 4.5% in data from intensive examinations of children. In a large study sponsored by the World Health Organization, Stevenson and colleagues surveyed 426,932 live and stillborn births and reported an overall frequency of major and minor

malformations of 12.7% in single births and 4.6% in multiple births.[40] Tasnadi et al. reported an incidence of CVM of 1.2% among 3,573 3-year-old children studied. These included VM and/or AVM in 0.45%, CM (port-wine skin lesion) in 0.42%, LM/primary lymphedema in 0.14%, and mixed form CVM showing phlebectasia, nevus, and limb length discrepancy in 0.34%.[41]

CVMs have a male-to-female ratio of 1:1, and VMs are the most common type. Among VMs, the extratruncular type is the most frequent lesion and presents in either diffuse or localized forms.[37] Eifert et al. reported the prevalence of deep venous anomalies among 257 VMs; phlebectasia was the most frequent (36%), followed by aplasia or hypoplasia of the deep venous trunks (8%) and venous aneurysms (8%).[42] However, more than 70% of CVMs are mixed, and these complex forms can include arterial, capillary, venous, or lymphatic elements. When both extratruncular and truncular LMs are combined, their overall incidence is close to that of VM, if not higher.[37]

ETIOLOGY

A number of genetic and chromosomal abnormalities have been implicated in the development of CVMs. These have been associated with (1) exposure to damaging chemical compounds during the first trimester of pregnancy; (2) infections such as rubella, cytomegalic inclusion disease, herpesvirus, and toxoplasmosis; (3) thalidomide and other drugs such as aminopterin, cyclophosphamide, quinine, anticonvulsant drugs, cortisone, and corticotropin; and (4) alcohol, tobacco, and cocaine abuse. Maternal diseases and exposures including goiter, diabetes mellitus, thyroid disease, tuberculosis, hypoxia, and carbon monoxide and lead poisoning have also been identified as potential causes of CVMs.[39,40,43]

Although most CVMs are sporadic, autosomal dominant inheritance of mutated genes has been confirmed to cause some CVMs based on genetic studies of families.[37,38,44-49] These mutated genes encode for tyrosine kinase receptors and intracellular signaling molecules.[49] The endothelial-specific angiopoietin receptor TIE2/TEK, located on 9p21, was identified to cause familial mucocutaneous CVMs.[49] Further studies showed that somatic mutations in angiopoietin receptor gene TEK led to the loss of TIE2 receptor function.[50] This in turn upregulated expression of other vascular endothelial growth factors, such as βTGF and βFGF, resulting in the development of VMs.[51]

Vascular endothelial growth factor (VEGF) has been found to induce penetration of capillary vessels into the avascular epidermis.[52] A defective response of endothelial cells to VEGF as the consequence of abnormal signaling of VEGF receptors results in CVMs if the differentiation is abnormal and there is an arrest in the development of normal vascular tissue. The persistence of the embryonic vascular system also causes additional abnormal development.

Recently a high susceptibility loci within the HLA locus on chromosome 6p21.32 has been identified with development of truncular VMs. Due to deletion or duplication, the number of copy number variations is significantly associated with an increased chance to develop truncular VMs. The region contains 211 known genes.[53-57] In addition, the increased expression of matrix metalloproteinase-9 in intramuscular VM lesions suggests that VMs have the ability for angiogenesis to provoke invasive growth while expanding slowly due to the increase in hydrostatic pressure.[58] Progesterone receptors in VMs are also suspected to cause the progression of lesions when hormonal levels change.[59]

EMBRYOLOGY

When the embryo begins its exponential growth, an equivalent growth of the vascular system is required to deliver nutrition and oxygen necessary for the proper development of the fetus. If growth of vascular structures does not occur, there is a high risk for development of CVM.[60-63] The long complex process of angiogenesis increases the risk of developmental defects in comparison to other tissues from the same mesodermal origin, such as bone, muscle, and connective tissue. Embryonic blood vessels originate from the blood island of Pander, which represents the masses of vasoformative cells that undergo a complicated process of evolution.[33] Undifferentiated capillary plexus becomes the initial vasculature; subsequently, some capillaries undergo regression and coalescence with others to form a reticular structure. This reticular structure is efficient to meet the embryo's needs during the early, rapid-growth stage of embryogenesis. This extratruncular stage occurs before the final truncular stage, during which formation of the actual artery, vein, and lymphatic trunks occurs to complete the differentiation. The characteristics of the embryonic cells change drastically between the extratruncular and truncular stages.[2,7,9] The clinical behavior of the vascular defect depends on the stage at which arrested development occurs. Any defect occurring before the truncular stage maintains the embryonic characteristics of mesenchymal cells.

Extratruncular Lesions

Extratruncular CVMs represent arrested development during early embryonic life, while the vascular system is in the reticular stage.[33] These embryonic remnants of mesodermal origin retain the characteristics of mesenchymal cells (angioblasts) and have the potential to grow and proliferate when stimulated internally (e.g., by menarche, pregnancy, hormonal release) or externally (e.g., by trauma, surgery). Therefore all extratruncular lesions, regardless of type, carry a significant risk of recurrence after treatment and can grow rapidly.[64] By nature, an extratruncular lesion behaves like an infiltrating process, invading the surrounding structures. Because bones, muscles, soft tissues, and blood vessels all originate from the same mesoderm, there is no plane of partition between them. Therefore such a lesion, whether diffuse or circumscribed, produces a pressure effect on the surrounding tissues, in addition to the hemodynamic impact on the affected vascular system.

Truncular Lesions

Truncular CVMs arise when arrested development occurs later, during the vascular trunk formation stage of embryonic

development.[33] Truncular lesions have lost the embryonic characteristics of the mesenchymal cells, together with the potential to grow and proliferate. These lesions do not carry the same risk of recurrence as extratruncular lesions, but they are generally associated with more serious hemodynamic consequences.[65,66]

Based on pathology, truncular lesions are further divided into obstructive and dilated lesions.[1,7-9] All truncular lesions appear as formed vessels with various degrees of developmental defects, ranging from incomplete or immature lesions (aplasia or hypoplasia) to overdeveloped lesions (hyperplasia). A truncular VM may present as a persistent fetal vessel that does not involute normally (e.g., sciatic vein, marginal or embryonic vein) or as a defective vessel trunk (e.g., vein web, venous aneurysm/ectasia), resulting in stenosis, complete obstruction, or dilatation.[37,67,68]

PATHOPHYSIOLOGY

In terms of pathophysiologic significance, CVMs can be divided into two types: those with mechanical impacts on surrounding structures, producing compression and/or infiltration effects, and those with a hemodynamic impacts on the affected circulation. The relative significance of these variants depends on the type of CVM as well as its embryologic subtype.

Extratruncular Lesions

In general, all extratruncular lesions have both mechanical and hemodynamic impacts. The initial mechanical impact is generally of little significance; compression and infiltration become more significant as the lesion grows. With enlargement, a simple lesion can produce serious damage and become life-threatening, for example, by causing airway obstruction.

In general, the hemodynamic impact is usually far more serious than the mechanical impact.[69-71] High-flow CVMs (e.g., AVMs) have a greater hemodynamic impact than low-flow lesions (e.g., VMs), because the arteriovenous shunts do not have the resistance of the normal capillary system.[72,73]

Truncular Lesions

All truncular lesions, regardless of type, have mainly hemodynamic impacts, the significance of which depends on the type of CVM. For example, the impact of a truncular LM that manifests clinically as primary lymphedema remains limited to the lymphatic transportation system, seldom involving the accompanying venous system.[74-77] In contrast, a truncular VM affecting the lower extremity (e.g., femoral vein aplasia) can present with more serious hemodynamic impacts, resulting in chronic venous insufficiency.[78-81] When venous insufficiency is combined with lymphatic insufficiency in the case of a mixed CVM, the impact (e.g., phlebolymphedema) is even more serious.[82-85]

Among truncular VMs, a venous aneurysm situated between two segments of normal vein is a potential source of venous thrombosis and pulmonary embolism, especially when the deep system is involved. The most common symptoms are a painful mass and localized swelling. In some cases, a massive pulmonary embolism is the first symptom. The incidence of venous aneurysms is similar in men and women.[37] In our experience with 39 venous aneurysms in 30 patients, the majority were located in the deep system of the lower extremities, with 5 in the internal jugular vein and 4 in the superficial venous system.[86] Diagnosis was made by phlebography, color-flow duplex scanning, and/or magnetic resonance imaging (MRI). The size of the aneurysms ranged from 1.7 to 6 cm. Three patients had deep venous thrombosis, and three had pulmonary embolism.

In children, venous dilatation is most common in the internal jugular vein and is most noticeable during crying or other physical effort.

Truncular ("fistulous") AVMs, although rare, have the most powerful impact on the vascular system. The shunting of arterial blood to the venous system may result in a substantial degree of steal from distal arterial vessels, as well as extra-loading to the proximal and distal venous system.[87,88] These effects in turn may produce chronic venous hypertension distal to the lesion and high output cardiac failure.[38]

Secondary Organ Impact

CVM may also impact related tissues or organs. For example, an intraosseous CVM can stimulate the epiphyseal plate and induce abnormal long-bone growth, resulting in leg-length discrepancy.[89-91] Compensatory scoliosis with or without pelvic tilt can impact gait and/or the cardiopulmonary system. Other systems may also be affected.

CLINICAL PRESENTATION

The clinical presentations of all CVMs (both extratruncular and truncular) depend on the vascular system involved and whether the lesion is localized or diffuse. They may affect the arterial, venous, lymphatic, or capillary system as independent lesions or as mixed types (HLM). A complete examination is usually sufficient to establish a diagnosis, although imaging is sometimes required to determine lesion extent. In small children the diagnosis may be more difficult, as it may take some time for the lesion to become fully identifiable.[37,38,92-94]

Capillary Malformations

A CM appears as a port-wine stain on the skin with a distinctive color; it is different from the common vascular birthmark known as nevus flammeus neonatorum. Birthmarks are pinkish discolorations affecting the nuchal region ("stork bite") or the face along the eyelids, forehead, or lips ("angel's kiss"). In contrast, CMs can present anywhere on the body and can range from small localized lesions to extensive lesions covering the skin in multiple areas. CMs are often accompanied by other abnormal physical findings beneath the skin, heralding other CVMs. For example, a CM in the face is a warning sign for an intracranial CVM known as Sturge-Weber syndrome, with ipsilateral ocular and leptomeningeal vascular malformations.[95-98]

Venous Malformations

VMs present at birth as soft bluish swellings located near the skin surface, although some are not initially distinctive.[21,22] They are easily compressible and enlarge when the affected area is dependent or with a Valsalva maneuver. VMs in the extremity are easily collapsed when the leg is elevated to allow venous drainage. They usually present as slowly growing solitary lesions, but there may be multiple lesions, either localized or extensively infiltrative. VMs are associated with various degrees of pain and stiffness, especially in the morning but are generally not tender. The symptoms respond to compression therapy. However, when the lesions involve underlying muscle, bone, abdominal viscera, or the central nervous system, they may be complicated by secondary symptoms.[37,81]

VMs in the head and neck region are usually unilateral, with a mass effect that causes significant distortion of the features and facial asymmetry. VMs involving the tongue, palate, and oropharynx often result in significant deformity, including dental malocclusion, and represent a potential life-threatening condition if they encroach on the upper airway together with laryngopharyngeal lesions. VMs affecting the limb are often associated with leg-length discrepancy caused by long-bone growth disturbance when they extend into muscle and bone, resulting in compensatory pelvic tilt and scoliosis. Others can cause pathologic fractures, hemarthrosis, ankyloses, or degenerative arthritis. VMs can occur anywhere in the gastrointestinal (GI) tract, affect any or all layers of the bowel wall, and cause chronic bleeding.

Thrombosis and pulmonary embolism, sometimes fatal, can occur because of the presence of phlebectasias or aneurysms.[37,99]

Lymphatic Malformations

LMs present in the extremity as diffuse (primary lymphedema) or localized swelling (lymphangioma).[25,26] The swelling with lymphangioma ranges from a well-localized sponge-like condition to a diffuse infiltrating condition affecting large areas and having a varying consistency, depending on whether the lesion's components are macrocystic or microcystic. LMs are generally asymptomatic and neither tender nor painful until complications such as lymph leak or bleeding occur. However, LMs affecting the oral mucosa and tongue are often accompanied by pain, swelling, or bleeding, with mucosal vesicles.

Proptosis, amblyopia, strabismus, or even loss of vision can manifest with a periorbital LM. Difficulty chewing, talking, and breathing can occur because of overgrowth of the mandible, maxilla, or tongue as a result of an LM affecting the face or cervical region. Skeletal overgrowth or pathologic fracture of a long bone can also be caused by an LM affecting bone metabolism (e.g., Gorham syndrome).[100-102]

Arteriovenous Malformations

Small AVMs present at birth often remain obscure until they progress and become local swellings accompanied by symptoms and signs of arteriovenous shunting, including local hyperthermia, a thrill, bruit, and/or visibly dilated veins.[23,24] Ischemic changes and ulceration of the skin can develop distal to the shunt, often with intractable pain and intermittent bleeding. Distal gangrene is likely if the arterial insufficiency is severe, and high-output cardiac failure is unavoidable if a large AVM is not treated.[38,73]

Combined Vascular Malformations (Hemolymphatic Malformations)

Both the primary lesion and the secondary effects of HLM, including KTS[103-106] and PWS[107-109], are a mixture of each type of CVM involved (e.g., CM, LM, VM, and/or AVM).[27,37,110,111] Overgrowth of affected soft and skeletal tissue as a secondary phenomenon induced by the CVM is more distinctive; the port-wine stain's characteristic pattern over the lateral side of the involved extremity often extends to the buttock or thorax. Underlying LMs infrequently accompany various skin conditions and consist of vesicles, which often become symptomatic with leakage or infection.

Limb swelling caused by an HLM represents phlebolymphedema, a mixed condition with varying degrees of lymphatic and venous insufficiency.[83-85] Chronic lymphatic insufficiency usually manifests as primary lymphedema, while chronic venous insufficiency relates to insufficiency of the marginal vein (MV). The MV is an embryonic tissue remnant which fails to involute and is often visible or palpable as a large dilated vein along the lateral aspect of the lower extremity (see Fig. 171.2I). Its distal portion may be associated with sequelae of chronic venous insufficiency (stasis dermatitis, ulcer), secondary to venous reflux resulting from a lack of venous valves, known as avalvulosis.[37,112] Therefore all venous disorders, including varicose veins, thrombophlebitis, and pulmonary embolism, are major clinical signs of a VM involved with an HLM. In addition, the existence of the MV often heralds coexisting deep venous anomalies and warrants proper investigation.

Soft tissue and skeletal hypertrophy or hypotrophy ("vascular bone syndrome") are secondary effects of the primary lesion in the affected limb. They are often obvious at birth and can be progressive. HLMs affecting the extremity carry a higher risk of involvement of other intraperitoneal, retroperitoneal, intrathoracic, and mediastinal organs. Depending on the CVM, the clinical findings may include cardiopulmonary, musculoskeletal, GI, genitourinary, or gynecologic symptoms. Infrequently, the lesion presents with a distinctive condition such as hematuria, hematochezia, chyluria, chylorrhea, chylothorax, or pleural effusion. Occasionally, it presents with vague symptoms such as constipation, malabsorption syndrome, bladder outlet obstruction, or recurrent infection.

DIAGNOSIS

General Principles

The majority of CVMs can be detected in early childhood based on a heightened clinical suspicion when a child presents with abnormal swelling and disfigurement. A careful history and physical examination often provide enough clues to make a

BOX 171.2 Diagnostic Tests for Congenital Vascular Malformations

Noninvasive to Minimally Invasive Studies

- Duplex ultrasonography
- Magnetic resonance imaging—T2-weighted study
- Radioisotope lymphoscintigraphy
- Computed tomography with contrast and three-dimensional reconstruction
- Bone scanogram
- Whole-body blood pool scintigraphy (transvenous angioscan using radioisotope-tagged red blood cells)
- Transarterial lung perfusion scintigraphy (transarterial angioscan using radioisotope-tagged microsphere albumin)
- Air plethysmography
- Magnetic resonance venography or arteriography
- Magnetic resonance lymphangiography
- Indocyanine green lymphangiography
- Ultrasound lymphangiography

Selective Invasive Studies

- Standard, selective, or superselective arteriography
- Ascending, descending, or segmental phlebography
- Percutaneous direct-puncture angiography: arteriography, phlebography, or lymphography
- Contrast (classic) lymphangiography

presumptive clinical diagnosis. By nature, a CVM may appear anywhere in the body, either as a predominant lesion or as a mixed anomaly. To further confuse the clinician, these lesions may change due to internal or external stimulations. One CVM might suggest other hidden lesions scattered throughout the body, so any evaluation should include a full-body investigation.[113,94,114]

The initial diagnostic workup should start by ruling out infantile hemangioma and then identifying the type and subtype of CVM.[113] Following the history and physical examination, the appropriate combination of noninvasive or minimally invasive tests should be performed (Box 171.2). This often results in a diagnosis. Invasive tests can generally be deferred to a later time if the diagnosis needs refinement, if surgical or other invasive therapeutic measures are being considered, or if the symptoms merit further investigation.

Because AVMs are potentially limb- or life-threatening, their evaluation is different; a full assessment of their status is recommended as early as possible, regardless of the patient's age.[115,116]

Children younger than 2 years should have only those procedures necessary for diagnosis. However, when the child has a condition that warrants earlier intervention (abnormal long-bone growth with leg-length discrepancy), the lesion is located in a limb- or life-threatening area, or it compromises vital functions, invasive tests should be included to start early treatment.[113,117]

Physical Examination

Inspection and palpation of all skin surfaces, including the genitalia, should be performed in a well-lit environment. Although the majority of VMs and LMs present as single lesions, a physical evaluation for both conditions should be made to assess their relative significance. Auscultation (for bruit) and palpation (for thrills and pulse character) are helpful to assess the presence and extent of an AVM.

The examination should be done with the patient in the standing and supine positions, and posture and gait should be evaluated to assess the dynamic impact of the lesion. Involvement of the skin, soft tissue, and bone should be assessed so that positive findings will not be missed.[91] The limb elevation test should be performed in all extremity CVMs. With this test, VMs may demonstrate dramatic emptying of the venous lakes or veins during leg elevation.[113] In VMs, the findings of acute and chronic complications and their sequelae should be investigated.

The evaluation of an AVM should include not only its hemodynamic impact on the distal and proximal arterial and venous systems, but also its effects on the central cardiovascular system, in addition to involvement of the lymphatic system.[35,64]

Imaging

The imaging evaluation aims to identify the type and subtype (extratruncular or truncular) of CVM and to confirm or rule out the presence of other CVMs. In most cases, the diagnosis of CVM can be made with noninvasive or minimally invasive studies.[113] These studies distinguish CVM from infantile hemangioma. Invasive studies are reserved for therapeutic planning or for the diagnosis of aggressive AVMs.

Minimally Invasive Studies

Imaging for CVM assessment includes magnetic resonance imaging (MRI),[118,119] duplex ultrasonography,[37,81,92,120] and preferably whole-body blood pool scintigraphy (WBBPS) if feasible.[121] If LM is suspected, radioisotope lymphoscintigraphy is added.[122,123] For an AVM, contrast computed tomography with three-dimensional (3D) reconstruction is essential.[124] T2-weighted MRI is the "gold standard" for VMs, and when used together with duplex ultrasonography, most other CVMs can be distinguished. WBBPS (a transvenous angioscan using radioisotope-tagged red blood cells) can detect small amounts of abnormal blood pooling throughout the body, and is valuable not only to confirm the presence of a VM but also to exclude an LM. This test is also used in the follow-up of multisession treatments (Fig. 171.3).

Transarterial lung perfusion scintigraphy (TLPS) is a transarterial angioscan with radioisotope-tagged microsphere albumin. It measures the percentage of blood volume shunted by AVMs located in the extremities. TLPS is valuable in detecting microshunting AVMs common in PWS, as is conventional arteriography (Fig. 171.4).

Ultrasonographic lymphangiography, magnetic resonance lymphangiography, and indocyanine green lymphangiography may be useful in candidates for lymphovenous reconstruction.[113,37,92,125-130]

Invasive Studies

The role of invasive studies in CVM evaluation is limited because the majority can be diagnosed by noninvasive tests. Nonetheless,

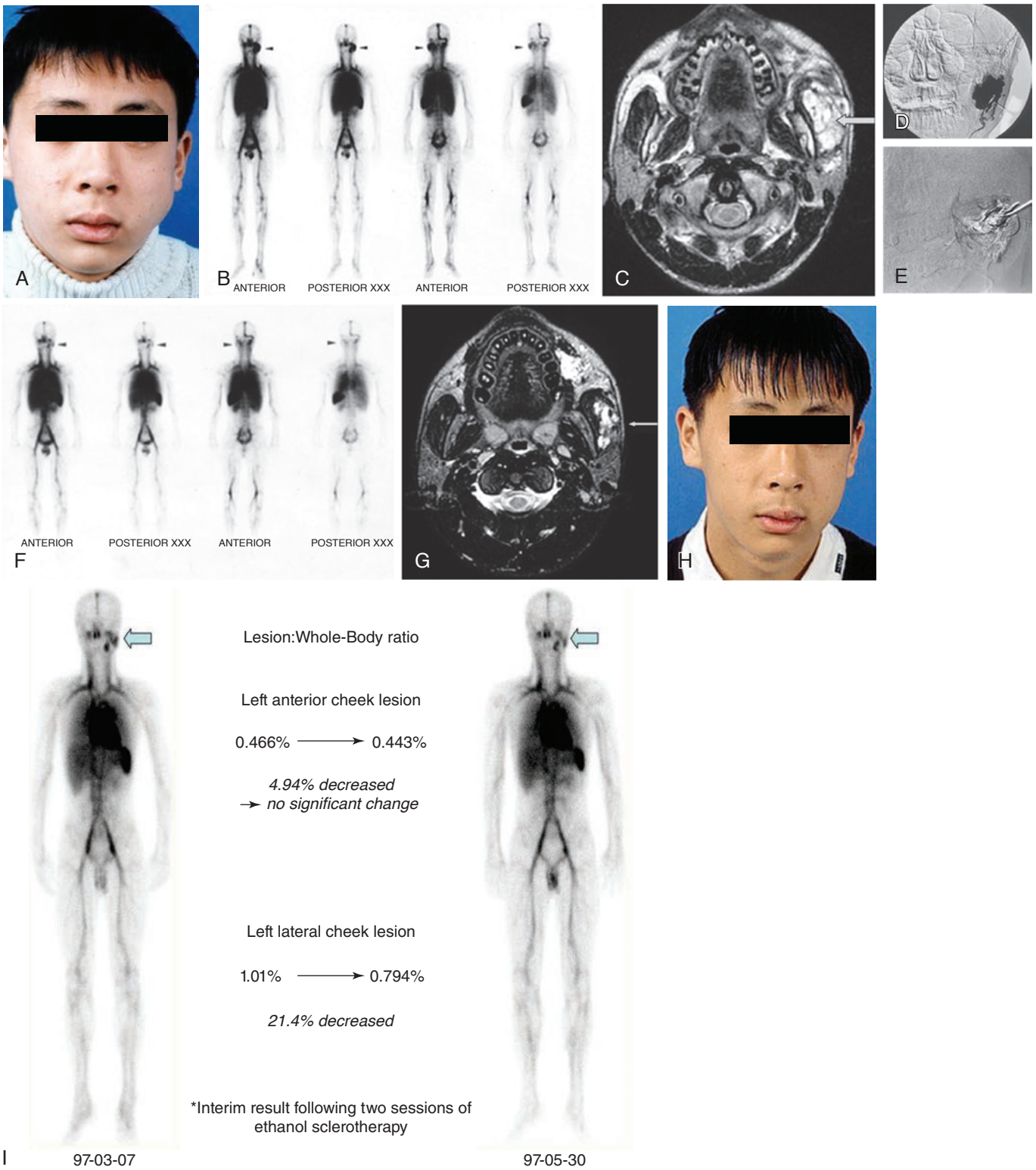

Figure 171.3 Role of Whole-Body Blood Pool Scintigraphy (WBBPS). (A–I) Qualitative and quantitative analysis of a venous malformation (VM). Photograph (A) demonstrates a VM affecting the left cheek and presenting as diffuse swelling. WBBPS (B) delineates abnormal blood pooling along the left cheek (*arrows*). T2-weighted MRI (C) reveals a large VM (*arrow*), compatible with other test findings. Based on the findings of percutaneous direct-puncture angiography (D), ethanol sclerotherapy (E) was carried out successfully. Both WBBPS (F) and MRI (G) findings demonstrate an excellent response (*arrows*) at interim follow-up. The swelling along the left cheek has completely disappeared (H). The quantitative measurement of the efficacy of therapy (I) is compatible with the qualitative findings (F).

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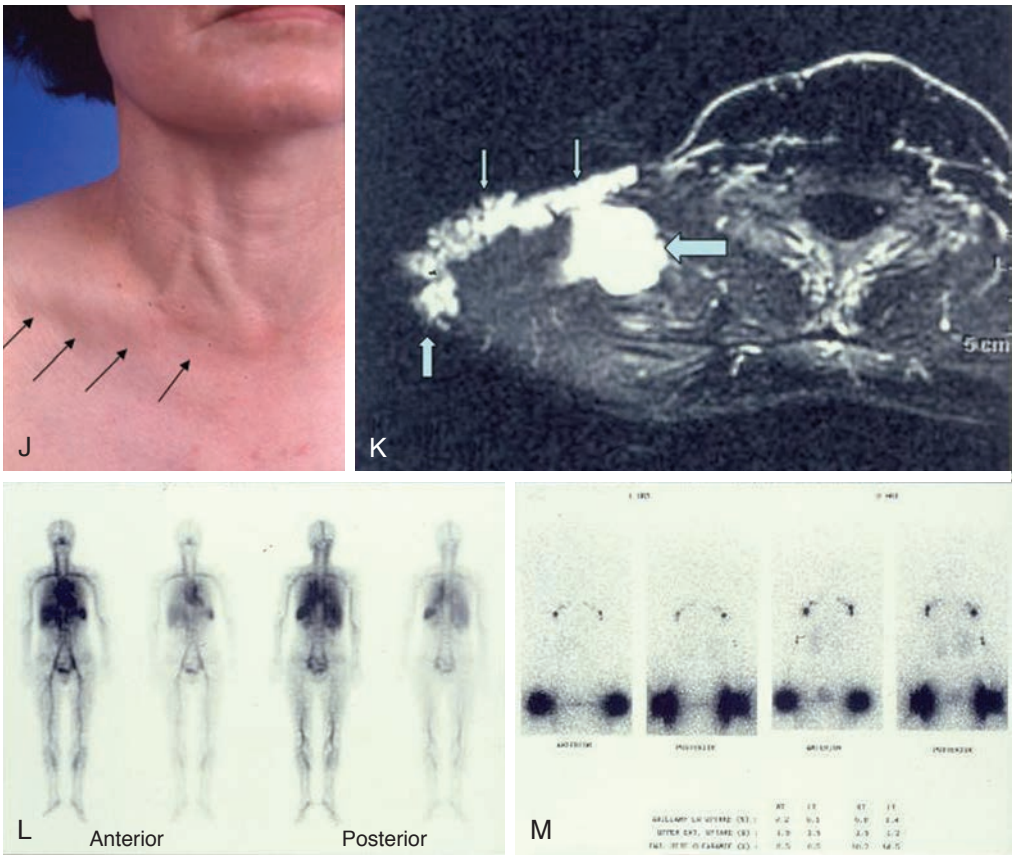

Figure 171.3, cont'd (J–M) Differential diagnosis of VM and lymphatic malformation (LM). Photograph depicts diffuse swelling over the right clavicular region (*arrows* in J), with vague but steady pain extending to the root of the neck and to the right shoulder. Clinically, this was considered a VM, based on an increase in size during the Valsalva maneuver. T2-weighted MRI shows findings typical of a VM (*arrows* in K). However, there was a strong clinical suspicion of an LM owing to its location in the common site of infiltrating, extratruncular LMs. WBBPS (L) does not show pooling in these areas, ruling out a VM. Radionuclide lymphoscintigraphy findings (M) illustrate a completely normal lymph transporting system.

they remain the gold standard, particularly for AVMs.[113] Selective arteriography is mandatory for the diagnosis of AVMs and as a roadmap for treatment. In the case of VMs, ascending, descending, or segmental phlebography serves as a guide for diagnosis and treatment. In patients with LMs, percutaneous lymphangiography is infrequently needed but occasionally performed to evaluate the extent of an extratruncular lesion.[28,122] In general, traditional lymphangiography is no longer used owing to its potential to damage lymphatic vessels secondary to inflammation produced by oil-based contrast, unless indicated specifically for reconstructive surgery.

Evaluation of Affected Systems

Leg-length discrepancy secondary to abnormal long-bone growth should be evaluated by bone scan, as described in the section entitled Congenital Vascular Bone Syndrome. Coagulation studies are not routinely included in the evaluation of CVMs, but may be required in cases of extensive extratruncular VMs and large marginal veins, especially when venous thrombosis is suspected. The use of coagulation studies is discussed more fully in the section entitled Coagulopathy: Thrombosis and Fibrinolysis.[17,37,99]

Differentiating Congenital Vascular Malformations From Infantile or Neonatal Hemangioma

Even though the overall incidence of CVM is much lower than that of hemangioma,[5,41,131] differentiating CVM from hemangioma should be the first step in the diagnosis of CVMs.[132,133] Hemangiomas are usually not present at birth, appear suddenly during the neonatal period as rapidly growing tumors, and ultimately involute. Hemangiomas are more common in females (3–5 : 1 female:male ratio). In contrast, a CVM is always present at birth, although it may not be apparent. Gender distribution is equal, and it grows commensurate with body growth. In most cases a history and physical examination will distinguish a CVM from a hemangioma; the distinction is confirmed by noninvasive studies. Tissue biopsy is rarely needed.

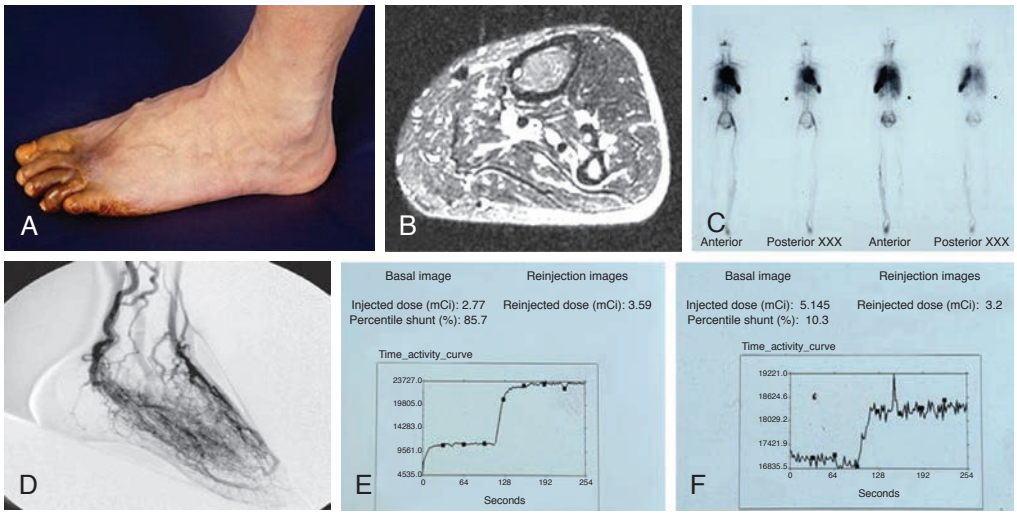

Figure 171.4 Role of Transarterial Lung Perfusion Scintigraphy (TLPS). (A) Ischemic left foot with impending necrosis of two toes. The local condition deteriorated rapidly after arteriovenous malformations (AVMs) affecting the pedal arterial arch were treated with coil embolization of the feeding artery. (B) MRI findings in the lower leg are compatible with an AVM affecting the foot only. (C) Whole-body blood pool scintigraphy shows the hyperdynamic status of the arterial system originating from the AVM in the foot. (D) Arteriography reveals massive shunting through the AVM. (E) Before treatment, the shunting percentage of blood measured with TLPS is 85.7%. (F) After multisession ethanol sclerotherapy, the shunting is effectively reduced to 10.3% on repeat TLPS. TLPS is a reliable test not only to assess the severity of AVMs, but also to follow the response to therapy. It is also useful to find hidden micro-AVMs, often exceeding the reliability of arteriography.

TREATMENT

General Principles

During the last century, limited knowledge about the natural history and biologic behavior of CVMs often contributed to poor outcomes following an overaggressive surgical approach—in particular surgery performed on extensive, unresectable lesions.[134,135] As a result of these poor outcomes, for many years surgery was limited to situations in which it was the only option (bleeding control, significant hemodynamic compromise, severe disturbances in bone growth, and disfiguring lesions). Eventually, new concepts and classification systems provided a better understanding of CVMs, and recognition of the fundamental differences between extratruncular and truncular lesions led to better management principles.

Extratruncular lesions grow and will recur unless the lesion nidus is completely destroyed. They should thus be treated aggressively. In contrast, truncular CVMs lack the potential for proliferation, and the same aggressive approach is not justified. Some can be handled conservatively until they become hemodynamically significant. Intervention should be performed only for symptoms and in situations such as thromboembolism, chronic venous insufficiency, and ulceration.[37,78,81,112] For best results, a multidisciplinary team of experts should review every CVM, and the treatment plan should be derived by team consensus following an appropriate diagnostic workup[115] (Boxes 171.3 and 171.4).[37,38,117]

The lateral embryonic or marginal vein deserves special attention.[90,91,136] Its treatment is discussed in the section entitled Klippel-Trenaunay Syndrome.

BOX 171.3 Indications for Treatment of Extratruncular Congenital Vascular Malformations

- Hemorrhage
- High-output heart failure (arteriovenous shunting malformation)
- Secondary ischemic complications (arteriovenous shunting malformation)
- Secondary complications of chronic venous hypertension (venous malformation)
- Lesions located in life-threatening (e.g., proximity to airway) or vital function–threatening (e.g., seeing, eating, hearing) region
- Disabling pain
- Functional impairment
- Cosmetically severe deformity
- Vascular-bone syndrome
- Lesions located in a region with a potentially high risk of complications (e.g., hemarthrosis, deep venous thrombosis, pulmonary embolism)
- Lymph leak with or without infection
- Recurrent sepsis (local or general)

Arteriovenous and Venous Malformations

All AVMs should be considered potentially life- or limb-threatening lesions necessitating an early, aggressive approach (Fig. 171.5).[23,24] A "controlled" approach minimizing damage to adjacent areas is preferable, but in certain situations, limb sacrifice may be necessary.[37,38]

VMs are less dangerous and may not require treatment.[31,81,137,117,37] When the risk-benefit ratio favors treatment, as in those which threaten vital functions or produce vascular bone syndrome, less aggressive options (e.g., foam/liquid

sclerotherapy) should be performed.[66,16] In pediatric patients, VM without bone involvement can usually be monitored until the child reaches age 6 years or is mature enough to tolerate diagnostic and treatment procedures.[113,117]

Order of Treatment

The treatment strategy should focus on the hemodynamic derangements associated with the primary malformation first, followed by treatment of secondary disorders. This can involve either reconstructive or ablative/excisional surgery. Corrective surgery for the sequelae of secondary hemodynamic consequences may follow. When severe CVMs result in a nonfunctional limb, early amputation should be considered.[37,38]

BOX 171.4 Components of a Multidisciplinary Team for the Management of Congenital Vascular Malformations

- Vascular surgery
- Pediatric surgery
- Plastic and reconstructive surgery
- Orthopedic surgery
- Anesthesiology
- Pathology
- Physical medicine and rehabilitation
- Otolaryngology
- Head and neck surgery
- Cardiovascular medicine
- Psychiatry
- General medicine
- Interventional radiology
- Diagnostic radiology
- Nuclear medicine
- Dermatology

Nonsurgical/Endovascular Therapy

Endovascular therapy, primarily embolization and sclerotherapy, is now accepted as the treatment of choice for surgically *inaccessible* extratruncular lesions, such as the diffuse, infiltrating type beyond the deep fascia with involvement of muscle, tendon, and bone.[37,38,117] In cases where surgery is anticipated, adjunctive endovascular therapy can be performed pre- and postoperatively to improve the safety and effectiveness of surgery.[117,138]

Sclerotherapy and Embolotherapy

Liquid sclerosants are now used as the major therapeutic tool for the treatment of CVMs. Frequently used sclerosants include ethanol, polidocanol, and sodium tetradecyl sulfate. Embolotherapy agents include coils, glue, and particles. *N*-Butyl cyanoacrylate (NBCA) and Onyx are useful as preoperative therapy to reduce morbidity prior to the surgical excision of AVM or VM.[139,140] Specific indications and techniques for the use of these agents can be found in Chapter 173.

Surgical Therapy

Excision is the only option for complete removal of a CVM, but generally requires extensive surgery with high morbidity.

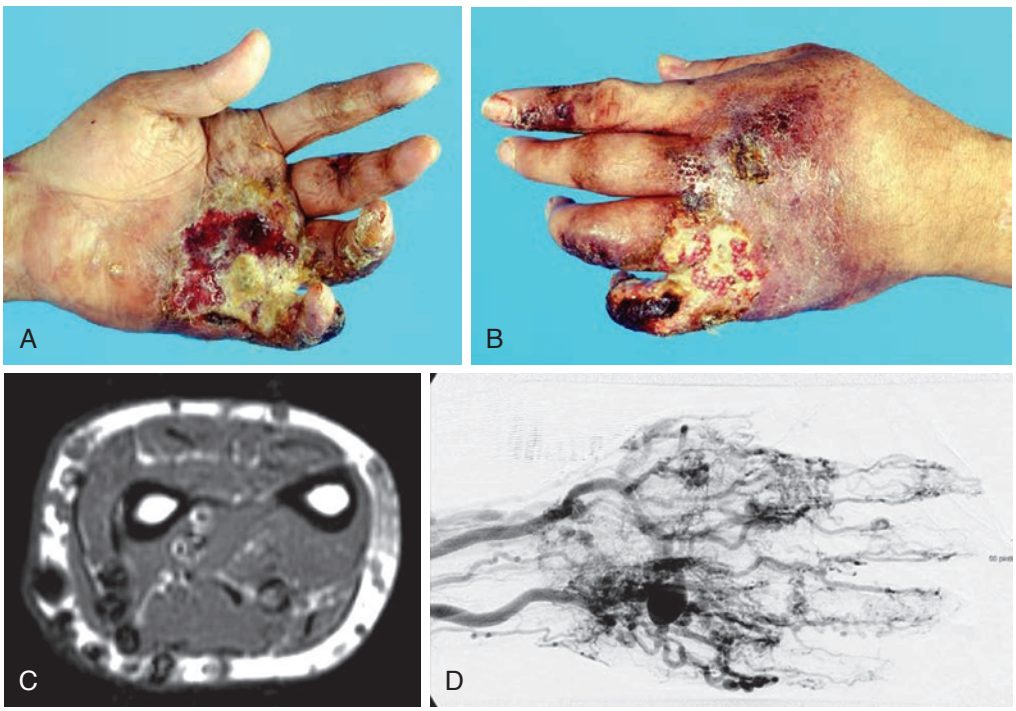

Figure 171.5 Natural Course of Arteriovenous Malformation (AVM), With Impending Limb Loss. (A and B) Ultimate outcome of a neglected AVM affecting the left hand and fingers. Stealing of arterial blood from the distal arterial trees by the AVM eventually leads to chronic arterial insufficiency and subsequent ischemia and gangrene. The hand and fingers are now in jeopardy, with great risk of major tissue loss. MRI (C) and arteriography (D) show evidence of massive shunting, making treatment more difficult.

Incomplete resection can result in recurrence. Therefore ideal candidates for surgical excision are limited to those with localized lesions.[37] Truncular VM lesions with involvement of the iliac veins or IVC can be managed surgically—for example, using segmental resection of the involved vein combined with various reconstruction techniques.[141-144] Venous aneurysms of veins such as the popliteal or femoral vein can be managed with resection and bypass/transposition using a new vein segment, or partial tangential resection and aneurysmorrhaphy. Valve function restoration is also technically feasible with vein valve transplant or transposition.[145-147] Indications and techniques for specific procedures can be found in Chapter 172.

SPECIFIC VASCULAR MALFORMATIONS AND CONDITIONS

Congenital Vascular Bone Syndrome: Angio-Osteodystrophy

CVBS is a group of syndromes associated with abnormal long bone growth caused by CVMs in childhood. Abnormal circulation around and/or inside the bone from CVMs results in angio-osteo-hypertrophy or angio-osteo hypotrophy.[89,91] Limb overgrowth is always due to hypervascularization, either by macroshunts or by microshunts.[148-150] Among VM, the presence of a marginal vein (MV) is known to cause angio-osteo-hypertrophy. Undergrowth with bone shortening may be induced by bone compression from abnormal vascular masses or reduction of arterial inflow from arterial hypoplasia. Tissue and bone growth factors may also be involved.[151] In one study of patients with VMs, the incidence of long-bone lengthening by CVBS was 19% and shortening was 7%. Among patients with AVMs, lengthening occurred in 49% and shortening in 4%.[89]

The diagnosis of limb length difference can be confirmed by plain x-rays and bone scans. Duplex ultrasonography together with MR or CT will confirm the intraosseous localization of the CVM.[152] Evaluation should be performed expeditiously so that treatment can be undertaken before the epiphyseal plate is closed between ages 16 and 18.[37,80] Alternatively, removal of the CVM in early childhood may retard bone growth and correct limb length discrepancy. In some cases, orthopedic procedures may also be required.[89-91,148,149]

Klippel-Trénaunay Syndrome

The typical patient with KTS has the following clinical features: (1) port-wine stain that may be localized to a relatively small area or involve the lateral aspect of one or more extremities; (2) limb hypertrophy or gigantism, manifested by an extremity that is longer and larger in circumference than the healthy extremity; (3) presence of large clusters of varicose veins extending throughout the entire extremity; and (4) a large lateral venous collector called the vena marginalis lateralis/marginal vein (MV), which usually drains into the pelvic veins. All patients with KTS have three CVM components, including VM, LM, and CM.[84,92,103-106]

The large majority of KTS patients can be managed with conservative measures such as compression (gradient elastic stockings with 35 to 45 mm pressure) and sclerotherapy. However, some patients have pain from large venous varicosities, as well as ulceration, thrombosis, and pulmonary embolism. In these cases, excision of large varicose clusters will relieve symptoms. Prior to excision, imaging should be performed to ensure that the deep system is present, as 8% of patients with KTS have either atresia or hypoplasia of this system. We recommend surgery in two or three stages, and the use of a tourniquet to eliminate or decrease bleeding. Beginning 2 months after surgery, sclerotherapy using either liquid or foam should be used to eliminate residual varicosities.[37,112]

A large marginal vein should be excised in its entirety when the deep system is patent, using segmental resection through several incisions. Large perforators, often 8 to 10 mm in diameter, connecting to the deep system, should be ligated to prevent profuse bleeding.[103-106]

Because patients with KTS may also have venous aneurysms or enlarged phlebectatic veins in the deep venous systems, imaging such as CTV and MRI should be performed to identify these and treat the sequelae as indicated.[92]

Growth discrepancies in the extremities can lead to disabling skeletal sequelae in early adolescence. For this reason, children with KTS should have orthopedic evaluations and the proper measures taken to prevent scoliosis.

In some patients, lymphangioma cause significant problems, including swelling leading to deformity, repeated episodes of lymphangitis, lymph leakage through the perineum, lymphatic blisters, and cosmetic concerns.

Parkes Weber Syndrome

PWS is a condition first described in 1907 with clinical features similar to those of KTS. As initially described, the syndrome consisted of varicose veins, limb hypertrophy, and port-wine stain, but with a clearly detectable pulsation and thrill. The difference between PWS and KTS is based mainly on the presence of AVM in PWS, and therefore a different clinical course with different prognosis.[107-109] However, using radioactive isotopes (transarterial lung perfusion scan), some investigators have detected arteriovenous (AV) shunting among the patients previously diagnosed as KTS, blurring the difference between the two syndromes. The presence of significant AV shunting in a symptomatic patient with PWS warrants treatment by embolization.[37,92]

Coagulopathy: Thrombosis and Fibrinolysis

Extratruncular VM are associated with coagulopathy because of stasis of blood within the abnormal structures, which leads to the activation of the coagulation cascade.[153,154] This condition is known as localized intravascular coagulopathy (LIC). It is followed by fibrinolysis, which is reflected in elevated levels of fibrin degradation products such as plasmin derived D-dimer

epitopes.[155,156] Microthrombi in LIC form stonelike structures called "phleboliths," which can be detected by palpation when the VM is located superficially or visualized on plain x-rays when located in deep VM.[155,157]

LIC can result in thromboembolic events, including deep vein thrombosis (DVT), pulmonary embolism (PE), and subsequent chronic pulmonary hypertension. Furthermore, this relatively benign local condition can progress to disseminated intravascular coagulation (DIC) with life-threatening hemorrhage and multiorgan system failure. Events known to trigger the conversion of the LIC to DIC include sclerotherapy, surgical resection, bone fracture, prolonged immobilization, and pregnancy or menstruation.[157-161] The presence of phleboliths may therefore represent an indication for anticoagulation, especially when the accompanying lesion is large and extensive.[162,163]

All patients with VMs should undergo testing for hypercoagulable state as part of their routine diagnostic evaluation. Large and/or multifocal VMs with significant elevations of D-dimer levels are strongly suggestive of coagulation disorders. Extensive VMs affecting an extremity with low fibrinogen levels are suggestive of an increased risk for bleeding, particularly if surgery or sclerotherapy is anticipated. We recommend management with low molecular weight heparin (LMWH).[164,165]

LONG-TERM FOLLOW-UP ASSESSMENT

The clinical behavior of every vascular malformation depends on the stage of embryogenesis at which developmental arrest occurs. Therefore as mentioned previously, the entire extratruncular lesion is destined to grow whenever there is adequate stimulation. All CVMs affecting the extremity should be closely observed during the child's growth until the epiphyseal plate has closed. Female patients have much higher risks of deterioration or revival of the lesion, owing to menarche, pregnancy, or hormonal therapy.[89] A dormant lesion (e.g., microshunting AVM) may become clinically active, changing its clinical characteristics in this setting. Trauma or surgery can also trigger activity in a previously quiet lesion, stimulating it to grow rapidly. Hence lifetime follow-up at regular intervals is necessary in all treated or untreated lesions, especially after pregnancy. Periodic follow-up evaluation, including radiographic studies and various noninvasive studies, is essential for proper long-term care.[37,38]

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172 CHAPTER

Congenital Vascular Malformations: Surgical Management

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INTRODUCTION

The proper diagnosis and treatment of vascular anomalies has long been impeded by misused terminology. Advances in our understanding of these disorders led to the creation of a biological classification system, formally adopted by the International Society of the Study of Vascular Anomalies in 1996 and updated in 2014.[1-4] This classification scheme divides these anomalies into vascular tumors and vascular malformations based on physical characteristics, natural history, and cellular features. Vascular tumors are true neoplasms that arise from cellular hyperplasia, while vascular malformations are congenital lesions originating from errors of embryonic development of blood vessels. Vascular tumors include infantile hemangioma, kaposiform hemangioendothelioma, and tufted angioma. Vascular malformations can be further subdivided based on vascular channel type (capillary, lymphatic, venous, arterial, or combinations thereof) or by flow (slow vs. fast). Slow flow lesions include capillary malformations (CM), lymphatic malformations (LM), and venous malformations (VM). Examples of fast flow lesions include arteriovenous fistulas (AVF) and arteriovenous malformations (AVM). Combined malformations (such as Klippel-Trenaunay and CLOVES [congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal abnormalities] syndromes) consist of two or more types of vascular malformations and can be associated with other anomalies.[1,4]

Correct identification of the type of anomaly present in a vascular malformation is paramount to appropriate treatment selection. Consequently, lesions must be properly imaged prior to procedural planning. Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are the most common modalities used to determine the extent of the malformation. Angiography can also be useful for delineation of AVM, demonstrating the nidus and its feeding vessels, along with flow characteristics.[5,6] For those with lymphatic anomalies, lymphoscintigraphy may be useful for demonstration of lymphedema, while digital subtraction lymphangiography and magnetic resonance lymphangiography can best delineate the alternate anatomy and dysfunction of the central conducting lymphatics.[7-9] Additional information regarding appropriate diagnostic evaluations for vascular malformations can be found in Chapter 171.

Vascular malformations are primarily treated with sclerotherapy or surgical excision. Conservative treatment such as compression garments can help control symptoms of bulky disease and lymphedema. Recently, rapamycin inhibitors have

Abstract

Vascular anomalies are classified into two groups: vascular tumors and vascular malformations. In addition, vascular malformations can be further subdivided based on vascular channel type (capillary, lymphatic, venous, arterial, or combinations thereof) or by flow (slow vs. fast). Correct identification of the type of vascular anomaly is paramount to appropriate treatment selection, and imaging should generally be obtained prior to planned procedures to define the extent of the malformation. These lesions are primarily treated with either sclerotherapy or surgical excision. Complete surgical resection may not be achievable, and lesions may require multiple or staged procedures, sometimes in combination with sclerotherapy.

Keywords

vascular malformation
lymphatic malformation
venous malformation
arteriovenous malformation

been used to successfully treat several types of vascular anomalies, including LM, venous lymphatic malformations (VLM), and capillary lymphatic/venous malformations (CLVM).[10]

Preoperative sclerotherapy or embolization may decrease intraoperative blood loss and increase the likelihood of achieving a safe and successful surgical procedure.[11-15] General principles for resection have been well described by Upton and Taghinia.[16] One should avoid the creation of a large scar that may be as unaesthetically pleasing as the original malformation. Tourniquets should be used for extremity lesions to limit blood loss. Vital structures should also be tagged and avoided to prevent functional loss. Limiting administration of paralytics allows for the use of intraoperative nerve monitoring. Incisions should be closed without tension and drains used to prevent accumulation of fluid postoperatively.

Complete surgical resection may not be achievable, and lesions may require multiple or staged procedures. Resection is generally performed to improve contour and mobility, decrease infectious risk, and for pain relief rather than purely for cosmetic purposes.

This chapter addresses the surgical treatment of vascular malformations. Endovascular treatments, including sclerotherapy, are addressed in Chapter 173.

SURGICAL TREATMENT OF LOW-FLOW MALFORMATIONS

Capillary Malformations

Capillary malformations are present at birth and typically appear as flat, pink-red cutaneous lesions. They can be associated with underlying soft tissue and skeletal overgrowth, other internal abnormalities, or as part of combined malformations. Resection is not usually necessary for isolated CM, and treatment consists primarily of flashlamp pulse-dye laser therapy for cosmetic purposes. They may, however, be partially resected during debulking procedures for underlying venous or lymphatic malformations.

Lymphatic Malformations

Lymphatic malformations are often classified as macrocystic (diameter >1 cm), microcystic (diameter <1 cm), or a combination of both. This description of the type of LM, along with its location and extent, is useful when determining treatment options.[17] Presentation can vary from a localized mass to a diffuse anomaly. LM are unique among vascular anomalies in that they not only can serve as a source of infection, causing cellulitis or bacteremia, but they also are affected by illness occurring elsewhere in the body, increasing in size in response to infection. Cervicofacial LM in the head and neck region are common and can present with breathing and swallowing difficulties. Congenital anomalies of the central lymphatics can present with chylothorax or chylous ascites, respiratory compromise, malnutrition and hypoproteinemia, lymphopenia, and bony erosion.[18] Intralesional bleeding may also occur secondary to trauma or an abnormal venous connection. Cutaneous involvement of LM manifests as reddish-purple to black vesicles, which can leak serosanguinous fluid.

In general, LM that are predominantly macrocystic are more amenable to sclerotherapy, while those that are microcystic in nature often require resection. Lesions with poor response to sclerotherapy can also be resected. Massive LM, even when predominantly macrocystic, are often best treated with resection since shrinkage after sclerotherapy may not be sufficiently satisfying. Asymptomatic lesions can be observed. Indications for treatment include deformity, dysfunction, leakage into body cavities or from the skin, and recurrent infections. Since these procedures may be lengthy, operative intervention should be delayed until 6 months of age unless the airway is threatened.

Operative Treatment

Subcutaneous LM can cause considerable tissue expansion, and thus for larger lesions, a lenticular excision should be made. As much involved skin as possible (i.e., with creases, dimpling, or vesicles) should be included in the excision to prevent rupture of lymphatic cutaneous vesicles at a later time. The remaining overlying skin and subcutaneous tissue is then dissected off the underlying LM as flaps. The appearance of an LM is similar to fat but has a distinguishable texture. In situations where there is no normal subcutaneous tissue and the LM extends into the dermis, a deep subdermal dissection plane can be created to ensure sufficient vascularity. An intraoperative nerve stimulator is helpful, particularly when the LM encompasses neurovascular structures. Since LM are not malignant lesions, the entirety of the lesion need not be removed, and care should be taken to preserve any vital structures. Subsequent operations may be necessary to remove residual LM or re-contour areas following the initial resection (Fig. 172.1A-C). However, re-operations can be much more difficult because of scar tissue and loss of planes, so every effort should be made to be as thorough as possible at the initial operation. Moreover, depending on how much LM is left behind, any residual lesion may re-expand in the months following surgery. Closed suction drains are placed in the wound to absorb lymphatic leakage, and excision of redundant skin may be required to close the skin in a cosmetic fashion. Complex flaps may be required to provide adequate tissue coverage and cosmetic reconstruction.[19]

Treatment of symptomatic abdominal and pelvic LM can be challenging, and sclerotherapy is effective for macrocystic lesions. Microcystic lesions can be observed or partially resected, avoiding removal of major associated viscera when possible. LM of the gastrointestinal (GI) tract can cause pain and obstruction, and bowel resection may be required for symptomatic relief. Splenic involvement is common; splenectomy should be limited to patients who develop massive or symptomatic splenomegaly or hypersplenism.

Management of leakage from lymphatic anomalies can be difficult. Chylous pleural effusions from thoracic LM can sometimes be treated with chemical or mechanical pleurodesis. LM of the pericardium causing pericardial fluid accumulation can be treated by pericardial window or repeated pericardiocentesis by needle or indwelling catheter. Nonoperative

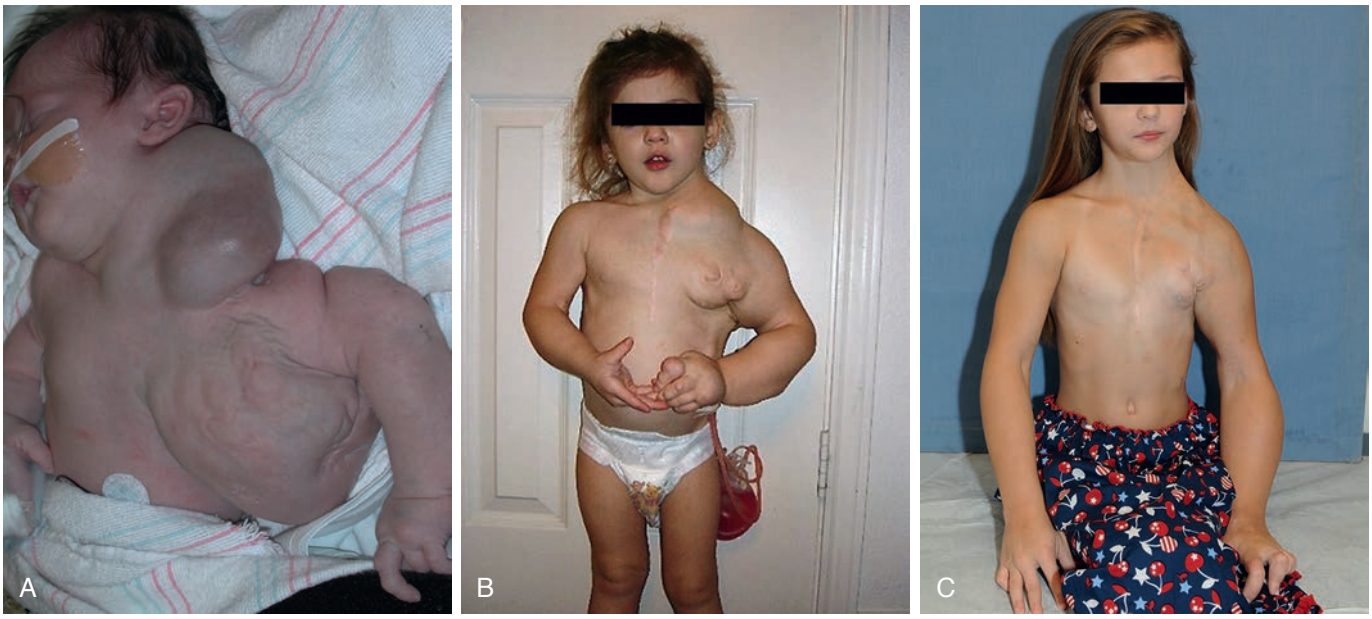

Figure 172.1 (A) Lymphatic malformation of left neck, axilla, mediastinum, and upper extremity in baby girl, shortly after birth. (B) Girl, age 3, following multiple sclerotherapy and debulking procedures. (C) Girl, now age 10, active in dance and other activities.

management aimed at decreasing the total volume of lymph fluid with octreotide, low-fat diets, or total parental nutrition may reduce thoracic duct flow. Ligation or embolization of the thoracic duct can be useful, but this should be done with caution in those with diffuse lymphatic anomalies, as outflow obstruction may exacerbate symptoms. In some rare cases, shunt procedures can provide palliation.

LM can occur in the subcutaneous tissue of the penis, and lymphedematous swelling of the penis not controlled by wrapping can be excised. The entire thickness of the subcutaneous tissue should be removed to minimize recurrent swelling.

Postoperative Management

Closed suction drains are left until output is minimal to prevent seromas and hematomas that may delay healing and induce wound disruption. These can remain in place for weeks to months, so patients should be warned preoperatively regarding the duration of drainage.

Cutaneous vesicles from unexcised lymphatic channels may occur within the surgical scar following resection, but they can be controlled by local intravesicular sclerotherapy or CO_2 laser treatment. They can be resected, but due to their extensive nature, recurrence is common. Consequently, to prevent development of vesicles, the uninvolved dermis should be advanced over the resection bed and any involved skin excised during the procedure.

Venous Malformations

Venous malformations may be present at birth and typically grow with the patient, although symptoms may not arise for some time. They may expand with dependent position and Valsalva maneuver. Stasis in VM can lead to phlebothrombosis, causing pain and swelling. In addition, VM of the bone and joints can lead to fractures and hemarthroses. VM involving the muscle can also present with pain and swelling, which are exacerbated by the dependent position and exertion, and can cause associated skeletal problems, including fracture, overgrowth, deformation, or undergrowth.[20]

Asymptomatic VM can be managed initially with compressive garments to minimize thrombotic episodes, and some patients feel improvement with daily low-dose aspirin. Surgery is reserved for symptomatic lesions, cosmesis, or functional impairment, but prior to any operation, coagulation studies should be obtained, as localized intravascular coagulation can occur.[21] Those VM that are well-localized are most amenable to surgical excision (Fig. 172.2A-D). Large lesions can be debulked if they are causing uncontrolled pain, significant limb length discrepancy, bleeding, severe cosmetic problems, impairment in function, or limitation of range of motion. Lesions that cannot be entirely resected may be treated with sclerotherapy, and preoperative sclerotherapy can also be performed to decrease blood loss and shrink the lesion.

VM of the GI tract can occur anywhere from mouth to anus. Blue rubber bleb nevus syndrome (BRBNS) is a rare disorder characterized by multifocal venous malformations, most commonly involving the skin and GI tract (Figs. 172.3A-C).[22] Skin lesions have the appearance of tiny "blue rubber nipples" and can be numerous. Lesions in the GI tract can cause intussusception, which is manifested by intermittent abdominal discomfort. Some lesions may never cause symptoms and require no intervention, and moderate fecal blood loss can often be managed conservatively with iron supplementation. Severity and frequency of bleeding can be decreased with stool softeners and avoidance of constipation. Exsanguinating hemorrhage is rare. However, those with significant anemia, particularly requiring

Figure 172.2 (A) Two-year old boy with large venous malformation of lower back. (B) Resection of venous malformation demonstrating creation of flaps. (C) Venous malformation following resection. (D) Child at 2-month follow-up.

blood transfusions, or an acute small bowel obstruction may warrant an operation.

Operative Treatment

For extremity VM, the use of a tourniquet can decrease intraoperative blood loss. VM have fragile, dysplastic vessels and permeate into surrounding tissues, which can result in significant blood loss with dissection.[23] Cutting through a VM produces a surface resembling a sponge, and bleeding is difficult to control with cautery, clamps, or sutures. Hemostatic devices such as bipolar sealers, electrocautery, and ultrasonic scalpels can be useful. Involved skin should be incorporated in the incision as much as possible. VM can also act as a tissue expander, leading to redundant skin once excised, and a large amount of involved skin can be removed with the specimen. Flaps are raised in all directions from the incision (see Fig. 172.2B). When lesions involve the dermis or are just below the dermis, flaps should be made as thinly as possible without devascularization of the skin. Care should be taken to preserve nerves, tendons, and joint cavities; and closed-suction drains are placed in the flap. Large resection areas can be covered by local or distant flaps, or by the use of skin grafts.

For those with blue rubber bleb nevus syndrome affecting the GI tract, VM can be removed with a combination of wedge

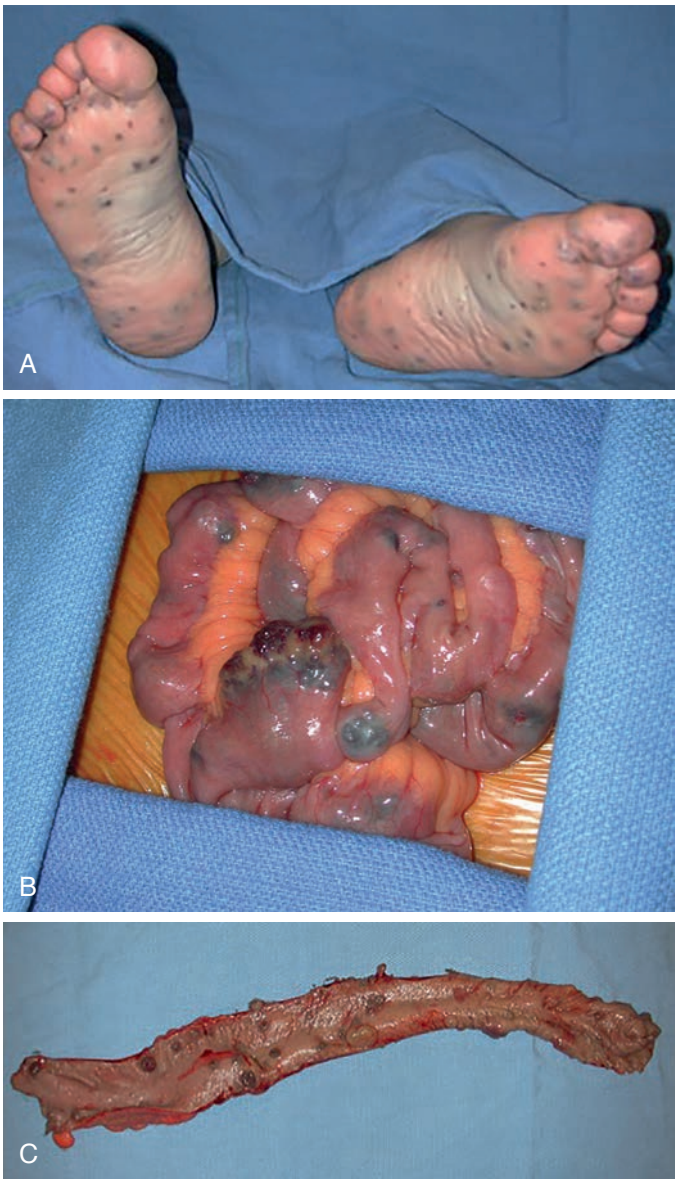

Figure 172.3 (A) Patient with blue rubber bleb nevus syndrome, with multiple venous malformations (VMs) of the foot. (B) Multiple VM in the intestine. (C) Densely populated VM in resected bowel.

bowel resection, band ligation, polypectomy, suture-ligation of narrow-based polypoid lesions, and segmental bowel resection (see Fig. 172.3B and C). It is preferable to remove individual lesions rather than sections of intestine, since lesions are distributed throughout the gut. Intraoperative endoscopy, from mouth-to-anus, identifies lesions that may not be seen externally or palpable. Serosal sutures or dye stain can be used to mark these lesions.

Diffuse and densely located VM, involving large continuous segments of bowel, require more than simple excision, and can be managed by colectomy, anorectal mucosectomy, and coloanal pull-through.[24]

Anorectal VM can be associated with an ectatic inferior mesenteric vein, which can siphon blood flow from the portal vein.[25] This causes stagnation of blood resulting in portomesenteric thrombosis and resultant portal hypertension. Patients with rectal VM should be screened for this anomaly, and if found, it can be ligated proximally to prevent thrombosis.

While bulky VM of the scrotum may be amenable to sclerotherapy, repeated sessions should be avoided to minimize radiation, and thus surgical resection is preferable. Sclerotherapy of labial VM can be performed as long as female gonads are shielded. Debulking is best undertaken after puberty, although massive lesions can be debulked earlier. Sclerotherapy of the clitoris should be avoided; clitoral VM can be resected, but care should be taken to avoid neurovascular injury.

Postoperative Management

Lesions not completely excised can re-canalize and enlarge, requiring additional procedures or sclerotherapy.[26] Postoperative complications include hematoma, partial skin necrosis, and persistent edema. Drains are left in place until fluid outflow is minimal.

SURGICAL TREATMENT OF HIGH-FLOW MALFORMATIONS

Arteriovenous Malformations

Arteriovenous malformations are characterized by abnormal connections between feeding arteries and draining veins. They may begin as only a pink stain, but they can expand during pregnancy or puberty or secondary to local trauma. Expansion can lead to skin ischemia and local steal phenomenon, resulting in pain, ulceration, functional impairment, nerve compression, soft tissue and bony destruction, and bleeding. These symptoms necessitate treatment.[13,27] Large AVM can also cause high output cardiac failure, which requires early intervention. Asymptomatic lesions can be observed, although it is preferable to treat before the AVM progresses.

Operative Treatment

Management of AVM includes embolization alone or in combination with surgical excision. Preoperative embolization of the nidus is followed by surgical resection in 2 to 3 days, since rapid expansion can occur during the period between embolization and resection (Fig. 172.4A and B).[13] Unless the surgeon is sure that the entire AVM has been removed, the proximal feeding arteries should not be embolized or ligated, as these provide the only avenue to reach the nidus of the AVM for subsequent embolization. Occlusion of the primary vessels will result in recruitment by the nidus of other nearby arteries, allowing the AVM to recur and progress. Embolization can also be used for palliation in persistent AVM.

The goal of the operation is complete excision to normal margins with removal of both the nidus of the AVM and involved skin. Focal AVM can be excised with good long-term control.[28] In addition, diffuse lesions have higher recurrence rates and are more difficult to treat, as residual tissue can form collaterals and re-expand.[29] Intraoperative Doppler examination and recognition of the bleeding pattern at the margin are also useful

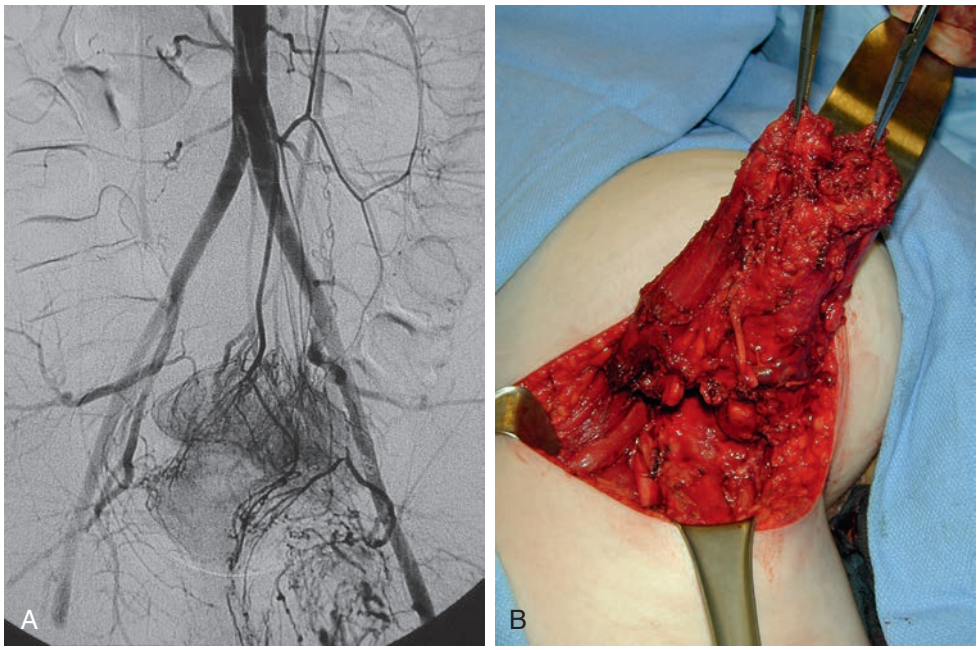

Figure 172.4 (A) Angiogram of diffuse arteriovenous malformation (AVM) of the gluteus maximus muscle, prior to preoperative embolization. (B) Excision of AVM.

guidelines for resection. Intraoperative frozen sections have not proven useful in determining the extent of resection.[13] Reconstruction immediately following resection may require skin grafts or local, regional, or microvascular free flaps.[13,28-30] Large excisions that do not allow for primary closure can be managed with vacuum-assisted closure devices or tissue transfer techniques. For difficult extremity AVM, particularly those with loss of function, amputation can be performed.

AVM of the thoracic and abdominal cavity are managed with a combination of sclerotherapy and open resection. Most AVM of the chest are intrapulmonary and can be associated with hereditary hemorrhagic telangiectasia. They can be managed with partial pulmonary resection. AVM of the GI tract are rare.[31,32] Most patients present with GI bleeding. Bleeding may be temporized with embolization, but recurrent or serious bleeding requires a formal resection. Splenic hilum or parenchymal lesions are uncommon, but they can be managed with splenectomy.[33,34] Pancreatic AVM can cause portal hypertension and eventual GI bleeding. Straightforward cases can be controlled with embolization, but permanent control may require complete resection, such as a pancreaticoduodenectomy.[35-39] More complex hepatic AVM may require hepatectomy or hepatic transplantation. Congenital arterioportal fistulae can cause ascites, abdominal pain, GI bleeding, or malabsorption.[40] Hepatectomy or surgical ligation of the fistula can be performed if transcatheter embolization fails.[41-43]

Urinary tract AVM can cause hematuria, hypertension, and flank pain.[44] Localized lesions can be resected.[45,46] AVM of the genitals can be managed with embolization and resection. AVM of the buttock often involves the gluteal muscles. These can be resected if embolization fails to control symptoms.

Postoperative Management

Patients should be followed long-term since lesions can recur. Reported rates of recurrence range from 8% to 93%.[29,30] Early signs of recurrence include erythema, superficial telangiectasias, swelling, pulsation, bleeding, or Suen sign (rapid soft tissue rebound upon palpation).

SURGICAL TREATMENT OF COMBINED VASCULAR MALFORMATIONS

Diseases with combined vascular malformations include Klippel-Trenaunay syndrome (KTS), Parkes Weber syndrome (PWS), and CLOVES syndrome and present within a wide-ranging spectrum. KTS is a slow flow combined capillary-lymphatico-venous malformation associated with prominent soft tissue and bony hypertrophy of one or more extremities.[47-49] Capillary malformations may be large, multiple, or develop lymphatic vesicles, which may weep or bleed. Lymphedema is a common complaint. The deep venous system can be absent or hypoplastic, and often anomalous superficial veins will develop in the extremity, including the primitive lateral embryonic vein of Servelle. These anomalous veins can cause cellulitis, pain, edema, and bleeding and are at risk for thrombophlebitis and as a source of pulmonary emboli.[50] These veins should be imaged prior to treatment.

Parkes Weber Syndrome is a fast-flow lesion characterized as a capillary-arteriovenous malformation (CAVM) or capillary arteriovenous fistulae (CAVF) and involves the upper and lower

extremities.[51] Congestive heart failure can develop secondary to the AVM and fistulae and may necessitate embolization of these.

CLOVES syndrome is characterized by congenital lipomatous overgrowth, vascular malformations, epidermal nevi, seizures, scoliosis, and skeletal/spinal anomalies.[52,53] Lipomatous masses on the trunk and flank can be present at birth, and extend into the mediastinum, pleural cavity, retroperitoneum, and paraspinal-intraspinal space. These can cause physical deformity and functional impairment (Fig. 172.5A). For example, large hands, macrodactyly, widened triangular feet, and "sandal gap" toes are extremity abnormalities found in these patients. Anomalous veins are also present in the extremities and along the thoracic wall and have been shown to cause pulmonary embolism.[54]

Nonoperative management with compression therapy can improve symptoms of pain, swelling, and heaviness from chronic venous insufficiency and lymphedema. Routine use of compression garments is started around age 4 to 5 years. Pneumatic compression devices can be used while sleeping or recumbent, but they are expensive. Anomalous veins were historically managed with resection, but endovenous laser ablation is now the more common therapeutic modality.

Operative Management

Soft tissue overgrowth can be managed by debulking and contour resections, which are typically done as staged procedures (see Fig. 172.5B-D).[55,56] The most common areas of debulking are the trunk, genitalia, perineum, buttock, and lower extremity. Asymptomatic lesions extending into the mediastinum or thoracic cavity are managed conservatively. Because of the risk of thromboembolism, patients should be considered for preoperative

Figure 172.5 (A) Patient with congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal abnormalities (CLOVES) syndrome, with mixed malformation of right upper extremity and chest wall, limiting range of motion. (B) Lenticular incision was created and malformation removed off muscle fascia. Note that the incision does not cross the axilla or elbow joint. (C) Closure of incision by adjacent tissue advancement technique. (D) At 14 months follow-up, patient now has improved mobility in upper extremity.

and postoperative anticoagulation and temporary inferior vena cava filter placement. Preoperative imaging is critical to determine if overgrowth is extrafascial or intrafascial, because injury to major neurovascular structures and immobility can occur with debulking of intrafascial overgrowth. Hypertrophy of the extremity can result in limb-length discrepancy that may require epiphysiodesis.

Debulking should be tailored to address the specific problematic areas of each patient and to remove as much excess bulk and weight as possible. The most extensive areas are usually addressed first. Blood loss and transfusions can be minimized by using tourniquets and intraoperative cell saver machines. A lenticular excision is used when excess tissue is present and should incorporate cutaneous lesions as anatomic options allow. The skin is incised down to the subcutaneous tissue and then skin flaps are raised. Areas with malformation that involves or is adjacent to the dermis require cautious dissection of flaps to avoid devascularization. The flap dissection should be limited to a maximum circumference of 180° to enhance flap viability and minimize postoperative wound complications. Once flaps are raised, the abnormal tissue between the muscle fascia and skin is removed. Drains are then placed in the wound bed, and skin flaps are reapproximated. The overgrowth acts as a tissue expander and often allows a large amount of excess skin to be removed. Amputation of an extremity may be necessary for palliation for unrelenting symptoms or destroyed fixed joints.

Postoperative Management

Patients should be counseled prior to resection regarding delayed postoperative healing and the protracted use of closed-suction drains. Because of altered circulation and poor lymphatic drainage, tissue in these patients makes for poor flaps, and wound healing can take several weeks to months. Drains are removed once output decreases to approximately 10 to 15 mL/day. Lymphatic vesicles may appear in and around the scar postoperatively and can be treated by laser therapy.

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173 CHAPTER

Congenital Vascular Malformations: Endovascular Management

DANIEL M. O'MARA and CLIFFORD R. WEISS

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INTRODUCTION

Vascular anomalies comprise a collection of disorders characterized by abnormal blood vessel growth. The need for accurate characterization of these lesions has led to the development of a classification system based on biologic behavior that has been approved by the International Society for the Study of Vascular Anomalies (ISSVA) and is widely accepted in the medical community.[1,2] It broadly divides vascular anomalies into nonneoplastic lesions (i.e., vascular malformations) and neoplastic lesions (i.e., vascular tumors) (Table 173.1).

Vascular malformations are the more common anomaly, comprising approximately two-thirds of all vascular anomalies; they are congenital, nonneoplastic lesions that develop secondary to defects in vasculogenesis.[3,4] Vascular malformations are further subdivided into low- and high-flow lesions based on their hemodynamic characteristics. Low-flow vascular malformations are composed of capillaries (capillary malformation), veins (venous malformation), lymphatics (lymphatic malformation [LM]), or a combination (venolymphatic malformation). High-flow vascular malformations are characterized by a direct communication between arterial and venous vessels without an intervening capillary bed (arteriovenous malformations [AVMs] and arteriovenous fistulas [AVFs]).

Vascular tumors are neoplastic vascular anomalies defined by the presence of abnormal endothelial proliferation. Overall, the most common vascular tumor is the infantile hemangioma, which is benign and characteristically involutes over time.[5] Angiosarcoma and epithelioid hemangioendothelioma are examples of malignant vascular tumors and require oncologic evaluation and treatment.[5]

This chapter focuses on the diagnosis and treatment of vascular malformations, the vascular anomalies most commonly treated by endovascular specialists.

Abstract:

Congenital vascular malformations comprise a diverse group of anomalies that are defined by abnormal non-neoplastic growth of blood vessels. Vascular malformations are broadly divided into low-flow and high-flow lesions based on their hemodynamic characteristics. Minimally invasive endovascular therapies have been developed for many of the vascular malformations. Sclerotherapy is currently the first-line therapy for low-flow lesions, and arterial, venous, and/or percutaneous embolization serves as neoadjuvant (pre-surgical) or primary treatment for high-flow lesions.

Keywords

Venous malformation
lymphatic malformation
arteriovenous malformation
arteriovenous fistula
sclerotherapy
embolization

TABLE 173.1 Classification of Vascular Anomalies by the International Society for the Study of Vascular Anomalies

VASCULAR MALFORMATION		VASCULAR TUMOR		
Slow Flow	High Flow	Benign	Locally Aggressive or Borderline	Malignant
Capillary malformation	Arteriovenous malformation	Infantile hemangioma	Kaposiform hemangioendothelioma	Epithelioid hemangioendothelioma
Venous malformation	Arteriovenous fistula	Congenital hemangioma	Retiform hemangioendothelioma	Angiosarcoma
Lymphatic malformation		Tufted angioma	Papillary intralymphatic angioendothelioma	
Mixed malformation		Spindle cell hemangioma Pyogenic granuloma	Composite hemangioendothelioma Kaposi sarcoma	

ISSVA. International Society for the Study of Vascular Anomalies Classification of Vascular Anomalies. http://issva.org/classification; 2014 Accessed December 2016; Wassef M, Blei F, Adams D, et al. Vascular anomalies classification: Recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics*. 2015;136(1):e203-e214.

TABLE 173.2 Typical Magnetic Resonance Imaging Features of Vascular Anomalies

	IH	VM	LM	AVM	AVF
Solid mass	Yes	No	No	No	No
Phlebolith	No	Yes	No	No	No
Enhancement	Avid, homogenous	Variable	None (cyst periphery)	Avid, serpiginous	Avid, serpiginous
DCE-MRA	Arterial	Venous	None	Arterial with early venous drainage	Arterial with early venous drainage

AVM, Arteriovenous malformation; *AVF,* arteriovenous fistula; *DCE-MRA,* dynamic contrast-enhanced magnetic resonance angiography; *IH,* infantile hemangioma; *VM,* venous malformation; *LM,* lymphatic malformation.

DIAGNOSIS OF VASCULAR MALFORMATIONS

The diagnosis of vascular malformations can be confusing due to their relative rarity and overlapping clinical and imaging features. Because of this confusion, suspected vascular malformations are often referred to centers with a dedicated multidisciplinary vascular anomaly team for diagnostic workup and treatment.[6] It is common to seek consultation from experts in the fields of dermatology, plastic surgery, neurosurgery, vascular surgery, and diagnostic and interventional radiology. At our institution, the vascular anomaly team classifies vascular malformations according to an established visual pathway, known as the S.E. Mitchell vascular anomalies flowchart (SEMVAFC) (Fig. 173.1),[6] which combines clinical and imaging findings to accurately identify lesions. In some cases, syndromes associated with vascular malformations, such as Parkes-Weber syndrome and Klippel-Trénaunay syndrome (KTS), can be identified with SEMVAFC.

Vascular malformations can be imaged with duplex ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and conventional angiography. Patients are often first evaluated with US, which has the advantages of wide availability, lack of ionizing radiation, patient comfort, and real-time hemodynamic characterization. However, US is limited by a small field of view that may exclude portions of a larger vascular malformation. MRI is the preferred examination for most lesions, given its wide field of view, excellent soft tissue resolution, and ability to assess enhancement characteristics (Fig. 173.2).[7] Accurate classification is assisted by the addition of dynamic contrast-enhanced magnetic resonance angiography (DCE-MRA), which produces imaging of the lesion in the arterial, capillary, venous, and delayed venous phases.[8] MRI is also useful after treatment to judge changes in size and flow characteristics.

Our MRI protocol for vascular anomalies includes multiplanar fat-saturated T2-weighted, T1-weighted, and fat-saturated precontrast and postcontrast T1-weighted sequences (Fig. 173.3). MRA is an integral component of the postcontrast portion of the examination and is typically performed with contrast-enhanced time-resolved angiography with interleaved stochastic trajectories (TWIST) sequence.[8] The typical MRI appearance of common vascular anomalies is reviewed in Table 173.2 and discussed in detail in the following sections.

TREATMENT OF LOW-FLOW VASCULAR MALFORMATIONS

Introduction

The two most common low-flow vascular malformations encountered in clinical practice are venous malformations (VMs) and LMs.

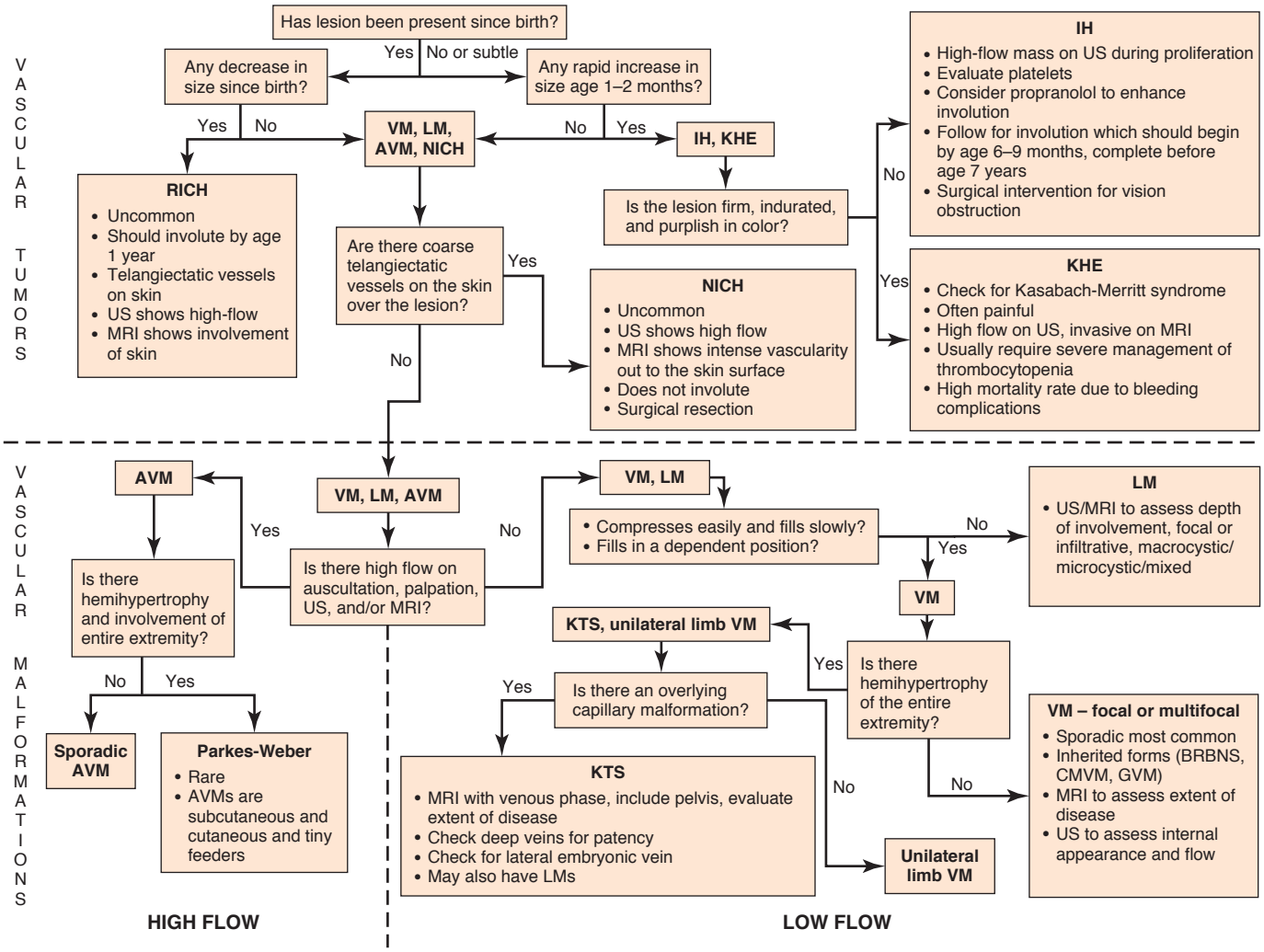

Figure 173.1 S. E. Mitchell vascular anomalies flow chart. *AVM,* Arteriovenous malformation; *BRBNS,* blue rubber bleb nevus syndrome; *CMVM,* cutaneomucosal venous malformation; *GVM,* glomuvenous malformation; *IH,* infantile hemangioma; *KHE,* Kaposiform hemangioendothelioma; *KTS,* Klippel-Trénaunay syndrome; *LM,* lymphatic malformation; *MRI,* magnetic resonance imaging; *NICH,* noninvoluting congenital hemangioma; *RICH,* rapidly involuting congenital hemangioma; *US,* ultrasonography; *VM,* venous malformation. (Reproduced from Tekes A, Koshy J, Kalayci TO, et al. S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): a visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies. *Clin Radiol*. 2014;69(5):443-457.)

VMs are uni- or multilocular lesions composed of postcapillary, endothelium-lined venous channels with abnormal mural smooth muscle. Most VMs occur sporadically; however, 1% to 2% may be inherited as an autosomal dominant trait.[9] Glomuvenous malformation (GVM), cutaneomucosal venous malformation (CMVM), cerebral cavernous VM, and blue rubber bleb nevus syndrome (BRBNS) are examples of hereditary diseases that can result in multiple lesions.[10,11] VMs range from small solitary lesions localized to the skin and subcutaneous tissues to diffuse masses that extend across multiple tissue planes and encase vascular, nervous, and visceral structures. VMs most commonly arise in the head and neck but can also affect the trunk and extremities. On physical examination, superficial VMs appear as compressible, bluish, nonpulsatile masses (Figs. 173.4 and 173.5). Lesions can expand with increased local venous pressure, as may result from dependency or with a Valsalva maneuver. Calcified phleboliths are characteristic and may be found via palpation or imaging. Common complications of VMs include pain and swelling related to phlebothromboses, infection, and psychosocial issues related to disfigurement. Additional morbidities are related to the specific location of the VM. For example, lesions in the head and neck may compromise respiration, speech, deglutition, and vision. VMs in the extremities can cause gait instability and limit mobility. Lesions within the gastrointestinal and genitourinary tracts can cause intraluminal hemorrhage resulting in acute and chronic anemia.

LMs are benign unilocular or multilocular cystic lesions composed of dysplastic endothelium-lined lymphatic channels. Cysts vary in size and may be classified as macrocystic (individual cysts >1-2 cm), microcystic, or mixed. The majority of lesions are sporadic, although some lesions are associated with Turner and Noonan syndromes.[12,13] Similar to other vascular malformations, LMs are usually diagnosed at birth or during the first

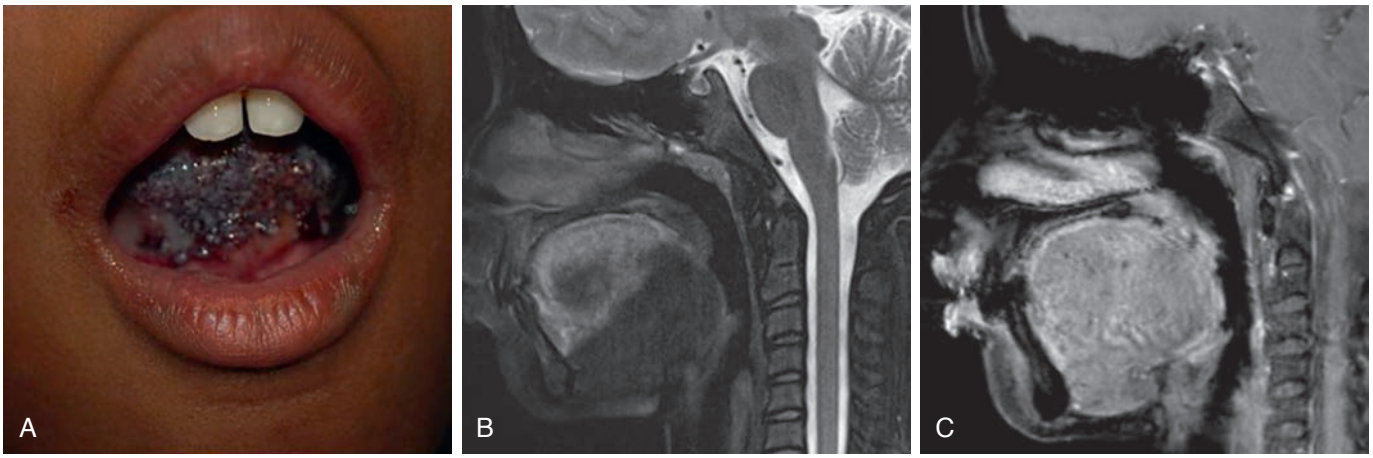

Figure 173.2 (A) An 11-year-old female with LVM of the tongue, status post–tongue reduction surgery and prior laser treatment. Recurrence of numerous small blue-black cystic lesions on her tongue. They weep clear lymphatic and bloody fluid. (B, C) Sagittal T2-weighted image of the tongue shows increased T2 signal in the intrinsic tongue muscles, which are mildly enhanced in the contrast-enhanced T1-weighted sagittal image (C). Magnetic resonance imaging (MRI) is helpful for identifying the depth of infiltration in this superficial lesion. (Reproduced from Tekes A, Koshy J, Kalayci TO, et al. S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): a visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies. *Clin Radiol*. 2014;69(5):443-457, Fig. 11.)

few years of life, but they may occasionally present later, in childhood, adolescence, or adulthood. The majority of LMs occur in the head and neck, but lesions are also found in the chest, axillae, and perineum. On physical examination, macrocystic LMs in the superficial soft tissues are palpable as cystic, rubbery, or ballotable masses (Fig. 173.6). Cutaneous LMs appear as small vesicles that discharge clear or milky lymphatic fluid when ruptured. A microcystic LM may simply appear as an area of soft tissue overgrowth. Intralesional hemorrhage is a common complication and typically results in pain and swelling. LMs may also enlarge and become painful in the presence of systemic infections. Like other vascular malformations, LMs in the head and neck can cause airway compromise.[14] Lesions deep in the chest and abdomen can cause pleural, pericardial, and peritoneal chylous effusions.[15]

Imaging

In general both VMs and LMs appear isointense to skeletal muscle on T1-weighted imaging and hyperintense on T2-weighted imaging, although intralesional hemorrhage will result in variable T1 and T2 signals depending on the age of blood products (Figs. 173.4–173.6). VMs and macrocystic LMs are cystic in appearance, whereas microcystic LMs appear as solid masses. VMs will characteristically demonstrate foci of signal void, corresponding to phleboliths, and will enhance during the venous phase of dynamic MRA. The cystic channels of LMs do not contain phleboliths or enhance internally during MRA, but the channels may contain fluid levels related to prior hemorrhage, and the peripheries of the cysts can enhance.[7] Duplex ultrasound is useful to diagnose vascular malformations in the prenatal setting, to differentiate high- and low-flow lesions, and to monitor for complications such as thrombosis and hemorrhage. Sonographically, vascular malformations appear as hypoechoic or anechoic fluid- or debris-filled cystic lesions. Phleboliths in VMs will appear as hyperechoic foci with posterior acoustic shadowing. Low-flow lesions typically exhibit essentially no flow on Doppler analysis.

Therapy Overview

Typically low-flow vascular malformations will grow and become more symptomatic over time. Treatment is often indicated to ameliorate pain, functional impairment, or disfigurement. Therapeutic options range from palliative to surgical measures. Compression garments can be used to decrease blood stagnation and swelling associated with vascular malformations in the extremities. Pharmacotherapy with aspirin and low-molecular-weight heparin (LMWH) may decrease the risk of thrombotic complications.[16] However, these measures do not decrease the overall disease burden, and more invasive therapies are usually indicated. Among the various minimally invasive and surgical options, percutaneous sclerotherapy has emerged as the first-line treatment.[10,11,17]

Sclerotherapy

Sclerotherapy involves percutaneously placing needles into the cystic spaces of a vascular malformation; they are then filled with an endothelium-damaging agent, or sclerosant. The goal of this therapy is to cause fibrosis and eventual contraction of the vascular malformation. This technique has been shown to be safe and effective for treating low-flow vascular malformations throughout the body.[18,19]

Preintervention Assessment

Patients who are being considered for sclerotherapy should ideally first be assessed in the clinic setting. A careful history

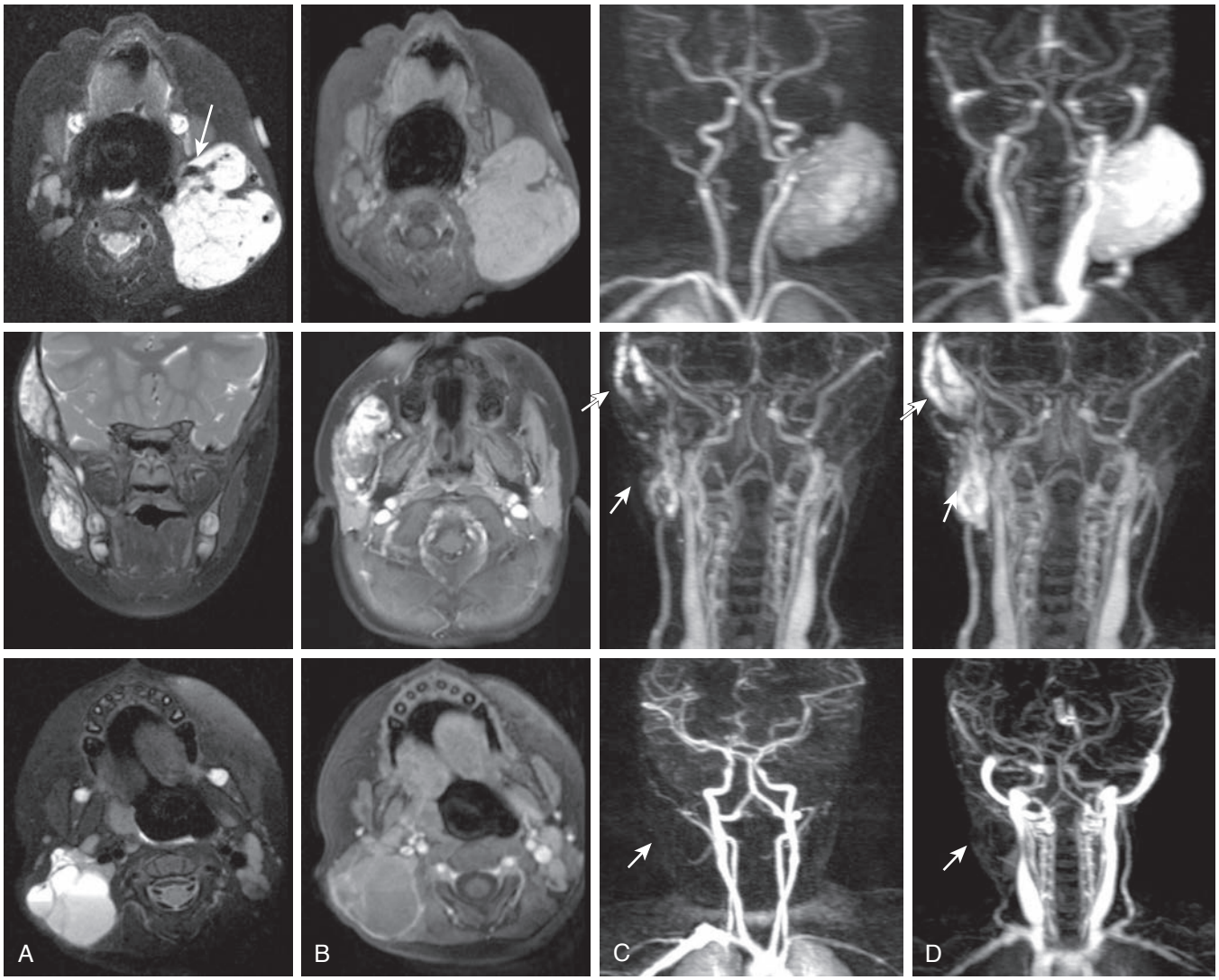

Figure 173.3 Top row: Infantile hemangioma (IH). (A) Axial T2-weighted fat-saturated image (B) and axial T1-weighted postcontrast fat-saturated image demonstrating a well-demarcated T2 hyperintense mass with clean borders and homogeneous internal enhancement. Note the serpiginous internal flow void *(arrow)* (A) from an arterial feeder. Coronal TWIST demonstrates avid enhancement in the arterial phase (C) with a feeder from the external carotid artery and lack of washout during the venous phase (D). Note the venous drainage to the left subclavian vein. *Middle row:* Venous malformation (VM). (A) coronal T2-weighted fat-saturated image demonstrates a predominantly T2 hyperintense mass infiltrating the right masticator and temporalis muscle. Note multiple small round T2 dark foci, representing phleboliths. (B) Axial T1-weighted postcontrast fat-saturated image demonstrates strong but somewhat heterogeneous internal enhancement. (C, D) Coronal TWIST demonstrates progressively increasing enhancement during the venous phase *(arrows)*. There was no enhancement in the arterial phase (not shown). *Bottom row:* Lymphatic malformations (LMs). (A) Axial T2-weighted fat-saturated image demonstrates a lobular multicystic mass with a fluid–fluid level in the soft tissues of the right lower neck. Axial T1-weighted postcontrast fat-saturated image (B) demonstrates enhancement of the cyst wall only without any internal enhancement. Lack of internal enhancement distinguishes LMs from VMs. The layering bright T1 signal is likely due to internal hemorrhage. Coronal TWIST did not demonstrate enhancement in the arterial or in the venous phase *(arrows)* (C, D). (Reproduced from Higgins LJ, Koshy J, Mitchell SE, et al. Time-resolved contrast-enhanced MRA (TWIST) with gadofosveset trisodium in the classification of soft-tissue vascular anomalies in the head and neck in children following updated 2014 ISSVA classification: first report on systematic evaluation of MRI and TWIST in a cohort of 47 children. *Clin Radiol.* 2016;71(1):32-39, Fig. 1.)

and physical examination should be performed. A preintervention MRI should be obtained and reviewed with the primary goals of defining the extent of treatable (nonthrombosed) disease and identifying critical nearby structures that could be damaged during sclerotherapy. Details of the treatment approach, risks, benefits, postoperative expectations, and length of treatment should be clearly discussed with the patient.

VMs continuously undergo cycles of spontaneous thrombosis and thrombolysis in a phenomenon called localized intravascular coagulopathy (LIC).[16] Although anticoagulants and platelet

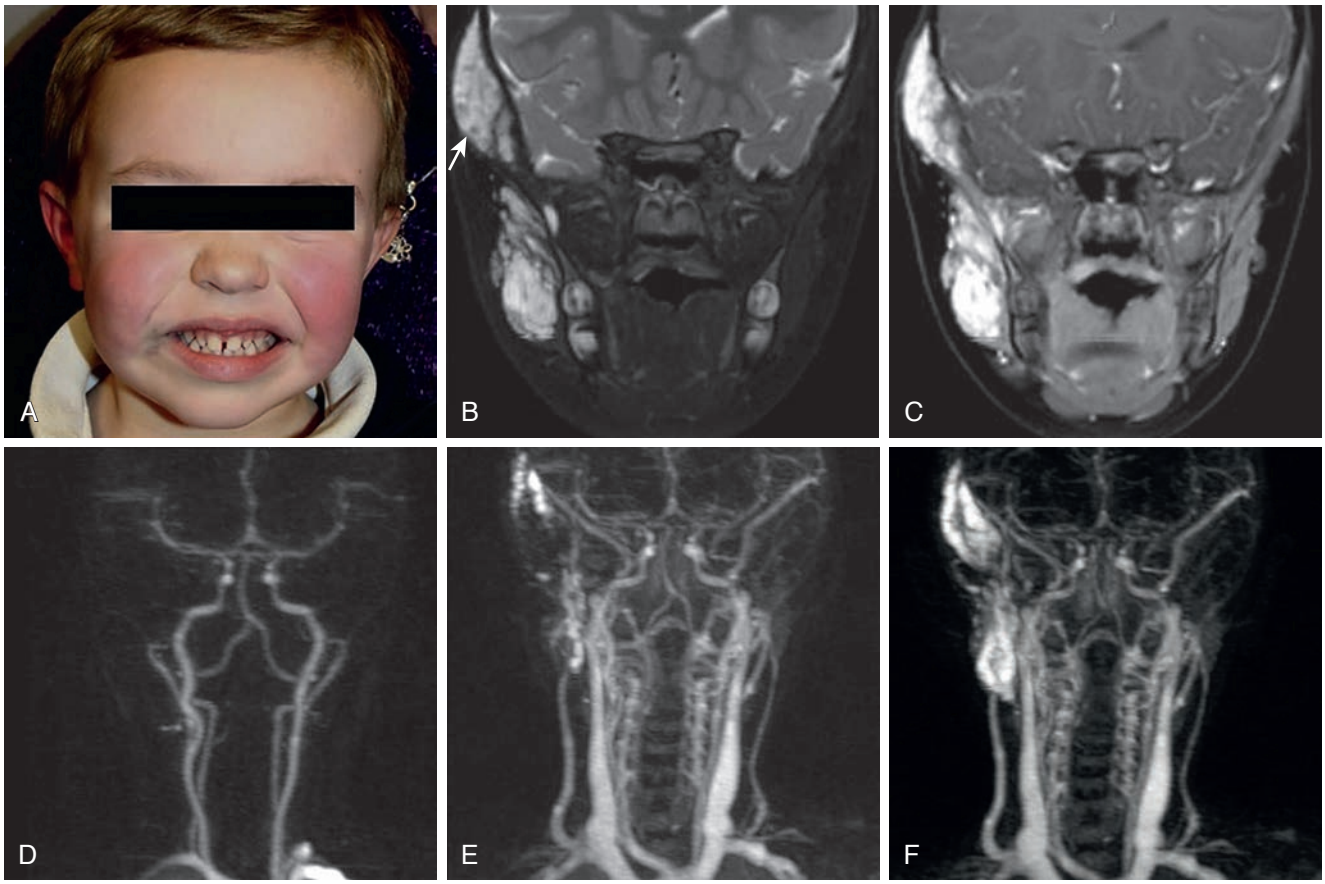

Figure 173.4 Venous malformation (VM). (A) A 4-year-old male with blue discoloration of his right cheek and the corner of right lip; it was noted to have been present since birth and was stable. Note that the right cheek is fuller than the left. The lesions are soft and compressible. (B, C) Coronal images show infiltration of the right temporalis muscle and right masticator space by a T2 bright (B) and enhancing mass (C). Note the T2 dark round foci in (B), representing phleboliths *(arrow)*. (D–F) Dynamic contrast-enhanced magnetic resonance angiography (DCE-MRA) demonstrates no enhancement in the arterial phase (D). Enhancement starts in the venous phase (E) and progressively increases in the delayed venous phase (F), which is typical for VMs. (Reproduced from Tekes A, Koshy J, Kalayci TO, et al. S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): a visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies. *Clin Radiol*. 2014;69(5):443-457, Fig. 6.)

inhibitory medications are not typically withheld prior to the procedure, LIC is common with large VMs, causing elevation of D-dimer, hypofibrinogenemia, and thrombocytopenia.[20] Immediately after sclerotherapy, LIC can progress to disseminated intravascular coagulopathy (DIC), and basic coagulation parameters (complete blood count, prothrombin time/international normalized ratio, partial thromboplastin time, fibrinogen, and D-dimer measurements) should therefore be obtained prior to interventions for large VMs. Patients with signs of LIC are prescribed LMWH for 10 days before and 10 days after the procedure. This therapy corrects the coagulopathy by halting the abnormal consumption of fibrinogen.

Patient comfort and immobility are important considerations during sclerotherapy; treatments are therefore generally performed in conjunction with general anesthesia. Patients who have cardiac, pulmonary, or other diseases that increase their risk for perioperative morbidity or mortality due to anesthesia should be identified and thoroughly evaluated by an anesthesiologist prior to undergoing sclerotherapy.

Technical Details

Sclerotherapy is best performed in an angiography suite. The patient should be positioned on the angiography table such that the area of interest can be safely and easily accessed by the operator. A preliminary US can be performed to identify the optimal skin entry sites, which are then prepped in sterile fashion. The procedure is considered "clean," and antibiotic prophylaxis is recommended.[21] Typical agents include intravenous cefazolin, and, for the penicillin-allergic patient, vancomycin or clindamycin.

Once preparations are complete and the patient is adequately sedated, US is used to guide a 21- or 22-gauge needle into the vascular malformation (Fig. 173.6). Several needles can be placed during a single procedure to treat multiple noncommunicating components of a lesion concurrently. In the case of a VM, intralesional placement of a needle is confirmed with blood return upon aspiration and digital subtraction angiography (DSA). DSA is used both to estimate the capacity of the lesion

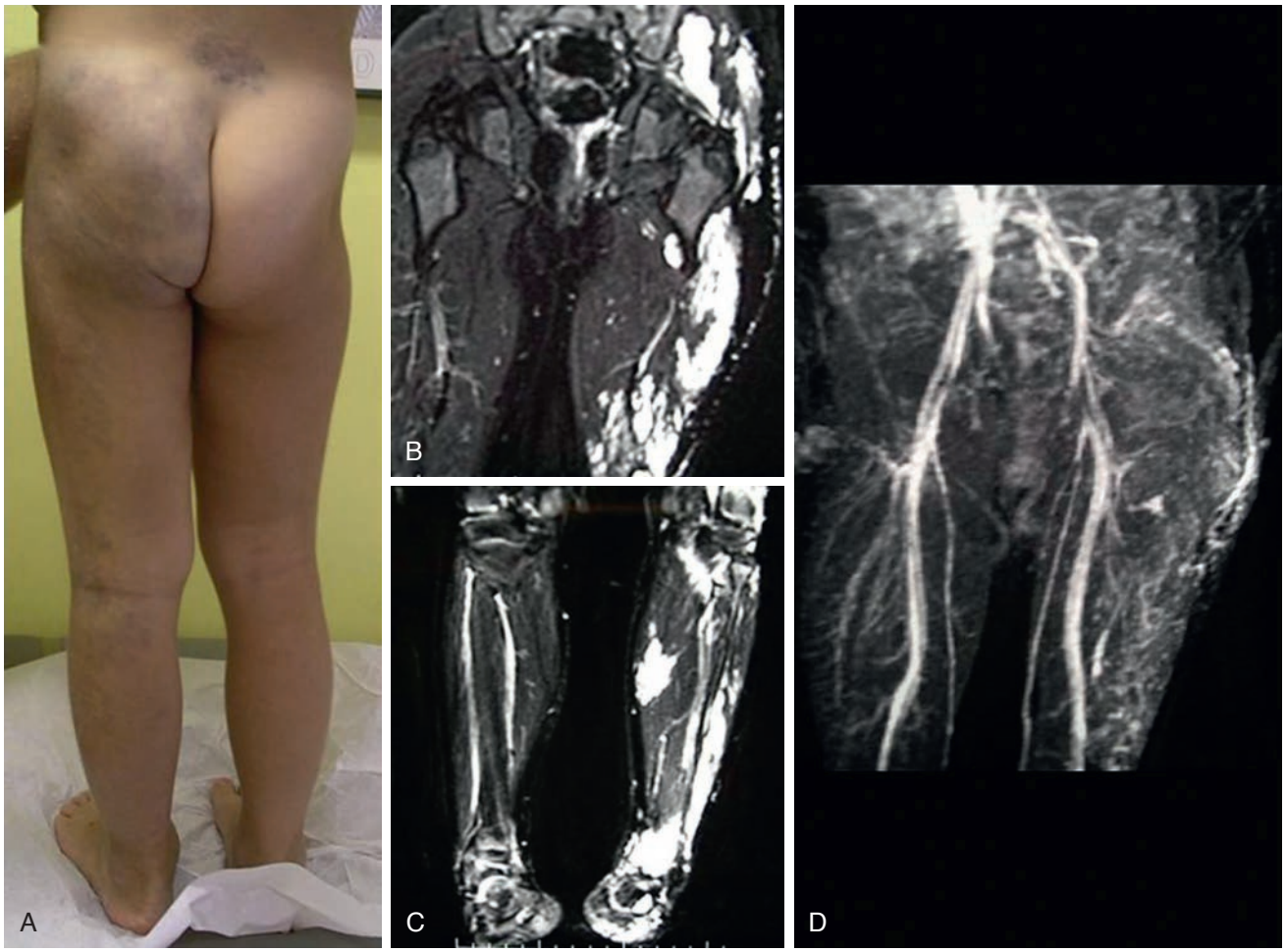

Figure 173.5 Venous malformation (VM). (A) A 4-year-old female with extensive blueness in her left leg and buttock region. She had no leg-length discrepancy on measurement. (B, C) Coronal T2-weighted image shows an extensive VM infiltrating the muscle groups in the left lower extremity and buttock. Note infiltration in the skin. (D) Dynamic contrast-enhanced magnetic resonance angiography (DCE-MRA) shows enhancement of the VM in the venous phase. (Reproduced from Tekes A, Koshy J, Kalayci TO, et al. S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): a visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies. *Clin Radiol.* 2014;69(5):443-457, Fig. 13.)

and to determine the presence of rapidly draining veins, which, if present, must be closed via manual pressure or coil or glue embolization to allow adequate sclerosant dwell time. A negative-contrast-technique sclerosant is hand-injected into the vascular spaces under fluoroscopic guidance. Commonly used sclerosants for the treatment of VMs include ethanol, sodium tetradecyl sulfate (often foamed), ethanolamine oleate, and more recently bleomycin.[22-24] The sclerosant is allowed to dwell within the lesion for a period of time, typically 15 to 20 minutes. Once the target dwell time is reached, the syringe is disconnected and the lesion assessed for venous return. If venous return is present, DSA is repeated to assess for residual disease and additional sclerosant is injected as needed. Once the treated area is closed and no venous return is noted, the needle is removed and the skin site is cleaned and dressed.

Sclerotherapy is also used for the treatment of macrocystic LMs. Needles are placed into the cystic spaces of the lesion, and lymphatic fluid is then completely aspirated and partially replaced with a sclerosant. In the case of larger macrocysts, placement of a drainage catheter and repeated infusions of sclerosant over several consecutive days may be necessary to close the cyst. Commonly used sclerosants for the treatment of LMs include doxycycline and bleomycin, although there are reports of using other agents such as ethanol, sodium tetradecyl sulfate, and OK-432 (Picibanil).[22,25] For microcystic LMs, bleomycin has been used with some success.[26] Microcystic LMs refractory to sclerotherapy can be considered for surgical resection.

Postintervention Care and Complications

Patients should be monitored in a postprocedure care unit as they recover from anesthesia. Procedure-related inflammatory pain and swelling are expected, and pain management, icing, and elevation of the treated area are routinely implemented during the recovery period. Steroids are often given to control swelling, particularly when the treated lesion is in the head

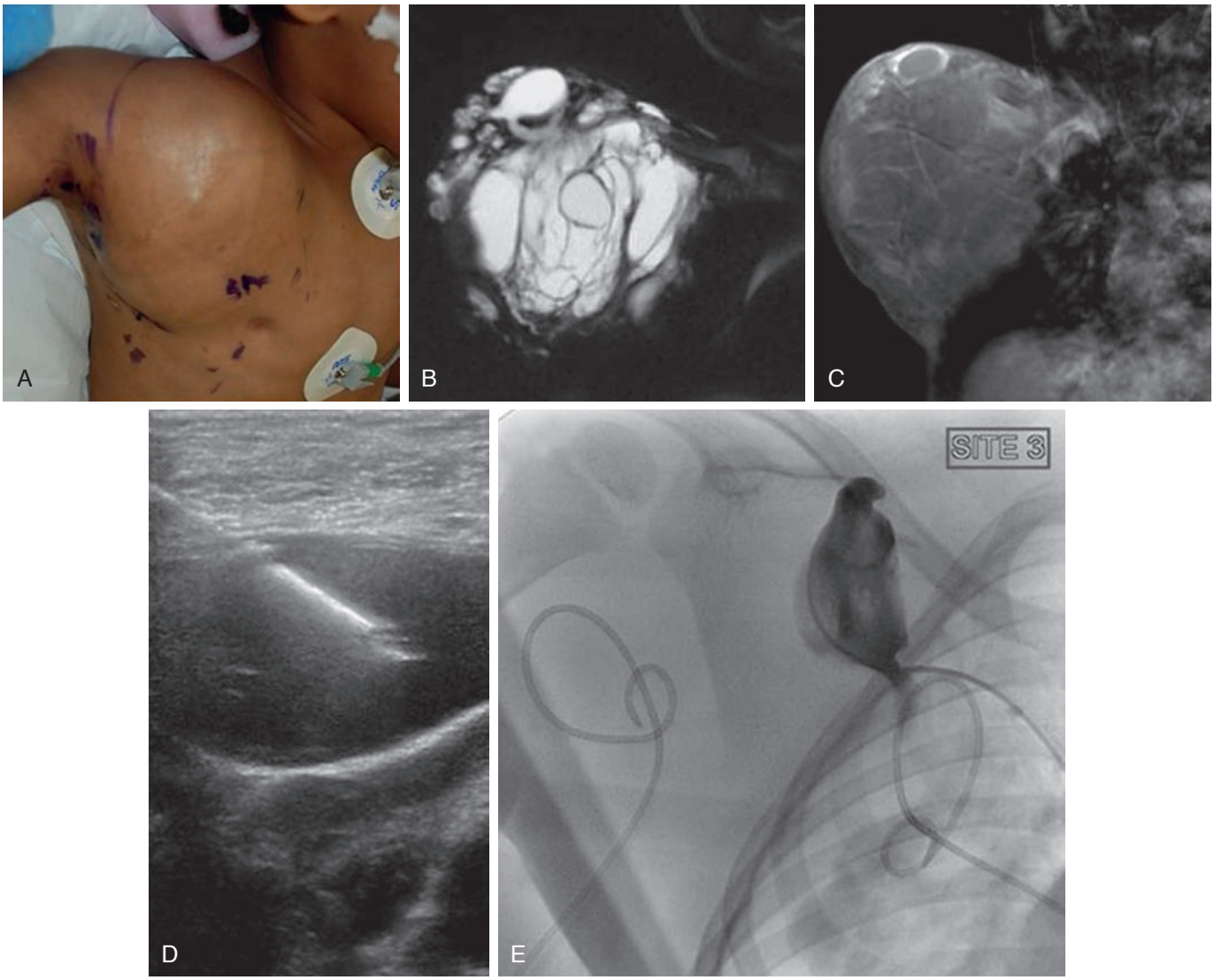

Figure 173.6 Lymphatic malformation (LM). (A) A 4-year-old male with a large mass on his right shoulder/chest wall. It was first noted soon after birth, and he underwent surgical debulking at that time. (B, C) A known LM that had recently grown larger. (C) Coronal T2-weighted image with fat saturation shows a T2 bright multicystic/septate large mass that shows enhancement of only the cyst walls and septa, typical for LMs. The relatively large size of each cyst qualifies for a macrocystic LM. (D) Ultrasound during percutaneous access demonstrates a macrocystic LM. (E) Injection of contrast medium into one of three macrocysts being treated with doxycycline sclerotherapy. (Reproduced from Tekes A, Koshy J, Kalayci TO, et al. S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): a visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies. *Clin Radiol*. 2014;69(5):443-457, Fig. 7.)

or neck or in an area susceptible to compartment syndrome, such as the forearm or leg. Most patients who undergo sclerotherapy are admitted for overnight observation and pain management.

Patients should be evaluated in the clinic 1 week following the procedure to assess for complications and again in 1 to 2 months after MRI has been performed to assess for reductions in symptoms and lesion size. Decreased T2 signal and enhancement are additional radiographic findings that are expected following sclerotherapy.[27] Successful treatment is often incremental, and large multifocal lesions will likely require additional procedures. In many cases clinical results are seen long before imaging results appear significant. As the goal of therapy is to treat the patient's symptoms, treatment can often be stopped despite little change on MRI.

The majority of complications are related to unintentional extravasation of sclerosant outside the lesion.[22] Extravasation is of particular concern during the treatment of superficial VMs because it may result in irritation, blistering, and necrosis of the adjacent skin or mucosal surface. It is paramount that the fluoroscopic images and skin site be carefully examined during the injection phase of treatment in order to detect and minimize extravasation. Extravasation appears as a blush of contrast material outside the lumen of the lesion on fluoroscopy. Any

instance of extravasation necessitates the immediate cessation of sclerosant injection. Skin necrosis is usually heralded by blanching, erythema, or other discoloration of the skin at the end of the procedure. Patients with suspected cutaneous complications should be examined frequently in the clinic and standard wound care, including topical antibiotics and clean dressings, should be practiced. Patients with areas of large or deep ulceration should be referred to a wound care specialist.

Hematuria, a consequence of sclerosant-induced hemolysis, is another common complication, particularly when large doses of sclerosant and intravenous contrast material are used. Placement of a urinary catheter is helpful to detect and monitor this complication, which tends to be a minor transient finding that resolves with oral and intravenous hydration.[28]

Acute compartment syndrome is an uncommon complication that can arise when the treated lesion is located in a fascia-bound compartment, such as a muscular compartment in an extremity. Inflammatory swelling causes high intracompartmental pressures and insufficient blood supply to the muscles and nerves. Recognition of the intracompartmental location of a lesion is important for proper treatment planning, as the inflammatory response can be mitigated by the avoidance of excessive treatment. Postprocedurally, ice packs should be applied and tight circumferential dressings avoided. Steroid therapy (e.g., intravenous dexamethasone) can be considered for patients who do not respond to more conservative measures.

Additional Endovascular Techniques and Other Therapies

Magnetic Resonance Imaging–Guided Sclerotherapy

The majority of sclerotherapy procedures can be performed with ultrasound and fluoroscopy for image guidance. Both of these modalities are easy to use and widely available. However, some vascular malformations, such as those deep in the abdomen or beneath scar or bone, are not adequately visualized or targeted with US. If these lesions require treatment, interventional MRI should be considered. The technique commonly relies on steady-state free precession imaging, which is a gradient echo–based MRI technique that provides real-time sequences for needle targeting and the monitoring of sclerosant delivery.[29-31] Large initial investments in equipment and MR-specific training are necessary prerequisites that currently hinder widespread usage of this useful technique.

Coil and Glue Embolization

Permanent embolic agents, such as coils and glue (e.g., N-butyl cyanoacrylate), can be used for percutaneous closure of draining veins and capacious venous spaces that are not responding to sclerotherapy.[32,33] Glue can be injected into vascular malformations through a percutaneous needle, whereas coils require placement of an endovascular catheter. Preoperative coil and glue embolization of VMs can be performed to reduce surgical morbidity and promote complete surgical excision by reducing disease volume and intraoperative blood loss.

Laser Therapy

Laser photocoagulation is an option to treat facial VMs.[34] Electro-optical synergy, a technique that combines laser light and radiofrequency energy, has also been effective.[35] Laser treatments can be combined with sclerotherapy to treat lesions with superficial and deep components.

Sirolimus

Ideally vascular malformations could be treated noninvasively by medical therapies that target the cellular pathways promoting abnormal vascular growth. In particular, inappropriate activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway is associated with some vascular anomalies, and the mTOR pathway has been proposed as a target for therapy.[36,37] Sirolimus, a compound that inhibits the mTOR pathway, has been approved by the US Food and Drug Administration for the treatment of lymphangioleiomyomatosis, which is also associated with abnormal activation of mTOR. More recently, a prospective phase II clinical trial has demonstrated sirolimus to be efficacious and safe in treating complicated vascular anomalies that were refractory to other therapies, including medication, interventional procedures, and surgery.[36]

TREATMENT OF HIGH-FLOW VASCULAR MALFORMATIONS

Introduction

High-flow vascular malformations include *AVM and AVF. AVMs* are high-flow vascular anomalies composed of a complex primitive network of arterial and venous channels (a nidus)—a network that bypasses the normal capillary bed. Arterial inflow is diverted via these shunts into draining veins, resulting in local and occasionally systemic hemodynamic disturbances such as tissue ischemia and venous hypertension. AVMs occur in the central nervous system, limbs, trunk, and viscera.[11,17] Like that of other vascular malformations, the diagnosis of AVMs can usually be made based on history and clinical examination alone.[38] On physical examination, an AVM is commonly detected as a warm palpable mass with overlying skin discoloration and an associated palpable thrill and bruit (Fig. 173.7).[11,17,38,39] In advanced stages, AVMs can cause ulceration of the surrounding soft tissues, bleeding, and high-output heart failure. The Schöbinger staging system subclassifies AVMs according to biologic behavior and clinical effects; it is useful for determining the progression of disease (Table 173.3).[40] The Yakes classification system sorts AVMs by angioarchitecture and suggests specific endovascular treatment options for each subtype (Table 173.4).[41]

AVFs are characterized by a direct connection between an artery and a vein without the presence of an intervening nidus.[42] AVFs can be acquired or congenital, but only congenital lesions are considered vascular malformations. Trauma is the most common cause for AVFs. Congenital AVFs are rare lesions that commonly manifest in infancy as high-output heart failure and are known to occur in certain anatomic locations, such as the

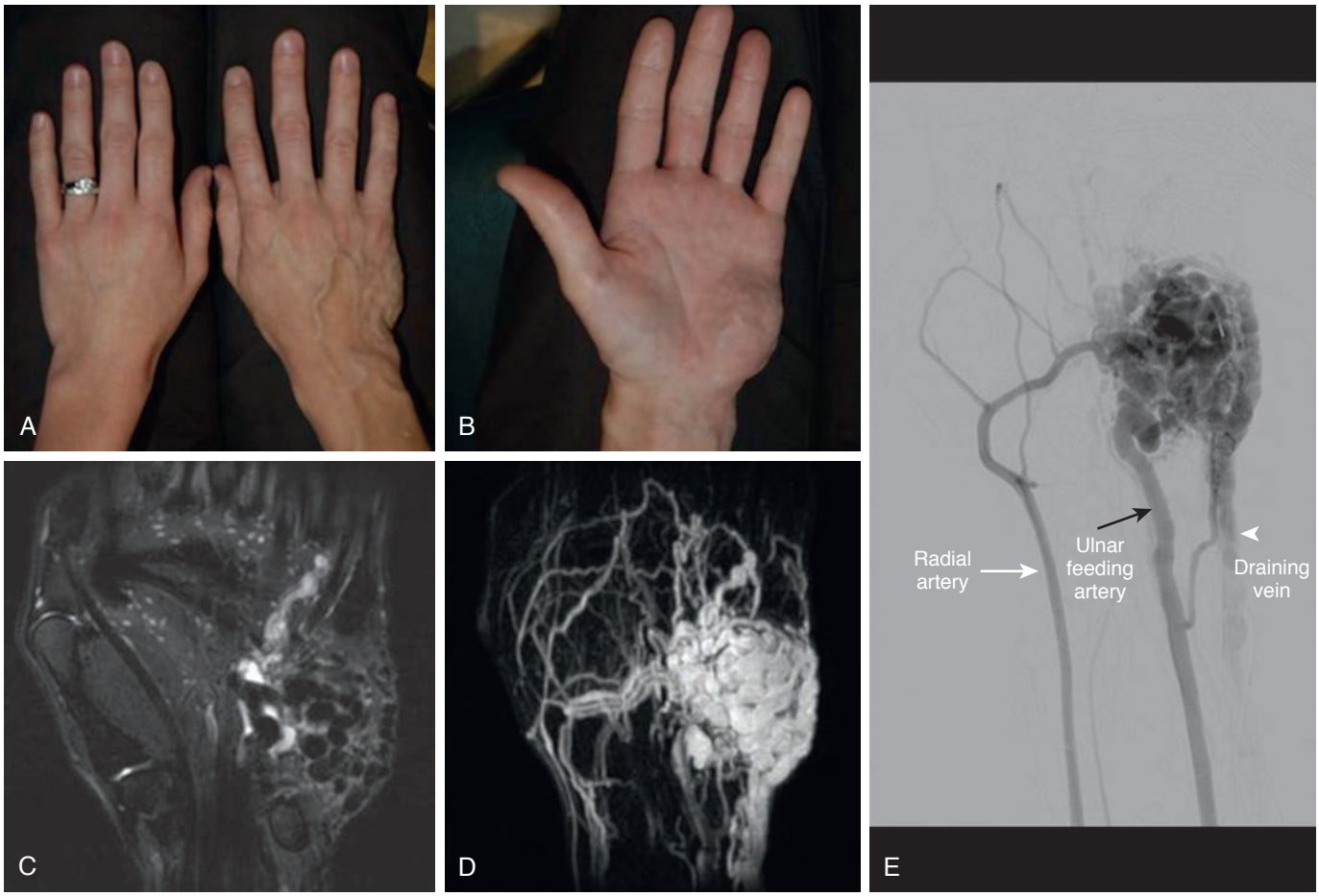

Figure 173.7 Arteriovenous malformation (AVM). (A) A 30-year-old female with a swollen pulsatile mass on the hypothenar eminence of her right hand. View of the dorsal surface of the patient's right hand compared with the left. Note the enlarged draining veins and relatively larger size of the right hand. (B) Note the mass on the hypothenar eminence of the right hand's palmar surface. (C) Coronal T2-weighted image with fat saturation demonstrates a serpiginous tangle of flow voids indicating high flow and infiltration the hypothenar eminence and subcutaneous fat. Note the absence of associated soft-tissue mass. (D) Magnetic resonance angiogram demonstrates strong enhancement of the AVM with arterial feeder from the ulnar artery and venous drainage into the basilic vein. (E) Angiogram demonstrating predominant ulnar feeder *(black arrow)* to the AVM. Note early venous drainage to the basilic vein *(arrowhead)*. Enlargement of the ulnar artery becomes more conspicuous when it is compared with a normal radial artery *(white arrow)*. The draining vein is also patulous *(arrowhead)*. (Reproduced from Tekes A, Koshy J, Kalayci TO, et al. S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): a visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies. *Clin Radiol*. 2014;69(5):443-457, Fig. 9.)

TABLE 173.3 Schöbinger Staging of Arteriovenous Malformations

Stage	Clinical Findings
I (Quiescence)	Warm areas of pink-blue discoloration, shunting on Doppler ultrasonography
II (Expansion)	Mass associated with thrill and bruit
III (Destruction)	Mass associated with ulceration, bleeding, pain
IV (Decompensation)	Lesion associated with cardiac decompensation

Shobinger R. In: Proceedings of International Society for the Study of Vascular Anomalies Congress, Rome I, June 23–26, 1996.

vein of Galen malformation of the deep cerebral venous system. AVFs in the extremities may be associated with ischemic complications distal to the arteriovenous shunt, such as claudication, rest pain, and ulceration.[42] AVFs detected on physical examination typically present as a pulsatile masses with an associated bruit.

Imaging

Imaging of an AVM or AVF is usually indicated to evaluate the extent of disease. Gray-scale and Doppler US demonstrate the abnormal network of vascular channels that make up the nidus and connect the feeding arteries to the draining veins. The feeding arteries have high-velocity diastolic (low resistance) blood flow resulting from the lack of a normal capillary bed

TABLE 173.4 Yakes Arteriovenous Malformation Classification

Type	Description	Treatment
I	Direct AVF	Mechanical occluding devices (e.g., coils, plugs)
IIa	Typical AVM nidus	Transcatheter and direct puncture ETOH embolization
IIb	AVM nidus with shunt into an aneurysmal vein	Transcatheter and direct puncture ETOH embolization or coiling the aneurysmal outflow vein
IIIa	Aneurysmal vein whereby the vein wall is the nidus with single outflow vein	Coiling OF the aneurysmal single outflow vein
IIIb	Same as IIIa but with multiple outflow veins	Coiling OF each outflow vein
IV	Infiltrative form of AVM	Transcatheter embolization and direct puncture embolization (50% ethanol and nonionic contrast mixture)

AVF, Arteriovenous fistula; *AVM,* arteriovenous malformation; *ETOH,* ethanol.
Yakes WF. Yakes' AVM classification system. *J Vasc Intervent Radiol*. 2015;26(2):S224.

between the arteries and veins.[43] The draining veins demonstrate pulsatile high-velocity (arterialized) flow.[43]

Given its wide field of view, MRI is the preferred imaging modality for assessing a large AVM (Fig. 173.7). MRI can determine the extent of the lesion as well as its proximity to critical structures.[11,17,38] In general AVMs appear as T1 and T2 hypointense serpentine flow voids that demonstrate postcontrast enhancement during the arterial phase of MRA.[38,39,43] There may be surrounding edema, fibrin deposition, and tissue overgrowth. Conventional angiography has the advantages of high spatial and temporal resolution and is therefore the most accurate modality to identify and differentiate the feeding arteries, nidus, and draining veins.

Ultrasound examination of an AVF demonstrates the abnormal direct connection between an artery and vein without a nidus. The feeding artery has low-resistance flow, and the draining vein has arterialized flow. Aliasing around the AVF can occur, representing perivascular thrill. MRA similarly demonstrates the abnormal arteriovenous connection with early filling of the draining vein.

Treatment of Arteriovenous Malformations

AVMs are recalcitrant lesions with an inherent ability to persist despite therapeutic intervention. The main treatment options for AVMs are surgical resection and endovascular embolization.[11,17,38,44] Both therapies target the nidus of the lesion with the goal of eliminating the abnormal arteriovenous shunt. When the nidus is completely removed, surgical resection is associated with a reduced recurrence rate. However, the architecture of the nidus if often complex, making complete surgical resection difficult.[38,45] In these cases, embolization may be performed either as a primary treatment or as neoadjuvant therapy prior to surgical resection.[11,17,38,42,45]

Endovascular closure can be quite challenging and should be attempted only after careful study of the lesion's vascular anatomy. Treatment should be directed at the nidus, which can be difficult to identify due to the presence of multiple tortuous feeding arteries that overlap and obscure the more distal areas of shunting. Treatment of the nidus results in improved long-term outcomes and fewer complications.[46]

Embolization can be performed by approaching the AVM from the arterial side or the venous side. In approaching from the arterial side, the main feeding artery of the AVM is selected with a guiding catheter. A microcatheter is then advanced to subselect the distal branches just proximal to the arteriovenous site of shunting. A sclerosant agent like ethanol or a semiliquid embolic agent like N-butyl cyanoacrylate or ethylene vinyl alcohol copolymer (Onyx) is then injected.[38,46-48] Additional branches are subselected and treated as needed.

A venous approach is possible when there is a single draining vein or venous sac. When there are multiple draining veins, treatment from the venous side is unlikely to be successful. However, when possible, the venous approach is often preferred, as the risk of nontarget embolization of normal nutrient arteries is decreased. Additionally, treatment of the venous side often decreases the number of arterial feeders, which makes complete obliteration of the nidus more feasible.[49] The technique involves subselection of the draining vein with a catheter. Prior to the injection of a sclerosant or liquid embolic agent, the venous outflow can be occluded with a balloon catheter to prevent uncontrolled spread of the embolic/sclerosant agent. When a large sac is present, N-butyl cyanoacrylate and coils are typically used to fill the capacious channel.

When transarterial or transvenous access is not possible and the AVM is in an amenable location, direct percutaneous access and treatment of the lesion can be performed.[11,17,38] Liquid agents, semiliquid agents, and coils can all be delivered through the percutaneously placed needles.

Approximately 57% of AVMs treated with surgical resection and embolic therapy will recur within the first year following treatment, and approximately 98% of AVMs will enlarge or recur within 5 years following treatment.[38,45] The patient should therefore be followed regularly for at least 5 years. Additional interventions should be performed when lesions recur or cause symptoms.

Complications of arterial side embolization are typically related to treatments performed too proximally in the arterial feeder. Proximal treatment provides ineffective therapy; it also increases the risk of nontarget embolization of normal nutrient arteries and leads to loss of future arterial access to the nidus and recruitment of the collateral vessels that foster growth of the AVM.[11,17,38]

Treatment of Arteriovenous Fistulas

Acquired AVFs commonly resolve spontaneously within a few months, allowing for a conservative approach consisting of serial

imaging and clinical evaluation. Congenital AVFs and AVFs with large fistulous connections that do not close spontaneously require more invasive measures. Treatment options include surgical or endovascular repair.[42] Endovascular placement of a covered stent over the fistula is the most common approach. When there is a long fistulous tract, coil embolization is another possible approach.[50]

SYNDROMES ASSOCIATED WITH VASCULAR MALFORMATIONS

A number of syndromes are associated with vascular malformations (Table 173.5). These include KTS, BRBNS, unilateral limb VM, mucocutaneous VMs, Sturge-Weber syndrome, Proteus syndrome, congenital lipomatous overgrowth, vascular malformations, epidermal nevi (CLOVE) syndrome, and Maffucci and Gorham-Stout syndromes, all of which are associated with low-flow vascular malformations.[51] Parkes-Weber syndrome (PWS); hereditary hemorrhagic telangiectasia (HHT); and Cobb, Wyburn-Mason, Bannayan-Riley-Ruvalcaba, and Cowden syndromes are associated with high-flow vascular malformations.[51] The following discussion delves into some of the more commonly encountered syndromes associated with vascular malformations.

Klippel-Trénaunay Syndrome

KTS is characterized by the clinical triad of capillary malformation of the skin (port wine stain), low-flow (capillary-venous-lymphatic) vascular malformation, and local soft tissue and bony overgrowth.[52,53] KTS is diagnosed by the presence of at least two out of three of these clinical elements. The syndrome is typically sporadic, although familial cases have been reported.[54] The vascular malformation can occur anywhere in the body but typically manifests as a persistent embryonic vein.[43,52] The lateral marginal vein (also known as the vein of Servelle) is the most common anomalous vein.[55] Similar to other low-flow vascular malformations, the lymphatic and vascular malformations present in KTS may be treated with percutaneous sclerotherapy. Patients with superficial valveless varices may experience limb swelling and pain and can be treated with compression garments and intravenous laser therapy. The deep venous system can also be anomalous (hypoplasia, aplasia, valvular incompetence), and patency and adequacy of the deep system should be confirmed prior to occlusion of superficial varices to avoid exacerbating venous insufficiency.[56]

TABLE 173.5 Syndromes Associated With Vascular Malformations

Syndromes Associated With VMs
Klippel-Trénaunay
Blue rubber bleb nevus
Maffucci
Syndromes Associated With CMs
Klippel-Trénaunay
Sturge-Weber
Syndromes Associated With LMs
Gorham
Syndromes Associated With AVMs
Parkes-Weber
Hereditary hemorrhagic telangiectasia
Bannayan-Riley-Ruvalcaba

AVMs, Arteriovenous malformations; *CMs,* capillary malformations; *LMs,* lymphatic malformations; *VMs,* vascular malformations.

Parkes-Weber Syndrome

PWS is characterized by a congenital AVF with associated varicosities and overgrowth (Fig. 173.8).[52] A red vascular skin stain (also known as a "pseudocapillary malformation") may be present, representing part of the high-flow vascular malformation rather than a true capillary malformation.[53] PWS can affect any limb but most commonly occurs in the lower extremity.[57] Varicosities form as a result of high-flow shunting from the AVF. Lymphedema and lymphatic vesicles can be seen in the skin. High-output congestive heart failure can result if there are multiple AVFs. Conservative management of PWS is preferred, as invasive therapies can worsen the vascular shunting through an AVF.[53] In complicated cases, such as those associated with intractable pain or heart failure, superselective arterial embolization of the AVF can be performed.[53]

Hereditary Hemorrhagic Telangiectasia

HHT, also known as Osler-Weber-Rendu disease, is an autosomal dominant disorder characterized by the presence of AVMs in multiple organ systems including the brain, lung, liver, and gastrointestinal tract.[11,58] The diagnosis of HHT is made clinically on the basis of the Curaçao criteria, which assess for the presence of epistaxis, telangiectasias, visceral lesions, and an associated family history (a first-degree relative with HHT).[59] The HHT diagnosis is considered definite if three or four criteria are present, possible or suspected if two criteria are present, and unlikely if fewer than two criteria are present. Recurrent and severe epistaxis related to mucocutaneous telangiectasia is the most common presentation. Treatment of HHT is aimed at decreasing the amount of hemorrhage and minimizing complications. In the case of acute hemorrhage, volume resuscitation with intravenous fluid or blood products may be needed. Patients with chronic anemia should receive iron supplementation. Patients with pulmonary AVMs may have symptoms of dyspnea, hemoptysis, hemothorax, and stroke.[60] Pulmonary AVMs with feeding arteries measuring greater than 2 to 3 mm in diameter should undergo transarterial embolization with retrievable permanent embolics.[58] Hepatic involvement in HHT ranges from small telangiectasias to large AVMs.[61] Intrahepatic shunting is the result of solitary or multiple abnormal connections between the hepatic artery and portal vein, hepatic artery and hepatic vein, and portal vein and hepatic vein. Patients who experience

Figure 173.8 (A) Foot and lower leg of a 24-year-old male with Parkes-Weber syndrome. Note thickened skin lesions as outlined by *white arrows*. Similar changes are also noted in the anterior lower shin. (B) Lateral arteriogram of the foot from a popliteal injection. Note hypervascularity of the arteriovenous malformation (AVM) nidus *(white arrows)* underneath the thickened skin lesions on photo (A). Note that the dorsalis pedis artery is the feeding artery *(black arrow)*. The posterior tibial artery *(arrowhead)* is marked for orientation purposes. (C) Selective arterial phase on the dorsum of the foot on a lateral view. Note the catheter in the dorsalis pedis artery *(black arrow)*. The AVM nidus (*white arrows*) demonstrates early arterial enhancement with an early draining vein *(arrowhead)*. (D) Selective arterial phase on the dorsum of the foot on an anteroposterior view. Note the microcatheter in the distal part of the feeding artery *(black arrow)* supplying the nidus of the AVM *(white arrows)*. The draining vein is marked with an *arrowhead*. (Reproduced from Tekes A, Koshy J, Kalayci TO, et al. S.E. Mitchell Vascular Anomalies Flow Chart (SEMVAFC): a visual pathway combining clinical and imaging findings for classification of soft-tissue vascular anomalies. *Clin Radiol*. 2014;69(5):443-457, Fig. 15.)

complications—such as high-output cardiac failure, portal hypertension, and encephalopathy—should receive medical therapies directed at those conditions (e.g., diuretics, beta blockers, antiarrhythmics).[61] Patients who have progressive worsening of their clinical condition despite medical therapy should be considered for invasive treatment, including transarterial embolization and orthotopic liver transplantation. Cerebral AVMs may be treated with transarterial embolization, stereotactic radiation, or surgery or a combination of methods.[58] Gastrointestinal AVMs are managed with endoscopic photoablation or electrocautery, although episodes of severe acute gastrointestinal hemorrhage may necessitate segmental bowel resection.[58]

CONCLUSION

Vascular malformations are nonneoplastic vascular anomalies that are subdivided into low-flow and high-flow lesions. Common low-flow vascular malformations are VMs and LMs, which are most commonly treated with percutaneous sclerotherapy. High-flow malformations include AVMs and AVFs, which are treated with surgery, endovascular intervention, or both.

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Additional information regarding the new classification system.

A complete reference list can be found online at www.expertconsult.com.

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174 CHAPTER

Acquired Arteriovenous Fistulas

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The earliest description of an arteriovenous fistula (AVF), the abnormal communication between an artery and vein, is attributed to William Hunter, who in 1761 reported two cases of brachial AVFs following attempted phlebotomy. He also described the adaptive enlargement of the artery and veins proximal to the AVF, as well as the associated hissing noise ("bruit") and tremulous motion ("thrill").[1,2]

AVFs were infrequently identified and diagnosed until the introduction of high-speed projectiles during 19th-century conflicts, which altered the magnitude and complexity of military injuries. Successive military conflicts and the increase in blunt, penetrating, and iatrogenic trauma among civilians have resulted in a greater number of vascular injuries (VIs) and, as a consequence, acquired AVFs.[3-9]

Keywords

Acquired arteriovenous fistulas
Etiology
Pathogenesis
Operative and Endovascular Repair

ETIOLOGY AND INCIDENCE

AVFs can be either congenital or acquired. Vascular malformations, including congenital AVFs, are discussed in Chapters 171, 172, and 173. The focus of this chapter is acquired AVFs, including those caused by trauma and the small number which occur spontaneously, usually from erosion or rupture of an atherosclerotic or infected aneurysm into an adjacent vein.

Traumatic Arteriovenous Fistulas

The anatomic distribution of VIs and AVFs is related to the mechanism of injury and varies between military personnel and civilians. Blast injuries due to improvised explosive devices (IEDs) account for 73% of VIs among military personnel, whereas penetrating trauma due to gunshot wounds (GSWs) or stab wounds (SWs) account for the majority (61.7%) of civilian VIs reported to the National Trauma Data Bank.[10,11] In an article by Robbs et al. which included 210 civilian traumatic AVFs, SWs accounted for 63%, whereas GSWs accounted for 26% and blunt trauma for 1%.[12] AVFs due to SWs involve the cervicomediastinal arteries in 54% to 75% of cases and most frequently (21%) the common carotid artery. Although extremity and abdominal penetrating VIs occur with almost equal frequency (40% vs. 32%) in the civilian population, in the military population VIs predominate in the extremities. This is secondary to the use of protective body armor. Acquired AVFs involve the upper and lower extremities in 22% and 20% of cases, respectively, whereas thoracic and abdominal AVFs are encountered in 4% of patients.[12-14]

Iatrogenic Arteriovenous Fistulas

Iatrogenic injuries that cause AVFs usually result from percutaneous cardiac and vascular procedures, central venous catheterization, orthopedic procedures on the lumbar spine and knee, diagnostic kidney and liver biopsies, and percutaneous insertion of biliary and urinary drainage catheters. The right common femoral artery (CFA) remains the most common site of iatrogenic injury (37%) in the lower extremities.[15] The increase in the number of percutaneous interventions being performed would be expected to result in a greater number of iatrogenic AVFs. However, the use of smaller gauge (21- vs. 18-gauge) angiographic needles inserted under ultrasound (US) guidance has significantly reduced the number of access site complications from 3.4% (using fluoroscopy) to 1.4 % (with US) in patients undergoing predominantly cardiac angiography.[16] US guidance reduced access site complications by 43% in patients undergoing peripheral interventions. Whether the addition of closure devices will further reduce femoral access site complications remains uncertain.[17]

Spontaneous Arteriovenous Fistulas

First described by Syme in 1831, rupture or erosion of an atherosclerotic, inflammatory, or mycotic aortic or iliac aneurysm into the inferior vena cava (IVC) (Fig. 174.1), iliac vein (Fig. 174.2), or retroaortic left renal vein (Fig. 174.3) can result in spontaneous AVFs.[18-23] There have been a few isolated case reports of spontaneous AVFs in patients with syphilitic aortitis, HIV arteritis, and Marfan and Ehlers-Danlos syndromes.[19,24]

Arteriovenous Fistulas in Specific Locations

Carotid Artery Arteriovenous Fistulas

Carotid artery injury constitutes 5% to 11% of all arterial injuries and usually results from SWs or GSWs, therapeutic or diagnostic catheterization, or blunt trauma to the skull or cervical spine. A fistula between the carotid artery and the internal jugular vein or its tributaries occurs following 4% to 27% of such injuries.[7,12,14,25-28]

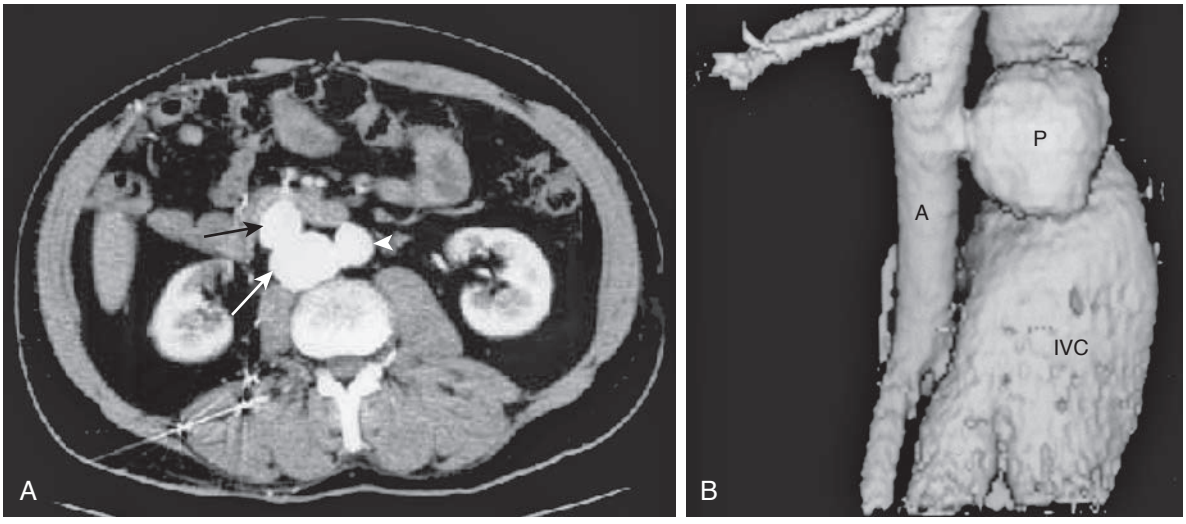

Figure 174.1 (A) Axial CT scan demonstrating the aorta *(arrowhead)*, pseudoaneurysm *(white arrow)*, and inferior vena cava *(black arrow)*. (B) Three-dimensional reconstruction of the CT scan of a traumatic aortocaval fistula demonstrating a pseudoaneurysm *(P)*, enlarged inferior vena cava *(IVC)*, and aorta *(A)*.

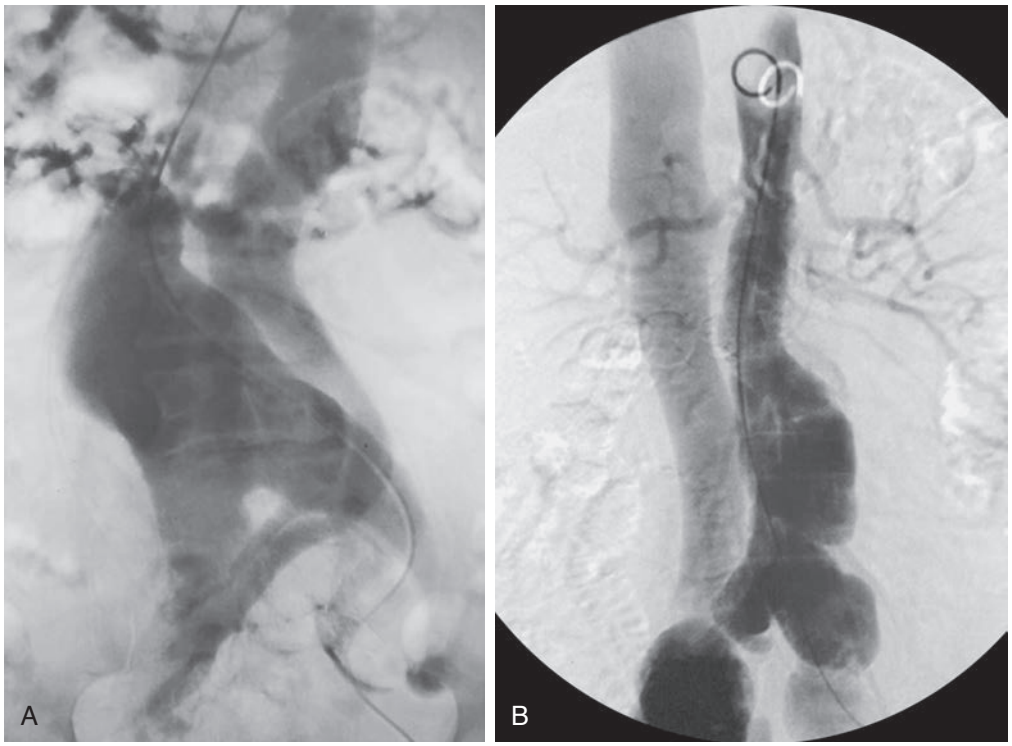

Figure 174.2 (A) Aortogram of a patient with an aortic aneurysm and spontaneous aortocaval fistula treated surgically. (B) Aortogram demonstrating an aortic aneurysm and bilateral iliac aneurysms associated with an arteriovenous fistula between the right common iliac artery and vein treated with an aortic endograft.

Vertebral Artery Arteriovenous Fistulas

Vertebral artery (VA) AVFs occur in 0.7% to 7.4% of cases of penetrating trauma. The AVF is usually between the VA, its muscular or radicular branches, and the internal jugular and/or vertebral veins. Iatrogenic injury during operative procedures on the cervical spine and catheterization of the internal jugular vein accounts for approximately ⅔ of cases, and cervical spine fractures due to blunt trauma, chiropractic manipulation, or closed head injury, GWs, and SWs for the remaining ⅓.[29-31]

Axillary and Subclavian Arteriovenous Fistulas

Approximately 3% of all neck- and chest-penetrating trauma is associated with injury to the subclavian vein (44%), artery (39%), or both (17%).[32] Inadvertent puncture of the carotid or subclavian arteries occurs in up to 8.4% of cases of attempted central venous catheterization,[25,26] and the incidence of AVFs following subclavian vein catheterization is estimated at 0.58%.[33] Penetrating axillary artery injuries and fractures of the clavicle or first rib are rare causes of AVFs.[32,34-36]

Brachial, Radial, and Ulnar Arteriovenous Fistulas

Upper extremity trauma accounts for 25% to 40% of all VIs.[7,13] The brachial and forearm arteries are involved in 10% to 22% of cases.[6] The radial and ulnar arteries are frequently used for cardiac interventions; AVFs occur in 0.02% to 0.04% of cases. Peripherally inserted central catheters (PICC lines) may also be complicated by AVFs.[37-40]

Femoral Arteriovenous Fistulas

Penetrating injuries due to GSWs, SWs, shrapnel injuries from IEDs, or long bone fractures may result in femoral AVFs.[6,7,41-43] The incidence of AVFs as a result of such injuries varies considerably between the military and civilian populations. In a review of 558 AVFs due to military injuries, 28% involved the superficial femoral or profunda femoris arteries,[14] whereas in a civilian series of AVFs predominantly due to SWs, the CFA was involved in 12% of cases (Fig. 174.4).[12] Sporadic cases of spontaneous AVFs between the superficial femoral artery and vein have also been described.[24] Despite the less frequent use of the CFA as the preferred access site for cardiac and vascular interventions, it remains the most common site of iatrogenic AVFs, with an incidence of 0.06% to 0.86% when diagnosed by physical exam but 2.8% using duplex US.[41,42] Femoral AVFs are slightly more frequent after interventional than diagnostic procedures. The majority of AVFs close spontaneously: in one study, only 11% became symptomatic and required operative repair (OR).[44] Femoral and external iliac artery AVFs are a rare complication of endovenous laser ablation for varicose veins.[45,46] The risk factors predisposing to iatrogenic femoral AVFs are listed in Box 174.1.

Popliteal Arteriovenous Fistulas

Popliteal AVFs have similar etiologies to femoral AVFs. They account for approximately 16% of AVFs reported in the Vietnam registry and 5% to 14% of civilian AVFs.[12,14,47] Blunt trauma associated with comminuted femoral and proximal tibial fractures

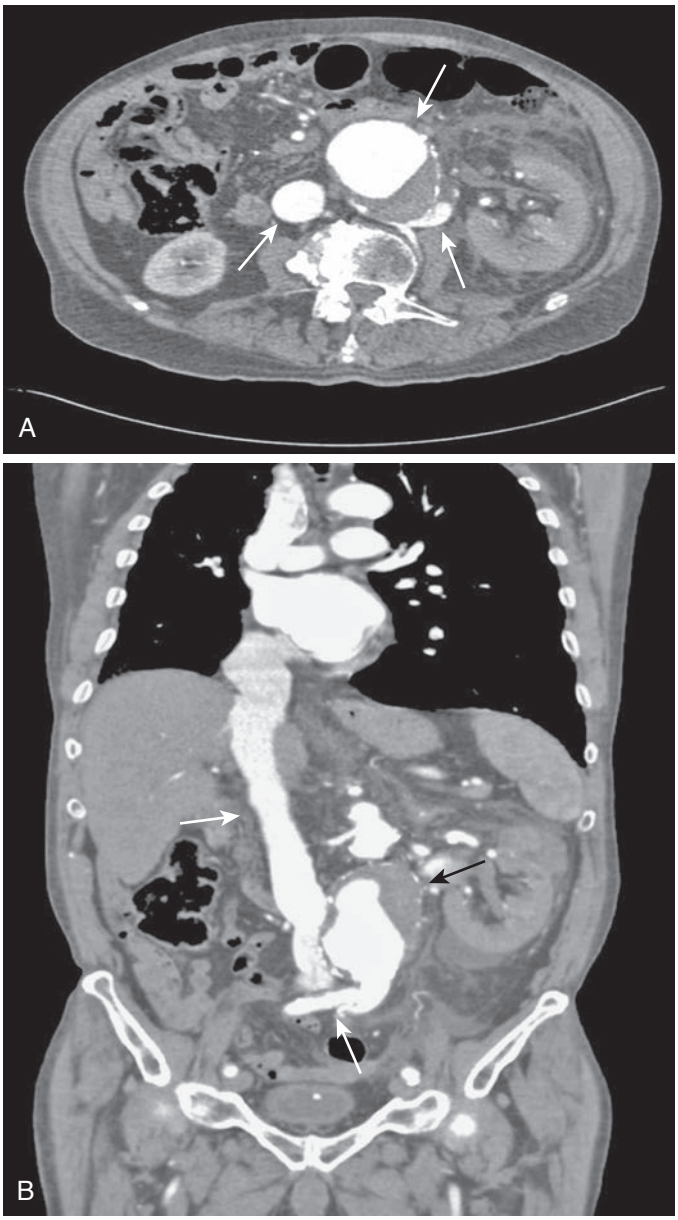

Figure 174.3 (A) Axial CT scan demonstrating an aortorenal arteriovenous fistula. Contrast material is present in the abdominal aortic aneurysm *(top arrow)*, inferior vena cava *(left arrow)*, and retroaortic left renal and lumbar veins *(right arrow)*. (B) Sagittal reconstruction of the CT scan in (A) showing contrast material in the aneurysm *(black arrow)*, inferior vena cava *(top white arrow)*, and retroaortic left renal and lumbar veins *(bottom white arrow)*.

and orthopedic procedures on the knee may also be complicated by AVFs (Fig. 174.5).[48,49] The number of iatrogenic popliteal AVFs can be expected to increase, due to the more frequent use of popliteal access for interventions to treat deep vein thrombosis and chronic venous insufficiency.

Tibial and Peroneal Arteriovenous Fistulas

AVFs of the tibial and peroneal arteries are a recognized complication of comminuted fractures, blast fragment injuries, balloon catheter thrombectomy, and atherectomy of the tibial vessels.[50,51] Approximately 24% of the AVFs reported in the Vietnam registry occurred in the tibial and peroneal arteries.[14] The more frequent use of retrograde tibial access to recanalize occluded lower extremity arteries in patients with critical limb ischemia (CLI) may increase the risk of AVFs in these locations.[52-56]

BOX 174.1 Factors Predisposing to Iatrogenic Femoral Arteriovenous Fistula

Female gender	Age >65
Emergency procedures	Sheath size >8 F
Intensity of anticoagulation	High body mass index
Low distal puncture	Severe femoral atherosclerosis
Hypertension	Left-sided/multiple punctures
Prosthetic grafts	Hostile groin

Aorto-iliac Arteriovenous Fistulas

Rupture or erosion of an AAA into the IVC accounts for 80% to 90% of acquired aortocaval fistulas (ACFs). GSWs, shrapnel, or SWs account for the remaining 10% to 20% (see Fig. 174.1).[18-22] Less commonly, iatrogenic injury during peripheral arterial or cardiac catheterization or lumbar disk surgery and, rarely, blunt trauma have been associated with ACFs.[57-60] Iliac AVFs account for 0.4% to 1.4% of AVFs and are usually the result of penetrating trauma or lumbar disc surgery.[12,14,61]

VI occurs in up to 0.05% of lumbar disc procedures. Anatomic anomalies, such as a low aortic bifurcation at L4-L5 (18%) and degenerative changes of the anterior spinal ligament, may contribute to VIs in this location.[62-64] VIs at the L3-L4 disc space predominantly involve the aorta and IVC; the majority of iliac VIs occur with L4-L5 and L5-S1 disc space surgery. The common iliac arteries, which lie immediately anterior to the L4-L5 lumbar disc space, are the most commonly injured vessels (right CIA 43%; left CIA 29%).[65,66]

Renal Arteriovenous Fistulas

The majorities of renal AVFs occur after renal biopsies but can result from trauma, surgery, percutaneous interventions, tumors, inflammation, or erosion of an aneurysm directly into a vein. The incidence of biopsy-associated renal AVFs range from 9% to 18%. Factors predisposing to biopsy-related renal AVFs include use of a large-bore needle, lack of radiologic guidance when performing the biopsy, medullary penetration, and the presence of atherosclerotic vessels.[67,68] Other causes of renal AVFs include placement of percutaneous nephrostomy tubes (Fig. 174.6), laser lithotripsy, and mass ligation of the renal pedicle.[67-70] Aortic and renal artery aneurysms may also erode into a retroaortic or normally located renal vein or its tributaries.[22,23] Isolated renal AVFs due to blunt and penetrating trauma are uncommon.[71]

Splenic, Hepatic, and Mesenteric Arteriovenous Fistulas

Penetrating injuries involving the splenic, hepatic, superior, and inferior mesenteric arteries or their tributaries may result in fistulas between their contiguous veins, the portal vein, hepatic veins, or the IVC.[72-85] Splenic AVFs may result from blunt or penetrating intraabdominal trauma, mass ligation of the splenic pedicle, iatrogenic injury during splenoportography, and, rarely,

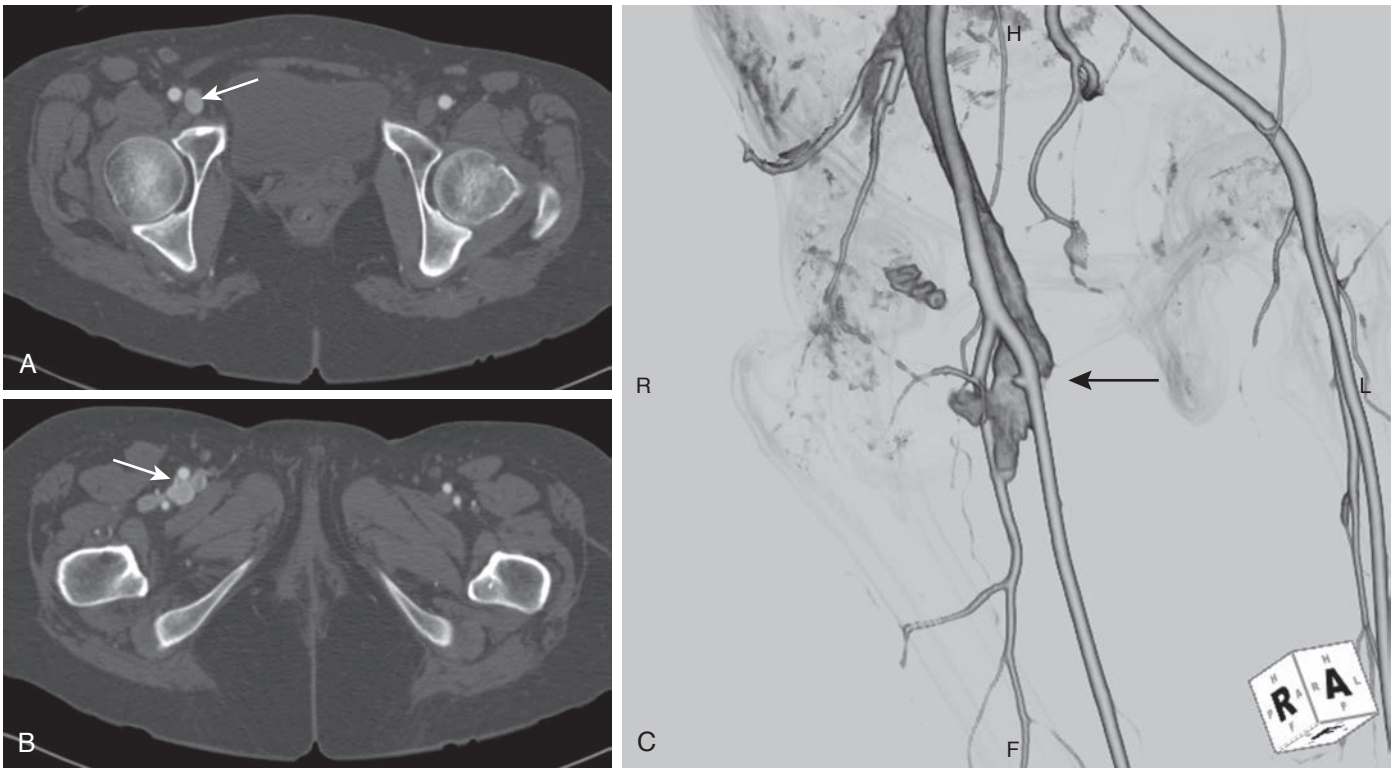

Figure 174.4 (A) Axial CT pelvis with intravenous contrast in a patient with history of prior cardiac catheterization demonstrates opacification of the right common femoral vein *(arrow)* on the arterial phase image. (B) More inferiorly, a small vascular connection *(arrow)* is noted between the right superficial femoral artery and femoral vein consistent with an arteriovenous fistula. (C) Three-dimensional reconstructed image demonstrates the small right superficial femoral arteriovenous fistula *(arrow)*.

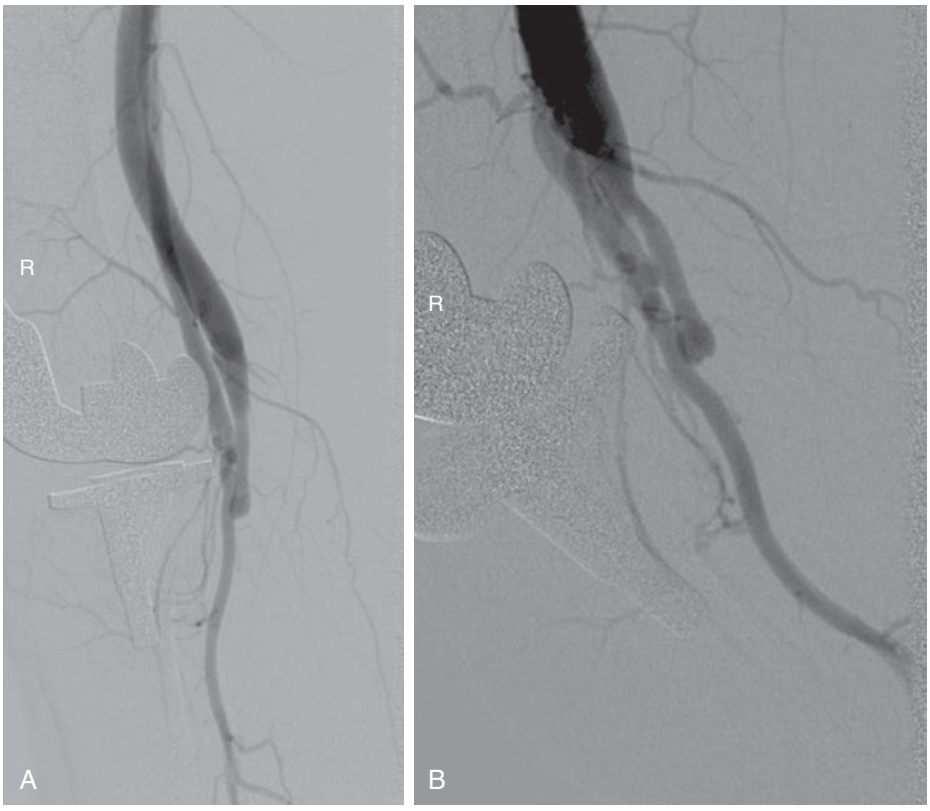

Figure 174.5 (A) Digital subtraction angiography of a patient status post knee arthroplasty demonstrates a right popliteal arteriovenous fistula. There is early venous filling of the popliteal vein during the arterial phase angiogram. (B) Magnification view demonstrates similar findings.

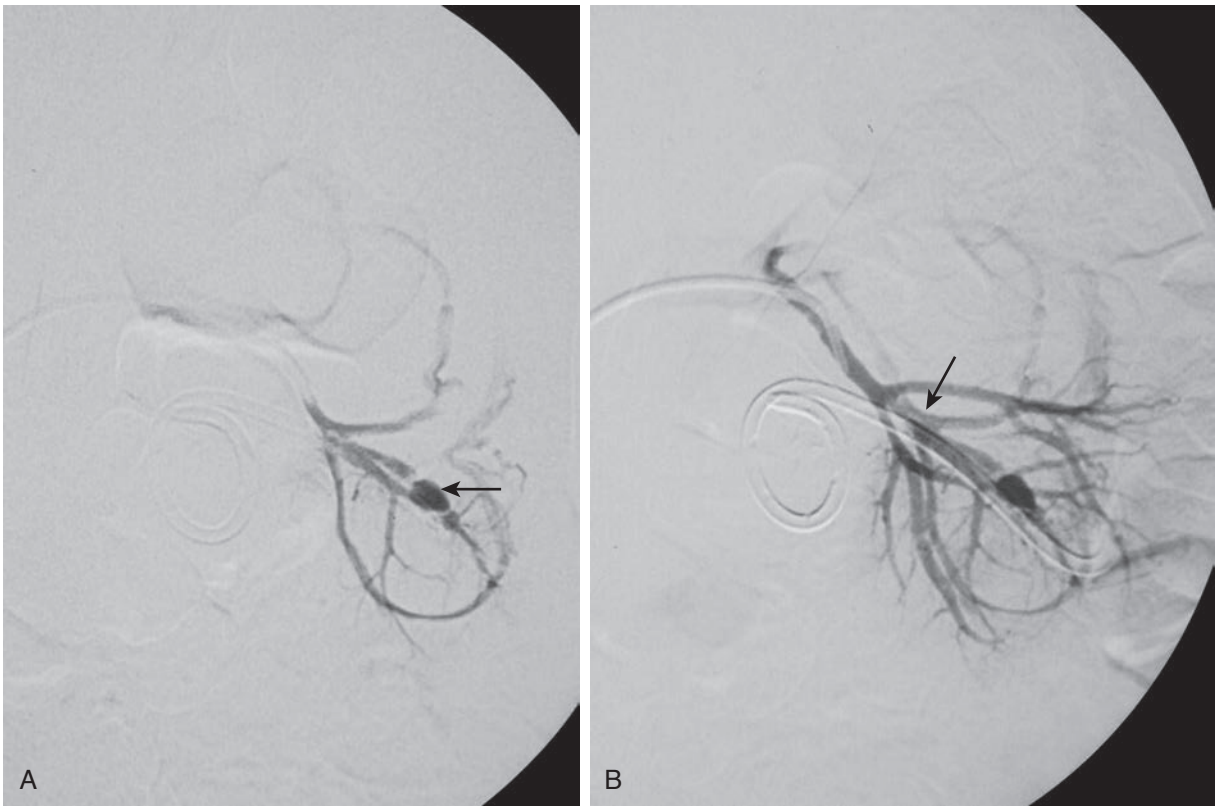

Figure 174.6 Selective left renal arteriography in a patient status post percutaneous left nephrostomy demonstrates a pseudoaneurysm *(arrow)* arising from a left lower pole renal branch (A) with early venous filling *(arrow)* from an arteriovenous fistula (B).

erosion of a pancreatic pseudocyst into the splenic artery and vein.[73-77] Forty-four percent of splenic AVFs are due to rupture of a noncalcified splenic artery aneurysm (SAA) into an adjacent vein; this may be the first indication of the presence of an SAA.[5,77-83] Hepatic AVFs are most commonly the result of penetrating or vehicular trauma but may occur after percutaneous needle biopsy, transhepatic diagnostic catheterizations, biliary drainage, or TIPS procedures (Fig. 174.7).[77-83] Hepatic AVFs may be either intrahepatic or extrahepatic and occur in 5.4% of patients after percutaneous needle biopsy.[77-83] Hepatic artery aneurysms (HAAs) and carcinomas may also erode into an adjacent vein, resulting in an AVF.[79,86,87] AVFs of the superior and inferior mesenteric arteries are rare and are usually the result of penetrating trauma, iatrogenic injuries, or mass ligation of the vascular pedicle during bowel resection.[84,85]

PATHOPHYSIOLOGY

The natural history of an AVF is determined by the diameter of the artery and vein, the size and location of the fistula, the adequacy of the collateral circulation, and the competence of the distal venous valves. AVFs may close spontaneously, decrease in size, or progressively enlarge as a result of degenerative changes within the arterial wall.[88,89]

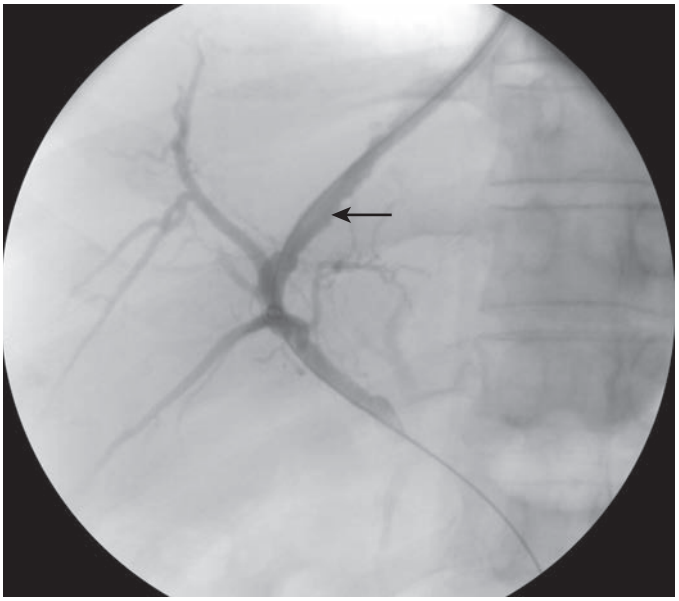

Figure 174.7 Angiography through the vascular sheath during a transjugular intrahepatic portosystemic shunting procedure demonstrates inadvertent puncture of the right hepatic artery with a fistula to the right hepatic vein *(arrow)*.

Fistula Size and Flow

Holman and Taylor established that antegrade flow in the artery distal to an AVF was maintained when the cross-sectional area of the fistula was ≤1.5 times the diameter of the inflow artery but was diminished or reversed when the fistulous opening exceeded the diameter of the inflow artery by greater than threefold.[90] Flow in the artery proximal to the fistula increased up to fivefold if the fistula was ≥1.5 the arterial diameter and eightfold if the opening was greater than 3 times the diameter of the inflow artery.[91] Flow rates of greater than 350 mL/min are associated with failure of a fistula to close spontaneously.[41] Iatrogenic femoral AVFs are usually small with low flow rates and therefore infrequently result in congestive heart failure (CHF). The larger-diameter sheaths used for aortic and complex peripheral and venous interventions, TIPS procedures, and orthopedic instrumentation of the lumbar spine and the knee may result in larger defects and AVFs with higher flow rates, and greater risk of cardiac decompensation.

Chronic Changes

In chronic AVFs the increase in hemodynamic shear stress results in attenuation of the arterial wall, accompanied by calcification and lipid deposition in the inflow artery. These structural changes result in elongation, tortuosity, and ultimately aneurysmal dilatation at the site of the fistula.[92-94] The adjacent vein also dilates and becomes tortuous and thickened or "arterialized" with pulsatile flow. The structural changes in the artery and vein become evident at approximately 2 months and established by 15 months but appear to be reversible if the AVF is repaired within 2 years.[92-94] The direction of flow in the artery distal to an AVF is determined by the size of the fistula. Flow is usually antegrade with small fistulas but is reversed with larger defects, owing to the increase in collateral flow distal to the fistula. The high venous pressure at the site of the fistula results in dilatation and valvular incompetence of the distal vein, producing chronic venous insufficiency.

Cardiac Effects

In patients with large AVFs, the increase in preload results in cardiomegaly and dilatation of the aorta and vena cava proximal to the fistula. These structural changes may develop within weeks to months or progressively increase over months to years. Young healthy males are more likely to compensate for the increase in preload than older individuals, but, ultimately, if left untreated, high-output CHF ensues.[89]

CLINICAL PRESENTATION

History

Symptoms in patients with large AVFs may arise from increased venous return (CHF), diversion of arterial blood flow (ischemia), or venous hypertension (varicosities, edema). An antecedent history of trauma, catheter-based interventions, or AAA should be elicited in all patients. The majority (75%) of patients with small AVFs are asymptomatic. The most common symptoms are thrill or bruit (61%-96% of cases) or a pulsatile mass (20%-52% of cases).[12,14] The acute onset of abdominal or back pain is the presenting complaint in 70% to 80% of patients with spontaneous aortic and iliac AVFs. Other symptoms and signs may occur as a function of the location of the AVF. Although CHF is most commonly associated with aortic and iliac AVFs, symptoms of cardiac decompensation may occur in patients with large extremity, visceral, or carotid AVFs.[95]

Physical Examination

Neck and Upper Extremities

A rapidly expanding or pulsating hematoma, carotid bruit or thrill, and dilated neck veins suggest the diagnosis of a carotid-jugular AVF. Neurologic deficits due to embolization or shunting of blood through the fistula may also be present.[13,28] The clinical diagnosis of vertebral AVFs is often unsuspected because only 50% of patients present with overt signs or symptoms of injury; neurologic symptoms are rare. Subclavian, axillary, and brachial AVFs may manifest with pulse deficits, blood pressure abnormalities, arm swelling, dilated venous tributaries, hand ischemia, or a pulsatile mass with a thrill and bruit. Radial and ulnar AVFs are usually asymptomatic and manifest as a thrill or bruit over a small pulsatile mass and, rarely, digital embolization.

Lower Extremities

A careful examination of the groin and lower extremity for evidence of an expanding or pulsatile hematoma and/or a thrill or bruit should be performed. Temporary compression of the artery proximal to the fistula should result in slowing of the heart rate and a reduction in pulse pressure (Nicoladoni-Branham sign). Leg swelling with dilated or varicose veins, pigmentation, and ulceration may be present in more chronic cases. Although signs and symptoms of arterial ischemia are rare, the presence of peripheral pulses and segmental blood pressures should be documented. Pedal access–related fistulae between the crural arteries and their venae comitantes usually present incidentally as a small mass with an overlying thrill and bruit.[96]

Chest and Abdomen

A pulsatile mass or pronounced aortic pulsation with an epigastric thrill or bruit is suggestive of an ACF. A holosystolic murmur is present in 75% of ACFs, although it may be absent if there is a large amount of thrombus present within the aneurysm. A thrill is palpable in 25% of patients.[19-22,74] In patient with AVFs to the aorta or iliac arteries following lumbar disc surgery, symptoms may not manifest until months to years after the event. In these cases a lower abdominal bruit may be the only finding. Signs of CHF and lower extremity venous hypertension are characteristic findings in patients with larger fistulas.[97]

Small renal AVFs are usually discovered incidentally by the presence of a bruit over the kidney. Blood flow through larger renal AVFs may approach 60% to 82% of total ipsilateral flow and result in ischemia of a significant portion of the kidney, leading to hypertension.[68] Patients with spontaneous aortorenal

AVFs may present with abdominal pain, hematuria, proteinuria, renal impairment of varying severity, a varicocele, non–contrast-enhancing "silent" left kidney, and hemodynamic instability[22,98] These patients often present late because they are first evaluated for hematuria by the urologist.[99]

The clinical findings in patients with visceral AVFs include jaundice, hepatosplenomegaly, prominent venous collaterals, and epigastric bruits. Hematochezia and hematuria due to rupture of mucosal veins in the rectum and bladder may be present in 11.5% to 35% of cases.[100]

DIAGNOSTIC EVALUATION

Radiographs should be obtained in all patients with suspected AVFs for evidence of prior trauma (bullet or metal fragments), abnormal calcifications, and signs of CHF. The diagnostic algorithm then proceeds to noninvasive imaging to identify the characteristics of the AVF, with either duplex US, computed tomographic angiography (CTA), or magnetic resonance angiography (MRA). Depending on the outcomes of these, additional testing, such as ankle-brachial indices or venous or carotid duplex imaging, are obtained. A 12-lead electrocardiogram and/or two-dimensional echocardiogram may be obtained if CHF is suspected. Catheter-based angiography and/or cardiac catheterization are reserved for treatment and/or diagnostic uncertainty. Endoscopy may be indicated in patients with active gastrointestinal bleeding or a history of bleeding from esophageal varices or gastric ulceration.

Color-Flow Duplex Ultrasound Imaging

Duplex ultrasound (DUS) imaging is an appropriate initial choice for the diagnosis of acquired chronic AVFs. Characteristic findings include visualization of the AVF and a color mosaic in the tissues at the level of the fistula. Loss of triphasic arterial waveforms proximal to the fistula, diminished or reversal of flow in the distal artery, and continuous high-velocity flow in the vein cephalad to the fistula are the usual Doppler findings (Fig. 174.8).[67,68,101] The diagnostic accuracy of DUS is highly technician dependent and may be difficult to perform in the

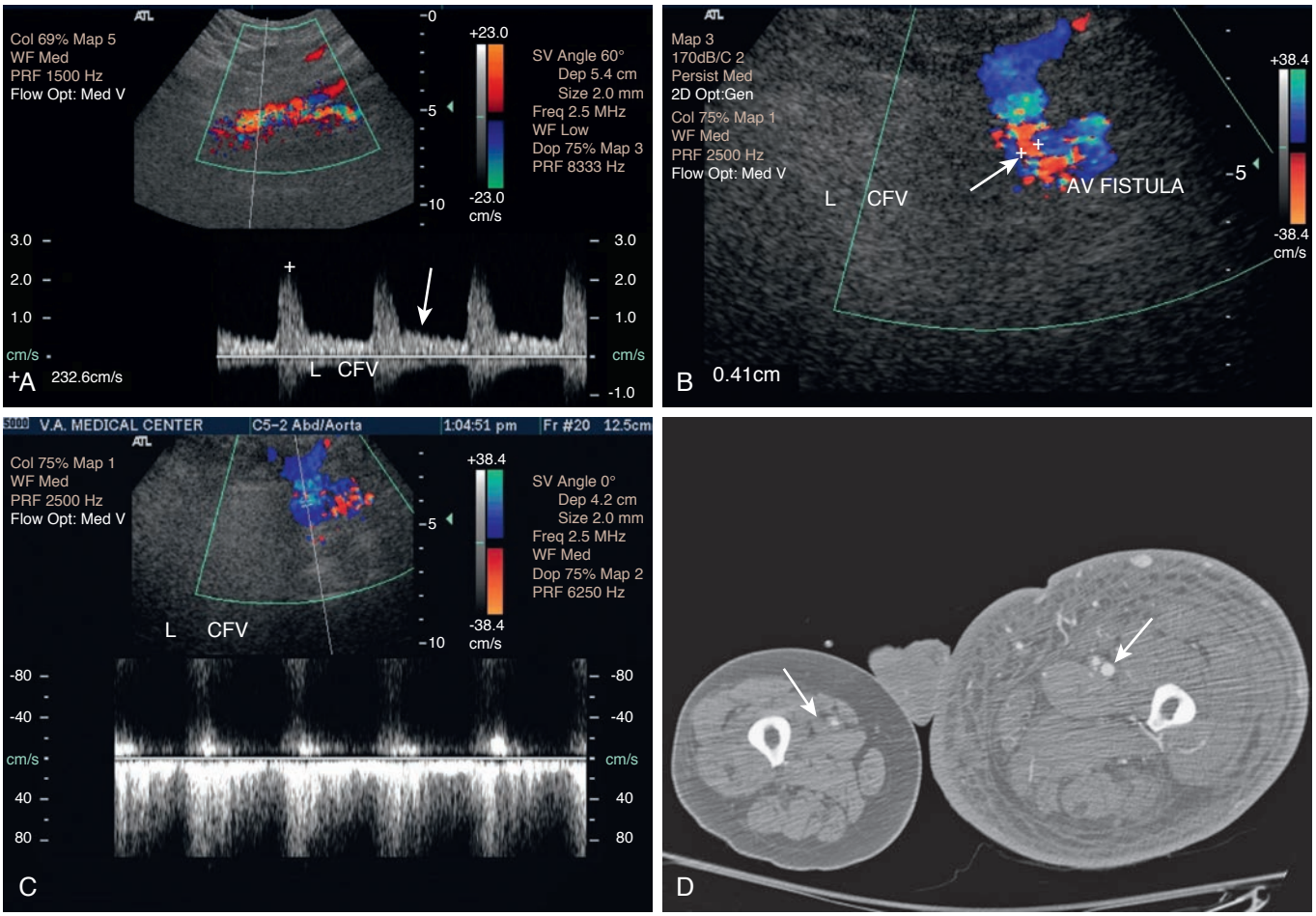

Figure 174.8 Ultrasound image and CT scan of a patient with a large common femoral AVF. Loss of triphasic waveforms is observed in the common femoral artery (CFA) proximal to the fistula (A); a large connection is demonstrated by the white arrow between the CFA and common femoral vein (CFV) (B); a pulsatile and reverse flow is seen in the CFV distal to the fistula (C); and early enhancement of superficial femoral vein *(white arrow)* on the side with an AVF (D).

presence of open wounds, subcutaneous air, hematoma, fractures, obesity, and interference from anatomic structures.[102]

Computed Tomography Angiography

CTA is an appropriate diagnostic tool for evaluation of patients with suspected AVFs because it is minimally invasive, accurate, and operator independent and allows for repeat follow-up exams. In prospective studies evaluating arterial injuries, CTA has been shown to be comparable to digital subtraction angiography (DSA) with a sensitivity of 90% to 95% and specificity of 99% to 100%.[103-107] The major limitations of CTA are exposure to ionizing radiation, the risk of contrast-induced nephrotoxicity (CIN), interference from vessel wall calcification, and the degradation of image quality by metallic, motion, and shoulder streak artifacts. However, the incidence of such interference is believed to be approximately 1%.[106]

Magnetic Resonance Imaging and Angiography

MRI and MRA facilitate the diagnosis of AVF by delineating the underlying defect, measuring flow disturbances, and defining the relationship between the fistula and adjacent soft tissue structures.[105,108,109] Among the benefits of MRA are the absence of exposure to ionizing radiation and a mild side effect profile. However, its utility is limited by the inability to monitor acutely ill or severely injured patients, longer image acquisition times, and patient intolerance. Due to heating and object deflection by the magnetic field and radiofrequency gradients, patients with certain metals (either medical devices, or bullet or shrapnel fragments) cannot enter the MRI environment. Contrast-induced toxicity and the potential development of nephrogenic systemic fibrosis (NSF) in patients with renal impairment remain a concern.[110]

Digital Subtraction Angiography

DSA provides excellent spatial and temporal image resolution, permits rotational views, and is used for both diagnostic and therapeutic for acquired AVFs. The typical angiographic features of an AVF are early venous filling and failure to opacify distal arteries. A high-quality angiogram to identify the precise location of AVFs is essential for endovascular therapy (EVT). In cases where it may be difficult to locate the fistula by arteriography alone, simultaneous catheterization of both the affected artery and vein or balloon catheter occlusion of the inflow artery with contrast injection beyond the balloon can be helpful. DSA with carbon dioxide may be an alternative to conventional angiography in patients with a history of contrast reaction or chronic renal failure.[111]

PRINCIPLES OF MANAGEMENT

The goals of therapy for acquired AVFs consist of closure of the fistula, restoration of normal hemodynamic flow, and reestablishment and maintenance of vascular continuity.[112] Although venous repair was originally considered unnecessary, data from the conflicts in Afghanistan and Iraq suggest that repair of major extremity venous injuries is desirable to reduce the sequelae of venous hypertension and improve limb salvage.[113] The majority of patients with acquired AVFs have no or only mild symptoms and do not require an extensive preoperative work-up. Massive leg swelling and ulceration are controlled with diuretics, limb elevation, or compressive bandaging. Patients with ACFs in florid CHF may be admitted to the ICU preoperatively for optimization of cardiac function.

Conservative Treatment

The natural history of stable iatrogenic femoral AVFs is relatively benign, with 38% to 81% expected to close spontaneously by 1 year.[41,42,114] Therefore patients with small AVFs and normal cardiac function can be monitored with DUS for at least a year. Angiographically, 33% to 90% of renal AVFs resolve spontaneously between 6 weeks and 4 years after the initial diagnosis. This is not entirely unexpected because procedure-related renal AVFs are usually small.[67]

Compression Therapy

US-guided compression and compressive bandaging have been advocated as first-line treatment for small iatrogenic AVFs. Successful occlusion of an AVF is unlikely if the artery and vein are closely adherent, if the defect is large or located at an arterial bifurcation, or if the communication is deep and not amenable to superficial compression. The low success rate of US compression (0%-30%) and the prolonged duration of bandage compression required (15 ± 10 days), as well as the occurrence of local skin ulceration and DVT with the latter, argue against the use of this technique.[115-118]

Endovascular Therapy

Until recently, open surgery was the only option for treating AVFs after conservative therapy had failed. However, its morbidity and mortality and the ongoing advances in endovascular techniques have increased the use of EVT to treat VIs and AVFs. EVT is the treatment of choice for poor-risk surgical candidates, older stable patients with suitable anatomy, and patients with AVFs in surgically inaccessible locations.[119] EVT can be accomplished by transcatheter embolization, placement of a stent-graft, or a combination of the two modalities. Temporary balloon occlusion is a useful adjunct to control bleeding.

Embolization

Transcatheter embolization can be used to treat many AVFs.[67,68,120-127] Available embolic agents include autologous clot, gelatin sponges, microfibrillar collagen, polyvinyl alcohol particles, metal coils, detachable balloons, and liquid embolic agents such as N-butyl cyanoacrylate (n-BCA) and ethylene vinyl alcohol copolymer (Onyx). The choice of embolic agent depends on vessel size, the caliber of the delivery catheter, and whether repeated embolization is anticipated. Gelfoam is the preferred agent for temporary occlusion, and metallic coils and

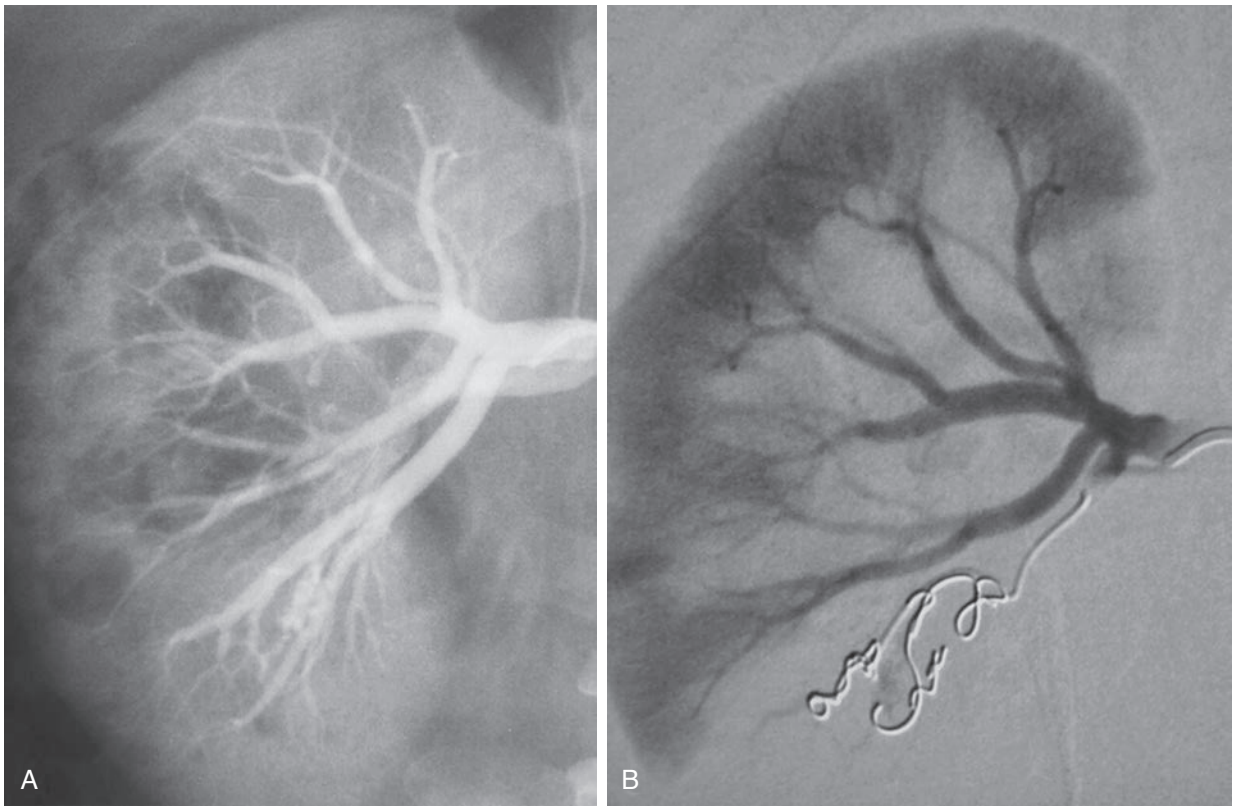

Figure 174.9 Selective right renal arteriogram demonstrating a communication between a branch of the renal artery and vein (A) that was successfully treated with coil embolization (B).

particles are used for permanent occlusion. Successful embolization requires accurate positioning of the catheter at the site of the AVF before delivering the occluding agent.[122,124] Microcoils and particulate agents deployed through coaxial microcatheters are ideal for treating small muscular and radicular branch cervical, renal, visceral, or extremity AVFs, with technical success rates of 89% to 92% (Fig. 174.9). Although a limited number of reports have been published on the embolization of visceral AVFs, principles similar to those used for the endovascular treatment of other AVFs can be applied.[122,125-129]

The major risk associated with transcatheter embolization of AVFs is embolization to arteries related to the fistula and to the lung, resulting in parenchymal or extremity ischemia or pulmonary embolism (Fig. 174.10). In high-flow fistulae, larger high radial force coils are deployed first to provide a scaffold for smaller-sized packing coils, to avoid inadvertent migration and embolization. Placement of a protective covered stent, Amplatzer plug, or temporary balloon occlusion device can reduce the risk of coil migration or embolization in these situations.[130] With careful technique, the extent of infarction related to catheter embolization of renal AVFs, for example, has been limited to less than 10% in more than 75% of patients.[68]

Covered Stent-Grafts

Covered stents can be used to bridge a fistula and preserve parent vessel flow in large-diameter AVFs. If a PSA is present, it is occluded with embolic material. A wide variety of stent-grafts have been used successfully to treat patients with acquired and spontaneous AVFs.[131-133] Because of the limited stent sizes currently available to treat tibial disease, use of a covered stent designed for the coronary arteries can be considered in AVFs involving the crural arteries.[35,119,134-137]

Penetrating injuries of the innominate, carotid, and subclavian arteries are anatomically amenable to EVT.[35,136] In a review of 54 published cases of endovascular treatment of carotid trauma, covered stents were deployed for carotid AVFs in 31% (17 of 54) of cases, with an 88% success rate.[135] AVFs also accounted for 21% of cases of subclavian trauma treated with covered stents over a 10-year period, by du Toit et al.[35]

The placement of covered stent-grafts to treat AVFs in the groin and around the knee joint, although technically feasible, has been avoided because of the perceived risk of kinking or bending in these locations. Because the CFA has been the access site for most angiographic interventions, placement of a covered stent was also believed to preclude its use for repeated procedures (Fig. 174.11).[138,139] However, the introduction of shorter length (12-28 mm) stent-grafts with a wider range of diameters has allowed for accurate bridging of an AVF in the CFA without crossing or impinging on the orifices of the SFA or profunda femoris arteries, while leaving the remaining uncovered CFA accessible for repeated interventions.[35,119,134-147]

Abdominal Endografts

Commercially available aortic endografts and their components, initially designed to treat patients with aorto-iliac (A-I) and thoracic aneurysmal disease, are currently used to treat aortic,

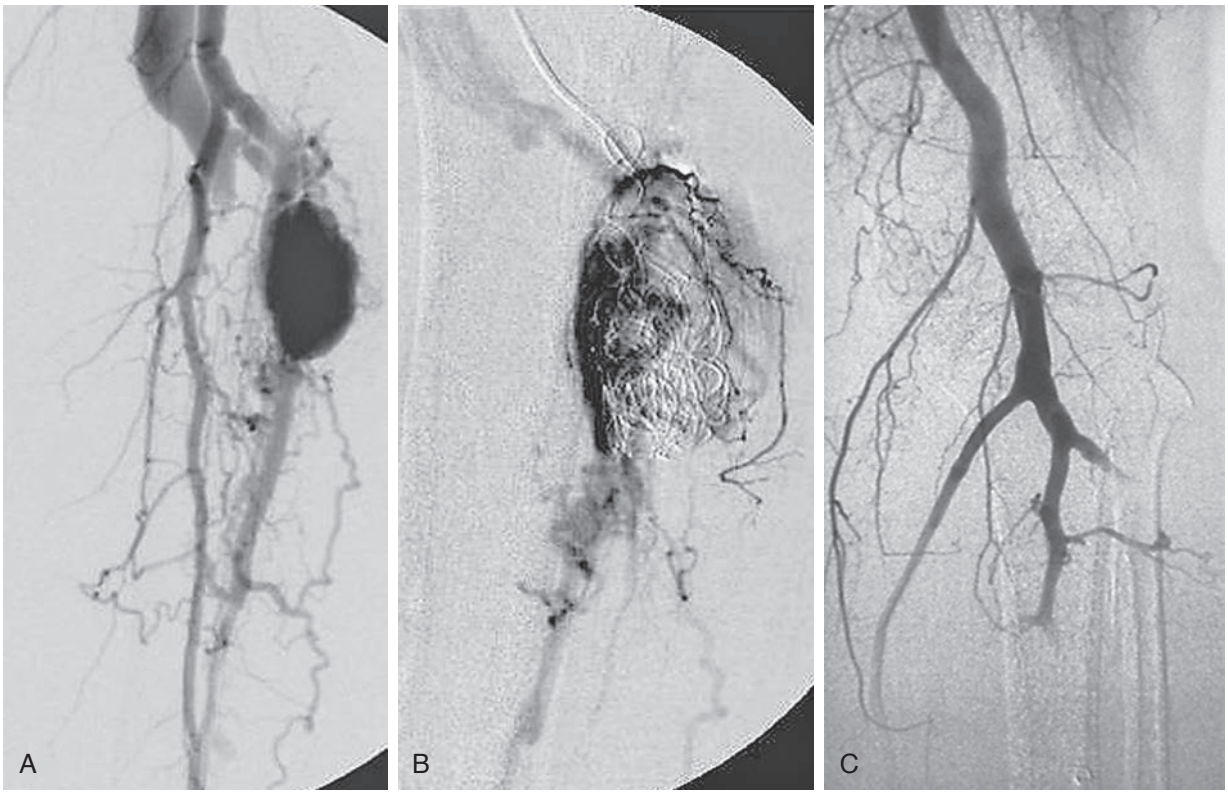

Figure 174.10 (A) Selective femoral angiogram demonstrating an arteriovenous fistula (AVF) between the anterior tibial artery and vein. (B) Coil embolization of the AVF. (C) Occlusion of the tibioperoneal trunk by a dislodged coil, resulting in severe limb ischemia requiring treatment with a popliteal-to-posterior tibial venous bypass graft.

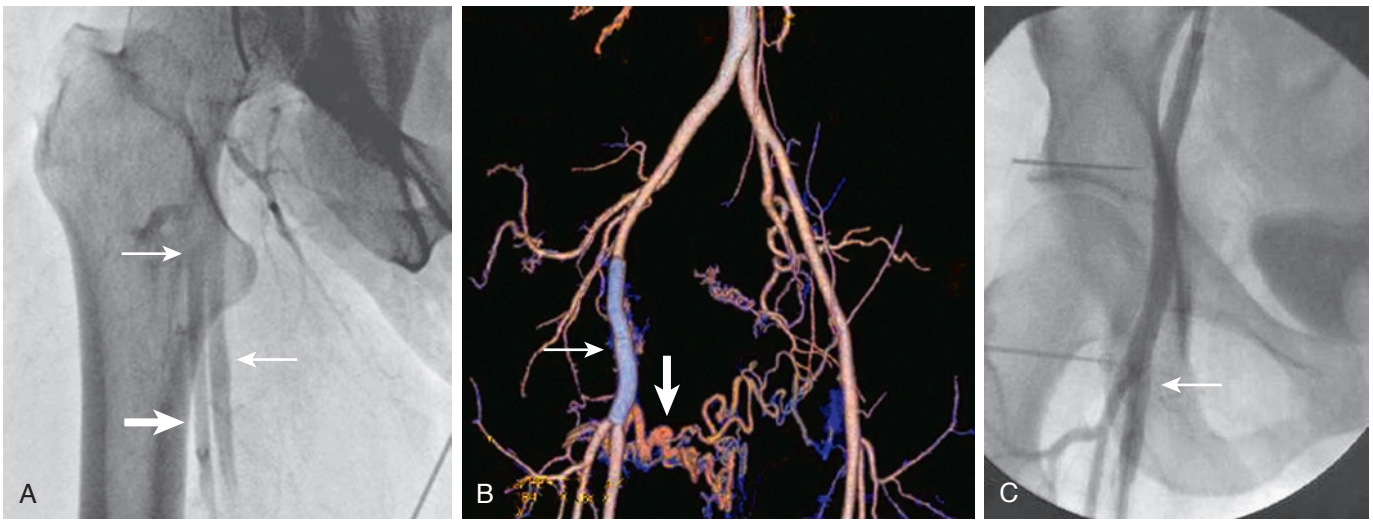

Figure 174.11 (A) Selective femoral angiogram demonstrating an arteriovenous fistula (AVF; *upper arrow*) at the common femoral bifurcation, outlining the superficial femoral vein *(middle arrow)* and artery *(lower arrow)*. (B) CT reconstruction showing persistence of the AVF *(vertical arrow)* below a covered stent-graft *(horizontal arrow)* used to treat common femoral stenosis after attempted operative repair of the fistula. (C) Selective femoral angiogram demonstrating closure of the fistula after placement of an additional covered stent-graft *(arrow)*.

iliac, and aortic arch branch vessel AVFs. AVFs of the descending thoracic aorta are rare but, when present, may be amenable to EVT.[119,143-146] The major limitations to the use of endografts to repair ACFs are similar to those that preclude their use in conventional aneurysm repair; the diameter, length, and angulation of the aortic neck, as well as the diameter and tortuosity of the access vessels. ARFs are also amenable to EVT. The depth of the pelvis and the presence of enlarged veins also make EVT a practical and safer option than open repair for most I-C and I-I AVFs.[148]

The introduction of smaller-diameter grafts and delivery systems has facilitated the management of younger patients with aortic and iliac trauma and AVFs, whose vessels are much smaller than older adults. Careful case selection and limiting graft oversizing has reduced the incidence of endoleaks, sac ruptures, and fistula persistence or recurrence in the short-term follow-up of small numbers of these younger patients.[119,145] The risk of air embolism and dislodgement of thrombotic material resulting in pulmonary embolism has led some surgeons to advocate prophylactic placement of a removable IVC filter or insertion of a second aortic prosthesis into the IVC to prevent this complication.[149]

Only case reports address the treatment of renal, splenic, hepatic, and mesenteric AVFs with covered stent-grafts, but coiling of these AVFs is generally effective while preserving flow in the parent vessel. Additional embolization of feeding vessels is usually required for larger AVFs to prevent endoleaks and recurrence or persistence of the fistula.[80,150,151] Amplatzer plugs have been successfully used to occlude splenic, renal, mesenteric, subclavian, and popliteal AVFs and those occurring after endovascular aneurysm repair in selected patients.[152]

Operative Repair

OR of AVFs is recommended for young, healthy patients, individuals with complex anatomy unsuitable for EVT, or when EVT has failed.

Carotid and Vertebral Arteriovenous Fistulas

Although AVFs involving vessels in zone II of the neck are repaired surgically, exposure of AVFs in zones I and III can be difficult. Median sternotomy or left lateral thoracotomy may be required. Exposure of the distal internal carotid artery (ICA), even with the recognized maneuvers used to improve exposure at the base of the skull, is associated with considerable morbidity. Therefore EVT is often the most appropriate treatment for these lesions.

AVFs in zone II are more amenable to OR. Treatment of AVFs involving the carotid arteries may include primary repair of the defect in the artery and vein, patch angioplasty, interposition grafting, or ligation. The majority of traumatic vertebral AVFs occur deep in the neck between the C2-C5 vertebrae and are difficult to treat surgically. Lesions involving the V-1 segment are the most surgically accessible. Ligation of the VA proximal to the AVF and transposition of the distal segment onto the CCA may be feasible in selected patients. Treatment of more complex lesions usually requires ligation of the VA and vein above and below the fistula, and a subclavian-VA vein bypass at the C1-C2 interspace, if the contralateral VA is atretic or occluded.[153]

Axillary and Subclavian Arteriovenous Fistulas

Exposure of subclavian and proximal axillary artery AVFs may require median sternotomy (40%), a supraclavicular incision (23%), combined supraclavicular and infraclavicular incisions (20%), or division of the clavicle (16%).[154] The axillary artery is exposed by an incision directly over the artery, beginning below the middle of the clavicle and extending into the deltopectoral groove. The extent of arterial injury determines the repair; damage from blast injuries or GSWs usually requires excision of the damaged artery and placement of an interposition graft, whereas lacerations or transections can be reapproximated and repaired primarily.

Lower Extremity Arteriovenous Fistulas

The OR of lower extremity AVFs is accomplished by isolating the involved artery and vein proximal and distal to the AVF in healthy tissue planes, separating the vessels, and repairing the defect primarily, with an autogenous or prosthetic patch or interposition graft. When the AVF involves the superficial femoral artery, application of a tourniquet can significantly reduce blood loss. The distal runoff should be carefully assessed, especially with GSWs and injuries from IEDs, where multiple arteries may be involved. If there is continuity of one or more of the infrageniculate arteries, ligation of the involved artery and vein may be undertaken.

Aortocaval and Iliac Arteriovenous Fistulas

Aortocaval (ACFs), A-I, and I-I AVFs are repaired using a midline or retroperitoneal incision, which can be extended into the chest if necessary. In patients with spontaneous ACFs secondary to AAA, the AAA and massively dilated IVC are readily recognizable, whereas a thrill with dilation of the aorta and IVC accompany traumatic or iatrogenic ACFs. Repair of the aorta is undertaken in standard fashion, with ligation of the connection to the IVC performed from inside the aorta (Fig. 174.12). Attempting to separate the IVC and aorta and repair the IVC externally can lead to extensive bleeding and should not be attempted. In 10% of patients the defect in the IVC is large enough that a prosthetic patch or interposition graft is required. Care should be taken to avoid air embolism or the dislodgement of thrombus into the IVC during surgical manipulations.

Iliocaval or I-I AVFs can be much more difficult to repair surgically due to their location deep in the pelvis and the presence of enlarged veins. Temporary balloon occlusion catheters can be placed in the iliac and femoral veins above and below the fistula to minimize blood loss before exposing the AVF. The defect in the IVC or iliac vein can then be repaired and arterial continuity reestablished.

Aortorenal Arteriovenous Fistulas

OR of aortorenal fistulae may require suprarenal aortic clamping to avoid injury to the renal artery and enlarged veins. AVFs

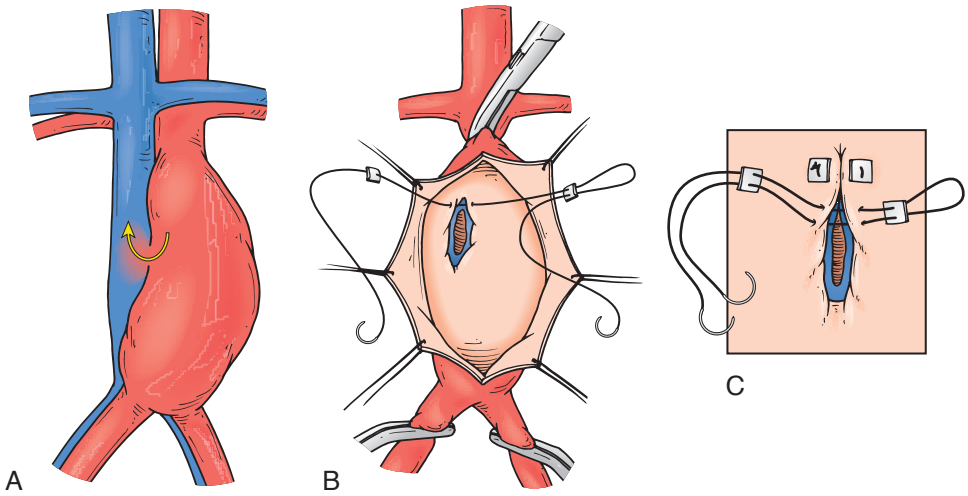

Figure 174.12 Schematic view of operative repair of an aortocaval fistula (A). The defect is closed from within the aneurysm sac (B,C). (From Crawford ES, et al. *Diseases of the Aorta: Including an Atlas of Angiographic Pathology and Surgical Technique*. Baltimore MD: Williams and Wilkins; 1984.)

associated with renal artery aneurysms or dissection are repaired in situ by aneurysmectomy with or without vein patch closure or aortorenal bypass.[155] Ex vivo repair may be required in selected cases of branch vessel involvement. Fistulae resulting from mass ligation of the renal pedicle are treated surgically by isolation and ligation of the renal artery and vein at their origins.

Visceral Arteriovenous Fistulas

Visceral AVFs are exposed via a midline or subcostal incision. The splenic artery in patients with AVFs is usually dilated and tortuous and can be controlled at its origin prior to treatment. Splenectomy is often performed for AVFs of the hilum or parenchyma.[75] The splenic vein should be ligated close to its junction with the superior mesenteric vein to minimize the risk of thrombus propagation into the portal vein. Exposure of arterioportal and arteriosystemic AVFs may require medial visceral rotation and/or thoracoabdominal extension of the incision to obtain proximal control of the celiac artery.

Definitive OR of hepatic AVFs depends on their location and etiology. Spontaneous AVFs may require placement of an interposition graft, with repair or ligation of the vein. In the case of a fistula resulting from a common HAA, proximal and distal ligation of the aneurysm is an option if collateral flow through the right gastric and gastroduodenal arteries is preserved. Lesions of the proper hepatic artery and its branches require either direct repair or a vein interposition graft to maintain hepatopetal flow. Ligation of the involved artery and segmental or partial hepatectomy may be required with intrahepatic AVFs.

Treatment options for AVFs involving the superior or inferior mesenteric arteries or their tributaries include interposition grafting or ligation and excision of the AVF if a tributary is involved and collateral flow can be preserved. Mesenteric AVFs following mass ligation of the gastric, inferior, or superior mesenteric vascular pedicles are treated by isolation and proximal ligation of the involved artery and vein.

TREATMENT OUTCOMES

In symptomatic patients, repair of A-C, I-C, or I-I AVFs are accompanied by almost immediate improvement in cardiac and pulmonary function. Normalization of renal function maybe delayed for 48 to 72 hours. Younger patients with high-output CHF can be expected to recover fully, whereas the recovery of older individuals with spontaneous AVFs is determined by preexisting comorbidities.[156,157] The comparison of treatment outcomes is listed in Table 174.1.

Operative Repair

OR of postcatheterization AVFs is successful in 89% to 96% of cases. However, in cases of unstable patients where emergent surgery is required, EVT may be safer.[41,42] Intraoperative blood loss, myocardial infarction, pulmonary embolism, stroke, and multisystem organ failure account for a morbidity rate of 36% and a mortality rate of 7.1% to 12% following OR of spontaneous ACFs. Long-term graft patency is 96% in surviving patients.[19-23,119,143-146,158,159] There are no large series documenting the treatment outcomes of OR for visceral AVFs. However, treatment outcomes can be inferred from the elective treatment of VAA; the mortality rate for elective procedures is approximately 5% and increases to 10% to 25% in patients with ruptured aneurysms. Similarly, limited information is available on the outcome of renal AVFs repaired surgically. The results from repair of renal artery aneurysms suggest that AVF repair can be undertaken with low morbidity and mortality rates in institutions with extensive experience treating these lesions.[160]

Endovascular Therapy

Stent-grafts alone or combined with embolization have been successfully deployed in 83.9% to 100% of selected patients with pseudoaneurysms or AVFs of the carotid, subclavian, and

TABLE 174.1 Results of Operative Repair and Endovascular Therapy for Vascular Injuries and Arteriovenous Fistulas

Year	Author	Number Patients AVFs ()	AVF Type	Mechanism of Injury	OR *N* (%)	EVT *N* (%)	Technical Success (%)	COMPLICATION RATE (%)		MORTALITY RATE (%)	
								OR	EVT	OR	EVT
2016	Orion et al.[a]	67	ACF/AIF/ARF	SP	41 (61)	26 (39)	94	36	46	12	19
2014	Nakad et al.[a]	54	ACF/AIF/ARF	SP, IAT, PT	50 (100)	54 (100)	96		35	12	0
2011	Davidovic et al.[a]	50	ACF/AIF/ARF	SP, IAT							
2011	Herrera et al.	36 (7)	CJ	PT		36 (100)	94.4		12.5		2.8
2009	du Toit et al.	19 (9)	CJ	PT		19	100		5.2		5.2
2008	Herrera et al.	18 (16)	VV, VJ	PT, IAT		17	88.9		5.5		0
2007	Schonholz et al.	54 (8[b])	CJ, CCF	BT, PT, IAT		54 (100)	94.5		9.3		
2016	Branco et al.	153	Ax-Subclavian	PT	135 (89)	18 (11)	94.4	25.5	0	27.8	5.6
2015	Naidoo et al.	31 (5)	Ax-Subclavian	PT	49 (100)	31 (100)	83.9	18	0		0
2012	Dubose et al.	160 (27)	Subclavian	PT, IAT, BT		160	96.9		3.1		0
2010	Sobnach et al.	50 (5)	Subclavian	PT		1	100		0		0
2008	du Toit et al.	57 (12)	Subclavian	PT		57	100		7		1.7
2013	Yousuf et al.	30	Femoral	IAT, PT	29	1	90		0	0	0
2005	Onal et al.	12	Femoral	IAT, PT	0	12			8.3	3.6	
1993	Franco et al.	55 (2)	Ilio/Femoral	IAT	55				25.4		

[a]All AVFs.

[b]8 CCFs (carotid cavernous) AVFs excluded.

ACF, Aortocaval; *AIF*, aortoiliac; *ARF*, aortorenal; *AVF*, arteriovenous fistula; *CJ*, carotid jugular; *EVT*, endovascular therapy; *IAT*, iatrogenic; *OR*, operative repair; *PT*, penetrating trauma; *SP*, spontaneous; *VV*, vertebro-vertebral; *VJ*, vertebro jugular.

Sobnach S, Nicol AJ, Nathire H, et al. An analysis of 50 surgically managed penetrating subclavian artery injuries. *Eur J Vasc Endovasc Surg*. 2010;39:155–159.
Yousuf KM, Bhagwani AR, Bilal N. Management of chronic traumatic arteriovenous fistula of the lower extremities. *Eur J Trauma Emerg Surg*. 2013;39(4):393–396.
Onal B, Ilgit ET, Koşar S, et al. Endovascular treatment of peripheral vascular lesions with stent-grafts. *Diagn Interv Radiol*. 2005;11(3):170–173.
Franco CD, Goldsmith J, Veith FJ, et al. Management of arterial injuries produced by percutaneous femoral procedures. *Surgery*. 1993;113(4):419–425.

axillary arteries. Early and late stent-graft occlusion (5%-10%), intimal thickening resulting in greater ≥50% (4%-20%) luminal stenosis, re-intervention rates of 6% to 12%, and mortality rates of 0% to 5.9% are the major complications of EVT in these patients. Although these data encompass the treatment outcomes of all types of cervical and upper extremity VIs and not only AVFs, they do provide some insight into the expected results of EVT for patients with these AVFs.[6,135-137,141,161-163]

In most cases, EVT is the treatment of choice for iatrogenic femoral, profunda femoris, and popliteal AVFs, with technical success rates ranging from 88% to 100%.[138,139,164] Whether the routine use of antiplatelet agents will limit intimal thickening and improve graft patency remains undetermined.[165-167] There are currently no long-term follow-up data addressing the use of complex tibial interventional approaches to treat AVFs in patients with CLI. Abdominal aortic endografts are successfully deployed in 84% to 94% of patients with ACFs, with morbidity and mortality rates of 12% to 46% and 0% to 19%, respectively.[158,168] Endoleaks and graft complications due to aortic remodeling, especially in younger patients, require continued monitoring.[158] Only 23% to 36% of renal AVFs require treatment. Transcatheter embolization alone or in combination with a stent-graft is accompanied by a success rate of 90%. Successful occlusion of VAAs can be achieved with coil embolization in 93.3% to 100% of cases, with an overall perioperative morbidity of 10% to 12.5% and mortality of 0.0% to 8.3%.[75,169-171] Multiple interventions are usually necessary to achieve this level of success treating VAAs, pseudoaneurysms, and AVFs.[128,172]

The endovascular treatment of SAAs is associated with 0% mortality but a 40% splenic infarction rate; embolization of HAAs, with a mortality rate of 11% without significant hepatic ischemia.[169]

Operative Repair Versus Endovascular Therapy

There are currently no prospective randomized controlled trials comparing EVT with OR in the management of patients with AVFs. Only a few studies with small numbers of patients are available for analysis. The initial results of EVT for AVFs appear promising; the complication rate is relatively low, but long-term follow-up data are limited.

Several vascular surgeons have advocated EVT as the optimal treatment of A-I and aortorenal AVFs because it is less invasive, associated with less blood loss and hemodynamic instability, can be used in surgically inaccessible locations, and has lower morbidity and mortality rates.[168,173] In contrast, Orion et al. in a meta-analysis of 67 patients with ACFs, 41 (61%) treated with OR and 26 (39%) with EVT, found no statistical differences in morbidity (46% vs. 36%) or mortality (19% vs. 12%) between OR and EVT, respectively.[158] Kotsikoris et al. reported a 7.1% mortality rate for patients with ACCFs undergoing OR.[159] OR, currently reserved for young healthy patients, individuals with unsuitable anatomy for EVT, and when EVT has failed, is curative and durable with 90% patency in surviving patients. The current literature suggests that, despite its recognized advantages, EVT cannot yet be recommended as the standard

of care for patients with aortic or iliac AVFs. Because of the small numbers of patients with acquired ACFs, there is little likelihood of a randomized controlled trial; a prospective registry may provide better comparative long-term outcome data.[174]

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CHAPTER 175

Hemodialysis Access: General Considerations and Strategies to Optimize Access Placement

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As the population ages and the incidence of diabetes rises, chronic kidney disease (CKD) and end-stage renal disease (ESRD) are increasingly common diagnoses in the United States. In 2015, data from the United States Renal Data System (USRDS) showed that 117,162 new patients began therapy for ESRD, whereas the prevalent dialysis population reached 661,648. Of note, after a sharp rise in the incidence of ESRD patients in the 1980s and 1990s, followed by a leveling off in 2000 and a peak in 2006, there has been a slight but steady decline through 2015 (Fig. 175.1). Despite this, the number of ESRD patients continues to rise by about 21,000 patients per year (Fig. 175.2), with a resulting rise in healthcare costs.[1] Medicare fee-for-service spending for ESRD patients increased by 1.6%, from $30.4 billion in 2012 to $30.9 billion in 2013, accounting for 7.1% of overall claims (Fig. 175.3). Not surprisingly, most of these costs occur during the transition from CKD to ESRD and are due to the high use of long-term catheters and frequent hospitalizations for permanent arteriovenous (AV) access failures, requiring thrombectomies, revisions, and repeated access placements.[2]

INITIATIVES AND GUIDELINES

In 1997, the National Kidney Foundation-Dialysis Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guidelines for Vascular Access were published in an effort to increase the

Abstract

This chapter reviews the current initiatives and guidelines regarding hemodialysis access placement. In accordance with these guidelines, with an access surgeon's perspective, the authors review the appropriate steps to optimizing access placement. The steps reviewed include: timing of access, pre-operative evaluation, selection of access location, surgical techniques, post-operative and long-term follow-up, and results.

Keywords

Hemodialysis access
Guidelines
Pre-operative evaluation
Surgical technique
Patency rates

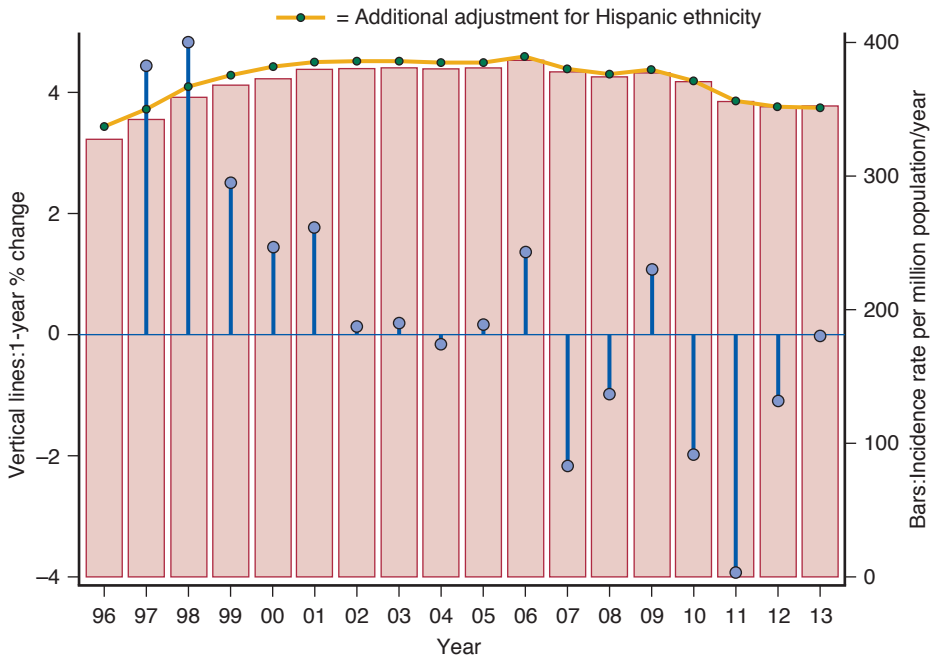

Figure 175.1 Trends in adjusted incidence rate (per million/year) of end-stage renal disease (ESRD) (*bars*; scale on the right), and annual change (%) in the adjusted incidence rate of ESRD (*lines*; scale on left) in the US population, 1996–2013. (Reproduced from United States Renal Data System [USRDS]. Incidence, prevalence, patient characteristics, and treatment modalities. In: USRDS 2015 annual report: Epidemiology of kidney disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD: 2015. Available at: http://www.usrds.org/2015/view/v2_01.aspx. Accessed 5/25/2016)

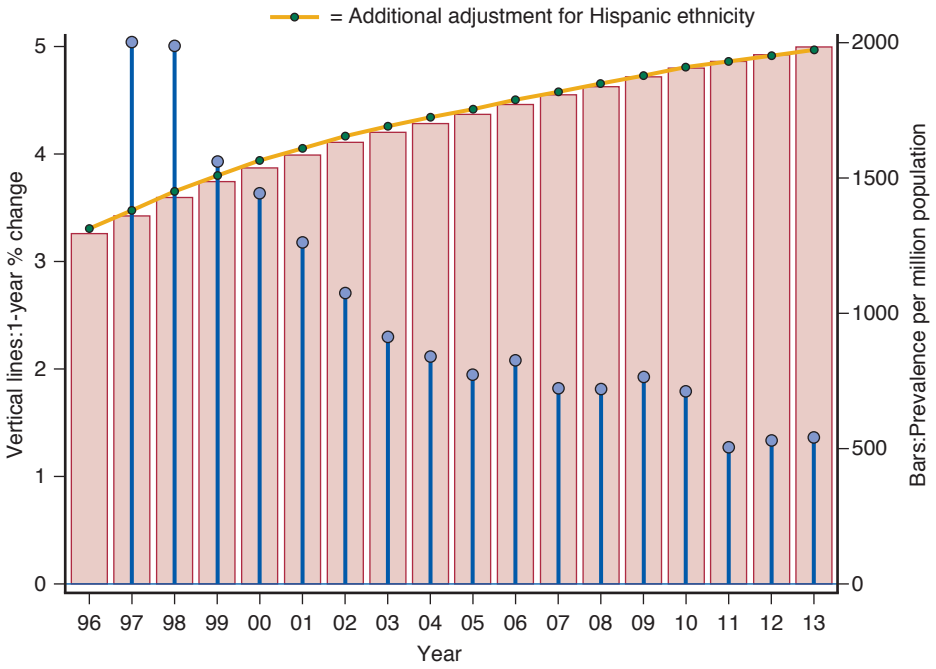

Figure 175.2 Trends in adjusted end-stage renal disease (ESRD) prevalence (per million) (*bars*; scale on the left), and annual change (%) in adjusted prevalence of ESRD (*lines*; scale on right), in the US population, 1996–2013. (Reproduced from United States Renal Data System [USRDS]. Incidence, prevalence, patient characteristics, and treatment modalities. In: USRDS 2015 annual report: Epidemiology of kidney disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD: 2015. Available at: http://www.usrds.org/2015/view/v2_01.aspx. Accessed 5/25/2016)

placement of autogenous AV access and prolong the use of created access by detection of dysfunction prior to thrombosis. These guidelines stress the early identification of patients with progressive kidney disease, identification and protection of potential native access construction sites, and development of multifaceted quality assurance programs to detect at-risk vascular access, track complication rates, and implement procedures that maximize access longevity. These original guidelines recommended that autogenous AV accesses should be constructed in at least 50% of all new hemodialysis patients and ultimately 40% of prevalent hemodialysis patients.[3]

In 2003, in an effort to reach the goals set forth by the NKF-KDOQI guidelines, the Centers for Medicare and Medicaid Services (CMS) recommended the adoption of a National Vascular Access Improvement Initiative (NVAII); in 2005, this was expanded to the Fistula First Breakthrough Initiative (FFBI). FFBI identified clinical and organizational changes that could be adapted and applied locally by nephrologists, dialysis personnel, access surgeons, and patients to increase the production and use of autogenous AV access. They also identified national system changes, which included reimbursement of autogenous AV access at a higher rate than prosthetic AV accesses and

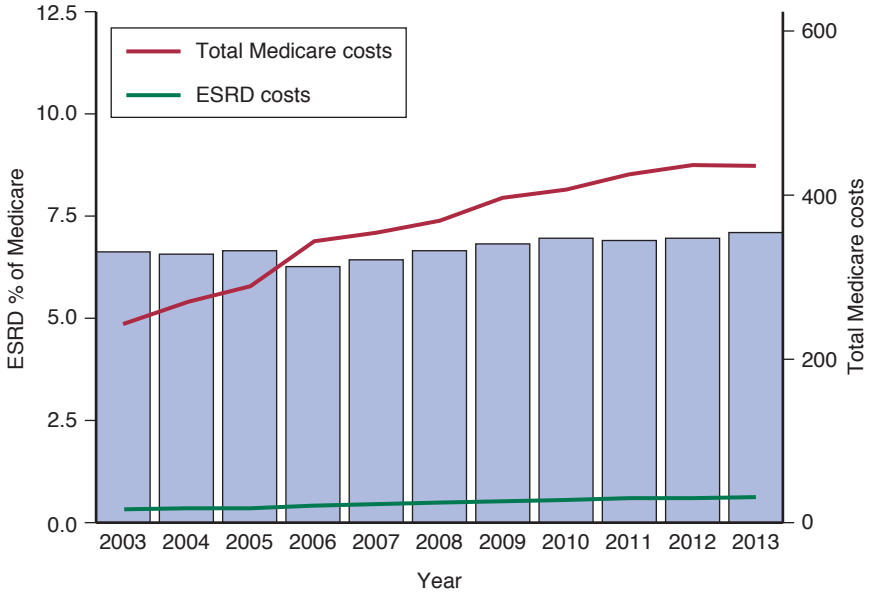

Figure 175.3 Trends in costs of the Medicare and end-stage renal disease *(ESRD)* program, 2003–2013. (Reproduced from United States Renal Data System [USRDS]. Medicare expenditures for persons with ESRD. In: USRDS 2015 annual report: Epidemiology of kidney disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD: 2015. Available at: http://www.usrds.org/2015/view/v2_11.aspx. Accessed 25 May 2016.)

catheters and reimbursement of preoperative vein mapping. As a result of their efforts, the national rate of autogenous access reached 40% prevalence by August 2005, followed by a steady-state incline until 2011, when it reached a plateau of about 60%.[4]

Recognizing that autogenous access may not be feasible in all dialysis patients, the FFBI recently transitioned to the Fistula First Catheter Last Workgroup Coalition (FFCL) to further focus on the development of tools and resources to help dialysis facilities and clinicians increase permanent access rates while also reducing catheter use. The FFCL coalition's current goals are to increase the utilization of autogenous AV access in all appropriate hemodialysis patients to 68%, decrease the use of long-term catheters for greater than 90 days to less than 10%, and to engage patients and all providers to work together to achieve these goals. These new goals emphasize decreasing the use of long-term catheters by changing the focus of dialysis access away from autogenous access in all patients to autogenous access in all appropriate patients. This allows the access surgeon to evaluate and act based on the individual needs of the patient; if the surgeon feels that autogenous access is not achievable or would unreasonably prolong the use of a long-term catheter, a prosthetic access should be placed.[5]

The Society for Vascular Surgery (SVS), recognizing the effect of decision making by the individual access surgeon on the successful construction of AV access, has sponsored two further initiatives. First, in 2002, the Committee on Reporting Standards published the recommended standards for reports dealing with AV hemodialysis access. The purpose of this document was to provide standardized definitions related to AV access procedures and to recommend reporting standards for patency and complications in order to permit meaningful comparisons among AV access procedures.[6] This was followed in 2008 by the clinical practice guidelines for the surgical placement and maintenance of AV hemodialysis access. After a multispecialty panel performed a systematic review of the literature, guideline recommendations were made in seven areas: (1) timing of referral to access surgeons, (2) operative strategies to maximize the placement of autogenous AV accesses, (3) first choice for the autogenous access, (4) choice of AV access when a patient is not a suitable candidate for a forearm autogenous access, (5) the role of monitoring and surveillance in AV access management, (6) conversion of a prosthetic AV access to a secondary autogenous AV access, and (7) management of the nonfunctional or failed AV access.[7] This chapter focuses on strategies to maximize successful access placement, whether autogenous or prosthetic.

TIMING OF REFERRAL

The NKF-KDOQI and the SVS Clinical Practice Guidelines both recommend that patients be referred to a vascular access surgeon for permanent dialysis access when their creatinine clearance is less than 25 mL/min. Once preoperative evaluation is completed, if the patient is felt to be an adequate candidate for autogenous AV access, the access should be constructed as soon as possible to give it adequate time to mature; ideally this should be greater than 6 months before the anticipated need for dialysis. However, since prosthetic access patency is limited by the duration of access placement, not time of access use, if a patient is felt to require a prosthetic access, the access placement should be delayed until 3 to 6 weeks prior to the initiation of dialysis.[3,7]

Early access placement, greater than 4 months before the initiation of dialysis, has been shown to decrease the risk of sepsis (relative risk [RR] 0.57) and death (RR 0.76) when compared with late access creation (less than 1 month before the initiation of dialysis or after initiation of dialysis), primarily by reducing the use of central venous hemodialysis catheters.[8] Despite this, nationwide data suggest that only 25% of hemodialysis patients initiate dialysis with permanent AV access. Lenz et al. reported

that 93% of patients in an academic medical center with a well-established dialysis unit and vascular surgery service initiated hemodialysis with the use of a central venous catheter. In a retrospective review, they identified the reason as inadequate predialysis care in 45% of patients, acute illness with failure to recover from an episode of acute renal failure in 31% of patients, and noncompliance with medical and surgical appointments in 17% of patients.[9] These studies stress the need for early referral and education for predialysis patients to prevent the use of central venous catheters and their subsequent complications.[8,9]

PREOPERATIVE EVALUATION

Thorough preoperative evaluation of the arterial and venous system is imperative if long-term, permanent AV access is to be placed successfully.

History and Physical Examination

A thorough history should include the dominant extremity, recent history of peripheral intravenous lines, sites of indwelling or previous central lines including pacemakers and defibrillators, all previous access procedures, any history of trauma or previous nonaccess surgery to the extremity, all comorbid conditions, and current medications. On physical examination, the brachial, radial, and ulnar arteries should be evaluated for compressibility and equality bilaterally. An Allen test should be performed to evaluate palmar arch patency. The superficial venous system should be evaluated with and without a venous pressure tourniquet in place, examining for distensibility and interruptions. The arm should be examined for prominent venous collaterals and edema, which may be signs of central venous stenosis.[3,7]

Medical Assessment

Multiple patient factors may play a role in AV access patency; these include age, sex, diabetes mellitus (DM), peripheral vascular disease (PVD), smoking, obesity, hyperparathyroidism (hPTH), anemia, and medications. The literature is split on many of these factors; however, best evidence to date suggests that all except sex and obesity have a negative impact on access patency rates (Table 175.1).[10] In the following paragraphs we review further some of the more studied factors that appear to negatively impact patency further.

Age

Published reports regarding age and its effect on AV access patency are mostly retrospective observational studies with conflicting results. However, these reports, along with a known shorter life expectancy for patients with ESRD, have raised the following question: Should proximal or prosthetic AV access be the first-line approaches in the elderly? To answer this, Lazarides et al. performed a meta-analysis, 13 studies in all, of dialysis outcomes in elderly patients (age range: 50 to 70 years), including studies that compared subgroups of elderly and nonelderly patients as well as forearm and upper arm accesses.

TABLE 175.1 Medical Factors Affecting Arteriovenous Access Patency

Factor	Level of Best Evidence	Best Evidence Suggests Effect of Patency
Age	Meta-analysis	Yes
Gender	Meta-analysis	No
Diabetes mellitus	Prospective series	Yes
Atherosclerosis	Prospective series	Yes
Smoking	Prospective series	Yes
Obesity	Prospective series	No
Parathyroid hormone	Prospective series	Yes
Anemia	Prospective series	Yes
Medications	Systematic review	Yes

They found a statistically significant higher rate of autogenous radial-cephalic direct AV access primary (OR 1.8), 1-year (OR 1.5), and 2-year (OR 1.4) failure in elderly patients compared with the nonelderly. They also found a statistically significant higher rate of autogenous brachial-cephalic direct upper arm access patency (RR 0.1) compared with autogenous radial-cephalic direct forearm access. They noted no statistical differences with the use of prosthetic access.[11] Based on these data, it is reasonable to recommend autogenous upper arm brachial-cephalic fistula or prosthetic access over distal radial-cephalic fistula.

Diabetes Mellitus

Published reports are mostly retrospective observational studies with similar results, stating that DM has a negative impact on AV access patency. These reports, along with a known increase in arterial calcification and atherosclerosis, have raised the following question: Should proximal or prosthetic AV access be the first-line approach in diabetics? To further evaluate the impact that DM has on the vasculature, Sedlack et al. compared preoperative noninvasive vascular mapping between diabetic and nondiabetic patients. They noted an increased number of arterial calcifications in diabetics but no difference in arterial diameter or the ability to place autogenous AV access; they did not evaluate long-term outcomes.[12] Looking at long-term outcomes in diabetic patients, Konner et al. noted an increased risk of thrombosis (0.03/patient year [PY] in nondiabetics vs. 0.07/PY in diabetics) and an increased risk of arterial steal (0.6/PY in nondiabetics vs. 7.0/PY in diabetics).[13] Further studies are needed in this area; however, given the current literature, surgeons should take inflow in diabetics as distal as possible to decrease the risk of arterial steal.

Smoking

Published reports are retrospective observational studies with similar results, stating that cigarette smoking significantly increases early and late failure of AV access.[14] ESRD patients

should be referred to a tobacco cessation program before placement of first-time or any new AV access.

Medications

Published reports are mostly observational studies that have yielded conflicting results. One of the largest studies to date, the Dialysis Outcomes and Practice Patterns Study (DOPPS), noted an improvement of autogenous access secondary patency (RR 0.56) with angiotensin-converting enzyme (ACE) inhibitors, an improved prosthetic AV access primary patency (RR 0.86) with calcium channel blockers, an improved prosthetic AV access secondary patency (RR 0.70) with aspirin, and a decreased prosthetic AV access primary patency (RR 1.33) with warfarin.[15] A study sponsored by the USRDS showed a decreased AV access patency with antiplatelet agents including ticlopidine, dipyridamole, and aspirin.[16] Others have shown that angiotensin receptor blockers (ARBs) combined with antiplatelet agents increased autogenous AV access patency by 84%, whereas ARBs alone improved prosthetic AV access patency by 59%.[17] At the present time there is a lack of consensus regarding the role of specific medications in improving AV access patency.

Arterial Assessment

If any abnormality is noted on the clinical arterial examination (absent or reduced pulse, positive Allen test, or asymmetrical arm pressures), the patient should be further evaluated with segmental pressures and duplex ultrasound scanning and/or pulse volume recordings (PVRs). For optimal outcome, no pressure gradient should be noted between the bilateral upper extremities, arterial diameter should be greater than or equal to 2.0 mm throughout the extremity, and a patent palmer arch should be present.[18] Any abnormality noted on noninvasive testing should prompt alternate site selection or be further evaluated with an arteriogram, which gives the surgeon the ability to both identify and possibly treat an arterial inflow stenosis. In patients nearing dialysis, the risk of contrast arteriography should be weighed against the need for access to mature before beginning dialysis. Renal protective agents should be used preceding arteriography; these include intravenous fluids, *N*-acetylcysteine, and sodium bicarbonate.[19-22]

Venous Assessment

If superficial veins cannot be visualized with a venous pressure tourniquet in place or any abnormality is noted on the superficial venous examination, the patient should be further evaluated with superficial venous duplex ultrasound vein mapping. Using venous duplex imaging, superficial veins should be examined for diameter, distensibility, and continuity. Minimal diameter for use of the forearm has been reported as low as 2.0 mm by Mendes et al., who noted a successful early maturation rate of 76%.[23] Using a minimal vein diameter of 2.5 mm, Silva et al. were able to perform 63% autogenous access with a 92% early maturation rate and 83% 1-year patency rate.[18] Using a minimal vein diameter of 3.0 mm, Huber et al. were able to perform 90% autogenous access with an 84% early maturation rate.[24]

Central venous stenosis should be suspected if there are any prominent venous collaterals or edema, a difference in extremity diameter, any history of previous central venous catheter placement, or multiple previous accesses in the planned extremity. If any of these abnormalities are identified, the patient should be examined first with deep venous duplex ultrasound imaging followed by venography if necessary.[3] Passman et al. compared duplex ultrasound and venography in 60 upper extremities of preoperative access patients. Five (8%) ultrasounds were nondiagnostic due to artifact from central venous catheters or incomplete visualization of the central venous system. Of the studies that were diagnostic, they noted 81% sensitivity and 97% specificity of duplex ultrasound imaging with no statistical difference as compared with venography. Venography should be performed for further evaluation and possible treatment in patients with either nondiagnostic or abnormal duplex ultrasound imaging.[25] As with arteriography, in predialysis patients the risk of contrast venography must be weighed against the need for access to mature in time for dialysis. Before venography, patients should be treated with intravenous fluids, N-acetylcysteine, and/or sodium bicarbonate.[19-22]

SELECTION OF ACCESS LOCATION

The various types of autogenous and prosthetic upper, lower, and body-wall AV access are listed in Box 175.1. In planning AV access, a few general principles apply (Fig. 175.4). For the purposes of this chapter, our focus is on upper extremity accesses. Further accesses are discussed in Chapter 176 .

1. Due to easier accessibility and lower infection rates, upper extremity access sites are used first, with the nondominant arm given preference over the dominant arm.
2. AV accesses are placed as far distally in the extremity as possible to preserve proximal sites for future accesses.
3. As long as the patient is deemed appropriate, given their superior patency rates and lower complication rates, autogenous AV accesses should always be attempted before a prosthetic AV access.
4. These autogenous access configurations should include, in order of preference, direct AV anastomosis, venous transpositions, and venous translocations.

Ultimately the following question remains: How does the surgeon decide who is an appropriate patient for autogenous access and who is not and should go straight to a prosthetic access? Multiple factors play a role in this decision, starting with the patient's medical assessment, as discussed earlier, including the patient's age, history of DM, PVD, smoking, hPTH, and anemia. Arterial and venous anatomy plays a major role in this decision and should be based on objective studies, including preoperative noninvasive duplex ultrasound and/or invasive venous and arterial imaging. The access surgeon should combine all of these factors in order to determine the feasibility of an autogenous access; the surgeon should also have a thorough discussion with the patient regarding the risks and benefits of autogenous and prosthetic access before arriving at a mutual decision.

BOX 175.1 Configurations of Arteriovenous Access

Forearm

Autogenous

- Posterior radial branch–cephalic wrist direct access (snuffbox fistula)
- Radial-cephalic wrist direct access (Brescia-Cimino-Appel fistula)
- Radial-cephalic forearm transposition
- Brachial (or proximal radial)–cephalic forearm looped transposition
- Radial-basilic forearm transposition
- Ulnar-basilic forearm transposition
- Brachial (or proximal radial)-basilic forearm looped transposition
- Radial-antecubital forearm indirect femoral vein translocation
- Brachial (or proximal radial)-antecubital forearm indirect looped femoral vein translocation
- Radial-antecubital forearm indirect saphenous vein translocation
- Brachial (or proximal radial)-antecubital forearm indirect looped saphenous vein translocation

Prosthetic

- Radial-antecubital forearm straight access
- Brachial (or proximal radial)-antecubital forearm looped access

Upper Arm

Autogenous

- Brachial (or proximal radial)–cephalic upper arm direct access
- Brachial (or proximal radial)-cephalic upper arm transposition
- Brachial (or proximal radial)-basilic upper arm transposition
- Brachial (or proximal radial)-brachial vein upper arm transposition
- Brachial (or proximal radial)-axillary (or brachial) upper arm indirect femoral vein translocation
- Brachial (or proximal radial)-axillary (or brachial) upper arm indirect saphenous vein translocation

Prosthetic

- Brachial (or proximal radial)-axillary (or brachial) upper arm straight access

Adapted from Sidawy AN, Gray R, Besarab A, et al. Recommended standards for reports dealing with arteriovenous hemodialysis accesses. *J Vasc Surg*. 2002;35:603-610.

Forearm Access

Cephalic Vein

For autogenous forearm access, use of the cephalic vein is preferred to the basilic vein secondary to its lateral location and the need for only minimal dissection. Possible sites of arterial inflow include the posterior branch of the radial artery in the "snuffbox," the trunk of the radial artery, the ulnar artery, and the brachial artery. The ulnar artery is usually not the first arterial option due to its distance from the cephalic vein. The access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to preserve more proximal sites of inflow for future accesses. Therefore in patients with an adequate posterior branch of the radial artery, an autogenous posterior radial branch–cephalic wrist direct access (snuffbox fistula) is performed (Fig. 175.5). In patients with an inadequate posterior branch of the radial artery but an adequate radial artery, an autogenous radial-cephalic wrist direct access (Brescia-Cimino-Appel fistula) is recommended. In either of these cases, if the cephalic vein is felt to be too deep, as seen in obese patients, or is not located in close proximity to the radial artery in the wrist, an autogenous radial-cephalic forearm transposition is performed (Fig. 175.6). If the radial artery is inadequate, the ulnar artery may provide an alternative distal inflow site; alternatively, the entire trunk of either the radial or the ulnar artery may provide an arterial source. If the radial and ulnar arteries are inadequate but the brachial or proximal radial arteries are adequate, an autogenous brachial (or proximal radial)-cephalic forearm looped transposition is performed.

Basilic Vein

When the cephalic vein is not felt to be adequate for an autogenous AV access, the basilic vein is the preferred alternative. Secondary to its medial location in the forearm, a transposition is always required. Possible sites of arterial inflow include the distal radial artery, the ulnar artery, the proximal radial artery, and the brachial artery. Use of the posterior branch of the radial artery is not possible secondary to the distance from the basilic vein. Similar to the cephalic vein, the AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to preserve more proximal sites of inflow for future accesses. Therefore when the radial artery is adequate, an autogenous radial-basilic forearm transposition is performed. If the radial artery is inadequate but the ulnar artery is adequate, an autogenous ulnar-basilic forearm transposition is performed. If the distal radial and ulnar arteries are inadequate, a more proximal segment may be used (autogenous proximal radial-basilic forearm looped transposition). If the radial and ulnar arteries are inadequate throughout but the brachial artery is adequate, an autogenous brachial-basilic forearm looped transposition is performed.

Alternate Vein

When the cephalic and basilic forearm veins are not felt to be adequate for autogenous AV access, translocations of the femoral and saphenous veins are appropriate alternatives. Further strategies for these complex autogenous accesses are described in Chapter 176.

Prosthetic Graft

If an adequate forearm vein is unavailable, a prosthetic AV forearm access is performed. Sources of arterial inflow include the distal or proximal radial artery or the brachial artery. Similar to autogenous access, the AV graft is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to preserve more proximal arteries for future accesses. Therefore when the distal radial artery is adequate, a prosthetic radial-antecubital forearm straight access is performed (Fig. 175.7). If the radial artery is inadequate but the brachial or proximal radial artery is adequate, a prosthetic brachial (or proximal radial)-antecubital forearm looped access is performed (Fig. 175.8A and B).

One of the interesting debates in this area is whether, after exhausting the forearm autogenous options, the surgeon should recommend a forearm prosthetic access before placing an upper arm autogenous access. As previously discussed in this chapter,

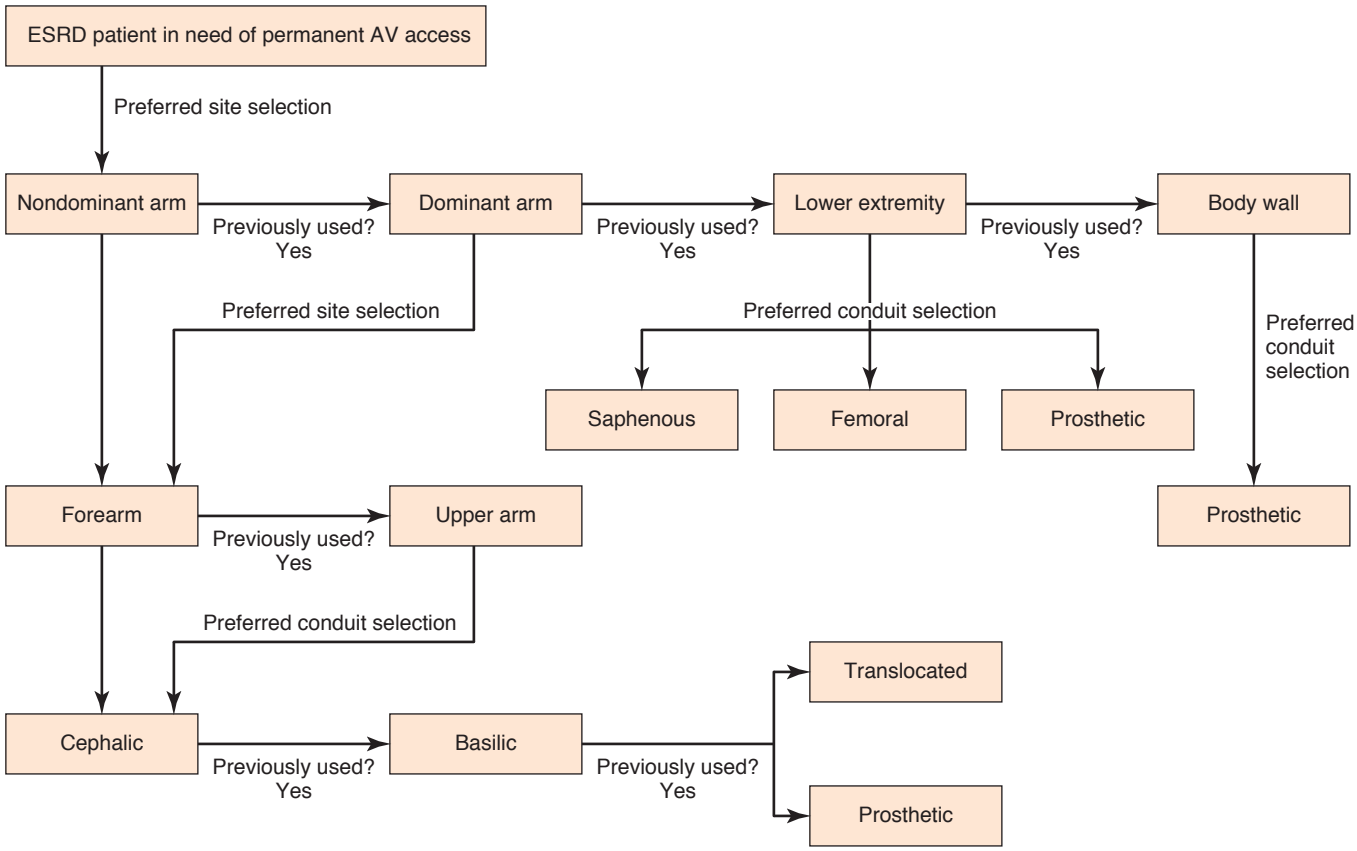

Figure 175.4 Algorithm: selection of access location. *AV,* Arteriovenous; *ESRD,* end-stage renal disease.

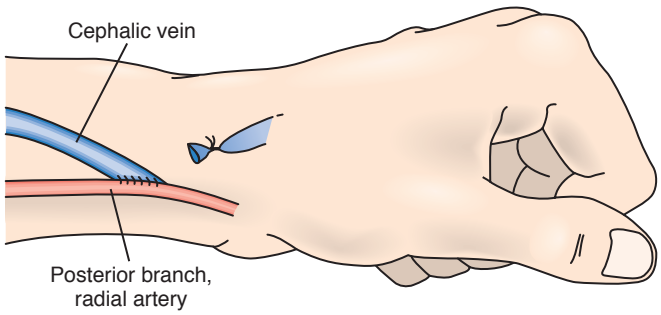

Figure 175.5 Autogenous posterior radial branch–cephalic wrist direct access (snuffbox fistula).

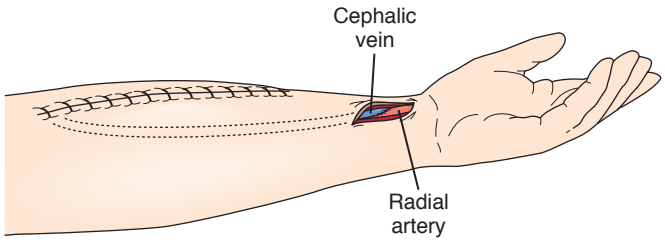

Figure 175.6 Autogenous radial-cephalic forearm transposition. (Reproduced from Silva MB, Hobson RW, Pappas PJ, et al. Vein transposition in the forearm for autogenous hemodialysis access. *J Vasc Surg*. 1997;26:981-988.)

the access surgeon should consider all of the patient and anatomic factors, particularly, the adequacy of the upper arm vein. A mutual decision should be made between the surgeon and patient after a thorough discussion about the risks and benefits of autogenous and prosthetic access. Most importantly, if a prosthetic forearm access is chosen, this should be considered a "bridge" to an autogenous upper arm access. Access surgeons should minimize the number of attempts to salvage the access with endovascular means to avoid damaging the venous outflow. A plan for eventual conversion of the forearm prosthetic access to a secondary autogenous access should be put in place; strategies include conversion of the prosthetic access mature outflow vein to an autogenous upper arm access or the identification of a new, remote site for autogenous access construction.[7]

Upper Arm Access

Cephalic Vein

When use of the forearm has been exhausted, efforts at access are directed to the upper arm. Similar to the forearm, use of the upper arm cephalic vein is preferred to the basilic vein secondary to its lateral location and need for only minimal dissection. For upper arm access, possible sites of arterial inflow include the proximal radial and brachial arteries; the AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to lower the risk of arterial steal. Therefore in patients with an adequate cephalic vein and an adequate proximal radial artery, an autogenous proximal radial-cephalic upper arm direct access is performed.

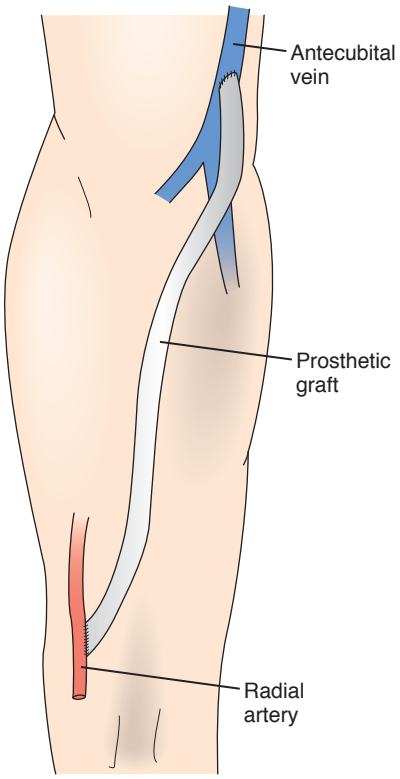

Figure 175.7 Prosthetic radial-antecubital forearm straight access.

If the proximal radial artery is inadequate and the brachial artery is adequate, an autogenous brachial-cephalic upper arm direct access is performed (Fig. 175.9). If the cephalic vein is felt to be too deep or is located far from the artery, an autogenous brachial (or proximal radial)-cephalic upper arm transposition is performed.

Basilic Vein

When the cephalic vein is felt to be inadequate for an autogenous AV access, the upper arm basilic vein is the preferred alternative. Secondary to its medial and deep location, transpositions are required for all accesses using the basilic vein. Similar to upper

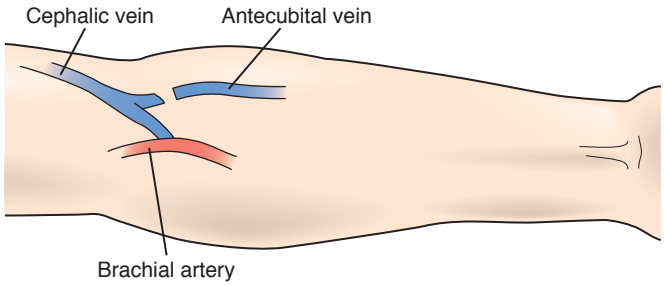

Figure 175.9 Autogenous brachial (or proximal radial)-cephalic upper arm direct access.

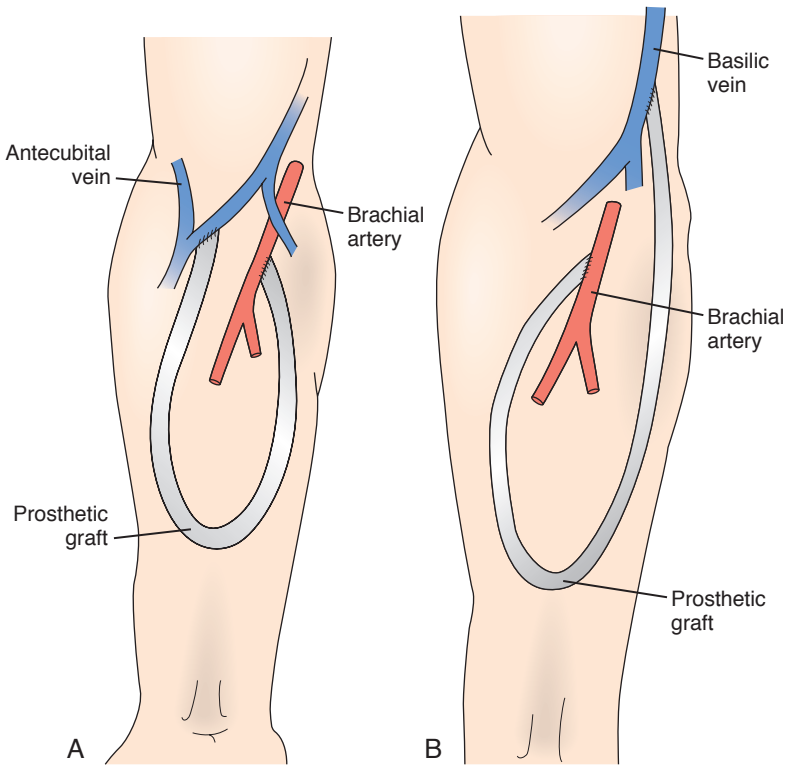

Figure 175.8 (A and B) Prosthetic brachial (or proximal radial)-antecubital forearm looped access.

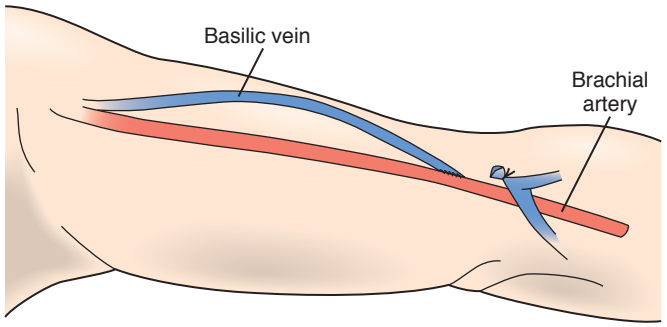

Figure 175.10 Autogenous brachial (or proximal radial)-basilic upper arm transposition.

arm cephalic vein AV accesses, possible sites of arterial inflow include the proximal radial and brachial arteries; the AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to lower the risk of arterial steal. Therefore in patients with an adequate basilic vein and an adequate proximal radial artery, an autogenous proximal radial-basilic upper arm transposition is performed. If the proximal radial artery is inadequate and the brachial artery is adequate, an autogenous brachial-basilic upper arm transposition is performed (Fig. 175.10).

Alternate Vein

When the cephalic or basilic veins are felt to be inadequate for upper arm autogenous access, brachial vein transpositions as well as femoral and saphenous vein translocations are appropriate alternatives. Further strategies for these complex autogenous accesses are described in Chapter 176 .

Prosthetic Graft

If no vein is available, an upper arm prosthetic AV access is performed. Similar to upper arm autogenous AV accesses, possible sites of arterial inflow include the proximal radial and brachial arteries; the AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to lower the risk of arterial steal. Therefore when the proximal radial artery is adequate, a prosthetic proximal radial-axillary vein (or brachial vein) upper arm straight access is performed. If the proximal radial artery is inadequate and the brachial artery is adequate a brachial-axillary vein (or brachial vein) upper arm straight access is performed (Fig. 175.11).

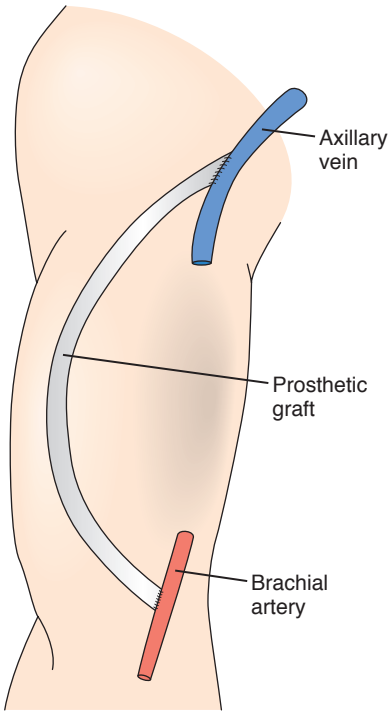

Figure 175.11 Prosthetic brachial (or proximal radial)-axillary (or brachial) upper arm straight access.

TECHNIQUE FOR PERMANENT ACCESS

Despite the multiple anatomic options for both autogenous and prosthetic AV accesses, the principles of surgical technique remain similar in all AV access procedures.

Autogenous Access

The following techniques are common to all autogenous vein accesses:

1. After identification of the vein, the distal end is transected and flushed with heparinized saline. This allows for evaluation of the caliber and extent of the vein and to identify any side branches.
2. With transposition accesses, the vein is completely dissected and mobilized, ligating all side branches, to its origin.
3. After controlling the artery, an arteriotomy of 4 to 6 mm maximal length is made. The length of the arteriotomy is limited to decrease the incidence of arterial steal.
4. The artery is flushed proximally and distally with heparinized saline to avoid thrombosis during the anastomosis.
5. The AV anastomosis is performed between the side of the artery and the end of the vein; this configuration decreases the subsequent risk of venous hypertension.
6. The AV anastomosis is performed using a 6-0 or 7-0 monofilament nonabsorbable continuous suture to avoid subsequent anastomotic dilation.
7. With nontransposed access, after completion of the anastomosis, large venous branches can be ligated through stab incisions. This encourages flow in the main venous segment, which may promote earlier maturation.

One-Stage Versus Two-Stage Transposed Access

Whether cephalic or basilic, forearm or upper arm, if autogenous AV access requires a transposition, this may be performed with either a one- or two-stage technique. The main benefit to a one-stage technique is obvious: the patient requires only one procedure and one anesthetic. However, if this access fails to mature, the patient has undergone an extensive dissection with no benefit, often leaving him or her reluctant to try again. A two-stage procedure begins with a direct anastomosis between

the intended artery and vein, followed by a 4- to 6-week waiting period to evaluate for maturity. If the vein appears to be maturing appropriately, the second stage, transposition of the vein, is performed. This requires transection of the vein just proximal to the anastomosis, followed by its mobilization and tunneling, followed by a new anastomosis in its transposed position. The benefits of the two-stage procedure are assuring that the vein will be mature and usable for hemodialysis access before performing an extensive dissection as well as easier dissection of the maturing vein during the transposition. The drawbacks again are obvious: this requires a second procedure and a second anesthetic, putting patients at increased risk of surgery.[26] Therefore we recommend performing this procedure in two stages only with small-caliber (<4 mm) veins.

Prosthetic Access

The following techniques are common to all prosthetic access:

1. The length of the arteriotomy does not have to be limited to 4 to 6 mm. The diameter of the graft will limit the incidence of arterial steal.
2. The artery is flushed proximally and distally with heparinized saline to avoid thrombosis during the anastomosis.
3. A 6-mm polytetrafluoroethylene (PTFE) prosthetic graft is used for conduit (see considerations further on).
4. The anastomoses are performed using a 6-0 or 7-0 monofilament nonabsorbable suture in a continuous manner.
5. Careful attention to sterile technique is paramount to avoid graft infections.

Choice of Prosthetic Material

A standard-wall 6-mm expanded PTFE (ePTFE) material is our choice for prosthetic access grafts. Variations in the standard ePTFE graft include thin-walled, extended stretch, external rings, various tapered configurations, and heparin coating. These are all meant to ease handling, provide external support, and improve patency rates. To date, there is only minimal evidence that any of these variations improve long-term results; therefore, use of these variations remains a matter of surgeon preference.[27,28]

Standard-wall grafts can be cannulated as early as 2 weeks; to improve this time further there has been recent development of early cannulation prosthetic grafts (Acuseal, W.L. Gore, Flagstaff, Arizona; Flixene Maquet-Atrium Medical, Rastatt Germany; and Vectra Bard, Covington, Georgia). They are generally constructed in three layers, with an elastomeric membrane sandwiched in between two layers of ePTFE material. This configuration hinders suture-line and dialysis needle bleeding, allowing for early cannulation reportedly as soon as 24 hours from implantation and thus offering the potential for either avoidance or early removal of short- and long-term dialysis catheters. Mean cannulation times have been reported in the literature from 2 to 15 days with minimal hematoma incidence; longer cannulation times were noted to be due to either surgeon or patient preference. Similar to other variations of prosthetic accesses, there is minimal evidence that this variation improves long-term results. Therefore use of this variation remains a matter of surgeon preference.[29-32]

POSTOPERATIVE FOLLOW-UP

From the time of its placement, autogenous AV access should be mature and ready for cannulation 12 weeks postoperatively and prosthetic AV access should be mature and ready for cannulation as early as 2 weeks postoperatively. If any access is noted to be failing to mature, it should be further examined with duplex ultrasound followed by venography if further information is necessary. Secondary procedures include open surgical procedures such as vein patches, interposition vein grafts, vein transposition to proximal arteries, branch ligations, vein superficialization, and endovascular procedures such as arterial and venous angioplasties. McLafferty et al. were able to identify treatable problems with 69% of failing autogenous accesses and successfully salvage the access to functional maturation in 83%.[33] Similarly, Berman et al. demonstrated an overall 10% improvement in achieving a successful autogenous AV access using close follow-up and secondary procedures.[34]

Despite the multitude of secondary procedures available, there are limited options for the treatment of generalized small-caliber veins that fail to dilate after AV access creation. Recent reports have discussed the use of balloon-assisted maturation (BAM); this is a procedure where repeated long-segment angioplasties are performed on the suboptimal outflow vein that is failing to dilate. By disrupting the venous wall, these serial angioplasties essentially transform the outflow vein into a larger-diameter "collagen tube."[35] Using this technique, Miller et al. reported successful maturation in 118 of 122 patients requiring an average of 2.6 procedures, with 15% 1-year primary and 77% 1-year secondary patency rates.[36] Similarly, DeMarco Garcia et al. reported an 85% maturation success rate and an 80% 1-year secondary patency rate.[37] Further reports have discussed the use of BAM at the time of AV access placement for outflow veins measuring less than 2 mm in diameter. Using this technique, Veroux et al. reported a mean fistula maturation time of 32 days, with a 5.2% reintervention rate over 7-month follow-up.[38] Challenges to both of these techniques include essentially converting an autogenous access into a prosthetic with subsequent similar long-term patency and reintervention rates of prosthetic access and the economics associated with repeated multiple procedures to achieve AV access success.[35]

LONG-TERM FOLLOW-UP

After initial maturation, the AV access should be monitored routinely while the patient is on dialysis. The preferred method of monitoring is a monthly determination of access flow by ultrasound dilution, conductance dilution, thermal dilution, or Doppler technique. Access flow less than 600 mL/min or access flow less than 1000 mL/min, which has decreased by 25% over 4 months, should be further evaluated with duplex ultrasound, followed by fistulogram if further information is necessary. Another method of access monitoring, more useful with prosthetic access, is measurement of static venous dialysis pressures; a graft-arterial ratio of greater than 0.75, graft-venous ratio of less than 0.5, or a progressive increase in the venous or arterial segment of more than 0.25 should be further evaluated

with duplex ultrasound followed by fistulogram if further information is necessary.[3,7] Measurements of dynamic venous pressures have been found to be relatively poor markers of autogenous or prosthetic access function. Other acceptable methods of access surveillance include measurement of prepump arterial dialysis pressure, measurement of access recirculation using urea concentrations or dilution techniques, evaluation of physical findings such as arm edema, altered characteristics of access thrill, notation of prolonged bleeding after needle removal, and duplex surveillance. Any abnormalities noted on fistulogram should be treated prophylactically with secondary procedures to prevent access failure.[3,7]

RESULTS

In order to accurately compare AV access procedures, standard definitions regarding patency are necessary and have been defined and published by the Committee on Reporting Standards of the SVS. To review, an AV access is functional only if it can deliver a flow rate of 350 to 400 mL/min without access recirculation to maintain a dialysis treatment time of less than 4 hours. Primary patency is the interval between the time of access placement and any intervention designed to maintain or reestablish patency, access thrombosis, or the time of measurement of patency. Assisted primary patency is the interval between the time of access placement and access thrombosis or the time of measurement of patency, including any intervening surgical or endovascular manipulation. Secondary patency is the interval between the time of access placement and access thrombosis, access abandonment, or the time of measurement of patency, including any intervening surgical or endovascular manipulations designed to reestablish functionality after access thrombosis.[6]

Using these definitions, autogenous AV access has consistently been shown to have excellent primary and secondary patency rates when compared with prosthetic AV access (Fig. 175.12).

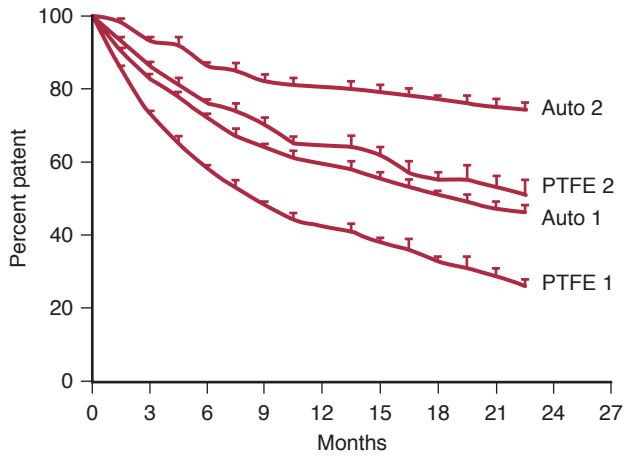

Figure 175.12 Primary and secondary patency rates of autogenous and prosthetic arteriovenous accesses. *PTFE,* Polytetrafluoroethylene. (Reproduced from Huber TS, Carter JW, Carter RL, Seeger JM. Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic review. *J Vas Surg.* 2003;38(5):1005-1011.)

One-year primary patency rates of autogenous AV access range from 43% to 85%[39-46] and 2-year primary patency rates range from 40% to 69%.[40,43,47,48] In comparison, 1-year primary patency rates of prosthetic AV access range from 40% to 54%[39,40,45,46] and 2-year primary patency rates range from 18% to 30%.[40,47,49] Similarly, secondary patency rates are superior in autogenous access, ranging from 46% to 90%[39,40,43-45] at 1 year and from 62% to 75%[40,47-49] at 2 years compared with prosthetic access, which ranges from 59% to 65%[39,40,43] at 1 year and from 40% to 60% at 2 years.[40,47,49] Also of note, in order to maintain these secondary patency rates, prosthetic AV access requires a higher number of interventions than autogenous AV access. To illustrate further the superior patency rates of autogenous access, Huber et al. performed a meta-analysis of the published literature from 1966 to 2001 and showed that primary patency rates for autogenous accesses were 72% at 6 months and 51% at 18 months, with corresponding primary patency rates for prosthetic AV access of 58% and 33%, respectively. Secondary patency rates for autogenous accesses were 86% at 6 months and 77% at 18 months with a corresponding secondary patency for prosthetic AV access of 75% and 55% (see Fig. 72.10), respectively.[40] These superior patency rates of autogenous access include basilic vein transpositions, which have demonstrated 1-year primary patency rates from 35% to 76%[39,42,44,50,51] and secondary patency rates from 47% to 90%, respectively.[39,44,50] Use of a two-stage technique for smaller-diameter (2.5 to 4.0 mm) basilic veins have demonstrated similar 1-year primary and secondary patency rates of 46%[52] and 84% to 96%, respectively.[53,54] These studies demonstrate that the use of the basilic vein in either a one- or two-stage procedure is a preferred alternative to prosthetic AV access when direct access is not available.

A common tradeoff for the higher long-term patency rates associated with autogenous AV access is higher primary failure rates due to failure of access maturation or primary thrombosis. Initial success rates leading to a functional AV access range from 55% to 97%.[41-44,47] These poor maturation rates do appear to correspond to the increasing use of small and suboptimal veins for autogenous access. This was demonstrated by Patel et al., who demonstrated that the use of preoperative duplex vein mapping and venography in the construction of autogenous access increased from 61% to 73%, with a corresponding decline in the functional maturation rate from 73% to 57%.[54]

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The United States Renal Data System (USRDS) is a national data system that collects, analyzes, and distributes about ESRD in the United States.

U.S. Renal Data System. USRDS 2015 Annual Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, Bethesda, MD: 2015. http://www.usrds.org.

NKF-K/DOQI Clinical Practice Guidelines originally published in 1997 and most recently updated in 2015 were published in an effort to increase autogenous arteriovenous access to 50% in all new ESRD patients and 40% overall prevalence of all ESRD patients. http://wwwkidney.org/professionals/KDOQI/guidelines.cfm.

Fistula First Catheter Last (FFCL) coalition's current goals are to increase autogenous AV access utilization in all appropriate hemodialysis patients to 68%, decrease the use of long-term catheters greater than 90 days to 10%, and to engage patients and providers to work together to achieve these goals. http://esrdncc.org/ffcl/.

The Committee on Reporting Standard of the Society for Vascular Surgery published recommended standards for reports dealing with arteriovenous access in order to standardize definitions related to access procedures and provide more meaningful comparisons.

Huber TS, Carter JW, Carter RL, Seeger JM. Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses:a systematic review. *J Vas Surg*. 2003;38(5):1005–1011.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 176

Hemodialysis Access: Complex

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Over the past decade, significant improvements have been made in quality of care and life expectancy for patients on hemodialysis. Consequently it is not uncommon for the surgeon to be confronted with patients who have "outlived" their arteriovenous (AV) access options in the upper extremities. In one study, nearly 7% of access placements were located at a site other than the upper extremity.[1] For many of these patients, quality of life and long-term survival depend primarily on the surgeon's ability to provide a functional and durable AV access. To meet this challenge, the access surgeon must have a number of complex vascular access procedures in his or her surgical armamentarium and must be aware of the advantages and disadvantages of each.

What is apparent from the available literature and our own anecdotal experience is that these complex access procedures are associated with a higher complication rate compared with AV access procedures of the upper extremity, and the management of these complications is generally more challenging. Although one might be tempted to avoid complex vascular access procedures by simply placing a tunneled dialysis catheter, the significant complications associated with chronic dialysis via a catheter are well established.[2–4] The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for vascular access recommend the use of a dialysis catheter only as a bridge to AV access placement or in patients with an extremely limited life expectancy.[5] Despite the challenges of complex AV access placement and the associated complications, their placement is usually justified and preferable to the use of a tunneled dialysis catheter.

GENERAL PRINCIPLES

In facing a complex access situation, the surgeon must obtain a complete access history and delineate the causes of prior failures. A careful investigation of the vascular anatomy is important to identify arterial or venous pathology that may affect access outcome. Although noninvasive vascular testing is useful, it may provide insufficient anatomic information on patients who have had multiple access procedures; therefore, contrast angiography and venography are often necessary. Only after a complete understanding of the history and anatomy can the surgeon consider all access options and create a long-term access strategy for the patient.

Abstract

When significant improvements in life expectancy and quality of life have been made in patients on hemodialysis, it is not uncommon for surgeons to be confronted with patients who have "outlived" their arteriovenous (AV) access options in the upper extremities . To meet this challenge, the access surgeon must have a number of complex vascular access procedures in his or her surgical armamentarium and must be aware of the advantages and disadvantages of each. This chapter discusses options and techniques for complex hemodialysis access placement including venous translocation and transposition, chest wall and lower extremity access placement, as well as newer technologies and techniques.

Keywords

complex access
hemodialysis
lower extremity dialysis access

Avoiding Complex Access

As noted earlier, the complication rate of AV access procedures of the lower extremity, chest wall, and other "exotic" access sites is high, and these complications are difficult to manage. Therefore one should ensure that alternatives in the upper extremity do not exist before resorting to these locations. Even though a patient has had multiple failed AV accesses in an extremity, a venogram may reveal an alternative vein, such as a paired brachial vein or a patent cephalic vein in the deltopectoral groove that can provide venous outflow for an additional access procedure in the extremity. Such options should be used before moving to sites outside the upper extremity (Fig. 176.1). If a central venous stenosis is present and the vessels in the upper extremity appear adequate for AV access placement, the surgeon should consider angioplasty and/or stenting of the central vein stenosis and then placement of an upper extremity access rather than proceeding with a complex access elsewhere. Although the primary patency of percutaneous central vein angioplasty is only 29% at 12 months, remedial angioplasty procedures either alone or with a stent are generally easy to perform and can extend the 12-month patency to more than 70% (Fig. 176.2).[6]

Selection of a Complex Access Site

Although algorithms have been developed that define a general order of preference for access placement in the upper extremity, the development of a similar algorithm for complex access placement is problematic, given the dearth of evidence-based literature related to these procedures. It is possible, however, to provide broad recommendations regarding the clinical situations in which a particular complex AV access procedure is most helpful and those in which it should be avoided. These recommendations are outlined in Table 176.1.

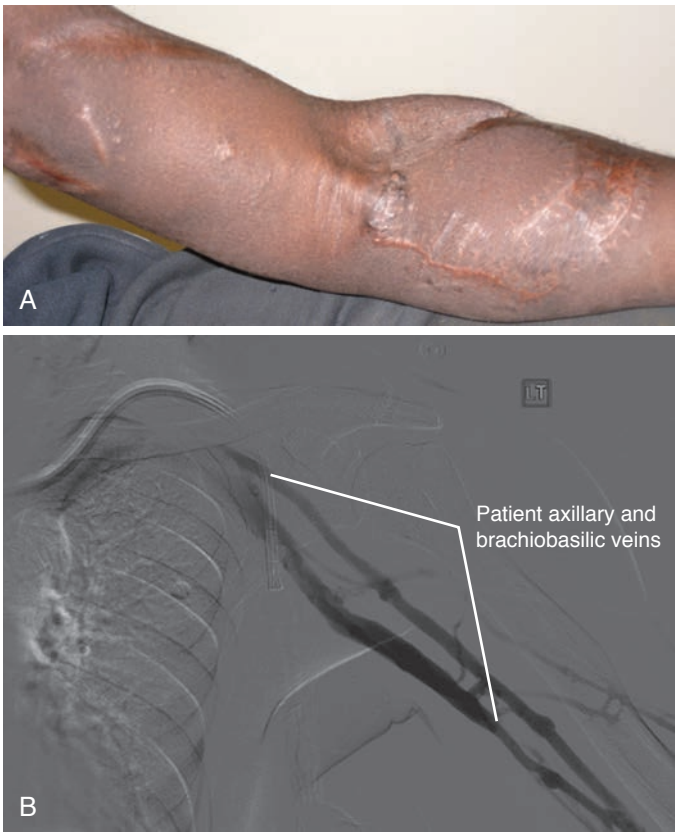

Figure 176.1 (A) Patient with failed prosthetic arteriovenous (AV) accesses in the left forearm and upper arm is referred for the establishment of a new access. (B) A venogram was obtained to determine whether any alternative to a "complex" access was available in the left upper extremity. Despite the two previous upper extremity AV access procedures, the brachiobasilic, axillary, and central veins were widely patent. A successful brachiobasilic transposition was performed.

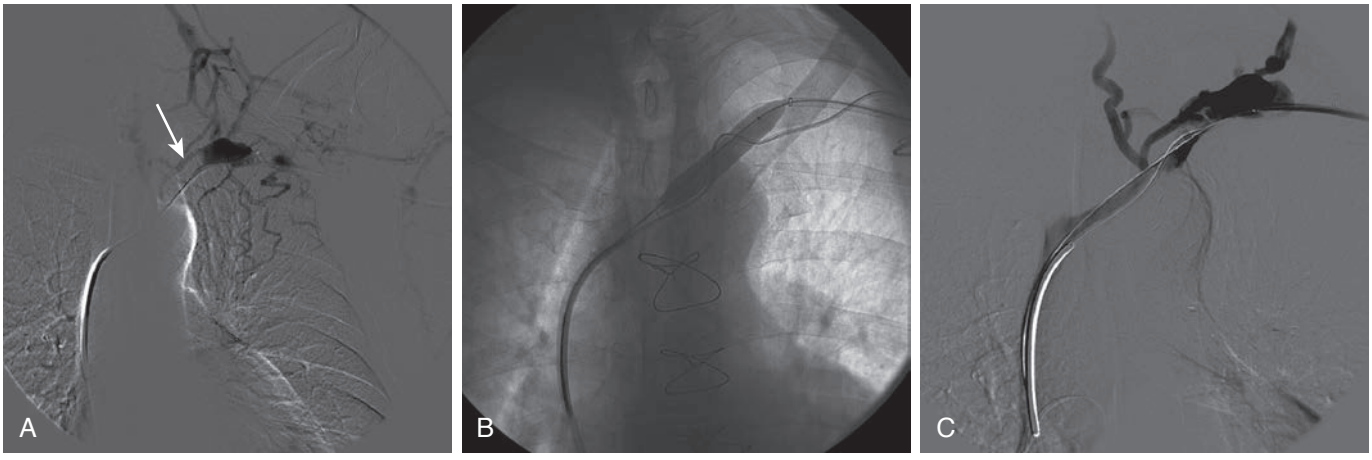

Figure 176.2 (A) Venography of the left upper extremity in a patient with an autogenous brachiocephalic arteriovenous access and symptoms of venous hypertension demonstrates chronic occlusion of the subclavian vein *(arrow)*. (B) The subclavian vein occlusion was crossed with a wire, and angioplasty was successfully performed with a high-pressure balloon. (C) Completion venography demonstrating patency of the central veins.

TABLE 176.1 Major Complex Access Procedures: Indications, Relative Contraindications, and Anatomic Requirements

Access Procedure	Specific Anatomic Requirements	Ideal Clinical Situation	Relative Contraindications
Autogenous femoral vein transposition	Patent femoral vein >3 mm in diameter Patent, noncalcified superficial femoropopliteal artery	Pediatric or young, healthy patients Patients who are hypercoagulable with no other autogenous access options Patients at high risk for infection (poor hygiene, immunosuppressed, multiple previous access infections)	Significant obesity of the thigh Patients who are elderly or "medically fragile" Access sites for temporary catheter placement not readily available Patients at high risk for access-related ischemia of the lower extremity
Prosthetic midthigh loop femoral-femoral access Prosthetic loop femoral-femoral access	Patent femoral or common femoral vein Patent, noncalcified superficial femoral artery (midthigh access) or common femoral artery	Patients who are elderly or have significant medical comorbidities	Patients at high risk for infection (poor hygiene, immunosuppressed, multiple previous access infections) Patients who are morbidly obese
Prosthetic chest wall access	Patent axillosubclavian artery and vein Patent central vein	Patients who are morbidly obese Patients at high risk for access-related limb ischemia	Patients who are reasonable candidates for autogenous or prosthetic thigh access procedures
Tunneled dialysis catheter	Patent central vein	Patients who are "medically fragile" or have limited life expectancy (<6 mo) Patients in whom all alternative access procedures have been expended	Patients who are candidates for an alternative complex access procedure (autogenous or prosthetic thigh or chest wall access)
Hemoaccess Reliable Outflow vascular access device	Guide wire access to a patent central vein Brachial artery >3 mm	A central venous stenosis/occlusion that precludes upper extremity autogenous or prosthetic access options Patients otherwise relegated to dialysis via a tunneled dialysis catheter	Active infection Systolic blood pressure <100 mm Hg Ejection fraction <20%

AUTOGENOUS ARTERIOVENOUS ACCESS

Several techniques have been described that use the saphenous and femoral veins to create autogenous AV accesses in the upper and lower extremities. These veins can be completely mobilized and disconnected both proximally and distally to create an access at a site remote from their origin (translocation). Alternatively, the distal portion of the vein can be mobilized and tunneled superficially, leaving the central portion of the vein connected to its normal anatomic position (transposition).

Given the high infection rate associated with AV access procedures of the lower extremity, use of the saphenous vein or femoral vein translocation or transposition procedures in the thigh is theoretically appealing. However, these operations have been associated with wound complications related to vein harvest and access-related ischemia or steal syndrome; therefore, their role in AV access procedures remains undefined, and they are not included in the KDOQI clinical practice guidelines.[5]

Translocation Procedures

The autogenous brachial artery–axillary vein fistula with saphenous vein or femoropopliteal vein translocation is an alternative to thigh access for patients with poor superficial upper extremity veins who are not candidates for a traditional upper extremity autogenous access. This access may also be indicated for patients with multiple failed upper extremity prosthetic AV accesses owing to infection or unexplained thrombosis.

Saphenous Vein–Forearm Translocation

Few studies have been published evaluating saphenous vein–forearm translocation for hemodialysis access. Secondary patency rates vary widely between the studies from 50% to 96% at 1 year and 66% to 84% at 2 years.[7–10] The infection rate is low, but has been quoted as high as 4%.[8] Since patency is not clearly defined in these saphenous vein–forearm translocation reports, it is unclear whether the patency results cited in those studies refers to functional patency. The saphenous vein can be translocated as a forearm loop configuration[7] or placed in a straight configuration from the radial artery to the antecubital vein.[8]

Femoropopliteal Vein–Arm Translocation

Results

Huber et al. reported a series of 30 patients who underwent translocated femoral vein–upper arm brachial axillary access.[11] They reported primary and secondary patency rates of 67% and 100% at 18 months. Although this procedure has the potential advantages of an autogenous access, they must be

balanced against a higher incidence of wound hematomas, compartment syndrome, and access-related upper extremity ischemia. Distal revascularization–interval ligation (DRIL) was employed to treat clinically significant access-related ischemia in 27% of patients in that series. Huber's group stressed the importance of using the contralateral rather than the ipsilateral saphenous vein for the DRIL procedure to reduce the risk of limb swelling and compartment syndrome.

Arm composite autogenous vascular access (ACAVA) using the great saphenous vein and the femoral vein has also been described.[12] The rationale for this technique was to decrease the diameter of the vein at the arterial anastomosis in hopes to minimize the rate of steal syndrome. At 12 months, the secondary patency rate was 81%. Of note, one patient developed steal syndrome.

Technique

Before harvesting the femoral vein, the surgeon must ensure that the patient has adequate arterial circulation to heal wounds from the vein harvest. Duplex ultrasonography of the lower extremity is necessary to confirm that the femoral vein is patent and has an adequate diameter (>6 mm).

A longitudinal skin incision is made over the brachial artery proximal to the antecubital fossa. The axillary vein is exposed through a single longitudinal incision in the axilla. To expose the femoral vein, an incision is made in the groin and extended distally along the medial border of the sartorius muscle. The vein is mobilized from the mid–popliteal fossa to the common femoral vein. Tributaries are ligated and divided. It is important to preserve the profunda vein to reduce the symptoms related to outflow obstruction. The reversed vein is connected to the brachial artery and axillary vein (Fig. 176.3). A closed suction drain is placed in the thigh wound, and the incisions are closed in layers.

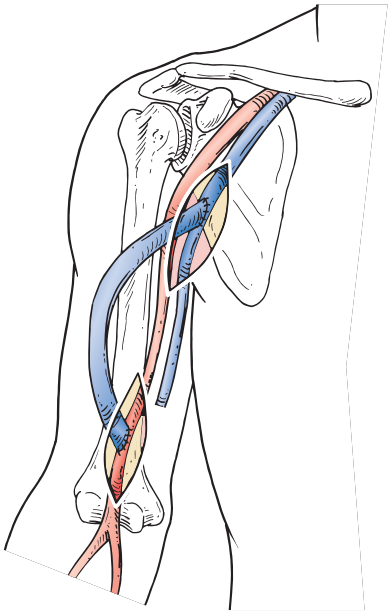

Figure 176.3 Brachioaxillary arteriovenous access using the reversed translocated femoral vein.

Transposition Procedures

Brachial Vein Transposition

Results

In 2004, Bazan and Schanzer reported two cases of autogenous brachial vein transposition in patients with inadequate superficial upper extremity veins for autogenous AV access creation.[13] No manifestations of venous hypertension occurred in either patient. After 1 year, both accesses were functional. Other series report secondary patency rates from 40% to 92% at 1 year. This procedure can be done as a single stage transposition[14] or with a two-stage technique.[15] One published series reported a 2-year patency of 55%.[16]

Technique

Although this technique has been described as a single-stage procedure, most reports recommend that brachial vein transposition be performed as a two-stage procedure whereby the AV anastomosis is created at the first stage, followed 6 weeks later by vein transposition. One-stage procedures are considered only in cases in which the brachial vein exceeds 4 mm in diameter. The first stage of the procedure involves making a longitudinal incision over the brachial pulse in the antecubital fossa in order to expose both the brachial artery and vein. When multiple brachial veins are present, the largest vein is used for the AV anastomosis. Use of the proximal radial artery, rather than the brachial artery, as the site for the AV anastomosis may reduce the risk of access-related limb ischemia. An end-to-side vein-to-artery anastomosis is performed using a running 6-0 polypropylene suture. The second stage is performed 4 to 6 weeks after the first to allow the vein wall to arterialize, thereby facilitating its mobilization. A longitudinal incision is made over the course of the brachial artery and vein in the upper arm to expose the entire brachial vein length from the antecubital fossa to the axilla.

The medial antebrachial cutaneous and median nerves are adjacent to the vein and must be protected from injury. Venous tributaries are individually suture-ligated. The anterior surface of the vein is marked to prevent twisting during transposition. The vein is divided near the AV anastomosis and passed through a subcutaneous tunnel created with a tunneling device. An end-to-end anastomosis of the vein is then performed. If the vein is too short to be transposed through a separate subcutaneous tunnel, it can be simply elevated by closing the fascia and subcutaneous tissue of the wound beneath it with interrupted 3-0 absorbable suture. A running 4-0 absorbable suture is used to close the skin over the vein containing the access. The access can be cannulated once the skin incision has completely healed, usually in about 3 weeks after the second-stage procedure.

Saphenous Vein Transposition

Results

The common femoral artery–saphenous vein loop transposition was first described in a single patient by May et al. in 1969.

Based on the limited number of series[17–19] reporting the outcome of saphenous vein translocation, the following conclusions can be drawn: (1) The use of skip incisions or endoscopic techniques to harvest the saphenous vein may decrease the wound complications associated with this procedure; (2) because the great saphenous vein does not readily dilate after access creation, only veins greater than 3 mm in diameter should be used and the vein must be tunneled just beneath the dermis to allow reliable cannulation of the access; (3) cannulation of the access must be delayed at least 6 weeks postoperatively to prevent puncture-site bleeding and hematoma; (4) the procedure may not be practical for patients who are morbidly obese or those with a large redundant pannus because access cannulation may require the patient to lie in the supine position and retract the pannus to expose the access.

Alomran et al. described an innovation of the GSV AVF in the form of a semipaneled graft, which aims to overcome the poor dilation of the GSV but requires harvest its entire length. This technique is labor-intensive because it involves longitudinal venotomy and open valvulotomy of the entire GSV and the creation of panels.[20]

Technique

The saphenous vein is exposed and mobilized from the saphenofemoral junction to the knee. Mobilization of the saphenous vein can be accomplished using skip incisions over the vein or an endoscopic vein harvest technique. The saphenous vein is transected distally at the knee, leaving the saphenofemoral junction intact. The saphenous vein is tunneled to form a subcutaneous loop and anastomosed to the superficial femoral artery.

Femoral Vein Transposition

Results

The largest experience with autogenous femoral artery–femoral vein transpositions was reported by Gradman et al. in two separate series.[21,22] The initial series reported the outcome for 25 patients who underwent the procedure. Ten of the accesses were narrowed or "banded" (i.e., flow-limited) at the time of the initial procedure to prevent postoperative access-related limb ischemia. Even with banding, limb ischemia necessitating additional surgery was common, occurring in 32% of patients. The primary and secondary patency rates at 12 months were 78% and 87%, respectively. The ankle-brachial index decreased an average of 0.21.[21]

In an effort to decrease the incidence of access-related limb ischemia, Gradman modified the technique and patient selection criteria.[22] The size of the arterial anastomosis was limited by inserting a 5-mm mandrel in the beveled vein and closing the excess vein with suture. The tapered vein was then anastomosed end to side to the distal superficial femoral artery. Patients with an ankle-brachial index less than 0.85 or absent pedal pulses were excluded. Prophylactic fasciotomies were performed in patients with weak or absent pedal pulses after access creation. The secondary patency rate was 94% at 2 years. With the modification in technique and patient-selection criteria, the occurrence of limb ischemia necessitating revascularization was reduced from 32% to 0%. Other studies report primary patency of 91% at 1 year and secondary patency of 84% at 2 years.[23] Complications of this technique includes distal limb ischemia, venous hypertension requiring fasciotomies, bleeding, and high-output heart failure.[24] Therefore, caution is necessary in creating this access in patients with congestive heart failure.

Technique

A preoperative assessment of the lower extremity arterial and venous anatomy with duplex ultrasonography is necessary.

The femoral vein is exposed and mobilized as described previously. In obese patients it is often necessary to mobilize the vein to the knee to gain adequate length. It is critical to preserve the profunda vein to prevent venous hypertension and compartment syndrome. The femoral vein is ligated distally and transected. The vein is brought through a subcutaneous tunnel lateral to the vein harvest incision and anastomosed to the superficial femoral artery in the distal thigh. The distal end of the femoral vein should be tapered to 4.5 to 5 mm, as outlined earlier (Fig. 176.4A).

In cases where the patient was considered at high risk for access-related limb ischemia or if he or she was significantly obese and superficialization of the vein provided inadequate

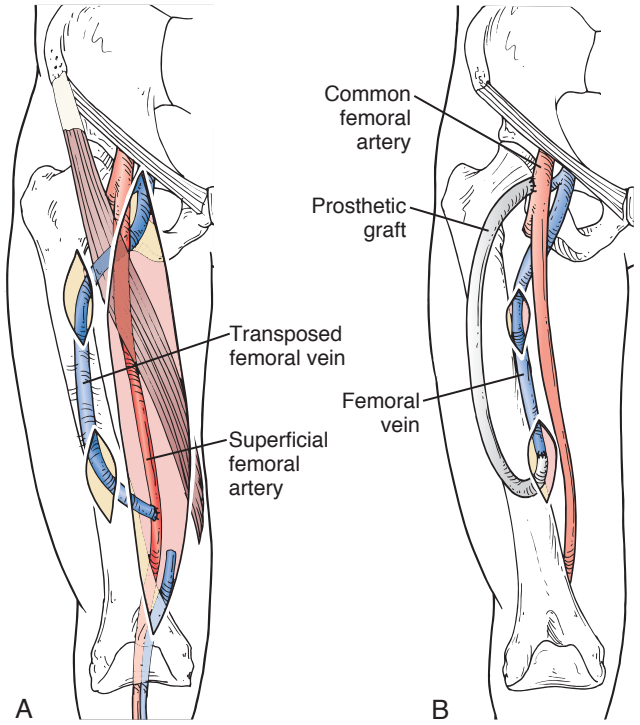

Figure 176.4 (A) Femoral vein transposition procedure. (To review the technique for exposing the femoral vein, see the section titled "Femoropopliteal Vein–Arm Translocation.") After the femoral vein has been exposed, it is transected in the popliteal fossa and mobilized to the common femoral vein, preserving the profunda vein. The femoral vein is passed posterior to the superficial femoral artery through a subcutaneous tunnel on the anterior thigh and anastomosed to the distal superficial femoral artery. (B) Composite femoral vein transposition and prosthetic access procedure. The 4- to 7-mm polytetrafluoroethylene graft is tunneled deeply to prevent needle cannulation of the prosthetic access and reduce infection. This technique is used in patients at high risk for access-related limb ischemia or in obese patients with inadequate vein length for superficialization.

length for cannulation, Gradman modified the technique by anastomosing a 4- to 7-mm polytetrafluoroethylene (PTFE) graft end to end to the femoral vein and tunneling the composite vein-graft laterally in the thigh in a loop configuration. The 4-mm end of the prosthetic graft was anastomosed end to side to the common femoral artery (Fig. 176.4B). The smaller portion of prosthetic limb of the access was tunneled deep in the subcutaneous tissue to prevent cannulation of it by dialysis technicians.

A modification of the femoral vein transposition technique has been described in patients with inadequate vein length.[25] Rather than passing the vein through a tunnel, the vein is elevated by approximating the subcutaneous tissue beneath the vein. The skin is approximated over the access using a subcuticular closure technique. After 4 to 6 weeks, the access is cannulated directly through the overlying scar.

Ankle Fistula. To date, there have only been a few case reports of ankle AV fistula formation either from the posterior tibial artery to saphenous vein or dorsalis pedis artery to saphenous vein. The procedure involves a cutdown at the ankle and end-to-side anastomosis of the greater saphenous vein to the artery. Preoperative assessment with digital pressures as well as angiogram should be performed to guide management. A patient with heavily calcified tibial vessels or absence of a palpable pulse would not be an ideal candidate for this type of fistula. Because of the paucity of literature regarding this procedure, no recommendations can be made regarding its efficacy.[26–29]

PROSTHETIC ARTERIOVENOUS ACCESS

Prosthetic Chest Wall and Cervical Arteriovenous Access

Sites for prosthetic AV access placement in the cervical region and on the chest wall are as follows: axillary artery–ipsilateral axillary vein loop access (Fig. 176.5A), axillary artery–contralateral axillary or jugular vein straight access ("necklace access"; Fig. 176.5B), and brachial artery–jugular vein straight access (see Fig. 176.5B). Although the prosthetic chest wall AV access was first described in 1978, the literature reporting the outcomes of this technique is limited primarily to case reports and small case series.[1,30–32]

Results

Necklace Access

In 1996, McCann reported outcomes for a series of 26 patients with prosthetic chest wall AV accesses.[31] He used a straight graft configuration from the axillary artery to the contralateral axillary or internal jugular vein. The secondary patency rate for AV accesses in his series was 60% at 2 years. In a more recent series, the primary and secondary patencies at 12 months were 72% and 89%, respectively.[33] All accesses in that series were monitored bimonthly with physical examination and ultrasound in order to detect access dysfunction prior to thrombosis. Because

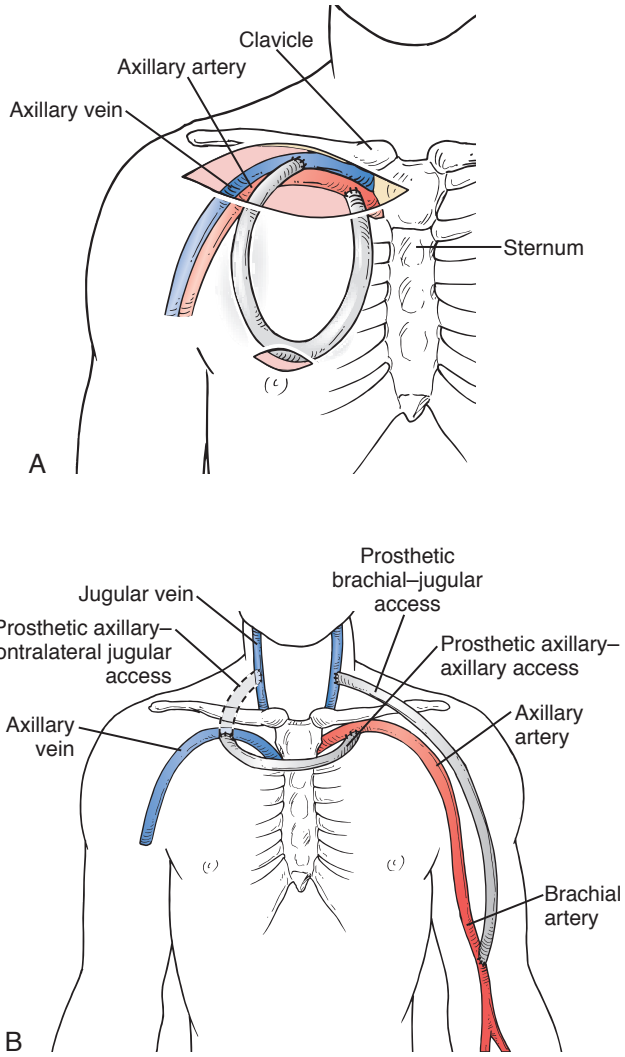

Figure 176.5 (A) Prosthetic axillary artery–axillary loop access. By situating the venous limb of the graft laterally on the chest wall and angling the venous anastomosis toward the central veins, subsequent percutaneous angioplasty is facilitated should a stenosis develop. (B) Prosthetic chest wall and cervical straight access options.

the arterial and venous anastomoses are oriented peripherally with the straight graft configuration, thrombectomy may require an incision near one or both anastomoses to effectively clear thrombus from the access and percutaneously treat an anastomotic stenosis.

Brachial to Jugular Access

Vega et al. reported a series of 51 prosthetic brachial artery–jugular vein accesses.[34] The secondary patency rate was 70% at 18 months, which is similar to the patency rate of axillary-axillary AV access. Other studies have reported a secondary patency of 93% at 1 and 2 years.[35] The prosthetic graft is tunneled over the ventral aspect of the shoulder and over the midclavicle. It is important to confirm patency of the jugular vein with a preoperative imaging study (Table 176.2).

Ipsilateral Axillary-Axillary Chest Wall Loop Access

Liechty et al. recently published their series of 67 prosthetic axillary-axillary loop access and reported primary and secondary

TABLE 176.2 Results of Cervical and Chest Wall Access

Series	Configuration	Number of Patients	SECONDARY PATENCY (%)		Infection (%)	Access-Related Ischemia (%)
			1-Year	2-Year		
McCann[31]	AA-cAV AA-cIJV	26	75	60	4	0
Jean-Baptiste et al.[32]	Loop AA-iAV	27	87	80	11	0
Kendall et al.[1]	Loop AA-iAV	34	59	37	15	0
Liechty et al.[36]	Loop AA-iAV	67	82	58	9	0
Vega et al.[34]	BA-IJV	51	74	63	2	0
Kim et al.[35]	BA-IJV	32	93	93	6	3

AA, Axillary artery; *BA*, brachial artery; *cAV*, contralateral axillary vein; *cIJV*, contralateral internal jugular vein; *iAV*, ipsilateral axillary vein; *IJV*, internal jugular vein.

patency rates of 81% and 58% at 2 years. The authors also explain that if there was central venous stenosis or occlusion, an attempt should be made to recanalize the central veins. If adequate results could not be obtained, they suggest placement of the HeRO graft (discussed later).[36] The looped graft configuration, which uses the ipsilateral axillary artery and vein, preserves the contralateral axillary vessels for future access placement. Should a subsequent stenosis develop at the venous anastomosis, this orientation toward the central veins will facilitate percutaneous intervention.

No case of access-related steal was noted in any of the three largest chest wall access series.[1,31,32] In each of these series, a number of axillary artery–axillary vein accesses were placed in patients in whom previous accesses in the ipsilateral extremity had caused hand ischemia. Based on this experience, it appears that a history of access-related hand ischemia does not preclude access placement based off the ipsilateral axillary artery.

Chest wall access appears to be associated with a lower infection rate than prosthetic AV access in the lower extremity. The infection rates range from 4% to 15%, which compares favorably with series reporting the outcome of prosthetic AV accesses based off vessels in the groin. Given the technical challenge and higher complication rate associated with prosthetic AV access placement in the thigh position in patients who are morbidly obese, chest wall access may be an attractive alternative in this situation. One potential disadvantage of chest wall access, however, is that proximal control of the axillary vessels can be extremely challenging if the graft becomes infected and needs to be excised.

Technique

Most patients considered for a chest wall or cervical AV access procedure have had previous central venous dialysis catheters and multiple upper extremity AV access procedures and interventions; therefore, it is important that patients undergo venography to confirm central venous patency before surgery. If the proximal axillary, subclavian, or brachiocephalic vein has recently undergone angioplasty or stenting, an alternative site for AV access should be considered, because recurrent stenosis following central venous intervention is common and may influence access patency.

The patient is placed in the supine position with the arm extended 90 degrees on an arm board. An incision is made one fingerbreadth below the clavicle from the sternoclavicular joint to the coracoid process. The pectoralis major muscle fibers are split. The clavipectoral fascia is divided, and the axillary vein is exposed and mobilized. The axillary artery lies beneath the vein. The artery is exposed at its exit from the thoracic outlet and mobilized to the pectoralis minor muscle. The pectoralis minor muscle is not divided. Branches of the axillary artery, such as the supreme thoracic artery, are ligated and divided as necessary to achieve adequate mobilization of the axillary artery. A 6-mm PTFE graft is tunneled in a loop configuration on the chest wall. Before tunneling of the graft, the patient is placed in the reverse Trendelenburg position to reposition the breast in a dependent location. This maneuver is performed to accurately determine graft length and is particularly important for patients with pendulous breasts. The graft is tunneled using a transverse counterincision made cephalic to the areola. The venous limb of the prosthetic graft is positioned laterally on the chest. The venous end of the graft is oriented nearly parallel to the axillary vein and directed centrally (see Fig. 176.5A). The arterial end of the graft is positioned perpendicular to the axillary artery. The graft is sewn end to side to the axillary artery and vein. Dialysis technicians are allowed to cannulate the access 2 to 3 weeks postoperatively.

Hemodialysis Reliable Outflow Vascular Access Device

For patients whose options for an upper extremity vascular access are precluded by a central venous stenosis or occlusion, the hemodialysis reliable outflow (HeRO) device (Hemosphere, Inc., Minneapolis, Minnesota) is a reasonable alternative to a lower extremity access or tunneled dialysis catheter. The HeRO device is composed of two components: a graft component, which is a 6-mm PTFE graft with a titanium coupler at one end, and a venous outflow component, which is a 19-Fr silicone catheter reinforced with a nitinol braid to prevent kinking. The graft component is anastomosed to an artery such as the brachial artery and is tunneled subcutaneously as a standard prosthetic

AV access. The venous outflow component does not require a venous anastomosis but rather is percutaneously placed into the right atrium via the internal jugular or subclavian vein. The graft and venous outflow components are tunneled subcutaneously to a counterincision in the deltopectoral groove, where they are connected with a titanium coupler (Fig. 176.6). The US Food and Drug Administration has approved the HeRO device for use in catheter-dependent patients with central venous stenosis or occlusion. Relative contraindications for HeRO device placement include a brachial artery diameter less than 3 mm, systolic blood pressure less than 100 mm Hg, active infection, and/or ejection fraction less than 20%.

Results

The initial study reporting results for the HeRO device was an industry-sponsored, multicenter, nonrandomized trial that included 36 patients who were receiving dialysis via a tunneled catheter due to a central venous stenosis or occlusion.[37] HeRO device outcomes were compared with the results of a meta-analysis of the tunneled dialysis catheter literature. The primary and secondary patency rates for the HeRO device at 8 months were 39% and 72%, respectively. A mean of 2.5 interventions were required annually to maintain patency of the HeRO device. No studies have directly compared outcomes of the HeRO device with those of other complex access procedures. The four centers involved in the original industry-sponsored trial subsequently reported their collective experience.[38] The primary and secondary patency rates at 1 year were 49% and 91%, respectively. A recent meta-analysis included 409 patients with primary and secondary patencies of 22% and 59% at 1 year. The incidence of steal syndrome was 6.3%.[39]

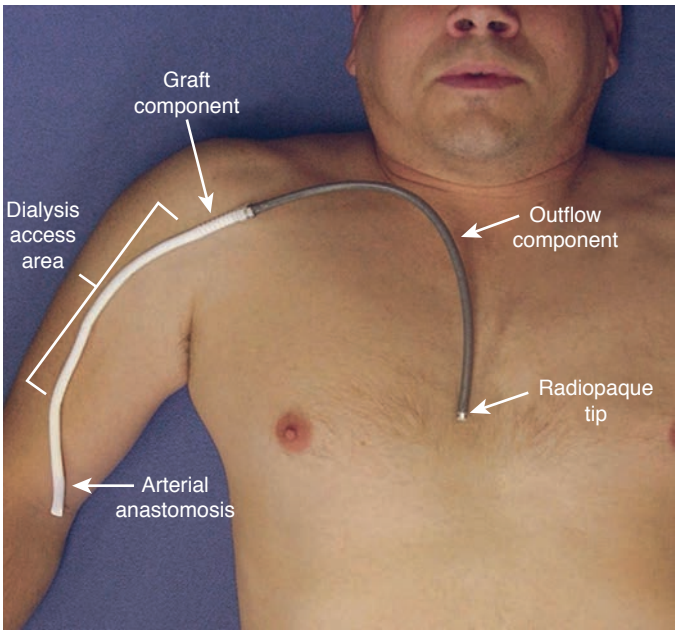

Figure 176.6 Placement of a device for hemodialysis reliable outflow (HeRO) vascular access. The silicone catheter component of the HeRO device is placed into the central veins using a similar technique to that of placing a tunneled dialysis catheter. To facilitate passage of the catheter component of the HeRO device, it may be necessary to dilate the tract with an over-the-wire angioplasty balloon. A tunneling device is used to pass the silicone catheter from the neck incision to the counterincision at the deltopectoral groove. An end-to-side anastomosis between the graft component and the distal brachial artery is performed and the graft is tunneled retrograde to the incision at the deltopectoral groove. Silicone catheter and graft components are connected using the titanium connector. (From Katzman HE, McLafferty RB, Ross JR, Glickman MH, Peden EK, Lawson JH. Initial experience and outcome of a new hemodialysis access device for catheter-dependent patients. *J Vasc Surg.* 2009;50:600-607.)

Technique

An operating room with both open surgical and endovascular intervention capabilities is required. The procedure is performed with the patient under general anesthesia. The patient is placed in the supine position with the upper extremity extended 90 degrees on an arm board and the head turned away from the side through which the HeRO device is to be implanted. An incision is made over the brachial pulse in the distal upper arm, and the brachial artery is exposed and mobilized. A counterincision for connecting the graft and catheter components is made in the deltopectoral groove. Using a tunneling device, the graft component of the HeRO device is brought through a subcutaneous tunnel from the exposed brachial artery into the counterincision. Ideally, the venous component of the HeRO device should be placed using a new venous stick under ultrasonic guidance. However, if both internal jugular and subclavian veins are occluded, an existing tunneled dialysis catheter can be wired and exchanged with the venous outflow component. To enable passage of the introducer sheath and silicone catheter through the established tract, it may be necessary to dilate the tract with an over-the-wire high-pressure angioplasty balloon. After dilation of the tract, a dilator/introducer sheath is inserted over the guidewire. The dilator and guide wire are removed and the silicone catheter is inserted using the tear-away sheath. Fluoroscopy is used to ensure correct positioning of the catheter tip in the right atrium. A tunneling device is used to pass the end of the venous component from the neck incision to the counterincision in the deltopectoral groove. After systemic heparin is administered, an end-to-side anastomosis between the graft and the distal brachial artery is performed in standard fashion. The graft and catheter are trimmed to the appropriate length at the incision in the deltopectoral groove and are then connected using the titanium connector. The clamps are removed and flow is established through the graft. A thrill should be palpable over the graft component of the access. After 2 to 4 weeks, the graft component of the device is accessed in the same manner as a conventional prosthetic AV access. Occasionally, it is necessary to exchange a functioning tunneled dialysis catheter for the venous component of the HeRO device over the wire, and there are no alternative sites to place a new tunneled catheter for dialysis while awaiting incorporation of the graft. In such cases, the author has used a Super HeRO adapter (Merit Medical, South Jordan, Utah) designed to connect an early cannulation graft, such as an Accuseal (W.L. Gore, Newark, Delaware) to the venous outflow component of the HeRO device. The graft can be cannulated immediately after HeRO placement and this eliminating the need for the placement of a tunneled dialysis catheter.

Prosthetic Lower Extremity Arteriovenous Access

The sites and graft configurations most commonly used for prosthetic access placement in the lower extremity are femoral artery–greater saphenous or femoral vein loop AV access and popliteal artery–greater saphenous or femoral vein straight AV access (Fig. 176.7).

For most surgeons, prosthetic lower extremity AV access is the preferred site once options in the upper extremity have been exhausted. Advantages of the procedure include the following: the operation is relatively simple to perform owing to the accessibility and size of the femoral vessels; patency rates for these accesses are comparable, if not superior, to those of upper extremity accesses; the surgical management of complications, such as graft infection and anastomotic stenosis, is easier than for chest wall accesses; and both of the patient's hands are free to self-cannulate the access or to perform activities during dialysis. The major disadvantages of the prosthetic lower extremity access are a higher infection rate compared with AV accesses in the upper extremity as well as an increased risk of lower extremity ischemia.

Results

A number of series reporting the outcome of prosthetic lower extremity AV accesses have been published. However, different methods of reporting outcomes prohibit the direct comparison of some results. Antoniou et al. published a meta-analysis discussing 660 upper-thigh AVGs and 60 midthigh grafts. The average secondary patency rates at 1 year were 71%, with an average 2-year secondary patency rate of 60%; there was no difference in the patency of upper-thigh grafts compared with midthigh grafts.[40] These investigators included only studies reporting outcomes using the convention established by the Committee on Reporting Standards for AV Accesses of the Society for Vascular Surgery and the American Association for Vascular Surgery (AAVS) (Table 176.3). The infection rates reported in thigh-access series ranged from 8% to 41%.[8,41–46] Two reports suggested that prosthetic thigh AV access may be associated with a high incidence of limb loss; however, neither study objectively documented access-related ischemia as the cause of limb loss.[41,47] Although other studies reported clinically significant access-related ischemia in up to 11% of cases, limb loss occurred in only 1% to 3% of cases.[42–46]

There are significant disadvantages of prosthetic femoral-femoral AV access for patients who are obese. The abdominal pannus that overlies the groin and the depth of the femoral vessels in obese patients not only make the placement procedure more technically difficult but also increase the risk of complications. The largest series of prosthetic femorofemoral AV accesses noted significantly higher rates of access reintervention in obese compared with nonobese patients.[41]

Reports have been published describing the technique and outcome in a series of patients who underwent prosthetic looped AV access based off the mid–superficial femoral artery and femoral vein in the midthigh rather than the groin (Fig. 176.8).[48,49] This modification avoids the node-bearing tissue and the panniculus and may, therefore, be associated with a lower infection rate. Furthermore, the prosthetic midthigh loop access also preserves the proximal femoral vessels for future access placement.

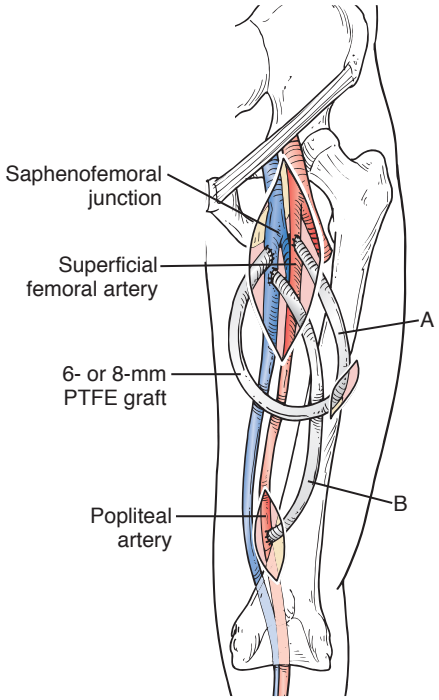

Figure 176.7 Prosthetic thigh access options: femorosaphenous loop access (A) and popliteosaphenous straight access (B). *PTFE,* Polytetrafluoroethylene.

Technique

Patients should undergo duplex ultrasonography of the femoral vessels before access placement to verify patency of the artery and vein and to determine the degree of calcification of the arterial wall. This is particularly important if a midthigh access is planned, because the superficial femoral artery is often diseased or significantly calcified. In selected cases, contrast angiography of the artery or vein may be necessary.

For a proximal loop graft, the femoral artery and great saphenous vein are exposed using a single longitudinal groin incision positioned over the femoral pulse. The proximal superficial femoral artery and greater saphenous vein near the saphenofemoral junction are mobilized for a distance of 3 to 4 cm. The superficial femoral artery is the preferred site for arterial inflow, but the common femoral artery can be used. The greater saphenous, femoral, or common femoral vein can be used as the site for the venous anastomosis. The same tunneling technique described for prosthetic forearm loop AV access is used for the placement of a prosthetic thigh access. Although some use an 8-mm PTFE graft for thigh access, we use a 6-mm graft to minimize the risk of access-related ischemia.

To expose the superficial femoral artery and femoral vein for the performance of midthigh loop access, an incision is made along the medial border of the sartorius muscle in the midthigh. This muscle is retracted to gain access to the femoral vessels. The superficial femoral artery and femoral vein are encircled with vessel loops. The graft is tunneled over the anterolateral thigh. This graft location facilitates graft cannulation

TABLE 176.3 Results of Complex Thigh and Upper Extremity Accesses

Access Type/ Series	Configuration	Number of Accesses	SECONDARY PATENCY (%)		Infection (%)	Wound Complications (%)	Access-Related Ischemia (%)
			1-Year	2-Year			
Prosthetic Thigh							
Cull et al.[41]	PTL	116	68	54	41	—	11
Taylor et al.[47]	PTL	45	52	47	11	—	16
Bhandari et al.[8]	PTL	49	85	82	35	—	0
Vogel et al.[47a]	PTL	126	62	—	20	—	0
Korzets et al.[42]	PTL	37	73	65	11	—	11
Englesbe et al.[43]	PTL	30	41	26	27	—	3
Khadra et al.[44]	PTL	74	74	63	16	—	3
Tashjian et al.[45]	PTL	73	83	83	22	—	2
Flarup et al.[48]	MTL	14	64	18	21	—	0
Scott et al.[49]	MTL	46	68	43	21	—	13
Autogenous Thigh							
Gradman et al.[21]	FV transposition	25	87	87	0	28	32
Gradman et al.[22]	FV transposition	22	100	94	0	0	0
Autogenous Upper Extremity							
Huber et al.[11]	BA-Ax FV translocation	30	100	100	0	40	27
Elwakeel et al.[16]	BA-BV transposition	21	76	55	5	0	0
Angle et al.[50]	BA-BV transposition	20	—	—	—	—	0
Casey et al.[14]	BA-BV transposition	17	40	40	—	—	—

Ax, Axillary vein; *BA*, brachial artery; *BV*, brachial vein; *FV*, femoral vein; *MTL*, midthigh loop; *PTL*, proximal thigh loop.

without requiring the patient to rotate the extremity externally. In most cases, the venous limb of the graft is situated medially and the arterial limb laterally on the thigh. In patients in whom the superficial femoral artery lies beneath the sartorius muscle, the lateral border of the muscle is mobilized and the arterial limb is tunneled lateral to it (see Fig. 176.8A).

CRYOPRESERVED VEIN ALLOGRAFTS

Cryopreserved vein allografts (cadaveric vein) have emerged as an option for AV graft reconstruction; however, indications for their use in hemodialysis access remains to be clearly defined. A recently published study discussed the use of cryopreserved vein allografts in 106 patients over a 10-year period. The investigators categorized the graft placement as central outflow (outflow to the subclavian vein, innominate vein, or right atrium), standard outflow (axillary vein, cephalic or basilic vein), or femoral outflow. The observed primary and secondary patency rates were 22.6% and 66%, respectively, at 1 year. The authors state that the potential benefit of a cryopreserved vein allograft over a prosthetic conduit is realized in patients with multiple repeat accesses and active infections (42% of patients in this series had history of active or recent infection).[51] The disadvantages of cryopreserved vein allografts are recurrent infection of the allograft and the dreaded complication of rupture, leading to loss of limb or life in our experience. Therefore this approach should be used only in select cases.

UNCONVENTIONAL VASCULAR ACCESS PROCEDURES

The literature describes a number of "exotic" AV access procedures used to obtain access when options in both the upper and lower extremities have been exhausted. These procedures are generally described in case reports; therefore, their durability and complication rates have not been established. However, their use may be justified when no other alternative exists.

Unconventional Chest or Abdominal Wall Access Procedures

In several case reports and small case series, direct surgical approaches to the central veins have been described for patients

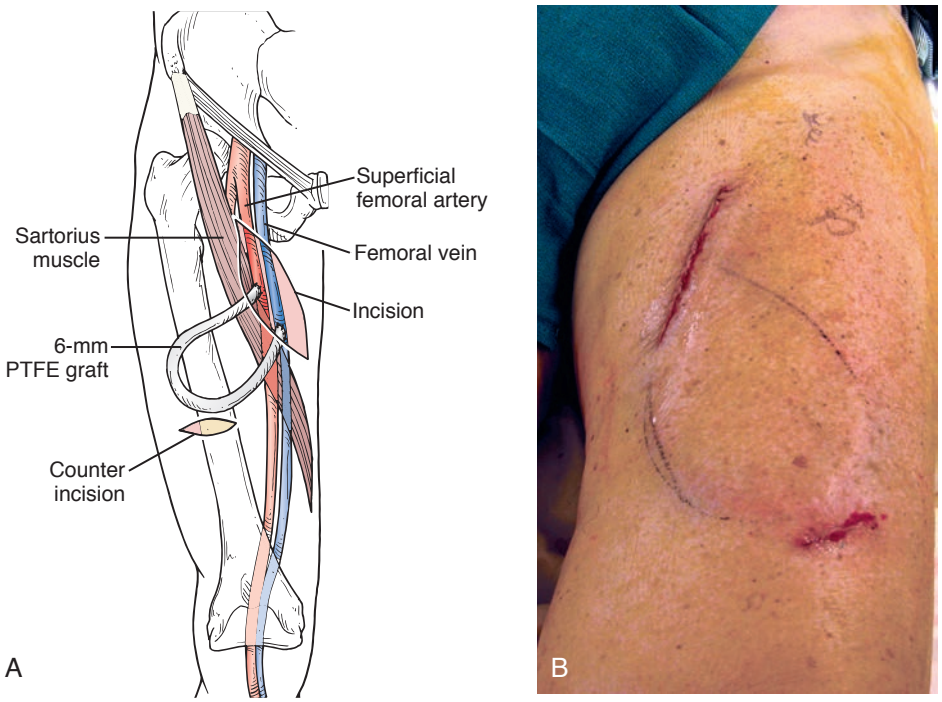

Figure 176.8 (A) Midthigh loop access with both graft limbs tunneled medial to the sartorius muscle. Alternatively, if the superficial femoral artery lies closer to the lateral edge of the muscle, the arterial limb can be passed lateral to the sartorius muscle. (B) Photograph demonstrating the location of the incisions for midthigh loop access placement and the relation of the midthigh loop access to the groin. *PTFE,* Polytetrafluoroethylene.

with central venous occlusion who require vascular access or have access-related venous hypertension. These include a bypass to the right atrial appendage through a third intercostal space, or "minipericardiotomy"; a right superficial femoral artery–superior vena cava (SVC) prosthetic access; and a femoral transposition combined with an iliac vein to a suprarenal vena cava bypass.[52–54]

Karp et al. have published a case report describing a prosthetic chest wall access from the axillary artery to the left renal vein.[55] The left renal vein was exposed through a left flank retroperitoneal incision. The prosthetic graft was tunneled on the chest wall lateral to the nipple and over the 12th rib. A polyurethane graft was used in this case to allow early cannulation of the access. Although several interventions were required to maintain access patency owing to graft kinking over the 12th rib, the access remained patent for 18 months.

The authors have placed a prosthetic external iliac–left renal vein access in a patient with no other access options. The left external iliac artery was exposed just proximal to the inguinal ligament, and the left renal vein was exposed through a retroperitoneal flank incision. To prevent kinking and allow early cannulation of the access, a ringed PTFE graft was used for the intra-abdominal graft segment, and a polyurethane graft was used on the abdominal wall. The access functioned without requiring intervention until the patient's death from a cardiac event 8 months postoperatively.

A prosthetic axillary artery–right atrium AV access in a patient with thrombosis of both the superior and inferior venae cavae has been described.[56,57] The right axillary artery is exposed through an infraclavicular incision, and a median sternotomy is used to expose the atrial appendage. An 8-mm PTFE graft is tunneled beneath the pectoralis muscles into the axilla along the midaxillary line. At the level of the ninth rib, the graft is turned medially and cephalad for subcutaneous tunneling to the infraclavicular incision and then medially and caudad to the fifth rib interspace at the sternal border. A space is created in the fifth interspace, and the graft is passed into the mediastinum. This long, tortuous course was chosen to provide a sufficient length in a subcutaneous location that would allow a large number of potential cannulation sites. The graft is anastomosed end to side to the axillary artery and to the right atrial appendage.

Arterial–Arterial Access Procedures

Bunger et al. reported the outcome of a series of 20 patients who underwent axillary artery–axillary artery interposition with PTFE grafts.[58] The interposition graft was looped on the chest wall and anastomosed end to end to the transected axillary artery (Fig. 176.9A). The diameter of the PTFE graft (range, 6 to 8 mm) was dictated by the size of the axillary artery. Operative or endovascular revision procedures were required in 30% of patients. The primary and secondary patency rates at 6 months were 90% and 93%, respectively; however, mean follow-up was only 7 months. Limb ischemia occurred in one patient whose access thrombosed, but it resolved after thrombectomy. No symptoms of limb ischemia occurred in the three other patients whose access thrombosed.

Zanow et al. recently reported a series of 36 arterioarterial prosthetic loop accesses.[59] Among their patients, 31 of the

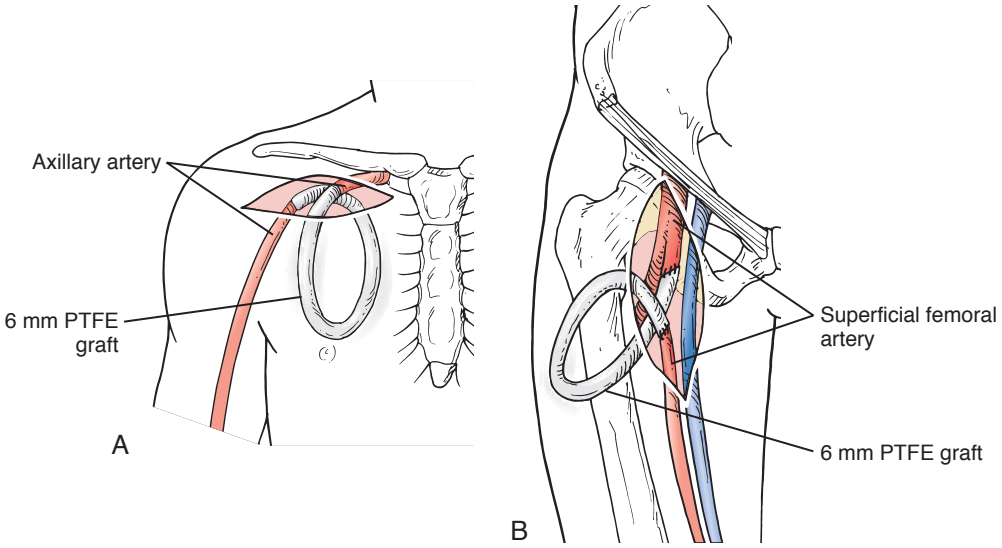

Figure 176.9 (A) Prosthetic axillary artery–axillary artery loop access. (B) Prosthetic femoral artery–femoral artery loop access. *PTFE,* Polytetrafluoroethylene.

accesses were based off the axillary artery and 5 were based off the femoral artery (see Fig. 176.9). In each case, the artery was divided and end-to-end anastomoses were used to interpose the prosthetic graft. The secondary patency rates were 96% at 1 year and 87% at 3 years. The authors noted that thrombosis of the femoral access resulted in severe limb ischemia requiring immediate thrombectomy, whereas occlusion of the axillary access caused only mild ischemia and was much better tolerated.

Salgado et al. described the technique of superficial femoral artery transposition for vascular access.[60] The technique involves the following steps: (1) transection of the sartorius muscle; (2) exposure and mobilization of the superficial femoral artery; (3) elevation of the superficial femoral artery by suturing the ends of the sartorius muscle and closing the subcutaneous tissue beneath the artery; and (4) closure of the skin over the artery. In their series of 14 patients, the authors did not report patency but rather found that these accesses "delivered 3215 hemodialysis treatments." Five needle cannulation complications were reported: bleeding due to arterial laceration ($n = 2$), pseudoaneurysm ($n = 2$), and infected pseudoaneurysm ($n = 1$). Three episodes of arterial thrombosis occurred.[60]

Lei et al. reported their series of 18 patients with superficial femoral to deep femoral artery loop access. In their study, indications for this procedure included an unsuitable upper and lower extremity deep vein, stenosis, or occlusion of upper extremity central veins, congestive heart failure, and prior access-related steal syndrome. Their primary and secondary patency rates were 94.5% and 88.8%, respectively, at 6 months; at 3 years they were 61% and 72%, respectively. Eight patients had postoperative leg swelling and there was one graft occlusion, but no lower extremity ischemia was reported. Preoperative assessment involves duplex imaging of the arteries and supplemental contrast angiography to define adequacy of the deep femoral artery as well as to rule out any arterial inflow or outflow lesions. The technique involves exposure of the superficial femoral and deep femoral arteries and subcutaneous placement of a 6-mm PTFE conduit as a loop. End-to-side anastomoses are performed from the graft to the vessels.[61]

Arterial–arterial access procedures may be considered in patients with previous access-related limb ischemia and high-output cardiac failure. It is important to note that these accesses cannot be used to infuse medications. Also, dialysis unit personnel should be instructed to hold pressure over the needle cannulation site for at least 20 minutes. The arterial–arterial access procedures do not provide flow rates as high as arterial–venous access procedures (Bunger noted a median flow rate of 165 mL/min). Since dialysis blood flow rates exceeding 400 mL/min can cause recirculation and arm pain, it may be necessary to run patients at slower blood flows for longer periods to deliver adequate dialysis treatment.

Unconventional Sites for Placement of a Tunneled Dialysis Catheter

Transthoracic Superior Vena Cava Catheters

Wellons et al. reported a series of 22 patients with bilateral internal jugular and subclavian vein occlusion who underwent placement of a tunneled dialysis catheter into the SVC via direct transthoracic puncture.[62] The catheters functioned from 1 to 7 months. The only major complications reported were hemothorax in one patient and pneumothorax in another. Both were successfully treated with tube thoracostomy.

In this procedure, a pigtail catheter is placed in the SVC via access from the femoral vein and a venogram of the SVC is performed. Anteroposterior and lateral fluoroscopic views of the SVC are obtained and used as a reference guide to pass an introducer needle from a point immediately cephalic to the head of the right clavicle to the SVC. Once the SVC is entered, a hydrophilic wire is placed into the inferior vena cava (IVC). A tunneled dialysis catheter is placed in the usual fashion.

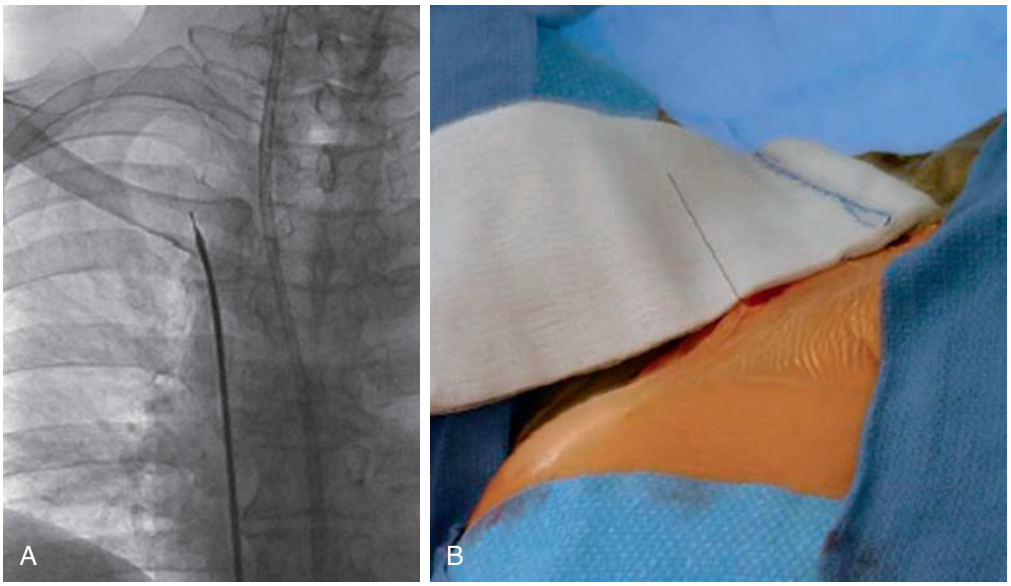

Figure 176.10 Inside-out-central venous access technique. (A) The sheath and needle or advanced to the point of obstruction in the superior vena cava. The needle and wire are then directed to the posterior aspect of the head of the clavicle. (B) The wire is then exteriorized and pulled through the skin of the supraclavicular fossa.

Another method recently described in the literature for placing a tunneled dialysis catheter through a SVC occlusion is the inside-out central venous access technique (IOCVA). This technique can be used to place a central venous catheter or the venous component (intravenous catheter) of the HeRO device as well. To cross the occluded SVC, the right common femoral vein is accessed. A 0.035 J-tipped guide wire is placed in the IVC with a 5-Fr angled tip catheter over the wire. Wire and catheter are navigated to the atrium and to the confluence with the occluded SVC. A 0.032-inch J-tipped guide wire is then placed at the level of the occlusion and the catheter is removed along with the 6-Fr hemostasis sheath. An 8-Fr SL0 sheath (SL0, Daig Inc., St. Jude Medical, St. Paul, Minnesota) is then placed with the tip next to the occlusion. A BRK transseptal needle (St. Jude Medical) is then placed in the dilator and a 0.018-inch steel core cut wire is placed inside the needle. Both the transseptal needle and steel wire are then directed from the IVC to the SVC, using lateral projections with angiography to make sure that the pathway does not go through the atrial appendage. The needle and wire are then directed to the posterior side of the clavicle. The wire is then exteriorized and pulled through the skin of the supraclavicular fossa. The SL-0 dilator and BRK needle are exteriorized as well. Wire and BRK needle are then removed from the groin and replaced with a 0.032-inch J-tipped guidewire via the dilator. Over this, wire balloon dilation using a 10-mm balloon is performed along the tract (see Fig. 176.10).[63]

Translumbar Inferior Vena Cava Catheters

An alternative technique for placing a tunneled dialysis catheter into the IVC is through a direct translumbar approach. Rajan et al. have reported a series of 58 translumbar IVC catheters, 37 of which were placed for hemodialysis access.[64] IVC thrombosis occurred in one case, and stenosis occurred in another. In several cases the catheter migrated into the subcutaneous soft tissues, retroperitoneum, or iliac veins, necessitating catheter repositioning. This was most commonly noted in obese patients. A case of retroperitoneal hematoma occurred secondary to catheter migration out of the IVC. In another study the cumulative patency rate was 52% at 6 months and 17% at 12 months. Infection of the catheter occurred in six cases.[65]

The catheter tip is positioned at the junction of the IVC and the right atrium; therefore, use of a long tunneled dialysis catheter is required. The patient is placed prone or in the left lateral decubitus position. A small stab incision is made 3 to 4 cm lateral to the midline and just above the right iliac crest at the L3 vertebral level. Through this incision, an 18-gauge long needle is inserted and advanced toward the IVC under fluoroscopic guidance. Once the translumbar needle has entered the IVC, a guidewire is placed. A second incision is made lower and lateral to the initial puncture site for the tunneled catheter. The catheter is then placed in the usual fashion.

Transhepatic Inferior Vena Cava Catheters

A percutaneous transhepatic approach has been used to place tunneled catheters in the IVC for hemodialysis. The outcome of this procedure has been reported in two series constituting a total of 57 catheters in 23 patients.[66,67] Thrombosis or malfunction of the catheter requiring catheter exchange was frequent in both series. In one series of 21 catheter placements, the complication rate was 29%, including one death from massive intraperitoneal hemorrhage. Although the average duration of dialysis via this route in the two series was 24 and 138 days, respectively, one patient was dialyzed for 599 days. Given the catheter maintenance problems associated with the transhepatic approach, this procedure should be used only as a last resort.

PEDIATRIC VASCULAR ACCESS

The preferred renal replacement therapies for the pediatric patient population are renal transplantation and peritoneal dialysis. According to the US Renal Data System (USRDS), approximately 38% of pediatric patients with end-stage renal disease receive a kidney transplant within the first year.[68] Hemodialysis is considered by many as a bridge to transplantation or as a treatment of last resort. Since the occurrence of end-stage renal disease is less common in children than adults and hemodialysis is not the preferred treatment modality, few surgeons have a sizable experience with pediatric vascular access. As a result, the literature on pediatric vascular access is limited to a few single-institution, retrospective reviews of experiences acquired over many years. Standard methods for reporting outcomes such as patency are not used for the majority of those reports. The chief limitation of the pediatric vascular access literature is the way in which studies define a pediatric patient. Most of the "pediatric" vascular access case series are primarily composed of adolescents whose body sizes approximate those of small adults rather than children. Given the limitations of the pediatric vascular access literature, it is difficult to determine the outcome of autogenous AV access procedures or to derive algorithms for vascular access for the small child younger than 10 years of age. Therefore only broad concepts related to vascular access for the pediatric patient population can be elicited from the available literature.

Kidney Disease Outcomes Quality Initiative Recommendations and Recent Trends

Given the technical challenges of autogenous or prosthetic AV access placement in very small children, the KDOQI guidelines recommend peritoneal dialysis or hemodialysis via a tunneled dialysis catheter for patients weighing less than 20 kg. Peritoneal dialysis or hemodialysis via a tunneled dialysis catheter is also recommended as a bridge to kidney transplantation if the transplant is expected to occur in less than 1 year. The KDOQI guidelines emphasize the importance of matching the length and diameter of the tunneled dialysis catheter to the size of the patient and provide a table for reference. Catheter placement considerations in pediatric patients are similar to those in adults. The most recent USRDS report shows that the rates of vascular access infection and hospitalization for infection/sepsis among hemodialysis patients younger than 10 years of age are increasing.[68] This is due in part to catheter infections resulting from patients spending more time on transplant waiting lists.

A commonly used argument against the placement of permanent access is the relative short time for renal transplantation. Catheter placement is used as a bridge to renal transplantation, which is the ideal goal of treatment, but this cannot always be achieved. Furthermore due to the finite life span of an allograft, planning for vascular access poses a unique challenge in this population. As a result, any intervention that could compromise future access must be avoided. Catheters frequently lead to stenosis or thrombosis of central veins, particularly in children who have smaller-diameter veins. These trends support the KDOQI recommendations that an autogenous or prosthetic AV access is preferred for pediatric patients on maintenance hemodialysis.[5]

Autogenous Arteriovenous Access

Autogenous AV access is considered the optimal hemodialysis access in pediatric patients. The outcomes in pediatric patients have been published for the following autogenous AV access procedures: radial-cephalic access, ulnar-basilic access, radial-basilic transposed access, brachial-basilic transposed access, brachial-cephalic access, and femorofemoral transposed access.[69–76] The secondary patency rates ranged from 70% to 98% at 2 years. However, in most of these series it is unclear whether early access failures and accesses that failed to mature were excluded from patency analysis. Nonmaturation of autogenous AV accesses in children reportedly occurs in as many as 33% of cases. For a pediatric patient with anatomy unsuitable for an autogenous access procedure, a prosthetic AV access can be placed. One study reported the outcome for prosthetic AV access in children to be equivalent to that in adults.[73]

Technique

The same considerations and diagnostic modalities used to select the appropriate autogenous or prosthetic AV access procedure in adults apply to children. The more distal anatomic sites should be used as a first access, preserving the more proximal sites for access later in life. There are key differences in the techniques used for AV access placement in children compared with adults. AV access placement is facilitated in pediatric patients by the use of microsurgical techniques and microsurgical instruments, adequate magnification, and an interrupted suture technique. The AV anastomosis is performed with 8-0 to 10-0 polypropylene suture. Second, to minimize vessel dissection and vasospasm, vascular control is obtained with a sterile tourniquet.[69,70]

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177 CHAPTER

Hemodialysis Access: Dialysis Catheters

KAREN WOO and VINCENT L. ROWE

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Central venous catheters play an important role in the treatment of patients with end-stage renal disease. Despite initiatives to improve fistula creation, more than 80% of patients initiated hemodialysis with a catheter, a number that has changed little over the past decade.[1] Central venous catheters for hemodialysis are categorized by their intended duration as either acute or chronic. Both acute and chronic hemodialysis catheters can be placed percutaneously; however, chronic catheters have a subcutaneous cuff at the skin exit site, whereas acute catheters do not. As a result, acute catheters are at higher risk for infectious complications and can easily become dislodged. Thus acute catheters should be placed only in hospitalized patients and used for a short duration, usually less than 4 weeks.[2] This time frame is in stark contrast to chronic catheters, which can be used for up to approximately 12 months.

This chapter focuses on tunneled hemodialysis catheters and their management, but the potential complications related to placement of acute non-tunneled hemodialysis catheters mirror

Abstract

Central venous catheters for hemodialysis are categorized by their intended duration, as either acute or chronic. Chronic hemodialysis catheters are placed in a tunneled fashion and have a subcutaneous cuff at their skin exit site for tissue ingrowth. Acute catheters do not have a cuff and are placed percutaneously without a tunnel. As a result, acute catheters are at higher risk for infectious complications and can easily become dislodged. Currently, chronic hemodialysis catheters are utilized as either a first line treatment option for hemodialysis or a bridge during permanent hemoaccess creation or revisions. This chapter will focus on tunneled hemodialysis catheters (THC) and indications for placement, technical considerations for insertion, and the management of the potential complications related to placement of the catheters.

Keywords

tunneled hemodialysis catheter
complications
infection
thrombosis
venography

those of tunneled hemodialysis catheters. However, because of the short duration of use of acute catheters, long-term complications are less frequent but infectious complications are more common.

INDICATIONS

The most common indication for placement of a tunneled hemodialysis catheter is for urgent hemodialysis while the patient is waiting for an autogenous arteriovenous fistula (AVF) to be created or to mature. Other indications include patients in whom an AVF or prosthetic arteriovenous graft (AVG) is not anatomically feasible or who are not operative candidates because of advanced comorbidities. Temporary hemoaccess is also indicated after revision of a permanent hemodialysis access for management of a complication (e.g., access revision for pseudoaneurysm formation or infection), after placement of a peritoneal dialysis catheter, and for a chronic ambulatory peritoneal dialysis patient requiring abdominal or inguinal surgery.

The benefits of tunneled hemodialysis catheters over AVF and AVG vascular access include immediate use for hemodialysis, uncomplicated and needle-free connection to the dialysis circuit, elimination of cannulation site complications, and simple insertion technique that can be performed by many different interventional specialists.[3]

TYPES OF CATHETERS

Early cuffed catheters were straight in configuration and stiff. Due to advances, the early catheter configurations have been largely supplanted by precurved flexible catheters with various tip designs.

Design Characteristics

Catheter designs aim to achieve one main goal: adequate dialysis clearance at a relatively high flow rate of 300 to 350 mL/min.[4] In addition, the phenomenon of recirculation must be minimized to ensure adequate clearance. The "arterial lumen" of the catheter is the outflow to the dialysis machine from the patient; the "venous lumen" is defined as the inflow from the machine back to the patient. Access recirculation is the reentry of dialyzed blood from the venous lumen directly into the arterial lumen, thus bypassing the systemic circulation and leading to inefficient dialysis.[5]

Design Categories

Numerous manufacturer modifications exist in an effort to satisfy the requirements of high flow rates and minimal recirculation. The modifications fall into four general categories.

Split Tip

Split-tip catheters have a double-lumen, single-body configuration in the midbody but separate into two distinct distal tips, each with side holes in all directions (Fig. 177.1A).

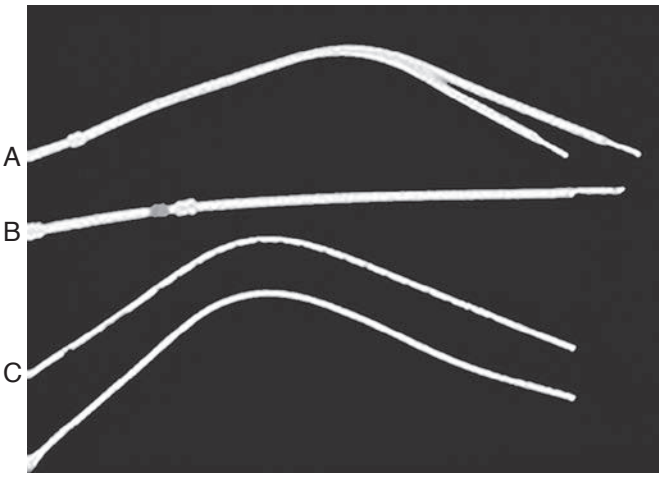

Figure 177.1 Three types of tunneled hemodialysis catheters: split-tip catheter (A), staggered-tip or step-tip catheter (B), and dual catheter (C). (From Richard HM, 3rd, et al. A randomized, prospective evaluation of the Tesio, Ash split, and Opti-flow hemodialysis catheters. *J Vasc Interv Radiol*. 2001;12:431–435.)

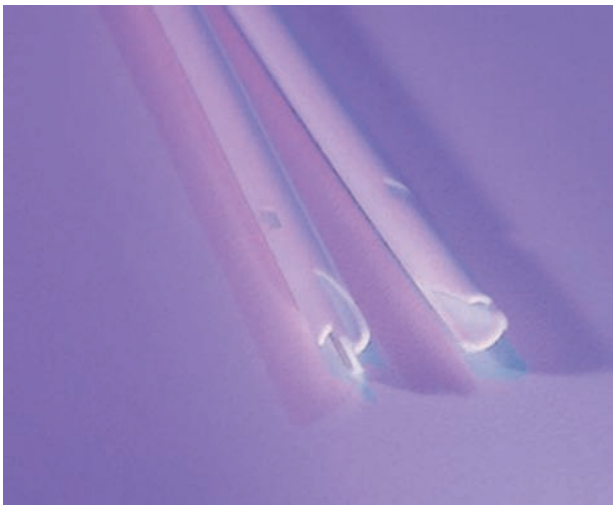

Figure 177.2 Tal Palindrome catheter. (Courtesy Covidien.)

Step Tip

The staggered-tip or step-tip catheter is a double-lumen, single-body catheter with the venous limb extending at least 2.5 cm beyond the inflow tip (see Fig. 177.1B).

Dual Catheter

The dual catheter design consists of two completely separate catheters that can be inserted in two different locations (see Fig. 177.1C).

Symmetric Tip

The Tal Palindrome (Covidien, Mansfield, Mass) is the only catheter that has a symmetric tip design with equal length of arterial and venous limbs and biased spiral ports. The design of the ports allows inflow to occur through the most proximal portion of the port and outflow to occur as a jet directed away from the catheter tip (Fig. 177.2).[6]

Numerous reviews directly compare performance of individual tunneled hemodialysis catheters with specific outcome variables of flow rate, recirculation time, and patency. Unfortunately, despite isolated beneficial characteristics of a particular catheter, no universal significant benefit has been demonstrated by one catheter over the competitors.[3-5,7] In one of the few randomized trials, a symmetric-tip catheter and a step-tip catheter demonstrated no difference in risks for thrombosis, infection, and overall catheter survival.[8]

PREOPERATIVE EVALUATION

History and Physical Examination

As with any clinical assessment, the proper preoperative evaluation of a patient begins with a detailed history and physical examination. Specific inquiries should include details such as prior long-term central line placement, prior AVF or AVG placement, prior tunneled hemodialysis catheter infections, history of a coagulation disorder, and history of a pacemaker. Physical examination of the neck and chest is critical. Evidence of a previously placed tunneled hemodialysis catheter, previous permanent accesses, upper extremity or facial edema, and ipsilateral venous distention with visible venous collaterals should alert the clinician to the possibility of central venoocclusive disease.

Numerous specialists have the skill set to properly place a tunneled hemodialysis catheter. However, there is a significant advantage in terms of continuity of care when the same practitioner places the tunneled hemodialysis catheter and the permanent access or when a team approach coordinates these procedures. There are a finite number of access sites available for both tunneled catheter and permanent access placement. Therefore a comprehensive plan that embraces all forms of hemodialysis access may provide maximum benefit of each crucial access site.

Central Venous Imaging

Color-Flow Venous Duplex Imaging

Noninvasive color-flow duplex imaging is the first line method of preoperative imaging for the tunneled hemodialysis catheter. Patency of internal jugular veins and axillary veins is easily identified with compression of the vein. However, as imaging moves toward the central chest, the air interface with the lung tissue, as well as obstructing bone structures, makes central vein imaging virtually impossible.

Magnetic Resonance Venography

Three-dimensional gadolinium-enhanced magnetic resonance venography (MRV) has been shown to be highly sensitive in identifying central vein occlusions and stenoses greater than 50% when directly compared with digital subtraction angiography.[9] Despite the accuracy of MRV, gadolinium must be administered with caution in patients with a glomerular filtration rate of less than 30 mL/min because of the risk of gadolinium-induced nephrogenic systemic fibrosis, which is rare even in this patient population, but has not been described in patients with normal renal function.

Computed Tomographic Venography

Computed tomographic venography (CTV) is similar to MRV in being able to image multiple vessels in the chest in one setting. However, CTV does have the advantages of being readily available in most medical centers, fast acquisition times, and fewer deleterious contrast agent concerns. In medical centers dedicated to use of this imaging modality for the evaluation of hemodialysis patients, anecdotal evidence points to an acceptable level of accuracy for the evaluation of central venous disease. A study of 18 patients comparing CTV and digital subtraction venography for the diagnosis of benign thoracic central venous obstruction demonstrated that CTV findings correlated closely with those of digital subtraction venography.[10]

Catheter-Based Contrast Venography

Catheter-based contrast venography remains the "gold standard" for diagnosis of central vein stenosis or occlusion. Contrast venography has the distinct advantage of allowing the clinician to initiate endovascular treatment if a significant stenosis is detected at the time of venography. In addition, it is often possible to perform catheter-based venography with a much smaller volume of contrast material than what is required for CTV, reducing the risk of nephrotoxicity.

CATHETER INSERTION

Site Selection

The right internal jugular vein is the preferred access site for tunneled hemodialysis catheter placement because it has the best patency, presumably owing to less kinking. In a prospective evaluation, factors affecting long-term survival of tunneled hemodialysis catheters were analyzed in a cohort of 812 catheters in 492 patients.[3] A tunneled hemodialysis catheter placed in the right internal jugular vein demonstrated significantly longer survival compared with one placed in the left internal jugular vein. Tunneled hemodialysis catheters placed in the femoral vein had the worst long-term survival. The subclavian vein should be avoided if possible to prevent catheter-induced subclavian stenosis, which would negatively affect the future placement of ipsilateral permanent access.[3,4]

A tunneled hemodialysis catheter from the right internal jugular vein should be 17 to 19 cm in length; catheters from the left are slightly longer. When femoral access is used, long catheters (24-31 cm) should be placed so that the tip can reach into the inferior vena cava to produce the best flow rates.

Technique

Tunneled hemodialysis catheter insertion should be performed in a procedure room under fluoroscopic guidance. Bedside placement is discouraged because of the need for proper sterility, the possibility of additional endovascular procedures (such as venography and venoplasty), and the requirement for fluoroscopy.

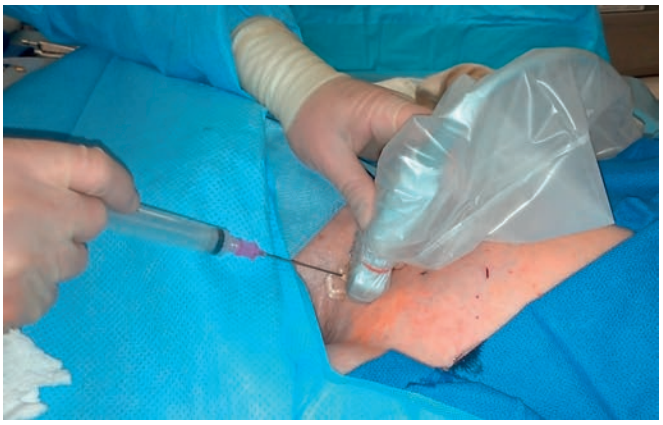

Figure 177.3 Ultrasound-guided puncture of the internal jugular vein with a micropuncture needle.

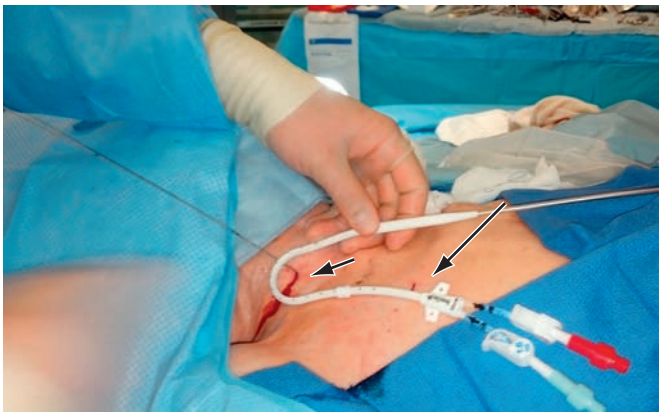

Figure 177.4 Placement of the tunneled hemodialysis catheter alongside the anticipated catheter course to determine where to position the exit site. Internal jugular vein puncture site *(short arrow)*; upper chest catheter exit site *(long arrow)*.

The procedure is usually performed under local anesthesia with conscious sedation. Preoperative antibiotic prophylaxis directed at gram-positive bacterial strains is administered before skin incision in each case. The skin is then prepared with isopropyl alcohol and chlorhexidine solutions.

Ultrasound evaluation with a sterile covered transducer confirms access vein patency. The site of vein cannulation should be 3 to 4 cm cephalad to the clavicle. Real-time ultrasound guidance is used to access the vein with a micropuncture 21-gauge needle, 0.018-inch guide wire, and 5F coaxial catheter (Fig. 177.3). After successful cannulation, the introducer and 0.018-inch wire are removed and exchanged for a 0.035-inch wire. A 1-cm skin incision is made surrounding the wire entry site (Fig. 177.4, *short arrow*). Fluoroscopic imaging should be used during all wire maneuvers to confirm wire position.

Because of the large size and stiff nature of most tunneled hemodialysis catheters, a moderate amount of forward pressure may need to be applied during insertion. It is highly advisable to have the guide wire course in the superior vena cava to inferior vena cava channel and not enter the right heart chambers. This is especially true for left-sided placement of a tunneled hemodialysis catheter. Because of the tortuous path from the left internal jugular to the heart, it is possible for the dilator to push the midportion of the guide wire, creating a loop that could perforate the side wall of the central vein. The incidence of this can be reduced by use of a stiffer wire than the one provided in the insertion kit and direct fluoroscopic visualization during passage of all dilators and sheaths over the wire.

Figure 177.5 Tunneling of the catheter subcutaneously from the chest incision to the neck incision anterior to the clavicle.

Figure 177.6 Dilatation of the track of the wire.

Antegrade Placement

A small incision is made on the anterior chest where the tunneled hemodialysis catheter is to exit the subcutaneous tunnel (see Fig. 177.4, *long arrow*). The exit site of the tunneled hemodialysis catheter should be inferior and lateral to the vein entry site. The exit site should also be positioned such that the felt cuff on the catheter shaft is 1 cm proximal to the exit site. Placement of the tunneled hemodialysis catheter alongside the anticipated catheter course is useful in determining where the exit site should be positioned. The tunneled hemodialysis catheter is then attached to the tunneling device and passed subcutaneously from the chest incision up through the vein entry site incision in the neck, traversing anterior to the clavicle en route (Fig. 177.5). The track of the wire is sequentially dilated, and the final introducer and peel-away sheath unit is inserted until the sheath is "hubbed" at the skin (Fig. 177.6). The introducer and wire are removed, and the tunneled hemodialysis catheter is inserted through the peel-away sheath (Fig. 177.7). Once the tunneled hemodialysis catheter is fully inserted, the peel-away sheath is withdrawn.

Figure 177.7 Insertion of the tunneled hemodialysis catheter through the peel-away sheath.

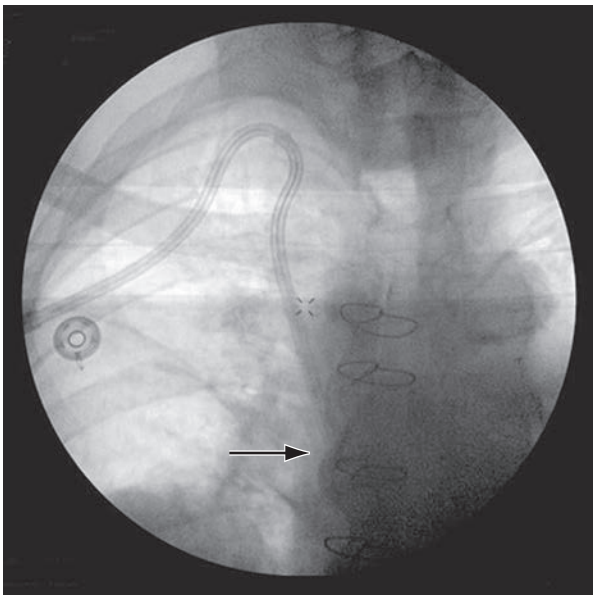

Figure 177.8 Chest radiograph demonstrating proper position of the tip of the tunneled hemodialysis catheter *(arrow)* at the level of the right mainstem bronchus.

Each lumen of the catheter is aspirated and flushed with dilute heparin (100 units of heparin sulfate per milliliter of normal saline). Both of these actions should be easily accomplished without resistance. If resistance is encountered, the catheter should be examined under fluoroscopy to rule out a kink in the path of the catheter or malpositioning of the tip. Ideally, the most distal tip of the catheter should be in the distal superior vena cava/proximal right atrium border. This preferred position corresponds to the shadow of the right mainstem bronchus (Fig. 177.8).

The chest wall and vein entry site incisions are closed with absorbable sutures, and the tunneled hemodialysis catheter is secured to the chest wall with nonabsorbable sutures. Each lumen of the tunneled hemodialysis catheter is filled with the manufacturer-indicated volume of concentrated heparinized saline (1000 units/mL) to protect against intracatheter thrombosis. In a meta-analysis comparing low doses (<5000 units/mL) heparin lock versus high-dose heparin (≥5000 units/mL), low-dose heparin was shown to be associated with a significantly lower risk of bleeding-related complications with no difference in the incidence of catheter thrombosis.[11] Sodium citrate 4% solution can be used in patients with heparin allergies.

Retrograde Placement

Tunneled hemodialysis catheters have been developed that can be placed in a "reverse-tunneled" or "retrograde" fashion; these catheters do not have ports attached initially. The catheter is inserted into the vein before tunneling in the same fashion as the standard tunneled hemodialysis catheter. The catheter is then tunneled from the neck incision to the chest incision, and the ports are attached after tunneling. The advantage of this type of insertion is that it allows precise positioning of the catheter tip.

Unconventional Catheter Sites

Patients who have exhausted conventional sites for vascular access may require placement of tunneled hemodialysis catheters in unconventional sites, such as the transhepatic and translumbar routes.

Translumbar catheters are generally placed with the patient in the prone position by percutaneous puncture of the inferior vena cava above the right iliac crest. The catheter is tunneled through a right lateral abdominal exit site. For transhepatic catheters, percutaneous access to the right or middle hepatic vein is obtained through the eighth intercostal space in the midaxillary line under fluoroscopic guidance. The catheter is then tunneled to a lateral anterior chest wall exit site. The tip of the catheter is positioned in the right atrium in both approaches.

The reported mean total catheter service lifespan of transhepatic and translumbar catheters in the literature ranges from 70 days to 1948 days.[12-14] In addition, unique to this type of access is the high rate of subsequent interventions for maintenance of adequate hemodialysis access. Two of the largest published series reported that more than 60% of their patients required at least one catheter exchange. Catheter migration, thrombosis, and infection are the most commonly reported reasons for catheter exchange.[12-15] Translumbar catheter exchanges may be more difficult than exchanges through the transhepatic approach because of retroperitoneal fibrosis that develops along the track.[12]

PERIOPERATIVE CARE AND COMPLICATIONS

The perioperative management of patients after placement of a tunneled hemodialysis catheter centers on the evaluation for and treatment of potential acute complications. In a compilation of data from 1794 central venous cannulations in critically ill patients, the overall complication rate was 7.1%.[16] Failure to place the central line and arterial puncture were the

most common mechanical complications, followed by pneumothorax. The keys to successful management of these complications are awareness, prompt recognition, and expeditious treatment.

Pneumothorax

An end-expiratory upright chest radiograph should be performed after placement of a tunneled hemodialysis catheter to confirm tip placement and to exclude a pneumothorax.[17] If acute, severe symptoms and signs of pneumothorax develop, a tube thoracostomy should be performed immediately and the patient should be given oxygen by mask. In the setting of tension pneumothorax, decompression of the pleural space with an intravenous catheter placed in the second intercostal space in the midclavicular line can be lifesaving. More frequently, the air leak is relatively small, and the pneumothorax develops during a period of several hours.

When a small pneumothorax is encountered (<20%) and there are no symptoms or signs of respiratory compromise, decrease in peripheral oxygen saturation, or hemodynamic impairment, a "watchful waiting" approach with repeated chest radiographs is appropriate.[18] If symptoms develop or there is an increase in the size of the pneumothorax on subsequent chest radiographs, tube thoracostomy should be performed. If the pneumothorax is initially noted to be large (>20%), tube thoracostomy should be performed regardless of whether symptoms are present

Hemothorax

A hemothorax can develop when the back wall of either a vein or artery and the parietal pleura are perforated by an advancing needle tip, dilator, or sheath.[19] The subclavian vein or artery, the innominate vein, or even the superior vena cava may be involved. The lack of effective tamponade combined with negative respiratory pressure may result in a large blood loss through a small puncture. Clinically, patients may develop respiratory compromise accompanied by dullness to percussion and decreased breath sounds on the affected side. A decreased hematocrit and evidence of fluid in the pleural cavity on the chest radiograph strongly support the diagnosis. Drainage of the pleural space with a tube thoracostomy is generally adequate therapy and should be performed for significant hemothorax to prevent entrapment of the lung. Rarely, bleeding must be controlled surgically or, if possible, percutaneously with the use of covered stents.

Wire Embolism

Wire embolism occurs when control of the wire is lost during the procedure or the guide wire is sheared off by the access needle as it is withdrawn. If resistance to wire removal is encountered, fluoroscopic imaging should be used, and removal of the wire and needle together as a unit may be required. Fortunately, guide wires can usually be removed fluoroscopically with use of a wire snare retrieval system.[20]

Cardiac Arrhythmia

Cardiac complications related to central venous catheterization are rare. Arrhythmia during placement of a tunneled hemodialysis catheter is associated with the guide wire irritating the myocardium. The problem can be minimized by use of guide wires that have distance markings and fluoroscopy to visualize the location of the tip of guide wires and catheters. If cardiac arrhythmias develop after the placement of a tunneled hemodialysis catheter, the catheter position should be checked fluoroscopically or with a chest radiograph and the catheter tip should be withdrawn if the tip is near or traversing the tricuspid valve. Rarely, in less than 1% of cases, patients will have arrhythmias that require chemical or electrical cardioversion.[21]

Cardiac Perforation

The soft, flexible hemodialysis catheters that are currently used are unlikely to perforate the heart. More common causes of cardiac perforation are guide wires, dilators, and rigid introducers. Cardiac perforation may result in acute pericardial tamponade from bleeding or fluid infusion into the pericardial space. Signs and symptoms of pericardial tamponade can develop rapidly and include shock and cyanosis with marked cervical venous distention. Tachycardia and muffled heart sounds are generally present, and a large globular cardiac silhouette may be present on a chest radiograph. Any intraluminal catheter devices should be removed and pericardiocentesis or a pericardial window created. If the tamponade recurs after pericardiocentesis or creation of a window, median sternotomy with formal cardiac repair may be necessary.

Thoracic Duct Laceration

Percutaneous catheterization of the superior vena cava through the left internal jugular or the subclavian approach carries a small risk of thoracic duct laceration. Cirrhotic patients are more prone to the development of this complication. If a lymphatic leak becomes apparent, the catheter should be removed and a pressure dressing should be applied. Nearly all such leaks resolve spontaneously.

Nerve Injuries

The brachial plexus is the nerve structure that is most vulnerable during percutaneous catheterization by virtue of its large size and proximity to the subclavian vein and artery.[22,23] Acute upper extremity pain referred along a neural anatomic pathway suggests impingement on the brachial plexus and necessitates immediate withdrawal of needles or catheters. Permanent injury is rare. The vagus, recurrent laryngeal, and phrenic nerves are also in proximity to the internal jugular vein but are small nerves and infrequently injured. The development of hoarseness after catheter placement suggests injury to the vagus or recurrent laryngeal nerve. Phrenic nerve injuries are generally asymptomatic and are incidentally identified on radiographic examination when an elevated hemidiaphragm is seen.[24] The development of Horner

syndrome has also been reported by inadvertent trauma to the stellate ganglion during percutaneous cannulation of the internal jugular vein.

Catheter Misplacement

In a prospective study of 1619 patients the incidence of catheter tip malposition, defined as extrathoracic or ventricular positioning, was 3.3%.[25] The use of fluoroscopy during catheter placement should eliminate the occurrence of catheter tip malposition. If there is a question as to the location of the tip of the catheter during placement, contrast material can be injected through the catheter under fluoroscopic guidance to help define the anatomy.

Venous

If the catheter tip is left in the subclavian, axillary, jugular, or hepatic vein, the catheter tip or turbulence generated during hemodialysis may cause intimal injury, which leads to thrombosis of the vein.[26] Stiff catheters or introducers left abutting the wall of the superior vena cava or more peripheral veins can also erode through the vessel wall and produce a hemomediastinum or hydromediastinum.

Arterial

Catheters may be inadvertently placed into the subclavian or carotid artery and go unrecognized. This is more common in a hypotensive or poorly oxygenated patient who may not have return of bright red, pressurized blood when an artery is punctured. Because tunneled hemodialysis catheters are generally placed on an elective basis, arterial placement is rare. If there is a question of arterial placement, the pressure can be transduced through the catheter to see if the waveform is arterial or venous. A sample from the catheter can also be sent for a blood gas analysis to determine if the values are consistent with an arterial or venous blood gas. If the injury is recognized in a timely fashion (<4 hours), most of the catheters placed in the carotid artery can be simply removed and pressure applied for a prolonged time (15-20 minutes).[27] If the injury is recognized later, the catheter should be removed in the operating room with open repair of the artery because the incidence of track formation and accumulation of thrombus on the catheter is increased.[27] Injuries to the subclavian artery are more difficult to compress because of the lack of bone structures to compress against and should be monitored closely for evidence of hemothorax. Open or endovascular repair of the artery may be required.[28]

LONG-TERM CARE AND COMPLICATIONS

The long-term management of tunneled hemodialysis catheters is primarily performed by the staff at the dialysis center where the patient receives dialysis. Patients with tunneled hemodialysis catheters usually do not come to the attention of the vascular surgeon unless a late complication of the catheter develops.

Air Embolism

Air embolism is a rare but potentially lethal complication of central venous catheterization that can be either an acute or a late complication.[19] In its late form, air embolism generally occurs when air enters the catheter either before attachment of the tubing or when the tubing becomes disconnected.[29,30] Air embolization can also occur through cracks in the catheter or its hub, as well as through the catheter track after the removal of a central venous catheter.[31] Patients should be instructed that in the event the catheter becomes disconnected or uncapped, a critical complication could result. Patients should be instructed to cap the open catheter with a thumb or finger and to call for help immediately. An occlusive dressing should be placed over the skin puncture site when the catheter is removed to allow adequate sealing of the track.

If sudden cardiorespiratory collapse develops in a patient with a tunneled hemodialysis catheter, air embolism must be strongly considered. Further embolization must be prevented by capping or clamping of the catheter while the patient is simultaneously placed in the Trendelenburg and left lateral decubitus position (Durant maneuver).[32] This position displaces air away from the pulmonic valve, which relieves the right ventricular outflow obstruction. The catheter can be advanced into the heart to aspirate the air.[33]

Catheter Embolism

Fractures can develop in the material of chronically indwelling catheters. This usually occurs at sites of stress, such as the thoracic inlet especially with catheters based in the subclavian vein.[34,35] Fractures can result in breaking off and embolization of the distal aspect of the catheter, which can typically be removed in the angiography suite with use of a wire snare retrieval system.[36]

Catheter Occlusion

Catheter occlusion occurs in 30% to 40% of patients with tunneled hemodialysis catheters.[37] Occlusion of the catheter generally is a consequence of the development of a fibrin sleeve or plug at the catheter tip. The ability to infuse fluid into the catheter but the inability to withdraw blood often indicates impending occlusion.

Prevention

Use of antithrombotic agents is not recommended to prevent catheter thrombosis. Low-dose warfarin is ineffective in reducing catheter thrombosis. Both therapeutic warfarin, titrated to an INR of 2 to 3, or aspirin 325 mg/day decrease the risk of catheter thrombosis but are associated with an unacceptable risk of gastrointestinal bleeding, particularly in the elderly.[38,39] A meta-analysis of 13 studies of heparin lock solutions versus all other types of catheter lock solutions, including citrate, recombinant tissue plasminogen activator, antibiotic with heparin, ethanol, and taurolidine (a novel antimicrobial agent used in Europe) with a total of 1883 subjects, demonstrated no difference in patency between heparin versus other lock solutions.[40]

Treatment

Local infusion of fibrinolytic agents has been used in the salvage of occluded central venous catheters.[41,42] Currently, alteplase is the only fibrinolytic agent that is approved for treatment of occluded central venous catheters. Most commonly, 2 mg of fibrinolytic agent in 2 mL of solution is injected and allowed to dwell in the catheter for 2 to 3 hours. The catheter is then irrigated and flushed, with removal of any residual clot. This process can be repeated until patency is restored. In a study of 815 catheter occlusion episodes, success was achieved in 77% of cases with the first infusion of alteplase and in an additional 10% of cases after the second infusion.[43] However, use of this technique may result in only a limited number of additional dialysis sessions before the treatment must be repeated. A study of 570 catheters during a 2.5-year period demonstrated a median of five to seven additional dialysis sessions after each treatment.[44] Guide wires should never be passed through catheters in an effort to relieve an obstruction because of the risk of dislodging part or all of the occlusion and causing an embolic event.

Because of the frequency of recurrent occlusion and the difficulty in delivery of a highly concentrated fibrinolytic agent to the fibrin sheath around the tip of the catheter, techniques have been developed to mechanically eliminate the fibrin sheath. These techniques generally involve the insertion of a wire snare device through another venous access site, such as the femoral vein, to strip the fibrin sheath from the catheter and remove it. In a study of 131 sheath-stripping procedures on 100 catheters, the technical success of the procedure was 95.6% and the mean primary patency after the first stripping was 89 days.[45] An alternative technique is to remove the catheter over a wire, then use an angioplasty balloon to rupture the sheath, and finally replace the catheter over the wire. A retrospective review of these two techniques compared with simple catheter exchange demonstrated no difference in patency.[46]

Central Venous Thrombosis

Catheter-related thrombus is present in approximately 30% of all patients with central venous catheters.[47] However, less than half of these thrombi are clinically significant.[47] The incidence of pulmonary embolus from catheter-related thrombus ranges from 0% to 17%, although catheter-related thrombus has rarely been reported to be the cause of death.[47] The more clinically significant implication of catheter-related thrombosis is its association with infection. In a study of patients with catheter-related *Staphylococcus aureus* bacteremia, 71% were found also to have central venous thrombus.[48] Nevertheless, the routine use of low-dose warfarin prophylaxis is not recommended.[49]

Venous thrombosis should be suspected in patients with tunneled hemodialysis catheters who present with arm, neck, or facial swelling; prominent collateral venous patterns; signs or symptoms of embolic complications; or unexplained fever. Duplex scanning generally is diagnostic, although venography is required on occasion for definitive diagnosis and determination of the extent of thrombosis. Conventional therapy consists of anticoagulation and elevation of the symptomatic arm. If possible, the catheter should be removed. Because patients with tunneled hemodialysis catheters often do not have other sites available for access placement, anticoagulation therapy with the catheter left in place can be considered.[50]

Central Venous Stenosis

Catheter-associated central vein stenosis develops as a result of injury to the intima of the vein by the catheter.[51] The association between subclavian vein cannulation for hemodialysis access and subsequent subclavian vein stenosis is well described.[52,53] The incidence of subclavian vein stenosis after placement of a tunneled hemodialysis catheter is significantly higher than that of internal jugular vein stenosis. In a study comparing venography in 50 patients dialyzed through a subclavian vein catheter and 50 patients dialyzed through an internal jugular vein catheter, 42% of patients in the subclavian group had a stenosis versus 10% in the jugular group.[54] As such, cannulation of the subclavian vein for hemodialysis access should be avoided if at all possible.

Presentation

Central vein stenosis can be completely asymptomatic. Often, an ipsilateral upper extremity access is created without knowledge of a central vein stenosis, which results in the rapid development of symptoms, the most common of which is arm edema. Patients with brachiocephalic vein stenosis can also present with facial edema. Other manifestations of central vein stenosis are aneurysmal dilatation of the extremity veins and the ipsilateral AVF, thrombosis of the access, inadequate dialysis, prolonged bleeding after use of the access, and superior vena cava syndrome.[51]

Treatment

Elevation and compression of the upper extremity can occasionally be enough to relieve the edema associated with central venous stenosis but is unlikely to be effective if there is an AV access on the ipsilateral extremity. NKF KDOQI guidelines recommend percutaneous transluminal angioplasty with or without stent placement as the preferred treatment for central venous stenosis.[2] In a small randomized study of percutaneous transluminal angioplasty and stent placement, 1-year primary patency in both groups was dismal at 12% and 11%, respectively.[55] However, the secondary patency at 1 year was 100% for percutaneous transluminal angioplasty and 78% for stenting. This marked difference in primary and secondary patency underscores the fact that multiple procedures are usually needed to maintain patency after endovascular management of central venous stenoses. Some authors have reported the use of custom-made paclitaxel-coated balloons with diameter up to 14 mm prolonging the restenosis interval from a median of 4 months with a standard balloon to 9 months with the paclitaxel-coated balloon.[56]

Catheter-Related Infection

There are three categories of catheter-related infection: exit site infection, tunnel infection, and bacteremia.[2] The NKF KDOQI

guidelines define an exit site infection as "inflammation confined to the area surrounding the catheter exit site, not extending superiorly beyond the cuff if the catheter is tunneled, with exudate culture confirmed to be positive." A tunnel infection is defined as "the catheter tunnel superior to the cuff is inflamed, painful, and may have drainage through the exit site that is culture positive." Finally, catheter-related bacteremia is defined as "blood cultures are positive for the presence of bacteria with or without the accompanying symptom of fever." The incidence of catheter-related bacteremia ranges from 0.6 to 6.5 episodes per 1000 catheter days.[57] Consequences of bacteremia include infective endocarditis and metastatic abscesses, the incidence of which increases when catheter salvage is attempted.[57]

Treatment

The predominant organism isolated from infected lines is gram-positive (52%-84%), with *S. aureus* making up 21% to 43%.[57] Ideally, the management of an infected hemodialysis catheter includes removal of the catheter.[57] Initial empirical antibiotic therapy should include broad-spectrum coverage of potentially resistant strains of gram-positive organisms as well as gram-negative organisms.[58] This coverage should be adjusted to a focused regimen when culture results become available. Amphotericin B or caspofungin, which has a more favorable toxicity profile, should be used if there is evidence of disseminated fungal infection or if patients demonstrate persistent fungemia after catheter removal.[49] Uncomplicated *S. aureus* catheter-related bacteremia is generally treated with 4 to 6 weeks of antibiotic therapy; gram-negative bacilli or enterococcus bacteremia is usually treated with 7 to 14 days of therapy. Bacteremia with *Candida* is usually treated with a minimum of 14 days of antibiotic therapy. Complicated bacteremia with septic thrombophlebitis or endocarditis is usually treated for 4 to 6 weeks and osteomyelitis for 6 to 8 weeks.[58]

Catheter exit site infections alone can usually be salvaged with topical and systemic antibiotics without the need for catheter replacement.[58] Presence of a tunnel infection or catheter-related bacteremia requires catheter removal with delayed placement of a permanent access. The NKF KDOQI Work Group recommends delay of placement of a new permanent access until culture results have been negative for at least 48 hours after cessation of antibiotic therapy.[2] Depending on the length of antibiotic therapy, this may or may not be reasonable. Strategies for catheter salvage include exchange over a wire and catheter salvage with or without antibiotic lock. A meta-analysis of 28 studies encompassing 1596 patients found that antibiotic lock solution and guide wire exchange had similar cure proportions that were both superior to systemic antibiotics alone.[59] Cure proportions were highest for coagulase-negative staphylococci, followed by gram-negative rods and *S. aureus*. Where catheter salvage has been described, it is associated with failure rates greater than 65%.[57] As such, the safest course of action is most often to remove the catheter.

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CHAPTER 178

Hemodialysis Access: Failing and Thrombosed

GEORGE H. MEIER

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Although placement of arteriovenous (AV) hemodialysis access is an important step in the management of patients with end-stage renal disease (ESRD), the maintenance and remediation of a failing or thrombosed AV access is almost as important. Dialysis access is a lifeline for ESRD patients, so access maturation and continued function are critical for these patients' overall well-being. The specific treatments for a nonmaturing or failing AV access may be slightly different from those for a thrombosed AV access; however, the long-term management of all dialysis patients centers on preserving the adequacy of their dialysis treatments for as long as possible with minimal intervention.

The flow disturbances and hemodynamic changes associated with an AV access can initiate an intimal hyperplasia (IH) response.[1-4] The IH occurs primarily at the outflow anastomosis of a prosthetic AV access (Fig. 178.1) and anywhere along the outflow vein in an autogenous AV access (Fig. 178.2). It can also involve the distant, ipsilateral central veins (e.g., subclavian), even in the absence of previous indwelling catheters.[5-7] Some patients develop intractable IH with the early onset of a critical stenosis, whereas others have a more limited response without any significant hemodynamic impact. The underlying mechanisms responsible for AV access IH are ill-defined, but the resulting lesions are common, occurring in the majority of patients with dialysis access, whether autogenous or prosthetic.

MEASURING ACCESS FUNCTION

The optimal management of a failing or thrombosed AV access is partially contingent upon detecting access dysfunction. The most common measurement of access function is urea clearance with dialysis, or Kt/V, where K is the rate of clearance of urea, calculated from the pre- and postdialysis measurements; t is the duration of dialysis; and V is the patient's urea distribution volume. In this fashion, the "dose" of dialysis in a given session

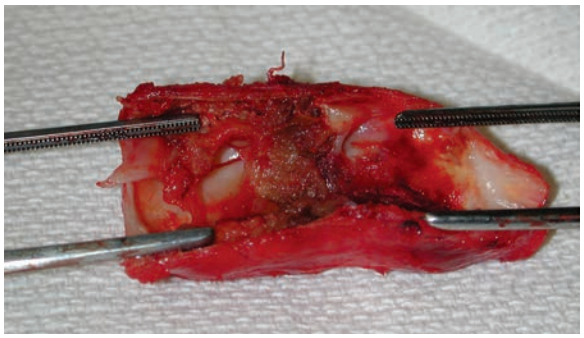

Figure 178.1 Surgical specimen demonstrating typical intimal hyperplasia at the venous anastomosis of prosthetic arteriovenous access.

Figure 178.2 Fistulagram demonstrating intimal hyperplasia throughout an upper arm arteriovenous access.

can be calculated objectively.[8-10] Kt/V is generally monitored to ensure that it remains over 1.2.

The function or quality of the AV access affects the maximum dialysis dose in several ways. First, adequate flows in the access are needed for the dialysis machine to function efficiently. Currently, high-flow dialysis is the norm in the United States, with pump speeds of 350 mL/min or more common. As long as the dialysis membranes can tolerate this high flow, the dose of dialysis can be given in a shorter time, reducing both costs and resources needed. Nonetheless, this high-flux technique requires much more efficient access function and is less tolerant of problems related to recirculation or high venous pressures. Recirculation, the retreatment of blood already filtered by the dialysis machine, can be insidious, often showing up as poorer solute clearances with each subsequent dialysis treatment.[11,12] Pressure limits are typically set on the dialysis machine; as a result, increasing venous pressures result in more prolonged dialysis because of efforts to reposition the efferent needle and thus remedy the high pressures.

Mechanisms of Access Failure

Flow Limitation

A functional AV access requires flow rates that exceed the pump speed of the dialysis machine by several-fold. With modern, high-flux dialysis, pump speeds may approach 500 mL/min. Thus flows of 1000 to 1200 mL/min are needed in the AV access to avoid recirculation.[13,14] In addition, adequate cardiac output is essential to maintain these flow rates. If cardiac output is marginal, decreased access flow may occur over the course of the dialysis session because of decreased preload associated with successful fluid removal during dialysis. Limitation of the access flow, by whatever mechanism, results in the recirculation of already dialyzed blood to the dialysis machine, greatly limiting the effectiveness of dialysis.[9,15,16] Recirculation can result when the afferent needle pulls blood that has just been returned to the patient via the efferent needle. This partially dialyzed blood is then dialyzed a second time, with decreased removal of substrate caused by lower concentrations in the partially dialyzed blood. This results in a decreased effective dialysis dose, with a longer duration of dialysis required to achieve the same clearance. There are several mechanisms by which recirculation can occur.

Venous Outflow Stenosis

The classic cause of recirculation is venous outflow stenosis, resulting in decreased flow through the AV access and increased recirculation of blood to the afferent needle. Regardless of the adequacy of arterial inflow, an outflow stenosis limits flow and increases recirculation. This is a common problem seen with failing prosthetic AV accesses.

Arterial Inflow Stenosis

Arterial inflow stenosis can similarly limit flow through the AV access, but in this case, both needles are distal to the stenosis. The limited arterial inflow results in recirculation from the distal efferent needle to the proximal afferent needle. This is a common mechanism of failure of autogenous AV access, occasionally leading to complete collapse of the outflow vein during dialysis.

Cannulation Location

Another important cause of recirculation is inadequate separation of the cannulation needles. Specifically, recirculation will occur if the needles are positioned too close together, even in the presence of a high access flow rate. Repeatedly puncturing the access at the same convenient location, rather than rotating puncture sites, can cause false aneurysms or pseudoaneurysms. If these are sufficiently large, recirculation can occur because of the stagnant flow within the pseudoaneurysm. In addition, these pseudoaneurysms are problematic because they are often the sites of infiltration and bleeding (Fig. 178.3).

Conduit Access Limitation

Although access flow is of fundamental importance, the conduit itself may be the cause of problems, or there may be secondary issues that limit the ability to puncture the AV access for reliable dialysis. If the vein is too deep or too small for reliable

Figure 178.3 Repeated cannulation at the same site resulted in a pseudoaneurysm associated with infiltration and ulceration.

cannulation, dialysis may be problematic, even with adequate flow. In a morbidly obese patient with ESRD, a vein of any size may be inadequate because of the depth of the overlying skin and soft tissue through which the vein must be cannulated.[17-19] In these patients, superficial transposition or elevation of the vein conduit may be necessary to allow maturation and reliable cannulation.[20-23]

CAUSES OF ACCESS FAILURE

Once dialysis access is established, the mode of failure is usually related to the type of access constructed. In the case of tunneled dialysis catheters, failure usually results from thrombus or the development of a fibrin sheath surrounding the catheter (see Chapter 177). For both autogenous and prosthetic AV accesses, the issue is often the development of venous outflow stenosis or stenosis of the autogenous access itself resulting from IH, leading to limited clearance.[24-28] Autogenous AV accesses may have limited patency after thrombectomy, so intervention is recommended before thrombosis occurs. Prosthetic accesses thrombose at a higher overall flow rate than autogenous accesses, but they may have better patency after thrombectomy. Thrombosed prosthetic accesses can often be remediated multiple times before they need to be abandoned.

As stated previously, IH is one of the unresolved issues affecting both the establishment and maintenance of a functional AV access. Although IH can occur anywhere in the outflow veins, certain anatomic factors can predispose to local or remote stenoses. For example, central venous stenosis is common in both autogenous and prosthetic AV accesses (Fig. 178.4). In the past, this was often attributed to the use of subclavian catheters, because the subclavian veins were the most common sites of central venous access.[29-31] In most modern dialysis centers, use of the subclavian veins for catheter access is avoided, specifically for this reason; yet there is still a high incidence of subclavian vein stenosis with upper extremity accesses. It is likely that the high flow across the subclavian vein at the thoracic inlet generates a perturbation in flow that leads to IH and stenosis. In this fashion, almost any vein used in the outflow of an AV access

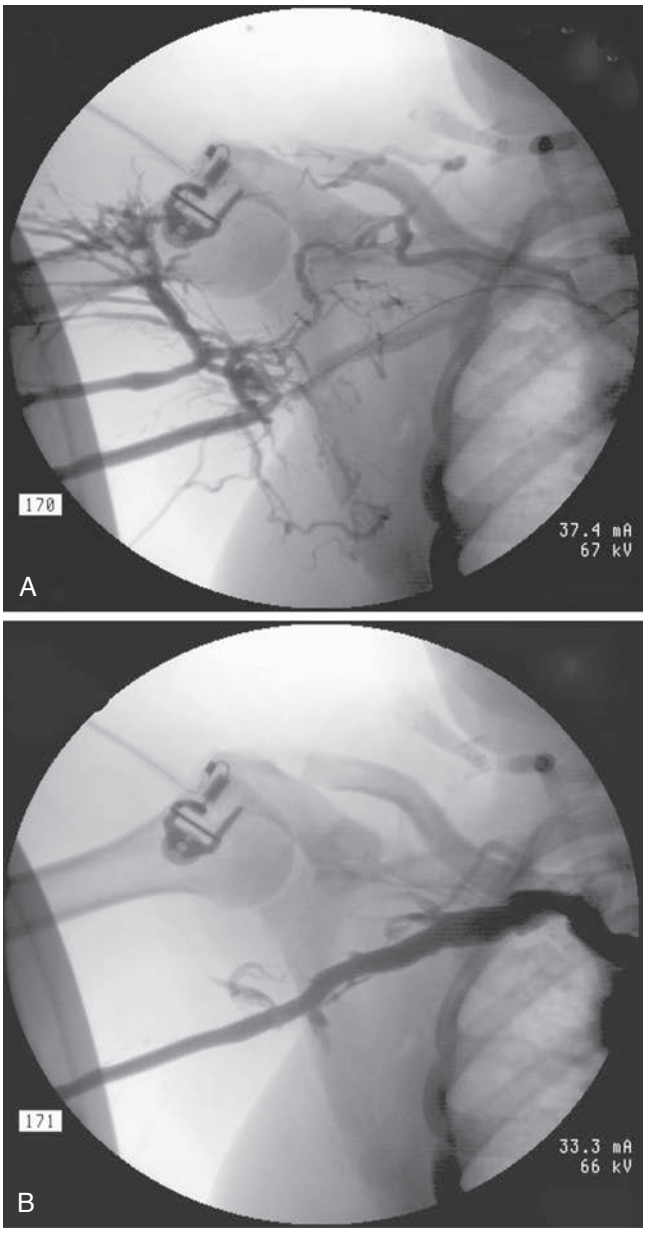

Figure 178.4 A stenosis in the axillary vein secondary to intimal hyperplasia is shown (A) before and (B) after successful treatment with an 8-mm high-pressure angioplasty balloon. Note the resolution of the venous collaterals.

can develop IH and stenosis. Another unavoidable factor is puncture of the conduit that leads to IH in autogenous conduits and to local tissue ingrowth in prosthetic accesses, simulating IH. Finally, IH occurs at the venous anastomosis of prosthetic AV access, theoretically aggravated by the excess turbulence associated with the size and compliance mismatch between the prosthetic graft and the outflow vein (see Chapter 5).

Detection of Access Failure

Clinical Evaluation

In many cases, clinical examination may be sufficient to assess access function with a reasonable degree of certainty. If an access is functioning well, a continuous thrill should be present near the arterial anastomosis, and it should be detectable for several

centimeters into the outflow vein. If a pulse is present near the venous outflow, then venous outflow stenosis is likely. In most cases, a thrill distal to an area of pulsatility suggests the location of the stenosis. Pseudoaneurysms of the access may result in local pulsatility in the areas of enlargement, independent of venous outflow issues. Only areas of normal diameter can be assessed by physical examination for pulsatility caused by venous outflow stenosis; aneurysmal or pseudoaneurysmal areas will often have increased pulsatility.

Collateral Veins or Edema

Collateral veins around areas of stenosis or occlusion are important indicators of elevated venous pressures. Typically this occurs around the shoulder or the anterior chest wall for upper extremity accesses as a result of a subclavian vein stenosis or occlusion. Thus the physical examination in these patients should include special attention to the head, neck, chest, and shoulder. Similarly, patients with a significant venous outflow stenosis without adequate collaterals may present with upper extremity edema alone.[32-34]

Access Bleeding

High venous pressures can lead to excessive access bleeding after removal of the cannulation needles, and this is often discovered by the dialysis center staff because of the prolonged time required to obtain hemostasis.[35-38] This may be the first indication of increased venous pressures and is a common indication for interrogating the access with either duplex ultrasound or venography. Venography may be better than ultrasound in this situation because it affords the opportunity to both diagnose and treat any venous outflow lesion (see the section on "Interventions for Failing Access"). The central vein stenoses responsible for the elevated pressures can lead to an insidious decrease in the access flow rates, often not recognized until later by the dialysis staff. Thus excessive access bleeding should initiate an evaluation that can lead to intervention before access failure; this is especially important for autogenous AV access.

Failure to Mature

The increased blood flow through the outflow vein of an autogenous AV access causes the vein to dilate and its wall to thicken or become "arterialized." Although this process varies by patient and specific vein, the outflow vein usually matures sufficiently for cannulation within 3 to 4 months of creation. When an autogenous AV access fails to mature, the underlying causes may be difficult to distinguish on clinical examination. In the presence of an arterial inflow stenosis, a good thrill may be present, but inadequate flow through the narrowed segment may prevent reliable cannulation with the venous return needle (i.e., efferent needle). Cannulation can be assisted by occluding the venous outflow using a tourniquet to allow maximum venous distention for the puncture; however, any residual outflow vein branches close to the site of stenosis may prevent distention and lead to an inability to cannulate the access. These collateral or "accessory" veins can also theoretically inhibit the maturation process of the main outflow vein by the diversion of blood away from the main channel, even in the absence of an arterial inflow stenosis. It is somewhat paradoxical that low resistance venous outflow improves dialysis function by preventing recirculation, although it can make access cannulation more difficult.

Inability to reliably cannulate an autogenous AV access for dialysis may also indicate that an access has failed to mature and may require revision, despite the fact that the vein may have dilated sufficiently (i.e., 6 mm). It is important to emphasize that the ability to reliably cannulate an access is also dependent on the experience of the individual performing the cannulation in addition to the quality of the access itself. Fragile, immature veins that have not become arterialized sufficiently to withstand the trauma of repeated cannulations may lead to hematomas around the needle access site. The presence of significant hematomas may lead to further problems cannulating the access (both autogenous and prosthetic) and predispose to the development of a stenosis. In other cases, the access vein may simply be too deep to allow easy cannulation. An open dialogue between the access surgeon and the dialysis center personnel is important to determine the cause of any cannulation difficulties to both optimize maturation and prolong the functional life of the access.

Assessment During Dialysis

There are several techniques for monitoring dialysis access function, all based upon the measurements of access flow, pressure, or flow resistance. From a practical standpoint, two methods predominate: measurement of static venous pressure and measurement of flow rate using ultrasound flow measurement.

Venous Pressure Measurement

Intimal hyperplasia static venous pressure is perhaps the easiest of the surveillance techniques and the most widely used in dialysis centers.[37,39-41] To measure this value, the dialysis pump is turned off, and the circuit is allowed to equilibrate. The venous (i.e., efferent) needle pressure is then used as the static venous pressure. Individual measurements that are greater than 50% of the mean arterial pressure are considered abnormal; however, the trends over time are more reliable and predictive than a single measurement. Specifically, if the static venous pressures increase over a series of measurements, investigation is indicated even if the 50% mean arterial pressure threshold is not achieved.

Flow Measurement

The second technique for assessment is using a Transonic Hemodialysis Monitor (Transonic Systems, Inc., Ithaca, New York) within the dialysis circuit.[42-44] Using this technique, a bolus of isotonic saline is injected into the blood stream and dilutes the blood and the corresponding ultrasound velocity. As the saline passes through the blood lines, a sensor registers an indicator curve that can be used to calculate the flow rate. There are several advantages of this technique. First, flow is measured by saline dilution with the needles reversed, producing a stable measure of access flow that is independent of the volume of the saline injected. Second, access recirculation can be assessed objectively at the same time with the same equipment using the needles in their normal orientation.[12,41,45-47] Therefore access flow and access recirculation can be assessed repeatedly over time to provide two independent measures of access function.

The development of an access stenosis is highly variable in onset. Some patients develop clinically significant stenosis within a few weeks of access creation, whereas others never develop a stenosis. Generally a flow rate of less than 600 to 800 mL/min predicts thrombosis in a prosthetic access, although the thresholds for autogenous accesses are not well defined.[15,44,48] The National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) Clinical Practice Recommendations for Vascular Access recommends further study and intervention when this threshold is achieved.[49] However, there is some suspicion that these rates may be too low, and that interrogation or intervention may be appropriate at a higher level (e.g., flow rates <900 mL/min). The KDOQI guidelines also recommend at least a monthly assessment of access flow using any number of techniques.

Duplex Ultrasound Access Surveillance

Although duplex ultrasound surveillance has been attempted for AV access, there are currently few data to suggest that it provides any real benefit in maintaining access function long term. Prospective trials of duplex ultrasound surveillance have not consistently demonstrated any patency benefit, with the limitation of a single study.[50] Duplex ultrasound can be useful in confirming any suspected abnormalities in access flow detected by physical examination, although it may not add much beyond a thorough examination by an experienced clinician. For this reason, duplex ultrasound for AV access is generally reserved for those situations in which the clinical examination is confusing or difficult.

Catheter-Based Contrast Imaging

Catheter-based contrast imaging is essential to any intervention to maintain or improve dialysis access function. Contrast imaging is, by definition, invasive because needle or catheter access involves skin puncture. In general, contrast imaging provides anatomic information rather than physiologic data, although access flow can be inferred from the anatomic images. For this reason, surveillance and monitoring are complementary to contrast imaging, with anatomic contrast imaging providing supporting evidence for the alteration of access function identified by physiologic monitoring techniques.[51,52] In addition, once the underlying anatomic defects are identified, intervention can be performed in the same setting as the diagnostic study. Performing the diagnostic and therapeutic procedures at the same time can avoid the risk of access failure during the intervening time associated with a staged approach.

INTERVENTIONS FOR FAILING ACCESS

Open Surgical Techniques

Revision for Stenoses

Open surgical revision of a stenotic segment within the AV access can improve both flow and function. The challenge is to define the underlying lesion responsible for the diminished flow. As with all access interventions, complete imaging from the arterial inflow to the central veins is necessary, and this is generally done at the time of operative revision. The advantage of simultaneous imaging is that questions concerning the access can be answered in "real time." Repeat imaging is often necessary to further define the relevant anatomy when the diagnostic imaging is performed at an earlier time.

Figure 178.5 Collateral veins with venous hypertension due to central venous stenosis associated with a tunneled dialysis catheter.

Surgical revision for stenosis is generally performed using an interposition graft or a patch angioplasty (Fig. 178.5). Both techniques have advantages and disadvantages, can be effective, and are widely used. The use of an interposition graft to bypass a stenosis at the venous outflow of a prosthetic access essentially re-sites the venous anastomosis, thereby limiting the length of available vein that can ultimately be used to construct any new permanent access. Patch angioplasty simply enlarges the area of stenosis without removing the local disease process (or consuming any available length of the vein), theoretically leading to a higher incidence of recurrent stenosis. However, results of these two techniques are largely equivalent.[53-55]

Revision for Other Problems

The presence of multiple outflow vein branches can limit the available vein length for cannulation and can inhibit the dilation of the main outflow vein during the maturation period. The significance of the collaterals may not be obvious at the time of initial access placement, but may become apparent if the access fails to enlarge above a large branch. In this situation, ligation of collateral branches may help maximize outflow through a single axial venous segment.

Translocation or elevation of a deep autogenous AV access may be necessary to allow successful needle cannulation. This is a common problem, particularly in obese patients with type 2 diabetes. In these patients, overlying fat and subcutaneous tissue may limit the ability to cannulate the autogenous access, even in the presence of high flow rates and a good outflow vein. Transposition to a more superficial location may allow access utilization that would otherwise be impossible.

The technique for superficial transposition is similar to that used in the second stage of a two-stage basilic vein transposition. In this situation, the depth of the vein from the skin is generally greater than its diameter. To reliably access the vein, the access should be within one vein diameter from the skin surface or within 6 mm as recommended by the KDOQI "rule of 6s," which is among their criteria for autogenous access cannulation (i.e., vein diameter—6 mm, depth from skin—6 mm, flow rate—600 mL/min).[56] There are two basic approaches to making the vein accessible. The first is to remove the fat and subcutaneous tissues overlying the vein and then re-approximate the subcutaneous tissues, which produces a shallower tissue depth to cannulate the access. The challenge in this technique is to somehow avoid developing scar tissue in the subcutaneous space that may limit needle access or generate IH. Bronder et al.[22] reported favorable results with this technique in a large series of patients.

The second technique involves transection of the vein, with superficial transposition and re-anastomosis. Although it may be possible to simply reattach the vein to its previous anastomosis, the access surgeon should be prepared to re-site the arterial anastomosis more proximally to accommodate any loss of vein length resulting from the new, superficial tunnel. This secondary surgical procedure, although generally not a major operation, may result in significantly greater morbidity than that associated with the original access procedure, given its potential for wound complications in obese patients. After transection of the vein, the longer segment is tunneled in a subcutaneous course. The vein is then carefully re-anastomosed to avoid unnecessary tension. As with the two-stage basilic vein transposition, the vein has already adapted to arterial pressure and flow, making the surgery safer and easier because the vein is somewhat easier to manipulate, although some venous hypertension is associated with the arterial communication. Any other abnormalities in the access can be addressed at the same time. In some cases, during maturation the vein may dilate and elongate, such that simple elevation without transection can be performed.

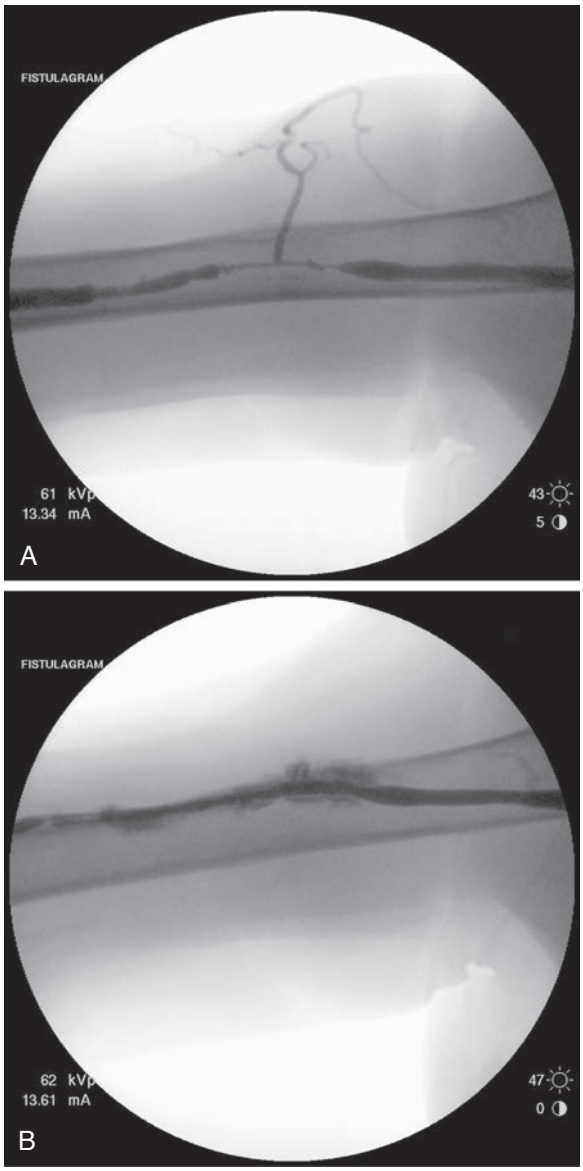

Figure 178.6 A diffuse, high grade stenosis in an autogenous access (A) with disruption and contrast extravasation (B) after balloon angioplasty with a high-pressure balloon.

Percutaneous Techniques

Percutaneous techniques for failing and thrombosed accesses are similar to those used in other vascular distributions. Once the complete circuit from the arterial inflow to the venous outflow has been imaged, specific approaches to the underlying pathology can be performed. Despite the similarities, the lesions encountered in AV access are much different from the arterial lesions, typically resulting from atherosclerosis. The fibrotic, rubbery stenoses characteristics of IH do not routinely dissect, like atherosclerotic stenoses, but more commonly tear or are disrupted as a result of the obligatory higher insufflations pressures (Fig. 178.6).

Balloon Angioplasty

Of all the percutaneous interventions performed on AV accesses, simple balloon angioplasty is the most common.[57-61] The balloon is placed within the area of stenosis and insufflated to a pressure that will eliminate any focal stenosis or "waist" seen on the distended balloon. The insufflation times are generally longer than those used in arterial disease, to allow more remodeling of the lesions to occur; this usually takes 2 to 3 minutes. Treatment is repeated until all areas of presumed outflow stenosis are adequately treated. Stenoses caused by IH routinely require high pressures to resolve, often 20 atmospheres or more. With these increased pressures, trauma to the vein can occur, which can stimulate the IH process, leading to recurrent stenoses. For this reason, some physicians advocate switching to a cutting balloon before high-pressure dilation,[62-66] allowing subsequent balloon angioplasty to be performed at much lower pressures.

A technique termed balloon-assisted maturation has been described to facilitate autogenous access maturation.[67-70] In this technique, the outflow vein is serially dilated with progressively larger balloons until a target vein diameter is achieved. The vein is allowed to heal between the serial dilations (hopefully without the development of IH), resulting in a larger venous

conduit once healing is complete. This approach was first described in 2001 by Turmel-Rodrigues et al.,[71] who reported a 97% success rate in 52 dysfunctional and 17 thrombosed forearm autogenous accesses with a mean age of 10 weeks. The corresponding primary and secondary success rates at 1 year were 39% and 79%, respectively. Subsequent authors have published similar results, advocating a policy of early intervention in patients with nonmaturing forearm autogenous accesses.[72] However, the long-term functional outcome of accesses treated by these techniques remains undefined.

Stenting

An intraluminal stent may be used to treat any residual stenoses or dissections after balloon angioplasty. However, in-stent restenosis is quite common with the use of bare metal stents.[73-75] More recently, covered stents have been used to prevent recurrent stenoses.[6,58,76-80] These devices are essentially fabric-covered stents designed to prevent the ingrowth of hyperplastic tissue, and thus avoid the early failures seen with bare metal stents. Notably, covered stents have been shown to have a patency advantage when treating stenoses at the venous anastomosis of prosthetic AV accesses, limited only by their expense.[58,76,79,81] Covered stents can also be used to prolong prosthetic AV access use in the presence of a large pseudoaneurysm or a degenerated graft.[82-87] Covered stents may allow continued needle punctures in previously aneurysmal (or pseudoaneurysmal) segments, with no apparent loss of patency. Although the durability of this method is not yet established, it may serve as a temporary bridge until further access or formal access revision can be performed.[88,89]

Hybrid Approach

Therapeutic endovascular procedures are often performed at the time of the diagnostic procedure, as outlined previously. Similarly, open, surgical revision can be performed at the same time as the diagnostic study if it is performed in an operating room, commonly a hybrid suite. The specific approach depends on the underlying pathology. A venous outflow stenosis may be treated by percutaneous techniques, whereas an arterial anastomotic stenosis may require open surgical revision. The catheter-based imaging can be performed in the operating room with either a portable C-arm or a fixed imaging system, and the choice of definitive intervention (open or endovascular) is dictated by the findings (Fig. 178.7). Thus hybrid procedures are often the most efficient for patients because all necessary treatments can be performed at the same session.

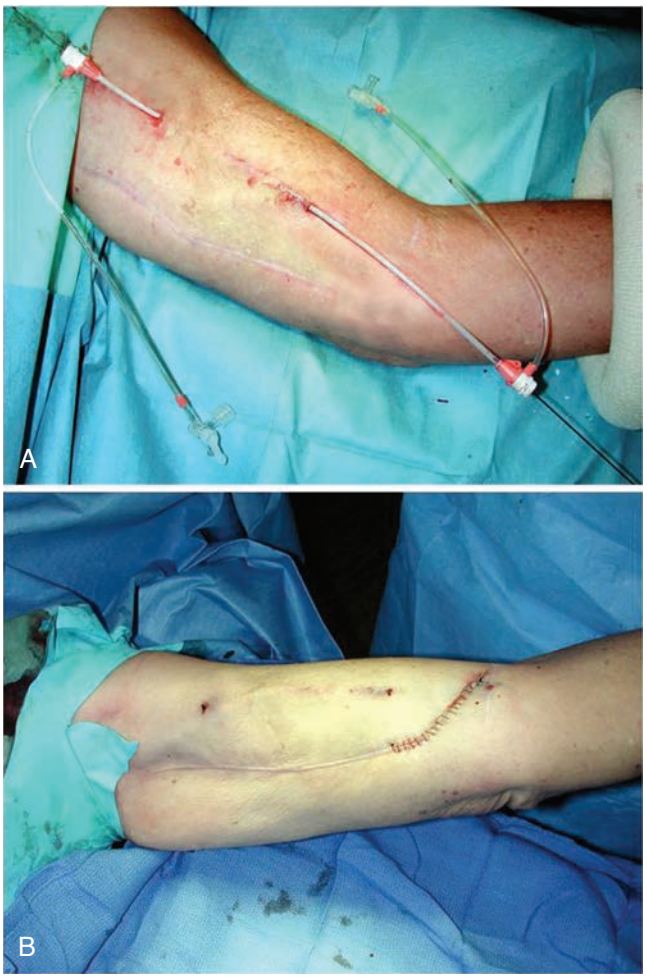

Figure 178.7 Patient with brachial-basilic autogenous arteriovenous access with stenoses at both the arterial anastomosis and within the outflow vein. A hybrid approach was performed, including (A) balloon angioplasty of the stenosis in the outflow vein and (B) open surgical revision of the arterial anastomosis.

INTERVENTIONS FOR THROMBOSED ACCESS

Autogenous Arteriovenous Access

The treatment of thrombosed AV accesses may be difficult, particularly for autogenous accesses. In this case, the endothelial surface may be significantly compromised, because thrombus rarely forms in native veins without some underlying abnormality. Thrombus removal (i.e., thrombectomy) often leads to recurrent thrombosis because the underlying flow surface is abnormal. This is further compounded by the trauma to the endothelial surface caused by the balloon thromboembolectomy catheter. For these reasons, open surgical thrombectomy has traditionally had limited value for autogenous AV accesses.[90-94] Palmer et al.[95] reported technical success in 7 of 10 patients with thrombosed autogenous accesses treated with an open, surgical approach. However, the corresponding 6-month primary and secondary patency rates were only 51% and 69%, respectively, for the accesses that were initially treated successfully. More recently, Cull et al.[96] reported excellent results and described a detailed technique to remove the thrombus. Although the role for surgical thrombectomy remains unresolved, it certainly merits consideration, and it is likely to be effective for limited or short-segment thrombotic occlusions.

Other series reported better results with percutaneous mechanical thrombectomy, but long-term data are still lacking.[97-100] Shatsky et al.[101] reported their experience using the Arrow-Trerotola device (Teleflex Medical, Research Triangle Park, North Carolina) in a series of 44 thrombosed autogenous accesses. Their primary patency rates were 38% at 6 months

and 18% at 12 months; secondary patency rates were 74% and 69% at 6 and 12 months, respectively. Although primary patency was limited, repetitive treatments seemed to be possible.

Prosthetic Arteriovenous Access

Prosthetic AV accesses tend to thrombose more frequently than autogenous accesses. Because the most common failure mode is IH at the venous anastomosis, they can usually be salvaged, providing long-term access without a significant disruption in a patient's dialysis schedule. In addition, prosthetic AV accesses tolerate balloon thrombectomy better than autogenous accesses because they do not have a viable endothelium, which is potentially susceptible to mechanical injury with thrombectomy, as in the case of autogenous accesses. Segments of the prosthetic graft itself can also be replaced as necessary to remediate any graft degeneration or localized soft tissue infections, oftentimes continuing the dialysis schedule using the residual, unaffected segment. A recent publication suggests that the shorter maturation times associated with prosthetic access (compared with autogenous accesses) may significantly reduce the number of catheter days for patients on dialysis, particularly with revisions performed with early access grafts.[102]

Open Surgical Techniques

The open, surgical treatment of a thrombosed AV access is predicated on the rapid removal of clot and definitive treatment of the underlying cause of failure. Most commonly, the access thrombosis is a result of venous outflow stenosis, although there are other mechanisms of failure. For example, a large pseudoaneurysm at a cannulation site may result in pooling of blood within the dilated segment with the stagnant flow leading to thrombosis. Similarly, inadequate arterial inflow may lead to graft thrombosis in the absence of venous outflow issues. Therefore the surgeon's first task is to determine the underlying cause of the thrombosis. The operative plan and the site of the incision are both dictated by the presumed underlying pathology.

The thrombus within an AV access can usually be removed using an appropriately sized balloon thromboembolectomy catheter; typically a 4F catheter is used for 6-mm diameter grafts. The location of the incision is based upon the anticipated revision. In the absence of any other obvious pathology, venous outflow stenosis is the probable cause and the focus of the likely revision. If the access has another significant obvious pathology, such as large pseudoaneurysms, it may be appropriate to incorporate this finding into the planning as well.

Once the access is cleared of thrombus, its full extent should be imaged from the arterial inflow to the venous outflow, including the central veins, ruling out any lesion that may predispose to a recurrent thrombosis. All venous anastomotic or outflow lesions should be repaired using conventional, open techniques. Patch angioplasty may be used to manage typical venous outflow stenosis (Fig. 178.8). This approach has the advantage of preserving the outflow vein, but it requires an extensive dissection in a scarred operative field. As an alternative, an interposition graft can be used to essentially re-site the venous anastomosis more proximally on the vein, avoiding scar tissue and providing the best-quality outflow.

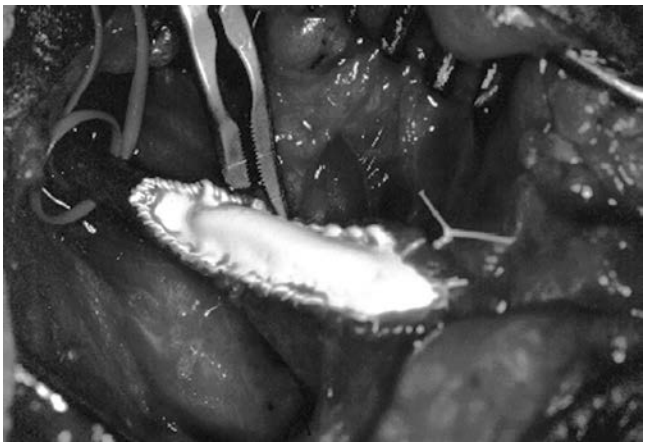

Figure 178.8 Surgical patch angioplasty using an expanded polytetrafluoroethylene patch at the venous anastomosis of a thrombosed prosthetic access.

Prosthetic AV accesses can usually be used for dialysis after open, surgical thrombectomy because there is often a sufficient length of the graft left undisturbed. For example, if the access-related problem occurs near the arterial anastomosis of a C-shaped configuration (e.g., brachial-axillary configuration), a distal segment closer to the venous anastomosis can be used for cannulation. Similar options for immediate cannulation may exist after open, surgical thrombectomy of autogenous accesses, but the need for a temporary catheter is likely increased.

Percutaneous Techniques

The use of percutaneous techniques for prosthetic access thrombosis was described in 1984 by Glanz et al.[103,104] in an effort to both avoid the loss of vein associated with surgical revision and to allow outpatient treatment. Since that time, the use of balloon angioplasty for venous outflow stenosis associated with AV access failure has grown dramatically. In these percutaneous techniques, the thrombus within the prosthetic access is generally removed as the first step, with treatment of underlying pathology as the second component.

Thrombolysis

The thrombus can be removed from the prosthetic access in a number of ways using percutaneous techniques. In most cases, crossed sheaths are placed within the clotted access, and a thrombolytic agent is infused to remove the bulk of the thrombus and provide some antegrade flow (Fig. 178.9).[105-111] Typically, 2 to 4 mg of tissue plasminogen activator is placed into the clot. The arterial and venous ends of the prosthetic access are intermittently occluded to allow the entire prosthetic graft (and thrombus) to be infused with lytic agent (Fig. 178.10). In the "lyse-and-wait" technique, the thrombolytic agent is given, and the patient is monitored in the holding area for a "return of flow."[107,110-113] In the "lyse-and-go" technique, the patient is immediately taken to the operating room or interventional suite for further percutaneous intervention. Typically an 8-mm

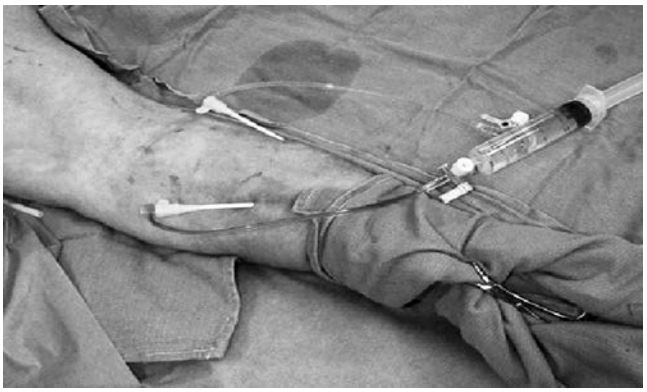

Figure 178.9 The crossed sheaths, typically used for endovascular treatment of a thrombosed prosthetic access, are shown with sheaths directed toward the arterial and venous ends.

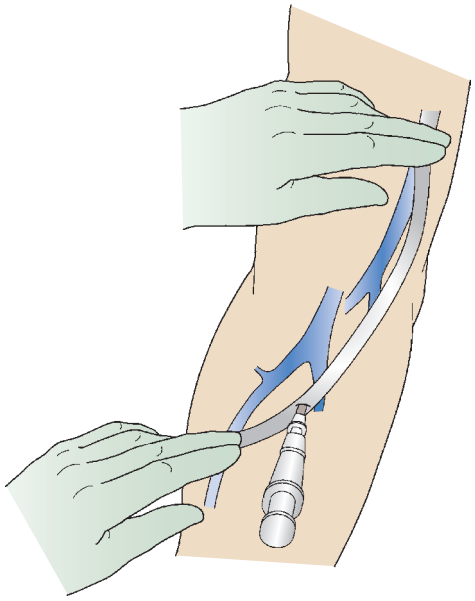

Figure 178.10 Thrombolytic agent is infused into the thrombosed prosthetic access, and both the arterial and venous ends are serially occluded to diffuse the agent throughout the thrombus.

by 8-cm high-pressure balloon (i.e., 8 × 80 balloon) is introduced through a sheath within the prosthetic access, and balloon angioplasty of the entire graft, including venous outflow, is performed. Any areas of residual stenosis are treated with balloon angioplasty using long-duration insufflations (typically >3 min). If there is a residual thrombus or "plug" at the arterial end, a balloon catheter is introduced through the venous sheath to facilitate extraction (Fig. 178.11). Any residual, partially lysed clot is further fragmented by repeat balloon angioplasty. Ultimately, the residual debris is released into the pulmonary circulation, although this is not usually associated with any systemic effects or complications.[114-118]

Alternatively, a mechanical thrombectomy device can be used alone or in combination with the lytic agent to debulk or remove thrombus within the prosthetic access. The most common devices used for this purpose are the AngioJet,[119-123] the Arrow-Trerotola device,[111,124,125] and the Hydrolyser (Cordis Corp, Bridgewater, New Jersey).[126-129] All these devices have their proponents, but none has proved superior in clinical settings.

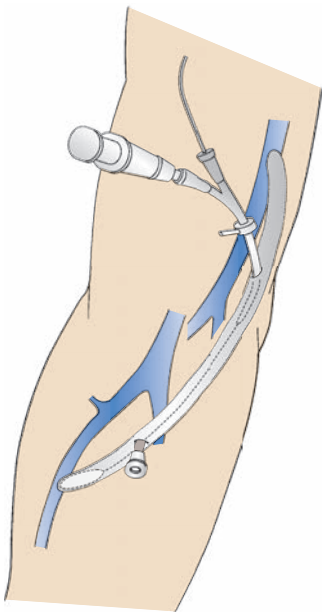

Figure 178.11 If a thrombus or plug persists at the arterial anastomosis, a conventional thromboembolectomy catheter can be passed through the sheath to facilitate removal.

Stenosis Treatment

Once the prosthetic AV access is cleared of thrombus, the next challenge is to treat the underlying cause of failure. Again, complete imaging from the arterial inflow to the superior vena cava is necessary to fully define the potential problems leading to the failure. Once the cause or causes have been defined, treatment is focused on the offending lesion(s). In general, a 6-mm prosthetic graft can easily tolerate balloon dilation to 8 mm. The fibrotic nature of IH may cause the offending lesion to recoil significantly, and thus prolonged high-pressure insufflations are often needed. Although ultra–high-pressure balloons may allow dilation of stubborn lesions in the venous outflow, tearing or disruption of the vein can occur with release of the balloon "waist." Some physicians advocate the use of cutting balloons followed by balloon angioplasty for refractory stenoses in an effort to better control the applied force (discussed previously).

Balloon angioplasty is appropriate for any significant central vein stenosis. Although balloon angioplasty alone in this situation is commonly associated with early recurrence, bare metal stents do not seem to provide any significant patency advantage because of recurrent IH within the stented segment or "in-stent" stenosis. Covered stents appear to improve patency for central venous lesions and should be considered for any recurrent lesions. Covered stents may also be beneficial in anastomotic venous outflow stenoses, which are more traditionally treated by balloon angioplasty alone. In a recent publication, Haskal et al.[130] showed that covered stents dramatically improved patency (51% in the covered stent group vs. 23% of those with balloon angioplasty alone at 6 months) in patients with failing

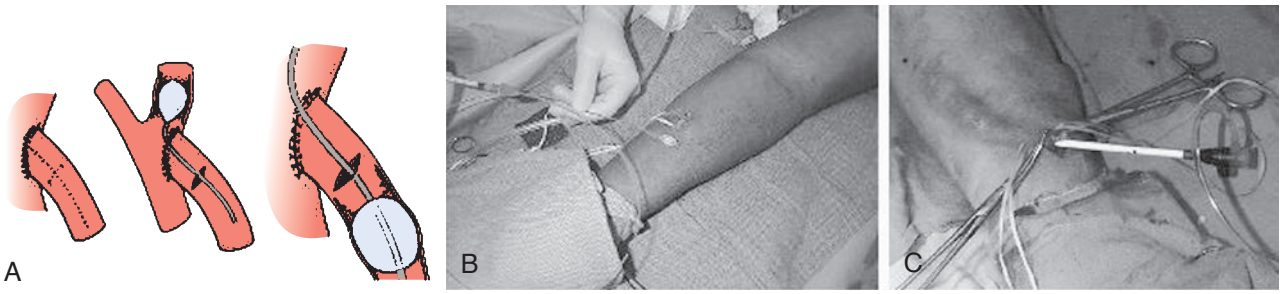

Figure 178.12 Hybrid technique for thrombectomy and angioplasty of a prosthetic arteriovenous access. (A) A thromboembolectomy catheter is passed proximally and distally through a small incision in the graft near the venous anastomosis. (B) Conventional balloon catheters are used for thrombectomy. (C) A sheath is then placed through the arteriotomy to facilitate imaging and potentially perform an endovascular intervention.

hemodialysis grafts. Although this overall patency difference is significant, the cost effectiveness of these relatively expensive devices is less clear.[131] Further studies also seem to support this concept,[78,83,132-134] but additional experience is needed to define their specific roles.

Hybrid Techniques

The two components of successful AV access thrombectomy are removal of the thrombus and treatment of the underlying cause of access failure. Removal of thrombus is often best achieved by open balloon thrombectomy; this can often be performed with the patient under local anesthesia with sedation and using a small incision over the prosthetic graft (Fig. 178.12). Once the thrombus is removed, complete imaging from the arterial inflow to the superior vena cava can be performed. With this approach, treatment of any remote, underlying lesion can be accomplished by techniques normally reserved for percutaneous treatment. The effectiveness of the thrombus removal with this hybrid approach is comparable to the open alternative, and no thrombus is left in the graft, thereby avoiding the potential to embolize into the pulmonary circulation, which may occur with the total percutaneous approach. Also, because thrombolytic agents are generally not used, the risk of bleeding (and bleeding complications) is decreased. Finally, any venous anastomotic stenoses can be treated with balloon angioplasty, thereby preserving the available length of the outflow vein, frequently compromised with the open, surgical approaches. In many ways, this hybrid procedure has the potential for improved results with reduced morbidity. Unfortunately, the published results of this hybrid technique are limited.[97,135,136]

TREATMENT OUTCOME

Unfortunately, there are few long-term data comparing these various approaches. The majority of the studies compare open, surgical thrombectomy for prosthetic access with the percutaneous approach.[137] Despite some limitations in the quality of the evidence, the outcomes for the two approaches appear to be comparable. The two variables that appear to have the most impact on outcome include the effectiveness of the thrombectomy and the treatment of the underlying cause of thrombosis rather than the specific approach. Most centers have already settled on their preferred techniques for the management of access thrombosis, and clinical protocols for management are often difficult to implement. Until alternative approaches are better validated, the "best" treatment will remain a topic of debate.

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179 CHAPTER

Hemodialysis Access: Nonthrombotic Complications

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The National Kidney Foundation Kidney Dialysis Outcomes Quality Initiative (KDOQI) 2006 Guidelines recognize the following access complications: bleeding, infection, aneurysm/pseudoaneurysm, seroma, access-related hand ischemia (ARHI), venous hypertension, and neuropathy.[1,2] Cardiopulmonary complications are also reviewed.

BLEEDING

Prolonged access-site bleeding and easy bruising are the most frequent complications. However, end-stage renal disease (ESRD) is also associated with increased rebleeding in peptic ulcer disease, spontaneous retroperitoneal bleeding, and hemorrhagic transformation of stroke.[3-8] Contributing factors include anemia, thrombocytopenia, acquired defects of primary hemostasis, repeated procedures, and antiplatelet and anticoagulant agents. With appropriate medical management, the risks can be minimized.

Etiology

Morgagni first described the association between bleeding and renal dysfunction.[9] Both platelet dysfunction and anemia play a role. At normal hematocrit levels, platelets and plasma reside at the vessel periphery, thus increasing contact with endothelium and facilitating activation and aggregation at sites of injury. In anemia, rheology changes.[10-12] When the hematocrit declines, there is an increase in nitric oxide (NO) activity, causing vasodilation and platelet inhibition.[13,14]

Moderate thrombocytopenia is common in ESRD but rarely causes significant bleeding. Increased bleeding is predominantly due to uremia-induced platelet dysfunction.[9,13-15] There is no

Abstract

Non-thrombotic complications are common in the hemodialysis population. Awareness of the complications, diagnostic tests, and interventions to treat are important, both for access maintenance and for overall care of the patient. This chapter discusses bleeding, access related infections, aneurysms, seromas, access-related hand ischemia, venous hypertension, neuropathy and cardiopulmonary complications.

Keywords

ARHI
Neuropathy
Bleeding
Aneurysms

direct relationship, but risk increases markedly when BUN is greater than 100 mg/dL (35.7 mmol/L). Uremia has been associated with defects at every stage of platelet function. Reduced expression of glycoprotein (GP) Ib impairs platelet adhesion to subendothelium,[16] and a conformational change in GP IIb-IIIa inhibits fibrinogen binding and platelet aggregation.[15] The content of dense granules is decreased, thus reducing the storage pool of platelet adenosine diphosphate (ADP) and serotonin[17] and increasing endothelial production of prostacyclin, which inhibits platelet activation.[11,18]

Many medications increase bleeding risk in CKD. Beta-lactam antibiotics (cephalosporins and penicillins) have prolonged half-lives and are only partially cleared by dialysis.[19] At high levels they cause platelet dysfunction. At extremely high levels, penicillins alter antithrombin III activity, causing heparin-like abnormalities.[20] Oral anticoagulation is common in CKD patients, as almost 20% have atrial fibrillation.[21] Most receive warfarin; however, use of novel oral anticoagulation (NOAC) agents is increasing.[22] NOACs are cleared by the kidney in varying degrees, and the initial safety and efficacy trials excluded dialysis patients.[23-27] A recent analysis of the Fresenius Medical Care North America ESRD database demonstrated that in comparison with warfarin, dabigatran and rivaroxaban are associated with a higher risk of bleeding, which can result in hospitalization or death.[22]

It should be noted that persistent or recurrent access-site bleeding should be evaluated for causes other than coagulopathy. Prolonged bleeding may be a sign of venous outflow stenosis, pseudoaneurysm formation, or access infection. At least 40% of fatal vascular access hemorrhages are preceded by a herald bleed or access infection within the prior 6 months.[28]

Treatment

There are several strategies to control bleeding and minimize surgical risk in patients with ESRD. The strategy is dictated by clinical circumstances and the urgency of intervention.

Active Bleeding and Emergent Surgery

Desmopressin (1-desamino-8-D-arginine vasopressin, or DDAVP) is a human-made form of the normal human hormone arginine vasopressin (the antidiuretic hormone, or ADH), a peptide containing nine amino acids. Compared with vasopressin, desmopressin's first amino acid has been deaminated, and the arginine at the eighth position is in the *dextro* rather than the *levo* form. DDAVP (0.3 to 0.4 μg/kg administered intravenously or subcutaneously) induces the rapid release of autologous von Willebrand factor (vWF) and factor VIII and transiently decreases the activity of protein C.[29-31] Tachyphylaxis typically develops after a second dose.[32] Platelet transfusion also works immediately but lasts for only 4 to 5 hours, as platelets become dysfunctional shortly after they enter a uremic environment.[13]

More prolonged effects can be obtained from cryoprecipitate, a plasma derivative rich in fibrinogen, vWF, and factor VIII that works within minutes. Maximal effects occur in 4 to 12 hours, lasting up to 24 hours.[13,33] The primary disadvantage is rare anaphylaxis or hemolysis.[13]

Persistent oozing during surgery or after dialysis may be secondary to heparin effects. If ACT is elevated, protamine can be administered, up to 1.5 mg/100 units of heparin, to reverse anticoagulant effect. Recombinant factor VIIa may be used "off label" as rescue; case reports describe success,[34-36] but it carries a risk of systemic thromboembolic complications.[37]

Elective Surgery

Preoperative planning should focus on minimizing platelet dysfunction and correcting anemia. Hemoglobin is below 10 g/dL in at least 20% of ESRD patients.[21] Adequate hematocrit provides a margin of safety and affects blood rheology, facilitating platelet function. Recombinant human erythropoietin induces erythropoiesis, thus correcting anemia,[13] but it takes several weeks to show an effect. Erythropoietin increases platelet expression of GP-IIb/IIIa and enhances platelet aggregation.[15,38] Platelet function can also be improved by scheduling surgery 24 hours after dialysis and by discontinuing antiplatelet medications 1 week prior.

Patients facing major operations may benefit from conjugated estrogens, 25 to 50 mg orally or 0.6 mg/kg per day IV for 5 consecutive days, which increase vWF synthesis, reduce protein S and NO, and correct bleeding time.[13,14,39-43] Effects are seen within 6 hours,[40] peak in 5 to 7 days, and last up to 14 days.[11] Transdermal estrogen administered 2 weeks prior (50 to 100 μg/24 hours) is an alternative.[14]

Postoperative Bleeding

Postoperative bleeding should be addressed by return to the operating room and exploration for surgically correctable causes. Pharmacologic adjuncts, particularly protamine sulfate, should be considered if the initial procedure involved heparin. DDAVP may also be helpful.

INFECTION

Infections are the second most frequent cause of death and loss of access site, occurring more commonly with prosthetic devices.[44-46] The risk of sepsis-related death is markedly increased in patients with CKD.[46] The Society for Vascular Surgery reporting standards recommend classifying infections as early (<30 days) or late (>30 days), culture-positive or culture-negative, and the site of infection (i.e., para-anastomotic, mid-AV access, outflow veins). Treatment is dictated by type and location of access, timing, and extent of infection. Grading of infection is as follows:

Grade 0: None
Grade 1: Resolved with antibiotic treatment
Grade 2: Loss of AV access because of ligation, removal, and bypass
Grade 3: Loss of limb

Bacteriology: Most access-related infections are due to single-organism gram-positive bacteria, *Staphylococcus aureus* predominating, Solitary gram-negative organisms account for 25%, with a small percentage being polymicrobial.[47,48]

Catheter Related: In comparison with autogenous AV fistulas, the risk of infection is highly dependent on type of access used:

2.2 ($P = .002$) for AV grafts, 13.6 ($P < .0001$) for tunneled catheters, and 32.6 ($P < .0001$) for temporary catheters.[46] Catheters, both temporary and tunneled, are the source of two-thirds of all infections and more than 80% of all bloodstream infections in hemodialysis patients.[46,49] In a study of 800 dialysis patients by the Centers for Disease Control and Prevention, use of a catheter, specific dialysis units, and malnutrition (albumin <3.5 g/dL) were identified as independent risk factors for sepsis.[50]

Epidemiology: Twenty percent of access loss is related to infection.[51] A prospective study found that the probability of infection at 1 year is 4.5% for autogenous AV fistulas versus 19.7% for prosthetic grafts.[52] A longitudinal cohort study of 4005 hemodialysis patients in the U.S. Renal Data System, found a RR for infection of 1.35 for prosthetic compared with autogenous grafts.[53]

Increased susceptibility to infection is related to impaired humoral and cellular immunity, nutritional deficiencies, frequent breaches of skin integrity, and the presence of prosthetic material.[53] Risk factors for infection include repeated cannulation, cannulation technique, poor hygiene, repetitive hospitalizations, duration of prosthetic AV access use, increased age, lower extremity location (18% vs. 1.6%; $P < .05$), and diabetes mellitus.[49,54] Gram-negative bacteria and associated remote infections or complications are more common with lower extremity prosthetic accesses (31% vs. 4%; $P = .003$).[41,42] The buttonhole technique is associated with higher infection rates than the rope-ladder technique or area techniques, due to inappropriate use of sharp needles after the tract has developed, inadequate use of disinfecting agents, and incomplete scab removal.[55,56]

Treatment

Broad-spectrum antibiotics should be initiated as soon as access-related infection is considered and tailored to the appropriate organisms as soon as possible. Most commonly, vancomycin and gentamicin are chosen because of their ease of dosing and spectrum of efficacy. In centers with a low prevalence of methicillin-resistant *S. aureus*, nafcillin, oxacillin, or cefazolin may be used.[57,58]

Autogenous Access: Most autogenous AV access infections are associated with cannulation issues or hematomas, with bacteriology similar to that seen in prosthetic infections. They may present with cellulitis or abscess. Most respond to a 2- to 4-week course of antibiotics, with surgery rarely necessary. Autogenous access with intraluminal endovascular devices requires a prolonged course (4 to 6 weeks) of parenteral antibiotics or may require resection of the prosthetic material.[46]

Prosthetic Access: Prosthetic access infections are more complex. Attempts at salvage are reasonable for limited infections, allowing uninterrupted dialysis, site preservation, limited catheter days, and decreased surgical complexity. Failure to improve with local resection may necessitate full graft excision. Greater than 50% of such infections involve only a discrete portion of the access.[59] Thigh graft infections are more likely to involve gram-negative bacteria (OR 10.22)[60] and distant seeding (15% vs. 3%, $P = .02$, OR 5.24).

Salvage is most frequently feasible when infection involves the midportion of the graft. Segmental resection is accomplished by exposure of uninfected graft, proximally and distally, and tunneling a new graft through clean tissue planes. The infected segment is then resected with the incisions left open. Early success is in excess of 90%,[61-63] but recurrent infection occurs in up to 20% of cases with secondary procedures needed in 19%. Another option includes use of a vacuum-assisted closure device after open surgical debridement.[64]

Anastomotic Infection: Anastomotic infections require aggressive therapy with complete graft excision to prevent disruption and hemorrhage.[65] Alternatively, subtotal graft excision may be considered with low-virulence organisms such as *Staphylococcus epidermidis.* This entails leaving a small cuff on the artery to decrease surgical dissection and complexity. Infection in the retained cuff has been reported in up to 17% of cases.[65] Brachial artery ligation, a last resort, is feasible in critically ill patients with grossly infected prosthetic grafts, with risk of hand ischemia dependent on the adequacy of the collateral circulation.[66] Cryopreserved vessels are an alternative to preserve the site. Matsuura achieved satisfactory 1-year primary patency (PP) and secondary patency (SP), 42%% and 68%, respectively, with a recurrent infection rate of only 2.3%.[67] Most infections presenting within days of access creation should usually be treated by complete graft excision.[46,61]

Thrombosed Grafts: Although removal of thrombosed AV grafts is not usually necessary[68] and can be technically challenging if such grafts are well incorporated, there are several studies demonstrating the potential for the thrombosed graft to serve as the source of infection.[65] One study found that 71% asymptomatic patients had positive indium scans, whereas 62% had perigraft purulence at the time of graft removal.[68] The decision to remove a thrombosed AV graft should be based on the classic signs of inflammation (rubor, dolor, calor, and tumor) combined with the absence of an alternative source of infection.

PSEUDOANEURYSM AND ANEURYSM

Pseudoaneurysms and true aneurysms create issues with cannulation difficulty, increased risk of thrombosis, pain, bleeding, cosmesis, and infection.[69] Progressive enlargement can compromise overlying skin; this may lead to rupture, which is sometimes fatal (Fig. 179.1).

Pseudoaneurysm

AV-access pseudoaneurysms develop due to trauma from repeated punctures or poor technique, with resultant perigraft hematoma formation in addition to increased intragraft pressures associated with outflow stenoses. Pseudoaneurysms occur in 2% to 10% of polytetrafluoroethylene (PTFE) AV grafts, more commonly in older grafts.[70] Surrounding tissue ingrowth limits pseudoaneurysm development, with poorly incorporated grafts at higher risk. Autogenous fistula pseudoaneurysms are less frequent but not rare.[71] Most are related to cannulation. Pseudoaneurysm changes should prompt a change in cannulation technique and

Figure 179.1 Symptomatic pseudoaneurysms with early skin erosion that appeared several years after creation of an autogenous proximal radiocephalic arteriovenous fistula.

location but is not a reason for intervention. Treatment is directed by complications.[70]

Treatment

Open: Interposition grafts involve resection of the segment with placement of interposition grafts or bypass around the lesion. This is most typical for prosthetic graft pseudoaneurysms. Although the new segment becomes incorporated, dialysis continues in incorporated segments. With extensive degeneration, options include a temporary tunneled catheter with replacement of all but anastomotic regions, or staged, segmental replacement, allowing use of the access while the new graft becomes incorporated but requiring two procedures. For extensive degeneration of an autogenous fistula, options include conversion to a graft ("graftula"), maintaining only the arterial anastomosis, and creating a new venous anastomosis. Another option is fistula reduction surgery with resection of a portion of the vein wall, typically over a 10-mm rubber catheter as a sizing dowel. This permits resection of the overlying skin and a short period of catheter access.

Endovascular: The advantages of endoluminal repair include lack of interruption of hemodialysis, avoidance of catheters, percutaneous procedures, and the ability to identify and treat concomitant venous stenosis, present in up to 73%.[69,72-74] Potential risks include stent-graft infection, continued difficulty of access due to the need to puncture the stent graft through the pseudoaneurysm, and persistent cosmetic issues. Barshes reported on 32 patients treated with Wallgraft, Viabahn, and Fluency self-expanding covered stents,[69] with 100% procedural success; PP was 82% and 28% at 30 days and 6 months, respectively. Although 73% of patients had resolution or a significant decrease in size of the pseudoaneurysms, 12.5% developed early thrombosis and 18.75% required additional interventions. Shah et al. found that simultaneous angioplasty of outflow stenosis was necessary in 56%, with 69.2% 6-month patency. Patients with skin erosions were at increased risk for failure due to infection (OR 5.0).[74] Florescu also identified infection as a significant risk of endovascular therapy, with infection occurring in 35% and thrombosis in 12%.[73] Although minimally invasive techniques are appealing, higher cost, risk of infection, and potential difficulty with access for dialysis without good long-term patency remain concerns.

True Aneurysm

Aneurysm formation in fistulas is seen adjacent to the anastomosis associated with hemodynamically significant stenosis, within cannulation areas, adjacent to stenoses midaccess, or next to vein junctions, valves, or rigid areas caused by prior catheters. Cannulation of the area should be discontinued with any type of aneurysm.

Treatment: The preferred treatment for postanastomotic aneurysms is relocation of the anastomosis to a more proximal site. Comparable SP can be achieved by balloon angioplasty of the stenotic anastomosis for small dilations, but this requires a longer time to resolution, leading to catheter use. Partial resection and patch angioplasty are alternatives. For aneurysms in the midportion, fistulogram should be performed to identify outflow stenoses that exacerbate aneurysm formation and can be treated with endovascular techniques. For diffuse degeneration, reduction of the lumen by partial aneurysmectomy is preferred. This requires a longitudinal incision along the length of the involved fistula. Woo reported reduction surgery in 19 patients with a median PP of 14 months.[75] Hossny found a cumulative patency of 85.7% at 1 year.[76] Pierce et al. reported a stapled revision in 12 cases[77] with no immediate wound complications, but 16.6% had problems, including thrombosis and persistent pain requiring ligation. Vo et al. reported 95% success, with a PP of 67% and SP 91% at 1 year, and 46% and 85% at 3 years.[78] Stapled repair can be performed with the Endo GIA stapler (Covidien, Mansfield, Massachusetts) or a TA stapler (Covidien, Norwalk, Connecticut). Reinforcement may be needed. Treatment for aneurysms along the venous outflow tract is angioplasty, with selective stenting.

Aneurysmal Degeneration of Inflow Artery

Arterial aneurysms are rare, as is arteriomegaly. Patients may present with distal embolization, ischemia, swelling, or a painful mass. Mestres et al. reported on 12 patients requiring intervention, with a median of 18.3 years of dialysis. Long-standing access with subsequent ligation or thrombosis and renal transplantation were associated factors.[79] Renal transplant and immunosuppression have been identified in association with arterial degeneration.[80,81] The decision to intervene depends on symptoms, aneurysmal size, patient comorbidities, and life expectancy. Radial artery pseudoaneurysms can be treated by ligation, whereas brachial or axillary aneurysms require bypass.

SEROMA

A perigraft seroma is a collection of sterile, clear, ultrafiltered serum surrounded by a nonsecretory fibrous pseudocapsule. Early seromas frequently resolve spontaneously and are not uncommon with prosthetic grafts. Chronic seroma is rare. Other noninfectious fluid collections include hematomas or lymphoceles. These complications are graded 0 to 3, as follows[2]:

Grade 0: No collection
Grade 1: Observed, resolved
Grade 2: Involves aspiration or surgical drainage
Grade 3: Results in loss of the graft

Most resolve without intervention.[82] Surgery is warranted when the seroma interferes with cannulation, continues to grow, or compromises overlying skin. Aspiration should be avoided, as it significantly increases the risk of graft infection and loss.

Etiology and Incidence: Seromas have been reported with both PTFE grafts and polyester fabric [82-84] at an incidence of less than 2%.[85-87] It is unclear whether location is a risk factor or facilitates recognition. Ladenheim et al. found a higher incidence, 36%, with gel-coated PTFE arteriovenous grafts[88] and concluded that they are not ideal for hemodialysis access.

The mechanism appears to involve increased graft porosity and failure of graft incorporation. Schanzer found that in prosthetic AV accesses, the seroma always occurs near the arterial anastomosis.[89] The active transudation of serum-like fluid can be observed when the prosthetic material is exposed at that point.[86] Several studies have suggested presence of a fibroblast growth inhibitor in patients' serum.[90-92] Histologic studies support this, as there are typically immature fibroblasts lining the graft.[83] Other theories include immunologic reaction, graft damage at implantation, and clinically occult infection.

Presentation: Ultrasound can help distinguish a seroma from a hematoma. Seromas generally appear within 1 month, are painless, and enlarge over time, leading to cannulation difficulty or thinning of the skin.[87] Surgical exploration reveals a fibrous pseudomembrane filled with serous or gelatinous material surrounding the prosthesis. There may also be visible graft sweating.[86,89]

Treatment: Blumenberg et al. reviewed 279 cases treated by 320 surgeons.[84] Treatment included serial aspiration, observation, incision and drainage, cyst removal, and prosthetic graft replacement. Graft replacement yielded the highest cure rate at 92%. Observation and aspiration had similar success (68% vs. 69%), but aspiration led to infection or thrombosis in 8%. Cyst removal had a 72% success rate, with infection or thrombosis in 12%. Incision and drainage had a 53% success rate, with seroma persistence in 40% and infection or thrombosis in 7%. Graft excision and cyst excision are recommended, with changing prosthetic material and rerouting through new anatomic planes. Dauria et al. reported 100% success with focal excision and bypass.[85]

Although most investigators advocate graft excision,[84,85,89,90,93] several reports suggest access preservation.[86,87,94-96] Rhodes described placement of microfibrillar collagn (Avitene; Bard Davol Inc., Warwick, Rhode Island) in the perigraft space.[95] Similarly, an 84% success was reported with fibrin sealing for PTFE grafts.[86] Borrero and Doscher report salvage by pseudocapsule excision.[87] Gargiulo et al. reported success with percutaneous Dacron-covered stents and closed suction drainage.[96]

ARHI or steal syndrome was initially described in 1969 by Storey et al.[97] It has been increasingly recognized as an uncommon but devastating complication of access. Access construction reduces digital blood flow in up to 80% of cases; however, only a few develop symptomatic ischemia.[98] Some coolness and tingling is present in up to 10%,[99] with many resolving in a few weeks. Significant ischemia incidence ranges from 1% to 2% with autogenous access at the wrist[100-103] and 4% to 8% in those with brachial-based access.[100,102-104]

Steal can be limb-threatening and must be promptly evaluated and treated if clinically significant. It is graded as follows[105]:
Grade 0: No symptoms
Grade 1: Mild—cool extremity, few symptoms, flow augmentation with access occlusion
Grade 2: Moderate—intermittent ischemia only during dialysis, claudication
Grade 3: Severe—ischemic pain at rest, tissue loss

Intervention is unnecessary for grades 0/1, sometimes needed for grade 2 and mandatory for grade 3.

Pathophysiology and Risk Factors

Creation of an access substantially alters flow dynamics and resistance in the extremity. The arterial inflow supplies two competing circuits—the low-resistance access proximally and the high-resistance peripheral vascular bed distally. The amount and direction of flow is determined by relative resistances and collateral circulation. A "physiologic steal" or reversal of flow in a portion of the arterial tree distal to the anastomosis is common after access creation. Kwun demonstrated reversal of flow in 73% of autogenous accesses and 91% of prosthetic accesses.[106] Reversal is neither necessary nor sufficient to cause distal ischemia.[107,108] Ischemia results from inadequate collateral circulation and inability of the arterial tree to meet increased demand. Under normal circumstances, the vascular system compensates via increased cardiac output (CO) and vasodilatation.[109] Diseased vessels do not vasodilate,[110,111] and stenosis leads to decreased distal perfusion pressure. Hypotension during dialysis further decreases perfusion and explains symptoms during treatment. ARHI is locoregional hypoperfusion secondary to inadequate arterial compensation.[112]

Risk factors for ARHI include diabetes, peripheral artery disease (PAD), coronary artery disease (CAD), brachial-based (proximal) access, female gender, history of ARHI, and multiple previous access procedures.[108,113-116] Hyperglycemia decreases shear-induced vasodilation, which is critical to both collateral recruitment and inflow artery remodeling.[110,111,117] Atherosclerosis increases the likelihood of flow-limiting inflow lesions and peripheral resistance. Brachial-based accesses increase flow relative to wrist accesses[118] and decrease resistance to flow in the AV access.

Prevention: The ideal strategy is prevention, which entails a thorough preoperative assessment and risk-factor evaluation. No test reliably predicts the development of ARHI. Although patients with a preoperative digital brachial index (DBI) less than 1.0 are more likely to develop steal, there is no cutoff below which steal is inevitable.[114] Similarly, Goff et al. found that an intraoperative DBI less than 0.6 had 100% sensitivity and 18% PPV for predicting eventual ARHI.[119]

Preoperative examination should include measurement of bilateral upper extremity blood pressures and an Allen test. Patients with an incomplete palmar arch with radial artery

dominance should not undergo radial artery–based fistula creation. In those with a questionable Allen test due to skin tone, a handheld continuous-wave Doppler can assess perfusion.[120] Berman et al. showed that only 0.3% of those who had a normal preoperative arterial examination could have been identified by additional physiologic testing and concluded that routine testing is not justified.[121] If patients have a blood pressure differential greater than 20 mm Hg,[121] that extremity should not be used unless the underlying problem can be corrected.

In high-risk patients, operative strategy may be adjusted to minimize the risk of ARHI. Brachial-based accesses are more likely to develop distal ischemia.[102,108,113] Consequently use of the proximal radial artery is preferable,[116] with 89% maturation and 84% 1 year patency with proximal forearm arteries.[122] Alternatively, axillary artery inflow in high-risk patients decreases ARHI, based on the larger capacity and smaller pressure drop across the anastomosis.[123]

Diagnosis

Clinical Presentation: Patients may present with a wide spectrum of signs/symptoms depending upon the severity of ischemia. ARHI may manifest as numbness, burning pain, and severe weakness within hours of access creation.[104] Acute ARHI (<24 hours) is rare but more likely with prosthetics.[124,125] Most symptoms develop over weeks to months[125] and occasionally years after access creation.[126-128] Symptoms range from coolness and paresthesias, to rest pain and weakness. Physical examination reveals a cool extremity, pallor, cyanosis, delayed capillary refill, absent pulses/signals, diminished sensation, weak grip, ulceration, or gangrene. Improvement with access compression confirms the diagnosis and predicts a good response to revision.[129]

Differential includes carpal tunnel syndrome (CTS), venous hypertension, and ischemic monomelic neuropathy. When the clinical picture is unclear, ischemia should be presumed until proven otherwise. The one exception is acute presentation, immediately after access creation, when ischemic monomelic neuropathy (IMN) must be considered.

Diagnostic Testing: Multiple studies support the diagnosis, but none is definitive. These include digital pressure measurement, photoplethysmography (PPG), pulse oximetry, color duplex ultrasound, and angiography (all performed with/without access compression). PPG is simple to perform and is recommended. Most access patients have both a reduction in digital pressure and flow reversal in distal arteries, whereas only a few are symptomatic.[98,106,107] Modaghegh et al. attempted to define clinically relevant thresholds for DBI and pulse oximetry and found that a DBI of less than 0.7 was 100% sensitive but only 73% specific. With respect to pulse oximetry, they identified a threshold of 94% (sensitivity 80%, specificity 92.5%).[130] Many patients have preserved flow at rest and become ischemic only during dialysis. In 16.6% of Berman's series, in digital waveforms flattened only during dialysis.[121] Lazarides et al. utilized the postoperative systolic pressure index (SPI, postoperative forearm pressure divided by contralateral forearm pressure) to identify a group of patients at risk. They found that 14% had mild to moderate ischemic symptoms and an SPI less than 0.4. This group was followed closely, with 50% improving over time, as did the SPI; the remaining patients required revision. An SPI less than 0.5 was predictive of abnormal NCS and indicated significant ischemia. These investigators recommend serial SPI and NCS to identify patients at risk and suggest that the deterioration of NCS should be considered an indication for revision.[104]

Angiography and duplex ultrasound help to determine the mechanism of ARHI (Figure). Inflow stenosis is a factor in 15% to 20% of cases.[103,121,131,132] Therefore angiography should be the first step in intervention and should include imaging the aortic arch to hand (Fig. 179.2). Duplex ultrasound with access flow measurements should also be obtained to determine flow rates—high (autogenous >800 mL/min, prosthetic >1200 mL/min[127]) or low—to facilitate the planning of intervention.

Treatment

Deciding which patients need intervention requires judgment. Transient, mild symptoms[99,133] often resolve within a few weeks[134] and can be managed expectantly with reassessment, warming, and antihypertensive reduction.[135] Patients experiencing ischemic pain with arm activity or during hemodialysis are at greater risk and need closer monitoring. Once severe symptoms are present (progressive numbness or pain, pallor of the hand, diminished sensation, ischemic ulcers, progressive dry gangrene, decreased motor function, or atrophy of the hand muscle), swift intervention is critical.[133] Typically symptoms occur with gradual tissue loss; if this is ignored, however, there is a rapid final deterioration leading to necrosis and gangrene.

The goal of treating ARHI is twofold: symptom resolution and access preservation. These include two basic strategies: access-flow reduction and augmentation of distal arterial flow. Options include banding, revision using distal inflow (RUDI), proximalization of arterial inflow (PAI), distal revascularization with interval ligation (DRIL), and angioplasty. Ligation is a last resort in those with limited life expectancy, severe tissue loss, or a poorly functioning access.

Reduction of Access Flow

Banding or Flow-Limiting Procedures: These procedures entail the creation of a stenosis in the AV access near the arterial anastomosis, which is accomplished via suture plication, placement of a single narrowing tie, or wrapping with a constrictive prosthetic cuff. This alters the relative resistance of the access and the peripheral vascular bed such that a higher proportion of the arterial inflow is directed toward the hand. It can be difficult to determine the precise degree of stenosis that will eliminate ischemia without endangering access patency; consequently results have been variable, both in terms of symptomatic improvement and access preservation (Table 179.1).

Many early series based the degree of banding on intraoperative assessment of distal perfusion without attention to access flow. Odland et al. found 100% symptom resolution with 62% patency at 6 months and 38% at 1 year with banding and PPG monitoring with a target endpoint digital artery pressure of 50 mm Hg or DBI of 0.6.[100] DeCaprio et al. described 11

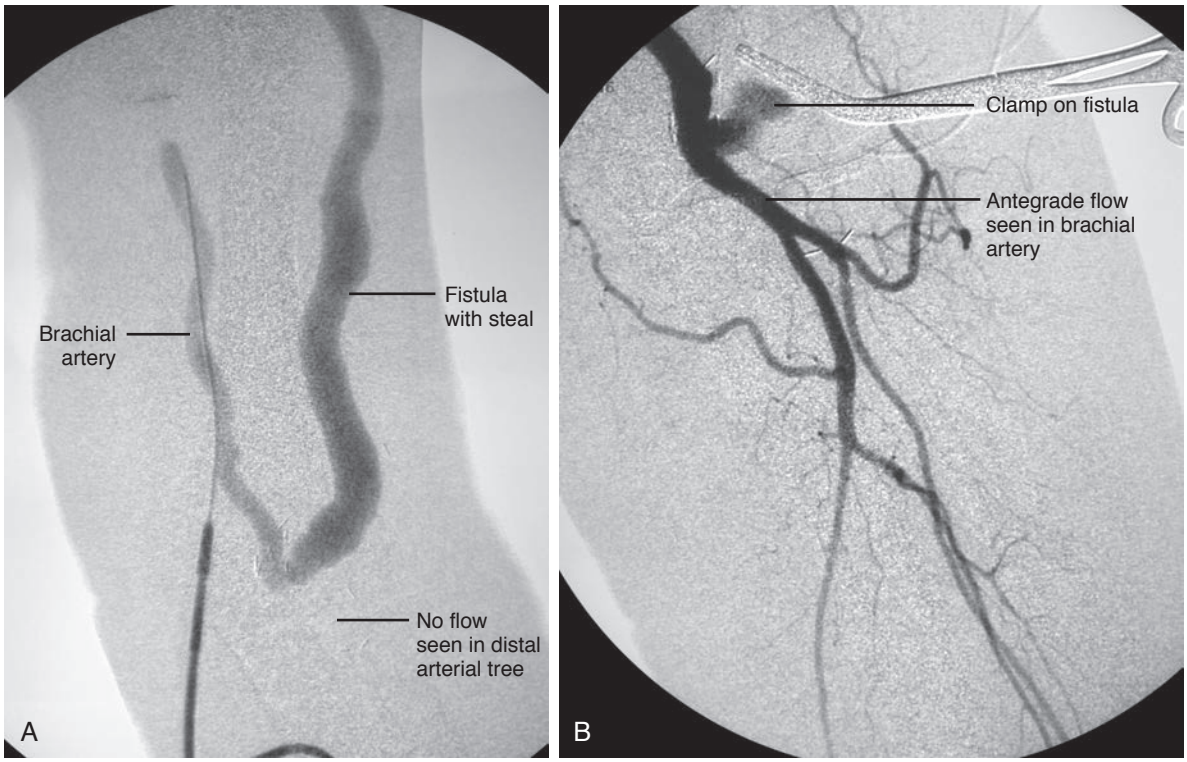

Figure 179.2 Arteriogram of a patient with steal syndrome with and without arteriovenous access compression. Note visualization of the distal brachial artery and forearm vessels with compression.

patients titrated to a pressure of 50 mm Hg with 91% symptom improvement but 91% access loss within a week.[131] Recent studies report superior results when access flow is monitored intraoperatively. Zanow achieved 86% symptoms relief and 84% patency at 1 year.

Although flow monitoring has proven beneficial,[127,136-139] access flow rates appear to be most important in prosthetic grafts. In Zanow's study, 12-month patency rates for autogenous accesses were better than those for AV grafts (91% ± 4% vs. 58% ± 12%; $P < .001$). On final analysis, access flow of 700 mL/min is an important cutoff for maintenance of access patency (38% vs. 74% patency), suggesting the reason for earlier failures with banding.[100,131,145,147]

Despite favorable results using intraoperative physiologic testing and flow monitoring, it is important to realize that anesthesia-induced changes can make these tests inaccurate. Consequently a number of groups now advocate using minimally invasive limited ligation endoluminal-assisted revision (MILLER)[149] for banding. This method uses a 4- to 5-mm endoluminal balloon placed percutaneously as a sizing dowel. A small incision is made near the anastomosis, allowing a suture to be secured around the access with the balloon inflated. Miller and colleagues achieved significant clinical improvement in 89% of 114 patients with an early thrombosis rate of only 4.4%.[145]

Revision Using Distal Inflow (RUDI): RUDI was proposed by Minion et al. in 2005[150] but had been previously described.[151] RUDI involves ligation of the fistula at the arterial anastomosis with reestablishment of flow from a more distal artery via bypass or translocation of a vein side branch (Fig. 179.3). The decision to use ulnar or radial artery is based on quality of the vessel, with preference for supply to nondominant hand. This decreases flow through the access by reducing the diameter of the fistula and taking inflow from a smaller vessel. The native arterial flow is preserved and the fistula rather than the extremity is placed at risk.

Recent case series demonstrate promising results. In a series of 20 patients, Misskey et al. achieved symptom resolution in 90% with 1-year PP and SP of 58% and 84%, respectively.[152] Leake and coworkers reported 89% clinical improvement and 95% access preservation in 19 patients. However, 22% experienced bleeding and 5.6% developed surgical site infection.

Direct Augmentation of Peripheral Flow

Proximalization of Arterial Inflow (PAI): PAI, described by Zanow et al.,[153] involves ligation of the AV anastomosis and conversion of inflow to a more proximal level using a small-caliber (4 to 5 mm) prosthetic interposition (Fig. 179.4). Some degree of flow limitation is imposed by the interposition. Uninterrupted dialysis continues via the vein. This relies on the proximal artery having a larger diameter, higher capacity, and lower pressure drop across the AV anastomosis at similar access flow rates. The primary advantage is preservation of the native artery's continuity.

Zanow et al. reported complete resolution of symptoms in 84% and significant improvement in 16% of their patients. Access PP was 87% at 12 months and 67% at 36 months.[153] In a subsequent series, Thermann and Wollert reported immediate clinical success in 90% and sustained improvement in 82% at 19 months.[154] Patients with severe tissue loss did particularly

TABLE 179.1 Banding Outcomes Based on Type of Intraoperative Assessment Tool

Author	Year	Pts (*n*)	Prosthetic (%)	Banding Technique	Intraop Assessment Tool	Significant Symptom Relief	Early Thrombosis *n* (%)	Follow-Up (Months)
Zanow et al.[127]	2006	78	12	Plication + cuff	Access flow	67 (86)	6 (8)[a]	25 (1–73)
Thermann et al.[136]	2007	15	13	Plication + cuff	Access flow	10 (67)	0	18 (6–70)
Van Hoek et al.[137]	2009	9	0	Polyester cuff	Access flow, PPG	9 (100)	0	30
Shemesh et al.[138]	2010	7	0	PTFE cuff	Access flow	7 (100)	0	23 (6–41)
Wang et al.[139]	2013	7	29	Dilator-Assisted	Access flow, pulse ox, distal pulse, angiogram	7 (100)	0	7 (2–12)
Shintaku et al.[140]	2015	5	0	MILLER	Access flow, pulse ox, angiogram	2 (40)	0	NS
Khalil and Livingston[141]	1988	4	100	Plication	Distal pulse	4 (100)	0	13 (8–22)
Odland et al.[100]	1991	16	100	Plication	PPG	16 (100)	5 (31)[b]	NS
DeCaprio et al.[131]	1997	11	100	Steel clips	PPG	10 (91)	9 (82)	18 (6–70)
Stary and Thaow[142]	2002	4	0	Dacron cuff	Access thrill	4 (100)	0	NS
Schneider et al.[143]	2006	6	0	PTFE T-band	None	5 (83)	0	NS
Yaghoubian and de Virgilio[144]	2009	7	0	Plication	Distal pulse/signal	7 (100)	0	9 (4–18)
Miller et al.[145]	2010	114	20	MILLER	Thrill, angiogram[c]	101 (89)	5 (4.4)	11 (0.25–37)
Smith et al.[146]	2013	6	0	Dacron cuff	PPG	6 (100)	0	14 (2–36)
Leake et al.[147]	2015	37	29	NS	None	28 (75)	4 (11)	NS
Patel et al.[148]	2015	26	0	Plication	Distal pulse/signal, angiogram	24 (92)	0	NS
Shukla et al.[132]	2015	20	5	MILLER	Angiogram	15 (75)	1 (5)	NS

[a]Thrombosis within 6 months.
[b]Thrombosis within 3 months.
[c]Access flow measurement was used only in the last 20 patients in the series.
Results of banding procedures according to type of intraoperative tool used to assess banding adequacy. The top half of the chart (pink) represents those studies in which the degree of banding was controlled by monitoring access flow rates, whereas the bottom half of the chart (blue) represents studies in which no access flow monitoring was used. Early thrombosis occurred within 30 days unless otherwise specified.
MILLER, Minimally invasive limited ligation endoluminal-assisted revision; *NS*, not specified; *PPG*, photoplethysmography; *PTFE*, polytetrafluoroethylene.

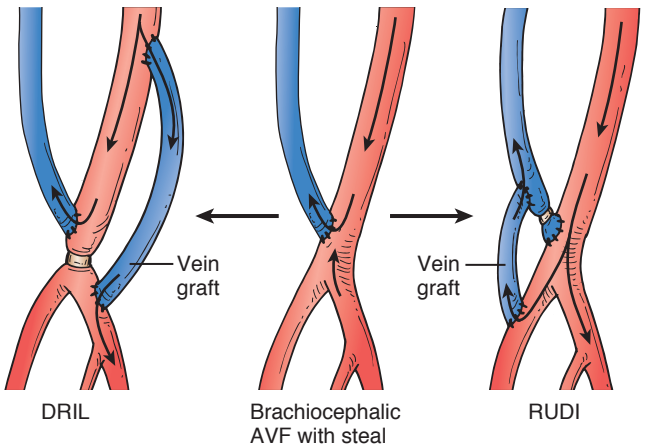

Figure 179.3 The anatomic configurations of the distal revascularization and interval ligation *(DRIL)* and revision using distal inflow *(RUDI)* procedures are illustrated for the treatment of hand ischemia or steal syndrome after an autogenous brachiocephalic arteriovenous access. *AVF*, Arteriovenous fistula.

poorly; 12 patients had 19 access thromboses and 7 required ligation for persistent symptoms.

Distal Revascularization–Interval Ligation (DRIL): DRIL was first described by Schanzer et al. in 1988.[134] Since then multiple publications have reported impressive results[121,147,155-157] and many consider it the procedure of choice.[157,158] DRIL entails the creation of a bypass originating proximal to the access anastomosis and terminating distal to it, with ligation of the artery distal to the anastomosis (see Fig. 179.3). This prevents retrograde flow from the distal vessels and creates a low-resistance pathway for blood to reach the peripheral vascular bed. Recent data suggest that the pressure augmentation from ligation contributes only 10% of the benefit of the DRIL[159] and may be avoided if circulation is adequately improved with bypass. An area of reduced pressure called a pressure sink exists in the artery just proximal to the anastomosis.[160,161] This exists because the large capacitance of the venous outflow causes pressure to

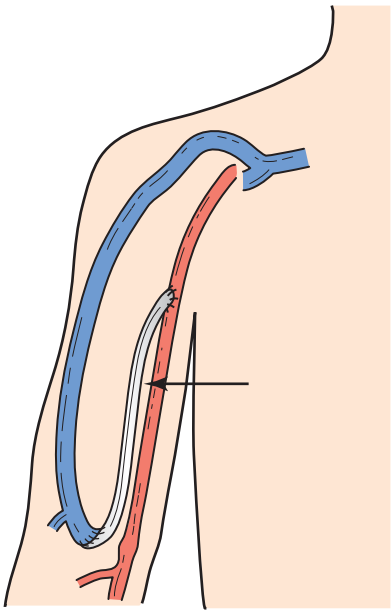

Figure 179.4 Proximalization of arterial inflow. The original arteriovenous access anastomosis.

fall rapidly, reaching central venous pressure within 1 cm of the anastomosis. Locating the origin of the bypass 7 to 10 cm above the inflow anastomosis avoids this pressure sink.

Long-term results are excellent. Schanzer et al. described 13 of 14 patients with complete recovery,[99] 82% 1-year access patency, and 100% bypass patency. Berman et al. described 21 patients with limb salvage and access patency of 100% and 94%, at 18 months.[121] Knox et al. found 90% resolution of ischemia and 15 of 20 digital ischemic lesions healed[162]; 1-year access patency was 83% and bypass graft patency was 80% at 4 years. Aimaq et al. reported a 5-year access patency of 67.1% for autogenous, 40% for prosthetic, and 97% for arterial bypass grafts.[157]

Drawbacks to DRIL include its invasiveness and perioperative mortality rates as high as 6.8%,[147] with wound complication rates of 9% to 19%.[152,155,156,162] ARHI patients are particularly frail, with a 1 year mortality of 30% in multiple series[121,155,156]—higher than that of typical ESRD patients,[163] reflecting the presence of advanced comorbid conditions. The second drawback is dependence of the hand on the bypass. However, long-term bypass patency is excellent and, in rare instances of occlusion, limb salvage is achievable via either a repeat bypass or access ligation.[155,156,162,164]

Distal Radial Artery Ligation (DRAL): Flow reversal is significant in a subset of patients with radial-cephalic AV accesses. In these cases, retrograde flow through the intact palmar arch results in inadequate digital flow. This is palmar arch steal syndrome (PASS), which is treated with ligation or coil embolization of the distal radial artery.[165-167] It is critical to evaluate patency of the ulnar artery and palmar arch prior to ligation.[166]

Treatment Selection: Treatment should be individualized based on life expectancy, severity of disease at presentation, access utility, access flow rate, future access options, and availability of conduit. RUDI, DRIL, and PAI all have good outcomes but require more extensive surgery, with morbidity and mortality exceeding those of ligation or banding.[147] Consequently the latter are better suited to patients with limited life expectancy. If a patient is healthy enough to warrant access salvage, the next factor is the severity of ischemia and risk of limb loss. If the patient has extensive tissue loss, a more definitive solution is needed. DRIL is ideally suited to this situation,[157,158,168] whereas banding is best avoided. Banding is most likely to require repeated interventions to be effective.[132,147] In extreme cases, ligation may be the best option for limb salvage.

Access-specific factors are also important. Although most cases of ARHI occur in association with high access flow rates (autogenous >800 mL/min, prosthetic >1200 mL/min),[127] flow rates are normal or low in up to one-third of patients.[108,135] Flow reduction such as banding and RUDI are suited to high-flow ARHI. However, when ARHI occurs with low or normal flow, the underlying pathology is more likely inadequate collateral circulation or atherosclerotic disease. These conditions are best treated via revascularization (DRIL, PAI, or angioplasty). Availability of autogenous conduit also affects choice of intervention. Both RUDI and DRIL traditionally require autogenous conduit, whereas PAI is typically uses PTFE.

VENOUS HYPERTENSION

Venous hypertension is a significant issue because it impacts access patency and function and causes disabling edema. Most cases are secondary to central venous stenosis (CVS) or occlusion.[169,170] The prevalence of CVS is unknown, as many patients have adequate collateral flow and consequently remain asymptomatic. CVS has been identified in 17% to 26% of patients undergoing venography for failing access or arm edema.[171-174] CVS threatens the current access and risks loss of the extremity for future access. Prevention, early recognition, and definitive treatment are crucial.

Etiology: CVS is primarily caused by catheters. Despite the efforts of the Fistula First Catheter Last Workgroup Coalition, 80.2% of patients begin dialysis with catheters.[175] Longer catheter duration is correlated with stenosis,[176,177] but catheters utilized for less than 1 month are also associated with CVS.[178-180] Subclavian access has the highest rate, 40% to 50%, whereas IJ is less than 10%.[181-183] The presumed etiology is chronic endothelial trauma due to catheter motion with cardiac and respiratory cycles.[181,184] In resected specimens, the stenosis contains fibrous tissue and neointimal fibromuscular hyperplasia.[185] The same process occurs with implantable cardiac rhythm devices[186,187]; however, only 7% to 10% of ESRD patients have such devices.[188,189] Caution should be exercised in placing access ipsilateral to cardiac devices with intravenous wires.

Although catheters account for most CVS, up to 10% of CVS occurs without catheter use.[190,191] The exact mechanism is unclear; however, is likely due to increased blood flow, natural anatomic narrowing, and valves. In a series of 30 CVS, Glanz et al. noted that most occurred in the subclavian vein between clavicle and first rib or in the axillary vein where it is compressed by chest wall during abduction.[173] Morosetti et al. used

intravenous ultrasound (IVUS) to demonstrate hyperplastic venous valves in a patient with no previous catheter use and severe stenosis at the distal cephalic arch.[192] This narrowing causes turbulent blood flow and venous deformation, which causes intimal smooth muscle cell proliferation in in vitro models.[193]

Diagnosis

Clinical Presentation: Presentation is dictated by degree of collateral flow, site of obstruction, and status of peripheral venous valves. Patients with robust collaterals and competent valves may be asymptomatic.[176] Consequently it is extremely important to maintain a high index of suspicion in considering access creation, particularly with a history of prior catheters. Often the only physical signs are scars and dilated shoulder collaterals (Fig. 179.5). In many cases, declining access function and prolonged needle-hole bleeding are the only indications of CVS.

Symptomatic venous hypertension may manifest immediately after access placement or in a delayed fashion.[172] The typical presentation is swelling, tenderness, and pain. However, severe cases may cause cyanosis, stasis, and ulceration.[194] Some edema is normal after construction of a new AV access. The magnitude varies depending on configuration, with more proximal accesses causing more swelling that typically subsides within a few weeks. Persistent swelling beyond 1 to 2 weeks requires additional assessment, as up to 25% will be associated with central stenosis.[172]

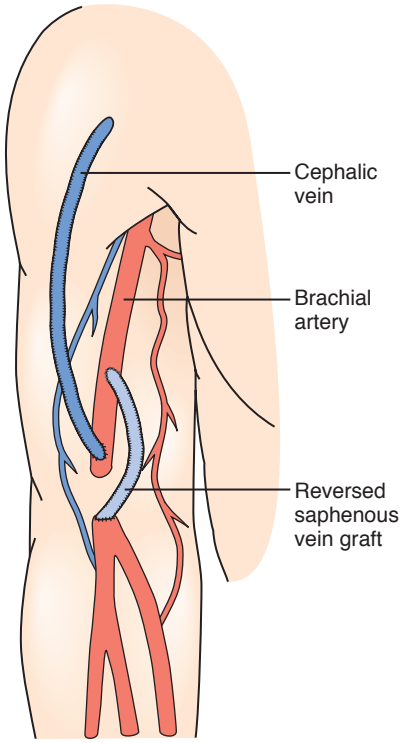

Figure 179.5 Diagram of brachiocephalic arteriovenous access and brachial artery bypass with interval brachial artery ligation and division. (Redrawn from Knox R, Berman SS, Hughes JD, et al. Distal revascularization–interval ligation: a durable and effective treatment for ischemic steal syndrome after hemodialysis access. *J Vasc Surg*. 2002;36:250–256.)

Atypical venous hypertension can occur. Pillai et al. reported bleeding esophageal varices from SVC occlusion related to a HeRO graft.[192] Kiernan et al. reported increased intraocular pressure related to a fistula in a patient with brachiocephalic vein occlusion, retrograde flow in the jugular, inferior petrosal sinus, cavernous sinus, and superior ophthalmic veins, which resolved with ligation.[195] Samaniego et al. described venous congestive encephalopathy and facial swelling, which resolved with ligation, in a patient with innominate occlusion, hypoplastic contralateral transverse sinus, and engorged cerebral veins.[196]

Diagnostic Testing: Duplex ultrasound is recommended for patients with a history of proximal vein cannulation, particularly subclavian lines.[120] However, more proximal subclavian or innominate lesions may be inadequately visualized.[197] KDOQI guidelines mandate venography before the creation of a permanent access in patients with prior subclavian lines.[198] If central venous occlusion is confirmed, placement of AV access in the ipsilateral limb should be avoided.

Duplex is preferred for early-onset edema after autogenous access creation to avoid cannulation of the new access, damage to the thin-walled vein, or bleeding from unincorporated prosthetic graft. However, duplex will not identify central stenoses.[120,199,200] Patients with persistent edema or edema developing after 2 weeks should undergo venography. Venography, while the gold standard,[198] can underestimate the degree of stenosis. Extensive collateral vessels are sometimes the only indication of an underlying lesion. IVUS should be used as an adjunct in those with high clinical suspicion despite absence of an obvious stenosis.

Treatment

Management is controversial. Ligation is well tolerated and provides symptomatic relief but sacrifices a functional access and leaves the ipsilateral extremity unavailable for future access. Given the finite number of access options, attempts at salvage should be made when possible.

Endovascular Intervention: KDOQI recommends percutaneous transluminal angioplasty (PTA) as primary therapy (Fig. 179.6).[201] However, the decision to intervene should not be made lightly and should only be made for symptomatic patients. Histologic analysis demonstrates that recurrent venous lesions have more aggressive neointimal hyperplasia compared with primary lesions.[202] Consequently the natural history of central venous angioplasty and stenting is characterized by frequent restenosis and reintervention. When Renaud et al. implemented a policy of withholding treatment for asymptomatic high-grade (>70%) CVS, they found better patency than with treatment of symptomatic cases without any decrease in access patency.[203]

PTA is the treatment of choice. Immediate success is 82% to 89%,[173,174,204] but long-term outcomes are poor. PP rates drop to 23% to 55% at 6 months, and by 12 months patency is 12% to 43%.[173,174,204,205] With multiple repeat interventions, the APP improves to 64% to 82%.[204,206-208] This results from more elastic recoil in central veins than peripheral veins.[209]

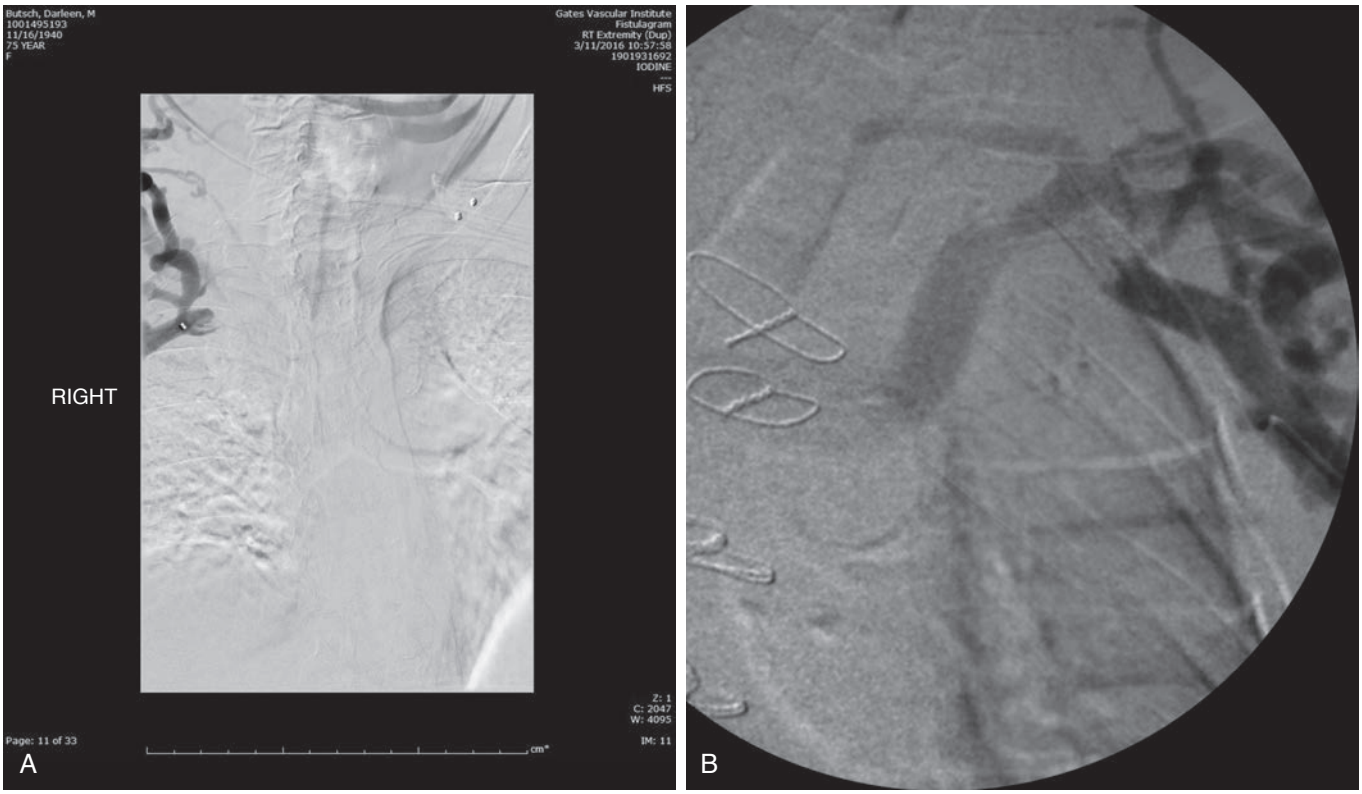

Figure 179.6 Distended collateral veins on physical examination and fistulagram with central occlusion/stenosis.

Kovalik et al. have shown that degree of elastic recoil predicts response to angioplasty. In their series, lesions with greater than 50% recoil had poor long-term patency (2.9 months) but improved with stenting (8.6 months). If recoil was less than 50%, angioplasty results were better (7.6 months) but worse after stenting (4.2 months). They concluded that elastic lesions are more likely to benefit from stenting and that stents should be avoided in nonelastic lesions.[210]

Multiple studies have examined benefits of primary and selective stenting. Stenting increases immediate technical success from 90% to 100%.[171,204,211,212] However, 1-year PP ranges from 11% to 56%, with the majority less than 25%.[171,204,205,207,208,212] Bakken et al. compared PTA with stenting, finding equivalent 1-year PP (29% PTA; 21% stenting) and APP (73% PTA; 46% stenting); therefore their study suggested that stenting does not improve patency.[204] Maya et al. reported 1-year PP 19% for stents ($n = 23$) and 20% for PTA ($n = 32$). Although results were equivalent, the investigators concluded that stents were advantageous in elastic lesions because selective stenting would skew results in favor of PTA.[207]

The most frequent cause of stent failure is intimal hyperplasia, which is particularly robust in the hemodialysis outflow tract.[202] Consequently several groups have proposed stent grafts. Early results are promising, with 12-month PP 40% to 67% and APP 80% to 86%.[213-216] Nevertheless stent grafts should be used with caution in central veins as they have the potential to cover major venous confluences and collaterals. Verstandig et al. reported exclusion of the internal jugular vein in 77%.[214] When considering stent grafts for CVS, the benefit of improved patency must be weighed against potential loss of future dialysis catheter insertion sites.

A few technical points: High-pressure, less-compliant balloons 1 to 2 mm larger than adjacent veins with inflation times greater than 2 minutes should be used. Flexible self-expanding, stents are preferable. Stents should be extended more peripherally than centrally to achieve stability and prevent central displacement. Placement of a guidewire in the IVC prevents stent embolization to the heart or pulmonary artery in the event of undersizing and facilitates removal by snare when necessary. There may be a role for drug-coated balloons (DCBs); however, data are limited. Massmann et al. recently reported a small series with custom-made paclitaxel-coated balloons to treat 10 patients. DCBs demonstrated improved freedom from target lesion revascularization (5 months vs. 10 months, $P = .025$).[217] Stenting remains the best adjunctive therapy for residual stenosis and early (<3 months) recurrence. Although most cases of CVS are due to intrinsic lesions, a subset are due to extrinsic compression.[190,218,219] These will have a poor response to endovascular therapy and are prone to stent fracture and collapse. Therefore it is crucial to maintain a high index of suspicion, particularly for lesions at the costoclavicular junction.[219]

Open Surgical Techniques: Surgical treatment has substantial morbidity and is reserved for patients untreatable with angioplasty/stenting.[201] Open reconstruction provides symptom relief and 1-year patency of 75% to 88%.[220-224] Techniques include direct reconstruction, decompression, and bypass. Bilateral venography is essential to planning. Surgical repair was first described with a spiral saphenous vein graft,[225] later

popularized by Doty et al., with 87.5% patency at 23-year follow-up (mean 10.9 years).[226] In modern series, CVS is most commonly managed via prosthetic bypass, with outflow including right atrium, femoral vein, saphenous vein, ipsilateral internal jugular vein, and contralateral jugular vein.[227] Another option is jugular turndown in which the IJ is divided high in the neck and anastomosed to the ipsilateral subclavian vein.[228] This frequently requires clavicle resection and precludes future use of the IJ for temporary access. In the setting of a high-flow access, banding can be done in addition to improve the inflow-outflow balance.[190,229,230] El-Sabrout and Duncan described prosthetic axillary–right atrial bypass[231] with 89% symptom resolution and 100% graft patency at 1.5 to 52 months (mean 15.4 months). Sottiurai et al. performed brachial or axillary to IJ bypass using 8- to 10-mm PTFE grafts[223] with 100% symptom resolution and 86% graft patency at 31 months (range 10–87). Grimm et al. performed axillary-femoral bypass with 8- to 10-mm ringed PTFE.[230] Upper extremity swelling improved in all; however, three patients developed lower extremity swelling and one required fistula ligation.

Arteriovenous access–related venous hypertension is a particularly challenging problem and is expected to become more common as the dialysis population grows. Angioplasty and stenting remain first-line, but open surgical techniques have an important place in management and should be considered prior to abandoning a functional access.

NEUROPATHY

Approximately two-thirds of patients have preexisting peripheral neuropathy at initiation of dialysis.[232-234] Diabetes is predictive for development of neuropathy after access creation.[235] Specific access-related neuropathy has four grades of severity[2]:

Grade 0: Asymptomatic

Grade 1: Mild—intermittent changes (pain, paresthesia, numbness with sensory deficit)

Grade 2: Moderate—persistent sensory changes

Grade 3: Severe—sensory changes, progressive motor loss (motion, strength, muscle wasting)

Types of Neuropathy and Management

Neuropathy is categorized into three groups in CKD: (1) systemic disease neuropathies, which develop gradually and involve painless, progressive, symmetrical sensorimotor polyneuropathy[168]; (2) mononeuropathies, related to compression, compartment syndromes, and entrapment; and (3) ischemic monomelic neuropathy, which occurs acutely after AV access creation.

Systemic Disease Neuropathy

Diabetic Polyneuropathy: In the United States, 46% of dialysis patients are diabetic (Dialysis Outcomes and Practice Patterns Study [DOPPS]). Diabetic neuropathy with large fiber demyelination typically affects lower extremities with numbness, paresthesias, and pain. Ndip et al. found that 79% of diabetic dialysis patients with foot ulceration have peripheral neuropathy.[236]

Uremic Polyneuropathy: Uremia is the most common cause of neuropathy in dialysis patients; it is present in 50% to 70% and is more common in men.[237,238] It improves with hemodialysis and may resolve with transplantation.[238-241] Axonal degeneration with secondary segmental demyelination is identified and is most severe distally.[237,242-245] Hyperkalemia affects symptom severity.[246] Physical findings include impaired vibratory sensation in the lower extremities, loss of deep tendon reflexes in the Achilles tendon, and loss of distal touch and position sense. It is important to be aware of these neuropathies considering access-related neurologic changes.

Compressive Mononeuropathies

CTS is 10 times more frequent in hemodialysis patients.[247] Warren and Otieno first reported CTS in a hemodialysis patient in 1975,[248] and numerous studies since have shown an increased prevalence, 0.6% to 30%.[249] Time since hemodialysis initiation is associated with CTS, 46% to 50% at 5 years and 50% at 10 years.[250-252] The etiology of increased risk is not understood but thought to be partially due to serum beta$_2$-macroglobulin deposition as amyloid in periarticular tissues, a molecule not cleared by hemodialysis.[249,251,253,254] A more recent study identified 12 patients with early onset CTS after access creation and without amyloid deposition but with venous hypertension.[255] These investigators suggested that venous hypertension with congestion led to median nerve compression and chronic irritation of the carpal ligament with resultant thickening. There are conflicting data as to whether access side impacts on CTS development.[251,256] Systemic factors include uremia, expanded extracellular fluid volume causing irritation of the ligament, and nerve ischemia.[186,187] Pseudoaneurysms and hematomas can also cause nerve compression.[257] Symptoms include tingling dysesthesias in the median nerve distribution, worse at night or during dialysis.[237] Exacerbation with dialysis is related to relative ischemia with venous hypertension and tunnel edema.[251,258] Rapid improvement is expected with early intervention.[259,260] Once motor or sensory deficits develop, symptoms respond more poorly.[261] Ulnar nerve compression at the elbow and wrist is also seen in hemodialysis patients.[249,262-264] Symptoms include pain or sensory changes in the ulnar aspect of the hand, weakness of the adductor pollicis, and weakness with finger adduction and abduction.

Ischemic Monomelic Neuropathy

IMN is rare, occurring in 0.5% of access creations[265-268] and resulting from acute vascular compromise of neurologic structures.[269] Bolton initially described IMN,[270] with Wilbourn coining the term.[271] Delayed recognition/intervention leads to irreversible, profound neurologic deficits in the median, radial, and ulnar nerves.[265] Most cases occur in older diabetics with preexisting peripheral neuropathy, peripheral arterial disease, and brachial-based access. It has never been reported in accesses originating distal to the brachial artery.[269,272,273]

Presentation can be confounded by anesthesia. Within hours of surgery, patients develop acute pain, weakness, or paralysis of the hand and forearm muscles, often with prominent sensory loss and dysesthesias. The hand is warm, with a palpable pulse

or audible signal in distal radial and ulnar arteries.[237,269,272-274] Pain is out of proportion to clinical findings, which differentiates IMN from ARHI. Digital pressure index is higher than 0.3.[275] Diagnosis is frequently delayed, with symptoms attributed to anesthesia, patient positioning, or surgical trauma.[275] Patients with acute limb pain, weakness, and sensory loss in the immediate postoperative period should be assessed for direct nerve injury or compression from hematoma. Most nerve injury from anesthesia occurs more gradually during days to weeks and is more focal with regard to symptoms.[276]

IMN is related to preexisting marginal perfusion to nerves, compromised by additional flow diversion by the access.[275] Prevalence of brachial artery involvement suggests that IMN is due to the inability of this vessel to vasodilate and compensate for increased access demands. The resultant low-level ischemia does not translate to muscle or skin viability issues, nor does it present as ARHI. However, it results in severe irreversible ischemic nerve injury if not promptly treated. The ischemic threshold of peripheral nerves is lower than that of muscle.[266] Dyck et al. found the antecubital area to be a "watershed" for the vasa nervorum of the three nerves of the upper limb. Electrophysiologic studies support the concept of nerve ischemia as the etiology. Nerve conduction studies done 1 hour after AV access creation demonstrate acute, reversible, changes with motor conduction block and conduction slowing due to myelin retraction from the node of Ranvier.[269] Axonal loss of motor and sensory nerves occurs late, consistent with degenerative types of polyneuropathy, and sensory amplitudes are more severely affected.[266] Evidence of denervation is more severe distally, with a proximal gradient.[275] Because IMN is a form of ARHI limited to the nerves, treatment includes access ligation or emergent augmentation of flow. Even with rapid intervention, paralysis and pain may be only partially resolved or may become permanent.[273-277]

CARDIOPULMONARY COMPLICATIONS

Cardiovascular complications, including CHF, pulmonary hypertension (PH), and coronary steal remain the leading causes of morbidity and mortality in patients with ESRD. Patients with CKD also have accelerated atherosclerosis related to comorbidities such as hypertension, diabetes mellitus, uremic dyslipidemia, and increased asymmetric di-methylarginine (ADMA), a nitrous oxide synthase inhibitor. AV access construction itself is associated with an increased risk of cardiovascular death.

Congestive Heart Failure: CHF is present in approximately one-third of new dialysis patients.[278] Associated factors include chronic volume overload, arterial hypertension, cardiovascular calcification, valvular disease, increased arterial stiffness, anemia, inflammation, access flow volumes, and arrhythmias.[279] High access flow (Qa) may predispose to CHF in patients with marginal cardiac function. Left atrial diameter and CO increase within 3 to 14 days of fistula creation.[280] LV mass and left atrial area also increase significantly within 3 months.[281] Abassi et al. found a 40% increase in CO and suggested that a Qa/CO ratio greater than 0.3 increases the risk for high-output cardiac failure.[282] The Qa/CO ratio is significantly higher in patients with upper arm access in comparison with forearm access, and 1 in 10 patients with upper arm access are in the danger zone (Q/CO >0.3) for developing CHF.[283] Not all studies have found a relationship between AV access and CHF. In a review of the U.S. Renal Data System morbidity and mortality data, no association was seen between AV access and CHF or acute coronary syndrome as compared with catheter access.[284]

Treatment includes banding, ligation, or restriction of flow if the access is determined to contribute. Some advocate decreasing access flow to less than 300 mL/min, while NKF-KDOQI provides no guidelines. Ligation leads to complete loss of access, and banding may jeopardize the access. Inflow reduction by distalization for high-flow accesses (>1600 mL/min) was proposed by Chemla, who demonstrated 77% access patency and 100% CHF symptom resolution with a decrease in CO from 8 ± 3.1 to 5.6 ± 1.71 L/min.[285]

Coronary Steal Syndrome

The internal mammary artery (IMA) is frequently utilized in coronary revascularization. However, in patients with ipsilateral AV access, the access may steal from the coronary circulation. Proximal subclavian stenosis predisposes to coronary steal. A high-flow access without inflow stenosis may lead to coronary steal. CTA is recommended to assess the subclavian artery prior to coronary reconstruction and to avoid potential complications. Kato et al. demonstrated retrograde flow in the IMA with a high-flow fistula by angiography.[286] Minami found correctable reversal of flow by fistula compression at coronary revascularization and addressed the situation by using the IMA as a free graft.[287] Feldman et al. compared patients with access ipsilateral and contralateral to IMA bypasses. They found risk of a first cardiac event greater in patients with ipsilateral access (HR 2.92, $P = .008$) and a trend toward higher mortality with ipsilateral access.[288] Cuthbert et al. found that 28% of patients with ipsilateral access developed clinical or physiologic evidence of malperfusion while on hemodialysis and concluded that access ipsilateral to IMA bypass should be avoided.[289] If coronary steal is detected in a limb with ipsilateral AV access and a patent IMA graft, evaluation of the subclavian artery is mandatory, as correction of stenosis may result in symptom resolution without access sacrifice. Flow directionality can also be assessed by duplex ultrasonography prior to IMA harvesting.

Embolization of Stents to Heart and Pulmonary Arteries

Physiologic variations in vein wall diameter, stent undersizing, and lack of adherence of the stent to the wall may lead to embolization. Complications include tricuspid regurgitation, acute myocardial infarction, pulmonary infarction, and cardiogenic shock from embolization to the right atrium, right ventricle, and pulmonary arteries.[290]

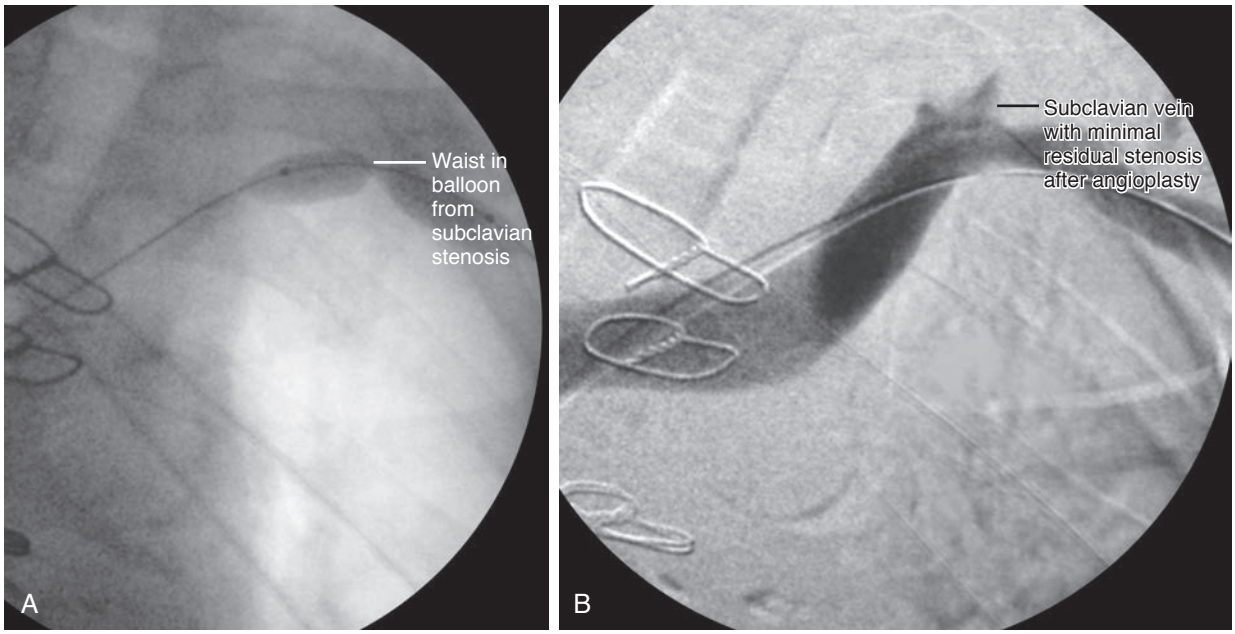

Figure 179.7 (A) Angioplasty of subclavian vein stenosis in a patient with an ipsilateral autogenous AV access and venous hypertension. (B) Completion venogram after subclavian vein angioplasty that demonstrated no residual stenosis.

Pulmonary Hypertension

PH is a progressive, fatal disease with a significant decrease in survival (mortality 30.8% vs. 3.5%) associated with increased CO, which increases in prevalence soon after access creation (40%) and regresses after access closure.[282]

PH is precipitated by volume overload, left ventricular failure, arterial hypertension, increased flow from the access, metabolic changes, and potentially recurrent embolization from the access and from access salvage procedures. Patients with CKD have acquired endothelial cell dysfunction, reducing their ability to tolerate the elevated CO associated with access creation. Nakhoul et al. found elevated endothelin in all dialysis patients, with 48% having PH.[291] Those with PH had greater CO than those without. Temporary access closure resulted in a decrease in CO and systolic pulmonary artery pressure (PAP), suggesting that increased venous return was a factor.

Havlucu et al. found a correlation with systolic PAP and arteriovenous fistula (AVF) flow by Doppler ultrasonography, reversible with AVF compression from 36.8 ± 10.7 to 32.8 ± 10.5 mm Hg.[292] Yigla et al. found PH in 37% of AV access patients, in no peritoneal dialysis patients, and in 1 patient with renal insufficiency. CO was also significantly higher—6.9 L/min versus 5.5 L/min—in patients on hemodialysis. He reported that PAP increased in 66% of patients after beginning hemodialysis and concluded that long-term hemodialysis and AV access creation are associated with PH by affecting pulmonary vascular resistance and CO. Recurrent embolization appears less important[293] Harp evaluated the relationship of access thrombectomy and found PH in 52% of all dialysis patients after at least one thrombectomy versus 26% in patients without ESRD. ESRD was associated with a 2.7-fold increase risk of PH, but thrombectomy itself was not a factor.[294] Hsieh et al. evaluated the impact of repetitive endovascular thrombectomy in a prospective fashion and were unable to demonstrate any correlation.[295]

Treatment includes anticoagulants, diuretics, digoxin, oxygen, and calcium antagonists. Vasodilators and antiproliferative agents may also be utilized. Access ligation or flow reduction should be considered in patients with a poor response to medical management. Alternative modes of dialysis or transplant should be considered. Patients with underlying severe heart failure or preexisting PH should be considered for alternative access or for catheter or peritoneal dialysis rather than AV access creation.

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CHAPTER 180

Epidemiology and Natural History of Vascular Trauma

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INTRODUCTION

Vascular injury is a major cause of death and disability in society, with trauma being the principal etiology. Despite the establishment of mature trauma systems to improve delivery of prompt and effective treatment, as well as innumerable technological advances with improved clinical outcomes and expanded application of data collection systems, the burden of traumatic injuries continues to increase in society. Unfortunately, there has been a progressive increase in trauma-related deaths over time, with an overall increase of 21% between 2000 and 2010.[1] In the United States, trauma is the number one cause of death for patients between the ages of 1 and 46, and is the third highest overall cause of mortality across all age groups.[1] As of 2014, traumatic injury by any mechanism was the number one cause of years of potential life lost at 31.7% and accounted for nearly 200,000 deaths overall.[2] Certainly, mortality from trauma is complex, with outcomes predicated on the extent and nature of sustained injuries. Nonetheless, hemorrhage is overwhelmingly the agent of death in most instances. From a military perspective, vascular injury with associated hemorrhage is the leading cause of potentially preventable wartime mortality, despite improved strategies aimed at rapid transport, point-of-injury hemorrhage control, and early operative intervention.[3,4] For both civilian and military environments, long-term disability from limb loss, chronic pain, and posttraumatic stress disorder impact many

victims, adding to the societal burden incurred from vascular trauma.[5]

While our ability to diagnose and treat vascular injuries has substantially improved over time, our overall impact on this incidence and prevalence has been lacking. This dismal reality underscores the complex nature of traumatic injury and the myriad factors that influence its incidence in society. Although applied rigorously to many disease processes that impact public health, an epidemiologic approach to the characterization and management of traumatic vascular injury has not been extensively explored. According to the World Health Organization, epidemiology is defined as the **study** of the **distribution** and **determinants** of **health-related states or events** in **specified populations**, and the **application** of this study to the control of health problems. While traditionally applied to the study of communicable and noncommunicable disease processes, epidemiologic principles can be applied to the study of any process that impacts the health of a population, including vascular injury.

An epidemiologic approach to vascular injury has several potential benefits, particularly as it relates to civilian trauma. At a national level, elucidating the various socioeconomic, geopolitical, and cultural factors influencing trauma can serve as a basis for broad public health initiatives, policy change, and other efforts aimed as mitigating the impact of trauma on at-risk populations. Additionally, the application of epidemiologic principles to vascular injury aims to more accurately classify and risk-stratify various injury patterns through improved data gathering and scoring methodologies, to assess for local and regional differences in terms of volume and case mix, and to track changes over time. Through the recognition of regional differences, these metrics can serve as a vehicle for change at the institution, trauma system, and regional legislative levels.

The purpose of this chapter is to provide a framework for understanding the protean factors that influence vascular injury in society from an epidemiologic standpoint. Providing a historical context, with perspective from the transformative influence of military trauma over the past century, will serve to highlight changes over time affecting the broader delivery of trauma care. Additionally, contemporary efforts employed to characterize the natural history of vascular injury and track outcomes, particularly specific injury patterns, will be explored.

The Origins of Vascular Injury Management

Major vascular trauma commonly manifests with hemorrhage, and, arguably, the initial principles of surgical practice evolved around the control of bleeding. The earliest reported description of vessel injury management came in the 2nd century, where Galen explored techniques of vessel ligation. However, the knowledge was not applied in practice until the 16th century, when a French military surgeon, Ambroise Páre, resurrected this lost knowledge.[6] Beyond this timeframe and for the next 400 years, vascular injury management was limited to major amputation and vessel ligation.

However, beginning in the late 19th and early 20th centuries, novel techniques to directly repair vessel injuries began to emerge. In 1902, a French surgeon named Alexis Carrel popularized techniques for arterial anastomosis, facilitating countless subsequent innovations in multiple surgical disciplines. This work would later earn him the Nobel Prize in Physiology or Medicine in 1912.[6] Additionally, new medical techniques and principles, such as antisepsis, antibiotics, and improved anesthetics, facilitated a widespread revolution in the management of vascular injury. The experiences reported from the major modern conflicts, starting with World War I, provide a highlight of the evolution and key milestones in vascular trauma management. Table 180.1 provides a summary of the reported wartime experiences and outcomes, including the overall and treatment-related amputation rates. Despite growing experience with vascular repair, the techniques for vascular anastomosis and interposition grafting by the turn of the century, widespread application of these techniques was lacking, likely due to insufficient training, equipment, and the high incidence of complications.[6] Additionally, infrastructure to facilitate the timely diagnosis and delivery of definitive treatment was not well established, negating the feasibility of limb salvage efforts (Fig. 180.1A).

Evolution Through Military Conflict

The incidence, nature, and management of vascular injury, and in fact all aspects of trauma, are often described within the framework of major periods of conflict or war. The sheer volume and severity of trauma associated with combat provides a unique opportunity to study the natural history of vascular injury patterns, create novel surgical techniques, and implement systemic change aimed at the mitigation of risk. However, the changing nature of warfare over time inherently influences the incidence, severity, and distribution of vascular injury patterns, requiring ongoing evolution of our techniques and practices. Providing a historical framework for the evolution of wartime vascular injury management allows for the understanding of the contemporary epidemiology, natural history, and management of vascular injury in both modern conflict, as well as within the civilian realm.

A classic paper by DeBakey et al. characterizes the vascular injury burden during World War I and II, noting an incidence of vascular injury during both wars of approximately 1%. Of the 2471 arterial injuries documented during World War II, only 81 underwent attempted repairs, with an amputation rate of 36%. In 40 patients, an attempt was made to repair larger arterial disruptions using vein interposition grafts; unfortunately, the amputation rate was 50% for this cohort. There was overwhelmingly a routine posture toward ligation of vessels in the majority of patients. Although this practice was understood to be less than ideal, it was deemed to be necessary given resource constraints of this era.[7]

The Korean War experience beginning in 1952 resulted in an increased incidence of vascular injuries at approximately 2% of all casualties relative to previous conflicts. This may reflect improved evacuation methods during this conflict utilizing rotary wing aircraft, increasing the number of patients with vascular injuries surviving to definitive surgical therapy. There was a paradigm shift in the management of vascular injuries witnessed during this era, with 88% undergoing an attempt at

TABLE 180.1 Epidemiology of Combat-Related Vascular Injuries, Management, and Amputation Rates

Conflict	No. of Injuries	Incidence (%)	Philosophy	Amputation Rate (%)	Attempted Repair[a]	Method of Repair	Incidence of Repair Type (%)[b]	Post-Repair Amputation Rate (%)
World War I Makins[123]	1202	0.4	Ligate artery and vein (even if uninjured)	19-70[c]	39 (3.2%)	Ligation artery Ligation artery and vein Lateral suture	57 40 3	28 20-90 20
World War II DeBakey et al.[7]	2471	0.96	Repair only minor injuries, no routine vein ligation	49	121 (5%)	Ligation Lateral suture Primary anastomosis Vein graft	66 3 0.6 1.6	50 35 50 58
Korea Hughes[10]	304	2.4	Repair with lateral suture or anastomosis	13	269 (88%)	Ligation Lateral suture Primary anastomosis Artery-vein graft[d]	12 12 48 27	51 3 9 24
Vietnam Rich[13] McNamara[124]	1000	2	Vascular repair with vein graft, vein repair	13	930 (93%)	Ligation Lateral suture Primary anastomosis Vein graft	1.5 9 38 46	33 0 7.4 13
Global War on Terror Dua[51] White[23]	1570	12	Vascular repair with vein graft, vein repair, damage control, and shunts	14	339 (65%)[e]	Ligation Lateral suture Primary anastomosis Vein graft Prosthetic graft	35 12.4 9.4 38 2.9	2 2 0 15 21

[a]Excluding injuries managed with initial ligation.
[b]Totals may not equal 100% because of cases that were uncategorized or labeled "other."
[c]The widely reported WWI amputation rate of 19% (Makins) included up to 70% nonacute lesions, and the actual amputation rate based on smaller series appears to be 45%-70%.
[d]Wide use of homografts and reported amputation rates of 33% with arterial graft versus 12% with vein graft.
[e]Among 523 vascular injuries in 497 patients from Dua et al.

primary repair/anastomosis (60%) or interposition graft (27%).[6,8] While early reconstruction strategies employed cadaveric femoral artery as an interposition graft conduit,[9] this was largely abandoned after some time due to an increased failure and amputation rate (33%) compared with vein grafts (12%).[8] Several more comprehensive reports on successful arterial repair performed during the Korean War followed, including classic papers from Colonel Carl Hughes, which gained the attention of the Office of the Army Surgeon General.[10-12] Hughes demonstrated an impressive reduction in the amputation rate among 269 repairs—from 40% in World War II to 13% during the Korean War. While improvements in casualty evacuation during the Korean War were achieved, significant time delays and resuscitation requirements remained the primary Achilles heel of successful vascular injury management.[10] Despite the increased surgical capabilities brought to bear in the management of vascular injury during this time frame, the overall burden of vascular injury and its effect on mortality remained obscure.

The Vietnam War ushered in several significant advances in vascular injury management. Arguably the most important achievement of the era was the creation of the Vietnam Vascular Registry, which provided the ability to characterize injury patterns and outcomes following intervention. Rich et al.[13] published landmark reports of the first 500 and 1000 patients, documenting the preference for attempted repair in the majority (93%) of injuries and describing longer term repair patency and amputation rates. In total, this registry captures nearly 10,000 vascular injuries in over 7500 injured warfighters.[6] Another key accomplishment was the increased emphasis on routine repair of venous injuries as a vital component of limb salvage strategies, albeit controversial.[14,15]

For decades to follow, the vascular injury experience of these previous wars was thought to be unapproachable with regard to the duration of conflict and the number of injuries. With more than 8000 deaths and approximately 50,000 combat-related injuries in more than a decade of modern warfare (http://www.icasualties.org), the Global War on Terror (GWOT) has proved to be a formidable and sustained military campaign. During this conflict, modern advances have allowed a concerted effort to reduce deaths from potentially survivable vascular injuries and to improve the quality of functional extremity salvage (i.e., saving life *and* limb).[16]

The development of the Joint Theater Trauma System has improved surgical care and reduced mortality by implementing clinical practice guidelines and performing outcomes research emerging from the Joint Theater Trauma Registry (JTTR). The GWOT Vascular Initiative is a comprehensive registry designed to study patterns of vessel injury and methods of vascular repair, and to provide more complete long-term analysis of patient outcomes.

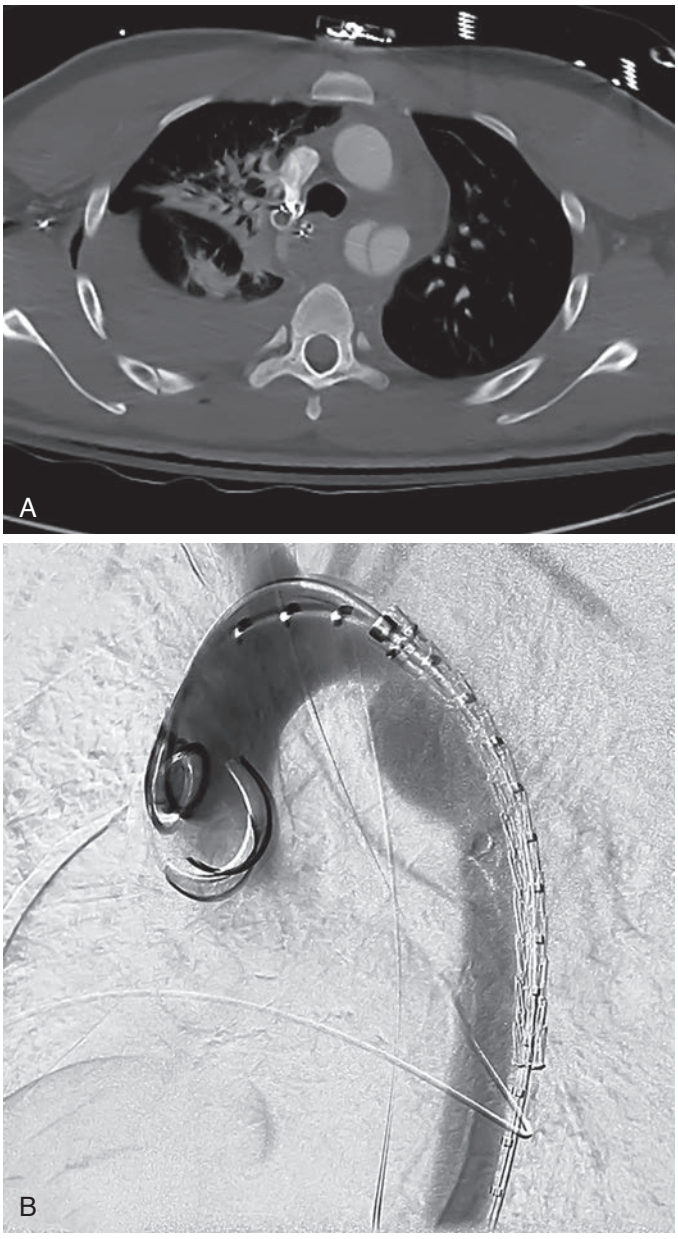

Figure 180.1 Blunt Aortic Injury. (A) Computed tomography angiogram demonstrating type III blunt aortic injury with pseudoaneurysm. (B) Conventional angiography demonstrating an aortic pseudoaneurysm immediately prior to thoracic endovascular aortic repair.

At the beginning of the GWOT, the US Department of Defense implemented a testing, training, and fielding program for battlefield tourniquets.[17-19] Although widespread tourniquet use began with trepidation, the forward deployment of surgical capabilities has provided for limited tourniquet duration, thus increasing the effectiveness of tourniquets and reducing the rate of associated complications. The effectiveness of early tourniquet application observed in Iraq and Afghanistan has led to doctrinal changes that have produced a surge of patients with vascular injuries who, in the past, would not have reached a field hospital alive (see Fig. 180.1B).[20,21] The application of tourniquets for extremity vascular injury is now routine and has been formalized in the Tactical Combat Casualty Care (TCCC) guidelines.[22]

Of interest, the 12% incidence of vascular injuries based on data from the JTTR is the highest ever reported during wartime. Certainly the widespread application of tourniquets contributes to this statistic; however, improved detailed data collection as well as a shift in injury mechanism from conventional weaponry to the improvised explosive devices (IEDs) likely impacts this as well.[23] Additionally, the widespread use of body armor in conjunction with increased exposure to IEDs has led to an epidemiologic shift in injury patterns, with a proportionally higher rate of extremity vascular injury (53%) and a decreased rate of major truncal vascular injury (15%). Interestingly, there has been an increased incidence of vascular ligation (35%) compared to that of the Korean and Vietnam War era, underscoring the devastating nature of many of the extremity wounds in modern warfare, which negate the opportunity for attempts at limb salvage.[23]

Other modern advances include the selective application of surgical adjuncts, such as temporary vascular shunts that facilitate delayed definitive vascular repair in scenarios of polytrauma and the routine performance of fasciotomies to minimize the incidence of undiagnosed compartment syndrome.[24-29] Progress in the management of increasing complex vascular injury patterns and the associated management of complex soft tissue wounds through closed negative pressure wound therapy, has been impressive.[30] Also, the application of endovascular technologies for the diagnosis and treatment of certain types of vascular, pelvic, and solid organ war-related injuries has become more widespread and generally accepted as a mainstay of surgical care.[31-33]

Despite tremendous achievements that have inexorably altered the natural history of vascular injury and its impact on morbidity and mortality, it is challenging to draw definitive comparisons between modern and historical conflicts with regard to "killed in action," "died of wounds," and other outcome measures given the heterogeneity not only due to the technological advancements but also to the changing tactical environment and the subsequent injury patterns. Nonetheless, many warfighters continue to succumb to potentially survivable injuries on the battlefield. In several contemporary studies evaluating combat-related mortalities from Operation Enduring Freedom and Operation Iraqi Freedom, approximately 15% to 25% of casualties were deemed to have potentially survivable injury patterns at the time of autopsy, of which 80% to 87% are attributed to hemorrhage.[3,16,34,35] This not only underscores the lethality of vascular injury and hemorrhage, but also alludes to the fact that viable strategies for more timely intervention remain elusive.

Data Repositories and Registries

One of most important factors in understanding the epidemiology and patterns of vascular injuries and trauma is the collection of large samples with thorough and reliable data. This has traditionally been done by single centers performing chart review analyses during long periods or by the analysis of wartime experience with limited follow-up data. Developments in computerized databases, automated data collection, and the

establishment of trauma systems with dedicated registrars have facilitated the collection and analysis of large and multicenter trauma data. An early example and model for future development was the establishment of the Vietnam Vascular Registry, with subsequent landmark reports on the epidemiology and outcomes of a wide variety of vascular injuries.[13] The recognized importance of the prospective collection of data from wartime experiences led to the establishment of the Joint Theater Trauma System and the JTTR, which continue to collect critical information from combat operations in Iraq and Afghanistan. The past decade has also seen the establishment of the National Trauma Data Bank (NTDB) by the American College of Surgeons. The NTDB is the largest trauma registry ever assembled, and as of the 2015 annual report, it contains more than 6 million records from 746 trauma centers in North America, of which nearly 500 are level I or level II centers. This rich data source has allowed detailed descriptive data and adequately powered statistical analysis of a wide variety of vascular injuries and related traumatic disease. The NTDB data are subject to extensive auditing, with an edit check program that aims to ensure data quality and accuracy. Submission data are also rigorously standardized. A data dictionary—the National Trauma Data Standard—commissioned by the federal government and established by the ACSCOT Subcommittee on Trauma Registry Programs, allows for uniform data collection across institutions and serves as the standard for data submission to the NTDB.

While robust in its breadth and depth, the NTDB does possess certain limitations that influence its ability to accurately characterize the epidemiology of traumatic injury, particularly certain vascular injury patterns. One limitation is that nonadmitted patients are uniformly not captured in this database. This is of particular importance in the context of vascular injury, as patients that die without transport to a treatment facility are not captured. Thus, major vascular injuries where exsanguination results in rapid demise are likely underrepresented in the NTDB. This creates an inherent selection bias for more stable, less severely injuried patients, confounding analyses aimed to characterize the epidemiology and natural history of vascular injury, particularly truncal injury patterns. The NTDB is also not a true population-based data set, as the data set only reflects experience at participating institutions, which inherently are biased in favor of large-volume, urban trauma centers. Hence, the experience of nonparticipating facilities, likely smaller community and rural hospitals capable of locally treating less severe injury patterns, will not be reflected in the NTDB data set. While capturing certain in-hospital complications, the database does not fully characterize the outcomes following vascular injury and is limited to in-hospital outcomes and complications.

The PROspective Vascular Injury Treatment (PROOVIT) registry, supported by the American Association for the Surgery of Trauma, has been established to address key limitations of the NTDB, in an effort to better characterize the natural history and outcomes of civilian vascular injury patterns. The initial publication of this data set included 542 patients from 14 centers from March 2013 to February 2014, in whom 484 sustained arterial injuries and 71 experience isolated venous injuries. The additional strengths of this database include the capture of key elements of prehospital care, such as the application of tourniquets, which was seen in 20% of patients within this series.[36]

Vascular Injury Classification and Scoring

The ideal vascular injury classification and scoring system has yet to be developed, probably because of the wide variation in traumatic vascular disease and the associated outcomes. Standard injury scoring systems, such as the Injury Severity Score (ISS), the Revised Trauma Score (RTS), and the Trauma and Injury Severity Score (TRISS), fail to accurately and reliably capture the impact of major vascular injury on morbidity and mortality.[37,38] Beyond this, the myriad factors that influence mortality—independent of the injury itself—cannot be effectively captured using ISS, specifically. In a study by Markov, mortality rates for patients with ISS >15 following civilian versus military-related vascular trauma with similar injury patterns was 40% and 10%, respectively, further underscoring the limitations of ISS to characterize vascular injury outcomes.

For battlefield or combat-related vascular trauma, it is probably most useful to categorize injuries according to a three-tiered system based on the wound location and the ability to achieve hemorrhage control. This system also can be easily applied to civilian vascular trauma. Peripheral or extremity wounds (tier 1) are located distal to the axillary artery or vein (upper) or the common femoral artery or vein (lower), and are responsible for the smallest percentage (14%) of modern battlefield deaths due to bleeding.[39] This has largely been attributed to the widespread distribution and use of tourniquets or pressure packing, which is performed in 56% of combat casualties. Proximal groin or axillary wounds (tier 2) are now categorized as junctional wounds and are often not amenable to either direct pressure or tourniquets. This has led to the development and wide deployment of advanced hemostatic dressings and the search for junctional hemorrhage control devices.[39] The third category (tier 3) is intracavitary wounds to the thorax or abdomen and pelvis, resulting in noncompressible truncal hemorrhage (NCTH). This has been identified as the most difficult and deadly source of hemorrhage on the battlefield, and NCTH has been identified as the etiology in 67% of battlefield deaths from hemorrhage.[39] This categorization scheme is most useful for penetrating or battlefield trauma, but it can be applied to any vascular trauma with associated hemorrhage.

The American Association for the Surgery of Trauma Organ Injury Scaling (AAST-OIS) system is the most widely used grading system for traumatic injuries and is well validated for predicting the outcomes and the need for intervention in solid organ injuries. AAST-OIS tables are currently also available for traumatic vascular injuries, including cervical, thoracic, abdominal, and peripheral. This grading system is organized primarily around the exact identity of the vessel rather than the severity of the vascular injury or the degree of hemorrhage or ischemia, and thus provides little additional information about treatment or outcomes. Additional classification systems have been developed to better characterize the natural history, to guide

TABLE 180.2 Homicide Rates by Country

Country	Indicator	YEAR								
		2005	2006	2007	2008	2009	2010	2011	2012	2013
Honduras	Count	3212	3118	3588	4455	5280	6236	7104	7172	6757
	Rate	46.6	44.3	50.0	60.8	70.7	81.8	91.8	91.0	84.3
United States of America	Count	16,740	17,309	17,128	16,465	15,399	14,722	14,661	14,827	12,253
	Rate	5.6	5.8	5.6	5.4	5.0	4.7	4.7	4.7	3.8
United Kingdom	Count	896	863	873	760	714	753	646	644	602
	Rate	1.5	1.4	1.4	1.2	1.2	1.2	1.0	1.0	1.0
Japan	Count	643	619	574	646	506	465	442	428	370
	Rate	0.5	0.5	0.5	0.5	0.4	0.4	0.3	0.3	0.3
Hong Kong	Count	34	35	18	36	47	35	17	27	62
	Rate	0.5	0.5	0.3	0.5	0.7	0.5	0.2	0.4	0.9
France	Count	976	879	993	1,021	819	796	856	784	777
	Rate	1.6	1.4	1.6	1.6	1.3	1.3	1.3	1.2	1.2
South Africa	Count	18,528	19,202	18,487	18,148	16,834	15,940	15,609	16,259	17,068
	Rate	38.4	39.3	37.3	36.1	33.1	31.0	29.9	30.7	31.9
Australia	Count	259	281	255	261	263	231	244	254	249
	Rate	1.3	1.3	1.2	1.2	1.2	1.0	1.1	1.1	1.1
Colombia	Count	17,086	16,119	15,423	14,911	15,454	15,013	15,803	14,670	15,419
	Rate	39.6	36.8	34.7	33.0	33.7	32.3	33.5	30.7	31.8
Puerto Rico	Count	771	748	731	807	894	983		978	
	Rate	20.5	19.9	19.6	21.6	24.0	26.5		26.5	
Mexico	Count	9921	10,452	8867	14,006	19,803	25,757	27,213	25,967	23,063
	Rate	9.0	9.3	7.8	12.2	17.0	21.8	22.8	21.5	18.9
Brazil	Count			44,625	45,885	44,518	43,272	46,177	53,054	53,646
	Rate			23.5	23.9	23.0	22.2	23.3	26.5	26.5

Rate = Number homicides per 100,000 in the population.
Data source: United Nations Office on Drugs and Crime.

treatment, and to predict outcomes for specific injury patterns, such as blunt carotid and aortic injuries.[40,41]

For major extremity fractures and soft tissue injury, several scoring systems have been developed to characterize the "mangled extremity." The most commonly described include the Mangled Extremity Severity Score, the Mangled Extremity Syndrome Index, the Predictive Salvage Index, and the Limb Salvage Index.[42] Although they contain different components, the presence of vascular injury and limb ischemia is a universal key variable. In addition to providing an objective classification system for epidemiologic purposes, these scores have been studied for their ability to predict the need for extremity amputation in both civilian and military settings.[42,43] Although they have been correlated with the need for amputation, prospective trials have found that they lack adequate predictive ability to be used for individual patients and did not correlate with limb salvage when arterial reconstruction was performed.[43]

Contemporary Civilian Vascular Injury

Violence in Society

The epidemic of urban violence is a scourge on society and largely contributes to the burden of vascular injuries seen at treatment facilities. Homicide rates clearly reflect the overall violence in society and are loosely linked to the incidence of vascular injury; therefore, they reflect on global and regional trends, which provides a framework for understanding the impact on local trauma systems. Table 180.2 shows the rates of homicide for select nations over time. In the United States, the homicide rate in 2013 was 3.8 per 100,000 in the population. In comparison, the rates in Honduras, the United Kingdom and Japan were 84, 1, and 0.3 per 100,000, respectively, which underscores the wide variation in different nation states.[44] Regional variations are even more pronounced. According to FBI statistics for 2015, the homicide rate in St. Louis was a staggering 50 per 100,000, which is greater than 10 times the national average. In the United States, gun violence is the principal agent of death in 60% of cases (Table 180.3), compared to 11% for bladed weaponry. This contrasts strikingly with the United Kingdom, where firearm-related homicide is a low 7%, reflecting strict gun control policies.

Epidemiologic Patterns and Trends

The exact incidence and distribution of vascular injury mechanisms may vary widely between centers, depending on the setting (urban vs. rural) and population served. According to a recent

TABLE 180.3 Homicide by Mechanism

Country	Mechanism	YEAR 2005	2006	2007	2008	2009	2010	2011	2012
United States of America	Firearm %	61%	59%	59%	58%	60%	60%	59%	60%
	Sharp %	12%	11%	11%	12%	12%	12%	12%	11%
	Other %	28%	30%	30%	31%	28%	28%	30%	30%
Honduras	Firearm %				79%	81%	83%	84%	
	Sharp %				15%	14%	12%	10%	
	Other %				6%	5%	5%	6%	
United Kingdom	Firearm %		8%	7%	6%	7%	10%	7%	
	Sharp %		38%	37%	40%	35%	37%	39%	
	Other %		54%	56%	54%	58%	54%	54%	
Australia	Firearm %	13%	15%	13%	12%	13%	17%	17%	17%
	Sharp %	36%	38%	43%	43%	41%			
	Other %	51%	47%	44%	46%	46%			
Colombia	Firearm %	70%	72%	71%	71%	78%	78%	77%	
	Sharp %	11%	11%	11%	13%	13%	14%	14%	
	Other %	20%	17%	18%	16%	9%	8%	9%	

Data source: United Nations Office on Drugs and Crime.

NTDB analysis of all trauma admissions, the incidence of vascular trauma is 1.6% for adults and 0.6% for pediatric patients, which is significantly lower than the 6% to 12% incidence among combat casualties.[23,28] However, the reported incidence of major vascular injury is likely to be an underestimate, as mentioned previously, and does not include patients who die at the trauma scene. In one analysis of autopsy reports of 552 trauma deaths identified, penetrating injury was the reported mechanism in 42% of patients, with approximately 80% dying from hemorrhage. Of the patients who had vital signs in the field, 26% were identified has having major vessel disruption.[45] The majority of prehospital or immediate deaths from vessel disruption were due to aortic injury (55%), and most (78%) were associated with death within 15 minutes of injury.

While blunt trauma accounts for approximately half of trauma deaths, vascular injury due to blunt trauma is relatively uncommon, with death from blunt vascular injury being relatively rare.[45] The most lethal blunt vascular injury pattern involves laceration or transection of the thoracic aorta, accounting for approximately 10% of all trauma-related prehospital deaths.[46] While many patients will succumb to this injury pattern immediately, those who survive to undergo definitive care fare well, with an injury-specific mortality rate of 12%.[47]

Major vascular disruption or bleeding continues to be associated with approximately 25% of early trauma deaths, and some important modern epidemiologic trends have been identified. The average age of all trauma patients and those with vascular injury is steadily increasing, with a 10-year increase in the average age of trauma patients between 1996 and 2004.[48] Thus, the classically described "young and healthy" trauma patient is being replaced with more elderly patients who have a higher incidence of preexisting vascular disease that may increase the risk for vessel injury and may alter treatment options.

Factors Influencing the Natural History of Vascular Injury

Most vascular injury patterns mandate prompt treatment in order to optimize outcomes. That treatment may come in the form of definitive treatment or temporizing measures aimed at facilitating a safe delay in care. The most significant improvements in vascular injury management over the past century have addressed these key factors. The development of a robust network of emergency medical services that can provide rapid transport and basic or advanced life support measures are an essential component of modern trauma care. One study from the United Kingdom demonstrated a decreased ratio of prehospital to in-hospital deaths over an 8-year period (1996 to 2004) from 1.5 to 0.75, underscoring the improved efficiency of prehospital EMS.[48] Gunst et al. reported consistent findings where decreased transport times and advances in prehospital care resulted in more critically injured patients surviving until arrival at a hospital, particularly those with nonsurvivable injury patterns. This led to a temporal shift in early in-hospital trauma deaths toward an earlier time point. When these early deaths were scrutinized, 76% were deemed nonsurvivable.[49] While these statistics do not support the claim that decreased transport times lead to increased survival, at a minimum it does confirm the ability of prehospital EMS to provide for the potential salvage of critically injured patients that would have otherwise died in the prehospital setting.

For severely injured patients, damage control techniques, including abbreviated surgery, the application of endovascular techniques, balanced resuscitation, and temporary intravascular shunts (both arterial and venous) have been associated with major reductions in both mortality and limb loss.[50-52] These innovations have altered the classic trimodal distribution of trauma-related mortality toward more of a bimodal distribution,

with a significantly decreased incidence of late deaths beyond 24 hours.[49]

Arguably the most significant development in modern vascular surgery is the emergence of endovascular techniques for managing vascular disease, and these techniques are now being extended to traumatic injuries. Although initially applied to injuries for which open repair was highly morbid (thoracic aorta) or provided limited exposure (distal carotid, subclavian artery), endovascular techniques for temporizing acute control of hemorrhage, or as definitive management, can be applied to a wide array of arterial and venous injury patterns.[33,53-55] A national analysis demonstrated a 27-fold increase in the use of endovascular therapy, and this was associated with a decrease in morbidity, hospital stay, and mortality.[52] Endovascular techniques have, even now, been extended to the combat setting, and include vena cava filter placement, embolization (58% of nonfilter treatment procedures), and stent placement (30%). Technical success of these procedures is 90% to 100% and provides a definitive, minimally invasive treatment option.[56]

Impact of Age and Gender on Vascular Injury

One of the largest determinants of risk for traumatic injury is age, with the overwhelming burden impacting young adults. According the 2015 NTDB report, traumatic injury progressively increases beginning at age 14, peaking at approximately age 21, and progressively declining thereafter. The majority of overall traumatic injuries are due to motorized vehicles between patient ages of 14 and 49, with falls as the dominant injury mechanism in all other age groups. While penetrating injury due to firearms accounts for less than onethird of injuries in the peak age demographic, the case fatality rate is nearly 4 times greater at approximately 15%. More than 70% of traumatic injuries in the peak age group occur in males, with up to 90% for penetrating extremity wounds.[57]

The overall incidence of vascular injury in the pediatric population (age <16) is 0.6%, compared to 1.6% in adults, based on a recent NTDB analysis.[58] Injuries to vessels in the thorax were approximately 7 times lower in children compared to adults. Penetrating injury patterns were less common in children (41.8%) compared to adults (51.2%).[58] However, a smaller single institution series reported a higher proportion of penetrating injuries in children at 67%, likely reflecting regional variation and low sample size.[59] Unfortunately, firearm and stab wounds accounted for the majority of penetrating injuries in children, with a mortality rate of 20% for those injured by a gun.[58]

The upper extremity was the most common location of pediatric vascular injury (37.9%), with most injuries involving either the radial or ulnar arteries (22%). The upper extremity is also the most common site of penetrating vascular injury for both adults and children. With regard to blunt injury patterns, the upper extremity (33%) and chest (33%) are the most common sites of blunt vascular injury in children and adults, respectively.[58] The amputation rates for both children and adults were similar.

The incidence of vascular injury in the geriatric population (mean age 70 years) is similar to that of the pediatric population, at 0.7%. There is still a gender bias toward injury in males at 60%, albeit less pronounced than in the younger adult population. Blunt mechanisms (MVC and falls) account for the overwhelming majority of injuries (84%), with blunt thoracic aortic injury being most frequent (39%). Crude mortality rates were significantly higher in the geriatric population compared to younger adults (44% vs. 22%), with injury to the thorax carrying a high mortality rate of 66%. With respect to penetrating injuries, the forearm vessels are most commonly injured (31.5%). Amputation rates following extremity vascular injury were similar in both the geriatric and younger adult populations.[60]

Ethnicity and Socioeconomic Factors

Disparity in healthcare outcomes has been extensively documented for multiple disease processes, with traumatic injury being no exception. Beyond outcomes, there is also a disparate distribution in the burden of traumatic injury within society, based on race and socioeconomic status. The effect of race and insurance status has been explored in multiple studies, with most indicating pronounced effects.[57,61-65] However, there appears to be a lack of uniformity across various injury patterns.

In a large review of the NTDB from the years of 2001 to 2005, Haider et al. demonstrated marked differences in the incidence of penetrating trauma as a function of both race and insurance status. The overall incidence of penetrating injury in this sample was 8.7%. For insured patients, the incidence by race was as follows: white = 3.1%, black = 18.3%, and Hispanic = 11.7%. For uninsured patients, a similar distribution was seen: white = 7.4%, black 31%, and Hispanic = 21.8%. Unadjusted mortality rates were statistically different for white, black, and Hispanic patients at 5.7%, 8.2%, and 9.1%, respectively. When stratified by insurance status these findings persisted, with mortality rates for uninsured white, black, and Hispanic patients at 7.9%, 11.4%, and 11.3%, respectively. These findings continued to persist despite adjustment for injury severity and demographic variables.[61]

Several authors point to heterogeneity within the trauma population as a potentially confounding factor in explaining outcomes based on race and insurance status. In an effort to control for this, Crandall et al. analyzed the outcomes in a more homogeneous population involving patients who sustained isolated lower extremity vascular injury. Mortality rates were higher for uninsured patients (31.7% vs. 21.5%); however, when stratified by mechanism, only penetrating injury remained significant. In a risk-adjusted model, race remained a predictor of increased mortality following penetrating lower extremity vascular injury in blacks (odds ratio [OR] 1.45, P = .03).[57] In another study evaluating outcomes of pedestrians struck by motor vehicles, Maybury demonstrated that blacks (OR 1.22) and Hispanics (OR 1.33) had a significantly higher mortality rate than whites utilizing a multivariate risk-adjusted model, with uninsured status also as an independent predictor of increased mortality.[65] The explanation for these outcome disparities prove challenging and may, in part, reflect physiologic and environmental variables that are not appropriately captured within the NTDB. Nonetheless, these findings highlight the

need for further investigation, and support the development of outreach programs aimed at minimizing the impact of traumatic injury on at-risk populations.

Mechanisms of Injury, Ballistics, and Biomechanics

The clinical presentation, pattern of associated injuries, need for intervention, and outcomes after traumatic vascular injury will be highly dependent on the mechanism of injury and the specific characteristics of that mechanism. For blunt injury, this mainly involves the velocity or forces of impact, the use of restraints or protective devices, and the primary anatomic areas that sustain the brunt of the kinetic forces. In addition, patients sustaining blunt trauma may suffer penetrating-type vascular injury from impalements, cuts from glass or sharp debris, and punctures by fractured bone fragments. The most common blunt mechanism associated with major vascular injury is motor vehicle collision, and injury to the vessel typically results from stretching and shearing forces, or from vascular avulsion (usually due to rapid deceleration).[66] Several additional etiologic factors have been proposed, including the generation of a sudden spike in intravascular pressure, creating wall stress, tear, or rupture, as well as forward inertial deceleration of blood impacting the anterior vessel wall ("water-hammer" effect).[66,67]

For penetrating trauma, the wounds can be primarily classified as due to stab/puncture or from missiles/projectiles that are typically firearms related. Stab and puncture wounds result in direct vascular injury without significant transmission of kinetic energy or damage to surrounding tissues. Missiles may injure vascular structures by direct laceration or by the transfer of energy due to proximity, with an impact kinetic energy (iKE) related to the mass (M) and velocity (V) of the projectile ($iKE = \frac{1}{2} MV^2$). Rarely, missiles or fragments can enter the lumen of the arterial or venous system and embolize, resulting in luminal occlusion and distal ischemia. Terms such as "high velocity" are often used, but are frequently poorly defined or misunderstood, and there are multiple projectile characteristics, such as shape, deformity, fragmentation, pitch, and yaw, that are of equal importance to, or more important than, the velocity.[68] Additional injury to surrounding tissue has been attributed to both the "sonic wave" and the stretching of tissue due to the pressure wave ("temporary cavity"), which are considerations that have been used to justify excessive tissue debridement or vessel resection. However, subsequent study has found that the effect of the sonic wave is negligible, and the size of the temporary cavity is smaller (11× the diameter of the missile) than previously described (up to 30× diameter).[68] Jahnke et al. examined the arteries from vascular wounds in the Korean War and excised the injured segment as well as a 1-cm margin of grossly normal vessel.[11] They demonstrated histologic evidence of injury that extended through the 1 cm of normal-appearing vessel. Similarly, histologic vessel injury was demonstrated in samples from the Vietnam War, but showed no correlation with the outcome of repair. Excessive debridement of grossly normal vessel or surrounding tissues is not required, even with the ballistics of so-called high-velocity wounds. Finally, particular mention should be made of shotgun injuries. Although shotguns are classified as low velocity, the resultant tissue injury due to diffuse tearing, contusion, and devascularization from multiple pellets can be significantly greater than even that of high-velocity gunshots.[69,70] Although less common than stab or gunshot mechanisms, they have been associated with vascular injury in up to 25% of wounds, and the degree of injury is highly correlated with the type of pellet and the effective weapon–victim range.[69] Shotgun pellets are notorious for creating vessel micropunctures that are difficult to diagnose even by examination or imaging studies.[71]

Blast injury, such as that seen with improvised explosive devices in the wars in Iraq and Afghanistan, has its own unique wounding pattern and mechanisms. The overall mechanism is a combination of blunt force trauma, penetrating fragment injuries, and potentially thermal injury. Blast injuries in modern combat series now outnumber standard gunshot wounds and account for 73% of vascular injuries among wounded soldiers. Blast effects are classified as primary (direct blast pressure), secondary (penetrating fragments), tertiary (collision with objects or vehicles), and quaternary (thermal injury). The relative distribution of each varies by the type of explosive, enclosed versus outdoors, and the presence of protective equipment. The majority of vascular and other injuries are due to secondary and tertiary blast effect (81%). Blast-induced extremity vascular injury with coexisting fracture is associated with a 50% amputation rate with attempts at limb salvage and a 77% amputation rate overall.[72] Blast injuries may also occur with civilian incidents, such as terrorist bombings, and vascular injuries have been identified in up to 10% of victims.

EPIDEMIOLOGY AND NATURAL HISTORY OF SPECIFIC VASCULAR INJURIES

The epidemiology for major traumatic vascular injuries will vary widely by injury location, mechanism, and the specific blood vessel involved. Similarly, the natural history and outcomes of these injuries will vary widely by these factors as well as by the specific size and degree of injury to the vessel. As many of these injuries are rapidly fatal or are immediately managed by either ligation or repair, the evolution and long-term outcome of untreated vascular injury is inherently poorly understood. Currently available clinical data on their natural history mainly come from the experience with nonoperative management of blunt internal carotid artery injuries and asymptomatic extremity artery injuries.[73,74] Also, there are limited data from several animal models on the development and progression of traumatic vascular injuries.[67] Table 180.4 shows a summary of the known natural history and potential life- or limb-threatening complications that may develop after either blunt or penetrating major vascular trauma. Clinically, occult injuries, such as narrowing/vasospasm, small intimal flap or pseudoaneurysm, and minor arteriovenous fistulae may resolve without operation in up to 86% of cases, and only 2% overall require operative intervention.[70,74] More significant injuries will frequently progress and

TABLE 180.4 Natural History of Various Types of Vascular Injuries and Potential Future Complications

Injury Type	Natural History[a]	Complications
Penetrating or Iatrogenic		
Laceration	Pseudoaneurysm or thrombosis	Ischemia, rupture, embolization
Contusion	Stenosis, thrombosis	Ischemia, embolization
Arteriovenous fistula	Increase in size and flow	"Steal" syndromes, heart failure
Blunt		
Intimal dissection or thrombosis (<25%)	Spontaneous resolution	None unless progression
Intimal dissection or thrombosis (>25%)	Pseudoaneurysm, thrombosis	Rupture, ischemia
Pseudoaneurysm	Increase in size	Rupture, embolization
Thrombosis	Occlusion, recanalization	Ischemia, stenosis
Arteriovenous fistula	Increase in size and flow	"Steal" syndromes, pseudoaneurysm
Transection	Thrombosis, pseudoaneurysm	Ischemia, compartment syndrome

[a]Natural history without intervention and assuming initial hemorrhage control.

may present with life- or limb-threatening disease without initial definitive treatment.

Neck

The incidence of vascular injury in the neck is 20% with penetrating trauma and approximately 1% in blunt trauma in civilian series, with the majority of injuries involving the carotid artery.[40,75] However, there is marked difference in the epidemiology and treatment paradigms of blunt versus penetrating carotid artery injuries. The overall incidence of diagnosed carotid artery injury is 0.2%, with 41% due to penetrating trauma versus 59% from blunt mechanisms.[76] Interestingly, a series examining missed arterial injuries identified the carotid as the most common site (39%).[77] Based on a review of the NTDB, the majority of carotid artery injuries are located in the internal carotid (37%) and less commonly the common carotid (20%), with mixed injuries the least common (10%). However, unspecified injuries accounted for 33% of documented carotid injuries.[76]

The majority of blunt carotid artery injuries are due to stretch from hyperflexion/extension with rotation and are located in the distal internal carotid artery.[75,76] Bilateral carotid artery injury or associated vertebral artery injury is present in 20% to 50% of cases. This injury pattern is usually associated with high-velocity motor vehicle crashes and multisystem injury (79%), including a 50% incidence of severe brain injury.[76,78] The increased utilization of routine computed tomography (CT) angiography for trauma has resulted in a surge of blunt carotid artery injury diagnoses.[40] The primary predictors of outcome are the grade of injury, the degree of associated injuries, and the development of neurologic symptoms. Mortality of up to 50% has been reported, but the injury-associated mortality is 15%, and the incidence of severe neurologic deficits among survivors is 16%.[39,75,78]

Vertebral artery injury is relatively uncommon, accounting for 1% to 7% of penetrating neck injuries and 1% of blunt injuries.[40,79] While mortality from isolated vertebral artery injury is approximately 10% to 20%, the mortality increases to 50% when combined carotid–vertebral artery injury is present. The majority of vertebral artery injuries (78%) have an associated cervical spine fracture, and the incidence of vertebral artery injury is up to 40% when a cervical spine fracture is present.[40,78] The incidence of posterior circulation stroke with blunt vertebral artery injury has been reported to be as high as 24%, with an 8% attributed mortality rate. However, aggressive screening with early diagnosis by CT angiography was associated with a reduction in the stroke risk from 14% to 0%.[80]

Truncal Injury

Noncompressible Truncal Hemorrhage

Injuries to named vessels of the thorax or abdomen from either blunt or penetrating mechanisms are highly morbid, with a large percentage of patients dying before they reach a hospital. A study of 1203 battlefield casualties in Iraq and Afghanistan found no survivors among those with injury to a named abdominal or thoracic vessel.[81] Even for pediatric patients, who are typically more tolerant to injury and hemorrhage, mortality approaches 100% with thoracic vascular injuries and hemodynamic instability at presentation. However, exsanguinating hemorrhage may not necessarily involve injury to named vascular structures. NCTH, irrespective of injury pattern carries a high associated mortality, accounting for 60% to 70% of potentially preventable mortality in the civilian setting.[82] From experience during Operation Enduring and Iraqi Freedom, 24% of deaths were deemed survivable, of which 42% were due to NCTH, accounting for 10% of all combat-related deaths.[16,34] Unlike peripheral or junctional vascular trauma, these injuries are not amenable to direct compression or simple inflow occlusion (tourniquet) in the prehospital or emergency department phase; therefore, they have been the focus of great interest and innovation. Critical concepts or interventions for patients with NCTH are (1) minimizing delays in transfer from the emergency department to the operating room; (2) permissive hypotension until vascular control is obtained; (3) balanced or "hemostatic" resuscitation with the early use of plasma; (4) procoagulant adjuncts, such as tranexamic acid; and (5) the use of damage control surgery techniques and intravascular shunts when indicated.[50,83]

In an effort to alter the natural history of this highly lethal injury pattern, novel strategies are being developed, which are particularly aimed at the prehospital phase of care. Resuscitative endovascular balloon occlusion of the aorta has emerged as a viable adjunct in the management of patients with NCTH.[33,53]

This intervention is minimally invasive, potentially obviating the need for heroic intervention, such as open aortic cross-clamping, and can be applied in the prehospital arena. Experience with this technique is increasing, with the development of new technologies and devices to increase safety and feasibility. The AAST Aortic Occlusion for Resuscitation in Trauma and Acute Care Surgery (AORTA) Registry was established in 2013 to prospectively track outcomes of patients undergoing any form of aortic occlusion including REBOA.[84]

Thorax

Thoracic Aorta

The majority of thoracic vascular injury (90%) is due to penetrating trauma, with 28% of penetrating aortic injuries in the thoracic portion.[85] In a landmark study of 5760 vascular injuries, Mattox et al found that 14% involved the thoracic aorta, of which 86% were due to penetrating mechanisms.[86] Thoracic aortic injuries can be classified into several groups, including intrapericardial/ascending (8% to 27%), aortic arch (8% to 18%), and descending thoracic (11% to 21%).[87]

Blunt trauma of the descending thoracic aorta is the most frequently diagnosed and encountered blunt thoracic vascular injury with 98% of these injuries occurring at the ligamentum arteriosum or just distal to the origin of the left subclavian artery (Fig. 180.2).[88] The most common mechanisms of injury are motor vehicle accidents (driver's chest decelerates against the steering wheel), falls from a height with impact on a hard surface, and impact from a large mass. Additionally, blunt aortic injury is identified in up to 30% of airplane crash victims.[89] Injuries are classified as follows: intimal tear (grade I), large intimal flap or intramural hematoma (grade II), pseudoaneurysm (grade III), and rupture (grade IV).[41,90]

Blunt trauma to the ascending aorta occurs from sudden displacement of the intact sternum or displacement of the fractured or dislocated sternum onto the anterior surface of the ascending aorta. Several injuries can occur: a subadventitial hematoma, a subintimal hematoma or tear, or a complete tear with pseudoaneurysm formation or free rupture.[46] Another injury to the ascending aorta from blunt trauma is a torsion tear caused by the sudden rotation of the heart apex posteriorly with a spiral tear starting above the aortic valve. Most (98%) of these die at the scene from pericardial tamponade or exsanguination and, thus, rarely survive to hospital diagnosis or repair.[46,91]

In contemporary practice, blunt thoracic aortic injuries are managed primarily with thoracic endovascular aortic repair (TEVAR). A landmark multicenter study by Fabian et al (AAST-1) in 1997 characterized the traditional approach to blunt thoracic aortic injuries, with 35% undergoing clamp and sew repair, and 65% having repair with cardiopulmonary bypass.[75] Mortality was 31%, and the paraplegia rate was 9%. In a recent multi-center experience, TEVAR was utilized in 76% of cases, with overall and aortic-related mortality rates of 8.6% and 2.5%, respectively, and paraplegia in a mere 0.5%.[92] Additionally, the literature supports delayed repair of stable injuries (grade I to III), particularly in the presence of significant associated injuries.[47,92] Endovascular repair has also been extended to patients with acute penetrating thoracic injury or delayed complications, such as pseudoaneurysm or arteriovenous fistula.[56] Finally, nonoperative management of select patients with low-risk injuries (grade I/II) or with prohibitive surgical risk is becoming more widely accepted.[47,92,93]

Great Vessels

Injury to the great vessels (innominate, brachiocephalic, proximal subclavian) is frequently fatal (90% occur within 30 minutes) due to hemorrhage or associated injury to the airway, heart, or aortic arch.[87] Additionally, mortality rates of 70% to 80% have been reported for isolated subclavian artery injuries.[55,94,95] The incidence of great vessel injury is approximately 5% with gunshot wounds, and 2% with stab wounds; it is extremely uncommon (<1%) in blunt trauma.[60,87] In a large autopsy study of trauma deaths, 12.7% of deaths were due to injury to the aorta or great vessels, and no patient with a penetrating wound survived to hospital arrival compared with 5% of blunt injuries.[46] Many patients will have multiple-vessel injury (65%), and the majority (77%) present with clear signs of hemorrhage or a large and expanding hematoma.[96] Operative approaches are dependent on individual surgeon and institution preferences, but typically involve a median sternotomy or left thoracotomy. High patency rates (>90%) have been described with both vein and prosthetic repairs, with no significant incidence of prosthetic graft infection reported.[94,96] Ligation of the subclavian arteries may be performed in select cases and is frequently well tolerated because of collateral circulation.[95,68] Experience with TEVAR for blunt thoracic aortic injury involving routine coverage of the left subclavian artery supports this claim, with only a 4% to 5% incidence of left arm ischemic symptoms. Long-term functional deficits among survivors are attributed to the central nervous or brachial plexus injuries more than to the vascular injury.[94]

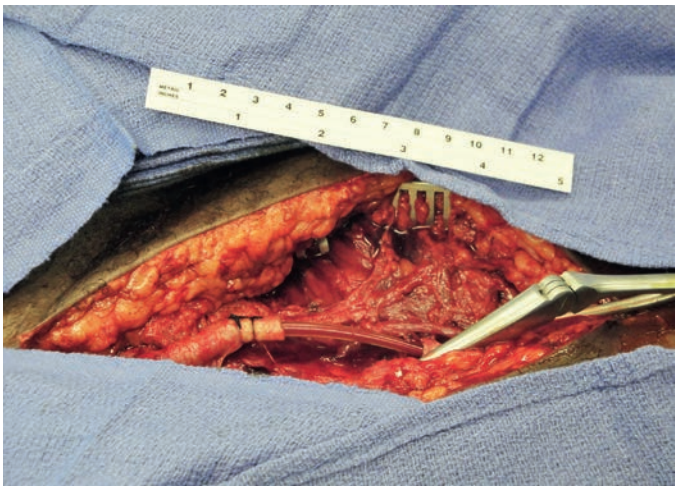

Figure 180.2 Temporary Vascular Shunt. Injury to the superficial femoral artery from a gunshot wound. Due to concomitant injury, temporary shunting was performed using an Argyle shunt to maintain limb viability while more life-threatening injuries were managed.

Axillosubclavian Vessels

Although the proximal subclavian vessels are primarily mediastinal structures, the distal subclavian and proximal axillary vessels cross anatomic zones including the chest, neck, and extremity. Proximal subclavian injuries adhere to the principles described before for great vessels, but axillosubclavian injuries often have a different presentation and complicating factors. Among modern combat casualties, the incidence of upper extremity vascular injury is 1.7%, and 23% of these involve the axillary or subclavian vessels.[97] The majority of civilian injuries are due to penetrating trauma (55% to 75%) and are most common in shotgun wounds (18%), followed by gunshots (10%) and stab wounds (9%).[70] Concomitant vein injury is present in onethird of patients.[98] Blunt axillosubclavian injuries are rare and are due to either shear forces or clavicle fracture with nearly universal presence of nerve injury or fracture.[99] Limb function is often severely impaired, but this is primarily due to the high incidence (40% to 100%) of associated brachial plexus injury.[98] Amputation is ultimately required in 3% to 15% and mortality is up to 25%, with worse outcomes among the blunt injuries patterns.[99]

There is increasing interest in, and successful reports of, endovascular management of these injuries, particularly for pseudoaneurysms and arteriovenous fistulae. A series of 57 patients with long-term follow-up demonstrated stenosis in 20% and occlusion in 12%; all were managed percutaneously with no limb ischemia or loss.[55] Additionally, these techniques have been shown to decrease hospital length of stay and have a high degree of technical success approaching 100%.[55] These techniques may also be extended to so-called unstable patients and, in fact, may achieve faster hemorrhage control in systems that are prepared for emergent endovascular intervention.[56]

Abdomen

In a large series of 5760 vascular injuries, 34% involved abdominal vasculature and 24% involved multiple vessels.[86] The majority of abdominal vascular injuries were due to penetrating mechanisms (89%), with 36% of patients having multiple vessel injury.[100,101] Hemodynamic instability or complete arrest requiring emergency department thoracotomy has been reported in up to 15% of patients.[102] There appears to be a relatively equal distribution of the type of vessel injured, with vein injuries in 53% versus arterial injuries in 47%.[102] Approximately half (53%) of patients had two or more abdominal vessels injured, with mortality increasing from 45% with one vessel to 60% and 73% with two and three vessels injured, respectively.[102] The most commonly injured major vessels were the inferior vena cava (IVC) and branches (52%), the aorta and branches (35%), the superior mesenteric artery (SMA) and branches (45%), and the portal or hepatic venous system (22%).[100,101] The reported high mortality rates of 30% to 60% highlight the need for early diagnosis and intervention, with 70% to 89% of deaths attributed to bleeding.[100] Hypotension was present in 25% of patients and is one of the strongest independent predictors of death (OR, 4.5 to 18).[100]

The major abdominal vasculature is located in the retroperitoneum; therefore, injuries may present with contained retroperitoneal hematomas rather than free bleeding. A four-zone anatomic classification for retroperitoneal hematomas based on the vasculature is commonly used: zone 1 (central) contains the aorta and vena cava, zone 2 (lateral) contains the renal vessels, zone 3 (pelvic) contains the iliac vessels, and zone 4 (hepatoportal) contains the portal vein and retrohepatic vena cava. Zone 3 predominates in blunt trauma (70%), whereas zone 2 is most commonly seen in penetrating injury (50%).[103] Retroperitoneal hematomas are associated with morbidity of up to 60%, and with mortality from 13% to 40%.[103]

Abdominal Aorta (Zone 1)

Blunt injury to the abdominal aorta is rarely seen, and the majority of these injuries probably result in prehospital death from bleeding or severe associated injuries. Injury to the abdominal aorta represents only 5% of aortic injuries and was identified in 9% of all fatal aortic injuries from vehicular trauma.[104] More than half (56%) of the fatalities involved transection of the aorta and have been associated with the deceleration and hyperflexion with lap belt restraints.[104] Only 25% of patients will have abdominal wall bruising or injury, and the most common early signs are arterial insufficiency (81%), acute abdomen (55%), and weakness or paralysis (47%).[104] These injuries are virtually always in the infrarenal aorta, most commonly at the junction with the inferior mesenteric artery or the iliac bifurcation.[66,104] An intimal flap with distal dissection is the most common pathologic lesion (57%), followed by thrombosis (40%) and pseudoaneurysm (15%).[104] Mortality is 20% to 40% and increases to 83% with advanced age (>65 years).[102,104]

Penetrating abdominal aortic injury is most frequently due to gunshot wounds (78%) and carries an overall survival of less than 50%.[102] Approximately 30% will present in extremis with no measurable blood pressure, and up to 21% may require emergency department thoracotomy.[85] The location of injury is most commonly infrarenal (45%), followed by suprarenal (37%) and subdiaphragmatic (18%).[105] Injury to the suprarenal aorta is particularly difficult and highly morbid, although Mattox et al reported survival in 10 of 28 (36%) patients.[106] Overall mortality rates of 33% to 81% have been reported.[85,106] Although modern trauma management principles have been found to have no impact on the high mortality of these injuries, a study from San Diego found that mortality decreased from 78% to 40% when the patient was brought directly to the operating room (bypassing the emergency department) for resuscitation.[85,105]

Inferior Vena Cava (Zone 1)

Although the IVC is part of the lower pressure venous system, injuries cause rapid exsanguination unless they are contained or immediately controlled. Excluding mesenteric vessels, the IVC is the most commonly injured major abdominal vessel, representing 6.7% of all penetrating vascular injuries and 3.4% of blunt injuries.[60] The majority of injuries (>90%) are due to penetrating mechanisms and are located in the infrarenal cava

(85%). Approximately half of patients will present with hypotension.[107] Associated visceral injuries are present in 90% of patients and include injury to the duodenum (31%), liver (29%), and pancreas (26%).[107]

Mortality with isolated IVC injury is reported as high as 70% and increases to 78% in combination with another venous injury.[102] However, survival of up to 96% is reported among patients with an isolated infrarenal IVC injury and no hemodynamic instability.[107] Data from combat injuries of the IVC in Vietnam found that the majority underwent surgical repair (72%) versus ligation (19%), with a 23% mortality rate. IVC injury in the wars in Iraq and Afghanistan accounts for 1.4% of all vascular injuries, with approximately 50% undergoing ligation versus shunting with delayed repair or immediate repair in the remainder.[23]

Celiac and Mesenteric Vessels (Zone 1)

Traumatic injuries to the celiac trunk, SMA, or superior mesenteric vein are extremely uncommon and represent only 0.01% to 0.1% of all vascular injuries.[108] Similarly, low incidences have been reported from recent large series of battlefield injuries (0.19% celiac, 0.83% SMA).[23] A much higher incidence of 6.3% was demonstrated in a large NTDB series, but this probably includes branch vessels and more distal mesenteric injuries.[60] The majority of visceral artery injuries are due to penetrating trauma, representing 90% to 95% of celiac artery and 52% to 77% of SMA injuries.[108,109] Associated injuries are the rule, with a mean of 4.2 injuries per patient and with 35% of patients having a coexisting superior mesenteric vein injury.[108] The clinical presentation is typically either hemodynamic instability or peritonitis, with a mean estimated blood loss of 8.5 liters.[109] Mortality is 20% to 40%, with most deaths due to intraoperative or early postoperative bleeding (71%), and later postoperative complications (29%).[100,108] Mortality is directly correlated to both the injury severity and the number of coexisting vessel injuries.[85,100]

Renal Vessels (Zone 2)

Although renal injuries are relatively common with both blunt and penetrating trauma, true renovascular injury is much less common. For blunt mechanisms (incidence of 0.08%), a distinction should be made between renal parenchymal injury involving the segmental vessels or renal avulsion (AAST-OIS grade 4 to 5 injuries) and primary renovascular injury that is usually due to stretching and subsequent dissection or thrombosis. The injury mechanism is equally distributed between blunt (49%) and penetrating (51%).[110] Associated abdominal injuries are present in 77%. Nephrectomy was required in 51% of penetrating injury, with a mortality of 30%.[111]

Iliac Vessels (Zone 3)

Iliac vascular injury is uncommon, with an overall incidence of less than 1% representing 14% of civilian penetrating arterial injuries and 2% of combat vascular injuries.[112,113] Iliac artery and vein injuries are a particular challenge because of the difficulties of exposure and obtaining distal control in the deep pelvis. Injuries to the main vessels are predominantly due to gunshot wounds (86% to 95%), and 56% will have multiple iliac injuries.[113] The majority (68%) of injuries that survive to hospital admission are to the common or external iliac vein, and 32% involve the iliac arteries. Mortality with iliac vessel injury is 28% to 49%, and appears to be decreased with the use of damage control techniques including intravascular shunts.[50] Injuries to branch vessels or the internal iliac vessels are most commonly due to blunt trauma with an associated pelvic fracture. Injury to the main iliac or femoral vessels with pelvic fracture is exceedingly rare (0 of 429 patients in one series). Several series have identified the control of pelvic hemorrhage as the most frequent preventable cause of death from bleeding, and surgical intervention with packing or iliac artery ligation may be required.

Hepatoportal Vessels (Zone 4)

Injuries to the hepatoportal system are highly morbid because of common factors including massive hemorrhage, associated pancreaticoduodenal injury, difficult surgical exposure, and surgeon inexperience with these uncommon injuries. Injury to the hepatic veins or retrohepatic vena cava occurred in 9% and portal vein in 5% of abdominal vascular injuries; and 94% are due to penetrating trauma.[100] Among patients with injury to the IVC, there is a 19% incidence of combined injury with the portal vein.[107] Portal vein injuries are 92% fatal in association with other portal triad injuries, and 100% fatal with hepatic artery injury. Injuries of the retrohepatic vena cava have an associated mortality of 70% to 100% even with various shunt or exclusion techniques.[107] Injury of the retrohepatic vena cava (88%) and injury of the portal vein (69%) represent two of the top three causes of death from abdominal vascular trauma.[100]

Extremity

Extremity trauma is extremely common in all settings from both blunt and penetrating mechanisms, accounting for approximately 1% to 2% of all civilian trauma.[60] Vascular injury is more common in the lower extremities (66%) versus upper (34%).[28] In contrast, approximately 50% of modern combat injuries involve the extremities, with 75% due to blast mechanisms.[114] Although blunt mechanisms account for the large majority of overall extremity injuries, penetrating trauma mechanisms cause most (60% to 80%) extremity vascular injuries.[115]

Prehospital management of extremity vascular injury in military conflict has evolved significantly during OEF/OIF, with the widespread use of tourniquets beginning in 2005 as well as commonplace use of hemostatic dressings. Tourniquet use resulted in a staggering reduction in the prehospital death rate from 23.3 deaths per year to 3.5 deaths per year, for an overall reduction in potentially survivable death of 85%.[39] Currently, extremity vascular injury accounts for 13.5% of potentially survivable vascular injuries in modern conflicts.[39]

Isolated civilian extremity trauma with vascular injury carries a 10% risk of mortality or limb loss, and this risk is higher for penetrating mechanism and more proximal vessel injury.[116] Blunt extremity vascular injury is associated with an 18% amputation

rate and a 10% mortality rate.[115] With adjustment for other variables, lower extremity vascular injury is independently associated with an increased amputation rate (OR, 4.3) and higher mortality (OR, 2.2).[117]

Temporary intravascular shunt use is increasingly applied in the context of polytrauma, with contemporary series reporting its use in 9% of civilian vascular injuries and up to 24% of combat extremity vascular injuries (see Fig. 180.2).[28,118] In the largest published combat series of temporary intravascular shunts, patency varied widely from 86% for proximal injuries to 12% for distal vessels.[28] Despite the varied patency rates, early limb salvage in this population was 88% for distal shunts and 95% for proximal shunt placement (P = not significant) and is comparable to the reported limb salvage rates of 75% to 100% in civilian series.[118]

Upper Extremity

A recent analysis of the NTDB found that the upper extremities were the site of 27% of all civilian vascular injuries. Approximately 25% of blunt extremity vascular injuries are in the arm, with 50% located in the brachial artery. Among patients who required upper extremity amputation, the most commonly injured vessel was the brachial artery (12% of patients).[60] Compartment syndrome is present or may develop in 21% and is associated with multiple vessel injuries and open fractures. Mangled extremity predictive scoring systems have been found to be less predictive of outcomes for upper extremity injury, and limb salvage has been demonstrated in 90% of patients. Blunt injury is associated with a significantly higher amputation rate (20%) and mortality compared with penetrating mechanisms.[115]

Contemporary military experience reveals an overall incidence of upper extremity arterial injury in 30% to 34% of patients, with 11% proximal (brachial artery) and 19% distal (radial or ulnar).[23,97] Associated injuries to the ulnar or median nerve are present in up to 50%, and functional outcomes are mainly related to the associated nerve injuries rather than to the vascular trauma.[119] Associated injuries to the ulnar or median nerve are present in up to 50%, and functional outcomes are mainly related to the associated nerve injuries rather than to the vascular trauma.[119]

The majority of upper extremity vascular injuries in both civilian and military trauma are to the forearm vessels, including the radial and ulnar arteries.[60,97,117] Penetrating trauma is the cause of up to 81% of injuries, but stab wounds are more common than gunshot injury (opposite of the lower extremity).[117] Blunt radial or ulnar injury is almost always seen with a coexisting fracture of the forearm or elbow dislocation (95%) and is associated with higher mortality and limb loss.[115] Injury to forearm nerves and bone or soft tissue is the primary determinant of the ultimate functional outcome.[119]

Lower Extremity

Femoropopliteal Vessels

The majority of penetrating extremity wounds are to the lower extremity (71%) and have a 10% incidence of vascular injury versus 1% for blunt trauma.[70,73,115] Most femoral artery injuries are due to penetrating trauma, but blunt trauma is now the predominant cause (61%) of popliteal injury.[120] Knee dislocations are particularly high risk, with up to a 30% incidence of popliteal artery injury.[121] Femoral artery injuries represent 14% of all lower extremity vascular injuries from blunt trauma and 42% from penetrating.[60,115] An NTDB analysis of 651 patients demonstrated injury to the common femoral artery (CFA) in 18%, the superficial femoral artery (SFA) in 28%, and the popliteal in 36%.[116] The most feared complications vary by injury site, with bleeding of greater concern in more proximal injuries (CFA and SFA) and limb loss due to ischemia of greatest concern with popliteal injuries. Up to 46% of CFA and SFA injuries have an associated injury to the femoral vein, and 40% to 50% of popliteal injuries are combined.[120] Between 7% and 25% of patients will have an associated nerve injury, and long-term function is related to the nerve and soft tissue injuries more than to the vascular trauma. An analysis of almost 30,000 patients with vascular injury from the NTDB found that among patients who required lower extremity amputation, the popliteal artery was the most commonly injured vessel (28% of patients).[60] The majority of deaths due to extremity hemorrhage in both the civilian and military populations are from injuries to the femoral vessels. After adjustment for confounding factors, femoral or popliteal vascular injury is associated with increased mortality (OR, 2.2) and limb loss (OR, 4.3).[117]

Tibioperoneal Vessels

The true incidence of tibioperoneal vessel injury is unknown as the majority are likely to be clinically silent. Tibioperoneal vessels represent the majority (63%) of blunt lower extremity vascular injuries, 10% of penetrating leg trauma, and 44% among combat casualties.[23,60,115] Among patients with isolated lower extremity trauma with vascular injury, the posterior tibial artery is injured in 13% and the anterior tibial artery is injured in 8.6% (combined injury in 1.1%).[116] Whereas observation or ligation for isolated single-vessel injury is universally well tolerated, up to 50% of multivessel injuries develop symptoms of limb ischemia and are associated with an OR of 5.2 for amputation.[116,122] Associated injuries include tibial or fibular fractures in 64%, severe soft tissue injury in 32%, and nerve injury in 36%.[122] Amputation is required in approximately 10% of patients and is twice as frequent with blunt trauma as with penetrating trauma. The overall mortality is less than 5% and is 3 times less common than in more proximal arterial injuries.[122]

SUMMARY

Vascular injury remains a common source of morbidity and mortality in both military and civilian settings. While significant progress is evident, the overall blight of traumatic injury remains a scourge on society. The greatest opportunity to influence outcomes does not stem from improvements in prehospital care, innovation in technique and therapeutics, or surgical capabilities, but rather from efforts targeting injury prevention. An epidemiologic approach to trauma and vascular injury serves

to identify the complex factors that influence the incidence and prevalence in society. This establishes the foundation for public health and legislative initiatives aimed at mitigating the impact on at-risk populations. Improved data gathering through registries and databases—using standardized metrics and outcomes measures—is important to accurately characterize injury across the spectrum of care. Overall, a more systematic and comprehensive approach is warranted to minimize impact on the individual, on society, and on our healthcare system as a whole.

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A complete reference list can be found online at www.expertconsult.com.

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181 CHAPTER

Vascular Trauma: Head and Neck

BENJAMIN W. STARNES and ZACHARY M. ARTHURS

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Cervical vascular injuries are notoriously difficult to evaluate and to manage, mostly secondary to complex anatomy confined to a relatively narrow anatomic space. The initial evaluation of these patients is often obscured by associated injuries to the head, chest, or abdomen. In addition, signs of cerebral ischemia, cranial nerve deficits, or cervical nerve compression may not be present on initial evaluation. The evaluation and appropriate management of this injury pattern have been controversial and continue to evolve. Advances in noninvasive imaging (primarily computed tomography [CT]) have revolutionized the evaluation of stable patients with cervical vascular injuries, aerodigestive injuries, and associated fractures. In addition, endovascular surgery has added another facet to the care of these trauma patients. Injuries to the distal internal carotid artery, proximal common carotid artery, subclavian artery, or vertebral arteries are now amenable to endovascular methods to arrest hemorrhage, to exclude dissections and pseudoaneurysms, or to assist with open repair. This chapter addresses the presentation, evaluation, and treatment of cervical vascular injuries.

CAROTID ARTERIES

Penetrating Injury

After penetrating cervical trauma, cervical blood vessels are the most commonly injured structures in the neck and account for a 7% to 27% stroke rate and a 7% to 50% mortality.[1] In this population, 80% of deaths are stroke related.

Abstract

Cervical vascular injuries are notoriously difficult to evaluate and to manage, mostly secondary to complex anatomy confined to a relatively narrow anatomic space. The initial evaluation of these patients is often obscured by associated injuries to the head, chest, or abdomen. In addition, signs of cerebral ischemia, cranial nerve deficits, or cervical nerve compression may not be present on initial evaluation. The evaluation and appropriate management of this injury pattern have been controversial and continue to evolve. Advances in noninvasive imaging (primarily computed tomography [CT]) have revolutionized the evaluation of stable patients with cervical vascular injuries, aerodigestive injuries, and associated fractures. In addition, endovascular surgery has added another facet to the care of these trauma patients. Injuries to the distal internal carotid artery, proximal common carotid artery, subclavian artery, or vertebral arteries are now amenable to endovascular methods to arrest hemorrhage, to exclude dissections and pseudoaneurysms, or to assist with open repair. This chapter addresses the presentation, evaluation, and treatment of cervical vascular injuries.

Keywords

Injury
Penetrating
Blunt
Cerebrovascular
Carotid
Vertebral
Subclavian
Endovascular
Cervical
Venous

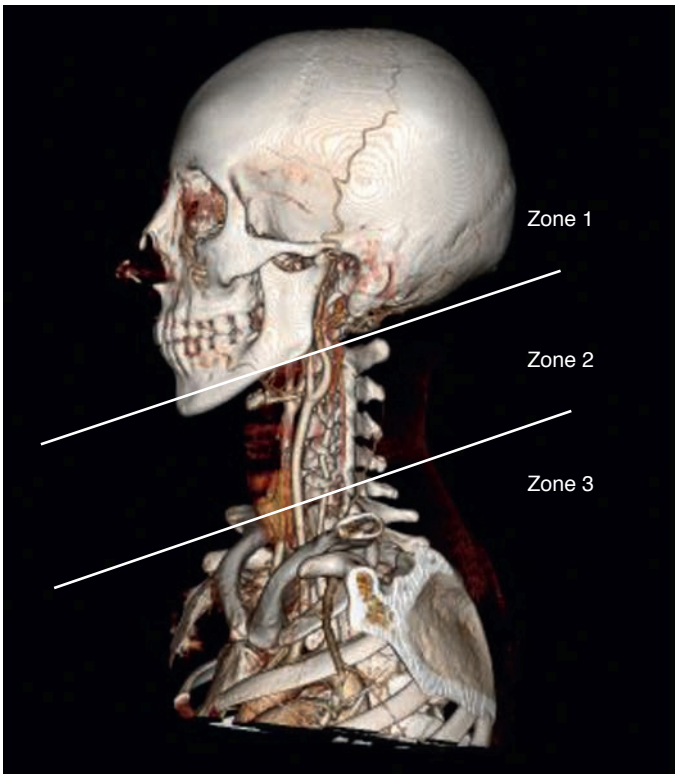

Figure 181.1 Anatomic zones of the neck for penetrating neck injuries.

Clinical Presentation

The neck has classically been divided into three zones that dictate diagnostic evaluation and treatment[2] (Fig. 181.1):

- Zone I: below the cricoid cartilage—proximal control obtained in the chest.
- Zone II: between the cricoid cartilage and the angle of the mandible—proximal and distal control obtained in the neck.
- Zone III: above the angle of the mandible—distal control difficult to obtain.

Zone II is the most commonly injured (47%), followed by zone III (19%) and zone I (18%). It is not uncommon for the injury to traverse two zones of the neck.[3] In addition to location, the physical examination triages patients on the basis of "hard signs" of vascular injury (mandating exploration) and "soft signs" of vascular injury (observation vs. further diagnostic evaluation). Hard signs include shock, refractory hypotension, pulsatile bleeding, bruit, enlarging hematoma, and loss of pulse with stable or evolving neurologic deficit. Soft signs include history of bleeding at the scene of injury, stable hematoma, nerve injury, proximity of injury track, and unequal upper extremity blood pressure measurements. Ninety-seven percent of patients with hard signs have a vascular injury as opposed to only 3% with soft signs.[3]

On the basis of mechanism of injury, gunshot wounds are more likely to cause a large neck hematoma and vascular injury (27%) compared with stab wounds (15%).[3] Shotgun wounds, blast injuries, and transcervical (crossing midline) gunshot wounds have a higher rate of vascular injury and should be approached with a high index of suspicion. Associated injuries to the tracheobronchial tree, esophagus, and spinal cord are present in 1% to 7% of patients.[3] In addition to hard signs of a vascular injury, patients may present with hard signs of a tracheobronchial injury (respiratory distress or air bubbling from the wound), mandating operative exploration. Other soft signs of cervical neck injury include painful swallowing, subcutaneous emphysema, hematemesis, and signs of nerve injury (cranial nerves IX, X, XI, and XII) or brachial plexus injury (axillary, musculocutaneous, radial, median, and ulnar nerves). A focused and detailed clinical evaluation reliably identifies patients with vascular injuries that require treatment. A physical examination with normal findings has a negative predictive value of 90% to 100% for vascular injuries.[4]

Special consideration should be given to patients who present with coma, a dense hemispheric stroke, or documented carotid thrombosis. The treatment of this specific injury pattern has come full circle from revascularization in the 1950s, to routine ligation in the 1970s, followed by revascularization as the current mainstay of treatment. In the 1970s, authors reported only a few patients with dense hemispheric stroke who developed hemorrhagic stroke after revascularization, leading to the recommendation of internal carotid artery ligation distal to the thrombus.[5-7] Follow-up studies demonstrated that the extent of anoxic brain injury (not hemorrhagic conversion of the injury), development of reperfusion injury, cerebral edema, and resultant uncal herniation accounted for patients with worsening neurologic status and death.[8,9] However, to date, there is no preoperative marker other than time (>24 hours from time of injury) that predicts those patients unlikely to benefit from revascularization. Early revascularization has consistently demonstrated improvement or stabilization of neurologic symptoms in patients with dense hemispheric strokes (100%), even in patients who present obtunded (50%).[1,10]

Diagnostic Evaluation

Patients with hard signs of a vascular injury should proceed to the operative suite. All patients should have plain radiographs of the neck and chest to determine the track of the injury and to diagnose occult hemothoraces or pneumothoraces. There have been several advances in the treatment of penetrating neck injuries, and data are now sufficient to support selective exploration in hemodynamically stable patients who do not have hard signs of a vascular or tracheobronchial injury. Exploration of cervical injuries based on platysma muscle penetration carries an unacceptably high negative exploration rate of 50% to 90%.[11]

CT is the modern workhorse for trauma evaluation and should be the initial diagnostic step in evaluating patients with penetrating neck injuries who do not have hard signs of vascular or aerodigestive injury. Contrasted axial imaging with reformatting software allows exact determination of the injury track, vascular injuries, proximity to the esophagus and trachea, spinal fractures and cord involvement, and extension into the head or chest (Fig. 181.2). In the setting of penetrating cervical injuries, computed tomographic angiography (CTA) has a 90% sensitivity and 100% specificity for vascular injuries that require treatment.[12,13] CTA may be limited secondary to missile fragments (especially shotgun injuries) or bone fragments obscuring

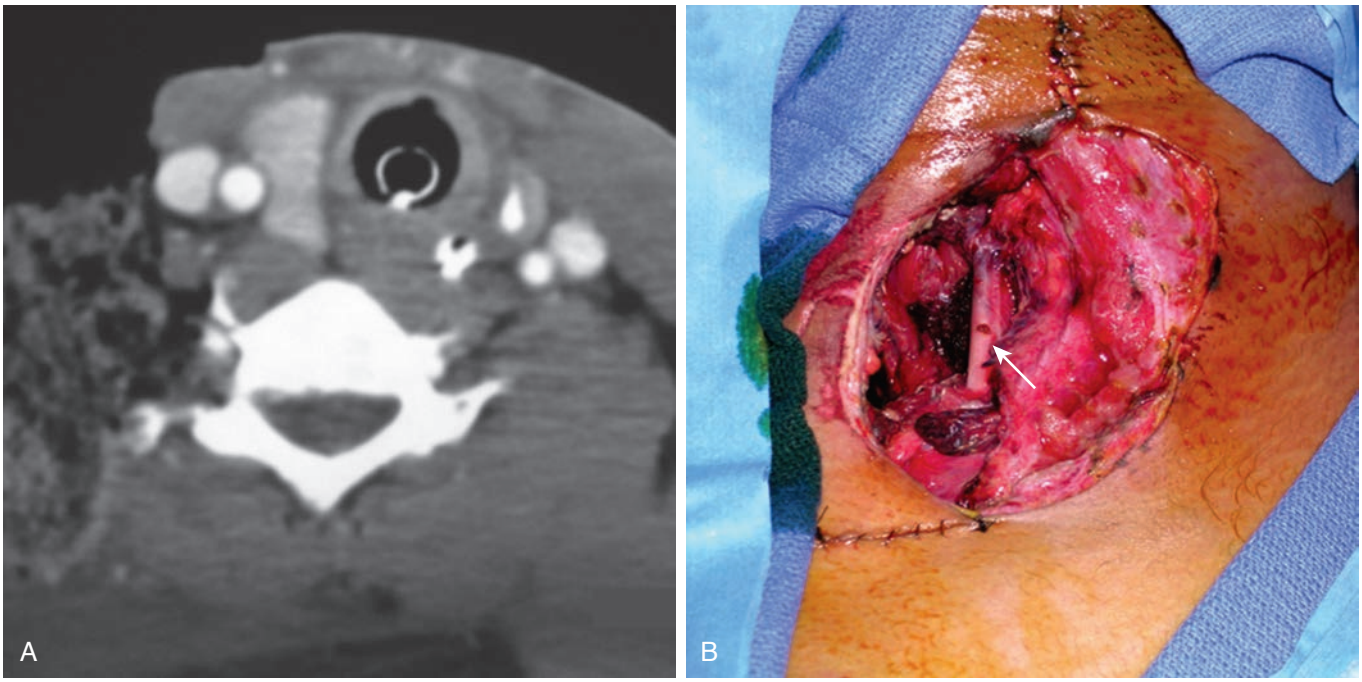

Figure 181.2 This patient sustained a high-velocity gunshot wound to zone I of the neck. On initial evaluation, he did not have hard signs of a vascular injury. (A) Computed tomographic angiography demonstrates no injury to the internal jugular vein or common carotid artery. In addition, there is no injury to the aerodigestive tract. (B) The patient's wound was débrided in the operative suite; the *arrow* marks the cords of the brachial plexus.

the cervical vasculature; arteriography should be used for these patients as a confirmatory study. Ultrasonography has been used for penetrating neck trauma, but its utility is limited to zone II neck injuries.[14] In addition, subcutaneous air, fragments, and hematomas make ultrasound less reliable.

Medical Treatment (Nonoperative Management)

Occult injuries (intimal flaps, dissections, and pseudoaneurysms) identified during evaluation for penetrating cervical injury should be managed just as those caused by blunt trauma (detailed later). Isolated intimal flaps are rare in penetrating trauma, and dissections occur in only 2% of cases. Pseudoaneurysms are the most common occult injury identified. Large pseudoaneurysms should be considered for early intervention, whereas small pseudoaneurysms should be treated with antithrombotic therapy and early follow-up imaging. The natural history of these lesions is not known; however, patients should be closely monitored for development of embolic symptoms.

Endovascular Treatment

An endoluminal approach to neck injuries may avoid the morbidity of median sternotomy, a high thoracic incision, or difficult dissection at the base of the skull. Another benefit is that endoluminal therapy can be performed under local anesthesia, allowing the provider direct assessment of the patient's neurologic status. For zone I and zone III injuries, endovascular exclusion of a pseudoaneurysm, partial transection, or arteriovenous fistula remains a viable option based on the location of injury and the patient's clinical status. Self-expanding covered stents can be safely delivered to these locations with limited morbidity.[15-18] Zone II injuries should be approached with operative repair.

Surgical Treatment

Proximal and Distal Control in the Neck

Obtaining control of the injury in each zone presents unique challenges. All patients should have their proximal thighs (potential vein conduit) and chest (potential proximal control) prepared into the operative field. Zone I injuries that are manifested with hard signs may be approached through a cervical incision, but a median sternotomy or high anterolateral thoracotomy will be required to obtain proximal control. If the patient is in shock, endovascular attempts at proximal control should not delay performing a median sternotomy. Depending on the patient's hemodynamics and the location of injury, proximal control of the great vessels may be performed from a femoral approach in the operative suite with balloon occlusion (a large 33-mm compliant balloon catheter). Alternatively, if the proximal vessel can be visualized from a cervical approach but not secured with a vascular clamp, a compliant balloon or Fogarty catheter can be passed retrograde for temporary proximal control. After the vessel is properly exposed, the balloon can be replaced with a vascular clamp.

An overt injury in zone II can be readily approached through a cervical incision and repair performed under direct visualization. The most common vessel injured by penetrating mechanisms is the internal jugular vein, followed by the common carotid artery. The operative feasibility, ability to examine the aerodigestive tract, and relatively low risk to exploration in this region

favor open exploration over endovascular techniques in emergent situations.

Hemorrhage from a zone III injury can be devastating, and an immediate operative exploration through a cervical incision can be used first to control inflow and to assess the injury pattern. Even after subluxation of the mandible and division of the posterior belly of the digastric muscle, the distal extent of the injury may not be visualized. If the vessel is transected with inadequate length for clamp application, distal control can be obtained by placing a Fogarty balloon (No. 3-4) within the vessel lumen. If the vessel is lacerated, a sheath can be placed in the common carotid artery and a Fogarty catheter can be passed antegrade through the injury to control backbleeding. After the Fogarty balloon is inflated, arteriography can be performed through the side arm of the sheath to delineate the injury with respect to the skull base and further guide operative exposure. After hemorrhage is arrested, the surgeon must decide whether to proceed with operative repair, embolization of the carotid artery, endoluminal stenting, or temporary shunting or to return the patient to the intensive care unit for resuscitation, imaging of the brain, and delayed repair. If a damage control approach is used, the patient should have serial imaging to evaluate evolving cerebral edema, and cerebral perfusion pressures should guide further resuscitative maneuvers.

Surgical Repair of Cervical Vessels

After the injury has been delineated and controlled, the surgeon must decide whether to ligate, repair, or temporarily shunt the vessel. The internal jugular vein and external carotid artery may be ligated with limited morbidity. Ligation of the internal carotid artery results in a 45% mortality,[1] and it should be reserved only for injuries at the base of the skull that are not amenable to reconstruction. Clean-based lacerations caused by stab wounds may be repaired primarily; however, gunshot wounds, fragmentation wounds, and shotgun injuries typically require reconstruction of the common carotid or internal carotid artery. Shunts should be used in patients who are already at risk of cerebral hypoperfusion secondary to shock and to all injuries of the internal carotid artery. If the distal clamp can be placed below the carotid bulb, the internal carotid artery will receive adequate backbleeding through the external carotid artery. Heparin (50 units/kg) should be given before clamps are placed.

The greater saphenous vein has good size match with the internal carotid artery and, when used as an interposition graft, has demonstrated excellent patency and limited infectious risk. The external carotid artery can also be transposed to the internal carotid artery for injuries in the proximal internal carotid. In addition, superficial femoral artery can be used in the common or internal carotid artery but requires an additional reconstruction in the lower extremity with polytetrafluoroethylene (PTFE).[19] PTFE or Dacron typically has a better size match than the greater saphenous vein in the common carotid artery, and in this location, there is no difference in patency rates between the conduits. In the setting of associated aerodigestive injuries, autogenous conduits should be used, the esophageal repair should be drained away from the vascular repair, and a muscle pedicle (cervical strap muscles, omohyoid muscle, digastric muscle, or sternal head of the sternocleidomastoid) should be placed between the two repairs.

After repair of the vascular injury, all patients must be monitored for signs of cerebral edema and intracranial hypertension. If a clinical neurologic examination cannot be performed, direct intracerebral pressure monitoring or serial head imaging should be obtained.

Blunt Cerebrovascular Injuries

The overall incidence of blunt cerebrovascular injury (BCVI) has been universally reported as less than 1% of all trauma admissions for blunt trauma, but this relatively small population of patients has stroke rates ranging from 25% to 58% and mortality rates of 31% to 59%.[20-22] The variability in incidence of BCVI is 0.19% to 0.67% for unscreened populations compared with 0.6% to 1.07% for screened populations.[20]

Clinical Presentation

The recognition and treatment of BCVI have dramatically evolved during the past 2 decades. As imaging technology has improved with respect to both image quality and acquisition times, its use has become a fundamental diagnostic tool in blunt trauma evaluation. Paralleling advances in noninvasive imaging, a heightened awareness of BCVI has emerged. Through aggressive screening, these injuries have increasingly been recognized before devastating neurologic ischemia results.

Mechanism of Blunt Cerebrovascular Injury

Three basic mechanisms of injury are encountered: (1) extreme hyperextension and rotation, (2) a direct blow to the vessel, and (3) vessel laceration by adjacent bone fractures.[23] The most common mechanism causing blunt carotid injury is hyperextension of the carotid vessels over the lateral articular processes of C1-3 at the base of the skull, which is typically a result of high-speed automobile crashes. There are also scattered case reports of chiropractic manipulation[24] and rapid head turning with exercise causing BCVI.[25] A direct blow to the artery typically occurs in the setting of a misplaced seat belt across the neck during a motor vehicle crash or in the setting of hanging. This injury pattern typically occurs in the proximal internal carotid artery as opposed to the distal aspect. Basilar skull fractures involving the petrous or sphenoid portions of the carotid canal can injure the vessel at this location.

Common mechanisms of injury associated with BCVI include motor vehicle crash (41% to 70%), direct cervical blow (10% to 20%), automobile versus pedestrian (12% to 18%), fall from height (5% to 15%), and hanging events (5%).[20,22] Most common associated injuries at the time of diagnosis include closed head injuries (50% to 65%), facial fractures (60%), cervical spine fractures (50%), and thoracic injuries (40% to 51%).[20,22]

Signs and Symptoms of Blunt Cerebrovascular Injury

Case reports, as early as 1967, described BCVI with recognized symptoms of cerebral ischemia, and all patients were symptomatic

at the time of diagnosis.[26] Carotid injuries typically are manifested with a contralateral sensory or motor deficit, decreased mental status, or neurologic deficits not explained by closed head injury. A carotid-cavernous fistula may be manifested with orbital pain, proptosis, hyperemia, cerebral swelling, or seizure. Depending on whether the vessel is occluded or whether the resultant injury is a nidus for embolic events, the symptoms may be variable. Patients typically have coexisting traumatic brain injuries that may mask signs and symptoms of BCVI.

Patients may present to the trauma center with obvious signs of BCVI; however, many patients are initially asymptomatic and subsequently develop symptoms after a latent period. Several authors have reported times from 1 hour to several weeks after injury before the development of symptoms.[27-30] Evaluating an unscreened trauma population, Berne et al. found a median time to diagnosis of 12.5 hours for survivors of BCVI and 19.5 hours for nonsurvivors, suggesting a sufficient window of opportunity for diagnosis and treatment.[22] Neither admission Glasgow Coma Scale score nor baseline neurologic examination correlates with subsequent development of symptoms attributed to BCVI.

Screening for Blunt Cerebrovascular Injury

Although there is no consensus on the ideal screening protocol, several authors have found associations with signs, symptoms, and risk factors identified on admission. The first and most comprehensive screening protocol was initiated at the Denver Health Medical Center. The criteria are listed in Table 181.1.[20,31] With this screening protocol, the authors reported an overall BCVI incidence of 0.86%. Exactly 4.8% of all trauma patients were screened on the basis of defined risk criteria, and 18% of screened patients were found to have an injury. Fifty-two percent of these screened patients were asymptomatic. Neurologic morbidity was 16%, and BCVI-associated mortality was 15%.[20] Using the Memphis criteria (see Table 181.1), they found an incidence of 1.03%; 3.5% of all blunt trauma patients were screened, and 29% of screened patients were found to have an injury.[32] Both screening regimens mandated four-vessel cerebral angiography if the patient met at least one of the screening criteria.

Several authors have evaluated a more restricted screening protocol in an effort to reduce the cost of screening and to limit the number of examinations with normal findings. A cervical seat belt sign has been evaluated in several prospective studies and has not been found to be predictive of BCVI.[20,33] Biffl et al. performed a multivariate analysis on a prospectively screened population and found four independent risk factors for BCVI, listed in Table 181.1.[34] Patients with one factor had a 41% risk of BCVI; two factors, 56% to 74%; three factors, 80% to 88%; and all four factors, 93%. However, 20% of patients with BCVI did not have any of the four risk factors. The bulk of the available literature supports an appropriate screening protocol for BCVI, and all major trauma centers should have predetermined screening criteria for BCVI.

Diagnostic Evaluation

Duplex Ultrasound

Duplex scanning has been evaluated in multiple trauma centers for diagnosis of BCVI. In the evaluation of carotid artery stenosis, duplex ultrasound is limited when lesions of less than 60% stenosis are evaluated; likewise, duplex ultrasound will not often

TABLE 181.1 Screening Criteria for Blunt Cerebrovascular Injury

	Denver Criteria[a]	Memphis Criteria[b]	Modified Criteria[c] (Odds Ratio)
Signs and symptoms	Arterial hemorrhage or expanding hematoma	Neurologic examination findings not explained by brain imaging	GCS score <6 (1.98)
	Cervical bruit	Horner syndrome	
	Neurologic examination findings inconsistent with head CT findings	Neck soft tissue injury (seat belt sign, hanging, or hematoma)	
	Stroke on follow-up head CT		
	Focal neurologic deficit		
Risk factors	Le Fort II or III fracture pattern	Le Fort II or III fracture pattern	Le Fort II or III fracture pattern (3.7)
	Basilar skull fracture with involvement of the carotid canal	Basilar skull fracture with involvement of the carotid canal	Petrous fracture (2.64)
	Diffuse axonal injury with GCS score <6	Cervical spine fracture	Diffuse axonal injury (3.09)
	Cervical spine fracture		
	Near-hanging with anoxic brain injury		

CT, Computed tomography scan; *GCS*, Glasgow coma scale.

[a]Modified from Biffl WL, Moore EE, Ryu RK, et al. The unrecognized epidemic of blunt carotid arterial injuries: early diagnosis improves neurologic outcome. *Ann Surg*. 1998;228:462-470.

[b]Modified from Miller PR, Fabian TC, Croce MA, et al. Prospective screening for blunt cerebrovascular injuries: analysis of diagnostic modalities and outcomes. *Ann Surg*. 2002;236:386-393; discussion 393-395.

[c]Modified from Biffl WL, Moore EE, Offner PJ, et al. Optimizing screening for blunt cerebrovascular injuries. *Am J Surg*. 1999;178:517-522.

TABLE 181.2 Blunt Cerebrovascular Injury Grading Scale

Injury Grade	Angiographic Findings	Stroke Risk (%)	Mortality (%)
I	Luminal irregularity or dissection; intramural hematoma with <25% luminal narrowing	3	11
II	Dissection or intramural hematoma ≥25% of the lumen	11	11
III	Pseudoaneurysm	33	11
IV	Vessel occlusion	44	22
V	Vessel transection	100	100

Modified from Biffl WL, Moore EE, Offner PJ, et al. Blunt carotid arterial injuries: implications of a new grading scale. *J Trauma*. 1999;47:845-853.

identify small intimal tears or nonocclusive dissections. It is often difficult to obtain adequate visualization of the internal carotid artery at the base of the skull, where the majority of these injuries occur. The sensitivity of duplex ultrasound for detection of BCVI ranges from 38% to 86%[29,35]; therefore, it should not be used as a screening modality.

Digital Subtraction Angiography

Selective digital subtraction angiography (DSA) has, in the past, been considered the diagnostic "gold standard" for screening patients with suspected BCVI. The Denver group proposed an angiographic grading system for BCVI (Table 181.2), which has become the standard for reporting BCVI.[36] Most important, the grading scale held prognostic value for patients' future risk of subsequent stroke.

There are several limitations of DSA that make it a difficult diagnostic tool. First and foremost, it is an invasive procedure with technical limitations and a complication profile that carries a risk of stroke (<1.0%).[20] Performing screening DSA on all patients at risk of BCVI may impose a large economic and workload burden on the angiography suite; some institutions cannot support this type of demand.

Computed Tomographic Angiography

Helical CTA offers several potential advantages over conventional DSA and should now be considered the gold standard diagnostic modality. It is a noninvasive study that can be obtained in less than 5 minutes, and, as opposed to cerebral angiography, CTA obtains three-dimensional images of the vessel wall (Fig. 181.3). In addition, the workup of blunt trauma patients will inevitably involve CT imaging of the head, chest, abdomen, or all of these. CTA of the carotid-vertebral circulation can easily be obtained during this examination, sacrificing little in time (60 seconds per scan), contrast burden (approximately 100 mL), or radiation exposure.

The ability to use CTA for screening depends on the quality of the scanner at the host institution. Using early-generation single-slice and four-slice CT scanners, two prospective comparative studies (performed by the Denver and Memphis groups) found CTA to have a sensitivity of 47% to 68% and specificity of 67% to 99% compared with DSA.[32,37] CTA missed 55% of grade I, 14% of grade II, and 13% of grade III injuries.[37] CTA technology rapidly improved during the ensuing years, such that the number of detectors progressively increased and postimaging processing became readily available. Bub et al. prospectively compared multidetector CTA (four- and eight-slice scanners) with DSA and found a sensitivity of 83%to 92% and a specificity of 88% to 98% from three different radiologists.[38] The interobserver reliability was also higher for CTA than for DSA.

In 2005 Biffl et al. reported their experience using 16-slice CTA for the diagnosis of BCVI, and contrary to the prior study in Denver disqualifying early-generation CT scanners, DSA was not used as the gold standard.[39] During an 11-month period, 331 patients were screened, and 5.4% were diagnosed with BCVI. In this final study, CTA scans with normal findings were followed with clinical observation, and no patients developed neurologic symptoms consistent with delayed presentation of missed BCVI. All abnormal examination findings were confirmed with DSA. Of the 18 injuries identified by CTA, 17 were correctly graded, whereas one patient was upstaged to grade III on DSA (a small pseudoaneurysm was not identified on CTA; false-positive rate of 1.2%).[39] In 2006 a prospective comparative study validated 16-slice CTA as a primary screening modality for BCVI.[40] In this report, CTA was performed in addition to DSA in 162 consecutive patients; 20 carotid and

Figure 181.3 This three-dimensional computed tomographic angiography reconstruction with bone subtraction demonstrates occlusion of the right internal carotid artery. This patient presented with a zone II neck hematoma and a seat belt mark across the right side of the neck after an automobile crash. The *arrow* marks the occlusion at the origin of the internal carotid artery.

26 vertebral injuries were diagnosed. In that population, this resulted in an incidence of 1.25% and a screening yield of 28%, which is comparable with historic controls. CTA and DSA were 100% concordant for blunt carotid injuries, resulting in a sensitivity of 100% and a specificity of 100%.[40] This is the only study comparing conventional 16-slice CTA directly with DSA and demonstrating equivalence. On the basis of these findings, a minimum of 16-slice CTA should be considered the primary screening modality for BCVI. However, many authorities still remain passionate that DSA should be the primary screening test of choice for patients with BCVI.[41]

In 2009 the initiation of a CTA-based screening and diagnostic program at one institution, along with interdisciplinary standardized treatment guidelines, reduced the time to diagnosis of BCVI 12-fold and the institutional stroke rate due to BCVI 4fold. The authors concluded that this effect may be due to earlier diagnosis and initiation of definitive therapy.[42]

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) is an attractive noninvasive modality because of the resolution of images obtained in this anatomic region, the infinite number of projections of the vessel, and the ability to assess the intracranial architecture for signs of stroke.[43,44] Limitations include availability and the time required for image acquisition. This modality is thus impractical in a trauma patient with multiple competing injuries. In comparative studies of DSA versus MRA, MRA performs poorly, with sensitivities of 50% to 95%.[32,45] The latest report is from 2002, and improved technology may therefore change the role of MRA in BCVI.

Medical Treatment

The mainstay for treatment for BCVI is antithrombotic therapy; however, there are no randomized controlled trials to support this recommendation. Fabian et al. reported the first prospective observational study demonstrating improved neurologic outcome associated with early use of antithrombotic therapy.[21] Their analysis revealed the benefit of heparin therapy for decreasing the rate of neurologic deterioration after symptoms developed and decreasing the rate of new neurologic events. Heparin therapy was associated with a dramatic reduction in neurologic morbidity (29%) compared with no treatment (73%). Biffl et al. confirmed that patients benefited from early anticoagulation, documenting the greatest benefit to patients who were asymptomatic at the time of heparinization.[20] In the asymptomatic group, only one patient developed subsequent stroke. On analysis of the symptomatic cohort, 93% of patients had improvement in their neurologic deficits with anticoagulation compared with only 67% without anticoagulation. On the basis of these two studies, anticoagulation became the first line of treatment of BCVI.

Complications associated with anticoagulation range from 25% to 54% in the trauma population.[20] Most concerning is intracranial hemorrhage, but more common are gastrointestinal bleeds, retroperitoneal hemorrhage, blunt solid organ injury with hemorrhage, and rebleeding from surgical wounds. Eachempati et al. noted that few patients were able to receive heparin therapy at the time of BCVI diagnosis (14%), and they found a complication rate of 16% among those who received heparin therapy.[46] Because of the complication profile of full anticoagulation therapy, several authors have focused on antiplatelet therapy as an alternative to traditional anticoagulation.

A prospective comparison of antiplatelet therapy with anticoagulation for BCVI does not exist. There is one study by Biffl et al. that reported anticoagulation (heparin with transition to Coumadin) to be superior to antiplatelet therapy (aspirin or clopidogrel), with stroke rates of 1% versus 9%.[20] Several follow-up studies have failed to confirm this result. Miller et al. found that resultant stroke rates after BCVI treated with heparin therapy and antiplatelet therapy (5% and 3%, respectively) were similar.[47] Follow-up studies further demonstrated no difference in stroke rates for those patients treated with heparin (5% to 8%) compared with those treated with antiplatelet therapy (3% to 7%).[31,32,48]

Either heparin or antiplatelet therapy can be used with similar results. If the patient has no contraindications to anticoagulation, a prudent protocol would be heparin therapy (goal activated partial thromboplastin time of 50 to 60 seconds) and transition to Coumadin (goal international normalized ratio of 2.0) for 3 months. Antiplatelet therapy should be used for the same time period.

All patients who are medically treated should undergo serial CTA or DSA at 1-week and 3-month follow-up. At 3-month follow-up, one can expect 72% of grade I injuries to completely heal.[49] Grade II injuries are fairly evenly distributed: 33% improve, 33% are stable, and 33% progress to pseudoaneurysms.[49] Grade III injuries tend either to remain unchanged (50%) or to enlarge (40%). Grade IV injuries universally did not improve and probably do not warrant follow-up imaging after discharge.[49]

Endovascular Treatment

Endovascular therapy has primarily been reserved for evolving dissections that are surgically inaccessible, pseudoaneurysms that persist or enlarge after antithrombotic treatment, or patients with worsening neurologic symptoms on medical therapy. When patients develop a symptomatic injury, a pseudoaneurysm, or a chronic dissection, endoluminal treatment with either a bare or covered stent is an alternative to open repair.[50,51] Balloon-expandable and self-expanding stents have been used in this location, and in all cases, apposition of the dissection to the wall was achieved with no neurologic events reported.[51,52]

Follow-up imaging of BCVI treated with antithrombotic therapy is imperative. Pseudoaneurysms are unlikely to resolve with medical management,[53] and 33% of acute nonocclusive dissections treated with anticoagulation develop pseudoaneurysms on follow-up arteriography.[21] These lesions have a low risk of rupture, but they tend to be the source of chronic embolic events or thrombosis.[54,55]

Because of the potential for embolic stroke and their failure to resolve with antithrombotic therapy, pseudoaneurysms that fail to resolve, enlarge, or result in ischemic complications should be excluded from the cerebral circulation. Based on the location of these injuries in the distal internal carotid artery, endovascular therapy offers several advantages over open repair. Self-expanding

covered stents can be safely delivered to these locations with limited morbidity.[15-18]

Initial reports from Parodi et al. relied on balloon-expandable bare Palmaz stents (Cordis Johnson & Johnson, Miami Lakes, Florida) to cover the orifice of the pseudoaneurysm.[56] Covering the orifice will typically promote thrombosis of the pseudoaneurysm, but if the sac fails to thrombose, an option has been to coil embolize the sac through the interstices of the bare stent.[57] In these series the mean follow-up was 3.5 years without neurologic sequelae, but thrombosis and embolic potential, as well as the potential for restenosis, remain a concern after endovascular placement of devices in the carotid artery.[58] Although thromboembolic complications are most common immediately after stent placement, patients should be committed to lifelong follow-up for unforeseen complications, such as stent fracture.[59] Post-stent therapy is variable, but on extrapolation of data from carotid artery stenting for atherosclerotic disease, a regimen of dual antiplatelet therapy (aspirin and clopidogrel) appears adequate to prevent stent thrombosis and embolic ischemic events.[60] If antiplatelet therapy is discontinued, stent thrombosis and resultant stroke are inherent risks.[16]

The enthusiasm for carotid stenting for BCVI paralleled advances in carotid stenting platforms used for carotid artery stenosis. There are several positive case reports followed by sporadic case series in the literature. However, Cothren et al. provided a sobering report highlighting the risk of stent thrombosis. They evaluated blunt carotid pseudoaneurysms (grade III) persisting 7 to 10 days after injury in 46 patients; 92% were asymptomatic. Twenty-three patients were excluded with carotid Wall stents, and 23 patients were treated with either antiplatelet or anticoagulation therapy.[61] Three (13%) periprocedural ischemic complications occurred. Eight (45%) in the carotid stent group experienced carotid artery occlusion during follow-up, and only 1 (4%) in the medical treatment group experienced carotid artery occlusion.[61] This is the highest rate of carotid stent occlusion published, and it demonstrates the challenges of stenting a dissected artery at the skull base.

As opposed to the experience of Cothren et al., Edwards et al. placed 22 carotid stents for BCVI; 18 patients had pseudoaneurysms, and 4 patients were treated for extensive dissections. They experienced no periprocedural complications. Twelve patients were treated with postprocedural antiplatelet therapy, and eight received anticoagulation. With a mean angiographic follow-up of 7 months, none were occluded (100% patency).[49] The variance in outcomes can be explained by the challenges of treating this injury pattern.

Follow-up for this patient cohort is imperative, and further prospective studies with long-term follow-up are needed to determine the risks and efficacy of carotid stents for BCVI. Compliance with medications and follow-up surveillance should be considered in planning appropriate therapy for trauma patients.

Surgical Treatment

The indications for surgical intervention parallel those for endovascular intervention.[21,62] Patients with evolving dissections, pseudoaneurysms that persist or enlarge after antithrombotic treatment, or patients with worsening neurologic symptoms should undergo repair. Whether an open repair or endovascular repair is used should be based on the patient's associated injuries, the location of the injury, the ability to comply with the antiplatelet regimen, and the ability to achieve long-term follow-up.

Schievink et al. have addressed blunt carotid pseudoaneurysms with operative repair in 22 patients.[63] To exclude the lesions, 5 patients required carotid ligation, 13 underwent resection with reconstruction, and 4 required cervical to intracranial carotid bypass. In their series, two patients experienced ischemic stroke, and the most common complication was cranial nerve neurapraxia secondary to high surgical exposure. This series illustrates the difficulty of treating these lesions at the base of the skull and the resultant morbidity.

If the injury is located at the base of the skull, the only option for treatment may be endovascular exclusion. When the lesion is located in the proximal internal carotid or common carotid artery, the vessel should be approached by an anterior exposure. The vessel may be repaired primarily or, more commonly, by patch angioplasty with either greater saphenous vein or prosthetic material.

VERTEBRAL ARTERIES

Vertebral artery injuries are rare occurrences, with an incidence of 0.20% to 0.77% of all trauma admissions.[20,21] Although injuries to the first portion (V1) of the vertebral artery are readily accessible, those to the second portion (V2, within the bony foramen of the cervical canal), the third portion (V3, as the vessel exits the bony foramen and enters the base of the skull), and the fourth portion (V4, intracranial segment to the basilar artery) can be extremely difficult to control.

Clinical Presentation

Penetrating injuries are most commonly due to gunshot wounds and stab wounds.[64] Life-threatening hemorrhage is rare from an isolated vertebral injury (mortality, 4%); however, penetrating injuries frequently involve the common carotid artery, subclavian artery, internal jugular vein, and subclavian vein, which may be life threatening. Patients typically are asymptomatic or complain of associated neurologic injury secondary to either compression from hematoma or direct injury.[64]

The most common mechanism for blunt vertebral artery injury is fracture of the transverse foramen through which the vessel courses (vertebrae C2-6).[65] The vertebral vessels are relatively fixed throughout the vertebral canal, making the V2 segment susceptible to hyperextension and stretch injuries. Because of the rich collateral circulation in the neck, unilateral vertebral artery injuries are often asymptomatic in 80% of cases. With regard to dissections, patients may complain of subtle neck pain or posterior headache. Vertebrobasilar ischemia may be manifested with protean symptoms, including dizziness, vertigo, nausea, tinnitus, dysarthria, dysphagia, ataxia, visual deficits, and hoarseness. The degree of ischemia is determined by the extent of distal propagation into the basilar or posterior

inferior cerebellar arteries. Patients with bilateral vertebral artery injuries may present with more severe symptoms: coma, fixed pupils, and loss of respiratory drive. Approximately 25% of patients will have bilateral blunt vertebral artery injuries, and 33% will have an associated blunt carotid injury.[66]

Diagnostic Evaluation

Vertebral artery injury typically is manifested with penetrating neck injury. If the patient presents with refractory shock, with hard signs of a vascular injury, or with hard signs of a tracheal injury (continuous air bubbling from the wound), the management is straightforward, and the injury should be diagnosed in the operating room. Plain films in the emergency department are useful for determining the track of the missile and any foreign bodies within the wound. Hemodynamically stable patients with a normal Glasgow Coma Scale score who do not have hard signs of a vascular injury should undergo CTA of the neck. The provider should also include the head and chest in the evaluation of the injury to fully evaluate associated injuries and to identify the track of the missile or knife. This mechanism of injury should also prompt a high suspicion for aerodigestive injuries, which may require additional evaluation (bronchoscopy, rigid esophagoscopy, or upper gastrointestinal swallow studies).

Blunt vertebral artery injuries were originally diagnosed by DSA, and the same grading criteria (see Table 181.2) were applied to the vertebral artery as for the carotid artery. In contrast to blunt carotid injuries, grade of blunt vertebral artery injuries does not correlate with increasing risk of stroke. The stroke risk of blunt vertebral artery injuries is 20% irrespective of grade.[66] The same controversy about screening and imaging surrounds the evaluation of blunt vertebral artery injuries. The same screening criteria used for blunt carotid trauma (see Table 181.1) are applied to blunt vertebral artery injuries; however, cervical spine fracture is the only factor that is independently associated with blunt vertebral artery injuries (odds ratio, 14.5).[34]

All imaging modalities are less accurate for diagnosis of blunt vertebral artery injuries compared with carotid injuries. Duplex evaluation of the vertebral vessels is extremely limited; however, with color-flow imaging, the operator can assess for vessel patency. MRA has the previously stated limitations in the setting of trauma. In the evaluation of blunt vertebral artery injuries, CTA has a sensitivity and specificity of 40% to 60% and 90% to 97%, respectively.[38] If there is a high index of suspicion based on cervical fracture, a confirmatory study should be obtained. MRA is an acceptable option when it is available; however, if concern persists, DSA should be performed.

Medical Treatment

Medical management has no role for penetrating injuries, but it does have a role for blunt injuries identified during the diagnostic evaluation. The posterior circulation stroke rate attributed to blunt vertebral artery injury is 24%, with an associated mortality of 8%.[66] Symptomatic patients should be treated with heparin and monitored for hemorrhagic conversion with serial neurologic examinations. Heparin therapy was first evaluated in asymptomatic patients and found to reduce neurologic events in the posterior circulation from 20% to 35% (no anticoagulation) to 0% to 14% (heparin therapy).[47,66] In patients who could not tolerate anticoagulation, the efficacy of heparin was similar to that of aspirin. Follow-up studies increasingly used aspirin secondary to the bleeding complications associated with heparin therapy. Miller et al. treated 43 vertebral artery injuries; 32 patients received aspirin or clopidogrel, and only 8 patients received heparin therapy.[47] None of the patients developed stroke. Symptomatic patients or those patients without contraindications to anticoagulation should be treated with 3 to 6 months of anticoagulation with radiographic follow-up. Asymptomatic patients should be treated with either 3 to 6 months of anticoagulation or dual antiplatelet therapy; data are insufficient for one treatment to be recommended at this time.

Endovascular Treatment

Endovascular treatment of the vertebral artery is used for uncontrolled hemorrhage not controlled with surgery, backbleeding from the V3 segment, pseudoaneurysm, and symptomatic patients who cannot tolerate anticoagulation (Fig. 181.4). The endovascular technique of crossing the vertebral artery confluence at the basilar artery is technically challenging, but when possible, both proximal and distal ends of the transected or lacerated vessel should be treated with embolization. If the vessel is intact, the injury may be crossed from an antegrade approach, allowing embolization of both the outflow and inflow (trap-door technique). In nearly half of vertebral artery injuries evaluated with endovascular techniques, the vessel was thrombosed and required no treatment at all.[67] Preservation of the vertebral artery may be a concern when other extracranial blood supply has also been compromised. In these complex cases, endovascular stenting of the vertebral artery has been performed as a salvage procedure.[47] There are no data to support routine stenting for blunt vertebral artery injuries.

Surgical Treatment

Operative management is reserved for patients with active bleeding from the vertebral artery at the time of neck exploration. In a review of the largest series of penetrating vertebral artery injuries, 50% of patients who underwent open exploration required postoperative endoluminal embolization to arrest bleeding or to control arteriovenous fistulas.[67] Controlling the vertebral artery can be challenging for even the most experienced trauma or vascular surgeon. Unilateral surgical ligation results in a stroke rate of 3% to 5%.[68]

The approach is the same as that described previously for exploration of the carotid artery. Once the sternocleidomastoid muscle has been retracted laterally, the V1 segment can be visualized by transecting the sternocleidomastoid muscle from the sternum and clavicle. Next, the internal jugular vein is identified, and laterally, the scalene fat pad is divided vertically, with care taken to identify and protect the phrenic nerve coursing lateral to medial across the anterior scalene muscle. Division

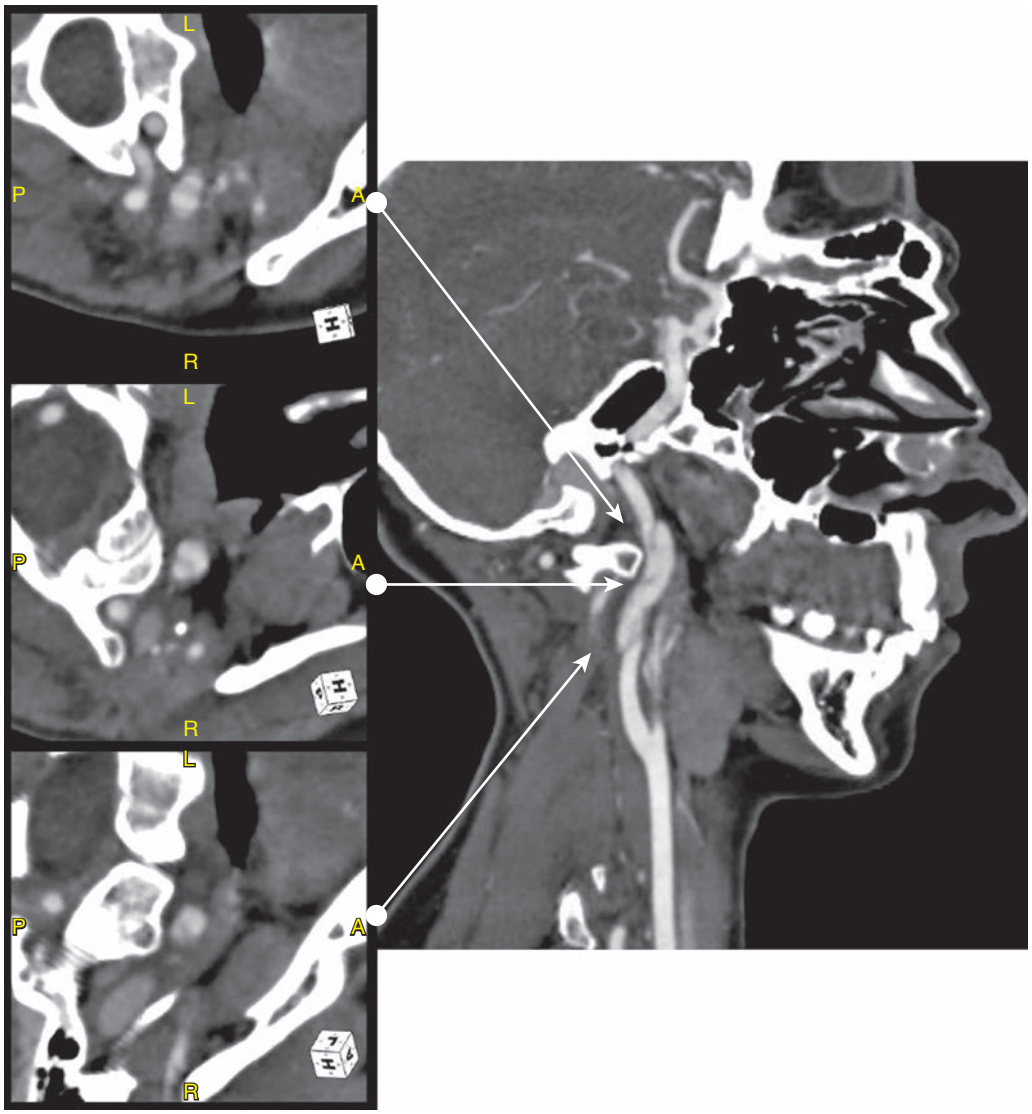

Figure 181.4 Patient suffered a high-speed motor vehicle accident with resultant bilateral internal carotid artery dissections. She was treated with antiplatelet therapy, and then repeat axial imaging on hospital day 7 demonstrated a complex right internal carotid artery dissection which extends up to C1. The dissection measures 3.8 cm in length, and the axial images at three separate locations demonstrate a patent flow lumen.

of the anterior scalene muscle from the first rib allows visualization of the first portion of the subclavian artery and the origin of the vertebral artery, thyrocervical trunk, and internal mammary artery. On the right side, the recurrent laryngeal nerve should be protected, and care should be taken on the left side to avoid injury to the thoracic duct. Partial manubrium and clavicle resection can gain exposure in this location.

The V2 segment is more challenging to control, and most surgeons should simply ligate the proximal V1 segment as repair of the vertebral artery is futile and exposure of the V2 segment is fraught with venous bleeding. Exposure of V2 involves retracting the sternocleidomastoid muscle laterally, dividing the omohyoid muscle, and retracting the carotid sheath medially. Identification of the cervical spinal bodies and the associated prevertebral fascia is mandatory. The sympathetic chain ganglia should be protected as they course through this region. Longitudinal opening of the anterior longitudinal ligament and paraspinous muscles allows identification of the transverse process of the spinal bodies. Removal of the anterior aspect of the transverse processes by use of a handheld rongeur allows exposure of the vertebral artery. Posterior to the vessel lie the cervical nerve roots. Hemorrhage in this location should be controlled with proximal ligation of V1. Bone wax can be packed into the bony canal, and postoperative embolization of the distal vertebral artery may be performed if needed.

Most vascular and trauma surgeons are unfamiliar with the V3 segment at the base of the skull. Rather than a timely dissection, the patient may be better served by proximal ligation of the V1 segment, packing of the wound (with bone wax, gauze, or balloon occlusion), and then endoluminal embolization. To expose the V3 segment for ligation, the incision is extended posteriorly behind the ear onto the mastoid process.[69] The

sternocleidomastoid muscle is retracted medially and may be divided from the skull base. During this step, the spinal accessory nerve should be identified and preserved. The transverse process of C1 is identified anterior and below the mastoid process. The muscle attachments to C1 and C2 are cleared with a periosteal elevator, and then, after resection of the lateral process of C1, the vertebral artery is exposed.

SUBCLAVIAN ARTERY

Injuries to the thoracic outlet are extremely lethal. Prehospital mortality is 50% to 80%, and of those who survive transport, 15% die during treatment.[70]

Clinical Presentation

Blunt injuries to the subclavian vessels are extremely rare, but when they occur, patients typically have associated clavicular fractures, mediastinal injuries, and pulmonary contusions. Penetrating injuries account for the majority of trauma to the subclavian vessels; in one US trauma center, gunshot wounds accounted for 74% and stab wounds accounted for 26% of injuries.[71] These patients often present to the emergency department in cardiac arrest, and consideration for resuscitative thoracotomy must be based on time from injury and signs of life. Those patients who survive transport may present with hard signs of vascular injury as described earlier, which mandate immediate operative exploration. All other patients with soft signs of a vascular injury should have further diagnostic evaluation. A normal radial pulse does not reliably exclude an upper extremity vascular injury. Concomitant cervical and thoracic injuries are common in 70% of patients.

The upper extremities rarely suffer from ischemia because of the intense collateral circulation; the long-term morbidity of these injuries is secondary to brachial plexus injuries. Brachial plexus injuries can be caused by penetrating injuries that directly transect nerve roots; blunt injuries that result in shear or traction forces; and operative exposure, which can result in iatrogenic injury. Blunt injury to the brachial plexus is typically secondary to stretch injuries to the upper extremity or bone fractures.

Diagnostic Evaluation

In the unstable patient, there are few options other than immediate exploration, but because of the fibrous attachments surrounding the subclavian vessels, injuries will frequently result in a contained extrapleural hematoma that may extend into the supraclavicular fossa. If time allows, CTA can be invaluable to identify the location of injury and to evaluate the mediastinum. Hemodynamically stable patients with asymmetrical pulses or neurologic deficits should undergo evaluation with CTA, including the chest, neck, and upper extremity. Injury to the axillary vessels can range from intimal disruption to pseudoaneurysms, dissection, and even thrombosis. In addition, axial imaging will appropriately evaluate the mediastinum, cervical vasculature, and associated bone fractures.

Medical Treatment

Intimal disruptions and dissections that are not flow limiting should be treated with clinical observation. Anticoagulation or antiplatelet therapy may be added at the discretion of the surgeon. If the patient develops embolic symptoms, antithrombotic therapy should be instituted with arteriography of the injury.

Endovascular Treatment

Endovascular treatment in this area can obviate the need for an extensive dissection at the base of the neck. Covered stent-grafts have been increasingly used in this location, with several authors reporting immediate technical success for treatment of pseudoaneurysms, lacerations, arteriovenous fistulas, and even complete transections (Fig. 181.5).[72-74] Approximately 42% to 50% of patients are candidates for endovascular treatment.

These injuries may be approached from a transfemoral, transbrachial, or combined technique. Acute thromboses in patients with malperfusion symptoms can be treated through a retrograde brachial approach, and after flow is restored, a covered stent can be used to treat the injury. Most transected vessels can be crossed with a hydrophilic wire. Undoubtedly, endovascular techniques reduce the morbidity of operative exposure and potential nerve injury in a blood-stained field. There are relatively few contraindications to this approach. The patient must be hemodynamically stable. Some consider a large supraclavicular hematoma with brachial plexus compression a relative contraindication; however, the injury may be treated with a covered stent followed by hematoma evacuation in a controlled field.

The mobility and compression between the first rib and clavicle raise concern about long-term patency in the young trauma population; it is imperative to observe these patients for late sequelae. In addition, endovascular repair does not preclude stent explantation with formal open repair; this approach would ideally reduce the potential for iatrogenic nerve injury in the acute setting. In one of the largest reported series, three early stent thromboses were encountered in 56 patients.[72] All three were opened with a secondary intervention, and no patient experienced upper extremity ischemia.[72] Endovascular therapy in the thoracic outlet offers a less invasive, rapid treatment and has the added benefit of avoiding injury to the brachial plexus, which has long-term implications for a functional recovery.

Surgical Treatment

Injuries to the thoracic outlet can be difficult to expose in an acute setting; it is important to prepare the neck, chest, and groin into the surgical field. Proximal control requires either a median sternotomy for the innominate and right subclavian arteries or a high left anterolateral thoracotomy with potential clavicular resection for the left subclavian artery. Rather than direct exploration of the hematoma, a remote occlusion balloon can be placed either from the groin or retrograde from the brachial artery. In doing so, the surgeon can perform arteriography, and with

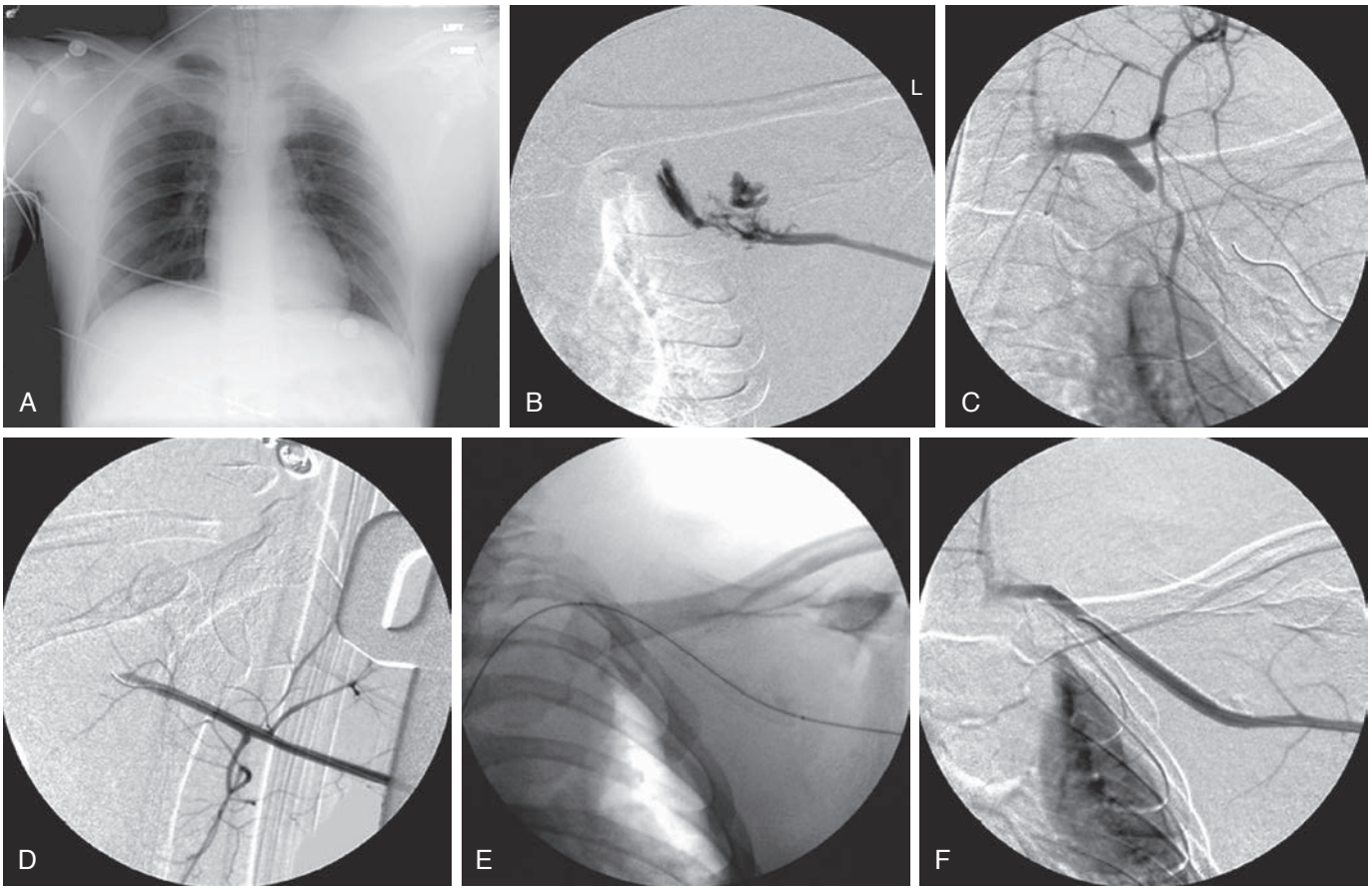

Figure 181.5 Blunt subclavian artery transection. (A) The patient presented with a large stable hematoma in the supraclavicular fossa extending into the axilla after a high-speed motorcycle crash. The chest radiograph demonstrates the soft tissue density over the left clavicle. (B) From the left brachial approach, there is extravasation at the level of the subclavian to axillary artery junction. (C) From the right groin, left subclavian artery selective angiography was performed. (D) A curved Glidewire was used to cross the transection. (E) Once the transection was crossed, the brachial wire was snared within the hematoma, obtaining femoral-brachial wire access. The transection was treated with a covered stent. (F) Completion angiogram demonstrates complete exclusion of the transected segment and no residual extravasation.

proximal control, the operative tempo changes from emergent to semiurgent. Either an endovascular treatment can ensue, or the surgeon can proceed with a meticulous dissection at the base of the neck and avoid either a sternotomy or thoracic incision.

If the patient is in extremis, subclavian artery ligation rarely results in upper extremity ischemia. When the vessel is repaired, the injury typically requires an interposition graft. PTFE works well in this location and has excellent patency.[75,76] If the field is grossly contaminated, saphenous vein, internal jugular vein, and superficial femoral artery have all been used in this location. Nearly 50% of penetrating subclavian injuries will have an associated subclavian vein injury in addition to the arterial injury.[75]

CERVICAL VENOUS INJURIES

Venous injuries to the neck and thoracic outlet are invariably due to penetrating injuries. Blunt venous injuries are extremely rare and should be considered with sternal and clavicle fractures. Venous injuries to the internal jugular vein occur in 20% of penetrating neck trauma, and subclavian vein injuries occur in 50% of penetrating subclavian injuries.[76,77]

Clinical Presentation

When patients present in extremis, the venous injury is typically identified in the operative suite. Isolated venous injuries are manifested with hard or soft signs of a vascular injury, but patients are rarely hypotensive.[78]

Diagnostic Evaluation

The diagnostic evaluation should parallel the evaluation described before for each arterial anatomic region. If the patient undergoes CTA for a suspected vascular injury, delayed acquisition (ranging from 30 seconds to 3 minutes) will provide improved imaging of the venous anatomy once the contrast material has cleared the associated arterial anatomy.

Endovascular Treatment

Endovascular stents have increasingly been used in the central venous system for subclavian and superior vena cava chronic thromboses. The efficacy of covered stents for venous trauma has been described only in case reports, with good technical results.[79,80] This technology will be increasingly used for isolated venous injuries in hemodynamically stable patients.

Surgical Treatment

The surgical approach to each vein is identical to the arterial exposure described earlier. If the patient has hard signs of a vascular injury and is in extremis, the neck and subclavian veins can be ligated with limited morbidity. If the internal jugular vein is ligated, the patient should be monitored for cerebral edema, but this is a rare occurrence even with bilateral internal jugular vein ligation. Internal jugular vein reconstructions (with either spiral vein grafts or externally reinforced PTFE) in the setting of bilateral neck dissections have an 18-month patency of 64%; elevated stump pressures (>30 mm Hg) may improve patency.[81] When the subclavian vein is ligated, the upper extremity should be elevated and placed in compression; transient edema typically resolves during the course of 7 to 10 days, and long-term venous stasis is rare.[77] Simple lacerations of the vein can be repaired with lateral venorrhaphy if less than 50% of the wall is involved.[77] All repairs are at risk of eventual thrombosis; mechanical and chemical thromboprophylaxis should be considered. Extensive vein repairs (end to end, venous interposition, or spiral/panel grafts) typically do not have a role in penetrating neck injuries (as opposed to lower extremity injuries) when time is critical.

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CHAPTER 182

Thoracic Vascular Trauma

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INTRODUCTION

Thoracic injuries are common sequelae of both blunt and penetrating trauma, with blunt thoracic injuries proving responsible for approximately 8% of all trauma admissions in the United States, with motor vehicle crashes being the most common mechanism.[1-4] Penetrating injuries are also commonly encountered, with one report from a high-volume, urban trauma center[3] identifying penetrating chest trauma among 7% of all trauma admissions and 16% of all penetrating trauma admissions overall.

Despite the prevalence of thoracic injury following trauma, the majority of patients presenting with these injuries will not require thoracic operative intervention. Appropriate utilization of tube thoracostomy and comprehensive inpatient management will prove definitive treatment for the majority of patients with these injuries. Even among penetrating mechanisms, only 14% of stab wounds and 15% to 20% of gunshot wounds to the chest require operative intervention for thoracic injury.[3]

It is important to note, however, that vascular injury occurring within the thoracic region continues to be associated with high mortality,[1-4] with many patients likely not surviving to reach a facility capable of providing care.[5-7] Among those who do present to trauma centers, however, the continued evolution of imaging capabilities and improved approaches for nonoperative and operative management continue to improve the care of these patients.[5-8] Significant progress has been made over the last two decades in the diagnosis and treatment of thoracic vascular injuries. This paradigm shift includes the widespread use of computed tomography angiography (CTA) for diagnosis, aggressive blood pressure control, delayed repair for stable patients, adoption of endovascular repair as the treatment modality of choice for anatomically suitable candidates, and medical management of minimal aortic injuries. These advances have significantly improved the outcomes of patients with thoracic vascular trauma. Nevertheless, the effective treatment of these injuries requires careful consideration of treatment dilemmas, thoughtful decision-making, a comprehensive appreciation of

Abstract

Blunt thoracic aortic injury (BTAI) and major thoracic vascular injuries remain serious events following trauma. Considerable advances have been made in the diagnosis, medical management, and operative repair of these injuries. In particular, endovascular adjuncts have emerged as critical tools in appropriate selected patients.

Keywords

aortic injury
thoracic
vascular
trauma
injury
endovascular

anatomic relationships within the thoracic cavity, and prompt operative intervention when indicated. This chapter summarizes the current diagnosis and management of thoracic vascular injuries.

Presentation and Evaluation

Any patient with significant blunt chest trauma or penetrating injury around the thoracic cavity is at risk for vascular injury. The patient may provide useful history, but often this information is provided by prehospital personnel. The mechanism of injury, time from injury, vital signs, and neurologic status at the scene, as well as any changes during transport, are critical. With blunt injury specifics, such as prolonged extrication, the location and degree of occupant compartment vehicle deformation may provide useful information. With penetrating trauma, the specific details are typically vague and often unreliable.

Evaluation proceeds according to the Advanced Trauma Life Support guidelines, and potentially life-threatening conditions are immediately treated. As with any trauma patient, thorax trauma may necessitate intubation for airway control. While these patients require evaluation and imaging for potential neurologic, intraabdominal, or extremity trauma, the discussion herein will focus largely on the diagnosis and characterization of thoracic vascular injuries. Physical examination, which should be performed both rapidly and thoroughly, has been shown to be reliable and can often help make the diagnosis. The presence of distended neck veins, tracheal deviation, subcutaneous emphysema, chest wall instability, absent breath sounds, or muffled heart sounds may all provide crucial information. Likewise, the absence of an upper extremity pulse suggests a proximal arterial injury. Vital signs should be frequently monitored with careful observation of the work of breathing and arterial saturation. Overall, the most common thoracic injuries are hemothorax and/or pneumothorax. However, rapid diagnosis of vascular injury is likely paramount to success in most instances.

Penetrating thoracic trauma in a hemodynamically unstable patient warrants operative intervention. The decision regarding surgical exposure may be problematic, especially if there is concomitant abdominal injury. Clinical judgment is paramount in this situation. The hemodynamically stable patient may benefit from additional imaging, especially chest computed tomography, which provides more detailed and organ-specific information.[9]

IMAGING

Plain radiography of the chest remains the most commonly utilized initial radiographic imaging following thoracic trauma. An adequate plain film should make the diagnosis of any large hemothorax or pneumothorax. Since screening chest x-rays (CXRs) are usually performed supine, however, hemothorax can be somewhat difficult to adequately diagnose. Haziness of one hemithorax, when compared with the other, may be the only real radiographic sign. If this is of any substance, a chest tube should be placed.

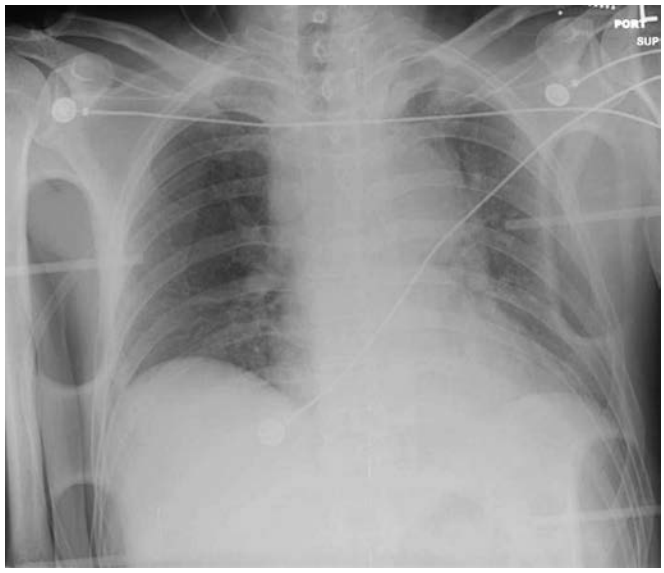

Figure 182.1 Chest radiograph of a patient with blunt thoracic aortic injury showing a widened mediastinum and obliteration of the aortic knob.

A CXR may also allow the clinician to evaluate the mediastinum for the possibility of a blunt traumatic aortic injury (BTAI; Fig. 182.1). A variety of clinical findings may prove suggestive of BTAI, including widened mediastinum, apical capping, or loss of normal radiographic cardiac or aortic arch silhouette. It is important to note, however, that plain chest radiography in this setting is neither specific nor sensitive for the presence of BTAI. A recent study by Gutierrez and colleagues[10] at Los Angeles County Hospital found that among 3728 trauma patients admitted to their facility over 2 years, 200 patients (5.4%) had an abnormal CXR on arrival. From the same overall group, 17 BTAIs were identified by CTA. Only seven of the CTA-confirmed BTAI patients had any mediastinal abnormality on CXR, for a sensitivity of CXR of only 41%. These findings highlight an improved understanding that CXR alone is not a reliable screening modality for BTAI. They also emphasize the need for careful consideration of other factors—including mechanism of injury—in determining those who need subsequent CTA imaging after trauma.

In the modern era, CTA has become a tool of trauma evaluation that is liberally employed. Computed tomography (CT) protocols that utilize angiographic contrast are ubiquitous to initial evaluation protocol of most major trauma centers, and have specific benefits with regard to the diagnosis and characterization of vascular injury. This imaging modality, particularly with the advent of advanced multi-slice imaging capabilities, affords both precise evaluation of the aorta and other vascular structures of the chest. Postimaging processing can also rapidly and effectively provide good resolution—three-dimensional evaluation of the thoracic vascular structures.[11-13] CTA of a patient with BTAI is shown in (Fig. 182.2). Intravascular ultrasound (IVUS) provides real-time, 360-degree imaging of the aorta using a high-frequency (10 MHz), miniature ultrasound probe placed through a femoral arterial sheath (Fig. 182.3).[14] IVUS is a useful tool for evaluation of traumatic aortic injury,

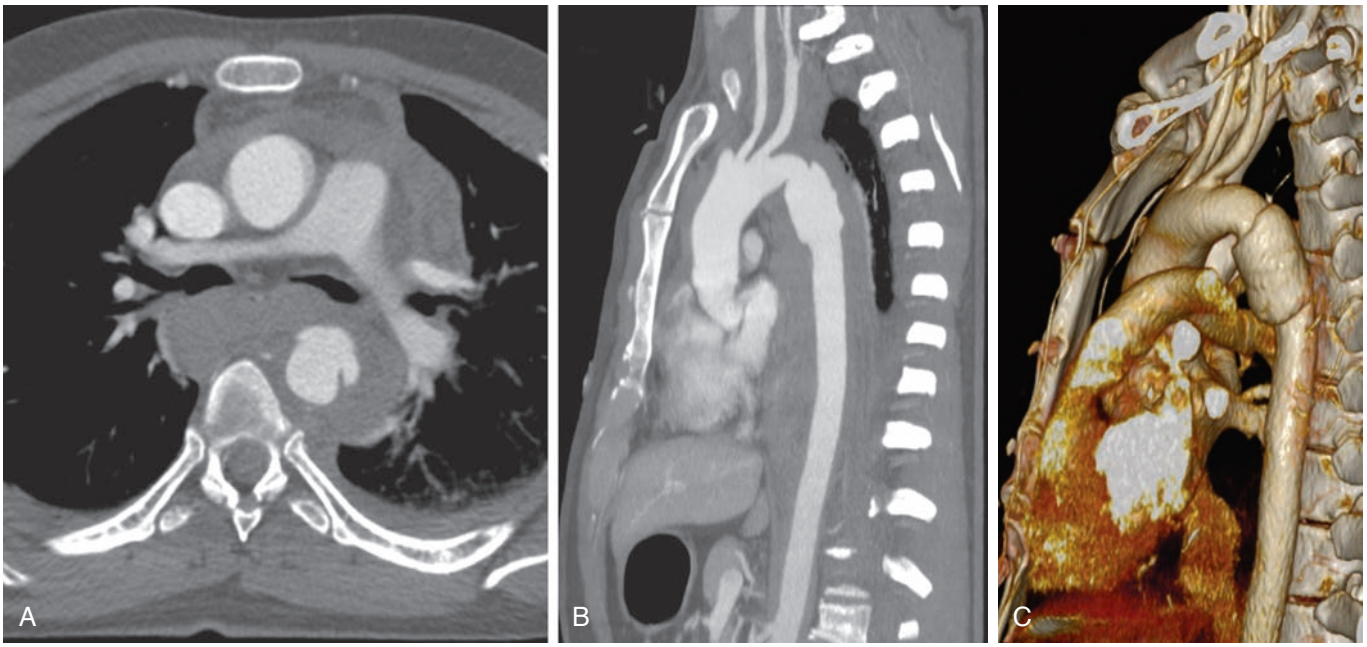

Figure 182.2 Computed tomography angiography of a patient with blunt thoracic aortic injury. (A) Axial view demonstrating the injury and periaortic hematoma. (B) Sagittal view demonstrating the typical location of the injury at the isthmus distal to the left subclavian artery. (C) Three-dimensional computed tomography reconstruction.

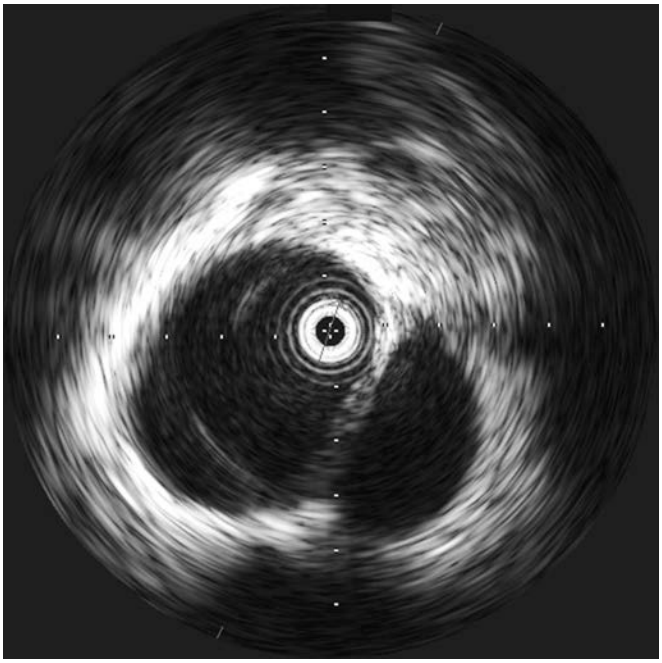

Figure 182.3 Intravascular ultrasound image of a patient with blunt thoracic aortic injury demonstrates a pseudoaneurysm.

especially in cases with equivocal CTA, or in cases of periaortic hematomas in the absence of a direct sign of aortic injury.[15] IVUS does not require contrast or radiation and can be performed concurrently using the same femoral puncture as angiography. The disadvantages of IVUS are additional cost (capital equipment and disposable catheter), larger sheath, and operating room time.[16]

Angiography, once considered the "gold standard" for diagnosis, remains a valuable imaging modality in the management of patients with thoracic vascular trauma. However, it has taken on a therapeutic, rather than purely diagnostic, role, given the wide utilization of CTA. Today, angiograms are more commonly performed in the operating room at the time of definitive repair. Disadvantages include invasive nature, cost, use of intravenous contrast, access site complications, and the need to transport the patient to an angiography suite or operating room (CTAs are commonly performed in the emergency center). There is a small incidence of false-positive angiograms from known anatomic abnormalities, such as ductus diverticulum and aberrant brachiocephalic arteries.[17,18]

Indications for Emergent Operation

While the vast majority of traumatic thoracic injuries can be managed nonoperatively, surgery may be indicated emergently, urgently, or in a delayed fashion. Indications for emergent operation thoracic exploration include shock with a penetrating chest injury, initial chest tube output of 1500 cc, or persistent chest tube output of 250 cc/h for 3 hours. There is likely a linear relationship between the total amount of thoracic hemorrhage and mortality, necessitating a familiarity of the treating surgeon with the most common exposures that will be required in an emergent setting. The patient's overall clinical condition and astute surgical judgment are of paramount importance when deciding to operate and what type of surgical exposure or approach to utilize.

Open Surgical Exposure/Incisions

There are several surgical approaches to the thorax, each with advantages and disadvantages for emergent trauma applications.

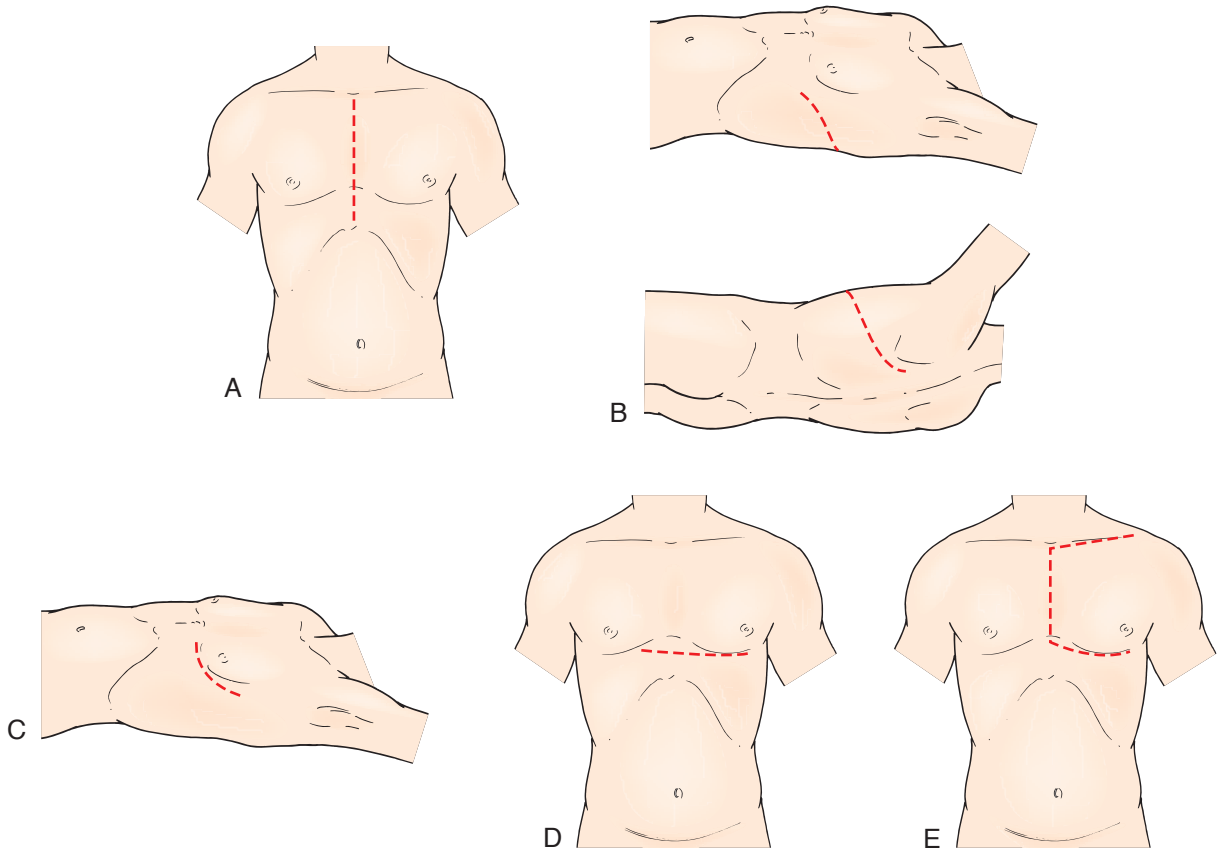

Figure 182.4 Incisions for thoracic trauma. (A) Median sternotomy with right or left neck extensions can be used to treat injuries to the heart, proximal aorta, innominate, and left carotid arteries. (B) Left posterolateral thoracotomy for repair of descending thoracic aortic injuries. (C) Left anterolateral thoracotomy for patients in extremis (ED thoracotomy); also provides access to the left subclavian artery. (D) Extension of the anterolateral thoracotomy to the opposite chest as a "clamshell" incision. (E) "Book" thoracotomy.

The surgeon should be familiar will all of them, and the clinical situation should determine the choice of incision. Hemodynamically unstable patients may not tolerate lateral positioning, as it may exacerbate hypotension. In addition, in the emergent exploration of the unstable trauma patient, the only imaging is likely to be portable chest radiograph. In this scenario, the surgeon will have limited knowledge of potential mediastinal involvement, the projectile's path, or additional cavitary involvement. With penetrating thoracic trauma, there is the possibility of injury to adjacent body regions, such as the abdomen and neck. Therefore, a thoracic incision must prove versatile in accommodating flexibility in the conduct of operation. In this setting, incision selection requires careful consideration of the appropriate extensions that can be made to best optimize exposure and control options.

In the stable patient, additional imaging data is more likely to have been obtained. Armed with better understanding of the location and nature of injury, a better decision regarding optimal therapy can be formulated. In the modern endovascular age, this information may facilitate the effective utilization of less-invasive adjuncts. However, knowledge of open surgical options and defaults remain paramount. If open exploration or repair is selected, the choice of incision should be guided by the CT findings.[19]

Commonly employed open operative approaches include anterolateral thoracotomy, posterolateral thoracotomy, and even bilateral thoracotomy (or "clamshell thoracotomy") and median sternotomy (Fig. 182.4). The anterolateral approach is perhaps the most expedient—and extending it across the midline affords excellent exposure to both pleural spaces, the anterior mediastinum and nearly the full complement of thoracic vascular structures. Likewise, the incision can be continued as a celiotomy for abdominal exploration and is preferred over the posterolateral approach in the patient in shock. The main disadvantage of the anterolateral approach is exposure of posterior thoracic structures. By extending the ipsilateral arm and placing a bump to elevate the thorax approximately 20 degrees, the incision can be carried to the axilla—a maneuver that will improve posterior exposure. The posterolateral thoracotomy affords optimal exposure of the hemithorax, especially the posterior structures, and is the standard incision for most elective thorax operations. Its lack of versatility limits the usefulness in trauma, but is the preferred approach to repair any injury pattern that also involves intrathoracic tracheoesophageal injuries. Sternotomy provides excellent access to the heart, proximal great vessels, and anterior mediastinum. This particular incision is versatile—and can be extended as an abdominal, periclavicular, or neck

incision. The "trap door" incision is rarely used, since left-sided thoracic vessels can be approached via sternotomy with extension.[20]

Operative Techniques

Thoracic vascular injuries after significant trauma rarely occur in isolation, particularly after penetrating mechanisms. Therefore, it is useful to appreciate a few key nonvascular operative techniques that may be required during emergent operative exploration. Among patients requiring emergent thoracic exploration, between 20% and 30% will need a pulmonary resection, which ranges from wedge resections to major anatomic resections.[21,22] Pneumonorrhaphy, wedge resection, tractotomy, and formal anatomic resection are all techniques that can be utilized to manage pulmonary parenchymal injury. The trauma surgeon should be facile with all of these techniques, and the choice of a particular one is driven by the patient's clinical condition and the extent and location of the pulmonary injury. The widespread adoption of a variety of surgical staplers has facilitated tractotomy and pulmonary resections. Pneumonorrhaphy is the simplest technique and is applicable to superficial pulmonary lacerations. These can be closed with a running simple or mattress suture. Injuries near the lung periphery can be excised by a stapled wedge resection. The lung is mobilized, any adhesions are lysed, and the inferior pulmonary ligament may need to be divided to improve lower lobe exposure. A stapled wedge resection is performed by grasping the parenchyma with a lung clamp and firing the stapler to excise the peripheral tissue. Tractotomy is rapid and ideal for through-and-through parenchymal injuries.[23] Placing the jaws of the stapler through the tract and firing it will open the tissue. Bleeding vessels or air leaks can then be individually ligated. Tissue thickness will determine the appropriate size staples, and at times, the staple line needs to be over sewn with a running suture.

More centrally located injuries, especially those close to the hilum, require special consideration. Precise understanding of the pulmonary vasculature and hilar anatomy are necessary to safely perform a stapled resection for centrally located injuries. If a nonanatomic resection is precluded, as with extensively damaged lung parenchyma, a formal lobectomy is necessary. Hilar injuries present a significant challenge. Hemorrhagic shock is invariably present, and the injury necessitates pneumonectomy, which carries a prohibitive mortality. Several techniques can be used to obtain hilar control, including lung torsion, manual compression, and application of a vascular clamp. Manual compression followed by clamping is the most widely used. Very proximal hilar injures are particularly problematic, and opening the pericardium will occasionally allow vascular control.

MANAGEMENT OF SPECIFIC THORACIC VASCULAR INJURIES

Blunt Thoracic Aortic Injury

BTAI remains the second-most frequent cause of mortality after blunt force.[24,25] A recent autopsy study conducted by Teixeira and colleagues at Los Angeles County Hospital identified thoracic aortic injury (TAI) as a contributor in onethird of automobile accident deaths. National Vital Statistics data suggest that the majority of deaths due to BTAI after these blunt mechanisms occur prior to the arrival to a hospital facility.[26]

Among patients who survive to receive care, continued medical advances have improved the ability to expediently diagnose and effectively treat TAI. Thoracic endovascular aortic repair (TEVAR) has emerged as the primary treatment modality utilized for TAI among amenable patients, gradually replacing traditional open repair (OR) as the dominant surgical treatment modality.[13,27-41] Among patients with severe BTAI, the subsequent use of TEVAR has been associated with improved morbidity and mortality compared with traditional OR approaches.[13,27-30] Given these results, and following a 2011 analysis of the accumulated literature, the Clinical Practice Guidelines from the Society for Vascular Surgery (SVS) suggested that "endovascular repair be performed preferentially over open surgical repair or nonoperative management."[38]

Diagnosis

The clinical presentation of TAI can vary considerably. On arrival to a treating facility, patients may be asymptomatic or complain of pain in the chest or radiating to the neck, back, or shoulder. Hemodynamics may range from normotensive to frank shock, with hypotension being a common sign.[42]

The initial diagnostic test of choice is the plain CXR, which has a number of findings that are suggestive—but not confirmatory—of the diagnosis. On initial plain radiography, a widened or otherwise abnormal appearing mediastinum may be seen in up to 93% of patients with TAI.[43,44] Various definitions have been utilized to define pathologic widening of the mediastinum on plain radiography. These have included an 8 cm wide mediastinum at the level of the aortic knob, or a width at the same level that exceeds 25% of the total chest width.[43,44] It is imperative, however, that any visualized abnormality undergo advanced imaging, particularly in the context of suspicious mechanisms of injury. It is also important to appreciate that a normal plain chest radiograph does not exclude TAI and—as previously discussed—has a low sensitivity for this purpose.[10]

Over the last decade, CTA of the chest has emerged as the most commonly employed initial imaging tool for the diagnosis of or evaluation for BTAI, with a high documented sensitivity (95% to 100%) and concomitant high negative predictive value (99% to 100%) following trauma.[45-47] False positives do occur, however, particularly among lower grade injuries. In an examination of patients undergoing traditional angiogram after CTA, Bruckner and colleagues noted that CTA had an appreciably low specificity of 40% and a positive predictive value of only 15%.[47] Despite these findings, the majority of studies have validated the utilization of CTA after trauma due to the high sensitivity and ability to exclude blunt TAI with very high negative predictive value when CTA is utilized in this setting.[45-47]

Classification/Grading

BTAIs represent a spectrum of lesions that range from intimal tears to free rupture. The mechanism often involves rapid deceleration, where the greatest point of strain is at the aortic isthmus (Fig. 182.5). Classification is based on the extent of injury to the anatomic layers of the aortic wall. Based on imaging, BTAI is classified into four grades: intimal tears (grade 1); intramural hematoma (grade 2); pseudoaneurysm (grade 3); and rupture (grade 4; Fig. 182.6).[30,38] Grade 1 injuries do not cause an external aortic contour abnormality and are best visualized on CTA or IVUS. Angiograms in grade 1 patients can be interpreted as normal. Injuries involving the media, such as intramural hematomas or dissections, are considered grade 2. Grade 2 injuries cause an abnormality in the aortic contour and can be visualized on CTA, IVUS, or angiography. Pseudoaneurysms and ruptures (grade 3 and 4) are easily visualized with all imaging modalities. Additional classification systems based on contemporary imaging have also been proposed.[30,48-52] Accurate diagnosis (grade) of BTAI is critical because it affects management decisions and is an important tool in evaluating outcomes.

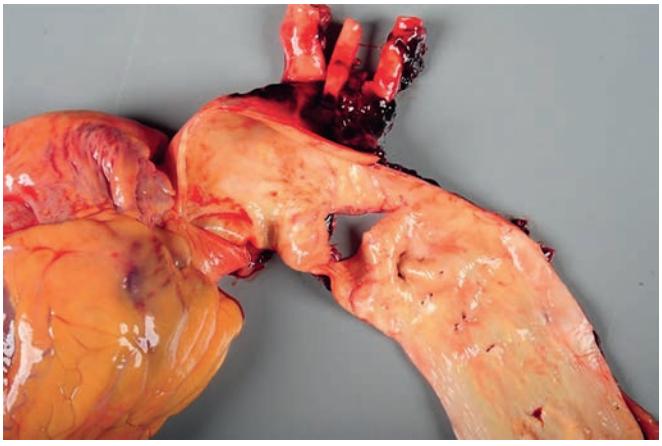

Figure 182.5 Postmortem aorta with injury in the descending aorta at the isthmus.

Blunt Thoracic Aortic Injury Treatment—Medical Therapy

Immediate management of all BTAI injuries, either as definitive therapy or during preparation for repair, includes aggressive blood pressure control. Effective pharmacologic suppression of aortic pressure fluctuations is utilized to reduce the stress on the injured aortic wall. These efforts have been shown to potentially reduce the risk of aortic rupture after BTAI diagnosis from 12% to 1.5%.[53] For grade 1 injuries, medical management alone is the mainstay of definitive therapy. For grade 2, 3, and 4 injuries, the SVS guidelines suggest medical management be utilized as a bridge to subsequent repair.

The optimal blood pressure goal and control regimen has not been well established, with different institutions having proposed various approaches. Fabian et al.[54] suggested the use of an intravenous beta-blocker to keep blood pressure at or below a recommended figure of 100 mm Hg or a mean below 80 mm Hg. The group also proposed the addition of an intravenous vasodilator if the beta-blocker was adequate on its own, as a monotherapy to control blood pressure. At our institution, we utilize a target goal of less than 120 mm Hg systolic blood pressure, most commonly achieved with titrated continuous beta-blockade infusion as tolerated.

It is important to consider that specific patterns of associated traumatic injury may affect the ability to employ medical therapy for BTAI. Specifically, patients with traumatic brain injury requiring optimization of cerebral perfusion pressure (CPP) may require elevation of blood pressure to optimize neurologic outcome. This required elevation is counter to the medical management of BTAI and may necessitate earlier intervention for aortic injury to facilitate optimal brain injury outcome. Given the common complexity of severely injured trauma patients, it is advisable that all discussions about the appropriateness of medical therapy and timing of potential BTAI repair be undertaken in a collaborative fashion by the key stakeholders in care.

The managing team must also remain vigilant for other indications to abort medical therapy, including obvious signs of malperfusion or possible early progression of BTAI while undergoing medical management. In the largest retrospective, multicenter series of BTAI patients to date, the Aortic Trauma

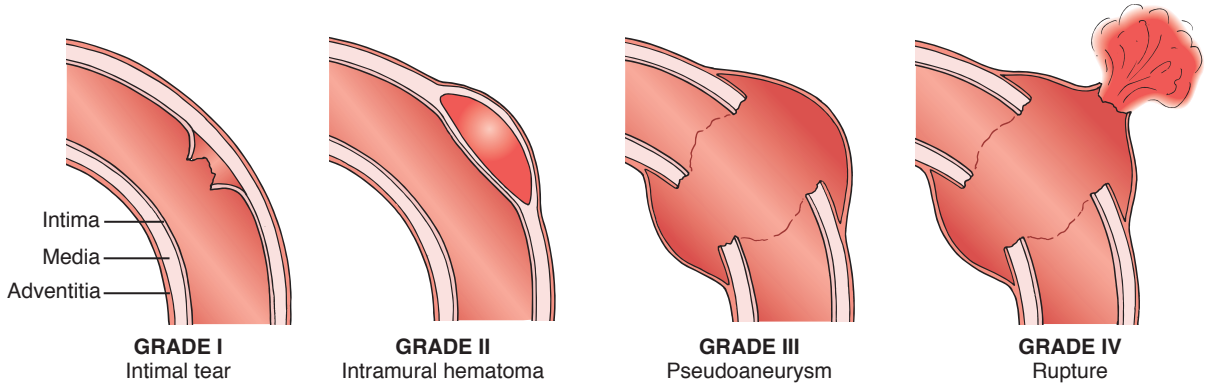

Figure 182.6 Classification of traumatic aortic injury.

Foundation (ATF) study group noted that medical therapy alone was selected for 32.2% of patients. Only two in-hospital failures of medical therapy were noted in the population studied, both undergoing subsequent endovascular salvage repair without complication.[13]

Blunt Thoracic Aortic Injury Repair

While prompt repair of BTAI is preferred, existing data suggest that selective delayed repair may result in optimal outcomes.[31] This approach is commonly required among trauma patients, requiring treatment of more immediately life-threatening injuries, such as laparotomy or emergent craniotomy—a common occurrence among the severely injured cohort.[5,13] Until definitive intervention for BTAI is undertaken, medical management of blood pressure control is performed in an appropriate intensive care. The subsequent timing of definitive repair is then individualized for the specific patient through a multidisciplinary, decision-making process.

Once the optimal timing of intervention for the individual patient has been established, endovascular repair has emerged as the mainstay of subsequent definitive BTAI treatment in the modern era. The evolution in endovascular technologies occurring over the last decade or more has afforded that TEVAR can be safely and effectively performed in the majority of patients with BTAI. In the largest multicenter retrospective BTAI examination to date, conducted by the ATF between 2008 and 2013,[13] TEVAR was the treatment utilized for 76.4% of the 382 BTAI patients studied, with only 23.6% requiring OR.

Documented improved outcomes following TEVAR for the treatment of BTAI are due both to increased experience with endovascular approaches to treatment and device advances. The first endovascular device approved by the US Food and Drug Administration (FDA) for the treatment of thoracic aortic aneurysms was the Thoracic Aortic Graft (TAG; W.L. Gore & Associates, Flagstaff, Arizona) in 2005. This device was initially used for TEVAR in patients with BTAI in an off-label indication. Subsequent introduction of a variety of on-label FDA approved devices in 2008 has increased the tools available for definitive treatment of these injuries by effective endovascular means.

The technique utilized for endovascular repair at our institution has been described previously.[28] In summary, all endovascular procedures are performed under general anesthesia in a hybrid operating room equipped with fixed imaging equipment (Axiom, Siemens Medical, Malvern, Pennsylvania). Intraoperatively, the abdomen and bilateral groins are prepped in standard fashion. An arch aortogram is performed through femoral access, and the location of the injury is confirmed. The cerebrovascular anatomy is evaluated based on the arch angiogram, especially if left subclavian artery coverage is planned. IVUS is used selectively based on the discretion of the attending surgeon. The patient is anticoagulated using a weight-based heparin protocol if there are no contraindications. Otherwise, a smaller dose of heparin (3000 to 5000 units) is administered.

The thoracic device is selected based on CT images according to the manufacturer's sizing recommendations. Measurements are made based on two-dimensional, thin-cut axial CT scans with IV contrast. The device is delivered and deployed using a standard technique without any pharmacologic adjunct; extension pieces may be deployed as indicated. The subclavian artery is covered, as needed, to obtain a proximal landing zone or gain better apposition with the lesser curvature of the aortic arch. We maintain a policy of selective delayed subclavian artery revascularization for such cases.[55] Postdeployment balloon angioplasty is performed selectively when incomplete apposition of the graft at the proximal landing zone is noted. The heparin is then reversed with protamine. Postoperatively, patients are returned to the surgical-trauma intensive care unit and discharged following stabilization of their other injuries**.** A diagnostic and completion angiogram of a patient with a grade III BTAI is shown (Fig. 182.7). A follow-up CTA shows successful exclusion of the aneurysm.

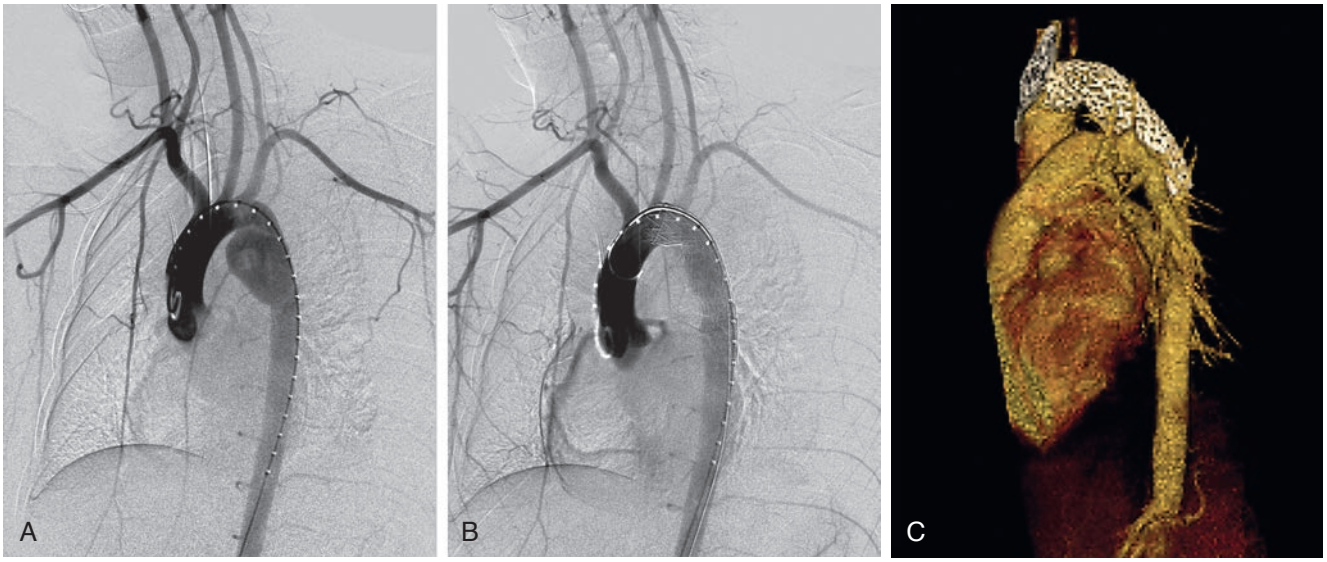

Figure 182.7 (A) Diagnostic and (B) completion angiography of a patient with a grade III blunt thoracic aortic injury. (C) Follow-up computed tomography angiography shows successful exclusion of the aneurysm.

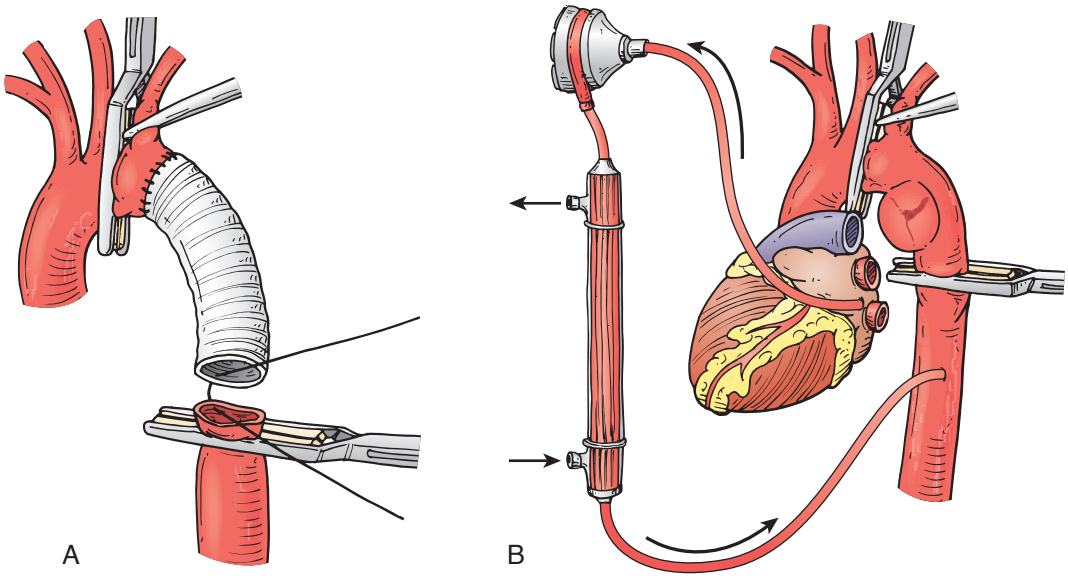

Figure 182.8 Open repair of blunt thoracic aortic injury can be performed using a (A) clamp and sew technique or (B) distal aortic perfusion.

Select patients with unsuitable anatomy or other confounding factors may continue to require open surgical repair. In the modern era, OR is reserved for specific scenarios. Among patients showing signs of hemodynamic compromise and the need for emergent repair, not all facilities will have the capability to martial endovascular resources in the required time frame to optimize outcome. While rapid mobilization of endovascular resources is inherent to many modern trauma centers, local capabilities must be considered.

Other considerations in selecting OR include the consideration of patients anatomically unfavorable for TEVAR. The foremost criteria determining the need for OR is the absence of an adequate proximal landing zone to allow for proper "seal" of the site of injury by the device. In approximately 40% of BTAI patients, left subclavian artery coverage is required to achieve this objective.[13] Available data suggest that the majority of trauma patients requiring left subclavian artery coverage in this setting will have good short- and mid-term outcomes without the need for subsequent bypass.[13,55] Other anatomical criteria that may preclude the ability to safely conduct TEVAR for BTAI include small or diseased iliofemoral vessels, with diameters of these vessels less than 7 mm being a risk factor for access site complications, including dissection, rupture, and hematoma formation.

When OR is required, a number of approaches can be considered to facilitate BTAI treatment, depending on the site and length of the descending thoracic aorta involved. Given that the most commonly encountered location of BTAI is in the region of the isthmus, a left posterolateral thoracotomy to enter the chest through the fourth space is usually the most expedient and optimal incision choice. Once the chest is opened, the initial objective is to acquire proximal and distal control around the area of injured thoracic aorta. The proximal clamp is typically applied between the left common carotid and left subclavian arteries, while the distal clamp is placed at some point on the distal descending thoracic aorta distal to the zone of injury (Fig. 182.8A).

Depending on the clinical scenario and patient condition, a distal aortic perfusion strategy should be expediently developed. The most expeditious technique is "left-heart bypass," which can be performed through cannulation of the left inferior pulmonary vein and distal thoracic aorta (see Fig. 182.8B). Rarely, the proximal clamp positioning is untenable. In this scenario, full cardiopulmonary bypass (CPB) is advisable, commonly through a femoral artery and a femoral vein cannulation. If total circulatory arrest is warranted, then careful venting of the left ventricle during times of cooling and rewarming is crucial.

One of the caveats, which is often problematic for the polytrauma patient, is the need for systemic anticoagulation with the use of bypass. For left-heart bypass, this is achieved through administration of intravenous heparin at a dose of 1 mg/kg to achieve an activated clotting time (ACT) of more than 200 seconds. In cases where full bypass is required, heparin is used at a dose of 4 mg/kg to achieve an ACT of greater than 480 seconds. Once the patient is on bypass and the perfusion circuit is satisfactory, the periaortic hematoma is incised, the extent of injury explored, and the ensuing aortic repair undertaken. It is paramount that the aortic adventitia is incorporated into the subsequent suture lines, as this layer provides the majority of the tensile strength of the aorta. The patient is gradually rewarmed during the latter phase of the anastomosis to facilitate removal of the clamps at a moderate degree of hypothermia (32°C to 34°C). Once the clamps are off, the patient is weaned off the bypass until adequate hemostasis is achieved and the wound is closed in its respective layers.

A significant consideration when undertaking open BTAI repair is spinal cord protection and the importance of distal aortic perfusion in minimizing the risk of postoperative

paraplegia.[56] Several potential strategies designed to mitigate the risk of postoperative paraplegia have previously been described in the literature.[57-61] Perhaps the most significant contributor to spinal cord ischemia occurs as a result of aortic clamping and subsequent occlusion of critical segmental spinal cord arterial branches. Important factors in determining the incidence of immediate onset or delayed paraplegia following aortic repair include duration of cross-clamping, level and length of aortic segment excluded by clamping, duration of systemic hypotension, cerebrospinal fluid pressure, distal aortic pressure, and the number of intercostals ligated during repair.[62] Multiple adjuncts have helped lower the incidence of paraplegia following aortic repair for BTAI, including cerebrospinal fluid drainage, administration of steroids, generalized and localized hypothermia, as well as reattachment of key intercostal arteries during the conduct of repair.[59-62]

Postoperative Management

The hemodynamic state of the patient is closely monitored following the procedure, and meticulous care is provided for any other trauma they have experienced. Significant vigilance must be maintained for any of the common complications that can arise following aortic trauma, including bleeding, infection, and neurologic changes. Long-term data on durability and major complications is limited to less than 10 years, as widespread adoption of TEVAR did not occur until the mid-2000s. Knowledge of optimal follow-up practice is, subsequently, limited. At present, the follow-up surveillance strategy utilized at our center includes clinical examination and CT at 1, 6, and 12 months, and yearly thereafter.

Potential Complications of Thoracic Endovascular Aortic Repair

Current data suggest that in comparison to OR, TEVAR may reduce early death, paraplegia, renal insufficiency, transfusions, reoperation for bleeding, cardiac complications, pneumonia, and length of hospital stay.[13,30-32] In their landmark 2008 report, Demetriades and colleagues of the AAST BTAI study group[32] documented significant improvements in BTAI care associated with the transition from open to TEVAR. In their examination of 193 patients with BTAI, they found that TEVAR was associated with significantly decreased transfusion requirements and lower mortality compared with OR. The more contemporary findings from the ATF study group experience support these findings, with a significantly lower PRBC requirement (mean 5.9 vs. 3.1 units, $P < .002$) in the first 24 hours and a lower overall mortality (8.6% vs. 19.7%, $P = .021$) and aortic-related mortality (13.1% vs. 2.5%, $P = .003$) among TEVAR treated patients compared with open counterparts.[13]

The common concerns for paralysis and stroke that have been associated with OR appear to also be mitigated with the increasing use of TEVAR. In the aforementioned ATF multicenter study of 382 BTAI patients,[13] only 1 paralysis following TEVAR was noted, occurring in an 81-year-old male requiring 20-cm device coverage of the thoracic aorta. Likewise, stroke was a very rare occurrence, identified in only two patients, ages 62 and 85, respectively. Both required coverage of the left subclavian artery to facilitate TEVAR. These findings support the safety profile for TEVAR in the setting of BTAI, but suggest that older patients with possible native atherosclerotic burden and BTAI patterns requiring more extensive endograft coverage may increase risk of ischemic complications.

Access- and device-related complications also appear to be rare complications of TEVAR in contemporary practice. This improvement in safety profile has emerged as a benefit of increased experience and improvements in device technology. In the older 2008 report of the AAST BTAI study group, the investigators noted a significant rate of specific TEVAR-related complications.[32] Demetriades and his group found that 18.4% of patients undergoing TEVAR had some form of stent graft-specific complication, most notably endoleak at 13.6%. The continued advancement of endovascular technologies since this report, including the increasing utilization of FDA-approved devices specific to aortic trauma, has improved the ability to avoid these adverse events following TEVAR. In the more contemporary published experience of the ATF Study Group, which captured the treatment of 382 BTAI patients, a significantly decreased risk of TEVAR-related complications was documented.[13] This group noted six malpositions of the endograft at initial TEVAR occurred (3.0%) and a post-TEVAR endoleak rate of 2.5%. Only one delayed stent migration was noted. In addition, just two access site complications (one pseudoaneurysm, one persistent bleeding requiring intervention) were identified. Among the six defined TEVAR treatment failures encountered in this large series, all underwent subsequent salvage with reintervention (two repeat TEVAR, four OR). The ATF study group identified only one patient treated with repeat TEVAR who suffered aortic-related mortality. No other mortalities were observed among the TEVAR failures.

Although increasingly rare in the modern era, it is important to note that complications during or after TEVAR remain possible in specific settings. Excessive oversizing or undersizing of endografts can lead to propagation of aortic injury or failure to achieve adequate seal. Patient-specific anatomical issues may also contribute, including the presence of a tight curvature of the aortic arch, native atherosclerotic burden and the aforementioned diameter limitations of iliac access vessels.

Outcomes After Blunt Thoracic Aortic Injury Management

The largest multicenter retrospective study of BTAI outcomes conducted to date included 382 patients from nine American College of Surgeons verified Level I trauma centers in North America.[13] This study, a collaborative effort conducted under the auspices of the ATF, captured a distribution of BTAI grades of injury (94 grade 1 injuries [24.6%], 68 grade 2 [17.8%], 192 grade 3 [50.3%], and 28 grade 4 [7.3%]). Overall in-hospital mortality for all patients with BTAI was 18.8% (nonoperative management 34.4%, OR 19.7%, TEVAR 8.6%), with an aortic-related mortality of 6.5% (nonoperative management 9.8%, OR 13.1%, TEVAR 2.5%).

Among the ATF BTAI study patients, the majority of aortic-related deaths (18/25) occurred prior to the opportunity for completion of OR or TEVAR. Of the seven patients who died after OR (3) or TEVAR (4), all had an Injury Severity Score (ISS) in excess of 25, consistent with severe polytrauma. Using multivariate logistic regression, the investigators found that the independent predictors of aortic-related mortality included higher overall ISS and higher grade of BTAI injury. On multivariate regression, TEVAR utilization proved the only variable protective against aortic-related mortality.

Remaining Controversies and Future Directions

The current SVS guidelines for BTAI management[38] provide an evidence-based, consensus-derived grading system and suggested course of treatment. These guidelines represent the most comprehensive effort in BTAI care optimization yet conducted by a major medical organization. The SVS guidelines do, however, have some limitations—including the fact that they are specific to the aortic lesion alone. Potential future improvements include further refinement of injury grading paradigms, standardization of care, and the establishment of effective prospective long-term follow-up mechanisms. A number of initiatives are actively underway to promote these needed advances.

Several investigators have suggested that greater scrutiny of specific elements of BTAI-related imaging may provide an important key to defining optimal type and timing of treatment. Both the Vancouver simplified grading system[57] and the alternate classification scheme proposed by Osgood et al.[34] have promoted the importance of more detailed aortic lesion dimension assessments, parameters not specifically included in SVS criteria, as crucial to determining the need for TEVAR. Initial work by investigators at the University of Maryland[35] has also demonstrated that associated secondary signs of injury available on CTA of the chest may require further consideration. Specifically, this group has highlighted that the presence of extensive mediastinal hematoma and large left hemothorax may prove important hallmarks of impending aortic rupture. In a 15-year retrospective study of 331 patients with BTAI, we examined CTA imaging variable to determine predictors of rupture. We found that injury grade was a predictor of aortic-related mortality. Contrary to the Maryland study, we found that pseudoaneurysm size, lesion/normal aortic diameter ratio, and mediastinal hematoma location and size were not predictors of aortic-related mortality.

There has also been debate regarding what some investigators term "minimal aortic injuries."[34] Optimal management of these BTAI patients, which include grade 1 and 2 injuries, has been debated. Some groups have suggested that these "minimal aortic injuries" do not universally require TEVAR, an approach that conflicts with the present SVS clinical practice guideline suggestions. The findings from research conducted at several high-volume centers, however, suggest a nonoperative approach to initial care of this range of BTAI is safe.[34,35] In the aforementioned ATF study, researchers retrospectively compared grade 1 and 2 injuries treated with TEVAR. They found no significant difference in in-hospital outcomes between patients managed with medical therapy alone or TEVAR.[13] While this existing data suggest that the nonoperative management of SVS grade 2 injuries is safe, the natural history beyond discharge is not well-defined. These patients will require effective longitudinal follow-up and study, ideally in the context of a multicenter study.

Another challenge includes consideration of the fact that BTAI patients commonly have significant associated injuries that are pertinent to overall outcome. In some instances, the optimal care of these associated injuries proves counter to optimal BTAI care. The need to maintain an optimal cerebral perfusion pressure among patients with brain injury, for instance, contrasts with the pharmacologic blood pressure impulse control recommended to minimize wall stress in the injured thoracic aorta. An optimal algorithm should incorporate some consideration of associated injuries into individualized BTAI care.

Ideal timing of BTAI treatment is a remaining issue that requires further study. The results of the American Association for the Surgery of Trauma Aortic Injury Study Group, reported in 2009, suggested that improved outcomes were associated with initial medical management, including blood pressure pulse pressure optimization.[31] This group found that patients treated in a delayed (>24 hours) fashion, after this period of optimization, had improved survival compared with BTAI patients treated operatively within less than 24 hours. There remains a need, however, to adequately define whether specific risk factors associated with BTAI represent a higher risk for early aortic rupture and need for more emergent repair.

Finally, the long-term durability of endovascular devices used for BTAI treatment remains to be determined. Improved conformability to aortic contour and various fixation element changes are attractive features of modern devices. The ongoing study of branched graft devices may soon obviate the need for coverage of the left subclavian artery during TEVAR entirely. However, this remains an unresolved issue of BTAI care. Optimal graft sizing and graft utilization in pediatric patients—or patients with small aortic diameters—are also inadequately studied issues. These challenges are augmented by the fact that optimal device indications and utilization has primarily been subjected only to industry-funded study. These issues require more objective investigation in a large, multicenter fashion.

Vascular Injuries to the Aortic Arch Vessels and Thoracic Outlet Vasculature

While TAI is perhaps the hallmark thoracic vascular injury, a wide variety of traumatic pathologies at various locations within the chest can be encountered.[63] The majority of these injuries are initially diagnosed with contrast-enhanced CT, now ubiquitous to initial trauma evaluations. As with TAI, the patient condition and associated injuries remain considerations in defining optimal management of identified vascular injuries. For unstable patients requiring immediate surgical intervention, particularly after penetrating mechanisms, initial open repair approaches are commonly utilized. The aforementioned issues

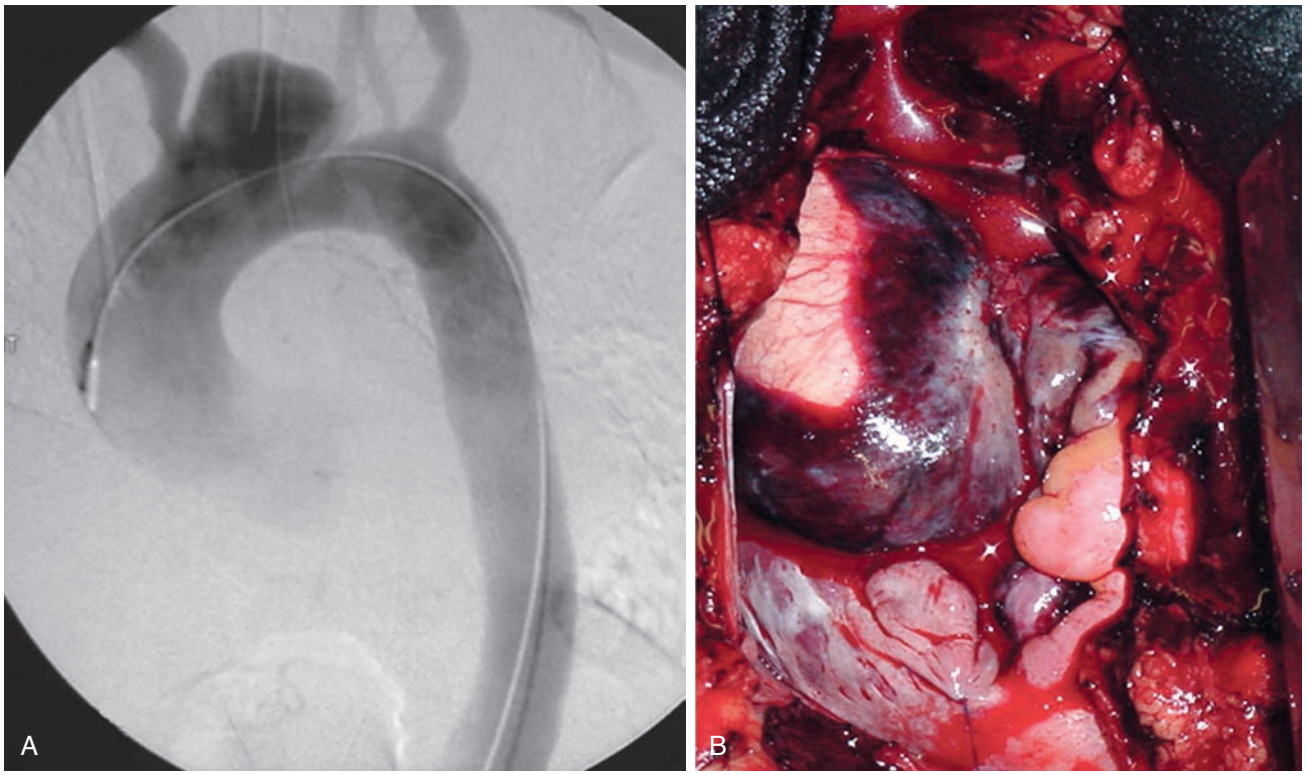

Figure 182.9 Blunt trauma to the aortic arch. (A) Diagnostic arch angiogram shows a large pseudoaneurysm. (B) Intraoperative photograph after median sternotomy. (Courtesy Dr. Anthony L. Estrera.)

regarding initial incision and subsequent extensile options should be considered carefully in these instances.

Ascending Aorta and Transverse Arch

Rupture of the ascending and transverse aortic arch is uncommon, but the exact incidence is unknown due to the lethality of these injuries. A widened mediastinum and cardiac tamponade are frequently associated with ascending aortic ruptures. Repair of these injuries requires a median sternotomy, CPB, and systemic heparinization (Fig. 182.9). Management of the aortic tear may be primary or with an interposition graft. Special attention should be paid to the status of the aortic valve. Injuries to the aortic arch may require hypothermic circulatory arrest and associated antegrade and retrograde cerebral perfusion techniques. Survival depends primarily on the severity of associated injuries.[64-66]

Innominate Artery

Rupture of the innominate artery is the second-most common thoracic arterial injury following blunt trauma. Innominate artery injuries can generally be repaired via a median sternotomy with a right cervical extension when necessary. Blunt injury typically involves the base of the innominate artery, and this is most expeditiously repaired with a bypass from the ascending aorta to the distal innominate artery, followed by oversewing of the innominate stump (Fig. 182.10). Division of the innominate vein is occasionally required for exposure, and shunts or CPBs are often not required. Avoidance of the injured area until completion of the bypass leads to a technically easier repair.[67,68]

Left Common Carotid Artery

The surgical approach to injuries of the proximal left carotid artery mirrors that of the innominate artery—a sternotomy with a left cervical extension, if needed. With injuries of the left carotid origin, bypass graft repair is generally preferred over an end-to-end reanastomosis.[69] The management of a carotid injury in the setting of neurologic disturbances is controversial. Generally, if the patient is evaluated soon after injury, revascularization is recommended because hypotension (rather than ischemic infarct) is the most likely cause of morbidity.[70] Chapter 156 contains additional information on carotid injuries. Recently, traumatic carotid lesions have been managed with endovascular techniques. An endovascular approach is especially useful for extensive lesions with involvement near the skull base, where obtaining proximal and distal vascular control may result in increased morbidity. The goal of endovascular therapy is the elimination of a fistula, aneurysm, or stenosis while preserving native flow to the brain. There have been multiple reports on the successful management of traumatic carotid injuries with endovascular techniques.[66-73] However, the use of stents introduces new considerations, such as the probability of late in-stent thrombosis. The administration of postprocedural medications, such as aspirin and clopidogrel, can minimize the incidence of in-stent thrombosis.[74,75]

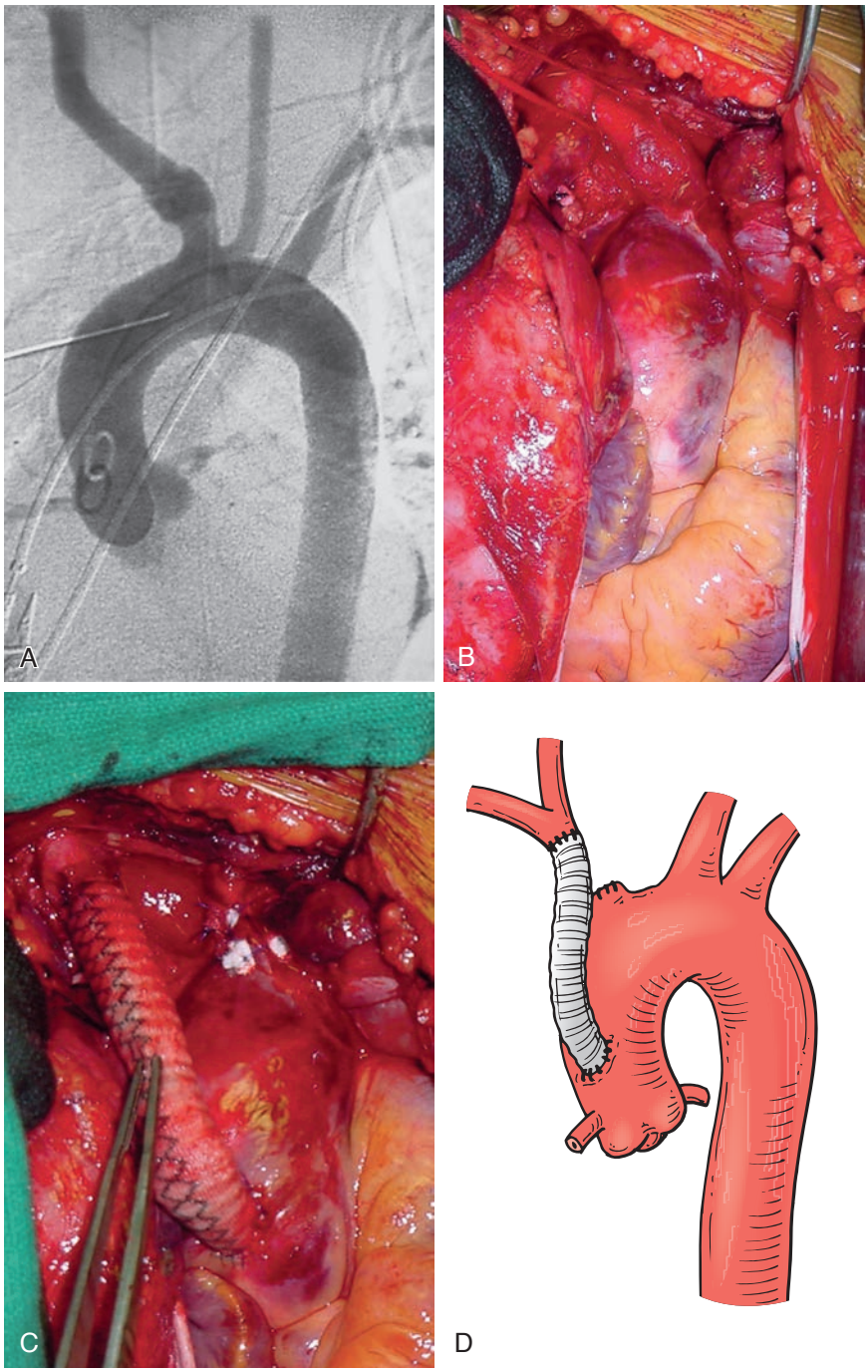

Figure 182.10 Repair of innominate artery injury. (A) Diagnostic angiogram. (B) Intraoperative image showing blunt injury to the proximal innominate artery. (C and D) Placement of an ascending aorta to innominate artery bypass with oversewing of the innominate artery stump. (Courtesy Dr. Anthony L. Estrera.)

Subclavian Vessels

Injuries to the subclavian vessels are usually caused by penetrating wounds. Subclavian vascular injuries require preoperative imaging (generally CTA) for appropriate incision planning. Injuries to the right subclavian artery are best addressed via a median sternotomy with a right cervical extension. Proximal control of left-sided subclavian injuries can be obtained via a left anterolateral thoracotomy. A separate supraclavicular incision can be used for distal control. These two incisions can be connected with a sternotomy to facilitate exposure. This incision should be used sparingly because of reports of postoperative "causalgia" neurologic symptoms.[69] In addition, the second or third portion of the subclavian artery can usually be exposed without the need for clavicular resection or sternotomy.

Endovascular approaches to innominate, intrathoracic carotid, and subclavian arterial injuries have been described in both blunt and penetrating trauma (Fig. 182.11).[76-78]

As with TAI, endovascular capabilities are increasingly being utilized to effectively treat vascular injuries to the vessels of the thoracic arch and thoracic inlet.[62,79-82] Available data suggest that, among appropriately selected patients, endovascular treatment is associated with improved outcome for injuries in these areas—which often represent challenging open exposures for

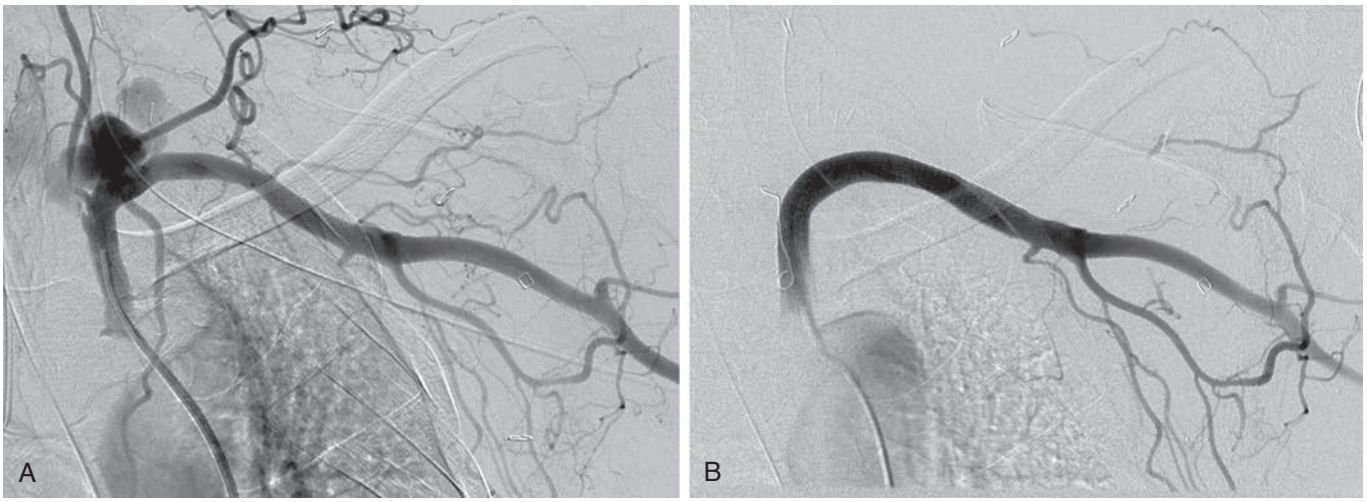

Figure 182.11 (A) Selective left subclavian angiogram of a patient after a stab wound shows a pseudoaneurysm. (B) After coil embolization of the left vertebral artery, endovascular repair of the left subclavian artery injury was performed using a covered stent graft. (Courtesy Dr. Kristofer M. Charlton-Ouw.)

control and repair. In a recent study conducted by Branco and colleagues, investigators found that endovascular treatment of axillo-subclavian injuries was associated with lower in-hospital mortality and surgical site infections than counterparts undergoing open repair of these injuries.[79] A subsequent report used a large cohort of patients from the National Trauma Databank to compare matched populations of vascular injured patients undergoing open or endovascular repair.[80] The study found that outcomes were improved across a wide range of vascular thoracic vascular injuries. Additional literature supports these findings.[63,81] While this evidence suggests that endovascular repair modalities may have improved outcomes compared to open repair of a variety of thoracic vascular injuries during the initial hospitalization, there remains a significant paucity of long-term outcomes. There remains a need to capture this data in order to better define if endovascular repair is to be considered definitive or simply a temporizing/damage control adjunct over the lifespan of a young trauma patient. To this end, the PROspective Vascular Injury Treatment (PROOVIT) registry, developed under the auspices of the American Association for the Surgery of Trauma, is capturing data in a multicenter, multinational fashion to better define the optimal management and follow-up of these injuries.[63]

CONCLUSION

Thoracic vascular injuries remain significant challenges of modern trauma vascular care. Significant strides have been made with regard to diagnostic and initial management capabilities—facilitated by improvements in contrast-enhanced CT imaging and endovascular treatment modalities. There remains, however, a need to better define optimal grading systems and long-term outcomes after these injuries. Ongoing efforts in this regard, including the Aortic Trauma Foundation Prospective Multi-Center, Multi-National TAI registry and the PROOVIT registry, promise to advance additional understanding about the optimal diagnosis, management, and follow-up of these injuries.

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183 CHAPTER

Vascular Trauma: Abdominal

DEMETRIOS DEMETRIADES and KENJI INABA

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Abstract

Abdominal vascular injuries are the most common cause of death after penetrating abdominal trauma. Accurate diagnosis, rapid surgical exposure and control, and the definitive management of these injuries may challenge the skills and judgment of even the most experienced surgeons. These can be made even more complex by any associated intraabdominal injuries. Rapid transportation to a trauma center, early recognition of the injuries, early surgical intervention, excellent knowledge of the anatomy, and good surgical judgment are critical for optimizing patient survival.

Keywords

Trauma
Injury
Shunt
REBOA
Damage Control Surgery
Coagulopathy

Abdominal vascular injuries are the most common cause of death after penetrating abdominal trauma. Accurate diagnosis, rapid surgical exposure and control, and the definitive management of these injuries may challenge the skills and judgment of even the most experienced surgeons. These can be made even more complex by any associated intraabdominal injuries. Rapid transportation to a trauma center, early recognition of the injuries, early surgical intervention, excellent knowledge of the anatomy, and good surgical judgment are critical for optimizing patient survival.

SURGICAL ANATOMY

For vascular trauma purposes, the abdomen is conventionally divided into the intraperitoneal and retroperitoneal areas. The retroperitoneum is further divided into four distinct zones (Fig. 183.1):

- Zone 1, which includes the midline retroperitoneum extending from the aortic hiatus to the sacral promontory. This zone is subdivided into the supramesocolic and inframesocolic areas. The supramesocolic area contains the suprarenal aorta and its major branches (celiac axis, superior mesenteric artery [SMA], and renal arteries), the supramesocolic inferior vena cava (IVC) with its major branches, and the superior mesenteric vein (SMV). The inframesocolic area contains the infrarenal aorta and IVC.
- Zone 2 (left and right), which includes the kidneys, paracolic gutter, and renal vessels.
- Zone 3, which includes the pelvic retroperitoneum and contains the iliac vessels.
- Zone 4, which includes the perihepatic area containing the retrohepatic IVC and hepatic veins.

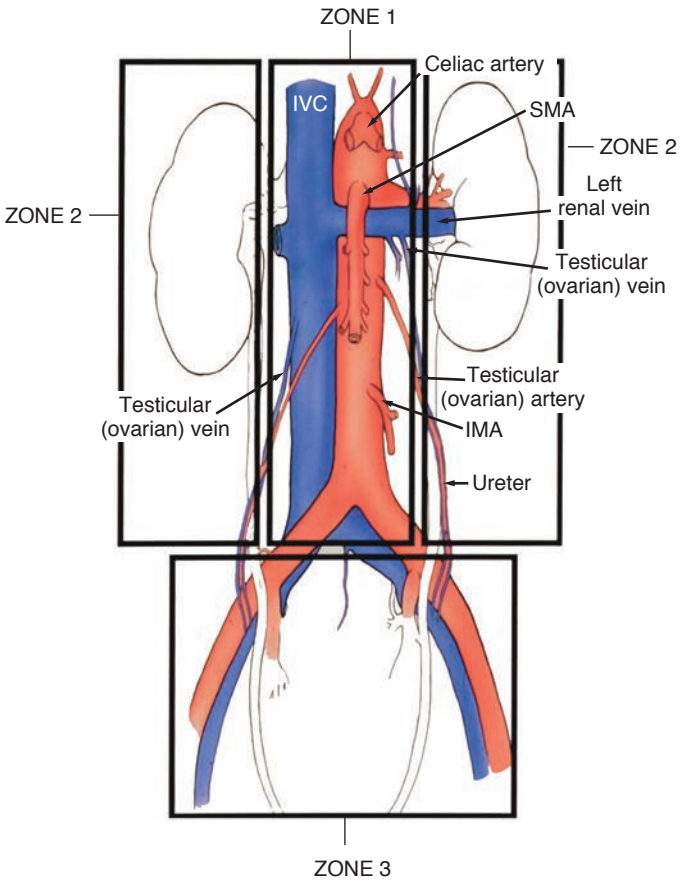

Figure 183.1 Retroperitoneal Vascular Zones. Zone 1 includes the midline vessels from the aortic hiatus to the sacral promontory; zone 2 includes the paracolic gutter and the kidneys; and zone 3 includes the pelvic retroperitoneum. *IMA*, Inferior mesenteric artery; *IVC*, inferior vena cava; *SMA*, superior mesenteric artery.

EPIDEMIOLOGY

Penetrating trauma is responsible for most abdominal vascular injuries and accounts for approximately 90% of cases in urban trauma centers.[1] Low-velocity missiles cause direct injury to the vessel. High-velocity missiles and blast can also cause injury by means of a shock wave and transient cavitation. These injuries may manifest as early or late thrombosis, in addition to hemorrhage.

In patients who undergo exploratory laparotomy for injury, the incidence of vascular trauma is 14.3% for gunshot injuries,[2] 10% for stab wounds,[3] and 3% for blunt injuries.[4]

Blunt abdominal trauma may cause vascular injuries by one of three mechanisms:

1. Rapid deceleration, as occurs in high-speed vehicular collisions or falls from height; this can cause avulsion or intimal tearing and subsequent thrombosis.
2. Direct anteroposterior crushing, from a seat belt or a direct blow to the anterior abdomen.
3. Direct laceration of a major vessel by a bone fragment, for example with severe pelvic fractures.

Abdominal arterial and venous injuries occur with the same incidence. In a review of 302 abdominal vascular injuries from our center, the incidence of arterial injuries was 49% and that of venous injuries was 51%.[1] The most commonly injured abdominal vessel was the IVC, accounting for 25% of injuries, followed by the aorta (21%), iliac arteries (20%), iliac veins (17%), SMV (11%), and SMA (10%). Overall, patients with penetrating trauma who sustained a vascular injury had an average of 1.7 vascular injuries per patient.[1]

CLINICAL PRESENTATION

Many patients with major abdominal vascular injuries die at the scene. Of the patients who are transported to a hospital, approximately 14% lose vital signs en route or on arrival in the emergency department.[1] The clinical presentation depends on the injured vessel, the size and type of injury, the intraperitoneal or retroperitoneal location of injury, the presence of associated injuries, and the time elapsed.

Penetrating injuries to the abdomen associated with hypotension and abdominal distention are highly suggestive of vascular injury. Asymmetric femoral pulses may indicate iliac artery injury. Many patients may be normotensive on admission only to decompensate a few minutes later. Some patients present in a hemodynamically stable condition because of thrombosis of the vessel or containment of the bleeding in the retroperitoneum. In most cases the diagnosis is made intraoperatively.

DIAGNOSTIC EVALUATION

In most patients with abdominal vascular injuries, no investigations are needed because of the altered hemodynamics and obvious need for immediate laparotomy. For penetrating injuries, hemodynamic instability, peritonitis on examination, or an unevaluable patient mandates immediate laparotomy and any vascular injuries will be diagnosed intraoperatively.[5] Whenever possible, plain radiographs should be obtained (Fig. 183.2) for localizing any bullet fragments. If the patient does not require immediate laparotomy and is to undergo a trial of nonoperative management, CT would be the next diagnostic evaluation and has excellent sensitivity and specificity for vascular injury (Figs. 183.3A and B, and 183.4). For blunt trauma, peritonitis or hemodynamic instability with a positive abdominal FAST exam requires immediate laparotomy. For unstable patients with negative FAST, a diagnostic peritoneal aspirate is performed to exclude a false negative FAST and other sources of bleeding are sought. This includes the retroperitoneum, ideally imaged using CT (Fig. 183.5).

TREATMENT

Prehospital Treatment

The most important factor for the survival of salvageable patients with vascular injuries is rapid transportation to a trauma center, followed by immediate surgical control of the bleeding.

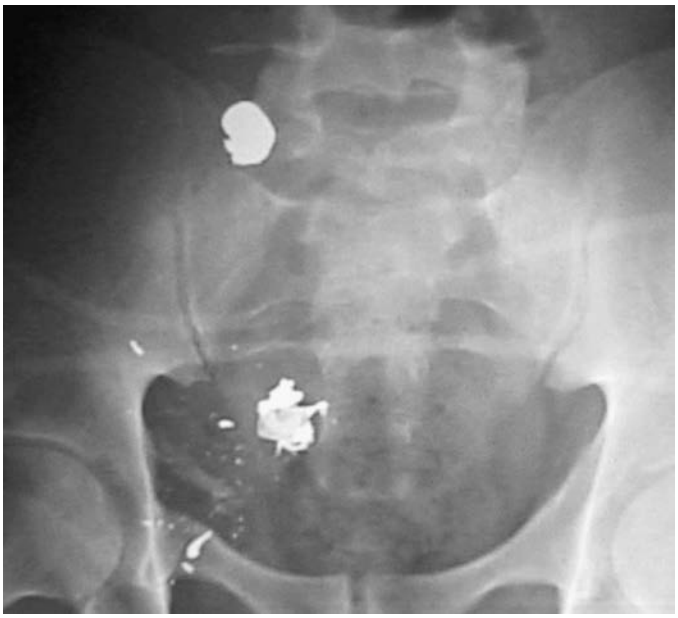

Figure 183.2 The pelvic location of the missile on the abdominal radiograph, combined with hypotension, is highly suggestive of an iliac vascular injury.

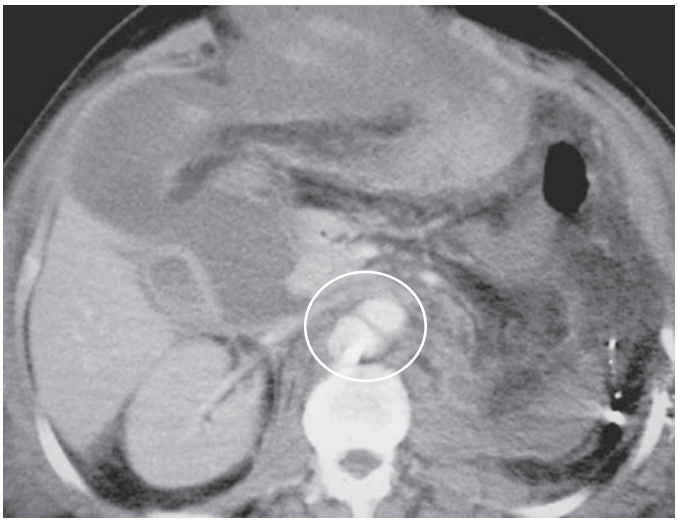

Figure 183.4 Postoperative computed tomography scan of a patient with a gunshot wound shows an abdominal aortic false aneurysm *(circle)*.

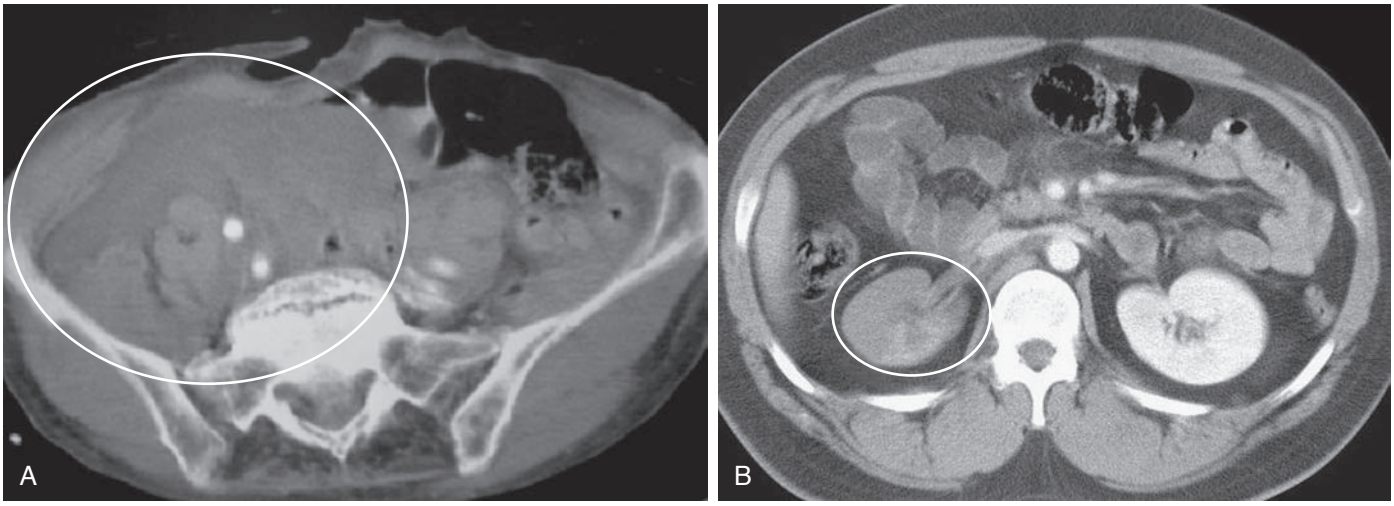

Figure 183.3 (A) Computed tomography (CT) scan of a traffic accident victim shows a large pelvic hematoma *(circle)* due to injury of the right common iliac artery. (B) CT scan with intravenous administration of contrast material in a high-speed traffic accident patient shows poor uptake of the contrast agent in the right kidney because of occlusion of the renal artery *(circle)*.

Figure 183.5 A 5-year-old child presented with a severe pelvic fracture and absent right femoral pulse. Angiography shows a complete occlusion of the right common iliac artery *(arrow)*.

Prehospital advanced life support has no place in penetrating trauma, especially in an urban environment. A policy of "scoop and run" is currently the recommended approach. The role of prehospital intravenous fluid administration is controversial; some studies show improved survival with fluid restriction and others show no effect on survival.[6-8] Experimental work on abdominal aortic injuries has shown that, in the presence of uncontrolled bleeding, aggressive fluid resuscitation increases mortality and the rate and volume of hemorrhage.[9,10] However, avoidance of all fluid resuscitation in near-fatal hemorrhage may result in cardiac arrest before bleeding is controlled.[11] It seems that some degree of controlled hypotension is beneficial and prevents massive exsanguination while avoiding the risk of cardiac arrest due to massive blood loss and severe hypotension.[9,12] Experimental work suggests that a systolic pressure of 80 to 90 mm Hg is the optimal pressure in the presence of active vascular bleeding.[13]

Emergency Department Treatment

The extent of resuscitation required in the emergency department depends on the clinical condition of the patient. For patients arriving in cardiac arrest, endotracheal intubation and a resuscitative thoracotomy should be performed in the emergency department. A left anterolateral thoracotomy through the fourth to fifth intercostal space is performed, the thoracic aorta is cross-clamped, and the heart is resuscitated. If cardiac activity returns, the operation is completed in the operating room. The survival rate after resuscitative thoracotomy for abdominal vascular injuries is approximately 2%.[1]

An attractive alternative to resuscitative thoracotomy for patients with suspected intraabdominal vascular injury, particularly in the pelvis, is endoluminal aortic occlusion with use of a percutaneous balloon inserted through the femoral artery.[14,15] The balloon is inflated in the distal thoracic aorta. The aortic occlusion reduces intraabdominal bleeding and facilitates resuscitation. Experimental work comparing endoluminal balloon aortic occlusion to thoracotomy with aortic clamping in a model of hemorrhagic shock showed that aortic balloon occlusion was associated with increased central perfusion pressures with less physiologic disturbance,[16] and clinical experience with this technique is rapidly increasing.

In all other patients with suspected vascular injuries, large-bone intravenous catheters should be placed in the upper extremities or the central veins of the thoracic inlet. Femoral vein catheters should be avoided in case the victim has an injury to the IVC or the iliac veins. As discussed earlier, the concept of controlled hypotension should be borne in mind, and aggressive fluid resuscitation should be avoided. Except for patients in cardiac arrest or at risk for imminent cardiac arrest, endotracheal intubation should be avoided in the emergency department because rapid sequence induction is often associated with cardiovascular decompensation.

Surgical Treatment

General Principles

All possible steps should be taken to mitigate heat loss and hypothermia. All infused fluids should be prewarmed to 40°C to 42°C, and the patient's extremities should be covered with a warming blanket. Rapid infusion devices should be ready, and the blood bank should be notified. After a vascular injury is identified, the aggressive replacement of shed blood with products in a 1:1:1 ratio directed by a massive transfusion protocol has been demonstrated to improve outcomes. The patient's entire torso, from the neck to the knees, should be prepared and draped. Although the initial incision is a full midline laparotomy, additional thoracotomy or saphenous vein harvesting may become necessary. The surgical team should be ready, and the skin preparation should be performed before induction of anesthesia because it is often associated with rapid hemodynamic decompensation in these patients.

Some surgeons have advocated a preliminary left thoracotomy and aortic cross-clamping to prevent cardiovascular collapse after anesthesia and laparotomy.[19,20] The effectiveness of this procedure has been challenged by other authors.[21] We believe that this approach should be considered only for patients at risk of imminent cardiac arrest. A thoracotomy is an additional traumatic insult that may aggravate hypothermia and coagulopathy and has little effect on the control of bleeding from major venous injuries. We advocate an immediate laparotomy, temporary control of bleeding by direct compression, and aortic cross-clamping, if necessary, at the diaphragm. In our experience, this is almost always possible, even in obese patients. To facilitate aortic exposure, division of the left crus of the diaphragm may

be necessary. In cases where a retroperitoneal hematoma extends high toward the aortic hiatus, infradiaphragmatic exposure of the aorta is difficult, and a left thoracotomy may be necessary for aortic control.

Endoluminal aortic occlusion, as described before, is promising but still underused. The use of this technique intraoperatively can reduce the need for thoracotomy for proximal vascular control. In addition, it may make the exploration of anatomically difficult, upper zone 1 hematomas safer and easier. Training of surgeons in the use of this technique may add a useful tool to the armamentarium available for the management of these complex cases.

Retroperitoneal Hematoma

The management of retroperitoneal hematomas depends on the mechanism of injury. As a general rule, almost all hematomas due to penetrating trauma should be explored, irrespective of size. Underneath a small hematoma, there is often a vascular or hollow viscus perforation. The only exception to this recommendation is a contained zone 4 retrohepatic hematoma. Surgical exploration of the retrohepatic vena cava or the hepatic veins is extremely challenging and in most cases will be detrimental because these contained venous injuries do very well with nonoperative management.

Retroperitoneal hematomas due to blunt trauma rarely require exploration because of the very low incidence of underlying vascular or hollow viscus injuries requiring surgical repair.[22] If the hematoma is in zone 1, it should be explored. However, in patients with zone 2 hematomas, surgical exploration may result in the unnecessary loss of the kidney. Similarly, exploration of a stable zone 3 hematoma due to pelvic fractures may cause severe bleeding that is uncontrollable. Exploration of zone 2 and 3 retroperitoneal hematomas should therefore be limited to patients with expanding, pulsatile, or leaking hematomas. In addition, zone 3 pelvic hematomas associated with an absent ipsilateral femoral pulse should also be explored because of the potential for an iliac artery injury. Paraduodenal hematomas also require exploration to exclude an underlying duodenal injury. Finally, hematomas at the root of the mesentery in the presence of ischemic bowel may harbor an injury to the SMA and should be explored. Exploration of these hematomas is technically difficult and potentially dangerous and should not be performed in the absence of ischemic bowel. Unexplored hematomas should be evaluated postoperatively using color-flow Doppler studies (which may be difficult because of bowel gas), CT angiography, or catheter-based angiography. With the advancement of endovascular technology and the availability of hybrid operating rooms with angio-interventional capabilities, there is now the option to perform on-table diagnostic angiography instead of opening a contained retroperitoneal hematoma. Any significant injuries may be managed endovascularly, if amenable, with stenting or embolization. This approach has the additional advantages of keeping the retroperitoneum intact, especially important in the presence of associated hollow viscus injuries.

Once the hematoma is open, in the presence of severe active bleeding, the immediate priority is to control the bleeding by direct compression. After this critical task is achieved, the next step is to identify the bleeding vessel and obtain proximal and distal control. If control is difficult or the patient is severely hypotensive, the abdominal aorta can be compressed digitally or with an aortic compressor at the aortic hiatus. After dissection of the peritoneum over the aorta and, if necessary, division of the left crus of the diaphragm (at the 2-o'clock position to avoid bleeding), the aorta can be cross-clamped. Endoluminal aortic occlusion with a percutaneously placed catheter balloon, as described before, is an attractive but still underused alternative.

The exploration of the area of bleeding or hematoma should proceed systematically. Each anatomic zone requires a different technical maneuver. Zone 1 supramesocolic bleeding or hematoma is the most difficult to approach because of the dense concentration of major vessels (aorta, celiac artery, SMA, renal vessels, IVC), the difficult exposure of many of these vessels, and the difficult proximal control of the infradiaphragmatic aorta. For some injuries, the only safe way to achieve proximal aortic control is through a left thoracotomy or with endoluminal aortic occlusion. The supramesocolic aorta, along with the origins of its major branches, is best exposed by mobilization and medial rotation of the viscera in the left upper abdomen. The first step of this approach is to divide the peritoneal reflection lateral to the left colon, the splenic flexure of the colon, and the spleen. The fundus of the stomach, spleen, tail of the pancreas, colon, and left kidney are then rotated to the right. This maneuver provides exposure of the aorta, origin of the celiac axis, SMA, and left renal vessels (Fig. 183.6). Some surgeons prefer not to include the left kidney in the medial rotation.[23] However, for injuries involving the posterior wall of the aorta, inclusion of the left kidney in the visceral rotation

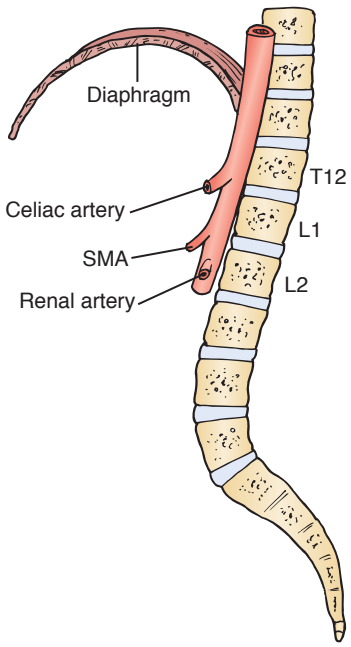

Figure 183.6 Left medial visceral rotation provides good exposure of the supramesocolic aorta and the origin of the celiac axis, superior mesenteric artery *(SMA)*, and left renal vessels.

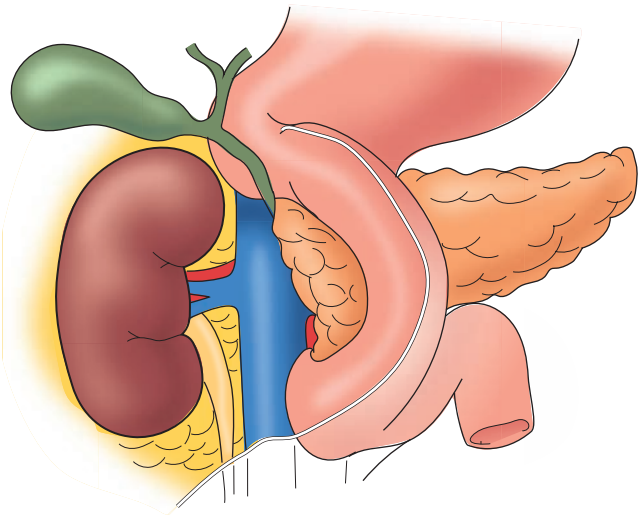

Figure 183.7 Medial visceral rotation of the right colon and hepatic flexure and Kocherization of the duodenum and pancreas provide excellent exposure of the inferior vena cava and the origins of the renal veins. (From Buckman RF, Pathak AS, Badellino MM, Bradley KM. Injuries of the inferior vena cava. *Surg Clin North Am*. 2001;81:1431-1447.)

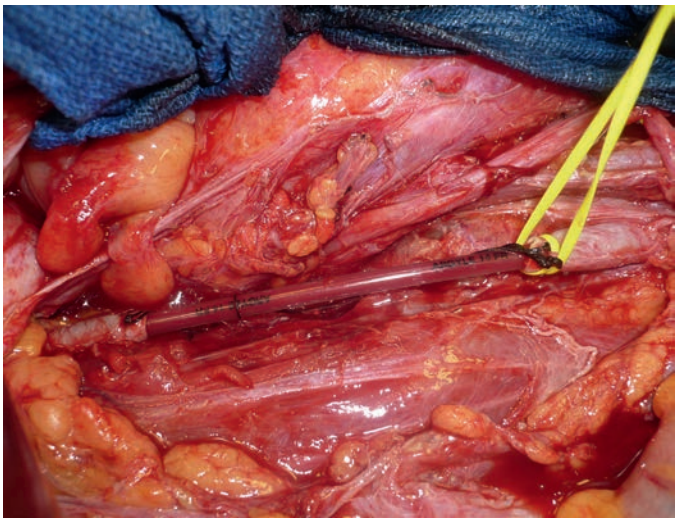

Figure 183.8 Temporary arterial shunt for damage control in a hemodynamically unstable patient with a gunshot wound and complete transection of the iliac artery.

improves the exposure. In suspected supramesocolic IVC injuries, zone 1 should be explored through a medial rotation of the right colon and hepatic flexure and Kocher mobilization of the duodenum and head of the pancreas (Fig. 183.7). The inframesocolic zone 1 area can be approached by retracting the transverse colon cephalad and displacing the small bowel to the right. The peritoneum over the aorta and IVC is then incised, and the vessels are exposed. An alternative approach is medial rotation of the right or left colon.

Zone 2 bleeding or hematoma is explored by mobilization and medial rotation of the right colon, duodenum, and head of the pancreas on the right side or the left colon on the left side. The source of bleeding in zone 2 is the renal vessels or the kidneys.

Zone 3 vessels are explored by dissection of the paracolic peritoneum and medial rotation of the right or left colon. In some cases, direct dissection of the peritoneum over the vessels can provide the necessary exposure.

The reconstruction of major vessels with synthetic grafts in the presence of intestinal spillage poses significant risks for graft infection. Copious irrigation before graft placement, use of autologous graft material whenever possible, and omental wrapping or soft tissue coverage for polytetrafluoroethylene (PTFE) grafts will reduce the risk of infection.

Damage Control Procedures

Many patients with major abdominal vascular injuries require massive blood transfusions, are hypotensive, and become severely hypothermic, acidotic, and coagulopathic intraoperatively. Persistent attempts to definitively reconstruct the injury are ill advised and will result in increased mortality. These patients should undergo early damage control and definitive reconstruction at a later stage when their physiology improves. Earlier reports recommended that damage control procedures be considered in patients in extremis who had exhausted their physiologic reserves and were in danger of irreversible shock and death. However, to be effective, damage control should not be a procedure of last resort but should be considered at a much earlier stage, before the patient becomes severely hypotensive and coagulopathic.[24] This concept is even more important in patients with major comorbidities, such as older age or chronic medical problems, and in suboptimal environments, such as small community hospitals or combat zones.

With the damage control approach, all complex venous injuries are ligated, arterial injuries are shunted,[25] and any diffuse retroperitoneal or parenchymal bleeding is controlled by tight gauze packing. If commercially produced vascular shunts are not available, temporary intraluminal shunts can be constructed from sterile intravenous or nasogastric tubing.[26] The shunt is secured with proximal and distal ligatures (Fig. 183.8). The abdomen is then closed temporarily with a prosthetic material or vacuum dressing techniques (Fig. 183.9), and the patient is transferred to the intensive care unit (ICU) for further resuscitation. The abdomen should never be closed primarily because of the very high incidence of abdominal compartment syndrome. The patient is returned to the operating room after resuscitation and stabilization for definitive vascular repair and abdominal wall closure.

Endovascular Techniques

Endovascular techniques have revolutionized the management of blunt thoracic aorta and other arterial injuries.[27] Hybrid operating rooms (Fig. 183.10) with angiographic radiology capabilities provide an opportunity to improve the management of abdominal vascular injuries by either temporary control of life-threatening bleeding or definitive care with angioembolization or stenting. In the appropriate cases the combination of endovascular adjuncts and open surgery may be lifesaving.

Figure 183.9 Temporary closure of the abdomen with the negative pressure dressing technique. After damage control procedures, the abdomen should never be closed primarily because of the risk of abdominal compartment syndrome.

Figure 183.10 Hybrid operating rooms allow combined open surgical and endovascular procedures.

The role of endovascular techniques in penetrating abdominal vascular trauma, which is almost always associated with severe active bleeding, is usually limited. However, the use of endoluminal balloons for temporary proximal aortic control can be a useful adjunct during open surgery. In addition, endovascular techniques may be the best therapeutic intervention in most cases with delayed vascular complications such as aneurysms, arteriovenous fistulae, and arterial occlusions.

Abdominal Compartment Syndrome

The normal intraabdominal pressure in the resting supine position is near zero. Elevation of the intraabdominal pressure greater than 12 mm Hg constitutes a diagnosis of intraabdominal hypertension.[28] A pressure that exceeds 20 mm Hg in addition to organ dysfunction results in abdominal compartment syndrome. Abdominal compartment syndrome is characterized by a tense abdomen, tachycardia with or without hypotension, respiratory dysfunction with high peak inspiratory and plateau pressures in mechanically ventilated patients, and oliguria. However, significant organ dysfunction may begin long before classic abdominal compartment syndrome is manifested.

All patients with severe abdominal trauma, especially vascular trauma, are at risk for development of abdominal compartment syndrome. Major risk factors include massive blood transfusions, prolonged hypotension, hypothermia, aortic cross-clamping, damage control procedures, and closure of the abdominal wall. After severe trauma, the abdomen should never be closed under tension. Similarly, after damage control procedures, the abdominal wall fascia should not be closed because progressive postoperative bowel edema will frequently result in abdominal compartment syndrome.

The diagnosis of abdominal compartment syndrome is based on clinical examination and intraabdominal pressure measurements. All high-risk patients and those in whom abdominal compartment syndrome is suspected clinically should be monitored closely with serial intraabdominal pressure measurements. The intraabdominal pressure can be measured reliably through the bladder catheter. The catheter is used to empty the bladder. Approximately 20 mL of sterile saline is injected back into the bladder to allow pressure transduction without the false elevation in pressure expected from bladder wall tension in a full bladder. The pressure is then measured through the catheter by either a simple water column or a commercial pressure transduction device. Definitive management requires surgical decompression. In general, pressures higher than 20 to 30 mm Hg are considered strong indicators for surgical decompression of the abdomen. If organ dysfunction is present, the pressure threshold may be lower. The abdomen can be opened in the operating room or even in the ICU if necessary. Temporary abdominal wall closure can be achieved with the use of a commercially available vacuum closure device, or a sterile x-ray cassette cover, laparotomy sponges, closed suction drains, and sticky drapes can be used to accomplish temporary coverage (see Fig. 183.9). When the bowel edema improves, usually within 2 to 3 days, the patient is returned to the operating room for definitive abdominal wall closure.

SPECIFIC VASCULAR INJURIES

Abdominal Aorta Injuries

Anatomy

The aorta descends into the retroperitoneum between the two crura of the diaphragm at the T12-L1 level and bifurcates into the common iliac arteries at the L4-L5 level, which approximately corresponds to the level of the umbilicus. The first branches of the abdominal aorta are the phrenic arteries that originate from its anterolateral surface. Immediately below is the celiac trunk that originates from the anterior surface of the aorta, and 1 to 2 cm below that is the SMA, followed by the renal arteries 1 to 1.5 cm below the origin of the SMA and finally, the inferior mesenteric artery (IMA), 2 to 5 cm above the bifurcation.

Mechanism of Injury

Blunt injury to the abdominal aorta is extremely rare, diagnosed in 0.04% of all blunt trauma admissions.[29] Fractures of the thoracolumbar spine and seat belt injuries are associated with an increased risk of abdominal aortic injuries.[29,30] Intimal dissection and thrombosis are the most common lesions in patients reaching the hospital alive. False aneurysms occur less frequently. Patients with free ruptures die at the scene and rarely receive medical care.[30,31] In a review of 28 cases with blunt abdominal aortic injuries, intimal tears or large intimal flaps were the most common lesion (60%), followed by free rupture (30%) and pseudoaneurysm (10%).[32]

Penetrating injuries are by far the most common cause of abdominal aortic injuries. In a review of 1218 patients with abdominal gunshot injuries from our center, there were 33 abdominal aortic injuries (2.7%). In 529 knife wounds to the abdomen, the aorta was injured in 1.5%.[33] The infrarenal aorta is injured in 50% of patients, the supraceliac aorta in 25%, and the aorta between the celiac trunk and the renal arteries in 25% of patients.[34]

Clinical Presentation

The clinical presentation depends on the mechanism of injury (blunt or penetrating), type of aortic injury, presence of free intraperitoneal bleeding or retroperitoneal hematoma, associated injuries, and time elapsed since the injury. In blunt trauma, two-thirds of patients have acute symptoms of bleeding or visceral or lower extremity ischemia. The diagnosis is made during the initial hospitalization by means of CT or angiography or at laparotomy. In one-third of cases the diagnosis is made many months or even years after the injury.[29-31]

The clinical presentation of penetrating aortic injuries is usually dramatic. Many victims die at the scene. Of those who are treated, approximately 28% have an unrecordable blood pressure, and approximately 21% require a resuscitative thoracotomy.[33] In approximately 18% of cases the bleeding is temporarily contained in the retroperitoneum and the patients are normotensive on admission.[34] On rare occasions the injury is missed at operation only to manifest at a later date as a false aneurysm or arteriovenous fistula (see Fig. 183.4).

Management

Almost all patients with penetrating aortic injuries require open repair. In blunt trauma the management depends on the location and type of the injury. Many patients with small intimal tears can safely be managed nonoperatively. More severe blunt injuries with free rupture or large intimal flaps require open or endovascular repair.[32] In a National Trauma Data Bank analysis of 436 patients with blunt abdominal aortic injuries, 394 patients (90%) were managed nonoperatively and 29 (7%) underwent endovascular repair, with only 13 patients (3%) undergoing open aortic repair or extraanatomic bypass.[35]

Endovascular Treatment

Endovascular management has a definitive role in selected cases of infrarenal aortic injury. Patients with limited infrarenal aortic dissection, large intimal flaps, false aneurysms, or aortocaval fistulae have been treated successfully with angiographically placed stents.[36,37]

Surgical Treatment

The surgical exposure of the vascular structures in zone 1 is achieved by medial visceral rotation, as described in the section on retroperitoneal hematoma (see Fig. 183.6). For high supramesocolic injuries, a left thoracotomy may be necessary for cross-clamping of the aorta. Approximately 93% of patients with penetrating trauma have other associated intraabdominal injuries, the most common being injuries to the small bowel (45%), colon (30%), and liver (28%).[33] Before any definitive management that requires a prosthetic graft, all enteric spillage should be controlled and the peritoneum should be washed out. Lateral aortorrhaphy is possible in most cases. More complex repairs with prosthetic grafts may be necessary.[38] Many authors do not consider the presence of enteric spillage a contraindication to the use of prosthetic material.[38]

Mortality

The prognosis of abdominal aortic injuries after blunt trauma is significantly better than that of injuries due to penetrating trauma. The reported overall mortality in blunt trauma is approximately 30%.[35]

The mortality after penetrating trauma in two large series with 146 patients was 67%.[33,38] In another series of 57 patients with gunshot wounds, the mortality rate was 85%.[39] Suprarenal aortic injuries have a significantly worse outcome than infrarenal injuries.[34] The mortality in patients undergoing emergency center resuscitative thoracotomy is almost 100%.[33,34] The prognosis of penetrating abdominal aortic injuries is significantly better than that of injuries to the thoracic aorta, most likely owing to the retroperitoneal containment of bleeding in abdominal injuries. In a comparison of 67 abdominal aortic injuries with 26 thoracic aortic injuries, the mortality rates were 76% and 92%, respectively.[33]

Celiac Artery Injuries

Anatomy

The celiac artery originates from the anterior wall of the abdominal aorta, immediately below the aortic hiatus, at the level of T12-L1 (see Fig. 183.6). The main trunk is 1 to 1.5 cm long, and at the upper border of the pancreas it has three branches (the tripod of Haller): the common hepatic artery, left gastric artery, and splenic artery. Because of the extensive fibrous, ganglionic, and lymphatic tissues that surround the trunk, surgical dissection may be tedious.

Mechanism of Injury

Injuries to the celiac artery are rare and almost always due to penetrating trauma. In a review of 302 abdominal vascular injuries, the celiac artery was involved in 10 cases (3.3%).[1]

Surgical Treatment

The surgical exposure can be achieved either by direct dissection over the upper abdominal aorta through the lesser sac or by medial rotation of the upper abdominal viscera, as described previously. The rotation does not need to include the left kidney. The celiac artery can be ligated without ischemic sequelae to the stomach, liver, or spleen because of the rich collateral circulation of these organs. The left gastric and splenic arteries may also be ligated with impunity. Ligation of the common hepatic artery is usually well tolerated because of adequate supply from the portal vein and the gastroduodenal artery.

Mortality

The reported mortality rate of celiac artery injuries ranges from 38% to 75%.[40] However, among the 50 collectively reported cases of celiac artery injuries, most patients had other vascular injuries that contributed to the high mortality.

Superior Mesenteric Artery Injuries

Anatomy

The SMA originates from the anterior surface of the aorta, immediately below the celiac artery, behind the pancreas at the L1 level (see Fig. 183.6). It then proceeds over the uncinate process of the pancreas and the third part of the duodenum and enters the root of the mesentery. The SMA has the following branches: inferior pancreaticoduodenal artery, middle colic artery, arterial arcade with 12 to 18 intestinal branches, right colic artery, and ileocolic artery. SMA injuries are divided into four zones[41]:

- Zone 1, between the aortic origin and the inferior pancreaticoduodenal artery.
- Zone 2, between the inferior pancreaticoduodenal artery and the middle colic artery.
- Zone 3, distal to the middle colic artery.
- Zone 4, the segmental intestinal branches.

As a general rule, ligation of the SMA in zones 1 and 2 results in severe ischemia of the small bowel and right colon. Ligation of zones 3 and 4 may result in localized ischemia of the small bowel requiring segmental resection.

Mechanism of Injury

The SMA is second to the renovascular system as the most commonly injured abdominal vessel after blunt trauma. Blunt trauma is responsible for between 10% and 20% of all SMA injuries[42,43] and can cause thrombosis of the artery by a direct blow, crushing of the abdomen, or seat belt injuries. Deceleration injuries may cause avulsion of the vessel from its origin in the aorta or intimal tear and subsequent thrombosis. Penetrating injuries are the most common mechanism of injury. Because of the anatomic location of the artery, multiple significant associated injuries are common.[44]

Clinical Presentation

The clinical presentation depends on the mechanism of injury, nature of the vascular injury, presence of associated intraabdominal injuries, and time elapsed since injury. Isolated thrombosis of the SMA due to blunt trauma may be missed during the initial evaluation, only to manifest at a later stage with bowel necrosis. Most patients with penetrating trauma present in severe shock. Patients with contained hematomas may be normotensive or mildly hypotensive on admission.

Surgical Treatment

The operative findings may include various degrees of hemoperitoneum, hematoma around the SMA, ischemic bowel, or any combination of these (Fig. 183.11).

After temporary control of the bleeding by direct compression and, if necessary, cross-clamping of the aorta, the SMA should be explored.

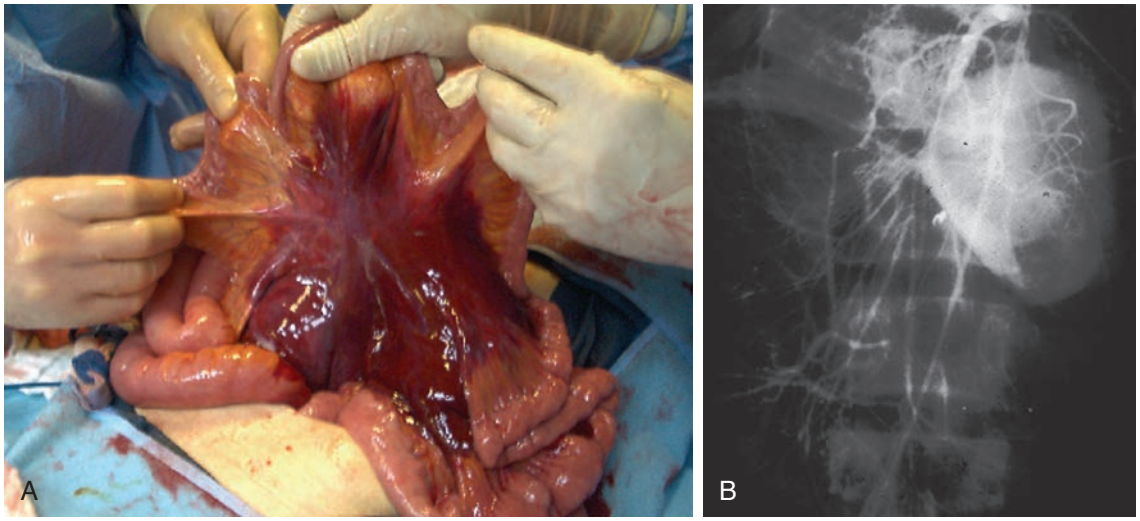

Figure 183.11 (A) Traffic accident victim with a large hematoma at the base of the mesentery found at laparotomy. This is suggestive of a superior mesenteric artery (SMA) injury and needs to be evaluated by angiography, preferably postoperatively. (B) Postoperative angiography shows a large SMA false aneurysm.

Exposure

Exposure of the retropancreatic SMA can be achieved by medial rotation of the left colon, gastric fundus, spleen, and tail of the pancreas, as described earlier. The kidney does not need to be rotated unless injury to the posterior wall of the aorta is suspected. In cases of severe bleeding when immediate exposure is critical, stapled division of the neck of the pancreas may provide fast and direct exposure of the SMA and the portal vein. Exposure of the infrapancreatic SMA can be achieved by cephalad retraction of the inferior border of the pancreas and direct dissection, or it can be achieved through the root of the small bowel mesentery by incising and dissecting the tissues to the left of the ligament of Treitz. An extensive Kocher maneuver may be required to expose this segment of the SMA. More distal sections of the SMA can be approached directly.

Exploration of a hematoma at the root of the mesentery is always a difficult and potentially dangerous task, even in the hands of experienced surgeons. In penetrating trauma or blunt trauma with ischemic bowel, all hematomas around the SMA should be explored. However, it is our practice and recommendation not to explore stable hematomas after blunt trauma in the absence of bowel ischemia. In these patients the SMA is evaluated postoperatively by means of angiography or CT angiography (see Fig. 183.11B).

Operative Management

Sharp partial transections of the SMA, such as those inflicted by knife wounds, can be managed by lateral arteriorrhaphy with 6-0 vascular sutures. This approach is possible in approximately 40% of cases.[45] Because mobilization of the SMA is restricted by the surrounding dense neuroganglionic tissue and its multiple branches, an end-to-end anastomosis is rarely possible.

Depending on the site of SMA injury, the condition of the patient, and the color of the bowel, these injuries can be managed by ligation or an interposition graft. Ligation of the SMA distal to the middle colic artery is associated with a moderate risk of bowel ischemia. Ligation of the proximal SMA results in ischemic necrosis involving the small bowel and the right colon. The first 10 to 20 cm of the jejunum may survive through collaterals from the superior pancreaticoduodenal artery. Ligation of the SMA proximal to the origin of the inferior pancreaticoduodenal artery may preserve critical collateral circulation to the proximal jejunum and is preferable to a more distal ligation. Ligation of the proximal SMA should be performed only in the presence of necrotic bowel. Ligation should be avoided in all other circumstances because of the catastrophic consequences of short bowel syndrome. In patients in critical condition with severe hypothermia, acidosis, and coagulopathy, a damage control procedure with a temporary endoluminal shunt should be considered.[46]

Definitive reconstruction is performed at a later stage after resuscitation and normalization of the patient's physiologic parameters. The reconstruction can be performed with a saphenous vein or PTFE graft between the distal stump of the SMA and the anterior surface of the aorta. In the presence of an associated pancreatic injury, the vascular anastomosis should be performed away from the pancreas, and every effort should be made to protect it from pancreatic enzymes by use of omentum and surrounding soft tissues (Fig. 183.12).

Postoperative Considerations

Postoperatively, the patient should be monitored closely for any signs of bowel ischemia. The threshold for second-look laparotomy within the first 24 hours of operation should be low. Failure to improve postoperatively and the persistence of metabolic acidosis despite adequate fluid resuscitation should prompt re-exploration of the abdomen to rule out bowel ischemia. Some authors practice mandatory second-look laparotomy. Damage control techniques allow inspection of the bowel through the transparent material used for temporary closure of the abdomen.

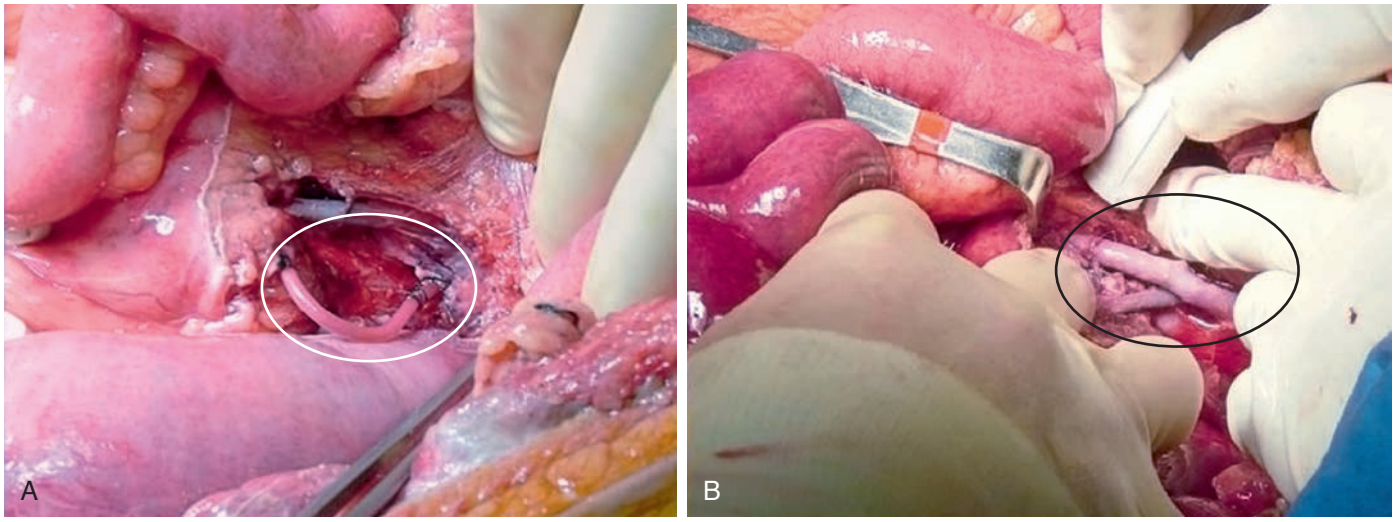

Figure 183.12 (A) Damage control with a temporary endoluminal shunt *(circle)* of the superior mesenteric artery. (B) Definitive reconstruction with a saphenous vein graft *(circle)* 18 hours later.

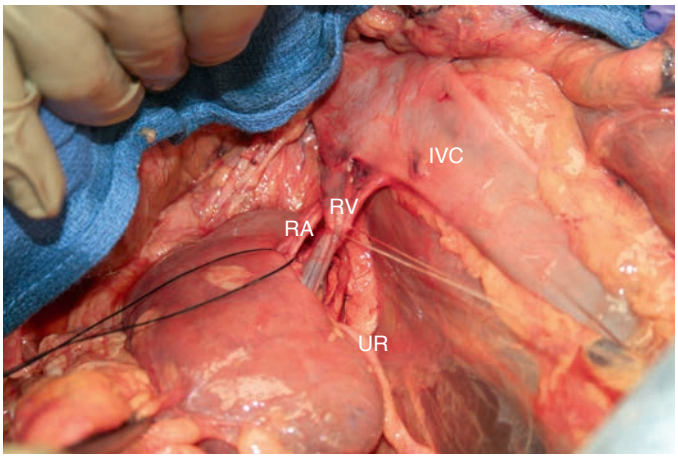

Figure 183.13 Anatomy of the Hilum of the Right Kidney. Note the position of the renal artery *(RA, black ligature)* behind the renal vein *(RV, white ligature)* and inferior vena cava *(IVC)*. *UR*, Ureter.

Figure 183.14 Angiography shows an intimal tear of the right renal artery *(circle)* due to a fall from a height. Management with an endovascular stent was successful.

Mortality

The mortality directly related to SMA injuries is difficult to assess because most patients have multiple severe injuries, including other major vascular injuries. The reported mortality varies from 33% to 68%.[42,43,45,47]

Renovascular Injuries

Anatomy

The renal arteries originate from the aorta at the L2 level (see Fig. 183.6). The right renal artery emerges at a slightly higher level and is longer than the left and courses under the IVC. Approximately 30% of the population has more than one renal artery, often an accessory one to the lower pole of the kidney. The renal veins lie in front of the renal arteries (Fig. 183.13). The left renal vein is significantly longer than the right and courses in front of the aorta. It has collateral branches from the left gonadal vein inferiorly, the left adrenal vein superiorly, and a descending lumbar vein posteriorly.

Mechanism of Injury

Renal artery injuries account for approximately 0.05% of all blunt trauma admissions.[48] The left renal artery is 1.3 to 1.6 times more likely to be injured than the right renal artery.[48,49] It has been suggested that the right renal artery is protected from deceleration injuries because of its course underneath the IVC.[50] Rapid deceleration accidents may cause intimal tears and subsequent arterial thrombosis at a later stage. In approximately 50% of cases with blunt renal artery injury, there is thrombosis or an intimal flap (Fig. 183.14; see also Fig. 183.3B). Avulsion of the artery occurs in 12% of cases.[51] In 9% to 14% of renovascular injuries, the renal artery is involved bilaterally.[49,51]

Clinical Presentation

The diagnosis of renovascular injury after penetrating trauma is almost always made intraoperatively. However, in blunt trauma, the diagnosis is usually made during routine CT evaluation of the abdomen (Fig. 183.15; see also Fig. 183.3). The clinical presentation is subtle and nondiagnostic, and the diagnosis is often delayed. In earlier reports, when CT evaluation of the abdomen was not as common, up to 50% of patients did not receive timely treatment because of delayed diagnosis.[51] Abdominal contrast-enhanced CT is highly sensitive in diagnosing renovascular trauma and should be the first line investigation (see Fig. 183.3).[52] In addition, CT provides useful information about associated injuries.

Endovascular Treatment

Endovascular treatment may play an important role in selected cases of blunt renovascular trauma, and it should be considered the first-line therapeutic option in patients in stable condition with intimal tears, acute occlusions, false aneurysms, and arteriovenous fistulae (see Fig. 183.15). The experience with this technique is still limited, and the follow-up is short. However, it is very promising and most likely will increase the number of patients undergoing revascularization.[53-55] In a National Trauma Data Bank study covering the period 1993–2001, none of the 517 blunt renal artery injuries were managed with endovascular techniques.[48] In a more recent study from the same data bank, covering the period 2004–09, only 3.2% were managed with endovascular stenting.[56] This reluctance to pursue endovascular treatment might be due in part to the frequently delayed diagnosis, which is considered by many surgeons a contraindication for revascularization.

Surgical Treatment

The management of renovascular injuries depends on the mechanism of injury, time of diagnosis, ischemia time, general condition of the patient, and presence of a contralateral normal kidney. In penetrating injuries the diagnosis is almost always made early during exploratory laparotomy, and depending on the extent of the injury and the condition of the victim, reconstruction of the vessels or nephrectomy is performed.

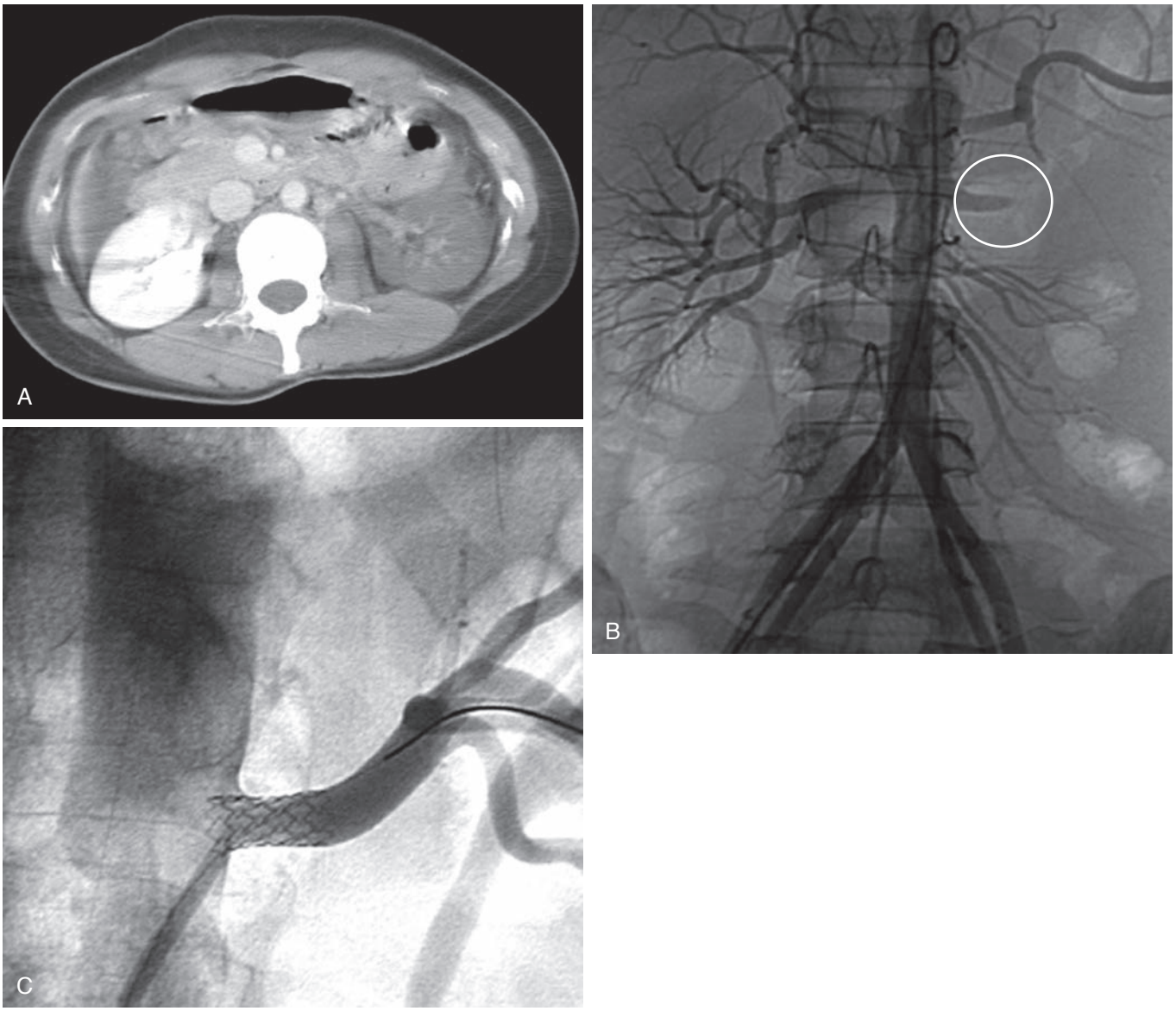

Figure 183.15 (A) Computed tomography scan shows a nonfunctioning left kidney after a traffic injury. (B) Angiography shows complete thrombosis of the renal artery *(circle)*. (C) Revascularization with an angiographically placed endovascular stent.

Revascularization

As a general rule, all zone 2 hematomas resulting from penetrating trauma should be explored. The only exception may be a stable perinephric hematoma away from the hilum.[57] However, in blunt trauma the management of renal artery injuries is complicated by the often-delayed diagnosis and prolonged ischemia of the kidney. Renal function is severely affected after 3 hours of total ischemia and 6 hours of partial ischemia, although with collateral circulation from the renal capsule or surrounding soft tissues, kidney function may be preserved despite prolonged ischemia.[52]

In stable patients diagnosed with renovascular trauma within 4 to 6 hours of injury, the general recommendation is revascularization.[52,58] However, revascularization is rarely performed, even in patients with no other injuries. In a study based on the National Trauma Data Bank, which is maintained by the Committee on Trauma of the American College of Surgeons, only 9% of the 517 patients with renal artery injury due to blunt trauma underwent revascularization. Of the remaining cases, 73% had no kidney exploration, and 18% underwent immediate nephrectomy. In the group of 87 patients with isolated renal artery injuries, 8% underwent revascularization, 8% had early nephrectomy, and 84% were observed. Multiple regression analysis adjusting for age, Injury Severity Score, and severe associated injuries showed that patients treated with revascularization had a significantly longer ICU and hospital stay than observed patients did.[48] In patients with bilateral injuries or injury to a solitary kidney, some authors recommend revascularization even up to 20 hours after the injury.[58] However, most surgeons will avoid revascularization in patients diagnosed more than 6 hours after trauma, unless the injury involves both kidneys

or a solitary kidney. The results after revascularization are generally disappointing, and successful surgical revascularization has been reported mainly by surgeons with extensive experience in renovascular surgery. The cumulative success rate of revascularization is 28%.[49] Even after successful revascularization, subsequent hypertension develops in 12% to 57% of patients, and most require elective nephrectomy.[49,58,59] The overall poor long-term results have led some authors to suggest that revascularization should be considered only in patients with bilateral renal artery occlusion or those with injury to a solitary kidney.[49,58]

Nonoperative management is certainly an acceptable option, especially in patients with delayed diagnosis, those with other major extraabdominal injuries or significant hemodynamic instability, and those with a contralateral normally functioning kidney. In a National Trauma Data Bank review of 778 cases with blunt renal artery injuries, most patients (62%) were managed without any intervention. Of patients managed nonoperatively, 32% to 40% develop renovascular hypertension.[49,51,56,58] In most patients the hypertension develops within 1 year of the injury, with a mean of approximately 3 months.[49]

The advancement of endovascular techniques has opened new horizons in the management of these injuries. We recommend liberal revascularization with endovascular techniques because of the safety of this approach and the potential for renal salvage even after prolonged ischemia. Even if late hypertension develops, medical management and nephrectomy are effective ways to address this problem. If stenting is not possible, we advocate observation and long-term monitoring for hypertension. Surgical revascularization should be considered only in renovascular injuries diagnosed intraoperatively, provided the patient's condition is stable enough to tolerate the procedure, or in the rare case of bilateral injuries or injury to a solitary kidney.

Surgical Reconstruction

Surgical reconstruction of a renal artery injury can be achieved by simple arteriorrhaphy, vein patch, resection and anastomosis, and interposition grafting. For complex, time-consuming arterial reconstructions, the kidney should be perfused intermittently with iced heparinized lactated Ringer solution or University of Wisconsin solution. Postrevascularization administration of mannitol may improve the parenchymal blood flow and alleviate the reperfusion injury.

Venous Injuries

Renal vein injuries can be managed by lateral venorrhaphy if feasible. Extensive injuries should be managed by ligation. Complex reconstruction, especially in a hemodynamically unstable patient, should be avoided. Ligation of the left renal vein near the IVC is well tolerated because of venous drainage through the left gonadal vein, left adrenal vein, and lumbar veins.

Mortality

The true mortality rate of renovascular injuries is difficult to estimate because there are other major injuries in most cases. The reported mortality rate varies from 0% to 57%.[52] The mortality in renovascular injuries due to blunt trauma is low because of the occlusive nature of most arterial injuries.[48]

Inferior Mesenteric Artery Injuries

Anatomy

The IMA originates from the anterior surface of the aorta 3 to 4 cm above the aortic bifurcation. It provides blood supply to the left colon, sigmoid, and upper part of the rectum. It communicates with the SMA through the marginal artery of Drummond.

Mechanism of Injury

Injuries of the IMA are rare. They are almost always due to penetrating trauma and account for 1% of all abdominal vascular injuries.[1]

Surgical Treatment

The diagnosis of IMA injury is made intraoperatively. Ligation is well tolerated, and no cases of colorectal ischemia have been reported in trauma cases.

Iliac Vascular Injuries

Anatomy

The abdominal aorta bifurcates into the two common iliac arteries at the L4-L5 level. The common iliac arteries divide into the external and internal iliac arteries over the sacroiliac joint. The ureter crosses over the bifurcation of the common iliac artery.

The common iliac veins join at the L5 level, below the level of the aortic bifurcation and underneath the right common iliac artery, to form the IVC (Fig. 183.16).

Mechanism of Injury

Penetrating trauma is by far the most common cause of iliac vascular injuries. Approximately 10% of patients who undergo laparotomy for gunshot wounds and 2% of patients with laparotomies due to stab wounds have iliac vascular injuries.[60] Injury

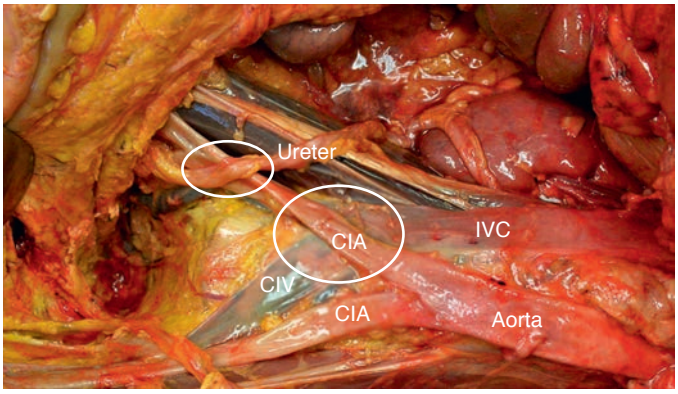

Figure 183.16 Anatomy of the Iliac Vessels. Note the confluence of the two common iliac veins *(CIVs)* behind the proximal right common iliac artery *(CIA, large circle)*. Also note the position of the ureter over the bifurcation of the common iliac artery *(small circle)*. *IVC*, Inferior vena cava.

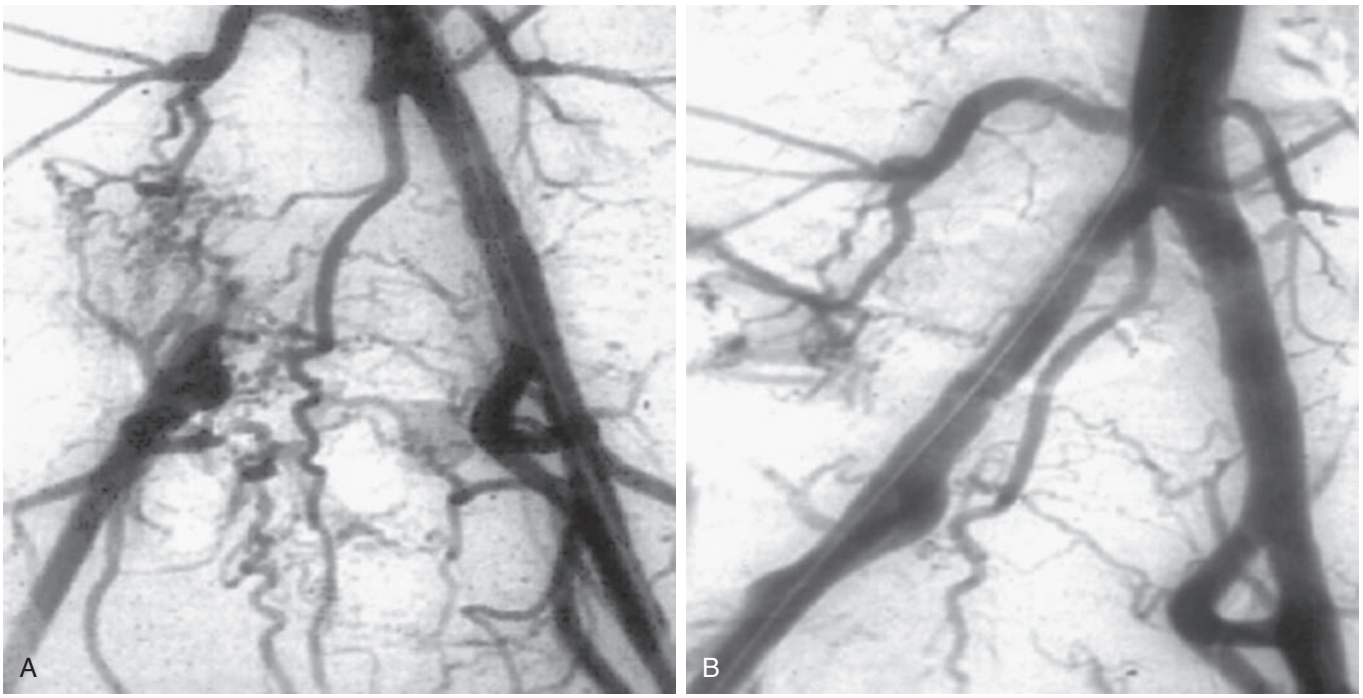

Figure 183.17 (A) Right common iliac artery thrombosis in a 16-year-old patient diagnosed many months after a motor vehicle accident. (B) Management with an endovascular stent was successful.

to the common or external iliac artery due to blunt trauma is not common, although there are many case reports. Direct laceration of the iliac vessels from a pelvic fracture or stretching of the iliac artery over the pelvic wall, resulting in intimal tear and subsequent thrombosis, is the usual mechanism of injury after blunt trauma (see Fig. 183.5).[61] Approximately 26% of patients with iliac vascular injuries have combined arterial and venous injuries.[60] Penetrating injuries usually involve the common iliac vessels, whereas blunt trauma usually affects branches of the internal iliac artery.

Clinical Presentation

The presence of a penetrating injury in the lower abdomen associated with severe hypotension and abdominal distention is highly suggestive of iliac vascular injuries. An absent or diminished femoral pulse in a patient with penetrating abdominal trauma or pelvic fracture is diagnostic of an injury to the common or external iliac artery. In rare cases of blunt trauma, thrombosis of the iliac artery may not be diagnosed during the initial workup because of the subtle clinical symptoms. In blunt trauma the diagnosis modality of choice is CT angiography.

Endovascular Treatment

Endovascular techniques may play an important role in selected cases of iliac artery injury, especially after blunt trauma. Patients with false aneurysms, arteriovenous fistulae, or large intimal tears with or without thrombosis may benefit from angiographically placed endovascular stents (Fig. 183.17).[62,63] Because of its safety and low complication rate, this should be the first line therapeutic option in elective cases in patients with subacute or chronic traumatic lesions of the common or external iliac arteries.

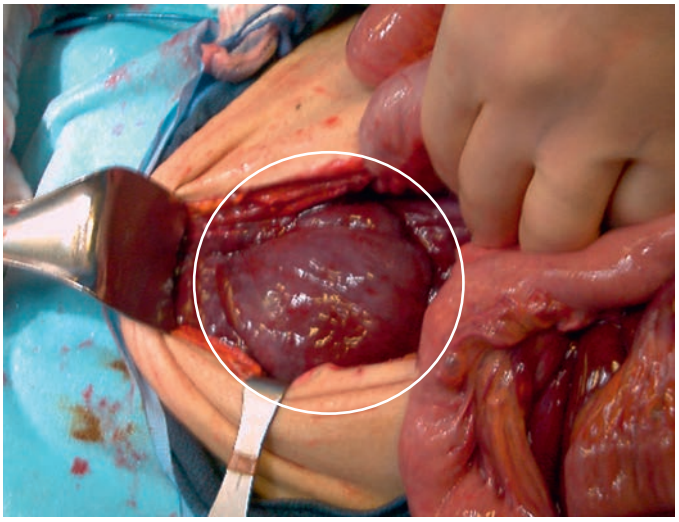

Figure 183.18 Large hematoma in the pelvis *(circle)* after a gunshot wound. This is highly suggestive of an iliac vascular injury, and proximal control should be obtained as soon as possible.

Surgical Treatment

Exposure

The operative findings may include free intraperitoneal bleeding, a zone 3 pelvic hematoma, or a combination of the two (Fig. 183.18). Zone 3 hematomas due to blunt trauma should be explored only if there is associated intraperitoneal leak, if they are expanding rapidly, or if there is an absent or diminished femoral pulse. In penetrating trauma, all hematomas should be explored. Any active bleeding is initially exposed by direct dissection of the overlying peritoneum, although medial rotation

of the right or left colon may provide better exposure. The ureter, which crosses over the bifurcation of the common iliac artery, should be identified and protected during the dissection. In addition, care should be taken to avoid iatrogenic injury to the iliac veins that lie directly under the arteries. Isolation and control of the internal iliac artery are essential in arterial injuries because bleeding may persist despite proximal and distal control. If exposure of the distal iliac vessels is difficult, especially in male patients with a narrow pelvis, extension of the midline incision by adding a transverse lower abdominal incision or longitudinal incision through the inguinal ligament may be necessary.[60]

Arterial Injuries

Small arterial injuries can be repaired with 4-0 or 5-0 vascular sutures, with care taken to avoid significant stenosis of the vessel. If necessary, a vein or PTFE patch can be used to avoid stenosis. In most gunshot injuries and in all patients with blunt trauma, reconstruction by an end-to-end anastomosis or with a prosthetic graft (6 to 8 mm) is usually necessary. Local heparin solution should be administered to prevent thrombosis during the repair. The need for systemic anticoagulation intraoperatively remains debated; however, it should not be used if there are concomitant injuries such as a traumatic brain injury. A balloon-tipped catheter should always be passed proximally and distally to remove any clots. Complex arterial reconstructions with an extraanatomic bypass or with a mobilized internal iliac artery have little or no role in the acute management of trauma. Extraanatomic bypass should be considered only in late cases with severe purulent peritonitis or infected grafts. There is evidence that the presence of enteric contamination is not a contraindication to synthetic graft use.[64] However, many vascular surgeons still recommend that an extraanatomic bypass be considered in the presence of significant enteric contamination. If prosthetic material is used, it is important that any enteric spillage be controlled and that the peritoneal cavity be meticulously cleaned before prosthetic graft repair.

It is the authors' opinion that ligation of the common or external iliac arteries should never be performed, even for damage control in patients in critical condition. Ligation is poorly tolerated by most patients and is associated with a high incidence of limb loss, and subsequent attempts to revascularize the leg may cause severe reperfusion injury and organ failure or death. In patients who need damage control, flow can be restored with a temporary intraluminal shunt (see Fig. 183.8); definitive reconstruction of the vessel is performed at a later stage when the patient's condition has stabilized.

Venous Injuries

Iliac venous injuries can be technically more challenging than arterial injuries because of the difficult exposure caused by their location behind the arteries (see Fig. 183.16). This problem is even more difficult on the right side because of the location of the right common iliac artery and the confluence of the two common iliac veins behind the right common iliac artery. Despite these difficulties, the recommendation to transect the iliac artery to access the underlying vein[65] is extreme and should not be performed. In most cases, careful mobilization and retraction of the artery provides satisfactory exposure of the vein. Ligation and division of the internal iliac artery may be helpful in providing better exposure. Repair of the iliac veins by means of lateral venorrhaphy should be considered only if it can be performed without producing major stenosis. Ligation is generally preferable to a repair that produces severe stenosis because of the risk of thrombosis and pulmonary embolism.[60] Complex reconstruction with spiral grafts or prosthetic materials, especially in a critically ill patient, is not recommended. Ligation is usually well tolerated, although patients may develop transient leg edema. On rare occasion, ligation results in massive edema of the leg and compartment syndrome that requires fasciotomy. The management of iliac venous injuries in the presence of associated iliac artery injuries is even more controversial. We do not recommend complex venous reconstruction because patients with combined arterial and venous injuries are invariably in extremely critical condition, and any procedures that prolong the operation or increase blood loss should be avoided. However, many authors recommend venous reconstruction with patch venoplasty or PTFE grafts, although there is no evidence of improved outcome with this approach.

Compartment Syndrome

Many patients with iliac vascular injuries develop extremity compartment syndrome. In this case, fasciotomy should be performed without delay, often before arterial reconstruction. However, the role of prophylactic fasciotomy is controversial and has been challenged by many authors. Prophylactic fasciotomy is a major procedure that is often associated with increased bleeding due to coagulopathy and increased venous pressures.[66,67] If fasciotomy is not performed, the patient should be monitored closely with frequent clinical examinations and compartment pressure measurements. Fasciotomy should be performed at the first signs of compartment syndrome.[60] Perioperative administration of mannitol may play a beneficial role in reducing the effects of reperfusion injury and inhibiting the development of compartment syndrome and the need for fasciotomy.[67,68]

Mortality

The reported overall mortality varies from 30% to 50% in arterial injuries and 25% to 40% in venous injuries. In isolated iliac vascular injuries, the mortality is approximately 20% for arterial injuries and approximately 10% for venous injuries.[60]

Inferior Vena Cava Injuries

Anatomy

The IVC is formed by the confluence of the two common iliac veins in front of the L5 vertebra and underneath the right common iliac artery. It ascends over the spine to the right of the aorta; at the level of the renal veins it deviates farther to the right, courses behind the liver, crosses the diaphragm, and, after a short course of 2 to 3 cm in the chest, drains into the right atrium of the heart. In its course, the IVC receives four or five pairs of lumbar veins, the right gonadal vein, the renal veins, the right adrenal vein, the hepatic veins, and the phrenic

veins. All lumbar veins are below the renal veins, and except for the right adrenal vein, there are no other venous branches between the renal veins and hepatic veins. Besides the three major hepatic veins, there are six to eight accessory veins inferiorly. Some of the accessory veins are large and may bleed profusely in the case of injury or iatrogenic avulsion.

Mechanism of Injury

The IVC is the most commonly injured abdominal vessel and accounts for approximately 25% of abdominal vascular injuries.[1] Blunt trauma is responsible for approximately 10% of IVC injuries, and it usually involves the retrohepatic segment of the vein.[69] In approximately 18% of patients with penetrating IVC injuries, there is an associated aortic injury.[70]

Clinical Presentation

More than half the patients with IVC injuries who reach the hospital alive are hypotensive, and approximately 18% require emergency thoracotomy.[70,71] Many patients with contained hematomas may be hemodynamically stable on admission. The diagnosis is almost always made intraoperatively.

Surgical Exposure

Many injuries to the IVC, especially those involving the infrarenal IVC, present with stable hematomas because of the low existing pressures within the IVC. As a rule, all hematomas due to penetrating trauma should be explored. An exception to this approach is the stable retrohepatic hematoma. Exploration of these hematomas is extremely difficult and may lead to uncontrollable hemorrhage and death. The infrarenal and juxtarenal IVC are best exposed by mobilization and medial rotation of the right colon, the hepatic flexure of the colon, and the duodenum (see Fig. 183.7). Exposure of the retrohepatic IVC is technically challenging and usually requires extensive mobilization of the liver by dividing its ligaments and extending the incision to include a right subcostal incision, right thoracotomy, or sternotomy. In our experience, addition of a subcostal incision provides excellent exposure and is the preferred initial step. If this is insufficient to allow access to the injury, a median sternotomy is performed. This provides excellent exposure to the injured structures, and if total hepatic vascular occlusion or an atriocaval shunt is required, it allows access to the right atrium as well as the suprahepatic vena cava. Alternatively, if the patient already has a right thoracotomy, connecting this incision to the laparotomy and incising the diaphragm circumferentially, leaving sufficient cuff for reconstruction, allows excellent exposure to all of these structures. These additional incisions should be considered only if perihepatic packing is not effective in controlling the hemorrhage. In cases in which packing is not effective and the additional incisions are not sufficient for adequate visualization and repair of the IVC or hepatic veins, more radical maneuvers including hepatic vascular isolation, an atriocaval shunt, or division of the liver should be considered.

Hepatic Vascular Isolation

Hepatic vascular isolation involves cross-clamping of the infradiaphragmatic aorta, suprahepatic IVC, infrahepatic IVC above the renal veins, and portal triad. Failure to clamp the aorta as a first step may result in severe hypotension and possible cardiac arrest due to the reduced venous return after occlusion of the IVC. The suprarenal IVC can be cross-clamped in the space between the superior surface of the liver and the diaphragm. However, with a juxtahepatic venous injury, this maneuver may worsen the injury if it is done incorrectly. As discussed previously, accessing the suprahepatic IVC through a sternotomy or right thoracotomy[71] may be preferable because this will also improve exposure of the injury, facilitating what is under even the best of conditions a challenging repair. Even with hepatic vascular isolation, some backbleeding can be anticipated.

Atriocaval Shunt

The atriocaval shunt requires placing a tube through a purse-string suture in the appendage of the right atrium and directing it into the IVC, distal to the caval injury. Tourniquets should be applied around the intrapericardial IVC and the suprarenal IVC.[72] A large-bore thoracostomy tube or a large endotracheal tube with clamp occlusion of the proximal end and one or two holes created to correspond to the endoatrial part of the tube can be used as a shunt. If an endotracheal tube is used, the inflated balloon can replace a tourniquet around the suprarenal IVC (Fig. 183.19). This is preferable to dissection around the IVC for tourniquet placement. Although numerous reports have highlighted the extremely poor results with atriocaval shunts, in our experience, patients have survived when the shunt was used early. This approach entails a major escalation of the operation, but in appropriate cases, it should be used early in the operation.

Division of the Liver

Another option is to divide the liver along the gallbladder-IVC plane to provide direct exposure to the IVC. This approach increases bleeding, especially in an already coagulopathic patient, and should be avoided except when the liver is already severely injured and the IVC can be exposed with minimal dissection.

Surgical Options

In most patients the IVC can be repaired by lateral venorrhaphy with 3-0 or 4-0 vascular suture material (Fig. 183.20). Most posterior caval wounds can be exposed and repaired by rotating the IVC. In some patients with anterior and posterior caval injuries, the posterior wound can be exposed and repaired from within the vein by extending the anterior wound. Ligation of the vein should be considered in hemodynamically unstable patients with severe infrarenal injuries or when repair produces major stenosis. Ligation of the suprarenal IVC is not an acceptable option because it results in renal failure. In unstable patients an intravascular shunt should be used to temporize.

Postoperatively, patients with IVC ligation should have their lower extremities wrapped with firm elastic bandages and elevated. Most patients develop temporary edema that subsides within a few weeks. However, some patients develop extremity compartment syndrome and require fasciotomy.

In patients with severe IVC stenosis after lateral venorrhaphy, there is a risk of thrombosis and pulmonary embolism. If this

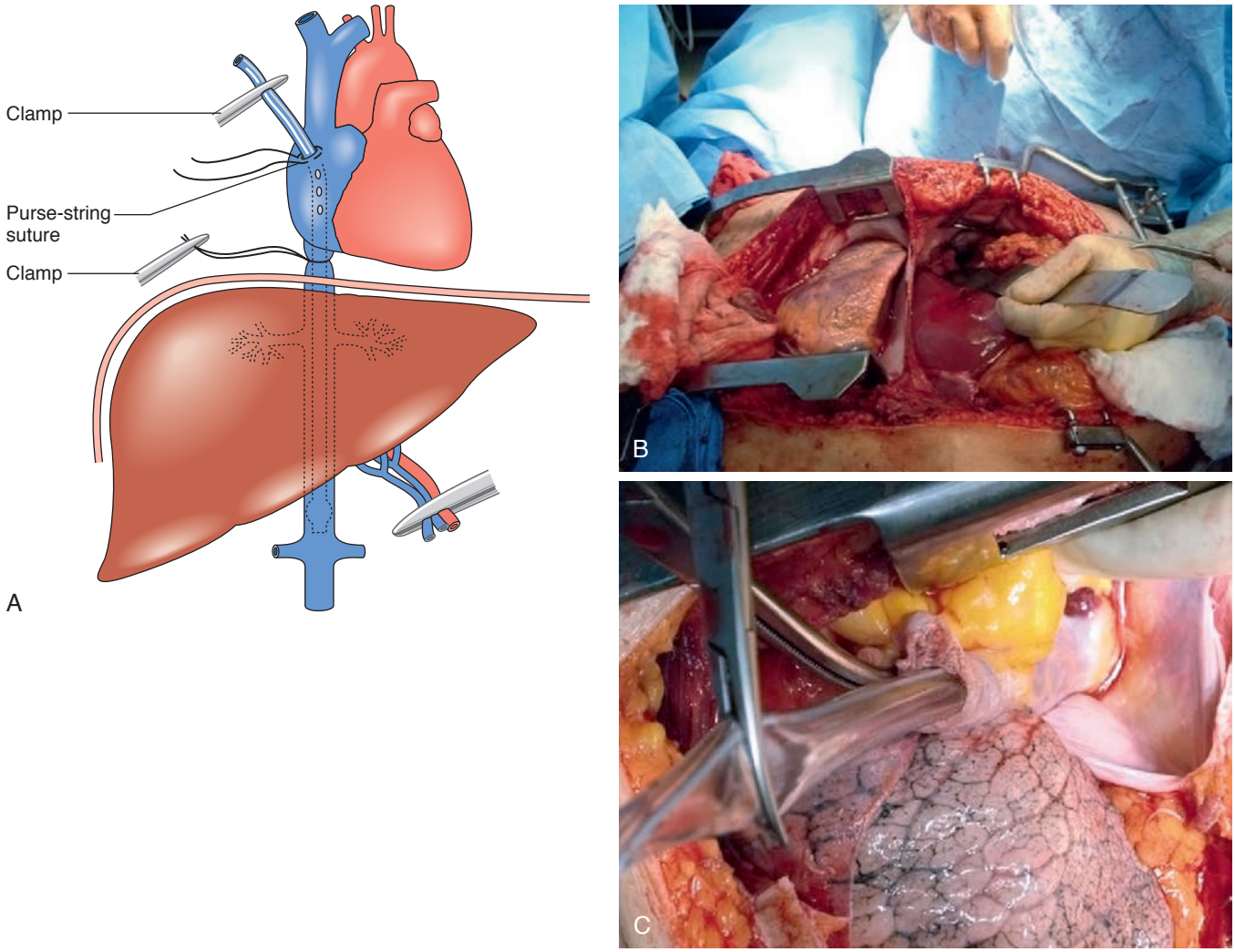

Figure 183.19 (A) Atriocaval shunt for severe retrohepatic inferior vena cava (IVC) injuries. An endotracheal tube is placed through a purse-string suture in the right atrial appendage, and the cuff is inflated above the renal veins. A tourniquet is applied in the intrapericardial IVC. Note the extra holes in the endoatrial part of the tube. This technique should be considered when liver packing does not control hemorrhage. (B) Median sternotomy with laparotomy in preparation for atriocaval shunt placement. (C) Insertion of the shunt through the right atrium.

cannot be avoided, a caval filter or clips should be deployed above the site of stenosis.

Mortality

Approximately half the patients with IVC injuries die before reaching medical care, and among those who arrive at the hospital with signs of life, the mortality ranges between 20% and 57%.[69] In a study of 136 cases with IVC injuries, Kuene et al.[69] reported an overall mortality of 52%. In patients reaching the operating room alive, the mortality was 35%. The mortality was significantly higher in suprarenal injuries.

Portal Venous System Injuries

Anatomy

The portal vein is 6 to 10 cm long and is formed by the confluence of the SMV and the splenic vein behind the neck of the pancreas, to the right of L2, and to the left of the IVC. It passes behind the first part of the duodenum and enters the hepatoduodenal ligament. In the hepatoduodenal ligament, it courses between and behind the common bile duct to the right and the hepatic artery to the left. In the hilum of the liver, it splits into right and left branches. The portal vein has no valves and provides approximately 80% of the hepatic blood flow. The SMV trunk crosses over the third part of the duodenum and the uncinate process of the pancreas. It then passes behind the neck of the pancreas, where it joins the slightly smaller splenic vein to form the portal vein. The splenic vein courses along the superior border of the pancreas and drains the inferior mesenteric vein, just before the confluence with the SMV.

Mechanism of Injury

Injury to the portal vein trunk is relatively rare and is found in approximately 1% of patients undergoing laparotomy for trauma.[73] More than 90% of portal vein injuries are due to penetrating trauma. Because of its proximity to other major

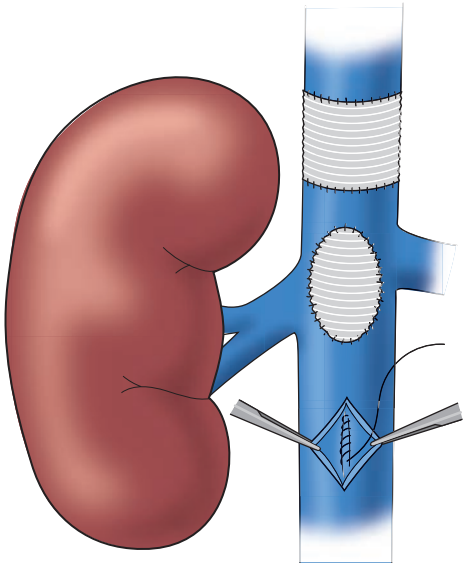

Figure 183.20 Injuries to the inferior vena cava can be managed with lateral venorrhaphy, patch repair or interposition graft. Perirenal and suprarenal injuries should not be ligated.

vessels, the incidence of associated vascular injuries is high, ranging from 70% to 90% of cases.[74]

Clinical Presentation

Most patients with penetrating injuries to the portal venous system present with signs of hemorrhagic shock and require emergency laparotomy. In blunt trauma the injury usually involves the SMV and is due to a direct blow to the abdomen or deceleration forces. These mechanisms often result in thrombosis of the vessels and occasionally avulsion and bleeding. In cases with thrombosis, the diagnosis is delayed and is often made on CT.

Surgical Treatment

The operative findings usually include a combination of local hematoma and various degrees of hemorrhage. Exposure of the retropancreatic portal vein and its major branches can be achieved by mobilization and medial rotation of the right colon and hepatic flexure of the colon and extensive Kocher mobilization of the duodenum. However, this approach often does not provide satisfactory exposure, especially in patients with associated injuries to the SMA. In these cases, stapled division of the neck of the pancreas provides excellent exposure and should be considered early (Fig. 183.21). The suprapancreatic portal vein can be exposed by a combination of mobilization and medial rotation of the right colon and hepatic flexure and a Kocher maneuver.

The portal vein and SMV should be repaired if this can be achieved with lateral venorrhaphy. Complex reconstructive procedures, such as interposition grafts, are rarely feasible or advisable because of the patient's poor condition. Approximately 80% of patients have other vascular injuries that contribute to blood loss and coagulopathy. Complex reconstruction should be undertaken only in patients with associated hepatic artery injury that cannot be repaired. Ligation of both the portal vein and the hepatic artery is not compatible with life. In these cases, reconstruction of the portal vein with a saphenous vein graft should be considered.[74]

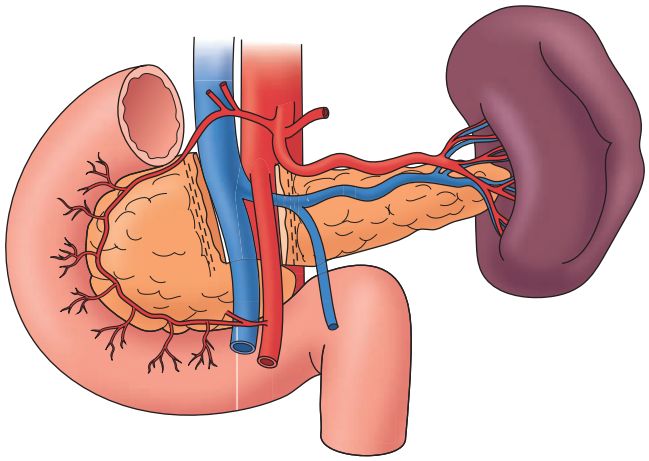

Figure 183.21 Stapled division of the neck of the pancreas provides good exposure of the retropancreatic portal vein and the superior mesenteric vessels.

Ligation of the portal vein with a patent hepatic artery is compatible with life, and the survival ranges from 55% to 85%.[75,76] After ligation of the portal vein or SMV, the bowel becomes massively edematous, and patients can develop patchy bowel wall necrosis. The abdomen should never be closed primarily because, without exception, all patients develop abdominal compartment syndrome. Temporary abdominal wall closure should be performed. Second-look laparotomy should be performed in 24 to 72 hours to check the viability of the bowel.

Postoperatively, massive fluid replacement is required because of sequestration in the splanchnic bed. During the next few days, there is significant improvement of bowel edema due to enlargement of the collateral circulation, and abdominal wall closure may be possible. Experience with the long-term effects of portal ligation is limited, but there is evidence that most survivors do not develop portal hypertension.[73,75,76]

Mortality

The mortality in portal vein injuries is high and ranges between 50% and 72%.[1,75,76] Most patients have other major injuries, making it difficult to assess the mortality directly related to isolated portal vein injuries.

ADVANCES IN THE MANAGEMENT OF ABDOMINAL VASCULAR INJURIES

There have been some significant advances in the management of abdominal vascular injuries in the past decade. The policy of "scoop and run" and early surgical control of bleeding have now become the standard of care and have improved survival in patients with vascular injuries. The concept of damage control has gained popularity and acceptance, and as a result, many patients with vascular injuries have been saved. The recognition of abdominal compartment syndrome and the use of temporary

abdominal wall closure are also important steps in improving outcomes. Endovascular technology has revolutionized the management of selected patients with specific vascular occlusions, arteriovenous fistulae, and false aneurysms. Hybrid operating rooms with angiographic radiology capabilities provide an opportunity to improve the management of abdominal vascular injuries by either temporary control of life-threatening bleeding with endovascular balloon tamponade or definitive care with angioembolization or stenting. The development of intraoperatively placed sutureless, expandable stent-grafts during open surgery is promising and may allow quick and safe vascular reconstruction. Finally, research into powerful new hemostatic agents is promising, and these agents may have a major impact on the management of abdominal vascular injuries.

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A complete reference list can be found online at www.expertconsult.com.

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CHAPTER 184

Vascular Trauma: Extremity

DAVID S. KAUVAR and LARRY W. KRAISS

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This chapter covers the diagnosis and management of vascular injuries to the extremities. Information relating to the epidemiology and pattern of extremity vascular injury is contained in Chapter 180 of this book. The focus is on arterial injuries distal to the deltopectoral groove (axillary artery and distal) and the inguinal ligament (common femoral artery and distal) resulting from blunt and penetrating noniatrogenic trauma. The assessment and management of such injuries continues to evolve, and this chapter's emphasis remains on capturing recent data while retaining elements describing traditional (and in most cases still useful) management techniques.

EPIDEMIOLOGY AND PATTERN OF INJURY

Trauma represents a leading cause of morbidity and mortality around the world.[1] The overall incidence of trauma and vascular injuries is increasing, and although vascular injuries are present in only 1% to 2% of injured patients, these patients account for a far greater share of morbidity, mortality, and resource utilization than those without such injuries.[2,3] In modern series, vascular injuries to the extremities occur in 0.5% to 1% of

Abstract

This chapter covers the diagnosis and management of vascular injuries to the extremities. Information relating to the epidemiology and pattern of extremity vascular injury is contained in Chapter 180 of this book. The focus is on arterial injuries distal to the deltopectoral groove (axillary artery and distal) and the inguinal ligament (common femoral artery and distal) resulting from blunt and penetrating noniatrogenic trauma. The assessment and management of such injuries continues to evolve, and this chapter's emphasis remains on capturing recent data while retaining elements describing traditional (and in most cases still useful) management techniques.

Keywords

Extremity
Injury
Trauma
Artery
Vein
Shunt

TABLE 184.1 Overview of Extremity Arterial Injury Epidemiology From Large Retrospective Studies

Author	Year	Total *N*	Arterial Injury	Extremity Arterial Injury	Penetrating	Upper Extremity	Lower Extremity	Comment
Mattox et al.[4]	1989	Not reported	5,760	1961 (34%)	87%	859 (44%)	1102 (56%)	Vascular injuries only
Barmparas et al.[5]	2010	1,380,563	22,089 (1.6%)	9937 (45%)	5068 (51%)	5855 (59%)	4082 (41%)	National Trauma Data Bank
Loh et al.[2]	2011	2,157	50 (2.3)	14 (28%)	20 (40%)	6 (43%)	8 (57%)	
Perkins et al.[3]	2012	5,823	256 (4.4%)	87 (34%)	46 (53%)	41 (47%)	46 (53%)	
DuBose e al.[6]	2015	Not Reported	483	240 (50%)	179 (37%)	100 (21%)	240 (59%)	PROOVIT (AAST) Registry

PROOVIT, PROspective Observational Vascular Injury Treatment.

injured patients but account for 20% to 50% of all vascular injuries (Table 184.1).[2-5] As is typical for the general population of injured patients, those with extremity vascular injuries tend to be young, with average ages in the 30s, and predominantly (70% to 90%) male (Table 184.1).[2-4,6]

Mortality

Extremity vascular injuries result from blunt and penetrating mechanisms with nearly equal frequency. Patients with blunt injuries experience mortality rates between 2% and 5%, whereas penetrating injuries generally result in fewer deaths.[7] The discrepancy is predominantly due to a greater incidence of concomitant nonvascular injuries in blunt trauma patients. Perkins et al.[3] reported double the rate of packed red blood cell use and massive transfusion as well as a hospital length of stay three times longer in patients with blunt injuries than with penetrating, indicating a more severe overall injury complex. In some instances mortality can be attributed to the extremity vascular injury itself, and in such cases penetrating injuries to proximal extremity arteries predominate. Dorlac et al.[8] identified 14 cases of prehospital exsanguination from isolated extremity vascular injuries. All of these injuries resulted from penetrating mechanisms, and 79% of patients exsanguinated from an artery proximal to the knee or elbow. Similar results were noted in an autopsy study by Bilgen et al.,[9] who found that a penetrating mechanism was responsible for 95% of lethal extremity vascular injuries and that 84% of these injuries were to proximal arteries. We performed a study of isolated lower extremity arterial injuries, revealing a 2.8% mortality rate with 78% of deaths due to penetrating trauma. Proximal arterial injuries resulted in greater mortality than distal ones.[10]

Amputation

Amputation rates in patients with extremity vascular injury range from 7% to 30%, with most amputations performed in patients with blunt mechanisms.[3,10] The high amputation rates seen in patients with blunt vascular injuries to the extremities can be attributed to the high-energy mechanism of such injuries and the resultant amount of damage to bone, nerve, and soft tissue, and not typically to the vascular injury itself.[10-15] Amputation is much more common when the lower extremity is involved and is most common at the popliteal level in the lower extremity and with arterial injury at the forearm level in the upper extremity.[5,7,10,14,]

Location of Injury

In large series examining both blunt and penetrating mechanisms, arterial injuries occur with nearly equal frequency in the upper and lower extremities.[4-6,16,] In the upper extremity, regardless of mechanism, the most frequently injured arterial level is that of the forearm vessels. In the lower extremity, however, mechanism influences the arterial injury pattern, with the popliteal artery most frequently injured in blunt trauma and the superficial femoral artery (SFA) most frequently injured in penetrating trauma (Fig. 184.1). A blunt mechanism of injury is seen more frequently in lower extremity than in upper extremity arterial injuries, and lower extremity injuries have accordingly higher incidences of associated tissue injuries, complications, and mortality.[16]

Associated Tissue Injuries

In extremities sustaining arterial injuries, other tissues are injured with varying frequency, based on the mechanism and arterial level of injury. In general, fractures are seen with high frequency in blunt limb trauma, with rates as high as 80% to 100% in some series.[17,18] In penetrating trauma, fractures are seen in only 15% to 40% of limbs with an arterial injury.[18-20] Regardless of mechanism, fractures, especially comminuted ones, consistently represent a risk factor for amputation when they are found in association with extremity vascular injury.[10,15,17-19,]

The incidence of named venous injury concomitant with extremity arterial trauma ranges between 15% and 35%. The presence of a vein disruption does not consistently predict amputation, and there is no broad consensus as to whether such injuries should be repaired and whether failing to do so predisposes the patient to long-term morbidity. Long-term limb

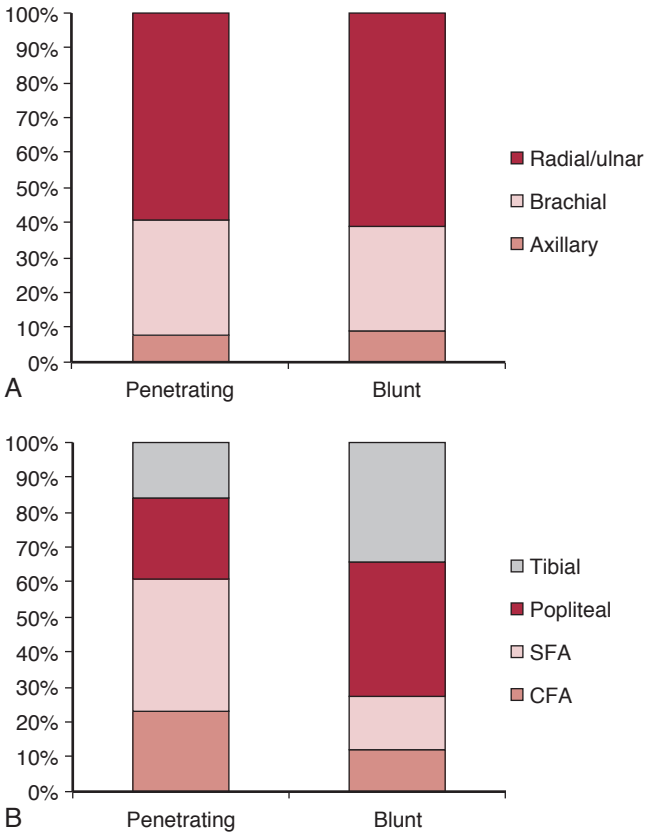

Figure 184.1 Relative frequency of injury to upper extremity (A) and lower extremity (B) arteries resulting from blunt and penetrating trauma. *CFA,* Common femoral artery; *SFA,* superficial femoral artery. (Data from references 4, 5, 8, and 17.)

edema in particular appears to be unrelated to whether a venous injury was repaired or not.[17]

The presence of a peripheral nerve injury associated with extremity vascular trauma can be difficult to detect acutely, and thus such injuries may be underreported in most of the literature on extremity vascular trauma. For the lower extremity, most studies report rates around 10%; upper extremity vascular trauma is associated with a much higher incidence of nerve injury, around 40% to 50%. Like concomitant vein injuries, a nerve injury does not predict amputation, even in severely injured limbs.[21]

Significant soft tissue disruption often accompanies extremity vascular trauma. As with nerve injuries, the incidence appears to be higher in the upper extremity, reported as 40% to 70%, than in the lower extremity, for which rates are typically reported to be 30%. The presence of a significant soft tissue deficit does appear to correlate with amputation in lower extremity arterial trauma.[15,17,18,]

DIAGNOSIS AND WORKUP

The efficient diagnosis and rapid localization of extremity vascular injuries are of great importance in the evaluation of a trauma patient. In cases in which a patient presents with "hard signs" of vascular (primarily penetrating arterial) injury, the existence and location of the injury are generally obvious, and the next step in management is operative exploration and repair.[22] The diagnosis of injuries in patients presenting with only "soft signs" of vascular injury is more challenging, and such patients typically require specific diagnostic testing in addition to the secondary trauma survey (Box 184.1). Conventional catheter-based angiography, once considered the "gold standard" for the preoperative diagnosis and localization of extremity vascular injuries, has been largely supplanted by other diagnostic techniques.

BOX 184.1 Clinical Signs of Extremity Arterial Injury

Hard Signs

- Absent distal pulse
- Palpable thrill or audible bruit
- Actively expanding hematoma
- Active pulsatile bleeding

Soft Signs

- Diminished distal pulse
- History of significant hemorrhage
- Neurologic deficit
- Proximity of wound to named vessel

Physical Examination and Doppler Indices

A number of studies speak to the diagnostic sensitivity of the combination of physical examination and measurement of Doppler-derived blood pressures in detecting extremity arterial injuries resulting from penetrating trauma. Frykberg et al.[23] studied 310 patients with penetrating injuries to the extremities, most presenting with proximity of the wound to a major vascular structure as the sole outward sign of vascular injury. Physical examination alone identified 21 of 23 major arterial injuries, most patients with an injury presented with more than one hard sign, and all patients with hard signs were found to have a significant injury. This resulted in a positive predictive value of physical examination alone of 100% and a negative predictive value of 99%. A prospective study in which routine angiography was used to screen for arterial injury in patients with soft signs was performed by Weaver et al.[24] They found that proximity alone was a poor predictor of significant arterial injury, with no surgically significant arterial injuries identified in the population in whom proximity was the sole angiographic indication. They also found that an isolated Doppler-derived pressure index of 0.99 or less (arterial pressure distal to presumed injury/normal brachial arterial pressure) had a sensitivity of 82% and a specificity of 40% for the detection of a significant arterial injury. These results were confirmed in a similar study by Schwartz et al.,[25] who found a sensitivity of 86% for a pressure index of less than 1.0. In both of these studies, a pulse deficit in the injured extremity correlated very well with the presence of a significant arterial injury. For upper extremity injuries and in situations in which both lower extremities are injured, the pressure used to calculate an "injured extremity index" may be obtained from any uninjured extremity with reliability similar to that of the ankle-brachial index.[24,25]

Fewer specific data are available on the reliability of physical examination and Doppler indices in detecting arterial injury in blunt extremity trauma, but the excellent results in penetrating injuries have been extrapolated to this population. Rozycki et al.[14] cited a 66% rate of pulse diminishment and a 31% rate of pulselessness in a population of bluntly injured extremities with arterial injuries. In a series of 500 blunt popliteal artery injuries, Wagner et al.[17] similarly reported a pulselessness rate of 94% and a diminished pulse rate of 4%.

All patients presenting with trauma to the extremities and hard signs of arterial injury should have those injuries surgically explored in an expeditious manner. Patients presenting with soft signs should undergo a complete pulse examination and a measurement of Doppler pressures in the injured limb distal to the suspected injury for the calculation of a pressure index. If the index is less than 1.0, a further diagnostic and localization study should be performed. The proximity of an extremity wound to a named vessel alone should not prompt a localization study in the absence of a diminished or absent pulse or a Doppler index of less than 1.0.

Computed Tomographic Angiography

Computed tomographic angiography (CTA) is the diagnostic modality most frequently used to identify and localize extremity arterial injuries, having largely supplanted catheter-based angiography (Figs. 184.2 and 184.3). Most seriously injured patients undergo contrasted CT scans as part of their initial evaluation, and scans are frequently completed within minutes of a patient's presentation to a trauma center. CTA offers the benefit of imaging the bone and soft tissues of the injured extremity simultaneously with arterial interrogation. In addition, CTA can assist in the diagnosis of major venous injuries if a delayed phase scan is performed.

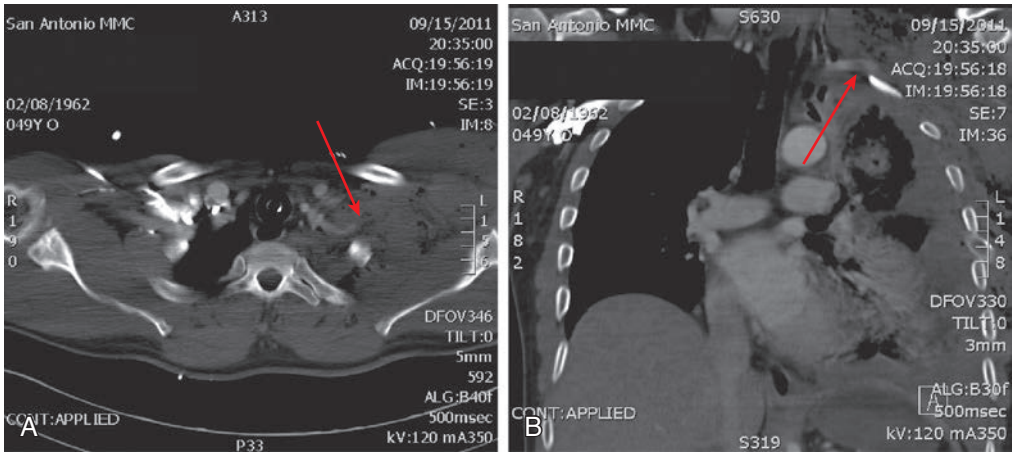

Figure 184.2 Computed tomographic angiography images from a patient sustaining a gunshot wound to the left shoulder with a pulseless left upper extremity. Note abrupt truncation of the left subclavian artery as it enters a large hematoma (A, *arrow*). Coronal reconstruction images reveal occlusion with intraluminal filling defect at the thoracic outlet (B, *arrow*).

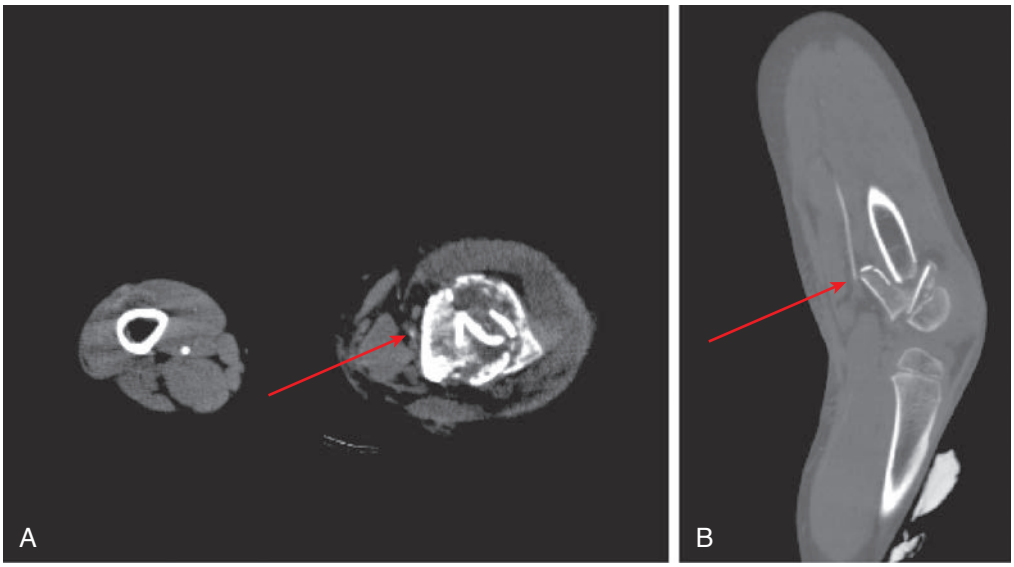

Figure 184.3 Computed tomographic angiography images from a patient sustaining blunt trauma to the left lower extremity with comminuted femur fracture. Note diminutive (likely spasm) left superficial femoral artery at the level of the fracture (A, *arrow*) just proximal to its abrupt truncation, seen best on reconstructed images (B, *arrow*).

Patterson et al.[26] reviewed nine studies published from 2001 to 2009 covering 540 patients undergoing CTA to diagnose extremity arterial injuries. There was a total of seven missed injuries, for a rate of 1.3%. The sensitivities reported in the nine studies averaged greater than 95%, with specificities greater than 90%. A prospective study by Inaba et al.[27] of patients with both blunt and penetrating extremity trauma and clinical "soft signs" revealed 100% sensitivity and specificity for arterial injury detection. Seamon et al.[28] performed a study in which 21 patients received CTA followed by conventional angiography. The criterion for entry was a Doppler index of less than 0.9 in the injured extremity. CTA identified nine injuries, all confirmed at operation or by conventional angiography. No significant arterial injuries were found with conventional angiography after being missed on CTA, although three cases of arterial spasm were discovered in this manner and treated nonoperatively. In this prospective study, CTA was obtained within minutes, whereas angiography took more than 2 hours on average. CTA was also associated with a cost savings of more than $15,000 per patient.

CTA has some limitations in the evaluation of limb trauma with some studies reporting inconsistent contrast opacification of the arterial system if the timing of the intravenous bolus is not optimal. In addition, imaging artifact from metal fragments can limit diagnostic utility. In patients with a large number of fragments, such as those with shotgun injuries, conventional angiography may offer better diagnostic capability than CTA.[27] Despite these limitations, CTA should be considered the initial diagnostic and localization modality of choice in stable patients with blunt or penetrating extremity trauma presenting with soft signs of extremity arterial injury. Conventional angiography should be reserved for unique cases and intraoperative use.

Duplex Ultrasonography

The use of duplex ultrasonography (DUS) in the diagnosis of extremity vascular trauma has been limited, especially with the increasing use of CTA. DUS can be time-consuming and operator specific, but the existing data regarding the technique deserve mention here. Bynoe et al.[29] studied a mixed population of 198 blunt and penetrating extremity trauma patients. All had a wound in proximity to a major vessel and underwent DUS. In cases in which DUS was inconclusive or the trauma surgeon thought more information was needed, arteriography was performed. DUS identified 22 major arterial injuries, 12 to the SFA. Only two injuries were missed (one diagnosed on angiography and the other during a surgical wound débridement); both were due to shotgun wounds. The sensitivity and specificity of DUS for the diagnosis of arterial injury were 95% and 98%, respectively. Bergstein et al.[30] performed a similar study in which 67 penetrating extremity trauma patients with soft signs of arterial injury or proximity underwent arteriography followed by DUS. Four arterial injuries were identified on angiography with only half also seen on DUS, making the sensitivity only 50% compared with a gold standard of arteriography. Finally, Gagne et al.[31] published a small study in which only four arterial injuries were prospectively identified, three discovered only by arteriography and one only by DUS, confirming the questionable reliability of DUS in the trauma setting. In this study, however, DUS was also compared with contrast venography for the detection of venous injuries. DUS identified seven injuries, four of which were missed by venography, which captured only one injury (to a calf vein) missed by DUS.

Although DUS is inexpensive and noninvasive, it is unreliable for the detection of arterial injuries in extremity trauma. CTA remains the most appropriate initial study for this purpose. DUS may have a role in the detection of occult venous injuries and should be considered an adjunctive imaging modality in extremity trauma. In addition, DUS may have a role in the surveillance of known injuries selected for nonoperative management (see later).

TREATMENT PRINCIPLES

Nonoperative Management

The presence of an arterial injury in a traumatized extremity does not necessarily mandate surgical therapy. When blunt and penetrating injuries to distal branches of the axillary and common femoral arteries are diagnosed with CTA, nonoperative management can be successful in up to 70% of cases.[32] Stain et al.[33] reported on 45 extremity arterial injuries noted on angiography and treated initially without surgical exploration. Injuries included small, non–flow-limiting intimal defects and flaps, small pseudoaneurysms, and arteriovenous fistulas. None produced distal ischemia or extravasation. Of these 45 injuries, 31 (69%) were proximal to the knee or elbow. None of the 45 progressed to require operative intervention after a mean of more than 5 weeks of follow-up.

Dennis et al.[34] presented a series of extremity trauma patients including 44 patients with an arterial injury identified on angiography at presentation and undergoing initial nonoperative management. Requirements included a lack of distal ischemia or extravasation and a defect smaller than 2 cm. Of the 44, 4 (9%) developed new or enlarging pseudoaneurysms within one month of injury and went on to repair. Additionally reported were 309 patients with injuries in proximity to a major vessel. These patients were evaluated without angiography and observed clinically. Four (1.3%) eventually developed hard signs of injury (all within 1 week) and had operative repair. No long-term limb morbidity resulted from their approach in either group.

These results confirm the lack of necessity for routine arteriography and suggest that nonoperative management of selected arterial injuries is reasonable, but a high index of suspicion for the possible development of pseudoaneurysm or ischemic complication is necessary during a period of close clinical follow-up. Injuries identified on imaging that may be considered for observation include those that produce no active hemorrhage or distal ischemia, such as small intimal tears or flaps, pseudoaneurysms, and arteriovenous fistulas. Serial surveillance with an appropriate imaging modality such as CTA or DUS is recommended; early repair might be more appropriate if prospects for follow-up are uncertain.

Endovascular Therapy

The use of endovascular techniques to treat vascular injuries has increased significantly over the past 2 decades. From 2000 to 2003, there was a nearly fourfold increase in the percentage of arterial injuries treated by endovascular means. This same period saw a greater than 30-fold increase in the use of stent-grafts to treat arterial trauma.[35] The growth in endovascular treatment has been less pronounced for extremity injuries than for axial arterial trauma, and endovascular therapy is currently applied more frequently in blunt than in penetrating trauma and in lower extremity than in upper extremity injuries. It appears to have similar or improved outcomes compared with open repair of extremity arterial injuries despite being applied in patients with a significant burden of associated injuries and medical comorbidities.[36,37]

Endovascular treatment is most appropriate when the morbidity difference between the open and endovascular procedures is greatest. This is most often the case in the setting of injuries to junctional vessels (such as the subclavian and iliac).[38] In such cases, the use of endovascular balloon occlusion for proximal vascular control may obviate the need for opening a body cavity. If the traumatic vascular lesion can be safely traversed with a guide wire, definitive endovascular treatment is possible in some cases.

Stent-grafts have been successfully deployed to treat arterial injuries manifesting with hemorrhage and occlusion.[39] The greatest experience is in the iliac and subclavian vessels, and reported short-term results are promising.[40,41] Catheter-directed embolization with coils and glue has been used to treat smaller vessels and seems particularly successful when it is used for the treatment of small pseudoaneurysms and arteriovenous fistulas of the crural and deep femoral branch arteries.[42,43]

With endovascular equipment and skills in increasingly ready supply, their broader application in the treatment of extremity vascular injuries seems inevitable. Enthusiasm for their use should be tempered by the fact that there are few to no long-term data available on the outcomes when these techniques are used "off-label" to treat such injuries. Every limb trauma patient is different, and the most appropriate treatment should be determined on a case-by-case basis through close communication between the trauma surgeon and endovascular provider. If an institution is to have the capability to apply endovascular techniques to emergently treat extremity trauma patients, it must be prepared with the ready availability at all hours of the equipment and expertise necessary to maximize the benefits of these techniques.

Open Surgical Management

Open surgical control and repair remain the mainstays of the management of most extremity vascular injuries. If possible, operations should be performed on a table amenable to fluoroscopic imaging to facilitate orthopedic fixation and on-table angiography if needed. The extremity should be prepared and draped widely to facilitate exposure of inflow and outflow vessels, typically circumferentially in the case of extremity injuries. If the need for a vein graft is anticipated, the proposed harvest site should be included in the prepared operative field. Conventional practice is to obtain saphenous vein grafts from uninjured extremities to preserve collateral venous drainage. This dogma is not supported by good-quality data, however, and it may be appropriate to harvest conduit from an injured extremity if there is no venous injury present or if the vessel to be harvested is well peripheral to the site of injury.

The general principles of establishing proximal and distal vascular control and restoring in-line flow to a suitable outflow bed are the same for the treatment of traumatic lesions as for any other vascular defect. Because traumatic vascular injuries frequently present with significant hemorrhage, the ability to expeditiously achieve vascular control is paramount. A tourniquet can be used to provide rapid control of inflow until surgical proximal arterial control can be obtained. To ensure adequate exposure for control and repair, incisions are typically made longitudinally, directly over the target vessel, proximal and distal to the injury. Once vascular control is achieved, incisions can be extended as needed to expose the zone of vascular injury. In some cases of extremity injury, control may need to be obtained proximal to the extremity itself. Such cases lend themselves well to the endovascular placement of an occlusion balloon to achieve proximal control. If this is not possible, upper extremity control may require infraclavicular or supraclavicular incisions to expose the subclavian vessels. Retroperitoneal or inguinal ligament–splitting incisions may be required for proximal control in the lower extremity. Many trauma patients may be unable to tolerate systemic anticoagulation because of ongoing hemorrhage or associated injuries. In these patients, local anticoagulation with heparinized saline injection directly into the injured vessel proximal and distal to the injury may be used.

Wide débridement of contaminated and nonviable tissue within the zone of vascular injury should be performed. During débridement, an assessment of the availability of healthy tissue to cover the vascular repair should be made; as such, coverage is essential to prevent desiccation and possible anastomotic breakdown or graft disruption. Tissue coverage may require coordination with other services operating on the injured extremity. The injured vessel should be débrided to healthy-appearing tissue before a final plan for vascular repair is made. Intimal injury can extend beyond what is appreciated by an injured vessel's outward appearance. Before heparinization and repair, inflow and outflow vessels should undergo gentle balloon catheter thrombectomy to confirm patency. A subjective assessment should be made of the bleeding forward and backward from the injured vessel, and if it is not thought to be adequate, a search for additional flow-compromising injuries should be undertaken.

In general, provided the patient's physiologic status will tolerate it, arterial injuries should undergo urgent surgical repair with the goal of restoring inline distal flow. In some cases, however, acute ligation of an injured extremity artery may be the most feasible acute option. Sometimes this may be done with a plan for formal revascularization when the patient's overall condition stabilizes. If an artery proximal to the elbow or knee

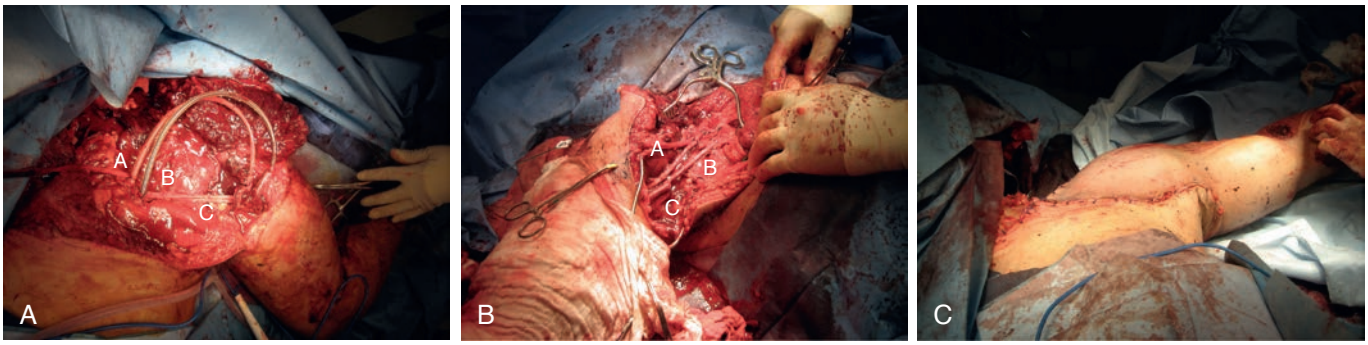

Figure 184.4 (A) Open scapulothoracic dissociation (torso to the left) before return to normal anatomic length with axillary arterial *(A)* and venous *(B)* shunts in place. Note brachial plexus component *(C)* on significant stretch before reduction. (B) After reduction, fixation, and interposition vein grafts to the axillary artery *(A)* and vein *(B)*, the brachial plexus *(C)* is returned to its typical anatomic position and tension. (C) Normal-appearing external shoulder anatomy is restored after skin closure.

is ligated, the extremity distal to the injury should be observed extremely closely for signs of developing ischemia, which should prompt immediate formal revascularization or shunting (or amputation if neither of these can be safely performed).[44,45]

Once the extent of the arterial injury is known, three options exist for repair. In some cases, a short injured segment can be resected circumferentially and enough of the vessel freed proximally and distally to perform a spatulated end-to-end anastomosis. In other cases, a single arteriotomy can be débrided and a patch angioplasty performed. If neither of these is feasible, an interposition graft of appropriate length is indicated. Results of vein grafts are good, with 30-day patency rates of around 90%. Most occlusions occur within the first week, suggesting technical problems as the etiology for graft failure.[46] All open traumatic wounds are considered contaminated, and the preferred conduit for repair of vascular injuries is autologous saphenous vein. Infections involving prosthetic grafts are notoriously difficult to manage, resulting in high rates of graft explantation and amputation. These issues are exacerbated when there is inadequate soft tissue graft coverage.[47,48] It is generally accepted that the poor long-term patency seen with prosthetic grafts used for chronic occlusive disease will manifest in trauma patients as well.[49] Feliciano et al.[48] reported an early (≤30 days) graft occlusion rate of more than 6% in a series of 175 extremity arterial prosthetic grafts, with an additional 6% of grafts occluding after 30 days. The prosthetic arterial grafts most at risk for thrombosis were placed in smaller vessels. Despite the perception of a high failure rate, the use of prosthetic conduits remains controversial, and no long-term patency data are available. A short-segment prosthetic graft may be considered to repair an uncontaminated (typically blunt) arterial injury to a proximal vessel such as the axillary or common femoral artery, where size match with the saphenous vein may be a problem.

Temporary Shunting

The civilian use of temporary shunts to expeditiously restore flow before definitive vascular repair has grown out of initial military surgical experiences with the technique in the Vietnam War.[50] The technique has gained wide acceptance as a temporizing measure allowing for distal perfusion during fracture stabilization before formal vascular repair or as an adjunct to damage control management of a patient unable to undergo definitive repair acutely (Fig. 184.4). In reports of shunts used to allow orthopedic fixation, arterial shunt dwell times have been in the range of 1 to 3 hours, with patency rates approaching 100% in the absence of the use of systemic anticoagulation.[51-53] Dwell times are predictably longer when shunts are placed as part of damage control management, typically ranging from 12 hours to over 24 hours, allowing time for resuscitation and physiologic stabilization before definitive vascular repair. Despite higher limb injury severity in such damage control patients, shunt patency and limb salvage results are equivalent to those seen when arteries are shunted to allow for orthopedic stabilization.[52,54] Although infrequently used, arterial shunts placed in the forearm and tibial vessels have poor patency (12% vs. 86% for proximal shunts), as presented in a recent military report.[55] Shunts placed in the venous system fare surprisingly well in terms of patency, despite the absence of systemic anticoagulation and dwell times of up to a few hours. In a combined review of two recent military reports, only a single episode of thrombosis was noted among 14 shunted vein injuries (93% patency).[55,56]

Venous Repair Versus Ligation

The decision whether to repair or to ligate major extremity venous injuries remains controversial. There has been no consistently reported association between major venous ligation and eventual amputation. Conventional wisdom has been that vein repairs are highly likely to acutely thrombose, a conclusion supported by data from Timberlake et al.,[57] who performed DUS on 138 patients with venous repairs. They found that between 24 and 96 hours from operation, all repairs had occluded. The high incidence of acute thrombosis of venous repairs is supported by data from Smith et al.,[58] who reported 45% occlusion rate at 72 hours. The occlusion of venous repairs may be transient, however, as they found that at 12 weeks, more than 85% of the vein repairs were patent.

The development of limb edema is seen as the primary potential adverse outcome when a major extremity venous injury

is ligated. The development of edema is more common when ligation is performed at the popliteal than at the femoral level, with transient swelling seen in up to 90% of ligated popliteal and 50% of ligated femoral injuries. Repair reduces the transient edema by about half, to 50% and 29%, respectively.[57] Nearly all patients, regardless of the status of the injured vein, experience near-complete resolution of edema by the time of or shortly after discharge from the hospital.[57,59,60] Edema is far less common after ligation of major upper extremity veins.

Venous thromboembolism is also a risk after major extremity venous injury, and the rate of deep venous thrombosis in patients undergoing major venous ligation appears to be approximately twice that of patients undergoing repair. There is no clear indication of whether the thrombi seen in this population are the result of the venous ligation, however, and the rates of pulmonary embolism are similar between patients undergoing ligation and repair.[61]

The decision to repair or to ligate a major extremity vein injury should be made in the context of the patient's overall physiologic condition. If it is safe to take the time required to repair an injury, it is reasonable to attempt to do so. End-to-end anastomosis, lateral suture venorrhaphy, patch venoplasty, and interposition grafting are all viable options for repair, depending on the anatomy of the injury. Ligation should be performed if the patient's condition will not tolerate the additional operative time. Regardless of whether ligation or repair is performed, a period of leg elevation and gentle compression can help reduce the incidence of postoperative edema and possibly eventual venous insufficiency.

SPECIFIC ARTERIAL INJURIES

Axillary Artery

Mechanism and Pattern

The axillary artery is predominantly injured in penetrating trauma,[44,62] with the proximal, middle, and distal divisions injured with similar frequency.[62] The artery is located in close proximity to the brachial plexus, and nerve injuries are seen in more than a third of patients sustaining axillary injury.[62,63]

Diagnostic Considerations

Deficiencies in distal pulses and frank ischemic changes are not universally seen in proximal upper extremity arterial injuries, and a deficit is appreciated in only about two thirds of patients with injury to the axillary artery.[44,64] A high clinical index of suspicion should be maintained when a patient has an injury in proximity to the course of the axillary artery, especially if there is evidence of a concomitant brachial plexus injury. Doppler indices and vascular imaging with CTA or angiography can be useful in making the diagnosis.

Surgical Considerations

Because the proximal portion of the vessel is relatively fixed and cannot be significantly mobilized longitudinally, injuries to the axillary artery are most commonly primarily repaired or treated with an interposition graft.[44,62,63] Owing to the proximal location of the axillary artery near the thoracic outlet, certain injuries in hemodynamically stable patients may be amenable to stent-graft treatment if the lesion can be safely traversed with a wire. The endovascular procedure can be performed antegrade by the femoral approach or retrograde by the ipsilateral brachial approach.[39-41,65]

Brachial Artery

Diagnostic Considerations

A pulse deficit is appreciated in three quarters of patients with an injury to the brachial artery.[44] The arterial injury is frequently associated with fractures of the humerus and dislocations of the elbow (especially in children), so a high clinical index of suspicion is warranted when these skeletal injuries are present.

Surgical Considerations

The brachial artery's course is generally straight, and the vessel can be extensively mobilized and can be repaired with an end-to-end anastomosis in up to 50% of cases; most of the remaining injuries are treated with an interposition graft.[20,44,66]

Radial and Ulnar Arteries

Diagnostic Considerations

Radial and ulnar artery injuries are manifested with corresponding pulse deficits more than 80% of the time and can be associated with significant soft tissue trauma.[20] Part of the diagnostic evaluation of a patient with suspected forearm arterial injury is a Doppler-based Allen test to confirm joint radial and ulnar contribution to the anastomoses of the palmar arches.

Surgical Considerations

If only one of the forearm arteries is injured and an Allen test reveals a patent palmar arch, the injured artery may be safely ligated. If the palmar arch is not patent in the absence of the contribution of the injured artery, the artery should be repaired. In instances in which both the radial and ulnar arteries are injured, preference should be given to repair of the ulnar artery, as it is most commonly the dominant contributor to the perfusion of the hand. The forearm arteries are commonly amenable to mobilization and end-to-end repair.

Femoral Arteries

Diagnostic Considerations

Clinically apparent distal ischemia or pulse deficit is noted in more than 90% of femoral arterial injuries.[45] Although hard signs of arterial injury are common, a high clinical index of suspicion should be maintained in cases of penetrating injury to the groin or proximal thigh. An injury to the PFA may not itself produce diminished distal perfusion, but such injuries can be manifested with an expanding thigh hematoma. A low threshold for the use of CTA or other vascular imaging modality should be maintained.

Surgical Considerations

The CFA is most commonly repaired with a short-segment interposition graft or a vein patch. Injuries to the CFA should be explored with circumferential dissection and control of the CFA and proximal SFA and PFA to ensure that a small back-wall injury is not missed (Fig. 184.5). The PFA can be ligated in an unstable patient, but it should be repaired if the patient's physiologic condition will tolerate because of the vessel's role in collateralization of the leg (Fig. 184.6). Injuries to branches of the PFA are frequently amenable to endovascular embolization.

The SFA is typically repaired with an interposition graft, but if sufficient length can be attained by longitudinal mobilization, end-to-end anastomosis can be performed.

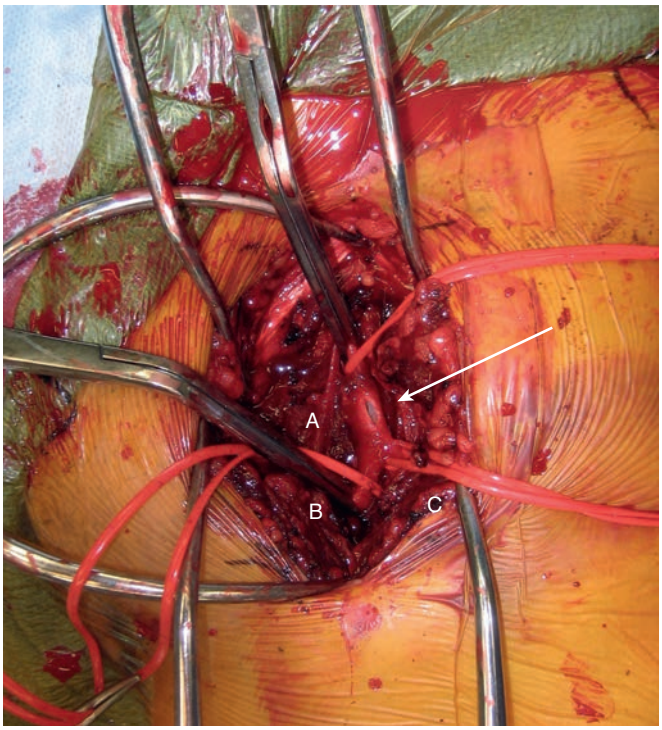

Figure 184.5 Stab wound to the common femoral artery (CFA). In addition to the traumatic anterior CFA laceration *(arrow)*, this vessel also had a smaller, full-thickness, posterior laceration. Note circumferential dissection and loop control of the CFA *(A)*, superficial femoral artery *(B)*, and proximal profunda femoris artery *(C)*. The posterior laceration was primarily repaired with interrupted sutures and the anterior laceration was repaired with a vein patch to prevent loss of luminal diameter.

Popliteal Artery

Diagnostic Considerations

Diminished or absent pulses are features of nearly all blunt and most penetrating popliteal injuries.[17] Because of the close association of popliteal injury with fractures and dislocations of the knee, an arterial injury should be suspected in patients with such skeletal injuries unless their physical examination findings and noninvasive evaluation are completely normal (Fig. 184.7).

Surgical Considerations

In nearly all instances, the most appropriate exposure of the injured popliteal artery is through separate medial above- and below-knee incisions. Although they do not allow direct access to the retrogeniculate popliteal artery, these incisions allow proximal and distal vascular control and extension to the SFA and crural arteries, and they permit a number of options for arterial repair. Medial exposure of the popliteal artery directly behind the knee should be avoided because the necessary division of the semimembranosus and semitendinosus tendons invites considerable morbidity. Rarely, a posterior approach to the popliteal may be used to treat an arterial injury that is known to be focal and behind the knee, but most injured patients cannot be safely placed in the required prone position, and it is frequently difficult to know the true extent of arterial injury preoperatively. Because of the relatively fixed location and nature of the exposure of the popliteal artery, primary anastomosis is not typically possible, and the majority of injuries require an interposition graft.[67]

Injury to the popliteal artery, especially when resulting from blunt trauma, carries the highest amputation rate of any arterial disruption of the lower or upper extremity.[5,10,19,68]

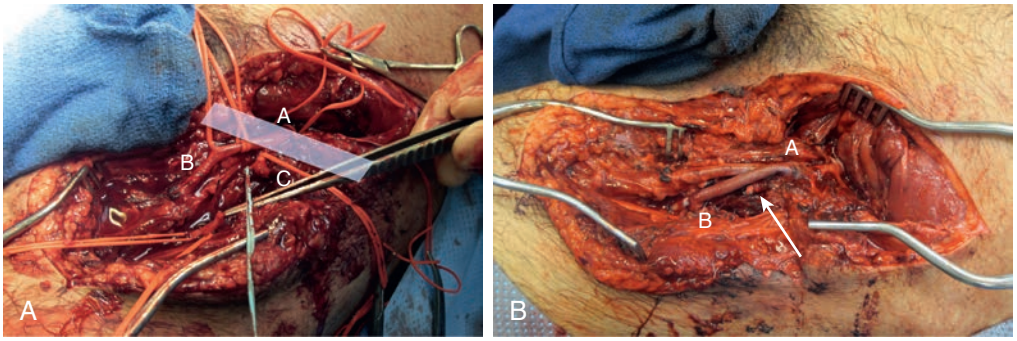

Figure 184.6 (A) Gunshot wound resulting in transection and segmental loss of the proximal profunda femoris artery. Control of the common femoral *(A)*, superficial femoral *(B)*, and proximal profunda femoris *(C)* arteries has been obtained. The distal profunda is at the forceps tip. The patient had a high femoral bifurcation, necessitating division of the inguinal ligament *(shaded box)* to achieve proximal control. (B) To preserve the most proximal profunda branches, repair was achieved through a common femoral *(A)* to profunda *(B)* interposition graft *(arrow)* with ligation of the proximal profunda stump *(arrow)*.

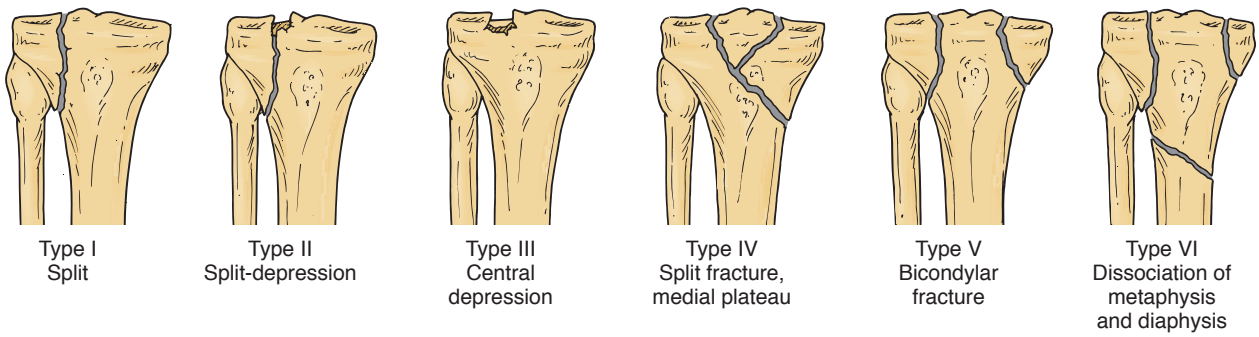

Figure 184.7 Schatzker classification of tibial plateau fractures. The type IV fracture pattern is associated with injury to the popliteal artery.

Although amputation rates have decreased in recent times, popliteal injuries should be reconstructed promptly and with great care, because failure to promptly restore adequate distal perfusion or to identify thrombosis in a repaired vessel may lead to limb loss. Clinical conditions predisposing to amputation in a large series of blunt popliteal injuries are presented in Table 184.2.

TABLE 184.2 Amputation Rates in Association With Perioperative Risk Factors in Blunt Popliteal Artery Trauma ($N = 100$)

Risk Factor	Present (%)	Absent (%)	*P* Value[a]
Severe soft tissue injury	13/31 (42)	2/69 (3)	<.0001
Deep soft tissue infection	9/17 (53)	6/83 (7)	<.0001
Preoperative ischemia	15/64 (23)	0/36 (0)	<.001
Preoperative delay >6 h	10/40 (25)	5/24 (21)	NS
Preoperative delay >12 h	2/14 (14)	13/50 (26)	NS
Systemic anticoagulation	6/71 (8)	9/29 (31)	<.01
Primary arterial repair	3/49 (6)	12/51 (24)	<.05
Palpable pedal pulse within 24 h	4/55 (7)	11/45 (24)	<.05
Trifurcation arterial injury	6/29 (21)	9/71 (13)	NS
Popliteal vein injury	6/29 (21)	9/71 (13)	NS
Ligation of venous injury	2/6 (33)	4/23 (17)	NS
Fasciotomy (operative or delayed)	11/61 (18)	4/39 (10)	NS
Delayed fasciotomy	1/4 (25)	14/96 (15)	NS
Preoperative compartment syndrome	2/17 (12)	13/83 (16)	NS

[a]Two-tailed Fisher exact test.
NS, Not statistically significant.
Modified from Wagner WH, Calkins ER, Weaveret FA, et al. Blunt popliteal artery trauma: 100 consecutive cases. *J Vasc Surg*. 1988;7:736.

Tibial Arteries

Diagnostic Considerations

Most patients with tibial arterial injuries present with a pulse deficit and, if multiple arteries are involved, clinically apparent ischemic changes of the foot.[69-71] Arterial injury should be suspected in cases of high-energy trauma to the tibia, especially in patients with complex fracture patterns and significant soft tissue disruption.

Surgical Considerations

It is widely accepted that disruption of a single tibial artery does not require reconstruction. Very low amputation rates have been consistently reported when such isolated injuries are observed or ligated.[69-72] In cases of multiple arterial injuries or single injuries with clinically ischemic limbs, repair of at least one tibial vessel should be performed.[73] Standard surgical approaches to the tibial arteries should be used, and if calf fasciotomies have been or are to be performed, these exposures of the anterior and deep posterior compartments can be used to access the injured vessels. Most tibial artery injuries require interposition grafting; however, end-to-end anastomosis is possible if the injury is focal. Because some isolated tibial artery injuries are not clinically apparent on presentation, late pseudoaneurysms and arteriovenous fistulas can develop. These can frequently be treated by endovascular means.[43]

OTHER CONSIDERATIONS

Compartment Syndrome and Fasciotomy

For a detailed discussion of the pathophysiology and clinical features of compartment syndrome, refer to Chapter 102. The classically described diagnostic signs of the five *p*'s (pain with passive motion, pallor, poikilothermia, paresthesia, and pulselessness) represent late signs of compartment syndrome and are frequently absent or obscured in trauma patients because of distracting injuries and altered mental status. The true incidence of clinically relevant compartment syndrome after modern extremity vascular injury is unknown because of the widespread use of prophylactic fasciotomy. This practice has developed as it has become accepted that the development of compartment syndrome portends a poor limb outcome.[74,75]

Approximately 40% of patients with lower extremity arterial injury will receive a fasciotomy, with most of these performed within hours of initial revascularization. Performance of a

fasciotomy concomitant with or soon after lower extremity revascularization is associated with a fourfold reduction in eventual amputation and other complications.[76] Lower extremity fasciotomies are performed more commonly for penetrating than for blunt trauma and are most commonly performed when the popliteal artery is injured, followed closely by the femoral arteries. The performance of a fasciotomy is most strongly predicted by the presence of a fracture or dislocation, a vein or nerve injury, or multiple arterial injuries.[75,76]

In the upper extremity, compartment syndrome principally results from arterial injury proximal to the elbow, most frequently to the brachial artery. Approximately 20% of patients with brachial artery injuries will be diagnosed with compartment syndrome, and as with the lower extremity, the syndrome is more common in penetrating trauma. Multiple arterial injuries and fracture predict the development of upper extremity compartment syndrome, but unlike in the lower extremity, vein and nerve injuries do not.[74]

Early calf or forearm fasciotomy should be considered in all patients, with restoration of distal perfusion after ischemia resulting from trauma, especially if multiple fractures or arterial injuries are present. Fasciotomy will be of greater potential benefit with longer ischemic time. Thigh or upper arm fasciotomies should be considered for proximal arterial injuries, especially if there is a proximal venous occlusion and outflow is not restored. Although fasciotomies complicate wound management and may require additional operative procedures to include possible split-thickness skin grafting, their benefits, even when performed prophylactically, outweigh these risks.

Vascular Injury in the Mangled Extremity

Injured extremities with severe trauma to multiple tissue types (some combination of skin, muscle, nerve, and bone) present a difficult clinical problem. Such "mangled extremities" can present with one or more arterial injuries and the decision regarding whether to perform primary amputation or to attempt limb salvage has been a source of debate for decades. The Mangled Extremity Severity Score (MESS) has been devised as a decision aid (Box 184.2).

A MESS of 7 or higher correlates well with primary amputation of the upper[77,78] or lower[79,80] extremity. Ischemia is a component of the MESS, but the degree of bone loss and soft tissue disruption has greater bearing on the decision to perform primary amputation.[11,13] Neither the MESS nor any of the numerous other extremity injury scores accurately predict functional outcomes in severe limb trauma.[81-83] In addition, long-term functional status does not appear to be affected by limb amputation in a patient with severe lower extremity injury.[21,84]

Patients with mangled extremities and arterial injuries should undergo initial multidisciplinary consultation with the inclusion of a vascular surgeon. If an initial attempt at limb salvage is planned, vascular reconstruction should be performed, provided the graft or repair can be covered with viable tissue. In general, an attempt at initial limb salvage and early revascularization is appropriate. The need for reconstruction of arterial injuries should not be considered an indication for primary amputation, except in select instances, including cases of multiple-level or very long arterial injuries, requiring extensive reconstruction or physiologic compromise precluding the long reconstructive procedure. The general principle that a patient's life should not be sacrificed for the sake of an injured limb holds true in all cases. In cases of limbs with multiple tissue injuries, shunts can be used to temporize and allow early fracture stabilization or continued resuscitation (so-called vascular damage control), followed by vascular reconstruction when physiologic condition allows.

BOX 184.2 Mangled Extremity Severity Score

Skeletal/Soft Tissue Injury	
Low energy (stab; simple fracture; pistol gunshot wound)	1
Medium energy (open or multiple fractures, dislocation)	2
High energy (high-speed motor vehicle accident or rifle gunshot wound)	3
Very high energy (high-speed trauma + gross contamination)	4
Limb Ischemia	
Pulse reduced or absent but perfusion normal	1[a]
Pulseless; paresthesias, diminished capillary refill	2
Cool, paralyzed, insensate, numb	3[a]
Shock	
Systolic blood pressure always >90 mm Hg	0
Hypotensive transiently	1
Persistent hypotension	2
Age	
<30 years	0
30-50 years	1
>50 years	2

[a]Score doubled for ischemia >6 h.
Modified from Helfet DL, Howey T, Sanders R, Johansen K. Limb salvage versus amputation. Preliminary results of the Mangled Extremity Severity Score. *Clin Orthop Relat*. 1990; Res 256:80-86.

Intra-arterial Drug Injection

The accidental injection of therapeutic or illicit drugs into a peripheral artery is an uncommonly encountered but potentially devastating clinical phenomenon. The upper extremity is most commonly involved and the brachial is the most commonly injected artery. Injection is immediately followed by distal perfusion of the drug with an ensuing intense intra-arterial inflammatory response. Clinically, severe pain, often accompanied by edema, numbness, discoloration, cyanosis, or mottling of the skin, is seen as endothelial inflammation proceeds to microvascular thrombosis. These findings are most prominent distally. Pulses may be present at the wrist, but signals in the hand and digits are usually absent. The diagnosis of intra-arterial drug injection is primarily made clinically, but DUS can be used to ascertain patency of proximal arteries. Angiography can promote further thrombosis and is not generally recommended.

The treatment of intra-arterial drug injection is supportive, aiming to reduce inflammation and stasis and to prevent propagation of thrombosis. Revascularization is not considered

BOX 184.3 Suggested Therapeutic Regimen for Acute Intra-arterial Drug Injection

- Systemic intravenous anticoagulation with heparin
- Dexamethasone 4 mg intravenously every 6 h to reduce inflammation and to stabilize cellular membranes
- Dextran 40 intravenously at 20 mL/h to prevent platelet aggregation and thrombosis
- Appropriate pain control, including opiates as needed
- Elevation of the extremity to reduce edema
- Aggressive physical therapy to minimize contractures

a viable option because the primary pathophysiologic mechanism consists of distal microvascular thrombosis and resulting soft tissue damage. A suggested therapeutic regimen for acute intra-arterial drug injection is presented in Box 184.3.[85,86]

The treatment regimen is continued until the condition resolves or is fully stabilized, typically 3 to 7 days. Débridement of ischemic tissue is deferred pending clear demarcation. Long-term occupational therapy is frequently necessary to maximize the restoration of limb function. Various other treatments for intra-arterial drug injection have been reported, including the use of nerve blocks, local and systemic vasodilators, and thrombolytic agents. Experience with these modalities is confined to small groups of patients.[87] The role of thrombolytic therapy in the treatment of intra-arterial drug injection has yet to be defined.

Infectious sequelae can complicate cases of intra-arterial drug injection. Localized soft tissue infections resulting from injection with contaminated needles or superinfections of ischemic tissue should be treated by standard methods, with parenteral antibiotics and surgical drainage and débridement as necessary. Another potential infectious complication is the development of a mycotic aneurysm at the site of injection. This is manifested as a tender mass overlying a major vessel, but it is not always pulsatile. DUS or CT angiography can help make the diagnosis and can assist with operative planning (Fig. 184.8). The surgical treatment of mycotic aneurysms can be ligation and resection or arterial reconstruction. The clinical consequences of ligation without reconstruction should be considered, and ligation with delayed reconstruction if clinically apparent distal ischemia develops is an acceptable treatment. If reconstruction is attempted, autogenous conduit should be used if at all possible, and the anastomoses and graft bed should be in tissue planes uninvolved with infection. Frequently, graft courses will be extra-anatomic (i.e., obturator bypass, laterally tunneled femoral bypass). Grafts should be covered with viable muscle, and local flaps may be required. When operating on a patient with intra-arterial drug injection, the surgeon should maintain vigilance for broken needles within the soft tissue. Injury to the surgeon from these may result in the transmission of diseases such as human immunodeficiency virus infection and hepatitis if the patient is affected.[88]

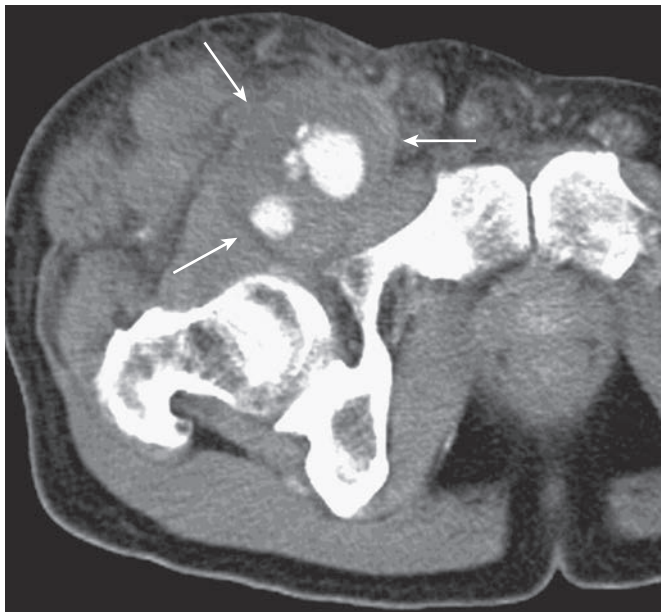

Figure 184.8 Computed tomographic angiography demonstrating a mycotic aneurysm *(arrows)* of the right femoral and external iliac arteries in a patient with a history of heroin injection into the right groin. Note thick aneurysm wall and multilobed morphology. (From Lee W, Mossop PJ, Little AF, et al. Infected (mycotic) aneurysms: spectrum of imaging appearances and management. *Radiographics*. 2008;28:1853-1868.)

Extremity Frostbite

The distal tissue necrosis seen in severe cold exposure injuries results from the combination of direct cellular destruction by freezing and thawing and severe peripheral vasospasm with resultant small-vessel thrombosis after rewarming. This combination of pathophysiologic factors frequently results in eventual irreversible necrosis necessitating partial digital amputation. Similar to intraarterial drug injection, the vascular problem manifested in frostbite primarily involves thrombosis within the digital arteries, capillaries, and venules and is not amenable to surgical treatment. Local, intraarterial, catheter-directed thrombolysis has been used as an adjunct to close observation, limb rewarming, and wound care, which are the mainstays of the treatment of extremities with severe frostbite. Bruen et al.[89] performed catheter-directed thrombolysis in six patients with extremity frostbite and distal ischemia. They noted an 80% decrease in eventual amputations versus historical controls not undergoing catheter-directed thrombolysis. Outcomes after catheter-directed thrombolysis were better if the procedure was performed within 24 hours of presentation.

In cases of acute frostbite, catheter-based diagnostic angiography of all distal extremities with clinically apparent ischemia (absent pulses, skin cyanosis) should be considered. If distal perfusion defects are present that are not solely due to vasospasm (i.e., persistent after vasodilator challenge with papaverine or nitroglycerin), intra-arterial catheter-directed thrombolysis with recombinant tissue plasminogen activator should be considered. Treatment is initiated through an infusion catheter placed in a proximal extremity vessel (typically the brachial, superficial femoral, or popliteal artery) and should be continued for up to 48 hours, with repeated diagnostic angiography performed at 8- to 12-hour intervals and catheter-directed thrombolysis discontinued when angiography reveals no residual perfusion

defects. Multiple extremities can be treated simultaneously through multiple arterial access points with the cumulative dose of tissue plasminogen activator administered (0.5 to 1.0 mg/h) divided between the affected extremities. Unfractionated heparin is administered at 500 units/h through each arterial sheath for the duration of treatment.

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A complete reference list can be found online at www.expertconsult.com.

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185 CHAPTER

Conditions Arising From Repetitive Trauma and Occupational Vascular Problems

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Upper extremity work-related injuries are a major societal problem in regard to disability, cost, and loss of work days. Occupational injuries affecting the shoulders, arms, and hands have been recognized for nearly 300 years and are generally categorized into injuries caused by accidents or injuries resulting from long-standing repetitive tasks.[1] Injuries in the latter category are due to small but additive amounts of tissue damage sustained from repetitive motions; they are known collectively as cumulative trauma disorders. According to 2011 data released by the US Bureau of Labor Statistics, injuries sustained from repetitive motion often result in longer duration of time away from work compared with other classes of injury.[2] Although most of these injuries affect the musculoskeletal system, injuries to arteries and veins are known to occur.[3] Work-related vascular injuries develop from excessive or exaggerated activity involving the shoulders, arms, or hands. Box 185.1 lists arterial disorders associated with occupational trauma.

MANUAL LABOR INJURIES

Hand-Arm Vibration Syndrome

The first cases of this injury were reported by Loriga in 1911 among Italian miners presenting with "dead finger."[4] Hamilton in 1918 made the connection between cold-induced blanching and numbness of the hands and use of pneumatic drills by stonecutters in Indiana.[5] Subsequent work by Taylor and Pelmear[6] and Ashe et al.[7] firmly established hand-arm vibration syndrome as a discrete clinical entity.

The disease has been referenced by many names, from the original dead finger to Raynaud of occupational origin, traumatic vasospastic disease, and vibration-induced white finger. The current designation hand-arm vibration syndrome (HAVS) was introduced to reflect that the extent of involvement is more of the upper extremity than just the digit. Regardless of the name,

Abstract

Occupational Vascular Problems Abstract

Upper extremity work-related injuries represent a society-level problem with regard to disability, cost, and loss of work days. Repetitive motions and long-term exposure to vibration, cold, and trauma can cause tissue damage and vascular injury resulting in long-term injury and disability. This chapter serves to describe the etiology, presentation, diagnosis, and management of upper extremity occupational vascular disorders.

Keywords

Raynaud syndrome
hand ischemia
digital ischemia
vibration injury
exposure injury

BOX 185.1 Arterial Disorders Associated With Occupational or Recreational Activities

Manual Labor

Hand-arm vibration syndrome
Hypothenar hammer syndrome

Exposure

Acro-osteolysis
Electrical burns
Extreme thermal injuries

Athletic

Chronic hand ischemia
Quadrilateral space syndrome
Humeral head compression of the axillary artery
Thoracic outlet syndrome

the common initial symptoms are those of Raynaud phenomenon secondary to prolonged use of vibrating mechanical tools.

Clinical Findings and Risk Factors

The Taylor and Pelmear staging system is presented in Table 185.1.[6] In the early stages, vibration injury may be manifested as slight tingling and numbness. Later, the tips of one or more fingers experience attacks of blanching, usually precipitated by cold. With continued progression, the affected area increases in size, and the blanching extends to the entire finger. Attacks of white finger typically last approximately 1 hour and terminate with reactive hyperemia (red flush) and often considerable pain. Prolonged exposure may induce bluish black cyanosis in the affected fingers. Only approximately 1% of cases progress to ulceration or gangrene.[8]

Vibrating handheld machines (e.g., pneumatic hammers and drills, grinders, and chain saws) have been implicated in hand-arm vibration syndrome. Such injury potential is not restricted to a few types of tools but applies to a variety of situations in which workers' hands are subjected to transmission of vibration energy.[9] There appears to be a linear relationship between the acceleration exposure dose (amount of acceleration and years of exposure) and the onset and severity of hand-arm vibration syndrome.[10]

The exact mechanism of injury is unknown. The frequency and intensity of vibration affect the extent of damage to the endothelium.[11] Local platelet adhesion seems to be an important factor in arterial occlusion. It has been shown that sympathetic hyperactivity, in combination with local factors such as vibration-induced hyperresponsiveness of the digital vessels to cold, may be responsible for the finger-blanching attacks.[12] In those with exposure to vibration injury, appearance of symptoms has also been correlated to smoking status.[13] Lower levels of serotonin, as well as polymorphism variants of the HTR1B, have also been shown to increase susceptibility to symptoms.[14]

Diagnosis

Key features in the history include use of vibrating tools and symptoms of Raynaud phenomenon. For a vasospastic condition, the most promising single objective test is cold provocation and recording of the time until digital temperature recovers (see Chapter 20). Digital artery occlusion is best detected by recording the systolic pressure of the affected fingers with transcutaneous Doppler ultrasound[15-17] or duplex scanning.[18] In advanced disease, arteriography is helpful. Barker and Hines[19] documented arterial occlusion by brachial arteriography in workers who complained of hand blanching and attacks of numbness. Other authors have reported on the use of arteriography in this injury.[20-22] Use of MRA is described by Poole and Cleveland to differentiate HAVS from hypothenar hammer syndrome.[23]

Arteriographic changes in hand-arm vibration syndrome can include multiple segmental occlusions of the digits and a corkscrew configuration of vessels in the hands.[22] The extent of digital artery occlusion appears dependent on the frequency and duration of exposure.[24] Of 80 workers (chippers) with hand-arm vibration syndrome investigated at the Blood Flow Laboratory at Northwestern University, 25 (31%) exhibited a significant reduction in systolic pressure in one or more digits.[25] In 6 of the 25 workers, arteriography showed digital artery occlusion (Fig. 185.1). Incompleteness of the palmar arch was seen not only in the symptomatic hand but also in the contralateral, asymptomatic one. Raynaud phenomenon was present in 73 of 80 workers (91%). Abnormal cold response was observed in 53% of these workers (Fig. 185.2).

TABLE 185.1 Stages of Hand-Arm Vibration Syndrome

Stage	Condition of Digits	Work and Social Interference
0	Vibration exposure but no signs or symptoms	No complaints
0T	Intermittent tingling	No interference with activities
0N	Intermittent numbness	No interference with activities
1	Blanching of 1 or more fingertips, with or without tingling and numbness	No interference with activities
2	Blanching of 1 or more fingers with numbness, usually in winter	Slight interference with home and social activities; no interference with work
3	Extensive blanching; frequent episodes in summer and winter	Definite interference at work, at home, and with social activities; restriction of hobbies
4	Same as stage 3: extensive blanching, most fingers involved, frequent episodes in summer and winter	Same as stage 3, but occupation changed to avoid further vibration exposure because of the severity of signs and symptoms

Modified from Taylor W, Pelmear PL, eds. *Vibration White Finger in Industry.* New York: Academic Press; 1975.

Figure 185.1 Arteriogram of the hand in a vibratory tool worker. Occlusion of the digital arteries *(arrow)* is apparent.

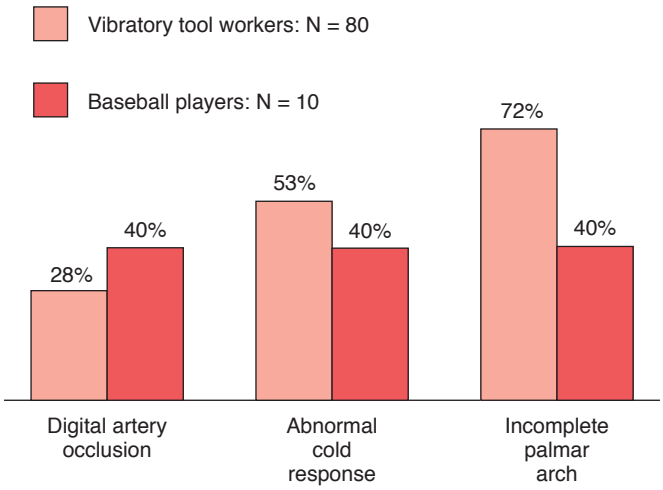

Figure 185.2 Incidence of digital artery occlusion, abnormal cold response, and incomplete palmar arch by Doppler examination in vibratory tool workers and baseball players. (From Bartel P, Blackburn D, Peterson L, et al. The value of non-invasive tests in occupational trauma of the hands and fingers. *Bruit*. 1984;8:15.)

Treatment and Prevention

With onset of neurovascular symptoms that interfere with social or work activities, the initial treatment is discontinuation of use of vibratory tools.[10] In advanced cases a calcium channel blocker such as nifedipine (30-120 mg daily) may be useful. Calcium antagonists inhibit the response of arterial smooth muscle to norepinephrine and have been reported to be

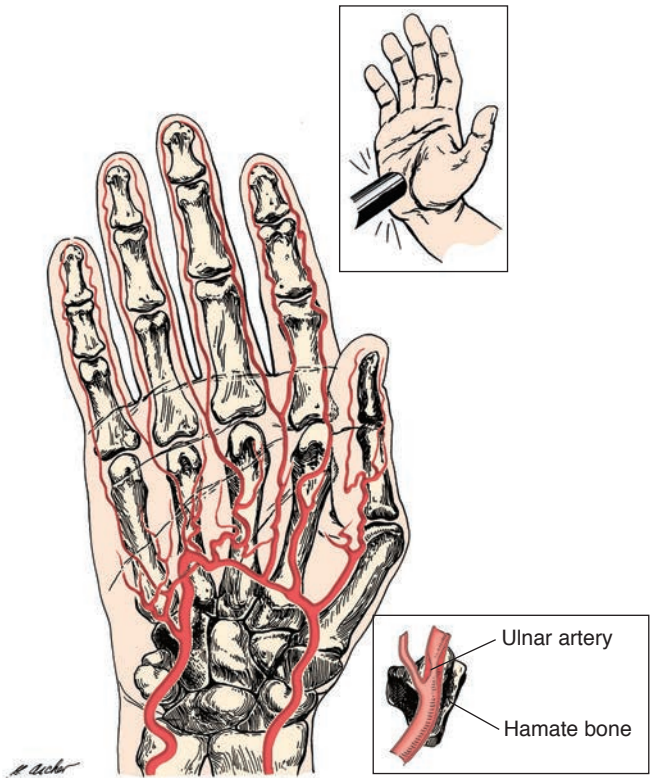

Figure 185.3 Mechanism of ulnar artery injury *(upper inset)* in a patient with hypothenar hammer syndrome. The terminal branch of the ulnar artery is vulnerable to injury because of its proximity to the hamate bone *(lower inset)*.

effective.[26] Intravenous infusion of a prostanoid (prostaglandin E1, prostacyclin, or iloprost) is usually reserved for patients with digital gangrene.[27] Surgical treatment, such as cervical sympathectomy or digital sympathectomy, is rarely needed.

Prevention is likely to be more effective than treatment. Personal protective equipment, such as gloves that limit exposure to cold and dampen transmission of vibration, should be used. Standards that limit the dose and duration of exposure to vibration have been set in place for factories and workplaces in the United States and internationally.[10]

Hypothenar Hammer Syndrome

Etiology and Incidence

The anatomy of the ulnar artery at the hypothenar eminence makes it vulnerable to injury with repetitive use of the palm of the hand in activities that involve pushing, pounding, or twisting. The ulnar artery and nerve travel in a tunnel known as Guyon canal that is bound by the pisiform and hamate bones. In this region, the ulnar artery is superficial and covered only by skin, subcutaneous tissue, and the palmaris brevis muscle (Fig. 185.3). Use of the palm as a hammer compresses the artery against the hook of the hamate bone, which acts as an anvil.

Von Rosen (1934)[28] and Guttani (1772)[29] published the original reports of the disease, but it was Conn et al.[30] who first recognized the anatomic mechanism of injury and coined the term *hypothenar hammer syndrome*. Mechanics, factory

workers, carpenters, masons, and any laborers who habitually use their hands as a hammer are at risk for the disease.[31-33]

The incidence of this rare entity is not precisely known because it is likely underrecognized. In Little and Ferguson's study of 79 mechanics, 14% had evidence of ulnar artery occlusion but none had symptoms severe enough to seek medical attention.[31] Studies focusing on cases of hypothenar hammer syndrome among referrals to tertiary centers for hand ischemia have found an incidence of 1.1% to 1.6%.[33,34]

The type of arterial abnormality observed often depends on the nature of the vessel injury but includes thrombotic occlusion, aneurysm formation, or both. Vasospasm and damage to the intima can result in platelet aggregation and thrombus formation.[35] Damage to the media can lead to aneurysmal degeneration of the artery (Fig. 185.4), although this occurs less frequently. Thrombus formation can also occur within the aneurysm itself and lead to distal embolization.

Research by Ferris et al.[34] demonstrated that, in addition to vascular damage from repetitive trauma, underlying vessel abnormalities may also be responsible. Histologic examination of 19 resected ulnar arteries showed hyperplastic proliferation of the intima or media and disruption of the internal elastic lamina suggestive of fibromuscular dysplasia. In 13 patients for whom bilateral angiograms were available, 12 of 13 (92%) showed an abnormality in the contralateral asymptomatic ulnar artery. On the basis of this evidence, they proposed that the etiology of hypothenar hammer syndrome depends on the presence of underlying ulnar artery fibromuscular dysplasia with superimposed repetitive palmar trauma.

Figure 185.4 Arteriogram of the hand of a carpenter. Note the aneurysm of the ulnar artery *(arrow)* caused by repetitive trauma from using the hand as a hammer.

Clinical Findings and Diagnosis

Patients typically present with Raynaud phenomenon. However, several key features distinguish hypothenar hammer syndrome from similar syndromes.[35] There is a preponderance of male smokers with a concomitant history of repetitive trauma to the hand.[33] The distribution is asymmetrical, often involving only the dominant upper extremity. The cyanosis and pallor phases can occur, but the hyperemic redness is usually lacking.[32] The digits affected tend to be the ulnar three fingers, with a distinct lack of involvement of the thumb.[32,34]

Physical examination may reveal cool or mottled digits; severe cases present with ischemic ulcers. A callus may be present over the hypothenar eminence. The result of Allen test is often positive, indicating ulnar artery occlusion. On occasion, an aneurysm is observed as a pulsatile mass in the hypothenar eminence.

Noninvasive imaging studies such as duplex ultrasound and contrast-enhanced computed tomography or magnetic resonance imaging have been used to make the diagnosis of hypothenar hammer syndrome.[36-38] However, the "gold standard" imaging modality in hypothenar hammer syndrome remains invasive arteriography. Arteriography is extremely useful in diagnosis and planning of surgical treatment because it defines the type of vascular lesion (spasm, aneurysm, occlusion), shows the site and extent, and identifies the anatomy of the palmar arch and significant collateral vessels. A corkscrew pattern is typically observed in affected vessels.[34] Regardless of which imaging modality is used, proximal arterial segments should be included in the examination to rule out upstream sources of embolization.

Treatment

The majority of patients with hypothenar hammer syndrome will improve with nonsurgical interventions.[33] Conservative measures include smoking cessation and hand protection involving avoidance of exposure to cold environments and avoidance of further trauma. Medical therapy consists of calcium channel blockers and antiplatelet drugs. Anticoagulation has been used in cases of digital necrosis.

Surgical therapy is reserved for severe cases of digital ischemia or the presence of an aneurysm. Simple ligation of an aneurysm can be performed if there is adequate collateral circulation. More often, surgical intervention requires resection with primary reconstruction or vein graft interposition. One study suggests the use of arterial interposition graft as well.[39] Several large case series report that a majority of patients have improvement in symptoms of hand ischemia after reconstruction and that long-term results are satisfactory.[34,40-42]

EXPOSURE INJURIES

Occupational Acro-Osteolysis

Wilson et al.[43] first described this disease in workers exposed to polyvinyl chloride. Many of these workers experienced ischemic symptoms in the hand, with resorption of the distal phalangeal tufts, similar to that seen with scleroderma. The

dominant initial symptoms are those of Raynaud syndrome. A few reports of angiography in this syndrome document damage to the digital arteries.[44-46] Findings include multiple stenoses and occlusions of the digital arteries along with nonspecific hypervascularity adjacent to the areas of bone resorption. The reason for the hypervascularity is not clear, but it may be related to stasis of contrast medium in digital pulp arteries secondary to shortening and retraction of the fingers. Some of these digits were clubbed, a finding that has also been associated with hypervascularity in the fingertips. Treatment is supportive.

Electrical Burns

Electrical energy inflicts tissue destruction in relation to the voltage applied. Currents less than 1000 V cause injuries limited to the immediate underlying skin and soft tissue. High voltage (>1000 V) usually causes extensive damage as the current travels from the point of entry to the point of exit. No tissue is immune to the devastating effects of high-voltage injury, and arterial injury may occur. The upper extremity, especially the hand, is involved more often than are other parts of the body because of its grasping function. The arterial injury is often manifested by arterial necrosis with thrombus or bleeding, and gangrene of the digits occasionally develops.

Bookstein[44] described the angiographic changes in the upper extremity after electrical injury, including extensive occlusion of the ulnar and digital arteries and thrombosis of the radial artery. Arterial spasm may also be present. Later, damage to the media may cause aneurysm formation. Fig. 185.5 shows a brachial artery aneurysm in a patient who had sustained electrical burns 9 months earlier. Treatment and salvage of the upper extremity depend on the associated soft tissue and bone injuries.[47]

Figure 185.5 Aneurysm of the brachial artery in an electrician who had sustained a high-voltage electrical burn 9 months previously.

Reconstruction with free flap due to local vascular damage has been described.[48] Occlusion of a major artery documented by arteriography requires bypass grafting, and good results have been reported.[49]

Extreme Thermal Injuries

Vasomotor disturbances in the hands of individuals exposed to extreme chronic thermal trauma are typically manifested as Raynaud syndrome. Workers at highest risk for thermal injuries are those in a profession in which their hands are subjected to chronic exposure to cold, such as slaughterhouses, canning factories, and fisheries.[50,51] Epidemiologic studies examining this dilemma are limited. Swedish military trainees exposed to extreme cold for up to 14 months were found to have reduced sensation to temperature changes as well as vibrotactile stimulus; however, there were no alterations in the finger systolic blood pressure.[52] These symptoms were documented to be present by sensory testing at 4 months; however, symptoms such as cold intolerance and white fingers were present 4 years after initial injury.[53] The action of alternating ice-cold and hot exposure, use of plastic gloves in cold exposure, and long-term exposure to cold seem to be identifiable risk factors. Treatment is supportive.

ATHLETIC INJURIES

Athletes, particularly professionals who engage in strenuous or exaggerated hand or shoulder activity, may be susceptible to upper extremity ischemia as a result of arterial injury. Hand ischemia is often manifested as Raynaud syndrome, symptoms of sudden arterial occlusion, or embolization to the digits. Injury can occur anywhere along the course of the upper extremity from the subclavian artery to the digital vessels. Recognized syndromes occur anatomically at the thoracic outlet, the quadrilateral space, and the humeral head and in the hand. The exact incidences of these syndromes are unknown. The majority of reported arterial injuries in the elite athlete involve baseball players; however, vascular injury has been reported in such sports as karate, volleyball, handball, Frisbee, lacrosse, golf, weightlifting, and butterfly swimming.[54,55]

Hand Ischemia

Clinical Findings and Risk Factors

The mechanisms of hand ischemia fall into two main categories: direct digital artery injury and embolization from a proximal source in the upper extremity. Hand activity in any sport can cause blunt-force injury to the arteries[56]; however, direct digital arterial trauma is encountered more often in handball players, baseball catchers, and practitioners of karate. Fig. 185.6 illustrates occlusion of the palmar arch in a Frisbee player; ischemia of all fingers occurred suddenly after he caught the Frisbee. It has been suggested that handball players with more than 200 hours of accumulated playing time are at greater risk for symptomatic alterations in perfusion.[57,58] In a study of Basque handball players, 57% of those who play, 77% of federated players in the senior category, and 87% of professionals sustain injury to the arteries

Figure 185.6 Occlusion of the palmar arch in a Frisbee player *(arrow)*. Because of this injury, there is poor filling of contrast medium in the second, third, fourth, and fifth fingers.

of the hand and fingers.[59] In a study of beach volleyball players, both time spent playing and female gender were risk factors for developing hand ischemia symptoms.[60]

Baseball players, particularly catchers because of the tremendous and frequent impact of the baseball, are predisposed to the development of chronic hand ischemia. Many catchers exhibit Raynaud symptoms, especially in the off-season when they engage in outdoor activity in cool autumn or winter weather. Lowrey[61] reported decreased digital perfusion to the index finger of the glove hand in 13 of 22 baseball catchers examined by Doppler flow and the Allen test. Of 10 professional catchers studied in that author's laboratory, 40% had evidence of digital artery occlusion.[61]

Another form of hand ischemia occasionally observed in baseball pitchers is compression of the digital artery by Cleland ligament. These ligamentous structures are found on the palmar surface of the digits and span from the phalanx to the subcutaneous tissue (Fig. 185.7). The proposed mechanism is compression of the digital vessels with hyperextension of the proximal interphalangeal joints.

Treatment

Treatment of hand ischemia depends on the clinical findings. With acute injury, a conservative approach involving intravenous infusion of dextran and pain control is in order. Medical therapy for digital ischemia includes purine derivatives such as pentoxyfylline, calcium channel blockers, and analgesics for pain control.[59] Botulinum toxin (Botox) injection has emerged as an alternative to surgical intervention for digital ischemia due to vasospasm. In case series, Botox injection into the neurovascular bundle of the fingers results in 75% to 100% improvement of pain and healing of digital ulceration in 48% of patients.[62] Surgical intervention is indicated for severe symptoms not alleviated by conservative management. Digital periarterial sympathectomy was shown to be successful in a cohort of handball players with severe symptoms.[59] Release of Cleland ligament has been successful in relieving digital artery compression in baseball pitchers as well.[63] Preventing injury is important and can be accomplished by the use of gloves with padding and other protective devices.[61]

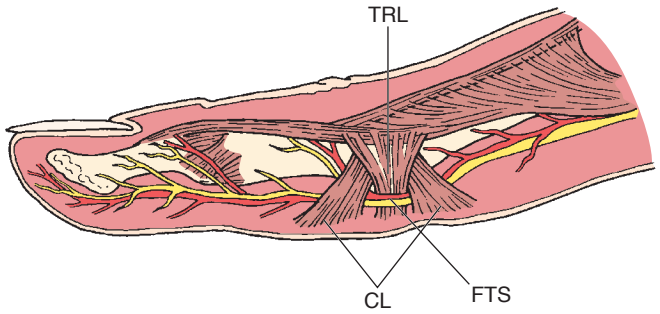

Figure 185.7 With the proximal interphalangeal joint in hyperextension, Cleland ligament may compress and occlude the vascular supply to the fingertip. *CL,* Cleland's ligament; *FTS,* flexor tendon sheath; *TRL,* transverse retinacular ligament.

Quadrilateral Space Syndrome

The quadrilateral space is defined as the area bordered by the teres minor superiorly, the humeral shaft laterally, the teres major inferiorly, and the long head of the triceps muscle medially (Fig. 185.8).[64] Found within this space are the posterior humeral circumflex artery and the axillary nerve.

Cahill and Palmer[65] first reported in 1983 the diagnosis and surgical treatment of 18 patients with this entity. Compression of the posterior humeral circumflex artery within this space occurs with the arm in the "cocked" position (abduction and external rotation). Chronic compression and trauma to this artery in overhand motion athletes, particularly pitchers and volleyball players, can lead to aneurysmal dilatation or occlusion (Fig. 185.9). Aneurysms in this location are prone to distal embolization in the hand.[66,67]

Experience with nine patients at the Mayo Clinic suggests a new classification of quadrilateral space syndrome into vascular and neurogenic etiologies. Vascular quadrilateral space syndrome (vQSS) is caused by repetitive mechanical trauma to the posterior circumflex humeral artery resulting in thrombosis and/or aneurysmal degeneration leading to distal embolization. vQSS is most often seen in overhead athletes. Neurogenic QSS (nQSS) is caused by fixed structural impaction of the quadrilateral space by fibrous bands or space-occupying lesions. This occurs from

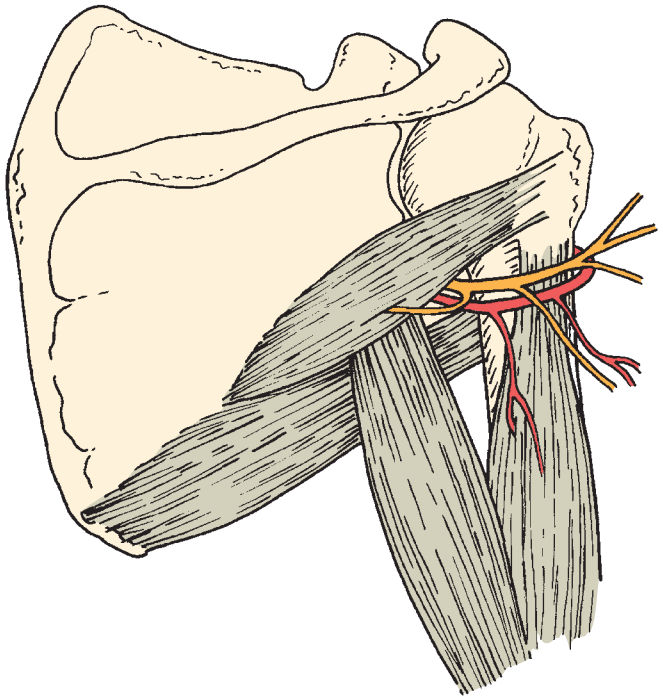

Figure 185.8 The posterior humeral circumflex artery and axillary nerve traverse the interval of the quadrilateral space.

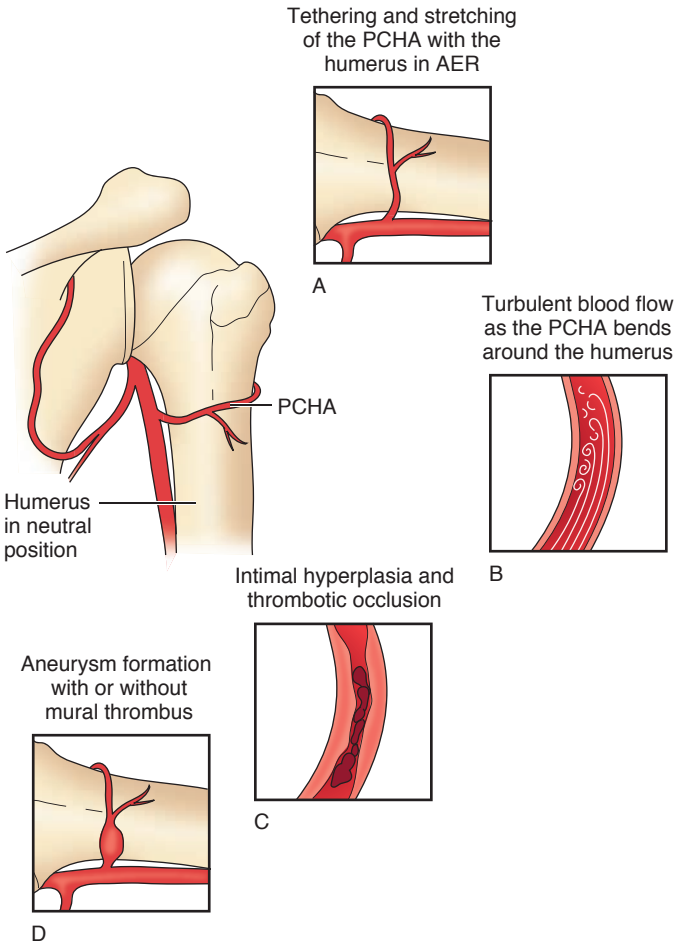

Figure 185.9 Proposed mechanism for posterior circumflex humeral artery degeneration and thrombosis: (A) The posterior circumflex humeral artery stretches around the neck of the humerous similar to a stretched rubber band leading to intimal injury and weakening of the vessel wall. (B) The repetitive pulley movement likely leads to turbulent blood flow within the bend around the humeral neck. (C) These changes lead to intimal hyperplasias, thrombotic occlusion, and (D) aneurysmal formation. (From Brown SAN, Doolittle DA, Bohanon CJ, et al. Quadrilateral space syndrome: the Mayo Clinic experience with a new classification system and case series. *Mayo Clin Proc*. 2015;90(3):362–394.)

repetitive microtrauma to connective tissue in the quadrilateral space and can be seen in recreational athletes, such as swimmers, or in occupations requiring some overhead movement. Presentation can include muscle atrophy, paresis, paresthesia, poorly localized shoulder pain, or tenderness with palpation of the quadrilateral space.[68]

For vQSS, thrombolytic therapies may be used initially to dissolve the distal emboli, but surgery to treat the aneurysm should then be addressed. Surgical treatment of aneurysms in this location involves ligation of the posterior humeral circumflex artery.[69] The anterior and posterior humeral circumflex arteries provide blood supply to the humeral head, and at least one of the two vessels must be preserved or repaired to prevent avascular necrosis. Many athletes return to practice after operation, and surgical treatment may be supplemented with 3 to 6 months of anticoagulation.[68]

Treatment of nQSS can initially be conservative with oral antiinflammatory medications, physical therapy, and limitation of activities; however, surgical decompression involving neurolysis and excision of fibrous bands or other space-occupying lesions often allows patients to return to full activity without pain or limitation after several weeks.[68]

Humeral Head Compression of the Axillary Artery

Lord and Rosati[70] first reported compression of the third portion of the axillary artery by the head of the humerus. With overhead throwing or striking motions in which the arm is abducted and externally rotated, there is downward compression of the humeral head against the axillary artery.[66,71] Sonographic studies have demonstrated the impedance of flow through the axillary artery by the humeral head with these overhand motions.[72]

Symptoms typically include arm fatigue and loss of pitch velocity after several innings. Finger numbness, Raynaud syndrome, and cutaneous embolization can be seen as well. Evaluation includes duplex studies and arteriography with the arm at rest and in the provocative position.

Treatment is based on extent of injury. For those with compression of the artery alone, modification of throwing motion has resulted in improvement of symptoms. Saphenous vein patch angioplasty has been used for those whose symptoms do not improve.[73,74] In patients with structural injury to the vessel, resection with saphenous vein bypass has been performed either anatomically tunneled or extraanatomically above the pectoralis minor. Long-term results are good, and many of the athletes treated at major centers are able to return to competition after rehabilitation.[74-76]

Thoracic Outlet Syndrome

Athletes who engage in overextended shoulder motion, such as baseball pitchers, butterfly swimmers, weightlifters, and oarsmen, are potential candidates for thoracic outlet compression. Although not as common as neurogenic and venous thoracic outlet syndrome, injuries to the subclavian artery have been reported in these athletes. Because a comprehensive review of thoracic outlet syndrome is provided elsewhere (see Chapters 120-124), only a brief discussion as it relates to athletic activities is given here.

Clinical Findings and Risk Factors

Compression of the subclavian or axillary artery can occur at the scalene muscles, costoclavicular space, or pectoralis minor muscle. A significant portion of cases of arterial thoracic outlet syndrome are due to underlying bone abnormalities, such as a cervical rib or anomalous first rib; but in athletes, hypertrophy of the scalene muscles or pectoralis minor muscles can lead to symptoms as well.[74] With chronic compression and vessel wall damage, a spectrum of disease can develop, including thromboembolism, occlusive disease, and aneurysm formation.

Although arterial thoracic outlet syndrome has been recognized for more than 2 centuries, the association with elite athletes has only been recent. Tullos et al.[77] in 1972 reported an axillary artery thrombus secondary to compression by the pectoralis minor in a major league pitcher. In 1978 Strukel and Garrick[78] reported on three competitive baseball pitchers with thoracic outlet compression. However, until the 1986 report of Fields et al.[79] on athletic injury in the thoracic outlet, the injury had received little attention. In their fascinating report, they describe a major league pitcher who suffered a catastrophic stroke resulting from subclavian artery thrombosis with proximal clot propagation.

Symptoms are similar to those previously described in humeral head compression of the axillary artery and include arm fatigue, loss of pitch velocity, finger numbness, Raynaud syndrome, and cutaneous embolization. It is often difficult to make the diagnosis, and evaluation by an orthopedic surgeon to rule out musculoskeletal abnormalities is useful. Duplex scanning and transcutaneous Doppler studies with the athlete in the pitching position help to detect compression of the subclavian or axillary artery. A definitive diagnosis is established by arteriography with positional exposure (Fig. 185.10).

Treatment

Treatment depends on the extent of injury. Nonbone compression alone can be treated by division of the offending muscle or tendon.[73] If an anomalous first rib or cervical rib is the culprit, a transaxillary approach can be used for decompression. If the subclavian artery requires reconstruction because of severe occlusive disease or aneurysmal disease, combined supraclavicular and infraclavicular incisions provide better exposure. Saphenous vein is the preferred conduit for bypass, although prosthetic grafts or the femoral vein can also be used.[74,80] Long-term patency rates are good, approaching 90% to 100%. The ability to return to competition after repair is not well documented.

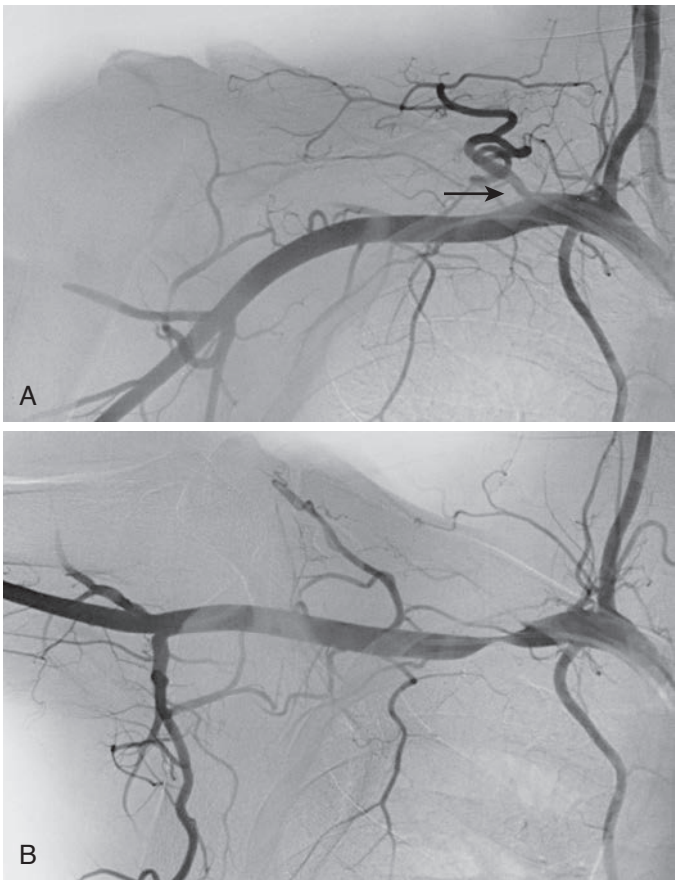

Figure 185.10 (A) Arteriogram of the right subclavian artery including the thyrocervical trunk *(arrow)* in a professional baseball pitcher. No injury is seen when the arm is placed in neutral position. (B) There is compression of the subclavian artery and occlusion of the thyrocervical trunk when the arm is placed in the pitching position (hyperabduction).

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Brown SN, Doolittle DA, Bohanon CJ, et al. Quadrilateral space syndrome: the mayo clinic experience with a new classification system and case series. *Mayo Clin Proc*. 2015;90(3):382–394.

New classification system for quadrilateral space syndrome explaining the differences between vascular and neurogenic etiologies, and the best treatment options for each process.

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Nasu Y, Kurozawa Y, Fujiwara Y, et al. Multicenter study on finger systolic blood pressure test for diagnosis of vibration-induced white finger. *Int Arch Occup Environ Health*. 2008;81:639.

This contemporary multicenter study demonstrates the sensitivity and specificity of noninvasive systolic blood pressure measurements to make the diagnosis of hand-arm vibration syndrome. Included are the techniques of performing this testing.

A complete reference list can be found online at www.expertconsult.com.

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186 CHAPTER

Special Techniques in Pediatric Vascular Surgery

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INTRODUCTION

Although conditions afflicting the extracardiac vascular system during infancy and childhood have been described for well over two centuries, a comprehensive literature dedicated to the management of pediatric vascular surgery patients remains lacking. Despite the presence of a number of textbooks devoted to the focused topic of pediatric cardiac surgery, a unified resource collating common themes and describing surgical techniques and principles does not exist for vascular surgery of children and the young adult. This can partly be explained by the range of vascular surgery conditions encountered in the modern era of pediatric surgery and by the diversity of providers who render treatment in this therapeutic area. Beyond pediatric surgeons with expertise in advanced vascular surgery reconstruction, adult vascular surgeons, pediatric and adult cardiothoracic surgeons, transplant surgeons, urologists, plastic surgeons, and adult general surgeons may all at one time or another operate on the blood vessels of pediatric patients. It is our hope in this introductory chapter to provide a broad overview of concepts and techniques that are particularly relevant to the pediatric population and that may prove useful to those who, either rarely or frequently, may be called upon to treat the vascular problems of this unique age group.

HISTORICAL BACKGROUND

One might trace the origins of pediatric vascular surgery to the 16th century when Guido Guidi first described a congenital vascular malformation after observing pulsatile varices protruding from a young man's scalp.[1] Giovanni Morgagni, a precocious Italian anatomist and a pioneer in the development of pediatric surgery, was instrumental in further expanding this early experience with vascular anomalies. His original description of coarctation of the thoracic aorta in 1760 was just one of his many original discoveries.[2] Sixty years later, August Meckel reported the associated collateral circulation and rib erosion that is seen in this condition.[3] In 1835 Schlessinger was the first to discover that aortic coarctation is not limited to the aortic isthmus[4] and, later in the same century, Pierre-Carl Pontain reported on arterial hypertension as a pathophysiologic consequence of coarctation.[5] Although much less frequently encountered, constriction of the subisthmic aorta was noted by Schlessinger during his autopsy of a 15-year-old girl whose distal thoracic aorta was nearly obliterated.[6] Quain reported a similar malady of the abdominal aorta in a 50-year-old man in 1847.[5] The first clinical recognition of renovascular hypertension in a child was in 1938 by Wyland Leadbetter and Carl Burkland.[7] They further noted that removal of the child's kidney,

which had become ischemic from fibromuscular dysplasia, corrected the hypertension. These are just a few of the myriad discoveries that have provided a framework for our current understanding of many pediatric vascular disorders.

For many years, operative repair of vessels in infants was deemed too hazardous to undertake.[8] Thomas Starzl overcame this barrier in July 1967 with his pioneering efforts to complete the first successful pediatric liver transplant. This operation, carried out on a 19-month-old child with a large hepatoma necessitating multiple vascular anastomoses, was a major milestone in pediatric vascular surgery.[9] Further technical advances were developed by Dean, Stanley, and Fry in their landmark work on pediatric patients with renovascular hypertension.[10,11] Over the past 3 to 4 decades, pediatric, cardiac, and vascular surgeons have continued to accrue significant clinical and technical experience that has translated into more consistent results and allowed more sophisticated vascular reconstructions to be undertaken in infants and children.

BASIC PRINCIPLES

William Ladd and Robert Gross are often cited as the founders of pediatric surgery, and much of the current-day training of pediatric surgeons can be traced to these two men and their many pioneering contributions. Publication of their textbook *Abdominal Surgery of Infancy and Childhood* in 1941 was instrumental in establishing pediatric surgery as a unique and independent surgical subspecialty.[12] This text emphasized the paramount importance of gentle tissue handling, one of William Halsted's fundamental surgical principles, when operating on children. Although there are many similarities between children and adults regarding surgical management and operative technique, there are also a number of important differences that warrant highlighting. These range from fluid management and anesthetic concerns to issues related to the future growth of organs and their surrounding critical elements. From a vascular surgical standpoint, one must take into consideration that as an infant or child grows, the demands on blood vessels will also increase.

Timing of Surgery

If clinically permissible, vascular reconstruction in small infants should be delayed to allow for further development as reconstructing vessels less than 2 mm in diameter is technically challenging and has been associated with comparatively inferior results. For example, deferring renal revascularization in children with renovascular hypertension until the child is at least 3 years old has been shown to increase the likelihood of a successful outcome.[13] Fortunately, the incidence of neonatal hypertension is quite low, ranging from 0.2% to 2%,[14] and prolonging the use of antihypertensive medications in an effort to delay surgery has not been associated with significant long-term adverse effects.[15] However, occasionally, it can prove challenging to control high blood pressure in an infant, given the variable onset and duration of oral antihypertensive medications as well as unpredictable responses to these agents. Persistent, uncontrolled hypertension in these young patients can lead to congestive heart failure and cardiogenic shock, which may compel surgical reconstruction of the renal arteries regardless of the child's age. Although the preference is to defer surgical repair until the patient is of appropriate age and size, renal artery reconstruction has been safely performed in the very young; the University of Michigan has described their successful treatment of a 3-month-old, 4700-g baby with bilateral renal artery occlusions.[13]

In contrast, the recommendation to delay the surgical correction of renovascular hypertension, early repair of thoracic coarctation is typically advised, given low reported perioperative mortality rates and a relatively low risk of reintervention or recurrent coarctation following reconstruction.[16] More importantly, early repair minimizes the incidence of vascular dysfunction and persistent hypertension.[17]

Anticoagulant and Antiplatelet Agents

The management of antithrombotic therapy in children has both similarities and important differences from that in adults. The major distinctions in the pediatric population relate to their dynamic and evolving coagulation system, age-dependent distribution and clearance of antithrombotic drugs, limited vascular access and the impact of this on monitoring efforts, the limited availability of medications in liquid formulations, dietary differences complicating oral vitamin K antagonists (VKAs), and general compliance issues.[18]

Unfractionated heparin has been used safely in children for decades. As in adults, heparin is typically systemically administered intraoperatively when vessels are temporarily clamped. A bolus dose of 75 to 100 units/kg results in a therapeutic activated partial thromboplastin time (aPTT) in 90% of children.[18] However, this percentage may in fact be an overestimation because aPTT therapeutic ranges are calculated using adult plasma and aPTTs are slightly elevated at baseline in young children. As such, the therapeutic range in a neonate correlates to a reduced relative increment in aPTT compared with adults; as a result, aPTT values correctly predict therapeutic heparin concentrations only 70% of the time.[19] Consequently, maintenance doses are age dependent, with infants requiring an increased hourly dose (28 units/kg per hour) compared with children older than 1 year of age (20 units/kg per hour).

Protamine sulfate can be safely given to reverse heparin intraoperative anticoagulation in the pediatric population. It is typically administered at a rate of 1.0 mg/100 units of heparin received. Given that neonates and young children have a more rapid clearance of heparin compared with adults, protamine is typically not administered in these age groups.[13,18] Avoiding protamine administration and allowing heparin to wear off over the early postoperative period confers an additional theoretical benefit of minimizing thrombotic events in particularly small-caliber blood vessels.

Similar to adults, postoperative anticoagulation regimens in children have evolved over the past decade. This is due to both difficulties inherent to the use of VKAs and the advent of newer agents such as low-molecular-weight heparin (LMWH) and novel oral anticoagulants (NOACs). VKAs can be particularly

problematic in newborns, given their decreased levels of vitamin K–dependent coagulation factors. The fact that VKAs are available only in tablet form, and that vitamin K is nearly absent from breast milk but typically present in infant formula, further complicates their use.[20] LMWH has now become the preoperative and postoperative anticoagulant agent of choice in the pediatric population. This class of drugs is appealing, given a decreased need for monitoring compared with VKAs, minimal drug-drug interactions, and a reduced risk of heparin-induced thrombocytopenia.[21] However, LMWH has considerable dose variability in children, which can result in fluctuations in antithrombin levels. In addition, the general unpopularity of frequent cutaneous injections obligated by LMWH therapy has led some centers to begin trialing NOACs. Although quite promising, the data on the use of NOACs in children remains limited at present and their appropriate role in this population remains to be defined.[22]

Antiplatelet drugs have been used for decades in children. If reconstructing very small vessels, aspirin is typically administered intraoperatively through a nasogastric tube to minimize the chance of thrombus formation at anastomotic sites.[13] Doses ranging from 1 to 5 mg/kg have been deemed safe.[18] Reye syndrome is rare in this setting because its association with aspirin is at much higher dosage levels (>40 mg/kg).[23] Clopidogrel has been used more frequently in recent years, particularly in children with heart disease. One randomized trial indicated that clopidogrel at a dose of 0.2 mg/kg per day was efficacious in young children.[24]

Pediatric Anesthesia and Perioperative Care

The subspecialty of pediatric anesthesia owes much of its foundation and progress to M. Digby Leigh, who published the first dedicated text on the discipline in 1947.[25] Although the full breadth of content pioneered by Leigh and further developed by subsequent generations of pediatric anesthesiologists is well beyond the scope of this chapter, there are several basic principles worth mentioning.

First, given that a neonate's ability to main normothermia is inadequate, the operating room environment should be optimized to minimize a baby's heat loss. As part of this effort, the ambient room temperature should be maintained between 23°C and 25°C (80°F and 85°F), inhaled gases should be warmed and humidified, fluids should be delivered via a warming device, and a forced warm air delivery device or warming blanket should be used. Second, given the obvious size differences between young children and adults, a full complement of appropriately sized anesthesia-related equipment and devices (pulse oximeter probes, facemasks, tracheal tubes, suction catheters, laryngoscope blades, etc.) must be readily available.

A critical component of anesthesia administration to infants and young children is expertise in airway management. This skill set requires a detailed knowledge of the developmental anatomy and physiology of the pediatric skull, nose, and upper airway. Equally as important to safely performing facemask ventilation, laryngoscopy, and subsequent tracheal intubation is the ability to effectively address postoperative airway complications, some unique to the pediatric population. Laryngospasm, hypoxemia, croup, and aspiration are among the respiratory events that are responsible for nearly 50% of pediatric anesthesia complications.[26] In contrast to adults, the usual method of inducing anesthesia in children is with inhalational agents, typically nitrous oxide followed by sevoflurane. Upon emergence from anesthesia, the child is typically placed in the "recovery position" (lateral decubitus) because it promotes airway patency and is helpful should the child develop emesis. This latter complication is not trivial because postoperative nausea and vomiting are significantly more common in children than adults and, among other negative consequences, can delay discharge from the recovery room. In addition to proper positioning in the lateral recovery position to minimize the aspiration risk, children are often prophylactically administered an antiemetic along with dexamethasone, which can minimize both tracheal edema and postoperative vomiting.[27]

BASIC VASCULAR TECHNIQUES

As in the adult world, there are multiple elements that comprise any successful pediatric vascular surgery operation. Proper patient positioning, adequate exposure and lighting, optimal incision location and size, safe and effective clamp selection and placement, appropriate suture material and conduit choice, and technically sound anastomoses are all important for a positive outcome. Of course, the aforementioned factors are all of secondary significance behind selecting the correct procedure from the onset.

Vascular Instruments and Retractors

In general, vascular instruments used during pediatric reconstructions are similar to those typically used in the adult realm. However, small versions of forceps, clamps, Castroviejo needle holders, scissors, and other specialty instruments are available and can be helpful in manipulating smaller-sized pediatric blood vessels. For example, "baby" Jacobson or Potts bulldog clamps are useful atraumatic vascular clamps, and Yasargil or Heifitz clips can be particularly beneficial for small or fragile vessels at risk for tearing or prone to spasm. Delicate handling of tissue with Debakey and fine Gerald forceps is advised. Metzenbaum, Stevens tenotomy, and Potts or Dietrich scissors are useful for dissecting vessels as well as extending arteriotomies.

With regard to retractor systems, both self-retaining and handheld instruments are used much like in adult surgery. For abdominal procedures, typically a Thompson Pediatric Abdominal System (Thompson Surgical Instruments, Traverse City, Michigan) is used because its selection of lower-profile blades with variable depths and widths affords considerable versatility in young patients (Fig. 186.1). For the extremities and neck, Weitlaner retractors, which come in various sizes, are most commonly used.

Vascular Exposure and Clamping

Information relating to specific vascular exposures is beyond the scope of this chapter and will be described elsewhere in

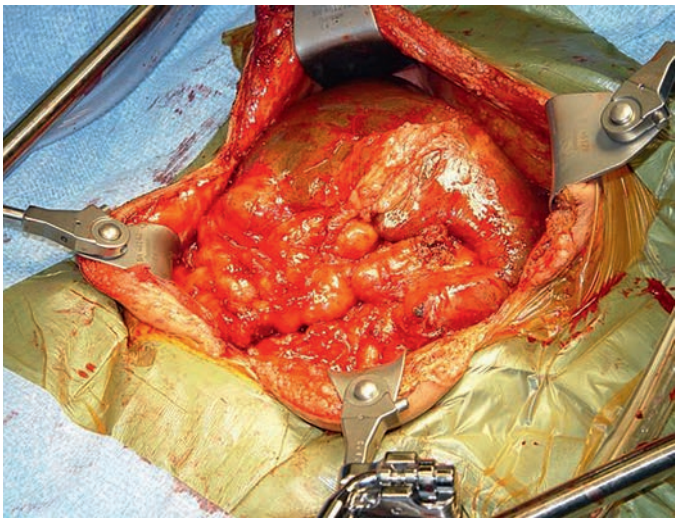

Figure 186.1 A Thompson Pediatric Abdominal Retractor System (Thompson Surgical Instruments, Traverse City, Michigan), due to its lower profile blades with variable depths and widths, provides excellent exposure to the abdominal contents in young patients.

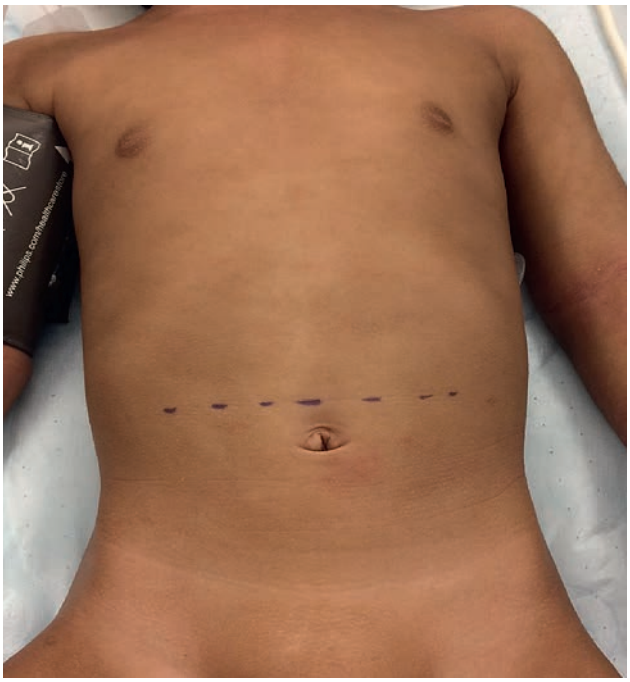

Figure 186.2 Proposed location of a transverse abdominal incision in a young child, which can provide better exposure of the abdominal aorta and viscera given the barrel-shaped nature of the abdomen.

this textbook. In general, exposure of the relevant blood vessels should be done in the most direct route possible and with the least amount of tissue manipulation. Broadly prepping the patient is recommended in the event that more complex exposure or vascular control than originally anticipated becomes necessary. Anatomic landmarks and key structures should guide the surgeon's incision and subsequent dissection. In the absence of a palpable pulse to further direct the course of the dissection, a Doppler probe should be used in the effort to avoid unnecessary tissue disruption and the creation of tissue flaps that may negatively impact wound healing. Given that the abdomen of young child is barrel shaped, a transverse incision often provides better exposure to the abdominal viscera and the abdominal aorta and its major branches than a midline incision (Fig. 186.2). There is also evidence that a transverse incision is less likely to develop fascial dehiscence compared with a vertical incision in children less than 1 year of age.[28]

Gentle handling of tissues is paramount in the effort to avoid vessel disruption, hematoma formation, and other bleeding complications. Particular caution should be undertaken in patients with known connective tissue disorder or in the setting of infected or dissected vessels. The clinical and anatomic scenario at hand should guide selection of appropriate clamp type and size. Applying clamps in a side-biting fashion should generally be avoided given the small caliber of pediatric vessels and the increased risk of "back-wall" suture placement with subsequent vessel thrombosis.

Arteriotomy Closure

Primary closure of an arteriotomy or venotomy in a pediatric patient is the simplest and most expedient means of arterial or venous reconstruction. However, given the small caliber of pediatric vessels and their need for future growth, primary closure can result in luminal narrowing with a hemodynamically significant stenosis. As such, similar to the situation with adult vascular reconstructions, judgment must be used in determining the safety and appropriateness of closing a given vessel primarily versus using a patch closure that may be necessary to ensure an adequate luminal size. Although a patch repair in adults is typically undertaken by beginning a running suture at each apex, some have advocated for an interrupted suture technique in children (see Figs. 59.39 and 59.40); such a strategy will theoretically better accommodate native vessel growth and luminal expansion over time. Similarly, the patch size should be made sufficiently large so as to not cause vessel constriction over time as the child grows. In one report of pediatric trauma patients less than 10 years of age and with a vascular injury, patch repair was the most common operative management strategy, being used 3 times more frequently than bypass grafting (28% vs. 9.6%).[29]

Arterial Replacement and Bypass Procedures

Several different techniques can be used to address young patients afflicted with aneurysmal degeneration or arterial occlusive disease. Although relatively infrequently encountered in children, connective tissue disorders, tuberous sclerosis, vessel infection, inflammatory middle aortic syndrome, and trauma are all examples of clinical conditions that may necessitate a major vascular reconstruction. Replacement of the diseased vessel with a bypass procedure is the most commonly performed revascularization procedure in these settings. Depending on the extent of vessel involvement, segmental resection and reconstruction with vessel reimplantation or primary end-to-end reanastomosis are additional options. Reimplantation has been used in the

Figure 186.3 Ostial stenosis of the left renal artery in a 4-year-old girl with renovascular hypertension. (From Stanley JC, Criado E, Upchurch GR Jr, Brophy PD, Cho KJ, Rectenwald JE. Pediatric renovascular hypertension: 132 primary and 30 secondary operations in 97 children. *J Vasc Surg.* 2006;44(6):1219-1228.)

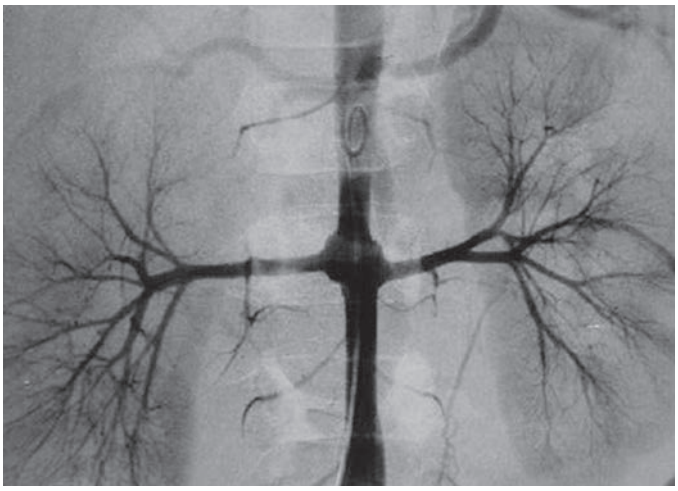

Figure 186.4 Bilateral renal artery–aortic implantations in a 7-year-old boy. Note the capacious aortic anastomoses from spatulation of the renal arteries. (From Stanley JC, Criado E, Upchurch GR Jr, Brophy PD, Cho KJ, Rectenwald JE. Pediatric renovascular hypertension: 132 primary and 30 secondary operations in 97 children. *J Vasc Surg.* 2006;44(6):1219-1228.)

surgical management of peripheral aneurysms, as well as for children with renovascular hypertension. This latter clinical entity typically develops from renal artery stenosis as a result of progressive medial dysplasia and intimal fibroplasia. The anatomic pattern where disease is limited to the renal ostia is particularly conducive to repair with renal artery implantation (Fig. 186.3). In a series of 97 children treated surgically for renovascular hypertension at the University of Michigan, reimplantation of the renal artery was the most common means of repair, being performed in 45% of procedures.[13] With this technique, the anterior and posterior aspects of the transected renal artery should be spatulated to ensure creation of a generous anastomosis. Typically, the renal artery is reimplanted onto the aorta; although infrequent, the iliac artery can be used if performing a renal autotransplantation. An aortic punch device can be helpful in fashioning a desired oval aortotomy that is at least twice the diameter of the renal artery. A tendency toward oversizing the aortotomy in this manner will decrease the chance of developing an anastomotic stricture over time (Fig. 186.4). As noted previously, an interrupted suture technique should be considered for the anastomosis unless the patient is a mature adolescent with normal-sized vessels. Medial mobilization of the kidney may be necessary to ensure the anastomosis is free of tension.

Peripheral aneurysms can often be treated by resection and primary end-to-end reanastomosis. This technique has been used for aneurysms of the renal, splanchnic, brachial, femoral, and popliteal arteries.[30] When using this technique, both vessel ends should be spatulated to increase the anastomotic circumference (see Fig. 139.41).

Reconstruction with a bypass or interposition graft adds complexity to the procedure, given the need for an additional anastomosis and important issues related to conduit selection. The most common indications for performing an arterial bypass or interposition graft in the extremity of a child are peripheral aneurysms and trauma. Traumatic causes include both blunt injury and iatrogenic injury, such as arterial disruption or thrombosis associated with percutaneous access or catheter placement. Abdominal aortic coarctation, also referred to as midaortic syndrome, and renovascular hypertension due to renal artery stenosis, on the other hand, are the most frequent indications for bypass grafting originating from the descending thoracic or abdominal aorta.

Children with abdominal aortic coarctation typically develop aortic narrowing in a supraceliac location and present during the first or second decade of life with refractory hypertension (Fig. 186.5A). Up to 80% of these children have coexisting splanchnic or renal artery occlusive disease. In rare cases the degree of obstruction can result in symptomatic mesenteric ischemia.[31] In the largest series to date of 53 children surgically treated for midaortic syndrome, Stanley and colleagues corrected the developmental narrowing with either a thoracoabdominal bypass graft ($n = 26$) or an interposition aortoaortic graft ($n = 3$).[32] Notably, more than half of the bypass procedures necessitated a concomitant renal or splanchnic revascularization procedure (see Fig. 186.5B). The conduit of choice for thoracoabdominal bypass grafting in this series was expanded PTFE because it was believed to be less likely to undergo postimplantation dilatation compared with Dacron. It is important that the graft be oversized in relation to the aortic diameter at the time of implantation to avoid the development of critical stenoses with future aortic growth. As such, 8- to 12-mm grafts, 12- to 16-mm grafts, and 14- to 20-mm grafts are recommended for use in young children, early adolescents, and late adolescents/adults, respectively. In contrast to graft diameter, the length of the graft is not as important as there is minimal longitudinal aortic growth after the age of 10. Although the long-term overall

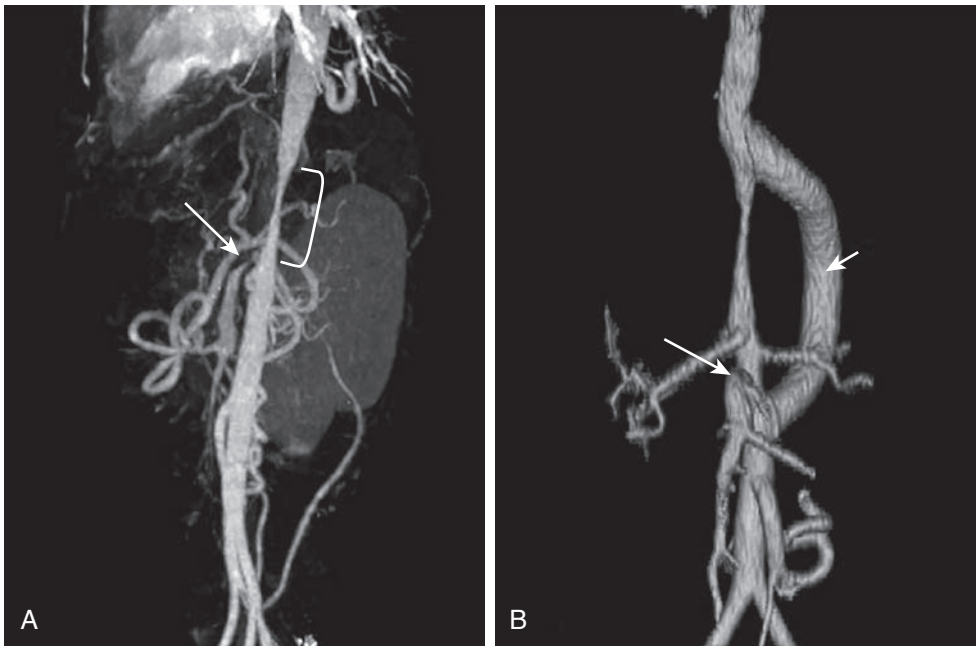

Figure 186.5 A, Midaortic syndrome *(bracket)* with superior mesenteric artery stenosis *(arrow)*. B, Thoracoabdominal bypass *(large arrow)* with aortic implantation of superior mesenteric artery *(small arrow)*. (From Stanley JC, Criado E, Eliason JL, Upchurch GR Jr, Berguer R, Rectenwald JE. Abdominal aortic coarctation: surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. *J Vasc Surg*. 2008;48(5):1073-1082.)

graft patency was excellent in Stanley's series (97% at 5 years), lifelong surveillance is necessary to ensure that reoperation for graft outgrowth, anastomotic stenosis, or failed visceral artery reconstruction is not required.[32]

The use of a prosthetic conduit in children is traditionally limited to major aortic reconstructions. Autogenous conduit, namely the great saphenous vein (GSV), is preferred for visceral and peripheral reconstructions. It is important to be aware that GSV grafts can undergo late expansion and even aneurysmal degeneration, especially if the vein is unsupported when used in young children. A review of 100 aortorenal grafts created with GSV revealed that 16% developed late aneurysmal dilatation or stenosis.[33] In a more recent series of 16 lower extremity bypass procedures undertaken with GSV in children, the vein grafts proved more durable, with only 11% demonstrating expansion over a 10-year follow-up period.[34] Given the risks of late weakening and aneurysmal degeneration, some advocate for supporting GSV grafts originating from the abdominal or pelvic vessels in a Dacron mesh wrap. Alternatively, some prefer to use the internal iliac artery as a conduit when originating a bypass from the aorta or iliac vessels because it offers greater long-term durability compared with GSV.[13] A novel and quite creative technique using the principles of tissue expansion has recently been developed for children with midaortic syndrome that can obviate the need for any of the aforementioned conduits.[35] By periodically inflating a tissue expander implanted posterior to the distal aorta over time, longitudinal growth of the distal aorta and iliac vessels is promoted, ultimately allowing for resection of the diseased segment of aorta and reconstruction with a primary end-to-end anastomosis (Fig. 186.6).

Endovascular

Paralleling the tremendous improvements in endovascular technology seen in adult cardiovascular care, recent technical advances have now made it possible to perform complex percutaneous arterial and venous interventions in infants and children. There are several fundamental differences in technique between adults and children with regard to contrast angiography. In general, contrast volume should not exceed 4 to 5 mL/kg in neonates or 6 to 8 mL/kg in infants. A hand injection technique, rather than power injection, is generally preferred when the patient is less than 15 kg to maximize control of the arterial bed opacification and minimize contrast reflux or excessive injection rates. Power injectors can safely be used in children weighing more than 15 kg, although the injection parameters are typically reduced to half the adult rates.[36] Systemic heparinization is usually administered following arterial access in children less than 15 kg to prevent femoral artery thrombosis. Access is usually gained with ultrasound guidance using a 21-gauge access needle and an 0.018-inch micropuncture wire.[37] A 3- to 5-Fr vascular sheath can then be placed for diagnostic and/or therapeutic interventions. An array of dedicated pediatric-length catheters has been developed to facilitate cannulation of the artery or vein of interest.

Complications related to percutaneous arterial access are generally uncommon, but their frequency can approach 10% in children younger than 1 year of age.[36] The most frequently reported complications include hematoma, dissection, thrombosis, pseudoaneurysms, and arteriovenous fistula. Vessel thrombosis as a result of vasospasm is of particular concern in

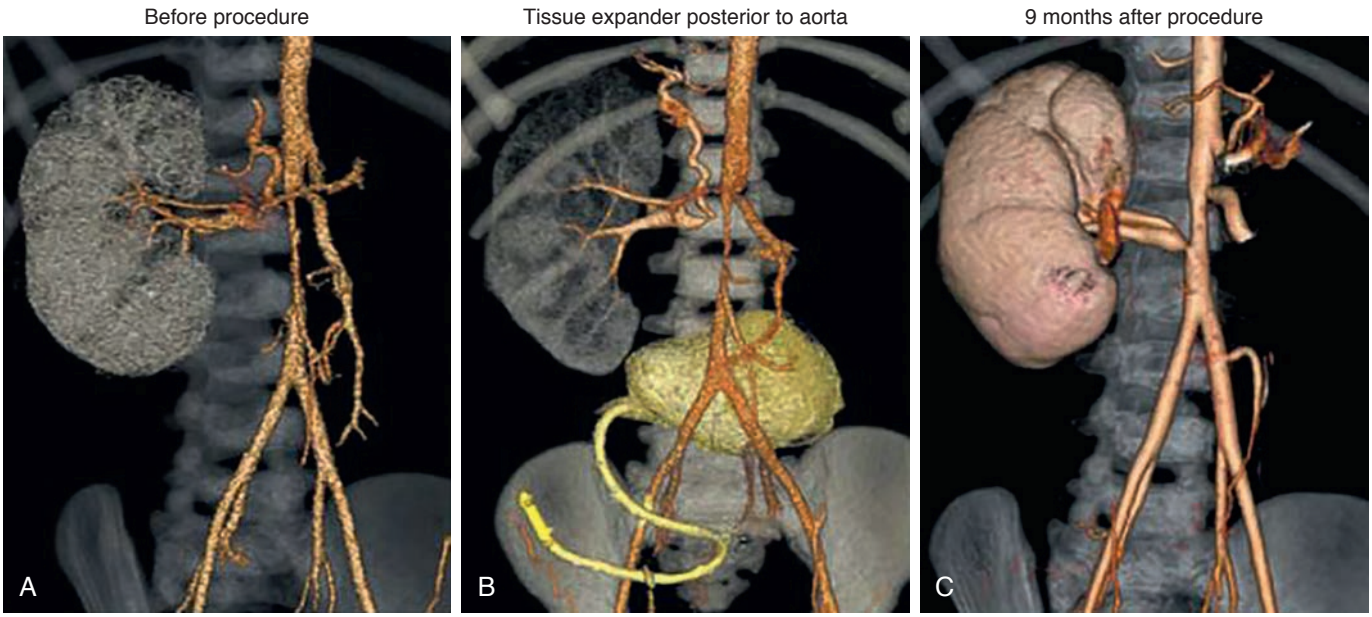

Figure 186.6 (A) Frontal angiographic view of 3-year-old girl with midaortic syndrome. (B) Placement of retroaortic tissue expander prior to aortic surgery. (C) Removal of tissue expander followed by primary aortic reconstruction. (From Kim HB, Vakili K, Modi BP, et al. A novel treatment for the midaortic syndrome. *N Engl J Med*. 2012;367(24):2361-2362.)

small patients (<15 kg); incidence rates as high as 16% have been reported.[38] Prophylactic intraarterial nitroglycerin (1 to 3 μg/kg) can be administered to help prevent this complication in small children.[36]

Percutaneous balloon angioplasty has been used as a treatment for children with renovascular hypertension for more than 20 years, with varying degrees of success. In one series of 33 patients, Shroff and colleagues achieved blood pressure control in only 54%, and 37% of the patients developed restenosis.[39] It is recommended to avoid placing stents in pediatric renal arteries unless there is significant elastic recoil after angioplasty or a postangioplasty dissection is identified. Hepatic artery stenosis can develop in up to 20% of pediatric liver transplant recipients,[40] and these lesions can also be successfully treated with percutaneous angioplasty techniques. Typically, balloons between 2 and 6 mm in diameter are used, and the associated complications include acute vessel dissection, vasospasm, and thrombosis.[41] The literature on this technique is limited to several case series, and currently no long-term data are available. Although balloon angioplasty of aortic coarctation in pediatric patients has been a safe and effective treatment option since the 1980s, its durability remains in question. In a series of 67 neonates and children with coarctation treated by endovascular means, 25% developed recoarctation requiring reintervention and 5% developed an aneurysm at the angioplasty site at long-term follow-up (median, 5 years).[42]

Much like in adults, endovascular procedural success in children will likely continue to improve as the associated technology becomes further advanced over time. This treatment modality will likely confer the benefit of decreased perioperative morbidity at the potential expense of lower longer-term durability, a trade-off that parallels the adult experience with endovascular surgery.

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Largest series of pediatric patients who underwent primary and secondary operations for renovascular hypertension. The authors not only report their operative outcomes but also share their surgical techniques and lessons learned.

A complete reference list can be found online at www.expertconsult.com.

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187 CHAPTER

Aortic and Arterial Aneurysms in the Pediatric Population

DAWN M. COLEMAN, JONATHAN L. ELIASON, and JAMES C. STANLEY

AORTIC ANEURYSMS 2439
NONAORTIC ARTERIAL ANEURYSMS 2442
SUMMARY 2447

Pediatric arterial aneurysms include many rare and heterogeneic diseases. Etiologies vary widely among the different types of aneurysms, with infection, inflammation, genetic disorders, and trauma being most common (Table 187.1). Aneurysms in children, with few exceptions, should be considered dangerous. Although optimal management strategies and established criteria for operative treatment remain ill defined, rupture and thrombosis are reported frequently enough to justify early intervention in most cases. Unfortunately, children having a systemic process responsible for their aneurysm carry the highest chance of rupture, but they are also at greatest operative risk. Many surgical procedures in the treatment of these aneurysms are complex, and management strategies based upon the specific arterial bed involved deserve individual review.

AORTIC ANEURYSMS

Aortic aneurysms are classically defined as enlargement (dilation) of the aorta's diameter greater than 1.5 times normal. Diagnosis of a pediatric aortic aneurysm requires a careful consideration of location and aortic size, for which standards are not well established. However, a contemporary retrospective series analyzed the results from 88 thoracic and 110 abdominal contrast material-enhanced computed tomographic examinations in children without known cardiovascular disease and determined a range of normal "effective diameters" of the aorta and common iliac arteries at multiple levels.[1] Aortic diameters exceeding the "normal" range were considered aneurysmal.

Etiologies of pediatric aortic aneurysm are quite diverse. Infectious aneurysms in the past accounted for nearly one-third of pediatric aortic aneurysms but are less commonly encountered in contemporary times, most often associated with umbilical artery catheterization.[2] Infectious aneurysms are typically saccular and may involve the thoracic aorta, abdominal aorta, and iliac vessels (Fig. 187.1). *Staphylococcus aureus* and *albus* are predominant organisms responsible for these infections. These aneurysms present most commonly during the first 2 years of life. In such cases, it is critical for infection to be quiescent if a prosthetic conduit is to be used for the aortic repair. Unfortunately, such an option does not exist in the face of many acutely expanding or ruptured infected aortic aneurysms. Noniatrogenic periaortic infections are also recognized as a rare cause of childhood aortic aneurysms.

Inflammatory aortic aneurysms are uncommon, being most often attributed to Takayasu aortoarteritis and in rare instances to Kawasaki disease, Behçet disease, and systemic lupus erythematosus.[3] While Takayasu aortitis more commonly results in aortic stenoses, related aneurysms do occur, typically involving the thoracic aorta.[4] They affect older children and adolescents.

Kawasaki disease (mucocutaneous lymph node syndrome) is characterized by a febrile state typically in young children having erythematous extremities, fingertip desquamation, conjunctivitis, and lymphadenopathy. The disease more commonly affects the abdominal segment of the aorta, usually during the first year of life. A critical component of Kawasaki disease is coronary artery aneurysm, affecting approximately a fifth of children with

Abstract

Pediatric arterial aneurysms are rare and heterogeneous. Aneurysms in children, with few exceptions, should be considered hazardous and while optimal management strategies and established criteria for operative treatment remain ill defined, rupture and thrombosis are reported frequently enough to justify early intervention in most cases. Individualized surgical treatment is often complex and must consider patient age and anatomic factors; these reconstructions may be undertaken with negligible perioperative morbidity and mortality. Given the predicted long life expectancy of most children affected with these aneurysms, the treatment must be thoughtfully planned and executed for durability and long-term follow-up is mandatory.

TABLE 187.1 Pediatric Aneurysms

Etiology	Principal Artery Affected	Histologic and Morphologic Character	Clinical Characteristics
I: Infection	Aorta, iliac arteries	Acute inflammatory infiltrates present initially, then chronic inflammation and fibrotic changes; saccular aneurysms	Umbilical artery catheterization, endocarditis, predisposing factors; fever, systemic infectious symptoms; untreated aneurysms often progress to rupture
II: Aortitis Takayasu disease	Aorta	Chronic inflammation with giant cells, vessel wall necrosis; saccular aneurysms	Signs and symptoms more often relate to stenotic disease than aneurysms, with the latter often remaining asymptomatic
III: Arteritis Behçet disease Systemic lupus Kawasaki disease Periarteritis nodosa	Renal, splanchnic, axillobrachial, iliofemoral arteries (Kawasaki: coronary arteries)	Chronic panmural inflammation and degeneration, late fibrosis; multiple small saccular aneurysms	Usually asymptomatic but may cause hematuria, perirenal hematomas or death with rupture (lupus, periarteritis nodosa); myocardial infarction or tamponade (Kawasaki), aneurysm thrombosis more common than rupture
IV: Genetic Arterial tortuosity Cutaneous Laxa syndrome Ehlers-Danlos syndrome Marfan syndrome Loeys-Dietz syndrome Tuberous sclerosis	Aorta, muscular arteries	Medial elastic tissue disorganization, mucinous deposits (cystic medial necrosis); solitary fusiform and saccular aneurysms	Aortic rupture or dissection relatively common; arteriography and vascular reconstructions may be hazardous in the face of active disease
V: Developmental: Idiopathic	Aorta, renal, iliofemoral arteries	Medial thinning and fibroplasia; solitary and multiple saccular aneurysms affecting arterial bifurcations most often	Usually asymptomatic; extremity aneurysms often present as painless, pulsatile mass
VI: Traumatic: Extravascular	Aorta, extremity arteries	Disruption of usually three layers of artery (pseudoaneurysm), thrombosis of small aneurysms Common; saccular aneurysms	Protean manifestations; aortic aneurysms often rupture; peripheral lesions often asymptomatic

an attending risk of acute thrombosis. Aneurysm regression with immunosuppression is well described in this disease, and reconstructions should be avoided in the face of active disease at the risk of anastomotic disruption or stenosis.[5]

A number of genetic diseases have been associated with the development of pediatric aortic aneurysms. The most common ones deserve comment. Tuberous sclerosis is an autosomal dominant disorder characterized by complex multiorgan involvement affecting the brain, retina, kidneys, heart, and skin, with vascular manifestations occurring less often. Hamartomas in multiple organ systems are a common feature, and central nervous system involvement occurs often with associated seizures and mental retardation. The vascular complications of this entity tend to occur in younger children. The abdominal and thoracic aorta are more commonly affected than peripheral arteries (Fig. 187.2). Nearly two dozen pediatric aortic aneurysms attributed to tuberous sclerosis have been reported.[6-8] Instances of rupture and death have been reported in both infancy and childhood.[6] Although the pathogenesis of the vasculopathy remains unclear, there is evidence for dysplastic and degenerative changes within the arterial wall and a loss of heterozygosity involving genes *TSC1* and *TSC2*.[6,9,10]

Ehlers-Danlos, Marfan, Loeys-Dietz, arterial tortuosity, and cutaneous laxa syndromes are more often associated with aortic root and thoracic aortic aneurysms or dissections in older children. Vascular (type IV) Ehlers-Danlos syndrome is an autosomal dominant disease resulting from a defect in the *COL3A1* gene responsible for type III collagen. The syndrome is associated with spontaneous rupture of hollow viscera, as well as large arteries such as the aorta. Aortic lesions are not rare in this syndrome.[11] An earlier report noted that of 132 vascular complications encountered in 24 patients, 17 had thoracic or abdominal aortic aneurysms, dissections, or ruptures.[12] Vascular repair in these patients may be hazardous because the arteries are extremely fragile, and reconstructions should be undertaken with extreme caution.

Marfan syndrome is due to an autosomal dominant disease resulting from a defect in the *FBN1* gene which leads to abnormal collagen cross-linking. Dilation of the aortic root, which may progress to aneurysmal degeneration, is a hallmark vascular feature of this syndrome. Although infantile disease is rare and children are less commonly affected than adults, it is noteworthy that 50% to 83% of children with Marfan syndrome exhibit aortic dilation, including 20% having aortic aneurysms. Neonatal

Figure 187.1 Infectious 2.2-cm infrarenal abdominal aortic aneurysm *(arrow)* and a 1.3-cm right iliac artery aneurysm *(arrow)* in a 2-week-old associated with umbilical catheterization and sepsis (computed tomography angiography).[2]

Figure 187.2 Multiple saccular aneurysms along the anteromedial aspect of the descending thoracic aorta in a 5-year-old with tuberous sclerosis.

Marfan syndrome, resulting primarily from de novo mutations, is a particularly severe and rapidly progressive phenotype of this genetic disease.[13-15]

Loeys-Dietz syndrome is an autosomal dominant connective tissue disorder resulting from a defect in the TGF-β pathway that causes abnormal pathway signaling, tissue friability, craniofacial abnormalities, and a characteristic panvasculopathy.[16,17] The vascular phenotype is characterized mainly by descending thoracic aortic and peripheral aneurysms, arterial tortuosity, and dissections. Progressive aneurysmal expansion and rupture are commonplace with this syndrome and operative therapy is pursued earlier rather than later in most cases. Beta-blocker and angiotensin II type I receptor blocker (ARB) therapy should be considered for both Marfan and Loeys-Dietz patients, to potentially reduce progressive aortic root dilation.[18,19]

Frequently no identifiable etiology can be ascribed to pediatric aortic aneurysms. These aneurysms are considered as idiopathic, as well as developmental or congenital, in origin. In cases of thoracic aortic aneurysms that do not meet criteria for Marfan or Loeys-Dietz syndromes ("nonsyndromic"), there are data to suggest that acceptance of a global phenotype is useful to stratify risk and guide clinical interventions, including pharmacologic means to lessen the rate of aneurysmal progression.[20] It is noteworthy that children having systemic, noncardiovascular features involving the craniofacial, ocular, or cutaneous tissues have aneurysms associated with more rapid enlargement.

In other children, these aneurysms may be attributed to post-stenotic turbulent flow causing aortic dilation. Such aneurysms are most often observed in children with thoracic isthmic coarctations or abdominal narrowings caused by abnormal fusion of the embryonic dorsal aortas during the fourth week of fetal development. In as much as concurrent peripheral aneurysms are common in these cases, it is likely that an unknown genetic defect, yet to be identified, that results in a major fault in the vessel wall formation.

Surgical interventions for aortic aneurysms in children include aneurysmectomy with interposition graft reconstructions, nonanatomic aorto-aortic bypasses, and closed or open aneurysmorrhaphy in selected children.[2] These reconstructions are often complex, given the frequency of splanchnic or renal artery branches originating from the aneurysms.

Aneurysmectomy with interposition graft aortic reconstruction is the most direct means of treating pediatric abdominal aortic aneurysms limited to the infrarenal aorta (Fig. 187.3).[2] The largest diameter graft that can safely be implanted should be used, but not one so large that slow flow along the grafts inner surface results in the accumulation of excess thrombus with the potential for thromboembolism. Large grafts placed in older children and adolescents allow for sufficient blood flow as adulthood is reached, and in infants and younger children a large conduit will permit further growth prior to the predicted need for reoperation as the child outgrows the initial reconstruction. In general, this translates to 6- to 10-mm grafts in newborns and small infants, 10- to 12-mm grafts in larger infants, 12- to 14-mm grafts in young children, and 14- to 20-mm grafts in older children and adolescents. Teflon (expanded polytetrafluoroethylene [ePTFE]) prostheses are favored over

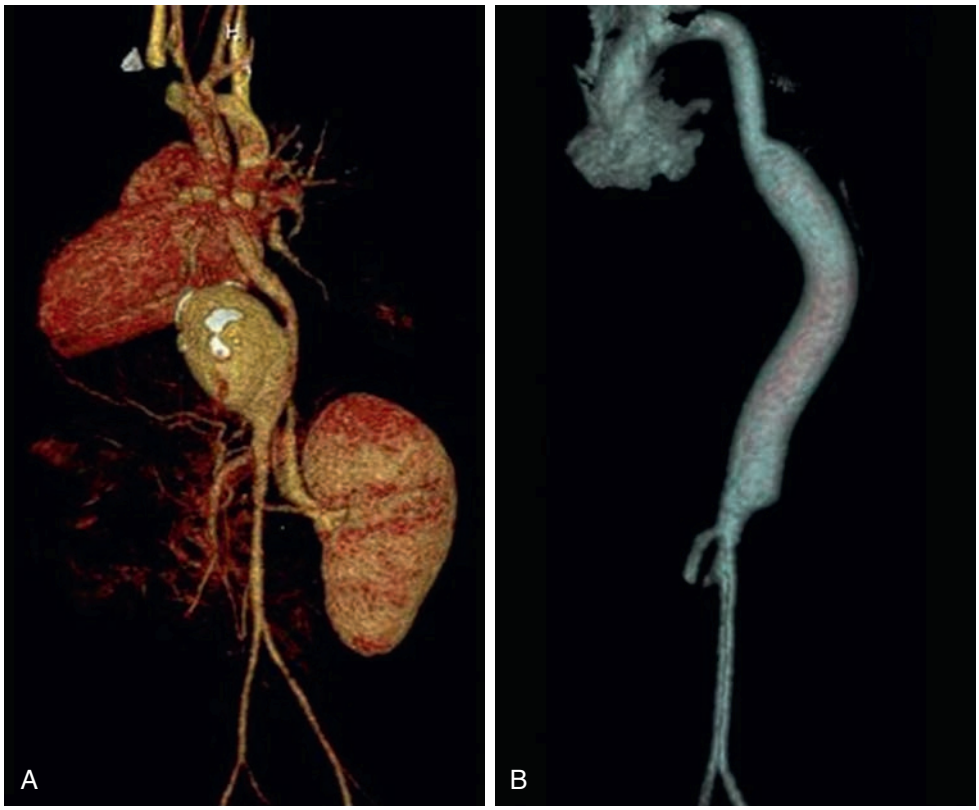

Figure 187.3 (A) Saccular 3.5-cm supraceliac mycotic aneurysm in a 20-month-old associated with infected umbilical artery catheterization (computed tomography angiography). (B) Magnetic resonance angiography following aneurysmectomy and repair with interposition 12-mm expanded polytetrafluoroethylene.[2]

woven or knitted Dacron (polyethylene terephthalate) due to the inherent postimplantation dilation of the latter conduits. Cryopreserved homografts may be an appropriate conduit in select children, although their long-term durability has not been established.[6,21]

Aneurysmectomy with nonanatomic aortic reconstructions in the form of thoracoabdominal or abdominal aorto-aortic and aorto-iliac bypasses are undertaken most often when splanchnic or renal arteries have their origins from the aneurysm itself, mandating their revascularization (Fig. 187.4).[2] Usually, the aortic reconstructions are undertaken first, before reconstructions of the branch arteries. This provides continuous flow to the pelvic and lower extremity tissues during respective splanchnic and renal artery reconstructions, and eventual aneurysmectomy.

The role of closed or open aneurysmorrhaphy in treating pediatric abdominal aortic aneurysms is ill defined.[2] Nevertheless, if the underlying basis of the aortic dilation can be eliminated, such as with post-stenotic aneurysms, the inexorable progression of aortic expansion following aneurysmorrhaphy may not occur. This assumes the residual aortic wall will remain stable. Although the latter may be reasonable, no long-term data exist to confirm such. Closed aneurysmorrhaphy is performed most often in treating small fusiform aortic aneurysms. Two specific circumstances negate the safe performance of closed aneurysmorrhaphy: (1) the first being the presence of thrombus or loose fibrinous debris lining the aneurysm sac, and (2) the second being an exceedingly large aneurysm in which the plicated wall would be difficult to collapse. In the latter setting, an open aneurysmorrhaphy with excision of a portion of the wall would be more appropriate (Fig. 187.5).

Endovascular aneurysm repair (EVAR) has a limited role in the definitive management of most pediatric abdominal aortic aneurysms. An exception to this tenet is the treatment of traumatic pseudoaneurysms in older adolescents in whom further aortic growth is unlikely, or in those emergent circumstances of an aortic disruption. Thoracic endovascular aneurysm repair (TEVAR) for thoracic aneurysm in select patients of appropriate age and size may be also appropriate, although caution exists in children with a progressive arteriopathy.

Surgical treatment of abdominal aortic aneurysms is successful in more than 90% of infants and young children.[2] This involves complex operative techniques that must take into account the child's growth potential, the aneurysm location and whether the splanchnic and renal arteries are involved. Regardless of the intervention undertaken, long-term follow-up is mandatory for all surgical interventions.

NONAORTIC ARTERIAL ANEURYSMS

The natural history of nonaortic pediatric arterial aneurysms remains ill defined, as is the categorization of these aneurysms.[22,23]

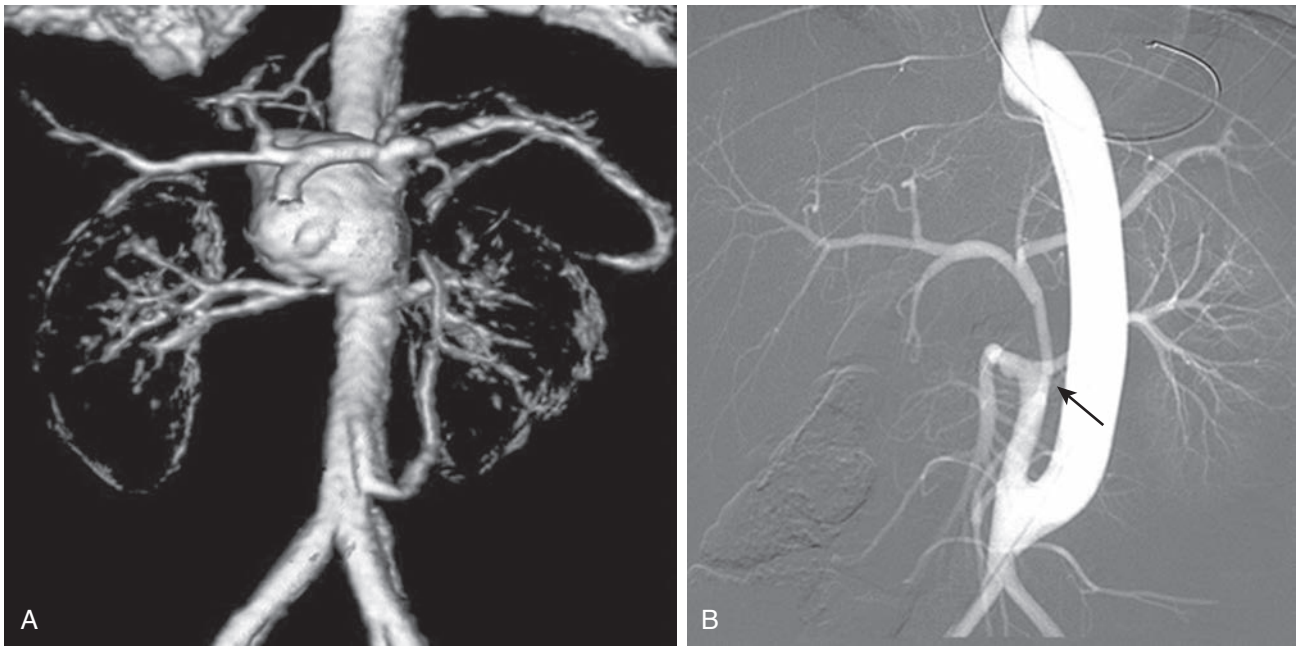

Figure 187.4 (A) Central abdominal aortic aneurysm with involvement of the celiac, superior mesenteric, and renal arteries associated with tuberous sclerosis in a 5-year-old boy (computed tomography angiography). (B) Treatment included aneurysmectomy, 14-mm expanded polytetrafluoroethylene thoracoabdominal bypass, aortic reimplantation of a left renal artery and superior mesenteric artery (SMA), and aortoceliac bypass with a hypogastric artery graft, all from the distal abdominal aorta *(arrow)*, as well as a right nephrectomy (digital subtraction arteriography).[2]

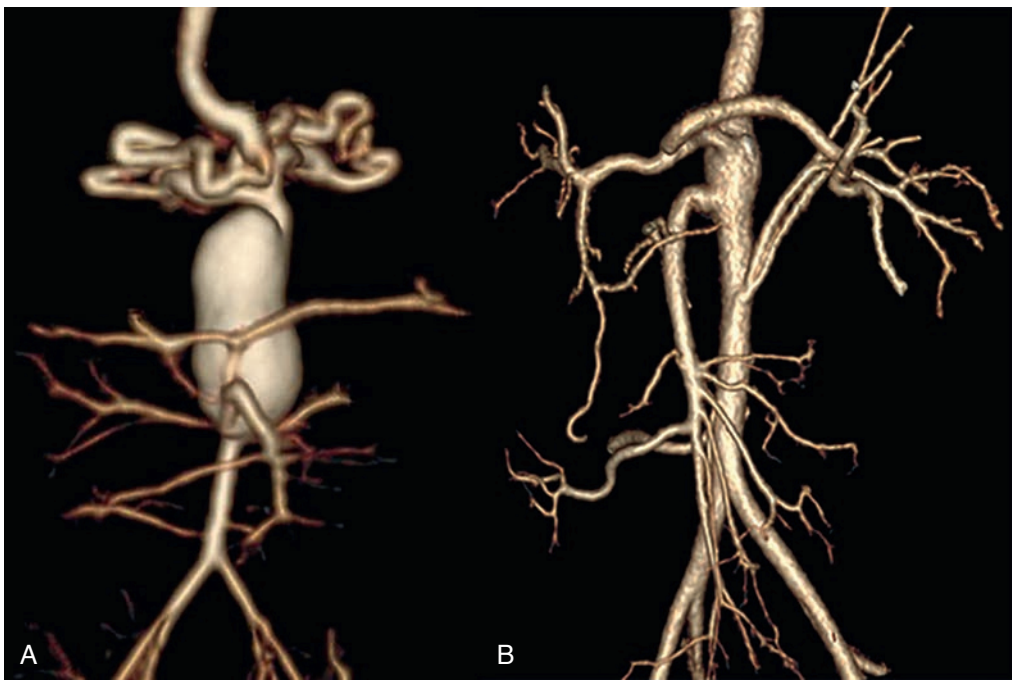

Figure 187.5 (A) Saccular 2-cm supraceliac aortic aneurysm with involvement of the celiac, superior mesenteric, and renal arteries associated with focal and nearly complete occlusion (coarctation) of the diaphragmatic aorta in a 6-month-old (computed tomography angiography). (B) Appearance following resection of the coarcted aortic segment with primary aorto-aortic reanastomosis, open aneurysmorrhaphy, and aortic reimplantation of one of the affected arteries with no evidence of progressive aortic dilation 7 years postoperatively.[2]

The risk of expansion, rupture, thrombosis, and distal thromboembolism of these nonaortic aneurysms warrant intervention in most instances. These peripheral arterial aneurysms are extremely uncommon but share etiologic risk factors similar to aortic aneurysms, including infection, inflammation, inherited vasculopathies, and trauma. In contrast to aortic aneurysms, neurofibromatosis 1 and fibromuscular dysplasia are often associated with nonaortic aneurysms in childhood. It is most appropriate to discuss peripheral arterial aneurysms by the vascular bed affected.

Extracranial cerebrovascular artery aneurysms have been previously defined by De Jong et al., who previously proposed that aneurysms in the region of the carotid bulb should be defined by a diameter greater than 150% of the normal common carotid artery or 200% of the normal internal carotid artery, and for the internal carotid artery dilations greater than 120% of a normal cross-section of the ipsilateral artery were considered aneurysmal.[24]

True aneurysms of the extracranial carotid artery are likely a manifestation of a genetic disorder, inflammatory disease, or traumatic pseudoaneurysms resulting typically from blunt injury, tonsillectomy, or iatrogenic vascular accessing injury (Fig. 187.6). The most commonly reported symptom is a pulsatile neck mass. Horner syndrome and cranial nerve dysfunction rates have been reported to be as high as 4.6% to 11%.[25] Given that the risk of central neurologic complication and rupture rates are reported to be as high as 42%, early surgical treatment is usually pursued.[26]

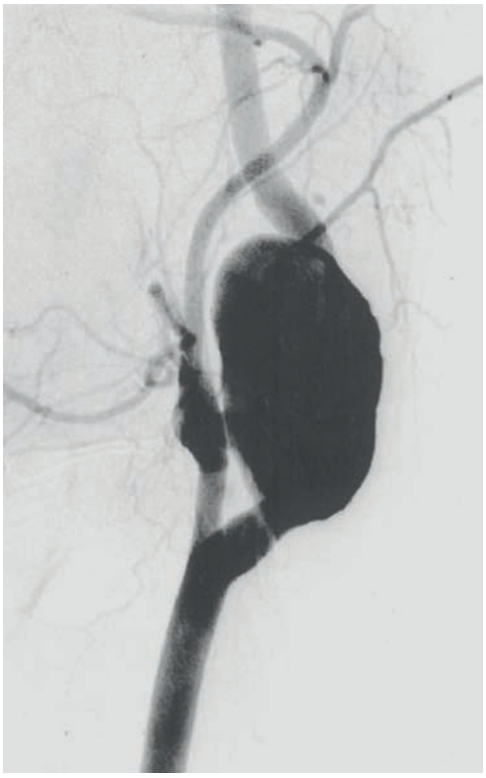

Figure 187.6 Carotid Artery Aneurysm. Preoperative angiogram demonstrating a traumatic 3-cm saccular internal carotid artery aneurysm with 11-mm fusiform ectasia of the external carotid artery.[22]

Aneurysmectomy with an interposition bypass is the most commonly described procedure in treating carotid artery aneurysms, using both autogenous and prosthetic conduits.[27,28] The authors favor the use of hypogastric artery given the risk of late aneurysmal deterioration of vein graft when placed in low resistance arterial beds with high diastolic flow.[29] Procedural morbidity has been associated with cranial nerve injury (4% to 22% incidence) and central neurologic complications, such as stroke (4% to 11% incidence).[25] Ligation may be considered in select patients but only with confirmation of an intact circle of Willis.[30] Endoluminal therapy with placement of covered stents may be appropriate in certain cases.[31,32]

Splanchnic artery aneurysms most commonly have a mycotic, inflammatory, traumatic, or connective tissue disease origin.[33-35] Abdominal pain is common, and luminal gastrointestinal bleeding has also been described.[36] Blunt and deceleration injuries to the liver and spleen can result in small pseudoaneurysms that may thrombose without clinical sequelae or be treated with endovascular embolization if symptomatic or associated with hematobilia. Nontraumatic aneurysms carry a greater risk of rupture and thromboses. Although surgical intervention to exclude an aneurysm and reestablish arterial continuity is ideal (Fig. 187.7), in cases of infection or most genetic diseases, vessel friability may preclude reconstruction, mandating ligation (Fig. 187.8) with reliance on collateral flow to lessen intestinal ischemic complications.[12,33]

Renal artery aneurysms are generally attributed to a connective tissue disorder or a congenital vasculopathy such as arterial dysplasia related to neurofibromatosis and fibromuscular dysplasia. A contemporary radiologic review of renal angiography performed for pediatric fibromuscular dysplasia and neurofibromatosis characterized the phenotype to include 12 cases (28%) of renal aneurysms with a background incidence of occlusive disease affecting 91% of patients (39/43).[37] The clinical relevance of these aneurysms remains ill defined, including the natural history and rupture risk. Pediatric renal artery aneurysms are mainly asymptomatic, although secondary renovascular hypertension and distal thromboembolization have been reported with flank pain and hematuria less common. Aneurysms are often saccular in appearance and occur most commonly at bifurcations. Surgical options for treating these aneurysms are complex and include angioplastic closure, bypass, or reimplantation of the affected artery following resection of the aneurysm (Fig. 187.9). The authors favor hypogastric artery for conduit in cases of aortorenal bypass for reasons aforementioned. Ethanol ablation and coil embolization may also be considered for distal, subsegmental, and cortical aneurysms.[38,39] Primary partial or complete nephrectomy may be required for irreparable disease, including multiple aneurysms not amenable to any form of reconstruction.[22] Closed aneurysmorrhaphy of small (2 to 3 mm diameter) renal artery aneurysms with fine monofilament suture may be appropriate for those aneurysms encountered during treatment of other larger, more clinically relevant aneurysms, or during renal artery revascularization for occlusive disease.

Upper extremity aneurysms most commonly result from trauma, including iatrogenic catheterization-related injury and

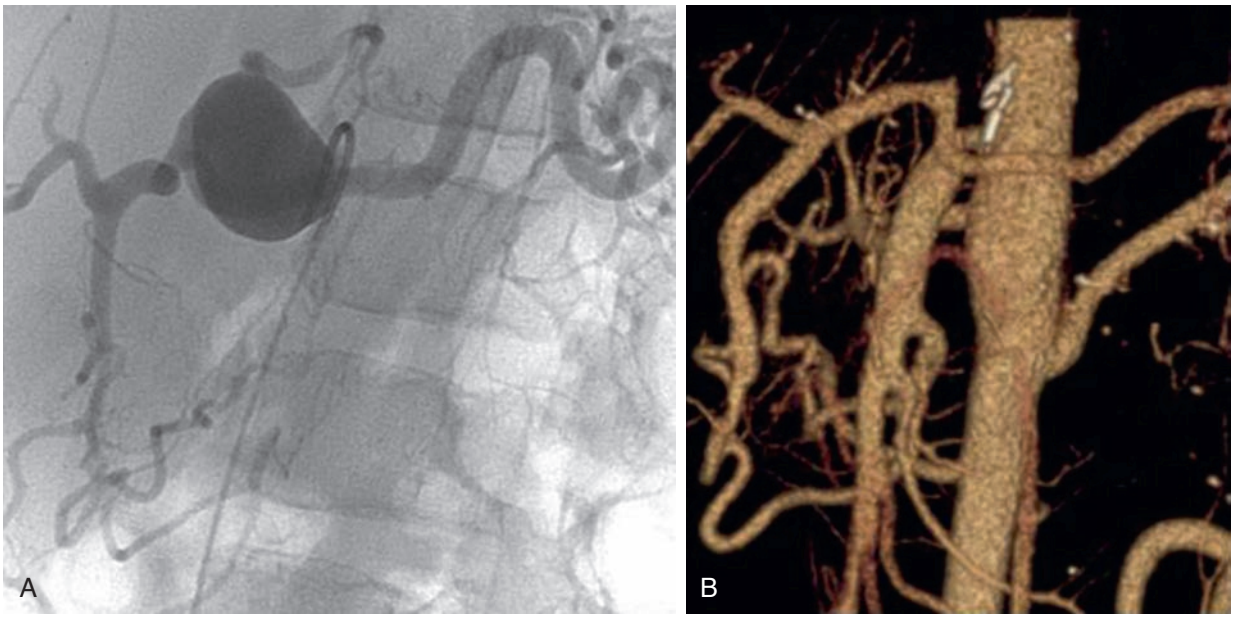

Figure 187.7 Celiac Artery Aneurysm. (A) Preoperative angiogram of a post-stenotic celiac artery aneurysm. (B) Postoperative computed tomographic arteriography image following resection of the aneurysm with primary end-to-end anastomosis of the proximal hepatic to proximal splenic artery.[22]

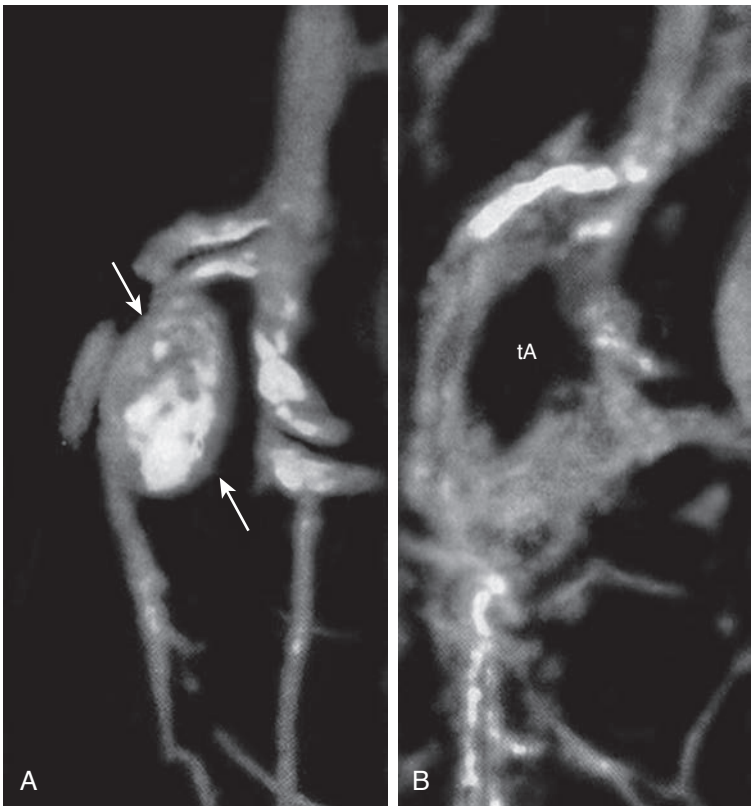

Figure 187.8 Superior Mesenteric Artery (SMA) Aneurysm. (A) SMA aneurysm in a child with Ehler-Danlos syndrome *(arrows)*. (B) Postoperative appearance of thrombosed aneurysm (tA) following proximal and distal ligation alone. (Upchurch GR Jr, Zelenock GB, Stanley JC. In: Rutherford RB, ed. *Splanchnic Artery Aneurysms, in Vascular Surgery*, 6th ed. Philadelphia, PA: Elsevier Saunders; 1973:20115.)

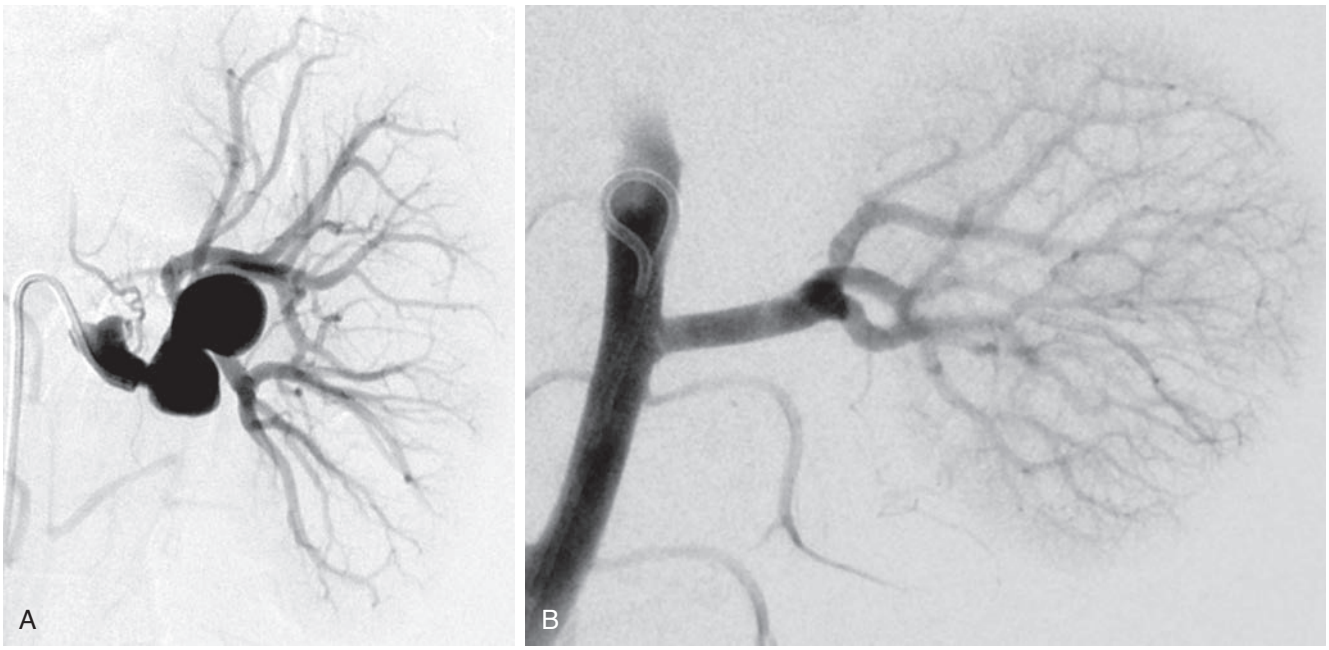

Figure 187.9 Renal Artery Aneurysm. (A) Preoperative angiogram of a 14-year-old with neurofibromatosis (NF1) demonstrating a severely ectatic and diffusely dysplastic left main renal artery with severe left renal artery ostial and distal stenosis associated with two bilobed distal left renal artery aneurysms. (B) Postoperative angiogram following aneurysm resection with ex vivo reconstruction requiring syndactolization of three segmental renal artery branches and aortorenal bypass with hypogastric artery.

the inflammatory arteritides, such as Kawasaki disease (Fig. 187.10). These aneurysms often present as a pulsatile mass, although pain and paresthesia have been reported.[22,40,41] Although rupture of noninfectious aneurysms is rare, the risk of distal hand and digit thromboembolism merits early surgical intervention.[40-43] Aneurysm resection distal to the axillary artery with revascularization by direct reanastomosis, bypass with reversed saphenous vein, or ligation pending the presence of adequate collateral vessels have all been well described with negligible morbidity and mortality.[40]

Lower extremity aneurysms most frequently involve the iliac arteries (Fig. 187.11), sharing similar etiologic risk factors with aortic aneurysm. Although mainly asymptomatic, these aneurysms have been reported to cause abdominal pain and lower quadrant abdominal mass.[44] Although internal iliac artery aneurysms may be safely ligated in the setting of robust pelvic collateralization, common and external iliac arteries require treatment with resection and reanastomosis, interposition grafting, aorto-iliac bypass, or plication. A prosthetic conduit is appropriate in this setting, recommended to be sized as large as possible to facilitate future growth without risking luminal thrombus and distal thromboembolism.[22,45] Cadaveric homografts may have a role in the management of infected iliac artery aneurysms.[46] Femoral pseudoaneurysms and true aneurysms (Fig. 187.12) are subject to acute thromboses and warrant early operative intervention. Arterial reconstructions following

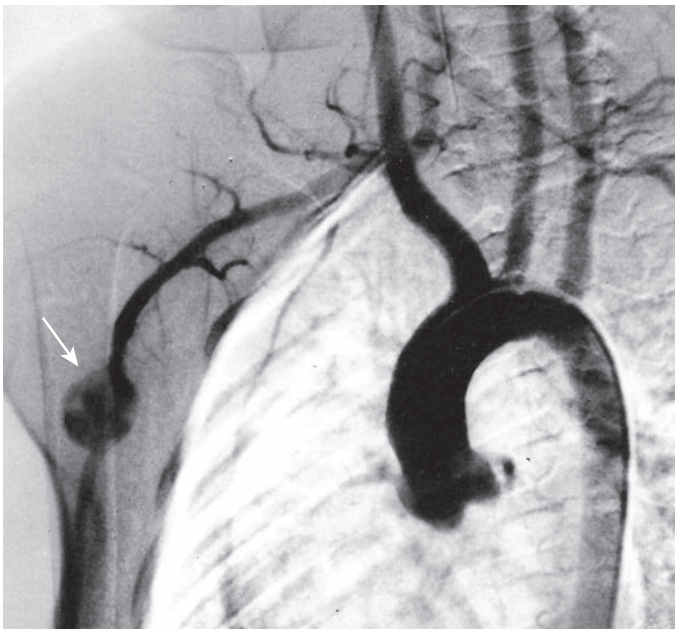

Figure 187.10 Brachial Extremity Aneurysm. Preoperative arteriogram of a 4-year-old with a right brachial artery aneurysm measuring 18 mm resulting from Kawasaki disease. (Stanley JC, Eliason JL. Pediatric arterial diseases. In: Coran AG, Adzick NS, Krummel TM, et al., eds.: *Pediatric Surgery*, 7th ed. Philadelphia, PA: Elsevier; 2012:1643.)

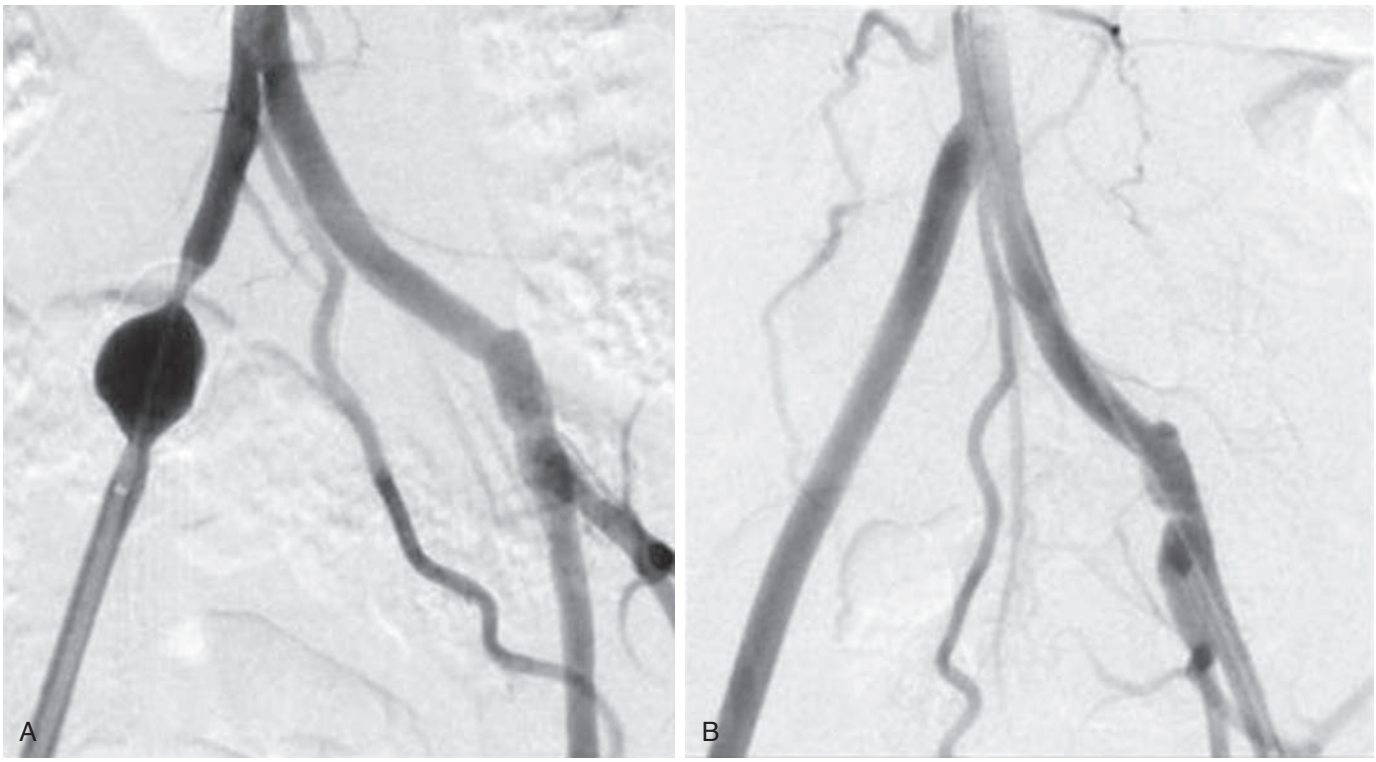

Figure 187.11 Iliac Artery Aneurysm. (A) Preoperative arteriogram of a child with a right common iliac artery aneurysm. (B) Postoperative arteriogram following aneurysm resection with aorto-iliac bypass using 7 mm polytetrafluoroethylene prosthesis.[22]

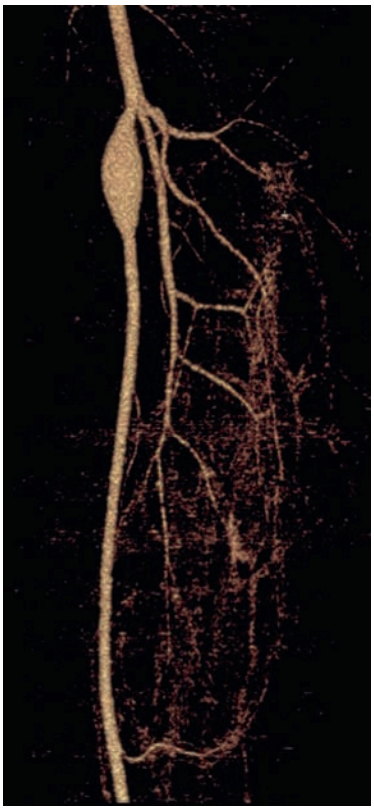

Figure 187.12 Superficial Femoral Artery Aneurysm. Superficial femoral artery aneurysm of unknown etiology in a 2-year-old treated by aneurysmectomy and interposition vein graft reconstruction.

aneurysmectomy in these cases usually use autologous vein conduits. In a contemporary series of nonaortic pediatric arterial aneurysms, no long-term difference in outcomes across vascular territories following operative repair was noted. Although no reinterventions were required following the treatment of extracranial cerebrovascular or extremity aneurysms in the University of Michigan experience, 15% of children treated for visceral aneurysms underwent later reoperations.[22]

SUMMARY

Pediatric aortic and arterial aneurysms represent a variety of complex diseases affecting multiple vascular territories. Individualized surgical treatment that considers patient age and anatomic factors may be undertaken with negligible perioperative morbidity and mortality. It is the authors' contention that a multidisciplinary team of vascular surgeons, pediatricians, radiologists, and anesthesiologists provide the best setting for the most optimal care of children with these aneurysms. Given the predicted long life expectancy of many children affected with these aneurysms, the treatment must be thoughtfully planned and executed, and long-term follow-up is mandatory.

SELECTED KEY REFERENCES

Eliason JL, Coleman DM, Criado E, Stanley JC. Surgical treatment of abdominal aortic aneurysms in infancy and early childhood. *J Vasc Surg*. 2016;64(5):1252–1261.

The largest contemporary single institution experience reporting on the clinical presentation and surgical management of 11 pediatric patients with aortic aneurysms. This study from the University of Michigan suggests that successful surgical management of AAAs in infants and young children requires careful execution of a diverse group of surgical techniques based on the etiology, the child's size and growth potential, and the aneurysm's location and coexisting branch involvement.

Davis FM, Eliason JL, Ganesh SK, Blatt NB, Stanley JC, Coleman DM. Pediatric nonaortic arterial aneurysms. *J Vasc Surg*. 2016;63(2):466–476.e1.

The largest contemporary single institution experience reporting on the clinical presentation and management of 41 children with 61 non-aortic aneurysms across diverse vascular beds. This study from the University of Michigan suggests that individualized surgical treatment, ranging from simple ligations to major arterial reconstructions, are durable and can be undertaken with minimal risk.

Sarkar R, Coran AG, Cilley RE, Lindenauer SM, Stanley JC. Arterial aneurysms in children: clinicopathologic classification. *J Vasc Surg*. 1991;13(1):47–56, discussion 56–47.

A relevant classification schema proposed for pediatric arterial aneurysms that considers (1) arterial infection, (2) giant-cell aorto-arteritis, (3) autoimmune connective tissue disease, (4) Kawasaki's disease, (5) Ehlers-Danlos syndrome or Marfan's syndrome, (6) other forms of noninflammatory medial degeneration, (7) arterial dysplasia, (8) congenital-idiopathic factors and (9) false aneurysms.

A complete reference list can be found online at www.expertconsult.com.

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188 CHAPTER

Pediatric Vascular Tumors

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INTRODUCTION

Four major types of primary pediatric tumors have been categorized: infantile hemangioma (IH), congenital hemangioma (CH), kaposiform hemangioendothelioma (KHE), and pyogenic granuloma. Although the majority of pediatric vascular tumors are benign, KHE is considered an intermediate tumor. Most of these tumors are seen in infants and children, except pyogenic granulomas, which can be seen at any age. Vascular tumors occur in many body locations and may cause pain and bleeding or destroy adjacent tissues. Systemic manifestations may include thrombocytopenia and anemia as a result of consumption coagulopathy, or congestive heart failure in the few patients with large high-flow lesions, particularly in the liver. Death is rare.[1,2]

Vascular tumors require differentiation from vascular malformations. Primary vascular and intermediate tumors can be present at birth and usually have proliferative endothelium. Vascular malformations occur from abnormal tissue growth, are present at birth (although not always evident), have quiescent endothelium, and generally grow as the child grows. Primary tumors and vascular malformations may look alike, with blue, red, or purple hues; and the lesions may be flat or raised.[3,4]

Secondary tumors that may surround major vessels are many and include soft tissue, cartilaginous or bony sarcomas, and benign or malignant neurogenic tumors, such as neuroblastoma or ganglioneuroma, among others.

Current management is multidisciplinary. History and physical examination, supplemented by imaging studies if needed, are important for identification and classification of primary tumors. Treatment may vary by tumor type, and biopsy is rarely necessary. Application of topical therapies, the use of antiangiogenic drugs, sclerotherapy, or laser therapy, and the role for surgical excision continue to evolve. For example, IH and CH are often observed, whereas the treatment of pyogenic granuloma is primarily surgical. Vascular anomaly or malformation centers have been created at many referral centers to centralize and coordinate care.[2,5] Similarly, resection of secondary tumors may involve pediatric, orthopedic, and oncologic surgeons and neurosurgeons alone or in combination, with vascular surgery involvement relegated to select patients with large or infiltrative tumors near the aorta or vena cava and their major branches, or the major head, neck or extremity vessels. In contrast to adult patients, major vascular reconstruction is uncommon in the pediatric population.

CLINICAL FEATURES

Infantile Hemangioma

The pathogenesis of IH is development from progenitor cells which normally would evolve into blood vessels.[6] The precursor cell seems to be a multipotent hemangioma-derived stem cell, which produces an erythrocyte-type glucose transporter

Abstract

Primary pediatric vascular tumors are mostly benign and occur in four major types: infantile hemangioma, congenital hemangioma, kaposiform hemangioendothelioma and pyogenic granuloma. Clinical presentation varies according to tumor type, but these can occur in many body locations, may cause pain and bleeding or tissue invasion with physiologic or aesthetic consequences. Systemic manifestations are rare but can be severe. Current management of such tumors is multidisciplinary and has evolved significantly over the last two decades. The purpose of this chapter is to discuss clinical features, diagnosis and management of pediatric vascular tumors.

Keywords

Infantile hemangioma
pediatric vascular tumors
kaposiform hemangioendothelioma
congenital hemangioma

(GLUT1).[7,8] These stem cells are similar to placental endothelium but genetically derived from the child.[9,10] Hypoxia is widely accepted as the primary stimulus for growth of IH.[11] Endothelial proliferation likely occurs from complex interactions between activated T cells, alterations in vascular endothelial growth factor receptor (VEGFR) expression, and the binding of endothelial growth factor A to VEGFR-2 receptors. Reduction in local antiangiogenic proteins may be another stimulus to tumor growth. Sometime between early infancy and 4 years of age, these tumors involute, the mechanism of which is unclear. Endothelial proliferation slows and apoptosis increases during this time, with potential triggers related to a decrease in proangiogenic maternal estrogens or an increase in angiogenesis inhibitors in the epidermis. The tumor is replaced by fat cells, which also derive from the aforementioned stem cells.[12-14]

IH is the most common neoplasm of infancy and affects white infants more often than dark-skinned children. Premature infants with low birth weight, particularly girls, have a higher risk of developing these tumors.[15] For every 500-g decrease below a 2500-g baby, the risk of IH increases 40%. Lesions tend to be solitary (80%) and involve the head and neck, trunk, or extremity in decreasing order of frequency. The tumors appear at median age of 2 weeks but may be evident as small pale, telangiectatic, or ecchymotic spots in nearly one-half of infants at birth.[15-17]

IH has a proliferative growth phase during the first 9 months of life, with most rapid growth in the first 8 weeks of life. Eighty percent of volumetric growth is achieved by age 5 months.[18,19] Tumor appearance during this stage varies based on whether it involves the superficial or deep dermis. If the tumor is in the superficial dermis, it appears bright red, but when deeper, the lesion either has a bluish or normal color. Many IHs are mixed with both superficial and deep components (Fig. 188.1A to C). Proliferation often slows by 5 to 6 months of age; however, in those with a primarily deep component, proliferation can be prolonged, sometimes up to 18 months of age. Subsequent growth coincides with growth of the child.[19] The involution phase begins by 1 year of age, at which point the tumor shrinks, the color fades, the center of the lesion pales, and the tumor softens. Involution is complete by 4 years of age in most children.[15] Some patients with a large deep component are left with fibrofatty tissue and redundant skin. Scarring is most often associated with ulcerative lesions. Telangiectasias and discoloration are other sequelae after lesion regression is complete.[18,20]

IHs may be multiple and involve the skin or liver. The cutaneous lesions are often less than 5 mm in diameter and domelike (see Fig. 188.1D). If more than five hemangiomas are present, the child has a 16% chance of harboring visceral lesions, with the most common extracutaneous location being the liver. The brain, gut, and lung are rarely involved. Most hepatic IH are small, discovered incidentally, and are classified as multifocal or diffuse. Multifocal hepatic hemangiomas are usually asymptomatic, although high-output cardiac failure by arteriovenous or portovenous shunting occurs rarely. Similar to cutaneous IH, involution begins by 1 year of age and often earlier in most children.[21,22]

Diffuse IHs can be seen in the liver and often does not need active treatment other than close observation. At times, large, diffuse IHs may replace much of the liver parenchyma and cause massive hepatomegaly. Compression of the inferior vena cava or upward pressure on the diaphragm with reduction of the pleural space causes respiratory symptoms or abdominal pain and pressure in select patients. High-output cardiac failure is rarely seen. Almost all infants with profound liver involvement develop hypothyroidism because this hemangioma expresses a deiodinase that inactivates thyroid hormone, necessitating thyroid-stimulating hormone monitoring.[23] The need for large doses of thyroid hormone may be great to reduce the risk of irreversible mental retardation seen with inadequate therapy. As the hemangioma regresses, the need for replacement therapy ebbs. Differential diagnosis includes hepatic arteriovenous malformation (AVM) and malignant neoplasm. Hemangiomas and AVMs exhibit fast-flow characteristics, with 90% of fast-flow lesions being hemangiomas and the remaining ones AVMs. Hepatoblastoma and metastatic neuroblastoma do not have the shunting characteristics of hemangioma.[22]

IHs may be associated with specific syndromes in which there are anomalies of the cardiovascular, gastrointestinal, and urogenital systems; brain or spinal cord; eye; or bone.

A child with a large, segmental midline lumbosacral region IH carries a 33% chance of having a spinal anomaly such as a tethered cord, lipoma, or intraspinal hemangioma (Fig. 188.2A). Magnetic resonance imaging (MRI) between 3 and 6 months of age is important to exclude spinal abnormality in these cases.[24] Lower body IH may be associated with urogenital anomalies or ulceration, myelopathy, bone deformities, anorectal malformations, arterial, and/or renal anomalies. This association is termed LUMBAR, and most children with these anomalies are girls. The IH is usually large, segmental, and superficial, has minimal postnatal growth, and often ulcerates. The hemangioma may be seen in the sacral or lumbar regions, the perineum and genitalia, or lower extremity.[25]

Segmental plaquelike IHs of the face may be associated with one or more anomalies in the brain or cerebrovascular system, heart, eye, sternum, or supraumbilical region, categorized as PHACES syndrome (see Fig. 188.2B). The acronym represents posterior fossa brain malformation, hemangioma, arterial anomalies, coarctation of the aorta and cardiac defects, eye abnormalities, and sternal clefting or supraumbilical raphe. Ninety percent of affected children are female. The most common anomaly is a cerebrovascular malformation in 72% of patients, and approximately 8% of infants sustain a stroke. PHACES is found in less than 3% of all patients with IH, and extracutaneous features in this group are seen in less than one-third of the children.[26] Similar to the LUMBAR association, most affected children are girls. Recognition of PHACE syndrome is critical because these patients have higher risk of complications and sequelae than those with isolated IH.

Rare lesions that can be confused with primary vascular tumors of infancy include arteriovenous malformation, infantile myofibromatosis, infantile fibrosarcoma, Enzinger intramuscular hemangioma, pilomatrixoma, neuroblastoma, and lymphoma.

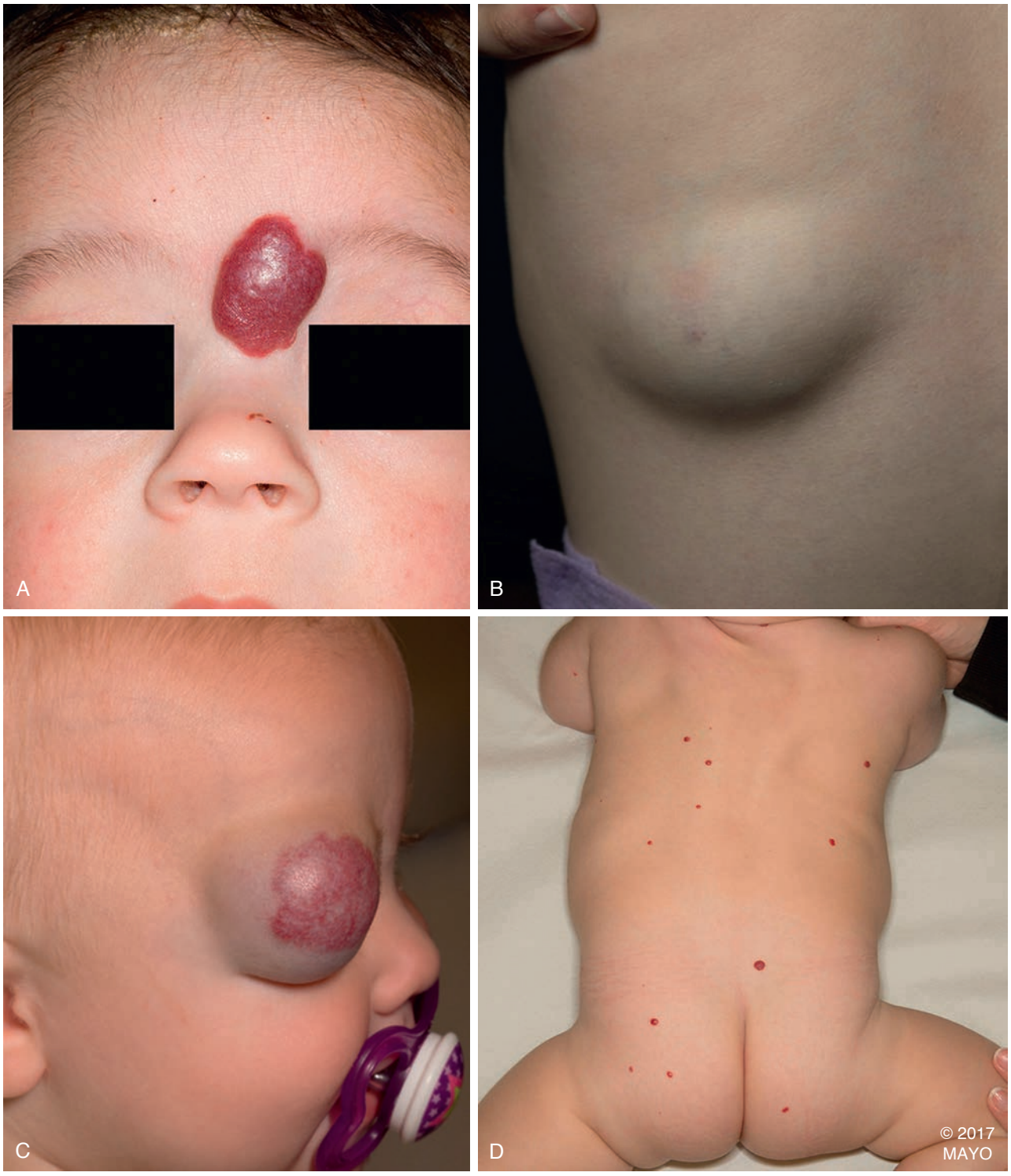

Figure 188.1 Various Types of Infantile Hemangioma. (A) Superficial lesion of the face. (B) Deep lesion of the trunk. Notice the difference in outward appearance and color. (C) A mixed lesion with both superficial and deep components. (D) Multifocal superficial lesions on the trunk and buttocks.

Congenital Hemangioma

CH is fully formed at birth and does not illustrate the postnatal growth of IH. This tumor is most often solitary, although multiple lesions have rarely been described and may range from 1 or 2 cm to more than 20 cm in diameter. CH has a red-violaceous color with coarse telangiectasias, central pallor, and a peripheral pale halo. Unlike IH, CH is more common in the extremities and has an equal sex distribution.[27-29]

CH has historically been defined as rapidly involuting or non-involuting. One small series suggests a third category, defined as partially involuting because some CHs show involution, however

Figure 188.2 Segmental lumbosacral (A) and facial (B) infantile hemangiomas. Such findings should raise suspicion of LUMBAR or PHACE associations.

not completely.[30] Rapidly involuting CH changes quickly after birth, with one-half the lesions completely regressed by 7 months of age and the others by 14 months. Rapidly involuting lesions are noted in the limbs or head and neck in 40% to 50% of cases and the trunk in 6% (Fig. 188.3).[27,28] Involution results in atrophic skin and little underlying subcutaneous adipose tissue, in contrast to regression of IH. Large CH may exhibit high-flow cardiac output. Thrombocytopenia has been reported with a large, rapidly involuting CH, but that association is not Kasabach-Merritt phenomenon (KMP; see later).[31] A solitary hepatic hemangioma in an infant represents a rapidly involuting CH. The lesions are discovered incidentally on prenatal or antenatal ultrasonography, and there is no association with cutaneous hemangiomas. They do not stain positive for GLUT1, a marker for IH.[32] Noninvoluting CHs persist long term, as the name implies, and involve the head or neck 43% of cases, the extremities in 38%, or the torso in 19%.[29]

Kaposiform Hemangioendothelioma

This rare vascular neoplasm has prevalence in infancy of 1 per 100,000, is reddish purple with an ill-defined border, and may be mistaken for ecchymosis on first glance (Fig. 188.4). Sixty percent of KHEs manifest in the neonatal period, and more than 90% are evident by infancy.[33] The tumor is usually greater than 5 cm in diameter, larger than the typical IH, and there may be hair noted in the involved skin, which tends to be a transient phenomenon. KHE has an equal sex distribution, is solitary, and affects the head or neck in 40% of children and the trunk or extremity in 30% each.[34] The lesion is locally invasive but does not metastasize. Multifocal cases are rare but should prompt biopsy when suspected. The natural history of this tumor is expansion in infancy and early childhood and then partial regression. Fibrosis occurs and may cause chronic pain and contractures. Many affected children exhibit KMP.[35] The syndrome is more common in children with large tumors and in those with visceral and muscle involvement.[36] KHE is pathologically similar to tufted angioma, the latter considered by some authors to be a milder form of this tumor.[37] Profound thrombocytopenia (<25,000/mm^3) and consumptive coagulopathy in this condition may prove life threatening in 12% to 24% of children.[35,36] An adult variant occurs and is male predominant, smaller in size but with similar distribution as children, and without risk of KMP.[38]

Pyogenic Granuloma

Pyogenic granuloma, also known as lobular capillary hemangioma, is a solitary red papule that averages 6.5 mm in diameter, rapidly grows, has a stalk, and is complicated by bleeding and ulceration (Fig. 188.5).[39,40] Sex distribution is 2:1 male to female, with mean age at onset of approximately 7 years. The lesion rarely occurs during the first year of life, and the prevalence is inversely correlated with age. Approximately 40% occur at age 5 years or less, another 30% between 5 and 10 years of age, and less than one-fourth after age 10. Nearly 90% of lesions

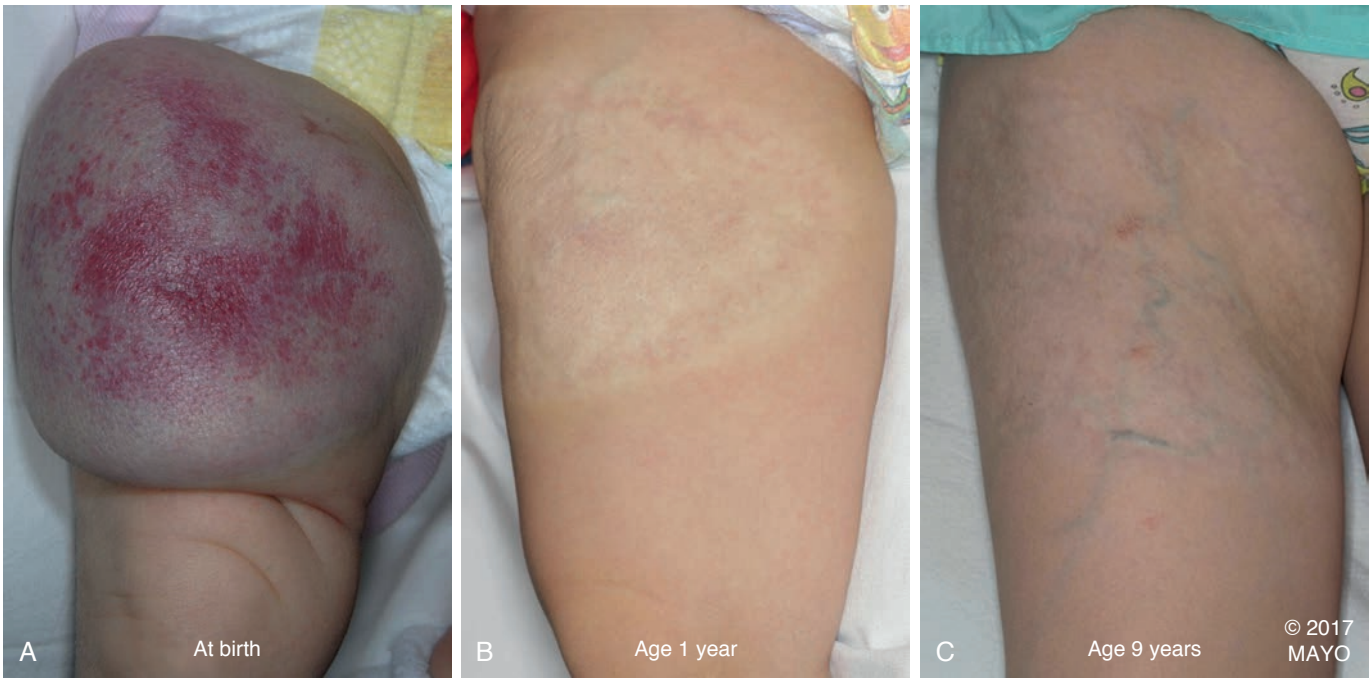

Figure 188.3 Images show progressive regression of a rapidly involuting congenital hemangioma of an extremity.

Figure 188.4 Kaposiform hemangioendothelioma of the extremity.

Figure 188.5 Typical appearance of pyogenic granuloma as a solitary red papule, which often has a stalk.

are cutaneous, with mucous membrane involvement in almost 12%. Distribution is head or neck in 62% of cases, trunk in 19%, upper extremity in 13%, and lower extremity in 5%. Head and neck lesions involve the cheek, oral cavity, scalp, forehead, eyelid, or lips, in decreasing order of frequency.[40] Pyogenic granuloma may be induced by trauma, insect bite, viral infection, or dermatologic disorder in one-fourth of patients.

DIAGNOSIS

Correct diagnosis of a vascular tumor of childhood is made by history and physical examination in 90% of patients. Assessment by handheld Doppler has utility in some cases, particularly if considering fast-flow lesions. When the diagnosis is unclear, radiographic imaging is often diagnostic but biopsy rarely proves necessary. Ultrasound and MRI are the primary imaging modalities when needed.[41]

Diagnosis of IH is made by history and physical examination in nearly all patients. Ultrasound shows a well-circumscribed hypervascular mass. Low-resistance arterial waveforms are present, and venous drainage is seen. MRI can be used if ultrasound imaging is equivocal, but MRI is rarely necessary. IH is seen as a parenchymal mass with dilated vessels and signal voids during the proliferative phase, unlike an arteriovenous malformation. The lesion is isointense on T1 sequences and hyperintense on T2 images and enhances homogeneously after the administration of contrast. An involuting IH is lobular and has adipose tissue and a reduced number of vessels, with signal void or enhancement.[41] MRI or MR angiography is used to image the brain and neck for children with PHACE syndrome. Echocardiography and

an eye examination are important adjuncts in this situation. Although ultrasound may be useful when LUMBAR associations are suspected, MRI often is needed to image the lumbosacral spine, abdomen, and pelvis. Choice of study is based on age of the infant or child and type of lesion.

Less than 1% of IHs require histopathologic evaluation for diagnosis. Biopsy is indicated if malignant disease is suspected or if the diagnosis remains unclear after the lesion is imaged. Microscopic evaluation of a proliferating lesion shows tightly packed capillaries with plump endothelial cells and minimal intervascular stroma. In contrast, an involuting lesion shows reduction in the number of capillaries that have enlarged channels, increased stroma, and fibrofatty tissue.[32,42,43] A hallmark of IH is that it shows GLUT-1 positivity throughout all stages of proliferation and involution.

CH remains a clinical diagnosis. When needed, the findings on ultrasound and MRI are similar to those of IH. Lesions demonstrate fast flow, shunting, and enhancement. Histopathologically, CH is differentiated from IH because CH does not immunostain for GLUT1.[32]

KHE can also be diagnosed by history and physical examination, but biopsy is often used to confirm diagnosis. MRI is used to confirm diagnosis and determine extent of disease. Lesions are infiltrative and hyperintense on T2 images and enhance with contrast. Subcutaneous stranding and ill-defined borders are common, and prominent vessels with hemosiderin cause signal voids.[41]

Histopathology shows an infiltrating lesion with lobules of spindled lymphatic endothelial cells, some of which may be dilated or have a glomeruloid appearance. Vessels contain thrombi and hemosiderin, and mitoses are uncommon. Tumors will immunostain positive for lymphatic markers D240 and PROX1.[32]

Pyogenic granuloma is suggested by its appearance, location, and association with trauma or other factors. Microscopic analysis shows an exophytic mass attached to a narrow stalk on low-power examination and a normal numbers of mast cells, in contrast to a proliferating IH. The superficial part of the tumor shows immature capillaries with interspersed fibroblastic tissue, similar to granulation tissue, and edema in the matrix. The deeper segment has proliferating capillaries arranged in a lobular pattern extending into the deep dermis, and a dense, fibrous stroma.[32]

MANAGEMENT

Infantile Hemangioma

Observation is the mainstay of management because most tumors are small and localized and do not involve esthetically or functionally important areas. Parents can be reassured by showing them examples of proliferative, involuting, and regressed lesions that were managed in other infants. Close observation is needed during the proliferative phase to be certain the tumor does not ulcerate or pose risk of destruction of adjacent important structures.[1,15]

Approximately 16% of lesions develop skin ulceration during the proliferative phase, at an average of 4 months of age.[44] Ulceration is more common on the lips, neck, anogenital, and other flexural regions; larger and segmental IHs are also at risk of ulceration (Fig. 188.6). Standard wound care is topical antibiotic and Vaseline, followed by gauze. These lesions may be very painful, so topical lidocaine may be needed. Topical pharmacotherapy may be appropriate treatment for small IHs that do not require systemic therapy. Topical corticosteroid, such as clobetasol, may prove effective for small, superficial lesions, although hypopigmentation and skin atrophy can occur. Application of timolol, a beta blocker, also has been proven effective for small, superficial lesions. Systemic absorption of the drug is possible if a large amount of medication is applied, particularly for large, deep lesions.[45]

Systemic therapy is indicated for large hemangiomas that cannot be treated with local injections and is considered when topical therapy has been ineffective. Several drugs have been used, including beta blockers, steroids, and antimetabolic agents.[1,15]

Propranolol is standard of care for IHs that cannot be treated by observation alone or with topical agents.[46] This medication is used when there is risk for complications to adjacent tissue, such as anatomic distortion, ulceration, or visual obstruction. Systemic steroids are reserved for those who do not respond to, or have a contraindication to, beta blockers. Propranolol is given 2 or 3 times daily with a usual total dosage of 2 mg/kg per day, although some lesions respond to a lower dose. Rarely is a higher dose needed. Propranolol is administered through the proliferative phase until at least 1 year of age. Most physicians taper the dose thereafter. Lesions that are deep or in critical areas, such as the nose or eye, may require treatment beyond 1 year. Treatment efficacy is best when the medication is started during the proliferative phase for children that require this therapy. Rebound tumor growth occurs if the medication is abruptly discontinued during the proliferative phase. Tolerance seems best when the drug dose is started at 1 mg/kg per day and slowly increased to 2 mg/kg per day. Approximately 90% of tumors stop growing or regress with systemic beta blocker therapy.[47] Medication side effects are uncommon but include bronchospasm, bradycardia, hypotension, hypoglycemia, seizures, and hyperkalemia. Risk of an adverse event is higher in preterm infants and children younger than 3 months of age. The cardiovascular, respiratory, electrolyte, and glucose effects of beta blockers need to be monitored, especially in premature infants or young children and those with airway disease.[48] Introduction of this medication in an inpatient setting is rarely required. Relative contraindications to propranolol include infants or children with reactive airway or congenital heart disease, or glucose abnormalities. Treatment should be on an individual basis. When there is concern about intracerebral abnormalities, such as in PHACE syndrome, guidance by a pediatric neurologist is helpful.[47,49]

If systemic beta-blocker or steroid therapy proves ineffective, third line systemic drugs such as interferon or vincristine are considerations but are rarely, if ever, used. These medications have a high risk of side effects; interferon is not recommended in children younger than 1 year of age because of the risk of neurologic problems such as spastic diplegia.[1,5,15]

Embolization is considered for large high-flow IHs that cause congestive heart failure, such as multifocal or diffuse hepatic hemangiomas that have macrovascular shunts, particularly when

Figure 188.6 Images of ulcerative infantile hemangioma on the neck (A) and upper back (B).

there is little or only partial response to systemic beta-blocker therapy. The goal of embolization is to provide prompt control of heart failure as the therapeutic benefits of systemic agents accrue. This treatment has little or no role in hepatic hemangioma without heart failure. Drug therapy is used post embolization until the child is approximately 1 year of age, when involution generally begins.

Pulsed dye laser therapy is primarily used to treat residual telangiectasia post involution but can also be used to treat areas of ulceration in lesions slow to respond to other treatments. Carbon dioxide laser has been used to treat subglottic hemangioma during the proliferative phase as drug treatment is initiated.[50,51-53]

Excision of proliferating lesions is rarely indicated, given the success of pharmacotherapy.[1,15] The tumor is highly vascular, so there is a risk blood loss. Anesthetic complications, scarring, and cosmesis in infants must be considered. A well-localized or pedunculated, ulcerated, or bleeding lesion may be excised if the resulting scar is esthetically placed and no worse than would be predicted if excision is done after involution is in process or complete. The ideal time for operative intervention is between 3 and 4 years of age. At this age the tumor is smaller and less vascular and it will no longer involute. In general, the deformity improves with time, which makes long-term memory of the procedure and self-esteem issues less likely.[1,15,20]

Circular hemangiomas with residual fibrofatty tissue or excess skin are best managed with circular excision and purse-string closure.[54] The resultant scar can be revised 6 to 12 months later and closed linearly. This technique reduces the length of the linear scar relative to the initial diameter of the hemangioma. Initial linear excision of a circular hemangioma generates a scar nearly 3 times the diameter of the tumor.

Congenital Hemangiomas

Most CHs are managed initially by observation. A rapidly involuting congenital hemangioma (RICH) is regressed by 1 year of age. Reconstruction with dermal, fat, or acellular dermis grafts is considered for atrophic scarring, best done before 4 years of age. Rarely, large lesions that cause high-output cardiac failure are treated by embolization or excision. Noninvoluting congenital hemangioma (NICH) is a stable lesion and does not respond to pharmacologic treatment. These lesions usually require resection.[1]

Kaposiform Hemangioendothelioma

Treatment depends on size of the KHE and presence of KMP. Patients without KMP are treated to minimize fibrosis, chronic pain, stiffness, and contractures. Surgical resection is applicable to small, localized lesions. However, these tumors are often large and infiltrative and involve multiple tissues, thereby preventing complete excision. Complete blood counts and coagulation factors need to be monitored to identify development of KMP. In the neonatal period, these blood tests are drawn at baseline and then approximately weekly thereafter in the stable infant, with gradual lengthening between blood draws. In those with KMP, blood tests are done more frequently, as indicated by the patient progress. If the KHE becomes larger, firmer, or more painful at any point during therapy, blood tests should be checked

emergently because this may be the harbinger of consumptive coagulopathy. The primary role for medical therapy is to treat KMP. Systemic therapy for KHE is used to prevent life-threatening complications in children with unresectable tumors or KMP. Corticosteroids are often started initially to stabilize patients with KMP, at doses of approximately 2 mg/kg per day followed by a taper. Other systemic therapy may include vincristine or interferon. Response to vincristine is seen in 90% of cases, interferon treatment in 50%, and corticosteroids in 10%.[55] Intravenous vincristine is dosed at 0.05 mg/kg weekly and continued for approximately 6 months until thrombocytopenic or coagulopathic problems resolve. The use of sirolimus has shown good efficacy in cases of KMP, and many experts favor this medication over vincristine because of its efficacy and the efficiency in treatment. The role of sirolimus is currently under study in a clinical trial.[56,57] Platelet transfusion should be avoided unless there is active bleeding or a surgical procedure is necessary. Transfused platelets may be trapped in the lesion and cause pain and swelling.[34] Improvement in KMP is an accepted biomarker of treatment response.

Pyogenic Granuloma

Pyogenic granuloma has been treated by curettage, electrocauterization, shave excision, laser therapy, or full-thickness excision. Of these, the most common treatment is shave excision followed by cautery. Incomplete treatment is fraught with regrowth of the lesion.[40,58] Topical beta blockers have been used to treat facial lesions in children.[59]

SECONDARY TUMORS

Full review of the types, diagnosis, imaging studies, and management strategies for infants or children with secondary tumors that may have vascular involvement is beyond the scope of this chapter. The general precepts of management, including multidisciplinary assessment, are similar to those in Chapter 194. In short, tumor type, location, and extent influence therapy and surgical approach. Even though segmental resection and replacement of major arteries and veins is uncommon, proximal and distal vascular control is important, should vessel injury and bleeding occur in the course of dissection. Autogenous patches or conduits are preferred, except in some cases of aortic or caval replacement. Interrupted sutures are necessary when an interposition or bypass graft is placed, to accommodate growth of the child. If visceral, renal, or supraaortic trunk grafts are necessary, hypogastric artery is generally preferred over saphenous vein because of long-term aneurysmal degeneration in the latter. This caveat is similar to how pediatric aortic branch vessel reconstructions are done for occlusive or aneurysmal disease. Figs. 188.7 and 188.8 highlight illustrative cases in which vascular surgeon involvement was needed.

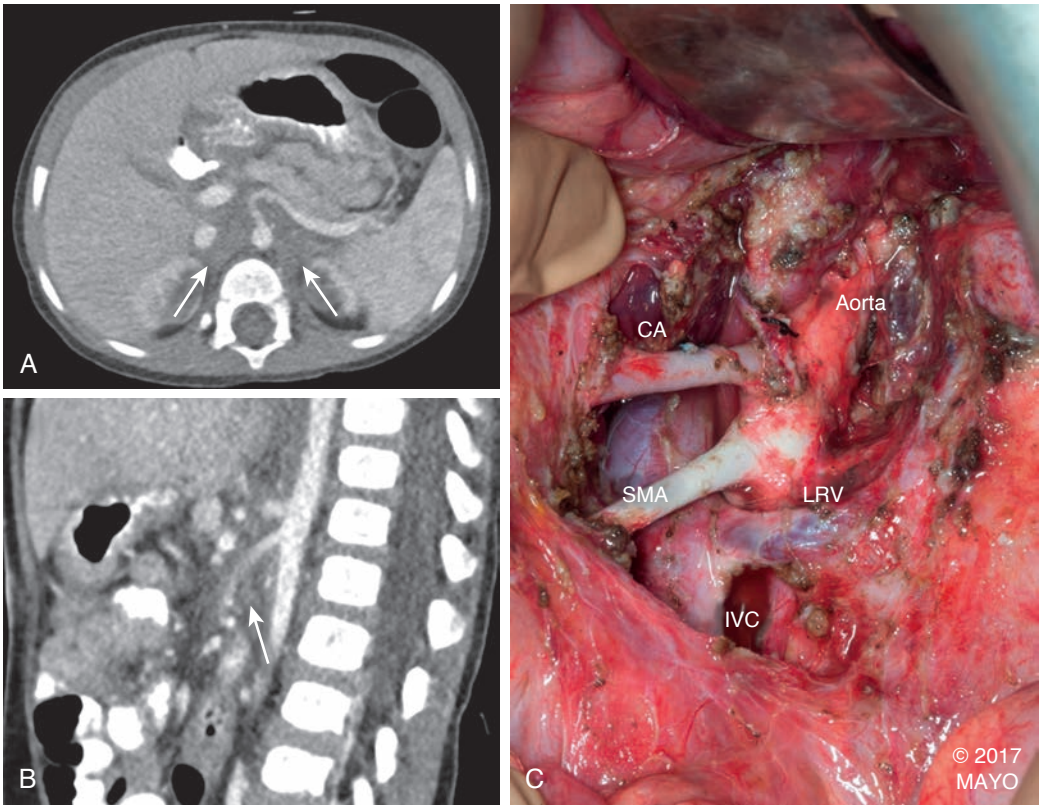

Figure 188.7 Infant with a neuroblastoma surrounding the paravisceral aorta, celiac, superior mesenteric, and left renal arteries and left renal vein, as shown by the *arrows* on axial and coronal CT images (A and B). The tumor could be separated from the aorta, branch arteries, and renal vein (C). *CA,* Celiac artery; *CT,* computed tomography; *IVC,* inferior vena cava; *LRV,* left renal vein; *SMA,* superior mesenteric artery.

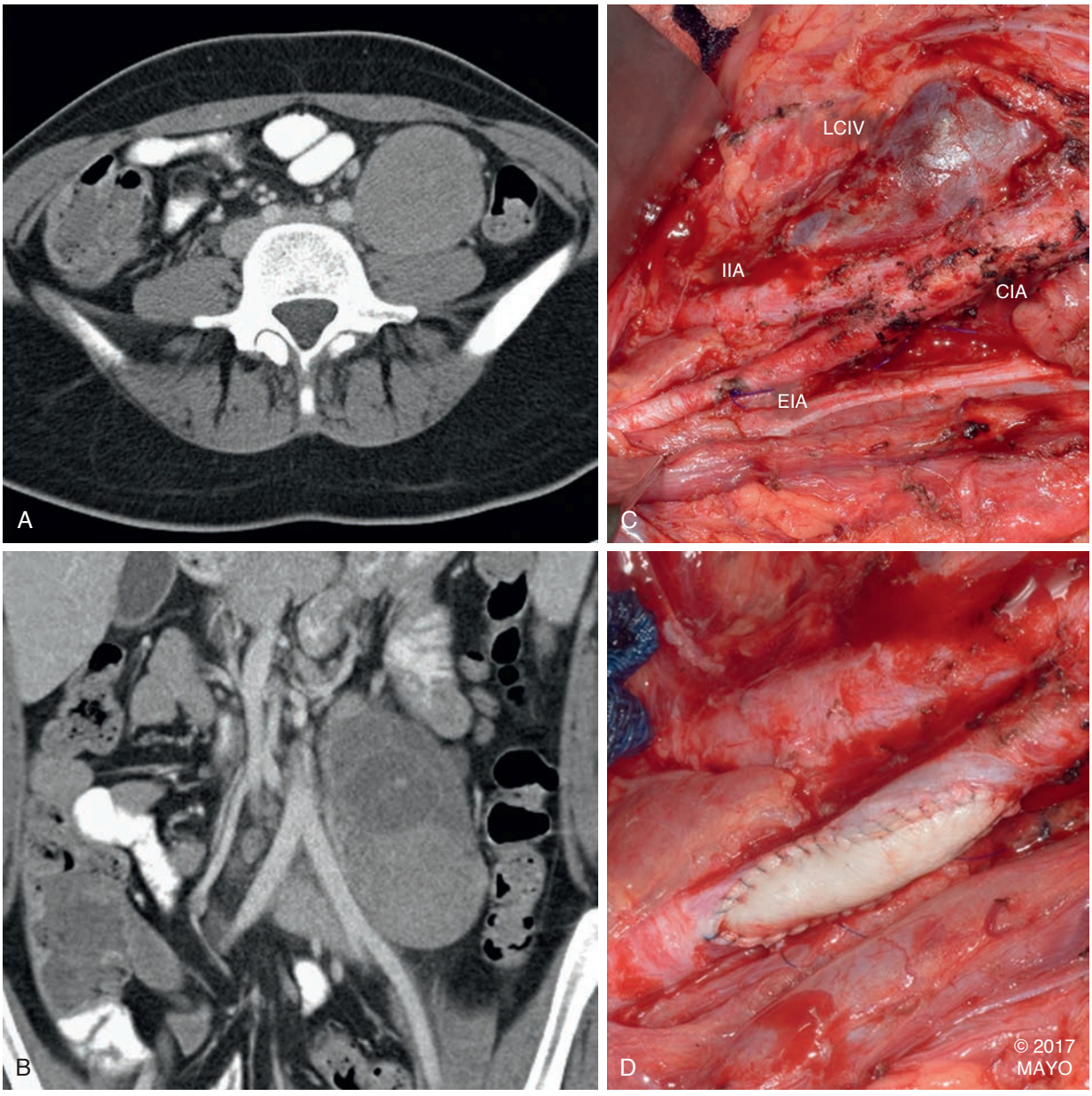

Figure 188.8 Large, lobulated left pelvic neuroblastoma abutting iliac vessels as shown on axial (A) and coronal (B) CT images. The tumor was resected but was adherent to the external iliac artery, which required a bovine patch for reconstruction (C and D). *CIA,* Common iliac artery; *CT,* computed tomography; *EIA,* external iliac artery; *IIA,* internal iliac artery; *LCIV,* left common iliac vein.

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189 CHAPTER

Vascular Trauma in the Pediatric Population

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INTRODUCTION

Pediatric trauma is the leading cause of death in children older than one year in the United States.[1] Although vascular injuries are infrequent, occurring in in 0.6% to 1% of trauma patients,[2,3] they constitute an important cause of mortality after trauma. Efforts to curb death and morbidity after automobile accidents, such as wearing seat belts and using car seats, have reduced mortality rates in this patient population, but has not significantly changed the *rate* of vascular injuries.[3,4] Overall, the most common cause of pediatric vascular injury is iatrogenic injury after peripheral interventions. Outside of the United States and Europe, warfare which does not discriminate civilians from combatants has also resulted in significant vascular injuries among noncombatants many of whom are, unfortunately, young children.[5,6]

The spectrum of treatment choices for vascular injuries includes expectant therapy, vessel ligation, direct vessel repair, or interposition graft repair. In adult patients, both endovascular and open vascular options are available. It is difficult to standardize the management of pediatric patients with vascular injuries due to a diverse set of factors. First, these vascular injuries are rare, occurring in less than 0.6% of pediatric patients who present with trauma.[2] Additionally, many different specialties participate in repair of these injuries ranging from pediatric surgeons, adult trauma and/or vascular surgeons, orthopedic surgeons, neurosurgeons to plastic surgeons.[3] Each specialty brings their unique perspective and background in how to deal with these injuries which makes arriving at a consensus difficult. Furthermore, pediatric vascular injuries are far more technically challenging to treat and this adds significant complexity to the choice of treatment for these injuries. The unique issues with these patients include size (diameter) of the injured vessel, spasticity of young vessels, and the choice of treatment must accommodate ongoing axial growth in this pediatric population. It is possible to apply the same principles and techniques of adult trauma to the older child but the younger child may require different approaches. In pediatric patients with vascular injuries, historically, definitive arterial reconstruction has not always been the preferred management approach. Ligation or expectant therapy (systemic heparin without repair) was the most common choice of treatment. Adverse outcomes, such as loss of axial growth leading to debilitating gait disturbances, limb overgrowth due to traumatic arteriovenous fistula (AVF), and amputation have prompted calls for a more aggressive approach in management of pediatric extremity vascular injuries.[2]

This chapter is structured to describe the multiple components associated with pediatric vascular injuries including epidemiology, diagnosis, treatment, and outcomes of these injuries.

EPIDEMIOLOGY

The reported incidence of any vascular injury among patients younger than 16 years is 0.6% in the US National Trauma Data bank.[2] This, however, does not account for iatrogenic injuries that are sustained during instrumentation for vascular or cardiac procedures. Although the exact prevalence of iatrogenic injuries is unknown, since these occur during hospitalization for admissions other than trauma, few case series have evaluated their experience with these type of injuries.[7-9] In tertiary pediatric hospitals, iatrogenic vascular injuries range from 33%[8] to 100%[7] of an institution's experience with pediatric vascular trauma. These penetrating vascular injuries can occur from misadventures during intravenous (IV) insertion, arterial puncture for blood gas analysis, transfemoral diagnostic or intervention procedures, umbilical artery catheterization or during surgery (e.g., during cardiopulmonary bypass operations or during orthopedic procedures). It is *estimated* that half of pediatric vascular injuries across all ages are iatrogenic penetrating injuries. The prevalence of iatrogenic injuries decreases with advancing age.[10] Neonates have the highest frequency of iatrogenic vascular injuries which then declines in the 2- to 6-year-old range (50% iatrogenic), followed by those children over 6 (33% iatrogenic).[11] Lin and colleagues identified four factors in their series of patients with iatrogenic injuries that were associated with increased risk of iatrogenic femoral complications.[10] These factors included age younger than 3, type of therapeutic intervention, ≥3 earlier catheterizations and the use of a 6F or larger guiding catheter.[10] Even with heparinization and use of appropriately sized catheters, the thrombosis rate ranges from 1% to 25%.[10,12] Both artery and vein accessed can be thrombosed after intervention. In a report of neonatal injuries after instrumentation, for example, two of seven patients presented with phlegmasia cerulea dolens who were interestingly successfully treated by leech therapy.[13]

Other causes of vascular trauma become more prevalent as a child's age increases and as noted above more than 2/3 of vascular injuries in children over the age of 6 are due to non-iatrogenic causes.[14] Mechanism of pediatric vascular injuries differs in and out of war zones. In review of National Trauma Data Bank, Barmpares et al. noted that the most common cause of trauma in children was motor vehicle accidents (24.3%).[2] Other causes of trauma included firearm injuries (19.6%), stab wounds (16.6%), and falls (11.8%).[2] Blunt injuries constituted the majority (57.7%) of injuries in this study of the US national trauma registry[2] which was similar to a Swedish registry data.[4] In most large contemporary single institution studies, penetrating causes were the most frequent causes of vascular injuries in children over 6 years of age.[3,9,15,16] It is observed that pediatric patients with blunt injury had an overall higher injury severity score than those presenting with penetrating injuries.[9] Needless to say in areas of the world in which children are exposed to warfare, these unfortunate children are more prone to sustain penetrating vascular injuries due to high-energy gunshot wounds and IEDs with complex wounds and combined bony and tissues injuries.[5]

Anatomic location of injuries is somewhat predicated on the mechanism of injury. Overall, however, the most common site of noniatrogenic vascular injuries in pediatric population is upper extremity vessels.[2,3,5,9,11,15,16] Penetrating upper extremity injuries are significantly more common than the truncal vessels, which include abdominal, thoracic, and cervical vessels. Among patients with blunt mechanism of injury, upper extremity vessel injuries constitutes a third of vascular injuries often combined with an orthopedic trauma.[2] In patients with noniatrogenic injuries, penetrating injuries are significantly more common in the vessels of the upper extremity than other vessels.[2,3,5,9,11,15,16] Truncal injuries however carry the highest mortality rates, in excess of 50%.[17,18] Most of these patients sustain concomitant significant organ injuries[17] and these patients have significantly higher injury severity scores (ISS) than patients with other injuries (e.g., 45.4 ± 19.8 vs. all injured patients 12.3 ± 11.7 in one study[9]). Truncal injuries significantly increase the odds of mortality independent of all other confounders.[9]

It should be noted that venous injuries are less common than arterial injuries and more difficult to diagnose in pediatric population. Combined arterial and venous injuries also significantly increase the odds of mortality. In most contemporary studies of pediatric vascular injuries, the most common site of observed venous injury was IVC[2,9,19] followed by other truncal vessels such a cervical veins,[17] portal veins,[20] and iliac veins.[18] The most commonly injured extremity vein is the femoral vein.[19] In one study of injuries to the truncal vessels, Hamner et al., noted a mortality rate of 67% among patients with IVC injury[20] making these injuries significantly morbid.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

Anatomical landmarks used to access arteries and veins in adults for insertion of large-bore IV catheters or arterial access are not as helpful in children, and this is one of the major contributing factors to iatrogenic injuries in children. In children, for example, there are reports of 12%[21] to 33%[22] minor overlap of femoral vein and artery which can lead to inadvertent arterial injury during venous access obtained without ultrasound guidance. Use of ultrasound during peripheral intervention has shown to significantly decrease complications after interventional procedures in adults,[23] but the effects of routine use of ultrasound on preventing these injuries among pediatric population merit further exploration.

Another significant contributor to the iatrogenic injuries is the size of vessels used for pediatric interventions. Using ultrasound, Warkentine et al., showed a significant correlation between size of the femoral artery and child's weight and body surface area.[21] In a large study of pediatric patients undergoing cardiac catheterization, the authors developed a risk scoring system for the prediction of serious adverse events (SAE) among these pediatric patients.[24] In this model, age <30 days and weight <2.5 kg, and procedures that required endovascular intervention (i.e., required larger sheaths) were highly predictive of SAEs that included vascular injuries.[24] These findings correlate well with the observation by Lin et al. noting a high correlation of vascular injuries with the use of larger (>6F) sheath.[10] The

effects of sheath size and complications afterward in pediatric population may be due to significant spasm encountered in these arteries after catheterization. In an older study, Mortensen has demonstrated complete arterial occlusion due to arterial spasm around a catheter in children.[25] It was observed by Franken and colleagues that size of catheter in relationship to the size of artery can significantly affect arterial spasm.[26] Franken and colleagues observed that when either catheter diameter was greater than 50% of arterial diameter or when catheter diameter was less than 1.9 mm smaller than arterial diameter significant spasm was observed.[26] The smaller size of pediatric vessels and highly spastic nature of these vessels can lead to spontaneous thrombosis and severe persistent vasospasm that may last for hours.[26] Other physiologic factors that contribute to arterial thrombosis in this patient population are related to the low intravascular volume and other medical conditions that exist in these children. Children requiring cardiac catheterization often suffer from low cardiac output that can also exacerbate thrombosis by relatively low flow to the distal tissue beds.

Iatrogenic and traumatic vascular injuries may lead to disruption, obstruction, or spasm of injured vessels. Obstruction of the vessel will lead to occlusion of the vessel and downstream ischemic symptoms that require urgent attention and restoration of flow. When vasospasm is suspected, conservative therapy after removal of the offending agents (e.g., a catheter) may be adequate to alleviate vasospasm and restore arterial flow. One of the most common pediatric vascular injuries is blunt brachial artery injury after supracondylar fracture. Arterial spasm after orthopedic injury may lead to ischemic arm after this injury. These injuries are often self-limiting and improve after orthopedic repair, and unless the arm is significantly ischemic, observation and conservative therapy may be equally effective as surgery (see later).[27] Adjuncts such as use of intra-arterial vasodilators such as papaverine may reverse spasm and restore blood flow if spasm does not improve. Warming the patients with injured lower extremity artery may also reverse arterial spasm.

Unique to vascular injuries is traumatic AVF due to iatrogenic or other traumatic causes. Since these fistulae are often asymptomatic initially, they may go undetected for years. These injuries can then lead to high-flow cardiac failure by gradual enlargement of the fistula communication and subsequent increase in demand for cardiac output. Flow disturbances due to these fistulae can lead to both high-pressure venous[28] and ischemic arterial ulcers[29] in the affected limb. Additionally, in certain cases, high flow to the affected extremity may lead to limb overgrowth. Once diagnosed, the majority of these AVFs can be ligated or coiled.

DIAGNOSTIC EVALUATION

Hard signs of vascular injury often seen in patients with penetrating vascular injuries, which include external bleeding and/or expanding hematoma, are reliable indicators of vascular injuries. When these signs are absent, the diagnosis of pediatric vascular injuries requires a high index of clinical suspicion and careful vascular examination. As noted above the majority of non-iatrogenic traumatic pediatric vascular injuries in countries at peace are due to blunt mechanisms.[2,4] Without evident hard signs of vascular injuries in many patients with blunt arterial injuries, the diagnosis of pediatric vascular injuries can be difficult and requires careful vascular exam. As in adults, examination of the affected and contralateral extremity includes skin color, capillary refill, and pulse examination even in the absence of actual vascular injuries, because, as noted previously, pediatric vessels are highly reactive and can go in spasm due to trauma leading to reduced or absent pulses. In one series of non-iatrogenic traumatic injuries, Myers and colleagues noted 26% of intraoperative spasm as the cause of low pulse exam in pediatric patients.[15] Additionally, combined orthopedic and arterial injuries, a very common occurrence in pediatric population, can lead to significant arterial spasm which can often be corrected after such injuries have stabilized.[16] It is therefore important in the multiply injured child, lacking hard signs of vascular injury, to address life-threating injuries first, resuscitate and warm the child, and then re-evaluate pulses to avoid unnecessary diagnostic tests and possible operative intervention.

In the absence of hard signs of vascular injury, serial exams using continuous wave hand-held Doppler can be an effective tool. Doppler can be used to listen to the pulse if it is absent but more importantly it can be used to measure ankle brachial index (ABI) in the injured extremity. Doppler can also be used for measurement of the injured extremity index (IEI), which similar to ABI, allows for the Doppler occlusion of an injured limb compared to a noninjured extremity. Katz and colleagues showed that ABI in children younger than 2 is not as reliable as in older children.[30] These authors observed that ABI is less than 1.0 until child is above 25 months of age or has attained a body surface area of greater than 0.5 m^2.[30] For this reason, Cannon et al. recommend using IEI in children instead of ABI and recommend strong consideration of poor perfusion as due to vascular injuries or systemic causes when IEI is less than 0.9 in children older than 2 and less than 0.88 in children 2 and under.[11] No direct comparisons of these two measurements are made in any study, but given the limitations of ABI in children younger than 2, IEI seems be a more accurate objective test of ischemia due to injury. Pulse oximetry has also been shown to be effective in following patients with arterial injury, for example, in those who have blunt brachial injury due to supracondylar fracture.[31] Regardless of the technique used, if resuscitation, warming, and correction of bony injuries does not correct the malperfusion of an injured limb, diagnostic tests should be used to identify the location and severity of the arterial injury.

Duplex ultrasound can identify the location and severity of these injuries in children suspected of vascular injuries. The specificity and sensitivity of arterial Duplex have been shown in many studies. It is suggested that Duplex can be the first investigation study in evaluating arteries and able to detect arterial injuries.[32] Duplex can also be highly useful in detection of cervical carotid injuries, but it cannot assess other more proximal or cephalad truncal injuries. Computed tomography (CT) angiogram (CTA) has been shown to be a very reliable study for detection of blunt truncal injuries, such as when a child has signs of direct trauma to neck, chest, or abdomen such as the seat belt sign.[33] CTA is often employed in patients

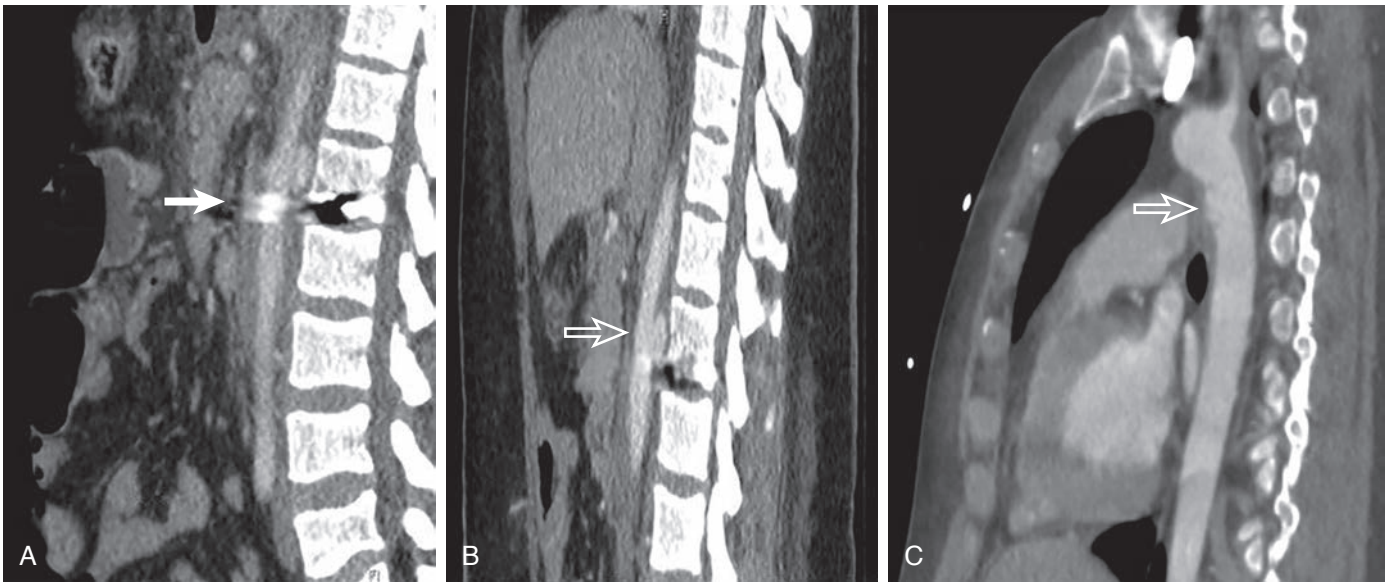

Figure 189.1 Utilization of CTA in detecting arterial truncal injuries; A and B are CTA of a 17 year-old-male shot through abdomen (*solid arrow* points bullet trajectory whereas *hollow arrow* points to aortic pseudoaneurysm due to heat/blast injury). (This was not appreciated during abdominal exploration.) (C) A thoracic aorta injury in a 16 year-old-male involved in a motor vehicle accident.

with multiple injuries and can often detect occult truncal injuries that were missed during physical exam or not appreciated due to the location of the injury (Fig. 189.1). CTA is not as useful in the detection of extremity arterial injuries in children. In such cases angiography may be indicated, while appreciating the significant risks of angiography in young children. Angiography is very useful in identifying the location of arterial injury and in distinguishing arterial injury from vasospasm. If diagnostic tests are not conclusive, in the setting of limb hypoperfusion, exploration of the suspected artery is indicated regardless of patient's age and size.

MANAGEMENT OF PEDIATRIC VASCULAR INJURIES

As noted previously many tenets of adult vascular trauma are applicable to pediatric patients. Similar to adult vascular trauma, the principles of care related to vascular injury include exposure of injured vessel, control of hemorrhage, and restoration of blood flow to the end organ. In that regard, several adjuncts in adult vascular trauma can be translated to the pediatric patients with vascular injuries. These include the following:

1. *Use of Temporary Vascular Shunts*—This adjunct has been quite useful in adult trauma by reducing the ischemia time and possible consequences of ischemia (e.g., nerve injury, muscle loss, compartment syndrome) while other injuries are treated. As with adult patients, a shunt should be inserted, after distal embolectomy and infusion of heparinized saline in the distal artery. Argyle shunts used for carotid surgery or a pediatric feeding tube can be used as a shunt in these smaller vessels.
2. *Role of Heparin*—Heparin is used extensively in adult vascular trauma provided there is no other contraindication to its use—such as excessive bleeding from poly-trauma or documented allergy to heparin. Heparin mediates platelet aggregation and decreases the propagation of formed thrombosis and may reduce formation of thrombosis in a narrowed spastic artery. The same principle applies to pediatric patients who should receive systemic heparin if there is no contraindication to its use. Temporary use of systemic heparin may also be used in cases of pediatric vascular injury where vasospasm has been a complicating factor, reducing distal outflow.
3. *Nonoperative management of arterial injuries*—In adults, minimal arterial disruption observed in patients with arterial injury is often managed nonoperatively. This may be the case of both blunt and minor penetrating vascular injuries identified during the work-up for vascular injury with CTA, angiogram, or Duplex. Similar to adults, if the distal circulation is intact, and the injury is minor (i.e., minimal vessel wall and intimal disruption or no active bleeding), the injured child can be observed. The basis of this practice is the observation by Stain and colleagues that these intimal injuries healed without any intervention during the follow up in adult patients.[34] Extrapolating from adult literature, it is reasonable to observe minor arterial injuries provided that there is intact distal circulation and the child can be observed carefully and monitored by follow-up imaging studies.

Lower Extremity Arterial Injuries

Historically, early exploration of pediatric vascular injuries was avoided unless there was an evidence of ongoing exsanguinating bleeding. However, poor long-term outcomes from

this conservative therapy strategy have led to more aggressive approaches with some recommending exploration even in the setting of vasospasm.[10] Although this approach may not be appropriate in all cases,[27] the consequences of delayed exploration and revascularization compel many surgeons to intervene and explore early to avoid these consequences. Operative management of the injured vessel in children is challenging as the vessels are spastic and small, and any repair must take into consideration the need for future axial and radial growth of blood vessels as well as the long-term patency of vascular repairs.[35] Management of the injured vessel should be coordinated with the other providers and should not jeopardize the injured children's survival. Management of pediatric vascular injuries should follow some of the basic tenets of adult vascular injuries. These include early diagnosis, definitive vascular repair or reconstruction, systemic heparinization, use of intravascular temporary shunts, use of embolectomy catheters, liberal use of fasciotomies and use of endovascular techniques to temporize bleeding (i.e., proximal balloon occlusion) or reestablish flow to the injured extremity if injured vessel size can accommodate endovascular options.

Management of Iatrogenic Vascular Injuries

Iatrogenic injuries may lead to complete or partial occlusion of an injured vessel. When this injury leads to complete occlusion, limb hypoperfusion can quickly set in with devastating circumstances. As noted previously, the conservative management of these injuries may lead to devastating long-term consequences perhaps due to the short "ischemic threshold" time beyond which limb quality deteriorates rapidly as shown in animal models.[36] In cases of arterial occlusion, arterial exploration, embolectomy, and patch angioplasty will lead to acceptable outcomes even in children younger than 2 years of age.[10]

If iatrogenic injury has not caused complete arterial occlusion, definitive repair can be delayed as long as the limb is well perfused. Small flaps and dissection often can be followed by serial exam and systemic heparinization to avoid arterial thrombosis. These patients must be monitored carefully and operated upon if the limb perfusion deteriorates. Interval repair of such injuries may also lead to acceptable outcomes,[10,12] but immediate restoration of perfusion should the gold standard.

Extracorporeal membrane oxygenation (ECMO) cannulation is a common cause of iatrogenic pediatric vascular injuries in tertiary pediatric centers.[37,38] These injuries that occur in about 20% to 52% of ECMO patients[38,39] can affect either femoral or carotid cannulation site.[37-39] Carotid injuries have shown to lead to cognitive disabilities which can be avoided by carotid repair after ECMO, and this has led centers to perform routine carotid reconstruction after ECMO, with good patency and neurologic outcomes.[37]

Management of Noniatrogenic Injuries

Management of noniatrogenic injuries is dependent on the location and mechanism of the injury. As noted previously the majority of vascular injuries after the age of 6 is related to noniatrogenic causes.[14] The epidemiology of these injuries was previously discussed.

Penetrating trauma to vascular injury requires immediate attention to temper blood loss and repair injured vessels in an attempt to save life and limb. High-energy penetrating blast injuries in urban warfare or war zone areas may require extensive soft tissue debridement, use of vascular shunts, and liberal use of fasciotomy while other injuries are addressed using a multispecialty approach to these injures as reported by Peck and colleagues.[40] The successful experience by these surgeons operating in Iraq and Afghanistan and reporting of 12 unfortunate children who sustained combat related injuries,[40] lends significant support to the philosophy of early diagnosis and operative management of vascular injuries in children.

The tenets of arterial repair, applicable to adult arterial injury, apply to children with the special consideration that children's vessels are smaller, spastic and any repair or interposition graft must accommodate the axial growth of the injured vessel and limb. Similar to adult injuries, if the injury is confined to a short segment of the arterial wall, primary repair of the injured artery with interrupted nonabsorbable polypropylene sutures is the procedure of choice. Patch angioplasty may be required in cases where simple repair is not possible due to lateral wall injuries. This type of repair avoids luminal growth issues at the anastomosis site and has been used with good success in low-velocity penetrating injuries and blunt injuries.[3,41] Patch angioplasty can be safely performed with a segment of noninjured greater saphenous vein (GSV).

Special considerations should be given to cases where interposition graft is required in children. The issues to consider are details pertinent to techniques of anastomosis creation, choice of suture material, and the type of conduit to accommodate the axial growth in children and avoid luminal narrowing at the anastomosis site. Since there is a need for these arteries to grow both axial and radial, the running-type suture technique commonly used in adults may not be ideal in pediatric population (Fig. 189.2). This type of suturing technique, in theory, may cause purse-string narrowing of the anastomosis and may hinder the radial expansion of the artery at the site of anastomosis. This has prompted some authors to recommend interrupted sutures instead of running sutures in pediatric patients.[42]

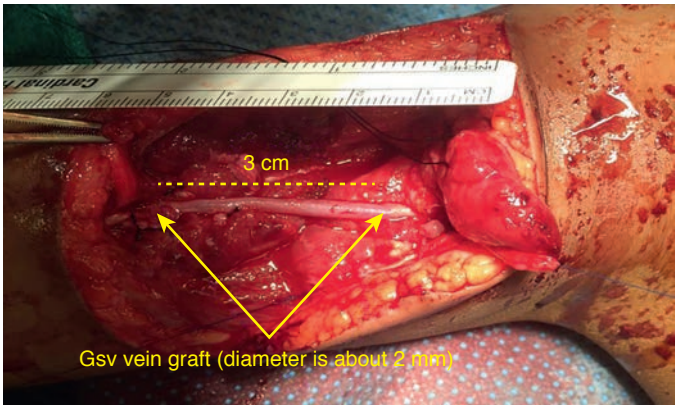

Figure 189.2 Penetrating injury to proximal brachial artery in a 7 YOM. Repaired with an interposition graft using grater saphenous and interrupted 8-0 prolene. (Courtesy of Dr. John Eidt.)

Although there are no comparative studies in pediatric patients comparing the types of anastomosis among pediatric patients, in animal studies, the use of running-type anastomoses has been shown to cause arterial narrowing in growing pigs at the site of anastomosis.[43] These authors also noted that nonabsorbable sutures were less thrombogenic than absorbable sutures.[43] These observations suggest that interrupted nonabsorbable sutures on a beveled anastomosis further enlarges the anastomotic connection between conduit and artery, may be the best method of arterial reconstruction in pediatric patients. The GSV has shown to be a durable conduit among children who underwent vascular reconstruction.[44] Therefore similar to adult trauma patients, the contralateral GSV should be the conduit of choice if an interposition graft is needed. This conduit should be preferentially used when there is high blast injury to the artery, which requires debridement of artery and the surrounding tissues to provide a clean and tension-free repair. In children, these types of injuries are often encountered in combat zones and invariably are associated with other injuries. In the setting of other injuries, a shunt can be used while complex neurologic and bony fractures are addressed.[40] It should be noted that dog bites in pediatric population could also present with both blunt and penetrating vascular injuries.[45] These devastating injuries, similar to high blast injuries, require significant tissue debridement and arterial injuries often with interposition graft.[46]

Early and liberal use of lower extremity four-compartment fasciotomy in patients with lower extremity ischemia has shown to decrease limb-related adverse outcomes.[47] This is universally practiced in wartime extremity injuries and is well described in the civilian pediatric literature.[3] This should be practiced in pediatric patients with lower extremity ischemia to improve the quality of limb salvage.

Special Case of Noniatrogenic Arterial Injuries—Blunt Brachial Artery Injury

Combined arterial and orthopedic injuries require a team approach. The majority of arterial injuries are improved once the orthopedic fracture is reduced. Blunt brachial artery injury is a common site of pediatric arterial injury where an orthopedic injury compromises the brachial artery. It occurs in the setting of a fall onto an outstretched hand and can be associated with neurovascular injury. Blunt brachial artery is the most common type of injury in a recent publication from Sweden[4] and is reported in 10% of children with supracondylar fracture[48] with potentially devastating consequences of upper extremity amputation and Volkman ischemic contracture. Stretch injuries to the artery, which can disrupt the vessel intima or impingement of the vessel by surrounding tissue, are the usual causes of this (Fig. 189.3). The presentation can range from normal to pulseless pink hand (PPH) to severe ischemia. After the orthopedic injury is corrected, pulses may return, obviating any necessity of intervention on the brachial artery. In patients with no pulse and evidence of ischemia after orthopedic reduction, the brachial artery must be explored and repaired in situ after thromboembolectomy or interposition graft with proximal GSV. Controversy exists about the best course of therapy among patients with PPH. Traditionally, PPH was managed expectantly with anticoagulation and serial exam of the hand that appeared well perfused (pink) and arterial exploration considered *only* if the patient developed neurologic signs of ischemia.[49] Other authors recommend arterial exploration for *every* case of PPH.[50] Although no prospective randomized trial exists, we suggest that there may be equipoise between observation and exploration for patients who present with isolated blunt brachial artery injury

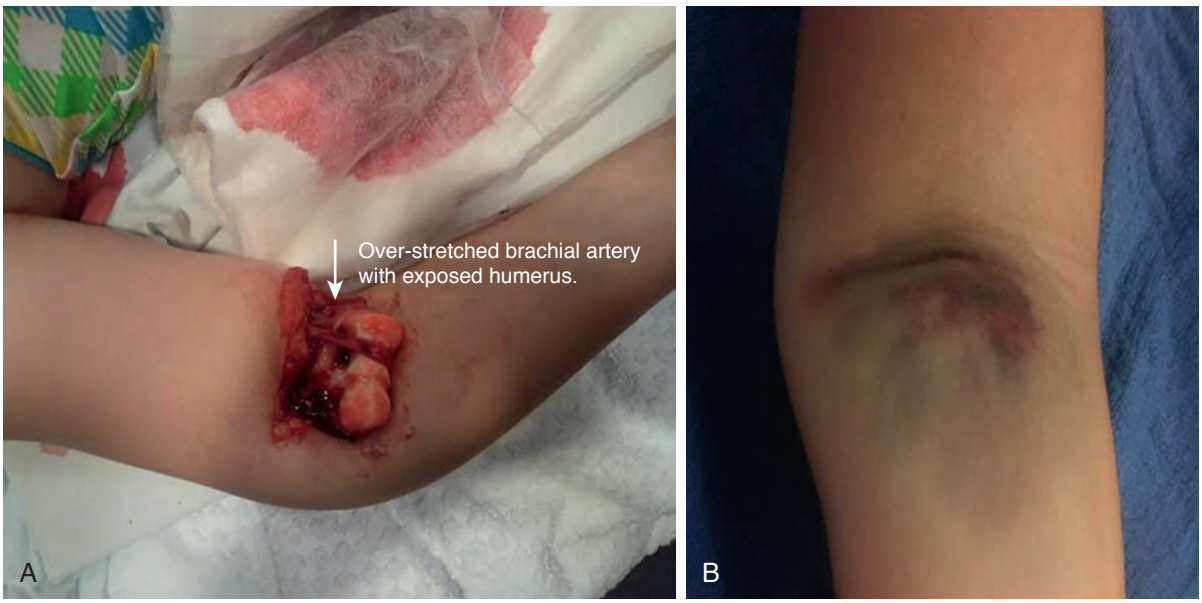

Figure 189.3 A common orthopedic injury is supracondylar fracture. Both of these patients presented with pulseless pink hand. Both improved after orthopedic repair. But patient in B required vascular exploration, embolectomy, and patch repair. (Courtesy of Dr. Timothy Ward, Dept. of Orthopedics, UPMC, Pittsburgh, PA.)

using a large administrative database.[27] This study was somewhat limited, however, being a retrospective analysis of an administrative database, and much clinical information beyond the index admission was not available.[27] Regardless of our findings in this publication, it is strong belief of this author that until level I prospective studies confirm that nonoperative management of pink pulseless hand does not affect long term limb function, a stable patient with PPH should be explored to evaluate the artery and repair the vessel as needed. Lack of pulses after orthopedic repair should therefore prompt exploration of the brachial artery and restitution of pulses with arterial repair or interposition graft.

Truncal Vascular Injuries

Similar to the adult, the injuries to the truncal vessels in children are life threatening and require immediate attention. The overall mortality rates of vascular injuries in US children is about 13% using NTDB.[2] These rates are significantly higher among patients with truncal arterial injuries.[2] Barmparas et al. observed a 16% to 41% mortality rate for truncal vessels: neck 16%, chest 41%, abdomen 25%.[2] In a large trauma center, Corneille et al. observed that *all* cases of mortality out of 116 children with significant vascular trauma were due to truncal arterial injuries.[9] The most important predictor of outcome in pediatric patients with truncal injuries is hemodynamics at the time of presentation with other factors affecting survival including caval injuries, anatomic location of the injury, and the mechanism of injury.[17] Unlike adult patients, blunt injury to the aorta is uncommon in pediatric population and, as this is typically accompanied with a variety of other injuries, is universally incompatible with survival.[17] In injured pediatric patients, due to the small diameter of injured arteries, endovascular options, commonly employed in adults with great success, are very limited.

These injuries can often be diagnosed with high resolution CTA without any need for angiography.[17] Most cases of pediatric thoracic aortic injuries and great vessel trauma are managed with open surgery. Thoracic aortic injuries are treated with clamp-and-sew technique without any significant adverse neurologic outcomes.[17,18,51] Although among patients with severe truncal artery injuries who present in shock outcomes are extremely poor, using this clamp and sew technique Allison et al. reported survival rates of 81% to 92% among patients who were hemodynamically stable at presentation with *no* paraplegia.[17] Similar to adults with blunt thoracic aorta, delayed repair with early initiation of beta-blocker therapy has shown a survival benefits to patients.[52] Smaller diameter thoracic stents can be used in some adolescent children with blunt thoracic artery injuries,[53] but long term results are lacking and should be used only cautiously (Fig. 189.4).

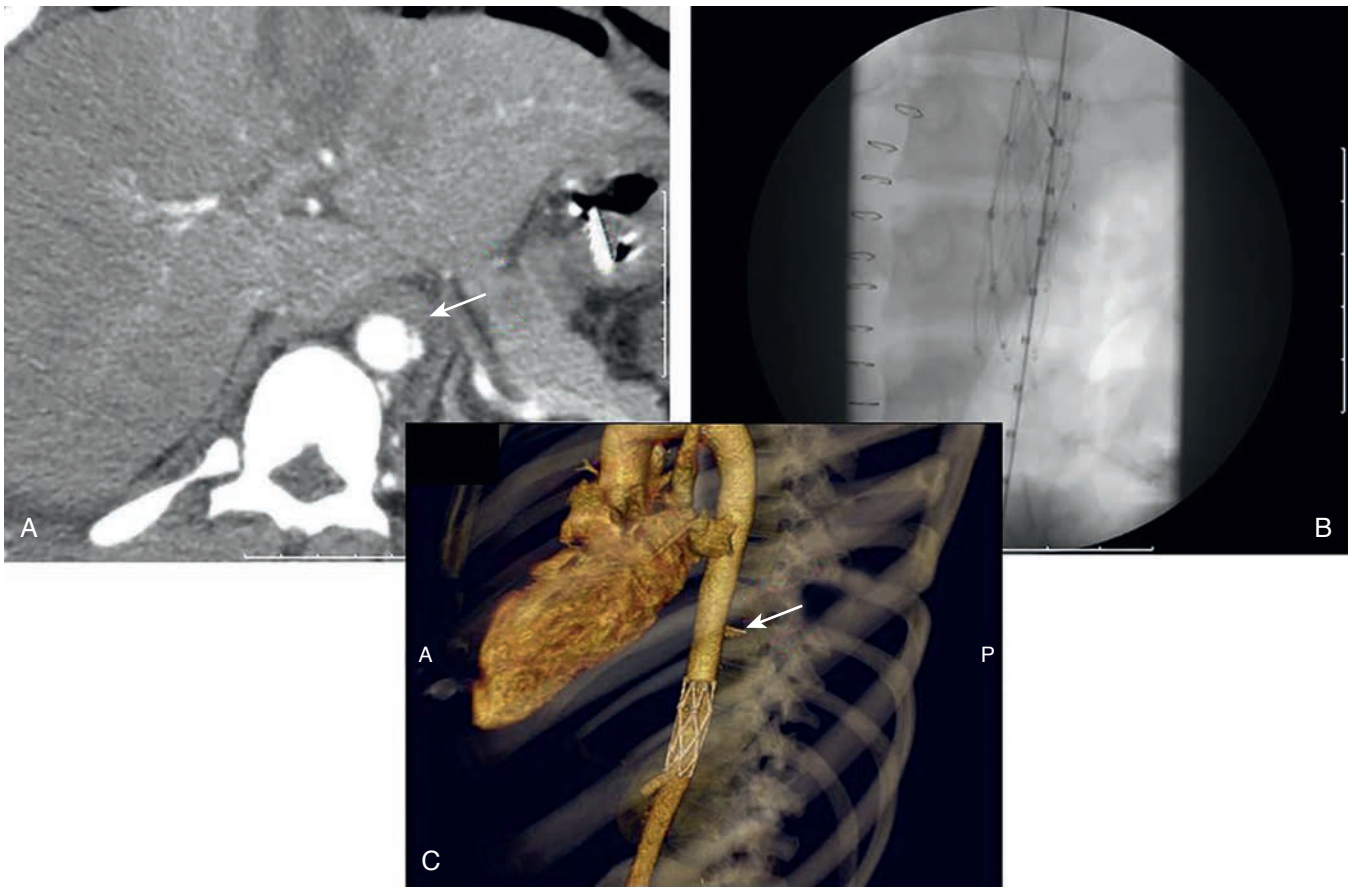

Figure 189.4 Endovascular repair of GSW to distal. (A) Thoracic aorta in a 14 YOM *(arrow)*. (B) This was successfully repaired. A few months later, follow up CT shows that the stent has migrated and covered celiac access (C, *arrow points* to the initial location of stent). (Courtesy of Dr. John Eidt.)

Management of abdominal vascular injuries is dictated by hemodynamic stability and the severity of associated injuries and thus ranges from suture repair of injured vessels to interposition replacement with a synthetic graft for aortic and caval injuries and use of GSV or hypogastric arteries for other intra-abdominal vascular injuries.

Mechanism of injury and anatomical location dictates the appropriate repair of cervical injuries. For lesions due to a penetrating mechanism and located in the anatomically accessible lesions (zone II), simple repair or interposition graft of injured vessel is possible. More proximal injuries (zone I) with penetrating injuries may require median sternotomy. More distal injuries (zone III) may be treated by ligation of the internal carotid artery or endovascular techniques (coiling or use of covered stent) if anatomically feasible to save the child's life. Blunt injuries to the carotid artery are more difficult to diagnose without a high definition CTA, but they rarely benefit from surgical intervention. These patients do worse than patients with penetrating injuries,[3] and treatment is often careful observation, antiplatelet therapy and serial imaging.[54] Injury to the innominate artery requires median sternotomy. This approach also allows exposure of the proximal right subclavian artery. The proximal left subclavian artery can be approached via left anterior lateral thoracotomy. Endovascular control of these proximal vessels with a balloon is gradually replacing the need for proximal control by these open techniques.

ROLE OF ENDOVASCULAR TECHNIQUES IN PEDIATRIC PATIENTS

As noted in the sections of iatrogenic injuries, endovascular interventions in children can be fraught with complications. The smaller vessels in children are also not suitable for large stent graft coverage. So, despite significant use of endovascular interventions for all forms of traumatic vascular injuries in adults, endovascular intervention plays a limited role in pediatric population and then, mainly in adolescents. The adolescent thoracic aorta, for example, can accommodate smaller diameter thoracic stent grafts,[53] but the majority of traumatic aortic injuries in children require open repair. Endovascular techniques can be used to control bleeding by placing a proximal balloon and therefore simplifying exposure; can also be used for embolization of inaccessible bleeding vessels (e.g., see above injuries to zone III cervical injuries); and in some cases there are reported cases of use of covered stents to manage traumatic carotid injuries in pediatric patients (Fig. 189.5).[55] Further smaller profile devices may increase the utilization of endovascular therapies in younger children in the near future.

POSTOPERATIVE MANAGEMENT AND OUTCOMES

Routine postoperative management of injured children requires collaboration with pediatric specialists who can better manage the details of care. With specific reference to traumatic vascular injuries, these patients require routine hourly vascular examination with any changes prompting immediate attention. Similar to adult trauma patients, and barring any medical contraindication, antiplatelet therapy is advisable. Although there are no clear scientific reasons for this, antiplatelet therapy may be beneficial to the injured vessel or the new anastomosis which is often devoid of endothelium and thus prone to platelet adhesion to the injured vessels. The duration of this therapy is not scientifically proven, but it appears that a short course (30 days) is adequate. Routine use of anticoagulation is not indicated and may cause bleeding, particularly in patients with polytrauma.

Other than routine pulse exam and clinical assessment, postoperative surveillance should be tailored to the vascular repair. The issues of appropriate postoperative surveillance beyond the index hospitalization and compliance of these trauma patients is multifaceted. The compliance of trauma patients for follow-up is low,[56] and since trauma care is provided with multiple services, the burden of compliance with follow-up is passed between services.[57] Additionally no clear surveillance follow-up protocol is agreed upon. Patients with thoracic aortic repair with thoracic stent should undergo annual CTA to evaluate the stented aorta until adulthood. Other than this type of injury, routine CT or CTA is not indicated. For lower extremity revascularization, simple pulse exam or IEI can detect a failing graft in the immediate postoperative period.[3] Duplex surveillance of the graft at one month postoperatively and then at routine intervals is advisable to expose early technical issues or stenosis or aneurysmal changes of the graft at later time points.

The difficulty with compliance and the low number of patients with pediatric trauma makes a discussion about long-term postoperative outcomes difficult. The discussion about long-term outcomes after pediatric vascular trauma therefore centers on retrospective case series or observational database studies. In-hospital mortality rates of these patients are reported to be 13.2%[2] with 2.4% of patients dying at the time of presentation to the emergency department based on the US National Trauma Data Bank Data.[2] In case series studies reported crude mortality rates which are similar (9.7%[9] to 12%[3] in two large case series). The highest mortality among the pediatric patients was among infants (18.2%) and of these, the highest mortality was among patients with chest vascular injuries.[2] The overall rate of in-hospital amputations was low but the highest amputation rates were observed among patients with brachial and popliteal artery injuries for upper and lower extremity injuries, respectively.[2] Lin et al., reported the long-term results of a series of 34 patients with iatrogenic injuries.[10] In this series, patients were followed for a mean follow up period of 38 months. No limb loss with surgical repair was occurred and gait disturbance was observed among the three patients who presented with chronic limb ischemia and gait disturbance.[10]

CONCLUSIONS AND FUTURE DIRECTIONS

Pediatric vascular trauma is currently managed by different groups of specialists with different training and backgrounds.

Figure 189.5 Iatrogenic injury during repair of orthopedic injury (A) that was repaired by a covered stent (B) in a 12 YOM patient with unstable patient with multi-trauma. Artery was repaired in few days—after patient improved—with an interposition graft and stent removal and evacuation of hematoma.

Klinkner and colleagues noted that vascular surgeons treated only 17% of pediatric vascular injuries.[3] Since these events are rare, there are no clear guidelines about algorithmic care of these patients. Most data reported here are based on evidence from animal studies, case series, and expert opinion. It is therefore imperative that in every institution, algorithmic care of these patients be developed by all the involved specialists and based on the best available data so all the involved specialties follow the same guidelines in taking care of these fragile patients. It is important that data for these cases be recorded in a registry dedicated to pediatric patients. The National Trauma Data Bank now collects demographic on these patients and Barmparas used this registry for a comprehensive review.[2] Ideally, collaborative efforts by vascular and trauma registries to collect data on vascular injuries, outcomes, and long-term follow-up may provide the best source of information for best quality care. Additionally, the US Military Medical Corps has been involved in many cases of pediatric vascular trauma since 2003. The information about their experience should be added to NTDB and any future vascular trauma registry to help translate their successful management techniques to the civilian pediatric population. Such a registry must also record the information about in-hospital neonatal vascular injuries and their outcomes. Given the significant advantages of the use of ultrasound among adult patients in reducing vascular injuries,[23] guidelines about use of this technology to reduce injuries in these pediatric patients should be investigated.

Despite the limitations of the data noted above, modern data emphasize aggressive operative management of vascular injuries in pediatric patients in clear contradistinction to the

historical, more conservative management approach. This approach, similar to adult vascular trauma, comprises a comprehensive team approach that includes bleeding control, vascular shunting to circumvent ischemia while other injuries are addressed, liberal use of fasciotomy for lower extremity injuries, and use of endovascular approaches as the definitive or contributive mode of treatment. Future research in the field of pediatric trauma should focus on creating endovascular approaches to both possibly mitigate the injury or ultimately treat the injury definitively. Such treatment options must accommodate the small size and expected growth of the arteries of these patients.

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A complete reference list can be found online at www.expertconsult.com.

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190 CHAPTER

Placement of AV Dialysis Accesses and Central Catheters in the Pediatric Patient

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BACKGROUND

Pediatric end-stage renal disease (ESRD) is a challenge for caregivers, nephrologists, and surgeons. Although 25.1% of pediatric patients initiating treatment for ESRD do so with index transplantation and 18.3% initiate with peritoneal dialysis, a large majority of patients (55.8%) utilize hemodialysis (HD) as their first modality of renal replacement therapy. Currently, the National Kidney Foundation's (NKF) Kidney Disease Outcome Quality Initiative (K-DOQI) guidelines recommend placing permanent HD access in all patients aged 0 to 19 who are greater than 20 kg and are not expected to receive a kidney transplant within 1 year.[1] Thus, patients expected to be on dialysis greater than 1 year that meet the age and size criteria should receive a permanent arteriovenous fistula (AVF). Over 50% of pediatric patients who initiate ESRD treatment with HD meet these criteria; however, approximately 90% of these suitable patients commence HD treatment via central venous catheters (CVCs).

The Fistula First Breakthrough Initiative (FFBI) was established in 2003 to improve the rates of arteriovenous fistula placement for HD. Combined with the FFBI, the K-DOQI practice guidelines set a goal of 40% AVF placement for first time access patients, and this goal was exceeded by 2011 with 60% fistula use. However, the FFBI does not specifically address the low rates of fistulas in the pediatric population. To combat this problem, the International Pediatric Fistula First Initiative (IPFFI) was established in 2005 with the aim of addressing the lack of AVF use in the pediatric population.[2] The IPFFI was a collaborative effort with the Midwest Pediatric Nephrology Consortium, whose aim was to increase awareness among pediatric providers (nephrologists, surgeons, and dialysis staff) that AVF is the preferred access method for long-term HD in pediatric patients. The initiative has penetrated the United States and evidence supporting fistula first placement in pediatric population is emerging. For example, the initiative's implementation with corresponding reduction in bloodstream infections has been demonstrated at

Children's Hospital at Downstate, SUNY Downstate Medical Center.[3]

INCIDENCE

The incidence of ESRD in patients aged 0 to 21 years old[a] was 1462 in the year 2013.[4] In comparison, the incidence in adults was 117,162 patients the same year. The incidence of ESRD in the pediatric population appears to have peaked in 2003 and has since then been steadily decreasing, although compared to the early 1980s and 1990s, the incidence curve has largely plateaued. Since its initiation of data collection in 1992, the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reports no significant change in the pattern of incidence of ESRD in pediatric population. When looking specifically at certain age groups, race, or gender, these rates are anticipated to remain stable.[5] The cumulative prevalence of ESRD in pediatric patients as of December 31, 2013 was 9921 children.

The United States Renal Data System (USRDS) reports HD as the most common index treatment for patients initialing care for ESRD; in 2013, 55.8% of pediatric patients initiated care with HD, 25.1% had preemptive transplantation, and 18.3% started with peritoneal dialysis.[4] Compared to adults, where index transplantations are rare, there is a wider distribution of index treatment modalities in the pediatric population. The index treatment for adults in 2013 was HD in 88.2%, peritoneal dialysis in 9%, and index transplantation in only 2.6% of patients. As many as 37% of children with ESRD underwent kidney transplantation within the first year of starting ESRD care during the time period of 2009 to 2013; this a slightly lower figure compared to the previous listing of 43.6%.

ETIOLOGY

The leading group of disorders responsible for ESRD in pediatric patients continues to be cystic/hereditary/congenital disorders accounting for 33% of cases in the current reporting period (compared to 28.6% in previous report). Glomerular diseases are the second leading etiology, responsible for 24.6% of cases (27% previously), followed by secondary glomerulonephritis in 12.9% of patients (Fig. 190.1). Looking at individual diagnoses, the most common causes of ESRD include focal glomerular sclerosis (12.7%), renal hypoplasia/dysplasia (9.8%), congenital obstructive uropathies (9.2%), and lupus nephritis (7.5%). In African American patients, there is a significantly higher percentage of children with certain nephropathies related to systemic diseases. For example, African American children make up 95% of all children affected with sickle cell nephropathy. In addition, AIDS nephropathy patients in the current reporting period are 97% African American, which is an increase from 91% in previous reporting years. Finally, among those affected by lupus nephropathy, 53% are African American (increased from 50% previously).

[a]While previous USRDS reports included patients aged 0 to 18 years old, the most recent report includes patients up to age 21 years.

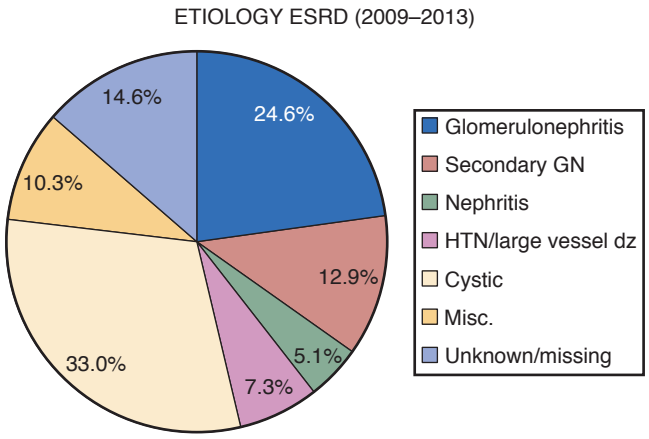


Figure 190.1 Primary reported etiology of End Stage Renal Disease *(ESRD)* in pediatric patients aged 0 to 21 years old, 2009 to 2013. *GN,* Glomerulonephritis; *HTN,* hypertension. (Adapted from United States Renal Data System: *2015 USRDS annual data report: epidemiology of kidney disease in the United States,* Bethesda, MD, 2015, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, chapter 8: table 8.1.)

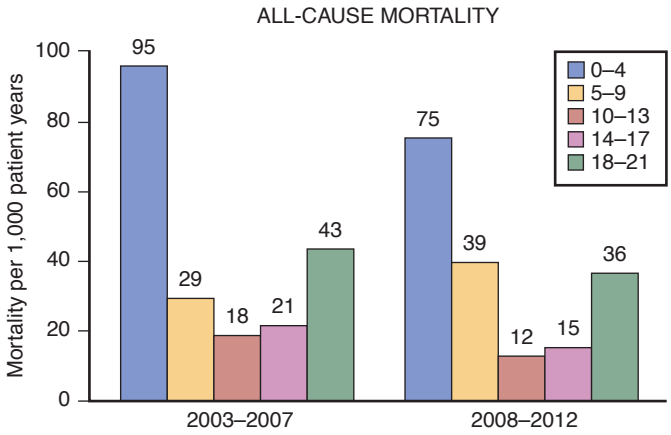


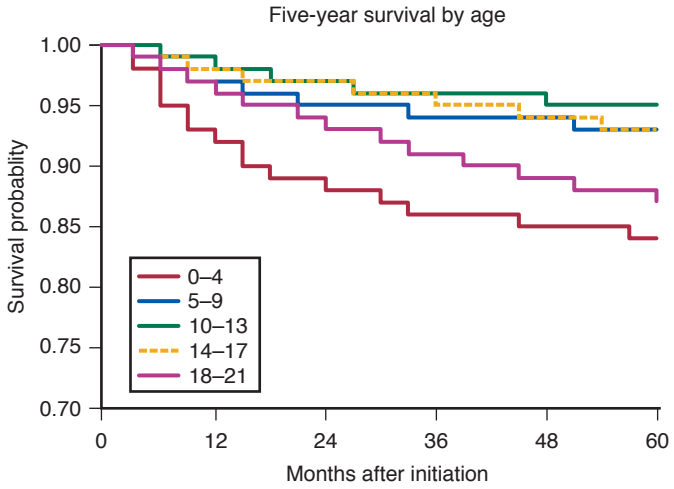
Figure 190.2 One-year adjusted all-cause mortality rates in pediatric patients with End Stage Renal Disease in 2003 to 2007 and 2008 to 2012 shown by age. *HD,* Hemodialysis; *PD,* peritoneal dialysis; *Tx,* transplant. (Source: United States Renal Data System: *2015 USRDS annual data report: epidemiology of kidney disease in the United States,* Bethesda, MD, 2015, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, chapter 8; USRDS ESRD Database. Incident dialysis and transplant patients defined at the onset of dialysis or the day of transplant without the 60-day rule; followed to December 31, 2013. Adjusted for age, sex, race, Hispanic ethnicity, and primary cause of ESRD. Ref: incident ESRD patients aged 0 to 21, 2010 to 2011.)

MORBIDITY AND MORTALITY

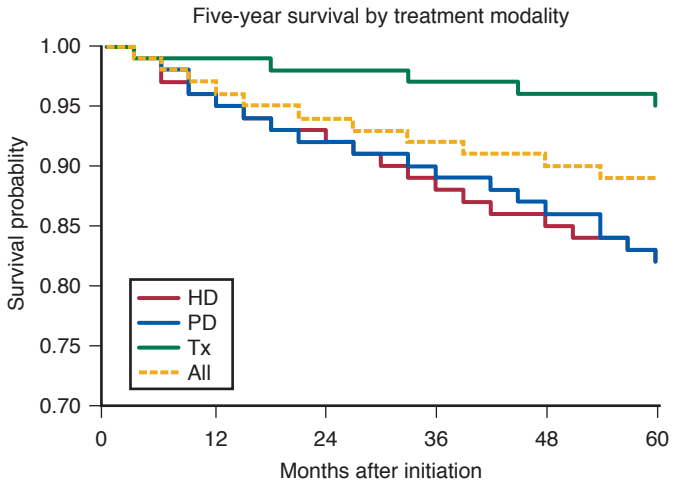
ESRD in children, as it does in the adults, confers an increased morbidity and mortality on those affected compared to the general population. The 2008 to 2012 all-cause mortality was 36 per 1000 patient-years, a 14.3% improvement over the previous time period. Although this rate is relatively low, the most affected are the youngest children. The mortality rates per 1000 patient-years is 75 cases for children aged 0 to 4 years, 39 for 5 to 9 year-olds, 12 for 10 to 13 year-olds, 15 for 14 to 17 year-olds, and 36 for 18 to 21 year-olds (Fig. 190.2).

HD patients also have a higher mortality compared to patients being treated with other modalities. The reported 1-year mortality rate in the 2008 to 2013 period for HD patients was 46 per 1000 patient-years compared to 35 per 1000 patient-years for peritoneal dialysis patients, and mortality is lowest for transplanted patients at 11 per 1000 patient-years.

The combined 5-year survival for pediatric ESRD patients evaluated from 2008 to 2012 was 89%, with the youngest age group having the lowest survival. The 5-year survival percentages were 84%, 93%, 95%, 93%, and 87% for children aged 0 to 4 years, 5 to 9 years, 10 to 13 years, 14 to 17 years, and 18 to 21 years, respectively (Fig. 190.3A). As expected, the 5-year survival is best for those who have undergone transplantation (95%), followed by peritoneal dialysis and HD, both with a 5-year survival of 82% (see Fig. 190.3B). The causes of mortality in pediatric patients are primarily cardiopulmonary issues and infections. Cardiopulmonary complications are responsible for 21% of all pediatric ESRD deaths, followed by infections of which bacterial infections cause 11.1% of deaths.



A



B

Figure 190.3 Adjusted 5-year survival in incident pediatric patients from 2004 to 2008 shown by age (A), and by treatment modality (B). *HD,* Hemodialysis; *PD,* peritoneal dialysis; *Tx,* transplant. (Source: United States Renal Data System: *2015 USRDS annual data report: epidemiology of kidney disease in the United States,* Bethesda, MD, 2015, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, chapter 8; USRDS ESRD Database. Incident dialysis and transplant patients defined at the onset of dialysis or the day of transplant without the 60-day rule; followed to December 31, 2013. Adjusted for age, sex, race, Hispanic ethnicity, and primary cause of ESRD. Ref: incident ESRD patients aged 0 to 21, 2010 to 2011.)

Rates of hospitalization are used as a surrogate for morbidity and a direct indicator of complications. Pediatric ESRD patients average 2005 admissions per 1000 patient-years; the most common causes again are cardiopulmonary issues, resulting in 374 admissions per 1000 patient-years, and infectious complications resulting in 606 admissions per 1000 patient-years.[4] Broken down into hospital admission by modality of treatment, patients who have undergone transplantation have the lowest admission rates at 276 per 1000 patient-years, followed by those on HD at 556 per 1000 patient-years and by those on peritoneal dialysis at 779 hospitalizations per 1000 patient-years.

PATIENT SELECTION

The inherent technical challenges unique to pediatric patients and shorter expected waiting time for transplantation access selection presents a dilemma. Incident access selection depends largely on information provided by caregivers, but it also relies on preconceived notions about HD, parent and caregiver biases, and the age and maturity of the patient.[6] Studies are limited but issues such as small patient size, having a maturing AVF or graft, and communications issues among stakeholders have been identified as limiting factors to successful autogenous fistula placement and use in pediatric patients.[7,8] Chand and colleagues identify several major barriers to successful AVF use including communication problems between providers, a lack of standardized referral practices for chronic kidney disease (CKD) patients, a lack of standardized accepting surgeon, as well as a lack of early communication between those placing and repairing fistulas (surgeons and interventional radiologists) and dialysis staff (nephrologists, nurse practitioners, dialysis nurses) regarding problematic fistulas.[8] Similarly, few studies have looked at psychosocial issues affecting access selection in this population.

Medical decisions can be complex and burdensome; however, when children are allowed to make a decision, long-term implications may not be well understood, although as patients become adolescents, studies have demonstrated decisions are made in conjunction with parents regarding care.[6] In our own practice, patients report fear of needles, inability to wear jewelry or participate in sports, and the ugly appearance of fistulas as barriers to fistula placement. Parents have their own concerns with fistula placement including the uncertainty of knowing what is best for their child despite receiving all the data supporting fistulas over catheters. Brittinger and colleagues evaluated patient discomfort with HD cannulation and 39% of pediatric patients reported no discomfort, 39% had a tolerable amount of discomfort, and only 22% reported significant discomfort; however, 95% of the participants also reported they would prefer not to revert to CVC for access.[9]

Pediatric patients are initiating HD treatment exclusively with a CVC over 80% of the time, a statistic largely unchanged in the last decade. This percentage is higher when considering those with maturing arteriovenous fistulas or grafts, elevating the percentage to 99.2% in patients aged 0 to 4 years, 98.5% in patients 5 to 9 years, 97.3% in patients 10 to 13 years, 92.2% in patients 14 to 17 years, and lowest at 90.4% among patients 18 to 21 years (Fig. 190.4A). The overall trend of catheter presence at index HD has changed very little since 2006 (see Fig. 190.4B). Similar to adults, pediatric fistula placement several months before renal replacement therapy initiation is ideal; thus, nephrologists and surgeons should communicate early about CKD patients such that surgery can be completed in a timely fashion and that fistulas are able to reach functional maturation. Currently, K-DOQI guidelines recommend all patients with CKD stage 4 (GFR <30 mL/min per 1.73 m^2) be referred for education about modality of ESRD treatment and that AVF be placed 6 months before the anticipated start of HD. Although the progression of CKD to ESRD can vary widely, providers should make early referrals whenever possible.

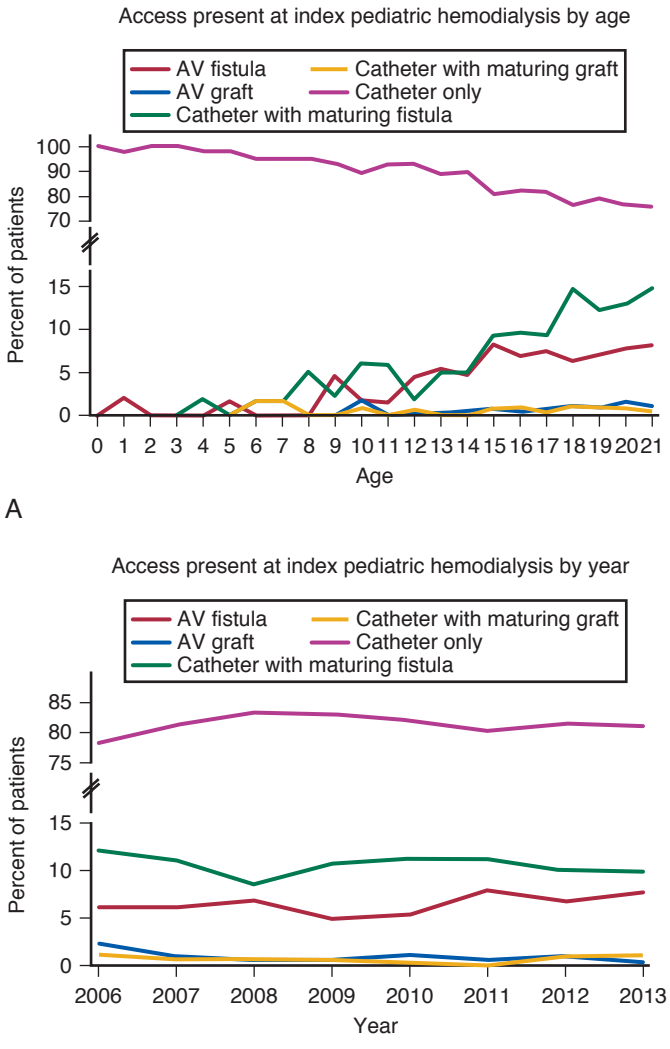


Figure 190.4 Vascular access present at initiation of incident pediatric hemodialysis by age (A) and by year (B). *HD,* Hemodialysis; *PD,* peritoneal dialysis; *Tx,* transplant. (Source: United States Renal Data System: *2015 USRDS annual data report: epidemiology of kidney disease in the United States,* Bethesda, MD, 2015, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Vol 2 ESRD chapter 8; USRDS ESRD Database. ESRD patients initiating hemodialysis in 2006 to 2013.)

TREATMENT WITH HEMODIALYSIS

Establishing access for HD is one of the main considerations in initiating treatment for patients of all ages. Issues, such as central venous stenosis and catheter-associated infections, were among the main concerns leading to the FFBI as well as the International Pediatric Fistula First Initiative. According to the NAPRTCS 2011 dialysis access data report, 78% of patients receiving HD had external percutaneous catheters, 0.3% had external AV shunts, 11.8% had internal fistulas, and 6.7% had internal arteriovenous grafts. Of the external percutaneous catheters, the majority (51.1%) were placed in the subclavian vein exacerbating associated central vein stenosis, 43.7% were placed in the jugular vein, and 4.2% in the femoral vein.[10] Up to 80% of central venous catheters in use are "permanent" catheters instead of "temporary," decreasing the urgency for autogenous AVF placement.[10] Despite the recognized efforts to increase AVF placement, use of external percutaneous catheters for HD at initiation of therapy has increased from 73% in 1992 to more than 90% of all HD access in 2010.[4]

CENTRAL VENOUS CATHETERS GENERAL CONSIDERATIONS

Specific reasons delineating the common use of permanent catheters for HD access are sparse, yet those describing complications of the catheters are abundant. Fadrowski and colleagues reported that 59% of patients followed by their center had central venous catheters.[7] The reasons given for catheter use included "small body size" in 18.8%, having "AVF/AVG maturing" in 7%, and having a "transplant scheduled" in 10.9% of the patients. Of those patients who listed having a pending transplant, 69% had in fact received a transplant within a year, yet 31% of them were still waiting for an organ while receiving HD via CVC. Another retrospective investigation by the same group looked at risks attributable to central venous catheters compared to fistulas in 12- to 18 year-old ESRD patients receiving HD for the year 2000.[11] The authors included 418 patients, 41% with AVF/AVG and 58% with CVC. The group discovered a significant higher relative risk among CVC patients with regard to all-cause hospitalization (RR 1.84 CI 1.38 to 2.44), hospitalizations due to infections (RR 4.74 CI 2.02 to 11.14), and complications of vascular access (RR 2.72 CI 2.00 to 3.69). The durability of central venous catheters remains inferior to fistulas, averaging from 4 to 12 months and in some cases as low as under a month.[12] Central venous catheter durability ranges from 0% to 62% at 1 year, and failure is attributed to infection (17% to 40%), thrombosis (33%), accidental extrusion (5% to 10%), and kinking, which is more common in smaller nonprecurved catheters or noncuffed catheters.[12,13]

A major complication of central venous catheters with long-lasting implications is central venous stenosis. In an attempt

to mitigate long-term damage, the K-DOQI guidelines have delineated the sequence of vein selection that is preferred in the event that a CVC is needed.[1] The recommendation of vein selection lists right internal jugular vein, right external jugular vein, left internal and external jugular veins, subclavian veins, femoral veins, and lastly and rarely used would be translumbar and transhepatic access to the IVC. Publications elucidating the prevalence of central venous stenosis link its occurrence to history of subclavian central venous catheter placement as commonly as 25% to 50%.[14] Finally, although the presence of a catheter seems to impair the long-term patency of AVF in adults,[10,15-17] this is not the case in pediatric patients as demonstrated in our investigations.[18] Thus, ipsilateral catheter is not a contraindication to fistula placement and efforts to replace catheters with fistulas would reduce the incidence of central venous stenosis.

CENTRAL VENOUS CATHETERS TECHNICAL CONSIDERATIONS

Central venous catheters by design are either temporary (non-tunneled) or permanent (tunneled), and these are often placed percutaneously under moderate sedation and local anesthetic. Tunneled catheters in pediatric population, however, often require general anesthesia to ensure patient compliance, which comes with its own set of potential complications and side effects. There is no evidence-based rule for catheter size selection, making establishing central venous access for HD a major challenge; compounding the issue is that commercially available precurved catheters are only supplied in larger sizes. Larger catheters offer higher volumes (and shorter times) during dialysis; however, the size of the child and his or her vessels limit the size of the catheter that can be used. Smaller catheters necessitate longer dialysis sessions due to slower flow rates; thus, the size must be large enough to be useful for dialysis but also small enough to be tolerated by the vessel. The authors created a catheter sizing formula that proved to be safe and is utilized in our practice: [Size (Fr) = Age ± 2]. Taking the age of the child and using it as the catheter's, diameter in French measurement and then reducing the size if the patient is small for their age or increasing the size if the child is larger than peers the same age. Precurved catheters available for the adult populations make percutaneous and subcutaneous tunneling possible; however, these catheters are largely unavailable in the smaller sizes for the youngest of pediatric ESRD patients. In these patients, placing a tunneled CVC usually means artificially creating the curve during placement and making one or more counter incisions (Fig. 190.5) over the access vessel for accurate and precise placement.

Figure 190.5 Twelve-year-old pediatric end stage renal disease patient who had a 10 French hemodialysis central venous catheter placed in the internal jugular vein. A 10-French catheter was selected due to the patient being smaller than peers her age, and a counter incision was necessary for proper placement.

AV ACCESS GENERAL CONSIDERATIONS

Autogenous arteriovenous fistulas are the preferred form of access for pediatric patients undergoing HD. Technical success has been demonstrated in a variety of autogenous AV accesses in both upper and lower extremities.[19-23] Early experience with autogenous fistula placement in children demonstrate lower patency rates as shown by Bagolan and colleagues with the placement of Cimino fistulas children from 1985 to 1994; their reported 4-year patency was 63.5%, and the complication rate was 35%, which thrombosis was the most common complication.[19] More recent publications have reported better outcomes. The authors have described factors affecting long-term patency of autogenous fistulas of 101 fistulas placed in 93 children with a mean age of 14 years (range 3 to 19), and weights ranging 12 to 131 kg.[18] At the time of surgery, 82% of the patients had a CVC catheter in place and were on HD for an average time of 18 months; furthermore, 24% of them had a history of multiple catheters. The group performed 43 radiocephalic, 29 brachiocephalic, 20 basilic vein transpositions, 9 femoral vein transpositions, and had an average follow up of 2.5 years. The reported primary and secondary patency at 2 years was 83% and 92%, respectively, and 65% and 83% at 4 years, respectively. Chand and colleagues showed that the implementation of IPFFI was feasible at their institution.[24] While not uniformly utilized, the use of the operating microscope has also been successful in children, with less primary fistula failures.[25,26]

AV ACCESS TECHNICAL CONSIDERATIONS

As with central line placement, the K-DOQI publishes guidelines for a structured approach for the placement HD access.[1] They report a preference for radiocephalic AVF followed by brachiocephalic AVF and lastly by basilic vein transposition. The techniques for standard radiocephalic, brachiocephalic, and basic vein transposition are widely described and can be applied to pediatric populations with some additional considerations for optimal results.

The initial consultation, similar to adults, starts with a complete history including previous central venous access use, a thorough physical exam with detailed vascular examination, and vein mapping on all patients. The operating surgeon should evaluate the vein mapping personally to determine vein suitability. Due to significant vasospastic response in pediatric patients, vein imaging should also be performed intraoperatively once the patient is placed under anesthesia. Size cutoffs of 2.0 mm for forearm veins, and 2.5 mm for upper-arm veins have had successful rates of maturation.[18] One of the attributes unique to pediatric vessels is their intense vasospastic response with handling; for example, tourniquet occlusion can be used for arterial control during fistula construction in lieu of arterial clamping. Loupe magnification (×2.5 or greater) should be standard in all pediatric fistulas. Sanabia and colleagues demonstrated 10% early failure rate, and 70% 5-year patency with the use of either operating microscope or loupe magnification.[26] Subsequently, Bourquelot and colleagues also published a lower primary fistula failure with use of microsurgery.[25] Standard end-to-side anastomosis using a continuous running monofilament suture is recommended, since interrupted suture placement is not imperative. Finally, vein transpositions (brachial or femoral in the event that superficial arm vasculature is not suitable) can be performed in either single or two-stage procedure. Kim and colleagues have described the use of two-stage basilic vein transposition with increased percentage of maturation (87%), lower failure rates (7%), and 91% 1-year patency rates.[27] Groin fistulas have also been successfully placed in pediatric populations, in the setting of unavailable upper extremities or patient preference as described by Gradman and colleagues with a technique similar to that described in adults.[20] Their reported primary patency was 100% and 96% at 1 and 2 years, respectively; secondary patency was reported to be 100%.

CONCLUSION

Establishing pediatric HD access is complex and has yet to become standardized. National data indicate that a large majority of patients initiate HD with CVCs despite results demonstrating that AVF are superior. Central venous catheters are associated with higher complications, more hospitalizations, and shorter lifespans when compared to AVF. Since the initiation of the IPFFI, there has been little change in fistula use for incident HD in the pediatric population. A handful of barriers to fistula placement have been identified, but these have yet to be addressed. Given that the majority of pediatric ESRD patients will outlive at least one transplant and return to HD, providers should steer away from using catheters as the primary treatment modality and avoid the life-long implications of catheter-related complications. Aside from emergent need for dialysis and those that already have a CVC with an impending transplant, CVC use should be largely curtailed. Finally, educational material, such as that used in the IPFFI, should be widely distributed to both providers and patients. Standardizing timing of referrals, improving communication among providers, and delineating pitfalls can greatly increase the prevalence of autogenous fistulas in this population.

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191 CHAPTER

Erectile Dysfunction

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DEFINITION

Erectile dysfunction (ED) is defined as the recurrent or consistent inability to obtain and/or maintain a penile erection sufficient for satisfactory sexual performance.[1] It is a common problem with significant negative effects on the quality of life of both the patient and his partner and is associated with poor relationship satisfaction, negative general health perceptions, and role limitations owing to physical and emotional problems.[2]

EPIDEMIOLOGY

Figures on the prevalence of ED vary; however, it is estimated that at least 20 million men in the United States experience the condition.[3] The Massachusetts Male Aging Study (MMAS) has reported a combined prevalence of ED in 52% of men over the age of 40, with an increase in the rate of moderate dysfunction from 17% to 34% and complete ED from 5% to 15%, between the ages of 40 and 70 years, respectively.[4] Another

Abstract

Erectile dysfunction is recurrent or consistent inability to obtain and/or maintain a penile erection for satisfactory sexual performance. It is a highly prevalent condition, affecting over 50% of men over the age of 40. Origin of ED may be psychogenic, neurogenic, endocrinologic, vasculogenic or drug induced, and is often multifactorial. There are a variety of diagnostic modalities which can be used to help identify the source of the issue. Treatment options include oral medications, injectables and surgical treatment. ED is a frequent comorbidity in men undergoing vascular surgery.

study, looking at data from the National Health and Nutrition Examination Survey (NHANES), reported a combined prevalence of ED in 18% of men over the age of 20 years, with an increase from 7% of the population between the ages of 20 and 29 years to 78% in those over 75 years of age.[5] The prevalence of ED appears to be similar among different ethnic groups, with a different population-based study demonstrating a 22% rate of ED in white men, 24% in black men, and 20% rate among Hispanic men all over 40 years of age.[6] Differences noted in the prevalence rates across these studies are partially due to nonstandardized definitions of the severity of ED, especially given the frequently subjective nature of this reported complaint.

PHYSIOLOGY OF PENILE ERECTION

The penis is a composite structure, including the paired dorsal corpora cavernosa and the ventral corpus spongiosum, which contains the urethra. The corpora cavernosa are surrounded by the tunica albuginea, a bilayered structure, which supports the cavernous tissue and provides the flexibility, rigidity and strength of the penis. The spongiosum lacks the outer layer of the tunica, allowing for a low-pressure urethra during erection. Blood flow to the penis typically originates from the internal pudendal artery, a branch of the internal iliac artery. Distally, it then becomes the common penile artery, where it subdivides into the dorsal, cavernosal, and bulbourethral arteries. Frequently accessory pudendal arteries arising from the external iliac, obturator, vesical, and femoral arteries contribute significantly to the arterial supply to the penis.[7] The cavernosal arteries effect tumescence of the penis and end at the helicine arteries, which open into the endothelium-lined lacunar spaces. Venous drainage begins within the lacunar spaces, which drain into subtunical venules and emerge as emissary veins. The deep venous system continues with these emissary veins draining into the cavernosal veins and deep dorsal or spongiosal veins until they join either the prostatic venous plexus or the internal pudendal veins. Superficial veins coalesce to form the superficial dorsal vein, which drains into the saphenous veins (Fig. 191.1).

Erection is the result of an integrative physiologic complex—comprising psychological, neuronal, hormonal, vascular, and cavernous smooth muscle systems—that begins in the brain. Relevant innervation to the penis includes somatic nerves, responsible for sensation and contraction of the bulbocavernosus and ischiocavernosus muscles, and the parasympathetic and sympathetic autonomic nerves located at levels S2-S4 and T12-L2, respectively, which are instrumental in tumescence. These segments form the hypogastric and pelvic plexi. The fibers that innervate the penis compose the cavernous nerve, which travels along the posterolateral aspect of the prostate and then accompanies the membranous urethra through the urogenital diaphragm.[8] The cavernous nerves then innervate the helicine arteries and trabecular smooth muscle.[9]

The cavernous smooth muscle plays a key role in erectile function and remains contracted in the flaccid state of the penis under α-adrenergic control. The erectile process begins with sexual stimulation, which increases parasympathetic activity

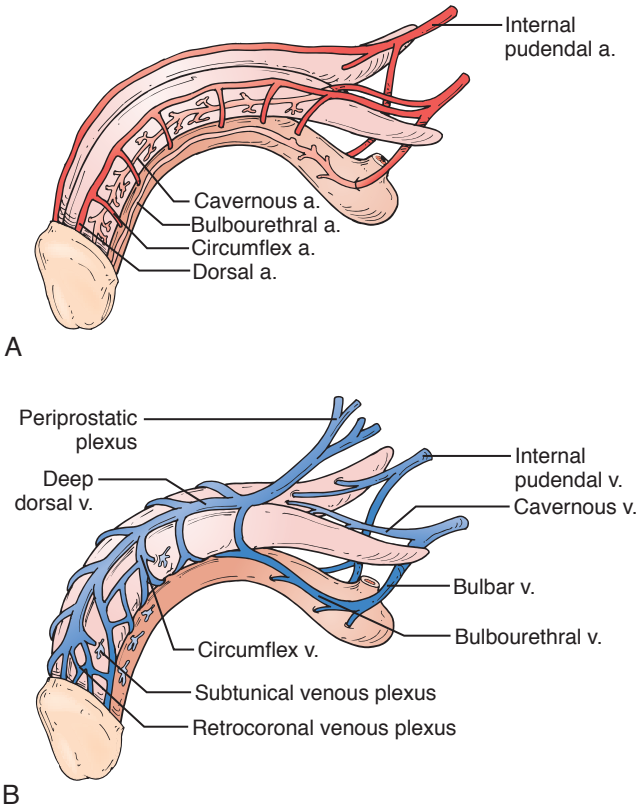

Figure 191.1 Penile Vascular Anatomy. (A) Penile arterial supply; (B) penile venous drainage. (Source: Wein AJ. *Campbell-Walsh Urology*, 10th ed. Philadelphia, PA: WB Saunders/Elsevier; 2011:691-692.)

and stimulates the release of neurotransmitters from cavernous nerve terminals or from the endothelium of the cavernosal arteries, resulting in relaxation of the penile smooth muscle.[10,11] This is mediated by the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway, ultimately resulting in increased blood flow through the penile arteries (Fig. 191.2).[12,13] This blood flow then expands the sinusoids, compressing subtunical venules and peripheral sinusoids and ultimately reducing venous outflow (veno-occlusive mechanism). This leads to an increase in intracavernous pressure, resulting in an erection.

PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

Given the interaction of the multiple different physiologic systems required for adequate erectile function, it is easy to appreciate that derangements in any one system can serve as a cause of ED. ED is classified according to its likely origin: psychogenic, neurogenic, endocrinologic, vasculogenic, and drug-induced. It is often multifactorial in nature.

Psychogenic Erectile Dysfunction

Psychogenic (nonorganic) ED is generally assumed to be ED predominantly or exclusively related to psychological or interpersonal factors.[14] It is estimated to play a role in 10% to 15%

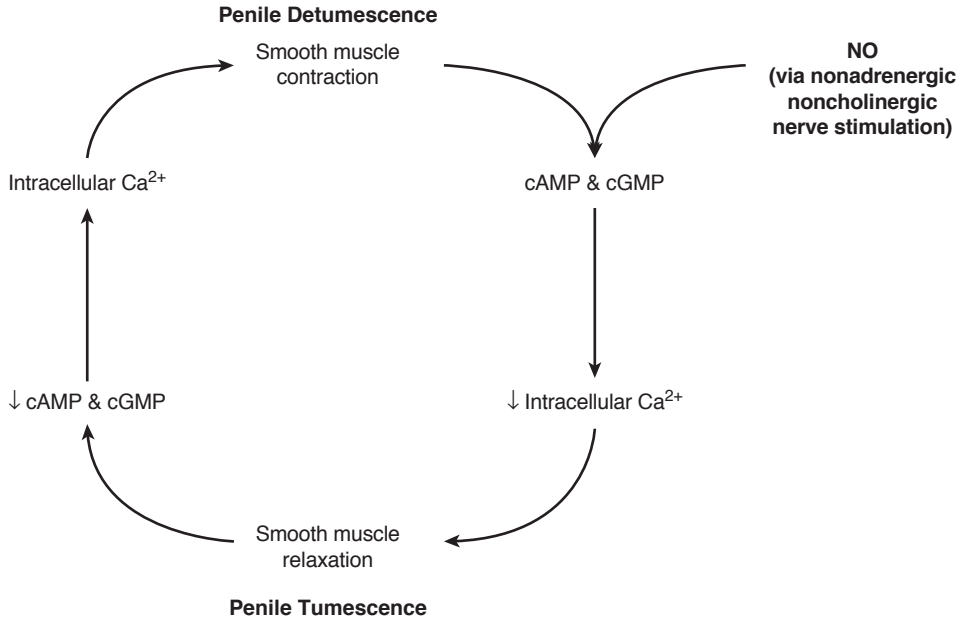

Figure 191.2 **Erectile Physiology.** *Ca^{2+},* Calcium; *cAMP,* cyclic adenosine monophosphate; *cGMP,* cyclic guanosine monophosphate; *NO,* nitric oxide.

of all men with ED. It has been further classified as either situational psychogenic ED, which is noted to be either partner-related, performance-related, or associated with psychological distress, or generalized psychogenic ED, secondary to a lack of sexual arousability or a disorder of sexual intimacy.[15] Psychogenic ED is an adrenaline-mediated phenomenon and is a diagnosis of exclusion, once physical (organic) factors have been ruled out. The clinical features include sudden-onset ED, with intermittency of function or a situational nature to the erectile problems, as well as reports of good nocturnal erections.[16]

Neurogenic Erectile Dysfunction

Neurogenic ED, an uncommon entity, is secondary to events disrupting central neural networks or the peripheral nerves involved in sexual function. It is further subclassified into supraspinal, spinal, and peripheral neurogenic ED.[17] Supraspinal ED is generally caused by tumor, stroke, Parkinson disease, dementia, or temporal lobe epilepsy.[17] Spinal causes include multiple sclerosis, spinal cord injury, transverse myelitis, myelodysplasia, and lumbar disc disease or surgery.[17-19] Peripheral causes include diseases associated with lower motor neuron lesions, trauma, pelvic pathology, and radical pelvic surgery.[17] Pelvic surgery, particularly radical prostatectomy, has a high risk of causing cavernous nerve injury and has been demonstrated to have a significant effect on erectile function.[20]

Endocrinologic Erectile Dysfunction

Androgens, specifically testosterone, have been linked to sexual desire, organic function, and erectile function. However, low serum testosterone has not been clearly linked to the presence or severity of ED.[21,22] Animal models have shown that testosterone is important in the regulation of the expression of nitric oxide synthase (NOS) and phosphodiesterase type 5 (PDE5) inside the penis.[23] Hyperprolactinemia, leading to the inhibition of luteinizing hormone (LH), is associated with low libido and possibly ED. Profound hypothyroidism (low LH levels) and profound hyperthyroidism (high estradiol levels) may be associated with sexual dysfunction.

Vasculogenic Erectile Dysfunction

ED and cardiovascular disease (CVD) share common risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, obesity, and smoking, leading to the concept that ED is another manifestation of vascular disease.[24] A large survey of over 7500 patients with hypertension and diabetes demonstrated ED in 67% of patients with hypertension alone, 71% of patients with diabetes alone, and 78% of patients with both conditions.[25] A Spanish study of over 2400 patients has demonstrated each of these to be independently associated with ED and age-adjusted odds ratios of having ED of 4.0 in diabetics, 1.58 with hypertension, 1.63 with high cholesterol, 2.63 with peripheral vascular disease, and 2.5 among smokers.[26] ED patients have also been noted to have significantly higher plasma levels of low-density lipoprotein (LDL) when compared with normal counterparts.[27]

The Princeton III consensus guidelines recognize ED as a strong predictor of CVD and specifically coronary artery disease (CAD).[28] Data from a meta-analysis of prospective cohort studies evaluating ED and the risk of CVD demonstrated a combined relative risk for men with ED for overall CVD of 1.48, 1.46 for CAD, 1.35 for stroke, and 1.19 for all-cause mortality.[29] Additionally, ED has been described as an independent marker of cardiovascular events and all-cause mortality after adjusting for age, weight, hypertension, diabetes, hyperlipidemia, and cigarette smoking.[30] ED is also an independent predictor of peripheral artery disease (OR 1.97), with a significant stepwise increase in prevalence of peripheral artery disease with increasing

severity of ED (28% of men with mild ED, 33% with moderate ED, and 40% with severe ED).[31]

A number of theories have been proposed to explain the pathophysiologic association between ED and CVD. Given that atherosclerosis is a systemic disease, with all vascular beds affected to some extent, the artery size hypothesis proposes that symptoms present at different time points according to the diameter of the arterial blood supply.[32] Accordingly, a 50% stenosis of the coronary arteries would amount to a near complete occlusion of the penile arteries despite an equal amount of total atherosclerotic plaque in both vessels. In addition to the flow-limiting stenosis, ED due to arterial insufficiency is related to lower oxygen tension in intracavernous blood.[33] This has been associated with possibly decreased prostaglandin E_1 (PGE_1) and E_2 formation, leading to transforming growth factor (TGF) β_1–induced collagenization of cavernous smooth muscle.[17,34] Increased connective tissue has been correlated with failure of the veno-occlusive mechanism required for good erectile function.[35]

Endothelial dysfunction serves as an additional link between ED and CVD. NO produced by the endothelium is necessary for the increased flow and vasodilation of the penile arteries, which is necessary for erection. In both ED and CVD, a deficiency of NO is brought about by impaired production or increased degradation, thereby decreasing the vasodilation and modulation of smooth muscle cells and inhibiting cellular adhesion.[36,37] Among ED patients without evidence of CVD, endothelial dysfunction has been noted within the penile vasculature but not in the small arteries of the forearm, indicating that endothelial dysfunction may occur earlier in the penile vasculature than in other vascular beds.[38]

ED has also been demonstrated to be a strong predictor of subsequent cardiovascular events. Data from the Prostate Cancer Prevention Trial (PCPT) demonstrated that incident ED was associated with a 25% increased likelihood of subsequent cardiovascular events during the 5-year study follow-up and that men with incident ED during the study period were at a 45% increased risk of cardiovascular events.[39] This association was similar to the risk associated with current smoking or a family history of myocardial infarction. Another study addressing men referred with ED and vasculogenic ED documented on penile ultrasonography demonstrated a 20% rate of abnormal stress echocardiography on cardiac evaluation.[40]

In addition to arterial causes, as indicated earlier, vasculogenic ED is also often the result of inadequate venous occlusion.[41] Corporal veno-occlusive dysfunction (CVOD) may be due to the development of large venous channels draining the cavernous tissue or to degenerative or functional changes in the tunica albuginea, as seen in Peyronie disease.[42,43]

Drug-Induced Erectile Dysfunction

Antihypertensives, psychotropics, and antiandrogens are the primary drug classes associated with ED. Among the antihypertensives, multiple studies have demonstrated significant increases in ED among patients on thiazides as compared with placebo.[44,45] Studies of β-adrenergic antagonists demonstrate mixed results with respect to potentially causing ED, with nonselective drugs such as propanolol showing clear associations with ED and agents with higher selectivity for the β_1 adrenoreceptor, such as acebutolol, showing a reduction in ED compared with placebo.[46] Angiotensin receptor blockers have been consistently shown to have proerectile effects.[47] Antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs), can negatively affect all steps of the sexual response cycle, most notably ejaculatory latency. Differences are noted in the incidence of ED among different medications, with higher rates noted in patients on paroxetine.[48] Antiandrogens cause partial or complete blockade of circulating androgens either by inhibiting their production or antagonism at the level of the androgen receptor; they are frequently used in the treatment of prostate cancer. Use of these medications is generally associated with decreased sexual desire, although medical castration with luteinizing hormone–releasing hormone agonists/antagonists and nonsteroidal anti-androgens such as flutamide or bicalutamide can also contribute to veno-occlusive dysfunction.[49] Other classes of drugs associated with ED include 5-alpha reductase inhibitors (finasteride, dutasteride) and digoxin.[50,51]

ASSESSMENT OF ERECTILE DYSFUNCTION

History and Physical Examination

Since ED is often multifactorial, the initial evaluation must include a complete medical, psychosocial, and sexual history.[52] Care should be taken to assess for signs and symptoms of possible underlying conditions, with a detailed review of current medications, to identify possibly reversible and treatable disorders causing ED. One study of over 270,000 ED patients demonstrated a 68% prevalence of a significant underlying condition at the time of ED presentation.[53]

Given the often sensitive subject matter, clinicians should consider using validated questionnaires in order to ease into the conversation, including the International Index of Erectile Function (IIEF) and the abridged five-item version of the IIEF, and the Sexual Health Inventory in Men (SHIM); these have been demonstrated to accurately diagnose and quantify the severity of the ED complaint.[54,55] Descriptive measures should be used for the rigidity and sustainability of erections during sexual arousal, intermittency or any situational aspect of erections, and the presence of nocturnal erections in order to further define underlying causes of ED. Patients complaining of sudden-onset ED with loss of sustaining capability and strong nocturnal erections are more likely to have nonorganic ED secondary to psychogenic causes. Frequently physical examination will not reveal a specific cause. A general examination, with evaluation of blood pressure, heart rate, abdominal pulsations, peripheral pulses, evaluation of male secondary sex characteristics including the presence of gynecomastia, and a focused genital examination should be performed.[52,56] Attention should be paid to the absence of femoral pulses, indicative of aortoiliac arterial occlusive disease. Genital examination should include examination of the penis, specifically the size and position of the urethral meatus, the

presence of tunical plaques, evaluation of testicular size and consistency, and a digital rectal examination in the appropriately aged man.[56]

Laboratory Evaluation and Adjunctive Testing

According to the International Consultation in Sexual Medicine (ICSM) committee, recommended laboratory tests to confirm the presence of underlying diseases include fasting blood glucose, a lipid profile, and serum testosterone levels, with optional examinations such as thyroid function testing based on the clinical scenario.[52,56] The Princeton III consensus statement recommends that all men over 30 years old with organic ED should be considered at increased CVD risk until recommended checks suggest otherwise; it further recommends a resting electrocardiogram and serum creatinine level in addition to the previously described testing in men without known CVD.[28] It also recommends, in consultation with a cardiologist or primary care physician, the performance of a thorough noninvasive of CVD status and, when indicated, invasive evaluation, including measurement of biomarkers and physiologic stress testing for ischemia or anatomic clarification using coronary computed tomographic angiography.[28]

Nocturnal penile tumescence (NPT) monitoring, used to study the quality of nocturnal erectile function, may be used both in a sleep laboratory setting and with a portable, home use device such as the Rigiscan (Timm Medical Technologies, Inc., Minneapolis, Minnesota).[57] In contemporary practice, its routine usefulness for diagnostic purposes is significantly limited.

Vascular Evaluation

Vascular studies in the patient with ED are designed to determine whether arteriogenic ED or veno-occlusive dysfunction is present.

Penile Brachial Pressure Index

The penile brachial pressure index (PBI) refers to the ratio of penile systolic to brachial systolic pressure and has been used to test for the presence of significant hemodynamic occlusive disease proximal to the penile arteries, thus contributing to ED. Penile systolic blood pressure is measured by applying a small blood pressure cuff to the base of the flaccid penis and measuring the systolic blood pressure with a Doppler probe. The validity of this technique in the evaluation of ED has been called into question, given significant interobserver variability, failure to measure pressure in the erect state, and concerns regarding the false-positive diagnosis of arterial insufficiency. Thus its use in the evaluation of ED is primarily a matter of history.[58,59]

Office Injection Testing

Intracavernosal injection (ICI) testing is performed by injection of a vasodilatory drug (or cocktail of drugs), combined with genital or audiovisual stimulation, in a clinical setting. The erectile response is then evaluated by a clinician to rate both the rigidity and duration of response. Patients are monitored for detumescence while in the office after the test is performed, and those who do not spontaneously detumesce within 1 hour of injection are given intracavernous injections of a diluted phenylephrine solution. Vasodilatory medications used include PGE_1 alone or a combination of medications including PGE_1, papaverine, and phentolamine. Although ICI testing has been used in an attempt to differentiate organic from psychogenic ED, it is now accepted that its only value is to define a functional veno-occlusive mechanism in men who develop a rigid and sustained erection.[60]

Failure to obtain a rigid erection may indicate vascular disease but may also be the result of an excessive sympathetic response associated with anxiety during ICI testing.[61] Currently the ICI test is seldom performed and generally considered to be obsolete.

Duplex Ultrasonography of the Penis

Duplex Doppler ultrasound (DDUS) of the penis is a reliable noninvasive diagnostic method for evaluating ED, allowing an objective quantification of the blood flow to the penis. It also provides a physiologic diagnosis to guide therapy in patients with a poor response to oral ED therapy, differentiates psychogenic versus organic ED, aids in the evaluation of the young man with primary ED or a history of pelvic trauma, and suggests the need for cardiovascular evaluation in the man with vasculogenic ED without overt CVD risk factors.[62]

Given the significant influence of psychological and environmental factors on erectile function, DDUS should be performed in a quiet, comfortable room, isolated from intrusion and distraction. An erection is then pharmacologically induced using ICI with vasoactive medications. If a good erection is not achieved, patients should be redosed to ensure maximal smooth muscle relaxation for accurate interpretation of the results. Rigidity and sustainability of the erection is noted by the examiner. DDUS is performed using a high-resolution linear array ultrasound transducer with a frequency between 7.5 and 12 MHz. With the patient in supine position, the penis is scanned and the locations of the left and right cavernosal arteries are identified. Peak systolic velocity (PSV), end-diastolic velocity (EDV) as well as resistive indices (RI) are measured. The penis is then evaluated using B-mode images to observe for the presence of tunical plaque (Peyronie disease), fibrosis, and the presence of calcification in either the vasculature or the plaque itself.

Various criteria have been suggested for normal PSV values, but it is generally accepted that a PSV below 25 cm/s suggests arteriogenic ED.[63] This level has been noted to have a sensitivity of 100% and specificity of 86% among patients with abnormalities on pudendal angiography.[64] A PSV of 35 cm/s decreases the sensitivity to 76%, but increases specificity to 92%.[65] Significant asymmetry of PSV, with a greater than 10 cm/s difference between right and left sides, suggests a significant atherosclerotic lesion or iatrogenic/surgical cause for a decrease in arterial flows.[65] Veno-occlusive dysfunction is evaluated using EDV in the presence of normal arterial inflow. Generally EDV of greater than 5 cm/s is accepted as the measurement at which CVOD is present (Fig. 191.3).[62,65] Given concerns for the specificity of EDV alone for the diagnosis of CVOD in patients with arterial insufficiency, RI has been used with a cut point

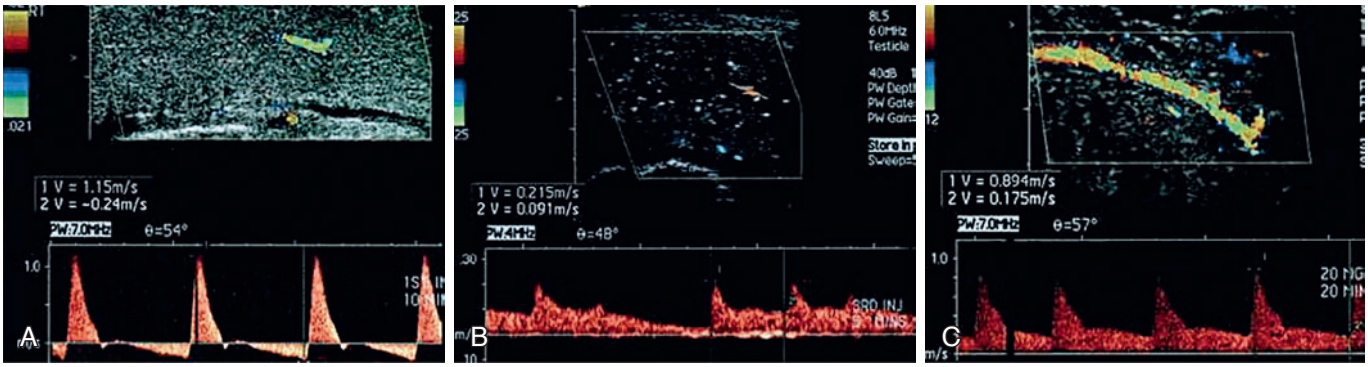

Figure 191.3 Color Doppler Duplex Ultrasound of the Penis. (A) Normal erectile hemodynamics: Doppler waveform analysis demonstrating cavernosal artery peak systolic velocity of 115 cm/s and end-diastolic velocity of −24 cm/s, representing normal erectile hemodynamics. (B) Mixed vasculogenic erectile dysfunction (ED): Doppler waveform analysis demonstrating cavernosal artery peak systolic velocity of 21.5 cm/s and end-diastolic velocity of 9.1 cm/s, indicating the presence of arterial insufficiency and corporal veno-occlusive dysfunction (CVOD). (C) Corporal veno-occlusive dysfunction: Doppler waveform analysis demonstrating cavernosal artery peak systolic velocity of 89.4 cm/s, and end-diastolic velocity of 17.5 cm/s. End-diastolic velocity greater than 6 cm/s indicates corporal veno-occlusive dysfunction. (Source: Wilkins CJ, Sriprasad S, Sidhu PS. Colour Doppler ultrasound of the penis. *Clin Radiol.* 2003;58(7):514-523.)

of less than 0.75 as abnormal.[62,66] It should be noted, however, that RI, calculated as the difference between PSV and EDV divided by the PSV, is ultimately dependent upon PSV. Patients with good arterial inflow and significantly elevated EDV may still have RI values within the normal range; therefore, RI alone should not be used for diagnostic purposes.

Dynamic Infusion Cavernosometry and Cavernosography

Dynamic infusion cavernosometry and cavernosography (DICC) is the most accurate assessment of erectile hemodynamics. Given the widespread availability of DDUS and the specialized equipment and training needed to perform DICC, its clinical use is limited, and it is now generally used mainly in (1) young, healthy men with a history of perineal or pelvic trauma being considered candidates for penile revascularization; (2) young men with ED failing erectogenic pharmacotherapy, presumed to be secondary to CVOD, who are faced with penile implant surgery as their only option; (3) young men with primary ED (who have never had a rigid erection) to rule out CVOD; (4) medicolegal cases where a definitive diagnosis is needed; and (5) patients with Peyronie disease and comorbid ED, where the presence of CVOD will ultimately change surgical management.[67]

Dynamic infusion cavernosometry involves placement of a butterfly needle in each corporal body, one connected to a pressure transducer and the other to a server-controlled pump for heparinized saline infusion.[67,68] After the injection of vasoactive drugs (in doses significantly higher than those used for DDUS), erection ensues and a number of parameters are recorded: (1) equilibrium pressure (in mm Hg) within the corpus cavernosum, which is an assessment of intracavernosal pressure (ICP) development within the corpus cavernosum 10 to 15 minutes after vasoactive agent injection; (2) cavernosal artery inflow gradient (in mm Hg), which is the difference between brachial artery systolic pressure and the cavernosal artery occlusion pressure, measured on both sides; (3) flow to maintain, defined as the flow of saline (mL/min) required to maintain a given ICP; and (4) pressure decay (in mm Hg/30 s), the pressure drop occurring over a 30-second period after raising the ICP to 150 mm Hg. Patients are pharmacologically redosed as needed to maintain flow or if pressure decay values are abnormal.[69] If the cavernosometry demonstrates CVOD, cavernosography may be performed, where a nonionic radio-opaque dye is injected intracavernosally and a radiograph obtained in order to demonstrate the site of venous drainage.

Standardized data for the results for DICC are not available. However, normal values are as follows: cavernosal artery occlusion pressure below 30 mm Hg, flow to maintain of less than 5 mL/min, and a pressure decay of less than 45 mm Hg over 30 seconds.[68] Although abnormal values aid in the diagnosis of CVOD following DICC, additional data are available in terms of the relationships between these parameters. Plotting the flow to maintain against the ICP graphically generates one of two patterns, a curvilinear pattern or a parabolic pattern. Patients with a linear pattern are generally accepted to have genuine evidence of CVOD, whereas those with a parabolic pattern generally have abnormal veno-occlusive parameters secondary to excess sympathetic tone.[67]

Selective Internal Pudendal Angiography/ Penile Angiography

Penile arteriography is an essential component of the evaluation for any patient under consideration for penile revascularization surgery. Such patients have (1) pure arterial insufficiency without CVOD, (2) a focal occlusion of one or both common penile or cavernosal arteries, (3) perforating branches traveling from the dorsal to the cavernosal artery, (4) at least one patent inferior epigastric artery (IEA) of sufficient length to serve as a donor artery, and (5) at least one patent dorsal artery to act as a recipient artery. Another indication is in patients with high-flow priapism, where angioembolization of the cavernosal artery–corpus cavernosal fistula is potentially curative.

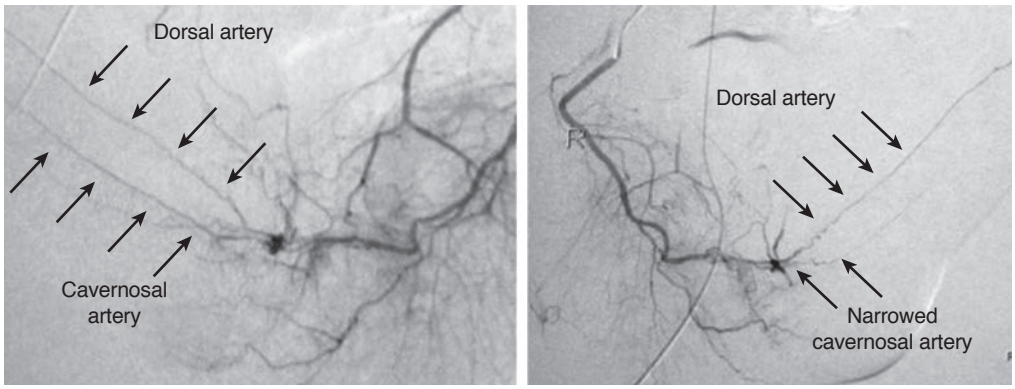

Figure 191.4 **Selective Internal Pudendal Angiography.** *Left image:* Normal internal pudendal angiogram demonstrating patent dorsal and cavernosal arteries of normal caliber. *Right image:* Internal pudendal angiogram demonstrating patent dorsal artery with occlusion of the cavernosal artery. (Images courtesy of Dr. Irwin Goldstein, MD, San Diego Sexual Medicine, Alvarado Hospital, San Diego, CA.)

A technically challenging and invasive procedure, pudendal/penile angiography requires an endovascular specialist with skill at cannulating both the internal pudendal arteries and the inferior epigastric arteries, which are used for revascularization.[62] Arterial inflow to the penis should be maximized with the use of ICI delivered vasoactive agent, which is usually administered prior to contrast injection. The timing of injection should allow for maximal arterial inflow to the penis but should not be administered at such a time point as to cause reduced arterial flow at full rigidity. Selective catheterization of the internal pudendal artery is performed to increase detail (Fig. 191.4).[70]

Despite the anatomic detail provided by arteriography, it represents only a road map and is not a functional test. Thus the results must be interpreted in light of the functional results obtained using DDUS and/or DICC.

TREATMENT OF ERECTILE DYSFUNCTION

Given the safe and effective oral therapies widely available for the treatment of ED, a process-of-care model has been established to guide the practitioner through a structured treatment algorithm (Fig. 191.5).[71] After ruling out adverse medication effects, patients with presumed organic ED are first referred for lifestyle modification, targeting the factors commonly associated with ED and frequently CVD, including smoking cessation, weight loss, and increased aerobic exercise. Numerous trials have demonstrated improvements in erectile function with smoking cessation, giving the clinician additional evidence to motivate a patient to quit smoking.[72] In a randomized controlled trial of obese Italian men, participants were randomized to receive (1) intervention based on detailed advice for a 10% weight loss (including diet and exercise) or (2) control, where no advice was given.[73] At 2-year follow-up, the patients in the intervention group had significant weight loss and reported significant improvements in erectile function defined by the IIEF.

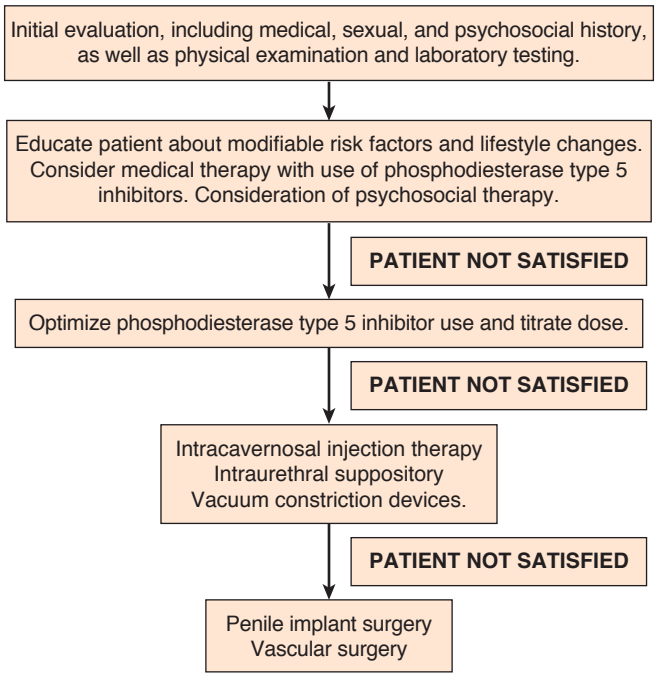

Figure 191.5 Process-of-care model for the treatment of erectile dysfunction (ED). A goal-oriented treatment approach to ED, with a stepwise escalation of therapeutic modalities in patients unsatisfied with treatment results.

Among patients with psychogenic ED, psychosocial interventions have demonstrated some improvement in erectile function when used in combination with sildenafil therapy, compared to sildenafil therapy alone.[74]

PDE5 inhibitors (PDE5i), described further on, complete the available first-line therapeutic modalities for ED. Vacuum constriction devices, although once considered first-line, are now generally considered a second-line treatment for ED, in addition to ICI and intraurethral alprostadil. Surgical therapy in contemporary practice is considered a third-line therapeutic modality and includes penile implant surgery and vascular reconstructive surgery.

Phosphodiesterase Type 5 Inhibitors

In 1998, the PDE5 inhibitor sildenafil citrate (Viagra, Pfizer Inc., New York) became the first oral drug for ED treatment to be approved by the U.S. Food and Drug Administration (FDA). It dramatically changed the treatment of ED compared with historic therapeutic modalities. Utilizing similar mechanisms of action, four PDE5 inhibitors have been approved to date by the FDA: sildenafil, vardenafil hydrochloride (Levitra or Staxyn, Bayer Pharmaceuticals Corp, West Haven, Connecticut, and GlaxoSmithKline, Philadelphia, Pennsylvania), tadalafil (Cialis, Lilly LLC, Indianapolis, Indiana), and avanafil (Stendra, Vivus Inc., Mountain View, California).

Mechanism of Action and Means of Use

As suggested by their name, PDE5 inhibitors work by inhibiting the PDE5 enzyme, which degrades cGMP, the downstream effector of NO. Prolonged activity of cGMP decreases intracellular calcium concentration and maintains smooth muscle relaxation, thus leading to an erection. Means of use for the tablets, including the time to maximum concentration and the half-life of each medication, vary (Table 191.1). The choice of the optimal PDE5 inhibitor for the individual patient is dependent upon the patient's sexual dynamics, particularly the frequency and predictability of sexual activity as well as the presence of comorbid conditions, which may potentially be treated with a daily dose of a PDE5 inhibitor such as tadalafil for concomitant benign prostatic hypertrophy (BPH).[75]

Outcomes

The majority of the drug trials in ED are short term, lasting less than 12 weeks. Across these studies, sildenafil was more effective than placebo, with per-patient sexual intercourse success rates of 69% (range 52% to 85%) versus 36% (range 19% to 68%), respectively.[76] Sexual intercourse success rates with vardenafil and tadalafil have been shown to be similar (68% and 69%, respectively), although no single published trial comparing all agents exists.[76] In pooled estimates, use of sildenafil, vardenafil, and tadalafil had an approximate 2.5-fold increased likelihood of improvement in erectile quality compared to placebo in general ED patients.[76] The ability of these agents to permit sexual intercourse depends upon the underlying etiology of ED, with men with psychogenic ED responding better than men with veno-occlusive dysfunction.[77]

TABLE 191.1 Pharmacokinetics of FDA-Approved Phosphodiesterase Type 5 Inhibitors

Generic Name	Trade Name	T_{max} (min)	$T_{½}$ (h)
Sildenafil	Viagra	60	4
Vardenafil	Levitra, Staxyn	42	4.5
Tadalafil	Cialis	120	17.5
Avanafil	Stendra	45	5.1

FDA, U.S. Food and Drug Administration; T_{max}, time required to attain maximal plasma concentration; $T_{½}$, half-life, time required for elimination of half of the medication from plasma.

Adverse Events and Contraindications

Side effect profiles tend to be similar among PDE5 inhibitors. The most commonly reported effects include headache, flushing, nasal congestion, heartburn, and temporary alteration in color vision, all of which can frequently be easily managed with other over-the-counter medications.[76] Other side effects include myalgia, nausea, diarrhea, vomiting, and dizziness with risk of serious cardiovascular events in 0.2% to 0.5% of patients on sildenafil, vardenafil or tadalafil versus 0.1% to 0.2% of those on placebo.[76] Among these medications, the incidence of adverse effects (range 24% to 34%) is similar, with discontinuation secondary to adverse effects ranging from 0.53.8% to 8%.[76] Ischemic nonarteritic optic neuropathy (NAION) and priapism have been rarely reported among users of PDE5 inhibitors, but no clear causal link has been established.[76]

PDE5 inhibitors are contraindicated in patients who use nitrate medications owing to a risk of severe hypotension.[78] Although not specifically indicated, patients with serious CVD should use PDE5 inhibitors with caution, primarily due to risks associated specifically with physical exertion (sexual activity) as opposed to risks posed by the PDE 5 inhibitors themselves. Vardenafil use is contraindicated among patients taking type 1A or type 3 antiarrhythmics and among those with prolonged QT syndrome.[79]

Intracavernosal Injection Therapy

Intracavernosal injection therapy (ICI) was accidentally discovered and first described for the treatment of ED in 1982; it is recognized as a safe and effective treatment strategy.[80] ICI is generally relegated to second-line therapy for ED and can prove effective in up to 90% of ED patients and in more than 50% of those who fail to respond to a PDE5 inhibitor.

Mechanism of Action and Means of Use

There are three main drugs (although many others exist) used in ICI: PGE_1, phentolamine, and papaverine. These medications are frequently used in combination (Trimix—PGE_1, phentolamine, papaverine; Bimix—phentolamine, papaverine) for increased efficacy and potency. PGE_1 (the FDA-approved version is known as alprostadil and marketed as Caverject, Pfizer, Inc., New York, or Edex, Actient Pharmaceuticals, Lake Forest, Illinois), activates prostaglandin receptors, resulting in an increase in the intracellular concentration of cyclic adenosine monophosphate (cAMP) in the cavernosal smooth muscle.[81] Phentolamine is a nonselective α-adrenoceptor antagonist, which induces relaxation of cavernosal smooth muscle.[82] Papaverine acts as a nonspecific PDE inhibitor and initiates an increase in both intracellular cAMP and cGMP, resulting in penile erection.[80] Use of ICI therapy involves direct injection of these vasoactive medications into the corpora cavernosa by the patient. The patient is trained to self-administer the medication at home. Responses are generally seen within 5 to 10 minutes, with dose-dependent changes in duration and rigidity of the erection.

Outcomes

Used in patients who generally have ED refractory to PDE5 inhibitor therapy, ICI therapy is highly efficacious, with an 89% response rate (patients able to achieve a penetration-hardness erection capable of sexual intercourse) and at least a 24% discontinuation rate across ED patients at 36-month follow-up.[83] Discontinuation rates and reasons vary according to the patient population and can be secondary to recovery of erections following radical prostatectomy, progression of ED such that the patient requires escalating medication doses, and declining interest in sexual activity. Patients with a history of radical prostatectomy, a combination radical prostatectomy, or pelvic radiation therapy, diabetes, and a long preexisting history (>5 years) of untreated ED are more likely to fail ICI therapy.[83] True failure of ICI therapy is generally a clinical indicator of the presence of cavernosal smooth muscle damage (veno-occlusive dysfunction).

Adverse Events and Contraindications

The predominant concern about ICI therapy is priapism. Other minor adverse effects include pain, ecchymosis, and hematoma formation. Priapism rates with ICI vary in the literature from 0.25% to 7.3%, with figures in the lower part of the range in centers with careful patient selection and superior patient education and counseling.[83] Aching or burning penile pain has been reported more often with the use of PGE_1. Reversal of a prolonged erection is accomplished with the intracavernosal administration of an α-adrenergic agonist agent (phenylephrine).

Intraurethral PGE_1 Suppository

Intraurethral PGE_1 in the form of alprostadil (known as Medicated Urethral System for Erection, or MUSE, Meda Pharmaceuticals Inc., Somerset, New Jersey) is an alternative method for delivering medication directly to the corporal bodies. The drug is absorbed through the urethral mucosa and into the corpora cavernosa, where it has a similar mechanism of action to intracavernosal alprostadil. A small plastic device is inserted into the urethral meatus by the patient, and the pellet is deposited into the urethra. The efficacy of MUSE is variable, with small trials suggesting superior efficacy for ICI versus MUSE.[84,85] Penile pain is reported in 33% of patients, with approximately 5% reporting urethral bleeding.[86]

Vacuum Constriction Devices

Vacuum constriction devices, also known as vacuum erection devices (VEDs), have been approved by the FDA since 1982.[87] VEDs consist of a suction cylinder and pump, which induces a vacuum around the corporal bodies, with a resultant increase in corporal blood inflow. This requires the application of a compression band around the base of the penis to restrict venous drainage and maintain rigidity. Compression rings cannot be left in place for longer than 30 minutes in order to avoid ischemic injury to cavernosal tissue. Patient satisfaction is generally low; up to 70% of men discontinue VEDs at a median of 1 month of use because its application is cumbersome and due to the cooler, cyanotic nature of the VED-erected penis.[88]

Penile Implant Surgery

Penile implant or penile prosthesis surgery, represents the first available treatment option for patients presenting with organic ED, with the first inflatable device described in 1973.[89] It remains an excellent option for patients who have attempted and failed to achieve satisfactory results with other modalities, have grown weary of second-line therapy use (ICI, intraurethral alprostadil, VED), or are not deemed candidates for vascular surgical options (see further on). Implants act solely to allow a patient to achieve a rigid erection on demand and have no effect on the patient's sensation, ability to ejaculate, or achieve orgasm.

Technical Considerations

There are two main classes of implants: malleable (or semirigid) and hydraulic (or inflatable). Semirigid prostheses consist of two malleable rods that are placed into the corpora cavernosa; they are manually shaped by the patient at the onset of sexual activity and are reshaped after sexual relations are completed. Inflatable implants are further subdivided and classified according to the configuration of the prosthesis: a two-piece inflatable, which consists of two cylinders attached to a scrotal pump; and a three-piece inflatable, which consists of two cylinders attached to a scrotal pump and a separate reservoir, which is generally placed extraperitoneally in the space of Retzius. Choice of implant is both surgeon- and patient-dependent. Malleable implants are less commonly employed in the modern implant era and tend to be implanted only occasionally with some uncommon exceptions. Our practice is to preferentially place three-piece implants, given their superior rigidity and girth, better concealability and zero rigidity in the deflated state. Two-piece implants are generally placed in patients who have an obliterated extraperitoneal space, have small bowel loops abutting the deep inguinal ring (patients who have undergone radical cystoprostatectomy), have a renal transplant, or have poor grip strength and may have difficulty deflating a three-piece implant.

Outcomes and Adverse Events

Patient and partner satisfaction are generally high following penile implant surgery, with satisfaction rates varying between 75% and 97% depending on the patient population and implant used.[89] This is mostly related to the excellent rigidity and spontaneity of these devices. The most significant complication of penile implant surgery is infection, with data from the most recent generation of penile prostheses varying from 0.7% to 3%.[90,91] Treatment of infection requires complete device removal, which can lead to difficulty with subsequent reimplantation due to scarring and decreased penile length and girth. Protocols for salvage implantation (infected device removal with simultaneous reimplantation) demonstrate an 84% success rate.[92] Other complications include component erosion (most often occurring in the infected implant), reservoir herniation, visceral erosion, device autoinflation, cylinder migration, and device malfunction.

Five-year mechanical failure rates range from 0% to 9% for currently available prostheses.[89]

Penile Revascularization Surgery

Given the myriad of causes for ED, penile revascularization (penile artery bypass surgery) currently serves as one of only two modalities with the potential to cure the ED patient without a future necessity for vasoactive medications or implant surgery (the other is crural ligation surgery). However, penile revascularization, unlike revascularization in patients with coronary disease or peripheral arterial insufficiency, is not successful in patients with CVD, as these patients have a significant underlying element of endothelial dysfunction and corporal smooth muscle dysfunction as the main factors leading to ED.[89] In addition, patients with ED secondary to diffuse atherosclerosis will have significant disease present in the small penile arteries, thereby ruling out the presence of an adequate recipient vessel.[93] Thus patient selection for revascularization surgery is of paramount importance, as it is most likely to be successful in a highly selected group of young men with an isolated arterial stenosis following pelvic trauma. Inclusion criteria for consideration for revascularization generally include young men (age is poorly defined, although most authorities would not revascularize men older than 40 years old), absence of vascular risk factors, absence of evidence for other etiologies of ED, absence of evidence of CVOD with evidence of pure arterial insufficiency (as described earlier), and the presence of focal occlusive disease in the common penile artery or cavernosal artery that is amenable to distal bypass by the previously outlined arteriographic criteria.[89,94]

Technical Considerations

The IEA has been identified as the ideal donor vessel for bypass. Although many bypass procedures have been identified (historically over 20 procedures in total), the most commonly utilized approach is to perform an IEA to dorsal artery bypass.[93] Given the paucity of data pertaining to the use of venous target vessels, the arterial revascularization adapted from Goldstein et al. is reported here (Fig. 191.6).[94,95]

A variety of scrotal incisions may be made to expose the dorsal artery at the base of the penile shaft. An abdominal incision is made to expose the rectus muscle, which is reflected medially, and the IEA is identified. It is then mobilized from its origin near the external iliac artery to a point near the umbilicus, where it is transected. It is then transferred through the posterior wall of the inguinal canal onto the dorsum of the penis. The abdominal incision is then closed. The adventitial layer of the distal aspect of the IEA and proximal aspect of the dorsal artery are stripped with microscissors, and a microsurgical simple interrupted anastomosis is performed with 10-0 nylon sutures. Following completion of the anastomosis and after achieving complete hemostasis, the penis is replaced in its anatomic position and the wound is closed.

Endovascular management of focal arterial occlusion has also been previously studied, with the majority of the reports published in the 1980s using balloon angioplasty without stenting.[96] Results are variable and poorly defined.

Outcomes and Complications

Data on outcomes following penile revascularization are sparse, with most studies limited by varying inclusion and exclusion criteria, lack of validated markers to evaluate success, and generally short-term follow-up.[93] In addition, the published studies have discrepant patient populations, use different anastomotic and bypass techniques, and frequently do not assess long-term patency. As a result, practice guidelines from the American Urological Association consider penile revascularization unproven and controversial.[97] Among these studies, subjective success rates vary depending on type or revascularization procedure, definition of successful outcome, and patient population; they range from 50% to 82% (Table 191.2).[98-103] Looking specifically at arterial revascularization surgery as already described, a recent review of 71 patients with 34-month mean follow-up demonstrated that 55% of men had IIEF scores qualifying them as having normal erectile function without the use of a PDE5 inhibitor.[98]

The most frequently reported complications include failure to improve erectile function, inguinal hernias, penile shortening,

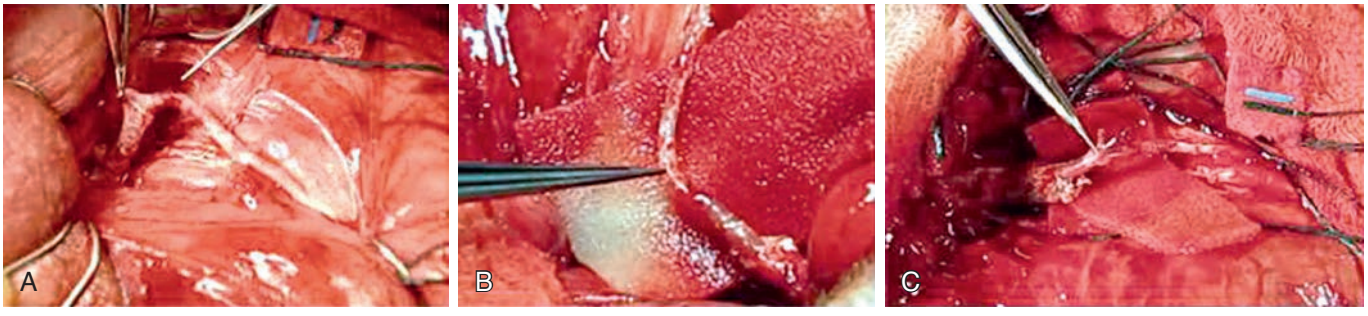

Figure 191.6 Penile Revascularization. (A) Isolated and mobilized dorsal artery of the penis just distal to the fundiform ligament; (B) transected inferior epigastric artery transferred to the dorsum of the penis; (C) microsurgical anastomosis between the inferior epigastric artery and the dorsal penile artery. (Images courtesy of Dr. Irwin Goldstein, MD, San Diego Sexual Medicine, Alvarado Hospital, San Diego, CA.)

TABLE 191.2 Most Recent Published Reports on Outcomes of Penile Revascularization

Report	Number of Patients	Follow-Up (Months)	Success Rate (%)
Vardi et al.,[99]	35	60	49
Kawanishi et al.,[100]	51	60	66
Munarriz et al.,[98]	71	35	55
Kayigil et al.,[102]	110	60	64
Zuckerman et al.,[103]	17	37	82

loss of penile sensation, and—in cases where arterialization of the dorsal vein was used—glans hyperemia.[89,98]

Surgery for Veno-Occlusive Dysfunction

Current guidelines from the American Urological Association, given an absence of clear data demonstrating benefit to patients, do not recommend surgery to limit the venous outflow from the penis.[97] CVOD is now considered the result of damage to the cavernosal smooth muscle; thus the venous leak is a symptom of an underlying pathology that is not generally correctable through venous ligation.[89,93] Despite this, venous ligation surgery has been attempted for decades, with poor long-term results. However, crural ligation surgery among highly selected young patients with isolated crural venous leak (generally secondary to blunt perineal trauma) has demonstrated some medium-term efficacy.[104] One study of 15 patients with a mean age of 29 years and isolated crural venous leak demonstrated on DICC resulted in unassisted sexual intercourse in 71% of men after crural ligation surgery and 93% of men reported improved erectile function as quantified by the IIEF.[104] This confirmed results from a similar population of 11 patients, with a mean age of 28 years, with 82% improvement in erectile function.[105]

FUTURE THERAPEUTIC STRATEGIES

Given the significant amount of ED research that has been performed over the past decade, increased understanding of the physiology of erection and pathophysiology of ED has identified a myriad of potential targets for the treatment of ED. Studies focusing on medications targeting the central nervous system as well as innovative methods for targeting the NO/cGMP pathway, as PDE5 inhibitors do, are currently ongoing.[106] Gene therapy, focusing on signaling pathways for penile erection, has been effective in improving ED in a variety of animal models.[107] Two of the more exciting and promising therapeutic modalities currently evaluated in man are described in the following paragraphs, including endovascular stenting and stem cell therapy.

Endovascular Stenting—ZEN Trial

Initial results from the ZEN (Zotarolimus-Eluting Peripheral Stent System for the Treatment of ED in Males with Suboptimal Response to PDE5I) trial were published in late 2012, looking at the safety and feasibility of a balloon-expandable drug-eluting stent for patients with atherosclerotic ED and focal internal pudendal artery stenoses.[108] Patients with atherosclerotic ED and a suboptimal response to PDE5 inhibition as well as specific clinical, DDUS, and angiographic factors were prospectively enrolled in this trial, with a safety endpoint of a major adverse event 30 days postprocedure and a feasibility endpoint of four-point improvement in IIEF erectile function domain scores in greater than 50% of patients at 3 months. A total of 30 subjects with a mean age of 60 years were studied and 45 stents were placed. The majority of patients had known cardiovascular risk factors. Safety endpoints were met in all subjects, with 59% of patients in an intention-to-treat analysis meeting the feasibility endpoint at 3 months (unchanged at 6 months). Restenosis greater than 50% of the posttreatment luminal diameter was noted in 34% of patients at 6-month follow-up (32 lesions evaluated). Longer-term results are pending.

Stem Cell Therapy

The use of pluripotent stem cells as a curative therapy for ED has been evaluated in a number of animal studies and is currently being investigated in at least one phase I human clinical trial.[109] Stem cells are believed to be able to differentiate into the various cell types instrumental in erectile function; therefore, it was hypothesized that systemic or ICI of stem cells may replenish lost or deteriorating tissues contributing to ED, although this mechanism has not been proven in animals. A number of stem cell types—derived from bone marrow, adipose tissue, skeletal muscle, embryonic cells, endothelial progenitor cells, and umbilical cord blood—have been used in rats, with promising results.[109] One report of seven human patients undergoing treatment and three control patients with a long history of diabetes (mean 29 years) and ED refractory to medical therapy investigated the benefit of ICI of umbilical cord blood stem cells. In the experimental group, six patients reported some increase in rigidity, with two able to achieve penetration and maintenance with use of 100 mg of sildenafil at 6-month follow-up, compared with no improvement in the control group.[110] Further research is obviously needed to prove the feasibility of this treatment modality.

ERECTILE DYSFUNCTION IN MEN UNDERGOING VASCULAR SURGERY

Prevalence of Erectile Dysfunction in the Vascular Surgery Population

Given the significant cardiovascular risk factors and comorbidities present among patients requiring vascular surgical interventions, it is not unexpected that ED is a frequent and common complaint among patients both before and after abdominal aortic aneurysm (AAA) repair and treatment of aortoiliac disease. One study, looking at the prevalence of ED among a population of 137 vascular surgery patients, identified a 90% rate of ED

(defined as IIEF erectile function domain score less than 25), with moderate or severe ED in 70% of cases.[111] Among patients with an untreated AAA, the rate of moderate or severe ED was 82%. Another study looking at self-reports of preoperative sexual dysfunction in 56 AAA patients using SHIM scores described a 27% rate of ED in patients undergoing elective open AAA repair, 63% for those undergoing endovascular repair of AAA (EVAR), and 45% for those undergoing open repair for AAA rupture.[112] It should be noted that these figures are considerably higher than historically reported preoperative ED rates in AAA and aortoiliac occlusive disease patients, ranging from 22% to 39%, as previous studies had variable definitions of ED without the use of validated questionnaires or defined ED as only the most severe ED cases (IIEF erectile function domain score <11).[113,114]

Erectile Function Outcomes Following Definitive Therapy

Outcomes following AAA repair have recently been more extensively studied following a pair of randomized trials. The landmark Aneurysm Detection and Management (ADAM) study, randomized 1136 patients with 4.0- to 5.4-cm AAAs to surveillance versus immediate open repair.[115] Patients were evaluated by a nurse to rate their sexual function as normal versus impotent without the use of questionnaires. "Impotence" rates were significantly higher across patients randomized to immediate repair from 18 months to 4-year follow-up. Across groups, a steady and significant increase in ED was also noted, pointing to disease progression over time. Another rigorously performed study randomized 881 AAA patients to EVAR and open AAA repair and evaluated sexual function outcomes by use of the IIEF erectile function domain score.[116] Of note, patients had significant preoperative ED at baseline, with a mean IIEF score of 11.4 for the EVAR and 10.3 for the open group. At 1 year, there was a mean decline in IIEF of 2.5 and 2.3 for the EVAR and open groups, respectively, and a decline of 3 and 2.9 points, respectively, at 2 years, demonstrating no significant difference between the EVAR and open AAA repair groups. In a vasculopathic population such a decrease is likely age-related and not related to the surgical intervention.

ED rates after open and endovascular aortoiliac procedures have been evaluated in a single retrospective study of 116 patients following open aortoiliac reconstruction or percutaneous transluminal balloon angioplasty and/or stenting of the common and/or external iliac artery.[117] Patients were evaluated with the IIEF postoperatively and were asked to recall their sexual function before surgery. A significant decline in erectile function was recorded in both groups.

ED following vascular repair has been associated with bilateral internal iliac interruption during EVAR, as would be expected.[118] Internal iliac embolization prior to EVAR has also demonstrated significant increases in reported ED rates across a number of studies.[119] Therefore preservation of the internal iliac artery has been recommended when possible. In addition, adjunct internal iliac revascularization prior to EVAR may improve erectile outcomes, with reports of no change in sexual function and even improvement in erectile ability in a single patient following this procedure.[120]

Given these findings, it would be prudent for the vascular surgeon to consider counseling regarding erectile function changes following vascular surgical procedures. A previous report has shown that 91% of patients undergoing open AAA repair or EVAR do not recall receiving preoperative information regarding the risk of a possible negative impact on sexual function.[121]

CONCLUSIONS

ED is a highly prevalent condition and a potential marker for significant vascular disease; it is frequently unaddressed by vascular surgery practitioners despite the significant overlap of risk factors between ED and cardiovascular/peripheral vascular disease. Although treatment is often easily achieved with use of a PDE5 inhibitor, diagnostic evaluation in a subset of patients may help to better direct patient care and can provide prognostic information regarding potential response to therapy. Further study using validated instruments to quantify erectile function is needed in order to fully appreciate the effect of vascular reconstructive surgery on ED rates.

ACKNOWLEDGMENTS

We would like to gratefully acknowledge the assistance of Irwin Goldstein, MD, Director of Sexual Medicine at San Diego Sexual Medicine, Alvarado Hospital, San Diego, California, in providing us with images from selective internal pudendal arteriography and intraoperative photographs from his extensive experience with penile revascularization.

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CHAPTER 192

Complex Regional Pain Syndrome

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Complex regional pain syndrome (CRPS), previously called posttraumatic pain syndrome (PTPS), causalgia, or reflex sympathetic dystrophy (RSD), is one of the most poorly understood and frequently misdiagnosed entities encountered in clinical practice. This painful condition can develop after damage to peripheral nerves in a variety of settings. In susceptible patients, the initiating event may be relatively insignificant or even obscure.

EPIDEMIOLOGY/ETIOLOGY

The exact incidence of CRPS is unknown, but it has been estimated to occur in at least 1% to 12% of patients with peripheral nerve injury.[1] Others have reported that there are 50,000 new cases of CRPS in the United States annually.[2] CRPS has a male to female (particularly postmenopausal) ratio of 1:4 to 1:2, and is seen more commonly with increasing

Abstract

With the development of new arterial revascularization techniques, sympathectomy has ceased to be a routine method for improving arterial flow in patients with ischemia; however, with the development of video-assisted thoracoscopy, it has been increasingly used for the treatment of hyperhidrosis.

In this chapter we initially contextualize this surgical technique, describe the anatomical and physiologic aspects of the sympathetic nervous system, and analyze the current indications, techniques, results, and complications of both thoracic and lumbar sympathectomy.

Keywords

Sympathectomy
endoscopic sympathectomy
hyperhidrosis
quality of life
Raynaud syndrome
compensatory sweating
ischemia
complex regional pain syndrome

age.[3] Three causes of CRPS have been identified: traumatic, nontraumatic, and idiopathic.

Traumatic

Traumatic causes include fractures, dislocations, sprains, crush injury, burn, and iatrogenic injury. Most cases of CRPS are posttraumatic.[4] It occurs acutely in about 7% of patients with limb surgery, limb fractures, or other injuries. CRPS has been reported in 0.2% to 11% of patients with Colles fracture[5] and in 12% to 20% of patients with hemiplegia.[6] The incidence of CRPS type II (as defined later) has varied from as low as 1.5% in the Vietnam War to 8% in the Persian Gulf War[7] to as high as 32% in the Civil War.[8] CRPS has also been reported in patients with spinal cord and brain injuries, with an incidence of 5% to 12%.[7-9]

Recently, Hassantash and colleagues reported the results of a meta-analysis of causalgia, including 110 articles and 1528 cases[10] High-velocity missiles caused at least 77% of the injuries. The median nerve, alone or in combination with other nerves (56%), and the sciatic nerve (60%) were most commonly involved. In 92% of cases the nerve injury was incomplete.

Most cases resolve within the first year, with a smaller subset progressing to chronic stage. This is often associated with a change from "warm CRPS," where inflammatory characteristics dominate to "cold CRPS" in which autonomic features dominate.[11]

Nontraumatic

Nontraumatic causes include prolonged bed rest, neoplasm, metabolic bone disease, deep venous thrombosis, myocardial infarction, and stroke. The incidence of CRPS in patients with myocardial ischemia is between 5% and 20%.[1] Chronic painful conditions of the upper extremity subsequent to myocardial infarction have been grouped into a category designated *shoulder-hand syndrome.* These conditions have been reported in 15% of patients, but this percentage has been reduced significantly because of much more rapid post infarct mobilization.[9]

Idiopathic

In idiopathic CRPS, no cause can be identified.

CLASSIFICATION AND TERMINOLOGY

Box 192.1 lists more than 40 terms that describe CRPS. The most common include *causalgia*, both minor and major (*causalgia* is derived from the Greek *causos*, meaning "heat," and *algos*, meaning "pain"—that is, a burning pain)[10]; *minor* and *major traumatic dystrophy*, describing the intensity of the syndrome when it develops after an injury that does not damage a peripheral nerve; *shoulder-hand syndrome*, or RSD involving the entire upper extremity; and *Sudeck's atrophy*, a posttraumatic reflex dystrophy with bone involvement demonstrable on radiographs.

BOX 192.1 Terms Used to Describe Complex Regional Pain Syndrome (Causalgia and Posttraumatic Pain Syndromes)

- Acute atrophy of bones
- Algodystrophy
- Algoneurodystrophy
- Causalgia
- Causalgia-like states
- Chronic segmental arterial spasm
- Chronic traumatic edema
- Disuse phenomenon
- Homans minor causalgia
- Major causalgia
- Mimocausalgia
- Minor causalgia
- Mitchell causalgia
- Painful osteoporosis
- Peripheral trophoneurosis
- Posttraumatic dystrophy
- Posttraumatic fibrosis
- Posttraumatic neurovascular pain syndrome
- Posttraumatic osteoporosis
- Posttraumatic pain syndrome
- Posttraumatic painful osteoporosis
- Posttraumatic spreading neuralgia
- Posttraumatic sympathalgia
- Posttraumatic sympathetic dysfunction
- Posttraumatic sympathetic dystrophy
- Posttraumatic vasomotor disorders
- Reflex neurovascular dystrophy
- Reflex dystrophy
- Reflex dystrophy of the extremities
- Reflex nervous dystrophy
- Reflex sympathetic dystrophy
- Shoulder-hand syndrome
- Steinerocher shoulder-hand syndrome
- Sudeck atrophy
- Sudeck osteodystrophy
- Sudeck syndrome
- Sympathalgia
- Sympathetic neurovascular dystrophy
- Traumatic angiospasm
- Traumatic edema
- Traumatic neuralgia
- Traumatic vasospasm

To resolve the confusion surrounding the various terms used to describe this syndrome, Stanton-Hicks and associates convened a consensus committee of the International Association for the Study of Pain to discuss the nomenclature of causalgia and RSD.[12] As a result, the term *complex regional pain syndrome* was developed to replace the terms *causalgia* and *reflex sympathetic dystrophy.* CRPS includes a spectrum of conditions with somewhat similar clinical manifestations that often are grouped together for the sake of clinical utility.[13,14] Hallmarks of this syndrome include dysfunction and pain of a duration or severity out of proportion to what might be expected from the initiating event. The new classification scheme is based on a descriptive method that should allow future modifications to reflect new scientific findings.[13,14]

Summary of Key Features

Three components characterize CRPS:

1. *Complex:* This term denotes the dynamic and varied nature of the clinical presentation in a single person over time and among persons with seemingly similar disorders. It also reflects the autonomic, cutaneous, motor, inflammatory, and dystrophic changes that distinguish this syndrome from other forms of neuropathic pain.
2. *Regional:* This term describes the wide distribution of clinical symptoms and findings beyond the area of the original lesion,

and is considered a key characteristic of the syndrome. The distal part of a limb is usually affected, but occasionally CRPS occurs in other parts of the body (e.g., the face or torso) and may spread to other body parts.

3. *Pain:* The hallmark of CRPS is pain that is out of proportion to the initiating event. The designation refers to spontaneous burning pain and thermally or mechanically induced allodynia (i.e., pain from stimuli that are not normally painful).

Syndrome Types

Two types of CRPS have been recognized. Type I corresponds to the former term *RSD*, and type II corresponds to the former term *causalgia.* The definitions of CRPS types I and II contain criteria that exclude (1) pain and other findings that are physiologically, anatomically, and temporally appropriate to some form of injury, and (2) myofascial pain syndrome. The terms *sympathetically maintained pain* (SMP) and *sympathetically independent pain* (SIP) are used to describe types of pain that can be associated with a variety of pain disorders, including CRPS types I and II.

Diagnostic Criteria

The diagnostic criteria for CRPS type I, as adapted from Stanton-Hicks and coworkers[12] and Merskey and Bogduk,[15] are as follows:

- History of an inciting noxious event.
- Spontaneous pain, hyperalgesia, or allodynia beyond the territory of a single peripheral nerve and disproportionate to the initiating event.
- Edema, skin blood-flow abnormality, or abnormal sudomotor activity in the region of the pain that has developed since the initiating event.
- Absence of other conditions that would account for the degree of dysfunction and pain.

The diagnostic criteria for CRPS type II are as follows:

- History of a nerve injury.
- Spontaneous allodynia or pain is not necessarily limited to the region of the injured nerve.
- Edema, temperature and skin blood-flow changes, abnormal sudomotor activity, or motor dysfunction in the region of the pain that has developed since the original nerve injury.
- Absence of other conditions that would account for the degree of dysfunction and pain.

CRPS, NOS (not otherwise specified), is a subtype that describes patients who only partially meet the current criteria, but were diagnosed with CRPS under previous criteria.[15-18]

PATHOGENESIS

Theories and Components

Many theories have been proposed to explain CRPS, but none has been universally accepted. Most were developed to explain the causalgia associated with nerve injury (CRPS type II). Past theories included the artificial synapses theory by Doupe,[19] the vicious cycle of reflexes by Livingston,[20] and the gate control theory.[21] Presently, major theories which have been proposed to explain the causes/pathogenesis of CRPS include the following:

Exaggerated Local Inflammatory Response Theory/Neurogenic Inflammation

The painful affected limb is usually hot, red, swollen, and has reduced function, all of which are signs of inflammation. Recent studies have shown that inflammatory mediators (e.g., TNF-α and interleukin-6) are elevated in blister fluid and blood samples obtained from affected limbs.[22] This theory is supported by the fact that corticosteroids are often successful in the treatment of patients with acute CRPS. The reported efficacy of low-dose intravenous immunoglobulins (IVIG) could be due to an antiinflammatory effect.[23]

It has also been suggested that localized neurogenic inflammation may be involved in the production of vasodilation, acute edema, and increased sweating. Neuropeptides released from sensory neurons, cause skin reddening and swelling, which is seen in affected limbs.

Complex Regional Pain Syndrome as a Sympathetically Mediated Syndrome

There is a low centrally mediated sympathetic outflow to cutaneous vasoconstrictors in the affected limb, which may produce red and warm extremities.[24] It has been suggested that the permanent cold temperature in some cases of late CRPS may be due to endothelial rather than sympathetic dysfunction.[24] All four randomized controlled trials that were conducted to assess intravenous regional sympathetic block (IVRSB) have been negative.[24] Many clinicians using this method have demonstrated that it reduced pain in some patients,[24] and one wonders whether this effect was the result of the application of tourniquet. It should also be noted that local anesthetic application to the sympathetic ganglia (e.g., the stellate or lumbar sympathetic block) can relieve pain for the short term in selected patients;[24] however, repeated applications do not prolong that effect.[25] The SMP can be reduced by sympathetic blockade, particularly in the early stage of CRPS, but is rare in long-standing CRPS.[26]

Complex Regional Pain Syndrome as the Result of Limb Ischemia/Reperfusion Injury

CRPS-I is felt to be an abnormal inflammatory response to a deep tissue injury, producing a picture of a compartment syndrome with resultant, oxygen-free radical-induced microvascular dysfunction, further ischemia and inflammation, and nociceptor excitement.[24] Groeneweg et al.,[27] in a recent pilot study showed that tadalafil (a phosphodiesterase inhibitor), reduced pain in some CRPS patients with cold limbs. This was thought to be secondary to its vasodilator property.

Central Sensitization Theory

This theory is thought to be important in most chronic pain.[24] It is believed that *N*-methyl D-aspartate (NMDA) receptors may play an important role in central sensitization. In two

randomized clinical trials, low-dose IV ketamine (an NMDA antagonist) dramatically reduced CRPS pain, which may indicate an important role for such central sensitization.[24]

Complex Regional Pain Syndrome Secondary to Nerve Damage

The similarity of CRPS syndrome to small-fiber-predominant polyneuropathy stimulated the idea that regionally restricted small nerve fiber damage may occur in CRPS, rather than sympathetic dysfunction, and may be responsible for CRPS signs.[24] Studies of CRPS-amputated limbs and skin biopsies showed small fiber loss.[24] Therefore it is postulated that CRPS-I syndrome may, in fact, represent neuropathic pain syndrome.

Complex Regional Pain Syndrome as an Autoimmune Disorder

Goebel[24] and Blaes et al.[28] showed evidence for antineuronal autoantibodies in 30% and 90% of patients with CRPS. Goebel et al. also demonstrated, in a randomized clinical trial, that a single infusion of low-dose IVIG effectively reduces pain in patients with long-standing CRPS.

Cortical Reorganization Theory

Functional MRI studies over the last several years have shown that sensory representations of CRPS-affected limbs are altered, that the degree of this alteration corresponds to the pain intensity, and that reduction in pain is associated with normalization.[24] There are also changes in the motor cortex. CRPS patients often feel alienation from their affected limb; the limb can feel strange and disfigured. Computer-based graded motor imagery (GMI), which consists of exercise to train the brain in better recognizing the affected limb, can decrease swelling and pain in some CRPS patients.[24] The mirror therapy (advocated by McCabe et al.).[24,29] for the treatment of CRPS requires that the patient hides the affected limb behind a mirror that is placed perpendicular to the body midline. When looking into the mirror and performing bilateral synchronized gentle movement, the affected limb (the reflection of the unaffected limb in the mirror) has a normal look and moves normally. This therapy has been shown to minimize both early and late pain in these patients after stroke.

CLINICAL PRESENTATION

CRPS type I can occur in any age group, with a female-male ratio of 2 : 1. Although type I has been reported in children, it is not as disabling as in adults.

Symptoms and Signs

The clinical criteria for the diagnosis of CRPS, as outlined by Stanton-Hicks and colleagues,[12,14] are summarized in Fig. 192.1 and Box 192.2.[12,14]

BOX 192.2 Diagnostic Criteria for Complex Regional Pain Syndrome

Clinical Symptoms and Signs

- Burning pain hyperpathia or allodynia
- Temperature or color changes edema
- Hair or nail growth changes

Laboratory Results

- Thermometry or thermography bone radiography
- Three-phase bone scan quantitative sweat test response to sympathetic block

Interpretation

If total number of positive findings is
- >6: Reflex sympathetic dystrophy probable
- 3–5: Reflex sympathetic dystrophy possible
- <3: Reflex sympathetic dystrophy unlikely

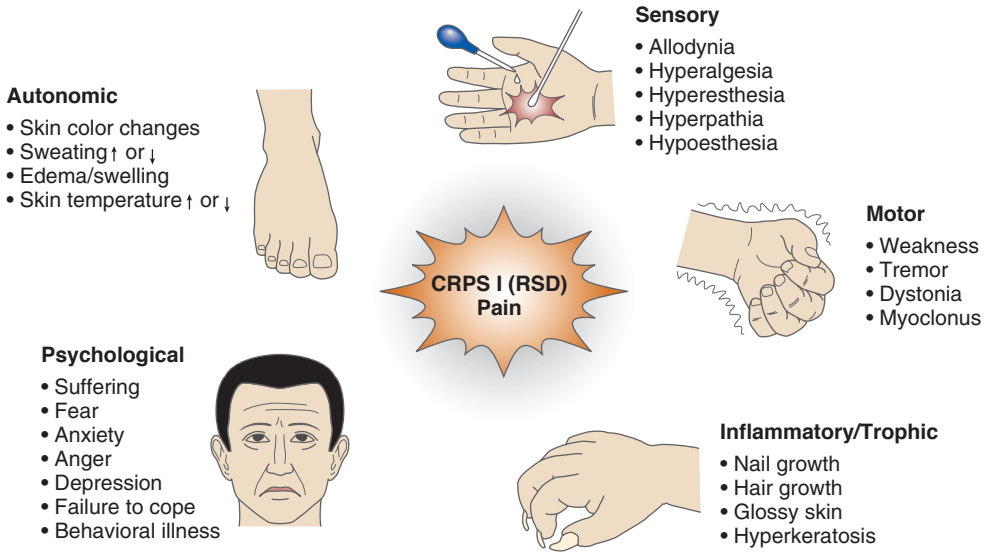

Figure 192.1 Clinical features of complex regional pain syndrome *(CRPS)* type I (reflex sympathetic dystrophy *[RSD]*).

Pain: Pain is a necessary symptom for the diagnosis of CRPS. It is located in the affected extremity and is disproportionate to what would be expected from the initial event. It may be spontaneous or evoked and is usually reported as burning or diffuse pain. The pain may also be described as throbbing or aching, intermittent or continuous, and exacerbated by physical or emotional stress. The pain is not consistent with the distribution of a peripheral nerve, even if the initial injury involved such a nerve. This important feature distinguishes CRPS from pain of other causes and from more specific neuropathic pain disorders. The patient often adopts a protective posture to guard the affected extremity.

Sensory Changes: Sensory changes of CRPS are usually reported at some stage and include allodynia and hyperesthesia in the region of the pain. Allodynia may occur in response to thermal stimulation (cold or warm), deep pressure, light touch, or joint movement.

Sympathetic Dysfunction: Sympathetic dysfunction in CRPS is reported as a sudomotor or vasomotor instability in the affected extremity compared with the unaffected extremity. This dysfunction may vary in severity at different times.

The patient may report that the extremity is warm and red or cold and blue, purple, or mottled. Veldman and associates reported that 92% of patients had altered skin temperature.[30] Sweating, particularly of the palms or soles, may be reported as increased, decreased, or unchanged. Normal sympathetic function may be present at certain times. Swelling can occur at any stage of the syndrome and is typically peripheral; it may be intermittent or permanent and may be exacerbated by the dependent position of the extremity. There can also be pitting or brawny edema.

Trophic Changes: Trophic changes of the skin may occur later in the course of the syndrome. The nails may be atrophic or hypertrophic. Hair growth and texture may be decreased or increased, and the skin may become atrophic. Motor dysfunction includes dystonia, tremor, and loss of strength of the affected muscle groups. Joint swelling and stiffness may also be reported, particularly of the digits.

Budapest Consensus Criteria

The Budapest Consensus Workshop introduced criteria to identify CRPS and rule out other neuropathic conditions. CRPS patients must report symptoms of, and show signs on physical examination, in the following categories: vasomotor, sensory, motor/trophic, and sudomotor/edema (Figs. 192.1 and 192.2; Box 192.3).

Comprehensive Adjunctive Clinical Tests

With the foregoing features in mind, the clinical evaluation can be enhanced by focusing on particular aspects or using adjunctive tests.

Sensory Examination: Sensory impairment can be positive (allodynia, mechanical and thermal hyperalgesia) or negative (hyperesthesia, hypalgesia). These sensory impairments can be localized (glove-like) or generalized. Quantitative sensory testing to confirm the clinical findings of sensory abnormalities can be applied; however, this is not specific for patients with CRPS.[31]

Figure 192.2 A patient with chronic complex regional pain syndrome exhibits dystonic posture of the right ankle along with trophic skin changes. (Figure 2 from Freedman M, Greis AC, Marino L, et al. Complex regional pain syndrome: diagnosis and treatment. *Phys Med Rehabil Clin N Am*. 2014;25(2):291-303, 293.)

BOX 192.3 Budapest Clinical Diagnostic Criteria for Complex Regional Pain Syndrome

1. Continuing pain that is disproportionate to any inciting event
2. Patient must report one symptom in three of the four following categories:
   a. *Vasomotor:* Temperature asymmetry and/or skin color changes and/or skin color asymmetry
   b. *Sensory:* Hyperesthesia and/or allodynia
   c. *Motor/trophic:* Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or tropic changes (hair, nail, and/or skin)
   d. *Sudomotor/edema:* Edema and/or seating changes and/or sweating asymmetry
3. Patient must exhibit one sign at the time of evaluation in two or more of the following categories:
   a. *Vasomotor:* Temperature asymmetry and/or skin color changes and/or asymmetry
   b. *Sensory:* Hyperalgesia to pin prick and/or allodynia to light touch and/or deep somatic pressure and/or joint movement
   c. *Motor/trophic:* Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, and/or skin)
   d. *Sudomotor/edema:* Edema and/or sweating changes and/or sweating asymmetry
4. No other diagnosis that better explains the signs and symptoms

Modified from Harden RN, Bruehl S, Perez RS, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. *Pain*. 2010;150(2):274.

Sudomotor Sympathetic Examination: Resting heat output can be estimated by skin impedance,[32] by quinizarin or cobalt blue testing,[33] or as part of the quantitative sudomotor axon reflex test,[34] which measures resting sweat output by hygrometry and changes evoked by iontophoresis of acetylcholine into the skin.[35] These tests are useful diagnostic tools, but they are difficult to conduct and are generally not recommended for the routine diagnosis of CRPS.[31,36]

Vasomotor Examination: Simultaneous temperature measurements of both the affected and unaffected extremities are taken

at corresponding anatomic sites. The temperature of the digit pads, palms, soles, forearms, and calves can be measured with noncontact thermometry or thermography. Serial measurements should be taken, because peripheral temperatures vary widely under normal circumstances. Skin perfusion can be evaluated visually or by pulse oximetry.

Motor Dysfunction: The presence of dystonia, tremor, and changes in strength can be measured clinically. Objective measurements should be taken (e.g., apposition and opposition pinch strength, grip, weight-bearing on the lower extremity).

Psychological Testing: Psychological testing has not been validated in CRPS. The psychiatrist generally uses familiar instruments as part of the initial assessment and follow-up.[37]

Neurophysiologic Testing: The diagnosis of CRPS type II requires a peripheral nerve lesion, and CRPS may develop following a central nervous system lesion (brain tumor or brain infarct). It is therefore important to confirm or exclude peripheral nerve and central nervous system lesions. Nerve conduction studies may show discrete abnormalities secondary to edema or peripheral vasoconstriction.[31] Distinct abnormalities exceeding 20% of normal values should be observed and may indicate a peripheral nerve lesion, which can be noted in patients with carpal tunnel syndrome or CRPS type II. Somatosensory evoked potentials after ulnar-median or tibial nerve stimulation testing are usually normal in patients with CRPS type I; however, these tests can be abnormal in patients with CRPS type II. Electromyograms are usually not performed in patients with CRPS, because they are painful and may exaggerate the pain of CRPS. Overall, these tests can be useful in the diagnosis of CRPS types I and II and to confirm peripheral nerve or central nerve system lesions; however, the findings are not specific.

Inflammatory Assessment: Neuroinflammatory mediators such as substance P, bradykinin, and calcitonin gene-related peptide are usually increased in patients with CRPS; however, other systemic inflammatory markers, such as C-reactive protein, erythrocyte sedimentation rate, and leukocyte count, are not elevated.[38]

DIAGNOSTIC EVALUATION

Radiographic Findings

The primary radiographic manifestations in patients with CRPS are diffuse osteoporosis with severe patchy demineralization, especially of the periarticular regions, and subperiosteal bone resorption.[31] However, these changes are late and nonspecific.

Three-Phase Bone Scans: Accelerated blood flow in the diseased limb combined with increased, diffuse activity during the blood-pool phase and increased periarticular uptake in the delayed static phase is considered pathognomonic for CRPS (Fig. 192.3). A meta-analysis of 19 articles on the use of three-phase bone scans in patients with CRPS revealed a poor sensitivity of 50%. Therefore many believe that bone scans are not accurate enough for the diagnosis of CRPS.[39]

Magnetic Resonance Imaging: Magnetic resonance imaging (MRI) may reveal characteristic findings during the course of the disease.[31] Skin thickening and changes in bone signal intensity in carpal and metacarpal bones, along with effusions in adjacent joints, may be related to the acute and early stages of CRPS. However, several studies have suggested that the consequences of surgery or trauma may mimic CRPS type I–like MRI findings; therefore, MRI is usually not used as a screening method, but it may be helpful in excluding other disease entities.

Figure 192.3 Three-phase bone scan in complex regional pain syndrome of the left hand, demonstrating osteopenia. (From Schurmann M, Gradl G, Rommel O. Early diagnosis in post-traumatic complex regional pain syndrome. *Orthopedics*. 2007;30:450-456.)

Diagnostic Sympathetic Blockade

The validity of a clinical diagnosis of CRPS can be greatly strengthened by a positive response to sympathetic blockade. If there is no relief from pain for the duration of the complete sympathetic blockade, the diagnosis of CRPS is less likely. A documented increase in skin temperature of 1°C to 3°C confirms the success of sympathetic blockade. Patients should be encouraged to quantify the degree of pain relief experienced (e.g., 100% relief, 50% relief). The degree of pain relief a patient experiences with such a blockade is an excellent predictor of how much relief can be expected from surgical sympathectomy.[40] Caution should be exercised, however, because sympathectomy can provide some degree of nonspecific relief of almost any pain, including ischemic pain.[40,41] CRPS pain is usually dramatically relieved by sympathetic blockade (almost always 75% to 100% relief), whereas relief of pain from other causes is usually only mild to moderate (25% to 50% at most).

Sympathetic blockade can be achieved by the intravenous delivery of an alpha-blocking agent (e.g., phentolamine), intravenous regional blockade with bretylium, Bier blockade, differential spinal blockade, epidural blockade, and local anesthetic blockade of the paravertebral lumbar sympathetic

chain. Many consider paravertebral lumbar blockade using lidocaine or bupivacaine most effective because it blocks both sensory and motor nerves.[40]

Differential Diagnosis

Causalgia-like pain can occur if a nerve is caught in a suture, entrapped by scar, or compressed by surrounding structures. Nerve entrapment must be considered when causalgia appears immediately after an operation. If peripheral nerve entrapment is the cause, there is often a "trigger point" where focal application of pressure causes sharp pain. The pain can be relieved by the infiltration of a small amount of local anesthetic at that point (see Chapter 45).

Patients who present with cutaneous signs and symptoms characteristic of early stages of CRPS are sometimes thought to have Raynaud syndrome; however, with Raynaud syndrome, the patient's symptoms should be episodic, related principally to cold exposure, and relieved by warmth. The pain of peripheral neuritis is often burning and associated with hyperesthesia and vasomotor phenomena. However, the clinical syndrome associated with peripheral neuritis is more anatomically diffuse and gradual in onset, and the patient has no history of trauma or another discrete precipitating event. Other conditions must be kept in mind, including inflammatory or infectious disorders, such as rheumatic arthritis, unilateral vascular occlusive disease, bone or soft tissue injury, thoracic outlet syndrome, compartment syndrome, and psychological disorders.

NONSURGICAL TREATMENT

In the past, when there was no effective treatment, CRPS frequently resulted in chronic invalidism, emotional deterioration, and drug addiction. Thus the proper treatment of CRPS is based on prevention and early recognition. For patients known to be susceptible to CRPS, such as those who have hemiplegia or myocardial infarction, early mobilization of an injured extremity is critical. When early sympathetic dystrophic changes occur, pain relief and active use of the hand, arm, or leg are indicated. Passive motion by physical therapists should be avoided because it may increase the pain and edema. Opiate analgesics, when needed, should be used conservatively. Splinting the hand in a functional position may help.

Few evidence-based treatment modalities for CRPS are available.[41-47] Treatment of CRPS usually requires a multidisciplinary approach, including a neurologist, anesthesiologist, vascular surgeon, orthopedic specialist, psychologist, and physical therapist.

Physical Therapy

Physical therapy should be considered not only essential but also the first line of treatment for patients with CRPS. Intensive physical therapy should be initiated, including full range-of-motion exercises and whirlpool exercises. Aggressive therapy should be avoided, however, because patients with CRPS have an exaggerated response to painful and nonpainful stimuli,[48] and any pain may exaggerate the syndrome. The primary objective of physical therapy is goal-oriented functional restoration, which includes (1) mobilization, swelling control, and isometric strengthening; (2) desensitization of the affected region; (3) stress loading, isotonic strengthening, range of motion, postural normalization, and aerobic conditioning; and (4) vocational rehabilitation.[14] Physical therapy should be combined with pharmacologic therapy.

Recently, Barnhoorn et al. reported on a randomized trial of pain exposure physical therapy (PEPT) compared with conventional treatment in CRPS syndrome type 1 and could not conclude that PEPT is superior to conventional treatment.[49]

Mirror Visual Feedback: Mirror visual feedback has been used in the early stages of CRPS type I. The effect of this therapy is based on findings that visual input from a moving, unaffected limb re-establishes the pain-free relationship between sensory feedback and motor execution of the affected limb. McCabe and coworkers reported good results in patients with early stages of CRPS type I.[29]

Recently, Vural et al. reported that in stroke patients with CRPS type 1, addition of mirror therapy to conventional stroke rehabilitation program provides more improvement in pain perception and motor functions of the upper limb, compared with conventional therapy without mirror therapy.[50]

Transcutaneous Electrical Nerve Stimulation: Transcutaneous electrical nerve stimulation (TENS) has been used to treat CRPS.[47,51] It may be tried before more aggressive treatment is attempted. In the hands of an experienced practitioner, the success or failure of TENS will be apparent by the third to fifth treatment.[51]

Acupuncture and Electroacupuncture: Chan and Chow reported on the use of acupuncture in more than 20 patients with CRPS after hand injuries.[52] A total of 14 patients experienced marked permanent improvement, and four had some improvement.

Pharmacologic Therapy

Pharmacologic therapy, particularly as it applies to early stages of CRPS, can be combined with intermittent sympathetic blockades and physical therapy. Drug therapy may require nonspecific analgesics, but these should be superimposed, only when necessary, on a "background" of medication designed to attenuate the symptoms by direct effect. Of these, phenytoin, amitriptyline, carbamazepine, and baclofen can be effective, and they are usually used in that order owing to increasing side effects. Tricyclic antidepressant amitriptyline hydrochloride (Elavil) is used in doses of 50 to 75 mg nightly.

Opioids: Opioids inhibit central nociceptive neurons through interaction with μ-receptors. There are no long-term studies of oral opioids in the treatment of neuropathic pain, including CRPS; however, the expert opinion of pain clinicians is that opioids should be part of a comprehensive pain regimen protocol. Opioids should be tried early in the course of CRPS, not as a "last resort."

Tricyclic Antidepressants: Tricyclic antidepressants are some of the best-studied drugs in the treatment of neuropathic pain, and they have shown an analgesic effect. They inhibit the reuptake

of monoaminergic transmitters. There is solid evidence that the reuptake and noradrenaline blocker amitriptyline and the selective noradrenaline blocker desipramine produce pain relief in several neuropathies.

GABA-Agonists: GABA-agonists such as gabapentin (Neurontin) have also been used in the treatment of CRPS. The action of gabapentin probably includes the inhibition of calcium channels.

α-Adrenergic Blocking Agents: The use of α-adrenergic blockers is based primarily on the fact that patients with CRPS have altered blood flow as a result of increased local secretion of norepinephrine and vascular endothelial hypersensitivity. Inhibition of the receptors leading to vascular dilation and increased blood flow may be helpful. Pain relief following intravenous phentolamine administration has been suggested as a diagnostic tool, as well as a prognostic guide for favorable response to sympathetic blockade.[44,53] Its 15-minute plasma half-life precludes its use as a therapeutic modality. Other medications include phenoxybenzamine and prazosin.[44,45] Phenoxybenzamine has antiadrenergic effects and is an irreversible α-antagonist and has been shown to be beneficial in treating CRPS. It is considered a third-line agent and works best in cases lasting less than 3 months.[53]

Oral β-Blocking Agents: Propranolol, which antagonizes serotonin, has been partially successful.[43,44]

Oral Calcium Channel Blocking Agents: These agents produce smooth muscle relaxation of the arteriole walls, leading to increased blood flow.

Bisphosphonate Therapy: This therapy is based on the concept that pain results from osteopenia as part of CRPS. These are potent inhibitors of osteoclastic activity, which are used for management of osteoporosis and other metabolic bone diseases. Their primary action is reduction of bone turnover.

With recent publication of results from a randomized clinical trial with neridronate,[54] there is fairly convincing evidence that various bisphosphonates can significantly relieve spontaneous and stimulus-evoked pain, improve functional status, and have an acceptable safety profile in patients with early disease (<6 months duration) and abnormal uptake in three-phase bone scintigraphy. Most studies had a short follow-up period, but in the largest and most recent study, improvement seen after neridronate treatment was sustained or even better over a follow-up period of at least 1 year. However, the doses required for long-term remission are quite high (100 mg neridronate or 90 mg pamidronate, each given IV 4 times over 10 days).[55]

Five randomized controlled trials have reported oral and IV alendronate and IV clodronate, pamidronate, and neridronate to be effective in improving physical function and reducing pain in patients with CRPS type 1, with tolerability and a good profile of safety.

Nonsteroidal Antiinflammatory Drugs: These drugs inhibit the enzyme cyclooxygenase (Cox), which leads to decreased production of the prostaglandins (which mediate inflammation and hyperalgesia) and thromboxanes that increase nociceptor sensitivity to painful stimuli and promote vascular constriction.

In most cases, patients are started on analgesics and NSAIDS and some guidelines recommend using the WHO ladder, except for strong opioids.[55] However, these are usually ineffective in sufficiently reducing pain; therefore, they are often followed by medications used for the treatment of neuropathic pain.

Steroid Therapy. These are potent antiinflammatory agents that decrease tissue edema, which decreases pain and improves joint motion. Prednisone, prednisolone, and methylprednisolone are commonly used.[44] The usual starting dose of prednisone is 60 mg/day. The dose is tapered every 3 days by 5 mg, so the total course of therapy lasts about 5 weeks.

Sympathetic Blockade

Because many patients experience at least a temporary response to nonoperative treatment in the early stages of CRPS, a common error in management is persisting with such treatments too long and shifting repeatedly from one to another. This subjects patients to wasted time and expense and prolonged suffering, and it may also compromise their chances of obtaining complete and lasting relief by surgical sympathectomy. Thus if the measures described earlier are not effective in relieving the patient's symptoms promptly, or if the symptoms are exacerbated over the course of several days, the physician should proceed directly to sympathetic blockade, which is both diagnostic and therapeutic.

An initial sympathetic blockade is appropriate in the early stage (<6 months) to confirm the diagnosis and test the procedure's therapeutic potential. The rapid pain relief gained from a sympathetic blockade can be extremely helpful psychologically. Also, the condition may be reversible at this stage, and complete remission can sometimes be achieved, particularly in patients who experience long-lasting relief from serial sympathetic blockade, thus allowing aggressive physical therapy. When relief is short-lived, however, repeated blockade is counterproductive and expensive. Sympathetic blockade of the affected extremity has been used as an alternative therapy for patients with CRPS, but proof of its effectiveness is scanty.[56]

Sympathetic blocks involve injection of local anesthetics along the lumbar sympathetic chain for lower limb CRPS, or stellate ganglion for upper limb CRPS, which is done under fluoroscopic guidance. A good response is categorized by an increase in temperature in the affected extremity, without a sensory or motor block, reduced pain, improved range of motion, and decreased allodynia.[57] If there is any short-term benefit, block can be repeated. These blocks are usually more beneficial in patients who demonstrate sympathetically mediated symptoms. Response duration and efficacy may vary. Success is expected to be greater in patients with SMP than in patients with sympathetic independent pain.[2]

Several uncontrolled studies have reported on the effect of sympathetic blockade in patients with CRPS. About 85% of patients reported positive results, but fewer patients (60%) reported long-term relief.[40,58] Other authorities have questioned the role of the sympathetic system in the pathogenesis of CRPS and therefore its role in treatment.[59,60] A Cochrane review of local anesthetic sympathetic blockade for CRPS concluded

that the published evidence is too scarce to support the use of sympathetic blockade as the "gold standard" treatment for CRPS.[61] However, it continues to be used at various centers worldwide.[62,63]

Rocha et al. reported the results of a double-blind randomized study of thoracic sympathetic block for the treatment of CRPS type 1. CRPS type 1 patients were treated with standardized pharmacologic and physical therapy and were randomized to either thoracic sympathetic block or control procedure as an add-on treatment. Clinical data, pain intensity and interference, pain dimensions, neuropathic characteristics, mood, upper limb function, and quality of life were assessed before, at 1 month, and 12 months after the procedure. Thirty-six patients were included, 17 of which had the thoracic sympathetic block. The average pain intensity was not significantly different between the two groups at 1 month. However, at 12 months, the average pain item was significantly lower in the thoracic sympathetic block group. In addition, the pain dimensions, evoked pain symptoms score, and depression scores were significantly lower in the thoracic sympathectomy block group at 1 and 12 months. However, the quality of life was only slightly improved by the thoracic sympathectomy block.[64]

Lumbar Sympathetic Blockade Technique

Complete sympathetic blockade may be obtained with a single injection of 15 mL of bupivacaine (Marcaine) at the level of L2. Better results may be obtained using two or even three needles, with one point inserted at L2 and the others at L3 and L4 (Fig. 192.4).

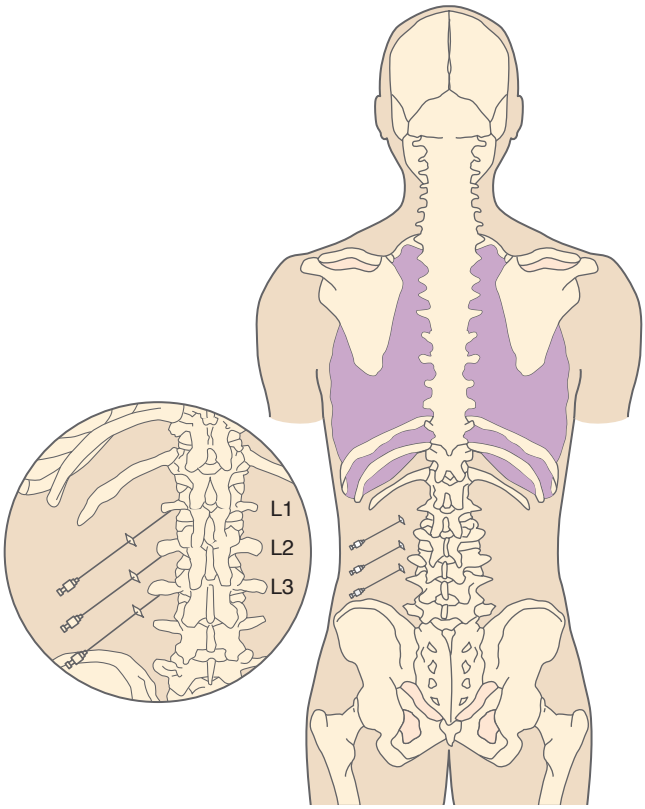

Figure 192.4 Lumbar sympathetic blockade (three-needle technique).

Epidural and Intrathecal Drug Therapy

Continuous epidural anesthesia or an intrathecal narcotic pump allows low-dose narcotics or local anesthetics to be administered, which may result in fewer systemic side effects than intravenous application. Local narcotic use can elevate the pain cycle, whereas the anesthetic agent provides a relatively selective sympathetic blockade. Successful outcomes with placement of an indwelling morphine pump[65] or the administration of continuous epidural anesthesia in conjunction with continuous passive motion[66] have been reported. Owing to the risk and cost of this modality, its use has been limited. Continuous epidural anesthesia also requires hospitalization and carries the risk of urinary retention, hypertension, and skin breakdown. Intrathecal morphine pumps are usually expensive and require refilling of the narcotic reservoir. One double-blinded controlled trial reported that epidural clonidine is beneficial in CRPS patients. Intrathecal baclofen therapy has been suggested for CRPS patients who are refractory to conventional modalities.[67]

Neuromodulation

Neuromodulation modalities include peripheral nerve, spinal cord, and thalamic stimulation. Implantable devices such as spinal cord stimulators are increasingly used in patients with intractable CRPS for symptomatic pain relief. In a prospective randomized controlled study, patients with CRPS who received spinal cord stimulation with physical therapy obtained greater pain relief and improvement in health-related quality of life than those who received physical therapy alone.[68,69]

Deer et al. and the Neuromodulation Appropriateness Consensus Committee (NACC) reported on neurostimulation of the spinal cord and peripheral nervous system in the treatment of chronic pain and ischemic diseases. They concluded that the appropriate neurostimulation is safe and effective in some chronic pain conditions and that clinical evidence and further technical refinements will continue to expand its use. The NACC will continue to facilitate the safety and efficacy of neurostimulation.[70]

Psychotherapy

Recently, the International Association for the Study of Pain consensus report recommended that patients with CRPS seek psychotherapy, including psychometric testing, if their pain persists beyond 2 months.[13] This includes the treatment of anxiety, depression, and personality disorders. Counseling, behavioral modification, relaxation therapy, biofeedback, group therapy, and self-hypnosis should be considered in these patients.

SYMPATHECTOMY

Once CRPS has been temporarily relieved by sympathetic blockade, the question arises whether to try to achieve this degree of relief more permanently by sympathectomy.

Indications

The decision to perform a sympathectomy depends on the clinical stage of the disease, the severity of symptoms, and the degree and duration of relief obtained by sympathetic blockade. This applies to both upper and lower extremity CRPS. For example, if a patient with pain of recent onset experiences pain relief from sympathetic blockade that lasts well beyond the known duration of the anesthetic agent used, it is advisable to continue with nonoperative measures. A patient whose condition has persisted for several months, whose pain is disabling, and who experiences nearly total relief from sympathetic blockade, but only for the typical duration of the anesthetic, may be considered a candidate for immediate surgical sympathectomy. A patient with symptoms of long duration (many months to years) and associated trophic changes, whose symptoms are less "classic" and less severe, and who receives only mild to moderate relief from sympathetic blockade should be advised that the long-term results are likely to be disappointing. These examples correspond to Drucker's three stages (over 6-month duration); this is deliberate because sympathectomy is, for the most part, best applied in stage 2 (3- to 6-month duration)—before progression to stage 3 and after stage 1 (first 3 months)—in patients who are unresponsive to nonoperative therapy.

For CRPS of the upper extremity, surgical cervical or dorsal sympathectomy (lower stellate ganglion and T2 and T3) is indicated, whether through the open or the thoracoscopic approach. For patients with CRPS of the lower extremity, lumbar sympathectomy is usually indicated. If surgical sympathectomy is limited to patients who obtain excellent relief from sympathetic blockade with local anesthetic, nearly 90% of patients experience long-term relief.[40,58,71]

Lumbar Sympathectomy

Anatomic Considerations

Sympathetic outflow to the lower extremities originates in spinal cord segments T10 to L3. Preganglionic fibers from these segments form extensive synaptic connections in paravertebral ganglia from L1 to S3 for innervation of the entire lower extremity and pelvic region. Sympathetic innervation of the foot and lower leg is conveyed primarily through the L2 and L3 ganglia; the proximal leg region is innervated primarily through the L1 to L4 ganglia. Overall, three lumbar ganglia are most commonly found, with fusion of the L1 and L2 ganglia most commonly accounting for the reduced number. Crossover fibers occur in 15% of patients, with most leaving via the fourth and fifth lumbar ganglia. For most clinical indications, L2 and L3 ganglionectomy is sufficient, but also removing L4 is advised to reduce the possibility of collateral reinnervation. Extensive ganglionectomy is usually not warranted and may result in ejaculatory disturbances in preclimacteric men when bilateral high ganglionectomies (i.e., including L1) are performed.

Chemical Sympathectomy

The high response rate achieved with percutaneous sympathetic blockade with local anesthetics led to attempts to achieve extended blockade with phenol or alcohol injections via the same approach. To accomplish this, the tips of three needles are placed against the bodies of the L2, L3, and L4 vertebrae (see Fig. 192.4). Their positions must be confirmed radiographically. In the lateral view, the needle points should barely reach the anterior border of the vertebral bodies. In the anteroposterior view, the points should lie over them. After proper needle positioning has been ascertained, 3 mL of 6.5% to 7% phenol dissolved in water, or 3 mL of absolute alcohol, is injected through each needle.

Experience with phenol lumbar sympathectomy is limited in the United States but is increasing. Long-term results have not been reported. The clinical impressions are that this approach produces a less complete and less durable effect than surgical sympathectomy. Chemical sympathectomy must not be taken lightly, because phenol or alcohol injections can cause significant inflammation and scarring, making subsequent surgical sympathectomy, if needed, difficult or unsafe.

Open Technique

The open technique for lumbar sympathectomy is illustrated in Fig. 192.5.

Laparoscopic Technique

The technique of laparoscopic lumbar sympathectomy has been described by several authorities (Figs. 192.6 and 192.7).[72,73] A 12- to 15-mm incision is made midway between the iliac crest and the costal margin at the anterior axillary line. This is carried down through the external and internal oblique muscles, which are separated along their respective fibers to reach the retroperitoneal space. Using blunt dissection, the areolar fatty tissue is dissected while the peritoneal sac is gently pushed forward, which creates a safe space for insertion of the distention balloon system into the retroperitoneum. The balloon is inflated under direct vision via a 30-degree scope introduced into the balloon trocar. A Hasson trocar is introduced into the space created and secured with two sutures to the fascia to avoid gas leakage. The space created is insufflated with carbon dioxide to a pressure of 10 to 12 mm Hg. Two or three additional 5-mm ports are inserted under direct vision into the retroperitoneal space along a line 2 to 3 cm posterior to the first trocar, at the mid and posterior axillary lines.

Decompression of the peritoneal cavity can also be accomplished using a Veres needle, which equalizes pressures. The surgeon and assistant should stand in front of the patient so they can clearly identify the peritoneal sac, which is pushed backward and medially, and the psoas muscle, which is in front and upward. The gonadal vessels and ureters should be clearly identified. The genitofemoral nerve is visualized descending obliquely along the psoas muscle. Two instruments are used for dissection, traction, clipping, and cutting, and a third instrument is sometimes used for retraction of the psoas muscle and for suction, if needed. The sympathetic chain is identified along the inner margin of the psoas muscle, and small communicating rami and blood vessels are divided with cautery, clips, and endoscissors. The sympathetic chain is then transected between clips at the level of L2 and L4. The retroperitoneal space is deflated, the trocars are removed, the fascia at

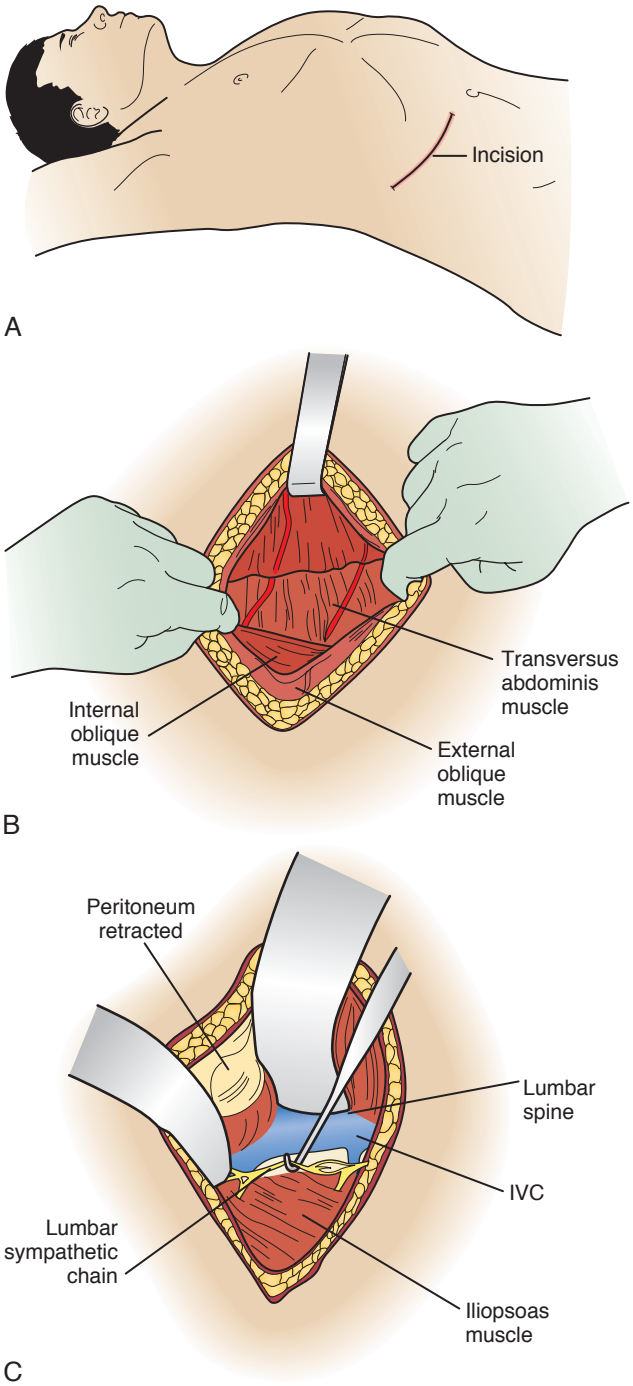

Figure 192.5 Open technique for lumbar sympathectomy. (A) Incision site. (B) The external oblique, internal oblique, and transversus abdominis muscles have been split and retracted. (C) The retracted peritoneum and position of the lumbar sympathetic chain. *IVC*, Inferior vena cava.

the large port site is sutured, and the skin incisions are closed.[72,73]

Results of Sympathectomy/Complex Regional Pain Syndrome

In Thompson's 1979 series, 82 patients with upper and lower extremity causalgia were treated with sympathectomy, and 93% had excellent or good pain relief.[21] Olcott and associates[71] reported 91% good to excellent results in 35 patients (17 upper extremity and 18 lower extremity). Some form of postsympathectomy neuralgia occurred in 4 (23%) of the upper extremity cases and in 12 (67%) of the lower extremity cases. In all instances, the neuralgia resolved spontaneously.

Mockus and coworkers reported 97% pain relief in 31 patients, which was sustained in 94%.[70] In nine patients with upper extremity causalgia, 12 dorsal sympathectomies were performed; in 22 patients with lower extremity causalgia, 23 lumbar sympathectomies were performed. In the nine patients who had dorsal sympathectomies, all nine (100%) had early pain relief, and eight patients (89%) had late pain relief. Of the 22 patients who underwent lumbar

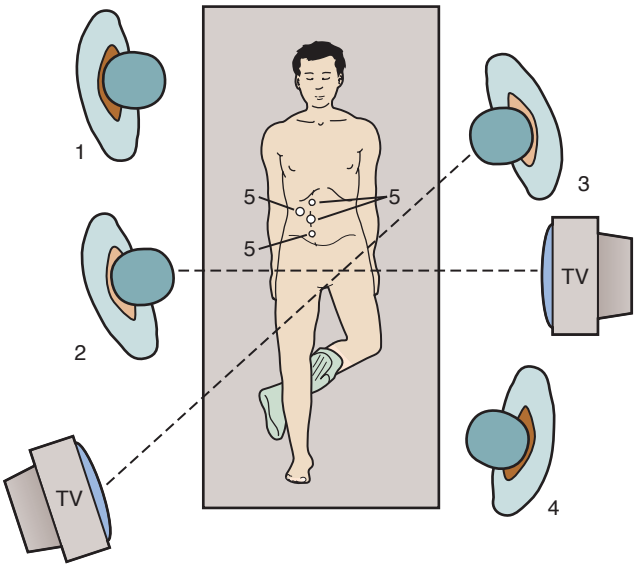

Figure 192.6 Diagram showing the positions of the camera operator *(1)*, surgeon *(2)*, assistant *(3)*, scrub nurse *(4)*, and port placements *(5)* for laparoscopic lumbar sympathectomy.

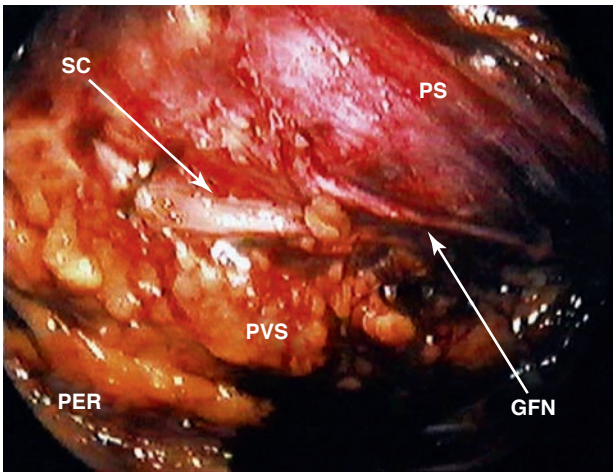

Figure 192.7 Retroperitoneoscopic view of the operative field. *GFN*, Genitofemoral nerve; *PER*, peritoneum; *PS*, psoas muscle; *PVS*, prevertebral space; *SC*, sympathetic chain. (From Beglaibter N, Berlatzky Y, Zamir O, et al. Retroperitoneoscopic lumbar sympathectomy. *J Vasc Surg*. 2002;35:815-817.)

sympathectomies, 21 patients (95%) had early and late pain relief. In a similar, more recent series of 28 patients, my colleagues and I reported 95% long-term success in patients who had experienced an excellent response to sympathetic blockade.[40]

An interesting subgroup of patients was identified in two of the aforementioned reports.[40,72] In the first series, patients with causalgia persisting after disk surgery enjoyed pain relief following sympathectomy equal to that in other patients.

Bandyk and associates reported sympathectomy results in 73 patients with CRPS type I (46 were video-assisted thoracoscopic and 37 were surgical lumbar sympathectomies).[58] At 3 months after sympathectomy, 90% of patients experienced a more than 50% reduction in pain, with pain severity scores decreasing from a mean of 8.7 before surgery to 3.4 after surgery. Overall, patient satisfaction was 77% and was not significantly influenced by patient age, CRPS duration, or extremity involvement (84% lumbar, 72% cervicodorsal).

Hassantash and colleagues reviewed 110 articles containing 1528 cases of causalgia.[10] Response to sympathetic blockades was noted in 88%, and 94% of patients undergoing sympathectomy were cured. However, in a recent Cochrane systematic review of the literature, Cepeda and associates analyzed patients who obtained at least 50% pain relief shortly after sympathetic blockade (30 minutes to 2 hours) and those with pain relief at 48 hours or longer after blockade.[61] They concluded that it was not possible to determine the effect of sympathetic blockade on long-term pain relief because the studies evaluated different outcomes.

Complications

Complications may include injury to the genitofemoral nerve, ureter, lumbar veins, aorta, and inferior vena cava. The most common complication is postsympathectomy neuralgia, which occurs in up to 50% of patients from 5 to 20 days after sympathectomy.[29,72,73] The cause is still speculative. The pain is characterized as an annoying "ache" in the anterolateral thigh region that is worse at night and is unaffected by activity or level of cutaneous stimulation. The discomfort responds to moderate analgesics and spontaneously remits within 8 to 12 weeks after onset.

Retrograde ejaculation can occur in 25% to 50% of male patients undergoing bilateral L1 sympathetic ganglionectomy.[74] This complication rarely occurs after unilateral ganglionectomy, especially when the surgeon takes care to preserve the first lumbar ganglion. Although potency should not be affected, many experienced surgeons insist that such derangements in sexual function do occur in men. Careful preoperative questioning about sexual function is important to evaluate any changes reported after lumbar sympathectomy.

Summary of Treatment Guidelines

The following are the generally accepted guidelines for the treatment of patients with CRPS type I:

Stage 1 (0 to 3 months): Physical therapy with or without TENS is usually useful. A local nerve or sympathetic blockade may be necessary for patients who experience severe pain and are unable to undergo physical therapy. If these measures fail, a course of steroid therapy should be given.

Stage 2 (3 to 6 months): Physical therapy, TENS, and steroid therapy should be combined. Sympathetic blockade and surgical sympathectomy should be considered if these measures fail.

Stage 3 (beyond 6 months): Steroid therapy or sympathetic blockade and surgical sympathectomy should be considered but may be unsuccessful. Neuromodulation (spinal cord stimulation) may be used. Manipulation of joint contractures under general anesthesia, antidepressants, and vocational guidance may be used.

OVERALL RESULTS OF TREATMENT

Most studies indicate that patients with early diagnosis and treatment (within 6 to 12 months) have an overall good outcome.[40,58,62,71] Most authorities also agree that spontaneous resolution can occur if CRPS is diagnosed and managed early.[40,58,62,71]

Failure to promptly recognize and treat CRPS type I results in irreversible changes, including wasting of skin and muscles, fixed joint contractures,[75] and severe demineralization of bone. It is generally believed that initiating treatment in the early stage carries a better prognosis. Patients who are diagnosed later are more refractory to treatment.[40,58,61] In patients with CRPS, restricted movement of the knee joint is very common. Patella baja (an abnormally low position of the patella) and changes in the mechanics of the tibiofemoral joint may occur, leading to chronic degeneration.[76]

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Bandyk DF, Johnson BL, Kirkpatrick AF, Novotney ML, Back MR, Schmacht DC. Surgical sympathectomy for reflex sympathetic dystrophy syndromes. *J Vasc Surg*. 2002;35:269–277.

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Beglaibter N, Berlatzky Y, Zamir O, Spira RM, Freund HR. Retroperitoneoscopic lumbar sympathectomy. *J Vasc Surg*. 2002;35:815–817.

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193 CHAPTER

Current Role of Sympathectomy (Upper and Lower)

NELSON WOLOSKER and PAULO KAUFFMAN

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Abstract

In this chapter, the authors present the anatomy and physiology of the sympathetic nervous system, as well as the pathophysiology of diseases due to its dysfunction, such as hyperhidrosis, long QT syndrome, Raynaud's syndrome and causalgia. The evolution of the technique of thoracic and lumbar sympathectomy, its difficulties and complications are described. Finally, the surgical indications for sympathectomy as well as its outcomes for each of these diseases is detailed. Sympathectomy is a procedure still widely used in clinical practice, despite the appearance of other therapeutic options for these diseases. It is important that the vascular surgeon is aware of which diseases and which type of patient sympathectomy is still well indicated, as well as the technical details that will lead to the best clinical results.

Keywords

sympathectomy
hyperhidrosis
Complex Regional Pain Syndrome
Long QT syndrome
Raynaud Syndrome

The effects resulting from the blockade of preganglionic and postganglionic neurons were first described in the late 19th century by Langley,[1] and several reports in that era described sympathectomy to treat epilepsy, goiter, and angina pectoris.[1-5] The first to use cervical sympathectomy to treat a patient with hyperhidrosis was Kotzareff in 1920.[6] In 1924, Hunter tried to use sympathectomy to reduce muscle tonus in patients with spastic paralysis; although this intervention did not show any beneficial effect on this condition, he observed increased in circulation in denervated limbs.[7] The first intervention in human lumbar sympathetic chain ganglia was performed by Diez to treat a patient with thromboangiitis obliterans (TAO). In 1924, Diez reported 100% success in treating 150 cases of upper limb TAO.[8] This led to the use of this intervention in treating Raynaud disease and other types of vasospastic disease. There was then a technical evolution in open surgery involving different surgical approaches to resect the sympathetic ganglia: supraclavicular (cervical),[9] axillary transthoracic,[10] dorsal (posterior),[11] dorsal midline,[12] and anterior transthoracic.[13] Leriche (1924) performed the same surgical operation to treat Raynaud disease. Better results than in TAO were observed with sympathectomy for spastic conditions.[14] By the end of the 1930s, the main indications for cervicothoracic sympathectomy had started to be delineated: hyperhidrosis, TAO, and vasospastic conditions. Until the 1960s, due to a lack of revascularization techniques, lumbar sympathectomy was widely used to treat lower limb peripheral artery diseases.

After the development of the thoracoscope, introduced by Jacobaeus in 1910,[15] Hughes in 1942 performed the first thoracoscopic sympathectomy.[16] Kux, in 1953, was the first to publish a large experience with this method.[17] However, despite the good results, for unknown reasons this technique did not achieve international acceptance for almost 30 years. In the 1980s, the endoscopic technique was used to perform sympathetic denervation in the upper limbs by a few groups of surgeons.[18] In the 1990s, advances in optical systems and instruments for thoracoscopic surgery made it possible to use video-assisted thoracoscopy to perform sympathectomy.[19] The low morbidity, good cosmetic results, decreased incidence of Horner syndrome, and short hospital stay prompted patients with hyperhidrosis to ask their physicians to help them by using video-assisted thoracoscopic sympathectomy (VATS).[20] The outcomes of VATS have been positive and VATS surgery is being increasingly performed. During the last 15 years, thousands of operations have been reported, which has led to technical improvements and better results.

ANATOMY

Sympathetic Ganglia

The motor sympathetic route is formed by three neurons (Fig. 193.1). The cell body of the first neuron is located in the sudomotor and vasomotor centers, mainly in the hypothalamus. Its axon projects along the dorsal longitudinal and spinovestibular fascicles to the cell body of the second neuron (preganglionic neuron), which is located in the intermediolateral nucleus of the spinal gray matter, between the first thoracic and second lumbar vertebrae. Its axon (the preganglionic fiber) exits the medulla through the ventral root of the spinal nerves and, through the white communicating branch, projects to the paravertebral ganglion, where it forms a synapse with the cell body of the third neuron, the postganglionic neuron. Its axon (the postganglionic fiber) leaves the sympathetic chain through the gray communicating branch into the spinal nerve and is distributed peripherally. The ganglia are also interconnected longitudinally by axons from preganglionic neurons that run rostrally or caudad to the neighboring ganglia of the chains.

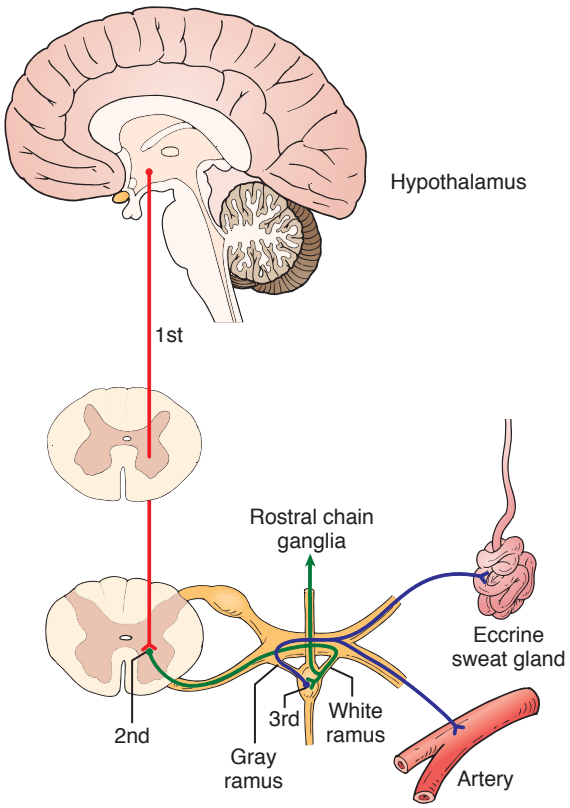

Figure 193.1 The motor sympathetic route. The cell body of the first neuron is located in the sudomotor and vasomotor centers, the second neuron (preganglionic neuron) is located in the intermediolateral nucleus of the spinal gray matter, and the third neuron (postganglionic neuron) is located in the paravertebral ganglia.

As in the somatic nervous system, the axon of the preganglionic neuron exits the segment in which its soma is located. There is one sympathetic paravertebral ganglion (G) for each spinal segment. The sympathetic fiber that originates from the ganglion innervates the area of the spinal nerve corresponding to that segment. Thus the second ganglion (G2) supplies sympathetic innervations for the structures of the second dermatome (D2).

In the neck, there are normally three ganglia in the sympathetic chain. The superior cervical ganglion results from the fusion of the first four sympathetic cervical ganglia; it is located at the level of the transverse process of the second and third cervical vertebrae and supplies the head and neck. The middle cervical ganglion is located at the level of the sixth cervical

vertebra. The inferior cervical ganglion is generally fused with the first thoracic ganglion (G1) to form the cervicothoracic ganglion (stellate ganglion), which is located anterior to the head of the first rib and covered by the pleura.

In the thoracic region, the ganglia of the sympathetic chain are positioned anteriorly to the transverse processes of the thoracic vertebrae and are covered by the parietal pleura. They are fewer in number than the spinal thoracic nerves because of the fusion of the first thoracic ganglion with the inferior cervical ganglion, fusion of the last thoracic ganglion with the first lumbar ganglion, and fusion of the thoracic ganglia with each other.

The greater, lesser, and least splanchnic nerves are formed by preganglionic fibers originating from the 5th to 12th thoracic medullary segments. They cross the corresponding sympathetic ganglia without forming synapses with them and end in the celiac, aorticorenal, and superior and inferior mesenteric ganglia. The major splanchnic nerve plays a particularly important role in visceral pain because of the large numbers of visceral afferent fibers it contains. Hence splanchnicectomy may be employed to treat unmanageable visceral pain, particularly in pancreatic diseases (cancer and pancreatitis).[21] In the past, thoracolumbar sympathectomies were performed to treat hypertension, a technique currently abandoned with the advent of modern antihypertensive drugs.[22]

Sympathetic Innervation of the Upper Limbs

The preganglionic fibers responsible for the innervation of the upper limbs originate from the second to eighth thoracic medullary segments, most of them below the fourth segment. The fibers enter the paravertebral sympathetic chain through the white communicating branches of the corresponding ganglia and have an ascending pathway in which a synapse is formed with cells located in the second thoracic ganglion, the stellate ganglion, and probably the middle cervical ganglion. It is of surgical interest that no preganglionic fibers enter the sympathetic chain above the first thoracic ganglion, which participates in innervation of the limb in only 10% of the cases.

In most patients, the thoracic sympathetic trunk is located in the middle of the intercostal space, on the bottom edge of the top rib or the top edge of the bottom rib.[23-25] Therefore when we section the sympathetic chain on two consecutive ribs, there is a high probability that we are making the sympathetic ganglion between them dysfunctional.[26]

Several anatomic landmarks have been used to determine the exact location of sympathetic interruption, including the thoracic ganglion (G), the vertebral level, and the intercostal space. More recently, a rib-oriented nomenclature has been suggested that refers to the rib level (R) instead of the vertebral level for sympathetic interruption.[26] This decision was based on too many patients having mediastinal fat that can obscure clear identification of the specific ganglia and because there are many anatomic variations in the ganglion anatomy. Information about the technique used for ganglionic interruption should also be included in the nomenclature, stating whether clipping, cauterization, or segment removal is performed. For this chapter, we use the ganglionic level as anatomic reference.

Sympathetic Innervation of the Lower Limbs

Sympathetic preganglionic fibers responsible for the innervation of the lower limbs originate from the 12th thoracic medullary segment to the 2nd lumbar segment and reach the sympathetic chain by white rami comunicantes, all having descendant paths.

Postganglionic fibers originate in cells of the lumbar and sacral ganglia. The fibers destined for the lumbar plexus come from the first three lumbar ganglia and those destined for the sacral plexus come from the fourth lumbar nerve and sacral ganglia. Therefore all postganglionic fibers that follow the sciatic nerve originate on ganglia located under the third lumbar nerve, since the greater number of synapses occur on fourth lumbar nerve.

It is known that there are no rami comunicantes under the second lumbar ganglion; therefore, the removal of the second and third lumbar sympathetic ganglia interrupts all preganglionic fibers to the sciatic nerve and consequently to the cutaneous territory located under the knee except the saphenous nerve territory, which originates from the lumbar plexus. To obtain thigh denervation it is necessary to remove the first lumbar ganglion. The removal of the fourth lumbar ganglion does not amplify the scope of denervation but interrupts the many postganglionic fibers destined for the sciatic nerve.

Sympathetic Innervation of the Ocular Structures

The sympathetic preganglionic fibers controlling the smooth muscles of the eye are rostral, from anterior roots of G1 and G2. The fibers enter the sympathetic chain by the corresponding ganglia but do not form synapses. The synapses are subsequently formed when they ascend to the superior cervical ganglion. The postganglionic fibers head toward the ocular-pupillary apparatus through the carotid plexus. Consequently resection of the stellate ganglion causes Horner syndrome (enophthalmos, myosis, and palpebral ptosis).

Sympathetic Innervation of the Cephalic Segment

Sympathetic innervation of the head and neck originates from the first to fifth thoracic medullary segments. The preganglionic fibers ascend the sympathetic chain and form synapses with the first thoracic ganglion and the inferior cervical ganglion. Most of the postganglionic fibers responsible for innervation of the face originate from G2, which implies that craniofacial sweating diminishes through G2 ablation.

Sympathetic Innervation of the Heart

Sympathetic innervation of the heart is supplied from the higher three heart nerves (superior, medial, and inferior) arising from the three cervical ganglia and from the sixth or seventh thoracic paravertebral ganglia. Most fibers converge at the cardiac plexuses. These nerves are more abundant in the fourth and fifth thoracic segments than at higher levels.

PHYSIOLOGY

The sympathetic chain supplies the smooth muscles of the blood vessels through adrenergic fibers and the sweat glands through cholinergic fibers. The vascular system differs from other systems in its lack of antagonistic innervation between sympathetic and parasympathetic vasoconstrictor fibers; thus vasodilation results from a decrease in sympathetic activity.

The autonomic nervous system has a considerable influence on vessels with a more developed smooth muscle layer of the vessel wall in relation to its caliber. Hence arterioles are most affected by sympathetic activity and the autonomic nervous system has great influence on skin circulation but is of little importance in great vessels and muscular arteries.

Eccrine sweat glands, which are responsible for hyperhidrosis, are innervated by the nonmyelinic C fibers of the sympathetic nerves, and acetylcholine is the chemical mediator. Local or systemic administration of cholinergic agents induces sweating, whereas the use of atropine blocks it. Although sweating in the palmar and plantar regions may result from emotional stimuli and abundant sweating is observed under clinical conditions in which catecholamines are released by the adrenal glands, administration of adrenergic agents by any route does not stimulate the sweat glands.[15] Blocking of preganglionic fibers does not stop sweating caused by stimulation of the postganglionic fibers, nor does the local administration of cholinergic agents. However, if postganglionic fibers are cut, such secretion will no longer occur through local stimulation by any pharmacologic agent. This is an exception to Cannon's law (which states that when one unit in a series of efferent neurons is destroyed, increased irritability to chemical agents is developed in the structure that has been isolated and the effect is greater in the part that is directly denervated). Heating of the skin may cause sweating in this situation through an unknown mechanism.

Different neural centers control the various types of sweat glands in a reflex manner. Thus emotional sweating is controlled by a cortical center, thermal sudoresis by a hypothalamic center, gustatory sudoresis by medullary nuclei, and spinal sweating by cells of the intermediate-lateral region of the spinal cord.

The nerve centers and pathways that control emotion-induced sweating are not fully known, although it seems that they are located in the frontal lobe. Emotion-induced stimuli can increase sweating, especially in the palmar and plantar regions.

Under baseline conditions, few impulses pass to the sweat glands, and nonsensory sweating (perspiration) is always present, partly because of the activity of the glands and partly because of loss of water through the epidermis.

INDICATIONS FOR CERVICOTHORACIC SYMPATHECTOMY

The current indications for cervicothoracic sympathectomy are limited to essential hyperhidrosis, selected cases of critical hand ischemia, complex regional pain syndrome (CRPS),[27] clinically refractory long QT syndrome,[28] and Raynaud syndrome.[29]

INDICATIONS FOR LUMBAR SYMPATHECTOMY

The current indications for lumbar sympathectomy are limited to essential plantar hyperhidrosis and selected cases of chronic critical ischemia of the legs with no conditions or revascularization. The few randomized trials that have been performed have not shown beneficial effects on amputation and mortality rates, improvement of rest pain, or the healing of ischemic ulcers, including diabetic ulcers.[30,31] Other less frequent indications are selected cases of Raynaud syndrome and CRPS.[32]

Idiopathic Hyperhidrosis

Hyperhidrosis, the production of excessive quantities of sweat believed to be the result of stimulation of the sympathetic nervous system at the central level, is typically limited to the palms, soles, or axillae in a symmetric manner.[33] It may also affect the craniofacial segment. Hyperhidrosis may arise during childhood, but it is more intense during adolescence, a transitional period of life with potential psychological stress associated with triggers of hormonal and sexual maturation. It may persist into adulthood but decreases in intensity in some patients.[22] Hyperhidrosis affects approximately 3% of the population; in 13% to 57% of patients it can be associated with a family history of hyperhidrosis.[34] Climate is not an etiologic factor, but hot weather exacerbates sweating.[35]

Palmar hyperhidrosis generally takes on greater clinical significance than plantar or axillary hyperhidrosis because it creates significant problems within the educational, social, professional, and affective spheres, which can worsen any emotional issues that such patients may already have.[36-38]

Plantar hyperhidrosis is frequently associated with palmar or axillary hyperhidrosis and is worsened by the use of closed shoes, which hinder evaporation and favor skin maceration. The constant dampness provides conditions for malodorous fungal or bacterial infections.[39]

Axillary hyperhidrosis tends to appear at puberty, with the increased production of sexual hormones. Symptoms of axillary hyperhidrosis are disabling both professionally and socially for almost all patients who seek surgical treatment.[40] Likewise, craniofacial hyperhidrosis and facial rubor may cause social phobia.[41,42]

Nonsurgical treatment should initially be attempted in all cases of hyperhidrosis. If results are inferior to patient expectations, sympathectomy should be considered. Besides oxybutynin, other alternatives include botulinum toxin injection[43] and glycopyrrolate.[44]

Sympathectomy is indicated for patients who do not experience an improvement in quality of life despite appropriate nonoperative treatment and are willing to accept the risks involved in surgical treatment (mainly compensatory hyperhidrosis).[45]

Ischemia of the Hand

Selected patients with ischemic hand pain or finger ulcers, particularly those with TAO and distal arterial obstruction, may benefit from sympathectomy (see Chapter 138).[46-48] Cervicodorsal sympathectomy has been used selectively in cases of critical hand ischemia to improve cutaneous vasodilation, control ischemic rest pain and vasomotor phenomena, and support healing of the skin in patients unresponsive to conservative management. However, no randomized comparison with other treatments is available, and because the disease can be improved by smoking cessation, it is difficult to judge the benefit of sympathectomy from published studies.[49,50]

Complex Regional Pain Syndrome

CRPS, also known as causalgia, reflex sympathetic dystrophy (RSD), posttraumatic pain syndrome, shoulder-hand syndrome, and Sudeck atrophy, is a term that has been used since 1994. It describes a regional pain condition that often occurs after injury, is disproportionate to the inciting event, and is associated with signs of vasomotor dysfunction and sudomotor activity (see Chapter 192).

When CRPS is left untreated, hyperalgesia, allodynia, signs of vasomotor dysfunction, and edema can be seen initially. After 3 to 6 months, there is increased pain, and sensory dysfunction and motor or trophic changes (or both) develop (dystrophic stage). Finally the pain decreases, but there are still sensory disturbances (atrophic stage).[51,52] Sympathetic blockade with local anesthesia has been used to control pain in selected patients. If it is effective, this technique can be repeated, together with physical therapy to recover functionality of the limb.[53] Peridural or intrathecal infusions of anesthetic drugs can be used in selected patients who do not respond to conservative treatment. Because of proximity to receptor sites, the therapeutic effect of intrathecal drug application lasts longer and the rate of systemic side effects is reduced. However, there are catheter-related technical problems, such as catheter dislocation, obstruction, kinking, and disconnection or rupture, as well as drug-related side effects.[54]

Spinal cord stimulation is efficacious in CRPS type I (level B recommendation) that is resistant to medication or other treatments. High-frequency transcutaneous electrical nerve stimulation and repetitive transcranial magnetic stimulation are noninvasive and suitable as preliminary or add-on therapies and provide satisfactory pain relief to many patients, including those resistant to medication or other therapies.[55]

Chemical sympathectomy with phenol or alcohol seems to have at best a temporary effect limited to cutaneous allodynia. Because studies reported in the literature have only a few patients and poorly defined outcomes, well-designed studies on the effectiveness of the procedure are needed.[56,57]

Sympathectomy can be used in selected patients who do not respond to nonsurgical treatment or in those who have good but transient benefit from pharmacologic sympathetic blockade (see Chapter 192).[58]

Long QT Syndrome

Long QT syndrome is an idiopathic congenital disorder characterized by a lengthened QT interval on the electrocardiogram associated with a high incidence of severe tachyarrhythmia, syncope, and sudden death; it often occurs at a young age. There is no clinical or radiologic evidence of heart disease. Severe episodes typically occur during intense physical exercise or emotional crises, which leads to the supposition that the sympathetic nervous system plays an active part in the genesis of the problem. The mortality rate in untreated patients reaches as high as 78%. Beta blockers are effective in preventing such crises in 75% to 80% of the cases.[59] Sympathectomy is only potentially indicated in patients who, even with appropriate clinical treatment, continue to have syncopal crises (about 20%-25% of these patients).[60,61]

Raynaud Syndrome

Raynaud disease and phenomenon are characterized by episodic spasm of arterioles, usually in the digits, with intermittent pallor or cyanosis, precipitated by exposure to cold, emotional upset, or drugs (see Chapter 141). The treatment of Raynaud syndrome is essentially nonoperative. Sympathectomy has been used in rare patients who, despite adequate clinical treatment, continue to have severe symptoms or trophic lesions that heal with difficulty. However, it is difficult to judge the benefit because randomized trials have not been performed and the natural history is variable.

SURGICAL TECHNIQUES

Open Surgery for Cervicothoracic Sympathectomy

Until the 1990s and before VATS, open surgery was the "gold standard" for cervicodorsal sympathectomy. Several approaches are available for open surgery, each with its own advantages and disadvantages. There are three main approaches, the paravertebral, transthoracic, and supraclavicular routes. Today the open technique is indicated only when VATS cannot be accomplished for technical reasons or an associated open operation is being performed.

The paravertebral route, mainly used by neurosurgeons, offers wide exposure of the sympathetic chain. However, it involves extensive dissection and the sectioning of several muscle bunches and requires a long period of recovery.[62]

The transthoracic axillary approach has the advantages of superior exposure, easier access to the sympathetic chain for wide incisions, lower risk of Horner syndrome, and good cosmetic results. The main complication is postsympathetic neuralgia, which is long-lasting and extends the recovery time.[63]

The supraclavicular approach requires an extrapleural access and thus allows the procedure to be completed bilaterally in a single operation. The resulting scar becomes virtually invisible in a short time, convalescence is fast with little pain, hospital stay is short, and surgical complication rates are low. The

disadvantage is that the stellate ganglion is the point of reference for identifying the sympathetic chain, and its simple manipulation can result in Horner syndrome, although in most cases transitory.[64]

Video-Assisted Thoracoscopic Sympathectomy

At present, VATS is considered the gold standard for cervicothoracic sympathectomy. Several approaches (one port, two ports, three ports, four ports, lateral, dorsal) are available, each with its own advantages and disadvantages.[65,66] An easy and practical technique (two ports) is described in the following paragraphs.

Instrumentation

The basic equipment includes a 15-degree angled thoracoscope, video camera with monitor, DVD recorder, light source, video endoscopic instruments, electrocautery (harmonic or not), and nerve hook and vascular clips.

Anesthesia

The patient usually undergoes double-lumen endotracheal general anesthesia, which makes it possible to stop the patient's ventilation and consequently to collapse the lung on the side that will undergo surgery. When necessary, bronchoscopy is used to verify tube positioning. A double-lumen endotracheal tube is used in patients undergoing resection of the fourth ganglion of the thoracic sympathetic chain. When thermoablation is performed on the second or third ganglion, a single-lumen tube may be used in conjunction with adequate control over lung ventilation. Long-acting anesthetic agents are avoided to allow immediate extubation at the end of the procedure.

Positioning

The patient is placed in dorsal decubitus semiseated position with the trunk raised approximately 45 degrees. Two small pads are placed under the shoulders to create a space between the axillae and the surgical table and to bring the shoulders forward, thereby avoiding distention of the brachial plexus when the arms are positioned in 90 degrees of abduction on the arm rests. Another pad under the knees and a securing strap at the hip level allow the legs to be positioned comfortably and stabilize the patient on the surgical table when it is rotated laterally to bring the sites for surgery forward (right or left).

Technique

In cases of hyperhidrosis, which represent more than 95% of the cases and in which thermoablation of only the third or fourth sympathetic ganglion is performed, two mini-incisions about 1 cm in length are made. The first incision is made on the anterior axillary line at the level of the fourth or fifth intercostal space to introduce a video camera. The second incision at the second or third intercostal space on the medial axillary line is used to introduce the surgical instruments (electric or ultrasonic bistoury, scissors, dissecting forceps, retractable hook, and aspirator) into the pleural cavity (Fig. 193.2). In cases where the stellate ganglion must be resected, a third mini-incision is made anterior to the posterior axillary line to facilitate the dissection.

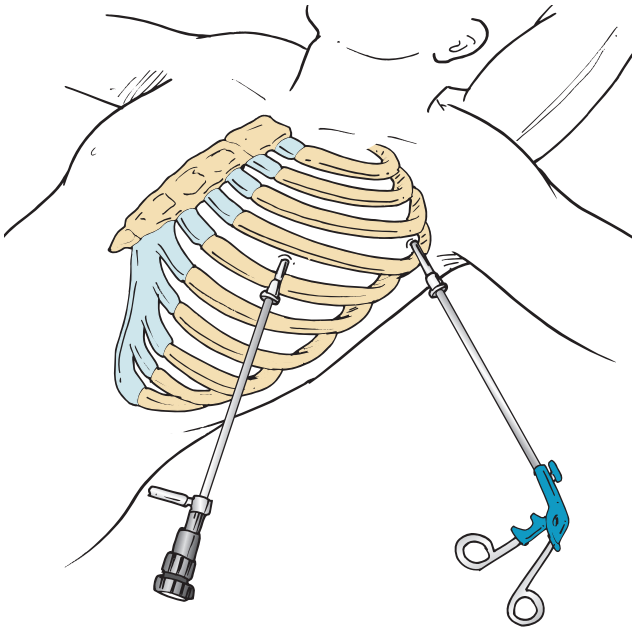

Figure 193.2 Port placement: one in the fourth or fifth intercostal space on the anterior axillary line and one in the medial axillary line in the second or third intercostal space.

Trocars 5.5 mm in diameter are introduced into all the incisions to keep the pathway open and protect the structures of the thoracic wall. Carbon dioxide insufflation into the pleural cavity has been used in some centers to improve surgical access. However, this procedure is not free of risk, and it may cause cardiovascular problems even when it is used at low pressure.[67] To avoid these complications, we have preferred to use open pneumothorax, which has proved to be sufficiently satisfactory.

The sympathetic chain is identified through the parietal pleura as a whitish, longitudinal, multinodular cord that forms a slight prominence in the lateroposterior region of the thoracic vertebrae, above the heads of the costal arches (Fig. 193.3). In elderly patients or individuals with a greater degree of fatty tissue, the sympathetic chain sometimes becomes difficult to distinguish. In such cases the chain is identified by touch with the endosurgical instruments (Fig. 193.4). The parietal pleura is sectioned above the chain and is also dissected by blunt separation. The communicating branches are coagulated and sectioned to the extent desired (Fig. 193.5). The chain is then sectioned above the costal arches and the segment isolated is cauterized (Fig. 193.6). Application of vascular clips to the main sympathetic trunk instead of thermoablation is an alternative.

After hemostasis is achieved, a 14- or 16-Fr aspiration probe is placed through the upper trocar and connected to a negative-pressure aspirator. The anesthetist is then asked to ventilate the collapsed lung until complete expansion has been achieved. This can be verified by direct viewing on the video monitor. The video camera and aspirating probe are then removed and the corresponding incision is sutured. Occlusive bandages are left on the surgical incisions for 24 hours. In the postanesthesia

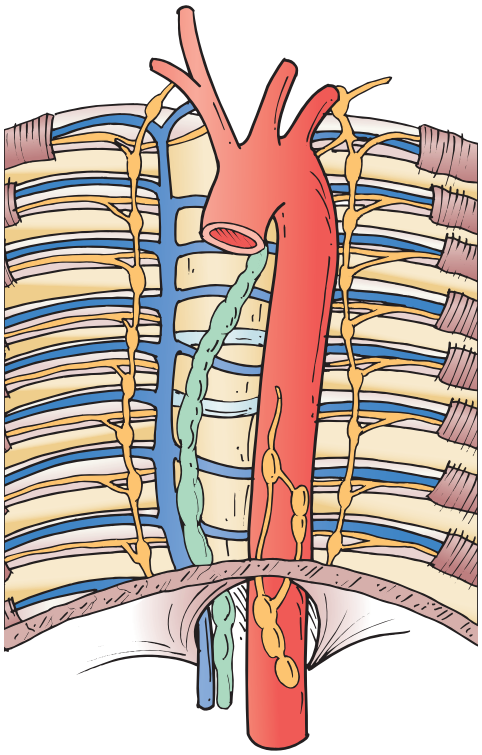

Figure 193.3 Sympathetic chain *(yellow)* coursing above the heads of the costal arches. The stellate ganglion is located anterior to the head of the first rib, the T2 ganglion is between the second and third ribs, the T3 ganglion is between the third and fourth ribs, and the T4 ganglion is between the fourth and fifth ribs.

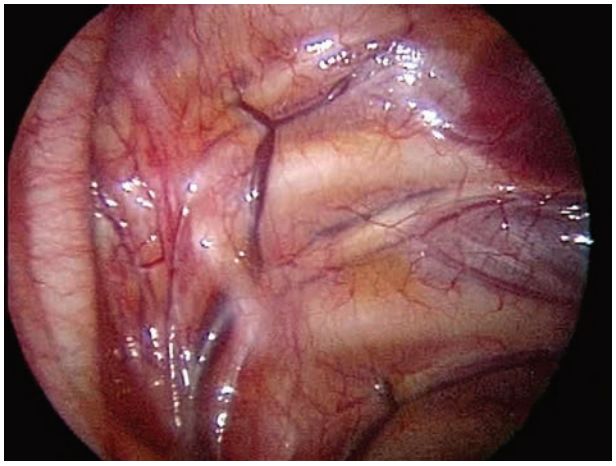

Figure 193.4 Thoracoscopic normal anatomy of the sympathetic chain *(arrow)*.

recovery room, chest radiography is requested to confirm and inspect expansion of the lung and check for possible residual pneumothorax.

Lumbar Sympathectomy

Open surgery performed through anterolateral extraperitoneal access provides a wide surgical field and allows for the execution of bilateral surgery with no need to change the patient's position on the surgical bed. As an alternative to conventional surgery,

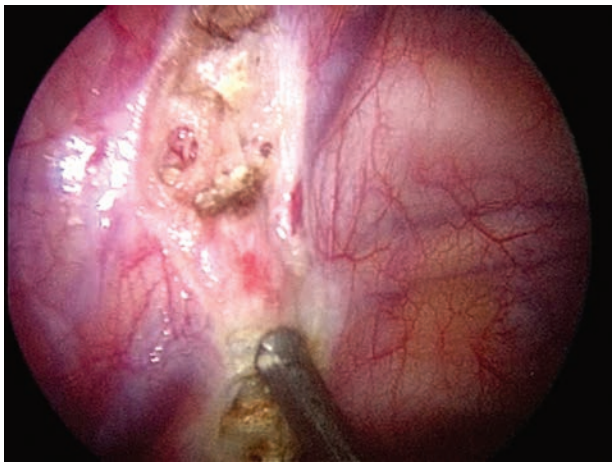

Figure 193.5 Sympathetic chain sectioned above and below the ganglia.

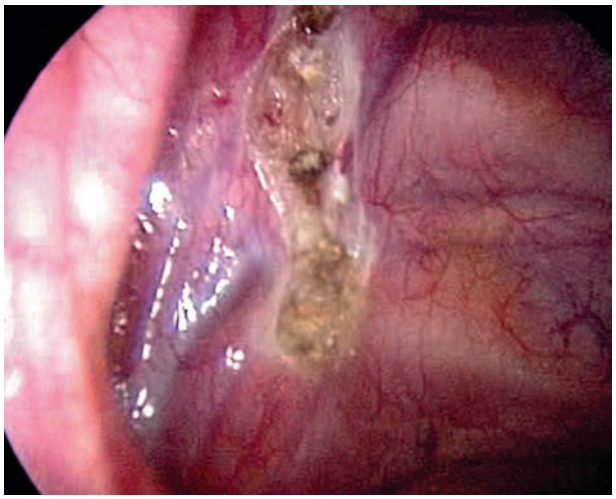

Figure 193.6 Sympathetic chain cauterized.

some services perform the sympathetic denervation through retroperitonioscopy, reporting minimal morbidity, short convalescence time, and similar effectiveness to open surgery.[68,69]

Chemical sympathectomy which consists in blocking the sympathetic nerve with phenol, has increased in application since Reid et al. in 1970 showed the procedure to be safe and effective in a large number of patients.[70] It is a fairly long-lasting method and as an advantage has the possibility to be repeated whenever necessary. Postsympathectomy neuralgia occurred in 9% of the cases in Reid et al.'s experience, a complication that is relatively frequent with surgical sympathectomy.

Technical Difficulties in Video-Assisted Thoracoscopic Sympathectomy

Pleural adhesions are found fairly frequently during thoracoscopy (3%-7%). Firm and extensive pleural adhesions caused by previous pleuropulmonary diseases may make it impossible to perform VATS. In such cases open surgery is the best option. Unfortunately such adhesions cannot be diagnosed preoperatively by routine chest radiography.[71]

The presence of an azygos lobe is an infrequent anatomic variation that involves an accessory pulmonary lobe at the apex of the lung, making it difficult or sometimes impossible to carry out VATS, particularly when the surgeon is not prepared for this contingency.[72] Preoperative chest radiography may identify this anomaly.[73]

Technical Alternatives for Video-Assisted Thoracoscopic Sympathectomy

Alternatives to ganglia resection are interruption of the chain without the removal of ganglia (sympathicotomy)[74] and blockade by endoscopic clipping,[75-77] a technique that can be reversed, within 10 days after intervention, by removal of the clips.[78,79] In both techniques, transmission of sympathetic impulses from the lower sympathetic ganglia through the stellate ganglia to the limbs is interrupted.

Sympathicotomy and thoracoscopic clipping are also acceptable. Early results are comparable to those of sympathectomy, but long-term results are unknown. Sympathicotomy is a good alternative when the anatomy is not appropriate for sympathectomy (large veins over the sympathetic chain). Clipping of the trunk has the potential benefit of unclipping (reverse operation) in case of intolerable compensatory hyperhidrosis. Large-scale prospective studies with long-term follow-up are needed in both techniques.

New alternatives based on emerging technology have been introduced for performing sympathectomy using an embryonic natural orifice: the transumbilical endoscopic surgery with a flexible endoscope. This novel procedure can reduce postoperative pain and afford even better cosmetic benefits by hiding the surgical incision in the umbilicus. It seems to be a safe and an efficacious alternative to the conventional approach.[80-82]

Contraindications to Video-Assisted Thoracoscopic Sympathectomy

The contraindications to VATS are lung infections that evolve with pleural effusion and require puncture or drainage, lung diseases that cause dense pleural adhesions (such as tuberculosis), previous thoracic surgery, thoracic radiotherapy, sinus bradycardia, and clinical conditions in which endotracheal anesthesia is contraindicated.[83] Obesity has also been considered a contraindication to VATS; even though overweight patients have a high degree of satisfaction with the operation, it may be difficult to identify the sympathetic chain when it is covered by a greater layer of adipose tissue. In addition, such patients have a higher risk of severe compensatory hyperhidrosis.[84]

TARGET GANGLIA

The extent of thermoablation, resection, or interruption of the sympathetic chain is an important subject in dealing with thoracic sympathectomy (Table 193.1).[85,86]

With improvements in surgical techniques for the treatment of hyperhidrosis, therapeutic success has been achieved even when sympathectomy is performed at levels distant from the stellate ganglion (G3 and G4 ganglia). This has corresponded to a significant reduction in the complications that were most feared before the advent of VATS: Horner syndrome and compensatory hyperhidrosis.

TABLE 193.1 Denervation Levels for Different Indications

Disease	Denervation Level
Palmar hyperhidrosis	G4 or G3
Axillary hyperhidrosis	G4
Craniofacial hyperhidrosis	G2
Facial rubor	G2
Plantar	L2 and L3
Complex regional pain syndrome	Stellate ganglion, G2, and G3
Vascular disease	Stellate ganglion, G2, and G3
Raynaud syndrome	Stellate ganglion, G2, and G3
Long QT syndrome	Left side, from the stellate ganglion to G4 or G5

Lumbar sympathectomy is a predominantly preganglionic type of surgery, since the fourth ganglion is not manipulated, because the majority of the pre- and postganglionic fibers synapse are in this level. It is generally agreed that resection of the first three lumbar ganglia produces denervation of the whole corresponding lower limb. However, although some have advocated removal of the second and third lumbar ganglia only, this approach limits the sympathetic denervation to the territory located under the knee, although the clinical results are similar to those obtained by longer resection. Further, saving of the first lumbar sympathetic chain, at least one side, prevents interference with the normal mechanisms of male ejaculation. In practice we found that the arrangement of the ganglia in this chain varied considerably. There are cases where the first three ganglia are perfectly identified and others where there are only two ganglia separated by a long chain segment. There have also been a few cases where there was only one identifiable ganglion, giving the impression that all of them had merged into one. Our approach has been to remove the chain from the crus of diaphragm to the level of the fourth lumbar vertebra, saving the first ganglion, which usually is included in diaphragmatic pillar fibers.[87,88]

Palmar Hyperhidrosis

In cases of palmar hyperhidrosis, physicians initially used to resect G2 and G3 ganglia with good results (anhidrosis); however, it was a difficult procedure associated with a high incidence of Horner syndrome and severe compensatory hyperhidrosis.[89] Subsequently, on the basis of the principle that interruption of the transmission of sympathetic impulses from the lower sympathetic ganglia through stellate ganglia resolves hyperhidrosis, thermoablation of G2 accelerated this procedure and gave similar results. However, intervention on the G2 ganglion

resulted in a high rate of compensatory hyperhidrosis (in more than 75% of the cases) because an extensive area is denervated, including the cephalic, cervical, and upper limb segments. This collateral effect has been responsible for dissatisfaction in 4% of patients.[90] To minimize this problem, thermoablation of G2 was initially replaced by thermoablation of G3 and currently G4, which has led to similar results of palmar anhidrosis but considerably decreased compensatory hyperhidrosis,[91] probably due to preservation of sympathetic tonus in the cephalic segment.

Patients who undergo G3 ablation usually have totally dry hands and need to use skin moisturizers, whereas patients who undergo G4 ablation have continued low levels of sweating (not hyperhidrosis but a little greater than normal physiologic levels), which is considered to be a therapeutic success.[92-94]

Axillary Hyperhidrosis

Resection of the second to fourth ganglia of the thoracic sympathetic chain was the first step in treating axillary hyperhidrosis.[95] It was replaced by thermoablation on G3 and G4[96] and then by single G4 thermoablation,[97] which results in excellent therapeutic success (anhidrosis), less severe compensatory hyperhidrosis, and a higher rate of satisfaction.

Craniofacial Hyperhidrosis or Facial Rubor

Sympathetic denervation of the face and head can be obtained by thermoablation of the G2 ganglion.[41] Sympathetic blockade of G3 with the use of clips is an alternative for these patients.[98]

Complex Regional Pain Syndrome, Vascular Disease, and Raynaud Syndrome

Sympathetic denervation of the upper limb must be as complete as possible if sympathectomy is used for these conditions. Hence the stellate ganglion, G2, and G3 should be included.[89] To avoid incomplete denervation of the limb, the communicating branches of T1 and the nerve of Kuntz have to be ablated as well.[99] This approach is always associated with the presence of Horner syndrome.

Long QT Syndrome

Sympathectomy is performed only on the left side, from the stellate ganglion to G4 or G5.[60,100,101]

RESULTS

Hyperhidrosis

The success rate in the abolition of hyperhidrosis (i.e., anhidrosis) is very high and ranges from 96% to 100% for palmar hyperhidrosis,[102,103] from 63% to 100% for axillary hyperhidrosis,[104] and from 87% to 100% for craniofacial hyperhidrosis.[105] In addition, quality-of-life analyses have demonstrated an "overall satisfaction" of around 90% 5 years after sympathectomy.[45,106,107]

Although it is nonspecific for the treatment of plantar hyperhidrosis, which is usually associated with palmar or axillary hyperhidrosis, VATS was shown to immediately reduce plantar sweating in more than 80% of patients; however, there is a reduction to smaller degrees of improvement (60%) during the 1-year period after surgery.[108]

There is no convincing anatomic-physiologic explanation for this improvement. Perhaps correction of palmar hyperhidrosis by the intervention leads to a greater emotional equilibrium, thereby lowering sympathetic nervous stimuli to the feet.

Recurrence of palmar or axillary hyperhidrosis has been reported in 1% to 13% of surgically treated patients and in 2% of the patients with craniofacial hyperhidrosis.[105] The main cause of the recurrence is technical failure. Reoperation is usually successful. Weak adhesions are found in these situations, but they do not cause significant difficulties for the procedure.

Transitory occurrence of sweating of variable intensity in the denervated segment during the first postoperative week (third to fifth postoperative days) is observed in 13% of the cases. It lasts for a maximum of 36 hours and is caused by the release of neurotransmitter at the end of the sympathetic postganglionic fibers as they degenerate.[109]

One adverse effect from sympathectomy is gustatory sudoresis. Its incidence is variable (ranging from 6% to 32%), and it is probably related to eating habits in different regions. In most cases it is of light to moderate intensity and does not interfere with quality of life.[110]

Compensatory hyperhidrosis consists of an increase in the severity of sweating in locations that were previously normal. This is the most frequent and most feared side effect of thoracic sympathectomy. Compensatory hyperhidrosis is present in almost all patients, and when severe (in 1%-4% of the cases), it is considered the main cause of patient dissatisfaction.[111] It occurs mainly on the abdomen, back, and thighs and becomes more uncomfortable on hot days, during physical exercise, and in hot work environments.[112] It may diminish over time, or the patient may learn to live with it.[113]

Compensatory hyperhidrosis has a high correlation with the level and extent of resection.[114] The higher the interruption or resection of the sympathetic chain, the more afferent fibers responsible for inhibition of sweating would be harmed, thereby causing a considerable increase in the quantity and intensity of compensatory hyperhidrosis. By performing thermoablation only in G4 ganglia for palmar or axillary hyperhidrosis, there is a significant decrease in the quantity and intensity of compensatory hyperhidrosis,[62] which leads to an improvement in quality of life. Another risk factor for compensatory hyperhidrosis is a high body mass index (BMI); this is why patients with a BMI greater than 25 should not be operated on. Because of the importance of compensatory hyperhidrosis, it is necessary to attempt medical treatment with anticholinergic drugs first and to operate only on those individuals who do not obtain significant results.[115] Furthermore, it is necessary to alert all patients with hyperhidrosis to this risk before they choose sympathetic denervation or an alternative technique and that treatment with anticholinergics is the best alternative for compensatory hyperhidrosis, although reasonable results are

achieved in only half of these patients.[116,117] The rate of compensatory hyperhidrosis and its severity are tolerated better by children, and their postoperative satisfaction is higher than that of adolescents and adults. Therefore VATS is indicated for children as early as possible.[118]

Another alternative that has been used in attempts to reduce the occurrence and intensity of compensatory hyperhidrosis is utilization of the two-stage unilateral or even the unilateral sympathectomy for the treatment of hyperhidrosis. With these procedures, the incidence and intensity of hyperhidrosis appears to be lower.[119–122]

Patients with poorer quality-of-life evaluations before surgery presented higher levels of improvement after sympathectomy. VATS is therefore considered an efficient therapeutic alternative for patients with initially poor quality-of-life evaluations.[123]

Vascular Diseases

Sympathectomy is seldom used at present to treat vascular insufficiency because of the availability of bypass and interventional procedures. When sympathectomy is used, it is performed for digital and palmar obstructions associated with necrotic lesions of the fingers.[124] In selected patients, sympathectomy has been reported to decrease pain and to assist in clinical treatment.[125,126]

Complex Regional Pain Syndrome

VATS is highly effective in reversing symptoms when it is performed early in the evolution of CRPS, at which time it has a success rate of 80% to 90%.[58] However, sympathectomy is ineffective if it is delayed until after joint contracture or nerve atrophy has occurred.[127] It should be used cautiously in clinical practice, in carefully selected patients, and only after other treatment options have failed.[32,128]

Long QT Syndrome

Favorable results from left thoracic sympathectomy in high-risk patients (preventing complications) have been demonstrated in the literature since the 1970s. VATS is associated with a significant reduction in the incidence of aborted cardiac arrest and syncope in high-risk patients with long QT syndrome compared with pre–left cardiac sympathetic denervation events, but changes in the QT interval after sympathectomy are variable and the clinical results cannot be fully predicted.[129] In a group of high-risk patients undergoing left cardiac sympathetic denervation, 46% remained asymptomatic; syncope occurred in 31%, aborted cardiac arrest in 16%, and sudden death in 7%.[59]

Raynaud Syndrome

The results of sympathetic denervation in cases of Raynaud syndrome are transitory.[130] Vasospastic episodes reappear within a short time, and dissatisfaction with the procedure is observed in almost 50% of patients.[131] This has led some authors to no longer recommend sympathectomy for such patients.[132]

BOX 193.1 Complications Associated With Thoracoscopic Sympathectomy

Common

Compensatory sweating (70%-100%)
Segmental atelectasis (1%-5%)
Pneumothorax (1%-5%)
Subcutaneous emphysema (1%-2%)

Rare (<1% of Cases)

Horner syndrome
Hemothorax
Pleural effusions
Injury to the vagus nerve
Injury to the phrenic nerve
Injury to the subclavian artery and vein

COMPLICATIONS OF VIDEO-ASSISTED THORACOSCOPIC SYMPATHECTOMY

Although VATS is a minimally invasive procedure, it is not free of risk. A detailed awareness of the technical difficulties and complications (Box 193.1) is important to improve the safety and outcomes of the procedure.[133]

Pneumothorax

The most common perioperative complication is pneumothorax. Most patients (75%) have some residual gas in the thorax at the end of the surgery. Small amounts of residual air in the pleural cavity remaining after sympathectomy are absorbed. However, when pulmonary fistulas are present, 1% to 3% of patients may require thoracic drainage.[134] Tension pneumothorax after surgery is rare. It results from direct injury to the lung at the time of trocar insertion or from tearing of an apical adhesion when the lung is depressed.[135]

Apical bullae may occasionally be found; they may rupture during anesthesia when high pulmonary insufflation pressure is used at the completion of the procedure. This complication can be prevented by careful reinsufflation at the end of the operation.[136] Subcutaneous emphysema around the trocar insertion site confined to the thoracic wall may occur in 2% to 7% of patients.[137] Treatment is conservative in the absence of pneumothorax.

Hemorrhage

Significant intraoperative hemorrhage is rare and mostly originates from intercostal vein disruption during dissection of the sympathetic chain. It may also occur at the trocar insertion site. Laceration of the subclavian artery and intercostal artery pseudoaneurysms requiring thoracotomy have been reported.[138]

Chylothorax

Chylothorax is an extremely rare complication resulting from laceration of the main or accessory thoracic duct.[139]

Cardiac Complications

Transitory bradycardia during sympathectomy occurs in 1.2% of the patients,[140] but it is usually self-limited and does not require intervention. Recovery takes place after a few minutes of clinical observation. Extensive thoracic sympathectomy may have a beta-blocker effect, leading to a moderate decrease in heart rate at rest and during maximal exercise.[141,142] Intraoperative cardiac arrest has been reported in only two patients during the surgical procedure, but they were both successfully resuscitated.[143]

Neurologic Complications

Severe postoperative pain is a common event, presenting in more than 95% of cases. It occurs independently of the electrocautery type. Most patients report acute pain, especially when breathing in deeply, for some hours after the operation, but a significant number complain of pain of lower intensity that is more constant in the dorsal region, which may occasionally require nonsteroidal anti-inflammatory agents for 2 weeks along with analgesics as necessary.[144]

Paresis and paresthesia in the upper limbs occurred in 2.9% of the patients as a result of tension of the brachial plexus caused by their position on the surgical table.[145] In most patients, these manifestations regressed within 3 days to 3 weeks.[146]

Horner syndrome is a side effect from complete sympathetic denervation of the upper limb when the stellate, G2, and G3 ganglia are resected.[48] However, in cases of hyperhidrosis in which only G3 or G4 is manipulated, this complication is rare.[147]

CAUSES OF FAILURE

Incomplete Denervation

Late activation of the intermediate ganglia (microscopic aggregates of ganglion cells distributed in the communicating branches or in the anterior roots of the cervical and brachial spinal nerves) may explain failures in the sympathetic denervation of the upper limbs.[13]

Regeneration

There is no evidence of regeneration of the sympathetic ganglion cells. However, if only the axis cylinder is sectioned, regeneration of new fibers from the ganglion cell may occur. This may have a negligible effect in operations where the paravertebral ganglia are removed.[63]

Functional Reorganization (Collateral Nerve Sprouting)

Degenerated fibers produce humoral substances that stimulate closely intact nerves to establish connections with denervated ganglion cells.[148] Hence cutting of only the preganglionic fibers responsible for the innervation of the upper limbs (the fibers that pass by the stellate ganglion on their pathway to the superior cervical ganglion) would give rise to favorable conditions for sprouting in the stellate ganglion.[149] Furthermore, there may be a functional connection between these branches and the ganglion cells in the spinal nerves, which would explain the return of sympathetic activity in the limb.

REVERSAL OF SYMPATHECTOMY

A small subset (currently less than 1%) of patients submitted to VATS for hyperhidrosis develop postoperative intense compensatory hyperhidrosis that is perceived as more debilitating than their initial complaints; therefore they seek medical assistance to reverse the sympathetic blockade. Studies in this area are still scarce, and the initial outcomes are poor, probably because of technical flaws.[150]

Promising technical advances with robotics technology have been achieved through implantation of a nerve graft using 10-0 nylon sutures on the epineurium.[151]

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A complete reference list can be found online at www.expertconsult.com.

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194 CHAPTER

Vascular Tumors and Their Management

BERNARDO C. MENDES and THOMAS C. BOWER

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INTRODUCTION

Over the past 15 years, surgical treatment of primary or secondary malignancies involving the arteries and veins has become more aggressive.[1-6] This is due in part to careful patient selection, improvement in surgical techniques and critical care, and the lack of curative adjuvant therapies. The primary challenge to management is the inability to diagnose these tumors at an early stage, in which case surgical resection would be more broadly applicable. This chapter reviews the selection of patients, surgical principles and management, the approach to, and technical aspects of, resection and replacement of major central and peripheral arteries and veins.

TUMOR TYPES

Tumors of the arteries and veins are classified by their origin. In general primary tumors arise from the media, often the smooth muscle. They rarely arise from the intima except for aortic sarcoma. Aortic tumors have been classified in two ways. Salm described three morphologic types of primary aortic tumors: polypoid or intraluminal, intimal, and adventitial.[7] Wright classifies both the polypoid and intimal types as intimal tumors and those of the adventitia as mural tumors.[8] Polypoid tumors are attached to the intima, grow intraluminally, and have a propensity to embolize. Intimal tumors are infiltrative and grow along the endothelial surface, which may result in large vessel branch occlusion. Adventitial or mural tumors grow beyond the confines of the aorta and invade adjacent structures. The majority of primary aortic tumors are of the intimal type, with equal distribution in the aortic segments. Staats and colleagues recently reported the clinicopathologic features of 26 aortic and iliofemoral sarcomas. Most of the aortic tumors originated in the abdominal (13) or thoracic segments (8). Interestingly, the diagnosis was not suspected clinically in any case. Poorly differentiated sarcomas were most common (13), followed by undifferentiated tumors (7). There were a small number of osteosarcomas, myxofibrosarcomas, and myxoid sarcomas that secondarily involved the arteries.[9] Secondary arterial involvement is also seen with head and neck, lung, musculoskeletal, colorectal, pancreatic, gynecologic, and retroperitoneal carcinomas or sarcomas.[10-13]

Primary and secondary tumors of the inferior vena cava (IVC) are shown in Table 194.1. Primary tumors of the superior vena cava (SVC) or peripheral veins are less common than those of the IVC.[1,5,14-16] Venous leiomyosarcoma is the most common primary tumor; it occurs more often than its arterial counterpart, is polypoid or nodular, and usually grows intraluminally, although it can extend through the adventitia and invade adjacent structures.[17,18] Similar to aortic sarcoma, distant metastases occur early and are present in at least half of patients at diagnosis.[1,19,20] These factors adversely affect survival.[1]

Retroperitoneal sarcoma is the most common malignancy to invade the infrarenal IVC, but it can invade any caval segment. Cancers of the viscera or solid organs invade the IVC segment in closest proximity. For example, cancers of the liver, pancreas, kidney, or adrenal glands invade the suprarenal segment.[17] Renal cell carcinoma (RCC) is the most common malignancy to exhibit intraluminal tumor thrombus, a feature present in 4% to 15% of patients. The thrombus is limited to the renal vein-caval

Abstract

Surgical treatment of malignancies involving the arteries and veins has become more aggressive, due in part to careful patient selection, improvement in surgical techniques and critical care, and the lack of curative adjuvant therapies. This chapter reviews the selection of patients, surgical principles and management, the approach to, outcomes and technical aspects of, resection and replacement of major central and peripheral arteries and veins.

Keywords

Vascular tumors
Inferior vena cava resection
graft replacement
leiomyosarcoma
renal cell carcinoma
tumor thrombus

TABLE 194.1 Tumors of the Vena Cava

Primary leiomyosarcoma
Secondary SVC tumors
Lung cancer with mediastinal adenopathy
Lymphoma
Follicular or medullary thyroid cancer
Teratoma
Thymoma
Angiosarcoma
Synovial cell carcinoma
Secondary IVC tumors
Retroperitoneal soft tissue tumors
Liposarcoma
Leiomyosarcoma
Malignant fibrous histiocytoma
Hepatic tumors
Cholangiocarcinoma
Hepatocellular carcinoma
Metastatic (e.g., colorectal)
Pancreaticoduodenal cancers
Secondary IVC tumors that may have tumor thrombus
Renal cell carcinoma
Pheochromocytoma
Adrenocortical carcinoma
Sarcomas of uterine origin
Leiomyomatosis
Endometrial stromal cell
Germ cell tumors
Embryonal
Teratocarcinoma

IVC, Inferior vena cava.

confluence in nearly half of this group. Extension into the suprarenal IVC occurs in 40% of patients, and the remaining 10% present with right heart involvement.[21-27]

CLINICAL PRESENTATION AND EVALUATION

Lymphovascular invasion is important to the pathologic staging of most malignancies. Hematogenous spread at the cellular level is the primary mechanism of metastasis for certain cancers and sarcomas, but arterial obstruction by tumor emboli is a recognized presentation of arterial tumors, albeit rarer than non-neoplastic emboli.[8,28-31] Upper or lower extremity, or brain involvement, are the most common locations of malignant embolization.[32] At times intimal or mural aortic sarcomas are misdiagnosed as aneurysms, focal dissection, an inflammatory process mimicking vasculitis, or an atherosclerotic lesion. Interestingly there are reports of aortic sarcoma originating within an aneurysmal sac after EVAR or immediately adjacent to a polyester aortic graft.[33-36] Similar to other advanced malignancies, at the time of diagnosis, the most common symptoms are nonspecific, such as malaise, fatigue, and unintentional weight loss.

Primary venous leiomyosarcoma more commonly involves the IVC than the peripheral veins, presents in women more than men, and occurs over a wide age range, with a mean age at presentation of 50 to 60 years.[1,14,15,19,37] Similar to primary aortic sarcoma, early detection is rare. Abdominal pain is the most common symptom, although many patients present with nonspecific symptoms, and metastases are present in 50% or more of patients when the diagnosis is made.[5,15,18] Cardiac symptoms, hepatic vein outflow obstruction causing Budd-Chiari syndrome, obstruction of renal vein outflow, or invasion of retroperitoneal muscles or nerves may occur with primary or secondary venous malignancies. Lower extremity deep vein thrombosis or edema is more common with peripheral vein tumors.[38]

A multidisciplinary team is paramount to manage patients with primary or secondary arterial or venous malignancies. Involvement of a medical or surgical oncologist is needed to guide adjuvant and surgical therapies. For example, neoadjuvant treatment is now offered to select patients with locally advanced pancreatic adenocarcinoma and vascular involvement to improve their candidacy for surgical resection. If a response is noted, radical resection is undertaken; this may involve revascularization of the portal vein and/or hepatic artery (Fig. 194.1). Oncologic, hepatobiliary, urologic, orthopedic, neurologic, and cardiothoracic surgeons often team with the vascular surgeon in operative planning and execution. Evaluation is directed at definition of the tumor type, its locoregional extent and distant metastases, and the severity of arterial or venous obstruction. Moreover, patient comorbidity and performance status (physical fitness) affect decision making for operation. In general surgical therapy is offered to patients with localized disease, good cardiopulmonary, hepatic and renal function, and few if any limitations in daily activities (performance status score of 0 or 1).[16]

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most common studies used to define location and extent of tumor, presence of distant metastases, and plan of operation. Arterial and venous phase imaging is important. Properly timed CT venography supplants the need for standard venography. MRI remains the imaging study of choice when there is an intracaval mass, in which case differentiation between tumor and bland thrombus is critical to patient management. Some groups, including our own, have used MRI to determine the likelihood of venous wall invasion from intracaval tumor thrombus. Psutka and Zini have both shown that residual adherent tumor thrombus to the caval wall increases the risk of recurrence and mortality.[26,27] Such preoperative differentiation influences operative planning and the need for caval replacement. Positron emission tomography (PET) is selectively used to define distant metastases for many primary and secondary tumors and has been used to diagnose aortic sarcoma.[39-41] Transesophageal echocardiography and ultrasound imaging are used selectively depending on tumor type and location, particularly if CT or MRI provide inadequate images of venous tumors. The Mayo Clinic group routinely obtains lower extremity ultrasonography of the deep veins for any patient with an IVC, iliac, or extremity tumor to exclude occult deep vein thrombosis. Recently, the authors have applied three-dimensional (3D) modeling for operative planning for complex tumors in close proximity to major vessels, soft tissues, bone, or nerves (Fig. 194.2).

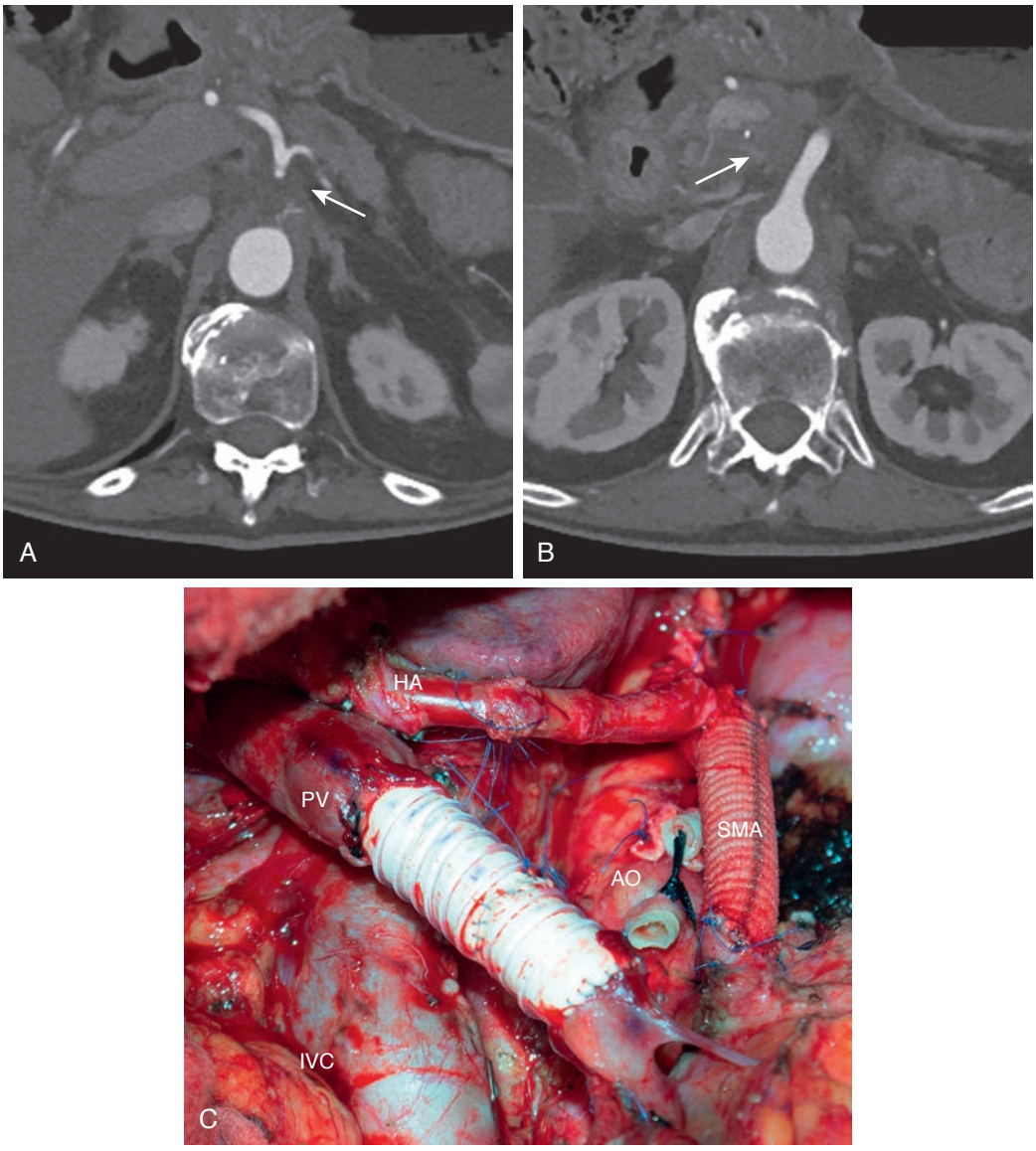

Figure 194.1 Axial computed tomography images showing encasement of the celiac artery (A, white arrow) and near-encasement of the superior mesenteric artery (B, white arrow) in a young, good-risk patient with locally advanced pancreatic adenocarcinoma who responded to neoadjuvant therapy. Tumor resection required reconstruction of the superior mesenteric artery (SMA). A superficial femoral artery graft was used to reconstruct the hepatic artery (HA) because of size match. The portal vein (PV) was reconstructed with a large-diameter externally supported polytetrafluoroethylene (PTFE) interposition graft (C). The portal vein was reconstructed first, with a longer graft to maintain liver blood flow; the hepatic artery was reconstructed later. The PTFE graft was foreshortened after the arterial reconstructions were completed. *IVC,* Inferior vena cava.

Medical risk assessment focuses on organ system function. Transthoracic echocardiography or cardiac stress studies, pulmonary function tests, and blood work for liver and renal function are commonly obtained. If major liver resection is anticipated, it is important to address the volume of liver remnant to avoid perioperative hepatic dysfunction. Physical fitness is essential if a major aortic, vena cava, or central artery or vein replacement is to be done. The risk of major adverse events and the capacity for patients to recover from surgery is negatively impacted if they have significant morbidities or limitations in daily activities (performance score ≥2). Patients with poor cardiopulmonary function or physical debility should not be offered operation in our opinion.

TREATMENT

The operative approach and treatment depend on the type, location, and extent of the tumor, the extent of venous obstruction, and the location of collaterals in patients with primary or secondary venous tumors. As with any vascular reconstruction, adequate exposure is essential, so the incision and approach must be chosen carefully and with input from the entire surgical team. 3D

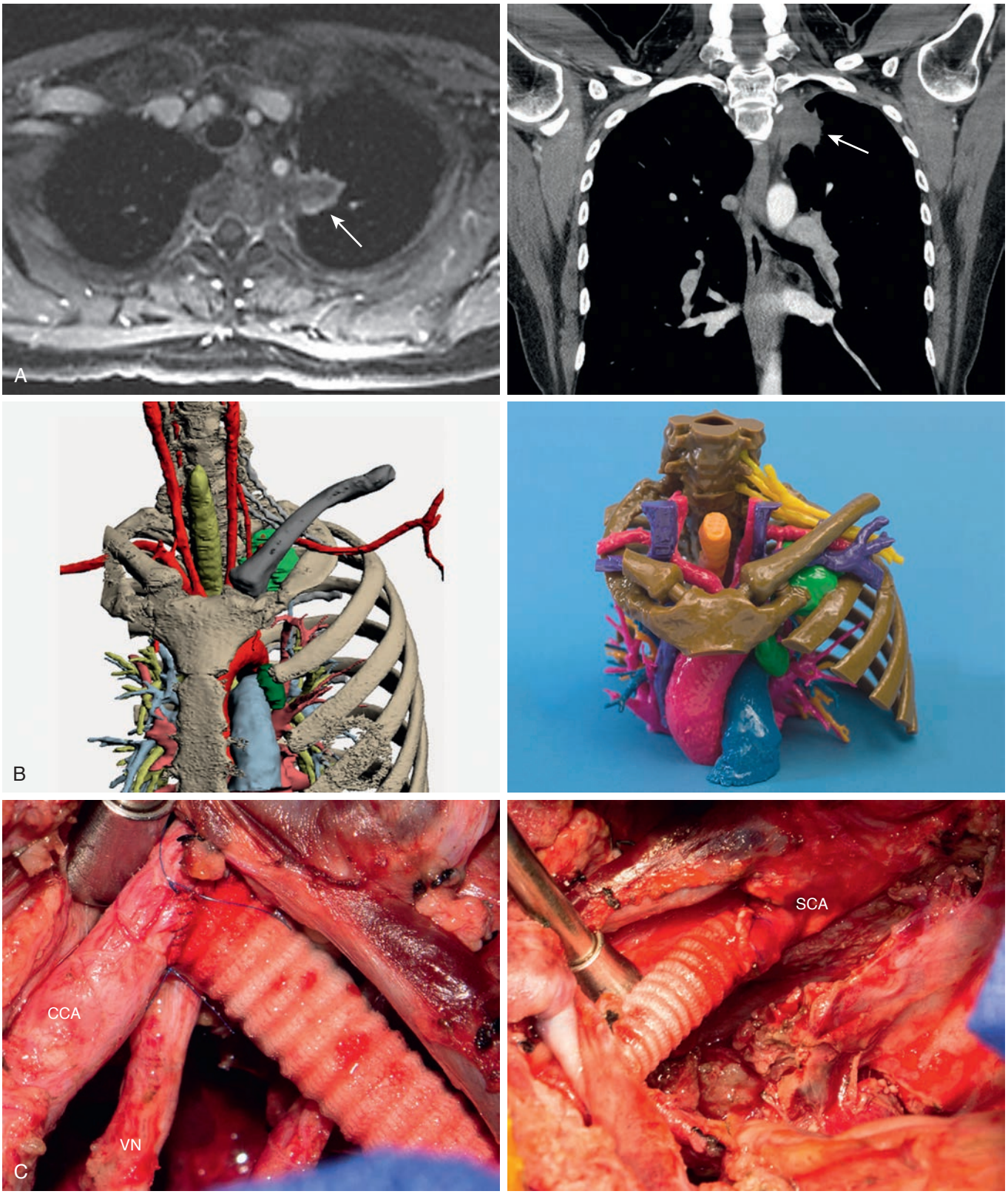

Figure 194.2 Left sided Pancoast tumor *(white arrows)* encasing the subclavian artery (A) and three-dimensional modeling (B) showing the relationship of the tumor *(green)* to the adjacent artery *(red)*, veins *(purple)*, brachial plexus *(yellow)*, and bony structures *(tan)*. The mass was resected, requiring replacement of the subclavian artery, as shown in (C). *CCA,* Common carotid artery; *SCA,* subclavian artery; *VN,* vagus nerve.

modeling is helpful when the tumor is in a difficult area, such as the thoracic inlet or outlet, the mediastinum, or the pelvis. Choice of incision is straightforward for most neck, mediastinal, and extremity operations but varies when vascular reconstruction is needed in the abdomen. The selection of midline, bilateral subcostal, modified Makuuchi, or thoracoabdominal incisions is determined based on the size and location of the tumor, body habitus including the costal flare, extent of the anticipated vascular replacement, and the level at which control of the aorta, vena cava, or branch vessels is needed. For example, a bilateral subcostal incision can be used to approach the upper abdominal aorta, visceral and renal arteries, portal vein, or suprarenal vena cava if the costal margin is wide. A full midline incision provides similar access and may be preferable for individuals with narrow costal margins. Either incision can be extended with a sternotomy for patients with RCC or similar cancers when tumor thrombus involves the right heart. This combination of incisions is also useful for patients with malignant obstruction of the suprahepatic and retrohepatic IVC, where there is venous congestion of the liver (Fig. 194.3).[1,4,5,14,16,17,42] A Makuuchi incision is favored by some surgical oncologists when radical pancreatic resection and vascular reconstruction are necessary. A low right thoracoabdominal incision (eighth or ninth interspace) affords excellent exposure of the vena cava and liver for patients with large malignant tumors involving the retrohepatic IVC.

If vascular involvement is confined to only part of the aortic wall or the iliac or peripheral artery, a prosthetic or bovine patch is used for repair. Aortic, supra-aortic trunk, carotid, visceral, and iliac artery replacement is done with a prosthetic graft unless resection involves the aerodigestive tract. In this case our preference is for a cryopreserved artery allograft or superficial femoral artery (SFA).[43-45] In the authors' experience, the latter seems to resist infection or anastomotic dehiscence better than saphenous vein, particularly when the carotid artery requires replacement during the resection of head and neck cancer with involvement of the aerodigestive tract and for

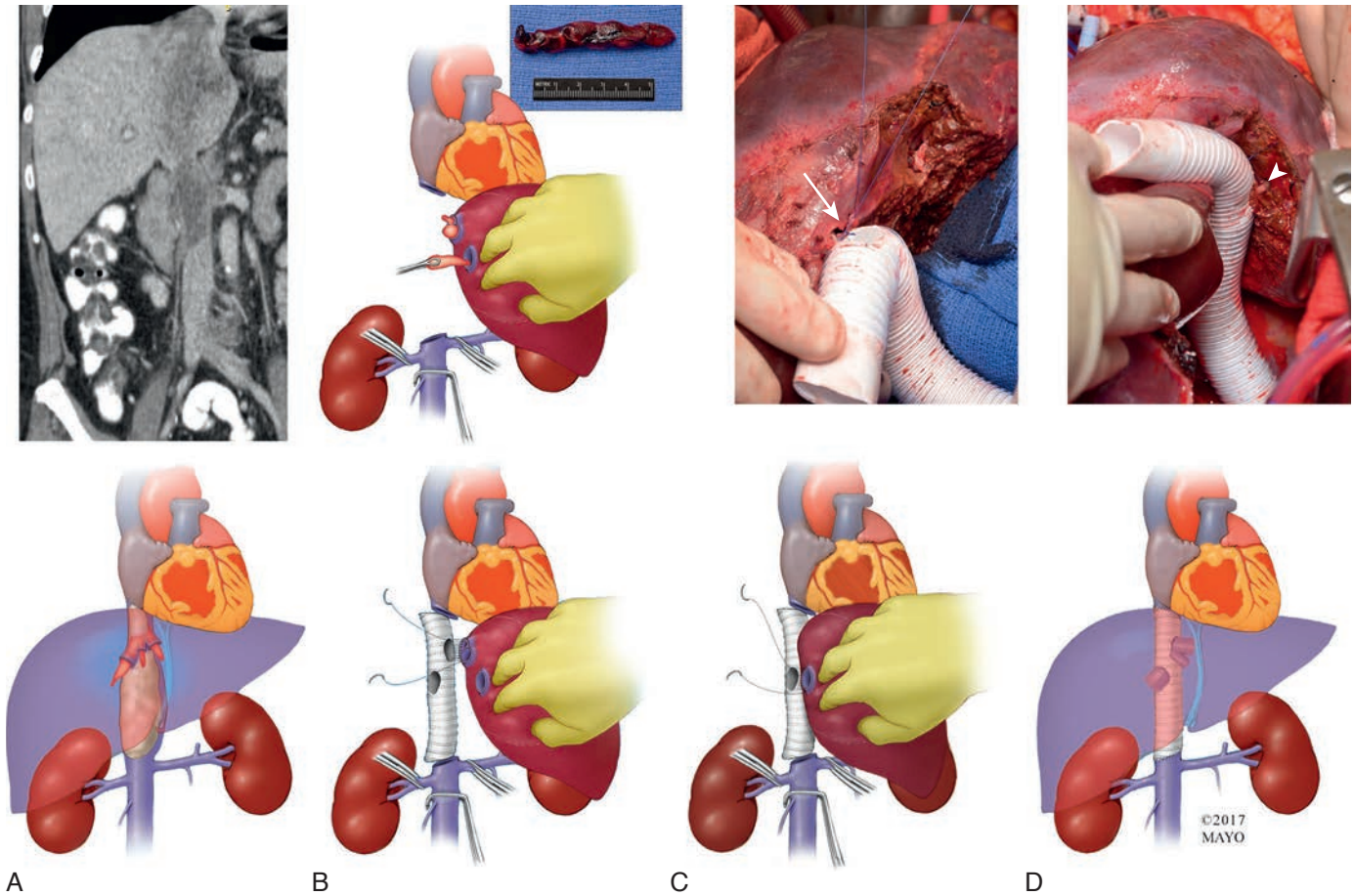

Figure 194.3 An infiltrative retrohepatic caval leiomyosarcoma extending from the cavoatrial junction to the renal vein; caval confluence as depicted vertically (A). The tumor invaded the hepatic veins, causing thrombosis, with resultant hepatic congestion. Operation was done with cardiopulmonary bypass. The tumor was resected and the liver rotated to allow removal of bland thrombus from each of the hepatic veins and some of their branches (B). The *left* and *middle* hepatic veins were reimplanted onto the externally supported polytetrafluoroethylene graft (*bottom* [B], and *top* [C, white arrow]). The right hepatic vein was reimplanted next (*bottom* [C] and *top* [D, arrowhead]). Note that the hepatic veins are not linearly oriented. The liver was placed in anatomic position, and the *upper* and *lower* caval anastomoses were completed (D), *bottom panel*.

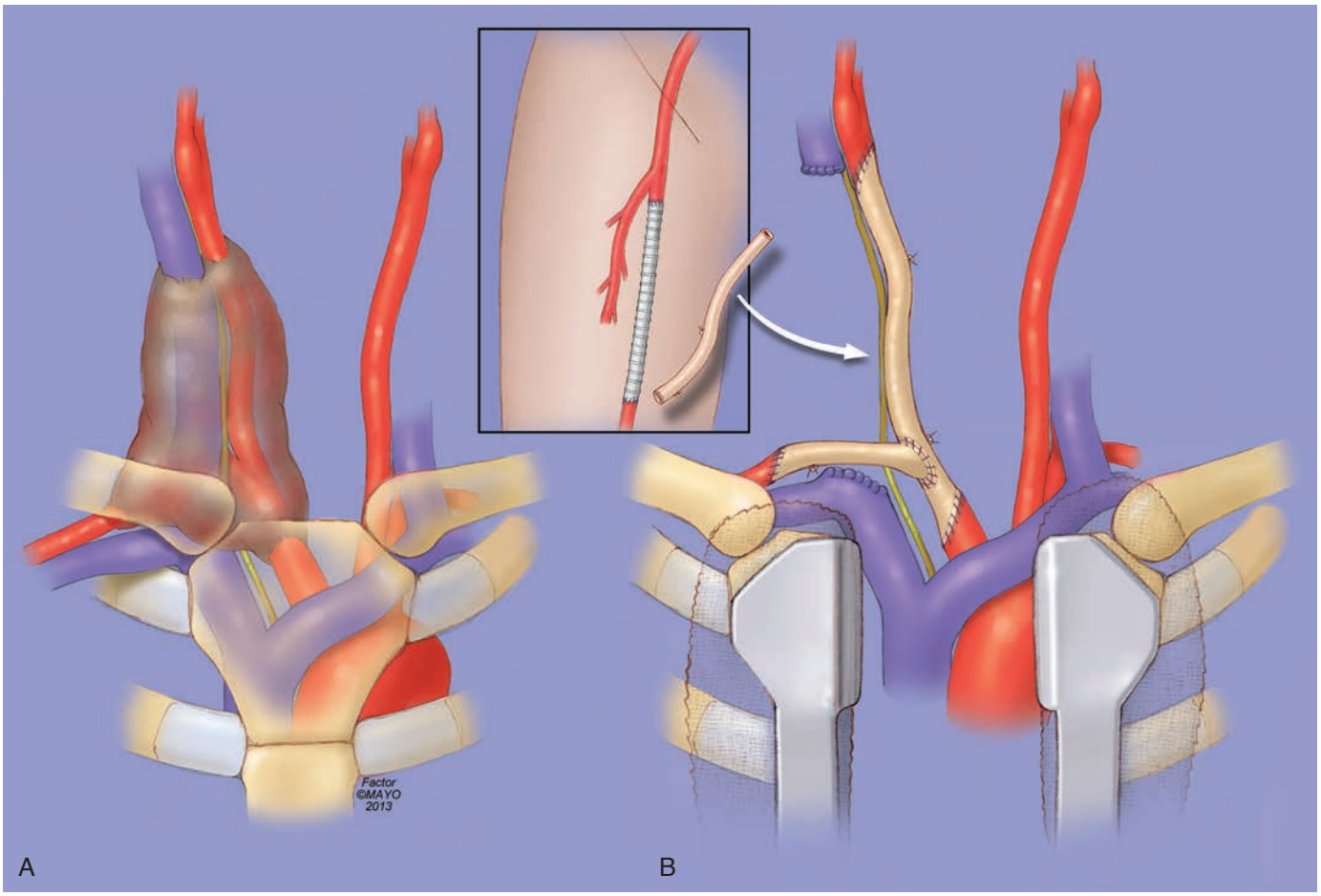

Figure 194.4 Patient with recurrent angiosarcoma encasing the common carotid, subclavian, and distal innominate arteries and the internal jugular vein, as shown schematically (A). The right superficial femoral artery (SFA) was harvested and used to reconstruct the carotid and subclavian arteries. The SFA was replaced with a prosthetic interposition graft (B). The left vertebral artery was dominant and the patient tolerated test balloon occlusion of the right vertebral artery; therefore, it was not reconstructed.

reconstruction of the hepatic and/or superior mesenteric artery in select patients with locally resectable pancreatic cancer. In these cases the SFA is replaced with a prosthetic interposition graft (Fig. 194.4). If a cryopreserved femoral artery allograft is used, it is best if the diameter is 7 mm or larger, as we have seen graft stenosis occur in smaller sized allografts. A few surgeons have used a thoracic aortic stent graft to facilitate resection of a tumor involving the aortic wall to obviate the need for aortic cross clamping. Tumor resection follows stent graft placement, and the aortic wall defect is buttressed with a patch.[46,47]

Our preference for vena cava or iliac vein replacement is a large-diameter externally supported PTFE graft.[5,16,17] The external support resists compression in the mediastinum or abdomen. Cryopreserved aortic grafts have been used by the authors to replace the IVC or iliac veins if concomitant intestinal resection is done. Others have used cryopreserved vein or bovine pericardial tube grafts in similar circumstances.[48-51] Portal vein replacement can be replaced with a prosthetic graft, or with left renal, jugular, femoral, or spiral saphenous vein conduits.[52-54] Patch venoplasty is preferred over large vein segmental resection and replacement whenever possible, and our preference is for a bovine pericardial patch. We accept as much as 60% involvement of the circumference of the IVC in which to resect and patch provided that the resection is limited to a small segment (4-7 cm length). It is imperative that the diameter of the patch be of adequate size to avoid stenosis. The diameter necessary is easily calculated based on the circumference of the normal vena cava, which geometrically is a cylinder. An IVC 20 mm in diameter in which 50% of the vein wall is resected will require a patch 30 mm in diameter (π or $3 \times$ vein diameter $\times$ % of the wall to be replaced. For this case, the calculation is made as $3 \times 20 \times 0.5$) (Fig. 194.5).[17]

Peripheral artery or vein replacement is done with a prosthetic graft or saphenous vein alone, in a spiral or panel graft configuration, or with a cryopreserved artery or vein. Choice of conduit is dependent on the size of the vessel, the length needed for reconstruction, and the availability of autogenous conduit (Fig. 194.6). If both artery and vein replacement is necessary, venous reconstruction is usually done first (Fig. 194.7). With chronic infrarenal IVC or long segment iliac or peripheral vein occlusion, vein replacement may not be necessary if collaterals are not

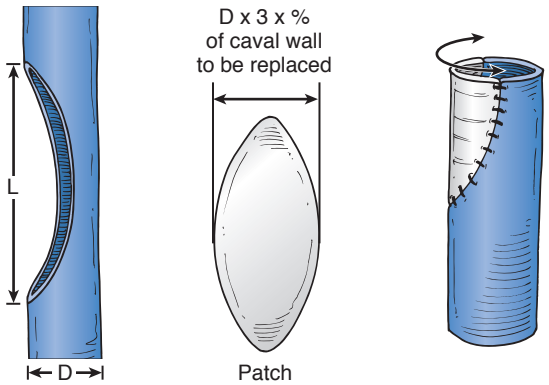

Figure 194.5 If closure of a caval defect will narrow the vein, a bovine pericardial patch is used. The diameter of the patch is estimated from the percentage circumference resected from the normal vena cava. See diagram for calculation. In most cases, the patch assumes a wide elliptical or circular configuration.

ligated during tumor resection.[21,55-58] In select cases, temporary arterial or venous shunting or bypass is utilized to maintain distal perfusion during resection of large musculoskeletal tumors before definitive vascular reconstruction.

REPLACEMENT OF THE INFERIOR VENA CAVA

At Mayo Clinic, any segment of the IVC is replaced if the majority of its circumference requires resection to achieve tumor-free margins and the vein is only partially obstructed by the malignancy. We prefer large-diameter, externally supported PTFE grafts and have found patency rates to be at least 90% in more than 110 patients who have now been treated at the Mayo Clinic.[5] Maximal diameter is 20 mm, which is sometimes smaller than the vena cava. Cryopreserved aortic allograft, femoral vein panel graft, and bovine pericardial tube grafts have been utilized in the few patients who required concomitant intestinal resection (Fig. 194.8). Others, including the University of California, Los Angeles (UCLA) group, prefer these conduits. The UCLA group favors smaller-diameter grafts because of the theoretical increase in blood flow velocity through the graft, which may enhance patency.[4] PTFE grafts are readily available and resist visceral compression. The rings of the graft are kept in immediate proximity to the anastomoses whenever possible to avoid late stenosis in the unsupported segment.

Infrarenal IVC replacement is straightforward, with the primary challenge being control of the iliac vein-caval confluence if resection extends to the caval bifurcation. There are a number of thin-walled or broad-based iliolumbar or sacral veins which cause troublesome bleeding if injured. This venous anatomy is highly variable, but often there is a large right iliolumbar vein at the junction of L5-S1. We long ago abandoned the use of arteriovenous fistulas to enhance patency for grafts in this position, given the good results seen with anticoagulation alone.[4,5,16,17,59] Resection of the pararenal IVC segment has been done without graft replacement but is hampered by a risk of renal failure, particularly if one kidney is resected with the tumor. Our preference is to reconstruct or reimplant remnant renal veins, including the left one, even if the branches of the left renal vein are preserved. The added operative time is minimal as compared with the consequence of renal failure from ligation of the left renal vein if a right nephrectomy has been done.

Special adjuncts are helpful when the retrohepatic or suprahepatic IVC requires resection and graft replacement, particularly if concomitant major liver resection and/or hepatic vein reconstruction is necessary. Total vascular isolation (TVI), selective use of venovenous or cardiopulmonary bypass (CPB) to maintain hemodynamics or protect the organs, choice of clamp position, ischemic preconditioning of the liver during hepatic resection, and ligation of the afferent and efferent lobar vessels during parenchymal division have all been used in our experience.[3-5,16,17,59-61] The specific steps with retrohepatic IVC replacement and concomitant liver resection are highlighted in previous publications by the authors.[17,59,61,62] TVI is initiated once the surgical team is prepared to transect the vena cava to complete the en bloc tumor resection. A temporary period of suprahepatic IVC clamping allows determination as to the need for venovenous bypass. Generally patients with good cardiopulmonary function tolerate systolic pressures of 100 mm Hg or higher without the need for venovenous bypass. If the initial test clamp results in lower pressures, intravenous volume loading is necessary. If the target of 100 mm Hg is not achieved within a few minutes, a cannula is placed in the infrarenal IVC at the gonadal vein confluence. Blood is circulated through an extracorporeal pump system to the jugular vein via a large-bore catheter. If the upper caval anastomosis is to the suprahepatic segment with incorporation of the remnant hepatic vein, the anastomosis will be challenging because the PTFE graft is stiff. Placement of the suprahepatic clamp in the immediate supradiaphragmatic extrapericardial position affords additional length and size of the vein orifice. A parachute technique may facilitate this anastomosis. One or more clamps are placed on the graft caudal to the anastomosis to allow hepatic venous drainage, but only after forebleeding is allowed by temporary release of the hepatic artery and portal vein clamp prior to completion of the anastomosis. Graft length is an important consideration, as the tendency is to cut the graft too long. This mistake is obviated by checking graft length during maximum inhalation and exhalation. We cut the graft primarily based on the inhalation length, as the upper and lower IVC will stretch. Reestablishment of blood flow is done after back bleeding and fore bleeding of the IVC has been performed with the patient in a head-down position, the lungs inflated to 30 mm Hg, and the graft filled with heparinized saline. The anastomosis is completed, the lower caval clamp is released, and the graft is de-aired to avoid embolism. To date, the warm liver ischemia time has been well tolerated by patients with these in situ reconstructive techniques.[3,16,60,61]

A few patients with infiltrative leiomyosarcomas or secondary tumors of the retrohepatic IVC occlude hepatic vein outflow and the liver becomes very congested. Mobilization of the liver and isolation of the suprahepatic IVC is risky because the liver parenchyma tears and bleeds easily. In these circumstances, cardiopulmonary bypass (CPB) and cooling have been utilized. The liver is fully mobilized once CPB is instituted. An atriotomy

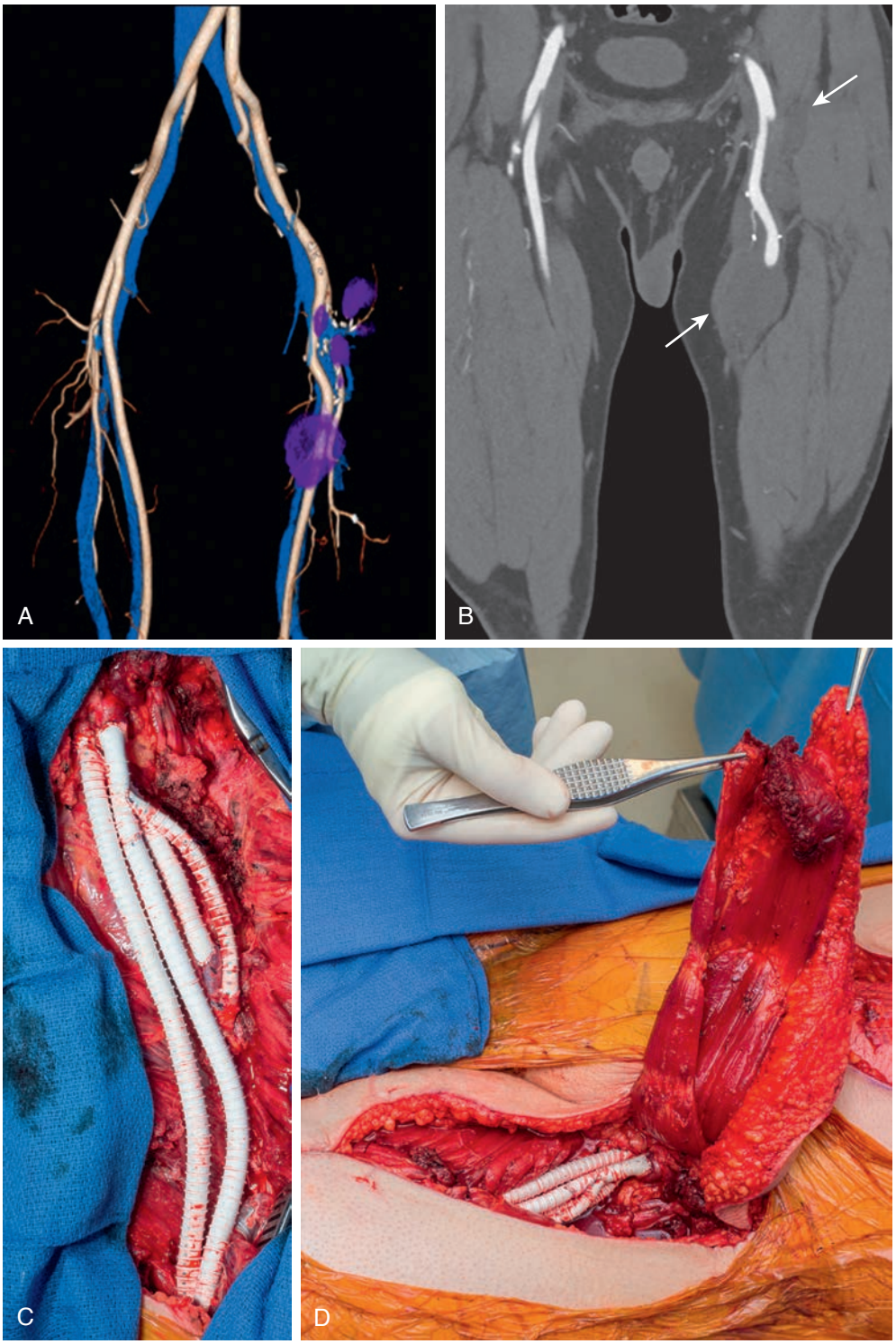

Figure 194.6 Patient with recurrent myxoid liposarcoma in the left groin and thigh, encasing the femoral arteries and veins (A and B). To achieve tumor-free margins (R0 resection), a wide resection was necessary. The common femoral artery and vein, deep femoral artery and vein, and superficial femoral artery and femoral vein required interposition grafts. Although autogenous reconstruction is preferable for peripheral veins, the patient did not have adequate conduit, necessitating the use of a prosthesis (C). Distal arterial and venous anastomoses were done first and the proximal venous anastomoses were completed next, followed by the common femoral artery anastomosis. A rectus abdominis flap was mobilized to cover the grafts and fill the soft tissue defect (D).

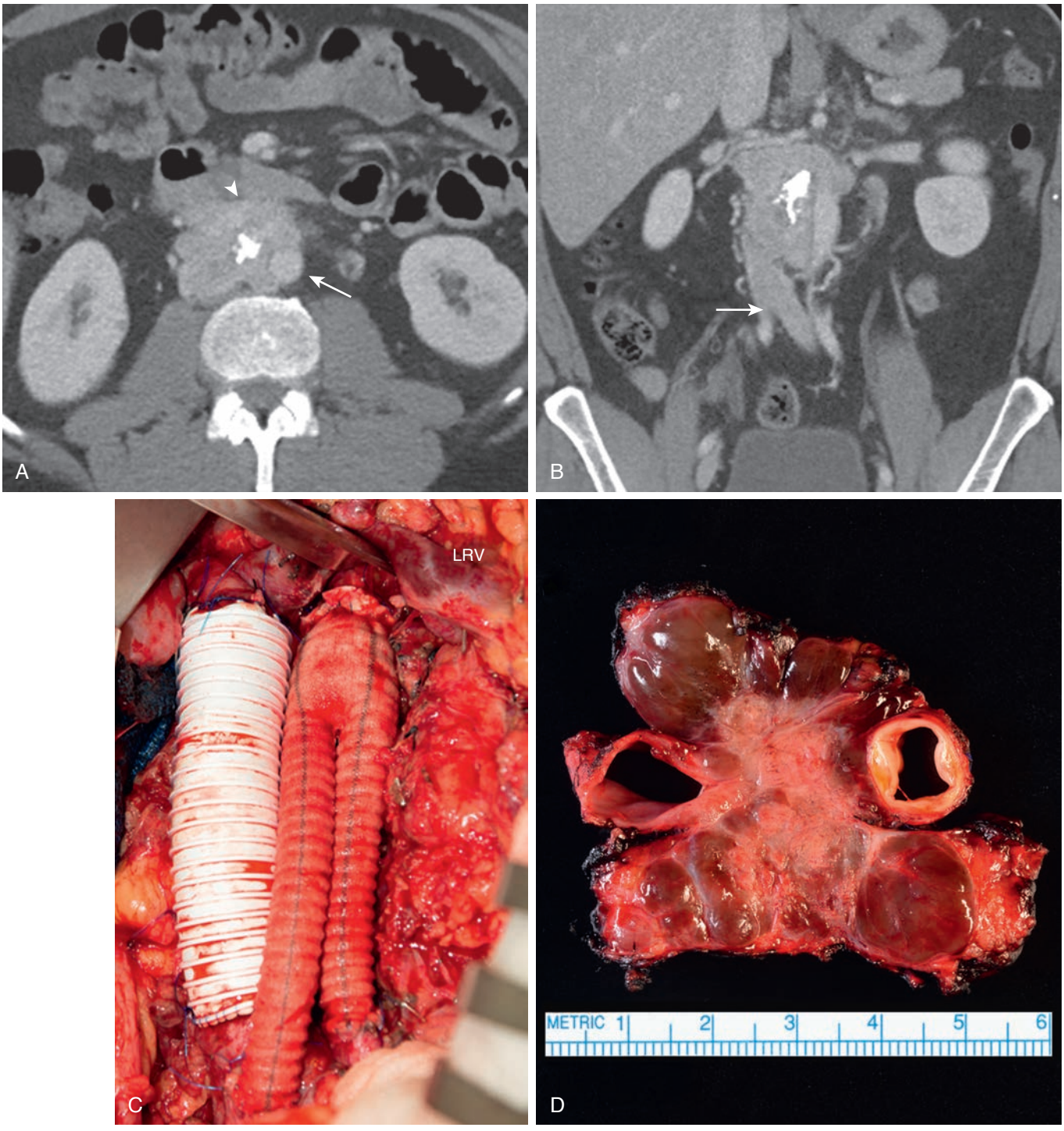

Figure 194.7 Paraganglioma encasing the infrarenal vena cava (A, *arrowhead*) with partial involvement of the aortic wall (A, *arrow*), as shown on CT (A) and (B), and on the pathologic specimen (D). The tumor extended to near the caval bifurcation, as shown by the *arrow* (B). The vena cava and the aorta required reconstruction (C). *CT,* Computed tomography; *LRV,* left renal vein.

allows examination of the upper extent of the tumor. The IVC is transected and the tumor and cava are resected with buttons cut around the hepatic veins. It is imperative that frozen sections show tumor-free margins. The remnant hepatic veins are reimplanted onto the caval graft; it is then placed in anatomic position and sewn to the cavoatrial junction and the infrahepatic IVC. The challenges are proper alignment of the hepatic veins on the graft, as they are not linear in orientation, and ensuring that the hepatic vein–graft suture lines and the raw liver surface are hemostatic in advance of the caval-graft anastomoses due to the inherent coagulopathy with CPB and hypothermia.

Others prefer ex situ hepatic resection and autotransplantation of the hepatic remnant if a complex vascular reconstruction is needed and the warm hepatic ischemia time is anticipated to be

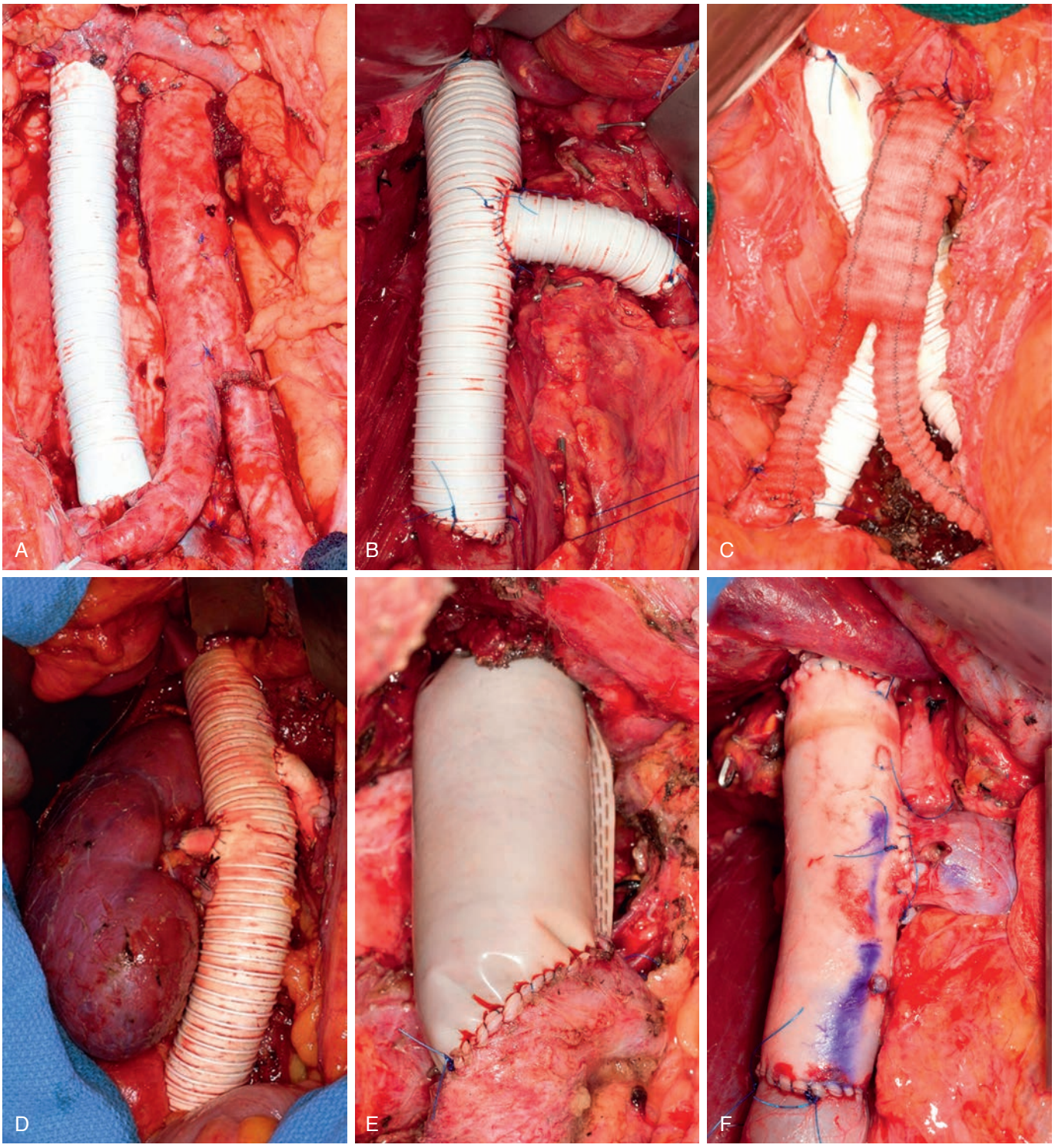

Figure 194.8 Inferior vena cava (IVC) and branch vein reconstructions can be done in many ways. (A) An infrarenal IVC graft. (B) Reconstruction of the infrahepatic and infrarenal IVC with a prosthetic interposition graft to the remnant left renal vein. (C) Bifurcated grafts used to reconstruct the infrarenal IVC, aorta, and common iliac arteries. Both renal veins were reconstructed together with caval replacement in (D). A bovine pericardial tube graft was used to reconstruct the infrahepatic IVC (E). A cryopreserved aortic allograft was used for caval replacement (F), as there was duodenal wall invasion. The remnant left renal vein was reimplanted.

long. Ex situ techniques allow time to perform difficult vascular anastomoses while protecting the liver but are fraught with higher perioperative mortality and liver failure rates than in situ reconstructions. Moreover, there is a low but real risk of liver failure, necessitating orthotopic liver transplantation. Further refinement in surgical technique, methods to mitigate ischemic liver injury, and new or better neoadjuvant therapies are needed to broaden applicability and improve outcomes in these patients.[3,16,60,61]

OUTCOMES

Patient outcome is dictated by operative risk; performance status; tumor type, location, and stage; and whether arterial and/or venous involvement is managed by primary closure, a patch, or an interposition graft.

Given the rarity of primary aortic or peripheral arterial malignancies, few surgical series are available.[12,28,32,63,64] The Mayo Clinic group reported outcomes in 13 patients diagnosed with primary angiosarcoma of the heart, aorta, or supra-aortic trunks spanning a 26-year period. Metastatic disease was present in 10 patients when diagnosis was made, and only 9 proved to have resectable disease. Of the nine patients, five underwent aortic resection and reconstruction and two each were treated by thromboendarterectomy or pericardiectomy and atrial septal resection with patch closure of the defect (Fig. 194.9). One patient had biopsy only. There were no early deaths but overall median survival was just 8 months. The surgically treated aortic sarcoma patients had median survival of 14 months, ranging from 1 to 75 months.[28] Carpenter et al. reported outcomes for 60 patients surgically treated for tumors arising from or secondarily involving the aorta or other major arteries.[12] Iliac artery involvement was noted in 37 patients (62%) and sarcoma was the most common pathology; of these, 12 patients required aortic resection, 8 were treated with graft replacement, and a patch or primary closure was used for the others. Early mortality was 5%. There were two intraoperative deaths and another from cardiac arrest within 24 hours of surgery. Two deaths were in patients with aortic tumors, and the third in a patient with sacral malignancy in which the aorta and iliac arteries required mobilization. The latter patient died from coagulopathy induced by bone and soft tissue hemorrhage. Graft patency was excellent over a mean follow-up of 20.5 months except for one patient with an SFA graft rupture and another with thrombosis of a prosthetic graft involving the common iliac artery.[12]

Comparison of outcomes for patients with IVC replacement is difficult because tumor types vary and surgeons lump patients treated by primary closure or patch angioplasty with those who need segmental resection and graft replacement. Moreover, the location of the IVC tumor influences risk.[18] The physiologic stress of a retrohepatic IVC graft replacement, particularly if hepatic veins require concomitant reconstruction, varies significantly from an individual who needs replacement of the infrarenal IVC. Mortality was 20% in the Kieffer series, but tumor size was large and 14 of the 20 patients had suprarenal IVC involvement, including 5 with invasion into the hepatic veins or heart.[15] By comparison, Ito reported no mortality among 20 patients surgically treated for PVL, but only 5 patients had graft replacement and only 1 had tumor above the hepatic veins.[14] Similarly, an Italian report indicated low mortality among 11 patients treated with graft replacement of the infrarenal IVC.[1,65] Contemporary series from Quinones-Baldrich et al., Hemming and colleagues, and Glebova and associates document low mortality despite increasingly complex operations (Table 194.2).[1-6,14,15,42,61,66,67] Overall 5-year survival has reached 50% in some series for primary or secondary IVC tumors. Among 124 patients from the Mayo Clinic who had segmental IVC resection and graft replacement, at 5 years, overall survival was 52%, disease-free survival 32%, and local progression-free survival 66%.[5] Other series report similar results. Although surgical resection may improve survival in select patients, more effective adjuvant therapies are needed if additional survival advantage is to be seen.

The greatest survival benefit is seen in patients surgically treated for RCC with intracaval tumor thrombus. Five-year survival rates between 40% and 60% are noted in several series, with sarcomatoid features, lymph node involvement, perinephric fat infiltration, distant metastasis, and residual tumor adherent to the IVC wall after thrombectomy adversely impacting outcome.[21-24,26,27,68-71] Extent of tumor thrombus is not as important as presence of metastases at time of operation or vascular margin status. Psutka and colleagues noted a 1.5-fold increase in mortality at 5 years if vascular margins proved positive on pathologic analysis, among a cohort of 304 patients. Five-year disease-specific survival reaches 40% to 71% for patients undergoing radical nephrectomy and IVC tumor thrombectomy in the absence of metastases, but falls considerably to 6% to 28% when metastatic disease is present.[25,26]

Concomitant liver resection increases the complexity of the operation significantly. Sarmiento and colleagues reported outcomes of 19 patients who underwent partial hepatectomy and segmental IVC resection and reconstruction. Cholangiocarcinoma was the most common tumor (nine patients), followed by metastases in five, sarcomas in three and hepatocellular carcinoma in two patients. Major hepatectomies (≥3 segments) were performed in 15 patients. Hepatic vascular isolation was needed in 13 patients, and all but 1 patient had IVC replacement with a PTFE graft. Despite a high complication rate (42%), there was only one perioperative death (5%). Median overall survival was 38 months.[61] These results are corroborated by a more recent publication by Hemming and colleagues.[3] Concomitant liver and IVC resection was performed in 60 patients, mostly for primary hepatic tumors. Graft replacement of the IVC was needed in 38 patients, 6 of whom required an ex vivo procedure, whereas the remaining 54 used varying degrees of vascular isolation. Perioperative mortality was 8%. Long-term survival was 89% and 35% at 1 and 5 years, respectively. These results support aggressive resection of hepatic tumors with IVC involvement.[3,60,61]

Adjuvant therapies have been slow to evolve for most primary or secondary IVC malignancies. Tyrosine-kinase inhibitors seem an effective treatment for patients with RCC, although they have not significantly impacted survival in patients with intracaval tumor thrombus.[72-75] An R0 tumor resection is always the goal, but select patients with retroperitoneal or IVC sarcomas may have their risk of locally recurrent disease lowered by radiation therapy. Some authors have shown benefit from combination of external beam and intraoperative radiation therapy in such cases.[76-79]

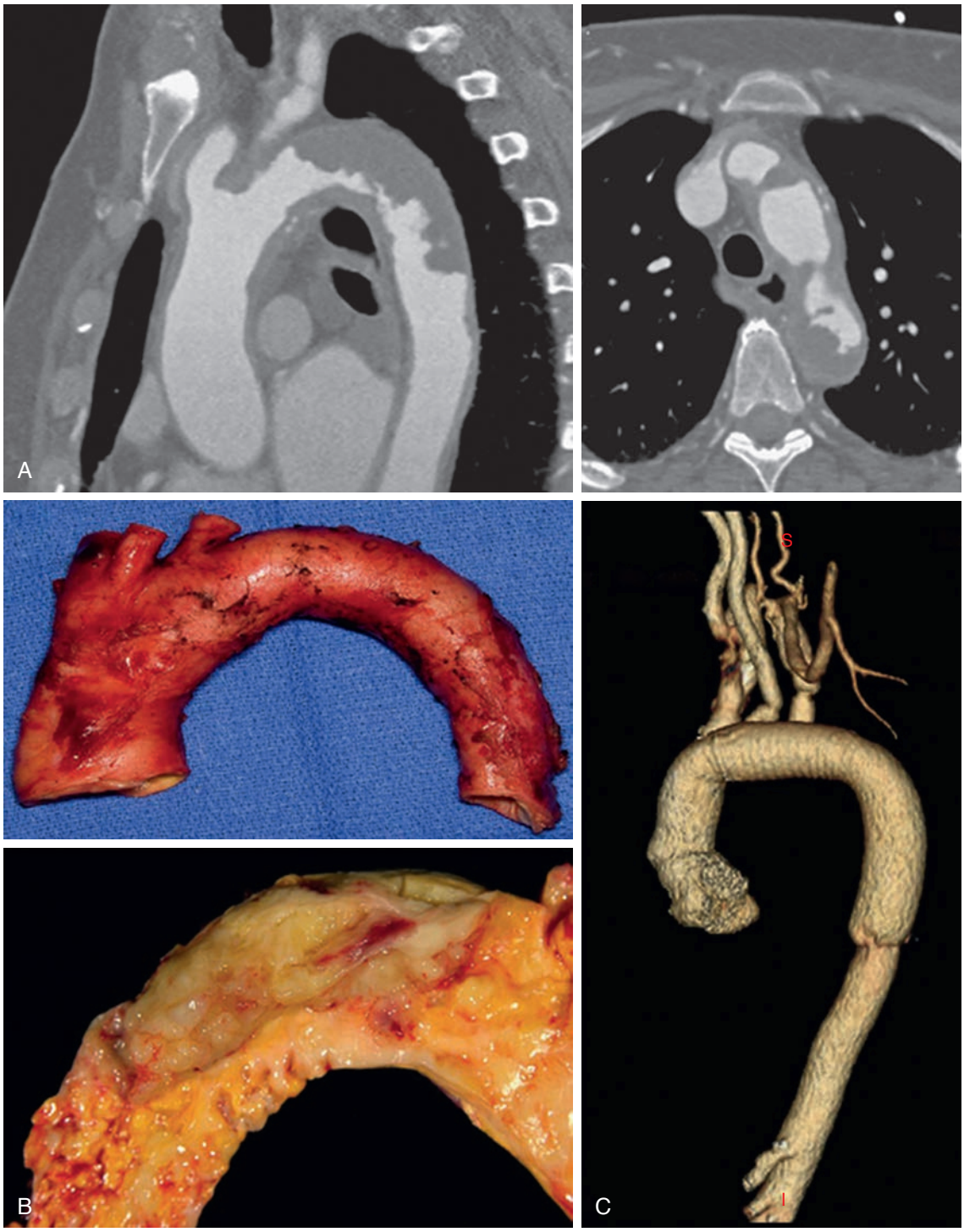

Figure 194.9 Sagittal and axial computed tomography (CT) images of an intimal sarcoma of the aortic arch and proximal descending thoracic aorta (A). Pathologic specimens (B) show no gross invasion through the adventitia but extensive intimal tumor. Postoperative CT angiogram (C) showing widely patent aortic graft with reconstructed supra-aortic trunks. (Modified from Fatima J et al. Primary angiosarcoma of the aorta, great vessels, and the heart. *J Vasc Surg*. 2013;57(3):756-764.)

Malignant obstruction of the SVC is most often caused by lung cancer with mediastinal adenopathy. Lymphoma, thyroid cancer, thymoma, and teratoma are the other etiologies. Most patients with malignant SVC obstruction are not surgical candidates, and treatment is palliative with stenting of the vein. If patients with localized disease undergo segmental SVC or innominate vein resection, our preference for venous reconstruction is a prosthetic graft (expanded PTFE).

Single-center experience with peripheral vein reconstruction for malignancy is rarer than that of the IVC. Sun and associates

TABLE 194.2 Contemporary Series of Primary and Secondary Inferior Vena Cava Malignancies

	N	TYPE		LOCATION			Liver Resection	Tumor size (cm)		Early Mortality n (%)
				IR	SR/RH	SH		Median	Graft	
Sarmiento et al. (2003)	19	Cholangiocarcinoma Metastatic Sarcoma HCC	9 5 3 2	0	19	0	19	—	18	1 (5)
Kieffer et al. (2006)	20	PVL		3	13	4	4	21	13	4 (20)
Ito et al. (2007)	20	PVL		6	13	1	1	10.7	5	0
Kuehnl et al. (2007)[a]	35	PVL Secondary	6 20	5 (4)	7 (3)	14 (2)	—	—	—	2 (6)
Delis et al. (2007)	12	Colorectal HCC Cholangiocarcinoma	6 4 2	0	12	0	12	—	12	0
Quinones-Baldrich et al. (2012)	47	PVL Secondary	30 17	9	18		—	11.6	27[b]	0
Hemming et al. (2013)	60	Cholangiocarcinoma HCC Metastases Other tumors	26 16 13 5	—	—	—	60	—	38	5 (8)
Benkirane et al. (2014)	26	RCC	26	—	—	—	—	10	26	1 (3.8)
Fabre et al. (2014)	37	PVL RCC Adrenocortical Sarcoma HCC Other tumors	2 11 8 6 2 8	8	15	14	—	—	14	2 (5.4)
Glebova et al. (2016)	63	RCC Sarcoma Germ cell tumor Paraganglioma Adrenocortical Other tumors	31 13 6 4 3 6	18	44	—	—	11.1	21	2 (3)
Illuminati et al. (2016)	18	PVL		—	—	—	—	—	18	0
Bower et al. (2015)[c]	110	PVL Secondary	36 74	28	14	1	32	10.5	110	2 (2)

[a]Nine SVC and 26 IVC tumors. The locations in the nine patients with grafts are shown in parentheses.
[b]Eight entire IVCs replaced with hepatic/renal vein reimplantation; six had suprarenal and pararenal IVCs replaced with seven renal vein reimplantations; four had infrarenal and pararenal IVCs replaced with four renal vein reimplantations.
[c]Multiple segments in the remainder.
HCC, Hepatocellular carcinoma; *IVC,* inferior vena cava; *IR,* infrarenal segment; *PVC,* primary venous leiomyosarcoma; *RCC,* renal cell carcinoma; *SR/RH,* suprarenal–retrohepatic segment; *SH,* suprahepatic segment.

from the Mayo Clinic reported the results of 28 reconstructions in 27 patients with iliac (19), lower extremity (6), and upper extremity (3) venous tumors spanning the period between 2000 and 2015. Prosthetic grafts were used in 17 patients, vein grafts in 7, and a cryopreserved graft in 1, with the remaining 3 reconstructions done with a patch. Early outcomes were good, with no 30-day mortality and few graft-related complications (infection in three). At a median follow-up of 4.4 years, 2- and 5-year primary patency rates were both 61%. Graft thrombosis occurred in five patients, four with prosthetic grafts, yielding an overall freedom from graft thrombosis of 87% at 5 years.[38] Similar results have been reported by others.[80]

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Bower TC, Nagorney DM, Cherry KJ, et al. Replacement of the inferior vena cava for malignancy: an update. *J Vasc Surg.* 2000;31(2):270–281.

The paper provides an in-depth analysis of the types and locations of the IVC tumors, analysis of outcomes, and detailed surgical techniques.

Fatima J, Duncan AA, Maleszewski JJ, et al. Primary angiosarcoma of the aorta, great vessels, and the heart. *J Vasc Surg*. 2013;57(3):756–764.

The Mayo Clinic experience in 13 patients diagnosed with primary angiosarcoma of the heart, aorta, or supra-aortic trunks spanning a 26-year period. Five of the nine patients underwent aortic resection and reconstruction and two each were treated by thromboendarterectomy or pericardiectomy and atrial septal resection with patch closure of the defect. There were no early deaths but overall median survival was just 8 months. The surgically treated aortic sarcoma patients had median survival of 14 months, ranging from 1 month to 75 months.

Hemming AW, Mekeel KL, Zendejas I, Kim RD, Sicklick JK, Reed AI. Resection of the liver and inferior vena cava for hepatic malignancy. *J Am Coll Surg*. 2013;217(1):115–124.

A large series of 60 patients treated with concomitant liver and inferior vena cava resection for primary and secondary hepatic tumors. A detailed technical description of different variations of the operation is provided. Ex vivo reconstruction was performed in six patients, and the other 54 procedures were performed with varying degrees of vascular isolation. The IVC was reconstructed in 38 patients using a tube graft. Perioperative mortality was 8% and actuarial 1- and 5-year survival rates were 89% and 35%.

Pouliot F, Shuch B, LaRochelle JC, Pantuck A, Belldegrun AS. Contemporary management of renal tumors with venous tumor thrombus. *J Urol*. 2010;184(3):833–841.

This paper summarizes the contemporary management of patients with renal cell cancer and venous tumor thrombus. The authors provide comparative outcome data between the largest studies with regard to median survival, disease-specific survival, and impact of metastases or no metastases on disease-specific survival.

Quinones-Baldrich W, Alktaifi A, Eilber F. Inferior vena cava resection and reconstruction for retroperitoneal tumor excision. *J Vasc Surg*. 2012;55(5):1386–1393.

The UCLA group describes 47 patients treated with IVC resection and tumor excision between 1990 and 2011. The majority of tumors were sarcomas, of which 30 were primary to the IVC. Eleven patients had primary repair, 9 had patch angioplasty, and 27 had circumferential resection and IVC replacement with a PTFE graft. Eighteen of the reconstructions with grafts included more than one caval segment. There was no mortality and a 10.6% major morbidity rate.

Salm R. Primary fibrosarcoma of aorta. *Cancer*. 1972;29(1):73–83.

Landmark paper on the morphologic types of aortic tumors.

Wachtel H, Gupta M, Bartlett EK, et al. Outcomes after resection of leiomyosarcomas of the inferior vena cava: a pooled data analysis of 377 cases. *Surg Oncol*. 2015;24(1):21–27.

This is a large pooled data analysis on IVC leiomyosarcomas. The dominant predictors of survival included margin status, tumor size, and radical resection.

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195 CHAPTER

Vascular Reconstruction in Oncologic Surgery

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PANCREATIC MALIGNANCIES

Pancreaticoduodenectomy

Pancreatic cancer is currently the fourth leading cause of death within the United States with 53,000 new cases and 41,780 deaths estimated for 2016.[1] Improving long-term survival remains the goal of care. Therefore surgery remains the pivotal portion of multidisciplinary care. Currently, preoperative resectability can be classified as follows: *unresectable* (metastatic disease/encasement of the superior mesenteric artery [SMA] or hepatic arteries, lack of venous reconstructive options); *borderline resectable* (superior mesenteric vein [SMV]/portal vein [PV] tumor-vessel interface ≥180 degree of vessel wall circumference, and/or reconstructable occlusion; SMA tumor-vessel interface <180 degree of vessel wall circumference; celiac artery [CA] tumor-vessel interface <180 degree of vessel wall circumference); or *resectable.*[2] Recent reports of successful SMA and hepatic artery reconstruction during resection of a pancreatic head malignancy (at times with total pancreatectomy) may provide successful surgical strategies in some patients with arterial involvement. Therefore venous resections, as well as arterial reconstruction, need be in the armamentarium of the pancreatic surgeon. Herein presented are the details of vascular reconstructions for resection of the pancreatic head.

When there is potential for a venous resection/reconstruction one should consider an artery-first approach.[3,4] Our preference is to dissect and ligate all SMA branches/perivascular connective tissue to the pancreas prior to undertaking SMV/PV clamping or venous resection. In brief, this technique can be accomplished by rotating the specimen to the left by widely mobilizing the right colon to fully expose the duodenum in its entirety and dividing the perivascular connective tissue along the SMA in a parallel fashion from caudal to cranial. Attachments between the SMA and uncinate are divided to expose the lateral border of the PV–SMV. After the specimen has been freed from the SMA the only tissue remaining should be venous attachments. Benefits include not only the potential for lower blood loss and

Abstract

Vascular resections and reconstructions are not uncommon during oncologic operations. Surgeons undertaking tumor extirpation should be aware of the potential need for vascular interventions and technically proficient in vascular procedures prior to entering the operating theatre. Herein, this chapter focuses on the technical aspects of vascular resection and reconstruction for pancreatic, hepatic and biliary malignancies as well as soft tissue sarcoma.

Keywords

Surgical Oncology
Hepatopancreatobiliary surgery
Portal vein resection
borderline resectable pancreatic cancer
Hilar Cholangiocarcinoma
soft tissue sarcoma

facilitation of an en-bloc resection but also increased mobility of the specimen and ease of venous resection.

Venous Resection and Reconstruction

The surgeon should have a clear understanding of the need for venous reconstruction based on high quality preoperative cross-sectional imaging (triple contrast phase along with thin cuts through the pancreas). Obliteration of the tumor/vessel fat plane interface or narrowing of the SMV/PV is suggestive of vascular abutment or involvement. True venous involvement of the SMV, PV, or their confluence can be confirmed either at the time of tunneling under the pancreatic neck or following the creation of the tunnel (at the time the surgeon is controlling vessels from the SMV/PV, SMA to the head of the pancreas and uncinate process). Vein resections can either be performed by excising the right lateral portion of the SMV or PV or a segment of the SMV, after gaining venous control. Generally, options to proceed include locally resecting a portion of the right lateral aspect of the SMV/PV (tangential resection) and repairing either with interrupted sutures in a transverse fashion or with a saphenous vein patch (Fig. 195.1), segmental resection and primary anastomosis, or segmental en-bloc resection of tumor and vein followed by placement of an interposition graft.[5] More recently, data suggest SMV or PV resection with primary end-to-end reconstruction or transverse venorrhaphy results in a greater patency rate as compared to lateral/longitudinal venorrhaphy, patch venoplasty or interposition grafting.[6]

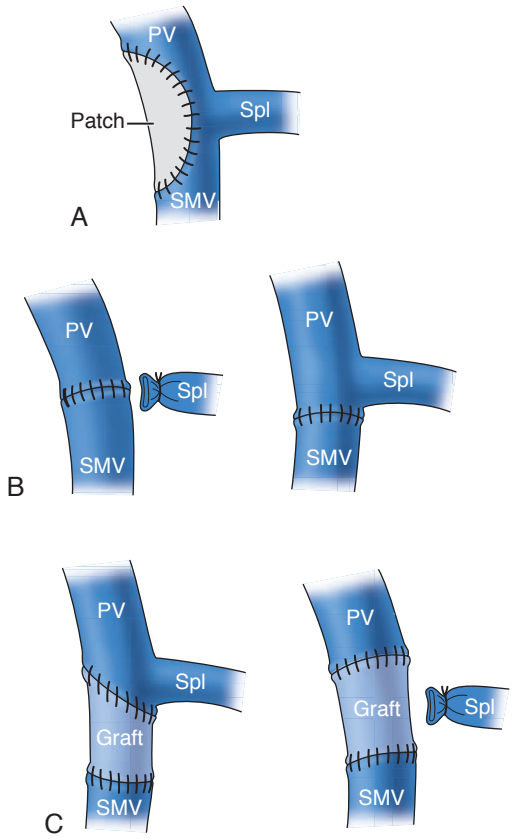

Figure 195.1 Venous Reconstruction Options Following Superior Mesenteric Vein/Portal Vein Resection During Proximal Pancreatectomy (A) tangential resection with patch repair, (B) primary anastomosis with/without splenic vein grafting, (C) interposition grafting with/without splenic vein grafting. (From Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg*. 2004;8:935–950.)

As a general principle, it is of paramount importance to critically analyze the site of tumor infiltration of the vein preoperatively and intra-operatively. Wide mobilization of the liver and retroperitoneum will allow approximately a 3-cm gap to be bridged by a primary end-to-end repair. Proximal vein involvement can typically be handled more easily, as the vessel diameter is large enough to create a sufficient anastomosis. However, in cases of venous involvement distal to the first jejunal branch, the decreasing diameter of the SMV may limit the technical possibility to perform a venous resection.[7] Occasionally, however, the SMV, PV, SV, and confluence will all be involved by tumor. This pattern of venous invasion may be found when resecting tumors of the pancreatic neck or medial aspect of the head of the pancreas. In such cases when all three venous structures are involved, a total pancreatectomy with SMV to PV reconstruction can be considered. In this setting, the venous gap may exceed 3 cm and interposition grafting may be required.

Please note, for all proximal pancreatectomies, the patient should have the groin sterilely prepped into the field and covered to allow access to the great saphenous vein (GSV) if venous reconstruction should be required.

Tangential Superior Mesenteric Vein/Portal Vein Resection With Saphenous Vein Patch

Tangential (right lateral SMV/PV partial resection) has become our preference when there is involvement of the medial aspect of the SMV/PV junction opposite to the splenic vein. Although certain circumstances preclude this technique and a formal segmental resection must be performed, if possible a tangential resection should be utilized. Key technical aspects of this procedure include proximal and distal control of the SMV/PV and splenic vein with vascular clamps, achieving a grossly negative margin of vein and constructing a vein patch. If there is a question of leaving a positive margin, a segmental resection should be utilized. Additionally, if only a small portion of the vein is required for resection the vascular clamps can be applied in a "V" format, angling in behind the involved area of vein. Note, if a larger portion of the vein is required, a Satinsky clamp can be applied parallel to the vein.

The GSV should always be harvested prior to PV clamping in order to expedite the reconstruction and limit the amount of portal flow disruption. It is paramount to plan and prioritize sequential steps to allow for safe and efficient venous repair. GSV harvest is accomplished by exposing the previously prepped groin and creating a longitudinal incision medial to the femoral artery. The GSV is then identified at its junction (saphenofemoral junction) with the femoral vein, mobilized distally for an appropriate length (5-6 cm), and ligated proximally and distally; this segment of GSV is then removed and placed in heparinized

saline. Note: close communication with the anesthesia team at the time of PV clamping is important to avoid potential hypotension and any diminished mesenteric venous flow.

To complete the vein patch, the GSV should be opened longitudinally, cut to size and spatulated. The valves should be lysed to avoid directional flow issues. Following clamping, the patch is then grafted using 5/0 or 6/0 prolene suture in a running technique (see Fig. 195.1). Finally, an air knot of 1/3 the diameter of the PV (growth factor) is tied in order to allow for venous distention.

Segmental Resection and Primary Anastomosis

Segmental resection with primary end-to-end anastomosis has proven to have the highest patency rates of all reconstruction methods. Certain factors must be appropriate in order to complete a primary end-to-end anastomosis following a segmental resection. First and foremost, the anastomosis must be created without tension. This can be facilitated by mobilization of the SMV (along the root of the small bowel mesentery) and PV (superior to the pancreas) by ligating and dividing small branches along the length of these vessels. Additionally, further length on the PV can be gained through hepatic mobilization. Therefore the right and left liver should be mobilized by incising the triangular and cardinal ligaments along with the hepatocolic and falciform ligaments. If further length is required, the midgut can also be mobilized by creating a dissection plane immediately anterior to the wall of the aorta and IVC. Such preparatory steps should precede the interruption of portal venous flow to avoid venous congestion.[9]

Proximal and distal control of the PV and SMV is then obtained with pediatric vascular clamps, the vein transected, and the specimen removed. The previous mobilization maneuvers should permit a tension-free primary anastomosis. Once an appropriate length is achieved, the anastomosis is undertaken utilizing a running 5/0 or 6/0 prolene suture on the back wall and simple suture repair on the front wall. Note: travel distance between each suture should be conservative. Finally, an air knot of 1/3 the diameter of the PV (growth factor) is tied in order to allow for venous swelling and to prevent an hour-glass formation of the anastomosis. Typically, a segmental defect of ≤3 cm can be repaired with a primary anastomosis using these principles (Fig. 195.2).

Segmental Resection and Interposition Grafting

For segmental resections of the PV or the SMV longer than 3 cm, we recommend the use of a vascular conduit as an interposition graft. Conduit selections include: autologous vein (left renal vein, internal jugular [IJ] vein), cryopreserved vein, bovine pericardium, peritoneum, and synthetic grafts. However, cryopreserved vein, bovine pericardium, peritoneum, and synthetic grafts are not considered optimal conduits for PV reconstruction. Our conduit preference for interposition grafting in the setting of pancreatectomy is autologous vein utilizing the left renal vein or splenic vein.

Left Renal Vein Graft

Traditionally, the left renal vein has been used to repair venous structures (PV, IVC or hepatic vein) during resection of hepatic hilar cholangiocarcinomas. Extrapolating this technique to the pancreas offers distinct advantages for venous reconstruction. Importantly, literature has shown the safety of distal left renal vein ligation, when ligated as close to the IVC as possible, therefore allowing the left kidney to drain through the gonadal and adrenal veins.[10] Advantages to this conduit include the ability to expose the vein within the same operative field and eliminating a second operative field as would be required to harvest the IJ vein.[10] Additionally, the caliber and wall thickness of the vein is similar to the PV, therefore providing ease in handling and suturing.[10]

Distally, the vein must be divided at the junction of the left gonadal and left adrenal veins. If chosen as a conduit it is critical to leave these veins intact to ensure adequate left renal drainage. Proximally, the vein is then divided flush with the IVC (Fig. 195.3). Division of the vein is undertaken with a linear (transverse anastomosis) stapling device. Generally, this conduit provides a 3- to 4-cm venous interposition. Following harvest, the venous segment should be maintained in heparinized saline until reconstruction. Interposition reconstruction should then be undertaken with 5-0 or 6-0 prolene suture in a running technique in an end-end fashion without spatulation (see Figs. 195.1 and 195.2).

Internal Jugular Vein Graft

IJ vein graft remains a valid option for segmental reconstruction. However, unlike the left renal vein, a separate surgical field is required. Harvest of the IJ vein is performed with the patient's head turned away from the surgeon and the neck slightly extended. An incision on the anterior border of the sternocleidomastoid muscle (SCM) is created and taken down to the carotid sheath. This can be facilitated by retracting the SCM laterally. Next, the carotid sheath should be entered and the facial vein ligated between ties. Next, the vagus nerve should be identified, keeping it free from injury. An appropriate length of IJ vein is then chosen and ligated between ties. Following harvest, the venous segment should be maintained in heparinized saline until reconstruction.

Interposition reconstruction should then be undertaken with 5-0 or 6-0 prolene suture in a running technique in an end-end fashion without spatulation (see Figs. 195.1 and 195.2).

Splenic Vein Preservation Versus Ligation

Splenic vein preservation is possible. However, preservation of the splenic vein significantly limits the mobilization of the PV and may prevent primary anastomosis of the SMV/PV following segmental resection if the tumor is opposite the splenic vein orifice. Thus, total pancreatectomy with SMV/PV end-to-end anastomosis may be the best option when all three vessels are encased. However, if there is excess distance to bridge then choosing a segment of splenic vein from the

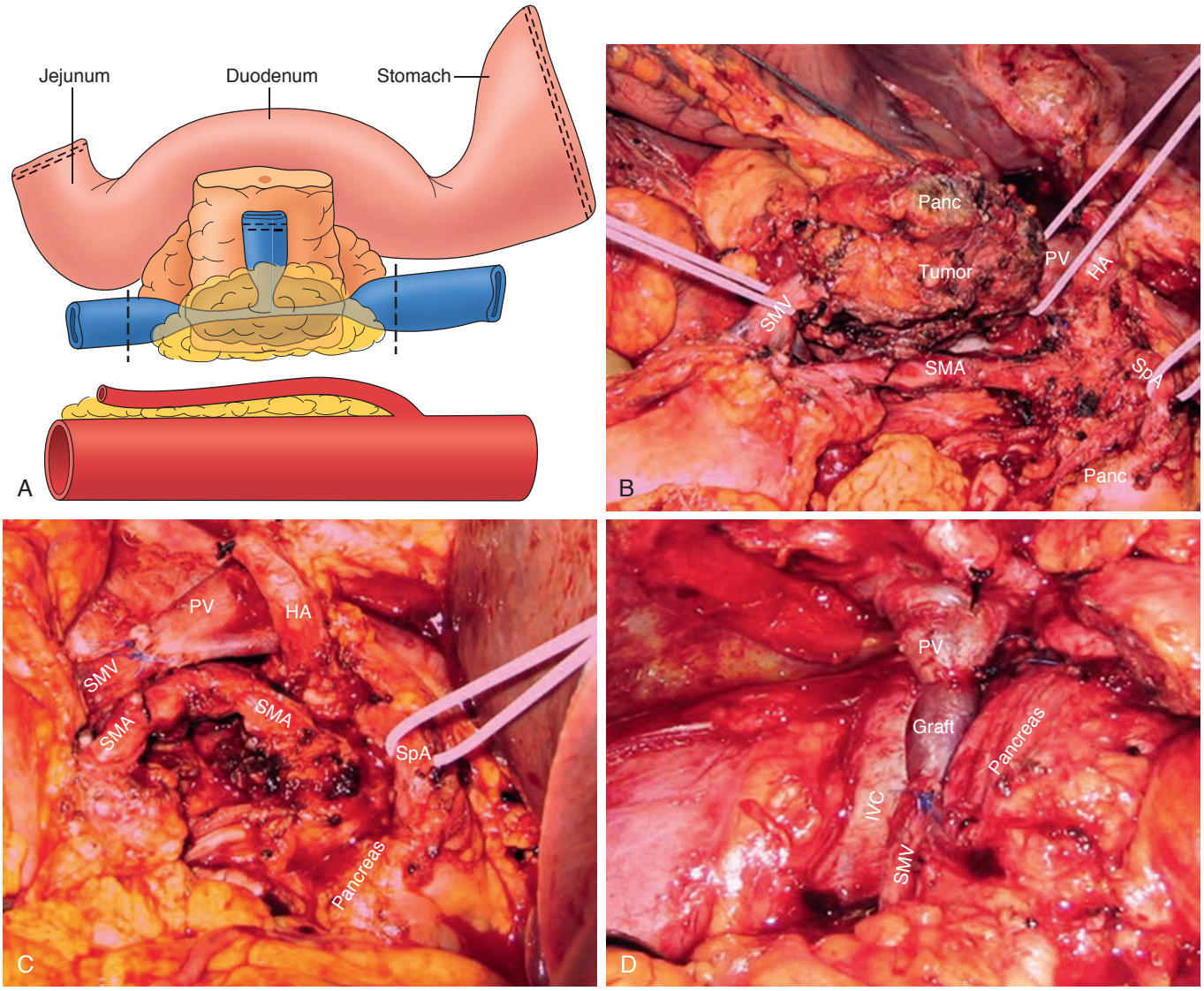

Figure 195.2 (A) Schematic of the completed dissection, tumor remains only adherent to SMV/PV. (B) Completion of dissection, tumor remains only attached to SMV/PV. (C) Completed segmental resection with primary anastomosis. (D) Completed segmental resection with autologous vein grafted anastomosis. *PV,* Portal vein; *SMV,* superior mesenteric vein. (From Strasberg SM, Sanchez LA, Hawkins WG, Fields RC, Linehan DC. Resection of tumors of the neck of the pancreas with venous invasion: the "Whipple at the Splenic Artery (WATSA)" procedure. *J Gastrointest Surg.* 2012;16:1048–1054.)

distal pancreas to use as a secondary splenic vein graft can be performed.[5]

Arterial Resection

To date, the oncologic benefit of arterial resection for pancreatectomy remains unclear. Historically, arterial resection was associated with high morbidity and has thus been considered a contraindication. More recently, Perinel et al. have published results of a cohort of patients who underwent planned arterial resection and reconstruction during pancreatectomy. This cohort was then compared to those who required only venous resection and those who required no vascular resection. The primary selection criteria for arterial resection was the possibility of achieving a complete resection based on the extent of axial encasement, the absence of tumor invasion at the origin of celiac trunk and SMA, and a free distal arterial segment to allow for reconstruction. Six SMA, two celiac trunk, four common hepatic artery, and two replaced right hepatic artery resections were undertaken with the preferred arterial reconstruction being a splenic artery transposition. There were no statistically significant differences in the incidence, grade, and type of complications in the three groups. Planned arterial resection for PDA may now be able to be performed safely. However, that said, 7/14 and 2/14 patients in the arterial resection group developed metastatic and two loco-regional recurrences, respectively.[11]

Please note, this study is presented as hypothesis generating and should not be taken as standard of care. A clear limitation to

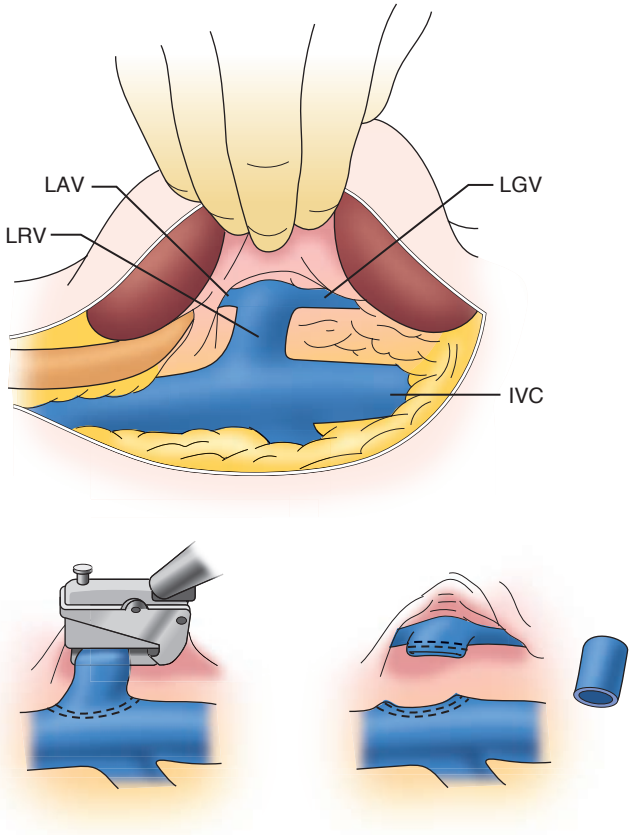

Figure 195.3 Left renal vein conduit. *IVC,* Inferior vena cava; *LAV,* left adrenal vein; *LGV,* left gonadal vein; *LRV,* left renal vein. (Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

this data remains the small sample size and heterogenous patient population, therefore contributing to unclear oncologic benefit.

Postoperative Considerations and Oncologic Outcomes

Postoperatively, patients do not require anticoagulation with heparin; however, it is our practice to start antiplatelet therapy (aspirin) on the first postoperative day and continue such antiplatelet therapy indefinitely. Doppler ultrasound imaging on postoperative day 2 or 3 is useful to detect any flow abnormalities that may require additional anticoagulation. Reported rates of venous thrombosis after reconstruction range from 0% to 44% and vary according to the repair[6]: longitudinal venorrhaphy was recently documented as 25%, patch repair 31%, and interposition grafting 44%. Transverse venorrhaphy and primary repair had a 0% thrombosis rate at a median follow-up of 316 days.[6]

With respect to oncologic efficacy, literature has shown equivalence between those who undergo SMV/PV resection to those who do not. In an assessment of long-term survival, 110 patients who had undergone SMV/PV resection were matched and compared to 181 patients who did not require venous resection. Median survival was 23.4 versus 26.5 months ($P = .177$), respectively.[5] Additionally, in a more recent study, comparing outcomes between patients who did and did not undergo venous resection at the time of pancreaticoduodenectomy, postoperative complications (55.7% vs. 50%), R0 resection (65% vs. 76%), and median overall survival (21.6 months vs. 19.7 months) were found to be similar.[12] Therefore in properly selected patients, venous resection during pancreaticoduodenectomy should be undertaken if technically feasible.

Celiac Axis Resection/Appleby Procedure

Involvement of the celiac axis by pancreatic body tumors is no longer considered an absolute contraindication to resection. In highly selected patients, resection is feasible and relies on collateral circulation through the gastroduodenal artery (GDA) to maintain hepatic arterial perfusion. However, we would note that in the setting of locally advanced pancreatic adenocarcinoma, we recommend the commencement of systemic therapy prior to the consideration of surgical exploration. Our current algorithm implements FOLFIRINOX or Gemcitabine/Abraxane followed by serial cross-sectional imaging. In the lack of an objective response, further neo-adjuvant radiotherapy may be employed.

That being said, if resection is deemed appropriate and the celiac axis remains grossly involved with tumor, an Appleby procedure can be performed. This allows for en-bloc resection of the common hepatic, celiac, and splenic arteries in combination with a distal pancreatectomy and splenectomy. Of paramount importance, adequate flow through the GDA must be determined prior to celiac axis resection and preserved to allow for continued hepatic arterial perfusion via retrograde flow to the proper hepatic artery.

The general operative principle for this procedure is the assessment of resectability by determining adequacy of retrograde blood flow through the GDA by isolating the celiac axis, common hepatic artery, and GDA. The common hepatic artery is then clamped. Flow in the proper hepatic artery and GDA is assessed by palpation and Doppler flow. The presence of a strong pulse/signal will allow resection to proceed.

Once deemed resectable, the common hepatic artery is clamped and divided. Transfixing sutures are placed at the superior and inferior borders of the pancreas and the pancreas is divided at the pancreatic neck. The celiac axis should then be exposed, clamped, and divided utilizing a prolene suture ligature. Standard distal pancreatectomy, splenectomy can then ensue.

HEPATIC AND BILIARY MALIGNANCIES

Despite advances in novel chemotherapeutics, biologic agents and immunotherapy, the best chance for cure and long-term survival for hepatic and biliary malignancies is surgical resection with negative margins. Even with improvements in regional hepatic therapies, patients who are deemed unresectable have overall worse survival than those who have a chance at curative

resection. However, regional nodal involvement often determines oncologic outcome beyond a technically successful resection. Historically, vascular invasion for hepatic and biliary tumors was considered a contraindication to surgical resection and thus conceived with high skepticism, as the risks of an operative intervention were felt to far outweigh the benefits.

However, with technical advances over time, combined hepatectomy and vascular resection as a means to obtain negative margins for many hepatobiliary malignancies has become acceptable. Most of the published literature of vascular resection and surgical outcomes comes from hilar cholangiocarcinoma (Klatskin tumors) due to the infiltrative nature of this malignancy (involvement of adjacent vascular structures within the hilum). Therefore this chapter uses hilar cholangiocarcinoma as an example to demonstrate the fundamental elements and operative approach of oncologic vascular surgery and reconstruction in hepatic and biliary malignancies.

Cholangiocarcinoma is the most common cancer of the biliary tree, accounting for 3% of gastrointestinal cancers.[9] Although many present with advanced disease, 50% to 70% of patients will be considered for curative resection. These particular cases present unique challenges as the disease can extend longitudinally along the hepatic ducts and obtaining a negative margin is often difficult. Resection of the extrahepatic biliary tree in conjunction with hepatic resection has become the standard of care.[10,11] The infiltrative nature of the tumor and the anatomic proximity of a Klatskin tumor to the PV, hepatic arteries, and IVC predisposes it to vascular involvement. Therefore hepatic surgeons must be facile in perihepatic vascular reconstruction of the PV, hepatic artery, or retrohepatic IVC in cases of locally advanced cholangiocarcinoma.

It goes without saying that these combined resections are associated with higher morbidity and mortality rates. Given the high morbidity of such surgical resection and complex decision making in this disease, management at high volume centers within a multidisciplinary team experienced in both surgical and perioperative management of these diseases is highly recommended.

General Considerations and Surgical Principles

In the management of hilar cholangiocarcinoma, it is of highest importance to define tumor resectability preoperatively. Management of these tumors with vascular reconstruction begins with a standard oncologic work-up, including preoperative cross-sectional imaging with either triphasic computed tomography (CT) or magnetic resonance imaging/cholangiopancreatography (MRI/MRCP) to assess the extent of vessel involvement. Variant vascular anatomy and ductal vascular relationships must be defined for preoperative planning for successful resection and vascular reconstruction. It is paramount to confirm vessel accessibility above and below the tumor level for vascular anastomosis. Additionally, it has become our practice to also obtain a preoperative duplex ultrasound to assess for vascular involvement.

The general principles of vascular reconstruction apply. It is essential to preoperatively address the need for vascular access, ability to establish proximal/distal control, and select appropriate conduits for vessel reconstruction in each patient individually. In general, guidelines for liver resections include a future liver remnant (FLR) of greater than 0.6% of total body weight (greater in the pretreated or cholestatic liver).[11,12] It is therefore recommended to obtain volumetric assessment preoperatively to avoid postoperative complication and liver insufficiency/failure, even more so in planned resections in conjunction with vascular reconstruction. In cases of borderline FLR, preoperative portal vein embolization (PVE) has been used as an important adjunct. In such cases, PVE should be performed 4 to 6 weeks before resection to allow time for adequate hypertrophy.

Portal Vein Reconstruction

Reconstruction of the PV in conjunction with hepatectomy was first described in the Western literature by Blumgart in 1990 for hilar cholangiocarcinoma.[15] Several years after, a "no-touch en bloc resection" technique[16,17] for hilar cholangiocarcinoma was described by Neuhaus and his colleagues.

Studies have shown histologic invasion in greater than one-third of cases in which the PV has been resected.[18] Although occult invasion does not often occur, the distance between the leading edge of cancer cells to the outer layer of the adventitia is usually less than 1 mm in most cases. With that, PV resection is the most common vascular resection performed for hilar cholangiocarcinoma and considered a means to obtain negative margins and thus a better chance of long-term survival. Preoperative planning and understanding the portal venous anatomy as well as the position of the hepatic artery in relation to it is key for successful outcomes.[19,20]

In general, primary end-to-end anastomosis is preferred compared to interposition grafting. To perform a primary anastomosis, complete mobilization of the proximal main PV to the level of the pancreas is recommended (as described above under pancreatectomy). For right-sided hepatectomies, a minimum of 1.0 cm segment of the PV prior to branching point is required for clamp placement and anastomosis.[9] Anastomosis of the left PV can almost always be performed in an end-to-end fashion as the left PV is accessible and should be performed before the liver itself is transected. If needed, anastomosis can be performed after parenchymal transection (Fig. 195.4).

As left-sided resections usually require a more extended resection, the right posterior sectoral branch becomes the general target for anastomosis. This reconstruction is usually performed after transection of the liver. If the main PV does not reach, common autologous vein grafts including left renal, femoral, jugular, and even hepatic vein from the resected liver can be used (see Fig. 195.3).[21-25] If no native veins are available, synthetic or cryopreserved grafts can be used but, if possible, should be avoided due to risk of infection and thrombosis.

Long-term survival when using PV resection depends entirely on the ability to achieve negative margins. Therefore with aggressive surgical care, the number of resectable and, therefore, curable patients has increased over time. Morbidity of combined resection with concomitant vascular reconstruction has improved

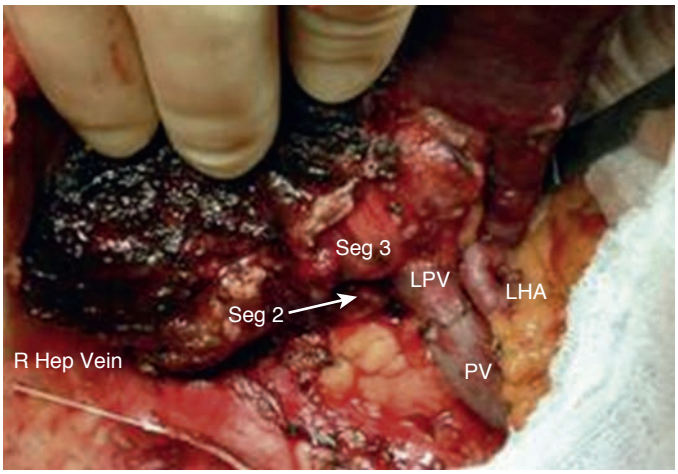

Figure 195.4 The tumor has been resected with a right trisectionectomy with bile duct resection and PV resection. The main PV has been anastomosed to the left PV. *LHA,* Left hepatic artery; *LPV,* left portal vein; *PV,* portal vein; *R Hep Vein,* right hepatic vein. (From Berumen J, Hemming A. Vascular reconstruction in hepatic malignancy. *Surg Clin N Am*. 2016;96:283–298.)

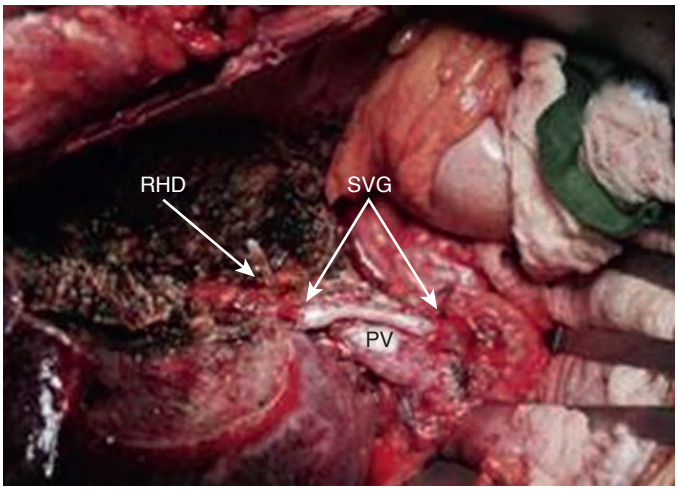

Figure 195.5 Extended left hepatectomy for hilar cholangiocarcinoma has been performed. The hepatic artery has been resected with a saphenous vein graft placed from the proper hepatic artery to the right hepatic artery several millimeters before it divides into anterior and posterior divisions. *PV,* portal vein; *RHD,* right hepatic duct; *SVG,* saphenous vein graft. (From Berumen J, Hemming A. Vascular reconstruction in hepatic malignancy. *Surg Clin N Am*. 2016;96:283–298.)

over the last decade. Several studies have shown that patients undergoing combined hepatectomy and PV resection with negative margins have similar outcomes to patients with negative margins undergoing hepatic resection alone.[9,18-20] Most recent reports have shown improved outcomes with perioperative mortality up to 33% in early studies in the 1990s and early 2000s to current reports of 0% to 5%, similar to liver resections without PV resection.[18,29,30]

Hepatic Artery Resection

In contrast to PV resection, data on hepatic artery reconstruction is more limited and long-term survival benefits have not been clearly described. However, an increasing number of series have successful outcomes of hepatectomies and PV/hepatic artery reconstruction in a selected patient population.

Most cases in which a hepatic artery resection in indicated, the artery is involved at its bifurcation and thus necessitates combined PV resection. Prior to any arterial reconstruction, it is of highest importance to review the anatomic variation in case native vessels are needed. As with the PV reconstruction, assessment of adequate clamping space for proximal and distal control sites and options for suitable grafts need to be made preoperatively. Arterial reconstruction should be performed after completion of PV reconstruction, which is usually done after the specimen is removed and the liver is transected. To perform a tension-free end-to-end primary anastomosis, the artery must be fully mobilized.[31] The preferred conduit for interposition graft is the GSV (Fig. 195.5).[32] Other options include the radial or splenic artery, however these should only be considered in the absence of a suitable saphenous vein.

Although originally studies demonstrated worse long-term outcomes with a higher operative mortality of up to 55%,[34,35] more recent outcomes from high volume centers with experience have shown acceptable results combining arterial and PV reconstruction. Nagino et al.[23] report the largest series of 50 patients who underwent combined PV and arterial reconstructions with an operative mortality rate of only 2%. With advanced microsurgical techniques, 32 of their cases were performed in a primary end-to-end, fashion, 11 with a saphenous vein and radial artery interposition graft, and 2 using a left or right gastric artery. R0 resection was achieved in 66%, with 1-, 3-, 5-year survival rates of 78%, 36%, and 30%, respectively.[23]

Inferior Vena Cava Resection

IVC involvement has traditionally been a contraindication to resection for hepatic and biliary malignancies given the poor postoperative outcomes. However, with improved techniques for liver resection and perioperative management, tumors involving the IVC and hepatic veins are now considered resectable in select patients with hepatic malignancies with acceptable morbidity and mortality.

Caval reconstruction depends, as with any other vascular reconstruction, on the degree and extent of involvement. If feasible, primary resection with a side-bite clamp with primary anastomosis or patch repair can be considered.[36] Otherwise, complete replacement of the vena cava with a synthetic or biological graft should be considered. For complete caval replacement generally speaking, the IVC should be exposed above and below the tumor and resection can be performed along with the parenchymal resection after vascular control has been obtained. Primary end-to-end repair may be feasible with a resected portion up to 3 cm. However, larger defects should be reconstructed using synthetic or biologic graft material. Reconstructive options include an interposition graft with a large caliber (18-22 mm) polytetrafluoroethylene (PTFE) ringed graft or a bovine pericardium patch if the caval defect is less than 1/3 the circumference. Contrary to what one might think,

there is no clinical evidence that using synthetic material leads to higher risks of infection in these vascular reconstructions.[37-40]

IVC resection and reconstruction has been associated with higher morbidity and mortality[38,40] rates but this risk has been accepted given its benefits in experienced hands and lack of alternative curative approaches. The largest series by Hemming and colleagues[42] included 60 patients over a study period of 16 years. In their study, defects of greater than 5 cm were repaired with autologous vein, bovine pericardium, or Gore-Tex. More than half of their patient population required full reconstruction with a Gore-Tex graft. Perioperative mortality was 8% and 3-year survival 35%.[43] Others have reported similar perioperative mortality rates ranging from 11% to 19% with a 5-year survival of 22% to 38%.[37-47] These results demonstrate that combined liver and IVC resection proves to be beneficial in fit and highly selected patients. Nevertheless, these radical resections should only be executed at highly specialized centers with experienced hepatobiliary surgery and liver transplantation and capacity of perioperative ICU and interventional radiology.

Renal cell carcinoma has a predilection for tumor growth into the IVC. For local involvement, tumor thrombectomy after proximal and distal control of the IVC can be performed. However, for more extensive tumor involvement, vena caval resection and reconstruction may be required.

SOFT TISSUE SARCOMA

Soft tissue sarcoma (STS) is a rare, heterogeneous group of tumors of mesenchymal origin, comprising over 50 histologic subtypes and representing 1% of all adult cancers.[48] The underlying oncogenesis of these tumors varies widely amongst the various subtypes. The most commonly affected site is the extremity (approximately 40% of cases)[49]; however, STS may arise anywhere in the body. STS is often locally aggressive and as such often involves multiple anatomic structures. Complete surgical resection is the mainstay of treatment and the only potentially curative therapy. Owing to the infiltrative nature of these tumors, local recurrence had historically been the pitfall of treatment[50-52] and highlights the need to achieve wide, microscopically negative margins. Management is best handled at high volume centers within a multidisciplinary team experienced in both surgical and medical treatment of this disease.

The surgical management of STS is further complicated when major vasculature is involved. Any major blood vessel or vascular bundle may require resection in order to remove all disease. Amputation was historically considered the ideal procedure to achieve local control.[53,54] Since the hallmark study by Rosenberg and colleagues in 1982 demonstrating similar oncologic outcomes of limb-preserving surgery in combination with adjuvant radiation as compared to amputation alone,[55] limb preservation has become the modern standard of care. It is often the case that a major blood vessel must be resected in order to achieve this goal. Limb preservation thus necessitated the development of techniques to reconstruct major blood vessels after extensive en-bloc oncologic resections. Recent literature has defined this field as "oncovascular surgery."[56] Both resection and reconstruction require careful planning among a team of experienced oncologic and vascular surgeons given the complex anatomy and locations of these tumors.

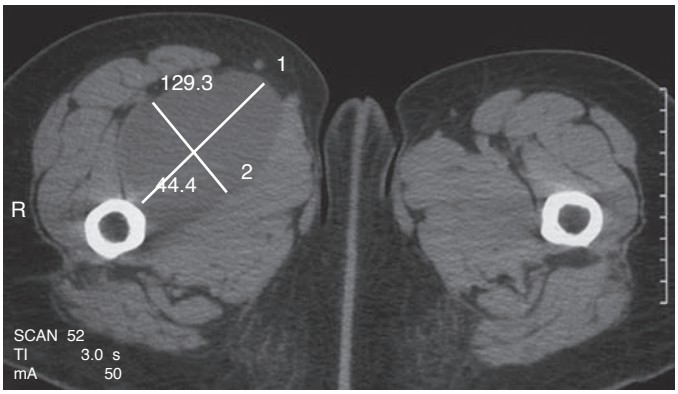

Figure 195.6 Preoperative CT image demonstrating a well-demarcated liposarcoma of the medial compartment of the right thigh. Surrounding soft tissue structures are well delineated from tumor. (From Karakousis C. Tumor in the medial thigh. In: *Atlas of Operative Procedures in Surgical Oncology*, New York: Springer Science + Business Media; 2015:327, Chapter 48, Fig. 48.7.)

General Considerations and Surgical Principles

Management of STS requiring concomitant vascular reconstruction begins with a standard oncologic workup, including appropriate staging. Each case should be individualized to the specific histologic type and managed within a multidisciplinary team. When vascular reconstruction is necessary, cross-sectional imaging with either contrast-enhanced CT or MRI is sufficient to delineate anatomic details such as involved vessels, modification to normal blood flow patterns, development of collaterals, and presence of intravascular thrombus (Fig. 195.6). MRI is particularly useful in defining involvement of soft tissues adjacent to vascular structures.[56,57] Adjuvant imaging modalities such as duplex ultrasonography can be helpful in select cases but often do not add significant information to the operative plan.

Considerations that are essential to address preoperatively include the need for vascular access, ability to establish proximal/distal vascular control, possible endovascular adjuncts, and specific strategies for reconstruction of the involved blood vessels.[56] Technique, extent of vascular resection, and choice of conduit vary widely among the literature and are often based on surgeon preference.[58-70] The most common materials utilized for oncovascular reconstructive surgery are summarized in Table 195.1. Short- and long-term patency rates of vascular bypass in STS resection are comparable to those performed for atherosclerosis,[58-70] thus emphasizing that the presence of STS itself does not significantly alter the vascular outcome of these procedures. Endovascular adjuncts may be performed pre- or postoperatively to optimize conduit patency and outcomes. Preoperatively, embolization of vessels perfusing hostile surgical fields such as large pelvic tumors has been employed to help manage predicted intraoperative bleeding.[71] Postoperative endovascular interventions may also be utilized to provide secondary patency and extend the life of a functioning vascular conduit.

TABLE 195.1 Materials Utilized for Arterial/Venous Reconstruction

Autologous vein
• Great saphenous vein • Femoral vein • Splenic vein • Jugular vein • Left renal vein
Cadaveric, cryopreserved vein
Cadaveric, cryopreserved artery
Bovine pericardium
Synthetic conduit
• Polytetrafluoroethylene (PTFE) • Polyethylene terephthalate (Dacron)

The extent of vascular resection and subsequent reconstruction is based upon the extent of the lesion, the predicted patient morbidity, and the preoperative venous anatomy. When curative resection is the goal, all involved vascular structures must be completely removed to achieve negative margins. In difficult anatomic regions where dissection may lead to massive hemorrhage and vascular involvement is unclear, the decision can be made to shave the tumor away from major vessels as opposed to a formal resection (Fig. 195.7). Although in some instances safer, this technique may leave behind residual microscopic disease along the adventitia. For arterial resections, reconstruction must always be performed given the inevitability of limb ischemia if adequate perfusion is not restored. If less than 50% of the vessel circumference is resected, patch angioplasty is an acceptable option. More extensive lesions require formal arterial bypass.

Venous resection with subsequent reconstruction is less definitively managed, with multiple options based on the clinical scenario. Veins which are chronically occluded or in the periphery of the surgical field can be sacrificed via ligation without significant effect on preservation of the limb[72,73] and is well tolerated (Fig. 195.8). Likewise, preoperative imaging displaying abundant venous collaterals can allow for ligation of major veins with similarly good outcomes.[59,66,67] Without evidence of collaterals or preoperative occlusion, the decision to reconstruct major veins is debated in the literature. Proponents of venous reconstruction cite that it adds very little morbidity to the overall procedure, while simultaneously acting as prophylaxis to severe postoperative venous hypertension with sequelae similar to that of a post-thrombotic syndrome.[61] Arguments against venous reconstruction make note that if assessed in the early postoperative period, venous conduits are often occluded,[69] although this is not a consistent finding in all series.[62] Authors have also argued that incidence of postoperative edema does not vary with or without venous reconstruction.[69] Furthermore, even in cases where edema from venous ligation is present, it can often be managed with standard medical treatments such as limb elevation and compression.[67,74] If a flap repair is used to cover the surgical defect, functional venous collaterals may also develop in the postoperative period and render venous reconstruction unnecessary.[75] Overall, it is acceptable to perform venous reconstruction when indicated but is not a surgical necessity.

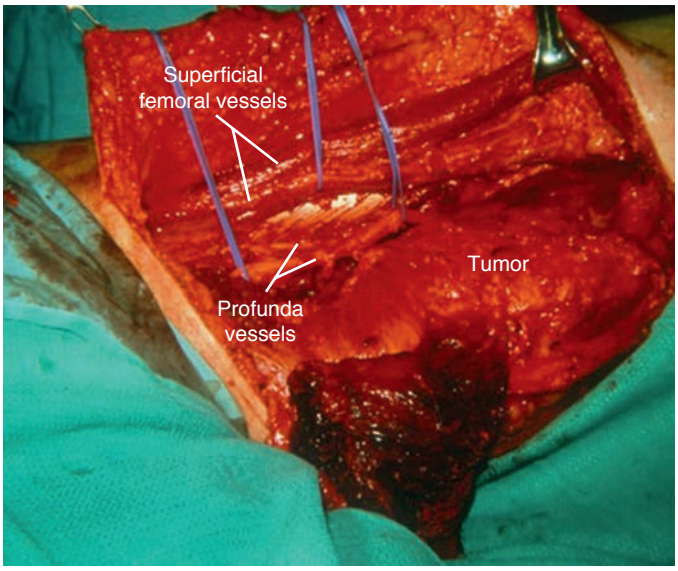

Figure 195.7 Dissection of a medial thigh sarcoma away from the superficial femoral and profunda femoris arteries. (From Karakousis C: Tumor in the medial thigh. In *Atlas of Operative Procedures in Surgical Oncology*, New York, 2015, Springer Science + Business Media; Chapter 48, p. 327, Fig. 48.8.)

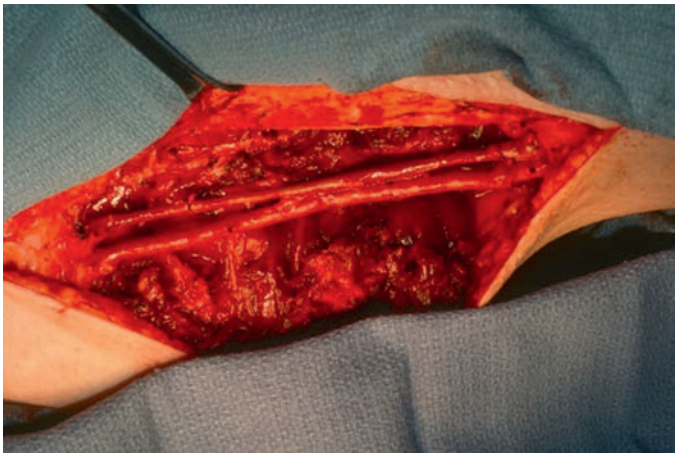

Figure 195.8 Resection of the femoral artery and vein with isolated arterial reconstruction. In the setting of chronic occlusion or well-developed collaterals, veins may be ligated without significant impact on limb preservation. (From Karakousis C. Tumor in the anterior thigh. In: *Atlas of Operative Procedures in Surgical Oncology*, New York: Springer Science + Business Media; 2015:321, Chapter 47, Fig. 47.19.)

Extremity Soft Tissue Sarcoma

The extremity is the most common location of STS, and in approximately 3% of cases a major neurovascular bundle is involved.[56] Historically, 47% of STS cases localized to the extremity resulted in amputation.[75] At that time, incomplete resections and local recurrence rates exceeded 60%[75] and thus did not provide a satisfactory oncologic outcome. Since the advent of adjuvant radiotherapy, amputation rates more recently approximate 0% to 8% as limb-sparing procedures evolved

to become the standard of care.[62,76] Importantly, limb salvage with vascular reconstruction offers comparable local tumor control,[62,68,69] and overall survival[76] as compared to amputation. Functional outcomes and quality of life are improved with limb-sparing procedures,[77] which is particularly important given the relatively young mean age of patients with STS.

Any major upper or lower extremity vessel may be involved in STS, and thus thorough knowledge of both the vascular anatomy and possible bypass options is a prerequisite to optimal patient outcomes. In order to achieve negative margins, the extent of the resection may be more significant than originally planned based on preoperative imaging. Thus, the ability to be flexible in regards to an operative plan is also paramount. The predominant site of STS is the lower extremity and therefore the vast majority of resections subsequently involve a lower extremity bypass. Upper extremity vascular resection and reconstruction is rare, but when performed most commonly involves the brachial artery.[68] Most if not all permutations of arterial reconstructions of the extremity are represented in the literature.[68,69,74] A list of common arterial reconstructions are represented in Table 195.2; however, various combinations may be required to restore adequate limb perfusion.

Choice of conduit in vascular reconstruction of the extremity after STS resection is based upon surgeon preference. For arterial reconstructions, most centers utilize autologous vein whenever possible as it provides lower rates of infection.[62,77] The GSV is the most commonly used autologous conduit given its length and ease of accessibility; however, several reports have illustrated good outcomes with the femoral vein as well.[68,78] When possible, the graft should be harvested from the contralateral limb so as not to worsen limb edema on the side of the primary resection, which commonly disrupts native venous tributaries and lymphatics. To date, there are no published studies demonstrating improved patency of venous over synthetic grafts after STS resection as has been the case in similar non-oncologic vascular procedures. The failure to recapitulate this finding is likely based upon underpowered sample sizes when studying this rare disease, and as such autologous vein should be considered a superior conduit overall. Anecdotally, synthetic conduits have been employed in a larger proportion of venous reconstructions as compared to arterial; however, autologous vein is also a suitable option for venous repair as well.

Outcomes with respect to vascular reconstructions for limb preservation are exceedingly good, as evidenced by limb salvage rates of over 90% in nearly all published studies. Five year arterial patency approximates 55% to 80%.[61-63] Venous patency rates are more variable and less well characterized. In general, thrombosis is more common in venous reconstructions secondary to the low flow state of this system. The clinical significance of these events is typically negligible, as most episodes of venous thrombosis are successfully managed with systemic anticoagulation alone. The most common morbidities related to vascular reconstructions after STS resection are wound infection, skin flap necrosis, limb edema, hematoma, and graft thrombosis.[61-63] Early arterial thrombosis is quite rare but necessitates reintervention to restore perfusion to the extremity, which typically involves revision and/or complete reconstruction of the vascular conduit.

Patients with STS who undergo limb-preserving surgery with adjuvant radiotherapy have similar long-term outcomes as those who undergo limb amputation. Five year overall survival approximates 40% to 65%.[61-63] The success of STS resection is incumbent upon complete removal of disease, and as such most reports achieve R0 (margin negative) or R1 (microscopically positive margin) resections in nearly all cases.[61-63] This has only been made possible by modern advances in vascular bypass, which permit safe clearance of even questionably involved structures. At one time, local recurrences plagued the surgical management of STS. With current limb-preserving techniques and radiotherapy, local recurrence has diminished from over 60%,[3] to approximately 16%.[61-63]

TABLE 195.2 Common Reconstructive Bypasses of the Lower Extremity

Femoropopliteal
Iliofemoral
Femorofemoral
Popliteopopliteal
Popliteotibial
Tibiotibial
Saphenofemoral (venous)

Retroperitoneal Soft Tissue Sarcoma

Retroperitoneal STS represents a particularly challenging surgical disease, which is only further complicated when the aorta, IVC, or both are involved. Retroperitoneal STS comprises 15% of all cases of sarcoma.[56] As with other anatomic locations, these tumors are locally aggressive and invade nearby vital structures. These tumors are often asymptomatic until they achieve a sufficient size to cause compression of local structures, and as such typically involve multiple organs. Multivisceral resections (defined as the removal of two or more organs) are frequently required to achieve negative margins.[59,67] When the aorta or IVC are involved, additional concerns arise as both structures must be resected if a curative surgery is planned.

Preoperative workup must focus specifically on identifying the extent of vascular and solid organ involvement. Tumors may present anywhere from the aortic hiatus and retrohepatic IVC superiorly to the common iliac bifurcation inferiorly. Extension into the pelvis makes adequate exposure and safe dissection more difficult, and in some cases impossible. When the aorta or IVC are involved, consideration must be given to the possible need for cardiopulmonary or veno-venous bypass. The potential need for postoperative renal replacement therapy (RRT) must also be considered if the renal vasculature requires resection or a formal nephrectomy is a possibility. Therefore we favor obtaining preoperative split function renal testing. Based on the extent of the tumor, a tentative but specific operative plan must be developed in order to make preparations for the vascular reconstruction.

With respect to vascular reconstruction, involvement may comprise the artery alone, vein alone, or a combination of the two. Similar to vessels in the extremity, if less than 50% of the

vessel circumference is resected, angioplasty (primary or patch) is a reasonable option.[64] Both synthetic and autologous materials can be used for this purpose.[64] In the setting of bowel resection, which is common in retroperitoneal STS, some centers opt to avoid synthetic materials.[64] Good results have been reported with the use of cryopreserved autologous vein, saphenous vein, femoral vein, and IJ vein.[64] If greater than 50% of the vessel circumference is involved, a formal resection and reconstruction must be performed to avoid compromising flow. Both the aorta and the IVC may be reconstructed utilizing autologous or synthetic conduits.[70] Given the large diameter of both vessels, synthetic conduits are generally the first line choice. These offer several advantages, including avoidance of donor site morbidity, ease of matching vessel diameter, and a shorter procedure. When large en-bloc resections are required, concomitant replacement of the aorta and IVC can be performed and has been done so with favorable results.[18] Similarly, reimplantation of one or both renal vessels on either side of the conduit can be performed if necessary.[70] For situations in which IVC reconstruction is exceedingly difficult or dangerous, the IVC can be ligated. Up to half of these patients will develop subsequent venous hypertension and lower extremity edema if collaterals are poor.[79] Similarly to reconstructions in the extremity, the two exceptions to this are if occlusive thrombus is present proximal to the resected vein segment preoperatively, or significant venous collaterals have been identified on cross-sectional imaging. In either of these scenarios, the IVC can be ligated without significant sequelae.

Postoperative management after retroperitoneal STS resection has the potential for high morbidity given the multivisceral component, extensive dissection required to achieve negative margins, and prolonged time spent in the operating room to perform the necessary vascular reconstruction. Mortality is notably rare[67] but is certainly a more significant concern as compared to resection of extremity STS. Patency of the reconstructed aorta and IVC is very good as a result of the large diameter of these vessels, with overall graft patency rates of approximately 90% at 2 years follow-up.[69] Common early postoperative morbidities include hemorrhage, wound infection, prolonged ileus, and renal insufficiency.[69] Hemorrhage may resolve without intervention or may be a harbinger of significant complication, in some cases necessitating revision of the vascular conduit.[67] Late complications include abscess formation and ureteral stenosis.[67]

Oncologic outcomes for retroperitoneal STS involving major blood vessels are comparable to those of the extremity only if complete resection with negative surgical margins is achieved. In other words, patients with retroperitoneal STS after R1 resections have worse outcomes than patients with R0 resections. In the largest series to date assessing retroperitoneal STS resection with major blood vessel involvement, R0 resection yielded 2- and 5-year survival rates of 90% and 66.7%, respectively. However, patients with an R1 resection had a mean survival of 21 months, and R2 resections had 8 months mean survival.[20] Local recurrence in this series approximated 18% for complete resections.[67] Neoadjuvant and adjuvant therapies vary widely among centers, but nearly all patients will receive some variant of adjunctive treatment.

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CHAPTER 196

Chronic Exertional Compartment Syndrome

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Chronic exertional compartment syndrome (CECS) is a nonatherosclerotic cause of claudication that is often referred to a vascular surgeon. As the name implies, it is exercise-induced leg pain that usually presents in young, active patients such as athletes and military personnel. Symptoms are generally confined to the compartment of the leg that is affected and are reproducible to timing, distance, and the intensity of exercise.

HISTORY

CECS was first described in 1912 by Edward Wilson during an expedition to the South Pole.[1] In his diary he described his symptoms, which are consistent with anterior compartment syndrome. Various descriptions were offered until G. E. Mavor published his article regarding a professional soccer player in Aberdeen, Scotland, who complained of pain in the anterior compartments of both legs during exercise. In addition, he had paresthesias associated with the pain in his foot. Mavor ultimately performed the first published fasciotomy for CECS. Interestingly, his repair was completed with a fascia lata graft to close the defect. The operation worked so well that after he performed it on the contralateral leg, the patient was able to resume his soccer career.[2]

ETIOLOGY

The exact mechanism is unknown but CECS is believed to arise from increased compartment pressure (ICP) resulting in transient muscular ischemia within the enclosed myofascial space during endurance training.[3,4] In contrast to an acute compartment syndrome, in which the pressure remains elevated, in CECS the pressure dissipates over time and the symptoms resolve. Theories that have been proposed to explain the development of ischemia include arterial spasm, microcirculatory obstruction, and arteriolar and venous collapse due to pressure disturbances.[5] Studies on normal muscle reveal a 20% increase in muscle size secondary to increased blood volume and exercise.[6] In addition, fascial thickening and hypertrophy have been postulated to account for this syndrome.[7] However, some studies, including those by Amendola, have found that pain is not related to ischemia on nuclear medicine blood flow imaging; in their study of patients with CECS utilizing MRI did not

Abstract

Chronic exertional compartment syndrome is a nonatherosclerotic cause of claudication in the young patient. It is present in highly active athletes and soldiers, involving increased intracompartmental pressures (ICMPs) during activity. Its diagnosis relies on a heightened clinical suspicion, physical examination, and compartment pressure measurements after exercise. Treatment involves a fasciotomy of the affected compartment.

Keywords

claudication in young patients
compartment pressure
non-atherosclerotic leg pain

find ischemic changes in all of the patients with elevated pressures.[8]

EPIDEMIOLOGY

Risk factors include anabolic steroid use, with resultant muscle hypertrophy and abnormal biomechanics during running that favor increased load bearing by various compartments of the leg.[9,10] The estimated prevalence of CECS in patients with exercise-induced leg pain is 10% to 60% in relation to the diagnostic criteria utilized.[11] In a study of 150 athletes with exercise-induced leg pain, CECS was the most common condition (34%), followed by stress fracture of the tibia, accounting for 25%.[12] Most patients with CECS present with pain in the anterior and lateral compartments and 70% to 80% of these will have bilateral symptoms. Studies have not revealed a difference in males and females and the median age of presentation is 20 years.[13] The condition is often seen in military personnel and recruits. Waterman and colleagues reviewed the military health database over an 8-year period and identified 611 patients who underwent 754 surgical procedures. Of these procedures 77.4% involved only the anterior or lateral compartment. Symptom recurrence after treatment was 44.7%, and 27.7% of these individuals were unable to return to full activity. Surgical failure was associated with perioperative complications, activity limitations, and persistence of preoperative symptoms. The investigators concluded that CECS was a substantial contributor to lower extremity disability in the military population.[14]

In a systematic review among athletes, runners and soccer players were most prone to develop CECS. In addition, the presence of deep posterior compartment syndrome in this young population is associated with higher rates of surgical failure.[15]

DIFFERENTIAL DIAGNOSIS

A history of reproducibly developing pain in a compartment of the leg with exercise in a young, active person is typically seen. The pain can be described as burning or aching. In patients referred to a vascular specialist, the main diagnosis that should be considered is popliteal entrapment syndrome (PES). Although patients may describe similar symptoms as seen in CECS, often a diminished pulse is not noted with provocative maneuvers; subsequent noninvasive studies will generally fail to identify popliteal compression. Other etiologies of exercise-induced leg pain—such as stress fracture and medial tibial stress syndrome (shin splints)—can be ruled out by physical examination and x-ray imaging. Other nonatherosclerotic etiologies that should be considered include cystic adventitial disease of the popliteal artery and thromboangiitis obliterans (Buerger disease). Both of these conditions, along with atherosclerosis, are not generally seen in this young, active population.

ANATOMY

The leg is divided into four compartments: anterior, lateral, superficial, and deep posterior. The structures located within the anterior compartment include the deep peroneal nerve, anterior tibial artery, tibialis anterior, and extensor muscles of the toes. The lateral compartment contains the superficial peroneal nerve and the peroneus longus and brevis muscles. The superficial posterior compartment contains the gastrocnemius and soleus muscles and the sural nerve. The deep posterior compartment contains the tibial nerve, posterior tibial artery, peroneal artery, tibialis posterior muscle, and flexors of the toes.

CLINICAL PRESENTATION AND DIAGNOSIS

CECS should be suspected in a young, active patient with reproducible symptoms that occur with endurance training and resolve with rest. In this patient population, in addition to the symptoms already described, exercise history may reveal neurologic symptoms based on the involved compartment. For example, for the most common compartments affected, the patient may describe weakness with dorsiflexion (anterior compartment, deep peroneal nerve), numbness of the dorsum of the foot (lateral compartment, superficial posterior compartment), or, more rarely, weakness of plantarflexion (posterior compartment, tibial nerve).

Physical examination is unrevealing at rest. The individual compartments may feel firm or be tender to deep palpation, and fascial hernias may be present as well.[3] Neurologic examination should focus on the suspected, specific compartment and nerve involved to identify chronic irritation. The pulse examination and resting ankle-brachial indices will be normal in these individuals.

The definitive diagnosis of CECS is established by invasive measurement of intracompartmental pressures (ICMPs). A handheld device is available (Stryker catheter, Kalamazoo, Michigan) that allows rapid measurement (Fig. 196.1). With this device, the pressure can be measured in the compartments of interest. The classic diagnostic criteria described by Pedowitz are as follows: ICMP before exercise 15 mm Hg; 1 minute after exercise, greater than 30 mm Hg; and 5 minutes after exercise, greater than 20 mm Hg.[16] The exercise regimen described in studies is often variable and inconsistent. A more recent protocol developed by Roscoe in the United Kingdom involves continuously measured ICMP before, during, and after participants exercise on the treadmill. A standardized exercise protocol was utilized, and the investigators compared patients with a suspicion for CECS with healthy volunteers. The protocol included measuring beyond 5 minutes of exercise and to maximal tolerable pain as the individuals tested went through three phases of exercise carrying a weighted backpack and with varying grades on the treadmill. When the investigators compared their technique, they found a higher sensitivity and specificity for the diagnosis of CECS.[11]

Recent studies have investigated the use of MRI to diagnose CECS. Ringler performed a validation study with MRI in 76 patients referred for pain induced by a lower extremity exercise; as a result, 23 patients met the clinical diagnostic criteria for CECS. Utilizing a T2-weighted intensity ratio of 1.54 and correlating with ICMP measurements, the sensitivity of MRI

Figure 196.1 Intracompartmental pressure measurement.

was 87% and specificity was 62%. Others have also had promising results with MRI and described the benefit of visualizing fascial thickening and edema as well muscle hypertrophy.[17] Other modalities such as near-infrared spectroscopy (NIRS) have been investigated as well. This technique is able to noninvasively measure the tissue oxygen saturation with a sensitivity similar to that of MRI.[18] All of these modalities are promising, but ICMP is the current "gold standard" for the diagnosis of CECS.

MANAGEMENT

Nonsurgical

Most patients are initially offered a trial of decreasing or stopping the physical activities that trigger the symptoms. Cessation of eliciting activities usually resolves all symptoms; but in this patient population, who are often high-performance athletes, it is not a realistic option. Multiple nonsurgical interventions have been described for the treatment of CECS, including the use of insoles and orthotics to correct excessive pronation, running on softer surfaces, physical therapy, icing, warm therapy, nonsteroidal anti-inflammatory drugs, and even local lidocaine injections.[10,13,19] All nonsurgical treatments have had little success; surgical intervention with compartment decompression is the only reliable option that can return these patients to prior activity levels.

Surgical

Surgical compartmental release is accepted as the only effective treatment of CECS. The goal of the intervention is to decrease the ICMP by increasing the volume of the affected compartments. Multiple fasciotomy techniques have been used, including subcutaneous and endoscopic fasciotomy, as well as fasciectomy, with similar results. This outpatient procedure can be performed under local, regional, or general anesthesia. A compressive dressing is usually applied in the operating room, and we prescribe graded compression stockings (15-20 mm Hg) for the first 14 days after the surgery for patient comfort.

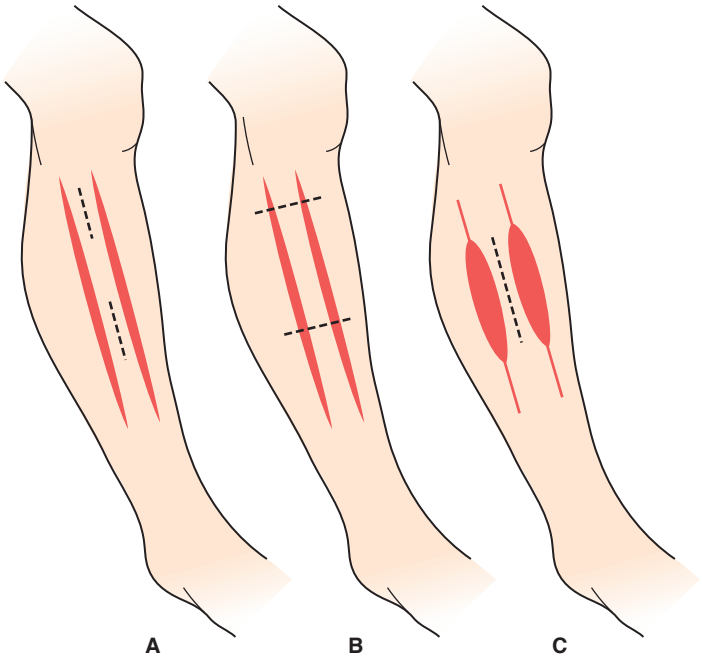

Figure 196.2 Schematic representation of alternate anterior and lateral compartment release techniques. See text below for details. *Dotted line:* skin incision.

Anterior and Lateral Compartment Fasciotomy

Following the technique described by Rorabeck in 1983, the compartments are released by using two 4-cm vertical skin incisions separated by a 15-cm skin bridge. The incisions are centered between the fibula and the crest of the tibia and a plane is developed between both incisions. Decompression of the anterior and lateral compartments is achieved by retracting the skin and incising the fascia 1 cm medial and lateral to the intermuscular septum (Fig. 196.2A). A similar decompression can be achieved by performing a single 5 cm skin incision over each compartment and incising the underlying fascia subcutaneously with Metzenbaum scissors (Fig. 196.3). Another technique employs two transverse skin incisions to perform subcutaneous

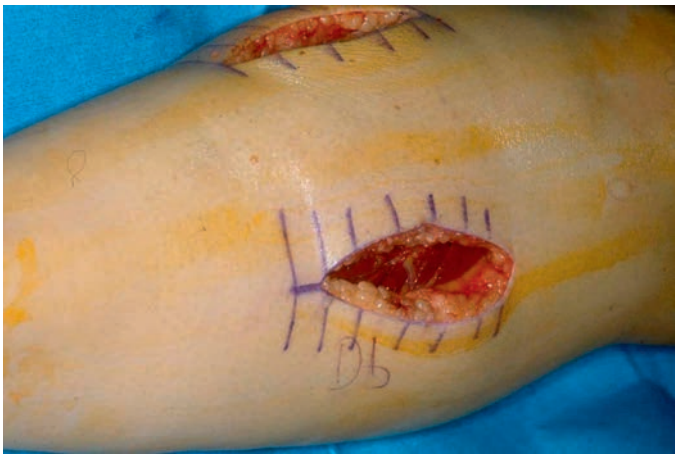

Figure 196.3 Anterior and lateral compartment fasciotomy.

fasciotomy of the anterior and lateral compartments (see Fig. 196.2B).

Open fasciectomy of the anterior and lateral compartments is performed using a single incision lateral to the edge of the tibia. After raising subcutaneous flaps of appropriate length, the fascia of both the anterior and lateral compartments is exposed and an approximately 6- by 2-cm ellipse of fascia is removed. This procedure is usually combined with fasciotomies performed by incising the fascia proximally and distally in order to achieve complete compartment release while the fascia overlying the intermuscular septum is left intact (see Fig. 196.2C).

Posterior Compartments Release

One or two vertical incisions are made behind the posteromedial edge of the tibia. The greater saphenous vein and the saphenous nerve are identified, mobilized if needed, and protected during the procedure. The fascia is incised and, in order to decompress the deep posterior compartment, the tibial attachments of the soleus are taken down so as to expose the deep posterior compartment fascia. The fascia overlying the deep posterior compartment is incised, exposing the flexor digitorum longus and decompressing the compartment.

Endoscopic Compartmental Release

Similar to the technique of subfascial endoscopic perforator surgery (SEPS), endoscopic compartmental release has been described. A transverse incision is made in the proximal leg just medial to the fibular head and a dissection plane is created into the loose areolar tissue just superficial to the fascia where the balloon dissector is inserted. The balloon is advanced to the distal leg and inflated in order to create a cavity within the fascial cleft. The fascia overlying the anterior and lateral compartments is released under direct visualization.[20]

To release the superficial and deep posterior compartments, a skin incision is made proximally on the medial aspect of the leg; the balloon is advanced into the loose subcutaneous tissue just above the fascia, inflated, and removed after developing the cavity. Using endoscopic scissors and under direct visualization, the fascia overlying the superficial posterior compartment as well the fascia of the deep posterior compartment are released directly off the edge of the tibia.[20]

POSTOPERATIVE MANAGEMENT AND COMPLICATIONS

The patient is instructed to perform range-of-motion and stretching exercises, and we do not place limitations on weight bearing postoperatively. Patients are encouraged to ambulate early after the procedure. Vigorous activities such as running and participating in team sports are not recommended for the first 2 weeks to ensure skin healing. Activities are gradually advanced and the patient is expected to return to full activity in 6 to 8 weeks.

The most frequent complication is postoperative neurologic dysfunction, specifically superficial peroneal neuritis, which affects up to 5% of patients. Infection, seroma, hematoma, DVT and wound dehiscence are rare in this patient population.

OUTCOMES

Although surgical treatment is accepted as the only effective treatment option for CECS, outcomes are not universally positive. Furthermore, there is no standardized tool, questionnaire, or metric to report the efficacy of the intervention, making the evaluation of success across published cases series difficult. Earlier reports described resolution of symptoms in almost 100% of cases, but recent papers report success rates below 50%.[21,22] In the military population, 25% of patients are unable to return to active duty even after surgical treatment.[14] Interestingly, 84% of patients are satisfied with the results of the procedure at short- and midterm follow-up.[15] Overall, the estimated clinical success rate of compartmental release for CECS is around 66%.[15]

Recurrent symptoms are reported by 5% to 10% of patients, and approximately 6% of patients undergo revision surgery.[23] Incomplete or inadequate compartment decompression as well extensive scarring are the usual reasons for revision surgery.

Multiple studies have investigated predictors of surgical failure after all of the described procedures (fasciotomy, fasciectomy, endoscopic fasciotomy), which have yielded similar results. Based on anatomy, the diagnosis of CECS of the posterior compartment is associated with the poorest outcomes.[23,24] Satisfaction after the procedure and return to the previous level of activity does not correlate with preoperative ICMP values.[23] However, chronicity and a longer duration of symptoms are associated with worse outcomes. Poor outcomes have also been found among female athletes, but the underlying reason for this finding is unknown.[24]

CECS is an unusual cause of claudication in the young patient, and every vascular surgeon should understand the presentation, diagnosis, and treatment of this pathology. In contrast to older patients with claudication due to atherosclerosis, the symptoms of CECS occur with more strenuous exercise, and we should understand that cessation of activity is not a reasonable recommendation for this patient population. However, it is also

important to appreciate that even though the procedure is not complex, the surgical outcomes are not uniformly positive.

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197 CHAPTER

Development and Operation of Multispecialty Cardiovascular Centers

MICHAEL R. GO, JEAN E. STARR, and BHAGWAN SATIANI

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INTRODUCTION

A service line strategy has long been used by medical centers to counter inefficiency in provision of multidisciplinary care, improve quality, and capitalize on high-frequency diseases with well-reimbursed treatments. Common examples are neuroscience, cancer, and wound care services. The concept of a vascular service line has existed since World War II,[1] and organized cardiovascular (CV) centers have existed in civilian hospitals since the 1980s.

However, service line strategies involving multiple specialties can be a challenge in academic medical centers (AMCs), where departmental silos can splinter the care of a single patient. For example, vascular disease can be managed by vascular surgery, vascular medicine, interventional radiology, and cardiology.[2] These difficulties may also arise in community hospitals, where turf battles between private groups may exist.

Currently, the multispecialty CV center remains a priority of health system leaders,[3] but the forces shaping their evolution are changing rapidly in the contemporary healthcare environment. Successful multispecialty CV centers are adapting, whereas others are losing market share. Vascular diseases in particular represent a strategic priority for CV centers because of the projected growth in demand for services, disruptive technology, prevailing poor care coordination, and a lack of integration with cardiac disorders.[4] In this chapter, we will review early examples of multispecialty CV centers and the impact of changes in market forces, consider development and operational aspects, appraise trends within existing CV centers, and look ahead into the future.

Abstract

A service line strategy has long been used by medical centers to counter inefficiency in provision of multidisciplinary care, improve quality, and capitalize on high-frequency diseases with well-reimbursed treatments. However, service line strategies involving multiple specialties can be a challenge in academic medical centers, where departmental silos can splinter the care of a single patient. For example, vascular disease can be managed by vascular surgery, vascular medicine, interventional radiology, and cardiology. These difficulties may also arise in community hospitals, where turf battles between private groups may exist. The multispecialty cardiovascular center remains a priority of health system leaders, but the forces shaping their evolution are changing rapidly in the contemporary healthcare environment. The successful cardiovascular center of the future must be multidisciplinary and patient centered, empower physicians and other leaders to participate fully in governance and business decisions, design quality of care guidelines, abandon siloed care, and move to collaborative models.

Keywords

Multidisciplinary vascular center
cardiovascular service line
heart and vascular institute
vascular surgery
multidisciplinary collaboration

EARLY EXAMPLES OF MULTISPECIALTY CARDIOVASCULAR CENTERS

An early concept of a vascular center was described by Elkin and DeBakey in 1943:

> *The problem of supplying competent specialized care by experienced personnel for large numbers of casualties with vascular injuries was solved in World War II by the establishment in the Zone of Interior of vascular centers to which surgeons experienced in vascular surgery were attached and in which other surgeons could be trained. To these centers were sent patients with vascular injuries and diseases. The establishment of these centers made it possible to carry out the necessary treatment of such patients with an economy of equipment, personnel, and effort which would have been impossible had the patients been scattered through a large number of hospitals. It also permitted the observation of patients with vascular injury and disease in numbers far beyond those of any similar previous experience. Careful and detailed records were kept and analysis of data derived therefrom permitted deductions and conclusions which could not be gained from the small series of cases previously observed by surgeons in civilian practice.*[1]

Even in the midst of war, these surgeons had the foresight to recognize and address the challenges and opportunities facing a service line strategy, all the while paying equal attention to the clinical care, teaching, and research missions. The War Department set up the first vascular center at Ashford General Hospital in West Virginia. It was, indeed, a true multispecialty CV center consisting of a surgeon, assistant surgeon, two medical officers, a cardiologist, a physiotherapist, and an officer to supervise reconditioning after treatment had concluded.

Modern CV centers do not have to deal with the volumes of military injuries that Ashford General Hospital did but instead must navigate an increasingly complex environment with a shifting regulatory landscape, decreasing reimbursement, demands for transparency and quality measures, and interspecialty competition. However, CV centers are well suited for multispecialty collaboration. Emphasis on one organ system, high volumes and visibility, and a major source of revenue for health systems have led to initiatives to undertake new care models with reimbursement tied to varying incentives through novel strategies, such as Medicare demonstration projects. With increasing employment of all CV specialties by health systems, the task of getting multiple specialties to agree on protocols and quality metrics has become possible. Modern vascular centers that employed CV specialists arose in the 1980s and include the Mayo Vascular Center.[5]

The birth of the Mayo Vascular Center in 1987 arose from the recognition that because multiple clinical departments were involved in the diagnosis and treatment of most vascular diseases, diagnostic testing suites and physician clinics became physically and administratively distinct and spread across the campus. As the Mayo Vascular Center developed a national referral base, these separations introduced significant inefficiency. The strategic vision of the founders of the Center prioritized a "one-stop" patient experience and openness to any interested specialties. This represented an early recognition of patient satisfaction as a quality metric, as well as the potential for competition between specialties in the vascular space.

Initially, large private health systems were unable to duplicate the Mayo experience, which is unique both geographically as well as organizationally, following a foundation model for physician-hospital alignment.[6] However, as the fee-for-service model evolved into the health maintenance organization (HMO) era in the 1980s and 1990s, then to the present value-based payment (VBP) system in which cost containment and value are emphasized, academic, private, and foundational model CV centers have found success, and their strategic visions have dramatically changed and increased in complexity.

FORCES SHAPING THE EVOLUTION OF CONTEMPORARY MULTISPECIALTY CARDIOVASCULAR CENTERS

The United States spends more than any other country on healthcare, and by 2020 US healthcare expenditures are projected to exceed 20% of the gross domestic product.[7] Inefficiencies in US healthcare are widely viewed as opportunities to contain costs, particularly in the government-sponsored Medicare and Medicaid programs. Regulators and the public are increasing focus on value, transparency, and definitions of quality. Total demand for CV services is increasing rapidly as the population ages, while a specialty physician shortage looms.[4,8] What started out as a marketing tactic aimed at increasing market share has now evolved into a holistic focus on quality, efficiency, transparency, patient satisfaction, and cost, almost all driven by changing reimbursement systems. Health systems still continue to fight for market share to compensate for diminishing revenue. This is the difficult environment in which the contemporary multidisciplinary CV center must succeed. Hospital systems and physicians alike should weigh the advantages and disadvantages before undertaking the process of CV center formation (Table 197.1).

Changes in Demographics and Care Delivery

The number of board-certified vascular surgeons in the United States has remained relatively stable, and in 2010 there were, by one estimate, fewer than 3000. This number is projected to grow linearly over the next 3 decades to approximately 3500 in 2040.[9] Simultaneously, the general population will continue to expand rapidly, and the elderly population even more quickly over the coming years. Vascular surgeons are one of the smaller physician workforces, yet they take care of a disease that is part of the leading cause of death in the United States. A vascular surgeon shortage looms, and this has and will continue to shape the makeup of the vascular provider pool and the

TABLE 197.1 Pros and Cons of Establishing a Multidisciplinary Cardiovascular (CV) Center

Pros	Cons
• Common CV disease process • Demand for CV care is increasing • Ease of access for patients with multiple medical problems • Ease of access for referring physicians • Improved relationship and influence with payers • Decreased duplication of services and expenses • Improved quality oversight • Consolidated marketing strategy • Development of a CV scorecard to measure success	• Consolidation of services may require capital expenditures for physical facility • Physician engagement may be difficult due to diminished autonomy and interspecialty conflicts • May be seen as hostile to medical education and research • Change in reporting structure (especially academic medical centers) • Difficulties in aligning compensation among specialists • Challenges to aligning procedural privileging • Patients still require other services so not completely self-reliant

TABLE 197.2 Essential Components of a Multidisciplinary Cardiovascular (CV) Center

1. Medical/surgical specialties:
   a. Vascular and endovascular surgery
   b. Cardiothoracic surgery
   c. Cardiology: interventional and noninvasive
   d. Radiology: interventional and noninterventional
   e. Vascular medicine
   f. Anesthesiology
   g. Podiatry
   h. Neurology/neuroradiology
   i. Endocrinology (including lipid metabolism)
   j. Wound care specialist
2. Vascular nursing
3. Noninvasive vascular laboratory
4. Noninvasive cardiac laboratory
5. Rehabilitation: cardiac and vascular diseases
6. Prevention and wellness screening programs
7. Research
8. Education

modes of delivery of vascular care.[8] Because vascular care is also provided by cardiologists, interventional radiologists, and vascular medicine specialists, a multidisciplinary CV center makes an ideal organization in which to provide comprehensive services to patients with a common pathology (Table 197.2).

Although still relatively rare before the age of 50 years, by age 80 the prevalence of peripheral arterial disease (PAD) rises to 20%. By 2030, 180,000,000 people are estimated to have at least one risk factor for PAD.[9] Thus, as the elderly population continues to expand faster than younger segments,

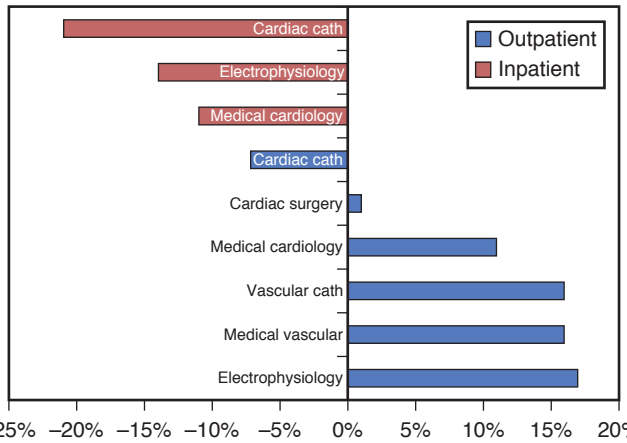

Figure 197.1 Cardiovascular Volume Growth Projections by Subservice Line 2013 to 2018.

the prevalence of PAD will continue to increase sharply, and the number of PAD procedures will increase accordingly (Fig. 197.1). Furthermore, these elderly patients are living longer, requiring treatment over longer periods of time, and all the while accumulating more comorbidities that affect PAD treatment outcomes.[10]

Despite these demographic changes, management of these aging and increasingly complex patients moves more and more into the outpatient arena. The rate of inpatient PAD interventions declined from 209.7 to 151.6 per 100,000 Medicare beneficiaries between 2006 and 2011, whereas the rate of outpatient interventions increased from 184.7 to 228.5.[11] With the shift to outpatient care, significant increases in office-based procedures are also occurring.

Paradoxically, medical innovation has largely focused on inpatient treatments. Costs for inpatient care continue to rise and make up the "lion's share" of Medicare expenditures for PAD[12]; this highlights the disconnect between increasing outpatient volumes and a focus on inpatient care. Given the push by multiple stakeholders, it is likely that financial incentives for outpatient care, preventive medicine, and population health management will drive the design of multispecialty CV centers in the future. For example, the safety, patient satisfaction, and financial viability of endovascular procedures performed in the outpatient setting has already been established.[13]

Competition

Market forces have played a significant role in the evolution of many multispecialty centers that focus on common or historically well-reimbursed diseases including CV, orthopedic, and neurologic diseases, especially in the outpatient arena (Fig. 197.2). For example, in the 1990s, the number of programs offering coronary artery bypass grafting (CABG) increased by 30%. More than 80% opened within 30 miles of an existing program, and 55% opened within 10 miles. Every new program established in a freestanding "heart" facility opened within 20 miles of an existing program. New cardiac surgery programs established from 1993 to 2004 led to little increased access

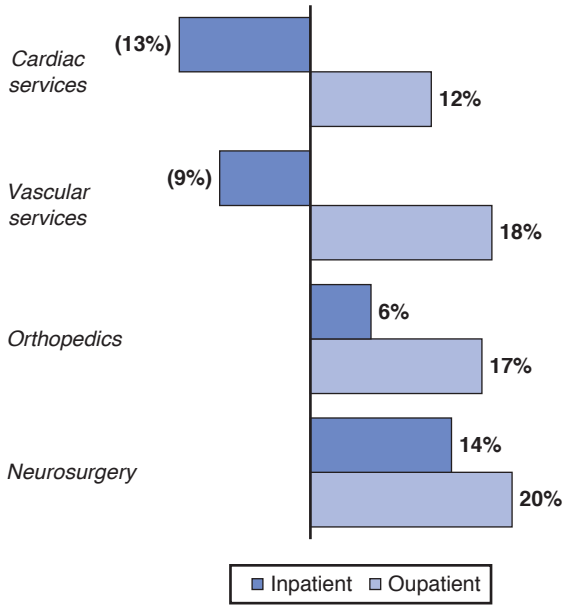

Figure 197.2 **All Payer Growth in Major Service Line Volume Projections 2014 to 2019.** The left side shows negative growth and the right side shows positive growth.

and substantial duplication of services.[14] At the same time, CABG volume overall was decreasing and there was mounting evidence that centers with lower CABG volumes had poorer outcomes.[15] Ultimately, the competition in this environment made it very difficult for many CABG programs to maintain durable independent success.

The evolution of disruptive technology, such as endovascular aneurysm repair (EVAR), has also increased competition among multispecialty CV centers. In many regions, as EVAR diffused from early adopters to academic centers to the community, the total volume of EVAR cases became distributed over an increasing number of centers. Again, this was in spite of data suggesting that high-volume centers had better outcomes.[16] The rapid growth of programs in proximity, decreasing procedural volumes, and the need for volume at individual centers to maintain quality outcomes and financial success has led to intense competition but has not necessarily improved access to specialty care in all communities.

Reimbursement and Quality of Care

Assorted reimbursement models have been proposed and implemented rapidly as our healthcare system struggles to balance cost, outcomes, and value. Pay-for-performance models offer only modest incentives for quality improvement over fee-for-service models and drive the use of evidence-based practice while emphasizing patient satisfaction. The assumption is that higher quality leads to fewer encounters, more durable outcomes, and therefore lower cost, an assumption that may not be valid and also one that depends heavily on the definition of quality. The definition of quality can vary significantly, particularly if one moves from an individual perspective to a community or population perspective. Individual patient outcomes have always been the physician's measure of quality. Quality and value were viewed as synonymous. However, in this era of cost containment, the definition of value has evolved to include much more. Not only are patient outcomes a part of this new value equation but so is patient (customer) satisfaction and experience, efficiency, and cost management. To this end, calculating the value of a multispecialty CV system has become important to the public, payers, and regulators.

As part of the trend toward financial transparency and value estimation, Medicare in 2008 began the Physician Feedback Program. Not yet publicly reported, this program collects data on quality, cost, and resource use on a hospital and provider level and provides participants with their data in comparison to their peers. In addition to this reporting, a VBP modifier is in development, which would provide for differential payment for fee-for-service Medicare services based on quality of care and costs incurred by providers. With all this currently or soon-to-be publicly available data, multispecialty CV centers must balance meeting metrics while staying true to their core mission.

DEVELOPMENT OF A MULTISPECIALTY CARDIOVASCULAR CENTER

To position themselves to provide for population health, successful health systems are altering their strategies. Optimizing CV specialist access at high-volume, critical locations is important so that there is a balance between offering access at outreach sites yet not short changing primary sites.[17] Ideally, the right patients should be seen by the right specialist at the right time in the most cost-effective manner. Although "on demand" presence is rarely possible because of limited physician capacity, considerable management skills are needed to use CV specialists appropriately. This may include streamlining scheduling practices, reducing no-shows, and prioritizing patient convenience by offering hours convenient for them.

When multiple specialties are involved, there is always going to be jockeying for an advantage between groups. Managing these highly charged conflicts takes a skillful leader. Experience, temperament, and trust are prime attributes to seek in any leader, but especially in a complex, changing environment. A physician co-leader working with an administrator may provide the best value (Fig. 197.3). Almost 75% of surveyed CV centers had either a "dyad" (physician leader and an administrator) or a "triad" (administrator and two physician specialists) leading the center.[18] The team leading a CV center, as a whole, must possess critical skills such as project management, strategic and operational awareness, financial proficiency, and competence in addressing quality of care issues. The biggest challenges are aligning incentives and achieving shared values and expectations so that all stakeholders agree to be accountable to each other. It is essential that these are written down and agreed upon by all members.

In AMCs the duality of reporting to the academic department as well as the CV center creates confusion regarding accountability.[2] Although it may be possible to eliminate the duplicate reporting in nonacademic, highly integrated health systems,

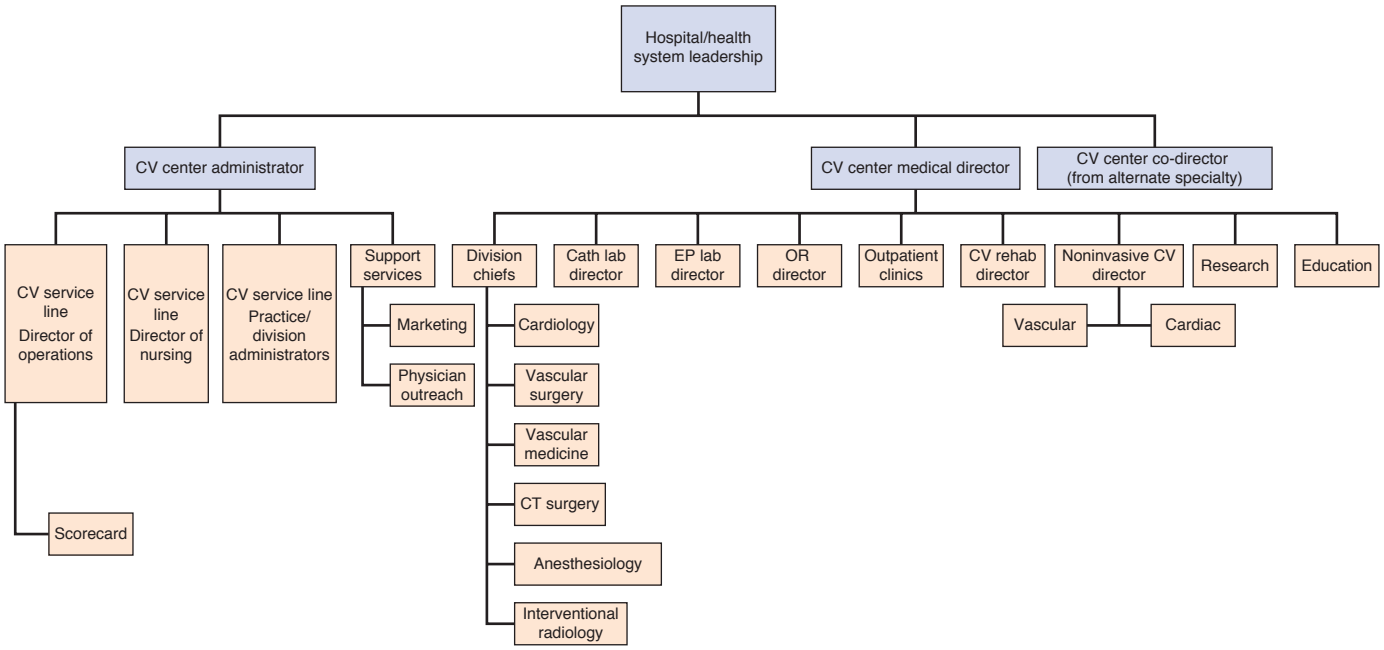

Figure 197.3 Suggested governance of a CV center (dyad or triad). *CT,* Cardiothoracic; *CV,* cardiovascular; *EP,* electrophysiology; *OR,* operating room.

long-standing barriers and fear of disruption of traditional cost-accounting systems make it difficult in AMCs.

Another pitfall in a CV center is agreeing on privileges for procedures because procedural volumes required for "competence" vary by specialty. Agreement must be reached by reviewing relevant specialty guidelines and favoring a higher bar, then negotiating to train each other to achieve competence. This can happen only if incentives for compensation are transparent, fair, based upon valid benchmarks, and agreed upon unanimously. After internal competition between specialties is eliminated or minimized, all specialists can concentrate on growing the business regardless of who does the work.

Finances and Compensation

As more CV specialists become fully employed by health systems, the financial management must itself be completely integrated. A dedicated budget and a single profit and loss statement for all CV operations must be in place. This allows the pressures on revenues such as increasing costs, decreasing reimbursement, more risk-based payments, and changing payer mix to affect all specialties. Although volume, commonly measured by work relative value units, is still the dominant component of physician compensation, an increasing share is tied to quality of care and performance. If the CV center is designing a compensation system to align multiple specialties, shared incentives must be encouraged so that some percentage of compensation is based on team, unit, service line, or system performance. Similarly, at-risk incentives may include metrics such as quality measures, use, readmissions, patient access, cost control, good citizenship, and outreach activities. As an example, if there is a group performance incentive, a CV specialist who travels to an outreach site and generates referrals for others in the group while her own procedural productivity suffers should share equally in the group bonus if productivity targets are met or exceeded. These incentives should be perfectly transparent to all the involved clinicians. Multispecialty collaboration is unlikely to succeed if a specialty or individual feels that their income is more at risk than the others.

Operational Issues

A culture of excellence is vital for a CV center to succeed but requires a commitment from physician and nursing staff. Because of the competition for CV patients both locally and regionally, CV centers need to differentiate themselves based upon quality outcomes, price, access, reputation, and rankings. Achieving well-known designations for excellence requires the organizational commitment of everyone from leadership to support staff, in addition to investment in personnel and computer resources. Common CV sought designations include: US News and World report (Heart and Heart Surgery category),[19] Health Grades,[20] which gives out specialty awards annually, Thomson Reuters, which publishes hospitals that meet certain CV benchmarks with its top 100,[21] Intersocietal Accreditation Commission accreditation for vascular laboratories, echocardiography and nuclear medicine,[22] and American Heart Association recognition for ST-elevation myocardial infarction referral centers. Many insurance companies and professional society databases also confer various awards for excellence in specialty care.[23] These designations require sophisticated computer programs and staff to enter, collect, analyze, and report data.

The governance structure of the CV institute must ensure that responsibility and accountability for the service line is designated to clearly appointed personnel. The "dyad" model combines the clinical experience of a physician with a skilled administrator. The difficulty in executing a vision or strategic plan occurs because of ambiguous lines of responsibility.

Regardless, the structure must allow proper representation of all parties (see Fig. 197.3).

There are several options for designing an operations hierarchy. Several layers of vertical bureaucracy existing in most hospitals are not well suited to single service line organizations. A matrixed structure allows expedited decision making, quicker execution of strategic plans, and better patient outcomes and quality of care. However, this reporting structure consists of a CV leader but no clear and direct responsibilities for all the divisions or departments within the service line.[24] This model requires all parties to be cooperative at all levels, and obtaining consensus may delay time-sensitive decisions. In an integrated operating structure most, if not all, reports occur directly to leaders of a service line or subservice line within a CV center. This structure is more complex because of the number of personnel and functions reporting to very few individuals, but decision making can be more efficient. There is no "one-size-fits-all" governance hierarchy that will work in every system. The management structure chosen must fit the local culture while satisfying basic organizational needs.

AMCs have traditionally operated with a hierarchical structure partly because the decision-making power rests with a dean and a department chair and partly because AMCs are cautious about taking risks with new models of care. However, foundation model-based institutions such as the Mayo Clinic have changed to patient-centric, integrated models of care in view of the move to value-based reimbursement, more emphasis on quality of care, increased transparency, and regulatory pressures. In bringing several specialties in CV centers into a single service line, many challenges are faced because of disruption of the existing power structure, medical education, resident training, and most importantly internal competition and compensation models. Not all AMCs are well suited for disruptive change.[25] Skilled leadership is required to integrate clinical, research, education, and administrative functions into a tightly knit, efficient unit focused on patient care, best outcomes, growth, and external competition.

THE CURRENT STATE OF MULTISPECIALTY CARDIOVASCULAR CENTERS

A recent survey of CV center administrators showed that AMCs, nonteaching community hospitals, and teaching community hospitals each constitute one-third of all CV centers.[18] Half of CV centers are associated with greater than 500 beds, and 60% are either regional or multistate systems, suggesting the need for organizational resources and capacity. It must be recognized that the creation of a larger entity such as a CV center poses new challenges in terms of governance and operations to any healthcare system, which should be anticipated (Table 197.3).

To better understand the current status of multidisciplinary CV centers in this country, existing community and AMC program administrators and lead physicians were contacted for telephone interviews. Designations for current CV centers range

TABLE 197.3 Challenges and Solutions for Cardiovascular (CV) Centers

Challenge	Possible Solutions
Appropriate leadership	1. Select a knowledgeable, representative, and accepted leadership unit in place 2. Establish a culture of integrity, transparency, and accountability 3. Mission and vision statements after input from all stakeholders 4. Responsibilities are specific and not ambiguous
Organizational chaos	1. Require physician leadership training 2. Integrate employed and affiliated physicians 3. Fashion a systemwide service line 4. Integrate inpatient and outpatient services 5. Control costs associated with newly formed service line associated center
Interspecialty silos and conflicts	1. Minimize internal competition while maximizing referrals and volumes for all 2. Avoid cannibalization 3. Design a transparent, fair compensation system that rewards not only individual productivity but team goals
Turf battles	1. Affirm a multispecialty team approach to cardiovascular diseases 2. Broad agreement to train each other when possible 3. Train multidisciplinary nurse specialists, patient schedulers, and other care givers 4. Cross specialty strategy, privileging, and quality of care committee 5. Educate trainees on the advantages of cooperation
Integration	1. Common charge-master and pool technical and professional revenue 2. Single profit and loss statement 3. Cross specialty practice guidelines and value analysis 4. Compensation incentives partly based upon group or subservice line performance and system goals 5. Physicians completely embedded in the governance model
Variation in care among specialties	1. Standardization of clinical and operational protocols 2. Institute a standing multidisciplinary quality assurance (mortality and morbidity) and case monitoring conference 3. Participate in national registries such as Vascular Quality Initiative (VQI) by the Society for Vascular Surgery or National Surgical Quality Improvement Program (NSQIP) by the American College of Surgeons or similar program

from "center of excellence" and "service line" to "institute," implying varying degrees of integration. Service lines tend to bring together specialties with a common clinical focus under one administrative umbrella, with the aim of initiating cost-savings maneuvers and promoting collaboration among specialists. Centers of excellence seem to venture beyond operational integration and clinically cooperate on various levels with regard to physical facilities, scheduling, and referrals. Institutes imply the highest level of integration with financial interdependence between the member specialties and an increased level of collective fiscal responsibility by the specialties.

The impetus to establish a multidisciplinary CV center varies but was generally consistent with the reasons stated earlier. Administrators tended to cite business reasons as motivators, such as greater procedural volume, access to patients, and better bargaining power with payers. Improved system accessibility for patients and better patient outcomes were also mentioned. Although physicians claimed these same patient-centered inspirations, preservation of specialty specific referrals and practice patterns remained important to them. Despite this, most CV centers were inclusive of cardiology and vascular surgery; cardiothoracic surgery, interventional radiology, neurology, neurosurgery, and vascular medicine were involved on a more varying basis. Overall, CV centers seemed to have a higher level of integration when a variety of physicians were engaged at the inception of the CV center and improved patient care was the ultimate objective.

The presence of a common CV center administrator was a typical theme, but this person's responsibilities and decision-making authority varied from functioning as a simple coordinator to one with full strategic and operational capabilities. Physician leadership was always incorporated to some degree but ranged from one to several directors, typically from a variety of specialties. Commonly, a cardiologist was the appointed physician leader. The amount of physician responsibility also ranged from an assigned title to involvement in operations including active planning and frequent team meetings.

Many CV centers approached were still in a state of continued development and refinement of their programs. The more recent adapters tended to have service line–type programs by aligning the involved specialties through administrative functions. This included managing personnel issues and processing requests for new equipment acquisition, among many other tasks. Individual specialties maintained their separate financial structures and oversight programs (quality, physician recruitment, reimbursement, etc.). Clinical activities were typically also independent, although there were some CV centers whose specialists shared a common outpatient clinic or inpatient procedural area.

In general, academic divisions contacted continued to report and be accountable to their respective departments. It was rare to encounter an AMC where individual divisions had traded the traditional departmental structure for a disease-based configuration, unless special circumstances existed, such as a previously established multispecialty practice or the availability of a large amount of external funding. Departments also seemed unwilling to sacrifice their components (and sometimes the more lucrative ones) to a disease-specific center. Community hospitals tended to have similar concerns, with specialists remaining loyal to their private practices and groups, rather than wanting to create a whole new financial structure and give up total operational and fiscal control.

No matter the base structure of a CV center, most have developed some type of tool for measuring success. Key performance indicators (KPIs) are the norm in CV centers operated by both academic and community hospital systems,

TABLE 197.4 Key Performance Indicators in Creating a Cardiovascular (CV) Scorecard

Focus	Focus of Metrics	Examples of Metrics
Customer	1. Patient 2. Employee 3. Referring physician	• Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS), care pathways, average wait times to access • Attrition rate, satisfaction survey metrics • Referral rates, survey metrics
Clinical/education	1. Quality 2. Research 3. Education	• Outcomes by specialty, shared performance measures, concurrence with guidelines, door to door times, core measures met • Grant volumes and dollars, presentations, publications • Peer-reviewed publications • Scientific presentations—local, regional and national • Performance in "in-training" and board examinations • Results of accreditation site visits • Outcomes of National Resident Matching Program (NRMP)
Organizational	1. Leadership 2. Strategy/business development 3. Financial performance 4. Marketing initiatives 5. Operational efficiency	• Quality of care indicators, financial performance, market share • Market share, payer mix, physician alignment • Inpatient and outpatient volumes, accounts receivables, physician productivity, monitoring of value based payments, net profitability measures by specialty, return on investment • Patient intake by geographical area and zip code, success of differentiation strategies, online analytics (bounce and conversion rates) • Case mix index, supply chain efficiency, readmission rates, no show rates, unit or procedure room use rates, staff productivity

whether they are administrative or clinical (Table 197.4). A scorecard should be built based on the organization's mission, vison, and values in order to better communicate strategy to the key stakeholders. KPIs should be reviewed regularly to gauge success. Examples of CV scorecard projects are endless and may include increasing local/regional market share, improving patient throughput in the ambulatory setting, employer of choice programs, and reintervention rates for endovascular interventions.

Healthcare marketing is a specialty and in competitive markets is a multi-million dollar budget item for CV centers. Although there are several important metrics in gauging success of marketing plans, market share is a critical number to follow over time. Market penetration is monitored by analyzing patients served, discharges, and revenue in specific regions. Occasionally in CV centers that exist largely in name only, without true integration in operations and finance, care givers themselves may be unaware that a named CV center exists, making one wonder how effective their marketing plans have been. This emphasizes the importance of staff engagement on all levels to promote a healthier patient experience and the success of centers of excellence.

FUTURE DIRECTIONS

With mergers and acquisitions of hospitals and health systems will come consolidation of services focused on reducing variations in care and eliminating wasteful tests and procedures, all to produce better quality healthcare with reduced cost.[26] Specialties providing care to the vascular patient will be persuaded to work together with greater efficiency, and physicians will be credentialed according to experience and skills rather than specialty-specific requirements. Difficult as it may be, sharing of knowledge must be mutually acknowledged as being a necessity. Best practices and specialty guidelines must be shared and disseminated throughout all clinical areas.

On the surface, the multidisciplinary CV center seems well suited to achieve success in bundled and accountable care reimbursement models. By giving providers defined payments for "episodes of care," bundling emphasizes clinical performance and the use of evidence-based medicine but also rewards efficiency of care delivery and multispecialty cooperation. Systems that can achieve quality outcomes with the least redundancy and waste should succeed. Furthermore, by including continuums of care in certain "episodes" (e.g., defining an episode as admission through a surgery and then 90 days postdischarge), systems are forced to invest not only in procedural or inpatient care but also postacute and outpatient care. The Bundled Payments for Care Improvement Initiative (BPCI) sponsored by the Center for Medicare and Medicaid Innovation (a product of the Affordable Care Act) has targeted 48 disease areas in which to roll out bundled payments; fully one-third are CV diseases.

The Accountable Care Organization (ACO) model further broadens the scope of cost-containment efforts to the community and population level. Instead of individual episodes of care, disease outcomes at the population level are emphasized. Successful treatment of chronic outpatient diseases and delivery of effective preventative care are rewarded. In addition to the quality care delivery and system efficiency incentivized by bundled payments, effective resource use across a community, geographic region, or population is rewarded by the ACO. The Centers for Medicare and Medicaid (CMS) recently reported that since 2012, Medicare ACOs have grown to more than 477 nationwide and currently are serving nearly 8.9 million beneficiaries.[27] Besides large health systems, physicians are leading consolidation of single or multispecialty vascular and cardiac groups and are also well positioned to succeed in competing for the CV patient. A national survey of ACOs showed that 51% were physician led and 33% were jointly led by physicians and hospitals.[28] Furthermore, physicians constituted a majority of the governing board in 78% of ACOs. Each of these evolving reimbursement models rewards a different type of multispecialty CV system, and development of a successful center requires intimate knowledge of the local and national reimbursement environment and the direction in which it is likely to move.

Patients increasingly affected by cost shifting to higher deductibles will move toward being better consumers, seeking out online reviews about quality and price transparency. Nonemergency procedures performed in the expanding outpatient arena will compete for price and quality. Similarly, Hospital Consumer Assessment of Healthcare Providers and Services (HCAHPS) metrics now used as part of value-based reimbursement will likely also begin to be used in outpatient centers. CV centers of the future will also join the technology revolution by allowing vascular patients to access their electronic medical records, including imaging and test results. Consumer expectations for access to care are also changing quickly. The ease of access to services at one click for transportation, groceries, laundry, and retail care has changed consumer behavior to where "on-demand" access is expected. Similarly, online scheduling convenience will be expected and require upgrading scheduling platforms and physician portals. The concept of a "just in time" strategy to decrease waste and improve efficiency will become common as health systems grapple with innovative ways of using technology to increase access to vascular specialists at multiple locations.

CONCLUSION

Factors that should lead to the long-term success of any CV center are those that characterize the best health systems today: enlightened leadership, excellent patient care, demonstrated outcomes and quality, cutting-edge research and innovation, and committed physicians who have access to the latest technology.

The successful CV center of the future must be multidisciplinary and patient-centered, empower physicians and other leaders to participate fully in governance and business decisions, design quality of care guidelines, and abandon siloed care, and move to collaborative models. Only then will there be a truly shared commitment to collaborative growth in the construction of the CV center of the future.

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CHAPTER 198

Development and Successful Operation of an Outpatient Vascular Center

KRISHNA MOHAN JAIN

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INTRODUCTION

Endovascular procedures were traditionally performed in the hospital where the patient was observed overnight following the procedure; this gradually transitioned to the patient being discharged on the same day.[1] Once the safety and efficacy of these procedures was established for the hospital-based setting, studies were conducted by multiple investigators that documented the safety, cost efficiency, and efficacy of conducting endovascular procedures in a dedicated outpatient office.[2-4] The deficit reduction act of 2005 included the provision for the Center for Medicare and Medicaid Services (CMS) to reimburse endovascular procedures in the office setting. Same-day discharge of the patient after these procedures helps reduce the cost of the procedure.[1] Other insurance companies followed CMS and now provide the same coverage. Thus, endovascular procedures can now be conducted in outpatient vascular centers. There are three types of outpatient centers that a patient may consider

Abstract

In 2005, the deficit reduction act allowed the reimbursement of procedures performed in office-based endovascular labs. Initially, the majority of procedures were performed to manage hemodialysis access. Subsequently, peripheral angioplasty and related procedures became reimbursable through the Center for Medicare and Medicaid Services (CMS). This has resulted in more than 500 labs opening in the country managed by vascular surgeons, interventional cardiologists, radiologists, and nephrologists. Of the commonly performed endovascular procedures, only endovascular repair of abdominal aortic aneurysm and carotid stent are not reimbursable when done in the office. There is no accreditation requirement by CMS for reimbursement, but individual states have different requirements. The physician receives a global fee that is a combination of a technical component and a professional component.

Key Words

office based lab
angioplasty
angioplasty and stenting
critical limb ischemia
dialysis access
atherectomy
venous ablation
venous stenting
vena cava filter

for endovascular procedures: a hospital-associated outpatient center, an ambulatory surgery center, or an office-based vascular center.

Outpatient vascular centers can be established by a hospital or by office-based practitioners. In hospital-developed outpatient centers, the hospital is paid under the outpatient prospective payment system, and each physician bills separately for professional services rendered. At a privately owned ambulatory surgery center (ASC), the "facility fee" is paid to the ASC for the surgical procedure and the provider is paid the "facility rate" based on the surgical procedure performed. In an office setting, Medicare and other insurance companies pay at the "nonfacility" rate. This nonfacility fee is a combination of technical and professional fees. An office-based center or laboratory is defined as a procedural suite within an office and is an extension of the office where patients are seen and treated. The office-based center is not specialty specific and the elements described in this chapter can be applied to all specialties. Office-based centers are currently owned by vascular surgeons, interventional cardiologists, interventional radiologists, and interventional nephrologists.

REGULATIONS

Office-based centers, in contrast to ASCs, do not have well-defined regulations guiding their operation. Instead, the centers are mostly regulated by state law (Table 198.1), because there are currently no federal guidelines for an office-based center. These regulations mostly pertain to anesthesia, radiology, and the Occupation Safety and Health Administration (OSHA).

Anesthesia

Regulations pertaining to anesthesia depend on the degree of sedation administered to the patient. In most states there is no requirement for an anesthesiologist to be present for minimal to moderate sedation. Many states, including New York,[5] require the presence of anesthesia personnel if moderate to severe sedation is needed for the procedures being performed. Different accrediting bodies may also have specific requirements regarding anesthesia that must be followed for the center to be accredited.

Radiology

Each state has different regulations governing the radiology suite in the office. Not all states require lead lining of the lab if a C-arm is being used. Some states mandate that only a certified radiology technician can operate the C-arm. The lab should follow the state law related to C-arm inspection, lead lining, staffing, and training regulations. In addition, there may be regulations governing the integrity of lead aprons and dosimeters.

Occupation Safety and Health Administration

OSHA regulations need to be followed diligently. This requires compliance training, policies and procedures, employee handbooks, and forms for recording incidents (needle sticks, etc.). The complete set of regulations can be found at www.osha.gov.

TABLE 198.1 Comparison of Ambulatory Surgery Center and Office-Based Labs

	ASC	Office-Based Lab
Payment methods	Bill facility fee and professional fee	Global payment (nonfacility)
Procedures allowed	All ASC approved procedures can be performed	Limited number of procedures
Physician usage	Other practitioners can use	Only practitioners seeing the patients in that office
Ownership	Multiple physicians can own it	Lab must typically be owned by physicians who are seeing patients and operating on them
Licensing	CMS and state license required	No license needed
Capital investment	Higher capital outlay for construction and equipment	Reasonable capital outlay
Oxygen requirements	Built in gas/oxygen supply and wall suction required	Oxygen cylinder
Size of facility	Bigger facility required	Depending on expected volume, smaller space can suffice
Regulations	Comply with federal and state laws	Comply with state laws
Services cost	Higher professional services cost at outset	Minimal cost
Staffing cost	Higher staffing cost; different staffing ratio	Office staff can be used in addition to added personnel
Monthly cost	Higher monthly costs	Lower cost
Accreditation requirements	Accreditation required	Not required except in certain states
Certification requirements	Certificate of Need required in many states	No Certificate of Need required
Transfer regulations	Transfer agreement required	Not needed, desirable if the practitioner is not a surgeon

ASC, Ambulatory Surgery Center; *CMS*, Center for Medicare and Medicaid Services.

COMPONENTS FOR SUCCESS

Office for Patients

Office-based outpatient interventional centers are defined as locations where patients traditionally see physicians or surgeons to discuss and diagnose their clinical needs. The office must

have the basic requirements of space and personnel, such as examination rooms for patients to be seen, and nursing staff to provide patient care, among other requirements.

Noninvasive Vascular Lab

A noninvasive vascular lab is needed to support the office-based practice and the endovascular laboratory suite. An ultrasound machine that can reliably perform imaging of the venous system and peripheral arterial system including the aorta, carotids, and visceral arteries is required. The same machine can be used to access arteries and veins in the endovascular suite. Different probes may be required to access the tibial and radial arteries. A Doppler machine to do wave forms and measure ankle and toe pressures is required to assess circulation in the extremities. Additionally, the appropriate equipment is required to conduct photoplethysmography of digital vessels to check the digital circulation in patients with the Reynaud phenomenon, vascular steal in dialysis patients, and occlusive disease in diabetics. The lab should be certified by the Intersocietal Accreditation Commission or the American College of Radiology.

Endovascular Lab

Almost all the percutaneous endovascular procedures currently being performed in the hospital can be safely conducted in the office-based lab.[6,7] Because there are limited resources in the office as compared to hospital, patient selection is crucial in optimizing results and intent to cause no harm. The absolute contraindications to treating a patient would be the need for general anesthesia, the need for hospital admission due to comorbidities, the need for prolonged observation postprocedure, or severe allergy to dye.[4] Relative contraindications for patients would include the weight of patient exceeding 400 pounds or a patient with decreased pain tolerance, if conscious sedation is not available. Endovascular repair of an aortic aneurysm and carotid stenting cannot be performed in an office-based lab and are not reimbursable in the office-based setting. In a pilot study (not published), endovascular repair of infrarenal aneurysms was safely done in the office-based lab in appropriately selected patients. However, until a larger study is conducted, this procedure should not be performed in the office-based setting.

Types of Procedures

Hemodialysis Access–Related Procedures (See Chapter 177)

Catheter insertions (temporary or permanent): Insertion of catheters should be avoided as much as possible[8] because of inherent complications like infection and stenosis caused by the catheters. Patients needing urgent dialysis without a functioning access will need catheters and these can be easily placed in the office setting.

Catheter removal: If the state regulations allow, a midlevel operator can be trained to remove catheters.

Fistulogram: There is no indication for doing a fistulogram on a predetermined schedule.[9] The following indications should be used for the procedure: (1) decreased blood flow, (2) increased venous pressure, (3) increased bleeding after removal of the needle, (4) ultrasound-proven hemodynamically significant stenosis, (5) inability to access the vein, (6) increased recirculation time, or (7) decreased urea clearance.

Fistulogram intervention (See Chapter 178): Once a fistulogram is performed, the most common intervention carried out is angioplasty of stenosis. Routine placement of stents is not recommended. Two covered stents, the Flair[10-12] (Bard Peripheral Vascular, Inc., Tempe AZ) and Viabahn stents (W.L Gore and Associates, Inc., flagstaff AZ), are approved by the Food and Drug Administration (FDA) to be used at the site of stenosis in graft vein anastomosis. Stents should be used only if there is elastic recoil after angioplasty, recurrent lesions within 3 months of the procedure, or in treating grade 2 or 3 hematomas. A stent should not be placed at the site of cannulation. Intrastent stenosis is very difficult to treat; therefore, following current best practices is advised. Additional concerns for stent use include migration or fracture of the stent. The use of laser atherectomy of stenosis at the dialysis access stent is currently not FDA approved, so it should not be done. If large branches are stealing the blood from the main access, coil embolization can be done[13] and may help improve blood flow through the main vein. Finally, if the fistula is not maturing, a fistulogram and angioplasty are appropriate. There is no reimbursable code for balloon-assisted maturation of a fistula.[14,15] Patients should not have balloon angioplasty at scheduled intervals without medical necessity.

Percutaneous thrombectomy: If a dialysis graft or fistula thromboses, it can be declotted using percutaneous,[16] chemical, and mechanical thrombectomy.[17] In cases of thrombosis in arteriovenous grafts,[18] angioplasty of graft vein anastomosis is almost invariably required[19] post thrombectomy.

Central venous stenosis management: Many patients present with swelling of the arm or other manifestations of higher venous pressure because of central venous stenosis. The narrowing may occur due to previous catheters or the presence of a pacemaker/defibrillator on the ipsilateral side.[20] Correction of these areas of stenosis requires large high-pressure balloons. Bare metal and covered stents are used more frequently in treating central vein stenosis.[21]

Inflow arterial stenosis: Blood flow in the access may be diminished due to proximal arterial stenosis. This can be corrected by angioplasty using a retrograde approach through the access or by using an antegrade approach via the femoral artery.

Peripheral Arterial Procedures

Diagnostic arteriogram: An arteriogram may be performed for carotid artery disease, renal artery stenosis, lower extremity ischemia, or visceral ischemia. A diagnostic arteriogram can be performed and billed for any vessel in the body except the coronary arteries. The procedure can be done via a femoral, brachial,[22] radial,[23] or tibial approach. Femoral artery access is

the most common approach. Prior to the procedure, kidney function should be assessed and in cases where renal function is compromised, an appropriate hydration protocol should be used. In patients with moderate to severe renal impairment, CO_2 angiography should be performed.[24] In cases of morbid obesity or hostile groin, a brachial or radial approach can be used. The complication rate is higher with the brachial approach compared to the radial approach.[22] Closure devices are used based on physician preference. Although there is no significant decrease in postprocedure bleeding when these devices are used, the time to discharge is often diminished.[25]

Arterial Intervention

Carotid: Stenting is not reimbursable.

Renal: Renal angioplasty and stent can be performed using appropriate indications.[26]

Visceral: Angioplasty and stenting of superior mesenteric and celiac arteries can be performed with results comparable to open procedures.[27]

Aorta: Angioplasty of the aorta is seldom indicated.

Iliac artery: Angioplasty and stenting of iliac arteries results in satisfactory long-term results. Atherectomy at this anatomical location is not proven to be clinically beneficial and is not reimbursable.[28]

Superficial femoral artery, popliteal artery, and infrapopliteal arteries: Intervention in this segment of blood vessels is the most common procedure performed in many labs, often done to relieve critical limb ischemia. Documentation of prior noninvasive vascular lab studies is desirable to justify the intervention. Angioplasty,[28] stenting,[29] and atherectomy[30-32] are all performed in these vessels. Stents crossing the knee joint are not advised because of increased incidence of stent fracture. There are currently no FDA-approved stents for infrapopliteal arteries. Various atherectomy devices are used, including directional, orbital, or laser devices. Long-term results using these devices are not currently available, because most of the data ends at 1-year post procedure. In the latest advances, drug eluting balloons,[33] new design stents, and drug-coated stents[33-36] are showing promising results. A retrograde tibial approach is being used to cross lesions when an antegrade method fails or in cases where the patient has a hostile groin.[37-39]

Upper extremity arterial stenosis: Stenosis in the subclavian,[40] axillary, brachial, radial, and ulnar arteries can be managed by angioplasty and stent when indicated. There is currently not enough data to support atherectomy in these arteries.

Venous Procedures

Venous stenosis in the iliac and femoral veins due to post-thrombotic obstruction or external compression, that is, May Thurner syndrome, can be detected using venography and intravenous ultrasound (IVUS). There is an increasing body of literature supporting the use of angioplasty and stenting of these lesions (see Chapter 161). Neglen et al.[41] have shown long-term patency of venous stents and sustained clinical symptom relief. Ganelin et al.[42] demonstrated the safety of this procedure in an office-based setting. Currently there is no FDA-approved stent to treat venous stenosis, but there are two ongoing trials testing the efficacy and safety of vein-specific stents. The stents needed are usually large, 14 to 28 mm in size. This also requires stocking larger balloons that are not usually kept in the lab. IVUS is proving to be more accurate than venography in diagnosing venous stenosis.[43] Results of thrombolytic therapy of iliac vein thrombosis in the office have been reported, and will likely soon be considered safe in the office setting. Finally, vena cava filters can be inserted and removed safely in the office-based lab.[44]

Port Insertions

Ports for chemotherapy, nutrition, or antibiotic therapy can be inserted as long as the patient is not on Coumadin. In many hospitals, ports are exclusively inserted by interventional radiologists or operating surgeons. However, ports can also be placed in office-based labs, where same-day service can be provided for port insertion.[6]

Venous Center

Use of an outpatient venous center to primarily manage superficial venous reflux has gained wide acceptance among physicians and patients. These centers specialize in endovenous ablation, microphlebectomy, sclerotherapy, and evolving new techniques like foam and glue injections for truncal venous insufficiency.[45] The venous center can be developed with or without an accompanying endovascular center. However, improved efficiency can be gained when venous centers are combined with an endovascular center, because patients who do not have complete symptomatic relief after ablation of veins causing superficial venous reflux may benefit from further intervention. They may also be candidates for interrogation of iliac and femoral veins using venogram and intravenous ultrasound and subsequent treatment with angioplasty and stenting. Providing treatment for all types of vascular conditions at one location improves the safety and convenience for the patient, because their physician is the same for both procedures.

Additional Services

Vascular Medicine

Management of peripheral vascular disease starts with medical management and may end in surgical intervention in some patients.[46] Even after intervention it is crucial to have optimal medical management. All vascular surgeons devote greater than 80% of their time to medical management of patients with peripheral artery disease (PAD). However, in a busy practice, a vascular medicine specialist can dedicate 100% of their time to managing the risk factors in patients with PAD, freeing the surgeon to dedicate more of their time to surgery. A vascular medicine specialist can coordinate programs dedicated to helping patients stop smoking and control weight with supervised exercise. With the continuous advent of new drugs and the need to treat hypertension, diabetes, and hyperlipidemia, it is challenging to keep up with all the medical advances. Most, though not all, patients have primary care physicians. However,

increasing regulatory demands prevent these doctors from spending enough time with patients whose health could be improved with closer monitoring of their risk factors. A vascular medicine service supporting the office-based lab can ensure patients are provided the most current medical treatment available and provide the personalized care these patients need to improve their health.

Wound Care Center

Ideally a vascular center would work closely with a wound care center.[47] Patients seen in the office with wounds can have the extremity revascularized in the office-based setting followed by wound care in the wound care center. If the practice is large enough, it can also own the wound center. Wound centers may also direct new patients into the vascular practice. If the limb can be revascularized in the office-based lab, followed by wound management in the wound care center, this can avoid a hospital admission, which is inherently more expensive.

Screening Program

Providing a screening program to patients for various endovascular diseases should be part of the comprehensive services provided to the patient population with peripheral vascular disease.[48] Screening for aortic aneurysms, PAD, and carotid disease is routinely done, both by primary care physicians and cardiovascular specialists. Since 2007, Medicare reimburses for abdominal aortic aneurysm (AAA) screening in men over 55 years of age with a family history of AAA, all men above the age of 65, and women 65 years or older with a family history of AAA or history of smoking. Specific screening guidelines vary among clinical societies. PAD screening and carotid screening are often done in tandem. In the life-line screening program, the prevalence of PAD and carotid artery disease was 4.1% and 3.9% respectively.[49] As many as 18.8% of patients with PAD also have carotid artery disease. Most patients who have an abnormal ankle brachial index will have mild atherosclerotic disease. Although mild disease can be managed medically, patients with severe disease will need endovascular intervention. Providing a screening program for endovascular diseases in an office-based laboratory increases the awareness of disease among patients in addition to positioning the practice as a leader in managing PAD, both of which benefit the practice.

Building a Center

Business Plan

Before embarking on developing an outpatient office-based endovascular suite, it is crucial to have a business plan.[4] This involves collecting clinical data, financial analysis, creating a pro forma, and projections. The physician needs to assess at the current volume of percutaneous procedures in each category that can be performed in the office, and anticipate what new procedures will be offered once the endovascular suite is opened. Each procedure has a different code and reimbursement that needs to be determined and incorporated into the business plan. A realistic expectation of growth based on the last 3 years of clinical practice should be determined. The capital expense and cost of disposable items and devices needs to be calculated and accounted for based upon the anticipated volume of patients. The largest expenses relate to the purchase of a building, capital equipment, cost of devices, and the cost of labor. If it is a new practice it may be advisable to build the practice prior to opening an office-based lab.

Building

The endovascular center needs to be in conjunction with the existing office space. A typical center is usually 2500 to 3500 square feet in area. The center will need the following areas: (1) a reception area, which can be combined with existing reception spaces; (2) a preoperative and recovery room with one or two reclining chairs for dialysis patients, and three to five beds for peripheral and venous procedures; (3) an endovascular suite that is lead lined, one or two depending on the anticipated patient volume; (4) a storage area for equipment and supplies; (5) a decontamination area; (6) a manager/coordinator's office; and (7) a nurses station.

Equipment

One of the biggest challenges facing the startup of the lab is financing. Most labs choose to buy the necessary equipment outright. However, many companies are willing to lease the capital equipment to the lab. Depending on the financial strength of the group, equipment can be procured in either manner. A list of equipment necessary for the endovascular suite and venous center can be found in Tables 198.2 and 198.3, respectively. For radiology equipment, another consideration is the choice between a C-arm and a fixed system, which depends on personal preference, types of cases anticipated, and the cost of the equipment. Currently available C-arms with vascular software provide adequate image quality for almost all procedures done in the office. One limitation is morbidly obese patients. C-arms have in increased risk of radiation to the patient, physician, and staff. Therefore, appropriate measures[50] should be taken to limit the radiation exposure.[51] Fixed systems may be better for renal intervention, procedures in morbidly obese patients, and carotid angiography. However, for dialysis-related cases a fixed system is harder to use because of positioning of the patient in relationship to the x-ray tube. It is better to buy new equipment rather than used or refurbished equipment, because the success of the center depends upon the functionality of these pieces of equipment. Purchase of equipment to perform ultrasound is highly recommended because ultrasound guidance for entering vessels during arterial and venous procedures is known to decrease complication rates. One of the complications of these procedures is postprocedure bleeding, and the most common cause for transfer to the hospital is bleeding after femoral artery catheterization. Thus, it is highly recommended that ultrasound be used to access arteries and veins,[52] but it is rarely required during fistulograms.

Supplies and Medications

Various supplies and medications are required for a functional endovascular center (Tables 198.4 and 198.5). The amount and brand of theses supplies to be stocked is at the discretion

TABLE 198.2 Equipment for the Endovascular Suite

In the Lab
C-arm/Fixed overhead system
Radiolucent table
Power injector
Ultrasound machine
Monitoring equipment
Overhead surgical light
Surgical instruments
Arm board
Portable oxygen tanks
Suction machine
Procedure table for instruments
Preoperative and Postoperative Area
Wheel chair
Reclining chair
Beds/stretcher
AED
Monitors
Crash cart
Miscellaneous
Furniture
Computers
Blanket warmer
Autoclave
Emergency battery backup
Lead aprons, hats, and glasses
PAC image storing
Emergency generator
Storage racks
Data collection software
EHR

AED, Automated external defibrillator; *EHR,* electronic health record; *PAC,* picture archiving and communication;

TABLE 198.3 Equipment for the Venous Center

Radiofrequency ablation machine/Laser machine
Table
Pump
Ultrasound machine

TABLE 198.4 Supplies

Preparation for Procedure
Surgical packs
Lead apron
Lead lined and sterile gloves
Booties, lead lined hats, and regular hats
Arterial and Venous Procedures
Vascular access kit
Catheter and wires
Sheaths
Support catheters
Crossing devices
Angioplasty balloons
Stents (bare metal and covered)
Atherectomy device
Inflation device
Intravenous ultrasound catheter
Closure device
Snare
Dialysis Related Procedures
Dialysis permanent and temporary catheters
Over the wire Fogarty catheter
Other Procedures
Ports
Stents
Intracaval filters
Filter retrievable kits

TABLE 198.5 Medications

Contrast solution
Intravenous fluid
Fentanyl
Versed
Heparin
Protamine sulfate
Local anesthetic agent
Other drugs if anesthesiology is providing sedation
Local hemostatic agents

of the endovascular center and the procedures that the center plans to perform.

Staffing

Acquiring new staff for the endovascular or venous center depends on the current number of staff members in the office. Some of the tasks, like scheduling, billing, and patient registration, can be performed by the current staff. The staff needed exclusively for the lab include a manager (if there is no business manager in the office), a registered nurse, a scrub technician, a radiology technician/medical assistant trained in using the C-arm, and another medical assistant to interact with patients

and carry out miscellaneous duties in the pre- and postprocedure area. If an anesthesiologist is providing sedation, they will have their own staff.

Electronic Health Record, Picture Archiving, and Communication System (PACS)

Data management in the office is currently being mandated by government and private insurance companies. It is important to have an electronic health record (EHR) and data management tool that can seamlessly interact. The data management tool should be able to provide patient demographics, risk factors, clinical findings, procedures performed, outcomes, and participate in a registry. For the functioning of the lab, the data management system should be able to track procedures, inventory, supplies used per procedure, clinical monitoring, image management, and billing. The clinical, business, and quality indicators have to work seamlessly. Total transparency is critical to the success of the lab; payers will need to see this data to reimburse for services provided by the office. Because there is no peer review for office-based procedures, payers are inherently suspicious of doctors performing unnecessary procedures. Only a strong data management program can help challenge that bias. All of the images produced during procedures need to be stored and archived for quality, follow-up, and legal requirements in a picture archiving and communication system (PACS). Ideally the data should be accessible from a remote site as well.

The EHR should have the following elements: (1) full history and physical exam including vascular exam, noninvasive vascular lab findings, indication for the procedure, pre- and postprocedure medications including antiplatelet drugs, anticoagulants, and statins; (2) procedure notes including site verification, type of anesthesia, vital signs during the procedure, the amount of radiation, and the amount of contrast; (3) equipment used including wires, catheters, balloons, stents, and other devices; (4) technical details of the procedure and medications administered; (5) a report should generate for the referring provider; and (6) documentation of follow-up visits/phone calls to document the outcomes of the procedure.

Biomedical and Electrical

There should be enough plugs and power to supply all electrical equipment in the room. Some devices may need a 220-V connection. There should also be an emergency generator. All equipment should be serviced at recommended intervals and have a sticker to identify the date of the last service. Portable oxygen should be available. A portable suction machine should also be available; wall suction is not required.

Accreditation

There are currently no organizations equipped to specifically accredit office-based endovascular centers. Various labs have received accreditation from different entities like The Joint Commission (JACHO), Accreditation Association for Ambulatory Health Care (AAAHC), and the American Association for Accreditation of Ambulatory Surgery Facilities (AAAASF). To ensure safe, effective, consistent, and comparable care at all office-based endovascular centers, an organization needs to be developed to specifically accredit these labs. Some of the principles used by the JACHO and other agencies could also apply in certifying these labs. All the procedures performed are percutaneous and no body cavities are opened. The procedures are very similar in nature and do not require elaborate, complex, or varied monitoring tools. In the accreditation process, none of these organizations look at indications and outcomes, which should be considered to ensure the safety and efficacy indicated by the accreditation. However, excessive regulatory burden will make office-based labs too difficult and expensive to operate, and thus oversight of these centers by a specific organization is essential.

Running a Center

Medical Records

With a good EHR, medical records should be completed in a timely manner. These records include history and physical, preoperative plan and discussion with the patient, informed consent, procedure notes, record of anesthesia, postprocedure recovery records, and follow up. By law, patients must have access to some part of their records via the Internet. Inaccurate medical records can result in poor or dangerous care of the patient and result in legal complications.

Policies and Procedures

The policy and procedures manual is the brain of your practice. It defines your best practices, and describes the conduct of the procedure and standard set by the lab to be followed for optimal outcomes. The policies need to be followed by staff and physicians alike. A clear definition and description of the procedures, equipment needed to carry out the procedure, and conduct of the procedure should be detailed in the manual. If there is a complication, there should be a plan established to manage each complication. This would include emergency protocols and transfer protocols. If there are state or accreditation body requirements, these will be defined in the manual and followed accordingly.

Coding Compliance

Overcoding and undercoding are both illegal under federal law. Every year there are changes in coding for office-based procedures. The lab should have a certified coder who remains updated with the various changes. Periodic audits performed internally or by a third party are highly recommended because the cost of inaccurate coding is significant.

Billing

Billing can be done internally or outsourced depending on the current practice of the office. If the billing is outsourced, it is critical to ensure the billing is done in a timely manner and there is appropriate follow-up with insurance companies and patients in case an insurance company requires more data to be submitted. The charges should be set in a reasonable manner keeping the Medicare allowable charges in mind. A policy should be established for dealing with overdue bills if there is precipitous drop in collection of bills greater than 90 days past due. If

preauthorization from the insurance company is required, it should be obtained before the procedure is performed; otherwise the insurance company will not pay and a potentially very dissatisfied patient will be left with a large bill. Because patients are more frequently required to provide copayments, the lab should take these into account when assessing cash flow.

Data Management

Data within a medical practice exists in many forms, including administrative and clinical records, which consist of both image and text files. A good EHR is crucial in providing quality care. There is need for software that can manage office notes, ultrasound and x-ray images, medications, inventory, billing outcomes, and be able to transmit data to a registry. The data should be contemporaneous, easy to access, and in a format that can be analyzed. Most of the commercially available generic EHRs are not suited to good data management, and thus there is a need for new carefully designed data management software.

Quality Control

To ensure the quality of the practice, data should be analyzed at regular intervals. There should be monthly meetings of physicians and staff to look at all untoward incidents and complications. Root cause analysis should be carried out for major or unexpected complications and appropriate measures should be taken to avoid them in the future.

The data should be compared to national results published in peer-reviewed journals. Indications for the procedure should be clearly delineated and should follow the published guidelines. If the lab is part of a registry,[53] data should be compared to other centers to make sure there are no significant deviations. Some states have regulations that require reporting of serious complications, unplanned transfer to the hospital, transmission of blood-borne pathogens, and any deaths that occur within 30 days of the procedure.

Outcome Measurement

Outcome measurement is important for marketing, quality control, and success of the practice. When establishing your practice, one can quote the results from the literature to patients while getting informed consent. As the practice matures, patients will want to know the results from your specific practice or with a specific physician. With appropriate data collection, the operators in the lab should be able to provide these results. Outcomes can only be measured if the patient has appropriate follow-up after the procedure. The best marketing tool you have is your results. If the lab is a part of a registry, outcomes can be compared internally between practice physicians and externally with other labs. Measurement of outcomes includes success of the procedure, complications, death, and long-term follow up. Different parameters may need to be measured for different procedures. These outcomes are well defined in the literature and should be comparable to the procedures being carried out in the hospital. One goal of the office-based lab should be to surpass the hospital outcomes because there is inherent efficiency in the office and nosocomial infections should not be part of the complications. The Vascular Quality Initiative under the auspices of the Society for Vascular Surgery has become an important tool in measuring outcomes in a hospital setting[53] and is currently being adapted to office-based endovascular labs.

Management of Complications

There are very few reports describing complications observed in the office-based setting. However, complications should be similar to those encountered in the hospital setting (Table 198.6). Due to limited resources, there should be written protocols to manage complications. In the most comprehensive report published,[6] the overall complication rate in 6458 procedures was 0.8%. The specific rates were: venous 2.2%; diagnostic aortogram 1%; arteriogram and intervention 2.7%; fistulogram 0.5%; catheters 0.3%; and venous filter related 2%. Twenty-six patients out of 2822 required hospital transfer and 10 patients needed an operation. As expected, operative site bleeding/hematoma was the most common reason to transfer the patient. There was no 30-day mortality rate related to the procedures. Oskui et al. also published data supporting the safety of these procedures in the office-based setting.[54] A protocol should be established concerning how serious complications will be handled. Specific personnel should be identified as responsible for calling 911 to enable patient transfer to the hospital. Ideally, the patient should be transferred to the hospital where the vascular surgeon has privileges. If a nonvascular surgeon is performing the procedure and the patient needs to be transferred, the interventionist should have an arrangement with the receiving hospital or a vascular surgeon to manage any complications. A written transfer agreement with the hospital is not required.

TABLE 198.6 Types of Complications Observed Following Endovascular Procedures

Access Site Complications	Target Site Complications	Anesthesia Complications	Cardiac Complications	Device Related Complications	Other Complications
Active Bleeding	Rupture	Hypoxia	Myocardial infarction	Retained wire	Syncope
Pseudoaneurysms	Dissection	Need to intubate	Arrhythmia	Broken catheter	Seizure
Hematoma	Occlusion			Catheter embolization	Renal failure
Closure of vessel	Thromboembolism			Stent migration	
Embolism					
Infection					

Marketing

Enjoy what you do and let the world know it is your passion. Marketing is not advertising; advertising is part of marketing. All marketing is local and the key to any marketing program is communication. There are various ways to communicate your message. The easiest and most cost-effective (free) method is to interact with local referring physicians. To market the vascular center, the center needs to know its own outcomes, strengths, and weaknesses. Great outcomes speak for themselves. Let consumers know your strengths and figure out a way to get rid of weaknesses. Data should be collected and shared appropriately with referring physicians and patients. The age-old teaching of availability, affability, and ability has stood the test of time. If a patient's dialysis access is clotted and you can take care of it "now," you will have a strong relationship with the nephrologist and the dialysis center. If you also thank the nephrologist, and the patient is dialyzed without missing a treatment, you have won the physician's confidence and referrals for a long time. With staff and patient turnover, the success of your practice relies on successful marketing. In other words, marketing is an ongoing process.

Marketing starts with you and your staff. If the patient and the referring physician have a good experience with you and your staff, they will become your ambassadors. The physician and the staff should dress professionally, act professionally, provide information in a brochure form and online, and be polite and accessible. The center should be clean and inviting, a place where patients would like to return.

Avenues for Marketing

Personal contacts: It is important to let referring physicians know what you do. You will be surprised how often they send you a patient but do not truly understand the variety of care you can provide. For the success of the center, key specialties to contact besides primary care are nephrologists, cardiologists, gynecologists, interventional radiologists, emergency room physicians, and podiatrists. In many hospitals, cardiologists and interventional radiologists do not perform peripheral arterial interventions, thus your center is the ideal place for these procedures to occur. Personal contact can be made by phone or in person. A brochure sent to the referring physician with information pertaining to the procedures done in the center is an inexpensive way of keeping physicians aware of your center's capabilities. The center could also create a newsletter for physicians, which would serve as a continual reminder of the care you provide. You can also educate physicians and patients, making your center an important part of the endovascular field in your area.

Local meetings: These meetings could be physician meetings, social meetings (i.e., rotary club), or patient-oriented meetings. You should be able to explain what you do. Most people do not know the basic premise of office-based procedures. You could also arrange educational meetings for physicians, other midlevel providers, and patients.

Print media: The local newspaper is always looking for articles about the latest advances in medicine. You could write an article or arrange for an interview regarding a new procedure you are offering. Advertising in print media is declining rapidly as the penetration of this media is on the decline. However, if a newspaper has a strong presence in your community, an advertisement may be worthwhile, although it likely has decreasing returns.

Audio and visual media: Advertising on radio is more cost effective than TV. If you have a venous center, this medium is crucial to its success. There are opportunities in every community where local radio and TV stations have a need for a medical segment. Approach these stations and offer your services to educate the public. If a new technology becomes available, arrange for an interview.

Internet: This medium continues to grow at the fastest pace. A comprehensive website is essential to any modern-day practice. It should include pertinent information about the center and educational material about the procedures you do. The site should be regularly assessed for accuracy and updated as the medical information evolves. There are various social media outlets that can be used for advertising. It is best to work with marketing people who understand this medium.

Research: Not every practice wants to participate in research. If you know your data and you are doing clinical research, you can publish it. The data you publish can be shared with your referral base. This builds trust and confidence in your abilities. Currently there is very little data in the published literature about office-based endovascular procedures, thus the field needs data and is willing to support genuine research efforts.

If you decide to advertise, you need to follow certain guidelines as advocated by the American Medical Association (AMA) code of medical ethics, opinion 5.02. Be careful to abide by federal regulatory standards that apply to commercial advertising, and make only objective and factually supportable claims about experience, competence, and quality. Avoid aggressive high-pressure tactics and refrain from using testimonials that do not reflect typical patient outcomes. Be careful when claiming to have treated a particular ailment successfully in a large number of cases, because this can imply a certainty of results or create unjustified patient expectations. Finally, eschew claims of unique medical skills unless this is true for a particular geographic area.

Radiation

Radiation safety[51,55] is an important part of all the safety measures undertaken in the office-based lab. Appropriate precautions need to be taken to minimize exposure of the patient, operator, and staff in the room. This includes appropriate lead shielding as required for the room and that all personnel need to wear appropriate lead-lined aprons, thyroid shield, head cover, and lead-lined glasses. Everyone should pass a radiation safety test every 2 years and records should be maintained. Radiation badges should be worn and checked at regular intervals. For younger members of the team, the potential cumulative dose over a lifetime should be assessed and managed.

Patient Satisfaction

It is paramount for the success of these centers to have a very high satisfaction rate, because this impacts the patient return rates. In a patient satisfaction survey administered in an office-based laboratory, two questions were asked: (1) were they satisfied and (2) will they return to the office if another procedure is needed; in these surveys the patient satisfaction rate was 98% to 99%.[4,6] There are many reasons patients cited for being highly satisfied. They see the same staff every time, there is no hospital maze to navigate, no hospital registration, no preprocedure workup in most patients, the time spent in the center is significantly less than in the hospital, access is easier for the patient, and the results are comparable to a hospital-based procedure. The main reason patients may not be satisfied is occasional poor pain control in the office-based setting if conscious sedation is not used judiciously. There are currently no standard surveys available that assess patient satisfaction in these centers. An example of a patient satisfaction survey can be found in Box 198.1.

Evaluation of the Center by Physicians

A quarterly evaluation of marketing efforts, screening programs, outcomes, complications, rates of hospital transfer, and financial data should be performed by the physicians in the group. At these meetings, the minutes should be documented and maintained. In case of a sentinel event, an emergency meeting of all parties concerned, including the medical director of the center, should occur. If the center is failing to meet its own goals, root cause analysis should be conducted and any appropriate actions should be taken. A quarterly profit/loss report is crucial for the financial viability of the center. As new devices come to the market, a cost analysis should be completed before procuring the device for the center. Processes should be streamlined to enhance the effectiveness of the center. Various operators should have a consensus about device use to minimize the number of products on the shelf. Finally, the center should not offer inferior care as compared to the community standard based on cost.

BOX 198.1 Sample Patient Satisfaction Survey

Using the number scale described below, please circle the appropriate number to indicate your agreement with each statement:
1. Highly disagree
2. Moderately disagree
3. Agree
4. Moderately agree
5. Highly agree

Were you satisfied with our care?
1 2 3 4 5
If you need another procedure will you come back to our office?
1 2 3 4 5
Have you had a similar procedure in the hospital?
Yes No
If yes, where will you prefer to have your next procedure?
Hospital Office
If not in the hospital, what are the reasons?
Poor pain control
Did not feel safe
Staff was not competent
Other reason:_____

Future

The future of outpatient office-based endovascular labs is bright. As healthcare payers continue to demand efficiency and institute a value-based payment system, office-based care will have an increased demand because it has proven to be safe, cost effective, and patient friendly. In the future, payments to physicians will be made under the Medicare Access and Children's Health Insurance Program (CHIP) Reauthorization Act, Public law No. 114-10 Act (MACRA). Starting in 2019, physician payment will be provided through a new merit-based incentive payment system (MIPS). An increasing number of patients are demanding outpatient services as demonstrated by the success of ASCs providing endoscopy, plastic, and ophthalmology services. However, there is a paucity of data supporting the efficient use of outpatient vascular centers. As more data becomes available, the value of these centers will be recognized by patients and payers alike, making these centers the preferred location for treatment of peripheral vascular disease.

ACKNOWLEDGMENT

The authors thank John Munn MD, Mark Rummel MD, Dan Johnston MD, Syed Alam MD, and staff for all the work they do in the office-based vascular center, Chris Longton RN for providing business management of the center, Laura Bauler PhD for her help with the manuscript, and Jeff Smith Esq. for legal guidance.

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This paper reported the largest series of patients having percutaneous endovascular procedures in the office in a safe manner while achieving very high patient satisfaction.

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199 CHAPTER

Essentials and Value of a Vascular Registry to the Practice

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INTRODUCTION

Registries contain troves of information, generally collected in the course of routine clinical practice. The usefulness or value of that information depends on many issues but primarily whether it is used for a purpose consistent with the intent of the registry and whether the registry data are regarded as valid. This chapter will summarize the characteristics of registries, and examine how they might—or might not—add value to the practice of vascular surgery. A comprehensive review of medical registries is also available.[1]

WHAT IS THE DEFINITION OF A MEDICAL REGISTRY?

Although most practitioners intuitively understand the concept, it is useful to unambiguously define a medical registry. Some have applied the term to almost any database that collects information about patients or clinical events. However, there are specific characteristics that make a collected data set a true registry. The most useful definition was advanced by Solomon in 1991 and subsequently subscribed by many others:

> *A systematic collection of a clearly defined set of health and demographic data for patients with specific health characteristics, held in a central database for a predefined purpose.*[2,3]

Understanding the predefined purpose of the registry is paramount, as this will govern downstream decisions about which data should be collected.[4] Others have termed this predefined purpose as the *Inclusion Principle*—or the defining feature of the registry and the information it collects. In other words, what characteristic(s) of a patient or medical event qualifies it for registry inclusion?[5]

One way of operationalizing this definition has been termed the **MDR-OK** model:[5]

Mergeable data facilitates aggregation of information submitted from various individual sources that can be combined into a larger, more representative, data set.

Data set standardization means that the same characteristics are collected on every patient or case included in the registry. The predefined purpose of the registry will inform the process

Abstract

Registries can vary widely in scope and content but generally reflect collections of "real-world" clinical data accumulated in the course of routine care. Thus, registry data differ from that collected by randomized controlled trials in important ways. Although possibly less accurate or robust in terms of consistency and accuracy, registry data are arguably generalizable to more patients than conclusions drawn from randomized controlled trials. This chapter reviews the characteristics of registries, highlights advantages vs disadvantages and discusses the role registry data can play in improving the quality of vascular surgical care.

Keywords

Levels of evidence
Generalizability
Quality improvement
Vascular Quality Initiative
ACS-NSQIP
Vascunet

of selecting the characteristics to be collected for later analysis. Adherence to collecting a clearly defined standardized data set should reduce the subsequent problem of missing information during analyses. Completeness of data collection is a key factor in determining the quality or external validity of a registry.

Rules for data collection provide guidelines for translating raw source data into definitions established by the registry. These guidelines are typically contained in a protocol and data dictionary developed during conception of the registry. Observance of these rules will ensure that data in the registry are reproducible and consistent, even if collected by different people at different times in different locations about different patients or events. The degree to which these rules are complied with affects the consistency of a registry which is a measure of internal validity. Examples of this process are mapping blood pressure information into a registry data element such as "Hypertension" or creatinine values into a data element termed "Renal Insufficiency."

The aforementioned characteristics are fundamental to a **M**edical **D**ata **R**egistry. Several additional features may enhance the value of a registry:

Observation over time means that a registry collects longitudinal patient data, which are then linked to the initial patient record.

Knowledge of outcomes may allow a registry to indicate which characteristics collected as part of the initial registry record are more or less likely to lead to a particular clinical outcome. It is important to recognize that the outcome in question must be as carefully defined and standardized as any of the initial data elements. Outcomes assessment may be determined actively (by their specific addition to the registry by its participants) or passively (by linkage to administrative data). An example of the latter is tracking vital status by using a common identifier such as a social security number to link the initial registry record with the Social Security Death Index.

The diversity of medical registries arises from the various reasons or predefined purposes for their existence. Registries have been generally categorized according to their inclusion principle, their intended function, or both.[6] Categories based on the inclusion principle might be disease-based, procedure- or therapy-based, or population-based. A more functional classification would be research, quality measurement, or quality improvement. A single registry might be classified under multiple schemes. For instance, a disease- or population-based registry might primarily exist to facilitate clinical research, while a procedure-based registry might be used to measure and improve quality. Other registries—often operated by regulatory agencies—exist for purposes of public reporting.

WHY DO REGISTRIES EXIST?

Like virtually all physicians, vascular surgeons strive to provide the best outcomes for their patients. To do this, information is needed about which procedures or treatments work best for which patients at which times. It is an axiom of quality improvement that "you can't improve what you don't measure." Registries measure activities that occur during routine clinical care, as opposed to information derived from randomized clinical trials,

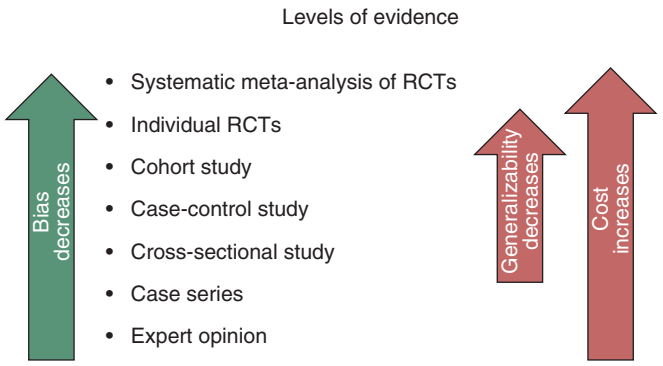


Figure 199.1 Relationship of bias in medical evidence relative to generalizability and cost. *RCT,* Randomized controlled trials.

which are in reality experiments designed to answer specific questions or test explicitly stated hypotheses.

Further, in recent years, many payers have restricted the use of new or evolving technology unless the results of these procedures are followed carefully in registries.[7,8] The FDA is also exploring use of medical registries for purposes of postapproval device surveillance.[9]

There is a well-recognized hierarchy of medical evidence based primarily on whether the conclusion delivered by a particular type of study is felt to be biased (Fig. 199.1).[10,11] Systematic meta-analyses of related randomized controlled trials (RCTs) are regarded as the highest quality evidence followed by individual RCTs themselves. Randomization is the feature that minimizes bias introduced by known and unknown confounders. *Internal validity* refers to the confidence that a study's results are free from bias and therefore more likely to reflect a true difference between the comparison groups.[1] However, randomization also requires that true uncertainty exist in the minds of the investigators and participants as to the superiority of one treatment assignment—a concept known as clinical equipoise. Well-designed and run RCTs also tend to have highly developed protocols that precisely define data elements and study outcomes, as well as a schedule of study visits that optimize data collection and outcome ascertainment. The high regard for results produced by RCTs owes primarily to randomization but also to their highly structured, reliable study protocols.

However, RCTs have numerous drawbacks. Randomization is unethical in situations where clinical equipoise does not exist, no matter how valuable or useful the answer might be. The highly restrictive inclusion/exclusion criteria of RCTs may raise questions about whether the results apply to the broader population of patients seen in routine clinical practice. The degree to which a study's conclusions can be generalized to a broader population is termed *external validity*.[1] Finally, the elaborate structure that makes RCTs valuable also makes them expensive—too expensive to use to answer every clinical question of interest. Because RCTs tend to be mounted to answer a focused question, their infrastructure is typically not preserved or recycled to answer additional or subsequent related questions.

The disadvantages of RCTs create the niche and rationale for medical registries. Randomization is not a prerequisite for

enrollment, so there are rarely ethical objections. Maintaining confidentiality of protected health information (PHI) is usually the major concern with registries. Systematic and broad registration of patients or events according to the predefined inclusion principle should make registry-based results more generalizable to everyday patients and minimize selection bias. The large case volume accumulated by many registries allows detection of relatively low-frequency events that are unlikely to be recognized in an RCT. Broad participation also facilitates benchmarking, which is the comparison of an individual or group's performance to the average performance (or best performance) of another. Benchmarking is a purpose typically not fulfilled by RCTs.

Highly structured protocols and elaborate infrastructure do not have to be features exclusive to RCTs, but they do tend to increase the expense of creating, running, and participating in a registry. On the other hand, registries are typically intended to last for many years, and may serve as platforms for multiple studies, making them more economical in the long term.

WHAT DETERMINES THE VALUE OF A REGISTRY?

The quality of data collected and maintained by a registry is the greatest determinant of that registry's value.[4] Registry data quality has been defined as the "totality of features and characteristics of a data set that bear on its ability to satisfy the needs that result from the intended use of the data." Two major attributes of registry data quality are recognized: **completeness** and **accuracy**.[3]

Completeness is a measure of the extent to which all data eligible for registry entry have actually been included. Since one of the major advantages of registries are their increased representativeness or broad inclusion of relevant cases, any concern that a registry's data is not inclusive or representative will lower its value and raise questions of selection bias. Lack of completeness is a threat to a registry's external validity or generalizability. These issues may be more likely to affect procedure-based as opposed to disease-based registries, as well as those that depend on self-reported data as opposed to data entry by a third party or automatic process.[12] Lack of completeness would severely compromise the value of a registry established for the purpose of public reporting. Another issue that may affect a registry's external validity is cost of participation. If cost becomes a barrier to participation, data that are entered into the registry may be less representative, again raising the possibility of selection bias.[12]

Accuracy refers to the degree to which registered data conform to reality, or a predetermined gold standard.[3] Flaws in data accuracy will primarily affect a registry's internal validity or confidence that conclusions based on registered information are free from bias or error.

A registry can increase its internal and external validity by establishing user-friendly data-handling processes (ease of entry, clear dictionaries and help text, etc.) in the design of the registry, as well as quality control measures that assess data accuracy after the entry (some form of auditing).[3,4,13] An appropriately focused auditing strategy or policy should be a feature of all high-quality registries. The nature and scale of the audit should be consistent with the registry's purpose and will ideally test for both completeness and accuracy.

Concerns about validity pertain to all types of registries, whether they exist primarily for research or other clinical purposes. For instance, a registry's signal about poor clinical outcomes may be dismissed if there is suspicion that the underlying data are suspect.[14]

There is also a tension between registry complexity and both internal and external validity. Typically the more complex registries will collect and contain more clinical information, theoretically increasing their value since they can analyze the relationship of more clinical characteristics with outcomes than registries that contain simpler data sets. A hierarchy of data for arthroplasty registries has been described that can be extrapolated to other clinical, procedure-based registries.[15]

- Level 1—Simple demographics, date of procedure, dx, type of procedure, medical device info, surgeon and hospital identifier
- Level II—Patient clinical characteristics, surgical technique, intraoperative events/processes
- Level III—PROs, clinical or functional outcomes, economic data
- Level IV—Radiographic assessments (possibly by a central imaging core)

Obviously a registry collecting Level III or IV information will have much richer data and be able to address a wider variety of clinical questions than a registry that only contains Level I information. At first glance, it may appear to deliver greater value. However, a complex registry that strives to collect detailed information but sacrifices representativeness or has quality issues because of complicated or confusing data entry processes may ultimately not be as useful as a simpler registry. In general, a registry should be no more complex than necessary to meet its stated purpose.

At inception and throughout its life cycle, a registry must address and balance multiple issues that create tension between its value and validity. Although registries are not typically as costly as RCTs, they are frequently not subsidized or externally funded. Thus even a relatively low-cost registry may be very expensive for some centers or groups.

WHERE DO REGISTRIES FIT AS MEDICAL EVIDENCE?

As mentioned earlier, there is a hierarchy of medical evidence ranging from systematic reviews of randomized controlled trials regarded as the most authoritative to isolated case reports regarded as least authoritative. RCTs are so highly regarded because they are prospectively designed as focused clinical experiments and the randomization allocation minimizes the possibility that the trial outcomes will be affected by confounding influences. However, RCTs cannot address every issue for which we need data to help guide clinical decision-making.

TABLE 199.1 Types of Registry-Based Studies

Study Design	Level of Evidence (for a Registry Study)	Sample Selection	Advantages	Disadvantages
COHORT	High	An "exposure" defines the cohort, which is then followed prospectively for an "outcome" of interest	Temporal relationship between "exposure" and "outcome" established	Bias still possible but largely related to the structure of the registry
CASE-CONTROL	Medium	An "outcome" defines the cohort of cases. Controls are matched to cases based on prespecified matching criteria.	Useful to study possible exposures associated with rare outcomes	No temporal relationship established between exposure and outcome; selection bias possible when selecting matching criteria for controls
CROSS-SECTIONAL	Low	Inclusion of a subject in the sample determined by existence of either the exposure or the outcome	Can establish prevalence of a practice/condition or the mere coexistence of the exposure and outcome	No temporal relationship established

While data from registries do not represent the highest level of evidence, they do provide valuable information that cannot be obtained from any other source. There are essentially three types of studies that leverage registry data (Table 199.1).[15] The highest level registry-based study is the cohort analysis. A cohort study selects its sample prospectively based on an exposure of interest (also known as the independent variable) and then follows that sample over time to detect an outcome of interest (dependent variable). Cohort studies establish a temporal relationship between the exposure and outcome, and results are typically described in terms of a survival analysis, such as a Kaplan-Meier curve.

Case-control studies use registry data to identify patients who have a particular outcome of interest (cases) and then look for characteristics associated with that outcome by assembling a control cohort that resembles the cases based on prespecified matching criteria. Properly done, large case-control studies use already collected registry data to provide important information not available through any other method. The case-control study does not establish a temporal relationship between possible risk factors and the outcome, and the matching process is a possible source of bias.

Registries can also provide prevalence information through cross-sectional studies in which an exposure and outcome are determined simultaneously. An example would be an analysis of the proportion of AAA treated with endovascular repair at any given time.

Differences between registry data and those collected in the course of a randomized controlled trial are important to recognize.[4] First, subject enrollment into a trial is typically strictly controlled occurring only after stringent assessment of carefully defined, prospectively applied inclusion and exclusion criteria. Enrollment criteria for registry entry are usually not so strict (giving registries a "real-world" flavor), but then the possibility that ineligible subjects are included may corrupt the relationship between a particular characteristic and outcome. Also, treatment allocation in a registry is almost never random, so the factors governing the choice of one type of treatment over another are frequently unknown.

Because participants in randomized trials are so valuable, follow-up for adverse events and clinical outcomes is typically active and aggressive. This type of information may only find its way into registries passively and can produce problems with missing data in terms of outcomes of interest. For that matter, outcome ascertainment in a formal trial is frequently blinded to the treatment allocation but not necessarily so in a registry. When an outcome of interest such as mortality is definitive and not open to interpretation, linkage to administrative databases may alleviate this problem. For less definitive outcomes, the possibility of ascertainment bias remains a significant issue in registries.

Because registry data are often affected by various confounders (e.g., selection bias, ascertainment bias, inconsistent treatment protocols and others that may not be recognized), data analysis can be complicated. Numerous statistical methods to account for known confounding have been developed, including adjustment techniques, regression analysis, instrumental variable analysis, and various types of propensity-matching.[15]

For the clinician evaluating a registry-based article, a standardized approach can be useful, as outlined here.[4]

1. Generalizability. Are the enrollment criteria clearly specified? If so, are the registry patients similar to my patients?
2. Relevance. Is the purpose of the registry clearly stated, and are the data pertinent to the question being posed?
3. Quality. Does the registry have procedures in place to assess the accuracy and completeness of its data? This information is typically found in a publication describing the registry and its operation, frequently cited in the Methods section.
4. Meaningful outcomes. How objective are the criteria used to define the outcome of interest? Were outcomes determined systematically? This is especially important if a comparison group is included. There should be an equal opportunity or likelihood to identify the outcome in the comparison group.

5. Follow-up. This property is closely related to the previous question. Poor or inconsistent follow-up will result in many cases of missing data.
6. Characterization of the comparison group. Cohort and case-control registry studies compare outcomes between different groups of subjects. It is important to understand whether these groups are different in ways besides the defined exposure variable. This is typically the area where many of the more sophisticated statistical and analytic techniques are applied, because the subjects were not assigned to the case or control groups randomly.

A *randomized registry trial* is an effort to leverage the existing infrastructure of high-quality registries and still gain the powerful advantages of randomization.[16] A randomized registry trial is a clinical experiment targeting a specific question conducted within the context of a registry, thus avoiding the time-consuming and expensive task of creating the infrastructure necessary to answer the question. During a randomized registry trial, a "randomization module" unique to the question at hand is applied at the time of registry entry. Randomized registry trials still require informed consent and equipoise regarding the risks or benefits to the patient of allocation to one group or the other.

Probably the best example of a randomized registry trial is the TASTE (Thrombus Aspiration in ST Elevation MI) study performed in Scandinavia.[17,18] This study randomized patients experiencing STEMI to a specific attempt at thrombus aspiration during percutaneous coronary intervention (PCI) versus standard PCI alone. Enrollment was relatively straightforward, since STEMI patients in Scandinavia are typically entered into the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART), a well-developed registry. Following informed consent, patients were randomly allocated to thrombus aspiration or standard PCI. The outcome was "hard" (mortality at 30 days) and ascertained by querying SWEDEHEART. Most patients agreed to participate, and the incremental cost of enrolling a patient in the TASTE study, as opposed to just the underlying registry, was $50.[18] Thrombus aspiration was found not to provide a survival advantage, compared with standard PCI for STEMI.[17]

Existing Vascular Surgery Registries (Table 199.2)

Vascular Quality Initiative

The Vascular Quality Initiative (VQI) sponsored and administered by the Society for Vascular Surgery (SVS) is the largest vascular-focused registry family in the United States, with more than 370 participating centers, more than 2500 providers from multiple specialties, and nearly 300,000 cases entered in 12 distinct procedure-related registries as of June 2016 (Fig. 199.2). The purpose of the VQI registries is to provide information regarding indications, patient characteristics, procedure performance, and clinical outcomes that will support quality improvement efforts.[19] The participating centers are also organized into 17 regional groups, most of which have in-person semiannual meetings to facilitate more informal sharing of best practices and lessons learned (see Fig. 199.2).[20]

The SVS VQI is organized as a Patient Safety Organization (PSO), which is a legal entity defined by the Patient Safety Act of 2005. As long as it meets certain statutory requirements concerning confidentiality and operates according the rules specified by the Patient Safety Act, institutions participating in the PSO can transmit PHI to the registry without obtaining informed consent. By law, a PSO's primary purpose must be quality improvement, so there are also provisions in the Patient Safety Act that promote transparent reporting of adverse outcomes and prevent use of the data for disciplinary or corrective action. Thus information regarding clinical outcomes and processes of care—also termed Patient Safety Work Product—can only be publicly distributed in de-identified fashion. Public comparison of performances between identified centers or providers is also prohibited.

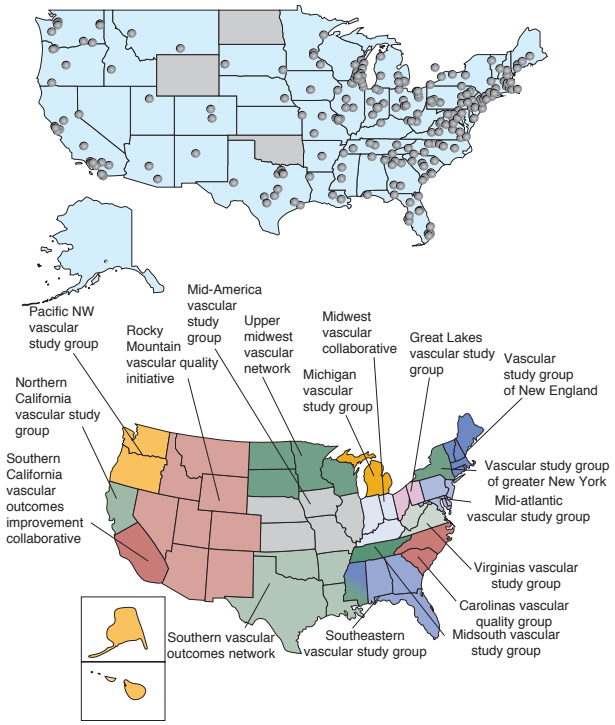
VQI participants enter clinical data into a commercially operated web-based data platform. The method of data collection is not prescribed, allowing flexibility in workflows that can be tailored to each individual center. Thus some centers have providers enter data at the point of care, others rely on employed data coordinators, and some use commercial data abstraction services.

As mentioned earlier, completeness of case capture and accuracy are the key determinants of registry validity. The VQI requires that all cases eligible for registry entry be submitted—a

TABLE 199.2 Vascular Registries

Registry NSQIP	Sponsor	Strengths	Limitations
VQI	Society for Vascular Surgery	100% data collection, extensive procedural detail, 1-year follow-up	Cost, data completeness, complexity
NSQIP	American College of Surgeons	Systematic data collection approach; rigorous auditing	Limited clinical detail, sampling, limited long-term follow-up
Vascunet	European Society for Vascular Surgery	Multitude of countries and regions represented	Heterogeneous data input policies and completeness
National Cardiovascular Data Registry	American College of Cardiology	Extensive detail on peripheral vascular intervention, multidisciplinary	Limited detail on non-PVI procedures

NSQIP, National Surgical Quality Improvement Program.



Total procedures captured (as of 6/1/2016)	298,303
Peripheral vascular intervention	93,996
Carotid endarterectomy	68,466
Infra-inguinal bypass	30,947
Endovascular AAA repair	27,326
Hemodialysis access	25,450
Carotid artery stent	11,183
Supra-inguinal bypass	10,508
Open AAA repair	8,322
Thoracic and complex EVAR	6,426
IVC filter	5,541
Leg amputations	5,399
Varicose vein	4,739

Figure 199.2 Status of the Society for Vascular Surgery Patient Safety Organization as of June 2016. There were 379 participating centers from 46 states and the Canadian province of Ontario organized into 17 regional quality groups. *EVAR,* Endovascular aneurysm repair.

process that is audited by the review of claims records. The lack of a requirement for individual patient-informed consent also facilitates completeness of case capture. The VQI does not systematically audit a random sample of records for accuracy of specific data, but rather uses statistically targeted auditing. According to this policy, centers or specific case records may be audited based on their apparent outlier status, depending on the analysis.

Another important distinctive of the VQI is a requirement for follow-up of outcomes approximately 1 year after the procedure. While this requirement significantly raises the effort necessary to participate in the VQI (increased complexity), the registry can thus provide information about which patients undergoing vascular intervention are most likely to have sustained benefit (as opposed to simply surviving the perioperative period). Since many vascular procedures are performed for preventive (e.g., asymptomatic carotid stenosis or intact AAA) or lifestyle (e.g., claudication) indications, knowing which patients are likely to survive long enough to benefit from the intervention is critical information during preoperative decision-making.

American College of Surgeons National Surgical Quality Improvement Program

The National Surgical Quality Improvement Program (NSQIP) is operated by the American College of Surgeons (ACS) and is patterned after the earlier Veterans Administration Surgical Quality Improvement Program (VASQIP).[21-23] In its current form, it offers several options for participation, depending on the size of the hospital and associated resources for data collection. NSQIP contains a procedure-targeted vascular module.[24] Under this option, a hospital collects 100% of procedures performed defined by a specific subset of vascular CPT codes. Procedure data are abstracted by trained personnel who are periodically audited by NSQIP. A number of procedure-relevant outcomes are captured, but follow-up is limited to 30 days after surgery.

National Veterans Administration Surgical Quality Improvement Program

This registry served as the prototype for the American College of Surgeons National Surgical Quality Improvement Program mentioned previously.[21] The two programs function very similarly, except that this program is restricted to United States Veterans Administration hospitals.

Vascunet

Vascunet is a collection of international registries (or audits) organized by the European Society for Vascular Surgery.[25,26] The participating countries are Australia, Denmark, Finland, Germany, Hungary, Iceland, Italy, New Zealand, Norway, Spain, Sweden, Switzerland, and the United Kingdom. Each country operates its own registry, which can vary in types of procedures and data elements collected, as well as length of follow-up. Case registration is not always mandatory.

For the Scandinavian registries, vital status and relatively long-term follow-up can be obtained through linkage with national administrative databases. Although not comprehensive nor covering all countries participating in Vascunet, formal auditing for data capture and consistency have been performed in Hungary[27] and Sweden[28] with acceptable results.

For some registries reporting is mandatory, and for others it is voluntary. In the United Kingdom, reporting is mandatory and data are collected for the purposes of public reporting of outcomes following AAA, carotid endarterectomy (CEA), and lower extremity procedures. Public reports for both hospitals and individual consultant surgeons are released.[29]

The Vascunet collaboration has published several articles describing variation in indications and outcomes for AAA,[30,31] popliteal aneurysm,[32] infrainguinal bypass surgery,[33] and CEA.[34,35] Other reports have highlighted the challenges of reconciling and harmonizing data from numerous national registries in order to properly leverage the large numbers of cases that can be pooled by such collaborations.[36]

National Cardiovascular Data Registry

The National Cardiovascular Data Registry (NCDR) administered by the American College of Cardiology operates a suite of registries mostly focused on cardiac procedures. In 2014, the NCDR launched its PVI Registry to collect lower extremity arterial catheter-based interventions, carotid stent, and endarterectomy procedures.[37]

ROLE OF MEDICAL REGISTRIES IN QUALITY IMPROVEMENT

Most registries established for QI purposes (VQI, ACS-NSQIP, VASQIP) return information to their participants in the form of benchmarking (crude and risk-adjusted). ACS-NSQIP and VQI also make available de-identified data sets that allow focused QI research into a particular topic. VQI also facilitates customized querying of an individual site's own data through an online analytics engine incorporated into the web-based data entry platform.

Within the context of the SVS VQI, information from the registries serves as the substrate for separate and distinct quality improvement efforts. The VQI is governed by its participants, who commission the Patient Safety Organization (owned and operated by the SVS) to analyze the registry data in order to uncover variations in practice performance and clinical outcomes in order to identify opportunities to improve vascular care. The VQI communicates these findings to its participants in the form of Center Opportunity Profile for Improvement (COPI) reports, along with other report formats informing individual providers of their performance in selected areas, such as smoking cessation counseling or prescription of antiplatelet/statin medication at discharge.

An individual COPI report focuses on a particular clinical issue or outcome such as surgical site infection (SSI) after lower extremity bypass or stroke/death following carotid intervention. A multivariable model predicting the outcome of interest is developed based on nationwide data from the relevant VQI registry. This multivariable model is then used to predict the likelihood of the outcome occurring for a given center, which is then compared with the observed frequency of the outcome at that center, in the form of an observed/expected (O/E) ratio. Individualized feedback to participating centers is then provided, along with information regarding the rates of risk factors or clinical characteristics associated with the outcome of interest. When these risk factors or clinical characteristics are modifiable, the center could potentially improve its performance through attention to these particular factors through a change in process of care. For other risk factors that may not be modifiable (e.g., patient co-morbidities), knowledge of these characteristics could assist in optimizing patient selection for a particular procedure or making the informed consent process more relevant for an individual patient.

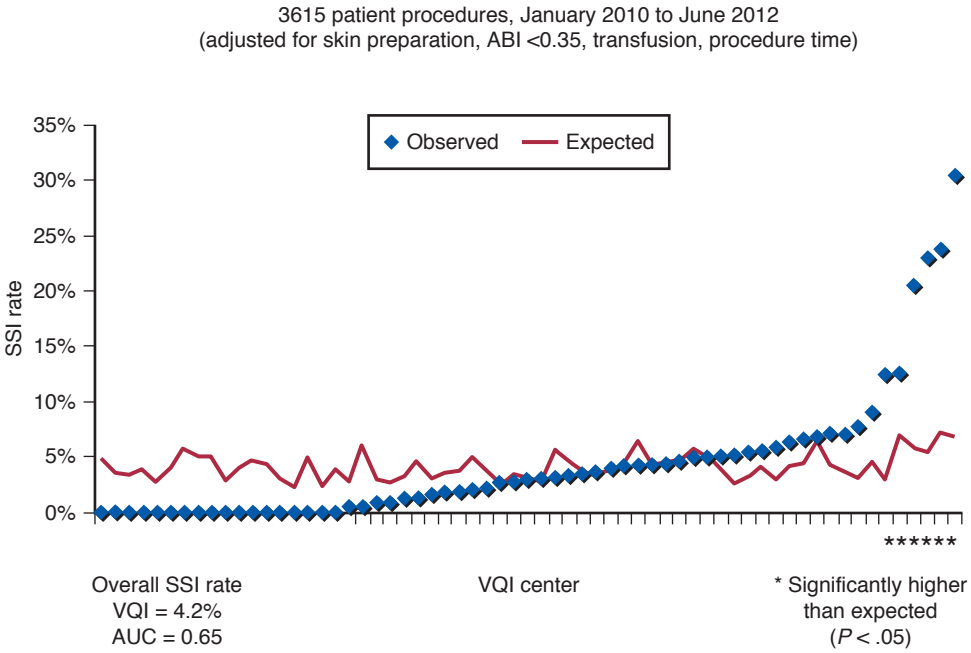
The impact of the VQI COPI report for SSI after lower extremity bypass is presented as an example.[38] SSI is an outcome of interest following lower extremity bypass and is specifically captured by VQI at the time of discharge after the index procedure. Significant variation in the occurrence of SSI was noted, ranging from 0% to 30% (Fig. 199.3). The multivariable model identified low ABI, increased operative time, transfusions, and use of a nonchlorhexidine skin preparation agent as risk factors for SSI; the latter three are potentially modifiable process measures (Fig. 199.4). The COPI report for each center participating in the lower extremity bypass registry reported that center's O/E ratio for SSI and whether the O/E ratio was significantly different. Each center also received information about the prevalence of pertinent risk factors for SSI specific to their patients (see Fig. 199.4).

Following the release of the SSI COPI report, there was a significant increase in use of chlorhexidine for skin preparation, a reduction in transfusions, and reduced operating time. There was a trend toward reduced SSI, which was not statistically significant nationwide. However, there was a statistically significant decline in SSI among centers that had the greatest increase in chlorhexidine usage (Fig. 199.5).

The VQI has released other COPI reports focusing on length of stay (LOS) after elective CEA and endovascular aneurysm repair (EVAR), with corresponding reductions in LOS among participating centers (Fig. 199.6).

The initial experience with VASQIP showed a relatively dramatic improvement in surgical quality (27% and 45% reductions in 30-day mortality and major morbidity, respectively) within the VA system, coinciding with delivery of individualized feedback regarding outcomes.[39] It is very common to see reports of improved quality connected to registry participation.[12] However, these reports typically are not controlled for secular trends in overall improvement in care, and the observed quality improvement may not be a direct result of registry participation.

There is now increasing recognition that simply providing information about a center's performance may not result in consistently improved performance.[14] Two recent reports that did control for an overall secular improvement in care indicated that the rate of improvement in mortality or major morbidity among centers participating in NSQIP did not exceed the observed rate of improvement in the same outcomes among centers that did not participate in NSQIP.[40,41] The current interpretation of these potentially sobering reports is that some form of organized quality improvement process must be implemented in response to the data to truly drive improved performance.[14,42] Such QI processes may take the form of Plan-Do-Study-Act (PDSA)



Variable	*OR*	*95% CI*	*P*
ABI <0.35	1.54	1.03–2.30	<.04
Procedure time >220 minutes	2.11	1.05–4.23	<.04
Transfusion >2 units pRBCs	3.30	2.17–5.02	<.001
Chlorhexidine w / wo alcohol prep	0.53	0.35–0.79	.002

ABI, ankle-brachial index; *CI*, confidence interval; *OR*, odds ratio; *pRBCs*, packed red blood cells; *w/wo*, with or without.

Figure 199.3 Variation in surgical site infection *(SSI)* following lower extremity bypass in individual vascular quality initiative *(VQI)* centers between January 2010 and June 2012. Rates of SSI ranged from 0% to 30%. Six centers were statistical outliers with high O/E ratios *(asterisks)*. Independent risk factors for SSI after lower extremity bypass in the VQI between January 2010 and June 2012. (From Kalish et al. *J Vasc Surg.* 2014 [Reference 35].)

cycles, LEAN, or Six Sigma programs operating at the local center level. So while robust reliable data, often collected through a registry, is **necessary** for quality improvement, it may not be **sufficient**.[14]

PUBLIC REPORTING OF REGISTRY DATA

There is a strong presumption that the public has a right to information about surgical quality performance in order to make the most informed choices regarding where to obtain healthcare. To this end, public reporting of surgical outcomes may be desirable. On the other hand, there is concern that public access to quality performance information will reduce the willingness of providers and centers to be forthright when discussing adverse events, thereby compromising quality improvement efforts that are widely believed to be enhanced by assurances of confidentiality.[43]

When evaluating a registry, it is important to know whether the data are used for public reporting, as there may be conditions applied to the collection and reporting of the data that will affect its validity and the overall confidence in the data. Information about how outliers are identified and confirmed should be available to both participants and consumers of the information. At a minimum, reports of mortality and morbidity should be risk-adjusted so that hospitals and providers caring for sicker, more complex patients are not unfairly labeled as subpar because of the expected higher incidence of adverse outcomes occurring in this higher risk population.

Two prominent examples of public reporting of cardiovascular outcomes are the New York State Cardiac Registries[44] and the Vascular Services Quality Improvement Program (VSQIP) in the United Kingdom, covering AAA, CEA, and lower extremity PAD procedures.[45,46] Registration of all eligible patients is mandatory in both programs and both programs report both hospital-specific and surgeon-specific risk-adjusted outcomes.

COPI	VQI wound infection rate			3.6%	SVS PSO
	Center name				
	Your center's number of procedures			21	
	Your center's wound infection rate			28.6%	
	Your center's wound infection expected rate			5.9%	
	Observed rate vs. expected rate			Rates significantly different $P < .01$	
	Predictors of wound infection			**Your center**	
VQI Average	Chlorhexidine skin prep **60%**	Transfusion ≥3 units **5.8%**	Procedure time >220 minutes **50%**	Improvement opportunity	
	Higher is better	**Lower is better**	**Lower is better**		
Your center	57%	33%	71%	Significantly higher infection rate than expected. Switch to chlorhexidine. Reduce number of transfusions.	

Note: This patient safety work product generated within the SVS PSO,LLC, is considered privileged and confidential.

Figure 199.4 Example of Center Opportunity Profile for Improvement *(COPI)* report regarding surgical site infection (SSI) after lower extremity bypass to a fictional vascular quality initiative *(VQI)* center. In this center's case, the observed (28.6%) to expected (5.9%) SSI rate is statistically high ($P < .01$). Increasing chlorhexidine use, reducing transfusions, and shortening procedure times represent opportunities for changes in the process of care that would be predicted to lower future SSI rates. *SVS PSO,* Society for Vascular Surgery Patient Safety Organization. (Courtesy of Society for Vascular Surgery Patient Safety Organization.)

Following the onset of public reporting, risk-adjusted cardiac surgery mortality in New York fell 41%.[44] In an attempt to determine if public reporting in New York was associated with a differential impact on mortality, comparison with other states who did not publicly report outcomes showed that New York's outcomes were significantly better, with a calculated odds ratio for short-term mortality of 0.66.[44] There is some controversy as to whether public reporting has produced risk aversion (thus potentially denying high-risk patients needed care) among New York hospitals and surgeons; data have been published supporting both sides of the issue.[44]

Similar concerns have been raised in the United Kingdom, and Karthikesalingam et al.[46] have advanced strong arguments specifically against surgeon-specific outcomes reporting. Important points include the fact that case numbers for individual surgeons are much lower than hospital-specific numbers, leading to greater statistical uncertainty. Also, they note the possibility of risk aversion and unfair attribution of any particular patient's death to an individual surgeon in an era where team-based care is increasingly emphasized and recognized as correlating with patient outcomes.

Defenders of public reporting recognize that such a practice introduces unwanted incentives to maximize the risk profile or underreport mortality. Rigorous external auditing assessing both completeness and accuracy is necessary to maintain the confidence of both public and the healthcare community in these registries.[44]

Registries such as the SVS VQI are organized under legislation (Patient Safety Act of 2005) that specifically prohibits the public release of hospital- or surgeon-specific outcomes. PSOs are intentionally designed to foster the free exchange of information between hospitals and providers in order to promote the transparency and dissemination of best practices/lessons learned. The primary purpose of the SVS VQI is to improve quality, not to inform the public of the specific performance of individual hospitals or surgeons.

THE FUTURE OF MEDICAL REGISTRIES

In our opinion, medical registries—even more specifically vascular registries—are here to stay. The information they provide is distinctly different from formal RCTs. Their data represent a real-world experience that can be extremely valuable, assuming the data contained in the registry are believable.[6] Many important clinical questions can only be answered by the systematic collection of clinical data obtained during the routine delivery of vascular care—especially information that allows characterization of relatively low-frequency events unlikely to be seen in statistically valid numbers by any single center or practitioner.[12]

Cost is the primary challenge facing clinical registries. The more complex registries collect and analyze information at a granular level that can support detailed and valuable analyses. But the more complex registries are more expensive in terms of infrastructure, as well as the time and effort required by sites to enter the data. As the value of registries is increasingly recognized by regulatory agencies and industry and third-party payers, it is likely that the cost of participation will be

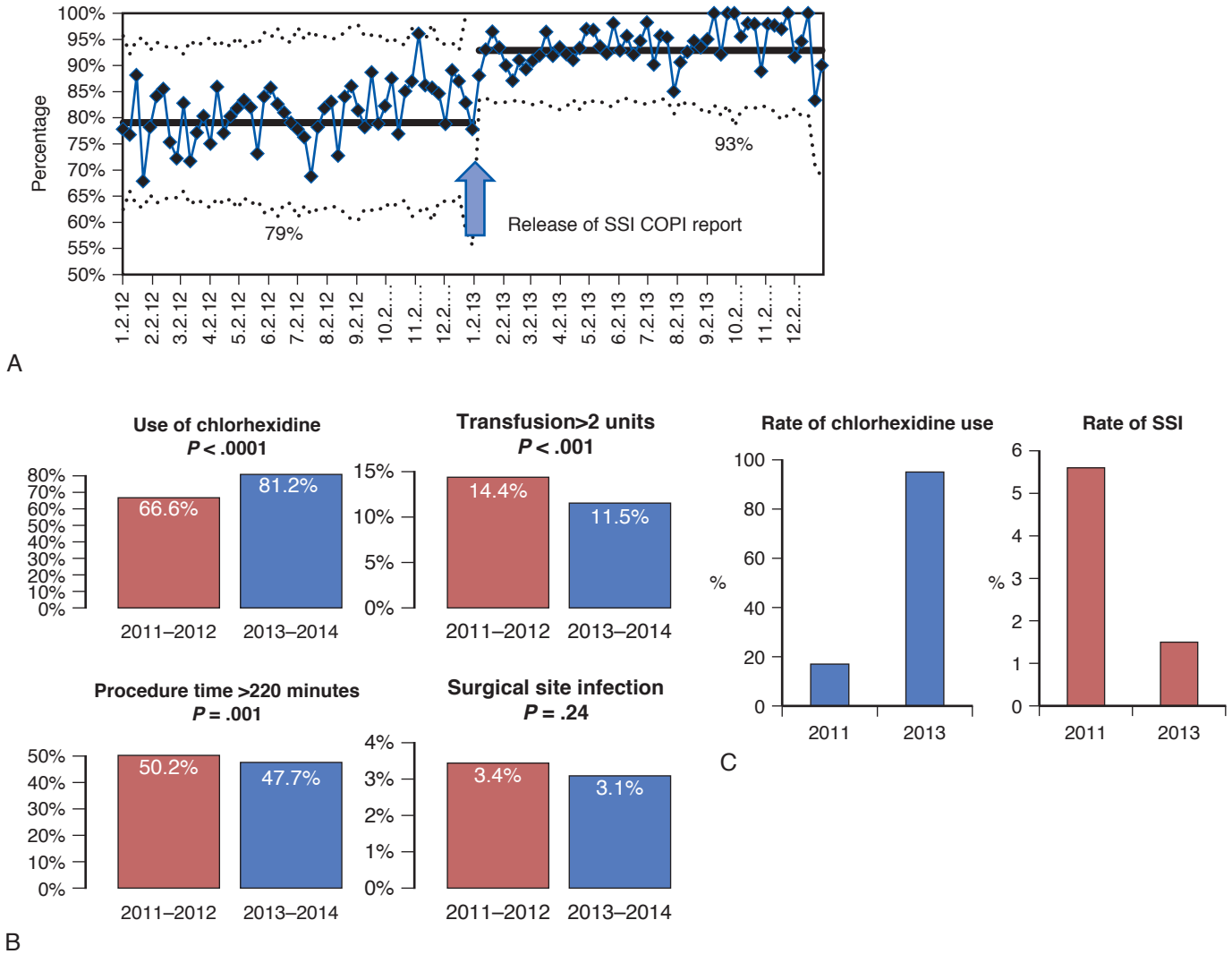


Figure 199.5 **Impact of Surgical Site Infection Center Opportunity Profile for Improvement *(SSI COPI)* Report in the Vascular Quality Initiative (VQI).** (A) Statistical process control chart showing the rate of chlorhexidine use across the VQI before and after the release of the SSI COPI report *(blue arrow)*. (B) There were significant beneficial changes in chlorhexidine use, transfusion practice, and procedure time following release of the SSI COPI report. Coincidentally, SSI rates across the VQI decreased, but not to a statistically significant degree. (C) Among select VQI centers who had the greatest increase in chlorhexidine use (low to high utilizers), a statistically significant decrease in SSI rate was observed. (Courtesy of Society for Vascular Surgery Patient Safety Organization.)

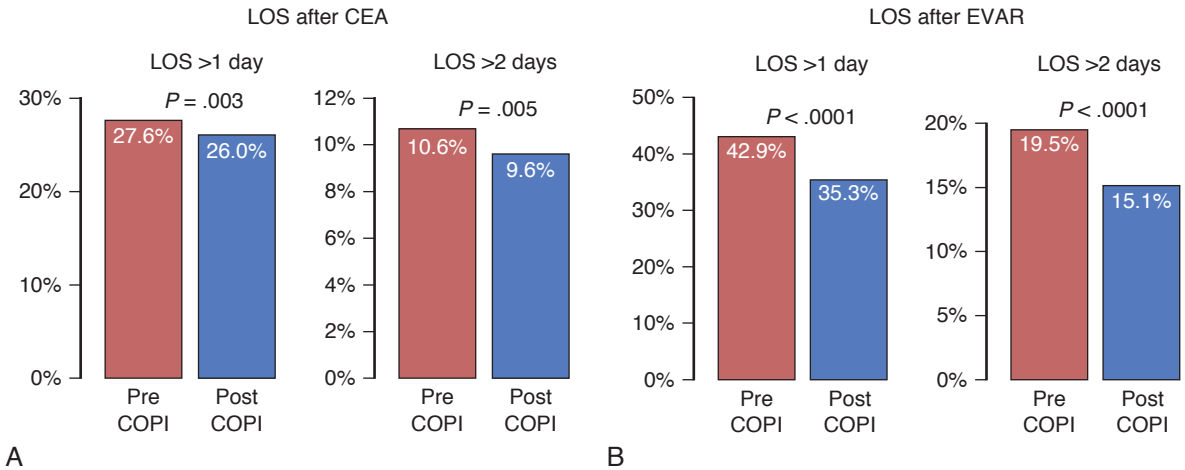


Figure 199.6 Impact of Center Opportunity Profile for Improvement *(COPI)* reports focusing of length of stay *(LOS)* after carotid endarterectomy (*CEA*; A) and elective endovascular aneurysm repair (*EVAR*; B). (Courtesy of Society for Vascular Surgery Patient Safety Organization.)

subsidized.[12] Alternatively, participation may be motivated by policies of payers or regulatory agencies that will give preferred status to registry participants.

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CHAPTER 200

Marketing a Vascular Surgery Practice

RUSSELL HOWARD SAMSON

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With the changing nature of healthcare, the competition for patients by hospital systems, private practices, and other entities is intensifying. Now most vascular surgeons are competing for patients not only with other vascular surgeons but also with physicians in other specialties. To some degree, then, marketing has become an imperative for vascular practices to survive. However, many medical professionals may be uncomfortable with marketing, comparing such activities to those of used car salespersons. However, if other physicians are unaware of the vascular surgeon's prowess and expertise, then they will be unlikely to refer their patients to that surgeon. Furthermore, if patients are unaware of the surgeon's experience or reputation, they will be less likely to consult with that doctor. Nor will they be as trusting of the surgeon's opinions and advice. This applies even to surgeons who get their referrals through the reputation of the university or hospital in which they work.

Accordingly, it behooves all vascular surgeons to consider marketing of some form. This does not necessarily imply high expense or sometimes distasteful television advertisements. Rather, marketing can be done in ways that, in and of itself, result in improved patient care and outcomes.

This chapter outlines the five principles of marketing to both patients and referring physicians: **Discovery, Strategy, Solutions, Implementation, and Review**. The vascular surgeon needs to understand what constitutes a marketing plan and how to evaluate its effectiveness. Not all marketing can achieve positive results, and poorly planned strategies can be costly and inefficient and even have a contrary result.

DISCOVERY

An essential aspect of marketing is self-discovery. There are two fundamental questions to ask oneself. First the vascular surgeon has to know what is the goal of a marketing campaign. Is the goal to simply increase new patients or is the goal to increase a specific type of new patient? For example, is it patients with a specific type of insurance, such as Medicare, or rather cash pay cosmetic clients? Is it patients with a specific vascular condition, such as patients with venous disease or perhaps abdominal aortic aneurysms? In general, targeted marketing will be more efficient and more likely to succeed. For some practices the object may be to maintain the current volume of established patients. Second, one has to look inward to identify what makes the individual surgeon or practice unique or marketable. Usually this will be because the surgeon has specific experience in certain procedures. However, it may be his or her reputation in the community as a caring physician. It could be contributions to local community charities or other nonmedical activities. It may be worthwhile to provide current patients with a brief questionnaire to identify why they first came to see the surgeon and why they are continuing as a patient. The office staff will also be able to provide this information because they are usually well aware of patients' regard for their doctor. This knowledge becomes even more important when marketing a multiperson practice where some individuals will not be as marketable as others. If this is the case the program may decide to highlight the practice reputation rather than one of its high-profile individuals.

Discovery also involves assessing potential market competitors. This will include not only other specialists who treat vascular conditions, such as cardiologists and interventional radiologists, but also dermatologists, podiatrists, and many general practitioners. Although not directly competitive, health insurers, hospitals, and multispecialty groups and accountable care organizations will also impact the vascular surgeon's ability to recruit patients. For example, a hospital with its own vascular surgeons may contract with a local business to provide all health services for that company's employees, thus excluding those

Abstract

Marketing is key to a successful practice. This chapter describes the general concepts necessary to establish a marketing campaign.

Keywords

discovery
strategy and solutions
internal marketing
external marketing
implementation

employees from the available pool of potential patients. Similarly, the demographics of a community also need to be taken into account when assessing the market potential. Certainly, a more aged community would be more likely to provide the patient population most suited to a vascular surgeon. As a corollary, a young population may be more appropriate for a practice trying to increase market share of patients with spider veins. Information about the market potential can be obtained from the local chamber of commerce.

Once the "competition" has been identified, it is also important to attempt to discern why they are successful. What attributes do they have that the practice does not possess? Similarly, what does the practice offer that they do not? Analyze also all aspects of their marketing. It may not be profitable, for example, to compete with television advertisements if their budget for such marketing far exceeds the vascular surgeons' own available funds.

STRATEGY AND SOLUTIONS

The strategy for marketing can be divided into internal marketing efforts and an external marketing campaign. However, the vascular surgeon must first assess the budget that he or she would be willing to spend. Television and newspaper advertisements can be very expensive. Furthermore, although large groups may be able to afford a marketing consultant, most individual or small practices will need to rely on partnering with other like-minded physicians, organizations, or institutions. Some insurance companies will advertise their medical panel in direct mailing as well as newspaper advertisements. A local hospital may be willing to advertise a unique aspect of the surgeon's practice. The local medical society may be willing to co-host a lecture series promoting that activity. The Society for Vascular Surgery has also prepared multiple documents on how to market a vascular practice. The society also has produced patient information brochures that are extremely useful for marketing purposes.

Most vascular surgeons who are already in practice will realize that the majority of patients come to them by direct referral from other physicians. Accordingly, it is imperative that, at a minimum, the surgeon must make networking with local referring physicians a priority. Therefore giving lectures at hospital grand rounds, socializing in the doctor's lounge, and becoming active on hospital or medical society committees are all important ways to improve patient referrals. Educational dinner meetings for referring doctors are an excellent method of demonstrating special techniques or therapies that the surgeon offers. The Society for Vascular Surgery has provided templates for how to run such a meeting, including how to analyze the effectiveness of the evening.

INTERNAL MARKETING

Other than referrals from other physicians, patient word of mouth comments are the most beneficial. Internal marketing to established patients enhances the potential for these patients to encourage new patients to come to the practice. Furthermore, it maintains loyalty to the practice and ensures that patients will return for regular follow-ups. A list of methods to provide internal marketing is included in Box 200.1.

However, it is usually beneficial for the practice to first develop a branding identity. This may include a logo or a catch phrase. Even an individual surgeon may benefit from a logo design. After this has been created, it should be used on all publications, stationery, clinical reports, brochures, and so on. Examples of internal marketing include patient education brochures; letters or electronic communication such as emails or text messages (provided that they are Health Insurance Portability and Accountability Act [HIPAA] compliant) informing patients of needed return visits or tests; and communications about upcoming lectures or new advances in vascular therapy that may benefit the patient. Telephone on-hold audio information about a new procedure or therapy can be more useful than music. Often overlooked, but extremely important, is ensuring that the office staff is polite, friendly, professional, and fully supportive of the practice identity. A rude front desk person can make all marketing meaningless! Similarly, an unkempt or untidy office or a habit of untimely patient appointments will be equally detrimental.

In this new electronic age, a website is almost essential. Many patients will turn to the web for information about the practice, including the physician's credentials, as well as general information such as the practice address and phone number. The website will also provide an opportunity to provide valuable information about the various conditions that patients will be inquiring about. Accordingly, a well-constructed professional website may enhance the practice reputation, as well as providing an important opportunity to market the practice. It will be extremely beneficial if the site is optimized by the major search engines to appear prominently on their web searches.

EXTERNAL MARKETING

Opportunities for external marketing abound. Many of these are listed in Box 200.2. However, some of these can be extremely expensive, such as television advertisements and billboards. Furthermore, television and radio, as well as newspaper advertisements, need to be repetitive and run over a prolonged period before they will have any effect. In general, practices advertising arterial therapies will probably not benefit from many of these. On the other hand, practices advertising cosmetic services for

BOX 200.1 Internal Marketing Opportunities

- Practice brochure CV of each physician and his/her special expertise
- Medical information brochures (e.g., AAA, varicose veins, carotid endarterectomy)
- Stationery with practice logo and catch phrase
- On-hold audio information
- Patient recall letters
- Product packaging (e.g., stockings) with logo
- Website
- Email newsletters
- Training the staff to best represent the practice
- Staff uniforms with practice logo

BOX 200.2 External Marketing

- Website
- Newspaper and magazine ads
- Free standing inserts for magazines and newspapers
- Radio and television commercials
- Billboards
- Promotions
- YouTube videos
- Direct mail postcards
- Yellow Page ads
- Val-Pak coupons
- External signage
- Facebook
- Twitter
- Blogs
- Dinner and hospital lectures

varicose veins may be obliged to use these methods because competitors may be using these approaches. It is important for practices to realize that external marketing to patients will also be seen by referring physicians. This can work to the practice's advantage if the marketing is performed in a tasteful and professional manner. Referring physicians may not have realized that the practice offered the services that are being advertised.

One form of advertising on television that is extremely effective and free, is to be interviewed as a local expert. Local channels frequently look toward local doctors to add commentary about a medical news item. Accordingly, making oneself available to the local channels can be very helpful.

Vascular screenings at health fairs are another method of advertising that can be effective and helpful for patients, if advertised and performed in a professional manner. Screening advertisements should not imply that patients are at risk if they do not attend. Nor should the benefits be exaggerated.

Social media such as Facebook and Twitter are increasingly being used to market medical practices. For these to be effective, they need to be updated frequently with compelling information. This can be time consuming for the practice, and therefore the assistance of a professional agency may be beneficial. Vascular surgeons also need to pay attention to the multitude of physician-rating agencies and websites where patients rate their doctors. A few malicious patient reviews can be very damaging to the surgeon's reputation. On the other hand, mention by one of the more widely known companies such as Castle Connolly can be helpful.

Finally, as managed care organizations increasingly control where patients receive their treatment, vascular surgeons need to make sure that they are included in these organizations' roster of specialists. In most cases it will be beneficial to prove that the practice not only delivers quality care but that it is cost-efficient. Therefore the practice must be knowledgeable about data such as hospital length of stay, cost of services, return to surgery, and hospital readmissions.

IMPLEMENTATION

Most internal marketing can easily be achieved without any professional assistance other than perhaps the development of a catch phrase or branding logo. As already described, the Society for Vascular Surgery provides information on how to market, as well as patient education and physician education brochures, as a valuable service to members. However, for internal marketing to be effective, someone in the practice has to spend the time to make sure that it is effective.

On the other hand, it is probably advisable that practices embarking on external marketing hire an advertising agency to assist in developing a marketing campaign. For example, although the practice can quite easily create a YouTube video, an unprofessional video may be counterproductive. Furthermore, creating media for newspaper advertisements, and especially television, will usually require significant expertise and expense. Although using an advertising agency is costly, a well-constructed marketing plan that is appropriately budgeted and executed should provide the desired results in a cost-effective manner. Practices must understand that even though they have hired an outside agency a hands-off approach, leaving everything up to that agency, will not work. The practice will have to invest time educating the agency about the practice, its goals, and the medical information the practice wishes to convey in its advertising. Failure to oversee the agency's work may result in embarrassing and counterproductive media content.

Identifying an advertising agency that is best suited to the practice can be difficult. However, it is generally advisable to use a local company because that agency will be more likely to know the intricacies of the local market. On the other hand, there are now multiple companies advertising their services on the web. However, these usually offer generic advice and content that may not work in the practice's community.

REVIEW

Perhaps reviewing the advertising is as important as discovery. It is critical to know whether the advertising is working or not and whether the practice is getting its "bang for the buck." This is especially so if a large amount of capital outlay was required. There are many metrics that can be analyzed to evaluate the benefit of advertising. The billing office can provide information on the numbers of new patients according to age, gender, disease process, insurance carrier, and other demographics such as patients' zip code. Similarly, the income derived from these new patients is also critical information. It is clearly not cost-efficient to spend $10,000 on an advertisement that generates only $2000 in revenue.

Other methods should also be used to determine what aspects of the advertising are most or least effective. For example, if a newspaper advertisement is placed for a cosmetic vein therapy, the ad could offer a discount if the patient brings in the advertisement. These inducements may not be practical for other forms of advertising. Accordingly, the most effective method is to request new patients complete a brief questionnaire about why the patient chose the practice or physician. Because patients will often have a primary and secondary reason or sometimes even a third reason for coming to the practice, these questions have to be very carefully developed. For

example, a patient may be referred to the practice by the primary physician but made the appointment only after they saw an advertisement in the newspaper or were encouraged by a friend or relative. In addition, if the practice is advertising in multiple print media it does not help to simply ask whether they saw a practice advertisement. Rather, there needs to be a checkbox for each magazine or newspaper in which that advertisement appears. An analysis of patients' experience in the office after their appointment is also very helpful in assessing internal marketing. For example, questions about the cleanliness of the office, waiting times, or their overall experience with the physician may unmask areas for potential improvement. Because some patients may be unwilling to complete these questionnaires, it may be helpful to offer the opportunity for them to win a small monthly prize for those completing these forms.

It is advisable that the practice performs the review process on a regular basis. This will allow manipulation of the various marketing materials to better conform to changing conditions. However, the benefits of a marketing campaign may take some time to manifest.

SUMMARY

Although some vascular surgeons consider marketing distasteful, almost all are marketing their practices in one way or another. Furthermore, vascular surgery has become a highly competitive field as nonsurgeons increasingly become involved in treating vascular conditions. To some degree, then, marketing has become an imperative for vascular surgeons' practices to survive. This chapter provides an overview of what is necessary for a marketing effort. How a vascular surgeon goes about marketing will be dependent on local factors, as well as their own priorities, abilities, and finances.

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The Society for Vascular Surgery has produced many videos that help vascular surgeons to develop marketing programs

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The SVS also has produced video and marketing tools for branding